

## **I. THERAPEUTIC CLASS**

KEYTRUDA (pembrolizumab) is an antineoplastic agent, monoclonal antibody.

## **II. COMPOSITION**

### ***IIa. Active Ingredients***

Pembrolizumab

### ***IIb. Inactive Ingredients***

L-histidine  
L-histidine hydrochloride monohydrate  
Sucrose  
Polysorbate 80  
Water for injection

## **III. CLINICAL PHARMACOLOGY**

### ***IIIa. Mechanism of Action***

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumor cells to inhibit active T-cell immune surveillance. KEYTRUDA is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumor cells. By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.

In preclinical murine models, combinations of an anti-mouse PD-1 antibody plus a TKI have demonstrated enhanced anti-tumor activity compared to either agent alone.

### ***IIIb. Pharmacokinetics***

The pharmacokinetics of pembrolizumab was studied in 2993 patients with various cancers who received doses in the range of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. There are no clinically meaningful differences in pharmacokinetics of pembrolizumab across indications.

#### ***IIIb-1. Absorption***

KEYTRUDA is dosed via the IV route and therefore is immediately and completely bioavailable.

#### ***IIIb-2. Distribution***

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

#### ***IIIb-3. Metabolism***

Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its clearance.

#### **IIIb-4. Elimination**

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the terminal half-life ( $t_{1/2}$ ) is 22 days (32%).

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration ( $C_{max}$ ), trough concentration ( $C_{min}$ ), and area under the plasma concentration versus time curve at steady state ( $AUC_{ss}$ ) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Following administration of pembrolizumab 200 mg every 3 weeks in patients with cHL, the observed median  $C_{min}$  at steady-state was up to 40% higher than that in other tumour types treated with the same dosage; however, the range of trough concentrations is similar. There are no notable differences in the median  $C_{max}$  between cHL and other tumour types. Based on available safety data in cHL and other tumour types, these differences are not considered clinically meaningful.

#### **IIIb-5. Special Populations**

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild or moderate hepatic impairment, and tumor burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure. Pembrolizumab exposure with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients ( $\geq 3$  to 17 years) are comparable to those of adults at the same dose.

##### Renal Impairment

The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild ( $GFR < 90$  and  $\geq 60$  mL/min/1.73 m<sup>2</sup>) or moderate ( $GFR < 60$  and  $\geq 30$  mL/min/1.73 m<sup>2</sup>) renal impairment compared to patients with normal ( $GFR \geq 90$  mL/min/1.73 m<sup>2</sup>) renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients with normal renal function. KEYTRUDA has not been studied in patients with severe ( $GFR < 30$  and  $\geq 15$  mL/min/1.73 m<sup>2</sup>) renal impairment. [See *Dosage and Administration (VI- Renal Impairment)*.]

##### Hepatic Impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild and moderate hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN and TB >1.5 to 3 x ULN and any AST, respectively, as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST  $\leq$ ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with severe (TB >3 x ULN and any AST) hepatic impairment. [See *Dosage and Administration (VI- Hepatic Impairment)*.]

### **IIIc. Pharmacodynamics**

Based on the modeling of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy and safety between the doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.

In peripheral blood of patients who received KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or 3 weeks, an increased percentage of activated (i.e., HLA-DR+) CD4+ and CD8+ T-cells was observed after treatment at all doses and schedules without an increase in the circulating T-lymphocyte number.

### **IIId. Clinical Studies**

#### **Melanoma**

##### **KEYNOTE-006: Controlled trial in melanoma patients naïve to treatment with ipilimumab**

The efficacy of KEYTRUDA was investigated in KEYNOTE-006, a multicenter, controlled, Phase III study for the treatment of unresectable or metastatic melanoma in patients who were naïve to ipilimumab and who received no or one prior systemic therapy. Patients were randomized (1:1:1) to receive KEYTRUDA at a dose of 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab (n=278). Randomization was stratified by line of therapy, ECOG performance status, and PD-L1 expression status. The study excluded patients with autoimmune disease or those receiving immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection. Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter.

Of the 834 patients in KEYNOTE-006, 60% were male, 44% were ≥65 years (median age was 62 years [range 18-89]) and 98% were white. Sixty-six percent had no prior systemic therapies and thus received study therapy as first-line treatment whereas 34% had one prior therapy and thus received study therapy as second-line treatment. Thirty-one percent had an ECOG PS of 1 and 69% had an ECOG PS of 0. Eighty percent of patients were PD-L1 positive (PD-L1 membrane expression in ≥1% of tumor and associated immune cells as assessed prospectively by an immunohistochemistry assay with the 22C3 anti-PD-L1 antibody) and 18% were PD-L1 negative. Sixty-five percent of patients had M1c stage, 32% had elevated LDH and 9% had brain metastases. BRAF mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumors, 139 (46%) were previously treated with a BRAF inhibitor. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumors [RECIST 1.1]). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 1 summarizes key efficacy measures.

**Table 1: Response to KEYTRUDA 10 mg/kg every 2 or 3 weeks  
in Patients with Ipilimumab-Naïve Advanced Melanoma in KEYNOTE-006**

| Endpoint                                                    | KEYTRUDA<br>10 mg/kg every<br>3 weeks<br>n=277 | KEYTRUDA<br>10 mg/kg every<br>2 weeks<br>n=279 | Ipilimumab<br><br>n=278      |
|-------------------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------|
| <b>OS*</b>                                                  |                                                |                                                |                              |
| Number (%) of patients with event                           | 92 (33%)                                       | 85 (30%)                                       | 112 (40%)                    |
| Hazard ratio <sup>†</sup> (95% CI)                          | 0.69 (0.52, 0.90)                              | 0.63 (0.47, 0.83)                              | ---                          |
| p-Value <sup>‡</sup>                                        | 0.00358                                        | 0.00052                                        | ---                          |
| Median in months (95% CI)                                   | Not reached<br>(NA, NA)                        | Not reached<br>(NA, NA)                        | Not reached<br>(13, NA)      |
| <b>PFS<sup>§</sup> by IRO<sup>¶</sup></b>                   |                                                |                                                |                              |
| Number (%) of patients with event                           | 157 (57%)                                      | 157 (56%)                                      | 188 (68%)                    |
| Hazard ratio <sup>†</sup> (95% CI)                          | 0.58 (0.47, 0.72)                              | 0.58 (0.46, 0.72)                              | ---                          |
| p-Value <sup>‡</sup>                                        | <0.00001                                       | <0.00001                                       | ---                          |
| Median in months (95% CI)                                   | 4.1 (2.9, 6.9)                                 | 5.5 (3.4, 6.9)                                 | 2.8 (2.8, 2.9)               |
| <b>Best Overall Response<sup>§</sup> by IRO<sup>¶</sup></b> |                                                |                                                |                              |
| ORR % (95% CI)                                              | 33% (27, 39)                                   | 34% (28, 40)                                   | 12% (8, 16)                  |
| Complete response %                                         | 6%                                             | 5%                                             | 1%                           |
| Partial response %                                          | 27%                                            | 29%                                            | 10%                          |
| <b>Response Duration<sup>#</sup> by IRO<sup>¶</sup></b>     |                                                |                                                |                              |
| Median in months (range)                                    | Not reached<br>(2.0+, 22.8+)                   | Not reached<br>(1.8+, 22.8)                    | Not reached<br>(1.1+, 23.8+) |
| % ongoing at 12 months <sup>▷</sup>                         | 79%                                            | 75%                                            | 79%                          |

\* Based on second interim analysis

† Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model

‡ Based on stratified Log rank test

§ Based on first interim analysis

¶ IRO = Independent radiology plus oncologist review using RECIST 1.1

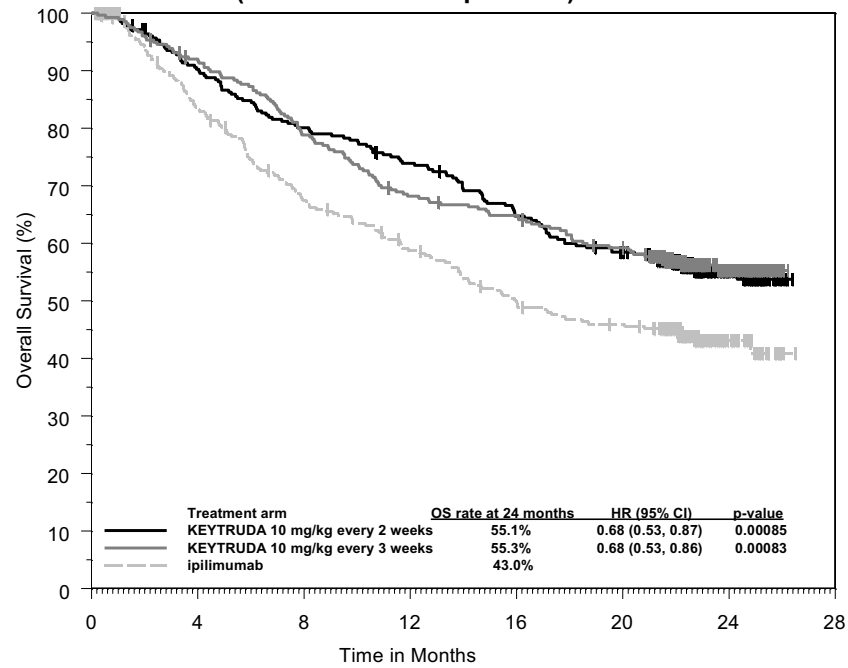
# Based on patients with a best overall response as confirmed complete or partial response from the final analysis

▷ Based on Kaplan-Meier estimates

NA = not available

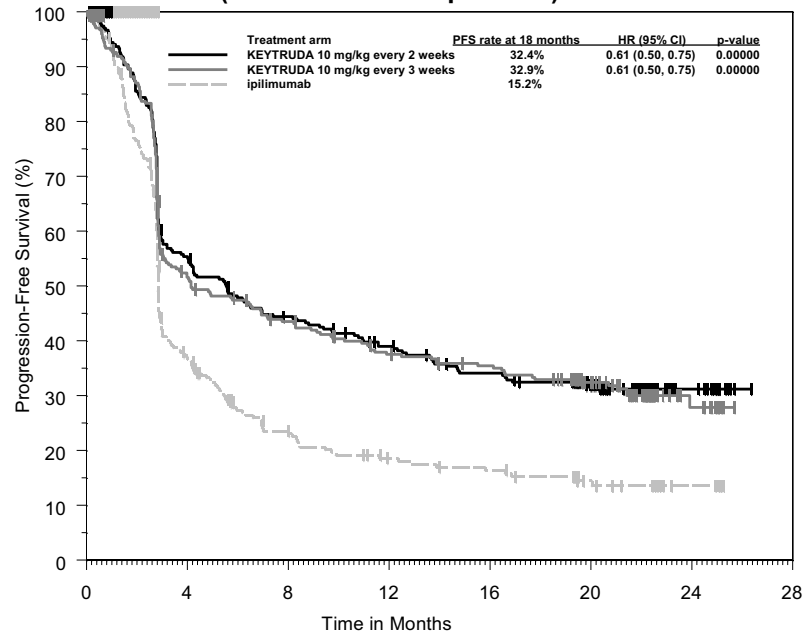
The final analysis was performed after all patients had at least 21 months of follow-up. The final OS analysis was performed after 383 patient events (119 for KEYTRUDA 10 mg/kg every 3 weeks, 122 for KEYTRUDA 10 mg/kg every 2 weeks and 142 for ipilimumab). The OS HRs vs. ipilimumab were 0.68 (95% CI: 0.53, 0.86; p<0.001) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks and 0.68 (95% CI: 0.53, 0.87; p<0.001) for patients treated with KEYTRUDA 10 mg/kg every 2 weeks. The OS rate at 18 months and 24 months were 62% and 55% respectively for KEYTRUDA 10 mg/kg every 3 weeks, 60% and 55% respectively for KEYTRUDA 10 mg/kg every 2 weeks, and 47% and 43% respectively for ipilimumab. At the final analysis, a long-term PFS analysis was performed based on 566 patient events (183 for KEYTRUDA 10 mg/kg every 3 weeks, 181 for KEYTRUDA 10 mg/kg every 2 weeks and 202 for ipilimumab). The PFS HRs vs. ipilimumab were 0.61 (95% CI: 0.50, 0.75) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks and 0.61 (95% CI: 0.50, 0.75) for patients treated with KEYTRUDA 10 mg/kg every 2 weeks. (See Figures 1 and 2.) The percentage of responders with an ongoing response at 18 months was 68% for KEYTRUDA 10 mg/kg every 3 weeks, 71% for KEYTRUDA 10 mg/kg every 2 weeks and 70% for ipilimumab.

**Figure 1: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-006 (Intent to Treat Population)**



| Number at Risk                   |     | Time in Months |     |     |     |     |    |   |
|----------------------------------|-----|----------------|-----|-----|-----|-----|----|---|
| KEYTRUDA 10 mg/kg every 2 weeks: | 279 | 249            | 221 | 202 | 176 | 156 | 44 | 0 |
| KEYTRUDA 10 mg/kg every 3 weeks: | 277 | 251            | 215 | 184 | 174 | 156 | 43 | 0 |
| ipilimumab:                      | 278 | 213            | 170 | 145 | 122 | 110 | 28 | 0 |

**Figure 2: Kaplan-Meier Curve for Progression-Free Survival (Based on IRO) by Treatment Arm in KEYNOTE-006 (Intent to Treat Population)**



|                                  |     | Time in months |     |    |    |    |    |   |
|----------------------------------|-----|----------------|-----|----|----|----|----|---|
| Number at Risk                   |     |                |     |    |    |    |    |   |
| KEYTRUDA 10 mg/kg every 2 weeks: | 279 | 148            | 116 | 98 | 82 | 52 | 16 | 0 |
| KEYTRUDA 10 mg/kg every 3 weeks: | 277 | 136            | 111 | 91 | 84 | 60 | 13 | 0 |
| ipilimumab:                      | 278 | 88             | 48  | 34 | 29 | 16 | 5  | 0 |

#### Sub-population analysis by BRAF mutation status

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were BRAF wild type, BRAF mutant without prior BRAF treatment and BRAF mutant with prior BRAF treatment. The PFS hazard ratios (HRs) (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.61 (95% CI: 0.49, 0.76) for BRAF wild type, 0.52 (95% CI: 0.35, 0.78) for BRAF mutant without prior BRAF treatment, and 0.76 (95% CI: 0.51, 1.14) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.68 (95% CI: 0.52, 0.88) for BRAF wild type, 0.70 (95% CI: 0.40, 1.22) for BRAF mutant without prior BRAF treatment, and 0.66 (95% CI: 0.41, 1.04) for BRAF mutant with prior BRAF treatment. ORR for pooled KEYTRUDA vs. ipilimumab was 38% vs. 14% for BRAF wild type, 41% vs. 15% for BRAF mutant without prior BRAF treatment, and 24% vs. 10% for BRAF mutant with prior BRAF treatment.

#### Sub-population analysis by PD-L1 status

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were PD-L1 positive vs. PD-L1 negative. The PFS HRs (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.53 (95% CI: 0.44, 0.65) for PD-L1 positive patients and 0.87 (95% CI: 0.58, 1.30) for PD-L1 negative patients. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.63 (95% CI: 0.50, 0.80) for PD-L1 positive patients and 0.76 (95% CI: 0.48, 1.19) for PD-L1 negative patients.

#### KEYNOTE-002: Controlled trial in melanoma patients previously treated with ipilimumab

The efficacy of KEYTRUDA was investigated in KEYNOTE-002, a multicenter, controlled study for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor. Patients were randomized (1:1:1) to receive KEYTRUDA at a dose of 2 (n=180) or 10 mg/kg (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine, temozolomide, carboplatin, paclitaxel, or carboplatin+paclitaxel). The study excluded patients with autoimmune disease or those receiving immunosuppression; a history of severe or life-threatening immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; previous severe hypersensitivity to other monoclonal antibodies; a history of pneumonitis or interstitial lung disease; HIV, hepatitis B or hepatitis C infection.

Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced independently-verified progression of disease after the first scheduled disease assessment were able to crossover and receive 2 mg/kg or 10 mg/kg of KEYTRUDA every 3 weeks in a double-blind fashion.

Of the 540 patients in KEYNOTE-002, 61% were male, 43% were ≥65 years (median age was 62 years [range 15-89]) and 98% were white. Eighty-two percent of patients had M1c stage, 73% had at least two and 32% had three or more prior systemic therapies for advanced melanoma. Forty-five percent had an ECOG PS of 1, 40% had elevated LDH and 23% had a BRAF mutated tumor. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1) and OS. Secondary efficacy outcome measures were PFS (as assessed by Investigator using RECIST 1.1), ORR and response duration. Table 2 summarizes key efficacy measures in patients previously treated with ipilimumab. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomized to the chemotherapy arm, 55% crossed over and subsequently received treatment with KEYTRUDA.

**Table 2: Response to KEYTRUDA 2 mg/kg or 10 mg/kg Every 3 Weeks  
in Patients with Unresectable or Metastatic Melanoma in KEYNOTE-002**

| Endpoint                                                    | KEYTRUDA<br>2 mg/kg every<br>3 weeks<br>n=180 | KEYTRUDA<br>10 mg/kg every<br>3 weeks<br>n=181 | Chemotherapy<br><br>n=179 |
|-------------------------------------------------------------|-----------------------------------------------|------------------------------------------------|---------------------------|
| <b>OS*</b>                                                  |                                               |                                                |                           |
| Number (%) of patients with event                           | 123 (68%)                                     | 117 (65%)                                      | 128 (72%)                 |
| Hazard ratio <sup>†</sup> (95% CI)                          | 0.86 (0.67, 1.10)                             | 0.74 (0.57, 0.96)                              | ---                       |
| p-Value <sup>‡</sup>                                        | 0.117                                         | 0.011 <sup>è</sup>                             | ---                       |
| Median in months (95% CI)                                   | 13.4 (11.0, 16.4)                             | 14.7 (11.3, 19.5)                              | 11.0 (8.9, 13.8)          |
| <b>PFS<sup>§</sup> by IRO<sup>¶</sup></b>                   |                                               |                                                |                           |
| Number (%) of patients with event                           | 129 (72%)                                     | 126 (70%)                                      | 155 (87%)                 |
| Hazard ratio <sup>†</sup> (95% CI)                          | 0.57 (0.45, 0.73)                             | 0.50 (0.39, 0.64)                              | ---                       |
| p-Value <sup>‡</sup>                                        | <0.0001                                       | <0.0001                                        | ---                       |
| Median in months (95% CI)                                   | 2.9 (2.8, 3.8)                                | 2.9 (2.8, 4.7)                                 | 2.7 (2.5, 2.8)            |
| Mean in months (95% CI) <sup>#</sup>                        | 5.4 (4.7, 6.0)                                | 5.8 (5.1, 6.4)                                 | 3.6 (3.2, 4.1)            |
| <b>PFS<sup>§</sup> by INV<sup>Ⓟ</sup></b>                   |                                               |                                                |                           |
| Number (%) of patients with event                           | 122 (68%)                                     | 112 (62%)                                      | 157 (88%)                 |
| Hazard ratio <sup>†</sup> (95% CI)                          | 0.49 (0.38, 0.62)                             | 0.41 (0.32, 0.52)                              | ---                       |
| p-Value <sup>‡</sup>                                        | <0.0001                                       | <0.0001                                        | ---                       |
| Median in months (95% CI)                                   | 3.7 (2.9, 5.4)                                | 5.4 (3.8, 6.8)                                 | 2.6 (2.4, 2.8)            |
| Mean in months (95% CI) <sup>#</sup>                        | 5.8 (5.2, 6.4)                                | 6.5 (5.8, 7.1)                                 | 3.7 (3.2, 4.1)            |
| <b>Best Overall Response<sup>§</sup> by IRO<sup>¶</sup></b> |                                               |                                                |                           |
| ORR % (95% CI)                                              | 21% (15, 28)                                  | 25% (19, 32)                                   | 4% (2, 9)                 |
| Complete response %                                         | 2%                                            | 3%                                             | 0%                        |
| Partial response %                                          | 19%                                           | 23%                                            | 4%                        |
| <b>Response Duration<sup>§</sup> by IRO<sup>¶</sup></b>     |                                               |                                                |                           |
| Median in months (range)                                    | 22.8<br>(1.4+, 25.3+)                         | Not reached<br>(1.1+, 28.3+)                   | 6.8<br>(2.8, 11.3)        |
| % ongoing at 12 months <sup>à</sup>                         | 73%                                           | 79%                                            | Not reached <sup>ò</sup>  |

\* Based on final analysis

† Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

‡ Based on stratified Log rank test

§ Based on second interim analysis

¶ IRO = Independent radiology plus oncologist review using RECIST 1.1

# Restricted mean progression-free survival time based on follow-up of 12 months

Ⓟ INV = Investigator assessment using RECIST 1.1

§ Based on patients with a best overall response as confirmed complete or partial response from the final analysis

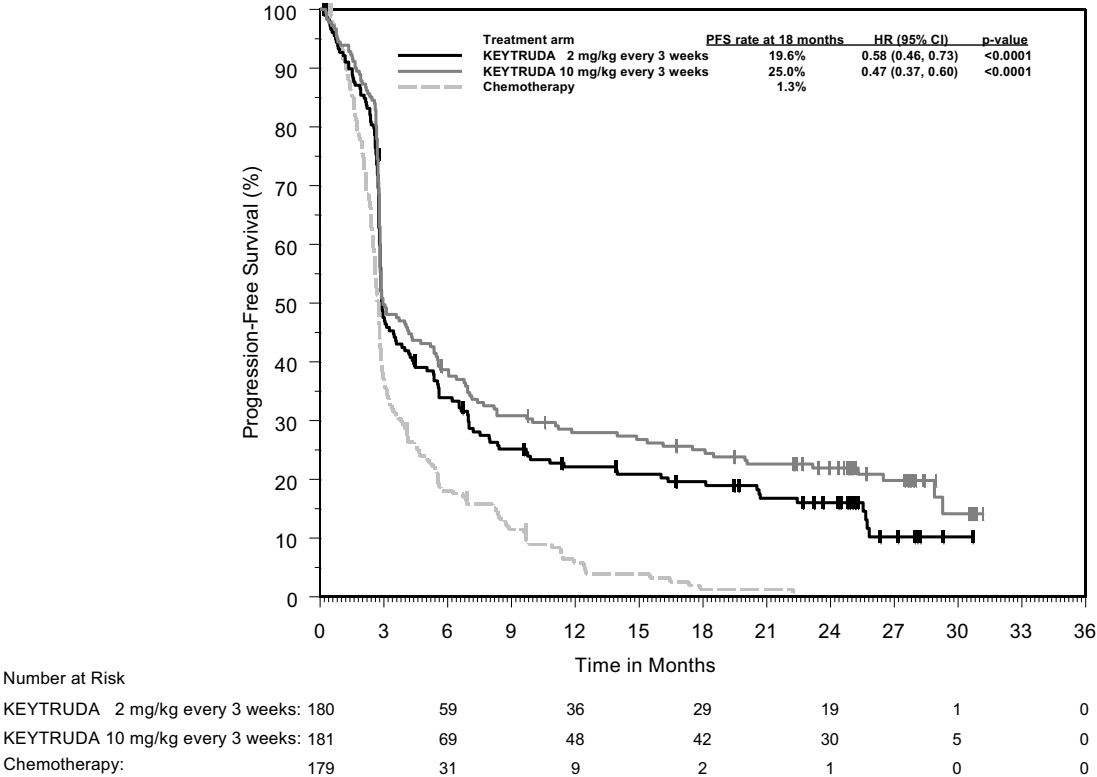
à Based on Kaplan-Meier estimates

è Not statistically significant after adjustment for multiplicity

ò The maximum follow-up for ongoing patients in the chemotherapy arm is 11.3 months; patients continue to be followed

At the final analysis, a long-term PFS analysis was performed based on 466 PFS events (150 for KEYTRUDA 2 mg/kg every 3 weeks; 144 for KEYTRUDA 10 mg/kg every 3 weeks and 172 for chemotherapy). The PFS HRs vs. chemotherapy were 0.58 (95% CI: 0.46, 0.73) for patients treated with KEYTRUDA 2 mg/kg every 3 weeks and 0.47 (95% CI: 0.37, 0.60) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks (Figure 3).

**Figure 3: Kaplan-Meier Curve for Progression-Free Survival (Based on IRO) by Treatment Arm in KEYNOTE-002 (Intent to Treat Population)**



**KEYNOTE-001: Open-label study in melanoma patients**

The efficacy of KEYTRUDA was also investigated in an uncontrolled, open-label study for the treatment of unresectable or metastatic melanoma. Efficacy was evaluated for 276 patients from two defined cohorts of KEYNOTE-001, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor) and another which included patients naïve to treatment with ipilimumab. Patients were randomized to receive KEYTRUDA at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Exclusion criteria were similar to those of KEYNOTE-002.

Of the 89 patients receiving 2 mg/kg of KEYTRUDA who were previously treated with ipilimumab, 53% were male, 33% were ≥65 years of age and the median age was 59 years (range 18-88). All but two patients were white. Eighty-four percent of patients had M1c stage and 8% had a history of brain metastases. Seventy-eight percent of patients had at least two and 35% had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population.

Of the 51 patients receiving 2 mg/kg of KEYTRUDA who were naïve to treatment with ipilimumab, 63% were male, 35% were ≥65 years of age and the median age was 60 years (range 35-80). All but one patient was white. Sixty-three percent of patients had M1c stage and 2% had a history of brain metastases. Forty-

five percent had no prior therapies for advanced melanoma. BRAF mutations were reported in 39% of the study population.

The primary efficacy outcome measure was ORR as assessed by independent review using confirmed responses and RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including complete response, partial response and stable disease), response duration, PFS, and OS. Tumor response was assessed at 12-week intervals. Table 3 summarizes key efficacy measures in patients, previously treated or naïve to treatment with ipilimumab, receiving KEYTRUDA at a dose of 2 mg/kg based on a minimum follow-up time of 30 months for all patients.

**Table 3: Response to KEYTRUDA 2 mg/kg Every 3 Weeks in Patients with Unresectable or Metastatic Melanoma in KEYNOTE-001**

| Endpoint                              | KEYTRUDA 2 mg/kg every 3 weeks in patients previously treated with ipilimumab<br>n=89 | KEYTRUDA 2 mg/kg every 3 weeks in patients naïve to treatment with ipilimumab<br>n=51 |
|---------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <b>Best Overall Response* by IRO†</b> |                                                                                       |                                                                                       |
| ORR %, (95% CI)                       | 26% (17, 36)                                                                          | 35% (22, 50)                                                                          |
| Disease Control Rate %‡               | 48%                                                                                   | 49%                                                                                   |
| Complete response                     | 7%                                                                                    | 12%                                                                                   |
| Partial response                      | 19%                                                                                   | 24%                                                                                   |
| Stable disease                        | 20%                                                                                   | 14%                                                                                   |
| <b>Response Duration§</b>             |                                                                                       |                                                                                       |
| Median in months (range)              | 30.5 (2.8+, 30.6+)                                                                    | 27.4 (1.6+, 31.8+)                                                                    |
| % ongoing at 24 months¶               | 75%                                                                                   | 71%                                                                                   |
| <b>PFS</b>                            |                                                                                       |                                                                                       |
| Median in months (95% CI)             | 4.9 (2.8, 8.3)                                                                        | 4.7 (2.8, 13.8)                                                                       |
| PFS rate at 12 months                 | 34%                                                                                   | 38%                                                                                   |
| <b>OS</b>                             |                                                                                       |                                                                                       |
| Median in months (95% CI)             | 18.9 (11, not available)                                                              | 28.0 (14, not available)                                                              |
| OS rate at 24 months                  | 44%                                                                                   | 56%                                                                                   |

\* Includes patients without measurable disease at baseline by independent radiology

† IRO = Independent radiology plus oncologist review using RECIST 1.1

‡ Based on best response of stable disease or better

§ Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=23 for patients previously treated with ipilimumab; n=18 for patients naïve to treatment with ipilimumab

¶ Based on Kaplan-Meier estimation

Results for patients previously treated with ipilimumab (n=84) and naïve to treatment with ipilimumab (n=52) who received 10 mg/kg of KEYTRUDA every 3 weeks were similar to those seen in patients who received 2 mg/kg of KEYTRUDA every 3 weeks.

**KEYNOTE-716: Placebo-controlled trial for the adjuvant treatment of patients with completely resected Stage IIB or IIC melanoma**

The efficacy of KEYTRUDA was investigated in KEYNOTE-716, a multicenter, randomized, double-blind, placebo-controlled trial in patients with completely resected stage IIB or IIC melanoma. A total of 976 patients were randomized (1:1) to receive KEYTRUDA 200 mg or the pediatric (≥12 years old) dose of KEYTRUDA 2 mg/kg intravenously (up to a maximum of 200 mg) every three weeks (n=487) or placebo (n=489) for up to one year until disease recurrence, or until unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 8<sup>th</sup> edition (AJCC) T stage. Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. Patients with active autoimmune disease or a medical condition that required immunosuppression or

mucosal or ocular melanoma were ineligible. Patients underwent imaging every 6 months for 1 year from randomization, every 6 months from years 2 to 4, and then once in year 5 from randomization or until recurrence, whichever came first.

Among the 976 patients, the baseline characteristics were: median age of 61 years (range: 16 to 87), 39% age 65 or older; 60% male; and 93% ECOG PS of 0 and 7% ECOG PS of 1. Sixty-four percent had stage IIB and 35% had stage IIC.

The primary efficacy outcome measure was investigator-assessed recurrence free survival (RFS) in the whole population, where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurred first. The secondary outcome measures were distant metastasis-free survival (DMFS) and OS in the whole population. DMFS and OS were not formally assessed at the time of this analysis.

The trial initially demonstrated a statistically significant improvement in RFS for patients randomized to the pembrolizumab arm compared with placebo. These efficacy results are summarized in Table 4.

**Table 4: Efficacy Results in KEYNOTE-716**

| <b>Endpoint</b>                   | <b>KEYTRUDA<br/>200 mg every<br/>3 weeks<br/>n=487</b> | <b>Placebo<br/><br/>n=489</b> |
|-----------------------------------|--------------------------------------------------------|-------------------------------|
| <b>RFS</b>                        |                                                        |                               |
| Number (%) of patients with event | 54 (11%)                                               | 82 (17%)                      |
| RFS rate at 18 months             | 85.8%                                                  | 77%                           |
| Median in months (95% CI)         | NR (22.6, NR)                                          | NR (NR, NR)                   |
| Hazard ratio* (95% CI)            | 0.65 (0.46, 0.92)                                      |                               |
| p-Value (stratified log-rank)     | 0.00658                                                |                               |

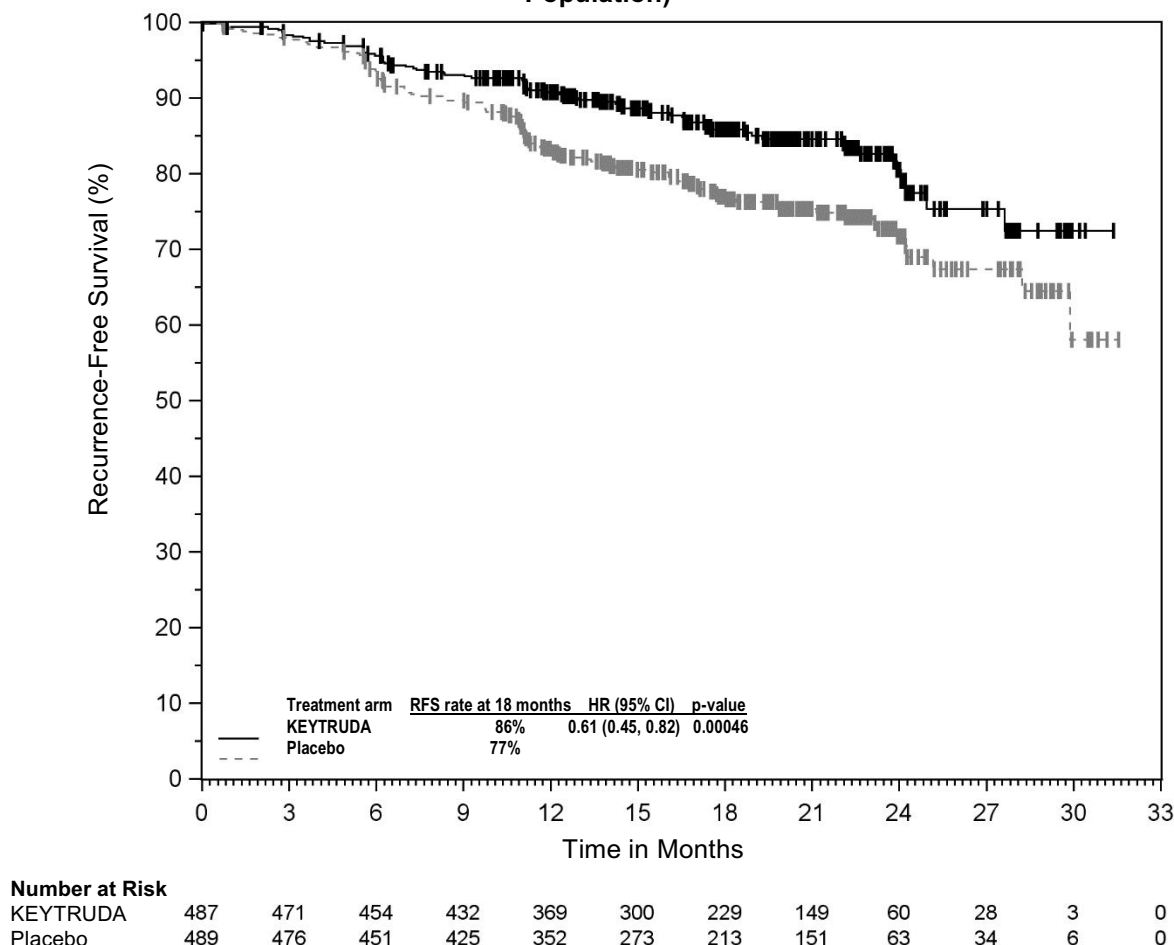
\* Based on the stratified Cox proportional hazard model

NR=not reached

A pre-specified sensitivity analysis of RFS that included new primary melanomas was consistent with the primary RFS analysis, with an HR of 0.64 (95% CI: 0.46, 0.88).

An updated RFS analysis was performed with a median follow-up of 20.5 months (range: 4.6 to 32.7 months). At the time of this analysis, the hazard ratio in patients randomized to pembrolizumab versus patients randomized to placebo was 0.61 (95% CI: 0.45, 0.82) with 72/487 (14.8%) events and 115/489 (23.5%), respectively. These efficacy results are summarized in Figure 4.

**Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716 (Intent to Treat Population)**



**KEYNOTE-054: Placebo-controlled trial for the adjuvant treatment of patients with completely resected Stage III melanoma**

The efficacy of KEYTRUDA was evaluated in KEYNOTE-054, a multicenter, randomized double-blind, placebo-controlled trial in patients with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma. A total of 1019 patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=514) or placebo (n=505), for up to one year until disease recurrence, or until unacceptable toxicity. Randomization was stratified by AJCC stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated). Patients must have undergone lymph node dissection and, if indicated, radiotherapy within 13 weeks prior to starting treatment. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually.

Among the 1019 patients, the baseline characteristics were: median age of 54 years (25% age 65 or older); 62% male; ECOG PS of 0 (94%) and 1 (6%). Sixteen percent had stage IIIA; 46% had stage IIIB; 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (≥4 positive lymph nodes); 50% were BRAF

V600 mutation positive and 44% were BRAF wild type; 84% had PD-L1 positive melanoma with tumor proportion score (TPS  $\geq 1\%$ ) according to an investigational use only (IUO) assay.

The primary efficacy outcome measures were investigator-assessed RFS in the whole population and in the population with PD-L1 positive tumors. The secondary outcome measures were DMFS and OS in the whole population and in the population with PD-L1 positive tumors. OS was not formally assessed at the time of these analyses. The trial initially demonstrated a statistically significant improvement in RFS (HR 0.57; 98.4% CI 0.43, 0.74; p-Value < 0.0001) for patients randomized to the KEYTRUDA arm compared with placebo at its pre-specified interim analysis. Updated efficacy results with a median follow-up time of 45.5 months are summarized in Table 5 and Figures 5 and 6.

**Table 5: Efficacy Results in KEYNOTE-054**

| Endpoint                          | KEYTRUDA<br>200 mg<br>every<br>3 weeks<br>n=514 | Placebo<br><br>n=505 |
|-----------------------------------|-------------------------------------------------|----------------------|
| <b>RFS</b>                        |                                                 |                      |
| Number (%) of patients with event | 135 (26%)                                       | 216 (43%)            |
| RFS rate                          | 82%                                             | 73%                  |
| Median in months (95% CI)         | NR                                              | 20.4 (16.2, NR)      |
| Hazard ratio* (98% CI)            | 0.57 (0.43, 0.74)                               |                      |
| p-Value (stratified log-rank)     | <0.0001                                         |                      |
| <b>DMFS</b>                       |                                                 |                      |
| Number (%) of patients with event | 173 (34%)                                       | 245 (49%)            |
| DMFS rate at 42 months            | 65%                                             | 49%                  |
| Median in months (95% CI)         | NR (49.6, NR)                                   | 40.0 (27.7, NR)      |
| Hazard ratio* (95% CI)            | 0.60 (0.49, 0.73)                               |                      |
| p Value (stratified log rank)     | < 0.0001                                        |                      |

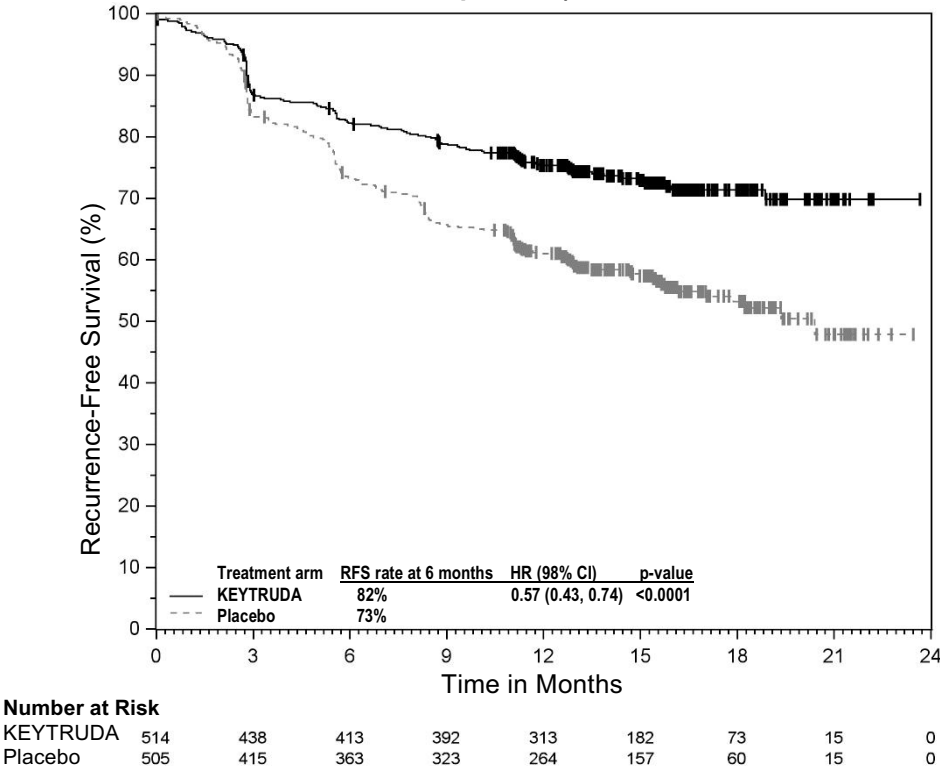
\* Based on the stratified Cox proportional hazard model  
NR = not reached

For patients in the whole population, the RFS rate at 42 months was 60% in the KEYTRUDA arm and 41% in the placebo arm (HR was 0.59 [95% CI: 0.49, 0.70]).

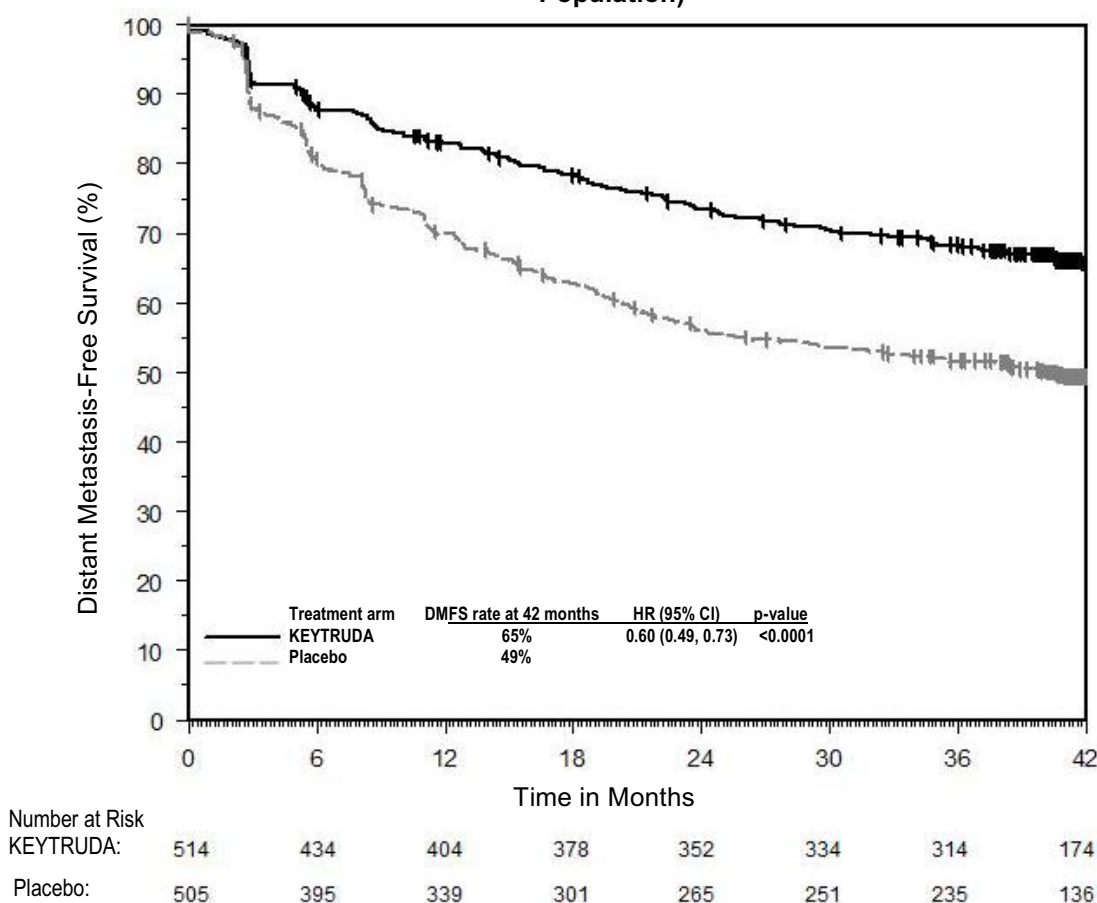
For patients with PD-L1 positive tumors, the RFS rate at 42 months was 61% in the KEYTRUDA arm and 44% in the placebo arm (HR was 0.59 (95% CI: 0.49, 0.73)). Additionally, pre-defined subgroup analyses were performed in patients whose tumors were PD-L1 negative, BRAF mutation positive, or BRAF mutation negative. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression or BRAF mutation status. The RFS HR for KEYTRUDA was 0.46 (95% CI: 0.27, 0.77) for patients with PD-L1 negative tumors. The RFS HR was 0.52 (95% CI: 0.40, 0.66) for patients with BRAF mutation positive tumors, and 0.67 (95% CI: 0.51, 0.88) for patients with BRAF mutation negative tumors.

For patients with PD-L1 positive tumors, the DMFS rate at 42 months was 67% in the KEYTRUDA arm and 52% in the placebo arm (HR was 0.61 (95% CI: 0.49, 0.76); p < 0.0001). Additionally, pre-defined subgroup analyses were performed in patients whose tumors were PD-L1 negative, BRAF mutation positive, or BRAF mutation negative. The DMFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression or BRAF mutation status. The DMFS HR for KEYTRUDA was 0.49 (95% CI: 0.28, 0.83) for patients with PD-L1 negative tumors. The DMFS HR was 0.51 (95% CI: 0.39, 0.68) for patients with BRAF mutation positive tumors, and 0.73 (95% CI: 0.55, 0.98) for patients with BRAF mutation negative tumors.

Figure 5: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054 (Intent to Treat Population)



**Figure 6: Kaplan-Meier Curve for Distant Metastasis Free Survival in KEYNOTE-054 (Intent to Treat Population)**



### Non-Small Cell Lung Carcinoma

#### KEYNOTE-189: Controlled trial of combination therapy in non-squamous NSCLC patients naïve to treatment

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in a multicenter, randomized, active-controlled, double-blind trial, KEYNOTE-189. Key eligibility criteria were metastatic non-squamous NSCLC, no prior systemic treatment for metastatic NSCLC, and no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Patients were randomized (2:1) to receive one of the following regimens:

- KEYTRUDA 200 mg with pemetrexed 500 mg/m<sup>2</sup> and investigator's choice of cisplatin 75 mg/m<sup>2</sup> or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed 500 mg/m<sup>2</sup> intravenously every 3 weeks.
- Placebo with pemetrexed 500 mg/m<sup>2</sup> and investigator's choice of cisplatin 75 mg/m<sup>2</sup> or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by placebo and pemetrexed 500 mg/m<sup>2</sup> intravenously every 3 weeks.

Treatment with KEYTRUDA continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression by BICR or beyond discontinuation of pemetrexed if the patient was clinically stable and deriving clinical benefit as determined by the investigator. For patients who completed 24 months of therapy or had a complete response, treatment with KEYTRUDA could be reinitiated for disease progression and administered for up to 1 additional year. Assessment of tumor status

was performed at Week 6 and Week 12, followed by every 9 weeks thereafter. Patients receiving placebo plus chemotherapy who experienced independently-verified progression of disease were offered KEYTRUDA as monotherapy.

Among the 616 patients in KEYNOTE-189 (410 patients in the KEYTRUDA combination arm and 206 in the placebo plus chemotherapy arm), baseline characteristics were: median age of 64 years (49% age 65 or older); 59% male; 94% White and 3% Asian; 43% and 56% ECOG performance status of 0 or 1 respectively; 31% with PD-L1 TPS <1%; and 18% with treated or untreated brain metastases at baseline. A total of 67 patients in the placebo plus chemotherapy arm crossed over to receive monotherapy KEYTRUDA at the time of disease progression and 18 additional patients received a checkpoint inhibitor as subsequent therapy.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time was 10.5 months (range: 0.2 – 20.4 months). Table 6 summarizes key efficacy measures.

**Table 6: Response to KEYTRUDA, Pemetrexed, and Platinum Chemotherapy in Patients with Non-Squamous NSCLC in KEYNOTE-189**

| Endpoint                               | KEYTRUDA +<br>Pemetrexed +<br>Platinum<br>Chemotherapy<br>n=410 | Placebo +<br>Pemetrexed +<br>Platinum<br>Chemotherapy<br>n=206 |
|----------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------|
| <b>OS</b>                              |                                                                 |                                                                |
| Number (%) of patients with event      | 127 (31%)                                                       | 108 (52%)                                                      |
| Hazard ratio* (95% CI)                 | 0.49 (0.38, 0.64)                                               |                                                                |
| p-Value <sup>†</sup>                   | <0.00001                                                        |                                                                |
| Median in months (95% CI)              | Not reached<br>(NA, NA)                                         | 11.3<br>(8.7, 15.1)                                            |
| <b>PFS</b>                             |                                                                 |                                                                |
| Number (%) of patients with event      | 245 (60%)                                                       | 166 (81%)                                                      |
| Hazard ratio* (95% CI)                 | 0.52 (0.43, 0.64)                                               |                                                                |
| p-Value <sup>†</sup>                   | <0.00001                                                        |                                                                |
| Median in months (95% CI)              | 8.8 (7.6, 9.2)                                                  | 4.9 (4.7, 5.5)                                                 |
| <b>Objective Response Rate</b>         |                                                                 |                                                                |
| ORR <sup>‡</sup> % (95% CI)            | 48% (43, 53)                                                    | 19% (14, 25)                                                   |
| Complete response %                    | 0.5%                                                            | 0.5%                                                           |
| Partial response %                     | 47%                                                             | 18%                                                            |
| p-Value <sup>§</sup>                   | <0.0001                                                         |                                                                |
| <b>Response Duration</b>               |                                                                 |                                                                |
| Median in months (range)               | 11.2<br>(1.1+, 18.0+)                                           | 7.8<br>(2.1+, 16.4+)                                           |
| % with duration ≥6 months <sup>¶</sup> | 81%                                                             | 63%                                                            |
| % with duration ≥9 months <sup>¶</sup> | 59%                                                             | 44%                                                            |

\* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Based on patients with a best overall response as confirmed complete or partial response

§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status

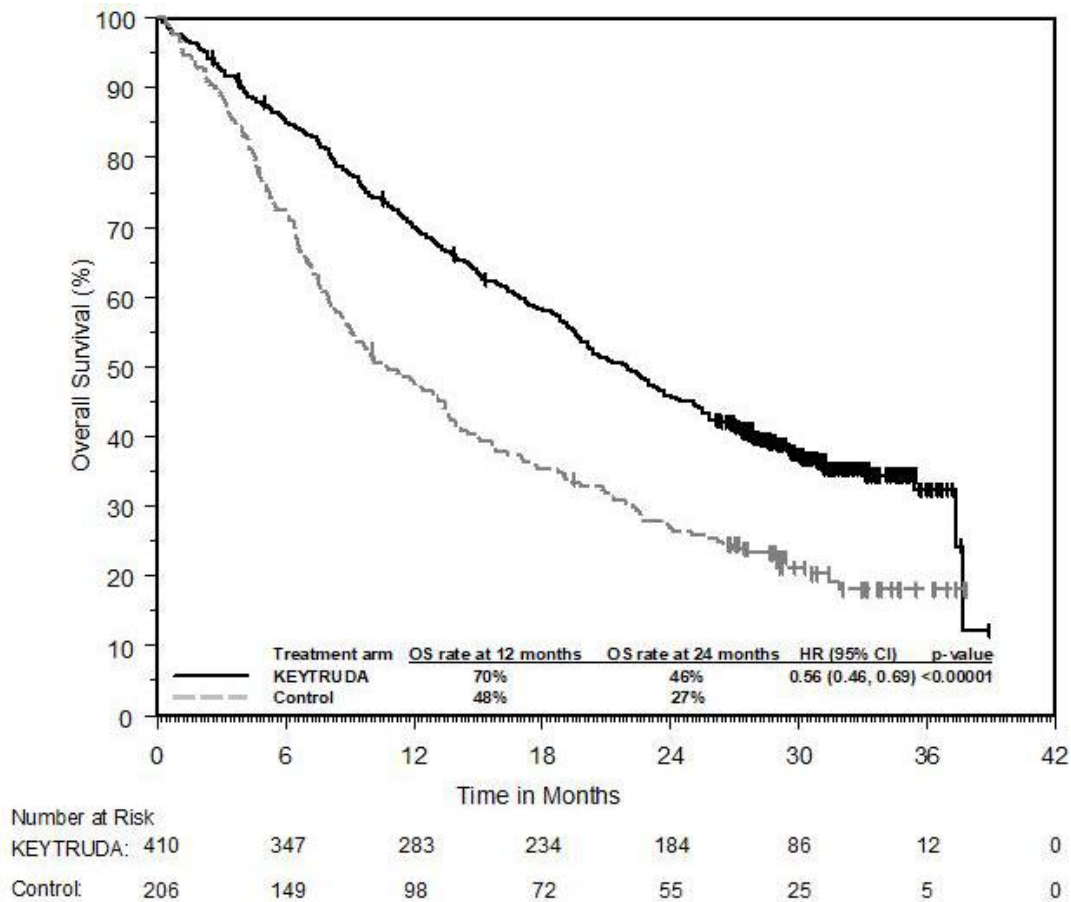
¶ Based on Kaplan-Meier estimation

NA = not available

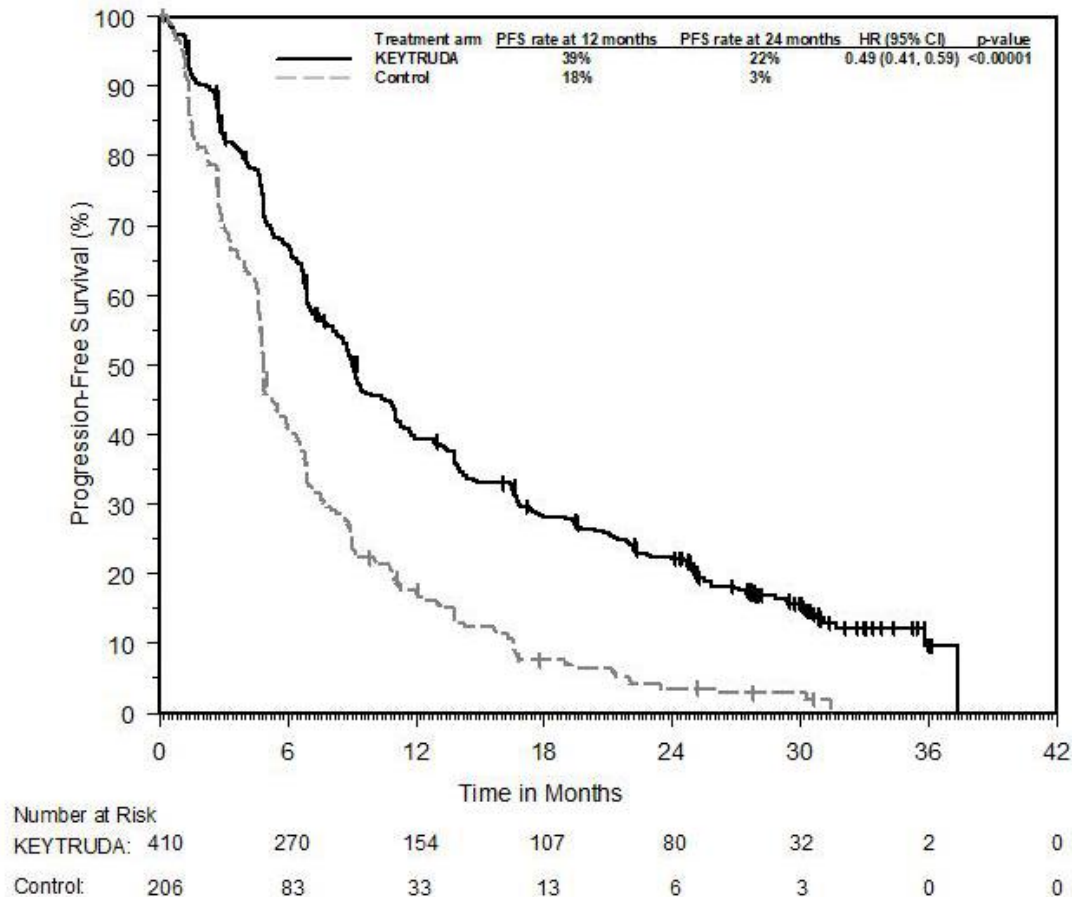
The final OS analysis was performed at a median duration of follow-up of 18.8 months after 421 patient events (258 for KEYTRUDA combination arm and 163 for the placebo plus chemotherapy arm). Median OS was 22.0 months (95% CI: 19.5, 24.5) for the KEYTRUDA combination arm and 10.6 months (95% CI: 8.7, 13.6) for the placebo plus chemotherapy arm. The OS HR was 0.56 (95% CI: 0.46, 0.69;  $p < 0.00001$ ). At final analysis, a PFS analysis was performed based on 534 patient events (337 for the KEYTRUDA combination arm and 197 for the placebo plus chemotherapy arm). The median PFS was 9.0 months (95% CI: 8.1, 10.4) for the KEYTRUDA combination arm and 4.9 months (95% CI: 4.7, 5.5) for the placebo plus chemotherapy arm. The PFS HR was 0.49 (95% CI: 0.41, 0.59,  $p < 0.00001$ ). See Figures 7 and 8.

The ORR at the final analysis was 48% for the KEYTRUDA combination arm and 20% for the placebo plus chemotherapy arm. The median duration of response was 12.5 months (range 1.1+, 34.9+) for the KEYTRUDA combination arm and 7.1 months (range 2.4, 27.8+) for the placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 53% at 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 27% in patients who received placebo plus chemotherapy.

**Figure 7: Kaplan-Meier curve for Overall Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)**



**Figure 8: Kaplan-Meier curve for Progression-Free Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)**



Patient-reported outcomes were assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13. Exploratory analyses of patients receiving pembrolizumab combination therapy showed stable EORTC QLQ-C30 Global Health Status/QoL at Week 12 and Week 21 vs declines in patients receiving placebo plus chemotherapy. There was a trend toward a prolonged time to deterioration in the EORTC QLQ-LC13/QLQ-C30 endpoint of cough, dyspnea or chest pain observed for patients receiving pembrolizumab combination therapy.

**KEYNOTE-407: Controlled trial of combination therapy in squamous NSCLC patients naïve to treatment**

The efficacy of KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC, regardless of tumor PD-L1 expression status, and no prior systemic treatment for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS <1% [negative] vs. TPS ≥1%), investigator's choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m<sup>2</sup> on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m<sup>2</sup> on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.

- Placebo and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m<sup>2</sup> on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m<sup>2</sup> on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks.

Treatment with KEYTRUDA or placebo continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (BICR), unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year.

Patients in the placebo arm were offered KEYTRUDA as monotherapy at the time of disease progression.

Assessment of tumor status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter. The major efficacy outcome measures were progression-free survival and objective response rate (ORR) as assessed by BICR using RECIST 1.1 and overall survival. An additional efficacy outcome measure was duration of response as assessed by BICR using RECIST 1.1.

A total of 559 patients were randomized: 278 patients to the KEYTRUDA arm and 281 to the placebo arm. The study population characteristics were: median age of 65 years (range: 29 to 88); 55% age 65 or older; 81% male; 77% White; ECOG performance status of 0 (29%) and 1 (71%); and 8% with treated brain metastases at baseline. Thirty-five percent had tumor PD-L1 expression TPS <1% [negative]; 19% were from the East Asian region; and 60% received paclitaxel.

In KEYNOTE-407, there was a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomized to placebo with carboplatin and either paclitaxel or nab-paclitaxel (see Table 7).

**Table 7: Efficacy Results in KEYNOTE-407**

| <b>Endpoint</b>                               | <b>KEYTRUDA<br/>Carboplatin<br/>Paclitaxel/Nab-paclitaxel<br/>n=278</b> | <b>Placebo<br/>Carboplatin<br/>Paclitaxel/Nab-paclitaxel<br/>n=281</b> |
|-----------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------|
| <b>OS</b>                                     |                                                                         |                                                                        |
| Number of events (%)                          | 85 (31%)                                                                | 120 (43%)                                                              |
| Median in months (95% CI)                     | 15.9 (13.2, NA)                                                         | 11.3 (9.5, 14.8)                                                       |
| Hazard ratio* (95% CI)                        | 0.64 (0.49, 0.85)                                                       |                                                                        |
| p-Value (stratified log rank)                 | 0.0008                                                                  |                                                                        |
| <b>PFS</b>                                    |                                                                         |                                                                        |
| Number of events (%)                          | 152 (55%)                                                               | 197 (70%)                                                              |
| Median in months (95% CI)                     | 6.4 (6.2, 8.3)                                                          | 4.8 (4.2, 5.7)                                                         |
| Hazard ratio* (95% CI)                        | 0.56 (0.45, 0.70)                                                       |                                                                        |
| p-Value (stratified log rank)                 | <0.0001                                                                 |                                                                        |
| <b>Overall Response Rate</b>                  |                                                                         |                                                                        |
| ORR <sup>‡</sup>                              | 58%                                                                     | 38%                                                                    |
| (95% CI)                                      | (52, 64)                                                                | (33, 44)                                                               |
| <b>Response Duration</b>                      |                                                                         |                                                                        |
| Median duration of response in months (range) | 7.7 (1.1+, 14.7+)                                                       | 4.8 (1.3+, 15.8+)                                                      |
| % with duration ≥6 months <sup>‡</sup>        | 62%                                                                     | 40%                                                                    |

\* Based on the stratified Cox proportional hazard model

† At the initial interim analysis (n=101 for KEYTRUDA combination therapy, n=102 for placebo), a statistically significant difference was observed; ORR was 58% [95% CI (48, 68)] and 35% [95% CI (26, 45)] for placebo, p=0.0004

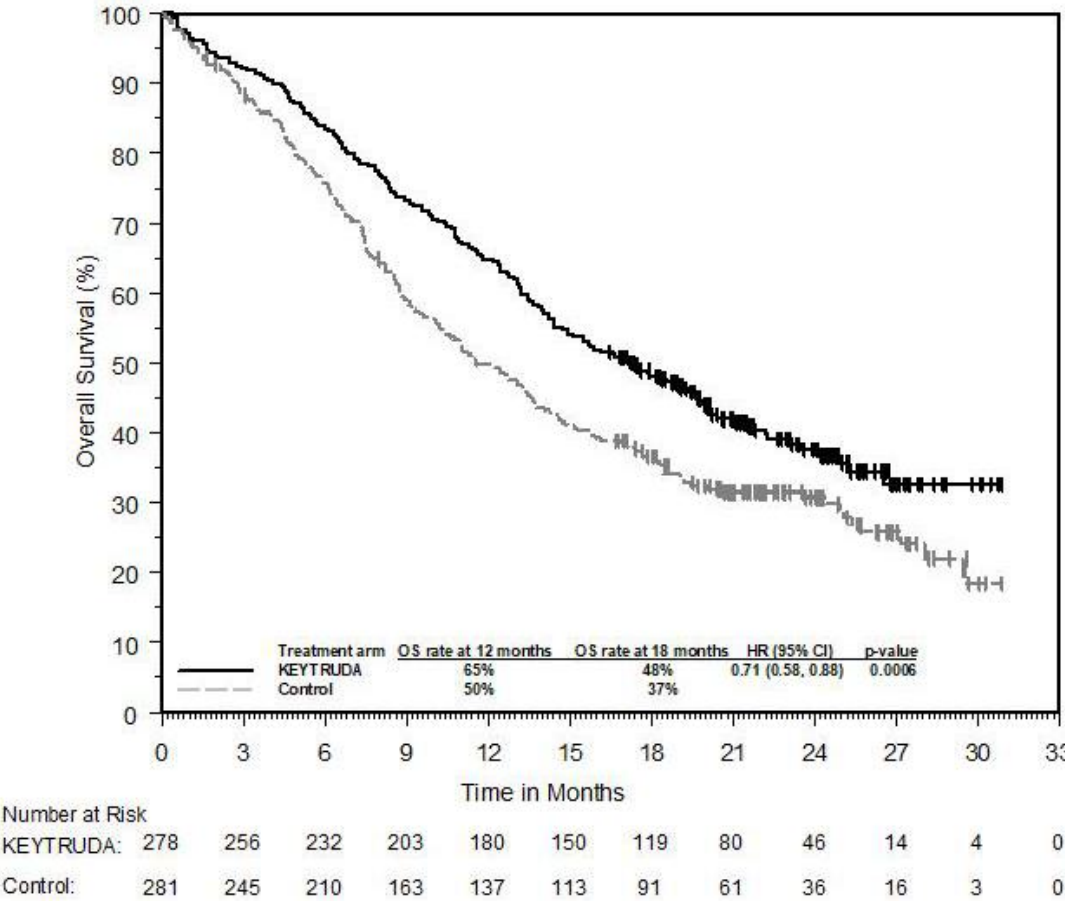
‡ Based on Kaplan-Meier estimation

NA = not available

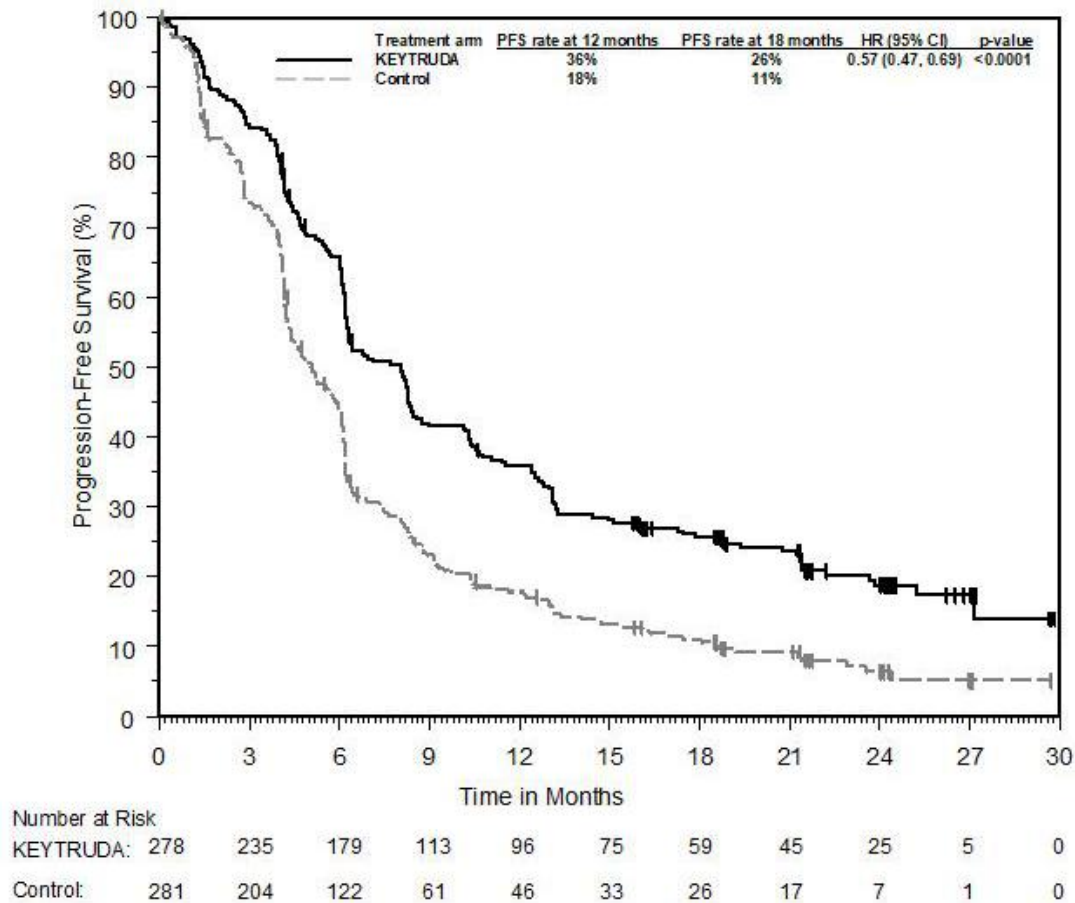
The final OS analysis was performed at a median duration of follow-up of 14.3 months after 365 patient events (168 for KEYTRUDA combination arm and 197 for placebo plus chemotherapy arm). Median OS was 17.1 months (95% CI: 14.4, 19.9) for the KEYTRUDA combination arm and 11.6 months (95% CI: 10.1, 13.7) for the placebo plus chemotherapy arm. The OS HR was 0.71 (95% CI: 0.58, 0.88; p=0.0006). At final analysis, a PFS analysis was performed based on 469 patient events (217 for the KEYTRUDA combination arm and 252 for the placebo plus chemotherapy arm). The median PFS was 8.0 months (95% CI: 6.3, 8.4) for the KEYTRUDA combination arm and 5.1 months (95% CI: 4.3, 6.0) for the placebo plus chemotherapy arm. The PFS HR was 0.57 (95% CI: 0.47, 0.69, p<0.0001). See Figures 9 and 10.

The ORR at the final analysis was 63% for the KEYTRUDA combination arm and 38% for the placebo plus chemotherapy arm. The median duration of response was 8.8 months (range 1.3+, 28.4+) for the KEYTRUDA combination arm and 4.9 months (range 1.3+, 28.3+) for the placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 64% and 38% at 6 and 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 44% and 25% in patients who received placebo plus chemotherapy.

Figure 9: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407



**Figure 10: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407**



**KEYNOTE-042: Controlled trial of NSCLC patients naïve to treatment**

The efficacy of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, randomized, controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumours expressed PD-L1 (TPS  $\geq 1\%$ ) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx™ Kit, and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=637) or investigator's choice platinum-containing chemotherapy (n=637; including pemetrexed+carboplatin or paclitaxel+carboplatin. Patients with non-squamous NSCLC could receive pemetrexed maintenance). Patients were treated with KEYTRUDA until unacceptable toxicity or disease progression. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 9 weeks for the first 45 weeks, and every 12 weeks thereafter.

Among the 1274 patients in KEYNOTE-042, baseline characteristics were: median age 63 years (45% age 65 or older); 71% male; 64% White and 30% Asian; 19% Hispanic or Latino; and 31% and 69% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (39%) and non-squamous (61%); M0 (13%), M1 (87%); and treated brain metastases (6%). Forty-seven percent of patients had TPS  $\geq 50\%$ , and 53% had TPS 1 to 49%.

The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR as assessed by blinded independent central review (BICR) using RECIST 1.1. Table 8 summarizes key efficacy measures for the entire ITT population (TPS  $\geq$  1%).

**Table 8: Efficacy Results (PD-L1 TPS  $\geq$  1%) in KEYNOTE-042**

| Endpoint                                 | KEYTRUDA<br>200 mg every<br>3 weeks<br>(n=637) | Chemotherapy<br><br>(n=637) |
|------------------------------------------|------------------------------------------------|-----------------------------|
| <b>OS</b>                                |                                                |                             |
| Number (%) of patients with event        | 371 (58%)                                      | 438 (69%)                   |
| Hazard ratio* (95% CI)                   | 0.81 (0.71, 0.93)                              |                             |
| p-Value <sup>†</sup>                     | 0.002                                          |                             |
| Median in months (95% CI)                | 16.7 (13.9, 19.7)                              | 12.1 (11.3, 13.3)           |
| <b>PFS<sup>‡</sup></b>                   |                                                |                             |
| Number (%) of patients with event        | 507 (80%)                                      | 506 (79%)                   |
| Hazard ratio*. <sup>§</sup> (95% CI)     | 1.07 (0.94, 1.21)                              |                             |
| Median in months (95% CI)                | 5.4 (4.3, 6.2)                                 | 6.5 (6.3, 7.0)              |
| <b>Overall Response Rate<sup>‡</sup></b> |                                                |                             |
| ORR %. <sup>§</sup> (95% CI)             | 27% (24, 31)                                   | 27% (23, 30)                |
| Complete response %                      | 1%                                             | 1%                          |
| Partial response %                       | 27%                                            | 26%                         |
| <b>Response Duration<sup>‡,¶</sup></b>   |                                                |                             |
| Median in months (range)                 | 20.2<br>(2.1+, 31.2+)                          | 8.3<br>(1.8+, 28.1)         |
| % with duration $\geq$ 18 months         | 53%                                            | 30%                         |

\* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

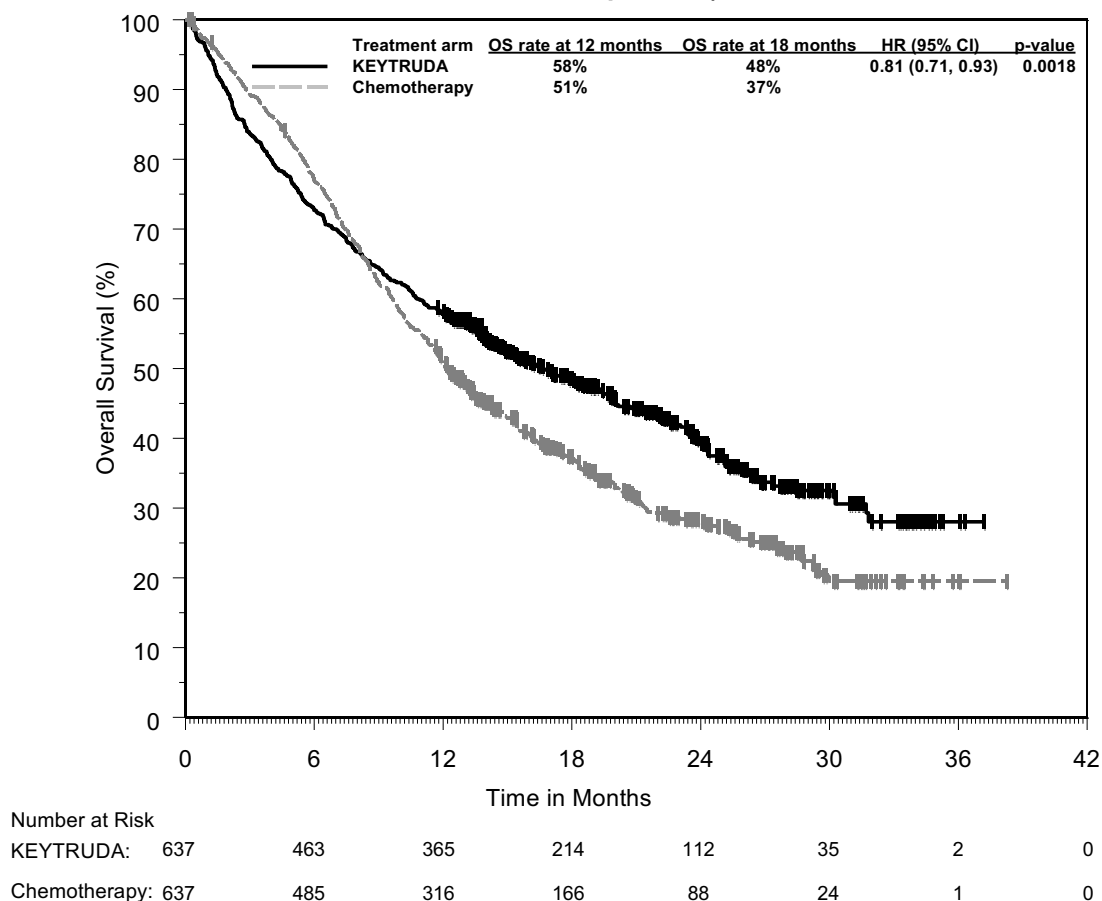
<sup>†</sup> Based on stratified Log rank test

<sup>‡</sup> Assessed by BICR using RECIST 1.1

<sup>§</sup> Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints

<sup>¶</sup> Based on patients with a best overall response as confirmed complete or partial response; based on Kaplan-Meier estimates

**Figure 11: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS  $\geq$  1%, Intent to Treat Population)**



#### KEYNOTE-024: Controlled trial of NSCLC patients naïve to treatment

The efficacy of KEYTRUDA in previously untreated patients with NSCLC was also investigated in KEYNOTE-024, a multicenter, randomized, controlled trial. The study design was similar to that of KEYNOTE-042, except that only patients with metastatic NSCLC whose tumors expressed PD-L1 with TPS of 50% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx™ Kit were eligible. Patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Patients with non-squamous NSCLC could receive pemetrexed maintenance). Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA. Assessment of tumor status was performed every 9 weeks.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White and 15% Asian; and 35% and 65% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (18%) and non-squamous (82%); M1 (99%); and brain metastases (9%).

The primary efficacy outcome measure was PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 9 summarizes key efficacy measures for the entire ITT population.

**Table 9: Efficacy Results in KEYNOTE-024**

| <b>Endpoint</b>                        | <b>KEYTRUDA<br/>200 mg every<br/>3 weeks<br/>n=154</b> | <b>Chemotherapy<br/><br/>n=151</b> |
|----------------------------------------|--------------------------------------------------------|------------------------------------|
| <b>PFS*</b>                            |                                                        |                                    |
| Number (%) of patients with event      | 73 (47%)                                               | 116 (77%)                          |
| Hazard ratio <sup>†</sup> (95% CI)     | 0.50 (0.37, 0.68)                                      |                                    |
| p-Value <sup>‡</sup>                   | <0.001                                                 |                                    |
| Median in months (95% CI)              | 10.3 (6.7, NA)                                         | 6.0 (4.2, 6.2)                     |
| <b>OS</b>                              |                                                        |                                    |
| Number (%) of patients with event      | 44 (29%)                                               | 64 (42%)                           |
| Hazard ratio <sup>†</sup> (95% CI)     | 0.60 (0.41, 0.89)                                      |                                    |
| p-Value <sup>‡</sup>                   | 0.005                                                  |                                    |
| Median in months (95% CI)              | Not reached<br>(NA, NA)                                | Not reached<br>(9.4, NA)           |
| <b>Objective Response Rate*</b>        |                                                        |                                    |
| ORR % (95% CI)                         | 45% (37, 53)                                           | 28% (21, 36)                       |
| Complete response %                    | 4%                                                     | 1%                                 |
| Partial response %                     | 41%                                                    | 27%                                |
| <b>Response Duration<sup>§,¶</sup></b> |                                                        |                                    |
| Median in months (range)               | Not reached<br>(1.9+, 14.5+)                           | 6.3<br>(2.1+, 12.6+)               |
| % with duration ≥ 6 months             | 88%                                                    | 59%                                |

\* Assessed by BICR using RECIST 1.1

† Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

‡ Based on stratified Log rank test

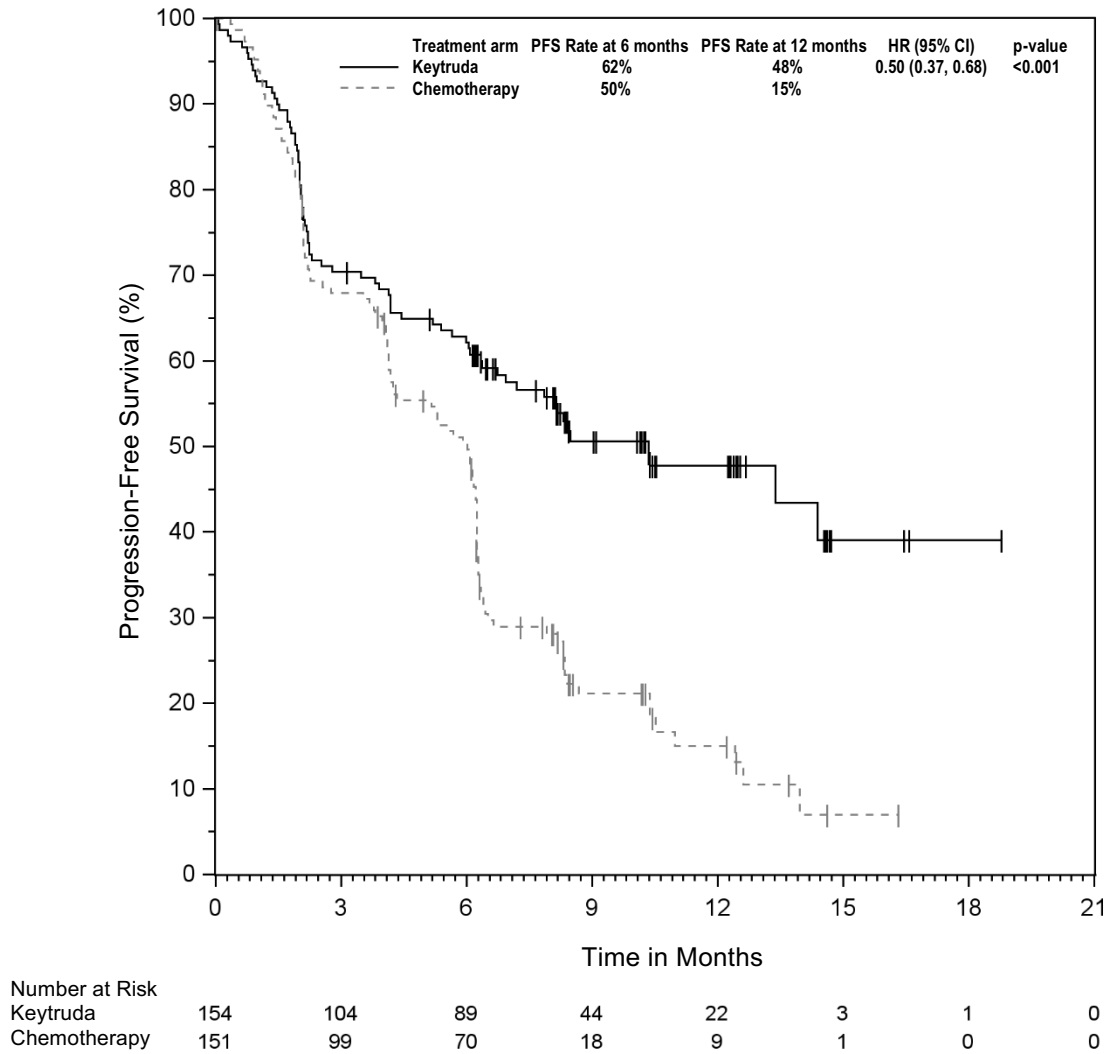
§ Based on patients with a best overall response as confirmed complete or partial response

¶ Based on Kaplan-Meier estimates

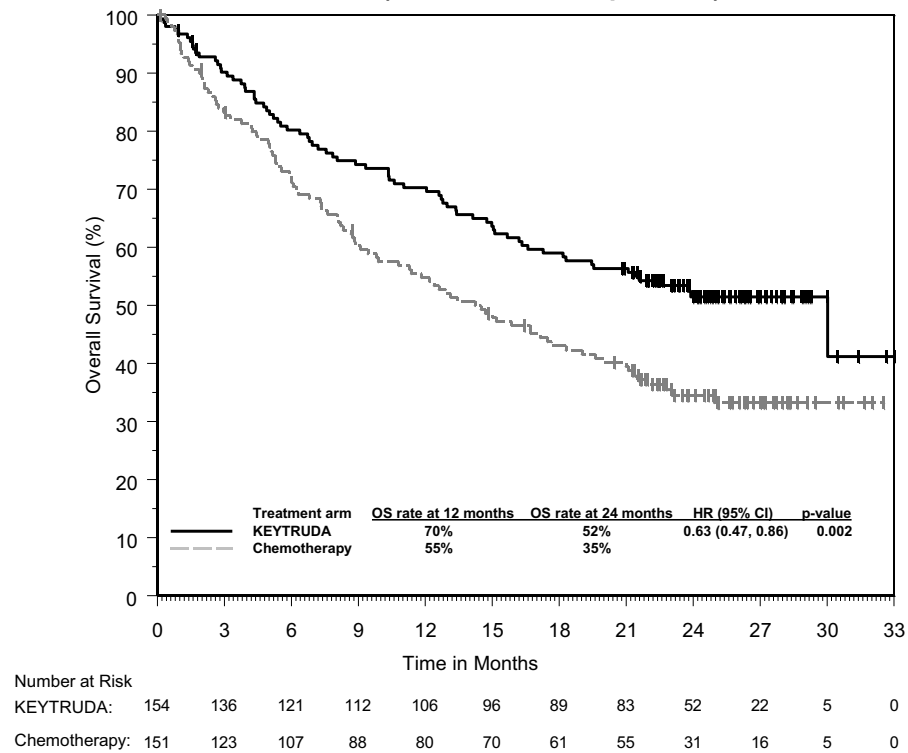
NA = not available

The final OS analysis was performed at a median follow-up of 25 months after 169 patient events (73 for KEYTRUDA and 96 for chemotherapy). Median OS was 30.0 months (95% CI: 18.3, NA) for KEYTRUDA and 14.2 months (95% CI: 9.8, 19.0) for chemotherapy. The OS HR was 0.63 (95% CI: 0.47, 0.86; p=0.002). See Figure 13.

Figure 12: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



**Figure 13: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)**



The improved benefit as assessed by PFS, OS, ORR, and response duration for KEYTRUDA as compared to chemotherapy in the population studied was associated with improvements in health-related quality of life (HRQoL). The change from baseline to Week 15 showed a meaningful improvement in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 global health status/QoL score for patients receiving KEYTRUDA compared to chemotherapy (difference in LS means = 7.82; 95% CI: 2.85, 12.79; two-sided p=0.002). The time to deterioration in the EORTC QLQ-LC13 composite endpoint of cough, dyspnea, and chest pain was prolonged for patients receiving KEYTRUDA compared to chemotherapy (HR = 0.66; 95% CI: 0.44, 0.97; two-sided p=0.029), where deterioration is defined as a confirmed 10-point or greater score decrease from baseline in any one of these three symptoms.

#### KEYNOTE-010: Controlled trial of NSCLC patients previously treated with chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, randomized, controlled trial. Key eligibility criteria were advanced NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression TPS of 1% or greater by a clinical trial assay version of the PD-L1 IHC 22C3 pharmDx™ kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Patients were randomized (1:1:1) to receive 2 mg/kg (n=344) or 10 mg/kg (n=346) of KEYTRUDA every 3 weeks or 75 mg/m<sup>2</sup> of docetaxel every 3 weeks (n=343). Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Assessment of tumor status was performed every 9 weeks.

Among the 1033 patients in KEYNOTE-010, baseline characteristics were: median age 63 years (42% age 65 or older); 61% male; 72% White and 21% Asian; and 34% and 66% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (70%); M1 (91%); brain metastases (15%); and the incidence of genomic aberrations was EGFR (8%) or ALK (1%). Prior

therapy included platinum-doublet regimen (100%); patients received one (69%), or two or more (29%) prior therapies.

The primary efficacy outcome measures were OS and PFS as assessed by an independent review committee using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 10 summarizes key efficacy measures for the entire ITT population (TPS  $\geq 1\%$ ) and for the subgroup of patients with TPS  $\geq 50\%$ . Kaplan-Meier curves for OS (TPS  $\geq 1\%$  and TPS  $\geq 50\%$ ) are shown in Figures 14 and 15.

**Table 10: Response to KEYTRUDA 2 or 10 mg/kg Every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010**

| Endpoint                          | KEYTRUDA<br>2 mg/kg every<br>3 weeks | KEYTRUDA<br>10 mg/kg every<br>3 weeks | Docetaxel<br>75 mg/m <sup>2</sup> every<br>3 weeks |
|-----------------------------------|--------------------------------------|---------------------------------------|----------------------------------------------------|
| <b>TPS ≥1%</b>                    |                                      |                                       |                                                    |
| Number of patients                | 344                                  | 346                                   | 343                                                |
| <b>OS</b>                         |                                      |                                       |                                                    |
| Number (%) of patients with event | 172 (50%)                            | 156 (45%)                             | 193 (56%)                                          |
| Hazard ratio* (95% CI)            | 0.71 (0.58, 0.88)                    | 0.61 (0.49, 0.75)                     | ---                                                |
| p-Value†                          | <0.001                               | <0.001                                | ---                                                |
| Median in months (95% CI)         | 10.4 (9.4, 11.9)                     | 12.7 (10.0, 17.3)                     | 8.5 (7.5, 9.8)                                     |
| <b>PFS‡</b>                       |                                      |                                       |                                                    |
| Number (%) of patients with event | 266 (77%)                            | 255 (74%)                             | 257 (75%)                                          |
| Hazard ratio* (95% CI)            | 0.88 (0.73, 1.04)                    | 0.79 (0.66, 0.94)                     | ---                                                |
| p-Value†                          | 0.068                                | 0.005                                 | ---                                                |
| Median in months (95% CI)         | 3.9 (3.1, 4.1)                       | 4.0 (2.6, 4.3)                        | 4.0 (3.1, 4.2)                                     |
| <b>Overall Response Rate‡</b>     |                                      |                                       |                                                    |
| ORR %§ (95% CI)                   | 18% (14, 23)                         | 18% (15, 23)                          | 9% (7, 13)                                         |
| <b>Response Duration†,¶,¶</b>     |                                      |                                       |                                                    |
| Median in months (range)          | Not reached<br>(0.7+, 20.1+)         | Not reached<br>(2.1+, 17.8+)          | 6.2<br>(1.4+, 8.8+)                                |
| % ongoing                         | 73%                                  | 72%                                   | 34%                                                |
| <b>TPS ≥50%</b>                   |                                      |                                       |                                                    |
| Number of patients                | 139                                  | 151                                   | 152                                                |
| <b>OS</b>                         |                                      |                                       |                                                    |
| Number (%) of patients with event | 58 (42%)                             | 60 (40%)                              | 86 (57%)                                           |
| Hazard ratio* (95% CI)            | 0.54 (0.38, 0.77)                    | 0.50 (0.36, 0.70)                     | ---                                                |
| p-Value†                          | <0.001                               | <0.001                                | ---                                                |
| Median in months (95% CI)         | 14.9 (10.4, NA)                      | 17.3 (11.8, NA)                       | 8.2 (6.4, 10.7)                                    |
| <b>PFS‡</b>                       |                                      |                                       |                                                    |
| Number (%) of patients with event | 89 (64%)                             | 97 (64%)                              | 118 (78%)                                          |
| Hazard ratio* (95% CI)            | 0.58 (0.43, 0.77)                    | 0.59 (0.45, 0.78)                     | ---                                                |
| p-Value†                          | <0.001                               | <0.001                                | ---                                                |
| Median in months (95% CI)         | 5.2 (4.0, 6.5)                       | 5.2 (4.1, 8.1)                        | 4.1 (3.6, 4.3)                                     |
| <b>Overall Response Rate‡</b>     |                                      |                                       |                                                    |
| ORR %§ (95% CI)                   | 30% (23, 39)                         | 29% (22, 37)                          | 8% (4, 13)                                         |
| <b>Response Duration†,¶,¶</b>     |                                      |                                       |                                                    |
| Median in months (range)          | Not reached<br>(0.7+, 16.8+)         | Not reached<br>(2.1+, 17.8+)          | 8.1<br>(2.1+, 8.8+)                                |
| % ongoing                         | 76%                                  | 75%                                   | 33%                                                |

\* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† Based on stratified Log rank test

‡ Assessed by BICR using RECIST 1.1

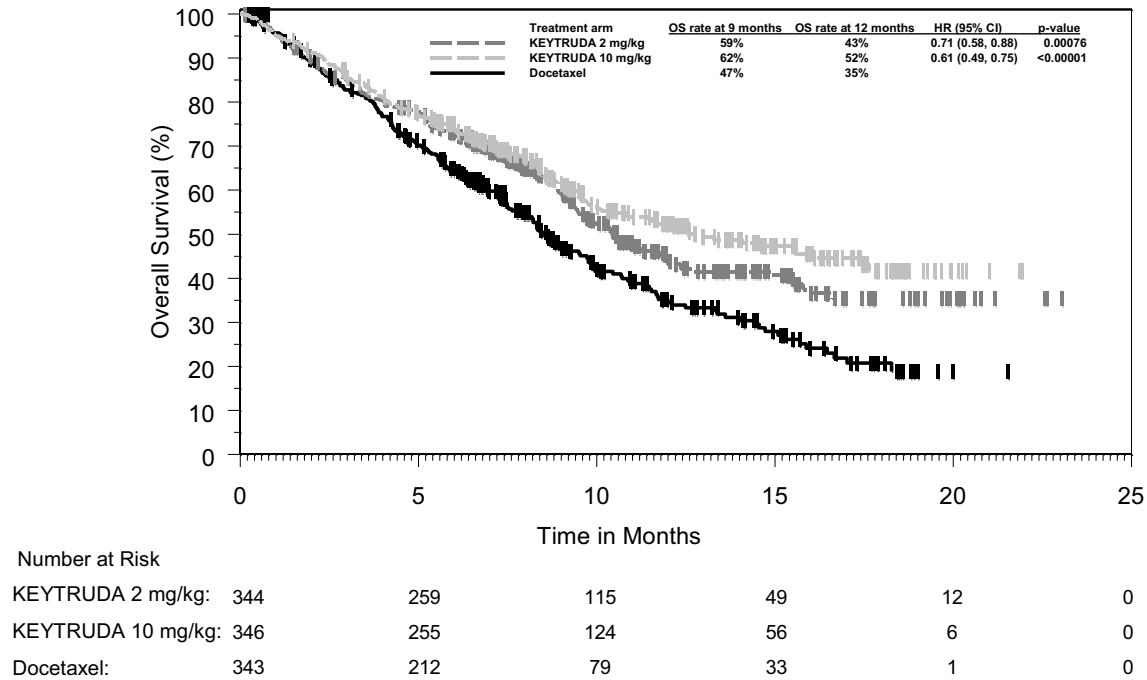
§ All responses were partial responses

¶ Based on patients with a best overall response as confirmed complete or partial response

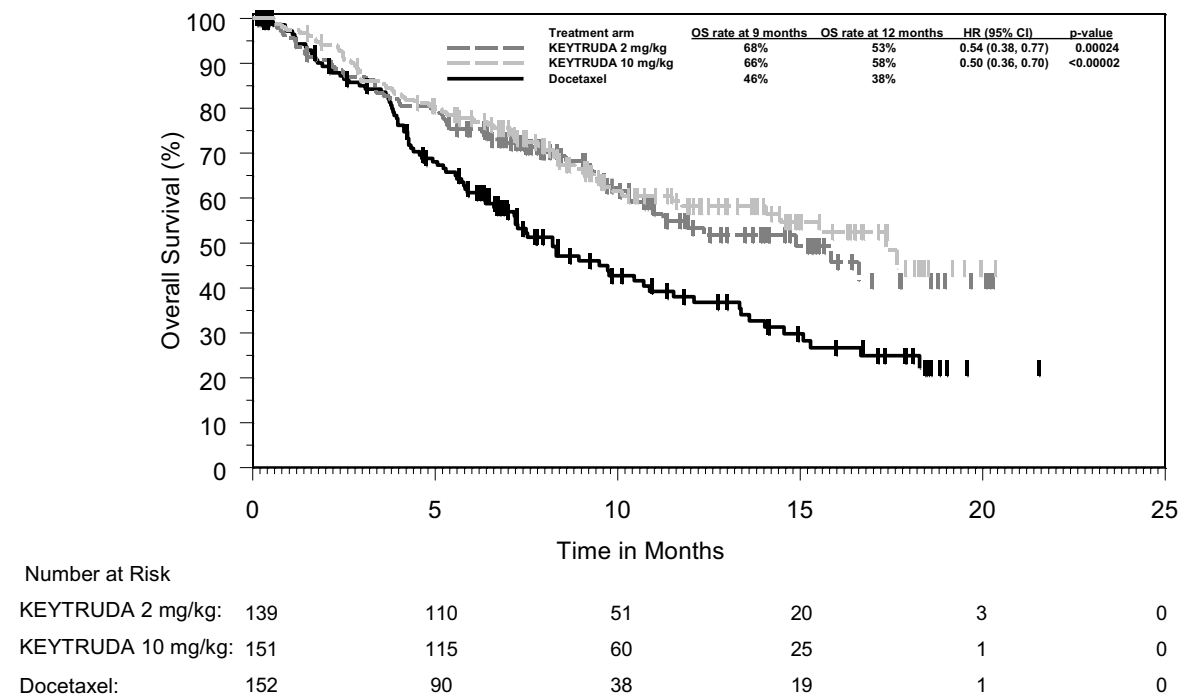
# Includes 30, 31, and 2 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

⦿ Includes 22, 24, and 1 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

**Figure 14: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS  $\geq$  1%, Intent to Treat Population)**



**Figure 15: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS  $\geq$  50%, Intent to Treat Population)**



Efficacy results were similar for the 2 mg/kg and 10 mg/kg KEYTRUDA arms. Efficacy results for OS were consistent regardless of the age of tumor specimen (new versus archival).

**KEYNOTE-001: Open-label study in NSCLC patients previously treated with chemotherapy**

The efficacy of KEYTRUDA was also investigated in a multicenter, open-label, randomized, dose-comparative cohort of KEYNOTE-001. Patients had advanced NSCLC that was PD-L1 positive, with progression of disease following treatment with platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations had disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. Patients were randomized to receive 10 mg/kg of KEYTRUDA every 2 (n=69) or 3 (n=87) weeks until disease progression or unacceptable toxicity. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR (according to RECIST 1.1 as assessed by blinded independent central review) and duration of response.

The prevalence of patients with a PD-L1 expression TPS greater than or equal to 50% among screened patients with NSCLC as ascertained retrospectively by the companion diagnostic PD-L1 IHC 22C3 pharmDx™ kit was 26%. Among the randomized patients with tumor samples evaluable for PD-L1 expression, 61 had TPS greater than or equal to 50%. The baseline characteristics for this population included: median age 60 years (34% age 65 or older); 61% male; 79% White; and 34% and 64% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous and non-squamous (21% and 75%, respectively); M1 (98%); brain metastases (11%); and one (25%), two (31%), or three or more (44%) prior therapies. The mutation status among patients was EGFR (10%), ALK (0%), or KRAS (16%).

Efficacy results for NSCLC patients treated with 10 mg/kg every 2 or 3 weeks in KEYNOTE-001 are summarized in Table 11.

**Table 11: Response to KEYTRUDA 10 mg/kg Every 2 or 3 Weeks in Previously Treated NSCLC Patients with PD-L1 Expression TPS ≥50% (n=61)**

| Endpoint                      |                           |
|-------------------------------|---------------------------|
| <b>Best Overall Response*</b> |                           |
| ORR %, (95% CI)               | 43% (30, 56)              |
| Complete response             | 2%                        |
| Partial response              | 41%                       |
| <b>Response Duration†</b>     |                           |
| Median in months (range)      | Not reached (2.1+, 13.4+) |
| % ongoing                     | 65%‡                      |
| <b>Time to Response†</b>      |                           |
| Median in months (range)      | 2.1 (1.4, 6.2)            |
| <b>PFS§</b>                   |                           |
| Median in months (95% CI)     | 6.3 (2.1, 10.7)           |
| 6-month PFS rate              | 53%                       |
| <b>OS§</b>                    |                           |
| 12-month OS rate              | 60%                       |

\* Based on all patients treated (n=61), with assessment by independent review and RECIST 1.1

† Based on patients (n=26) with a confirmed response by independent review

‡ Includes 17 patients with ongoing responses of 6 months or longer

§ Based on all treated patients (n=61)

Similar ORR results were observed in another group of patients (n=25) with TPS greater than or equal to 50% receiving KEYTRUDA at a dose of 2 mg/kg every 3 weeks in KEYNOTE-001.

KEYNOTE-671: Controlled trial for the neoadjuvant and adjuvant treatment of patients with resectable NSCLC

The efficacy of KEYTRUDA in combination with platinum-containing chemotherapy given as neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in KEYNOTE-671, a multicenter, randomized, double-blind, placebo-controlled trial. Key eligibility criteria were previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8<sup>th</sup> edition, regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by stage (II vs. III), tumor PD-L1 expression (TPS  $\geq 50\%$  or  $< 50\%$ ), histology (squamous vs. non-squamous), and geographic region (East Asia vs. non-East Asia).

Patients were randomized (1:1) to one of the following treatment arms:

- Treatment Arm A: neoadjuvant KEYTRUDA 200 mg on Day 1 in combination with cisplatin 75 mg/m<sup>2</sup> and either pemetrexed 500 mg/m<sup>2</sup> on Day 1 or gemcitabine 1000 mg/m<sup>2</sup> on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, KEYTRUDA 200 mg was administered every 3 weeks for up to 13 cycles.
- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m<sup>2</sup> and either pemetrexed 500 mg/m<sup>2</sup> on Day 1 or gemcitabine 1000 mg/m<sup>2</sup> on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, placebo was administered every 3 weeks for up to 13 cycles.

All study medications were administered via intravenous infusion. Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed at baseline, Week 7, and Week 13 in the neoadjuvant phase and within 4 weeks prior to the start of the adjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed every 16 weeks through the end of Year 3, and then every 6 months thereafter.

The primary efficacy outcome measures were OS and investigator-assessed event-free survival (EFS). Secondary efficacy outcome measures were pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent pathology review (BIPR).

A total of 797 patients in KEYNOTE-671 were randomized: 397 patients to the KEYTRUDA arm and 400 to the placebo arm. Baseline characteristics were: median age of 64 years (range: 26 to 83), 45% age 65 or older; 71% male; 61% White, 31% Asian, and 2.0% Black. Sixty-three percent and 37% had ECOG performance of 0 or 1, respectively; 30% had Stage II and 70% had Stage III disease; 33% had TPS  $\geq 50\%$  and 67% had TPS  $< 50\%$ ; 43% had tumors with squamous histology and 57% had tumors with non-squamous histology; 31% were from the East Asian region.

Eighty-one percent of patients in the KEYTRUDA in combination with platinum-containing chemotherapy arm had definitive surgery compared to 76% of patients in the platinum-containing chemotherapy arm.

The trial demonstrated statistically significant improvements in OS and EFS for patients randomized to KEYTRUDA in combination with platinum-containing chemotherapy followed by KEYTRUDA monotherapy compared with patients randomized to placebo in combination with platinum-containing chemotherapy followed by placebo alone. At a pre-specified interim analysis (median follow-up time of 21.4 months (range: 0.4 to 50.6 months)) the EFS HR was 0.58 (95% CI: 0.46, 0.72;  $p < 0.0001$ ), the pCR rate was 18% vs. 4% ( $p < 0.0001$ ) and the mPR rate was 30% vs. 11% ( $p < 0.0001$ ) for patients randomized to pembrolizumab in combination with platinum-containing chemotherapy followed by pembrolizumab monotherapy compared with patients randomized to placebo in combination with platinum-containing chemotherapy followed by placebo alone. At the time of this analysis, OS results were not mature with only 46% of pre-specified OS events in the overall population. Table 12 summarizes key efficacy measures at a median follow-up time of

29.8 months (range: 0.4 to 62.0 months). The Kaplan-Meier curves for OS and EFS are shown in Figures 16 and 17.

**Table 12: Efficacy Results in KEYNOTE-671**

| <b>Endpoint</b>                              | <b>KEYTRUDA with<br/>chemotherapy/KEYTRUDA<br/>n=397</b> | <b>Placebo with<br/>chemotherapy/Placebo<br/>n=400</b> |
|----------------------------------------------|----------------------------------------------------------|--------------------------------------------------------|
| <b>OS</b>                                    |                                                          |                                                        |
| Number of patients with event (%)            | 110 (28%)                                                | 144 (36%)                                              |
| Median in months* (95% CI)                   | NR (NR, NR)                                              | 52.4 (45.7, NR)                                        |
| Hazard ratio† (95% CI)                       | 0.72 (0.56, 0.93)                                        |                                                        |
| p-Value‡                                     | 0.00517                                                  |                                                        |
| <b>EFS</b>                                   |                                                          |                                                        |
| Number of patients with event (%)            | 174 (44%)                                                | 248 (62%)                                              |
| Median in months* (95% CI)                   | 47.2 (32.9, NR)                                          | 18.3 (14.8, 22.1)                                      |
| Hazard ratio† (95% CI)                       | 0.59 (0.48, 0.72)                                        |                                                        |
| <b>pCR</b>                                   |                                                          |                                                        |
| Number of patients with pCR                  | 72                                                       | 16                                                     |
| pCR Rate (%), (95% CI)                       | 18% (14.5, 22.3)                                         | 4% (2.3, 6.4)                                          |
| Treatment difference estimate (%), (95% CI)§ | 14% (10.1, 18.7)                                         |                                                        |
| <b>mPR</b>                                   |                                                          |                                                        |
| Number of patients with mPR                  | 120                                                      | 44                                                     |
| mPR Rate (%), (95% CI)                       | 30% (25.7, 35.0)                                         | 11% (8.1, 14.5)                                        |
| Treatment difference estimate (%), (95% CI)§ | 19% (13.9, 24.7)                                         |                                                        |

\* Based on Kaplan-Meier estimates

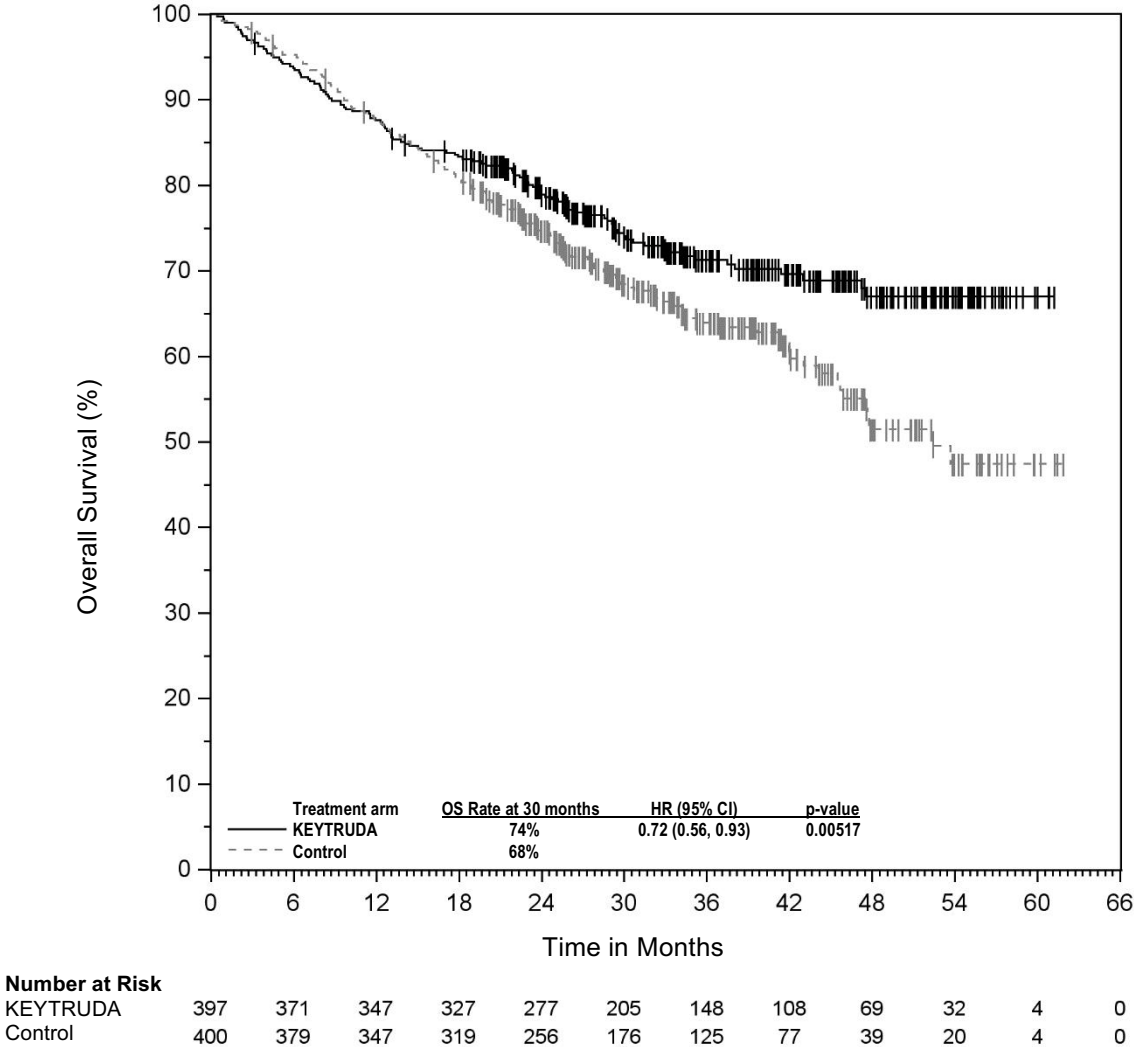
† Based on Cox regression model with treatment as a covariate stratified by stage, tumor PD-L1 expression, histology, and geographic region

‡ Based on stratified log-rank test

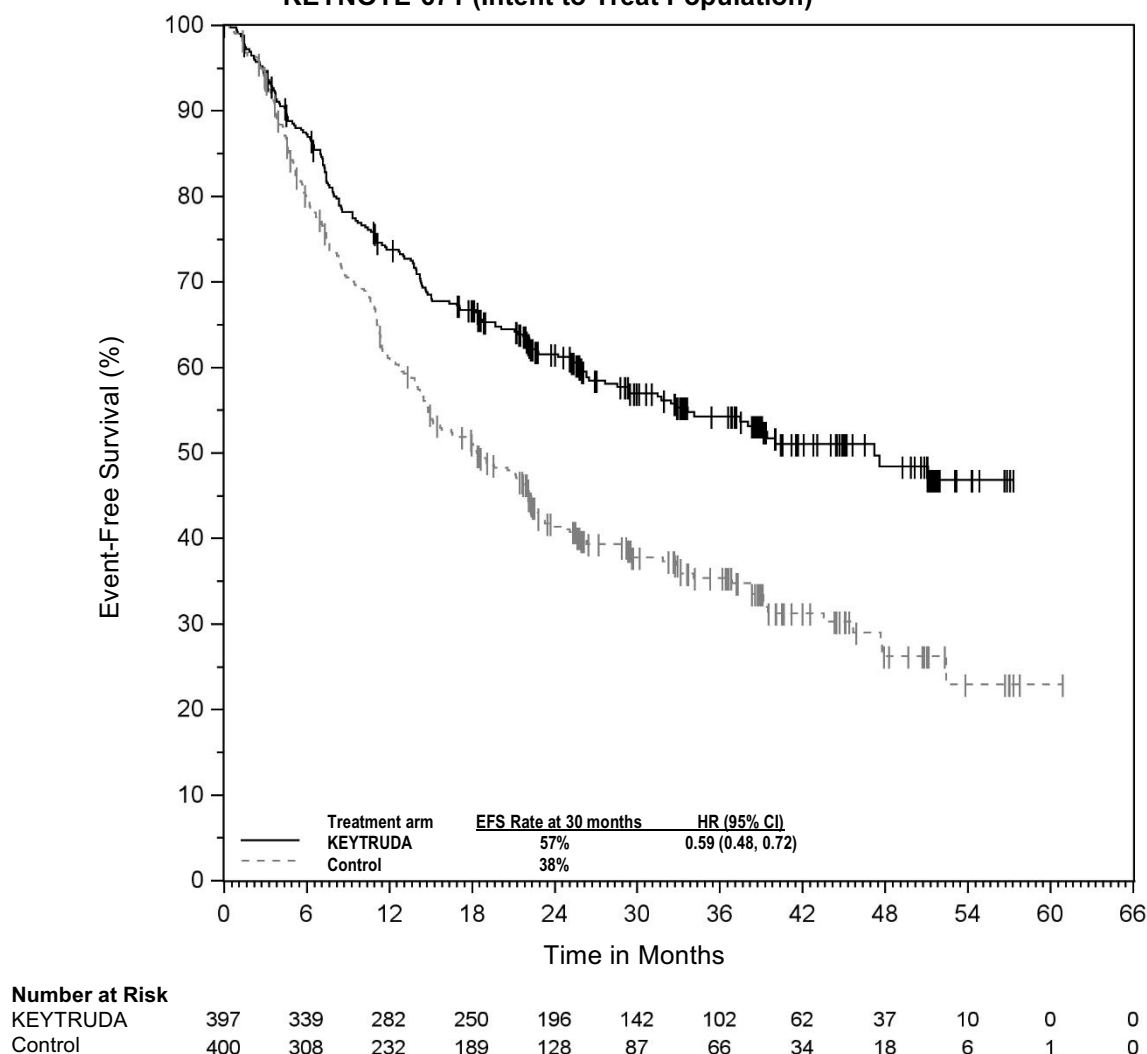
§ Based on Miettinen and Nurminen method stratified by stage, tumor PD-L1 expression, histology, and geographic region

NR = not reached

Figure 16: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)



**Figure 17: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)**



**KEYNOTE-091: Controlled trial for the adjuvant treatment of patients with resected NSCLC**

The efficacy of KEYTRUDA was investigated in KEYNOTE-091, a multicenter, randomized, triple-blind, placebo-controlled trial. Key eligibility criteria were completely resected stage IB (T2a  $\geq$  4 cm), II, or IIIA NSCLC by AJCC 7<sup>th</sup> edition, regardless of tumor PD-L1 expression status, no prior neoadjuvant radiotherapy and/or neoadjuvant chemotherapy, and no prior or planned adjuvant radiotherapy for the current malignancy. Patients may or may not have received adjuvant chemotherapy. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 4 cycles of adjuvant chemotherapy were ineligible. Randomization was stratified by stage (IB vs. II vs. IIIA), adjuvant chemotherapy (no adjuvant chemotherapy vs. adjuvant chemotherapy), PD-L1 status (TPS <1% [negative] vs. TPS 1-49% vs. TPS  $\geq$ 50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomized (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST 1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity, or approximately one year (18 doses). Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first year, then every 6 months for years 2 to 3, and then annually up to the end of year 5. After year 5, imaging is performed as per local standard of care.

Among the 1177 patients in KEYNOTE-091 (590 patients in the KEYTRUDA arm and 587 in the placebo arm), baseline characteristics were: median age of 65 years (range: 31 to 87), 53% age 65 or older; 68% male; and 77% White, 18% Asian. Sixty-one percent and 39% had ECOG performance of 0 or 1, respectively. Fourteen percent had stage IB (T2a  $\geq$  4 cm), 57% had stage II, and 29% had stage IIIA disease. Forty percent had tumor PD-L1 expression TPS <1% [negative], 32% had TPS 1-49%, 28% had TPS  $\geq$ 50%, and 86% received adjuvant chemotherapy. Fifty-one percent were from Western Europe.

The primary efficacy outcome measures were investigator-assessed disease-free survival (DFS) in the overall population and in the population with tumor PD-L1 expression TPS  $\geq$ 50%, where DFS was defined as the time between the date of randomization and the date of first recurrence (local/regional recurrence, distant metastasis), a second malignancy, or death, whichever occurred first. Secondary efficacy outcome measures were investigator-assessed DFS in the population with tumor PD-L1 expression TPS  $\geq$ 1%, and OS in the overall population and in the populations with tumor PD-L1 expression TPS  $\geq$ 50% and TPS  $\geq$ 1%.

The trial demonstrated a statistically significant improvement in DFS in the overall population at a pre-specified interim analysis for patients randomized to the KEYTRUDA arm compared to patients randomized to the placebo arm. At the time of analysis, OS results were not mature (18% with events in the overall population). The median follow-up time was 32.4 months (range: 0.6 to 68 months). Efficacy results are summarized in Table 13 and Figure 18.

**Table 13: Efficacy Results in KEYNOTE-091**

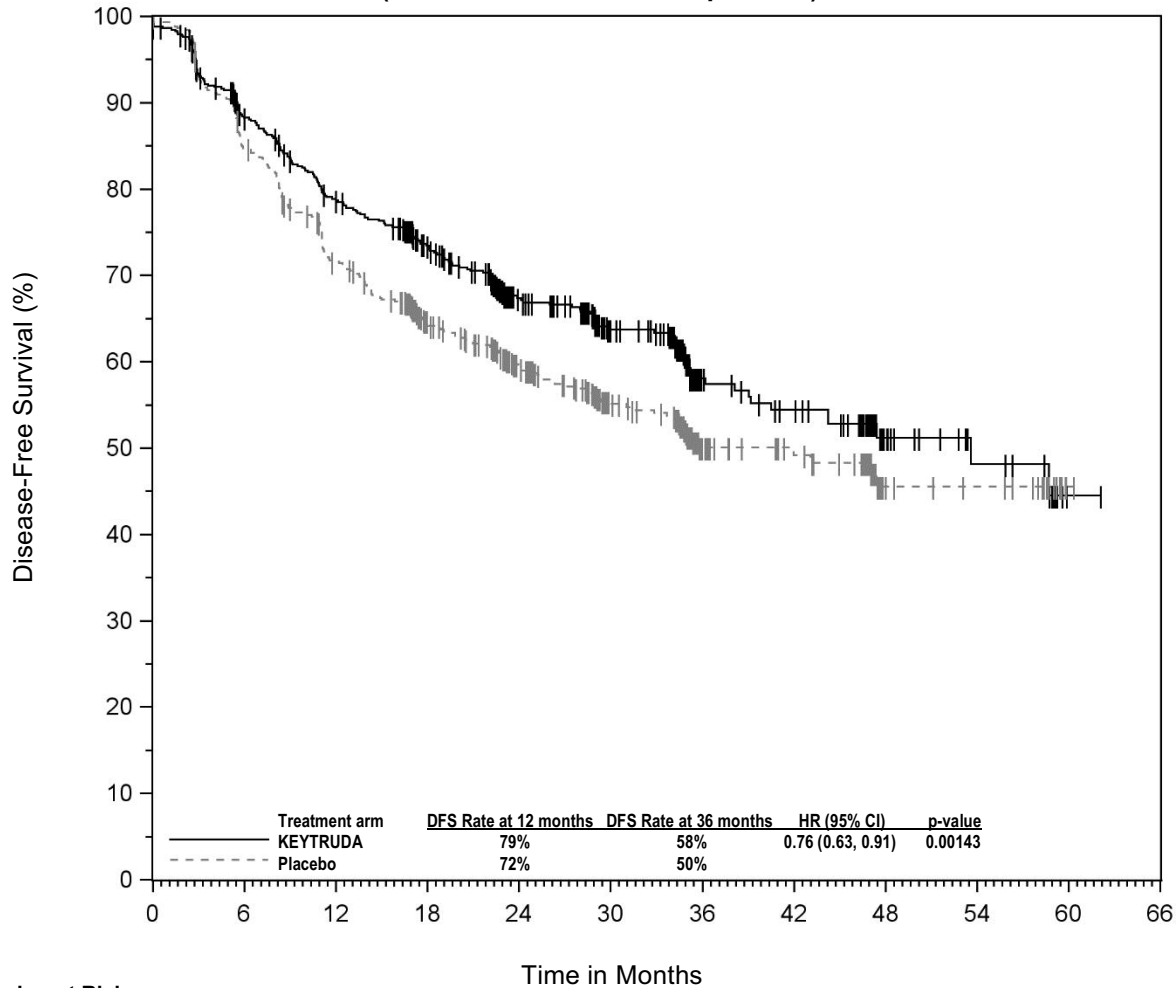
| <b>Endpoint</b>                   | <b>KEYTRUDA<br/>200 mg every<br/>3 weeks<br/>n=590</b> | <b>Placebo<br/><br/>n=587</b> |
|-----------------------------------|--------------------------------------------------------|-------------------------------|
| <b>DFS (Overall)</b>              |                                                        |                               |
| Number (%) of patients with event | 212 (36%)                                              | 260 (44%)                     |
| Hazard ratio* (95% CI)            | 0.76 (0.63, 0.91)                                      |                               |
| p-Value <sup>†</sup>              | 0.0014                                                 |                               |
| Median in months (95% CI)         | 53.6 (39.2, NR)                                        | 42.0 (31.3, NR)               |

\* Based on the multivariate Cox regression model

<sup>†</sup> Based on the permutation test with multivariate Cox regression model

NR = not reached

**Figure 18: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in KEYNOTE-091 (Overall Intent to Treat Population)**



| Number at Risk |     |     |     |     |     |     |    |    |    |    |   |
|----------------|-----|-----|-----|-----|-----|-----|----|----|----|----|---|
| KEYTRUDA       | 590 | 493 | 434 | 358 | 264 | 185 | 82 | 70 | 28 | 16 | 1 |
| Placebo        | 587 | 493 | 409 | 326 | 241 | 160 | 72 | 57 | 22 | 18 | 1 |

### **Malignant Pleural Mesothelioma**

#### **KEYNOTE-483: Controlled study of combination therapy in patients with untreated unresectable advanced or metastatic malignant pleural mesothelioma (MPM)**

The efficacy of pembrolizumab in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-483, a multicentre, randomised, open-label, active-controlled study. Key eligibility criteria were unresectable advanced or metastatic MPM with no prior systemic therapy for advanced/metastatic disease. Patients were enrolled regardless of tumour PD-L1 expression. Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by histological subtype (epithelioid vs. non-epithelioid). Patients were randomised (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- Pembrolizumab 200 mg with pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles, followed by pembrolizumab 200 mg every 3 weeks (n=222). Pembrolizumab was administered prior to chemotherapy on Day 1.
- Pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles (n=218).

Treatment with pembrolizumab continued until disease progression as determined by the investigator according to modified RECIST 1.1 for mesothelioma (mRECIST), unacceptable toxicity, or a maximum of 24 months. Assessment of tumour status was performed every 6 weeks for 18 weeks, followed by every 12 weeks thereafter.

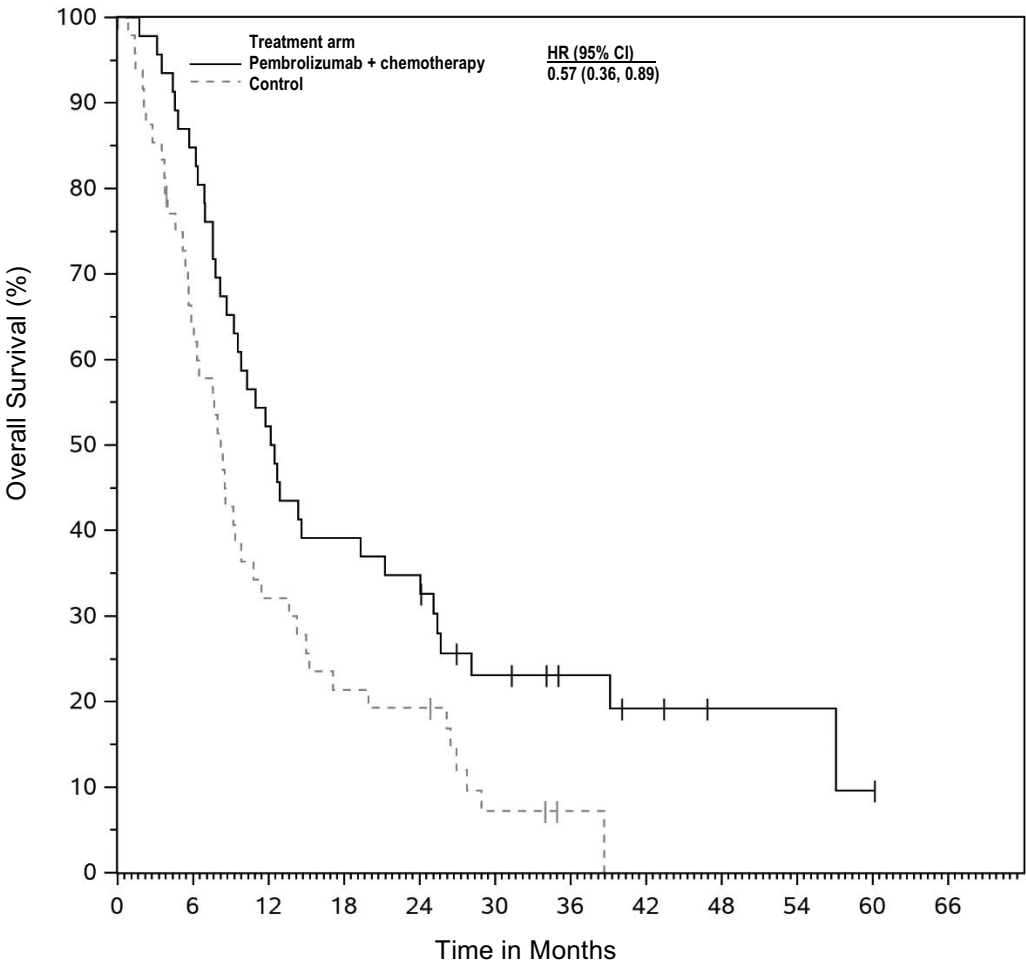
Among the 95 patients with non-epithelioid histology in KEYNOTE-483, baseline characteristics were: median age of 71 years (range: 48-85 years of age) with 76% age 65 or older; 83% male; 85% White, 15% not reported or unknown; 1% Hispanic or Latino and 44% and 56% ECOG performance status of 0 or 1, respectively.

The primary efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using mRECIST. The study demonstrated statistically significant improvement in the overall population in OS [HR 0.79; 95% CI 0.64, 0.98; p-Value 0.0162] and PFS [HR 0.80; 95% CI 0.65, 0.99; p-Value 0.0194] at the final analysis and ORR [52% (95% CI 45, 59) vs. 29% (95% CI 23, 35); p-Value < 0.00001] at the interim analysis in patients randomised to pembrolizumab in combination with chemotherapy compared with patients randomised to chemotherapy alone. Table 14 summarises key efficacy measures and Figures 19 and 20 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up time of 9.8 months (range: 0.9 to 60.3 months) in the patients with non-epithelioid malignant pleural mesothelioma.

**Table 14: Efficacy results in KEYNOTE-483 for patients with non-epithelioid malignant pleural mesothelioma**

| Endpoint                                                                                          | Pembrolizumab<br>200 mg every 3 weeks +<br>Pemetrexed +<br>Platinum Chemotherapy<br>(n=46) | Pemetrexed +<br>Platinum Chemotherapy<br>(n=49) |
|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>OS</b>                                                                                         |                                                                                            |                                                 |
| Number (%) of patients with event                                                                 | 37 (80%)                                                                                   | 44 (90%)                                        |
| Hazard ratio* (95% CI)                                                                            | 0.57 (0.36, 0.89)                                                                          |                                                 |
| Median in months† (95% CI)                                                                        | 12.3 (8.7, 21.2)                                                                           | 8.2 (5.8, 9.8)                                  |
| <b>PFS</b>                                                                                        |                                                                                            |                                                 |
| Number (%) of patients with event                                                                 | 36 (78%)                                                                                   | 38 (78%)                                        |
| Hazard ratio* (95% CI)                                                                            | 0.47 (0.29, 0.77)                                                                          |                                                 |
| Median in months† (95% CI)                                                                        | 7.1 (4.5, 9.8)                                                                             | 4.5 (4.0, 6.4)                                  |
| <b>Objective response rate</b>                                                                    |                                                                                            |                                                 |
| ORR % (95% CI)‡                                                                                   | 41% (27, 57)                                                                               | 6% (1, 17)                                      |
| <b>Response duration†</b>                                                                         |                                                                                            |                                                 |
| Median in months (range)                                                                          | 11.1 (1.3+, 38.9+)                                                                         | 4.0 (2.4+, 5.2)                                 |
| * Based on Cox regression model with Efron's method of tie handling with treatment as a covariate |                                                                                            |                                                 |
| † From product-limit (Kaplan-Meier) method for censored data                                      |                                                                                            |                                                 |
| ‡ Based on the exact method for binomial data                                                     |                                                                                            |                                                 |

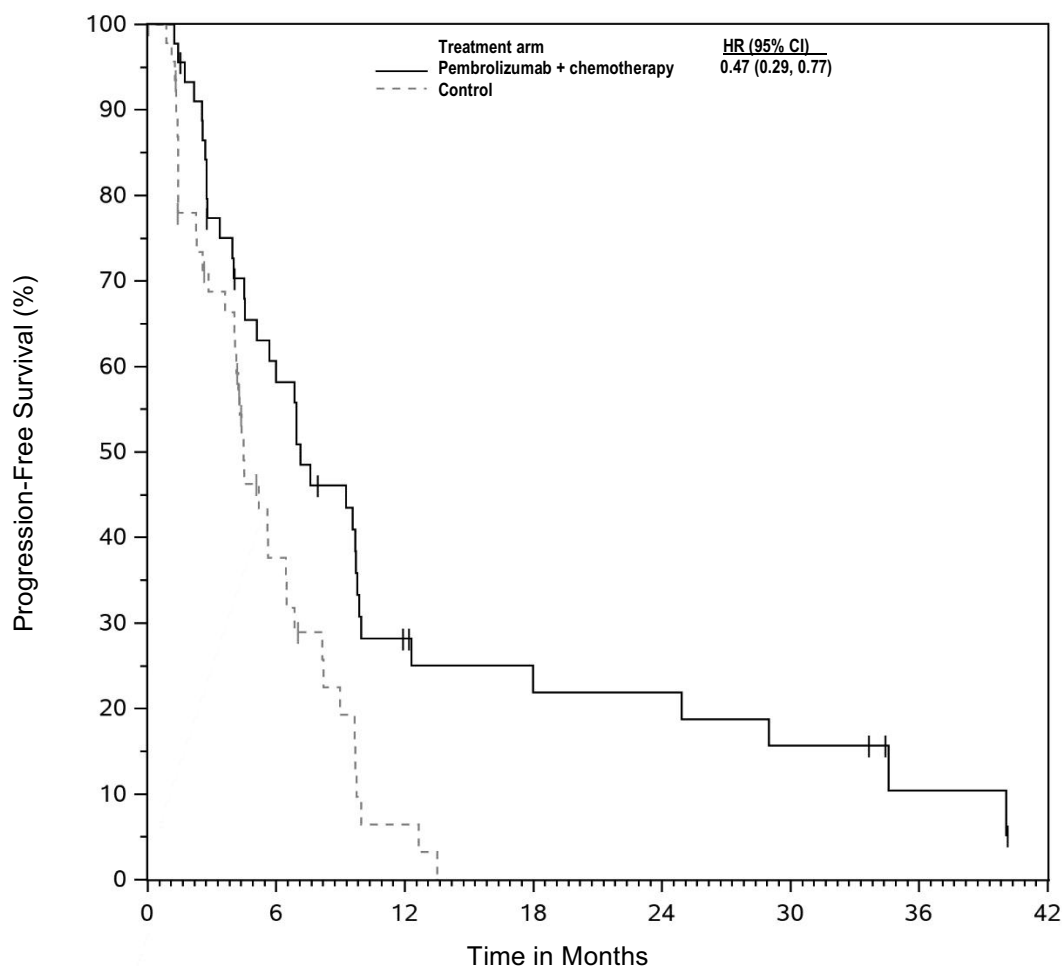
Figure 19: Kaplan-Meier curve for overall survival in patients with non-epithelioid MPM in KEYNOTE-483



Number at Risk

|                              |    |    |    |    |    |   |   |   |   |   |   |   |
|------------------------------|----|----|----|----|----|---|---|---|---|---|---|---|
| pembrolizumab + chemotherapy | 46 | 39 | 24 | 18 | 16 | 9 | 6 | 4 | 2 | 2 | 1 | 0 |
| Control                      | 49 | 30 | 15 | 10 | 9  | 3 | 1 | 0 | 0 | 0 | 0 | 0 |

**Figure 20: Kaplan-Meier curve for progression-free survival in patients with non-epithelioid MPM in KEYNOTE-483**



**Number at Risk**

|                              |    |    |    |   |   |   |   |   |
|------------------------------|----|----|----|---|---|---|---|---|
| pembrolizumab + chemotherapy | 46 | 24 | 10 | 7 | 7 | 5 | 2 | 0 |
| Control                      | 49 | 13 | 2  | 0 | 0 | 0 | 0 | 0 |

**Head and Neck Cancer**

**KEYNOTE-689: Controlled study for the neoadjuvant and adjuvant treatment of patients with resectable locally advanced HNSCC**

The efficacy of KEYTRUDA was investigated in KEYNOTE-689, a randomized, multicenter, open-label, active-controlled study conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor stage by AJCC 8<sup>th</sup> edition (III vs. IVA) and PD-L1 status (TPS  $\geq$  50% vs. TPS < 50%).

Patients were randomized (1:1) to one of the following treatment arms:

- Treatment arm A: Neoadjuvant KEYTRUDA 200 mg for 2 cycles prior to surgical resection. Within 6 weeks following surgery, KEYTRUDA 200 mg for 3 cycles in combination with either radiation + 3 cycles of concomitant cisplatin 100 mg/m<sup>2</sup> every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery. This was followed by KEYTRUDA 200 mg every 3 weeks for up to 12 cycles.

- Treatment arm B: No neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, either radiation + 3 cycles of concomitant cisplatin 100 mg/m<sup>2</sup> every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery.

High-risk pathologic features are defined by evidence of positive margins or extranodal extension following surgical resection.

Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as assessed by BICR, until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed 12 weeks after end of RT ± cisplatin treatment and then every 3 months until the end of Year 3; then every 6 months thereafter up to the end of Year 5. In arm A, 89% of the patients had surgery compared to 88% in arm B. In arm A, 29% of patients received cisplatin plus radiation and 46% received radiation alone. In arm B, 40% of patients received cisplatin plus radiation and 39% received radiation alone.

Among the 714 patients in KEYNOTE-689, 682 (96%) had tumors that expressed PD-L1 with a CPS ≥ 1 based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 682 patients were: median age of 60 years (range: 22 to 87), 33% age 65 or older; 79% male; 78% White, 13% Asian and 2.5% Black; 43% had ECOG PS of 1, and 79% were former/current smokers. Four percent of patients' tumors were HPV-positive, and 26% had Stage III disease, 74% had Stage IVA disease.

The primary efficacy outcome measure was EFS by BICR defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant disease progression or recurrence, or death due to any cause. Secondary primary malignancy was not considered an event. Additional efficacy outcome measures were mPR as assessed by BIPR, OS, and pCR as assessed by BIPR.

The study demonstrated a statistically significant improvement in EFS (HR 0.73; 95% CI: 0.58, 0.92; p-Value 0.00411) in patients randomized to pembrolizumab in combination with radiation with or without concomitant cisplatin compared to those randomized to radiation with or without concomitant cisplatin at the first pre-specified interim analysis in the overall population. OS at interim analysis was not formally tested. Table 15 summarizes key efficacy results for the pre-specified subgroup of patients whose tumors expressed PD-L1 with a CPS ≥ 1 at a median follow-up time of 27.0 months (range: 0.5 to 66.5 months). Figures 21 and 22 show the Kaplan-Meier curves for EFS and OS.

**Table 15: Efficacy Results in KEYNOTE-689 for Patients with PD-L1 Expression (CPS ≥ 1)**

| Endpoint                          | KEYTRUDA 200 mg<br>every 3 weeks<br>with<br>RT with or without<br>Cisplatin<br>n=347 | RT with or<br>without Cisplatin<br>n=335 |
|-----------------------------------|--------------------------------------------------------------------------------------|------------------------------------------|
| EFS                               |                                                                                      |                                          |
| Number (%) of patients with event | 128 (37%)                                                                            | 156 (47%)                                |
| Median in months* (95% CI)        | 59.7 (37.9, NR)                                                                      | 29.6 (19.5, 41.9)                        |
| Hazard ratio† (95% CI)            | 0.70 (0.55, 0.89)                                                                    |                                          |
| p-Value‡                          | 0.00140                                                                              |                                          |
| OS                                |                                                                                      |                                          |
| Number (%) of patients with event | 106 (31%)                                                                            | 128 (38%)                                |
| Median in months* (95% CI)        | NR (NR, NR)                                                                          | 61.8 (49.2, NR)                          |
| Hazard ratio† (95% CI)            | 0.72 (0.56, 0.94)                                                                    |                                          |

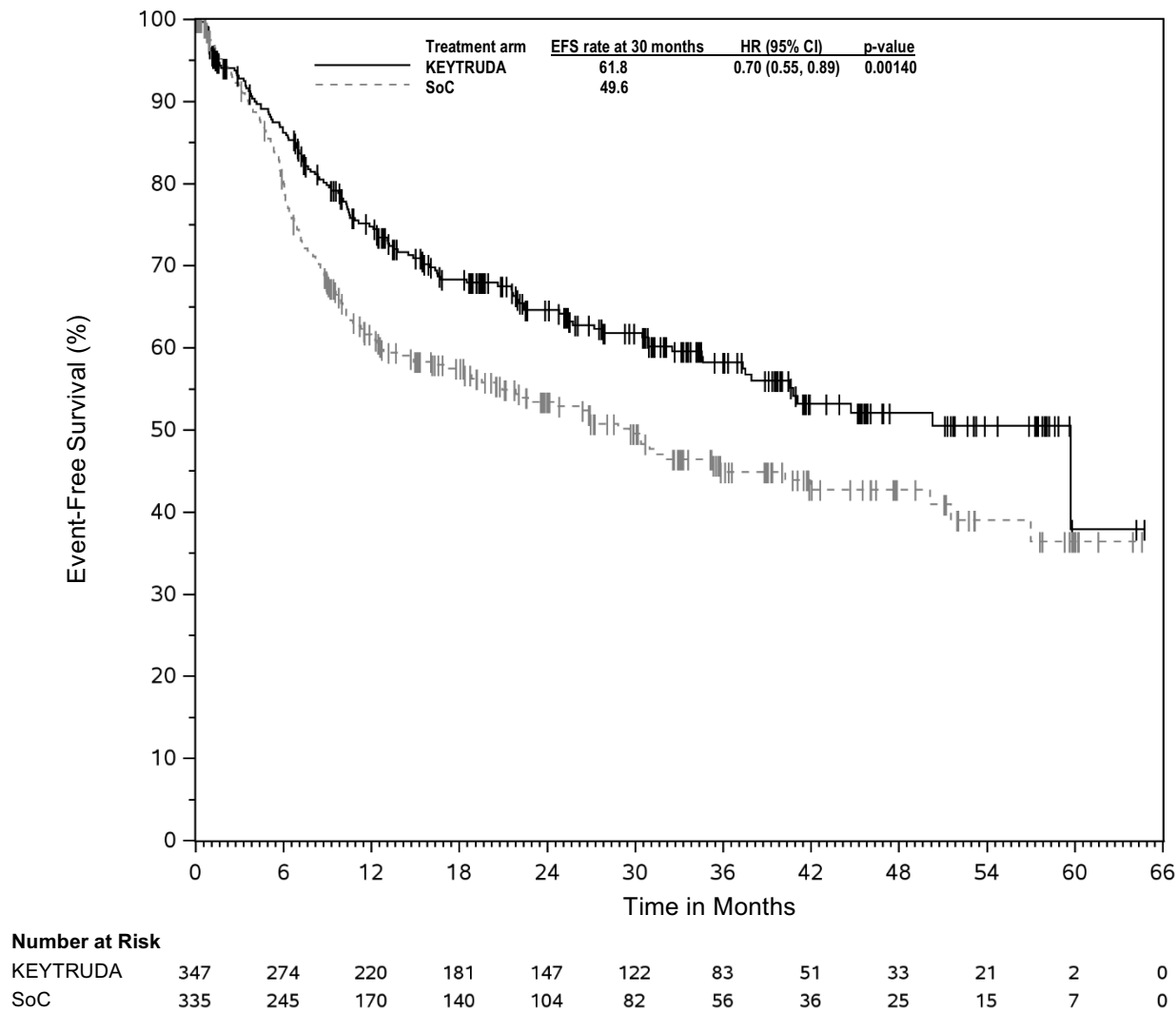
\* From product-limit (Kaplan-Meier) method for censored data

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site and tumor stage

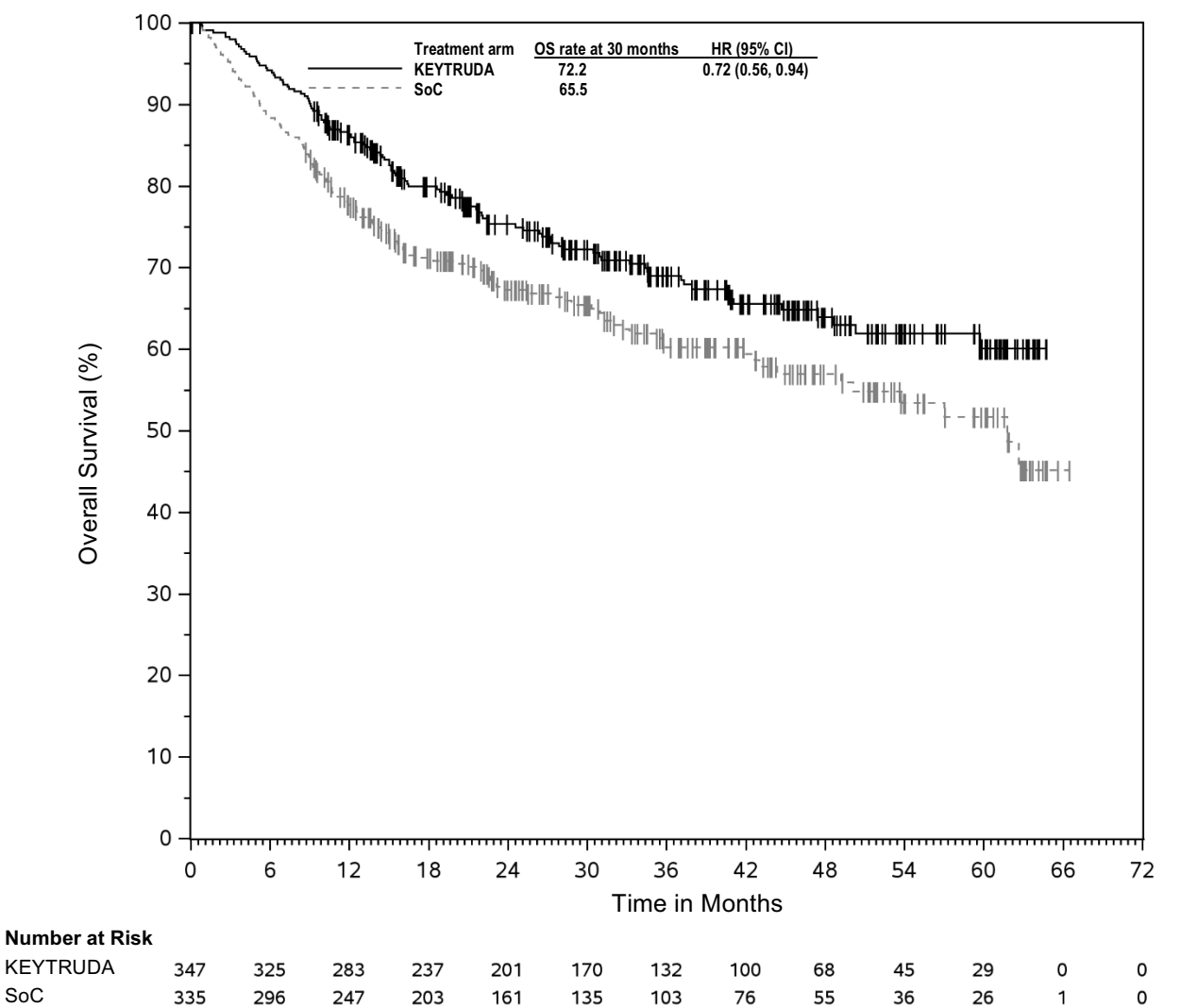
‡ One-sided p-Value based on log-rank test stratified by primary tumor site and tumor stage: Compared to a one-sided p-Value boundary of 0.0124

NR = not reached

Figure 21: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-689 for Patients with PD-L1 Expression (CPS ≥ 1)



**Figure 22: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-689 for Patients with PD-L1 Expression (CPS ≥ 1)**



**KEYNOTE-048: Controlled trial of first-line monotherapy or combination therapy in HNSCC**

The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%) based on the PD-L1 IHC 22C3 pharmDx™ kit, HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). Patients were randomized 1:1:1 to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks
- KEYTRUDA 200 mg intravenously every 3 weeks, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m<sup>2</sup> intravenously every 3 weeks, and FU 1000 mg/m<sup>2</sup>/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)
- Cetuximab 400 mg/m<sup>2</sup> intravenously as the initial dose then 250 mg/m<sup>2</sup> intravenously once weekly, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m<sup>2</sup> intravenously every

3 weeks, and FU 1000 mg/m<sup>2</sup>/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)

Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months. A retrospective re-classification of patients' tumor PD-L1 status according to CPS using the PD-L1 IHC 22C3 pharmDx™ kit was conducted using the tumor specimens used for randomization.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) sequentially tested in the subgroup of patients with CPS ≥20, the subgroup of patients with CPS ≥1, and the overall population.

The study population characteristics were: median age of 61 years (range: 20 to 94), 36% age 65 or older; 83% male; 73% White, 20% Asian and 2.4% Black; 61% had ECOG PS of 1; and 79% were former/current smokers. Twenty-two percent of patients' tumors were HPV-positive, 23% had PD-L1 TPS ≥50%, and 95% had Stage IV disease (Stage IVA 19%, Stage IVB 6%, and Stage IVC 70%). Eighty-five percent of patients' tumors had PD-L1 expression of CPS ≥1 and 43% had CPS ≥20.

The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis in the overall population. The trial also demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to KEYTRUDA as a single agent compared to those randomized to cetuximab in combination with chemotherapy. At the time of the interim analysis, there was no significant difference in OS between the KEYTRUDA single agent arm and the control arm for the overall population. Table 16 and Figure 23 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

**Table 16: Efficacy Results for KEYTRUDA plus Platinum/Fluorouracil  
in KEYNOTE-048**

| Endpoint                          | KEYTRUDA<br>200 mg every 3 weeks<br>Platinum<br>FU<br><br>n=281 | Cetuximab<br>Platinum<br>FU<br><br>n=278 |
|-----------------------------------|-----------------------------------------------------------------|------------------------------------------|
| OS                                |                                                                 |                                          |
| Number (%) of patients with event | 197 (70%)                                                       | 223 (80%)                                |
| Median in months (95% CI)         | 13.0 (10.9, 14.7)                                               | 10.7 (9.3, 11.7)                         |
| Hazard ratio* (95% CI)            | 0.77 (0.63, 0.93)                                               |                                          |
| p-Value†                          | 0.0067                                                          |                                          |
| PFS                               |                                                                 |                                          |
| Number of patients with event (%) | 244 (87%)                                                       | 253 (91%)                                |
| Median in months (95% CI)         | 4.9 (4.7, 6.0)                                                  | 5.1 (4.9, 6.0)                           |
| Hazard ratio* (95% CI)            | 0.92 (0.77, 1.10)                                               |                                          |
| p-Value†                          | 0.3394                                                          |                                          |
| Objective Response Rate           |                                                                 |                                          |
| ORR‡ (95% CI)                     | 36% (30.0, 41.5)                                                | 36% (30.7, 42.3)                         |
| Complete response rate            | 6%                                                              | 3%                                       |
| Partial response rate             | 30%                                                             | 33%                                      |
| Response Duration                 |                                                                 |                                          |
| Median in months (range)          | 6.7 (1.6+, 30.4+)                                               | 4.3 (1.2+, 27.9+)                        |

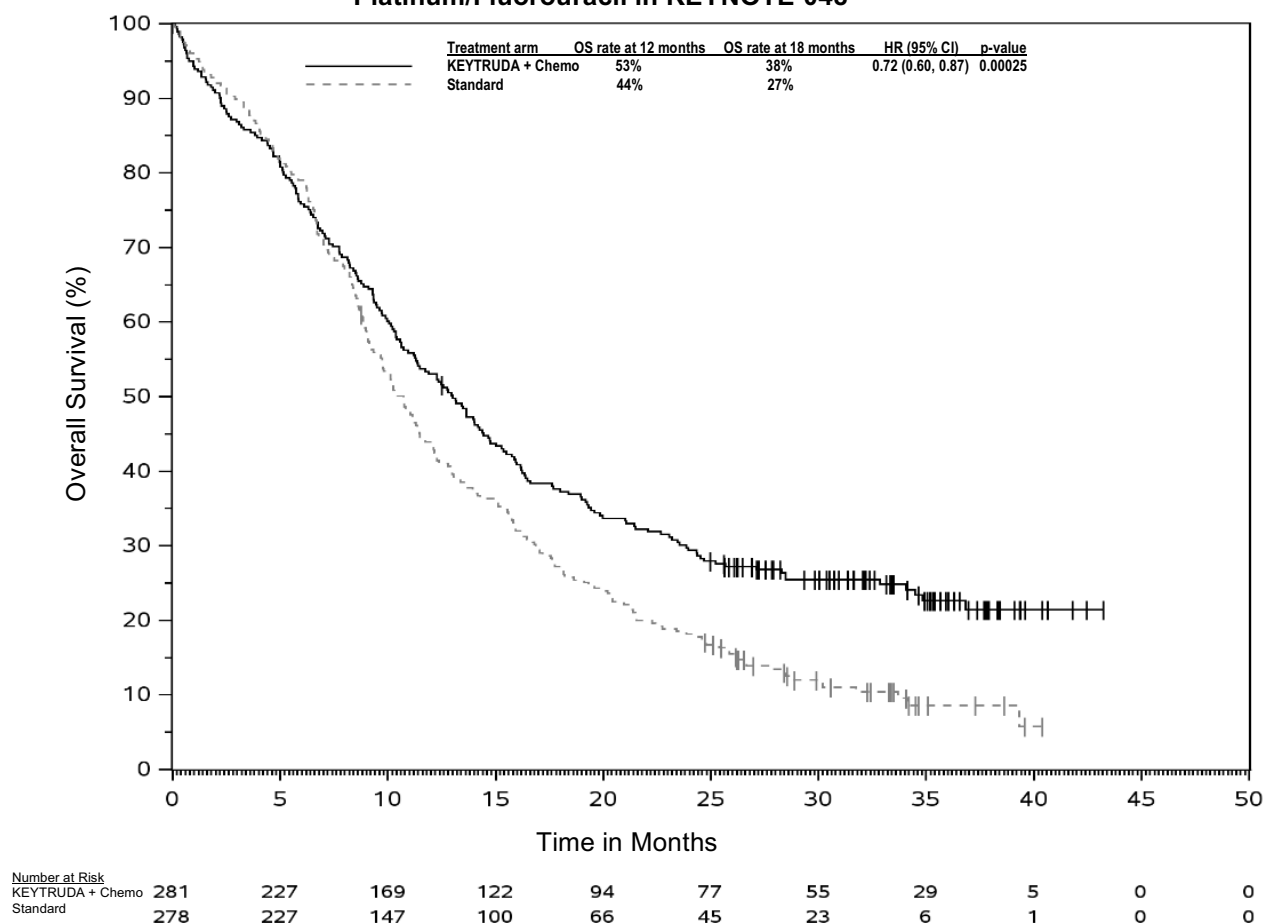
\* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Response: Best objective response as confirmed complete response or partial response

In KEYNOTE-048, OS HRs for patients randomized to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS  $\geq 1$  (HR 0.71, 95% CI: 0.57, 0.88), CPS  $\geq 20$  (HR 0.69, 95% CI: 0.51, 0.94). The OS HRs at final analysis with a median follow-up of 11.4 months were similar to those obtained at the pre-specified interim analysis and in addition, demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS  $\geq 1$  and CPS  $\geq 20$ : ITT (0.72, 95% CI: 0.60, 0.87), CPS  $\geq 1$  (0.65, 95% CI: 0.53, 0.80), CPS  $\geq 20$  (0.60, 95% CI: 0.45, 0.82).

**Figure 23: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048\***



\*Median follow-up of 11.4 months at protocol-specified final analysis.

Table 17 summarizes efficacy results for KEYTRUDA as a single agent in the subgroups of patients with CPS  $\geq 1$  HNSCC and CPS  $\geq 20$  HNSCC. Figure 24 summarizes the OS results in the subgroup of patients with CPS  $\geq 1$  HNSCC.

**Table 17: Efficacy Results for KEYTRUDA as a Single Agent  
in KEYNOTE-048 (CPS ≥1 and CPS ≥20)**

| Endpoint                  | CPS ≥1                                        |                                      | CPS ≥20                                       |                                      |
|---------------------------|-----------------------------------------------|--------------------------------------|-----------------------------------------------|--------------------------------------|
|                           | KEYTRUDA<br>200 mg every 3 weeks<br><br>n=257 | Cetuximab<br>Platinum<br>FU<br>n=255 | KEYTRUDA<br>200 mg every 3 weeks<br><br>n=133 | Cetuximab<br>Platinum<br>FU<br>n=122 |
| OS                        |                                               |                                      |                                               |                                      |
| Number of events (%)      | 177 (69%)                                     | 206 (81%)                            | 82 (62%)                                      | 95 (78%)                             |
| Median in months (95% CI) | 12.3 (10.8, 14.9)                             | 10.3 (9.0,11.5)                      | 14.9 (11.6, 21.5)                             | 10.7 (8.8, 12.8)                     |
| Hazard ratio* (95% CI)    | 0.78 (0.64, 0.96)                             |                                      | 0.61 (0.45, 0.83)                             |                                      |
| p-Value†                  | 0.0171                                        |                                      | 0.0015                                        |                                      |
| PFS                       |                                               |                                      |                                               |                                      |
| Number of events (%)      | 225 (88%)                                     | 231 (91%)                            | 113 (85%)                                     | 111 (91%)                            |
| Median in months (95% CI) | 3.2 (2.2, 3.4)                                | 5.0 (4.8, 5.8)                       | 3.4 (3.2, 3.8)                                | 5.0 (4.8, 6.2)                       |
| Hazard ratio * (95% CI)   | 1.15(0.95, 1.38)                              |                                      | 0.99 (0.75, 1.29)                             |                                      |
| Objective Response Rate   |                                               |                                      |                                               |                                      |
| ORR‡ (95% CI)             | 19% (14.5, 24.4)                              | 35% (29.1, 41.1)                     | 23% (16.4, 31.4)                              | 36% (27.6, 45.3)                     |
| Complete response rate    | 5%                                            | 3%                                   | 8%                                            | 3%                                   |
| Partial response rate     | 14%                                           | 32%                                  | 16%                                           | 33%                                  |
| Response Duration         |                                               |                                      |                                               |                                      |
| Median in months (range)  | 20.9 (1.5+, 34.8+)                            | 4.5 (1.2+, 28.6+)                    | 20.9 (2.7, 34.8+)                             | 4.2 (1.2+, 22.3+)                    |

\* Based on the stratified Cox proportional hazard model

† Based on a stratified log-rank test

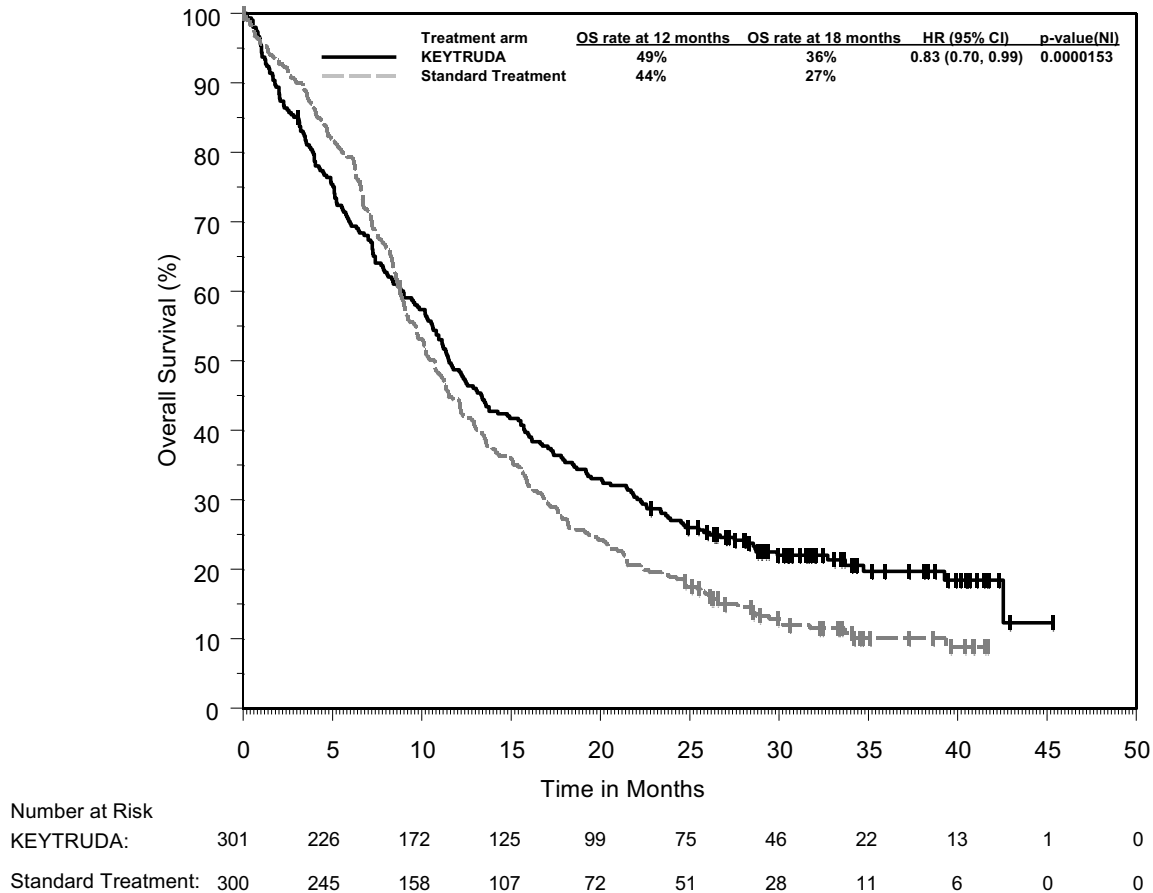
‡ Response: Best objective response as confirmed complete response or partial response

The final OS analysis was performed for patients with CPS ≥1 with a median follow-up of 11.4 months from the pre-specified interim analysis. Median OS was 12.3 months (95% CI: 10.8, 14.3) for KEYTRUDA as a single agent and 10.3 months (95% CI: 9.0, 11.5) for cetuximab in combination with chemotherapy, with an HR of 0.74 (95% CI: 0.61, 0.90).

The final OS analysis was performed for patients with CPS ≥20 with a median follow-up of 12.2 months from the pre-specified interim analysis. Median OS was 14.8 months (95% CI: 11.5, 20.6) for KEYTRUDA as a single agent and 10.7 months (95% CI: 8.8, 12.8) for cetuximab in combination with chemotherapy, with an HR of 0.58 (95% CI: 0.44, 0.78).

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.90 (95% CI: 0.68, 1.18). The final OS analysis was performed for patients with CPS 1-19 with a median follow-up of 10.3 months. At the final analysis, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.86 (95% CI: 0.66, 1.12).

**Figure 24: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1)**



\*Median follow-up of 11.2 months at protocol-specified final analysis.

**KEYNOTE-012: Open-label study in HNSCC patients previously treated with chemotherapy**

The efficacy of KEYTRUDA was investigated in 192 patients with recurrent and/or metastatic HNSCC, regardless of tumor human papilloma virus (HPV) status (33% positive), enrolled in a multicenter, non-randomized, open-label multi-cohort study (KEYNOTE-012). One cohort (n=132) was included regardless of PD-L1 tumor status. Efficacy is reported for a subgroup of 110 patients with recurrent and/or metastatic HNSCC that progressed on or after treatment with platinum-containing chemotherapy and cetuximab, and for a subgroup of 64 patients with recurrent and/or metastatic HNSCC that progressed on or after treatment with platinum-containing chemotherapy without prior cetuximab. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=53), or 200 mg every 3 weeks (n=121) until disease progression or unacceptable toxicity. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 64 patients with disease progression after platinum-containing chemotherapy without prior cetuximab, the baseline characteristics were median age 60 years (28% age 65 or older); 77% male; 75% White, 20% Asian, and 3% Black; 88% had M1 stage disease; and 33% and 67% had an ECOG performance status 0 and 1, respectively. Thirty-six percent of patients had two or more lines of therapy in the recurrent and/or metastatic setting.

Among the 110 patients with disease progression after platinum-containing chemotherapy and cetuximab, the baseline characteristics were median age 60 years (34% age 65 or older); 85% male; 75% White, 14% Asian, and 7% Black; 87% had M1 stage disease; and 27% and 73% had an ECOG performance status 0 and 1, respectively. Eighty percent of patients had two or more lines of therapy in the recurrent and/or metastatic setting.

Efficacy results are summarized in Table 18.

**Table 18: Efficacy Results in Patients with HNSCC**

| Endpoint                        | Previously treated with platinum without cetuximab | Previously treated with platinum and cetuximab |
|---------------------------------|----------------------------------------------------|------------------------------------------------|
|                                 | n=64                                               | n=110                                          |
| <b>Objective Response Rate*</b> |                                                    |                                                |
| ORR %, (95% CI)                 | 20% (11, 32)                                       | 15% (9,23)                                     |
| Complete response               | 5%                                                 | 4%                                             |
| Partial response                | 16%                                                | 11%                                            |
| <b>Response Duration</b>        |                                                    |                                                |
| Median in months (range)        | Not reached (1.8+, 21.8+) <sup>‡</sup>             | Not reached (2.4+, 18.7+) <sup>†</sup>         |
| % with duration ≥ 6-months      | 83% <sup>§</sup>                                   | 79% <sup>¶</sup>                               |
| <b>Time to Response</b>         |                                                    |                                                |
| Median in months (range)        | 2.0 (1.6, 11.1) <sup>‡</sup>                       | 3.7 (1.6, 16.7) <sup>†</sup>                   |
| <b>PFS*</b>                     |                                                    |                                                |
| Median in months (95% CI)       | 2.1 (1.9, 3.7)                                     | 2 (1.9, 2.1)                                   |
| 6-month PFS rate                | 31%                                                | 20%                                            |
| <b>OS*</b>                      |                                                    |                                                |
| 6-month OS rate                 | 70%                                                | 53%                                            |
| 12-month OS rate                | 46%                                                | 34%                                            |

\* Assessed by blinded independent central review using RECIST 1.1

† Based on patients (n=16) with a confirmed response by independent review

‡ Based on patients (n=13) with a confirmed response by independent review

§ Based on Kaplan-Meier estimates; includes 10 patients with responses of 6 months or longer including 3 patients with responses of 12 months or longer

¶ Based on Kaplan-Meier estimates; includes 11 patients with responses of 6 months or longer including 1 patient with response of 12 months or longer

There were objective responses in patients regardless of HPV tumor status.

### **Urothelial Carcinoma**

#### ***KEYNOTE-A39: Controlled trial of combination therapy with enfortumab vedotin in urothelial carcinoma patients***

The efficacy of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-A39, an open-label, multicenter, randomized, active-controlled trial that enrolled 886 platinum-eligible patients with unresectable or metastatic urothelial carcinoma. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression, active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7%

with associated diabetes symptoms. Patients were considered cisplatin-ineligible if they had at least one of the following criteria: glomerular filtration rate 30-59 mL/min, ECOG PS  $\geq 2$ , Grade  $\geq 2$  hearing loss, or NYHA Class III heart failure. Patients randomized to the gemcitabine and platinum-based chemotherapy arm were permitted to receive maintenance immunotherapy. Randomization was stratified by cisplatin eligibility (eligible or ineligible), PD-L1 expression [high (CPS  $\geq 10$ ) or low (CPS  $< 10$ )], and liver metastases (present or absent). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle.
- Gemcitabine 1000 mg/m<sup>2</sup> on Days 1 and 8 and investigator's choice of cisplatin 70 mg/m<sup>2</sup> or carboplatin (AUC 4.5 or 5 mg/mL/min according to local guidelines) on Day 1 of each 21-day cycle.

Treatment with KEYTRUDA and enfortumab vedotin continued until RECIST v1.1-defined progression of disease, unacceptable toxicity or, for KEYTRUDA, a maximum of 35 cycles (up to approximately 2 years). Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. Assessment of tumor status was performed every 9 weeks for 18 months and then every 12 weeks thereafter. The major efficacy outcome measures were PFS as assessed by BICR according to RECIST v1.1 and OS. Additional outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 and time to pain progression (TTPP).

The study population characteristics were: median age of 69 years; 77% male; and 67% White. Ninety-five percent had M1 disease, and 5% had M0 disease. Seventy-three percent had a primary tumor in the lower tract, and 27% of patients had a primary tumor in the upper tract. Fifty-four percent were cisplatin-eligible, 58% were PD-L1 high, and 72% of patients had visceral metastases, including 22% with liver metastases. Twenty percent had normal renal function, and 37%, 41% and 2% were characterized with mild, moderate, or severe renal impairment, respectively. Ninety-seven percent had ECOG PS of 0-1 and 3% had ECOG PS of 2. Eighty-five percent of patients had transitional cell carcinoma (TCC) histology, 2% had TCC with other histology, and 6% had TCC with squamous differentiation.

Thirty-two percent of patients receiving KEYTRUDA in combination with enfortumab vedotin went on to receive subsequent cancer-related therapies, compared to 70% in the gemcitabine and platinum-based chemotherapy arm. Thirty-two percent of patients in the gemcitabine and platinum-based chemotherapy arm received maintenance immunotherapy, and 26% received immunotherapy as first subsequent therapy after disease progression.

The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomized to KEYTRUDA in combination with enfortumab vedotin compared with patients randomized to gemcitabine and platinum-based chemotherapy. Efficacy results were consistent across all pre-specified patient subgroups.

The median follow-up time for 442 patients treated with KEYTRUDA and enfortumab vedotin was 17.3 months (range: 0.3 to 37.2 months). Efficacy results are summarized in Table 19 and Figures 25 and 26.

**Table 19: Efficacy Results in KEYNOTE-A39**

| <b>Endpoint</b>                            | <b>KEYTRUDA<br/>200 mg every<br/>3 weeks in<br/>combination with<br/>enfortumab<br/>vedotin<br/>n=442</b> | <b>Gemcitabine +<br/>Platinum<br/>Chemotherapy<br/>with or without<br/>maintenance<br/>immunotherapy<br/>n=444</b> |
|--------------------------------------------|-----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>OS</b>                                  |                                                                                                           |                                                                                                                    |
| Number (%) of patients with event          | 133 (30%)                                                                                                 | 226 (51%)                                                                                                          |
| Median in months (95% CI)                  | 31.5 (25.4, NR)                                                                                           | 16.1 (13.9, 18.3)                                                                                                  |
| Hazard ratio* (95% CI)                     | 0.47 (0.38, 0.58)                                                                                         |                                                                                                                    |
| p-Value <sup>†</sup>                       | <0.0001                                                                                                   |                                                                                                                    |
| <b>PFS</b>                                 |                                                                                                           |                                                                                                                    |
| Number (%) of patients with event          | 223 (50%)                                                                                                 | 307 (69%)                                                                                                          |
| Median in months (95% CI)                  | 12.5 (10.4, 16.6)                                                                                         | 6.3 (6.2, 6.5)                                                                                                     |
| Hazard ratio* (95% CI)                     | 0.45 (0.38, 0.54)                                                                                         |                                                                                                                    |
| p-Value <sup>†</sup>                       | <0.0001                                                                                                   |                                                                                                                    |
| <b>Objective Response Rate<sup>‡</sup></b> |                                                                                                           |                                                                                                                    |
| ORR <sup>§</sup> % (95% CI)                | 68% (63.1, 72.1)                                                                                          | 44% (39.7, 49.2)                                                                                                   |
| p-Value <sup>¶</sup>                       | <0.0001                                                                                                   |                                                                                                                    |
| Complete response                          | 29%                                                                                                       | 12%                                                                                                                |
| Partial response                           | 39%                                                                                                       | 32%                                                                                                                |
| Stable Disease                             | 19%                                                                                                       | 34%                                                                                                                |
| Disease Control Rate <sup>#</sup>          | 86%                                                                                                       | 78%                                                                                                                |
| <b>Response Duration</b>                   |                                                                                                           |                                                                                                                    |
| Median in months (range)                   | NR<br>(2.0+, 28.3+)                                                                                       | 7.0<br>(1.5+, 30.9+)                                                                                               |
| % with duration ≥6 months <sup>Ⓟ</sup>     | 86%                                                                                                       | 61%                                                                                                                |
| % with duration ≥12 months <sup>Ⓟ</sup>    | 67%                                                                                                       | 35%                                                                                                                |
| % with duration ≥18 months <sup>Ⓟ</sup>    | 60%                                                                                                       | 19%                                                                                                                |

\* Based on the stratified Cox proportional hazard regression model

† Two-sided p-Value based on stratified log-rank test

‡ Includes only patients with measurable disease at baseline

§ Based on patients with a best overall response as confirmed complete or partial response

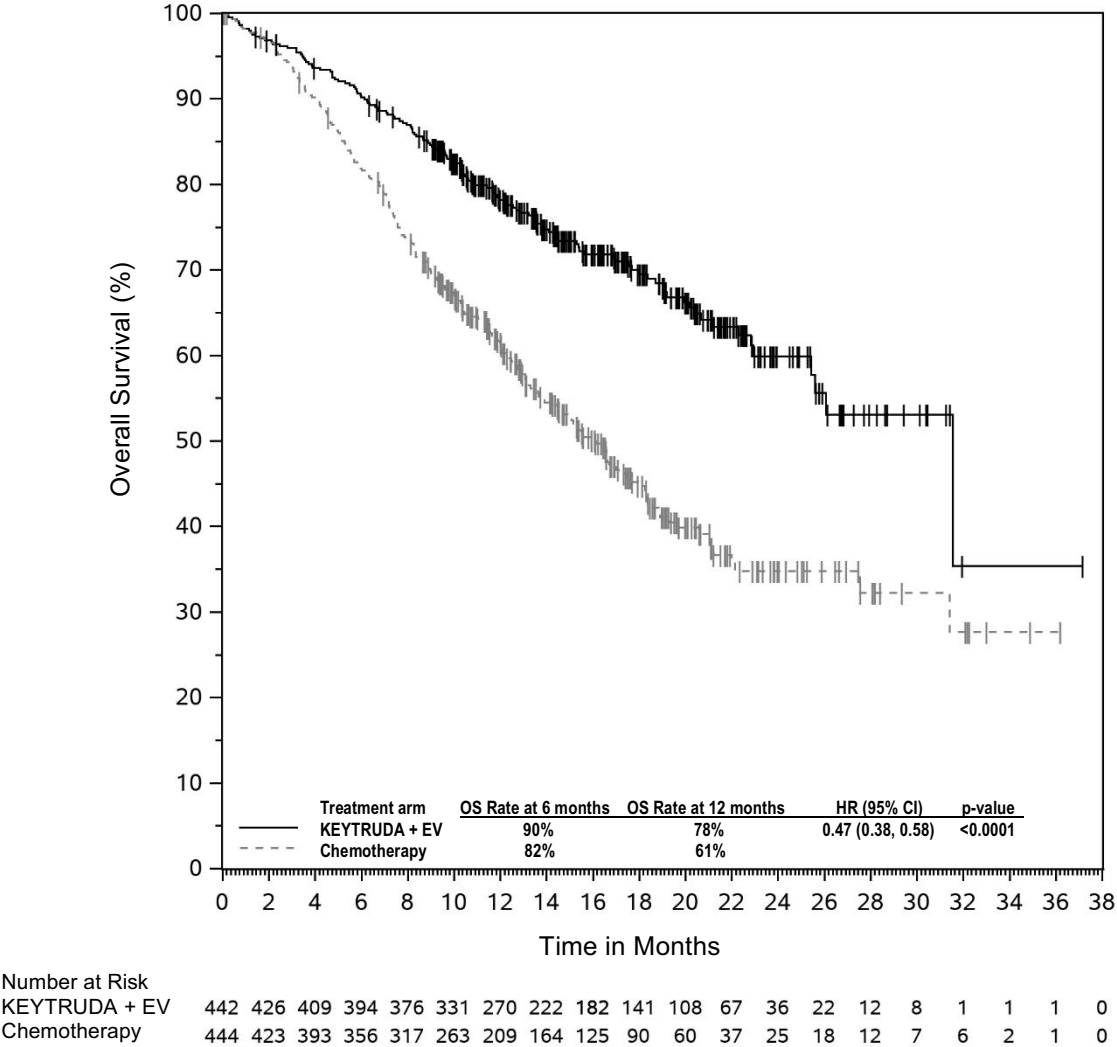
¶ Two-sided p-Value based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases

# Based on best response of stable disease or better

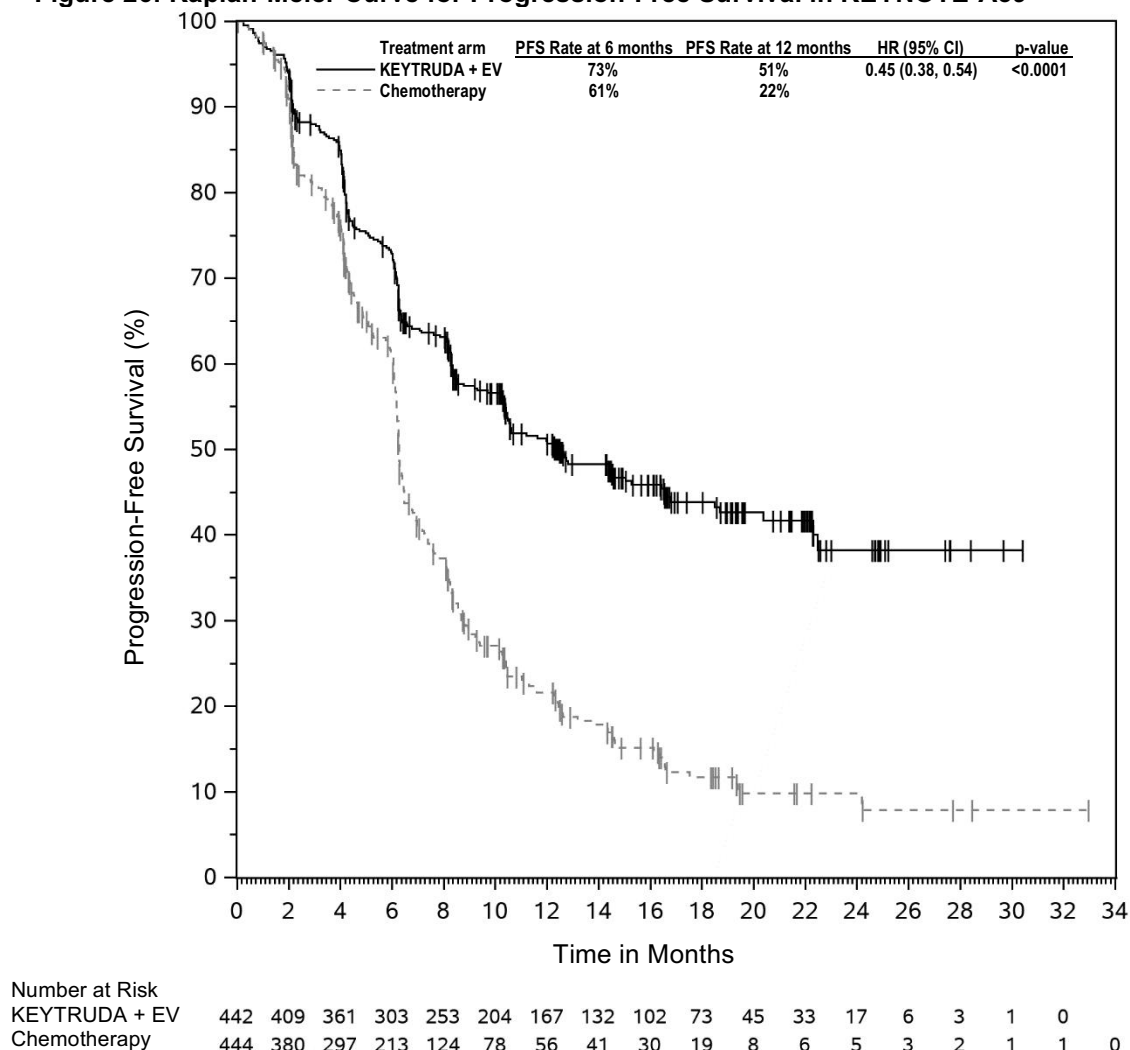
Ⓟ Based on Kaplan-Meier estimation

NR = not reached

Figure 25: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A39



**Figure 26: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A39**



**KEYNOTE-045: Controlled trial in urothelial carcinoma patients previously treated with platinum-containing chemotherapy**

The efficacy of KEYTRUDA was evaluated in KEYNOTE-045, a multicenter, randomized (1:1), active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m<sup>2</sup> (n=84), docetaxel 75 mg/m<sup>2</sup> (n=84), or vinflunine 320 mg/m<sup>2</sup> (n=87). Patients received KEYTRUDA until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1 and duration of response.

Among the 542 randomized patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 57% ECOG performance status of 1 or greater; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumor in the lower tract and 14% had a primary tumor in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy as the most recent line of therapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

At a pre-specified interim analysis, the median follow-up time for 270 patients treated with KEYTRUDA was 10.3 months. The study demonstrated statistically significant improvements in OS and ORR for patients randomized to KEYTRUDA as compared to chemotherapy (Table 20). There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. Efficacy results are summarized in Table 20.

**Table 20: Efficacy Results in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy**

| Endpoint                                         | KEYTRUDA<br>200 mg every<br>3 weeks<br>n=270 | Chemotherapy<br><br>n=272 |
|--------------------------------------------------|----------------------------------------------|---------------------------|
| OS                                               |                                              |                           |
| Number (%) of patients with event                | 155 (57%)                                    | 179 (66%)                 |
| Hazard ratio* (95% CI)                           | 0.73 (0.59, 0.91)                            |                           |
| p-Value†                                         | 0.002                                        |                           |
| Median in months (95% CI)                        | 10.3 (8.0, 11.8)                             | 7.4 (6.1, 8.3)            |
| PFS‡                                             |                                              |                           |
| Number (%) of patients with event                | 218 (81%)                                    | 219 (81%)                 |
| Hazard ratio* (95% CI)                           | 0.98 (0.81, 1.19)                            |                           |
| p-Value†                                         | 0.416                                        |                           |
| Median in months (95% CI)                        | 2.1 (2.0, 2.2)                               | 3.3 (2.3, 3.5)            |
| Objective Response Rate‡                         |                                              |                           |
| ORR % (95% CI)                                   | 21% (16, 27)                                 | 11% (8, 16)               |
| Complete response                                | 7%                                           | 3%                        |
| Partial response                                 | 14%                                          | 8%                        |
| p-Value§                                         | 0.001                                        |                           |
| Response Duration±¶                              |                                              |                           |
| Median in months (range)                         | Not reached (1.6+, 15.6+)                    | 4.3 (1.4+, 15.4+)         |
| Number (%#) of patients with duration ≥6 months  | 41 (78%)                                     | 7 (40%)                   |
| Number (%#) of patients with duration ≥12 months | 14 (68%)                                     | 3 (35%)                   |

\* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

† Based on stratified Log rank test

‡ Assessed by BICR using RECIST 1.1

§ Based on method by Miettinen and Nurminen

¶ Based on patients with a best overall response as confirmed complete or partial response

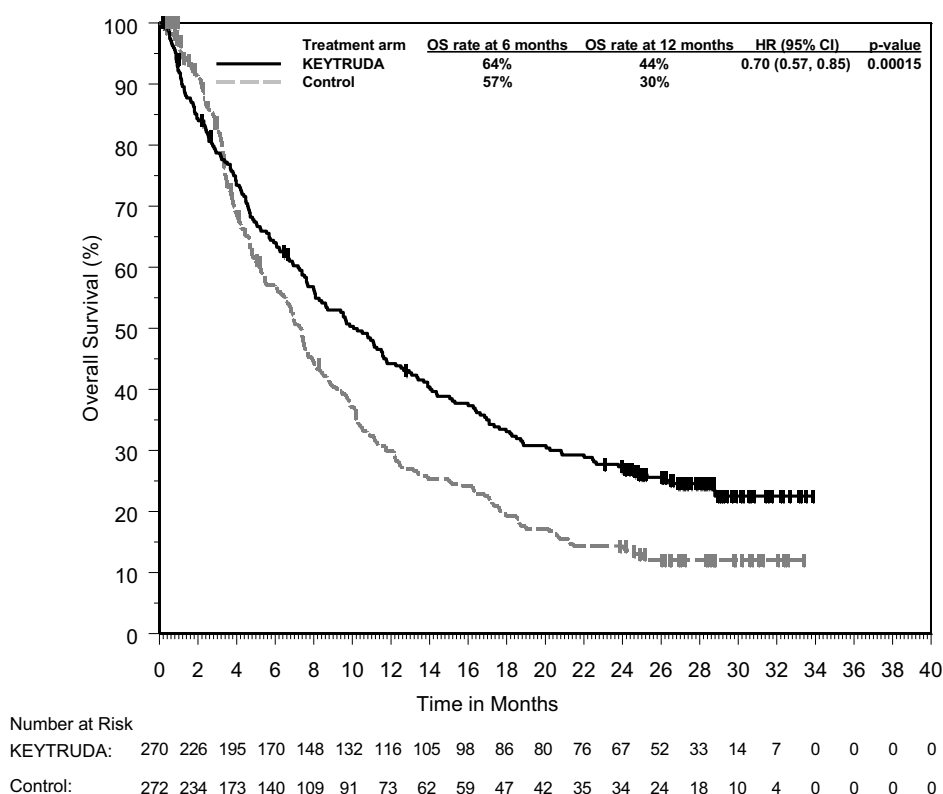
# Based on Kaplan-Meier estimation

The final OS analysis was performed 13.6 months after the interim analysis with 419 patient events (200 for KEYTRUDA and 219 for chemotherapy). Median OS was 10.1 months (95% CI: 8.0, 12.3) for

KEYTRUDA and 7.3 months (95% CI: 6.1, 8.1) for chemotherapy. The OS HR was 0.70 (95% CI: 0.57, 0.85;  $p < 0.001$ ). See Figure 27. In the final analysis there was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS.

At the final analysis, among the 57 responding patients who received KEYTRUDA vs. 30 responding patients who received chemotherapy, the median response duration was not reached (range 1.6+ to 30.0+ months) in patients who received KEYTRUDA, vs. 4.4 months (range 1.4+ to 29.9+ months) in patients who received chemotherapy. In patients who received KEYTRUDA, 84% had responses of 6 months or longer and 68% had responses of 12 months or longer (based on Kaplan-Meier estimation) vs. 47% who had responses of 6 months or longer and 35% who had responses of 12 months or longer (based on Kaplan-Meier estimation) in patients who received chemotherapy. The complete and partial response rates were 9% and 12%, respectively in patients who received KEYTRUDA vs. 3% and 8%, respectively in patients who received chemotherapy.

**Figure 27: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-045 (Intent to Treat Population)**



Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30. A prolonged time to deterioration in the EORTC QLQ-C30 global health status/QoL score was observed for patients treated with pembrolizumab compared to investigator's choice chemotherapy (HR 0.70; 95% CI 0.55-0.90). Over 15 weeks of follow-up, patients treated with pembrolizumab had stable global health status/QoL scores, while those treated with investigator's choice chemotherapy had a decline in global health status/QoL scores. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

KEYNOTE-052: Open-label trial in urothelial carcinoma patients ineligible for cisplatin-containing chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-052, a multicenter, open-label trial of patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST 1.1 and duration of response. Efficacy is reported for patients who had the opportunity for at least 2 post-baseline scans representing at least 4 months of follow-up.

Among 370 patients with urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy, baseline characteristics were: median age 74 years (82% age 65 or older); 77% male; and 89% White and 7% Asian. Eighty-eight percent had M1 disease, 12% had M0 disease. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Reasons for cisplatin ineligibility included: baseline creatinine clearance of <60 mL/min (50%), ECOG performance status of 2 (32%), ECOG performance status of 2 and baseline creatinine clearance of <60 mL/min (9%), and other (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss; 9%). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy. Eighty-one percent had a primary tumor in the lower tract, and 19% of patients had a primary tumor in the upper tract.

Among the 370 patients, 30% (n = 110) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 110 patients were: median age 73 years, 68% male, and 87% White. Eighty-two percent had M1 disease, and 18% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 18% of patients had a primary tumor in the upper tract. Seventy-six percent of patients had visceral metastases, including 11% with liver metastases. Reasons for cisplatin ineligibility included: 45% with baseline creatinine clearance of <60 mL/min, 37% with ECOG performance status of 2, 10% with ECOG 2 and baseline creatinine clearance of <60 mL/min, and 8% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

At a pre-specified interim analysis, the median follow-up time for 370 patients treated with KEYTRUDA was 11.5 months. Efficacy results are summarized in Table 21. The data presented for subjects with PD-L1 CPS ≥10 are based on a subgroup analysis in a single-arm trial. A randomized, controlled confirmatory trial is ongoing.

**Table 21: Efficacy Results in Patients with Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy**

| Endpoint                        | All Subjects<br>n=370     | PD-L1 CPS ≥10<br>N=110    |
|---------------------------------|---------------------------|---------------------------|
| <b>Objective Response Rate*</b> |                           |                           |
| ORR %, (95% CI)                 | 29% (24, 34)              | 47% (38, 57)              |
| Disease control rate†           | 47%                       | 67%                       |
| Complete response               | 8%                        | 19%                       |
| Partial response                | 21%                       | 28%                       |
| Stable disease                  | 18%                       | 20%                       |
| <b>Response Duration</b>        |                           |                           |
| Median in months (range)        | Not reached (1.4+, 27.9+) | Not reached (1.4+, 26.5+) |
| % with duration ≥ 6-months      | 82%‡                      | 82%                       |
| <b>Time to Response</b>         |                           |                           |
| Median in months (range)        | 2.1 (1.3, 9.0)            | 2.1 (1.3, 4.7)            |
| <b>PFS*</b>                     |                           |                           |
| Median in months (95% CI)       | 2.3 (2.1, 3.4)            | 4.9 (3.8, 10.8)           |
| 6-month PFS rate                | 34%                       | 49%                       |
| <b>OS</b>                       |                           |                           |
| Median in months (95% CI)       | 11.5 (10.0, 13.3)         | 18.5 (12.2, NA§)          |
| 6-month OS rate                 | 67%                       | 76                        |

\* Assessed by BICR using RECIST 1.1

† Based on best response of stable disease or better

‡ Based on Kaplan-Meier estimates; includes 85 patients with responses of 6 months or longer

§ not available

The final ORR analysis was performed 9.9 months after the interim analysis with 106 ORR events for all patients [median follow-up of 11.4 months (range: 0.1, 41.2 months)]. ORR was 29% (95% CI: 24, 34) and 47% (95% CI: 38, 57), respectively for all subjects and subjects with CPS ≥10. The complete and partial response rates were 9% and 20%, respectively in all subjects and 20% and 27%, respectively in subjects with CPS ≥10. At the final analysis among the responding patients, the median response duration was 30.1 months (range 1.4+ to 35.9+ months) in all subjects (n=106) and not reached (range 1.4+ to 35.4+ months) in subjects with CPS ≥10 (n=52). Responses of 6 months or longer (based on Kaplan-Meier estimation) were 81% and 82%, respectively for all subjects and subjects with CPS ≥10.

### **Classical Hodgkin Lymphoma**

#### ***KEYNOTE-204: Controlled study in patients with relapsed or refractory classical Hodgkin lymphoma (cHL)***

KEYNOTE-204 was a randomized, open-label, active-controlled trial conducted in 304 patients with relapsed or refractory cHL. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or >5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Randomization was stratified by prior auto-SCT (yes vs. no) and disease status after frontline therapy (primary refractory vs. relapse less than 12 months after completion vs. relapse 12 months or more after completion). Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks
- Brentuximab vedotin (BV) 1.8 mg/kg intravenously every 3 weeks

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or a maximum of 35 cycles. Disease assessment was performed every 12 weeks. The major efficacy outcome measures were PFS and ORR as assessed by BICR according to the 2007 revised International Working Group (IWG) criteria.

Among KEYNOTE-204 patients, the baseline characteristics were median age 35 years (16% age 65 or older); 57% male; 77% White; and 61% and 38% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 2 (range 1 to 11). Forty-two percent were refractory to the last prior therapy and 29% had primary refractory disease. Thirty-seven percent had undergone prior auto-HSCT, 5% had received prior BV, and 39% had prior radiation therapy.

The median follow-up time for 151 patients treated with KEYTRUDA was 24.9 months (range: 1.8 to 42.0 months). Efficacy results are summarized in Table 22.

**Table 22: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma**

| Endpoint                                          | KEYTRUDA<br><br>200 mg every<br>3 weeks<br>n=151 | Brentuximab<br>vedotin<br>1.8 mg/kg every<br>3 weeks<br>n=153 |
|---------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------|
| <b>PFS</b>                                        |                                                  |                                                               |
| Number of patients with event (%)                 | 81 (54%)                                         | 88 (58%)                                                      |
| Median in months (95% CI)                         | 13.2 (10.9, 19.4)                                | 8.3 (5.7, 8.8)                                                |
| Hazard ratio* (95% CI)                            | 0.65 (0.48, 0.88)                                |                                                               |
| p-Value†                                          | 0.0027                                           |                                                               |
| <b>Objective Response Rate</b>                    |                                                  |                                                               |
| ORR‡ (95% CI)                                     | 66% (57.4, 73.1)                                 | 54% (46.0, 62.3)                                              |
| Complete response                                 | 25%                                              | 24%                                                           |
| Partial response                                  | 41%                                              | 30%                                                           |
| p-Value§                                          | 0.0225                                           |                                                               |
| <b>Response Duration</b>                          |                                                  |                                                               |
| Median in months (range)                          | 20.7 (0.0+, 33.2+)                               | 13.8 (0.0+, 33.9+)                                            |
| Number (%¶) of patients with duration ≥ 6 months  | 66 (80%)                                         | 34 (60%)                                                      |
| Number (%¶) of patients with duration ≥ 12 months | 48 (62%)                                         | 23 (50%)                                                      |
| Number (%¶) of patients with duration ≥ 24 months | 11 (47%)                                         | 7 (43%)                                                       |

\* Based on the stratified Cox proportional hazard model

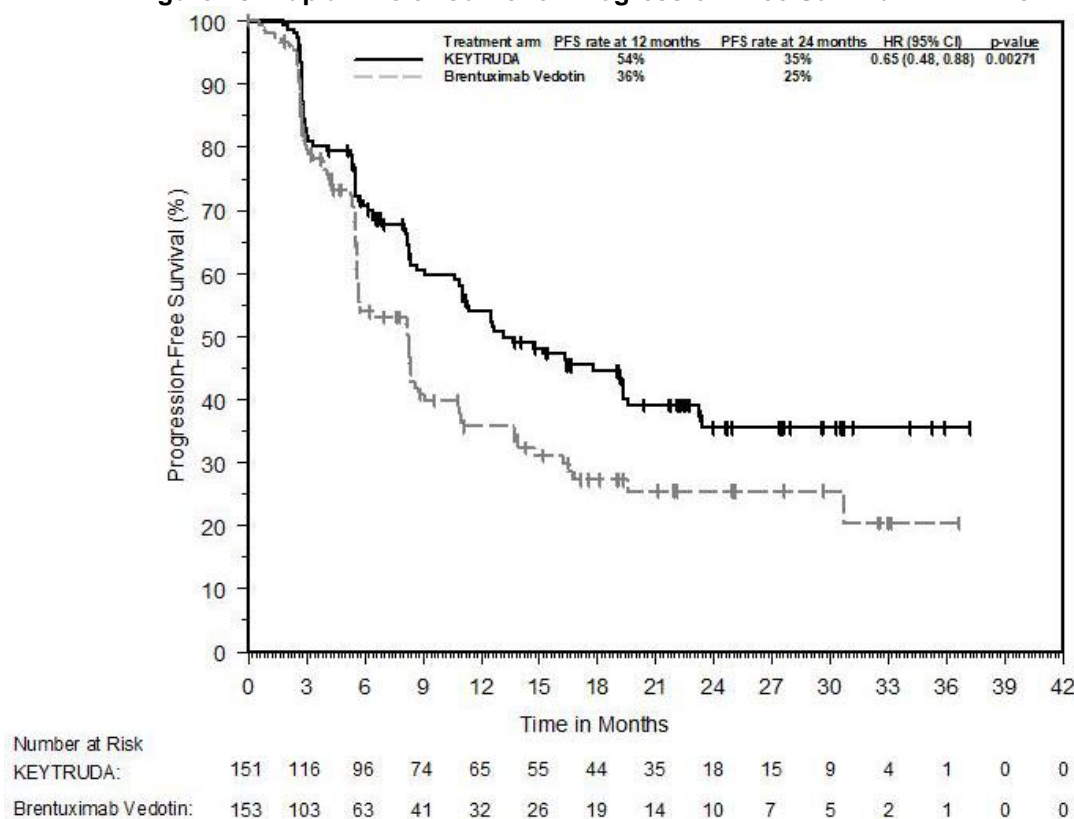
† Based on stratified log-rank test

‡ Based on patients with best overall response as complete response or partial response

§ Based on Miettinen and Nurminen method stratified by prior auto-SCT and disease status

¶ Based on Kaplan-Meier estimation

**Figure 28: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-204**



Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ C30 global health status/QoL was observed for patients treated with pembrolizumab compared to BV (HR 0.40; 95% CI: 0.22-0.74). Over 24 weeks of follow-up, patients treated with pembrolizumab had an improvement in global health status/QoL compared to BV which showed a decline (difference in Least Square (LS) means = 8.60; 95% CI: 3.89, 13.31; nominal two-sided p=0.0004). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

**KEYNOTE-013 and KEYNOTE-087: Open-label studies in patients with refractory classical Hodgkin lymphoma, or those who have relapsed after greater than or equal to 3 prior lines of therapy**

The efficacy of KEYTRUDA was investigated in 241 patients with refractory classical Hodgkin lymphoma, or who have relapsed after 3 or more prior lines of therapy, enrolled in two multicenter, nonrandomized, open-label studies (KEYNOTE-013 and KEYNOTE-087). Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic hematopoietic stem cell transplant within the past 5 years (or greater than 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial. Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=31) or 200 mg every 3 weeks (n=210) until unacceptable toxicity or documented disease progression. Response was assessed using the revised lymphoma criteria by PET CT scans, with the first planned post-baseline assessment at Week 12. The major efficacy outcome measures (ORR, CRR, and duration of response) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria. Secondary efficacy outcome measures were PFS and OS.

Among KEYNOTE-013 patients, the baseline characteristics were median age 32 years (6% age 65 or older), 58% male, 94% White; and 45% and 55% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 5 (range 2 to 15). Eighty-seven percent were refractory to at least one prior therapy, including 39% who were refractory to

first-line therapy. Seventy-four percent of patients had received Auto-SCT, 26% were transplant ineligible; and 42% of patients had prior radiation therapy.

Among KEYNOTE-087 patients, the baseline characteristics were median age 35 years (9% age 65 or older); 54% male; 88% White; and 49% and 51% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range 1 to 12). Eighty-one percent were refractory to at least one prior therapy, including 34% who were refractory to first-line therapy. Sixty-one percent of patients had received Auto-SCT, 38% were transplant ineligible; 17% had no prior brentuximab, vedotin use; and 37% of patients had prior radiation therapy.

Efficacy results are summarized in Table 23.

**Table 23: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma**

| Endpoint                        | KEYNOTE-013                            | KEYNOTE-087                     |
|---------------------------------|----------------------------------------|---------------------------------|
|                                 | n=31                                   | n=210                           |
| <b>Objective Response Rate*</b> |                                        |                                 |
| ORR %, (95% CI)                 | 58% (39.1, 75.5)                       | 71% (64, 77)                    |
| Complete remission              | 19%                                    | 28%                             |
| Partial remission               | 39%                                    | 43%                             |
| <b>Response Duration*</b>       |                                        |                                 |
| Median in months (range)        | Not reached (0.0+, 26.1+) <sup>†</sup> | 16.6 (0.0+, 39.1+) <sup>‡</sup> |
| % with duration ≥ 6-months      | 80% <sup>§</sup>                       | 74% <sup>¶</sup>                |
| % with duration ≥ 12-months     | 70% <sup>#</sup>                       | 59% <sup>♯</sup>                |
| <b>Time to Response</b>         |                                        |                                 |
| Median in months (range)        | 2.8 (2.4, 8.6) <sup>†</sup>            | 2.8 (2.1, 16.5) <sup>‡</sup>    |
| <b>PFS*</b>                     |                                        |                                 |
| Median in months (95% CI)       | 11.4 (4.9, 27.8)                       | 13.6 (11.1, 16.7)               |
| 6-month PFS rate                | 66%                                    | 72%                             |
| 9-month PFS rate                | ---                                    | 61%                             |
| 12-month PFS rate               | 48%                                    | 52%                             |
| <b>OS</b>                       |                                        |                                 |
| 6-month OS rate                 | 100%                                   | 99.5%                           |
| 12-month OS rate                | 87.1%                                  | 96.1%                           |

\* Assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria

<sup>†</sup> Based on patients (n=18) with a response by independent review

<sup>‡</sup> Based on patients (n=149) with a response by independent review

<sup>§</sup> Based on Kaplan-Meier estimation; includes 9 patients with responses of 6 months or longer

<sup>¶</sup> Based on Kaplan-Meier estimation; includes 84 patients with responses of 6 months or longer

<sup>#</sup> Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer

<sup>♯</sup> Based on Kaplan-Meier estimation; includes 60 patients with responses of 12 months or longer

The improved benefit as assessed by ORR, CRR, and response duration in the KEYNOTE-087 population was accompanied by overall improvements in health-related quality of life (HRQoL) as assessed using the

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the European Quality of Life Five Dimensions Questionnaire (EQ-5D). Relative to subjects with stable disease or progressive disease, subjects with a complete or partial response had the largest improvement and the highest proportion with a 10 point or greater increase in their EORTC QLQ-C30 global health status/QoL score, as well as, had the largest improvement in their EQ-5D utility and VAS scores from baseline to Week 12.

### **Colorectal Cancer**

#### **KEYNOTE-177: Controlled trial for first-line treatment of patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC**

The efficacy of KEYTRUDA was investigated in KEYNOTE-177, a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup> (or levoleucovorin 200 mg/m<sup>2</sup>), and FU 400 mg/m<sup>2</sup> bolus on Day 1, then FU 2400 mg/m<sup>2</sup> over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m<sup>2</sup> on first infusion, then 250 mg/m<sup>2</sup> weekly.
- FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup> (or levoleucovorin 200 mg/m<sup>2</sup>), and FU 400 mg/m<sup>2</sup> bolus on Day 1, then FU 2400 mg/m<sup>2</sup> over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m<sup>2</sup> on first infusion, then 250 mg/m<sup>2</sup> weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The primary efficacy outcome measures were PFS assessed by BICR according to RECIST v1.1 and OS. Secondary outcome measures were ORR and DoR.

A total of 307 patients were enrolled and randomized to KEYTRUDA (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range: 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an ECOG PS of 0 and 48% had an ECOG PS of 1. Mutation status: 25% BRAF V600E, 24% KRAS/NRAS. For 143 patients treated with chemotherapy, 56% received mFOLFOX6 with or without bevacizumab or cetuximab and 44% received FOLFIRI with or without bevacizumab or cetuximab.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy at an interim analysis. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis, with an additional 12 months of follow-up, in which 60% of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA. The median follow-up time was 38.1 months (range: 0.2 to 58.7 months). Table 24 and Figures 29 and 30 summarize the key efficacy measures for KEYNOTE-177.

**Table 24: Efficacy Results for First-line Treatment in Patients with MSI-H CRC in KEYNOTE-177**

| Endpoint                                    | KEYTRUDA<br>200 mg every 3 weeks<br>n=153 | Chemotherapy<br>n=154 |
|---------------------------------------------|-------------------------------------------|-----------------------|
| <b>PFS</b>                                  |                                           |                       |
| Number (%) of patients with event           | 82 (54%)                                  | 113 (73%)             |
| Median in months (95% CI)                   | 16.5 (5.4, 32.4)                          | 8.2 (6.1, 10.2)       |
| Hazard ratio* (95% CI)                      | 0.60 (0.45, 0.80)                         |                       |
| p-Value†                                    | 0.0002                                    |                       |
| <b>OS‡</b>                                  |                                           |                       |
| Number (%) of patients with event           | 62 (41%)                                  | 78 (51%)              |
| Median in months (95% CI)                   | NR (49.2, NR)                             | 36.7 (27.6, NR)       |
| Hazard ratio* (95% CI)                      | 0.74 (0.53, 1.03)                         |                       |
| p-Value§                                    | 0.0359                                    |                       |
| <b>Objective Response Rate</b>              |                                           |                       |
| ORR (95% CI)                                | 44% (35.8, 52.0)                          | 33% (25.8, 41.1)      |
| Complete response rate                      | 11%                                       | 4%                    |
| Partial response rate                       | 33%                                       | 29%                   |
| <b>Response Duration</b>                    |                                           |                       |
| Median in months (range)                    | NR (2.3+ - 41.4+)                         | 10.6 (2.8 - 37.5+)    |
| % of patients with duration<br>≥ 6 months¶  | 97%                                       | 88%                   |
| % of patients with duration<br>≥ 12 months¶ | 85%                                       | 44%                   |
| % of patients with duration<br>≥ 24 months¶ | 83%                                       | 35%                   |

\* Based on Cox regression model

† Based on log-rank test (compared to a significance level of 0.0177)

‡ Based on final analysis

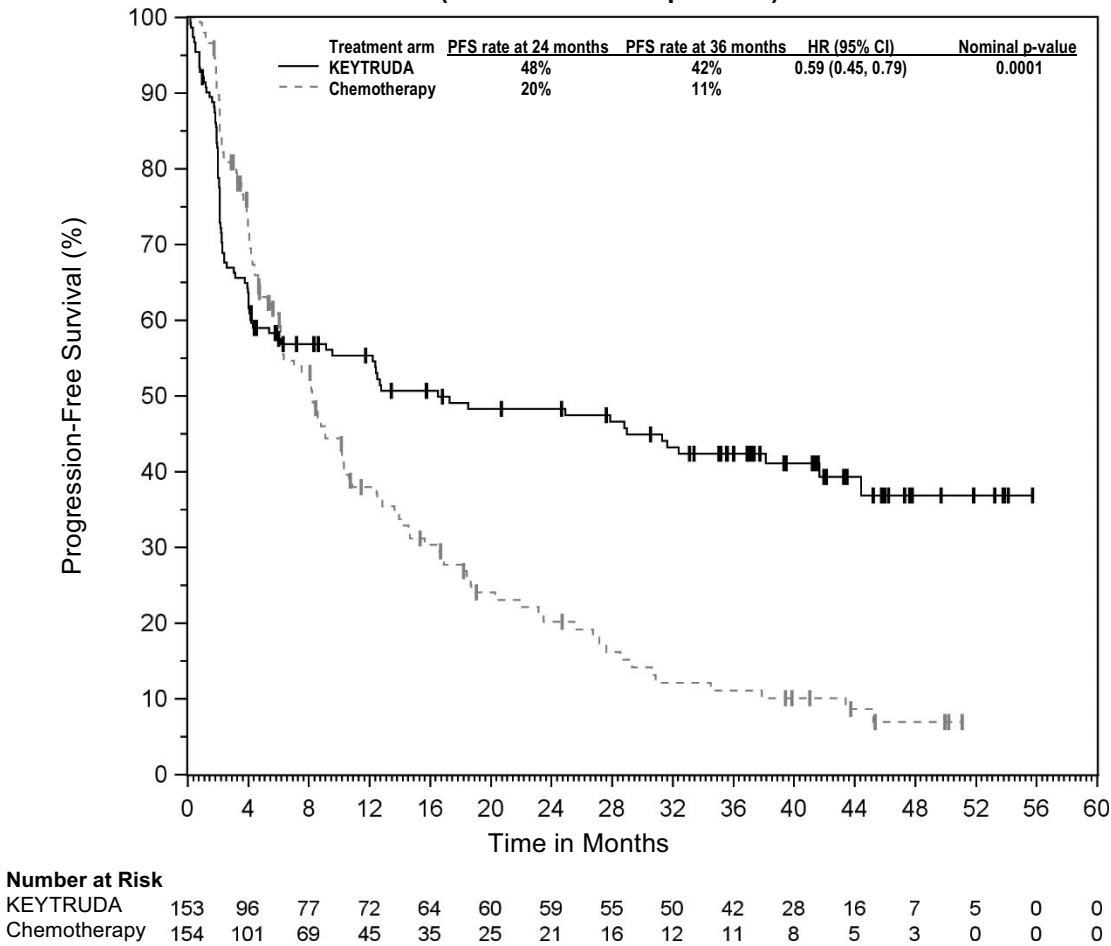
§ Not statistically significant after adjustment for multiplicity

¶ Based on Kaplan-Meier estimation

NR=not reached

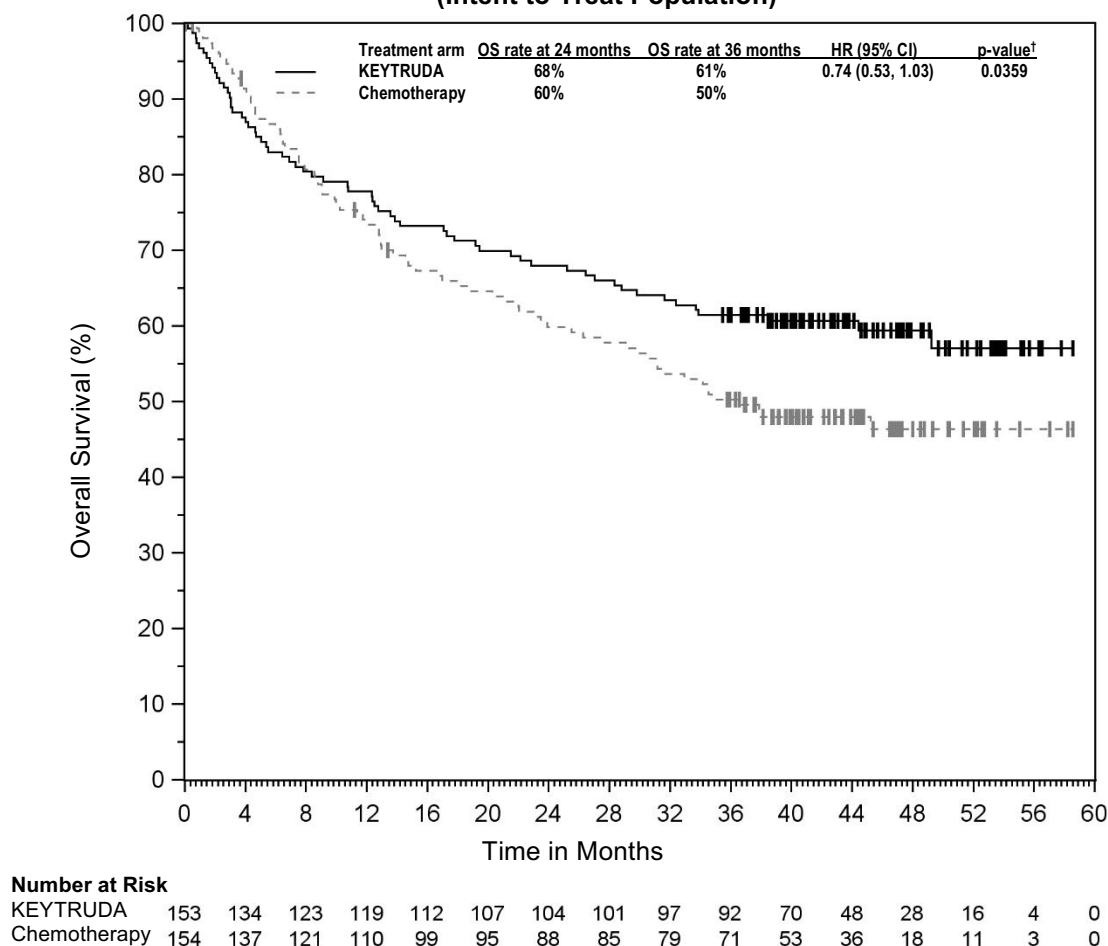
At the final analysis, there were a total of 203 PFS events (86 for KEYTRUDA; 117 for chemotherapy). The median PFS was 16.5 months (95% CI: 5.4, 38.1) for the KEYTRUDA arm and 8.2 months (95% CI: 6.1, 10.2) for the chemotherapy arm. The PFS HR vs. chemotherapy was 0.59 (95% CI: 0.45, 0.79, nominal p=0.0001) (Figure 29). The ORR at the final analysis was 45% for the KEYTRUDA arm and 33% for the chemotherapy arm. The median duration of response was not reached (range: 2.3+, 53.5+) for the KEYTRUDA arm and 10.6 months (range: 2.8, 48.3+) for the chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 84% at 24 months or longer in the KEYTRUDA arm vs. 34% in the chemotherapy arm.

Figure 29: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)\*



\* At the time of the protocol-specified final analysis.

**Figure 30: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)\***



\* At the time of the protocol-specified final analysis.

† Not statistically significant after adjustment for multiplicity.

Exploratory analyses of patient-reported outcomes (PROs) using EORTC QLQ-C30 show improvement in global health status/quality of life, functioning (i.e., physical, role, social) and fatigue in patients treated with KEYTRUDA compared to a decline for patients treated with chemotherapy at pre-specified Week 18. Improvements from baseline in global health status/quality of life continued through Week 45 for patients treated with KEYTRUDA. In addition, a prolonged time to deterioration in global health status/QoL (HR 0.61; 95% CI: 0.38-0.98), physical (HR 0.50; 95% CI: 0.32-0.81) and social functioning (HR 0.53; 95% CI: 0.32-0.87), and fatigue (HR 0.48; 95% CI: 0.33-0.69) was observed for patients treated with KEYTRUDA compared to chemotherapy. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

### Cervical Cancer

#### KEYNOTE-A18: Controlled study of combination therapy with CRT in patients with high-risk, locally advanced cervical cancer

The efficacy of KEYTRUDA in combination with cisplatin and external beam radiation therapy (EBRT) followed by brachytherapy (BT) was investigated in KEYNOTE-A18, a multicenter, randomized, double-blind, placebo-controlled study that enrolled 1060 patients with locally advanced cervical cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. There were 601 patients with FIGO (International Federation of Gynecology and Obstetrics) 2014 Stage III-IVA (tumor involvement of the lower vagina with or without extension onto pelvic sidewall or

hydronephrosis/non-functioning kidney or has spread to adjacent pelvic organs) with either node-positive or node-negative disease and 459 patients with FIGO 2014 Stage IB2 - IIB (tumor lesions >4 cm or clinically visible lesions that have spread beyond the uterus but have not extended onto the pelvic wall or to the lower third of vagina) with node-positive disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by planned type of EBRT (Intensity-modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT] vs. non-IMRT and non-VMAT), stage at screening of cervical cancer (FIGO 2014 Stage IB2-IIB vs. Stage III-IVA), and planned total radiotherapy dose ([EBRT + BT dose] of <70 Gy vs. ≥70 Gy as per equivalent dose [EQD2]). Patients were randomized (1:1) to one of the two treatment arms:

- KEYTRUDA 200 mg IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m<sup>2</sup> IV weekly (5 cycles, an optional sixth infusion could be administered per local practice) and radiotherapy (EBRT followed by BT), followed by KEYTRUDA 400 mg IV every 6 weeks (15 cycles)
- Placebo IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m<sup>2</sup> IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by placebo IV every 6 weeks (15 cycles)

Treatment continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Assessment of tumor status was performed every 12 weeks for the first two years, every 24 weeks in year 3, and then annually.

Among the 601 patients with FIGO 2014 Stage III - IVA disease enrolled in KEYNOTE-A18, the baseline characteristics were: median age of 51 years (range: 22 to 87); 16% age 65 or older, 36% White, 1% Black, 34% Asian; 38% Hispanic or Latino; 68% ECOG performance status of 0 and 32% ECOG performance status of 1; 93% with CPS ≥1; 71% had positive pelvic and/or positive para-aortic lymph node(s), 29% had neither positive pelvic nor para-aortic lymph node, 86% IMRT or VMAT EBRT, 90% ≥70 Gy (EQD2). Eighty-four percent had squamous cell carcinoma and 16% had non-squamous histology.

The primary efficacy outcomes were PFS (as assessed by investigator according to RECIST v1.1 or histopathologic confirmation) and OS. The study demonstrated statistically significant improvements in PFS [0.70 (95% CI 0.55, 0.89; p-Value 0.0020)] from the first pre-specified interim analysis and OS [0.67 (95% CI 0.50, 0.90; p-Value 0.0040)] from the second pre-specified interim analysis in the overall population for patients randomized to KEYTRUDA with CRT compared to placebo with CRT. Table 25 summarizes key efficacy measures from the second pre-specified interim analysis in patients with FIGO 2014 Stage III - IVA disease with median follow-up time of 26.6 months (range: 0.9 to 41.7 months).

The Kaplan-Meier curves in patients with FIGO 2014 Stage III - IVA disease for OS and PFS based on this analysis are shown in Figures 31 and 32, respectively.

**Table 25: Efficacy results in KEYNOTE-A18 for patients with FIGO 2014 Stage III - IVA cervical cancer**

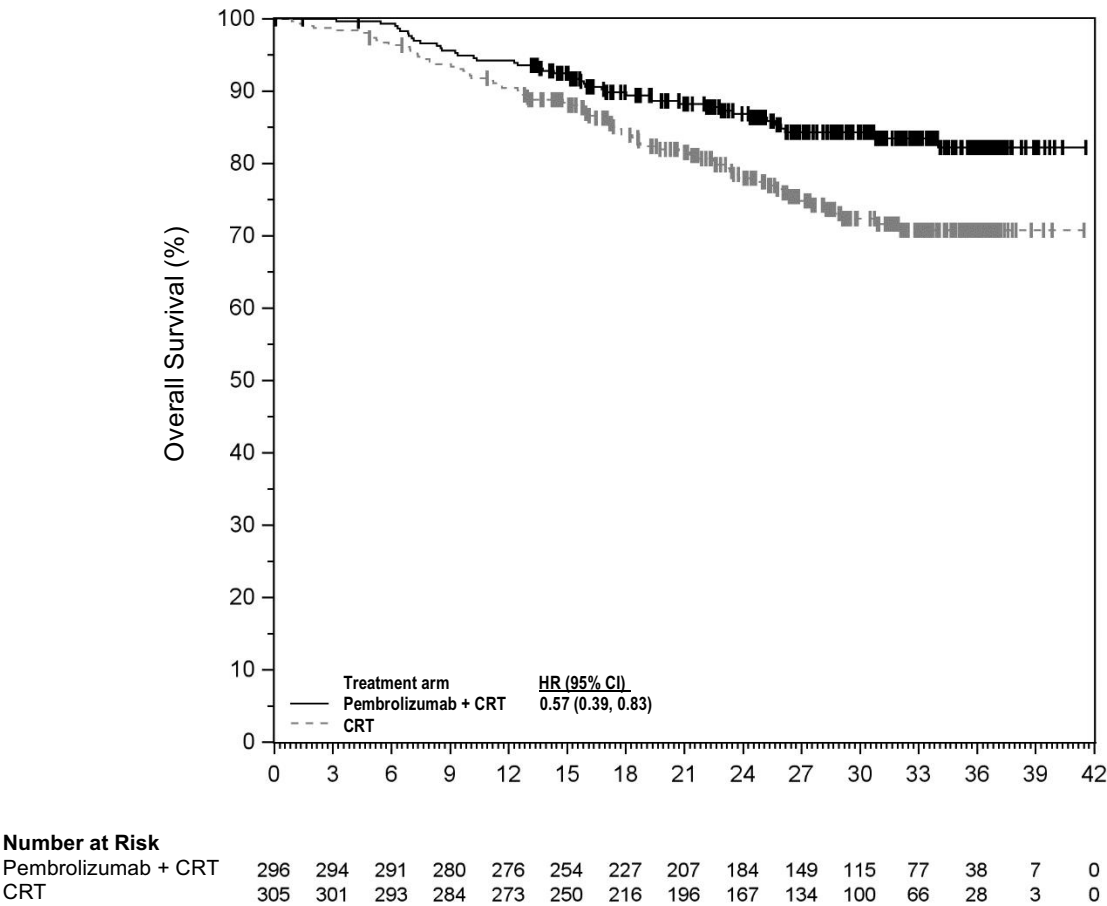
| Endpoint                          | KEYTRUDA<br>200 mg every 3 weeks<br>and 400 mg every<br>6 weeks with CRT<br>n=296 | Placebo<br><br>with CRT<br>n=305 |
|-----------------------------------|-----------------------------------------------------------------------------------|----------------------------------|
| OS                                |                                                                                   |                                  |
| Number of patients with event (%) | 43 (15%)                                                                          | 73 (24%)                         |
| Median in months (95% CI)         | NR (NR, NR)                                                                       | NR (NR, NR)                      |
| Hazard ratio* (95% CI)            | 0.57 (0.39, 0.83)                                                                 |                                  |
| PFS by Investigator               |                                                                                   |                                  |
| Number of patients with event (%) | 79 (27%)                                                                          | 125 (41%)                        |
| Median in months (95% CI)         | NR (NR, NR)                                                                       | NR (26.3, NR)                    |
| Hazard ratio* (95% CI)            | 0.57 (0.43, 0.76)                                                                 |                                  |

\* Based on the unstratified Cox proportional hazard model

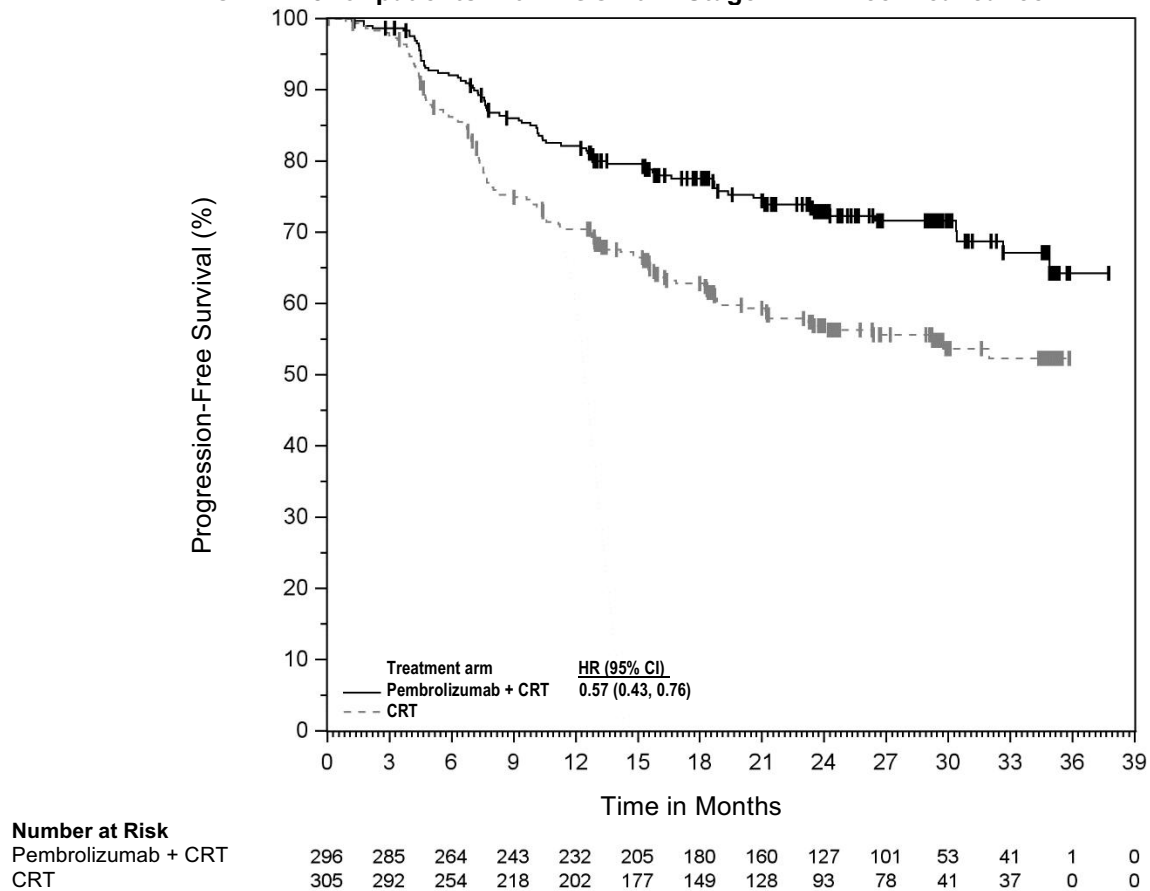
CRT = Chemoradiotherapy

NR = Not reached

Figure 31: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-A18 for patients with FIGO 2014 Stage III - IVA cervical cancer



**Figure 32: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-A18 for patients with FIGO 2014 Stage III - IVA cervical cancer**



**KEYNOTE-826: Controlled study of combination therapy in patients with persistent, recurrent, or metastatic cervical cancer**

The efficacy of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicenter, randomized, double-blind, placebo-controlled study that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent. Patients were enrolled regardless of tumor PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥10). Patients were randomized (1:1) to one of the two treatment groups:

- Treatment Group 1: KEYTRUDA 200 mg plus chemotherapy with or without bevacizumab
- Treatment Group 2: Placebo plus chemotherapy with or without bevacizumab

The investigator selected one of the following four treatment regimens prior to randomization:

1. Paclitaxel 175 mg/m<sup>2</sup> + cisplatin 50 mg/m<sup>2</sup>
2. Paclitaxel 175 mg/m<sup>2</sup> + cisplatin 50 mg/m<sup>2</sup> + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m<sup>2</sup> + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m<sup>2</sup> + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. The option to use bevacizumab was by investigator choice prior to randomization. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Week 9 and then every 9 weeks for the first year, followed by every 12 weeks thereafter.

Of the 617 enrolled patients, 548 patients (89%) had tumors expressing PD-L1 with a CPS  $\geq 1$  based on the PD-L1 IHC 22C3 pharmDx™ Kit. Among these 548 enrolled patients with tumors expressing PD-L1, 273 patients were randomized to KEYTRUDA in combination with chemotherapy with or without bevacizumab, and 275 patients were randomized to placebo in combination with chemotherapy with or without bevacizumab. The baseline characteristics of these 548 patients were: median age of 51 years (range: 22 to 82), 16% age 65 or older; 59% White, 18% Asian, and 1% Black; 37% Hispanic or Latino; 56% and 43% ECOG performance status of 0 or 1, respectively; 63% received bevacizumab as study treatment; 21% with adenocarcinoma and 5% with adenosquamous histology; for patients with persistent or recurrent disease with or without distant metastases, 39% had received prior chemoradiation only and 17% had received prior chemoradiation plus surgery.

The primary efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and duration of response, according to RECIST v1.1, as assessed by investigator. At a pre-specified interim analysis, the study demonstrated statistically significant improvements in OS (HR 0.64; 95% CI 0.50, 0.81; p-Value = 0.0001) and PFS (HR 0.62; 95% CI 0.50, 0.77; p-Value < 0.0001) for patients whose tumors expressed PD-L1 with a CPS  $\geq 1$  randomized to pembrolizumab in combination with chemotherapy with or without bevacizumab compared to placebo in combination with chemotherapy with or without bevacizumab. The study also demonstrated statistically significant improvements in OS and PFS in the overall population. Table 26 summarizes key efficacy measures for patients whose tumors expressed PD-L1 with a CPS  $\geq 1$  in KEYNOTE-826 at the final analysis with a median duration of follow-up of 21.3 months. The Kaplan-Meier curves for OS and PFS based on the final analysis are shown in Figures 33 and 34.

**Table 26: Efficacy Results in KEYNOTE-826 for patients with PD-L1 expression (CPS ≥ 1)**

| Endpoint                                 | KEYTRUDA<br>200 mg every 3 weeks<br>plus Chemotherapy* with<br>or without bevacizumab<br>n=273 | Placebo<br><br>plus Chemotherapy* with or<br>without bevacizumab<br>n=275 |
|------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| OS                                       |                                                                                                |                                                                           |
| Number (%) of patients with event        | 153 (56%)                                                                                      | 201 (73%)                                                                 |
| Median in months (95% CI)                | 28.6 (22.1, 38.0)                                                                              | 16.5 (14.5, 20.0)                                                         |
| Hazard ratio <sup>†</sup> (95% CI)       | 0.60 (0.49, 0.74)                                                                              |                                                                           |
| p-Value <sup>‡</sup>                     | < 0.0001                                                                                       |                                                                           |
| PFS                                      |                                                                                                |                                                                           |
| Number (%) of patients with event        | 171 (63%)                                                                                      | 220 (80%)                                                                 |
| Median in months (95% CI)                | 10.5 (9.7, 12.3)                                                                               | 8.2 (6.3, 8.5)                                                            |
| Hazard ratio <sup>†</sup> (95% CI)       | 0.58 (0.47, 0.71)                                                                              |                                                                           |
| p-Value <sup>‡</sup>                     | < 0.0001                                                                                       |                                                                           |
| Objective response rate                  |                                                                                                |                                                                           |
| ORR <sup>¶</sup> % (95% CI)              | 69% (63, 74)                                                                                   | 51% (45, 57)                                                              |
| Complete response                        | 26%                                                                                            | 15%                                                                       |
| Partial response                         | 43%                                                                                            | 36%                                                                       |
| Response duration                        |                                                                                                |                                                                           |
| Median in months (range)                 | 19.2 (1.3+, 40.9+)                                                                             | 10.4 (1.5+, 40.7+)                                                        |
| % with duration ≥ 12 months <sup>#</sup> | 56                                                                                             | 45                                                                        |
| % with duration ≥ 24 months <sup>#</sup> | 48                                                                                             | 30                                                                        |

\* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

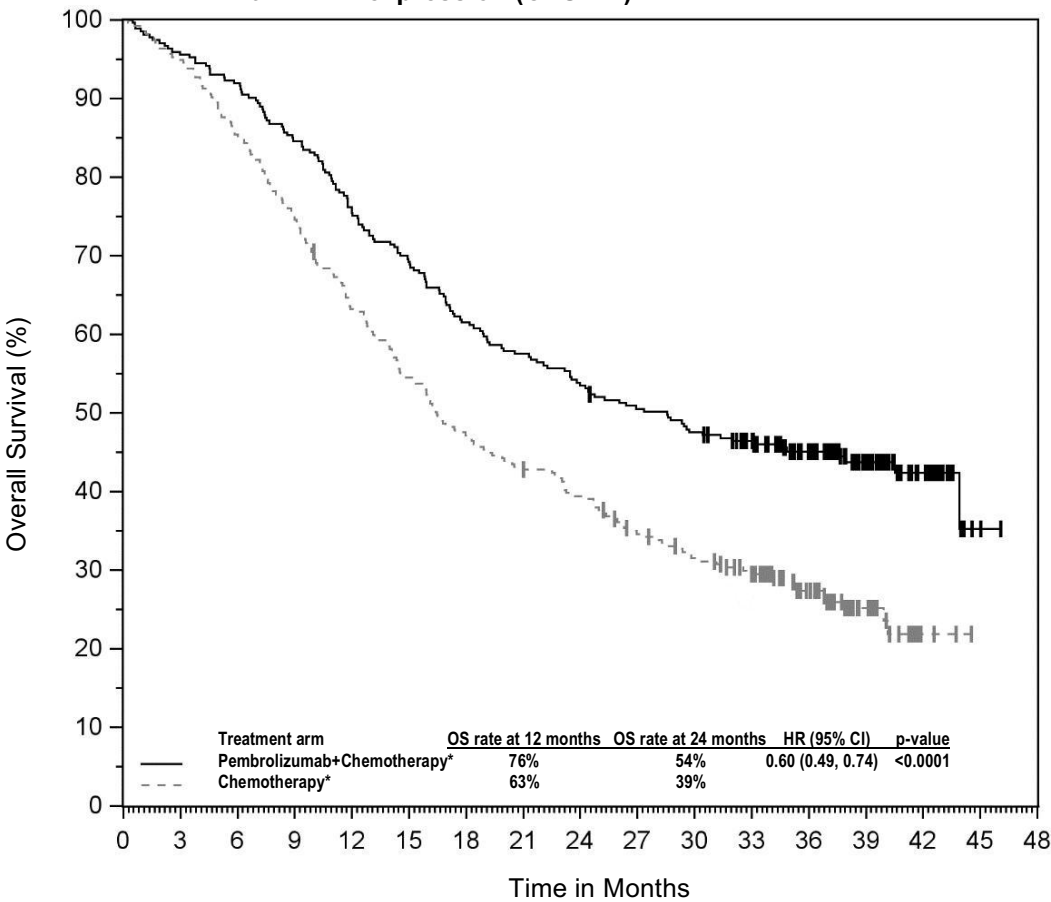
† Based on the stratified Cox proportional hazard model

‡ Nominal p-Value based on stratified log-rank test

¶ Response: Best objective response as confirmed complete response or partial response

# Based on Kaplan-Meier estimation

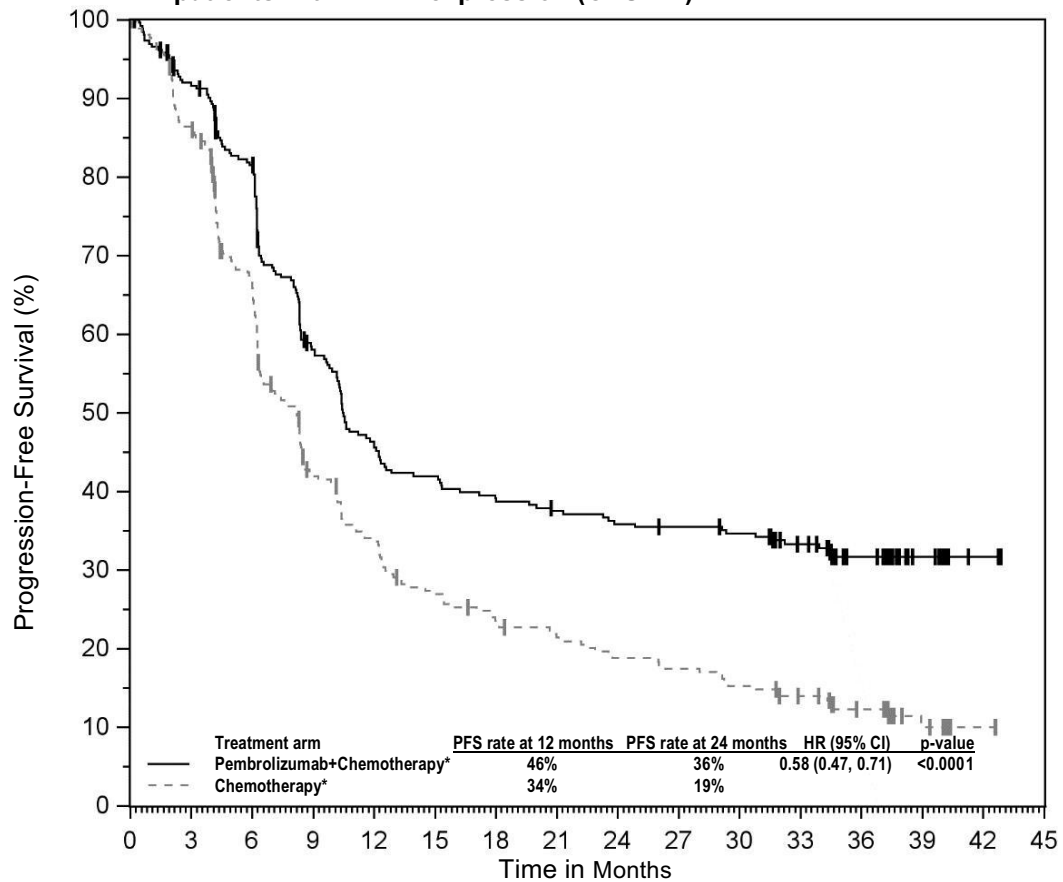
**Figure 33: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥ 1)**



| Number at Risk              |     |     |     |     |     |     |     |     |     |     |     |     |    |    |    |   |   |
|-----------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|---|---|
| Pembrolizumab+Chemotherapy* | 273 | 261 | 251 | 231 | 206 | 189 | 168 | 157 | 146 | 136 | 128 | 116 | 90 | 52 | 22 | 2 | 0 |
| Chemotherapy*               | 275 | 261 | 235 | 207 | 173 | 149 | 129 | 117 | 107 | 91  | 81  | 68  | 45 | 24 | 3  | 0 | 0 |

\* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

**Figure 34: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥ 1)**



| Number at Risk              |     |     |     |     |     |     |    |    |    |    |    |    |    |    |   |   |
|-----------------------------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|---|---|
| Pembrolizumab+Chemotherapy* | 273 | 238 | 208 | 144 | 113 | 104 | 97 | 92 | 88 | 86 | 83 | 70 | 46 | 25 | 6 | 0 |
| Chemotherapy*               | 275 | 229 | 170 | 103 | 81  | 64  | 55 | 49 | 43 | 40 | 35 | 28 | 18 | 7  | 2 | 0 |

\* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

**Renal Cell Carcinoma**

***KEYNOTE-426: Controlled trial of combination therapy with axitinib for first-line treatment of patients with advanced RCC***

The efficacy of KEYTRUDA in combination with axitinib was investigated in a randomized, multicenter, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced RCC, regardless of PD-L1 tumor status and International Metastatic RCC Database Consortium (IMDC) risk group categories. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Randomization was stratified by risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”). Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks in combination with axitinib 5 mg orally, twice daily. Patients who tolerated axitinib 5 mg twice daily for 2 consecutive treatment cycles (i.e., 6 weeks) with no >Grade 2 treatment-related adverse events to axitinib and with blood pressure well controlled to ≤ 150/90 mm Hg were permitted dose escalation of axitinib to 7 mg twice daily.

Dose escalation of axitinib to 10 mg twice daily was permitted using the same criteria. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.

- Sunitinib 50 mg orally, once daily for 4 weeks and then off treatment for 2 weeks.

Treatment with KEYTRUDA and axitinib continued until RECIST 1.1-defined progression of disease as verified by BICR or confirmed by the investigator, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Administration of KEYTRUDA and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at baseline, after randomization at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter. Chemistry and hematology laboratory tests were performed at each cycle.

Among the 861 patients in KEYNOTE-426 (432 patients in the KEYTRUDA combination arm and 429 in the sunitinib arm), baseline characteristics were: median age of 62 years (range: 26 to 90); 38% age 65 or older; 73% male; 79% White and 16% Asian; 99.9% had a Karnofsky Performance Score (KPS) of  $\geq 70\%$ ; patient distribution by IMDC risk categories was 31% favorable, 56% intermediate and 13% poor.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR according to RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time for 432 patients treated with KEYTRUDA and axitinib was 13.2 months (range: 0.1 – 21.5 months). Table 27 summarizes key efficacy measures. Improvements in OS, PFS and ORR were shown consistently across all tested subgroups, including subgroups by IMDC risk category and PD-L1 tumor expression status.

**Table 27: Response to KEYTRUDA and Axitinib in Patients with Advanced RCC in KEYNOTE-426**

| Endpoint                                                      | KEYTRUDA<br>with axitinib<br>n=432 | Sunitinib<br>n=429   |
|---------------------------------------------------------------|------------------------------------|----------------------|
| OS                                                            |                                    |                      |
| Number of patients with event (%)                             | 59 (14%)                           | 97 (23%)             |
| Median in months (95% CI)                                     | Not reached (NA, NA)               | Not reached (NA, NA) |
| Hazard ratio* (95% CI)                                        | 0.53 (0.38, 0.74)                  |                      |
| p-Value <sup>†</sup>                                          | 0.00005                            |                      |
| 12-month OS rate (95% CI)                                     | 90% (86, 92)                       | 78% (74, 82)         |
| 18-month OS rate (95% CI)                                     | 82% (77, 86)                       | 72% (66, 77)         |
| PFS                                                           |                                    |                      |
| Number of patients with event (%)                             | 183 (42%)                          | 213 (50%)            |
| Median in months (95% CI)                                     | 15.1 (12.6, 17.7)                  | 11.0 (8.7, 12.5)     |
| Hazard ratio* (95% CI)                                        | 0.69 (0.56, 0.84)                  |                      |
| p-Value <sup>†</sup>                                          | 0.00012                            |                      |
| ORR                                                           |                                    |                      |
| Overall response rate <sup>‡</sup> (95% CI)                   | 59% (54, 64)                       | 36% (31, 40)         |
| Complete response                                             | 6%                                 | 2%                   |
| Partial response                                              | 53%                                | 34%                  |
| p-Value <sup>§</sup>                                          | <0.0001                            |                      |
| Response Duration                                             |                                    |                      |
| Median in months (range)                                      | Not reached (1.4+, 18.2+)          | 15.2 (1.1+, 15.4+)   |
| Number (% <sup>¶</sup> ) of patients with duration ≥6 months  | 161 (88%)                          | 84 (81%)             |
| Number (% <sup>¶</sup> ) of patients with duration ≥12 months | 58 (71%)                           | 26 (62%)             |

\* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Based on patients with a best overall response as confirmed complete or partial response

§ Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region

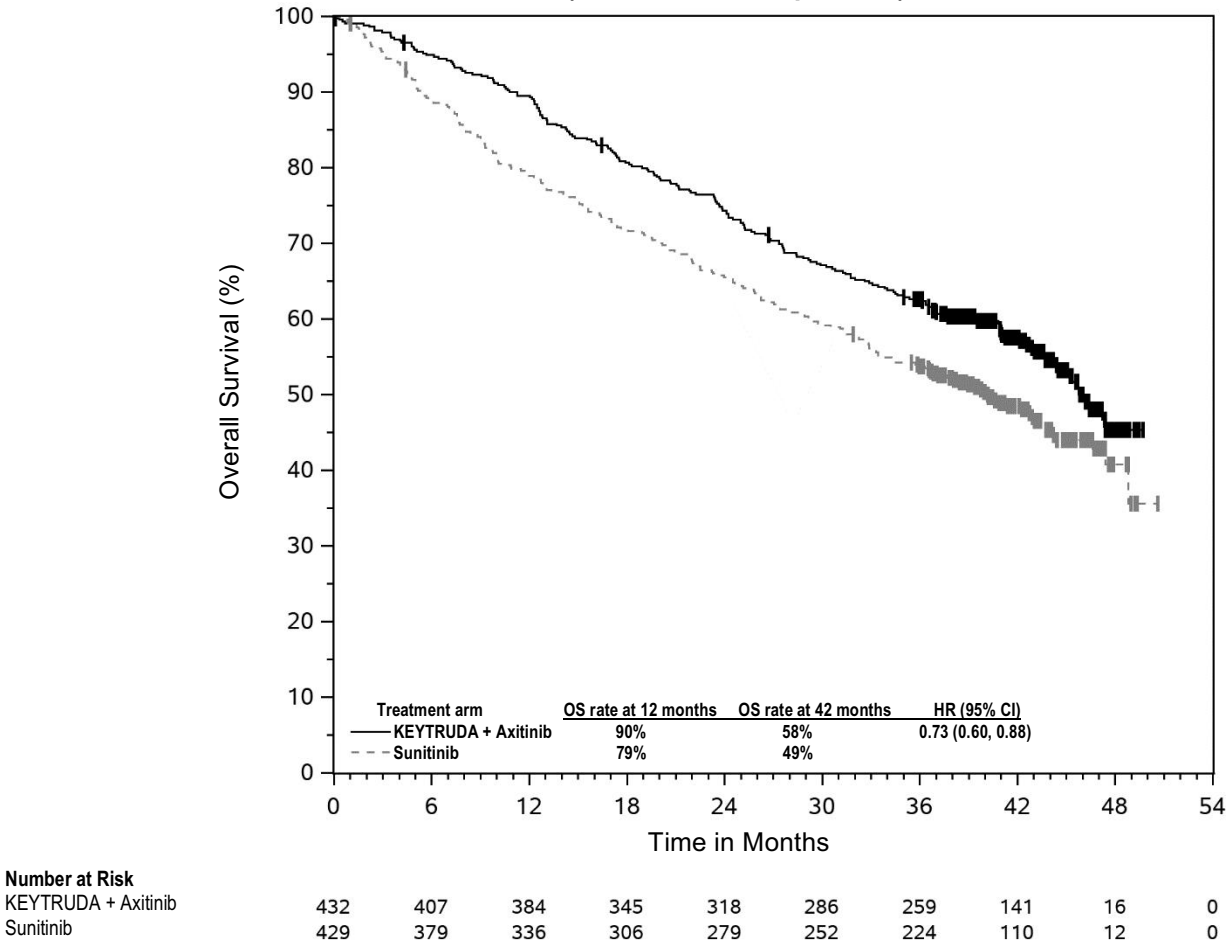
¶ Based on Kaplan-Meier estimation

NA = not available

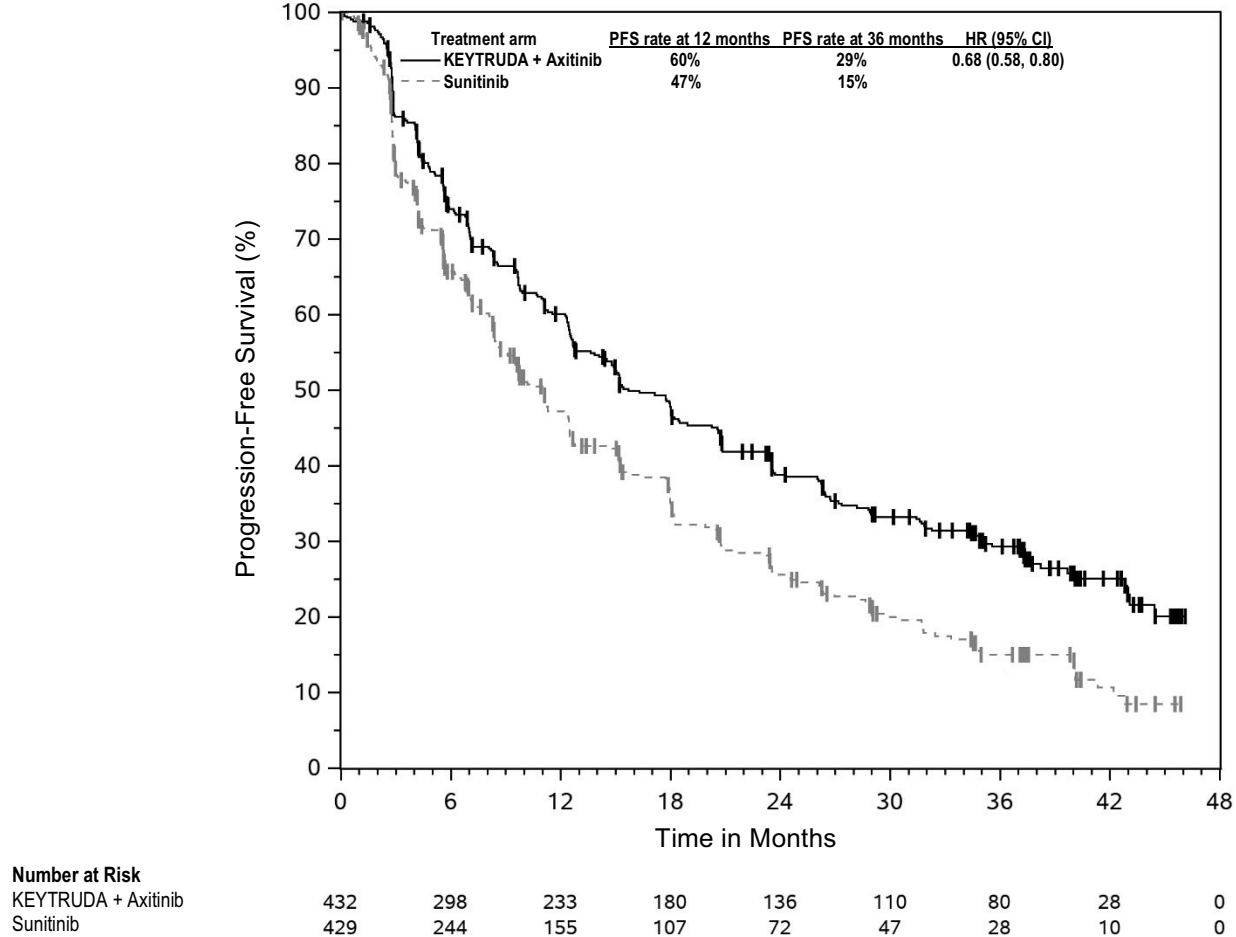
The protocol-specified final OS analysis was performed at a median duration of follow-up of 37.7 months after 418 patient events (193 in the KEYTRUDA and axitinib arm and 225 in the sunitinib arm). Median OS was 45.7 months (95% CI: 43.6, NA) in the KEYTRUDA and axitinib arm and 40.1 months (95% CI: 34.3, 44.2) in the sunitinib arm. The OS HR was 0.73 (95% CI: 0.60, 0.88). The 12-month OS rates were 90% (95% CI: 86, 92) in the KEYTRUDA and axitinib arm and 79% (95% CI: 75, 83) in the sunitinib arm. The 24-month OS rates were 74% (95% CI: 70, 78) in the KEYTRUDA and axitinib arm and 66% (95% CI: 61, 70) in the sunitinib arm. The 36-month OS rates were 63% (95% CI: 58, 67) in the KEYTRUDA and axitinib arm and 54% (95% CI: 49, 58) in the sunitinib arm. The 42-month OS rates were 58% (95% CI: 53, 62) in the KEYTRUDA and axitinib arm and 49% (95% CI: 44, 53) in the sunitinib arm. At final analysis, a PFS analysis was performed based on 587 patient events (286 in the KEYTRUDA and axitinib arm and 301 in the sunitinib arm). The median PFS was 15.7 months (95% CI: 13.6, 20.2) in the KEYTRUDA and axitinib arm and 11.1 months (95% CI: 8.9, 12.5) in the sunitinib arm. The PFS HR was 0.68 (95% CI: 0.58, 0.80).

The ORR at the final analysis was 60% in the KEYTRUDA and axitinib arm and 40% in the sunitinib arm. The median duration of response was 23.6 months (range: 1.4+ to 43.4+) in the KEYTRUDA and axitinib arm and 15.3 months (range: 2.3 to 42.8+) in the sunitinib arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 71%, 59%, 49%, and 45% at 12, 18, 24, and 30 months, respectively, in patients with confirmed response in the KEYTRUDA and axitinib arm, vs. 62%, 46%, 37%, and 32% in patients with confirmed response in the sunitinib arm.

**Figure 35: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)**



**Figure 36: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)**



**KEYNOTE-581: Controlled trial of combination therapy with lenvatinib for first-line treatment of patients with advanced RCC**

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-581, a multicenter, open-label, randomized trial conducted in 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by geographic region (North America versus Western Europe versus “Rest of the World”) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable versus intermediate versus poor risk).

Patients were randomized (1:1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily.
- Lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily.
- Sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks.

Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by BICR using RECIST 1.1. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 8 weeks.

Among the 1069 patients in KEYNOTE-581 (355 patients in the KEYTRUDA with lenvatinib arm, 357 patients in the lenvatinib with everolimus arm, and 357 patients in the sunitinib arm), the study population characteristics were: median age of 62 years (range: 29 to 88 years); 42% age 65 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by IMDC risk categories was 33% favorable, 56% intermediate and 10% poor, and by MSKCC risk categories was 27% favorable, 64% intermediate and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

The primary efficacy outcome measure was PFS based on BICR using RECIST 1.1. Key secondary efficacy outcome measures included OS and ORR. The trial demonstrated statistically significant improvements in PFS, OS, and ORR in patients randomized to KEYTRUDA in combination with lenvatinib compared with sunitinib. The median overall survival follow-up time was 26.6 months. Pre-specified interim analysis efficacy results for KEYNOTE-581 are summarized in Table 28. Consistent results were observed across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumor expression status.

**Table 28: Efficacy Results in KEYNOTE-581**

| Endpoint                          | KEYTRUDA<br>200 mg every<br>3 weeks<br>and Lenvatinib<br>n=355 | Sunitinib<br><br>n=357 |
|-----------------------------------|----------------------------------------------------------------|------------------------|
| PFS                               |                                                                |                        |
| Number of patients with event (%) | 160 (45%)                                                      | 205 (57%)              |
| Median in months (95% CI)         | 23.9 (20.8, 27.7)                                              | 9.2 (6.0, 11.0)        |
| Hazard ratio* (95% CI)            | 0.39 (0.32, 0.49)                                              |                        |
| p-Value†                          | <0.0001                                                        |                        |
| OS                                |                                                                |                        |
| Number of patients with event (%) | 80 (23%)                                                       | 101 (28%)              |
| Median in months (95% CI)         | NR (33.6, NR)                                                  | NR (NR, NR)            |
| Hazard ratio* (95% CI)            | 0.66 (0.49, 0.88)                                              |                        |
| p-Value†                          | 0.0049                                                         |                        |
| 12-month OS rate (95% CI)         | 91% (88, 94)                                                   | 80% (76, 84)           |
| 18-month OS rate (95% CI)         | 87% (83, 90)                                                   | 74% (69, 79)           |
| 24-month OS rate (95% CI)         | 79% (74, 83)                                                   | 70% (65, 75)           |
| Objective Response Rate           |                                                                |                        |
| ORR‡ (95% CI)                     | 71% (66, 76)                                                   | 36% (31, 41)           |
| Complete response rate            | 16%                                                            | 4%                     |
| Partial response rate             | 55%                                                            | 32%                    |
| p-Value§                          | <0.0001                                                        |                        |
| Response Duration¶                |                                                                |                        |
| Median in months (range)          | 26 (1.6+, 36.8+)                                               | 15 (1.6+, 33.2+)       |

\* Based on the stratified Cox proportional hazard model

† Two-sided p-Value based on stratified log-rank test

‡ Response: Best objective response as confirmed complete response or partial response

§ Nominal p-Value. At the earlier pre-specified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing KEYTRUDA plus lenvatinib with sunitinib, (odds ratio: 3.84 (95% CI: 2.81, 5.26), p-Value <0.0001)

¶ Based on Kaplan-Meier estimates

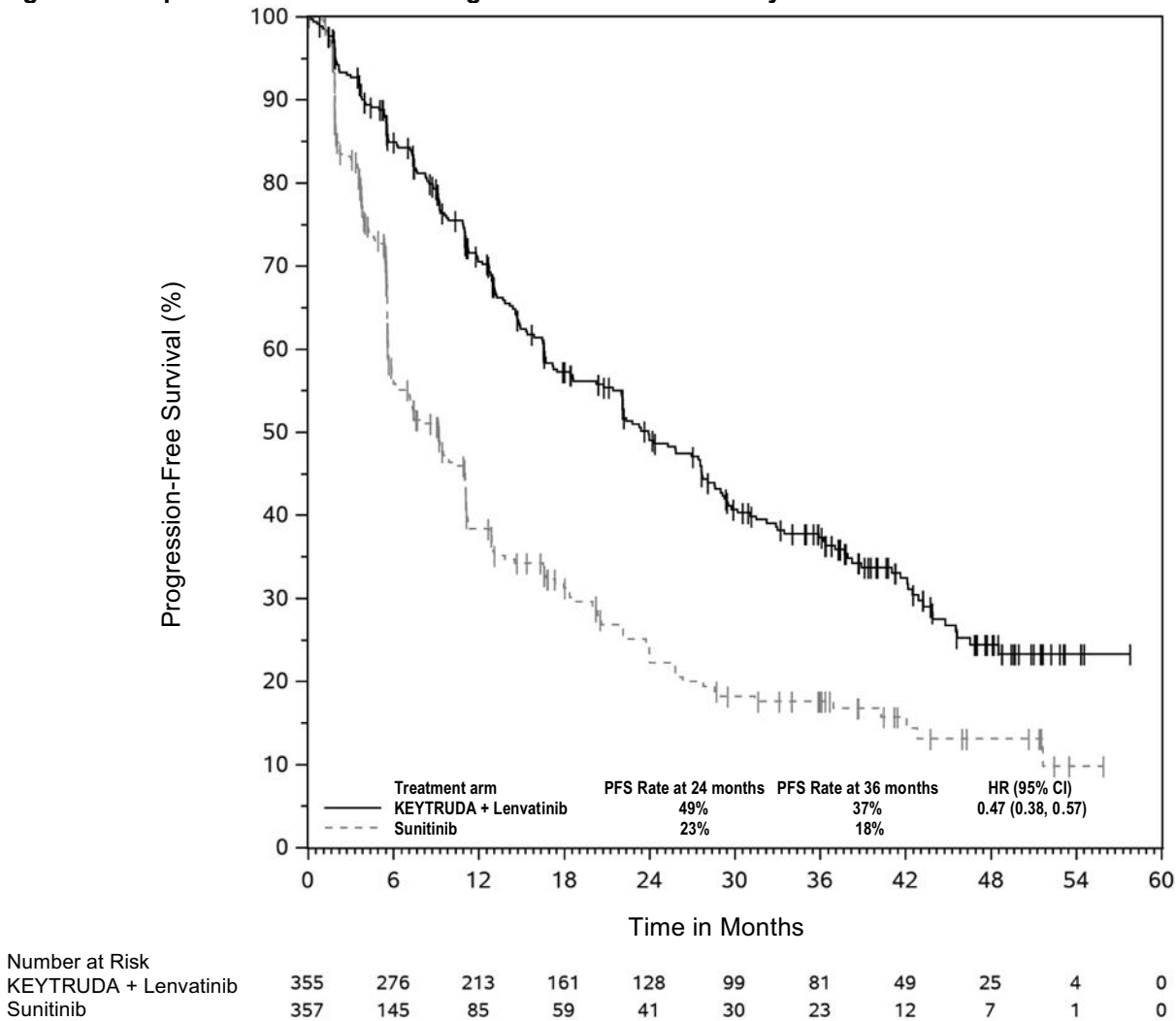
NR = not reached

At the protocol-specified final analysis, median follow-up was 49.4 months. The PFS analysis was performed with 207 patient events for KEYTRUDA in combination with lenvatinib and 214 patient events for sunitinib. The median PFS was 23.9 months (95% CI: 20.8, 27.7) for KEYTRUDA in combination with lenvatinib and 9.2 months (95% CI: 6.0, 11.0) for sunitinib. The PFS HR was 0.47 (95% CI: 0.38, 0.57, nominal p<0.0001). At the final OS analysis there were 149 patients events for KEYTRUDA in combination with lenvatinib and 159 patients events for sunitinib. Median OS was 53.7 months (95% CI: 48.7, NE) for KEYTRUDA in combination with lenvatinib and 54.3 months (95% CI: 40.9, NE) for sunitinib. The OS HR was 0.79 (95% CI: 0.63, 0.99; nominal p<0.0424). The OS analysis was not adjusted to account for subsequent therapies, in which 195/357 (54.6%) patients in the sunitinib arm and 56/355 (15.8%) patients in the pembrolizumab plus lenvatinib arm received subsequent systemic anti-PD-1/PD-L1 therapy. OS may be confounded by the difference in subsequent therapies. See Figures 37 and 38.

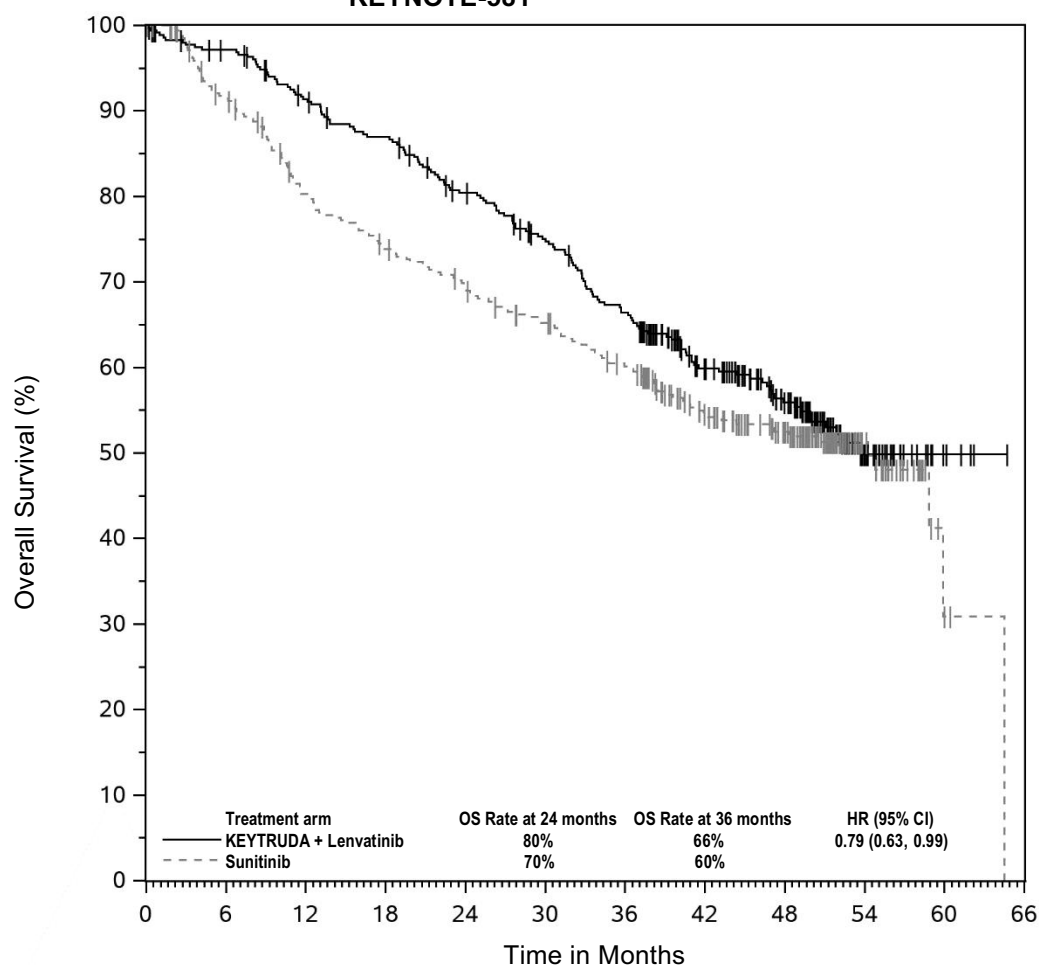
The ORR was 71% for KEYTRUDA in combination with lenvatinib and 37% for sunitinib. The complete response rates were 18% for KEYTRUDA in combination with lenvatinib and 5% for sunitinib. The median duration of response was 26.7 months (range: 1.64+, 55.92+) for KEYTRUDA in combination with lenvatinib and 14.7 months (range: 1.64+, 54.08+) for sunitinib. The percentage of patients with ongoing responses

based on Kaplan-Meier estimation were 56% and 41% at 24 and 36 months or longer in patients who received KEYTRUDA in combination with lenvatinib vs. 32% and 24% in patients who received sunitinib.

Figure 37: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-581



**Figure 38: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-581**



|                       |     |     |     |     |     |     |     |     |     |    |   |   |
|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|---|---|
| Number at Risk        |     |     |     |     |     |     |     |     |     |    |   |   |
| KEYTRUDA + Lenvatinib | 355 | 338 | 313 | 296 | 269 | 245 | 216 | 158 | 117 | 34 | 5 | 0 |
| Sunitinib             | 357 | 308 | 264 | 242 | 226 | 208 | 188 | 145 | 108 | 33 | 3 | 0 |

**KEYNOTE-B61: Open-label trial of combination therapy with lenvatinib in patients with advanced/metastatic non-clear cell RCC in the first-line setting**

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-B61, a multicenter, open-label, single-arm trial that enrolled 160 patients with advanced/metastatic non-clear cell RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 400 mg every 6 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily. Treatment continued until unacceptable toxicity or disease progression. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was considered by the investigator to be deriving clinical benefit. KEYTRUDA was continued for a maximum of 24 months; however, lenvatinib could be continued beyond 24 months.

Among the 158 treated patients, the baseline characteristics were: median age of 60 years (range: 24 to 87 years), 71% male; 86% White, 8% Asian, and 3% Black; 22% and 78% of patients had a baseline KPS of 70 to 80 and 90 to 100 respectively; histologic subtypes were 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other; patient distribution by IMDC risk categories

was 35% favorable, 54% intermediate and 10% poor; Common sites of metastases in patients were lymph node (65%), lung (35%), bone (30%), and liver (21%).

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included DOR and PFS (as assessed by BICR using RECIST 1.1), and OS. Efficacy results are summarized in Table 29. Clinical activity was observed regardless of the histological subtype.

**Table 29: Efficacy Results in KEYNOTE-B61**

| Endpoint                        | KEYTRUDA<br>400 mg every 6 weeks<br>and Lenvatinib<br>n=158 |
|---------------------------------|-------------------------------------------------------------|
| <b>Objective Response Rate*</b> |                                                             |
| ORR†, (95% CI)                  | 51% (43, 59)                                                |
| Complete response               | 8%                                                          |
| Partial response                | 42%                                                         |
| Stable disease                  | 32%                                                         |
| Disease control rate            | 82%                                                         |
| <b>Response Duration*‡</b>      |                                                             |
| Median in months (range)        | 19.5 (1.5+, 23.5+)                                          |
| % with duration ≥6 months       | 89%                                                         |
| % with duration ≥12 months      | 76%                                                         |
| % with duration ≥18 months      | 51%                                                         |
| <b>Time to Response</b>         |                                                             |
| Median in months (range)        | 2.8 (2.5, 15.2)                                             |
| <b>PFS*</b>                     |                                                             |
| Median in months (95% CI)       | 17.9 (15.1, 22.1)                                           |
| 12-month PFS rate (95% CI)      | 64% (56, 71)                                                |
| 18-month PFS rate (95% CI)      | 48% (39, 56)                                                |
| <b>OS</b>                       |                                                             |
| Median in months (95% CI)       | NR (NR, NR)                                                 |
| 12-month OS rate (95% CI)       | 82% (75, 87)                                                |
| 18-month OS rate (95% CI)       | 73% (65, 79)                                                |

\* Assessed by BICR using RECIST 1.1

† Based on patients with a best overall response as confirmed complete or partial response

‡ Based on Kaplan-Meier estimates

NR = not reached

***KEYNOTE-564: Placebo-controlled study for the adjuvant treatment of patients with resected RCC***

The efficacy of KEYTRUDA was investigated as adjuvant therapy for RCC in KEYNOTE-564, a multicenter, randomized, double-blind, placebo-controlled study in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate high-risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high-risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥4 weeks prior to the time of screening. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=496) or placebo (n=498) for up to 1 year until disease recurrence, or until unacceptable toxicity.

Randomization was stratified by metastasis status (M0, M1 NED), within M0 group, further stratified by ECOG PS (0,1), and geographic region (US, non-US). Patients underwent imaging every 12 weeks for the first 2 years from first dose, then every 16 weeks from year 3 to 4, and then every 24 weeks annually.

Among the 994 patients, the baseline characteristics were: median age of 60 years (range: 25 to 84), 33% age 65 or older; 71% male; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-four percent were N0; 84% had no sarcomatoid features; 86% were pT2 with Grade 4 or sarcomatoid features or pT3; 8% were pT4 or with nodal involvement; and 6% were M1 NED. Baseline characteristics and demographics were generally comparable between the KEYTRUDA and placebo arms.

The primary efficacy outcome measure was investigator-assessed DFS. The key secondary outcome measure was OS. The study demonstrated statistically significant improvements in DFS and OS for patients randomized to the KEYTRUDA arm compared with placebo. Generally, consistent results were observed across pre-specified subgroups. Efficacy results are summarized in Table 30 and Figures 39 and 40.

**Table 30: Efficacy Results in KEYNOTE-564**

| Endpoint                           | KEYTRUDA<br>200 mg every<br>3 weeks<br>n=496 | Placebo<br><br>n=498 |
|------------------------------------|----------------------------------------------|----------------------|
| <b>DFS*</b>                        |                                              |                      |
| Number (%) of patients with event  | 109 (22%)                                    | 151 (30%)            |
| Median in months (95% CI)          | NR                                           | NR                   |
| Hazard ratio <sup>‡</sup> (95% CI) | 0.68 (0.53, 0.87)                            |                      |
| p-Value                            | 0.0010 <sup>§</sup>                          |                      |
| 12-month DFS rate (95% CI)         | 86% (82, 89)                                 | 76% (72, 80)         |
| 24-month DFS rate (95% CI)         | 77% (73, 81)                                 | 68% (64, 72)         |
| <b>OS<sup>†</sup></b>              |                                              |                      |
| Number (%) of patients with event  | 55 (11%)                                     | 86 (17%)             |
| Median in months (95% CI)          | NR                                           | NR                   |
| Hazard ratio (95% CI) <sup>‡</sup> | 0.62 (0.44, 0.87)                            |                      |
| p-Value                            | 0.0024 <sup>§</sup>                          |                      |
| 12-month OS rate (95% CI)          | 99% (97, 99)                                 | 98% (96, 99)         |
| 24-month OS rate (95% CI)          | 96% (94, 98)                                 | 94% (91, 96)         |
| 36-month OS rate (95% CI)          | 94% (91, 96)                                 | 90% (86, 92)         |
| 48-month OS rate (95% CI)          | 91% (88, 93)                                 | 86% (83, 89)         |

\* Median follow-up time was 23.9 months (range: 2.5 to 41.5 months).

† Median follow-up time was 55.8 months (range: 2.5 to 74.5 months).

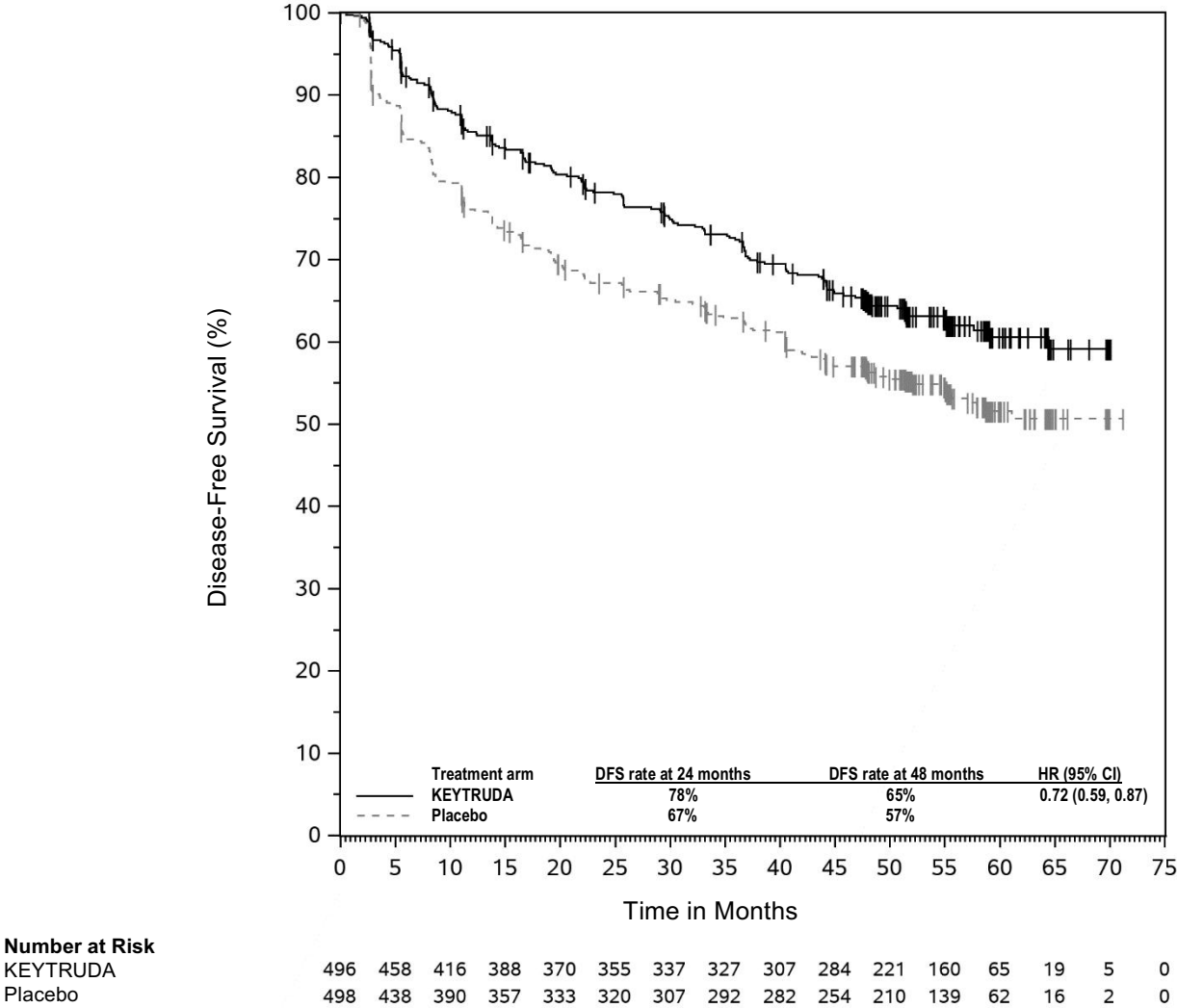
‡ Based on the stratified Cox proportional hazard model

§ Based on stratified log-rank test

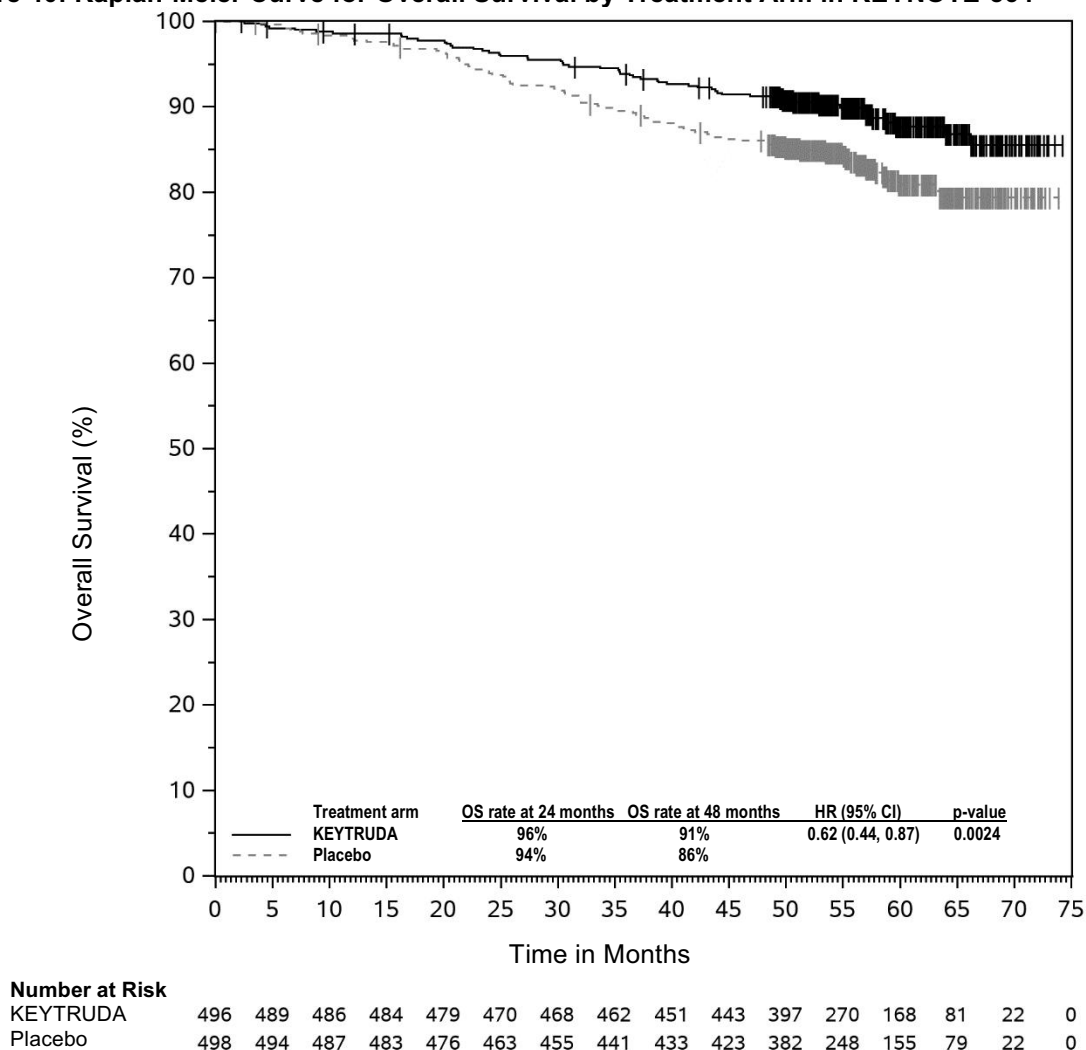
NR = not reached

At a pre-specified interim analysis (median follow-up time was 55.8 months (range: 2.5 to 74.5 months)), the updated DFS HR was 0.72 (95% CI: 0.59, 0.87). The updated 12-month DFS rates were 86% (95% CI: 82, 88) in the KEYTRUDA arm and 76% (95% CI: 72, 80) in the placebo arm. The updated 24-month DFS rates were 78% (95% CI: 74, 82) in the KEYTRUDA arm and 67% (95% CI: 63, 71) in the placebo arm. The 36-month DFS rates were 72% (95% CI: 68, 76) in the KEYTRUDA arm and 63% (95% CI: 58, 67) in the placebo arm. The 48-month DFS rates were 65% (95% CI: 60, 69) in the KEYTRUDA arm and 57% (95% CI: 52, 61) in the placebo arm.

Figure 39: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in KEYNOTE-564



**Figure 40: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-564**



## Endometrial Carcinoma

### KEYNOTE-868/NRG-GY018: Controlled trial of combination therapy for treatment of patients with primary advanced or recurrent endometrial carcinoma

The efficacy of KEYTRUDA in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868, a multicenter, randomized, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma including those with dMMR and pMMR tumors. Patients had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting. Patients who had received prior adjuvant chemotherapy were eligible if their chemotherapy-free interval was at least 12 months. Patients with endometrial sarcoma, including carcinosarcoma, or patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy. Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg every 3 weeks, paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by KEYTRUDA 400 mg every 6 weeks for up to 14 cycles.
- Placebo every 3 weeks, paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by placebo every 6 weeks for up to 14 cycles.

All study medications were administered as an intravenous infusion on Day 1 of each treatment cycle. Treatment continued until disease progression, unacceptable toxicity, or a maximum of 20 cycles (up to approximately 24 months). Patients with measurable disease who had RECIST-defined stable disease or partial response at the completion of cycle 6 were permitted to continue receiving paclitaxel and carboplatin with KEYTRUDA or placebo for up to 10 cycles as determined by the investigator. Assessment of tumor status was performed every 9 weeks for the first 9 months and then every 12 weeks thereafter.

Among the 810 randomized patients, 222 (27%) had dMMR tumor status and 588 (73%) had pMMR tumor status.

The dMMR population characteristics were: median age of 66 years (range: 37 to 86), 55% age 65 or older; 79% White, 9% Black, and 3% Asian; 5% Hispanic or Latino; 64% ECOG PS of 0, 33% ECOG PS of 1, and 3% ECOG PS of 2; 61% had recurrent disease and 39% had primary or persistent disease; 5% received prior adjuvant chemotherapy and 43% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (24% grade 1, 43% grade 2, 14% grade 3), adenocarcinoma NOS (11%), and other (8% including dedifferentiated/undifferentiated, serous, and mixed epithelial).

The pMMR population characteristics were: median age of 66 years (range: 29 to 94), 54% age 65 or older; 72% White, 16% Black, and 5% Asian; 6% Hispanic or Latino; 67% ECOG PS of 0, 30% ECOG PS of 1, and 3% ECOG PS of 2; 56% had recurrent disease and 44% had primary or persistent disease; 26% received prior adjuvant chemotherapy and 41% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (17% grade 1, 19% grade 2, 16% grade 3), serous (26%), adenocarcinoma NOS (10%), clear cell carcinoma (7%), and other (5% including mixed epithelial and dedifferentiated/undifferentiated).

The primary efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1. Secondary efficacy outcome measures included OS, ORR, and DoR. The trial demonstrated statistically significant improvements in PFS for patients randomized to KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy in both the dMMR and pMMR populations. The median follow-up time was 13.6 months (range: 0.6 to 39.4 months) and 8.7 months (range: 0.1 to 37.2 months) in the dMMR and pMMR populations, respectively. OS endpoint was not formally assessed within multiplicity control. OS maturity was 12.2% in the dMMR population and 16.8% in the pMMR population. Among the patients who had been randomized to receive placebo in combination with chemotherapy and discontinued from the study, 55% from the dMMR population and 45% from the pMMR population subsequently received post-study therapies that incorporated anti-PD-1/PD-L1 therapy. Table 31 and Figures 41 and 42 summarize the efficacy results for KEYNOTE-868 by MMR status.

**Table 31: Efficacy Results in KEYNOTE-868**

| Endpoint                                | dMMR Population                            |                                           | pMMR Population                            |                                           |
|-----------------------------------------|--------------------------------------------|-------------------------------------------|--------------------------------------------|-------------------------------------------|
|                                         | KEYTRUDA<br>with<br>chemotherapy*<br>n=110 | Placebo<br>with<br>chemotherapy*<br>n=112 | KEYTRUDA<br>with<br>chemotherapy*<br>n=294 | Placebo<br>with<br>chemotherapy*<br>n=294 |
| PFS                                     |                                            |                                           |                                            |                                           |
| Number (%) of<br>patients with<br>event | 29 (26%)                                   | 60 (54%)                                  | 95 (32%)                                   | 138 (47%)                                 |
| Median in<br>months (95% CI)            | NR (30.7, NR)                              | 8.3 (6.5, 12.3)                           | 13.1 (10.6, 19.5)                          | 8.7 (8.4, 11.0)                           |
| Hazard ratio <sup>†</sup><br>(95% CI)   | 0.34 (0.22, 0.53)                          |                                           | 0.57 (0.44, 0.74)                          |                                           |
| p-Value <sup>‡</sup>                    | <0.0001                                    |                                           | <0.0001                                    |                                           |
| OS                                      |                                            |                                           |                                            |                                           |
| Number (%) of<br>patients with<br>event | 10 (9%)                                    | 17 (15%)                                  | 45 (15%)                                   | 54 (18%)                                  |
| Median in<br>months (95% CI)            | NR (NR, NR)                                | NR (NR, NR)                               | 28.0 (21.4, NR)                            | 27.4 (19.5, NR)                           |
| Hazard ratio <sup>†</sup><br>(95% CI)   | 0.55 (0.25, 1.19)                          |                                           | 0.79 (0.53, 1.17)                          |                                           |
| p-Value <sup>§</sup>                    | 0.0617                                     |                                           | 0.1157                                     |                                           |

\* Chemotherapy (paclitaxel and carboplatin)

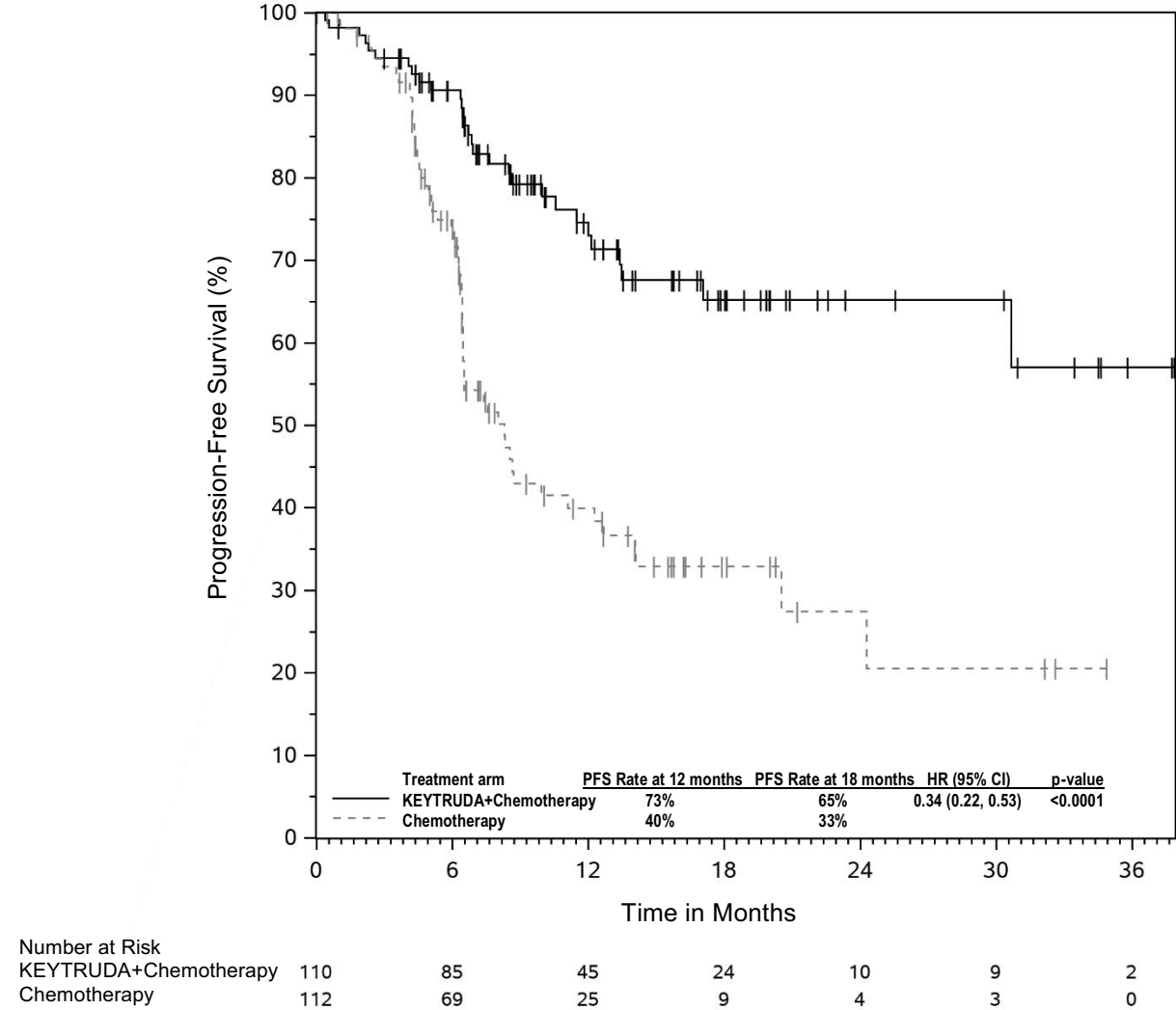
† Based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test (compared to an alpha boundary of 0.00207 for dMMR and 0.00116 for pMMR)

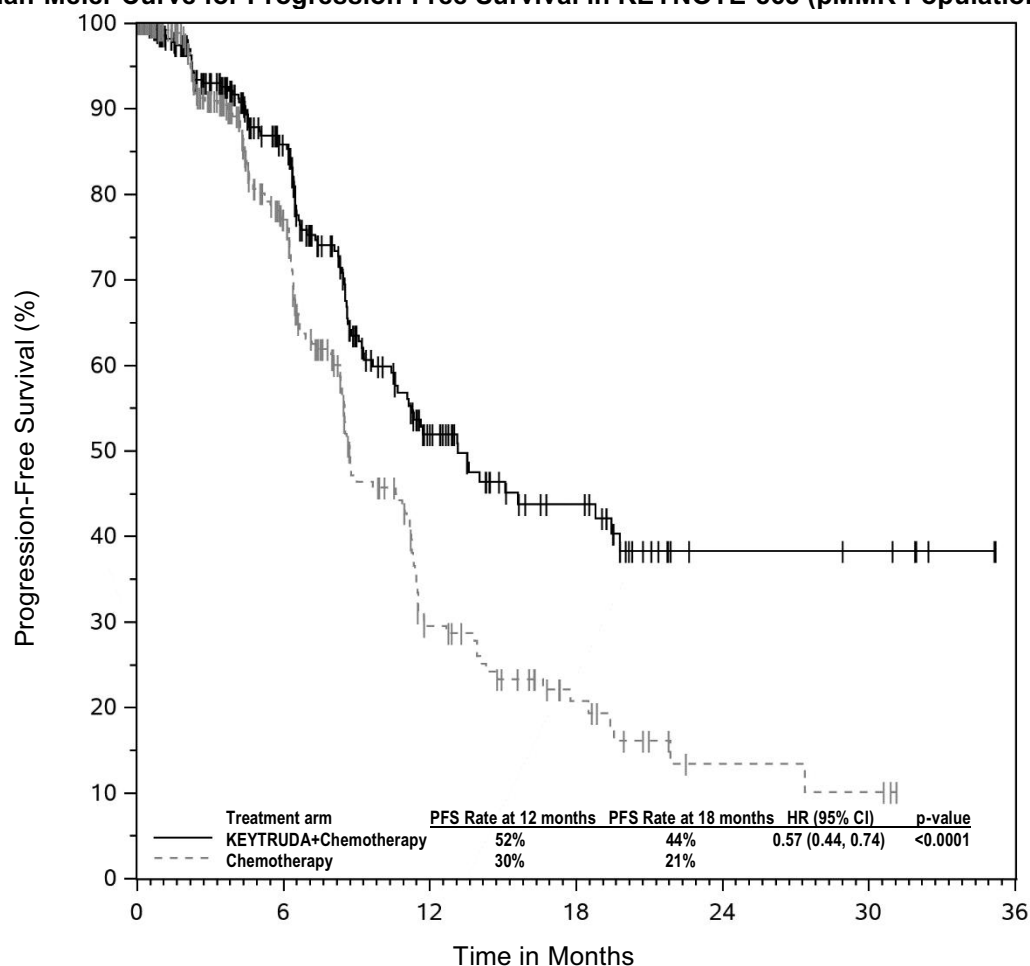
§ Nominal p-Value; no multiplicity adjustment

NR=not reached

Figure 41: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)



**Figure 42: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)**



|                       |     |     |    |    |   |   |   |
|-----------------------|-----|-----|----|----|---|---|---|
| Number at Risk        |     |     |    |    |   |   |   |
| KEYTRUDA+Chemotherapy | 294 | 162 | 57 | 29 | 7 | 6 | 0 |
| Chemotherapy          | 294 | 144 | 36 | 15 | 4 | 3 | 0 |

**KEYNOTE-146: Open-label study of combination therapy in patients with endometrial carcinoma**

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in a non-randomized, multicenter, open-label, multi-cohort trial KEYNOTE-146, conducted in 108 patients with endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. The trial excluded patients with active autoimmune disease or medical conditions that required immunosuppression.

Patients received KEYTRUDA at a dose of 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator. Clinically stable patients who were considered by the investigator to be deriving clinical benefit were permitted to remain on treatment beyond RECIST-defined disease progression. Patients could be treated with KEYTRUDA for up to 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 6 weeks until week 24, followed by every 9 weeks thereafter. The major efficacy outcome measures were ORR and duration of response, as assessed by blinded independent central review (BICR) using RECIST 1.1.

Among the 108 patients, 87% (n= 94) had tumors that were not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), 10% (n=11) had tumors that were MSI-H or dMMR, and in 3% (n=3) the status was not known. The baseline characteristics of the 94 patients with tumors that were not MSI-H or dMMR were: median age of 66 years with 62% age 65 or older; 86% White, 6% Black, 4% Asian, 3% other

ances; and ECOG PS of 0 (52%) or 1 (48%). All 94 of these patients received prior systemic therapy for endometrial carcinoma: 51% had one, 38% had two, and 11% had three or more prior systemic therapies.

Efficacy results are summarized in Table 32.

**Table 32: Efficacy Results in Patients with Endometrial Carcinoma that is Not MSI-H or dMMR**

| Endpoint                                 | KEYTRUDA<br>with lenvatinib<br>n=94* |
|------------------------------------------|--------------------------------------|
| <b>Best Overall Response<sup>†</sup></b> |                                      |
| ORR %, (95% CI)                          | 38.3% (29, 49)                       |
| Complete response                        | 10.6%                                |
| Partial response                         | 27.7%                                |
| Stable Disease                           | 40.4%                                |
| Disease Control Rate                     | 78.7%                                |
| <b>Response Duration<sup>†</sup></b>     |                                      |
| Median in months (range)                 | NR (1.2+, 33.1+) <sup>‡</sup>        |
| % with duration ≥6 months                | 76% <sup>§</sup>                     |
| % with duration ≥12 months               | 51% <sup>¶</sup>                     |
| <b>Time to Response</b>                  |                                      |
| Median in months (range)                 | 1.4 (1.1, 8.0)                       |
| <b>PFS<sup>†</sup></b>                   |                                      |
| Median in months (95% CI)                | 5.4 (4.4, 7.6)                       |
| 6-month PFS rate                         | 49%                                  |
| 12-month PFS rate                        | 33%                                  |
| <b>OS</b>                                |                                      |
| Median in months (95% CI)                | 16.4 (13.5, 25.9)                    |
| 12-month OS rate                         | 70%                                  |

\* Median follow-up time of 18.7 months

† Assessed by BICR using RECIST 1.1

‡ Based on patients (n=36) with a response by independent review

§ Based on Kaplan-Meier estimates; includes 25 patients with responses of 6 months or longer

¶ Based on Kaplan-Meier estimates; includes 8 patients with responses of 12 months or longer

+ Denotes ongoing

NR = not reached

**KEYNOTE-775: Controlled study of combination therapy in advanced endometrial carcinoma patients previously treated with systemic chemotherapy**

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a randomized, multicenter, open-label, active-controlled study conducted in patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Participants may have received up to 2 platinum-containing therapies in total, as long as one was given in the neoadjuvant or adjuvant treatment setting. The study excluded patients with endometrial sarcoma carcinosarcoma, pre-existing Grade ≥ 3 fistula, uncontrolled BP (> 150/90 mmHg), significant cardiovascular impairment or event within previous 12 months, or patients who had active autoimmune disease or a medical condition that required immunosuppression. Randomization was stratified by MMR status (dMMR or pMMR [mismatch repair proficient]) using a validated IHC test. The pMMR stratum was further stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily.
- Investigator's choice consisting of either doxorubicin 60 mg/m<sup>2</sup> every 3 weeks, or paclitaxel 80 mg/m<sup>2</sup> given weekly, 3 weeks on/1 week off.

Treatment with KEYTRUDA and lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for pembrolizumab, a maximum of 24 months. Administration of study treatment was permitted beyond RECIST-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. A total of 121/411 (29%) of the pembrolizumab and lenvatinib-treated patients received continued study therapy beyond RECIST-defined disease progression. The median duration of the post-progression therapy was 2.8 months. Assessment of tumor status was performed every 8 weeks.

A total of 827 patients were enrolled and randomized to KEYTRUDA in combination with lenvatinib (n=411) or investigator's choice of doxorubicin (n=306) or paclitaxel (n=110). The baseline characteristics of these patients were: median age of 65 years (range: 30 to 86), 50% age 65 or older; 61% White, 21% Asian, and 4% Black; ECOG PS of 0 (59%) or 1 (41%), and 84% with pMMR tumor status and 16% with dMMR tumor status. The histologic subtypes were endometrioid carcinoma (60%), serous (26%), clear cell carcinoma (6%), mixed (5%), and other (3%). All 827 of these patients received prior systemic therapy for endometrial carcinoma: 69% had one, 28% had two, and 3% had three or more prior systemic therapies. 37% of patients received only prior neoadjuvant or adjuvant therapy.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures included ORR, as assessed by BICR using RECIST 1.1. At the pre-specified interim analysis, with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), the study demonstrated a statistically significant improvement in OS and PFS. The prespecified final OS analysis with approximately 16 months of additional follow-up duration from the interim analysis (overall median follow-up time of 14.7 months [range: 0.3 to 43.0 months]) was performed without multiplicity adjustment. Efficacy results by MMR subgroups were consistent with overall study results. PFS, ORR and response duration results at the interim analysis and OS results at final analysis are summarized in Table 33. Kaplan-Meier curves for final OS and interim PFS analyses are shown in Figures 43 and 44, respectively.

**Table 33: Efficacy Results in KEYNOTE-775**

| Endpoint                                   | KEYTRUDA<br>200 mg every 3 weeks<br>Lenvatinib<br>n=411 | Chemotherapy*<br><br>n=416 |
|--------------------------------------------|---------------------------------------------------------|----------------------------|
| <b>OS</b>                                  |                                                         |                            |
| Number (%) of patients with event          | 276 (67%)                                               | 329 (79%)                  |
| Median in months (95% CI)                  | 18.7 (15.6, 21.3)                                       | 11.9 (10.7, 13.3)          |
| Hazard ratio <sup>†</sup> (95% CI)         | 0.65 (0.55, 0.77)                                       |                            |
| p-Value <sup>‡</sup>                       | < 0.0001                                                |                            |
| <b>PFS<sup>§</sup></b>                     |                                                         |                            |
| Number (%) of patients with event          | 281 (68%)                                               | 286 (69%)                  |
| Median in months (95% CI)                  | 7.2 (5.7, 7.6)                                          | 3.8 (3.6, 4.2)             |
| Hazard ratio <sup>†</sup> (95% CI)         | 0.56 (0.47, 0.66)                                       |                            |
| p-Value <sup>‡</sup>                       | < 0.0001                                                |                            |
| <b>Objective response rate<sup>§</sup></b> |                                                         |                            |
| ORR <sup>§</sup> % (95% CI)                | 32% (27, 37)                                            | 15% (11, 18)               |
| Complete response                          | 7%                                                      | 3%                         |
| Partial response                           | 25%                                                     | 12%                        |
| p-Value <sup>¶</sup>                       | < 0.0001                                                |                            |
| <b>Response duration<sup>§</sup></b>       |                                                         |                            |
| Median in months <sup>#</sup> (range)      | 14.4 (1.6+, 23.7+)                                      | 5.7 (0.0+, 24.2+)          |

\* Doxorubicin or Paclitaxel

† Based on the stratified Cox regression model

‡ One-sided nominal p-Value for final analysis based on stratified log-rank test. At the pre-specified interim analysis of OS with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), statistically significant superiority was achieved for OS comparing the combination of pembrolizumab and lenvatinib with chemotherapy (HR: 0.62 [95% CI: 0.51, 0.75] p-Value < 0.0001)

§ At pre-specified interim analysis

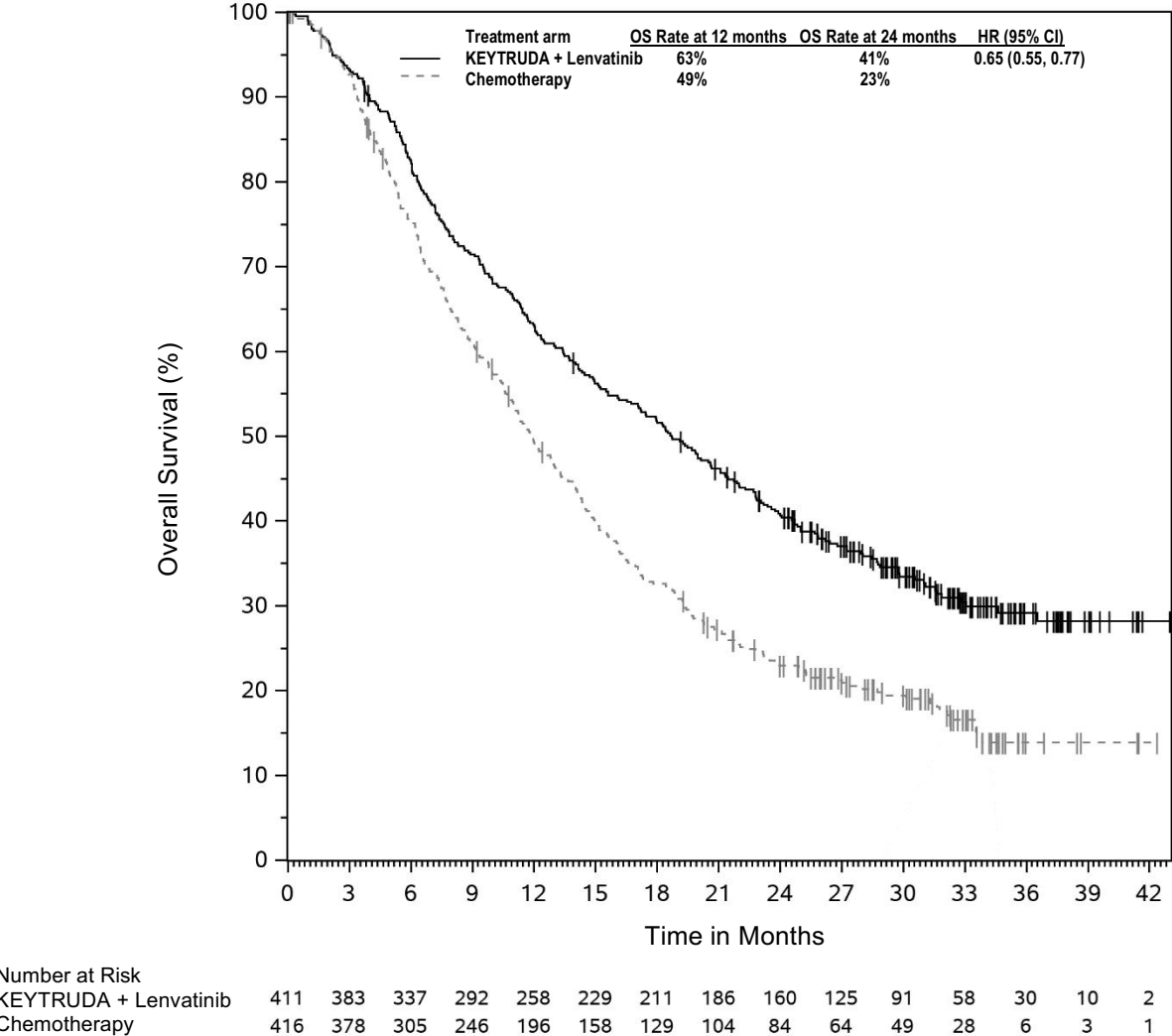
‡ One-sided p-Value based on stratified log-rank test

§ Response: Best objective response as confirmed complete response or partial response

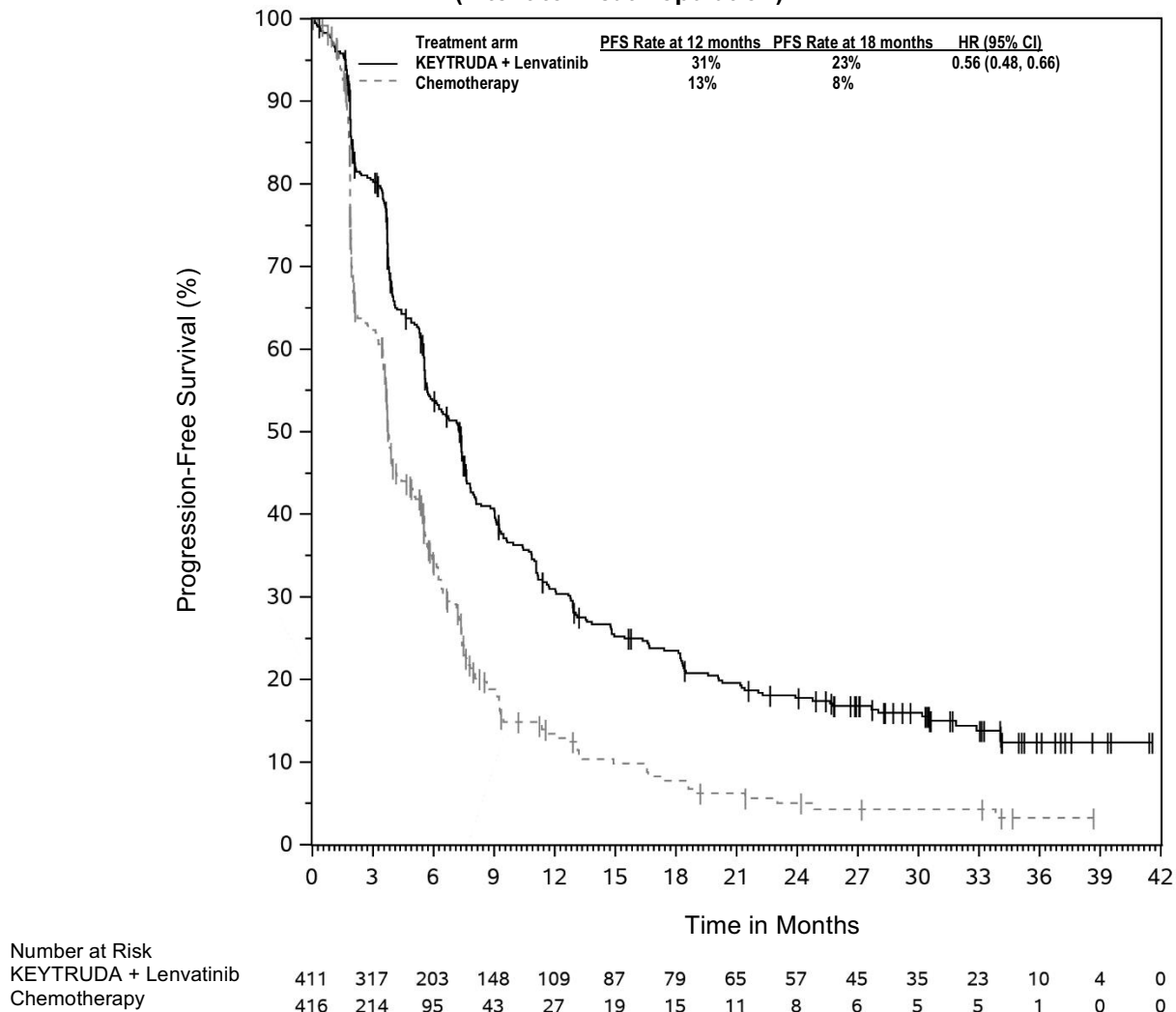
¶ Based on Miettinen and Nurminen method stratified by MMR Status, ECOG performance status, geographic region, and history of pelvic radiation

# Based on Kaplan-Meier estimation

Figure 43: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-775 (Intent to Treat Population)



**Figure 44: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-775 (Intent to Treat Population)**



### Esophageal Cancer

#### KEYNOTE-590: First-line treatment of locally advanced unresectable or metastatic Esophageal Cancer/Gastroesophageal Junction

The efficacy of KEYTRUDA was investigated in KEYNOTE-590, a multicenter, randomized, placebo-controlled trial that enrolled 749 patients as a first-line treatment in patients with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. Patients with active autoimmune disease, a medical condition that required immunosuppression, or known HER-2 positive GEJ adenocarcinoma patients were ineligible. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m<sup>2</sup> IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m<sup>2</sup> IV per day on Day 1

to Day 5 of each three-week cycle, or per local standard for 5-FU administration, for up to 24 months.

- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m<sup>2</sup> IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m<sup>2</sup> IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration, for up to 24 months.

Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue beyond the first RECIST v1.1-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks.

Among the 749 patients in KEYNOTE-590, 383 (51%) had tumours that expressed PD-L1 with a CPS  $\geq$  10. The baseline characteristics of these 383 patients were: median age of 63 years (range: 28 to 89), 41% age 65 or older; 82% male; 34% White and 56% Asian; 43% had an ECOG PS of 0 and 57% had an ECOG PS of 1. Ninety-three percent had M1 disease and 7% had M0 disease. Seventy-five percent had a tumor histology of squamous cell carcinoma, and 25% had adenocarcinoma.

The primary efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST 1.1 in squamous cell histology, CPS  $\geq$  10, and in all patients. The study demonstrated a statistically significant improvement in OS and PFS for all pre-specified study populations. In all patients randomized to KEYTRUDA in combination with chemotherapy, compared to chemotherapy the OS HR was 0.73 (95% CI 0.62-0.86) and the PFS HR was 0.65 (95% CI 0.55-0.76). Secondary efficacy outcome measures were ORR and duration of response, according to RECIST 1.1 as assessed by the investigator.

Table 34 summarizes the key efficacy measures from the pre-specified analysis in patients whose tumours expressed PD-L1 with a CPS  $\geq$  10 in KEYNOTE-590 performed at a median follow-up time of 13.5 months (range: 0.5 to 32.7 months). The Kaplan-Meier curves for OS and PFS are shown in Figures 45-50.

**Table 34: Efficacy Results for KEYTRUDA plus chemotherapy in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)**

| Endpoint                                      | KEYTRUDA<br>200 mg every 3 weeks<br><br>Cisplatin<br>5-FU<br>n=186 | Placebo<br><br>Cisplatin<br>5-FU<br>n=197 |
|-----------------------------------------------|--------------------------------------------------------------------|-------------------------------------------|
| <b>OS</b>                                     |                                                                    |                                           |
| Number (%) of patients with event             | 124 (66.7%)                                                        | 165 (83.8%)                               |
| Median in months* (95% CI)                    | 13.5 (11.1, 15.6)                                                  | 9.4 (8.0, 10.7)                           |
| Hazard ratio† (95% CI)                        | 0.62 (0.49, 0.78)                                                  |                                           |
| p-Value (stratified log-rank)                 | <0.0001                                                            |                                           |
| <b>PFS‡</b>                                   |                                                                    |                                           |
| Number (%) of patients with event             | 140 (75.3%)                                                        | 174 (88.3%)                               |
| Median in months* (95% CI)                    | 7.5 (6.2, 8.2)                                                     | 5.5 (4.3, 6.0)                            |
| Hazard ratio†(95% CI)                         | 0.51 (0.41, 0.65)                                                  |                                           |
| p-Value (stratified log-rank)                 | <0.0001                                                            |                                           |
| <b>Objective Response Rate‡</b>               |                                                                    |                                           |
| ORR % (95% CI)                                | 51.1% (43.7, 58.5)                                                 | 26.9% (20.8, 33.7)                        |
| Complete response rate                        | 5.9%                                                               | 2.5%                                      |
| Partial response rate                         | 45.2%                                                              | 24.4%                                     |
| p-Value (Miettinen-Nurminen)                  | <0.0001                                                            |                                           |
| <b>Response Duration†,§</b>                   |                                                                    |                                           |
| Median duration of response in months (range) | 10.4 (1.9, 28.9+)                                                  | 5.6 (1.5+, 25.0+)                         |
| % of patients with duration ≥6 months*        | 80.2%                                                              | 47.7%                                     |
| % of patients with duration ≥12 months*       | 43.7%                                                              | 23.2%                                     |
| % of patients with duration ≥18 months*       | 33.4%                                                              | 10.4%                                     |

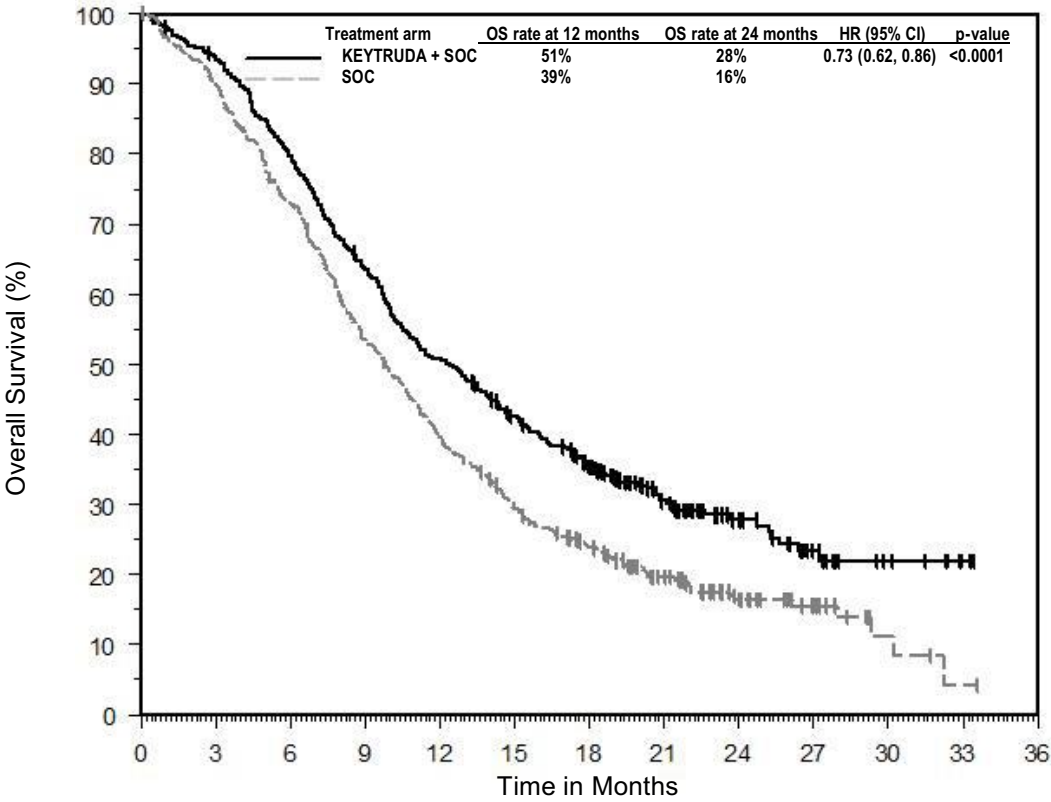
\* Based on Kaplan-Meier estimation

† Based on the stratified Cox proportional hazard model

‡ Assessed by investigator using RECIST 1.1

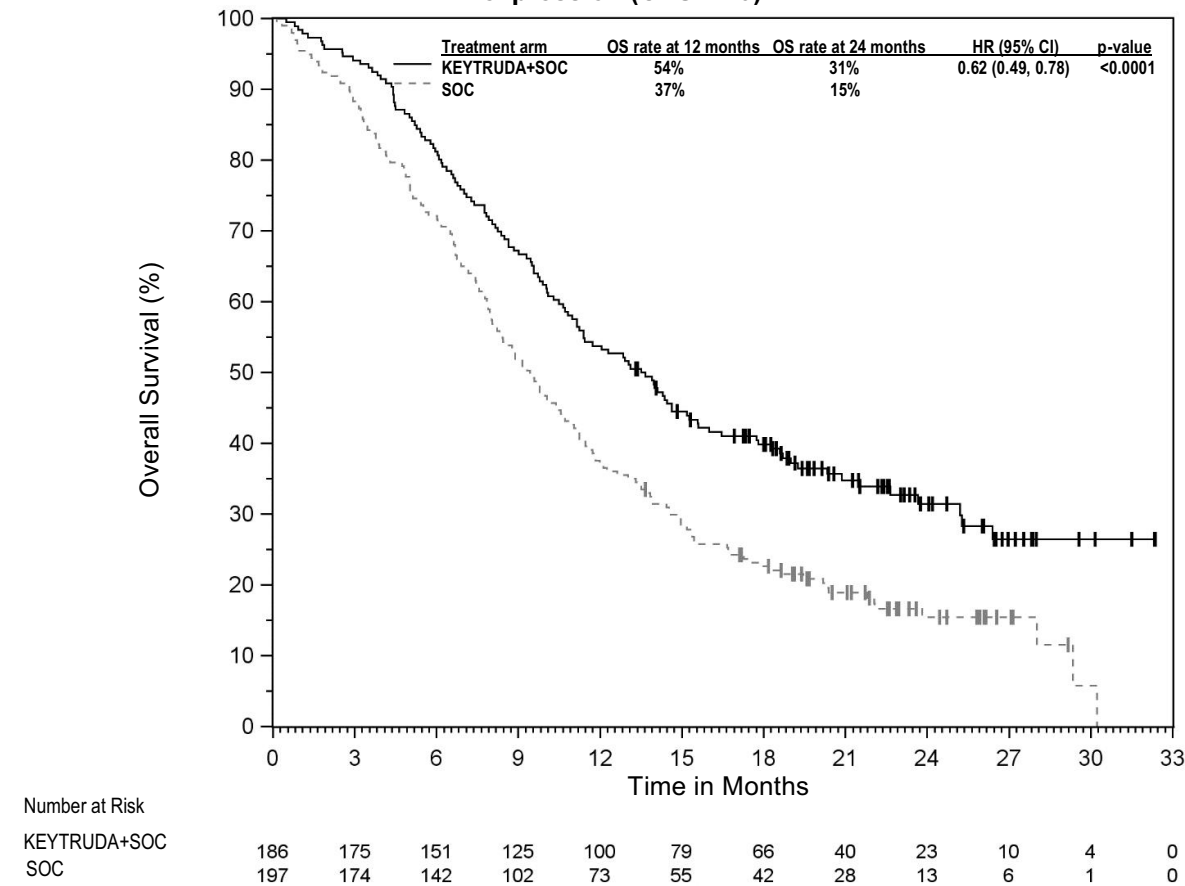
§ Based on patients with a best overall response as confirmed complete or partial response

Figure 45: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590

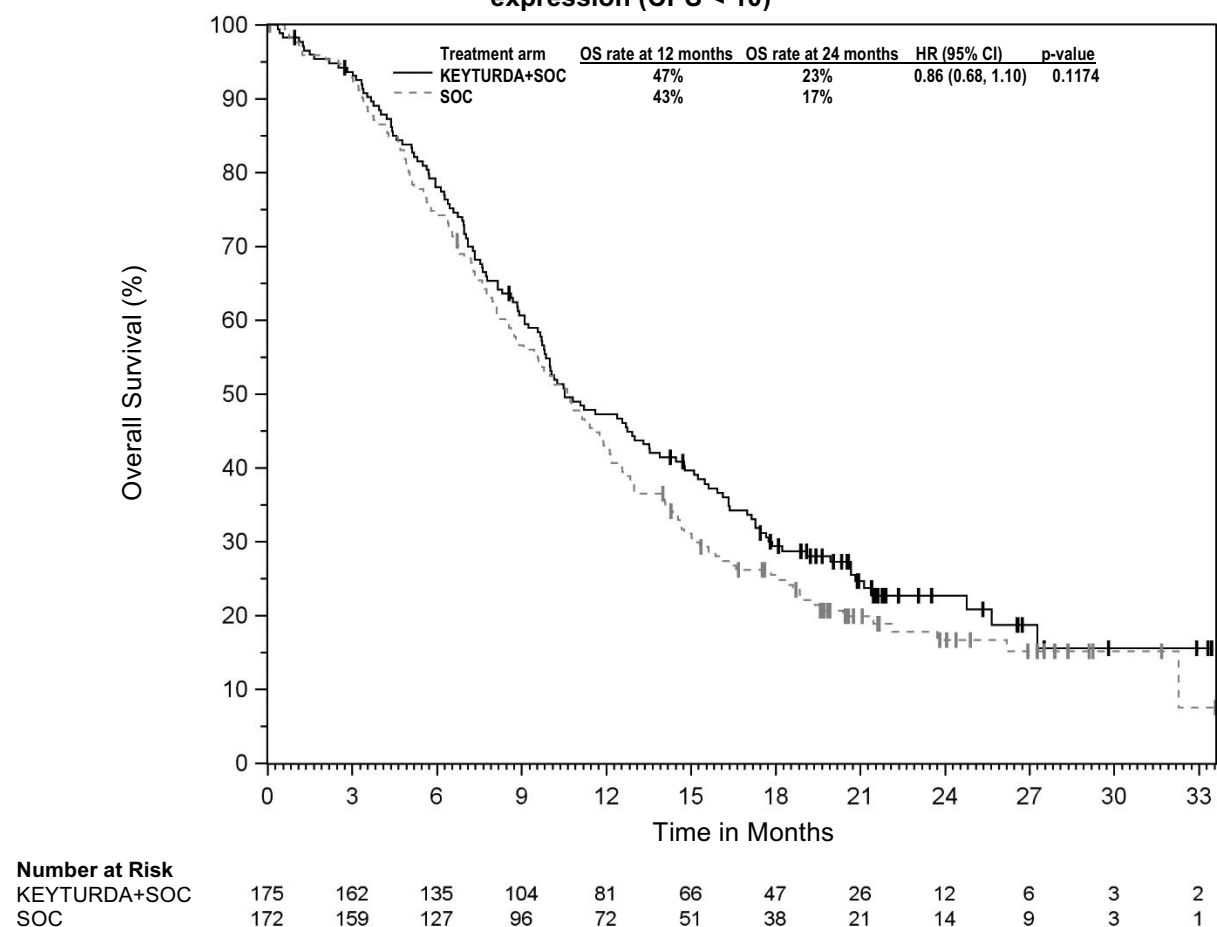


|                 |     |     |     |     |     |     |     |    |    |    |   |   |   |
|-----------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|---|---|---|
| Number at Risk  |     |     |     |     |     |     |     |    |    |    |   |   |   |
| KEYTRUDA + SOC: | 373 | 348 | 295 | 235 | 187 | 151 | 118 | 68 | 36 | 17 | 7 | 2 | 0 |
| SOC:            | 376 | 338 | 274 | 200 | 147 | 108 | 82  | 51 | 28 | 15 | 4 | 1 | 0 |

Figure 46: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)



**Figure 47: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS < 10)**



#### Exploratory Analysis

In patients with PD-L1 CPS<10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the KEYTRUDA arm and 10.6 months (95% CI: 8.8, 12.0) for the placebo arm, with an HR of 0.86 (95% CI: 0.68, 1.10).

Figure 48: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590

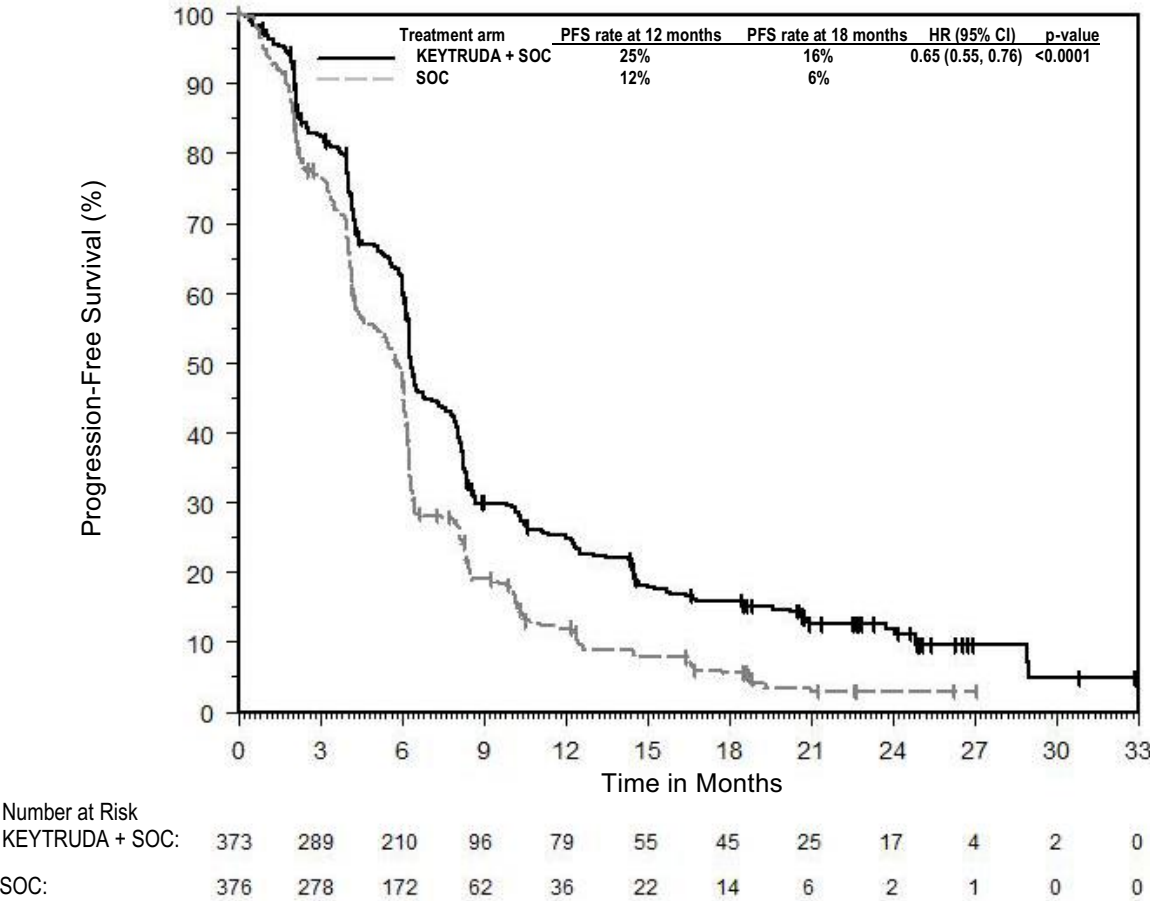
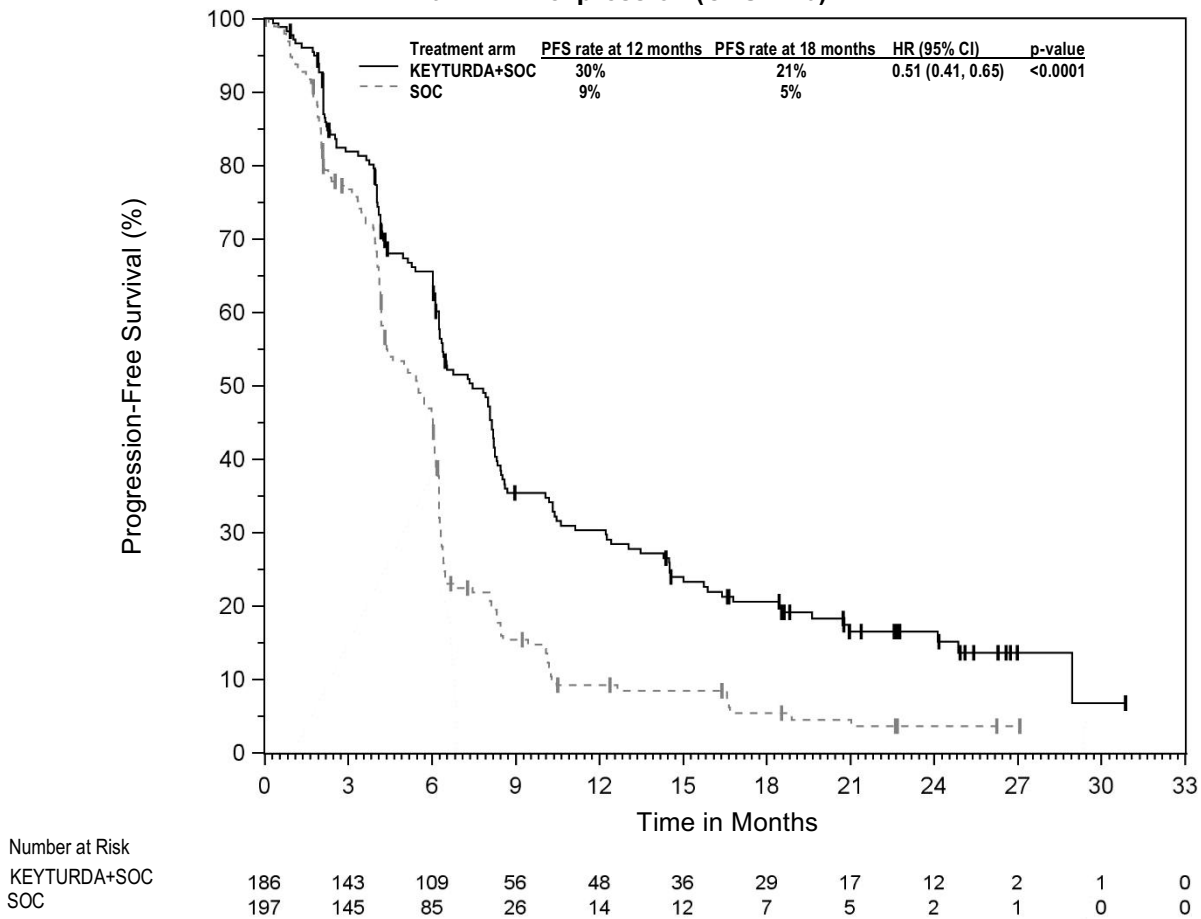
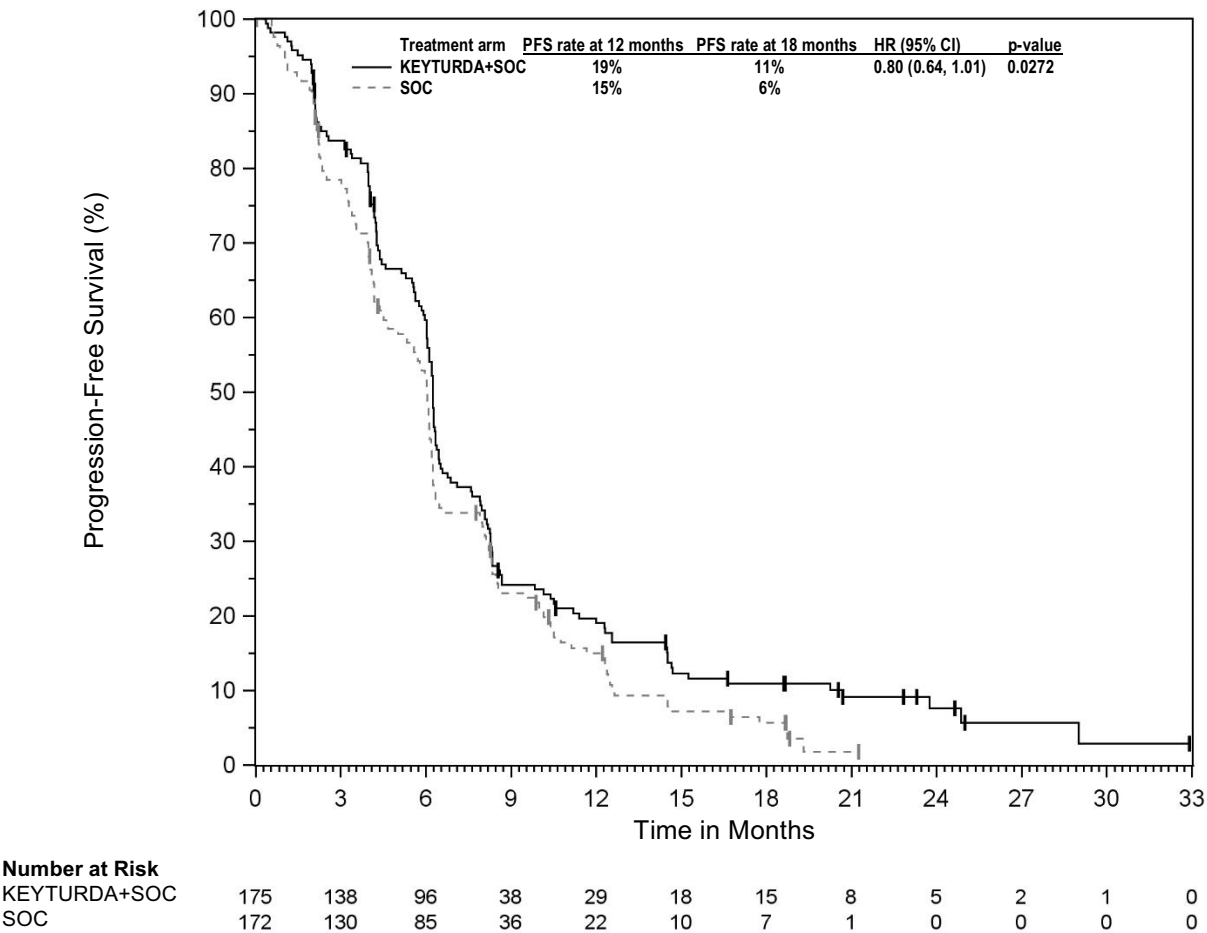


Figure 49: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)



**Figure 50: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS < 10)**



*Previously treated recurrent locally advanced or metastatic Esophageal Cancer*

**KEYNOTE-181: Controlled trial in esophageal cancer patients previously treated with systemic therapy**

The efficacy of KEYTRUDA was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Patients with HER2/neu positive esophageal cancer were required to have received treatment with approved HER2/neu targeted therapy. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive either KEYTRUDA 200 mg every 3 weeks or investigator's choice of any of the following chemotherapy regimens, all given intravenously: paclitaxel 80-100 mg/m<sup>2</sup> on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m<sup>2</sup> every 3 weeks, or irinotecan 180 mg/m<sup>2</sup> every 2 weeks. Randomization was stratified by tumor histology (esophageal squamous cell carcinoma [ESCC] vs. esophageal adenocarcinoma [EAC]/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Treatment with KEYTRUDA or chemotherapy continued until

unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue beyond the first RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measure was OS evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS  $\geq 10$ , and all randomized patients. Additional efficacy outcome measures were PFS, ORR, and DoR, according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

A total of 628 patients were enrolled and randomized to KEYTRUDA (n=314) or investigator's treatment of choice (n=314). Of these 628 patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS  $\geq 10$ . Of these 167 patients, 85 patients were randomized to KEYTRUDA and 82 patients to investigator's treatment of choice [paclitaxel (n=50), docetaxel (n=19), or irinotecan (n=13)]. The baseline characteristics of these 167 patients were: median age of 65 years (range: 33 to 80), 51% age 65 or older; 84% male; 32% White and 68% Asian; 38% had an ECOG PS of 0 and 62% had an ECOG PS of 1. Ninety percent had M1 disease and 10% had M0 disease. Prior to enrollment, 99% of patients had received platinum-based treatment and 84% had also received treatment with a fluoropyrimidine. Thirty-three percent of patients received prior treatment with a taxane.

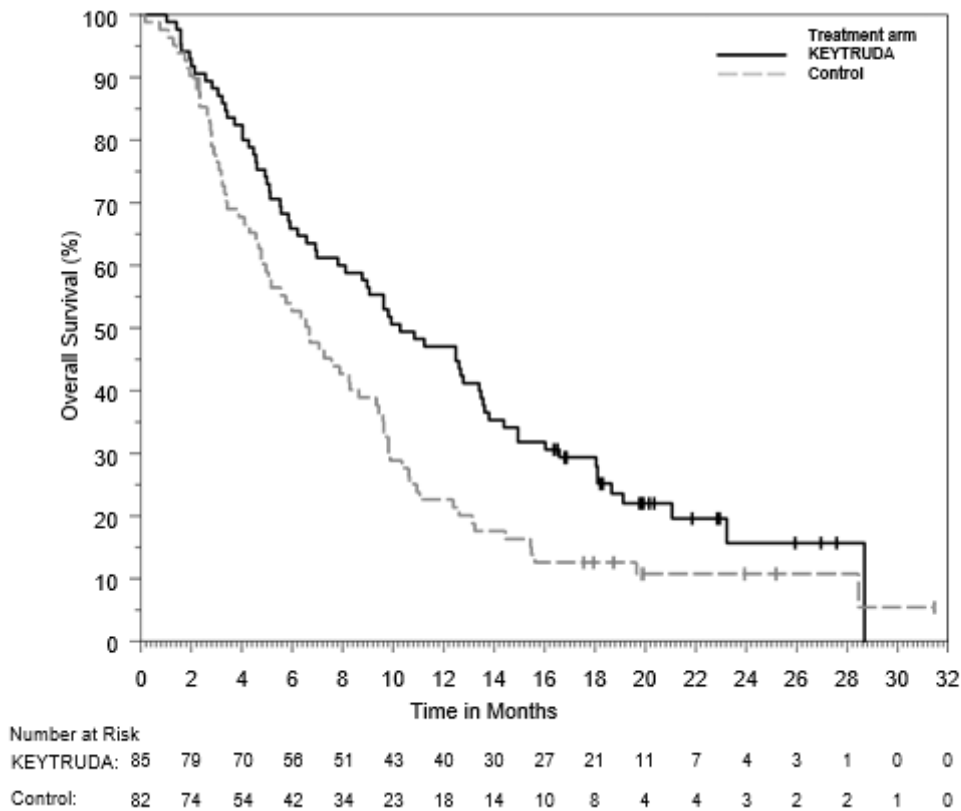
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS  $\geq 10$ , and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS  $\geq 10$ ), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 35 and Figure 51 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS  $\geq 10$ .

**Table 35: Efficacy Results in Patients with Recurrent or Metastatic ESCC (CPS  $\geq 10$ ) in KEYNOTE-181**

| Endpoint                                      | KEYTRUDA<br>200 mg every<br>3 weeks<br>n=85 | Chemotherapy<br><br>n=82 |
|-----------------------------------------------|---------------------------------------------|--------------------------|
| <b>OS</b>                                     |                                             |                          |
| Number (%) of patients with event             | 68 (80%)                                    | 72 (88%)                 |
| Median in months (95% CI)                     | 10.3 (7.0, 13.5)                            | 6.7 (4.8, 8.6)           |
| Hazard ratio* (95% CI)                        | 0.64 (0.46, 0.90)                           |                          |
| <b>PFS</b>                                    |                                             |                          |
| Number (%) of patients with event             | 76 (89%)                                    | 76 (93%)                 |
| Median in months (95% CI)                     | 3.2 (2.1, 4.4)                              | 2.3 (2.1, 3.4)           |
| Hazard ratio* (95% CI)                        | 0.66 (0.48, 0.92)                           |                          |
| <b>Objective Response Rate</b>                |                                             |                          |
| ORR (95% CI)                                  | 22 (14, 33)                                 | 7 (3, 15)                |
| Number (%) of complete responses              | 4 (5)                                       | 1 (1)                    |
| Number (%) of partial responses               | 15 (18)                                     | 5 (6)                    |
| Median duration of response in months (range) | 9.3 (2.1+, 18.8+)                           | 7.7 (4.3, 16.8+)         |

\* Based on the Cox regression model stratified by geographic region (Asia vs. ex-Asia)

**Figure 51: Kaplan-Meier Curve for Overall Survival in KEYNOTE-181 (ESCC CPS  $\geq 10$ )**



### Triple-Negative Breast Cancer

#### KEYNOTE-522: Controlled study of neoadjuvant and adjuvant treatment of patients with high-risk early-stage TNBC

The efficacy of KEYTRUDA in combination with carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide, given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in Study KEYNOTE-522, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were newly diagnosed previously untreated high-risk early-stage TNBC (tumor size  $>1$  cm but  $\leq 2$  cm in diameter with nodal involvement or tumor size  $>2$  cm in diameter regardless of nodal involvement), regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomization was stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

Patients were randomized (2:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- **Arm 1:**
  - Four cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
    - Carboplatin
      - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen  
**or** AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen **and**
    - Paclitaxel 80 mg/m<sup>2</sup> every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen

- Followed by four additional cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
    - Doxorubicin 60 mg/m<sup>2</sup> **or** epirubicin 90 mg/m<sup>2</sup> every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **and**
    - Cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
  - Following surgery, 9 cycles of KEYTRUDA 200 mg every 3 weeks were administered.
- **Arm 2:**
    - Four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
      - Carboplatin
        - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen **or** AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen **and**
      - Paclitaxel 80 mg/m<sup>2</sup> every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen
    - Followed by four additional cycles of preoperative placebo every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
      - Doxorubicin 60 mg/m<sup>2</sup> **or** epirubicin 90 mg/m<sup>2</sup> every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **and**
      - Cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
    - Following surgery, 9 cycles of placebo every 3 weeks were administered.

Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precludes definitive surgery, disease recurrence in the adjuvant phase, or unacceptable toxicity.

The major efficacy outcome measures were pCR rate and EFS. pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome measure was OS.

A total of 1174 patients were randomized: 784 patients to the KEYTRUDA arm and 390 patients to the placebo arm. The study population characteristics were: median age of 49 years (range: 22 to 80), 11% age 65 or older; 99.9% female; 64% White, 20% Asian, 5% Black, and 2% American Indian or Alaska Native; 87% ECOG PS of 0 and 13% ECOG PS of 1; 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumor 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 75% of patients were overall stage II and 25% were stage III.

The trial demonstrated a statistically significant improvement in pCR, EFS, and OS at pre-specified analyses for patients randomized to KEYTRUDA in combination with chemotherapy followed by KEYTRUDA monotherapy compared with patients randomized to placebo in combination with chemotherapy followed by placebo alone. Efficacy results are summarized in Table 36 and Figures 52 and 53.

**Table 36: Efficacy Results in Patients with High-Risk Early-Stage TNBC in KEYNOTE-522**

| Endpoint                                    | KEYTRUDA with chemotherapy/KEYTRUDA | Placebo with chemotherapy/Placebo |
|---------------------------------------------|-------------------------------------|-----------------------------------|
| <b>pCR (ypT0/Tis ypN0)*</b>                 | <b>n=401</b>                        | <b>n=201</b>                      |
| Number of patients with pCR                 | 260                                 | 103                               |
| pCR Rate (%), (95% CI)                      | 64.8 (59.9, 69.5)                   | 51.2 (44.1, 58.3)                 |
| Treatment difference (%) estimate (95% CI)† | 13.6 (5.4, 21.8)                    |                                   |
| p-Value                                     | 0.00055                             |                                   |
| <b>EFS‡</b>                                 | <b>n=784</b>                        | <b>n=390</b>                      |
| Number of patients with event (%)           | 123 (16%)                           | 93 (24%)                          |
| 24 month EFS rate (%), (95% CI)             | 88 (85, 90)                         | 81 (77, 85)                       |
| Hazard ratio (95% CI)§                      | 0.63 (0.48, 0.82)                   |                                   |
| p-Value¶                                    | 0.00031                             |                                   |
| <b>OS#</b>                                  | <b>n=784</b>                        | <b>n=390</b>                      |
| Number of patients with event (%)           | 115 (15%)                           | 85 (22%)                          |
| 36-month OS rate (%), (95% CI)              | 90 (87, 91)                         | 87 (83, 90)                       |
| 60-month OS rate (%), (95% CI)              | 87 (84, 89)                         | 82 (77, 85)                       |
| Hazard ratio (95% CI)§                      | 0.66 (0.50, 0.87)                   |                                   |
| p-Value¶                                    | 0.00150                             |                                   |

\* Based on a pre-specified pCR interim analysis (compared to a significance level of 0.003)

† Based on Miettinen and Nurminen method stratified by nodal status, tumor size, and choice of carboplatin

‡ Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052) with a median follow-up time of 37.8 months (range: 2.7 to 48 months)

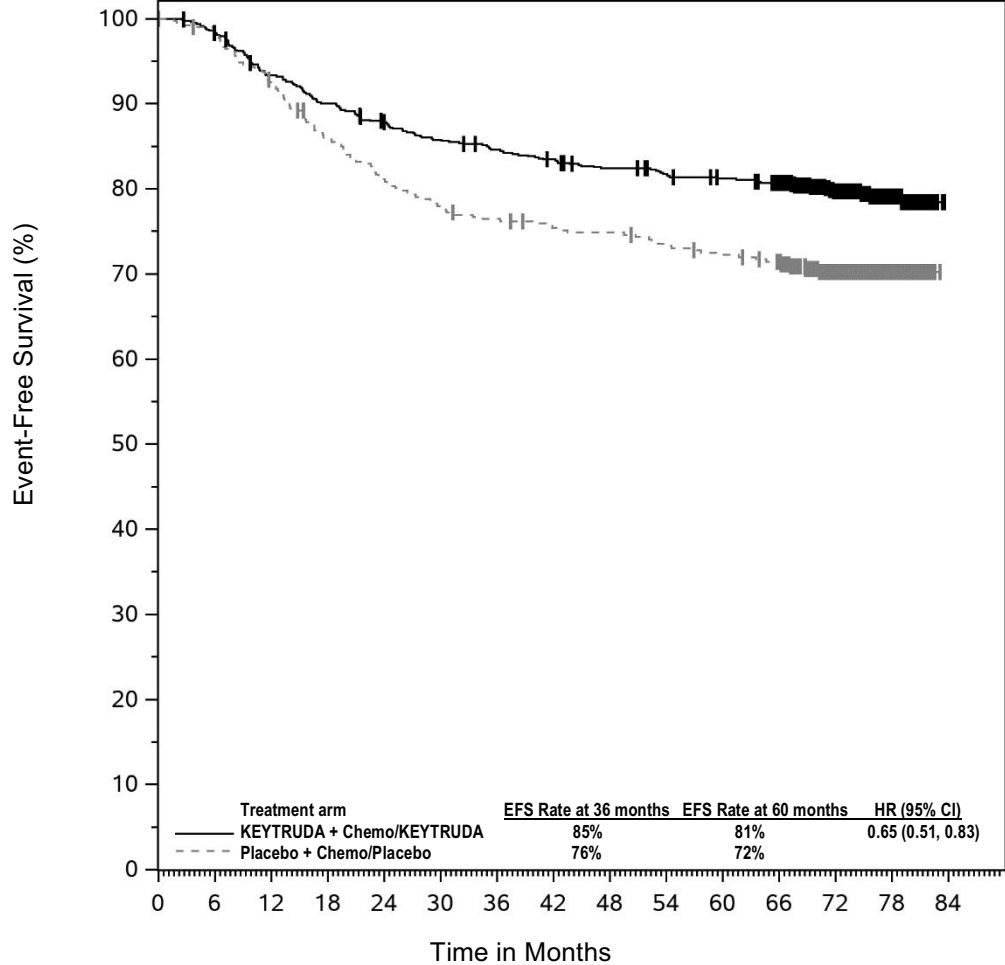
§ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status, tumor size, and choice of carboplatin

¶ Based on log-rank test stratified by nodal status, tumor size, and choice of carboplatin

# Based on a pre-specified OS interim analysis (compared to a significance level of 0.0050) with a median follow-up time was 73.1 months (range: 2.7 to 83.9 months)

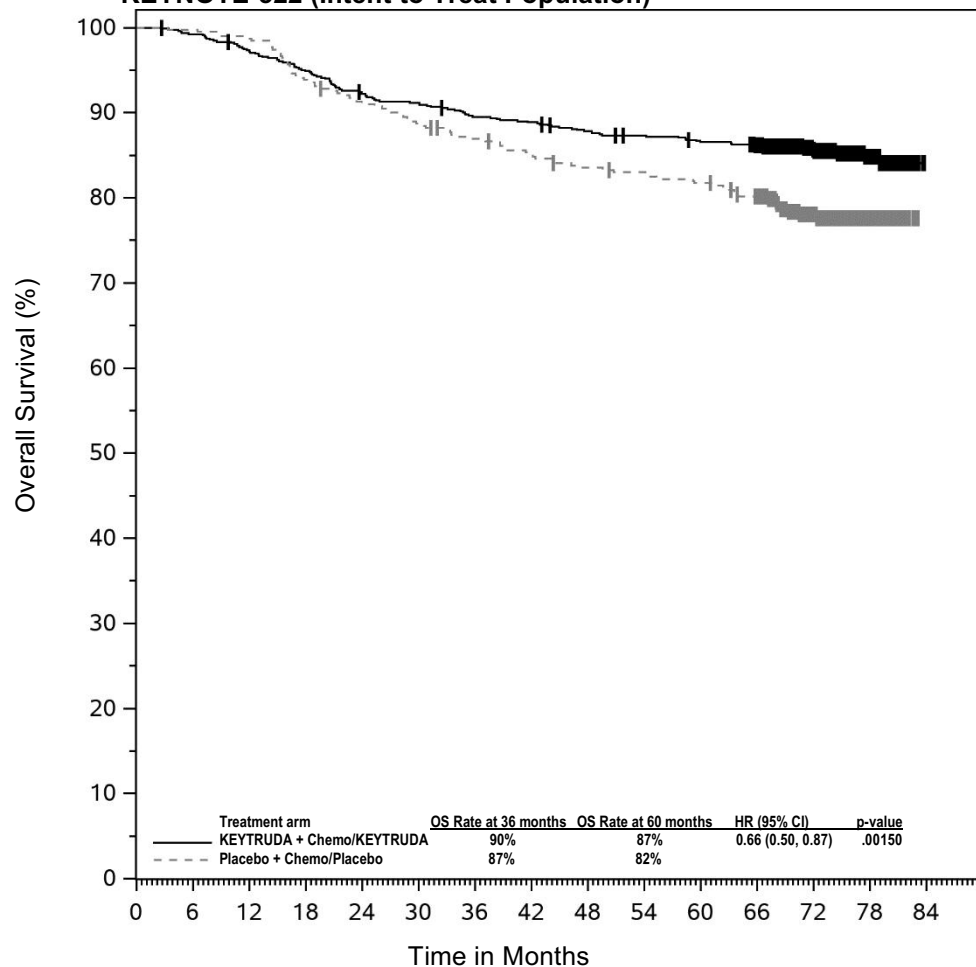
In a pre-specified interim analysis (median follow-up time was 73.1 months (range: 2.7 to 83.9 months), the EFS HR was 0.65 (95% CI: 0.51, 0.83). The 36-month EFS rates were 85% (95% CI: 82, 87) in the KEYTRUDA arm and 76% (95% CI: 72, 80) in the placebo arm. The 60-month EFS rates were 81% (95% CI: 78, 84) in the KEYTRUDA arm and 72% (95% CI: 67, 76) in the placebo arm.

Figure 52: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



|                           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |   |  |  |  |  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|--|--|--|--|
| Number at Risk            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |   |  |  |  |  |
| KEYTRUDA + Chemo/KEYTRUDA | 784 | 769 | 728 | 702 | 681 | 665 | 654 | 644 | 633 | 625 | 618 | 602 | 409 | 164 | 0 |  |  |  |  |
| Placebo + Chemo/Placebo   | 390 | 382 | 358 | 330 | 312 | 300 | 293 | 287 | 285 | 278 | 273 | 264 | 178 | 76  | 0 |  |  |  |  |

**Figure 53: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)**



|                           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |   |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|
| Number at Risk            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |   |
| KEYTRUDA + Chemo/KEYTRUDA | 784 | 777 | 760 | 742 | 720 | 712 | 698 | 693 | 683 | 677 | 670 | 656 | 448 | 176 | 0 |
| Placebo + Chemo/Placebo   | 390 | 389 | 385 | 366 | 354 | 345 | 336 | 328 | 321 | 318 | 313 | 300 | 199 | 82  | 0 |

**KEYNOTE-355: Controlled study of combination therapy in patients with locally recurrent unresectable or metastatic TNBC**

The efficacy of KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin was investigated in Study KEYNOTE-355, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, and which had not been previously treated with chemotherapy. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomization was stratified by chemotherapy treatment (paclitaxel or nab-paclitaxel vs. gemcitabine and carboplatin), tumor PD-L1 expression (CPS  $\geq 1$  vs. CPS  $< 1$ ) based on the PD-L1 IHC 22C3 pharmDx™ kit, and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no).

Patients were randomized (2:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA 200 mg on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m<sup>2</sup> on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m<sup>2</sup> on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

- Placebo on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m<sup>2</sup> on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m<sup>2</sup> on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m<sup>2</sup> and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Treatment with KEYTRUDA or placebo continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter.

The major efficacy outcome measure were OS and PFS as assessed by BICR using RECIST 1.1, in patients with tumor PD-L1 expression CPS  $\geq 10$ . Additional efficacy outcome measures were ORR, DOR, and DCR (stable disease for at least 24 weeks, or complete response, or partial response) in patients with tumor PD-L1 expression CPS  $\geq 10$  as assessed by BICR using RECIST 1.1.

A total of 847 patients were randomized: 566 patients to the KEYTRUDA arm and 281 patients to the placebo arm. The study population characteristics were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy-five percent of the patients had tumor PD-L1 expression defined as CPS  $\geq 1$  and 38% had tumor PD-L1 expression CPS  $\geq 10$ .

In KEYNOTE-355, there was a statistically significant improvement in OS and PFS in patients with tumor PD-L1 expression CPS  $\geq 10$  randomized to KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin compared with patients randomized to placebo in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin. The trial also demonstrated a clinically meaningful improvement in ORR and DoR.

Efficacy results are summarized in Table 37 and Figures 54 and 55.

**Table 37: Efficacy Results for Patients with TNBC with PD-L1 Expression CPS ≥10**

| Endpoint                          | KEYTRUDA<br>with chemotherapy*<br>n=220 | Placebo<br>with chemotherapy*<br>n=103 |
|-----------------------------------|-----------------------------------------|----------------------------------------|
| OS†                               |                                         |                                        |
| Number of patients with event (%) | 155 (70%)                               | 84 (82%)                               |
| Median in months (95% CI)         | 23.0 (19.0, 26.3)                       | 16.1 (12.6, 18.8)                      |
| Hazard ratio‡ (95% CI)            | 0.73 (0.55, 0.95)                       |                                        |
| p-Value§                          | 0.0093                                  |                                        |
| 24-month OS rate (%) (95% CI)     | 48.2 (41.4, 54.6)                       | 34.0 (25.0, 43.1)                      |
| PFS¶, #                           |                                         |                                        |
| Number of patients with event (%) | 136 (62%)                               | 79 (77%)                               |
| Median in months (95% CI)         | 9.7 (7.6, 11.3)                         | 5.6 (5.3, 7.5)                         |
| Hazard ratio‡ (95% CI)            | 0.65 (0.49, 0.86)                       |                                        |
| p-Value§                          | 0.0012                                  |                                        |
| Objective Response Rate¶, #       |                                         |                                        |
| ORR, (95% CI)                     | 53% (46, 59)                            | 41% (31, 51)                           |
| Complete response                 | 17%                                     | 14%                                    |
| Partial response                  | 35%                                     | 27%                                    |
| Response Duration¶, #             |                                         |                                        |
| Median in months (95% CI)         | 12.8 (9.9, 25.9)                        | 7.3 (5.5, 15.4)                        |
| % with duration ≥6 monthsβ        | 82%                                     | 60%                                    |
| % with duration ≥12 monthsβ       | 56%                                     | 38%                                    |

\* Chemotherapy: paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin

<sup>†</sup> Based on the pre-specified final analysis

<sup>‡</sup> Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no)

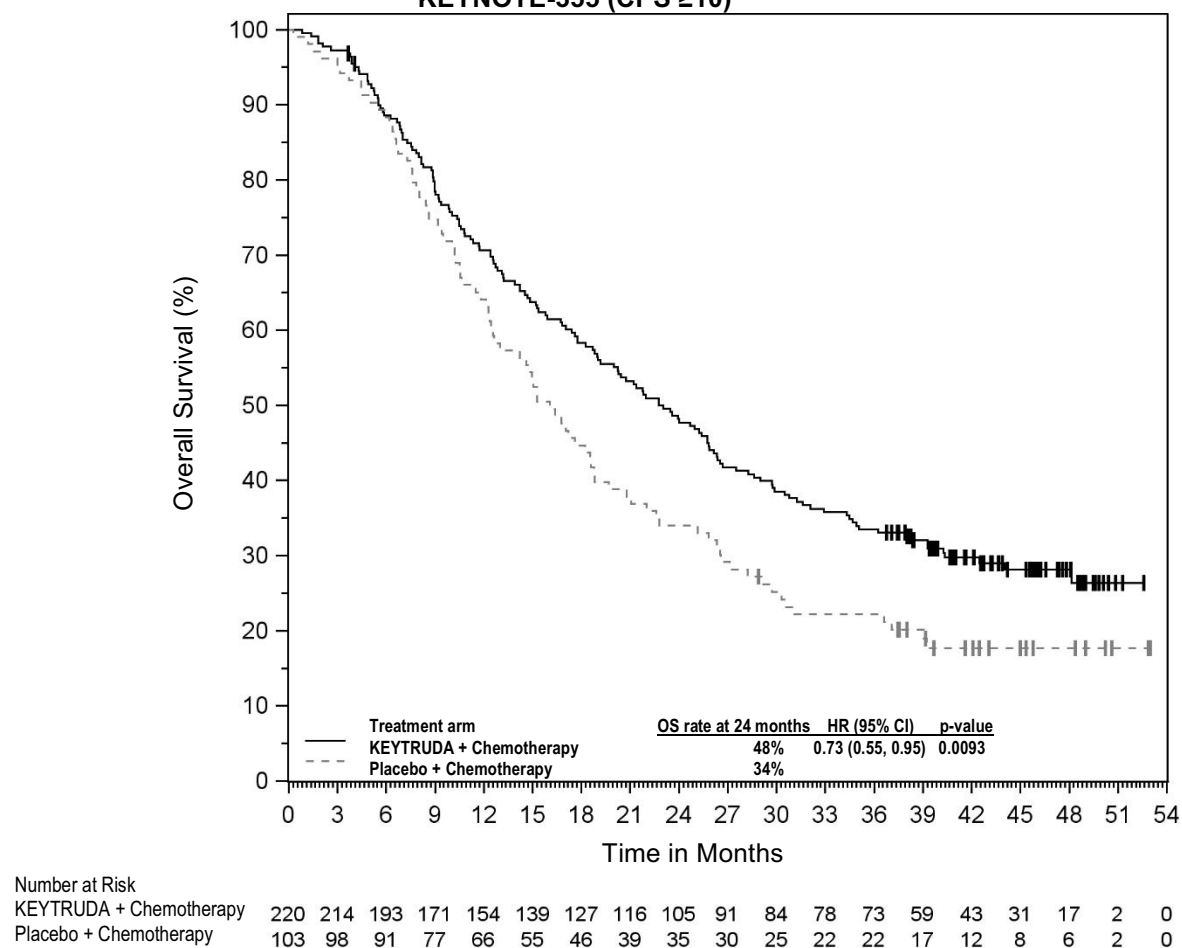
<sup>§</sup> One-sided p-Value based on log-rank test stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no)

<sup>¶</sup> Assessed by BICR using RECIST 1.1

<sup>#</sup> Based on a pre-specified interim analysis

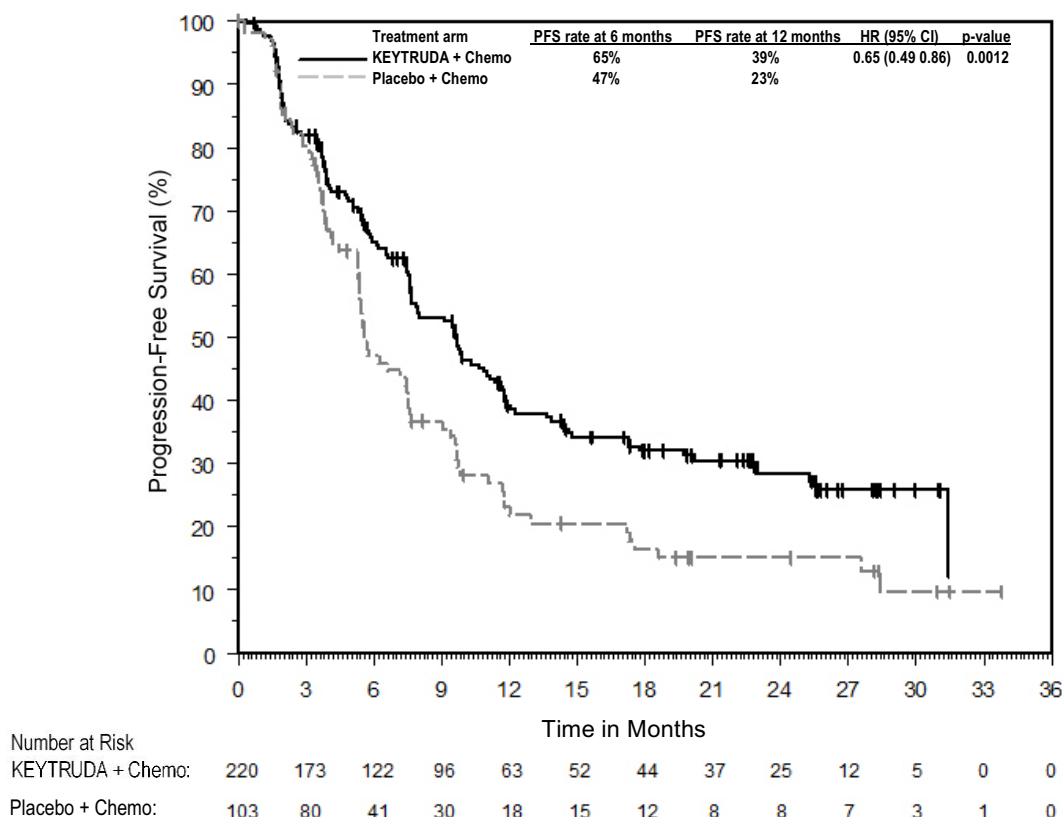
<sup>β</sup> From product-limit (Kaplan-Meier) method for censored data

Figure 54: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-355 (CPS ≥10)\*



\*Based on the pre-specified final analysis

**Figure 55: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-355 (CPS ≥10)\***



\*Based on a pre-specified interim analysis

The impact of the addition of KEYTRUDA to chemotherapy on patient-reported outcomes were assessed using the EORTC QLQ-C30, EORTC QLQ-BR23 and EuroQol EQ-5D. Results from each measure showed that the addition of KEYTRUDA to chemotherapy did not result in a decrease in health-related quality of life through 15 weeks of follow-up.

### Gastric Cancer

#### KEYNOTE-859: Controlled trial of combination therapy in HER2-negative gastric cancer patients naïve to treatment

The efficacy of KEYTRUDA in combination with fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-859, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 patients with HER2-negative advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Prior neoadjuvant and/or adjuvant therapy was allowed if it was completed at least 6 months prior to randomization. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression or patients who had received prior treatment with immune checkpoint inhibitors were ineligible. Randomization was stratified by PD-L1 expression (CPS ≥1 or <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/ Israel/ North America/ Australia, Asia or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week cycle:

- KEYTRUDA 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m<sup>2</sup> and 5-FU 800 mg/m<sup>2</sup>/day for 5 days (FP) or oxaliplatin 130 mg/m<sup>2</sup> and capecitabine 1000 mg/m<sup>2</sup> bid for

14 days (CAPOX) for up to 35 cycles. Duration of cisplatin or oxaliplatin treatment could be capped at 6 cycles as per local country guidelines. KEYTRUDA was administered prior to chemotherapy on Day 1 of each cycle.

- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m<sup>2</sup> and 5-FU 800 mg/m<sup>2</sup>/day for 5 days (FP) or oxaliplatin 130 mg/m<sup>2</sup> and capecitabine 1000 mg/m<sup>2</sup> bid for 14 days (CAPOX) for up to 35 cycles. Duration of cisplatin or oxaliplatin treatment could be capped at 6 cycles as per local country guidelines. Placebo was administered prior to chemotherapy on Day 1 of each cycle.

Treatment with KEYTRUDA and chemotherapy or placebo and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Assessment of tumor status was performed every 6 weeks.

Among the 1,579 patients in KEYNOTE-859, 1,235 (78%) had tumours that expressed PD-L1 with a CPS  $\geq 1$  based on the PD-L1 IHC 22C3 pharmDx™ kit. The baseline characteristics of the 1,235 patients with tumour PD-L1 expression CPS  $\geq 1$  included: median age of 62 years (range: 24 to 86), 40% age 65 or older; 70.4% male; 55.5% White; 33.1% Asian; 36.5% ECOG PS of 0 and 63.5% ECOG PS of 1. Ninety-six percent of patients had metastatic disease (stage IV) and 4% had locally advanced unresectable disease. Five percent (n=66) had tumours that were MSI-H. Eighty-six percent of patients received CAPOX.

The primary efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DOR as assessed by BICR using RECIST v1.1.

The study demonstrated a statistically significant improvement in OS (HR 0.78; 95% CI 0.70, 0.87; p-Value < 0.0001), PFS (HR 0.76; 95% CI 0.67, 0.85; p-Value < 0.0001) and ORR (51% [95% CI 47.7, 54.8] vs 42% [95% CI 38.5, 45.5]; p-Value 0.00009) in patients randomized to KEYTRUDA in combination with chemotherapy compared with placebo in combination with chemotherapy in the overall population. The median follow-up time was 12 months (range: 0.1 to 45.9 months). Table 38 summarizes key efficacy results for the pre-specified subgroup of patients whose tumors expressed PD-L1 with a CPS  $\geq 1$  and Figures 56 and 57 show the Kaplan-Meier curves for OS and PFS.

**Table 38: Efficacy Results for KEYNOTE-859 for patients with PD-L1 expression (CPS ≥ 1)**

| <b>Endpoint</b>                    | <b>KEYTRUDA<br/>200 mg every 3 weeks<br/>Fluoropyrimidine and<br/>Platinum<br/>Chemotherapy<br/>n=618</b> | <b>Placebo<br/>Fluoropyrimidine and<br/>Platinum<br/>Chemotherapy<br/>n=617</b> |
|------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| <b>OS</b>                          |                                                                                                           |                                                                                 |
| Number (%) of patients with event  | 464 (75%)                                                                                                 | 526 (85%)                                                                       |
| Median in months* (95% CI)         | 13.0 (11.6, 14.2)                                                                                         | 11.4 (10.5, 12.0)                                                               |
| Hazard ratio <sup>†</sup> (95% CI) | 0.74 (0.65, 0.84)                                                                                         |                                                                                 |
| p-Value <sup>‡</sup>               | <0.0001                                                                                                   |                                                                                 |
| <b>PFS</b>                         |                                                                                                           |                                                                                 |
| Number (%) of patients with event  | 443 (72%)                                                                                                 | 483 (78%)                                                                       |
| Median in months* (95% CI)         | 6.9 (6.0, 7.2)                                                                                            | 5.6 (5.4, 5.7)                                                                  |
| Hazard ratio <sup>†</sup> (95% CI) | 0.72 (0.63, 0.82)                                                                                         |                                                                                 |
| p-Value <sup>‡</sup>               | <0.0001                                                                                                   |                                                                                 |
| <b>Objective Response Rate</b>     |                                                                                                           |                                                                                 |
| ORR <sup>§</sup> (95% CI)          | 52% (48.1, 56.1)                                                                                          | 43% (38.7, 46.6)                                                                |
| Complete response rate             | 10%                                                                                                       | 6%                                                                              |
| Partial response rate              | 42%                                                                                                       | 37%                                                                             |
| p-Value <sup>¶</sup>               | 0.00041                                                                                                   |                                                                                 |
| <b>Response Duration</b>           |                                                                                                           |                                                                                 |
| Median in months (range)           | 8.3 (1.2+ - 41.5+)                                                                                        | 5.6 (1.3+ - 34.2+)                                                              |
| % with duration ≥ 12 months*       | 41%                                                                                                       | 26%                                                                             |

\* Based on Kaplan-Meier estimation

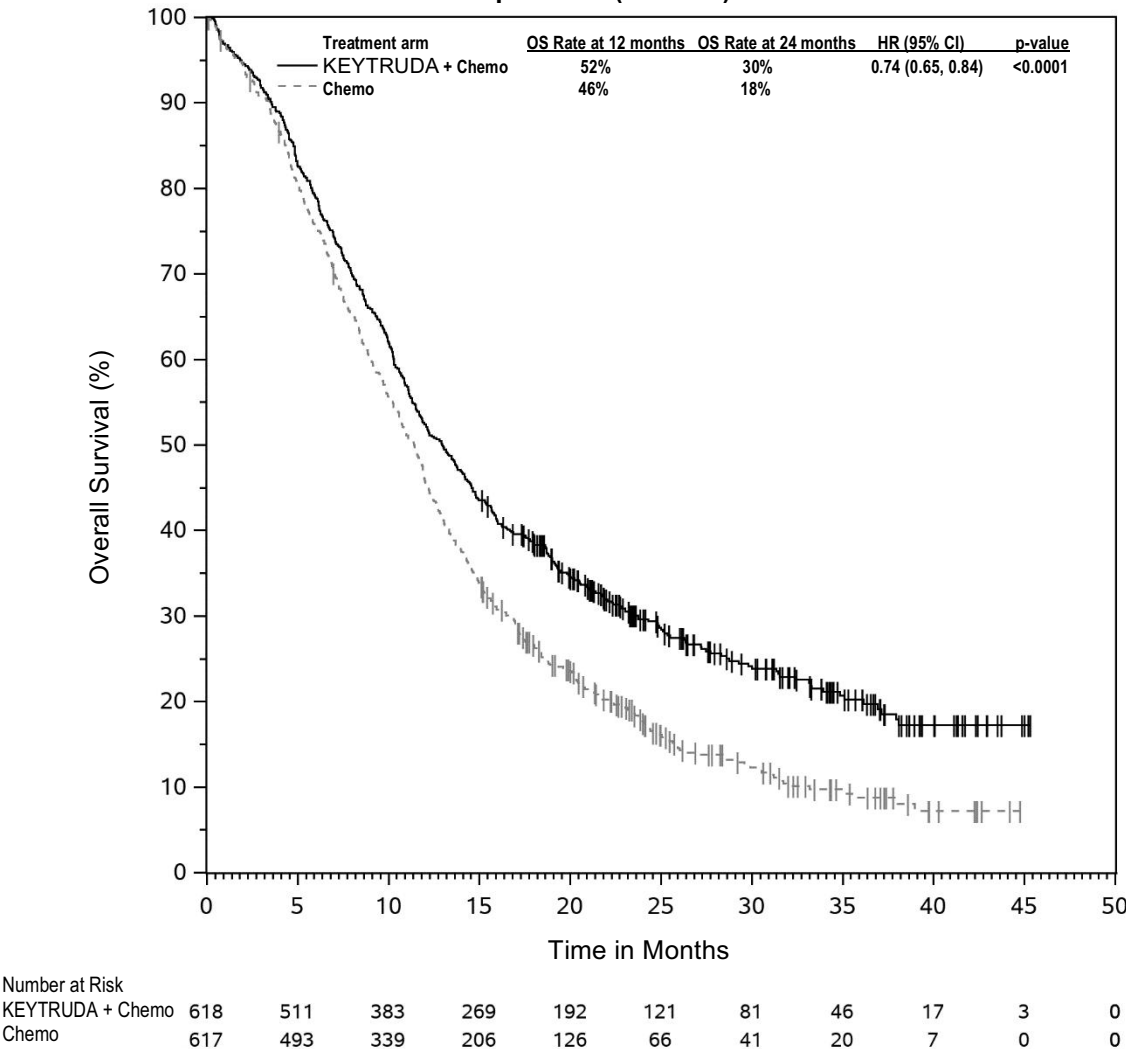
† Based on the stratified Cox proportional hazard model

‡ One-sided p-Value based on stratified log-rank test

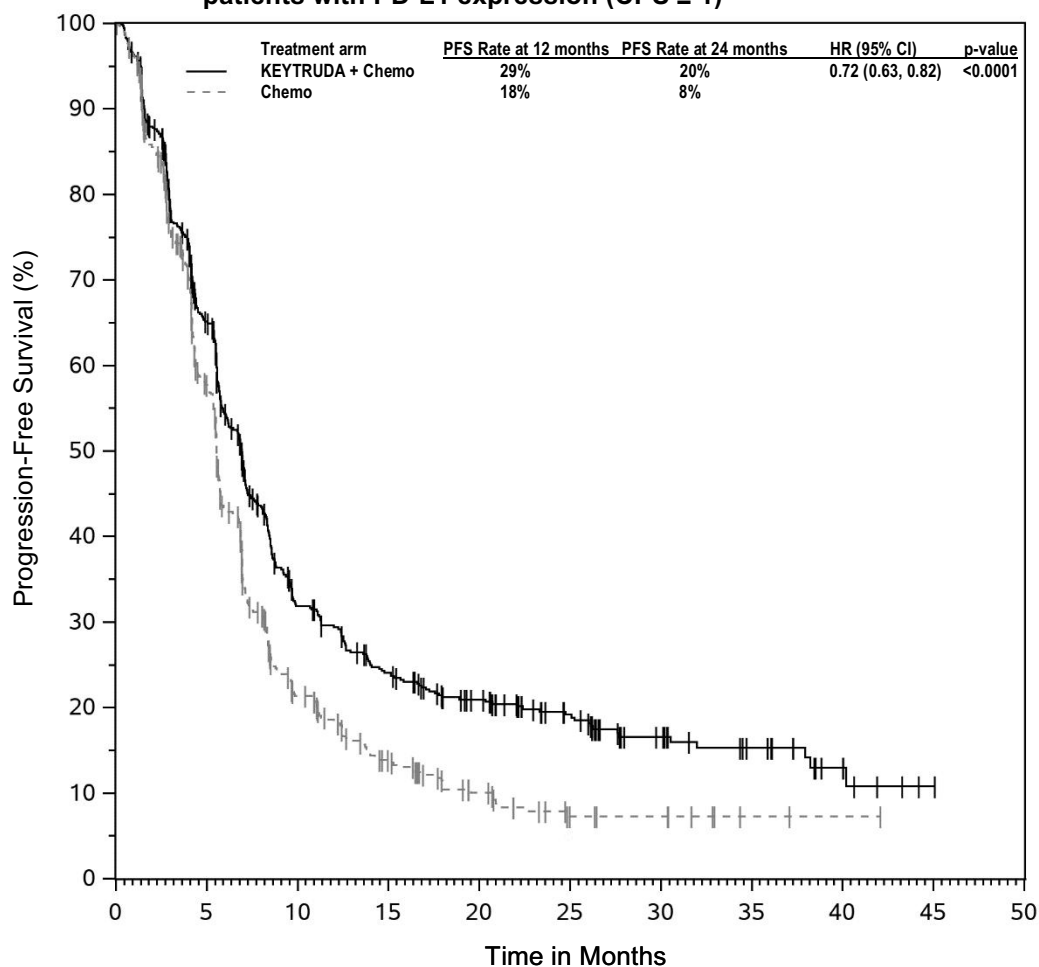
§ Response: Best objective response as confirmed complete response or partial response

¶ One-sided p-Value based on stratified Miettinen & Nurminen method

**Figure 56: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859 patients with PD-L1 expression (CPS ≥ 1)**



**Figure 57: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-859 patients with PD-L1 expression (CPS ≥ 1)**



**Number at Risk**

|                  |     |     |     |     |    |    |    |    |   |   |   |
|------------------|-----|-----|-----|-----|----|----|----|----|---|---|---|
| KEYTRUDA + Chemo | 618 | 356 | 156 | 112 | 82 | 57 | 33 | 21 | 8 | 1 | 0 |
| Chemo            | 617 | 317 | 97  | 51  | 26 | 11 | 8  | 2  | 1 | 0 | 0 |

An analysis was performed in KEYNOTE-859 in patients whose tumors expressed PD-L1 with a CPS ≥ 1 to < 10 or CPS ≥ 10 in both arms (see Table 39).

**Table 39: Efficacy results by PD-L1 expression in KEYNOTE-859**

| Endpoint        | KEYTRUDA combination therapy<br>n=337 | Chemotherapy<br>n=345 | KEYTRUDA combination therapy<br>n=279 | Chemotherapy<br>n=272 |
|-----------------|---------------------------------------|-----------------------|---------------------------------------|-----------------------|
|                 | <b>CPS ≥ 1 to &lt; 10</b>             |                       | <b>CPS ≥ 10</b>                       |                       |
| OS HR (95% CI)  | 0.83 (0.70, 0.98)*                    |                       | 0.65 (0.53, 0.79)†                    |                       |
| PFS HR (95% CI) | 0.83 (0.70, 0.99)*                    |                       | 0.62 (0.51, 0.76)†                    |                       |
| ORR§ (95% CI)   | 45% (39.7, 50.6)                      | 42% (37.0, 47.7)      | 61% (54.6, 66.3)                      | 43% (37.1, 49.1)      |

\* Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on unstratified Cox proportional hazard model

† Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on stratified Cox proportional hazard model

§ Response: Best objective response as confirmed complete response or partial response

KEYNOTE-811: First-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma

The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 698 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS  $\geq 1$  or  $< 1$ ), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/ Israel/ North America/ Australia, Asia or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week cycle:

- KEYTRUDA 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m<sup>2</sup> for up to 6 cycles and 5-FU 800 mg/m<sup>2</sup>/day for 5 days (FP) or oxaliplatin 130 mg/m<sup>2</sup> up to 6-8 cycles and capecitabine 1000 mg/m<sup>2</sup> bid for 14 days (CAPOX). KEYTRUDA was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.
- Placebo, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m<sup>2</sup> for up to 6 cycles and 5-FU 800 mg/m<sup>2</sup>/day for 5 days (FP) or oxaliplatin 130 mg/m<sup>2</sup> up to 6-8 cycles and capecitabine 1000 mg/m<sup>2</sup> bid for 14 days (CAPOX). Placebo was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.

Treatment with KEYTRUDA, trastuzumab and chemotherapy or placebo, trastuzumab and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Treatment was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Assessment of tumor status was performed every 6 weeks.

Among the 698 patients randomized in KEYNOTE-811, 594 (85%) had tumors that expressed PD-L1 with a CPS  $\geq 1$ . PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. The population characteristics of these 594 patients were: median age of 63 years (range: 19 to 85), 43% age 65 or older; 80% male; 63% White, 33% Asian, and 0.7 % Black; 42% ECOG PS of 0 and 58% ECOG PS of 1. Ninety-eight percent of patients had metastatic disease (stage IV) and 2% had locally advanced unresectable disease. Ninety-five percent (n=562) had tumors that were not MSI-H, 1% (n=8) had tumors that were MSI-H, and in 4% (n=24) the status was not known. Eighty-five percent of patients received CAPOX.

The primary efficacy outcome measures were PFS, based on BICR using RECIST 1.1, and OS. Secondary efficacy outcome measures included ORR and DoR, based on BICR using RECIST 1.1.

In the overall population, a statistically significant improvement in OS (HR 0.80; 95% CI 0.67, 0.94; p-Value=0.004), at final analysis, and PFS (HR 0.72; 95% CI 0.60, 0.87; p-Value=0.0002), at a pre-specified interim analysis, was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy.

At a pre-specified interim analysis conducted on the first 264 patients randomized in the overall population (133 patients in the KEYTRUDA arm and 131 in the placebo arm), a statistically significant improvement in the objective response rate (74.4% vs 51.9%, representing a 22.7% difference; 95% CI (11.2, 33.7); p-Value<0.0001) was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy.

A pre specified subgroup analysis indicated that adding KEYTRUDA to trastuzumab and chemotherapy demonstrated a greater benefit in the population of patients whose tumors express PD-L1 with a CPS of  $\geq 1$ .

Efficacy results at the final analysis for the pre-specified subgroup of patients whose tumors expressed PD-L1 with a CPS  $\geq 1$  are summarized in Table 40 and Figures 58 and 59.

**Table 40: Efficacy Results for KEYNOTE-811 with PD-L1 Expression CPS  $\geq 1$**

| <b>Endpoint</b>                               | <b>KEYTRUDA<br/>200 mg every<br/>3 weeks<br/>Trastuzumab<br/>Fluoropyrimidine<br/>and Platinum<br/>Chemotherapy<br/>n=298</b> | <b>Placebo<br/><br/>Trastuzumab<br/>Fluoropyrimidine and<br/>Platinum<br/>Chemotherapy<br/>n=296</b> |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| <b>OS</b>                                     |                                                                                                                               |                                                                                                      |
| Number (%) of patients with event             | 226 (76%)                                                                                                                     | 244 (82%)                                                                                            |
| Median in months (95% CI)                     | 20.1 (17.9, 22.9)                                                                                                             | 15.7 (13.5, 18.5)                                                                                    |
| Hazard ratio* (95% CI)                        | 0.79 (0.66, 0.95)                                                                                                             |                                                                                                      |
| p-Value <sup>†</sup>                          | 0.0062                                                                                                                        |                                                                                                      |
| <b>PFS</b>                                    |                                                                                                                               |                                                                                                      |
| Number (%) of patients with event             | 221 (74%)                                                                                                                     | 226 (76%)                                                                                            |
| Median in months (95% CI)                     | 10.9 (8.5, 12.5)                                                                                                              | 7.3 (6.8, 8.4)                                                                                       |
| Hazard ratio* (95% CI)                        | 0.72 (0.60, 0.87)                                                                                                             |                                                                                                      |
| p-Value <sup>†</sup>                          | 0.0003                                                                                                                        |                                                                                                      |
| <b>Objective Response Rate</b>                |                                                                                                                               |                                                                                                      |
| ORR <sup>‡</sup> (95% CI)                     | 73% (67.7, 78.1)                                                                                                              | 58% (52.6, 64.1)                                                                                     |
| Complete response rate                        | 17%                                                                                                                           | 10%                                                                                                  |
| Partial response rate                         | 56%                                                                                                                           | 48%                                                                                                  |
| Difference (95% CI) <sup>§</sup>              | 15% (7.1, 22.2)                                                                                                               |                                                                                                      |
| p-Value <sup>§</sup>                          | <0.0001                                                                                                                       |                                                                                                      |
| <b>Response Duration</b>                      | n=218                                                                                                                         | n=173                                                                                                |
| Median in months (range)                      | 11.3 (1.1+, 60.8+)                                                                                                            | 9.6 (1.4+, 60.5+)                                                                                    |
| % with duration $\geq 6$ months <sup>¶</sup>  | 75%                                                                                                                           | 68%                                                                                                  |
| % with duration $\geq 12$ months <sup>¶</sup> | 49%                                                                                                                           | 42%                                                                                                  |

\* Based on the unstratified Cox proportional hazard model

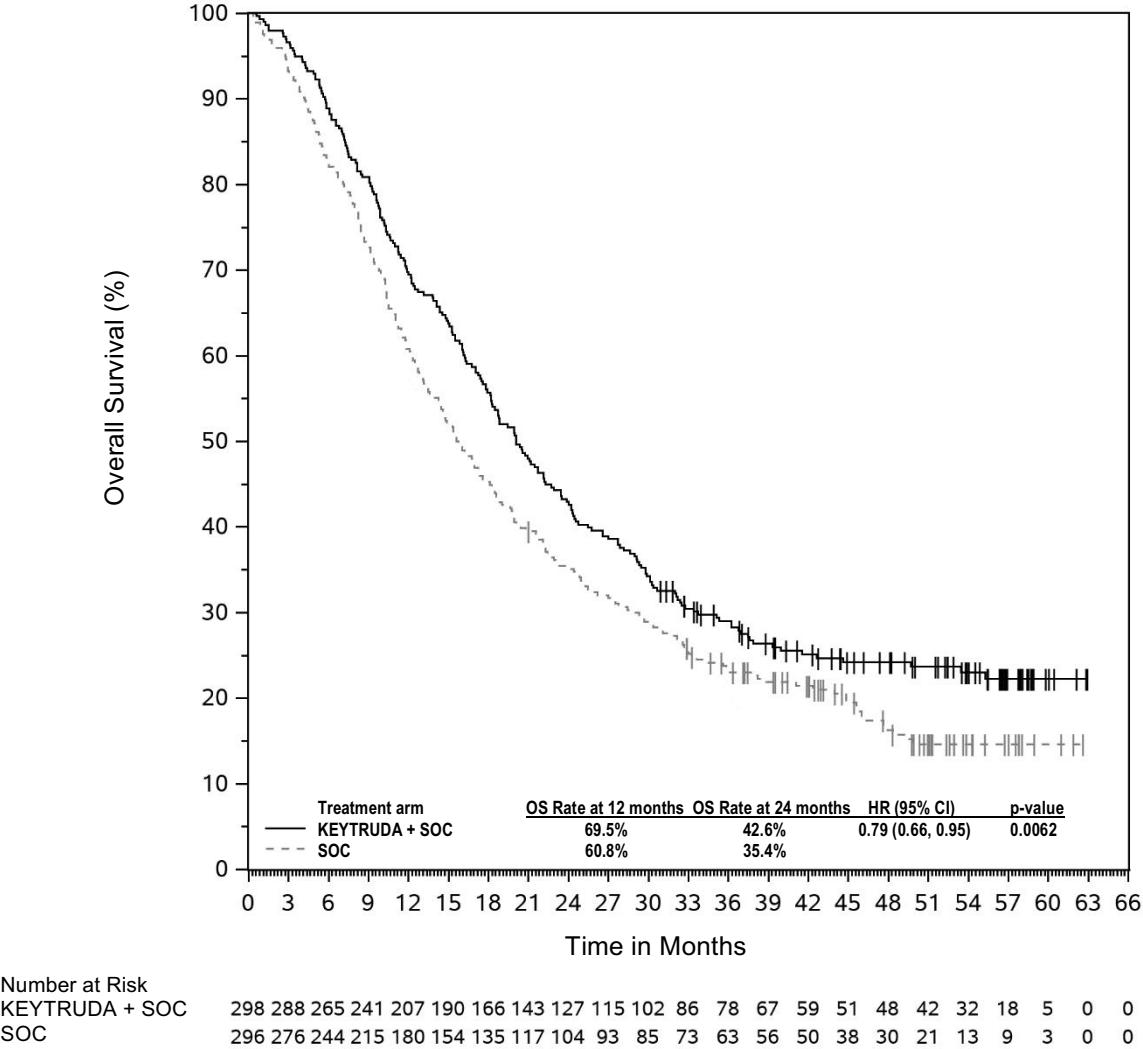
† Based on unstratified log-rank test; p-value is nominal p-value

‡ Response: Best objective response as confirmed complete response or partial response

§ Based on unstratified Miettinen and Nurminen method; p-value is nominal p-value

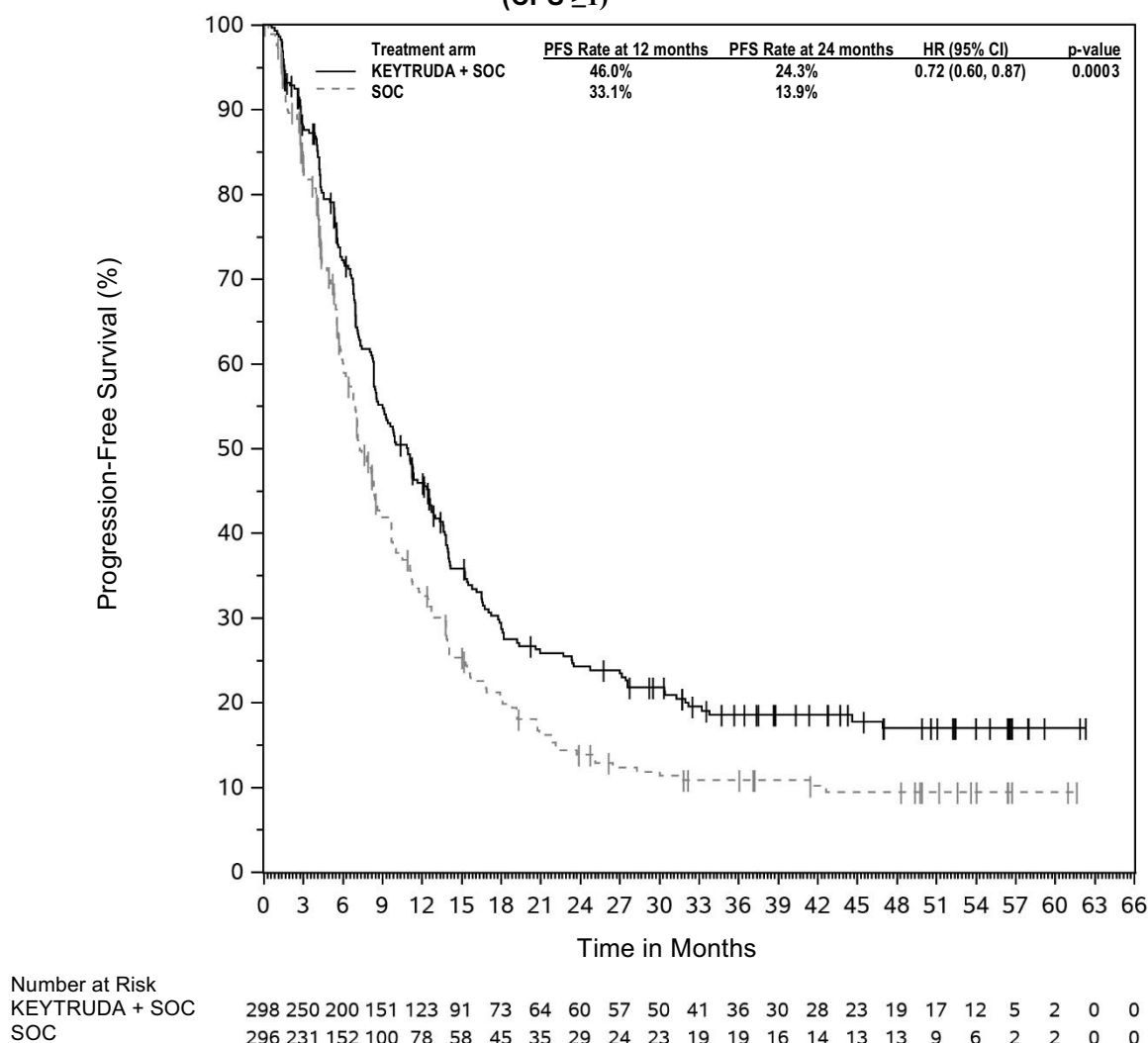
¶ Based on Kaplan-Meier estimation

Figure 58: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)



\*Based on the pre-specified final analysis

**Figure 59: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)**



\*Based on the pre-specified final analysis

### Biliary Tract Carcinoma

#### KEYNOTE-966: Controlled trial of combination therapy in patients with locally advanced unresectable or metastatic biliary tract carcinoma

The efficacy of KEYTRUDA in combination with gemcitabine and cisplatin was investigated in KEYNOTE-966, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1069 patients with locally advanced unresectable or metastatic BTC, who had not received prior systemic therapy in the advanced disease setting. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by region (Asia vs. non-Asia), locally advanced vs. metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomized (1:1) to one of the two treatment groups:

- KEYTRUDA 200 mg on Day 1 plus gemcitabine 1000 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup> on Day 1 and Day 8 every 3 weeks.

- Placebo on Day 1 plus gemcitabine 1000 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup> on Day 1 and Day 8 every 3 weeks

All study medications were administered via intravenous infusion. Treatment was continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment was continued for a maximum of 35 cycles, or approximately 24 months. For cisplatin, treatment could be administered for a maximum of 8 cycles and for gemcitabine, treatment could be continued beyond 8 cycles.

Administration of KEYTRUDA with chemotherapy was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Assessment of tumor status was performed at baseline and then every 6 weeks through 54 weeks, followed by every 12 weeks thereafter.

The study population characteristics were median age of 64 years (range: 23 to 85), 47% age 65 or older; 52% male; 49% White, 46% Asian; 46% ECOG PS of 0 and 54% ECOG PS of 1; 31% of patients had a history of hepatitis B infection, and 3% had a history of hepatitis C infection.

The primary efficacy outcome measure was OS and the secondary efficacy measures were PFS, ORR and DOR as assessed by BICR according to RECIST v1.1.

Table 41 and Figures 60 and 61 summarize the efficacy results for KEYNOTE-966.

**Table 41: Efficacy Results in Patients with BTC in KEYNOTE-966**

| Endpoint                                   | KEYTRUDA<br>200 mg every<br>3 weeks with<br>gemcitabine/cisplatin<br>n=533 | Placebo with<br>gemcitabine/cisplatin<br><br>n=536 |
|--------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------|
| <b>OS*</b>                                 |                                                                            |                                                    |
| Number (%) of patients with event          | 414 (78%)                                                                  | 443 (83%)                                          |
| Median in months (95% CI)                  | 12.7 (11.5, 13.6)                                                          | 10.9 (9.9, 11.6)                                   |
| Hazard ratio <sup>†</sup> (95% CI)         | 0.83 (0.72, 0.95)                                                          |                                                    |
| p-Value <sup>‡</sup>                       | 0.0034                                                                     |                                                    |
| <b>PFS§</b>                                |                                                                            |                                                    |
| Number (%) of patients with event          | 361 (68%)                                                                  | 391 (73%)                                          |
| Median in months (95% CI)                  | 6.5 (5.7, 6.9)                                                             | 5.6 (5.1, 6.6)                                     |
| Hazard ratio <sup>†</sup> (95% CI)         | 0.86 (0.75, 1.00)                                                          |                                                    |
| p-Value <sup>‡</sup>                       | 0.0225                                                                     |                                                    |
| <b>Objective Response Rate§</b>            |                                                                            |                                                    |
| ORR <sup>¶</sup> (95% CI)                  | 28.7% (24.9, 32.8)                                                         | 28.5% (24.8, 32.6)                                 |
| Number (%) of complete responses           | 11 (2.1%)                                                                  | 7 (1.3%)                                           |
| Number (%) of partial responses            | 142 (26.6%)                                                                | 146 (27.2%)                                        |
| p-Value <sup>#</sup>                       | 0.4735                                                                     |                                                    |
| <b>Duration of Response*, <sup>‡</sup></b> |                                                                            |                                                    |
|                                            | n=156                                                                      | n=152                                              |
| Median in months (range)                   | 8.3 (1.2+ - 33.0+)                                                         | 6.8 (1.1+ - 30.0+)                                 |
| % with duration ≥6 months                  | 65%                                                                        | 55%                                                |
| % with duration ≥12 months                 | 38%                                                                        | 27%                                                |
| % with duration ≥24 months                 | 18%                                                                        | 6%                                                 |

\* Results at the pre-specified final OS analysis

† Based on the stratified Cox proportional hazard model

‡ One-sided p-Value based on a stratified log-rank test

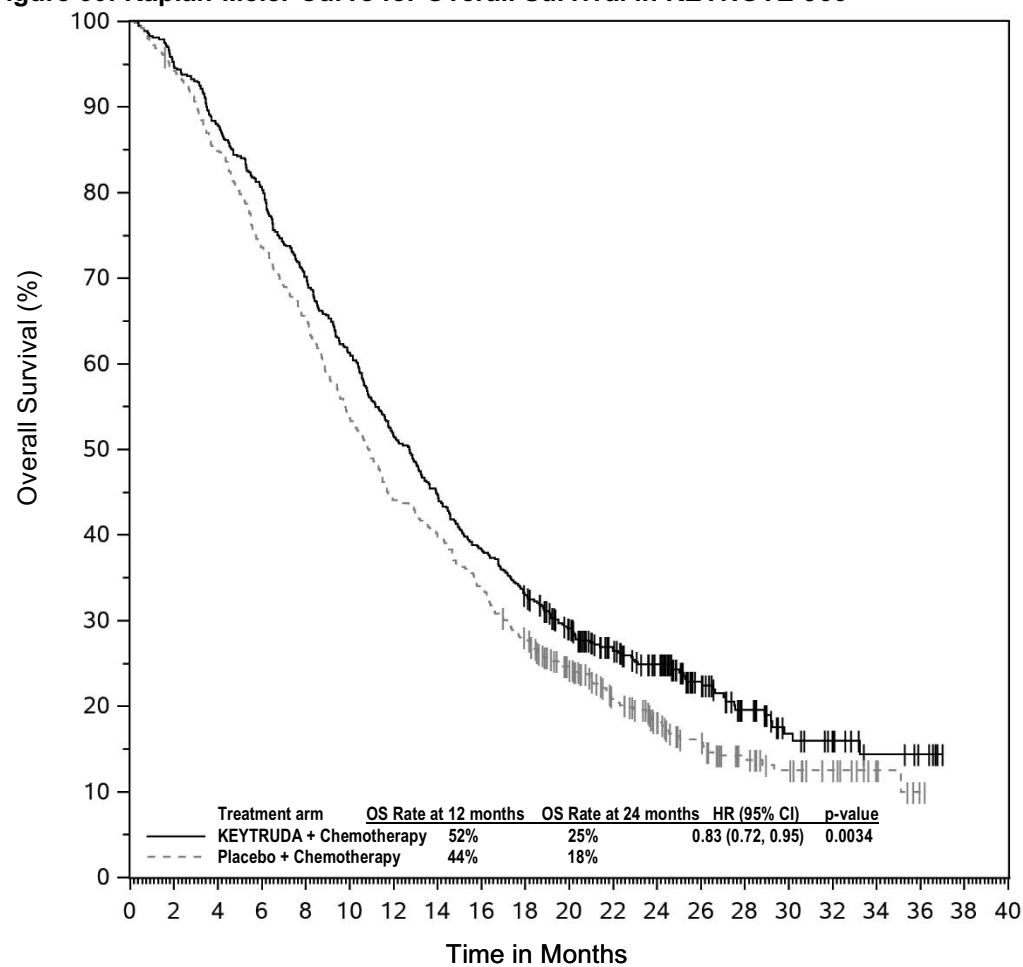
§ Results at pre-specified interim analysis

¶ Confirmed complete response or partial response

# One-sided p-Value based on the stratified Miettinen and Nurminen analysis

♢ Based on Kaplan-Meier estimate

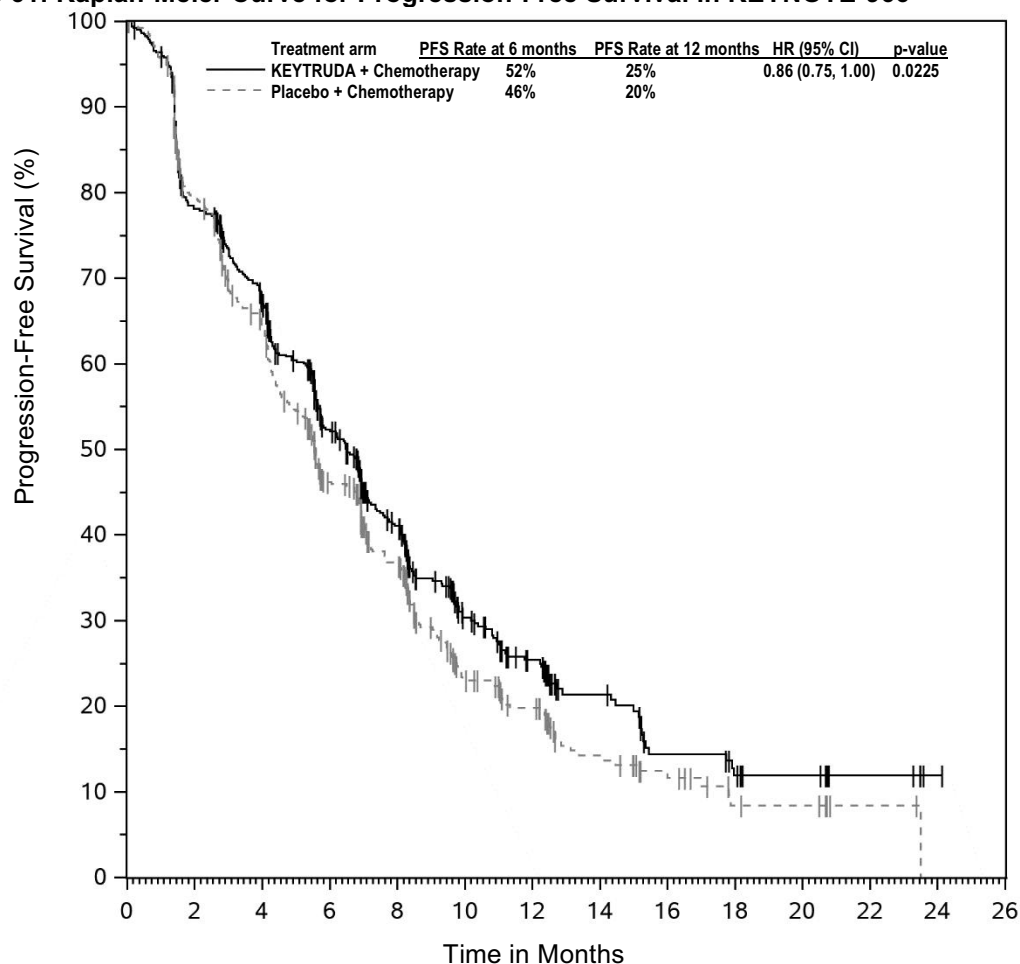
Figure 60: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966\*



|                         |     |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |    |
|-------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|
| Number at Risk          |     |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |    |
| KEYTRUDA + Chemotherapy | 533 | 505 | 469 | 430 | 374 | 326 | 275 | 238 | 204 | 175 | 142 | 108 | 88 | 56 | 35 | 21 | 16 |
| Placebo + Chemotherapy  | 536 | 504 | 454 | 394 | 349 | 287 | 236 | 213 | 181 | 148 | 115 | 81  | 59 | 43 | 28 | 20 | 14 |

\*Based on the pre-specified final OS analysis

**Figure 61: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-966\***



|                         |     |     |     |     |     |    |    |    |    |    |    |   |   |   |
|-------------------------|-----|-----|-----|-----|-----|----|----|----|----|----|----|---|---|---|
| Number at Risk          |     |     |     |     |     |    |    |    |    |    |    |   |   |   |
| KEYTRUDA + Chemotherapy | 533 | 403 | 336 | 238 | 163 | 91 | 62 | 33 | 19 | 14 | 10 | 5 | 1 | 0 |
| Placebo + Chemotherapy  | 536 | 411 | 323 | 211 | 147 | 70 | 51 | 25 | 16 | 7  | 6  | 2 | 0 | 0 |

\*Based on the pre-specified interim analysis data cut-off

From baseline to Week 18, pre-specified exploratory patient-reported outcomes (PROs) using the EORTC QLQ-C30 (global health status/quality of life, physical functioning, role functioning), EORTC QLQ-BIL21 (pain and jaundice scores), and EQ-5D-5L visual analog scale (VAS) for patients receiving KEYTRUDA in combination with gemcitabine/cisplatin were similar to those treated with placebo and gemcitabine/cisplatin. From baseline to Week 18, health-related quality of life (HRQoL) was maintained when KEYTRUDA was added to gemcitabine/cisplatin.

#### Immunogenicity

In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks, 36 (1.8%) of 2034 evaluable patients tested positive for treatment-emergent antibodies against pembrolizumab of which 9 (0.4%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralizing antibody development.

## **IV. NONCLINICAL TOXICOLOGY**

### **Chronic Toxicity**

The safety of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose toxicity study in Cynomolgus monkeys administered IV doses of 6, 40 or 200 mg/kg once a week in the 1-month study and once every two weeks in the 6-month study, followed by a 4-month treatment-free period. No findings of toxicological significance were observed and the no observed adverse effect level (NOAEL) in both studies was  $\geq 200$  mg/kg, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg, respectively. The exposure multiple between the NOAEL and a human dose of 200 mg was 74.

### **Carcinogenesis**

The carcinogenic potential of pembrolizumab has not been evaluated in long-term animal studies.

### **Mutagenesis**

The genotoxic potential of pembrolizumab has not been evaluated.

### **Reproduction**

Animal reproduction studies have not been conducted with KEYTRUDA. The central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that administration of KEYTRUDA during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

### **Development**

Developmental toxicity studies have not been conducted with pembrolizumab. There were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat dose toxicity studies.

## **V. INDICATIONS**

### *Melanoma*

KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC or III melanoma who have undergone complete resection.

### *Non-Small Cell Lung Carcinoma*

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic non-squamous non-small cell lung carcinoma (NSCLC), with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA as monotherapy is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumour Proportion Score (TPS)  $\geq 1\%$ ] as determined by a validated test, with no EGFR or ALK genomic tumor aberrations, and is:

- stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic

KEYTRUDA as monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD-L1 with a  $\geq 1\%$  TPS as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA.

KEYTRUDA is indicated for the treatment of patients with resectable (tumors  $\geq 4$  cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adult patients with Stage IB (T2a  $\geq 4$  cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy.

#### *Malignant Pleural Mesothelioma*

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma (MPM).

#### *Head and Neck Cancer*

KEYTRUDA as monotherapy is indicated for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumors express PD-L1 [Combined Positive Score (CPS)  $\geq 1$ ].

KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

KEYTRUDA as monotherapy is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS)  $\geq 1$ ] as determined by a validated test.

KEYTRUDA as monotherapy is indicated for the treatment of patients with metastatic or unresectable recurrent HNSCC with disease progression on or after platinum-containing chemotherapy.

#### *Urothelial Carcinoma*

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS)  $\geq 10$ ] as determined by a validated test.

This indication is approved based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

#### *Classical Hodgkin Lymphoma (cHL)*

KEYTRUDA as monotherapy is indicated for the treatment of adult and pediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

#### *Colorectal Cancer*

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) in adults.

#### *Cervical Cancer*

KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS  $\geq 1$ ) as determined by a validated test.

#### *Renal Cell Carcinoma*

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of patients with advanced RCC.

KEYTRUDA, as monotherapy, is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

#### *Endometrial Carcinoma*

KEYTRUDA, in combination with carboplatin and paclitaxel, followed by KEYTRUDA as monotherapy, is indicated for the treatment of patients with primary advanced or recurrent endometrial carcinoma.

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.

#### *Esophageal Cancer*

KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic carcinoma of the esophagus or HER2 negative gastroesophageal junction adenocarcinoma (tumor center 1 to 5 centimeters above the gastroesophageal junction) that is not amenable to surgical resection or definitive chemoradiation, in adults whose tumors express PD-L1 with a CPS  $\geq 10$ , as determined by a validated test.

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS)  $\geq 10$ ] as determined by a validated test, with disease progression after one prior line of systemic therapy.

#### *Triple-Negative Breast Cancer*

KEYTRUDA is indicated for the treatment of adult patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 (CPS  $\geq 10$ ) as determined by a validated test.

#### *Gastric Cancer*

KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS  $\geq 1$ .

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS  $\geq 1$ .

### *Biliary Tract Carcinoma*

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

## **VI. DOSAGE AND ADMINISTRATION**

### **General**

#### **Patient Selection**

If specified in the indication, select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression, MSI-H or dMMR tumor status [see V. *Indications*].

PD-L1 expression should be evaluated using the PD-L1 IHC 22C3 pharmDx™ kit or equivalent.

MSI or MMR tumor status should be evaluated using a validated test.

#### **Recommended Dosing**

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- 200 mg every 3 weeks or
- 400 mg every 6 weeks.

For use in combination, see the prescribing information for the concomitant therapies. When administering KEYTRUDA as part of a combination with intravenous chemotherapy, KEYTRUDA should be administered first.

For urothelial carcinoma patients treated with KEYTRUDA in combination with enfortumab vedotin, administer KEYTRUDA after enfortumab vedotin when given on the same day.

For urothelial carcinoma patients treated with KEYTRUDA in combination with enfortumab vedotin, the recommended initial dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) as an intravenous solution on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.

For RCC patients treated with KEYTRUDA in combination with axitinib, see the prescribing information regarding dosing of axitinib. When used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer [see *Clinical Studies (IIIId)*].

For endometrial carcinoma and RCC patients treated with KEYTRUDA in combination with lenvatinib, the recommended initial dose of lenvatinib is 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumor size or small new lesions within the first few months followed by tumor shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression should remain on treatment until disease progression is confirmed.

For adjuvant treatment of melanoma, NSCLC, or RCC, KEYTRUDA should be administered for up to one year or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 39 weeks or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of high-risk early-stage TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.

For the neoadjuvant and adjuvant treatment of resectable locally advanced HNSCC, patients should be treated with neoadjuvant KEYTRUDA as monotherapy for 2 doses of 200 mg every 3 weeks or 1 dose of 400 mg or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA in combination with radiation with or without concomitant cisplatin for 3 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks followed by KEYTRUDA as monotherapy for 12 doses of 200 mg every 3 weeks or 6 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA monotherapy as neoadjuvant treatment should not receive KEYTRUDA in combination with radiation with or without concomitant cisplatin as adjuvant treatment.

**Dose Modifications**

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described in Table 42.

**Table 42: Recommended Dose Modifications [see *Precautions (VIII)*]**

| <b>Adverse reactions</b>                                                                                                                                                | <b>Severity</b>                                                                                                                                                             | <b>Dose modification</b>                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Immune-mediated pneumonitis                                                                                                                                             | Moderate (Grade 2)                                                                                                                                                          | Withhold until adverse reactions recover to Grades 0-1*                                                                                                                                                                                                                 |
|                                                                                                                                                                         | Severe or life-threatening (Grades 3 or 4) or recurrent moderate (Grade 2)                                                                                                  | Permanently discontinue                                                                                                                                                                                                                                                 |
| Immune-mediated colitis                                                                                                                                                 | Moderate or severe (Grades 2 or 3)                                                                                                                                          | Withhold until adverse reactions recover to Grades 0-1*                                                                                                                                                                                                                 |
|                                                                                                                                                                         | Life-threatening (Grade 4) or recurrent severe (Grade 3)                                                                                                                    | Permanently discontinue                                                                                                                                                                                                                                                 |
| Immune-mediated nephritis                                                                                                                                               | Moderate (Grade 2)                                                                                                                                                          | Withhold until adverse reactions recover to Grades 0-1*                                                                                                                                                                                                                 |
|                                                                                                                                                                         | Severe or life-threatening (Grades 3 or 4)                                                                                                                                  | Permanently discontinue                                                                                                                                                                                                                                                 |
| Immune-mediated endocrinopathies                                                                                                                                        | Severe or life-threatening (Grades 3 or 4)                                                                                                                                  | Withhold until adverse reactions recover to Grades 0-1*<br><br>For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered |
| Immune-mediated hepatitis<br><br>For liver enzyme elevations in RCC patients treated with combination therapy with axitinib, see dosing guidelines following this table | Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 to 5 times upper limit of normal (ULN) or total bilirubin >1.5 to 3 times ULN                         | Withhold until adverse reactions recover to Grades 0-1*                                                                                                                                                                                                                 |
|                                                                                                                                                                         | AST or ALT >5 times ULN or total bilirubin >3 times ULN                                                                                                                     | Permanently discontinue                                                                                                                                                                                                                                                 |
|                                                                                                                                                                         | For patients with liver metastases who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥50% relative to baseline and lasts ≥1 week | Permanently discontinue                                                                                                                                                                                                                                                 |
| Immune-mediated skin reactions or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)                                                                    | Severe skin reactions (Grade 3) or suspected SJS or TEN                                                                                                                     | Withhold until adverse reactions recover to Grades 0-1*                                                                                                                                                                                                                 |
|                                                                                                                                                                         | Severe skin reactions (Grade 4) or confirmed SJS or TEN                                                                                                                     | Permanently discontinue                                                                                                                                                                                                                                                 |
| Other immune-mediated adverse reactions                                                                                                                                 | Based on severity and type of reaction (Grade 2 or Grade 3)                                                                                                                 | Withhold until adverse reactions recover to Grades 0-1*                                                                                                                                                                                                                 |
|                                                                                                                                                                         | Severe or life-threatening (Grades 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome                                                                            | Permanently discontinue                                                                                                                                                                                                                                                 |
|                                                                                                                                                                         | Life-threatening (Grade 4) or recurrent severe (Grade 3)                                                                                                                    | Permanently discontinue                                                                                                                                                                                                                                                 |
| Infusion-related reactions                                                                                                                                              | Severe or life-threatening (Grades 3 or 4)                                                                                                                                  | Permanently discontinue                                                                                                                                                                                                                                                 |

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Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v.4)

- \* If corticosteroid dosing cannot be reduced to  $\leq 10$  mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued.

In patients with cHL with Grade 4 hematological toxicity, KEYTRUDA should be withheld until adverse reactions recover to Grades 0-1.

In patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST  $\geq 3$  times ULN but  $< 10$  times ULN without concurrent total bilirubin  $\geq 2$  times ULN, withhold both KEYTRUDA and axitinib until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib prescribing information.
- If ALT or AST  $\geq 10$  times ULN or  $> 3$  times ULN with concurrent total bilirubin  $\geq 2$  times ULN, permanently discontinue both KEYTRUDA and axitinib and consider corticosteroid therapy.

When administering KEYTRUDA in combination with lenvatinib, interrupt one or both to manage adverse reactions as appropriate. No dose reductions are recommended for KEYTRUDA. For management of adverse reactions, withhold, dose reduce, or discontinue lenvatinib in accordance with the instructions in the lenvatinib Product Information.

### **Preparation and Administration**

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEYTRUDA is a clear to slightly opalescent, colorless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Do not freeze the infusion solution.
- Chemical and physical in-use stability has been demonstrated for up to 42 days at 2°C to 8°C or 23°C to 27°C.
- The product does not contain preservative. Aseptic handling should be ensured during the preparation of infusion. The diluted product should be used immediately. If not used immediately, diluted solutions of KEYTRUDA may be stored at room temperature for up to 12 hours. Diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from dilution of KEYTRUDA to completion of infusion should not exceed 7 days. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- Translucent to white proteinaceous particles may be seen in the diluted solution. Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5  $\mu$ m in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Discard any unused portion left in the vial.

### **Pediatric Patients**

In melanoma and cHL, the recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks.

### **Renal Impairment**

No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment.

### **Hepatic Impairment**

No dose adjustment is needed for patients with mild or moderate hepatic impairment. KEYTRUDA has not been studied in patients with severe hepatic impairment.

## **VII. CONTRAINDICATIONS**

None.

## **VIII. PRECAUTIONS**

### **Immune-mediated adverse reactions**

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA. Immune-mediated adverse reactions can occur after discontinuation of treatment. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA. *[See Dosage and Administration (VI) and Adverse Reactions (XIV- Clinical Trials Experience).]*

#### Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (XIV- Clinical Trials Experience)]*. Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis. *[See Dosage and Administration (VI) and Immune-mediated adverse reactions above.]*

#### Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (XIV- Clinical Trials Experience)]*. Monitor patients for signs and symptoms of colitis and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis. *[See Dosage and Administration (VI) and Immune-mediated adverse reactions above.]*

#### Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (XIV- Clinical Trials Experience)]*. Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes. Administer corticosteroids (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1-2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA. *[See Dosage and Administration (VI) and Immune-mediated adverse reactions above.]*

#### Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA [see *Adverse Reactions (XIV- Clinical Trials Experience)*]. Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis. [See *Dosage and Administration (VI)* and *Immune-mediated adverse reactions above*.]

#### Immune-mediated endocrinopathies

Adrenal insufficiency (primary and secondary) has been reported in patients receiving KEYTRUDA. Hypophysitis has also been reported in patients receiving KEYTRUDA. [See *Adverse Reactions (XIV- Clinical Trials Experience)*.] Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes. Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated, withhold KEYTRUDA for moderate (Grade 2), withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis. [See *Dosage and Administration (VI)* and *Immune-mediated adverse reactions above*.]

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA [see *Adverse Reactions (XIV- Clinical Trials Experience)*]. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment; therefore, monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism. [See *Dosage and Administration (VI)*, *Adverse Reactions (XIV- Clinical Trials Experience)*, and *Immune-mediated adverse reactions above*.]

For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered.

#### Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids [see *Dosage and Administration (VI)*].

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. [See *Dosage and Administration (VI)*.]

#### Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, vasculitis, hypoparathyroidism, gastritis, hemolytic anemia and pericarditis. The following were reported in other clinical studies with KEYTRUDA or in postmarketing use: myocarditis, sclerosing cholangitis, exocrine pancreatic insufficiency, cystitis noninfective, and myocarditis-myositis-myasthenia gravis overlap syndrome.

Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in postmarketing use.

#### *Transplant-related adverse reactions*

Solid organ transplant rejection has been reported in the postmarketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection in these patients.

Acute graft-versus-host-disease (GVHD), including fatal GVHD, after treatment with KEYTRUDA has been reported in patients with a history of allogeneic hematopoietic stem cell transplant (HSCT). Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

#### **Elevated liver enzymes when KEYTRUDA is given in combination with axitinib for RCC**

When KEYTRUDA is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC [see *Adverse Reactions (XIV)*]. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. Follow medical management guidelines for both drugs. [See *Dosage and Administration (VI)* and the prescribing information for axitinib.]

#### **Increased mortality in patients with multiple myeloma when KEYTRUDA is added to a thalidomide analogue and dexamethasone**

In two randomized clinical trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

#### **Infusion-related reactions**

Severe infusion reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA [see *Dosage and Administration (VI)*]. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; premedication with antipyretic and antihistamine may be considered.

### **IX. PREGNANCY**

There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. KEYTRUDA is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment with KEYTRUDA and for at least 4 months after the last dose of KEYTRUDA.

### **X. NURSING MOTHERS**

It is unknown whether KEYTRUDA is secreted in human milk. Because many drugs are secreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue KEYTRUDA, taking into account the benefit of breast-feeding for the child and the benefit of KEYTRUDA therapy for the woman.

## **XI. PEDIATRIC USE**

### **Pediatric Patients**

In KEYNOTE-051, 161 pediatric patients (62 children ages 6 months to less than 12 years and 99 adolescents ages 12 years to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive or MSI-H advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 4 doses (range 1-35 doses), with 138 patients (86%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety profile in these pediatric patients was similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of pediatric patients) were pyrexia, vomiting, headache, abdominal pain, anemia, cough, and constipation.

Efficacy for pediatric patients with melanoma and cHL is extrapolated from the results in the respective adult populations [see *Clinical Studies (IIIId)*].

## **XII. USE IN THE ELDERLY**

### **Geriatric Patients**

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population.

Data from patients  $\geq 65$  years are too limited to draw conclusions on cHL population.

Data are limited in patients  $\geq 75$  years for chemotherapy combination in patients with esophageal carcinoma.

## **XIII. DRUG INTERACTIONS**

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA to treat immune-mediated adverse reactions. [See *Precautions (VIII)*.] Corticosteroids can also be used as premedication, when KEYTRUDA is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

## **XIV. ADVERSE REACTIONS**

### **Clinical Trials Experience**

The safety of KEYTRUDA was evaluated in 2799 patients in controlled and uncontrolled studies. The median treatment duration was 4.2 months (range 1 day to 30.4 months) including 1153 patients treated for greater than or equal to six months and 600 patients treated for greater than or equal to one year.

KEYTRUDA was discontinued for treatment-related adverse reactions in 5% of patients. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA. Of these treatment-related SAEs, the most common were pneumonitis, colitis, diarrhea and pyrexia.

**Immune-mediated adverse reactions [see Precautions (VIII)]:**

Immune-mediated adverse reactions are presented based on 2799 patients with melanoma and NSCLC. The safety profile was generally similar for patients with melanoma and NSCLC. Table 43 presents the incidence of immune-mediated adverse reactions by Grade that occurred in patients receiving KEYTRUDA.

**Table 43: Immune-Mediated Adverse Reactions**

| Adverse Reaction                | KEYTRUDA<br>2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks<br>n=2799 |             |             |             |             |
|---------------------------------|----------------------------------------------------------------------------|-------------|-------------|-------------|-------------|
|                                 | All Grades (%)                                                             | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) | Grade 5 (%) |
| <b>Hypothyroidism*</b>          | 8.5                                                                        | 6.2         | 0.1         | 0           | 0           |
| <b>Hyperthyroidism†</b>         | 3.4                                                                        | 0.8         | 0.1         | 0           | 0           |
| <b>Pneumonitis‡</b>             | 3.4                                                                        | 1.3         | 0.9         | 0.3         | 0.1         |
| <b>Colitis</b>                  | 1.7                                                                        | 0.4         | 1.1         | <0.1        | 0           |
| <b>Adrenal Insufficiency</b>    | 0.8                                                                        | 0.3         | 0.3         | <0.1        | 0           |
| <b>Hepatitis</b>                | 0.7                                                                        | 0.1         | 0.4         | <0.1        | 0           |
| <b>Hypophysitis</b>             | 0.6                                                                        | 0.2         | 0.3         | <0.1        | 0           |
| <b>Nephritis§</b>               | 0.3                                                                        | 0.1         | 0.1         | <0.1        | 0           |
| <b>Type 1 Diabetes Mellitus</b> | 0.2                                                                        | <0.1        | 0.1         | 0.1         | 0           |

\* In individual studies of patients with HNSCC treated with KEYTRUDA as monotherapy (n=909) the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with KEYTRUDA in combination with platinum and 5-FU chemotherapy (n=276) the incidence of hypothyroidism was 15.2%, all of which were Grade 1 or 2. In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2. In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hypothyroidism was 21% (all Grades) with 0.2% Grade 3.

† In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hyperthyroidism was 12% (all Grades) with 0.2% Grade 3.

‡ In individual studies of patients with NSCLC treated with KEYTRUDA as monotherapy (total n=2602), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. In cHL patients treated with KEYTRUDA as monotherapy, the incidence of pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively.

§ In patients with non-squamous NSCLC treated with KEYTRUDA 200 mg in combination with pemetrexed and platinum chemotherapy (n=405) the incidence of nephritis was 1.7% (all Grades) with 1.0% Grade 3 and 0.5% Grade 4.

**Endocrinopathies:** The median time to onset of adrenal insufficiency was 5.3 months (range 26 days to 16.6 months). The median duration was not reached (range 4 days to 1.9+ years). Adrenal insufficiency led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Adrenal insufficiency resolved in 5 patients. The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 patients. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 patients. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA due to hypothyroidism.

**Pneumonitis:** The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.

**Colitis:** The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 patients.

**Hepatitis:** The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 patients.

**Nephritis:** The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 patients.

## Other adverse events

### Melanoma

Table 44 summarizes the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA in KEYNOTE-006. The most common adverse events (reported in at least 15% of patients) were arthralgia and cough.

**Table 44: Adverse Events Occurring in ≥10% of Patients Treated with KEYTRUDA and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grade 3]) (KEYNOTE-006)**

|                                                        | KEYTRUDA<br>10 mg/kg every 2 or<br>3 weeks<br>n=555 |                 | Ipilimumab<br>3 mg/kg every 3 weeks<br>n=256 |                 |
|--------------------------------------------------------|-----------------------------------------------------|-----------------|----------------------------------------------|-----------------|
| Adverse Events                                         | All Grades<br>(%)                                   | Grade 3*<br>(%) | All Grades<br>(%)                            | Grade 3*<br>(%) |
| <b>Musculoskeletal and Connective Tissue Disorders</b> |                                                     |                 |                                              |                 |
| Arthralgia                                             | 18                                                  | 0               | 10                                           | 1               |
| Back pain                                              | 12                                                  | 1               | 7                                            | 1               |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b> |                                                     |                 |                                              |                 |
| Cough                                                  | 17                                                  | 0               | 7                                            | 0               |
| <b>Skin And Subcutaneous Tissue Disorders</b>          |                                                     |                 |                                              |                 |
| Vitiligo                                               | 11                                                  | 0               | 2                                            | 0               |

\* Of these ≥10% adverse events, none was reported as Grade 4.

Table 45 summarizes the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA at a dose of 2 mg/kg in KEYNOTE-002. The most common adverse event (reported in at least 20% of patients) was pruritus.

**Table 45: Adverse Events Occurring in  $\geq 10\%$  of Patients with Melanoma Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (KEYNOTE-002)**

|                                                        | <b>KEYTRUDA<br/>2 mg/kg every 3 weeks<br/>n=178</b> |                        | <b>Chemotherapy<br/>n=171</b> |                        |
|--------------------------------------------------------|-----------------------------------------------------|------------------------|-------------------------------|------------------------|
| <b>Adverse Event</b>                                   | <b>All Grades (%)</b>                               | <b>Grades 3-4* (%)</b> | <b>All Grades (%)</b>         | <b>Grades 3-4* (%)</b> |
| <b>Gastrointestinal Disorders</b>                      |                                                     |                        |                               |                        |
| Abdominal pain                                         | 13                                                  | 2                      | 8                             | 1                      |
| <b>Skin And Subcutaneous Tissue Disorders</b>          |                                                     |                        |                               |                        |
| Pruritus                                               | 25                                                  | 0                      | 8                             | 0                      |
| Rash                                                   | 13                                                  | 0                      | 8                             | 0                      |
| <b>Metabolism and Nutrition Disorders</b>              |                                                     |                        |                               |                        |
| Hyponatremia                                           | 11                                                  | 3                      | 5                             | 1                      |
| <b>Musculoskeletal and Connective Tissue Disorders</b> |                                                     |                        |                               |                        |
| Arthralgia                                             | 15                                                  | 1                      | 10                            | 1                      |

\* Of these  $\geq 10\%$  adverse events, none was reported as Grade 4 in patients receiving KEYTRUDA at 2 mg/kg. Hyponatremia was reported as Grade 4 in one patient receiving chemotherapy.

Overall, the safety profile was similar across all doses and between patients previously treated with ipilimumab and patients naïve to treatment with ipilimumab.

#### *Resected Melanoma*

Among the 969 patients with resected melanoma enrolled in KEYNOTE-716 and 1019 patients with resected melanoma enrolled in KEYNOTE-054, the adverse reactions were generally similar to those occurring in patients with unresectable or metastatic melanoma or NSCLC.

#### *Non-Small Cell Lung Carcinoma*

##### *Combination Therapy*

Table 46 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA, pemetrexed, and platinum chemotherapy in KEYNOTE-189. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel in KEYNOTE-407 were generally similar to those occurring in patients in KEYNOTE-189 with the exception of alopecia (46%) and arthralgia (21%).

**Table 46: Adverse Events Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA with Pemetrexed and Platinum Chemotherapy and at a Higher Incidence than in Patients Receiving Placebo with Pemetrexed and Platinum Chemotherapy (Between-Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (KEYNOTE-189)**

|                                                             | <b>KEYTRUDA +<br/>Pemetrexed +<br/>Platinum<br/>Chemotherapy<br/>n=405</b> |                                | <b>Placebo +<br/>Pemetrexed +<br/>Platinum<br/>Chemotherapy<br/>n=202</b> |                                |
|-------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------|--------------------------------|
| <b>Adverse Events</b>                                       | <b>All<br/>Grades*<br/>(%)</b>                                             | <b>Grades 3-<br/>4<br/>(%)</b> | <b>All<br/>Grades<br/>(%)</b>                                             | <b>Grades 3-<br/>4<br/>(%)</b> |
| <b>General Disorders and Administration Site Conditions</b> |                                                                            |                                |                                                                           |                                |
| Fatigue                                                     | 41                                                                         | 6                              | 38                                                                        | 2.5                            |
| Asthenia                                                    | 20                                                                         | 6                              | 24                                                                        | 3.5                            |
| <b>Gastrointestinal Disorders</b>                           |                                                                            |                                |                                                                           |                                |
| Diarrhea                                                    | 31                                                                         | 5                              | 21                                                                        | 3.0                            |
| <b>Blood and Lymphatic System Disorders</b>                 |                                                                            |                                |                                                                           |                                |
| Neutropenia                                                 | 27                                                                         | 16                             | 24                                                                        | 12                             |
| <b>Skin and Subcutaneous Tissue Disorders</b>               |                                                                            |                                |                                                                           |                                |
| Rash                                                        | 20                                                                         | 1.7                            | 11                                                                        | 1.5                            |

\* Graded per NCI CTCAE v4.03

#### *Neoadjuvant and Adjuvant Therapy for Resectable NSCLC*

Adverse events occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy adjuvant treatment in KEYNOTE-671, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.

#### *Monotherapy*

Table 47 summarizes the adverse events that occurred in at least 10% of previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-042. The most common adverse events (reported in at least 15% of patients) were dyspnea and cough. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-024 and previously treated patients in KEYNOTE-010 were generally similar to those occurring in patients in KEYNOTE-042.

**Table 47: Adverse Events Occurring in  $\geq 10\%$  of NSCLC Patients Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-5]) (KEYNOTE-042)**

|                                                        | <b>KEYTRUDA<br/>200 mg every 3 weeks<br/>n=636</b> |                           | <b>Chemotherapy<br/>n=615</b> |                           |
|--------------------------------------------------------|----------------------------------------------------|---------------------------|-------------------------------|---------------------------|
| <b>Adverse Event</b>                                   | <b>All Grades*<br/>(%)</b>                         | <b>Grades 3-5<br/>(%)</b> | <b>All Grades<br/>(%)</b>     | <b>Grades 3-5<br/>(%)</b> |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b> |                                                    |                           |                               |                           |
| Dyspnea                                                | 17                                                 | 2.0                       | 11                            | 0.8                       |
| Cough                                                  | 16                                                 | 0.2                       | 11                            | 0.3                       |
| <b>Endocrine Disorders</b>                             |                                                    |                           |                               |                           |
| Hypothyroidism                                         | 12                                                 | 0.2                       | 1.5                           | 0                         |

\* Graded per NCI CTCAE v4.03

### *Adjuvant Therapy for Resected NSCLC*

Among the 580 patients with resected NSCLC treated with KEYTRUDA in KEYNOTE-091, the adverse reactions were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as monotherapy with the exception of hypothyroidism (21%) and hyperthyroidism (11%).

### Other Cancers

#### Monotherapy

Adverse events occurring in patients with HNSCC, urothelial carcinoma, cHL, CRC, esophageal cancer, or adjuvant treatment of RCC were generally similar to those occurring in patients with melanoma or NSCLC.

#### Combination Therapy

##### Malignant Pleural Mesothelioma

Among the 241 patients with MPM treated with KEYTRUDA in combination with pemetrexed and platinum chemotherapy in KEYNOTE-483, the adverse events were generally similar to those occurring in other patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy.

##### Head and Neck Cancer

In patients with HNSCC receiving KEYTRUDA as neoadjuvant treatment, continued as adjuvant treatment in combination with RT with or without cisplatin and then as monotherapy, the adverse event occurring in at least 20% of patients and at a higher incidence ( $\geq 2\%$  difference) of Grades 3-4 severity for KEYTRUDA plus RT with or without cisplatin compared to RT with or without cisplatin was weight loss (14% vs. 10%).

In patients with HNSCC receiving KEYTRUDA plus chemotherapy (platinum and 5-FU), adverse events occurring at a greater severity (Grade 3-4) and at a higher incidence ( $\geq 2\%$  difference) compared to cetuximab plus chemotherapy (platinum and 5-FU) were: fatigue (7% vs. 4.9%), mucosal inflammation (10% vs. 5%), and stomatitis (8% vs. 3.5%).

##### Urothelial Carcinoma

Among patients with locally advanced or metastatic urothelial carcinoma receiving KEYTRUDA plus enfortumab vedotin, adverse events were generally similar to those observed in patients receiving KEYTRUDA or enfortumab vedotin as monotherapy. The incidence of rash maculo-papular with the combination was 36% all Grades (10% Grades 3-4), which is higher than observed in KEYTRUDA monotherapy.

##### Gastric Cancer

In patients with gastric cancer receiving KEYTRUDA plus chemotherapy (fluoropyrimidine and platinum), adverse events occurring in at least 20% of patients and at a higher incidence ( $\geq 2\%$  difference) of Grades 3-4 severity compared to placebo plus chemotherapy (fluoropyrimidine and platinum) were: anemia (12% vs. 10%), platelet count decreased (7% vs. 5%).

In patients with gastric cancer receiving KEYTRUDA plus trastuzumab and chemotherapy (fluoropyrimidine and platinum), adverse events occurring in at least 20% of patients and at a higher incidence ( $\geq 2\%$  difference) of Grades 3-4 severity compared to placebo plus trastuzumab and chemotherapy (fluoropyrimidine and platinum) were: vomiting (4.6% vs. 1.9%), anemia (14% vs. 12%), decreased platelet count (14% vs. 10%), and lymphopenia (13% vs. 9%).

##### Cervical Cancer

In patients with cervical cancer receiving KEYTRUDA plus CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]), adverse events occurring at a higher incidence ( $\geq 2\%$  difference) of Grades 3-5 severity for KEYTRUDA plus CRT compared to placebo plus CRT was leukopenia (13% vs. 11%).

In patients with cervical cancer receiving KEYTRUDA plus chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab, adverse events occurring at a higher incidence ( $\geq 2\%$  difference) of Grades 3-5 severity for KEYTRUDA plus chemotherapy with or without bevacizumab

compared to placebo plus chemotherapy with or without bevacizumab were: anemia (30% vs. 27%), neutropenia (12% vs. 10%), thrombocytopenia (8% vs. 5%), asthenia (3.6% vs. 1.6%).

### Esophageal Cancer

The safety of KEYTRUDA, in combination with cisplatin and FU chemotherapy was investigated in KEYNOTE-590, a multicenter, double-blind, randomized (1:1), placebo-controlled trial for the first-line treatment in patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation [see *Clinical Studies (III)*]. A total of 740 patients received either KEYTRUDA 200 mg (n=370) or placebo (n=370) every 3 weeks for up to 35 cycles, both in combination with up to 6 cycles of cisplatin and up to 35 cycles of FU.

The median duration of exposure was 5.7 months (range: 1 day to 26 months) in the KEYTRUDA combination arm and 5.1 months (range: 3 days to 27 months) in the chemotherapy arm.

KEYTRUDA was discontinued for adverse events in 15% of patients. The most common adverse events resulting in permanent discontinuation of KEYTRUDA ( $\geq 1\%$ ) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). Adverse events leading to interruption of KEYTRUDA occurred in 67% of patients. The most common adverse events leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (19%), fatigue/asthenia (8%), decreased white blood cell count (5%), pneumonia (5%), decreased appetite (4.3%), anemia (3.2%), increased blood creatinine (3.2%), stomatitis (3.2%), malaise (3.0%), thrombocytopenia (3%), pneumonitis (2.7%), diarrhea (2.4%), dysphagia (2.2%), and nausea (2.2%).

Tables 48 and 49 summarize adverse events and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-590.

**Table 48: Adverse Events Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA in KEYNOTE-590**

| Adverse Event                   | KEYTRUDA<br>200 mg every 3 weeks<br>Cisplatin<br>FU<br>n=370 |                    | Placebo<br><br>Cisplatin FU<br>n=370 |                    |
|---------------------------------|--------------------------------------------------------------|--------------------|--------------------------------------|--------------------|
|                                 | All Grades*<br>(%)                                           | Grades 3-4†<br>(%) | All Grades*<br>(%)                   | Grades 3-4†<br>(%) |
| <b>Gastrointestinal</b>         |                                                              |                    |                                      |                    |
| Nausea                          | 67                                                           | 7                  | 63                                   | 7                  |
| Constipation                    | 40                                                           | 0                  | 40                                   | 0                  |
| Diarrhea                        | 36                                                           | 4.1                | 33                                   | 3                  |
| Vomiting                        | 34                                                           | 7                  | 32                                   | 5                  |
| Stomatitis                      | 27                                                           | 6                  | 26                                   | 3.8                |
| <b>General</b>                  |                                                              |                    |                                      |                    |
| Fatigue‡                        | 57                                                           | 12                 | 46                                   | 9                  |
| <b>Metabolism and Nutrition</b> |                                                              |                    |                                      |                    |
| Decreased appetite              | 44                                                           | 4.1                | 38                                   | 5                  |
| <b>Investigations</b>           |                                                              |                    |                                      |                    |
| Weight loss                     | 24                                                           | 3.0                | 24                                   | 5                  |

\* Graded per NCI CTCAE v4.03

† One fatal event of diarrhea was reported in each arm.

‡ Includes asthenia, fatigue

**Table 49: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Esophageal Cancer Patients Receiving KEYTRUDA in KEYNOTE-590**

| Laboratory Test*               | KEYTRUDA<br>200 mg every 3 weeks<br>Cisplatin<br>FU |                 | Chemotherapy (Cisplatin<br>and FU) |                 |
|--------------------------------|-----------------------------------------------------|-----------------|------------------------------------|-----------------|
|                                | All Grades <sup>†</sup><br>%                        | Grades 3-4<br>% | All Grades <sup>†</sup><br>%       | Grades 3-4<br>% |
| <b>Hematology</b>              |                                                     |                 |                                    |                 |
| Anemia                         | 83                                                  | 21              | 86                                 | 24              |
| Neutropenia                    | 74                                                  | 43              | 71                                 | 41              |
| Leukopenia                     | 72                                                  | 21              | 73                                 | 17              |
| Lymphopenia                    | 55                                                  | 22              | 53                                 | 18              |
| Thrombocytopenia               | 43                                                  | 5               | 46                                 | 8               |
| <b>Chemistry</b>               |                                                     |                 |                                    |                 |
| Hyperglycemia                  | 56                                                  | 7               | 55                                 | 6               |
| Hyponatremia                   | 53                                                  | 19              | 54                                 | 19              |
| Hypoalbuminemia                | 52                                                  | 2.8             | 52                                 | 2.3             |
| Increased creatinine           | 45                                                  | 2.5             | 42                                 | 2.5             |
| Hypocalcemia                   | 44                                                  | 3.9             | 38                                 | 2               |
| Hypophosphatemia               | 37                                                  | 9               | 31                                 | 10              |
| Hypokalemia                    | 30                                                  | 12              | 34                                 | 15              |
| Increased alkaline phosphatase | 29                                                  | 1.9             | 29                                 | 1.7             |
| Hyperkalemia                   | 28                                                  | 3.6             | 27                                 | 2.6             |
| Increased AST                  | 25                                                  | 4.4             | 22                                 | 2.8             |
| Increased ALT                  | 23                                                  | 3.6             | 18                                 | 1.7             |

\* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/cisplatin/FU (range: 345 to 365 patients) and placebo/cisplatin/FU (range: 330 to 358 patients)

† Graded per NCI CTCAE v4.03

#### Renal Cell Carcinoma

##### In Combination with Axitinib (KEYNOTE-426)

The most common adverse events that occurred in at least 20% of previously untreated patients with RCC receiving KEYTRUDA and axitinib in KEYNOTE-426 were diarrhea, hypertension, fatigue, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia syndrome, nausea, ALT increased, AST increased, dysphonia, cough and constipation.

In KEYNOTE-426, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed in previously untreated patients with RCC receiving KEYTRUDA in combination with axitinib. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either KEYTRUDA (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT >3 times ULN, and of those patients with recurrence of ALT >3 times ULN, all recovered. There were no Grade 5 hepatic events. [See *Dosage and Administration (VI) and Precautions (VIII).*]

##### In Combination with Lenvatinib (KEYNOTE-581)

Table 50 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

**Table 50: Adverse Events Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Sunitinib (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (KEYNOTE-581)**

|                                                        | <b>KEYTRUDA +<br/>lenvatinib<br/>n=352</b> |                                | <b>Sunitinib<br/>n=340</b>    |                                |
|--------------------------------------------------------|--------------------------------------------|--------------------------------|-------------------------------|--------------------------------|
| <b>Adverse Events</b>                                  | <b>All<br/>Grades*<br/>(%)</b>             | <b>Grades 3-<br/>4<br/>(%)</b> | <b>All<br/>Grades<br/>(%)</b> | <b>Grades 3-<br/>4<br/>(%)</b> |
| <b>Gastrointestinal Disorders</b>                      |                                            |                                |                               |                                |
| Diarrhea                                               | 61                                         | 10                             | 49                            | 5                              |
| Nausea                                                 | 36                                         | 2.6                            | 33                            | 0.6                            |
| Vomiting                                               | 26                                         | 3.4                            | 20                            | 1.5                            |
| Constipation                                           | 25                                         | 0.9                            | 19                            | 0                              |
| Abdominal pain                                         | 21                                         | 2.0                            | 8                             | 0.9                            |
| <b>Vascular Disorders</b>                              |                                            |                                |                               |                                |
| Hypertension                                           | 55                                         | 28                             | 41                            | 19                             |
| <b>Endocrine Disorders</b>                             |                                            |                                |                               |                                |
| Hypothyroidism                                         | 47                                         | 1.4                            | 26                            | 0                              |
| <b>Metabolism and Nutrition Disorders</b>              |                                            |                                |                               |                                |
| Decreased appetite                                     | 40                                         | 4.0                            | 31                            | 1.5                            |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b> |                                            |                                |                               |                                |
| Dysphonia                                              | 30                                         | 0                              | 4.1                           | 0                              |
| <b>Investigations</b>                                  |                                            |                                |                               |                                |
| Decreased weight                                       | 30                                         | 8                              | 9                             | 0.3                            |
| <b>Renal and Urinary Disorders</b>                     |                                            |                                |                               |                                |
| Proteinuria                                            | 30                                         | 8                              | 13                            | 2.9                            |
| <b>Skin and Subcutaneous Tissue Disorders</b>          |                                            |                                |                               |                                |
| Rash                                                   | 27                                         | 3.7                            | 14                            | 0.6                            |
| <b>Musculoskeletal and Connective Tissue Disorders</b> |                                            |                                |                               |                                |
| Arthralgia                                             | 28                                         | 1.4                            | 15                            | 0.3                            |
| <b>Nervous System Disorders</b>                        |                                            |                                |                               |                                |
| Headache                                               | 23                                         | 0.6                            | 16                            | 0.9                            |

\* Graded per NCI CTCAE v4.03

#### Endometrial Carcinoma

In Combination with Chemotherapy (KEYNOTE-868)

In patients with endometrial carcinoma receiving KEYTRUDA plus chemotherapy (paclitaxel and carboplatin), adverse events were generally similar to those observed with KEYTRUDA alone or chemotherapy alone with the exception of rash maculo-papular (13% all Grades; 2% Grades 3-4).

In Combination with Lenvatinib (KEYNOTE-775 and KEYNOTE-146)

Table 51 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-775. Adverse events occurring in patients with endometrial carcinoma receiving KEYTRUDA in combination with lenvatinib in KEYNOTE-146 were generally similar to those occurring in patients in KEYNOTE-775.

**Table 51: Adverse Events Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Doxorubicin or Paclitaxel (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (KEYNOTE-775)**

|                                                             | KEYTRUDA +<br>lenvatinib<br>n=406 |                  | Doxorubicin or<br>paclitaxel<br>n=388 |                  |
|-------------------------------------------------------------|-----------------------------------|------------------|---------------------------------------|------------------|
| Adverse Events*                                             | All<br>Grades <sup>†</sup><br>(%) | Grade 3-4<br>(%) | All<br>Grades <sup>†</sup><br>(%)     | Grade 3-4<br>(%) |
| <b>Vascular Disorders</b>                                   |                                   |                  |                                       |                  |
| Hypertension                                                | 64                                | 37.9             | 5.2                                   | 2.3              |
| <b>Endocrine Disorders</b>                                  |                                   |                  |                                       |                  |
| Hypothyroidism                                              | 57                                | 1.2              | 0.8                                   | 0                |
| <b>Gastrointestinal Disorders</b>                           |                                   |                  |                                       |                  |
| Diarrhea                                                    | 54                                | 8                | 20                                    | 2.1              |
| Nausea                                                      | 50                                | 3.4              | 46                                    | 1.3              |
| Vomiting                                                    | 37                                | 2.7              | 21                                    | 2.3              |
| Abdominal pain                                              | 20                                | 2.5              | 14                                    | 1.3              |
| <b>Metabolism and Nutrition Disorders</b>                   |                                   |                  |                                       |                  |
| Decreased appetite                                          | 45                                | 8 <sup>‡</sup>   | 21                                    | 0.5              |
| <b>Investigations</b>                                       |                                   |                  |                                       |                  |
| Decreased weight                                            | 34                                | 10               | 6                                     | 0.3              |
| Increased ALT                                               | 21                                | 4.6              | 5                                     | 0.8              |
| <b>General Disorders and Administration Site Conditions</b> |                                   |                  |                                       |                  |
| Fatigue                                                     | 33                                | 5                | 28                                    | 3.1              |
| Asthenia                                                    | 24                                | 6                | 24                                    | 3.9              |
| <b>Musculoskeletal and Connective Tissue Disorders</b>      |                                   |                  |                                       |                  |
| Arthralgia                                                  | 31                                | 1.7              | 8                                     | 0                |
| <b>Renal and Urinary Disorders</b>                          |                                   |                  |                                       |                  |
| Proteinuria                                                 | 29                                | 5                | 2.8                                   | 0.3              |
| <b>Infections</b>                                           |                                   |                  |                                       |                  |
| Urinary tract infection                                     | 26                                | 3.9              | 10                                    | 1.0              |
| <b>Nervous System Disorders</b>                             |                                   |                  |                                       |                  |
| Headache                                                    | 25                                | 0.5              | 9                                     | 0.3              |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>      |                                   |                  |                                       |                  |
| Dysphonia                                                   | 23                                | 0                | 0.5                                   | 0                |
| <b>Skin and Subcutaneous Tissue Disorders</b>               |                                   |                  |                                       |                  |
| Palmar-plantar<br>erythrodysesthesia<br>syndrome            | 21                                | 2.7              | 0.8                                   | 0                |

\* The median duration of study treatment was 7.6 months (range: 1 day to 26.8 months). The median duration of exposure to KEYTRUDA was 6.9 months (range: 1 day to 25.8 months) compared to 3.4 months (range: 1 day to 25.8 months) for chemotherapy.

<sup>†</sup> Graded per NCI CTCAE v4.03

<sup>‡</sup> There was one Grade 5 (0.2%) reported.

Discontinuation of KEYTRUDA, lenvatinib or both due to an adverse reaction (Grades 1-4) occurred in 30% of patients; 15% KEYTRUDA, and 11% both drugs. The most common adverse reactions leading to discontinuation of KEYTRUDA were diarrhea, increased ALT, and intestinal obstruction (each 1.0%). Refer to the lenvatinib prescribing information for lenvatinib discontinuation information.

Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 69% of patients; KEYTRUDA was interrupted in 50%, and both drugs were interrupted in 31% of patients. The most

common adverse reactions leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were diarrhea (8%), increased ALT (3.9%), hypertension (3.4%), increased AST (3.2%), decreased appetite (2.2%), fatigue (2.2%), urinary tract infection (2.2%), proteinuria (2.0%), and asthenia (2.0%). Refer to the lenvatinib prescribing information for lenvatinib interruption information.

#### Triple-Negative Breast Cancer

**KEYNOTE-522:** Controlled study of neoadjuvant and adjuvant treatment of patients with high-risk early-stage TNBC

In patients with high-risk early-stage TNBC receiving KEYTRUDA in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide), given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment, adverse events occurring in at least 20% of the patients and at a higher incidence ( $\geq 5\%$  difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide), given as a neoadjuvant treatment and continued alone as adjuvant treatment were diarrhea (41% vs. 34%), rash (30% vs. 24%), pyrexia (28% vs. 19%), and decreased appetite (23% vs. 17%). Of these adverse events, Grades 3-4 events were diarrhea (3.2% vs. 1.8%), rash (1.8% vs. 0.3%), pyrexia (1.3% vs. 0.3%), and decreased appetite (0.9% vs. 0.3%).

**KEYNOTE-355:** Controlled study of combination therapy in patients with locally recurrent unresectable or metastatic TNBC

In patients with TNBC receiving KEYTRUDA in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin), adverse events occurring in at least 20% of the patients and at a higher incidence ( $\geq 5\%$  difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin) were diarrhea (28% vs. 23%), decreased appetite (21% vs. 14%), and rash (20% vs. 12%). Of these adverse events, Grades 3-4 events were diarrhea (1.8% vs. 1.8%), decreased appetite (0.8% vs. 0.4%), and rash (0.8% vs. 0.0%).

#### **Biliary Tract Carcinoma**

In patients with BTC receiving KEYTRUDA plus chemotherapy (gemcitabine and cisplatin), adverse events occurring at a higher incidence ( $\geq 5\%$ ) compared to placebo plus chemotherapy were pyrexia (26% vs. 20%), rash (17% vs. 9%), pruritus (15% vs. 10%) and hypothyroidism (9% vs. 2.6%). Of these adverse events, Grades 3-4 events were pyrexia (2.3% vs. 0.9%), rash (0.6% vs. 0.4%), pruritus (0.0% vs. 0.0%) and hypothyroidism (0.2% vs. 0.0%).

#### **Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of KEYTRUDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Musculoskeletal and connective tissue disorders:* arthritis

*Eye disorders:* Vogt-Koyanagi-Harada syndrome

*Immune system disorders:* hemophagocytic lymphohistiocytosis

*Nervous system disorders:* optic neuritis

## **XV. OVERDOSAGE**

There is no information on overdosage with KEYTRUDA. The maximum tolerated dose of KEYTRUDA has not been determined. In clinical trials, patients received up to 10 mg/kg with a similar safety profile to that seen in patients receiving 2 mg/kg.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

#### **XVI. APPEARANCE & AVAILABILITY**

Clear to slightly opalescent, colorless to slightly yellow solution.

Each 4 ml vial contains 100 mg pembrolizumab.

#### **XVII. STORAGE**

Store in a refrigerator (2°C to 8°C; 36°F to 46°F).

Protect from light. Do not freeze. Do not shake.

For storage conditions after reconstitution or dilution of the medicinal product, see *Dosage and Administration* (VI).

#### **XVIII. SHELF-LIFE**

Please refer to expiry on the outer carton.

#### **XIX. MANUFACTURED BY**

MSD International GmbH  
T/A MSD Ireland (Carlow)  
Dublin Road, Carlow,  
Co. Carlow, Ireland

#### **XX. PACKED AND RELEASED BY**

Merck Sharp & Dohme B.V.  
Waarderweg 39, Haarlem, 2031 BN  
Netherlands

#### **XXI. PRODUCT REGISTRATION HOLDER**

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Date of revision: 11 June 2026

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