Clinical Trial Protocol

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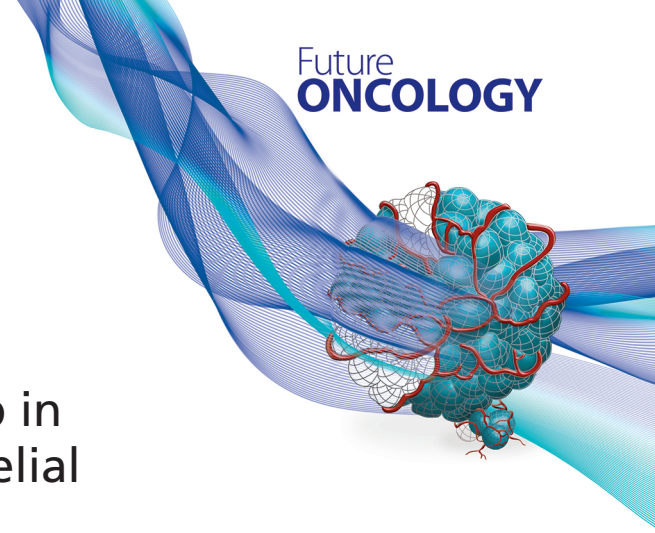

PIVOT-10: Phase II study of bempegaldesleukin plus nivolumab in cisplatin-ineligible advanced urothelial cancer

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The choice of first-line therapy for patients with metastatic urothelial cancer (mUC) is based on cisplatin-eligibility and programmed death-ligand 1 (PD-L1) status. For patients with mUC who are ineligible for cisplatin and with low PD-L1 expression, chemotherapy-based regimens are the only approved first-line option. In a Phase I/II trial of the chemotherapy-free regimen, bempegaldesleukin (BEMPEG; NKTR-214) plus nivolumab, patients with locally advanced or mUC experienced tumor responses regardless of baseline PD-L1 expression (objective response rates: 50 and 45% in patients with PD-L1-positive and -negative tumors, respectively). The Phase II PIVOT-10 study (NCT03785925), evaluates efficacy and safety of first-line BEMPEG plus nivolumab in cisplatin-ineligible patients with locally advanced or mUC. Most patients will have low PD-L1 expression. Primary end point: objective response rates (including complete response).

Lay abstract: When people are diagnosed with advanced urothelial (bladder) cancer, they are often given a type of chemotherapy, called cisplatin, as their first treatment. However, some people are not able to receive cisplatin. For these people, especially if their cancer has a low level of the protein called programmed death-ligand 1 (PD-L1), treatment options are limited. This protein helps the body's natural immune system to defend itself against infections and disease, including cancer. Patients with a low level of PD-L1 protein in their cancer typically have a poor outlook. This article presents information on a clinical trial called PIVOT-10. This trial will test how well a new drug that modifies the immune system, called bempegaldesleukin (BEMPEG; NKTR-214) combined with a drug that blocks PD-1, nivolumab, works as an initial treatment for patients with advanced urothelial cancer who cannot receive cisplatin. Most patients will have a low PD-L1 tumor expression level. The main assessment will be overall response rate, which measures the percentage of patients experiencing shrinkage or disappearance of their cancer after receiving treatment. PIVOT-10 will also check the safety of BEMPEG and nivolumab and the impact of the treatment combination on survival.

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Keywords: bempegaldesleukin • cisplatin-ineligible • IL-2 pathway • immune checkpoint inhibitor combinations • immunotherapy • metastatic urothelial cancer • nivolumab • NKTR-214 • PD-L1 • PD-L1 negative

Background

Bladder cancer is the tenth most common cancer type worldwide [1] and is more common in men, in whom it is the sixth most common cancer and ninth leading cause of cancer-related death [1]. In the USA, it is estimated that there will be 81,400 new cases and 17,980 deaths in 2020 [2]. Bladder cancer comprises a number of different histological variants, among which urothelial cancer (UC) is the predominant type, accounting for approximately 90% of bladder cancer cases in the USA and Europe [3]. In addition, UC can arise in sites within the urinary tract other than the bladder, such as the urethra, renal pelvis and ureter [4].

Historically, the standard first-line treatment of advanced UC has involved the use of cytotoxic chemotherapy, specifically cisplatin-based regimens. Median overall survival (OS) with standard first-line platinum-based chemotherapy regimens is estimated at 9–15 months [5–8]. Many patients with advanced UC are ineligible to receive cisplatin based on the existence of at least one of the following clinical factors: Eastern Cooperative Oncology Group (ECOG) performance status of 2, creatinine clearance less than 60 ml/min, grade ≥2 hearing loss, grade ≥2 neuropathy and/or New York Heart Association Class III heart failure [9]. These patients are often treated in the first-line setting with carboplatin-based combinations, most commonly gemcitabine/carboplatin, which is, however, considered less effective than cisplatin-based chemotherapy. In a meta-analysis, the risk ratio for achieving an objective response was 1.34 (p = 0.02) in favor of cisplatin-based chemotherapy [10]. Thus, for patients with advanced UC who are not eligible to receive cisplatin, the choice of clinically beneficial first-line treatment options has been historically limited.

The past few years have seen a growing number of immune checkpoint inhibitors (ICIs) approved for the treatment of advanced UC. In the first-line setting, monoclonal antibodies against programmed death-ligand 1 (PD-L1), atezolizumab and programmed death-1 (PD-1), pembrolizumab, have been approved by the US FDA and EMA. Atezolizumab was granted accelerated approval by the FDA in April 2017 for the first-line treatment of patients with advanced UC who were not eligible to receive cisplatin based on results of the single-arm IMvigor210 study (n = 119) [11]. One month later, pembrolizumab was also granted accelerated approval by the FDA in the same patient population based on results of the single-arm KEYNOTE-052 trial [12,13]. The primary end point in each of these studies was objective response rate (ORR), which reached 23% (95% CI: 16–31%) in patients receiving atezolizumab [11] and 29% (95% CI: 24–34%) in patients receiving pembrolizumab [13]. Rates of complete response (CR) were 9% for both drugs and responses were observed in patients regardless of tumor PD-L1 status [11,13]. However, in mid-2018, based on the results of two ongoing confirmatory Phase III clinical trials (IMvigor130 [NCT02807636] and KEYNOTE-361 [NCT02853305]), the FDA and EMA revised the approved first-line indications for atezolizumab and pembrolizumab in advanced UC. Preliminary data from these studies showed reduced survival rates in patients with low baseline PD-L1 expression compared with patients receiving chemotherapy [14,15]. These concerning observations led to both regulatory agencies restricting the use of atezolizumab and pembrolizumab in the first-line setting to cisplatin-ineligible patients with high levels of PD-L1 expression (≥5% on tumor immune cells for atezolizumab and combined positive score [CPS] ≥10 for pembrolizumab, as determined by an FDA-approved test) [16–19]. For patients who are not eligible to receive any platinum-containing chemotherapy, the FDA (but not EMA) approved the use of atezolizumab or pembrolizumab regardless of PD-L1 status given the lack of alternative treatment options [16,18]. More recently, avelumab received FDA approval as maintenance therapy in patients with advanced UC who have not experienced disease progression while receiving first-line platinum-containing chemotherapy based primarily on a statistically significant OS benefit observed with the addition of avelumab to best supportive care in the JAVELIN Bladder 100 trial [20,21]. The approved indication did not include a requirement for PD-L1 expression; however, the survival benefit in the JAVELIN Bladder 100 study appeared to be driven largely by the PD-L1+ population (hazard ratio [HR]: 0.56 vs 0.86 in the PD-L1- population) [21]. ICIs are also approved for use following progression of advanced UC after first-line chemotherapy; these ICIs include atezolizumab, pembrolizumb, nivolumab (NIVO), durvalumab and avelumab [21–23].

Despite the treatment advances established by ICIs for advanced UC, many patients do not achieve durable responses across first- and second-line settings. This suggests that additional therapies may be required to enhance the efficacy of ICIs. Furthermore, there is no successful chemo-sparing regimen for PD-L1-low patients expected to be approved in the near future. Thus, there is a considerable unmet need for new first-line treatments with demonstrated clinical benefit in low PD-L1 expressing tumors, which account for approximately 70% of cisplatin-ineligible patients with metastatic UC [11,19]. While there is potential for change of NCCN guidelines based on results from key trials [20,24,25], the regulatory-approved standard of care for this indication still remains the FDA benchmark. Optimizing ICI therapy by exploring combinations with other immunotherapy agents is therefore of significant interest.

Targeting interleukin-2 for cancer therapy

IL-2 is a naturally occurring cytokine that has a crucial role in the immune response. It signals via the IL-2 receptor, which exists in monomeric, dimeric or trimeric forms. Immune effector cells, such as $CD8^+$ and $CD4^+$ T cells and natural killer (NK) cells express the intermediate affinity IL-2 receptor dimer, which comprises CD122 (IL-2Rβ) and CD132 (the common cytokine receptor γ chain) subunits [26,27]. Tregs, whose function is to regulate the immune response, express the high-affinity IL-2 receptor trimer, which is composed of CD25 (IL-2Rα), in addition to CD122 and CD132.

Given its ability to increase the numbers of cytotoxic T cells and NK cells, IL-2 was explored as a potential immunotherapeutic to enhance the body's anticancer immune response. In fact, high-dose IL-2 is generally hailed as one of the earliest immuno-oncology agents showing efficacy in metastatic disease. However, while high-dose IL-2 (aldesleukin) monotherapy can achieve complete and durable responses in solid tumors such as metastatic renal cell carcinoma and metastatic melanoma, its use has historically been limited by its short half-life, the use of high doses and toxicities that require specialist inpatient drug administration [28,29].

Bempegaldesleukin (NKTR-214)

Bempegaldesleukin (BEMPEG; NKTR-214) is an investigational CD122-preferential IL-2 pathway agonist. BEMPEG was engineered to signal preferentially through the IL-2 intermediate affinity receptor (IL-2Rβγ) found on $CD8^+$ effector T cells and NK cells as opposed to the high-affinity receptor (IL-2Rαβγ) found on Tregs (Figure 1). Its prodrug design, in which IL-2 is releasably conjugated to an average of six polyethylene glycol (PEG) moieties, allows for the slow sequential release of the PEG moieties following administration. This results in the generation of active species and sustained and controlled activation of the IL-2 pathway, which allows for less frequent dosing, a more favorable safety profile than high-dose IL-2 and outpatient administration [30–32].

Preclinical studies in murine tumor models have demonstrated that treatment with BEMPEG, as a single agent or in combination with ICI therapy, resulted in the expansion and mobilization of $CD8^+$ T cells into the tumor microenvironment [32]. *In vivo*, BEMPEG showed enhanced antitumor activity compared with the recombinant IL-2, aldesleukin, even when given less frequently and at lower doses [30,32].

In the first-in-human clinical study (EXCEL; NCT02869295), BEMPEG monotherapy was administered to patients (n = 28) with locally advanced or metastatic solid tumors, including UC (n = 1) [31]. BEMPEG was well tolerated, with the most common treatment-emergent adverse events (AEs) being fatigue (71%), flu-like symptoms (68%), pruritus (64%) and hypotension (57%). Based on predefined dose-limiting toxicity criteria, the maximum tolerated dose was identified as 0.009 mg/kg every 3 weeks administered intravenously (iv.) over 15 min. Of note, there was no evidence of immune-mediated AEs (except for one case of hypothyroidism) or organ-related inflammation (e.g., colitis, pneumonitis, dermatitis, hepatitis, endocrinopathies). Best objective response was stable disease, which occurred in 54% of patients. Encouragingly, BEMPEG induced proliferation and activation of $CD4^+$ T cells, $CD8^+$ T cells and NK cells in the blood and meaningful immune changes in the tumor, including infiltration of $CD8^+$, $CD4^+$ T cells and NK cells, without inducing Tregs. BEMPEG increased numbers of PD-1-expressing $CD8^+$ T cells in the tumor microenvironment; PD-1 has been shown to identify tumor-reactive T cells in infiltrating tumors [31]. Furthermore, BEMPEG upregulated expression of the gene encoding PD-L1, which is of interest as low baseline levels of PD-L1 may predict poor response to ICIs [33]. Based on a strong mechanistic rationale, as well as the biological activity and tolerability of BEMPEG, including non-overlapping toxicities with approved ICIs, clinical studies were initiated with BEMPEG combined with the approved anti-PD-1 inhibitor, NIVO.

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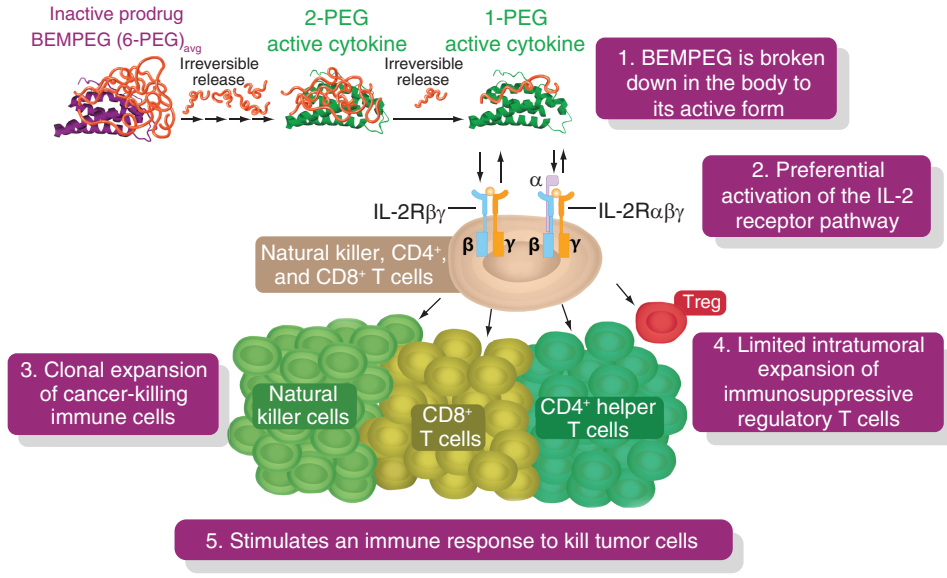

Figure 1. Mechanism of action of bempegaldesleukin. BEMPEG is an investigational CD122-preferential IL-2–pathway agonist. It consists of recombinant human IL-2 conjugated with an average of six releasable chains of PEG. **(A)** Sequential loss of PEG chains in the body yields a series of increasingly active IL-2 conjugates to achieve a sustained concentration of active drug and stable activity. **(B)** The location of the PEG chains directs BEMPEG to preferentially signal through the heterodimeric IL-2 receptor beta gamma complex (IL-2Rβγ; CD122/CD132) over the heterotrimeric IL-2Rαβγ complex. **(C & D)** This leads to clonal expansion of $CD8^+$ and $CD4^+$ T cells and natural killer cells without unwanted expansion of Tregs in the tumor microenvironment. **(E)** By leveraging the clinically validated IL-2 pathway, BEMPEG may stimulate an antitumor immune response.
BEMPEG: Bempegaldesleukin; PEG: Releasable polyethylene glycol.
Reproduced with permission from © Nektar Therapeutics, San Francisco, CA [30].

The ongoing Phase I/II open-label, multicenter, dose-escalation and -expansion study PIVOT-02 (NCT02983045) is investigating the combination of BEMPEG plus NIVO in patients with locally advanced or metastatic solid tumors, including UC. The dose-escalation phase (part 1) involved evaluation of the safety and tolerability of BEMPEG plus NIVO, including defining the maximum tolerated dose and/or recommended Phase II dose (RP2D). The RP2D was determined to be BEMPEG 0.006 mg/kg in combination with NIVO 360 mg, both administered every 3 weeks [34]. In part 2 of the study, the safety and efficacy of the combination at the RP2D was assessed in cohorts of five different tumor types: melanoma, renal cell carcinoma, non-small-cell lung cancer, UC and triple-negative breast cancer. Preliminary data show that BEMPEG plus NIVO was well tolerated with encouraging signs of clinical benefit for patients with advanced or metastatic UC who were ineligible for first-line cisplatin or who refused standard-of-care treatment (SOC; n = 41) [35]. Among the 27 patients who were evaluable for efficacy (at least one post-baseline scan), BEMPEG plus NIVO was associated with an investigator-assessed ORR of 48% (44% for cisplatin-ineligible patients and 55% for those who refused SOC). Deep responses were demonstrated, with five CRs (19%) and a median 78% tumor shrinkage among responders. Responses were observed regardless of baseline tumor cell PD-L1 expression, with ORRs of 50% and 45% in patients with PD-L1 positive (≥1% by anti-PD-L1 immunohistochemistry [IHC] assay) and PD-L1 negative tumors (<1% by IHC), respectively [35]. Importantly, of 13 paired-tissue samples, seven of ten samples that were PD-L1 negative (<1% expression) at baseline converted to PD-L1 positive (≥1% expression) by week 3 of treatment; three of these seven patients had partial response (PR), two had stable disease and two had disease progression [35]. The remaining three samples remained PD-L1 positive from baseline to week 3. Of the total (n = 41), 88% of patients experienced at least one treatment-related AE (TRAE), with low-grade cytokine-related events (flu-like symptoms [71%], fatigue [56%], rash [46%], pruritis [32%]) being the most common. Grade 3 TRAEs occurred in 15% of patients, including flu-like symptoms (5%) and hypotension (2%). The rate of discontinuations was low, with only four patients discontinuing treatment due to a TRAE. There were no treatment-related deaths. These preliminary data supported

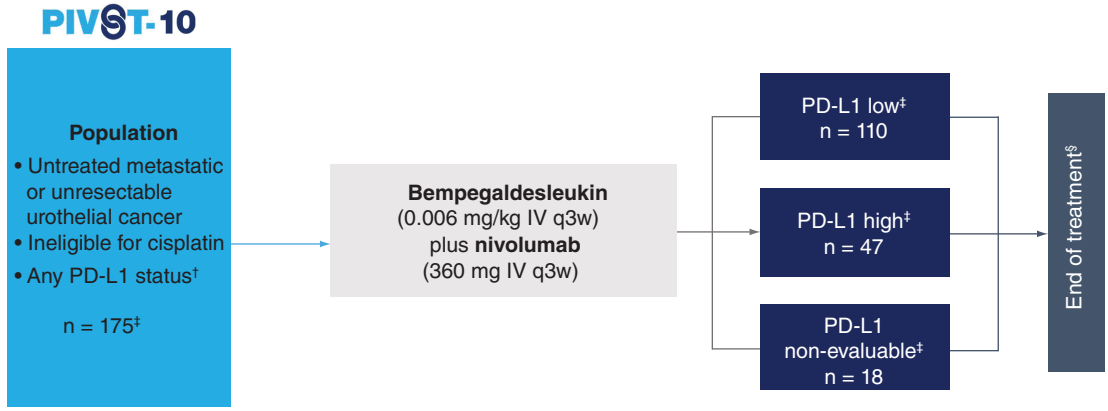

Figure 2. PIVOT-10 study design.
†PD-L1 status is determined at enrollment based on PD-L1 IHC 22C3 pharmDx assay: low PD-L1 expression is defined as a CPS <10; high PD-L1 expression is defined as CPS ≥10.
‡The study protocol called for enrollment to stop once ≥110 patients with low tumor PD-L1 expression were enrolled and had received at least one dose of BEMPEG plus NIVO. The study was designed to enroll a maximum of approximately 205 patients, including 30 patients who had received gemcitabine plus carboplatin according to a previous protocol amendment and 175 patients who will receive BEMPEG plus NIVO regardless of tumor PD-L1 status. Based on previous urothelial cancer-specific PD-L1 data [10,11,15,29], it is estimated that 70% of patients would have low tumor PD-L1 expression and the remaining 30% would have high tumor PD-L1 expression; thus, it is estimated that there would be 110 PD-L1 low, 47 PD-L1 high and 18 PD-L1 non-evaluable patients.
§Treat for up to 2 years until progressive disease per RECIST v1.1, loss of clinical benefit, death, unacceptable toxicity, symptomatic deterioration, investigator or patient decision to discontinue treatment, patient withdrawal of consent, loss to follow-up, or study termination.
BEMPEG: Bempegaldesleukin; CPS: Combined positive score; IHC: Immunohistochemistry; IV: intravenous; NIVO: Nivolumab; PD-L1: Programmed death-ligand 1; q3w, every 3 weeks; RECIST v1.1: Response Evaluation Criteria In Solid Tumors version 1.1.

the further evaluation of BEMPEG plus NIVO in patients with advanced or metastatic UC and informed the Phase II PIVOT-10 trial described here. In addition, the combination of BEMPEG plus NIVO is being evaluated in Phase III studies in muscle-invasive bladder cancer (NCT04209114), metastatic melanoma (NCT03635983) and advanced renal cell carcinoma (NCT03729245).

PIVOT-10 study

We report the design and methodology for an ongoing Phase II study of BEMPEG plus NIVO for the first-line treatment of cisplatin-ineligible patients with locally advanced or metastatic UC regardless of tumor PD-L1 expression (PIVOT-10; NCT03785925). PIVOT-10 has enrolled at more than 120 sites in over 20 countries across five continents.

Study design & objectives

PIVOT-10 is a Phase II, multicenter, single-arm study investigating the combination of BEMPEG plus NIVO in cisplatin-ineligible patients with locally advanced or metastatic UC (Figure 2). Tumor PD-L1 status is assessed at baseline using the PD-L1 IHC 22C3 pharmDx assay. Low tumor PD-L1 expression is defined as CPS <10 and high tumor PD-L1 expression is defined as CPS ≥10. The assay has been clinically validated in the pembrolizumab KEYNOTE-052 study and approved for use with pembrolizumab in UC [12,13,18,36]. The predefined criteria for stopping enrollment is after at least 110 patients with low tumor PD-L1 expression are enrolled and receive at least one dose of BEMPEG plus NIVO (regardless of the number of patients with high tumor PD-L1 expression enrolled).

Approximately 175 patients will be treated with BEMPEG plus NIVO. Patients will receive BEMPEG 0.006 mg/kg iv. plus NIVO 360 mg iv. on day 1 of each 3-week cycle. Patients will be treated until disease progression (by Response Evaluation Criteria In Solid Tumors version 1.1 [RECIST v1.1]), loss of clinical benefit, death, unacceptable toxicity, symptomatic deterioration, investigator or patient decision to discontinue treatment,

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Box 1. PIVOT-10 study end points

Primary end point
ORR† per BICR in patients with low PD-L1 expression.
Secondary end points
In all treated patients†:
- ORR and DOR per BICR;
- ORR and DOR per investigator assessment;
- Safety and tolerability.

In patients with low PD-L1 expression†:
- DOR per BICR;
- ORR and DOR per investigator assessment.

Exploratory end points
In all treated patients:
- PFS† per BICR;
- Overall survival;
- Activity of BEMPEG plus NIVO on immune-related RECIST v1.1;
- Immunological effects and immunogenicity of BEMPEG plus NIVO;
- Pharmacokinetics of BEMPEG plus NIVO;
- Patient-reported outcomes:
  - EORTC QLQ-C30;
  - FACIT (GP5 item);
  - EQ-5D-3L and visual analogue scale.

In patients with low PD-L1 expression:
- PFS† per BICR;
- Overall survival;
- Rate of tumor conversion from low to high PD-L1 expression and correlation with treatment response.

In patients with high PD-L1 expression†:
- DOR, ORR and PFS per BICR;
- DOR and ORR per investigator assessment;
- Overall survival.

†DOR, ORR and PFS will be evaluated per RECIST v1.1.
BEMPEG: Bempegaldesleukin; BICR: Blinded independent central review; DOR: Duration of response; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer QoL Questionnaire; EQ-5D-3L: Three-level EuroQol five-dimensional questionnaire; FACIT: Functional Assessment of Chronic Illness Therapy; NIVO: Nivolumab; ORR: Objective response rate; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; RECIST v1.1: Response Evaluation Criteria In Solid Tumors version 1.1.

patient withdrawal of consent, loss to follow-up, or study termination; or for a maximum of 2 years. Treatment is permitted beyond disease progression for patients with stable or improved performance and clinical status if the investigator perceives the patient to be benefiting from treatment.

The safety profile of BEMPEG has been well characterized. Cytokine toxicities common to IL-2 treatment, including fever, myalgia, chills and rash, may be mitigated using antihistamines, paracetamol and/or non-steroidal anti-inflammatory drugs. All patients are required to follow the protocol-specified hydration guidelines to mitigate the risk of hypotension.

The primary objective is to evaluate the antitumor activity of BEMPEG in combination with NIVO by assessing the ORR in patients with low PD-L1 expression by blinded independent central review (BICR). Secondary objectives include ORR (RECIST v1.1) in all treated patients by BICR; duration of response (DOR) by RECIST v1.1 in all treated patients and in patients whose tumors have low PD-L1 expression by BICR; and ORR and DOR (RECIST v1.1) per investigator assessment in all treated patients and in patients whose tumors have low PD-L1 expression. The safety and tolerability of the BEMPEG plus NIVO combination will also be evaluated. Progression-free survival (PFS) by BICR and OS are exploratory end points. The complete list of study objectives, including exploratory end points, is detailed in Box 1.

Key eligibility criteria

Study participants are required to have histologically or cytologically confirmed inoperable, locally advanced (T4b, any N; or any T, N2–3) or metastatic (M1, Stage IV) UC of the renal pelvis, ureter, urinary bladder, or urethra and measurable disease per RECIST v1.1. They must be aged ≥18 years, provide written consent and have an ECOG

performance status of ≤2. Participants must be ineligible to receive cisplatin based on the presence of at least one of the following: impaired renal function defined as a creatinine clearance ≥30 but <60 ml/min; grade ≥2 hearing loss (Common Terminology Criteria for Adverse Events [CTCAE] v5.0); grade ≥2 peripheral neuropathy (CTCAE v5.0); ECOG performance status of 2. Archival or fresh tumor tissue samples are required for determination of PD-L1 status at enrollment. Participants should not have received: prior systemic chemotherapy; investigational agents for inoperable, locally advanced or metastatic UC; or treatment with agents that target the IL-2 pathway; anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T-lymphocyte-associated antigen-4 antibody, or any other agent specifically targeting T-cell costimulation or immune checkpoint pathways. Patients with active autoimmune disease or who require systemic immunosuppressive drugs or those who have active brain metastases are excluded. A full list of eligibility criteria can be found in Supplementary Table 1.

Study assessments

Tumor response and disease progression end points will be determined by BICR and the investigator according to RECIST v1.1 (see Box 1). Patients will be assessed for response until progression of disease or treatment discontinuation, whichever occurs later.

All patients will have tumor measurements taken at baseline and every 9 weeks (±7 days) for the first 12 months, every 12 weeks (±7 days) thereafter and at the end of treatment. For patients who continue treatment beyond progression, scans will be performed every 9 weeks (±7 days) for the first 12 months of treatment post-progression, then every 12 weeks (±7 days) in the second year of treatment post-progression. Tumor assessments in the long-term follow-up period should be performed every 90 days (±10 days) from the last scan and are only needed if the patient discontinued treatment without radiographic disease progression. Tumor response will be evaluated using RECIST v1.1 as the primary and immune-related RECIST as an exploratory measure.

Radiographic assessments of the chest, abdomen and pelvis are required for all tumor measurements using either MRI or computed tomography scans every 9 weeks (±7 days) for the first 12 months following by every 12 weeks (±7 days). The same assessment method and technique for acquiring images must be used throughout the study to characterize each identified and reported lesion at each tumor measurement. These radiologic assessments will be made at the investigator site and images will be submitted to a central imaging center for BICR. An MRI of the brain should be done at screening to determine presence or absence of brain metastases at baseline. If the screening image is negative, additional brain imaging is not required unless clinically indicated.

Safety assessment will encompass an ongoing review of AEs, including incidence of treatment-emergent AEs, incidence of TRAEs, serious AEs, AEs leading to drug discontinuation, clinical laboratory tests, vital signs, physical examination, electrocardiograms and baseline echocardiograms. Reporting of AEs will begin after the first dose of BEMPEG plus NIVO and will continue until 100 days after the last dose. Severity of AEs will be determined using the National Cancer Institute CTCAE v5.0 guidelines. The relationship of each AE to BEMPEG and/or NIVO will be evaluated by the investigator. Ongoing AEs will be monitored until resolution, patient loss to follow-up, patient death, or the final follow-up visit, whichever comes first. Safety data for the first 20 patients who receive at least two cycles of BEMPEG plus NIVO (6 weeks) will be included in the initial planned safety review conducted by the Independent Data Monitoring Committee.

Health-related quality of life (QoL) assessments will also be conducted. The three-level version of the EuroQol Group's EQ-5D (EQ-5D-3L), EORTC QoL Questionnaire (QLQ-C30) and the Functional Assessment of Cancer Therapy GP5 are to be completed by patients at screening, every 3 weeks while on treatment and at follow-up.

Biomarker assessments will be carried out using tumor tissue and blood samples. Blood samples will be assessed for immune activation and tumor factors that support the mechanism of action of BEMPEG combined with NIVO, including, changes in cytokines and soluble CD25 (which is a specific pharmacodynamic biomarker for BEMPEG). Blood samples will also be used for pharmacokinetic analyses to measure plasma concentrations of BEMPEG and its metabolites and serum concentrations of NIVO, using pharmacokinetic parameters such as maximum concentration (C_{max}), time to C_{max}, area under the curve, clearance, volume of distribution and half-life. A mandatory tumor biopsy will be collected during screening and an optional tumor biopsy will be collected in cycle 1 around week 3. These samples will be used to evaluate on-treatment changes in PD-L1 status and for exploration of predictive biomarkers of response and resistance to immunotherapy.

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Statistical analysis methods

The total patient enrollment should be approximately 205 patients, including 175 patients who will receive BEMPEG plus NIVO and 30 patients who received gemcitabine plus carboplatin under a previous amendment of the study protocol. Patients in the gemcitabine plus carboplatin arm, which was intended to serve as a reference arm, will continue to receive this combination and be included in the study population for reference purposes.

The sample size was determined by the PD-L1 low population. Based on experiences in the KEYNOTE-052 study, which used the PD-L1 IHC 22C3 assay for assessment of PD-L1, it is expected that 70% of patients would have low tumor PD-L1 expression and the remaining 30% would have high tumor PD-L1 expression (CPS $\geq$10%) [12]. It is estimated that the study population would comprise approximately 110 patients with low tumor PD-L1 expression, 47 patients with high tumor PD-L1 expression and 18 patients with unevaluable PD-L1 status.

Populations for analysis include: the treated population (all patients who receive at least one dose of study drug); PD-L1 low population (all patients with low tumor PD-L1 expression [CPS <10] who receive at least one dose of study drug); and the PD-L1 high population (all patients with high tumor PD-L1 expression [CPS $\geq$10] who receive at least one dose of study drug).

ORR is defined as the percentage of patients with a confirmed best objective response of CR or PR, determined by BICR using RECIST v1.1. The ORR and its corresponding 95% exact CI will be calculated by the Clopper–Pearson method. DOR is defined for patients who have a confirmed CR or PR as the date from first documented CR or PR per RECIST v1.1 to the date that disease progression (as assessed by BICR) or death due to any cause are documented, whichever comes first. The median DOR will be estimated using the Kaplan–Meier method, with corresponding 95% CI and range values. PFS and OS will be estimated using the Kaplan–Meier method. PFS is defined as the time interval between the first dose and the first documented tumor progression occurrence (using RECIST v1.1 per BICR) or death due to any cause, whichever comes first. OS is defined as the time interval between first dose and death due to any cause. All safety data will be summarized for the treated population.

Conclusion

For patients with locally advanced or metastatic UC, immune modulation is an attractive therapeutic approach. However, further to the growing success of ICIs in this population, the combination of BEMPEG plus NIVO may broaden the benefits for those who are ineligible to receive cisplatin, especially for patients with low-expressing PD-L1 tumors. In addition to providing a chemotherapy-free option, this first-in-class combination with a manageable safety profile has demonstrated deep and durable responses. Encouraging efficacy and safety results were observed in the PIVOT-02 study evaluating the combination of BEMPEG plus NIVO in cisplatin-ineligible patients with metastatic UC, with responses observed regardless of baseline tumor cell PD-L1 expression. Thus, this combination addresses a high unmet need in the PD-L1-negative population. PIVOT-10 will further evaluate the antitumor activity of this combination by assessing the ORR in approximately 175 cisplatin-ineligible patients with locally advanced or metastatic UC. Findings of deep and durable responses may support the use of BEMPEG plus NIVO in this setting in clinical practice. Importantly, PIVOT-10 will further explore this treatment combination in cisplatin-ineligible patients with advanced UC and tumors with low PD-L1 expression, a population which is currently underserved by novel immune therapeutics.

Infographic

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download this infographic in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0795

Author contributions

RA Huddart, AO Siefker-Radtke, AV Balar, MA Bilen, T Powles, A Bamias, D Castellano, MF Khalil, MS Van Der Heijden, VS Koshkin, DW Pook, M Özgüroğlu, L Santiago, B Zhong, D Chien, W Lin, MA Tagliaferri and Y Loriot conceived, designed, or planned the study. RA Huddart, AO Siefker-Radtke, AV Balar, MA Bilen, T Powles, A Bamias, D Castellano, MF Khalil, MS Van Der Heijden, VS Koshkin, DW Pook, M Özgüroğlu, L Santiago, B Zhong, D Chien, W Lin, MA Tagliaferri and Y Loriot drafted, critically reviewed or revised the manuscript for important intellectual content. All authors reviewed the final version and are in agreement with the content and approved of the decision to submit.

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Bamias has also served as an advisor/consultant to AstraZeneca, Bristol-Myers Squibb, MSD, Pfizer and Pierre Fabre; and on the Speaker's Bureau for AstraZeneca, Bristol-Myers Squibb, Novartis and Pfizer. DE Castellano received institutional research funding from Janssen Oncology and travel expenses from AstraZeneca, Bristol-Myers Squibb, F Hoffmann–La Roche and Pfizer. DE Castellano has also served as a consultant/advisor to Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, F Hoffmann–La Roche/Genentech, Ipsen, Janssen Oncology, Lilly, MSD Oncology, Novartis, Pfizer, Pierre Fabre and Sanofi. MF Khalil has received research funding from and has also served as a consultant/advisor to Bristol-Myers Squibb. MS Van Der Heijden has received institutional research funding from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb and F Hoffmann–La Roche; and travel expenses from Astellas Pharma, F Hoffmann–La Roche, MSD Oncology and Novartis. MS Van Der Heijden has also served as a consultant/advisor to Astellas Pharma, AstraZeneca/MedImmune, Bristol-Myers Squibb, F Hoffmann–La Roche, Janssen, MSD Oncology and Seattle Genetics. VS Koshkin has served as a consultant/advisor to Janssen. DW Pook has received institutional research funding from Astellas Pharma, Bayer, Bristol-Myers Squibb, Exelixis, F Hoffmann–La Roche, Medivation, Merck Sharp & Dohme and Pfizer; honoraria from Astellas Pharma, Ipsen and Novartis; and travel expenses from Astellas Pharma, Bristol-Myers Squibb and Pfizer. DW Pook has also served as a consultant/advisor to Bristol-Myers Squibb, Merck Sharp & Dohme and Pfizer. M Özgüroğlu has no financial interests to disclose. L Santiago, B Zhong, D Chien, W Lin and MA Tagliaferri are employees of and have ownership interest (including stock, patents, etc.) in, Nektar Therapeutics. Y Loriot has received institutional research funding from AstraZeneca, Boehringer Ingelheim, Clovis Oncology, CureVac, Exelixis, Incyte, Janssen Oncology, Medivation, MSD Oncology, Nektar, Oncogenex, Pfizer and Sanofi; honoraria from Pfizer and Sanofi; and travel expenses from Astellas Pharma, AstraZeneca, F Hoffmann–La Roche, Janssen Oncology, MSD Oncology and Seattle Genetics. Y Loriot has also served as an advisor/consultant to Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, F Hoffmann–La Roche, Janssen, MSD Oncology and Seattle Genetics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, informed consent has been obtained from the participants involved.

Summary points

Background

- Chemotherapy-based regimens are the only approved first-line therapeutic options for patients with metastatic urothelial cancer (mUC), who are ineligible to receive cisplatin and have low programmed death-ligand 1 (PD-L1)-expressing tumors.
- Approximately 70% of cisplatin-ineligible patients with advanced UC have tumors with low PD-L1 expression.
- Few therapies have demonstrated statistically significant efficacy advantages in cisplatin-ineligible patients with low PD-L1 expression; thus, there is a high unmet need for new therapy options in this setting.

Bempegaldesleukin (NKTR-214)

- Bempegaldesleukin (BEMPEG; NKTR-214) is a CD122-preferential IL-2 pathway agonist that has been engineered to signal preferentially through the IL-2 intermediate affinity receptor (IL-2R$\beta\gamma$) found on $CD8^+$ effector T cells and natural killer cells as opposed to the high-affinity receptor (IL-2R$\alpha\beta\gamma$) found on Tregs.
- The ongoing Phase I/II PIVOT-02 study is investigating the chemotherapy-free combination of BEMPEG plus nivolumab (NIVO) in patients with locally advanced or metastatic solid malignancies, including UC. Preliminary results for patients with advanced or metastatic UC (n = 41) demonstrate encouraging efficacy and safety:
  - Among 27 patients who were evaluable for efficacy, objective response rate (ORR) was 48%, including a complete response rate of 19%;
  - Conversion of 70% of tumors from PD-L1 negative (<1% expression) at baseline to PD-L1 positive (≥1% expression) on treatment;
  - Manageable safety profile with the most common treatment-related adverse events being low-grade cytokine-related events (flu-like symptoms [71%], fatigue [56%], rash [46%], pruritis [32%]).

PIVOT-10

- PIVOT-10 (NCT03785925) is a Phase II study that is evaluating the safety and efficacy of BEMPEG plus NIVO in cisplatin-ineligible patients with locally advanced or metastatic UC regardless of PD-L1 expression.
- Eligible patients have histologically or cytologically confirmed inoperable, locally advanced or metastatic UC with measurable disease, be aged ≥18 years and have Eastern Cooperative Oncology Group performance status of ≤2.
- Study participants will receive BEMPEG 0.006 mg/kg intravenously plus NIVO 360 mg intravenously every 3 weeks and will be treated for a maximum of 2 years.
- The primary objective is ORR per Response Evaluation Criteria In Solid Tumors version 1.1 by blinded independent central review in patients with low PD-L1 expression; secondary objectives include ORR and duration of response in all treated patients and in patients whose tumors have low PD-L1 expression; safety and tolerability will also be assessed.
- The study protocol specified that approximately 175 patients would be enrolled and treated with BEMPEG plus NIVO, including 110 patients with low tumor PD-L1 expression.
- Based on the results of the PIVOT-10 trial, BEMPEG plus NIVO has the potential to address a high unmet need for an effective and well tolerated treatment for patients with cisplatin-ineligible advanced or metastatic UC with low tumor PD-L1 expression.
- This trial is being conducted in more than 120 sites in over 20 countries across five continents; for participating trial sites, please visit: https://clinicaltrials.gov and search NCT03785925.

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Article details

Title of article

PIVOT-10: Phase 2 study of bempegaldesleukin plus nivolumab in cisplatin-ineligible advanced urothelial cancer

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Article URL

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Trial registration number

NCT03785925

Primary objectives/rationale

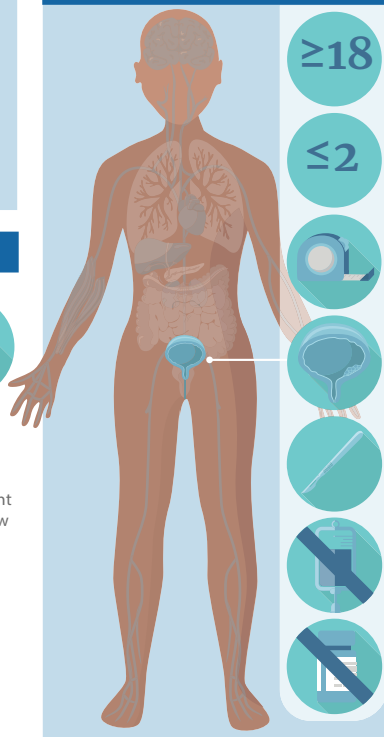
Primary objective

Evaluate the antitumor activity of BEMPEG plus NIVO in patients with low PD-L1 tumor expression

Secondary key objectives

Evaluate the antitumor activity, as well as safety and tolerability, of BEMPEG plus NIVO

Key eligibility criteria



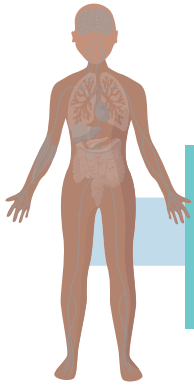
- ≥18: Age ≥18 years
- ≤2: ECOG PS ≤2
- Measurable disease per RECIST 1.1
- Histologically or cytologically documented inoperable, locally advanced or metastatic urothelial carcinoma
- Fresh biopsy or archival tissue
- No prior systemic chemotherapy or investigational agent for inoperable, locally advanced or metastatic urothelial cancer
- Ineligible for cisplatin

Study design and treatment

~175 participants | Global | Open-label | Multicenter | Single-arm Phase 2

Patients are being treated until disease progression, loss of clinical benefit, death, unacceptable toxicity, symptomatic deterioration, investigator or patient decision to discontinue treatment, patient withdrawal of consent, loss to follow up, or study termination, or for a maximum of 2 years

Study endpoints will be assessed in all treated patients as well as patients whose tumors have low PD-L1 expression (defined as CPS <10)



Population
- Untreated metastatic or unresectable urothelial cancer
- Ineligible for cisplatin
- Any PD-L1 status

n≈175

→ Bempegaldesleukin (0.006 mg/kg IV q3w) plus nivolumab (360 mg IV q3w)

→ PD-L1 low n≈110 | PD-L1 high n≈47 | PD-L1 non-evaluable n≈18

→ End of treatment

Outcome measures/endpoints

Primary endpoint:
ORR in patients with low tumor PD-L1 expression by BICR

Secondary endpoints:
ORR and DOR in all treated patients and patients with low tumor PD-L1 expression by BICR and investigator assessment; safety and tolerability

Glossary

BEMPEG: Bempegaldesleukin; BICR: Blinded independent central review; CPS: Combined Positive Score; DOR: Duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; IV: intravenous; NIVO: Nivolumab; ORR: Objective response rate; PD-L1: Programmed cell death ligand 1; q3w: Every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors.