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Salvage Therapy With Multikinase Inhibitors and Immunotherapy in Advanced Adrenal Cortical Carcinoma

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Background: Median overall survival is 12 to 15 months in patients with metastatic adrenal cortical carcinoma (ACC). Etoposide, doxorubicin, and cisplatin with or without the adrenolytic agent mitotane is considered the best first-line approach in this context, but has limited activity and no curative potential; additional salvage therapeutic options are needed.

Methods: Fifteen total patients with recurrent/metastatic ACC were treated with single-agent multikinase inhibitors (MKI) (n = 8), single-agent PD-1 inhibition (n = 8), or cytotoxic chemotherapy plus PD-1 inhibition (n = 4) at our institution as later-line systemic therapies in efforts to palliate disease and attempt to achieve a therapeutic response when not otherwise possible using standard approaches.

Results: Two of 8 patients (25%) treated with single-agent MKI achieved a partial response (PR), including 1 PR lasting 23.5 months. Another 3 patients (38%) had stable disease (SD); median progression-free survival (PFS) with single-agent MKI was 6.4 months (95% confidence interval [CI] 0.8—not reached). On the other hand, 2 of 12 patients (17%) treated with PD-1 inhibitors (either alone or in combination with cytotoxic chemotherapy) attained SD or better, with 1 patient (8%) achieving a PR; median PFS was 1.4 months (95% CI 0.6-2.7).

Conclusions: Our single-institution experience suggests that select ACC patients respond to late-line MKI or checkpoint inhibition despite resistance to cytotoxic agents. These treatments may be attractive to ACC patients with limited other therapeutic options. The use of MKI and immunotherapy in ACC warrants prospective investigation emphasizing parallel correlative studies to identify biomarkers that predict for response.

Key Words: adrenal cortical carcinoma, adrenocortical carcinoma, adrenal cancer, tyrosine kinase inhibition, checkpoint inhibition, immunotherapy

While benign tumors of the adrenal gland are common, adrenal cortical carcinoma (ACC) is extremely rare, with an incidence in the range of 0.7 to 2.0 cases per 1 million per year [1,2]. Surgical resection is the cornerstone of initial management [3,4]. The adrenolytic agent

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mitotane is often considered in patients with resected ACC with high-risk features in the adjuvant setting [5,6] but carries a significant side effect burden [7].

Unfortunately, ACC is highly malignant; roughly half of patients initially present with stage III or IV disease [3]. Further, the majority of patients eventually develop recurrent disease, after which the median overall survival (OS) is approximately 12 to 15 months [8]. The standard of care in the advanced setting was established by Fassnacht et al in the FIRM-ACT trial in 2012, which compared streptozocin plus mitotane to etoposide, doxorubicin, and cisplatin plus mitotane (EDP-M) [8]. EDP-M demonstrated a superior progression-free survival (PFS) in the trial (5.0 vs 2.1 months; $P < 0.001$), but there was no significant difference in OS between the 2 study groups (14.8 vs 12.0 months, respectively; $P = 0.07$). The response rate with EDP-M was also modest at 23%, and >75% of patients progressed within 1 year of starting therapy.

Other salvage therapy options for patients ACC include oral etoposide, oral cyclophosphamide, and several gemcitabine combinations, all of which have dismal response rates [9-11]. Mitotane also has poor efficacy as a single-agent [12]. Hence, there is a desperate need for effective salvage therapies for advanced ACC that progresses through first-line EDP therapy. The rationale for PD-1 inhibition in ACC includes the presence of demonstrable *PD-L1* expression and tumor-infiltrating lymphocytes in ACC samples, as well as the intermediate mutational burden, which correlates with checkpoint blockade efficacy in other tumor types [13-16]. Multikinase inhibitors (MKI) have been tested in advanced ACC, with modest efficacy [17-20].

In our practice, we have used MKI and checkpoint inhibitors as salvage therapies in ACC when patients desire more treatment, have reasonable performance status, and have progressed through standard salvage regimens. Herein we describe a cohort of patients who were treated with MKI and/or immunotherapy for recurrent/metastatic (R/M) ACC, detailing their clinical responses, toxicity, PFS, and OS.

Methods

Patients

This single institution retrospective cohort study was approved by the Mayo Clinic Institutional Review Board. Patients were included in the study if they were ≥18 years old at diagnosis of R/M ACC from January 1, 2012 to November 1, 2018 and were treated at Mayo Clinic Rochester with either MKI or checkpoint inhibitors. The diagnosis of ACC was required to be histologically confirmed by at least 1 expert endocrine pathologist at our institution. Standard European Network for the Study of Adrenal Tumors (ENSAT) was used to define stage [21]. Characteristics, treatment details, and dates of diagnosis, locoregional recurrence, metastasis, and death were obtained from review of the medical record. Adjuvant mitotane refers to mitotane started within several months of curative-intent surgery, regardless of recurrence status.

T_0 refers to the date of ACC recurrence, or the date of diagnosis for patients who initially presented with metastatic disease (stage IV). The first line of treatment was defined as first treatment after T_0, irrespective of whether salvage surgery was performed or not. Subsequent lines of treatment were delineated thereafter. The lines and duration of therapy where abstracted from the medical record. Best response to treatment was characterized on the basis of review of radiologic images by the study authors, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria [22]. Imaging was performed at Mayo Clinic Rochester for all patients in the study. Objective response rate (ORR) was defined as the proportion of patients achieving partial response (PR) or better. Clinical benefit rate (CBR) was defined as the proportion of patients achieving stable disease or better.

Cabozantinib, Lenvatinib, and pembrolizumab were obtained through insurance or via patient assistance programs if the patients' insurance did not approve the medications. Patients were counseled on the off-label nature of the therapies.

Statistics

PFS was estimated using the Kaplan-Meier method for patients treated with MKI and pembrolizumab (either alone or in combination with cytotoxic chemotherapy) from the time of treatment initiation until RECIST tumor progression or death, with patients who remained alive and progression-free censored at the time of last follow-up (through January 27, 2020). OS was estimated using the Kaplan-Meier method and defined as the time from treatment initiation to death from any cause for the 2 principal treatment groups (ie, MKI and pembrolizumab), with patients who remained alive censored at the date of last follow-up. OS was also calculated from T_0 to death for the entire cohort. OS was summarized at 1, 2, and 3 years from T_0. Median PFS and OS were also summarized, along with 95% confidence intervals (CI). Median follow-up time was calculated using the reverse Kaplan-Meier method [23]. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, US) or R version 3.4.2 (R Core Team, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Results

Patient characteristics

Fifteen patients (denoted MC1 to MC15) were treated at our institution with MKI and/or immunotherapy for R/M ACC. Eight patients (53%) were treated with single-agent MKI, whereas 12 patients (80%) were treated with pembrolizumab, either as a single-agent or in combination with cytotoxic chemotherapy (ie, cyclophosphamide or gemcitabine/docetaxel). Five of the 15 patients (MC3, MC4, MC7, MC13, and MC15) were treated both with single-agent MKI and single-agent pembrolizumab as separate lines of therapy during the follow-up period.

The median age at diagnosis for the cohort was 43 (range 19-62). Eight patients (53%) were male. Two patients had known germline mutations: 1 (MC8) with mutated *TP53* (c.1010G>A, p.R337H; known pathogenic variant causing Li-Fraumeni syndrome) 1 (MC12) with mutated *CDKN2A* (c.197A>C, p.His66Pro; associated with familial melanoma syndromes; patient had a personal history of melanoma and strong family history of cancer) [24].

At diagnosis, ENSAT stage was as follows: stage I (n = 1, 7%), stage II (n = 4, 27%), and stage III (n = 5, 33%), whereas 5 patients (33%) presented with metastatic disease (stage IV). Other baseline and treatment characteristics are shown in Table 1.

The minority of patients (n = 5, 33%) received adjuvant mitotane therapy for their primary treatment. Median time from diagnosis to T_0 in the 10 patients without metastatic disease at diagnosis was 7.5 months (range 4.5-21.7). Four of the 5 patients (80%) who presented with metastatic disease underwent palliative debulking surgery. Five of 15 patients (33%) had Cushing's features at diagnosis and were managed with metyrapone (n = 3) and ketoconazole (n = 2).

The median follow-up time from diagnosis was 83.0 months (95% CI 22.5-83.0). During the follow-up period, 10 patients (67%) died.

Conventional chemotherapy regimens

The majority of patients received etoposide, doxorubicin, and cisplatin (EDP) as the first-line regimen for R/M disease (n = 9, 60%). Two others (13%) were treated with EDP-M, for a combined total of 11 patients (73%) receiving first-line EDP-based therapy. One patient (13%) received single-agent mitotane for R/M disease. One patient was treated with high-dose interleukin-2 for what was initially thought to be renal cell carcinoma at an outside institution but upon review at our institution was demonstrated to be ACC and treated as

Table 1. Demographic and treatment characteristics

Characteristic	N (%) or Median (Range) Total N = 15
Gender	
Male	8 (53)
Female	7 (47)
Age at diagnosis	43 (19-62)
Cushing's syndrome at diagnosis	5 (33)
Stage at diagnosis	
I	1 (7)
II	4 (27)
III	5 (33)
IV	5 (33)
Primary surgery	
Yes	14 (93)
No	1 (7)
Adjuvant radiation	
Yes	2 (14)
No	12 (86)
Missing	1
Adjuvant mitotane	
Yes	5 (36)
No	9 (64)
Missing	1
First line salvage treatment	
EDP	9 (60)
EDP-M	2 (13)
Mitotane	1 (7)
Other	3 (20)

Abbreviations: EDP, etoposide, doxorubicin, cisplatin; M, mitotane.

such thereafter. Ten of the 11 patients treated with EDP or EDP-M had available response information; 6 (60%) had a PR to first-line EDP-based salvage therapy.

Fourteen of 15 patients (93%) received second-line therapy. Median time between the start of first line therapy and the start of second line therapy was 7.5 months (range 0.7–21.2). In the second line, eight patients (57%) received gemcitabine-based regimens. The remaining 6 patients (43%) received other therapies, including oral etoposide (n = 2, 14%), MKI/immunotherapy (n = 1, 7%), mitotane (n = 1, 7%), EDP (n = 1, 7%), and oral cyclophosphamide (n = 1, 7%) in the second line. Thirteen patients (87%) received third-line therapy, the majority (n = 8, 62%) with MKI/immunotherapy.

Salvage multikinase inhibitor therapy

Eight patients (53%) in total were treated with single-agent MKI. Seven of these patients (88%) received lenvatinib, whereas 1 (12%) received cabozantinib. Responses were as follows: 2 PR, 3 stable disease (SD), and 3 progressive disease (PD), for a CBR of 63% and ORR of 25%. Duration of therapy and best-response for these 8 patients is depicted in Fig. 1A and Table 2.

One of the patients who achieved a PR (MC3) received lenvatinib as his ninth line of therapy (after previously progressing on pembrolizumab). Chest computed tomography (CT) scans demonstrating the PR of his lung metastasis while on lenvatinib are shown in Fig. 2. Interestingly, he maintained this PR for 23.5 months before discontinuing therapy and subsequently progressing (Fig. 1A). In addition, MC14 received lenvatinib as first-line therapy for R/M ACC, achieved a PR, and remains alive on lenvatinib monotherapy 5 months later.

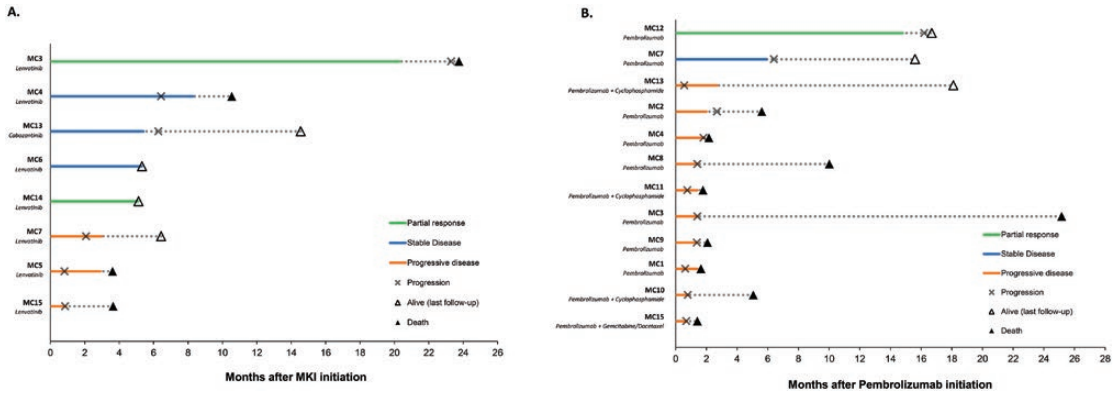

Figure 1. Swimmer's plot demonstrating the duration of treatment, best objective response, and survival from the date of initiation of multikinase inhibitors (**A**) and pembrolizumab (**B**) in the cohort of patients (indicated on the left). Colors of the line indicate the best response on treatment. The length of the colored line indicates the duration of time the patient was on treatment. Disease progression is indicated by X. Vital status at the time of last follow-up (alive vs dead) is indicated by the triangles. Dotted lines indicate follow-up time.

There were other notable clinical courses in patients treated with single-agent MKI: MC13 had SD on cabozantinib lasting 6 months after previously progressing through EDP, gemcitabine/docetaxel and cyclophosphamide plus pembrolizumab; MC4 had SD with lenvatinib as third-line therapy that lasted 6 months before further disease progression. (Fig. 1A).

Six of the 8 patients (75%) received mitotane prior to initiating MKI therapy. Median time from cessation of mitotane to initiation of MKI therapy was 239 days (range 48-579). In the 2 patients who achieved a PR with lenvatinib, MC3 and MC4, the time off mitotane was 385 and 252 days, respectively. None of the 8 patients were on steroidogenesis inhibitors during MKI therapy.

During the follow-up period, median time on MKI was 5.2 months (range 0.9-20.3), with 2 patients (25%) alive and continuing on MKI therapy at the time of last follow-up. Median PFS for patients treated with single-agent MKI, from the time of initiation, was 6.3 months (95% CI 0.8—not reached). Median OS from the time of MKI initiation was 17.2 months (95% CI 3.6—not reached) (Fig. 3A).

Salvage immunotherapy

In total, 12 patients (80%) were treated with the PD-1 inhibitor pembrolizumab, either alone or in combination with cytotoxic chemotherapy (Fig. 1B, Table 2). Eight of these patients (67%) were treated with single-agent pembrolizumab. Four (33%) were treated with cytotoxic chemotherapy (oral cyclophosphamide, n = 3; gemcitabine and docetaxel, n = 1) and concurrent pembrolizumab. Five of 12 patients (42%) were on steroidogenesis inhibitors (metyrapone, n = 3; ketoconazole, n = 2) while receiving pembrolizumab.

In the 8 patients who were treated with single-agent pembrolizumab, responses were as follows: 1 PR, 1 SD, and 6 PD. After treatment with the combination of cytotoxic chemotherapy plus pembrolizumab, all 4 patients had PD. Taken together, 1 patient (8%) had PR, 1 (8%) had SD, and 10 (83%) had PD, equating to a CBR of 17% and ORR of 8%.

The only objective response to single-agent checkpoint blockade occurred in MC12, who had a PR after 3 cycles of single-agent pembrolizumab. Representative chest CT scans are shown in Fig. 4. Interestingly, this patient had a germline *CDKN2A* mutation. He remained on pembrolizumab for 15 months until he developed significant transaminitis due to immune-related hepatitis, leading to discontinuation (see the following discussion), and then subsequent progression. Median time on pembrolizumab for all patients in this

Table 2. Reponses to treatment with multikinase inhibitors and immunotherapy

Treatment	Total N = 15[a]
Multikinase inhibitor (MKI), n (%)[b]	8 (53)
Earliest line of treatment, n (%)[c]	
1	2 (25)
3	2 (25)
4	1 (13)
5	1 (13)
6	1 (13)
9	1 (13)
Length of treatment (months), median (range)	5.2 (0.9-20.3)
Response, n (%)[c]	
Partial response	2 (25)
Stable disease	3 (38)
Progressive disease	3 (38)
Pembrolizumab, n (%)	8 (53)
Earliest line of treatment, n (%)[c]	
2	1 (13)
3	2 (25)
4	3 (38)
5	1 (13)
8	1 (13)
Length of treatment (months), median (range)	1.6 (1.4-14.8)
Response, n (%)[c]	
Partial response	1 (13)
Stable disease	1 (13)
Progressive disease	6 (75)
Pembrolizumab + cytotoxic chemotherapy, n (%)[d]	4 (27)
Earliest line of treatment, n (%)[c]	
3	4 (100)
Length of treatment (months), median (range)	1.1 (0.7-2.7)
Response, n (%)[c]	
Partial response	0 (0)
Stable disease	0 (0)
Progressive disease	4 (100)

[a]Five patients were counted twice in this table. MC4 received lenvatinib followed by pembrolizumab. MC15 received lenvatinib followed by pembrolizumab + gemcitabine/docetaxel. MC3 and MC7 received pembrolizumab followed by lenvatinib. MC13 received pembrolizumab + cyclophosphamide followed by cabozantinib.
[b]MKI includes lenvatinib and cabozantinib.
[c]Percentages calculated from the number of patients with the corresponding type of treatment.
[d]Cytotoxic chemotherapy includes cyclophosphamide (n = 3) and gemcitabine/docetaxel (n = 1).

cohort was 1.4 months (range 0.7-14.8). Three of 12 patients (25%) were alive at the time of last follow-up, but all 3 having discontinued pembrolizumab for either progression or toxicity. Median PFS for patients treated with single-agent pembrolizumab from the time of initiation was 1.4 months (95% CI 0.6-2.7). Median OS from the time of initiation of pembrolizumab was 5.3 months (95% CI 1.6—not reached) (Fig. 3B).

Toxicities of treatment with MKI/immunotherapy

Two patients (20%) experienced dose-limiting toxicities related to immunotherapy, but no patients had dose-limiting toxicity attributable to single-agent MKI. As previously mentioned, 1 patient (MC12) developed immune-related hepatitis, which resolved with corticosteroids and discontinuation of pembrolizumab. Another patient (MC10) developed dyspnea while on pembrolizumab plus cyclophosphamide in the setting of recent radiation to chest. While thought to be temporally consistent with radiation-induced pneumonitis, immunotherapy was indefinitely stopped for concern of immune-related pneumonitis [25], and their symptoms resolved shortly thereafter.

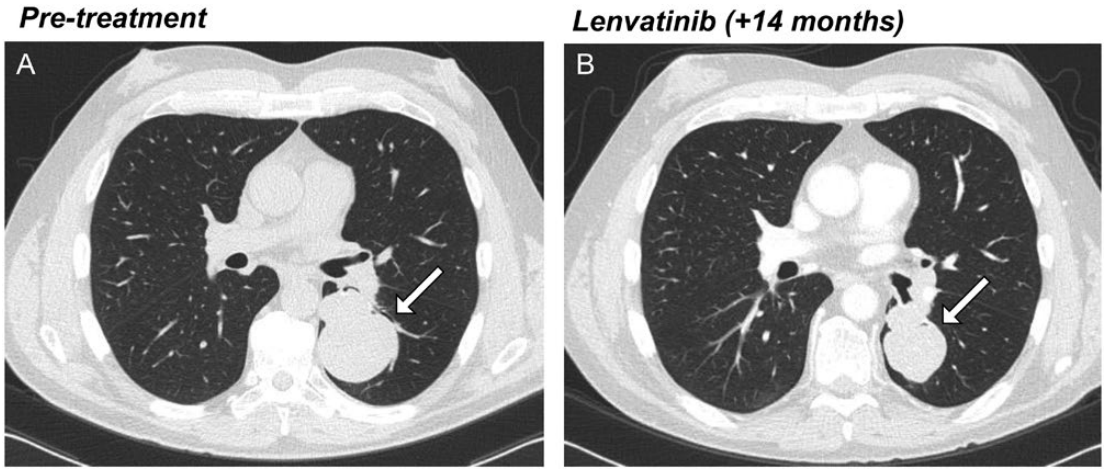

Figure 2. Patient MC3 was a 51-year-old male treated with lenvatinib as their ninth line of therapy. Previous therapies were as follows: EDP, gemcitabine, capecitabine, cyclophosphamide, mitotane, etoposide, docetaxel, and pembrolizumab. (**A**) Disease burden prior to starting lenvatinib. (**B**) The patient had a partial response of their lung metastasis on chest CT, shown here after 14 months of continuous lenvatinib. They went on to receive lenvatinib for another 6 months, for a total of 20.3 months, before discontinuing therapy and experiencing disease progression shortly thereafter at 23.5 months.

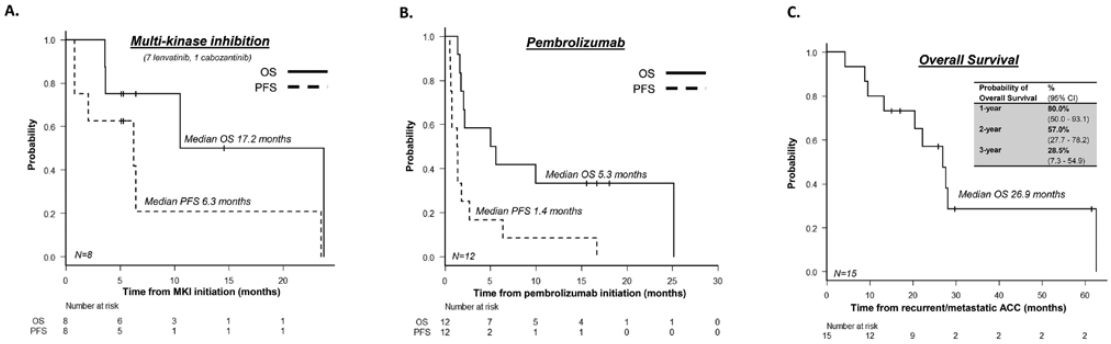

Figure 3. Progression-free survival (PFS) and/or overall survival (OS) were calculated from the date of initiation of multikinase inhibition (MKI), pembrolizumab, and the time of diagnosis of R/M ACC (T_0) using the Kaplan-Meier method, respectively. (**A**) PFS and OS from the time of initiation of MKI therapy for the 8 patients treated with MKI. (**B**) PFS and OS from the time of initiation of pembrolizumab for the 12 patients treated with either single agent pembrolizumab (n = 8) or pembrolizumab plus cytotoxic chemotherapy (n = 4). (**C**) Median OS for the entire cohort of 15 patients from T_0 was 26.9 months (95% confidence interval, 9.5-62.6). Probability of OS at 1, 2, and 3 years after T_0 is shown.

Overall survival for the entire cohort

Ten of the 15 patients (67%) died during the follow-up period; all 10 deaths were in the setting of progressive disease. The median OS from T_0 (time of R/M disease) was 26.9 months (95% CI 9.5–62.6) (Fig. 3C).

Discussion

Development of effective therapy in advanced ACC is hampered by the rarity of the disease and the complexity of the tumor biology [4,26]. Recent studies have suggested that key drivers include insulin-like growth factor 1 receptor signaling, Wnt-β-catenin signaling, and disturbance of the p53/Rb pathway, among others [4,27,28]. These insights will hopefully lead to novel interventions in the coming years.

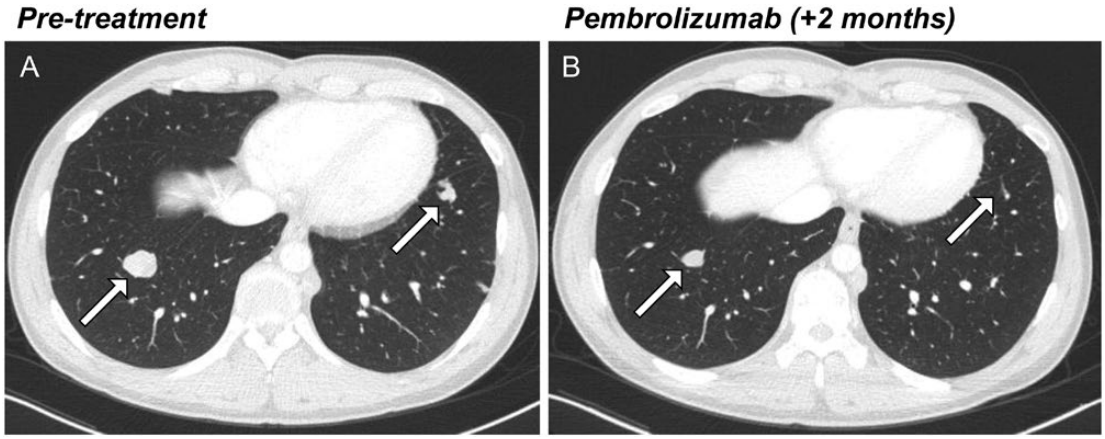

Figure 4. Patient MC12 was a 30-year-old male treated with single-agent pembrolizumab as the second line of therapy after EDP. Interestingly, he harbored a germline *CDKN2A* mutation (c.197A>C, p.His66Pro). (**A**) Disease burden prior to the start of pembrolizumab. (**B**) After 3 cycles (2 months later), the patient had a partial response of the lung metastasis on chest CT. They received pembrolizumab for another 12 months (14.8 months total) before developing laboratory evidence of immune-related hepatitis. Pembrolizumab was discontinued indefinitely, and he was treated with corticosteroids, with prompt resolution. However, he progressed shortly thereafter (16.7 months from the time of initiation of pembrolizumab).

Yet, a recent randomized phase III trial enrolling 139 patients showed no significant effect for linsitinib (OSI-906), an oral small molecule inhibitor of both insulin-like growth factor 1 receptor and the insulin receptor, compared to placebo in metastatic ACC, highlighting the dogged resilience of this tumor to our best understanding of important biological players [29]. Even mitotane, which has been used in ACC for decades, is not without controversy, given that it is a potent inducer of cytochrome P450-3A4, and thereby alters the efficacy of other therapies, including MKI [7, 30].

The utility of MKI like lenvatinib (VEGFR, FGFR, PDGFR, RET, and c-KIT), pazopanib (VEGFR, PDGFR, and c-KIT), and cabozantinib (VEGFR, RET, and c-MET) in other endocrine cancers has prompted their off-label use in metastatic ACC, as well as an ongoing prospective phase II trial for cabozantinib (clinicaltrials.gov identifier: NCT03370718) [31-33]. While previous trials using MKI in advanced ACC had limited success [17-20], herein we observed a remarkably durable PR lasting 2 years in a heavily pretreated patient with lenvatinib, as well as a PR in another patient using lenvatinib as their first-line of therapy for metastatic disease. Further, several patients who progressed quickly on other cytotoxic treatments had SD lasting months, suggesting that there is a subset of patients who could potentially derive benefit from MKI in the metastatic setting.

In our group, we are very sensitive to the possible confounding negative effect of prior mitotane therapy on the potential for benefit from MKI therapy [30]. Consequently, we strive to delay mitotane use in patients with metastatic ACC until after MKI therapy. We also strive to delay MKI therapy for as long as achievable after cessation of prior mitotane therapy. It is possible that this strategy may in part contribute to our more favorable experience than previously reported in MKI trials—wherein MKI therapy was most often initiated shortly after mitotane use. This could also reflect a selection bias where patients with more indolent disease were able to tolerate longer periods off-treatment between mitotane and MKI. Further investigation is required to draw definitive conclusions on whether the mitotane-induced disruption of MKI pharmacokinetics plays an important role in determining response.

The impact of checkpoint inhibitors spanning the oncology landscape has naturally lead to their investigation in ACC [34]. The JAVELIN trial assessed the PD-L1 inhibitor avelumab in 50 patients with previously treated metastatic ACC [35], but the ORR was a dismal 6%;

median PFS was a sobering 2.6 months (95% CI 1.4-4.0). Another recent trial conducted by Raj et al showed the results of treating 39 patients with single-agent pembrolizumab in R/M ACC. The ORR was 23%, with a small subset of patients achieving durable responses [36]. This dovetails with our findings here; there is likely a very small but noteworthy group of patients who derive benefit for checkpoint inhibition, but the majority have no response [37]. It is notable that the latter trial, as well as a recent case report, demonstrated microsatellite-high and/or mismatch repair deficiency may be a predictive biomarker of response to immunotherapy in ACC [36,38]. Interestingly, our patient who attained a durable PR with pembrolizumab had a germline *CDKN2A* mutation (encoding $p16^{INK4}$ and $p14^{ARF}$), which has been associated with improved response to checkpoint blockade in metastatic melanoma [24,39].

However, to highlight the knowledge gap that must be bridged to better understand immunotherapy efficacy spanning oncology, there was no difference in ORR based on PD-L1 staining, tumor infiltrating lymphocyte score, or tumor mutational burden in the study by Raj et al [36]. As such, the unique biological features of ACC that may hamper immunotherapy efficacy and are potentially targetable, such as immunosuppressive signaling in the tumor microenvironment and steroid secretion by malignant ACC cells, is highly of interest. Clearly, there is a critical need to develop adjunct therapies that work in concert with immunotherapy [40,41].

In point of fact, combinations of MKI with checkpoint inhibitors are being studied in several cancers. The rationale for these combinations is that MKI (eg, lenvatinib) modulate a variety of interferon-signaling related genes and thereby activate CD8+ T cells in the tumor microenvironment [42]. Clinical evidence for potential synergy between these agents includes evidence from several recent phase II trials in advanced endometrial carcinoma and metastatic renal cell carcinoma, wherein the combination of lenvatinib plus pembrolizumab had an ORR of 40% and 67%, respectively [43,44]. This combination could be the subject of future prospective investigation in ACC.

The long median OS in our study is noteworthy (median OS 26.9 vs 12–15 months in FIRM-ACT) [8]. However, our cohort likely represents a group of patients selected to be exceptional responders to salvage treatment, including a younger presenting age than the typical median (43 years in our study vs 55 in the National Cancer Data Base), access to tertiary medical center, and higher than expected response to first-line salvage therapy (60% in our study vs 23% in FIRM-ACT) [8,45,46]. Even so, our results are potentially important because they demonstrate that a small subset of patients respond to MKI and/or immunotherapy. Obviously, these treatments do not come without a cost; immunotherapy in particular has well documented, occasionally fatal immune-mediated toxicities [47]. Indeed, several patients in our study had worrisome adverse events, which unfortunately lead to the discontinuation of pembrolizumab in the one patient who had a durable PR.

To make progress, it will be vitally important to perform high-throughput correlative studies on patient samples (ie, with genomic, transcriptomic, and immune-phenotypic data) in future prospective studies to determine if there are subgroups primed to respond to any of these treatment modalities. Likewise, understanding how to prevent and mitigate toxicity, particularly from immune-related adverse events, is an urgent need [48]. The grim prognosis of metastatic ACC continues, but perhaps using novel methods to identify subsets of patients who may benefit from MKI and/or immunotherapy, as well as investigating therapies that augment the activity of MKI and immunotherapy could represent steps toward progress.

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Additional Information

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Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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