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Randomized phase 3 study of the anti-disialoganglioside antibody dinutuximab and irinotecan vs irinotecan or topotecan for second-line treatment of small cell lung cancer

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ABSTRACT

Introduction: Topotecan is approved as second-line treatment for small cell lung cancer (SCLC). Irinotecan is also frequently used given its more convenient schedule and superior tolerability. Preclinical studies support disialoganglioside (GD2) as an SCLC target and the combination of dinutuximab, an anti-GD2 antibody, plus irinotecan in this setting. We tested dinutuximab/irinotecan versus irinotecan or topotecan as second-line therapy in relapsed/refractory (RR) SCLC.

Materials and methods: Patients with RR SCLC and Eastern Cooperative Oncology Group performance status 0–1 were randomized 2:2:1 to receive dinutuximab 16–17.5 mg/m^2 intravenous (IV)/irinotecan 350 mg/m^2 IV (day 1), irinotecan 350 mg/m^2 IV (day 1), or topotecan 1.5 mg/m^2 IV (days 1–5) in 21-day cycles. The primary endpoint was overall survival (OS); secondary endpoints were progression-free survival (PFS), objective response

Abbreviations: GD2, disialoganglioside; NB, neuroblastoma.

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rate (ORR; complete response [CR] + partial response [PR]), and clinical benefit rate (CBR; CR + PR + stable disease). Safety/tolerability were also assessed.

Results: A total of 471 patients were randomized to dinutuximab/irinotecan (n = 187), irinotecan (n = 190), or topotecan (n = 94). Age, sex, performance status, prior therapies, and metastatic disease sites were similar between groups. Survival and response rates were not improved for patients receiving dinutuximab/irinotecan versus those receiving irinotecan or topotecan (median OS 6.9 vs 7.0 vs 7.4 months [$p = 0.3132$]; median PFS 3.5 vs 3.0 vs 3.4 months [$p = 0.3482$]; ORR confirmed 17.1% vs 18.9% vs 20.2% [$p = 0.8043$]; and CBR 67.4% vs 58.9% vs 68.1% [$p = 0.0989$]), respectively. Grade 3/4 adverse events (≥5% receiving dinutuximab/irinotecan) included neutropenia, anemia, diarrhea, and asthenia.

Conclusions: Dinutuximab/irinotecan treatment did not result in improved OS in RR SCLC versus irinotecan alone. Irinotecan administered every 21 days demonstrated comparable activity to topotecan administered daily × 5 every 21 days. ClinicalTrials.gov Identifier. NCT03098030.

1. Introduction

Small cell lung cancer (SCLC) is a high-grade, aggressive neuroendocrine cancer that accounts for 10% to 15% of all lung cancers [1,2]. Most patients have an initial response to first-line platinum-based doublet chemotherapy with or without radiotherapy. However, only 25% of patients with limited-stage disease experience durable benefit, and SCLC will progress in virtually all patients with extensive-stage disease [3]. The clinical benefit of second-line treatment is modest, with the majority of patients dying within 1 year of relapse. When this trial was initiated, topotecan was the only US Food and Drug Administration (FDA)-approved agent for second-line treatment of SCLC even though the response rate is 15% to 20% and duration of response (DOR) is generally short [4,5]. Since then, additional second- and subsequent-line therapies, including nivolumab, pembrolizumab, and lurbinectedin, have demonstrated activity in relapsed/refractory (RR) SCLC and have either obtained FDA approval or are contained within guideline recommendations for therapy [6–8]. Immunotherapy has also advanced into the first-line management of SCLC [9,10], which ultimately led to withdrawal of approval for pembrolizumab and nivolumab in the second line. The role of lurbinectidin has been questioned after the negative results of a regimen of lurbinectidin and doxorubicin failed to demonstrate superiority over topotecan or cyclophosphamide/doxorubicin/vincristine in this setting [11].

Irinotecan, another topoisomerase-I inhibitor, is approved in Japan for initial treatment of extensive-stage SCLC based on results of a phase 3 trial in which irinotecan plus cisplatin had superior overall survival (OS; vs cisplatin plus etoposide) [12]. Irinotecan has also shown good antitumor activity in patients with relapsed SCLC in several phase 2 studies and is listed by the National Comprehensive Cancer Network as an option for second-line treatment of SCLC [13,14].

Gangliosides such as disialoganglioside (GD2) participate in cell–cell recognition and adhesion as well as in signal transduction [15]. GD2 is expressed on the cell surface of all tumors of neuroectodermal origin and by all melanomas and to a variable degree by osteosarcoma, soft-tissue sarcomas, brain tumors, breast cancer, bladder cancer, and SCLC [16].

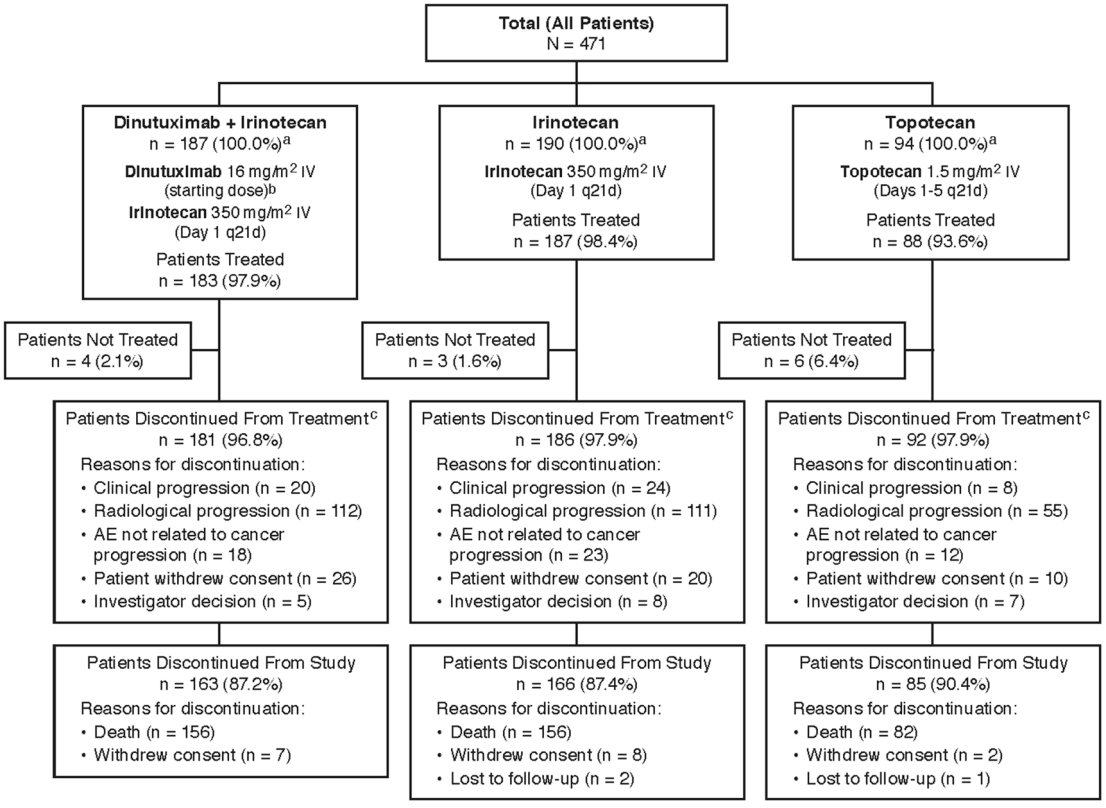

Fig. 1. Schema and patient disposition. AE, adverse event. [a] Percentage was calculated using the number of patients randomized as the denominator. [b] Dose escalation was to occur if maximal pain with prior dose was ≤ grade 1 or grade 2/3 that in the view of the Investigator was adequately managed, and the drug was otherwise tolerated. A starting dose of 16 mg/m^2 IV, with an increase of 1.5 mg/m^2 was allowed in a cycle to reach a maximum dose of 17.5 mg/m^2.

GD2 promotes malignant phenotypes in SCLC and plays a role in proliferation, invasion, and migration of tumor cells [17]. Anti-GD2 monoclonal antibodies (mAbs) suppress proliferation of GD2-expressing SCLC cells, induce apoptosis and enhance the apoptotic effects of chemotherapeutic drugs including SN-38, the active metabolite of irinotecan [18]. The addition of an anti-GD2 mAb resulted in an almost 8-fold enhancement of SN-38 cytotoxicity.

Dinutuximab, approved for the treatment of high-risk pediatric neuroblastoma (NB) in combination with interleukin-2, retinoic acid, and granulocyte–macrophage colony-stimulating factor, is a chimeric anti-GD2 mAb that preferentially binds to GD2 and induces lysis of GD2-expressing tumor cells through antibody-dependent cell-mediated and complement-dependent cytotoxicity [19,20]. In preclinical and in vitro studies, dinutuximab reduced the growth of GD2-expressing human SCLC cell lines [21,22]. The major toxicity of dinutuximab is pain, which is dose and schedule dependent. Abdominal pain is the most frequently described complication, though peripheral sensory and motor neuropathy can also occur. Prior studies appear to demonstrate that pain may be more severe and frequent in adult patients [15]. Combination of an anti-GD2 mAb with various anticancer drugs in vitro substantially enhanced cytotoxicity, even in cell lines expressing only low-to-moderate levels of GD2 [23]. In a phase 2 study evaluating dinutuximab versus temsirolimus in combination with irinotecan/temozolomide in pediatric NB, the combination with dinutuximab was active and tolerable [24]. Based on the high level of GD2 expression in SCLC, the preclinical activity of dinutuximab in SCLC, the activity of irinotecan as a single agent in RR SCLC, and the demonstrated ability to combine these agents in pediatric NB, we studied the combination of dinutuximab/irinotecan in SCLC compared with single-agent irinotecan or topotecan.

2. Materials and methods

2.1. Study design

The trial was an international, open-label, randomized, phase 3 study of second-line dinutuximab/irinotecan compared with irinotecan or topotecan alone in patients with RR SCLC (NCT03098030, EudraCT 2017–000758-20; Fig. 1). A lead-in phase involved intrasubject dose escalation (n = 12) to evaluate the safety/tolerability of dinutuximab in combination with irinotecan [25]. The study was conducted in accordance with Good Clinical Practice International Council for Harmonization guidelines and the Declaration of Helsinki and study protocol was approved by local Institutional Review Boards/Independent Ethics Committees. All patients provided written informed consent.

After completion of the lead-in phase, patients were randomized 2:2:1 to receive irinotecan (Group A), dinutuximab/irinotecan (Group B), or topotecan (Group C) and stratified by DOR to prior platinum treatment (relapse-free period < 3 or ≥ 3 months). Those in Group A or Group B received irinotecan 350 mg/m^2 on day 1 of each cycle. Patients in Group B also received dinutuximab on day 1 of each cycle beginning with a starting dose of 16 mg/m^2 intravenous (IV) with a maximum dose of 17.5 mg/m^2. Dinutuximab dose escalation and de-escalation occurred based on safety/tolerability. Prior to each dinutuximab dose, patients received IV hydration and premedication with antihistamines and antipyretics. From cycle 2 on, premedication with opioid analgesics (morphine or morphine equivalent) was considered if the patient had experienced pain in a prior cycle. For patients receiving dinutuximab and irinotecan, subjects were to continue with dinutuximab alone on schedule if irinotecan is terminated for toxicity or, if dinutuximab was terminated for toxicity, irinotecan would continue on schedule. Patients in Group C received topotecan 1.5 mg/m^2 IV for 5 consecutive days in each cycle. For all arms of the study, drugs were to be continued as long as they were tolerated and there was no progression of disease.

2.2. Study population

Eligible patients were adults aged ≥ 18 years with histologically or cytologically confirmed SCLC (undifferentiated small cell carcinoma arising in or consistent with lung origin) and documented relapse or disease progression during/after first-line platinum-based therapy.

Patients were allowed 1 prior regimen of a platinum-based doublet. In addition, eligible patients were required to have Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, life expectancy of ≥ 12 weeks, and adequate bone marrow and hepatic function. Patients with brain metastases were allowed if they completed definitive brain therapy, were asymptomatic and radiologically stable, and currently not receiving corticosteroids or radiation. As determined by the individual investigators, candidates for re-treatment with the original platinum-based regimen as second-line therapy were excluded.

2.3. Statistical Methods

The primary endpoint was OS; ([date of death – date of randomization] + 1) in patients randomized to dinutuximab/irinotecan versus those treated with irinotecan and topotecan alone. The secondary objectives were progression-free survival (PFS), objective response rate (ORR; complete response [CR] + partial response [PR]), clinical benefit rate (CBR; CR + PR + stable disease), and toxicity in patients treated with dinutuximab/irinotecan versus those treated with irinotecan or topotecan alone.

A 2:2:1 randomization scheme was chosen to maximize statistical power for the primary efficacy comparison (dinutuximab combination vs irinotecan). A total 306 deaths in these 2 groups would provide approximately 80% power to detect a hazard ratio (HR) of 0.725 or a 2.3-month gain in median OS (from 6 to 8.3 months); this calculation was based on a log-rank test (2-sided alpha = 0.05). If ≥ 82 deaths occurred in the topotecan group, the power would be approximately 65% to detect the same HR of 0.725 or a 2.3-month gain in median OS (6 to 8.3 months) with the combination versus topotecan alone (a secondary objective). Overall, a total of approximately 460 patients (184 each in the dinutuximab/irinotecan and single-agent irinotecan groups and 92 in the topotecan group) was expected to yield the requisite number of deaths assuming uniform enrollment over 10 months and a follow-up period of 14 months.

Descriptive statistics (number, mean, SD, median, minimum, and maximum) were used for continuous variables and frequency distributions and percentages for discrete variables. A closed, hierarchical testing procedure was used to control the overall false-positive rate at 5% (2-sided) for the primary comparison of dinutuximab/irinotecan versus irinotecan. The primary efficacy endpoint (OS) was to be tested first and, if it achieved statistical significance, the secondary endpoints were to be tested in the following sequence: PFS, ORR, and CBR.

The primary analysis of OS was performed in the intention-to-treat (ITT) analysis set, using a stratified log-rank test (2-sided, alpha = 0.05) to evaluate the difference between survival curves for the dinutuximab/irinotecan group versus the irinotecan group. Stratification was by duration of response to prior platinum therapy (<3 months, ≥ 3 months). Similarly, the stratified log-rank test was used to compare OS for the dinutuximab/irinotecan group versus for the topotecan group.

Median OS and PFS in each treatment group and the corresponding 2-sided 95% CIs were estimated using the Kaplan-Meier method [26]. Treatment effect on OS was estimated by the HR and 95% CI using the Cox proportional hazards model, stratified by patient response to prior platinum therapy. ORR was calculated by treatment group for ITT and efficacy evaluable patients. Both confirmed and unconfirmed CR/PR and CBR were evaluated along with 2-sided 95% exact CIs. Patients were classified as having stable disease if assessed as stable disease (or better) ≥ 6 weeks after the first dose date. All safety endpoints were summarized using descriptive statistics. An independent Data Monitoring Committee met regularly to review the evolving data from the study.

Table 1
Baseline Demographics and Disease Characteristics (ITT).

Variable Statistic/ Category[a]	Dinutuximab + Irinotecan (n = 187)	Irinotecan (n = 190)	Topotecan (n = 94)	Total (N = 471)
Age, years				
Median	61.0	61.5	62.0	61.0
Min, max	27, 84	31, 85	34, 84	27, 85
Age group, n (%)				
< 65 years	117 (62.6)	123 (64.7)	54 (57.4)	294 (62.4)
≥ 65 years	70 (37.4)	67 (35.3)	40 (42.6)	177 (37.6)
Sex, n (%)				
Male	142 (75.9)	147 (77.4)	68 (72.3)	357 (75.8)
Race, n (%)				
White	113 (60.4)	106 (55.8)	54 (57.4)	273 (58.0)
African American	1 (0.5)	2 (1.1)	3 (3.2)	6 (1.3)
Asian	28 (15.0)	34 (17.9)	18 (19.1)	80 (17.0)
Hispanic or Latino	5 (2.7)	2 (1.1)	4 (4.3)	11 (2.3)
ECOG PS,[b] n (%)				
0	36 (19.3)	39 (20.5)	17 (18.1)	92 (19.5)
1	147 (78.6)	148 (77.9)	71 (75.5)	366 (77.7)
Region,[c] n (%)				
North America	31 (16.6)	32 (16.8)	16 (17.0)	79 (16.8)
Western Europe	46 (24.6)	52 (27.4)	22 (23.4)	120 (25.5)
Central/ Eastern Europe	34 (18.2)	24 (12.6)	22 (23.4)	80 (17.0)
Russia and Ukraine	49 (26.2)	43 (22.6)	18 (19.1)	110 (23.4)
Asia-Pacific	27 (14.4)	39 (20.5)	16 (17.0)	82 (17.4)
Tobacco use, n (%)				
No	22 (11.8)	12 (6.3)	12 (12.8)	46 (9.8)
Yes	165 (88.2)	178 (93.7)	82 (87.2)	425 (90.2)
p value	0.1122			
Former	91 (48.7)	111 (58.4)	59 (62.8)	261 (55.4)
Current	74 (39.6)	67 (35.3)	23 (24.5)	164 (34.8)
Number of pack-years,[d] n	160	172	81	413
Mean (SD)	43.4 (26.8)	44.8 (32.0)	41.9 (24.8)	43.7 (28.7)
Median	40.00	38.50	38.50	40.00
Min, max	0.5, 150.0	3.6, 176.0	5.0, 141.0	0.5, 176.0
SCLC stage at initial diagnosis, n (%)				
Limited	42 (22.5)	43 (22.6)	23 (24.5)	108 (22.9)
Extensive	145 (77.5)	146 (76.8)	71 (75.5)	362 (76.9)
Missing	0	1 (0.5)	0	1 (0.2)
Brain metastases	22 (11.8)	28 (14.7)	16 (17.0)	66 (14.0)
Patients reporting pain, n (%)	74 (39.6)	62 (32.6)	29 (30.9)	165 (35.0)
Mean (SD) (scale 1–10)	3.9 (2.2)	3.8 (1.9)	3.6 (1.6)	3.8 (2.0)
Median (min, max)	3.5 (1, 10)	4.0 (1, 8)	3.0 (1, 8)	4.0 (1, 10)
DOR to prior platinum treatment, n (%)				
< 3 months	120 (64.2)	126 (66.3)	57 (60.6)	303 (64.3)
≥ 3 months	67 (35.8)	64 (33.7)	37 (39.4)	168 (35.7)
Best response to prior treatment, n (%)				
Complete response	3 (1.6)	10 (5.3)	5 (5.3)	18 (3.8)
Partial response	94 (50.3)	88 (46.3)	40 (42.6)	222 (47.1)
Stable response	28 (15.0)	38 (20.0)	16 (17.0)	82 (17.4)
Progressive disease	56 (29.9)	44 (23.2)	28 (29.8)	128 (27.2)
Not applicable	1 (0.5)	1 (0.5)	0	2 (0.4)
Unknown	5 (2.7)	9 (4.7)	5 (5.3)	19 (4.0)

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; max, maximum; min, minimum; SCLC, small cell lung cancer.

[a] Percentages were calculated using the number of patients in the column heading as the denominator.

[b] Baseline was defined as the last measurement obtained prior to first dose for patients in Part 1 or randomization for patients in Part 2.

[c] North America includes United States and Canada. Western Europe includes Spain, France, United Kingdom, and Italy. Central/Eastern Europe includes Bulgaria, Georgia, Hungary, Lithuania, Poland, and Slovakia. Asia-Pacific includes Australia, Taiwan, Thailand, South Korea, Hong Kong, India, Philippines, and Malaysia.

[d] Number of pack-years was defined as number of packs per day × number of years using cigarettes/chewing tobacco.

The charter included provisions for early termination of the trial.

3. Results

A total of 471 patients were randomized to dinutuximab/irinotecan (n = 187), irinotecan (n = 190), or topotecan (n = 94; Fig. 1). Demographics and baseline characteristics were similar across treatment groups (Table 1). The mean age was 61.6 years, and most patients were male (75.8%), white (58.0%), and had an ECOG PS of 1 (77.7%) at baseline. Most patients (76.9%) had extensive-stage SCLC at diagnosis with mean time from diagnosis to date of first dose of 9.5 months and 4.1 weeks from documented relapse/progression; 14% of patients had a history of brain metastases. Overall, most patients (64.3%) had a DOR to prior platinum therapy of < 3 months and PR was the best response for approximately half (47.1%) of patients. Thirty-five percent of patients reported pain at the time of study entry (Table 1).

3.1. Efficacy

The HR for the OS comparison between dinutuximab/irinotecan and irinotecan was 1.12 (95% CI: 0.90–1.40; $p = 0.3132$) and was 1.05 (95% CI: 0.80–1.37; $p = 0.7233$) for dinutuximab/irinotecan versus topotecan (Fig. 2). Median OS ranged from 6.9 to 7.4 months and median PFS ranged from 3.0 to 3.5 months across groups. Best overall response, ORR, and CBR results also were similar between groups, as were DOR results (Table 2).

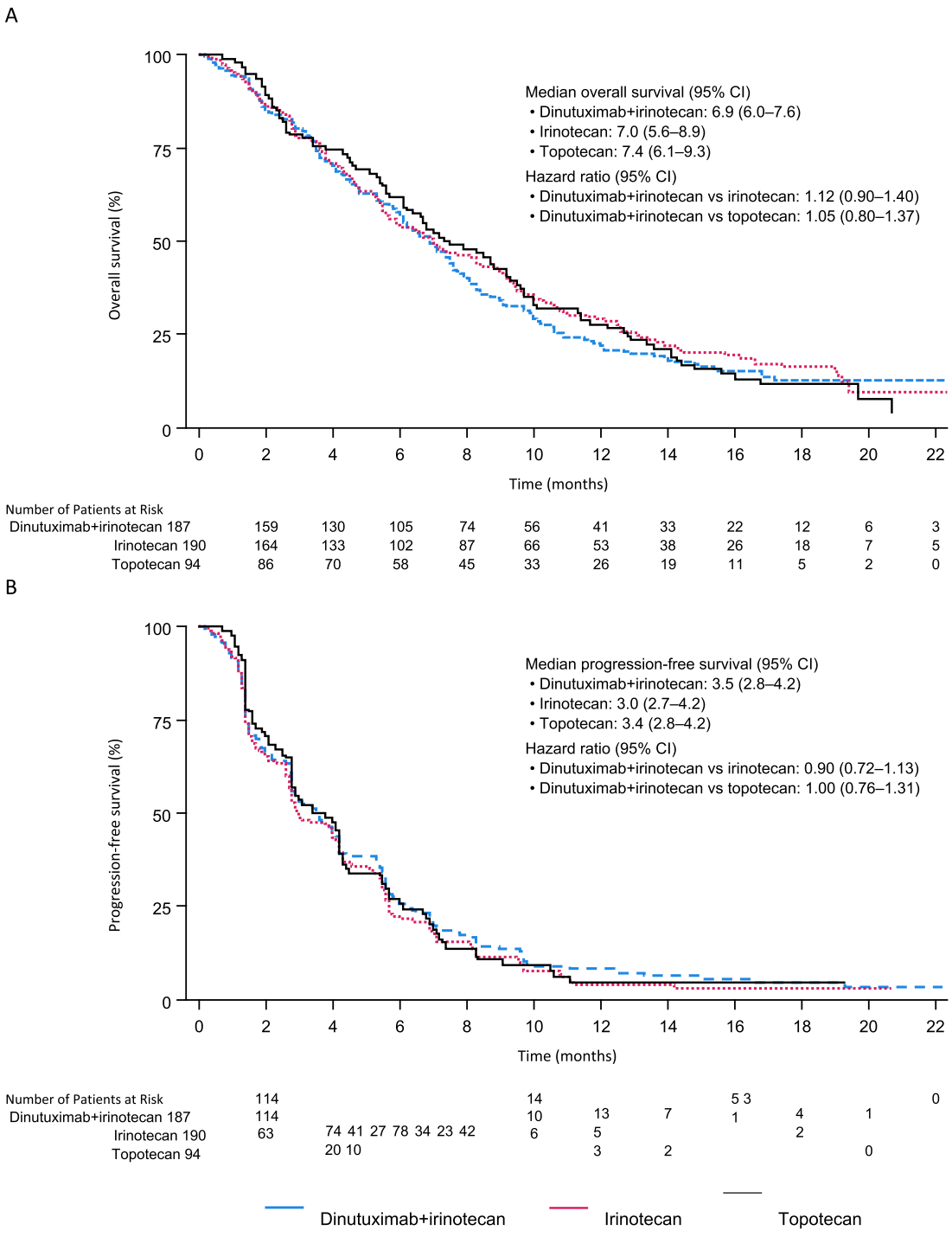

Fig. 2. Overall survival and progression-free survival for patients with SCLC. (*A*) Overall survival (ITT population). (*B*) Progression-free survival (ITT population). ITT, intention-to-treat; SCLC, small cell lung cancer.

3.2. Safety/Tolerability

The most commonly reported toxicities were diarrhea (64.5%, 62.0%, and 14.8%), anemia (36.6%, 29.4%, and 65.9%), abdominal pain (44.8%, 12.8%, and 10.2%), and nausea (44.3%, 47.1%, and 25.0%) in patients in the dinutuximab/irinotecan, irinotecan, and topotecan groups, respectively (Table 3). The most commonly reported adverse events (AEs) in the dinutuximab containing arm were abdominal pain (38.3%), diarrhea (28.4%), and nausea (27.9%). The majority of patients in all treatment groups required pain medication although the use of any pain medication (94.0%, 61.0%, 52.3%) and opioid medication (42.1%, 24.6%, 10.2%) was higher in the dinutuximab/irinotecan group than in the irinotecan and topotecan groups.

The most commonly reported grade ≥ 3 treatment-emergent AEs were neutropenia (24.0%, 16.6%, and 40.9%) and anemia (7.1%, 9.6%, and 35.2%) in the dinutuximab/irinotecan, irinotecan, and topotecan groups, respectively. The most commonly reported dinutuximab-related grade ≥ 3 toxicities were neutropenia (10.4%) and abdominal pain (9.3%). There were 20 treatment-attributable deaths in the combination arm (10.9%) versus 15 (8.0%) and 6 (6.8%) in the irinotecan and topotecan arms, respectively.

Table 2
Summary of BOR, ORR, and CBR (ITT Population).

Response[a]	Dinutuximab + Irinotecan (n = 187)	Irinotecan (n = 190)	Topotecan (n = 94)
BOR, n (%)			
CR	1 (0.5)	4 (2.1)	2 (2.1)
CRu	0	1 (0.5)	0
PR	31 (16.6)	32 (16.8)	17 (18.1)
PRu	13 (7.0)	10 (5.3)	4 (4.3)
Stable disease	81 (43.3)	65 (34.2)	41 (43.6)
Progressive disease	41 (21.9)	46 (24.2)	18 (19.1)
Not evaluable	1 (0.5)	4 (2.1)	0
ORR (confirmed)			
CR/PR, n (%) (95% CI)[b]	32 (17.1) (12.0–23.3)	36 (18.9) (13.6–25.3)	19 (20.2) (12.6–29.8)
Odds ratio (95% CI)[c]	–	0.87 (0.51–1.47)	0.84 (0.44–1.59)
p value[d]	–	0.5987	0.5892
CBR (unconfirmed + confirmed)			
CR/CRu/PR/PRu/ stable disease, n (%) (95% CI)[b]	126 (67.4) (60.2–74.0)	112 (58.9) (51.6–66.0)	64 (68.1) (57.7–77.3)
Odds ratio (95% CI)[c]	–	1.43 (0.94–2.19)	0.99 (0.58–1.68)
p value[d]	–	0.0989	0.9605

BOR, best overall response; CBR, clinical benefit rate; CR, complete response; CRu, complete response unconfirmed; ITT, intention-to-treat; ORR, overall response rate; PR, partial response; PRu, partial response unconfirmed.

[a] Percentage was calculated using the number of patients in the column heading as the denominator.

[b] Exact 2-sided 95% CI estimated using Clopper-Pearson method.

[c] Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥ 3 months). An odds ratio > 1 indicates an advantage for the dinutuximab combination treatment group.

[d] *P* value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥ 3 months).

4. Discussion

There has been relatively little progress in the treatment of SCLC over the last several decades. Over 20 years elapsed between the approval (since withdrawn) of topotecan for the treatment of RR SCLC and the approval of nivolumab for the same indication, despite evidence that it was not superior to topotecan in this setting [27]. Similarly, although lurbinectedin was recently approved for the management of RR SCLC, it also has yet to demonstrate superiority to topotecan. Only in the initial management of extensive disease have the anti–programmed cell death-1 agents, durvalumab and atezolizumab, combined with chemotherapy demonstrated superiority over chemotherapy alone [9,10].

The decision to evaluate dinutuximab in SCLC was supported by several by several factors including a novel target, demonstrated preclinical activity, and tolerability in another patient population. There are several possibilities as to why this study failed to demonstrate efficacy. First, the dose was substantially less than that used in the pediatric NB population. In DISTINCT, patients received only a single dose of 17.5 mg/m2 per cycle (totaling ≈ 32 mg/cycle) versus 4 doses of 17.5 mg/m2 per cycle in the NB study [24]. There have been 4 previous studies of anti-GD2 antibodies in adults, all in melanoma [28–31]. The doses and schedules used in these studies varied widely. In the study by Saleh et al, which used a single-dose regimen, the plasma disappearance curve of dinutuximab fit a 2-compartment model [28]. The mean half-life (t1/2) α was 24 ± 1 h, and the mean t1/2β was 181 ± 73 h [28].

These findings would indicate that fractionated dosing in adults is unnecessary. Based on this observation, as well as anticipated issues of patient acceptability, the single-dose regimen was advanced.

Another potential reason for lack of efficacy is that the agent may not have been able to penetrate the large tumor masses. In an in vitro study, Kendra et al noted that the agent could only penetrate 20 cell layers [32].

In the pediatric NB and the adult melanoma studies, dinutuximab was generally combined with cytokines (eg, interleukin-2) [29,31]. It is possible that such combinations are required for activity of the agent, either alone or with chemotherapy. Finally, because dinutuximab is a "targeted therapy", it is appropriate to ask whether the target was actually present. Prior studies have demonstrated a high prevalence of GD2 expression in SCLC [18]; however, we did not perform an actual assessment for the presence and intensity of the target by immunohistochemistry. Further research is needed to determine whether alternate dosing regimens (eg, a higher dose, multiple doses per cycle, or combination with cytokines) or a need to demonstrate the presence of high GD2 expression may have impacted the results.

Of note, this randomized trial demonstrated a comparable level of activity for once every three week dosing for irinotecan compared with the daily × 5 days dosing for topotecan. While not meeting the statistical requirements of equivalence this finding could have relevance for future studies given the greater acceptability and common use of the irinotecan schedule.

5. Conclusions

The combination of dinutuximab and irinotecan did not demonstrate improved activity in RR SCLC. Further development of dinutuximab in SCLC will require insight into the optimal dose/schedule, the presence of the target, and the ability of the agent to penetrate tumors.

6. Prior presentation

DISTINCT study data were presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program, Abstract 9017, Poster 210.

CRediT authorship contribution statement

Martin J. Edelman: Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing. **Mikhail Dvorkin:** Resources, Writing – review & editing. **Konstatin Laktionov:** Resources, Writing – review & editing. **Alejandro Navarro:** Resources, Writing – review & editing. **Oscar Juan-Vidal:** Resources, Writing – review & editing. **Vadim Kozlov:** Resources, Writing – review & editing. **Gil Golden:** Project administration, Data curation, Writing – review & editing. **Odette Jordan:** Project administration, Data curation, Writing – review & editing. **CQ Deng:** Project administration, Data curation, Writing – review & editing. **Dmitriy Bentsion:** Resources, Writing – review & editing. **Christos Chouaid:** Resources, Writing – review & editing. **Hristo Dechev:** Resources, Writing – review & editing. **Afshin Dowlati:** Resources, Writing – review & editing. **Natalia Fernández Núñez:** Resources, Writing – review & editing. **Olexandr Ivashchuk:** Resources, Writing – review & editing. **Ivane Kiladze:** Resources, Writing – review & editing. **Tsira Kortua:** Resources, Writing – review & editing. **Natasha Leighl:** Resources, Writing – review & editing. **Aleksandr Luft:** Resources, Writing – review & editing. **Tamta Makharadze:** Resources, Writing – review & editing. **YoungJoo Min:** Resources, Writing – review & editing. **Xavier Quantin:** Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Martin J. Edelman received support for manuscript (no compensation) from Precision Oncology; received grants or contracts from Amgen, Merck, Nektar, and Windmil; received consulting fees from Flame and Kanaph; was compensated for lecture by Regeneron/Sanofi; was compensated for webinar by Precision Oncology; received patent

Table 3
Most Common Adverse Events (Incidence ≥ 10% for Any Grade) From the Safety Analysis Set.

Adverse Event, n (%)[a]	Dinutuximab + Irinotecan (n = 183)		Irinotecan (n = 187)		Topotecan (n = 88)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any event	183 (100)	141 (77.0)	183 (97.9)	130 (69.5)	86 (97.7)	76 (86.4)
Hematologic toxicities						
Anemia	67 (36.6)	13 (7.1)	55 (29.4)	18 (9.6)	58 (65.9)	31 (35.2)
Neutropenia	59 (32.2)	44 (24.0)	47 (25.1)	31 (16.6)	45 (51.1)	36 (40.9)
Thrombocytopenia	18 (9.8)	7 (3.8)	13 (7.0)	0	22 (25.0)	16 (18.2)
Leukopenia	30 (16.4)	15 (8.2)	22 (11.8)	7 (3.7)	12 (13.6)	4 (4.5)
Gastrointestinal toxicities						
Diarrhea	118 (64.5)	29 (15.8)	116 (62.0)	39 (20.9)	13 (14.8)	2 (2.3)
Nausea	81 (44.3)	4 (2.2)	88 (47.1)	3 (1.6)	22 (25.0)	1 (1.1)
Vomiting	65 (35.5)	9 (4.9)	57 (30.5)	6 (3.2)	6 (6.8)	1 (1.1)
Decreased appetite	60 (32.8)	5 (2.7)	58 (31.0)	6 (3.2)	23 (26.1)	0
Constipation	16 (8.7)	0	16 (8.6)	0	13 (14.8)	0
Pain-related toxicities						
Abdominal pain	82 (44.8)	18 (9.8)	24 (12.8)	5 (2.7)	9 (10.2)	3 (3.4)
Pain in extremity	31 (16.9)	3 (1.6)	5 (2.7)	1 (0.5)	3 (3.4)	0
Non-cardiac chest pain	24 (13.1)	5 (2.7)	8 (4.3)	1 (0.5)	5 (5.7)	0
Headache	21 (11.5)	2 (1.1)	12 (6.4)	2 (1.1)	4 (4.5)	0
Other toxicities						
Alopecia	49 (26.8)	1 (0.5)	33 (17.6)	0	10 (11.4)	0
Asthenia	44 (24.0)	13 (7.1)	39 (20.9)	12 (6.4)	25 (28.4)	6 (6.8)
Fatigue	36 (19.7)	7 (3.8)	48 (25.7)	17 (9.1)	16 (18.2)	7 (8.0)
Cough	28 (15.3)	4 (2.2)	16 (8.6)	0	9 (10.2)	0
Dyspnea	27 (14.8)	8 (4.4)	18 (9.6)	4 (2.1)	13 (14.8)	5 (5.7)
Weight decreased	24 (13.1)	0	25 (13.4)	1 (0.5)	8 (9.1)	2 (2.3)
Pyrexia	19 (10.4)	1 (0.5)	10 (5.3)	0	13 (14.8)	0
Increased blood LDH	19 (10.4)	1 (0.5)	6 (3.2)	1 (0.5)	5 (5.7)	0
Pneumonia	12 (6.6)	7 (3.8)	11 (5.9)	9 (4.8)	9 (10.2)	4 (4.5)
Hyperglycemia	8 (4.4)	1 (0.5)	4 (2.1)	0	9 (10.2)	4 (4.5)

LDH, lactate dehydrogenase.
[a] Percentage was calculated using the number of patients in the column heading as the denominator. Medical Dictionary for Regulatory Activities version 22.1 was used for coding.

application for epigenetic therapy to increase susceptibility to radiopharmaceuticals from Andarix; was a consultant and was compensated for participation in a Data Safety Monitoring Board or Advisory Board for Syndax, was compensated for participation in a Data Safety Monitoring Board for Astra-Zeneca, GSK, Seattle Genetics, and Takeda; served as Chair, Scientific Advisory Board, Lung Cancer Foundation of America (uncompensated); and holds stock options in Andarix and Biomarker Strategies. Mikhail Dvorkin has nothing to declare. Konstatin Laktionov has nothing to declare. Alejandro Navarro received consulting fees from Boehringer Ingelheim, BMS, and Pfizer; received payment or honoraria for lectures, presentations, speakers bureaus, and manuscript writing or educational events from Roche and AstraZeneca; received payment for expert testimony from Oryzon Genomics and MedSIR; received support for meeting attendance and/or travel from Boehringer Ingelheim, Pfizer, Roche; and participated on a Data Safety Monitoring Board or Advisory Board for Oryzon Genomics. Oscar Juan-Vidal received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Abbvie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Pfizer, Roche/Genentech, and Takeda; received payment for expert testimony from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Merck Sharp & Dohme. Vadim Kozlov has nothing to declare. Dmitriy Bentsion has nothing to declare. Christos Chouaid has nothing to declare. Hristo Dechev has nothing to declare. Afshin Dowlati received an institutional grant to support the study from United Therapeutics and participated on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, BMS, Eli Lilly, G1 Therapeutics, Ipsen, Janssen, Merck, and Seattle Genetics. Natalia Fernández Núñez has nothing to declare. Olexandr Ivashchuk has nothing to declare. Ivane Kiladze has nothing to declare. Tsira Kortua has nothing to declare. Natasha Leighl has nothing to declare. Aleksandr Luft has nothing to declare. Tamta Makharadze has nothing to declare. YoungJoo Min has nothing to declare. Xavier Quantin has nothing to declare. Gil Golden is an employee and stockholder of United Therapeutics Corporation. Odette Jordan is an employee of United Therapeutics Corporation. CQ Deng is an employee of United Therapeutics Corporation. Leonard Lionnet has nothing to declare.

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