Clinical Trial Protocol

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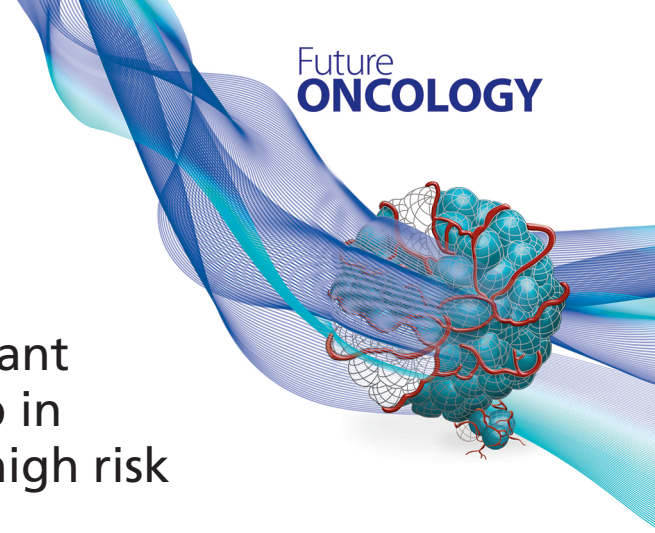

PIVOT-12: a Phase III study of adjuvant bempegaldesleukin plus nivolumab in resected stage III/IV melanoma at high risk for recurrence

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Bempegaldesleukin (BEMPEG: NKTR-214) is an immunostimulatory IL-2 cytokine prodrug engineered to deliver a controlled, sustained and preferential IL-2 pathway signal. Nivolumab (NIVO), a PD-L1 inhibitor, has been shown to prolong survival in patients with advanced melanoma and recurrence-free survival in the adjuvant setting. PIVOT-02 showed that BEMPEG plus NIVO was well-tolerated and demonstrated clinical activity as first-line therapy in metastatic melanoma. PIVOT-12 is a randomized, Phase III, global, multicenter, open-label study comparing adjuvant therapy with BEMPEG plus NIVO versus NIVO alone in adult and adolescent patients with completely resected cutaneous stage III/IV melanoma at high risk of recurrence. The primary objective is to compare the efficacy, as measured by recurrence-free survival, of BEMPEG plus NIVO versus NIVO.

Lay abstract: Following surgery, patients with advanced melanoma may require further treatment to reduce the likelihood of disease recurrence. Nivolumab (NIVO), a checkpoint inhibitor, reduces the risk of melanoma recurrence by enhancing the ability of the immune system to fight disease. Despite the availability of NIVO and other therapies, many patients with melanoma still experience disease recurrence after surgery. This article presents information on a clinical trial named PIVOT-12, which aims to assess the effectiveness of a new investigational drug called bempegaldesleukin that modifies the immune system and is given with NIVO to patients with stage III/IV melanoma following surgery. The main end point being measured is recurrence-free survival, which measures the time between a patient starting the study and the date of disease recurrence.

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Melanoma is the most serious form of skin cancer, and its incidence is continuing to rise throughout the world [1–3]. The prognosis, treatment and associated survival rates of primary cutaneous melanoma are dependent on the characteristics of the tumor (thickness and ulceration), presence of lymph node involvement and the presence or absence of distant metastases, as set out by the most recent, 8th edition, of the American Joint Committee on Cancer (AJCC) staging system [4,5]. Surgical resection alone has proven insufficient to cure many patients with stage III or IV melanoma; therefore, adjuvant systemic therapy is recommended to improve recurrence-free survival (RFS) rates for patients at a higher risk of recurrence [1,6].

For patients with unresectable or metastatic melanoma, the introduction of immune checkpoint inhibitors (ICI) has revolutionized the treatment landscape [6,7]. The PD-1 inhibitors, pembrolizumab and nivolumab (NIVO) and the combination of NIVO with the CTLA-4 inhibitor, ipilimumab, are now considered standard-of-care options for these patients [6,7]. The investigational combination of NIVO plus relatlimab, a LAG3 blocking antibody, has also shown clinical benefit compared with NIVO alone as first-line treatment of advanced melanoma [8].

The ICIs are also recommended as adjuvant therapy in resectable stage III and/or stage IV melanoma following complete resection [9–11]. Ipilimumab was the first ICI to be approved in the adjuvant setting based on results of the European Organization for Research and Treatment of Cancer (EORTC) 18071 study that showed that high-dose ipilimumab improved RFS, distant metastasis-free survival (DMFS) and overall survival (OS) in comparison to a placebo, in patients with completely resected stage III melanoma (stage IIIA>1 mm, stage IIIB/C; AJCC v7) [12–14]. Subsequently, the Phase III CheckMate 238 trial demonstrated the superiority of NIVO over ipilimumab in completely resected stage IIIB/C or stage IV melanoma (AJCC v7) [15,16]. NIVO demonstrated significant and sustained benefits in RFS compared with ipilimumab, with a median follow-up of 51.1 and 50.9 months, respectively. RFS at 4 years was 51.7% (95% CI: 46.8–56.3) in the NIVO group and 41.2% (95% CI: 36.4–45.9) in the ipilimumab group, with a hazard ratio (HR) of 0.71; p = 0.0003. OS at 4 years was 77.9% (95% CI: 73.7–81.5) in the NIVO group and 76.6% (95% CI: 72.2–80.3) with ipilimumab (HR: 0.87 [95% CI: 0.66–1.14]; p = 0.31) [15]. In addition, NIVO was better tolerated than ipilimumab with a lower rate of grade ≥3 treatment-related adverse events (TRAEs) (14.4 vs 45.9%) [16] and health-related quality-of-life was maintained for patients on NIVO treatment over the long-term follow-up period [17].

The Phase III EORTC 1325/KEYNOTE-054 trial of pembrolizumab versus placebo in patients with resected stage III (stage IIIA >1 mm, stage IIIB/C; AJCC v7) melanoma showed that adjuvant pembrolizumab resulted in a sustained and clinically meaningful improvement in RFS at a median of 3 years of follow-up [18]. The 3-year RFS was 63.7% (95% CI: 59.2–67.7) in the pembrolizumab group compared with 44.1% (95% CI: 39.6–48.4) for placebo (HR: 0.56 [95% CI: 0.47–0.68]; p < 0.001) [18]. Moreover, the 3.5-year DMFS was reported at 65.3% (95% CI: 60.9–69.5) and 49.4% (95% CI: 44.8–53.8) in the pembrolizumab group versus placebo (HR: 0.60 [95% CI: 0.49–0.73]; p < 0.001) [19]. Recent data also suggest a role for adjuvant pembrolizumab after complete resection in patients with high-risk stage II melanoma [20].

Adjuvant *BRAF*/*MEK*-targeted therapy with dabrafenib/trametinib has also been shown to prolong RFS and DMFS in patients with resected stage III (stage IIIA>1 mm, stage IIIB/C; AJCC v7) melanoma with *BRAF* V600-activating mutations [21] and is a recommended treatment option in this patient group [6,7].

Of note, while all these trials included a subset of patients with stage III disease deemed sufficiently high risk to warrant adjuvant treatment, the definitions of 'high-risk' stage III disease differed across trials. Furthermore, all trials used the 7th edition of the AJCC staging manual; this version was recently replaced by the 8th edition, where the number of stage III subgroups based on prognosis was revised from three (A–C) to four (A–D) [4]. A notable difference between the AJCC 7th and AJCC 8th edition is the prognosis for patients with stage IIIA disease; stage IIIA disease as defined by AJCC 7th edition staging, comprises a higher risk group than stage IIIA as defined by AJCC 8th edition staging (5-year melanoma-specific survival 78 vs 93%) [5].

Up to 48% of patients who have received adjuvant treatment for resected stage III or stage IV melanoma will still experience disease recurrence by 4 years [15,19]. Attempts to improve outcomes with the addition of ipilimumab to adjuvant anti-PD1 therapy have demonstrated conflicting results. A Phase III trial (CheckMate 915) comparing the addition of low-dose ipilimumab (1 mg/kg every 6 weeks) to NIVO did not improve RFS compared with NIVO alone in patients with completely resected stage IIIB–D or stage IV melanoma (AJCC v8) [22]. However, in

a randomized Phase II trial, conventionally dosed ipilimumab (3 mg/kg every 3 weeks) plus NIVO was superior to NIVO alone in patients with resected stage IV melanoma [23].

As such, there remains interest in researching novel adjuvant therapy combinations that have the potential to reduce or further delay recurrence and extend survival in patients with resected high-risk melanoma without adding substantial toxicity. Deeper understanding of patient characteristics and markers of response may uncover opportunities to deliver personalized treatment approaches for patients with resectable melanoma.

IL-2 pathway in cancer

IL-2 is an endogenous cytokine produced by immune cells and has important regulatory functions in immune response [24]. Harnessing the immune system to target tumor cells via the IL-2 pathway has been an approach successfully used to treat cancer [24]. High-dose IL-2 is an approved treatment for metastatic melanoma, with an overall response rate (ORR) reaching 23% [25]. Patients who are responsive achieve durable antitumor activity [25] and longer survival times (65 months in responders vs 10 months in the overall population) [26]. Data from a retrospective chart review of patients with metastatic melanoma or renal cell carcinoma treated with high-dose IL-2 suggests that clinical benefit may be underestimated [27]. However, treatment is associated with serious adverse events (AEs), including vascular leak syndrome; thereby, limiting its use to specialized centers that administer IL-2 in the in-patient setting [28].

IL-2 regulates the balance between immunostimulation and immunosuppression. The IL-2 pathway is activated when IL-2 binds to the IL-2 receptor (IL-2R). The pleiotropic effects of IL-2 signaling are mediated through the different IL-2R configurations made up of different receptor subunits including α, β and γ [24]. When IL-2 binds to the intermediate-affinity heterodimer IL-2Rβγ, expressed by naive and memory $CD4^+$ and $CD8^+$ T cells and natural killer (NK) cells, this leads to desired expansion of these immune effector cells to help the immune system target cancer cells. However, IL-2 also binds to the high-affinity heterotrimer IL-2Rαβγ, which is expressed constitutively by Tregs and type-2 innate lymphoid cells, leading to expansion of Tregs and unwanted downregulation of the immune response [29,30]. Engineering an agent to have biased IL-2 receptor binding has the potential to result in an improved immunostimulatory profile.

Bempegaldesleukin (BEMPEG: NKTR-214)

Bempegaldesleukin (BEMPEG: NKTR-214) is an immunostimulatory IL-2 cytokine prodrug that has been engineered to deliver a controlled, sustained and preferential IL-2 pathway signal (Figure 1) [31–35]. It comprises recombinant human IL-2 conjugated with an average of six releasable chains of polyethylene glycol moieties (PEG), which prevents rapid systemic immune activation upon administration [35,36]. The progressive release of these PEG chains yields a series of increasingly active IL-2 conjugates, which result in sustained concentrations of active drug and stable activity within the body [35,36]. The location of PEG chains at the IL-2/IL-2R α interface interferes with binding to IL-2 to the high-affinity IL-2Rα, while leaving binding to low-affinity IL-2Rβ unperturbed [36]. As such, BEMPEG preferentially binds the heterodimeric IL-2R βγ complex (predominantly expressed on NK cells and $CD8^+$ T cells), over the heterotrimeric IL-2R αβγ complex (predominantly expressed on immunosuppressive Tregs) [35,36].

In animal models, BEMPEG has been shown to induce an increased proliferation and infiltration of $CD8^+$ T cells and NK cells with limited expansion of Tregs, in the tumor microenvironment [36–38]. In the first-in-human Phase I EXCEL trial (ClinicalTrials.gov: NCT02869295) of BEMPEG monotherapy, the therapy proved to be well-tolerated, thereby allowing for outpatient administration, and showed clinical activity including tumor shrinkage and durable disease stabilization in heavily pretreated patients with advanced solid tumors [31]. There were significant increases in $CD4^+$ T cells, $CD8^+$ T cells and NK cells, demonstrating activation of the IL-2 pathway and subsequent robust immune activation [31]. BEMPEG plus NIVO has also been shown to enhance tumor programmed death-ligand-1 (PD-L1) expression, providing a rationale for further exploration of this combination in other malignancies [32].

The Phase I/II PIVOT-02 trial (ClinicalTrials.gov: NCT02983045) demonstrated that the combination of BEMPEG plus NIVO was well-tolerated and produced durable responses that deepened over time [32]. The dose-escalation phase included patients with advanced solid tumors and determined a recommended Phase II dose (RP2D); BEMPEG 0.006 mg/kg plus NIVO 360 mg every 3 weeks [32]. One of the Phase II dose-expansion cohorts evaluated the efficacy and safety of BEMPEG plus NIVO in patients with previously untreated metastatic

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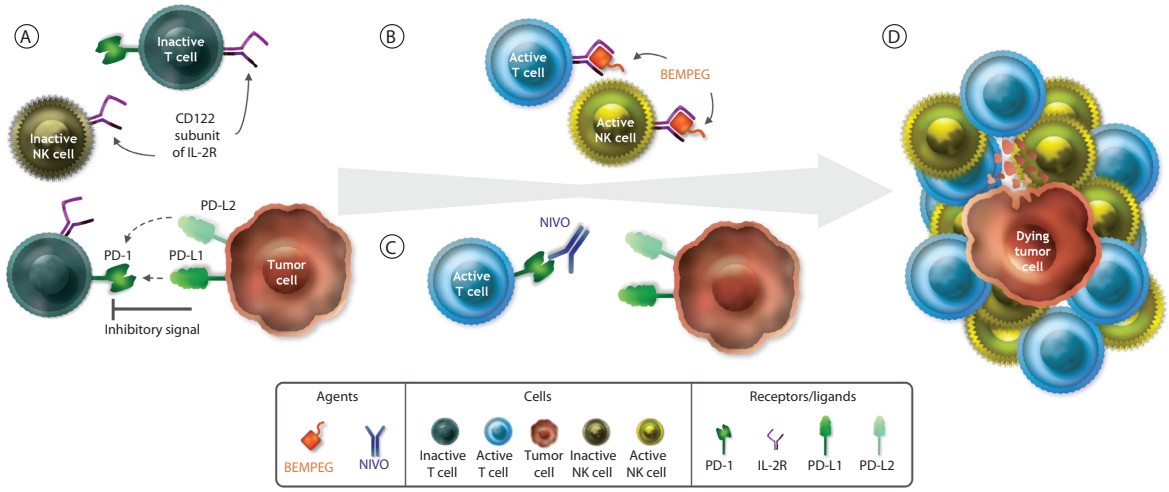

Figure 1. Mechanism of action of BEMPEG. BEMPEG is an immunostimulatory IL-2 cytokine prodrug that has been engineered to deliver a controlled, sustained and preferential IL-2 pathway signal. It comprises recombinant human IL-2 conjugated with an average of six releasable chains of PEG. BEMPEG plus NIVO demonstrates antitumor activity through the activation of cytotoxic function of immune cells. **(A)** An immunosuppressive TME and PD-1 and PD-L1/2 signaling support tumor growth [32]. **(B)** BEMPEG preferentially binds the CD122 subunit of the IL-2 receptor and expands effector T cells and NK cells over immunosuppressive Tregs in the TME [31,33]. **(C)** NIVO blocks PD-1 on T cells, restoring their cytotoxic function and enabling a potential antitumor response [34]. **(D)** BEMPEG plus NIVO leverage two clinically validated complementary immune-oncology pathways to create the potential for a greater antitumor response [31,35].
BEMPEG: Bempegaldesleukin; NK: Natural killer; PEG: Releasable polyethylene glycol; TME: Tumor microenvironment.

melanoma [39]. A total of 41 patients were enrolled in this trial. In the 38 patients who were evaluable for efficacy, with a median duration of follow-up of 29 months, the ORR was reported at 52.6% (20/38) and the complete response rate at 34.2% (13/38); additionally, the median progression-free survival was 30.9 months (95% CI: 5.3 – not estimable) [39]. Grade ≥3 TRAEs and immune-related AEs occurred in 17.1 and 4.9% of patients, respectively [39]. Most TRAEs resolved without intervention or were mitigated by over-the-counter oral or topical treatments [39]. No grade 3 hypotension was observed in the melanoma cohort [39]. The most common TRAEs were flu-like symptoms, rash, fatigue, pruritus, arthralgia and nausea [39]. Exploratory, early treatment blood biomarkers ($CD8^+$ polyfunctional strength difference and eosinophils) correlated with treatment response [39] and may help identify patients who may benefit the most from treatment if validated by ongoing research. The novel therapeutic combination of BEMPEG plus NIVO received 'breakthrough therapy' designation from the US FDA for the treatment of patients with previously untreated, unresectable or metastatic melanoma [32,39]. The PIVOT-02 findings are being confirmed in an ongoing randomized, registrational, Phase III trial in previously untreated patients with unresectable or metastatic melanoma (PIVOT IO 001; ClinicalTrials.gov: NCT03635983) [40]. Findings from preliminary studies such as PIVOT-02 lay the foundation for the exploration of BEMPEG plus NIVO as adjuvant treatment in patients with melanoma after complete resection.

PIVOT-12 study

PIVOT-12 (ClinicalTrials.gov: NCT04410445) is a randomized, Phase III, global, open-label study to compare adjuvant therapy of BEMPEG combined with NIVO versus NIVO alone in adult and adolescent (≥12 years of age) patients with completely resected stage IIIA with lymph node metastasis >1 mm, stage IIIB/C/D or stage IV cutaneous melanoma who are at high risk for recurrence. The trial is a multicenter study, with close to 200 active or planned sites in 16 countries across four continents. An open-label study design was chosen as the different dosing schedules used in each treatment arm would require addition placebo infusion visits. Additionally, the adverse events experienced with BEMPEG would likely lead to unblinding of study treatments.

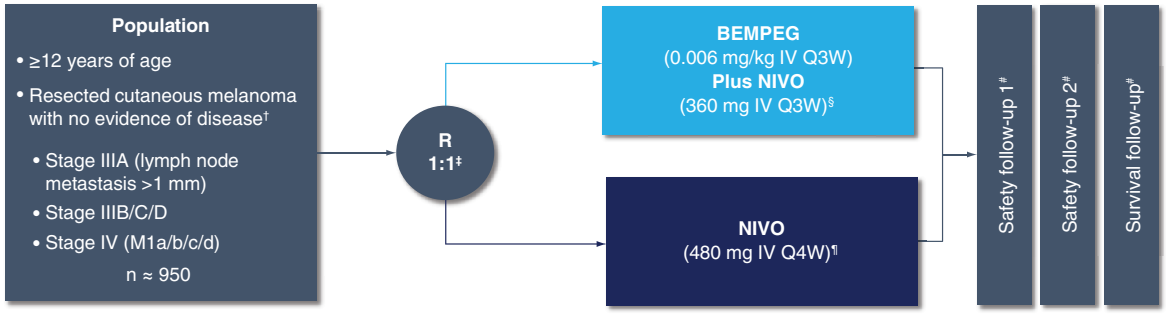

Figure 2. Phase III PIVOT-12 study design.
†By AJCC 8th edition.
‡Randomization is stratified by PD-L1 expression status on tumor cells (≥1 vs <1% vs indeterminate/not evaluable) and disease stage per AJCC 8th edition at screening (stage IIIA/IIIB vs stage IIIC vs stage IIID/IV).
§NIVO 4.5 mg/kg iv. Q3W for patients <40 kg.
¶NIVO 6.0 mg/kg iv. Q4W for patients <40 kg.
#Safety follow-up one: 30 (± 7) days after the last dose of all study treatment(s); safety follow-up two: 100 (± 7) days after the last dose of all study treatment(s); survival follow-up: Q12W (± 14 days) following safety follow-up visit two or 100 (± 7) days after the last dose of study treatment.
AJCC: American Joint Committee on Cancer; BEMPEG: Bempegaldesleukin (NKTR-214); iv.: Intravenous; PD-L1: Programmed death-ligand-1; Q3W: Every 3 weeks; Q4W: Every 4 weeks; Q12W: Every 12 weeks; R: Randomized.

Background & rationale

Adjuvant therapy with NIVO has shown promising results in adult patients with melanoma with involvement of lymph nodes, or with metastatic disease who have undergone complete resection, leading to longer RFS [15,16]; however, further reducing recurrence and extending survival remains the ultimate treatment goal. The immunogenic properties of BEMPEG with the induction of tumor-infiltrating lymphocytes and upregulation of the PD-1/PD-L1 axis makes BEMPEG a potentially promising combination therapy for use with ICIs that target and inhibit the PD-1/PD-L1 pathway [31,35]. Moreover, the side-effect profile of BEMPEG generally does not overlap with that of ICIs [31,41], further supporting the use of BEMPEG as a potentially complementary combination partner with ICIs.

Study design & objectives

The purpose of PIVOT-12 is to compare the efficacy and safety of BEMPEG plus NIVO versus NIVO alone in patients with completely resected stage IIIA with lymph node metastasis >1 mm, stage IIIB/C/D or stage IV cutaneous melanoma with no evidence of residual disease who are at high risk for recurrence (Figure 2). The definition for 'high risk' in this study is based on melanoma-specific survival data according to AJCC 8th edition staging classification. Although patients with stage IIIA disease appear to have favorable melanoma-specific survival [41], it has been acknowledged that patients with lymph node metastasis >1 mm have a worse prognosis than those with less lymph node involvement [5,42,43]. Therefore, patients with stage IIIA melanoma with lymph node metastasis >1 mm are also considered to be at high risk of recurrence and are included in this study.

All patients (or their legal guardian) must provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered part of the patient's standard care. The study will comprise a screening phase, a treatment phase and a long-term follow-up phase. During the screening phase, patients' eligibility will be assessed (see eligibility criteria below). Patients who consent to participate in the clinical study, but are not subsequently randomized, are classified as screen failures.

Following screening, eligible patients will be randomized (1:1) to receive BEMPEG 0.006 mg/kg in combination with NIVO 360 mg as intravenous (iv.) infusions every 3 weeks (Q3W; administered sequentially) or NIVO 480 mg monotherapy as an iv. infusion every 4 weeks (Q4W). Patients will be stratified by PD-L1 expression status on tumor cells (≥1 vs <1% vs indeterminate/not evaluable), as determined by PD-L1 immunohistochemistry using the 28–8 PharmaDx assay (Dako, an Agilent Technologies, Inc. company, CA, USA) and disease stage per AJCC 8th edition at screening (stage IIIA/IIIB vs stage IIIC vs stage IIID/IV). The number of patients with indeterminate/not evaluable PD-L1 status will be capped at a maximum of 25% of the total patient population. Patients will be treated for up to 1 year (a maximum of 17 cycles for the experimental arm and 13 cycles for the control arm)

Table 1. PIVOT-12 study end points.

Primary end point
• RFS by BICR in patients in all treated patients
Secondary end points
• OS in all treated patients
• DFMS (investigator-assessed and BICR) in patients who are stage III at study entry
• PFS2 in all treated patients
• Safety and tolerability
• Patient-reported outcomes (EORTC QLQ-C30; global health/quality of life and physical functioning subscales)
• RFS by BICR based on PD-L1 expression
• RFS per investigator assessment

BICR: Blinded independent central review; DMFS: Distant metastasis-free survival; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer QoL Questionnaire; OS: Overall survival; PFS2: Progression-free survival after the next line of treatment; RFS: Recurrence-free survival.

or until disease recurrence, death, unacceptable toxicity, investigator or patient decision to discontinue treatment, patient withdrawal of consent, loss to follow-up or study termination.

The BEMPEG study dose was determined by considering the clinical safety profile and evidence of robust immune system activation observed at the RP2D of 0.006 mg/kg iv. Q3W in the PIVOT-02 (ClinicalTrials.gov: NCT02983045) study [31]. The body weight-adjusted dose of 0.006 mg/kg is expected to provide similar exposure to BEMPEG in adults and adolescents; therefore, there is no adjusted dosage for adolescents. NIVO 360 mg Q3W is used in the experimental arm because this is the RP2D identified for the combination with BEMPEG in the PIVOT-02 study [31] and is being investigated in multiple studies of this combination, including in metastatic melanoma. NIVO 480 mg Q4W has been chosen for the control arm because this regimen is globally approved for adjuvant melanoma [10]. For adolescent patients with a body weight <40 kg, NIVO dosing will be weight-based adjusted to 4.5 mg/kg Q3W or 6.0 mg/kg Q4W in the BEMPEG plus NIVO arm and NIVO monotherapy arm, respectively.

The long-term follow-up phase comprises two safety follow-up visits and survival follow-up visits that will continue until withdrawal of consent, death, loss to follow-up or study termination by the sponsor. The first safety follow-up visit should occur 30 (± 7) days after the last dose of all study drug(s) or when the decision is made to discontinue treatment. The second visit should occur 100 (± 7) days after the last dose of all study treatment(s). Survival follow-up will be required for all patients, either via telephone or in-person, every 12 weeks (± 14 days). End of study is defined as no more than 5 years after randomizing the last patient or the sponsor's decision to terminate the study, whichever comes first. The estimated primary completion date is July 2027.

The primary objective is to compare the efficacy of BEMPEG in combination with NIVO to NIVO alone by assessing RFS per blinded independent central review, up to 5 years. RFS is defined as the time between the date of randomization and the date of first recurrence, new primary melanoma or all-cause death. Key secondary objectives include OS in all treated patients; DMFS, defined as the time between randomization and the date of first distant metastasis or death due to any cause, whichever occurs first, in patients who are stage III at study entry; and safety and tolerability. The complete list of trial end points is presented in Table 1.

Key eligibility criteria

Patients are required to have histologically confirmed stage IIIA (at least one lymph node metastasis measuring >1 mm at greatest diameter), stage IIIB/C/D or stage IV (M1a/b/c/d) cutaneous melanoma by AJCC 8th edition at study entry that has been completely surgically resected within 12 weeks prior to randomization. Sentinel node biopsy is sufficient to determine stage; completion of lymph node dissection is not required for enrollment. Patients must be ≥12 years of age when signing the informed consent form, except where local regulations, countries and/or institutional policies do not allow patients <18 years of age to participate. Patients must provide written informed consent, follow the study procedures and have an Eastern Cooperative Oncology Group performance status of 0 or 1 (≥17 years of age) or a Lansky Performance Score of ≥80% (12–16 years of age, inclusive). Tumor tissue from a biopsy or resected disease must be provided to determine PD-L1 expression status at enrollment. Patients with ocular or uveal melanoma or mucosal melanoma; an active, known or suspected autoimmune disease; a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent); or other immunosuppressive medications within 14 days of randomization will be excluded from the study. Patients must not have received: prior therapy for melanoma (except surgery for melanoma and/or adjuvant radiation for CNS lesions); prior treatment with interferon, talimogene laherparepvec, IL-2-directed therapy, anti-PD-1, anti-PD-L1,

anti-PD-L2, anti-CD137 or anti-CTLA-4 antibody or any other antibody or drug specifically targeting T-cell costimulation or ICI pathways; or treatment with an investigational agent or device within 28 days prior to randomization is not allowed. The full eligibility criteria are presented in Supplementary Table 1.

Statistical analysis

Approximately 950 patients (475 per treatment arm) will be enrolled in the study. The sample size is calculated to power the comparison of RFS between the two treatment arms in the intent-to-treat (ITT) population. A total of 400 RFS events are needed for the final analysis. Two formal interim analyses of RFS are planned for this study.

Primary analysis

A log-rank test, stratified by disease stage and PD-L1 status, will be used to compare RFS between the two treatment arms in the ITT population. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the HR and corresponding 95% CI. The Kaplan–Meier method will be used to further evaluate RFS.

Secondary analysis

If RFS by blinded independent central review is statistically significant at any of the planned analyses, the OS end point will be analyzed when the follow-up time is at least 5 years for all patients. The secondary analysis of OS in the ITT population will be conducted using a two-sided log-rank test stratified by randomization stratification factors only if the primary analysis of RFS claims significance. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the HR and corresponding 95% CI. The Kaplan–Meier method will be used to summarize OS further. Other secondary time-to-event end points will be analyzed similarly to OS.

Conclusion & future perspectives

ICIs have become the standard of care for unresectable and metastatic melanoma and have transformed the treatment landscape [6,7]. In patients with resectable disease at a high risk of recurrence, adjuvant use of ICIs have been shown to improve RFS and DMFS [12–16,18,19]; survival benefits have also been demonstrated with ipilimumab [12,14], but not for anti-PD1-targeted agents [15,16,18,19]. However, there remains a need to improve the RFS for these patients. BEMPEG is an immunostimulatory IL-2 cytokine prodrug that has been engineered to deliver a controlled, sustained and preferential IL-2 pathway signal [31]. The Phase I/II PIVOT-02 trial (ClinicalTrials.gov: NCT02983045) demonstrated that the combination of BEMPEG plus NIVO was well-tolerated and produced durable responses that deepened over time in patients with previously untreated metastatic melanoma [32,39]. PIVOT-12 will evaluate the efficacy of adjuvant BEMPEG combined with NIVO in patients with completely resected cutaneous melanoma who are at high risk for recurrence. The findings from this study may support the use of this combination treatment approach in the adjuvant setting for resectable melanoma in clinical practice.

Executive summary

Background

- For patients with metastatic melanoma, surgical resection remains a first-line treatment for eligible individuals; however, adjuvant therapies may be required for those at high risk for recurrence.
- The adjuvant use of checkpoint inhibitors, including nivolumab (NIVO) and pembrolizumab, have shown good efficacy, but up to 48% of patients experience disease recurrence within 4 years.
- There remains a need for novel adjuvant therapy combinations that benefit patients with resected melanoma.

Bempegaldesleukin (NKTR-214)

- Bempegaldesleukin (BEMPEG: NKTR-214) is an immunostimulatory IL-2 cytokine prodrug that has been engineered to deliver a controlled, sustained and preferential IL-2 pathway signal.

Nivolumab

- NIVO is a human immunoglobulin G4 monoclonal antibody that binds to programmed death receptor-1, subsequently blocking the pathway and inducing an antitumor response.

PIVOT-12 study design

- PIVOT-12 (ClinicalTrials.gov: NCT04410445) is a randomized, open-label, global, multicenter study comparing the combination of BEMPEG 0.006 mg/kg intravenous (iv.) every 3 weeks (Q3W) plus NIVO 360 mg iv. Q3W with NIVO monotherapy 480 mg iv. every 4 weeks in adults and adolescents (≥12 years of age) with completely resected

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stage IIIA with lymph node metastasis >1 mm, stage IIIB/C/D or stage IV cutaneous melanoma with no evidence of disease who are at high risk for recurrence.

- Patients will be treated up to approximately 1 year (maximum of 17 cycles for the experimental arm and 13 cycles for the control arm) or until disease recurrence, death, unacceptable toxicity, investigator or patient decision to discontinue treatment, patient withdrawal of consent, loss to follow-up or study termination.
- End of study is defined as no more than 5 years after randomizing the last patient or the sponsor's decision to terminate the study, whichever comes first.

PIVOT-12 study objectives

- The primary objective is to compare the efficacy, as measured by recurrence-free survival by blinded independent central review, of BEMPEG plus NIVO versus NIVO.
- The secondary objectives include overall survival, distant metastasis-free survival, progression-free survival after the next line of treatment, safety and tolerability, patient-reported outcomes and the predictive strength of programmed death-ligand 1 as a biomarker.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-1286

Infographic

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download the infographic in your browser, please click here.

Author contributions

All authors met the criteria for authorship set forth by the International Committee of Medical Journal Editors and were involved in the manuscript's conception, preparation and approval.

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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 patients involved.

Data sharing statement

Nektar is committed to sharing anonymized individual patient-level data and supporting clinical documents from eligible studies with qualified scientific researchers. These requests are reviewed and approved by an independent review panel. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

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