Abstract 1548

PROPEL: A phase 1/2 trial of bempegaldesleukin (BEMPEG; NKTR-214) plus pembrolizumab in lung cancer and other advanced solid tumours

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Bempegaldesleukin, in combination with pembrolizumab, is an investigational combination therapy and is not currently approved by the US FDA or other regulatory authorities

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Background: CPIs and Unmet Need in Advanced NSCLC

- CPIs have become a standard treatment for many cancers, including advanced NSCLC[1]
- However, they have shown limited efficacy as a single agent in patients with low or no (negative) PD-L1 expression[2]

There is an unmet need for novel immunotherapy agents for patients who are unlikely to respond to CPI (with low or negative PD-L1 expression) and to provide deeper, prolonged responses in those who do respond

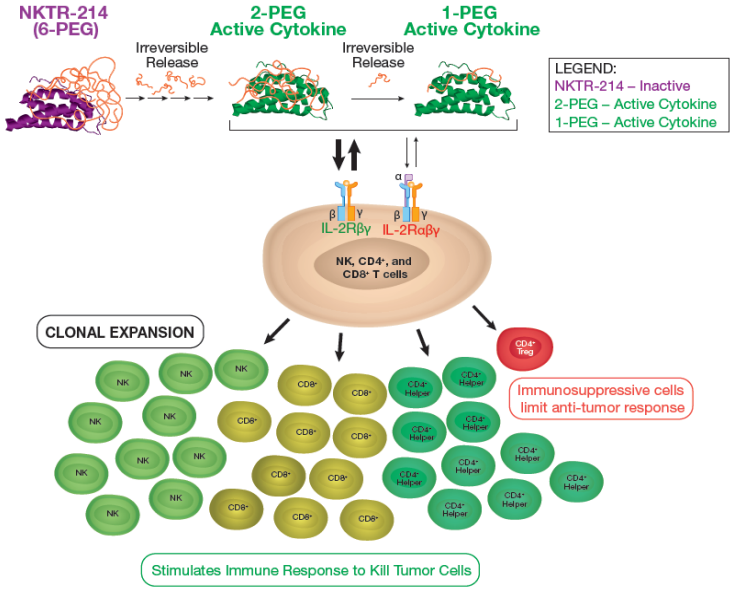
1L, first line; CPI, checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

1. NCCN Clinical Practice Guidelines in Oncology in NSCLC: version 6.2020; June 15, 2020; 2. Garon EB, et al. *N Engl J Med* 2015;372:2018–2028.

Background: Bempegaldesleukin

- Bempegaldesleukin (BEMPEG; NKTR-214) is a first-in-class CD122-preferential IL-2 pathway agonist[1–4]
- It directly activates and expands effector T cells and natural killer cells without increases in immunosuppressive regulatory T cells[1,2,5]

Mechanism of Action of BEMPEG[3,4]



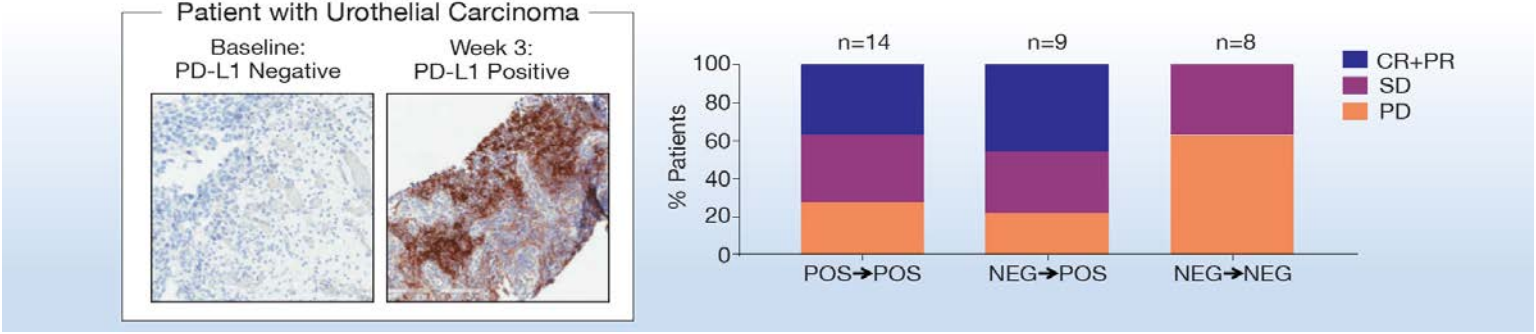
CD, cluster of differentiation; CPI, checkpoint inhibitor; IL, interleukin; NK, natural killer cell;
NSCLC, non-small cell lung cancer; PEG, releasable polyethylene glycol; PD-L1, programmed death-ligand 1; Treg, T-regulatory cell.

1. Bentebibel SE, et al. *Cancer Discov* 2019;9:711–721; 2. Sharma M, et al. *Nat Commun* 2020;11(1):661; 3. Diab A, et al. *J Clin Oncol* 2018;36(15 suppl):3006;
4. Charych DH, et al. *PLoS ONE* 2017;12(7):e0179431; 5. Charych DH, et al. *Clin Cancer Res* 2016;22:680–690.

Background: Bempegaldesleukin Plus Nivolumab

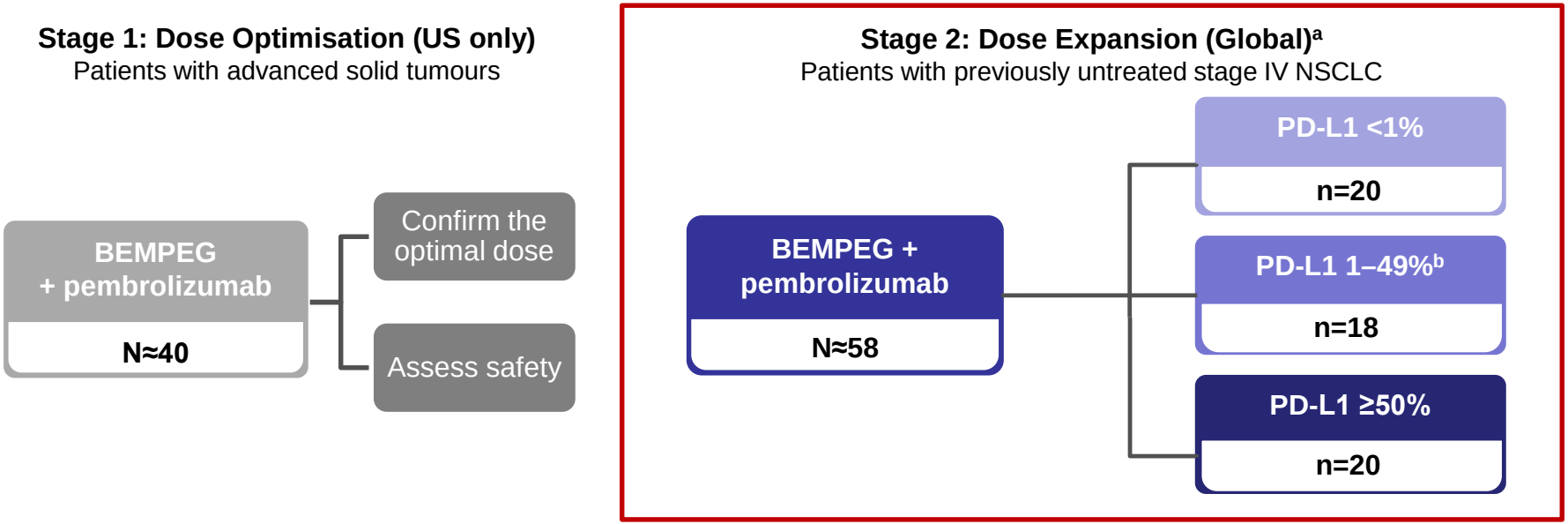
- BEMPEG has previously been combined with nivolumab, demonstrating promising efficacy[1,2]
- This combination has been shown to convert baseline tumours from PD-L1 non-expressing to PD-L1 expressing[1]

BEMPEG plus nivolumab-induced conversion of tumours from PD-L1– to PD-L1+ is associated with clinical benefit[1]



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 tumour 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.
1. Diab A, et al. *Cancer Discov* 2020;10(8):1158-73; 2. Diab A, et al. *J Clin Oncol* 2018;36(15 suppl):3006.

PROPEL: Phase 1/2 Study Design



[a]Patients will be treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, lost to follow up, investigator or patient decision to discontinue treatment, withdrawal of consent or termination of the study by the sponsor. [b]In France, patients in subgroup PD-L1 < 1-49% will be excluded.
PD-L1, programmed death-ligand 1; Q3W, every 3 weeks.
ClinicalTrials.gov. NCT03138889. https://clinicaltrials.gov/ct2/show/NCT03138889. Accessed January 7, 2021.

Study Assessments

Safety assessments include adverse events, clinical laboratory tests, vital signs and physical exams

Blood samples for pharmacokinetic analyses from all patients

Systemic and tumour tissue-based pharmacodynamic effects of BEMPEG plus pembrolizumab

Blood samples (plasma and serum) for exploratory biomarker analyses for CVA characterisation at baseline and at the time of a new CVA event

Tumour assessments every 9 weeks ± 7 days from Cycle 1, Day 1

CVA, cerebrovascular accident.

Endpoints

Stage 1: Dose Optimisation (US only)[a]

Patients with advanced solid tumours

Primary endpoints

- Safety and tolerability
- RP2D/MTD
- Optimal dosing schedule

Secondary endpoints

- ORR, CBR, DOR, TTR, PFS, OS
- Assess the association between efficacy measures and PD-L1 expression in tumours

Stage 2: Dose Expansion (Global)[a]

Patients with previously untreated stage IV NSCLC

Primary endpoints

- ORR

Secondary endpoints

- Safety and tolerability
- CBR, DOR, TTR, PFS, OS
- Assess the association between efficacy measures and PD-L1 expression in tumours

[a]All efficacy parameters assessed by RECIST v1.1 expect OS.

CBR, clinical benefit rate; DOR, duration of response; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid tumours; TTR, time to response.RP2D, recommended Phase 2 dose.

Key Eligibility Criteria

- Age ≥18 years
- Measurable disease per RECIST 1.1
- Advanced solid tumours
- ECOG PS of 0 or 1
- Life expectancy >12 weeks
- Patients must not have progressed within 6 months of receiving radiation, surgery, adjuvant, neoadjuvant, or systemic therapy for cancer treatment
- Oxygen saturation ≥ 92% on room air for all indications
- Tumour tissue sample: fresh or archival
- Patients with brain metastases are eligible if certain criteria are met

Dose-expansion cohort (NSCLC)

- Histologically or cytologically confirmed diagnosis of stage IV NSCLC
- No known EGFR, ROS1, BRAF v600E or ALK genomic tumour aberrations
- Must not have received prior treatment for metastatic NSCLC or immunotherapy, including IL-2 therapy
- Must undergo a brain MRI at screening

ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IL, interleukin; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid tumours; ROS1, c-ros oncogene 1.

Eligible Tumour Types

Tumour type	Stage	Line of treatment (metastatic setting)	PD-L1 status
DOSE OPTIMISATION			
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 IV (metastatic)**	**1st**	**Any**

PD-L1, programmed death-ligand 1.

Conclusions: Study Status

- The Phase 1/2 PROPEL study (NCT03138889) evaluates safety and tolerability and assesses the preliminary clinical benefit of the investigational CD122-preferential IL-2 pathway agonist, BEMPEG plus pembrolizumab[1,2]

- As of December 17, 2020, the PROPEL study has completed its enrollment in the NSCLC Dose Expansion part of the study
  - Expansion of this study and new study arms are planned and will be open to enrollment soon

- The trial is registered with ClinicalTrials.gov, NCT03138889, and the European Clinical Trials Register, 2019-003474-35

NSCLC, non-small cell lung cancer.

1. ClinicalTrials.gov. NCT03138889. https://clinicaltrials.gov/ct2/show/NCT03138889. Accessed January 7, 2021; 2. Charych D, et al. *PLoS One* 2017;12:e0179431.

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