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ORIGINAL ARTICLE

Nivolumab and sunitinib in patients with advanced bone sarcomas: A multicenter, single-arm, phase 2 trial

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Abstract

Background: Herein, we present the results of the phase 2 IMMUNOSARC study (NCT03277924), investigating sunitinib and nivolumab in adult patients with advanced bone sarcomas (BS).

Methods: Progressing patients with a diagnosis of BS were eligible. Treatment was comprised of sunitinib (37.5 mg/day on days 1–14, 25 mg/day afterword) plus nivolumab (3 mg/kg every 2 weeks). Primary end point was progression-free survival rate (PFSR) at 6 months based on central radiology review. Secondary end points were overall survival (OS), overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and safety.

Results: A total of 46 patients were screened, 40 patients entered the study, and 38 underwent central radiological review and were evaluable for primary end point. Median age was 47 years (range, 21–74). Histologies include 17 (43%) osteosarcoma, 14 chondrosarcoma (35%, 10 conventional, four dedifferentiated [DDCS]), eight (20%) Ewing sarcoma, and one (2%) undifferentiated pleomorphic sarcoma. The PFSR at 6 months was 42% (95% confidence interval [CI], 27–58). With a median follow-up of 39.8 months (95% CI, 37.9–41.7), the median PFS and OS were 3.8 months (95% CI, 2.7–4.8) and 11.9 months (95% CI, 5.6–18.2). ORR by RECIST was 5%, with two of 38 partial responses (one of four DDCS and one of 17 osteosarcoma), 19 of 38 (50%) stable disease, and 17 of 38 (45%) progressions. Grade ≥3 adverse events were neutropenia (six of 40, 15%), anemia (5/40, hypertension (6/40, 15%), 12.5%), ALT/AST elevation (5/40, 12.5%), and pneumonitis (1/40, 2.5%). Seventeen percent of patients discontinued treatment due to toxicity, including a treatment-related grade 5 pneumonitis

Conclusion: The trial met its primary end point in the BS cohort with >15% of patients progression-free at 6 months. However, the toxicity profile of this regimen was relevant.

KEYWORDS
anti-angiogeninic, bone, dedifferentiated chondrosarcoma, Ewing sarcoma, immunotherapy, nivolumab, osteosarcoma, PD-L1 inhibitor, sarcoma, sunitinib

INTRODUCTION

Systemic treatment for advanced bone sarcoma (BS) progressing after upfront chemotherapy is challenging, with best results still leveraging on the use of ifosfamide both for Ewing sarcoma[1] and osteosarcoma,[2,3] whereas evidence is limited in dedifferentiated chondrosarcoma (DDCS),[4] conventional chondrosarcoma[5] and other ultra-rare BS.[6]

Addressing the potential role of immunotherapy and treatment with multi-tyrosine kinase inhibitors (MTKIs) is crucial to potentially improve clinical outcomes in patients with advanced bone sarcomas.[7]

Regorafenib, a MTKI, targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), the c-kit (CD117), and the rearranged during Transfection receptors. Regorafenib was investigated in the REGOBONE and SARC024 trials,[8,9] demonstrating a median progression-free survival (PFS) of 14.8 weeks in Ewing sarcoma,[10] a median PFS of 3.6 months in osteosarcoma,[11] and a nonprogressive rate at 3 months of 54%, significantly better than results with placebo in chondrosarcoma.[12] In the CABONE trial, the use of cabozantinib, a MTKI with activity against MET receptor, also known as hepatocyte growth factor receptor (HGFR), and VEGFR, among others, was associated with a median PFS of 4.4 months in Ewing sarcoma and 6.7 months in osteosarcoma.[13] Similarly, a retrospective series with pazopanib, another MTKI, showed median PFS of 6 months for osteosarcoma,[14] and prolonged disease stabilization in DDCS.[15]

In the challenging field of advanced relapsed BS, treatments based on immune checkpoint inhibitors (ICI) monotherapy, as in SARC028 trial with pembrolizumab, failed to show significant activity without patient selection. Indeed, predictive biomarkers that may

help in identifying patients likely to benefit from immunotherapy, including ICI, are high tumor mutation burden (TMB), presence of tumor-infiltrating immune cells, including T cells, natural killer (NK) cells, and lower percentage of myeloid-derived suppressor cells (MDSCs).[16] Unfortunately, BS is usually characterized by the absence of positive predictors of immunotherapy activity. Indeed, BS on average show very low TMB: 0.79–1.96 mutations/Mbase in osteosarcoma,[11,17–19] ~0.2 mutations/Mbas in Ewing sarcoma[19,20] and <5 mutations/Mbase in chondrosarcoma with some correlation with grade.[21] Recently, an article assessing targeted DNA sequencing, showed that DDCS, as compared with conventional chondrosarcoma, had a higher TMB.[22] With respect to tumor immune infiltrate, it is well known that osteosarcoma and Ewing sarcoma have both limited CD8+/Tia1,[23–26] which are associated with better prognosis in osteosarcoma[23] and Ewing sarcoma,[27] with a possible role envisioned for macrophage-directed therapy.[28–31] Furthermore, osteosarcoma lacks programmed death-ligand 1 (PD-L1) expression on tumor cells,[23,24] with a small proportion of cases immune-hot according to a recent multi-omic study.[32] On the other hand, approximately 40% of DDCS were PD-L1–positive, exclusively in the dedifferentiated component.[33] Tumor angiogenesis is one of the proposed mechanisms of immune evasion, and there is a growing list of immune cells exhibiting the dual capacity of promoting immunosuppression and angiogenesis.[34] Sunitinib is a multi-agent tyrosine kinase inhibitor (TKI)[34,35] that targets multiple proangiogenic and angiogenesis-related receptors, such as platelet derived growth factor receptor α, KIT, stem cell factor, and vascular endothelial growth factor receptor 3. By inhibiting these receptors, sunitinib can reduce the production of growth factors that support tumor angiogenic supply and tumor growth, leading to potential antitumor effects in BS. Additionally, sunitinib can also affect tumor immunity by blocking cytokines that suppress T-cell activation and proliferation. Sunitinib immunomodulation was shown active in soft tissue sarcoma (STS),[35] and it was associated with full dendritic cell maturation in a preclinical osteosarcoma model.[28]

We therefore hypothesized that an antiangiogenic agent might act synergistically with anti–PD-1 compounds for the treatment of BS. In this phase 1/2 multicenter European study, the combination of sunitinib and nivolumab was investigated in patients with advanced STS and BS. The study aimed to assess the safety, tolerability, and potential antitumor effects of this novel therapeutic approach (IMMUNOSARC, NCT03277924).

The results of the phase 1b part, including both STS and BS cohorts, and the STS cohort of the phase 2 part of this study were already reported,[35] showing that sunitinib plus nivolumab is an active scheme with manageable toxicity in the treatment of selected patients with advanced STS, with almost half of patients free from progression at 6 months. Here, we present the results of the BS cohort of the phase 2 part of the IMMUNOSARC trial.

MATERIALS AND METHODS

Study design and subjects

In this multicenter phase 1b/2, single-arm prospective clinical trial, patients 18–80 years old with advanced BS were considered for eligibility and enrolled in eight centers in Spain and Italy belonging to the Spanish Group for Research on Sarcoma and the Italian Sarcoma Group (Figure 1). Central pathology review was mandatory before

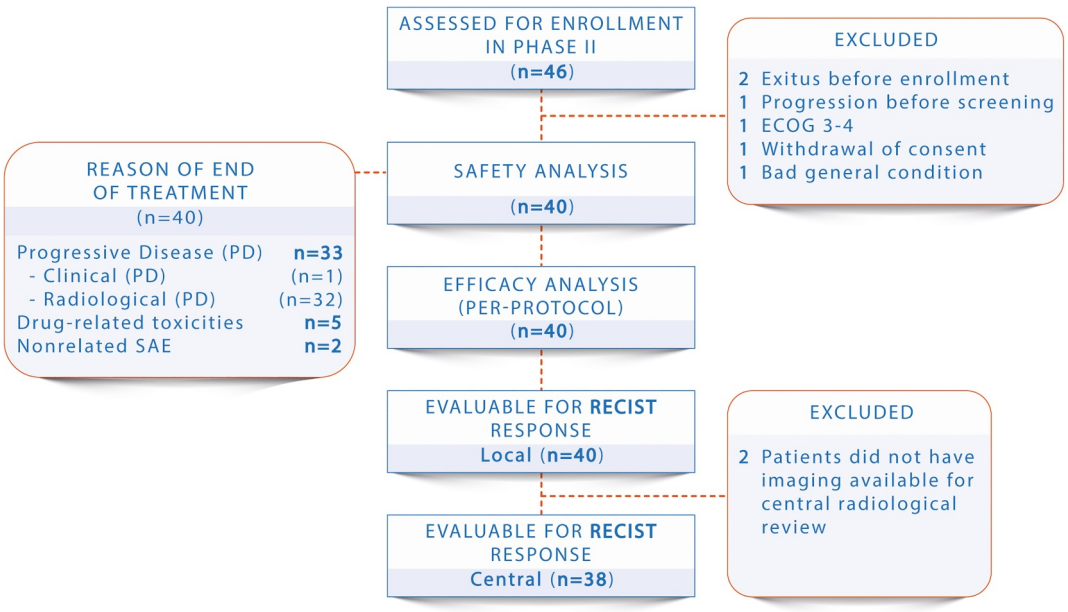

FIGURE 1 CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors.

accrual. Patients had to be progressing in the previous 6 months according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Eligible patients were divided into two cohorts: one for STS and another for BS. In the BS cohort, eligible histotypes were osteosarcoma/high-grade bone sarcoma, Ewing sarcoma, conventional chondrosarcoma, and DDCS. A maximum of three previous lines of chemotherapy for advanced disease were permitted. Other relevant inclusion criteria are described in Table S1.

Regulatory and ethics committee approvals were obtained from each country and participating institution. All patients provided written informed consent before participating in the study.

Procedures

As per de-escalation level (dose level −1) of the phase 1 part, oral sunitinib was administered at 37.5 mg on the first 14 days (induction) and from then on at 25 mg per day, continuously.

Nivolumab was given at 3 mg/kg intravenously starting from day 15 and every 2 weeks thereafter.[35] This was the recommended phase 2 dose from the phase 1 part of the study.

Local and mandatory independent central radiology review was performed. Tumor assessment was done every 8 weeks by computed tomography scan or by magnetic resonance imaging in accordance with RECIST 1.1, as described.[35]

For translational purposes, tumor biopsies were required at baseline and at week 13, and blood samples were collected at baseline, day 1 of week 3, day 1 of week 13, and at each radiological evaluation.

Outcomes

The primary end point for the phase 2 part of the study was 6-month PFSR according to RECIST 1.1 based on centralized radiologic review. The secondary end points were: PFS, overall survival (OS), overall response rate (ORR) according to RECIST 1.1, toxicity profile according to Common Terminology Criteria for Adverse Events (CTCAE) 4.0, and tissue samples (tissue and blood) collection at different time points, to contribute to translational studies.

Toxicity

In addition to toxicity grading as indicated above, the incidence of red blood cell and platelet transfusions, use of granulocyte colony stimulating factors, episodes of neutropenic fever, and episodes of neurotoxicity, hospitalizations, and treatment delays were also registered.

CTCAE grade 1–5 adverse events (AEs) were reported for all study drug-related side effects. Nonstudy drug-related serious AEs (SAEs) were also reported.

Statistical analysis

The sample size was determined for a one-arm, one-stage survival design based on the Brookmeyer and Crowley like test for the primary end point of 6-month PFSR.[36] The statistical test for survival probability was based on a nonparametric estimation of survival distribution.

IMMUNOSARC was a basket study that included both bone and soft tissue sarcomas. The statistical assumptions were based on European Organisation for Research and Treatment of Cancer data, which indicated that second-line active regimens in sarcoma patients are those able to achieve a 6-month PFSR of over 14%.[37] Furthermore, in osteosarcoma and high-grade chondrosarcoma, the most frequently encountered subtypes within this bone cohort, the most effective existing regimens show a median progression of 3–4 months, whereas the less effective regimens range from 1 to 2 months.[38] These data were used to determine our estimations for the null hypothesis (H0) and the alternative hypothesis (H1). Specifically, within this population, a 6-month PFSR of 5% was considered not promising (H0), whereas a 6-month PFSR of 15% was deemed promising (H1). With a 0.10 type I error α and a power of 0.80, 38 patients were needed in this cohort. The estimated accrual time was 24 months.

The intention-to-treat (ITT) population included patients who had provided written informed consent, with central pathology confirmation, and fulfilled all the inclusion criteria and none of the exclusion criteria. The per-protocol (PP) population (efficacy) included patients fulfilling the ITT population criteria, and additional patients who had received sunitinib in the induction phase and at least one dose of nivolumab. The safety population included all patients of the ITT population who had received at least one dose of sunitinib. The local radiologically evaluable population includes all patients of the ITT population who underwent at least one radiological assessment (Figure 1). The central radiologically evaluable population included all patients with radiological imaging available for central imaging review.

Time-to-event variables were measured from the date of enrollment and were estimated according to the Kaplan–Meier method. Comparisons between the variables of interest were performed by the log-rank test. For variables not available at baseline (i.e., RECIST), a landmark analysis was performed. False discovery rates were applied to regulate multiple comparisons. Other statistical methods are as described previously.[35]

RESULTS

From November 27, 2017 to November 23, 2018, 46 patients with advanced and progressing BS were assessed for eligibility in the phase 2 BS cohort (see CONSORT diagram, Figure 1). Six patients were excluded after screening (Figure 1). Forty patients of this cohort were eligible for the study, which defined the per-protocol safety population (Figure 1). All these patients were radiologically evaluable in the phase 2 part according to RECIST 1.1 and local review (local

radiologically evaluable population) (Figure 1). In two patients, DICOM images for central radiological revision were not available. Therefore, 38 patients were included in the central radiologically evaluable population and evaluable for the primary end point of the study (Figure 1).

Patient demographics are depicted in Table 1. The cutoff date for the final data analysis for phase 2 was March 15, 2022. At that time, all patients had discontinued treatment. Of the 40 patients who started the experimental treatment, 33 (83%) discontinued due to progression, and seven (17%) due to toxicity. The latter included treatment-related grade 3 anemia ($n = 1$), grade 3 malaise and fatigue ($n = 1$), grade 3 oral mucositis ($n = 1$), grade 3 transaminitis ($n = 1$), and grade 5 pneumonitis ($n = 1$). In two patients, reason for discontinuation was nontreatment-related toxicity: grade 3 nephrostomy infection ($n = 1$) and grade 5 pulmonary thromboembolism ($n = 1$) (Figure 1).

The median elapsed time between the previous progression and study entry was 1.15 months (range, 0.47–5.47).

TABLE 1 Demographics and clinical characteristics of 40 patients with advanced, progressing, bone sarcoma.

	No. (%)
All	40 (100)
Median age, years (range)	47 (21–74)
Sex (M/F)	27 (67)/13 (32)
Stage	
Locally advanced	4 (10)
Metastatic	36 (90)
Histology	
Osteosarcoma	17 (42)
Chondrosarcoma	10 (25)
Grade 2	6 (60)
Grade 3	4 (40)
Ewing sarcoma	8 (20)
Dedifferentiated chondrosarcoma	4 (10)
Undifferentiated pleomorphic sarcoma	1 (2)
ECOG PS baseline	
0	11 (27)
1	29 (72)
Resectable	
Yes	2 (5)
No	38 (95)
Previous lines of treatment	
1–2	29 (72)
>2	11 (27)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; M, male.

At a median follow-up of 39.8 months (95% CI, 37.9–41.7), 28 of 38 (73.7%) patients experienced progression according to central assessment, and 29 of 40 (72%) patients died. The 6-month PFSR according to centralized (primary end point) and local radiologic assessments was 42% (95% CI, 27–58) and 32% (95% CI, 18–47), respectively (Figure 2; Table 3). The median PFS for central and local assessments was 3.8 (95% CI, 2.7–4.8) and 3.7 months (95% CI, 2.7–4.7), respectively (Table 4).

The median OS was 11.9 months (95% CI, 5.6–18.2) and the proportion of patients alive at 6, 12, and 18 months was 73% (95% CI, 59–87), 47% (95% CI, 30–65), and 37% (95% CI, 20–54), respectively (Figure 3).

According to central radiologic review, there were two RECIST partial responses (PRs) among 38 centrally assessable patients representing an ORR of 5%, 19 stable disease (SD) (50%), and 17 progressive disease (PD) (45%) (Figure 4). PRs were observed in one patient with DDCS and one patient with chondroblastic osteosarcoma.

The median duration of response was 29 months (range, 8–51) for PRs and 7 months (range, 1–51 months) for SD (Figure 5). The longest response, >4 years, was observed in one of four patients with DDCS (Figure 5).

The 1-year OS was 100%, 65%, and 29% for patients with RECIST PR, SD, and PD, respectively ($p = .012$).

According to local assessment, there was one of 40 (3%) complete response (CR) in one DDCS (lasting more than 4 years) and there were three of 40 (8%) PRs (one osteosarcoma, lasting 8.4 months; another osteosarcoma lasting 5.6 months; one Ewing sarcoma lasting 1.9 months); SDs were 21 (53%), and PDs 15 (38%). The median duration of response was 7 months (2-49 months) for patients with CR or PR.

Toxicity

The most frequent all-grade treatment-related hematological toxicities (Table 2) were leukopenia (37.5%), neutropenia (37.5%), thrombocytopenia (37.5%), and anemia (35.0%), whereas the most common nonhematological adverse events were hypertension (62.5%), fatigue (62.5%), diarrhea (45.0%), and mucositis oral (45.0%). The most frequent grade 1/2 toxicities were fatigue (55.0%), hypertension (47.5%), diarrhea (45.0%), mucositis oral (40.0%), thrombocytopenia (32.5%), leukopenia (27.5%), neutropenia (22.5%), and anemia (22.5%). Grade ≥3 consisted in neutropenia (15%), hypertension (15%), anemia (12.5%), ALT increased (12.5%), AST increased (12.5%), and leukopenia (10.0%). There was one (2.5%) grade 5 pneumonitis. All other treatment-related adverse events were reversible. Notably, seven (17%) patients ended treatment due to toxicity (Figure 1).

In total, 326 sunitinib and 318 nivolumab 2-week cycles were administered in 40 patients of the PP population, with a median of 6.5[1–27,39] and 6[1–25,39] cycles of sunitinib and nivolumab per patient, respectively. The median dose intensity for sunitinib and nivolumab

TABLE 2 Drug-related toxicity in 40 patients with bone sarcoma undergoing sunitinib and nivolumab (highest grade per patient).

	Any grade, No. (%)	Grade 1–2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	Grade 5, No. (%
Hematological					
Leukopenia	15 (37.5)	11 (27.5)	4 (10.0)	0	0
Neutropenia	15 (37.5)	9 (22.5)	6 (15.0)	0	0
Thrombocytopenia	15 (37.5)	13 (32.5)	1 (2.5)	1 (2.5)	0
Anemia	14 (35.0)	9 (22.5)	5 (12.5)	0	0
Lymphocytopenia	8 (20.0)	6 (15.0)	2 (5.0)	0	0
Febrile neutropenia	1 (2.5)	1 (2.5)	0	0	0
Nonhematological					
Hypertension	25 (62.5)	19 (47.5)	6 (15.0)	0	0
Fatigue	25 (62.5)	22 (55.0)	3 (7.5)	0	0
Diarrhea	18 (45.0)	18 (45.0)	0	0	0
Mucositis oral	18 (45.0)	16 (40.0)	2 (5.0)	0	0
Nausea	15 (37.5)	15 (37.5)	0	0	0
ALT increased	10 (25.0)	5 (12.5)	3 (7.5)	2 (5.0)	0
Skin disorders	9 (22.5)	9 (22.5)	0	0	0
AST increased	7 (17.5)	2 (5.0)	3 (7.5)	2 (5.0)	0
Creatinine increased	6 (15.0)	6 (15.0)	0	0	0
Vomiting	6 (15.0)	6 (15.0)	0	0	0
PPE syndrome	5 (12.5)	4 (10.0)	1 (2.5)	0	0
Dyspepsia	5 (12.5)	5 (12.5)	0	0	0
Anorexia	4 (10.0)	4 (10.0)	0	0	0
Fever	4 (10.0)	4 (10.0)	0	0	0
GGT increased	4 (10.0)	4 (10.0)	0	0	0
Weight loss	4 (10.0)	3 (7.5)	1 (2.5)	0	0
ALP increased	3 (7.5)	3 (7.5)	0	0	0
Hair color changes	3 (7.5)	3 (7.5)	0	0	0
Hypotension	3 (7.5)	3 (7.5)	0	0	0
Dry mouth	3 (7.5)	3 (7.5)	0	0	0
Periodontal disease	3 (7.5)	3 (7.5)	0	0	0
Bronchopulmonary hemorrhage	2 (5.0)	2 (5.0)	0	0	0
Dizziness	2(5.0)	2 (5.0)	0	0	0
Dysgeusia	2 (5.0)	2 (5.0)	0	0	0
Headache	2 (5.0)	2 (5.0)	0	0	0
Hypocalcemia	2 (5.0)	2 (5.0)	0	0	0
Malaise	2 (5.0)	0	2 (5.0)	0	0
Pneumonitis	1 (2.5)	0	0	0	1 (2.5)
Body pain	1 (2.5)	1 (2.5)	0	0	0
Constipation	1 (2.5)	1 (2.5)	0	0	0
Dry eye	1 (2.5)	1 (2.5)	0	0	0
Dysphagia	1 (2.5)	0	1 (2.5)	0	0
Dysphonia	1 (2.5)	1 (2.5)	0	0	0

TABLE 2 (Continued)

	Any grade, No. (%)	Grade 1–2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	Grade 5, No. (%
Epistaxis	1 (2.5)	1 (2.5)	0	0	0
Esophagitis	1 (2.5)	1 (2.5)	0	0	0
Gastric hemorrhage	1 (2.5)	0	1 (2.5)	0	0
Hypomagnesemia	1 (2.5)	1 (2.5)	0	0	0
Hypothyroidism	1 (2.5)	1 (2.5)	0	0	0
Insomnia	1 (2.5)	1 (2.5)	0	0	0
Lung infection	1 (2.5)	1 (2.5)	0	0	0
Neuropathy	1 (2.5)	1 (2.5)	0	0	0
Face and thorax acne	1 (2.5)	1 (2.5)	0	0	0
Hypercholesterolemia	1 (2.5)	1 (2.5)	0	0	0
Hypertransaminasemia	1 (2.5)	0	1 (2.5)	0	0
Hypertriglyceridemia	1 (2.5)	1 (2.5)	0	0	0
Hyperuricemia	1 (2.5)	1 (2.5)	0	0	0
Lower extremity strengthless	1 (2.5)	1 (2.5)	0	0	0
Tinnitus	1 (2.5)	1 (2.5)	0	0	0
Trismus	1 (2.5)	1 (2.5)	0	0	0
Thromboembolic event	1 (2.5)	0	1 (2.5)	0	0
Weight gain	1 (2.5)	1 (2.5)	0	0	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysesthesia.

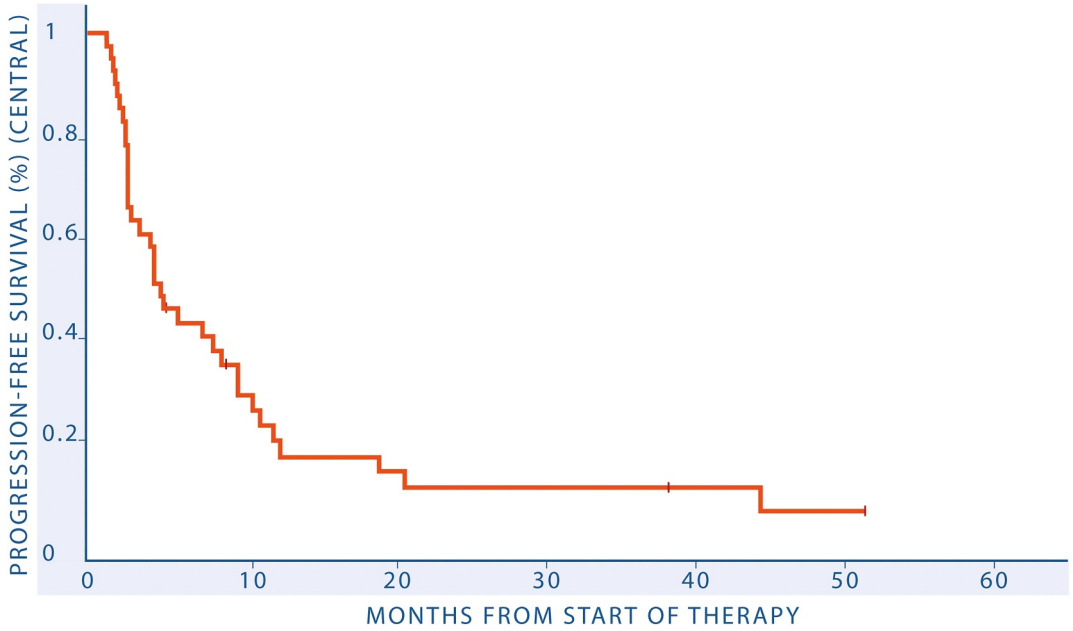

FIGURE 2 Progression-free survival in 38 patients with relapsed bone sarcomas undergoing sunitinib and nivolumab.

was 96% (71–100) and 100% (57–100), respectively. One (2.5%) patient had dose reductions and 23 (57%) had dose interruptions of sunitinib, whereas 19 (47%) patients had dose delays of nivolumab.

Univariate analysis of PFS showed no difference according to age or number of previous lines of treatment (Table 3). Objective responses and PFSR by histology are presented in Table 4.

TABLE 3 PFS and OS univariate analysis.

	No.	Median PFS (months) (95% CI)	PFS at 6 months, % (95% CI)	p	Median OS (months) (95% CI)	OS at 18 months, % (95% CI)	p
All	40	3.8 (2.7-4.8)	42		11.9 (5.6–18.2)	37 (20–54)	
Age (years)				.058			.18
0–47	21	3.5 (1.2 to 5.8)	28 (8–47)		11 (5.9–16.2)	25 (4–45)	
>47	19	8.4 (3.6 to 13.3)	58 (36–80)		29 (3–33.7)	52 (27–77)	
Sex				.69			.78
Male	27	3.7 (1.2–6.2)	37 (19–55)		11.8 (8–15.6)	47 (15–80)	
Female	13	7.1 (1.9–12.3)	54 (27–81)		15.6 (2.9–28.2)	33 (14–52)	
ECOG				.54			.69
0	11	4.3 (3.6–4.9)	36 (8 to 65)		15.7 (15.4–15.9)	44 (7–81)	
1	29	3.7 (0–8.2)	45 (26–63)		9.2 (4.5–14)	34 (15–53)	
Stage				.17			.10
Metastatic	36	3.7 (2.6–4.8)	38 (22–55)		12.8 (7.7–15.9)	31 (14–49)	
Locally A	4	10.5 (0–30)	75 (32–100)		20.8 (NA)	75 (32–100)	
Resectable				.91			.96
Yes	2	3.8 (NA)	50 (0–100)		11.8 (NA)	50 (0–100)	
No	38	3.7 (2.5–5)	42 (26–58)		11.9 (5.7–18)	37 (19–54)	
Line of Tx				.28			
1–2	29	4.4 (1.5–7.2)	45 (26–63)		11.9 (4.3–19.4)	35 (16–54)	.6
3	11	2.8 (1–4.6)	36 (8–65)		11(0–22.4)	45 (10–81)	

Abbreviations: A, advanced; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; OS, overall survival; PFS, progression-free survival; Tx, treatments.

TABLE 4 Histology and PFS.

Histology	No.	Centrally assessed median PFS (months)
All	40	
Osteosarcoma	17	3.5 (95% CI, 1.1–6)
Conventional chondrosarcoma	10	9.5 (95% CI, 0–19.3)
Ewing sarcoma	8	5.4 (95% CI, 0.4–10.5)
Dedifferentiated chondrosarcoma	4	1.8 (95% CI, NA)
Undifferentiated pleomorphic sarcoma	1	NA

Abbreviations: CI, confidence interval; NA, not applicable; PFS, progression-free survival.

DISCUSSION

This international single-arm phase 2 trial of sunitinib plus nivolumab in advanced and progressing BS, including osteosarcoma, Ewing sarcoma, conventional chondrosarcoma, and DDCS, obtained a promising 6-month PFS rate of 42% with a median PFS of 3.8 months. These results are consistent with second and further-line treatment regimens with drugs considered active in BS,[1,3,37] and the primary end point was met (i.e., >15% PFSR at 6 months).

Despite those outcomes, this was a hypothesis-generating trial, aiming to explore signals of activity of this combination that could eventually be integrated into future trials. Indeed, some patients had either durable response (i.e., a PR lasting >4-year in one of four DDCS patients and ~1 year in one of 17 osteosarcoma patients) or remained progression-free for >20 months (two of 10 conventional chondrosarcoma, one of eight Ewing sarcoma, and one of four dedifferentiated chondrosarcoma), supporting the tolerance of this combination for an extended period of time.

Limitations of this study include the different biology and growth rates of the different histologic diagnoses of enrolled patients, and the fact that a relatively low number of patients for each histotype was too small to draw solid conclusions on the efficacy in term of PFS of the combination of sunitinib plus nivolumab for a specific subtype (Table 4). Although ORR overall was low, and might not considered the better end point with immunotherapy or TKIs combination, it should be noted that dimensional responses were reported for DDCS and chondroblastic osteosarcoma, with longer median PFS and disease stabilization in conventional chondrosarcoma and Ewing sarcoma, similar to other reports.[39] In a difficult clinical context such as this, the observed tumor stabilization was important, and

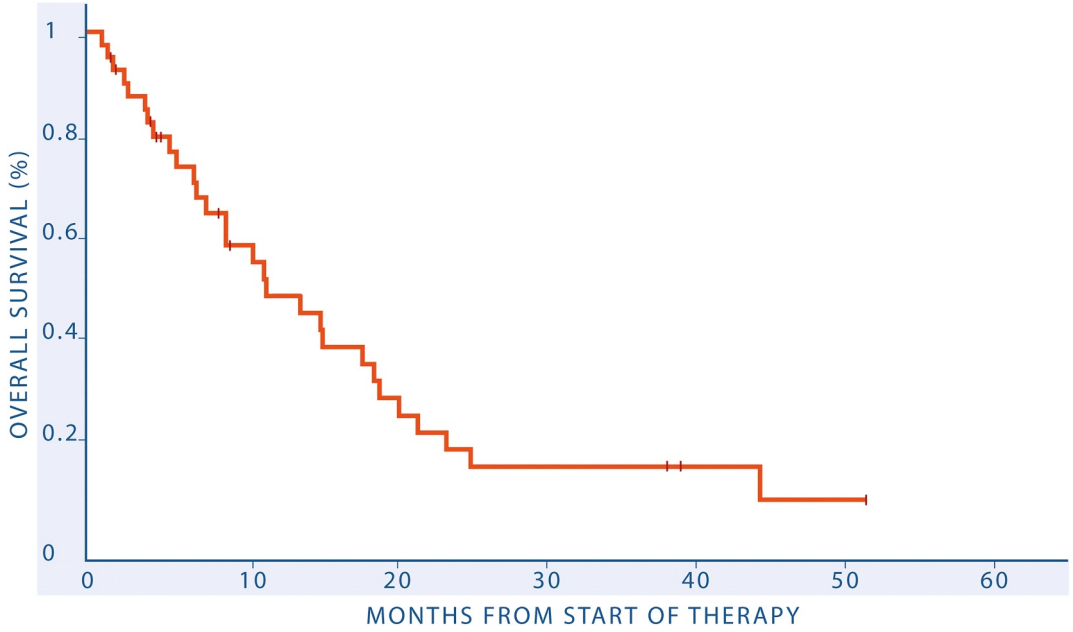

FIGURE 3 Overall survival in 40 patients with relapsed bone sarcomas undergoing sunitinib and nivolumab.

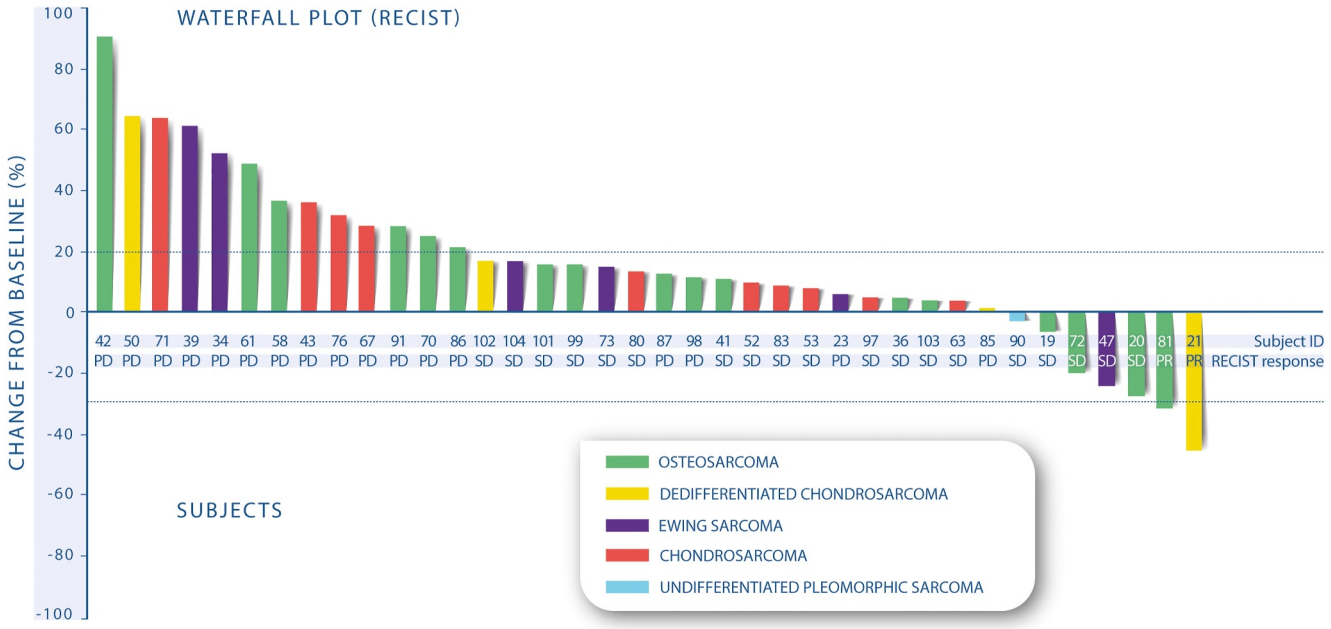

FIGURE 4 Response to treatment by patient according to RECIST 1.1. All evaluable patients (n = 40) are shown. Tumor diameter was measured in millimeters. The dashed lines represent 20% increase in diameter and 30% decrease in diameter (RECIST progression and response cutoffs, respectively). *No size variation. RECIST, Response Evaluation Criteria in Solid Tumors.

approximately 40% of the patients remained progression–free for more than 5 months, which qualifies as active treatment in the setting of high-grade sarcomas.[38–42] More complex is the interpretation of these data for the conventional chondrosarcoma patients. Although progression according to RECIST 1.1 (per inclusion criteria in the 6 months before enrollment) may not select chondrosarcoma patients with aggressive biology, it was reported that patients with unresectable and/or metastatic chondrosarcoma have poor prognoses, with a median PFS of <4 months after first-line chemotherapy.[43,44]

With regard to systemic treatments in advanced BS, in a recent review of 27 trials of systemic treatments for patients with osteosarcoma relapsed, including chemotherapy and TKI, the median PFS was 3 months (range, 1.2–19.4).[3] Similar results are reported in Ewing sarcoma, with both chemotherapy[1] and TKIs.[37] In this respect, the present combination might be regarded as a further option,

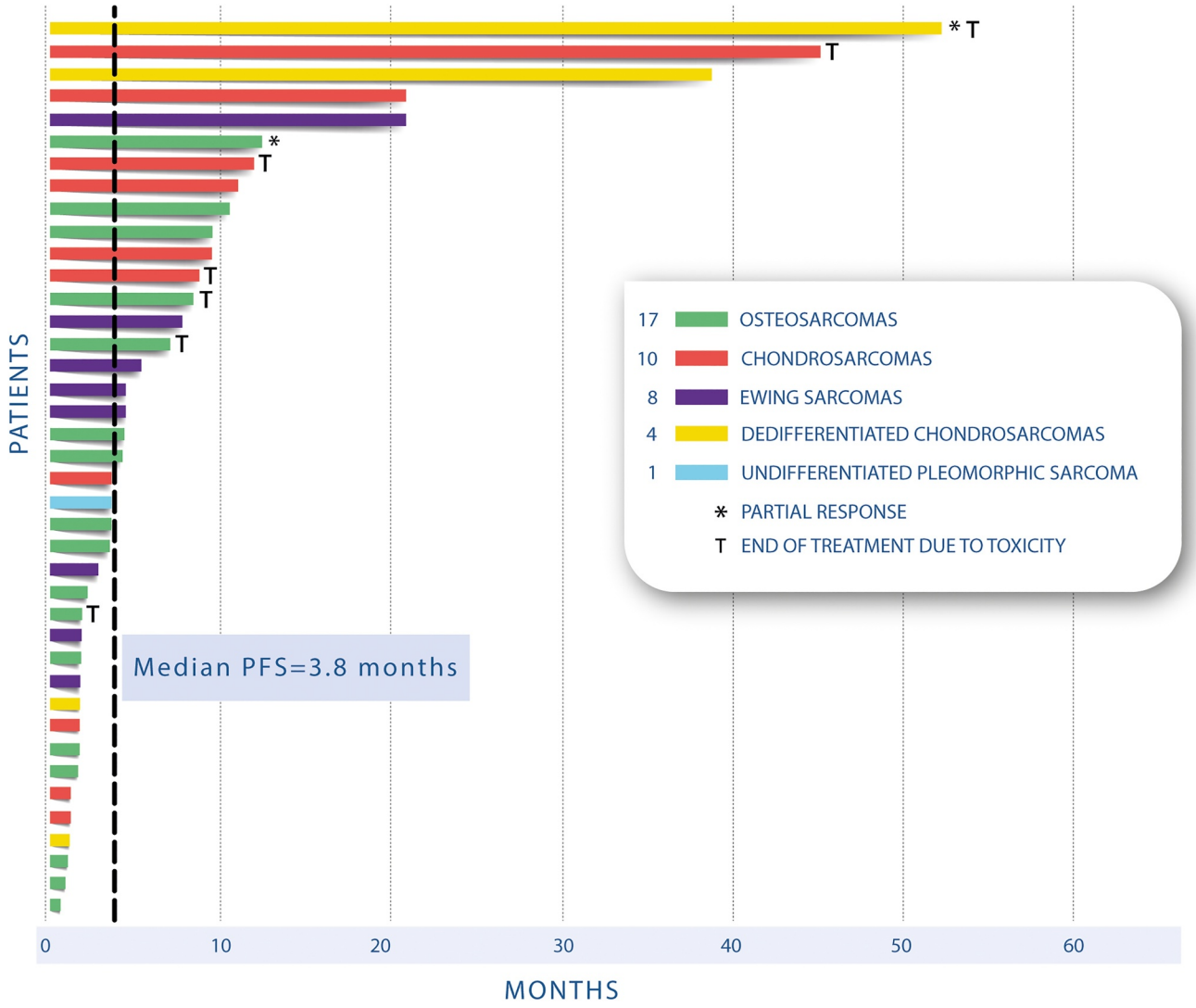

FIGURE 5 Progression-free survival rate to treatment by patient based on RECIST central radiological assessment. Each patient in the efficacy population is represented as bars (n = 40). The vertical dashed line represents the median progression-free survival. The stars represent patients achieving RECIST objective responses. The arrows represent patients nonprogressing in the last central radiological assessment. RECIST, Response Evaluation Criteria in Solid Tumors.

although discussion on economic evaluation of immunotherapy over chemotherapy is still ongoing.[45] In patients with conventional chondrosarcoma durable clinical benefit in 40.7% (11 of 27) patients, including two PRs, was observed with INBRX-109, an antibody drug targeting a specific receptor (DR5).[43] Controlled clinical trials with ivosidenib (AG-120), a selective inhibitor of mutant IDH1, are ongoing.[44]

A few clinical trials have assessed immunotherapy (ICI) in BS, including patients with osteosarcoma, Ewing sarcoma, and DDCS. Pembrolizumab has shown to have antitumor activity, regardless of PD-L1 expression in tumor biopsies, with a PR reported in a one of 22 (5%) patients with osteosarcoma.[24,39] Similarly, nivolumab has been found to be safe and well-tolerated in patients with advanced or unresectable BS,[25] but no objective response was observed in 11 and 13 patients with Ewing sarcoma and osteosarcoma, respectively.[25] On the other hand, a dimensional response (PR) was described in a patient with Ewing sarcoma with the combination of nivolumab and ipilimumab, but it only lasted 3 months.[26] The roles of PD-1 and PD-L1 inhibitors in conventional chondrosarcoma, and DDCS in particular, are less understood than in other sarcoma types, even though there are anecdotal responses to immune agents in conventional chodrosarcoma[46] and in one of five patients with DDCS (20%).[39]

In our study, sunitinib was used in monotherapy for 2 weeks and as an immunomodulator at a dose lower than the approved, in combination with nivolumab. The treatment of sarcoma cells with sunitinib can indeed exert significant changes on immune cell subsets toward immune activation, leading to dendritic cell (DC)-based cross-priming of IFN-γ–producing effector T cells and reduced regulatory T-cell induction.[28] This rationale apparently did not translate into a greater antitumor effect of the combination of sunitinib and nivolumab in terms of tumor shrinkage. How combination approach compares to current options and monotherapy can only be addressed in

controlled prospective trials. However, although sunitinib is approved for treating gastrointestinal stromal tumors, there are no controlled trials to date assessing sunitinib as monotherapy in BS, and it has been explored off-label for other types of BS, including osteosarcoma, showing some activity based on retrospective analyses.[47] Therefore, one might argue that, at least with present data for osteosarcoma and Ewing sarcoma patients,[8–15,48] regorafenib and cabozantinib might be better combined with ICI, as shown for kidney cancer.[49]

Approximately half of the patients experienced grade 1–2 hypertension, whereas grade 3–4 hypertension was reported in 15% of the patients. Grade 3–4 hematological toxicity was also reported (neutropenia, 15%; anemia, 12.5%). Notably, one (2.5%) grade 5 pneumonitis (toxic death) was reported, and 17% of the patients discontinued their treatment due to side effects.

Side effects observed with sunitinib plus nivolumab were consistent with those reported for most of immunotherapy and TKI combinations.[50] In this regard, one of the limitations of this study is the lack of patient-reported outcome (PROs) data. PROs and quality of life should be integrated in future trial design.

Improving patient selection when investigating the activity of immunotherapy in BS beyond histology is surely crucial, before embarking in new prospective studies. In this respect, identification of sarcomas with tumor-infiltrating T cell, M2-polarized macrophage, DC, and NK subpopulations, might help to select BS patients most likely responsive to immunotherapy. An increased number of tumor-infiltrating T cells and PD-L1 expression in metastases as compared with primary tumors was shown in osteosarcoma,[50] suggesting accessibility for T cells; this finding might imply that osteosarcoma patients with metastatic disease could benefit from T-cell–based immunotherapy.[51] Other combinations such as nivolumab with CTLA-4 inhibitors, such as ipilimumab, displayed a higher activity than nivolumab monotherapy in selected STS subtypes, such as undifferentiated pleomorphic sarcoma,[52] and might have a potential role for osteosarcoma as well.[53,54] Results of doxorubicin and pembrolizumab trials in chemo-naive sarcoma patients were recently published.[55] This trial included three cases with conventional chondrosarcoma, with no dimensional responses observed. Clinical trials combining immunotherapy and chemotherapy, methotrexate, doxorubicin, and cisplatin, in chemo-naive osteosarcoma patients are ongoing (NCT03277924, NCT04351308) and will verify the hypothesis that standard chemotherapy can be combined with ICI as part of up-front therapy at diagnosis. DC-targeted drugs, including toll-like receptor (TLR)-3 inhibitors might improve the therapeutic armamentarium of osteosarcoma. Results of intratumoral injection of the TLR-4 agonist glycopyranosyl lipid A in stable-emulsion formulation have been reported, showing promising activity in the setting of STS in combination with radiotherapy.[56]

Overall, further research is needed to better understand the potential benefits of immunotherapy in BS and identify biomarkers of response to these treatments. Based on this phase 1/2 trial finding, a correlative study with the NanoString PanCancer immune profiling panel in pre- and posttreatment biopsies is ongoing. An international expansion phase 2 trial in patients with selected sarcoma histotypes, DDCS among BS, is currently enrolling (NCT03277924).

In conclusion, the present study met its primary end point, showing an interesting, durable, disease control with sunitinib plus nivolumab in some patients with progressive, advanced BS, and promising anecdotal results in the orphan setting of DDCS. A translational study is ongoing to seek predictive markers in patients included in this trial.

AUTHOR CONTRIBUTIONS

Emanuela Palmerini: Data curation, investigation, writing–original draft, validation, supervision, and funding acquisition. **Antonio Lopez Pousa**: Investigation, validation, and writing–review and editing. **Giovanni Grignani**: Validation and writing–review and editing. **Andres Redondo**: Investigation, validation, and writing–review and editing. **Nadia Hindi**: Investigation, validation, writing–original draft, and writing–review and editing. **Salvatore Provenzano**: Investigation, validation, and writing–review and editing. **Ana Sebio**: Investigation, validation, and writing–review and editing. **Jose Antonio Lopez Martin**: Conceptualization, investigation, validation, and writing–review and editing. **Claudia Valverde**: Investigation, validation, and writing–review and editing. **Javier Martinez Trufero**: Investigation and writing–review and editing. **Antonio Gutierrez**: Investigation, validation, data curation, formal analysis, writing–review and editing, software, and project administration. **Enrique de Alava**: Investigation, validation, and writing–review and editing. **Maria Pilar Aparisi Gomez**: Investigation, validation, methodology, and writing–review and editing. **Lorenzo D'Ambrosio**: Investigation, validation, and writing–review and editing. **Paola Collini**: Investigation, validation, and writing–review and editing. **Alberto Bazzocchi**: Investigation, formal analysis, and writing–review and editing. **David S. Moura**: Investigation, validation, and writing–review and editing. **Toni Ibrahim**: Investigation, validation, and writing–review and editing. **Silvia Stacchiotti**: Investigation, validation, and writing–review and editing. **Javier Martin Broto**: Conceptualization, funding acquisition, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Emanuela Palmerini has served on advisory boards for Daiichi Sankyo, Deciphera Pharmaceuticals, Eusa Pharma, and SynOx Therapeutics. Giovanni Grignani reports grants and personal fees from PharmaMar, grants from Novartis, and personal consulting fees from Lilly, Pfizer, Bayer, and Eisai. Andres Redondo reports grants and personal fees from PharmaMar; personal fees from Lilly, Novartis, Amgen, AstraZeneca, and Tesaro; grants and personal fees from Roche; and grants from Eisai. Nadia Hindi reports grants, personal fees, and nonfinancial support from PharmaMar; personal fees from Lilly; grants from Eisai and Novartis; and research funding for clinical studies (institutional) from PharmaMar, Eli Lilly, AROG, Bayer, Eisai, Lixte, Karyopharm, Deciphera, GlaxoSmithKline, Novartis, Blueprint, Nektar, Forma, Amgen, and Daiichi Sankyo. Salvatore Provenzano reports personal fees for consultancy from Italfarmaco and Boehringer Ingelheim; and the spouse employed in AstraZeneca. Silvia Stacchiotti reports personal financial interests including honoraria, consultancy, or advisory role from Agentus, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Deciphera, Ikena, Gentili, GlaxoSmithKline, Ipsen, Nec Oncolimmunity, Novartis, Pharmamar, Pharma Essentia, Regeneron Springworks, and Servier; and institutional financial interests from Abbisko, Adaptimmune, Advenchen, Bayer, Blueprint, Boehringer Ingelheim, Daiichi Sankyo, Deciphera, EISAI, Epizyme, Foghorn, Hutchinson, Inhbrix, Karyopharm, Novartis, Pharmamar, RainThera, and Springworks. Jose Antonio Lopez Martin reports honoraria for advisory board participation and travel support from PharmaMar, Eli Lilly, Bayer, Eisai, Novartis, Bristol-Myers Squibb, MSD, Roche, Celgene, Pierre Fabre, Pfizer, GlaxoSmithKline, Daiichi Sankyo, Amgen, and Chobani. Javier Martinez Trufero reports honoraria for advisory board participation and travel support from PharmaMar, Eli Lilly, Eisai, Merck Sharp & Dohm, Merck, GlaxoSmithKline, and Roche. Lorenzo D'Ambrosio reports advisory board participation for Boehringer Ingelheim, AstraZeneca, PSI CRO Italy, and GlaxoSmithKline; and travel support from PharmaMar, GlaxoSmithKline, and AstraZeneca. Enrique de Alava reports personal fees and nonfinancial support from Roche, Bristol-Myers Squibb, and PharmaMar; and personal fees from Bayer. David S. Moura reports institutional research grants from PharmaMar, Eisai, Immix BioPharma, and Novartis outside the submitted work; travel support from PharmaMar, Eisai, Celgene, Bayer, and Pfizer, and personal fees from Tecnopharma. Javier Martin Broto reports research grants from PharmaMar, Eisai, Immix BioPharma, and Novartis; honoraria for advisory board participation and expert testimony from PharmaMar, Eli Lilly, Bayer, and Eisai; and research funding for clinical studies (institutional) from PharmaMar, Eli Lilly, AROG, Bayer, Eisai, Lixte, Karyopharm, Deciphera, GlaxoSmithKline, Novartis, Blueprint, Nektar, Forma, Amgen, and Daiichi Sankyo. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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