YONDELIS® (trabectedin)
YONDELIS – Infusion Duration Less Than 24 Hours in Advanced Soft Tissue Sarcoma

SUMMARY

- The recommended dose of YONDELIS is 1.5 mg/m^2 administered as an intravenous (IV) infusion over 24 hours through a central venous line every 21 days (3 weeks), until disease progression (PD) or unacceptable toxicity.[1]
  - *Hepatic Impairment:* The recommended dose is 0.9 mg/m^2 in patients with moderate hepatic impairment (bilirubin levels greater than 1.5 times to 3 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than 8 times the ULN). Do not administer YONDELIS to patients with severe hepatic impairment (bilirubin levels above 3 times the ULN, and any AST and ALT).[1]
- A phase 2 study compared 2 YONDELIS dosing regimens (1.5 mg/m^2 as a 24-hour IV infusion every 3 weeks [Q3W] vs 0.58 mg/m^2 as a 3-hour IV infusion every week [QW] for 3 weeks of a 4-week cycle) in patients with unresectable/metastatic liposarcoma (LPS) or leiomyosarcoma (LMS) after failure of anthracycline and ifosfamide therapy. Median time to progression (TTP), the primary endpoint, was 3.7 months vs 2.3 months (*P*=0.0302), in favor of the Q3W 24-hour arm. Median progression-free survival (PFS) was 3.3 months vs 2.3 months (*P*=0.0418) for the Q3W 24-hour arm vs the QW 3-hour arm, respectively. Median overall survival (OS) was 13.9 months vs 11.8 months (*P*=0.1920), respectively. PFS and OS endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established. A higher incidence of grade 3 AST elevations and grade 3/4 neutropenia, thrombocytopenia, ALT elevations, nausea, and vomiting occurred in the Q3W 24-hour arm.[2]
- Please refer to the DOSAGE AND ADMINISTRATION section of the full Prescribing Information.

CLINICAL DATA

To provide the most relevant information, the summary below is limited to a phase 2 study that compared 2 YONDELIS dosing regimens in patients with advanced LMS/LPS. Additional phase 2 studies in soft tissue sarcoma (STS) in which YONDELIS was administered as a 3-hour infusion are included in the OTHER RELEVANT LITERATURE section.

Phase 2 Study in Advanced LMS/LPS Comparing YONDELIS Q3W 24-hour Regimen vs QW 3-hour Regimen

Demetri et al (2009)[2] evaluated the efficacy and safety of YONDELIS in patients with unresectable/metastatic LPS or LMS after failure of prior anthracycline and ifosfamide therapy (N=270).

Study Design/Methods

- Phase 2, randomized, open-label, multicenter study
- Patients were ≥18 years of age with LPS or LMS and had unresectable and/or metastatic relapse or PD following treatment with an anthracycline- and ifosfamide-containing regimen (combined or sequential).
- Patients were randomly assigned 1:1 to receive the following via central venous access:
  - YONDELIS 1.5 mg/m^2 IV infusion over 24 hours Q3W (n=136) OR
  - YONDELIS 0.58 mg/m^2 IV infusion over 3 hours QW for 3 weeks of a 4-week cycle (n=134)
- Dexamethasone 20 mg IV was administered 30 minutes prior to YONDELIS as antiemetic prophylaxis.

- Treatment was continued until PD, unacceptable toxicity, or consent withdrawal. Treatment was permanently discontinued after 2 additional cycles following confirmation of a complete response. Patients who experienced PD were permitted to crossover to the alternate treatment schedule.
- Dose modifications for adverse events (AEs) were standardized in the study protocol.
- **Primary efficacy endpoint:** TTP (defined as time from randomization to PD or death due to PD)
- **Secondary efficacy endpoints:** PFS, OS, overall response rate according to Response Evaluation Criteria in Solid Tumors, and duration of response

Results

Patient Characteristics

- Baseline demographics were similarly distributed between treatment arms.
- Overall, 65.6% of patients had LMS and 34.4% of patients had LPS. Patients had received a median of 1 (range, 0-6) prior therapy for advanced disease, and 93% of patients had metastatic disease.
- The median number of cycles was 5 cycles (range, 1-37) in the Q3W 24-hour arm and 2 cycles (range, 1-21) in the QW 3-hour arm.

Efficacy

- Efficacy Endpoints are summarized in the table below:

Efficacy Endpoints[2]

	Q3W 24-h n=136	**QW 3-h n=134**	**HR (95% CI)**	***P*-value**
Median TTP[a], months	3.7	2.3	0.734 (0.554-0.974)	0.0302
Median PFS, months	3.3	2.3	0.755 (0.574-0.992)	Nominal[b] 0.0418
Median OS, months	13.9	11.8	0.843 (0.653-1.090)	Nominal[b] 0.192
ORR, %	5.6	1.6	–	–

[a]Primary endpoint.
[b]These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.
Abbreviations: CI, confidence interval; h, hour; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; QW, every week; TTP, time to progression.

Safety

- The most common grade 3/4 hematologic toxicity was neutropenia (Q3W 24-hour, 47%; QW 3-hour, 14%), followed by thrombocytopenia (Q3W 24-hour, 11%; QW 3-hour, approximately 6%) and anemia (Q3W 24-hour, 8%; QW 3-hour, 9%).
  - Neutropenia and thrombocytopenia were transient, with a recovery of 7 days for neutropenia and 5-7 days for thrombocytopenia.
  - Granulocyte colony-stimulating factor support was given to 28% of patients in the Q3W 24-hour arm and 12% of patients in the QW 3-hour arm.
  - Febrile neutropenia was reported in 0.8% of patients in each arm.
- The most common grade 3/4 biochemical toxicities were transient, noncumulative increases in AST or ALT, with a median duration of 7-8 days (3.5 days for AST in the Q3W 24-hour arm).
  - Grade 3 ALT: 45% in the Q3W 24-hour arm vs 9% in the QW 3-hour arm
  - Grade 4 ALT: 2% in the Q3W 24-hour arm vs 0% in the QW 3-hour arm
  - Grade 3 AST: 32% in the Q3W 24-hour arm vs 3% in the QW 3-hour arm
  - No grade 4 AST events occurred in either arm.

- Severe bilirubin elevations were uncommon (<1% were grade 3 events in both treatment arms).
- Drug-related death was reported in 3.1% and 2.3% of patients in the Q3W 24-hour and QW 3-hour arms, respectively.
- The most common grade 3/4, treatment-related, nonhematologic AEs (>2% of patients in either treatment arm) are summarized in the table: Most Common Grade 3/4 Treatment-Related, Nonhematologic AEs

Most Common Grade 3/4 Treatment-Related, Nonhematologic AEs[a,2]

	Q3W 24-h n=130 n (%)	QW 3-h n=130 n (%)
Abdominal pain	6 (5)	6 (5)
Back pain	4 (3)	4 (3)
Dyspnea	5 (4)	8 (6)
Fatigue	10 (8)	9 (7)
Nausea	7 (5)	3 (2)
Vomiting	7 (5)	2 (2)

[a]>2% of patients in either treatment arm.
Abbreviations: AEs, adverse events; h, hour; Q3W, every 3 weeks; QW, every week.

OTHER RELEVANT LITERATURE

Additional phase 2 and phase 3 studies in patients with STS evaluating the use of YONDELIS administered as a 3-hour infusion, either as a single agent[3,4] or in combination with doxorubicin,[5-7] have been conducted.

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 11 September 2024.

REFERENCES

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