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A phase II, open-label, single-arm trial of pembrolizumab for recurrent meningioma and solitary fibrous tumor

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Abstract

Background. Atypical and anaplastic meningiomas account for 20% of all meningioma cases. Solitary fibrous tumor (SFT) is a type of soft tissue sarcoma with similar attributes to meningioma. For patients with refractory or recurrent disease after previous surgery or radiotherapy, there is no effective treatment. Pembrolizumab, an anti-programmed cell death 1 (PD-1) antibody, is an effective treatment for various solid tumors. PD-1 ligand is highly expressed in aggressive meningiomas. We aimed to assess the effectiveness of pembrolizumab in treating meningioma and SFT recurrence after surgery and radiation therapy.

Methods. This prospective single-arm phase II trial comprised 15 patients with recurrent meningioma and 3 with anaplastic SFT, treated at a single institution during 2018 to 2022. The study was terminated due to a lack of efficacy and slow accrual. The primary endpoint was 6-month progression-free survival (PFS-6).

Results. Median progression-free survival (PFS) was 2.6 months, and median overall survival (OS) was 40 months. The 6- and 12-month PFS were both 11.1%. The 6- and 12-month OS were 94.4% and 61.1%, respectively. According to the Response Assessment in Neuro-Oncology (RANO) criteria, the overall response rate was 11%, with 2 patients achieving stable disease and 2 with partial response. Three patients (16.7%) developed grade 3 toxicity.

Conclusions. Our results showed that pembrolizumab failed to improve PFS-6 in patients with aggressive meningioma or anaplastic SFT. However, two patients, one with atypical meningioma and one with anaplastic SFT, achieved a partial response. More clinical studies are needed to identify which subset of patients may benefit from this treatment.

Key Points

- Pembrolizumab did not improve PFS-6 in patients with aggressive meningioma or SFT.
- Two patients achieved partial response.
- Our results suggest that some patients may benefit from this treatment.

Almost 40% of all primary brain tumors and 55% of nonmalignant brain tumors are meningiomas, that arise from arachnoid cells.[1] Atypical meningioma (WHO grade II) and anaplastic meningioma (WHO grade III) account for 20% of all meningioma cases.[2] Solitary fibrous tumor (SFT) (previously classified as hemangiopericytoma) is a type of soft tissue sarcoma originating from pericytes located in cerebral capillary walls.[2] Meningioma and SFT are both meningeal tumors and cannot be distinguished on imaging. The mainstay treatment for these intracranial tumors is surgery and radiation therapy.[3,4]

Importance of the Study

This single-arm phase II trial assessed the effectiveness of pembrolizumab in treating meningioma and solitary fibrous tumor (SFT) recurrence after surgery and radiation therapy. 15 patients with recurrent meningioma and 3 with anaplastic SFT were included in the study. Median PFS was 2.6 months, and median overall survival (OS) was 40 months. The 6- and 12-month PFS were both 11.1%. The 6- and 12-month OS were 94.4% and 61.1%, respectively. According to the Response Assessment in Neuro-Oncology (RANO) criteria, the overall response rate was 11%, with 2 patients achieving stable disease and 2 with partial response. Our results showed that pembrolizumab failed to improve PFS-6 in patients with aggressive meningioma or anaplastic SFT. However, two patients, one with atypical meningioma and one with anaplastic SFT, achieved partial response. More clinical studies are needed to identify which subset of patients may benefit from this treatment.

For patients with refractory or recurrent disease after previous surgery or radiotherapy, there is no standard of care and no effective therapy, and the 6-month progression-free survival (PFS) is poor.[5]

Earlier studies exploring diverse systemic therapies, such as various chemotherapies, hormonal therapies, interferon Alfa-2b, and molecularly targeted therapies have shown unsatisfactory outcomes.[6] Relatively more encouraging results have been observed with sunitinib, bevacizumab, and a focal adhesion kinase inhibitor.[6–8]

Pembrolizumab is an anti-programmed cell death 1 (PD-1) antibody, which acts to block the PD-1 inhibition on T cells, subsequently producing an enhanced immune response. It is an effective treatment for various solid tumors, with a positive correlation between PD-1 ligand (PD-L1) expression and response to treatment.[9,10]

PD-L1 expression is enhanced in anaplastic meningioma.[11] Due to its high expression, and the correlation between its presence and tumor response in other tumors, we sought to explore the efficacy of pembrolizumab for refractory atypical/anaplastic meningiomas and anaplastic SFT.

Two recently published studies evaluated the efficacy of two anti-PD-1 agents (nivolumab and pembrolizumab) in treating patients with high-grade meningiomas.[11,12] Although nivolumab failed to yield a significant improvement in PFS-6, it did reach 42.4%, and some patients did show response to treatment.[11] The second study on pembrolizumab reported a PFS-6 rate of 48%, hinting at a potential utility in this setting.[12]

Herein, we present the results from our phase II trial on the effectiveness of pembrolizumab in the treatment of recurrent or progressive meningioma and anaplastic SFT.

Methods

Study Design and Patients

This prospective, single-arm, open-label, interventional study comprised 18 adult patients (age 18 or older) with histologically or radiologically proven recurrent or progressive meningioma (grades I to III) or anaplastic SFT who were treated in a single institution from 2018 to 2022. All patients had documented disease progression after previous treatment with surgery and radiation therapy. Patients were recruited at least 6 months after treatment with stereotactic radiosurgery. Enrolled patients were required to have a Karnofsky perfomance scale (KPS) of 50 and above, and a projected life expectancy of at least 4 months. There were no limits on prior treatment lines.

The study protocol was written prior to the publication of the WHO 2021 brain tumor classification; therefore the tumors were classified according to the WHO 2016 classification.

Main exclusion criteria included the presence of cerebral nervous system (CNS) metastases and/or carcinomatous meningitis, and additional progressive malignancy that required active treatment, an active autoimmune disease or known immunodeficiency requiring active treatment, or prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. Patients requiring more than 2 mg of dexamethasone per day were also excluded.

All patients provided informed consent. The study was approved by the local IRB committee (RMC-0173-16, NCT03016091). The study was an independent investigator-initiated study, supported by a grant from MSD Pharmaceutical.

Study Procedures

Patients received IV pembrolizumab, at a dose of 200 mg, every 3 weeks, until disease progression or intolerable toxicity or up to 2 years of treatment. Patients who were clinically stable or improved were allowed to continue treatment beyond radiographic progression.

The study protocol was written prior to the publication of Response Assessment in Neuro-Oncology (RANO) meningioma criteria and subsequently at that time, there were no designated specific criteria for meningioma. Therefore, we mentioned the RECIST 1.1 criteria in protocol,[13] as used for solid tumors. However, post hoc analysis was performed with the RANO meningioma criteria and the results presented in this paper are according to these criteria.[14]

All patients underwent a baseline neurologic and clinical exam, MRI scan, and quality-of-life (QOL) assessment with a dedicated questionnaire. Clinical and neurological exams were performed every treatment cycle. MRI scans were repeated every 2 months.

QOL was measured using two questionnaires: the European Organization of for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) version 3.0[15] and the Quality-of-Life Questionnaire brain

cancer module (QLQ-BN20).[16] Questionnaires were completed at baseline, and then at every treatment cycle.

Biomarker Analyses

PD-L1 staining—PD-L1 expression was tested on tumor cells, using biopsy material obtained from previous surgeries. Samples were analyzed at QualTek Molecular Laboratories using PD-L1 IHC staining with Merck mouse monoclonal antibody clone 22C3 (catalog number, SK006; Merck & Co., Inc., Kenilworth, NJ). Staining intensity was scored with 0 as negative or trace, 1 as weak, 2 as moderate, and 3 as high. Samples were scored by board-certified pathologists with documented training/pathologist concordance for scoring PD-L1 IHC. The pathologist was blinded to patients' responses.

Tumor-infiltrating lymphocyte (TIL) assessment—The assessment was performed on biopsy material obtained from previous surgeries. Samples were analyzed at QualTek Molecular Laboratories. A morphological assessment of the presence or absence of TILs within the tumor nets was performed. The expression of TILs was graded on the basis of their density from 0 to 3. A score of 0 for <1 TIL per high power field (HPF) on average, a score of 1 for 1 to 10 TIL per HPF on average, a score of 2 for 11 to 20 TIL per HPF on average, and a score pf 3 for >20 TIL per HPF on average.

Outcomes

The main efficacy endpoint focused on the 6- and 12-month PFS rates. This choice was based on the observation that a significant proportion of meningioma patients with recurrent or refractory disease typically experience tumor progression before the 6-month landmark.[4,17] In addition, this endpoint has been chosen for other relevant trials, such as the sunitinib trial, making it easier to estimate the pembrolizumab effect in comparison to other drugs. The secondary efficacy endpoints were overall survival (OS) and overall PFS as they are both standard assessment of clinical benefit in subjects with recurrent or progressive meningioma, and overall response rate, which is considered a marker for clinical benefit. Overall safety and adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical Analysis

Twenty-five patients were required for the analysis to have 80% power to detect improvement in PFS-6 from 5% to 25% with a significance level of 0.05, and accounting for a 10% drop-out rate. The study was terminated after accrual of 18 patients, due to slow accrual and lack of efficacy.

Time-to-event analyses used the Kaplan–Meier method starting from the initiation of study therapy. The data were analyzed using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, N.Y., United States) and R, version 4.2.1 (R Foundation for Statistical Computing).

Results

Eighteen patients (9 males, 9 females) comprised the study group (enrolled between 2018 and 2022). Of them, three patients were diagnosed with anaplastic SFT and 15 patients with meningioma. Demographics and baseline patient characteristics are provided in Table 1. The study was terminated by the investigator and the sponsor due to lack of efficacy and slow accrual during the study period.

All patients were heavily pretreated: the median number of surgeries before enrollment was three and the median number of radiation treatments was 2. None of the patients received systemic treatments before the study period. The median functional status was 60. Only one patient was under steroid treatment at the time of enrollment (dexamethasone 2 mg).

Study Treatment and Clinical Outcomes

Median follow-up was 22 months. A median of 5 treatment cycles was given with a range of 1 to 24 cycles. One patient with anaplastic SFT completed 24 cycles of treatment. In the remainder of the patients, treatment was discontinued due to tumor progression. None of the patients discontinued due to treatment toxicity. At the time of the last follow-up, four patients had died.

Median PFS was 2.2 months, the 6- and 12-month PFS were both 11.1%. Median OS was 40 months, and the 6- and 12-month OS were 94.4% and 61.1%, respectively (Table 2).

According to the RANO criteria, two patients achieved partial response: one had anaplastic SFT and received treatment with pembrolizumab for two years; the other had atypical meningioma and received treatment for one year. Two other patients showed a short time of stable disease,

Table 1. Demographic and Clinical Information of Study Group Patients

Characteristic	Number
Total number of patients	18
Age (yr)	64.5 (28–84)
Sex (M/F)	9/9
KPS at baseline	60 (50–90)
Tumor type	
Recurrent grade I meningioma	3 (17%)
Atypical meningioma	11 (61%)
Anaplastic meningioma	1 (5%)
Anaplastic solitary fibrous tumor	3 (17%)
Multifocal disease	14 (78%)
Number of previous surgeries	3 (2–7)
Number of previous radiation therapy courses	2 (1–3)
Number of previous systemic therapies	0

*Data are expressed as median (range) or *n* (%).

one with grade 1 refractory meningioma and the other with grade 2 atypical meningioma. The remaining patients progressed under treatment (Table 2). According to the protocol, we were allowed to continue treatment after radiographic progression if we suspected that the radiographic picture presented immunotherapy pseudo-progressions as treatment effect. If further follow-up imaging revealed tumor progression, treatment was discontinued. This explains why several patients received treatment beyond progression.

Patients' responses according to histology are presented in Figure 1.

Table 2. Treatment outcomes (according to RANO)

Follow-up (months)	16.5 (2.2–48)
Treatment duration (months)	1.5 (1–24)
Number of cycles	5 (1–24)
Best response	
PR	2 (11%)
SD	2 (11%)
ORR	11%
PD	14 (78%)
PFS (months)	
Number of events	18
Median	2.2
Overall survival (months)	
Number of events	9
Median	40

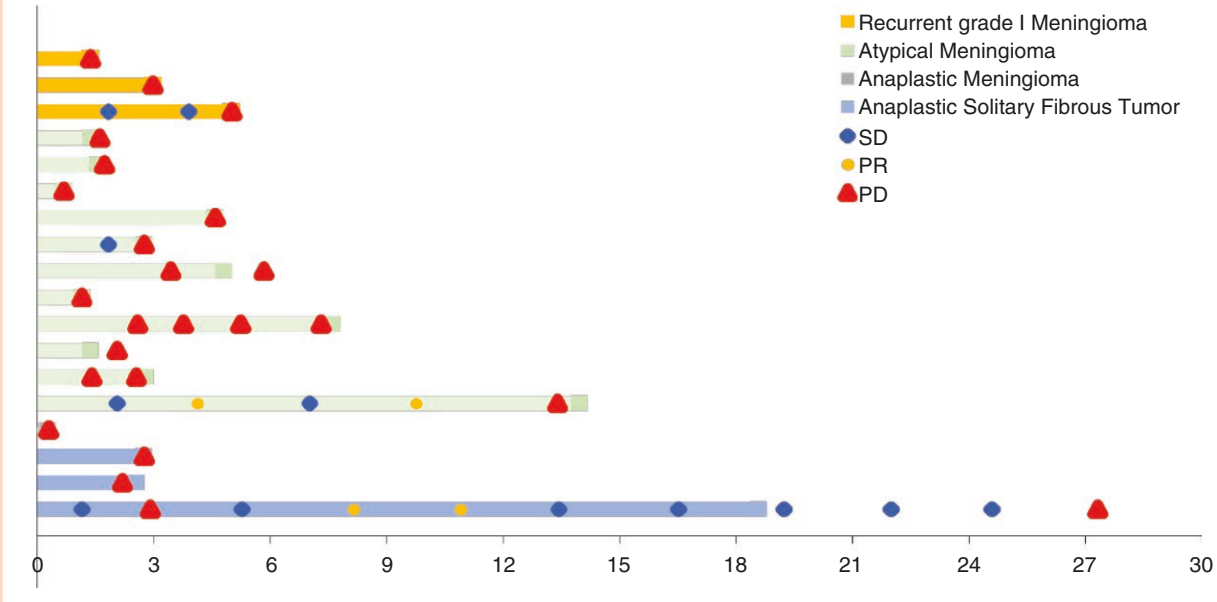
*Data are expressed as median (range) or *n* (%).
Abbreviations: ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Biomarker Analyses

Immunostaining for PD-L1 was performed on 10 samples and was positive only in 2 cases. The two patients who had positive PD-L1 staining progressed on treatment, and no correlation was found between PD-L1 immunostaining and disease response. There was no correlation between tumor-infiltrating lymphocyte (TIL) density and disease response.

Safety and QOL

Treatment was generally well tolerated, with the exception of three patients (16.7%) who developed grade 3 toxicity (hyperglycemia, diarrhea, and fatigue). In two of the patients who developed grade 3 toxicity, treatment was interrupted, they were treated with steroids and treatment was resumed later successfully. The third patient had progressive disease and therefore treatment was not resumed. Table 3 summarizes the adverse events.



Abbreviations: SD = stable disease, PR = partial response, PD = progressive disease.
Each horizontal line represents the treatment period per patient

Figure 1. Response by histology. Each horizontal line represents the treatment period per patient. PD = progressive disease, PR = partial response, SD = stable disease.

Table 3. Adverse events

Adverse event (grade)	Number (%)	Adverse event (grade)	Number (%)
Fatigue		Elevated TSH	
1	7 (39%)	1	0
2	3 (16.7%)	2	1 (5.5%)
3	1 (5.5%)	3	0
Insomnia		Hyperglycemia	
1	1 (5.5%)	1	0
2	0	2	0
3	0	3	1 (5.5%)
Diarrhea		Elevated amylase	
1	2 (11%)	1	0
2	1 (5.5%)	2	1 (5.5%)
3	1 (5.5%)	3	0
Constipation		Headache	
1	4 (22%)	1	1 (5.5%)
2	0	2	0
3	0	3	0
Nausea		Dizziness	
1	7 (39%)	1	1 (5.5%)
2	0	2	0
3	0	3	0
Abdominal pain		Cough	
1	4 (22%)	1	1 (5.5%)
2	0	2	0
3	0	3	0
Rash		Mouth dysesthesia	
1	2 (11%)	1	1 (5.5%)
2	0	2	0
3	0	3	0
Elevated liver enzymes			
1	0		
2	2 (11%)		
3	0		

We did not find significant changes in any of the QOL scales measured by QLQ-C30 and QLQ-BN20 questionnaires at baseline and through the treatment period.

Discussion

The standard of care for patients with aggressive meningioma and anaplastic SFT includes surgery and radiotherapy. Since there are no effective treatments for patients with refractory disease, the development of new treatment options is imperative.

In this phase II study, we evaluated the efficacy of pembrolizumab, an anti-PD-1 antibody, for patients with recurrent or refractory meningioma or anaplastic SFT. Based on data collected prior to trial termination, the trial's primary endpoint was not met, hinting at limited efficacy for pembrolizumab in this setting. Despite not reaching the study's primary endpoint, it is important to note that two patients did achieve partial response according to the RANO criteria.

Our results show lower PFS-6 compared to 2 recent studies that examined the efficacy of anti-PD-1 agents on meningioma patients.[13,14] A possible reason for the lower PFS-6 rate of 11.1% in our study compared to the study by Bi et al.[11] could be explained by the relative severity of disease in the patients recruited to our study. Moreover, our study patients had documented progression after previous lines of therapy, while Brastianos et al.[12] also included patients who had residual disease with no evidence of progression. The severe condition of the patients included in our study is also reflected by the inclusion of patients who had a KPS $\geq$ 50, while the other two studies recruited

patients in a better condition, with a KPS ≥ 70 or similarly an ECOG-performance status of ≤2.

In several solid tumors, including lung and melanoma, PD-L1 expression was found to correlate with response to pembrolizumab treatment.[9] High expression was also previously reported in anaplastic meningioma.[10] This was not true in our study. Out of 10 patients tested, 2 had positive staining for PD-L1 and both had tumor progression on treatment with pembrolizumab. Additionally, no correlation was found between TIL density and disease response. While these findings are limited due to the small sample size, they are in line with previous studies that did not find a significant correlation between PDL-1 staining and response to treatment.[12] Unfortunately, other tests of correlations with further known predictors of response, such as tumor mutation burden or microsatellite instability were not performed because of the low number of remaining tissue samples. Importantly, case reports have shown that immune checkpoint inhibitors can be effective in patients with aggressive meningiomas and impaired DNA mismatch repair (MMR) genes.[18,19]

The main limitation of this study was the small number of patients and the fact that meningioma and anaplastic SFT patients were grouped and analyzed together. An additional limitation was the introduction of pembrolizumab only after multiple lines of prior therapy and exclusively among poor-performance patients, which raises the important question of whether earlier treatment may lead to greater efficacy, either as a single-agent or in combination with radiotherapy. Such combinations have shown promising results in other tumors.[20] Another limitation of the study is the lack of classification based on newer methylation profiles and DNA/RNA sequencing.[21,22]

A RANO review published in 2014 supports the standardization of PFS-6 as an endpoint for meningioma clinical studies and defined a threshold of PFS-6 < 30% for as worthy of further clinical investigation for grade II/III meningiomas.[5] Our study was unfortunately far from this endpoint, making it a negative trial. However, we do see this pilot trial as an opportunity to further investigate the role of immunotherapy in meningioma, possibly earlier in the course of the disease and in combination with other treatment modalities.

In conclusion, our findings show that treatment with the anti-PD-1 agent pembrolizumab failed to improve PFS-6 in patients with aggressive meningioma or anaplastic SFT. Notably, however, two patients—one with atypical meningioma and one with anaplastic SFT—achieved partial response. Further clinical studies are required to identify which subset of meningioma may benefit from this treatment.

Keywords

meningioma | solitary fibrous tumor | pembrolizumab | PD-1 | immunotherapy

Lay Summary

Meningiomas and solitary fibrous tumors are types of brain tumors that can sometimes look alike. Pembrolizumab is a drug that helps the immune system fight cancer and has been effective for other cancers. This study aimed to see if pembrolizumab could help patients with these specific brain tumors. To do this, they treated 15 patients with meningioma and solitary fibrous tumors that had come back after previous treatments. Their results showed that the drug did not change how fast tumors grew after treatment. Only a few patients saw some benefit, 2 patients had tumors that did not grow and two other patients had tumors that shrank a bit. Three patients had serious side effects. The authors of this study concluded that pembrolizumab did not work well for most patients with these tumors.

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Conflict of interest statement

The authors have no other conflicts of interest related to the study.

Authors' Contributions

D. Limon: Conceptualization, investigation, methodology, data analysis, visualization, writing—original draft, and writing—review and editing. A. Amiel: Investigation, data analysis, writing—review and editing. S. Even Haim: Data analysis, visualization, writing—original draft, and writing—review and editing. N. Gordon: Conceptualization, data analysis, visualization, writing—review and editing. R. Tschernichovsky: Writing—review and editing. S. Stemmer: Conceptualization, writing – review and editing. O. Gal: Writing—review and editing. Y. Laviv: Writing—review and editing. A. Kanner: Writing—review and editing. T. Siegal: Conceptualization, investigation, methodology, writing—original draft, and writing—review and editing. S. Yust-Katz: Conceptualization, investigation, methodology, data analysis, visualization, writing—original draft, and writing—review and editing.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval

The study was approved by the local IRB committee (RMC-0173-16, NCT03016091).

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