PRODUCT NAME
YONDELIS® 1 mg for Injection

DOSAGE FORMS AND STRENGTHS
Powder for concentrate for solution for infusion.

YONDELIS® drug product is provided as a sterile lyophilized white to off-white powder.

Each vial contains 1 mg of trabectedin.

1 mL of reconstituted solution contains 0.05 mg of trabectedin (see *Instructions for Use and Handling and Disposal*).

INN: Trabectedin; CAS Registry No.: 114899-77-3

Chemical Name: (CAS): (1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-spiro[6,16 (epithiopropanoxymethano)-7,13-imino-12*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'(2'*H*)-isoquinolin]-19-one.

Molecular Formula: The molecular formula is $C_{39}H_{43}N_3O_{11}S$.

Molecular Weight: The molecular weight of trabectedin is 761.84 g/mol.

Solubility: Trabectedin is hydrophobic, and has a low solubility in water. Trabectedin solubility is enhanced in acidic media.

For excipients, see *List of Excipients.*

CLINICAL INFORMATION
Indications
YONDELIS® is indicated for the treatment of adult patients with advanced soft tissue sarcoma (STS), after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

YONDELIS® in combination with pegylated liposomal doxorubicin hydrochloride (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

Dosage and Administration
YONDELIS® must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other health professionals specialized in the administration of cytotoxic agents.

Posology
For the treatment of soft tissue sarcoma (STS), the recommended starting dose is 1.5 mg/m^2 body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles.

For the treatment of ovarian cancer, YONDELIS® is administered every three weeks as a 3-hour infusion at a dose of 1.1 mg/m^2, immediately after PLD 30 mg/m^2. To minimize the risk of PLD infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent PLD infusions may be administered over a 1-hour period. (See also PLD package insert for specific administration advice).

All patients must receive corticosteroids e.g. 20mg of dexamethasone intravenously 30 minutes prior to PLD (in combination therapy) or YONDELIS® (in monotherapy); not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed. The following criteria are required to allow treatment with YONDELIS®:

- Absolute neutrophil count (ANC) ≥ 1,500/mm^3
- Platelet count ≥ 100000/mm^3
- Hemoglobin ≥ 9 g/dL
- Bilirubin ≤ upper limit of normal (ULN)
- Alkaline phosphatase of non-osseous origin ≤ 2.5 x ULN (consider hepatic isoenzymes 5-nucleotidase or gamma glutamyl trans-peptidase (GGT), to distinguish if the elevation could be osseous in origin)
- Albumin ≥ 25 g/L
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤ 2.5 x ULN
- Creatinine clearance ≥ 30 mL/min;
    - Combination therapy for ovarian cancer: serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L) or creatinine clearance ≥ 60 mL/min
- Creatine phosphokinase (CPK) ≤ 2.5 x ULN

The same criteria as above must be met prior to re-treatment. Otherwise treatment must be delayed for up to 3 weeks until the criteria are met.

Additional monitoring of hematological parameters bilirubin, alkaline phosphatase, aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.

The same dose should be given for all cycles provided that no grade 3 – 4 toxicities are seen and that the patient fulfils the re-treatment criteria.

Dose adjustments during treatment

Prior to re-treatment, patients must fulfill the baseline criteria defined above. If any of the following events occur at any time between cycles, the dose must be reduced one level, according to table 1 below, for subsequent cycles:

- Neutropenia < 500/mm^3 lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia < 25,000/mm^3
- Increase of bilirubin > ULN and/or alkaline phosphatase > 2.5 x ULN
- Increase of aminotransferases (AST or ALT) > 2.5 x ULN (monotherapy) or > 5 x ULN (combination therapy), which has not recovered by day 21

- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the dose may be further reduced (see below). Colony stimulating factors can be administered for hematologic toxicity in subsequent cycles according to local standard practice.

Table 1: Dose modification table for YONDELIS® (as single agent for soft tissue sarcoma (STS) or in combination for ovarian cancer) and PLD

	Soft tissue sarcoma	**Ovarian cancer**	
	YONDELIS®	YONDELIS®	PLD
Starting dose	1.5 mg/m^2	1.1 mg/m^2	30 mg/m^2
First reduction	1.2 mg/m^2	0.9 mg/m^2	25 mg/m^2
Second reduction	1 mg/m^2	0.75 mg/m^2	20 mg/m^2

See the PLD package insert for more detailed information on PLD dose adjustments.

In the event that further dose reductions are necessary, treatment discontinuation should be considered.

Duration of treatment
In clinical trials, there were no pre-defined limits to the number of cycles administered. Treatment continued whilst clinical benefit was noted. YONDELIS® has been administered for 6 or more cycles in 29.5% and 52% of patients treated with the monotherapy and combination dose and schedule respectively. The monotherapy and combination regimens have been used for up to 38 and 21 cycles respectively. No cumulative toxicities have been observed in patients treated with multiple cycles.

Paediatric population
As no efficacy was observed, YONDELIS® should not be used in children below 18 years with paediatric sarcomas (see *Pharmacodynamic Properties*).

Elderly
No specific studies in older people have been performed. Overall 20% of the 1,164 patients in the integrated safety analysis of monotherapy clinical trials were over 65 years. Of the 333 patients with ovarian cancer who received trabectedin in combination with PLD, 24% were 65 years of age or older and 6% were over 75 years. No relevant differences in the safety profile were seen in this patient population. It seems that plasma clearance and distribution volume of trabectedin are not influenced by age. Therefore, dose adjustments based uniquely on age criteria are not routinely recommended.

Hepatic impairment
No studies with the proposed regimen have been conducted in patients with liver dysfunction. Thus, data are not available to recommend a lower starting dose in patients with hepatic impairment. However, special caution is advised and dose adjustments may be necessary in these patients since systemic exposure is probably increased and the risk of hepatotoxicity might be

increased. Patients with elevated bilirubin must not be treated with YONDELIS® (see *Warnings and Precautions*).

Renal impairment
Studies including patients with renal insufficiency (creatinine clearance < 30 mL/min for the monotherapy, and < 60 mL/min for the combination regimen) have not been conducted and therefore YONDELIS® must not be used in this patient population (see *Warnings and Precautions*). Considering the pharmacokinetic characteristics of trabectedin (see *Pharmacokinetic Properties*), no dose adjustments are warranted in patients with mild or moderate renal impairment.

Method of administration
Intravenous administration through a central venous line is strongly recommended (see *Warnings and Precautions* and *Instructions for Use and Handling and Disposal*).

For instructions on reconstitution and dilution of the medicinal product before administration, see *Instructions for Use and Handling and Disposal.*

Soft tissue sarcoma
Intravenous infusion over 24 hours with a three-week interval between cycles.

Ovarian cancer
Intravenous infusion over 3 hours after PLD 30 mg/m2 as a 90-minute intravenous infusion.
For PLD dosage administration instructions, see local manufacturers' prescribing information.

Contraindications
YONDELIS® should not be administered to nursing mothers (see *Pregnancy, Breast-feeding and Fertility*).

YONDELIS® should not be administered to patients with known hypersensitivity to any of its components.

YONDELIS® should not be administered to patients with an active serious or uncontrolled infection.

Warnings and Precautions
Hepatic impairment
Patients must meet specific criteria on hepatic function parameters to start treatment with YONDELIS®. Since systemic exposure to trabectedin is increased due to hepatic impairment and therefore the risk of hepatotoxicity might be increased, patients with clinically relevant liver diseases should be closely monitored and the dose adjusted if needed. Patients with elevated bilirubin at the time of initiation of a new treatment cycle must not be treated with trabectedin (see *Dosage and Administration*).

Renal impairment

Creatinine clearance must be monitored prior to and during treatment. Trabectedin as a single agent must not be used in patients with creatinine clearance < 30 mL/min or in patients treated in combination with PLD with creatinine clearance < 60 mL/min (see *Dosage and Administration*).

Myelosuppression
Grade 3-4 hematologic laboratory abnormalities (neutropenia, leukopenia, thrombocytopenia and anemia) were very commonly (>10%) reported in Phase 2 and 3 clinical studies of patients with STS and ovarian cancer treated with YONDELIS®. Among patients with STS with Grade 3-4 decreased neutrophil counts, the first median value of Grade 3 severity was observed at Day 12, followed by recovery to Grade 2 by Day 24. Abnormalities in neutrophil counts were non-cumulative, including in patients who received prolonged treatment with trabectedin (≥6 cycles).

Among patients with ovarian cancer with Grade 3-4 decreased neutrophil counts, neutrophil count nadir occurred at a median of 15 days and recovered within a week.

A full blood cell count including differential and platelet count must be performed at baseline, weekly for the first two cycles and then once between cycles (see *Dosage and Administration*). YONDELIS® should not be administered to patients with baseline neutrophil counts of less than 1500/mm^3, platelets count of less than 100000/mm^3 or hemoglobin < 9 g/dL. If neutropenia (ANC < 500/mm^3) lasting more than 5 days or neutropenia associated with fever or infection, or thrombocytopenia (platelet counts < 25000/mm^3) occur, dose reduction is recommended (see *Dosage and Administration*).

Supportive care/colony stimulating factors should be administered if needed according to institutional guidelines.

Nausea and vomiting
Grade 3 or 4 vomiting and nausea were reported commonly. All patients must be premedicated with corticosteroids such as dexamethasone. Additional anti-emetics may be administered as needed (see *Dosage and Administration* and *Interactions*).

Rhabdomyolysis and severe CPK elevations (> 5 x ULN)
In Phase 2 and 3 clinical studies of patients treated for STS, CPK elevations (Grade 3-4) in association with renal failure, rhabdomyolysis, and other muscle-related toxicities such as myositis, muscle weakness or muscle pain were observed in 4% of patients (n=31). Of these, four patients had fatal outcomes; two due to rhabdomyolysis and two due to renal failure. In total rhabdomyolysis was reported in four patients (0.5%).

Rhabdomyolysis has been uncommonly reported and severe CPK elevations were observed in 2% of patients treated with YONDELIS® in combination with PLD usually in association with myelotoxicity, severe liver function test abnormalities or renal failure.

Therefore, CPK should be closely monitored with strict adherence to treatment guidelines during the treatment phase and prior to re-treatment. Trabectedin must not be used in patients with CPK > 2.5 ×ULN (see *Dosage and Administration*). If rhabdomyolysis occurs, supportive measures

such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Treatment with YONDELIS® should be discontinued until the patient fully recovers.

Caution should be taken if medicinal products associated with rhabdomyolysis (e.g., statins) are administered concomitantly with trabectedin, since the risk of rhabdomyolysis may be increased.

Liver function test (LFT) abnormalities
Reversible acute increases in AST and ALT have been reported in patients treated with YONDELIS® monotherapy or in combination with PLD. Grade 3 or 4 transaminase elevations occurred very commonly; Grade 4 transaminase elevations occurred commonly. The median time to the occurrence of ALT or AST increase to Grade 3 or 4 levels was 8 days. Elevated levels decreased to below Grade 3 or 4 in about 8 days. Transaminase elevations were non-cumulative and decreased in magnitude and incidence with each subsequent cycle. Patients with increases in AST, ALT or alkaline phosphatase between cycles may necessitate dose reduction (see *Dosage and Administration*). YONDELIS® must not be used in patients with elevated bilirubin at the time of initiation of cycle. Bilirubin elevations that occurred since the previous dose should be reviewed for cause prior to next dosing, and dose reduction considered (see *Dosage and Administration*).

Cardiac dysfunction
In a Phase 3 clinical study of patients treated for liposarcoma or leiomyosarcoma who received prior anthracyclines, cardiac dysfunction (including cardiac failure, cardiac failure acute, congestive heart failure, cardiomyopathy, ejection fraction decreased, diastolic dysfunction, left ventricular dysfunction or right ventricular dysfunction) occurred in 20 (5.2%) of 378 patients receiving YONDELIS®, 15 (4%) of whom developed Grade 3 or 4 cardiac dysfunction. One patient suffered fatal cardiac failure. In the dacarbazine group (n=172), cardiac dysfunction occurred in 4 (2.3%) patients, 2 (1.2%) of whom reported Grade 3 events. No cardiac dysfunction events in this treatment group were reported with a Grade 4 event or an event that led to death.

Protocol specified assessments of left ventricular ejection fraction (LVEF) [echocardiogram or multigated acquisition (MUGA)] at baseline and at the time of treatment discontinuation were obtained in 251 patients (66%) receiving YONDELIS® and in 100 patients (58%) receiving dacarbazine. Absolute decreases of LVEF ≥15% at the end of treatment or an absolute decrease of ≥5% if the ejection fraction was lower than the normal range were similar for the YONDELIS® group (13.5%) and dacarbazine group (11%) despite the greater increase in overall exposure for the YONDELIS® group (median 4 cycles within YONDELIS® group versus 2 cycles within the dacarbazine group).

Multivariate analyses (MVA) revealed cardiac risk factors associated with YONDELIS®.

In the treatment of L-type sarcomas using monotherapy, a MVA of data from a single Phase 3 study demonstrated that prior cumulative anthracycline dose of $\geq$300 mg/m^2 and baseline LVEF less than the lower limit of normal (<LLN) were risk factors for the development of cardiac-related treatment-emergent adverse events (TEAEs). A MVA from an integrated data set of 11 studies conducted using monotherapy for various solid tumors, demonstrated that age

≥65 years and history of cardiovascular disease were also associated with an increased risk of cardiac-related TEAEs. A MVA evaluating data from 2 ovarian cancer studies in which combination therapy was used (trabectedin+DOXIL [pegylated liposomal doxorubicin hydrochloride]) showed an increased risk of cardiac-related TEAEs for patients with a history of prior cardiac medication use.

Patients with LVEF < LLN, prior cumulative anthracycline dose of ≥300 mg/m^2, or a history of cardiovascular disease may be at increased risk of cardiac dysfunction. Conduct a thorough cardiac assessment including determination of LVEF by echocardiogram or MUGA scan before initiation of YONDELIS® and at 2 to 3-month intervals thereafter until YONDELIS® is discontinued.

Patients should be monitored for cardiac-related adverse events or myocardial dysfunction, particularly patients who have a higher risk of cardiomyopathy due to prior anthracycline exposure, the presence of symptoms of decreasing cardiac function, history of cardiovascular disease or advanced age (≥65 years). For patients with Grade 3 or 4 cardiac adverse events indicative of cardiomyopathy or for patients with a LVEF that decreases below the LLN (assessed as either an absolute decrease of LVEF of ≥15% or <LLN with an absolute decrease of ≥5%), YONDELIS® should be discontinued.

Injection site reactions
The use of central venous access is strongly recommended (see *Dosage and Administration*). Patients may develop a potentially severe injection site reaction when trabectedin is administered through a peripheral venous line.

There have been few reported cases of trabectedin extravasation, with subsequent tissue necrosis requiring debridement. There is no specific antidote for extravasation of trabectedin. Extravasation should be managed by local standard practice.

Drug interactions
Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) and such combinations should be avoided if possible. In addition, aprepitant and systemic fluconazole should be used with caution during YONDELIS® treatment. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (see *Dosage and Administration*).

Caution should be taken if medicinal products associated with hepatotoxicity are administered concomitantly with trabectedin, since the risk of hepatotoxicity may be increased. The concomitant use of trabectedin with alcohol must be avoided.

Capillary leak syndrome (CLS)
Cases of CLS have been reported with YONDELIS® including some cases with a fatal outcome. If symptoms of possible CLS develop, such as unexplained edema with or without hypotension, reassess albumin level. A rapid decline in albumin level may be indicative of CLS. If a diagnosis

of CLS is confirmed after exclusion of other causes, discontinue YONDELIS® and promptly initiate CLS treatment according to institutional guidelines (see *Dosage and Administration*).

Allergic reactions
During postmarketing experience, rare cases of hypersensitivity reactions, with very rare occurrence of fatal outcome, have been reported in association with trabectedin administration either alone or in combination with PLD (see *Contraindications* and *Adverse Reactions*).

Men and women of childbearing potential
Women of childbearing potential must use effective contraception during treatment and 3 months thereafter. Men who are fertile must use effective contraception during treatment and 5 months after treatment (see *Pregnancy, Breast-feeding and Fertility*).

Immediately inform the treating physician if a pregnancy occurs.

PLD special warnings and special precautions for use
See PLD manufacturer's prescribing information for special warnings and precautions regarding PLD.

Interactions
Effects of other substances on trabectedin
A population analysis based on sparse-sampling data from a Phase 3 study demonstrated that the plasma clearance of trabectedin was decreased by approximately 31% in 86 patients who were co-administered PLD 30 mg/m^2 compared to 745 patients enrolled in 14 studies who received trabectedin alone. Data from a separate Phase 1 study, in which full pharmacokinetic profiles for trabectedin were obtained for 16 patients who received trabectedin 0.9 to 1.3 mg/m^2 in combination with PLD 30 mg/m^2, indicated a comparable (i.e., a mean difference of 16 %) plasma clearance of trabectedin as for the same doses of trabectedin given as a single agent.

Results from the population pharmacokinetic analyses (n=831 subjects) indicated that the plasma clearance of trabectedin was 19% higher in patients who received any concomitant dexamethasone administration relative to those who did not.

Since trabectedin is metabolized mainly by CYP3A4, the metabolic clearance of trabectedin is likely to be decreased in patients who are co-administered drugs that potently inhibit the activity of this isoenzyme. Similarly, the co-administration of trabectedin with potent inducers of CYP3A4 may increase the metabolic clearance of trabectedin.

Two drug-drug interaction Phase 1 studies have confirmed trends toward increased and decreased trabectedin exposures when administered with ketoconazole and rifampin, respectively.

In a drug-drug interaction study (n=8) with ketoconazole, a potent CYP3A4 inhibitor, systemic exposure of trabectedin was increased by approximately 21% (C_{max}) and 66% (AUC_{last}), when trabectedin was given concomitantly with ketoconazole (total daily dose of 400 mg). Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent

CYP3A4 inhibitors (e.g. oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) and such combinations should be avoided if possible. In addition, aprepitant and systemic fluconazole should be used with caution during YONDELIS® treatment. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (see *Dosage and Administration*).

In a drug-drug interaction study (n=8) with rifampin, a potent CYP3A4 inducer, systemic exposure of trabectedin was decreased by approximately 22% (C_{max}) and 31% (AUC_{last}), when trabectedin was given concomitantly with rifampin (total daily dose of 600 mg). Therefore, the concomitant use of trabectedin with strong CYP3A4 inducers (e.g., rifampin, phenobarbital, Saint John's Wort) should be avoided if possible.

In vitro preclinical studies have shown trabectedin is a substrate of multiple efflux transporters including P-gp, MRP2 and potentially MRP3 and MRP4, but not BCRP. Concomitant administration of inhibitors of P-gp, e.g., cyclosporine and verapamil, may alter trabectedin distribution. The clinical relevance of this interaction e.g., for CNS toxicity, has not been established and caution should be exercised when concomitantly administering trabectedin with inhibitors of P-gp.

The potential for other compounds to displace trabectedin from its plasma protein binding is considered to be very limited on the basis of *in vitro* data.

Impact of trabectedin on co-administered drugs
In vitro, trabectedin does not induce or inhibit major cytochrome P450 enzymes.

A population analysis based on sparse-sampling data from a Phase 3 study demonstrated that the plasma pharmacokinetics of PLD 30 mg/m^2 are similar when co-administered with trabectedin 1.1 mg/m^2 (86 patients) and when given alone (80 patients).

Maximal total and unbound trabectedin plasma levels reached in STS patients are about 1.8 and 0.05 nM, respectively, and in relapsed ovarian cancer patients are about 10.3 and 0.26 nM, respectively, and are only present during infusion, i.e., during day 1 of a 3-week treatment cycle; a clinically relevant inhibition of transporters by trabectedin at this low concentration level is not expected.

In view of the extremely low trabectedin plasma levels relative to the physiological levels of plasma proteins, the potential for trabectedin to displace other compounds from their plasma protein binding is considered to be very unlikely.

Pregnancy, Breast-feeding and Fertility
Pregnancy
No sufficient clinical data on exposed pregnancies are available. However, based on its known mechanism of action, trabectedin may cause serious birth defects when administered during pregnancy. Trabectedin crossed the placenta when administered to pregnant rats. The use of

trabectedin during pregnancy is not recommended. If pregnancy occurs during treatment, the patient must be informed of the potential risk to the fetus (see *Non-Clinical Information*).

Women of childbearing potential must use effective contraception during treatment and 3 months thereafter. Men who are fertile must use effective contraception during treatment and 5 months after treatment (see *Warnings and Precautions* and *Non-Clinical Information*).

Immediately inform the treating physician if a pregnancy occurs.

If pregnancy occurs during treatment genetic counseling should be considered.

Breast-feeding
It is not known whether trabectedin is excreted in human milk. The excretion of trabectedin in milk has not been studied in animals. Breast-feeding is contraindicated during treatment and 3 months thereafter (see *Contraindications*).

Fertility
Trabectedin can have genotoxic effects. Advice on conservation of oocytes or sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with YONDELIS®.

Genetic counseling is also recommended for patients wishing to have children after therapy.

Effects on Ability to Drive and Use Machines
No studies on the effects of the ability to drive and to use machines have been performed. However, fatigue or asthenia has been reported in patients receiving trabectedin. Patients who experience any of these events during therapy must not drive or operate machines.

Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of trabectedin based on the comprehensive assessment of the available adverse event information. A causal relationship with trabectedin cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Monotherapy
YONDELIS® in monotherapy in advanced STS.

In Phase 2 and 3 studies in patients with STS receiving YONDELIS® at the recommended dose (N=755), adverse reactions of Grade 3 or 4 severity were reported in 57% of patients, with 14% being classified as serious. The most common adverse reactions (≥20%) of any severity grade were anemia, increases in AST/ALT, leukopenia, neutropenia, nausea, fatigue, blood alkaline phosphatase increased, blood albumin decreased, thrombocytopenia, vomiting, blood creatinine increased, constipation, decreased appetite, blood creatine phosphokinase increased, diarrhea,

dyspnea, headache, and pyrexia. Fatal adverse reactions have occurred in 2.3% of patients. They were often the result of a combination of events including myelosuppression, febrile neutropenia (some with sepsis), hepatic dysfunction, renal or multiorgan failure, and rhabdomyolysis.

The table below displays the adverse reactions reported in ≥ 1% of patients according to the standard MedDRA system organ class. Both adverse reactions and laboratory values have been used to provide frequencies. Adverse reactions are presented in order of decreasing frequency.

Table 2: Adverse reactions reported in ≥1% of patients with soft tissue sarcoma in clinical trials (Phase 2 and 3) assigned to the recommended regimen [1.5 mg/m^2, 24 hour infusion every 3 weeks (24-h q3wk)]

	All Grades	---- Toxicity Grade ----		
System/Organ Class Adverse Reaction	N=755 %	Grade 3 %	Grade 4 %	Grade 3-4 %
Blood and lymphatic system disorders				
Anemia*(N=754)	96.3	16.3	0	16.3
Leukopenia*(N=648)	77.9	27.6	11.0	38.6
Neutropenia*(N=709)	73.8	26.4	22.4	48.8
Thrombocytopenia*(N=753)	50.5	7.2	10.0	17.1
Febrile neutropenia	3.8	3.4	0.3	3.7
Lymphopenia	4.5	1.9	0.1	2.0
Investigations				
Alanine aminotransferase increased*(N=754)	92.6	34.9	3.4	38.3
Aspartate aminotransferase increased*(N=753)	89.0	23.2	1.9	25.1
Blood alkaline phosphatase increased*(N=753)	62.9	1.9	0	1.9
Blood albumin decreased*(N=669)	62.8	4.3	0	4.3
Blood creatinine increased*(N=752)	42.4	3.2	0.8	4.0
Blood creatine phosphokinase increased*(N=597)	31.3	2.8	2.8	5.7
Blood bilirubin increased*(N=754)	19.4	1.7	0.1	1.9
Weight decreased	8.1	0.1	0	0.1
Gamma-glutamyltransferase increased	1.9	1.1	0.1	1.2
Gastrointestinal disorders				
Nausea	73.8	7.0	0.1	7.2
Vomiting	44.4	6.4	0.5	6.9
Constipation	35.9	0.7	0.3	0.9
Diarrhea	26.2	1.3	0	1.3
Abdominal pain	16.2	3.3	0.3	3.6
Dyspepsia	6.2	0	0	0
Stomatitis	6.1	0.1	0	0.1
Abdominal pain upper	5.0	0.3	0	0.3
General disorders and administration site conditions				
Fatigue	65.0	8.5	0.8	9.3
Pyrexia	20.4	0.4	0.3	0.7
Edema peripheral	19.6	0.8	0	0.8

Asthenia	8.6	1.5	0	1.5
Injection site reaction	8.5	0.9	0	0.9
Edema	3.6	0.4	0	0.4
Infections and infestations				
Infection	4.5	1.2	0.4	1.6
Pneumonia	3.6	2.0	0	2.0
Catheter site infection	2.8	1.5	0	1.5
Sepsis	1.9	0.4	1.5	1.9
Respiratory, thoracic and mediastinal disorders				
Dyspnea	22.8	4.5	0.7	5.2
Metabolism and nutrition disorders				
Decreased appetite	31.7	1.6	0.3	1.9
Dehydration	9.3	2.6	0	2.6
Musculoskeletal and connective tissue disorders				
Back pain	13.2	1.2	0	1.2
Arthralgia	11.8	0.1	0	0.1
Myalgia	9.9	0.3	0	0.3
Rhabdomyolysis	1.1	0.1	0.9	1.1
Vascular disorders				
Hypotension	5.7	0.9	0.7	1.6
Flushing	3.6	0	0	0
Nervous system disorders				
Headache	22.1	0.4	0	0.4
Dizziness	9.1	0.3	0	0.3
Dysgeusia	6.9	0	0	0
Paresthesia	4.1	0	0	0
Peripheral sensory neuropathy	3.8	0.1	0	0.1
Skin and subcutaneous tissue disorders				
Alopecia	4.0	0.1	0.1	0.3
Psychiatric disorders				
Insomnia	10.7	0.1	0	0.1

Notes:
*Percentages calculated with the number of subjects per lab test name with data as denominat
or
Fatal Sepsis and Rhabdomyolysis events (Toxicity Grade 5) are summarized under Toxicity Grade 4.
Injection site reaction includes the following Preferred Terms: Catheter site pain, Catheter site inflammation, Injection site pain, Catheter site erythema, Catheter site pruritus, Catheter site swelling, Infusion site extravasation, Catheter site edema, Catheter site related reaction, Infusion site pain, Injection site bruising, Injection site reaction, Catheter site bruise and Infusion site reaction
Pneumonia includes the following Preferred Terms: Lung infection, Lobar pneumonia and Pneumonia
Sepsis includes the following Preferred Terms: Clostridium difficile sepsis and Sepsis.
Lymphopenia includes the following Preferred Terms:
Lymphopenia and Lymphocyte count decreased.
Toxicity grade is based on NCI common toxicity criteria, version 4.0.
Adverse reactions reported any time from the first treatment dose to within 30 days after last treatment dose are included.
Incidence is based on the number of subjects, not the number of events.
Adverse reactions are coded using MedDRA version 16.0.

Blood and lymphatic system disorders

Neutropenia and Infection:

In study ET743-SAR-3007, 6% of patients (n=22) in the YONDELIS® group and 2% of patients (n=3) in the dacarbazine group had selected infections of febrile neutropenia, sepsis, or septic shock in the setting of neutropenia of any grade. In the YONDELIS® arm, there were 9 patients (2%) with neutropenic sepsis or septic shock of which 4 patients had fatal outcomes. There were no sepsis-related deaths in the dacarbazine group.

Thrombocytopenia-bleeding:

In study ET743-SAR-3007, bleeding events associated with Grade 3-4 decreases in platelet counts were infrequent i.e. 3% patients in the YONDELIS® group versus 5% patients in the dacarbazine group. There were no thrombocytopenic bleeding events leading to death in either treatment group.

In phase 2 and 3 clinical studies serious bleeding events associated with grade 3-4 decreases in platelet counts within the same treatment cycle occurred in <1% of patients.

Hepatobiliary disorders

AST/ALT increases:

Transient Grade 3 and Grade 4 increases of AST and ALT were observed. In Phase 2 clinical trials of patients assigned to the recommended treatment regime in several cancer types including STS, the median time to reach the peak values was 5 days for both AST and ALT. Most of the values had decreased to Grade 1 or resolved by day 14 - 15 and less than 2% of cycles had recovery times longer than 25 days. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time.

In study ET743-SAR-3007 incidence of Grade 3-4 ALT and AST laboratory abnormalities, were higher in the YONDELIS® group versus the dacarbazine group (32% and 17% versus 0.6% and 1.2% respectively). Transaminase elevations were managed by YONDELIS® dose reductions and delays (see *Warnings and Precautions*).

Hyperbilirubinemia:
Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset.

Severe liver injury:
In study ET743-SAR-3007, 33% of patients in the YONDELIS® group had a Grade 3 event and 2% had Grade 4 events related to liver injury which were mainly laboratory abnormalities in liver function tests (LFT). Severe drug-induced liver injury (AST/ALT>3×ULN, total bilirubin ≥2×ULN, ALP <2×ULN prior to and including the day of first occurrence of total bilirubin elevation ≥2×ULN, and no alternative explanation) was rare; with 3 patients in the YONDELIS® arm, neither of which progressed to liver failure. There were no deaths due to liver injury in this study.

In the Phase 2 and 3 clinical studies, manifestations of severe liver injury were uncommon with an incidence of 1%. Individual signs and symptoms included jaundice, hepatomegaly and liver pain. Mortality in the presence of hepatic injury occurred in less than 1% of patients.

Rhabdomyolysis and CPK elevations:
In study ET743-SAR-3007, CPK elevations of any grade were observed in 33% of patients treated with YONDELIS® versus 9% in the dacarbazine arm. In the YONDELIS®group 24 patients (6%), and one patient (<1%) in the dacarbazine group reported Grade 3-4 increases in CPK levels. Of the 24 patients in the YONDELIS® group, 6 patients had muscular weakness, myositis or musculoskeletal pain and four patients had rhabdomyolysis. Rhabdomyolysis was fatal for 2 patients. There were no deaths in the dacarbazine group due to rhabdomyolysis associated with elevated CPK (Grade 3-4).

Other adverse reactions
Hepatic failure:
Rare cases of hepatic failure (including cases with fatal outcomes) have been reported in patients with serious underlying medical conditions treated with trabectedin. Some potential risk factors that may have contributed to increased trabectedin toxicity observed in these cases were dose management inconsistent with recommended guidelines, potential CYP3A4 interaction due to multiple competing CYP3A4 substrates or CYP3A4 inhibitors, or lack of dexamethasone prophylaxis.

Combination therapy
YONDELIS® in combination with PLD in advanced ovarian cancer

The following safety profile of YONDELIS® is based on the evaluation of a Phase 3 clinical trial OVA-301 of 663 patients with advanced relapsed ovarian cancer who receive either PLD

(30 mg/m^2) followed by YONDELIS® (1.1 mg/m^2) every 3 weeks or PLD alone (50 mg/m^2) every 4 weeks. The combination of YONDELIS® with PLD was given to 333 patients in this trial. In the combination arm, the median number of cycles given was 6.0 cycles (range: 1 to 26) for a median of 19 weeks. In the PLD only arm, the median number of cycles given was 5.0 cycles (range: 1 to 22) for a median of 20 weeks. Most adverse reactions were managed with dose reductions or delays (see *Dosage and Administration*).

Most patients treated with YONDELIS® can be expected to have adverse reactions of any grade (99%) with 25% reporting adverse reactions of Grade 3 or 4 severity. The most common adverse reactions, reported in ≥20% of patients treated with YONDELIS® in combination with PLD were neutropenia, leukopenia, anemia, thrombocytopenia, anorexia, nausea, vomiting, constipation, diarrhea, abdominal pain, stomatitis, palmar-plantar erythrodysesthesia syndrome, pyrexia, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased and blood alkaline phosphatase increased.

The most common adverse reaction, reported ≥ 5% leading to drug discontinuation was neutropenia.

Fatal adverse reactions have occurred in 0.9% of patients. They were often the result of a combination of events including pancytopenia, febrile neutropenia (some with sepsis), hepatic dysfunction, renal or multiorgan failure, and rhabdomyolysis.

In the YONDELIS®+PLD arm, non-white (mainly Asian) patients had a higher incidence than white patients in Grade 3 or 4 adverse reactions (96% versus 87%), and serious adverse reactions (44% versus 23% all grades). The differences were mainly observed in relation with neutropenia (93% versus 66%), anemia (37% versus 14%) and thrombocytopenia (41% versus 19%). However, the incidences of clinical complications related to hematological toxicity such as severe infections or bleeding, or those leading to death or treatment termination, were similar in both subpopulations.

Adverse reactions reported among patients treated with YONDELIS® in combination with PLD during clinical studies that occurred at a rate ≥ 1% are shown in Table 3 below.

Table 3: Adverse reactions in ≥ 1% of patients with ovarian cancer treated with YONDELIS® in combination with PLD

Adverse Reaction System Organ Class Preferred Term	**YONDELIS®+ PLD (n = 333) %**			**PLD (n = 330) %**		
	Any (%)	**Grade 3**	**Grade 4**	**Any (%)**	**Grade 3**	**Grade 4**
Infections and infestations						
Neutropenic infection	1	1	0	0	0	0
Neutropenic sepsis	1	< 1	< 1	0	0	0
Blood and lymphatic system disorders						

Adverse Reaction System Organ Class Preferred Term	YONDELIS®+ PLD (n = 333) %			PLD (n = 330) %		
Neutropenia	77	29	34	38	14	8
Leukopenia	48	25	8	26	7	3
Anemia	48	10	3	25	5	1
Thrombocytopenia	36	10	8	8	2	1
Febrile neutropenia	8	6	2	2	2	<1
Pancytopenia	2	2	1	0	0	0
Bone marrow failure	2	< 1	1	< 1	< 1	0
Granulocytopenia	2	1	< 1	0	0	0
Metabolism and nutrition disorders						
Dehydration	5	2	1	5	2	0
Hypokalemia	11	4	< 1	8	1	0
Anorexia	32	2	0	26	3	< 1
Psychiatric disorders						
Insomnia	10	0	0	5	0	0
Nervous system disorders						
Headache	16	1	0	8	< 1	0
Peripheral sensory neuropathy	5	0	0	3	0	0
Dysgeusia	5	< 1	0	3	0	0
Syncope	2	2	0	< 1	0	0
Cardiac disorders						
Palpitations	4	< 1	0	0	0	0
Left ventricular dysfunction*	1	< 1	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	15	3	< 1	10	2	< 1
Cough	12	0	0	12	0	0
Pulmonary embolism	5	1	2	2	1	1
Pulmonary edema	1	0	0	0	0	0
Gastrointestinal disorders						
Nausea	74	10	0	42	4	0
Vomiting	56	12	< 1	30	4	0
Constipation	32	2	0	28	2	0
Diarrhea	26	2	0	19	2	0
Abdominal pain	20	1	0	33	5	< 1
Stomatitis	20	1	0	33	5	< 1
Dyspepsia	13	< 1	0	11	1	0
Hepatobiliary disorders						

Adverse Reaction System Organ Class Preferred Term	YONDELIS®+ PLD (n = 333) %			PLD (n = 330) %		
Hyperbilirubinemia	16	1	0	7	1	0
Hepatotoxicity	2	1	0	< 1	0	0
Skin and subcutaneous tissue disorders						
Hand-foot syndrome	24	4	0	54	18	1
Skin hyperpigmentation	6	0	0	3	0	0
Alopecia	12	0	0	14	< 1	0
Rash	11	0	0	17	1	0
Musculoskeletal, connective tissue, and bone disorders						
Musculoskeletal pain	4	< 1	0	3	< 1	0
Myalgia	5	< 1	0	3	0	0
Renal and urinary disorders						
Renal failure acute	2	1	< 1	1	1	0
General disorders and administration site conditions						
Pyrexia	20	1	0	13	1	0
Fatigue	46	8	< 1	36	5	< 1
Asthenia	17	2	0	12	2	0
Mucosal inflammation	12	2	0	19	6	0
Edema peripheral	9	1	0	8	0	< 1
Edema	3	< 1	0	1	0	0
Catheter site pain	3	0	0	0	0	0
Catheter site erythema	2	0	0	0	0	0
Catheter site inflammation	2	0	0	1	0	0
Investigations						
Alanine aminotransferase increased	55	29	2	9	1	0
Aspartate aminotransferase increased	40	6	1	10	1	<1
Blood alkaline phosphatase increased	23	1	0	8	1	0
Blood creatine phosphokinase increased	7	1	1	3	0	0
Blood creatinine increased	6	< 1	< 1	6	< 1	0

Adverse Reaction System Organ Class Preferred Term	YONDELIS®+ PLD (n = 333) %			PLD (n = 330) %		
Gamma-glutamyltransferase increased	4	2	0	2	0	0
Bilirubin conjugated increased	1	0	0	0	0	0

* All patients reporting Left ventricular dysfunction, after discontinuation of study therapy improved.

Rhabdomyolysis
The following clinically significant adverse reaction was observed in less than 1% of patients treated with YONDELIS® in combination with PLD: rhabdomyolysis (YONDELIS® + PLD ≤ 1% (Grade 3; 0%, Grade 4; ≤ 1%), and PLD alone 0%).

Allergic reactions
During clinical trials, hypersensitivity was reported in 2% of patients receiving trabectedin either alone or in combination with PLD, and most of these cases were Grade 1 or 2 in severity.

During postmarketing experience, rare cases of hypersensitivity reactions, with very rare occurrence of fatal outcome, have been reported in association with trabectedin administration either alone or in combination with PLD (see *Contraindications* and *Warnings and Precautions*).

Extravasation and tissue necrosis
During clinical studies and post-marketing surveillance, a few cases of trabectedin extravasation with subsequent tissue necrosis requiring debridement have been reported (see *Warnings and Precautions*).

Septic shock
Cases of septic shock, some of which were fatal, have been uncommonly reported in clinical studies and postmarketing experience, in patients treated either with monotherapy or combination therapy.

Postmarketing data
In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 4). In the table, frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports
Not known	Cannot be estimated from the available data.

In Table 4, adverse reactions are presented by frequency category based on spontaneous reporting rates and by frequency category based on incidence in clinical trials or epidemiology studies, when known.

Table 4: Adverse reactions identified during postmarketing experience with YONDELIS®		
System Organ Class **Adverse Reaction**	**Frequency Category Estimated from Spontaneous Reporting Rates**	**Frequency Category Estimated from Clinical Trials with YONDELIS®**
Vascular disorders		
Capillary leak syndrome	Not known	Uncommon

Overdose

Symptoms and signs

There is limited data on the effects of trabectedin overdose. The major anticipated toxicities are gastrointestinal, bone marrow suppression and hepatic toxicity.

Treatment

There is no specific antidote for trabectedin currently available. In the event of an overdose, patients should be closely monitored and symptomatic supportive care measures instituted as required.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic agent, ATC code: L01CX01

Mechanism of action

Trabectedin binds to the minor groove of DNA, bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle.

Trabectedin has been shown to exert antiproliferative *in vitro* and *in vivo* activity against a range of human tumor cell lines and experimental tumors, including malignancies such as sarcoma, breast, non-small cell lung, ovarian and melanoma.

In vitro and *in vivo* xenograft models have shown additive or synergistic effects when YONDELIS® was combined with doxorubicin.

Pharmacodynamic effects

Electrocardiogram

The effects of trabectedin on the QT/QTc interval were evaluated in a single-blind placebo controlled, sequential design study in patients with locally advanced or metastatic solid tumors who received ≤ 3 prior lines of chemotherapy. In this study, 75 patients received placebo (saline solution) and trabectedin (1.3 mg/m^2) as 3-h IV infusions on days 1 and 2, respectively. This study showed no patients with a QTc exceeding 500 ms or a time-matched increase from baseline in QTc that exceeded 60 ms at any time point. A therapeutic dose of trabectedin did not prolong the QTc interval.

Absolute Neutrophil Count (ANC)
An association was observed between the time course of ANC during treatment and trabectedin plasma concentrations, suggesting higher trabectedin exposure may increase the incidence and severity of neutropenia (see *Warnings and Precautions*).

Alanine Amino Transferase (ALT)
Serum ALT elevation during trabectedin administration is transient and non-cumulative following subsequent cycles of trabectedin treatment. The magnitude of the transient serum ALT elevation after trabectedin administration is dependent on the dose, but not on the duration of the infusion. The elevation of serum ALT does not appear to be associated with trabectedin exposure at the recommended dose. A liver protection effect of dexamethasone has been demonstrated when treating cancer subjects with trabectedin.

Total bilirubin
An association between the incidence of total bilirubin toxicity Grade ≥ 2 and trabectedin plasma AUC and C_{max} has been observed (see *Warnings and Precautions*).

Clinical studies
Monotherapy
The clinical efficacy and safety of trabectedin for the treatment of patients with leiomyosarcoma or liposarcoma (L-sarcoma) was demonstrated in Study ET743-SAR-3007, a Phase 3, randomized controlled study of trabectedin versus dacarbazine in patients with advanced L-type sarcoma. Patients in the study had been previously treated in any order with at least an anthracycline and ifosfamide containing regimen, or an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen. Three hundred eighty four (384) patients were randomized to the trabectedin group [1.5 mg/m^2 once every 3 weeks (q3wk 24-h)] and 193 patients to the dacarbazine group (1 g/m^2 once every 3 weeks). The median patient age was 56 years (range 17 to 81), 30% were male, 77% Caucasian, 12% African American and 4% Asian.

Major prognostic factors were well balanced among patients; 73% had leiomyosarcomas, 27% liposarcomas and all patients had an ECOG score of ≤1. The majority of patients in both treatment groups received 2 prior lines of chemotherapy and the median time since last disease progression was less than 1 month (0.85 month).

Patients in the trabectedin and dacarbazine arms received a median of 4 and 2 cycles respectively.

The primary efficacy endpoint of the study was overall survival (OS) with final analysis to occur at the time of 376 observed death events. The major secondary endpoints based upon investigator assessment of disease response were Progression Free Survival (PFS), Objective Response Rate (ORR), Duration of Response (DOR), and Time to Progression (TTP). The disease response criteria were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

With a median survival follow-up of 21.2 months, 381 patients died (258 [67%] in the trabectedin treatment group and 123 [64%] in the dacarbazine treatment group). The median OS was 13.7 months (95% CI: 12.2, 16.0) for the trabectedin treatment group and 13.1 months (95% CI: 9.1, 16.2) for the dacarbazine treatment group. The HR was 0.927 (95% CI: 0.748, 1.150; p=0.4920), which represents a 7.3% reduction in the risk of death for patients in the trabectedin treatment group. Other efficacy results from study ET743-SAR-3007 at the time of the interim analysis are presented in the table below. The PFS results were audited through a retrospective review by independent radiologists.

Table 5: Efficacy results from study ET743-SAR-3007

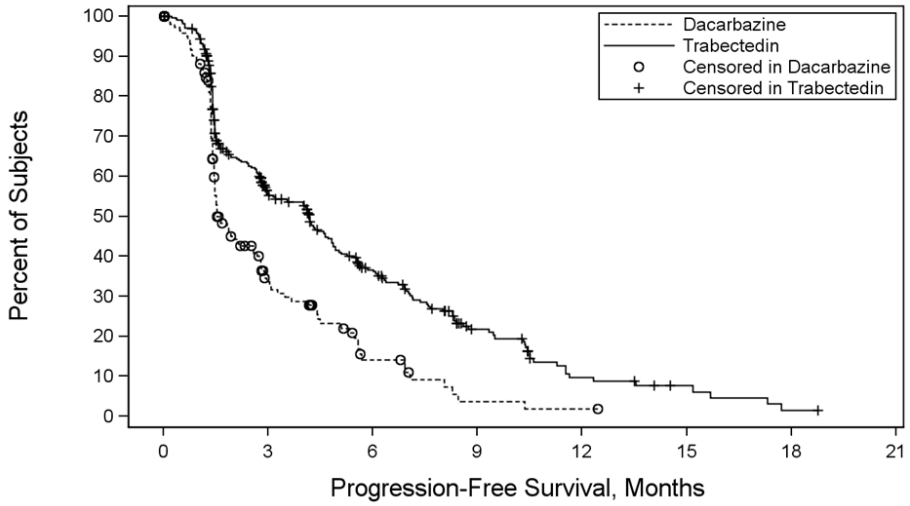
Efficacy endpoint	**Trabectedin**	**Dacarbazine**
N: ITT patients	345	173
Progression free survival[a]		
Events n (%)	217 (63%)	112 (65%)
Median (95% CI) (months)	4.21 (2.99, 4.83)	1.54 (1.48, 2.60)
HR (95% CI)[b]	0.550 (0.436, 0.696)	
p-value[c]	< 0.0001	
Time to Progression		
Events n (%)	205 (59%)	112 (65%)
Median (95% CI) (months)	4.24 (3.22, 4.93)	1.54 (1.48, 2.60)
HR (95% CI)[b]	0.522 (0.412, 0.661)	
p-value[c]	< 0.0001	
Objective Response Rate (ORR; CR+PR)		
Objective response rate n (%)	34 (10%)	12 (7%)
ORR (95% CI)[e]	(6.9, 13.5)	(3.6, 11.8)
OR (95% CI)[d]	1.467 (0.717 - 3.197)	
p-value[d]	0.3269	
Duration of Response (CR+ PR)		
n: response-evaluable patients	34	12
Median[c] (95% CI) (months)	6.47 (3.58, 7.62)	4.17 (2.14, NE)
HR (95% CI)[b]	0.471 (0.168, 1.318)	
p-value	0.1415	
Clinical Benefit Rate (CBR)		
CBR, n (%)	118 (34%)	32 (19%)
CBR 95% CI[e]	(29.2, 39.5)	(13.0, 25.1)
OR (95% CI)[d]	2.291 (1.446 - 3.692)	
p-value[d]	0.0002	

Table 5: Efficacy results from study ET743-SAR-3007

Efficacy endpoint	Trabectedin	Dacarbazine
N: ITT patients	345	173
Duration of stable disease		
n (%): patients with best response of stable disease	177 (51%)	60 (35%)
Events, n (%)	90 (51%)	35 (58%)
Median (95% CI), months	6.01 (4.86, 6.97)	4.17 (2.89, 5.49)
HR (95% CI)[b]	0.449 (0.300, 0.673)	
p-value[c]	0.0001	

[a] Based on Investigator assessment.
[b] Hazard ratio is estimated using Cox proportional hazards model with treatment group as the only covariate A hazard ratio <1 indicates an advantage for trabectedin
[c] P-value is based on unstratified log rank test.
[d] Based on Fisher′s exact test.
[e] ORR 95% CI is based on Fisher′s exact CI;
CR=Complete Response; CRu=Complete response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=hazard ratio; ITT=intent to treat, OR=odds ratio; CBR=Clinical Benefit Rate
Note: Objective response rate (ORR) is defined as the proportion of subjects who achieved a CR or PR as best response
Clinical benefit is defined as subject whose best overall response is CR, PR, or SD >=18wks.

Figure 1: Kaplan-Meier Curve of Progression-Free Survival



In Study ET743-SAR-3007, M.D. Anderson Symptom Inventory (MDASI) scores were used to assess patient's perceived symptom burden (symptom severity, and symptom interference

relating to physical and mental function) and to determine the impact of treatment on symptom change or stability. The MDASI scores demonstrated low levels of symptoms at baseline in both trabectedin and dacarbazine groups; which were maintained for the duration of therapy without any meaningful difference between treatment groups.

Randomized study ET743-STS-201 evaluated the efficacy and safety of trabectedin in patients with locally advanced or metastatic liposarcoma or leiomyosarcoma, whose disease had progressed or relapsed after treatment with at least anthracyclines and ifosfamide. In this trial trabectedin was administered either at 1.5 mg/m^2 as a 24-hour intravenous infusion every 3 weeks or at 0.58 mg/m^2 weekly as a 3-hour intravenous infusion for 3-weeks of a 4-week cycle. There were no pre-defined limits to the number of cycles administered. Treatment continued while clinical benefit was noted. No cumulative toxicities were observed in patients treated with multiple cycles. The protocol specified final TTP analysis showed a 26.6% reduction in the relative risk of progression for patients treated in the 24-h q3wk group (Hazard Ratio = 0.734 CI 0.554 - 0.974). Median TTP values were 3.7 months (CI: 2.1 - 5.4 m) in the 24-h q3wk group and 2.3 months (CI: 2.0 - 3.5 m) in the 3-h qwk group (p = 0.0302). No significant differences were detected in overall survival (OS). Median OS with the 24-h q3wk regime was 13.9 months (CI: 12.5 - 18.6) and 60.3% of patients were alive at 1 year (CI: 52.0 - 68.5%).

Additional efficacy data are available from 3 single-arm Phase 2 trials with similar populations treated with the same regime. These trials evaluated a total of 100 patients with lipo and leiomyosarcoma and 83 patients with other types of sarcoma.

Results from an expanded access program for patients with STS show that among the 903 patients assessed for OS, the median survival time was 11.9 months [95% CI: 11.2, 13.8]. The median survival by histology tumor type was 16.2 months [95% CI: 14.1, 19.5] for patients with leiomyosarcomas and liposarcomas, and 8.4 months [95% CI: 7.1, 10.7] for patients with other types of sarcomas. The median survival for patients with liposarcoma was 18.1 months [95% CI: 15.0, 26.4] and for patients with leiomyosarcoma 16.2 months [95% CI: 11.7, 24.3].

Combination therapy

The safety and efficacy of YONDELIS® in combination with PLD in patients with relapsed ovarian cancer were demonstrated in an open-label, active control, multicenter, randomized Phase 3 study. This study included 672 patients randomized to receive either YONDELIS® (1.1 mg/m^2 i.v. for 3 hours) administered after PLD® (30 mg/m^2 i.v for 90 min) every 3 weeks or PLD (50 mg/m^2 i.v. for 90 min) every 4 weeks.

The median age of the patients in the study was 57 years (range 26;87), 78% were Caucasian, 20% Asian and 2% Black/other. The baseline demographics and disease characteristics are provided in table 6 below:

Table 6: Summary of patients baseline and disease characteristics

	YONDELIS® + PLD N = 337	**PLD N = 335**
Median age (range)	56 (26;82)	58 (27;87)
Baseline ECOG		

performance status (%)		
0	68	57
1	29	39
2	3	3
Platinum sensitivity (%)		
Platinum sensitive	65	63
Platinum resistant	35	37
Prior Taxane therapy (%)	80	81
Platinum free interval (PFI)*	n (%)	n (%)
<6	118 (35)	124 (37)
≥6-12	123 (37)	90 (27)
≥12	95 (28)	121 (36)

*PFI: end of last platinum therapy to time of progression.

The clinical benefit of YONDELIS® + PLD was observed in PFS and ORR, with a trend in survival in favor of the combination arm at the time of the final analysis.

The primary endpoint, PFS, was significantly longer in patients treated with YONDELIS® in combination with PLD® compared with those treated with PLD alone (median PFS: 7.3 vs. 5.8 months respectively). Treatment with YONDELIS® + PLD resulted in a 21% risk reduction for disease progression compared to PLD alone [HR = 0.79; 95% CI (0.65;0.96), p = 0.0190].

The final survival analysis was performed based on 522 events with a median follow up of 47.4 months. Efficacy results are summarized in Table 7.

Table 7: Efficacy of YONDELIS® in combination with PLD in the treatment of patients with ovarian cancer (Study OVA-301)

	YONDELIS®+PLD	**PLD**	p-value
Independent radiologist review	n = 328	n = 317	
Median PFS (95% CI) months*	7.3 (5.9; 7.9)	5.8 (5.5; 7.1)	0.0190[a]
Hazard ratio (95% CI)	0.79 (0.65; 0.96)		
ITT population	n = 337	n = 335	
Objective response rate (%)	27.6	18.8	0.0080[b]
Odds ratio**	1.646 (1.144-2.367)		
Median duration of response (months)*	7.9 (7.4; 9.2)	7.7 (6.5; 9.0)	0.8203 [a]

	YONDELIS®+PLD	PLD	p-value
Hazard ratio (95% CI)	0.95 (0.62; 1.46)		
Independent oncologist review	n = 336	n = 335	
Median PFS (95% CI) months*	7.4 (6.4; 9.2)	5.6 (4.2; 6.8)	0.0008 [a]
Hazard ratio (95% CI)	0.72 (0.60; 0.88)		
Objective response rate (%)	30.4	19.1	0.0009 [b]
Odds ratio**		1.846(1.290-2.641)	
Overall survival (OS) (Final analysis n = 522 events)			
All randomized	n = 337	n = 335	
Median OS (95% CI) (months)	22.2 (19.3-25.0)	18.9 (17.1-21.5)	0.0835
Hazard ratio[a]	0.86 (0.72-1.02)		
Overall survival in platinum sensitive population (Final analysis n = 316 events)			
	n = 218	n = 212	
Median OS (95% CI) (months)	27 (24.1-31.4)	24.1 (20.9-25.9)	0.1056
Hazard ratio[a]	0.83 (0.67-1.04)		
Overall survival in platinum resistant population (Final analysis n = 206 events)			
	n = 119	n = 123	
Median OS (95% CI) (months)	14.2 (11.1-16.8)	12.4 (10.6-14.8)	0.5452
Hazard ratio[a]	0.92 (0.70-1.21)		

* Based on Kaplan Meier estimates; a hazard ratio < 1 indicates an advantage for YONDELIS®+PLD

** Odds ratio > 1 indicates advantage for (YONDELIS® +PLD) calculated with Cochran-Mantel-Haenszel.

[a] Log rank test

[b] Fisher's exact test

Based on independent oncologist review, patients who had platinum free intervals (PFI) less than 6 months had similar PFS between the two arms with both showing median PFS of 3.7 months [HR = 0.89 (95% CI: 0.67-1.20)]. ORR was 14.3% in the YONDELIS® +PLD arm vs. 11.4% in the PLD monotherapy arm. For patients who had PFI > 6 months, median PFS was 9.7 months in the YONDELIS®+PLD arm compared with 7.2 months in the PLD monotherapy arm [HR = 0.66 (95%CI 0.51-0.85), p-value = 0.0010]. ORR rate was 39.2% in the YONDELIS®+PLD arm vs. 23.6% in the PLD monotherapy arm.

In the final analysis, the treatment effect on overall survival was more pronounced in the YONDELIS®+PLD combination vs. PLD alone in patients with PFI ≥ 6 months (platinum-sensitive population: 27.0 vs. 24.1 months, HR = 0.83, CI : 0.67-1.04) than in those with PFI < 6 months (platinum-resistant population: 14.2 vs. 12.4 months, HR = 0.92, CI : 0. 70-1.21).

In the multivariate analyses including PFI, the treatment effect was statistically significant favoring the YONDELIS®+PLD combination over PLD alone (PFS, p = 0.0157; OS, p = 0.0285).

Pharmacokinetic Properties

Systemic exposure after intravenous administration as a constant rate intravenous infusion is dose proportional at doses up to and including 1.8 mg/m^2. The pharmacokinetic profile of trabectedin is consistent with a multiple-compartment disposition model, including a terminal half-life in plasma of 175 hours. The concentrations of trabectedin in plasma do not accumulate when administered every 3 weeks.

Distribution

Trabectedin has a large volume of distribution (greater than 5000 L), consistent with extensive distribution into peripheral tissues.

Trabectedin is extensively bound to plasma alpha-1 acid glycoprotein and albumin. The mean free (unbound) fraction in plasma is 2.23% and 2.72% at a total plasma concentration of 10 ng/mL and 100 ng/mL, respectively.

In vitro preclinical studies have shown trabectedin is a substrate of multiple efflux transporters including P-gp, MRP2 and potentially MRP3 and MRP4, but not BCRP. Preclinical models suggest P-gp, MRP2, and MRP3 are involved in the hepatic efflux of trabectedin metabolites and have an important and partially redundant function in protecting from trabectedin-mediated (liver) toxicity.

Metabolism

Trabectedin is extensively metabolized. Cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for the oxidative metabolism of trabectedin at clinically relevant concentrations. The contribution of other P450 enzymes to the metabolism of trabectedin cannot be ruled-out. No appreciable glucuronidation of trabectedin has been observed.

Elimination

The mean (SD) recovery of total radioactivity was 58% (17%), and 5.8% (1.73%) in the feces (24 days) and urine (10 days), respectively, after a dose of radiolabeled trabectedin was administered to 8 cancer patients. Negligible quantities (< 1% of the dose) of unchanged drug are excreted in the feces and in urine. The clearance of trabectedin in whole blood is approximately 35 L/h. This value is approximately one-half the rate of human hepatic blood flow. Thus the trabectedin extraction ratio can be considered moderate. The inter-patient variability of the population estimate for plasma clearance of trabectedin was 49% and intra-patient variability was 28%.

Special populations
A population pharmacokinetic analysis indicated that the plasma clearance of trabectedin is not influenced by total body weight (range: 36 to 148 kg), body surface area (range: 0.9 to 2.8 m^2), age (range: 19 to 83 years), or gender.

Pediatrics (18 years of age and younger)
The pharmacokinetics of trabectedin have been investigated in pediatric patients (age range: 2 years to 18 years, N=30) with refractory solid tumors, including sarcomas. Pharmacokinetic parameters in the pediatric population were similar to those previously observed in adults given the same dose per body surface area (see *Dosage and Administration*).

Elderly (65 years of age and older)
Results from population pharmacokinetic analyses indicate that the plasma clearance and distribution volume of trabectedin are not influenced by age. Thus, adjustment of the starting dose of trabectedin due to potential age-related changes in its pharmacokinetic properties is not recommended (see *Dosage and Administration).*

Renal impairment
There is no relevant influence of renal function measured by creatinine clearance on trabectedin pharmacokinetics within the range of values (≥ 30.3 mL/min) present in the patients included in the clinical studies. No data are available in patients with a creatinine clearance of less than 30.3 mL/min. The low recovery (< 9% in all studied patients) of total radioactivity in the urine after a single dose of ^{14}C-labelled trabectedin suggests that renal impairment would have little influence on the elimination of trabectedin or its metabolites.

Hepatic impairment
Administration of YONDELIS® as a single 3-hour infusion to patients with hepatic dysfunction (total bilirubin >1.5 to ≤3 times the ULN and AST and ALT <8 times the ULN) indicated that hepatic impairment is associated with increased trabectedin exposure. The geometric mean ratio for dose normalized C_{max} was 1.40 in subjects with hepatic dysfunction (administered 0.58 mg/m^2 [n=3] or 0.9 mg/m^2 [n=3]), compared with subjects with normal hepatic function (administered 1.3 mg/m^2 [n=9]) and 1.97 for dose normalized AUC_{last}.

Other populations
Race/ethnicity
A population pharmacokinetic analysis of a limited number of subjects showed that race and ethnicity are not expected to have clinically relevant effects on trabectedin pharmacokinetics. A Phase 1 study in a limited number of subjects showed that trabectedin plasma concentrations observed in the Japanese population at a dose of 1.2 mg/m^2 were similar to those obtained in the Western population at 1.5 mg/m^2.

Non-Clinical Information
Pharmacology/Toxicology
Preclinical data indicate that trabectedin has limited effect on the cardiovascular, respiratory and central nervous system at exposures below the therapeutic clinical range, in terms of AUC.

The effects of trabectedin on cardiovascular and respiratory function have been investigated *in vivo* (anesthetized Cynomolgus monkeys). A 1-hour infusion schedule was selected to attain maximum plasma levels (C_{max} values) in the range of those observed in the clinic. The plasma trabectedin levels attained were 10.6 ± 5.4 ng/mL (C_{max}), similar to those reached after administration of 1.1 mg/m^2 in 3 hour-infusion (C_{max} of 7.9± 2.0 ng/mL).

Myelosuppression and hepatoxicity were identified as the primary toxicity for trabectedin. Findings observed included hematopoietic toxicity (severe leukopenia, anemia, and lymphoid and bone marrow depletion) as well as increases in liver function tests, hepatocellular degeneration, intestinal epithelial necrosis, and severe local reactions at the injection site.

In mice, rats, rabbits and monkeys, dose-dependent local inflammation was regularly observed at the injection site after i.v. injection particularly after repeated cycles. In repeated dose toxicity studies in Cynomolgus monkeys, severe thrombophlebitis with extensive perivascular inflammation and fibrosis generally with pronounced necrosis, also affecting surrounding tissues was observed after the fourth cycle, and led to premature sacrifice or death in some animals. These adverse effects were observed when trabectedin was administered to animals less than 3 kg. Mortalities were seen at 0.42 mg/m^2 and above (see *Dosage and Administration Pediatrics*).

Renal toxicological findings were detected in multi-cycle toxicity studies conducted in monkeys. These findings were secondary to severe local intolerance at the administration site (i.e., catheter tip location), with severe damage of surrounding tissues (e.g., the kidneys) and therefore uncertainly attributable to trabectedin; however, caution must be exercised in the interpretation of these renal findings, and treatment-related toxicity cannot be excluded.

Carcinogenicity and mutagenicity
Trabectedin is genotoxic both *in vitro* and *in vivo*. Long-term carcinogenicity studies have not been performed.

Fertility
Fertility studies with trabectedin were not performed but limited histopathological changes were observed in the gonads in the repeat dose toxicity studies. Considering the nature of the compound (cytotoxic and mutagenic), it is likely to affect the reproductive capacity.

PHARMACEUTICAL INFORMATION

List of Excipients
Phosphoric acid (for pH adjustment)
Potassium dihydrogen phosphate
Potassium hydroxide (for pH adjustment)
Sucrose

Incompatibilities
YONDELIS® must not be mixed or diluted with medicinal products except those mentioned in *Instructions for Use and Handling and Disposal*.

Shelf Life
3 years
After reconstitution, chemical and physical stability has been demonstrated for 30 hours up to 25ºC. After dilution, chemical and physical stability has been demonstrated for 30 hours up to 25ºC. The total hold time between initial reconstitution and end of treatment should not be longer than 30 hours.

From a microbiological point of view, the reconstituted solution should be diluted and used immediately. If not diluted and used immediately, in-use storage times and conditions prior to use of the reconstituted product are the responsibility of the user and would normally not be longer than 24 hours at 2ºC to 8ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

Storage Conditions
Keep out of the sight and reach of children.

Store in a refrigerator (2ºC - 8ºC).

For storage conditions of the reconstituted and diluted medicinal product, see *Shelf Life*.

Nature and Contents of Container
YONDELIS® is supplied in a Type I colourless glass vial with a butyl stopper covered with an aluminium flip-off seal.

Each vial contains 1 mg of trabectedin.

Each outer carton contains one vial.

Instructions for Use and Handling and Disposal
Preparation for intravenous infusion
YONDELIS® reconstitution and dilution of the reconstituted solution must be conducted under aseptic conditions in a manner consistent with recommended safe procedures for handling cytotoxic compounds.

Instructions for reconstitution
Each vial containing 1 mg of trabectedin is reconstituted with 20 mL of sterile water for injections. A syringe is used to inject sterile water for injections into the vial. Shake the vial until complete dissolution. The reconstituted solution results in a clear, colorless to brownish yellow solution, essentially free of visible particles.

This reconstituted solution contains 0.05 mg/mL of trabectedin. It requires further dilution and is for single-use only.

Instructions for dilution

The reconstituted solution should be diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion. The required volume should be calculated as follows:

$$\text{Volume (mL)} = \frac{\text{BSA } (m^2) \times \text{individual dose } (mg/m^2)}{0.05 \text{ mg/mL}}$$

BSA = Body Surface Area

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 500 mL of normal saline 0.9% solution for infusion or dextrose 5% solution for infusion if administration is to be made through a central venous line. For infusion times exceeding 4 hours, an infusion set with a 0.2 micron polyethersulfone (PES) in-line filter can be used to further reduce the risk of exposure to adventitious pathogens that may be introduced during solution preparation.

If central venous access is not feasible and a peripheral venous line has to be used, the reconstituted solution may be further diluted in an infusion bag containing ≥ 1000 mL of normal saline 0.9% solution for infusion or dextrose 5% solution for infusion.

After administration of the PLD infusion, the intravenous line should be flushed well with 5% dextrose in water (D_5W) before administration of YONDELIS®. PLD must not be mixed with saline.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. After reconstitution and dilution, chemical and physical stability has been demonstrated for 30 hours up to 25ºC. The reconstituted solution should be diluted and used immediately. The total elapsed time between initial reconstitution and end of treatment should not be longer than 30 hours.

Instructions for handling and disposal

YONDELIS® is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised during handling. Procedures for proper handling and disposal of cytotoxic medicinal products must be followed. YONDELIS® should be handled and disposed of in a manner consistent with other anticancer drugs. Accidental contact with the skin, eyes or mucous membranes must be treated immediately with copious amounts of water.

Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic medicinal products

No incompatibilities have been observed between YONDELIS® and Type 1 glass vials, polyvinylchloride (PVC) and polyethylene (PE) bags and tubing, PE and polypropylene mixture bags, polyisoprene reservoirs, and titanium or plastic resin implantable vascular access systems.

MANUFACTURER

Baxter Oncology GmbH

Kantstraβe 2,
33790 Halle/ Westfalen,
Germany.

PRODUCT REGISTRATION HOLDER
Johnson & Johnson Sdn Bhd
Lot 3 & 5, Jalan Tandang, 46050 Petaling Jaya, Selangor, Malaysia.

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