Title of Trial: An open-label, randomized, phase II study in subjects with extensive disease, small cell lung cancer (ED-SCLC) after an initial response (complete response or partial response) to platinum-based therapy to determine the effect of EMD 273066 following low-dose cyclophosphamide on disease progression and survival versus best supportive care alone

Investigational Product: EMD 273066

Trial No.: EMR 62206-017

Study Centers: This study was conducted in 41 centers in 7 countries; Israel, Italy, Poland, Russia, Switzerland, Germany and Spain.

Trial Initiation Date: May 2007

Trial Completion Date: January 2011

Development Phase: Phase 2

Publications (references): None

Study Objectives:

The primary objective of this study was to assess whether exposure to EMD 273066 administered after low-dose cyclophosphamide following an objective response to initial induction therapy in subjects with SCLC would increase the proportion of subjects with progression free survival (PFS) at 6 months following randomization when compared with subjects given best supportive care (BSC) alone.

Secondary objectives were as follows:

- To estimate overall survival at 12 and 18 months (from beginning of first-line, platinum-based chemotherapy).
- To estimate median time to progression after randomization.
- To characterize the safety and tolerability of treatment with low-dose cyclophosphamide followed by EMD 273066.
- To collect additional immunogenicity data from subjects exposed to EMD 273066.
- To determine the objective response rate in subjects receiving second-line chemotherapy after disease progression

Methodology:

This was a parallel group, unblinded, randomized (1:1.5 ratio) open-label study of BSC without anti-neoplastic therapy versus low-dose cyclophosphamide (CTX) followed by EMD 273066

in subjects with ED-SCLC. Subjects were stratified by the extent of initial response to the first line platinum-based chemotherapy (complete response or partial response) defined by the investigator as per RECIST v1.0 and, in accordance with Protocol Amendment 1,administration of prophylactic cranial irradiation (yes or no). Prior to Protocol Amendment 1, subject evaluation started at Week 13 after initiation of first-line, platinum-based chemotherapy (between Days 22 and 28 after the fourth cycle).

Subjects were to undergo response assessment by computed tomography (CT) or magnetic resonance imaging (MRI) according to RECIST v1.0. If a complete response or partial response was confirmed, eligibility for randomization required completion of screening procedures necessary to meet inclusion and exclusion criteria. Randomized subjects were to begin treatment within 3 to 5 weeks after the last infusion of first-line chemotherapy.

After the implementation of the Protocol Amendment 1 further screening procedures, study randomization and start of study treatment was scheduled based on whether the subject was given elective prophylactic cranial irradiation (PCI) as follows:

1. No PCI:

- Inclusion and exclusion procedures were to begin at Week 13-15 after initiation of first line platinum-based chemotherapy.

- Eligible randomized subjects were to begin study treatment within 3-5 weeks (Week 15-17) after four 3-week cycles of first line platinum-based chemotherapy.

2. PCI to be given:

- PCI could be given in twice-daily fractionation for a total dose of 20 Gy administered within 3 weeks (Week 13-15) after four 3-week cycles of first line platinum-based chemotherapy.

- Inclusion and exclusion procedures were to begin 2 weeks following PCI followed by up to 2 weeks of rest (Week 16-18 after four 3-week cycles of first line platinum-based chemotherapy).

- Eligible randomized subjects were to begin study treatment within 5-7 weeks (Week 17-19) after four 3-week cycles of first line platinum–based chemotherapy.

Subjects were randomly assigned to 1 of 2 treatment groups:

- **Group A:** Subjects were to receive six 3-week cycles of low-dose CTX followed by EMD 273066 during the Consolidation Phase. Low-dose CTX, 300 mg/m^2 was to be administered intravenously (IV) on Cycle Day 1 followed 22-28 hours later by EMD 273066, 1.5 mg/m^2 by 4-hour IV infusion on each of 3 consecutive days (Cycle Days 2-4) followed by 17 days (Cycle Days 5-21) without study treatment to complete one 3-week Consolidation Cycle. Upon completion of these cycles, subjects who had not experienced disease progression were to enter the Maintenance Phase and receive low-

dose CTX followed 22-28 hours later by 1 infusion of EMD 273066, 1.5 mg/m2 or the lowest dose received during the Consolidation Phase every 3 weeks until disease progression.

- **Group B:** BSC without anti-neoplastic therapy until disease progression.

Subjects were to be followed until disease progression (defined as an increase in measurable disease by CT according to RECIST v1.0). CT scans (thoracic and abdominal) were to be performed every 6 weeks during the Consolidation Phase unless there was a need for an earlier evaluation to document disease status in an individual subject. Abdominal MRI scans instead of CT scans were acceptable for the purposes of this study. During the Maintenance Phase, CT or MRI scans were also to be performed every 6 weeks.

Number of Subjects (Planned and Analyzed):

A total of 110 subjects with a complete or partial response to first-line, platinum-based chemotherapy was planned for this study; 109 subjects were actually included in the All Subjects Analysis Set. The datasets analyzed in this study were as follows:

Data Analysis Sets - All Subjects Analysis Set

Analysis Sets Number (%) of Subjects	KS-IL2 N=65	BSC N=44	Overall N=109
All subjects analysis set	65 (100.0)	44 (100.0)	109 (100.0)
Intent-to-treat analysis set	64 (98.5)	44 (100.0)	108 (99.1)
Safety analysis set	64 (98.5)	44 (100.0)	108 (99.1)
Biomarker analysis set	64 (98.5)	40 (90.9)	104 (95.4)
Per-protocol analysis set	55 (84.6)	31 (70.5)	86 (78.9)

Diagnosis and Main Criteria for Inclusion/Exclusion: For inclusion in the study, all of the following inclusion criteria had to be fulfilled:

- Signed written informed consent.
- ≥ 18 years of age.
- Histologically documented SCLC.
- Radiologically demonstrated ED-SCLC by thoracic and abdominal CT or MRI scan prior to induction chemotherapy.
- Received 4 cycles of platinum-based, first-line chemotherapy (12 weeks) with or without PCI and without thoracic irradiation.
  - PCI given in 2 Gy twice-daily fractionation for a total dose of 20 Gy within 3 sweeks following the fourth 3-week course of first-line chemotherapy.

Note: prior to the Protocol Amendment 1 this criterion was "Received 4 cycles of platinum based, first-line chemotherapy (12 to 14 weeks) without thoracic irradiation."

- Experienced a response to platinum-based, first-line chemotherapy (complete response orpartial response as assessed by the Investigator according to RECIST v1.0) compared to findings shown prior to induction therapy.

  Note: prior to the Protocol Amendment 1 this criterion was "Experienced a response to platinum-based, first-line chemotherapy (complete response or partial response as assessed by the Investigator according to RECIST v1.0 shown after second and fourth course of induction chemotherapy) compared to findings shown prior to induction therapy."

- Confirmatory CT or MRI scans and cranial CT scan within 4 weeks prior to starting study treatment.

  - When elective PCI was not to be given, subject had to be able to begin study treatment 3-5 weeks after completion of platinum-based, first-line chemotherapy (week 15-17).

  - When elective PCI was given, subject had to be able to begin study treatment 5-7 weeks after completion of platinum-based, chemotherapy (week 17-19).

    Note: prior to the Protocol Amendment 1 this criterion was "Be enrolled and begin treatment 3-5 weeks after completion of platinum-based, first-line chemotherapy."

- Life expectancy ≥ 4 months.

- Eastern Clinical Oncology Group (ECOG) performance status ≤ 2 at study entry.

- No clinical history of significantly impaired renal function or chronic kidney disease. Must have an estimated glomerular filtration rate ≥ 50 mL/min determined by the Cockcroft-Gault formula.

- No significant hematologic abnormalities, including white blood cell (WBC) count ≥ 2.5 × 103/µl (or total granulocytes ≥ 1 × 103/µl), absolute lymphocyte count (ALC) ≥ 0.5 × 103/µl, platelet count ≥ 100 000, and hemoglobin level ≥ 9 g/dl.

- No significant hepatic abnormalities, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × the upper limit of normal (ULN) or ≤ 5 × ULN in case of liver metastasis, and total bilirubin < 1.5 × ULN.

- No significant electrolyte abnormalities, including serum sodium, potassium, and phosphorus within normal limits.

- Serologic testing within 4 weeks prior to starting study treatment with negative results for hepatitis C virus (HCV), human immunodeficiency virus (HIV), and hepatitis B virus (HBV) demonstrated by negative hepatitis B core antibody (HBcAb) and hepatitis surface antigen (HbsAg).

- Negative urine beta-human chorionic gonadotropin (HCG) pregnancy test and willingness to use effective contraception for both male and female subjects for the study duration and 1 month thereafter if of procreative potential; non-lactating females.

Study Treatment:

For subjects assigned to the low-dose CTX followed by EMD 273066 treatment regimen (Treatment Group A): Consolidation Phase therapy included CTX 300 mg/m2 administered per institutional guidelines on Day 1 followed by EMD 273066, 1.5 mg/ m2, administered as a 4-hour IV infusion on Days 2-4 (first dose administered on Day 2, beginning 22-28 hours after CTX administration) followed by 17 days without study treatment, during each cycle for up to 6 cycles. Thereafter, Maintenance Phase treatment was administered every 3 weeks (300 mg/m2 CTX IV administered per institutional guidelines on Day 1 followed 22-28 hours later by EMD 273066 administered as a 4-hour IV infusion on Day 2 at 1.5 mg/m2 or lowest dose administered during the Consolidation Phase).

For EMD 273066-exposed subjects prophylaxis and/or treatment of fever and flu-like symptoms were required. Paracetamol 650 mg po given in combination with indomethacin 50 mg po was administered to all subjects beginning 2 hours prior to the start of the EMD 273066 infusion, and repeated every 8 hours until 24 hours after completion of EMD 273066 infusions.

Alternative treatment for fever and flulike symptoms with other antipyretics and NSAIDS in subjects for whom paracetamol or indomethacin was contraindicated (i.e., allergy, gastric disorder, renal insufficiency, etc) was left to the discretion of the investigator.

The duration of subject participation included a Screening Phase (up to 5-7 weeks prior to treatment), a Consolidation Phase (a maximum of 18 weeks), and a Maintenance Phase (until disease progression).

Criteria for Evaluation:

Efficacy:

- Estimate PFS rate at 6 months after randomization.

- Estimate overall survival time.

- Estimate survival rates at 12 and 18 months (from beginning of first-line therapy).

- Estimate median time to progression (after randomization) or death due to progressive disease.

- Determine immunogenicity.
- Determine response rate following second-line chemotherapy.

Safety:

- Vital signs (pulse rate, respiratory rate, blood pressure, body weight and body temperature).
- Electrocardiograms (ECGs).
- Physical examination.
- AEs and SAEs graded by the NCI CTCAE version 3.0.
- Clinical laboratory test values.
- Discontinuations/withdrawals for reasons other than disease progression.
- ECOG performance status.

Statistical Methods:

The primary objective of this phase II, proof of concept (POC) study was to estimate and compare the PFS rate at 6 months after subjects received first-line platinum-based chemotherapy consisting of 4 courses of induction therapy and are then randomized (1:1.5 ratio) to treatment with BSC or low-dose CTX followed by the test agent EMD 273066 for consolidation and maintenance therapy. A review of published studies indicated that BSC 6-month PFS rate point estimates vary between approximately 10% and 30%, in similar target populations.

For this study it was assumed that 6-month PFS rate for BSC would approximate to 15-25% for subjects with a complete response or partial response after four courses of first-line platinum-based induction chemotherapy. A clinically relevant and meaningful improvement in 6-month PFS rate was assumed to be at least 20% above the BSC estimates.

A total sample size of 110 subjects was estimated for this study. Subjects were allocated in a 1:1.5 randomization allocation to BSC (n=44) or CTX followed by EMD 273066 (n=66). This sample size would achieve 80% power to detect a clinically meaningful difference between the null hypothesis that BSC and CTX followed by EMD 273066 6-month PFS rates are between 15-25%, with the alternative hypothesis that the EMD 273066 6-month progression proportion was 34-46%, using a 1-sided Chi-square test (with continuity correction) at significance level 10% (≤ 0.10). Exploratory survival analysis was also to be utilized to examine both the PFS rate at 6 months after randomization, as well as the secondary objectives of the estimates of overall survival rates at 12 and 18 months from the beginning of induction therapy and the time to progression after randomization. Descriptive and graphical summaries (median values and

90% confidence intervals) were prepared for the primary and secondary time-dependent endpoints. Safety and tolerability were assessed using descriptive statistics.

Results:

Subject Disposition: All 109 subjects in the All Subjects Analysis Set discontinued from the study due to the reasons outlined below:

Disposition of Subjects – All Subjects Analysis Set

Subject Status Number (%) of Subjects	KS-IL2 N=65	BSC N=44	Overall N=109
Subjects discontinued	65 (100.0)	44 (100.0)	109 (100.0)
Main reason for discontinuation:			
Disease progression	50 (76.9)	39 (88.6)	89 (81.7)
Adverse event	7 (10.8)	1 (2.3)	8 (7.3)
Withdrawal of consent	5 (7.7)	2 (4.5)	7 (6.4)
Protocol violation	0	1 (2.3)	1 (0.9)
Death	2 (3.1)	1 (2.3)	3 (2.8)
Other	1 (1.5)	0	1 (0.9)

Demographics and Baseline Characteristics: No notable differences were observed between treatment groups with regard to baseline demographic characteristics. All subjects were Caucasian; most were male (75 subjects, 69.4%). The mean age of subjects was 60.0 years (range: 32 to 81 years). All subjects had a tumor response after first-line platinum therapy at randomization; 106 subjects (98.1%) had a partial response and two subjects (1.9%) had a complete response. Most subjects (82 subjects, 75.9%) were not treated with PCI therapy; 26 subjects (24.1%) received PCI therapy.

Efficacy Results: The main efficacy findings for this study are summarized for the ITT Analysis Set below.

Summary of Key Efficacy Findings – ITT Analysis Set

	KS-IL2 N=64	BSC N=44	Hazard Ratio N=108
Primary efficacy endpoint			
At risk at 6 months: n (%)	3 (4.7)	3 (6.8)	
6-months PFS rate (%)	6.37	12.22	
2-sided 80% CI	(2.89, 11.76)	(6.19, 20.44)	
Secondary efficacy endpoints			
Median PFS (months)	1.51	1.41	1.01
2-sided 80% CI	(1.41, 1.68)	(1.41, 1.71)	(0.76, 1.34)
Median overall survival (months)	12.25	14.08	1.10
2-sided 80% CI	(10.87, 13.90)	(12.02, 15.21)	0.84, 1.44
At risk at 12 months: n (%)	31 (48.4)	27 (61.4)	
12-months survival rate (%)	52.13	61.36	
2-sided 80% CI	(43.73, 59.88)	(51.25, 69.99)	
At risk at 18 months: n (%)	13 (20.3)	12 (27.3)	
18-months survival rate (%)	23.54	29.22	
2-sided 80% CI	(16.92, 30.81)	(20.73, 38.22)	
Median time to progression (months)	1.54	1.48	1.03
2-sided 80% CI	(1.41, 1.81)	(1.41, 1.71)	0.76, 1.39
Best overall response			
Partial response	1 (1.6)	0	
Stable disease	22 (34.4)	15 (34.1)	
Disease progression	38 (59.4)	23 (52.3)	
Not evaluable	3 (4.7)	4 (9.1)	
Withdrew due to TEAE or other reason	0	2 (4.5)	

The primary objective of this study was not met. Exposure to EMD 273066 after low-dose CTX following an objective response to initial induction therapy in subjects with SCLC did not increase the percentage of progression-free subjects at 6 months after randomization when compared with subjects given BSC alone. The PFS rate at 6 months in the KS-IL2 group was lower than that observed in the BSC group (6.37% vs 12.22%).

The median PFS time was similar in the KS-IL2 and BSC groups (1.5 and 1.4 months, respectively). The hazard ratio for PFS (1.01) indicated that subjects in both treatment groups had a similar risk of disease progression or death.

The median time to progression was similar in the KS-IL2 and BSC groups (1.54 and 1.48 months, respectively); the hazard ratio (1.03) indicated a similar risk of disease progression in both groups.

The median overall survival time was shorter in the KS-IL2 group than in the BSC group (12.25 vs. 14.08 months, HR 1.10). The overall survival rates at 12 months and 18 months were lower in the KS-IL2 group than the BSC group (12 months: 52.13% vs 61.36%; 18 months: 23.54% vs 29.22%).

Best overall tumor responses to second-line treatment were generally similar in both treatment groups. A partial response was observed in one subject in the KS-IL2 group. Stable disease occurred to a similar extent in both treatment groups (34.4% of subjects in the KS-IL2 group

vs 34.1% of subjects in the BSC group). Disease progression occurred slightly more frequently in the KS-IL2 group than the BSC group (59.4% vs. 52.3% of subjects, respectively).

The ECOG performance status of subjects at the end of study was the same as observed at baseline for most subjects; however, a worsening in ECOG performance status from baseline to end of study was observed in approximately one third of subjects in each treatment group (32.7% in the KS-IL2 group and 35.0% in the BSC group) while an improvement from baseline to end of study was observed in just one patient in the KS-IL2 group.

Subgroup analyses of efficacy endpoints by PCI subgroup were generally unremarkable given that most subjects did not receive PCI prior to treatment initiation. PCI subgroup results indicated that subjects who received PCI had lower risks of disease progression or death in the KS-IL2 group compared with the BSC group; however, no conclusions can be drawn given the low number of subjects in this subgroup. In general, results in the non-PCI group followed the same trends as those reported for the overall population given that most subjects were included in that subgroup.

In conclusion, exposure to EMD 273066 after low-dose CTX following an objective response to initial induction therapy in subjects with SCLC had no statistically significant effect on PFS rates at 6 months when compared to BSC. Furthermore, it did not improve the PFS time, overall survival rates at 12 and 18 months, overall survival time or time to progression when compared with BSC. EMD 273066 was comparable to BSC with regard to best overall tumor responses to second-line treatment.

Safety Results: An overview of treatment-emergent adverse events (TEAEs) that occurred during the study is presented below.

Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

Number (%) Subjects	**KS-IL2 N=64**	**BSC N=44**	**Overall N=108**
TEAE	59 (92.2)	21 (47.7)	80 (74.1)
EMD 273066 related TEAE	49 (76.6)	NA	49 (45.4)
CTX-related TEAE	15 (23.4)	NA	15 (13.9)
NCI CTCAE Grade 3 and 4 TEAE	48 (75.0)	10 (22.7)	58 (53.7)
EMD 273066 related NCI CTCAE Grade 3 and 4 TEAE	31 (48.4)	NA	31 (28.7)
CTX-related NCI CTCAE Grade 3 and 4 AE	10 (15.6)	NA	10 (9.3)
Serious TEAEs	10 (15.6)	8 (18.2)	18 (16.7)
EMD 273066 related serious TEAEs	1 (1.6)	NA	1 (0.9)
CTX-related serious TEAEs	0	NA	0
NCI CTCAE Grade 3 and 4 serious TEAEs	9 (14.1)	7 (15.9)	16 (14.8)
EMD 273066 related NCI CTCAE Grade 3 and 4 serious TEAEs	1 (1.6)	NA	1 (0.9)
CTX-related NCI CTCAE Grade 3 and 4 serious TEAEs	0	NA	0
TEAEs leading to discontinuation	9 (14.1)	NA	9 (8.3)
TEAEs with fatal outcome	3 (4.7)	3 (6.8)	6 (5.6)

AE = adverse event; SAE = serious adverse event.

Most subjects (95 subjects, 88.8%) in the ITT Analysis Set died during the study or follow-up period; 55 subjects (87.3%) from the KS-IL2 group and 40 subjects (90.9%) from the BSC group. Three of these subjects died within 28 days of the last dose of EMD 273066. The

primary cause of death was disease progression (94.7% of subjects), which occurred to a similar extent in both treatment groups. Overall, TEAEs occurred in a greater percentage of subjects in the KS-IL2 group than the BSC group (92.2% vs 47.7%). During the Consolidation Phase, the most frequent TEAE by preferred term was pyrexia, which occurred exclusively in the KS-IL2 group (37.5% of subjects) and lymphopenia, which occurred in 42.2% of subjects in the KS-IL2 group vs one subject (2.3%) in the BSC group. During the Maintenance Phase, TEAEs occurred in 4.6% of subjects; 6.3% in the KS-IL2 group and 2.3% in the BSC group; individual TEAEs occurred in no more than one subject in either group.

EMD 273066 related TEAEs occurred in 76.6% of subjects in the KS-IL2 group. During the Consolidation Phase, the most frequent EMD 273066 related TEAEs by preferred term were pyrexia, lymphopenia, lymphocyte count decreased and pruritis, which occurred in 35.9, 25.0, 14.1 and 12.5% of subjects in the KS-IL2 group, respectively. During the Maintenance Phase, EMD 273066 related TEAEs occurred in 4.7% of subjects in the KS-IL2 group; individual events occurred in no more than one subject. CTX-related TEAEs occurred in 21.9% of subjects in the KS-IL2 group. During the Consolidation Phase, the most frequent by preferred term was lymphopenia (10.9%). During the Maintenance Phase, one CTX-related TEAE of lymphocyte count decreased occurred in one subject in the KS-IL2 group.

NCI CTCAE grade 3 and 4 TEAEs occurred in a greater percentage of patients in the KS-IL2 group than the BSC group (75.0% vs 22.7%). EMD 273066 related NCI CTCAE grade 3 or 4 TEAEs occurred in 48.4% of subjects in the KS-IL2 group. During the Consolidation Phase, the most frequent EMD 273066 related NCI CTCAE grade 3 or 4 TEAEs by preferred term were lymphopenia and lymphocyte count decreased, which occurred in 25.0% and 14.1% of subjects, respectively. One EMD 273066 related NCI CTCAE grade 3 TEAE (lymphocyte count decreased) occurred in one subject during the Maintenance Phase. CTX-related NCI CTCAE grade 3 or 4 TEAEs occurred in 15.6% of subjects in the KS-IL2 group, all during the Consolidation Phase. These consisted of lymphopenia, lymphocyte count decreased and fatigue, which occurred in 10.9%, 3.1% and 1.6% of subjects, respectively.

Serious TEAEs occurred in a lower percentage of patients in the KS-IL2 group (15.6%) than the BSC group (15.6% vs 18.2%). NCI CTCAE grade 3 and 4 serious TEAEs also occurred in a lower percentage of subjects in the KS-IL2 group than the BSC group (14.1% vs 15.9%). During the Consolidation Phase, the most frequent serious TEAE, and NCI CTCAE grade 3 or 4 serious TEAE, by preferred term was general physical health deterioration, which occurred in two subjects in the KS-IL2 group and one subject in the BSC group. Remaining serious TEAEs occurred in no more than one subject in any treatment group. One NCI CTCAE toxicity grade 3 serious TEAE (squamous cell carcinoma of the skin) occurred in one subject in the KS-IL2 group during the Maintenance Phase, which was not related to EMD 273066 treatment. One EMD 273066 related NCI CTCAE toxicity Grade 3 serious TEAE (rash generalized) occurred in one subject in the KS-IL2 group during the Consolidation Phase only.

TEAEs that led to a fatal outcome occurred in six subjects (5.6%); three subjects (4.7%) in the KS-IL2 group and three subjects (6.8%) in the BSC group; none were considered related to treatment and all but two were considered related to disease progression. The events in the KS-

IL2 group occurred within 7 to 16 days of start of EMD 273066 treatment while those in the BSC group occurred within 16 to 82 days of the start of BSC treatment.

TEAE that led to study treatment discontinuation occurred in 14.1% of subjects in the KS-IL2 group, all during the Consolidation Phase. The most frequent TEAEs that led to study treatment discontinuation were general physical health deterioration and rash generalized, each of which occurred in two subjects. Remaining events occurred in no more than one subject in this group.

Other Safety Data: Vital signs and ECG data were unremarkable. Laboratory data indicated more notable changes from baseline in laboratory parameters in the KS-IL2 group than the BSC group. The most notable hematology finding was a transient decrease in mean ALC values on Day 4 of each treatment cycle with EMD 273066 in the KS-IL2 group ranging from 0.767to 1.353 × 109/L. A shift in ALC values from NCI CTCAE grade 0 or 1 at baseline to grade 3 post treatment occurred in 58% of subjects in the KS-IL2 group, compared with just one subject (2%) in the BSC group. A shift in ALC values from grade 0 at baseline to grade 4 post treatment also occurred in one subject in each group. It should be noted that the mean ALC changes from baseline were reversible as mean ALC values had returned to baseline levels by the end of the study.

The most notable clinical chemistry findings were substantially increased mean AST, ALT and ALP values of 57.1 U/L (± 170.0), 64.3 U/L (± 88.6) and 37.1 U/L (± 55.3), respectively, on Day 8 of the first treatment cycle with EMD 273066 in the KS-IL2 group; further less notable increases were also observed at later cycles. However, mean AST, ALT and ALP changes from baseline to the end of the study were notably lower: 13.7 U/L (± 87.8), 6.5 U/L (± 23.7) and 21.3 U/L (± 32.2), respectively, in the KS-IL2 group, indicating a return to baseline levels. No conclusions can be drawn from these results given the large variances in data reported.

Furthermore, changes from baseline in AST and ALT values to NCI CTCAE grade 3 or 4 post treatment occurred infrequently and there were no changes from baseline in ALP values to NCI CTCAE grade 3 or 4 post-treatment. Five subjects (7.8%) in the KS-IL2 group and one subject (2.3%) in the BSC group had a concurrent shift in AST or ALT from Grade 0 to Grade 3 or 4. Three subjects in the KS-IL2 group had concurrent shifts in AST and ALT from Grade 0 at baseline to Grade 3 post-treatment that were considered treatment-related TEAEs; all resolved or resolved with sequelae. An additional subject in the KS-IL2 group had a shift in AST from Grade 0 at baseline to Grade 4 post-treatment concurrently with a shift in ALT from Grade 0 at baseline to Grade 3 post-treatment, which were not considered TEAEs; this subject subsequently died due to general deterioration. One subject in the BSC group had a concurrent shift in AST and ALT from Grade 0 at baseline to Grade 3 at the end of study visit; this was not considered a TEAE. In addition, one subject in the KS-IL2 group had a shift in AST from Grade 0 at baseline to Grade 3 at the end of study visit that was considered a treatment-related TEAE; no follow-up laboratory result was provided for this TEAE, which was ongoing at the end of the study.

Conclusions:

Exposure to EMD 273066 after low-dose CTX following an objective response to initial induction therapy in subjects with SCLC had no statistically significant effect on PFS rates at 6 months when compared to BSC. Furthermore, it did not improve the PFS time, overall survival rates at 12 and 18 months, overall survival time or time to progression when compared with BSC. EMD 273066 was comparable to BSC with regard to best overall tumor responses to second-line treatment.

Administration of EMD 273066 after low-dose CTX therapy resulted in a notable increase in known EMD 273066-related TEAEs, mostly lymphopenia and pyrexia events, compared to treatment with BSC. Serious TEAEs were less frequent in subjects treated with EMD 273066 than in those treated with BSC and only one subject experienced a known EMD 273066 related serious TEAE of generalized rash. Notable laboratory findings of decreased ALC and increased AST, ALT and AST with EMD 273066 administration are known IL2 effects.