PIVOT-10: A phase 2 study of bempegaldesleukin (NKTR-214) in combination with nivolumab (NIVO) in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer

TPS589

Robert A. Huddart[1], Arlene O. Siefker-Radtke[2], Arjun V. Balar[3], Mehmet A. Bilen[4], Thomas Powles[5], Aristotelis Bamias[6], Daniel E. Castellano[7], Maged F. Khalil[8], Michiel S. Van Der Heijden[9], Vadim S. Koshkin[10], David W. Pook[11], Mustafa Ozguroglu[12], Linda Santiago[13], Bob Zhong[13], Pao-Chen Li[13], Margit C. Tagliaferri[13], Wei Lin[13], Mary A. Tagliaferri[13], Yohann Loriot[14]

[1]The Royal Marsden NHS Foundation Trust, Surrey, UK; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Perlmutter Cancer Center – New York University Langone Health, New York, NY; [4]Emory University School of Medicine, Atlanta, GA; [5]Barts Cancer Institute, Queen Mary University of London, Royal Free NHS Trust, London, UK; [6]Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece; [7]Hospital Universitario 12 de Octubre, Madrid, Spain; [8]Lehigh Valley Hosp Network, Allentown, PA; [9]The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [10]University of California San Francisco, San Francisco, CA; [11]Monash Health, Melbourne, Australia; [12]Cerrahpaşa School of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey; [13]Nektar Therapeutics, San Francisco, CA; [14]Institute Gustave Roussy, Université Paris-Sud, Université Paris-Saclay, Villejuif, France

BACKGROUND

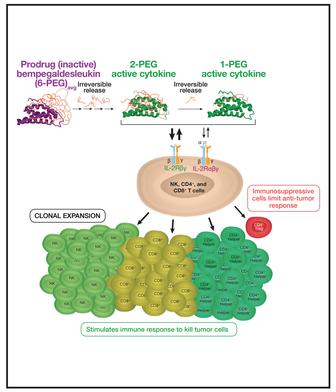
- Cisplatin-based chemotherapy is the standard of care (SOC) for first-line locally advanced or metastatic urothelial cancer.[1] However, about 50% of patients are ineligible due to poor performance status, impaired renal function, or co-morbidity.[1]
- Checkpoint inhibitors have been approved for patients who are ineligible to receive cisplatin, but their use is limited to patients whose tumors express high levels of programmed death -ligand 1 (PD-L1; high PD-L1 expression is defined as either a combined positive score [CPS] ≥10 or PD-L1 ≥5% expression on immune cells).[2,3]
- Approximately 70% of cisplatin-ineligible patients have tumors with low PD-L1 expression.[4,5]
- There is a high unmet need for new treatments for patients with advanced urothelial cancer and low PD-L1 expression, who are ineligible for cisplatin.

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 programmed death-1 (PD-1) expression **(Figure 1)**.[6,7]
- In a phase 1/2 study (PIVOT-02), BEMPEG plus nivolumab (NIVO) demonstrated encouraging efficacy **(Figure 2)** and a manageable safety profile in patients who were either ineligible for cisplatin, or who refused the SOC.[8]
  - Objective response rate (ORR) was 48%.
  - Deep responses were observed with a complete response (CR) rate of 19% (median 78% tumor shrinkage among responders).
  - Responses were observed regardless of baseline tumor PD-L1 expression, with an ORR of 50% in patients with PD-L1-positive* tumors and 45% in patients with PD-L1-negative* tumors.
  - 70% (7 of 10) of matched tumor biopsies converted PD-L1 status from negative at baseline to positive on treatment.
  - Most common treatment-related adverse events (TRAEs) were low-grade cytokine-related events (flu-like symptoms [71%], fatigue [56%], rash [46%], pruritis [32%]).
  - Grade 3 TRAEs occurred in 15% of patients.
- BEMPEG plus NIVO offers a potential novel combination immunotherapy for patients with advanced urothelial cancer regardless of baseline tumor PD-L1 status.

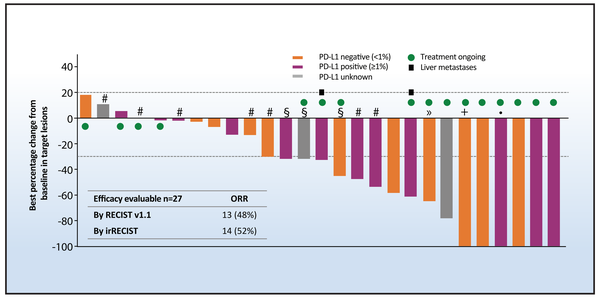
*PD-L1 status was evaluated using the 28-8 PharmDx assay; negative was defined as <1% of tumor cells with PD-L1 expression on immunohistochemistry (IHC); positive was defined as ≥1% of tumor cells with PD-L1 expression on IHC.

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 in first-line patients with advanced urothelial cancer (PIVOT-02)



Horizontal dotted lines indicate the thresholds for PD (20%) and PR (−30%) according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.
#Best overall response is PD. +Best overall response is PR with ~100% reduction of target lesions. §Best overall response is unconfirmed PR. •Best overall response is confirmed PR with unconfirmed CR. »Best overall response is PD by RECIST v1.1, but PR by irRECIST.
At data cut-off (12 March 2018), one patient was excluded for non-eligibility (no target lesion), and three patients were discontinued prior to the first scan (one due to patient decision; one due to clinical progression; one due to death from disease); 10 patients were pending their first scan in the database. PD-L1 status was evaluated using the 28-8 PharmDx assay; negative was defined as <1% of tumor cells with PD-L1 expression by immunohistochemistry; positive was defined as at least 1% of tumor cells with PD-L1 expression by immunohistochemistry.
CR, confirmed response; irRECIST, immune-related RECIST; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response.

Siefker-Radtke A, et al. J Clin Oncol 2019;37(7 suppl):388.

STUDY

Design

- PIVOT-10 is a Phase 2 global, multicenter, single-arm study of BEMPEG plus NIVO in patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin **(Figure 3)**.
- Approximately 175 patients will receive BEMPEG 0.006 mg/kg intravenously (IV) plus NIVO 360 mg IV on Day 1 of each 3-week cycle.
- Patients will be treated until disease progression (by RECIST v1.1), loss of clinical benefit, death, unacceptable toxicity, symptomatic deterioration, investigator's decision to discontinue treatment, patient withdrawal of consent, loss to follow-up, pregnancy, or study termination; or for a maximum of 2 years.
  - Treatment is permitted beyond progression for patients with stable or improved performance and clinical status, if the investigator perceives the patient to be benefitting from treatment.

Objectives

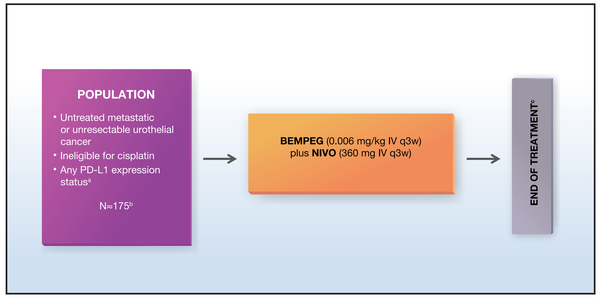
Primary

- Evaluate the antitumor activity of BEMPEG plus NIVO by assessing the ORR by RECIST v1.1 per blinded independent central review (BICR) in patients whose tumors have low PD-L1 expression.

Secondary

- Evaluate the effect of BEMPEG plus NIVO by assessing:
  - ORR (RECIST v1.1) per BICR in all treated patients
  - Duration of response (DOR; RECIST v1.1) per BICR in all treated patients and in patients whose tumors have low PD-L1 expression
  - ORR and DOR (RECIST v1.1) per investigator assessment in all treated patients and in patients whose tumors have low PD-L1 expression.
- Evaluate safety and tolerability of BEMPEG plus NIVO.

Figure 3. PIVOT-10 study design



[a]PD-L1 status is determined at enrollment based on PD-L1 IHC 22C3 pharmDx assay: low PD-L1 expression is defined as combined positive score (CPS) <10; high PD-L1 expression is defined as CPS ≥10.
[b]Study enrollment will stop once at least 110 patients whose tumors have low PD-L1 expression have been enrolled and received at least one dose of BEMPEG/NIVO. A maximum of approximately 205 patients will be enrolled, including 30 patients who received gemcitabine/carboplatin on a previous protocol amendment and 175 patients who will receive BEMPEG/NIVO regardless of PD-L1 status (assuming 110 PD-L1 low; 47 PD-L1 high, and 18 PD-L1 non-evaluable).
[c]Treat for up to 2 years until PD per RECIST version 1.1 or unacceptable toxicity; follow-up for safety, PD per RECIST 1.1 and survival.
IV, intravenous; PD, progressive disease; PD-L1, programmed death-ligand 1; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; q3w, every 3 weeks.

Eligibility criteria

Key inclusion criteria

- Histologically or cytologically documented urothelial cancer that is inoperable, locally advanced (T4b, any N; or any T, N2–3) or metastatic (M1, Stage IV).
- Measurable disease per RECIST v1.1.
- No prior systemic chemotherapy or investigational agent for inoperable locally advanced or metastatic urothelial cancer.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
- Ineligible for cisplatin defined as one or more of the following:
  - Impaired renal function defined as a creatinine clearance ≥30 but <60 mL/min
  - Grade ≥2 hearing loss (CTCAE v5.0)
  - Grade ≥2 peripheral neuropathy (CTCAE v5.0)
  - ECOG performance status of 2.
- Archival or fresh tumor tissue available for PD-L1 testing.

Key exclusion criteria

- Active autoimmune disease or requirement for systemic immune suppressive agents.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, agents that target IL-2 pathway, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
- Active brain metastases.

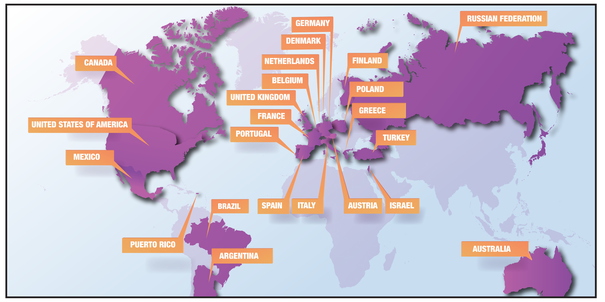
Assessments and follow-up

- On-study clinic visits occur every 3 weeks:
  - Study drug administration
  - Safety assessments
  - Health-related quality-of-life assessments
  - Blood samples for pharmacokinetic and biomarker assessments
  - Administration of IV fluids per hydration guidelines.
- Systemic and tumor tissue-based pharmacodynamic effects of BEMPEG plus NIVO will be evaluated.
- Tumor assessments will be performed at baseline and every 9 weeks (±7 days) for the first 12 months, then every 12 weeks (±7 days) until RECIST progression or treatment discontinuation.
- Long-term follow-up for safety, disease progression, survival, health-related quality of life, and subsequent therapies continues until withdrawal of consent, death, loss to follow-up, or study termination.

Status

- PIVOT-10 study is open for enrollment, with more than 100 active or planned sites globally **(Figure 4)**.
- Please visit ClinicalTrials.gov and search for NCT03785925 to find out the latest information on this study.

Figure 4. Countries with active or planned PIVOT-10 clinical trial sites



ACKNOWLEDGEMENTS

We would like to thank all patients, their families and the investigators who are participating in this study. We also thank Dako for collaborative development of the PD-L1 IHC 28-8 pharmDx assay, and Bristol-Myers Squibb (Princeton, NJ). This study is sponsored by Nektar Therapeutics, San Francisco, CA. Medical writing assistance was provided by Alison Lovibond PhD CMPP, and was funded by Nektar Therapeutics.

REFERENCES

1. Bellmunt J, *et al. Ann Oncol* 2014;25(suppl 3):iii40–iii48.
2. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech, Inc.; 2018.
3. Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014–2018.
4. Balar AV, *et al. Lancet* 2017;389:67–76.
5. Balar AV, *et al. Lancet Oncol* 2017;18:1483–1492.
6. Charych DH, *et al. Clin Cancer Res* 2016;22:680–690.
7. Bentebibel SE, *et al. Cancer Discov* 2019;9:711–721.
8. Siefker-Radtke A, *et al. J Clin Oncol* 2019;37(7 suppl):388.

Poster presented at the American Society for Clinical Oncology Genitourinary Cancers Symposium (ASCO-GU), February 13–15, 2020, San Francisco, CA. Corresponding author Prof. Robert A. Huddart: robert.huddart@icr.ac.uk