Cabazitaxel Versus Topotecan in Patients with Small-Cell Lung Cancer with Progressive Disease During or After First-Line Platinum-Based Chemotherapy

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Introduction: Patients with small-cell lung cancer (SCLC) typically respond well to initial chemotherapy. However, relapse invariably occurs, and topotecan, the only approved second-line treatment option, has limited efficacy. Taxanes have activity in SCLC, and cabazitaxel is a second-generation taxane with potential for enhanced activity in chemorefractory malignancies.

Methods: Patients with SCLC who relapsed after initial platinum-based chemotherapy were randomly assigned to receive cabazitaxel 25 mg/m^2 every 21 days or topotecan 1.5 mg/m^2 on days 1–5 every 21 days. Two patient subgroups, defined by chemosensitive and chemo-resistant/refractory disease, were assessed in combination and separately.

Results: The safety profile of cabazitaxel and topotecan was consistent with previous studies, and despite considerable toxicity in both arms, no new safety concerns were identified. Patients receiving cabazitaxel had inferior progression-free survival compared with topotecan (1.4 versus 3.0 months, respectively; two-sided $p < 0.0001$; hazard ratio = 2.17, 95% confidence interval = 1.563–3.010), and results were similar in both the chemosensitive and chemorefractory subgroups. No complete responses were observed in either arm, and no partial responses were observed in the cabazitaxel group. The partial response rate in the topotecan arm was 10%. Median overall survival was 5.2 months in the cabazitaxel arm and 6.8 months in the topotecan arm (two-sided $p = 0.0125$; hazard ratio = 1.57, 95% confidence interval = 1.10–2.25).

Conclusion: Cabazitaxel, a next-generation taxane, had inferior efficacy when compared with standard-dose topotecan in the treatment of relapsed SCLC. Topotecan remains a suboptimal therapy, and continued efforts to develop improved second-line treatments are warranted.

Key Words: Cabazitaxel, Phase 2, Small-cell lung cancer, Relapse, Topotecan.

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Small-cell lung cancer (SCLC) constitutes 12%–14% of all lung cancers, and is characterized by a rapid doubling time, a high growth fraction, and early development of systemic metastases.[1,2] While initially quite responsive to chemotherapy, resistance invariably develops. As a result, SCLC has a poor prognosis, with a median survival without treatment of 2 to 4 months.[3] With treatment, disease extent is considered the most reproducible prognostic factor. Two-year survival rates range from 20% to 40% for limited-stage disease (restricted to one lung or local tissues/lymph nodes) and 5% or less for extensive-stage disease (metastatic to contralateral lung or other sites).[1–3]

Platinum-based chemotherapy is first-line standard of care for SCLC. Etoposide with cisplatin or carboplatin is the most commonly used regimen,[2–4] although irinotecan plus carboplatin is an alternative option.[2,5] Despite high response rates to first-line chemotherapy, most patients with SCLC experience rapid relapse.[6] Patients with relapsed SCLC can

be categorized into two groups: those who relapse during or within 3 months of first-line therapy are considered chemorefractory (or resistant), and have a response rate to second-line chemotherapy of less than or equal to 10%; those who relapse after 3 months or more have chemosensitive disease, and have a response rate to second-line chemotherapy of ~25%.[2] Although several chemotherapies have demonstrated single-agent activity in relapsed SCLC, topotecan is currently considered to be the standard treatment.[2,7] In phase III trials in relapsed SCLC, topotecan treatment resulted in longer overall survival (OS) compared with best supportive care (26 versus 14 weeks)[8] and better symptom control versus a cyclophosphamide–doxorubicin–vincristine regimen.[9] Across several studies of patients with relapsed SCLC, median survival time has ranged from 14 to 35 weeks.[7] Therefore, new second-line therapies are needed to improve survival in patients with relapsed SCLC.

The first-generation taxanes, docetaxel and paclitaxel, have shown activity as first- or second-line single-agent treatments in SCLC.[10–12] In a phase II study of paclitaxel in patients with extensive-disease SCLC, 11 patients (34%) had a partial response (PR) and six patients (19%) had stable disease.[10] In another phase II study of paclitaxel, the overall response rate was 53%.[12] In a phase II study of docetaxel in previously treated patients with SCLC, seven patients (25%) had a PR and seven patients (25%) had stable disease.[11]

Cabazitaxel is a second-generation taxane that has demonstrated activity in the second-line treatment of chemotherapy-resistant solid tumors.[13,14] In particular, in the pivotal phase III TROPIC trial in patients with metastatic castration-resistant prostate cancer progressing after docetaxel therapy, cabazitaxel plus prednisone had superior efficacy versus mitoxantrone plus prednisone, including significantly longer OS and progression-free survival (PFS),[13] leading to regulatory approval worldwide. Interestingly, unlike other taxanes, cabazitaxel crosses the blood–brain barrier,[15] which could be therapeutically beneficial in cancers, such as SCLC where brain metastases are common. The paucity of therapeutic options and activity of taxanes in SCLC, the ability of cabazitaxel to cross the blood–brain barrier, and the activity of cabazitaxel in chemorefractory tumors provide a compelling rationale to assess cabazitaxel as a treatment for SCLC.

This phase II study evaluated the efficacy of cabazitaxel versus topotecan in patients with SCLC that had progressed during or after first-line platinum-based chemotherapy.

PATIENTS AND METHODS

Study Population

Eligible patients had histologically/cytologically documented locally advanced or metastatic SCLC that relapsed during or after first-line platinum-based chemotherapy. Patients were aged greater than or equal to 18 years, had measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1[16] and an Eastern Cooperative Oncology Group performance status less than or equal to one. Patients were required to have received no more than one prior chemotherapy regimen, and to have adequate hematologic and organ function. Exclusion criteria included: prior topotecan or taxane treatment; prior chemotherapy, radiotherapy (except for bone pain palliation), or surgery within 28 days; treatment with any investigational drug within 30 days; uncontrolled metastases of the central nervous system; known leptomeningeal metastases; other invasive neoplasm requiring ongoing therapy; unresolved adverse event (AE) of grade greater than one (except alopecia) resulting from prior anticancer therapy (according to National Cancer Institute Common Terminology Criteria [NCI CTCAE] v4.03);[17] or myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association Class III or IV congestive heart failure, stroke or transient ischemic attack within 6 months before study enrollment.

The study was conducted according to the Declaration of Helsinki with approval from ethics committees at each institution. Patients provided written informed consent.

Study Design

This was a phase II, open-label study (ARD12166; NCT01500720, ClinicalTrials.gov). Patients were randomly assigned (1:1) to receive cabazitaxel or topotecan. Patients were divided evenly into two subgroups depending on whether their disease had progressed (by RECIST 1.1) either greater than or equal to 90 days after completing first-line chemotherapy (chemosensitive subgroup) or during or up to 90 days after completing first-line chemotherapy (chemorefractory subgroup). Patients were also stratified by the presence of brain metastases and serum lactate dehydrogenase (LDH) concentration.

The primary endpoint was PFS, defined as time from randomization to documented tumor progression or death from any cause, whichever came first. Secondary endpoints included disease progression-free rate at week 12, response rate, duration of response, OS, and safety. Progression and response were defined per RECIST 1.1.

Study Treatment

Cabazitaxel 25 mg/m^2 was administered as a 1-hour intravenous (IV) infusion on day 1 every 21 days. Topotecan 1.5 mg/m^2 was administered as a 30-minute IV infusion on days 1–5 every 21 days. For cabazitaxel, premedication included an antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or equivalent), a steroid (dexamethasone 8 mg or equivalent) and an H2 antagonist (ranitidine 50 mg or equivalent). Premedications were administered by IV infusion at least 30 minutes before each cabazitaxel dose. If IV antihistamines were not available, premedication for hypersensitivity could be administered per local practice. Antiemetic prophylaxis with ondansetron, granisetron or dolasetron, or per local practice for topotecan, was permitted. Supportive care with granulocyte colony-stimulating factor (G-CSF) could be considered in both treatment arms, in accordance with ASCO guidelines.[18]

Safety Assessments

The safety population was defined as all randomized patients who received at least one dose of cabazitaxel or topotecan during the treatment period. Patients had a full health evaluation before treatment initiation. On-study safety assessments

included: physical examinations, AE monitoring, hematology, blood chemistry, coagulation and urine analysis, and 12-lead electrocardiograms. AEs and laboratory data were graded using NCI CTCAE v4.03.[17] Safety assessments were also performed within 22–30 days after the final dose of study treatment. In the follow-up period, ongoing serious and treatment-related AEs and concomitant medications were monitored until recovery from the AE or stabilization of the patient's condition.

Efficacy Assessments

The intent-to-treat population was defined as all randomized patients according to treatment arm. Tumors were assessed at baseline and every 6 weeks during treatment using abdominal and chest computerized tomography or magnetic resonance imaging. Brain computerized tomography or magnetic resonance imaging was performed every 6 weeks to follow metastases found at baseline or if new lesions were suspected. If study treatment was discontinued before disease progression, tumor assessments continued every 6 weeks until radiological progression or study cut-off, whichever came first. For imaging reviews, the same processes and technology (MEDIAN Technologies) were used at the investigator sites, and centrally.

Statistical Analysis

PFS, OS, and duration of response in the cabazitaxel and topotecan arms were compared using log-rank tests, stratified by brain metastases and LDH level. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated using the Cox proportional hazard model, stratified using the same factors described above. Median PFS and OS and corresponding 95% CIs were calculated using Kaplan–Meier estimates. Progression-free rate at week 12 and response rate were compared between treatment arms using a χ^2 test. A logistic regression model was used for additional exploratory analyses. The study sample size was chosen to enable a 30% risk reduction in hazard rate to be detected in the primary endpoint for the treatment arm versus the control arm, assuming a median PFS of 4.0 months in the control arm and 5.7 months in the experimental arm, based on a log-rank test with a one-sided 10% significance level. Based on these assumptions, 172 eligible patients (86 per arm) and 142 PFS events were needed to achieve 80% power for the study.

RESULTS

Patient and Disease Characteristics

Overall, 179 patients were randomized (Supplementary Figure S1, Supplemental Digital Content, http://links.lww.com/JTO/A848). In the total population, 70% were male, median age was 61 years, and all but one patient had an Eastern Cooperative Oncology Group performance status of 0 or 1 (Table 1). Approximately half of patients (51%) were considered chemosensitive. Most patients (94%) had metastatic disease at study entry, and the most frequent metastatic sites were lung, lymph node, and liver. Brain metastases were present in 28% of patients. Median time from initial diagnosis to study treatment was 8.6 months. Patient demographics and baseline disease characteristics were balanced across treatment groups.

Treatment Exposure

Ninety and 89 patients were randomly assigned to receive cabazitaxel or topotecan, of which 89 and 88 patients received treatment, respectively. The median number of treatment cycles with cabazitaxel or topotecan, respectively, was 2.0 versus 4.0 in the overall group, 2.0 versus 3.0 in the chemorefractory subgroup, and 2.5 versus 4.0 in the chemosensitive subgroup (Supplementary Table S1, SDC, http://links.lww.com/JTO/A848). Dose delays (study dose given later than 3 days after the scheduled time in any cycle) were required by 12 patients (13%) who received cabazitaxel, compared with 45 patients (51%) who received topotecan. Dose reductions were required by 18 patients (20%) who received cabazitaxel, compared with 33 patients (38%) who received topotecan. Among treated patients, cabazitaxel or topotecan was discontinued by 88 patients (99%) and 87 patients (99%), respectively, and the most frequent reasons for discontinuation in both arms were disease progression (cabazitaxel, 79%; topotecan, 57%) and AE (cabazitaxel, 16%; topotecan, 27%).

Survival

Median PFS was 1.4 months in the cabazitaxel arm versus 3.0 months in the topotecan arm (HR = 2.17, 95% CI = 1.563–3.010; two-sided $p < 0.0001$). Results were similar in both the chemosensitive and chemorefractory subgroups (Fig. 1). The progression-free rates at week 12 for cabazitaxel and topotecan were, respectively, 19% versus 53% in the overall group ($p < 0.0001$), 29% versus 63% in the chemosensitive subgroup ($p = 0.0011$), and 9% versus 42% in the chemorefractory subgroup ($p = 0.0004$).

Median OS in the total population was 5.2 months with cabazitaxel versus 6.8 months with topotecan (HR = 1.57, 95% CI = 1.10–2.25; two-sided $p = 0.0125$), and trends were similar in the chemosensitive and chemorefractory subgroups (Fig. 2).

Potential heterogeneity of the treatment effect was analyzed in a subgroup analysis of PFS and OS. A subgroup effect on both PFS and OS trended toward topotecan for most factors tested (Fig. 3).

Response

Overall, 152 patients had measurable lesions present at baseline and were evaluable for tumor response (73 in the cabazitaxel arm, 79 in the topotecan arm). No patient had a complete response. No patient receiving cabazitaxel had a PR, compared with eight PRs (10%) in the topotecan arm (8% and 12% in the chemorefractory and chemosensitive subgroups, respectively). In the overall population, stable disease was recorded as best response in 16 patients (22%), who received cabazitaxel (14% and 29% of chemorefractory and chemosensitive patients, respectively) and 50 patients (63%), who received topotecan (57% and 69% of chemorefractory and chemosensitive patients, respectively; Table 2).

Safety

In the safety population, 80 cabazitaxel-treated patients (90%) had a treatment-emergent adverse event (TEAE) of any grade, compared with 83 topotecan-treated patients (94%). Grade 3/4 TEAEs occurred in 52 patients (58%) in

TABLE 1. Patient Demographics and Baseline Disease Characteristics by Treatment Arm in the Overall Population and in Chemorefractory and Chemosensitive Subgroups

	Overall Population		Chemorefractory Subgroup		Chemosensitive Subgroup	
	Cabazitaxel (*n* = 90)	Topotecan (*n* = 89)	Cabazitaxel (*n* = 45)	Topotecan (*n* = 43)	Cabazitaxel (*n* = 45)	Topotecan (*n* = 46)
Median age, years (range)	60 (37–82)	62 (27–80)	58 (37–76)	60 (27–80)	62 (40–82)	65 (33–80)
ECOG PS, *n* (%)						
≤1	90 (100)	88 (98.9)	45 (100)	43 (100)	45 (100)	45 (97.8)
2	0	1 (1.1)	0	0	0	1 (2.2)
Patient subgroup, *n* (%)						
Chemorefractory	45 (50.0)	43 (48.3)	45 (100)	43 (100)	0	0
Chemosensitive	45 (50.0)	46 (51.7)	0	0	45 (100)	46 (100)
LDH concentration, *n* (%)						
≤ULN	46 (51.1)	46 (51.7)	18 (40.0)	17 (39.5)	28 (62.2)	29 (63.0)
>ULN	44 (48.9)	43 (48.3)	27 (60.0)	26 (60.5)	17 (37.8)	17 (37.0)
Median time from initial diagnosis to study treatment, months (range)[a]	8.7 (3–56)	8.5 (3–36)	6.8 (3–56)	7.1 (3–17)	10.7 (5–22)	10.5 (5–36)
Extent of disease at study entry, *n* (%)						
Metastatic	87 (96.7)	81 (91.0)	44 (97.8)	41 (95.3)	43 (95.6)	40 (87.0)
Locoregional	3 (3.3)	8 (9.0)	1 (2.2)	2 (4.7)	2 (4.4)	6 (13.0)
Number of organs involved at baseline, *n* (%)						
1–3	46 (51.1)	35 (39.3)	21 (46.7)	13 (30.2)	25 (55.6)	22 (47.8)
4–5	38 (42.2)	45 (50.6)	19 (42.2)	25 (58.1)	19 (42.2)	20 (43.5)
6–8	6 (6.7)	9 (10.1)	5 (11.1)	5 (11.6)	1 (2.2)	4 (8.7)
Brain metastases, *n* (%)	25 (27.8)	25 (28.1)	13 (28.9)	12 (27.9)	12 (26.7)	13 (28.3)
Other most common sites of metastasis, *n* (%)						
Lung	88 (97.8)	83 (93.3)	44 (97.8)	39 (90.7)	44 (97.8)	44 (95.7)
Lymph node	76 (84.4)	76 (85.4)	39 (86.7)	39 (90.7)	37 (82.2)	37 (80.4)
Liver	43 (47.8)	45 (50.6)	24 (53.3)	24 (55.8)	19 (42.2)	21 (45.7)
Bone	28 (31.1)	34 (38.2)	18 (40.0)	19 (44.2)	10 (22.2)	15 (32.6)
Adrenal gland	24 (26.7)	26 (29.2)	8 (17.8)	14 (32.6)	16 (35.6)	12 (26.1)

[a]Patients with available data: total population, cabazitaxel *n* = 89 and topotecan *n* = 88; chemosensitive subgroup, cabazitaxel *n* = 44 and topotecan *n* = 45.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

the cabazitaxel arm, and in 63 patients (72%) in the topotecan arm. In the cabazitaxel arm, the most frequent nonhematologic TEAEs of any grade were fatigue (29%), diarrhea (19%), decreased appetite (18%), and vomiting (18%; Table 3). In the topotecan arm, the most frequent nonhematologic TEAEs of any grade were dyspnea (25%), fatigue (25%), asthenia (20%), and decreased appetite (15%).

The most frequent hematologic AE was febrile neutropenia/neutropenic infection/neutropenic sepsis (cabazitaxel 18% versus topotecan 24%). The most frequent grade ≥ 3 hematologic laboratory abnormalities with cabazitaxel were neutropenia (57%), leukopenia (52%), and lymphopenia (39%), and with topotecan were neutropenia (78%), leukopenia (65%), and thrombocytopenia (45%; Table 3). G-CSF use was comparable in both treatment arms: therapeutic G-CSF was administered to 25 patients (28%) in the cabazitaxel arm and 23 patients (26%) in the topotecan arm; prophylactic G-GCF was administered to 53 patients (60%) in the cabazitaxel arm and 49 patients (56%) in the topotecan arm.

In the cabazitaxel arm, 36 patients (40%) experienced a serious TEAE, compared with 41 patients (47%) in the topotecan arm. Grade ≥ 3 serious TEAEs occurred in 35 patients (39%) treated with cabazitaxel, compared with 39 patients (44%) treated with topotecan. The most frequent serious TEAEs of any grade with cabazitaxel were febrile neutropenia/neutropenic infection/neutropenic sepsis (13%), and hyponatremia (3%), and with topotecan were febrile neutropenia/neutropenic infection/neutropenic sepsis (18%), thrombocytopenia (11%), anemia (7%), and pneumonia (7%).

During the treatment period (from start of treatment until 30 days after the final dose), there were 12 deaths in the cabazitaxel arm and 13 deaths in the topotecan arm, of which five and seven deaths, respectively, were due to an AE. Deaths were considered related to treatment in two patients receiving cabazitaxel (both due to neutropenic infection) and in four patients receiving topotecan (three with febrile neutropenia/neutropenic infection, and one with cardiopulmonary failure).

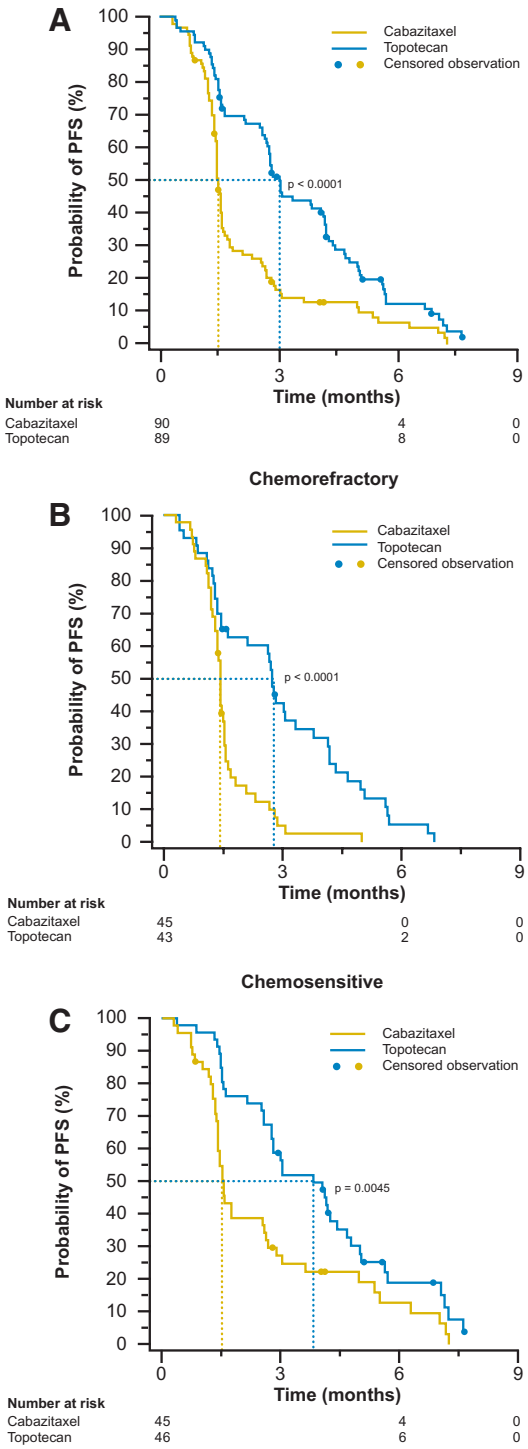

FIGURE 1. PFS. *A*, Intent-to-treat population. *B*, Chemorefractory subgroup. *C*, Chemosensitive subgroup. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

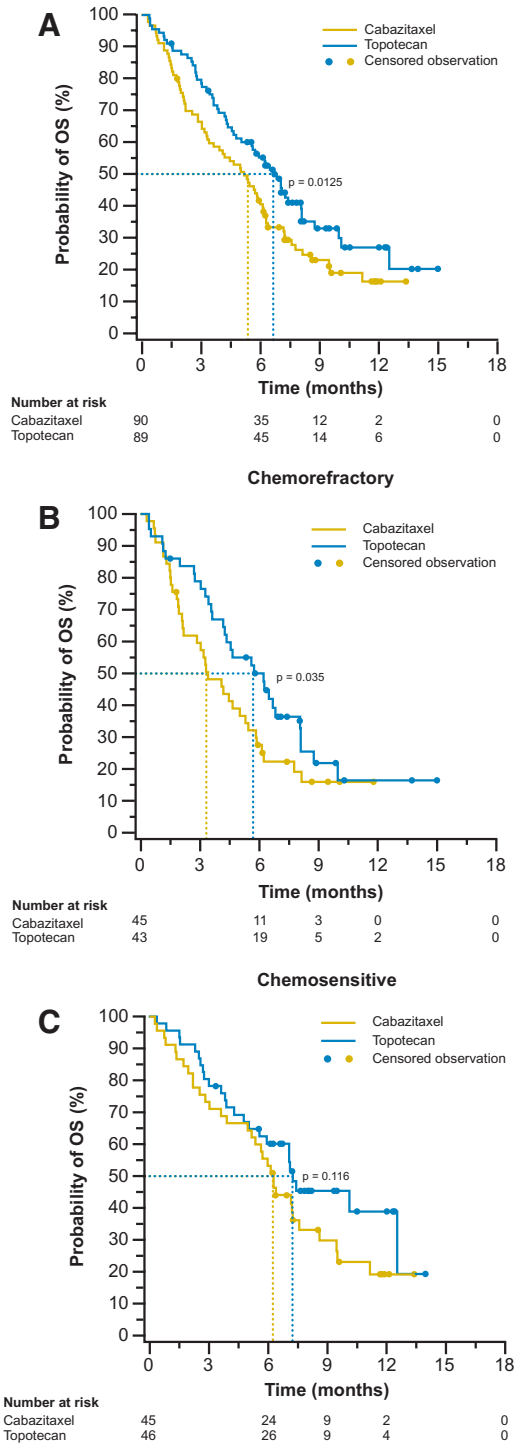

FIGURE 2. OS. *A*, Intent-to-treat population. *B*, Chemorefractory subgroup. *C*, Chemosensitive subgroup. CI, confidence interval; HR, hazard ratio; OS, overall survival.

DISCUSSION

In the late 1990s, topotecan replaced the cyclophosphamide–doxorubicin–vincristine regimen as standard second-line treatment for SCLC based on its similar efficacy in patients with chemosensitive SCLC (response rate 24%, median OS 25 weeks) and better symptom control.[9] Confirmation that topotecan prolonged survival and improved quality of life in patients with relapsed SCLC compared with best supportive care followed in 2006,[8] leading to regulatory approval in this

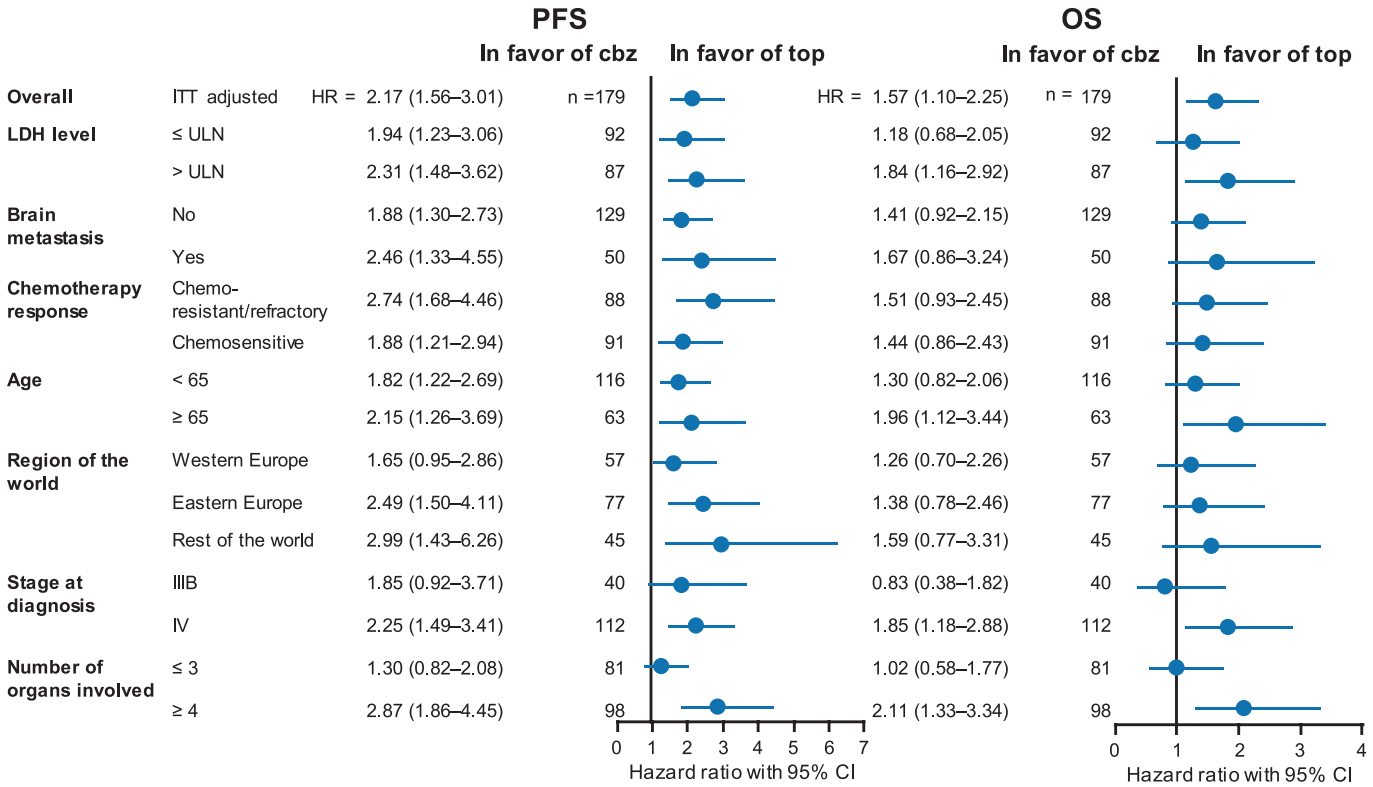

FIGURE 3. Subgroup analysis of PFS and OS in patients treated with cabazitaxel or topotecan. Overall Cox model was stratified for brain metastases and lactate dehydrogenase (LDH) level, as specified at randomization. Cox models for subgroups were not stratified. CI, confidence interval; ITT, intent-to-treat; ULN, upper limit of normal; PFS, progression-free survival; OS, overall survival; cbz, cabazitaxel; top, topotecan.

TABLE 2. Objective Tumor Response Rates in the Overall Tumor-Evaluable Population and in Chemorefractory/Chemosensitive Subgroups

	Overall Population		Chemorefractory Subgroup		Chemosensitive Subgroup	
Response, *n* (%)	**Cabazitaxel (*n* = 73)**	**Topotecan (*n* = 79)**	**Cabazitaxel (*n* = 35)**	**Topotecan (*n* = 37)**	**Cabazitaxel (*n* = 38)**	**Topotecan (*n* = 42)**
Complete response	0	0	0	0	0	0
Partial response	0	8 (10.1)	0	3 (8.1)	0	5 (11.9)
Stable disease	16 (21.9)	50 (63.3)	5 (14.3)	21 (56.8)	11 (28.9)	29 (69.0)
Disease progression	51 (69.9)	18 (22.8)	28 (80.0)	11 (29.7)	23 (60.5)	7 (16.7)
Not evaluable/missing data	6 (8.2)	3 (3.8)	2 (5.7)	2 (5.4)	4 (10.5)	1 (2.4)

indication.[19] Since then, however, no other single agent or combination has shown a significant benefit over topotecan. Although amrubicin (an anthracycline) demonstrated superior activity versus topotecan in a phase II trial in Japanese patients, no survival benefit was observed in phase II and III trials performed in Western populations.[20–22] Results from a recent phase III study in Japanese patients suggest that a cisplatin–etoposide–irinotecan regimen is superior to topotecan in relapsed SCLC that is sensitive to first-line treatment, and this regimen has the potential to become standard second-line chemotherapy. However, increased toxicity was noted in the combination arm. To date, these data have been presented only in abstract form, and full publication is awaited.[23]

First-generation taxanes have shown modest activity in the treatment of relapsed SCLC. In phase II studies of paclitaxel administered alone or in combination with other agents in patients with previously treated SCLC, overall response rates have ranged from 24–73%.[24–27] Similarly, docetaxel treatment in the second-line setting resulted in an overall response rate of 25%,[11] although in a trial in patients with limited or extensive-stage disease, a docetaxel/gemcitabine combination was reported to be inactive.[28] However, no taxane-based regimen has emerged as being significantly more effective than established treatments.[19] Cabazitaxel is a second-generation taxane developed to overcome resistance to first-generation taxanes,[29] and has shown comparable antitumor activity to

TABLE 3. Most Frequently Reported TEAEs (> 10% in Either Arm) in the Safety Population, Irrespective of Relation to Study Treatment, and Hematologic Laboratory Abnormalities

	Cabazitaxel (n = 89)		Topotecan (n = 88)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TEAE	79 (88.8)	52 (58.4)	83 (94.3)	63 (71.6)
Fatigue	26 (29.2)	7 (7.9)	22 (25.0)	7 (8.0)
Dyspnea	9 (10.1)	3 (3.4)	22 (25.0)	3 (3.4)
Febrile neutropenia/neutropenic infection/neutropenic sepsis	16 (18.0)	16 (18.0)	21 (23.9)	20 (22.7)
Asthenia	11 (12.4)	2 (2.2)	18 (20.5)	7 (8.0)
Diarrhea	17 (19.1)	2 (2.2)	9 (10.2)	0
Decreased appetite	16 (18.0)	2 (2.2)	13 (14.8)	1 (1.1)
Vomiting	16 (18.0)	1 (1.1)	7 (8.0)	0
Nausea	14 (15.7)	2 (2.2)	11 (12.5)	0
Abdominal pain	10 (11.2)	2 (2.2)	3 (3.4)	0
Cough	10 (11.2)	1 (1.1)	8 (9.1)	0
Constipation	8 (9.0)	0	9 (10.2)	0
Headache	6 (6.7)	0	9 (10.2)	0
Back pain	9 (10.1)	1 (1.1)	5 (5.7)	0
Hematologic laboratory abnormalities				
Anemia	83 (94.3)[a]	3 (3.4)[a]	87 (98.9)	23 (26.1)
Leukopenia	70 (79.5)[a]	46 (52.3)[a]	82 (93.2)	57 (64.8)
Neutropenia	60 (68.2)[a]	50 (56.8)[a]	77 (87.5)	69 (78.4)
Lymphopenia	68 (77.3)[a]	34 (38.6)[a]	63 (71.6)	28 (31.8)
Thrombocytopenia	52 (59.1)[a]	4 (4.5)[a]	81 (92.0)	40 (45.5)

[a]Eighty-eight patients in the cabazitaxel arm had samples available for analysis.
TEAE, treatment-emergent adverse events.

docetaxel in docetaxel-sensitive tumor models and increased potency versus docetaxel in taxane-resistant tumor models.[30]

In this study, cabazitaxel failed to demonstrate improved efficacy versus topotecan in patients with SCLC that had progressed during or after first-line platinum-based chemotherapy. In fact, cabazitaxel treatment resulted in a significantly shorter PFS and shorter OS than topotecan. Median OS seen with topotecan in this study (7.2 months) is similar to that reported in previous studies.[8,9] Patient and disease characteristics were well balanced between treatment arms. Furthermore, analysis of PFS and OS in patient subgroups, defined by LDH level, presence of brain metastasis, age, global region, stage at diagnosis or number of organs involved, consistently favored topotecan treatment over cabazitaxel, suggesting no heterogeneity of treatment effect. Objective response rates and progression-free rate at week 12 also favored the topotecan arm. It is currently unclear why cabazitaxel treatment resulted in a lower overall response rate compared with single-agent treatment with first generation taxanes in SCLC.[10–12,27]

In previous studies, frequent cabazitaxel-associated AEs have included hematologic events, such as anemia, leucopenia, and neutropenia, in addition to gastrointestinal disturbances and fatigue.[13,14,31–33] The safety profile of cabazitaxel in this study was consistent with previous studies and no new safety concerns were identified. However, in this study, the toxicity of both treatments was considerable. The rate of febrile neutropenia/neutropenic infection/neutropenic sepsis was 18% and 24% in the cabazitaxel and topotecan arms, respectively, despite 60% and 56% receiving prophylactic G-CSF. Dose delays and reductions were also common in both arms. Despite the observed survival benefit, treatment with the "traditional" topotecan regimen resulted in four treatment-related deaths, which is certainly a concern for a palliative treatment where the survival benefit is modest.

Overall, this randomized, phase II study suggests that cabazitaxel 25 mg/m^2 administered every 3 weeks, although relatively well tolerated in patients with relapsed SCLC, had inferior efficacy compared with topotecan 1.5 mg/m^2 administered on days 1–5 every 3 weeks. Results do not justify further investigation of cabazitaxel treatment in this disease. While it is clear that cabazitaxel is an inferior second-line treatment in patients with SCLC, topotecan remains a suboptimal therapy, and efforts to improve treatment in this setting remain warranted.

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