P-042

Progression-free survival and biomarker correlates of response with BEMPEG plus NIVO in previously untreated patients with metastatic melanoma: Results from the PIVOT-02 study

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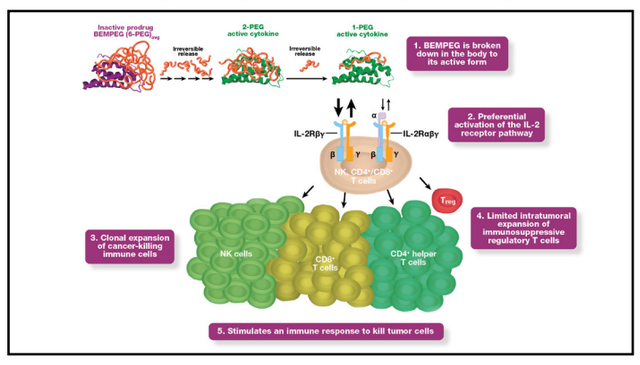
BACKGROUND

BEMPEG signals preferentially through the IL-2R pathway



- Bempegaldesleukin (BEMPEG; NKTR-214) is a CD122-preferential IL-2 pathway agonist shown to increase tumor-infiltrating lymphocytes, T-cell clonality, and PD-1 expression[1,2]
- BEMPEG plus the checkpoint inhibitor (CPI) nivolumab (NIVO) has been shown to convert tumors from PD-L1(–) at baseline to PD-L1(+) on treatment[3]
- Low levels of baseline tumor-infiltrating lymphocytes[4–6] and T-cell inflammation[7] are predictive of a poor response to CPIs

CD, cluster of differentiation; IL-2(R), interleukin-2 (receptor); NK, natural killer cell; PEG, releasable polyethylene glycol; Treg, regulatory T cell.

BEMPEG plus NIVO in metastatic melanoma

- Despite CPI therapy as an effective treatment option, an unmet needs exists for novel therapies that produce deep and durable responses in more patients with metastatic melanoma
- The safety and clinical activity of BEMPEG plus NIVO were evaluated in PIVOT-02, a multicenter phase 1/2 study in multiple solid tumors[3]
  - Encouraging safety and preliminary clinical activity were seen in first-line metastatic melanoma, including durable responses that deepened over time[3,8]
- BEMPEG plus NIVO received FDA Breakthrough Therapy Designation in July 2019 for patients with previously untreated, unresectable or metastatic melanoma
- We present clinical results from PIVOT-02 (NCT02983045) in previously untreated patients with metastatic melanoma, including mPFS and exploratory biomarkers of response
  - These data were first presented at the SITC Annual Meeting, November 9–14, 2020[9]

PATIENTS

Patient demographics and disease characteristics

	Total (N=41)
Sex	
Female	17 (41.5)
Male	24 (58.5)
Age (years)	
Median (range)	63 (22–80)
ECOG performance status	
0	32 (78.0)
1	9 (22.0)
PD-L1 status[a]	
PD-L1 positive ≥1%	24 (58.5)
PD-L1 negative <1%	14 (34.1)
Unknown	3 (7.3)

	Total (N=41)
***BRAF* mutation status**	
Mutant (V600E, V600K)	13 (31.7)
Wild-type or non-V600 mutation	27 (65.9)
Unknown	1 (2.4)
Serum lactate dehydrogenase[b]	
Normal	29 (70.7)
Elevated >ULN[c]	12 (29.3)
Stage (7th edition AJCC)	
M1a	5 (12.2)
M1b	16 (39.0)
M1c	20 (48.8)
Liver metastases[d]	
Yes	11 (26.8)
No	30 (73.2)

Data cutoff: 1SEPT2020. All numbers are n (%) unless otherwise specified.

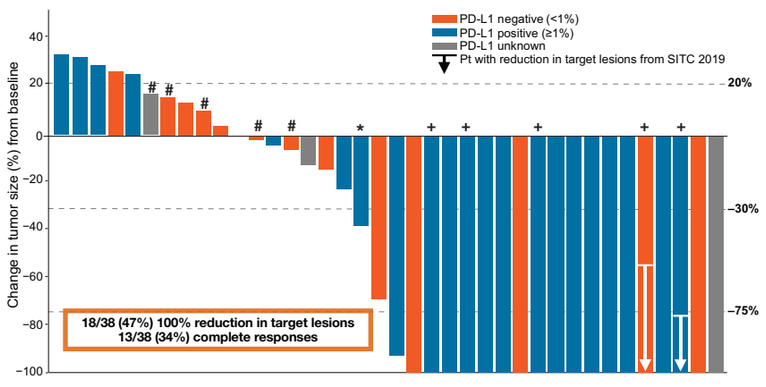
[a]PD-L1 status determined by PD-L1 IHC 28-8 pharmDx (Dako, an Agilent Technologies, Inc. company, Santa Clara, CA) on fresh or archival tumor; for patients with insufficient tumor tissue for central analysis, local pathology data for PD-L1 status at baseline were substituted. [b]Based on maximum value prior to dosing. [c]Eight patients with ≥2X ULN. [d]One patient with liver metastases was not evaluable for efficacy.

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

- 41 patients with previously untreated stage IV melanoma were enrolled and received ≥1 dose of BEMPEG plus NIVO
- As of September 1, 2020, 38 patients were efficacy evaluable, defined by the protocol as patients with ≥1 post-baseline scan (3 patients discontinued prior to the first scan due to an unrelated TEAE [n=1] and patient decision [n=2]); all patients are now off treatment

RESPONSE

Stage IV 1L melanoma: Best overall response by independent radiology

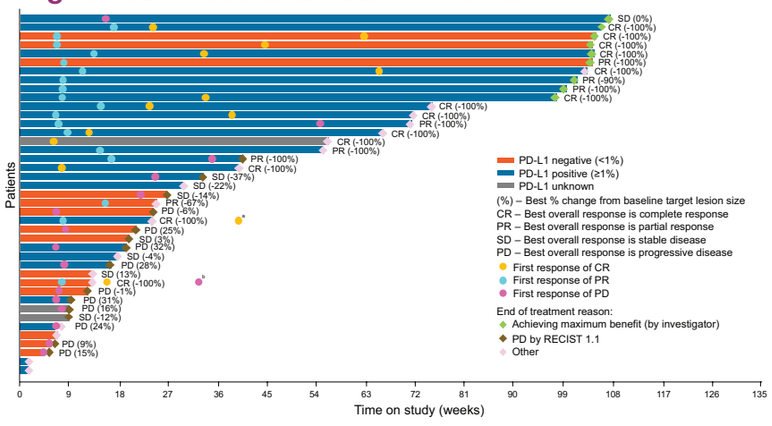


1L Melanoma (n=38 Efficacy Evaluable) Median 29.0 Months of Follow-up	
Confirmed ORR (CR+PR) , n (%)	20 (53)
CR	13 (34)
PD-L1 negative (n=13)	5 (39)
PD-L1 positive (n=22)	14 (64)
PD-L1 unknown (n=3)	1 (33)
LDH >ULN (n=11)	5 (46)
Liver metastases (n=10)	5 (50)
Median % change in tumor size from baseline	–78.5
Median time to response (months)	2.0
Median time to CR (months)	7.9

All 5 responses in patients with liver metastases were CRs

Data cutoff: 1SEPT2020. Response-evaluable population includes eligible patients with measurable disease (per RECIST v1.1) at baseline and ≥1 post-baseline tumor assessment. All objective responses are confirmed. #Best overall response is progressive disease due to nontarget lesion progression or presence of new lesion. *Best overall response is SD. +Best overall response is PR. CR for target lesion, non-target lesion still present. CR complete response; LDH, lactate dehydrogenase; ORR, objective response rate; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; ULN, upper limit of normal.

Responses with BEMPEG plus NIVO were durable and deepened over time
Stage IV 1L melanoma: ORR 53% with CR 34%



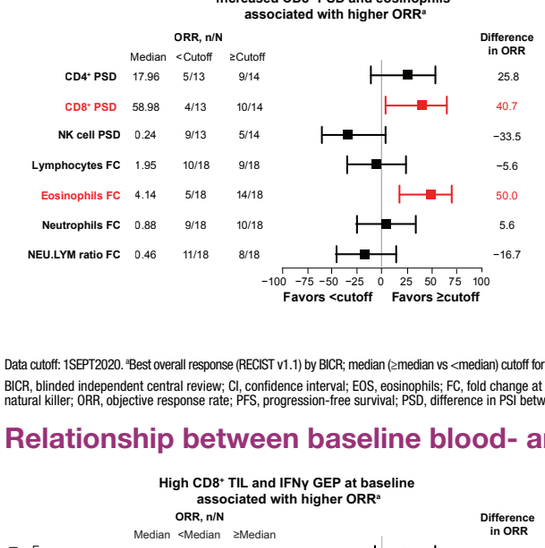
1L Melanoma (N=41; n=38 Efficacy Evaluable)	
Median duration of follow-up (months)	29.0
Median number of cycles (range)	9 (1–35)
Number of cycles ≥6, n (%)	29 (70.7)
Patients with ongoing responses, n (%)	16 (80.0)
Median duration of response (months)	NE

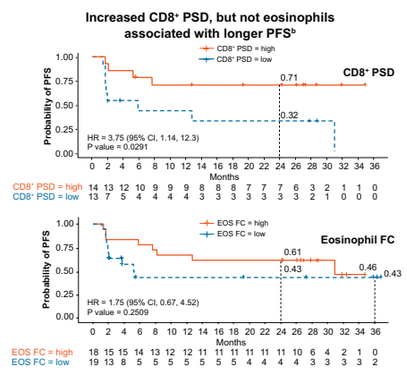
Data cutoff: 1SEPT2020. [a]Patient achieved PR in Mar 2018; EoT in Jul 2018; achieved CR in Oct 2018. [b]Patient achieved PR in Mar 2018; EoT in May 2018 due to patient decision (quality of life issues); achieved CR in May 2018; disease relapse in Sept 2018 due to new lesion (brain).

CR complete response; EoT, end of treatment; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

EXPLORATORY BIOMARKERS

Relationship between on-treatment (day 8) blood biomarkers in matched samples and response

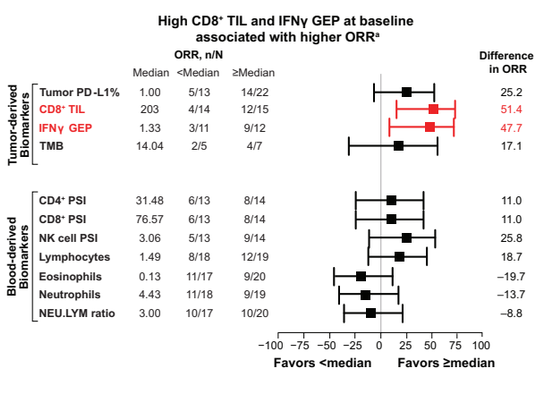


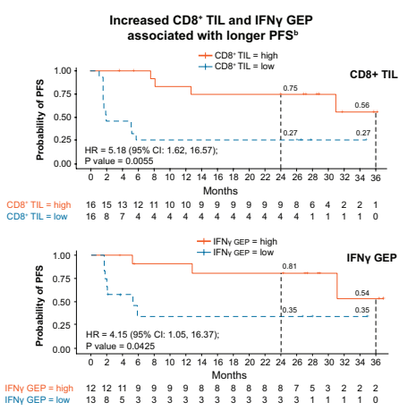


Data cutoff: 1SEPT2020. [a]Best overall response (RECIST v1.1) by BICR; median (≥median vs <median) cutoff for markers; efficacy-evaluable population, n=38. [b]CD8+ TIL and IFNγ GEP (high vs low by median cutoff); safety population (N=41).

BICR, blinded independent central review; CI, confidence interval; EOS, eosinophils; FC, fold change at C1D8 vs C1D1; GEP, gene expression profile; HR, hazard ratio; NEU.LYM ratio, neutrophil to lymphocyte ratio; NK, natural killer; ORR, objective response rate; PFS, progression-free survival; PSD, difference in PSI between C1D1 and C1D8; PSI, polyfunctional strength index, using IsoPlexis technology; TIL, tumor-infiltrating lymphocyte.

Relationship between baseline blood- and tumor-derived biomarkers and response



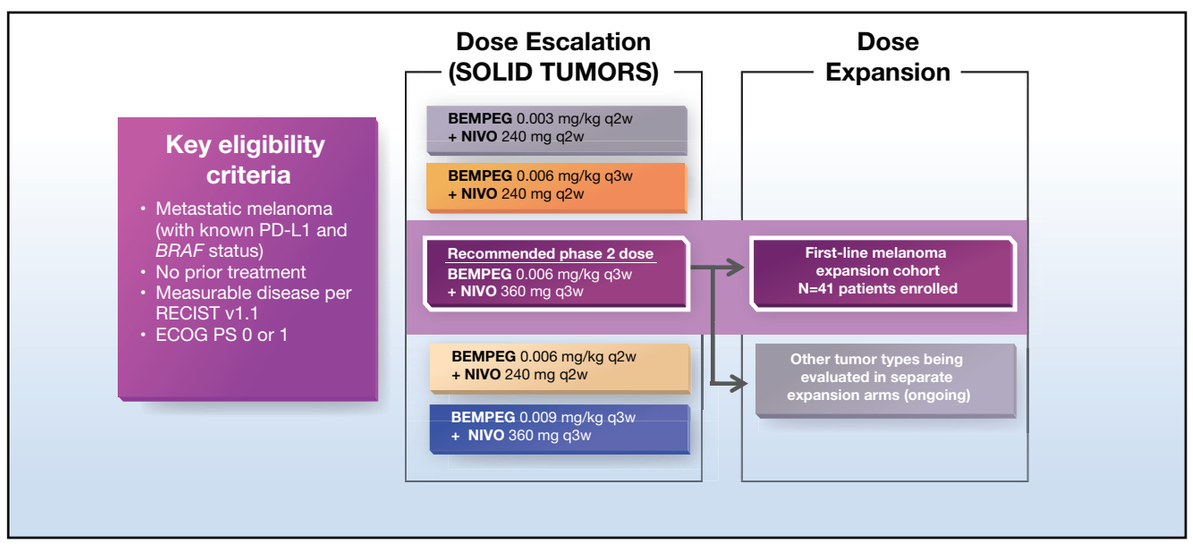


Data cutoff: 1SEPT2020. [a]Best overall response (RECIST v1.1) by BICR; median (≥median vs <median) cutoff for markers; efficacy-evaluable population, n=38.
[b]CD8+ TIL and IFNγ GEP (high vs low by median cutoff); safety population (N=41).

BICR, blinded independent central review; CI, confidence interval; GEP, gene expression profile; NEU.LYM ratio, neutrophil to lymphocyte ratio; NK, natural killer; ORR, objective response rate; PFS, progression-free survival; PSI, polyfunctional strength index, using IsoPlexis technology; TIL, tumor-infiltrating lymphocytes; TMB, tumor mutational burden.

STUDY DESIGN

PIVOT-02 phase 2 expansion cohort in first-line metastatic melanoma



Primary endpoints	Selected secondary and exploratory endpoints
• Safety and tolerability • ORR per RECIST assessed every 8 weeks[a]	• PFS • OS • Duration of response • Clinical benefit rate • Exploratory biomarkers in blood and tumor

[a]Tumors were assessed by blinded independent central radiology (BICR) and local investigator. BICR was used for the primary analysis, which required radiologic imaging scans to be submitted to a central location and reviewed by independent radiologists who were not involved in the treatment of the patients.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

SAFETY

Safety of BEMPEG plus NIVO was consistent with previous reports

Preferred Term[a], n (%)	Total (N=41)
Grade 3/4 treatment-related AEs	7 (17.1)[b]
Acute kidney injury	2 (4.9)
Atrial fibrillation[c]	2 (4.9)
Dizziness, dyspnea, hyperglycemia, hypernatremia, hypoxia	1 each (2.4)
Grade 1/2 treatment-related AEs (>30% listed below)	
Flu-like symptoms[d]	33 (80.5)
Rash[e]	29 (70.7)
Fatigue	27 (65.9)
Pruritus	20 (48.8)
Nausea	19 (46.3)
Arthralgia	19 (46.3)
Decreased appetite	15 (36.6)
Myalgia	15 (36.6)
Any imAE (Grade ≥3) (nephritis and renal dysfunction, diabetes mellitus/hyperglycemia treated with insulin)	2 (4.9)
Patients who discontinued BEMPEG or NIVO due to a treatment-related AE (blood creatinine increased, cerebrovascular accident, malaise, peripheral edema, pharyngitis)	5 (12.2)
Treatment-related deaths	**0**

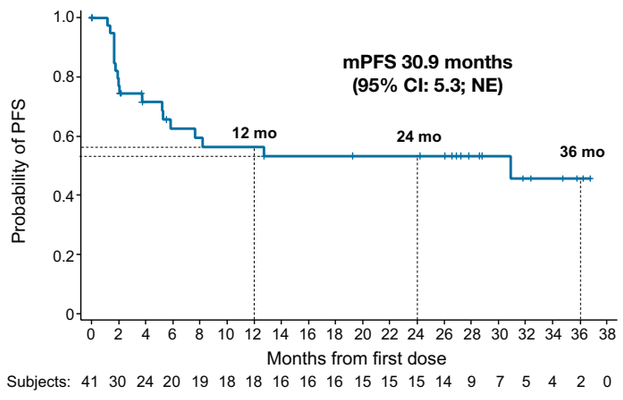
As of September 1, 2020, no new treatment-related AEs had been reported since September 25, 2019 (SITC 2019 cutoff)

Data cutoff : 1SEPT2020. Per-protocol, the safety-evaluable population is defined as patients with ≥1 dose of study treatment. [a]Patients are only counted once under each preferred term using the highest grade. [b]Patients with ≥2 G3/4 TRAEs are only counted once. [c]One patient with previous history of atrial fibrillation since 2015; one patient experienced atrial fibrillation 1 month after last dose of study drug. [d]Flu-like symptoms included the following preferred terms: chills, influenza-like illness, pyrexia. [e]Rash included 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.

AE, adverse event; BEMPEG, bempegaldesleukin; imAE, immune-mediated adverse event; NIVO, nivolumab; SITC, Society for Immunotherapy of Cancer.

SURVIVAL

mPFS 30.9 months (95% CI: 5.3; NE) at median follow-up of 29.0 months

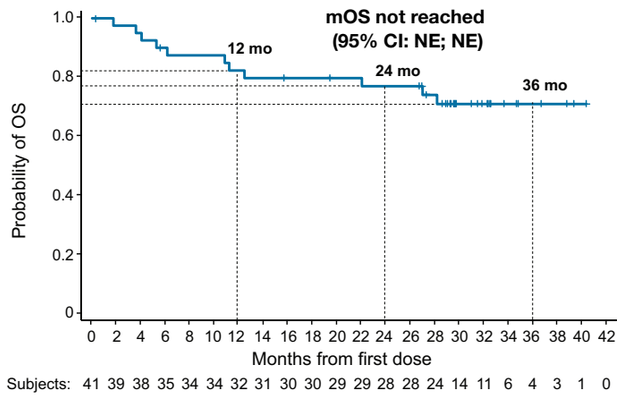


Kaplan–Meier Estimate of PFS by BICR (RECIST v1.1)	Total (N=41)
Rate at 12 months, % (95% CI)	56.2 (38.4; 70.6)
Rate at 24 months, % (95% CI)	53.1 (35.4; 67.9)
Rate at 36 months, % (95% CI)	45.5 (25.5; 63.5)

Data cutoff: 1SEPT2020. Intent-to-treat population (N=41).

BICR, blinded independent central radiology; CI, confidence interval; NE, not evaluable; (m)PFS, (median) progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

mOS not reached (95% CI: NE; NE) at median follow-up of 29.0 months



Kaplan–Meier Estimate of OS	Total (N=41)
Rate at 12 months, % (95% CI)	82.3 (66.4; 91.1)
Rate at 24 months, % (95% CI)	77.0 (60.4; 87.3)
Rate at 36 months, % (95% CI)	70.9 (53.5; 82.8)

Data cutoff: 1SEPT2020. Intent-to-treat population (N=41).

CI, confidence interval; NE, not evaluable; (m)OS, (median) overall survival.

CONCLUSIONS

- In previously untreated patients with metastatic melanoma in PIVOT-02:
  - BEMPEG plus NIVO achieved deep and durable responses, with an ORR of 53%, a CR rate of 34%, and a mPFS of 30.9 months
  - BEMPEG plus NIVO was well tolerated; TRAEs were predictable and consistent with previous reports
  - Non-invasive, on-treatment exploratory biomarkers (CD8+ PSD and eosinophils) demonstrated potential predictive value for response, before radiologic evidence was observed
- Registrational phase 3 trials evaluating BEMPEG plus NIVO are enrolling in first-line metastatic melanoma (PIVOT IO 001; NCT03635983) and adjuvant melanoma (PIVOT-12; NCT04410445)

ABBREVIATIONS

1L, first-line; BEMPEG, bempegaldesleukin (NKTR-214); CI, confidence interval; CPI, checkpoint inhibitor; CR, complete response; FDA, U.S. Food and Drug Administration; IL-2(R), interleukin-2 (receptor); (m)OS, (median) overall survival; NE, not evaluable; NIVO, nivolumab; ORR, objective response rate; PD-(L)1, programmed death-(ligand) 1; PFS, progression-free survival; PSD, difference in polyfunctional strength index between cycle 1 day 1 and cycle 1 day 8; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse events; Treg, regulatory T cell.

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