Kidney Cancer 5 (2021) 181–187
DOI 10.3233/KCA-210128
IOS Press

Research Report

Phase Ib/II trial of Ibrutinib and Nivolumab in Patients with Advanced Refractory Renal Cell Carcinoma[1]

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Received 12 July 2021
Accepted 27 October 2021
Pre-press 8 November 2021
Published 3 December 2021

Abstract.
BACKGROUND: Although immune checkpoint inhibitor-based therapy has improved the outcomes of many patients with metastatic renal cell carcinoma (mRCC), most eventually develop disease progression. Newer agents that modulate immune response can possibly potentiate checkpoint inhibitor therapy. The ITK/ETK/BTK inhibitor ibrutinib has been reported to inhibit myeloid derived suppressor cells in preclinical models and to potentiate immunotherapy. We conducted an investigator-initiated trial of ibrutinib plus the PD1 inhibitor nivolumab in mRCC patients, particularly in those previously exposed to immune checkpoint inhibitors.
METHODS: Eligible patients had mRCC of any histologic subtype, completed at least one line of prior systemic therapy which could have included prior immunotherapy, and had acceptable end-organ function with ECOG performance status of 0–2. Treatment consisted of nivolumab 240 mg intravenously every 2 weeks plus ibrutinib 560 mg (dose level 0) or 420 mg (dose level -1) orally once daily. Cycle length was 28 days. Dose limiting toxicity (DLT) was defined as any Grade 3 or higher adverse event (AE) attributable to therapy. After identification of the recommended phase 2 dose (RP2D), up to 19 patients were enrolled to an expansion cohort to further evaluate toxicities and any early evidence of efficacy. The primary endpoints of the trial were establishment of RP2D and progression-free survival (PFS).
RESULTS: A total of 31 patients were enrolled, 6 to dose level 0, 7 (of which one was not evaluable for DLT) in dose level -1, and 18 in the expansion cohort. Median age was 60 years (range, 36–90), most had clear cell histology ($n = 27$; 87%), and most had prior immune checkpoint inhibitor therapy ($n = 28$; 90%). Three patients experienced one DLT each, all in dose level 0 (all Grade 3), namely elevated lipase, hypoalbuminemia, and nausea. No DLTs were seen in dose level –1 which was declared the RP2D. The most common Grade 3 or higher AEs include anemia ($n = 5$), lymphocyte count decrease (4), nausea (2), and hypotension (2). Of 28 patients evaluable for response, one patient (3.6%) had a complete response, 2 (7.1%) had a partial response, and 11 (39.2%) had stable disease, for an objective response rate of 10.7% (95% CI: 3.7%–27.2%) and a disease control rate of 50% (95% CI: 32.6%–67.4%). All responders had received prior immune checkpoint inhibitor therapy. Median PFS was 2.5 months (95% CI, 1.9 – 4.8) while median OS was 9.1 months (95% CI, 6.6 –19.0).

[1]Results were presented in part at the American Society of Clinical Oncology Annual Meeting 2018 in Chicago, IL. USA.

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CONCLUSIONS: Ibrutinib at a dose of 420 mg orally once daily in combination with nivolumab 240 mg IV every 2 weeks is feasible and tolerable in mRCC patients. No unique immune-related AEs were observed. Anti-tumor activity was seen in patients previously exposed to PD-1 targeted therapy.

INTRODUCTION

Renal cell carcinoma is estimated to result in 13,780 deaths in 2021 in the United States, with approximately 76,000 new diagnoses expected [1]. The treatment of metastatic renal cell carcinoma (mRCC) has evolved substantially during the last decade, in large part due to the successful use of vascular endothelial growth factor (VEGF) receptor inhibitor therapies and immune check point inhibitor (ICI) therapies studied largely in clear cell mRCC patients [2–6, 18, 19]. For most patients with mRCC, ICIs are an established component of frontline combination regimens [4, 5]. Unfortunately, some patients experience either primary refractoriness while most will eventually experience disease progression despite initial clinical benefit, with a median progression free survival (PFS) following frontline immunotherapy ranging from 11.5–15 months [4, 5].

Myeloid derived suppressor cells (MDSCs) inhibit T-cell activation and proliferation and can play a role in reducing the effectiveness of ICI [7]. Human and murine MDSCs highly express Bruton's tyrosine kinase (BTK), which can be inhibited potently by ibrutinib, a small molecule approved for the treatment of hematologic malignancies [8]. Through inhibition of BTK phosphorylation in MDSCs, ibrutinib reduced generation of MDSCs and enhanced the efficacy of anti-PD-L1 therapy in a murine breast cancer model. Ibrutinib also inhibits other kinases, including ETK/BMX, ITK, and BLK. In a preclinical study of 90 human RCC tumor specimens and 30 normal tissues, ETK expression by IHC was found to be increased in RCC as compared to normal controls and there was a positive correlation between ETK expression and increasing clinical stage, grade and metastasis [9]. Additionally, inhibition of ITK by ibrutinib preferentially inhibits Th2 response in favor of Th1 response [10], which has been found to favor an antitumor immune response with ICIs [11].

These preclinical data suggest that ibrutinib may have clinical activity in mRCC, and in particular may play a role in enhancing the efficacy of ICIs [9–11]. To further explore this hypothesis, we conducted a prospective, investigator-initiated, open-label, non-randomized, single-center Phase Ib study of ibrutinib combined with the programmed cell death protein 1 (PD1) inhibitor nivolumab in patients with mRCC.

METHODS

Patients & treatment

Adult patients (≥18 years old) with any histologic subtype of metastatic renal cell carcinoma, measurable and/or evaluable disease, ECOG performance status of 0–2, adequate hematologic, renal, and hepatic function, and who had completed at least one prior line of systemic therapy were eligible for inclusion. Cycles of treatment were 28 days and included ibrutinib taken orally (PO) daily combined with nivolumab 240 mg intravenously (IV) every 2 weeks. Treatment with ibrutinib in combination with nivolumab continued for a maximum of one year or until tumor progression, unacceptable or intolerable toxicity, patient withdrawal for any reason, or physician choice. Continuing single agent nivolumab for a maximum of one year was allowed for patients who were unable to receive the doublet due to toxicity or patient preference per physician discretion. All patients receiving at least one cycle of therapy, regardless of dose level, were evaluable for response and were assessed for the primary endpoint of PFS. Patients were clinically assessed every 4 weeks. Imaging was assessed at baseline and every 8 weeks, with response and progression evaluated by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [12].

All research was reviewed and approved by the University of California Davis Institutional Review Board (IRB approval # 895892). All patients provided written, informed consent in accordance with the Helsinki Declaration.

ClinicalTrials.gov Identifier: NCT02899078.

The trial protocol is available in Supplement 1.

Trial design, end points, and statistics

The study involved a limited dose-finding lead in, during which 6 patients were enrolled to the first

dose level (DL) with ibrutinib 560 mg PO daily and nivolumab 240 mg IV every 2 weeks (DL 0). Dose-limiting toxicity (DLT) was defined as a common terminology criteria for adverse events (CTCAE, version 4) Grade 3 or higher event attributed to treatment, and was assessed after 1 cycle of treatment. To be evaluable for DLT, patients must have received at least three weeks of ibrutinib. If DLTs occurred in 2 or more patients at DL 0, enrollment of an additional 6 patients at DL –1 with ibrutinib at 420 mg PO daily and unchanged nivolumab dosing was planned. If DLT was observed in 2 or more of the first 6 patients at DL –1, the trial would be discontinued. The study proceeded to an expansion cohort with a goal of a total of 24 patients if no DLTs were observed in DL 0 or if no more than 1 DLT was seen at DL –1.

The planned sample size for the primary objective of PFS to evaluate preliminary efficacy was determined based on the CheckMate-025 trial which randomized 821 previously treated patients with mRCC to nivolumab 3 mg/kg IV every 2 weeks or 10 mg everolimus PO daily until progression or unacceptable toxicity [2]. In that study, progression-free survival (PFS) at 6 months was approximately 40% with nivolumab. Assuming ibrutinib combined with nivolumab would increase the PFS rate from 40 to 70% at the 6-month timepoint, it was determined a sample size of 25 patients would provide 90% power and one-sided alpha level 0.034 to detect this difference, with a critical value of 15 or more patients out of 25 experiencing PFS at 6 months. To account for attrition, a total of 31 patients were planned for accrual. All patients enrolled in the study were to be included in the efficacy assessment. Secondary objectives were to provide assessments of the objective response rate (ORR) based on RECIST criteria by investigator assessment, overall survival (OS), and safety based on NCI CTCAE of this treatment combination.

Overall survival was calculated using the Kaplan-Meier method as the duration from start of treatment to death by any cause, and PFS as the duration from start of treatment to progression or death. Censoring was applied at the date of last contact for living patients in OS estimation, and alive/progression-free patients for PFS. The ORR was estimated along with the 95% Wilson-Score confidence interval [17]. Data evaluation and analysis was completed using Excel (Microsoft Corp, 2020) and Prism (GraphPad Software, 2020), and SAS (SAS Institute, Cary, NC).

Table 1
Patient characteristics

Patient characteristic	No.	(%)
Total Enrolled Patients	31	N/A
Median age at enrollment [range], years	60 [36–90]	N/A
Median number of prior therapies	2 [1–10]	N/A
Sex		
Female	8	25.8%
Male	23	74.2%
Primary Ethnicity		
Hispanic or Latino	2	6.5%
Non-Hispanic	29	93.5%
Primary Race		
African American	1	3.2%
American Indian or Alaska Native	1	3.2%
Asian	2	6.5%
White	27	87.1%
ECOG Performance Status		
0-1	26	83.8%
2	5	16.1%
Histology		
Clear Cell	27	87.1%
Non-Clear Cell	4	12.9%
Prior Checkpoint Inhibitor Treatment		
Yes	28	90.3%
No	3	9.7%
Prior VEGF Targeted Treatment		
Yes	22	71%
No	9	29%
Prior Nephrectomy		
Yes	26	83.9%
No	5	16.1%
Ibrutinib Dose		
Dose Level 0 (560 mg)	6	19.4%
Dose Level –1 (420 mg)	25	80.6%

Abbreviation: N/A – not applicable.

RESULTS

Patient characteristics

At the time of data cut-off, a total of 31 patients were enrolled and 28 patients treated for at least 1 cycle, including 6 in DL 0, 7 in phase II DL –1, and 18 in the expansion cohort at dose level –1. The median age was 60 (range: 36–90). Most patients were of male sex. Most patients had received prior immune checkpoint inhibitor therapy ($n = 28$; 90.3%), with only 1 patient having received prior nivolumab plus ipilimumab combination therapy, and 26 (83.9%) had undergone prior nephrectomy. Patients had received a median of 2 prior lines of systemic therapy (range: 1–10) Clear cell RCC was the most common histology, comprising 27 (87%) patients. Of nccRCC patients, 1 had collecting duct RCC, and the remaining 3 patients had poorly differentiated RCC that could not be characterized as clear cell. Demographic data are summarized in Table 1.

Safety

In the dose-finding lead-in, 3 DLTs were noted in the DL 0 cohort. One patient experienced DLT of Grade 3 nausea attributed to either nivolumab or ibrutinib. Another patient had DLT of Grade 3 lipase elevation attributed to nivolumab; this patient was asymptomatic and lipase levels resolved upon discontinuation of treatment. A third patient had Grade 3 hypoalbuminenia as a DLT. Thus, DL –1 was opened per protocol design. Six patients were originally enrolled to DL –1; however, one of these patients was not evaluable for DLT (the patient did not complete at least three weeks of ibrutinib) due to symptomatic disease progression and was therefore replaced. Thus, there were a total of 7 patients enrolled in DL –1. No DLTs were observed at this dose level. Therefore, DL –1 was identified as the RP2D. Among all 31 patients, the most common adverse effects (AEs) were anemia (Any Grade: $n = 11$, 35.5%. Grade 3–4: $n = 5$, 16.1%), lymphocyte count reduction (Any Grade: $n = 12$, 38.7%. Grade 3–4: $n = 4$, 12.9%), and fatigue (Any Grade: $n = 18$, 58.0%. Grade 3–4: $n = 0$, 0%). All adverse events attributable to protocol therapy are listed in Table 2.

Response and survival outcomes

Of 31 patients enrolled, 3 were not evaluable for response, as they withdrew from the trial before completion of the first cycle: one withdrew consent prior to treatment, 1 continued to have progression of a symptomatic malignant pleural effusion and changed preference to hospice care on day 16 of cycle 1, and one discontinued treatment of day 5 of cycle 1 due to need for neurological surgery for cord compression and did not continue on trial. Of the 28 patients evaluable for response, ORR was 10.7% (95% CI: 3.7%–27.2%). One patient (3.6%) had a complete response (CR), two patients (7.1%) had a partial response (PR), and 11 patients (35.5%) had stable disease (SD). All patients with objective responses had ccRCC. In terms of exposure to ICI, the patient who experienced a CR had previously been treated with pembrolizumab, and both patients with PRs had previously been treated with nivolumab. For the 3 (10.7%) patients without prior immune checkpoint inhibitor exposure, best response was SD. Median time to best response was 51 days (range: 20–160 days). Visual depiction of responses and outcomes are available in the Supplementary Material as waterfall plot (Supplementary Figure 1) and swimmer's plot (Supplementary Figure 2). Median PFS was estimated to be 2.5 months (95% CI, 1.9–4.8). At 6 months, PFS was estimated at 25% (95% C, 11.1%–41.8%), and at 12 months, it was 11.4% (95% CI, 2.5%–28.0%). Median OS was 9.1 months (95% CI, 6.6–19.0). Median change in RECIST target lesion size was +7.5% (Range: –100% to +98%).

Follow-up

Median follow-up was 29.9 months. At time of data cut-off, 3 (10.7%) patients with prior immune checkpoint inhibitor exposure had experienced long-term anti-neoplastic response. One patient experienced a grade 4 aspartate aminotransferase (AST) elevation after 2 cycle requiring treatment discontinuation, but was found to have a CR and remains cancer-free after 45 months. Another developed pneumonitis after 10 cycles with SD, and continues to have stable lesions on imaging while off therapy at 43 months. Another patient with SD continues maintenance nivolumab off-trial at 26 months. Seven (25.0%) additional patients experienced progressive disease but remain alive at the time of analysis.

DISCUSSION

This single-arm investigator-initiated trial demonstrated that the combination of the BTK inhibitor ibrutinib with the PD1 inhibitor nivolumab is feasible, relatively safe, and has manageable toxicities at the RP2D in mRCC patients. Protocol therapy was reasonably tolerated, with similar AEs to that reported in prior studies of ibrutinib [13, 14] and nivolumab [2, 4]. There also appeared to be no unique immunotherapy-related toxicities observed, or no observed potentiation of known adverse events attributable to checkpoint inhibitor therapy.

Although the study did not meet its target of a 6 month PFS rate of 70%, intriguingly a small number of patients appeared to derive clinical benefit from this novel combination. It must be noted that the high PFS goal was developed in a disease context that rapidly evolved during the course of the trial. When the study was originally designed, nivolumab had just been approved as second line therapy of mRCC as a result of the CheckMate 025 trial, which enrolled checkpoint inhibitor-naïve patients. In contrast, >90% of the patients enrolled in our study had prior immune checkpoint inhibitor exposure, and patients had received a median of 2 prior lines of systemic therapy (range 1–10). Thus, we believe that the

Table 2
Adverse effects of any grade

Category	Grade 1	Grade 2	Grade 3	Grade 4	Total No. of Events
Fatigue	7	11			18
Lymphocyte count decreased	2	6	4		12
Anemia	3	3	5		11
Hyperuricemia	8				8
Anorexia	4	3			7
Diarrhea	7				7
Nausea	4		2		6
Rash, maculo-papular	2	2	1		5
Arthralgia	3	2			5
Dry Mouth	5				5
White blood cells decreased	5				5
Hypoalbuminemia	1	2	1		4
Dizziness	3		1		4
Vomiting	3		1		4
Generalized muscle weakness	2	2			4
Mucositis, oral	3	1			4
Edema, limbs	4				4
Platelet count decrease	4				4
Hypotension	1		1	1	3
Abdominal Pain	2		1		3
Creatinine increased	1	2			3
Fever	1	2			3
Constipation	2	1			3
Myalgia	2	1			3
Infection		1	1		2
Lipase increased		1	1		2
Aspartate aminotransferase increased	1			1	2
Dysgeusia		2			2
Alkaline phosphatase increased	1	1			2
Blood bilirubin increased	1	1			2
Dyspnea	1	1			2
Oral Pain	1	1			2
Bruising	2				2
Cough	2				2
Headache	2				2
Pruritis	2				2
Esophagitis			1		1
Alanine aminotransferase increased				1	
Anxiety		1			1
Dry Eyes		1			1
Dry Skin		1			1
Edema, face		1			1
Epistaxis		1			1
Hemoptysis		1			1
Hematuria		1			1
Hyperthyroidism		1			1
Pericardial effusion		1			1
Pneumonitis		1			1
Thrombotic event		1			1
Weight loss		1			1
Activated partial thromboplastin time prolonged	1				1
Hyperhidrosis	1				1
Hypocalcemia	1				1
Hyponatremia	1				1
Nasal Congestion	1				1
Pericarditis	1				1
Rhinnorhea	1				1
Rash, acneform	1				1
Rectal hemorrhage					0

remarkable response seen in a select few patients who previously experienced progression during treatment with immune checkpoint inhibition warrants further investigation.

The rapidly evolving nature of the mRCC therapeutic landscape with the establishment of several immunotherapy doublet regimens as the frontline standard of care in clear cell histology makes it more difficult for novel doublets to gain a foothold, except in the context of patients who have had prior checkpoint inhibitor therapy but are now experiencing tumor progression. To date, one retrospective study has evaluated re-challenge with immunotherapy in patients with mRCC. Evaluating 69 patients who had received ICIs in at least 2 separate lines of therapy, the study found that patients received either single-agent ICI or ICI combined with targeted therapy upon re-challenge [15]. Patients were found to have an ORR of 23% on re-challenge. The likelihood of response was higher among patients who had previously responded to ICI therapy, albeit with limited numbers for evaluation. Prospectively, a Phase II study of lenvatinib plus pembrolizumab allowed patients to have received prior CPI therapy. In this study of 91 evaluable patients, an ORR of 51% was noted [16]. Median progression-free survival was 11.7 months and median duration of response was 9.9 months. Since the study was a single-arm trial, it is not possible to determine how much of the efficacy observed in this study is derived from re-challenge of immunotherapy rather than the addition of lenvatinib.

This trial is limited by a heavily pre-treated and largely ICI-refractory patient population, lack of a control arm, and small sample size that preclude more definitive conclusions on the combination's efficacy. Given the aforementioned retrospective evaluation of ICI rechallenge demonstrating an ORR of 23%, it is possible that the ORR observed in this study could be attributable to nivolumab alone. In addition, in the absence of molecular correlative studies, which were not possible due to the logistic difficulties associated with obtaining additional tumor tissue during treatment, it is unclear whether the presumed mechanism of action of ibrutinib in inhibiting MDSCs and thus enhancing or recapturing nivolumab efficacy truly contributed to the modest clinical benefit observed.

In conclusion, ibrutinib at a dose of 420 mg orally once daily in combination with nivolumab 240 mg IV every 2 weeks is feasible and tolerable in mRCC patients. Anti-tumor activity was seen in a small subset of patients previously exposed to PD1-targeted therapy. Further evaluation of MDSC modulation as a therapeutic strategy in mRCC is warranted.

ACKNOWLEDGMENTS

We thank Jerry and Susan Knapp for their generous support of clinical research and this study at the UC Davis Comprehensive Cancer Center.

FUNDING

This investigator-initiated trial was funded by Pharmacyclics LLC, an AbbVie company, and the UC Davis Comprehensive Cancer Center (P30-CA093373).

AUTHOR CONTRIBUTIONS

Mamta Parikh contributed to the performance, interpretation of data and writing of this article.

Matthew E Tenold contributed to the interpretation of data and writing of this article.

Lihong Qi contributed to the interpretation of data and statistical analysis.

Frances Lara and Daniel Robles contributed to the performance of this study and data generation.

Frederick J Meyers contributed to the interpretation of data and writing of this article

Primo N. Lara contributed to the conception, performance, interpretation of data and editing of this article.

CONFLICT OF INTEREST

Primo N. Lara is Editor-in-Chief and Mamta Parikh is an Associate Editor of this journal. They were not involved in the peer-review process nor had access to any information regarding its peer-review. The authors have no other conflicts of interest to report.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/KCA210128.

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