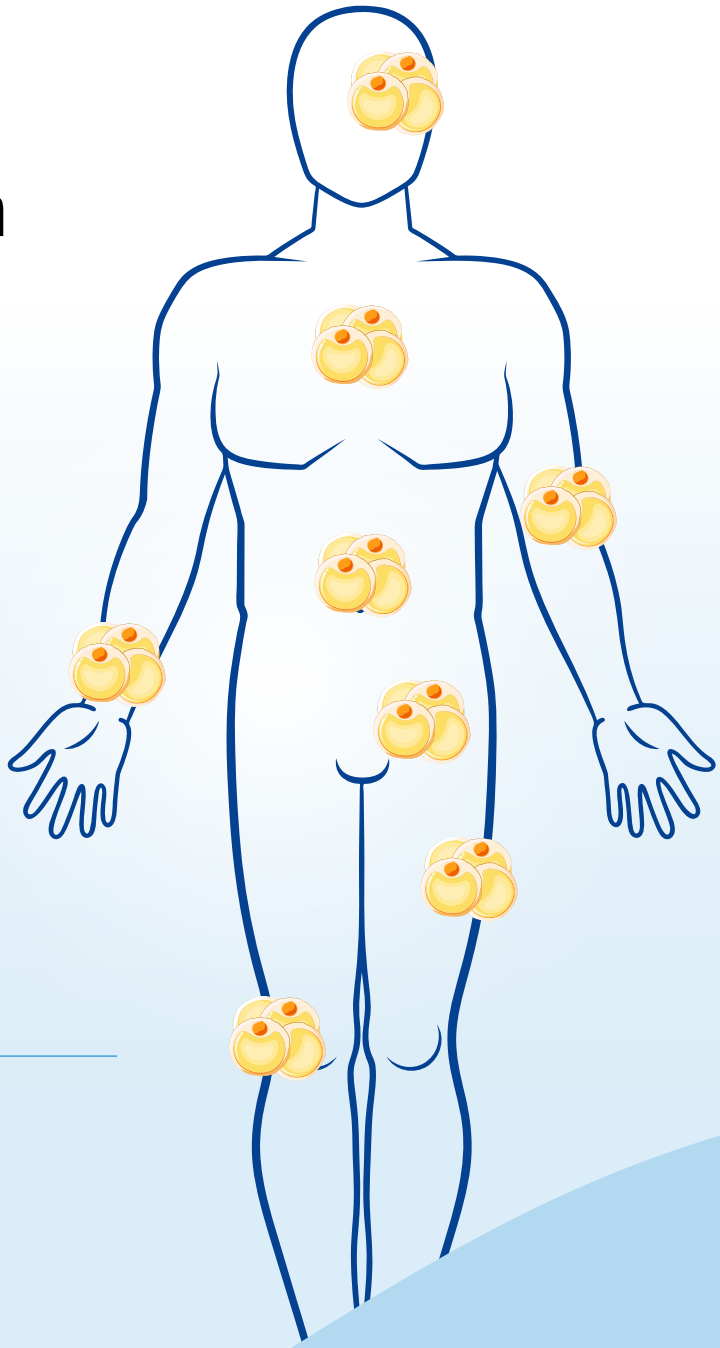
Sarcoma
Medical Education



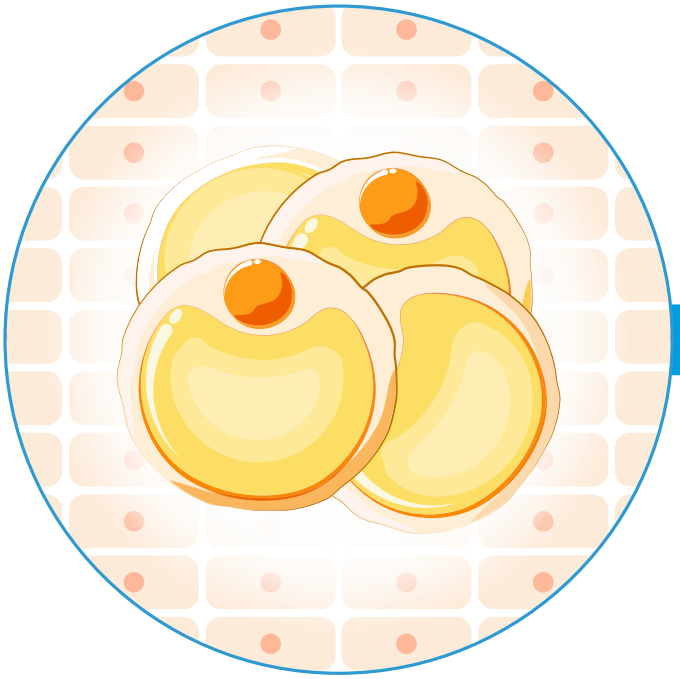
LIPOSARCOMA

Dr. Bernd Kasper

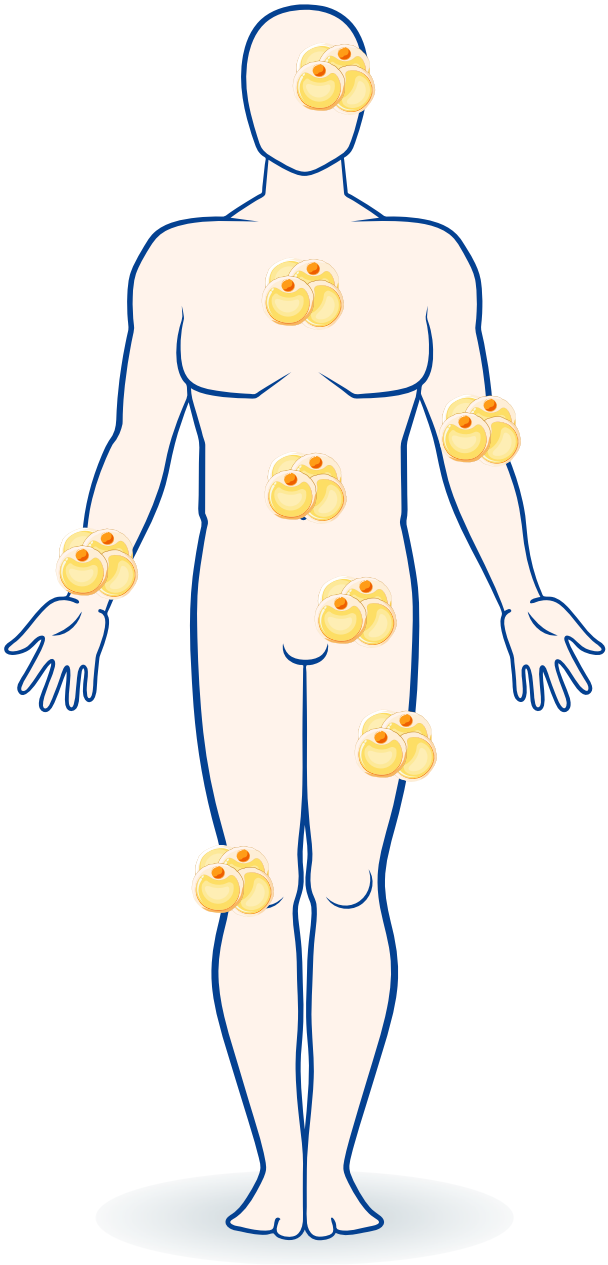
LIPOSARCOMA

What is liposarcoma?

Rare tumours arising from adipose tissue[1]



Account for 15 to 20% of all soft tissue sarcomas[1]



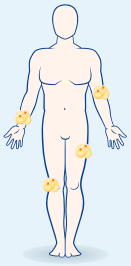
Liposarcoma can arise in any part of the body[1]

Subtypes of liposarcoma

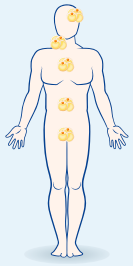
Liposarcomas can be classified into distinct histopathological subtypes[2–4]

Atypical lipomatous tumours (ALT) and **Well-differentiated** liposarcoma (WDLPS)

- **40-45%** of all liposarcomas[2]
- Locally aggressive with **virtually no risk of metastasis**[2,4]
- **ALT:** extremities[5]

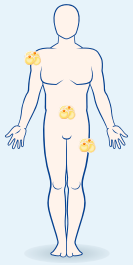


- **WDLPS:** retroperitoneum, paratesticular region, mediastinum or head and neck region[5]



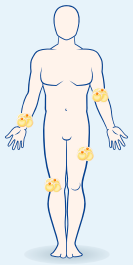
Dedifferentiated liposarcoma (DDLPS)

- Up to **90%** arise de novo and the remaining **10%** as a dedifferentiated recurrence of WDL/ALT[6]
- **High-grade** and **aggressive** disease[6]
- Retroperitoneum and deep soft tissue of proximal extremities[6]



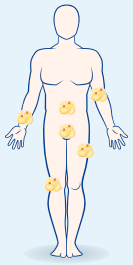
Myxoid liposarcoma (MLPS)

- **30%** of all liposarcomas[1,5,7]
- Typically more chemo- and radio-sensitive[1]
- **Disproportionately high metastatic** pattern[1,5,7]
- Extremities of **young adults**[1,5,7]



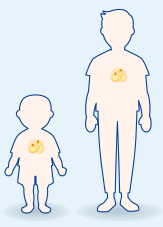
Pleomorphic liposarcoma (PLPS)

- **5%** of all liposarcomas[2,5,8]
- **Aggressive** subtype[2,8]
- **Distant metastases** in up to **50%** of cases[1,4]
- Mainly in the extremities, followed by retroperitoneum and abdomen[5]



Myxoid pleomorphic liposarcoma (MPLPS)

- **Exceptionally rare** and **aggressive**[9]
- Mixture of histologic features from conventional MLPS and PLPS[9]
- In **children** and **adolescents**[9]
- Mainly in the mediastinum[9]



Diagnosis and management of liposarcoma

All decisions regarding management should be made on an individual basis and by multidisciplinary teams with experience in treating this rare tumour type[1]

DIAGNOSIS

Imaging

- **Magnetic resonance** imaging in the extremities, pelvis and trunk[10]
- **Standard radiographs** to rule out a bone tumour[10]
- **Computed tomography** has a role in the diagnosis of retroperitoneal liposarcomas[10]

Biopsy

- **Multiple core needle biopsies** followed by histologic examination and molecular studies[10]

Staging

- **Computed tomography** scan of the thorax, abdomen and pelvis[10]

An accurate diagnosis is essential to plan an individualised treatment strategy[1,4]

LOCALISED LIPOSARCOMA

Surgery

Surgery should be offered as initial management when there is a possibility of complete resection[1]

- Preoperative radiotherapy can be discussed in patients with a low-intermediate grade liposarcoma[1,10]
- Preoperative chemotherapy to be reserved for patients with good PS and borderline resectable or recurrent retroperitoneal sarcomas where tumour shrinkage may improve surgical outcomes[5]

ADVANCED/METASTATIC LIPOSARCOMA

Chemotherapy

Main chemotherapeutic agents for the treatment of liposarcoma[4]	
First line	Anthracycline-based regimens
Second and later lines	Ifosfamide, dacarbazine, gemcitabine, docetaxel, trabectedin and eribulin

PS: Performance Status

TRABECTEDIN*

Trabectedin is the **most extensively studied agent** to date in advanced liposarcoma[12].

Consistent efficacy shown in more than **400 patients** with liposarcoma[12].

Randomised Phase III study comparing trabectedin and dacarbazine: Results in 147 patients with advanced liposarcoma[13]

- **Effectiveness - 45% reduction** in the **risk of disease progression or death**[13]
- **Tolerability - 40% of** trabectedin patients (vs 16%) were able to receive **extended treatment courses** of 6 or more cycles[13]

Positive outcomes confirmed by **real-world evidence** studies[14-18]. Efficacy from the most recent study in 155 liposarcoma patients mainly treated in 2nd line (≈60%):[15]

- Median PFS: 8.8 months
- Median OS: 30 months

Additional clinical studies and case reports in **different subtypes of liposarcoma** have confirmed trabectedin:[11,17-22]

- Achieves long-term tumour control[11,19]
- Preserves QoL[11,19]
- Is well tolerated[20]

Trabectedin is a **logical choice for second-line treatment of liposarcoma,** since it is able to achieve the treatment goal for most patients in this setting of long-lasting tumour control with a preserved QoL[18]

*Yondelis® (trabectedin) Product Information

PFS: progression-free survival; **OS:** overall survival ; **QoL:** quality of life

AUSTRALIA - MINIMUM PRODUCT INFORMATION

YONDELIS® (trabectedin) 0.25 mg or 1 mg powder for solution for infusion

INDICATIONS: YONDELIS® is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

CONTRAINDICATIONS: Hypersensitivity to trabectedin, or to the excipients; Concurrent serious or uncontrolled infection; Breast-feeding; Combination with yellow fever vaccine.

PRECAUTIONS: Use in hepatic impairment: Patients with elevated serum bilirubin levels must not be treated with YONDELIS®; Use in renal impairment: YONDELIS® must not be used in patients with creatinine clearance < 30 mL/min; Neutropaenia and sepsis: YONDELIS® should not be administered to patients with baseline neutrophil counts of less than 1.5 x 10^9/L; Thrombocytopaenia: YONDELIS® should not be administered to patients with baseline platelets count of less than 100 x 10^9/L; Nausea and vomiting; Rhabdomyolysis and severe CPK elevations (> 5 x ULN): YONDELIS® must not be used in patients with CPK2.5 x ULN.

Hepatotoxicity: YONDELIS® must not be used in patients with elevated bilirubin or those with AST, ALT or alkaline phosphatase > 2.5 x ULN; Cardiac dysfunction including cardiac failure, congestive heart failure, decreased ejection fraction, diastolic dysfunction, and right ventricular dysfunction can occur with YONDELIS®; Injection site reactions: Patients may develop a potentially severe injection site reaction when YONDELIS® is administered through a peripheral venous line. YONDELIS® extravasation may cause tissue necrosis requiring debridement; Allergic reactions; Capillary Leak Syndrome (CLS). Caution should be taken with co-administration of YONDELIS® with medicinal products associated with hepatotoxicity as the risk of hepatotoxicity may be increased. Co-administration with phenytoin or live attenuated vaccines (such as yellow fever vaccine) is not recommended. Fertile females must use effective contraception during treatment and 3 months thereafter. Fertile males must use effective contraception during treatment and 5 months after treatment.

INTERACTIONS: Co-administration with strong CYP3A4 inhibitors should be avoided since they may affect the plasma concentration of YONDELIS®. Alcohol consumption must be avoided during treatment with YONDELIS® due to the hepatotoxicity of the medicinal product. Concomitant administration with P-gp inhibitors may alter the distribution and/or elimination of YONDELIS® therefore caution should be taken.

ADVERSE REACTIONS: Most common: neutropenia, nausea, vomiting, increase in AST/ALT, anaemia, fatigue, thrombocytopenia, anorexia, diarrhoea, leukopenia, blood alkaline phosphatase increased, blood creatinine increased, blood creatine phosphokinase increased, constipation, decreased appetite, cough, dyspnoea, headache, pyrexia, peripheral oedema, abdominal pain, hypokalaemia, dehydration, white blood cell count decreased, neutrophil count decreased, platelet count decreased, dizziness, back pain, pain in extremity, arthralgia, myalgia, insomnia and anxiety.

DOSE AND METHOD OF ADMINISTRATION: YONDELIS® must be reconstituted and further diluted by a healthcare professional prior to intravenous infusion. Pre-infusion medications should be administered to provide anti-emetic and hepatoprotective effects. The recommended dose of YONDELIS® is 1.5 mg/m^2 according to Body Surface Area (BSA), administered as an intravenous infusion over 24 hours with a three-week interval between cycles (q3wk). Administration through a central venous line is strongly recommended.

Refer to full PI for management of dose adjustments and more information. Date of First Approval: 21 April 2021

Please review Product Information before prescribing. The Product Information can be accessed at www.ebs.tga.gov.au

PBS Information: This Product is not PBS listed

MALAYSIA - ABBREVIATED PRODUCT INFORMATION (API)

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

INDICATIONS AND USAGE:

- 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 specialised in the administration of cytotoxic agents

RECOMMENDED DOSE AND SCHEDULE:

- 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
- All patients must receive corticosteroids e.g. 20 mg 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

ADVERSE REACTIONS:

- The most common adverse reactions (≥20%) of any severity grade were anaemia, 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, diarrhoea, dyspnoea, 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

CONTRAINDICATIONS:

- YONDELIS® should not be administered to nursing mothers
- 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:

- Use in hepatic impairment: Use in renal impairment: YONDELIS® must not be used in patients with creatinine clearance < 30 mL/min;
- Myelosuppression: 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 haemoglobin < 9 g/dL;
- 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
- Rhabdomyolysis and severe CPK elevations: YONDELIS® must not be used in patients with CPK > 2.5 x ULN;
- Liver Function Test (LFT) abnormalities: YONDELIS® must not be used in patients with elevated bilirubin;
- Cardiac dysfunction including cardiac failure, cardiac failure acute, congestive heart failure, cardiomyopathy, ejection fraction decreased, diastolic dysfunction, left ventricular dysfunction and right ventricular dysfunction; Injection site reactions: Patients may develop a potentially severe injection site reaction when YONDELIS® is administered through a peripheral venous line;
- Allergic reactions; Capillary Leak Syndrome (CLS). Caution should be taken with co-administration of YONDELIS with medicinal products associated with hepatotoxicity as the risk of hepatotoxicity may be increased

DRUG INTERACTIONS:

- Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors

USE IN SPECIFIC POPULATIONS:

- The use of YONDELIS® in pregnant women is not recommended

For more information please refer to the full product information at this link.

SINGAPORE - ABBREVIATED PRODUCT INFORMATION (API)

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

INDICATIONS AND USAGE:

- YONDELIS® is indicated for the treatment of patients with advanced or metastatic liposarcoma or leiomyosarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients

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 personnel specialised in the administration of cytotoxic agents

RECOMMENDED DOSE AND SCHEDULE:

- The recommended starting dose is 1.5 mg/m² body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles. Administration through a central venous line is strongly recommended
- All patients must be premedicated with corticosteroids such as dexamethasone 20 mg IV, 30 minutes before each infusion; not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed

ADVERSE REACTIONS:

- 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

CONTRAINDICATIONS:

YONDELIS® should not be administered:

- To nursing mothers
- To patients with known hypersensitivity to any of its components
- To patients with an active serious or uncontrolled infection
- In combination with yellow fever vaccine

WARNINGS AND PRECAUTIONS:

- Use in hepatic impairment: YONDELIS® should not be used in patients with elevated bilirubin at the time of initiation of a new treatment cycle
- Use in renal impairment: YONDELIS® must not be used in patients with creatinine clearance < 30 mL/min;
- Myelosuppression: YONDELIS® should not be administered to patients with baseline neutrophil counts of less than 1500/mm3, platelets count of less than 100000/mm³ or haemoglobin < 9 g/dL;
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USE IN SPECIFIC POPULATIONS:

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For more information please refer to the full product information at this link.

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