

Following a treatment course and the completion of any necessitated treatment delays, the grades of toxicities that occurred during that course were reviewed and the dose for the next treatment course was modified for the following toxicities or patient cumulative treatment history:

- grade 3-4 neutropenia,
- grade 4 thrombocytopenia,
- grade 3-4 clinically significant, non-hematologic toxicity (excluding grade 3 nausea),
- total lifetime cumulative dose of doxorubicin, or comparable dose of epirubicin plus doxorubicin, is  $\geq 450$  mg/m<sup>2</sup>. To calculate the dose of epirubicin comparable to doxorubicin (in patients treated previously with epirubicin), the epirubicin cumulative dose should be divided by two.

#### **Concomitant Medication/Treatment**

All concomitant medication taken during the study were recorded in the case report form (CRF) with indication, daily dose and dates of administration. If a drug is administered prophylactically, this was noted

#### **8.4 Criteria For Efficacy**

The primary criteria of efficacy were response rate and response duration in patients with measurable disease. The secondary criteria were the time to response, the time to progression, survival, and the assessment of disease related symptoms. Definitions were as follows:

**Measurable disease** - Malignant lesions measurable in two dimensions with clearly defined margins by diagnostic studies (CT or MRI scan or ultrasound with at least one diameter  $\geq 2$  cm; chest X-ray with at least one diameter  $\geq 2$  cm), or a palpable lymph node lesion with at least one diameter  $\geq 2$  cm (verified by a scan, or by ultrasound, or X-ray, or by a second physician, when possible). A skin lesion must have one diameter  $\geq 1.0$  cm and must be confirmed by photograph (with scale).

**Evaluable disease** - Lesions with margins that are not clearly defined or that are measurable in one dimension only, lesions with the largest diameter  $< 2$  cm, abdominal lesions that are palpated but not measured, hepatomegaly.

**Non-measurable, non-evaluable disease** - ascites, pleural effusion, pericardial effusion, bone or bone marrow metastases, leptomeningeal metastases, lymphangetic metastases, previously irradiated lesions.

**Complete response (CR)** - complete disappearance of all known measurable and evaluable disease determined by 2 measurements not less than 4 weeks apart.

**Partial response (PR)** - greater than 50% decrease in the sum of the products of the greatest length and perpendicular width of all measurable lesions for at least 4 weeks with no simultaneous increase in a known lesion (>25%) or appearance of new lesions or increase in evaluable disease during this period.

**Response rate (RR)** - the percentage of the total of evaluable patients which have a complete or partial response.

**Time to Response** - the time from the first infusion to the time of initial documented response.

**Time to Progression** - the time from first dose administration to the time of the first documented progression.

**Response Duration** - the time from the initial documented response to the first sign of progression.

**Stable/No response** - state of response which is less than partial or progression and lasts for at least 8 weeks.

**Progression** - greater than 25% increase in measurable disease, reappearance of measurable disease, clear worsening of evaluable disease, appearance of any new lesions including brain metastases even if there is response outside of the brain or significant worsening of condition presumed to be related to malignancy.

### **Symptoms of Disease Evaluation**

Data was collected on patients' self-assessed scores for nine symptoms of disease, at baseline and prior to each course of therapy. (Appendix B) The patient was told: "Mark one box for each symptom to indicate how much you have experienced that symptom during the past three weeks or since your last treatment."

Each symptom was scored on a 4 point ordinal scale as follows:

1. Not at All 2. A Little 3. Quite A Bit 4. Very Much.

The analysis of longitudinal symptom data used the General Estimating Equations (GEE) methodology. The analysis focused on three of the nine symptoms, Shortness of Breath, Cough, and Chest Pain.

### 8.5 Patient Demographics

Two hundred and eleven patients were enrolled at 45 centers. Thirteen were in Canada, 20 in the United States, 8 in continental Europe, 3 in the United Kingdom and 1 in South Africa. Twelve patients were enrolled but not treated due to either refusing consent, progressive disease, going on another regimen or not meeting eligibility criteria. One hundred and seven patients were received topotecan and 104 received the active control combination. Greater than 70% of the patients in each arm completed the study. Ten topotecan patients and 13 CAV patients withdrew secondary to adverse events. Eighteen patients were not assessed beyond baseline. These patients had lesions that were considered non-evaluable or withdrew due to adverse events. A total of 28 patients on each arm were considered in violation, primarily due to NCS metastases, prior or concomitant chemotherapy, concomitant severe non-malignant medical problems, or not having the baseline lesions measured within the proscribed time.

In the intent to treat population the patients had the following characteristics:

Characteristic	Topotecan n=107	CAV n=104
Female	43 %	32 %
male	61 %	71 %
Age < 40 years	1 %	0 %
Age ≥ 65 years	39 %	39 %
White	93.5 %	95.2 %

Non-white	6.5 %	4.8 %
Mean weight	74.2 kg	74.7 kg
Weight range	40-159	36-117
Mean Body Surface Area	1.83	1.84
BSA range	1.36-2.50	1.22-2.42
Limited Disease at entry	17 %	15 %
Prior radiation	62 %	56 %
Prior Surgery	14 %	28 %
Prior Cranial Irradiation	25 %	23 %
Performance Status < 2	77 %	81 %
Liver Metastases	40 %	40 %
Brain Metastases	11 %	23 %
First regimen with platinum plus etoposide	77 %	79 %
First Line Response as CR	44 %	41 %
Time to Progression, median	24.4 weeks	22.9 weeks
Maximum Lesion diameter > 5 cm	48 %	49 %

### 8.6 Efficacy Results

Note that all cited results were based on calculations from a SAS dataset that was converted using DBMSCopy software to DBF format. The DBF format files were then imported into MS Access 7.0 and analyzed using structured queries. Discrepancies between calculated values and the sponsor's reported values were discussed with the sponsor, until a mutually satisfactory agreement was reached on what the data results were.

Topotecan showed activity in patients with SCLC that was similar to that seen for the active control regimen of CAV in terms of the primary

endpoints of response rate and duration of response and the secondary endpoints of time to progression, time to response, and survival.

In both arms of the study, the majority of patients received the intended dose and were able to complete the study.

**Exposure to Intended Dose**

Parameter	Topotecan	CAV
Patients	107	104
Courses administered	422	343
Received intended dose	75 % of courses	78 % of courses
Courses delayed beyond 25 days	27 %	16 %
Courses reduced dose	38 %	29 %
Patients considered non-evaluable	15 %	19 %

**Results of Primary and Secondary Efficacy Objectives**

Parameter	Topotecan	CAV
Response rate-1 <sup>c</sup> Endpoint	24.3% (95 % CI 16.2-32.4)	18.3 % (95 % CI 10.8-25.7)
Complete Response (CR)	0%	1 %
Median Duration of Response, weeks-1 <sup>c</sup> Endpoint	14.4 (95% CI 13.1-18.0)	15.3 (95% CI 13.1-22.1)
Median Time to Progression, weeks-2 <sup>c</sup> Endpoint	13.3 (95% CI 11.4-16.4)	12.3 (95% CI 11.0-14.1)
Median Time to Response, weeks-2 <sup>c</sup> Endpoint	6.2 (95% CI 5.7-6.4)	6.1 (95% CI 5.6-6.9)
Median Survival, weeks-2 <sup>c</sup> Endpoint	25.0 (95% CI 20.6-29.6)	24.7 (95% CI 21.7-30.3)

The difference in response rates was 6 % (95 % CI 5-17%)

## Per cent Patients Stating Improvement on a Symptom Scale

(Questionnaire is available as Appendix B)

Symptom	Topotecan	CAV
Shortness of Breath	29 %	7 %
Cough	26 %	13 %
Chest Pain	26 %	17 %
Hemoptysis	27 %	36 %
Anorexia	29 %	18 %
Insomnia	33 %	19 %
Hoarseness	32 %	11 %
Fatigue	24 %	9 %
Interference with Daily Activity	28 %	11 %

The symptoms described and measured in the study are disease related, and reported improvements in the symptoms should be interpreted in view of the natural history of the disease, which is rapid progression. The consistent improvement in 8 of 9 scales that favored topotecan over control is notable, and could provide supporting evidence of patient benefit. Even though there was a clear trend to better symptom improvement on the topotecan arm, the ability to quantify subjective categories is limited. Unlike pain scales where a distance may be measured or dose of analgesia compared at various times, the rating of symptoms into broad categories is useful and suggestive, but is difficult to analyze in this case. The circumstances for asking the questions were not clearly stated, the interpretation of the categories in each country and culture may be different, and the assignment of ordinal values to the categories may not reflect the degree of change from one state to another. The time to worsening of symptoms was also calculated by the sponsor using Kaplan-Meier curves, and there was divergence in favor of topotecan for shortness of breath and anorexia, but the statistical significance is subject to the

same limitations as the symptom improvement scale. The effects of receiving therapy for 5 days rather than one day with the concomitant administration of symptomatic medications and the potential benefit of increased contact with a health care provider cannot be measured, but may factor into the subjective impressions relating to the questionnaire responses.

### 8.7 Adverse Events

The most significant toxicity was hematologic toxicity, which was anticipated. There were 69% of the topotecan patients who had at least one episode of Grade 4 neutropenia, 30% with Grade 4 leukopenia, 29% with Grade 4 thrombocytopenia and 14% with Grade 4 anemia. The comparable numbers for the CAV arm were 51 % for neutropenia, 42 % for leukopenia, 5% for thrombocytopenia, and 20 % for anemia.

The clinical manifestations were that 70% of patients in the topotecan arm received systemic antibiotics in 34% of courses. Suspected infection was present in 28 % of patients and 9% of courses. There were 5 cases of Grade 4 sepsis and 3 deaths. In the CAV arm the comparable numbers were 60% of patients received systemic antibiotics in 35% of courses. Suspected infection occurred in 25% of patients and 13% of courses. There were 4 cases of Grade 3 or 4 sepsis and 1 death. There was no trend to cumulative toxicity in either arm.

G-CSF was used in 6% of topotecan courses and 8.5 % of CAV courses. Platelet transfusions were given in 6% of topotecan courses and 0.6 % of CAV courses. Red cell transfusions were given in 24 % of topotecan courses and 12 % of CAV courses. These results are summarized in the following table.

**Hematologic Toxicity in Study 090**

Parameter	Topotecan	CAV
Patients with Grade 4 neutropenia	69 %	51 %
Patients with Grade 4 leukopenia	29 %	42 %
Patients with Grade 4 thrombocytopenia	29 %	5 %
Patients with Grade 4 anemia	14 %	20 %

Patients that received systemic antibiotics	70 %	60 %
Courses with systemic antibiotics	34 %	35 %
Patients with suspected infection	28 %	25 %
Courses with suspected infection	9 %	13 %
Patients with Grade 3 or 4 sepsis	5 %	4 %
Deaths with sepsis	3 %	1 %
Courses with G-CSF	6 %	8.5 %
Courses with platelet transfusion	6 %	0.6 %
Courses with red cell transfusion	24 %	12 %

### Non-hematologic toxicities

The major non-hematologic toxicities were related to the gastrointestinal system, fatigue, and alopecia. They were experienced by the majority of patients in the majority of courses for both study arms and were considered by the investigators to be possibly or definitely related to therapy. This is summarized in the table below.

Toxicities experienced by patients

Parameter	Topotecan	CAV
Patients with non-heme toxicity	93 %	94 %
Course with non-heme toxicity	89 %	88 %
Patients with therapy related	80 %	85 %

Courses with therapy related	76 %	76 %
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Toxicities that occurred in greater than 10% of courses are summarized in the following table:

**Toxicities that occurred in > 10% of courses**

Toxicity	Topotecan		CAV	
	Total	SAE	Total	SAE
Alopecia	37 %	-	23 %	-
Nausea	30 %	2.4 %	25 %	2.0 %
Fatigue	29 %	3.8 %	37 %	3.2 %
Coughing	22 %	0.9 %	18 %	0 %
Emesis	18 %	0.7 %	13 %	0.9 %
Dyspnea	18 %	4.8 %	18 %	7.9 %
Anorexia	16 %	0.9 %	20 %	1.7 %
Constipation	16 %	0.2 %	12 %	0 %
Asthenia	11 %	3.3 %		
Headache			12 %	0.6 %

If the toxicity is restricted to those considered to be possibly or definitely related to therapy, toxicities that occurred in greater than 10 % of courses are summarized in the following table:

**Toxicities that occurred in > 10% of courses thought to be therapy related**

Toxicity	Topotecan		CAV	
	Total	SAE	Total	SAE

Alopecia	37 %	--	23 %	-
Fatigue	26 %	2.4 %	32 %	2.6 %
Nausea	22 %	1.4 %	21 %	2.0 %
Emesis	13 %	0.5 %	10 %	0.9 %
Anorexia	11 %	0.2 %	15 %	1.2 %

There was no evidence of cumulative toxicity in either arm.

### 8.8 Deaths on Study

There were 14 patients (13.1%) who died within 30 days of receiving topotecan. Four patients died due to hematologic toxicity. Eight patients died due to progressive disease. The remaining patients' deaths were ascribed to other medical conditions. There were 8 patients (7.7 %) who died within 30 days of receiving CAV. Two patients died due to hematologic toxicity and four patients died due to progressive disease. The other two deaths were ascribed to other medical conditions.

### 8.9 Withdrawals Due to Adverse Experiences

A minority of patients in each arm withdrew due to adverse experiences, with approximately an equal number considered related to study drug. These are displayed in the following table.

Withdrawals due to adverse experiences

Parameter	Topotecan	CAV
Patients withdrawn subsequent to AE	9.3 %	12.5 %
Patients withdrawn subsequent to therapy related	8.4 %	8.6 %

AE		
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The nature of the adverse events were similar in both arms, being primarily due to hematologic toxicity in patients with advanced disease.

### 8.10 Summary Comments

In study 090, 211 patients with SCLC, of which 210 had a previous response to chemotherapy (one had stable disease) were randomized to receive either topotecan at 1.5 mg/m<sup>2</sup> daily x 5 every 21 days or a combination of cyclophosphamide, doxorubicin and vincristine. The patients were considered sensitive in that their disease had not progressed for at least 60 days following the last treatment. About 1/6 of the patients had limited disease at the time of entry, the rest had extensive disease. Both regimens were able to provide some measure of patient benefit as evidenced by tumor response and subjective reporting of palliation of disease related symptoms in a similar manner.

#### Results of Primary and Secondary Efficacy Objectives

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Response rate-1 <sup>o</sup> Endpoint	24.3% (95 % CI 16.2-32.4)	18.3 % (95 % CI 10.8-25.7)
Complete Response (CR)	0%	1 %
Median Duration of Response, weeks-1 <sup>o</sup> Endpoint	14.1 (95% CI 13.1-18.4)	15.3 (95% CI 13.1-22.1)
Median Time to Progression, weeks-2 <sup>o</sup> Endpoint	13.3 (95% CI 11.4-16.4)	12.3 (95% CI 11.0-14.1)
Median Time to Response, weeks-2 <sup>o</sup> Endpoint	6.2 (95% CI 5.7-6.4)	6.1 (95% CI 5.6-6.9)
Median Survival, weeks-2 <sup>o</sup> Endpoint	24.7 (95% CI 19.7-28.9)	24.4 (95% CI 21.3-29.3)

The toxicity was somewhat greater for those patients treated with topotecan, and consistent with current prescribing information. There was no evidence that the toxicity was cumulative, and in the majority of cases was manageable. There are clear risks associated with the administration of cytotoxic chemotherapy, particularly hematologic toxicity. On balance, the potential for patient benefit would justify the risk, although only a minority of patients had objective responses or subjective improvements in disease related symptoms while the vast majority experienced toxicity that was considered to be possibly or definitely related to therapy. The likelihood of achieving a tumor response, however, exceeds the likelihood of having a serious adverse event for patients that are categorized as sensitive, making the administration of cytotoxic chemotherapy, and in particular topotecan a reasonable therapeutic option for patients with SCLC that are considered sensitive to chemotherapy and who are candidates for second line therapy.

### 9.0 Non-Comparator Supportive Studies

There were three supportive open label phase II studies that enrolled patients that were both sensitive and refractory. These were designated studies 014, 053 and 092. There was a difference in the definition of sensitive patient between these studies and 090 in that to be considered sensitive, a patient should not have progressed within 90 days (in contrast to 60 days) since the last chemotherapy.

Study 014 was a multicenter non-comparator study conducted in Europe by the EORTC. 101 patients were enrolled, of which 45 were considered sensitive. The primary endpoint in this study was response. The responses were as follows:

Study 014 Response Data

Population	CR	PR	Total (95% CI)
All patients n = 101	6.9 %	10.9 %	17.8 % (10.36-25.29)
Sensitive Patients n = 45	11.1 %	20 %	31.1 % (18.17-46.65)
Refractory Patients n = 55	3.6 %	3.6 %	7.3 % (2.02-17.59)