YONDELIS® (trabectedin)
Use of YONDELIS in Adult Patients With Advanced Liposarcoma or Leiomyosarcoma

SUMMARY

- A phase 3, randomized, multicenter study (SAR-3007) evaluated the use of YONDELIS vs dacarbazine in patients with advanced liposarcoma (LPS) or leiomyosarcoma (LMS) previously treated with an anthracycline and at least 1 additional systemic therapy.[1,2]
  - At the final analysis of overall survival (OS) after 381 OS events, median OS in the LPS subgroup was similar in the YONDELIS and dacarbazine groups (12.6 months vs 13.1 months, respectively; [hazard ratio (HR)] 1.05; *P*=0.826).[2] In the LPS subgroup, YONDELIS significantly improved progression-free survival (PFS) compared with dacarbazine (median 3.0 months vs 1.5 months, respectively; HR 0.55; 95% confidence interval [CI], 0.3-0.9; *P*=0.0093).[1,2]
  - In the LPS subgroup, grade 3-4 toxicities were predominantly lab-related hematologic toxicities and increases in hepatic transaminases.[2]
- A phase 3, randomized, multicenter study (LMS-04) evaluated the efficacy and safety of doxorubicin alone vs a combination of doxorubicin and YONDELIS, followed by maintenance YONDELIS in patients with metastatic or unresectable uterine or extrauterine LMS who had not received chemotherapy previously.[3,4]
  - At the time of analysis (median, 55 months), the median PFS was 12 months in the doxorubicin-YONDELIS group vs 6 months in the doxorubicin group (HR, 0.37; 95% CI, 0.26-0.53).
  - The median OS was 33 months in the doxorubicin-YONDELIS group vs 24 months in the doxorubicin group (HR, 0.65; 95% CI, 0.44-0.95).
  - Grade 3 or 4 adverse events (AEs) were significantly higher in the doxorubicin-YONDELIS group compared to the doxorubicin group (97% vs 56%, *P*<0.001).
- Additional phase 2 and 3 prospective studies that included adult patients with advanced soft tissue sarcoma (STS) of various histologies, including LPS, have been published.[5-14]
- Data have been reported from an open-label, single-arm, expanded access program (EAP) study in patients with pretreated, relapsed/refractory STS (including LPS and LMS).[15,16] One retrospective analysis of the EAP described outcomes in patients who received long-term (≥6 months) YONDELIS.[16]

CLINICAL DATA

There are no prospective clinical studies of YONDELIS in which enrollment was limited to adult patients with advanced LPS. To provide the most relevant information, the summary below is limited to a phase 3 study in adult patients with advanced LPS or LMS who received prior chemotherapy.

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

Demetri et al (2015)[1] evaluated the efficacy and safety of YONDELIS vs dacarbazine in patients with locally advanced or metastatic LPS or LMS previously treated with an anthracycline and at least 1 additional systemic therapy (N=518).

Study Design/Methods

- Phase 3, randomized, multicenter, open-label, active-controlled, parallel-group study
- Patients were randomized 2:1 to receive:
  - YONDELIS 1.5 mg/m^2 intravenously (IV) via central venous access over 24 hours every 21 days with dexamethasone 20 mg IV as premedication (n=384) or
  - Dacarbazine 1 g/m^2 IV over 20-120 minutes every 21 days (n=193)
- Dose modifications for AEs were standardized in the study protocol.
- **Primary endpoint:** OS

- **Secondary endpoints:** PFS, time to progression, objective response rate, duration of response, and safety
- **Additional secondary endpoint:** patient-reported outcomes as assessed by the MD Anderson Symptom Inventory questionnaire[17]
- The endpoints of clinical benefit rate (defined as the sum of complete responses, plus partial responses, plus stable disease [SD] for at least 18 weeks) and duration of SD were added to the statistical analysis plan as preplanned analyses to characterize prolonged disease control.
- The study was designed with a preplanned interim OS analysis after 188 deaths, which was to occur concurrently with the final analysis of PFS.
- A subgroup analysis in patients with LPS was conducted.[2]

Results

Patient Characteristics

- At the time of final OS analysis, 577 patients were randomized, of which 154 (27%) were in the LPS group.
- Baseline patient and disease characteristics at final OS are presented in the Table: Baseline Characteristics in the LPS Subgroup.

Baseline Characteristics in the LPS Subgroup[2]

	YONDELIS (n=102)	Dacarbazine (n=52)
Median age (range), years	56.5 (18.0-81.0)	53 (17.0-74.0)
LPS histology		
Myxoid ± round cell, n (%)	42 (41.2)	19 (36.5)
Pleomorphic, n (%)	11 (10.8)	5 (9.6)
Dedifferentiated, n (%)	49 (48.0)	28 (53.8)
Baseline ECOG PS score		
0, n (%)	51 (50.0)	26 (50.0)
1, n (%)	51 (50.0)	26 (50.0)
Lines of prior chemotherapy		
1, n (%)	24 (23.5)	15 (28.8)
2, n (%)	47 (46.1)	26 (50.0)
3, n (%)	21 (20.6)	2 (3.8)
4, n (%)	7 (6.9)	5 (9.6)
>4, n (%)	3 (2.9)	4 (7.7)
Mean (SD) time from initial diagnosis to randomization, months	54.3 (54.6)	56.5 (49.5)
Mean (SD) time from last disease progression to randomization, months	1.3 (1.3)	1.0 (0.9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LPS, liposarcoma; SD, standard deviation.

- At the time of interim OS analysis/final PFS analysis, 518 patients were randomized, of which 93 patients in the YONDELIS group and 47 patients in the dacarbazine group had LPS.[1]

Efficacy

- The final analysis of OS was performed after 381 OS events had occurred (clinical cutoff date of January 5, 2015). Median OS in the LPS subgroup was similar in the YONDELIS and dacarbazine groups (12.6 months vs 13.1 months, respectively [HR 1.05; 95% CI, 0.69-1.60]; *P*=0.826).[2]

- Subsequent anticancer therapy was used in the majority of patients in the LPS subgroup (64%). Post-protocol therapy in the YONDELIS vs dacarbazine treatment groups included pazopanib (16.7% vs 19.2%), dacarbazine (24.5% vs 7.7%), gemcitabine (13.7% vs 21.2%), and docetaxel (9.8% vs 17.3%), respectively. Additional therapies included radiation (13.7% vs 17.3%) and surgery (5.9% vs 15.4%).

- The final analysis of PFS was conducted at the time of the interim OS analysis after 329 PFS events (clinical cutoff date of September 16, 2013). In the LPS subgroup, YONDELIS (n=93) significantly improved median PFS compared with dacarbazine (n=47) (3.0 months vs 1.5 months, respectively [HR 0.55; 95% CI, 0.3-0.9]; *P*=0.0093).[1,2]
- Table: Secondary Endpoints in LPS Subgroup provides an analysis of secondary endpoints.[2]

Secondary Endpoints in LPS Subgroup[a,2]

	YONDELIS (n=93)	Dacarbazine (n=47)
Best overall response		
CR, n (%)	0	0
PR, n (%)	8 (8.6)	3 (6.4)
SD, n (%)	40 (43.0)	14 (29.8)
PD, n (%)	32 (34.4)	17 (36.2)
ORR, n (%)	8 (8.6)	3 (6.4)
	OR=1.380; 95% CI, 0.311-8.459; *P*=0.7508	
CBR, n (%)	26 (28.0)	7 (14.9)
	HR=2.218; 95% CI, 0.833-6.584; *P*=0.0957	

[a]Final analyses of secondary endpoints were conducted at the time of interim OS analysis.
Abbreviations: CBR, clinical benefit rate (CR + PR + SD ≥18 weeks); CI, confidence interval; CR, complete response; HR, hazard ratio; LPS, liposarcoma; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

- In an analysis of patient-reported outcomes among all patients, patients in both treatment groups had low baseline symptom burden. Low levels of symptoms and functional interference were maintained throughout the study in both groups.[17]

Safety

- In the LPS subgroup, the median number of treatment cycles and the proportion of patients with prolonged treatment courses (≥6, ≥9, or ≥12), were higher in the YONDELIS group compared with the dacarbazine group.
- Reported toxicities are presented in Table: Grade 3-4 Adverse Events in ≥5% of Patients in the LPS Subgroup.

Grade 3-4 Adverse Events in ≥5% of Patients in the LPS Subgroup[2]

	YONDELIS (n=102)	Dacarbazine (n=45)
Total patients with grade 3-4 adverse event, n (%)	76 (74.5)	25 (55.6)
Hematological		
Neutropenia, n (%)	38 (37.3)	11 (24.4)
Leukopenia, n (%)	25 (24.5)	9 (20)
Thrombocytopenia, n (%)	19 (18.6)	8 (17.8)
Anemia, n (%)	13 (12.7)	8 (17.8)
Nonhematological		
Fatigue, n (%)	4 (3.9)	0
Nausea, n (%)	2 (2.0)	1 (2.2)
Vomiting, n (%)	4 (3.9)	1 (2.2)
Abdominal pain, n (%)	0	3 (6.7)

	YONDELIS (n=102)	Dacarbazine (n=45)
Dehydration, n (%)	3 (2.9)	1 (2.2)
Febrile neutropenia, n (%)	7 (6.9)	1 (2.2)
Laboratory values		
ALT increase, n (%)	28 (27.5)	0
AST increase, n (%)	14 (13.7)	0
Creatinine phosphokinase increase, n (%)	5 (4.9)	0
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LPS, liposarcoma.		

Phase 3 Study in Patients With Advanced Leiomyosarcoma (LMS-04)

Pautier et al (2024)[3] evaluated the efficacy and safety of doxorubicin alone vs a combination of doxorubicin and YONDELIS, followed by maintenance YONDELIS, as a first-line treatment in adult patients with metastatic or unresectable uterine or extrauterine LMS who had not received chemotherapy previously (N=150).

Study Design/Methods

- Phase 3, randomized, multicenter, open-label study.
- Patients were randomized 1:1 to receive:
  - Doxorubicin group: doxorubicin alone (75 mg/m² IV over 10-15 minutes) once every 3 weeks with lenograstim (150 µg/m²/day subcutaneously) from day 3 to day 9, for up to six cycles (n=76)
  - Doxorubicin-YONDELIS group: doxorubicin (60 mg/m² IV over 10-15 minutes) followed by YONDELIS (1.1 mg/m² IV over 3 hours) once every 3 weeks, with pegfilgrastim (6 mg subcutaneously) on day 2, for up to six cycles (n=74).
- In patients without disease progression in the doxorubicin-YONDELIS group, YONDELIS alone (1.1 mg/m²) was continued for up to 17 cycles.
- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, secondary PFS, disease control rate, response rate, duration of response, and safety

Results

Patient Characteristics

- A total of 150 patients were randomized, with 76 assigned to the doxorubicin group and 74 to the doxorubicin-YONDELIS group.
- Among the 150 patients, 67 had uterine LMS, and 83 had soft-tissue LMS.
- The key characteristics of the patients are presented in the Table: Key Demographic and Clinical Characteristics.

Key Demographic and Clinical Characteristics[3]

Characteristics	Doxorubicin (n=76)	Doxorubicin-YONDELIS (n=74)
Median age (range), years	64 (53-69)	59 (52-68)
Sex, n (%)		
Female	59 (78)	53 (72)
ECOG PS score, n/N (%)[a]		
0	45/74 (61)	47/70 (67)
1	29/74 (39)	23/70 (33)
Median no. of cycles received (IQR)		
Induction therapy	6 (4-6)	6 (6-6)

Maintenance therapy	NA	10.5 (4-17)

[a]Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. Patients were required to have an ECOG performance-status score of less than 2. Data were missing for two patients in the doxorubicin group and for four in the doxorubicin-YONDELIS group.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status, IQR; interquartile range; NA, not available.

Efficacy

- At a median follow-up of 55 months, the median PFS was 12 months in the doxorubicin-YONDELIS group vs 6 months in the doxorubicin group (HR, 0.37; 95% CI, 0.26-0.53).
- At the time of analysis, a total of 107 patients had died (47 in the doxorubicin-YONDELIS group, 60 in the doxorubicin group).
- The median OS was 33 months in the doxorubicin-YONDELIS group vs 24 months in the doxorubicin group (HR, 0.65; 95% CI, 0.44-0.95).
- At 2 years, the PFS in the doxorubicin-YONDELIS group was 30% (95% CI, 21-42) vs 3% (95% CI, 1-9) in the doxorubicin group; the OS in the doxorubicin-YONDELIS group was 68% (95% CI, 57-78) vs 49% (95% CI, 38-60) in the doxorubicin group.
- The time to second disease progression was 26 months in the doxorubicin-YONDELIS group vs 13 months in the doxorubicin group (HR, 0.46; 95% CI, 0.32-0.65).

Safety

- A total of 149 patients received at least 1 cycle of treatment and were included in the safety analysis (doxorubicin-YONDELIS group, n=74; doxorubicin group, n=75).
- Patients in the doxorubicin-YONDELIS group experienced increased toxicity, with a higher incidence and severity of adverse hematologic events compared to the doxorubicin group.[4]
- Grade 3 or 4 adverse events were significantly higher in the doxorubicin-YONDELIS group vs the doxorubicin group (97% vs 56%, $P<0.001$).
- The proportion of patients experiencing neutropenia, anemia, thrombocytopenia, and febrile neutropenia was higher in the doxorubicin-YONDELIS group vs the doxorubicin group.
- Grade 3 or 4 liver cytolysis was reported in 34 (46%) patients in the doxorubicin-YONDELIS group vs 2 (3%) patients in the doxorubicin group. No cases of chronic liver dysfunction were reported.
- Serious adverse events were reported in 37 patients in the doxorubicin-YONDELIS group vs 20 patients in the doxorubicin group.
- No treatment-related deaths were reported in the doxorubicin-YONDELIS group, and one treatment-related death (cardiac failure) was reported in the doxorubicin group.

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 03 February 2025.

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