

Bempegaldesleukin plus nivolumab in first-line renal cell carcinoma: results from the PIVOT-02 study

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ABSTRACT

Background Immune checkpoint inhibitor-based combinations have expanded the treatment options for patients with renal cell carcinoma (RCC); however, tolerability remains challenging. The aim of this study was to evaluate the safety and efficacy of the immunostimulatory interleukin-2 cytokine prodrug bempegaldesleukin (BEMPEG) plus nivolumab (NIVO) as first-line therapy in patients with advanced clear-cell RCC. **Methods** This was an open-label multicohort, multicenter, single-arm phase 1/2 study; here, we report results from the phase 1/2 first-line RCC cohort (N=49). Patients received BEMPEG 0.006 mg/kg plus NIVO 360 mg intravenously every 3 weeks. The primary objectives were safety and objective response rate (ORR; patients with measurable disease at baseline and at least one postbaseline tumor response assessment). Secondary objectives included overall survival (OS) and progression-free survival (PFS). Exploratory biomarker analyses: association between baseline biomarkers and ORR.

Results At a median follow-up of 32.7 months, the ORR was 34.7% (17/49 patients); 3/49 patients (6.1%) had a complete response. Of the 17 patients with response, 14 remained in response for >6 months, and 6 remained in response for >24 months. Median PFS was 7.7 months (95% CI 3.8 to 13.9), and median OS was not reached (95% CI 37.3 to not reached). Ninety-eight per cent (48/49) of patients experienced ≥1 treatment-related adverse event (TRAE) and 38.8% (19/49) had grade 3/4 TRAEs, most commonly syncope (8.2%; 4/49) and increased lipase (6.1%; 3/49). No association between exploratory biomarkers and ORR was observed. Limitations include the small sample size and single-arm design.

Conclusions BEMPEG plus NIVO showed preliminary antitumor activity as first-line therapy in patients with advanced clear-cell RCC and was well tolerated. These findings warrant further investigation.

INTRODUCTION

Immunotherapies, particularly immune checkpoint inhibitors (ICIs), have dramatically changed the treatment landscape for patients with advanced renal cell carcinoma (RCC).^{1,2} Approved first-line treatments for these patients include an ICI combined with

Key messages

What is already known on this topic

- There remains a need for better-tolerated, immune checkpoint inhibitor-based combination treatments for patients with advanced renal cell carcinoma (RCC).
- Bempegaldesleukin (BEMPEG) is an immunostimulatory interleukin (IL)-2 prodrug that has been engineered to deliver a controlled, sustained, and preferential IL-2 pathway signal, with the goal of stimulating an antitumor immune response while minimizing toxicity.
- Phase 1 of the PIVOT-02 study showed that combination treatment with BEMPEG plus nivolumab was well tolerated and had encouraging clinical activity in solid tumors, including patients with RCC, warranting further investigation in a dose-expansion cohort.

What this study adds

- These data demonstrate the preliminary safety and efficacy of this novel immunotherapy combination in patients with advanced clear-cell RCC.

How this study might affect research

- These results provide rationale for the ongoing phase three trial in previously untreated patients with advanced or metastatic RCC (PIVOT 09; NCT03729245).

a vascular endothelial growth factor receptor (VEGFR)-targeted tyrosine kinase inhibitor (TKI; eg, nivolumab (NIVO) plus cabozantinib³ and pembrolizumab plus axitinib^{4,5} or lenvatinib⁶) or ICI combinations (eg, NIVO plus ipilimumab^{7,8}). However, ICI-TKI and ICI-ICI combinations are difficult to tolerate. Rates of grade 3/4 treatment-related adverse events (TRAEs) are high (>48%), 15%–25% of patients experience TRAEs leading to treatment discontinuation, and TRAEs necessitating dose modification are common.^{3–7} As such, there remains a need

for better-tolerated, ICI-based combination treatments that extend treatment benefit to more patients.

The International Metastatic RCC Database Consortium (IMDC) risk assessment criteria were established based on data from patients treated with VEGFR-TKI therapy but they have also been used for ICI-based therapy decision making.⁹ Historically, patients with IMDC favorable risk have angiogenesis-driven disease and respond well to VEGFR-TKI.¹⁰ Identifying which patients will achieve durable responses, and ultimately live longer with ICI-based regimens, is an unmet need.¹¹ Interleukin (IL)-2 is an extensively studied cytokine with immunostimulatory and immunosuppressive effects. Treatment with high-dose IL-2 (aldesleukin) produces durable responses in approximately 5% of patients with metastatic clear-cell RCC,¹² and data from a multi-institutional clinical registry (PROCLAIM) of 810 patients demonstrated median overall survival (OS) of 63 months in patients with IMDC favorable risk.¹³ However, severe toxicity experienced with the administration of high-dose IL-2, such as capillary leak syndrome, which is brought about by the IL-2 mechanism of action along with the pharmacokinetic and pharmacodynamic properties of high-dose IL-2, necessitates inpatient administration at specialized centers.¹⁴ High-dose IL-2 treatment, while stimulating the immune system by activating effector T cells and natural killer cells, also promotes the expansion of regulatory T cells, which play an immunosuppressive role in the tumor microenvironment.¹⁵ This, combined with the tolerability profile, has led to limited clinical use of high-dose IL-2 and prevented it being combined with other immunotherapies.

Bempegaldesleukin (BEMPEG, NKTR-214) is an immunostimulatory IL-2 prodrug that has been engineered to deliver a controlled, sustained, and preferential IL-2 pathway signal, with the goal of stimulating an antitumor immune response while minimizing toxicity and allowing for outpatient administration.^{16–18} The location of the polyethylene glycol chains directs BEMPEG to preferentially bind the dimeric IL-2 receptor $\beta\gamma$ complex (predominantly expressed on natural killer cells and CD8⁺ T cells) over the trimeric IL-2 receptor $\alpha\beta\gamma$ complex (predominantly expressed on immunosuppressive regulatory T cells).^{17, 18} In both animal models and patients with advanced solid tumors, BEMPEG has been shown to induce immunological changes,^{16–19} including preferential expansion and activation of CD8⁺ T cells and natural killer cells, and limited expansion of regulatory T cells in the tumor microenvironment.²⁰ Treatment with BEMPEG monotherapy was well tolerated in heavily pretreated patients with advanced solid tumors.¹⁶ Taken together, these factors support the evaluation of BEMPEG in combination with an ICI.

The phase 1/2 PIVOT-02 study (NCT02983045) established the recommended phase 2 dose of combination treatment with BEMPEG plus NIVO and demonstrated encouraging clinical activity in solid tumors, including RCC.^{21, 22} Data from the phase 2 part of PIVOT-02 has demonstrated encouraging antitumor activity in patients

with previously untreated metastatic melanoma¹⁹ and advanced/metastatic urothelial carcinoma.²³ This regimen is well tolerated with a predictable safety profile related to TRAEs and immune-mediated AEs.^{19, 21} The objective of this study was to evaluate the safety and efficacy of BEMPEG in combination with NIVO as first-line therapy in patients with advanced or metastatic clear-cell RCC.

METHODS

Study design and treatment

PIVOT-02 is a non-randomized, open-label, international, multicenter, multi-cohort, phase 1/2 study. In the phase two single-arm dose-expansion cohorts, patients received intravenous BEMPEG 0.006 mg/kg plus NIVO 360 mg administered every 3 weeks for up to 2 years or until documented disease progression, death, unacceptable toxicity, symptomatic deterioration, patient/investigator's decision to discontinue treatment, patient withdrawal of consent, loss to follow-up, or study termination by the sponsor. Dose reduction of BEMPEG, but not NIVO, was permitted.

The study was conducted in accordance with the Declaration of Helsinki, the US Food and Drug Administration regulations, and the International Council for Harmonization Good Clinical Practice guidelines. All patients provided written informed consent before the conduct of any study procedures.

Patients

Eligible patients had histologically confirmed, advanced (not amenable to surgery) or metastatic RCC (American Joint Committee on cancer stage IV) with a clear-cell component, including tumors with sarcomatoid features. Patients had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 and were ≥ 18 years of age with an Eastern Cooperative Oncology Group performance status of 0 or 1. No prior systemic therapy for advanced or metastatic RCC was allowed.

Patients were required to have archival or fresh tumor tissue (within 6 months) for assessment of programmed death ligand-1 (PD-L1) expression at baseline. Patients were excluded if they had received prior immunotherapy, including IL-2 agents, in any of the neoadjuvant, adjuvant, or advanced settings; had active, known, or suspected autoimmune disease requiring systemic immunosuppressive agents; or had an active infection requiring antimicrobial therapy, active brain metastases, or a known additional malignancy that was progressing or required active treatment.

Study objectives and assessments

The primary objective of the study was to evaluate the safety and objective response rate (ORR) following treatment with BEMPEG plus NIVO. ORR was defined as the percentage of patients with a best response of complete response (CR) or partial response (PR) by RECIST V.1.1.

Secondary objectives were to evaluate the efficacy of the combination using OS and progression-free survival (PFS), clinical benefit rate (CBR; a CR, PR, or stable disease ≥ 7 weeks), and duration of response (DOR).

Safety was evaluated in all patients (safety population) who received at least one dose of study drug, and AEs were categorized per the National Cancer Institute's Common Terminology Criteria for Adverse Events V.4.03. All efficacy endpoints other than PFS and OS were analyzed in the response-evaluable population (all patients with measurable disease per RECIST V.1.1 at baseline and at least one post-baseline tumor response assessment). Response assessments were performed at screening, every 8 weeks (± 7 days), and at end of treatment. Patients with an unconfirmed PR/CR required a confirmatory scan 4 weeks after the previous scan. Long-term follow-up for survival occurred every 3 months. All safety and efficacy endpoints were evaluated by local investigator assessment.

Analyses between dichotomous biomarker categories measured in baseline tumor biopsies and ORR were explored. Tumor biomarkers associated with response to ICIs were selected for analyses and assessed at baseline (including PD-L1 expression on tumor cells by immunohistochemistry (IHC) (by 28–8 PharmDx assay, Dako, an Agilent Technologies, Inc. company, Santa Clara, California, USA), interferon gamma (IFN- γ) gene-expression profile (GEP), CD8⁺ tumor-infiltrating lymphocytes (TIL) by IHC, and tumor mutational burden (TMB); see online supplemental information) for additional methods^{24–26}). Tumors were defined as PD-L1 negative ($< 1\%$ tumor cell expression), positive ($\geq 1\%$ tumor cell expression), or unknown (indeterminate/non-evaluable).

Statistical analysis

The study was designed to enroll a minimum of 26 patients in the phase 2 cohort at the recommended phase 2 dose of BEMPEG plus NIVO. Analyses reported here also include patients with RCC treated at the recommended phase 2 dose of BEMPEG plus NIVO during the dose escalation period in phase 1 of the study. Baseline characteristics and safety data were summarized by descriptive statistics and frequency tables. The Clopper–Pearson method was used to calculate response rates with two-sided 95% confidence intervals (CIs). DOR, PFS, and OS were evaluated by the Kaplan–Meier method. DOR and PFS data for patients without disease progression (per RECIST V.1.1) and alive, or with unknown status, were censored at the time of the last tumor assessment prior to new anti-cancer therapy. Statistical analyses for biomarker evaluations included calculation of the difference in response rates with 95% CIs between biomarker-defined groups. For the primary analysis, all efficacy and safety endpoints were analyzed up to and including the cut-off date (January 8, 2021). Statistical analyses were performed with SAS (V.9.4) and Prism V.8.0 (GraphPad Software, San Diego, California, USA).

Table 1 Baseline characteristics of all enrolled patients

	Total N=49
Male sex; n (%)	38 (77.6)
Median age (range), years	61 (40–78)
ECOG PS score; n (%)	
0	30 (61.2)
1	19 (38.8)
Prior nephrectomy; n (%)	46 (93.9)
Histology; n (%)	
Clear cell	49 (100)
PD-L1 status*; n (%)	
Negative $< 1\%$	31 (63.3)
Positive $\geq 1\%$	14 (28.6)
Unknown	4 (8.2)
IMDC risk group; n (%)	
Favorable	17 (34.7)
Intermediate	22 (44.9)
Poor	10 (20.4)
Prior radiotherapy; n (%)	7 (14.3)
Time from initial diagnosis to start of study treatment, median years (range)	1.57 (0.1–18.4)
Stage at initial diagnosis; n (%)	
I	8 (16.3)
II	9 (18.4)
III	9 (18.4)
IV	18 (36.7)
Unknown	5 (10.2)
Time from diagnosis of metastasis or locally advanced disease to start of study treatment, median months (range)	2.1 (0.7–48.8)

Data cut-off: January 8, 2021.

*PD-L1 status by immunohistochemistry: PD-L1-negative defined as $< 1\%$ tumor cell staining; PD-L1-positive defined as $\geq 1\%$ tumor cell staining.

ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium; PD-L1, programmed death ligand-1.

RESULTS

Patients

Between April 3, 2017, and February 26, 2018, 49 patients (phase 1, n=11; phase 2, n=38) were enrolled at 10 sites across the US and Italy. Baseline demographic characteristics are shown in [table 1](#). All patients were evaluable for safety and response.

At data cut-off (January 8, 2021), all patients had ended treatment. BEMPEG was discontinued for the following reasons: progressive disease by RECIST (n=31); AE (n=6); maximum 2-year treatment duration reached (n=7); patient decision (n=1); clinical progression (n=1); and

**Table 2** Incidence of TRAEs*

Event, n (%)	Advanced RCC N=49	
	Any grade	Grade 3–4
TRAEs	48 (98.0)	19 (38.8)
TRAEs with an incidence \geq 20% (any grade) or more than one patient at grade 3–4		
Fatigue	37 (75.5)	2 (4.1)
Pyrexia	24 (49.0)	1 (2.0)
Chills	24 (49.0)	0
Influenza-like illness	24 (49.0)	0
Pruritus	24 (49.0)	0
Nausea	23 (46.9)	0
Rash	19 (38.8)	0
Decreased appetite	19 (38.8)	1 (2.0)
Arthralgia	17 (34.7)	1 (2.0)
Edema peripheral	16 (32.7)	0
Diarrhea	15 (30.6)	0
Vomiting	15 (30.6)	0
Myalgia	14 (28.6)	1 (2.0)
Headache	11 (22.4)	0
Hypothyroidism	11 (22.4)	0
Rash maculopapular	11 (22.4)	0
Cough	10 (20.4)	0
Hypotension	10 (20.4)	2 (4.1)
Syncope	4 (8.2)	4 (8.2)
Increased lipase	3 (6.1)	3 (6.1)
Hyponatremia	2 (4.1)	2 (4.1)

Data cut-off: January 8, 2021.

*The incidence of TRAEs from any component of the study treatment is shown. Patients are only counted once under each preferred term using the highest grade; some patients may have experienced more than one event.
RCC, renal cell carcinoma; TRAE, treatment-related adverse event.

physician decision (n=3). Reasons for discontinuation from NIVO are shown in online supplemental figure 1.

The median duration of exposure to BEMPEG was 7.2 months (range, 0–25.8), with a median of 9.0 (range, 1–35) treatment cycles. The median duration of exposure to NIVO was 6.3 months (range, 0–25.8), with a median of 9.0 (range, 1–35) treatment cycles.

Primary analysis: safety

Ninety-eight per cent (48/49) of patients experienced at least one TRAE during treatment (table 2), and 38.8% (19/49) of patients experienced grade 3/4 TRAEs, with the most frequent events (occurring in at least one patient) being syncope (8.2%; 4/49), increased lipase (6.1%; 3/49), fatigue (4.1%; 2/49), hyponatremia (4.1%; 2/49), and hypotension (4.1%; 2/49) (table 2). All AEs,

regardless of causation, are included in online supplemental table 1.

TRAEs leading to discontinuation of either study drug occurred in 12.2% (6/49) of patients (6 patients: pneumonitis (n=2), increased alanine aminotransferase, increased aspartate transaminase, cerebrovascular accident, deep vein thrombosis, peripheral edema, peripheral sensory neuropathy, and pulmonary embolism (n=1 each)). TRAEs leading to any dose reduction of BEMPEG were observed in seven patients (14.3%; 7/49).

Serious TRAEs occurred in 22.4% (11/49) of patients (online supplemental table 2), with the most frequent serious TRAEs (occurring in more than one patient) being fever (6.1% (3/49 patients)) and cerebrovascular accident (4.1% (2/49 patients)). Immune-mediated AEs are shown in online supplemental table 3. There were no treatment-related deaths.

Primary analysis: ORR

After a median duration of follow-up of 32.7 months, investigator-assessed ORR (response-evaluable population) was 34.7% (17/49; 95% CI 21.7 to 49.6) (table 3), including 3/49 CRs (6.1%) and 14/49 PRs (28.6%; figure 1). Of the 17 patients with response, 14 patients continued to respond for over 6 months, 12 patients continued to respond for over 12 months, and 6 patients continued to respond for at least 24 months. The median time to response was 4.0 months (range 1.3–8.8).

ORR by IMDC risk score was 52.9% (9/17) in favorable-risk patients, 31.8% (7/22) among intermediate-risk patients, and 10.0% (1/10) in poor-risk patients. When combining the intermediate-risk and poor-risk patient groups, the ORR was 25.0% (8/32) (table 3).

Secondary analysis: DOR, CBR

Among responding patients, the median DOR was 26.1 months (95% CI 8.2 to not reached); Kaplan-Meier estimates of response are summarized in table 3.

CBR was 73.5% (36/49) in the overall RCC population (response-evaluable), 94.1% (16/17) in favorable-risk patients, 68.2% (15/22) in intermediate-risk patients, and 50.0% (5/10) in poor-risk patients (table 3).

Secondary analysis: survival

The median PFS was 7.7 months (95% CI 3.8 to 13.9; figure 2A; safety population). PFS probabilities were 39.4% (95% CI 25.6% to 52.9%) at 12 months and 24.1% (95% CI 13.0% to 37.0%) at 24 months (online supplemental table 4).

Median PFS among IMDC favorable-risk patients was 12.2 months (95% CI 5.2 to 16.4), for intermediate-risk patients was 7.1 months (95% CI 1.8 to 21.3), and for poor-risk patients was 2.9 months (95% CI 0.8 to not reached) (online supplemental table 4).

Median OS was not reached (95% CI 37.3 to not reached; figure 2B and online supplemental table 5).

Table 3 Objective response per RECIST V.1.1 by investigator review by IMDC risk score (response-evaluable population; n=49*)

	IMDC risk score				Total
	Favorable	Intermediate	Poor	Intermediate/poor	
Patients, n	17	22	10	32	49
ORR (CR+PR)	9 (52.9)	7 (31.8)	1 (10.0)	8 (25.0)	17 (34.7)
95% CI	27.8 to 77.0	13.9 to 54.9	0.3 to 44.5	11.5 to 43.4	21.7 to 49.6
CR	2 (11.8)	1 (4.5)	0	1 (3.1)	3 (6.1)
PR	7 (41.2)	6 (27.3)	1 (10.0)	7 (21.9)	14 (28.6)
SD	7 (41.2)	8 (36.4)	4 (40.0)	12 (37.5)	19 (38.8)
CBR (CR+PR+SD≥7 weeks)	16 (94.1)	15 (68.2)	5 (50.0)	20 (62.5)	36 (73.5)
PD	1 (5.9)	7 (31.8)	5 (50.0)	12 (37.5)	13 (26.5)
Time to response, median months†	4.0	4.1	1.6	3.8	4.0
Time to CR, median months†	4.7	1.4	–	1.4	3.5
Duration of response, median months†	13.0	26.1	NE	NE	26.1
Proportion of patients with response lasting at least 6 months (95% CI)†	77.8 (36.5 to 93.9)	85.7 (33.4 to 97.9)	100.0 (100.0 to 100.0)	87.5 (38.7 to 98.1)	82.4 (54.7 to 93.9)
Proportion of patients with response lasting at least 12 months (95% CI)†	55.6 (20.4 to 80.5)	85.7 (33.4 to 97.9)	100.0 (100.0 to 100.0)	87.5 (38.7 to 98.1)	70.6 (43.1 to 86.6)
Proportion of patients with response ≥24 months (95% CI)†	33.3 (7.8 to 62.3)	71.4 (25.8 to 92.0)	100.0 (100.0 to 100.0)	75.0 (31.5 to 93.1)	51.5 (25.7 to 72.3)

Data cut-off: January 8, 2021. Numbers are n (%) unless otherwise specified.

*Response-evaluable population includes patients who have measurable disease (per RECIST V.1.1) at baseline and have at least one postbaseline assessment of tumor response.

†Based on patients who responded. The median duration of response and the proportion of patients with response are from Kaplan-Meier estimates.

CBR, clinical benefit rate; CR, complete response; IMDC, International Metastatic RCC Database Consortium; NE, not estimable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Exploratory biomarker analyses

In the exploratory biomarker univariate analyses (data cut-off May 15, 2020), patients were grouped by baseline PD-L1 expression in tumor cells $\geq 1\%$ vs $< 1\%$ group (n=46), CD8⁺ TIL ≥ 73 cells/mm² (median of n=43 patients) vs < 73 cells/mm², TMB ≥ 3.51 mutations per megabase (median of n=19) vs < 3.51 mutations per megabase, or IFN- γ GEP ≥ 0.59 (median of n=37) vs < 0.59 ; no statistical difference was observed in ORR between the two groups based on each biomarker (online supplemental figure 2).

DISCUSSION

The international, multicenter PIVOT-02 trial showed that the novel immunostimulatory IL-2 cytokine/ICI combination of BEMPEG plus NIVO produced durable responses in some patients (response > 12 months in 71% of responding patients) with advanced, favorable-risk and intermediate-risk clear-cell RCC. The safety profile of the combination treatment was predictable, consistent with that of the individual compounds,^{21 27} and consistent with the safety profile reported in other PIVOT-02 cohorts.^{19 23} No new safety signals were identified. BEMPEG has been engineered as a prodrug to deliver a controlled and sustained IL-2 pathway signal and thereby overcome some of the challenges of high-dose IL-2 therapy, namely high toxicity requiring inpatient administration and intensive monitoring at centers with extensive experience administering this treatment. Capillary leak syndrome, a

serious AE associated with high-dose IL-2 therapy, was not observed in this cohort. The most frequently observed AEs with BEMPEG plus NIVO were mostly grade 1 or 2 in severity and included flu-like symptoms (fatigue, fever, chills, and influenza-like illness) and pruritus that were mostly transient and manageable using standard treatment protocols. Thyroid dysfunction is the most common immune-mediated AE observed with IL-2 therapy,²⁸ and in this cohort, the most common immune-mediated AE with BEMPEG plus NIVO was hypothyroidism (10 of 49 (20%); all grade 1 or 2; these rates are consistent with those reported in other PIVOT-02 cohorts.^{19 23} The rate of grade 3/4 TRAEs with the combination reported here (39%) compares favorably with reported rates from large randomized trials of other combination treatments in this patient population, including NIVO plus ipilimumab (48%),⁷ NIVO plus cabozantinib (61%),³ pembrolizumab plus axitinib (63%),⁴ and pembrolizumab plus lenvatinib (72%).⁶ The rate of AEs leading to discontinuation of combination treatment reported here (12%) is lower than that reported with ICI-TKI and ICI-ICI combinations (15%–25%^{3–7}).

Thirty-five per cent of patients achieved an objective response with BEMPEG plus NIVO in this small phase 2 study. This ORR is similar to that reported with ICI monotherapy (pembrolizumab, 34%²⁹; NIVO, 32%³⁰) but notably lower than ORRs with ICI-TKI combinations (NIVO plus cabozantinib, 56%³; and pembrolizumab plus axitinib,

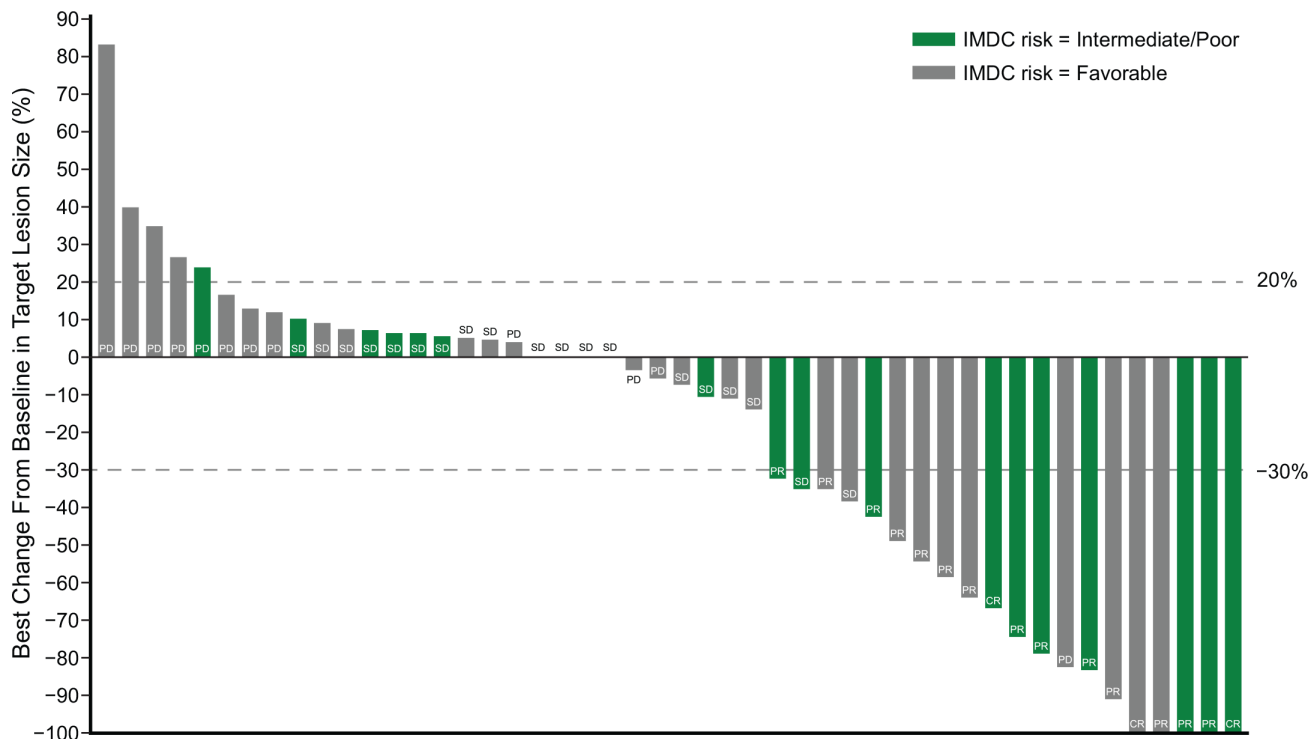


Figure 1 Efficacy of BEMPEG plus NIVO (investigator assessment). Waterfall plot of maximum change in tumor size from baseline (response-evaluable population*; n=49). Data cut-off: January 8, 2021. *Response-evaluable population includes patients who have measurable disease (per RECIST V.1.1) at baseline and have at least one postbaseline assessment of tumor response. BEMPEG, bempegaldesleukin; IMDC, International Metastatic RCC Database Consortium; NIVO, nivolumab; RECIST, Response Evaluation Criteria in Solid Tumors.

60%⁵ or lenvatinib, 71%⁶) and ICI–ICI combinations (NIVO plus ipilimumab, 39%⁷). Responses were durable in patients achieving a response with BEMPEG plus NIVO with a median DOR of 26 months, and 71% of responding patients having a response that lasted more than 12 months. These results, while preliminary and based on a small sample size, are consistent with median response durations reported in recent studies with ICI–TKI combinations, ranging from 20 to 26 months.^{3,5,6}

The median PFS observed with BEMPEG plus NIVO in this trial, 7.7 months, was lower than reported with other ICI based therapies in phase three trials.^{3,5–7} Although median OS was not yet reached in the overall population or favorable-risk population in this PIVOT-02 cohort, median OS was encouraging in intermediate- (38 months) and poor-risk (26 months) patients.

In PIVOT-02, objective responses were observed across all IMDC risk groups, with patients in the favorable-risk category treated with BEMPEG plus NIVO demonstrating higher ORR (53% vs 32% vs 10%) and longer median PFS (12.2 vs 7.1 vs 2.9 months) than those in the intermediate- and poor-risk categories, respectively. Data from the PROCLAIM database has shown that favorable-risk/intermediate-risk RCC patients treated with high-dose IL-2 had better outcomes than poor-risk patients; CBR were higher, and OS duration was longer in favorable-risk/intermediate-risk patients, with the most durable OS observed in the favorable-risk group.¹³ In patients with favorable-risk disease in CheckMate 214, the ORR with

NIVO plus ipilimumab was 30% (CR, 12%) compared with 52% (CR, 6%) in the sunitinib arm.⁷ The 53% ORR and 12% CR rate in the favorable-risk group with BEMPEG plus NIVO is encouraging in this risk group and provides support for investigating the combination of an ICI with an agent such as BEMPEG that modulates the tumor microenvironment. For these favorable-risk patients, novel treatment combinations with comparable or better efficacy than anti-VEGF therapy, but with an improved tolerability profile, are desirable. The lower ORR observed in the 10 patients with poor-risk features is consistent with RCC literature,³¹ although the limited number of poor-risk patients should be considered when interpreting the findings. A better understanding of how to identify patients who will benefit from ICI-based combinations, across risk-groups, is needed.

Exploratory biomarker analysis suggested that the ORR was not associated with any of the baseline biomarkers assessed, including baseline PD-L1 status. The association between baseline PD-L1 status, as well as other biomarkers, and clinical outcomes will be further explored in ongoing studies.

The small sample size of this cohort, and the lack of a comparator arm, are limitations of the trial, as is the potential for selection bias as patients were enrolled from a small number of academic specialty centers. DOR data should be interpreted with caution, given that the results are derived from Kaplan-Meier estimates in the 17 patients with a response. However, this study had a

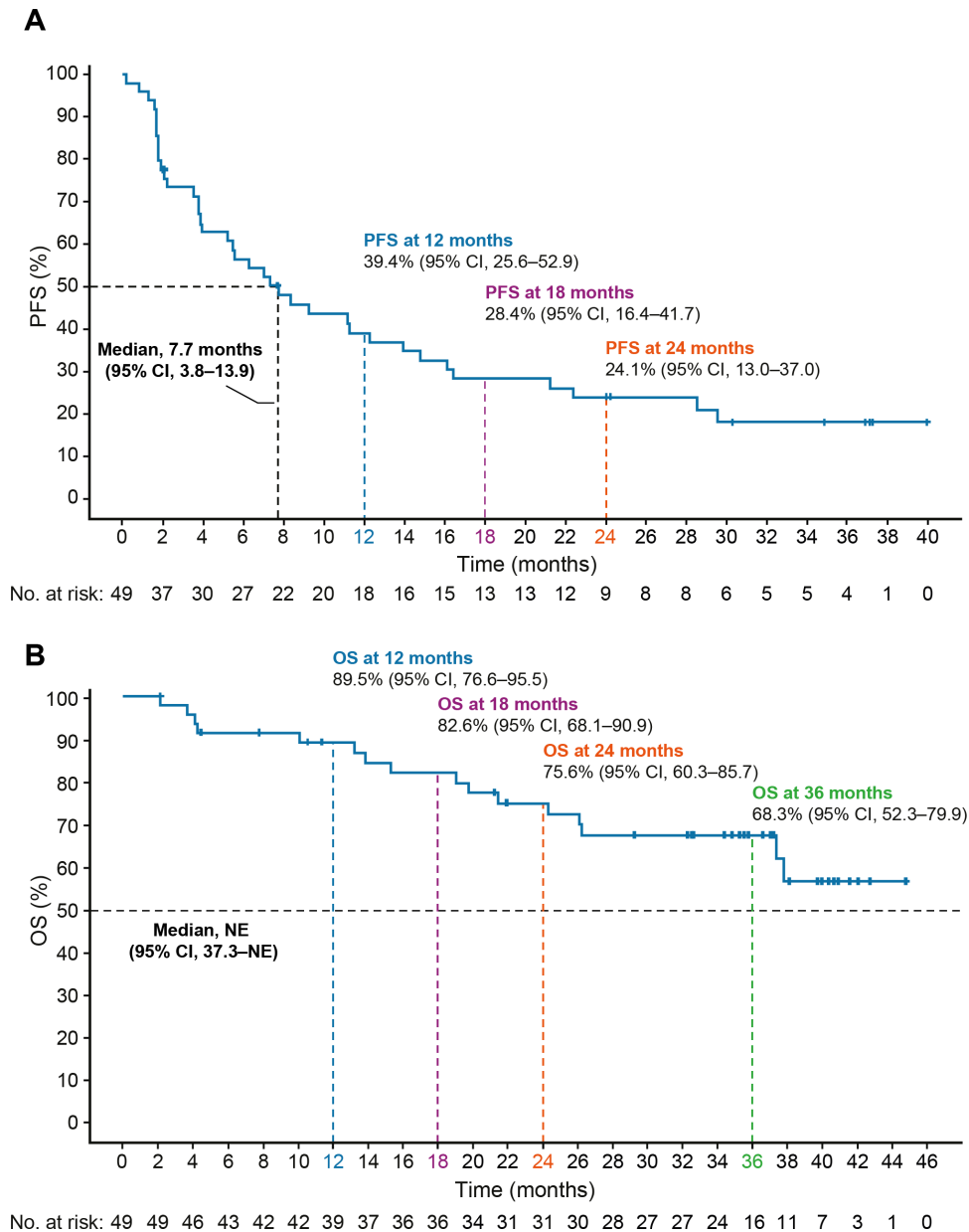


Figure 2 Efficacy of BEMPEG plus NIVO. (A) Kaplan-Meier estimates of progression-free survival by investigator assessment and (B) overall survival (safety population; n=49). Data cut-off: January 8, 2021. BEMPEG, bempegaldesleukin; NIVO, nivolumab; NE, not estimable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

relatively long duration of follow-up (32 months). Rates of previous nephrectomy in this study were high (97%) and minimally higher than reported in recent studies in metastatic RCC (~70%–80%).^{3 4 6} Ongoing studies will help elucidate the clinical benefits of adding BEMPEG to NIVO as first-line therapy in patients with advanced or metastatic RCC.

CONCLUSIONS

In conclusion, our results provide preliminary evidence of the safety and efficacy of BEMPEG plus NIVO in patients with advanced or metastatic RCC with a clear-cell component. The findings reported here are currently undergoing

validation in an ongoing randomized, registrational, phase three trial in previously untreated patients with advanced or metastatic RCC (PIVOT 09; NCT03729245). The combination of BEMPEG plus NIVO is also being investigated as part of a triplet regimen in combination with a TKI (cabozantinib or axitinib) in a phase 1/2 trial in patients with previously untreated advanced or metastatic RCC (PIVOT IO 011; NCT04540705).

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Data availability statement Data from this study may be shared with qualified researchers, upon request.

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