YONDELIS® (trabectedin)
YONDELIS - Alternative Dexamethasone Dosing

SUMMARY

- YONDELIS is indicated for the treatment of patients with unresectable or metastatic liposarcoma (LPS) or leiomyosarcoma (LMS) who received a prior anthracycline-containing regimen.[1]
- 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 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]
- Administer dexamethasone 20 mg IV 30 minutes prior to each dose of YONDELIS.[1]
- Alternative dexamethasone dosing regimens, including the use of lower doses of IV dexamethasone[2-5] and oral dosing regimens[2,4-8], have been described in the literature.
- Please refer to the DOSAGE AND ADMINISTRATION and CLINICAL STUDIES sections of the full Prescribing Information.

CLINICAL DATA

Phase 2 Studies

Phase 2 studies evaluating the use of alternative dexamethasone dosing regimens during treatment with YONDELIS in patients with soft tissue sarcoma (STS) are summarized in the table below.

Alternative Dexamethasone Dosing Regimens in Patients with STS in Phase 2 Studies[a]

Author	Study Design	Dosing Regimen	Key Efficacy Results	Key Safety Results
Martin-Broto et al (2016)[7,8]	Randomized, open-label, parallel-group study in pts with locally advanced nonresectable or metastatic STS (N=115)	• YONDELIS[b] 1.1 mg/m^2 IV over 3 hrs through central port followed by DOX 60 mg/m^2 IV; Dex 4 mg po q12 hrs on day -1 and Dex 20 mg IV 30 min prior to YONDELIS **OR** • DOX 75 mg/m^2 IV Both treatments given Q3W for 6 cycles in absence of PD or unacceptable toxicity	Median f/u: 13 mo for YONDELIS + DOX vs DOX alone, respectively **Primary Endpoint:** • Median PFS: 5.7 mo vs 5.5 mo (*P*=0.45) **Additional Endpoints:** • Median OS: 13.3 mo vs 13.7 mo (*P*=0.41) • Response: PR, 17% in both groups; SD, 53% vs 47% (*P*=0.77) • Study was D/C'd for futility after interim analysis	Grade 3-4 AEs with significantly higher incidence with YONDELIS + DOX vs DOX alone: Bilirubin ↑ (29% vs 12%; *P*=0.002), asthenia (25% vs 4%; *P*=0.002), ALT ↑ (19% vs 0; *P*<0.001), thrombocytopenia (18% vs 2%; *P*=0.016), and AST ↑ (8% vs 0; *P*=0.007) Deaths: 4 (2 in each arm) involving liver/renal failure (YONDELIS + DOX, n=1) and septic shock/neutropenia (remaining 3 pts)

Paz-Ares et al (2012)[6]	Multicenter study w/ phase 1 (double-blind, randomized, crossover) and phase 2 (pts choose +/- Dex) components in pts w/ previously treated unresectable, advanced, or metastatic STS; due to toxicity, modified to open-label w/mandatory Dex (N=41)	• YONDELIS[b] 1.3-1.65 mg/m^2 IV over 3 hrs Q3W plus Dex or PL in 1st cycle w/ alternate in 2nd cycle, and w/ pt's choice subsequently • Dex tx consisted of 4 mg po q12 hrs x 7 doses starting 24 hrs prior to YONDELIS plus 20 mg IV 30 min prior to YONDELIS	Median f/u: 21.2 mo **Primary Endpoint:** • ORR (n=35): 3% (1 PR; 51% had SD) **Additional Endpoints:** • Median PFS: 2.1 mo • Median OS: 10.2 mo • Estimated 1-yr OS: 41%	Grade 3-4 AEs: ALT ↑ (66%), AST ↑ (56%), neutropenia (51%), lymphopenia (51%), leukopenia (39%), vomiting (27%), anemia (22%), thrombocytopenia (22%), febrile neutropenia (15%), fatigue (12%), creatinine ↑ (7%), renal failure NOS (7%), nausea (10%), CPK ↑ (5%), bilirubin ↑ (5%) Tx-related deaths: n=4 Effect of Dex: • After 1st interim safety analysis, all drug-related deaths and most non-fatal drug-related SAEs occurred in pts treated with PL • Lower rates of AST/ALT ↑, neutropenia, and thrombocytopenia in pts treated with Dex
Garcia-Carbonero et al (2005)[4]	Open-label, single-arm, multicenter study in chemo-naïve pts with advanced, unresectable STS (N=36)	• YONDELIS[b] 1.5 mg/m^2 IV over 24 hrs Q3W • Dex 10 mg IV or po before YONDELIS (5 pts did not receive steroid)	Median f/u: 25 mo **Primary Endpoint:** • ORR (n=35): 17.1% (1 CR and 5 PR) • MR: n=1 **Additional Endpoints:** • Median PFS: 1.6 mo • Estimated 1-yr PFS: 21% • Median OS: 15.8 mo • 1-yr OS: 72% • Median DOR: 16.5 mo	Grade 3-4 AEs: Transient ALT ↑ (36%), transient AST ↑ (34%), neutropenia (33%), leukopenia (22%), nausea (14%), vomiting (14%), fatigue (11%), CPK ↑ (3%), anemia (3%) Additional AEs: Grade 1-2 AP ↑ (39%), grade 1-2 bilirubin ↑ (6%) D/C due to tx-related AEs: 2 pts (persistent AP ↑ on day 35)
Garcia-Carbonero et al (2004)[2]	Open-label, single-arm, multicenter study in pts with previously treated recurrent or metastatic STS (N=36)	• YONDELIS[b] 1.5 mg/m^2 IV over 24 hrs Q3W until PD or w/d due to toxicity • Dex 10 mg IV or po before YONDELIS (6 pts did not receive steroid)	Median f/u: 38.6 mo **Primary Endpoint:** • ORR: 8% (1 CR and 2 PR) **Additional Endpoints:** • Median TTP: 1.7 mo	Grade 3-4 AEs: Leukopenia (43%), neutropenia (34%), AST ↑ (26%), ALT ↑ (20%), thrombocytopenia (17%), anemia (9%), febrile neutropenia (6%), nausea (6%),

			• Median OS: 12.1 mo	bilirubin ↑ (3%), CPK ↑ (3%), vomiting (3%)
Monk et al (2012)[3]	Open-label, single-arm, 2-stage study in chemo-naïve pts with advanced uterine LMS (N=20)	• YONDELIS[b] 1.5 mg/m^2 IV over 24 hrs Q3W until PD, toxicity, or pt refusal • Dex 10 mg IV 30 min before YONDELIS	Median number of cycles: 2 (range, 2-29) **Primary Endpoint:** • ORR: 10% (2 PR; 50% had SD) **Additional Endpoints:** • Median PFS: 5.8 mo • Median OS: >26.1 mo (not reached) • Study closed prior to second stage because response criteria not reached	Grade 3-4 AEs: Neutropenia (n=16; 1 infection); leukopenia (n=11); thrombocytopenia (n=3); metabolic events (n=3); ALT ↑ (n=2); anemia (n=1); gastrointestinal and vascular events (n=1 each) W/D's due to AEs: n=1

[a]Studies in each section are presented by descending number of patients.
[b]YONDELIS was administered via a central venous line.
Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; chemo, chemotherapy; CPK, creatine phosphokinase; CR, complete response; D/C, discontinue or discontinuation; Dex, dexamethasone; DOR, duration of response; DOX, doxorubicin; EFT, Ewing's family tumor; f/u, follow-up; hrs, hours; IV, intravenous; LMS, leiomyosarcoma; min, minutes; mo, months; MR, minor response; NOS, not otherwise specified; ORR, overall response rate; OS, overall survival; OTS, osteosarcoma; PD, progressive disease; PFS, progression-free survival; PL, placebo; po, orally; PR, partial response; pts, patients; q, every; Q3W, every 3 weeks; SAEs, serious adverse events; SD, stable disease; STS, soft tissue sarcoma; TTP, time to progression; tx, treatment; w/, with; w/d, withdrawal.

OTHER RELEVANT LITERATURE

Grosso et al (2006)[5] evaluated the effect of dexamethasone premedication on the safety of YONDELIS in 54 previously-treated patients with advanced sarcoma. Patients received YONDELIS on a compassionate basis at a dose of 1000-1650 µg/m^2, either as a 3-hour (n=15) or 24-hour infusion (n=39) via central venous access every 3 weeks. Routine antiemetic premedication included IV dexamethasone (8-20 mg) and ondansetron. The initial 23 patients received YONDELIS with routine antiemetic prophylaxis alone, which did not include steroids on the day before therapy, but only on day 0 and possibly on day +1 (Group 1). Thirty-one patients received YONDELIS with steroid premedication (dexamethasone 4 mg orally twice daily) on the day before the YONDELIS infusion (Group 2). Hepatic and hematologic toxicity was reduced in the group who received dexamethasone premedication compared with the group who did not, as shown in the table below.

Hepatic and Hematological Toxicity in Patients With or Without Dexamethasone Premedication[5]

	Patients		Cycles	
	YONDELIS + Dexamethasone Premedication (n=31) n (%)	**YONDELIS without Dexamethasone Premedication (n=23) n (%)**	**YONDELIS + Dexamethasone Premedication (n=31) n (%)**	**YONDELIS without Dexamethasone Premedication (n=23) n (%)**
Grade 3/4 AST/ALT elevation	1 (3%)	16 (70%)	1 (<1%)	23 (34%)
Grade 3/4 neutropenia	3 (10%)	9 (39%)	3 (2%)	16 (23%)
Grade 3/4 thrombo-cytopenia	-	8 (35%)	-	17 (25%)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.				

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 14 January 2025.

REFERENCES

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