PROPEL: A phase 1/2 trial of bempegaldesleukin (NKTR-214) in combination with pembrolizumab in patients with advanced solid tumors

Poster: 127TiP

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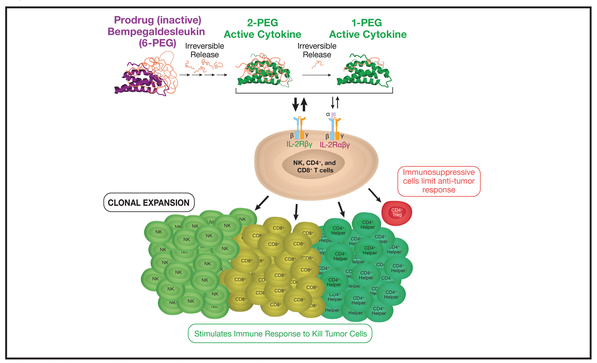
BACKGROUND

- Checkpoint inhibitors (CPIs) are activators of the immune system with proven capabilities of prolonging survival;[1–3] they form part of standard treatment for many advanced solid tumors, including non-small cell lung cancer (NSCLC).
- CPIs directed against programmed cell death receptor-1 (PD-1), such as pembrolizumab (pembro), depend on PD-1 ligand (PD-L1) expression and pre-existing T-cell infiltration within the tumors for optimal efficacy.[4,5]
  - In NSCLC, the objective response rate (ORR) with pembro monotherapy was 19% in an unselected patient population, with strong PD-L1 expression (≥50%) associated with higher ORR, longer progression-free survival and longer overall survival.[6]
- There is an unmet need in NSCLC for more effective CPI combinations to broaden, deepen, and prolong responses, especially for patients with poor prognostic features or negative predictive clinical factors for CPI benefit, including PD-L1-negative(–) status.

BEMPEG

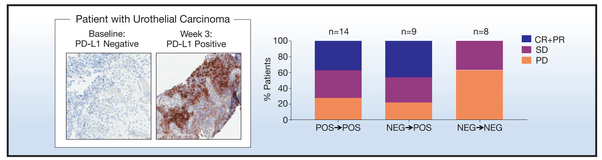
- Bempegaldesleukin (BEMPEG; NKTR-214) is a CD122-preferential interleukin-2 (IL-2) pathway agonist shown to increase tumor-infiltrating lymphocytes, T-cell clonality, and PD-L1 expression **(Figure 1)**.[7,8]
- Safety and clinical activity of BEMPEG plus the CPI, nivolumab (NIVO), were evaluated in PIVOT-02, a multicenter phase 1/2 study in various advanced solid tumors.[9–13]
  - The combination was tolerable and showed encouraging clinical activity, regardless of baseline PD-L1 status,[12] with durable responses that deepened over time.[13]
  - The recommended phase 2 dose (RP2D) was defined as BEMPEG 0.006 mg/kg plus NIVO 360 mg q3w.[9] However, proactive implementation of adverse event management guidelines may allow for higher doses of BEMPEG to be used in future studies.
  - BEMPEG plus NIVO was shown to convert baseline tumors from PD-L1(–) to PD-L1(+),[9–12] which was associated with clinical benefit **(Figure 2)**.[9]
  - Based on these data, BEMPEG + NIVO received Breakthrough Therapy Designation from the US Food and Drug Administration for patients with previously untreated, unresectable or metastatic melanoma.
- In this Phase 1/2 dose-optimization and -expansion trial, we will evaluate the safety and tolerability, and efficacy of BEMPEG plus pembro in patients with locally advanced or metastatic solid tumors, including NSCLC.

Figure 1. Mechanism of action of BEMPEG



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

Figure 2. BEMPEG plus NIVO-induced conversion of tumors from PD-L1– to PD-L1+ is associated with clinical benefit[7]



31 patients were available with matched baseline and week 3 results for PD-L1 status. Of these, 17 were PD-L1 negative at baseline. PD-L1 was assessed on tumor cells using a validated 28-8 method. Example image shown for a patient with urothelial carcinoma at baseline and week 3, 20x magnification.
CR, complete response; NEG, negative; PD, progressive disease; PD-L1, programmed cell death ligand-1; POS, positive; PR, partial response; SD, stable disease.

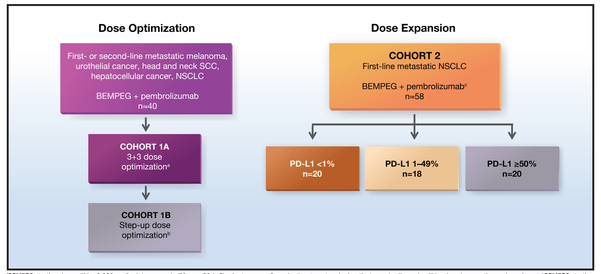
Diab A, *et al. J Clin Oncol* 2018;36(15 suppl):3006.

STUDY

Design

- PROPEL is a Phase 1/2 multinational trial of BEMPEG plus pembro in patients with locally advanced or metastatic solid tumors **(Figure 3)**.
- In the dose-optimization part (United States only), patients with selected advanced or metastatic solid tumors will be treated with escalating doses of BEMPEG plus pembro according to a 3+3 (Cohort 1a) or step-up (Cohort 1b) design to determine the maximum tolerated dose (MTD).
- In the dose-expansion part (global; Cohort 2), patients with untreated advanced or metastatic NSCLC, regardless of PD-L1 status, will be treated with BEMPEG plus pembro.
  - Patients will be stratified according to PD-L1 status: PD-L1 negative (<1% staining on tumor cell by immunohistochemistry), PD-L1 low/intermediate (1–49%), and PD-L1 highly positive (≥50%).

Figure 3. Study design



[a]BEMPEG starting dose will be 0.008 mg/kg intravenously (IV) over 30 (±5) minutes every 3 weeks (treatment cycle duration); pembrolizumab will be dosed as per the package insert. [b]BEMPEG starting dose will be the previously tolerated dose from the 3 + 3 dosing schema as determined by the Safety Review Committee (SRC) – it will be administered IV over 30 (±5) minutes every 3 weeks (treatment cycle duration); this dose may increase at each cycle for individual patients by increments of 0.002 mg/kg; pembrolizumab will be dosed as per the package insert. [c]BEMPEG starting dose will be 0.006 mg/kg IV over 30 (±5) minutes every 3 weeks (treatment cycle duration); pembrolizumab will be dosed as per the package insert. Based on the SRC's review of data from Cohort 1, additional patients in this cohort may receive the dose as established by the dose optimization cohorts. NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; SCC, squamous cell carcinoma.

Assessments

- Safety assessments will include adverse events, clinical laboratory tests, vital signs, physical exams, and electrocardiograms.
- Blood samples for pharmacokinetic analyses will be collected from all patients.
- Systemic and tumor tissue-based pharmacodynamic effects of BEMPEG plus pembro will be evaluated.
- Tumor measurements will be performed every 9 weeks ± 7 days.

Objectives

Primary objectives

- Part 1 (dose optimization):
  - To evaluate the safety and tolerability of BEMPEG plus pembro.
  - To define the MTD/RP2D and optimal dosing schedule of BEMPEG plus pembro.
- Part 2 (dose expansion):
  - To determine the ORR by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 of BEMPEG plus pembro in patients with untreated advanced or metastatic NSCLC.

Secondary objectives

- To evaluate safety and tolerability of BEMPEG plus pembro in patients with untreated advanced or metastatic NSCLC (dose expansion only).
- To assess the preliminary efficacy of BEMPEG plus pembro.
  - Measured as ORR, duration of response, clinical benefit rate, time to response, progression-free survival (all according to RECIST version 1.1), and overall survival.

Eligibility criteria

Key inclusion criteria

- Age ≥18 years.
- Measurable disease per RECIST 1.1.
- Tumor type as defined in **Table 1**.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Received no more than one prior line of systemic therapy for locally advanced or metastatic cancer.
- Oxygen saturation ≥92% on room air (all indications); oxygen saturation ≥90% on room air for lung cancer considered to be due to lung metastasis.
- Life expectancy >12 weeks.
- Adequate organ function.
- Tumor tissue sample: fresh or archival.
- Patients with brain metastases are eligible if certain criteria are met.

Key exclusion criteria

- Prior IL-2 therapy (dose expansion cohort only).
- Prior treatment with an immune CPI for advanced/metastatic disease.
- Active, known, or suspected autoimmune disease.
- Evidence of clinically significant interstitial lung disease or active noninfectious pneumonitis.
- History of unstable or deteriorating cardiac disease.

Table 1. Eligible tumor types

Tumor type	Stage	Line of treatment (metastatic setting)	PD-L1 status
DOSE OPTIMIZATION			
Melanoma	Stage III (unresectable) or Stage IV (metastatic)	1st and 2nd	Any
Urothelial carcinoma	Locally advanced or metastatic	1st and 2nd	Any
Head and neck squamous cell carcinoma	Recurrent and unresectable or metastatic	1st and 2nd	Any
Hepatocellular carcinoma	Locally advanced or metastatic	1st and 2nd	Any
Non-small cell lung cancer	Stage IV (metastatic)	1st and 2nd	Any
DOSE EXPANSION			
Non-small cell lung cancer	**Stage IIIb (recurrent) or Stage IV (metastatic)**	**1st**	**Any**

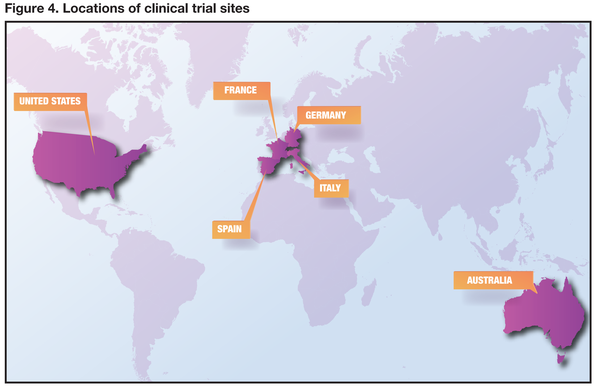
Dose expansion only (1L NSCLC)

- Histologically or cytologically confirmed diagnosis of advanced or metastatic NSCLC.
- Tumor tissue (fresh or archival) available for central PD-L1 testing.
- Must not be eligible to receive epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-directed therapy.
- Must not have received prior treatment for advanced or metastatic NSCLC.
  - Prior adjuvant and/or neoadjuvant treatment is allowed.
- Must not have progressed on or within 6 months of completing adjuvant PD-L1 therapy.
- Must undergo a brain magnetic resonance imaging at screening.

Status

- Enrollment is ongoing in the United States, and will open shortly for the dose-expansion cohort in Europe and Australia **(Figure 4)**.
- The trial is registered with ClinicalTrials.gov, NCT03138889, and the European Clinical Trials Register, 2019-003474-35.

Figure 4. Locations of clinical trial sites



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