YONDELIS® (trabectedin)
YONDELIS – Neutropenia

SUMMARY

- Neutropenic sepsis, including fatal cases, can occur with YONDELIS.[1]
- Assess neutrophil count prior to administration of each dose of YONDELIS and periodically throughout the treatment cycle. Withhold or reduce dose of YONDELIS based on severity of adverse reaction.[1]
- In the phase 3 registration study (SAR-3007)[2] in patients (N=550) with advanced liposarcoma (LPS) or leiomyosarcoma (LMS) previously treated with an anthracycline and ≥1 additional systemic therapy, the incidence of grade 3 or 4 neutropenia, based on laboratory values, in patients receiving YONDELIS was 43% (161/378). The median time to the first occurrence of grade 3 or 4 neutropenia was 16 days (range, 8 days to 9.7 months); the median time to complete resolution of neutropenia was 13 days (range, 3 days to 2.3 months). Febrile neutropenia (fever ≥38.5°C with grade 3 or 4 neutropenia) occurred in 18 patients (5%) treated with YONDELIS. Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%).[1]
- In a retrospective, pooled analysis of 19 phase 2 clinical studies evaluating YONDELIS as single-agent therapy in patients (N=1132) with advanced solid tumors, grade 3-4 neutropenia was observed in 36.2% of patients.[3]
- Please refer to the DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, PATIENT COUNSELING INFORMATION, and PATIENT INFORMATION sections of the full Prescribing Information.

CLINICAL DATA

To provide the most relevant information, the summary below is limited to a phase 3 study and a large, retrospective analysis of 19 phase 2 studies. Additional studies reporting the occurrence of neutropenia are included in the OTHER RELEVANT LITERATURE section.

Phase 3 Study in Patients with Advanced LPS or LMS (SAR-3007)

Demetri et al (2016)[1,2] evaluated the efficacy and safety of YONDELIS vs dacarbazine in patients (N=550) with unresectable, locally advanced or metastatic LPS or LMS previously treated with an anthracycline and at least 1 additional systemic therapy. Patients were randomized 2:1 to YONDELIS (1.5 mg/m^2 intravenously [IV] via central venous access over 24 hours every 21 days; n=378) or dacarbazine (1 g/m^2 IV over 20-120 minutes every 21 days; n=172). All patients treated with YONDELIS were required to receive dexamethasone 20 mg IV injection 30 minutes prior to the start of each YONDELIS infusion. Major prognostic factors were well balanced among patients, and most patients received ≥2 prior lines of chemotherapy. The median duration of exposure to YONDELIS was 13 weeks (range, 1 to 127 weeks), with 30% of patients exposed for >6 months and 7% of patients exposed for >1 year.

The incidence of neutropenia is listed below in Table: Neutropenia in Phase 3 Study.

Neutropenia in Phase 3 Study[a,1]

	YONDELIS[b]		Dacarbazine[b]	
	All Grades	Grades 3-4	All Grades	Grade 3-4
Neutropenia	66%	43%	47%	26%

[a]Incidence based on the number of patients who had both baseline and at least 1 on-study laboratory measurement.
[b]YONDELIS group (range, 373 to 377 patients) and dacarbazine group (range, 166 to 168 patients).

In the YONDELIS arm, the median time to first occurrence of grade 3 or 4 neutropenia was 16 days (range, 8 days to 9.7 months); the median time to complete resolution of neutropenia was 13 days (range, 3 days to 2.3 months). Febrile neutropenia (fever ≥38.5°C

with grade 3 or 4 neutropenia) occurred in 18 patients (5%). Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%).

Among 158 patients in the YONDELIS arm with dose reductions due to adverse reactions, neutropenia (including febrile neutropenia) was reported in 8% of patients. Among 198 patients with dose interruptions due to adverse reactions, neutropenia was reported in 31% of patients.

Jones et al (2018)[4] conducted a post hoc subgroup analysis of the SAR-3007 study[2] to evaluate safety and efficacy amongst elderly patients (aged ≥ 65 years) treated with YONDELIS (n=93) compared to dacarbazine (n=35). Neutropenia was reported in 50% of elderly patients treated with YONDELIS compared to 31% treated with dacarbazine. Febrile neutropenia was reported in 2% of patients in the YONDELIS arm and 0% in the dacarbazine arm.

Retrospective, Pooled Analysis

Le Cesne et al (2012)[3] conducted a retrospective, pooled analysis of 19 phase 2 studies that included 1132 patients with advanced solid tumors who received YONDELIS IV via 1 of 3 schedules: 1.5 mg/m^2 as a 24-hour infusion once every 3 weeks (Q3W), 1.3 mg/m^2 as a 3-hour infusion Q3W, or 0.58 mg/m^2 as a 3-hour infusion for 3 consecutive weeks every 4 weeks. The majority of patients had soft tissue sarcoma (44%) or ovarian cancer (26.1%), and most patients had received prior chemotherapy (90.2%). Overall, a median of 3 YONDELIS cycles (range, 1 to 59 cycles) were administered over a median treatment duration of 9.4 weeks (range, 3.0 to 236.7 weeks). Overall, 9.8% of patients received prophylactic granulocyte colony-stimulating factor therapy during the studies.

Neutropenia was common as shown below in Table: Neutropenia in Pooled Analysis. In these studies, neutropenia demonstrated a reversible pattern and was rarely associated with fever (1.9%) or infection (1.8%). A total of 4.2% of patients discontinued treatment due to neutropenia.

Neutropenia in Pooled Analysis[a,3]

	1.5 mg/m^{2}Q3W 24-hr (n=570)			**1.3 mg/m^{2}Q3W 3-hr (n=258)**			**0.58 mg/m^{2}QW 3-hr (n=304)**			**Total (N=1132)**		
Grade	**1-2**	**3**	**4**	**1-2**	**3**	**4**	**1-2**	**3**	**4**	**1-2**	**3**	**4**
%	27.3	26.6	23.9	36.4	15.9	19.4	40.9	8.6	1.3	33.0	19.3	16.9

Abbreviations: Q3W 24-hr, 24-hour infusion every 3 weeks; Q3W 3-hr, 3-hour infusion every 3 weeks; QW 3-hr, 3-hour infusion for 3 consecutive weeks every 4 weeks.
[a]Data obtained from a total of 19 phase 2 clinical trials.

OTHER RELEVANT LITERATURE

Hing et al (2008)[5] developed a pharmacokinetic-pharmacodynamic model using data from 699 patients treated with YONDELIS to characterize the onset and duration of neutropenia. The study found that the severity of neutropenia was affected by the dose of YONDELIS and the frequency of administration, but not the duration of the infusion (1-, 3- or 24-hour infusions). In addition, the model demonstrated that neutropenia was reversible, of short duration, and noncumulative.

The occurrence of neutropenia during treatment with YONDELIS has also been described in other published studies.[6-10] Another study evaluated the role of body mass index as a risk

factor for YONDELIS-related toxicity, including neutropenia, in patients with soft tissue sarcoma.[11]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 24 September 2024.

REFERENCES

1. YONDELIS (trabectedin) [Prescribing Information]. Horsham, PA: Janssen Products, LP;https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/YONDELIS-pi.pdf.

2. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized, multicenter clinical trial. *J Clin Oncol*. 2016;34(8):786-793.

3. Le Cesne A, Yovine A, Blay JY, et al. A retrospective pooled analysis of trabectedin safety in 1,132 patients with solid tumors treated in phase II clinical trials. *Invest New Drug*. 2012;30(3):1193-1202.

4. Jones RL, Demetri GD, Schuetze SM, et al. Efficacy and tolerability of trabectedin in elderly patients with sarcoma: subgroup analysis from a phase III, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. *Ann Oncol*. 2018;29(9):1995-2002.

5. Hing J, Perez-Ruixo JJ, Stuyckens K, et al. Mechanism-based pharmacokinetic/pharmacodynamic meta-analysis of trabectedin (ET-743, Yondelis) induced neutropenia. *Clin Pharmacol Ther*. 2008;83(1):130-143.

6. Gadducci A, Grosso F, Scambia G, et al. A phase II randomised (calibrated design) study on the activity of the single-agent trabectedin in metastatic or locally relapsed uterine leiomyosarcoma. *Br J Cancer*. 2018;119(5):565-571.

7. Rubio MJ, J Lecumberri M, Varela S, et al. Efficacy of trabectedin in metastatic uterine leiomyosarcoma: a retrospective multicenter study of the Spanish ovarian cancer research group (GEICO) [abstract]. *Int J Gynecol Cancer*. 2018;28:1173.

8. Buonadonna A, Benson C, Casanova J, et al. A noninterventional, multicenter, prospective phase IV study of trabectedin in patients with advanced soft tissue sarcoma. *Anticancer Drugs*. 2017;28(10):1157-1165.

9. Jones RL, Maki RG, Patel PR, et al. Safety and efficacy of trabectedin when administered in the inpatient versus outpatient setting: clinical considerations for outpatient administration of trabectedin. *Cancer*. 2019;125(24):4435-4441.

10. Kobayashi H, Iwata S, Wakamatsu T, et al. Efficacy and safety of trabectedin for patients with unresectable and relapsed soft-tissue sarcoma in Japan: a Japanese musculoskeletal oncology group study. *Cancer*. 2020;126(6):1253-1263.

11. Vincenzi B, Badalamenti G, Armento G, et al. Body mass index as a risk factor for toxicities in patients with advanced soft-tissue sarcoma treated with trabectedin. *Oncology*. 2018;95(1):1-7.