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

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BACKGROUND

• Cisplatin-based chemotherapy is the standard of care (SOC) for first-line locally advanced or metastatic urothelial cancer; however, about 50% of patients are ineligible due to poor performance status, impaired renal function, or co-morbidities.
• Checkpoint inhibitors have been approved for patients who are ineligible to receive cisplatin but use a limited to patients whose tumors express high levels of programmed death ligand 1 (PD-L1). High PD-L1 expression is used as a surrogate endpoint for overall survival (OS).
• Approximately 70% of cisplatin-ineligible patients have tumors with low PD-L1 expression.
• 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.

BEPEMG

• BEMPEG has a high affinity for CD122, which is not present on CD8+ T-cells, but is mainly present on CD4+ T-cells, natural killer (NK) cells, and B-cells.
• Bemegaldesleukin (BEMPEG; NKTR-214) is a CD122-preferential, interleukin-2 (IL-2) pathway agonist shown to increase tumor-infiltrating lymphocytes (TILs), clonality and progression-free survival (PFS) with PD-L1 expression (Figure 1).
• 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.

STUDY

Design

• PIVOT-10 is a Phase 2, global, multicenter, single-arm study of BEMPEG plus NIVO in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin (Figure 2).
• Approximately 175 patients will receive BEMPEG 0.5 mg/kg intravenously (IV) plus NIVO 350 mg every 4 weeks on Day 1 of each 28-day cycle. Patients will be treated until disease progression (by RECIST v1.1), loss of clinical benefit, death, unacceptable toxicity, detection of investigator’s choice of secondary endpoint (progression-free survival [PFS]), withdrawal of consent, loss to follow-up, or study termination.
• Treatment is permitted beyond progression for patients with stable or improved performance status and clinical status, if the investigator perceives the patient to be benefiting from treatment.

Objectives

• Evaluate the antitumor activity of BEMPEG plus NIVO by assessing the ORR by RECIST v1.1 in patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin.
• Evaluate the effect of BEMPEG plus NIVO by assessing:
  - ORR (by IrRECIST v1.1) in BICR in all treated patients and in patients with tumors that have low PD-L1 expression
  - ORR and ORR (RECIST v1.1) in investigator assessment in all treated patients and in patients with tumors that have low PD-L1 expression.
• Evaluate safety and tolerability of BEMPEG plus NIVO.

Eligibility criteria

• Histologically or cytologically documented urothelial cancer that is irresistible, locally advanced (T4b, any N; or any T, N2–3), or metastatic (M1, Stage IV).
• ECOG performance status of 0–3.
• No prior systemic chemotherapy or investigational agent for inoperable locally advanced (T4b, any N; or any T, N2–3) or metastatic (M1, Stage IV). Patients with prior treatment who are determined to be disease stable during the 4 weeks prior to the start of treatment (or 8 weeks if prior treatment of <4 weeks) may be included.
• Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
• No prior systemic chemotherapy or investigational agent for inoperable locally advanced (T4b, any N; or any T, N2–3; or any T, N1–2b) or metastatic (M1, Stage IV).
• Measurable or evaluable disease by RECIST v1.1.
• No prior checkpoint inhibitor therapy.
• No prior anti-PD-L1 or anti-PD-1 therapy within 2 weeks of the first dose of study treatment.
• Adequate bone marrow, hepatic, and renal function.
• No prior investigational agent for inoperable locally advanced (T4b, any N; or any T, N2–3; or any T, N1–2b) or metastatic (M1, Stage IV).
• Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
• Measurable or evaluable disease by RECIST v1.1.
• No prior systemic chemotherapy or investigational agent for inoperable locally advanced (T4b, any N; or any T, N2–3; or any T, N1–2b) or metastatic (M1, Stage IV).
• Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
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Key exclusion criteria

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

Assessments and follow-up

• On-study visits occur every 3 weeks:
  - Study drug administration
  - Safety assessments
  - Health-related quality-of-life assessments
  - Biopsies for sequential pathological and immunomarker assessments
  - Administration of IV fluids per hydration guidelines.

• Patients who are not treated may discontinue due to side effects, disease progression, 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.
• Please visit ClinicalTrials.gov and search for NCT03785925 to find out the latest information on this study.

REFERENCES

1. The Royal Marsden NHS Foundation Trust, Surrey, UK; 2. The University of Texas MD Anderson Cancer Center, Houston, TX; 3. Weill Cornell Medicine, New York, NY; 4. The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; 5. University of California San Francisco, San Francisco, CA; 6. Monash Health, Melbourne, Australia; 7. Cerrahpasa Medical Faculty, Istanbul, Turkey; 8. Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece; 9. Hospital Universitario La Paz, Madrid, Spain; 10. The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; 11. University of California San Francisco, San Francisco, CA; 12. Cerrahpa Medical Faculty, Istanbul, Turkey.