2.0 SYNOPSIS

Name of the Sponsor: Nektar Therapeutics	**Individual Study Table Referring to Part of the Dossier:**	**For National Authority Use Only**
Name of Finished Products: bempegaldesleukin (NKTR-214 drug product); Keytruda®	**Volume:**	
Name of Active Ingredients: bempegaldesleukin (NKTR-214 drug substance) pembrolizumab (anti-programmed cell death protein 1 [anti-PD-1] antibody)	**Page:**	

Title of Study:

A Phase 2/3, Randomized, Open-label Study to Compare Bempegaldesleukin Combined with Pembrolizumab Versus Pembrolizumab Alone in First-Line Treatment of Patients with Metastatic or Recurrent Head and Neck Squamous-Cell Carcinoma with PD-L1 Expressing Tumors (PROPEL-36)

Investigators and Study Centers:

One patient was dosed in this study [redacted] at Nebraska Methodist Hospital, Omaha, NE, USA. The study was discontinued on 16 June 2022.

Sites that screened or enrolled patients:

- Attikon University General Hospital, Athens, Greece [redacted]
- Universitätsklinikum Salzburg, Landeskrankenhaus, Salzburg Austria [redacted]
- ASST degli Spedali Civili di Brescia - Spedali Civili di Brescia, Lombardia, Italy [redacted]

See Appendix 16.1.4

Publications: none

Study Period:	**Development Phase:**
First patient registered: 23 February 2022 Study completion date: 16 June 2022	2/3

Objectives:

Primary Objectives

- To compare the overall survival (OS) of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.
- To compare the objective response rate (ORR) of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.

Secondary Objectives

- To compare progression-free survival (PFS) of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.
- To compare time to deterioration in global health status/quality of life, pain, and swallowing of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.
- To compare mean change from baseline in global health status/quality of life of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.
- To compare the overall safety and tolerability of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.

[redacted]

[redacted]

Rationale for the Change in Planned Analyses

On 14 March 2022, Nektar Therapeutics and Bristol Myers Squibb (BMS) reported that their PIVOT-IO-001 study did not meet its primary endpoint of demonstrating an efficacy advantage from addition of bempegaldesleukin to nivolumab therapy in patients with previously untreated inoperable or metastatic melanoma. On 14 April 2022, negative topline results from both PIVOT-09 (renal cell carcinoma) and PIVOT-10 (urothelial cancer) studies were reported. Based on these 3 large negative studies, Nektar Therapeutics and SFJ Pharmaceuticals, Inc. in consultation with the study Independent Data Monitoring Committee (DMC) made the decision to discontinue the PROPEL-36 trial on 21 April 2022 (16.2.4.3). At the time of termination, 1 patient was enrolled and treated in this study, so no summaries are produced; patient-level demographics, disposition and adverse event (AE) listings are provided.

Methodology:

This was planned to be a multicenter, randomized, open-label, Phase 2/3 study to evaluate the efficacy and safety of bempegaldesleukin combined with pembrolizumab compared with pembrolizumab monotherapy in patients with recurrent or metastatic head and neck squamous-cell carcinoma (HNSCC) with positive PD-L1 expression (combined positive score [CPS] $\geq$ 1).

The study used an adaptive design based on prespecified criteria and an independent, external DMC was to monitor efficacy and safety, approximately twice per year. The first planned interim analysis was to address futility. Enrollment was to pause for approximately 4 months after approximately 200 patients had been randomized, and the first interim analysis was to occur at least one month after the last patient of the Phase 2 portion had been randomized in the study. If the ORR passed the prespecified futility boundary, the Phase 3 portion of the study was to begin with an expected 300 additional patients to be randomized. The second interim analysis was to be conducted when approximately 500 patients had been randomized and about 231 OS events had been observed. At the second interim analysis, if the OS efficacy boundary had been crossed, the trial would have been stopped for efficacy. Otherwise, conditional power was to be calculated to determine the OS event size for final analysis.

Patient randomization was at a 1:1 ratio to receive 1 of 2 treatments:

- Arm A: Bempegaldesleukin plus pembrolizumab every 3 weeks (q3w) for up to 35 cycles (approximately 2 years).
- Arm B: Pembrolizumab monotherapy q3w for up to 35 cycles (approximately 2 years).

Randomization was stratified according to the following factors:

1. Disease status (metastatic vs recurrent only).
2. PD-L1 tumor expression determined by PD-L1 immunohistochemistry (IHC) 22C3 PharmDx (CPS $\geq$ 20 vs CPS 1-19) at either a local or the central laboratory.

   Note: CPS = the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100; specimen PD-L1 expression: CPS $\geq$ 1.
3. Human papillomavirus (HPV) status for oropharyngeal cancer determined by p16 IHC (positive vs negative). For patients with cancers of the oral cavity, hypopharynx, and larynx, HPV status was considered HPV negative.

Any patients attaining a complete response could consider stopping study drug if they met criteria for holding therapy. Patients who stopped study drug after receiving 35 cycles (approximately 2 years) for reasons other than disease progression or intolerability, or patients who attained a complete response and stopped study drug would have been eligible for up to 17 cycles (approximately 1 year) of retreatment upon experiencing Investigator-determined radiographic disease progression. The decision to retreat was at the discretion of the Investigator only if the patient met the criteria for retreatment and the trial was ongoing.

After the end of treatment, each patient was to be followed for 90 days after the last dose of all study drug(s) for AE monitoring, including serious AEs (SAEs) and AEs of special interest (AESIs). Patients who discontinued for reasons other than centrally verified disease progression were to have post-treatment follow-up for disease status until disease progression was verified by the central imaging vendor, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All patients were to be followed for OS until death, the patient withdrew consent, the patient was lost to follow-up, or the study was terminated by the Sponsor.

The Sponsor estimated that the study would be fully enrolled within approximately 25 months. Analyses were anticipated at the following times (relative to the first patient's randomization date): approximately 14 months for the first interim analysis, approximately 32 months for the second interim analysis, and approximately 38 to 52 months for the final analysis for OS.

Number of Patients Planned:

Approximately 500 patients (250 per arm).

Number of Patients:

The results in this report pertain to 1 patient [redacted], who received 2 study-drug cycles.
7 patients were screened, 2 patients randomized, 1 patient dosed; 16.2.4.2

Sex: [redacted]

Age: [redacted]

Ethnicity (Race): [redacted]

16.2.4.1

Diagnosis and Main Criteria for Eligibility (Key Inclusion Criteria):

- Had histologically or cytologically-confirmed recurrent or metastatic HNSCC that was considered incurable by local therapies.
  - No prior systemic therapy for recurrent or metastatic disease. Systemic therapy given as part of multimodal treatment for locally advanced disease was allowed if completed more than 6 months prior to signing consent.
  - The eligible primary tumor locations were oropharynx, oral cavity, hypopharynx, and larynx.
  - Patients could not have a primary tumor site of nasopharynx (any histology) and/or unknown primary.
- Had measurable disease based on RECIST 1.1 as determined by the local site Investigator. Tumor lesions situated in a previously irradiated area were considered measurable if progression had been shown in such lesions since irradiation.
- ECOG Performance Status of 0 or 1.
- Tumor tissue from a core, incisional, or excisional biopsy (fine needle aspirates were not acceptable) to the central laboratory for determination of PD-L1 status (if not determined at local laboratory) and exploratory biomarker analyses. A newly obtained biopsy was strongly preferred, but archival tumor biopsy could have been used and provided.
- The tumor must have had positive PD-L1 expression (ie, CPS $\geq$ 1) as determined with a PD-L1 IHC 22C3 PharmDx diagnostic kit at either a local or central laboratory.
- Patients with oropharyngeal cancer must have had results from testing of HPV status defined as p16 IHC testing using CINtec® p16 Histology assay. For patients with oral cavity, hypopharynx, or larynx cancers, HPV testing by p16 IHC was not required as by convention these tumor locations are assumed to be HPV negative.

Test Product, Dose and Mode of Administration, Batch Number:

- Bempegaldesleukin 0.006 mg/kg intravenous (IV) infusion every 3 weeks (q3w):

[redacted]	[redacted]	[redacted]

- Pembrolizumab 200 mg IV infusion q3w:

[redacted]	[redacted]	[redacted]

Duration of Treatment:

- Treatment was to be given for 35 cycles (approximately 2 years) following the date of the first dose of study drug/s or until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator decision to discontinue treatment, patient decision to discontinue treatment or withdraw consent, loss to follow-up, or Sponsor decision to terminate the trial.
- Following the Sponsor's decision to end the trial, treatment was discontinued after Patient [redacted] received 2 cycles.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Pembrolizumab 200 mg IV infusion q3w (N/A)

Criteria for Evaluation:

Efficacy: The primary efficacy measurements were to be OS and ORR by the blinded independent central review (BICR). The key secondary efficacy measurement was to be PFS by BICR.

Safety: Safety was assessed by review of the 1 randomized and treated patient's data [redacted].

Statistical Methods: Per the Statistical Analysis Plan (SAP) v.2.0 (16.1.9), no summary data was produced. Safety data were compiled from listings derived from the case report form (CRF).

Summary and Conclusions:

[redacted]

Safety Results

The patient experienced 1 Grade 1 adverse event of cough (16.2.7). Per investigator, cough was assessed as related to pembrolizumab. The company/Sponsor medical assessment attributed causality to the combination of bempegaldesleukin + pembrolizumab (data on file).

Conclusions:

One patient received 2 cycles of the study drugs (bempegaldesleukin 0.006 mg/kg IV and pembrolizumab 200 mg IV) before the bempegaldesleukin program was discontinued and the study was terminated. The patient experienced a Grade 1 AE of cough. No SAEs were reported.

Date of Report:	27 July 2022