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Phase II Clinical Trial evaluating the activity and tolerability of Pazopanib in patients (pts) with advanced and/or metastatic liposarcoma (LPS). A joint Spanish Sarcoma Group (GEIS) and German Interdisciplinary Sarcoma Group (GISG) Study

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BACKGROUND

Liposarcomas (LPS) are soft tissue sarcoma (STS) which account for at least 20% of all STS in adults. They can be further classified into histologically and biologically different subtypes: well-differentiated LPS/de-differentiated LPS (40%), myxoid or round cell LPS (about 45%) and pleomorphic LPS (5-10%).

Few therapeutic options are currently available for patients (pts) with unresectable, locally advanced, or metastatic STS including anthracyclines, ifosfamide, trabectedine, gemcitabine, dacarbazine or docetaxel. Following the positive results of the phase III study PALETTE, Pazopanib, a multikinase inhibitor, has been added to the arsenal as second or later line treatment for advanced non-adipocytic soft-tissue sarcoma. In the previous 4-stratum phase II study, the LPS stratum was closed after the first stage because of a PFS at 12 weeks of 17% (3 out of 17 patients did not progressed after 12 weeks). After central pathologic review, 2 other patients initially classified as other STS were found to have LPS with stable disease at 12 weeks (5/19: 26% PFS12w), thus fulfilling criteria for cohort expansion. Unfortunatelly, by that time the phase II study had been completed and in the PALETTE study patients with LPS were excluded. Therefore data on the LPS cohort remain inconclusive.

This open-label, non-randomized, multicenter, two-step phase II clinical trial was designed to assess the activity of pazopanib in second or further line in patients with advanced LPS in two independent cohorts: well-differentiated/ dedifferentiated (WD/DD cohort A) and myxoid/round-cell (M/RC cohort B) LPS.

METHODS

Primary objective: progression-free survival (PFS) assessed 12 weeks after start of treatment. (According the RECIST criteria 1.1) by local and central review.
Secondary Endpoints: median PFS, Time to progression (TTP), Overall survival (OS), Objective tumor response (RR), Duration of response, Clinical benefit rate (CBR), Grown Modulation Index (GMI) and Safety profile (according CTCAE, version 4.0)

* Study design: A Simon two-stage design was applied (P1 = 40%; P0 = 20%; alpha = .1) with an estimation sample size of 37 evaluable patients for each cohort.
Patients had CT scan assessments at baseline, w6, w12 and every 8w thereafter. Local and central radiological review was performed.

* Main inclusion/exclusion criteria:Pts ≥18 years old, ECOG 0-1, with high- or intermediate-grade LPS (excluding pleomorphic) with locally advanced or metastatic measurable disease (per RECIST 1.1) were eligible. Pts had to be unsuitable or should have failed at least one line of systemic therapy but no more than 3 lines. **Central pathologic review was performed before study entry** to confirm diagnosis and assign the patient into one of the two cohorts.

* Treatment: All patients received pazopanib 800 mg once daily until tumor progression, unacceptable toxicity, death, or pt's withdrawal.

RESULTS

52 patients were enrolled at 12 centers in Spain and Germany between January 2013 and July 2015.
Cohort B was closed after 15 patients because of lack of activity, while cohort A was completed up to 37 pts. 1 patient from cohort B was excluded for the per protocol population because the patient had received less than 3 weeks of treatment.

Patient baseline characteristics
28 patients (53.8%) were male and median age was 58.3 years. Patients in cohort B were younger, with primary tumours more likely to arise in the extremities and with metastasis at study entry. They also had more frequently achieved an objective response to previous chemo than patients in cohort A.

Table 1. Baseline characteristics

	Cohort A	Cohort B	Total
Median age (years)	61.4 (38.5-88)	49.1 (25.4-73.5)	57.6 (25.4-88)
Sex (Male)	22 (59.5%)	6 (40%)	28 (53.8%)
ECOG 0 vs 1	22 (59.5%) vs 15 (40.5%)	8 (57.1%) vs 6(42.9%)	30 (58.8%) vs 21 (41.2%)
Primary tumor			
Extremities	2 (5.8%)	13 (92.8%)	15 (30.6%)
Retroperitoneum	27 (65.7%)	1 (7%)	28 (57.1%)
Time from first treatment to study entry (years)	4.4 (0.1-25.2)	5.6 (1.7-17.2)	4.7 (0.1-25.2)
Metastasis at study entry	13 (35.1%)	10 (66.7%)	23 (44.2%)
Best response to previous chemo			
CR+PR	4 (14.8%)	7 (58.3%)	11 (28.2%)
SD	12 (44.4%)	3 (25.1%)	15 (38.5%)
Cycles of previos chemo	8 (1-74)	17 (6-41)	12 (1-74)

According to local assessment and intention to treat (ITT) PFS at 12w was 43.2% for cohort A and 13.3% for cohort B and according to central asessment 32.4% for cohort A and 6.7% for cohort B.

Table 2. PFS at 6 and 12 weeks by ITT

LOCAL				
6 weeks	SD	24 (64.9%)	5 (33.3%)	29 (55.8%)
	PD	13 (3.1%)	10 (66.7%)	23 (44.2%)
12 weeks	SD	16 (43.2%)	2 (13.3%)	18 (34.6%)
	PD	21 (56.8%)	13 (86.7%)	34 (65.3%)
CENTRAL				
6 weeks	PR	3(8.1%)	1 86.7%)	4 (7.7%)
	SD	16 (43.2%)	4 (26.7%)	20 (38.5%)
	PD	18 (48.6%)	10 (66.7%)	28 (53.8%)
12 weeks	PR	2 (5.4%)	0	2 (3.8%)
	SD	10 (27%)	1 (6.7%)	11 (21.2%)
	PD	25 (67.6%)	14 (93.3%)	39 (75%)

PR Partial response SD Stable disease PD progressive disease

Median PFS was 15 weeks (3.7 months) for cohort A and 8.57 weeks (2.1 months) for cohort B according to local assessment (p 0.01), while according central assessment median PFS was 16 weeks (4 months) for cohort A and 7.71 weeks (1.9 months) for cohort B.

Median OS was 80.29 weeks (20 months) for cohort A and 71.29 weeks (17 months) for cohort B. 28 patients (53.8%) of the total population were still alive at the time of analysis. In 91% of the patients disease progression was the cause of death.

Fig.1 PFS according to local assesment and ITT. Kaplan-Meier

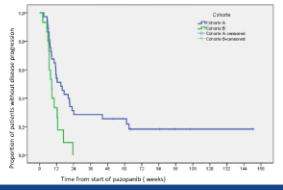
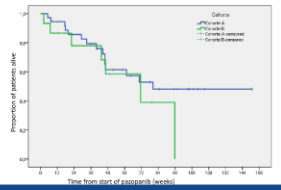


Fig 2. Overall survival (ITT). Kaplan-Meier



Growth Modulation Index (GMI)
There was enough information from 31 patients for this analysis, thus, results should be considered with caution.
The median GMI was 0.4 (0.1-3.4) for the total population, 0.6 (0.1-2.9) for cohort A and 0.2 (0.1-3.4) for cohort B (p 0.14).

Patients with GMI>1.33 had a larger non-progression rate at 12 weeks, and longer median PFS but GMI>1.33 wasn´t predictive of a longer overall survival.

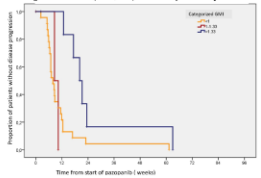
Table 3. Stratified GMI

	Cohort A	Cohort B	Total
<1	14 (70%)	9 (81.8%)	23 (74.1%)
1-1.33	2 (10%)	0	2 (6.5%)
>1.33	4 (20%)	2 (18.2%)	6 (19.4%)

Table 4. PFS at 12 weeks (local, ITT) and OS by stratified GMI

	<1	1-1.33	>1.33	
PR/SD at week 12	3 (13%)	0	5 (83.3%)	p 0.02
PD at week 12	20 (87%)	2 (100%)	1 (16.6%)	
median PFS (weeks)	7.8 (5.1-10.3)	8.57	20.14 (15.3-24.9)	p0.008
median OS (weeks)	70.4 (40.7-100)	*	46.29 (40-52.5)	p0.83

Fig 3. Median PFS (local, ITT) stratified by GMI. Kaplan-Meier.



Toxicity profile was similar to other previously reported studies. 28.8% presented at least one toxicity (all grades) and 5 (9.6%) had a grade 3 toxicity. The most commonly reported event was astenia in 12 patients (23%)

CONCLUSIONS

This study corroborates that pazopanib is well tolerated and is potentially active in the treatment of Well-differentiated/Dedifferentiated LPS as it is in other sarcoma subtypes, but not in Myxoid/Round Cell LPS.

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