
sitc
1985
35th ANNIVERSARY
2020
Reimagined
2020
SITC
NOVEMBER 9–14
sitc
Society for Immunotherapy of Cancer

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

Adi Diab[1], Scott S. Tykodi[2], Gregory A. Daniels[3], Michele Maio[4], Brendan D. Curti[5], Karl D. Lewis[6]; Sekwon Jang[7], Ewa Kalinka[8], Igor Puzanov[9], Alexander I. Spira[10], Daniel C. Cho[11], Shanhong Guan[12], Erika Puente[12], Ute Hoch[12], Sue L. Currie[12], Tuan Nguyen[12], Wei Lin[12], Mary A. Tagliaferri[12], Jonathan Zalevsky[12], Mario Sznol[13], Michael E. Hurwitz[13]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Seattle Cancer Care Alliance, Seattle, WA, USA; [3]University of California, La Jolla, CA, USA; [4]Azienda Ospedaliera Universitaria Senese, Siena, Italy; [5]Providence Cancer Institute and Earle A. Chiles Research Institute, Portland, OR, USA; [6]University of Colorado, Aurora, CO, USA; [7]Inova Schar Cancer Institute, Fairfax, VA, USA; [8]Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland; [9]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [10]Virginia Cancer Specialists, Fairfax, VA, USA; [11]NYU Medical Oncology Associates, New York, NY, USA; [12]Nektar Therapeutics, San Francisco, CA, USA; [13]Yale School of Medicine, New Haven, CT, USA

Presenter Disclosure Information:

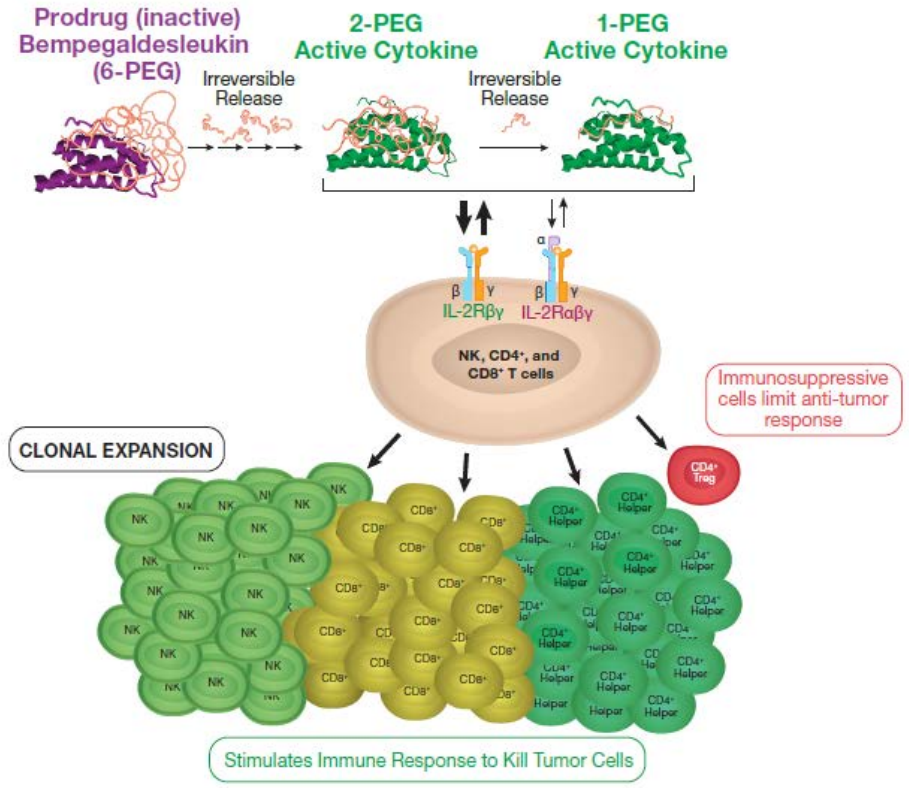
Adi Diab, MD, The University of Texas MD Anderson Cancer Center

The following relationships exist related to this presentation:

- Consulting or advisory role: Apexigen, Array, BMS, Celgene, CureVac, Dragonfly, Iovance, Nektar, Memgen
- Research funding (institution): Idera, Nektar, Pfizer, BMS , Apexigen

Bempegaldesleukin in combination with nivolumab is an investigational combination and is not currently approved by the FDA

BEMPEG Signals Preferentially Through The Interleukin-2 Receptor 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 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] is predictive of a poor response to CPIs

CPI, checkpoint inhibitor; IL, interleukin; NK, natural killer; PD-(L)1, programmed death-(ligand) 1; Treg, regulatory T cell.

1. Charych D, et al. *PLoS One* 2017; 12: e0179431; 2. Bentebibel SE, et al. *Cancer Discov* 2019;9:711–21; 3. Diab A, et al. *Cancer Discov* 2020;10:1158–73; 4. Daud AI, et al. *J Clin Oncol* 2016;34:4102–09; 5. Daud AI, et al. *J Clin Invest* 2016;126:3447–52; 6. Tumeh PC, et al. *Nature* 2014;515:568–71; 7. Ayers M, et al. *J Clin Invest* 2017;127:2930–40.

BEMPEG Plus NIVO in Metastatic Melanoma

- Despite CPI therapy as an effective treatment option, there is an unmet need for therapies to produce durable and deeper responses in more patients with metastatic melanoma
- Safety and clinical activity of BEMPEG plus NIVO was evaluated in PIVOT-02, a multicenter phase 1/2 study in multiple solid tumors[1]
  - Encouraging preliminary clinical activity and safety data were seen in metastatic melanoma, including durable responses that deepened over time[1,2]
- BEMPEG plus NIVO received FDA Breakthrough Therapy Designation in July 2019 for patients with previously untreated, unresectable or metastatic melanoma
- **Here, we report the updated results from PIVOT-02 (NCT02983045) in previously untreated patients with metastatic melanoma, including median PFS and biomarker correlates of response**

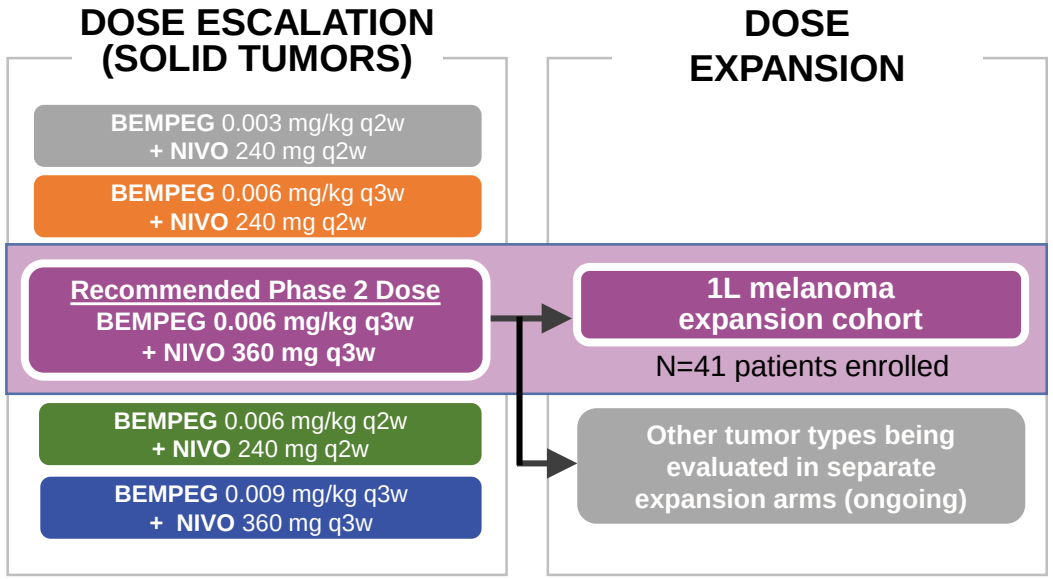
CPI, checkpoint inhibitor; FDA, U.S. Food and Drug Administration; PFS, progression-free survival.

1. Diab A, et al. *Cancer Discov* 2020;10:1158–73; 2. Diab A, et al. Oral presentation at SITC 2019:O35.

PIVOT-02 Study Schema

KEY ELIGIBILITY CRITERIA

- Metastatic melanoma (with known PD-L1 and *BRAF* status)
- No prior treatment
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1



Primary endpoints

- Safety and tolerability
- ORR per RECIST assessed every 8 weeks[a]

Selected secondary and exploratory endpoints

- PFS
- OS
- Duration of response
- Clinical benefit rate
- Biomarkers in blood and tumor

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

[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; PFS, progression-free survival; TEAE, treatment-emergent adverse event; SOC, standard of care.

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 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.

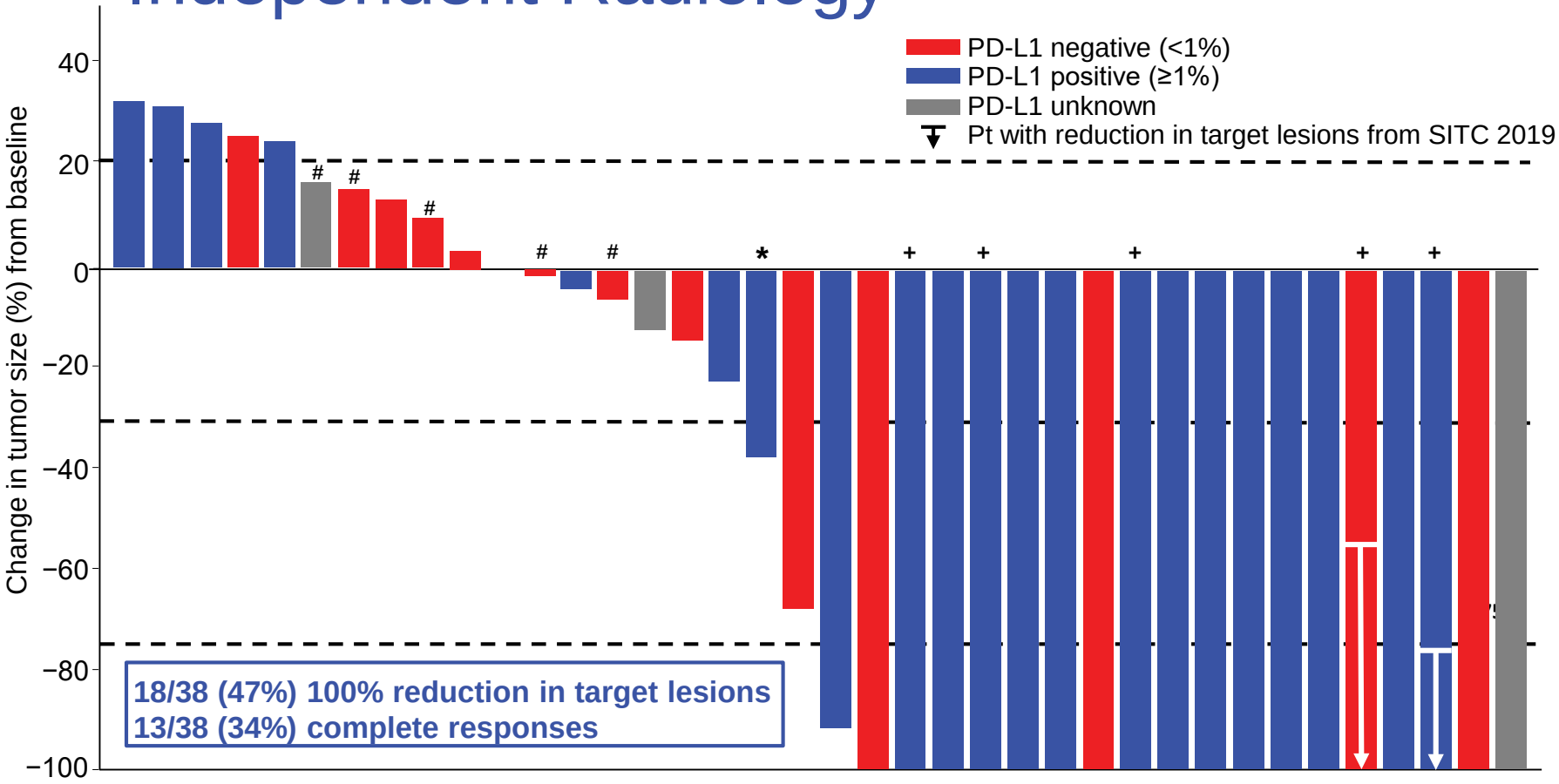
Safety of BEMPEG Plus NIVO was Consistent With Previous Reports

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**

No new treatment-related AEs reported since SITC 2019

Data Cutoff : 1SEPT2020. Per protocol, safety evaluable population is defined as patients with ≥1 dose of study treatment. [a]Patients are only counted once under each preferred term using 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 maculo-papular, rash maculovesicular, rash papular, rash pruritic, rash pustular, rash vesicular, exfoliative rash. AE, adverse event; imAE, immune-mediated adverse events.

Stage IV 1L Melanoma: Best Overall Response by Independent Radiology

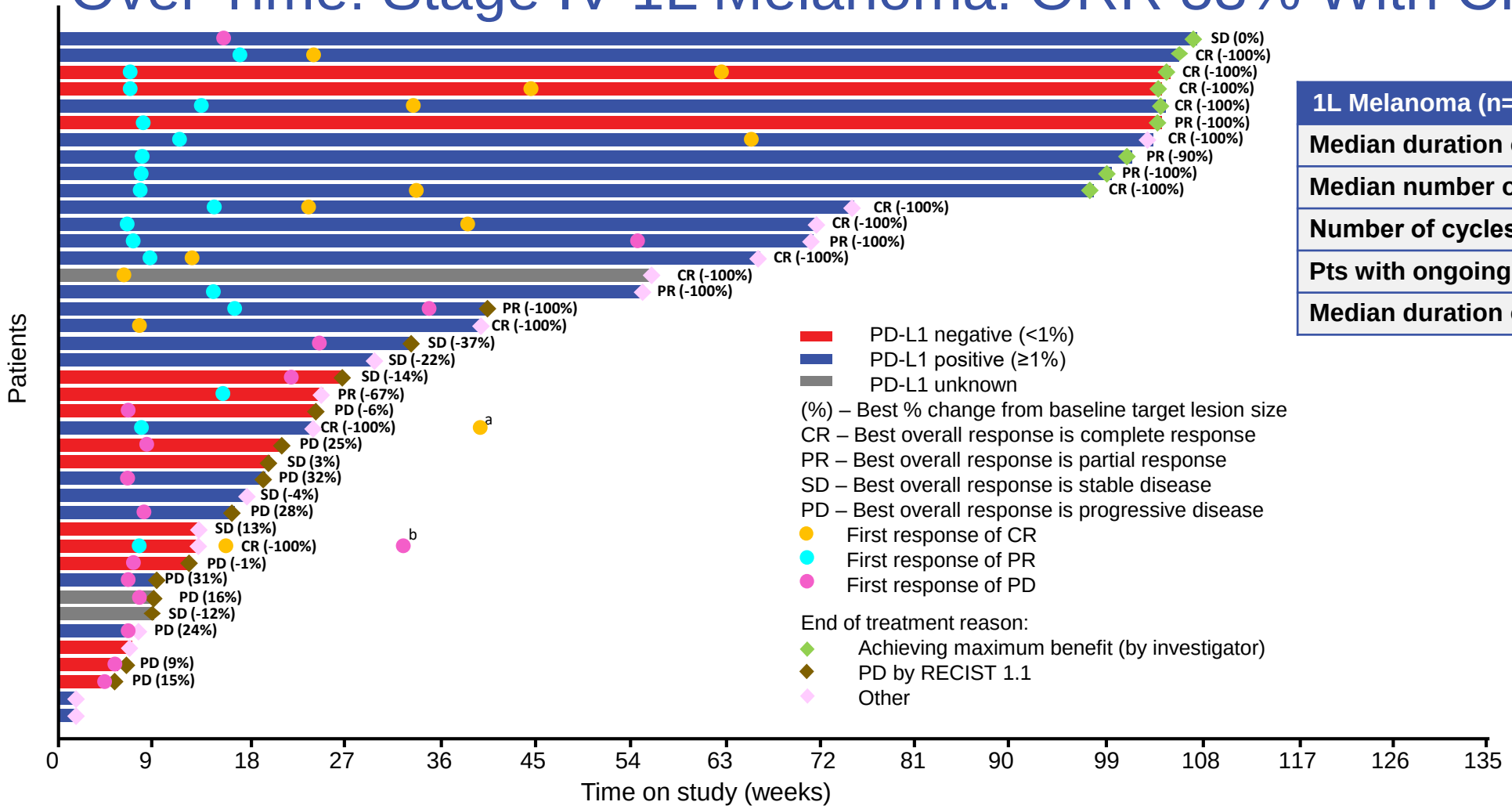


1L Melanoma (n=38 Efficacy Evaluable) Median 29.0 Months of Follow-up	ORR
Confirmed ORR (CR+PR)	**20 (53)**
CR	**13 (34)**
PD-L1 negative (n=13)	**5 (39)**
PD-L1 positive (n=22)	**14 (64)**
PD-L1 unknown (n=3)	**1 (33)**
LDH >ULN (n=11)	**5 (46)**
Liver metastases (n=10)	**5 (50)**
Median % reduction 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 1.1) at baseline and have ≥1 post-baseline tumor assessment. All objective responses are confirmed. #Best overall response is progressive disease due to non-target 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.

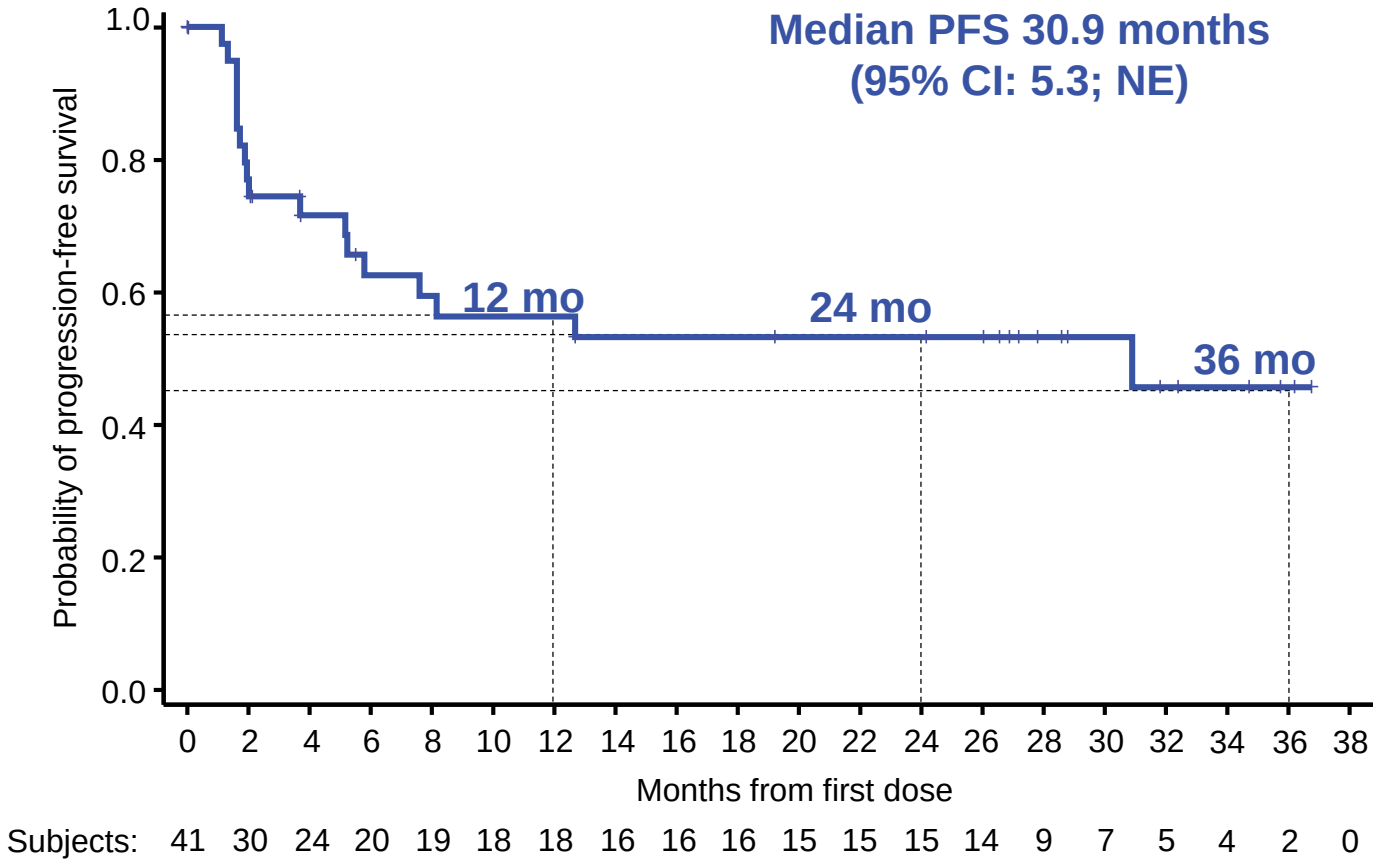
Responses With BEMPEG Plus NIVO Were Durable and Deepened Over Time: Stage IV 1L Melanoma: ORR 53% With CR 34%



1L Melanoma (n=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)
Pts 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 (QoL issues); achieved CR in May 2018; disease relapse in Sept 2018 due to new lesion (brain). EoT, end of treatment; NE, not estimable; PD-L1, programmed death-ligand 1.

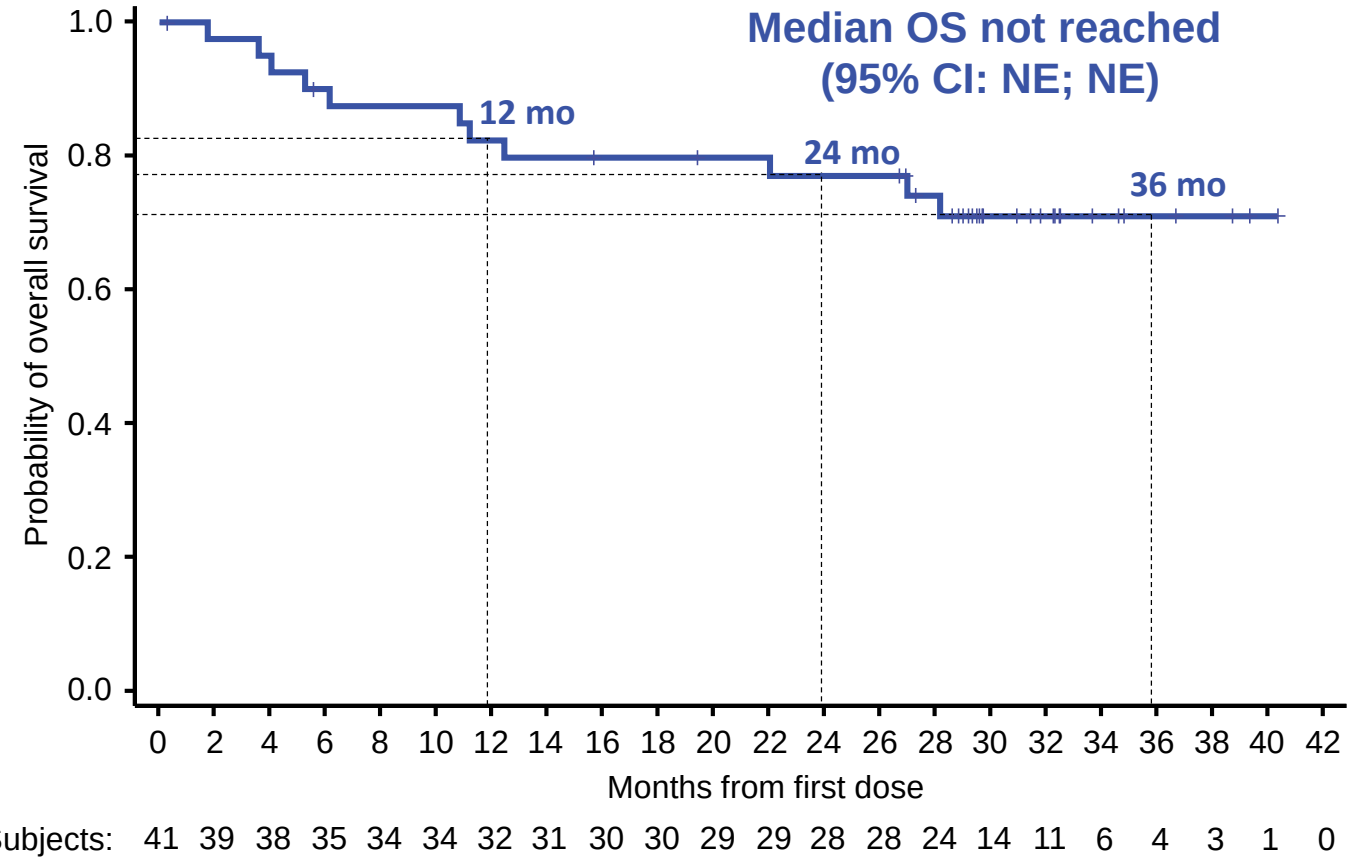
mPFS 30.9 Months (95% CI: 5.3; NE) at Median Follow-up of 29.0 Months



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.
BICR, blinded independent central radiology; NE, not estimable; mPFS, median progression-free survival.

mOS Not Reached (95% CI: NE, NE) at Median Follow-up of 29.0 Months

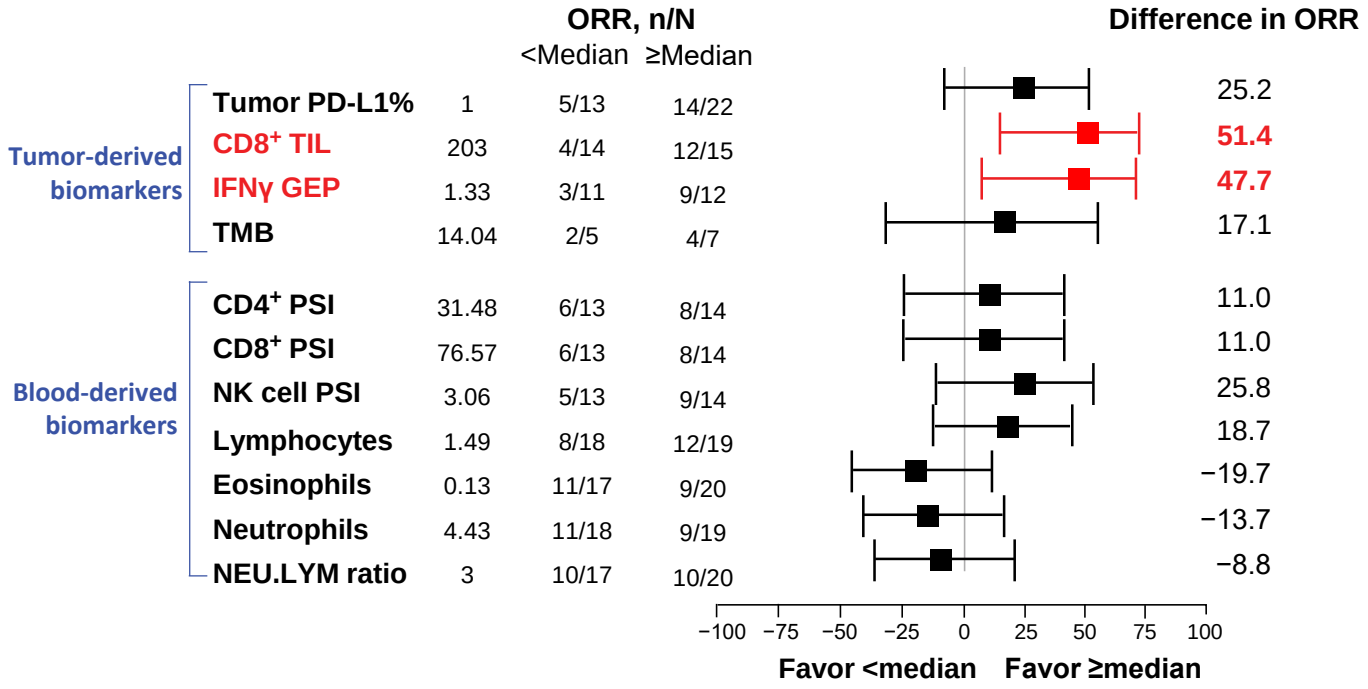


Kaplan–Meier Estimate of Overall Survival	Total (N=41)
Rate at 12 months, % (95% CI)	82.3 (66.4; 91.1)
Rate at 24 months, % (95% CI)	77.0 (60.4; 87.3)
Rate at 36 months, % (95% CI)	70.9 (53.5; 82.8)

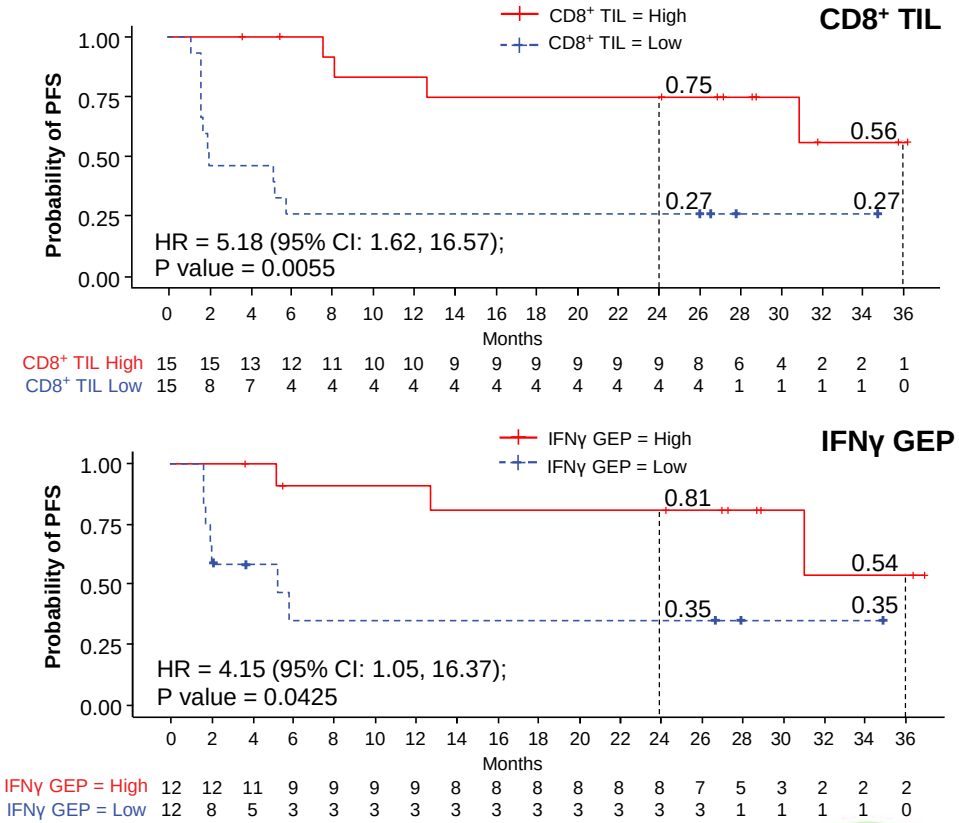
Data cutoff: 1SEPT2020.
NE, not estimable; mOS, median overall survival.

Relationship Between Baseline Biomarkers and Response

High CD8+ TIL and IFNγ GEP at baseline associated with higher ORR[a]



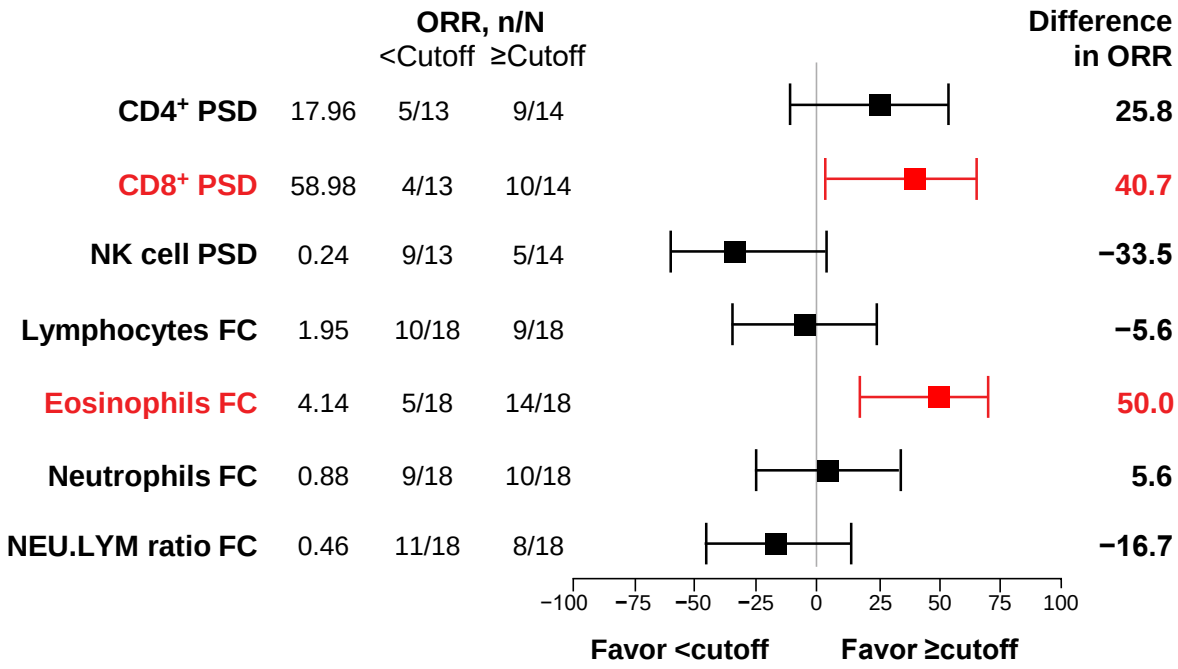
Increased CD8+ TIL and IFNγ GEP associated with longer PFS[b]



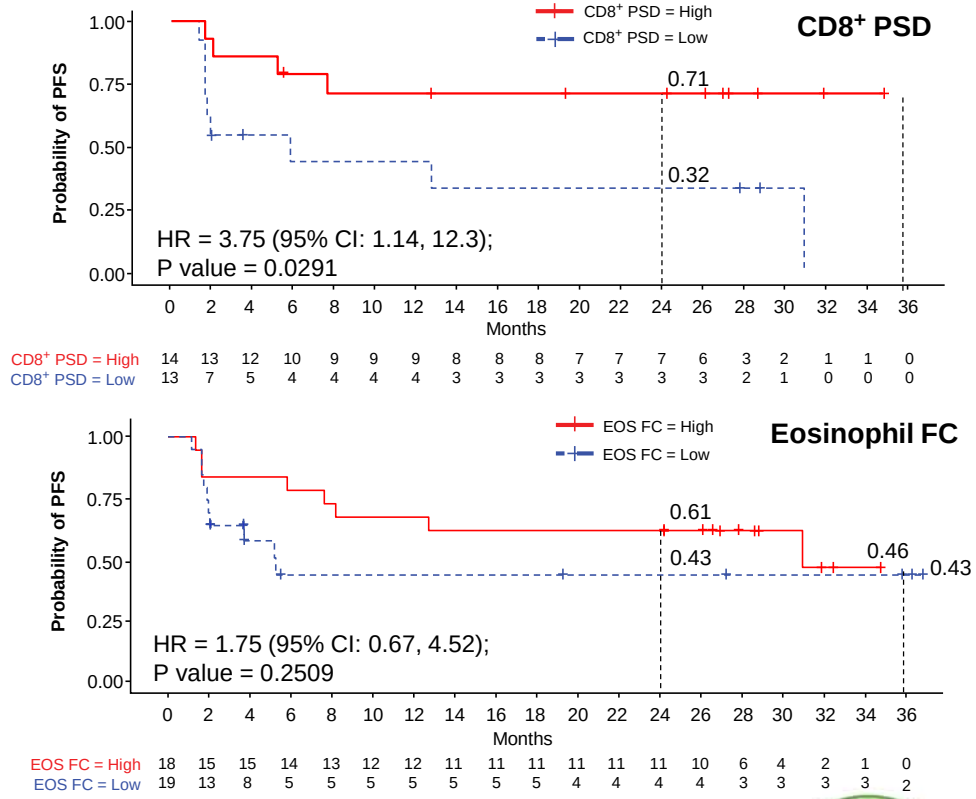
Data cutoff: 1SEPT2020. [a]Best overall response (RECIST 1.1) by BICR; median (≥median vs <median) cutoff for markers; efficacy-evaluable population, n=38. [b]CD8+ TIL and IFNγ GEP (high vs low by median cutoff); safety population (N=41). GEP, gene expression profile; NEU.LYM ratio, neutrophil to lymphocyte ratio; NK, natural killer; ORR, objective response rate; PFS, progression-free survival; PSI, polyfunctional strength index, using IsoPlexis technology; TIL, tumor-infiltrating lymphocyte; TMB, tumor mutational burden.

Relationship Between On-treatment (Day 8) Blood Biomarkers in Matched Samples and Response

Increased CD8+ PSD and eosinophils associated with higher ORR[a]



Increased CD8+ PSD, but not eosinophils associated with longer PFS[b]



Data cutoff: 1SEPT2020. [a]Best overall response (RECIST 1.1) by BICR; median (≥median vs < median) cutoff for markers; efficacy-evaluable population, n=38. [b]CD8+ PSD (high vs low by median cutoff); PFS, by BICR; safety population (N=41). EOS, eosinophils; FC, fold change at C1D8 vs C1D1; 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.

Conclusions

In previously untreated patients with metastatic melanoma in PIVOT-02:

- BEMPEG plus NIVO achieved deep and durable responses, with rates of complete response (34%) and median PFS (30.9 months) exceeding rates reported in clinical trials for approved treatments[1–6]
- BEMPEG plus NIVO is well tolerated; treatment-related AEs are predictable and consistent with previous reports
- Non-invasive, on-treatment biomarkers ($CD8^+$ PSD and eosinophils) predicted response to the combination, well before radiographic evidence
- This novel combination was awarded US FDA Breakthrough Therapy Designation
- 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)

1. Robert C, et al. *N Engl J Med* 2015;372:320–30; 2. Larkin J, et al. *N Engl J Med* 2019;381:1535–46; 3. Robert C, et al. *N Eng J Med* 2015;372:2521–32; 4.Ascierto PA, et al. *JAMA Oncol* 2019;5:187–94; 5. Larkin J, et al. *N Engl J Med* 2015;373:23–34; 6. Robert C, et al. *Lancet Oncol* 2019;20:1239–51.
AE, adverse event; FDA, U.S. Food and Drug Administration; PFS, progression-free survival; PSD, polyfunctional strength difference.

Acknowledgements

A special thank you to the patients, their families and all the study staff who are participating and have participated in the PIVOT-02 study

MD Anderson Cancer Center
- Adi Diab, MD
- Chantale Bernatchez, PhD
- Michael Wong, MD, PhD

Roswell Park Comprehensive Cancer Center
- Igor Puzanov, MD

Azienda Ospedaliera Universitaria Senese / UOC Immunoterapia Oncologica
- Michele Maio, MD

NYU Medical Oncology Associates,
- Daniel Cho, MD

University of Colorado Anschutz Cancer Center
- Karl Lewis, MD

Seattle Cancer Care Alliance
- Scott Tykodi, MD, PhD

University of California San Diego
- Greg Daniels, MD, PhD

Virginia Cancer Specialists
- Alexander Spira, MD

Inova Schar Cancer Institute
- Sekwong Jang, MD

Polish Mother's Memorial Hospital – Research Institute
- Ewa Kalinka, MD

Yale School of Medicine
- Michael Hurwitz, MD, PhD
- Mario Sznol, MD

Providence Cancer Institute
- Brendan Curti, MD

Study sponsored by Nektar Therapeutics & Bristol Myers Squibb
Medical writing assistance was provided by BOLDSCIENCE Inc. funded by Nektar Therapeutics


sitc
1985
35th ANNIVERSARY
2020
Reimagined
2020
SITC
NOVEMBER 9–14
sitc
Society for Immunotherapy of Cancer