A Randomized Phase II Study of MEDI0680 in Combination with Durvalumab versus Nivolumab Monotherapy in Patients with Advanced or Metastatic Clear-cell Renal Cell Carcinoma

Martin H. Voss[1], Arun A. Azad[2], Aaron R. Hansen[3], Jhanelle E. Gray[4], Sarah J. Welsh[5], Xuyang Song[6], Michael Kuziora[7], Lina Meinecke[7], Jorge Blando[7], Ikbel Achour[7], Yi Wang[8], Farzana L. Walcott[9], and Sjoukje F. Oosting[10]

ABSTRACT

Purpose: MEDI0680 is a humanized anti–programmed cell death-1 (PD-1) antibody, and durvalumab is an anti-PD-L1 antibody. Combining treatment using these antibodies may improve efficacy versus blockade of PD-1 alone. This phase II study evaluated antitumor activity and safety of MEDI0680 plus durvalumab versus nivolumab monotherapy in immunotherapy-naïve patients with advanced clear-cell renal cell carcinoma who received at least one prior line of antiangiogenic therapy.

Patients and Methods: Patients received either MEDI0680 (20 mg/kg) with durvalumab (750 mg) or nivolumab (240 mg), all intravenous, every 2 weeks. The primary endpoint was investigator-assessed objective response rate (ORR). Secondary endpoints included best overall response, progression-free survival (PFS), safety, overall survival (OS), and immunogenicity. Exploratory endpoints included changes in circulating tumor DNA (ctDNA), baseline tumor mutational burden, and tumor-infiltrated immune cell profiles.

Results: Sixty-three patients were randomized (combination, $n = 42$; nivolumab, $n = 21$). ORR was 16.7% [7/42; 95% confidence interval (CI), 7.0–31.4] with combination treatment and 23.8% (5/21; 95% CI, 8.2–47.2) with nivolumab. Median PFS was 3.6 months in both arms; median OS was not reached in either arm. Because of adverse events, 23.8% of patients discontinued MEDI0680 and durvalumab and 14.3% of patients discontinued nivolumab. In the combination arm, reduction in ctDNA fraction was associated with longer PFS. ctDNA mutational analysis did not demonstrate an association with response in either arm. Tumor-infiltrated immune profiles showed an association between immune cell activation and response in the combination arm.

Conclusions: MEDI0680 combined with durvalumab was safe and tolerable; however, it did not improve efficacy versus nivolumab monotherapy.

Introduction

Renal cell carcinoma (RCC) encompasses a range of malignancies derived from renal tubular epithelial cells and represents 2%–3% of all cancers with 338,000 new diagnoses each year (1, 2). The most common subtype is clear-cell renal cell carcinoma (ccRCC), which accounts for the majority of deaths due to kidney cancer (2). Multiple targeted therapies have been developed to treat ccRCC (1). Targets of approved agents include VEGF receptor, mTOR, and immune checkpoint proteins such as CTL-associated protein 4 (CTLA4), programmed death receptor 1 (PD-1), and programmed death receptor ligand-1 (PD-L1; ref. 1). In recent years, immune checkpoint inhibitors used in combination (e.g., nivolumab plus ipilimumab) or with antiangiogenic tyrosine kinase inhibitors (e.g., axitinib plus avelumab or pembrolizumab; cabozantinib plus nivolumab) have become the first-line standard of care for RCC in the United States, resulting in improved clinical benefit and prolonged survival for patients with metastatic disease (3, 4).

Nivolumab is a human IgG4 anti-PD-1 antibody. The randomized phase III clinical trial CheckMate 025 evaluated nivolumab versus the mTOR inhibitor everolimus in patients with advanced RCC who had previously progressed on antiangiogenic therapy (5, 6). Nivolumab demonstrated improved efficacy and safety compared with everolimus (6). The results of the Checkmate 025 trial led to the approval of nivolumab by the FDA in 2015 as a second-line treatment for metastatic ccRCC, following antiangiogenic treatment failure, shifting the standard of care for metastatic ccRCC toward immunotherapy-based treatments (7). However, about 35% (142/410) of patients treated with nivolumab experienced progressive disease (PD) as a best response, compared with 26% treated with everolimus (6), demonstrating a need for additional or novel treatment combinations (6).

[1]Memorial Sloan Kettering Cancer Center, New York, New York. [2]Monash Health, Melbourne, Australia. [3]Princess Margaret Cancer Centre, Toronto, Canada. [4]Moffitt Cancer Center, Tampa, Florida. [5]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom. [6]Clinical Pharmacology & Quantitative Pharmacology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland. [7]Translational Medicine, Oncology R&D, AstraZeneca, Gaithersburg, Maryland. [8]Early Oncology Biometrics, Oncology R&D, AstraZeneca, Gaithersburg, Maryland. [9]Oncology R&D, AstraZeneca, Gaithersburg, Maryland. [10]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

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Corresponding Author: Martin H. Voss, Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065. Phone: 646-888-4721; Fax: 646-227-2417; E-mail: vossm@mskcc.org

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Translational Relevance

In this phase II study, patients with clear-cell renal cell carcinoma (ccRCC) treated with the programmed death receptor 1 (PD-1) inhibitor MEDI0680 plus the programmed death receptor ligand-1 (PD-L1) inhibitor durvalumab had similar objective response rates compared with patients who received the PD-1 inhibitor nivolumab alone. The safety profile of MEDI0680 plus durvalumab was consistent with the known toxicity of PD-1/PD-L1 antibodies. In the combination arm, lower circulating tumor DNA (ctDNA) fraction was associated with improved progression-free survival, but not overall survival. ctDNA genomic alterations were not associated with response. Tumor-infiltrated immune cell profiles showed an association between immune cell activation and objective response in the combination arm. Combined blockade of PD-1 and PD-L1 does not result in additive efficacy over inhibition of PD-1 alone, suggesting that the PD-L1–CD80 interaction has a limited role in tumor immune evasion in ccRCC. Future combination strategies should explore targeting separate pathways.

Durvalumab is a fully human IgG1 mAb that blocks the binding of PD-L1 to PD-1 and cluster of differentiation 80 (CD80; ref. 8). In clinical studies, durvalumab has been evaluated as a monotherapy or in combination with other therapies for patients with various cancer types, demonstrating both safety and efficacy (8). One disadvantage of using PD-L1 inhibitors as monotherapy is that they do not block the binding of PD-L2 to PD-1 (9). A preclinical study demonstrated that PD-L2 was upregulated on tumor-associated macrophages following treatment with a PD-L1 inhibitor (9). Notably, PD-L1–targeted immuno-oncology agents have not demonstrated an overall survival (OS) benefit for patients with RCC (10). This may be due to the potential of PD-L2 to promote T-cell tolerance (10).

MEDI0680 is a humanized IgG 4κ mAb that binds to PD-1 expressed on the surface of T cells, blocking the interaction of PD-1 with PD-L1 and PD-L2 on tumor cells (11). The binding of PD-L1 and PD-L2 to the inhibitory PD-1 receptor expressed on T cells suppresses the cells' ability to mount an effective antitumor response (1, 12). In a first-in-human phase I study, MEDI0680 demonstrated a tolerable safety profile and preliminary clinical activity in patients with advanced solid malignancies, including RCC (11).

Suboptimal response rates with PD-1–directed monotherapy may be due in part to factors such as low PD-L1 expression and tumor mutational burden (13). Preclinical studies have also demonstrated that blocking PD-1 can increase the release of the proinflammatory cytokine IFNγ at the tumor site, which may then increase the expression of PD-L1 in various cancer cells (14, 15). In addition, PD-L1, when left uninhibited, can limit the antitumor response by binding to CD80 expressed on activated $CD8^+$ T cells, thereby restricting the role of CD80 in promoting T-cell survival, proliferation, and cytokine production (16). The hypothesis underlying the current trial was that simultaneous blockade of PD-1 using MEDI0680 and PD-L1 using durvalumab has the potential to improve efficacy relative to a blockade of PD-1 alone using nivolumab by blocking additional inhibitory interactions within the tumor microenvironment.

In the dose-escalation phase of this multicenter, open-label study in patients with advanced solid tumors, the combination of MEDI0680 with durvalumab was well tolerated, and a confirmed objective response rate (ORR) of 30% (9/30), including 3 of 4 patients with RCC was observed (17). In the phase II (dose expansion) part of this study, we evaluated the antitumor activity and safety of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in adults with ccRCC and assessed potential tumor-based biomarkers of response.

Patients and Methods

Patients

Eligible patients were aged ≥ 18 years and had advanced or metastatic RCC with a clear-cell component. Additional key inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) score of 0–1 and at least one measurable lesion. Patients had to have received 1–2 prior antiangiogenic therapy regimens, no prior immunotherapy, and a maximum of three systemic treatment regimens in the advanced or metastatic setting. Patients had to have evidence of radiographic progression on or after the last treatment regimen received and within 6 months prior to study enrollment. Patients had adequate organ and marrow function (defined in the Supplementary Materials and Methods). Key exclusion criteria included concurrent malignancies, active/prior autoimmune or inflammatory disorders within the past 3 years, and untreated central nervous system metastatic disease. Additional inclusion and exclusion criteria are available in the Supplementary Materials and Methods.

Study design

This randomized phase II, open-label, multicenter study of MEDI0680 in combination with durvalumab versus nivolumab monotherapy was conducted at 27 centers in six countries, including Australia, Canada, France, the Netherlands, the United Kingdom, and the United States. The study design is summarized in Supplementary Fig. S1. Stratification factors included the Memorial Sloan Kettering Cancer Center (MSKCC) risk group (prognostic score: 0 = favorable risk; 1 or 2 = intermediate risk; 3 = poor risk; ref. 18) and the status of PD-L1 expression on tumor cells (≤ 1% and > 1%). For determination of PD-L1 expression, archival tumor tissues or fresh tumor biopsies were evaluated by a central laboratory using the Ventana (SP263) IHC assay (Roche, catalog no. 790-4905). Patients were randomly assigned at a ratio of 2:1 to receive either 20 mg/kg of MEDI0680 with 750 mg of durvalumab or 240 mg nivolumab monotherapy. Each drug was administered intravenously every 2 weeks.

For patients receiving combination treatment, durvalumab was administered first. MEDI0680 was given approximately 30 minutes after completion of durvalumab infusion. Dose reductions of MEDI0680 and durvalumab were not permitted; however, holding doses or discontinuation in the case of treatment-related toxicity was allowed. Nivolumab dosing was based on the FDA-approved regimen described in the package insert. Patients could remain on study treatment for up to 2 years while tolerable and effective. Disease assessments were performed at baseline and every 8 weeks thereafter. Patients were followed for survival until the end of the study, regardless of additional treatments.

This study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and was consistent with the International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements. The study protocol was approved by an Institutional Review Board or independent ethics committee at each study site prior to initiation and enrollment. All patients provided written informed consent before participating in the study. This study was registered with ClinicalTrials.gov, number NCT03089645.

Endpoints

The primary endpoint was investigator-assessed ORR by RECIST version 1.1 (19), defined as the proportion of patients with a best overall response (BOR) category of confirmed complete response (CR) or partial response (PR). Secondary endpoints included safety, BOR, disease control, time to response, duration of response, progression-free survival (PFS), change from baseline in tumor size, OS, and the detection of anti-drug antibodies (ADA). Exploratory endpoints included blood tumor mutational burden (bTMB), changes in circulating tumor DNA (ctDNA), baseline genomic alteration profile, and baseline tumor-infiltrated immune profile in association with objective response.

Disease control was defined as the proportion of patients with a BOR of confirmed CR, PR, or stable disease (SD) maintained for ≥ 24 weeks. Duration of response was defined as the time from first documentation of objective response until first documentation of disease progression or death. Time to response was defined as the time from randomization until the first documentation of objective response. PFS was defined as the time from randomization until first documentation of disease progression or death, regardless of subsequent anticancer therapy received prior to progression. Change from baseline in tumor size was calculated as the percent change in target lesion sum of diameters at every postbaseline disease assessment. OS was defined as the time from randomization until death due to any cause. For PFS and OS analysis, patients free from progression and alive were censored at the last follow-up timepoint, respectively.

Safety

Safety was assessed by the presence of adverse events (AE) and serious AEs, as well as changes from baseline in laboratory parameters, vital signs, physical examination, and electrocardiogram results. AEs were coded by the Medical Dictionary for Regulatory Activities and preferred term, and AEs and laboratory values were graded according to the NCI Common Terminology Criteria for Adverse Events v4.03.

Statistical analysis

Up to 60 patients (40 patients in the MEDI0680 and durvalumab combination therapy arm and 20 patients in the nivolumab monotherapy arm) were planned for randomization at the selected combination dose. Assuming an ORR for nivolumab monotherapy of 21.5% (20), the sample size was chosen to detect a difference in ORR of 26.0% (i.e., an objective response of 47.5%) with 76% power at a one-sided significance level of 0.10. The 95% confidence interval (CI) of an ORR of 47.5% (19 responders/40 patients) based on the exact probability method is 31.5%–63.9%. Efficacy and safety analyses were based on the as-treated population, defined as all patients who received any dose of investigational product and were analyzed according to the treatment they received. The difference in ORR between arms was tested for significance using Fisher exact test.

Patients with missing overall response were counted as nonresponders. The median PFS and OS, along with their 95% CIs, were summarized by Kaplan–Meier curves. The differences in PFS and OS between treatment arms were tested for significance using a log-rank test. The HR with 95% CIs was estimated by Cox proportional hazards model controlling for prespecified stratification factors as explanatory variables.

A joint Bayesian predictive probability approach was developed to allow for continuous assessments of the delta (δ), or difference, of the ORR between the MEDI0680 and durvalumab combination and nivolumab. The target δ was set so as to demonstrate a 20% increase in the MEDI0680 and durvalumab combination ORR over the benchmark nivolumab ORR based on investigator assessments. Categorical data were summarized by the number and percentage of patients in each category. Continuous variables were summarized by descriptive statistics. SAS version 9.4 (SAS Institute Inc.) was used for data analyses.

Immunogenicity

Blood samples were assessed for the presence of ADAs in response to MEDI0680 using a previously described validated immunoassay (11). For durvalumab, clinical samples were evaluated for ADA via screening, confirmatory, titer, and neutralizing antibody assays. A homogeneous double-bridging electrochemiluminescence assay was used for ADA screening. Positive control (goat anti-durvalumab polyclonal antibody), negative control, and test samples were incubated with biotin-conjugated durvalumab and ruthenium-conjugated durvalumab to form an immunocomplex. The ADA immunocomplexes were captured on streptavidin-coated standard 96-well plates and signals were measured by an MSD Sector Imager (Meso Scale Diagnostics). A signal ≥ the established cutoff indicated the presence of ADAs in the sample. Samples for ADA assessment were collected during cycle 1 (study day 1), cycle 2 (study day 29 ± 3), cycle 5 (study day 113 ± 3), cycle 8 (study day 197 ± 3), cycle 11 (study day 281 ± 3), and during posttreatment and long-term follow-up. Patients who received ≥ 1 dose of both durvalumab and MEDI0680 and provided ≥ 1 posttreatment sample were evaluated, and immunogenicity results were analyzed descriptively by summarizing the proportion of patients who developed detectable anti-durvalumab or anti-MEDI0680 antibodies.

Biomarker analysis

ctDNA, bTMB, and genomic alterations

ctDNA was extracted centrally from plasma samples collected from both treatment arms, as described previously (21–23), and assayed using a GuardantOMNI Research Use Only next-generation sequencing assay (Guardant Health; ref. 23). This assay detects genomic alterations such as single-nucleotide variants, insertions, deletions, copy-number variants, fusions, and microsatellite instability (500 genes; 2.145 Mb; ref. 23). bTMB score was determined as described previously (23). Mean variant allelic frequency (VAF) was calculated at baseline and at 4 weeks following treatment. Percent change in mean VAF from baseline was determined, indicating percent change in ctDNA fraction. Reduction in ctDNA fraction ≥ 50% at 4 weeks versus baseline is defined as molecular response (MR; refs. 21, 24). Reduction in ctDNA fraction < 50% at 4 weeks versus baseline is defined as non-molecular response (non-MR; refs. 21, 24, 25).

IHC, multiplex immune fluorescence, and digital analysis

Tumor tissue sections from formalin-fixed paraffin-embedded blocks, derived from tumor biopsies at baseline or archival tumor samples, were processed by IHC for PD-L2 (Abcam; CAL28 clone) and by multiplex immunofluorescence (mIF) for CD8 (Ventana, SP239 clone), PD-L1 (Ventana, SP263 clone), PD-1 (Cell Signaling Technology, D4W2J clone), Ki-67 (Dako, MIB-1 clone), CD68 (Dako, PG-M1 clone), and cytokeratin (Dako, AE1/AE3 clone). Briefly, automated IHC protocols were performed on Ventana instruments (Roche Diagnostics, Ventana Medical Systems) employing 3,3′-diaminobenzidine as the chromogen. Immunostained slides were digitally scanned using an Aperio AT turbo scanner (Leica BioSystems) at 20× magnification. Digital images were viewed using Aperio ImageScope software version 12.1.0 (Leica

BioSystems) or VeriTrova software (AstraZeneca Computational Pathology GmbH). For mIF, a BOND Rx automated staining platform (Leica BioSystems) with a modified Opal protocol (Perkin-Elmer) was used. Imaging was performed on a Vectra Polaris multispectral imaging platform (Akoya Biosciences) in multispectral instrument mode. Digital images were imported into Developer XD software (AstraZeneca Computational Pathology GmbH) and analyzed for marker positive cells, which were reported as densities (cells/mm^2) using the program's cognition network technology, as described previously (26–28).

Data availability statement

The individual patient-level data generated in this study are not publicly available to protect patient privacy. Requests for data may be submitted through Vivli's web-based data request platform (www.vivli.org). A comprehensive explanation of AstraZeneca's data sharing policies is available at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Results

Patient demographics and clinical characteristics

As of June 12, 2020, 63 patients had been enrolled, randomly assigned a treatment, and treated (Supplementary Fig. S2). Forty-two patients were randomly assigned to receive MEDI0680 and durvalumab, and 21 were randomly assigned to receive nivolumab. Early in the study and prior to a protocol amendment, an additional 4 patients had been randomized to receive MEDI0680 20 mg/kg as monotherapy; this arm of the study was subsequently closed and replaced with the nivolumab arm due to a change in the standard-of-care treatment for ccRCC shortly after initiation of the study. All 4 patients discontinued treatment due to PD, withdrew from the study, and none of them were included in this analysis. The median duration of exposure for the 4 patients on MEDI0680 monotherapy was 24.1 weeks (range, 10.1–40.1).

Patient demographics and baseline disease characteristics are summarized in **Table 1**. Baseline patient and disease characteristics were generally well balanced between study arms, with several relevant exceptions: the percent of patients with PD-L1 expression ≤ 1% was higher in the MEDI0680 and durvalumab combination arm than in the nivolumab arm (88.1% vs. 61.9%), the median age was higher in the combination arm (64 vs. 58 years, respectively), and the prevalence of MSKCC favorable disease risk was lower in the combination arm (23.8% vs. 33.3%, respectively; **Table 1**). In addition, patients in the combination arm had a longer median time from initial diagnosis to study entry (38.3 vs. 14.1 months in the nivolumab arm; **Table 1**). The median number of prior anticancer treatments was 2.0 for both arms (**Table 1**).

Table 1. Patient demographics and baseline disease characteristics.

	MEDI0680 + durvalumab ($n = 42$)	Nivolumab ($n = 21$)
Median age (range), years	64.0 (39–80)	58.0 (38–80)
Sex, *n* (%)		
Male	33 (78.6)	15 (71.4)
Female	9 (21.4)	6 (28.6)
ECOG PS		
0	19 (45.2)	10 (47.6)
1	23 (54.8)	11 (52.4)
MSKCC risk classification, *n* (%)		
Favorable	10 (23.8)	7 (33.3)
Intermediate	30 (71.4)	13 (61.9)
Poor	2 (4.8)	1 (4.8)
PD-L1 expression, *n* (%)		
≤1%	37 (88.1)	13 (61.9)
>1%	5 (11.9)	8 (38.1)
Time from initial diagnosis to study entry		
n	40	19
Median (range), months	38.3 (2.9–236.8)	14.1 (6.7–155.2)
Number of prior anticancer therapies[a]		
Median (range)	2.0 (1–7)	2.0 (1–3)
Type of prior treatment		
n	42	21
Biologic	9 (21.4)	3 (14.3)
Immunotherapy	1 (2.4)	0
Chemotherapy	13 (31.0)	7 (33.3)
Radiation	15 (35.7)	5 (23.8)
Surgery	28 (66.7)	16 (76.2)
Other	21 (50.0)	12 (57.1)
Number of prior systemic therapies for metastatic disease[a]		
n	34	17
1	26 (76.5)	17 (100)
2	8 (23.5)	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed cell death ligand-1.

[a]Number of prior systemic therapies for metastatic disease is defined as number of lines of biologic, immunotherapy, chemotherapy, and other with treatment intent as definitive treatment or palliative for recurrent/metastatic disease.

Antitumor activity

The primary endpoint of investigator-assessed ORR was 16.7% (95% CI, 7.0–31.4) with MEDI0680 plus durvalumab and 23.8% (95% CI, 8.2–47.2) with nivolumab (**Table 2**), with no significant difference between the two treatment arms ($P = 0.513$; **Table 2**). CR was observed in 4.8% (2/42) of patients in the combination arm, with response durations of 21.5 and 11.1 months (**Table 2**). One patient with CR had multiple disease sites at baseline (lymph nodes, adrenal glands, nephrectomy bed, and diaphragm); the other patient with CR had renal fossa lesions at baseline. No patients in the nivolumab arm had a CR (**Table 2**). The nivolumab arm had a lower proportion of patients with PD (28.6% vs. 40.5%). For patients who achieved an objective response in the combination arm ($n = 7$) or in the nivolumab arm ($n = 5$), the median time to response was 1.8 months (95% CI, 1.7–9.1 months) and 1.8 months (95% CI, 1.6–7.3 months), respectively. The median duration of response was not reached in either arm; the longest duration of response was 23.5 months with the combination and 9.2 months with nivolumab (**Table 2**). The disease control rate at 24 weeks was 38.1% (16/42) with the combination and 38.1% (8/21) with nivolumab treatment (**Table 2**).

The ORR was not significantly different between treatment arms based on PD-L1 status (Supplementary Table S1). In PD-L1–negative patients (defined as expression ≤ 1%), the ORR was 13.5% (5/37) with combination treatment versus 15.4% (2/13) with nivolumab. In PD-L1–positive patients (defined as expression > 1%), the ORR was 40.0% (2/5) with combination treatment versus 37.5% (3/8) with nivolumab. Change in tumor burden over time is shown for individual patients in **Fig. 1**. The best change in the sum of target lesions from baseline for each patient is shown in **Fig. 2**. PFS was comparable between the combination and nivolumab arms (**Table 2**; Supplementary Fig. S3a).

Table 2. Disease response (as-treated population).

	MEDI0680 + durvalumab ($n = 42$)	Nivolumab ($n = 21$)
Best overall response, *n* (%)		
Complete response	2 (4.8)	0
Partial response	5 (11.9)	5 (23.8)
Stable disease	17 (40.5)	8 (38.1)
Unconfirmed partial response	2 (4.8)	0
Progressive disease	17 (40.5)	6 (28.6)
Not evaluable	1 (2.4)	2 (9.5)
Objective response, *n* (%)	7 (16.7)	5 (23.8)
95% CI	7.0–31.4	8.2–47.2
P value[b]	0.513	—
Median progression-free survival (95% CI), months	3.6 (2.0–5.5)	3.6 (1.9–13.0)
Median overall survival (95% CI), months	NR (NR–NR)	NR (12.0–NR)
Median time to response (range), months	1.8 (1.7–12.8)	1.8 (1.6–7.3)
Median duration of response (range), months	NR (9.5–23.5)	NR (1.9–9.2)
Disease control at ≥ 24 weeks, *n* (%)[a]	16 (38.1)	8 (38.1)
95% CI	23.6–54.4	18.1–61.6

Abbreviations: CI, confidence interval; NR, not reached.
[a]Complete and partial responses plus stable disease.
[b]As compared with nivolumab.

The median PFS for the as-treated population in the MEDI0680 and durvalumab arm was 3.6 months (95% CI, 2.0–5.5 months) versus 3.6 months (95% CI, 1.9–13.0 months) in the nivolumab arm (HR, 1.09; 95% CI, 0.58–2.04; $P = 0.789$). Median OS was not reached in either arm (**Table 2**; Supplementary Fig. S3b), and OS rates at 12 months were 75.2% (95% CI, 57.4-86.4) in the MEDI0680 and durvalumab arm and 83.6% (95% CI, 56.8-94.5) in the nivolumab arm.

Safety

In the combination arm, 64.3% (27/42) of patients discontinued treatment due to PD; in the nivolumab arm, 61.9% (13/21) patients discontinued treatment due to PD (Supplementary Fig. S2). The median duration of exposure was 16.0 weeks (range, 2.0–120.0) for MEDI0680 and durvalumab and 29.7 weeks (range, 2.0–78.1) for nivolumab. In the combination arm, 8 (19%) patients had at least one dose delay for MEDI0680, and 7 (16.7%) patients had at least one dose delay for durvalumab. In the nivolumab arm, 3 (14.3%) patients had at least one dose delay.

Treatment-related adverse events (TRAE) of any grade occurred in 92.9% of patients ($n = 39$) treated with the combination and 81.0% ($n = 17$) treated with nivolumab. TRAEs of grade 3–4 severity are summarized in **Table 3**. In the combination arm, Grade 3–4 MEDI0680-related AEs occurred in 26.2% ($n = 11$) of patients and grade 3–4 durvalumab-related AEs occurred in 23.8% ($n = 10$) of patients (**Table 3**). Grade 3–4 nivolumab-related AEs occurred in 23.8% ($n = 5$) of patients (**Table 3**). In total, 23.8% ($n = 10$) of patients discontinued MEDI0680 plus durvalumab due to an AE and 14.3% of patients ($n = 3$) discontinued nivolumab due to an AE (Supplementary Table S2).

Immunogenicity

Baseline and postbaseline ADA measurements for MEDI0680 were available for 40 and 39 patients, respectively. A total of 4 (10.0%) patients had an ADA-positive response at baseline and a total of 2 (5.1%) patients had an ADA-positive response to MEDI0680 postbaseline on cycle 5, day 1 (study day 112) and on cycle 2, day 1 (study day 31). No ADA-persistent positive responses were observed. Baseline and postbaseline ADA data for durvalumab were available for 41 and 39 patients, respectively. One patient (2.4%) had an ADA-positive response to durvalumab at baseline and 2 (5.1%) patients had an ADA-positive response to durvalumab post-baseline. ADA persistent-positive responses were observed in 2 patients.

Translational biomarker analysis

Sample sizes for translational biomarker analyses are summarized in Supplementary Table S3. Change in ctDNA was measured by percent change from baseline in mean VAF. ctDNA reductions were observed in several patients with CR and PR, in both treatment groups (**Fig. 3A** and **B**). In the combination and nivolumab arms, 27.5% (8/29) and 30% (3/10) of patients reported an MR, respectively (**Fig. 3B**). Only 1 patient with MR in the combination arm reported PD as their BOR (**Fig. 3B**). A subgroup analysis based on MR in relation to PFS and OS was performed in the MEDI0680 and durvalumab treatment arm only, due to sufficient sample size ($n = 29$). MR was observed in 8 patients (27.6%) and tended to be associated with a

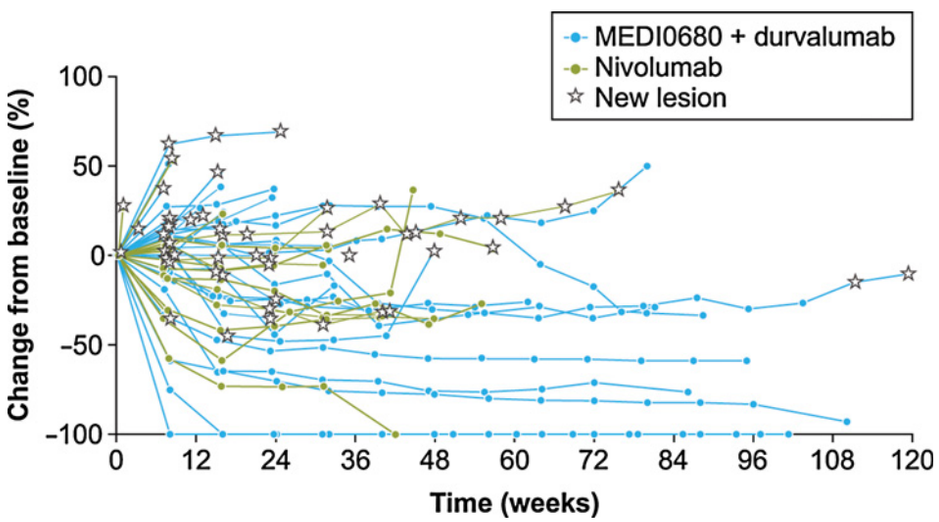

Figure 1.
Percentage change from baseline in target lesion sum of diameters (as-treated population).

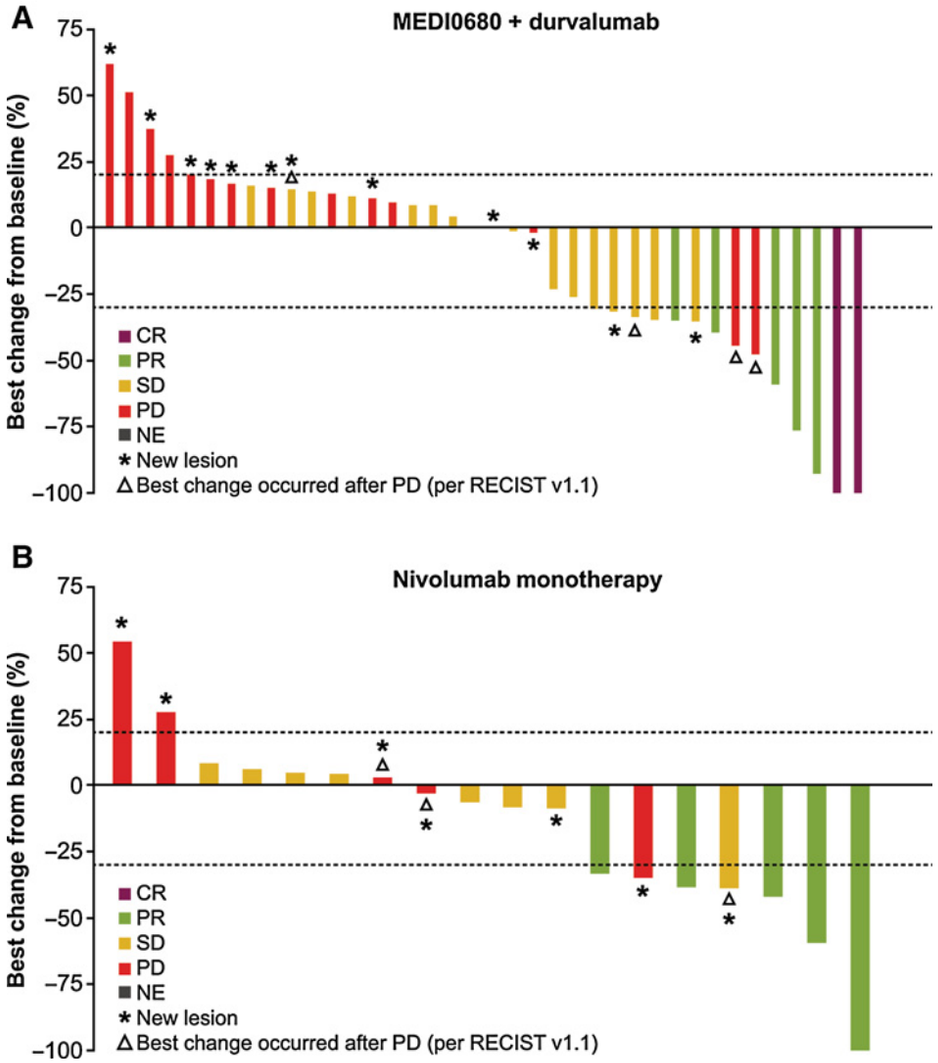

Figure 2.
Best percent change from baseline in target lesion sum of diameters for MEDI0680 with durvalumab (**A**), and nivolumab monotherapy (as-treated population; **B**). *New lesion occurred at the time best change from baseline achieved. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

longer median PFS (7.7 vs. 3.4 months; log-rank $P = 0.06$); however, no association with OS was observed (**Fig. 3C** and **D**).

Across both arms, the median peripheral bTMB score at baseline was 6.65 mut/Mb [combination arm: 6.700 mut/Mb (range, 0.96–14.36); nivolumab arm: 6.285 mut/Mb (range, 1.10–8.69)], consistent with previous observations showing relatively low TMB in patients with mRCC (29). No association between bTMB score at baseline as a continuous variable and response (CR or PR) was observed in either arm (Supplementary Fig. S4a). Applying a bTMB median cutoff of 6.65 mut/Mb (above median, $n = 10$; below median, $n = 10$) did not reveal an association with PFS or OS in the combination arm; this analysis could not be performed for the nivolumab arm due to an insufficient sample size ($n = 6$; Supplementary Fig. S4b and S4c).

The presence of genomic alterations derived from ctDNA analysis and obtained at baseline was not associated with response in either arm (Supplementary Fig. S4d). Pursuant to the hypothesis that the combination of MEDI0680 and durvalumab provides a more complete blockade targeting both PD-L2–PD-1 and PD-L1–PD-1 in comparison to anti-PD-1 nivolumab monotherapy, we evaluated the tumor-infiltrated immune profiles using mIF and IHC. Neither PD-L1 nor PD-L2 expression were associated with response in either arm (Supplementary Fig. S5). Immune-activated cells were associated with response in patients who received combination treatment, but not nivolumab treatment, although sample size differences between the arms must be considered when interpreting these findings. Tumors of patients with CR or PR were characterized by increased PD-1^+ immune cell and PD-1^+CD8^+ T-cell density (cells/mm^2) compared with patients who had SD ($n = 38$; $P < 0.05$), and a higher trend compared with PD (Supplementary Fig. S5). However, in patients who received nivolumab ($n = 21$), CD8^+ Ki67^+ ($\pm$ PD-1^+) T-cell density (cells/mm^2) showed a trend of association with response (Supplementary Fig. S5). Because of the small sample sizes in both arms, translational findings should be interpreted with caution, particularly in the nivolumab arm.

Discussion

The aim of the current study was to evaluate whether combined inhibition of PD-1 via MEDI0680 plus PD-L1 via durvalumab could improve antitumor immune response over that of PD-1 inhibition alone in patients with advanced or metastatic ccRCC. Treatment with the combination of MEDI0680 and durvalumab was safe and tolerable;

Table 3. Treatment-related AEs of grade 3–4 severity by drug (as-treated population).

	MEDI0680 + durvalumab ($n = 42$)					
	MEDI0680[a]		Durvalumab[a]		Nivolumab[a] ($n = 21$)	
n (%)	Grade 3–4	Any grade[b]	Grade 3–4	Any grade[b]	Grade 3–4	Any grade[b]
Patients with any treatment-related[b] AEs	11 (26.2)	39 (92.9)	10 (23.8)	39 (92.9)	5 (23.8)	17 (81.0)
Anemia	1 (2.4)	2 (4.8)	1 (2.4)	2 (4.8)	0	0
Immune-mediated enterocolitis	1 (2.4)	2 (4.8)	1 (2.4)	2 (4.8)	0	0
Immune-mediated pancreatitis	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Hepatocellular injury	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Amylase increased	1 (2.4)	2 (4.8)	1 (2.4)	2 (4.8)	1 (4.8)	0
Alanine aminotransferase increased	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	2 (9.5)
Aspartate aminotransferase increased	2 (4.8)	2 (4.8)	2 (4.8)	2 (4.8)	0	2 (9.5)
C-reactive protein increased	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Lipase increased	2 (4.8)	2 (4.8)	2 (4.8)	2 (4.8)	2 (9.5)	2 (9.5)
Transaminases increased	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Weight decreased	1 (2.4)	2 (4.8)	0	1 (2.4)	0	0
Hyponatremia	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Arthralgia	1 (2.4)	6 (14.3)	1 (2.4)	6 (14.3)	0	2 (9.5)
Myalgia	1 (2.4)	6 (14.3)	1 (2.4)	6 (14.3)	0	2 (9.5)
Encephalitis autoimmune	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Rash maculopapular	1 (2.4)	3 (7.1)	1 (2.4)	3 (7.1)	0	3 (14.3)
Rash popular	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	1 (4.8)
Adrenal insufficiency	0	0	1 (2.4)	1 (2.4)	0	0
Pancreatitis	0	0	1 (2.4)	1 (2.4)	0	1 (4.8)
Constipation	0	3 (7.1)	0	3 (7.1)	1 (4.8)	1 (4.8)
Hepatotoxicity	0	0	0	0	1 (4.8)	1 (4.8)
Hypophosphatemia	0	0	0	0	1 (4.8)	0
Renal tubular necrosis	0	0	0	0	1 (4.8)	1 (4.8)
Pneumonitis	0	1 (2.4)	0	1 (2.4%)	1 (4.8)	1 (4.8)

Abbreviation: AE, adverse event.
[a]As assessed by investigator.
[b]No treatment-related deaths were observed in this study.

however, it did not improve the ORR or PFS versus treatment with nivolumab alone. The ORR was numerically lower with MEDI0680 and durvalumab (16.7%) than with nivolumab (23.8%), but the difference was not statistically significant.

Differences in the ORR were not apparent between treatment arms when the analysis was stratified by PD-L1 expression. Notably, and despite the study design, the combination group enrolled patients with lower PD-L1 expression levels and less favorable MSKCC risk status, which highlights the challenges of effectively allocating arms in smaller randomized studies. Prior randomized studies of nivolumab in advanced RCC have shown a difference in outcomes based on MSKCC risk group and PD-L1 expression. A randomized phase III study of nivolumab monotherapy in patients with advanced RCC showed longer median OS in patients with favorable MSKCC risk scores [not reached (NR)], versus patients with intermediate MSKCC risk scores (21.8 months; 95% CI, 18.3–NR) and poor MSKCC risk (15.3 months; 95% CI, 96–22.4); however, no significant differences in ORR were observed between MSKCC risk groups (30). In addition, in a randomized phase II study of nivolumab monotherapy in patients with metastatic RCC, median OS in the PD-L1 ≥ 5% subgroup (NR; 95% CI, 13.4 months–NR) was longer compared with the PD-L1 < 5% subgroup (18.2 months; 95% CI, 12.7–26.0; ref. 31). Furthermore, ORR was higher for patients in the PD-L1 ≥ 5% subgroup (31% vs. 18%; ref. 31). However, a follow-up phase III study showed longer median OS in a subgroup of patients with < 1% PD-L1 expression (27.4 months; 95% CI, 21.4–NE) compared with the > 1% PD-L1 expression subgroup (21.8 months; 95% CI, 16.5–28.1; ref. 5). In the current study, a larger proportion of patients in the nivolumab arm had > 1% PD-L1 expression levels and lower MSKCC risk scores, which may have influenced the observed clinical outcomes. Therefore, the efficacy results should be interpreted with caution.

Although this study did not demonstrate superior antitumor efficacy of MEDI0680 in combination with durvalumab versus nivolumab in immunotherapy-naïve subjects with advanced or metastatic ccRCC, some clinical activity was reported. Two patients (4.8%) achieved CR with the combination treatment. Responses were durable, with the median duration not reached in either arm. The longest duration was 23.5 months with MEDI0680 and durvalumab and 9.2 months with nivolumab. While median PFS was 3.6 months in both arms, the rate of discontinuations was slightly higher in the MEDI0680 and durvalumab arm. The most frequently reported TRAEs were diarrhea, fatigue, pruritus, rash, and pyrexia. Aspartate aminotransferase increased was the only AE of special interest related to hepatotoxicity reported in ≥ 5% patients (combination arm, 4.8%; nivolumab arm, 14.3%). No hematologic toxicity or sustained hepatic, metabolic, renal, or endocrine toxicity was observed in this study and no patients died because of treatment-related toxicity.

Currently, there are no validated predictive biomarkers of response available for use in patients with RCC in clinical practice (32). No tissue or peripheral blood–based biomarker signature evaluated was clearly associated with favorable clinical outcomes in either arm. Multiparametric analyses did not reveal associations between bTMB or T-cell infiltration and response, as the ability to investigate either of these thoroughly was limited by sample sizes. The results of the ctDNA analysis, while not significant and limited by sample size, are of interest

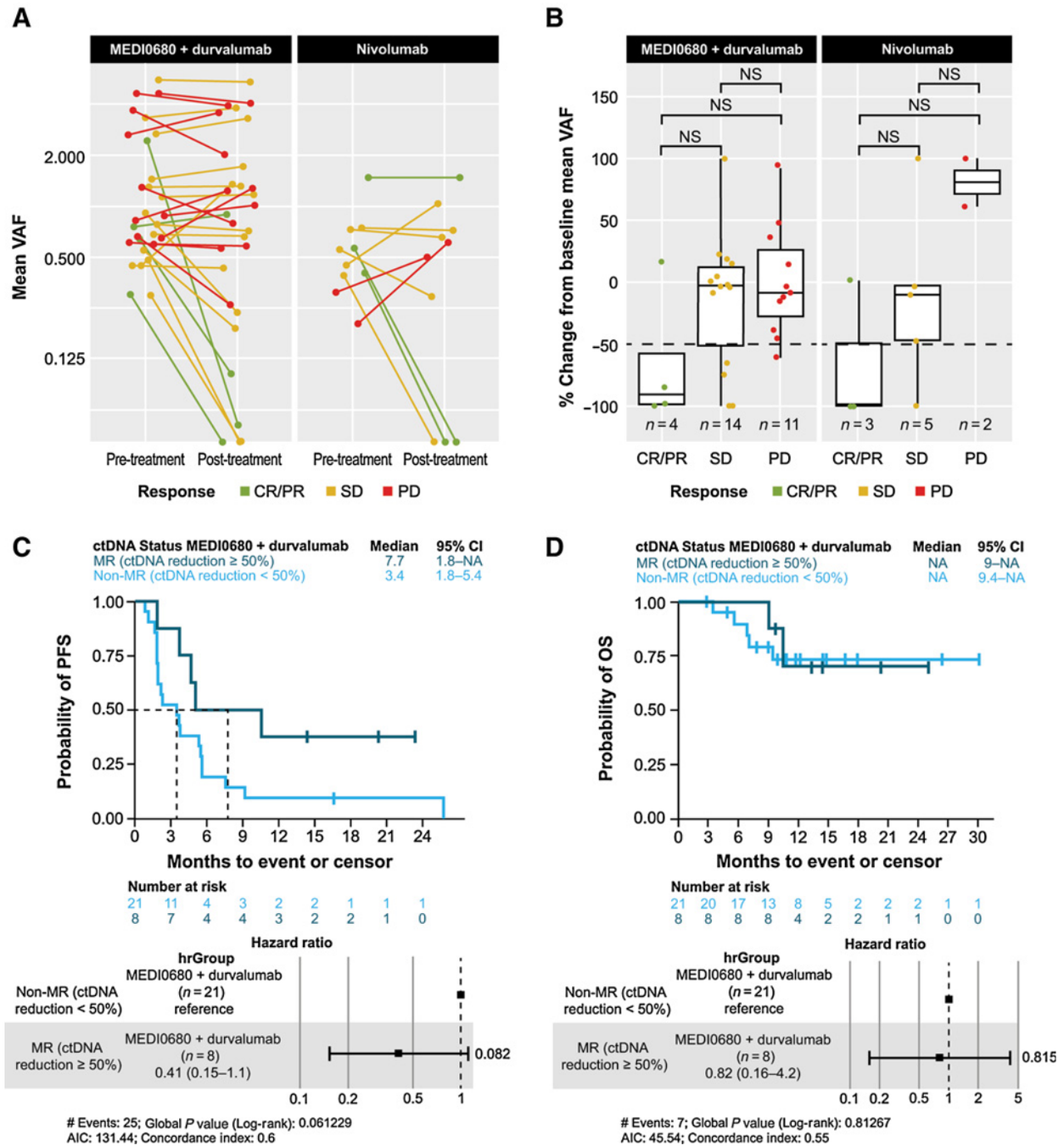

Figure 3.

Change in ctDNA mean VAF from baseline to week 4 (**A**) and percent change from baseline in mean VAF by clinical response (**B**). Subgroup analysis based on changes in ctDNA fraction using a 50% change from baseline cutoff in association with PFS (**C**), and OS (**D**) in the MEDI0680 + durvalumab arm. Reduction in ctDNA fraction ≥ 50% at 4 weeks versus baseline is defined as MR and reduction ctDNA fraction < 50% at 4 weeks versus baseline is defined as non-MR. AIC, Akaike Information Criteria; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; MR, molecular response; NA, not applicable; NS, not significant; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VAF, variant allele frequency.

and do warrant further investigation, particularly in larger clinical trials. Notably, we observed a trend in the combination arm where tumors containing activated T cells were more likely to respond to therapy. This is consistent with a previous study in mRCC demonstrating that tumors with activated immune profiles were more likely to respond to immunotherapy treatment compared with VEGF inhibitors (33). On the basis of the considerable complexity underlying the response to immunotherapy, additional comprehensive and integrated

approaches to identify suitable biomarkers of response in patients with RCC are needed (32).

In conclusion, while the safety profile of MEDI0680 and durvalumab was manageable and generally consistent with the known toxicity of the anti-PD-L1/PD-1 drug class, this study did not meet its primary endpoint. The combined blockade of PD-1 and PD-L1 did not improve efficacy over the inhibition of PD-1 alone for patients with advanced or metastatic ccRCC. Moreover, previous studies of the anti-CD80 mAb, galiximab, similarly demonstrated favorable safety profiles but low ORRs in patients with relapsed and refractory lymphomas when used as monotherapy. ORRs in those studies were 10.3% in patients with Hodgkin lymphoma (34) and 11% in patients with follicular lymphoma (35). Taken together, these results may suggest that the PD-L1–CD80 interaction does not have a significant role in tumor immune evasion in ccRCC, or that MEDI0680 does not provide adequate inhibition of the PD-1–CD80 interaction in patients with ccRCC. Future combination strategies could be explored combining agents that target PD-1 with others targeting alternative immunomodulatory pathways outside the PD-1/PD-L1 axis, such as CTLA-4 or VEGF.

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Authors' Contributions

M.H. Voss: Conceptualization, formal analysis, supervision, investigation, writing–original draft, writing–review and editing. **A.A. Azad:** Conceptualization, supervision, writing–review and editing. **A.R. Hansen:** Resources, data curation, writing–review and editing. **J.E. Gray:** Conceptualization, supervision, validation, investigation, methodology, writing–review and editing. **S.J. Welsh:** Investigation, writing–review and editing. **X. Song:** Conceptualization, formal analysis, investigation, methodology, writing–review and editing. **M. Kuziora:** Formal analysis, visualization, writing–review and editing. **L. Meinecke:** Resources, software, formal analysis, visualization, writing–original draft, writing–review and editing. **J. Blando:** Investigation, methodology, writing–review and editing. **I. Achour:** Conceptualization, formal analysis, supervision, visualization, methodology, writing–original draft. **Y. Wang:** Investigation, writing–review and editing. **F.L. Walcott:** Supervision, validation, investigation, visualization, project administration, writing–review and editing. **S.F. Oosting:** Investigation, writing–review and editing.

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