Original Article

Phase II Trial of Pembrolizumab in Patients with Platinum Refractory Germ Cell Tumors: A Hoosier Cancer Research Network Study GU14-206

Nabil Adra[1], Lawrence H. Einhorn[1], Sandra K. Althouse[2], Natraj R. Ammakkanavar[1], Dana Musapatika[3], Costantine Albany[1], David Vaughn[4], Nasser H. Hanna[1]

[1]Melvin & Bren Simon Cancer Center, Indiana University School of Medicine, Indianapolis, Indiana.

[2]Department of Biostatistics - Indiana University School of Medicine, Indianapolis, Indiana.

[3]Hoosier Cancer Research Network, Indianapolis, Indiana

[4]University of Pennsylvania Abramson Cancer Center, Philadelphia, Pennsylvania

Running head: Pembrolizumab in refractory germ cell tumors

Keywords: Testicular cancer; Germ cell tumor; Pembrolizumab; Immunotherapy; Checkpoint inhibitors

Corresponding Author:

Dr. Nabil Adra

Email: nadra@iu.edu

Address: 535 Barnhill Drive, RT 400, Indianapolis, IN 46202

Telephone: 317-944-5349; Fax: 317-944-3684

Number of manuscript pages: 15

Total number of words in abstract: 274

Total number of words in text: 2,195

Number of references: 28

Number of tables: 2

Number of figures: 1

Number of tables online only: 0

Number of figures online only: 0

This is the author's manuscript of the article published in final edited form as:
Adra, N., Einhorn, L. H., Althouse, S. K., Ammakkanavar, N. R., Musapatika, D., Albany, C., … Hanna, N. H. (2018). Phase II trial of pembrolizumab in patients with platinum refractory germ-cell tumors: a Hoosier Cancer Research Network Study GU14-206. Annals of Oncology, 29(1), 209–214. https://doi.org/10.1093/annonc/mdx680

Conflict of interest statement: the authors have no conflicts of interest to report

Funding: Merck & Co.

- Presented in part at the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, June 2017. Poster Discussion Session.

ABSTRACT

Background

Despite remarkable results with salvage standard-dose or high-dose chemotherapy about 15% of patients with relapsed germ-cell tumors (GCT) are incurable. Immune checkpoint inhibitors have produced significant remission in multiple tumor types. We report the first study of immunotherapy in patients with GCT.

Patients and Methods

Single arm phase 2 trial investigating pembrolizumab 200mg IV Q3weeks until disease progression in patients with relapsed GCT and no curable options. Patients age≥18 with GCT who progressed after first-line cisplatin-based chemotherapy and after at-least 1 salvage regimen (high-dose or standard-dose chemotherapy) were eligible. Centrally assessed programmed death-ligand 1 (PD-L1) on tumor and infiltrating immune cells was scored. Primary endpoint was overall response rate (ORR) using immune-related response criteria. Simon two-stage design with type I error 20% and power 80% was utilized.

Results

12 male patients were enrolled. Median age 38. All patients had non-seminoma. Primary site was testis (11) or mediastinum (1). Median AFP 615 (range,1-32,760) and hCG 4 (range,0.6-37,096). 6 patients had late relapse (>2years). Median number of previous chemotherapy regimens was 3. 6 patients received prior high-dose chemotherapy. 2 patients had positive PD-L1 staining (H-score 90 and 170). Median number of pembrolizumab doses was 2 (range,1-8). There were 6 grade 3 adverse

events. No immune-related adverse events were reported. No partial or complete responses were observed. 2 patients achieved radiographic stable disease for 28 and 19 weeks, respectively; both had continued rising AFP level despite radiographic stability and had negative PD-L1 staining.

Conclusion

This is the first reported trial evaluating immune checkpoint inhibitors in GCT. Pembrolizumab is well tolerated but does not appear to have clinically meaningful single-agent activity in refractory GCT.

Clinical trial information:NCT02499952.

Key Message

In this phase II trial, pembrolizumab was well tolerated but did not appear to have single agent activity in refractory germ cell tumors. Two patients had stable disease while the rest had progressive disease as best response. Programmed death-ligand 1 (PD-L1) staining was positive in 2 patients.

INTRODUCTION

Germ-cell tumors (GCT) are remarkably chemosensitive and up to 80% of patients with metastatic disease will be cured with cisplatin-based combination chemotherapy.[1] Patients who relapse after initial chemotherapy can still be cured with salvage therapy including salvage surgery, standard dose chemotherapy, or high-dose chemotherapy plus peripheral-blood stem cell transplant (PBSCT).[2-7] Despite the high cure rates with frontline and salvage chemotherapy, there remains a 15-20% cohort of patients with metastatic GCT who are incurable with the current therapeutic options. Novel therapeutic approaches are needed for these patients.

Monoclonal antibodies against programmed death 1 (PD-1) and its ligands (PD-L1 and PD-L2) have demonstrated robust activity and manageable toxicity in many advanced tumors including melanoma, lung, kidney, urothelial, and other malignancies.[8-11] Pembrolizumab is a highly selective, humanized monoclonal IgG4κ isotype antibody against PD-1 which can disrupt the engagement of PD-1 with its ligands and impede inhibitory signals in T cells.

Frequent PD-L1 expression has been reported in tumor samples from testicular cancer patients suggesting that these patients could potentially benefit from immunotherapy approaches with PD-1 or PD-L1 inhibition.[12] In addition, a prognostic value has been suggested for PD-L1 expression on testicular GCT indicating that patients with high PD-L1 expression were more likely to have poor clinical features and worse survival outcomes.[13] Case series have been reported regarding possible activity of PD-1 inhibitors in combination with chemotherapy in a small sample of 4 patients with platinum refractory GCT.[14]

Immune therapy with Pembrolizumab is a novel approach for salvage in patients with metastatic GCT. In a multicenter single-arm open-label phase II trial conducted within the Hoosier Cancer Research Network, we evaluated the efficacy and safety of pembrolizumab in patients with refractory GCT with no further curative treatment options.

PATIENTS AND METHODS

Patients

Eligible patients had histologically confirmed metastatic GCT (seminoma or non-seminoma histology) who progressed after first-line cisplatin-based chemotherapy and after at-least one salvage regimen: standard-dose chemotherapy or high-dose chemotherapy plus peripheral-blood stem-cell transplant. Relapsed patients who are not eligible for salvage chemotherapy (e.g. late relapse of disease) were also included in this study. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 was required (on a 5-point scale, with 0 indicating no symptoms and higher numbers indicating greater disability). Patients had measurable metastatic disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 and/or elevation of tumors markers (alpha-fetoprotein [AFP] and/or β-human chorionic gonadotropin [β-hCG]).[15] If a rising tumor marker was the only evidence of progressive disease, 2 consecutive rising values at least one week apart were required. Patients with treated brain metastases were eligible. Treatment with systemic corticosteroids or immunosuppressants within 7 days of first trial treatment was not permitted. All patients were required to provide archived tumor tissue from a biopsy or the original primary tumor for PD-L1 expression evaluation and other exploratory

analyses. Patients were eligible irrespective of PD-L1 staining result. Patients were ineligible if they had received anti-PD-1 or anti-PD-L1 therapy previously. Full eligibility criteria are listed in the trial protocol, available online with the full text of this article.

Pretreatment Evaluation

Pretreatment evaluation included complete history and physical examination, performance status, complete blood count, comprehensive metabolic profile, serum tumor markers (AFP and hCG), creatinine clearance, electrocardiogram, and computed tomography (CT) scan of the chest, abdomen, and pelvis.

Treatment Program

Planned treatment consisted of pembrolizumab 200mg administered intravenously (IV) every 3 weeks. Pembrolizumab was provided by Merck & Co., the supporter of this investigator initiated phase II trial. Treatment was continued until documented disease progression, development of unacceptable level of toxic effects, withdrawal of consent, decision by investigator to discontinue treatment, or the completion of 52 weeks of pembrolizumab therapy.

Evaluation of Response and Toxicity

Patients were assessed on day 1 of each 3-week cycle. A complete blood count, complete metabolic panel, and tumor markers were determined on day 1 of each cycle. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Tumor imaging was performed at baseline followed by every 6 weeks for the initial 18 weeks. Subsequently, imaging was spaced

to every 12 weeks until discontinuation of study drug. The full assessment schedule is provided in the trial protocol.

PD-L1 expression was assessed in formalin-fixed archived tumor samples at a central laboratory with the use of the commercially available PD-L1 IHC 22C3 assay. PD-L1 expression was scored as 0 (no staining), 1 (weak staining), 2 (moderate staining), 3 (intense staining) along with categorized PD-L1 combined positive score, defined as the percentage of PD-L1-expressing tumor and infiltrating immune cells relative to the total number of tumor cells (H-score).

Endpoints and Statistical Analysis

The primary endpoint was overall response rate (ORR) using immune related response criteria (irRC).[16] Secondary endpoints were ORR using RECIST version 1.1, to assess toxicity and tolerability of pembrolizumab, and to estimate the duration of disease response.[15] Exploratory objectives included assessment of prevalence of PD-L1 expression in tumor tissue and correlate with tumor response to treatment. Efficacy was assessed in the intention-to-treat population, which included all the patients who were assigned to the treatment group. Safety was assessed in the as-treated population, which included all the patients who received at least one dose of study treatment.

A Simon two-stage optimal design with type I error rate of 20% and power of 80% was utilized.[17] The null hypothesis was an ORR of ≤ 10% and the alternate hypothesis was ORR ≥ 15%. Consequently, 12 subjects were enrolled in the first stage. If no responses are determined in the initial stage, the study will be concluded. If at least 1

patient achieved a partial or complete response, then the treatment will be considered worthy of further investigation and 8 more subjects will be accrued in the second stage for a total sample size of 20 subjects. If there are 3 or more subjects with partial or complete response, then the treatment regimen would be considered a success. Statistical analyses were performed using SAS software, version 9.4. The data cutoff was February 2017. The study schema is depicted in figure 1.

RESULTS

Patient and Disease Characteristics

Twelve patients were enrolled between March and October 2016. Patient characteristics are provided in Table 1. Median age was 38 years (range, 27 to 55 years) and all patients were male. Primary tumor sites was testis in 11 patients (92%) and mediastinal non-seminoma in 1 patient (8%). All patients had non-seminoma histology. Tumor markers were elevated in all patients: AFP only in 3, hCG only in 3, both AFP and hCG were elevated in 6 patients. Metastatic sites included retroperitoneal lymph nodes in 5 patients, pulmonary metastasis in 9 patients, liver metastasis in 3 patients, brain and bone metastasis in 1 patient each. The median number of previous chemotherapy lines of treatment was 3 (range, 1 to 6). Six patients (50%) received prior high-dose chemotherapy and autologous stem-cell transplant as a previous line of therapy. Ten patients had received prior ifosfamide or paclitaxel-containing salvage chemotherapy regimens. Six patients (50%) had late relapse of disease defined as disease that relapsed more than 2 years after first-line cisplatin-based combination chemotherapy.

Treatment Administration

All 12 patients enrolled received at least one dose of pembrolizumab 200mg IV per study protocol. The median number of pembrolizumab doses was 2 (range, 1-8). Two patients received only 1 dose of pembrolizumab and had clear clinical disease progression at the time of the scheduled second dose. Eight patients received 2 doses of pembrolizumab and had disease progression at the 6 week interim evaluation. One patient received 6 doses and another patient received 8 doses of pembrolizumab.

Efficacy

No partial or complete responses were observed. Two patients achieved stable disease for 28 and 19 weeks, respectively. Both these patients had continued rising AFP values on treatment despite radiographic stability. One of these patients had late relapse with no response to previous salvage standard-dose chemotherapy (paclitaxel-ifosfamide-cisplatin [TIP] and paclitaxel-gemcitabine) before enrolling on this clinical trial. The second patient with radiographic stability did not have late relapse of disease and had slow progression after salvage standard-dose chemotherapy with TIP and gemcitabine-oxaliplatin. Ten patients had progressive disease as their best response. None of the patients on study had tumor marker decline while on treatment with pembrolizumab.

Per study protocol, at least 1 objective response was required to continue enrolling on the second stage of the study; therefore, the trial was closed at the completion of the first stage. At last follow-up, 6 of the 12 patients enrolled had died of disease progression.

Biomarker Analysis

Archival formalin-fixed paraffin-embedded tissue samples were available for correlative studies in all patients. Correlative studies were performed on samples from primary testicular tumor in 4 patients, retroperitoneal lymph nodes in 6 patients, bone metastasis biopsy sample in 1 patient, and lung metastasis biopsy sample in 1 patient. Immunohistochemistry staining of archival tumor samples was positive for PD-L1 expression in 2 patients: one patient with predominant embryonal carcinoma histology had 3+ staining in 30% of tumor cells formulating an H-score of 90. Another patient with predominant choriocarcinoma histology had 1+ staining on 50%, 2+ staining on 30%, and 3+ staining on 20% of tumor cells formulating an H-score of 170. Both these patients had progressive disease as their best response to therapy.

Toxicity

Pembrolizumab was tolerated by this patient population with 6 patients experiencing grade 3 adverse events. Four adverse events were possibly related to disease or study treatment. Grade 3 or higher and most commonly occurring adverse events are listed in Table 2. No grade 4 or 5 toxicities were observed. There were no immune-related adverse events observed.

DISCUSSION

In the current era, cisplatin-based combination chemotherapy will cure > 80% of patients with metastatic GCT.[18] 90% of patients with International Germ-Cell Cancer Collaborative Group (IGCCCG) good-risk disease will achieve cure with front-line chemotherapy. Patients with intermediate and poor-risk disease have less favorable outcomes and a significant proportion will relapse and require salvage therapy.[19]

High-dose chemotherapy plus PBSCT achieves cures in 60% of patients with relapsed metastatic GCT.[2, 3, 20] Patients who relapse after salvage standard-dose or high-dose chemotherapy have poor outcomes with no further curative options short of salvage surgery in patients with anatomically localized disease.[7, 21]

Understanding the mechanism(s) of resistance to treatment are desperately needed. Unfortunately, early studies with molecularly targeted therapies such as imatinib, sunitinib, thalidomide, and trastuzumab have yielded negative results.[22-25] More recently, studies with pazopanib have provided some signal of activity.[26]

Immunotherapy with PD-1 and PD-L1 inhibitors has demonstrated remarkable results in a variety of advanced solid malignancies after progression on standard-of-care treatment.[8-11] Preclinical investigations have shown that PD-L1 expression was present in 73% of all seminomas and 64% of non-seminomas.[12] Our study represents the first clinical trial investigating immunotherapy with checkpoint inhibitors as a novel approach in patients with platinum-refractory incurable GCT.

Pembrolizumab was tolerated in this study with no immune-related adverse events reported. Unfortunately, this clinical trial did not show clinical activity for pembrolizumab in patients with metastatic GCT who progressed after salvage chemotherapy. No objective responses were observed among the 12 patients enrolled; although 2 patients had radiographic stable disease for 28 and 19 weeks respectively, both had continued rising AFP level during treatment suggesting continued treatment resistance. PD-L1 expression was present on tumor samples from only 2 patients in this study. Both these patients had progressive disease as their best response.

Although this phase II trial investigated a novel approach for salvage in refractory GCT, there are limitations to report. The small cohort of patients limits the generalizability. Other studies are underway investigating single agent or combination checkpoint inhibition in patients with metastatic GCT. Immunohistochemistry staining for PD-L1 was performed on archival tumor tissues which may not represent the current immune status or the tumor microenvironment at the time of treatment with checkpoint inhibitor. In addition, PD-L1 expression from tumor metastatic sites was not performed and this might also be informative. The expression of PD-L1 is known to be dynamic and is regulated by extrinsic signaling such as release of interferon-γ by immune cells, loss of expression of tumor suppressor genes, or activation of the AKT-mTOR pathway.[27, 28] Moreover, this study was not a biomarker driven study since all patients were eligible irrespective of PD-L1 expression. Higher levels of PD-L1 expression have been associated with robust responses in certain advanced solid tumors such as melanoma and lung cancer but not in others.[10, 11] In addition, the protocol for this study mandated response assessment at 6 weeks, i.e. after 2 infusions of pembrolizumab at which time most patients had progressive disease. This might have been a short interval given our understanding that the immune checkpoint inhibitors have a median time to response of ≥ 2months.[8, 10] Nevertheless, patients on this study had clinical unequivocal rapid progression while on study treatment. Even though no immune-related adverse events were observed, the short duration of exposure to pembrolizumab with a median number of deliverable doses of 2 might influence that analysis.

In conclusion, this is the first reported clinical trial evaluating immune checkpoint inhibitors in testicular cancer. Single agent pembrolizumab did not demonstrate clinical benefit in this cohort of patients with refractory GCT. Further investigation requires evaluation of the mechanism of resistance and possible combination therapy.

ACKNOWLEDGEMENTS: none

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FIGURE LEGENDS

- Fig 1: Study schema

Table 1. Patient and Disease Characteristics

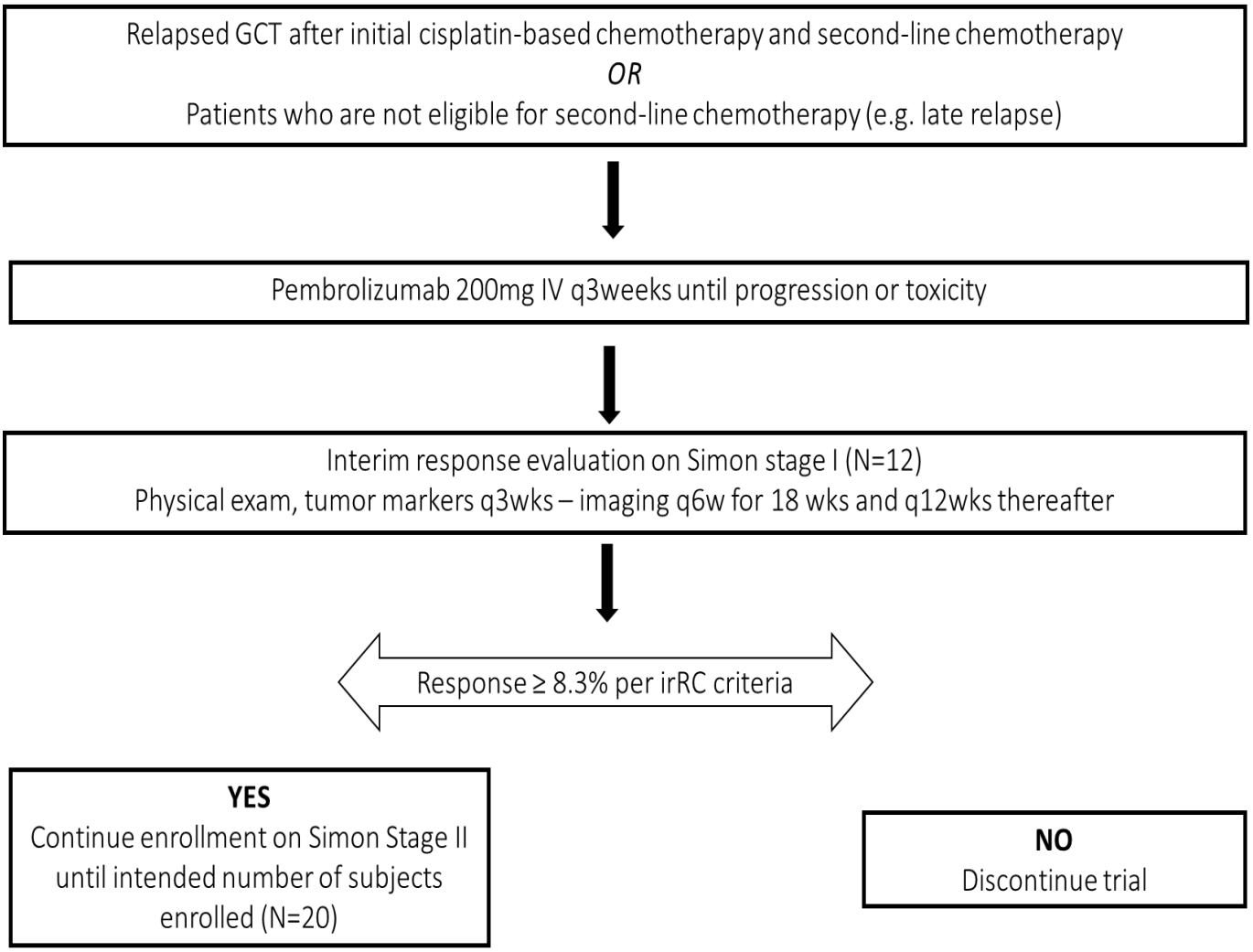
Characteristic	No. of Patients	%
Total patients	12	
Median age (range)	38 (27-55)	
Location of primary tumor		
• Testis	11	92%
• Retroperitoneum	0	0%
• Mediastinum	1	8%
Tumor histology		
• Seminoma	0	0%
• Non-seminoma	12	100%
Predominant histology		
• Choriocarcinoma	3	25%
• Embryonal carcinoma	5	42%
• Teratoma	1	8%
• Yolk Sac Tumor	3	25%
Metastatic site(s)		
• Retroperitoneum	5	42%
• Pulmonary	9	75%
• NPVM	5	42%
-Liver metastasis	3	25%
-Brain metastasis*	1	8%
-Bone metastasis*	1	8%
No. of previous chemotherapy regimens		
• 1	1	8%
• 2	0	0%
• 3	7	58%
• 4	2	17%
• 5	1	8%
• 6	1	8%
Late Relapse (> 2 years)	6	50%
Elevated Tumor Markers		
• AFP only	3	25%
• hCG only	3	25%
• AFP and hCG	6	50%
Median Serum AFP ng/mL (range)	615 (1-32,760)	
Median Serum hCG mIu/mL (range)	4 (0.6-37,096)	
ECOG performance status		
• 0	5	42%
• 1	7	58%

Abbreviations: NPVM, non-pulmonary visceral metastasis; AFP, alpha fetoprotein; HCG, human chorionic gonadotropin; IU, international unit; ECOG, Eastern Cooperative Oncology Group;
*Brain/bone imaging was not mandatory

Table 2. Common and Grade 3 or Higher Adverse Events Observed with Pembrolizumab Therapy

Adverse Event	Grade 1	Grade 2	Grade 3	Percent
Fatigue	4	2	0	50%
Nausea	4	1	0	42%
Vomiting	4	0	0	33%
Abdominal pain	2	0	1	25%
Diarrhea	3	0	0	25%
Skin and subcutaneous tissue disorders	2	0	1*	25%
Constipation	1	1	0	17%
Cough	2	0	0	17%
Dry skin	2	0	0	17%
Dyspnea	1	1	0	17%
Edema limbs	2	0	0	17%
Flank pain	0	2	0	17%
Flu-like symptoms	2	0	0	17%
Musculoskeletal and connective tissue disorder	1	1	0	17%
Non-cardiac chest pain	0	1	1	17%
Anemia	0	0	1	8%
Hyperglycemia	0	0	1	8%
Sciatic pain	0	0	1	8%
*Erythema at patch site				

Fig 1.


Relapsed GCT after initial cisplatin-based chemotherapy and second-line chemotherapy
OR
Patients who are not eligible for second-line chemotherapy (e.g. late relapse)
Pembrolizumab 200mg IV q3weeks until progression or toxicity
Interim response evaluation on Simon stage I (N=12)
Physical exam, tumor markers q3wks – imaging q6w for 18 wks and q12wks thereafter
Response ≥ 8.3% per irRC criteria
YES
Continue enrollment on Simon Stage II until intended number of subjects enrolled (N=20)
NO
Discontinue trial