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PHASE II STUDIES

Phase II study of avelumab in multiple relapsed/refractory germ cell cancer

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Summary

Background Germ cell tumors (GCTs) are highly curable diseases; however, not all patients can be cured. Patients in their second relapse have especially poor prognoses. PD-L1 expression is significantly higher in GCTs than in normal testicular tissue, and high PD-L1 expression is associated with a poor prognosis. This study aimed to determine the efficacy and safety of avelumab, a PD-L1 inhibitor, in patients with GCTs. *Methods* In this phase 2 study, patients with multiple relapsed and/or refractory GCTs were treated with avelumab at a dose of 10 mg/kg administered biweekly until progression or unacceptable toxicity. The primary endpoint was 12-week progression-free survival (PFS). Fifteen evaluable patients had to be enrolled in the first cohort, and if <8 of 15 patients had 12-week PFS, the study was to be terminated. Here, we report the results of the first stage of the trial. *Results* From November 2017 to January 2018, 8 patients with a median age of 29 years (range, 22 to 52 months) were enrolled. Patients were pretreated with a median of 5 (range, 1 to 6) previous lines of platinum-based therapies; 5 tumors (62.5%) were absolutely refractory to cisplatin, and 5 patients (62.5%) had visceral nonpulmonary metastases. At a median follow-up period of 2.6 months (range, 0.3 to 14.4), all the patients experienced disease progression, and 7 patients (87.5%) died. The twelve-week PFS was 0%, median PFS was 0.9 months (95% CI 0.5–1.9), and median OS was 2.7 months (95% CI 1.0–3.3). Avelumab was well tolerated, and no severe adverse events were observed. *Conclusions* This study failed to achieve its primary endpoint. Our data suggest a lack of avelumab efficacy in unselected multiple relapsed/refractory GCTs.

Keywords Avelumab · Germ cell tumors · Immune checkpoint inhibitors · PD-L1 expression · Refractory germ cell tumors

Introduction

Patients with germ cell tumors (GCTs) may potentially be cured by chemotherapy alone or chemotherapy followed by surgery (Einhorn 1990, Motzer, Geller et al. 1991, Einhorn 1993). With a first relapse, a cure can still be achieved with the use of platinum-based chemotherapy but only in 40–50% of cases [1–5]. Those patients who relapse after second-line therapy have, however, a very low chance for cure. They are usually treated with other chemotherapies not used previously [6, 7]. Anti PD1/L1 immune checkpoint inhibitors are novel, ground-breaking anticancer therapies. Several immune checkpoint inhibitors have already been approved for the treatment of patients with different types of cancer, such as urothelial, lung, renal, head and neck cancer, melanoma and Hodgkin's lymphoma. In some types of tumors, PD1/L1 expression is associated with the efficacy of PD1/L1 checkpoint inhibitors [8]. Data exist about increased efficacy in cases of PD-L1 expression in nonsmall cell lung cancer but not in renal cell carcinoma and melanoma [9–11]. PD-L1 overexpression was detected in 73% of

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seminomas and 64% of nonseminomatous tumors but not in normal testicular tissue [12]. Additionally, in another study using tissue samples from 140 GCT patients, the expression of PD-L1 was significantly higher in GCTs when compared with normal testicular tissue (mean quickscore [QS] = 5.29 vs. 0.32, $p < 0.0001$) [13]. The highest level of PD-L1 expression was detected in choriocarcinomas followed by embryonal carcinoma, teratoma, yolk sac tumor and seminoma. PD-L1 expression was shown to be associated with poor prognostic features, such as nonpulmonary visceral metastases, 3 or more metastatic sites or increased tumor markers. Patients with low PD-L1 expression presented with significantly better progression-free survival (PFS) (hazard ratio [HR] = 0.40, 95% CI 0.16–1.01, $p = 0.008$) and overall survival (OS) (HR = 0.43, 95% CI 0.15–1.23, $p = 0.040$) [13]. Moreover, we observed that PD-L1-expressing tumor-infiltrating lymphocytes (TILs) were prognostic in GCTs [14].

Avelumab is a fully human IgG1 anti-PD-L1 monoclonal antibody that targets PD-L1 and thus inhibits the interaction between PD-L1 and its receptors. This interaction leads to increased activity and quality of the tumor-specific T cell response, which results in higher antitumor activity. Avelumab has already demonstrated activity in different tumor types [15–18]. Based on the aforementioned data, we hypothesize that the PD-1/PD-L1 pathway could be efficiently targeted in GCT and lead to antitumor activity in patients with GCTs. The aim of this study was to assess the efficacy and safety of the anti-PD-L1 inhibitor avelumab in multiple relapsed/refractory testicular GCTs.

Patients and methods

Patients

Consecutive patients aged 18 years or older with multiple relapsed/refractory extracranial primary GCTs (either seminoma or nonseminoma) were eligible for the study. The patients had to be pretreated with cisplatin-based chemotherapy, and primary mediastinal GCTs in their first relapse could also be included. Other inclusion criteria included radiologically measurable disease; disease incurable with either surgery or chemotherapy; and adequate hematologic, liver and renal function (for details see clinicaltrials.gov). The main exclusion criteria were previous treatment with anti-PD1/L1 inhibitor and hypersensitivity to any compound of the drug. Patients with brain metastases could be included only when the brain metastases were controlled with local treatment (whole brain radiation, stereotactic radiation and/or surgery). The study protocol was reviewed and approved by the Ethical Committee of the National Cancer Institute in Bratislava, Slovakia. The study has been registered in the Database of Clinical Trials, and the ClinicalTrials.gov Identifier is NCT03403777. All the patients were required to provide written informed consent before enrollment.

Pretreatment evaluation

All the patients were thoroughly evaluated with a complete medical history, physical examination, and laboratory and disease assessment. Brain imaging and bone scans were performed only in symptomatic patients.

Drug administration

Avelumab was administered intravenously at 10 mg/kg every 2 weeks. Courses were repeated every 14 days until progression or unacceptable toxicity. Avelumab was administered as a 1-h intravenous infusion. The dose of avelumab was calculated based on the weight of the subject determined on the day prior to or the day of each dose administration. Premedication included H1 blockers and paracetamol (acetaminophen) 30 min before avelumab administration. Dose reduction to 3 mg/kg every 2 weeks was allowed, depending on the type and severity of toxicity encountered.

Duration of therapy

The treatment was administered until disease progression, unacceptable toxicity or complete response. In cases of a partial response after every 4 cycles (8 weeks), radical surgical resection was considered.

Evaluation of response and toxicity

A physical examination was performed and vital signs were assessed before each treatment cycle. Laboratory parameters, including serum tumor markers, were evaluated prior to every other cycle and one month after the end of treatment. Disease response assessment by CT scan was performed every 4 cycles (2 months).

The patients who received at least one dose of avelumab were evaluated for their response according to standard RECIST (Response Evaluation Criteria In Solid Tumors) Criteria version 1.1 [19]. Twelve-week PFS was the primary endpoint of the study [6]. The treatment was terminated in cases of disease progression, which was defined as significant marker progression (more than 50% increase) and/or radiological progression. Overall survival was measured from the initiation of therapy. Toxicity was assessed after

each cycle of therapy and scored using NCI-CTC Criteria (National Cancer Institute-Common Toxicity Criteria) version 4.1.

Role of sponsor

The sponsor of the study was the National Cancer Institute of Slovakia. Avelumab was provided by Merck/Pfizer for this investigator-initiated study. Merck/Pfizer had no influence on the study design, treatment evaluation and/or statistical analysis of the study data.

Statistical considerations

Statistical and analytical plan

This phase II study aimed to determine the efficacy of avelumab in patients with multiple relapsed/refractory GCT with a two-stage phase II design. The study was planned to accrue up to 43 eligible patients. The primary endpoint was 12-week PFS.

Study design, significance level and power

This was an open-label, nonrandomized, single-center phase II trial to study the efficacy and safety of avelumab in patients with multiple relapsed/refractory GCTs. The evaluation of eligible patients included all the patients who received at least one dose of the study drug. To determine the number of required patients, an optimal Simon two-stage design was used. Assuming a 12-week PFS of clinical interest ≥70% and a minimal 12-week PFS equal to 50%, a probability of 20% for rejecting an active drug combination (type II error), and a probability of 5% to further evaluate an ineffective drug combination (type I error), 15 evaluable patients were enrolled in the first cohort. If fewer than 8 patients among the first 15 patients were alive and progression-free at 12 weeks, the study would be terminated. If a PFS at 12 weeks occurred in at least 8 patients, the study would continue with a second cohort of another 28 patients. The treatment would be considered effective if a 12-week PFS was observed in ≥26 out of 43 patients.

Statistical analysis

The study population was summarized using the mean or median (range) for continuous variables and the frequency (percentage) for categorical variables. The median follow-up period was calculated as the median observation time among all the patients and among those still alive at the time of their last follow-up. The PFS was calculated from the date of starting the treatment with avelumab to the date of progression or death or to the date of the last follow-up. The OS was calculated from the date of starting the treatment with avelumab to the date of death or last follow-up. The PFS and OS were estimated using the Kaplan–Meier product-limit method. Statistical analyses were performed using NCSS 10 (2015) software (Hintze J, 2015, Kaysville, Utah, USA).

Table 1 Patient characteristics

	N	%
Patients	8	100.0
Histology		
Seminoma	0	0.0
Nonseminoma	8	100.0
Primary tumor		
Gonadal	7	87.5
Retroperitoneal	1	12.5
Mediastinal		
IGCCCG risk group before 1st line of therapy		
Good prognosis	2	25.0
Intermediate prognosis	3	37.5
Poor prognosis	3	37.5
Number of previous lines of therapy		
1 line	1	12.5
2 lines	2	25.0
>3 lines	5	62.5
Sensitivity to cisplatin		
Sensitive	3	37.5
Resistant	0	0.0
Refractory	5	62.5
Sites of metastases		
Retroperitoneum	3	37.5
Other lymphadenopathy	4	50.0
Brain	0	0.0
Liver	4	50.0
Lung	6	75.0
Bone	2	25.0
Visceral nonpulmonary metastases	5	62.5
Number of metastatic sites		
1	0	0.0
2	4	50.0
>3	4	50.0
Mean (range) of pretreatment markers		
AFP mIU/mL	4460 (0–33,218)	
βHCG IU/mL	18,221 (0–122,025)	
LDH (μkat/L)	15 (2–64)	

Abbreviations: *βHCG* beta-human chorionic gonadotropin, *AFP* alfa-fetoprotein, *LDH* lactate dehydrogenase, *IGCCCG* International Germ Cell Cancer Collaborative Group

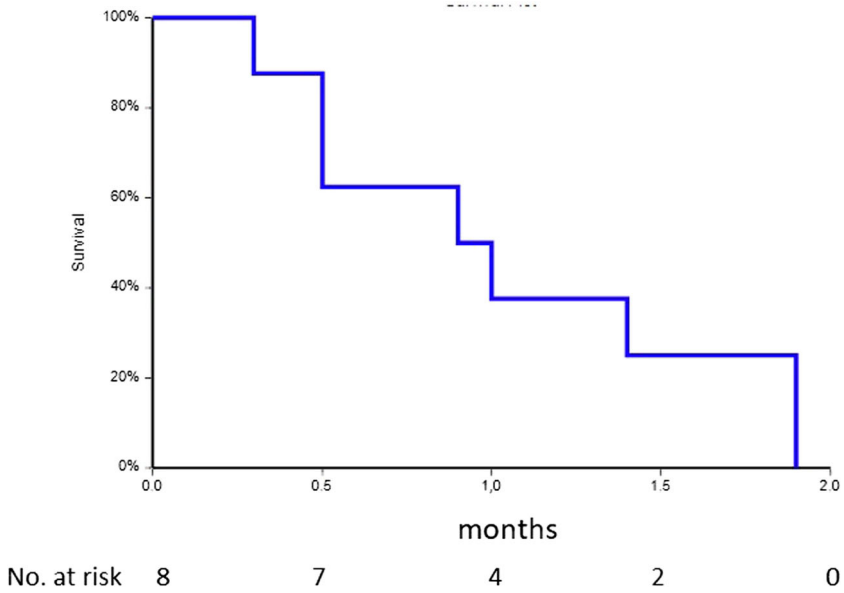

Fig. 1 Kaplan–Meier estimates of progression-free survival (median PFS = 0.9 months, 95% CI: 0.5–1.9)

Results

Patient characteristics

In total, 8 patients were enrolled in the study at the National Cancer Institute of Slovakia from November 2017 to January 2018. The patient characteristics are summarized in Table 1. The majority of patients had cancer of nonseminoma histology (1 embryonal carcinoma, 1 choriocarcinoma, 1 yolk sac tumor, 1 immature teratoma and 4 mixed germ cell tumor). All were heavily pretreated with a median of 5 (range, 1–6) previous lines of platinum-based chemotherapy. Two patients (25%) were pretreated with high-dose chemotherapy with autologous stem cell support. Five of 8 patients (62.5%) showed absolute platinum refractoriness [20], and 62.5% of patients had nonpulmonary visceral metastases. The median number of metastatic sites was 3 (range, 2–6). The median age was 29 years (range, 22–52 years). The median time from the diagnosis of metastatic disease to the start of avelumab was 44 months (range, 7–238 months). Six patients (75%) had ECOG PS (eastern cooperative oncology group performance status) 1, while two had ECOG PS 0.

Response and survival

The twelve-week PFS in the first 8 included patients was 0%; therefore, the study was terminated based on futility. According to the statistical design, 15 patients were enrolled in the first cohort, and if fewer than 8 patients were progression-free at 12 weeks on the study therapy, the study

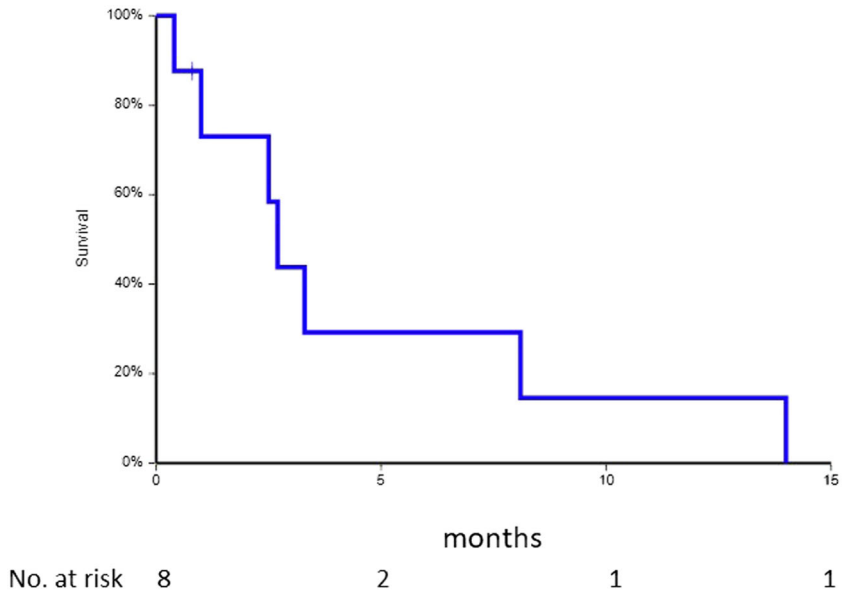

Fig. 2 Kaplan–Meier estimates of overall survival (median OS = 2.7 months, 95% CI: 1.0–3.3 months)

was to be terminated. Given that none of the first 8 patients were progression free at 12 weeks, the study was terminated prematurely. Even when all the subsequently included patients were progression free at 12 weeks, the primary endpoint could not be reached.

No objective response or disease stabilization was observed, and no patients achieved a tumor marker response, defined as more than a 50% decline. During a median follow-up period of 2.6 months (range: 0.3–14.4 months), all the patients experienced disease progression, and 7 (87.5%) died. The twelve-week PFS was 0%, median PFS was 0.9 months (95% CI 0.5–1.9 months) and median OS was 2.7 months (95% CI 1.0–3.3 months). The Kaplan–Meier PFS and OS survival curves are presented in Figs. 1 and 2**.** Three (37.5%) patients received subsequent treatment, including oral etoposide (2 patients) and cisplatin, etoposide and ifosfamide(1 patient). However, no treatment response was documented.

Adverse events

Avelumab was well tolerated by the population of patients with refractory GCTs. No serious adverse event (SAE) or grade 4 AEs were recorded. The grade 3 AEs included tumor-related pain ($N = 3$), anemia ($N = 1$), cachexia (N = 1), hypoalbuminemia (N = 1), thrombocytopenia (N = 1), acute urine retention (N = 1), dyspnea (N = 1) and fatigue (N = 1). None of the adverse events were related to avelumab administration.

Discussion

This phase II study failed to achieve its primary endpoint, and avelumab showed a lack of activity in this patient population. Avelumab showed good tolerability; however, no treatment response was observed, and patient survival was very short.

The introduction of cisplatin-based chemotherapy to the treatment of GCT substantially improved the outcome of this patient population; however, the treatment results of platinum-refractory GCT remain unsatisfactory. Numerous new treatment regimens, including targeted and biological therapies, have been evaluated in patients with refractory GCT; however, the activity of most new treatments is only modest, with a durable response observed in only a minute fraction of cases [21–25]. A meta-analysis of seven phase II trials analyzed the effectiveness of several agents used in monotherapy [6] and showed that the median PFS and OS were only 1.0 month and 4.7 months, respectively, which is consistent with the results of the present trial.

Immune checkpoint inhibitors are very promising in modern anticancer treatment and have shown efficacy with manageable toxicity in the treatment of different malignancies, including renal cell carcinoma, nonsmall cell lung cancer, melanoma and many others [8, 10, 11, 16, 18]. PD-L1 showed overexpression in GCTs and TILs in GCTs, and it is prognostic in this patient population, as well [12–14]. However, despite the biological rationale, avelumab failed to show clinically meaningful activity in patients with refractory GCTs. This observation is consistent with the results of similar phase II studies evaluating pembrolizumab or durvalumab with tremelimumab [26, 27], which contradicts previously published case reports and small series [28, 29]. One possible explanation may be that inhibition of the immune checkpoint is insufficient to abrogate immune tolerance in GCTs. A low mutation burden in GCTs [30] and consequent low number of neoantigens also could contribute to this lack of clinical meaningful activity. It seems that single or combined therapy with immune checkpoint inhibitors is associated with limited efficacy in refractory GCTs. However, we cannot exclude the possibility that the combination of immunotherapy with conventional chemotherapy and/or their application in earlier lines of treatment may be more efficacious.

In conclusion, this prospective phase II clinical trial failed to achieve its primary endpoint, and the data showed that avelumab lacked activity in unselected patients with multiple relapsed/refractory GCTs. New treatment strategies and the therapeutic challenge of new treatment targets, such as aldehyde-dehydrogenase or DNA methylation, are eagerly anticipated.

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Author contributions M-M, MC-C, U-DG and J-M participated in the conception and design of this study. D-S and M-R participated in data validation, and K-R, J-O, P-P, and Z-SM acquired, analyzed and interpreted the data. M-M drafted the article, and all the authors reviewed it critically for its important intellectual content.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All the procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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