YONDELIS® (trabectedin)
YONDELIS – Cardiovascular Events

SUMMARY

- Cardiomyopathy including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur with YONDELIS. In ET743-SAR-3007, a pivotal phase 3 study (SAR-3007)[1], a significant decrease in left ventricular ejection fraction (LVEF) was defined as an absolute decrease of ≥15% or below the lower limit of normal with an absolute decrease of ≥5%. Patients with a history of New York Heart Association (NYHA) Class II to IV heart failure or abnormal LVEF at baseline were ineligible. In the SAR-3007 study, cardiomyopathy occurred in 23 patients (6%) receiving YONDELIS and in 4 patients (2.3%) receiving dacarbazine. Grade 3 or 4 cardiomyopathy occurred in 15 patients (4%) receiving YONDELIS and in 2 patients (1.2%) receiving dacarbazine; cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS and in none of the patients receiving dacarbazine. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving YONDELIS was 5.3 months (range: 26 days-15.3 months).[2]
- Patients with LVEF < lower limit of normal, prior cumulative anthracycline dose of ≥300 mg/m^2, age ≥65 years, or a history of cardiovascular disease may be at increased risk of cardiac dysfunction. Assess LVEF by echocardiogram (ECHO) or multigated acquisition (MUGA) scan before initiation of YONDELIS and at 2- to 3-month intervals thereafter until YONDELIS is discontinued. Discontinue treatment with YONDELIS based on severity of adverse reaction.[2] Please refer to the YONDELIS Prescribing Information for additional information regarding permanent discontinuation of YONDELIS in patients who develop Grade 3 or 4 cardiac adverse events (CAEs) indicative of cardiomyopathy or decreases in LVEF below lower limit of normal.
- In a cardiac safety analysis of the pivotal phase 3 SAR-3007 study, heart failure and myocardial disorders were more frequent with YONDELIS vs dacarbazine (2.9% vs 0.6%, and 1.6% vs 0%, respectively); however, the proportion of patients with LVEF decline was comparable (13.5% vs 11%, respectively). A multivariate analysis identified advancing age, higher cumulative anthracycline dose (CAD), abnormal baseline LVEF, and cardiac medical history as independent risk factors of LVEF decline.[3]
- The effect of YONDELIS on the QT/QTc interval was evaluated in a phase 2 study in 75 patients who received placebo on day 1 and YONDELIS (1.3 mg/m^2) as a 3-hour intravenous (IV) infusion on day 2. None of the patients in the study had a QTc interval exceeding 500 msec or more than 60 msec increase from baseline, and no large changes in the mean QTc interval (ie, >20 msec) were observed.[2,4]
- Cardiac safety was evaluated in 3 retrospective analyses of drug-related CAEs pooled from phase 1-3 studies, spontaneously-reported cases, and pharmacovigilance databases.[5,6,7]
- Please refer to the DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and PATIENT COUNSELING INFORMATION sections of the full Prescribing Information.

CLINICAL DATA

To provide the most relevant information, the summary below is limited to prospective phase 3 and phase 2 studies and retrospective pooled analyses of phase 1-3 studies.

Prospective Studies

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

Demetri et al (2015)[1] conducted a randomized, open-label, multicenter study evaluating YONDELIS vs dacarbazine in patients with advanced LPS or LMS previously treated with an anthracycline and ≥1 additional systemic therapy (N=518). Patients were excluded from the study if they had a history of myocardial infarction within 6 months, history of NYHA Class II to IV heart failure, or abnormal LVEF at baseline. Patients were randomized 2:1 to receive YONDELIS (n=345) 1.5 mg/m^2 IV over 24 hours every 3 weeks (Q3W) via central line (premedication with dexamethasone 20 mg IV) or dacarbazine (n=173) 1 g/m^2 IV over 20-120 minutes Q3W. Patients received a median of 4 cycles of YONDELIS vs 2 cycles of dacarbazine.

Seven (2.1%) treatment-related deaths were reported in the YONDELIS arm, 1 of which was related to renal failure/cardiac arrest, and 1 of which was related to multiorgan failure.

Schuetze et al (2016)[3] conducted a cardiac safety analysis of YONDELIS vs dacarbazine in patients enrolled in the phase 3 study, SAR-3007. Data regarding previous anthracycline exposure, medical history, concomitant medications, baseline and end-of-treatment LVEF assessments, and CAEs were collected. At baseline, median CAD was 270 mg/m^2 in the YONDELIS group vs 241 mg/m^2 in the dacarbazine group. In the YONDELIS vs dacarbazine groups, 28.8% vs 24.4% of patients reported a cardiac medical history and 45.5% vs 35.5% were on cardiovascular therapy at the time of study entry. Baseline LVEF was less than the lower limit of normal in 5.3% of YONDELIS-treated patients and 7.6% of dacarbazine-treated patients.

Treatment-emergent cardiac disorders were observed in 15.1% of patients who received YONDELIS and 14.5% of patients who received dacarbazine, including arrhythmias in 9.5% and 7.0% of patients, respectively. Heart failure was more frequent with YONDELIS vs dacarbazine (2.9% vs 0.6%, respectively). Four of the 11 cases of heart failure reported with YONDELIS were drug-related and 8 patients recovered; cases were frequently confounded by concurrent AEs and/or prior cardiac history. Three cases of cardiomyopathy were reported in the YONDELIS arm; 2 of these were not drug-related and both patients recovered, while the third was possibly related to pneumonia (patient did not recover). One YONDELIS-treated patient with multiple cardiac comorbidities experienced fatal multiorgan failure which was associated with severely decreased LVEF (30%).

The proportion of patients with LVEF decline was comparable between treatment groups as shown in the table below.

Decreases in LVEF from baseline to end-of-treatment in SAR-3007[3]

	YONDELIS (n=378)	**Dacarbazine (n=172)**
Patients with baseline and final measurement, n (%)[a]	251 (66.4)	100 (58.1)
Absolute decrease ≥15%, n (%)	22 (8.8)	3 (3)
Less than LLN and absolute decrease ≥5%, n (%)	29 (11.6)	11 (11)
Satisfy either condition, n (%)	34 (13.5)	11 (11)

Abbreviations: LLN, lower limit of normal range.
[a]Percentages for total number of patients with baseline and final measurement were calculated with the number of patients treated in each treatment group as the denominator. Percentages were calculated with the number of patients with a baseline and final measurement as the denominator.

Among patients with LVEF decline, the median number of treatment cycles was 8.5 for YONDELIS vs 2 for dacarbazine. Overall survival and progression-free survival in patients with LVEF decline at the end of treatment were not worse compared with the total study population. A multivariate analysis identified the following independent risk factors of LVEF decline: higher CAD (≥300 mg/m^2), abnormal baseline LVEF, advancing age (≥65 years old), and cardiac medical history.

Phase 2 Sequential Design Study in Patients with Advanced Solid Tumors to Evaluate Effects on QT/QTc Interval

Thertulien et al (2012)[4] conducted a single-blind, multicenter, phase 2 sequential design study to evaluate the potential effects of YONDELIS on the QT/QTc interval, relative to placebo, in patients with locally advanced or metastatic solid tumor malignancies who had received up to 3 prior lines of chemotherapy (N=75). Patients enrolled in the study were 18-65 years of age, had a normal LVEF (in those previously treated with >260 mg/m^2 of anthracycline), a normal electrocardiogram (ECG), and were not smokers. All patients received a 3-hour IV infusion of placebo (normal saline) on day 1 and a 3-hour IV infusion of YONDELIS 1.3 mg/m^2 on day 2. Dexamethasone 20 mg IV (or equivalent) was administered 30 minutes prior to the 3-hour infusions on both days. ECGs were recorded periodically up to 8 hours after the placebo infusion and up to 24 hours after YONDELIS infusion.

Mean baseline QTcF intervals increased within 4 hours after initiation of placebo or YONDELIS therapy, but returned approximately to predose levels at the 8-hour timepoint. Small changes were observed in the mean QTcB intervals during the 24-hour period after initiation of placebo or YONDELIS therapy. None of the evaluable patients (n=72) in the study had a QTc interval exceeding 500 ms or had more than a 60 ms increase from baseline. Additionally, there were no large changes in the mean QTc interval (ie, >20 ms). Ninety-five percent (71/75) of patients experienced treatment-emergent adverse events, but there were no cardiac toxicities, ventricular arrhythmias (including ventricular fibrillation), or reports of sudden death. There were no clinically significant changes in laboratory assessments, vital signs, ECGs, and physical examination.

ADDITIONAL STUDIES EVALUATING CARDIAC SAFETY

Retrospective Pooled Analyses

Jones et al (2021)[5] conducted a retrospective pooled analysis of key cardiac-related treatment-emergent adverse events (cTEAEs) in ten phase 2 trials and one phase 3 trial (SAR-3007) evaluating YONDELIS monotherapy for soft tissue sarcoma (STS) and other solid tumors, and in two phase 3 trials evaluating YONDELIS in combination with pegylated liposomal doxorubicin (PLD) for recurrent ovarian cancer (ROC) as summarized below.

YONDELIS Monotherapy

Cardiac safety with YONDELIS monotherapy at a dose and regimen of 1.5 mg/m^2 IV over 24 hours Q3W was evaluated in a pooled analysis of ten phase 2 trials and one phase 3 trial in STS and other solid tumors (N=982). Cardiovascular medical history, categorized under the vascular disorder and/or cardiac disorder system organ class, was reported in 355/982 patients (36.2%). Results from multivariate analyses of cTEAEs when controlling for potential risk factors showed that patients with cardiovascular medical history (Risk Ratio [RR] 1.90; 95% confidence interval [CI], 1.24-2.91; *P*=0.003) and those aged ≥65 years (RR 1.78; 95% CI, 1.12-2.83; *P*=0.014) had an increased risk of cTEAEs.

cTEAEs were reported in 110/982 patients (11.2%) who received ≥1 YONDELIS dose, which included tachycardia (3.1%), palpitations (1.5%), LVEF decrease (1.3%), sinus tachycardia (1.0%), and congestive cardiac failure (1.0%). Median time from first dose of study drug to onset of first occurrence of a cTEAE was 40 days. In 65% of patients with cTEAE, the event was reported as resolved, with median time to resolution of 8 days. Thirty seven patients (3.8%) treated with YONDELIS experienced a Grade 3 or 4 cTEAE. Cardiac-related serious TEAEs were reported in 36 patients (3.7%); those most frequently reported (≥5 patients) included congestive cardiac failure (0.8%), pulmonary edema (0.6%), ejection fraction decreased (0.5%), cardiac failure (0.5%), and atrial fibrillation (0.5%). Six patients (0.6%) experienced a cTEAE leading to death.[5]

YONDELIS in Combination with PLD

Cardiac safety with combination therapy of YONDELIS+PLD (N=619), at a dose and regimen of YONDELIS 1.1 mg/m^2 IV over 3 hours Q3W co-administered with PLD 30 mg/m^2 IV over 90 minutes Q3W, was evaluated in comparison to PLD monotherapy (N=612) in a pooled analysis of two phase 3 trials in ROC. Prior cardiovascular medical history, categorized under the vascular and/or cardiac disorder system organ class, was reported in 45.6% of patients in the YONDELIS+PLD group and in 51.5% of patients in the PLD monotherapy group. Results from multivariate analyses of cTEAEs when controlling for potential risk factors showed increased risk of cTEAEs with YONDELIS+PLD compared with PLD monotherapy (RR 2.70; 95% CI, 1.75-4.17; *P*<0.0001). Patients with a history of prior cardiac medication use who received YONDELIS+PLD were also at increased risk of cTEAEs compared to those who received PLD monotherapy (RR 1.88; 95% CI, 1.16-3.05; *P*=0.010). Patients with a cumulative anthracycline dose of ≥300 mg/m^2 who received YONDELIS+PLD were at increased risk for a significant decrease in LVEF compared to patients who received PLD monotherapy (RR 0.54; 95% CI, 0.30-0.99; *P*=0.046).

cTEAEs were reported in 78/619 patients (12.6%) in the YONDELIS+PLD group and in 34/612 patients (5.6%) in the PLD monotherapy group, with LVEF decrease being the most commonly reported cTEAE (7.8% vs 4.2%, respectively). Palpitation was the only cTEAE reported with at least a 2% greater incidence in the YONDELIS+PLD group compared with the PLD monotherapy group (3.2% vs 1.0%). Median time from first study dose to onset of first occurrence of a cTEAE was 57 days with YONDELIS+PLD and 98 days with PLD monotherapy. Most patients in both groups had similar resolutions of cTEAEs (57.1% and 55.9%) and time to resolution (8 days). Grade 3 or 4 cardiac-related events were reported in 14 patients (2.3%) with YONDELIS+PLD and in 4 patients (0.7%) with PLD monotherapy; however, no cTEAEs were reported with an incidence of ≥1% in either group. Cardiac-related serious TEAEs were reported in 11 patients (1.8%) with YONDELIS+PLD and in 3 patients (0.5%) with PLD monotherapy. Congestive heart failure was reported in 3 patients (0.5%) with YONDELIS+PLD and in 1 patient (0.2%) with PLD monotherapy.[5]

Catherine et al (2021)[7] conducted a retrospective pooled analysis of CAEs from thirteen phase 1-3 studies (n=1061) published between 2010 and 2020 evaluating YONDELIS monotherapy or in combination with other agents in sarcoma, ovarian cancer, and other solid tumors. CAEs were reported in 36/1061 patients (3.4%). Palpitations and tachycardia were as frequent as heart failure, with arrhythmia and/or EKG modifications occurring in 11/36 cases and heart failure in 11/36 cases. Six of the heart failure cases were reported in patients receiving YONDELIS + PLD combination therapy, compared to 1 case of heart failure in patients receiving PLD alone. QT interval prolongation was reported in 5 cases, and 1 case of myocardial infarction in a patient receiving YONDELIS as monotherapy.

Lebedinsky et al (2011)[6] conducted a retrospective pooled analysis of drug-related CAEs from phase 1-3 studies, spontaneously-reported cases, and pharmacovigilance databases to evaluate cardiac safety of YONDELIS as summarized below. LVEF was monitored in

combination phase 1 studies with doxorubicin or PLD, as well as in a phase 3 study with PLD.

Phase 3 Study in Recurrent Ovarian Cancer (ROC)

In a phase 3 study (OVA-301) in patients with ROC, a slightly higher rate of CAEs was observed with YONDELIS in combination treatment with PLD vs PLD alone, primarily due to occurrence of grade 1 palpitations (4 events) in the combination arm. Clinically significant symptomatic CAEs (grade ≥2) were similar across arms: 11/333 patients (3.3%) in the YONDELIS with PLD group vs 6/330 patients (1.8%) in the PLD alone group. No deaths due to CAEs were observed.

Decrease in LVEF was comparable between arms in the phase 3 study: 6.6% in YONDELIS plus PLD arm vs 8.8% in PLD arm. Two of 42 patients (1 in each arm) with absolute LVEF decreases discontinued the study drugs.[6]

Pool of Phase 2 Studies

Analysis of patients within 19 single-agent, phase 2 studies, in which YONDELIS was administered as either a 3-hour infusion Q3W at a starting dose of 1.3 mg/m^2, a 24-hour infusion Q3W at a starting dose of 1.5 mg/m^2, or a 3-hour weekly infusion at a starting dose of 0.58 mg/m^2, showed CAEs in 20/1132 patients (1.8%); arrhythmias or rhythm abnormalities (n=13 [1.1%]) were the most common, usually consisting of grade 1-2 tachycardia (n=6) and grade 1 palpitations (n=4); 1 event was grade 3 atrial fibrillation and occurred in a patient treated with YONDELIS 1.5 mg/m^2 infused Q3W for 24 hours (previous cardiac history, including atrial fibrillation, irregular heart rate for 5 years, and a pacemaker). One patient with advanced ovarian cancer, who was treated with 3-hour weekly infusion of YONDELIS 0.58 mg/m^2, experienced grade 3 cardiac failure and died. In these phase 2 studies, drug exposure was found to be similar among those with and without CAEs.[6]

Pool of Phase 1 Studies

In 6 single-agent, phase 1 studies evaluating YONDELIS at doses ranging from 0.006-1.9 mg/m^2, given as 1-, 3-, 24-, or 72-hour IV infusions Q3W or every 4 weeks, CAEs (grade 4 cardiac arrest with severe pancytopenia and sepsis [n=1], grade 4 atrial fibrillation [n=2], and grade 1 tachycardia [n=1]) occurred in 4/283 patients (1.4%).

In 4 phase 1, combination studies evaluating YONDELIS with doxorubicin or PLD, CAEs (grade 1 sinus tachycardia in hypertensive patient and grade 1 ventricular dysfunction) occurred in 2/155 patients (1.3%).

In an analysis of LVEF in phase 1 combination studies, 5 patients treated with YONDELIS plus doxorubicin or PLD experienced decreases in LVEF; 3 discontinued PLD, but continued YONDELIS, with further increases in LVEF at the end of treatment in 3 patients.[6]

Postmarketing Experience

During single-agent YONDELIS postmarketing experience in Europe involving 2046 patients with STS, 4 CAEs (2 cardiac arrests and 2 cardiac failures; ~0.2%) occurred in patients with preexisting conditions (eg, cardiomegaly, cardiopathy, or prior chest wall radiotherapy).[6]

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 07 June 2023.

REFERENCES

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