TPS9601

# PIVOT IO 001 (CA045-001): A Phase 3, Randomized, Open-Label Study of Bempegaldesleukin (NKTR-214) Plus Nivolumab (NIVO) Versus NIVO Monotherapy in Patients With Previously Untreated, Unresectable or Metastatic Melanoma

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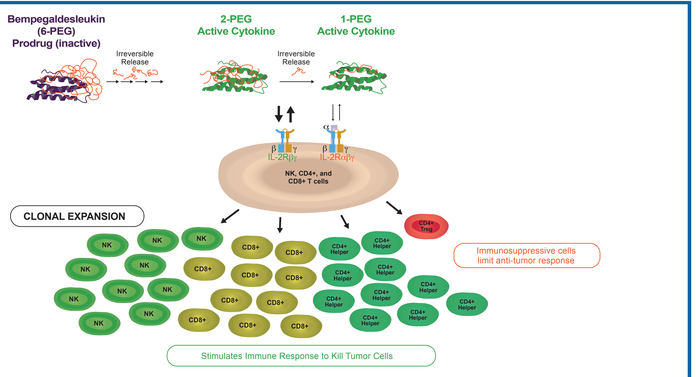
## Background

- Immune checkpoint inhibitors are a standard of care for patients with unresectable or metastatic melanoma, demonstrating durable survival benefit[1,2]
- High-dose interleukin-2 (IL-2) monotherapy has shown efficacy, including complete responses, in patients with metastatic melanoma. However, its use is limited by toxicities and inpatient drug administration[3]
- Bempegaldesleukin is a CD122-preferential IL-2 pathway agonist designed to provide sustained signaling through the IL-2βγ receptor (**Figure 1**)[4-6]

**Figure 1. Bempegaldesleukin preferential signaling through the IL-2βγ receptor pathway[4]**




IL-2, interleukin-2; NK, natural killer; PEG, polyethylene glycol; Treg, regulatory T cell.

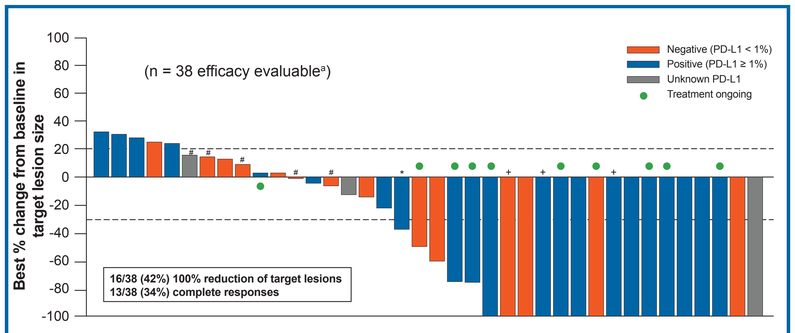
## PIVOT IO 001 Rationale

- In preclinical studies, the combination of bempegaldesleukin and an anti-programmed death 1 agent demonstrated a deeper and more sustained reduction in tumor growth compared with either therapy alone[5]

### PIVOT-02 (NCT02983045) bempegaldesleukin + NIVO combination study

- PIVOT-02 is an ongoing, phase 1/2 study evaluating the safety and efficacy of bempegaldesleukin + NIVO in a range of solid tumors[7]
  - In immuno-oncology–naive patients with melanoma, renal cell carcinoma, or urothelial carcinoma, the combination demonstrated clinical activity[8-10]
- In patients with previously untreated, metastatic melanoma, bempegaldesleukin + NIVO was well tolerated and demonstrated deep and durable responses (**Figure 2** and **Table 1**)[8,9]
  - Safety (n = 41; data cutoff date: October 1, 2018; median duration of follow-up: 7.2 months)[8]
    - Most common (> 50%) grade 1/2 treatment-related adverse events (TRAEs): flu-like symptoms (78%), rash (71%), and fatigue (63%)
    - Grade 3-4 TRAEs: 20%
    - Discontinuations due to TRAEs: 5%
  - Efficacy (n = 38 efficacy evaluable patients with ≥ 1 post-baseline scans; data cutoff date: March 29, 2019; median duration of follow-up: 12.7 months)[9]
    - Patients with ongoing responses = 80% (16 out of 20 responders)
    - Responses were observed across programmed death ligand 1 (PD-L1) expression levels (PD-L1 < 1% and PD-L1 ≥ 1%)

**Figure 2. PIVOT-02: best percent change from baseline in target lesion size with bempegaldesleukin + NIVO in patients with previously untreated, metastatic melanoma by independent radiology[9]**




[#]Best overall response is PD 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.
[a]Efficacy evaluable population includes patients who have measurable disease (per RECIST 1.1) at baseline and also ≥ 1 post-baseline assessment of tumor response. n = 41 ITT. 3 patients are excluded because they are not response evaluable: 1 patient discontinued treatment after 1 dose due to an unrelated AE (myocardial infarction); 1 patient discontinued treatment after 1 dose due to patient decision; 1 patient discontinued treatment after 3 doses due to patient decision.
AE, adverse event; CR, complete response; ITT, intent-to-treat; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

**Table 1. PIVOT-02: response rates to bempegaldesleukin + NIVO in patients with previously untreated, metastatic melanoma by independent radiology[9]**

| 1L Melanoma (n = 38 efficacy evaluable[a]) | ORR, n (%) |
|---|---|
| **Confirmed ORR (CR + PR)** | 20 (53) |
| CR | 13 (34) |
| DCR (CR + PR + SD) | 28 (74) |
| PD-L1 negative (n = 14) | 6 (43) |
| PD-L1 positive (n = 21) | 13 (62) |
| PD-L1 unknown (n = 3) | 1 (33) |
| LDH > ULN (n = 11) | 5 (45) |
| Liver metastases (n = 10) | 5 (50) |

[a]Efficacy evaluable population includes patients who have measurable disease (per RECIST 1.1) at baseline and also have ≥ 1 post-baseline assessment of tumor response.
1L, first-line; CR, complete response; DCR, disease control rate; LDH, lactate dehydrogenase; ORR, objective response rate; PD-L1, programmed death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; ULN, upper limit of normal.

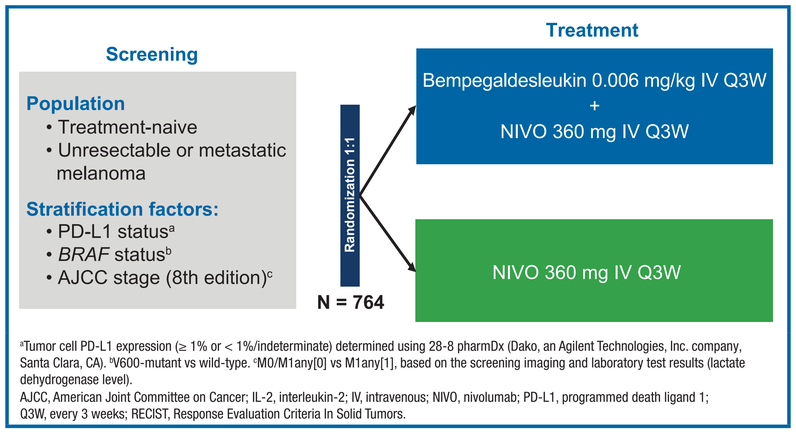
## PIVOT IO 001 Objective

- PIVOT IO 001 is designed to evaluate the efficacy and safety of bempegaldesleukin + NIVO in patients with previously untreated, unresectable or metastatic melanoma

## PIVOT IO 001 Study Design

- PIVOT IO 001 (NCT03635983) is a global, phase 3, randomized, open-label study of bempegaldesleukin + NIVO versus NIVO monotherapy in patients with previously untreated, unresectable or metastatic melanoma (**Figure 3**)

**Figure 3. PIVOT IO 001 study design**




[a]Tumor cell PD-L1 expression (≥ 1% or < 1%/indeterminate) determined using 28-8 pharmDx (Dako, an Agilent Technologies, Inc. company, Santa Clara, CA). [b]V600-mutant vs wild-type. [c]M0/M1any[0] vs M1any[1], based on the screening imaging and laboratory test results (lactate dehydrogenase level).
AJCC, American Joint Committee on Cancer; IL-2, interleukin-2; IV, intravenous; NIVO, nivolumab; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

- Key patient inclusion and exclusion criteria are shown in **Table 2**

**Table 2. PIVOT IO 001 key eligibility criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| • ECOG PS ≤ 1 (adults aged 18 years or older)/Lansky performance score ≥ 80% (minors aged 12-17 years only)<br>• Histologically confirmed unresectable or metastatic melanoma<br>• No prior systemic anticancer therapy for unresectable or metastatic melanoma<br>– Patients on prior adjuvant treatment with approved agents are eligible<br>• Patients having a recurrence < 6 months after completing adjuvant treatment are not eligible | • Active brain metastases or leptomeningeal metastases<br>• Uveal melanoma<br>• Active, known or suspected autoimmune disease |

ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria In Solid Tumors.

- Primary, secondary, and exploratory outcome measures are shown in **Table 3**

**Table 3. PIVOT IO 001 key study endpoints**

| Primary endpoints | Key secondary endpoints | Key exploratory endpoints |
|---|---|---|
| • ORR[a]<br>• PFS[a]<br>• OS | • ORR[b]<br>• ORR (biomarker population)[a,c]<br>• PFS[b]<br>• PFS (biomarker population)[a,c]<br>• OS (biomarker population)[c]<br>• DoR[b,d]<br>• TTR[b,d]<br>• Safety and tolerability | • Pharmacokinetics parameters<br>• Patient-reported outcomes |

[a]By BICR. [b]By investigator per RECIST 1.1. [c]Biomarker population includes all randomized participants who have biomarker data available at baseline. [d]By BICR per RECIST 1.1. BICR, blinded independent central review; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to response.

### PIVOT IO 001 recruitment status

- The trial is currently enrolling eligible patients (**Figure 4**)
- Estimated primary completion date: August 15, 2023

**Figure 4. Countries participating in PIVOT IO 001**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