ONLINE SUPPLEMENTAL FILE

The authors have provided this appendix to give readers additional information about their work. Supplement to: Tannir NM, Cho DC, Diab A, et al. Bempegaldesleukin plus nivolumab in first-line renal cell carcinoma: Results from a PIVOT-02 phase 2 cohort

Tannir NM, *et al. J Immunother Cancer* 2022; 10:e004419. doi: 10.1136/jitc-2021-004419

Contents

INVESTIGATORS

The following investigators participated in the PIVOT-02 study genitourinary cancer cohorts:

Arjun Balar	New York Medical College, Westchester Medical Center, NY, USA
Mehmet Bilen	Winship Cancer Institute of Emory University, Atlanta, GA, USA
Daniel Cho	New York Medical College, Westchester Medical Center, NY, USA
Adi Diab	The University of Texas MD Anderson Cancer Center, Houston, TX, USA
Mayer N. Fishman	H. Lee Moffit Cancer Center & Research Institute, Tampa, FL, USA
Jianjun Gao	The University of Texas MD Anderson Cancer Center, Houston, TX, USA
Giovanni Grignani	Candiolo Cancer Institute, FPO – IRCCS. Candiolo (TO), Italy
Michael Hurwitz	Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA
Nizar Tannir	The University of Texas MD Anderson Cancer Center, Houston, TX, USA
Arlene Siefker-Radtke	The University of Texas MD Anderson Cancer Center, Houston, TX, USA
Mario Sznol	Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA
James Larkin	Royal Marsden Hospital, Surrey, UK
Scott Tykodi	Seattle Cancer Care Alliance, WA, USA

SUPPLEMENTAL METHODS

Study oversight

Nektar Therapeutics sponsored the study and provided BEMPEG. Bristol Myers Squibb provided NIVO.

The study was designed by the authors and representatives of Nektar Therapeutics. The data were collected by staff at each site and monitored by the sponsor and a safety review committee.

The sponsor was involved in the analysis and interpretation of the data and the writing of the report. The authors had full access to the data and participated in its interpretation. Writing and editorial support was provided by BOLDSCIENCE Inc. and was funded by Nektar Therapeutics. All authors reviewed and approved the manuscript before submission for publication.

International Metastatic RCC Database Consortium risk score

IMDC risk score (favorable risk [IMDC score = 0], intermediate risk [IMDC score = 1 or 2], or poor risk [IMDC score = 3–6]) was determined by the total number present of the following six independent predictors of poor survival: Karnofsky performance status score of <80%; <1 year from initial diagnosis to treatment; anemia (hemoglobin concentration <lower limit of normal); hypercalcemia (corrected serum calcium concentration >upper limit of normal [ULN]); neutrophilia (neutrophil count >ULN); thrombocytosis (platelet count >ULN) (Heng DYC, et al. *J Clin Oncol* 2009;27:5794–9).

Biomarker assessments

Tumor biopsies were analyzed to correlate baseline high vs. low by median cutoff of: gene-expression levels (PanCancer Immune Profiling Panel, NanoString Technologies

Inc., Seattle, WA) for interferon (IFN)-γ gene-expression profile (based on expression levels of CD3D, IDO1, CCL5, CD2, CXCL13, IL2RG, HLA-E, CXCR6, LAG3, CXCL10, STAT1, GZMB, CXCL9, IFNγ, and PRF1), CD8 immunohistochemistry (mouse monoclonal [clone C8/144B] antibody purchased from Dako, Mosaic Laboratories, CA); and tumor mutational burden (FoundationOne CDx, Foundation Medicine, Cambridge, MA) to investigator-assessed objective response rate (Response Evaluation Criteria In Solid Tumors v1.1; response-evaluable population).

SUPPLEMENTAL TABLES AND FIGURES

Online supplemental table 1 Incidence of treatment-emergent adverse events (safety population)*

Event, n (%)	N=49	
	Any grade	**Grade 3–4**
Treatment-emergent AEs	49 (100.0)	28 (57.1)
TEAEs by preferred term with an incidence ≥20%		
Fatigue	40 (81.6)	2 (4.1)
Nausea	29 (59.2)	0
Pruritus	26 (53.1)	0
Pyrexia	24 (49.0)	1 (2.0)
Chills	25 (51.0)	0
Influenza-like illness†	24 (49.0)	0
Cough	22 (44.9)	1 (2.0)
Rash‡	22 (44.9)	0
Decreased appetite	21 (42.9)	1 (2.0)
Diarrhea	21 (42.9)	0
Arthralgia	19 (38.8)	1 (2.0)
Edema peripheral	19 (38.8)	0
Vomiting	18 (36.7)	0
Constipation	17 (34.7)	0
Headache	16 (32.7)	0
Myalgia	16 (32.7)	1 (2.0)
Dizziness	15 (30.6)	0
Hypotension	13 (26.5)	3 (6.1)
Rash maculopapular	13 (26.5)	0
Insomnia	12 (24.5)	0
Dyspnea	12 (24.5)	1 (2.0)
Dry skin	11 (22.4)	0
Hypothyroidism	11 (22.4)	0
Nasal congestion	11 (22.4)	0
Back pain	10 (20.4)	2 (4.1)
Upper respiratory tract infection	10 (20.4)	0

Data cutoff: January 8, 2021.

BEMPEG, bempegaldesleukin; NIVO, nivolumab; TEAE, treatment-emergent adverse event (defined as all AEs reported on-study regardless of relationship to study drug).

*The incidence of adverse events 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.

†Includes the following preferred terms: chills, influenza, influenza-like illness, pyrexia.

‡Includes the following preferred terms: erythema, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash maculovesicular, rash papular, rash pruritic, rash pustular, rash vesicular, exfoliative rash.

Online supplemental table 2 Incidence of serious adverse events considered related to treatment (safety population)

SAEs related to treatment, n (%)	**N=49**
SAEs	11 (22.4)
SAEs by preferred term*	
Pyrexia	3 (6.1)
Cerebrovascular accident	2 (4.1)
Adrenal insufficiency	1 (2.0)
Atrial fibrillation	1 (2.0)
Dehydration	1 (2.0)
Diabetic ketoacidosis	1 (2.0)
Hyponatremia	1 (2.0)
Hypotension	1 (2.0)
Infectious pleural effusion	1 (2.0)
Pneumonitis	1 (2.0)
Pulmonary embolism	1 (2.0)

Data cutoff: January 8, 2021.

*SAE was defined as any untoward medical occurrence that at any dose resulted in death; was life-threatening; required inpatient hospitalization or prolongation of an existing hospitalization; resulted in persistent or significant disability or incapacity; or was an important medical event that, based upon medical judgment, was considered to jeopardize the patient, and may require medical or surgical intervention to prevent one of the other outcomes listed above. SAEs considered related to study treatment by the investigator were collected from after the first dose of study treatment to within 100 days of NIVO discontinuation of NIVO and within 30 days of BEMPEG discontinuation. Some patients experienced more than one SAE but are counted in the total only once.

BEMPEG, bempegaldesleukin; NIVO, nivolumab; SAE, serious adverse event.

Online supplemental table 3 Incidence of immune-mediated adverse events (safety population)

imAEs by preferred term, n (%)	**N=49**	
	Any grade	**Grade 3–4**
Endocrine imAEs	10 (20.4)	0
Hypothyroidism	10 (20.4)	0
Adrenal insufficiency	1 (2.0)	0
Non-endocrine imAEs	5 (10.2)	3 (6.1)
Pneumonitis	2 (4.1)	1 (2.0)
Alanine aminotransferase increased	1 (2.0)	1 (2.0)
Aspartate aminotransferase increased	1 (2.0)	1 (2.0)
Autoimmune hepatitis	1 (2.0)	1 (2.0)
Diarrhea	1 (2.0)	0

Data cutoff: January 8, 2021.

imAE, immune-mediated adverse event; mUC, metastatic urothelial carcinoma; RCC, renal cell carcinoma.

Online supplemental table 4 PFS per RECIST v1.1 by local investigator assessment according to IMDC risk status (safety population; N=49)

	IMDC risk score			
	Favorable (n=17)	**Intermediate (n=22)**	**Poor (n=10)**	**Total (N=49)**
Patients with PFS event, n (%)	13 (76.5)	18 (81.8)	7 (70.0)	38 (77.6)
Patients censored, n (%)	4 (23.5)	4 (18.2)	3 (30.0)	11 (22.4)
Median PFS, months (95% CI)	12.2 (5.2–16.4)	7.1 (1.8–21.3)	2.9 (0.8–NE)	7.7 (3.8–13.9)
PFS rate at 12 months (95% CI)	50.2 (24.7–71.2)	36.4 (17.4–55.7)	30.0 (7.1–57.8)	39.4 (25.6–52.9)
PFS rate at 18 months (95% CI)	25.1 (7.8–47.3)	31.8 (14.2–51.1)	30.0 (7.1–57.8)	28.4 (16.4–41.7)
PFS rate at 24 months (95% CI)	18.8 (4.6–40.4)	27.3 (11.1–46.4)	30.0 (7.1–57.8)	24.1 (13.0–37.0)

Data cutoff: January 8, 2021.

CI, confidence interval; IMDC, International Metastatic RCC Database Consortium; PFS, progression-free survival; RCC, renal cell carcinoma.

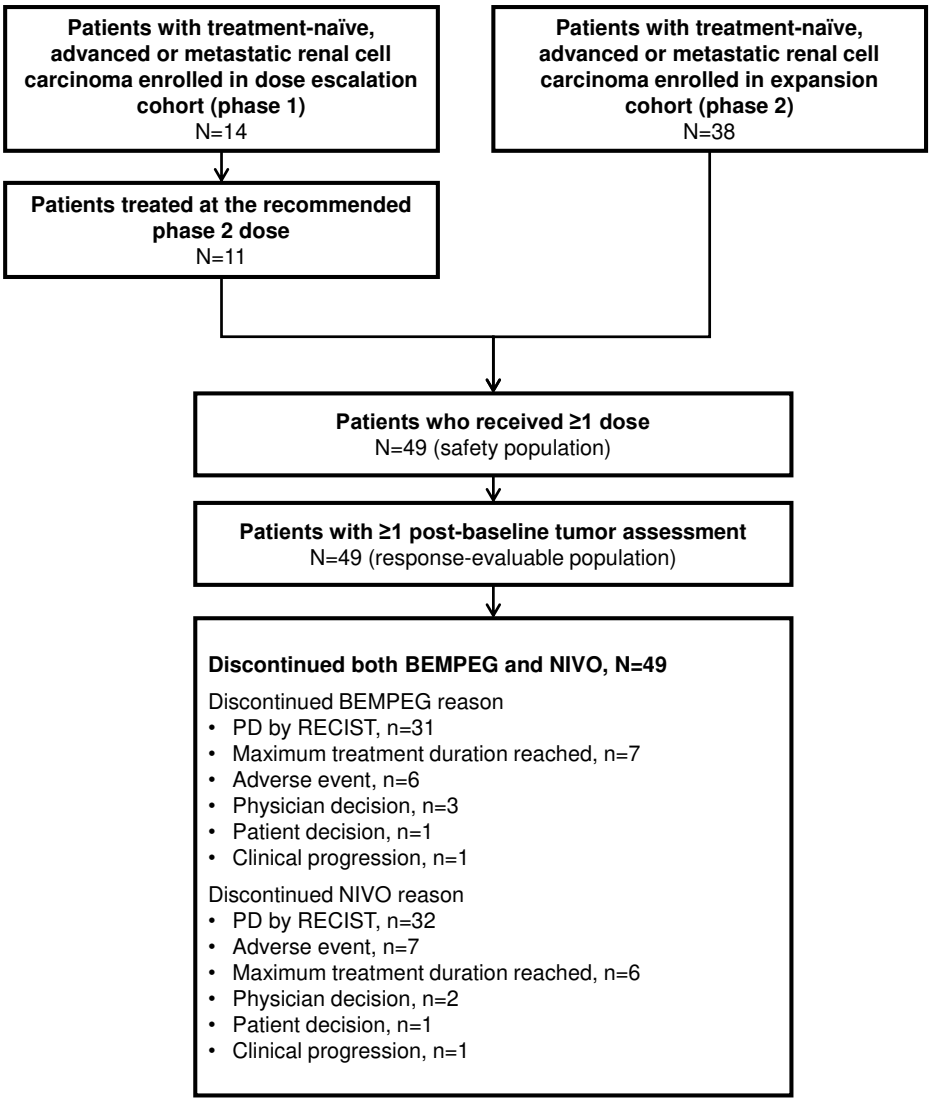
Online supplemental table 5 OS according to IMDC risk status (safety population; N=49)

	IMDC risk score			
	Favorable (n=17)	**Intermediate (n=22)**	**Poor (n=10)**	**Total (N=49)**
Patients with an OS event, n (%)	2 (11.8%)	9 (40.9%)	5 (50.0%)	16 (32.7)
Patients censored, n (%)	15 (88.2%)	13 (59.1%)	5 (50.0%)	33 (67.3)
Median OS, months (95% CI)	NE	37.7 (24.3–NE)	26.1 (4.2–NE)	NE (37.3–NE)
OS rate at 12 months (95% CI)	100.0 (100.0–100.0)	86.4 (63.4–95.4)	77.8 (36.5–93.9)	89.5 (76.6–95.5)
OS rate at 18 months (95% CI)	100.0 (100.0–100.0)	81.3 (57.4–92.6)	55.6 (20.4–80.5)	82.6 (68.1–90.9)
OS rate at 24 months (95% CI)	86.2 (55.0–96.4)	76.2 (51.8–89.4)	55.6 (20.4–80.5)	75.6 (60.3–85.7)
OS rate at 36 months (95% CI)	86.2 (55.0–96.4)	65.3 (40.4–81.9)	44.4 (13.6–71.9)	68.3 (52.3–79.9)

Data cutoff: January 8, 2021.

CI, confidence interval; IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma.

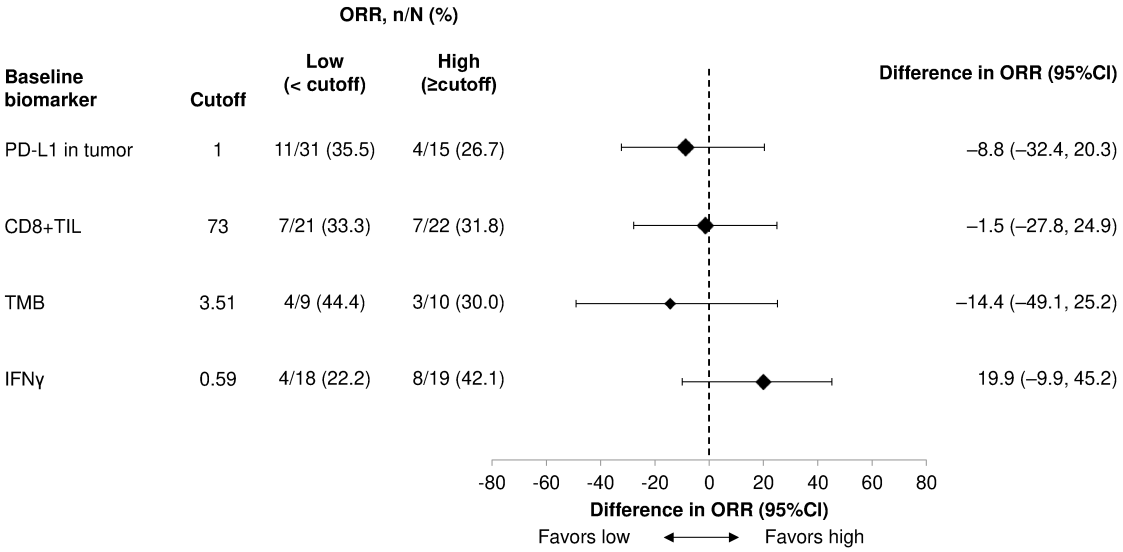
Online supplemental figure 1 Patient flow.



Data cutoff: January 8, 2021.

BEMPEG, bempegaldesleukin; NIVO, nivolumab; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

Online supplemental figure 2 Exploratory biomarker analyses. Relationship between baseline tumor biomarkers and objective response rate (Data cutoff: May 15, 2020)[a,b]



[a]For each biomarker evaluated, the number of patients with an objective response (CR or PR; n), by investigator response per RECIST v1.1, falling above and below the cutoff biomarker measurement, is presented. The denominator (N) is the number of patients evaluable for that biomarker. The differences in ORR for each dichotomous biomarker based on low or high are presented.

[b]Biomarkers were evaluated in baseline tumor samples: tumor PD-L1 expression by immunohistochemistry by PD-L1 IHC 28-8 PharmDx (Dako, an Agilent Technologies, Inc. company, Santa Clara, CA), expressed as a percentage of tumor cell expression (negative [low], <1% tumor cell expression; positive [high], ≥1% tumor cell expression); $CD8^+$ TIL by immunohistochemistry, cells/mm^2, IFNγ by gene-expression profile (Nanostring PanCancer Panel or HTG EdgeSeq Oncology Panel) and tumor mutation

burden (TMB) by mutations per megabase. $CD8^+$ TIL, IFNγ and TMB were dichotomized based on median values.