

Coordinated Pembrolizumab and High Dose IL-2 (5-in-a-Row Schedule) for Therapy of Metastatic Clear Cell Renal Cancer

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Abstract

Pharmacologic ligation of the interleukin-2 receptor and immune checkpoint blockade may change lymphocytes to induce regression of various cancers. This study addressed the safety and feasibility of the combination of interleukin-2 and pembrolizumab in the treatment of metastatic clear cell renal cancer. Nineteen out of twenty-seven patients had partial or complete responses. No accrual stops for safety were triggered.

Introduction: The ligation of the interleukin-2 (IL-2) receptor and immune checkpoint blockade may each alter lymphocytes, thereby inducing regression in various cancers. Single agent objective response rates of 14% to 25% have been reported for usual schedule 14-dose-in-a-row IL-2 therapy of metastatic clear cell renal cancer (ccRCC), with a notable subset of responses being durable. Pembrolizumab yielded a 33% response rate in patients with metastatic ccRCC.

Patients and Methods: This study addressed the safety and feasibility of the combination of IL-2 and pembrolizumab in the treatment of metastatic ccRCC. Subjects were treated with four 9-week blocks of therapy, receiving pembrolizumab every 3 weeks in all blocks and receiving 4 courses of 5-planned-doses high dose IL-2 in each of blocks 2 and 3. Safety was monitored by a Pocock boundary of study suspension and re-evaluation if exceeding a 15% dose limiting toxicity rate at $\alpha = 0.05$. The Simon 2-stage design tested for an alternative hypothesis response rate of at least a 45% vs. a null hypothesis rate of less than 20%, with $\alpha = 0.10$ and 90% power **Results:** No accrual suspension for safety was triggered. The objective response rate was 70% (19/27, 95% CI: 0.50-0.86). Nine patients responded after pembrolizumab alone and ten responded after the addition of IL-2. At a minimum follow-up of 23 months, 9 of the responding patients had no disease progression requiring additional treatment. **Conclusion:** The combination of 5-planned-dose-schedule high dose IL-2 and pembrolizumab is feasible, with a high response rate, justifying further exploration of this dual immune treatment of metastatic ccRCC.

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Keywords: Immunotherapy, Pembrolizumab, Interleukin-2, Clear cell kidney cancer

Introduction

Interleukin-2 (IL-2) has been utilized in the treatment of metastatic clear cell renal cancer (mCCRC) for decades. IL-2 binds

to an activating receptor (CD25/CD122/CD132; IL-2R $\alpha\beta\gamma$) on lymphocytes and is associated with a single-agent response rate of approximately 15% to 20% and a durable complete response rate of 5% to 7%¹⁻⁴. Standard schedule 14-in-a-row high-dose IL-2 has shown increased efficacy when compared to subcutaneous IL-2 and interferon in the treatment of metastatic kidney cancer and is therefore a key consideration for this indication for those meeting selection criteria.^{2,5-6} Immune checkpoint inhibition has more recently impacted the treatment of kidney cancer.⁷ The interaction between PD-1 (CD279) and its ligand PD-L1 (B7-H1, CD274) serves to induce and maintain immune tolerance, and blocking this interaction is an effective treatment strategy in many malignancies, including mCCRC.⁸⁻¹⁰ For example, the PD-1 inhibitor nivolumab was shown to have a second-line response rate of 25%, and a single agent response rate of 36% has

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been reported for the PD-1 inhibitor pembrolizumab.^{11,12} CTLA-4 mediates immunosuppression by binding to CD80 and CD86, limiting the immunostimulatory interaction of CD28 with these ligands.¹³ The combination of the CTLA inhibitor ipilimumab and nivolumab showed an objective response rate of 42% in patients with intermediate and poor risk disease. Notably, 11% of patients had complete responses. In addition, there is increasing evidence that some responses are durable, with 28% of patients remaining free from progression at 30 months.⁷ Finally, VEGF-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) based therapy has been widely utilized in the treatment of kidney cancer since the approval of sunitinib in 2006, and in 2019 the combination of the VEGF/TKI axitinib with the checkpoint inhibitors pembrolizumab or avelumab yielded response rates of 59.3% and 51.4%, respectively.¹⁴⁻¹⁷ More recently, the combination of cabozantinib and nivolumab has yielded a response rate of 55.7% and the combination of lenvatinib and pembrolizumab a response rate of 71.0%.^{18,19} As such, combinations with PD-1 therapy now represent a key component of the treatment landscape for mCCRC. Selection criteria for PD-1 combination treatment typically are less restrictive than the good risk concentration for standard high dose IL-2 monotherapy, with several PD-1/CTLA and PD-1/VEGF directed therapies having a higher relative impact in patients with intermediate risk or poor risk stratification.^{7,15,18,20}

Notably, the administration and side effect profiles of high-dose IL-2 and of anti-PD-1 therapy differ significantly. High-dose IL-2 requires a controlled setting with experienced staff and requires patients to have verified cardiac and pulmonary reserve. In addition, high-dose IL-2 has been associated with acute episodes of capillary leak syndrome as well as with significantly reduced neutrophil function.²¹ Pembrolizumab, in contrast, can be delivered in the outpatient setting, but is associated with risks of autoimmune adverse events which can have significant latency, and which can require prolonged treatment with immunosuppressive agents.^{22,23}

There may nonetheless be important synergies between IL-2 based therapy and checkpoint blockade. Cells which bear receptors for IL-2 stimulation may be modulated by checkpoint inhibition either directly or through other lymphocytes, and lymphocytes which are effectors of checkpoint inhibition may respond to IL-2.²⁴⁻²⁶ Interestingly, patients treated with anti-PD-1 therapy have been shown to undergo early intra-tumoral migration of lymphocytes, which would be then plausibly ripe for modulation via IL-2 therapy.²⁷ In fact, there is evidence that IL-2 may be efficacious following PD-1/L1 based therapy in patients with kidney cancer.^{28,29} Pegylated formulations of IL-2 such as NKTR-214 (bempegaldesleukin) have also been a topic of recent clinical testing, and there is preliminary data to suggest that the combination of this treatment with anti-PD-1 therapy may have utility in several solid malignancies.²¹ Finally, the ability of IL-2 to induce decades-long durable responses in a minority of patients gives it particular appeal as a partner agent. As such, we undertook a phase II single arm, single institution study of the combination of pembrolizumab and 5-in-a-row schedule high-dose IL-2 in the treatment of mCCRC.

In summary some the rationale for the PD-1 treatment lead in part of the treatment included these: Mechanistically, there could

be beneficial lymphocyte migration into the tumor²⁷; for toxicity evaluation, if there were events of rapid-onset auto-immune events as may occur in PD-1 therapy, those would not be confused with events unique to combination treatment; and for translational evaluation this would give the opportunity for study the changes of leukocyte phenotype from baseline to PD-1 exposure and then from *PD-1 exposed* to *combination exposed*, that is the particular IL-2 effect in this context.

Materials and Methods

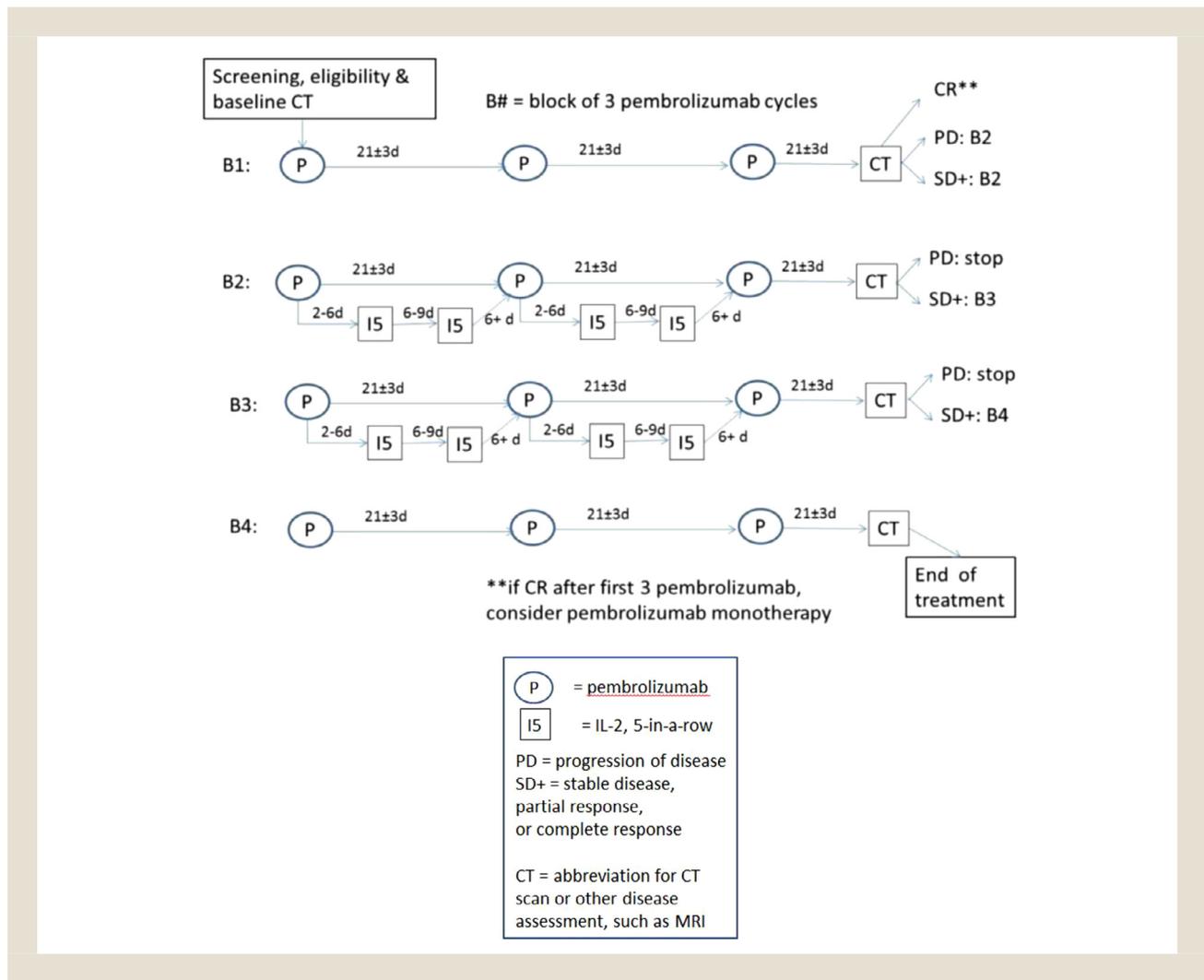
The trial was conducted at the Moffitt Cancer Center (Tampa, FL) with the approval of the Moffitt institutional review board. The Moffitt Cancer Center has extensive expertise in the delivery of IL-2. Patients were eligible if they had metastatic kidney cancer with a clear cell component and had measurable disease as per RECIST 1.1.³⁰ Patients were required to be relatively fit, with an ECOG performance status of 0 or 1.³¹ Patients also had to have acceptable laboratory parameters, including a creatinine of ≤ 1.5 times the upper limit of normal (ULN) or an estimated GFR of ≥ 60 , a hemoglobin of ≥ 9 g/dL, an absolute neutrophil count $\geq 1,500/\text{mcL}$, platelets $\geq 100,000$, total bilirubin ≤ 1.5 times ULN or direct bilirubin \leq ULN, and an AST ≤ 2.5 times ULN or ≤ 5 times ULN in patients with liver metastases. Finally, patients were required to have acceptable exercise stress testing or thallium stress testing within 3 months of treatment initiation unless a cardiologist deemed this unnecessary, and acceptable pulmonary function testing within 3 months of treatment initiation. Patients were excluded if they had active brain metastases, active autoimmune disease requiring systemic treatment within the past 2 years, more than 1 systemic therapy in the prior year, any therapy with IL-2 within 1 year, or therapy with anti-PD-1 or anti-PD-L1 agents at any time.

The primary objective of the study was to determine the anti-tumor activity of the treatment, as defined by a hypothesis of an objective response rate of at least 45% among ever-treated patients, and to determine whether the treatment could be delivered safely, as evaluated via a sequential toxicity boundary method.³² Secondary objectives included: (1) assessing the objective response rate for patients receiving at least 4 doses of pembrolizumab with 1 dose of IL-2, (2) assessing the objective response rate for patients receiving at least twenty doses of IL2 with at least 6 doses of pembrolizumab (half the planned doses), and (3) determining if the objective response rate and/or survival at 1 year were not more than 20% lower than that of matched controls identified in the PROCLAIM database of IL-2 treated patients. Exploratory objectives included an assessment of several correlative markers, which will be reported separately.

Patients received pembrolizumab at the standard dose and frequency of 200 mg every 3 weeks, with a total of 12 doses provided, organized as 4 blocks of 3 doses. Following the first and second doses of pembrolizumab in the second and third blocks of treatment (as detailed in Figure 1), patients underwent 2 weekly courses of treatment with 5-in-a row high-dose IL-2 (with each course consisting of 600,000 IU/kg of IL-2 given every 8 hours for up to 5 doses as tolerated). As such, patients were planned to receive 20 doses of IL-2 in the second and third 9-week blocks of treat-

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Figure 1 Protocol schema.



ment. Missed doses, for either medication, were not made up. Of note, this 5-in-a-row dose schedule has been shown to have relatively uniform dose delivery while maintaining a similar toxicity profile and response rates to the traditional 14-in-a-row schedule.³³

Patients underwent CT imaging at baseline, every 9 weeks during active treatment, and then every 2 to 3 months for 24 months.

A Simon 2-stage minimax design, with a 10% type I (alpha) error and a 90% power, was utilized to test the null hypothesis of an objective response rate of at most 20%, vs. an alternative hypothesis objective response rate of at least 45%.³⁴ The 95% confidence interval for the response rate was calculated using the Wilson score methods.³⁵ Patients were considered evaluable for the efficacy analysis if they received at least 1 dose of pembrolizumab and 1 dose of IL-2. In the initial stage, 15 patients were to be evaluated, and if 3 or fewer responded, the trial accrual was to be terminated. In the second stage, an additional 9 patients were to be evaluated, and if at least 8 patients responded between the 2 stages, the null hypothesis would be rejected. Up to 26 patients were to be enrolled, to allow for patients who were not evaluable.

A sequential boundary method was utilized to monitor dose-limiting toxicities.³² This accommodated an open-ended follow-up period for the earlier subjects while the latter were just starting. This was accomplished with a Pocock-type stopping boundary, yielding a probability of crossing the boundary of at most 0.05 when the rate of dose limiting toxicities was at the acceptable limit of 15%. Patients who had received at least 1 dose of pembrolizumab were included in the safety evaluation.

Results

A total of 27 patients enrolled in the study, of whom 26 received any study treatment. Baseline demographics and disease characteristics were as expected for a group of patients with advanced kidney cancer who were nonetheless fit enough to undergo a relatively intensive treatment protocol (Table 1). IMDC risk category was favorable for 37%, intermediate for 59%, and poor for 4%. The median age was 60, and 37% of patients were at least 65 years old. One patient had been previously treated with (standard schedule)

Table 1 Demographics and Disease Characteristics at Baseline (N = 27)

Characteristic	
Age	
Median (range) – years	60
<65 y - number (%)	17 (63)
Men sex - number (%)	22 (81)
IMDC prognostic risk - number (%)	
Favorable	10 (37)
Intermediate	16 (59)
Poor	1 (4)
Number with tumor at specific sites:	
Kidney	5
Renal bed	2
Lung or pleura	17
Liver	3
Bone	2
Adrenal	3
Any LN	14
Mediastinal LN	12
Other LN	7
Other*	7

* One each: Brain; pancreas; chest wall; gluteal; paraspinal; soft tissue of hip; retroperitoneum.

Table 2 Summary of Objective Responses

Objective response rate - number (%)	19 (70)
Best objective response - number (%)	
Complete Response	5 (19)
Partial Response	14 (52)
Stable disease	5 (19)
Progressive disease	2 (7)
Not Assessed	1 (4)*

* One patient did not receive any study treatment after baseline imaging was obtained

high-dose IL-2 several years before enrollment. Prior VEGFR-TKI treatment and progression were allowed, but actually none enrolled, so all the

Dose delivery for the planned up to 12 doses of pembrolizumab had a median of 12 doses – 14 subjects missed none – and average of 9.9 doses; for IL-2 planned up to 40 doses there was a median 25 doses and average 22.6, counting as 0 those courses in which the subject was not still on study or the subject was not even admitted.

As detailed in Table 2, 5 patients (19%) had a complete response to therapy, and 14 patients (52%) had a partial response, yielding an objective response rate of 70% (95% CI: 0.50-0.86), exceeding the response requirements to successfully reject the null hypothesis. Nine patients responded after pembrolizumab monotherapy was delivered in block one. Eight of these patients went on to receive high-dose IL-2, and 1 patient had very good disease response after monotherapy and declined to proceed with the administra-

tion of high-dose IL-2 due to other personal circumstances. Ten additional patients responded after treatment with the combination of IL-2 and pembrolizumab (9 patients after block 2 and 1 patient responded after block 3).

The objective response rate for patients receiving at least 4 doses of pembrolizumab and 1 dose of IL-2 was 77% (17/22, 95% CI: 0.54-0.91), and the objective response rate for patients receiving at least 6 doses of pembrolizumab plus at least twenty doses of IL-2 was 82% (14/17, 95% CI: 0.56-0.95). In addition, all patients in our study were alive at 1 year. While a formal comparison against matched controls in the PROCLAIM database was not carried out, the combination of 5-in-a-row high-dose IL-2 and pembrolizumab has a higher rate that appears to compare favorably to usual-14-in-a-row high-dose IL-2 alone.

The Kaplan-Meier estimate for progression free survival at 12 months was 63% (95% confidence interval 42% to 78%). Kaplan-Meier estimates for overall survival and progression-free survival are detailed in Figures 2 and 3, respectively.

As detailed in Figure 4, 9 patients (including 1 patient who received only pembrolizumab) continue without any further cancer-specific treatment for progression as of data cut-off, with a minimum follow-up of 23 months and a median follow-up of 27 months. Of the patients who have thus far progressed, 6 (1 with prior brain disease that was treated) progressed via the development of new brain metastases, making this the most common new site of progression. The latencies of the brain metastases detection, counting from start of treatment, were 182, 195, 211, 218, 293 and 793 days (indicated by the letter B in the figure).

Treatment-related adverse events are detailed in Table 3. No grade 5 events occurred. The most common grade 3 or 4 treatment-related events were decreased urinary output (37%), lymphopenia (26%), hypotension (33%), and hypophosphatemia (26%), all common in patients receiving various schedules of high dose IL-2.^{2,4-6,37-39} A formal cross-trial comparison of event-frequencies was not conducted.

Discussion

The primary objective of the study was met, as the response rate significantly exceeded that required to reject the null hypothesis. Notably, there was a relatively high rate (19%) of complete responses, and relatively high overall response rate (70%). As a point of reference, larger 14-in-a-row (standard, current label) schedule for high dose IL-2 had had randomized trial response rates of 23.2% (5) 25% (5b), 15% (2); and retrospective data set 15% (4); differences of patient selection among these, and vs. the present series are definitely acknowledged, although the intent for the present series was to have a “usual IL-2” type of patient selection. The objective response rate of 70% reported in the present study with the 5-in-a-row IL-2 schedule compares to a response rate of 24.5% in favorable risk patients treated with (mostly) standard schedule high-dose IL-2 alone as per the PROCLAIM registry, 26.0% in intermediate risk patients treated with high-dose IL-2 alone, and 17.2% in poor risk patients treated with high dose IL-2 alone.³⁶

One significant benefit of the treatment regimen was that a number of patients obtained long, unmaintained treatment-

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Figure 2 Overall survival with 95% confidence interval detailed.

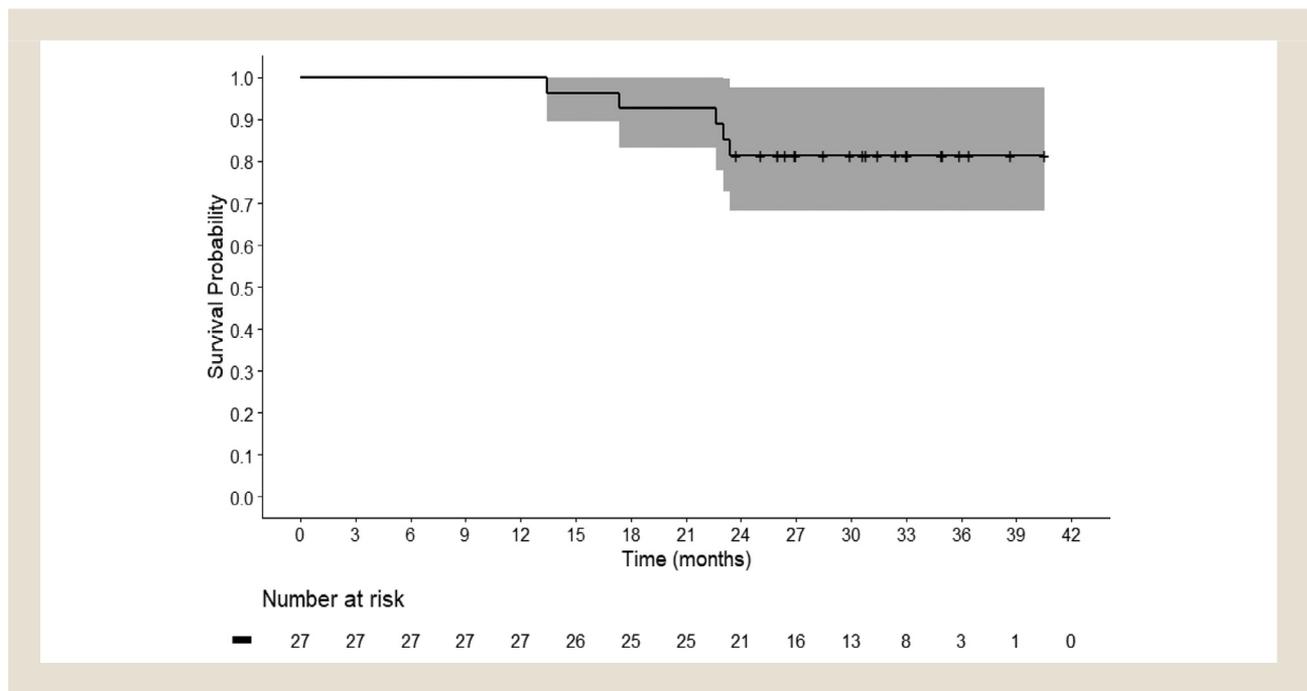
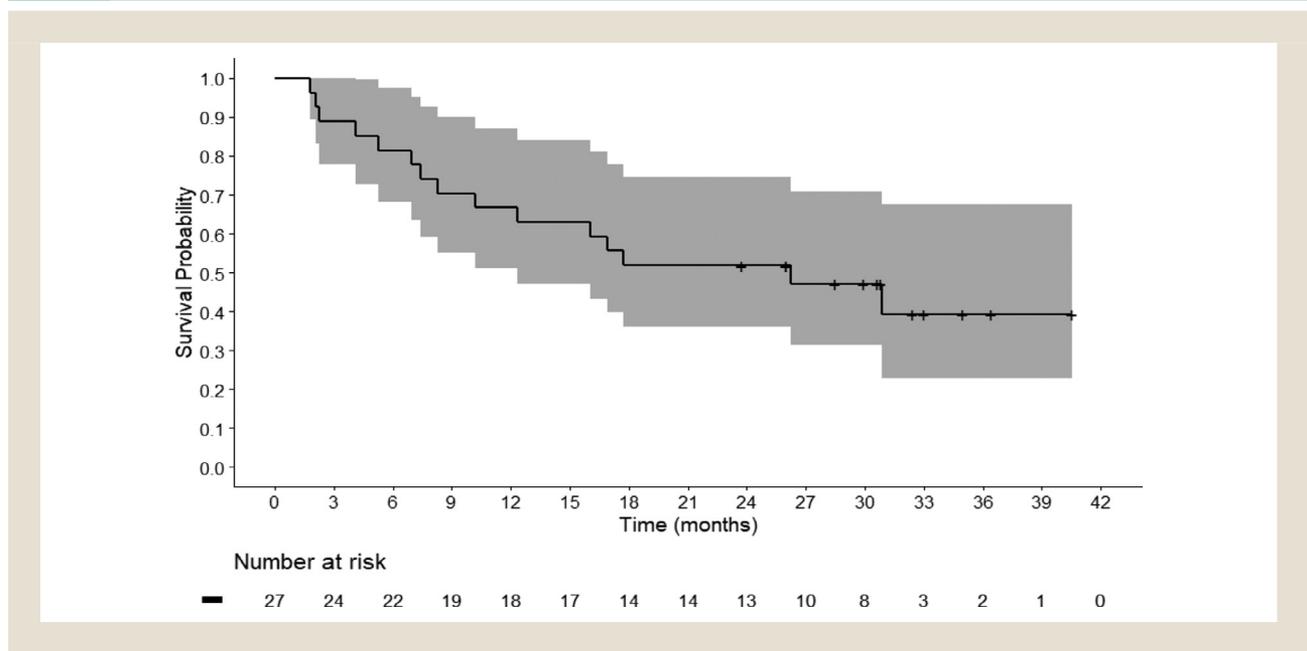


Figure 3 Progression free survival with 95% confidence interval detailed.



free intervals following study therapy, which is an outcome of increasing interest in cancer care.⁴⁰ In addition, the treatment met the pre-specified safety end points. These data did not show any large increase in autoimmune events with the combination of the 2 therapies. It is acknowledged that once the 2-part portion of the treatment started, attribution of any particular adverse event to 1 or the other of the medications could not be made definitively. The adverse events that were observed

appear to be consistent with the known side effect profile of the 2 medications.

Notably, there was a higher than anticipated incidence of brain metastases in the study population, but this finding may be due to the relatively small number of patients studied. At least 2 patients had regression of pulmonary lesions concurrently with progression in the brain, potentially indicating a difference in the anti-tumor effects of the treatment for brain metastases as compared to other

Figure 4 Time on treatment, subsequent survival off treatment, and overall survival Legend: Vertical striping: Time on combination pembrolizumab and IL-2. Thin horizontal line: Time on no treatment, and without any other medical therapy. Diagonal fill: Time on no medical treatment, but after a local therapy after study treatment, Letters indicate timing and type of initial post-study treatment: B: Brain metastasis treated with radiation or (B*) surgery and radiation, L: Local resection (1 renal radiofrequency ablation, 1 adrenal resection), X: Local treatment (mediastinal lymph node radiation therapy), M: Start of other medical therapy.

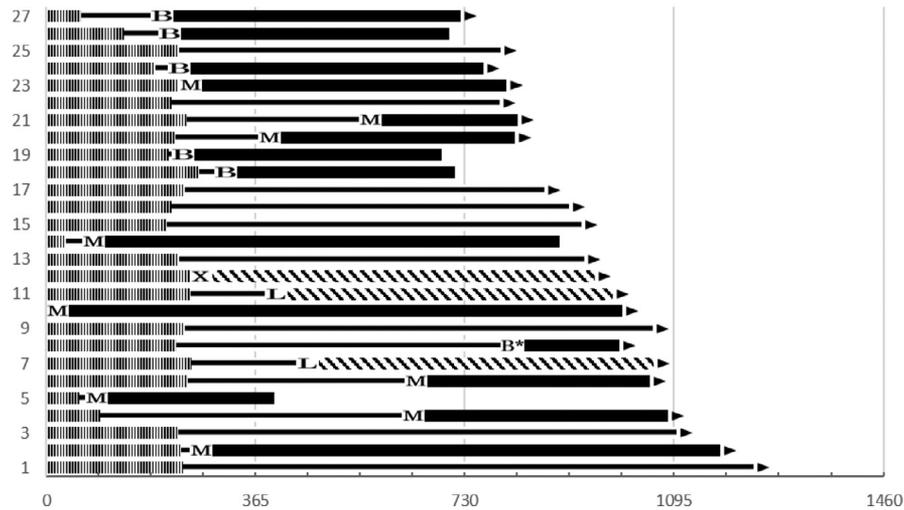


Table 3 Adverse Events Which are at Least Possibly Treatment-Related and Which Occurred in >10% of Patients (N=27)

Adverse Event – number (%)	Number of Patients (Percent)					Total
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
Decreased Urinary Output	1 (4)	0 (0)	9 (33)	1 (4)	0 (0)	11 (41)
Hypotension	0 (0)	0 (0)	8 (30)	1 (4)	0 (0)	9 (33)
Sinus tachycardia	4 (15)	2 (7)	2 (7)	0 (0)	0 (0)	8 (30)
Lymphocyte count decreased	0 (0)	0 (0)	0 (0)	7 (26)	0 (0)	7 (26)
Creatinine increased	0 (0)	3 (11)	4 (15)	0 (0)	0 (0)	7 (26)
Hypophosphatemia	0 (0)	0 (0)	7 (26)	0 (0)	0 (0)	7 (26)
Leukocytosis	0 (0)	0 (0)	6 (22)	0 (0)	0 (0)	6 (22)
Acute kidney injury	1 (4)	1 (4)	3 (11)	1 (4)	0 (0)	6 (22)
Rash maculo-papular	3 (11)	2 (7)	0 (0)	0 (0)	0 (0)	5 (19)
Hyponatremia	1 (4)	0 (0)	4 (15)	0 (0)	0 (0)	5 (19)
Blood bilirubin increased	0 (0)	0 (0)	4 (15)	0 (0)	0 (0)	4 (15)
Dyspnea	1 (4)	1 (4)	1 (4)	1 (4)	0 (0)	4 (15)
Arthralgia	0 (0)	1 (4)	3 (11)	0 (0)	0 (0)	4 (15)
Atrial fibrillation	0 (0)	1 (4)	3 (11)	0 (0)	0 (0)	4 (15)
Capillary leak syndrome	0 (0)	1 (4)	1 (4)	1 (4)	0 (0)	3 (11)
Dry skin	2 (7)	1 (4)	0 (0)	0 (0)	0 (0)	3 (11)
Pruritus	3 (11)	0 (0)	0 (0)	0 (0)	0 (0)	3 (11)
Fatigue	1 (4)	1 (4)	1 (4)	0 (0)	0 (0)	3 (11)
Fever	2 (7)	1 (4)	0 (0)	0 (0)	0 (0)	3 (11)

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sites of disease. The latencies from treatment start to identification of the brain lesions were at a minimum of 6 months, but not clustered at a point after pembrolizumab had stopped. While the efficacy of IL-2 in the treatment of brain metastases from clear cell renal cancer is not well-defined, anti-PD-1 therapy has been shown to have limited efficacy for central nervous system metastases from mCCRC.⁴¹ In practice, the treatment for brain metastases is primarily via surgery or radiation rather than systemic therapy.⁴²

The limitations of our study include the fact that it is a single arm, single institutional experience, and as such the generalizability of the results may be limited. In addition, rates of severe toxicity related to IL-2 may be lower at high-volume centers.⁴³ Further, the specific contribution of IL-2 to the response rate, or to the durability of response, particularly in those patients who had a response easily demonstrated after the first block of pembrolizumab monotherapy, remains undefined. While the response rate in our study was significant, other combinations such as axitinib and avelumab (51.4%), axitinib and pembrolizumab (59.3%), cabozantinib and nivolumab (55.7%), and lenvatinib and pembrolizumab (71.0%) also have impressive response rates, with eligibility criteria that were less strict and did not require dedicated cardiac or pulmonary function testing prior enrollment.^{14,15,18,19} Notably, however, no patients were excluded due to these screening evaluations in our study.

Conclusion

This study has demonstrated the feasibility and potential efficacy of combining high dose IL-2 and pembrolizumab in patients with mCCRC, potentially adding IL-2 to the list of suitable partners for anti-PD-1/L1 therapy in the treatment of this disease. A direct efficacy and toxicity comparison in a prospective, randomized multicenter format would serve to confirm this experience. The observed tolerability, response rate, and frequency of unmaintained durable response are encouraging. Other combinations, such as that of nivolumab with pegylated IL-2 formulations (NKTR, bempedalesleukin), and ALKS-4230 IL-2/IL2R $\alpha\beta\gamma$ combination, continue to be subjects of active investigation.^{21,44} Whereas aldesleukin has a half-life of between 13 and 85 minutes, bempedalesleukin has a pegylated prodrug that gradually generates an active cytokine that preferentially binds to IL2R $\beta\gamma$, thus minimizing stimulation of IL2R $\alpha\beta\gamma$ and T regulatory compartment.⁴⁵ As such, the specific immune changes and subsequently the anti-tumor effect of these 2 compounds may differ in practice. As additional effective combinations are found, ideal sequencing is another area of interest.⁴⁶ While our study evaluated the role of IL-2 and pembrolizumab in the first line, there may potentially be a role for this therapy as a salvage regimen following progression on PD-1 or on VEGF type treatments. In addition, whereas IL-2 is best studied in melanoma and in renal cancer, pembrolizumab is utilized in a wide variety of different tumor types and has efficacy in tumors of all types with microsatellite instability-high or mismatch repair deficient status.^{4, 47} IL-2 may therefore represent a partner agent that could be tested for a capacity to boost the durable response rate of pembrolizumab in a variety of tumor types. An analysis of laboratory and clinical factors correlated to treatment with pembrolizumab, interleukin-2 and response will be reported separately.

Clinical Practice Points

- IL-2 has a single-agent response rate of 15% to 20% and a durable complete response rate of 5% to 7%.
- A single-agent response rate of 36% has been reported for the PD-1 inhibitor pembrolizumab.
- There may be important synergies between these therapies, as cells which bear receptors for IL-2 stimulation may also be modulated by checkpoint inhibition, either directly or indirectly.
- The present single arm, single-institution study evaluated the combination of these 2 agents in patients with metastatic clear cell renal cancer.
- Subjects were treated with four 9-week blocks of therapy, receiving pembrolizumab every 3 weeks in all blocks and receiving 4 courses of high dose IL-2 in each of blocks 2 and 3.
- Nineteen out of 27 patients responded to therapy, including 9 patients who responded after pembrolizumab alone and ten patients who responded after the addition of IL-2.
- No accrual stop for safety was triggered.
- The combination of pembrolizumab and IL-2 if a safe, feasible, and potentially effective therapy for metastatic clear cell renal cancer.

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Disclosure

MF has participated as paid advisory board member for Merck and for Clinigen in relation therapies for metastatic kidney cancer.

CreDIT statement

Jonathan Chatzkel: Writing – original draft, Visualization, Investigation. **Michael J. Schell:** Methodology, Formal Analysis, Data Curation, Writing - review & editing, Visualization. **Jad Chahoud:** Writing – review & editing, Investigation. **Rohit Jain:** Writing – review & editing, Investigation. **Jingsong Zhang:** Writing – review & editing, Investigation. **Jennifer Swank:** Investigation; Steve Ludlow: Investigation. **Kristina Lombardi:** Investigation. **Yesenia Lucas:** Investigation. **Cortlin Croft:** Investigation. **Jennifer Rembisz:** Investigation. **Gigi Jameel:** Investigation. **Mayer Fishman:** Conceptualization, Writing – review & editing, Visualization, Project Administration, Funding acquisition, Investigation.

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