A Phase 3 Randomized Open-label Study Comparing Bempegaldesleukin (NKTR-214) Plus Nivolumab to Sunitinib or Cabozantinib (Investigator's Choice) in Patients With Previously Untreated Advanced Renal Cell Carcinoma

Abstract TPS4595

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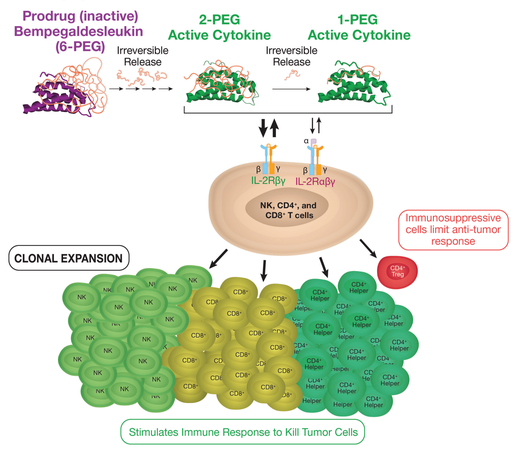
BACKGROUND

- High-dose interleukin-2 (IL-2; aldesleukin) has been an important therapy for advanced renal cell carcinoma (RCC) where it elicits immune-mediated durable responses, including complete responses and potential cure in up to 9% of treated patients[1-3]; however, its use is highly limited by its toxicity
- Bempegaldesleukin is a first-in-class IL-2 receptor pathway agonist that leverages the IL-2 pathway to stimulate peripheral and tumor immune responses (**Figure 1**)[4,5]
  - Inactive prodrug (IL-2 releasably conjugated to an average of 6 polyethylene glycol [PEG] polymers; 6_{avg}-PEG-IL-2)
  - The active cytokines (2-PEG-IL-2 and 1-PEG-IL-2) directly activate and expand effector T cells and natural killer (NK) cells by preferentially binding to the CD122 (IL-2Rβγ) subunit of the IL-2 receptor
  - Gradual release of PEG chains *in vivo* leads to sustained exposure to these active IL-2 cytokines

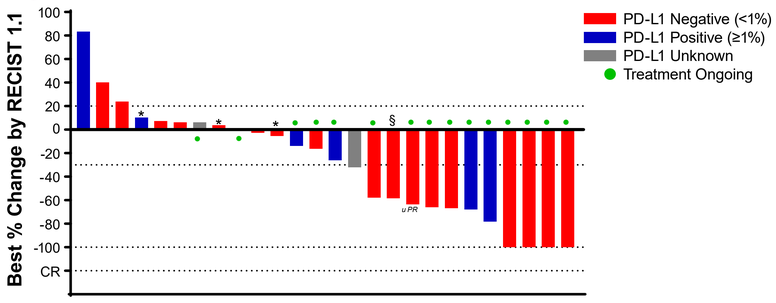
Figure 1: Bempegaldesleukin Preferential Signaling Through IL-2Rβγ



STUDY RATIONALE

- First-line therapy for advanced RCC is rapidly evolving, and preferred regimens[6] currently include:
  - Monotherapy with tyrosine kinase inhibitors (TKI) of angiogenesis (sunitinib or cabozantinib)[7,8]
  - Combination of immune checkpoint inhibitors (ICIs) (nivolumab + ipilimumab)[9]
  - Combination of TKI and ICI (axitinib + pembrolizumab or avelumab)[10,11]
- In a phase 2 clinical study, bempegaldesleukin + nivolumab demonstrated encouraging efficacy in frontline advanced RCC independent of PD-L1 status (**Figure 2**)[12]
  - Objective response rate (ORR) of 46% (12/26 patients with complete or partial response)
  - 53% (9/17) ORR in RCC patients with tumors lacking PD-L1 expression
- The combination of bempegaldesleukin + nivolumab was generally well tolerated among patients with different tumor types (N=283)[12]
  - Most common treatment-related adverse events (TRAEs) were low-grade cytokine-related events (flu-like symptoms [59%], rash [45%], fatigue [42%], pruritis [31%])
  - Grade ≥3 TRAEs 14%
  - Low rate of discontinuation due to TRAEs (2%)
- Bempegaldesleukin + nivolumab offers a potential novel combination immuno-oncology treatment option for patients with advanced RCC

Figure 2: Clinical Data in First-Line RCC Patients



Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria; -100% is PR for complete clearance of target lesions. CR is a complete response, "u": Unconfirmed. *Best overall response is PD (SD for target lesions, PD for non-target lesions). §Off study treatment with confirmed PR due to patient decision.
Data cut date – 29 May 2018 and median time on study (5.6 months; n=26). As of data cut date, 48 patients were enrolled and received at least one dose of bempeg + NIVO. Per the protocol, the initial assessment of efficacy was based on the first 26 patients who were efficacy evaluable defined as ≥ 1 post-baseline scan.

PIVOT-09: STUDY DESIGN

- Approximately 600 patients will be randomized 1:1 into two treatment arms (**Figure 3**)

Figure 3: Study Schema

Population

- Previously untreated advanced RCC
- Intermediate or poor IMDC prognostic score
- Tumor tissue available for PD-L1 testing
- Approximately 150 sites (US, Latin America, Russia, Asia Pacific)

Stratification Factors

- PD-L1 status (≥ 1% vs < 1% or indeterminate)
- Intermediate vs poor IMDC prognostic score
- TKI choice (sunitinib vs cabozantinib)

R 1:1 N=600

Arm A[a]
Bempegaldesleukin 0.006 mg/kg IV q3w + Nivolumab 360 mg IV q3w
[a]Maximum treatment duration 2 years

Arm B
Investigator's choice Sunitinib 50 mg po qd for 4 weeks, followed by 2 weeks off *OR* Cabozantinib 60 mg po qd

Co-Primary Endpoints

- ORR by BICR per RECIST v1.1
- OS

Secondary Endpoints

- PFS by BICR per RECIST v1.1
- AEs
- QoL
- PD-L1 biomarker

BICR, blinded independent central review; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; QoL, quality of life; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; q3w, every 3 weeks; qd, daily; TKI, tyrosine kinase inhibitor.

ELIGIBILITY

Key Inclusion Criteria

- Advanced RCC with clear cell component including tumors with sarcomatoid features
- Archival tissue (≤12 months) or fresh biopsy for PD-L1 test before randomization
- Measurable disease per RECIST v1.1 criteria (by local investigator)
- IMDC intermediate/poor risk (based on central laboratory results)
- Karnofsky Performance Status (KPS) ≥70%
- No prior systemic therapy (including neoadjuvant, adjuvant or vaccine therapy) for RCC
- Prior palliative radiotherapy ≥ 2 weeks before randomization
- LVEF >45% (≤60 days before randomization)

Key Exclusion Criteria

- Active autoimmune disease or requirement for systemic immune suppressive agents
- Additional malignancy that is progressing or requires active treatment (certain exceptions apply)
- Major surgery or radiotherapy ≤14 days of randomization
- Tumor invading the superior vena cava, other major blood vessels, or the GI tract
- Any evidence of endotracheal or endobronchial tumor ≤30 days of randomization
- Active infection requiring systemic therapy ≤14 days of randomization

ASSESSMENTS AND FOLLOW-UP

Clinical

- Clinic visits: 6-week cycles with 3-week visit schedule
  - Study drug administration
  - Safety assessments
  - Quality of life assessments
  - PK and biomarker assessments (primarily Arm A)
- Tumor assessments:
  - Screening: CT/MRI chest, abdomen, pelvis (CAP) and brain
  - Post randomization: CT/MRI CAP and brain if history or clinical symptoms of brain metastases
    - Frequency: every 9 weeks through week 54, then every 12 weeks until RECIST progression
- Safety follow up visit 30 days after last dose of study treatment
- Additional safety follow up 100 days after last dose of nivolumab (if applicable)
- Survival follow up approximately every 12 weeks
  - Includes collection of subsequent anticancer therapy and PFS2 data

Biomarkers and Pharmacokinetics

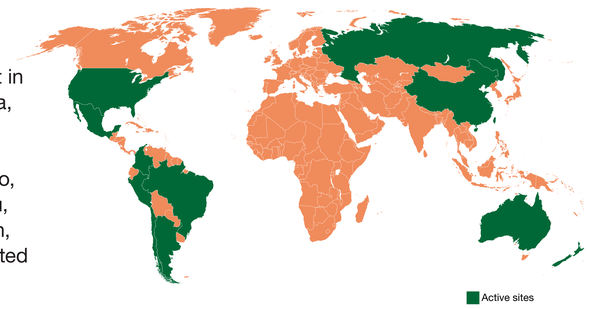
- Assessment of biomarkers potentially predictive of clinical responses to bempegaldesleukin combined with nivolumab or to TKI
- PK profiling of bempegaldesleukin and its metabolites (plasma) and nivolumab (serum)

STATISTICAL PLAN

- Study sample size accounts for the 2 co-primary efficacy endpoints: ORR and OS
- ORR analysis will occur when the first ~400 patients have a minimum follow-up of 6 months
- Overall Survival (OS) analysis will follow the promising zone adaptive design[13]
  - At the interim analysis for OS, an independent Data Monitoring Committee will set the number of OS events required in order to provide 90% conditional power for the final analysis
  - The target Hazard Ratio for OS is 0.65 (assuming median OS of 26.5 months for the control arm)

STATUS

- Study is open for enrollment
- For participating trial sites please visit https://clinicaltrials.gov, and search NCT03729245
- Planned enrollment in Argentina, Australia, Brazil, Chile, China, Colombia, Hong Kong, Mexico, New Zealand, Peru, Russian Federation, Singapore and United States



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