original reports

Nivolumab Plus Ipilimumab for Treatment-Naïv Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402)

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abstract

PURPOSE This study aimed to assess the efficacy of the combination of nivolumab (nivo) plus ipilimumab (ipi) as a first-line therapy with respect to the 12-month overall survival (OS) in patients with metastatic uveal melanoma (MUM) who are not eligible for liver resection.

METHODS This was a single-arm, phase II trial led by the Spanish Multidisciplinary Melanoma Group (GEM) on nivo plus ipi for systemic treatment-naïve patients of age > 18 years, with histologically confirmed MUM, Eastern Cooperative Oncology Group-PS 0/1, and confirmed progressive metastatic disease (M1). Nivo (1 mg/kg once every 3 weeks) and ipi (3 mg/kg once every 3 weeks) were administered during four inductions, followed by nivo (3 mg/kg once every 2 weeks) until progressive disease, toxicity, or withdrawal. The primary end point was 12-month OS. OS, progression-free survival (PFS), and overall response rate were evaluated every 6 weeks using RECIST (v1.1). Safety was also evaluated. Logistic regression and Cox proportional hazard models comprising relevant clinical factors were used to evaluate the potential association with response to treatment and survival. Cytokines were quantified in serum samples for their putative role in immune modulation/angiogenesis and/or earlier evidence of involvement in immunotherapy.

RESULTS A total of 52 patients with a median age of 59 years (range, 26-84 years) were enrolled. Overall, 78.8%, 56%, and 32% of patients had liver M1, extra-liver M1, and elevated lactate dehydrogenase. Stable disease was the most common outcome (51.9%). The primary end point was 12-month OS, which was 51.9% (95% CI, 38.3 to 65.5). The median OS and PFS were 12.7 months and 3.0 months, respectively. PFS was influenced by higher LDH values.

CONCLUSIONS Nivo plus ipi in the first-line setting for MUM showed a modest improvement in OS over historical benchmarks of chemotherapy, with a manageable toxicity profile.

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ASSOCIATED CONTENT

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Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults and remains to have poor prognosis with a 5 year overall survival (OS) rate of < 50%. This elevated mortality rate is caused by a high incidence of metastases[1] and lack of effective therapies.[2,3]

UM has a high tendency to metastasize to the liver.[4,5] When liver metastases develop, survival is reduced to < 6 months without treatment.[6] Chemotherapy and targeted therapies such as selumetinib have yielded poor results.[7,8] For instance, the PUMMA study, an international effort to determine benchmarks of progression-free survival (PFS) and OS, has pooled data from 29 trials published from 2000 to 2016, including a total of 912 patients. For medical treatments, the median OS was 9.3 months.[3] Patients with metastatic UM (MUM) have been systematically excluded from clinical trials with checkpoint inhibitors, and the results reported in retrospective series have not been encouraging.[9]

Immunobiological differences between UM and cutaneous melanoma (CM) might explain the differences in the treatment response to checkpoint inhibitors. First, the anatomy and the expression of soluble factors in the eye restrict the induction and expression of local immune responses.[10] Second, UM expresses lower levels of *CD8A* and programmed death ligand 1 (PD-L1) than most tumors included in the The Cancer Genome Atlas, both factors associated with the response to anti-PD1 drugs.[11] Third, T-lymphocytes in

CONTEXT

Key Objective

Assess the efficacy of the combination of nivolumab (nivo)/ipilimumab (ipi) as a first-line therapy in metastatic uveal melanoma (MUM).

Knowledge Generated

Among the 52 enrolled patients, the most common response was stable disease (51.9%) that was maintained for a median of 3.8 months. The overall disease control rate was 63.5 (95% CI, 50.4 to 76.5). We observed a median overall survival (OS) of 12.7 months (95% CI, 7.1 to 18.3) and a median progression-free survival of 3 months (95% CI, 2 to 4.1).

Relevance

Nivo/ipi showed promising OS results with a manageable toxicity profile that positions nivo/ipi as a promising first-line therapy for MUM.

liver MUM do not express PD-L1, showing the lack of adaptive immune resistance in MUM. Fourth, the tumor mutation burden, surrogate for tumor neoantigens, is extremely low in UM.[12]

Nivolumab (nivo) is a human immunoglobulin G4 anti-PD1 monoclonal antibody that acts through inhibition of adaptive immune resistance by blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2. It has already been approved for the treatment of various subtypes of malignancies, including CM. Ipilimumab (ipi) is a human IgG1 monoclonal antibody that binds to cytotoxic T-cell lymphocyte-4, inhibiting negative signals that downregulate T-cell activation and triggering their proliferation and infiltration in tumor tissues. Previous studies using single checkpoint inhibitors reported low efficacy in patients with MUM, but the combination of nivo and ipi was shown to be highly effective in metastatic CM, especially in tumors with low PD-L1 expression. Accordingly, this GEM-1402 trial, conducted by the Spanish Multidisciplinary Melanoma Group (GEM), aimed to assess the efficacy of nivo/ipi as a first-line therapy with respect to the 12-month OS in patients with MUM who are not eligible for liver resection.

METHODS

Patients and Study Design

This was a multicenter, open-label, single-arm, phase II study conducted between April 2016 and June 2017 at 10 centers in Spain. The database was locked in July 2019. This study was registered in the European Union Clinical Trials Register (EudraCT 2015-004429-15) and at ClinicalTrials.gov (identifier: NCT02626962). The study Protocol (online only) and any subsequent amendments were approved by the relevant institutional review boards or independent ethics committee at each institution, and the study was conducted in compliance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent.

Selection and Description of Patients

Patients with systemic treatment-naïve, histologically confirmed MUM were selected for the study. The inclusion criteria were age > 18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and progressive metastatic disease confirmed via cross-sectional imaging, defined as newly diagnosed metastatic disease or progression from previously diagnosed metastases. The exclusion criteria were prior systemic treatment for MUM including hepatic embolization or perfusion, concurrent autoimmune disease or a history of chronic or recurrent autoimmune disease, active malignancies within the previous 3 years, prior treatment with checkpoint inhibitors, and active brain metastases; see the Protocol.

Treatment Protocol

Each patient received intravenous (iv) nivo 1 mg/kg, administered over 60 minutes, in combination with iv ipi 3 mg/kg, administered over 90 minutes and every 3 weeks (once every 3 weeks) at four doses (cycles 1 and 2, each cycle = 6 weeks). Subsequently, patients received nivo iv 3 mg/kg over 60 minutes once every 2 weeks (cycle 3 and beyond, each cycle = 6 weeks). Treatment was continued until clinical or objective progression of disease (PD), unacceptable toxicity, or patient withdrawal. Treatment beyond initial PD was allowed at the investigator's criteria, given the cumulative evidence of clinical benefit following an initial progression (pseudoprogression/pseudoPD).[13] Therapies prohibited during the study period included immunosuppressants, corticoids at doses exceeding 10 mg/day of prednisone or equivalent, antitumor therapies, concurrent radiotherapy, and surgeries for malignant tumors (Protocol).

The tumor response was evaluated according to RECIST (v1.1) using computed tomography or magnetic resonance imaging once every 6 weeks for the first year and then once every 12 weeks thereafter until PD or treatment discontinuation, whichever occurred later.

Outcomes

The primary end point was the 12-month OS, defined as the time from the first dose to death from any cause in the intention-to-treat (ITT) population (n = 52). The secondary end points were investigator-assessed response rate and safety. The objective response rate evaluated according to RECIST 1.1 criteria was defined as the proportion of patients whose best overall response was complete response (CR) or partial response (PR). PFS was defined as the time from the first nivo dose to PD or death from any cause. Disease control rate was calculated as the percentage of patients whose best overall response was CR, PR, or stable disease (SD). SD was considered if maintained at least 6 weeks.

Adverse events (AEs) and treatment-related AEs (TRAEs) were monitored throughout the study period and graded according to the NCI Common Terminology Criteria for Adverse Events, v4·0. Liver toxicity was considered an AE of special interest, and an interim safety analysis was performed after 19 patients completed cycle 2.[14,15]

Cytokine Analysis

Cytokines were quantified in serum samples using a Luminex xMAP assay (Merck), incorporated into the MILLIPLEX MAP kits and run on Luminex 200, according to the manufacturer's instructions. The following cytokines were quantified: interferon-gamma (INFg), interleukin-10 (IL10), interleukin-12, p70 (IL12p70), interleukin-1beta (IL1b), interleukin-4 (IL4), interleukin-6 (IL6), interleukin-8 (IL8), tumor necrosis factor-alpha, vascular endothelial growth factor-A (VEGF-A), and transforming growth factor-beta. These biomarkers were chosen for their putative role in immune modulation/angiogenesis and/or earlier evidence of involvement in immunotherapy. Data were given in pg/mL.

Molecular Analysis

Genomic DNA was isolated from fresh tumor tissues and reference samples using the QIAamp DNA Mini Tissue Kit (Qiagen, Hilden, Germany). For Multiplex Ligation-dependent Probe Amplification (MLPA), a MLPA was carried out with 100 ng of DNA from tumor DNA and reference samples using the SALSA MLPA Probemix P027 UM kit (MRC Holland, Amsterdam, the Netherlands).

MLPA was performed using a 3130xl Genetic Analyzer (Applied Biosystems), and raw data were analyzed using Coffalyser.Net software (MRC Holland) to detect deletions and duplications in chromosomes 3 and 8.

Pyrosequencing assay was performed to detect mutations in codon 209 (exon 5) of the *GNAQ* and *GNA11* genes and in codon 625 (exon 14) of the *SF3B1* gene. DNA was amplified by polymerase chain reaction as previously described[16,17] (see Appendix 1, Molecular Analysis, online only).

Statistical Analysis

The sample size was determined using the SWOG One Arm Survival tool[18] and a Brookmeyer-Crowley type test.[19] To formulate the null hypothesis, we used data from 81 patients treated with first-line chemotherapy in three studies from the PUMMA meta-analysis.[20-22] The baseline characteristics of these pools of patients are summarized in Appendix Table A1 (online only). Assuming a null hypothesis of 1-year OS rate of 27% and an alternative hypothesis of 50% with a two-sided type I error of 5%, a power of 80%, and a 10% attrition rate, it was necessary to enroll 52 patients.

All statistical analyses complied with the CONSORT statement[23] and were performed with SPSS Statistics for Windows (v22 0, IBM Corp, Armonk, NY). Efficacy statistical analysis was performed per ITT. The OS and PFS were calculated using the Kaplan-Meier method with CIs at 95% (95% CI). A logistic regression model and a Cox proportional hazard model comprising relevant clinical factors were used to evaluate the potential association with the response to treatment and survival variables. Subjects without PFS events were censored at the date of last clinical evaluation, and those alive had OS censored at the date of the last reported contact. Variables with $P < .1$ in the univariate analysis were included in the model. Exclusive liver metastases versus liver and other location metastases were compared in the analysis of treatment response (Fisher's exact test) and OS and PFS (both with log-rank test). Safety analysis was performed in all patients who have received at least one dose of the study treatment.

RESULTS

Baseline Patient Characteristics

Overall, 61 patients were identified from nine hospitals between April 2016 and June 2017 of which 52 patients with a median age of 59.1 years (range, 26.1 to 84.3 years) were finally enrolled in this study (Fig 1). 55.8% were men. In total, 50 of the 52 patients underwent prior local therapy before study enrollment, including an enucleation procedure (n = 30), brachytherapy (n = 26), external radiotherapy (n = 4), or conservative surgery (n = 3).

The baseline ECOG performance status score was 0 and 1 in 84.6% and 15.4% of the patients, respectively. In total, 16 of 43 patients (37.2%) with known values had high levels of lactate dehydrogenase (LDH), with 7 (16.3%) having an LDH $\geq 2.5 \times$ Upper limit of normality (ULN). Alkaline phosphatase was normal in 76.9%. Up to 78.8% of patients presented with liver disease at baseline. The median number of liver metastases was 2 (range, 1-25), and the median size of the biggest liver metastases was 25 mm (range, 10-90 mm). 57.7% of the patients presented with extrahepatic disease. The baseline patient characteristics are detailed in Table 1.

Treatment Completion

At the data collection cutoff (July 9, 2019), the median follow-up was 13.4 months (range, 0.8-35.2 months).

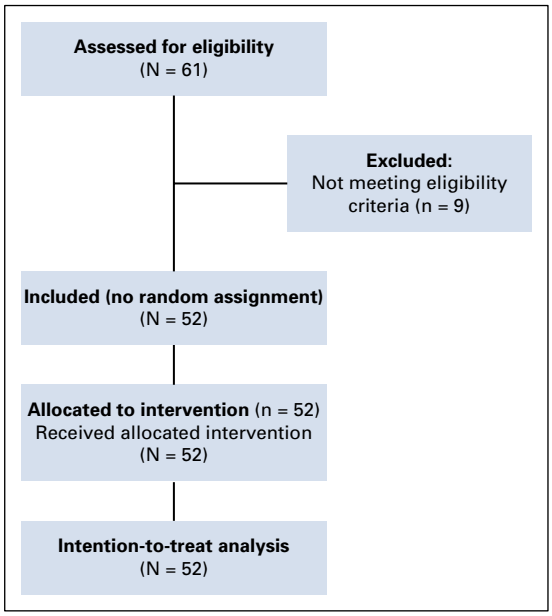

FIG 1. Patient inclusion flowchart.

There were four patients (7.7%) who were still on treatment. Patient discontinuation reasons included radiologically confirmed PD in 31 patients (59.6%); unequivocal clinical progression attributable to PD, two patients (3.8%); clinically unacceptable toxicity, 12 patients (23.1%); continuation of treatment judged as inappropriate by the principal investigator, two patients (3.8%); and patient's decision, one patient (1.9%) (some patients had more than one reason for discontinuation). Thirty-three patients completed the first two cycles of treatment with nivo/ipi, whereas 33 and 6 patients had treatment delays and omission of at least one dose, respectively.

Efficacy

In total, 6/52 (11.5%; 95% CI, 2.9 to 20.2) patients had an objective response (1 CR and 5 PRs) (Fig 2A-B). All responses appeared within the first 9 months after the start of treatment (median, range, 3.7, 2.91-10 months) and were maintained for a median of 15.6 months (95% CI, 1.6 to 33.8 months) (Fig 2A). Throughout the study period, SD was the most common outcome (51.9%; 95% CI, 38.3 to 65.5) (Fig 2A) and was maintained for a median of 3.8 months (95% CI, 0.1 to 21.5). We identified 10 patients with *pseudoPD* through the study (Appendix Fig A1, online only). Overall, the disease control rate was 63.5% (95% CI, 50.4 to 76.5), and most of the patients with PD (80.8%; 95% CI, 70.1 to 91.5) showed radiologically significant growth of their target lesions (Fig 2B-D). Logistic regression models for univariate analysis of treatment response and clinically significant variables did not show conclusive results, and thus, multivariate analysis was not feasible.

At the time of database lock, 38 patients died (32 because of PD, two who reported TRAEs described later, and four because of other causes). The median OS was 12.7 (95% CI, 7.1 to 18.3) months (Fig 3A), with 12- and 24-month OS rates of 51.9% (95% CI, 38.3 to 65.5) and 26.4% (14.2 to 38.6), respectively. Interestingly, OS in patients with exclusive liver metastasis (Fig 3B) was shorter than that in patients with metastasis in other locations beyond the liver (9.2 months *v* 23.5 months) and in those with both liver and other metastasis (15.5 months), but the difference was not significant ($P = .146$). The median PFS was 3.0 (95% CI, 2.0 to 4.1) months; 28.8% (95% CI, 16.5 to 41.1) and 19.2% (95% CI, 8.5 to 29.9) of patients were PD-free at 6 and 12 months, respectively (Fig 3C). The influencing factors of PFS (Table 2) included an LDH increased by at least 2.5 × ULN (HR: 6.1 [1.4 to 25.7]; $P < .015$).

Cytokine and Molecular Analysis

Analysis including specific cytokines suggested a possible association with OS at univariate level, including IL1b ($P = .022$), IL2 ($P = .083$), IL6 ($P = .027$), IL8 ($P = .05$), and VEGF-A ($P = .023$), but were not conclusive when all factors were assessed together (Table 2). Median values for IFNg and IL12p70 were also considered for categorization of patients, with similar results when multivariate approach was performed ($P = .116$ and $P = .325$, respectively).

Of 41 baseline tumor samples obtained from metastatic sites of disease, we were able to perform analysis of codon 209 of the *GNAQ* and *GNA11* genes and codon 625 of the *SF3B1* and MLPA analysis to detect deletions and duplications in chromosomes 3 and 8 in 25 patients (50% of total patients included). There were no significant differences for *GNAQ*, *GNA11*, and *SF3B1* mutations nor for chromosomal alterations regarding overall response rate (ORR), OS, or PFS (Fig 2C and Table 2).

Safety

All patients developed AEs (Appendix Table A2, online only), and TRAEs occurred in 49/52 patients (Table 3), with skin-related events being the most frequent (61.5%), followed by fatigue (57.7%) and liver-related events (36.5%). Treatment-related diarrhea occurred in 28.8% of patients. In total, 11 of the 19 patients with liver-related events also developed treatment-related diarrhea. Grade ≥ 3 TRAEs were reported in 30 patients (57.7%) (Table 3). Among 56 serious adverse events (SAEs), 30 were treatment-related and 23 resolved or improved according to the follow-up reports (Table 3 and Appendix Table A3, online only). The most frequent treatment-related SAEs (TRSAEs) included fever (four events), liver-related events (three events), and diarrhea (three events) (Table 3). Treatment-related deaths included one patient with thyroiditis and one with Guillain-Barré syndrome (Table 3). Other thyroid-associated TRSAEs included one more patient with thyroiditis (recovered) and two with impaired thyroid function.

TABLE 1. Demographics and Baseline Characteristics (N = 52)

Characteristic	n (%[a])
Sex	
Male	29 (55.8)
Female	23 (44.2)
ECOG PS	
0	44 (84.6)
1	8 (15.4)
Extraocular disease	
Metastatic disease at the time of UM diagnosis	4 (7.7)
At the time of UM recurrence (study baseline)	
Liver disease	41 (78.8)
Unilobular	10 (19.2)
Multilobular	28 (53.8)
Size of the biggest liver metastasis	
≤ 3 cm	23 (63.9)
> 3 cm and ≤ 8 cm	11 (30.6)
> 8 cm	2 (5.6)
Extrahepatic disease[b]	30 (57.7)
Lungs	22 (42.3)
Bone	9 (17.3)
Nodal	5 (9.6)
Brain (not active)	2 (3.8)
Others[c]	10 (19.2)
Prior local therapies	
Enucleation	30 (57.7)
Brachytherapy	26 (50.0)
External radiotherapy	4 (7.7)
Conservative surgery	3 (5.8)
Any	2 (4)
LDH: Median (range): 348.0 (155-6,200) IU/L	
Normal	27 (51.9)
Increased < 2.5 × ULN	9 (17.3)
Increased ≥ 2.5 × ULN	7 (13.5)
Not available	9 (17.3)
GGT: Median (range): 32.0 (12.0 to 803.0) IU/L	
Normal	34 (65.4)
Increased < 2.5 × ULN	8 (15.4)
Increased ≥ 2.5 × ULN	6 (11.5)
Not available	4 (7.7)
Alkaline phosphatase: Median (range): 78 (43.2 to 826.0) IU/L	
Normal	40 (76.9)
Increased (> ULN)	7 (13.5)
Not available	5 (9.6)
Genetic alterations #	
GNAQ	
WT	18 (72)
Mutant	7 (28)
GNA11	
WT	11 (44)
Mutant	14 (56)
SF3B1	
WT	22 (88)
Mutant	3 (12)
3p	
WT	7 (28)
Deletion	18 (72)
8q	
WT	6 (24)
Amplification	19 (76)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ULN, upper limit of normal; UM, uveal melanoma; WT, wild type.

[a]% overall sample (N = 52).

[b]Not exclusive.

[c]Other locations include lumbar (n = 2), perihepatic (n = 2), peritoneum (n = 2), skin (n = 1), pleura (n = 1), kidney (n = 1), and adrenal (n = 1); percentages of genetic alterations calculated over the number of evaluable patients in the molecular study (n = 25).

DISCUSSION

MUMs remain to have poor prognosis as no effective therapy has been established.[24] Immunotherapy has changed the paradigm of treatment for CM. However, the survival rates for UM have remained unchanged for

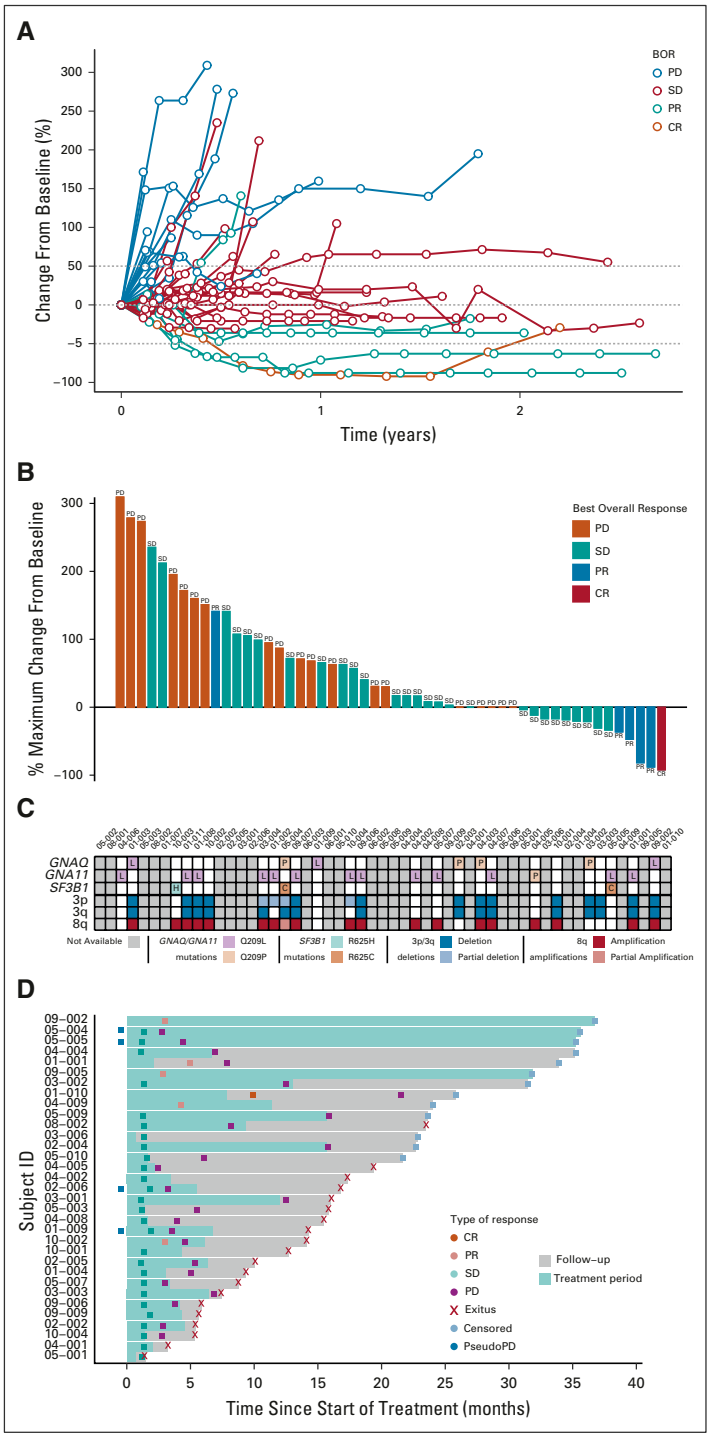

FIG 2. Treatment response. (A) Spider plot showing the radiological changes in the target tumor lesions from baseline through follow-up. *CR included a node as target lesion, not reaching 100% recovery from baseline. (B) Waterfall plot for maximum percentage change of the targeted lesions (RECIST). (C) Molecular substudy of genetic alterations in genes *GNAQ/GNA11* and *SF3B1*, deletions of chromosomal regions 3p/3q, and amplification of chromosomal region 8q. Patients are aligned with the waterfall plot of section B, allowing us to monitor the correlation between observed responses and molecular alterations in each patient. (D) Swimmer plot for all patients who had clinical benefit from treatment with the combination of nivo plus ipi. Patients with pseudoPD are pointed with blue dots. BOR, best objective response; CR, complete response; PD, progression disease; PR, partial response; SD, stable disease.

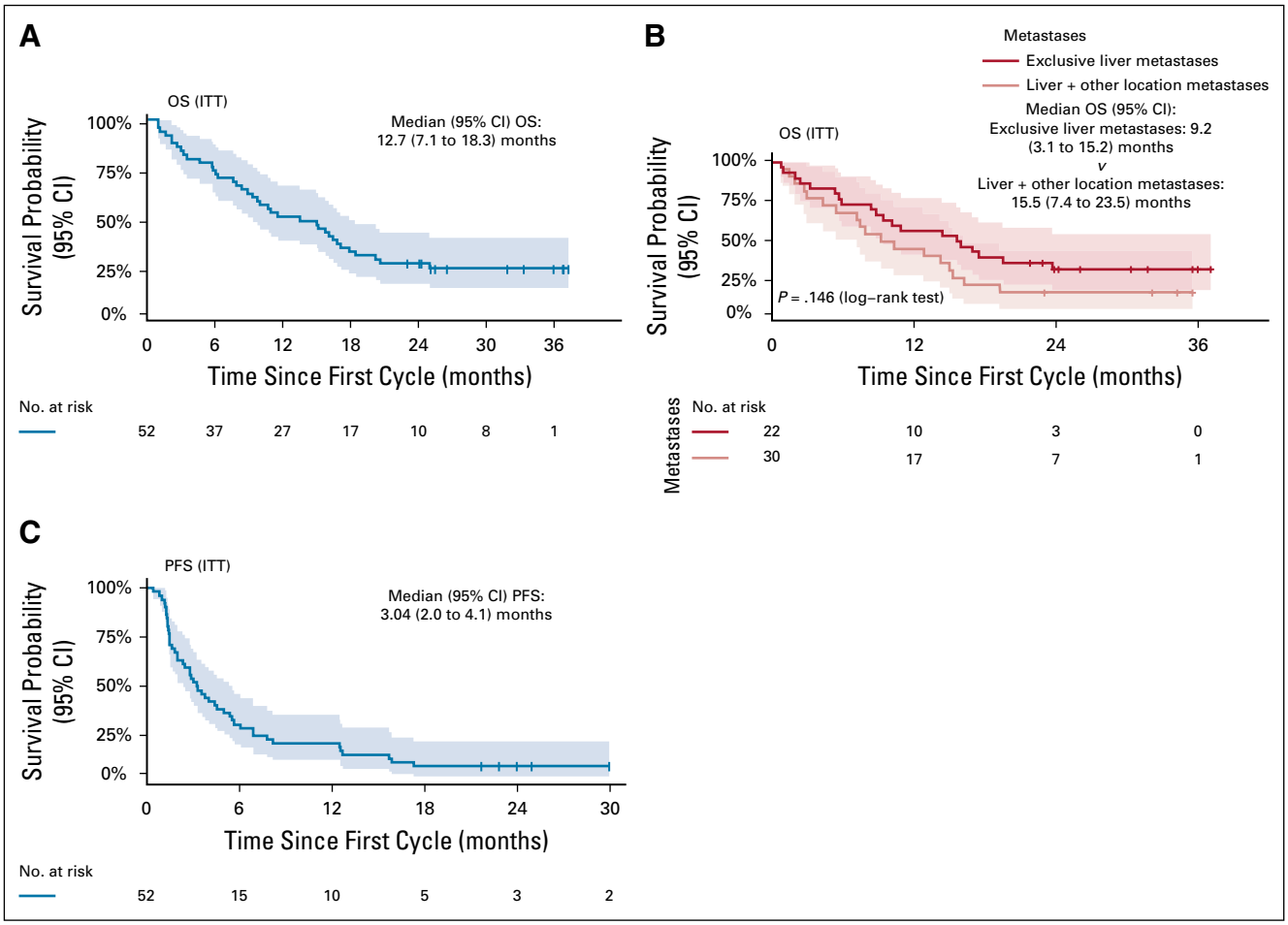

FIG 3. Kaplan-Meier curves for (A) overall survival (OS) in intention-to-treat (ITT) population and (B)according to the location of distant metastasis. (C) Kaplan-Meier curve for progression-free survival (PFS).

decades.[25,26] The largest retrospective series of anti-PD-1 and anti-PD-L1 published to date reported a 3% ORR and a median OS < 10 months.[12] Only 2 studies have reported final results on immunotherapy with ipi and reported OS rates of 6.8 months[27] and 9.8 months.[28] Johnson et al[29] also reported limited survival outcomes of pembrolizumab in 5 patients without high-volume liver metastasis. In the PUMMA meta-analysis,[3] systemic therapy was associated with a median OS of 9.3 months (95% CI, 8.4 to 10.1). Our results (median OS 12.7 months, 95% CI, 7.1 to 18.3) indicate a better prognosis of nivo/ipi than in other systemic therapies from PUMMA. However, our findings do not markedly differ from the liver-directed treatment subgroup in the meta-analysis (median OS 14.6 months, 95% CI 12.6 to 17.5). Another meta-analysis by Rantala et al[30] reported an OS of 0.91 years in chemotherapy-treated patients, whereas all liver-directed therapies showed an OS between 1.34 and 1.43 years. Our results should be interpreted with caution when compared to previous trials, which might have lower-/higher-risk patients. For instance, 64% of the patients enrolled in our study had M1a < 3 cm, whereas PUMMA included around 25% of these patients.

Two retrospective reports on nivo/ipi in pretreated patients with MUM showed a median OS of 14.2[31] and 16.1[32] months, superior to the estimates from the PUMMA meta-analysis. Also, the interim analysis of another phase II trial with the same combination (ClinicalTrials.gov identifier: NCT01585194) showed a 1-year OS of 62%.[33] Collectively, these findings justify further research with nivo/ipi combination in MUM.

Notably, 79% of patients in our study had liver metastases (28 of 41 with multilobular disease), and those with extrahepatic disease had better survival of 6 month difference, although not statistically significant. This differs from the PUMMA analysis, where patients with extrahepatic disease had a similar or even shorter survival than patients with liver-only metastasis. Liver-immunotherapy issues have also been reported for other cancers,[34,35] and it is still pending for responses, particularly for MUM. Correlative studies with fresh biopsies obtained before starting therapy trying to link pathogenic genetic alterations found in UM with treatment response have not shown statistically significant results (Fig 2C and Table 2). *SF3B1* mutations have been linked to alternative splicing events that could give rise to putative

TABLE 2. Overall Survival and Progression-Free Survival—Cox Proportional Hazard Models

		Overall Survival	Univariate			Multivariate		
Characteristic	**n**	**Median (95% CI)[a]**	**HR[b]**	**95% CI**	***P***	**HR[b]**	**95% CI**	***P***
LDH								
Normal	27	16.1 (13.8 to 18.3)	Reference	—	.026	Reference	—	.135
Increased < 2.5 × ULN	17	7.8 (4.5 to 11.2)	1.7	0.8 to 3.4	.162	1.2[c]	0.5 to 2.7	.730
Increased ≥ 2.5 × ULN	6	2.0 (0.3 to 3.7)	3.8	1.4 to 10.4	.009	3.5[c]	1.0 to 12.0	.046
GGT								
Normal	34	15.8 (13.4 to 18.2)	Reference	—	.032	Reference	—	.079
GGT increased	14	5.9 (2.6 to 9.1)	2.2	1.1 to 4.4		2.0[c]	0.9 to 4.4	
ECOG PS								
0	44	14.1 (8.1 to 20.2)	Reference	—	.076	Reference	—	.481
1	8	2.7 (1.6 to 3.9)	2.1	0.9 to 4.8		1.5[c]	0.5 to 4.6	
Extraocular disease at the time of UM recurrence								
Exclusive liver metastases	22	9.2 (3.1 to 15.2)	Reference	—	.245	—	—	—
Other locations	11	23.5 (2.0 to 45.0)	0.5	0.2 to 1.2	.100	—	—	—
Liver and other locations	19	15.5 (7.3 to 23.7)	0.7	0.4 to 1.5	.393	—	—	—
Size of liver metastasis								
≤ 3 cm	23	15.1 (10.2 to 20.0)	Reference	—	.030	Reference	—	.039
> 3cm	13	7.1 (1.9 to 12.3)	2.4	1.1 to 5.0		2.3[d]	1.0 to 5.2	
Cytokines								
IFNg > 6.61 (median)	16	15.5 (12.4 to 18.6)	Reference	—	.065	Reference	—	.116
IFNg ≤ 6.61 (median)	16	7.1 (4.1 to 10.2)	2.1	1.0 to 4.7		2.1[e]	0.8 to 5.4	
IL12p70 > 1.49 (median)	16	15.5 (12.4 to 18.6)	Reference		.061	Reference	—	.325
IL12p70 ≤ 1.49 (median)	16	5.8 (2.4 to 9.3)	2.2	1.0 to 5.0		1.6[e]	0.6 to 4.1	
IL1b	30	—	0.9	0.01 to 0.7	.022	0.0[f]	0.0 to 2.9	.151
IL2	30	—	0.7	0.5 to 1.0	.083	1.2[f]	0.7 to 2.1	.594
IL6	30	—	1.0	1.0 to 1.0	.027	1.0[f]	0.9 to 1.1	.864
IL8	30	—	1.0	1.0 to 1.1	.050	1.0[f]	1.0 to 1.1	.341
VEGF-A	30	—	1.0	1.0 to 1.0	.023	1.0[f]	1.0 to 1.0	.708
Genetic alterations								
GNAQ								
WT	18	7.83 (5.02 to 10.65)	2.168	0.72 to 6.57	.161	—	—	—
Mutant	7	15.11 (12.90 to 17.31)	Reference	—		—	—	
GNA11								
WT	11	14.12 (6.73 to 21.50)	0.787	0.32 to 1.94	.601	—	—	—
Mutant	14	7.83 (4.80 to 10.87)	Reference	—		—	—	
GNAQ/11								
WT	4	7.40 (0.00 to 19.07)	2.101	0.67 to 6.62	.195	—	—	—
Mutant	21	10.25 (0.66 to 19.84)	Reference	—		—	—	
SF3B1								
WT	22	8.76 (2.68 to 14.84)	3.602	0.47 to 27.30	.186	—	—	—
Mutant	3	0.00 (0.00 to 0.00)	Reference	—		—	—	
3p								
WT	7	14.25 (3.98 to 24.51)	0.856	0.33 to 2.24	.751	—	—	—
Deletions	18	7.40 (5.89 to 8.92)	Reference	—		—	—	

(continued on following page)

TABLE 2. Overall Survival and Progression-Free Survival—Cox Proportional Hazard Models (continued)

	Overall Survival		Univariate			Multivariate		
Characteristic	**n**	**Median (95% CI)[a]**	**HR[b]**	**95% CI**	***P***	**HR[b]**	**95% CI**	***P***
8q								
WT	6	10.25 (2.03 to 18.46)	0.684	0.23 to 2.05	.496	—	—	—
Amplification	19	8.76 (0.82 to 16.70)	Reference	—		—	—	

	Progression-Free Survival		Univariate			Multivariate		
Characteristic	**n**	**Median (95% CI)[a]**	**HR[b]**	**95% CI**	***P***	**HR[b]**	**95% CI**	***P***
Size of liver metastasis								
≤ 3 cm	23	3.7 (1.2 to 6.3)	Reference	—	.169	Reference	—	.804
> 3cm	13	1.9 (1.2 to 2.7)	1.6	0.8 to 3.3		1.1[g]	0.4 to 3.0	
LDH								
Normal	27	3.3 (1.4 to 5.2)	Reference	—	.054	Reference	—	.009
Increased < 2.5 × ULN	17	3.6 (2.2 to 5.0)	0.9	0.5 to 1.7	.774	1.7[h]	0.3 to 1.6	.379
Increased ≥ 2.5 × ULN	6	1.3 (0.8 to 1.8)	2.9	1.1 to 7.1	.024	6.1[h]	1.4 to 25.7	.015
GGT value								
Normal	34	3.6 (0.0 to 7.1)	Reference	—	.006	Reference	—	.084
GGT increased	14	1.4 (1.2 to 1.5)	2.6	1.3 to 5.1		2.2[h]	0.9 to 5.6	
Alkaline phosphatase								
Normal	40	3.6 (1.8 to 5.3)	Reference	—	.032	Reference	—	.636
Increased (> ULN)	7	1.4 (0.9 to 1.9)	2.5	1.1 to 5.7		1.3[h]	0.4 to 4.2	
Extraocular disease at the time of UM recurrence								
Exclusive liver metastases	22	1.5 (0.8 to 2.1)	Reference	—	.180	—	—	—
Other locations	11	5.0 (0.0 to 10.5)	0.5	0.2 to 1.1	.071	—	—	—
Liver and other locations	19	3.7 (2.3 to 5.1)	0.9	0.5 to 1.7	.775	—	—	—
Genetic alterations								
GNAQ								
WT	18	2.45 (0.80 to 4.10)	1.251	(0.48 to 3.26	.643	—	—	—
Mutant	7	2.78 (0.00 to 6.17)	Reference	—		—	—	
GNA11								
WT	11	3.57 (0.22 to 6.92)	0.787	0.32 to 1.94	.318	—	—	—
Mutant	14	1.98 (0.10 to 3.86)	Reference	—		—	—	
GNAQ/11								
WT	4	4.56 (0.33 to 8.80)	0.633	0.18 to 2.20	.465	—	—	—
Mutant	21	2.45 (0.96 to 3.93)	Reference	—		—	—	
SF3B1								
WT	22	2.45 (0.62 to 4.27)	0.636	0.18 to 2.20	.468	—	—	—
Mutant	3	2.78 (0.00; 6.59)	Reference	—		—	—	
3p								
WT	7	3.04 (1.51 to 4.57)	0.980	0.38 to 2.52	.966	—	—	—
Deletions	18	1.98 (0.15 to 3.82)	Reference	—		—	—	

(continued on following page)

TABLE 2. Overall Survival and Progression-Free Survival—Cox Proportional Hazard Models (continued)

Characteristic	Progression-Free Survival n	Progression-Free Survival Median (95% CI)[a]	Univariate HR[b]	Univariate 95% CI	Univariate P	Multivariate HR[b]	Multivariate 95% CI	Multivariate P
8q								
WT	6	3.57 (0.00 to 7.34)	0.960	0.37 to 2.47	.931	—	—	—
Amplification	19	2.45 (1.04 to 3.86)	Reference	—		—	—	

	Objective Response Rate n	Objective Response Rate Yes n (%)	Univariate HR[b]	Univariate 95% CI	Univariate P[i]	Multivariate HR[b]	Multivariate 95% CI	Multivariate P
Genetic alterations								
GNAQ								
WT	18	2 (11.1)	0.750	0.06 to 9.87	1.000	—	—	—
Mutant	7	1 (14.3)	Reference	—		—	—	
GNA11								
WT	11	2 (18.2)	2.889	0.23 to 36.87	.565	—	—	—
Mutant	14	1 (7.1)	Reference	—		—	—	
GNAQ/11								
WT	4	1 (25)	3.167	0.22 to 46.72	.422	—	—	—
Mutant	21	2 (9.5)	Reference	—		—	—	
SF3B1								
WT	22	3 (13.6)	—	—	.999	—	—	—
Mutant	3	0 (0)	—	—		—	—	
3p								
WT	7	0 (0)	—[j]	—[j]	.534	—	—	—
Deletions	18	3 (16.7)	Reference	—		—	—	
8q								
WT	6	0 (0)	—[j]	—[j]	.554	—	—	—
Amplification	19	3 (15.8)	Reference	—		—	—	

NOTE. Only factors with significant *P* values in univariate analysis are shown, except for results of *extraocular disease at the time of UM recurrence and genetic alterations* considered to have relevant clinical importance.

Abbreviations: AP, alkaline phosphatase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IL12p70, interleukin-12, p70; IL1b, interleukin-1beta; IL4, interleukin-4; IL6, interleukin-6; IL8, interleukin-8; INFg, interferon-gamma; LDH, lactate dehydrogenase; ULN, upper limit of normal; UM, uveal melanoma; VEGF-A, vascular endothelial growth factor-A; WT, wild type.

[a]Median estimated value in months, Kaplan-Meier method.

[b]Cox proportional hazard model.

[c]Multivariate analysis adjusted by sex and age (data available for n = 47).

[d]Multivariate analysis adjusted by sex, age, and ECOG PS (data available for n = 36).

[e]Multivariate analysis adjusted by sex, age, and ECOG PS (data available for n = 31).

[f]Multivariate analysis adjusted by sex, age, and ECOG PS (data available for n = 30).

[g]Multivariate analysis adjusted by sex, age LDH, GGT, and AP (data available for n = 30).

[h]Multivariate analysis excluding size of liver metastasis, adjusted by sex and age (data available for n = 45).

[i]Fisher's exact test.

[j]Not conclusive due to small sample size.

neoantigens, which might correlate with clinical benefit.[36] However, among the three patients identified with *SF3B1* mutations, one patient progressed and two patients showed SD (Fig 2C), with no clear correlation with treatment response.

The current study also explored the potential influence of a group of serum biomarkers within the prognostic approach. These findings must, however, be interpreted cautiously considering the small number of patients in some subgroups.

Regarding the safety profile, 49 patients (94.2%) reported TRAEs. Liver injury due to immune checkpoint inhibitors accounted for 36% of all TRAEs in the current study; four other events of hepatitis were also reported (2 > G3). These numbers are modest considering the high number of

TABLE 3. Treatment-Related Adverse Events (TRAEs) and Treatment-Related Serious Adverse Events (TRSAEs)

	TR-AEs				TR-SAEs				
	All TR-AEs		G3-G5 TR-AEs		All TR-SAEs		G3-G5 TR-SAEs		
Event	n	%[a]	n	%[a]	n	%[a]	n	% overall patients[a]	% overall TRAEs
Total	49	94.2	30	57.7	30	57.7	21	40.4	70
Skin-related events[b]	32	61..5	4	7.7	1	1.9	1	1.9	3.3
Fatigue	30	57.7	4	7.7	1	1.9	1	1.9	3.3
Liver toxicity/liver-related events[c]	19	36.5	11	21.2	3	5.8	3	5.8	10.0
Diarrhea	15	28.8	3	5.8	3	5.8	3	5.8	10.0
Fever	8	15.4	—	—	4	7.7	1	1.9	3.3
Nausea	7	13.5	—	—	—	—	—	—	—
Hypothyroidism	7	13.5	—	—	1	1.9	—	—	
Edema	4	7.7	—	—	—	—	—	—	—
Hypophysitis	4	7.7	—	—	1	1.9	—	—	
Hepatitis	4	7.7	—	—	2	3.8	2	3.8	
Vomiting	3	5.8	—	—	—	—	—	—	—
Thyroiditis	3	5.8	—	—	2	3.8	2	3.8	6.7
Constipation	3	5.8	—	—	—	—	—	—	—
Arthralgia	3	5.8	—	—	—	—	—	—	—
Pericarditis	—	—	—	—	1	1.9	—	—	—
Jaundice	—	—	—	—	1	1.9	1	1.9	3.3
Intestinal perforation	—	—	—	—	1	1.9	1	1.9	3.3
Hyponatremia	—	—	—	—	1	1.9	1	1.9	3.3
Hyperthyroidism	—	—	—	—	1	1.9	1	1.9	3.3
Guillain-Barré syndrome	—	—	—	—	2	3.8	2	3.8	—
Drug administration incidences[d]	—	—	—	—	3	5.8	—	—	—
Colitis	—	—	—	—	1	1.9	1	1.9	3.3
Anemia	—	—	—	—	1	1.9	1	1.9	3.3

NOTE. All severity of adverse events was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[a]Percentage calculated over the total number of patients included in the safety analysis (N = 52).
[b]Skin toxicity/skin symptoms: include rash and pruritus.
[c]Liver toxicity includes all events reported by the investigators as both liver toxicity per se and laboratory abnormalities compatible.
[d]Includes two drug administrations or treatment reported with incidences (quarantine) and 1 ipilimumab overdose.

patients affected with liver disease in our sample. Two deaths in patients who had TRAEs were reported. One patient (05-003) presented with Guillain-Barré syndrome after the third dose of treatment and discontinued accordingly; the patient died 15 months after the end of treatment due to PD. The second patient (05-008) discontinued treatment due to PD and died 7 months later due to PD and M1 within the brain. The safety profile of nivo/ipi in this study did not differ greatly from that seen in CM for which nivo/ipi is approved.

In conclusion, the combination of nivo and ipi showed promising OS results for UM. The toxicity profile was manageable and did not differ from that in CM. Interestingly, patients with extrahepatic disease, regardless of liver involvement, appear to benefit more from this treatment combination, an observation that should be validated in future studies. These results provide a strong rationale for further research on immunotherapy treatment combinations in UM.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX 1

Molecular Analysis

For GNAQ, GNA11, and SF3B1 analysis, DNA was amplified with specific primers flanking the codon 209 of the GNAQ and GNA11 genes, and codon 625 of the SF3B1 as previously described.[15,16] PCR was performed using the PyroMark PCR Kit (Qiagen, Maryland, Germany). The amplification conditions were an initial denaturation at 95°C for 15 minutes, 45 cycles consisting of denaturation at 95°C for 30 seconds, primer annealing at 65°C f (GNAQ and GNA11) or 56°C (SF3B1) for 30 seconds, primer extension at 72°C for 30 seconds, and a final extension at 72°C for 10 minutes. After PCR amplification, the amplicons were immobilized on Streptavidin Sepharose High Performance beads (GE Healthcare). Single-stranded DNA was prepared, and the sequencing primers annealed to the samples. The pyrosequencing reactions were conducted on the PyroMark Q24 instrument (Qiagen) and analyzed with PyroMark Q24MDx software. The nucleotide dispensation orders and the sequences to analyze for these hotspots were as follows:

Pyrosequencing Assay	Sequence to Analyze	Dispensation Order
Q209-GNAQ	CNAAGGTCAGA	GCGTAGTCAG
Q209-GNA11	GCNGGCCCCCCACATC	CGTCATGCACA
SF3B1	YGTAACACAACA	GTCTAGATGACAC

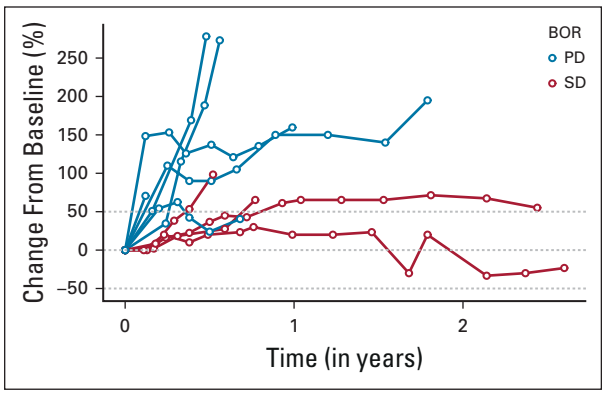

FIG A1. Spider plot showing the radiological changes in the target tumor lesions from baseline through follow-up of patients with pseudoPD.

TABLE A1. Baseline Characteristics of the Population Used to Calculate the Sample Size and Null Hypothesis Futility Threshold

		Null Hypothesis Population		
	Study Population	Carvajal et al[21]	O'Neill et al[20]	Pföhler et al[22]
Age	59	62	64	63
ECOG	0-1	0-1	0-1	0-2
Prior systemic therapy	0	0-2	0	0[b]
Metastasis	100%	96%	100%	100%
Hepatic	78.8%	—	—	100%
Extra hepatic	57%	—	—	43%
LDH level (increased)	32%	50%-74%[a]	27%	—
Number of patients (n)	52	52	15	14

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase

[a]Percentages range between 50% and 74% depending of the study arm.

[b]93% of patients were treated with treosulfan plus gemcitabine as first-line therapy.

TABLE A2. Adverse Events

	AEs			
	All AEs		G3-G4 AEs	
	n	%[a]	n	%[a]
All events	52	100	39	75.0
Skin toxicity/skin-related event[b]	30	57.7	5	9.6
Fatigue	35	67.3	6	11.5
Liver toxicity/liver-related events[c]	23	44.2	13	25.0
Diarrhea	19	36.5	4	7.7
Fever	15	28.8	2	3.8
Nausea	12	23.1	—	—
Hypothyroidism	10	19.2	—	—
Skin hypopigmentation	5	9.6	—	—
Abdominal pain	11	21.2	—	—
Anorexia	10	19.2	—	—
Cough	9	17.3	—	—
Headache	8	15.4	—	—
Vomiting	7	13.5	1	1.9
Clinical deterioration	7	13.5	4	7.7
Constipation	7	13.5	—	—
Arthralgia	7	13.5	—	—
Edema	6	11.5	—	—
Adrenal insufficiency	5	9.6	1	1.9
Upper respiratory infection	5	9.6	—	—
Back pain	5	9.6	—	—
Dyspnea	5	9.6	—	—
Hepatitis	4	7.7	2	—

NOTE. All severity of adverse events was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Abbreviation: AE, adverse event.

[a]Percentage calculated over the total number of patients included in the safety analysis (n = 52).

[b]Skin toxicity/skin symptoms include rash and pruritus.

[c]Liver toxicity includes all events reported by the investigators as both "liver toxicity" per se and laboratory abnormalities compatible.

TABLE A3. Serious Adverse Events

	Nontreatment-Related SAEs			
	All SAEs		G3-G5 SAEs	
	n	%[a]	n	%[a]
Abdominal pain	1	1.9	—	—
Ascitis	1	1.9	1	1.9
Back pain	1	1.9	—	—
Clinical deterioration	5	9.6	4	7.7
Cholecystitis	1	1.9	1	1.9
Confusion	1	1.9	—	—
Spinal disc herniation	1	1.9	—	—
Epigastric pain	1	1.9	—	—
Fever	4	7.7	—	—
General discomfort	1	1.9	1	1.9
Hyponatremia	1	1.9	1	1.9
Myalgia	1	1.9	1	1.9
Pneumonia	1	1.9	—	—
Progression of disease	3	5.8	3	5.8
Syncope	1	1.9	—	—
Sudden death	1	1.9	1	1.9
Vomiting	1	1.9	1	1.9
Total	26	50.0	14	26.9

Abbreviation: SAE, serious adverse event.

[a]Percentage calculated over the total number of patients included in the safety analysis (n = 52).