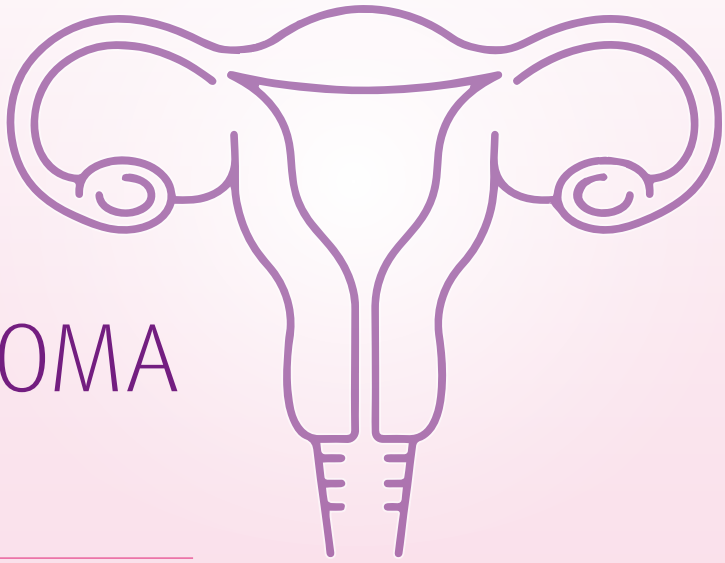
Sarcoma
Medical Education



UTERINE LEIOMYOSARCOMA (uLMS)

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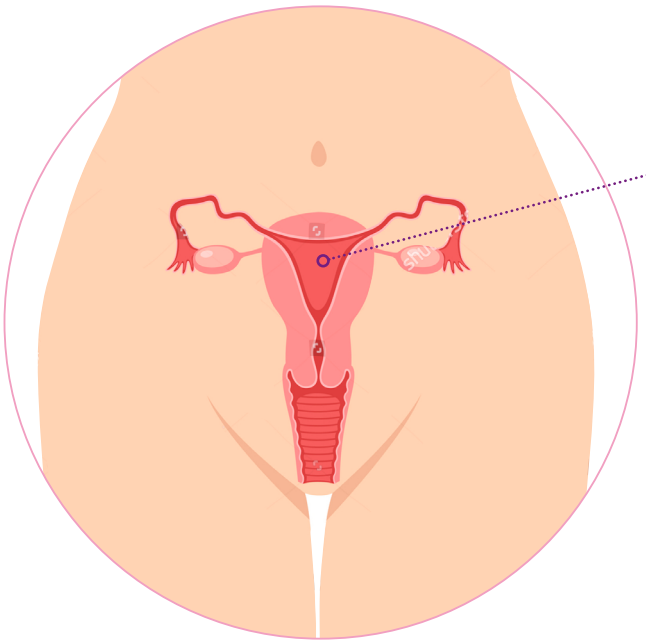
UTERINE LEIOMYOSARCOMA (uLMS)

What is uterine leiomyosarcoma?



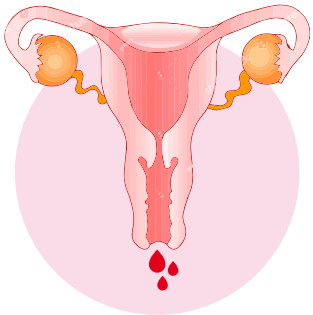
- **Rare** connective tissue tumour[1]
- Accounts approximately **1% of all uterine malignancies**[2]
- **Most common** form of uterine sarcoma[3]

Most uLMS[3,4]

- > 40 years of age
- perimenopausal period

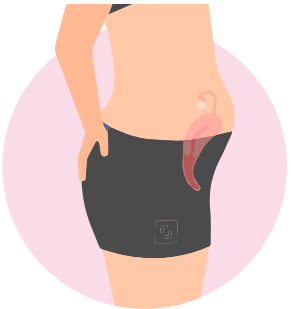
Symptoms[4,5]

56%



Abnormal uterine bleeding

54%



Palpable pelvic mass or enlarged uterus

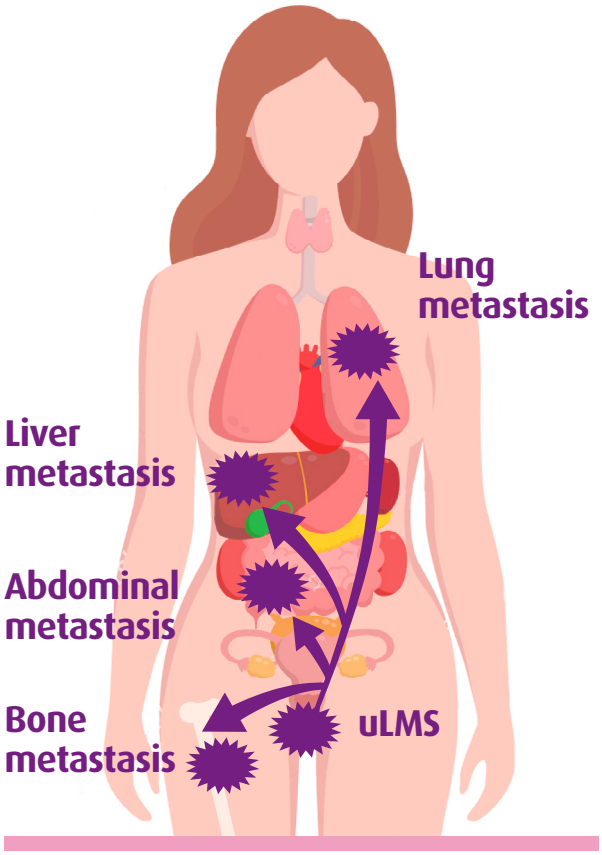
22%

Pelvic pressure or pain

?

Many patients remain asymptomatic

What is the prognosis of uterine leiomyosarcoma?

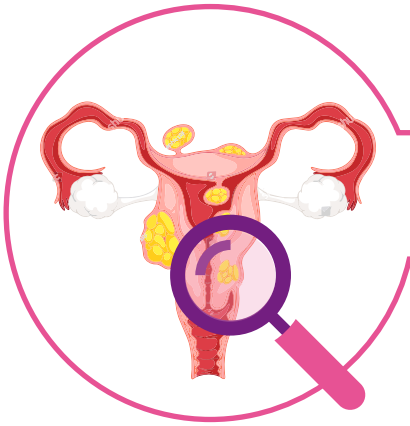


uLMS

- Highly aggressive tumour[5]
- Early hematogenous spread[2,5]
- Dissemination to extrapelvic sites (lung, abdominal, liver and bone metastases)[2,5]

5-year overall survival[5]	**25-76%**
Recurrence rates[5,6]	**45-75%**
Most common site of first recurrence[5,6]	**Lungs**

How is uterine leiomyosarcoma diagnosed and what means the risk of using uterine morcellation?



Benign uterine fibroids? or uLMS?

Preoperative distinction between fibroids and uLMS is difficult[3,4]

Uterine morcellation unknowingly in the setting of occult uterine sarcoma

Risk of tumour dissemination within the abdominopelvic cavity[2,4,5]

How is the uterine leiomyosarcoma treated?

Management of uLMS should be carried out in sarcoma reference centres[7]

LOCALISED uLMS

Surgery

- En bloc total hysterectomy[7] — RECOMMENDED
- SHOULD BE AVOIDED — Endoscopic supracervical hysterectomy, tumour enucleation or morcellation[4]

ADVANCED/METASTATIC uLMS

Surgery

Surgery aiming at complete resection seems to be the best strategy when local relapse or metastases of uLMS is diagnosed.

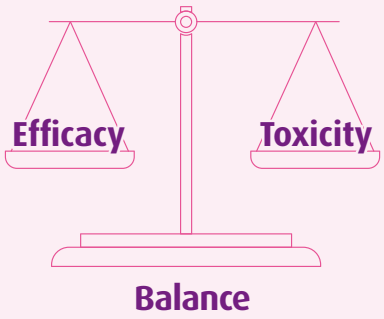
Chemotherapy = Increase of overall survival of women with metastatic LMS[8]

IMPORTANT[9]

Treatment goals

1. Make a tumour resectable (in selected cases)
2. Symptom control
3. Tumor stabilization with good quality of life

Choice of treatment



Main chemotherapeutic agents active in uLMS[6,8]

First-line therapy	▶ Anthracycline-based therapy
Second and later lines	▶ Gemcitabine +/- docetaxel; Gemcitabine +/- dacarbazine; Trabectedin; Pazopanib; Dacarbazine

ADVANCED/METASTATIC uLMS

Trabectedin*

More than a cytotoxic drug with immunomodulatory and antiangiogenic properties[10].

Contributes to a delayed response with a prolonged stabilization[10].

Indicated for the treatment of patients with unresectable or metastatic leiomyosarcoma who received a prior anthracycline-containing regimen[11].

Phase III trial: Significantly longer PFS versus dacarbazine in uLMS patients who had received prior anthracycline therapy[12].

Real-world evidence:
Clinical benefit in patients with recurrent/metastatic uLMS after failure to anthracycline-based therapy, especially when used in earlier lines[13].

- Manageable safety profile, including no cumulative toxicity[10,13].
- Improved efficacy when treatment is maintained until disease progression[6,14].
- Possible long-term therapy, with a high impact on survival and with a preserved quality of life[15].

Suitable choice when the treatment goal is **long-lasting tumour stabilisation** and **good patient quality of life**[16]

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 CPK 2.5 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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For more information please refer to the full product information at this link.

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