Below is a subgroup analysis by TTP from the end of first line chemotherapy. Topotecan appears to have more effect in patients with > 60 days TTP from the end of first line chemotherapy. In contrast to response rates, survival on the topotecan arm is trending in favor of the more "sensitive" group (> 60 days).

Table 30 Summary of survival, by time to progression from end of first line chemotherapy: ITT population

Survival (Weeks)	Treatment Group	
	ASC alone N=70	ASC + OT N=71
Time to progression ≤ 60 days	20	22
Median (95% C.I.)	13.2 (7.0, 21.0)	23.3 (10.7, 30.9)
Observed events	20 (100%)	19 (86.4%)
Censored events	0	3 (13.6%)
Log-rank p-value	0.0357	
Time to progression > 60 days	50	49
Median (95% C.I.)	14.4 (8.0, 21.1)	27.7 (17.6, 34.4)
Observed events	47 (94.0%)	44 (89.8%)
Censored events	3 (6.0%)	5 (10.2%)
Log-rank p-value	0.0975	

Data source: Table 13.1.1.6

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ON ORIGINAL

6.4.1 Clinical Microbiology

Not Applicable.

6.4.2 Sponsor's Efficacy Conclusions: Study #478

- The primary efficacy variable was overall survival. For the intent-to-treat population, median survival in the ASC alone group was 13.9 weeks compared with 25.9 weeks in ASC + OT group. The difference between the groups in overall survival was clinically and statistically significant (log-rank p=0.0104).
- For patients in the ASC + OT group, a response rate of 7.0% was recorded and stable disease was achieved in 44% of patients. Median time to progression for these patients was 16.3 weeks. In the ASC alone group 18 patients (25.7%) were alive after 6 months, compared to 34 patients (48.9 %) in the ASC + OT group.
- The primary objective of the study has been met by demonstrating that second-line oral topotecan extends survival in patients with relapsed resistant SCLC by a clinically and statistically significant margin.

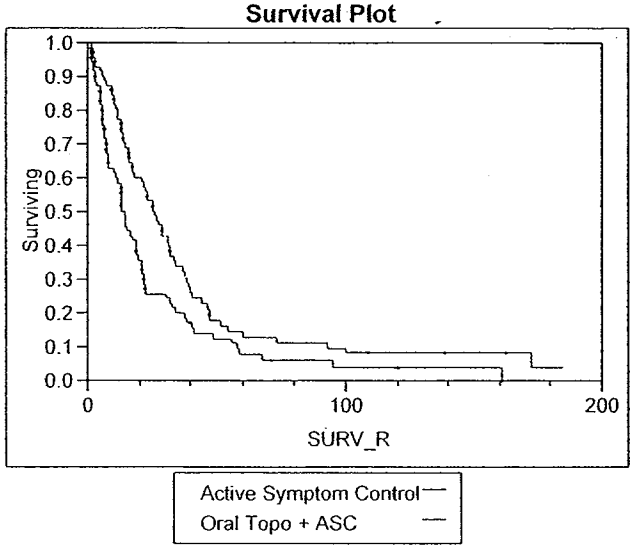
6.5 FDA's Assessment of Efficacy and Conduct of Study #478

FDA's Survival Analysis: General

The FDA analysis is based on the datasets submitted by the Sponsor. The FDA did not adjust any of the datasets for these analyses. Challenges in the stratification factors are described later in the review.

Oral topotecan improved the survival patients with small cell lung cancer (SCLC) (who had a prior complete or partial response to 1st-line chemotherapy and who > 45 days from the cessation of 1st-line chemotherapy). The median survival for oral topotecan was 25.9 weeks and 13.3 weeks for best supportive care; the log-rank p-value was 0.0104. These results match the Sponsor's presentation of the results.

Product-Limit Survival Fit
Survival Plot



Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
Active Symptom Control	13.3	10.3	18.6	6.3	30.4
Oral Topo + ASC	25.9	17.6	31.6	13.1	40.6
Combined	18.6	14.4	22.6	9.3	37.7

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.5644	1	0.0104
Wilcoxon	9.5318	1	0.0020

FDA's Survival Analysis: Stratification factors
Oral topotecan showed a consistent improvement in survival across the stratification factors (table below). The median survivals for the better prognostic groups were favored on the oral topotecan arm in comparison to the poor prognostic groups.

stratification factor	oral topotecan median survival weeks	best supportive care median survival weeks	log-rank p-value
Cessation from prior chemotherapy (days) $\leq$ 60	23.3	13.3	0.0357

stratification factor	oral topotecan median survival weeks	best supportive care median survival weeks	log-rank p-value
> 60	27.7	14.4	0.0975
Liver metastases			
absence	30.9	14.4	0.0071
presence	13.4	8	0.1674
Performance status (ECOG)			
0/1	29	18.6	0.0968
2	20.9	7.7	0.0146
Gender			
Female	38.7	14.4	0.0173
male	23.3	13.3	0.2702

FDA's Survival Analysis: age, stage, and cessation from prior chemotherapy (days) ($\leq$ 90 or > 90)

Oral topotecan showed a consistent improvement in survival with regard to age, stage of SCLC, and cessation from prior chemotherapy (days) ($\leq$ 90 or > 90) (table below).

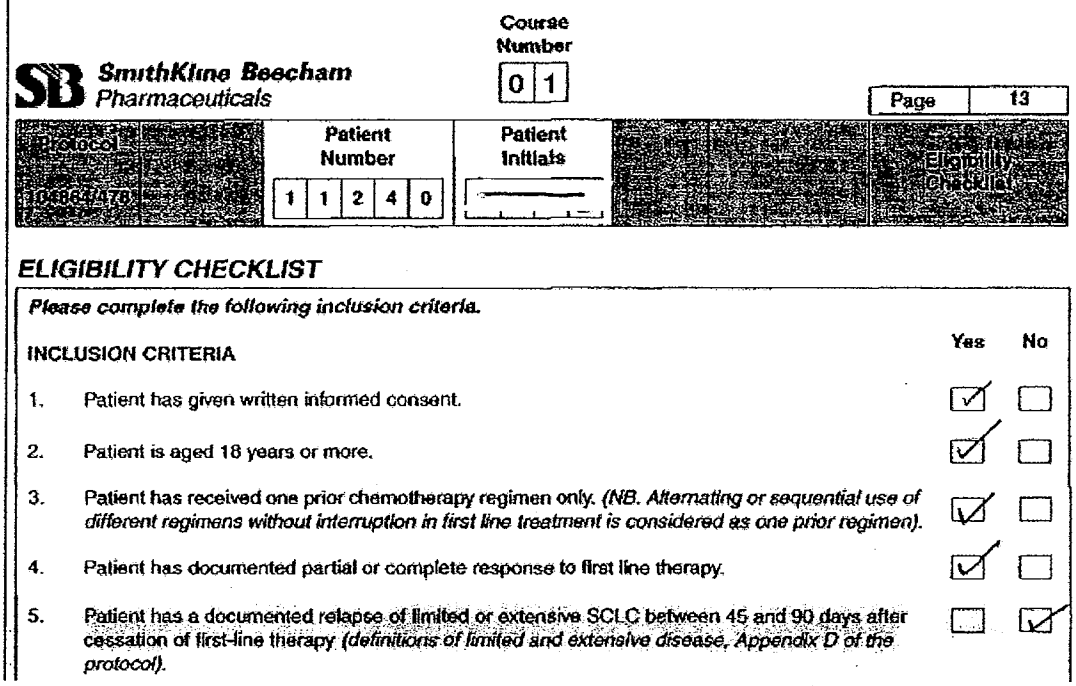
factor	oral topotecan median survival weeks	best supportive care median survival weeks	log-rank p-value
Age			
< 65 years	25.7	13.1	0.0796
$\geq$ 65 years	29.3	16.9	0.0733
Stage			
Limited	30.9	21	0.1412
Extensive	23.3	13.1	0.012
Cessation from prior chemotherapy (days)			
$\leq$ 90	22.7	14.4	0.0745
> 90	31.6	14.4	0.0.064

Eligibility: the number of days after cessation of first-line therapy

A search of the Sponsor's "Eligibility Check List" database55 for criterion #5, i.e., Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy, revealed that there three patients indicated with "No." The cases are in the table below. All the cases were from the best supportive care arm.

Patient #	N=no	Inclusion criterion #	Arm of study
478.046.11240	N	IN05	Active Symptom Control
478.072.11221	N	IN05	Active Symptom Control
478.094.85469	N	IN05	Active Symptom Control

Below is a portion of the CRF for patient #46.11240, showing the check-off "No."



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Protocol: 104864/476

Patient Number: 1 1 2 4 0

Patient Initials:

Eligibility Checklist

b(6)

ELIGIBILITY CHECKLIST

Please complete the following inclusion criteria.

INCLUSION CRITERIA		Yes	No
1.	Patient has given written informed consent.	☑	☐
2.	Patient is aged 18 years or more.	☑	☐
3.	Patient has received one prior chemotherapy regimen only. *(NB. Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).*	☑	☐
4.	Patient has documented partial or complete response to first line therapy.	☑	☐
5.	Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy *(definitions of limited and extensive disease, Appendix D of the protocol).*	☐	☑

On the bottom of the CRF is the following:

Do not admit the patient to this study if any "No" box has been marked.

55 Database elig.xpt received from Sponsor 10/2/2007

Below is a portion of the CRF for patient #72.11221 showing the check-off changed from "Yes" to "No."

On the bottom of the CRF is the following:

Do not admit the patient to this study if any "No" box has been marked.

Δ alp 00 635460256
Δ 26/10/04

Below is a portion of the CRF for patient #94.85469 showing the check-off changed from "Yes" to "No."

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Protocol	Patient Number	Patient Initials	Eligibility Checklist
104864/478	8 5 4 6 9		

b(6)

ELIGIBILITY CHECKLIST

Please complete the following inclusion criteria.

INCLUSION CRITERIA		Yes	No
1.	Patient has given written informed consent.	☑	☐
2.	Patient is aged 18 years or more.	☑	☐
3.	Patient has received one prior chemotherapy regimen only. *(NB. Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).*	☑	☐
4.	Patient has documented partial or complete response to first line therapy.	☑	☐
5.	Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy *(definitions of limited and extensive disease, Appendix D of the protocol).*	☑ 23.05.03	☐

On the bottom of the CRF is the following:

Do not admit the patient to this study if any "No" box has been marked.

According to protocol and the CRF, these patients were not eligible for study #478.

Unless these patients did not have relapsed SCLC, it appears that the disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy. If this is the criterion, searching the Jhoylink system database and the GSK derivation of TTP after cessation of first-line therapy finds more patients, who did not meet Eligibility criterion #5. There are eight patients (including the three describe above)—four from each arm.

Patient #	GSK Clintrial Data: Time to Progression from end of prior chemotherapy (days)		Comments
478.027.85397	34	Topotecan	
478.046.11240	14	Obs alone	Eligibility Check List" database for criterion #5
478.072.11197	39	Topotecan	
478.072.11221	43	Obs alone	Eligibility Check List" database for criterion #5
478.072.11222	43	Topotecan	
478.072.85487	16	Obs alone	
478.094.11180	44	Topotecan	
478.094.85469	43	Obs alone	Eligibility Check List" database for criterion #5

Excluding the three patients' CRF Eligibility CheckLists shown above, there was only one other patient with a discrepancy on the Eligibility CheckList page.

Below is a portion of the CRF for patient #27.85397, showing the check-off "Yes" but a number of days which was below the eligibility criterion.

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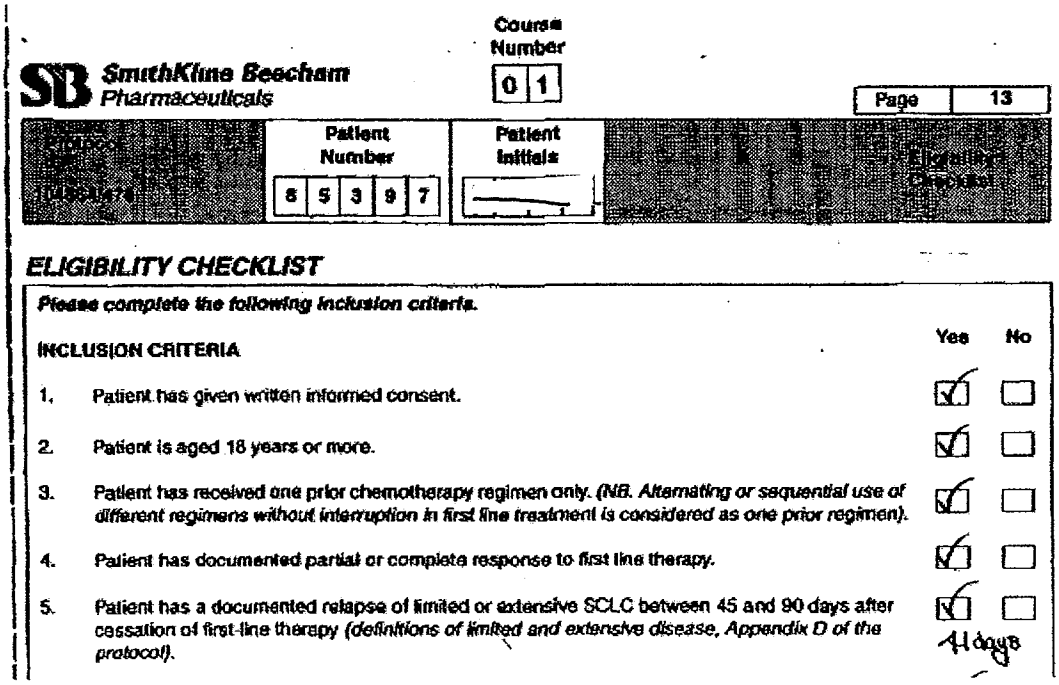

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Protocol No.	Patient Number	Patient Initials	Eligibility Checklist
[illegible]	8 5 3 9 7		

b(6)

ELIGIBILITY CHECKLIST

Please complete the following inclusion criteria.

INCLUSION CRITERIA	Yes	No
1. Patient has given written informed consent.	☑	☐
2. Patient is aged 18 years or more.	☑	☐
3. Patient has received one prior chemotherapy regimen only. *(NB. Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).*	☑	☐
4. Patient has documented partial or complete response to first line therapy.	☑	☐
5. Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy *(definitions of limited and extensive disease, Appendix D of the protocol).*	☑	☐

41 days

On the bottom of the CRF is the following:

Do not admit the patient to this study if any "No" box has been marked.

According to protocol and the CRF, these patients were not eligible for study #478.

"INCORRECT" CRFs: Eligibility Checklist

Amendment 2 changed Eligibility criterion #5 from relapse...between 45 and 90 days after cessation of first-line therapy to relapse...≥ 45 days after cessation of first-line therapy. The CRF was not amended. All the patients, accrued whose relapse was > 90 days after cessation of first-line therapy had "yes" checked-off as shown in the first example. There were 26 best supportive care patients, whose time after cessation of first-line therapy to relapse was greater than 90 days (range: 91-665 days) that the investigators entered into the Jhoylink system for registration and randomization. There were 31 oral topotecan patients, whose time after cessation of first-line therapy to relapse was greater than 90 days (range: 91-530 days) that the investigators entered into the Jhoylink system for registration and randomization. However, there were 14 patients who had notations on the CRF (7 best supportive care [whose time after cessation of first-line therapy to relapse was greater than 90 days range was 95-439 days]; 7 oral topotecan [whose time after cessation of first-line therapy to relapse was greater than 90 days range was 98-246 days]). These notations noted, amended, or corrected the criterion as shown in the other examples below. Thirteen of the 14 patients with notations on Eligility criterion #5 of the CRF were from the United Kingdom; the other patient was from Slovakia (a best supportive care patient). For the CRFs with dates associated with changes, the notations appear to have occurred about 5 days to 7 weeks after the randomizations; these notations appear to be associated with monitoring visits and changes entered by the monitor.56

In these cases, the protocol was correct and the patients were eligible but the CRF was incorrect.

Examples:

The number from Jhoylink registration and randomization system is used in the examples because this is what the Sponsor claims the investigator entered into the system.

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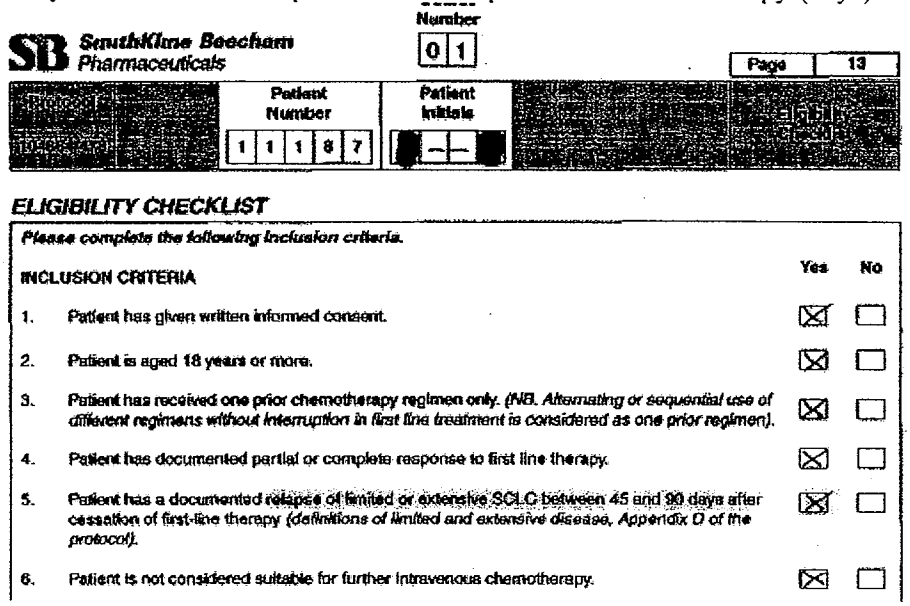
56 Amendment 0009, dated 8/6/2007; response by GSK to DSI request

The box is checked "yes." This applies to 43 cases

- Jhoylink duration of response from completion of 1st-line therapy (days): 665



SB SmithKline Beecham Pharmaceuticals

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Protocol	Patient Number	Patient Initials	Eligibility Checklist
104661/476	1 1 1 8 7	– –	

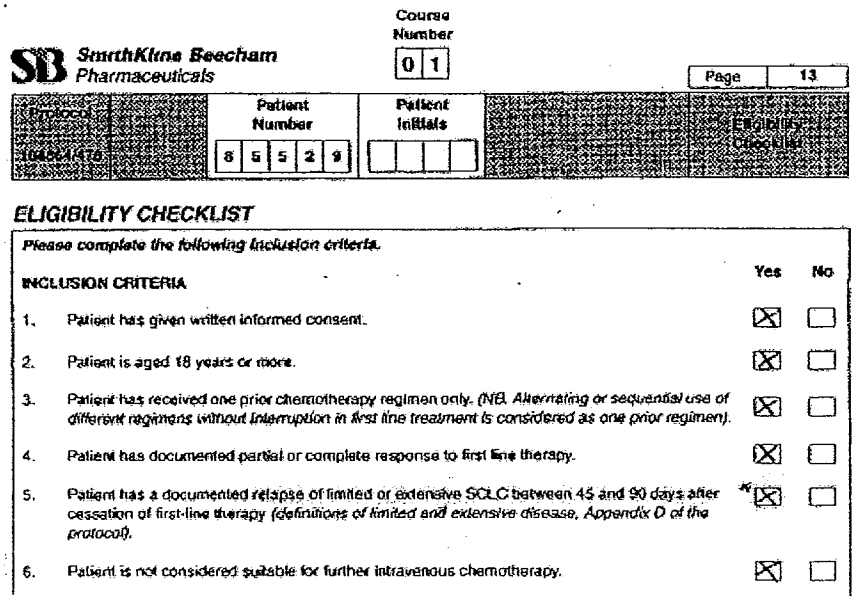
ELIGIBILITY CHECKLIST

Please complete the following inclusion criteria.

INCLUSION CRITERIA	Yes	No
1. Patient has given written informed consent.	☒	☐
2. Patient is aged 18 years or more.	☒	☐
3. Patient has received one prior chemotherapy regimen only. *(NB. Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).*	☒	☐
4. Patient has documented partial or complete response to first line therapy.	☒	☐
5. Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy *(definitions of limited and extensive disease, Appendix D of the protocol).*	☒	☐
6. Patient is not considered suitable for further intravenous chemotherapy.	☒	☐

The following are examples are notations made on the CRF, regarding this eligibility criterion.

- Jhoylink duration of response from completion of 1st-line therapy (days): 439



SB SmithKline Beecham Pharmaceuticals

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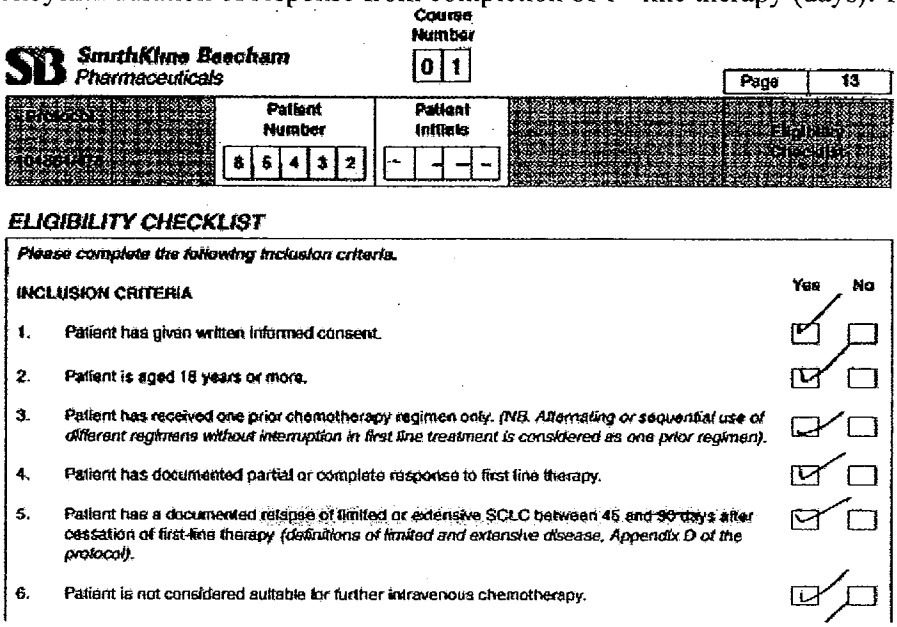
Protocol	Patient Number	Patient Initials	Eligibility Checklist
104661/476	8 5 5 2 9		

ELIGIBILITY CHECKLIST

Please complete the following inclusion criteria.

INCLUSION CRITERIA	Yes	No
1. Patient has given written informed consent.	☒	☐
2. Patient is aged 18 years or more.	☒	☐
3. Patient has received one prior chemotherapy regimen only. *(NB. Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).*	☒	☐
4. Patient has documented partial or complete response to first line therapy.	☒	☐
5. Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy *(definitions of limited and extensive disease, Appendix D of the protocol).*	☒	☐
6. Patient is not considered suitable for further intravenous chemotherapy.	☒	☐

- Jhoylink duration of response from completion of 1st-line therapy (days): 104



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Patient Number: 8 5 4 3 2

Patient Initials: - - - -

Eligibility Checklist

ELIGIBILITY CHECKLIST

Please complete the following inclusion criteria.

INCLUSION CRITERIA		Yes	No
1.	Patient has given written informed consent.	☑	☐
2.	Patient is aged 18 years or more.	☑	☐
3.	Patient has received one prior chemotherapy regimen only. *(NB. Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).*	☑	☐
4.	Patient has documented partial or complete response to first line therapy.	☑	☐
5.	Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy *(definitions of limited and extensive disease, Appendix D of the protocol).*	☑	☐
6.	Patient is not considered suitable for further intravenous chemotherapy.	☑	☐

- Jhoylink duration of response from completion of 1st-line therapy (days): 105

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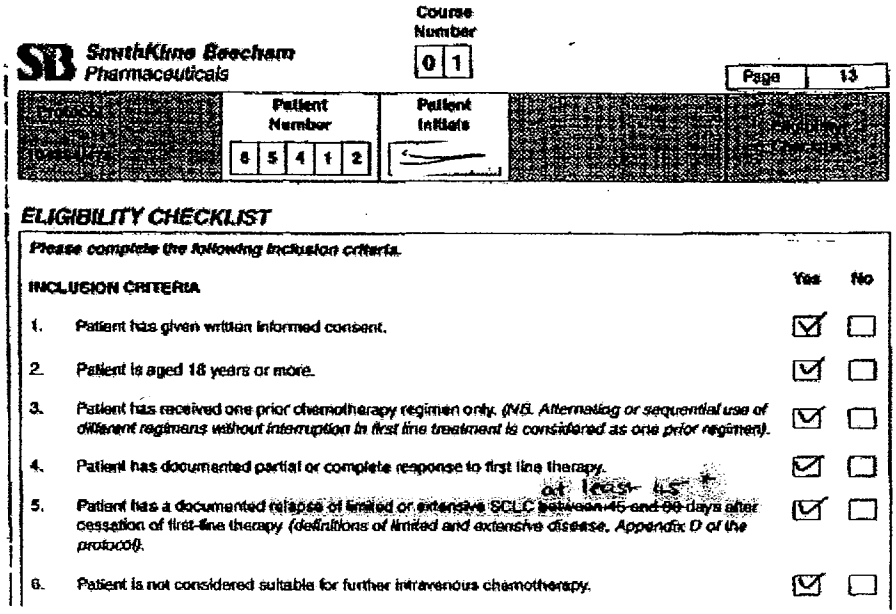

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Patient Number: 6 5 4 1 2

Patient Initials:

ELIGIBILITY CHECKLIST

Please complete the following inclusion criteria.

INCLUSION CRITERIA		Yes	No
1.	Patient has given written informed consent.	☑	☐
2.	Patient is aged 18 years or more.	☑	☐
3.	Patient has received one prior chemotherapy regimen only. *(NB. Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).*	☑	☐
4.	Patient has documented partial or complete response to first line therapy.	☑	☐
5.	Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy *(definitions of limited and extensive disease, Appendix D of the protocol).* at least 45 +	☑	☐
6.	Patient is not considered suitable for further intravenous chemotherapy.	☑	☐

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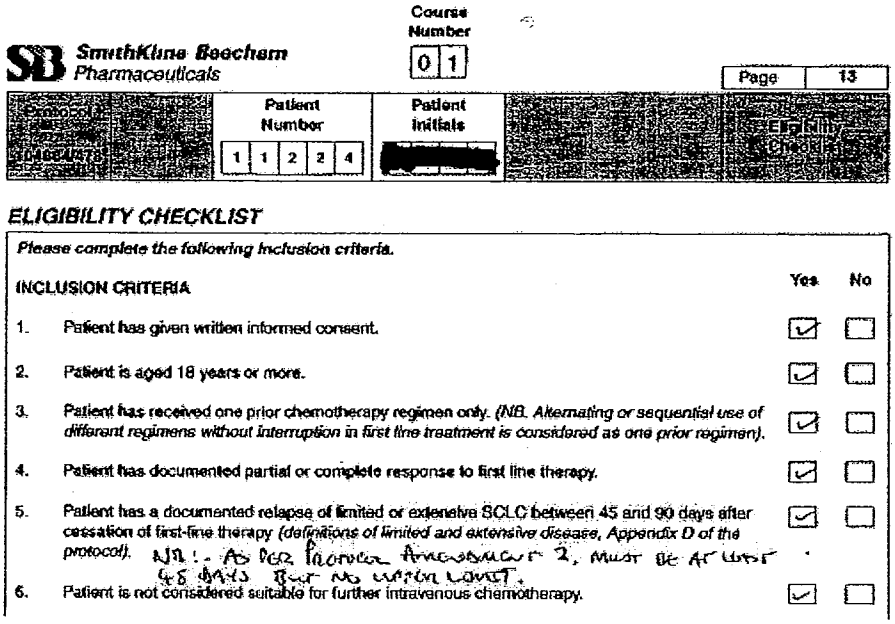
- Jhoylink duration of response from completion of 1st-line therapy (days): 121



SmithKline Beecham Pharmaceuticals

Course Number: 0 1

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Patient Number: 1 1 2 2 4

Patient Initials: [redacted]

ELIGIBILITY CHECKLIST

Please complete the following inclusion criteria.

INCLUSION CRITERIA		Yes	No
1.	Patient has given written informed consent.	☑	☐
2.	Patient is aged 18 years or more.	☑	☐
3.	Patient has received one prior chemotherapy regimen only. *(NB. Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).*	☑	☐
4.	Patient has documented partial or complete response to first line therapy.	☑	☐
5.	Patient has a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy *(definitions of limited and extensive disease, Appendix D of the protocol).* NB:- As per Protocol Amendment 2, must be at least 45 days but no upper limit.	☑	☐
6.	Patient is not considered suitable for further intravenous chemotherapy.	☑	☐

Stratification factor:

duration of response vs. time to progression from end of prior chemotherapy

SUMMARY OF TIME DURATION STRATIFICATION FACTOR IN STUDY 478

	UNITS: (≤ 60 DAYS OR > 60 DAYS)
Text of protocols: original, amendment 1, & amendment 2	Sections: 4.1 Number of Patients, 5.3.4 Stratification, 9.2 Method of Randomisation: duration of response to prior chemotherapy
Central Patient Registration and Randomization, original protocol	duration of response to first-line chemotherapy in days from cessation of first line therapy until documented relapse duration of the patient's response to first-line chemotherapy duration of the patient's response to first-line chemotherapy duration of response to first-line chemotherapy
Central Patient Registration and Randomization, amendment 1 & amendment 2	time in days from discontinuation of first line chemotherapy to relapse
Text of protocol: original, amendment 3	Sections: 4.1 Number of Patients, 5.3.4 Stratification, 9.2 Method of Randomisation: time to progression from end of prior chemotherapy57
Central Patient Registration and Randomization, amendment 3	time in days from discontinuation of first line chemotherapy to relapse
Study report	Synopsis, 5.4.5. Treatment Assignment, 5.8.8.1. Primary efficacy measure, Table 7: time to progression from end of prior chemotherapy 10. DISCUSSION AND CONCLUSIONS: time to progression from end of 1st-line chemotherapy
Publication58	treatment-free interval (TFI) after first-line therapy

57 This change was made approximately 3 months after the last patient was accrued to the study or this amendment had impact on the registration and randomization of zero patients

Duration of response, as a parameter, defines a measure of sensitivity to prior chemotherapy. TTP from cessation of 1st-line chemotherapy and treatment-free interval may not give a measure of sensitivity because it may include patients with stable disease or patients who progressed and received radiotherapy to a symptomatic site.

The stratification factor in the text of the protocol and the registration and randomization center procedures do not match.

APPEARS THIS WAY
ON ORIGINAL

58 O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cuceviá B, Juhasz G, Thatcher N, Ross GA, Dane GC, Crofts T. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006 Dec 1;24(34):5441-7

Investigator's Registration and Randomization Form

The form below was provided by GSK on 9/6/2007. This does not resolve whether it was duration of response or duration of response from completion of 1st line therapy. Note the difference in font-size for "days" and "(from completion of 1st line therapy)" compared to the rest of the document. This form may be the only documentation of what the investigator entered into the Jhoylink system.

SmithKline Beecham Protocol: Topotecan 478

Treatment Randomisation and Patient number allocation:

Centre No: ___ **Patient Initials:** ___ **CRF No:** _____

Confidential PIN code will be required before commencing the randomisation procedure.

Randomisation system telephone number:

Patient Eligibility

All screening procedures must have been completed and the patient's eligibility to be enrolled into protocol 478 fully assessed before performing the central randomisation procedure.

Information required during the Randomisation Procedure

i) Patient Date of Birth: __ / __ / __

ii) Gender: Male ☐
Female ☐

ii) Did the patient respond to 1st line chemotherapy?:
Yes ☐ Duration of Response ___ days
(from completion of 1st line therapy)
No ☐ ⇨ Not eligible for the protocol 478

iii) ECOG Performance Status:
0/1 ☐ 2 ☐
3 ☐⇨ Not eligible for the protocol 478

iv) Does the patient have liver metastases?.
Yes ☐
No ☐

Randomisation Outcome

Patient Randomisation No:___ ___ ___

Treatment Arm: **Active Symptom Control Alone** ☐
Active Symptom Control + Oral Topotecan ☐

Randomisation Performed by:(Print Name)_____ Date ___/___/___

SIGNED_____

NB. Please retain this form within the Study Investigator File.

The FDA requested the forms for all the patients registered and/or randomized on study #478 on Sept. 11 and Sept. 12, 2007. On Oct. 2, 2007, the Sponsor provided a partial response. The following is part of the Sponsor's response:

> "As of this morning's deadline, 25 of the 40 sites have responded conclusively to our inquiries. These 25 sites recruited 111 of the 141 patients into study 478 (79%). Only 7 of the 25 sites (three sites each in Bulgaria and the UK and one site in Russia) used the

optional randomization worksheets. Together, these seven sites recruited 39 patients into the study. Copies of the randomization worksheets have been submitted for 36 of these patients; all of these are being provided to the FDA."

"The 18 sites that confirmed that they did not use these forms recruited 72 patients into the study. Three additional sites did not remember using the forms, but confirmation requires the retrieval of the study files which could not be completed by today's deadline. Eleven sites have not responded and at one site, the investigator and sub-investigators are no longer at the institution and the department has been closed."

The Sponsor's commentary is noted but the instructions for the investigator at the bottom of the form, i.e., "NB. Please retain this form within the Study Investigator File."

Out of 40 sites surveyed about the forms, 25 sites responded. These 25 sites represented 111 patients. Only 7 of the 25 sites used the forms; 18 sites did not use the forms. Forms were provided from the following site numbers: 10, 29, 42, 49, 72, 73, and 74. From site #29, two forms were not provided; from site #72, one form was not provided. The 36 forms provided represent 26% of the patients on study #478. This was not a complete response in order to do an adequate review of what the investigators entered into the registration and randomization system.

There were discrepancies between the investigator filled-out form and the entries retrieved in the Jhoylink system data. This analysis is based on only 26% of the forms.

PATIENT NUMBER ARM	INVESTIGATOR FILLED OUT FORM	JOYLINK DATA	COMMENT
29.11243 Best supportive care	Liver met.::no **Medical Officer interpretation of handwriting: ask if present i/c liver, answered yes; u/s no liver mets now**	Liver met: yes	Stage in DEM database: Limited DEM database baseline liver metastasis (LM): no **Medical Officer: it is not known how the patient was stratified**
42.85412	Birth date: [redacted] Date: 6/7/02 "form completed retrospectively"	Year of birth 1941 Date: 4/5/02	DEM database has 1941

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PATIENT NUMBER ARM	INVESTIGATOR FILLED OUT FORM	JOYLINK DATA	COMMENT
72.11202	Date:2/24/2004	Date: 2/26/2004 Jhoylink systemFax[59]: 02-26-2004	
72.11221	No patient randomization number No selection of treatment arm	#100 Obs alone Jhoylink systemFax[60]: #100; Symptom Control alone	
72.11222	No selection of treatment arm	Topotecan Jhoylink systemFax[61]: Symptom Control + Topotecan	
72.85488	Duration of Response ~~33~~ 45 days Liver met.::no	Duration of Response: 45 Liver met.::yes	

59 PDF pages 282-294. of the Food and Drug Administration Estalishment Inspection Report of Pmf. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner

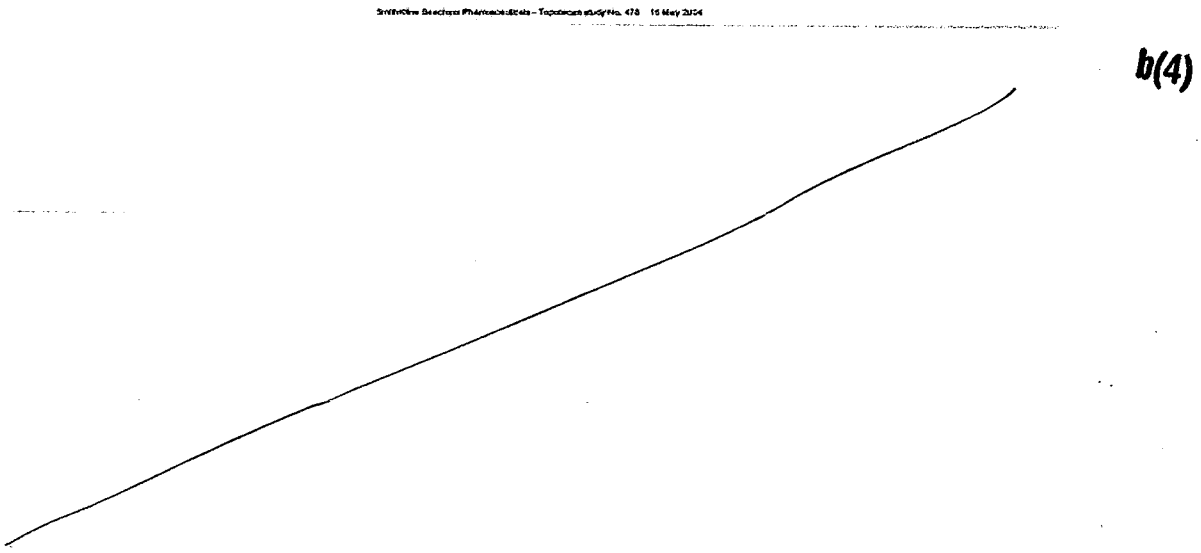
60 PDF pages 282-294. of the Food and Drug Administration Estalishment Inspection Report of Pmf. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner

61 PDF pages 282-294. of the Food and Drug Administration Estalishment Inspection Report of Pmf. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner

GSK provided a spreadsheet with Jhoylink entries on 9/18/2007. Below is a sample of the Jhoylink spreadsheet. The following is a statement by the Sponsor, regarding the relevance of this database to the dataset in the NDA:

> "Please note that the data provided by Jhoylink in this spreadsheet were not audited by GSK, nor were they used in the generation of the data in the study summaries and reports included in the original NDA [GSK used the monitored data from the case report forms (CRF) for this purpose]. As a consequence, there are a few discrepancies between the data provided by Jhoylink and those from the audited data provided in the CRFs. However, we are submitting this spreadsheet as it captured and accurately reflects the values entered by the investigators."

Note that age can be derived from the entry of the patient's birth date and the date of registration/randomization. However, for duration of response (from completion of 1st line therapy), there is a slot for entry of a number in days; there are no slots for entry of the dates for the completion of 1st line therapy and the date for disease recurrence/progression; in the CRF there is a slot for duration of response in weeks. The date on the top of the spreadsheet is May 16, 2004. The date for Amendment 3, which included changing in the text of the protocol from duration of response to prior chemotherapy (≤ 60 days or > 60 days) to time to progression from end of prior chemotherapy (≤ 60 days or > 60 days), is May 7, 2004. This sample documents that the investigator entered into the Jhoylink system a number and the Sponsor, at some time later, calculated from the CRF TTP from prior chemotherapy. The latter, i.e., the Sponsor's derivation, is what was submitted in the database in the NDA.



In the best supportive care arm, there were 29 entries into the Jhoylink system that underestimated the Sponsor's derivation of TTP from completion of 1st-line chemotherapy (-1 - -

1300 days); 13 of these were ≥ 14 days62. There were 26 entries that overestimated the Sponsor's derivation of TTP from completion of 1st-line chemotherapy (1 - 138 days); 8 of these were ≥ 14 days.

In the oral topotecan arm there 24 entries into the Jhoylink system that underestimated the Sponsor's derivation of TTP from completion of 1st-line chemotherapy (-1 - -1022 days); 11 of these were ≥ 14 days. There were 26 entries that overestimated the Sponsor's derivation of TTP from completion of 1st-line chemotherapy (1 - 86 days); 6 of these were ≥ 14 days.

According to the Sponsor, using 60 days as the stratification dividing line, **there were only five patients—all on the oral topotecan arm—who were stratified incorrectly (table below)**; four patients changed from a "good" prognostic group to a "bad" group; one patient changed from a "bad" prognostic group to a "good" group. However, if 90 days had been used as the stratification dividing line, there were 12 patients—2 on the oral topotecan arm and 10 on the best supportive care arm---who would have been stratified incorrectly; on the topotecan arm, one each had their resistant(bad)/sensitive(good) group changed; on the best supportive care arm, 8 changed from the "bad" prognostic group to the "good" and 2 changed from the "good" prognostic group to the "bad" group:

The table below shows the incorrectly stratified patients.

Centre No.	CRF No.	Treatment	Jhoylink Data: Response Duration from completion of 1st-line therapy (days)	GSK Clintrial Data: Time to Progression from end of prior chemotherapy (days)	Investigator entered value - GSK calculated values from CRF dates	Stratified correctly by Jhoylink to < 60 days > TTP from end of prior chemotherapy
17	85349	Topotecan	61	60	1	No
29	11241	Topotecan	63	55	8	No
72	85499	Topotecan	61	60	1	No
93	85466	Topotecan	59	90	-31	No
93	85468	Topotecan	80	46	34	No

Viewing the data in order of randomization did not suggest that the stratification factor of duration of response vs. time to progression from end of prior chemotherapy changed over time. There is no evidence that there was any training or monitoring for this discrepancy.

All the GSK Clinitrial Data for time to progression from end of prior chemotherapy matched the database in the DEM database except for one case:

62 The selection "14 days" was arbitrary and limits the discrepancies to what may be a significant incorrect entries.

Centre No.	CRF No.	GSK Clintrial Data: Time to Progression from end of prior chemotherapy (days)	DEM		PROGDAY, days
101	85463	90	478.101.85463	Active Symptom Control	109

A different stratification factor used by investigator sites

Different sites appeared to use either duration of response or time to progression from the end of prior chemotherapy. The FDA has verification of these differences for two sites.

Stratification factor: Duration of Response

According to the DSI inspector assigned to audit a Bulgaria site (72):

- "for subject stratification, subjects were stratified according to duration of response to prior chemotherapy versus time to progression per protocol amendment 3 which was approved after study completion at this site. The study protocol was not modified by this study site, rather by the sponsor."63
- "The CI's stated that the duration of response was determined by the date of response until the date of progression. It was explained by the site that Time of progression was determined by the last day of prior chemotherapy to the first day of progression. The CI stated that the data for time of progression was done through the sponsor's data analysis system."[64]

- "However, it was noted that the duration of response noted in weeks in the CRF and days on the Randomization confirmation **(Exhibit #16)** were not the same as those generated on the data listings. The CI stated that the data listings calculated by the sponsor used the time of progression equation even though, during the time of the study, the duration of response was captured."[65]

The table below is derived from the Bulgaria site (72

63 p. 5 of the Food and Drug Administration Estalishment Inspection Report of Pmf. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner
64 p. 8 of the Food and Drug Administration Estalishment Inspection Report of Pmf. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner
65 p. 8 of the Food and Drug Administration Establishment Inspection Report of Prof. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner

Centre Investigator or Location	CRF No.	Jhoylink Data Response Duration from completion of 1st-line therapy (days)	GSK Clintrial Data Time to Progression from end of prior chemotherapy (days)	Investigator entered value - GSK calculated values from CRF dates	duration of response from CANMED, days
72	11197	45	39	6	49
72	11198	45	45	0	49
72	11199	54	54	0	49
72	11200	240	102	138	224
72	11202	174	1196	-1022	1099
72	11221	48	43	5	49
72	11222	47	43	4	49
72	11223	48	53	-5	56
72	85487	50	16	34	42
72	85488	45	48	-3	42
72	85489	48	52	-4	49
72	85499	61	60	1	56
72	85500	47	46	1	49

The column to the far right is duration of response to prior chemotherapy taken out of the NDA database. The GSK data column matches the derived numbers in the database for TTP from 1st-line chemotherapy (data not shown). The data entered into Jhoylink system approximates duration of response more than TTP from 1st-line chemotherapy.

Patients were accrued from 3/29/2002 to 2/26/2004. This site was monitored regularly from 3/20/2002 to 4/14/2004.66 There does not appear to be any change in the pattern with monitoring. i.e., the first patient accrued had 50 days entered into the Jhoylink system and GSK changed it to 16 days; the last patient accrued had 174 days entered into the Jhoylink system and GSK changed it to 1196 days.

It appears that the investigator was entering duration of response into the Jhoylink system for stratification. Also, although this investigator site entered a large number of patients to the study, the investigator was not a co-author on the publication of the results.

66 Amendment 0009, dated 8/6/2007; response by GSK to DSI request

Stratification factor: Time to Progression from the end of prior chemotherapy

According to the DSI inspector assigned to audit a Ukraine site (92

- "The sub-investigator told me that he looked at the date that chemotherapy was stopped and started counting from that date. The method used at this site was time to progression rather than duration of response."67

The table below is derived from the Ukraine site (92).

Centre Investigator or Location	CRF No	Jhoylink Data: Response Duration from completion of 1st-line therapy (days)	GSK Clintrial Data: Time to Progression from end of prior chemotherapy (days)	Investigator entered value - GSK calculated values from CRF dates	duration of response from CANMED, days
92	11176	75	74	1	70
92	11177	63	63	0	63
92	11178	91	92	-1	49
92	11179	52	55	-3	91
92	11205	75	74	1	77
92	85470	51	50	1	49
92	85478	45	45	0	49
92	85479	51	50	1	49

The column to the far right is duration of response to prior chemotherapy taken out of the database. The GSK data column matches the derived numbers in the database for TTP from 1st-line chemotherapy (data not shown). The data entered into Jhoylink system approximates TTP from 1st-line chemotherapy more than duration of response.

Patients were accrued from 8/23/2002 to 1/30/2004. This site was monitored regularly from 2/20/2002 to 5/24/2005.68 There does not appear to be any change in the pattern with monitoring. i.e., the Jhoylink data and the GSK data were closely matched.

It appears that the investigator was entering tme to pogression from the end of prior chemotherapy into the Jhoylink system for stratification.

67 **E-mail From:** Saale, Mark; **Sent:** Wednesday, September 12, 2007 1:37 PM; **To:** Chu, Dan-My; **Subject:** RE: Inspection of Dr. Shparyk, Lviv, Ukraine
68 Amendment 0009, dated 8/6/2007; response by GSK to DSI request

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ON ORIGINAL

Stratification Factor: Liver Metastases at Baseline

The table below shows the number of patients in each arm with liver metastases according to the Jhoylink system, i.e., the registration and registration system for the study.

Jhoylink system data	
liver metastases:yes	
topotecan	Best supportive care
23	20

The table below shows the number of patients in each arm with liver metastases according to the DEM database. There were differences in the number patients with liver metastases in the two databases.

DEM database	
liver metastases:yes	
topotecan	Best supportive care
20	14

A comparison of both databases was performed. The table below shows the patients, who were stratified incorrectly according the presence or absence of liver metastases.

Jhoylink	Centre No.	CRF No.	Liver Mets	DEM	liver mets		comments
Obs alone	16	85364	No	478.016.85364	Y	Active Symptom Control	Limited disease on page 9 of the CRF, Disease Status-Screening Evaluation: there is no indication of liver mets; Jhoylink system database has "no" for liver mets.
Obs alone	17	85350	Yes	478.017.85350	N	Active Symptom Control	
Obs alone	22	85355	Yes	478.022.85355	N	Active Symptom Control	
Topotecan	27	85398	Yes	478.027.85398	N	Oral Topo + ASC	
Obs alone	29	11243	Yes	478.029.11243	N	Active Symptom Control	Jhoylink form: Liver met.:no; handwriting on form: ask if present i/c liver, answered yes; u/s no liver mets now

Jhoylink	Centre No.	CRF No.	Liver Mets	DEM	liver mets		comments
Topotecan	29	85388	Yes	478.029.85388	N	Oral Topo + ASC	Jhoylink form: liver met: yes
Obs alone	29	85406	Yes	478.029.85406	N	Active Symptom Control	Jhoylink form not submitted
Topotecan	35	11246	No	478.035.11246	Y	Oral Topo + ASC	
Topotecan	44	85435	Yes	478.044.85435	N	Active Symptom Control	
Obs alone	49	85511	Yes	478.049.85511	N	Active Symptom Control	Jhoylink form: liver met: yes
Topotecan	72	85488	Yes	478.072.85488	N	Oral Topo + ASC	Jhoylink form: liver met: no; Jhoylink system Fax : Metastase: Yes
Topotecan	73	85490	Yes	478.073.85490	N	Active Symptom Control	Jhoylink form: liver met: yes; treatment arm topotecan
Topotecan	81	85503	No	478.081.85503	Y	Oral Topo + ASC	
Obs alone	101	85465	Yes	478.101.85465	N	Active Symptom Control	
Obs alone	104	85458	Yes	478.104.85458	N	Active Symptom Control	

In 15 cases (10.6%), the randomization group assigned may have been different. With regard to the presence or absence of liver metastases, the patient information, which the investigators used at the time of data entry into the Registration and Randomization Center may have been different than the data derived from the baseline lesion data and entered into the DEM database.

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ON ORIGINAL

Stratification factor: Performance Status (ECOG)

The table below shows the number of patients in each arm with a respective performance status according to the Jhoylink system, i.e., the registration and registration system for the study.

	Jhoylink system data	
ECOG	topotecan	BSC
0	7	7
1	41	39
2	24	23

The table below shows the number of patients in each arm with a respective performance status according to the DEM database. There were differences in the number patients with regard to performances status in the two databases.

	DEM database	
Performance status	topotecan	BSC
0	8	6
1	44	41
2	19	23

A comparison of both databases was performed. The table below shows the differences in the recorded performance status and the patients, who were stratified incorrectly (in **bold**) according to performance status. According to the the protocol and the Jhoylink form, performance status stratification was by "0/1" and "2."

Jhoylink	Centre No.	CRF No.	ECOG	DEM	PS		comments
Topotecan	18	85552	1	478.018.85552	0	Oral Topo + ASC	
Topotecan	19	85363	1	478.019.85363	0	Oral Topo + ASC	
Topotecan	19	85555	1	478.019.85555	0	Oral Topo + ASC	
Obs alone	20	85537	0	478.020.85537	1	Active Symptom Control	
Topotecan	**44**	**85436**	**2**	**478.044.85436**	**1**	**Oral Topo + ASC**	
Topotecan	46	85431	0	478.046.85431	1	Oral Topo + ASC	
Obs alone	**47**	**85483**	**2**	**478.047.85483**	**1**	**Active Symptom Control**	

Jhoylink	Centre No.	CRF No.	ECOG	DEM	PS		comments
Topotecan	**49**	**85481**	**2**	**478.049.85481**	**1**	**Oral Topo + ASC**	
Obs alone	**49**	**85511**	**1**	**478.049.85511**	**2**	**Active Symptom Control**	**Jhoylink form: ECOG:0/1**
Obs alone	**72**	**85487**	**2**	**478.072.85487**	**1**	**Active Symptom Control**	**Jhoylink form: ECOG:2; Jhoylink system Fax: ECOG Status: 2**
Topotecan	**72**	**85488**	**2**	**478.072.85488**	**1**	**Oral Topo + ASC**	**Jhoylink form: ECOG:2; Jhoylink system Fax: ECOG Status: 2**
Topotecan	73	85490	0	478.073.85490	1	Active Symptom Control	Jhoylink form: ECOG:0/1
Obs alone	**94**	**85469**	**1**	**478.094.85469**	**2**	**Active Symptom Control**	
Topotecan	**103**	**11235**	**2**	**478.103.11235**	**1**	**Oral Topo + ASC**	

In 8 cases (5.7 %), the randomization group assigned may have been different.

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Stratification Factor: Gender or Sex

The gender (Jhoylink) and sex (DEM) for patients matched in both databases (data not shown).

Randomization Dates

There were five patients, whose randomization dates did not match in the Jhoylink system and the EFFICACY database in the NDA. Two patients had a difference of one day (478.027.85397 & 478.094.85471) between the databases. There was one patient (478.035.11246) whose dates differed by six days. There were two patients (in **bold**), who not only had the dates of randomization in the two databases different by several months (~9 months) but the randomization arms changed, too; the dates of birth of these two patients appear similar. These changes may have reduced the survival time by 9 months for the patient who was switched to best supportive care and increased the survival time by 9 months for the patient who was switched to oral topotecan.

Jhoylink	Centre No.	CRF No.	Randomisation	Rando No.	EFFICACY Database	RANDAT		comments
Topotecan	27	35397	12/19/2001	27	478.027.85397	12/18/2001	Oral Topo + ASC	same birth date
Topotecan	**73**	**85490**	**6/10/2002**	**61**	**478.073.85490**	**3/17/2003**	**Active Symptom Control**	**birth dates: [redacted] & [redacted] resp**
Obs alone	**73**	**85492**	**3/17/2003**	**93**	**478.073.85492**	**6/10/2002**	**Oral Topo + ASC**	**birth dates: [redacted] & [redacted], resp**
Obs alone	94	85471	3/27/2003	95	478.094.85471	3/28/2003	Active Symptom Control	same birth date
Topotecan	35	11246	8/11/2003	108	478.035.11246	8/5/2003	Oral Topo + ASC	same birth date

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Randomization: "Changes" in the treatment arm

Three patients were randomized to one arm in the Jhoylink system but appeared in another treatment arm in the NDA database. The table below shows the patients.

Jhoylink	Centre No.	CRF No.	DEM		comments
Topotecan	44	85435	478.044.85435	Active Symptom Control	
Topotecan	73	85490	478.073.85490	Active Symptom Control	Jhoylink form: treatment arm topotecan
Obs alone	73	85492	478.073.85492	Oral Topo + ASC	Jhoylink form: treatment arm Active Symptom Control

List of Patients with Randomization/Stratification Discrepancies

There were at least 32 patients (22.6%) who may have been stratified, registered, or randomized incorrectly; five patients had more than one discrepancy.

patient #	Arm	Randomization/stratification discrepancy
478.016.85364	Obs alone	Liver mets incorrectly stratified
478.017.85349	Topotecan	Stratified incorrectly by Jhoylink to < 60 days > TTP from end of prior chemotherapy
478.017.85350	Obs alone	Liver mets incorrectly stratified
478.022.85355	Obs alone	Liver mets incorrectly stratified
478.027.85397	Topotecan	disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy.
478.027.85398	Topotecan	Liver mets incorrectly stratified
478.29.11241	Topotecan	Stratified incorrectly by Jhoylink to < 60 days > TTP from end of prior chemotherapy
478.029.11243	Obs alone	Liver mets incorrectly stratified
478.029.85388	Topotecan	Liver mets incorrectly stratified
478.029.85406	Obs alone	Liver mets incorrectly stratified
478.035.11246	Topotecan	Liver mets incorrectly stratified
478.044.85435	Active Symptom Control	Liver mets incorrectly stratified Randomized: Topotecan in Jhoylink
478.046.11240	Obs alone	disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy. Eligibility Check List" database

patient #	Arm	Randomization/stratification discrepancy
		for criterion #5
478.047.85483	Obs alone	performance status/ECOG stratification
478.049.85481	Topotecan	performance status/ECOG incorrectly stratified
478.049.85511	Obs alone	Liver mets incorrectly stratified performance status/ECOG incorrectly stratified
478.072.11197	Topotecan	disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy.
478.072.11221	Obs alone	disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy.
478.072.11222	Topotecan	disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy.
478.072.85487	Obs alone	disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy. performance status/ECOG incorrectly stratified
478.072.85488	Topotecan	liver metastases incorrectly stratified performance status/ECOG incorrectly stratified
478.72.85499	Topotecan	Stratified incorrectly by Jhoylink to < 60 days > TTP from end of prior chemotherapy
478.073.85490	Active Symptom Control	Liver mets incorrectly stratified Randomized: Topotecan in Jhoylink The dates of randomization in the Jhoylink and the NDA databases differ by 9 months
478.073.85492	Oral Topo + ASC	Randomized: Obs alone in Jhoylink The dates of randomization in the Jhoylink and the NDA databases differ by 9 months
478.081.85503	Topotecan	Liver mets incorrectly stratified
478.93.85466	Topotecan	Stratified incorrectly by Jhoylink to < 60 days > TTP from end of prior chemotherapy
478.93.85468	Topotecan	Stratified incorrectly by Jhoylink to < 60 days > TTP from end of prior chemotherapy
478.094.11180	Topotecan	disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy.
478.094.85469	Obs alone	disqualifying factor was a relapse of < 45 days after the cessation of 1st-line therapy. performance status/ECOG incorrectly stratified
478.101.85465	Obs alone	Liver mets incorrectly stratified

patient #	Arm	Randomization/stratification discrepancy
478.103.11235	Topotecan	performance status/ECOG incorrectly stratified
478.104.85458	Obs alone	Liver mets incorrectly stratified

The results of the FDA statistician's (Dr. Chia-wen Ko) survival analysis after removing the discrepant cases is below:

- removal the 32 patients with discrepancies from the analysis:
- BSC+OT: median survival 25.8 (95% CI: 20.9 - 21.7) weeks with 49 deaths (out of n=54)
- BSC alone: median survival 18.6 (95% CI: 13.1 - 21.9) weeks with 52 deaths (out of n=55)
- P-value for un-stratified log-rank test comparing survivals = 0.1409
- Hazard ratio (un-stratified) = 0.74 (95% CI: 0.50 - 1.10)
- Conclusion: the addition of oral topotecan increased the median survival by 8 weeks. This advantage didn't reach statistical significance with only 101 deaths observed.

APPEARS THIS WAY
ON ORIGINAL

Staging Discrepancies

The table below list patients who were listed as limited disease but appear to have metastases that would define the stage as extensive.

Patients Listed as Limited Disease but have Extensive disease

patient	Arm	Comments
478.016.85364	Active Symptom Control	Efficacy database: liver mets:yes on page 9 of the CRF, Disease Status-Screening Evaluation: there is no indication of liver mets; Jhoylink system database has "no" for liver mets.
478.042.85414	Active Symptom Control	Efficacy database: liver mets:yes on page 9 of the CRF, Disease Status-Screening Evaluation: liver mets were documented; Jhoylink system database has "yes" for liver mets.
478.064.85530	Active Symptom Control	Lesions.xpt database: MTS PULM.BILAT on CRF patient has bilateral pulmonary mets;
478.103.11238	Oral Topo + ASC	Lesions.xpt database: BILATERAL SUPRARENAL; LEFT T4 HILL on CRF: bilateral suprarenal; pleural effusion present

APPEARS THIS WAY
ON ORIGINAL

Patients not considered suitable for further intravenous chemotherapy.

According to the O'Brien article, "Some patients who were randomly assigned to receive BSC alone withdrew consent and elected to receive standard intravenous chemotherapy. In all, 13 patients in each arm (18.3% on BSC and 18.6% on topotecan) received poststudy chemotherapy either alone or in combination with other therapy."69 Whatever the criteria to indicate that a patient was unsuitable for further IV chemotherapy at the time of disease progression was a different decision than used by either the 26 patients, the investigator or another physician, or a combination because there were some patients who received post study IV chemotherapy.

The Sponsor was queried about this issue of post study intravenous chemotherapy. The Sponsor had the following response:

> **GSK Response (7/26/2007):** As previously discussed, the route of administration of post-study chemotherapy was not captured in the CRF. The actual statement in the article by O'Brien, et al. is that "some patients who were randomly assigned to receive BSC alone withdrew consent and elected to receive standard intravenous chemotherapy. In all, 12 patients in each arm (18.3% on BSC and 18.6% on topotecan) received poststudy chemotherapy either alone or in combination with other therapy such as radiotherapy and surgery." Although the *intent* of these cases may have been to initiate intravenous post-study chemotherapy, the sentence about the actual receipt accurately reflects just "poststudy chemotherapy" since the route of administration was unknown to Dr. O'Brien as well."
>
> "Similar to the route of administration, the names of the post-study chemotherapy also were not captured in the CRF (Module 5 datasets for Study 478, Page 109), and thus are unavailable."

If the co-authors/physician-investigators of the O'Brien article did not know the route of administration of post study chemotherapy, it is not clear how this inference put in the article, as well as, was approved by all the authors, including GSK employees who were co-authors. Also, it is doubtful that Dr. O'Brien and the other co-authors, who were the doctors for some of the patients who received post study chemotherapy, did not know how they treated their patients post study.

From the Sponsor's databases, there were 14 patients randomized to ASC who were considered protocol violators and received chemotherapy; there were 13 ASC patients identified as having poststudy chemotherapy; except for one patient, they are the same patients. Nine of the 14 (64%) patients who received chemotherapy post study were patients of authors plus one additional patient in Protocol Violation database. DSI found one additional patient during the

69 O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cuceviá B, Juhasz G, Thatcher N, Ross GA, Dane GC, Crofts T. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006 Dec 1;24(34):5441-7

inspection--478.092.11176. DSI explained the situation with this patient with the following: ""Subject #11176, randomized to the ASC arm had withdrawn consent to be in the study but later received IV chemotherapy. The patient expired two weeks later. Per the FDA field investigator, the clinical investigators noted that they believed that post study IV chemotherapy was too harsh for this subject, but the subject and the family insisted on the subject receiving it.70 For the best supportive care arm there were 15 patients listed as receiving post study chemotherapy.

Patient #	arm	Action
478.019.85368	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.020.85537	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.042.85414	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy71
478.042.85415	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy72
478.043.11186	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.045.85417	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.063.85529	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.074.85496	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.074.85498	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.081.85502	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy73
478.081.85504	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.092.11176	Active Symptom Control	Found by DSI
478.092.11177	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy
478.101.85457	Active Symptom Control	Randomised to ASC but subsequently received chemotherapy74
478.122.85517	Active Symptom Control	Randomised to ASC but subsequently

70 Clinical Inspection Summary: Evaluation of Clinical Inspections, Sept. 17, 2007, NDA 20-981; Chu DM T through Salewski to Robertson K.
71 Confirmed by DSI as etoposide capsules. UK Spreadsheet; Inspector: Anthony Keller
72 Confirmed by DSI as IV cyclophosphamide and IV adriamycin. UK Spreadsheet; Inspector: Anthony Keller
73 Confirmed by DSI as carboplatin and etoposide. Clinical Inspection Summary: Evaluation of Clinical Inspections, Sept. 17, 2007, NDA 20-981; Chu DM T through Salewski to Robertson K.
74 Confirmed by DSI as lomustine capsules. Romanian Spreadsheet; Inspector: Anthony Keller

Patient #	arm	Action
		received chemotherapy

There were 13 patients randomized to the oral topotecan arm who received post study chemotherapy; two of these patients of one of the co-authors of the O'Brien article.

Patient #	arm	Action post study
478.018.85372	Oral Topo + ASC	Chemotherapy
478.018.85552	Oral Topo + ASC	Chemotherapy
478.019.85363	Oral Topo + ASC	Chemotherapy
478.034.85404	Oral Topo + ASC	Chemotherapy
478.034.85405	Oral Topo + ASC	Chemotherapy
478.042.11208	Oral Topo + ASC	Chemotherapy75
478.046.85431	Oral Topo + ASC	Chemotherapy
478.072.11222	Oral Topo + ASC	Chemotherapy76
478.072.85500	Oral Topo + ASC	Chemotherapy77
478.073.85492	Oral Topo + ASC	Chemotherapy
478.101.11232	Oral Topo + ASC	Chemotherapy78
478.104.11233	Oral Topo + ASC	Chemotherapy
478.121.85512	Oral Topo + ASC	Chemotherapy

75 Confirmed by DSI as etoposide capsules. UK Spreadsheet; Inspector: Anthony Keller
76 Not confirmed by DSI. According to the DSI inspector: "Regarding subject 87(11222), post chemo was recommended per condition however the subjects condition worsened and chemo was not done **(Exhibit #18).** Subject died shortly thereafter. According to the Sub investigator, prior to study enrollment patient was considered not suitable for further IV chemo because of the subjects difficulty in tolerating first line chemotherapy and was unable to complete cycles." p. 8-9 of the Food and Drug Administration Estalishment Inspection Report of Pmf. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner
77 Confirmed by DSI as cytoxan, adriamycin, vincristine (CAV) According to the DSI inspector: "I questioned the sub-investigator to the fact that post IV chemo conflicted with the protocol eligibility criterion that "patients not considered suitable for further intravenous chemotherapy". Dr. Kojuharova explained that at the time of screening for inclusionlexclusion, subject 78(85500) had a supraclavicular lymph node which prevented central venous access and the condition of the subject at the time was not suitable for further IV chemo. AAer having topotecan, the subject's condition was good and there was no longer presence of a lymph node and when the subject became sick again the IV. CAV regimen was the best in terms of Quality of life and most suitable." . p. 8-9 of the Food and Drug Administration Estalishment Inspection Report of Pmf. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner. Also in: Clinical Inspection Summary: Evaluation of Clinical Inspections, Sept. 17, 2007, NDA 20-981; Chu DM T through Salewski to Robertson K.
78 Confirmed by DSI as lomustine capsules. Romanian Spreadsheet; Inspector: Anthony Keller

Response rates in sensitive and resistant patients

The table below lists the Sponsor-indicated responders and compares the response in "sensitive" patients or patients predicted to have a second response to chemotherapy based on a greater than 90 days TTP from 1st-line chemotherapy and the response in "resistant" patients or patients predicted to be less likely to have a second response to chemotherapy based on a 90 day or less TTP from 1st-line chemotherapy.

Patient #	arm	Sensitive or resistant	Objective response	TTP from 1st-line chemoRx, days	Duration of response to 1st-line chemotherapy, days
478.072.11222	Oral Topo + ASC	<=90 Days	PR	43	49
478.072.85488	Oral Topo + ASC	<=90 Days	PR	48	42
478.072.85500	Oral Topo + ASC	<=90 Days	PR	46	49
478.092.11179	Oral Topo + ASC	<=90 Days	PR	55	49
478.046.85432	Oral Topo + ASC	> 90 Days	PR	122	98

The "sensitive" patients had a 3.3% objective response rate (1 of 30; 95% CI: -3.1%, 9.8%). The "resistant" had a 9.8% objective response rate (4 of 41; 9.8% (95% CI: 0.7%, 18.8%). The 95% CI for the difference in response rates was -4.7%, 17.6%.

The medical officer's calculations of the response results are corroborated in the O'Brien article as shown in the table below taken from the O'Brien article.79 Although the numbers and subgroups are present in the table below, the text of the article does not discuss the response rates from the perspective of resistant and sensitive patients or from the perspective of literature, particularly how the oral topotecan results are not consistent with the intravenous topotecan results (see discussion below).

Table 4. Response in the Oral Topotecan Group According to Length of Treatment-Free Interval

	Topotecan		Treatment-Free Interval							
	All (N = 71)		≤ 60 Days (n = 22)		> 60 Days (n = 49)		≤ 90 Days (n = 41)		> 90 Days (n = 30)	
Best Response	No.	%	No.	%	No.	%	No.	%	No.	%
CR	0		0		0		0		0	
PR	6	7	4	18	1	2	4	10	1	3
Total responders (CR + PR)	6	7	4	18	1	2	4	10	1	3
95% CI	2.33 to 15.67		5.2 to 40.3		0.05 to 10.9		2.7 to 23.1		0.08 to 17.2	
Stable disease	31	44	7	32	24	49	17	42	14	47
Progressive disease	24	34	7	32	17	35	12	29	12	40
Response not assessed	11	16	4	18	7	14	8	20	3	10

Abbreviations: CR, complete response; PR, partial response.

The results are the opposite of what one would expect, i.e., a response rate of resistant patients > sensitive, particularly in comparison with the intravenous topotecan formulation.80 According to Huber et al, the response rate in the sensitive patients is expected to be higher than in

79 O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cuceviá B, Juhasz G, Thatcher N, Ross GA, Dane GC, Crofts T. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006 Dec 1;24(34):5441-7

80 The Sponsor wrote that "The 60 day time point is within the range of time durations which separates the definition of resistant from sensitive disease." (7/19/2007). Using the Sponsor's cut-point of 60 days, the difference in response rates of "resistant" and "sensitive" patients increases more in the unexpected direction.

refractory patients; also, the median time to response is expected to be longer in the refractory patients than in the sensitive patients.81 The table below is take from Huber et al and illustrates the expected trend in response rates, i.e., response rates of sensitive patients > resistant patients, with intravenous topotecan.

TABLE 1 [illegible]

First author [ref]	Subjects n	CR	PR	OR %	SD %	Survival weeks*
Eckardt [9]						
Refractory	38†		1	2.6	45	20.4
Sensitive	36‡	3	4	19.4	36	26.6
Total	74			10.8	40.5	NR
von Pawel [10]						
Refractory	41†		1	2.4	NR	16.3
Sensitive	57‡	1	7	14.0	NR	25.7
Total	98			9.2	27	21.6
Ardizzoni [11]						
Refractory	47†	1	2	6.4	40	18.8
Sensitive	45‡	6	11	37.8	31	27.6
Total	92			21.7	35.9	21.6

CR: complete response; PR: partial response; OR: odds ratio; SD: stable disease; NR: not reported. *: median. †: patients who failed to respond or progressed within 90 days of first-line therapy were termed refractory. ‡: patients who relapsed after 90 days after first-line therapy were termed sensitive.

In their study with 1.25 mg/m2 IV topotecan, Huber and co-authors report, "As expected, the response rate was higher in the sensitive patients (17.1%) than in refractory patients (8.6%), and median time to response was longer for refractory patients (12.4 weeks) than for sensitive patients (6.4 weeks)." 82

According to the Sponsor, survival results fit more with the literature. However, although "sensitive" patients on the oral topotecan arm have a greater increase in median survival, only the survival results in "resistant" patients reach statistical significance; the survival results in "sensitive" patients trend in favor of oral topotecan. This is shown in the table below taken from the study #478 report.

81 Huber RM et al. Eur Respir J 2006; 27:1183-1189; the study was supported by an unrestricted grant from GlaxoSmithKline, Munich, Germany.
82 Huber RM et al. Eur Respir J 2006; 27:1183-1189; the study was supported by an unrestricted grant from GlaxoSmithKline, Munich, Germany.

Table 30 Summary of survival, by time to progression from end of first line chemotherapy: ITT population

Survival (Weeks)	Treatment Group	
	ASC alone N=70	ASC + OT N=71
Time to progression ≤ 60 days	20	22
Median (95% C.I.)	13.2 (7.0, 21.0)	23.3 (10.7, 30.9)
Observed events	20 (100%)	19 (86.4%)
Censored events	0	3 (13.6%)
Log-rank p-value	0.0357	
Time to progression > 60 days	50	49
Median (95% C.I.)	14.4 (8.0, 21.1)	27.7 (17.6, 34.4)
Observed events	47 (94.0%)	44 (89.8%)
Censored events	3 (6.0%)	5 (10.2%)
Log-rank p-value	0.0975	

Data source: Table 13.1.1.6

Using ≤ 90 days or > 90 days TTP from the end of 1st line chemotherapy as the definition of resistant disease or sensitive disease, gives similar trends in survival, i.e., a greater increase in median survival on the oral topotecan arm for the "sensitive" patients but none of the results for these two subgroups reach statistical significance.

≤ 90 days group (resistant)

Group	Median Time, weeks	Lower 95% CI	Upper 95% CI
Active Symptom Control	14.4	7.1	19.1
Oral Topo + ASC	22.7	13.4	27.7

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.1821	1	0.0745
Wilcoxon	2.9932	1	0.0836

> 90 days group (sensitive)

Group	Median Time, weeks	Lower 95% CI	Upper 95% CI
Active Symptom Control	14.4	6.6	22.4
Oral Topo + ASC	31.6	21.6	38.7
Combined	22.4	16.3	31.7

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.4274	1	0.0641
Wilcoxon	7.1259	1	0.0076

The response rate results in sensitive and resistant disease patients are not consistent with the survival data, the literature, and the results with the intravenous topotecan formulation.

Overall conclusions

- FDA did not have knowledge of the study at inception. FDA learned about the study after the study was completed.
- The study began as a study of resistant SCLC after 1st-line chemotherapy and transitioned to a study to include both resistant and sensitive SCLC
- The patient population had an undefined entry criterion which cannot be labeled, i.e., patients not considered suitable for further intravenous chemotherapy. The reasons intravenous chemotherapy may not be suitable for a patient was not captured on the case report form.
- The definition of "resistant" was left to the judgement of the investigator.
- There was no scientific or clinical basis for a stratification factor of duration of response of ≤ 60 days or > 60 days). In the text of the protocol this stratification factor was changed to time to progression from the end of prior chemotherapy after all the patients were accrued to the study
- Except for gender, all the stratification factors (time to progression from the end of prior chemotherapy; liver metastases [presence or absence]; performance status) had multiple discrepancies between what the investigator entered into the registration and randomization system and what was in the NDA database. There were also eligibility, randomization, and staging discrepancies.
- Study #478 planned to accrue 220 patients. The study was stopped early after 141 patients were accrued because of protracted recruitment and a diminishing number of centers and countries able to participate. The discussion about stopping the study with the European authorities and the FDA.
- On the oral topotecan arm, the response rates for patients who were defined as having "sensitive" and "resistant" SCLC were the reverse of what would be expected from the

literature and from the experience with intravenous topotecan. The "resistant" patients had a higher response rate than the "sensitive" patients.

- Radiological assessment of tumor response, and monitoring of hematology and chemistries was only routine on the oral topotecan arm.

- The data demonstrated a significant improvement in survival for patients on the oral topotecan arm compared to patients on the best supportive care arm. After removal of the known discrepant cases, there was still a survival benefit on the oral topotecan arm.

7 REVIEW OF SAFETY: STUDY #478

7.1 Sponsor's review of safety: Study #478

Title: An Open-Label, Multicentre, Randomised, Phase III Comparator Study of ASC alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC

STUDY #478 (tables and figures are from the Sponsor's 8/2006 meeting package); other information taken from the study report in the NDA.

Initiation Date: 16 Nov 2000
Early Termination Date: 30 Mar 2004
Revision of Patient Sample Size and Change in Stratification Factor[83]: 13 May 2004
Completion Date: 30 Sep 2004
Date of Report: April 2005

Exposure and Compliance with Oral Topotecan

Study	N	Number of Courses			Median Dose Intensity (mg/m^2/week)	Compliance[1]
		Total	Median	Range		
478	70	278	4	1-10	3.77	- 69 patients 90 – 100% - 1 patient <80%

1. Compliance defined as number of capsules taken relative to number of capsules dispensed.
N= number of patients in the oral topotecan arm.

Patients in the ASC alone group were not treated but were followed for the equivalent of a median of three courses (range 1 to 13).

83 The change in the stratification factor is not in the study report.

Table 31 Dose intensity of oral topotecan during each course of treatment: modified ITT population, ASC + OT group only

Course	ASC + OT			
	N	mean	median	Range
	Topotecan (mg/m²/week)			
1	70	3.60	3.83	1.96-4.03
2	59	3.62	3.83	1.90-4.50
3	50	3.56	3.83	2.19-5.17
4	37	3.70	3.83	2.50-5.17
5	25	3.68	3.83	1.92-5.71
6	20	3.89	3.83	3.10-5.17
7	6	4.32	3.97	3.83-5.17
8	4	4.72	4.50	3.83-6.03
9	4	3.73	3.36	3.01-5.17
10	1	3.83	3.83	3.83-3.83
Overall	70	3.61	3.77	2.08-4.72

Data source: Table 14.3.1

Summary of Oral Topotecan Dose Modifications and Reasons for Modification

	478
Total Courses[1]	206
Dose Delays[2] (%)	2.9
Hematologic	1.5
Nonhematologic	0
Others	1.4
Dose Reductions (%)	7.8
Hematologic	6.3
Nonhematologic	0.5
Others	1.0

1. After the first course of therapy.
2. ≥7 days.

In the ASC + OT group, dose reductions occurred in 7.8% of courses, principally due to haematological toxicity (6.3% of total courses). Similarly, 19.9% of topotecan courses were delayed, again mainly due to haematological toxicity (12.1% of total courses).

MEDICAL OFFICER NOTE: Dose delays in the table from the 9/2006 meeting package differs from the narrative in the study report submitted to the NDA.

The principal toxicities associated with topotecan treatment were hematological, and to ensure complete reporting of hematological toxicities, *these results were derived from the laboratory values recorded rather than the investigator reported hematological AEs.* Non-hematological toxicities consisted of treatment-emergent reported AEs

MEDICAL OFFICER NOTE: Where are the investigator reported hematological adverse events?

In the oral topotecan + BSC arm, grade 3 or 4 neutropenia occurred in 61.2% of patients, grade 3 or 4 leukopenia in 40.6% of patients, grade 3 or 4 thrombocytopenia in 37.7% of patients, and grade 3 or 4 anemia in 24.6% of patients.

In the BSC alone arm, grade 3 or 4 neutropenia occurred in 10.9% of patients, grade 3 or 4 leukopenia in 0 patients, grade 3 or 4 thrombocytopenia in 4.3% of patients, and grade 3 or 4 anemia in 6.4% of patients.

Sponsor's Note: The protocol-specified laboratory assessments and scheduled clinic visits in the oral topotecan + BSC arm conformed to standard medical evaluation procedures for patients receiving cytotoxic therapy. *Patients in the BSC alone arm were not expected to have laboratory assessments during this same post-randomization time period; for these patients, clinic visits were encouraged but not scheduled.*

MEDICAL OFFICER NOTE: The patients in the BSC alone arm, with regard to laboratory assessments and clinic visits, were handled differently than the topotecan arm.

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Table 33 Number (%) of patients with haematological toxicities at baseline and on-therapy: modified ITT population

Haematological Toxicity	n[1]	Worst Toxicity Grade 0	1	2	3	4
ASC alone						
Leukopenia						
baseline	67	65 (97.0%)	2 (3.0%)	0	0	0
on-therapy	47	40 (85.1%)	5 (10.6%)	2 (4.3%)	0	0
Neutropenia						
baseline	65	59 (90.8%)	1 (1.5%)	0	3 (4.6%)	2 (3.1%)
on-therapy	46	40 (87.0%)	1 (2.2%)	0	3 (6.5%)	2 (4.3%)
Thrombocytopenia						
baseline	66	60 (90.9%)	6 (9.1%)	0	0	0
on-therapy	47	40 (85.1%)	5 (10.6%)	0	2 (4.3%)	0
Anaemia						
baseline	67	29 (43.3%)	34 (50.7%)	2 (3.0%)	0	2 (3.0%)
on-therapy	47	14 (29.8%)	24 (51.1%)	6 (12.8%)	1 (2.1%)	2 (4.3%)
ASC + OT						
Leukopenia						
baseline	70	65 (92.9%)	4 (5.7%)	1 (1.4%)	0	0
on-therapy	69	7 (10.1%)	8 (11.6%)	26 (37.7%)	17 (24.6%)	11 (15.9%)
Neutropenia						
baseline	67	61 (91.0%)	2 (3.0%)	0	4 (6.0%)	0
on-therapy	67	6 (9.0%)	9 (13.4%)	11 (16.4%)	19 (28.4%)	22 (32.8%)
Thrombocytopenia						
baseline	70	64 (91.4%)	6 (8.6%)	0	0	0
on-therapy	69	13 (18.8%)	19 (27.5%)	11 (15.9%)	21 (30.4%)	5 (7.2%)
Anaemia						
baseline	70	34 (48.6%)	30 (42.9%)	3 (4.3%)	0	3 (4.3%)
on-therapy	69	4 (5.8%)	16 (23.2%)	32 (46.4%)	10 (14.5%)	7 (10.1%)

Data source: Table 14.5.1, Table 14.99.2

1. Number of patients with laboratory data.

Note that in study 478, laboratory assessment were not routinely done for patients randomized to the BSC alone arm.

Table 35 Number (%) of patients at each course with grades 3 and 4 neutropenia: modified ITT population, ASC + OT group only

Course	Neutropenia		
	n[1]	Grade 3	Grade 4
1	67	12 (17.9%)	15 (22.4%)
2	57	9 (15.8%)	9 (15.8%)
3	50	8 (16.0%)	5 (10.0%)
4	36	10 (27.8%)	0
5	25	3 (12.0%)	2 (8.0%)
6	19	2 (10.5%)	0
7	6	0	0
8	4	0	0
9	4	0	0
10	1	0	0
Total	67	19 (28.4%)	22 (32.8%)

Data source: Table 14.5.1

1. Number of patients with laboratory data

Table 36 Number (%) of patients at each course with grades 3 and 4 thrombocytopenia: modified ITT population, ASC + OT group only

Course	Thrombocytopenia		
	n[1]	Grade 3	Grade 4
1	69	13 (18.8%)	5 (7.2%)
2	57	11 (19.3%)	0
3	50	6 (12.0%)	0
4	37	1 (2.7%)	0
5	26	0	0
6	19	0	0
7	6	0	0
8	4	0	0
9	4	0	0
10	1	0	0
Total	69	21 (30.4%)	5 (7.2%)

Data source: Table 14.5.1

1. Number of patients with laboratory data

Table 37 Number (%) of patients at each course with grades 3 and 4 anaemia: modified ITT population, ASC + OT group only

Course		Anaemia	
	n[1]	Grade 3	Grade 4
1	69	1 (1.4%)	4 (5.8%)
2	58	3 (5.2%)	5 (8.6%)
3	50	4 (8.0%)	3 (6.0%)
4	37	2 (5.4%)	4 (10.8%)
5	26	2 (7.7%)	3 (11.5%)
6	19	0	3 (15.8%)
7	6	0	2 (33.3%)
8	4	1 (25.0%)	1 (25.0%)
9	4	0	1 (25.0%)
10	1	1 (100.0%)	0
Total	69	10 (14.5%)	7 (10.1%)

Data source: Table 14.5.1

1. Number of patients with laboratory data

Table 38 Time to onset and duration of grade 4 leukopenia, neutropenia and thrombocytopenia, and grade 3/4 anaemia: modified ITT population, ASC + OT group only

Toxicity: grade	n[1]	Courses	Onset (days)		Duration (days)		
		with Toxicity	median	range	median	range	> 7 days[2]
Leukopenia: 4	274	11 (4.0%)	13	8 – 15	5	1 – 8	2 (18.2%)
Neutropenia: 4	269	31 (11.5%)	15	8 – 23	6	1 – 13	7 (2.6%)
Thrombocytopenia: 4	273	5 (1.8%)	13	12 – 15	4	1 – 5	0
Anaemia: 3 or 4	274	40 (14.6%)	8	2 – 22	14	1 – 34	28 (10.2%)

Data source: Table 14.6.1

1. Number of courses with laboratory data.
2. Expressed as a percentage of the total number of courses.

Table 39 Summary of haematological nadirs: modified ITT population, ASC + OT group only

Variable	n[1]	Statistic	Mean (S.D.)	Median
WBC	274	Nadir (10^9/L)	3.6 (2.0)	3.3
	274	Day of nadir	13.4 (5.2)	15.0
	274	% decrease	50.4 (29.8)	54.2
Neutrophils	269	Nadir (10^9/L)	1.9 (1.6)	1.6
	269	Day of nadir	14.6 (5.1)	15.0
	263	% decrease	57.5 (31.6)	65.5
Platelets	273	Nadir (10^9/L)	153.8 (99.6)	140.0
	273	Day of nadir	14.9 (4.1)	15.0
	273	% decrease	41.9 (36.4)	47.8
Haemoglobin	274	Nadir (g/L)	95.4 (30.6)	99.0
	274	Day of nadir	15.4 (5.5)	15.0
	274	% decrease	18.8 (13.4)	19.8

Data source: Table 14.7.1
1. Number of courses with laboratory data.

Therapeutic Interventions - Study 478

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Table 41 Number (%) of patients/courses with fever, infection or sepsis: modified ITT population, ASC + OT group only

Complication/Intervention	ASC + OT	
	patients N=70	Courses N=278
Fever ≥ grade 2 or FN[1]	5 (7.1%)	5 (1.8%)
FN[1]	2 (2.9%)	2 (0.7%)
Fever ≥ grade 2 or FN[1] proximate to grade 4 neutropenia	1 (1.4%)	1 (0.4%)
Infection ≥ grade 2[2]	10 (14.3%)	11 (4.0%)
Infection ≥ grade 2[2] proximate to grade 4 neutropenia	3 (4.3%)	4 (1.4%)
Sepsis	3 (4.3%)	3 (1.1%)
Systemic antibiotic	27 (38.6%)	45 (16.2%)
Systemic I.V. antibiotic	15 (21.4%)	18 (6.5%)
I.V. antibiotic with ≥ grade 2 fever/ FN/infection proximate to grade 4 neutropenia or sepsis	6 (8.6%)	6 (2.2%)

Data source: Table 14.8.1

1. Excluding infection and sepsis.
2. Excluding sepsis.

Fever or infection proximate to grade 4 neutropenia in the oral topotecan + BSC group occurred in 4 (5.8%) patients in 5 (2.8%) courses. Sepsis occurred in 3 (4.3%) patients. Intravenous antibiotic use associated with episodes of fever, febrile neutropenia, or infection proximate to grade 4 neutropenia occurred for 6 patients in 6 (2.2%) courses.

No analysis of these events was performed for the BSC alone group since this information was not collected in the same systematic manner as that done for the oral topotecan arm. The summary of AEs showed that one patient in the BSC alone group experienced sepsis (grade 3). Eight (11.9%) patients in the BSC alone group experienced infections (excluding sepsis) of at least grade 2 severity.

The table below is only for the oral topotecan arrm. One patient received G-CSF in three cycles. Two patients received erythropoietin in four cycles. Twenty patients received red blood cell transfusions in 36 cycles. Five patients received platelet transfusions in eight cycles.

Table 22 Therapeutic Interventions for Hematological Toxicity Number (%) of Patients/Courses – Study 478

	Oral Topotecan + BSC	
	Patients (%)	Courses (%)
Intervention	n=70	n=276
Red blood cells	20 (28.6)	36 (13.0)
Platelets	5 (7.1)	6 (2.2)
G(M)-CSF	1 (1.4)	3 (1.1)
G-CSF as treatment	0	0
G-CSF as prophylaxis	1 (1.4)	3 (1.1)
Erythropoietin	2 (2.9)	4 (1.4)

No analysis of interventions for hematological toxicity was performed for the ASC alone group. None of the agents listed in the table above were administered to patients in the ASC alone group.

MEDICAL OFFICER NOTE: The use of hematologic growth factors was not described or recommended in the protocol.

Medications for palliation of SCLC symptoms and palliative radiotherapy were used more frequently in the ASC alone group (medications: 55 patients, 82.1%, and 42 patients, 60.0%, in the respective groups; palliative radiotherapy 17 patients, 25.4%, and 10 patients, 14.3%, in the respective groups). Transfusions were used more frequently in the ASC + OT group where they were required as support in patients with thrombocytopenia and/or anaemia.

MEDICAL OFFICER NOTE: The following statements conflict: 1) No analysis of interventions for hematological toxicity was performed for the ASC alone group. None of the agents listed in the table above were administered to patients in the ASC alone group and 2) Transfusions were used more frequently in the ASC + OT group where they were required as support in patients with thrombocytopenia and/or anemia.

On 8/30/2007, the Sponsor responded to the above concern with:

"In the Synopsis and in Section 7.3.3 "Palliative Care" of the Clinical Study Report (CSR) for Study 478, the statement "Transfusions were used *more* frequently in the ASC + OT group where they were required as support in patients with thrombocytopenia and/or anemia" is correct as this statement was made with reference to the palliative transfusions administered as part of the ASC for both treatment groups (Table 22 "Palliative care for SCLC symptoms; modified ITT population" of the CSR). The words "more frequently" are not meant to reflect a comparative statement based on statistical analysis. Rather, this was a clinical interpretation, an observation that the incidence seen in the ASC + OT group was greater than that experienced in the ASC only group. The claim on Page 87 of the CSR is correct that no analysis of interventions for hematological toxicity was performed for the ASC alone group as no chemotherapy was administered in the ASC only arm."

"Further, Table 12.17.1 shows that none of the agents listed in Table 40 were administered to patients in the ASC alone group, as this table reports medications given for reasons *other than* palliative care of the underlying SCLC (stated in the title of Table 12.17.1). Since Table 12.17.1 presents the transfusions administered for hematologic toxicity (e.g., reflecting the toxicity due to administered chemotherapy) and no chemotherapy was administered in the ASC alone arm, the number "0" was entered."

A total of 46 patients (68.7%) in the ASC alone group and 50 patients (71.4%) in the ASC + OT group had non-hematological AEs. Patients with the most commonly occurring AEs (≥10% of patients in either group) are summarized in the following table by toxicity grade.

Title: An Open-Label, Multicentre, Randomised, Phase III Comparator Study of ASC alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC

Preferred Term	Worst Toxicity Grade					Total
	Unknown	1	2	3	4	
ASC alone						**N=67**
Disease Progression	4 (6.0%)	0	0	1 (1.5%)	6 (9.0%)	11 (16.4%)
Dyspnoea	0	0	4 (6.0%)	5 (7.5%)	1 (1.5%)	10 (14.9%)
Cough	0	2 (3.0%)	5 (7.5%)	1 (1.5%)	0	8 (11.9%)
Fatigue	0	1 (1.5%)	3 (4.5%)	3 (4.5%)	0	7 (10.4%)
Nausea	0	2 (3.0%)	2 (3.0%)	0	0	4 (6.0%)
Diarrhoea	0	0	3 (4.5%)	0	0	3 (4.5%)
Vomiting	0	2 (3.0%)	0	0	0	2 (3.0%)
Pyrexia	0	1 (1.5%)	0	0	0	1 (1.5%)
Alopecia	0	0	0	0	0	0
ACS + OT						**N=70**
Nausea	0	11 (15.7%)	11 (15.7%)	1 (1.4%)	0	23 (32.9%)
Vomiting	0	4 (5.7%)	10 (14.3%)	2 (2.9%)	0	16 (22.9%)
Diarrhoea	0	2 (2.9%)	9 (12.9%)	3 (4.3%)	1 (1.4%)	15 (21.4%)
Fatigue	0	3 (4.3%)	7 (10.0%)	3 (4.3%)	0	13 (18.6%)
Cough	1 (1.4%)	2 (2.9%)	7 (10.0%)	1 (1.4%)	0	11 (15.7%)
Pyrexia	0	5 (7.1%)	3 (4.3%)	1 (1.4%)	0	9 (12.9%)
Dyspnoea	1 (1.4%)	1 (1.4%)	3 (4.3%)	1 (1.4%)	1 (1.4%)	7 (10.0%)
Alopecia	0	5 (7.1%)	2 (2.9%)	0	0	7 (10.0%)
Disease Progression	3 (4.3%)	0	1 (1.4%)	0	1 (1.4%)	5 (7.1%)

Although AEs were reported for similar numbers of patients in each treatment group, the profile of events was very different, as was to be expected. For patients in the ASC alone group, disease progression, dyspnoea and cough were the most commonly reported AEs,

occurring in 16.4%, 14.9% and 11.9% of patients respectively. For patients in the ASC + OT group, nausea, vomiting and diarrhoea were the most commonly reported AEs, occurring in 32.9%, 22.9% and 21.4% of patients respectively. Disease progression and dyspnoea occurred with a higher incidence and higher grade in the ASC alone group. Nausea, vomiting, diarrhoea, fatigue, pyrexia and alopecia occurred with a higher incidence in the ASC + OT group.

Table 43 Number (%) of patients with most frequently occurring (at least 5% of patients in either treatment group) AEs related to study treatment: modified ITT population, ASC + OT group only

Preferred Term	Worst Toxicity Grade 1	2	3	4	Total N=70
Nausea	10 (14.3%)	8 (11.4%)	1 (1.4%)	0	19 (27.1%)
Vomiting	3 (4.3%)	9 (12.9%)	1 (1.4%)	0	13 (18.6%)
Diarrhoea	2 (2.9%)	4 (5.7%)	3 (4.3%)	1 (1.4%)	10 (14.3%)
Fatigue	3 (4.3%)	5 (7.1%)	0	0	8 (11.4%)
Alopecia	5 (7.1%)	2 (2.9%)	0	0	7 (10.0%)
Pyrexia	4 (5.7%)	0	1 (1.4%)	0	5 (7.1%)
Anorexia	2 (2.9%)	3 (4.3%)	0	0	5 (7.1%)

Data source: Table 14.13.3

Serious Adverse Experiences

A total of 18 patients (25.7%) in the oral topotecan + BSC group and 18 patients (26.9%) in the BSC alone group had serious adverse events (SAEs) in the safety population. The most frequently reported SAEs in the oral topotecan + BSC group were thrombocytopenia (7.1%), leucopenia and neutropenia (4.3% each), and pulmonary embolism, neutropenic sepsis, and diarrhea (2.9% each). On the control arm, pulmonary embolism (1.5%) was the most common SAE. A total of 11 patients (15.7%) in the oral topotecan + BSC group had SAEs reported as related to study treatment.

MEDICAL OFFICER NOTE: For a group of patients not followed closely, the BSC arm had the same number of patients with serious adverse events as the topotecan arm.

Table 45 Reasons for dose delays after Course 1 (number (%) of courses): modified ITT population, ASC + OT only

Reason for Delay	ASC + OT N[1]=206
Haematological	25 (12.1%)
Non-haematological	2 (1.0%)
Haematological + non-haematological	0
Other (only)	12 (5.8%)
Unassigned	2 (1.0%)
Total	41 (19.9%)

Data source: Tables 14.19.1

1. Total number of courses after Course 1

Deaths

Table 48 Reported deaths by cause and time since randomisation: ITT population

Cause of Death	Treatment Group ASC N=67	ASC + OT N=70
Death ≤30 Days Since Randomisation		
Progressive disease	9 (12.9%)	1 (1.4%)
Haematological toxicity	0	2 (2.8%)
Non-haematological toxicity	0	1 (1.4%)
Other reasons	0	1 (1.4%)
Total	9 (12.9%)	5 (7.0%)
Total Deaths		
Progressive disease	66 (94.3%)	54 (76.1%)
Haematological toxicity	0	3 (4.2%)
Non-haematological toxicity	0	1 (1.4%)
Other reasons	1 (1.4%)	5 (7.0%)
Alive / Missing	3 (4.3%)	8 (11.3%)
Total	67 (95.7%)	63 (88.7%)

Data source: Table 14.99.3

Table 49 Number (%) of patients known to have died: modified ITT population, ASC + OT only

Cause of Death	Treatment Group ASC + OT N=70
Death ≤ 30 Days Since Last Dose	
Progressive disease	4 (5.7%)
Haematological toxicity	3 (4.3%)
Non-haematological toxicity	1 (1.4%)
Other reasons	3 (4.3%)
Total	11 (15.7%)
Death > 30 Days Since Last Dose	
Progressive disease	50 (71.4%)
Other reasons	1 (1.4%)
Total	51 (72.9%)
Death not recorded	8 (11.4%)

Data source: Table 14.15.1

A total of 11 patients (15.7%) died ≤30 days after receiving the last dose of study medication in the oral topotecan + BSC arm:
- 4 patients died from progressive disease.
- 3 patients died due to hematologic toxicities (attributed to study treatment).
- 1 patient died due to non-hematologic toxicity (diarrhea, possibly related to study treatment).
- 3 patients died due to other reasons (considered unrelated to study treatment).

Fifty of the 51 patients who died >30 days after the last dose of study medication died from disease progression. One patient died due to an "Other" reason, a chest infection prior to receiving topotecan that was not reported as an AE (possibly considered by the investigator as disease progression).

Table 31 Summary of Reported Deaths by Cause and Time from Randomization: ITT population - Study 478

Cause of Death	Oral Topotecan + BSC N=71	BSC Alone N=70
Death ≤30 Days Since Randomization		
All	5 (7.0%)	9 (12.9%)
Progressive disease	1 (1.4%)	9 (12.9%)
Hematological toxicity	2 (2.8%)	0
Non-hematological toxicity	1 (1.4%)	0
Other reasons	1 (1.4%)	0
Total Deaths		
All	63 (88.7%)	67 (95.7%)
Progressive disease	54 (76.1%)	66 (94.3%)
Hematological toxicity	3 (4.2%)	0
Non-hematological toxicity	1 (1.4%)	0
Other reasons	5 (7.0%)	1 (1.4%)
Alive / Missing	8 (11.3%)	3 (4.3%)

Table 50 Most frequently occurring (at least 2% of patients in either treatment group) SAEs: modified ITT population

Preferred Term	ASC alone		ASC + OT	
	Patients N=67 n (%)	Occurrences N	Patients N=70 n (%)	Occurrences n
At least one SAE	18 (26.9%)	19	18 (25.7%)	36
Disease progression	11 (16.4%)	11	5 (7.1%)	5
Thrombocytopenia	0	0	5 (7.1%)	5
Leukopenia	0	0	3 (4.3%)	3
Neutropenia	0	0	3 (4.3%)	3
Pulmonary embolism	1 (1.5%)	1	2 (2.9%)	2
Neutropenic sepsis	0	0	2 (2.9%)	2
Diarrhoea	0	0	2 (2.9%)	2

Data source: Tables 14.16.1, Table 14.17.1.

Table 51 Number (%) of patients with SAEs related to study treatment: modified ITT population, ASC + OT group only

Preferred Term	Worst Toxicity Grade					Total
	Unknown	1	2	3	4	
ASC + OT At least one SAE related to study treatment						N=70 11 (15.7%)
Thrombocytopenia	0	0	1 (1.4%)	2 (2.9%)	2 (2.9%)	5 (7.1%)
Neutropenia	1 (1.4%)	0	0	0	2 (2.9%)	3 (4.3%)
Leukopenia	0	0	1 (1.4%)	0	2 (2.9%)	3 (4.3%)
Neutropenic sepsis	0	0	0	0	2 (2.9%)	2 (2.9%)
Diarrhoea	0	0	0	1 (1.4%)	1 (1.4%)	2 (2.9%)
Infection	0	0	0	0	1 (1.4%)	1 (1.4%)
Lower respiratory tract infection	0	0	0	0	1 (1.4%)	1 (1.4%)
Pneumonia	1 (1.4%)	0	0	0	0	1 (1.4%)
Muscular weakness	0	0	0	1 (1.4%)	0	1 (1.4%)
Epistaxis	0	1 (1.4%)	0	0	0	1 (1.4%)

Data source: Table 14.16.3

Table 52 AEs leading to withdrawal: modified ITT population

Preferred Term	Worst Toxicity Grade 1	2	3	4	Total
ASC alone					**N=67**
Pulmonary embolism	0	0	0	1 (1.5%)	1 (1.5%)
ASC + OT					**N=70**
Leukopenia	0	0	0	2 (2.9%)	2 (2.9%)
Pulmonary embolism	0	0	0	2 (2.9%)	2 (2.9%)
Thrombocytopenia	0	0	1 (1.4%)	1 (1.4%)	2 (2.9%)
Diarrhoea	0	0	1 (1.4%)	1 (1.4%)	2 (2.9%)
Cerebrovascular accident	0	0	0	1 (1.4%)	1 (1.4%)
Disease progression	0	0	0	1 (1.4%)	1 (1.4%)
Infection	0	0	0	1 (1.4%)	1 (1.4%)
Neutropenia	0	0	1 (1.4%)	0	1 (1.4%)
Dyspnoea exacerbated	0	0	1 (1.4%)	0	1 (1.4%)
Neutropenic sepsis	0	0	1 (1.4%)	0	1 (1.4%)
Convulsion	0	1 (1.4%)	0	0	1 (1.4%)
Lymphadenopathy	0	1 (1.4%)	0	0	1 (1.4%)

Data source: Table 14.18.1

Table 53 Number (%) of patients with non-haematological laboratory toxicities of worst grade 3 and 4[1] at baseline and on-therapy: modified ITT population

Laboratory Variable	Baseline n[2]	Grade 3	Grade 4	On-therapy n[2]	Grade 3	Grade 4
ASC alone						
Albumin	57	0	0	37	0	0
Alkaline phosphatase	61	0	0	40	0	0
ALT	63	0	0	40	2 (5.0%)	0
AST	60	0	0	34	3 (8.8%)	0
Calcium	58	0	0	39	1 (2.6%)	3 (7.7%)
Magnesium	39	0	0	35	0	0
Potassium	60	0	0	40	2 (5.0%)	1 (2.5%)
Sodium	60	1 (1.7%)	0	40	2 (5.0%)	1 (2.5%)
Total bilirubin	65	0	0	39	1 (2.6%)	1 (2.6%)
Urea	55	0	0	34	1 (2.9%)	0
ASC + OT						
Albumin	63	0	0	64	1 (1.6%)	0
Alkaline phosphatase	67	0	0	66	1 (1.5%)	0
ALT	67	0	0	64	1 (1.6%)	0
AST	65	0	0	61	2 (3.3%)	0
Calcium	64	0	2 (3.1%)	63	0	5 (7.9%)
Magnesium	50	0	0	57	6 (10.5%)	1 (1.8%)
Potassium	68	1 (1.5%)	0	67	2 (3.0%)	1 (1.5%)
Sodium	68	4 (5.9%)	0	67	9 (13.4%)	4 (6.0%)
Total bilirubin	67	0	0	65	1 (1.5%)	0
Urea	60	0	0	58	1 (1.7%)	0

Data source: Table 14.23.1

1. Not all laboratory values of clinical concern were reported as AEs by the investigator
2. Number of patients with laboratory data

1. Patients were considered to have completed the study if the following conditions applied:
Study 478: the patient successfully completed screening, was randomized, and was not withdrawn due to an AE, protocol violation, lost to the study, or own request.

Table 54 Vital signs values outside pre-determined ranges pre- and post-dose: modified ITT population

Variable		Outside Normal Range		
		High		
		n (%)		N[1]
ASC alone				
Systolic blood pressure (mmHg)			**> 160**	
Observations	Pre-dose	7 (3.9%)		178
	Post-dose	3 (1.7%)		178
Patients	Pre-dose	2 (3.9%)		51
	Post-dose	2 (3.9%)		51
Diastolic blood pressure (mmHg)			**> 100**	
Observations	Pre-dose	0		178
	Post-dose	0		178
Patients	Pre-dose	0		51
	Post-dose	0		51
Heart rate (bpm)			**> 100**	
Observations	Pre-dose	11 (6.2%)		178
	Post-dose	4 (2.2%)		178
Patients	Pre-dose	3 (5.9%)		51
	Post-dose	4 (7.8%)		51
Temperature (°C)			**> 38.5**	
Observations	Pre-dose	0		176
	Post-dose	0		176
Patients	Pre-dose	0		49
	Post-dose	0		49

1. Number of patients/observations with data.

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Table 54 Vital signs values outside pre-determined ranges pre- and post-dose: modified ITT population (continued)

Variable		Outside Normal Range High n (%)		N[1]
ASC + OT				
Systolic blood pressure (mmHg)			**> 160**	
Observations	Pre-dose	14 (5.6%)		252
	Post-dose	5 (2.0%)		252
Patients	Pre-dose	4 (6.2%)		65
	Post-dose	2 (3.1%)		65
Diastolic blood pressure (mmHg)			**> 100**	
Observations	Pre-dose	0		252
	Post-dose	0		252
Patients	Pre-dose	0		65
	Post-dose	0		65
Heart rate (bpm)			**> 100**	
Observations	Pre-dose	9 (3.6%)		252
	Post-dose	21 (8.3%)		252
Patients	Pre-dose	2 (3.1%)		65
	Post-dose	11 (16.9%)		65
Temperature (°C)			**> 38.5**	
Observations	Pre-dose	0		245
	Post-dose	0		245
Patients	Pre-dose	0		64
	Post-dose	0		64

Data source: Table 14.24.1
1. Number of patients/observations with data.

In both treatment groups, the proportions of patients with systolic or diastolic blood pressure values, or with temperature or heart rate values outside the normal range were generally not greatly increased from pre-dose to post-dose. ***The variable with the largest changes was heart rate: in the ASC alone group, 5.9% of patients had an increased heart rate at baseline and 7.8% of patients had an increased heart rate post-treatment; in the ASC + OT group, 3.1% of patients had an increased heart rate at baseline and 16.9% of patients had an increased heart rate post-treatment.*** According to the Sponsor, these data confirm that topotecan does not adversely affect the vital signs.

MEDICAL OFFICER NOTE: Topotecan localized mainly in mitochondria.84 The experiments were done in HT-29 colon carcinoma cells and in a subline, HT-29/Mit, selected for resistance to mitoxantrone and overexpressing breast cancer resistance-associated protein. Whether topotecan localizes in myocardial mitochondia is not known at this time by the reviewer.

84 Croce AC, Bottiroli G, Supino R, Favini E, Zuco V, Zunino F. Subcellular localization of the camptothecin analogues, topotecan and gimatecan. Biochem Pharmacol. 2004 Mar 15;67(6):1035-45.

Seventy per cent of the patients on the oral topotecan arm completed the study compared to 53% of the patients on the best supportive care arm. The reasons for withdrawal from the study are in the table below.

Table 35 Patient Disposition

	Study 478	
	Oral Topotecan + BSC	BSC Alone
	N=71	N=70
	n (%)	n (%)
Completed the study[1]	50 (70.4)	37 (52.9)
Total withdrawn	21 (29.6)	33 (47.1)
Reason for withdrawal		
AE	13 (18.3)	9 (12.9)
Other	5 (7.0)	13 (18.6)
Protocol violation	0	7 (10.0)
Lost to follow-up	2 (2.8)	4 (5.7)
Ongoing	1 (1.4)	0
Missing reason	0	0

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7.1.1 Sponsor's Safety Conclusions

- In the ASC + OT group, the frequency of grade 3 or 4 haematological toxicities was in keeping with the known profile of oral topotecan: grade 3 or 4 neutropenia occurred in 61.2% of patients, grade 3 or 4 leukopenia in 40.6% of patients, grade 3 or 4 thrombocytopenia in 37.7% of patients and grade 3 or 4 anaemia in 24.6% of patients. Similarly, the incidence of fever, febrile neutropenia, infection and sepsis were as expected following treatment with topotecan: fever or infection proximate to grade 4 neutropenia occurred in 4 (5.8%) patients. Sepsis was reported for 3 (4.3%) patients.

- The numbers of patients who experienced AEs during the study was similar in each treatment group: 46 patients (68.7%) in the ASC alone group and 50 patients (71.4%) in the ASC + OT group.

- The AEs observed in the ASC + OT group during this study were consistent with the established safety profile of oral topotecan.

- A total of 18 patients (26.9%) in the ASC alone group and 18 patients (25.7%) in the ASC + OT group had SAEs. The reported incidence of disease progression was higher in the ASC alone group (11 patients, 16.4%) than in the ASC+ OT group (5 patients, 7.1%). The incidence of serious thrombocytopenia (5 patients, 7.1%), leukopenia (3 patients, 4.3%) and neutropenia (3 patients, 4.3%) was higher in the ASC + OT group, none of these events being reported in the ASC alone group.

- In total, 1 patient (1.5%) in the ASC alone group and 11 patients (15.7%) in the ASC + OT group were withdrawn from the study due to AEs in the modified ITT population. In the ASC alone group, one patient withdrew, due to a pulmonary embolism. In the ASC + OT group, the events most commonly leading to withdrawal were leukopenia, thrombocytopenia, pulmonary embolism and diarrhoea.

- In the modified ITT population, 67 patients (95.7%) in the ASC alone group and 62 patients (88.6%) in the ASC + OT group are known to have died at any time. In the modified ITT population, 11 patients (15.7%) in the ASC + OT died within 30 days of their last receipt of study medication; 51 patients (72.9%) died more than 30 days after last receipt of study medication. Three patients died within 30 days of their last receipt of study medication due to haematological toxicity and one due to nonhaematological toxicity.

- Monitoring of non-haematological laboratory data and measurement of vital signs showed no results of clinical significance for the ASC + OT group.

- Topotecan was well tolerated in these patients. The performance of the drug was entirely consistent with the established profile of the drug. The overall risks of being on

topotecan, particularly the risk of early death, were no greater than the risks of being on ASC. The treatment-specific non-haematological AEs (which are symptomatic) were generally mild, self-limiting and responsive to concomitant medications or to dose reduction in subsequent cycles. There were slightly more Grade 4 non-haematological 0AEs amongst those patients who received ASC alone than there were amongst patients who received ASC + OT.

7.2 FDA's review of safety: Study #478

Hematological toxicity

Oral topotecan has grade 3-4 hematological toxicity (neutropenia> thrombocytopenia>anemia).

Table 33 Number (%) of patients with haematological toxicities at baseline and on-therapy: modified ITT population

Haematological Toxicity	n[1]	Worst Toxicity Grade 0	1	2	3	4
ASC alone						
Leukopenia						
baseline	67	65 (97.0%)	2 (3.0%)	0	0	0
on-therapy	47	40 (85.1%)	5 (10.6%)	2 (4.3%)	0	0
Neutropenia						
baseline	65	59 (90.8%)	1 (1.5%)	0	3 (4.6%)	2 (3.1%)
on-therapy	46	40 (87.0%)	1 (2.2%)	0	3 (6.5%)	2 (4.3%)
Thrombocytopenia						
baseline	66	60 (90.9%)	6 (9.1%)	0	0	0
on-therapy	47	40 (85.1%)	5 (10.6%)	0	2 (4.3%)	0
Anaemia						
baseline	67	29 (43.3%)	34 (50.7%)	2 (3.0%)	0	2 (3.0%)
on-therapy	47	14 (29.8%)	24 (51.1%)	6 (12.8%)	1 (2.1%)	2 (4.3%)
ASC + OT						
Leukopenia						
baseline	70	65 (92.9%)	4 (5.7%)	1 (1.4%)	0	0
on-therapy	69	7 (10.1%)	8 (11.6%)	26 (37.7%)	17 (24.6%)	11 (15.9%)
Neutropenia						
baseline	67	61 (91.0%)	2 (3.0%)	0	4 (6.0%)	0
on-therapy	67	6 (9.0%)	9 (13.4%)	11 (16.4%)	19 (28.4%)	22 (32.8%)
Thrombocytopenia						
baseline	70	64 (91.4%)	6 (8.6%)	0	0	0
on-therapy	69	13 (18.8%)	19 (27.5%)	11 (15.9%)	21 (30.4%)	5 (7.2%)
Anaemia						
baseline	70	34 (48.6%)	30 (42.9%)	3 (4.3%)	0	3 (4.3%)
on-therapy	69	4 (5.8%)	16 (23.2%)	32 (46.4%)	10 (14.5%)	7 (10.1%)

Data source: Table 14.5.1, Table 14.99.2

1. Number of patients with laboratory data.

The grade 4 neutropenia had serious complications as follows:

Fever or infection proximate to grade 4 neutropenia in the oral topotecan + BSC group occurred in 4 (5.8%) patients in 5 (2.8%) courses. Sepsis occurred in 3 (4.3%) patients.Intravenous antibiotic use associated with episodes of fever, febrile neutropenia, or infection proximate to grade 4 neutropenia occurred for 6 patients in 6 (2.2%) courses.

With regard to hematological growth factors, the table below is only for the oral topotecan arrm. One patient received G-CSF in three cycles. Two patients received erythropoietin in four cycles. Twenty patients received red blood cell transfusions in 36 cycles. Five patients received platelet transfusions in eight cycles.

Table 22 Therapeutic Interventions for Hematological Toxicity Number (%) of Patients/Courses – Study 478

	Oral Topotecan + BSC	
	Patients (%)	Courses (%)
Intervention	n=70	n=276
Red blood cells	20 (28.6)	36 (13.0)
Platelets	5 (7.1)	6 (2.2)
G(M)-CSF	1 (1.4)	3 (1.1)
G-CSF as treatment	0	0
G-CSF as prophylaxis	1 (1.4)	3 (1.1)
Erythropoietin	2 (2.9)	4 (1.4)

The use of hematologic growth factors was not described or recommended in the protocol. The use of G-CSF was deleted from the proposed label of oral topotecan by the FDA. On Oct. 2, 2007, the Sponsor requested retention of this wording in the label. This was based on the guidance for the use of G-CSF in many clinical trials of IV topotecan and oral topotecan although there was no guidance for the use of G-CSF in study #478. On Oct. 8, 2007, the Sponsor wrote the following: [redacted] GSK has reviewed the data and agrees with the deletion of this statement."

Non-hematological toxicity

A total of 46 patients (68.7%) in the ASC alone group and 50 patients (71.4%) in the ASC + OT group had non-hematological AEs. Patients with the most commonly occurring AEs (≥10% of patients in either group) are summarized in the following table by toxicity grade.

Title: An Open-Label, Multicentre, Randomised, Phase III Comparator Study of ASC alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC						
Preferred Term	**Worst Toxicity Grade**					**Total**
	Unknown	**1**	**2**	**3**	**4**	
ASC alone						**N=67**
Disease Progression	4 (6.0%)	0	0	1 (1.5%)	6 (9.0%)	11 (16.4%)
Dyspnoea	0	0	4 (6.0%)	5 (7.5%)	1 (1.5%)	10 (14.9%)
Cough	0	2 (3.0%)	5 (7.5%)	1 (1.5%)	0	8 (11.9%)
Fatigue	0	1 (1.5%)	3 (4.5%)	3 (4.5%)	0	7 (10.4%)
Nausea	0	2 (3.0%)	2 (3.0%)	0	0	4 (6.0%)
Diarrhoea	0	0	3 (4.5%)	0	0	3 (4.5%)
Vomiting	0	2 (3.0%)	0	0	0	2 (3.0%)
Pyrexia	0	1 (1.5%)	0	0	0	1 (1.5%)
Alopecia	0	0	0	0	0	0
ACS + OT						**N=70**
Nausea	0	11 (15.7%)	11 (15.7%)	1 (1.4%)	0	23 (32.9%)
Vomiting	0	4 (5.7%)	10 (14.3%)	2 (2.9%)	0	16 (22.9%)
Diarrhoea	0	2 (2.9%)	9 (12.9%)	3 (4.3%)	1 (1.4%)	15 (21.4%)
Fatigue	0	3 (4.3%)	7 (10.0%)	3 (4.3%)	0	13 (18.6%)
Cough	1 (1.4%)	2 (2.9%)	7 (10.0%)	1 (1.4%)	0	11 (15.7%)
Pyrexia	0	5 (7.1%)	3 (4.3%)	1 (1.4%)	0	9 (12.9%)
Dyspnoea	1 (1.4%)	1 (1.4%)	3 (4.3%)	1 (1.4%)	1 (1.4%)	7 (10.0%)
Alopecia	0	5 (7.1%)	2 (2.9%)	0	0	7 (10.0%)
Disease Progression	3 (4.3%)	0	1 (1.4%)	0	1 (1.4%)	5 (7.1%)

Although AEs were reported for similar numbers of patients in each treatment group, the profile of events was very different, as was to be expected. For patients in the ASC alone group, disease progression, dyspnea and cough were the most commonly reported AEs, occurring in 16.4%, 14.9% and 11.9% of patients respectively. For patients in the ASC + OT group, nausea, vomiting and diarrhea were the most commonly reported AEs, occurring in 32.9%, 22.9% and 21.4% of patients respectively. Disease progression and dyspnea occurred with a higher incidence in the ASC alone group. Nausea, vomiting, diarrhea, fatigue, pyrexia and alopecia occurred with a higher incidence in the ASC + OT group.

Increases in Heart Rate

The two tables below are tabulations of vital signs on study #478.

In both treatment groups, the proportions of patients with systolic or diastolic blood pressure values, or with temperature or heart rate values outside the normal range were generally not greatly increased from pre-dose to post-dose. ***The variable with the largest changes was heart rate: in the ASC alone group, 5.9% of patients had an increased heart rate at baseline and 7.8% of patients had an increased heart rate post-treatment; in the ASC + OT group, 3.1% of patients had an increased heart rate at baseline and 16.9% of patients had an increased heart rate post-treatment.*** According to the Sponsor, these data confirm that topotecan does not adversely affect the vital signs. See table below.

Table 54 Vital signs values outside pre-determined ranges pre- and post-dose: modified ITT population

Variable		Outside Normal Range		
		n (%)	High	N[1]
ASC alone				
Systolic blood pressure (mmHg)			> 160	
Observations	Pre-dose	7 (3.9%)		178
	Post-dose	3 (1.7%)		178
Patients	Pre-dose	2 (3.9%)		51
	Post-dose	2 (3.9%)		51
Diastolic blood pressure (mmHg)			> 100	
Observations	Pre-dose	0		178
	Post-dose	0		178
Patients	Pre-dose	0		51
	Post-dose	0		51
Heart rate (bpm)			> 100	
Observations	Pre-dose	11 (6.2%)		178
	Post-dose	4 (2.2%)		178
Patients	Pre-dose	3 (5.9%)		51
	Post-dose	4 (7.8%)		51
Temperature (°C)			> 38.5	
Observations	Pre-dose	0		176
	Post-dose	0		176
Patients	Pre-dose	0		49
	Post-dose	0		49

1. Number of patients/observations with data.

Table 54 Vital signs values outside pre-determined ranges pre- and post-dose: modified ITT population (continued)

Variable		Outside Normal Range High n (%)	N[1]
ASC + OT			
Systolic blood pressure (mmHg)		**> 160**	
Observations	Pre-dose	14 (5.6%)	252
	Post-dose	5 (2.0%)	252
Patients	Pre-dose	4 (6.2%)	65
	Post-dose	2 (3.1%)	65
Diastolic blood pressure (mmHg)		**> 100**	
Observations	Pre-dose	0	252
	Post-dose	0	252
Patients	Pre-dose	0	65
	Post-dose	0	65
Heart rate (bpm)		**> 100**	
Observations	Pre-dose	9 (3.6%)	252
	Post-dose	21 (8.3%)	252
Patients	Pre-dose	2 (3.1%)	65
	Post-dose	11 (16.9%)	65
Temperature (°C)		**> 38.5**	
Observations	Pre-dose	0	245
	Post-dose	0	245
Patients	Pre-dose	0	64
	Post-dose	0	64

Data source: Table 14.24.1
1. Number of patients/observations with data.

Review of the vital signs of the patients on the topotecan, who had increased heart rates did not reveal a pattern associated with systolic pressures, diastolic pressures, pulse pressures, and temperatures. Review of the CRFs for these patients revealed: 1) at baseline the EKGs for all the patients were checked-off as "12-lead EKG normal/no clinically significant abnormalities" except for one patient (478.101.85461) who had "12-lead EKG clinical significant abnormalities: cardiac ischemia" on the CRF at baseline; and 2) at the time of the increase in heart rate, an EKG was either not done or the results of the EKG could not be found in the CRF. Review of the AE database did not reveal any anemia or any other adverse event to explain the increase heart rate. There was a patient (478.035.11246) with agitation at the time of the increased heart rate and there was another patient (478.101.85461) with a cerebral vascular accident and a number of electrolyte abnormalities

Overall safety conclusion:

- Hematological and non-hematological toxicities with the oral topotecan formulation are comparable to the experience with the intravenous topotecan formulation.

8 ADDITIONAL CLINICAL ISSUES

8.1 Special Populations

The table below shows the race distributions on the studies #478, #65, and #396. There was only one black patient (from Canada) entered on study #478. No conclusions about differing effects of Hycamtin capsules by race can be made.

	Study 478		Study 065		Study 396	
Baseline Characteristic	Oral Topotecan + BSC N=71 n (%)	BSC Alone N=70 n (%)	Oral Topotecan N=52 n (%)	IV Topotecan N=54 n (%)	Oral Topotecan N=153 n (%)	IV Topotecan N=151 n (%)
Race						
Caucasian	70 (98.6)	70 (100.0)	51 (98.1)	50 (92.6)	140 (91.5)	141 (93.4)
Black	1 (1.4)	0	1 (1.9)	1 (1.9)	4 (2.6)	1 (0.7)
Asian	0	0	0	1 (1.9)	8 (5.2)	8 (5.3)
Other	0	0	0	2 (3.7)	1 (0.7)	1 (0.7)

The intravenous formulation of topotecan has indications in ovarian, cervical, and small cell lung cancer. In the label for the intravenous formulation of topotecan, there is the following comment: "The effect of race on topotecan pharmacokinetics has not been studied."

8.2 Pediatrics

Not applicable. Small cell lung cancer is a smoking-related malignancy diagnosed in adults.

8.3 Advisory Committee Meeting

Not applicable.

8.4 Literature Review

DISEASE BACKGROUND

Each year over 170,000 new cases of lung cancer are diagnosed in the United States. Also, each year over 160,000 deaths from lung cancer occur. From 14% to 25% of lung cancer cases diagnosed are small cell lung cancer (SCLC).

The management of small cell lung cancer (NSCLC) is markedly different than non-small cell lung cancer. For the latter, surgical cure and radiotherapy for early stage disease, which is limited to the chest and mediastinum, are options. Small cell lung cancer (SCLC), which is an aggressive malignancy and disseminates systemically early, is responsive to chemotherapy and radiotherapy. The TNM classification system that is useful in NSCLC is not as predictive in

small cell lung cancer and is usually not used in SCLC. The SCLC is classified in two stages—limited and extensive. Overall, the median survival for patients with limited disease is 12-16 months and for patients with extensive disease is 8-10 months.[85,86,87] The table below describes much of the definitions, natural history, and treatment of SCLC.

	LIMITED STAGE	EXTENSIVE STAGE
Definition	tumor confined to one hemithorax and the regional lymph nodes the stage is based on a judgment as to whether all detectable tumor can be encompassed within a tolerable radiotherapy port, and therefore is a physiologic and anatomic definition	disease beyond these bounds of limited-stage
Proportion of patients with SCLC	~30%	~70%
Rx	Combination chemotherapy ± radiotherapy	chemotherapy
Median survival	12-16 months	8-10 months
Response to chemotherapy	~70%	
Prognosis of non-responders to chemotherapy	Poor Refractory disease Palliative Rx	
Prognosis of patients with response of long duration	Good Sensitive disease Further chemotherapy	

In general, limited stage SCLC is treated with chemotherapy plus radiotherapy to the chest disease. Extensive stage SCLC is treated with chemotherapy; radiotherapy is reserved for palliation of symptomatic disease and for patients, who achieve a complete response to chemotherapy and who then receive prophylactic cranial irradiation.

The table below (from DeVita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology, 6th edition, 2005) demonstrates the dissemination of the disease.

85 Source: original protocol for study #478.
86 Movsa B, Khuri FR, Kerstine K. Non-small-cell lung cancer. In: Cancer Management: a multidisciplinary approach,. Medical, surgical, & radiation oncology. 9th edition, 2005-2006 Edits: Pasdur R, Coia LR, Wagman LD. CMP Healthcare Media, Lawrence, KS, 2005. pp. 111-154
87 Glisson BS, Movsas B, Scott W.. Small-cell lung cancer, mesothelioma, and thymoma. In: Cancer Management: a multidisciplinary approach,. Medical, surgical, & radiation oncology. 9th edition, 2005-2006 Edits: Pazdur R, Coia LR, Wagman LD. CMP Healthcare Media, Lawrence, KS, 2005. pp. 155-173.

[redacted]

	Clinical Data		Autopsy Data		
Site	**All Patients**	**Single Site**	**LD at Presentation**	**ED at Presentation**	**All Patients**
Liver	21–36	6–7	60	73	69
Bone	27–41	9–13	45[a]	56[a]	54
Bone marrow	15–30	2–4	35	NA	NA
Adrenals	5–31	8–11	32	35	65
Brain	10–14	4–6	32	37–65	28–65
Retroperitoneal lymph nodes	3–12	NA	28	29	52
Mediastinal lymph nodes	66–80	80	73	83	87
Supraclavicular lymph nodes	17	5	NA	NA	42
Contralateral lung	1–12	1–4	14	8	27
Pleural effusion	16–20	2–7	28	30	NA
Subcutaneous tissues	5	NA	NA	NA	19 (and other soft tissues)
Pancreas	NA	NA	10–14	17	51

ED, extensive stage; LD, limited stage; NA, not available.
[a]Bone and bone marrow.
[Modified from Agiris A, Murren JR. Staging and prognostic factors in small cell lung cancer. In: Pass HI, Carbone DP, Johnson DH, et al., eds. *Lung cancer: principles and practice*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2004(*in press*).]

The natural history of the disease and the effect of the modalities of treatment are shown in the table below. Combination chemotherapy + chest radiotherapy are effective for limited stage SCLC. Combination chemotherapy alone gives the best results in extensive stage SCLC (from DeVita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology).

	Median Survival (Mo)		2- to 3-Y Survival Rate (%)	
Therapy	**Limited Disease[a]**	**Extensive Disease**	**Limited Disease**	**Extensive Disease**
Supportive care	3	1.5	—	—
Surgery	5–6[a]	—	4–5[a]	—
	11[b]		30–35[b]	
Thoracic radiotherapy	10[a]	—	10[a]	—
	3–9		2–7	
Single-agent chemotherapy	6	4	—	—
Combination chemotherapy	10–14	7–11	5–15	1–3
Combination chemotherapy with chest irradiation	15–26	7–11	10–40	1–2

[a]Operable patients in prechemotherapy era.
[b]Selected, carefully evaluated, pathologically staged patients.
(Modified from Morstyn G, Ihde DC, Lichter AS, et al. Small cell lung cancer 1973–1983: early progress and recent obstacles. *Int J Radiat Oncol Biol Phys* 1984;10:51; and ref. 61, with permission.)

In a comparison of surgery vs. radiotherapy in patients with operable SCLC, radiotherapy was superior (from DeVita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology).

			Survival Rate		
Group	**Patients**	**Mean Survival (Mo)**	**1 Y**	**2 Y**	**5 Y**
Surgery	71	6.5	21	4	1[a]
Radiotherapy	73	10[b]	22	10	4

[a]One patient unable to receive surgery; given irradiation.
[b]Significant survival difference ($P = .04$) in favor of radiotherapy.
(Modified from ref. 129.)

The benefit of chemotherapy added to the surgical adjuvant setting is shown below (from DeVita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology).

Adjuvant Therapy	Patients (n)	2-Y Survival Rate (%)
Chemotherapy	92	26
Placebo	61	8

(Data from refs. 247–250.)

The activity of numerous chemotherapeutic agents are shown in the table below (from DeVita, Hellman, & Rosenberg's Cancer: Principles & Practice of Oncology).

		No Prior Chemotherapy		Prior Chemotherapy	
Drug	**Dose (mg/m²)[a]**	**Patient (n)**	**% Response**	**Patient (n)**	**% Response**
Cyclophosphamide	1000	112	22	—	—
Ifosfamide	5000–8000	103	54	14	43
Doxorubicin	60	8	12	14	29
Epirubicin	100–120	182	48	—	—
Carboplatin	250–450	52	63	54	13
Cisplatin	50–120	—	—	118	14
Vincristine	1.5[b]	10	40	9	44
Vindesine	3–4[b]	—	—	50	24
Vinorelbine	30[b]	17	24	49	14
VP-16	100–300[c]	66	82	91	5
Teniposide	60–100[c]	109	52	80	22
Paclitaxel	250	75	45	24	29
Docetaxel	75–100	12	8	28	25
Irinotecan	100[b]	—	—	59	24
	350	—	—	32	16
Topotecan	1.5–2.0[c]	48	39	362	17

Gemcitabine	1000–1250[b]	31	48	64	19

Note: Response rates are weighted averages obtained from selected published trials that administered the chemotherapy drug intravenously in doses and schedules currently used. The duration of drug infusion was variable. Response rates should be regarded as approximate because patient populations were heterogeneous.
[a]Cycles repeated every 3 to 4 weeks unless otherwise specified.
[b]Treatment was given weekly or biweekly.
[c]Treatment was given daily or every other day for 3 to 5 days, repeated every 3 to 4 weeks.
(Modified from Agiris A, Murren JR. Advances in chemotherapy for small cell lung cancer. *Cancer J* 2001;7:228)

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Management (or unsuitable for IV chemotherapy) Issue

Treatment in patients with poor performance status[88]

> "Single agent chemotherapy in elderly patients and those with poor performance status was initially intended to provide a more tolerable treatment option. However, in comparisons of single-agent oral etoposide with combination chemotherapy regimens, patients assigned combination chemotherapy regimens not only lived longer but also had fewer side-effects. Therefore, combination chemotherapy remains the standard treatment in this setting. When the tolerability of standard dose etoposide and cisplatin remains a concern, options include dose reduction, substitution of carboplatin for cisplatin, or a combination of low-dose cisplatin, doxorubicin, vincristine, and etoposide."

According to Ardizzoni,[89]

> "Chemotherapy in the second line setting may provide symptom relief; however, many patients with relapsed SCLC have comorbidities, poor performance status (PS) scores, and often are elderly and, as a result, they may be unable to tolerate aggressive combination chemotherapy . In addition, many first-line chemotherapy regimens are associated with cumulative toxicities, including nephrotoxicity, neuropathy, and bone marrow suppression, and may limit the patient's ability to tolerate therapy on disease recurrence. Therefore, the cumulative toxicity profile of first-line treatments must also be considered when selecting treatments for managing recurrent disease."
>
> "Treatment of patients with relapsed SCLC who have adequate PS scores is based on the treatment-free interval and recovery from treatment-specific toxicities experienced in the first-line setting. For patients with a treatment-free interval >6 months, most oncologists use a reinduction strategy of platinum plus etoposide. The choice of treatment strategy in patients with treatment-free intervals <6 months is variable."
>
> "...many patients with recurrent SCLC are elderly and have multiple comorbidities (e.g., chronic obstructive pulmonary disease, coronary heart disease, arterial hypertension, diabetes) that may render them unable to tolerate intensive chemotherapy. Moreover, impaired end-organ function can significantly alter the pharmacokinetic and tolerability profiles of cytotoxic agents, and many oncologists have been reluctant to retreat these patients."

According to Chua,[90]

88 Jackman DM, Johnson BE. Lancet 2005;366:1385-96
89 Ardizzoni A. Topotecan in the Treatment of Recurrent Small Cell Lung Cancer: An Update. The Oncologist. 2004;9(suppl 6):4-13; Supported by GSK

"In conclusion, those regarded as elderly should be considered for treatment based on other clinical prognostic factors, chiefly performance status and presence of other co-morbidities rather than purely chronological age. Those with good performance status and minimal co-morbid illness should be treated in a similar manner to younger patients, preferably with a platinum-based regimen. Clinicians need to be cognisant of the higher risk of treatment toxicity and morbidity, and be prepared to offer supportive measures. On the other hand, older patients with other poor prognostic factors, such as poor performance status or significant comorbid illness, may still be considered for treatment, although in this setting the aim of treatment will be clearly be for palliative benefit."

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90 Chua YJ, Steer C, Yip D. Recent advances in management of small-cell lung cancer. Cancer Treatment Reviews. 2004;30:521-543

Resistant and Sensitive Small Cell Lung Cancer[91]

Introduction

Ardizzoni and co-authors defined two groups of previously treated SCLC patients, according to the probability of them responding to a second-line regimen. First, there were refractory patients, i.e., patients who did not respond to 1st-line therapy or who responded but progressed within 3 months from the end of treatment. Second, there were sensitive patients, i.e., patients who responded to 1st-line therapy but relapsed after a treatment-free interval of 3 or more months. Refractory SCLC patients rarely responded to 2nd-line single-agent chemotherapy and may only respond to true non-cross-resistant combination chemotherapy. In contrast, sensitive patients have more of a chance of responding to 2nd-line chemotherapy or perhaps to 1st-line chemotherapy rechallenge.

In their study, topotecan was administered as a 30-minute daily infusion at a dose of 1.5 mg/m2 for 5 consecutive days, every 3 weeks. The study was one of the largest phase II trials ever conducted with a single agent in the second-line treatment of this disease and the only study in which there was a prospective distinction between refractory and sensitive patients.

In the study, the type of prior chemotherapy did not appear to significantly influence treatment outcome. However, it was interesting to note that the response rate to topotecan was higher in patients who had been given prior topoisomerase II-directed agents (epipodophyllotoxins and anthracyclines) than in those who had not. This difference, although not statistically significant probably because of the small number of patients
in each subgroup, would be in agreement with preclinical data that suggest that resistance to topoisomerase II-targeting agents may induce collateral sensitivity to topoisomerase I drugs.

The table below shows that refractory SCLC is far less responsive (i.e., response rate: 6.3%) than sensitive SCLC (i.e., response rate: 37.3%). The drug used is intravenous topotecan.

91 In part, taken from Ardizzoni et al. J Clin Oncol 15:2090-2096, 1997

Table 2. Response Evaluation

	Refractory		Sensitive		Total	
	No.	%	No.	%	No.	%
Eligible	47	100	46	100	93	100
Not assessable	—		1	2.1	1	1.0
Assessable	47	100	45	100	92	100
CR	1	2.1	6	13.3	7	7.6
PR	2	4.2	11	24.0	13	14.1
OR	3	6.4	17	37.8	20	21.7
NC	19	40.4	14	31.1	33	35.9
PD	20	42.6	13	28.9	33	35.9
Early death	5	10.6	1	2.2	6	6.5

Abbreviations: OR, objective response; NC, no change; PD, progressive disease.

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The table below shows that response to 2nd-line IV topotecan was related to sensitivity to prior chemotherapy (i.e. sensitive vs refractory disease), the interval between the end of prior chemotherapy and the start of topotecan therapy (i.e., $\leq$6 months vs. > 6 months), and response to prior chemotherapy (i.e., CR + PR vs. no response). There were trends with gender and prior chemotherapy with anthracyclines or etoposide,

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TOPOTECAN IN THE SECOND-LINE TREATMENT OF SCLC

Table 3. Univariate Analysis of Prognostic Factors for Response to Topotecan

	No. Responders/ Eligible	%	P
Performance status			
0-1	16/76	21.0	NS
2	4/17	23.5	
Sex			
Male	16/64	25.0	NS
Female	4/29	13.8	
Age, years			
< 60	11/47	23.4	NS
≥ 60	9/46	19.6	
Sensitivity to prior CT			
Sensitive	17/46	37.0	.0008
Refractory	3/47	6.4	
No. of drugs in prior CT regimen			
≤ 3	11/54	20.3	NS
> 3	9/39	23.0	
Duration of prior CT, months			
≤ 6	15/76	19.7	NS
> 6	5/17	29.4	
Prior CT including			
Anthracyclines			
Yes	17/68	25.0	NS
No	3/25	12.0	
Etoposide			
Yes	20/86	23.2	NS
No	0/7	—	
Platinum compounds			
Yes	8/39	20.5	NS
No	12/54	22.2	
Interval between end of prior CT and start of topotecan, months			
≤ 6	8/72	11.1	.00001
> 6	12/21	57.1	
Response to prior CT			
CT + PR	19/70	27.1	.002
No response	1/23	4.3	

Abbreviations: CT, chemotherapy; NS, not significant.

The figure below demonstrates the survival difference between patients with sensitive and refractory SCLC patients to intravenous topotecan.

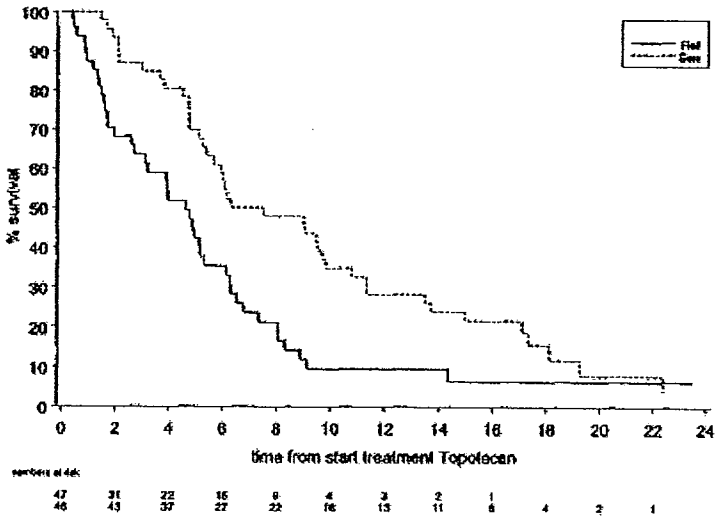

Fig 1. Actuarial survival according to prior treatment results. (——) Actuarial survival of refractory patients (median survival, 4.7 months). (------) Actuarial survival of sensitive patients (median survival, 6.9 months). Difference in survival between refractory and sensitive patients: $P = .0027$ (log-rank test of equality).

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MEDICAL OFFICER NOTE: In the table below, 90 days appears to be the dividing line between sensitive and resistant SCLC. In the von Pawel et al study,92 a minimum of 60 days was introduced in an ongoing two-arm, randomized trial *to make topotecan available* to a larger proportion of relapsed SCLC patients. There was no mention of the CAV arm or a general statement, making chemotherapy available to this subset of patients. Clinical and scientific evidence to support 60 days as a dividing line between sensitive and resistant SCLC is not available in the von Pawel et al article.

Definitions of sensitive and resistant disease in SCLC

SENSITIVE	RESISTANT
1st response > 34 weeks→ 2nd response in 15 of 19 (79%;) (median duration 32 wks [range: 22-53])93	1st response ≤ 34 weeks→ 2nd response in 8 of 18 (44%;) (median duration 17 wks [range: 6-48])94
1st response>8months →2nd response > 2 months95	1st response <8 months→2nd response < 2 months96
patients with an off-chemotherapy time >2.6 months responded (to VM-26) more frequently than the others *(P* = .016)97	
Rechallenge with the same drugs used in the initial chemotherapy still achieves around 50% response rate and about 3 months is the shortest time required from the end of previous chemotherapy in order to see frequent responses to reinduction98	
Abstract Responses were most common in patients who had responded to previous chemotherapy and who had not	Results patients who had been off chemotherapy < 90 days were less likely to respond *(P* = .03,

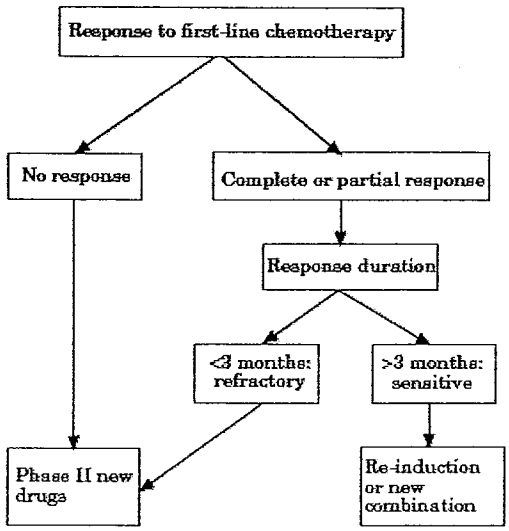
92 Von Pawel et al. Topotecan Versus Cyclophosphamide, Doxorubicin, and Vincristine for the Treatment of Recurrent Small-Cell Lung Cancer . *Clinical Oncology,* **17,** 658-667, 1999.
93 Postmus PE, Berendsen HH, van Zandwijk N, et al. Re-treatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. Eur J Cancer Clin Oncol 1987;23: 1409-1411.
94 Postmus PE, Berendsen HH, van Zandwijk N, et al. Re-treatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. Eur J Cancer Clin Oncol 1987;23: 1409-1411.
95 Vincent M, Evans B, Smith I. First-line chemotherapy rechallenge after relapse in small cell lung cancer. Cancer Chemother Pharmacol 1988;21:45-48.
96 Vincent M, Evans B, Smith I. First-line chemotherapy rechallenge after relapse in small cell lung cancer. Cancer Chemother Pharmacol 1988;21:45-48.
97 Giaccone et al. J Clin Oncol 6:1264-1270, 1988
98 Gioccone G. Eur J Cancer Clin Oncol. 1989;25:411-413
99 Johnson DH et al. J Clin Oncol 8:1613-1617, 1990

received any treatment in the 90 days before initiation of oral etoposide.99 Table 2 Time Off Chemotherapy: > 90 days Discussion Responses were most common in patients who had been off chemotherapy for at least 90 days and who had responded to previous treatment.	Fisher's exact test) 100 Table 2 Time Off Chemotherapy: < 90 days
CR ≥ 12 months101	
	refractory to chemotherapy as defined by either tumor growth during chemotherapy or the recurrence of a tumor within 3 months after the completion of chemotherapy or Chemotherapy-free interval: ≤90 days102
> 6 months following completion of 1st-line chemotherapy103	< 6 months after completion of 1st-line chemotherapy104
	"a period of 3 months for our definition of refractoriness to etoposide." "Refractoriness to etoposide was defined as lack of response to etoposide-containing frontline therapy, or ***progression during or within 3 months of the last dose of etoposide-containing frontline or second-line therapy***"105
sensitive patients, i.e., patients who responded to 1st-line therapy but relapsed after a treatment-free interval of 3 or more months106	refractory patients, i.e., patients who did not respond to 1st-line therapy or who responded but progressed within 3 months from the end of treatment107

100 Johnson DH et al. J Clin Oncol 8:1613-1617, 1990
101 Collard P, Weynants P, Francis C, et al. Treatment of relapse of small cell lung cancer in selected patients with the initial combination chemotherapy carboplatin, etoposide, and epirubicin. Thorax 1992;47:369-371.
102 Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 1992; 10:1225–1229
103 Greco FA. Treatment options for patients with relapsed small cell lung cancer. Lung Cancer 1993;(Suppl 1):S85-S89.
104 Greco FA. Treatment options for patients with relapsed small cell lung cancer. Lung Cancer 1993;(Suppl 1):S85-S89.
105 Perez-Solar R, Glisson BS, Lee JS, et al. 1996. Treatment of patients with Small Cell Lung Cancer refractory to Etoposide and Cisplatin with the Topoisomerase I poison Topotecan. Journal of Clinical Oncology, **14**, 2785-2790.
106 Ardizzoni et al. J Clin Oncol 15:2090-2096, 1997

s are those who have responded to first-line chemotherapy and relapsed after a treatment-free interval of ≥3 months108	r patients are those who have never responded to first-line chemotherapy or who have responded but progressed within 3 months from the end of induction treatment.109
chemosensitive (i.e., relapsed >90 days after firstline chemotherapy)110	chemorefractory (i.e., relapsed <90 days after first-line chemotherapy or did not respond) 111
Topotecan in the Treatment of Recurrent Small Cell Lung Cancer: An Update Andrea Ardizzoni *Oncologist* 2004; 9: 4-13 CME Quiz The preferred responses are highlighted. 2. The definition of a chemosensitive relapse in SCLC is: [Show hint!] a. A relapse that occurs >1 month after first-line chemotherapy. b. A relapse that occurs >2 months after first-line chemotherapy. c. A relapse that occurs >3 months after first-line chemotherapy. hint! **The efficacy and safety of topotecan in patients with recurrent SCLC have been demonstrated in several phase II studies (Table 1 +). These multicenter trials administered i.v. topotecan at a dose of 1.5 mg/m^2 on days 1–5 of a 21-day cycle (standard regimen). Enrolled patients had PS scores ≤2 and a mean age of 58 years at baseline. Topotecan was efficacious in both chemosensitive (i.e., relapsed >90 days after first-line chemotherapy) and chemorefractory (i.e., relapsed <90 days after first-line chemotherapy or did not respond) patients. Among chemosensitive patients, the ORR ranged from 14%–38%, with stable disease (SD) occurring in 16%–31% of patients. Median survival times among all patients in these studies ranged from 25–36 weeks. Among chemorefractory patients, the ORR was 2%–7%, with 5%–40% of patients achieving SD as a best response. The median overall survival time for patients with refractory disease was 16–21 weeks [18–21].**	
a prognostic distinction can be made between so called	a prognostic distinction can be made

107 Ardizzoni et al. J Clin Oncol 15:2090-2096, 1997; the study was supported by SmithKline Beecham Pharmaceuticals, Philadelphia, PA.
108 Ardizzoni A, Manegold C, Debruyne C, et al. European Organization for Research and Treatment of Cancer (EORTC) 08957 phase II study of topotecan in combination with cisplatin as second-line treatment of refractory and sensitive small cell lung cancer. *Clin Cancer Res* 2003;9:143–150.
109 Ardizzoni A, Manegold C, Debruyne C, et al. European Organization for Research and Treatment of Cancer (EORTC) 08957 phase II study of topotecan in combination with cisplatin as second-line treatment of refractory and sensitive small cell lung cancer. *Clin Cancer Res* 2003;9:143–150.
110 Ardizzoni A. Topotecan in the Treatment of Recurrent Small Cell Lung Cancer: An Update. The Oncologist. 2004;9(suppl 6):4-13; Supported by GSK
111 Ardizzoni A. Topotecan in the Treatment of Recurrent Small Cell Lung Cancer: An Update. The Oncologist. 2004;9(suppl 6):4-13; Supported by GSK

sensitive disease (patients with a response to first-line therapy and a treatment-free interval of at least 90 days) and refractory disease (patients with no response to first-line treatment or with relapse within 90 days)112	between so called sensitive disease (patients with a response to first-line therapy and a treatment-free interval of at least 90 days) and ***refractory disease (patients with no response to first-line treatment or with relapse within 90 days)***113
patients with so-called *sensitive disease*: those with a response to first-line therapy and a treatment-free interval of 90 days114	those with *resistant disease*: those with no response to first-line treatment or relapse within 90 days115
Sensitive patients (those who had a response to first-line therapy lasting 3 or more months) respond frequently to combination chemotherapy, which may be identical to first-line treatment116 Sensitive relapse SCLC patients are defined here as patients who have shown a response to induction treatment and a treatment-free interval of at least 3 months.	
Introductory text: patients who relapse more than 3 months after therapy eligibility criteria: date of progression being at least 60 days after completion of first-line chemotherapy. Discussion text:	

112 Ardizzoni A, Tiseo M. Small Cell Lung Cancer and Lack of Treatment Progress. Am Soc Clin Oncol Ed Book 423-427, 2007. Under potential conflicts of interest, Dr. Ardizzoni has listed honoraria from GlaxoSmithKline.
113 Ardizzoni A, Tiseo M. Small Cell Lung Cancer and Lack of Treatment Progress. Am Soc Clin Oncol Ed Book 423-427, 2007. Under potential conflicts of interest, Dr. Ardizzoni has listed honoraria from GlaxoSmithKline.
114 Tiseo M, Ardizzoni A. Current Status of Second-Line Treatment and Novel Therapies for Small Cell Lung Cancer. J Thorac Oncol. 2007;2: 764–772
115 Tiseo M, Ardizzoni A. Current Status of Second-Line Treatment and Novel Therapies for Small Cell Lung Cancer. J Thorac Oncol. 2007;2: 764–772
116 Huisman C, Postmus PE, Giaccone G, et al. Second-line chemotherapy and its evaluation in small cell lung cancer. *Cancer Treat Rev* 1999;25: 199–206.
117 Von Pawel et al. Topotecan Versus Cyclophosphamide, Doxorubicin, and Vincristine for the Treatment of Recurrent Small-Cell Lung Cancer . *Clinical Oncology*, 17, 658-667, 1999.

at least 60 days after initial therapy. The study was originally designed to recruit patients with at least 90 days between completion of first-line therapy and progression, but early in the study the criteria were amended.to make topotecan available to a larger proportion of relapsed SCLC patients.117	
IV topotecan label: responders who then subsequently progressed >/=60 days after completion of first-line therapy	
a treatment-free interval of ≥ 90 days118	
In reference to the van Pawel article (1999)—a randomised study of topotecan versus the established triple combination CAV (cyclophosphamide, Adriamycin, and vincristine) in patients with SCLC--"sensitive" to initial therapy (having a treatment-free interval of 90 days or more)119	
Patients and Methods section sensitive disease was defined as relapse ≥ 90 days after completion of first-line chemotherapy120	Introduction Primary refractory patients, whose tumors progress through initial chemotherapy or who experience relapse less than 90 days from the end of chemotherapy, have an especially poor prognosis121 Patients and Methods section Primary refractory disease was defined as relapse during first-line chemotherapy or less than 90 days after completing initial chemotherapy
patients who relapse 3 months after therapy are called *sensitive*. Patients with late relapses after receiving initial therapy may be retreated with the same induction regimen used initially122	Patients who relapse < 3 months after first-line therapy are commonly called *refractory*123
If more than 12 months has elapsed, it is worth retreating with the initial regimen. Where more than 3 months has	If the period to relapse has been less than 3 months, or the patient has progressed on

118 Page 12 of the protocol; in reference to a randomised study of topotecan versus CAV
119 Page 18 of Clinical Study Report for Study SK&F-104864/478
120 Masters GA, Declerck L, Blanke C et al. Phase II Trial of Gemcitabine in Refractory or Relapsed Small-Cell Lung Cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol. 2003;21:1550-1555
121 Masters GA, Declerck L, Blanke C et al. Phase II Trial of Gemcitabine in Refractory or Relapsed Small-Cell Lung Cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol. 2003;21:1550-1555
122 Simon GR, Wagner H. Small cell lung cancer. Chest 2003; 123 (supplement): 259S-271S
123 Simon GR, Wagner H. Small cell lung cancer. Chest 2003; 123 (supplement): 259S-271S

elapsed, patients may have greater than 30% probability of response to second-line treatment.124	induction chemotherapy, the prognosis is poor and patients are usually refractory to treatment.125
Those who had responded to previous treatment and relapsed 3 months or longer after completing such treatment are deemed sensitive126	Patients who did not respond to previous therapy or who relapsed within 3 months of completing therapy are judged refractory127
Editorial: a significantiy higher probability of response for those patients who had a treatment-free interval of more than 2.6 months Patients who had a treatment-free interval of more than 4.5 months had a higher probability of achieving a second response to the same chemotherapy as used in first-line so called sensitive patients at relapse, i.e. those with a response to first-line therapy and a treatment-free intewal of at least *90* days the sensitivity to the first-line treatment in combination with a progression free period of more than 3 months128	Editorial: those patients who relapsed within 4.5 months. resistant patients, i.e. no response to firstline treatment and relapse within 90 days.129
Introduction Patients with disease progression > 3 months after the last treatment of first-line therapy, which has induced an objective response, are classified as sensitive.130 Table 1 (footnote) Patients who relapsed after 90 days after first-line therapy were termed sensitive. Table 2 Time to relapse after first-line therapy ≥ 3 -- < 6 months sensitive	Introduction Patients developing disease progression within 3 months after first-line therapy are classified as refractory.131 Table 1 (footnote) Patients who failed to respond or progressed within 90 days of first-line therapy were termed refractory. Table 2 Time to relapse after first-line therapy < 3 months refractory

124 Chua YJ, Steer C, Yip D. Recent advances in management of small-cell lung cancer. Cancer Treatment Reviews. 2004;30:521-543
125 Chua YJ, Steer C, Yip D. Recent advances in management of small-cell lung cancer. Cancer Treatment Reviews. 2004;30:521-543
126 Jackman DM, Johnson BE. Lancet 2005;366:1385-96
127 Jackman DM, Johnson BE. Lancet 2005;366:1385-96
128 Postmus P. Second-line for small cell lung cancer: how-to-do-it? Lung Cancer. 2005 May;43(2):263-5
129 Postmus P. Second-line for small cell lung cancer: how-to-do-it? Lung Cancer. 2005 May;43(2):263-5

	the problem is the rapid development of drug resistance and the failure of second-line therapy to produce meaningful response rates and longer survival times, especially if the tumor fails to respond to primary treatment or there is rapid progression, within 3 months.132
2006 NCCN Second-line chemotherapy: Relapse > 2-3 mo up to 6 mo & Relapse > 6 mo133 Salvage Therapy Time from last therapy to relapse: if greater than 3 months has elapsed, expected response rates are approximately 25%134 2007 NCCN Subsequent chemotherapy: Relapse > 2-3 mo up to 6 mo & Relapse > 6 mo135 Salvage Therapy Time from last therapy to relapse: if greater than 3 months has elapsed, expected response rates are approximately 25%136	2006 NCCN Second-line chemotherapy: Relapse < 2-3 mo137 Salvage Therapy Time from last therapy to relapse: if this interval is less than 3 months, response to most agents or regimens is poor (10% or less)138 2007 NCCN Subsequent chemotherapy: Relapse < 2-3 mo139 Salvage Therapy Time from last therapy to relapse: if this interval is less than 3 months, response to most agents or regimens is poor (10% or less)140
	From page 20 (Inclusion Criteria) of the protocol (Amendment 3) in the NDA: Documented relapse of limited or extensive SCLC at least 45 days after the cessation of first-line chemotherapy indicative of

130 Huber RM et al. Eur Respir J 2006; 27:1183-1189; study was supported by a grant from GSK
131 Huber RM et al. Eur Respir J 2006; 27:1183-1189; study was supported by a grant from GSK
132 Lally BE, Urbanic JJ, blackstock AW, Miller AA, Perry MC. Small Cell Lung Cancer: Have We Made Any Progress Over the Last 25 Years? The Oncologist 2007;12:1096–1104
133 NCCN, Practice Guidelines in Oncology – v.1.2006: Small Cell Lung Cancer, SCL-C.
134 NCCN, Practice Guidelines in Oncology – v.1.2006: Small Cell Lung Cancer, MS 6.
135 NCCN, Practice Guidelines in Oncology – v.1.2007: Small Cell Lung Cancer, SCL-B.
136 NCCN, Practice Guidelines in Oncology – v.1.2007: Small Cell Lung Cancer, MS 6.
137 NCCN, Practice Guidelinesin Oncology – v.1.2006: Small Cell Lung Cancer, SCL-C.
138 NCCN, Practice Guidelinesin Oncology – v.1.2006: Small Cell Lung Cancer, MS 6.
139 NCCN, Practice Guidelinesin Oncology – v.1.2007: Small Cell Lung Cancer, SCL-B.
140 NCCN, Practice Guidelinesin Oncology – v.1.2007: Small Cell Lung Cancer, MS 6.

	resistant disease.
Those who had relapsed more than 3 months after completion of first-line therapy were termed 'sensitive'141	
Proposed oral topotecan label:	Proposed oral topotecan label:
from the Sponsor's Summary of the Day 45 Sponsor Presentation for Oral HYCAMTIN® (topotecan) Capsules, NDA 20-981: Dr. Pazdur asked whether the current IV label includes only sensitive disease patients. **Yes.** **MEDICAL OFFICER NOTE: Patients, who progressed 60-90 days after completion of 1st-line therapy, should be considered resistant.**	
Sponsor response dated 7/19/2007 "Progressive disease occurring within two to three month (60 to 90 days) of first-line therapy is the clinically-accepted, lower limit defining a level of residual chemosensitivity that would support or justify further chemotherapy." **MEDICAL OFFICER NOTE:** **This definition conflicts with the statement in the protocol (pages 7 & 16 in the original protocol; pages 10 & 18 in Amendment 3 protocol in NDA) that randomizing patients, who are sensitive to chemotherapy, to best supportive care is unethical.**	

b(4)

b(5)

The table above demonstrates the varied definitions of sensitive SCLC for patients, who relapse after 1st-line chemotherap, such as: 1) duration of response (CR + PR) > 6months or >8 months; 2) complete response of ≥ 12 months; 3) responders with a treatment-free intervals of > 3 months (or 90 days) or > 6 months; and 4) treatment-free intervals of >3 months or > 6 months. The fourth definition does not link objective response (CR or PR) to the treatment-free interval. It is possible that patients with stable disease (SD) could be included under the fourth definition.

However, in 1999, Huisman and co-authors wrote that it is not entirely clear how the 3-month split has been established and that prospective data on this question are lacking. [142] **Recently Tiseo and Ardizzonni wrote that the ≤ or > 90 day treatment-free interval definitions were designed many years ago and were based on small,**

141 Page 20 of Clinical Study Report SKF-104864/396
142 Huisman C, Postmus PE, Giaccone G, et al. Second-line chemotherapy and its evaluation in small cell lung cancer. *Cancer Treat Rev* 1999;25: 199–206.

retrospective studies. They continued with that the definitions have not been further assessed in larger patient series, nor has they been validated in prospective studies.143

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143 Tiseo M, Ardizzoni A. Current Status of Second-Line Treatment and Novel Therapies for Small Cell Lung Cancer. J Thorac Oncol. 2007;2: 764–772

A Comparison of Sensitive and Resistant SCLC: IV and oral topotecan

MEDICAL OFFICER NOTE: The figure below demonstrates the differences between the population originally targeted in a protocol and what was put in the final label of the drug. For both IV topotecan and oral topotecan, the original protocols limited the inclusion criteria to sensitive or resistant SCLC, respectively. The final label indications were open to both sensitive and resistant patient. populations. In the case of IV topotecan—a study for sensitive SCL, 60 days as the minimum was introduced into the study *to make topotecan available* to a larger proportion of relapsed SCLC patients. In the case of oral topotecan—a study for resistant SCLC, the study was amended to include patients with TTP post chemotherapy of > 90 days because the original window was proving to be too rigid and the definition of "resistant" was left to the judgement of the investigator.

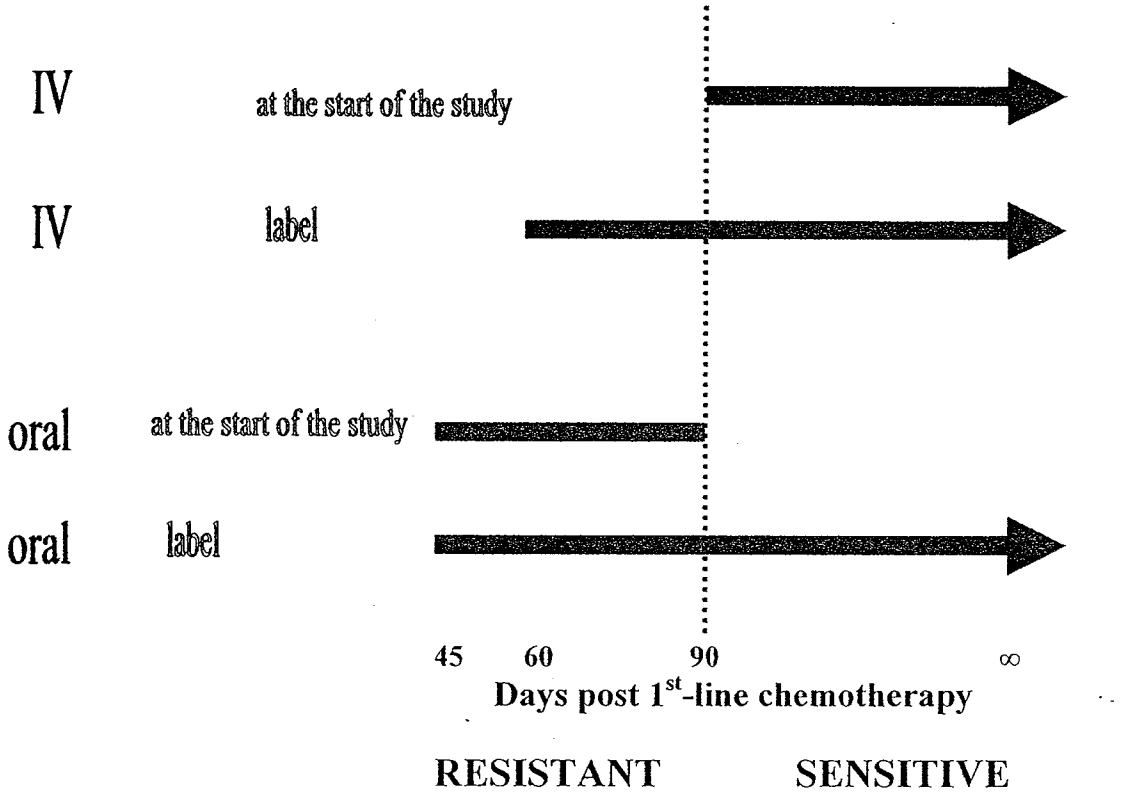

Figure. Patients populations as initially proposed and how labeled. Blue broad bars are IV topotecan (top two horizontal bars). Red broad bars oral topotecan (bottom two horizontal bars). The dashed vertical line separates resistant SCLC and sensitive SCLC.

Labels: A comparison oral topotecan (proposed) and IV topotecan (approved)

LABEL	ORAL (submitted in NDA)	INTRAVENOUS (approved)
Indication	[redacted]	small cell lung cancer *sensitive* disease after failure of first-line chemotherapy. In clinical studies submitted to support approval, *sensitive* disease was defined as disease *responding to chemotherapy* but subsequently progressing at least 60 days (in the Phase 3 study) or at least 90 days (in the Phase 2 studies) after chemotherapy **MEDICAL OFFICER NOTE: according to table above (Definitions of sensitive and resistant disease in SCLC), the domain of 60-90 days after chemotherapy is not sensitive disease.**
Pivotal clinical study		patients were considered *sensitive* to first-line chemotherapy (*responders* who then subsequently progressed >/=60 days after completion of first-line therapy). **MEDICAL OFFICER NOTE: according to table above (Definitions of sensitive and resistant disease in SCLC), the domain of 60-90 days after chemotherapy is not sensitive disease.**
Supportive clinical studies	[redacted]	*sensitive* (*responders* who then subsequently progressed >/=90 days after completion of first-line therapy) or *refractory* (no response to first-line chemotherapy or who *responded* to first-line therapy and then progressed within 90 days of completing first-line therapy).

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In general, in relapsed SCLC, patients with sensitive disease responded to 2nd-line chemotherapy more often than did patients with resistant disease (table below).

Response rates in sensitive and resistant SCLC

	SENSITIVE	RESISTANT
IV topotecan, n=104 CAV, n=106 Van Pawel144	24% 18%	
014 EORTC 014B 053 Perez-Solar145		7% 2% 2% 11%
Oral topotecan, n=52 IV topotecan, n=54146		23% 15%
IV topotecan *Ardizzoni et al.* 1997147	N=45 37% survival tended to be greater in sensitive patients in comparison to resistant patients.	N=47 6%
IV topotecan *Eckardt et al.* 1996148	N=52 16% survival tended to be greater in sensitive patients in comparison to resistant patients.	N=47 2%
IV topotecan *Depierre et al.* 1997149	N=57 14% survival tended to be greater in sensitive patients in comparison to	N=41 2%

144 Von Pawel et al. Topotecan Versus Cyclophosphamide, Doxorubicin, and Vincristine for the Treatment of Recurrent Small-Cell Lung Cancer . *Clinical Oncology,* 17, 658-667, 1999.
145 Page 19 of Study #478 study report
146 Page 20 of Study #478 study report
147 Ardizzoni A. Topotecan in the Treatment of Recurrent Small Cell Lung Cancer: An Update. The Oncologist. 2004;9(suppl 6):4-13
148 Ardizzoni A. Topotecan in the Treatment of Recurrent Small Cell Lung Cancer: An Update. The Oncologist. 2004;9(suppl 6):4-13

	resistant patients.	
Refers to IV topotecan from the *von Pawel et al.* 1999150	N=57 14% survival tended to be greater in sensitive patients in comparison to resistant patients.	N=41 2%
IV topotecan From the IV topotecan label: single arm studies	11% to 31%	2% to 7%
IV gemicitbine151	N=24 16.7% Survival was not different between the two groups	N= 18 5.6%
IV VM-26152	N=17 53%	N=16 12%
Oral VP-16153	N=14 64%	N=8 12.5%
Cisplatin + IV topotecan154	N=68 29% (1 CR)	N=42 24%

Ardizonni and co-authors wrote, "Refractory SCLC patients rarely respond to second-line single agent chemotherapy and may only respond to true "noncross resistant" combination-chemotherapy, whereas sensitive patients have a reasonable chance of responding to second-line chemotherapy or even to first-line chemotherapy rechallenge."155 However, Tiseo and Ardizzoni wrote that recent studies with either single-agent chemotherapy or combination chemotherapy, showed no difference in outcome between *sensitive* and *refractory* patients, and thus, as defined, have put the reliability of this prognostic classification under discussion.156

149Ardizzoni A. Topotecan in the Treatment of Recurrent Small Cell Lung Cancer: An Update. The Oncologist. 2004;9(suppl 6):4-13

150 Ardizzoni A. Topotecan in the Treatment of Recurrent Small Cell Lung Cancer: An Update. The Oncologist. 2004;9(suppl 6):4-13

151 Masters GA, Declerck L, Blanke C et al. Phase II Trial of Gemcitabine in Refractory or Relapsed Small-Cell Lung Cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol. 2003;21:1550-1555

152 Giaccone et al. J Clin Oncol 6:1264-1270, 1988; sensitive = > 2.6 months time from last chemotherapy; resistant = $\leq$ 2.6 months

153Johnson DH et al. J Clin Oncol 8:1613-1617, 1990

154Ardizzoni A, Manegold C, Debruyne C, et al. European Organization for Research and Treatment of Cancer (EORTC) 08957 phase II study of topotecan in combination with cisplatin as second-line treatment of refractory and sensitive small cell lung cancer. *Clin Cancer Res* 2003;9:143–150.

155Ardizzoni A, Manegold C, Debruyne C, et al. European Organization for Research and Treatment of Cancer (EORTC) 08957 phase II study of topotecan in combination with cisplatin as second-line treatment of refractory and sensitive small cell lung cancer. *Clin Cancer Res* 2003;9:143–150.

156 Tiseo M, Ardizzoni A. Current Status of Second-Line Treatment and Novel Therapies for Small Cell Lung

9 OVERALL ASSESSMENT

9.1 Conclusions

One non-blinded, randomized, controlled trial, demonstrating the efficacy and safety of Hycamtin capsules for the treatment of patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are ≥ 45 days post cessation of first-line chemotherapy has been submitted and reviewed. The pivotal trial was multicenter with only non-United States sites. The data submitted demonstrated that Hycamtin capsules has a survival benefit in small cell cancer patients (who have had a complete or partial response to first-line chemotherapy and who are ≥ 45 days post cessation of first-line chemotherapy) in comparison to a best supportive care control arm.

Hycamtin capsules showed a consistent improvement in survival in comparison to best supportive care across the stratification factors (i.e., cessation from prior chemotherapy (days) (≤ 60 or > 60), liver metastases (absence or presence), performance status (ECOG) (0/1 or 2) and gender (male or female). Hycamtin capsules improvement in survival with regard to age, stage of SCLC, and cessation from prior chemotherapy (days) (≤ 90 or > 90).

Study #478 was not designed and conducted under an IND; the FDA did not have knowledge about the study until noticed about the pre-NDA meeting in August 2006. The study was conducted in Europe and European authority. Study #478 did have challenges with regard to certain aspects of conduct of the trial (i.e., discrepancies in time to progression from the end of prior chemotherapy; liver metastases [presence or absence]; performance status; registration and randomization; and eligibility). Despite removal of 32 patients with discrepancies (the survival benefit of Hycamtin capsules in comparison to best supportive care remained. Also, on the Hycamtin capsules arm, the response rates for patients who were defined as having "sensitive" and "resistant" SCLC were the reverse of what would be expected from the literature and from the experience with intravenous topotecan; the "resistant" patients had a higher response rate than the "sensitive" patients.

The data submitted has demonstrated that Hycamtin capsules has satisfactorily demonstrated a consistent survival advantage compared to best supportive care in patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are ≥ 45 days post cessation of first-line chemotherapy in a randomized, non-blinded study.

Cancer. J Thorac Oncol. 2007;2: 764–772

9.2 Recommendation on Regulatory Action

Based on this review of NDA 20-981, Hycamtin capsules is clinically approvable for the treatment of patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are $\geq$ 45 days post cessation of first-line chemotherapy.

9.3 Recommendation on Postmarketing Actions

Not applicable.

9.4 Risk Management Activity

Not applicable.

9.5 Required Phase 4 Commitments

Not applicable.

9.6 Other Phase 4 Requests

Not applicable.

9.7 Labeling Review

See Sponsor final label (10/11/2007; amendment 00029).

9.8 Comments to Applicant

Not applicable.

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Robert White
10/12/2007 12:04:53 PM
MEDICAL OFFICER

Date	October 8, 2007
From	Ramzi Dagher, MD
Subject	Medical Team Leader Memo
NDA Number	20981
Drug	Hycamtin (topotecan)
Indication	patients with relapsed small cell lung cancer who had a complete or partial response and who are at least 45 days from the end of first-line chemotherapy
Recommendation	Approval

Recommendation

I recommend approval of this NDA for the following indication based on superiority in overall survival demonstrated in a randomized trial comparing oral topotecan plus best supportive care to best supportive care alone :

"patients with relapsed small cell lung cancer who had a complete or partial response and who are at least 45 days from the end of first-line chemotherapy"

The overall survival benefit demonstrated outweighs the risks exemplified by bone marrow suppression and diarrhea in this patient population.

Clinical Database and Findings

This recommendation is based on a randomized trial of oral hycamtin plus best supportive care compared to best supportive care alone. The SCLC patients had a prior complete or partial response to first-line chemotherapy, were not considered candidates for standard intravenous chemotherapy, and were at least 45 days from the end of first-line chemotherapy. Seventy-one patients were randomized to oral topotecan (2.3 mg/m^2/day administered for 5 consecutive days repeated every 21 days) and Best Supportive Care (BSC) and 70 patients were randomized to BSC alone. The primary objective was to compare the overall survival between the two treatment arms. Patients in the oral topotecan plus BSC group received a median of 4 courses of treatment and maintained a median dose intensity of 3.77 mg/m^2/week. The median patient age was approximately 60 years. All but one patient were Caucasian. The combination arm included 68% of patients who had extensive disease and 28% who had liver metastases. On the BSC arm, 61% of patients had extensive disease and 20% had liver metastases.

The topotecan plus BSC arm showed a clinically relevant and statistically significant improvement in overall survival compared with the BSC alone arm.

Survival results are shown in Table 1

Table 1. Overall Survival in Small Cell Lung Cancer Patients

	Treatment Group	
	ORAL HYCAMTIN + BSC (N = 71)	**BSC (N = 70)**
Median (weeks) (95% CI)	25.9 (18.3, 31.6)	13.9 (11.1, 18.6)
Hazard ratio (95% CI) Log-rank p-value	0.64 (0.45, 0.90) 0.0104	

BSC = Best Supportive Care.

N = total number of patients randomized.

CI = Confidence Interval.

Although objective tumor response rate and time to progression were measured on the topotecan arm, I do not recommend inclusion of this data in any labeling claim due to the lack of measurement in the concurrent comparator arm, the open label nature of the trial, and the lack of adjudication by an independent review committee.

In this randomized trial, the most commonly occurring clinically relevant grade 3 / 4 adverse events in the topotecan arm included neutropenia (61%), thrombocytopenia (37%), anemia (25%) and diarrhea (5%). The occurrence of adverse events was not routinely captured in the BSC arm and therefore I do not recommend inclusion of any safety information from the BSC arm in labeling.

In addition to this database of 71 patients who received oral topotecan plus BSC, an additional 682 patients received oral topotecan in 4 cliincal studies; one study in patients with recurrent non-small cell lung cancer and 3 studies in patients with recurrent small cell lung cancer. Safety findings in this database corroborate the findings in the randomized trial.

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/s/

Ramzi Dagher
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