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Weekly carboplatin plus paclitaxel chemotherapy in advanced melanoma patients resistant to anti-PD-1 inhibitors: a retrospective, monocentric experience

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Abstract

Immunotherapy with anti-PD-1 antibodies significantly improved the prognosis in advanced melanoma patients, but most of them develop primary or secondary resistance to the treatment. In this study, we evaluated efficacy and safety of a chemotherapy regimen with weekly carboplatin plus paclitaxel (wCP) in patients previously treated with anti-PD-1 antibodies. We retrospectively identified 30 patients with advanced melanoma treated at our Institute over the last eight years with wCP. The co-primary endpoints of the study were overall survival (OS) and progression-free survival (PFS). In addition, we evaluated treatment tolerability. For this patient cohort, median PFS and OS were 3.25 and 7.69 months, respectively. All included patients had previously received anti-PD-1 immunotherapy, most of them had ECOG PS 0–1, and only 5 patients had a BRAF V600 mutation. In univariable analysis, we observed shorter OS in patients with >2 involved metastatic sites, superficial spreading histology, and serum lactate dehydrogenase (LDH) values above the median. Liver metastases were associated with worse outcomes, while radiotherapy treatment of brain metastases was associated with improved OS. However, in a multivariable Cox regression model, only LDH above the median, superficial spreading histology, and female sex were significantly associated with worse OS. We reported grade 3 and 4 treatment-related toxicities in 4 and 0 patients, respectively. In conclusion, chemotherapy with wCP is a valid palliative treatment in advanced melanoma who progressed with anti-PD-1 antibodies.

Keywords Melanoma, Immunoresistance, Platinum-based chemotherapy, Palliative treatment

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Introduction

Treatment of advanced melanoma has been transformed by immunotherapies with immune checkpoint inhibitors (ICIs) that leads to clinically relevant improvement in overall survival (OS) shown in multiple randomized, phase 3 clinical trials. Moreover, adjuvant immunotherapy with ICIs reduces the risk of disease recurrence in high-risk patients [1]. Nevertheless, about 60% and 40% of the patients with advanced melanoma show primary resistance to ICI monotherapy and combination therapy, respectively, and a significant fraction of patients with initial partial response to ICIs would develop secondary resistance. For patients with resistance to ICI the prognosis remains poor, and additional evidence is needed to identify active treatment regimens able to improve clinical outcomes among these patients, in particular for BRAF wild-type melanoma [2].

So far, little data are available on efficacy of treatment regimens after immunotherapy failure, and options are often limited to phase 1 or 2 clinical trials with new checkpoint inhibitors or palliative chemotherapy [2]. Previous studies have evaluated either the addition of chemotherapy (CT) to ICI [3] or treatment with CT alone [4–7]. Dacarbazine, temozolomide and fotemustine are among the most frequently prescribed chemotherapeutic agents, used in a palliative intent despite modest response rates and minor benefit on survival outcomes. A recent study retrospectively assessed the outcome of patients who received CT after progression from anti-programmed death ligand (anti-PD)-1 antibody immunotherapy [4]. Unfortunately, favorable responses to CT after ICI failure were rare and most responses were short-lived, particularly in patients treated with a carboplatin plus paclitaxel combination [4]. Therefore, it is still unclear which palliative chemotherapy regimens are preferable among patients with advanced melanoma after progression on ICI.

Considering these observations, we retrospectively assessed the clinical efficacy and tolerability of a weekly carboplatin/paclitaxel (wCP) treatment regimen in patients refractory to anti-PD-1 immunotherapy.

Materials and methods

Patients We retrospectively collected clinical data of patients with advanced cutaneous or mucosal melanoma (inoperable stage III and stage IV), aged ≥ 18 years, formerly exposed to at least one anti-PD-1 agent (either nivolumab or pembrolizumab), regardless of the line and sequence of treatment, and then treated with wCP at our Institute. Patients were considered in the time frame from October 2015 to December 2023 (8 years). Anti-PD-1 treatment was administered either in the metastatic or adjuvant setting. BRAF-mutated patients who received BRAF plus MEK inhibitors were included if they also received ICI. Data regarding baseline demographic characteristics, previous anti-cancer treatments, response to therapy, and survival were retrieved from electronic medical records. Treatment response evaluation was performed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [8].

Patients were treated with a wCP regiment, i.e. paclitaxel 80 mg/m2 plus carboplatin AUC 2 on days 1, 8, and 15 for a 28-day cycle [9, 10]. This study was approved by the Institute Ethical Committee (n. 510/3, 2018) and conducted according to the Declaration of Helsinki.

Endpoints and data collection Co-primary endpoints were progression-free survival (PFS) and OS. PFS was defined as the time from the beginning of wCP treatment to disease progression or death. OS was defined as the time from the beginning of wCP treatment to death. Patients without an event were censored at the most recent follow-up date. Demographic, clinical, histological, and biochemical data were collected for all patients. The following characteristics of the tumor were considered: anatomic site of primary melanoma onset, BRAF mutations, melanoma staging according to the American Joint Stage Committee on Cancer (AJCC), number of sites and organs affected by second lesions, the presence/absence of brain or liver metastases, and serum lactate dehydrogenase (LDH) values. Patients were enrolled since 2015, and both the 7th and 8th version of the AJCC staging system were used.

Patient variables examined were: Eastern Cooperative Oncology Group Performance Status (ECOG PS), sex, age at start of the wCP treatment, previous treatments and comorbidities. To obtain information on vital status of patients, the Regional Internet Portal of Health and clinical records were used.

Statistical analysis Survival curves were estimated using the Kaplan-Meier product-limit method and were compared using the log-rank test. Median follow-up was estimated with the reverse Kaplan-Meier method. A univariable Cox regression analysis was performed to estimate hazard ratios (HR) and the relative 95% confidence intervals (CI). Variables included in the final multivariate model were selected according to their clinical relevance and/or statistical significance in the univariate analysis (cut off, $P=0.10$). Distribution of categorical and numerical variables was tested with the chi-squared test and the Wilcoxon rank-sum test, respectively. All analyses were performed using R Statistical Software (v4.2; R Core Team 2022) with the following packages: *survival*, *survminer*, *prodlim*, *ggplot2*, *ggpubr*, *gtsummary*.

Results

Clinical features of enrolled patients To investigate the efficacy and safety of wCP in melanoma patients resistant to anti-PD-1 immunotherapy, we analyzed 30 patients treated at our Institute over the last 8 years who had progressed on anti PD-1 treatment. As shown in Table 1, our cohort consisted of 21 men and 9 women with an average age of 71 years. Eleven patients had an initial diagnosis of nodular melanoma, 8 of superficial spreading melanoma, and the remaining 8 patients had other/unknown histology; among these, 3 cases of mucosal melanoma were included. Before starting the wCP therapy, 4 patients had an ECOG PS of 0 and 17 patients had ECOG PS of 1, while 9 patients showed ECOG PS≥2. Eighteen patients had at least one comorbidity. The BRAF V600 mutation was detected in 5 cases.

The disease burden was categorized as follows: patients with 2 or fewer sites of metastasis were classified as having a low disease burden, while patients with more than 2 metastatic sites were classified as having a high disease burden. Consequently, at baseline, 8 patients had a low disease burden, and 22 patients had a high disease burden. Brain or liver metastases were present in 10 and 12 patients, respectively. LDH value was available for 21 patients with a median value of 527 U/L.

Eleven patients received wCP in the second line of treatment, 15 in the third line, and 3 in the fourth line. Only one patient received wCP as a first line of treatment due to disease progression during adjuvant anti-PD-1 therapy. Three patients had received the combination of nivolumab and ipilimumab before wCP. Nineteen patients did not receive additional chemotherapy regimens, while 3 and 8 patients received dacarbazine or fotemustine, respectively, either before or after wCP. All the five BRAF-mutated patients enrolled in this study were treated with targeted therapy before wCP, and all the patients with brain metastasis underwent to radiotherapy, obtaining control of the brain disease at the beginning of treatment.

Four patients progressed from anti PD-1 treatment in the adjuvant setting. Nine patients had brain metastases before starting wCP treatment and underwent radiotherapy. In one patient, brain metastases were discovered during treatment with wCP, and this patient received radiotherapy during the wCP therapeutic period.

Outcomes of patients treated with wCP We evaluated PFS and OS in respect to the previous therapeutic schedules and as the best overall response. When evaluating radiological response to wCP, we observed that 10 patients achieved partial response (PR), 4 patients had stable disease (SD), and 15 patients had progressive disease (PD) (Table 2). Radiological response could not be assessed for one patient.

The median follow-up of our cohort was 35.7 months. We observed a median (m)PFS of 3.25 months (95% CI 2.56–7.1, Fig. 1A) and a mOS of 7.69 months (95% CI 4.31–15.7, Fig. 1B), respectively. In the univariable analysis, we found significantly longer PFS and OS in patients with low disease burden, with mPFS and mOS of 18.81 and 28.64 months, respectively, compared to 2.61 and 4.96 months in patients with high disease burden. However, this result was not confirmed in the multivariable analysis (Fig. 2; Tables 3 and 4). The presence of brain or liver metastases did not significantly impact survival outcomes, although liver metastases were associated with numerically worse OS in the univariable analysis. Receipt of brain radiotherapy had a positive prognostic effect (Fig. 3; Tables 3 and 4).

Differently from the inclusion criteria used in clinical trials, our study included patients in both good and poor clinical conditions. However, higher ECOG PS scores did not significantly affect survival outcomes (Tables 3 and 4).

LDH values were available only for 21 patients, with a median value of 527 U/L. LDH above median was significantly associated with worse PFS and OS in both univariable and multivariable analysis, with mPFS and mOS of 2.17 and 2.75 months, respectively, compared to mPFS of 6.15 and mOS of 9.96 months in patients with values below the median (Fig. 4). Additionally, female sex and superficial spreading histology were also associated with a negative prognosis.

Tolerability in patients treated with wCP

During the wCP regime, 19 patients developed grade 1–2 toxicity, and 4 patients had grade 3 toxicity. No grade 4 toxicity was recorded. The most frequently reported adverse events were hematologic, as 11, 2 and 5 patients developed anemia, thrombocytopenia and neutropenia, respectively, and neurological, in 9 patients. Non-hematologic grade 3 toxicity was reported only in one patient due to neurotoxicity, and only 2 patients discontinued treatment due to toxic effects (Table 5).

Discussion

Despite therapeutic advances in the treatment of metastatic melanoma, a significant proportion of patients are unresponsive to immunotherapies. Several studies have addressed the treatment of ICI-resistant melanoma, but no standard options are available so far. Subsequent therapeutic lines are represented by clinical trials with new compounds, whenever available, or by palliative chemotherapy. Multiple treatment combinations are currently under investigation in patients with advanced melanoma who developed resistance to anti-PD-1 immunotherapy. Notably, both pembrolizumab plus lenvatinib in the LEAP-004 study, and nivolumab plus relatlimab in the

Table 1 Patient characteristics first weekly carboplatin plus paclitaxel (wCP)

	N **= 30 pts[a]**	**%**
Age, y (range)	71	(59–75)
< 65	11	37
≥ 65	19	63
Sex		
Female	9	30
Male	21	70
ECOG PS		
0	4	13
1	17	57
2	8	27
3	1	3
Histology		
Nodular	11	37
Superficial spreading	8	27
Mucosal	3	10
Other/unknown	8	27
BRAF V600 mutation		
Mutation	5	17
No mutation	25	83
Other chemotherapy		
None	19	63
Post-CP	8	27
Pre-CP	3	10
Adjuvant treatment		
Dabrafenib/Trametinib	1	4
Nivolumab	4	13
None	25	83
Brain radiotherapy	10	33
Previous ICI		
anti-PD1	13	43
anti-PD1/anti-CTLA4 combination	3	10
sequential anti-PD1 /anti-CTLA4	14	47
Treatment line wCP		
1	1	3
2	11	37
3	15	50
4	3	10
Comorbidities		
Any	18	60
None	12	40
Liver metastasis		
Yes	12	40
No	18	80
Brain metastasis		
Yes	10	33
No	20	67
Metastatic sites, n		
> 2	18	60
1–2	12	40
Sites first wCP		
Brain	9	33
Lung	19	70
Lymph nodes	16	59

Table 1 (continued)

	N = 30 pts[a]	%
Liver	10	37
Bone	3	11
Kidney/adrenal gland	6	22
Spleen	3	11
Peritoneum	8	30
Skin/subcutaneous	6	22
Soft tissue	9	33
Another sites	2	7
Baseline LDH (range)	527	(308–718)
Unknown	9	30
Known	21	70

[a]median (IQR)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; CP, carboplatin plus paclitaxel; wCP, weekly carboplatin plus paclitaxel; ICI, immune checkpoint inhibitor; LDH, lactate dehydrogenase

Table 2 Best response to weekly carboplatin plus paclitaxel (wCP)

Best response to wCP	*N* = 30 pts	%
Complete response (RC)	0	0
Partial response (PR)	10	34
Stable disease (SD)	4	13
Progression disease (PD)	15	50
Not assessable (NA)	1	3

wCP, weekly carboplatin plus paclitaxel

RELATIVITY-020 study, showed promising efficacy in early phase clinical trials. Furthermore, treatment with the MEK inhibitor binimetinib showed efficacy in NRAS mutated melanoma [11–13].

The CP treatment regimen is also used in clinical practice, despite the availability of other agents such as dacarbazine, fotemustine or temozolomide. In this study, some patients received other chemotherapy regimens besides CP, but the aim of our study was to focus on the wCP treatment results. While previous studies have evaluated 3-weekly CP regimens, we leveraged a weekly regimen due to its better tolerability [6].

In a large retrospective, international study on 463 patients from 24 centers, the CP regimen was used in more than 30% of patients, albeit with low efficacy due to uncommon and short-lived responses [4]. On the other hand, in a recent retrospective study of seven advanced melanoma patients treated with CP therapy after progression on ICIs, platinum-based chemotherapy improved patients' response rates [6].

The efficacy of chemotherapy after failure of ICIs therapy has been evaluated in several other cancer types such as non-small cell lung cancer and urothelial carcinoma [14, 15]. In these tumor types, the combination of chemotherapy and immunotherapy showed antitumor efficacy. This association can induce cytolysis and inhibit cancer cell proliferation, and chemotherapy can also modulate the immune microenvironment [16]. However, these tumor types have been demonstrated to be more responsive to chemotherapy than melanoma, where the combination of chemotherapy and immunotherapy remains at the experimental stage, and it is not ready for being incorporated into routine clinical practice [3].

In our study, we evaluated the efficacy and tolerability of a wCP regimen in advanced melanoma patients after progression on anti-PD-1 immunotherapy. The mPFS of ~3 months and mOS of ~8 months in our cohort were consistent with previous literature data. We confirmed the poor prognostic role of baseline LDH, as patients with values above the median had poorer survival outcomes. It should be considered that LDH values reflect the burden and aggressiveness of the disease because this enzyme is involved in glycolysis and is aberrantly activated in neoplastic cells. Consequently, LDH values should be interpreted as an indicator of active tumor cells and of high tumor burden [17]. In this study, we relied on the LDH median value since patient blood tests were not centralized, and the upper limit of normal value was not available for all the patients. However, this analysis retained clinical relevance since it underlined the prognostic value of this biomarker for patients treated with palliative chemotherapy in a real world study.

Our preliminary results suggest that low tumor burden was associated with a positive prognostic effect, even if this result was not confirmed in a multivariable analysis. Due to the exploratory nature of these findings, and to the small number of patients in our cohort, it would be necessary to conduct a larger-scale evaluation to confirm this data. Indeed, in a previous study, we highlighted a more favorable trend and a greater response to anti-PD-1 treatment in low burden patients. We also found a better outcome to ICI treatment in the presence of lymph node, skin-subcutaneous, and lung metastases, while critical sites such as brain and liver were associated with worse outcomes [18]. Liver and brain lesions are considered less responsive to immunotherapy

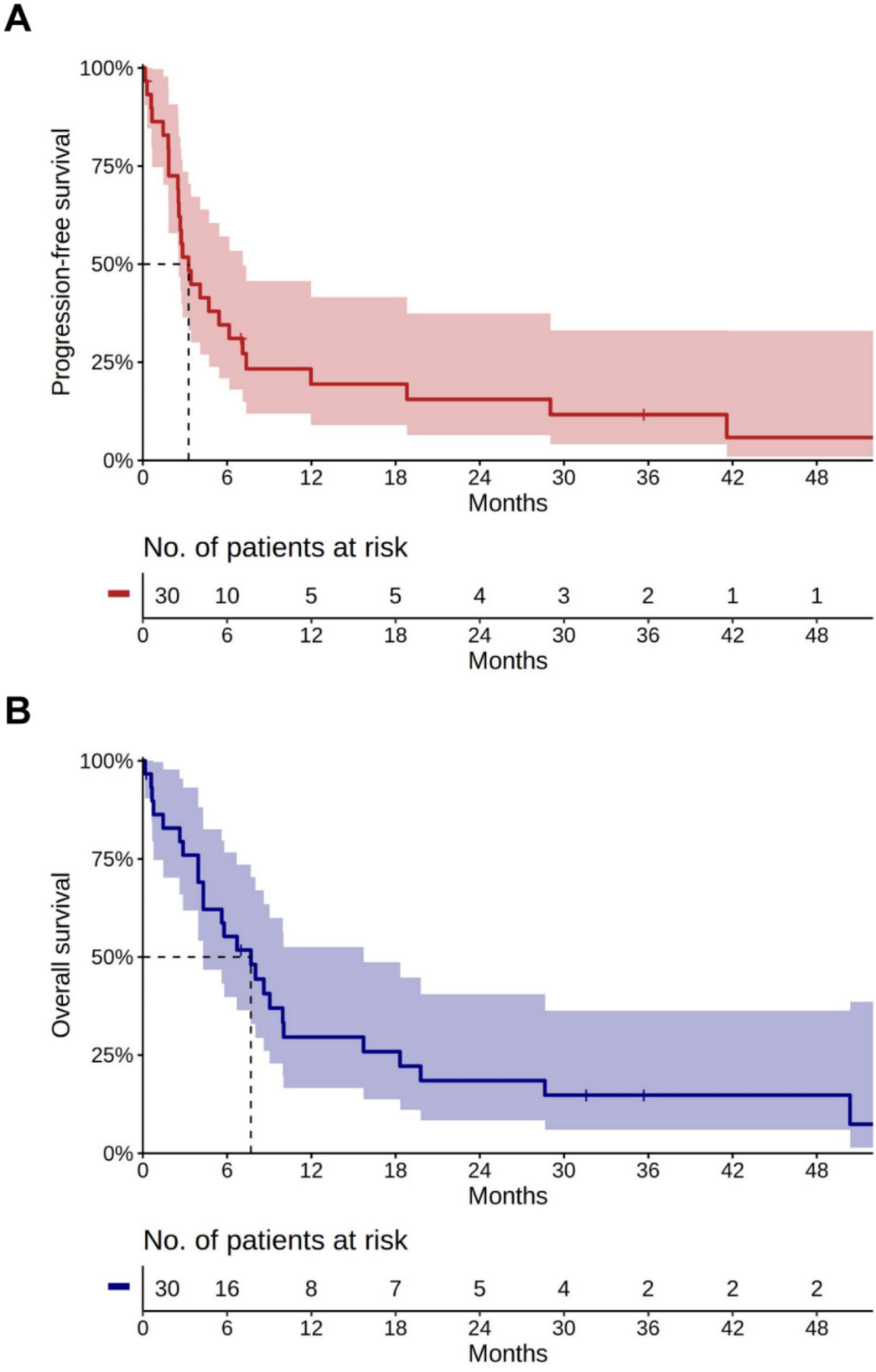

Fig. 1 Kaplan-Meier estimation of PFS and OS in the overall population **(A)** PFS in patients treated with wCP; median PFS was 3.25 months. **(B)** OS in patients treated with wCP; OS was 7.69 months. PFS: progression free survival; OS: overall survival; wCP: weekly carboplatin plus paclitaxel; CI: confidence interval; No: number

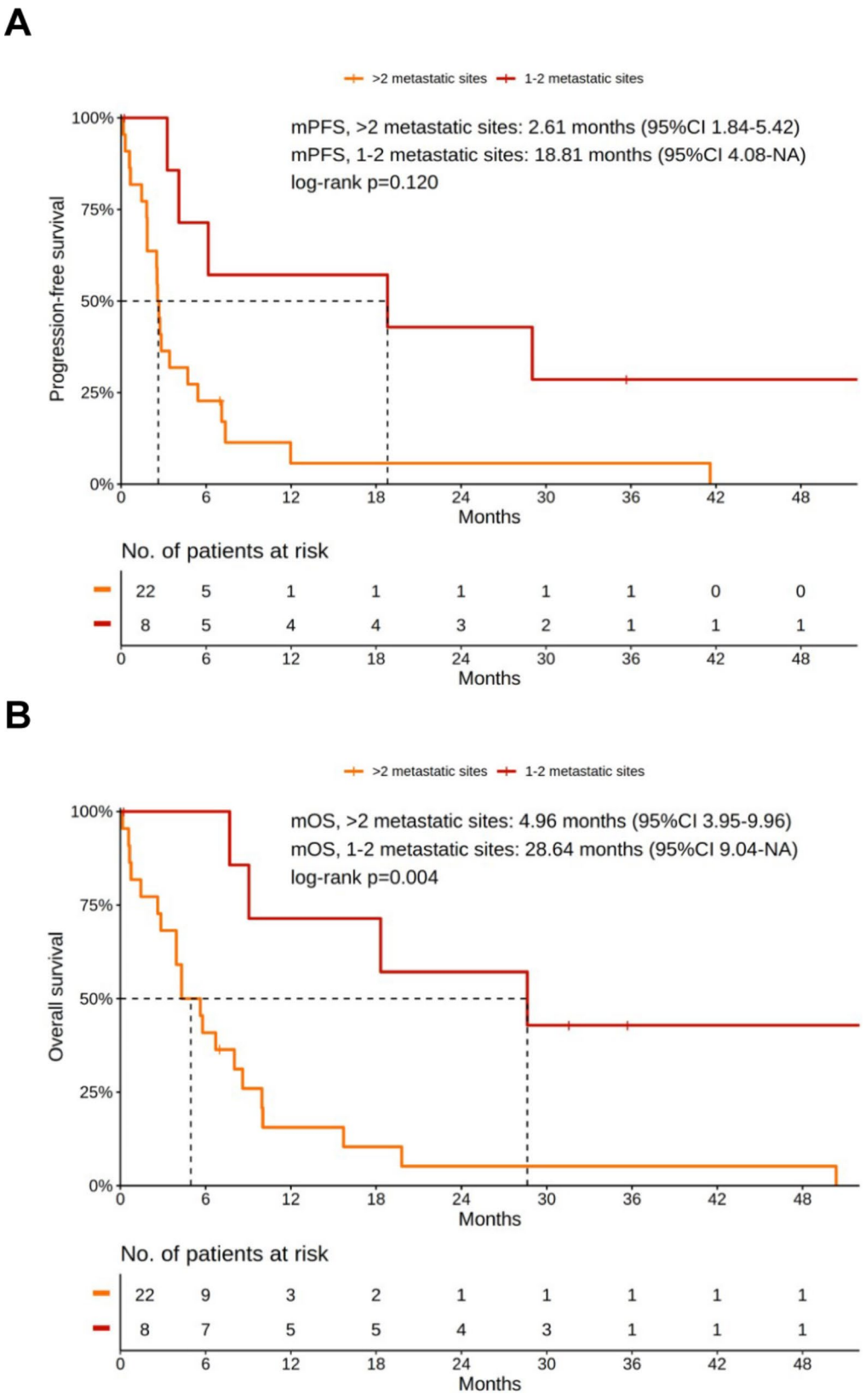

Fig. 2 PFS and OS according to burden disease in patients treated with wCP. **(A)** PFS in the whole study population according to burden disease. mPFS was of 18.81 months in patients with 1–2 metastatic site and of 2.61 months in patients with > 2 metastatic sites. **(B)** OS in the whole study population according to burden disease. mOS was 28.64 months in patients with 1–2 metastatic site and 4.96 months in patients with > 2 metastatic sites. PFS: progression free survival; OS: overall survival; wCP: weekly carboplatin plus paclitaxel; CI: confidence interval; mPFS: median PFS; mOS: median OS; No: number

Table 3 Univariate analysis of patient baseline characteristics before treatment with wCP

		Univariable, PFS		Univariable, OS	
		HR (95%CI)	***p***	**HR (95%CI)**	***p***
Sex	Females	-		-	
	Males	0.44 (0.19–1.01)	0.052	0.46 (0.19–1.10)	0.081
Age, y	< 65	-		-	
	≥ 65	1.03 (0.46–2.28)	> 0.9	1.08 (0.47–2.46)	0.9
ECOG PS	0–1	-		-	
	2–3	1.10 (0.46–2.64)	0.8	1.14 (0.47–2.77)	0.8
Histology	Nodular	-		-	
	superficial spreading	3.13 (1.09–8.97)	0.034	4.22 (1.39–12.8)	0.011
	Mucosal	1.66 (0.43–6.44)	0.5	2.19 (0.56–8.51)	0.3
	other/unknown	2.00 (0.65–6.12)	0.2	2.61 (0.84–8.14)	0.10
BRAF V600 mutation	Any	-		-	
	None	2.49 (0.73–8.47)	0.14	3.34 (0.78–14.4)	0.11
Adjuvant treatment	Any	-		-	
	None	1.54 (0.52–4.56)	0.4	1.62 (0.54–4.86)	0.4
Brain radiotherapy	Yes	-		-	
	No	3.13 (1.12–8.73)	0.030	2.60 (0.94–7.23)	0.067
Previous ICI	anti-PD1	-		-	
	anti-PD1/a-CTLA-4	0.47 (0.06–3.68)	0.5	0.90 (0.11–7.34)	> 0.9
	sequential anti-PD1/a-CTLA-4	1.18 (0.53–2.64)	0.7	1.26 (0.56–2.86)	0.6
Treatment line	≥ 3	-		-	
	1–2	0.75 (0.33–1.70)	0.5	0.76 (0.33–1.74)	0.5
Comorbidities	Any	-		-	
	None	0.06 (0.48–2.31)	0.9	1.29 (0.57–2.90)	0.5
Metastatic sites, n	> 2	-		-	
	1–2	0.29 (0.11–0.80)	0.017	0.22 (0.07–0.66)	0.007
Liver metastasis	No	-		-	
	Yes	1.90 (0.82–4.39)	0.13	2.07 (0.90–4.79)	0.089
Brain metastasis	No	-		-	
	Yes	0.63 (0.26–1.55)	0.3	0.66 (0.26–1.69)	0.4
Baseline LDH	LDH ≤ median	-		-	
	LDH > median	2.92 (1.13–7.56)	0.027	3.38 (1.29–8.88)	0.013
	Unknown	1.22 (0.43–3.46)	0.7	1.40 (0.48–4.10)	0.5

PFS, progression-free survival; OS, overall survival; HR, Hazard Ratio; CI, Confidence Interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; LDH, lactate dehydrogenase

compared to other metastatic sites. In the liver microenvironment, endothelial and Kupffer cells could favor the conversion of cytotoxic T lymphocytes into regulatory T cells [19]. Moreover, metastases in the liver are associated with a lower infiltration of CD8+T lymphocytes, resulting in lower sensitivity to ICIs [19]. In this study, while liver metastases were associated with numerically shorter survival outcomes, the data did not reach statistical significance likely due to the small size of our cohort. Similarly, the results for ECOG PS were not significant. It should be considered that we included in our cohort patients with poor ECOG PS. The decision to treat these patients was based on the careful evaluation of individual cases with the primary objective of palliating symptoms while offering a treatment that, based on our experience, demonstrates a favorable tolerability profile. However, we acknowledge that patients with ECOG PS>2 should generally be referred to palliative care and that active treatment over the last weeks before death should be avoided.

In CheckMate 204, the efficacy of the ipilimumab plus nivolumab combination was tested in patients with advanced melanoma, and it has been reported a rate of intracranial objective response of 55%. However, not all patients benefited from the combination which is characterized by significant toxicity (treatment-related adverse events of any grade occurred in the 36% of patients, with grade 3 or 4 events occurring in the 7% of patients and one death occurred for grade 5 immune-related myocarditis) [20]. In patients with symptomatic brain lesions, who take corticosteroids and have poor ECOG PS, outcomes are even worse, and the combination should not be proposed [20, 21]. Our study included 3 patients who experienced disease progression when treated with the

Table 4 Multivariate analysis of patient characteristics before treatment with wCP

	Multivariable, PFS		Multivariable, OS	
	HR (95%CI)	***p***	**HR (95%CI)**	***p***
Sex				
Females	-		-	
Males	0.08 (0.02–0.33)	< 0.001	0.10 (0.02–0.43)	0.002
Histology				
Nodular	-		-	
superficial spreading	2.82 (0.92–8.57)	0.068	4.45 (1.39–14.3)	0.012
Mucosal	0.98 (0.18–5.32)	> 0.9	2.67 (0.48–14.9)	0.3
other/unknown	0.53 (0.13–2.16)	0.4	1.04 (0.28–3.80)	> 0.9
Brain radiotherapy				
Yes	-		-	
No	11.8 (2.42–57.2)	0.002	4.77 (1.20–19.0)	0.026
Metastatic sites, n				
>2	-		-	
1–2	0.47 (0.12–1.87)	0.3	0.25 (0.06–1.12)	0.070
Liver metastasis				
No	-		-	
Yes	0.96 (0.26–3.49)	> 0.9	0.72 (0.19–2.70)	0.6
Baseline LDH				
LDH ≤ median	-		-	
LDH > median	5.64 (1.33-24.0)	0.019	5.14 (1.22–21.7)	0.026
Unknown	5.64 (1.04–30.6)	0.045	5.37 (0.96–30.1)	0.056

wCP: weekly carboplatin plus paclitaxel; PFS, progression-free survival; OS, overall survival; HR, Hazard Ratio; CI, Confidence Interval; LDH, lactate dehydrogenase

nivolumab plus ipilimumab combination. These patients, in the absence of V600 BRAF mutation or for progression with BRAF/MEK inhibitors, were only candidates for chemotherapy regimens. One patient had not yet undergone disease re-evaluation at the time of the last follow-up, while as a best response one patient obtained SD and the other a PR. In Italy, the ipilimumab plus nivolumab combination was made available by the regulatory agency since March 2022 and only for patients with untreated, advanced melanoma with brain metastases or PD-Ligand-1 expression lower than 1%. Our cohort dated back to October 2015 and some patients could not be treated with the combination.

In our study, all five patients BRAF V600 mutated were treated with BRAF and MEK inhibitors before the therapy with wCP, but this subgroup was very small and data on PFS and OS were not statistically significant.

In our population, we also included three patients with mucosal melanoma, to reflect a real world contest. While ICIs and targeted therapies have revolutionized the treatment of cutaneous melanoma, their impact on mucosal melanoma is weaker [22]. Therefore, chemotherapy is an alternative strategy in this subset of patients, and we thought it would be important to evaluate the result of the wCP treatment also in these patients.

Altogether, as the best response to treatment, we observed disease progression in half of the patients treated with wCP, but we also showed PR in 34% and SD in 13% of patients. The results are interesting, considering that our cohort included patients resistant to anti-PD-1, with brain and visceral metastases, with ECOG-PS 0–3 and, therefore, with a poor prognosis. Furthermore, two patients in PR are currently alive and with disease control in the absence of treatment. Therefore, this treatment regimens could be surely proposed to patients resistant to anti-PD-1, especially if they were male and presented with LDH values below the median.

The wCP scheme showed a good safety profile also in our patients who were previously subjected to different therapies. Most adverse events were grade 1–2 and the discontinuation of treatment for toxicities was necessary only for two patients. Thus, tolerability of the weekly schedule treatment permitted to treat patients with a PS greater than 0–1.

Our study highlights the possibility that patients with specific clinical characteristics, not responsive to anti-PD-1, may benefit from a chemotherapy treatment with wCP. Besides the advantage of good tolerability, the wCP schedule permits better patient monitoring, especially necessary for pre-treated patients in poor clinical conditions.

Our study needs confirmation on a larger population of patients, and it would be particularly important to specifically evaluate in a larger cohort the efficacy of wCP in the case of failure of the nivolumab plus ipilimumab combination in patients with BRAF wild type melanoma, for whom there are no alternative treatments [23].

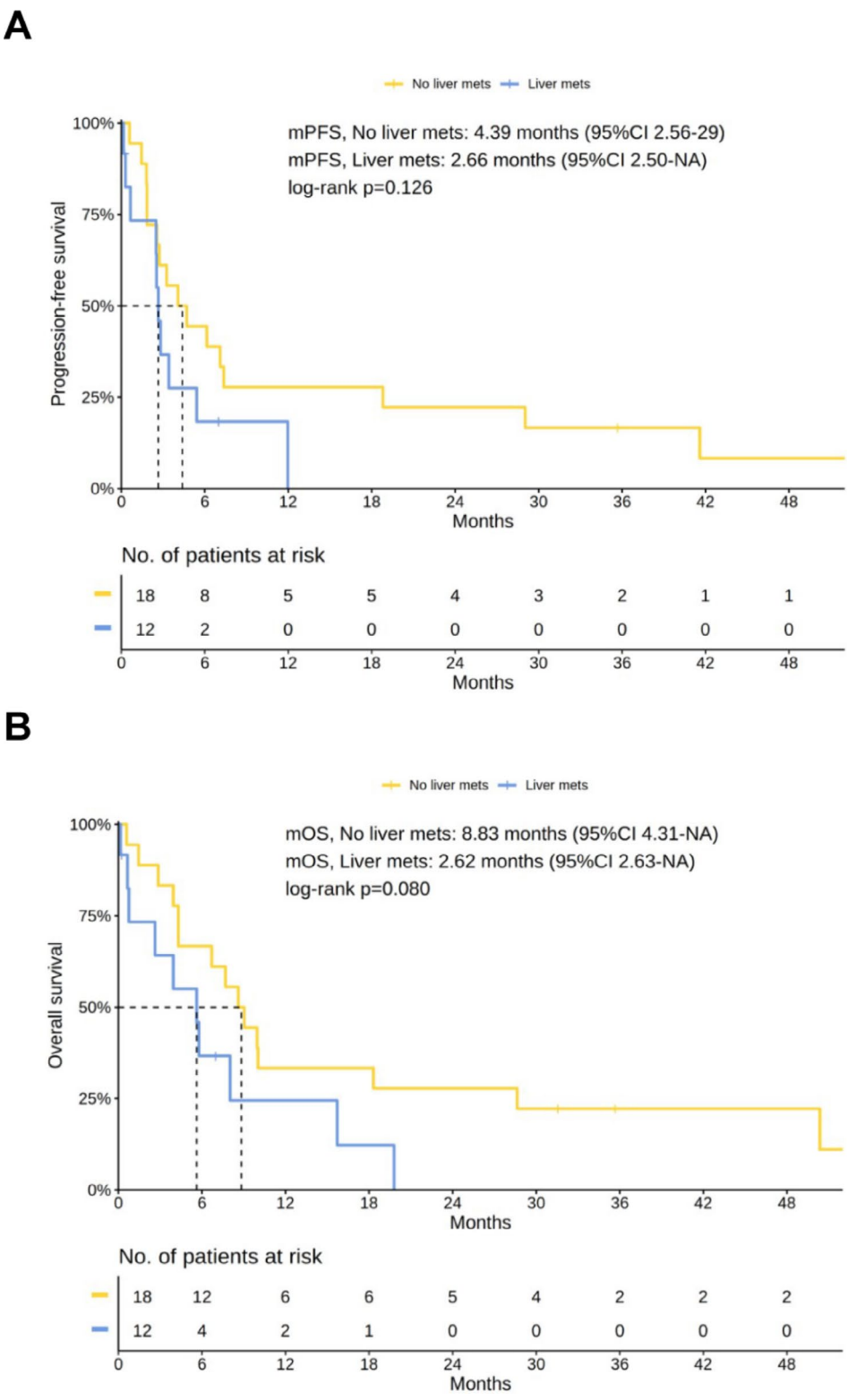

Fig. 3 PFS and OS according to presence/absence of liver metastasis in patients treated with wCP. **(A)** PFS in the whole study population according to presence/absence of liver metastasis. mPFS was of 4.39 months in patients without liver metastasis and of 2.66 months in patients with hepatic sites of disease. **(B)** OS in the whole study population according to presence/absence of liver metastasis. mOS was 8.83 months in patients without liver metastasis and 2.62 months in patients with hepatic sites of disease. PFS: progression free survival; OS: overall survival; wCP: weekly carboplatin plus paclitaxel; CI: confidence interval; mPFS: median PFS; mOS: median OS; mets: metastases; No: number

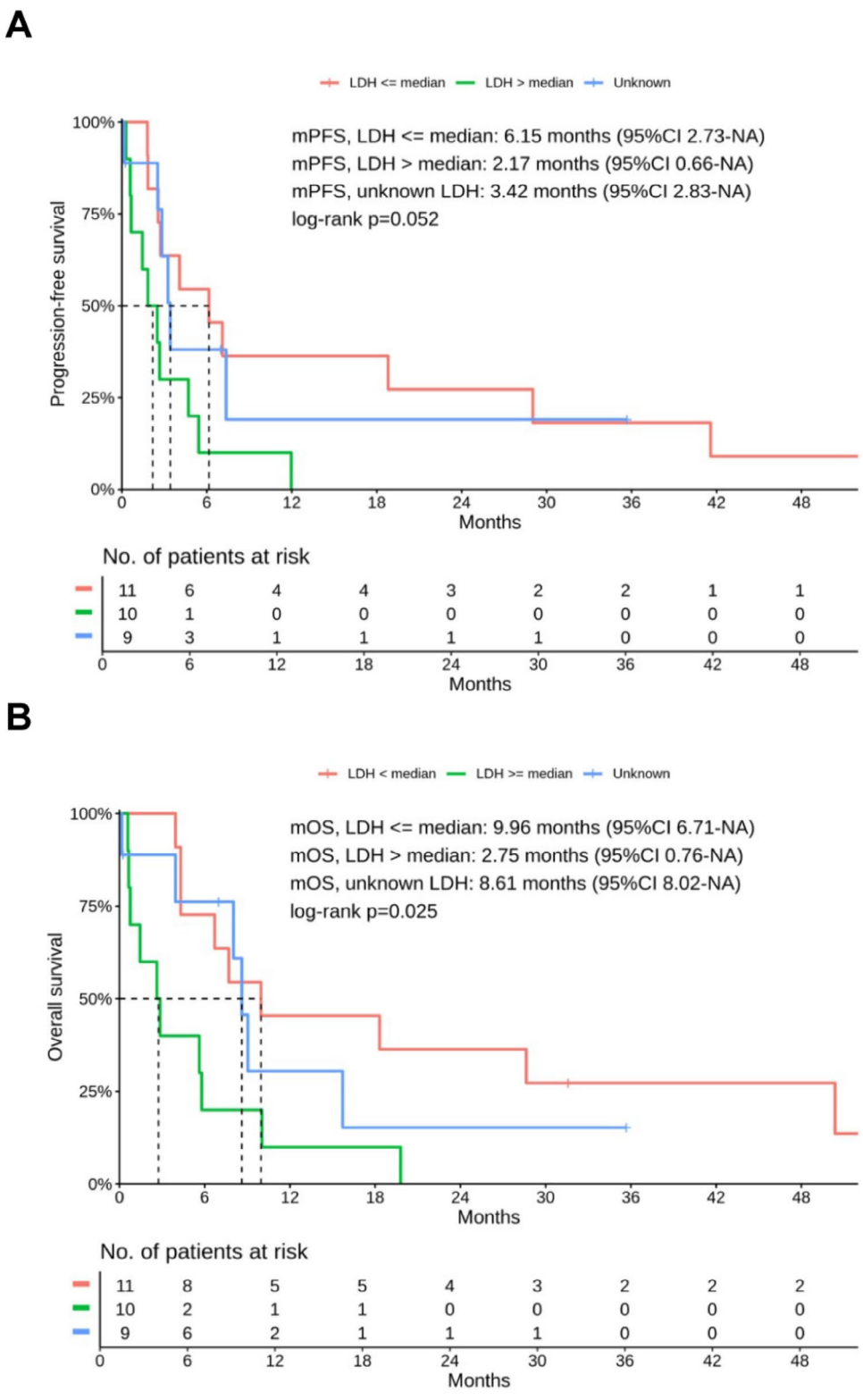

Fig. 4 PFS and OS according to LDH level in patients treated with wCP. **(A)** PFS in the whole study population according to LDH levels. mPFS was of 6.15 months in patients with LDH level less than median value and of 2.17 months in patients with LDH level greater than median value. In patients with unknown LDH value mPFS was 3.42 months. **(B)** OS in the whole study population according to LDH levels. mOS was 9.96 months in patients with LDH level less than median value and of 2.75 months in patients with LDH level greater than median value. In patients with unknown LDH value mOS was 8.61 months. PFS: progression free survival; OS: overall survival; LDH: lactate dehydrogenase; wCP: weekly carboplatin plus paclitaxel; CI: confidence interval; mPFS: median PFS; mOS: median OS; No: number

Table 5 Toxicities to weekly carboplatin plus paclitaxel (wCP)

	N pts	%
Toxicity to wCP	**23**	**76**
G1-2	19	82
G3	4	17
G4	0	0
Anemia	**11**	**36**
G1	7	23
G2	4	13
G3	0	0
G4	0	0
Thrombocytopenia	**2**	**6**
G1	1	3
G2	0	0
G3	1	3
G4	0	0
Neutropenia	**5**	**16**
G1	0	0
G2	2	6
G3	3	10
G4	0	0
Nausea/vomiting	**3**	**10**
G1	2	6
G2	1	3
G3	0	0
G4	0	0
Diarrhea	**3**	**10**
G1	3	10
G2	0	0
G3	0	0
G4	0	0
Constipation	**1**	**3**
G1	1	3
G2	0	0
G3	0	0
G4	0	0
Neurotoxicity	**9**	**30**
G1	4	13
G2	1	13
G3	1	3
G4	0	0
Asthenia	**5**	**16**
G1	3	10
G2	2	6
G3	0	0
G4	0	0
Another toxicity	**3**	**10**
G1	2	6
G2	1	3
G3	0	0
G4	0	0
Treatment discontinuation		
Yes	27	90
No	3	10
Reason of discontinuation		

Table 5 (continued)

	N pts	%
Toxicity	2	7
Progression disease	24	89
Another reason	1	4

wCP, weekly carboplatin plus paclitaxel; G, grade

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Author contributions
Conception/design: F.R.D.P., S.V., G.P. Provision of study material or patients: F.R.D.P., R.F., M.F.M., A.R.Z., Z.C.D.R., R.M., G.Pi., P.C. Collection and/or assembly of data: F.R.D.P., D.M., M.L.C. Data analysis and interpretation: F.R.D.P., D.M., C.M.F., P.M., F.D.G. Manuscript first writing: F.R.D.P., D.M., M.L.C., C.M.F., F.D.G. Manuscript revision: All authors.

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Data availability
The dataset analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethical Committee of IDI-IRCCS (protocol n. 510/3, 2018). As this is a retrospective analysis, authors made every effort to obtain written informed consent from each individual involved in the study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
FdG has been a speaker at BMS, and Novartis conference. PM had a consultant/advisory role for BMS, ROCHE Genentech, MSD, Novartis, AMGEN, Merck Serono, Pierre Fabre, INCYTE. The two authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All other authors declare no conflict of interest.

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