Phase I Dose-Escalation Results for the Delta-Like Ligand 3/CD3 IgG-Like T-Cell Engager Obrixtamig (BI 764532) in Patients With Delta-Like Ligand 3+ Small Cell Lung Cancer or Neuroendocrine Carcinomas

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ABSTRACT

PURPOSE We report phase I results for obrixtamig (BI 764532), a delta-like ligand 3 (DLL3)/CD3 IgG-like T-cell engager, in patients with previously treated DLL3-positive small cell lung cancer (SCLC), extrapulmonary neuroendocrine carcinomas (epNECs), or large cell neuroendocrine carcinoma of the lung (LCNEC-L).

METHODS Patients received escalating intravenous obrixtamig doses using four regimens: a fixed dose once every 3 weeks (A); a fixed dose once weekly (B1); a step-up dose once weekly for two weeks and target dose once weekly (B2); and a step-up dose once weekly for 3 weeks, target dose once weekly for 3 weeks, and once every 3 weeks thereafter (B3). The primary objective was maximum tolerated dose (MTD). Secondary objectives included safety, pharmacokinetics, and tumor response (RECIST v1.1).

RESULTS As of February 21, 2024, 168 patients received obrixtamig, 72% received ≥2 lines of previous anticancer therapy, and 51% received previous anti–PD-1/PD-L1 therapy. Seven dose-limiting toxicities occurred during MTD evaluation (Regimen A, n = 1; Regimen B2, n = 6). MTD was not reached. The most common treatment-related adverse event was cytokine release syndrome (any grade: 57%; grade ≥3: 3%); most cases occurred early and were reversible. Across all doses, regimens, and tumor types, the overall response rate (ORR) was 23% (95% CI, 17.4% to 30.2%), the median duration of response (DoR) was 8.5 months (95% CI, 6.2 to not reached), and the 6-month DoR rate was 70% (95% CI, 53% to 88%). All patients in Regimens B2/B3 received the minimum effective dose (≥90 μg/kg once weekly or once every 3 weeks), achieving an ORR of 28% (95% CI, 20.7% to 35.9%). With Regimens B2/B3, ORRs were 21% (95% CI, 12.9% to 33.1%), 27% (95% CI, 17.4% to 39.6%), and 70% (95% CI, 39.7% to 89.2%) for SCLC, epNECs, and LCNEC-L, respectively.

CONCLUSION The demonstrated tolerability and efficacy of obrixtamig regimens, administered as step-up followed by target doses of 90-1,080 μg/kg (once weekly or once every 3 weeks), in patients with heavily pretreated DLL3-positive tumors support further exploration in SCLC, epNEC, and LCNEC-L.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Neuroendocrine carcinomas (NECs), including small cell lung cancer (SCLC),[1,2] large cell neuroendocrine carcinoma of the lung (LCNEC-L),[3] and extrapulmonary NECs (epNECs),[4,5] are a highly heterogeneous group of aggressive cancers with poor prognosis.[6,7]

Standard first-line treatment for SCLC is platinum plus etoposide and an anti–PD-L1 antibody, but median progression-free survival (PFS; approximately 5 months) and overall survival (OS; approximately 12-13 months) are generally poor.[8,9] Subsequent therapy options, like topotecan and lurbinectedin, provide modest benefit, with median PFS typically <5 months.[10,11] Treatment for advanced LCNEC-L is usually based on SCLC or non–small cell lung cancer regimens, neither of which offer prolonged benefits.[12,13] Patients with epNECs are usually treated with first-line platinum plus etoposide or a fluorouracil-based regimen,[14] but the OS is usually <1 year.[15] Few second-line

CONTEXT

Key Objective

To determine the recommended dose and regimen for obrixtamig (BI 764532), a DLL3/CD3 IgG-like T-cell engager, in patients with previously treated DLL3-positive small cell lung cancer (SCLC), large cell neuroendocrine carcinoma of the lung, or extrapulmonary neuroendocrine carcinomas. Four regimens were assessed.

Knowledge Generated

Dose-limiting toxicities were reported in seven patients, most occurred during the initial step-up dose administration, and maximum tolerated dose was not reached. Cytokine release syndrome (CRS) was the most common treatment-related adverse event.

Relevance *(R.G. Maki)*

While a similar compound, tarlatamab, is now approved for SCLC, these data provide further support for DLL3-based therapy in both SCLC and other high-grade neuroendocrine tumors in need of novel therapeutics. It will be interesting to see if other routes of administration (ie, subcutaneous) can mitigate some of the CRS symptoms seen as a common adverse event in this study.*

*Relevance section written by *JCO* Associate Editor Robert G. Maki, MD, PhD, FACP, FASCO.

options are available, and outcomes are modest, at best. Therefore, new treatment options are needed for NECs.

Delta-like ligand 3 (DLL3) is an inhibitory Notch ligand that is minimally expressed in normal tissue, but frequently expressed on the cell surface of NECs, including approximately 80% of SCLC tumors,[16,17] approximately 75% of LCNEC-L tumors,[18] and up to approximately 80% of epNECs.[19] Its expression seems to be stable during treatment[20] and concordant across different disease sites.[21] Accordingly, DLL3 represents an attractive therapeutic target for these tumor types.

With the lack of benefit from the DLL3-targeted antibody-drug conjugates rovalpituzumab tesirine and SC-002 in SCLC and NECs,[22-25] attention turned to DLL3-targeted T-cell engagers (TCEs). In a phase I study of patients with pretreated SCLC (DeLLphi-300), the DLL3 TCE tarlatamab conferred an overall response rate (ORR) of 25% with a median duration of response (DoR) of 11.2 months (95% CI, 6.6 to 22.3); cytokine release syndrome (CRS) was the most common adverse event (AE).[26] To date, tarlatamab has not been assessed in clinical trials in patients with LCNEC-L or epNECs, other than neuroendocrine prostate cancer.[27]

Obrixtamig is a novel IgG-like TCE which binds to DLL3 on tumor cells and CD3 on T cells, activating T cells in the tumor microenvironment and leading to DLL3-dependent cytolysis of tumor cells.[28] NCT04429087 is an ongoing phase I dose-escalation/dose-expansion trial of obrixtamig in adults with locally advanced or metastatic DLL3-positive SCLC, epNEC, or LCNEC-L.[29] We report the phase Ia dose-escalation results.

METHODS

Patients

Patients 18 years and older had locally advanced or metastatic SCLC, LCNEC-L, or epNEC or small cell carcinoma of any other origin. Tumors were positive for DLL3 expression per central pathology review of archived tissue or an in-study biopsy. DLL3 testing was performed using the Ventana DLL3 (SP347) assay at the Roche Companion Diagnostics College of American Pathologists/Clinical Laboratory Improvement Amendments laboratory. Patients must have exhausted all treatments known to confer clinical benefit, including at least one line of platinum-based combination therapy. Further inclusion and exclusion criteria are described in Appendix 1 (online only).

Study Design

NCT04429087 is a multicenter, open-label phase Ia/Ib dose-escalation/dose-expansion trial; for the phase Ia dose-escalation part, patients were recruited from sites in Germany, Japan, Spain, and the United States.

Primary end points of the phase Ia part were maximum tolerated dose (MTD), defined as the highest dose with <25% risk of the true dose-limiting toxicity (DLT) rate being ≥33% during the MTD evaluation period, and the number of patients with DLTs in the MTD evaluation period. Separate MTDs were determined for each regimen.

Key phase Ia secondary end points were pharmacokinetics and objective response based on RECIST v1.1 according to investigator assessment.[30]

The study was conducted in accordance with the provisions of the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use—Good Clinical Practice, and local legislation. The protocol was approved by the relevant institutional review boards or ethics committees. All patients provided written informed consent.

Treatment

Four dosing regimens of obrixtamig infused intravenously (IV) over 2 hours were investigated (Appendix Fig A1, online only). Regimen A was a fixed once every 3 weeks dose on Day 1 of each cycle. Regimen B1 was a fixed once-weekly dose on Days 1, 8, and 15 of a 3-week cycle. As TCEs are associated with CRS, a step-up dosing strategy was adopted for Regimens B2 and B3 to mitigate CRS incidence and severity.[31] Regimen B2 included two step-up doses (on Days 1 and 8) followed by a fixed once-weekly dose on Day 1 of a 3-week cycle. Regimen B3 comprised three step-up doses once weekly for the initial 3 weeks, followed by the target dose once weekly for the next 3 weeks and then once every 3 weeks starting at Week 7. Regimens were assessed sequentially, starting with Regimen A with an obrixtamig starting dose of 0.03 μg/kg once every 3 weeks. Regimen B1 starting dose was based on matching exposure with a safe dose established in Regimen A. Subsequent cohorts of patients were switched from regimens B1 to B2 and B3, respectively, based on grade ≥2 toxicity because of CRS or related symptoms in the previous cohort. If grade ≥2 toxicity because of CRS or related symptoms occurred in the Regimen A or B1 cohorts using the fixed doses, the new cohorts were opened for Regimen B2 using two step-up dose(s). Similarly, based on Regimen B2 data, the step-up doses could be further modified, and additional new cohorts could be opened for Regimen B3 using three step-up doses. The target Regimen B2 and B3 step-up doses were determined after incorporating all available safety data.

To minimize potential CRS and infusion-related reaction (IRR) severity, patients were premedicated with a dose of oral/IV acetaminophen/paracetamol 1,000 mg, antihistamine equivalent to IV diphenhydramine 50 mg, and corticosteroids equivalent to prednisolone 100 mg or dexamethasone 16 mg.

Obrixtamig treatment was continued until disease progression, unacceptable toxicity, or other reasons requiring treatment discontinuation.

Study Assessments

Safety assessments included physical examination, vital signs, safety monitoring (vital signs and oxygen saturation) during and after drug administration, laboratory parameters, electrocardiogram, and incidences of AEs, serious AEs, AEs of special interest, AE severity (graded per Common Terminology Criteria for Adverse Events version 5.0), and causal relationship of AEs to obrixtamig. Per protocol, patients were hospitalized for mandatory observation for at least 24 hours for each step-up dose and the first target dose. The second target dose required observation for at least 8 hours. Thereafter, patients were observed in a clinical setting for at least 2 hours at the investigator's discretion. DLTs were defined by the criteria described in Appendix Table A1.

AEs of special interest included infusion reactions, CRS, and related neuropsychiatric events including potential immune effector cell–associated neurotoxicity syndrome (ICANS; a class-effect AE for drugs targeting/activating T cells). ICANS was graded according to the American Society for Transplantation and Cellular Therapy 2019 consensus guidelines.[32] A list of preferred terms classified as potential ICANS is provided in Appendix Table A2.

The MTD evaluation period was 3 weeks after the first administration of the target dose in Regimens A and B1. For Regimens B2 and B3, the MTD evaluation period included all step-up doses and was therefore extended from the initial dose up to 1 week after the first target dose. Tumor assessments were performed at screening (within 4 weeks before starting trial medication) and then every 6 weeks (42 days ± 7 days) starting from first obrixtamig administration until progressive disease (PD) or the start of subsequent anticancer treatment. Response was evaluated by the investigator per RECIST v1.1. Screening for CNS disease was not mandatory at baseline. Any new brain lesions detected during treatment in the absence of baseline scan were considered as PD by RECIST.

Statistical Analysis

Dose escalation was guided by a Bayesian logistic regression model, and the protocol allowed for lower or higher doses to be investigated, if they fulfilled the escalation with the overdose control principle.

This analysis included patients enrolled in the dose-escalation part of the trial. The data cutoff was February 21, 2024. Pharmacokinetic (PK) parameters were analyzed by noncompartmental analysis and summarized using descriptive statistics. Kaplan-Meier methods were used to estimate the median and percentiles for time-to-event end points, with 95% CIs calculated using the Brookmeyer and Crowley method. For objective response, 95% CIs were calculated using the Wilson method. Further analyses are described in Appendix 1.

RESULTS

Patients and Treatment

A total of 545 patients were screened for DLL3 positivity (SCLC, n = 281; LCNEC-L n = 44; epNEC n = 220), of whom 94%, 80% and 79% had DLL3-positive SCLC, LCNEC-L, and epNEC tumors, respectively. Between October 7, 2020, and

TABLE 1. Baseline Demographic and Disease Characteristics

Characteristic	Regimen A (n = 24)	Regimen B1 (n = 10)	Regimen B2 (n = 79)	Regimen B3 (n = 55)	All Patients (N = 168)
Age, years, median (range)	60 (46-78)	61 (44-66)	60 (32-81)	64 (35-77)	61 (32-81)
Sex, No. (%)					
Female	8 (33.3)	6 (60.0)	33 (41.8)	18 (32.7)	65 (38.7)
Male	16 (66.7)	4 (40.0)	46 (58.2)	37 (67.3)	103 (61.3)
Race, No. (%)					
White	18 (75.0)	8 (80.0)	64 (81.0)	51 (92.7)	141 (83.9)
Asian	6 (25.0)	2 (20.0)	11 (13.9)	3 (5.5)	22 (13.1)
Black or African American	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	2 (1.2)
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.6)
Multiple	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	2 (1.2)
ECOG performance status, No. (%)					
0	7 (29.2)	1 (10.0)	22 (27.8)	16 (29.1)	46 (27.4)
1	17 (70.8)	9 (90.0)	56 (70.9)	31 (56.4)	113 (67.3)
Missing	0 (0.0)	0 (0.0)	1 (1.3)	8 (14.5)	9 (5.4)
Tumor type, No. (%)					
SCLC	15 (62.5)	4 (40.0)	41 (51.9)	23 (41.8)	83 (49.4)
epNEC	7 (29.2)	5 (50.0)	32 (40.5)	27 (49.1)	71 (42.3)
LCNEC-L	2 (8.3)	1 (10.0)	6 (7.6)	5 (9.1)	1 4 (8.3)
Previous lines of anticancer treatment, No. (%)					
1	6 (25.0)	3 (30.0)	24 (30.4)	12 (21.8)	45 (26.8)
2	8 (33.3)	4 (40.0)	32 (40.5)	22 (40.0)	66 (39.3)
>2	10 (41.7)	3 (30.0)	23 (29.1)	19 (34.5)	55 (32.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	2 (1.2)
Previous use of PD1/PD-L1 blockers, No. (%)					
No	14 (58.3)	2 (20.0)	39 (49.4)	28 (50.9)	83 (49.4)
Yes	10 (41.7)	8 (80.0)	40 (50.6)	27 (49.1)	85 (50.6)
Metastases at baseline, No. (%)					
Brain	7 (29.2)	6 (60.0)	30 (38.0)	13 (23.6)	56 (33.3)
Liver	13 (54.2)	5 (50.0)	47 (59.5)	34 (61.8)	99 (58.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; epNEC, extrapulmonary neuroendocrine carcinoma; LCNEC-L, large cell neuroendocrine carcinoma of the lung; SCLC, small cell lung cancer.

February 12, 2024, 168 patients received obrixtamig; 24 received Regimen A (0.03-90 μg/kg once every 3 weeks), 10 received Regimen B1 (0.9-30 μg/kg once weekly), 79 received Regimen B2 (target dose: 90-1,530 μg/kg once weekly), and 55 received Regimen B3 (target dose: 90-1,080 μg/kg once weekly for 3 weeks, then once every 3 weeks from Week 7). Regimen B2 step-up doses were 30 and 90 μg/kg once weekly. Regimen B3 step-up doses were 10, 30, and 90 μg/kg once weekly. The switch from Regimens A to B1 was triggered by emerging PK data, whereas step-up dosing regimens B2 and B3 were initiated with the aim of increasing tolerability.

Baseline demographics and disease characteristics of all 168 patients are shown in Table 1.

At data cutoff (February 21, 2024), the median follow-up was 29 days (range, 3-408 days). Treatment was discontinued in 136 patients (81%), most commonly because of disease progression (n = 112 [67%]). Thirty-nine patients had died. Overall, the median number of treatment cycles was 3 (range, 1-35).

Safety and Tolerability

Seven DLTs occurred during the MTD evaluation period, six with Regimen B2 (9%) and one with Regimen A (4%; Appendix Table A3). MTD was not reached by the data cutoff. At data cutoff, MTD had not been reached for any regimen (Appendix 2).

All 168 patients received ≥1 dose of obrixtamig and were included in the safety population. Most patients (88%) had a treatment-related adverse event (TRAE), with 24% experiencing a grade ≥3 TRAE (Table 2). Treatment-emergent AEs are listed in Appendix Table A4. The most common TRAEs were CRS (57%), dysgeusia (23%), pyrexia (21%), asthenia (20%), and a transient decrease in lymphocyte counts (17%) lasting for a median of 8 days (95% CI, 7 to 12).

TABLE 2. TRAEs With Obrixtamig Monotherapy

TRAE	Regimen A (n = 24), No. (%)		Regimen B1 (n = 10), No. (%)		Regimen B2 (n = 79), No. (%)		Regimen B3 (n = 55), No. (%)		All Patients (N = 168), No. (%)	
TRAEs leading to dose reduction	1 (4.2)		0 (0.0)		3 (3.8)		0 (0.0)		4 (2.4)	
TRAEs leading to dose discontinuation	0 (0.0)		1 (10.0)		5 (6.3)		0 (0.0)		6 (3.6)	
TRAEs	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3
Any	19 (79.2)	5 (20.8)	6 (60.0)	2 (20.0)	76 (96.2)	27 (34.2)	47 (85.5)	6 (10.9)	148 (88.1)	40 (23.8)
CRS	11 (45.8)	0 (0.0)	3 (30.0)	0 (0.0)	54 (68.4)	3 (3.8)	28 (50.9)	2 (3.6)	96 (57.1)	5 (3.0)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	25 (31.6)	0 (0.0)	14 (25.5)	0 (0.0)	39 (23.2)	0 (0.0)
Pyrexia	3 (12.5)	0 (0.0)	1 (10.0)	0 (0.0)	18 (22.8)	0 (0.0)	13 (23.6)	0 (0.0)	35 (20.8)	0 (0.0)
Asthenia	4 (16.7)	0 (0.0)	1 (10.0)	1 (10.0)	16 (20.3)	0 (0.0)	13 (23.6)	0 (0.0)	34 (20.2)	1 (0.6)
Lymphocyte count decreased	3 (12.5)	3 (12.5)	0 (0.0)	0 (0.0)	22 (27.8)	16 (20.3)	3 (5.5)	2 (3.6)	28 (16.7)	21 (12.5)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	18 (22.8)	1 (1.3)	6 (10.9)	0 (0.0)	24 (14.3)	1 (0.6)
Nausea	4 (16.7)	0 (0.0)	2 (20.0)	0 (0.0)	9 (11.4)	0 (0.0)	7 (12.7)	0 (0.0)	22 (13.1)	0 (0.0)
AST increased	4 (16.7)	1 (4.2)	2 (20.0)	1 (10.0)	9 (11.4)	0 (0.0)	4 (7.3)	1 (1.8)	19 (11.3)	3 (1.8)
Decreased appetite	1 (4.2)	0 (0.0)	1 (10.0)	0 (0.0)	7 (8.9)	0 (0.0)	9 (16.4)	0 (0.0)	18 (10.7)	0 (0.0)
ALT increased	2 (8.3)	0 (0.0)	2 (20.0)	0 (0.0)	7 (8.9)	1 (1.3)	2 (3.6)	0 (0.0)	13 (7.7)	1 (0.6)
Anemia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	9 (11.4)	2 (2.5)	3 (5.5)	1 (1.8)	13 (7.7)	3 (1.8)
Vomiting	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	8 (10.1)	0 (0.0)	3 (5.5)	0 (0.0)	12 (7.1)	0 (0.0)

Abbreviations: CRS, cytokine release syndrome; G, grade; TRAE, treatment-related adverse event.

TRAEs were generally similar across Regimens B2 and B3 although CRS (51% and 68%) and reduced lymphocyte count (6% and 28%) incidences were lower with Regimen B3 than B2, respectively. The most common grade ≥3 TRAEs across all regimens were decreased lymphocyte count (13%), CRS (3%), anemia (2%), and increased aspartate transferase (2%).

At data cutoff, 105 patients (63%) had serious TRAEs, including two with grade 5 events, ICANS (Regimen B2; 1,530 μg/kg once weekly), and confusional syndrome (classified as Potential ICANS; Regimen B3; 720 μg/kg once weekly; Appendix Table A5). The Grade 5 ICANS event occurred in an 82-year-old man with NEC of the bladder and baseline brain metastases. The event occurred on Cycle 1 Day 16, the day after receiving the first 1,530 μg/kg once weekly dose of obrixtamig, and the patient died 16 days later. Autopsy findings not only were compatible with ICANS but also showed multiple viable metastatic lesions at known and previously unknown sites in the lung, right adrenal gland, and brain. The main cause of death was attributed to malignant neoplasm progression with evidence of moderate-grade cerebral edema and low-grade lymphocytic meningoencephalitis in the cerebrum, cerebellum, and brain stem; ICANS was considered as the secondary cause of death. The second grade 5 event occurred in a 65-year-old man with NEC of the colon. The patient was admitted with confusional syndrome (classified as Potential ICANS; Appendix Table A3) that started the day after the second step-up dose of 30 μg/kg once weekly, administered on Cycle 1 Day 8. The patient was treated with full supportive care, including increasing doses of corticosteroids and anakinra, but experienced further neurologic worsening and died 9 days later. Death was considered related to obrixtamig at the time of database lock. However, after autopsy, with findings of cerebral and cerebellar lymphangitic carcinomatosis, multiple hepatic and adrenal metastases, peritoneal effusion, and hemorrhagic petechial gastritis, the cause of death was changed and attributed to malignant neoplasm progression.

TRAEs leading to obrixtamig dose reduction or discontinuation occurred in four and six patients, respectively (Table 2). TRAEs leading to discontinuation were CRS, ICANS, and IRR (all Regimen B2; 30 μg/kg once weekly step-up dose); nervous system disorder (Regimen B2; 90 μg/kg once weekly step-up dose); dyspnea (Regimen B2; 720 μg/kg once weekly target dose); and asthenia (Regimen B1; 0.9 μg/kg once weekly).

CRS occurred at a median of 16 hours (range, 3-54 hours) after obrixtamig infusion and was mostly mild (grade 1 or 2, n = 91 [54%]); all cases were transient and resolved on treatment within a median of 2 days (range, 1-14 days). Thirty-three patients (20%) received corticosteroids or tocilizumab for CRS (Appendix Table A6). CRS predominantly occurred at the first two to three infusions of obrixtamig with Regimens B2 and B3; almost all episodes occurred during step-up dosing (Fig 1). Overall CRS rates in Regimens A and B1 (no step-up doses, maximum doses up to 90 μg/kg once every 3 weeks and 30 μg/kg once weekly, respectively) and Regimens B2 and B3 (doses up to 1,530 μg/kg once weekly and 1,080 μg/kg once weekly for 3 weeks [once every 3 weeks thereafter], respectively) were 46% and 30% and 68% and 51%, respectively.

Fifteen patients (9%) had treatment-related potential ICANS, of whom five (3%) had a grade ≥3 event. The most reported preferred terms for potential ICANS were confusional state (any, n = 7 [4%]; grade ≥3, n = 2 [1%]), ICANS (any, n = 4

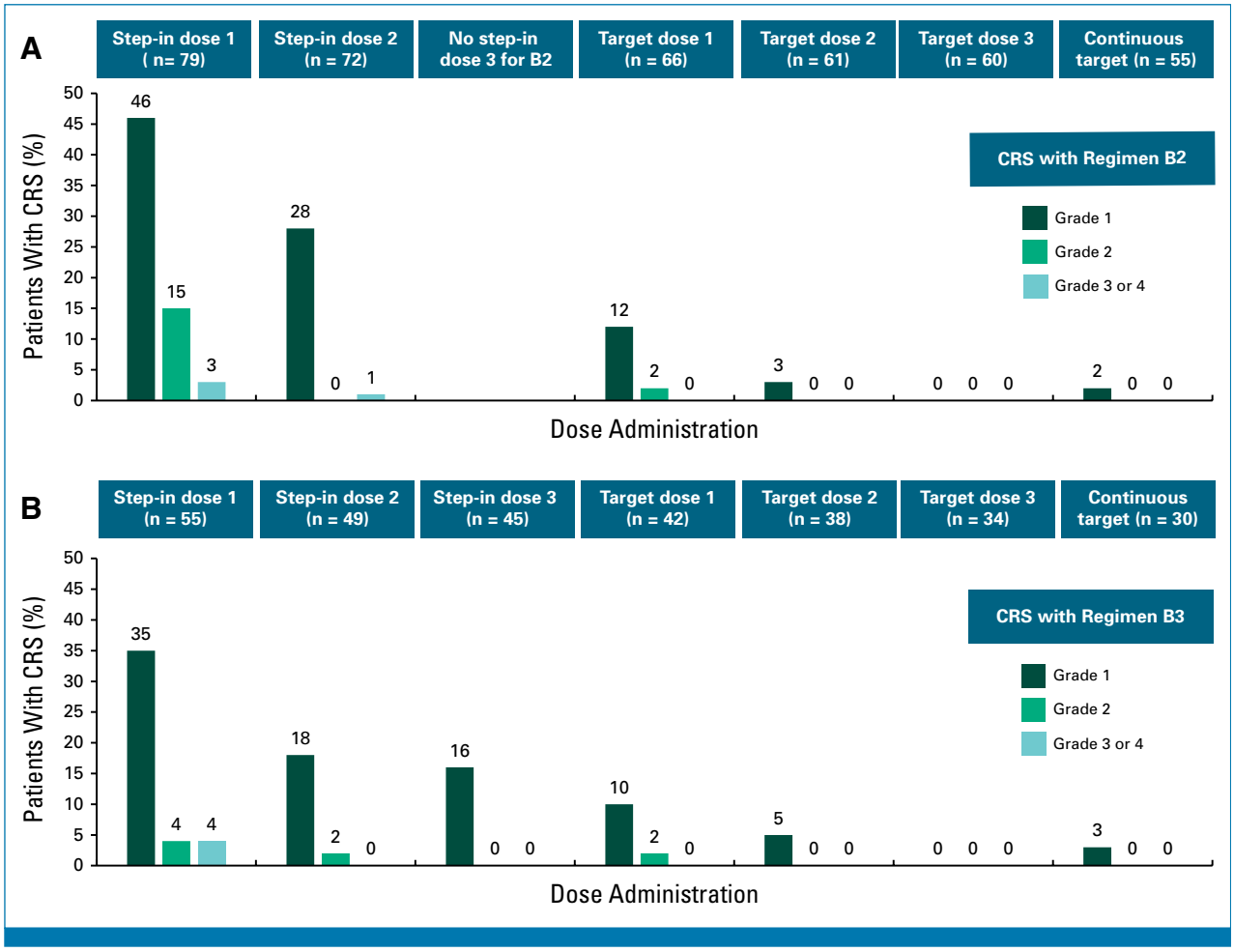

FIG 1. Incidence of CRS by administration of obrixtamig in patients treated with (A) Regimen B2 and (B) Regimen B3. CRS, cytokine release syndrome.

[2%]; grade ≥3, n = 2 [1%]), depressed level of consciousness (any, n = 3 [2%]; grade ≥3, n = 0), and disorientation (any, n = 2 [1%]; grade ≥3, n = 0; Appendix Table A7).

Efficacy

At data cutoff, 164 patients across all dose levels were evaluable for response, of whom 38 had partial responses (Fig 2A), giving an ORR across all doses, regimens, and tumor types of 23% (95% CI, 17.4% to 30.2%; Table 3). The median DoR was 8.5 months (95% CI, 6.2 to not reached; Table 3), with 6- and 9-month DoR rates of 70% (95% CI, 53% to 88%) and 49% (95% CI, 27% to 70%), respectively. The median DoR in patients with SCLC, epNEC, and LCNEC-L was 8.5 months, 6.2 months, and not reached, respectively. At data cutoff, 23 patients who responded to treatment were still receiving obrixtamig (Appendix Fig A2). The disease control rate (DCR), comprising complete response plus partial response, plus stable disease assessed ≥5 weeks after starting treatment, was 42% (95% CI, 34.8% to 49.7%).

Responses were seen in patients who received ≥90 μg/kg once weekly or once every 3 weeks obrixtamig. The ORR in evaluable patients who received ≥90 μg/kg once weekly or once every 3 weeks obrixtamig (n = 136) was 28% (95% CI, 21.1 to 36.0; Appendix Table A8). All patients in Regimens B2 (once weekly) and B3 (once weekly for 3 weeks, and once every 3 weeks thereafter) received ≥90 μg/kg obrixtamig and achieved an ORR of 27% (95% CI, 18.1 to 37.2) and 29% (95% CI, 18.7 to 43.0), respectively (Table 3, Fig 2B). The ORR by tumor type in Regimens B2 and B3 was 21% (95% CI, 12.9 to 33.1), 27% (95% CI, 17.4 to 39.6), and 70% (95% CI, 39.7 to 89.2) in patients with SCLC, epNEC, and LCNEC-L, respectively (Table 4). For epNEC, response rates by primary site of origin are shown in Appendix Table A9. In Regimens B2 + B3, the respective confirmed ORRs in patients with SCLC, epNEC, and LCNEC-L were 20% (95% CI, 11.6 to 32.4), 20% (95% CI, 11.3 to 31.8), and 44% (95% CI, 18.9 to 73.3), respectively (Appendix Table A10).

Pharmacokinetics

Based on available data in 138 patients (0.03-1,080 μg/kg once weekly or once every 3 weeks across four regimens), C_{max} and AUC for obrixtamig increased dose-proportionally.

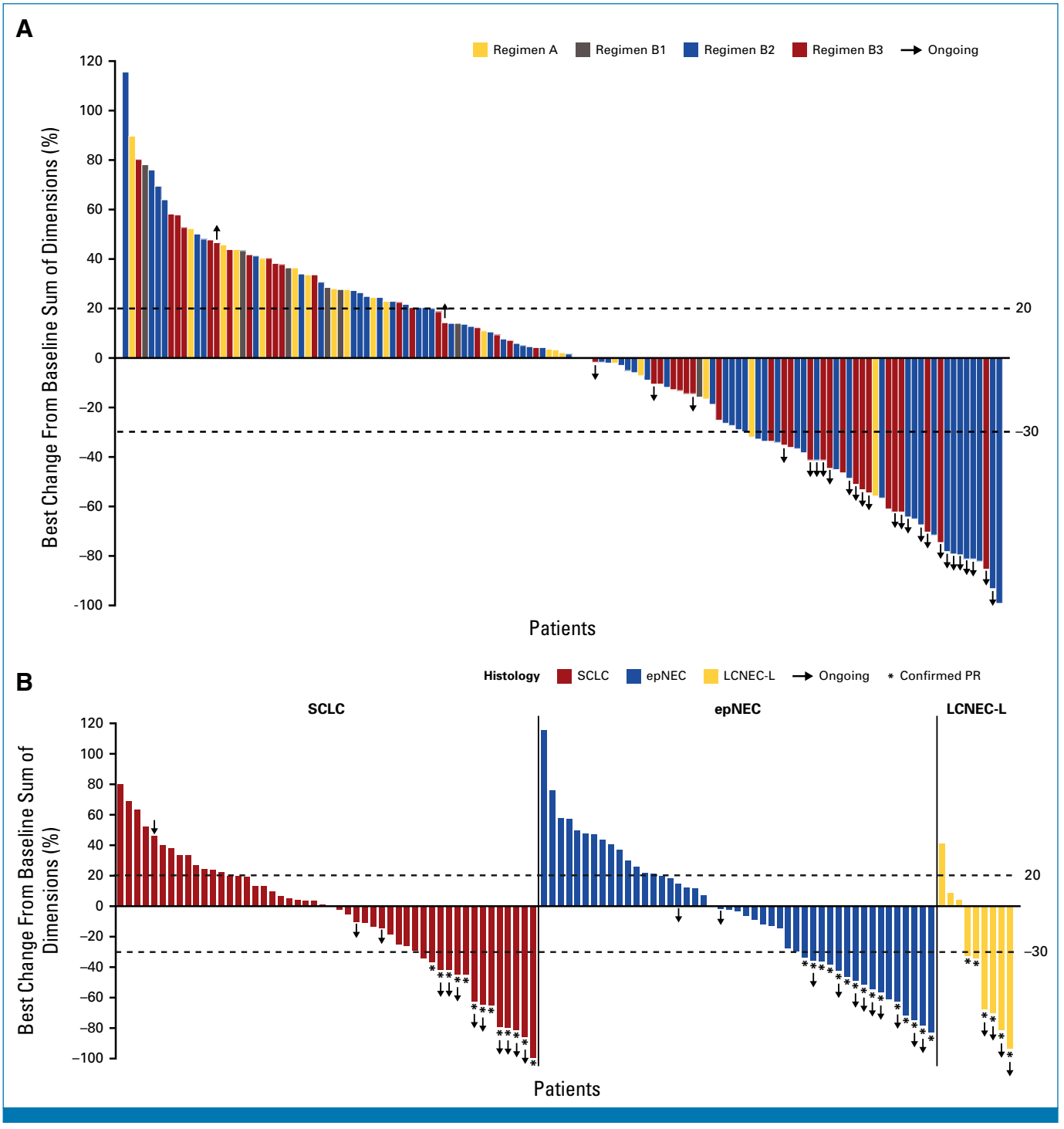

FIG 2. Antitumor effects of obrixtamig in patients with DLL3-positive SCLC, epNEC, and LCNEC-L. (A) Best percentage change in tumor dimensions from baseline for all assessable patients (investigator-assessed efficacy set). Of the 164 patients who started treatment 7 weeks before the data cutoff and were therefore included in the efficacy analysis set, 24 discontinued treatment before the first tumor assessment and were therefore excluded from waterfall plot analysis. A total of 140 of 164 patients had measurable tumors at baseline and postbaseline assessments. (B) Best percentage change in tumor dimensions from baseline in patients who received Regimen B2 or B3 (≥90 μg/kg obrixtamig once weekly and once weekly for 3 weeks [once every 3 weeks thereafter], respectively) by tumor type (investigator-assessed efficacy set). DLL3, delta-like ligand 3; epNEC, extrapulmonary neuroendocrine carcinoma; LCNEC-L, large cell neuroendocrine carcinoma of the lung; PR, partial response; SCLC, small cell lung cancer.

TABLE 3. Best ORR and DoR by Regimen in Evaluable Patients

Tumor Response	Regimen A[a] (n = 24)	Regimen B1[b] (n = 10)	Regimen B2[c] (n = 79)	Regimen B3[d] (n = 51)	Total[e] (n = 164)
ORR, No. (% [95% CI])	2 (8.3 [2.3 to 25.8])	0 (0.0 [0.0 to 27.8])	21 (26.6 [18.1 to 37.2])	15 (29.4 [18.7 to 43.0])	38 (23.2 [17.4 to 30.2])
DCR, No. (% [95% CI])	6 (25.0 [12.0 to 44.9])	1 (10.0 [1.8 to 40.4])	37 (46.8 [36.2 to 57.7])	25 (49.0 [35.9 to 62.3])	69 (42.1 [34.8 to 49.7])
Median DoR, months (95% CI)	19.4 (NC to NC)	NA	7.3 (4.2 to NC)	NC (NC to NC)	8.5 (6.2 to NC)[e]
6-month DoR rate, % (95% CI)	100.0 (100 to 100)	NA	63.0 (42 to 85)	NC (NC to NC)	70 (53 to 88)[e]
9-month DoR rate, % (95% CI)	100.0 (100 to 100)	NA	42.0 (20 to 65)	NC (NC to NC)	49 (27 to 70)[e]

Abbreviations: DCR, disease control rate; DoR, duration of response; NA, not appropriate; NC, not calculable; ORR, overall response rate.
[a]Dose range administered, 0.03-90.0 μg/kg once every 3 weeks.
[b]Dose range administered, 0.9-30.0 μg/kg once weekly.
[c]Step-up doses 30 μg/kg and 90 μg/kg once weekly; target dose range 90-1,530 μg/kg once weekly.
[d]Step-up doses 10 μg/kg, 30 μg/kg, and 90 μg/kg once weekly; target dose range 90-1,080 μg/kg once weekly for 3 weeks, and once every 3 weeks thereafter.
[e]All patients who achieved a partial response received obrixtamig at a dose of ≥90 μg/kg once weekly or once every 3 weeks.

The terminal half-life of obrixtamig was approximately 7 days (range, 5-10).

DISCUSSION

In this study, obrixtamig demonstrated manageable tolerability and encouraging efficacy in patients with DLL3-positive SCLC, epNEC, and LCNEC-L, with MTD not reached. Consistent with early-phase data for other DLL3-targeted TCEs,[33,34] the most common TRAEs were CRS and CRS-related (eg, pyrexia, asthenia, fatigue), neurologic (dysgeusia), and hematologic (decreased lymphocyte count) events. TRAEs were generally manageable, with low dose reduction and discontinuation rates (2% and 4%, respectively). Most patients received Regimen B2 or B3, and those receiving Regimen B3 had generally lower incidences of TRAEs, including CRS, than Regimen B2, with no dose reductions or discontinuations.

While CRS was the most common TRAE, most cases occurred during early cycles and the rates decreased with each step-up dose. CRS arose shortly after dosing (median 16 hours) and only lasted for a median of 2 days. CRS rates with obrixtamig (51%-68%) were similar to those observed with tarlatamab and MK-6070, another TCE (50%-60%).[33,35,36] Dysgeusia was the second most-frequent TRAE with obrixtamig (23%,

TABLE 4. Best ORR by Tumor Type in Patients Treated With Regimens B2 + B3

Unconfirmed ORR[a]	SCLC (n = 61)	epNEC (n = 59)	LCNEC-L (n = 10)	Total (n = 130)
ORR, No. (% [95% CI])	13 (21.3 [12.9 to 33.1])	16 (27.1 [17.4 to 39.6])	7 (70.0 [39.7 to 89.2])	36 (27.7 [20.7 to 35.9])
DCR, No. (% [95% CI])	26 (42.6 [31.0 to 55.1])	27 (45.8 [33.7 to 58.3])	9 (90.0 [59.6 to 98.2])	62 (47.7 [39.3 to 56.2])
CR, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)
PR, No. (%)	13 (21.3)	16 (27.1)	7 (70)	36 (27.7)
SD, No. (%)[b]	13 (21.3)	11 (18.6)	2 (20.0)	26 (20.0)
PD, No. (%)	22 (36.1)	21 (35.6)	1 (10.0)	44 (33.8)
Not evaluable, No. (%)[c]	13 (21.3)	11 (18.6)	0 (0)	24 (18.5)
Confirmed ORR[d]	SCLC (n = 55)	epNEC (n = 56)	LCNEC-L (n = 9)	Total (N = 120)
ORR, No. (% [95% CI])	11 (20.0 [11.6 to 32.4])	11 (19.6 [11.3 to 31.8])	4 (44.4 [18.9 to 73.3])	26 (21.7 [15.2 to 29.9])

Abbreviations: CR, complete response; DCR, disease control rate; epNEC, extrapulmonary neuroendocrine carcinoma; LCNEC-L, large cell neuroendocrine carcinoma of the lung; ORR, overall response rate; PR, partial response; SCLC, small cell lung cancer; SD, stable disease.
[a]Unconfirmed ORR analysis includes patients with a follow-up of ≥7 weeks since the start of treatment, including patients with ≥1 tumor assessment or patients who had no tumor assessment because of early toxicity, start of subsequent anticancer therapy, death, or any other reason.
[b]The minimum duration of stable disease was 5 weeks.
[c]Not evaluable: patients who did not have any tumor assessment because of early toxicity, start of subsequent anticancer therapy, death, or any other reason; or who had no other tumor assessment result than "not evaluable"; or who had only tumor assessment result of SD within 5 weeks from first treatment.
[d]Confirmed ORR analysis includes patients with a follow-up of ≥13 weeks since the start of treatment, including those patients with ≥2 tumor assessments or patients who did not have ≥2 tumor assessments because of early toxicity, start of subsequent anticancer therapy, death, or any other reason.

all grades 1 to 2), occurring at a similar frequency to that reported for tarlatamab in the DeLLphi-300 trial (22%).[33] The overall rate of potential ICANS with obrixtamig was 9% (grade ≥3, 3%). Neurologic AEs, including ICANS, are a class effect that physicians should be aware of during treatment with TCEs.

The ORR of 23% across all obrixtamig doses, regimens, and tumor types was promising, given that 72% of patients had received ≥2 previous therapies and 51% had received previous anti–PD-1/PD-L1 therapy. Notably, all responding patients received obrixtamig doses ≥90 μg/kg either once weekly or once every 3 weeks, which was considered the threshold for pharmacologic activity. Almost all the patients who received ≥90 μg/kg were treated with Regimen B2 (once weekly) or B3 (once weekly for 3 weeks, and once every 3 weeks thereafter), with ORRs of 27% and 29%, respectively. While DoR data are immature with 23 patients still on treatment, there is evidence that responses to obrixtamig are durable; the median DoR was 8.5 months (95% CI, 6.2 to calculable) with 70% (95% CI, 53% to 88%) and 49% (95% CI, 27% to 70%) DoR rates at 6 months and 9 months, respectively.

Across active dose ranges in Regimens B2 and B3, the confirmed ORR in patients with SCLC was 20% (95% CI, 11.6 to 32.4), which is nominally similar to that observed with other DLL3 TCEs.[26] While other studies of DLL3 TCEs might not have selected for DLL3 positivity, it should be noted that at screening, 94% of SCLC cases in our study were DLL3-positive. Furthermore, cross-trial comparisons of efficacy rates are confounded by differences in trial design and study population profiles. One particularly important difference between study designs is screening for the presence of brain metastases, which may occur in up to 80% of patients within 2 years of SCLC diagnosis.[37] In contrast to other phase I studies of DLL3 TCEs,[33,38] baseline radiologic screening for asymptomatic brain metastases was not required in the current trial. This approach permitted inclusion of patients with poor prognosis and high risk of early progression, while more closely resembling the current clinical standard of care in the real-world SCLC setting.

In contrast to clinical studies of other DLL3 TCEs, the current study assessed obrixtamig in multiple tumor types. In Regimens B2 and B3 at active dose levels, obrixtamig demonstrated highly encouraging confirmed ORRs of 20%, 20%, and 44% (Table 4 and Appendix Table A10) and confirmed DCRs of 44%, 45%, and 90% in patients with SCLC, epNEC, and LCNEC-L, respectively (Appendix Table A10). The response rate in LCNEC-L is especially encouraging, given the paucity of effective treatment options, particularly in second-line and later settings, where chemotherapy and immunotherapy have, at best, modest clinical activity.[3,39] The potential benefits provided by obrixtamig warrant further investigation in this setting. Interpretation of efficacy data was limited because of the open-label design of the trial with no comparator and because relatively few patients with LCNEC-L were recruited.

In conclusion, in the dose-escalation part of this phase I study, obrixtamig showed a manageable safety profile and encouraging signs of antitumor activity in patients with DLL3-positive advanced or metastatic SCLC, NEC, and LCNEC-L. Based on PK and tolerability, step-up dosing regimens with initially once weekly applications (eg, regimens B2 and B3) appeared most promising for further clinical development. Several obrixtamig clinical trials are currently recruiting patients, including phase I trials assessing it in combination with the anti–PD-1 antibody ezabenlimab for DLL3+ SCLC and NECs (ClinicalTrials.gov identifier: NCT05879978) and first-line standard of care in patients with DLL3+ NECs (ClinicalTrials.gov identifier: NCT06132113). Obrixtamig is also being assessed in other populations regardless of DLL3 positivity, including a phase II dose-selection trial in patients with pretreated SCLC, epNEC, or LCNEC-L (ClinicalTrials.gov identifier: NCT05882058) and in combination with single-agent chemotherapy (ClinicalTrials.gov identifier: NCT05990738) or first-line standard of care (ClinicalTrials.gov identifier: NCT06077500) for advanced SCLC. Results from these trials are eagerly anticipated.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase I Dose-Escalation Results for the Delta-Like Ligand 3/CD3 IgG-Like T-Cell Engager Obrixtamig (BI 764532) in Patients With Delta-Like Ligand 3+ Small Cell Lung Cancer or Neuroendocrine Carcinomas

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APPENDIX 1. METHODS

Inclusion and Exclusion Criteria

Key inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0-1 and at least one evaluable noncentral nervous system lesion, as defined by modified RECIST v1.1 criteria; patients must have failed on, or be ineligible for, available standard therapies including ≥1 line of chemotherapy; patients with small cell carcinomas must have previously received platinum-based therapy, must have had adequate organ function, and have to provide written informed consent.

Patients with brain metastases were permitted, provided that radiotherapy or surgery for brain metastases was completed ≥2 weeks before the first obrixtamig dose; patients with asymptomatic brain metastases were also allowed.

Key exclusion criteria were previous treatment with T-cell engagers or delta-like ligand 3–targeted therapies; persistent toxicity from previous treatment that had not resolved to grade ≤1 Common Terminology Criteria for Adverse Events (except for alopecia, grade 2 neuropathy, fatigue, or grade 2 endocrinopathies controlled by replacement therapy); diagnosis of immunodeficiency or receipt of immunosuppressive therapy within 7 days of first dose of obrixtamig; previous anticancer therapy within 3 weeks/5 half-life periods or extensive field radiotherapy within 2 weeks of first dose of obrixtamig; or known leptomeningeal disease.

Statistical Analysis

For each dosing regimen, a separate Bayesian logistic regression model using the escalation with overdose control (EWOC) principle was used during the escalation phase for dose level selection and maximum tolerated dose (MTD) estimation. Dose-limiting toxicity (DLT) probability estimates per dose level were summarized using the following intervals: under toxicity, 0.00-0.16; targeted toxicity, 0.16-0.33; and over toxicity, 0.33-1.00. MTD was defined as the highest dose with <25% risk of the true DLT rate being equal to or above 0.33 (EWOC criterion). Intrapatient dose escalation was allowed to dose levels cleared by the Safety Monitoring Committee.

APPENDIX 2. SUPPLEMENTARY RESULTS

Dose Escalation

Switch from fixed-dose Regimens A and B1 to Regimen B2 was triggered by occurrence of cytokine release syndrome and grade 2 immune effector cell–associated neurotoxicity syndrome (ICANS) in Regimen A after initial drug administration at 90 μg/kg once every 3 weeks.

Regimen B2 was introduced with two step-up doses of 30 and 90 μg/kg once weekly followed by the target dose. The target dose was escalated further from 90 μg/kg once weekly, and dose escalation continued until 1,530 μg/kg once weekly and then was stopped because of a grade 5 ICANS event and a flat dose-efficacy relationship. Overall, Regimen B2 was considered tolerable with appropriate safety management.

Regimen B3 was introduced based on accumulated safety data in Regimen B2 to further improve tolerability. Specifically, an additional step-up dose of 10 μg/kg once weekly was added. After 6 weeks, the schedule was switched from once weekly to once every 3 weeks to reduce patient burden for long-term use of obrixtamig. With the new step-up dosing design, obrixtamig was tolerable up to 1,080 μg/kg once weekly or once every 3 weeks (maximum dose tested). No DLTs were reported with Regimen B3.

Overall, both Regimens B2 and B3 were considered to have an acceptable safety profile with slightly better tolerability of Regimen B3. No clear efficacy differences were observed at target levels ranging from 90 to 1,080 μg/kg across Regimens B2 (once weekly) and B3 (once weekly for 3 weeks, once every 3 weeks thereafter).

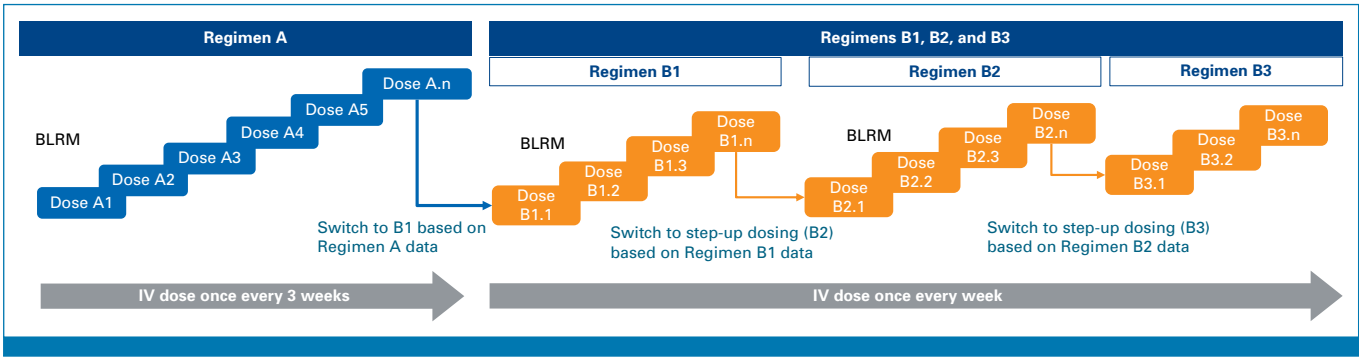

FIG A1. NCT04429087 study design. BLRM, Bayesian logistic regression model.

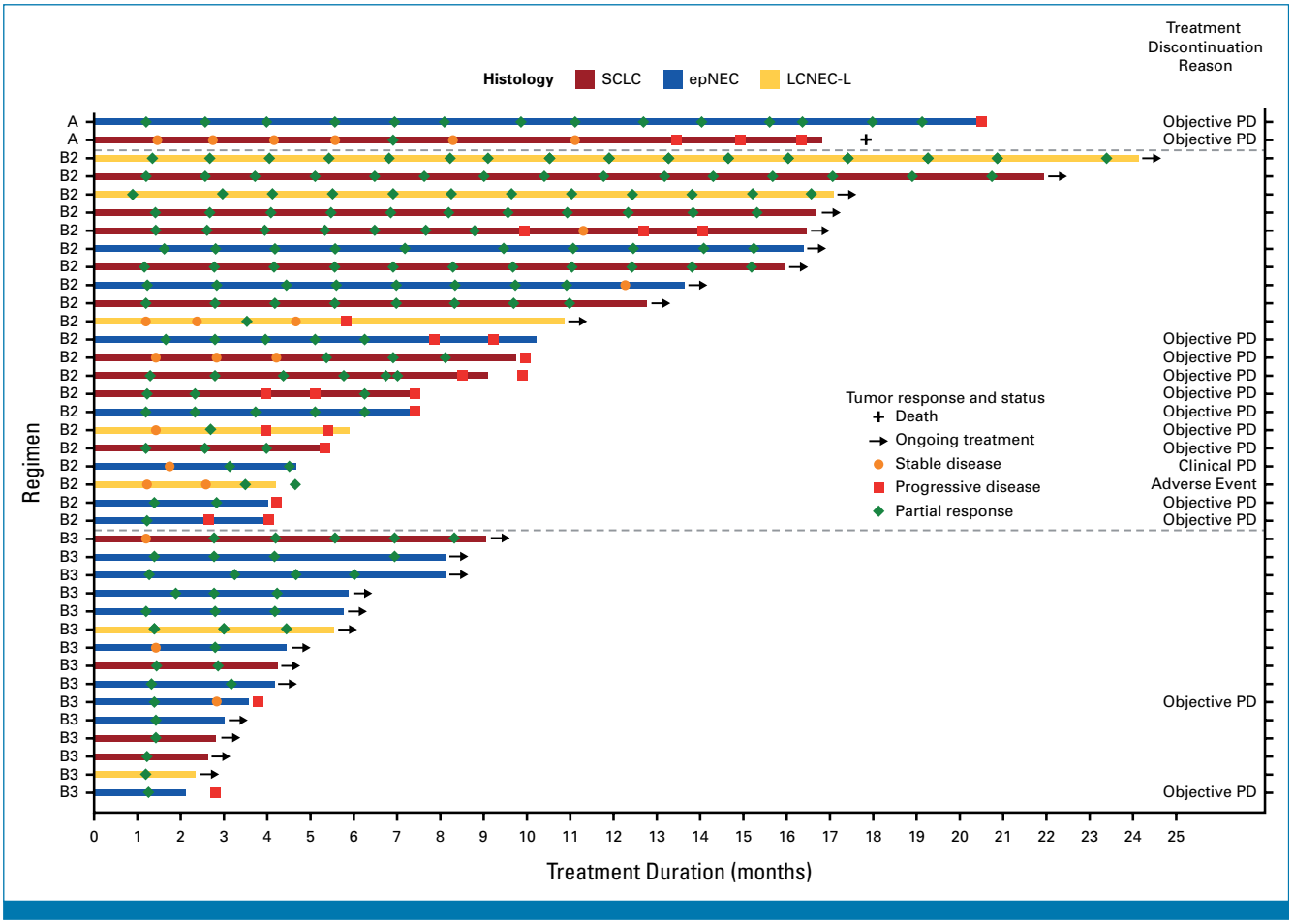

FIG A2. Swimmer plot by obrixtamig regimen. epNEC, extrapulmonary neuroendocrine carcinoma; LCNEC-L, large cell neuroendocrine carcinoma of the lung; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer.

TABLE A1. Overview of Dose-Limiting Toxicities

Category	Criteria
Nonhematologic	CRS/IRR CRS/IRR ≥CTC grade 4 CRS/IRR ≥CTC grade 3 if not resolved to grade 1 ≤ within 48 hours (despite appropriate intervention) Other nonhematologic AEs grade ≥3 except for Laboratory values unless they meet the criteria specified below Fatigue/asthenia; if present at baseline, there must be an increase of ≥2 grades lasting more than 7 days to qualify for DLT Grade 3 nausea or grade 3 vomiting or grade 3 diarrhea lasting ≤48 hours, which resolved to ≤grade 1 either spontaneously or with conventional medical intervention TLS grade 3 TLS grade 4 if clinically manageable and resolving within 24 hours Nonhematologic clinically significant laboratory value of CTC grade 4 Nonhematologic clinically significant laboratory value of CTC grade 3 if Hospitalization results from the laboratory value The abnormality persists for >72 hours despite appropriate interventions (eg, replacement therapy for electrolyte abnormalities, when indicated) Liver laboratory parameters: For patients with normal liver function at baseline (ALT, AST, and bilirubin within normal limits at baseline): An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample with the exclusion of causes because of underlying diseases and/or Marked peak aminotransferase (ALT and/or AST) elevations ≥10-fold ULN with the exclusion of causes because of underlying diseases and persistence for >72 hours despite appropriate treatment For patients with abnormal liver function at baseline (AST and/or ALT > ULN) An elevation of AST and/or ALT ≥5-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample, with the exclusion of causes because of underlying diseases and/or Marked peak aminotransferase (ALT and/or AST) elevations ≥10-fold ULN with the exclusion of causes because of underlying diseases and persistence for >72 hours despite appropriate
Hematologic	Hematologic toxicity CTC grade 4 (eg, neutropenia, thrombocytopenia, anemia) except for lymphopenia Anemia of any grade requiring red cell transfusion Thrombocytopenia of any grade requiring platelet transfusion Neutropenia of any grade requiring treatment with growth factors Grade 3 neutropenia with documented infection Grade 3 neutropenia lasting >3 days Febrile neutropenia Grade 3 thrombocytopenia (<50,000/mm^3)
Other	AE that leads to administration of <70% of the planned dose per cycle despite infusion interruption and infusion time prolongation AE that requires permanent discontinuation of obrixtamig Other toxicity considered significant enough to qualify as DLT in the opinion of the investigators, SMC, or sponsors

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; CTC, Common Terminology Criteria; DLT, dose-limiting toxicity; IRR, infusion-related reaction; SMC, Safety Monitoring Committee; TLS, tumor lysis syndrome; ULN, upper limit of normal.

TABLE A2. List of Potential ICANS Preferred Terms

Potential ICANS Preferred Terms		
(A-C)	(D-M)	(N-V)
Acquired deaf mutism	Delirium	New-onset refractory status epilepticus
Acquired epileptic aphasia	Delusion	Nightmare
Acute encephalitis with refractory, repetitive partial seizures	Delusion of grandeur	Ophthalmoplegia
	Delusion of parasitosis	Papilledema
	Delusion of reference	Paranoia
Agitation	Delusion of replacement	Paraparesis
Agraphia	Delusion of theft	Paresis
Altered state of consciousness	Delusional perception	Partial seizures
Anxiety	Depressed level of consciousness	Partial seizures with secondary generalization
Anxiety disorder	Depressive delusion	Peripheral nerve palsy
Anxiety disorder due to a general medical condition	Disorganized speech	Peripheral nerve paresis
	Disorientation	Persecutory delusion
Aphasia	Distractibility	Photosensitive seizure
Apraxia	Disturbance in attention	Postictal psychosis
Ascending flaccid paralysis	Dizziness	Poverty of speech
Ataxia	Dyscalculia	Preictal state
Atonic seizures	Dysgraphia	Presyncope
Autoimmune cerebellar ataxia	Encephalopathy	Psychomotor hyperactivity
Autoimmune encephalopathy	Epileptic encephalopathy	Quadriparesis
Automatism	Erotomanic delusion	Quadriplegia
Brain edema	Gait apraxia	Repetitive speech
Cerebellar ataxia	Generalized anxiety disorder	Restlessness
Cerebellar mutism	Hemiapraxia	Seizure
Cerebral ataxia	Hemiataxia	Seizure cluster
Change in seizure presentation	Hemiclonic seizure	Slow speech
Clonic convulsion	Hemiparesis	Somnolence
Cognitive disorder	Hemiplegia	Speech disorder
Communication disorder	Ictal bradycardia syndrome	Status epilepticus
Confusional arousal	Ictal central apnea	Stupor
Confusional state	Immune effector cell–associated neurotoxicity syndrome	Supranuclear palsy
Convulsions local		Syncope
Cytotoxic edema	Immune-mediated encephalopathy	Terminal agitation
	Irritability	Toxic leukoencephalopathy
	Jealous delusion	Transient aphasia
	Lack of spontaneous speech	Vasogenic cerebral edema
	Language disorder	
	Lethargy	
	Leukoencephalopathy	
	Memory impairment	
	Mental status changes	
	Micrographia	
	Mixed delusion	
	Monoparesis	
	Monoplegia	
	Muscle spasms	
	Mutism	
	Myofascial spasm	

Abbreviation: ICANS, immune effector cell–associated neurotoxicity syndrome.

TABLE A3. Patients with DLTs during the MTD Evaluation Period

Regimen and Dose Level, μg/kg	Obrixtamig Dose at DLT Onset, μg/kg	DLT Preferred Term	Grade	Serious	Study day at AE Start	Duration of DLT, days	Tumor Type
A 90 once weekly	90	Confusional state[a]	3	Yes	47	2	SCLC
B2 step-up 1,530 once weekly	1,530	ICANS[b]	5	Yes	16	16	epNEC
B2 step-up 270 once weekly	90	Nervous system disorder	3	Yes	10	9	SCLC
B2 step-up 270 once weekly	30	IRR	2	No	22	3	SCLC
B2 step-up 270 once weekly	30	CRS	4	Yes	2	4	SCLC
B2 step-up 360 once weekly	90	CRS	3	Yes	16	5	epNEC
B2 step-up 720 once weekly	30	ICANS	3	Yes	2	8	SCLC

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; epNEC, extrapulmonary neuroendocrine carcinoma; ICANS, immune effector cell–associated neurotoxicity syndrome; IRR, infusion-related reaction; MTD, maximum tolerated dose; SCLC, small cell lung cancer.

[a]Potential ICANS (Appendix Table A2).

[b]Attributed to progressive disease on autopsy; ICANS was considered a secondary cause of death.

TABLE A4. Overall Safety Profile and Most Common Treatment-Emergent AEs with Obrixtamig Monotherapy

AE	Regimen A (n = 24), No. (%)		Regimen B1 (n = 10), No. (%)		Regimen B2 (n = 79), No. (%)		Regimen B3 (n = 55), No. (%)		All Patients (N = 168), No. (%)	
AEs leading to dose reduction	1 (4.2)		0 (0.0)		3 (3.8)		0 (0)		4 (2.4)	
AEs leading to dose discontinuation	0 (0.0)		1 (10.0)		5 (6.3)		0 (0)		6 (3.6)	
AEs	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3
Any	24 (100)	14 (58.3)	10 (100)	6 (60.0)	79 (100)	50 (63.3)	54 (98.2)	22 (40.0)	167 (99.4)	92 (54.8)
Cytokine release syndrome	11 (45.8)	0.0	3 (30.0)	0 (0.0)	54 (68.4)	3 (3.8)	28 (50.9)	2 (3.6)	96 (57.1)	5 (3.0)
Asthenia	6 (25.0)	0 (0.0)	1 (10.0)	1 (10.0)	19 (24.1)	1 (1.3)	21 (38.2)	3 (5.5)	47 (28.0)	5 (3.0)
Dysgeusia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	28 (35.4)	0 (0.0)	16 (29.1)	0 (0.0)	45 (26.8)	0 (0.0)
Pyrexia	3 (12.5)	0 (0.0)	1 (10.0)	0 (0.0)	21 (26.6)	0 (0.0)	17 (30.9)	0 (0.0)	42 (25.0)	0 (0.0)
Nausea	4 (16.7)	0 (0.0)	5 (50.0)	0 (0.0)	21 (26.6)	1 (1.3)	8 (14.5)	0 (0.0)	38 (22.6)	1 (0.6)
Constipation	5 (20.8)	0 (0.0)	0 (0.0)	0 (0.0)	20 (25.3)	0 (0.0)	11 (20.0)	0 (0.0)	36 (21.4)	0 (0.0)
Decreased appetite	3 (12.5)	1 (4.2)	3 (30.0)	0 (0.0)	15 (19.0)	1 (1.3)	15 (27.3)	0 (0.0)	36 (21.4)	2 (1.2)
Fatigue	1 (4.2)	1 (4.2)	1 (10.0)	1 (1.0)	22 (27.8)	2 (2.5)	8 (14.5)	0 (0.0)	32 (19.0)	4 (2.4)
Anemia	1 (4.2)	0 (0.0)	1 (10.0)	0 (0.0)	17 (21.5)	5 (6.3)	11 (20.0)	5 (9.1)	30 (17.9)	10 (6.0)
Lymphocyte count decreased	3 (12.5)	3 (12.5)	0 (0.0)	0 (0.0)	23 (29.1)	17 (21.5)	3 (5.5)	2 (3.6)	29 (17.3)	22 (13.1)
AST increased	5 (20.8)	1 (4.2)	2 (20.0)	1 (10.0)	15 (19.0)	0 (0.0)	6 (10.9)	2 (3.6)	28 (16.7)	4 (2.4)
Back pain	2 (8.3)	0 (0.0)	3 (30.0)	0 (0.0)	12 (15.2)	0 (0.0)	8 (14.5)	2 (3.6)	25 (14.9)	2 (1.2)
Malignant neoplasm progression	4 (16.7)	4 (16.7)	3 (30.0)	3 (30.0)	14 (17.7)	13 (16.5)	2 (3.6)	1 (1.8)	23 (13.7)	21 (12.5)
Vomiting	2 (8.3)	0 (0.0)	2 (20.0)	0 (0.0)	14 (17.7)	0 (0.0)	4 (7.3)	0 (0.0)	22 (13.1)	0 (0.0)
ALT increased	3 (12.5)	0 (0.0)	2 (20.0)	0 (0.0)	11 (13.9)	2 (2.5)	4 (7.3)	1 (1.8)	20 (11.9)	3 (1.8)
Headache	4 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	11 (13.9)	0 (0.0)	1 (1.8)	0 (0.0)	16 (9.5)	0 (0.0)
Hyponatremia	1 (4.2)	0 (0.0)	2 (20.0)	0 (0.0)	9 (11.4)	3 (3.8)	3 (5.5)	1 (1.8)	15 (8.9)	4 (2.4)
Weight decreased	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	13 (16.5)	0 (0.0)	1 (1.8)	0 (0.0)	15 (8.9)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (11.4)	0 (0.0)	5 (9.1)	0 (0.0)	14 (8.3)	0 (0.0)
Dizziness	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (10.1)	0 (0.0)	4 (7.3)	0 (0.0)	14 (8.3)	0 (0.0)
Dyspnea	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	7 (8.9)	2 (2.5)	4 (7.3)	1 (1.8)	14 (8.3)	3 (1.8)
Edema peripheral	7 (29.2)	1 (4.2)	0 (0.0)	0 (0.0)	3 (3.8)	0 (0.0)	4 (7.3)	0 (0.0)	14 (8.3)	1 (0.6)
Arthralgia	3 (12.5)	0 (0.0)	1 (10.0)	0 (0.0)	6 (7.6)	0 (0.0)	3 (5.5)	0 (0.0)	13 (7.7)	0 (0.0)
COVID-19	2 (8.3)	0 (0.0)	1 (10.0)	0 (0.0)	9 (11.4)	0 (0.0)	1 (1.8)	0 (0.0)	13 (7.7)	0 (0.0)
Rash	4 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	9 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	13 (7.7)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (8.9)	0 (0.0)	5 (9.1)	0 (0.0)	12 (7.1)	0 (0.0)
Diarrhea	2 (8.3)	0 (0.0)	1 (10.0)	0 (0.0)	4 (5.1)	0 (0.0)	5 (9.1)	0 (0.0)	12 (7.1)	0 (0.0)
Insomnia	1 (4.2)	0 (0.0)	1 (10.0)	0 (0.0)	7 (8.9)	0 (0.0)	3 (5.5)	0 (0.0)	12 (7.1)	0 (0.0)
Lipase increased	2 (8.3)	1 (4.2)	1 (10.0)	0 (0.0)	6 (7.6)	1 (1.3)	3 (5.5)	0 (0.0)	12 (7.1)	2 (1.2)
Blood alkaline phosphatase increase	1 (4.2)	0 (0.0)	1 (10.0)	0 (0.0)	4 (5.1)	2 (2.5)	5 (9.1)	2 (3.6)	11 (6.5)	4 (2.4)
Pruritus	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.6)	0 (0.0)	4 (7.3)	0 (0.0)	11 (6.5)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	7 (8.9)	0 (0.0)	3 (5.5)	2 (3.6)	11 (6.5)	2 (1.2)
Confusional state	2 (8.3)	1 (4.2)	1 (10.0)	0 (0.0)	4 (5.1)	0 (0.0)	3 (5.5)	1 (1.8)	10 (6.0)	2 (1.2)
Hypokalemia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.6)	2 (2.5)	3 (5.5)	0 (0.0)	10 (6.0)	2 (1.2)
Dry skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.6)	0 (0.0)	3 (5.5)	0 (0.0)	9 (5.4)	0 (0.0)

Abbreviations: AE, adverse event; G, grade.

TABLE A5. Overall Frequency of Serious Treatment-Related Adverse Events

Preferred Term	All Grades, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	Grade 5, No. (%)
All treatment-related SAEs	105 (62.5)	69 (41.1)	23 (13.7)	10 (6.0)	1 (0.6)	2 (1.2)
Cytokine release syndrome	96 (57.1)	72 (42.9)	19 (11.3)	4 (2.4)	1 (0.6)	0 (0.0)
Immune effector cell–associated neurotoxicity syndrome	4 (2.4)	0 (0.0)	2 (1.2)	1 (0.6)	0 (0.0)	1 (0.6)
Infusion-related reaction	3 (1.8)	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Confusional state	2 (1.2)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
Neurotoxicity	2 (1.2)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Chest pain	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Drug-induced liver injury	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Dyspnea	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Facial paralysis	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorder	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviation: SAE, serious adverse event.

TABLE A6. Patients with CRS by Regimen and Highest Grade Treated with Corticosteroid or Tocilizumab

CRS Grade	Regimen A, No. (%)	Regimen B1, No. (%)	Regimen B2, No. (%)	Regimen B3, No. (%)	Total, No. (%)
Patients	24 (100)	10 (100)	79 (100)	55 (100)	168 (100)
All grades	11 (46)	3 (30)	54 (68)	28 (51)	96 (57)
1	9 (38)	1 (10)	39 (49)	23 (42)	72 (43)
2	2 (8)	2 (20)	12 (15)	3 (6)	19 (11)
3	0	0	2 (3)	2 (4)	4 (2)
4	0	0	1 (1)	0	1 (1)
5	0	0	0	0	0
CRS treated with corticosteroids or tocilizumab					
All grades	5 (21)	1 (10)	17 (22)	10 (18)	33 (20)
1	3 (13)	0	4 (5)	7 (13)	14 (8)
2	2 (8)	1 (10)	10 (13)	2 (4)	15 (9)
3	0	0	2 (3)	1 (2)	3 (2)
4	0	0	1 (1)	0	1 (1)
5	0	0	0	0	0

Abbreviation: CRS, cytokine release syndrome.

TABLE A7. Patients with Potential ICANS

Preferred Term	All Grade, No. (%)	Grade ≥3, No. (%)
Patients	168 (100)	168 (100)
Total patients with potential ICANS[a]	15 (9)	5 (3)
Confusional state	7 (4)	2 (1)
ICANS	4 (2)	2 (1)
Depressed level of consciousness	3 (2)	0
Disorientation	2 (1)	0
Agitation	1 (1)	0
Aphasia	1 (1)	1 (1)
Dizziness	1 (1)	0
Encephalopathy	1 (1)	0
Nervous system disorder	1 (1)	1 (1)
Presyncope	1 (1)	0
Somnolence	1 (1)	0

Abbreviation: ICANS, immune effector cell–associated neurotoxicity syndrome.

[a]Potential ICANS includes all patients reported as having ICANS (as reported by the investigator) plus patients with preferred terms classified as potential ICANS, by the study sponsor (Appendix Table A2), all considered treatment-related. Patients might have experienced multiple potential ICANS adverse events; therefore, the total number of preferred terms (n = 23) exceeds the number of patients with potential ICANS (n = 15).

TABLE A8. Best ORR by Dose Level and Tumor Type

	Obrixtamig Dose <90 μg/kg (once weekly or once every 3 weeks)			
Tumor Response	SCLC (n = 15)	epNEC (n = 10)	LCNEC-L (n = 3)	Total (n = 28)
ORR, No. (% [95% CI])	0 (0.0 [0.0 to 20.4])	0 (0.0 [0.0 to 27.8])	0 (0.0 [0.0 to 56.1])	0 (0.0 [0.0 to 12.1])
DCR, No. (% [95% CI])	1 (6.7 [1.2 to 29.8])	2 (20.0 [5.7 to 51.0])	1 (33.3 [6.1 to 79.2])	4 (14.3 [5.7 to 31.5])
CR, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)
PR, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)
SD, No. (%)[a]	1 (6.7)	2 (20.0)	1 (33.3)	4 (14.3)
PD, No. (%)	10 (66.7)	6 (60.0)	2 (66.7)	18 (64.3)
Not evaluable, No. (%)[b]	4 (26.7)	2 (20.0)	0 (0)	6 (21.4)
	Obrixtamig dose ≥90 μg/kg (once weekly or once every 3 weeks)			
Tumor Response	SCLC (n = 65)	epNEC (n = 61)	LCNEC-L (n = 10)	Total (n = 136)
ORR, No. (% [95% CI])	14 (21.5 [13.3 to 33.0])	17 (27.9 [18.2 to 40.2])	7 (70.0 [39.7 to 89.2])	38 (27.9 [21.1 to 36.0])
DCR, No. (% [95% CI])	28 (43.1 [31.8 to 55.2])	28 (45.9 [34.0 to 58.3])	9 (90.0 [59.6 to 98.2])	65 (47.8 [39.6 to 56.1])
CR, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)
PR, No. (%)	14 (21.5)	17 (27.9)	7 (70.0)	38 (27.9)
SD, No. (%)[a]	14 (21.5)	11 (18.0)	2 (20.0)	27 (19.9)
PD, No. (%)	23 (35.4)	22 (36.1)	1 (10.0)	46 (33.8)
Not evaluable, No. (%)[b]	14 (21.5)	11 (18.0)	0 (0)	25 (18.4)

Abbreviations: CR, complete response; DCR, disease control rate; epNEC, extrapulmonary neuroendocrine carcinoma; LCNEC-L, large cell neuroendocrine carcinoma of the lung; ORR, overall response rate; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SD, stable disease.

[a]The minimum duration of stable disease was 35 days.

[b]Not evaluable: patients who did not have any tumor assessment because of early toxicity, start of subsequent anticancer therapy, death, or any other reason; or who had no other tumor assessment result than "not evaluable"; or who had only tumor assessment result of CR/PR/SD within 35 days from first treatment.

TABLE A9. Best Overall Tumor Response and Disease Control by Primary Site of epNEC in Patients Who Received the Minimum Effective Dose of Obrixtamig (≥90 μg/kg once weekly or once every 3 weeks)

Tumor Response	GI	GU	Unknown Primary Origin	Other[a]	Total
Patients, No. (%)	32 (100)	20 (100)	7 (100)	1 (100)	60 (100)
ORR, No. (%)	8 (25)	7 (35)	1 (14)	0	16 (27)
DCR, No. (%)	14 (44)	11 (55)	2 (29)	0	27 (45)
CR	0	0	0	0	0
PR	8 (25)	7 (35)	1 (14)	0	16 (27)
SD[a]	6 (19)	4 (20)	1 (14)	0	11 (18)
PD, No. (%)	13 (41)	5 (25)	3 (43)	1 (100)	22 (37)
Not evaluable, No. (%)	5 (16)	4 (20)	2 (29)	0	11 (18)

Abbreviations: CR, complete response; DCR, disease control rate; GU, genitourinary; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Primary tumor site was recorded as nasal passage.

TABLE A10. Confirmed ORR by Tumor Type in Patients Treated With Regimens B2 + B3

Tumor Response	SCLC (n = 55)	epNEC (n = 56)	LCNEC-L (n = 9)	Total (n = 120)
ORR, No. (% [95% CI])	11 (20.0 [11.6 to 32.4])	11 (19.6 [11.3 to 31.8])	4 (44.4 [18.9 to 73.3])	26 (21.7 [15.2 to 29.9])
DCR, No. (% [95% CI])	24 (43.6 [31.4 to 56.7])	25 (44.6 [32.4 to 57.6])	8 (88.9 [56.5 to 98.0])	57 (47.5 [38.8 to 56.4])
CR, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)
PR, No. (%)	11 (20.0)	11 (19.6)	4 (44.4)	26 (21.7)
SD, No. (%)[a]	13 (23.6)	14 (25.0)	4 (44.4)	31 (25.8)
PD, No. (%)	18 (32.7)	21 (37.5)	1 (11.1)	40 (33.3)
Not evaluable, No. (%)[b]	13 (23.6)	10 (17.9)	0 (0)	23 (19.2)

Abbreviations: CR, complete response; DCR, disease control rate; epNEC, extrapulmonary neuroendocrine carcinoma; LCNEC-L, large cell neuroendocrine carcinoma of the lung; ORR, overall response rate; PR, partial response; SCLC, small cell lung cancer; SD, stable disease.

[a]The minimum duration of stable disease was 35 days.

[b]Not evaluable: patients who did not have any tumor assessment because of early toxicity, start of subsequent anticancer therapy, death, or any other reason; or who had no other tumor assessment result than "not evaluable"; or who had only tumor assessment result of CR/PR/SD within 35 days from first treatment.