TPS763

PIVOT-09: A phase 3 randomized open-label study of bempegaldesleukin (NKTR-214) plus nivolumab vs sunitinib or cabozantinib (investigator's choice) in patients with previously untreated advanced renal cell carcinoma (RCC)

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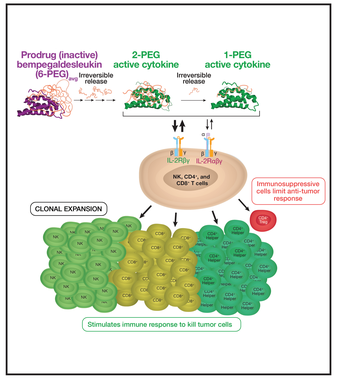
BACKGROUND

- 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 tumor regressions in up to 9% of treated patients.[1,2]
  - However, its use is limited by severe toxicity necessitating in-patient administration at specialist centers.[3]
- Bempegaldesleukin (BEMPEG; NKTR-214) is a first-in-class, CD122-preferential, IL-2 pathway agonist shown to increase tumor-infiltrating lymphocytes, T-cell clonality and programmed death-1 (PD-1) expression **(Figure 1)**.[4,5]
  - Biologic prodrug (IL-2 releasably conjugated to an average of 6 polyethylene glycol [PEG] polymers; 6-PEG_{avg}-IL-2).
  - The active cytokines (2-PEG-IL-2 and 1-PEG-IL-2) directly activate and expand effector T cells and natural killer cells, over immunosuppressive regulatory T cells, by preferentially binding to the CD122 subunit of the IL-2 receptor (IL-2Rβγ).
  - Gradual release of PEG chains *in vivo* leads to sustained exposure to these active IL-2 cytokines.

STUDY RATIONALE

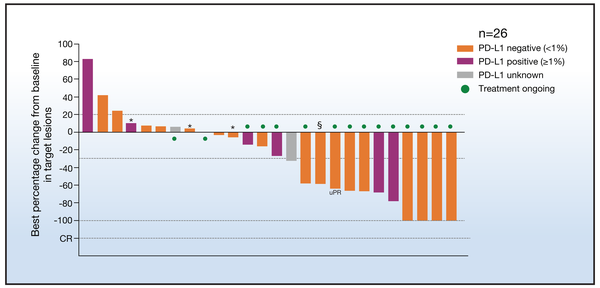
- First-line therapy for advanced RCC is rapidly evolving globally. Preferred regimens currently include:
  - Monotherapy with tyrosine kinase inhibitors (TKI) of angiogenesis (e.g. sunitinib, pazopanib, cabozantinib)
  - Combination of immune checkpoint inhibitors (CPI; nivolumab [NIVO] + ipilimumab)
  - Combination of TKI and CPI (axitinib + pembrolizumab or avelumab).
- In a phase 1/2 study (PIVOT-02), BEMPEG plus NIVO demonstrated encouraging efficacy **(Figure 2)** and a manageable safety profile in first-line advanced RCC independent of programmed death -ligand 1 (PD-L1) status.[6]
  - Objective response rate (ORR) of 46% (12/26 evaluable patients with complete or partial response).
    - ORR was 53% (9/17) for patients with PD-L1-negative (<1% PD-L1 expression by immunohistochemistry) RCC.
  - 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 occurred in 14% of patients.
  - There was a low rate of discontinuation due to TRAEs (2%).
- BEMPEG plus NIVO offers a potential novel combination immunotherapy for patients with advanced RCC, regardless of baseline tumor PD-L1 status.

Figure 1. Mechanism of action of BEMPEG



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

Figure 2. BEMPEG + NIVO as first-line treatment for patients with advanced RCC (PIVOT-02)



Horizontal dotted lines indicate the thresholds for progressive disease (PD), partial response (PR) and complete response (CR) according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1: –100% is PR for complete clearance of target lesions; CR is a complete response; uPR, unconfirmed PR.
*Best overall response is PD (stable disease [SD] for target lesions, PD for non-target lesions). §Off study treatment with confirmed PR due to patient decision.
At the data cutoff (29 May 2018), 48 patients with previously untreated advanced RCC were enrolled and had 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. As of data cutoff, median time on study was 5.6 months.

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

STUDY

Design

- PIVOT-09 is a Phase 3 global, multicenter, randomized, open-label study of BEMPEG plus NIVO vs investigator's choice of TKI (either sunitinib or cabozantinib) in patients with previously untreated advanced or metastatic RCC with a clear-cell component **(Figure 3)**.
- Approximately 600 patients will be randomized 1:1 between two treatment arms:
  - Arm A: BEMPEG 0.006 mg/kg intravenously (IV) every 3 weeks (q3w) combined with NIVO 360 mg IV q3w
  - Arm B: Investigator's choice of TKI monotherapy:
    - Sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off
    - Cabozantinib 60 mg orally once daily.

Endpoints

Co-primary

- ORR by blinded independent central review (BICR) per modified RECIST 1.1 (mRECIST 1.1) in patients with: (1) IMDC intermediate- or poor-risk scores; (2) IMDC all-risk scores.
- Overall survival (OS) in patients with: (1) IMDC intermediate- or poor-risk scores; (2) IMDC all-risk scores.

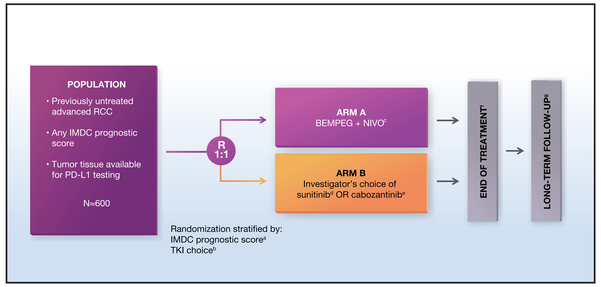
Key secondary

- Progression-free survival (PFS) by BICR per mRECIST 1.1 in patients with: (1) IMDC intermediate- or poor-risk scores; (2) IMDC all-risk scores.

Other secondary endpoints

- Adverse events.
- PD-L1 expression as a predictive biomarker for ORR, PFS, and OS.
- Quality-of-life.

Figure 3. PIVOT-09 study design



[a]Randomization is stratified by IMDC prognostic score: favorable (0) vs intermediate (1 or 2) vs poor (3–6); [b]Randomization is stratified by TKI choice: either sunitinib or cabozantinib; [c]BEMPEG 0.006 mg/kg IV q3w plus NIVO 360 mg IV q3w; maximum treatment duration of 2 years; [d]sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off; [e]cabozantinib 60 mg oral once daily; [f]treat until PD per mRECIST version 1.1 or unacceptable toxicity; [g]follow-up for safety, PD per mRECIST 1.1 and survival.
PD-L1 testing is carried out using the Dako PD-L1 IHC 28-8 pharmDx assay.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenous; PD, progressive disease; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; mRECIST 1.1, modified Response Evaluation Criteria In Solid Tumors version 1.1; q3w, every 3 weeks; TKI, tyrosine kinase inhibitor.

Eligibility criteria

Key inclusion criteria

- Advanced or metastatic RCC with clear cell component including tumors with sarcomatoid features.
- Archival or fresh tumor tissue available.
- Measurable disease per RECIST v1.1 (by local investigator).
- Any IMDC risk score (based on central laboratory results).
- Karnofsky Performance Status ≥70%.
- No prior systemic therapy (including neoadjuvant, adjuvant or vaccine therapy) for RCC.
- Prior palliative radiotherapy must be completed at least 2 weeks before randomization.
- Left ventricular ejection fraction >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 (exceptions apply).
- Major surgery ≤28 days of randomization.
- Tumor invading major blood vessels, or the gastrointestinal tract.
- Any evidence of endotracheal or endobronchial tumor ≤30 days of randomization.
- Active infection requiring systemic therapy within 14 days of randomization.

Assessments and follow-up

Clinical

- The treatment period is divided into 6-week cycles with a 3-week visit schedule:
  - Study drug administration
  - Safety assessments
  - Quality-of-life assessments
  - Blood samples for pharmacokinetic (PK) and biomarker assessments (Arm A).
- Tumor assessments will be performed at baseline and every 9 weeks (±7 days) through week 54, then every 12 weeks (±7 days) until BICR-confirmed disease progression (mRECIST 1.1) or treatment discontinuation (including treatment beyond progression), whichever is later.
- Long-term follow-up for safety and survival continues until withdrawal of consent, death, loss to follow-up or study termination.

Biomarkers and pharmacokinetics

- Tumor tissue from all patients will be collected at screening and analyzed for PD-L1 expression (using the Dako PD-L1 IHC 28-8 pharmDx assay), immune system-related genes, and proteins and mutations in cancer-related genes.
- For patients randomized to Arm A, blood samples will be collected for PK analysis of BEMPEG, its metabolites, and NIVO.
- Assessment of biomarkers potentially predictive of clinical responses will be assessed in tumor samples or peripheral blood (Arm A) taken at baseline and during treatment.

Status

- PIVOT-09 study is open for enrollment, with more than 100 active or planned sites globally **(Figure 4)**.
- Please visit ClinicalTrials.gov and search for NCT03729245 to find out the latest information on this study.

Figure 4. Countries with active or planned PIVOT-09 clinical trial sites

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