YONDELIS® (trabectedin)
YONDELIS - Administration Setting

SUMMARY

- The decision to administer YONDELIS in the inpatient or outpatient setting, including the use of an ambulatory pump, is at the discretion of the treating clinician.
- In the phase 3 pivotal study (SAR-3007)[1] in patients with advanced liposarcoma (LPS) or leiomyosarcoma (LMS) previously treated with an anthracycline and ≥1 additional systemic therapy, 73% (277/378) of patients in the YONDELIS group were administered their first dose as an outpatient and 27% (100/378) received their first YONDELIS dose in the inpatient setting. YONDELIS was administered via a central venous catheter and the administration setting (inpatient vs outpatient) was determined at the discretion of the investigator based on institutional preference or standard of care. A subset analysis demonstrated that efficacy and safety outcomes were similar when YONDELIS was administered in the outpatient or inpatient setting.[2]
- The administration of YONDELIS in the outpatient setting has been described in the literature.[3-7]
- As a vesicant, YONDELIS has the potential to cause necrosis, blistering, and pain when extravasation occurs, which may require surgical intervention, as evidenced by published reports.[2,8-16]

CLINICAL STUDY

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

Jones et al (2019)[2] conducted a subset analysis to compare the efficacy and safety of YONDELIS when administered in the inpatient vs outpatient setting during the phase 3 pivotal study (SAR-3007)[1].

Study Design/Methods[1,2]

- SAR-3007 was a phase 3, randomized, multicenter, open-label, active-controlled, parallel-group study.
- The study included patients with unresectable, locally advanced or metastatic LPS or LMS previously treated with at least a combination of an anthracycline and ifosfamide or an anthracycline and ≥1 additional cytotoxic chemotherapy regimen.
- Patients were randomized 2:1 to receive:
  - YONDELIS 1.5 mg/m^2 intravenously (IV) via central venous access over 24 hours every 3 weeks (Q3W) with dexamethasone 20 mg IV as premedication, or
  - Dacarbazine 1 g/m^2 IV over 20-120 minutes Q3W
- Patients randomized to the YONDELIS group received the 24-hour infusion in either an inpatient or outpatient setting, based upon institutional preference/standard of care.
- Institutions collected the site of YONDELIS administration for the first infusion, with the assumption that the site of care was unchanged for subsequent treatments.
- A subset analysis evaluated the efficacy, safety, and patient-reported outcomes of YONDELIS based on first infusion site of care.

Results of Subset Analysis[2]

- Among patients who received YONDELIS, 73% (277/378) received their first infusion in the outpatient setting and 27% (100/378) received their first infusion in the inpatient setting.

Baseline Characteristics

- Baseline demographics and disease characteristics were generally balanced across both inpatient and outpatient subgroups.

- The inpatient subgroup was found to have a higher population of elderly patients (aged ≥65 years) compared with the outpatient subgroup (36 patients [36%] vs 57 patients [21%], respectively) and with the overall study population (93 patients [25%]).
- No major differences in tumor histology, Eastern Cooperative Oncology Group
- (ECOG) performance status (PS) (ECOG PS), or lines of prior chemotherapy received were observed.
- A majority of the inpatient (n=77; 77%) and outpatient (n=199; 72%) subgroups were characterized as having LMS, having received ≥ 2 prior lines of chemotherapy, and having a similar likelihood of an ECOG PS of 0 or 1.
- 85% (n=85) and 89% (n=246) of patients in the inpatient and outpatient subgroups received ≥2 prior lines of chemotherapy, respectively.
- Treatment exposure was found to be similar in both groups, with a median of 4 treatment cycles administered in each.[2]

Efficacy

- Median progression-free survival was 4.1 months with inpatient administration vs 4.2 months with outpatient administration (hazard ratio [HR]: 0.90; *P*=0.49).
- Median overall survival was 14.3 months with inpatient administration vs 13.7 months with outpatient administration (HR: 0.89; *P*=0.40).
- No difference in clinical benefit rate (CBR; complete responses plus partial responses plus stable disease for ≥18 weeks) was demonstrated between the two subgroups: 33 inpatients (38%) (95% confidence interval [CI], 27.5%-39.5%) vs 84 outpatients (33%) (95% CI, 27.7%-49.0%; odds ratio [OR]=1.22 [95% CI, 0.71-2.08; *P*=0.44]).
- Objective response rate (ORR) was 14% (n=12; 95% CI, 5.2%-12.5%) for patients treated in the inpatient setting vs 8% (n=21; 95% CI, 7.3%-22.9%) for patients treated in the outpatient setting (OR=1.76; 95% CI, 0.75-3.95; *P*=0.15).
- There were no clinically meaningful differences in patient-reported outcomes as assessed by MD Anderson Symptom Inventory scores based on site of administration.[2]

Safety

- The most commonly reported treatment-emergent adverse events (AEs) in both inpatient and outpatient subgroups included nausea, fatigue, anemia and transaminase increases (Table: Most Commonly Reported Adverse Events).[2]

Most Commonly Reported Adverse Events (≥20% of patients)[2]

Adverse Event, n (%)	Inpatients (n=100)	Outpatients (n=277)
Nausea	73 (73)	212 (77)
Fatigue	63 (63)	199 (72)
Anemia	58 (58)	99 (36)
Alanine aminotransferase increased	54 (54)	133 (48)
Vomiting	47 (47)	126 (46)
Aspartate aminotransferase increased	43 (43)	99 (36)
Decreased appetite	38 (38)	103 (37)
Neutropenia	37 (37)	81 (29)
Constipation	34 (34)	107 (39)
Diarrhea	34 (34)	97 (35)
Peripheral edema	33 (33)	75 (27)
Cough	30 (30)	56 (20)
Headache	29 (29)	66 (24)
Neutrophil count decreased	28 (28)	68 (25)
Dyspnea	28 (28)	66 (24)
Blood alkaline phosphatase increased	28 (28)	59 (21)
Pyrexia	25 (25)	48 (17)
Hypokalemia	25 (25)	28 (10)
White blood cell count decreased	24 (24)	73 (26)
Thrombocytopenia	24 (24)	49 (18)

Adverse Event, n (%)	Inpatients (n=100)	Outpatients (n=277)
Platelet count decreased	22 (22)	41 (15)
Blood creatinine phosphokinase increased	20 (20)	37 (13)
Pain in extremity	20 (20)	29 (11)

- Grade 3-4 AEs occurred in 87 (87%) patients who received YONDELIS in the inpatient setting vs 219 (79%) patients who received YONDELIS in the outpatient setting. Grade 3-4 serious AEs were reported in 43% vs 33% of patients, respectively.
- Regardless of site of first infusion, the most common grade 3-4 AEs included increased transaminases, hematologic toxicities, nausea, and fatigue (Table: Grade 3 to 4 Reported Adverse Events).[2]

Grade 3 to 4 Reported Adverse Events (≥5% of patients)[2]

Adverse Event, n (%)	Inpatients (n=100)	Outpatients (n=277)
Alanine aminotransferase increased	29 (29)	82 (30)
Neutropenia	27 (27)	63 (23)
Anemia	26 (26)	41 (15)
Neutrophil count decreased	23 (23)	54 (20)
White blood cell count decreased	20 (20)	55 (20)
Aspartate aminotransferase increased	16 (16)	41 (5)
Platelet count decreased	15 (15)	24 (9)
Thrombocytopenia	14 (14)	25 (9)
Leukopenia	10 (10)	27 (10)
Nausea	10 (10)	16 (6)
Fatigue	9 (9)	23 (8)
Vomiting	8 (8)	15 (5)
Dehydration	6 (6)	12 (4)
Pulmonary embolism	6 (6)	6 (2)
Asthenia	6 (6)	1 (0.4)
Blood creatinine phosphokinase increased	5 (5)	17 (6)
Febrile neutropenia	5 (5)	13 (5)
Dyspnea	5 (5)	11 (4)
Hypokalemia	5 (5)	9 (3)
Catheter site infection	5 (5)	6 (2)
Hypoalbuminemia	5 (5)	2 (0.7)

- Catheter-related complications of any grade occurred at a similar frequency; reported in 16% (n=16) and 15% (n=42) of patients in the inpatient and outpatient setting, respectively (Table: Adverse Events from Catheter-Related Complications).[2]

Adverse Events from Catheter-Related Complications[2,a]

Adverse Event, n (%)	Inpatients (n=100)		Outpatients (n=277)	
	Total	Grade 3	Total	Grade 3
Catheter-related complications	16 (16)	6 (6)	42 (15)	14 (5)
Catheter site infection	5 (5)	5 (5)	14 (5)	6 (2)
Catheter site pain	7 (7)	0 (0)	12 (4)	3 (1)
Catheter site inflammation	1 (1)	1 (1)	7 (3)	0 (0)
Infusion site extravasation	0 (0)	0 (0)	5 (2)	2 (1)
Thrombosis in device	0 (0)	0 (0)	5 (2)	1 (0.4)
Soft-tissue necrosis	0 (0)	0 (0)	4 (1)	4 (1)
Catheter site erythema	1 (1)	0 (0)	3 (1)	0 (0)
Catheter site pruritis	1 (1)	0 (0)	3 (1)	0 (0)
Catheter site cellulitis	1 (1)	0 (0)	2 (1)	0 (0)
Catheter-site related reaction	0 (0)	0 (0)	1 (0.4)	0 (0)
Device breakage	0 (0)	0 (0)	1 (0.4)	1 (0.4)
Device component issue	2 (2)	1 (1)	1 (0.4)	0 (0)
Device occlusion	0 (0)	0 (0)	1 (0.4)	0 (0)

Adverse Event, n (%)	Inpatients (n=100)		Outpatients (n=277)	
	Total	Grade 3	Total	Grade 3
Infusion site erythema	0 (0)	0 (0)	1 (0.4)	0 (0)
Infusion site pain	0 (0)	0 (0)	1 (0.4)	0 (0)
Infusion site bruising	0 (0)	0 (0)	1 (0.4)	0 (0)
Infusion site hemorrhage	0 (0)	0 (0)	1 (0.4)	0 (0)
Injection site reaction	0 (0)	0 (0)	1 (0.4)	0 (0)
Medical device complication	0 (0)	0 (0)	1 (0.4)	0 (0)
Catheter site edema	1 (1)	0 (0)	0 (0)	0 (0)
Catheter site swelling	3 (3)	0 (0)	0 (0)	0 (0)
[a]No grade 4 or 5 catheter-related complications were reported for either subgroup.				

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 10 April 2024.

REFERENCES

1. Demetri GD, von Mehren M, Jones RL, et al. Protocol for: 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.

2. Jones RL, Maki RG, Patel SR, 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.

3. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol*. 2009;27(25):4188-4196.

4. Hoiczyk M, Grabellus F, Podleska L, et al. Trabectedin in metastatic soft tissue sarcomas: role of pretreatment and age. *Int J Oncol*. 2013;43(1):23-28.

5. Demetri G. ET-743: the US experience in sarcomas of soft tissues. *Anticancer Drugs*. 2002;13(Suppl. 1):S7-S9.

6. 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.

7. Runnebaum IB, Reichert D, Ringsdorf U, et al. Trabectedin plus pegylated liposomal doxorubicin (PLD) for patients with platinum-sensitive recurrent ovarian cancer: a prospective, observational, multicenter study. *J Cancer Res Clin Oncol*. 2018;144(6):1185-1195.

8. Theman TA, Hartzell TL, Sinha I, et al. Recognition of a new chemotherapeutic vesicant: trabectedin (ecteinascidin-743) extravasation with skin and soft tissue damage. *J Clin Oncol*. 2009;27(33):e198-e200.

9. Tortolano L, Gaudin A, Lemare F. From stinging to necrosis: application of the ALARM analysis to a trabectedin extravasation case. *Int J Clin Pharm*. 2013;35(5):938-939.

10. Vilasoa-Boo P, Martin-Vila A, Alvarez-Payero M, et al. Extravasation of trabectedin with tissue necrosis: case report. *Int J Clin Pharm*. 2013;35(5):910.

11. Azaïs H, Bresson L, Bassil A, et al. Chemotherapy drug extravasation in totally implantable venous access port systems: how effective is early surgical lavage? *J Vasc Access*. 2015;16(1):31-37.

12. Haslik W, Hacker S, Felberbauer FX, et al. Port-a-Cath® extravasation of vesicant cytotoxics: surgical options for a rare complication of cancer chemotherapy. *Eur J Surg Oncol*. 2015;41(3):378-385.

13. Polson K, Sullivan C, Houston M, et al. Optimizing safety in outpatient administration of trabectedin, a novel anticancer vesicant drug via continuous intravenous infusion. Poster presented at: 16th Annual Meeting of the Connective Tissue Oncology Society (CTOS); November 11-13, 2010; Paris, France.

14. Loverre T, De Mitri P, Scardigno D, et al. Management of extravasation in ovarian cancer patients receiving trabectedin. Abstract presented at: 13th Biennial Meeting of the International Gynecologic Cancer Society (IGCS); October 23-26, 2010; Prague. *Int J Gynecol Cancer.* 2010;20(suppl 2).

15. Yoshimi K, Wasa J, Otsuka M, et al. Differential diagnosis of trabectedin extravasation: a case report. *J Dermatology*. 2017;44(8):e200-e201.

16. Pluschnig U, Haslik W, Bayer G, et al. Outcome of chemotherapy extravasation in a large patient series using a standardised management protocol. *Support Care Cancer*. 2015;23(6):1741-1748.