

Study 014 Time to Event Endpoints in Weeks (95% CI)

Endpoint	Refractory	Sensitive	Total
Time to Resp.	5.6 (1.6-10.4)	7.0 (5.4-9.4)	6.3 (5.6-9.1)
Dur. of Resp.	30.7 (20.6-47.1)	20.7 (13.3-38.6)	30.7 (17.0-38.6)
Time to Prog.	8.3 (6.4-12.3)	17.7 (12.1-21.3)	57.9 (8.4-15.3)

Study 053 was a multicenter non-comparator study conducted in North America. A symptom questionnaire was included in the study design. 99 patients were enrolled, 52 of which were sensitive. The primary endpoint in this study was survival. The response data is as follows:

Study 053 Response Data

Population	CR	PR	Total (95% CI)
All patients n = 99	2 %	7.1 %	9.1 % (4.2-16.6)
Sensitive Patients n = 52	3.8 %	11.5 %	15.4 % (6.9-28.1)
Refractory Patients n = 47	0	2.1 %	2.1 % (0.05-11.3)

Not all patients had complete evaluations for symptom data, but of the 65 patients who were evaluable, there were 449 symptom assessments made. About 20% of the assessments described an improvement over baseline, 60% stability and 20 % were worse. There was no detectable difference between responders and non-responders.

Study 053 Time to Event Endpoints in Weeks (95% CI)

Endpoint	Refractory	Sensitive	Total
Time to Resp.	5.4	6.1 (5.1-7.4)	6.1 (5.4-6.6)
Dur. of Resp.	24.9	23.1 (14.6-31.3)	23.7 (21.7-31.3)
Time to Prog.	9.6 (6.1-11.7)	13.1 (11.0-18.1)	11.3 (9.3-13.1)

Study 092 was a multicenter non-comparator study conducted in Europe. 119 patients enrolled of which 71 were sensitive. The primary endpoint in this study was response. The response data is as follows:

Study 092 Response Data

Population	CR	PR	Total (95% CI)
All patients n = 119	2.5 %	5.0 %	7.6 % (2.81-12.31)
Sensitive Patients n = 71	4.2 %	7.0 %	11.3 % (5.0-21.0)
Refractory Patients n = 48	0	2.1 %	2.1 % (0.05-11.07)

Study 092 Time to Event Endpoints in Weeks (95% CI)

Endpoint	Refractory	Sensitive	Total
Time to Resp.	5.7	5.6 (3.9-6.6)	5.7 (5.4-6.6)
Dur. of Resp.	22.0	21.0 (12.6-36.0)	22.0 (17.1-23.3)
Time to Prog.	6.4 (6.0-8.1)	10.3 (7.6-11.9)	8.1 (7.0-10.0)

The toxicity data was similar for all three studies with the major toxicities being hematologic and the major non-hematologic toxicity being gastrointestinal.

10.0 Integrated Summary of Efficacy

Four hundred and twenty-six patients with Small Cell Lung Cancer were enrolled in four clinical studies to receive topotecan. Sixty of these patients were classified as responders for an overall response rate of 14.1 %. Fifty four (90 %) of these patients were classified prior to study entry as sensitive. In this group there were 10 CR and 44 PR. The data are summarized in the following table. Sensitivity data was missing for one patient

. This patient's best response was progression.

Response in all SCLC Patients

Population	CR n (%)	PR n (%)	Total n (% 95 % CI)
All patients n = 426	12 (2.8%)	48 (11.3 %)	60 (14.1 % CI 11.2-17.9 %)
Sensitive Patients n = 275 (64.5% of total)	10 (3.6 %)	44 (16 %)	54 (19.6 % CI 15.6-25.1 %)
Refractory Patients n = 150 (35.2 % of total)	2 (1.3 %)	4 (2.6 %)	6 (4 % CI 0.9-7.1 %)

Time to Event Endpoints in Weeks (95% CI)

Endpoint	Refractory	Sensitive	Total
Time to Resp.	5.7 (5.4-5.7)	6.4 (5.7-6.6)	6.1 (5.7-6.6)
Dur. of Resp.	24.9 (20.6-47.1)	17.1 (14.1-22.9)	18.4 (14.6-22.9)
Time to Prog.	7.7 (6.3-9.6)	12.6 (11.3-14.3)	11.1 (9.6-11.9)
Survival	14.0 (11.3-17.4)	24.9 (21.7-27.6)	20.7 (18.1-23.6)

The integrated data support the observation that there is antitumor activity of topotecan in SCLC. There is also a marked difference in response rate, time to progression, and survival between patients who are classified as sensitive and those that are classified as refractory. The overall response rate in any population will therefore reflect the percentage of patients who are classified as sensitive.

11.0 Integrated Summary of Safety

A total of 426 patients with relapsed or refractory SCLC received 1641 courses of topotecan at an intended dose of 1.5 mg/m²/day. The median dose intensity was 2.31 mg/m²/day, with a target of 2.5 mg/m²/day. There were dose reductions in 13% of the courses following course 1 and dose delays of greater than 7 days in 8.8 % of courses. The major toxicities were hematologic, as summarized in the following table:

Severe Hematologic toxicity in SCLC Patients

Parameter	Patients n= 426	Courses n=1641
Leukopenia	31.4 %	12.3 %
Neutropenia	74.3 %	39.1 %
Thrombocytopenia	28.1 %	10.6 %

Anemia	33.4 %	13.1 %
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Febrile Neutropenia

Parameter	Patients n= 426	Courses n=1641
Fever \geq Grade 2 or Febrile Neutropenia	8.2 %	3.4 %
Fever \geq Grade 2 or Febrile Neutropenia	4.0 %	1.6 %
Infection \geq Grade 2 with Grade 4 Neutropenia	12.9 %	4.5 %
Sepsis	3.8 %	1.2 %

Most Frequent Non-Hematologic Serious Adverse Events in SCLC Patients

Toxicity	%
Dyspnea	4.7
Pneumonia	4.2
Asthenia	3.1
Convulsions	2.1
Abdominal Pain	1.6
Diarrhea	1.4
Emesis	1.4
Pleural Effusion	1.2
Dehydration	0.7
Nausea	0.5

Adverse Events Leading to Withdrawal in SCLC Patients

Toxicity	%
Sepsis	2.1
Thrombocytopenia	1.6
Asthenia	1.4
Neutropenia	1.4
Pneumonia	1.2

Deaths

Treatment related deaths were reported in 5.2 % of patients and deaths within 30 days of treatment in 16.4 % of patients. 3.1 % of patients died

due to hematologic toxicity. In the total study population 80.5 % died due to progressive disease.

The toxicity profile, tolerance, withdrawals and deaths are manifestations of the inherent risks of receiving cytotoxic chemotherapy, and are consistent with previous experience with topotecan. The drug related death rate of 5.2 % is higher than that reported for patients with ovarian carcinoma (1.1%) in a population of comparable size. There are no apparent reasons related to the disease process or the mixed gender population that offer an explanation, but it is an observation that should not be overlooked and must be followed.

12.0 Summary of Advisory Committee Meeting - June 2, 1998

The following questions were submitted to the Oncology Drugs Advisory Committee prior to the meeting on June 2, 1998. Following presentations by the sponsor and by the Division, the Committee discussed and voted on responses to the questions. The responses follow the questions.

1. Study 090 does not provide evidence of a survival or time to progression benefit of Topotecan versus CAV, and it would be hard to document a clear survival effect of CAV in this setting. The evidence for benefit thus consists of a response rate and response duration. Does the response rate of 24% in this setting with a duration of response of 14 weeks, as presented for Trial 090, provide substantial evidence of efficacy in the second line treatment of patients with sensitive SCLC?

YES - 8

No - 1

2. Do the data on improvement in the disease-related symptom scale in Study 090 provide supportive evidence for the efficacy of Hycamtin (topotecan HCl) in the second-line treatment of patients with sensitive SCLC?

YES - 7

No - 1

Abstain - 1

3. Given the incidence and severity of hematologic toxicity outlined above, and considering the efficacy data outlined in the first two questions, is Trial 090 a well-controlled trial demonstrating the safety and efficacy of topotecan in the second-line treatment of sensitive SCLC?

YES - 6

No - 3

4. Should Hycamtin (topotecan HCl) be approved for second-line treatment of sensitive small cell lung cancer?

YES - 7

No - 2

Discussion: The Committee indicated that Hycamtin appears to provide an alternative to CAV therapy, and that the disease-related symptoms do show improvement. Adverse events are frequent, and there is concern that in using the 60 day relapse criterion for defining "sensitive" disease, more patients would be exposed to the toxicity without the possibility of benefit.

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13.0 General Summary with Recommended Regulatory Action

Topotecan given as an intravenous infusion at a dose of 1.5 mg/m²/day daily times 5 on a 21 day cycle has antitumor activity in SCLC. In a randomized controlled multicenter study it was at least as effective as a standard regimen of cyclophosphamide, doxorubicin, and vincristine (CAV) as measured by response rate, duration of response, time to progression and survival.

Topotecan monotherapy has demonstrated a response rate of 24.3% (95% CI 16.2-32.4) in the patients with sensitive disease treated in the Phase III study and a composite response rate of 19.6% (CI 15.6-25.1%) in sensitive patients from all trials (n=275). The median duration of response was 14.4 weeks (95% CI 13.1 to 18.0) in the Phase III study and 17.1 weeks (95% CI 14.1-22.9) for all patients with sensitive disease. The response rate is similar to that of the currently used standard regimen of CAV; the point estimate for response is better than CAV by 6% and the 95% confidence interval of the difference suggests it could be, at worst, 6% lower than CAV. In the 3 supporting studies, results from the same efficacy parameters were consistent. The dataset is enhanced by the size of the study population and the adequate power to make the statistical calculations. The following table summarizes the data from the comparative study.

Parameter	Topotecan(n=107)	CAV (n=104)
Overall Response Rate	24.3%	18.3%
Difference with 95% Confidence Interval	6%(-5.9 to 18%)	
Median Response Duration (weeks)	14.4 (13.1 to 18.0)	15.3 (13.1 to 23.1)
hazard-ratio (<i>Hycamtin</i> : CAV) with p-value	1.421 (0.73 to 2.76) p=0.300	
Median Time to Progression (weeks)	13.3 (11.4 to 16.4)	12.3 (11.0 to 4.1)
hazard-ratio (<i>Hycamtin</i> : CAV) with p-value	0.918 (0.69 to 1.22) p=0.552	
Median Survival (weeks)	25.0 (20.6 to 29.6)	24.7 (21.7 to 30.3)
hazard-ratio (<i>Hycamtin</i> : CAV) with p-value	1.039 (0.78 to 1.39) p=0.795	

N.B. The calculation for duration of response was based on the interval between first response and time to progression

The response rate is consistent with reported response rates for other regimens as second line therapy for SCLC. The Oncology Drugs Advisory Committee recommended at the meeting on June 2, 1998 that response rate and duration in this malignancy, which has a natural history of rapid

growth and patient demise in the setting of recurrent or refractory disease, provides evidence of efficacy.

The evidence supporting patient benefit for topotecan in this particular disease is not just response data but a combination of time to progression data, survival data, and symptom data.

Prior to the advent of chemotherapy for small cell lung cancer, placebo controlled studies to examine the effects of surgery or radiation, as reviewed by Zelen in 1973, showed in the first line setting a median survival of 12 weeks for patients with limited (one hemithorax) disease and 5 weeks for patients with extensive disease. Patients that relapse following a response to initial chemotherapy who do not receive further therapy, as described by Faiery et al., Tummerello et al., and others have a median survival of 6 to 10 weeks. As demonstrated for topotecan in the data with this submission, median survival for all patients receiving second line therapy was 20.7 weeks (95 % CI 18.1-23.6) and for patients with sensitive disease median survival was 24.9 weeks (95 % CI 21.7-27.6).

The survival benefit extended beyond the median values. The results of the Phase III data for patients treated with topotecan show a one year survival rate of 14 % (95 % CI 7.5-21). Pooled analysis of the three phase II studies of sensitive patients treated with topotecan showed a one year survival of 18% (95% CI 12-24).

The last point to support patient benefit is the improvement in scores on 9 scales of disease related symptoms seen in the Phase III study. On each scale between 1/5 to 1/3 of the patients who received topotecan reported improvement. The per cent of patients reporting improvement was numerically superior to the control arm of CAV on 8 of the 9 scales. Limitations on the rating instrument and methodology used for data gathering preclude formal statistical comparison. In addition, there was a delay based on Kaplan-Meier analysis in worsening of the scores on the scales for anorexia and shortness of breath in patients who received topotecan compared to the control arm of CAV.

The toxicity profile for topotecan in the small cell lung cancer studies was similar to that seen with cytotoxic chemotherapy in general and with previously published information and the current approved package insert. The major toxicities are hematologic, and can lead to severe, but temporary, marrow suppression with a 5% risk of death.

A patient with a classification of sensitive disease is far more likely to have a tumor response to topotecan (19.6 % (95% CI 15.6-25.1)) than a patient with refractory disease (4 % (95 %CI 0.9-7.1 %)). Overall the probability of having a drug related death (5%) is about the same as having a response for a patient that does not have sensitive disease; therefore,

growth and patient demise in the setting of recurrent or refractory disease, provides evidence of efficacy, if supported by other evidence.

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topotecan should not be recommended for patients who are not classified as having sensitive disease.

With tens of thousands of patients diagnosed every year with SCLC who have a high likelihood of having a relapse following initial treatment, the availability of another therapeutic option could positively impact on thousands of people annually. As experience is gained with the use of topotecan in addition to further experience with other available agents, it may be possible to attain better patient selection for each of the alternative therapies to minimize exposure to patients unlikely to gain any benefit, and therefore more likely to only experience toxicity, and to maximize exposure to those patients more likely to benefit from a particular regimen.

In summary, the natural history of rapid progression of relapsed sensitive small cell lung cancer almost universally leads to symptomatic deterioration and short median survival. Therapy that can alleviate the symptoms and prolong survival will have patient benefit. Tumor response rate for this particular disease entity is generally regarded as an appropriate surrogate for increased survival due to the natural history and the demonstration, as reviewed by Elias, Ettinger, Johnson, Sandler, and others, that agents that improve response rate tend to improve time to progression and survival. Whether response rate and response duration alone could provide adequate evidence of patient benefit and hence provide the sole basis for approval in this particular disease is a point which could be debated; however, in this NDA we have in addition time to progression data, survival data and symptom data which support response data and demonstrate clinical benefit. Topotecan was shown in a randomized controlled study with adequate power to provide benefits that were similar to or exceeded those provided by an active control regimen, CAV. Both regimens achieved measures of response, time to progression, median survival and had a positive impact on disease related symptoms that were consistent with other published studies and compared favorably with the natural history. Three additional studies with adequate numbers of patients with small cell lung cancer treated with topotecan provided statistical confirmatory support for the findings of the randomized study. For these reasons, approval for intravenous topotecan infusions on a daily x 5 schedule at a dose of 1.5 mg/m² for second line therapy of patients with small cell lung cancer who have sensitive disease is recommended.

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Bibliography

1. Aisner, J. Extensive-disease small-cell lung cancer: the thrill of victory; the agony of defeat. *J Clin Oncol* 14:658, 1996.
2. Beith, J.M., Clarke, S.J., Woods, R.L., et al. Long-term follow-up of a randomised trial of combined chemoradiotherapy induction treatment, with and without maintenance chemotherapy in patients with small cell carcinoma of the lung. *Eur J Cancer* 32A:438, 1996.
3. Blanke, C.D., Johnson, D.H. Treatment of small cell lung cancer. *Semin Thorac Cardiovasc Surg* 9:101, 1997.
4. Bunn, P.A., Jr., Carney, D.N. Overview of chemotherapy for small cell lung cancer. *Semin Oncol* 24:S7, 1997.
5. Bunn, P.A., Jr. Combination paclitaxel and platinum in the treatment of lung cancer: US experience. *Semin Oncol* 23:9, 1996.
6. Bunn, P.A., Jr. The North American experience with paclitaxel combined with cisplatin or carboplatin in lung cancer. *Semin Oncol* 23:18, 1996.
7. Carney, D.N. Carboplatin/etoposide combination chemotherapy in the treatment of poor prognosis patients with small cell lung cancer. *Lung Cancer* 12 Suppl 3:S77, 1995.
8. Darling, G.E. Staging of the patient with small cell lung cancer. *Chest Surg Clin N Am* 7:81, 1997.
9. Elias, A. Dose-intensive therapy for small cell lung cancer. *Chest* 107:261S, 1995.
10. Elias, A. Small cell lung cancer: state-of-the-art therapy in 1996. *Chest* 112:251S, 1997.
11. Elias, A. Dose-intensive therapy in small cell lung cancer. *Chest* 113:101S, 1998.
12. Ettinger, D.S. Ifosfamide in the treatment of small cell lung cancer. *Semin Oncol* 23:2, 1996.
13. Ettinger, D.S. New drugs for treating small cell lung cancer. *Lung Cancer* 12 Suppl 3:S53, 1995.
14. Ettinger, D.S. The place of ifosfamide in chemotherapy of small cell lung cancer: the Eastern Cooperative Oncology Group experience and a selected literature update. *Semin Oncol* 22:23, 1995.
15. Fairey AE, Baughan C, Williams CJ. Local irradiation for recurrence after initial chemotherapy in small-cell carcinoma of the lung (SCCL) (Meeting abstract). *Br J Cancer*; 65(Suppl 16):11 1992
16. Feigal, E.G., Cheson, B.D., Nelson, A.P. Clinical trials referral resource. *Clinical trials in lung cancer. Oncology (Huntingt)* 11:1686, 1997.
17. Ghaemmaghami, M., Jett, J.R. New agents in the treatment of small cell lung cancer. *Chest* 113:86S, 1998.
18. Giaccone, G. New drugs for the management of lung cancer. *Br J Hosp Med* 55:634, 1996.
19. Ihde, D., Souhami, B., Comis, R., et al. Small cell lung cancer. *Lung Cancer* 17 Suppl 1:S19, 1997.
20. Ihde, D.C. Small cell lung cancer. State-of-the-art therapy 1994. *Chest* 107:243S, 1995.
21. Johnson, B.E., Cortazar, P., Chute, J.P. Second lung cancers in patients successfully treated for lung cancer. *Semin Oncol* 24:492, 1997.

22. Johnson, B.E., Kelley, M.J. Biology of small cell lung cancer. *Lung Cancer* 12 Suppl 3:S5, 1995.
23. Johnson, D.H. Future directions in the management of small cell lung cancer. *Lung Cancer* 12 Suppl 3:S71, 1995.
24. Johnson, D.H. Small cell lung cancer in the elderly patient. *Semin Oncol* 24:484, 1997.
25. Kristensen, C.A., Jensen, P.B., Poulsen, H.S., Hansen, H.H. Small cell lung cancer: biological and therapeutic aspects. *Crit Rev Oncol Hematol* 22:27, 1996.
26. Loehrer, P.J., Sr. The role of ifosfamide in small cell lung cancer. *Semin Oncol* 23:40, 1996.
27. Lorigan, P., Lee, S.M., Betticher, D., et al. Chemotherapy with vincristine/ifosfamide/carboplatin/etoposide in small cell lung cancer. *Semin Oncol* 22:32, 1995.
28. Marchioli, C.C., Graziano, S.L. Paraneoplastic syndromes associated with small cell lung cancer. *Chest Surg Clin N Am* 7:65, 1997.
29. Midthun, D.E., Jett, J.R. Chemotherapy for advanced lung cancer. When to expect a response. *Postgrad Med* 101:187, 1997.
30. Murray, N. Importance of dose and dose intensity in the treatment of small-cell lung cancer. *Cancer Chemother Pharmacol* 40 Suppl:S58, 1997.
31. Murray, N. Treatment of small cell lung cancer: the state of the art. *Lung Cancer* 17 Suppl 1:S75, 1997.
32. Niklinski, J., Furman, M. Clinical tumour markers in lung cancer. *Eur J Cancer Prev* 4:129, 1995.
33. Perry, M.C. Future directions in the therapy of small cell lung cancer. *Chest Surg Clin N Am* 7:183, 1997.
34. Ranson, M., Thatcher, N. The importance of dose and schedule in chemotherapy for small cell lung cancer. *Anticancer Drugs* 6 Suppl 5:53, 1995.
35. Saka, H., Shimokata, K. Chemotherapy for small-cell lung cancer: more is not better. *Cancer Chemother Pharmacol* 40 Suppl:S107, 1997.
36. Salgia, R., Skarin, A.T. Molecular abnormalities in lung cancer. *J Clin Oncol* 16:1207, 1998.
37. Sandler, A.B. Current management of small cell lung cancer. *Semin Oncol* 24:463, 1997.
38. Sandler, A.B. Etoposide plus ifosfamide plus cisplatin in the treatment of small cell lung cancer. *Semin Oncol* 25:38, 1998.
39. Schiller, J.H., Cleary, J., Johnson, D. Lung cancer: review of the ECOG experience. Eastern Cooperative Oncology Group. *Oncology* 54:353, 1997.
40. Schiller, J.H. Topotecan in small cell lung cancer. *Semin Oncol* 24:S20, 1997.
41. Shepherd, F.A. The role of chemotherapy in the treatment of small cell lung cancer. *Chest Surg Clin N Am* 7:113, 1997.
42. Sing, A., Freudenberg, N., Kortsik, C., et al. Comparison of the sensitivity of sputum and brush cytology in the diagnosis of lung carcinomas. *Acta Cytol* 41:399, 1997.
43. Spiro, S.G. Clinical trials in lung cancer: nihilism versus enthusiasm [see comments]. *Thorax* 52:598, 1997.
44. Splinter, T.A. Introduction to the treatment of lung cancer. *Semin Oncol* 24:S12, 1997.

45. Testa, J.R., Liu, Z., Feder, M., et al. Advances in the analysis of chromosome alterations in human lung carcinomas. *Cancer Genet Cytogenet* 95:20, 1997.
46. Thomas, A.L., Woll, P.J. Cytotoxic dose-response relationships in small cell lung cancer. *Cancer Treat Rev* 23:191, 1997.
47. Tummarello D, Guidi F, Torresi U, Dazzi C, Cellerino. Teniposide (Vm26) As Second-Line Treatment For Small Cell Lung *Anticancer Res*; 10(2A):397-9 1990
48. Turrisi, A.T.r. Concurrent chemoradiotherapy for limited small-cell lung cancer. *Oncology (Huntingt)* 11:31, 1997.
49. Vuitch, F., Sekido, Y., Fong, K., et al. Neuroendocrine tumors of the lung. Pathology and molecular biology. *Chest Surg Clin N Am* 7:21, 1997.
50. Wagner, H., Jr. Radiation therapy in the management of limited small cell lung cancer: when, where, and how much? *Chest* 113:92S, 1998.
51. Warren, W.H., Gould, V.E. Differential diagnosis of small cell neuroendocrine carcinoma of the lung. *Chest Surg Clin N Am* 7:49, 1997.
52. Williams, C.L. Basic science of small cell lung cancer. *Chest Surg Clin N Am* 7:1, 1997.
53. Zelen, M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep (Part 3)* 4:31, 1973