

Ceralasertib plus Durvalumab in Chinese Patients with Advanced Solid Tumors: A Nonrandomized Clinical Trial

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Supplementary Methods

Adverse events of special interests were defined as: events of scientific and medical interest specific to the further understanding of the safety profile of durvalumab; these included but were not limited to events with a potential inflammatory or immune-mediated mechanism and which might require frequent monitoring and/or other therapy.

Dose-limiting toxicities included: Common Terminology Criteria for Adverse Events (CTCAE) grade 4 neutropenia (absolute neutrophil count <500 cells/mm³) lasting longer than 4 consecutive days; CTCAE grade 3 neutropenia (absolute neutrophil count ≥ 500 and <1000 cells/mm³) of any duration accompanied by fever $\geq 38.5^{\circ}\text{C}$ and/or systemic infection; CTCAE grade 3 thrombocytopenia (25000 to <50000 /mm³) with bleeding; any other confirmed grade 4 hematological toxicity by $\geq$ CTCAE v5.0 (repeat testing may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations); non-hematological grade 3 toxicities by $\geq$ CTCAE v5.0 including laboratory abnormalities (repeat testing may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations), QTc prolongation (>500 milliseconds), or colitis (irrespective of duration); any CTCAE grade 4 immune-related AE (irrespective of duration); any CTCAE grade 3 or 4 non-infectious pneumonitis (irrespective of duration); any CTCAE grade 3 immune-mediated AE, excluding colitis or pneumonitis, that does not downgrade to grade ≤ 2 within 3 days after onset despite maximal supportive care including systemic corticosteroids or downgrade to grade ≤ 1 within 14 days after onset of the event; any CTCAE grade ≥ 2 pneumonitis or interstitial lung disease that does not resolve to grade 1 within 3 days of the initiation of maximal supportive care; and any other toxicity that is clinically significant and/or unacceptable, does not respond to supportive care, results in a dose reduction, or is judged to be a DLT by the safety review committee.

Supplementary Results

Pharmacokinetics

The median time to peak concentration of ceralasertib occurred at 1.4 hours (range, 0.77–4.0) and 2.1 hours (range, 0.48–10.0) post-dose in cohorts 1 and 2, respectively, indicating that ceralasertib was rapidly absorbed after oral administration (**Supplementary Table S4**). The arithmetic mean $t_{1/2\lambda_z}$ was 7.4 hours (standard deviation [SD], 2.2) and 8.1 hours (SD, 3.0) in cohort 1 and 2, respectively. The geometric mean of the $C_{\max}$ was 7.8 $\mu\text{g/mL}$ (coefficient of variation [CV%], 29.0%) and 6.5 $\mu\text{g/mL}$ (CV%, 23.4%) and the geometric mean AUC_{last} was 48.8 h. $\mu\text{g/mL}$ (CV%, 37.8%) and 41.3 h. $\mu\text{g/mL}$ (CV%, 26.0%) in cohort 1 and 2, respectively.

Following multiple-dose administration, including up to 72 hours post-dose, the peak concentration of ceralasertib was reached after a median of 1.4 hours (range, 0.25–1.9) and 1.5 hours (range, 0.95–7.0) post-dose in cohort 1 and 2, respectively, indicating that, as with single-dose administration, ceralasertib was rapidly absorbed after oral administration. The arithmetic mean $t_{1/2\lambda_z}$ was 13.7 hours (SD, 4.1) and 14.3 hours (SD, 1.9) for cohort 1 and 2, respectively. The geometric mean AUC_{last} was 207 h. $\mu\text{g/mL}$ (CV%, 88.0%) and 227 h. $\mu\text{g/mL}$ (CV%, 51.3%) with a geometric mean maximum observed concentration of 10.2 $\mu\text{g/mL}$ (CV%, 30.7%) and 9.5 $\mu\text{g/mL}$ (CV%, 31.1%) in cohort 1 and 2, respectively. The mean temporal change parameter was 0.98 (SD, 0.41) and 0.92 (SD, 0.10) in cohort 1 and 2, respectively. The arithmetic mean accumulation ratio AUC and $C_{\max}$ were 1.52 (SD, 0.57) and 1.39 (SD, 0.49) in cohort 1 and 1.51 (SD, 0.17) and 1.46 (SD, 0.17) in cohort 2, indicating that limited accumulation occurred following multiple-dose administration of ceralasertib.

Supplementary Table S1. Dose intensity for ceralasertib and durvalumab.

	Cohort 1 Ceralasertib 240 mg BID (7-day) + durvalumab 1500 mg^a (n = 8)	Cohort 2 Ceralasertib 160 mg BID (14-day) + durvalumab 1500 mg^a (n = 6)
Relative dose intensity, median (range)		
Ceralasertib	100 (55–100)	100 (95–100)
Durvalumab	100 (88–100)	100 (88–100)

^aA single dose of durvalumab 1500 mg was given intravenously on day 1 of each 28-day cycle to each cohort. BID, twice daily.

Supplementary Table S2. Summary of treatment-related serious AEs.

Treatment-related SAEs, n (%)	Cohort 1 Ceralasertib 240 mg BID (7-day) + durvalumab 1500 mg^a (n = 8)	Cohort 2 Ceralasertib 160 mg BID (14-day) + durvalumab 1500 mg^a (n = 6)	Total (N = 14)
Anemia	0	1 (16.7)	1 (7.1)
Thrombocytopenia	0	1 (16.7)	1 (7.1)
Alanine aminotransferase increased	1 (12.5)	0	1 (7.1)
Aspartate aminotransferase increased	1 (12.5)	0	1 (7.1)
Mallory-Weiss syndrome	1 (12.5)	0	1 (7.1)
White blood cell count decreased	0	1 (16.7)	1 (7.1)

^aA single dose of durvalumab 1500 mg was given intravenously on day 1 of each 28-day cycle to each cohort.

The table includes adverse events with an onset date on or after the date of first dose of the investigational product up to and including 90 days following the date of last dose of investigational product, but prior to subsequent anti-cancer therapy. Patients with multiple occurrences are counted once per Preferred Term regardless of the number of occurrences.

BID, twice daily; SAE, serious adverse event.

Supplementary Table S3. TEAEs that occurred in cycle 0^a, in $\geq 20\%$ of total patients.

	Cohort 1 Ceralasertib 240 mg BID (7-day) + durvalumab 1500 mg (n = 8)	Cohort 2 Ceralasertib 160 mg BID (14-day) + durvalumab 1500 mg (n = 6)	Total (N = 14)
Any grade AE, n (%)			
Nausea	4 (50.0)	0	4 (28.6)
Vomiting	4 (50.0)	0	4 (28.6)
Anemia	2 (25.0)	1 (16.7)	3 (21.4)
Platelet count decreased	0	3 (50.0)	3 (21.4)
White blood cell count decreased	2 (25.0)	1 (16.7)	3 (21.4)

^aIn each cohort, a monotherapy lead-in period (cycle 0 of 7 or 14 days), prior to dosing with durvalumab, was included to investigate the PK profile and safety/tolerability of ceralasertib in Chinese patients.

AE, adverse event; BID, twice daily; PK, pharmacokinetic; SAEs, serious adverse events; TEAE, treatment-emergent adverse event.

Supplementary Table S4: PK parameters following single and multiple dosing of ceralasertib.

	Cohort 1 Ceralasertib 240 mg BID (7-day) + durvalumab 1500 mg[‡] (n = 8)	Cohort 2 Ceralasertib 160 mg BID (14-day) + durvalumab 1500 mg[‡] (n = 6)
Single-dose administration		
C_{max} (µg/mL)		
Geometric mean (CV%) ^a	7.8 (29.0)	6.5 (23.4)
Median (range)	7.6 (4.3–11.3)	6.4 (5.1–9.5)
t_{max} (h), median (range)	1.4 (0.77–4.0)	2.1 (0.48–10.0)
AUC_{last} (h·µg/mL)		
Geometric mean (CV%) ^a	48.8 (37.8)	41.3 (26.0)
Median (range)	46.7 (26.9–90.0)	37.1 (32.9–65.0)
t_{1/2λz} (h)		
Arithmetic mean (SD)	7.4 (2.2)	8.1 (3.0)
Median (range)	7.5 (5.1–11.2)	6.6 (6.2–11.5)
Multiple-dose administration		
C_{max,ss} (µg/mL)		
Geometric mean (CV%) ^a	10.2 (30.7)	9.5 (31.1)
Median (range)	8.9 (6.8–15.2)	9.4 (6.7–14.5)
t_{max} (h), median (range)	1.4 (0.25–1.9)	1.5 (0.95–7.0)
AUC_{last} (h·µg/mL)		
Geometric mean (CV%) ^a	207 (88.0)	227 (51.3)
Median (range)	206 (44.3–437)	205 (140–415)
t_{1/2λz} (h)^c		
Arithmetic mean (SD)	13.7 (4.1)	14.3 (1.9)
Median (range)	15.1 (6.7–18.2)	13.8 (12.4–17.5)
TCP		
Arithmetic mean (SD) ^b	0.98 (0.41)	0.92 (0.10)
Median (range)	1.0 (0.34–1.5)	0.93 (0.81–1.0)
AUC_{tau}(h·µg/mL)		
Geometric mean (CV%) ^a	74.9 (38.5)	76.5 (41.1)
Median (range)	69.4 (46.7–117)	74.7 (51.0–120)

	Cohort 1 Ceralasertib 240 mg BID (7-day) + durvalumab 1500 mg[†] (n = 8)	Cohort 2 Ceralasertib 160 mg BID (14-day) + durvalumab 1500 mg[†] (n = 6)
Accumulation ratio AUC ^c		
Arithmetic mean (SD)	1.5 (0.57)	1.5 (0.17)
Median (range)	1.3 (0.61–2.3)	1.5 (1.3–1.7)
Accumulation ratio C _{max}		
Arithmetic mean (SD)	1.4 (0.49)	1.5 (0.17)
Median (range)	128 (0.72–2.1)	1.5 (1.2–1.7)

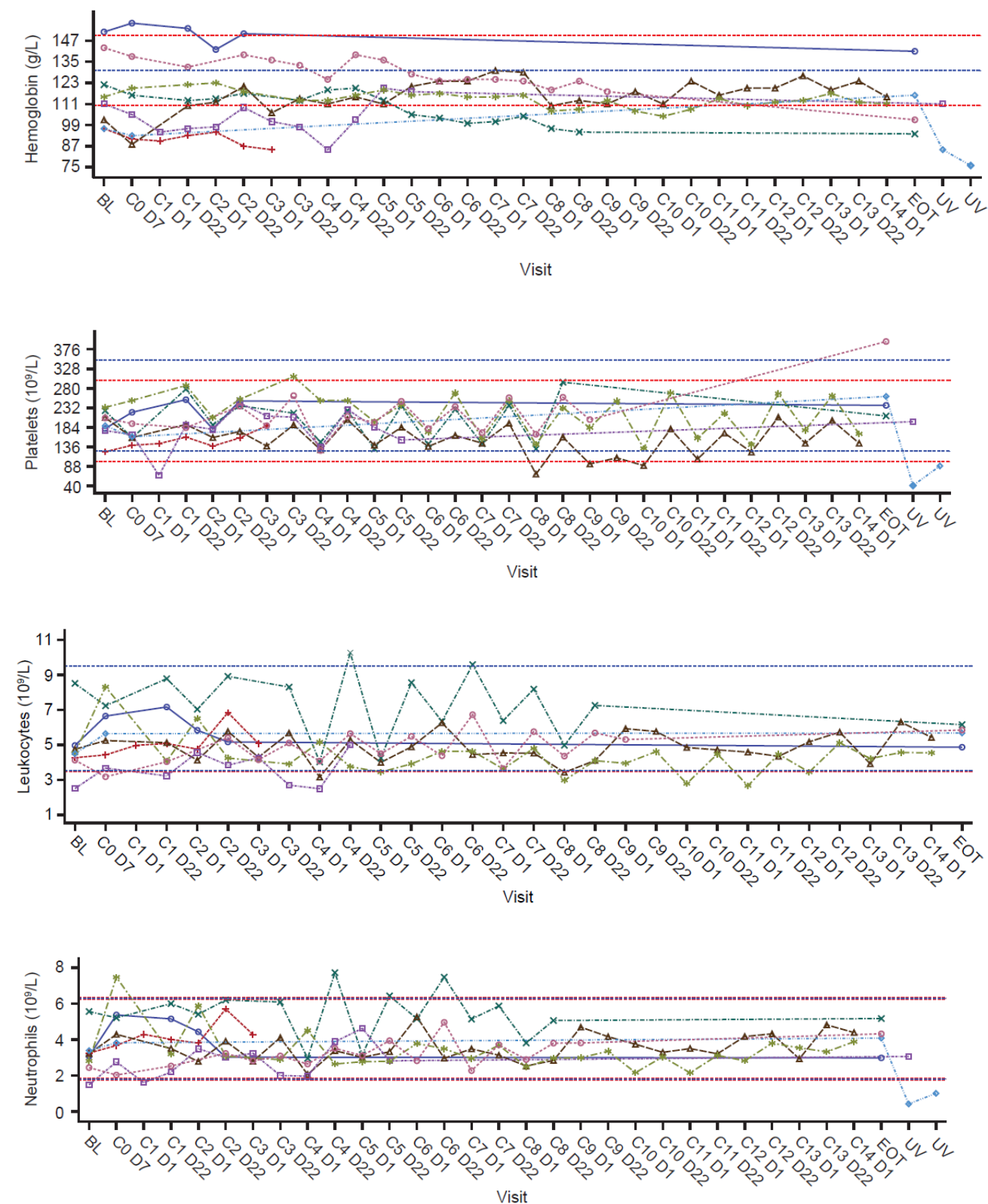
^aCalculated using log transformed data.

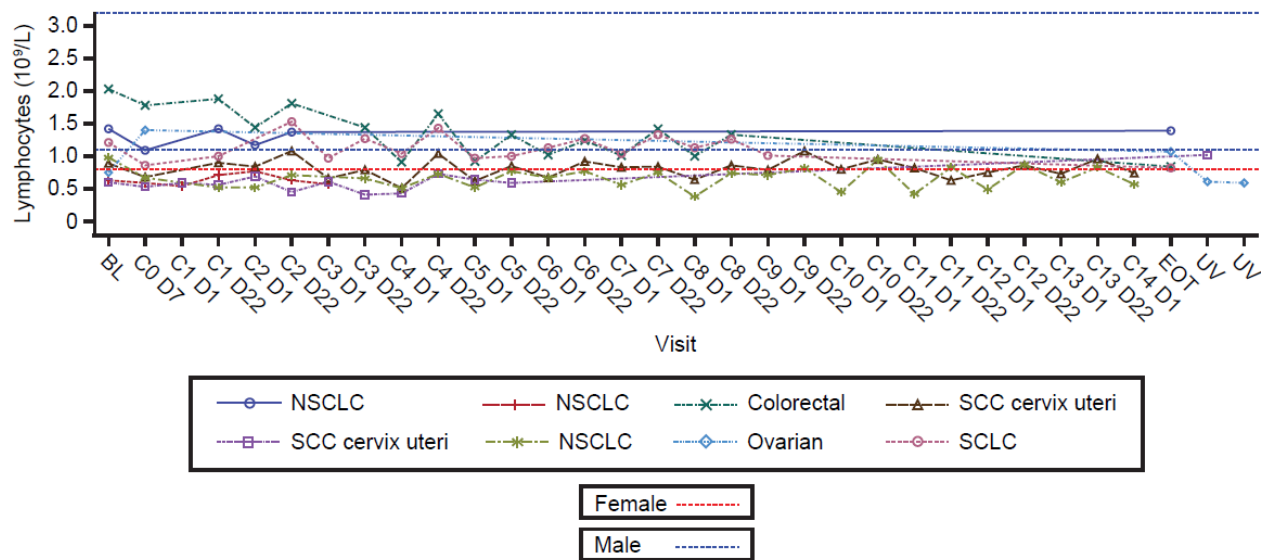
^bMissing data for n = 1 in cohort 1 and n = 3 in cohort 2.

^cA single dose of durvalumab 1500 mg was given intravenously on day 1 of each 28-day cycle to each cohort.

AUC, area under the concentration-time curve; AUC_{tau}, area under the concentration-time curve across the dosing interval; AUC_{last}, area under the concentration-time curve from time 0 to the last quantifiable concentration; BID, twice daily; C_{max}, maximum observed concentration; CV%, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; t_{1/2λz}, terminal elimination half-life; TCP, temporal change parameter; t_{max}, time to reach maximum observed plasma drug concentration.

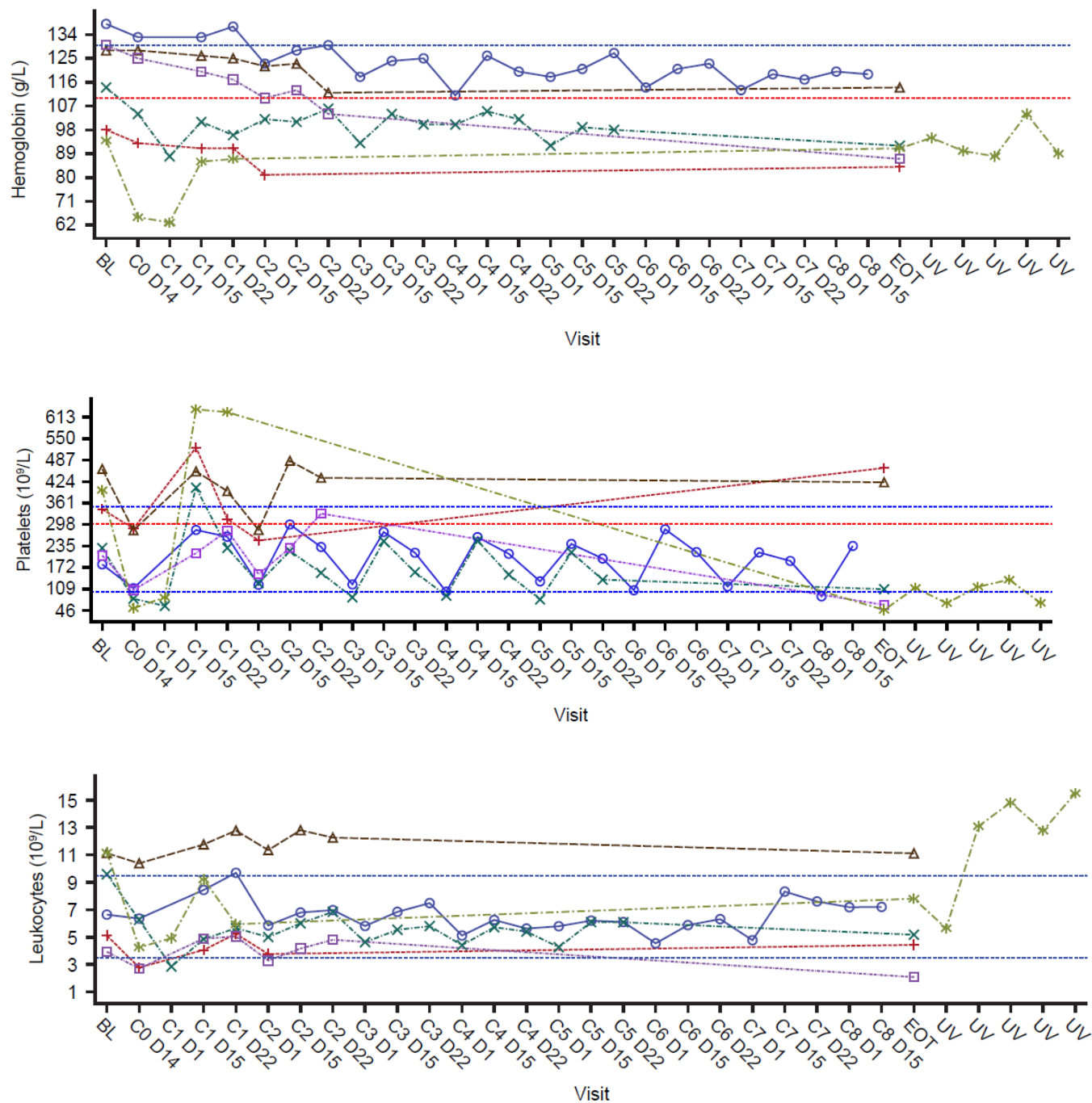
Supplementary Figure S1. Individual patient plots of hematological laboratory data in cohort 1.

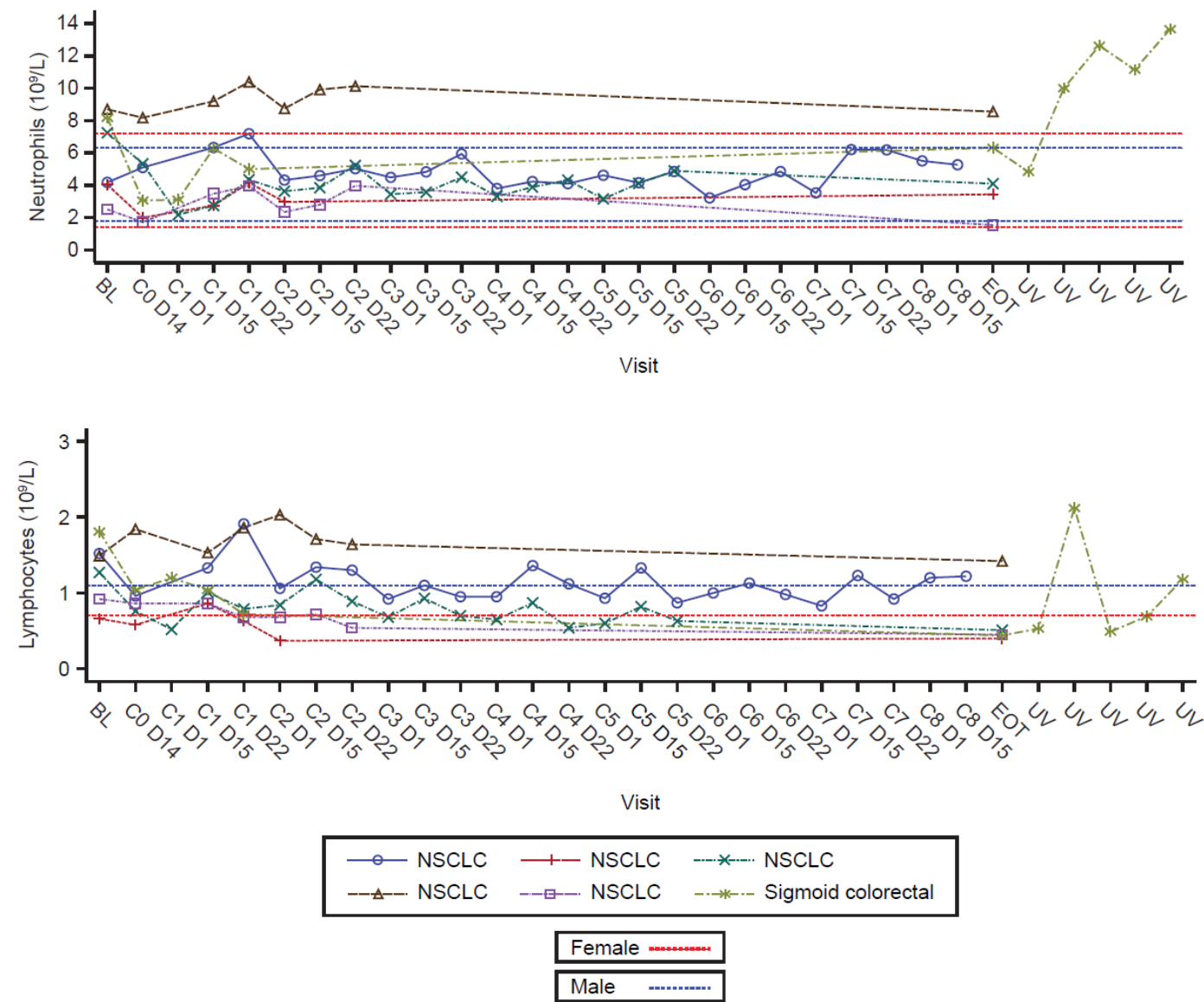




BL, baseline; C, cycle; D, day; EOT, end of treatment; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; UV, unscheduled visit.

Supplementary Figure S2. Individual patient plots of hematological laboratory data in cohort 2.

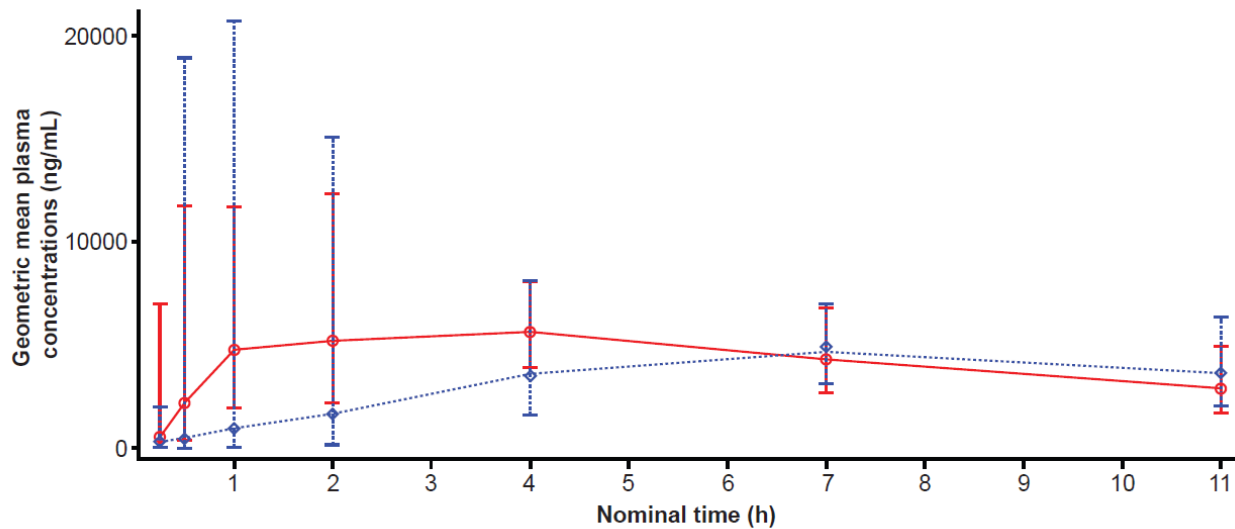




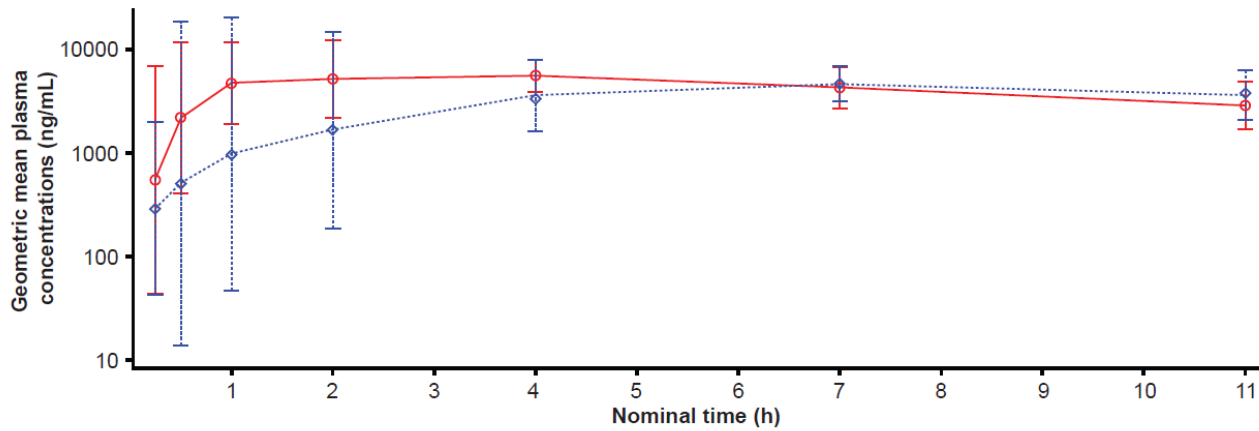
BL, baseline; C, cycle; D, day; EOT, end of treatment; NSCLC, non-small cell lung cancer; UV, unscheduled visit.

Supplementary Figure S3. Plasma concentrations versus time for ceralasertib after single dose administration at cycle 0 day 1 for (a) cohort 1 and (b) cohort 2; and after multiple dose administration at (c) cycle 0 day 7 for cohort 1 and (d) Cycle 0 day 14 for cohort 2.

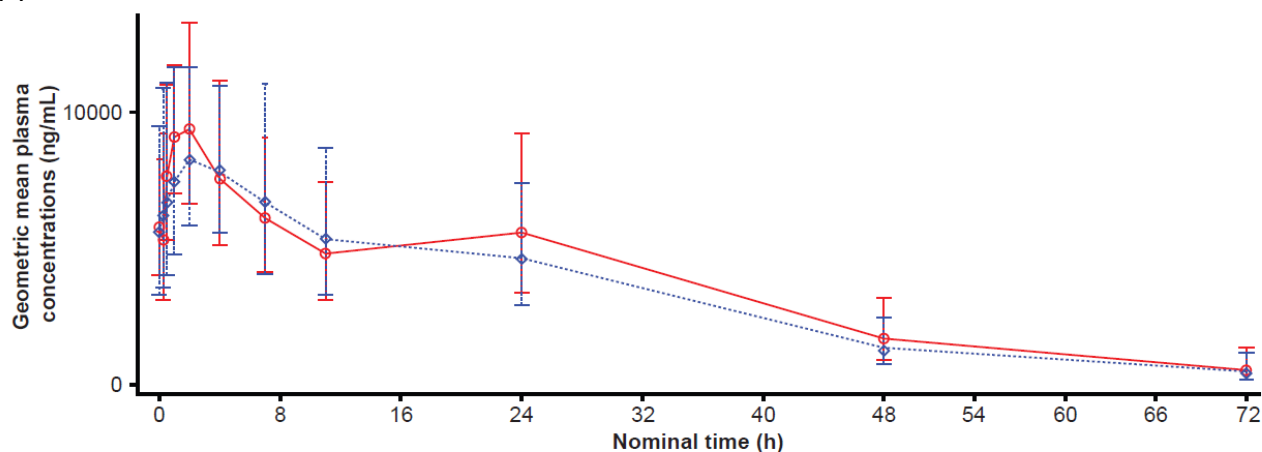
(a)



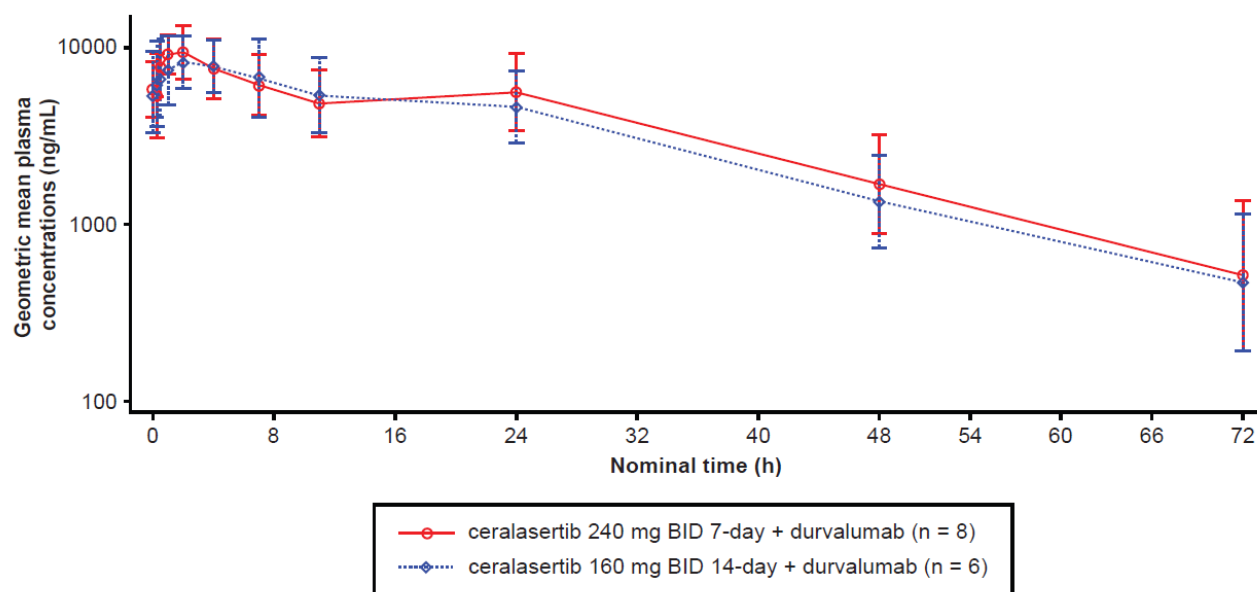
(b)



(c)



(d)



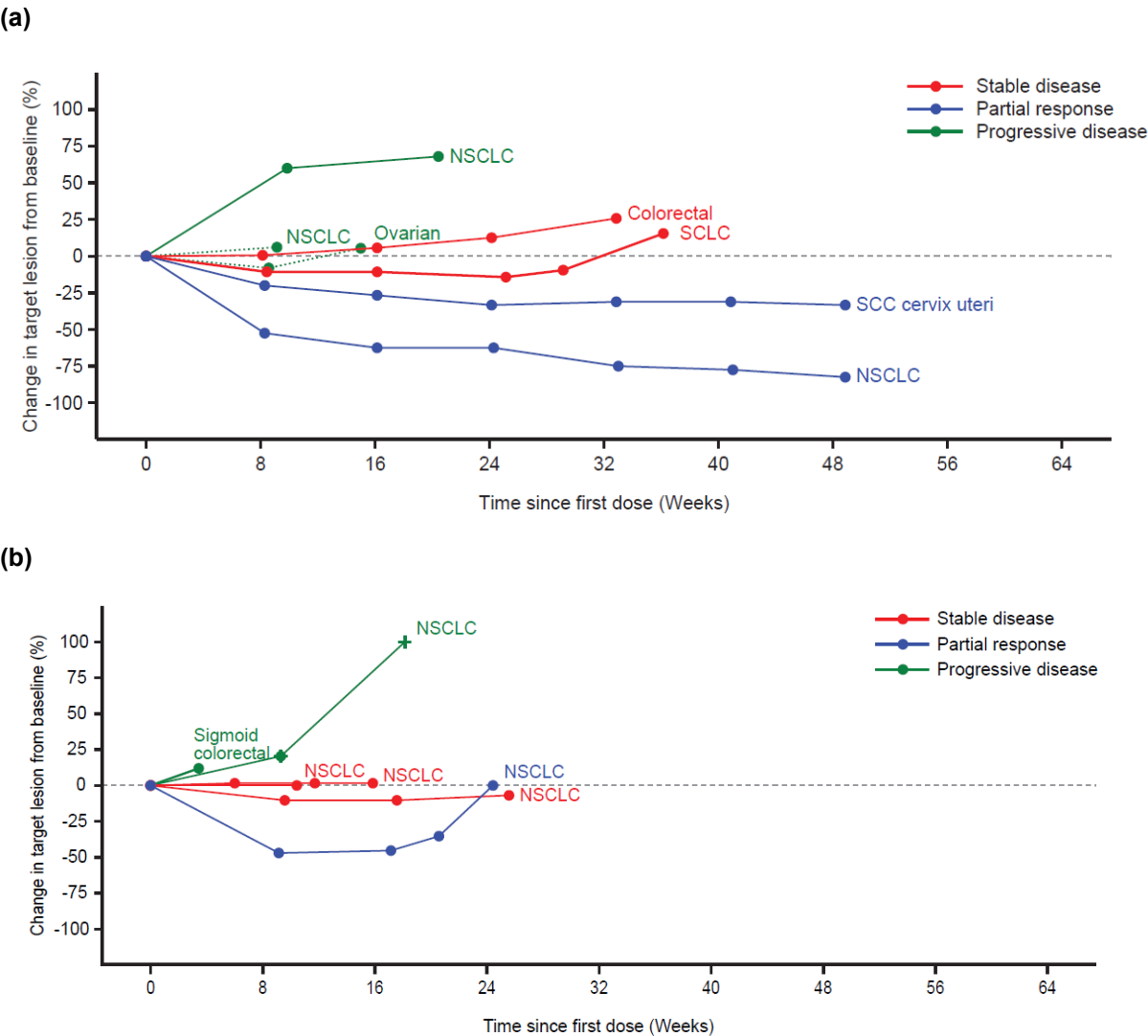
Vertical lines represent the geometric mean $\pm$ geometric SD (gSD), where the geometric mean was calculated as $\exp(\mu)$ where μ was the mean of the data on the natural log scale, and the gSD was calculated as $\exp(\sigma)$ where σ was the SD of the data on the natural log scale, i.e.

Geometric mean – gSD = $\exp(\text{mean}(\log(\text{PK concentration})) - \text{SD}(\log(\text{PK concentration})))$

Geometric mean + gSD = $\exp(\text{mean}(\log(\text{PK concentration})) + \text{SD}(\log(\text{PK concentration})))$

BID, twice daily.

Supplementary Figure S4. Percentage change from baseline in target lesion size over time in (a) cohort 1 and (b) cohort 2.



[+] denotes patient whose percentage change from baseline in tumor lesion exceeded 100%, and the spider plot was truncated for the patient at this point.

BID, twice daily; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; SCLC, small cell lung cancer.