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The clinical efficacy and safety of single-agent pembrolizumab in patients with recurrent granulosa cell tumors of the ovary: a case series from a phase II basket trial

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Authors' contributions:

JH and AN made significant contributions to conceptualization, project administration, data analysis and interpretation, and drafting, reviewing, and editing the majority of the original and final manuscript. AJ, SNW, AKS, LMR, MX, AA, DK, VS, BS, JR, and FY made significant contributions to project administration, data analysis and interpretation, and revising and reviewing the original and final manuscript.

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Abstract

Background—Treatment of recurrent, unresectable granulosa cell tumor (GCT) of the ovary can be challenging. Given the rarity of the tumor, alternative therapies have been difficult to evaluate in large prospective clinical trials. Currently, to our knowledge, there are no reports of the use of immune checkpoint inhibitors in GCT patients. Here, we present a case series of GCT patients treated with pembrolizumab who were enrolled in a phase II basket trial in advanced, rare solid tumors (Clinicaltrials.gov: NCT02721732).

Cases—We identified 5 patients with recurrent GCT (4 adult and 1 juvenile type); they had an extensive history of systemic therapy at study enrollment (range, 3–10), with most regimens resulting in less than 12 months of disease control. Pembrolizumab was administered in these patients, as per trial protocol. Although there were no objective responses according to the irRECIST guidelines, 2 patients with adult-type GCT experienced disease control for ≥ 12 months (565 and 453 days). In one, pembrolizumab represented the longest duration of disease control compared to prior lines of systemic therapy (565 days vs 13 months). In the other, pembrolizumab was the second longest systemic therapy associated with disease control (453 days vs 22 months) compared to prior lines of therapy. In this patient, pembrolizumab was discontinued following withdrawal of consent. PD-L1 expression was not observed in any baseline tumor samples. Pembrolizumab was well tolerated, with no grade 3 or 4 treatment-related adverse events.

Conclusions—Although our results do not support the routine use of pembrolizumab monotherapy in unselected GCT patients, some patients with adult-type GCT may derive a clinical benefit, with a low risk of toxicity. Future studies should investigate the role of immunotherapy and predictors of clinical benefit in this patient population.

Keywords

granulosa cell tumor of the ovary; pembrolizumab; immunotherapy; case report

Introduction

Granulosa cell tumors (GCTs) of the ovary represent 2%-5% of all ovarian neoplasms but comprise the majority (70%) of sex cord-stromal tumors[1, 2]. Given that most GCTs present at an early stage, intervention with tumor cytoreduction and surgical staging, with or

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without systemic adjuvant therapy, can be curative in many cases[3]. GCTs are classified as adult or juvenile type[3, 4]. Despite the favorable prognosis of adult-type GCT, recurrences are not uncommon, with relapses occurring even after 10 years[3–6]. In contrast, juvenile-type GCT tends to occur in younger patients and is typically more aggressive, with earlier recurrences[3, 5]. Regardless of the GCT type, cytoreductive surgery continues to be the mainstay of treatment for recurrent disease that is resectable with the addition of systemic chemotherapy, hormonal therapy, or radiation therapy[3, 7]. Unfortunately, patients with recurrent disease may require multiple surgical interventions and lines of systemic therapy, and responses to current systemic treatments are variable and limited[3, 6, 7]. Most patients with relapsed disease ultimately die of their disease, prompting a search for novel treatment modalities[3, 6, 7].

Immune checkpoint inhibitors have emerged as a treatment option for patients with malignancies such as metastatic melanoma and non-small cell lung carcinoma because they result in durable responses[8, 9]. Malignant cells may evade normal immune checkpoints through the programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway that downregulates cytotoxic T-cell activity, thus favoring tolerance and tumor growth. As an anti-PD-1 monoclonal antibody, pembrolizumab can inhibit this immune escape pathway. In addition, pembrolizumab has demonstrated impressive clinical responses in microsatellite instability-high or mismatch repair-deficient tumors[10]. Given the clinical benefit, the US Food and Drug Administration (FDA) approved pembrolizumab for microsatellite instability-high/mismatch repair-deficient tumors that had not responded to prior treatment in May 2017; this represents the first tissue-agnostic indication for drug approval. This new indication highlights that pembrolizumab’s anti-tumor effect may also benefit patients with other uncommon tumors.

Given the rarity of GCT, alternative therapies have been difficult to evaluate in large prospective clinical trials, and to our knowledge, no reports exist of immune checkpoint inhibitor use in these patients. We report a case series of 5 heavily pre-treated patients with recurrent GCT who received single-agent pembrolizumab as part of a phase II basket trial for patients with advanced rare malignancies.

Cases

Clinical trial design

We evaluated 5 patients with recurrent GCT who were enrolled in cohort 10 (“other rare tumor histologies” category) of an open-label, phase II basket Clinicaltrials.gov: (NCT02721732) at The University of Texas MD Anderson Cancer Center (Houston, Texas). In brief, this phase II trial examined the clinical efficacy and safety of single-agent pembrolizumab (200 mg IV every 3 weeks) in 10 pre-specified cohorts of advanced, rare tumors, regardless of PD-L1 status. Details of the trial design have been reported elsewhere[11], All trial patients had PD-L1 (H-score ≥ 42.5 denoted positivity) and tumor-infiltrating lymphocyte (TIL) characterization of tumor tissue that was correlated with treatment response, as described previously[11].

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Treatment response was evaluated using Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) guidelines on serial radiologic imaging at baseline, every 9 weeks for the first 6 months, and then every 12 weeks at the discretion of the investigator. Safety and tolerability were assessed by characterizing and grading adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events v403. This study received FDA and institutional review board approval, and all patients provided informed consent prior to enrollment.

The overall results of the phase II study and small cell neuroendocrine carcinoma of the female genital tract have been reported elsewhere[11, 12], In this case series, we report the outcomes of patients with relapsed GCT who had been treated with pembrolizumab monotherapy.

Patient characteristics

During the enrollment period of August 15, 2016–July 27, 2018, 5 patients with GCT of the ovary met the study inclusion criteria and provided informed consent to participate in the phase II trial. The baseline clinical and tumor characteristics of the 5 patients are shown in Table 1. Patients' ages ranged from 23 to 73 years, and most (4 of 5) had adult-type GCT. At baseline prior to treatment initiation, all patients had recurrent disease; 4 had disease contained within the abdominal or pelvic cavity, and the remaining patient (patient 2) also had lung metastases. Patients' treatment histories prior to pembrolizumab administration are shown in Table 2. They underwent a median of 2 (range, 2–5) and 7 (range, 3–10) prior cytoreductive surgeries and systemic therapies, respectively. The treatments with the longest duration of disease control after the first disease recurrence were carboplatin and paclitaxel, followed by anastrozole maintenance (9 months), single-agent anastrozole (13 months), carboplatin/docetaxel (52 months), carboplatin/taxane (8 months), and endoxifen (22 months) for patients 1–5, respectively. For patients 1, 3, and 4, these aforementioned systemic therapies were administered after optimal secondary tumor cytoreductive surgeries. Otherwise, the majority of these patients' prior regimens resulted in less than 12 months of disease control.

Treatment response and treatment-related adverse events

All patients were evaluable using irRECIST criteria; Figs. 1 and 2 demonstrate the greatest percentage changes in target tumor lesions and dynamic tumor volume changes over time, respectively. Patients 2 and 5 had stable disease as their best objective response, while patients 1, 3, and 4 had progressive disease, resulting in a clinical benefit rate of 40% (2 of 5). Patient 2 had stable disease after 3 cycles of treatment and derived clinical benefit for a duration of 565 days, until disease progression after cycle 25. Patient 5 had stable disease after 3 cycles of treatment and derived clinical benefit from pembrolizumab for a duration of 453 days, until withdrawal of consent after cycle 22. Patients 1, 3, and 4 all had progressive disease that was identified at the first on-treatment imaging scan after 3 cycles of pembrolizumab.

Three of the 5 patients experienced 1 or more treatment-related adverse events of any grade; none were grade 3 or 4. Two experienced immune-related adverse events: patient 2 had a

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grade 1 maculopapular rash that resolved after 47 days, and patient 5 had grade 2 hypothyroidism and required daily thyroid supplementation. Other non-immune treatment-related adverse events included fatigue (n = 1; patient 2), hyperthyroidism (n = 1; patient 2), nausea (n = 1; patient 4), and pruritus (n = 1; patient 5). Although unrelated to pembrolizumab therapy, a grade 3 hematoma from a tumor developed in patient 5 and resulted in a subsequent withdrawal of consent for further study participation.

PD-L1, TIL scoring, and somatic tumor mutations

Table 1 lists the PD-L1 H-scores and TIL scores of the 5 patients. One patient (patient 3) was not evaluable for PD-L1 H-scoring or TIL infiltration because of the absence of identifiable tumor cells on the specimen. For the remaining 4 patients, PD-L1 staining was absent (H-score of 0) and TIL infiltration was present in all baseline specimens. Patient 1 had a high number of TILs, patient 5 had a moderate number, and patients 2 and 4 had a low number.

Somatic tumor mutation gene panel results were available for 4 patients. Patients 1, 3, and 5 had *FoxL2* (c.402C>G p.C134W) mutations. In addition, patient 1 had an ATM (c.1010G>A p.R337H) mutation, while patient 5 had an *NFI* mutation (c.2158C>T p.R720W) and patient 2 had *TP53* mutations (c.733G>C p.G245R and c.490A>G p.K164E). Patient 4 had no detectable somatic mutations, and patient 3 did not undergo somatic tumor mutation gene panel testing.

Discussion

We present the first reported findings of the use of pembrolizumab monotherapy in recurrent GCT. Although no objective responses were seen among the 4 adult-type GCTs and 1 juvenile-type GCT, we observed stable disease, according to irRECIST criteria, in 2 patients that lasted for more than 12 months (patient 2: 565 days and patient 5: 453 days). Although the clinical benefit of pembrolizumab in these 2 patients may be overestimated because of the indolent nature of adult-type GCT, an examination of these patients' prior systemic therapies in the recurrence setting may provide context. Most prior lines of systemic therapy received in the recurrent setting in adult-type GCT patients resulted in a duration of disease control of less than 12 months. Furthermore, in patient 2, pembrolizumab provided a greater duration of disease control than did the best prior line of systemic therapy: single-agent anastrozole (565 days vs. 13 months, respectively). For patient 5, although the longest duration of disease control was 22 months with endoxifen, the other lines of therapy were not as beneficial, with the second longest duration of disease control being leuprolide (9 months). In patient 5's case, it is possible that pembrolizumab would have had an even longer duration of disease control, but treatment ended prematurely because of an unrelated grade 3 hematoma from a tumor bleed.

Interestingly, the 2 patients who had durable disease control also experienced immune-related adverse events that were attributable to pembrolizumab (maculopapular rash and hypothyroidism). This association between immune-related adverse events and relatively improved treatment response is suggestive of an active immune system, and this observation

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has been similarly reported in multiple studies[13–15]. Furthermore, pembrolizumab had low toxicity in patients with no grade 3 or 4 treatment-related adverse events.

The overall lack of objective anti-tumor response to pembrolizumab may be attributable to the absence of PD-L1 expression in the tumor microenvironment, as evidenced by the PD-L1 H-score of 0 in 4 of 5 patients' tumor samples (the remaining tumor sample being non-evaluable). With multiple definitions of PD-L1 positivity in the literature, PD-L1 status has been described as a predictive biomarker of response to PD-1 inhibitor monotherapy[16–18]. Although the presence of TILs has also been associated with improved response to PD-1 inhibitors, the absence of PD-L1 expression may explain the lack of anti-tumor response to pembrolizumab in patient 1, who had the highest TIL infiltration[17, 18], In addition, Mills et al. recently demonstrated that a minority of GCT patients had PD-L1 expression or TIL infiltration; the authors suggested that immune checkpoint inhibitors have a minimal role in the disease[19]. It should be noted, however, that the absence of PD-L1 expression does not preclude anti-PD-1 therapy, as the combination of CTLA4 and PD-1 inhibitors demonstrated a synergistic therapeutic response, independent of PD-L1 status[20, 21].

Somatic *FOXL2* mutations were present in 3 of the 4 adult-type GCT patients (the remaining patient had no available somatic mutation gene panel information). As a member of the forkhead transcription factor, *FOXL2* plays an integral role in normal granulosa cell development [22], The detection of the *FOXL2* (c.402C>G p.C134W) mutation in these patients is to be expected, as it is present in nearly all adult-type GCTs; this mutation is thought to be a driver of malignancy development and recurrence[23, 24], Patient 5 had 2 *TP53* mutations: 1 pathogenic (c.733G>C p.G245R) and the other a variant of unknown significance (c.490A>G p.K164E). Along with *TERT* and inactivated *KMT2D/MLL2* mutations, pathogenic *TP53* mutations have been implicated in relapsed adult-type GCT[25–27], Roze et al. performed whole-genomic sequencing on tumor samples from 33 patients and found pathogenic *TP53* mutations in tumors with the highest tumor mutational burden[26, 27]. Higher tumor mutational burden has been associated with a greater response to immune checkpoint inhibitors and may have been a contributing factor to disease control in patient 5[28]. Unfortunately, these patients did not undergo tumor mutational burden or MSI testing. Other somatic mutations detected in patients 2 (*ATM*) and 5 (*NF1*) were variants of unknown significance and are unlikely to be implicated in the response to pembrolizumab.

Relapsed GCT that is unresectable or metastatic continues to pose therapeutic challenges and has prompted a search for alternative treatments[3, 7]. The field of immunotherapy has revolutionized cancer therapeutics and has brought clinically durable treatment responses in multiple tumor types that have been refractory to conventional therapy[8, 9]. In gynecologic cancers, immune checkpoint inhibitors have led to improved treatment responses, resulting in FDA approval for the use of pembrolizumab for MSI-H endometrial cancer and PD-L1-positive cervical cancers. Furthermore, a recent trial of ipilimumab (a cytotoxic T-lymphocyte-associated protein 4 [CTLA4] inhibitor) and nivolumab (a PD-1 inhibitor) has demonstrated promising objective responses in patients with recurrent epithelial ovarian cancer (especially clear cell histologic type), irrespective of PD-L1 status[20]. Although the scope of the benefit of immune checkpoint inhibitors has expanded to include larger

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numbers of gynecologic malignancies, immunotherapy efficacy has been difficult to evaluate in GCT because of the rarity of the tumor.

Current treatment strategies for GCT are heterogeneous, including chemotherapeutic regimens (carboplatin/paclitaxel, BEP [bleomycin, etoposide, and cisplatin], CAP [cyclophosphamide, doxorubicin, and cisplatin], VBP [vinblastine, bleomycin, and cisplatin]), hormonal therapy (progestins, aromatase inhibitors, and gonadotropin-releasing hormone agonists), and radiation therapy with variable results, especially when combined with cytoreductive surgery[3, 7]. Vascular endothelial growth factor has been shown to be highly expressed on GCT tumors and has prompted the use of angiogenesis inhibitors (e.g., bevacizumab)[29–31]. In a phase II Gynecologic Oncology Group cooperative trial of bevacizumab in 36 patients with sex cord-stromal tumors (mostly GCTs), the authors demonstrated partial response and stable disease rates of 16.7% and 77.8%, respectively[31]. The median progression-free survival duration was 9.3 months[31]. In the recently published ALIENOR/ENGOT-ov7 multicenter randomized control trial, the authors found that the addition of bevacizumab to weekly paclitaxel improved objective response rates (from 25% to 44%) in a cohort of sex-cord stromal tumors (most of which were adult-type GCT)[32]. However, it did not improve progression-free survival[32]. As treatment options are limited, other agents, such as lurbinectedin, a selective RNA polymerase II inhibitor, were used in 4 of the 5 patients in our study (3 adult-and 1 juvenile-type GCT) prior to study enrollment. However, the treatment duration was short (2-6 cycles) because of disease progression or withdrawal of consent. Overall, the effectiveness of these systemic therapies vary; thus, cytoreductive surgery (when feasible) to no residual disease continues to be the most effective treatment option for patients with recurrent GCT.

Despite the lack of objective responses observed in this trial, some adult-type GCT patients derived clinical benefit, with a disease control duration of greater than 12 months. Thus, a further investigation to determine more accurate predictive markers of response to immunotherapy is warranted. Currently, there is an ongoing, open-label phase II basket trial (SWOG 1609; NCT02834013) of ipilimumab and nivolumab in rare solid tumors (including GCT). The SWOG 1609 trial also includes a planned biomarker evaluation (including whole exome sequencing, RNA sequencing, and multiplex immune profiling); we eagerly await the trial results.

The strengths of our study include the evaluation of the use of pembrolizumab in a rare cohort of GCT patients, correlated with translational PD-L1 and TIL data. Furthermore, tumor responses were objectively measured in an independent review by experienced radiologists using irRECIST criteria.

The small sample size, although expected because of GCT’s rarity, is a limitation of this study. Furthermore, given the differing tumor biologic characteristics of adult-type and juvenile-type GCTs, the efficacy of pembrolizumab may not be generalizable. Juvenile-type GCT represents a minority of GCT cases (approximately 5%) and thus presents an even greater challenge when evaluating new therapies in prospective clinical trials.

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In conclusion, we demonstrated that single-agent pembrolizumab is generally safe to use for GCT of the ovary. Although durable disease control may be observed, the routine use of pembrolizumab is unlikely to be effective at decreasing tumor burden in unselected patients with relapsed GCT, and more accurate biomarkers are needed to predict clinical benefit. Given the rarity of the tumor, genomic profiling of GCTs should be undertaken to identify pathways that can be targeted with novel investigational therapeutics.

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References

1. Schumer ST and Cannistra SA, Granulosa cell tumor of the ovary. J Clin Oncol, 2003. 21(6): p. 1180–9. [PubMed: 12637488]
2. Malmström H, et al., Granulosa cell tumors of the ovary: prognostic factors and outcome. Gynecol Oncol, 1994. 52(1): p. 50–5. [PubMed: 8307501]
3. Levin G, et al., Granulosa cell tumor of ovary: A systematic review of recent evidence. Eur J Obstet Gynecol Reprod Biol, 2018. 225: p. 57–61. [PubMed: 29665458]
4. Chen VW, et al., Pathology and classification of ovarian tumors. Cancer, 2003. 97(10 Suppl): p. 2631–42. [PubMed: 12733128]
5. Young RH, Dickersin GR, and Scully RE, Juvenile granulosa cell tumor of the ovary. A clinicopathological analysis of 125 cases. Am J Surg Pathol, 1984. 8(8): p. 575–96. [PubMed: 6465418]
6. Mangili G, et al., Long-term follow-up is crucial after treatment for granulosa cell tumours of the ovary. Br J Cancer, 2013. 109(1): p. 29–34. [PubMed: 23756859]
7. Gurumurthy M, Bryant A, and Shanbhag S, Effectiveness of different treatment modalities for the management of adult-onset granulosa cell tumours of the ovary (primary and recurrent). Cochrane Database Syst Rev, 2014. 2014(4): p. Cd006912.
8. Topalian SL, et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med, 2012. 366(26): p. 2443–54. [PubMed: 22658127]
9. Hodi FS, et al., Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med, 2010. 363(8): p. 711–23. [PubMed: 20525992]
10. Le DT, et al., Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science (New York, N.Y.), 2017. 357(6349): p. 409–413.
11. Naing A, et al., Phase 2 study of pembrolizumab in patients with advanced rare cancers. J Immunother Cancer, 2020. 8(1).
12. Frumovitz M, et al., Phase II study of pembrolizumab efficacy and safety in women with recurrent small cell neuroendocrine carcinoma of the lower genital tract. Gynecol Oncol, 2020.
13. Fujii T, et al., Incidence of immune-related adverse events and its association with treatment outcomes: the MD Anderson Cancer Center experience. Invest New Drugs, 2018. 36(4): p. 638–646. [PubMed: 29159766]

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14. Hua C, et al., Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. JAMA Dermatol, 2016. 152(1): p. 45–51. [PubMed: 26501224]
15. Hosoya K, et al., Association Between Early Immune-related Adverse Events and Clinical Outcomes in Patients With Non-Small Cell Lung Cancer Treated With Immune Checkpoint Inhibitors. Clin Lung Cancer, 2020.
16. Taube JM, et al., Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res, 2014. 20(19): p. 5064–74. [PubMed: 24714771]
17. Pardoll DM, The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer, 2012. 12(4): p. 252–64. [PubMed: 22437870]
18. Fujii T, et al., Biomarkers of response to immune checkpoint blockade in cancer treatment. Crit Rev Oncol Hematol, 2018. 130: p. 108–120. [PubMed: 30196907]
19. Mills AM, et al., Emerging biomarkers in ovarian granulosa cell tumors. Int J Gynecol Cancer, 2019. 29(3): p. 560–565. [PubMed: 30833441]
20. Zamarin D, et al., Randomized Phase II Trial of Nivolumab Versus Nivolumab and Ipilimumab for Recurrent or Persistent Ovarian Cancer: An NRG Oncology Study. J Clin Oncol, 2020: p. Jco1902059.
21. Curran MA, et al., PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A, 2010. 107(9): p. 4275–80. [PubMed: 20160101]
22. Cocquet J, et al., Evolution and expression of FOXL2. J Med Genet, 2002. 39(12): p. 916–21. [PubMed: 12471206]
23. Shah SP, et al., Mutation of FOXL2 in granulosa-cell tumors of the ovary. N Engl J Med, 2009. 360(26): p. 2719–29. [PubMed: 19516027]
24. Yanagida S, et al., Clinical and genetic analysis of recurrent adult-type granulosa cell tumor of the ovary: Persistent preservation of heterozygous c.402C>G FOXL2 mutation. PLoS One, 2017. 12(6): p. e0178989. [PubMed: 28594898]
25. Hillman RT, et al., KMT2D/MLL2 inactivation is associated with recurrence in adult-type granulosa cell tumors of the ovary. Nat Commun, 2018. 9(1): p. 2496. [PubMed: 29950560]
26. Da Cruz Paula A, et al., Genomic profiling of primary and recurrent adult granulosa cell tumors of the ovary. Mod Pathol, 2020.
27. Roze J, et al., Whole Genome Analysis of Ovarian Granulosa Cell Tumors Reveals Tumor Heterogeneity and a High-Grade TP53-Specific Subgroup. Cancers (Basel), 2020. 12(5).
28. Goodman AM, et al., Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther, 2017. 16(11): p. 2598–2608. [PubMed: 28835386]
29. Tao X, et al., Anti-angiogenesis therapy with bevacizumab for patients with ovarian granulosa cell tumors. Gynecol Oncol, 2009. 114(3): p. 431–6. [PubMed: 19524286]
30. Färkkilä A, et al., Vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 are highly expressed in ovarian granulosa cell tumors. Eur J Endocrinol, 2011. 164(1): p. 115–22. [PubMed: 21041381]
31. Brown J, et al., Efficacy and safety of bevacizumab in recurrent sex cord-stromal ovarian tumors: results of a phase 2 trial of the Gynecologic Oncology Group. Cancer, 2014. 120(3): p. 344–51. [PubMed: 24166194]
32. Ray-Coquard I, et al., Effect of Weekly Paclitaxel With or Without Bevacizumab on Progression-Free Rate Among Patients With Relapsed Ovarian Sex Cord-Stromal Tumors: The ALIENOR/ENGOT-ov7 Randomized Clinical Trial. JAMA Oncol, 2020.

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Highlights

- Pembrolizumab can provide durable disease control in patients with recurrent adult granulosa cell tumors.
- Pembrolizumab had an acceptable safety profile in patients with granulosa cell tumors.
- In this cohort, granulosa cell tumors of the ovary had low expression of PD-L1.

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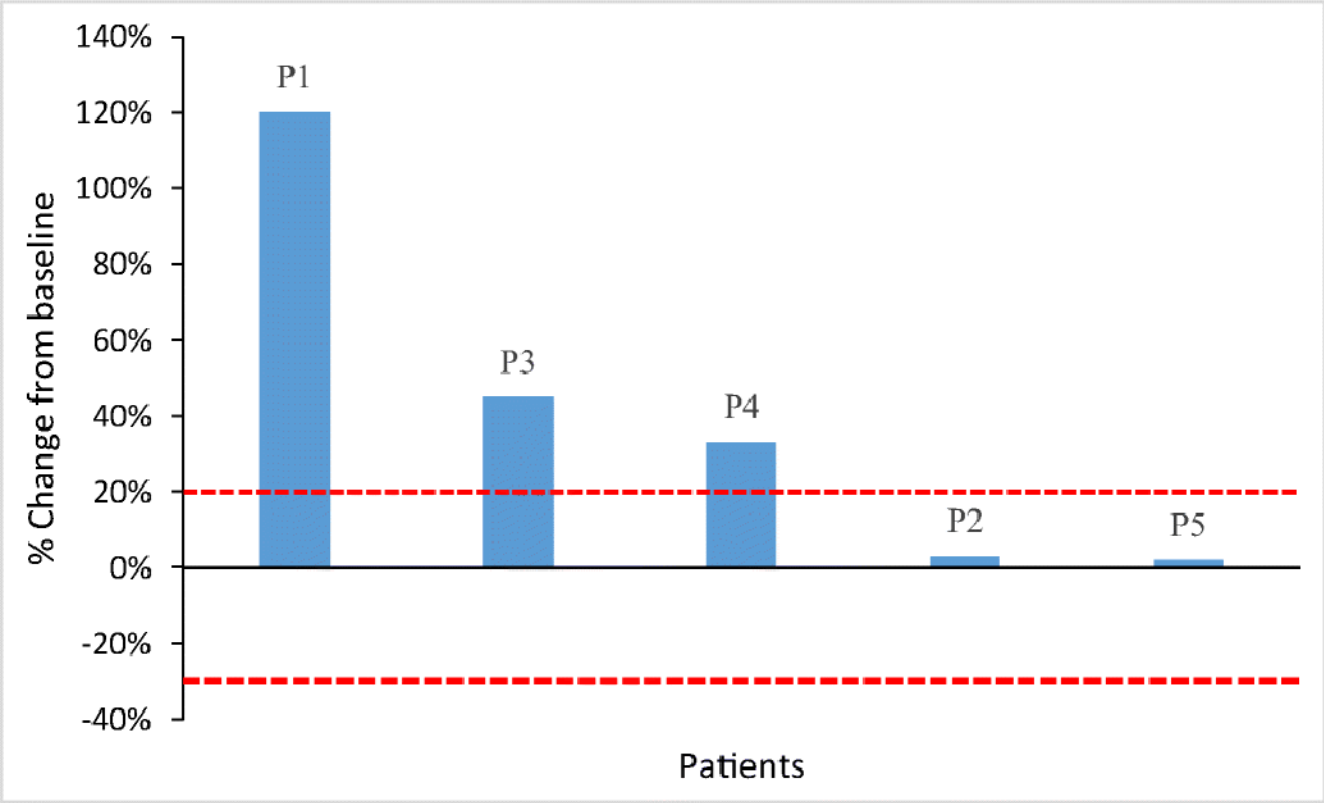

Fig 1:

Radiologic response to pembrolizumab in patients with granulosa cell tumor of the ovary. Waterfall plot illustrating the best objective response to pembrolizumab in the 5 patients (P1—5) using irRECIST criteria. Each bar represents a patient and shows the maximum percentage change from the baseline in the sum of the longest diameters of all target lesions and any new lesions while on pembrolizumab. The area above the upper red dotted line represents progressive disease (≥ 20% increase in the sum of the diameters of the target lesions compared with the baseline). The area between the upper and lower red dotted lines represents stable disease.

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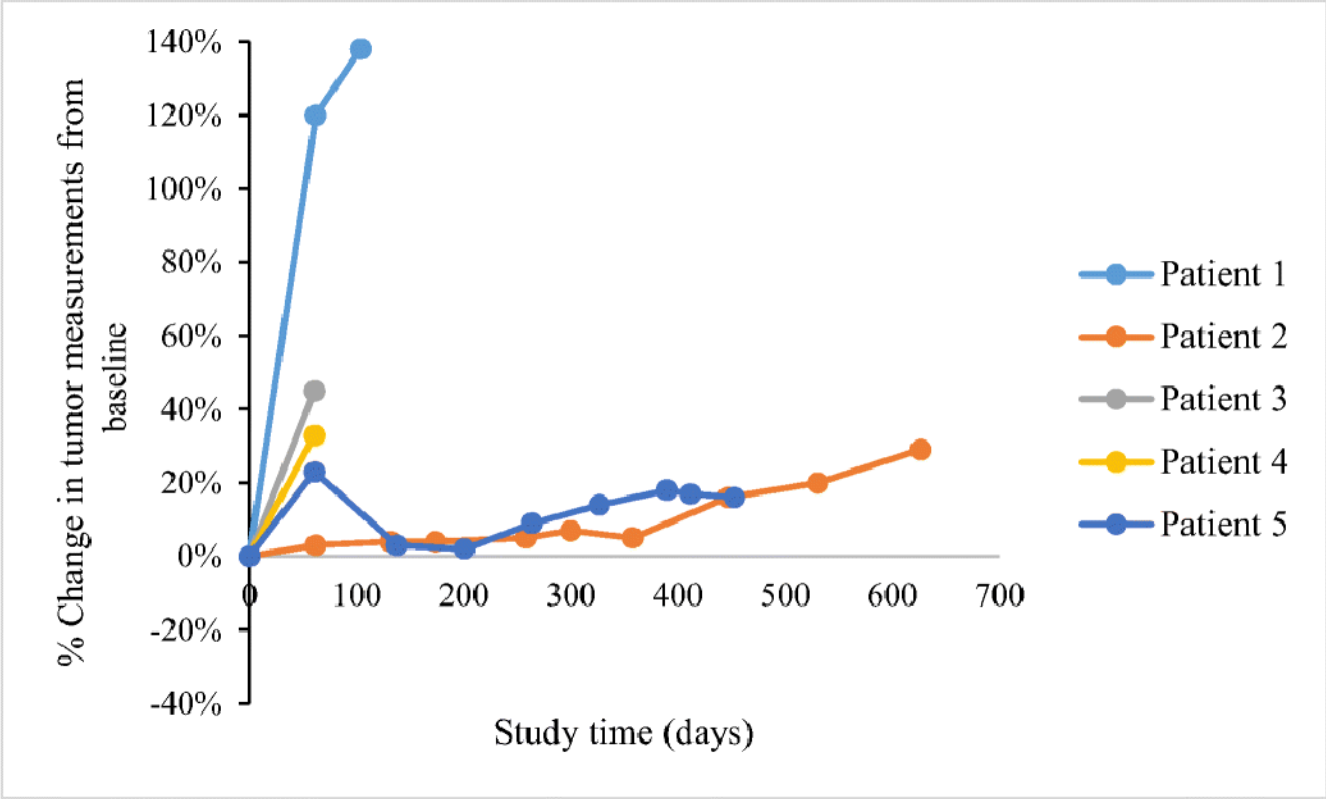

Fig 2:

Tumor response according to irRECIST criteria over time. This spider plot demonstrates the tumor measurements from the baseline using irRECIST criteria during the course of treatment with pembrolizumab in the 5 patients. Patients 1, 3, and 4 experienced disease progression as their best objective response, while patients 2 and 5 had stable disease. All patients experienced disease progression prior to stopping treatment except for patient 5, who withdrew consent.

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Table 1

Baseline clinical and tumor characteristics

Patient	Age (years)	GCT type	Years since initial diagnosis	ECOG PS	FIGO stage[1]	Metastatic sites[2]	PD-L1 H-score	TIL infiltration
1	54	Adult	16	1	IC1	A, P	0	3
2	38	Adult	12	0	I	A, L, P	0	1
3	73	Adult	26	1	IC	H, I, P, S	N/A[3]	N/A[3]
4	23	Juvenile	2	1	IIA	A, P	0	1
5	70	Adult	8	1	IIB	H, P	0	2

GCT = granulosa cell tumor, ECOG PS = Eastern Cooperative Oncology Group Performance Status, FIGO = International Federation of Gynecology and Obstetrics, PD-L1 = programmed cell death ligand-1, TIL = tumor-infiltrating lymphocyte, I = intestinal metastases, A = adenopathy, P = peritoneal metastases, L = lung metastases, H = hepatic metastases, S = splenic metastases, N/A = not applicable.

Percentage and intensity of PD-L1 membrane staining on a scale from 0 to 300, with ≥ 42.5 defined as the threshold for positivity of PD-L1. TIL = intensity of TILs within tumor nests on a scale of 0 to 3; 0 = absence of TILs, 1 = low number of TILs, 2 = moderate number of TILs, 3 = high number of TILs.

[1] FIGO 2015 staging.

[2] Sites of metastatic disease prior to treatment.

[3] Patient 3 had no tumor present in the tissue specimen for PD-L1 and TIL evaluation.

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Table 2

Prior treatments before pembrolizumab treatment

Patient	Prior RT	No. of prior cytoreductive surgeries	No. of prior systemic therapies	Prior systemic therapies[1]
1	Yes	5	7	1 – Letrozole[2] 2 – Carboplatin/paclitaxel, followed by anastrozole maintenance[*] 3 – Bevacizumab 4 – Leuprolide 5 – Tamoxifen 6 – Carboplatin/paclitaxel 7 – Lurbinectedin
2	No	2	7	1 – Carboplatin/paclitaxel[2] 2 – Carboplatin/paclitaxel/bevacizumab 3 – Bleomycin/etoposide/cisplatin 4 – Anastrozole[*] 5 – Leuprolide 6 – Megestrol 7 –Megestrol/tamoxifen
3	No	4	4	1 – Carboplatin/docetaxel[*] 2 – Carboplatin/paclitaxel 3 – Anastrozole 4 – Lurbinectedin
4	No	2	3	1 – Bleomycin/etoposide/cisplatin with exemestane[2] 2 – Carboplatin/paclitaxel followed by carboplatin/docetaxel[*] 3 – Lurbinectedin
5	No	2	10	1 – Carboplatin/paclitaxel[2] 2 – Carboplatin/paclitaxel 3 – Letrozole 4 – Leuprolide 5 – Bevacizumab 6 – Endoxifen[*] 7 – Temozolomide/methoxyamine 8 – Ixazomib/vorinostat 9 – Tamoxifen 10 – Lurbinectedin

RT = radiation therapy.

[1] Lines of systemic therapy are ordered chronologically.

[2] Postoperative adjuvant therapy following surgical staging.

[*] Longest duration of disease control following first disease recurrence.