P-047

PIVOT-12: A Phase 3 randomized study of adjuvant bempegaldesleukin (BEMPEG) plus nivolumab (NIVO) versus NIVO in completely resected cutaneous melanoma at high risk for recurrence

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BACKGROUND

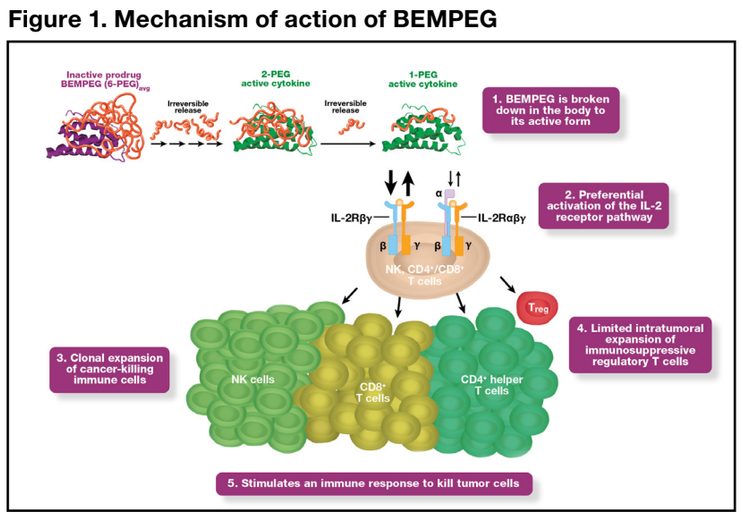
Adjuvant treatment of cutaneous melanoma

- Locally and regionally advanced cutaneous melanomas with lymph node involvement are at high risk for recurrence following surgical resection, which is associated with poor survival outcomes[1]
- Despite checkpoint inhibitor therapy as an effective adjuvant treatment option for resected stage III or IV cutaneous melanoma,[2] up to 48% of patients will have experienced disease recurrence by 4 years[3,4]
- There is an unmet need for novel adjuvant therapy combinations that have the potential to reduce or delay recurrence and extend survival in patients with resected cutaneous melanoma

BEMPEG signals preferentially through the IL-2R pathway

- Bempegaldesleukin (BEMPEG; NKTR-214) is a CD122-preferential IL-2 pathway agonist that has been engineered to deliver a controlled, sustained, and preferential IL-2 pathway signal[5]
- In animal models and in patients with cancer, BEMPEG induced increased proliferation and infiltration of $CD8^+$ cytotoxic T and natural killer cells without expansion of unwanted regulatory T cells in the tumor microenvironment (**Figure 1**)[6–8]
- In addition, BEMPEG has been shown to up-regulate PD-1, as well as its ligand PD-L1[6,8]
- BEMPEG plus nivolumab (NIVO) leverage two clinically validated complementary immuno-oncology pathways to create the potential for a greater antitumor immune response[8]

Figure 1. Mechanism of action of BEMPEG

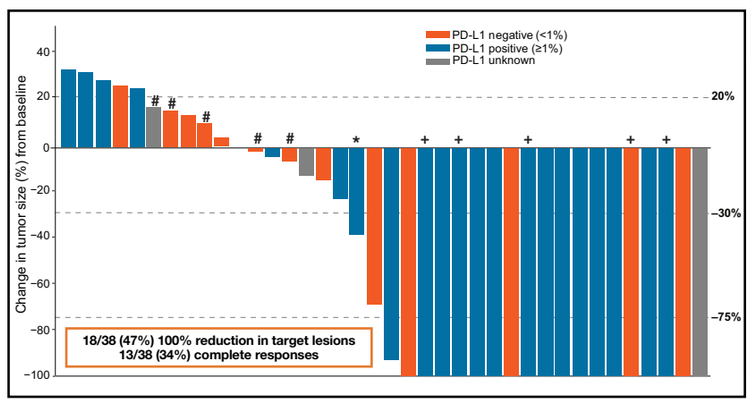


CD, cluster of differentiation; IL-2(R), interleukin-2 (receptor); NK, natural killer; PEG, releasable polyethylene glycol; Treg, regulatory T cell.

BEMPEG plus NIVO in melanoma

- The safety and clinical activity of BEMPEG plus NIVO were evaluated in the phase 2, first-line (1L) metastatic melanoma cohort of the PIVOT-02 trial (NCT02983045; N=41)[9]
  - Encouraging safety and preliminary clinical activity (**Figure 2**) were seen, including durable responses that deepened over time[9]
- BEMPEG plus NIVO received FDA Breakthrough Therapy Designation in July 2019 for patients with previously untreated, unresectable or metastatic melanoma
- PIVOT-12 (NCT04410445) is a registrational phase 3 trial evaluating BEMPEG plus NIVO as an adjuvant treatment after complete resection of melanoma in patients at high risk for recurrence

Figure 2. BEMPEG plus NIVO in stage IV 1L melanoma (PIVOT-02)[9]



1L Melanoma (N=41; n=38 efficacy evaluable) Median 29.0 months of follow-up	
Confirmed ORR (CR+PR), n (%)	20 (53)
CR, n (%)	13 (34)
Median PFS (mo)	30.9 (95% CI: 5.3; NE)
Median % change in tumor size from baseline	−78.5
Median time to response (mo)	2.0
Median time to CR (mo)	7.9

NCT02983045.

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, nontarget lesion still present. CI, confidence interval; CR complete response; mo, months; NE, not estimable; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

PIVOT-12: A PHASE 3 TRIAL OF BEMPEG PLUS NIVO IN ADJUVANT MELANOMA

Study design

- PIVOT-12 (NCT04410445) is a phase 3, global, multicenter, randomized, open-label study of BEMPEG plus NIVO as an adjuvant treatment for patients with completely resected cutaneous melanoma at high risk for recurrence (**Figure 3**)
- Approximately 950 patients will be randomized 1:1 to receive adjuvant BEMPEG plus NIVO (Arm A; 3-week cycles) or NIVO alone (Arm B; 4-week cycles)
- Patients will be treated for up to 1 year or until disease recurrence, death, unacceptable toxicity, decision by the investigator or patient to discontinue treatment, withdrawal of consent, loss to follow-up, or study termination

Objectives

Primary

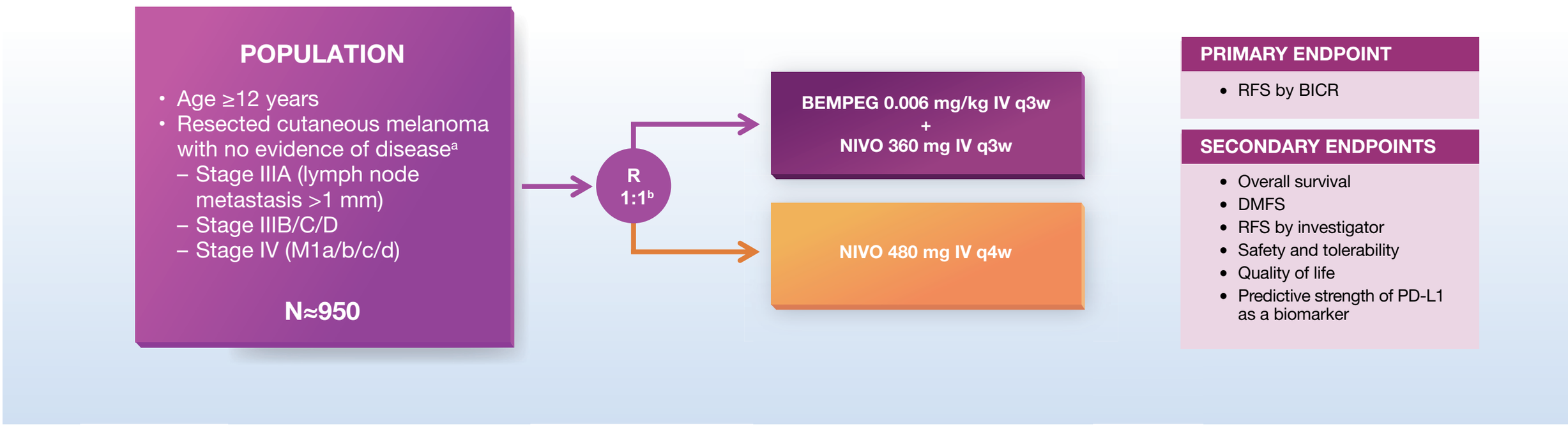
- Compare the efficacy of BEMPEG plus NIVO versus NIVO alone by assessing RFS[a] per BICR, up to approximately 60 months

Secondary

- Evaluate overall survival
- Evaluate DMFS[b] in patients with stage III disease at study entry
- Evaluate RFS per investigator assessment
- Assess the safety and tolerability of BEMPEG plus NIVO using the CTCAE v5.0
- Describe changes from baseline in patient-reported outcomes as assessed by the QLQ-C30 questionnaire
- Assess the predictive strength of PD-L1[c] expression as a biomarker, measured by RFS per BICR

[a]RFS was defined as the time between the date of randomization and the date of first recurrence, new primary melanoma, or all-cause death.
[b]DMFS was defined as the time between randomization and the date of first distant metastasis or date of death due to any cause, whichever occurs first.
[c]PD-L1 status determined by PD-L1 immunohistochemistry 28-8 pharmDx (Dako, an Agilent Technologies, Inc. company, Santa Clara, CA) on fresh or archival tumor.

Figure 3. PIVOT-12 study design – adjuvant therapy with BEMPEG plus NIVO in completely resected cutaneous melanoma at high risk for recurrence



NCT04410445.
[a]By American Joint Committee on Cancer (8th edition); [b]Randomization is stratified by PD-L1 status
BEMPEG, bempegaldesleukin (NKTR-214); BICR, blinded independent central review; DMFS, distant metastasis-free survival; IV, intravenous; NIVO, nivolumab; PD-L1, programmed death-ligand 1; q3w, every 3 weeks; q4w, every 4 weeks; R, randomized; RFS, recurrence-free survival.

Eligibility criteria

Key inclusion criteria

- ✔ Age ≥12 years (age ≥18 years where local regulations or institutional policies do not allow for patients age <18 years to participate)
- ✔ Histologically confirmed stage IIIA (lymph node metastasis >1 mm), IIIB/C/D, or IV (M1a/bc/d) cutaneous melanoma (AJCC, 8th edition) that has been completely surgically resected (no evidence of disease) within 12 weeks prior to randomization
- ✔ Tumor tissue must be provided for central analysis of PD-L1 expression
- ✔ Confirmed disease-free status documented by a complete physical examination and imaging studies within 28 days prior to randomization

Key exclusion criteria

- ✘ Prior therapy for melanoma (except surgery for melanoma and/or adjuvant radiation for central nervous system lesions)
- ✘ Prior treatment with interferon, talimogene laherparepvec, IL-2-directed therapy, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways
- ✘ History of ocular/uveal melanoma or mucosal melanoma
- ✘ Active, known, or suspected autoimmune disease
- ✘ Conditions requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization
- ✘ Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured

Status

- The PIVOT-12 study is open for enrollment, with close to 100 active or planned sites globally (**Figure 4**)
- Please visit ClinicalTrials.gov and search for NCT04410445 to find out the latest information on this study

Figure 4. Countries with active or planned PIVOT-12 clinical trial sites

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ABBREVIATIONS

1L, first-line; AJCC, American Joint Committee on Cancer; BEMPEG, bempegaldesleukin (NKTR-214); BICR, blinded independent central review; CD, cluster of differentiation; CTCAE, Common Terminology Criteria for Adverse Events; DMFS, distant metastasis-free survival; FDA, U.S. Food & Drug Administration; NIVO, nivolumab; PD-(L)1, programmed death-(ligand) 1; QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; RFS, recurrence-free survival.

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