Preliminary Results from PROPEL: A Phase 1/2 Study of Bempegaldesleukin (BEMPEG: NKTR-214) Plus Pembrolizumab With or Without Chemotherapy in Patients with Metastatic NSCLC

140P

E. Felip[1], D. Spigel[2], O.J. Juan-Vidal[3], J.T. Beck[4], C. Aguado de la Rosa[5], D. Johnson[6], E. Spath-Schwalbe[7], A. Reinacher-Schick[8], D. Rodriguez Abreu[9], M. Altan[10], N. Reinmuth[11], M. Edelman[12], M. Reck[13], Q. Zhao[14], S. Banerjee[14], S. Chaudhry[14], D. Chien[14], M. Tagliaferri[14], J. Zalevsky[15], A. Ganti[16]

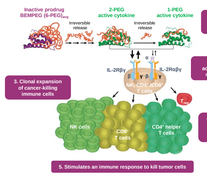
[1]Medical Oncology Service, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [2]Oncology Department, Sarah Cannon Research Institute, Nashville, TN, USA; [3]Medical Oncology Department, Hospital Universitari I Politècnic La Fe, Valencia, Spain; [4]Research Department, Highlands Oncology Group, Springdale, AR, USA; [5]Medical Oncology, Hospital Clínico San Carlos, Madrid, Spain; [6]Medical Oncology, Ochsner Medical Center, New Orleans, LA, USA; [7]Department of Hematology, Oncology, Gastroenterology and Palliative Care, Vivantes Klinikum Humboldt, Berlin, Germany; [8]Department of Oncology and Palliative Care, Lungenklinik Hemer, Hemer, Germany; [9]Medical Oncology Department, Hospital Universitario Insular de Gran Canaria, Gran Canaria, Spain; [10]Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [11]Thoracic Oncology, Asklepios Fachkliniken München-Gauting, Gauting, Germany; [12]Hematology and Oncology Department, Fox Chase Cancer Center, Philadelphia, MD, USA; [13]Thoracic Oncology Department, Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [14]Clinical Development, Nektar Therapeutics, San Francisco, CA, USA; [15]Research and Development, Nektar Therapeutics, San Francisco, CA, USA; [16]Hematology and Oncology Division, University of Nebraska Medical Center, VA Nebraska Western Iowa Health Care System, Omaha, NE, USA

BACKGROUND

- Checkpoint inhibitors have become a standard treatment for many cancers, including advanced NSCLC[1]
- However, CPIs have shown limited efficacy as a monotherapy in patients with low or no (negative) PD-L1 expression[2]
- There is therefore an unmet need for novel IO agents for patients who are unlikely to respond to CPIs (with low or negative PD-L1 expression) and to provide deeper, prolonged responses in those who do respond
- PROPEL is a Phase 1/2 global study (NCT03138889) of bempegaldesleukin (BEMPEG) + pembrolizumab, with or without CT, in patients with locally advanced/metastatic solid tumors

Here, we report safety data following dose-escalation (Cohort 1) and initial safety and efficacy of the IO doublet without chemotherapy in patients with untreated advanced/metastatic NSCLC, regardless of PD-L1 status (Cohort 2; dose-expansion)

BEMPEG: Preferential Signaling Through the IL-2 Receptor Pathway

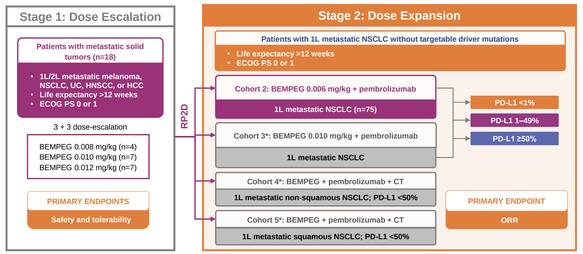


- BEMPEG is an immunostimulatory IL-2 cytokine prodrug, which has been engineered to deliver a controlled, sustained, and preferential IL-2 pathway signal[3,4]
- BEMPEG plus a CPI has been shown to convert baseline tumors from PD-L1 negative to PD-L1 positive[5-8]
- BEMPEG (0.006 mg/kg dose) plus either nivolumab or pembrolizumab is being evaluated in patients with metastatic or recurrent HNSCC (NCT04969861), metastatic melanoma (NCT03635983), adjuvant melanoma (NCT04410445), advanced renal cell carcinoma (NCT03729245), metastatic urothelial carcinoma (NCT03785925), and muscle-invasive bladder cancer (NCT04209114)

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

STUDY DESIGN AND METHODS

PROPEL: A Phase 1/2 Study



NCT03138889. *Enrollment ongoing. Pembrolizumab 200 mg IV q3w was administered across all cohorts. Study medications were administered until disease progression, death, unacceptable toxicity, symptomatic deterioration, lost to follow-up, investigator or patient decision to discontinue treatment, withdrawal of consent or termination of the study by the sponsor. Patients in Cohorts 4 and 5 received SOC platinum doublet chemotherapy in addition to the study medications noted for Cohort 2. In France, patients in subgroup PD-L1 <50% were excluded from Cohorts 2 and 3.
1L, first-line; 2L, second-line; BEMPEG, bempegaldesleukin; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IV, intravenous; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death ligand-1; q3w, every 3 weeks; SOC, standard of care; UC, urothelial cancer.

Study Procedures and Assessments

Safety and tolerability	Efficacy	PD-L1 status (Cohort 2)
AEs were assessed by CTCAE v5.0	Objective response per RECIST 1.1 by BICR targeting scans every 9 (±1) weeks	Local assessment was used for enrolment
Safety population: all patients who received ≥1 dose of treatment	Efficacy-evaluable population: patients with ≥1 post-baseline, on-treatment radiographic scans	Central assessment available for 91% of patients and was utilized for PD-L1 subgroup analyses when available

Data cut-off: October 29, 2021. Median follow-up for the dose-expansion Cohort 2: 12 months.
AE, adverse event; BICR, blinded independent central radiology; CTCAE, Common Terminology Criteria for Adverse Events; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors.

RESULTS

Patient Demographics and Disease Characteristics in the Dose-Escalation Cohort

		BEMPEG 0.008 mg/kg + pembrolizumab (n=4)	BEMPEG 0.010 mg/kg + pembrolizumab (n=7)	BEMPEG 0.012 mg/kg + pembrolizumab (n=7)
Median age, years (range)		59.5 (49–72)	68.0 (43–76)	65.0 (53–74)
Male sex, n (%)		2 (50.0)	3 (42.9)	2 (28.6)
ECOG PS, n (%)	0	3 (75.0)	2 (28.6)	5 (71.4)
	1	1 (25.0)	5 (71.4)	2 (28.6)
Cancer diagnosis, n (%)	Melanoma	2 (50.0)	3 (42.9)	4 (57.1)
	NSCLC	1 (25.0)	3 (42.9)	2 (28.6)
	UC	1 (25.0)	0	1 (14.3)
	HNSCC	0	1 (14.3)	0

BEMPEG, bempegaldesleukin; ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; UC, urothelial cancer.

TRAEs in the Dose-Escalation Cohort

TRAEs reported in >3 patients; n (%)	BEMPEG 0.008 mg/kg + pembrolizumab (n=4)		BEMPEG 0.010 mg/kg + pembrolizumab (n=7)		BEMPEG 0.012 mg/kg + pembrolizumab (n=7)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	4 (100.0)	2 (50.0)	7 (100.0)	4 (57.1)	7 (100.0)	4 (57.1)
Chills	2 (50.0)	0	2 (28.6)	0	6 (85.7)	0
Fatigue	2 (50.0)	0	6 (85.7)	3 (42.9)	3 (42.9)	0
Nausea	2 (50.0)	0	7 (100.0)	1 (14.3)	2 (28.6)	0
Pruritus	2 (50.0)	0	2 (28.6)	0	2 (28.6)	0
Diarrhea	1 (25.0)	0	4 (57.1)	2 (28.6)	1 (14.3)	0
Hypotension	1 (25.0)	0	2 (28.6)	1 (14.3)	2 (28.6)	0
Influenza-like illness	1 (25.0)	0	2 (28.6)	0	2 (28.6)	0
Pyrexia	1 (25.0)	0	7 (100.0)	0	4 (57.1)	0
Rash maculo-papular	1 (25.0)	0	1 (14.3)	0	2 (28.6)	1 (14.3)
Vomiting	1 (25.0)	0	4 (57.1)	0	1 (14.3)	0
ALT increased	0	0	2 (28.6)	0	2 (28.6)	0
Arthralgia	0	0	4 (57.1)	0	1 (14.3)	1 (14.3)
AST increased	0	0	2 (28.6)	0	2 (28.6)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BEMPEG, bempegaldesleukin; TRAE, treatment-related adverse event.

- No Grade 5 TRAEs were reported. One DLT (Grade 3 hypotension) was noted at the 0.010 mg/kg dose level within the first treatment cycle
- Four patients (4/14) at the highest dose levels required a dose reduction due to TRAEs (2/7 BEMPEG 0.010 mg/kg; 2/7 BEMPEG 0.012 mg/kg)
- BICR RECIST 1.1 responses were observed for 3 patients in the BEMPEG 0.010 mg/kg + pembrolizumab cohort (1L HNSCC [CR], 1L melanoma [PR], and 2L [refractory to pembrolizumab monotherapy] melanoma [PR])

Patient Demographics and Disease Characteristics in the Dose-Expansion Cohort

		PD-L1 status			All
		<1 (n=28)	1–49% (n=28)	≥50% (n=19)	(n=75)
Median age, years (range)		65.5 (46–83)	65.5 (51–80)	62.0 (40–79)	65 (40–83)
Male sex, n (%)		20 (71.4)	20 (71.4)	11 (57.9)	51 (68.0)
ECOG PS, n (%)	0	14 (50.0)	10 (35.7)	8 (42.1)	32 (42.7)
	1	14 (50.0)	18 (64.3)	10 (52.6)	42 (56.0)
Histology, n (%)	Squamous	13 (46.4)	13 (46.4)	4 (21.1)	30 (40.0)
	Non-squamous	15 (53.6)	15 (53.6)	15 (78.9)	45 (60.0)
Smoking status, n (%)	Current	9 (32.1)	8 (28.6)	6 (31.6)	23 (30.7)
	Former	17 (60.7)	18 (64.3)	11 (57.9)	46 (61.3)
	Non-smoker	2 (7.1)	2 (7.1)	2 (10.5)	6 (8.0)
Metastases, n (%)	Brain	4 (14.3)	1 (3.6)	1 (5.3)	6 (8.0)
	Liver	6 (21.4)	1 (3.6)	3 (15.8)	10 (13.3)
Stage at diagnosis, n (%)*	I–II	4 (14.3)	3 (10.7)	2 (10.5)	9 (12.0)
	III	2 (7.1)	6 (21.4)	0	8 (10.7)
	IV	21 (75.0)	19 (67.9)	17 (89.5)	57 (76.0)
Prior chemotherapy, n (%)		2 (7.1)	7 (25.0)	1 (5.3)	10 (13.3)

*One patient (PD-L1 status <1) had missing stage at diagnosis. ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1.

TRAEs in the Dose-Expansion Cohort

TRAEs reported in >10% of patients; n (%)	All (n=75)	
	Any Grade	Grade ≥3
Any	69 (92.0)	30* (40.0)
Pyrexia	25 (33.3)	0
Fatigue	19 (25.3)	3 (4.0)
Asthenia	15 (20.0)	1 (1.3)
Influenza-like illness	13 (17.3)	1 (1.3)
Pruritus	13 (17.3)	0
Nausea	12 (16.0)	0
AST increased	11 (14.7)	1 (1.3)
ALT increased	10 (13.3)	1 (1.3)
Arthralgia	10 (13.3)	1 (1.3)
Diarrhea	10 (13.3)	1 (1.3)
Hyperthyroidism	10 (13.3)	2 (2.7)
Lymphocyte count decreased**	10 (13.3)	7 (9.3)
Rash	10 (13.3)	2 (2.7)
Chills	8 (10.7)	0
Hypotension	8 (10.7)	1 (1.3)

Nine subjects (12%) reported ≥1 serious TRAE. *One Grade 5 TRAE of myasthenic syndrome was reported that was considered related to pembrolizumab only by the investigator; **Transient lymphocyte count decrease within the first 72 hours is a known result of BEMPEG treatment and is followed by lymphocytosis by Day 8.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

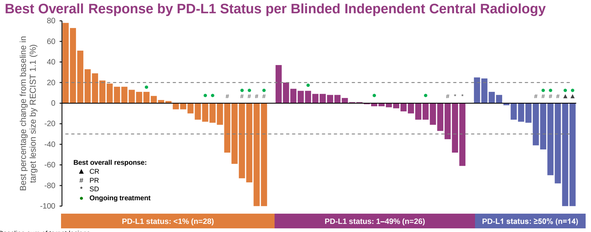
ORR by RECIST 1.1 per Blinded Independent Central Radiology

Median duration of response was not reached for patients with an objective response

Efficacy-evaluable population*		PD-L1 status			All
		<1 (n=28)	1–49% (n=27)	≥50% (n=15)	(n=70)
ORR, n (%)		5 (18)	1 (4)	6 (40)	12 (17)
Best response, n (%)	CR	0 (0)	0 (0)	2 (13)	2 (3)
	PR	5** (18)	1 (4)	4 (27)	10 (14)
	SD	6 (21)	14 (52)	4 (27)	24 (34)
	PD	16 (57)	11 (41)	4 (27)	31 (44)
	NE	1 (4)	1 (4)	1 (7)	3 (4)
DCR (CR + PR + SD), n (%)		11 (39)	15 (56)	10 (67)	36 (51)

*Five patients were not included in the efficacy-evaluable population; one patient (PD-L1 status 1–49%) had no post-baseline imaging due to an SAE of pulmonary embolus and four patients (all PD-L1 status ≥50%) had no post-baseline imaging due to an SAE of Lambert–Eaton syndrome (n=1), AEs of fatigue (n=1) and infusion reaction (n=1), or death due to myasthenic syndrome (n =1). **Two patients with a PR had a 100% reduction in target lesions from baseline.
AE, adverse event; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD-L1, programmed death ligand 1; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease.

Best Overall Response by PD-L1 Status per Blinded Independent Central Radiology



Baseline sum of target lesions			
Mean (standard deviation)	69.4 (43.9)	90.0 (43.8)	78.5 (39.7)
Median (range)	64.0 (10–208)	83.0 (15–220)	74.5 (26–166)

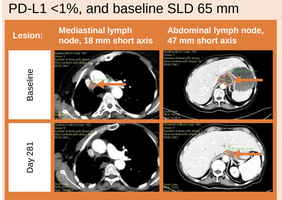
75% median reduction in baseline target lesions for patients with a RECIST 1.1 response

Two efficacy-evaluable patients (PD-L1 status 1–49%, n=1 [NE] and PD-L1 status ≥50%, n=1 [best response PD]) are not shown due to missing post-baseline target lesion measurements.
CR, complete response; NE, not evaluable; PD, progressive disease; PD-L1, programmed death ligand-1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

CASE VIGNETTES

Male patient (61 years) achieved a PR and 77% reduction in baseline target SLD

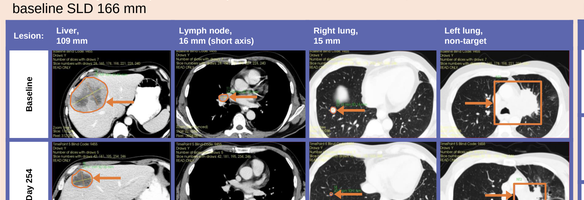
Medical history: Non-squamous NSCLC, PD-L1 <1%, and baseline SLD 65 mm



New abdominal lesion noted on Day 319. Patient continued study treatment beyond progression and target lesions remain stable (Day 442+)

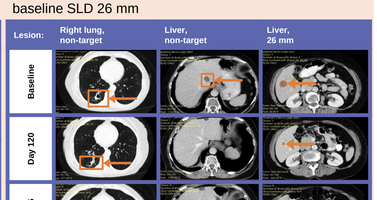
Male patient (55 years) achieved a PR and 76% reduction in baseline target SLD

Medical history: Widespread non-squamous NSCLC, PD-L1 80%, and baseline SLD 166 mm



Female patient (62 years) achieved a CR of target and non-target lesions

Medical history: Non-squamous NSCLC, PD-L1 91%, and baseline SLD 26 mm



*Based on further reduction at subsequent timepoint(s).
CR, complete response; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; PR, partial response; SLD, sum of longest diameters.

SUMMARY

- Preliminary evidence of clinical activity was observed with the chemotherapy-sparing IO doublet, BEMPEG 0.006 mg/kg + pembrolizumab, for patients with 1L metastatic NSCLC
  - In patients with PD-L1 status <1% at baseline (n=28): 18% ORR. Two patients with 100% reduction in target lesions and 3 patients with SD remain on treatment
  - In patients with PD-L1 status 1–49% at baseline (n=27): 4% ORR and 52% SD
  - In patients with PD-L1 status ≥50% at baseline (n=15): 40% ORR with 13% CR. Two additional patients with PRs remain on treatment
  - A 75% median reduction in baseline target lesions was observed in patients with a RECIST 1.1 response and a deepening reduction in target lesions over time
  - Median duration of response has not been reached for the patients with an objective response
- Compelling ORR by BICR for patients with PD-L1 negative (<1%) disease compared to historical data for pembrolizumab monotherapy[9]
- Notable CR rate by BICR for patients with PD-L1 high (≥50%) disease compared to historical data for pembrolizumab ±CT[10-12]
- BEMPEG 0.006 mg/kg + pembrolizumab was well tolerated in the 1L NSCLC setting
- Assessment of BEMPEG 0.006 mg/kg + pembrolizumab + CT is ongoing in patients with 1L NSCLC and PD-L1 status <50%

DISCLOSURES
The presenting author, Enriqueta Felip, reports Financial Interests, Personal, Advisory Board: Amgen, AstraZeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, GlaxoSmithKline, Janssen, Merck Sharpe & Dohme, Merck Serono, Peptomyc, Pfizer, Puma, Regeneron, Sanofi, Syneos Health, Takeda; Financial Interests, Personal. Invited Speaker: Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Janssen, Medscape, Merck Sharpe & Dohme, Merck Serono, Peervoice, Pfizer, Springer, Touch Medical; Financial Interests, Personal, Other: Medical Trends; Non-Financial Interests, Personal, Leadership Role, Dr. Felip is President Elect (2021–2023) of Spanish Society of Medical Oncology; Non-Financial Interests, Personal, Member, Dr. Felip is member of the ESMO Nominating Committee and Compliance Committee: ESMO; Non-Financial Interests, Personal, Member, Dr. Felip is member of the Scientific Committee: ETOP; Non-Financial Interests, Personal, Leadership Role, Dr. Felip is member of the Board of Directors and the Executive Committee (2017–2021): IASLC.

ABBREVIATIONS
1L, first line; 2L, second line; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BEMPEG, bempegaldesleukin; BICR, blinded independent central radiology; CD, cluster of differentiation; CPI, checkpoint inhibitor; CR, complete response; CT, chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; IL-2, interleukin-2; IL-2R, interleukin-2 receptor; IV, intravenous; IO, immunotherapy; NE, not evaluable; NK, natural killer; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand-1; PEG, polyethylene glycol; PR, partial response; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SAE, serious adverse event; SD, stable disease; SLD, sum of longest diameters; SOC, standard of care; TRAEs, treatment-related adverse event; T$_{reg}$, regulatory T cell; UC, urothelial cancer.

ACKNOWLEDGMENTS
We would like to thank all patients, their families, the investigators, and their staff for participating in this study. This study is funded by Nektar Therapeutics, San Francisco, CA, USA.

All authors contributed to and approved the poster. Medical writing assistance was provided by Suzanne Patel, PhD of BOLDSCIENCE Inc. Ltd., and was funded by Nektar Therapeutics.

REFERENCES
1. NCCN Clinical Practice Guidelines in Oncology in NSCLC; version 6.2020; June 15, 2020; **2.** Garon EB, et al. *N Engl J Med* 2015;372:2018–2028; **3.** Charych D, et al. *PLoS One* 2017;12:e0179431; **4.** Bentebibel SE, et al. *Cancer Discov* 2019;9:711–721; **5.** Diab A, et al. SITC 2018. Abstract O4; **6.** Siefker-Radtke AO, et al. *ASCO GU 2019*. Abstract 388; **7.** Hurwitz M, et al. *ASCO 2019*. Abstract 2623; **8.** Tolaney S, et al. CICON 2019. Poster A001; **9.** Hui R, et al. *Ann Oncol* 2017;28:874–81; **10.** Gadgeel S, et al. *J Clin Oncol* 2020;38:1505–1517; **11.** Mok TSK, et al. *Lancet* 2019;393:1819–1830; **12.** Gandhi L, et al. *New Engl J Med* 2018;378:2078–2092.