RESILIENT Part 2: A Randomized, Open-Label Phase III Study of Liposomal Irinotecan Versus Topotecan in Adults With Relapsed Small Cell Lung Cancer

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ABSTRACT

PURPOSE The phase III RESILIENT trial compared second-line liposomal irinotecan with topotecan in patients with small cell lung cancer (SCLC).

PATIENTS AND METHODS Patients with SCLC and progression on or after first-line platinum-based chemotherapy were randomly assigned (1:1) to intravenous (IV) liposomal irinotecan (70 mg/m² every 2 weeks in a 6-week cycle) or IV topotecan (1.5 mg/m² daily for 5 consecutive days, every 3 weeks in a 6-week cycle). The primary end point was overall survival (OS). Key secondary end points included progression-free survival (PFS) and objective response rate (ORR).

RESULTS Among 461 randomly assigned patients, 229 received liposomal irinotecan and 232 received topotecan. The median follow-up was 18.4 months. The median OS was 7.9 months with liposomal irinotecan versus 8.3 months with topotecan (hazard ratio [HR], 1.11 [95% CI, 0.90 to 1.37]; $P = .31$). The median PFS per blinded independent central review (BICR) was 4.0 months with liposomal irinotecan and 3.3 months with topotecan (HR, 0.96 [95% CI, 0.77 to 1.20]; nominal $P = .71$); ORR per BICR was 44.1% (95% CI, 37.6 to 50.8) and 21.6% (16.4 to 27.4), respectively. Overall, 42.0% and 83.4% of patients receiving liposomal irinotecan and topotecan, respectively, experienced grade ≥3 related treatment-emergent adverse events (TEAEs). The most common grade ≥3 related TEAEs were diarrhea (13.7%), neutropenia (8.0%), and decreased neutrophil count (4.4%) with liposomal irinotecan and neutropenia (51.6%), anemia (30.9%), and leukopenia (29.1%) with topotecan.

CONCLUSION Liposomal irinotecan and topotecan demonstrated similar median OS and PFS in patients with relapsed SCLC. Although the primary end point of OS was not met, liposomal irinotecan demonstrated a higher ORR than topotecan. The safety profile of liposomal irinotecan was consistent with its known safety profile; no new safety concerns emerged.

ACCOMPANYING CONTENT

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INTRODUCTION

Targeted therapies have redefined oncology management for many tumor types in recent years, but novel treatment options have remained elusive for patients with small cell lung cancer (SCLC).[1] SCLC is characterized by a rapid doubling time and early metastases,[2] and most patients present with extensive-stage or metastatic disease at diagnosis.[3,4] The aggressive nature of SCLC means that affected patients face a poorer prognosis than those with any other type of lung cancer. The five-year survival rate for SCLC is 7.2%, compared with 29.8%, 22.5%, and 18.6% for adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, respectively.[5]

First-line therapy for patients with metastatic SCLC (with etoposide and cisplatin or carboplatin, alone or combined with atezolizumab or durvalumab)[6] is associated with high response rates, but most patients relapse within 1-2 years,[7,8] and subsequent treatment options are limited. Currently, only two drugs are approved for second-line SCLC treatment: the topoisomerase I inhibitor, topotecan,[9,10] and the alkylating agent, lurbinectedin.[11-13] Topotecan is an established agent, but its modest antitumor activity is transient,

CONTEXT

Key Objective

Does liposomal irinotecan provide an overall survival (OS) benefit versus topotecan as second-line treatment for patients with small cell lung cancer (SCLC)?

Knowledge Generated

Liposomal irinotecan and topotecan demonstrated similar median OS in patients with SCLC who had progressed on or after first-line platinum-based chemotherapy. Although the primary end point of the study was not met, liposomal irinotecan demonstrated similar progression-free survival, a doubling of objective response rate and a reduced incidence of grade ≥3 related treatment-emergent adverse events (TEAEs) and TEAE-related discontinuations compared with topotecan.

Relevance *(T.E. Stinchcombe)*

This trial demonstrated the single activity and the adverse events associated with liposomal irinotecan, and additional trials of liposomal irinotecan are needed to define its role in SCLC. Antibody drug conjugates and bi-specific T-cell engagers are also being investigated in this disease.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

and its use is limited by myelosuppression and hematological toxicities.[8,14,15] Lurbinectedin was granted accelerated approval in 2020 for second-line use in adults with metastatic SCLC[11] on the basis of a manageable safety profile and an overall response rate of 35.2% in a phase II trial.[16] In the subsequent phase III ATLANTIS trial, lurbinectedin in combination with doxorubicin also showed activity in patients with relapsed SCLC, but the primary overall survival (OS) end point was not met versus physician's choice of topotecan or cyclophosphamide/doxorubicin/vincristine (hazard ratio [HR], 0.97; $P = .70$).[17] First-line immunotherapy in combination with chemotherapy modestly improved OS in both the CASPIAN and IMpower133 studies,[18,19] becoming a new standard of care. However, immunotherapy alone has shown limited efficacy in a small number of patients with SCLC in second-line treatment.[6] Thus, there remains an unmet need for novel efficacious second-line treatment options for patients with SCLC.

Nonliposomal irinotecan is an established component of the SCLC treatment landscape and acts by inhibiting the action of topoisomerase I, mainly via its active metabolite SN-38.[20,21] However, efficacy of nonliposomal irinotecan is limited by its short half-life and associated duration of exposure.[20,21] Liposomal irinotecan (ONIVYDE, ONIVYDE pegylated liposomal; historical names include nal-IRI, MM-398, or PEP02; Ipsen Biopharmaceuticals, Inc, Cambridge, MA) is a liposomal formulation that encapsulates irinotecan in a lipid bilayer vesicle, keeping it in circulation for longer than nonliposomal irinotecan before conversion to SN-38.[22,23] At equivalent doses, liposomal irinotecan demonstrates higher and sustained intratumoral levels of irinotecan and SN-38 relative to nonliposomal irinotecan.[20,21] Preclinical data suggest that the longer half-life relative to the nonliposomal formulation, and associated prolonged exposure may be more important than high peak concentrations for cytotoxic activity.[21]

RESILIENT (ClinicalTrials.gov identifier: NCT03088813) is a two-part phase II/III study to assess the safety, tolerability, and efficacy of liposomal irinotecan monotherapy as second-line treatment for patients with SCLC. In the phase II dose-expansion stage (part 1 of the study), liposomal irinotecan demonstrated promising antitumor activity, with no new safety signals.[24] The objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1)[25] and investigator assessment among 25 patients receiving liposomal irinotecan (70 mg/m^2 every 2 weeks in a 6-week cycle) was 44.0% (95% CI, 24.4 to 65.1). The liposomal irinotecan dose selected for part 2 of the study was based on the part 1 findings.[24]

Here, we report results from RESILIENT part 2, a randomized, open-label, phase III study that compared the efficacy and safety of liposomal irinotecan versus topotecan in patients with relapsed SCLC and progression on or after first-line platinum-based chemotherapy.

PATIENTS AND METHODS

Patients

Eligible patients were age ≥18 years with SCLC, confirmed by histopathology or cytology according to the International Association for the Study of Lung Cancer classification and radiologically confirmed disease progression on or after first-line platinum-based chemotherapy. In addition, patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 and a life expectancy of more than 12 weeks. Patients who had received one line of

immunotherapy (alone or in combination) as first- or second-line therapy were eligible, as were patients with asymptomatic radiologically stable CNS metastases.

A full list of the eligibility criteria is provided in the Data Supplement (online only).

Study Design and Treatment

Patients were randomly assigned (1:1) to receive intravenous (IV) liposomal irinotecan (70 mg/m^2 over 90 minutes, every 2 weeks in a 6-week cycle) or IV topotecan (1.5 mg/m^2 over 30 minutes daily for 5 consecutive days, every 3 weeks in a 6-week cycle). To manage myelosuppression, prophylactic granulocyte colony-stimulating factor was recommended for all patients receiving topotecan (in all cycles starting 24 hours after the last dose); use in patients receiving liposomal irinotecan was based on investigator discretion.

Treatments were allocated using a computerized interactive response technology system, with stratification by geographical region (North America *v* Asia *v* rest of world); platinum sensitivity status (resistant [progression within 90 days of completing first-line platinum-based therapy] *v* sensitive [all others]); performance status (ECOG PS score of 0 *v* 1); and receipt of prior immunotherapy (yes *v* no).

Trial therapies continued until radiologically determined disease progression per local radiology review and/or investigator assessment, per RECIST v1.1 criteria[25] (or Response Assessment in Neuro-Oncology Brain Metastases [RANO-BM][26] for CNS lesions) or unacceptable toxicity. All patients completed a 30-day follow-up assessment after permanent discontinuation of study treatment, after which they entered long-term follow-up and their survival status was monitored until death, loss to follow-up, withdrawal of consent, or study closure, whichever occurred first. A full list of reasons for withdrawal and discontinuation is provided in the Data Supplement.

End Points and Assessments

The primary end point in part 2 of RESILIENT was OS for liposomal irinotecan versus topotecan. OS was defined as the number of months from random assignment to the date of death due to any cause. Key secondary end points included progression-free survival (PFS; time from random assignment to first documented disease progression or death due to any cause, whichever occurred first) as per blinded independent central review (BICR) assessment, ORR (proportion of patients achieving complete or partial response) by BICR assessment, and the safety profile of liposomal irinotecan versus topotecan. A list of the per-protocol study end points is provided in the Data Supplement.

Tumor assessments were performed by computed tomography or brain magnetic resonance imaging at screening (baseline), every 6 weeks until progressive disease using RECIST v1.1 guidelines or RANO-BM for CNS lesions. Progressive disease was determined by local radiology review and/or by investigator assessment.

Adverse events (AEs) were recorded and coded using MedDRA (version 25.0), and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[27]

Trial Oversight

The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization Consolidated Guideline on Good Clinical Practice and the requirements of the US Food and Drug Administration and/or local regulatory authorities regarding the conduct of human clinical trials. The protocol was approved by the local institutional review board and independent ethics committees of the participating centers (Appendix Table A1, online only). Patients provided written informed consent at screening. Protocol amendments made after the study started are described in the protocol. The sponsor collaborated with senior authors on study design, gathering, analyzing, and interpreting results. The authors had access to all study data, reviewed and edited the manuscript, and had final responsibility for the decision to submit. The sponsor funded medical writing and editorial assistance.

Statistical Analysis

Efficacy was assessed in all randomly assigned patients according to the intention-to-treat (ITT) principle. Safety was assessed in all patients who received at least one dose of the trial regimen. The primary end point of OS was evaluated when at least 350 events were observed in 450 patients across the two treatment arms to provide at least 87% power to detect a HR of ≤0.714 (anticipated median OS 10.5 months for liposomal irinotecan *v* 7.5 months for topotecan) at an overall one-sided type level of 0.025. At the primary analysis, the one-sided type 1 error was controlled and allocated alpha of 0.024 per the Hwang-Shih-DeCani method.

The family-wise type 1 error rate was strictly controlled for secondary end points in a hierarchical approach. The statistical inference for PFS (by BICR) was only performed if the primary OS end point was statistically significant and the ORR if the PFS secondary end point was statistically significant.

Between-group differences in OS and PFS were assessed using a stratified log-rank test. Kaplan-Meier analysis was used to estimate median (95% CI) survival estimates, and HRs (95% CI) were estimated using stratified Cox proportional hazards models. Prespecified sensitivity analyses and subgroup analyses were conducted for OS and PFS. For the OS analysis, patients without observed death were censored according to the last recorded date alive. For the PFS analysis, patients with documented progressive disease or death after

two consecutive missed assessments, new anticancer therapy, treatment discontinuation, or loss to follow-up were censored at the time of the last adequate tumor assessment.

ORR and accompanying 95% CI were calculated and compared for the two treatment groups using the Cochran-Mantel-Haenszel method, incorporating region and platinum sensitivity stratification factors. Analyses were carried out using SAS software, version 9.4 or higher (SAS Institute, Inc, Cary, NC).

RESULTS

Patients

Between August 2019 and February 2021, 461 patients were randomly allocated to receive liposomal irinotecan 70 mg/m² (every 2 weeks in a 6-week cycle) (n = 229) or topotecan 1.5 mg/m² (for 5 consecutive days, every 3 weeks in a 6-week cycle) (n = 232); these patients comprised the ITT population (Fig 1). The safety population comprised 449 patients, of whom 226 received liposomal irinotecan and 223 received topotecan. As of data cutoff on February 8, 2022, seven patients (3.1%) in the liposomal irinotecan group and three (1.3%) in the topotecan group were still following the assigned trial regimen. The most common reason for premature discontinuation of the study medication was disease progression (149 patients [65.1%] in the liposomal irinotecan group and 158 [68.1%] in the topotecan group). Baseline demographics and clinical characteristics were generally balanced between groups; however, the proportion of patients with brain and/or CNS lesions was 24.5% in the liposomal irinotecan arm compared with 32.8% in the topotecan arm (Table 1).

All patients in both treatment arms had received prior chemotherapy, whereas 18.3% and 18.5% of patients receiving liposomal irinotecan and topotecan, respectively, had received prior immunotherapy (Table 1). The median (range) relative total dose intensity was 97.7% (1.1%-103.4%) and 88.4% (0.7%-102.7%). The median (range) number of treatment cycles (6-week cycle for both arms) was 2 (1-16) and 2 (1-14) and the median duration of treatment was 12.9 weeks (range 2.0-102.4) and 12.7 weeks (3.0-93.6) for patients receiving liposomal irinotecan and topotecan, respectively.

Among those included in the ITT population, 34.9% of patients receiving liposomal irinotecan and 44.0% of those receiving topotecan received subsequent anticancer therapy (Data Supplement, Table S1).

Efficacy

In the ITT population, the median OS was 7.9 months with liposomal irinotecan versus 8.3 months for topotecan

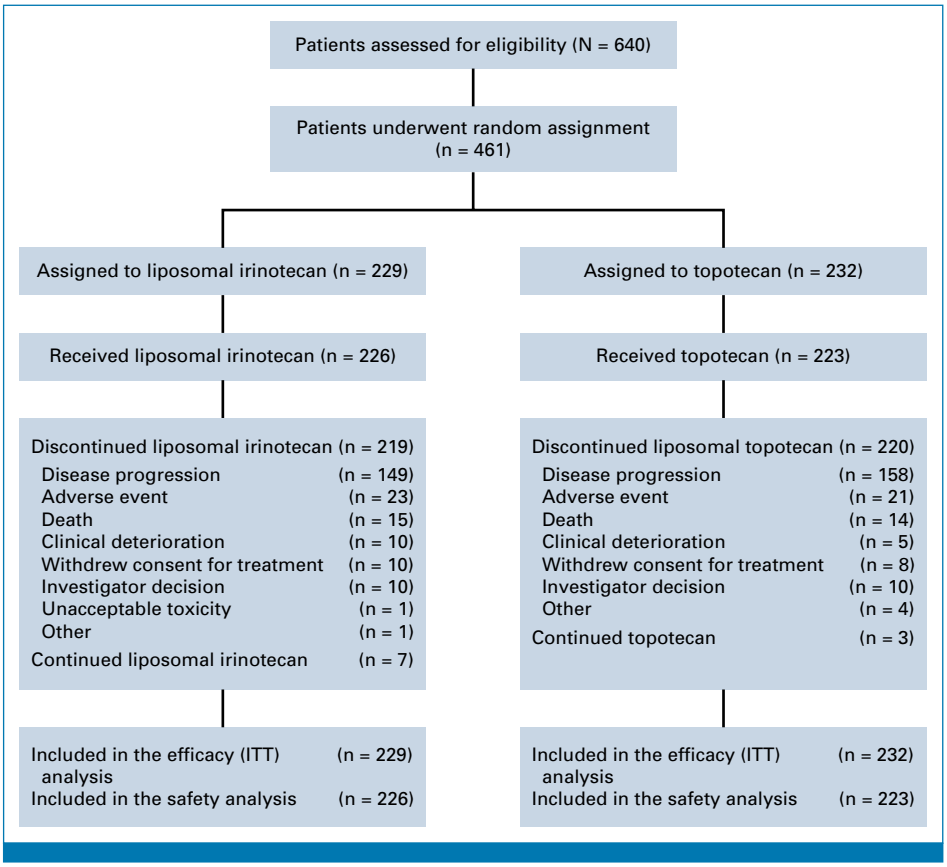

FIG 1. CONSORT diagram: eligibility, random assignment, and follow-up. ITT, intention-to-treat.

TABLE 1. Demographic and Disease Characteristics at Baseline

Characteristic	Liposomal Irinotecan (n = 229)	Topotecan (n = 232)	All Patients (N = 461)
Age, years			
Mean (SD)	62.9 (8.1)	61.7 (7.5)	62.3 (7.8)
Median (range)	63.0 (37.0-82.0)	62.0 (28.0-81.0)	62.0 (28.0-82.0)
Women, No. (%)	79 (34.5)	69 (29.7)	148 (32.1)
White, No. (%)	184 (80.3)	182 (78.4)	366 (79.4)
ECOG PS score, No. (%)			
0	59 (25.8)	59 (25.4)	118 (25.6)
1	169 (73.8)	173 (74.6)	342 (74.2)
Smoking status, No. (%)			
Current	72 (31.4)	76 (32.8)	148 (32.1)
Former	134 (58.5)	132 (56.9)	266 (57.7)
Never	23 (10.0)	24 (10.3)	47 (10.2)
Disease status, No. (%)			
Locally advanced	25 (10.9)	27 (11.6)	52 (11.3)
Metastatic	204 (89.1)	205 (88.4)	409 (88.7)
Key metastatic site(s), No. (%)			
Brain and/or CNS lesions	56 (24.5)	76 (32.8)	132 (28.6)
Hepatic	17 (7.4)	15 (6.5)	32 (6.9)
Bone and locomotor	51 (22.3)	58 (25.0)	109 (23.6)
Time since initial diagnosis, months			
Mean (SD)	9.9 (7.9)	8.7 (4.7)	9.3 (6.5)
Median (range)	7.9 (0.8-72.3)	7.7 (2.3-32.4)	7.8 (0.8-72.3)
Time since recent progression, months			
Mean (SD)	0.8 (1.0)	0.8 (1.1)	0.8 (1.2)
Median (range)	0.5 (0.0-12.2)	0.4 (0.0-12.2)	0.4 (0.0-12.2)
Prior radiotherapy, No. (%)			
Yes	114 (49.8)	121 (52.2)	235 (51.0)
Previous therapies, No. (%)			
Chemotherapy	229 (100.0)	232 (100.0)	461 (100.0)
Immunotherapy	42 (18.3)	43 (18.5)	85 (18.4)
Targeted therapy	1 (0.4)	1 (0.4)	2 (0.4)
Other	0 (0)	0 (0)	0 (0)
Best response to previous therapies, No. (%)			
Complete response	9 (3.9)	3 (1.3)	12 (2.6)
Partial response	104 (45.4)	114 (49.1)	218 (47.3)
Stable disease	48 (21.0)	43 (18.5)	91 (19.7)
Progressive disease	47 (20.5)	49 (21.1)	96 (20.8)
Nonevaluable	3 (1.3)	2 (0.9)	5 (1.1)
Unknown	18 (7.9)	21 (9.1)	39 (8.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; SD, standard deviation.

(HR for death, 1.11 [95% CI, 0.90 to 1.37]; P = .3094; Fig 2A). Similar 12- and 18-month OS rates were observed for both arms (31.1% *v* 32.5% and 16.1% *v* 20.9% for liposomal irinotecan and topotecan, respectively). In subgroup analyses, OS HRs for liposomal irinotecan versus topotecan were generally consistent with those for the overall population (Data Supplement, Fig S1).

Median PFS per BICR was similar for liposomal irinotecan versus topotecan (4.0 *v* 3.3 months; HR for disease progression or death, 0.96 [95% CI, 0.77 to 1.20]; nominal P = .7053; Fig 2B).

ORR per BICR was analyzed during the interim analysis (data cutoff August 11, 2021). Liposomal irinotecan was associated with a doubling of ORR compared with topotecan (44.1% *v*

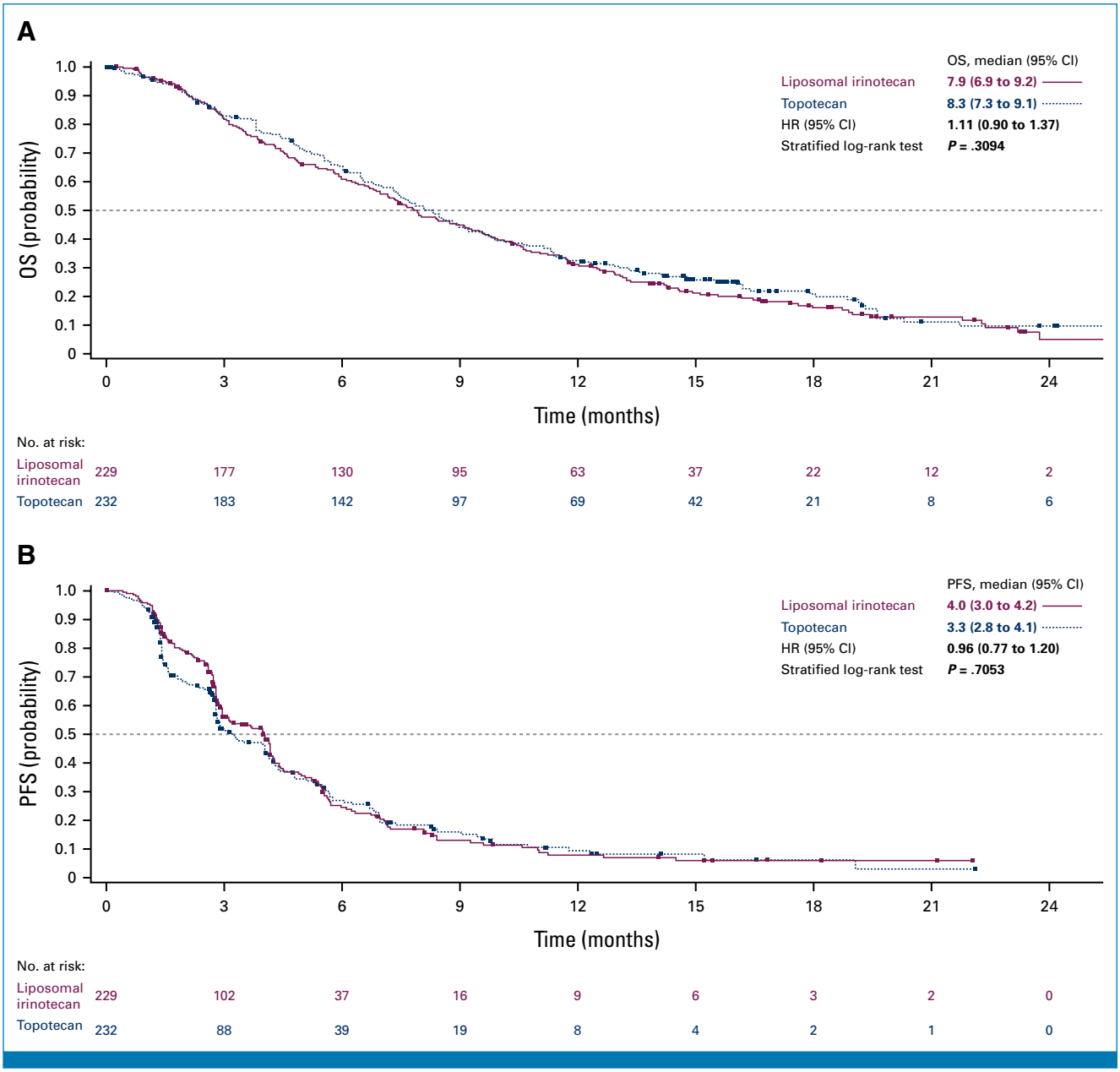

FIG 2. Kaplan-Meier Analysis of (A) OS and (B) PFS. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

21.6%; nominal $P < .0001$). Complete and partial responses were reported in 5.2% and 38.9% of patients receiving liposomal irinotecan, respectively, versus 3.0% and 18.5% of those receiving topotecan (Table 2). Median duration of response was similar for liposomal irinotecan and topotecan (4.1 *v* 4.2 months; Table 2).

Safety

Any-grade treatment-emergent adverse events (TEAEs) occurred in 96.0% and 99.1% of patients receiving liposomal irinotecan and topotecan, respectively (Table 3). The incidence of grade ≥3 TEAEs was lower in the liposomal irinotecan arm than in the topotecan arm (62.4% *v* 87.9%; Table 3), and the most common grade ≥3 TEAEs were diarrhea (13.7%), neutropenia (9.3%), and pneumonia (8.0%) for liposomal irinotecan and neutropenia (52.9%), anemia (33.6%), and thrombocytopenia (30.5%) for topotecan. Grade ≥3 related TEAEs occurred in 42.0% of patients receiving liposomal irinotecan and 83.4% receiving topotecan. The most common grade ≥3 related TEAEs were diarrhea (13.7%), neutropenia (8.0%), and decreased neutrophil count (4.4%) in the liposomal irinotecan arm and neutropenia (51.6%), anemia (30.9%), leukopenia, and thrombocytopenia (both 29.1%) in the topotecan arm (Table 3).

TABLE 2. Antitumor Activity Outcomes

Outcome	Liposomal Irinotecan (n = 229)	Topotecan (n = 232)
Best overall response, No. (%)		
Complete response	12 (5.2)	7 (3.0)
Partial response	89 (38.9)	43 (18.5)
Stable disease	68 (29.7)	98 (42.2)
Progressive disease	28 (12.2)	50 (21.6)
Not evaluable	29 (12.7)	32 (13.8)
Undefined	3 (1.3)	2 (0.9)
ORR, % (95% CI)		
CR + PR	44.1 (37.6 to 50.8)	21.6 (16.4 to 27.4)
Difference in ORR	22.3 (14.0 to 30.6); nominal $P < .0001$	
DoR, months		
Median (95% CI)	4.1 (3.1 to 4.3)	4.2 (2.9 to 4.8)

Abbreviations: CR, complete response; DoR, duration of response; ORR, objective response rate; PR, partial response.

Overall, 10.6% of patients receiving liposomal irinotecan and 10.3% of those receiving topotecan experienced TEAEs leading to treatment discontinuation (Table 3); related TEAEs leading to treatment discontinuation occurred in 4.9% and 4.0% of patients, respectively, and are summarized in the Data Supplement (Table S2). TEAEs leading to dose reduction occurred in 27.9% of patients receiving liposomal irinotecan and 46.6% of those receiving topotecan (Table 3). TEAEs leading to death occurred in 8.4% of patients in the liposomal irinotecan group and 4.0% of patients in the topotecan group; those deemed to be related to treatment occurred in 1.3% and 0.9% of patients, respectively (Data Supplement, Tables S3 and S4).

The details of TEAEs occurring in ≥10% of patients, TEAEs of grade ≥3 occurring in ≥5% of patients, serious TEAEs occurring in ≥2% of patients, and serious related TEAEs occurring in ≥2% of patients are summarized in the Data Supplement (Tables S5-S8, respectively).

DISCUSSION

Part 2 of the RESILIENT study demonstrated similar median OS and PFS for liposomal irinotecan compared with topotecan in patients with SCLC that had progressed on or after first-line platinum-based chemotherapy. Although the primary end point of OS was not met, there was a doubling of ORR (44.1% *v* 21.6%) with no overlapping confidence intervals in patients receiving liposomal irinotecan compared with those receiving topotecan. These results are consistent with RESILIENT part 1, in which 70 mg/m² liposomal

TABLE 3. Duration of Treatment, Cumulative Doses, and Overview of TEAEs

Outcome	Liposomal Irinotecan (n = 226)	Topotecan (n = 223)	All Patients (N = 449)
Duration of treatment, weeks, median (range)	12.9 (2.0-102.4)	12.7 (3.0-93.6)	NR
Total dose received, mg, median (range)	704.5 (1.5-6,195.0)	50.0 (0.1-359.4)	NR
Patients with a TEAE, No. (%)			
Any TEAE	217 (96.0)	221 (99.1)	438 (97.6)
Any treatment-related TEAE	195 (86.3)	214 (96.0)	409 (91.1)
Grade ≥3	141 (62.4)	196 (87.9)	337 (75.1)
Any TEAE leading to discontinuation	24 (10.6)	23 (10.3)	47 (10.5)
Any TEAE leading to dose reduction	63 (27.9)	104 (46.6)	167 (37.2)
Any serious TEAE	105 (46.5)	88 (39.5)	193 (43.0)
Leading to death	19 (8.4)	9 (4.0)	28 (6.2)
Treatment-related TEAE of grade ≥3 occurring in ≥5% of patients in all treatment arms, No. (%)			
Diarrhea	31 (13.7)	3 (1.3)	34 (7.6)
Neutropenia	18 (8.0)	115 (51.6)	133 (29.6)
Neutrophil count decreased	10 (4.4)	39 (17.5)	49 (10.9)
Leukopenia	9 (4.0)	65 (29.1)	74 (16.5)
WBC count decreased	9 (4.0)	24 (10.8)	33 (7.3)
Anemia	6 (2.7)	69 (30.9)	75 (16.7)
Platelet count decreased	3 (1.3)	39 (17.5)	42 (9.4)
Febrile neutropenia	3 (1.3)	13 (5.8)	16 (3.6)
Lymphopenia	2 (0.9)	15 (6.7)	17 (3.8)
Thrombocytopenia	1 (0.4)	65 (29.1)	66 (14.7)

Abbreviations: NR, not reported; SD, standard deviation; TEAE, treatment-emergent adverse event.

irinotecan (every 2 weeks in a 6-week cycle) demonstrated a median PFS of 3.98 months (95% CI, 1.45 to 4.24), an ORR of 44.0%, and a median OS of 8.08 months (5.16 to 9.82).[24]

The safety and tolerability of liposomal irinotecan was consistent with its known safety profile; the most frequent grade ≥3 related TEAE was diarrhea, which is consistent with data reported in RESILIENT part 1.[24] In this study, liposomal irinotecan compared with topotecan demonstrated a lower frequency of TEAEs leading to dose reduction, grade ≥3 TEAEs, and grade ≥3 related TEAEs. Overall, the frequency of hematological AEs was lower in patients receiving liposomal irinotecan than in those receiving topotecan. Hematological grade ≥3 related TEAEs such as neutropenia, anemia, thrombocytopenia, and febrile neutropenia occurred at a higher frequency in the topotecan arm; however, the rate of GI grade ≥3 related TEAEs was higher among patients receiving liposomal irinotecan.

The dichotomy between a doubling of response rate with liposomal irinotecan but no significant improvement in survival statistics is striking. Although slight imbalances in demographics were noted between cohorts, these differences are unlikely to contribute substantially to the observed dichotomy. Post-therapy treatment imbalances may also have played a role; however, a more probable explanation relates to the intrinsic biology of SCLC, which is notable for the widespread inactivation of two key cell cycle checkpoint regulators, *TP53* and *RB1*. The concomitant loss of these tumor suppressors promotes chromosomal instability and may contribute to the exceptional intratumoral heterogeneity of SCLC.[28] The higher response rate of liposomal irinotecan could reflect a more potent cytotoxic effect in which more sensitive cancer cells are killed but the most resistant survive. The latter of these may give rise to disease recurrence in a similar time course, regardless of the fraction of cancer cells killed. The substantially higher response rate together with less frequent severe treatment-related AEs support liposomal irinotecan as an attractive cytotoxic on which to consider future combination studies—with the goal of combining the high activity of liposomal irinotecan with agents that could extend the durability of the initial response. Further research will be needed to understand how and in which contexts liposomal irinotecan monotherapy, or novel liposomal irinotecan therapy combinations, might benefit patients with SCLC.

RESILIENT part 2 featured a large sample size and randomized study design with outcomes stratified across clinically relevant subgroups to allow the consistency of the results to be evaluated. Importantly, crossover between treatment arms was not permitted during active treatment but was allowed after treatment discontinuation. Furthermore, this trial included a population representative of clinical practice and included patients with platinum-resistant disease, prior immunotherapy, and brain and/or CNS metastases. However, this was an open-label study, which may confer a degree of confounding by indication.

The results of the RESILIENT study underline a persistent need for well-tolerated and efficacious treatment options in the second-line setting. In addition, with increasing uptake of first-line chemoimmunotherapy regimens, there is an emerging requirement to establish the efficacy of second-line therapies in patients who have received these regimens.[29] Since key genetic drivers of SCLC have yet to be identified, there is also a need for clinical trials to drive collection of tumor tissue for preclinical and clinical research and facilitate opportunities for targeted therapy. Improved understanding of SCLC biology on the basis of the differential expression of transcription factors may help to optimize treatment strategies and identify patients most likely to benefit from a specific approach.[30]

In conclusion, the phase III RESILIENT study showed similar median OS for liposomal irinotecan compared with topotecan in patients with SCLC who had progressed on or after first-line platinum-based chemotherapy. Although the primary end point was not met, liposomal irinotecan demonstrated similar PFS, a doubling of ORR, and reduced incidence of grade ≥3 related TEAEs and TEAE-related discontinuations compared with topotecan. This level of activity together with improved tolerability will support future combinatorial therapy research with liposomal irinotecan.

AFFILIATIONS

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DATA SHARING STATEMENT

Qualified researchers may request access to patient-level study data that underlie the results reported in this publication. Additional relevant study documents, including the clinical study report, study protocol with any amendments, annotated case report form, statistical analysis plan, and data set specifications may also be made available. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of study participants. Where applicable, data from eligible studies are available 6 months after the studied medicine and indication have been approved in the United States and European Union or after the primary manuscript describing the results has been accepted for publication, whichever is later. Further details on Ipsen's sharing criteria, eligible studies, and process for sharing are available here (https://vivli.org/members/ourmembers/). Any requests should be submitted to www.vivli.org for assessment by an independent scientific review board.

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A list of the RESILIENT trial investigators can be found in Appendix Table A1.

REFERENCES

1. Yuan M, Zhao Y, Arkenau HT, et al: Signal pathways and precision therapy of small-cell lung cancer. Signal Transduct Target Ther 7:187, 2022
2. Gustafsson BI, Kidd M, Chan A, et al: Bronchopulmonary neuroendocrine tumors. Cancer 113:5-21, 2008
3. Wang S, Zimmermann S, Parikh K, et al: Current diagnosis and management of small-cell lung cancer. Mayo Clin Proc 94:1599-1622, 2019
4. Xu L, Zhang G, Song S, et al: Surgery for small cell lung cancer: A Surveillance, Epidemiology, and End Results (SEER) survey from 2010 to 2015. Medicine 98:e17214, 2019
5. SEER*Explorer: An interactive website for SEER cancer statistics (2022). Surveillance Research Program, National Cancer Institute. https://seer.cancer.gov/statistics-network/explorer/
6. Hiddinga BI, Raskin J, Janssens A, et al: Recent developments in the treatment of small cell lung cancer. Eur Respir Rev 30:210079, 2021
7. Asai N, Ohkuni Y, Kaneko N, et al: Relapsed small cell lung cancer: Treatment options and latest developments. Ther Adv Med Oncol 6:69-82, 2014
8. O'Brien ME, Ciuleanu TE, Tsekov H, et al: Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 24: 5441-5447, 2006
9. HYCAMTIN (topotecan) for injection, for intravenous use [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020671s023lbl.pdf
10. HYCAMTIN 1 mg and 4 mg powder for concentrate for solution for infusion [summary of product characteristics]. https://www.ema.europa.eu/en/documents/product-information/hycamtin-epar-product-information_en.pdf
11. U.S. Food & Drug Administration: Press release: FDA grants accelerated approval to lurbinectedin for metastatic small cell lung cancer. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-lurbinectedin-metastatic-small-cell-lung-cancer
12. European Medicines Agency, European Medicines Agency decision, P/0446/2020, 1 December 2020 [product specific waiver for lurbinectedin (EMEA-002846-PIP01-20)]. https://www.ema.europa.eu/en/documents/pip-decision/p/0446/2020-ema-decision-1-december-2020-granting-product-specific-waiver-lurbinectedin-emea-002846-pip01_en.pdf
13. Jazz Pharmaceuticals Inc: ZEPZELCA (lurbinectedin) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213702s000lbl.pdf
14. Ardizzoni A, Hansen H, Dombernowsky P, et al: Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: A phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. J Clin Oncol 15:2090-2096, 1997
15. Horita N, Yamamoto M, Sato T, et al: Topotecan for relapsed small-cell lung cancer: Systematic review and meta-analysis of 1347 patients. Sci Rep 5:15437, 2015
16. Trigo J, Subbiah V, Besse B, et al: Lurbinectedin as second-line treatment for patients with small-cell lung cancer: A single-arm, open-label, phase 2 basket trial. Lancet Oncol 21:645-654, 2020
17. Aix SP, Ciuleanu TE, Navarro A, et al: Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): A multicentre, randomised, open-label, phase 3 trial. Lancet Respir Med 11:74-86, 2023
18. Paz-Ares L, Chen Y, Reinmuth N, et al: Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open 7:100408, 2022
19. Liu SV, Reck M, Mansfield AS, et al: Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). J Clin Oncol 39:619-630, 2021

20. de Man FM, Goey AKL, van Schaik RHN, et al: Individualization of irinotecan treatment: A review of pharmacokinetics, pharmacodynamics, and pharmacogenetics. Clin Pharmacokinet 57: 1229-1254, 2018
21. Kalra AV, Kim J, Klinz SG, et al: Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor prodrug conversion. Cancer Res 74:7003-7013, 2014
22. Drummond DC, Noble CO, Guo Z, et al: Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. Cancer Res 66:3271-3277, 2006
23. Ipsen Biopharmaceuticals Inc: Prescribing Information: ONIVYDE™ (irinotecan liposome injection), for intravenous use initial U.S. https://www.ipsen.com/websites/Ipsen_Online/wp-content/uploads/sites/9/2019/01/21083350/ONIVYDE_USPI.pdf
24. Paz-Ares L, Spigel DR, Chen Y, et al: RESILIENT part 1: A phase 2 dose-exploration and dose-expansion study of second-line liposomal irinotecan in adults with small cell lung cancer. Cancer 128: 1801-1811, 2022
25. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009
26. Lin NU, Lee EQ, Aoyama H, et al: Response assessment criteria for brain metastases: Proposal from the RANO group. Lancet Oncol 16:e270-e278, 2015
27. National Cancer Institute Division of Cancer Treatment & Diagnosis: Common Terminology Criteria for Adverse Events (CTCAE) v5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
28. Zhou H, Hu Y, Luo R, et al: Multi-region exome sequencing reveals the intratumoral heterogeneity of surgically resected small cell lung cancer. Nat Commun 12:5431, 2021
29. Das M, Padda SK, Weiss J, et al: Advances in treatment of recurrent small cell lung cancer (SCLC): Insights for optimizing patient outcomes from an expert roundtable discussion. Adv Ther 38: 5431-5451, 2021
30. Rudin CM, Brambilla E, Faivre-Finn C, et al: Small-cell lung cancer. Nat Rev Dis Primers 7:3, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

RESILIENT Part 2: A Randomized, Open-Label Phase III Study of Liposomal Irinotecan Versus Topotecan in Adults With Relapsed Small Cell Lung Cancer

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. RESILIENT Trial Investigator List

Country	Site Name	Principal Investigator
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	AZ Sint-Maarten	Marc Lambrechts
	UZ Leuven	Kristiaan Nackaerts
Brazil	Hospital de Caridade de Ijui	Fabio André Franke
	HGB—Hospital Giovanni Battista—Mãe de Deus Center	Alan Arrieira Azambuja
	Oncobio Servicos de Saude	Rodrigo Guimaraes
	Hospital de Câncer de Barretos—Fundação Pio XII	Josiane Mourao Dias
	INCA—Instituto Nacional de Câncer	Victor Santos
	Fundação Faculdade Regional de Medicina de São José do Rio Preto	Bruno Cezar Uchoa Junior
	Hospital Nossa Senhora da Conceicao	Gustavo Vasconcelos Alves
	CEPHO—Centro de Estudos e Pesquisas de Hematologia e Oncologia	Claudia Vaz de Melo Sette
China	The First Affiliated Hospital of Bengbu Medical College	Minghong Bi
	The First Hospital of Jilin University	Jiuwei Cui
	Beijing Cancer Hospital	Jian Fang
	Linyi Cancer Hospital	Jianhua Shi
	West China Hospital, Sichuan University	Ke Wang
	Guangdong Provincial People's Hospital	Zhen Wang
	Zhejiang Cancer Hospital	Xinmin Yu
France	Center Hospitalier de Saint-Quentin	Charles Dayen
	Hôpital Nord—CHU Marseille	Laurent Greillier
	CHU Brest—Hôpital Morvan	Gilles Quere
Germany	Evangelisches Krankenhaus Hamm gGmbH	Alexander Baraniskin
	Thoraxklinik Heidelberg gGmbH	Helge Bischoff
	Pius-Hospital Oldenburg	Frank Griesinger
	Universitaetsklinikum Freiburg	Cornelius Waller
Hungary	Jasz-Nagykun-Szolnok Megyei Hetenyi Geza Korhaz-Rendelointezet	Tibor Csoszi
	Tudogyogyintezet Torokbalint	Gabriella Galffy
	Bekes Megyei Kozponti Korhaz Pandy Kalman Tagkorhaza	Ibolya Laczo
	Semmelweis Egyetem	Gyorgy Losonczy
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	Med-Polonia Sp. z o.o.	Rodryg Ramlau

(continued on following page)

TABLE A1. RESILIENT Trial Investigator List (continued)

Country	Site Name	Principal Investigator
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	S.C Gral Medical S.R.L	Cristina Tiut
	S.C Medisprof S.R.L	Anghel Adrian Udrea
	S.C Radiotherapy Center Cluj S.R.L	Andrei Ungureanu
Russia	SPb SBIH "City Clinical Oncological Dispensary"	Nina Karaseva
	SBIH of Yaroslavl region "Regional Clinical Oncological Hospital"	Nikolay Kislov
	"VitaMed" LLC	Elena Poddubskaya
	SBHI of Kaluga Region "Kaluga regional clinical oncology dispensary"	Irina Rozhkova
	SBIH of Arkhangelsk region "Arkhangelsk Clinical Oncological Dispensary"	Ekaterina Solovyeva
	BHI of Omsk region "Clinical Oncology Dispensary"	Anastasia Zimina
Serbia	Clinical Hospital Center "Bezanijska kosa"	Zoran Andric
	Oncomed System	Vladimir Kovcin
	University Clinical Center Kragujevac	Marina Petrovic
	General Hospital Uzice	Zorica Radojevic
	Institute for Pulmonary Diseases of Vojvodina	Goran Stojanovic
South Korea	The Catholic University of Korea, Seoul St Mary's Hospital	SookHee Hong
	Asan Medical Center	Sang-We Kim
	Chungbuk National University Hospital	Ki Hyeong Lee
	The Catholic University of Korea, St Vincent's Hospital	Byoung Yong Shim
Spain	Hospital Universitario Virgen del Rocio	Miriam Alonso Garcia
	Hospital General Universitario Gregorio Marañon	Antonio Calles Blanco
	Hospital Regional Universitario de Malaga	Vanesa Gutierrez Calderon
	Hospital Universitari i Politecnic La Fe	Oscar Jose Juan Vidal
	Hospital General Universitario de Alicante	Bartomeu Massuti Sureda
	Hospital Universitari Vall d'Hebron	Alejandro Navarro Mendivil
	ICO l'Hospitalet—Hospital Duran i Reynals	Ramon Palmero Sanchez
	Hospital Universitario 12 de Octubre	Luis Paz-Ares Rodriguez
Taiwan	Tri-Service General Hospital	Ching-Liang Ho
	Changhua Christian Medical Foundation Changhua Christian Hospital	Sheng-Hao Lin
	Chang Gung Memorial Hospital, Linkou	Chien-Ying Liu
	National Taiwan University Hospital	Chih-Hsin Yang
Turkey	Trakya University Medical Faculty	Irfan Cicin
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(continued on following page)

TABLE A1. RESILIENT Trial Investigator List (continued)

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