Bempegaldesleukin Plus Nivolumab in Untreated Advanced Melanoma: The Open-Label, Phase III PIVOT IO 001 Trial Results

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ABSTRACT

PURPOSE Despite marked advances in the treatment of unresectable or metastatic melanoma, the need for novel therapies remains. Bempegaldesleukin (BEMPEG), a pegylated interleukin-2 (IL-2) cytokine prodrug, demonstrated efficacy in the phase II PIVOT-02 trial. PIVOT IO 001 (ClinicalTrials.gov identifier: NCT03635983) is a phase III, randomized, open-label study that builds on the PIVOT-02 results in first-line melanoma.

METHODS Patients with previously untreated, unresectable, or metastatic melanoma were randomly assigned 1:1 to receive BEMPEG plus nivolumab (NIVO) or NIVO monotherapy. Primary end points were objective response rate (ORR) and progression-free survival (PFS) by blinded independent central review and overall survival (OS). Secondary and exploratory end points included additional efficacy measures, safety, and pharmacokinetics (PKs) and pharmacodynamics analyses.

RESULTS In 783 patients (n = 391, BEMPEG plus NIVO; n = 392, NIVO monotherapy), the median follow-up was 11.6 months in the intent-to-treat population. The ORR with BEMPEG plus NIVO was 27.7% versus 36.0% with NIVO (two-sided $P = .0311$). The median PFS with BEMPEG plus NIVO was 4.17 months (95% CI, 3.52 to 5.55) versus 4.99 months (95% CI, 4.14 to 7.82) with NIVO (hazard ratio [HR], 1.09; 97% CI, 0.88 to 1.35; $P = .3988$). The median OS was 29.67 months (95% CI, 22.14 to not reached [NR]) with BEMPEG plus NIVO versus 28.88 months (95% CI, 21.32 to NR) with NIVO (HR, 0.94; 99.929% CI, 0.59 to 1.48; $P = .6361$). Grade 3-4 treatment-related adverse events (AEs) and serious AE rates were higher with the combination (21.7% and 10.1%, respectively) versus NIVO (11.5% and 5.5%, respectively). BEMPEG PK exposure and absolute lymphocyte count changes after BEMPEG plus NIVO were comparable between PIVOT IO 001 and PIVOT-02.

CONCLUSION The PIVOT IO 001 study did not meet its primary end points of ORR, PFS, and OS. Increased toxicity was observed with BEMPEG plus NIVO versus NIVO.

ACCOMPANYING CONTENT

Appendix
Data Supplement
Protocol

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INTRODUCTION

Immunotherapy combinations have revolutionized treatment and extended survival for patients with previously untreated, unresectable, or metastatic melanoma.[1-4] Although up to 60% of patients with advanced melanoma respond to immune checkpoint inhibitor regimens in the first-line setting, nearly 25% of these responders will eventually progress.[3-8] High-dose interleukin-2 (IL-2) monotherapy has shown efficacy, including durable complete responses (CRs), in patients with metastatic melanoma and is approved for this population in countries across the world.[9,10] However, its use is limited because of significant toxicities and the complex inpatient drug administration.[10]

Bempegaldesleukin (BEMPEG) is a pegylated IL-2 cytokine prodrug engineered to activate the clinically validated IL-2 pathway in a controlled and sustained fashion, with the goal of

CONTEXT

Key Objective

PIVOT IO 001 aimed to evaluate whether combination therapy with bempegaldesleukin (BEMPEG), a pegylated interleukin-2 (IL-2) cytokine prodrug, plus nivolumab (NIVO) improves safety and efficacy outcomes for patients with previously untreated unresectable or metastatic melanoma compared with NIVO monotherapy.

Knowledge Generated

BEMPEG plus NIVO combination therapy provided no additional clinical benefit compared with NIVO monotherapy in patients with previously untreated unresectable or metastatic melanoma. Although no new safety signals were found to be associated with the combination compared with previous reports, a higher incidence of AEs with a lack of added efficacy was noted with BEMPEG plus NIVO versus NIVO alone.

Relevance *(G.K. Schwartz)*

Despite promising science and phase II data, the addition of a pegylated IL-2 cytokine prodrug to a PD-1 checkpoint inhibitor did not improve clinical benefit over a PD-1 checkpoint inhibitor alone in patients with advanced melanoma.*

*Relevance section written by *JCO* Associate Editor Gary K. Schwartz, MD, FASCO.

preferentially activating and expanding effector CD8+ T cells and natural killer cells over immunosuppressive regulator T cells (Tregs) in the tumor microenvironment.[11-14] BEMPEG was designed with the intent to harness the benefits of IL-2 while overcoming the historical challenges with toxicity and allow for outpatient administration.

In the phase II PIVOT-02 study (ClinicalTrials.gov identifier: NCT02983045), BEMPEG plus nivolumab (NIVO) was well tolerated and demonstrated encouraging clinical activity in patients with previously untreated advanced melanoma. The study reported an objective response rate (ORR) of 52.6%, a CR rate of 34.2%, and, at the time of primary data lock, objective response for ≥12 months in 80.0% of responders.[15] To confirm and expand on these findings, a phase III, global, randomized, open-label study (PIVOT IO 001; ClinicalTrials.gov identifier: NCT03635983) was conducted to assess the efficacy and safety of BEMPEG plus NIVO compared with NIVO monotherapy in patients with previously untreated, unresectable, or metastatic melanoma. This publication has been summarized in an accompanying Plain Language Summary.

METHODS

Patients

Eligible patients were 12 years and older; had histologically confirmed stage III (unresectable) or stage IV (metastatic) melanoma (per the American Joint Committee on Cancer [AJCC] staging system, eighth edition), an Eastern Cooperative Oncology Group performance status score of 0 or 1 (18 years and older), or a Lansky performance score of ≥80% (aged 12-17 years); and were treatment-naive, with the exception of previous adjuvant and/or neoadjuvant treatment for melanoma with approved agents (eg, BRAF/MEK, ipilimumab [IPI], NIVO, pembrolizumab, or interferon). Patients who had recurrence within 6 months of completing adjuvant or neoadjuvant treatment were not eligible. Patients had measurable disease per RECIST 1.1.[16] Patients were excluded if they had active brain or leptomeningeal metastases, uveal melanoma, or an active, known or suspected autoimmune disease.

Study Design and Treatment

Patients were randomly assigned 1:1 to BEMPEG plus NIVO or NIVO monotherapy and stratified according to tumor cell PD-L1 status (≥1% *v* <1% or indeterminate, measured using PD-L1 IHC 28-8 PharmDx [Dako, an Agilent Technologies, Inc company, Santa Clara, CA]), *BRAF* mutation status (V600 mutation–positive *v* wild-type), and AJCC metastasis stage M0/M1any[0] (stage III any lactate dehydrogenase [LDH] or stage IV normal LDH) versus M1any[1] (stage IV elevated LDH). In the combination arm, BEMPEG was administered intravenously at a dose of 0.006 mg/kg, sequentially followed by intravenous NIVO administration at a dose of 360 mg, once every 3 weeks. NIVO monotherapy was administered intravenously at a dose of 360 mg once every 3 weeks. The use of NIVO 360 mg once every 3 weeks in this study allowed NIVO dosing frequency to align with BEMPEG. Dose reductions (BEMPEG only; dose reductions of NIVO were not allowed), delay, and discontinuation guidelines are described in the trial protocol (Protocol, online only). To mitigate the potential for BEMPEG-associated hypotension, a concern on the basis of previous trial experience, patients were provided with hydration guidelines, assessed for hydration and renal function within 24 hours before BEMPEG administration, and reminded of the hydration guidelines throughout each cycle.

End Points

Primary end points included ORR and progression-free survival (PFS), as determined by blinded independent central review (BICR) per RECIST 1.1, and overall survival (OS). Secondary end points included clinical benefit rate (CBR), duration of response (DOR), time to response (TTR), and safety (see the protocol online for end point definitions). Exploratory analyses include pharmacokinetics (PKs) and pharmacodynamic (PD) measures, such as BEMPEG exposure, absolute lymphocyte count (ALC), and soluble CD25 (sCD25) concentrations.

Trial Oversight

The trial was designed jointly by the sponsor (Bristol Myers Squibb) and partner (Nektar Therapeutics), along with a scientific steering committee. The trial met regulatory requirements and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by independent ethics committees and the institutional review board at each participating study site. Each participant provided written informed consent. Data were collected and analyzed by the sponsor and reviewed with the partner and all authors. An independent data and safety monitoring committee was established to provide oversight of safety and efficacy considerations to assess the benefit-risk profile of BEMPEG combined with NIVO. All authors were involved in the writing or critical review and editing of the manuscript and vouch for the fidelity of the trial to the protocol and for the accuracy and completeness of the data reported.

Statistical Analysis

The study planned for approximately 764 patients randomly assigned to account for three primary end points: ORR, PFS, and OS, with one-sided alpha allocations of .001, .03, and .019, respectively. The final analysis of ORR was performed in all randomly assigned patients with a follow-up of ≥6 months (ORR population) at the time of PFS final analysis. PFS and OS were evaluated in the intent-to-treat (ITT) population. For PFS, it was estimated that at least 375 events or deaths would yield 90% power to detect a hazard ratio (HR) of 0.7 at a two-sided alpha of .03. The first OS interim analysis, using Lan-DeMets alpha-spending function with O'Brien-Fleming boundary, was conducted at the time of PFS final analysis. ORR was compared between treatment arms using a stratified Cochran-Mantel-Haenszel test using the three stratification factors (PD-L1 status, *BRAF* status, and AJCC M stage). An associated odds ratio (OR) and 95% and 99.9% CIs were calculated. The ORR and corresponding 95% exact CI were calculated for each arm using the Clopper-Pearson method. PFS was compared between treatment arms using a stratified log-rank test. PFS HR and its two-sided 97% CI were estimated using a stratified Cox proportional hazards model. OS was analyzed similar to PFS. The median DOR and 95% CIs were estimated using the Kaplan-Meier method. Descriptive statistics of adverse events (AEs) graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0 were tabulated by treatment arm.

PK and PD Analyses Methods

ALCs were obtained by standard hematology procedures (complete blood count with differentials); sCD25 was quantified by a ligand binding assay using plasma samples. Longitudinal changes in sCD25, the soluble form of the IL-2 receptor alpha, were evaluated in the combination arm only. Extensive serial samples were collected from a subset of patients, and sparse sampling was performed for all patients in PIVOT IO 001 for PK evaluations (Appendix 1, online only). Plasma concentrations of BEMPEG were analyzed at Nektar Therapeutics using a validated electrochemiluminescence assay.

PK parameters for BEMPEG were derived by noncompartmental analysis methods using plasma concentration versus time data after the first dose administration of BEMPEG 0.006 mg/kg IV once every 3 weeks plus NIVO 360 mg IV once every 3 weeks (cycle 1) from the subset of patients who had extensive serial PK sampling. Actual sample collection times were used for the analyses. Within a dosing interval, the maximum observed plasma concentration (C_{max}) was recorded directly from experimental observations and area under the concentration-time curve from 0 to 96 hours ($AUC_{[0-96]}$) was calculated by the linear-up/log-down method in Phoenix WinNonlin (version 8.2). Plasma BEMPEG concentrations and PK parameters derived from PIVOT IO 001 were summarized and compared with those determined in PIVOT-02.

RESULTS

Patients

Between October 10, 2018, and December 17, 2021, 783 patients at 170 sites in 26 countries were randomly assigned to receive either BEMPEG plus NIVO (391 patients) or NIVO monotherapy (392 patients; Fig 1). Patient baseline characteristics were representative of a population with previously untreated, unresectable, or metastatic melanoma and were balanced between the two treatment arms (Table 1). At data cutoff (February 1, 2022), the median follow-up was 11.6 months (range, −0.90 to 37.4; calculated relative to the last patient last visit date of November 19, 2021) and 19.3 months (range, 6.0-37.4) for the ITT and ORR populations, respectively. A total of 387 of 391 patents in the BEMPEG plus NIVO arm and 382 of 392 in the NIVO arm received ≥1 dose of study treatment, which represent the safety populations (Fig 1). At data cutoff, 239 patients (62%) in the combination arm and 227 patients (59%) in the monotherapy arm had discontinued study treatment, mainly because of disease progression (>70% in each arm). The median duration of therapy was 4.14 (range, 0.0-24.9) months in the combination arm and 4.17 (range, 0.0-24.4) months in the monotherapy arm (Appendix Table A1, online only). The median number of doses was 6 (range, 1-35) in

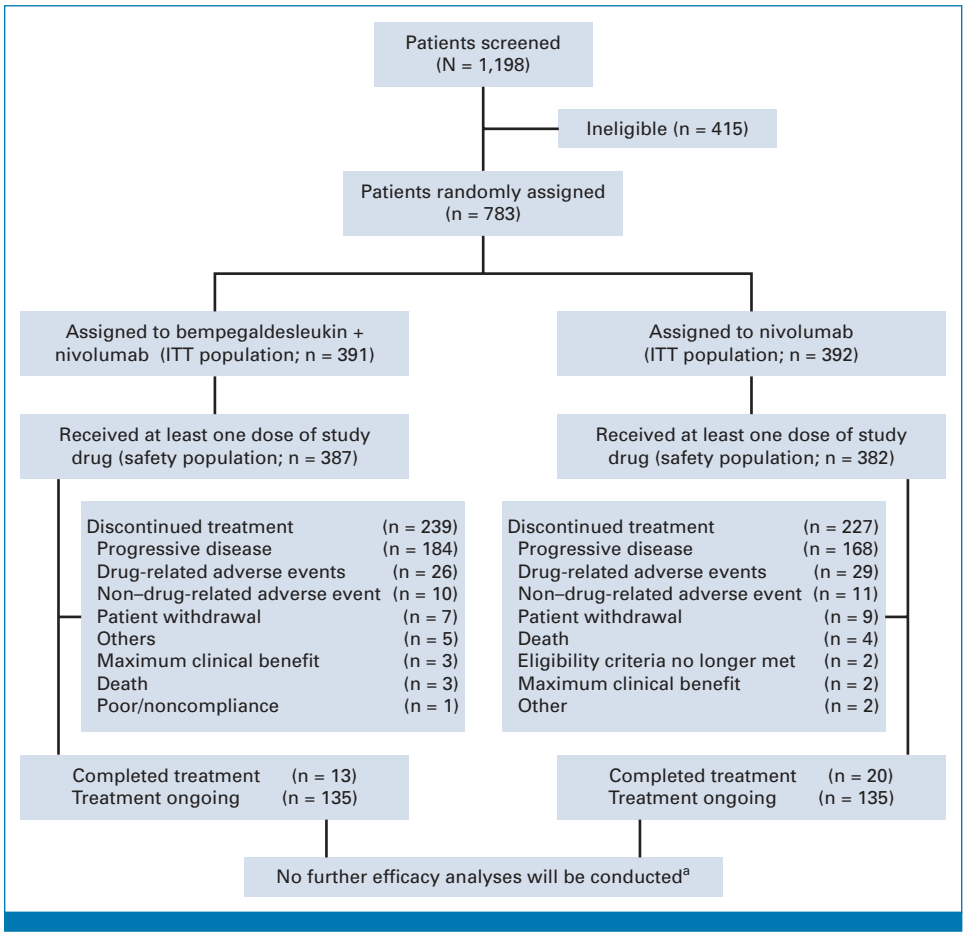

FIG 1. CONSORT diagram. [a]The PIVOT IO 001 study did not meet its primary end points of ORR and PFS by BICR and OS. BICR, blinded independent central review; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

patients who received BEMPEG plus NIVO and 7 (range, 1-35) in those who received NIVO alone (Table A1).

Efficacy

The ORR per BICR was 27.7% (95% CI, 22.4 to 33.4) with BEMPEG plus NIVO and 36.0% (95% CI, 30.3 to 42.0) with NIVO (OR, 0.66; 99.9% CI, 0.35 to 1.24; $P = .0311$; Table 2; Appendix Fig A1, online only). The best percent reduction from baseline in the sum of diameters of target lesions (per BICR) in all response evaluable patients in the ORR population is shown in Appendix Figure A2 (online only). CRs occurred in 8.1% of the patients in the BEMPEG plus NIVO arm and in 12.5% in the NIVO arm; the disease control rate was 56.1% and 58.5%, respectively (Table 2). The median TTR was similar between BEMPEG plus NIVO (2.17 months) and NIVO monotherapy (2.20 months). The median DOR was 29.67 months (95% CI, 18.89 to not reached [NR]) with the combination and NR (95% CI, 26.74 to NR) with NIVO.

The median PFS per BICR was 4.17 months (95% CI, 3.52 to 5.55) with BEMPEG plus NIVO and 4.99 months (95% CI, 4.14 to 7.82) with NIVO (HR, 1.09; 97% CI, 0.88 to 1.35; $P = .3988$). The 12-month PFS rates were 31.8% and 39.9%, respectively (Fig 2A). The median OS was 29.67 months (95% CI, 22.14 to NR) with BEMPEG plus NIVO and 28.88 months (95% CI, 21.32 to NR) with NIVO (HR, 0.94; 99.929% CI, 0.59 to 1.48; $P = .6361$). The 24-month OS rate in both arms was 55.5% (Fig 2B).

Across prespecified subgroups, HRs for PFS and the unweighted differences in ORR generally favored NIVO, but with no statistical significance (Appendix Figs A1 and A3, online only). On the basis of the ORR and PFS final analysis results, the study was unblinded to the study sponsor and scientific steering committee, and no further OS analyses beyond the first interim presented here will be conducted.

Safety

Any grade AEs of any cause during treatment occurred in 95.3% of the patients who received BEMPEG plus NIVO and in 91.9% of those who received NIVO; grade 3/4 AEs of any

TABLE 1. Baseline Characteristics

Characteristic	BEMPEG + NIVO (n = 391)	NIVO (n = 392)
Age, years, median (range)	62.0 (22-91)	61.0 (21-93)
Sex, No. (%)		
Female	162 (41.4)	163 (41.6)
Male	229 (58.6)	229 (58.4)
Prior adjuvant therapy, No. (%)[a]	32 (8.2)	47 (12.0)
Anti–CTLA-4 agents	4 (1.0)	6 (1.5)
Anti–PD-1 agents	9 (2.3)	12 (3.1)
BRAF inhibitors	1 (0.3)	6 (1.5)
MEK/NRAS inhibitors	1 (0.3)	6 (1.5)
Combination anti–PD-1 plus anti–CTLA-4	1 (0.3)	1 (0.3)
Combination BRAF plus MEK/NRAS inhibitors	1 (0.3)	2 (0.5)
Other investigational agents	0	1 (0.3)
Unassigned[b]	19 (4.9)	24 (6.1)
ECOG PS, No. (%)[c]		
0	294 (75.2)	274 (69.9)
1	96 (24.6)	116 (29.6)
2	1 (0.3)	2 (0.5)
Stratification factors, No. (%)		
Baseline PD-L1 status[d,e]		
<1%/indeterminate	191 (48.8)	197 (50.3)
≥1%	193 (49.4)	194 (49.5)
BRAF-mutation status[f]		
Mutant	159 (40.7)	163 (41.6)
Wild-type	232 (59.3)	229 (58.4)
AJCC v8 M stage[g]		
M0/M1any[0]	265 (67.8)	256 (65.3)
M1any[1]	126 (32.2)	136 (34.7)
Baseline LDH, No. (%)		
≤ULN	232 (59.3)	246 (62.8)
>ULN	156 (39.9)	144 (36.7)
≤2 × ULN	349 (89.3)	343 (87.5)
>2 × ULN	39 (10.0)	47 (10.0)

Abbreviations: AJCC, American Joint Committee on Cancer; BEMPEG, bempegaldesleukin; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; LDH, lactate dehydrogenase; M, metastatic; NIVO, nivolumab; NRAS, neuroblastoma rat sarcoma; ULN, upper limit of normal.

[a]Patients could receive more than one adjuvant therapy.

[b]Therapies that do not have an assigned category according to the data mapping dictionary (eg, various versions of interferon).

[c]Three patients were ECOG PS 0-1 at screening but presented as ECOG PS 2 at treatment.

[d]Patients with baseline status *not reported* or *not evaluable* were not included in this table. Because of a testing site error, seven patients were reported as *indeterminate* rather than *not evaluable* in the interactive response technology system and randomly assigned in the study.

[e]Tumor cell PD-L1 expression (≥1% or <1%/indeterminate) was determined using PD-L1 IHC 28-8 pharmDx (Dako, an Agilent Technologies, Inc company, Santa Clara, CA).

[f]*BRAF* V600–mutant versus wild-type.

[g]AJCC eighth edition M0/M1any[0] versus M1any[1], on the basis of the screening imaging and laboratory test results (LDH level). Mucosal melanomas were considered M1 for stratification.

cause occurred in 39.8% and 32.2%, respectively (Table 3). In patients who received BEMPEG plus NIVO versus those who received NIVO, treatment-related AEs (TRAEs) occurred in 88.6% and 69.1% and grade 3/4 TRAEs were 21.7% and 11.5%, respectively. TRAEs reported in ≥5% of patients are listed in Appendix Table A2 (online only). In addition, treatment-related serious AEs were observed in 14.0% and 6.8%, respectively. In the combination arm, the most frequently reported (>40%) categories for cytokine-associated AEs of any grade included flu-like symptoms

TABLE 2. Response by BICR per RECIST 1.1 in the ORR Population

Response	BEMPEG + NIVO (n = 271)	NIVO (n = 272)
ORR,[a] % (95% CI)	27.7 (22.4 to 33.4)	36.0 (30.3 to 42.0)
Confirmed BOR, No. (%)		
CR	22 (8.1)	34 (12.5)
PR	53 (19.6)	64 (23.5)
SD	77 (28.4)	61 (22.4)
PD	97 (35.8)	87 (32.0)
Undetermined[b]	22 (8.1)	25 (9.2)
DCR (CR + PR + SD), % (95% CI)	56.1 (50.0 to 62.1)	58.5 (52.4 to 64.4)
Estimated odds ratio (99.9% CI)	0.66 (0.35 to 1.24)	
P value[c]	.0311	
Median time to objective response, months (range)	2.17 (1.0-15.3)	2.20 (1.2-15.5)
Median DOR, months (95% CI)	29.67 (18.89 to NR)	NR (26.74 to NR)

NOTE. Database lock: February 1, 2022. The median follow-up is 19.3 months (range, 6.0-37.4) for the ORR population.
Abbreviations: BEMPEG, bempegaldesleukin; BICR, blinded independent central review; BOR, best overall response; CBR, clinical benefit rate; CMH, Cochran-Mantel-Haenszel test; CR, complete response; DCR, disease control rate; DOR; duration of response; NIVO, nivolumab; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]ORR population includes all randomly assigned participants who have a minimum follow-up of 6 months.
[b]Lesions were not evaluable mostly because of postscreening assessments not being performed.
[c]Two-sided *P* value from stratified CMH.

(66.4%), rash/pruritus (55.8%), and asthenic conditions (43.2%). Grade 3/4 hypotension occurred in five of the 387 patients (1.3%) receiving the combination therapy and one of the 382 patients (0.3%) receiving NIVO. Ischemic cerebrovascular events (ICEs) were observed across the BEMPEG clinical development program and followed closely in this trial. In total, 10 patients (2.6%) in the combination arm and three patients (0.8%) in the NIVO arm experienced an ICE of any grade; grade 3/4 events of ICEs occurred in five patients (1.3%) and two patients (0.5%), respectively. The most frequently reported immune-mediated AEs (imAEs) were hypothyroidism (18.9% and 12.0%), rash (13.2% and 6.8%), and hyperthyroidism (11.9% and 6.5%) in the combination and monotherapy arms, respectively.

A single-dose reduction of BEMPEG was required by 24 patients (6.2%), with 23 (95.8%) of these reductions being related to AEs of any grade; 4 (1.0%) were grade 3/4, including nausea and decreased neutrophil count and two syncope events (Table 3). AEs of any cause led to the discontinuation of any trial drug in 15.0% of patients in the combination arm (13.7% discontinued BEMPEG and continued with NIVO monotherapy) and in 11.8% of the patients treated with NIVO monotherapy. In the combination arm, TRAEs led to discontinuations in 39 patients (10.1%), of which 35 (89.7%) were BEMPEG discontinuations. In the NIVO monotherapy arm, 26 patients (6.8%) discontinued because of TRAEs. Overall, three deaths were considered by investigators to be treatment-related in the combination arm (Guillain-Barré syndrome; metabolic acidosis; pneumonitis, and liver failure), and one death was treatment-related in the NIVO monotherapy arm (myositis; Table 3).

PKs and PDs

In the combination arm, ALC initially decreased from baseline levels (cycle [C] 1, day [D] 1) around C1D3, peaked at C1D8, and returned close to baseline levels between C1D21 and C2D1 (day 22; Fig 3). NIVO monotherapy had a limited impact on modulating ALC compared with the BEMPEG plus NIVO combination. sCD25 increased by C1D5 (median 5.7-fold increase from baseline) and C1D8 (median 6.3-fold increase from baseline). While sCD25 levels decreased at C2D1 (day 22), they remained above baseline levels (median 1.9-fold increase from baseline; Fig 3). Increases in ALC and sCD25 demonstrated that BEMPEG was active in mediating immunomodulatory PD effects in the combination arm.

In PIVOT IO 001, the C_{max} and $AUC_{(0-96)}$ values of BEMPEG were 138 ng/mL and 5,391 ng × hour/mL, respectively, in the patient subset with extensive serial sample collections (Appendix Table A3, online only). Evaluation of the PK of BEMPEG and a summary of exposure comparisons between PIVOT IO 001 and PIVOT-02 are included in Appendix 1 (methods text and Appendix Figures A4 and A5 [online only]).

DISCUSSION

The phase III PIVOT IO 001 study did not meet its three primary end points of ORR, PFS, or OS with BEMPEG plus NIVO combination therapy, providing no added clinical benefit compared with NIVO monotherapy in patients with previously untreated, unresectable, or metastatic melanoma. This study found no new safety signals associated with the

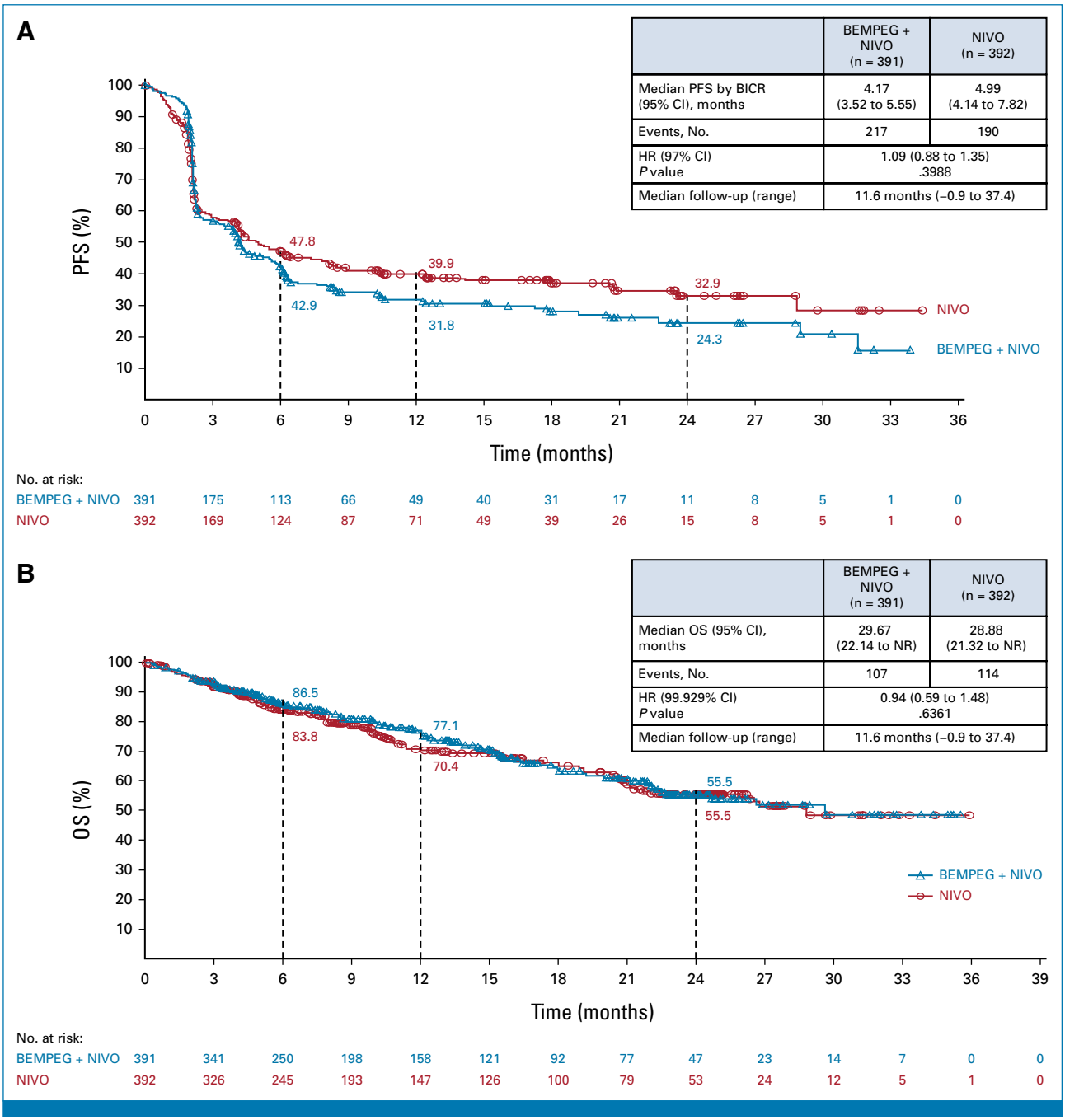

FIG 2. Kaplan-Meier estimates of (A) PFS per BICR and (B) OS in all patients. Database lock: February 1, 2022. The follow-up time is calculated relative to LPLV of November 19, 2021. The alpha allocated for PFS was .03, and that for OS was .019. Interim OS was tested using the group sequential testing procedure with O'Brien-Fleming alpha spending function. PFS was assessed by the primary definition of PFS per BICR, defined as the time between the date of random assignment and the date of first documented tumor progression, based on BICR assessment (per RECIST 1.1), or death because of any cause, whichever occurs first, before subsequent therapy. Statistical model for HR and *P* value: stratified Cox proportional hazards model and stratified log-rank test. The information fraction of events of OS is approximately 53%. BEMPEG, bempegaldesleukin; BICR, blinded independent central review; HR, hazard ratio; LPLV, last patient last visit; NIVO, nivolumab; NR, not reached; OS, overall survival; PFS, progression-free survival.

combination compared with the PIVOT-02 study[15] although a higher incidence of AEs with a lack of added efficacy was noted with BEMPEG plus NIVO versus NIVO alone. The higher incidence of TRAEs (eg, flu-like symptoms, hypotension, arthralgias, eosinophilia, and skin rash) with the combination provides evidence of the clinical activation of the IL-2 pathway. Moreover, it should be noted that rates of ICEs were higher with the combination than with NIVO

TABLE 3. Safety Summary

	BEMPEG + NIVO (n = 387)		NIVO (n = 382)	
Safety Parameter, No. (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-cause AEs	369 (95.3)	154 (39.8)	351 (91.9)	123 (32.2)
All-cause AEs leading to DC of any agent	58 (15.0)	34 (8.8)	45 (11.8)	23 (6.0)
TRAEs (30-day follow-up)	343 (88.6)	84 (21.7)	264 (69.1)	44 (11.5)
TRAEs leading to DC of any agent	39 (10.1)	23 (5.9)	26 (6.8)	17 (4.5)
TRAEs leading to DC of BEMPEG	35 (9.0)	19 (4.9)	NA	NA
Treatment-related SAEs	54 (14.0)	39 (10.1)	26 (6.8)	21 (5.5)
Dose reductions[a,b]	24 (6.2)		NA	
AEs leading to dose reductions	23 (5.9)	4 (1.0)[c]		
Treatment-related deaths[d]	3 (0.8)		1 (0.3)	
Cytokine-associated AE categories				
Arthralgia	85 (22.0)	3 (0.8)	61 (16.0)	2 (0.5)
Asthenic conditions	167 (43.2)	11 (2.8)	125 (32.7)	9 (2.4)
Elevated serum creatinine	14 (3.6)	0	19 (5.0)	0
Elevated transaminases	45 (11.6)	7 (1.8)	40 (10.5)	9 (2.4)
Eosinophilic disorders	58 (15.0)	7 (1.8)	6 (1.6)	0
Flu-like symptoms	257 (66.4)	5 (1.3)	109 (28.5)	5 (1.3)
Hypotension	37 (9.6)	5 (1.3)	6 (1.6)	1 (0.3)
Infusion-related reactions	51 (13.2)	2 (0.5)	10 (2.6)	0
Rash and pruritus	216 (55.8)	15 (3.9)	126 (33.0)	1 (0.3)
Tachyarrhythmias	6 (1.6)	1 (0.3)	5 (1.3)	2 (0.5)
imAEs category with ≥3%,[e,f] No. (%)				
Total imAEs	214 (55.3)	20 (0.5)	155 (40.6)	20 (0.5)
Hypothyroidism/thyroiditis	73 (18.9)	0	46 (12.0)	0
Rash[f]	51 (13.2)	6 (1.6)	26 (6.8)	0
Hyperthyroidism	46 (11.9)	0	25 (6.5)	0
Hypersensitivity[g,h]	15 (3.9)	1 (0.3)	8 (2.1)	1 (0.3)
Diarrhea/colitis[g]	11 (2.8)	5 (1.3)	14 (3.7)	6 (1.6)
Hepatitis[g]	6 (1.6)	3 (0.8)	12 (3.1)	8 (2.1)
Ischemic cerebrovascular events—all treated patients[e]				
Total No. of patients with an event	10 (2.6)	5 (1.3)	3 (0.8)	2 (0.5)
Cerebrovascular accident	6 (1.6)	1 (0.3)	1 (0.3)	0
Transient ischemic attack	2 (0.5)	0	0	0
Cerebral infarction	1 (0.3)	4 (1.0)	0	1 (0.3)
Ischemic stroke	1 (0.3)	0	2 (0.5)	0
Lacunar infarction	1 (0.3)	0	0	1 (0.3)

Abbreviations: AE, adverse event; BEMPEG, bempegaldesleukin; DC, discontinuation; imAE; immune-mediated adverse event; NA, not applicable; NIVO, nivolumab; SAE, serious adverse event; TRAE, treatment-related adverse event.

[a]All patients received one dose reduction.

[b]No dose reduction was allowed with NIVO.

[c]Nausea, decreased neutrophil count, and two syncope events.

[d]Treatment-related deaths: BEMPEG + NIVO: (1) Guillain-Barré syndrome, (2) metabolic acidosis, and (3) pneumonitis and liver failure; NIVO: myositis.

[e]No grade 5 events occurred.

[f]Includes events recorded between first dose and 100 days after last dose of study therapy.

[g]imAEs for which immune-modulating medication was initiated.

[h]Infusion-related reaction, anaphylactic reaction, hypersensitivity, anaphylactic shock.

monotherapy, which may be an important consideration when developing IL-2 pathway agonists in combination with current therapies for melanoma.

The PIVOT IO 001 study was conducted on the basis of the results from PIVOT-02, a nonrandomized, single-arm phase II study with a small sample size (41 patients with

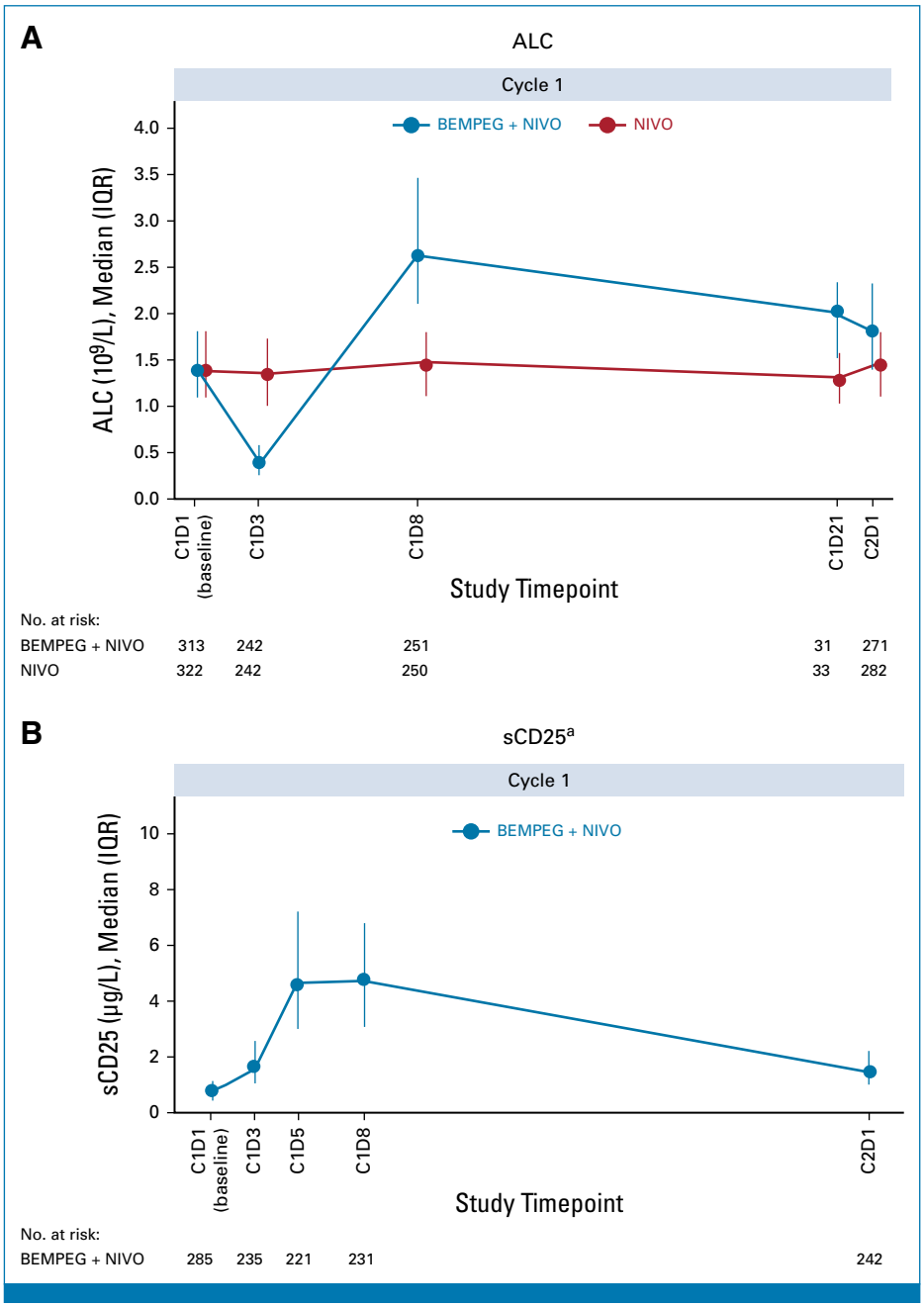

FIG 3. On-treatment longitudinal changes in ALC and sCD25. [a]sCD25 was not measured in the NIVO monotherapy arm. ALC, absolute lymphocyte count; BEMPEG, bempegaldesleukin; C, cycle; D, day; NIVO, nivolumab; sCD25, soluble CD25.

unresectable or metastatic melanoma) enrolled at 12 sites.[15] The design of the phase II trial could have possibly resulted in selection bias because of differences in enrollment and therefore a lack of generalizability that might have contributed in part to the disparate results in the current study. Although no formal cross-trial comparisons were conducted, the proportion of patients with a PD-L1 level ≥1% was numerically higher in PIVOT-02 (58.5%) compared with that in PIVOT IO 001 (49.4% in the BEMPEG plus NIVO arm).[15] Numerical differences in efficacy results were seen between the phase II and phase III studies of BEMPEG plus NIVO in advanced melanoma. In metastatic melanoma response-evaluable patients (n = 38) in the PIVOT-02 dose expansion study, the ORR by BICR was 52.6%, with 34.2% of patients experiencing CRs.[15] By contrast, the ORR by BICR for the combination arm in PIVOT IO 001 was 27.7%, with only 8.1% achieving CRs. The median PFS was 30.9 months (29.0 months follow-up) in PIVOT-02 versus 4.17 months (11.6 months follow-up) in the PIVOT IO 001 combination arm.[15] Overall efficacy results showed that NIVO monotherapy in PIVOT IO 001 performed similar to other modern trials using PD-1 monotherapy comparators.[2,5,17] In the

PIVOT-02 study, BEMPEG plus NIVO showed encouraging antitumor activity and relatively low rates of grade 3/4 TRAEs and imAEs in first-line treatment of patients with metastatic melanoma (n = 41).[15]

Increases in ALC and sCD25 demonstrated that BEMPEG was biologically active in mediating immunomodulatory PD effects. These observations were consistent with those observed in earlier stages of development.[17-19] Furthermore, the observed lymphopenia and subsequent lymphocytosis are consistent with the known characteristics of IL-2 and BEMPEG.[14,15,17-21] Although the dose of BEMPEG chosen for PIVOT IO 001 did not show single-agent antitumor activity, it was well-tolerated and associated with immune response in previous phase I and phase II studies.[14] Additional biomarker analyses are ongoing to further elucidate any potential mechanisms underlying the lack of added efficacy for BEMPEG plus NIVO versus NIVO monotherapy. Furthermore, exposure to BEMPEG was comparable in the phase II PIVOT-02 and phase III PIVOT IO 001 studies and, thus, did not appear to contribute to efficacy differences.

Currently available first-line standard immunotherapies (eg, NIVO with/without IPI, pembrolizumab, and NIVO plus relatlimab) for advanced melanoma have established high efficacy benchmarks that represent a challenge to developing new agents or combination therapies that can demonstrate improved outcomes in phase III trials.[2,5,22] Similar to BEMPEG plus NIVO, there are growing numbers of treatment regimens that have demonstrated efficacy and safety in phase I or II trials, yet fail to confirm those findings in larger, more robust phase III trials.[22-24] Multiple factors, such as evidence of single-agent activity in preclinical and early phase I/II studies, may help inform development of emerging therapies although no factor has been identified to predict success. Immuno-oncology is a dynamic field, and determining when to move an agent into a large phase III trial remains an active topic of discussion.[25] Furthermore, clinical evidence showing improved outcomes of new combination therapies compared with standard/benchmark therapies should result from more rigorous phase II studies (eg, randomized trials showing each agent's contribution to the treatment/disease, strong PD evidence of drug target activity, dose optimization through randomized dose finding studies), fulfilling a proof of principle requirement for further drug development.

The implications of the PIVOT IO 001 study results on other engineered IL-2 assets under development are currently unclear. It will be important to further assess the PD, mechanism of action, and biomarker results from this study to determine if the lack of enhanced efficacy with the combination is due to the challenges targeting the IL-2 pathway or due to the specific drug design of BEMPEG. The translational data generated from PIVOT IO 001 may inform the development of other IL-2 pathway agonists that are able to demonstrate efficacy in combination with checkpoint inhibitors.

In conclusion, the combination of BEMPEG plus NIVO as a first-line treatment for advanced melanoma did not improve the ORR, PFS, or OS compared with standard-of-care NIVO monotherapy.

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APPENDIX 1. PHARMACOKINETIC BEMPEGALDESLEUKIN ANALYSIS

An exploratory analysis evaluated the pharmacokinetics (PK) of bempegaldesleukin (BEMPEG) and compared the BEMPEG exposures from PIVOT IO 001 with those of PIVOT-02.

Blood samples were collected in all patients in PIVOT IO 001 for PK evaluations at six timepoints over the 3-week dosing interval after drug administration on cycle (C) 1 day (D) 1, as well as at predose, end of infusion, and 48 hours postdose in C5. These collections were considered sparse samples.

Extensive serial samples included blood samples collected at eight timepoints over the 3-week interval after drug administration on C1D1 for noncompartmental PK evaluations in a subset of patients.

Exposure to BEMPEG is displayed in Appendix Figures A4 and A5 (online only) for the subset of patients with extensive serial sampling and all patients in PIVOT IO 001, respectively. A summary of the C_{max} and $AUC_{(0\text{-}96)}$ PK parameters is given in Appendix Table A3.

Although samples were collected for nivolumab (NIVO) concentration assessments, a definitive population PK analysis for NIVO was not conducted on the basis of these study results. Still, an overlap in NIVO concentrations between the PIVOT-02 and PIVOT IO 001 studies was observed (Bristol Myers Squib, Data on file, October 2022).

TABLE A1. Cumulative Dose and Duration of Therapy

	BEMPEG + NIVO[a] (n = 387)		
Dose	BEMPEG (n = 387)	NIVO (n = 387)	NIVO[b] (n = 382)
Doses received, No., median (range)	6.0 (1-35)	6.0 (1-35)	7.0 (1-35)
Cumulative dose, median (range)	0.0362 mg/kg (0.006-0.213)	2,160 mg (360-12,600)	2,520 mg (360-12,600)
Duration of therapy, months, median (range)	4.14 (0.0-24.9)		4.17 (0.0-24.4)

Abbreviations: BEMPEG, bempegaldesleukin; NIVO, nivolumab.
[a]In the combination arm, BEMPEG was administered intravenously at a dose of 0.006 mg/kg, sequentially followed by intravenous NIVO administration at a dose of 360 mg, once every 3 weeks.
[b]NIVO monotherapy was administered intravenously at a dose of 360 mg once every 3 weeks.

TABLE A2. TRAEs

	BEMPEG + NIVO (n = 387), No. (%)		NIVO (n = 382), No. (%)	
TRAE ≥5%	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Pyrexia	132 (34.1)	1 (0.3)	7 (1.8)	0
Pruritus	103 (26.6)	1 (0.3)	58 (15.2)	0
Fatigue	98 (25.3)	3 (0.8)	58 (15.2)	1 (0.3)
Rash	95 (24.5)	10 (2.6)	44 (11.5)	0
Nausea	75 (19.4)	1 (0.3)	19 (5.0)	0
Arthralgia	68 (17.6)	3 (0.8)	28 (7.3)	1 (0.3)
Hypothyroidism	68 (17.6)	0	43 (11.3)	0
Influenza-like illness	63 (16.3)	3 (0.8)	1 (0.3)	0
Diarrhea	62 (16.0)	2 (0.5)	35 (9.2)	1 (0.3)
Infusion-related reaction	49 (12.7)	1 (0.3)	15 (3.9)	0
Eosinophilia	47 (12.1)	6 (1.6)	5 (1.3)	0
Hyperthyroidism	46 (11.9)	0	22 (1.3)	0
Asthenia	45 (11.6)	2 (0.5)	19 (5.0)	1 (0.3)
Decreased appetite	44 (11.4)	1 (0.3)	6 (1.6)	0
Myalgia	44 (11.4)	1 (0.3)	11 (2.9)	0
Vomiting	36 (9.3)	0	2 (0.5)	0
Hypotension	34 (8.8)	4 (1.0)	1 (0.3)	1 (0.3)
Headache	32 (8.3)	0	10 (2.6)	0
Chills	31 (8.0)	0	1 (0.3)	0
Dizziness	26 (6.7)	0	0	0
Rash maculopapular	26 (6.7)	1 (0.3)	13 (3.4)	0
Erythema	25 (6.5)	0	2 (0.5)	0
Increased alanine aminotransferase	24 (6.2)	2 (0.5)	22 (5.8)	3 (0.8)
Vitiligo	24 (6.2)	0	23 (6.0)	0
Dry skin	22 (5.7)	0	7 (1.8)	0
Face edema	21 (5.4)	2 (0.5)	0	0
Increased lipase	16 (4.1)	6 (1.6)	23 (6.0)	8 (2.1)
Increased amylase	13 (5.4)	5 (1.3)	20 (5.2)	4 (1.0)

Abbreviations: BEMPEG, bempegaldesleukin; NIVO, nivolumab; TRAE, treatment-related adverse event.

TABLE A3. Summary Statistics of BEMPEG PK Parameters in Cycle 1: PIVOT IO 001 Extensively Sampled PK Subset Versus PIVOT-02 Treated Population

PK Parameter (unit)		
Statistic	PIVOT IO 001	PIVOT-02
C_{max}		
Geo mean, ng/mL	138	122
No.	29	454
% CV	28	28
T_{max}		
Mean, hour	3.48	3.38
No.	29	454
Min-Max	0.517-24.0	0.170-49.7
$AUC_{(0\text{-}96)}$		
Geo mean, hour x ng/mL	5,391	4,556
No.	28	363
% CV	33	33

Abbreviations: BEMPEG, bempegaldesleukin; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo, geometric; Max, maximum; Min, minimum; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration.

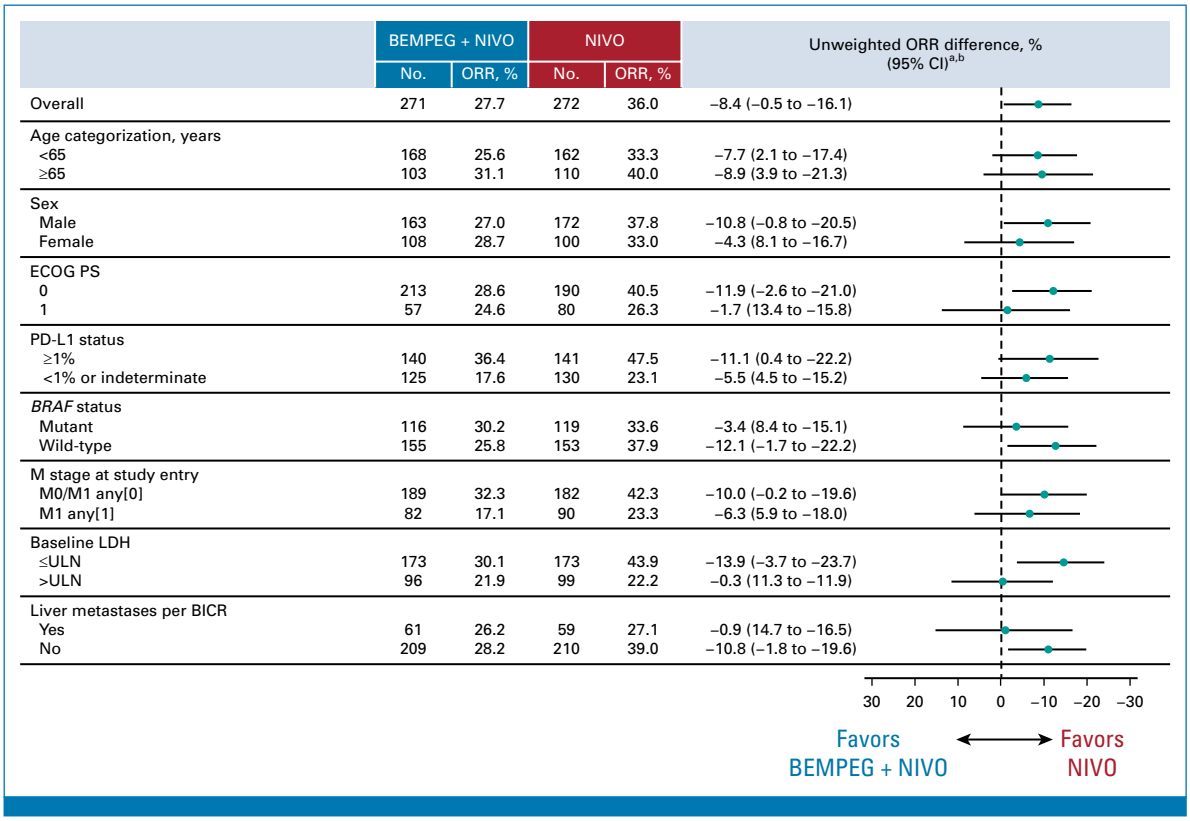

FIG A1. Subgroup analysis of ORR by BICR. Database lock: February 1, 2022. The median follow-up is 19.3 months (range, 6.0-37.4) for the ORR population. The alpha allocated for ORR was .001. [a]Two-sided 95% CI for unweighted difference was calculated using the Newcombe method. [b]Subset categories with <10 patients per treatment group are not included as ORR differences were not computed. BEMPEG, bempegaldesleukin; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; M, metastatic; NIVO, nivolumab; ORR, objective response rate; ULN, upper limit of normal.

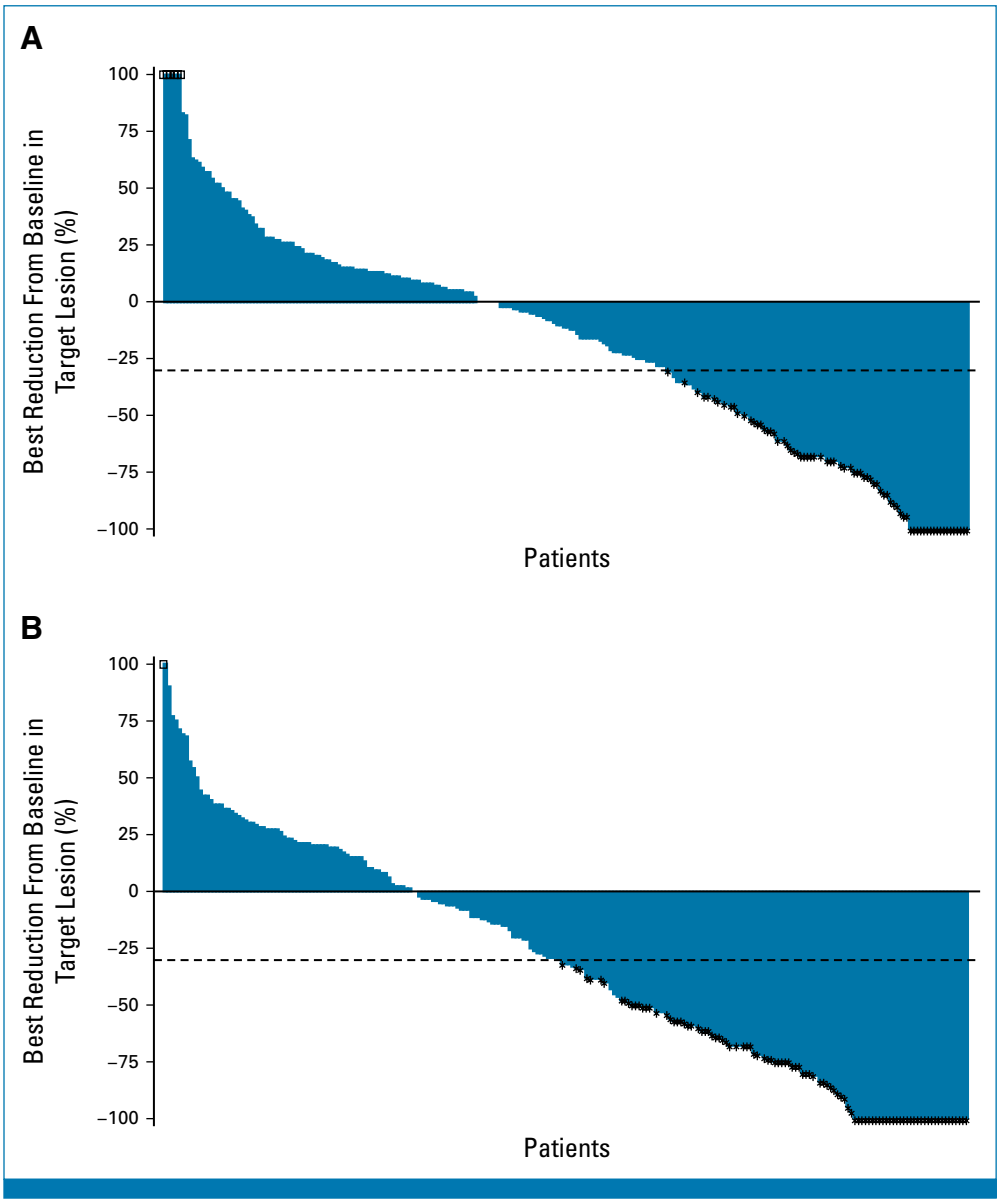

FIG A2. Waterfall plot of best % change from baseline in the sum of diameters of target lesions, per BICR—all response evaluable patients in the ORR population for (A) BEMPEG plus NIVO and (B) NIVO. Patients with target lesion at baseline and at least one postbaseline tumor assessment were included. Best change is maximum reduction in sum of diameters of target lesions (negative value means true reduction, and positive value means increase only observed over time). The horizontal reference line indicates the 30% reduction consistent with a RECIST 1.1 response. The asterisk symbol represents responders. The rectangle symbol represents % change truncated to 100%. BEMPEG, bempegaldesleukin; BICR, blinded independent central review; NIVO, nivolumab.

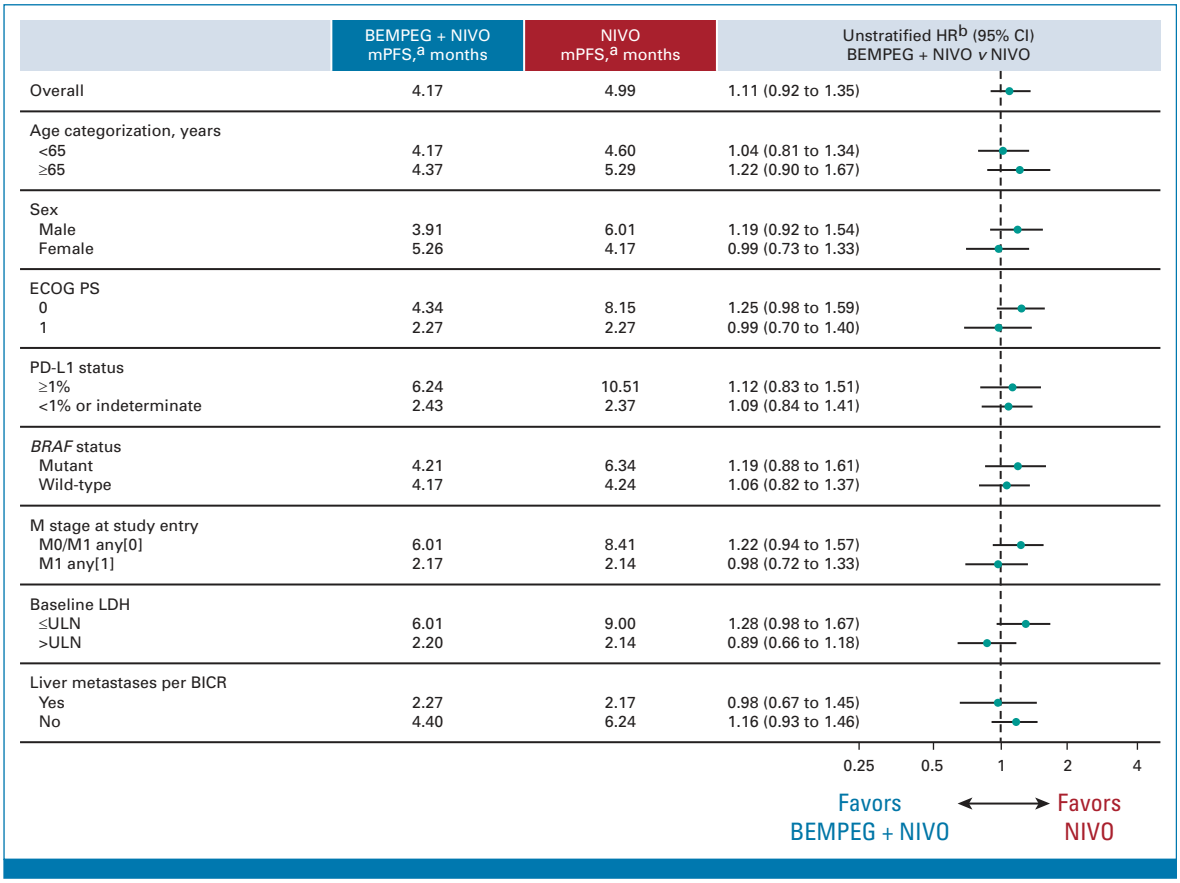

FIG A3. Subgroup analysis of PFS by BICR. Database lock: February 1, 2022. The median follow-up is 11.6 months (range, −0.9 to 37.4) for the ITT population. The follow-up time is calculated relative to LPLV of November 19, 2021. The alpha allocated for PFS was .03. [a]By the primary definition of PFS per BICR, defined as the time between the date of random assignment and the date of first documented tumor progression, on the basis of BICR assessment (per RECIST 1.1), or death because of any cause, whichever occurs first, before subsequent therapy. [b]HR and median are not computed for any subset category with <10 patients per treatment arm. BEMPEG, bempegaldesleukin; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intent-to-treat; LDH, lactate dehydrogenase; LPLV, last patient, last visit; M, metastatic; mPFS, median progression-free survival; NIVO, nivolumab; PFS, progression-free survival; ULN, upper limit of normal.

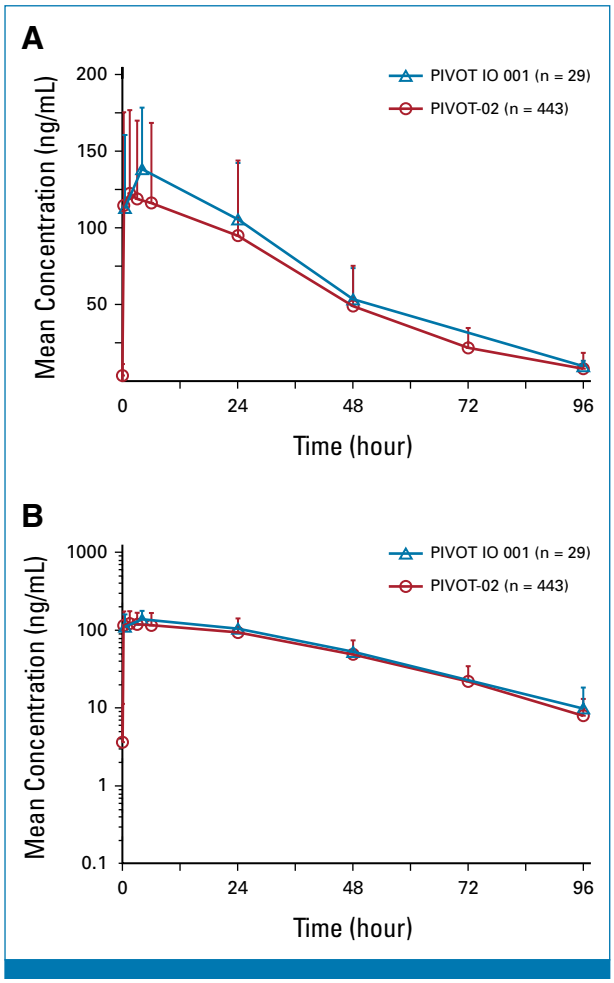

FIG A4. (A) Linear and (B) logarithmic linear plot of the mean (+SD) BEMPEG concentration profile versus time: PIVOT IO 001 extensively sampled PK subset versus the treated population of the PIVOT-02 trial. BEMPEG, bempegaldesleukin; PK, pharmacokinetic; SD, standard deviation.

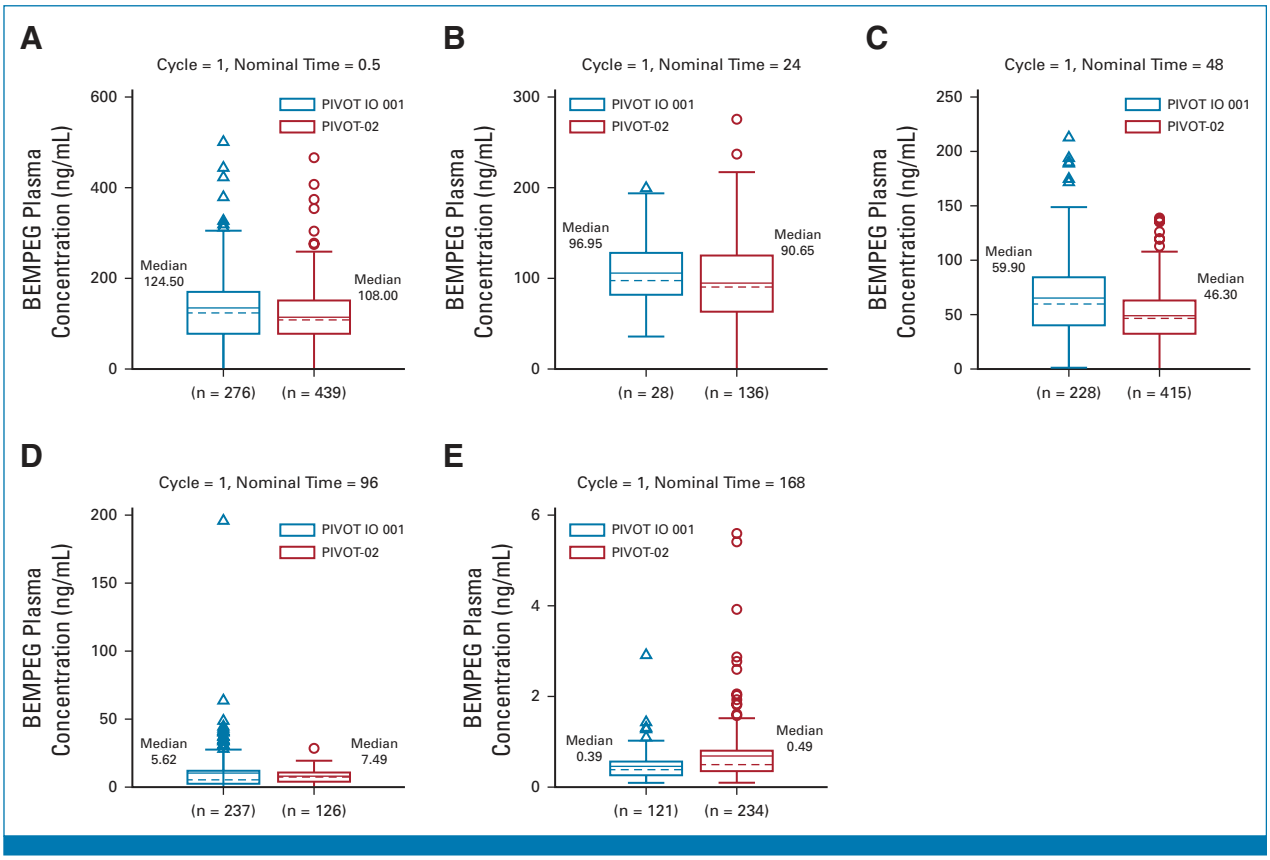

FIG A5. Box plot comparison of BEMPEG concentrations after administration of BEMPEG plus NIVO in PIVOT IO 001 and PIVOT-02 from all pharmacokinetics-evaluable patients at nominal times of (A) 0.5 hours, (B) 24 hours, (C) 48 hours, (D) 96 hours, and (E) 168 hours. BEMPEG, bempegaldesleukin; NIVO, nivolumab.