

# Continuous Infusion of Endostar Combined with Chemotherapy in Patients with Advanced or Recurrent Mucosal Melanoma: A Real-World Cohort Study

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## Research Article

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# Abstract

## Background

Mucosal melanoma is rare and has distinct clinical and genetic features. Even with advances in targeted and immune therapy, the survival of patients with advanced or recurrent mucosal melanomas remains poor. The standard treatment remains controversial and we conducted this real-world study aimed to test continuous intravenous Endostar infusion plus chemotherapy in this population in the first-line setting.

## Methods

Overall, 43 patients with advanced or recurrent mucosal melanoma treated at Fudan University Shanghai Cancer Center between April 2017 and August 2020 were retrospectively included. Patients received dacarbazine plus cisplatin or temozolomide plus cisplatin regimens per the investigators' preference. Endostar (105 mg/m<sup>2</sup>) was administered with continuous infusion for 168 hours (Civ 168h).

## Results

Of the 43 patients, 72.1% had metastatic disease, and the most common primary site was the gastrointestinal tract (51.2%). The most commonly observed mutations were *NRAS* (23.1%), *BRAF* (7.7%) and *CKIT* (5.1%). An objective response was observed in 12 (30.0%) of the 40 evaluable patients, and disease control was achieved in 31 (77.5%) patients. With a median follow-up of 17.6 months, the median progression-free survival (PFS) and overall survival (OS) were 4.9 and 15.3 months, respectively. Additionally, a high lymphocyte-to-monocyte ratio (LMR) ( $p=0.023$ , HR 0.29, 95% CI: 0.10-0.84) and *BRAF/KIT/RAS* mutation ( $p=0.028$ , HR 0.24, 95% CI: 0.07-0.86) were independently correlated with prolonged OS. Toxicity was manageable overall. Conclusion

## Continuous

Endostar infusion plus chemotherapy was effective and safe for the treatment of advanced or recurrent mucosal melanoma. A high LMR was correlated with favorable PFS and OS in this patient population.

## Background

Historically, the outcome of patients with advanced melanoma is dismal, with a median survival of 7.5 months.<sup>1</sup> In the past decade, with the advent of targeted therapy against the B-raf proto-oncogene (*BRAF*) and immune checkpoint inhibitors, the prognosis of melanoma has significantly improved. However, the clinical benefit of these therapeutic approaches is variable among different melanoma subtypes.<sup>2,3</sup> With more patients initially at advanced stage, low incidence of *BRAF* mutation (3-15%) and inferior activity (overall response rate [ORR], 23.3-37.1%) of immune checkpoint inhibitors (ICIs), the survival of patients with advanced or relapsed mucosal melanomas remains poor, and there is no defined standard first-line treatment strategy.<sup>4,5</sup> Additionally, due to demographic and ethnic disparities, mucosal melanoma represents only approximately 1.4% of all melanomas in the US but represents 22.6% of all melanomas in

China.<sup>6,7</sup> Data on mucosal melanoma remain limited, and most studies are derived from Asian countries due to ethnic disparities in prevalence.

Recombinant human endostatin (Endostar) has an additional 9-amino-acid sequence at the N-terminus of the protein and a six-histidine tag. Since 1997, Endostar has been reported to efficiently block angiogenesis and suppress tumor growth, with an acceptable safety profile in previous clinical studies.<sup>8-12</sup> In patients with advanced non-small-cell lung cancer (NSCLC), Endostar plus standard chemotherapy improved survival and was thus approved for the treatment of NSCLC by the State Food and Drug Administration of China in 2005.<sup>13</sup> In addition, preclinical and clinical investigations have demonstrated the benefit of Endostar in multiple malignancies, including gastrointestinal cancer, colorectal cancer, ovarian cancer, nasopharyngeal carcinoma and extensive-stage small-cell lung cancer (SCLC).<sup>14-22</sup>

Previously, a phase 2 study evaluated the efficacy and safety of Endostar plus dacarbazine in patients with metastatic melanomas and revealed superior progression-free survival (PFS, 4.5 vs. 1.5 months,  $p=0.013$ ) and overall survival (OS, 12.0 vs. 8.0 months,  $p=0.005$ ) in the Endostar group compared with the placebo group. Given the angiogenic nature of melanoma, the considerable survival benefit of Endostar combination treatment and the limited number of patients with mucosal melanoma in that study (7 in the placebo group and 9 in the Endostar group). Endostar-containing treatment strategies are worth further investigation in advanced mucosal melanoma.<sup>23</sup>

In the present study, we evaluated the efficacy and safety of Endostar plus polychemotherapy (dacarbazine/temozolomide and cisplatin) in a cohort of patients with advanced or relapsed mucosal melanoma. Endostar is commonly administered at 7.5 mg/m<sup>2</sup> once daily for 14 days, but this real-world cohort study aimed to evaluate the efficacy and safety of continuous Endostar infusion for 168 hours combined with chemotherapy. We also retrospectively analyzed the prognostic factors of this cohort and summarized our experience in treating patients with advanced or recurrent mucosal melanoma in the era of immunotherapy.

## Materials And Methods

### Study population

Patients with pathologically confirmed mucosal melanoma treated with Endostar-containing regimens in Fudan University Shanghai Cancer Center between April 2017 and August 2020 were retrospectively enrolled. Patients who were included in the present study also had advanced or recurrent disease, with a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1. The Endostar-containing regimens were either Endostar plus dacarbazine and cisplatin or Endostar plus temozolomide and cisplatin. Endostar was given by continuous infusion at a dosage of 105 mg/m<sup>2</sup> for 168 hours (Civ 168h) in the present study.

## Clinical indicators

The clinical features evaluated included baseline characteristics (sex, age, stage, serum lactate dehydrogenase (LDH) level, *KIT*, *BRAF* and *NRAS* mutation status, neutrophil-to-lymphocyte ratio [NLR], and lymphocyte-to-monocyte ratio [LMR]); treatment-related information (prior treatment, surgery, radiotherapy, response to treatment, treatment-related toxicities); and patient survival.

## Assessment and statistical analysis

Adverse events (AEs) were assessed by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Radiologic response was evaluated per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. ORR was defined as the proportion of patients achieving a complete response (CR) or partial response (PR). PFS refers to the interval from the first date of Endostar-containing treatment to date of radiologic progression, initiation of new treatment, patient death, or last follow-up. OS was calculated from the initiation of Endostar-containing treatment to patient death from any cause or last follow-up. Patients who were alive at the last follow-up were censored. Survival was calculated using the Kaplan-Meier method and compared by the log-rank test. Cox proportional hazards regression was applied to identify potential prognostic indicators. A P value of 0.05 or less (2-sided test) was considered significant. All these analyses were conducted with R software, version 3.3.3 (<http://www.R-project.org>) and SPSS 22.0 (SPSS Inc, Chicago, IL).

This study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center.

## Data availability

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

# Results

## Patient characteristics and treatment details

Of the 43 patients with advanced or recurrent mucosal melanoma, 17 (39.5%) were males, and 26 (60.5%) were females, with a median age of 61 years (25-74 years). The most common primary site was the gastrointestinal tract (n=22, 51.2%), followed by the sinonasal (n=14, 32.6%) and genitourinary tracts (n=6, 14.0%). A total of 32 (74.4%) patients had undergone surgical resection, of whom 18 had radical surgery (surgical resection margins negative on final pathology). Before initiation of Endostar-containing treatment, most patients had metastatic disease (n=31, 72.1%), and 12 (27.9%) had locally advanced disease that was deemed unresectable. The majority of patients (n=33, 76.7%) had normal LDH levels, while 9 (20.9%) patients had elevated LDH levels. *KIT*, *BRAF* and *NRAS* mutation status was available for all but four patients. More than half of the patients (25/39, 64.1%) did not have mutations in these genes. The most commonly observed mutation was *NRAS* (n=9, 23.1%), followed by *BRAF* (n=3, 7.7%) and *CKIT* (n=2, 5.1%). Of the three patients with *BRAF* mutations, one patient harbored the *BRAF* V600E mutation,

and the other two patients had the *BRAF* G606E and T599del mutations. The baseline patient characteristics are presented in Table 1.

The 43 patients received either Endostar plus temozolomide and cisplatin (n=24, 55.8%) or Endostar plus dacarbazine and cisplatin (n=19, 44.2%); this was the first-line treatment in most patients (40/43, 93.0%). Three patients had first-line anti-PD-1 treatment, and 11 patients received chemotherapy (paclitaxel or dacarbazine plus platinum) in the adjuvant setting. The median number of Endostar-containing treatment cycles was 4 (range: 1-6 cycles), and seven (16.3%) patients had chemotherapy dose adjustments due to drug-related toxicities. No patient discontinued Endostar during the treatment period.

## **Efficacy**

As of September 30, 2020, the median follow-up interval was 17.6 months (range 1.0-35.6 months). Of the 40 evaluable patients, an objective response was observed in 12 (30.0%) patients, four with CR (10%) and eight with PR (20.0%). Five responders (3 with anorectal primary sites and 2 with nasopharyngeal primary sites) received concurrent or sequential radiotherapy, and two received maintenance anti-PD-1 therapy following Endostar-containing treatment. Overall, disease control was achieved in 31 (77.5%) of the 40 patients. According to the primary site, the ORR was highest in those with disease originating from the sinonasal tract (38.5%, 5/13), followed by the genitourinary tract (28.6%, 2/7) and the gastrointestinal tract (25.0%, 5/20). Of the four patients with a CR, two had primary lesions located in the nasal cavity and paranasal sinuses, and two had primary lesions in the [anorectum](#). All four patients had locally advanced disease and underwent concurrent radiotherapy (the two patients with sinonasal melanoma underwent proton heavy ion radiotherapy).

As of the cutoff date, the median PFS was 4.9 months (95% confidence interval [CI]: 3.6 -10.3 months), and the median OS was 15.3 months (95% CI: 9.0 months - not available) for the entire cohort (Figure 1A and 1B). For the eight patients receiving concurrent/sequential radiotherapy or anti-PD-1 maintenance treatment, the median PFS was 12.1 months (95% CI: 4.0 - 20.0 months).

## **Univariate and multivariate survival analysis**

The NLR and LMR cutoffs were determined using receiver operating characteristic (ROC) curves to predict progression at 4.9 months. Univariate analysis was performed and showed that disease stage (p=0.015), previous surgery (p=0.050), liver metastasis (p=0.013), elevated LDH level (p=0.006), and LMR >3.45 (p=0.001) were associated with patient PFS. LMR >3.45 remained the only factor significantly correlated with longer PFS in the multivariate analysis (p=0.012, hazard ratio [HR] 0.28, 95% CI: 0.10-0.76); metastatic stage was adversely correlated with PFS (p=0.071, HR 2.5, 95% CI: 0.90-0.70), but the correlation was not statistically significant. With respect to OS, LMR >3.45 (p=0.023, HR 0.29, 95% CI: 0.10-0.84) and *BRAF*/*KIT*/*RAS* mutation (p=0.028, HR 0.24, 95% CI: 0.07-0.86) were independently correlated with prolonged OS.

## **Safety**

The most common AEs were hematologic AEs, including white blood cell count decreased (20/43, 46.5%), neutrophil count decreased (17/43, 39.5%), platelet count decreased (17/43, 39.5%) and anemia (7/43, 16.3%), as shown in Table 2. Other common AEs included nausea (14/43, 32.6%), vomiting (12/43, 27.9%), liver injury (3/43, 7.0%), fatigue (3/43, 7.0%) and kidney injury (3/43, 7.0%). Among all grade  $\geq 3$  AEs, platelet count decreased (8/43, 18.6%), white blood cell count decreased (6/43, 14.0%), and neutrophil count decreased (6/43, 14.0%) were the most frequently observed. Grade 3 hypertension and bleeding were observed (one each, 2.3%). No treatment-related deaths occurred.

### **Subsequent treatment**

As of Sep 30, 2020, 32 patients had experienced disease progression. Among them, 23 were subsequently treated with anti-PD-1/PD-L1 antibody alone or in combination with VEGFR-predominant tyrosine kinase inhibitors (TKIs); four underwent salvage chemotherapy, two patients harboring *BRAF* mutations were subsequently treated with vemurafenib, and one harboring a *KIT* mutation was treated with imatinib.

## **Discussion And Perspectives**

Mucosal melanoma is a distinct and rare subtype of melanoma that presents in unique and often concealed anatomic locations, which results in more advanced stage at diagnosis. Local recurrence and metastatic spread commonly occur after surgical resection, with recurrence rates as high as 50-90%.<sup>24</sup> Thus, the survival rate for this population is dismal overall. Due to the rarity, to date, no consensus guidelines have been formulated on the optimal systemic therapy for mucosal melanoma.

Dacarbazine and temozolomide are longstanding cytotoxic agents used in the treatment of advanced-stage melanoma. The ORRs in patients with metastatic melanoma are 12.1% and 13.1% with temozolomide and dacarbazine monotherapy, respectively.<sup>25</sup> Despite the increase in ORR with polychemotherapy, no significant improvement in OS has been detected.<sup>26</sup> Both agents are widely applied in patients with mucosal melanoma. However, limited efficacy data are available regarding these chemotherapeutic agents in mucosal melanoma patients. Although some evidence suggests that the response rate of mucosal melanoma is equivalent to that of cutaneous melanoma, worse outcomes have been reported in patients with mucosal melanoma treated with similar dacarbazine-based regimens.<sup>24,27</sup>

Previously, the efficacy and safety of the Endostar plus dacarbazine regimen was explored in a phase 2 randomized study in patients with metastatic melanoma. A response was observed in 5 of the 56 (8.9%) patients receiving Endostar plus dacarbazine treatment. The PFS and OS durations of this group were 4.5 and 12.0 months,<sup>23</sup> respectively, which were slightly lower than those of the present cohort (PFS, 4.9 months; OS, 15.3 months). Noticeably, different from this phase 2 study, which included all treated metastatic melanoma patients (16 [14.5%] of which were mucosal melanoma patients), our study applied combination chemotherapy and focused on patients with advanced or recurrent mucosal melanoma, a population with a devastating prognosis and limited treatment options. The results of our study indicate

the acceptable safety profile of the Endostar plus chemotherapy combination and highlight the promising activity of this combination.

Different from the conventional administration route, we used continuous Endostar infusion in addition to chemotherapy. Indeed, Endostar delivered by continuous intravenous injection has been explored previously. In a combined report from two phase 2 trials, Ma HL et al. described the favorable efficacy and safety profile of continuous intravenous Endostar (7.5 mg/m<sup>2</sup>/24 hours, 120 hours) in unresectable stage III NSCLC.<sup>28</sup> Continuous Endostar infusion (7.5 mg/m<sup>2</sup>/day or 15 mg/m<sup>2</sup>/day 1-14) has also been investigated in patients with metastatic acral melanoma. The preliminary results of this study were presented at ASCO 2015, demonstrating that dacarbazine in combination with continuous Endostar infusion was well tolerated and efficacious in the 20 patients involved, with an expected median PFS of approximately 6 months.<sup>29</sup> Further detailed data from this study are still awaited. Likewise, the real-world data of the present study showed the potential benefit of combining continuous Endostar infusion with chemotherapy in patients with advanced or recurrent mucosal melanoma. Notably, despite the median PFS of 4.9 months for the entire cohort, patients (n=8) receiving concurrent/sequential radiotherapy or anti-PD-1 maintenance treatment achieved a median PFS of 12.1 months (95% CI 4.0 - 20.0), which provides clues for further study.

Recently, the use of ICIs has been well established in melanoma, with pembrolizumab and nivolumab approved as standard first-line therapies in advanced cutaneous melanoma. However, the poor efficacy of ICIs has been reported in mucosal melanoma,<sup>3</sup> with an even more disappointing ORR in Chinese patients (ORR 0-13.3%).<sup>30,31</sup> More recently, toripalimab in combination with a multitarget tyrosine kinase inhibitor has demonstrated increased efficacy compared to that of current treatments. With an ORR of 48.3% and a median PFS of 7.5 months in mucosal melanoma in a phase I trial, toripalimab plus axitinib has achieved orphan-drug designation by US Food and Drug Administration.<sup>32</sup> Nevertheless, a similar combination, toripalimab plus vorolanib (CM082), exhibited an ORR of 22.2% in the preliminary results of a phase II trial.<sup>33</sup> Thus, more data are warranted to identify the optimal first-line treatment regimen for mucosal melanoma.

LMR, derived from routine blood tests, has been suggested to reflect the host immune system and correlate with clinical outcomes in various cancers.<sup>34-36</sup> In melanoma, LMR has been indicated as a prognostic predictor of advanced melanoma treated with chemotherapy or checkpoint inhibitors.<sup>37-39</sup> Few studies have focused on the correlation between LMR and the survival of patients with mucosal melanoma.<sup>40</sup> Our study suggests that a high LMR is a strong indicator for favorable PFS and OS in patients with advanced and recurrent mucosal melanoma. Future studies on incorporating the LMR into the prognostication process are warranted to better stratify patient risk. Additionally, specific therapies targeting systemic inflammation may be an effective option in patient subsets with a low LMR, which warrants further exploration.

In a previous cohort, the association of mutations and survival was investigated among patients with sinonasal mucosal melanoma,<sup>41</sup> and no impact of mutation was found on patient survival. Noticeably, in the present study, the multivariate analysis results suggested that mutations were associated with favorable OS but not PFS, which could be explained by the subsequent use of targeted therapies, such as imatinib and vemurafenib. Such individual examples were observed in this cohort. One patient harboring the *CKIT* mutation progressed after two cycles of Endostar-containing treatment and was given 8 cycles of imatinib plus nab-paclitaxel/carboplatin. He achieved a PR following this treatment and was alive at the cutoff of this study.

There are several limitations to this study. In addition to the retrospective nature of the study, the missing detailed information regarding the initial surgery, along with anti-PD-1 maintenance and radiotherapy, may have introduced difficulties and bias in the data analysis. Additionally, the number of patients included was small, and the follow-up period was relatively short. Nevertheless, the size of the study provided reasonable confidence in the findings despite the above limitations.

In summary, our study demonstrated the promising activity and acceptable safety profile of continuous Endostar infusion in combination with chemotherapy in the treatment of advanced or recurrent mucosal melanoma. These real-world data confirmed that a high LMR was correlated with favorable PFS and OS in this patient population. The detailed mechanisms of Endostar for the treatment of mucosal melanoma, its impact on the immune system and its use in combination with immunotherapy are worth investigations in the near future.

## **Declarations**

### **Acknowledgements**

Not applicable

### **Authors' contributions**

SYJ, XWZ and FJ drafted the manuscript. ZGL and XL supervised and revised the manuscript. All authors read and approved the final manuscript.

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### **Availability of data and materials**

All data of this study are available per the corresponding author's approval.

### **Ethics approval and consent to participate**

Not applicable.

## Consent for publication

All authors approved the final manuscript for publication.

## Competing interests

The authors declare that they have no competing interests.

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## Tables

Table 1  
Patient demographics and clinical characteristics.

	Number of patients	%
Age		-
Median (range)	61 (25–74)	-
Sex		
Male	17	39.5
Female	26	60.5
Stage		
Metastatic	31	72.1
Unresectable	12	27.9
Site		
Gastrointestinal tract	22	51.2
Sinonasal tract	14	32.6
Genitourinary tract	6	14.0
Metastases		
Liver	15	34.9
Lung	12	27.9
Bone	10	23.2
LDH level		
Elevated	9	20.9
Normal	33	76.7
NA	1	2.3
Mutation		
Wild type	25	64.1
BRAF*	3	7.7
CKIT	2	5.1
NRAS	9	23.1

\* BRAF mutations included BRAF V600E, BRAF G606E and T599del mutations.

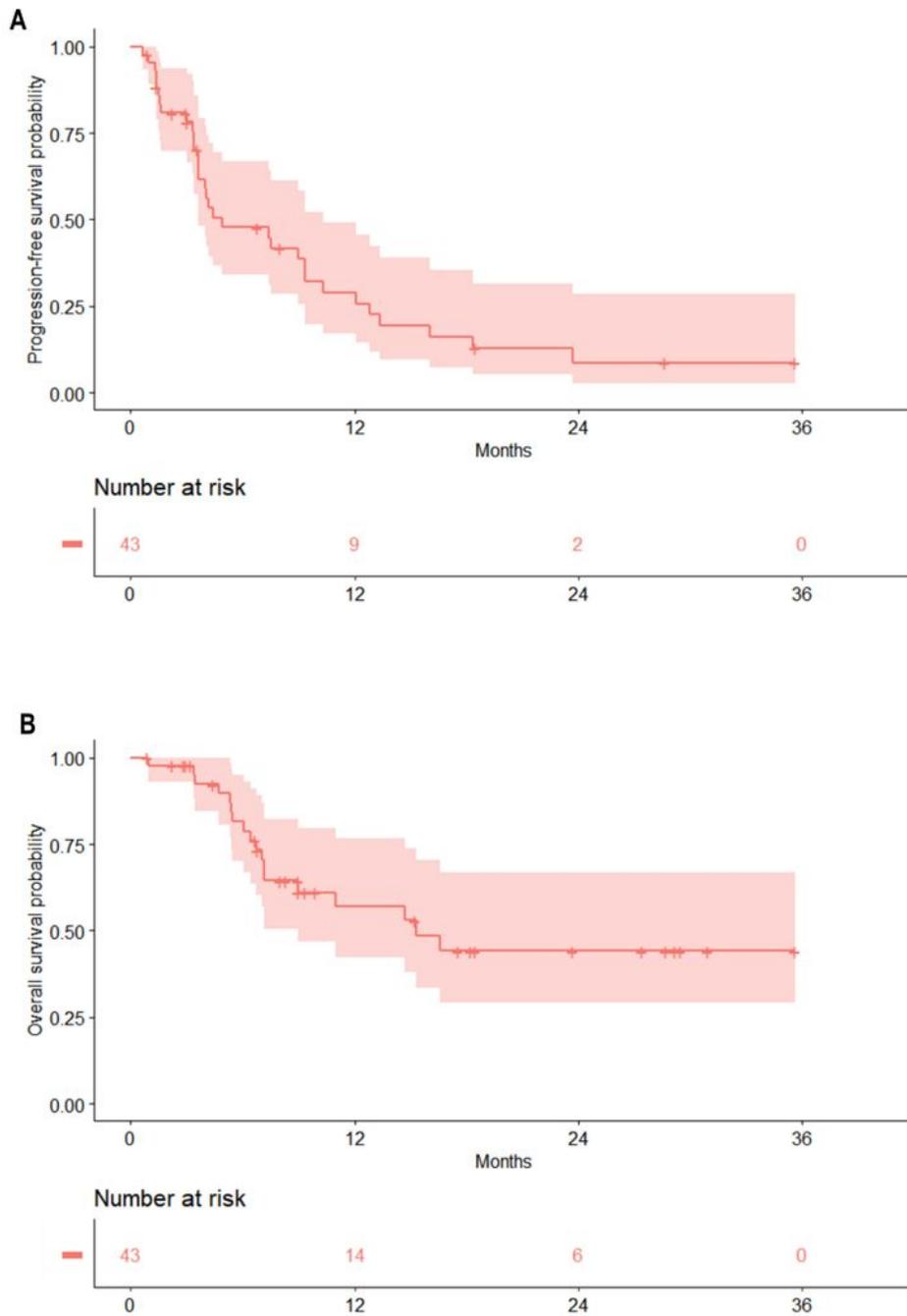
	Number of patients	%
NA	4	9.3
* BRAF mutations included BRAF V600E, BRAF G606E and T599del mutations.		

Table 2

Adverse events of any grade reported in at least 5% of patients and all reports of adverse events of grade 3–4.

Adverse event	Grade 1–2	Grade 3	Grade 4
White blood cell count decreased	14 (31.8%)	4 (9.1%)	2 (4.5%)
Neutrophil count decreased	11 (25.0%)	2 (4.5%)	4 (9.1%)
Platelet count decreased	9 (20.5%)	6 (13.6%)	2 (4.5%)
Anemia	5 (11.4%)	1 (2.3%)	1 (2.3%)
Nausea	11 (25.0%)	3 (6.8%)	0
Vomiting	10 (22.7%)	2 (4.5%)	0
Liver injury	2 (4.5%)	1 (2.3%)	0
Fatigue	3 (6.8%)	0	0
Kidney injury	3 (6.8%)	0	0
Hypertension	1 (2.3%)	1 (2.3%)	0
Paresthesia	3 (6.8%)	0	0
Bleeding	2 (4.5%)	1 (2.3%)	0

## Figures



**Figure 1**

Kaplan-Meier curve of progression-free survival (A) and overall survival (B) of the entire cohort.