MULTIDISCIPLINARY HEAD and NECK CANCERS SYMPOSIUM
EXTRAORDINARY CARE: Collaborative, Targeted, Diverse, Patient Centered
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A phase 2/3, randomized, open-label study of bempegaldesleukin plus 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)

T.Y. Seiwert[1], R.I. Haddad[2], D. Johnson[3], M. Gillison[4], U. Keilholz[5], M Tahara[6], J.P. Machiels[7], J. Deeken[8], V. Villaflor[9], Y. Su[10], T. Guthrie[11], D.M. Shin[12], K. De Block[13], A. Meirovitz[14], D. Chien[15], M.A. Tagliaferri[15], J. Zalevsky[16], K.J. Harrington[17]

[1]Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Division of Head and Neck Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [3]Medical Oncology, Ochsner Medical Center, New Orleans, LA, USA, [4]Thoracic/Head and Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA, [5]Comprehensive Cancer Center, Charité – Universitätsmedizin, Berlin, Germany, [6]Medical Oncology, National Cancer Center Hospital East, Chiba, Japan, [7]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, [8]Medical Oncology, Inova Schar Cancer Institute, Fairfax, VA, USA, [9]Department of Medical Oncology, City of Hope, Chicago, IL, USA, [10]Medical Oncology and Hematology Department, Nebraska Methodist, Omaha, NE, USA, [11]Medical Oncology Division, GenesisCare, Jacksonville, FL, USA, [12]Department of Medical Oncology and Hematology, Emory Winship Cancer Institute, Atlanta, GA, USA, [13]Oncology Department, AZ Sint-Maarten, Antwerp, Belgium, [14]Department of Oncology, Hadassah Medical Center, Jerusalem, Israel, [15]Clinical Development, Nektar Therapeutics, San Francisco, CA, USA, [16]Research and Development, Nektar Therapeutics, San Francisco, CA, USA, [17]Department of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK

BACKGROUND

- HNSCC represents the eighth most common cancer worldwide[1]
- PEMBRO, an ICI, is the preferred first-line therapy for advanced HNSCC alone in patients whose tumors express PD-L1 (CPS ≥1) or in combination with platinum-based chemotherapy in patients regardless of their tumor PD-L1 status[2,3]
  - However, 1-year survival rates with PEMBRO remain low (~50%), with or without chemotherapy[4]
  - Furthermore, some patients are ineligible for or refuse combination treatment with PEMBRO plus chemotherapy
- An unmet need remains for effective, chemotherapy-free, ICI-based therapy options for patients with advanced HNSCC
- Previous clinical studies have demonstrated clinical activity with IL-2 or IL-2-based immunotherapy in patients with HNSCC;[5–7] however, high toxicity rates and the requirement for in-patient administration at specialized centers have limited further clinical development

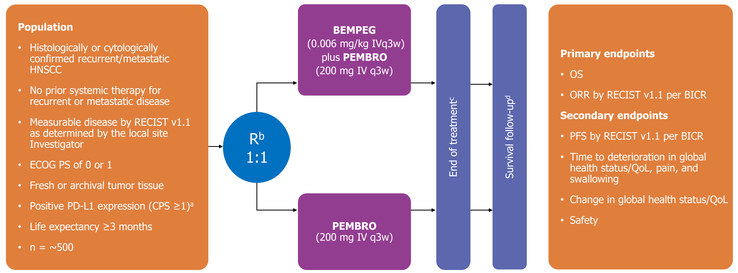
BEMPEG

- BEMPEG (NKTR-214) is an immunostimulatory IL-2 cytokine prodrug that has been engineered to deliver a controlled, sustained, and CD122-preferential IL-2 pathway signal **(Figure 1)**[8,9]
  - BEMPEG preferentially expands and activates $CD8^+$ T and NK cells, with limited expansion of unwanted immunosuppressive regulatory T cells, in the TME[8–11]
  - BEMPEG has been shown to convert baseline tumors from PD-L1-negative to PD-L1-positive as a single agent[8] and in combination with an ICI[12–15]
  - BEMPEG increases favorable antitumor gene expression and IFN-γ[10]
- BEMPEG in combination with NIVO leverages two clinically validated complementary immuno-oncology pathways to potentially enhance antitumor immune response[16]
  - In the PIVOT-02 study, BEMPEG plus NIVO elicited deep and durable responses in patients with immune-sensitive advanced solid tumors regardless of PD-L1 status[16]
  - In patients with advanced melanoma, ORR and CR rates were 53% and 34%, respectively, 47% of patients achieved 100% reductions in target lesions, and an extended median PFS of 30.9 months was observed **(Figure 2)**[10]
- BEMPEG plus NIVO received FDA Breakthrough Therapy Designation in July 2019 for patients with previously untreated, unresectable, or metastatic melanoma, and is under evaluation in registrational trials of patients with various solid tumors, including metastatic melanoma (NCT03635983), adjuvant melanoma (NCT04410445), advanced renal cell carcinoma (NCT03729245), metastatic urothelial carcinoma (NCT03785925), and muscle-invasive bladder cancer (NCT04209114)
- PROPEL-36 (NCT04969861) is a phase 2/3 study of BEMPEG in combination with PEMBRO vs PEMBRO alone in patients with previously untreated metastatic or recurrent PD-L1-positive HNSCC (CPS ≥1)

STUDY DESIGN

- The study will use an adaptive design based on prespecified criteria and an independent, external Data Monitoring Committee to monitor efficacy and safety
- Approximately 500 patients will be randomized 1:1 to receive BEMPEG plus PEMBRO or PEMBRO monotherapy every 3 weeks
- Patients will be treated for up to 35 cycles (~2 years) or until disease progression, death, unacceptable toxicity, a decision by the investigator or patient to discontinue treatment, withdrawal of consent, loss to follow-up, or study termination

PROPEL-36: A phase 2/3, multicenter study of BEMPEG plus PEMBRO vs PEMBRO alone in patients with previously untreated metastatic or recurrent PD-L1-positive HNSCC (CPS ≥1)



[a]Determined by PD-L1 immunohistochemistry 22C3 pharmDx assay (CPS ≥20 vs 1–19) at local or central laboratory; [b]Stratification factors: disease status (metastatic vs recurrent only); PD-L1 tumor status (CPS ≥20 vs 1–19); human papillomavirus status for oropharyngeal cancer determined by p16 immunohistochemistry (positive vs negative); [c]Patients will be treated for up to 35 cycles (~2 years; first course) until progressive disease, death, unacceptable toxicity, symptomatic deterioration, investigator or patient decision to discontinue treatment, patient withdrawal of consent, loss to follow-up, or study end. Patients who have stable disease, partial response, or complete response may be eligible for up to an additional 17 cycles (~1 year) of study treatment if there is investigator-determined radiographic disease progression by RECIST 1.1 after the initial treatment (ie, first course); [d]Until progressive disease, initiation of new anti-cancer therapy, death, patient withdrawal of consent, or study end. BEMPEG, bempegaldesleukin; BICR, blinded independent central review; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PEMBRO, pembrolizumab; PFS, progression-free survival; q3w, every 3 weeks; QoL, quality of life; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors.

OBJECTIVES

Primary objective

- To compare OS and ORR of BEMPEG plus PEMBRO vs PEMBRO alone

Secondary objectives

- To compare the following between BEMPEG plus PEMBRO vs PEMBRO alone:
  - PFS
  - Safety
  - Time to deterioration in global health status/QoL, pain and swallowing
  - Mean change from baseline in global health status/QoL

ELIGIBILITY CRITERIA

Key inclusion criteria

- ≥18 years of age on the day of providing informed consent
- Histologically or cytologically confirmed recurrent/metastatic HNSCC considered incurable by local therapies, with no prior systemic therapy for recurrent or metastatic disease[a]
  - Eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx
- Measurable disease by RECIST 1.1 as determined by the local site investigator
- ECOG PS of 0 or 1
- Fresh (strongly preferred) or archival tumor tissue samples[b]
- Tumor must have positive PD-L1 expression (CPS ≥1) as determined using the PD-L1 IHC 22C3 PharmDx diagnostic kit at either a local or central laboratory
- Patients with oropharyngeal cancer must provide HPV status based on p16 IHC testing using CINtec® p16 Histology assay[c]

Key exclusion criteria

- Disease that is suitable for local therapy administered with curative intent, or progressive disease within 6 months of completing curatively intended systemic treatment for locoregionally advanced HNSCC
- Radiation (or other non-systemic) therapy within 2 weeks of initiation of study drug, or not fully recovered from AEs due to a previous treatment (≤Grade 1 at baseline)[a,b]
- Life expectancy of <3 months and/or rapidly progressing disease (e.g., tumor bleeding, uncontrolled tumor pain) as determined by the investigator
- Known additional malignancy that is progressing or has required active treatment within 5 years of study drug[c]

[a]Systemic therapy given as part of multimodal treatment for locally advanced disease is allowed if completed more than 6 months prior to providing informed consent; [b]Tumor tissue must be from a core, incisional, or excisional biopsy (not fine needle aspirates) for determination of PD-L1 status at the central laboratory (if not determined locally), and for exploratory biomarker analyses; [c]If HPV status was previously tested using this method, no additional testing is required.

[a]Patients with Grade ≤2 neuropathy or alopecia are an exception to this criterion and qualify for the study; [b]If a patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy; [c]Except for curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, curatively resected in situ cervical cancer, and curatively resected in situ breast cancer.

STUDY STATUS

The PROPEL-36 study is open for enrollment, with ~185 sites across 26 countries planned

Please visit ClinicalTrials.gov and search for **NCT04969861** to find out the latest information on this study

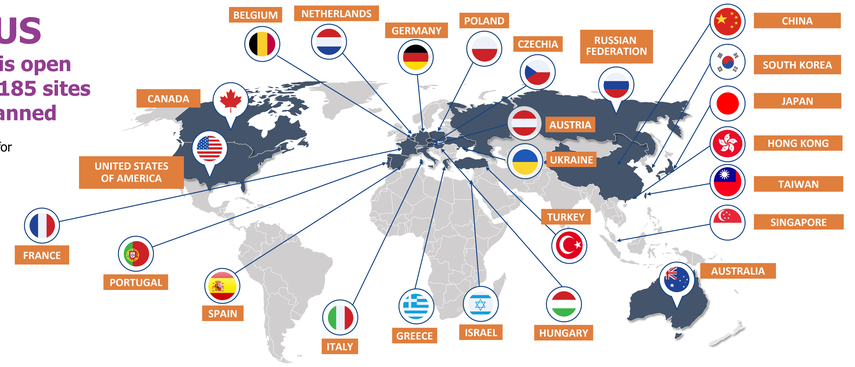
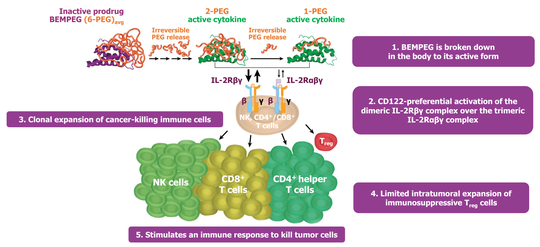
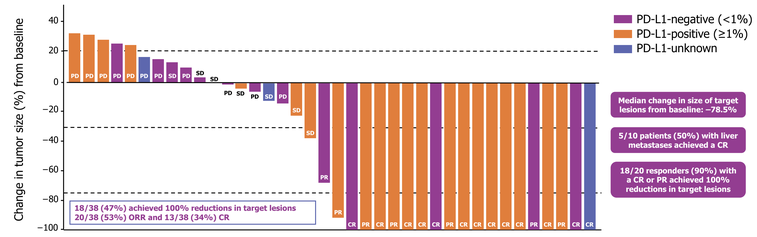


Figure 1. BEMPEG delivers a controlled, sustained, preferential IL-2 pathway signal



CD, cluster of differentiation; IL-2(R), interleukin-2 (receptor); NK, natural killer; PEG, releasable polyethylene glycol; T_{reg}, regulatory T cell.

Figure 2. BEMPEG plus NIVO in patients with advanced melanoma (PIVOT-02)[10]



Data cutoff: 1SEP72030. Response-evaluable population includes eligible patients with measurable disease (per RECIST 1.1) at baseline and have ≥1 post-baseline tumor assessment.
All objective responses are confirmed. CR, complete response; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; SD, stable disease.

REFERENCES

1. Sung H, et al. *CA Cancer J Clin* 2021;71:209–49; **2.** Keytruda (pembrolizumab) Prescribing Information. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s117,s118lbl.pdf; **3.** National Comprehensive Cancer Network (NCCN). NCCN clinical practice guideline: Head and neck cancers (v3.2021); **4.** Burtness B, et al. *Lancet* 2019;394:1915–28; **5.** De Stefani A, et al *Cancer* 2002;95:90–7; **6.** Matsijssen V, et al. *Ann Oncol* 1994;5:957–60; **7.** Cortesina G, et al. *Cancer* 1988;62:2482–5; **8.** Bentebibel S-E, et al. *Cancer Discov* 2019;9:711–21; **9.** Charych D, et al. *PLOS One* 2017;12:e0179431; **10.** Diab A, et al. *J Clin Oncol* 2021;39:2914–25; **11.** Charych DH, et al. *Clin Cancer Res* 2016;22:680–90; **12.** Hurwitz M, et al. ASCO 2019. Abstract 2623; **13.** Tolaney S, et al. CICON 2019. Poster A001; **14.** Siefker-Radtke A, et al. ASCO GU 2019. Abstract 388; **15.** Diab A, et al. ASCO 2018. Oral 3006; **16.** Diab A, et al. *Cancer Discov* 2020;10:1158–73.

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DISCLOSURES

Robert Haddad reports consulting/advisory role, BMS, Merck, Pfizer, Genetech, Astra Zeneca, and GSK; Research grant/funding, Merck, BMS, Pfizer, Genentech, GSK, and Astra Zeneca.

ABBREVIATIONS

AE, adverse event; BEMPEG, bempegaldesleukin; BICR, blinded independent central review; CD, cluster of differentiation; CPS, combined positive score; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, US Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; ICI, immune checkpoint inhibitor; IFN, interferon; IHC, immunohistochemistry; IL-2(R), interleukin-2 (receptor); NIVO, nivolumab; NK, natural killer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death ligand-1; PEG, releasable polyethylene glycol; PEMBRO, pembrolizumab; PFS, progression-free survival; PR, partial response; QoL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TME, tumor microenvironment; T_{regs}, regulatory T cell.