Additional efficacy analyses are summarized below:

i. **Lung Cancer Symptom Scale:** In Tax 320, the pattern mixture model for the longitudinal analysis of LCSS data found no significant difference between the docetaxel 75 mg/m^2 arm and the control arm (V/I). In Tax 317, the same model suggested benefit favoring docetaxel in the pain subscale for the docetaxel arm (100 and 75 mg/m^2 pooled), but there was no difference between the docetaxel 75 mg/m^2 subgroup and best supportive care.

ii. **Analgesic use:** In Tax 320, the proportion of patients on the docetaxel 75 mg/m^2 arm starting morphinic analgesics was not significantly different from the control arm (V/I). In Tax 317, fewer patients on the docetaxel 75 mg/m^2 arm started morphinic analgesics than those on the best supportive care/75 arm.

iii. **Change in performance status from baseline to last assessment on study:** No significant difference was observed in TAX 320 between the docetaxel 75 mg/m^2 arm and the control arm (V/I). The same analysis performed in TAX 317 did suggest a difference between docetaxel 75 mg/m^2 and best supportive care, favoring the docetaxel 75 mg/m^2 subgroup.

2. **Do the data on median time to progression, morphinic analgesic use, and mean change in performance status from baseline to last assessment presented in this sNDA adequately demonstrate that therapy with docetaxel 75mg/m^2 in second line treatment of NSCLC confers clinical benefit?**

YES = 4
NO = 7
ABSTAIN = 2

Safety

The following table summarizes treatment related mortality and major toxicities associated with docetaxel 75 mg/m^2 in both studies, relative to what is currently labeled for second-line treatment of patients with advanced breast cancer treated with 100 mg/m^2.

Adverse Event	TAX 317		TAX 320		Docetaxel Label (Breast Cancer)
	Docetaxel 75 mg/m^2	BSC (overall)	Docetaxel 75 mg/m^2	Control (V/I)	100 mg/m^2
Treatment Related Mortality	1.8%	NA	3.3%	3.4%	1.5%
Infection Grade 3-4	5.5%	5.0%	12.4%	9.2%	7.1%
Diarrhea Grade 3-4	3.9%	0%	1.7%	1.7%	6.3%
Asthenia Grade 3-4	18.2%	28%	12.4%	10.9%	14.9%
Sensory Neuropathy Grade 3-4	1.8%	3%	0.8%	3.4%	5.8%
Motor Neuropathy Grade 3-4	1.8%	3%	2.5%	0%	4.4%
Febrile Neutropenia	1.8%	NA	8.3%	0.8%	11.8%
Stomatitis Grade 3/4	1.8%	0%	1.7%	0.8%	7.8%
Fluid Retention Severe	0%	Not presented	3.3%	3.4%	6.5% (all tumor types)

3. **Do these data demonstrate acceptable safety associated with docetaxel when administered at a dose of 75 mg/m^2 in this population of patients with NSCLC?**

YES = 13
NO = 0
ABSTAIN = 0

4. **Is docetaxel 75 mg/m^2 approvable "for the treatment of patients with locally advanced or metastatic non-small cell lung carcinoma after failure of prior chemotherapy"?**

YES = 12
NO = 1
ABSTAIN = 0

8 Recommended Regulatory Action

Based on the data provided in the supplemental applications, s-NDA 20-449/ SE1-011, the following regulatory action is recommended. Product labeling has been revised in accordance with these recommendations.

I. Taxotere® (Docetaxel) should be approved for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. This indication is more specific than that proposed by the sponsor in the application because the ODAC expressed that it was important that labeling reflect the characteristics of the population that participated in the randomized, controlled trials in this application. Both studies required that patients have prior treatment with platinum-based chemotherapy, and the labeled indication will reflect that common feature of the participants.

APPEARS THIS WAY
ON ORIGINAL

/S/
Donna J. Griebel, MD

/S/ 12/17/99
Julie Beitz, MD

Appendix A

TAX 320 Further Therapy Tabulations

Gemcitabine					
Vinorelbine (Control)					
Pt.No	**No. of Cycles**	**Cycle Name**	**Best Resp**	**No. Other Regimens**	**Best Response other Regimens**
10077	1	061	PD	0	
10442	1	064	U	2	**PR (Vin)**
10460	1	061	NC (+VP-16)	0	
10463	1	063	PD	2	PD, U
10476	4	062-065	NC, U		
10489	2	063,064	NE,PD	3	PR(Taxol),NE,PD
10663	2	062	**PR (+ CDDP)**	0	
10688	3	061, 062, 063	PD	0	
Ifosfamide (Control)					
10019	1	065	PD	1	PD
10407	3	062,063,064	**PR**	1 (+1 H)	NC
10422	1	062	PD	0	
10515	2	061, 062	PD	0	
Docetaxel 100mg					
10058	1	064	NC	0	
10337	5	063, 064, 065, 066, 067	NE, PD	2	NE, PD; U, NC
10351	4	066,067,068, 069	NE, PD	1	U, PD
10426	1	061	PD	0	
10516	1	061	UK	0	
10654	1	061	UK	0	
10670	1	061	NC	0	
10679	2	061, 062	UK	1	NC
10686	1	063	PD	0	
Docetaxel 75mg					
10066	1	065	NC	0	

10329	3	062, 063, 064	NC	2	UK; NC
10355	7	062, 063, 064, 065, 066, 067, 068	NC	2	NC
10381	5	063, 064, 065, 066, 067	**PR**	0	
10396	2	061, 062	UK, PD	0	
10447	1	061	UK	1	UK, PD
10464	1	064	NC	1	NC
10652	1	061	PD	0	
10678	1	063	NC	0	

Paclitaxel

Vinorelbine (Control)

Pt.No	No. of Cycles	Cycle Name	Best Resp	No. Other Regimens	Best Response other Regimens
10076	2	061, 062	UK, PD	0	
10168	1	061	PD	0	
10183	1	061	PD	0	
10326 (+Carboplat)	2	061, 062	UK	2	NC
10333 (+Ifex)	1	061	UK	0	
10348	1	064	PD	1 (2 Hormonal including estramustine)	**PR (Cisplatin)** H = PR; PD on estramustine
10405	1	062	NE	1	NC
10463	1	064	UK	2	PD
10489	2	061, 062	**PR**	3	NE, PD; NE, PD; PD
10676	1	061	PD	0	

Ifosfamide (Control)

10019	2	061, 062	UK, PD	1	PD
10104 (+Carboplat)	1	061	PD	0	
10342	6	061, 062, 063, 065, 066, 067	NC	0	
10365	1	061	NC	2	NC; UK
10428	1	061	PD	0	

Docetaxel 100 mg					
10488	1	065	PD	1 (2 Hormonal including estramustine)	**PR (Cisplatin)** H=PR; PD on estramustine
Docetaxel 75 mg					
10095 (+Carboplat)	1	062	PD	0	
10184	1	061	UK	0	
10438	1	062	NC	1	NC
10447 (+Carboplat)	2	062, 063	UK, PD	1	UK
10457	1	062	PD	2 (1 Hormonal = estramustine)	UK PD (H=PD)

Docetaxel					
Vinorelbine (Control)					
Pt.No	**No. of Cycles**	**Cycle Name**	**Best Resp**	**No. Other Regimens**	**Best Response other Regimens**
10087	1	061	PD	0	
10092	2	061, 062	NE	0	
10326	6	065, 066, 067, 068, 069, 070	NC	2	UK; NC
10334	1	061	NE	0	
10387	2	063, 064	UK, PD	0	
10453	2	065, 066	UK	0	
10469	2	064, 065	NE, NC	1	NC
10489	2	062, 063	NE, PD	3	**PR (Taxol);** NE,PD; PD
Ifosfamide (Control)					
10651	2	061, 062	UK, PD	0	
10672	1	061	NC	0	
Docetaxel 100mg					

10508	2	062, 063	NC	1	UK
Docetaxel 75 mg					
10013 (+Doxil)	2	063, 067	UK, PD	2	NC; UK
10357	2	061, 062	NC	0	

Vinorelbine

Vinorelbine (Control)

Pt.No	No. of Cycles	Cycle Name	Best Resp	No. Other Regimens	Best Response other Regimens
10024	1	061	PD	0	
10442	1	061	PR	2	UK
10469	5	061, 062, 063, 064, 065	NC	1	NC
Ifosfamide (Control)					
10350	3	061, 062, 063	NC	0	
10360	1	061	UK		
10365	1	065	UK	2	NC
10394 (+Cisplat)	3	061, 062, 063	UK, NC	0	
10397 (+Carboplat)	1	061	NC	0	
10437	1	066	PR	0	
Docetaxel 100mg					
10011	1	061	NE	0	
10039	2	061, 062	UK, PD	0	
10070	1	061	NE	0	
10073	1	061	NE	0	
10102	1	061	PD	0	

10337	7	061- 067	NE, PD	2	NE, PD; NC
10344	1	061	NC		
10351	6	064, 065, 066, 067, 068, 069	UK, NC	1	NE, PD
10354	1	061	PD	0	
10393	1	061	UK	0	
10417 (+Carboplat)	2	061, 062	UK, PD	0	
10423	4	061, 062, 063, 064	NC	0	
10443	1	062	NC	(1=Immuno)	PD
10444	1	061	UK	0	
10468 (+Carboplat)	3	061, 062, 063	UK, PD	0	
10485	1	061	UK	0	
10508	1	063	UK	1	NC
10661	1	064	UK	0	
10679	2	061, 062	NC	1	UK
Docetaxel 75 mg					
10013	3	061, 062, 067	UK, NC	1	UK, PD
10025	1	061	PD	0	
10034	1	061	PD	0	
10040	1	061	PD	0	
10042	4	062, 063, 064, 065	UK	2 (1 Invest)	UK, UK
10052	1	061	NC	1	PD
10061	1	061	PD	0	
10079	3	062, 063, 064	UK, PD	1	PD
10080	1	061	NC	0	

10086	4	062, 063, 064, 065	NE, PD	1 (1H)	NE, PD (H=NE, PD)
10100	1	061	PD	0	
10171	1	061	NC	1(CGP69846A)	PD
10329	2	061, 062	UK	2	NC; NC
10343 (+Mito)	1	061	PD	0	
10355	1	061	NC	2 (1=Invest)	NC; NC
10364	3	062, 063, 064	NC	0	
10371 (+Mito)	2	061, 062	NC	0	
10375	1	063	PD	1	NC
10415	2	061, 062	UK, PD	0	
10427	1	062	PD	0	
10455	1	065	UK	0	
10457	2	062, 063	UK	2 (1=Invest=AG2 034) (+Estramustine)	PD; PD; PD
10464	1	061	NC	1	NC
10470	1	061	UK	1	UK
10475	1	062	PD	0	
10478 (+Carbo)	6	061-065*	PR	0	
10490	1	061	UK	0	
10650	1	061	NE	0	
10668 (+Carbo)	4	061, 062, 063, 064	PR	0	

Vinblastine +/- Mitomycin

Vinorelbine (Control)					
Pt.No	**No. of Cycles**	**Cycle Name**	**Best Resp**	**No. Other Regimens**	**Best Response other Regimens**
10356 (Mito Only)	4	061, 062, 063, 064	NC	0	
10382 (Vin+Mito)	2	061, 062	PD	0	
Ifosfamide (Control)					
10347 (Vin+Mito)	2	061, 062	NC	0	
10365 (Vin+Mito)	1	063	NC	3 (1=Invest)	NC;NE;UK
Docetaxel 100mg					
10029 (Vin+Mito)	1	062	UK	0	
10036 (Vin+Mito)	2	063, 064	NE	0	
10337 (Vin+Mito)	3	065, 066, 067	NC	2	NE, PD; NE, PD
10413 (Vin+Mito)	1	061	PD	0	
Docetaxel 75 mg					
10013 (*Mito+Carbo*)	1	067	UK	2	UK,PD; UK, PD
10035 (Vin+Mito)	2=Combo 3= Vinb only	061, 062; 063, 064, 065	NC NC	0	
10343 (*Mito+Navel*)	1	061	PD	0	
10371 (*Mito+Navel*)	2	061, 062	NC	0	

Ifosfamide
Vinorelbine (Control)

Pt.No	No. of Cycles	Cycle Name	Best Resp	No. Other Regimens	Best Response other Regimens
10326 (+VP-16)	2	063, 064	NC	2	UK; NC
10333 (+Taxol)	1	061	UK	0	
10405	2	061, 062	NC	1	NE
10326 (+VP-16)	1	065	PD	4	PR; NE, PD; NE, PD
Ifosfamide (Control)					
10003	1	061	NC	0	
Docetaxel 100 mg					
10017 (ICE)	1	061	PD	0	
10088 (+Methotrex)	1	061	PD	0	
10380	1	061	PD	0	
10502 (+Carboplat)	1	061	NC	0	
Docetaxel 75 mg					
10352 (+VP-16)	1	061	NE	0	
10375 (ICE)	1	061	NC	1	PD

Platinum

Vinorelbine (Control)

Pt.No	No. of Cycles	Cycle Name	Best Resp	No. Other Regimens	Best Response other Regimens
10326 (Carb + Taxol)	2	061, 062	UK	2	NC; NC
10348 (Cisplat +??Toremifene Hormonal)	3	061, 062, 063	PR	1 (+Estramustine)	PD; PD
10493 (Cisplat + VP)	1	061	UK	0	

10663 (Cisplat +Gem)	2	061, 062	**PR**	0	
10348 (Cisplat +??Toremifene Hormonal)	1	061	NE	0	
Ifosfamide (Control)					
10104 (Carbo+Taxol; Cis+Adr+CTX)	1;1	061, 062	PD;PD	0	
10377 (Cis+ CTX+Doxohabilin)	1	061	PD	0	
10394 (Cis+Navel)	3	061, 062, 063	NC	0	
10397 (Carbo+Navel)	1	061	NC	0	
10348 (Cisplat +??Toremifene Hormonal)	1	061	NC	1	**PR**
Docetaxel 100mg					
10017 (Carbo+Ifos+VP)	1	061	PD	0	
10038 (Carbo+VP)	1	061	NE	0	
10047 (?CAV; Cisplat+5FU)	1;1	061,061??	PD; PD	0	
10064 (Cispla+VP)	1	061?	NE	1	PD
10417 (Carbo+Navel)	2	064, 065	PD,UK	0	
10468 (Carbo+Navel)	3	061, 062, 063	UK, PD	0	
10488 (Cisplat +??Toremifene Hormonal)	3	061, 062, 063	**PR**	1 (+Estramustine)	PD (PD)
10502 (Carbo+Ifos)	1	061	NC	0	
Docetaxel 75 mg					
10013	1	067	UK	2	NC; UK,PD

(Carbo+Mito)					
10042 (Cisplat +??*Toremifene* Hormonal)	1	065?	UK	1	UK
10048 (Cisplat +??*Toremifene* Hormonal)	4	061, 062, 063, 064	**PR**	0	
10052 (Carboplatin ?+Navel)	1	061	PD	?1 (Navel)	NC
10079 (Cisplat +??Toremifene Hormonal)	1	061	PD	1	UK, PD
10086 (Cisplat +??Toremifene Hormonal)	2	061, 062	NE, PD	1	NE, PD
10095 (Carbo+Taxol)	1	062	PD	0	
10375 (?Cis+Ifos+VP?= ICE)	1	061	NC	1	PD
10402 (Carbo)	3	062, 063, 064	NC	1	UK
10447 (Carbo+Taxol)	2	062, 063	UK, PD	1	UK
10478 (Carbo+vinorel.)	6	061, 062, 063, 064, 065, 066	**PR**	0	
10498 (Carbo+VP)	1	061	NE	0	
10668 (Carbo+vinorel.)	3	061, 062, 063	**PR**	?1 (Single agent Navel)	NC?

Investigational

Vinorelbine (Control)

Pt.No	No. of Cycles	Cycle Name	Best Resp	No. Other Regimens	Best Response other Regimens
10348	3	061-063	**PR**	1	PD (PD)

??Cisplat+Toremifine ??				(+Estramustine)	
10683 ??Cisplat+Toremifine ??	1	061	**NE**	0	
Ifosfamide (Control)					
10365 (P53, immunotherapy)	1	064	NE	3	NC;NC;UK
10407 ??Cisplat+Toremifine ??	1	061	NC	1	**PR**
Docetaxel 100 mg					
10057 (Phase I 69846A)	1	062	PD	0	
10383 (Unconventional Chemo)	1	063	PD	0	
10391 (Perillyl Alcohol)	1	068	NC	0	
10443 (ISIS, immunotherapy)	1	063	PD	1	NC
10488 ??Cisplat+Toremifine ??	3	062, 063, 064	**PR**	1 (+estramustine)	PD (+PD)
10649 (PDX)	1	062	NC	0	
Docetaxel 75 mg					
10042 ??Cisplat+Toremifine ??	1	065	UK	1	UK
10048 ??Cisplat+Toremifine ??	4	061-064	**PR**	0	
10079 ??Cisplat+Toremifine ??	1	061	PD	1	UK, PD
10086 ??Cisplat+Toremifine ??	2	061, 062	NE, PD	1	NE, PD
10336 (Adenovirus P53, Immuno)	1	062	PD	0	

10355 (Metalloproteinase Inhibitor)	1	068	NC	2	NC; NC
10457 (AG2034)	1	064	PD	2 (+Estramustine)	PD; UK (PD)
10657 (Rhizoxin)	1	061	PD	0	
10658 (LY295501?=? diary/sulfonylurea)	4	061, 062, 063,064	NC	0?	

Summary of Chemo Regimens Administered with Response Reported Unknown or Not Evaluable:

	Control		TAX 100mg		TAX 75mg	
	No. Pt's	Cycles	No. Pt's	Cycles	No. Pt's	Cycles
Docetaxel	3	2,1,2	0	0	0	0
Docetaxel + Doxil	0	0	0	0	1	5?
Paclitaxel	2	1,1	0	0	1	1
Paclitaxel + Carbo	1	2	0	0	0	0
Paclitaxel + Ifos.	1	1	0	0	0	0
Gemcit.	1	4	4	5, 1, 1, 1	2	2, 1
CDDP + Etoposide	1	1	1	1	0	0
Carbo + Etoposide	0	0	1	1	1	1

Carbo + Mitomycin	0	0	0	0	1	1
CDDP + Toremifene	1	1	0	0	2	1, 2
CDDP + Vinorelbine	0	0	1	3	0	0
Vinorelbine	3	3,1,1	8	1,1,1,1, 11,1,1	9	4,3,4,2, 12,1,1,1
Mitomycin + Vinblastine	0	0	2	1,2	1	5
P53	1	1	0	0	0	0
Etoposide	0	0	1	1	1	1
Etoposide + Ifosfamide	0	0	0	0	1	1
Drug not Named	0	0	0	0	1	1

The numbers highlighted in the table are those in which more than 2 cycles were apparently administered, suggesting the possibility of some response, although it may have only been stable disease.

PD date could have been an earlier date if the follow-up examinations had been complete or performed on schedule:

Control	PD Date Assigned	Prior Assessment	Estimated TTP reduction (weeks)
10043	9/10/96 (006)	Last prior assessment cycle 003	3 weeks
10050	10/4/96 (006)	Baseline bone scan (Evaluable) not repeated until Cycle 006 = site of PD	6 weeks

10063	4/8/97	Brain Met's diagnosed FU2, no f/u exam's beyond cycle 003, including 004 until FU2, and no complete evaluation of all lesions after 000.	13 weeks (assuming 004 = 9/30/96, then a f/u should occur by 11/28/96)
10087	1/27/97 (004)	Bidimensionally measurable site not evaluated between 000 and 004.	6 weeks
10092	6/25/97 (010)	Last complete evaluations done cycle 006; none in 007, 008, 009.	6 weeks
10167	2/13/96 (003)	Site of PD not evaluated at cycle 002.	3 weeks
10326	12/13/95 (003)	Evaluation not done in cycle 002	3 weeks
10382	4/20/96 (003)	Evaluation not done in cycle 002	3 weeks
10435	12/20/96 (010)	No evaluation after cycle 005	9 weeks
10437	1/21/97 (FU2)	4.5 months after last evaluation in cycle 004 (9/4/96)	10 weeks
10460	10/3/96 (003)	No evaluation in cycle 002	3 weeks
10479	1/29/97 (004)	No evaluation in 001, 002, 003	6 weeks
10489	2/6/96 (005)	No evaluation in 004	3 weeks
10521	6/17/97 (003)	No evaluation in 002	3 weeks
Docetaxel 100 mg	**PD Date Assigned**	**Prior Assessment**	
10058	4/25/97 (FU 2)	3 months after FU1	4 weeks
10078	7/25/97 (FU 3)	5.5 months after 006 (2/13/97), with no scans in interim	14 weeks (f/u should occur by 4/10/97)
10103*	7/2/97 (cycle 004)	??5/10/97?? (cycle 002) Based on a bidimensionally measurable lesion becoming NE, before becoming bidimensionally measurable and evidence of PD at 7/2/97 CT again.	6 weeks
10166	2/10/97 (FU1)	6 months after cycle 010 (8/5/96) before exams are repeated and show PD.	17 weeks (f/u should occur by 9/30/96)
10351	6/25/96 (008)	Last assessed cycle 004 (3/26/96)	6 weeks
10417	8/7/96 (005)	Last assessed cycle 002 (6/14/96)	3 weeks
10423	9/4/96 (006)	Last assessed cycle 002 (6/5/96)	6 weeks
10488	4/25/96 (FU2)	Last assessed cycle 006 (1/3/96)	7 weeks
10504	11/8/96 (FU 2)	Last assessed cycle 004 (8/1/96)	3 weeks (f/u should occur by 10/17/96)
10508	1/21/97 (FU2)	Last assessed cycle 006 (10/29/96)	4 weeks (f/u should occur by 12/24/96)
10516	1/29/97 (005)	Last assessed in cycle 002 (12/16/96) when the lesion was 20% bigger.	3 weeks

Docetaxel 75 mg	PD Date Assigned	Prior Assessment	
10013	8/9/96 (010)	Last assessment done cycle 006 (4/30/96)	6 weeks
10046	7/5/96 (003)	Last assessment at done at baseline (4/12/96)	3 weeks
10331	11/17/95 (003)	Last assessment at done at baseline (9/27/95)	3 weeks
10346	7/31/96 (FU2)	Last assessment in cycle 006 (4/10/96) when lesion was 10% increased in size	8 weeks (f/u should occur by 6/6/96)
10432	7/31/96 (003)	Last assessment done at baseline (5/2/96)	3 weeks
10438	9/27/96	Baseline bone lesion considered evaluable with CT was not reassessed until cycle 003 (8/8/96) when it was considered NE because it was new imaging – MRI. Reassessment cycle 004 with MRI was assessed PD (9/27/96)	6 weeks
10464	9/24/96 (003)	Last assessment done at baseline (7/18/96)	3 weeks
10478	11/12/96 (003)	Last assessment done at baseline (9/25/96)	3 weeks
10506	2/5/97 (FU2)	Last assessment done at cycle 006 (09/26/96)	11 weeks (f/u should occur by 11/21/96)
10669	10/23/97 (FU1)	Last assessment cycle 008 (7/10/97)	7 weeks (f/u should occur by 9/4/97)
10677	10/30/97 (FU2)	Last assessment in cycle 006 (06/03/97)	13 weeks (f/u should occur by 7/29/97)

TAX 320 The docetaxel patients counted by the reviewer as SAE's Infection and Neutropenic fever are listed below. Those bolded appear in sponsor's lists of febrile neutropenia and neutropenic infection submitted in correspondence November 15, 1999. Those in parentheses are in sponsor's list for that category. Those not bolded and not in parentheses are additional patients that were reported to have febrile neutropenia in the SAE narratives, but appear in neither list.

Docetaxel 100 mg Infection SAE	Docetaxel 100 mg Neutropenic Fever SAE	Docetaxel 75 mg Infection SAE	Docetaxel Neutropenic Fever SAE
10007	**10007**	10006	(10006)
10011	10011	10018	10018
10016	**10021**	10026	10029
10021	10054	10035	10079
10045	(10062)	10042	10100
10062	10064	10044	(10346)
10078	**10166**	10079	(10364)
10083	**10188**	10099	(10379)
10102	(10327)	10331	**10395**
10103	**(10353)**	10339	(10475)
10166	(10385)	10395	(10490)
10169	10391	**(10410)**	(10658)
10177	(10423)	10415	(10689)
10178	**10443**	10416	
10188	**10458**	(10419)	
10335	(10474)	10438	
10344	(10484)	10472	
10353	(10486)	10499	
10366	**10491**	10501	
10372	**10495**	10514	
10409	(10659)	10520	
10417	**(10661)**	**10668**	
10443	(10662)		
10444	**(10680)**		
10458	(10686)		
10466			
10468			
10477			
10491			
10495			
10655			
10661			
10670			
10675			
10682			

TAX 320 Neurologic SAE Narratives

Pt. 10058 (docetaxel 100 mg) who was treated with 5 cycles of docetaxel was found to have progressive neuropathy sensory and motor that was attributed to radiation neuropathy superimposed on docetaxel neuropathy. PET and MRI showed no tumor.

Pt. 10325 (docetaxel 100 mg) was admitted on Day 5 of Cycle 3 with weakness, dehydration and stomatitis. This was apparently coded neuromotor. Four days later, after discharge from the hospital she collapsed while shopping from hyovolemia and hyopotension.

Pt. 10417 (docetaxel 100 mg) was admitted on Cycle 1 Day 8 with hypotension, confusion and infection. The confusion was likely related to underlying sepsis.

Pt. 10468 (docetaxel 100 mg) was admitted on Day 32 of Cycle 2 with dyspnea, delirium and pneumonia. Her condition reportedly improved and the delirium was likely secondary to underlying infection, and possibly hypoxia.

Pt. 10517 (docetaxel 100 mg) was admitted on Day 24 of Cycle 1 with increased dyspnea and loss of consciousness. She died the same day.

Pt. 10457 (docetaxel 75 mg) was admitted on Cycle 2 Day 15 with generalized shaking and unsteady gait. MRI and CT revealed no etiology. Alcohol was mentioned as a potential contributing factor. The symptoms resolved in 3 days.

Pt. 10461 (docetaxel 75 mg) was admitted on Day 5 of Cycle 3 for a fall. The patient was afebrile, had no neutropenia and was not thought to be septic. MRI was negative and the fall was attributed to a stroke. The patient died 8 days later. There was no autopsy.

TAX 320 Stomatatis SAE's

Docetaxel 100 mg:

1. Pt. 10325 was admitted on Day 5 of Cycle 3 with stomatitis, dehydration, and weakness.

2. Pt. 10327 was admitted on Day 8 of Cycle 2 with mucositis, dehydration and neutropenia. She was treated with IV antibiotics.

3. Pt. 10486 was admitted on Cycle 3 Day 8 with mucositis, dehydration, fever, and neutropenia.

TAX 320 Diarrhea SAE Narratives

Docetaxel 100 mg (n=5)

1. Pt. 10011 was admitted to the hospital on Day 8 of Cycle 1 with diarrhea, fever, and neutropenia.

2. Pt. 10007 was admitted to the hospital with fever on Day 11 of cycle 5. Stool culture was positive for C. difficile. *Diarrhea was not coded with this report, however.*

3. Pt. 10062 was admitted on Day 7 in Cycle 1 with vomiting, diarrhea, fever and neutropenia. On Day 19 of Cycle 3 she was hospitalized with small bowel obstruction and UTI, preceded by severe vomiting x 5 days.

4. Pt. 10192 was admitted Cycle 1 Day 8 with diarrhea, vomiting, dehydration, hypotension and neutropenia.

5. Pt. 10409 was admitted on Day 8 of Cycle 1 with diarrhea, vomiting, and chills. Blood cultures were positive for E. coli and enterobacter. He was readmitted on Day 6 of Cycle 3 with diarrhea, fever, and neutropenia. Blood and stool cultures were positive.

Docetaxel 75 mg; (n=3)

1. Pt. 10042 was admitted on Day 8 of Cycle 1 with grade 4 diarrhea, neutropenia, and sepsis.

2. Pt. 10339 was admitted to the hospital on Cycle 3 Day 10 with diarrhea.

3. Pt. 10410 was admitted on Cycle 2 Day 5 with diarrhea, vomiting, dehydration, pre-renal azotemia, and hyperglycemia.

TAX 320 Vomiting SAE Narratives

Docetaxel 100 mg (n=8)

1. Pt. 10062 was admitted on Day 7 in Cycle 1 with vomiting, diarrhea, fever and neutropenia. On Day 19 of Cycle 3 she was hospitalized with small bowel obstruction and UTI, preceded by severe vomiting x 5 days.

2. Pt. 10178 was admitted on Day 22 of Cycle 4 with vomiting, dehydration and pain.

3. Pt. 10094 was admitted on Day 6 of Cycle 2 with a neurocortical event and vomiting. CT head revealed intracranial metastases.

4. Pt. 10192 was admitted Cycle 1 Day 8 with vomiting, diarrhea, dehydration, hypotension, and neutropenia.

5. Pt. 10409 was admitted on Day 8 of Cycle 1 with vomiting, diarrhea, and chills. Blood cultures were positive for E. coli and enterobacter. He was readmitted on Day 6 of Cycle 3 with diarrhea, fever, and neutropenia. Blood and stool cultures were positive.

6. Pt. 10436 was admitted on Day 5 of Cycle 1 with vomiting. PD was diagnosed.

7. Pt. 10458 was admitted on day 3 of Cycle 2 with vomiting and abdominal pain. CT revealed abdominal pelvic mass obstructing small bowel.

8. Pt. 10174 was admitted for 23 hour observation on Day 5 of Cycle 1 for vomiting and dehydration. *This was not counted as an SAE as it was not a full admission.*

Docetaxel 75 mg (n=3)

1. Pt. 10410 was admitted on Cycle 2 Day 5 with vomiting, diarrhea, dehydration, pre-renal azotemia, and hyperglycemia.

3. Pt. 10415 was admitted on Day 12 of Cycle 3 with vomiting, asthenia, fatigue, and neutropenic sepsis.

3. Pt. 10475 was admitted on Day 9 of Cycle 2 with vomiting and fever.

Vinorelbine (n=1)

1. Pt. 10459 was admitted on Day 1 Cycle 1 with vomiting. This was a problem during a second admission Day 21 of Cycle 1.

TAX 320 Pneumonia SAE Narratives

Docetaxel 100 mg (n=14)

1. Pt. 10011 was admitted on Day 8 of Cycle 1 with neutropenic fever, diarrhea and RLL pneumonia. (possible)
2. Pt. 10021 was admitted on Day 10 Cycle 1 with pneumonia, neutropenic fever and dyspnea. Pneumonia considered (not related.)
3. Pt. 10078 admitted on Day 12 of Cycle 3 with pneumonia (not related).
4. Pt. 10083 admitted on Day 15 of Cycle 2 with bilateral interstitial infiltrates and fever and hypoxia. (considered possibly related)
5. Pt. 10103 was admitted on Day 15 of Cycle 2 with cough and pneumonia (possible).
6. Pt. 10166 was admitted on Day 10 of Cycle 3 with neutropenia and pneumonia (probable).
7. Pt. 10169 was admitted on Day 15 of Cycle 1 with progressive dyspnea and pneumonia (remote).
8. Pt. 10177 was admitted on Day 8 of Cycle 3 with left lung infiltrates and neutropenia. Pneumonia considered (probable)
9. Pt. 10335 was admitted on Day 8 of Cycle 1 with LUL pneumonia (possible).
10. Pt. 10344 was admitted on Day 16 of Cycle 1 with fever and RLL infiltrate. Sputum culture positive (remote).
11. Pt. 10465 admitted Day 12 of Cycle 4 with pneumonia (possible).
12. Pt 10468 admitted Day 32 of Cycle 2 with pneumonia (POSSIBLE).
13. Pt 10491 admitted day 8 of Cycle 2 with neutropenia and pneumonia (remote).
14. Pt 10661 was admitted on Day 8 of Cycle 5 with neutropenic fever and pneumonia.

Docetaxel 75 mg (n=9)

1. Pt 10018 was admitted on Day 13 of Cycle 5 with pneumocystis carinii pneumonia. (not related.)
2. Pt. 10035 was admitted on Day 13 of Cycle 1 with neutropenia and pneumonia (possibly related).
3. Pt. 10099 was admitted on Day 4 of Cycle 2 for respiratory infection (possible)
4. Pt. 10331 was admitted on Day 20 of Cycle 6 with pneumonia. (not related)
5. Pt 10419 admitted on Day 5 of Cycle 1 with dyspnea and pneumonia (not related).
6. Pt. 10472 admitted Day 5 of Cycle 2 with pneumonia (remote).
7. Pt. 10499 admitted Day 14 of cycle 1 with septic shock and pneumonia (possible).
8. Pt 10520 was admitted Day 5 of Cycle 1 with neutropenia and pneumonia (not related).
9. Pt. 100668 was admitted on Day 13 of cycle 3 with febrile neutropenia and discharged the next day, but readmitted one day later with RLL pneumonia. (probable)

Control (N=5)

1. Pt. 10101 was admitted on Day 4 of Cycle 2 with fever and Left lung infiltrates.
2. Pt. 10302 admitted Day 14 of Cycle 1 with neutropenia and pneumonia (probable).-
3. Pt. 10384 was admitted on Day 11 of Cycle 2 with post obstructive pneumonia (not related).
4. Pt. 10429 admitted Day 14 of Cycle 1 with neutropenic pneumonia (probable.)

5. Pt 10483 admitted on Day 16 of Cycle 6 with pneumonia (not related).

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AUG - 9 1999

Medical Officer 45-Day Review of NDA #20449 SE1 Nos. 11

1. General Information

SE1 No. 11 (Second line Non-Small Cell Lung Carcinoma)

Submission date: December 23, 1998 Fast Track Submission
June 23, 1999 Rolling NDA Final Submission

(First line Non-Small Cell Lung Carcinoma)

Submission date: June 30, 1999

Drug Name:	Docetaxel
Trade Name:	Taxotere®
Sponsor:	Rhône Poulenc Rorer
Pharmacologic category:	Taxane
Dose/Route of Administration:	60 - 100 mg/m^2 infused intravenously over 60 minutes.

2. Proposed Indication

SE1 No. 11 (Second line Non-Small Cell Lung Carcinoma)

Taxotere (docetaxel) for Injection Concentrate is indicated for the treatment of patients with locally advanced or metastatic Non-Small Cell lung Cancer ***after failure of prior chemotherapy.***

DOSAGE AND ADMINISTRATION
The recommended dose of TAXOTERE is 60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks.

(First line Non-Small Cell Lung Carcinoma)

Taxotere (docetaxel) for Injection Concentrate is indicated for the treatment of patients with ***chemotherapy-naïve*** locally advanced or metastatic Non-Small Cell lung Cancer.

DOSAGE AND ADMINISTRATION
The recommended dose of TAXOTERE is 60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks.

3. NDA Submission

SE1 No. 11 (Second line Non-Small Cell Lung Carcinoma)

This supplement was submitted under a Fast-Track designation and was a rolling submission. The final submission, which completed the application and started the

review clock, is dated June 23, 1999. One hundred twenty-nine volumes were submitted in December 1998. Those volumes included the final study report and data from TAX 320. The June 1999 submission consisted of seven volumes containing the final study report and data from the second pivotal trial for second line treatment of non-small cell lung carcinoma, TAX 317. The data from both studies were submitted electronically. Case Report Forms from TAX 320 were submitted in volumes 68-129, and those for TAX 317 in blue volumes 14-25.

The two pivotal phase 3 randomized, controlled trials that provide the primary safety and efficacy data both enrolled participants with unresectable locally advanced or metastatic non-small cell lung carcinoma whose disease had progressed during or after treatment with platinum based chemotherapy and who had an ECOG performance status ≤ 2. Patients were stratified for best response to prior platinum therapy (progression vs. other) and ECOG status (0-1 vs. 2). The primary endpoint in both trials was median survival.

TAX 320: (Open label; Twenty-seven U.S. sites)
ARMS: A = Taxotere 100 mg q 21 d (N = 125)
B = Taxotere 75 mg q 21 d (N = 125)
C = Vinorelbine 30 mg/m^2 Days 1, 8, 15 q 21 d
OR Ifosfamide 2 g/m^2 Days 1-3 q 21 d
(N = 123)

Reviewer Comment: Five of the 23 active sites entered 53.9% (201/373) of the patients who participated in this study. Those investigators/sites were:

Frank Fossella, MD	*US00418*	*N=53*	*(MD Anderson)*
Russell Devore, MD	*US01525*	*N=48*	*(Vanderbilt)*
Ronald Neal Kerr, MD	*US01966*	*N=42*	*(Texas Oncology)*
Jeffrey Crawford, MD	*US02002*	*N=32*	*(Duke)*
Ronald Natale, MD	*US01990*	*N=26*	*(USC/Norris)*

Exploratory Comparisons Among Treatment Sites – Mean Survival and Mean Censored for Further Chemotherapy Survival:

	TAX 100		*TAX 75*		*813*	
	Survival	*Censored*	*Survival*	*Censored*	*Survival*	*Censored*
Fosella	*244*	*210 (-14%)*	*260*	*209 (-20%)*	*288*	*162 (44%)*
*Devore**	*238*	*180 (-24%)*	*294*	*192 (-35%)*	*172*	*107 (-38%)*
*Kerr**	*133*	*115 (-14%)*	*152*	*89 (-42%)*	*170*	*109 (-36%)*
Crawford	*207*	*187 (-10%)*	*202*	*181 (-10%)*	*265*	*172 (-35%)*
Natale	*203*	*188 (-7%)*	*269*	*181 (-33%)*	*311*	*172 (-45%)*

TAX 317: (Open label; 50 North American and European sites)
ARMS: A = Taxotere 75 mg* q 21 d (N = 104)
B = Best Supportive Care (N = 100)

* The study was initiated with a docetaxel dose of 100 mg/m^2 on November 23, 1994, but a protocol amendment (#6) issued on January 31, 1997 lowered the dose to 75 mg/m^2 because of higher than expected toxic death rate. Patients on active treatment at the time of the amendment underwent a dose reduction. Fifty-five of the total 104 docetaxel patients participating in this study (and 49 best supportive care patients) were entered after the protocol amendment was issued.

Reviewer Comment: The four investigators/centers with the highest accrual were:

Frances Shepherd, MD	*CA00073*	*N=58*	*(Toronto)*
Rodryg Ramlau, MD	*PL00049*	*N=15*	*(Poland; Poznan?)*
Karin Mattson, MD	*FI00066*	*N=12*	*(Finland)*
Richard Gralla, MD	*US00174*	*N=11*	*(Oschner; LA)*

There were two additional investigators from Toronto who accrued patients to TAX 317:

Ronald Louis Burkes, MD	*CA00121*	*N=8*	*(Toronto)*
Ronald Feld, MD	*CA00120*	*N=2*	*(Toronto)*

For the purposes of a site visit, the three Toronto sites accrued 68/204 (33%) of this study's population.

Review Issues Raised by the Sponsor's Proposed Labeling:

1) Survival Claims:

- *TAX 317 is not included in the Second Line Non-Small Cell Lung Carcinoma Data in the Proposed Efficacy section for this disease in the label.*
- *The only survival data presented is that censored for subsequent chemotherapy*
- *The only censored for subsequent chemotherapy survival data discussed in the text is the survival at one year, and the lack of significant difference in median survival is not mentioned in the text, although it is shown in the table. The table presentation of the primary endpoint of median survival is not readily understandable. There is no discussion of whether the difference in %survival at one year is significant when each docetaxel arm is compared to control (the pre-specified analysis of survival – median survival - compared each docetaxel arm to control), although the confidence intervals are provided. The only p-value provided, with a reference to "significance" was when the additional unplanned comparison of the combined docetaxel arms was made with the control in an analysis of %1-year survival.*

2) *Response:*
   - ➢ *Both ITT and evaluable analyses are presented*
   - ➢ *The N responding is prominently displayed as the response rate, instead of the percent. The percent is lower than the N responding, and this could be misleading.*
   - ➢ *A combined docetaxel treatment groups vs. the control analysis comparison is presented. This may not have been a pre-specified analysis.*

3) *TTP*
   - ➢ *Both ITT and evaluable analyses are presented*
   - ➢ *The analysis presented in the table appears to show that the only significant difference in TTP is between the docetaxel 100mg and control arm. They do a combined analysis of the two docetaxel arms vs. control that is significant, and was probably not pre-specified.*

4) *Quality of Life*
   - ➢ *The longitudinal analysis tables are presented in the label.*
   - ➢ *They claim significant differences favoring docetaxel 100mg in patient total score, observer total score, fatigue, and lung cancer symptoms. Docetaxel 75mg is not mentioned, except in a closing comment that in responders or patients with stable disease there was "a clear improvement in QoL with both D/100 and D75".*

A table summarizing the sponsor's efficacy analyses is shown below. Pre-specified endpoints are enclosed in heavy crossbars, while those analyses that were not pre-specified are enclosed in dashed crossbars.

TAX 320

	TAX 100	TAX 75	Active Control
MEDIAN SURVIVAL	**5.5 month**	**5.7 months**	**5.6 months**
95% CI	**4.6, 6.6**	**5.1, 7.9**	**4.3, 7.9**
Separate Docetaxel Comparisons	**Log-Rank=NS**	**Log-Rank=NS**	
% 1 year Survival	21%	32%	19%
Separate Docetaxel Comparisons	Log-Rank = NS	Log-Rank = NS	
% 1 year Survival Censoring Pt's Not Lost to follow-up		(lost = 10)	(lost = 5)
Separate Docetaxel Comparisons		***Chi-Square p=0.046***	
Median Survival Censored at	6.6 month	5.8 month	5.4 month

Subsequent Chemorx			
95% CI	5.0, 7.9	5.2, 8.0	4.2, 7.9
Separate Docetaxel Comparisons	?	?	?
% 1 year Survival Censoring at Subsequent Chemorx	32%	32%	10%
95% CI	22, 43	20, 44	1, 18
Separate Docetaxel Comparisons	Log-Rank P=0.13	Log-Rank P= 0.12	
Response Rate (Secondary Endpoint)	**10.5%**	**6.5%**	**0.8%**
95% CI	5.9, 17.6	3.0, 12.7	0.0, 5.2
Separate Docetaxel Comparisons	**Fisher's Exact Test p=0.001**	**Fisher's Exact Test p=0.036**	
Time to Progression *Stat. Plan*:Censored at last assessment before further chemotherapy or radiotherapy *Study Report*: Censored at last assessment before further chemo, not radiotherapy AND Excluding patients without Non-small Cell Lung carcinoma	8.4 weeks	8.5 weeks	7.9 weeks
95% CI	6.7, 11.0	6.7, 11.0	6.9, 11.0
26 week K-M % Progression	19%	17%	8%
95% CI	12, 26	10, 24	3, 13
Separate Docetaxel Comparisons (???for the 26 week analysis??)	**Log-Rank p=0.044**	P=0.093	—
Duration of Response	32.1 weeks	39.3 weeks	25.6 weeks
Log-Rank	NS	NS	
Pre-specified Secondary Quality of Life Endpoints: Changes from baseline in LCSS scores ECOG PS Body Weight	LCSS = 84% compliance at Baseline	LCSS = 73% compliance at Baseline	LCSS = 73% compliance at Baseline

Analgesic Use			
Separate Docetaxel Comparisons – LCSS total score ANCOVA	0.2 (NS Longitudinal) (NS Pattern Mixture)	NS, NS, NS	
Fatigue Separate Docetaxel Comparisons ANCOVA	0.03 (0.07, 0.06)	NS, NS, NS	
Symptoms **Separate Docetaxel Comparisons ANCOVA**	0.03 (0.08, 0.09)	NS, NS, NS	
Factor 1 and Factor 1A ANCOVA	0.02 (NS. NS) 0.03 (NS, NS)	NS, NS, NS NS, NS, NS	
Observer LCSS Total Score	0.05, 0.05, 0.05	NS, NS, NS	
Observer Pain	0.05, 0.07, 0.08	NS, NS, NS	
PS, Weight, Analgesic USE	????	????	

TAX 317

	TAX 100/75	TAX100	TAX 75	BSC
MEDIAN SURVIVAL **Stat Plan-** to the date of death or date of last contact if death is unknown **Study Report** – censored at the date of last contact if lost to follow-up, date of *further anti-tumor therapy including chemo and surgery and immunorx.*	**7.2 months**	5.9 months	9.0 (vs. 4.6 m) n=55	**4.7 months** n=49 (4.6 mo. for n=49)
95% CI	**5.5, 9.2**		**5.5, 13.1**	**3.7, 6.0** (3.7, 6.1 for n=49)
Log Rank	**P=0.14**	**NS**	***P=0.016***	
Wilcoxon rank test	**P=0.06**			
% 1 year Survival	28%		40% (vs. 16%)	23% (16% for n=49)
95% CI	(19, 38)		(26, 54)	(13, 32) {(3, 30) for N=49}
P=	?NS?		??	

Response Rate	**5.8%**	6.3%	5.5% (1.4, 16.1)	
Duration of Response **Stat Plan** – Censor for further chemo, radiation, and surgery **Study Report** - Censored for chemo and surgery only	26.1 weeks	23.9 weeks (n=3)	26.1 weeks (n=3)	
TTP **Stat Plan** - Censored at date of last assessment prior to further therapy including chemo, immunotx, surgery, and radiation Study Report – Censored for all of the above except radiation	**10.6 weeks**	9.1 weeks	12.3 weeks n=55	**6.7 weeks** **n=49 for TAX 75 comparison**
95% CI	**7.6, 12.1**		(9.0, 18.3)	**6.0,7.3** {(6.0, 9.3) for n=49}
Log-Rank	**P<0.001**	0.037	P=0.004	
% 26-week non-PD	16%			5%
95% CI	8, 23			0, 10
Pre-specified Secondary Quality of Life Endpoints: Changes from baseline in LCSS/EORTC scores ECOG PS Body Weight Analgesic use				
"Tumor Related Medication" Incidence of administration	62% *p=0.02*			77%
"Tumor Related Non-Pain Medication"	30% *(p<0.01)*	31% (p=0.04)	29% (p=0.06)	49%
"Tumor Related Pain Medication - Morphine"	32% *p=0.01*	NS	26% P<0.01	49%
"Tumor Related Pain Medication – Non-Morphine"	39% *p=0.03*	NS	31% p<0.01	55%
Radiotherapy (% patients who were treated at least	26% p=0.09	(37%)	16%	37%

once during study or follow-up)			*p<0.01*	(41% in the B-75)
Mean change in PS from baseline in last PS	0.56 SE=0.09 p=0.11	0.45 SE=0.14 NS	0.65 SE=0.13 p<0.05	0.80 (SE=0.11) 1.09 SE+0.16 in B-57
% Patients with weight loss ≥ 10%	7% P=0.07	12%	2% p<0.01	15% (8% vs.D100) (22% vs. D75)
QoL LCSS	75% Baseline			68% Baseline
EORTC	93%			89%

Supportive Phase 2 Studies:

There are six supportive phase 2 studies submitted in this application. Four employed a docetaxel dose of 100 mg/m^2. Two, CHI-202 and TAX241, utilized lower docetaxel doses – 75 mg/m^2 and 60 mg/m^2, respectively.

(First line Non-Small Cell Lung Carcinoma)

Fifty volumes were submitted. The electronic submission

This supplement was submitted June 30, 1999. Fifty volumes were submitted. The data from the pivotal study was submitted electronically. Case Report Forms from TAX 308 for patients who died and discontinued due to adverse event were submitted under Item 12, volumes 12-1 to 12-23.

There is only one phase 3 randomized, controlled trial submitted in this application that provides the primary safety and efficacy data (TAX 308) for docetaxel in the treatment of patients with unresectable locally advanced (Stage IIIb or relapsed after surgery or radiotherapy) or metastatic non-small cell lung carcinoma with no history of prior chemotherapy for their disease. The patients enrolled in this study and had an WHO performance status ≤ 2. Patients were stratified before randomization according to disease extent. Patients were recruited so that 2/3 would be treated on the docetaxel arm and 1/3 would be in the best supportive care only arm. The primary endpoint was median survival.

The trial that provides the primary safety and efficacy data is:

TAX 308: (Open label; 15 European sites, 1 USA, 1 Mexico)

ARMS:	A = Taxotere 100 mg/m^2 q 21 d (+ BSC)	(N = 137)
	B = Best Supportive Care	(N = 70)

Reviewer Comment: The three investigators/centers with the highest accrual were all located in Poland:

Pluzanska	*PL00022 (Warsaw?)*	*N=46*
Roskowski	*PL00020 (Warsaw?)*	*N=43*
Krzakowski	*PL00012 (Lodz?)*	*N=37*

Together, these investigators accrued 61% of the patients in this study. Sixty percent of the patients these three centers accrued had stage IIIB disease (74% of the PL00022, 61% of the PL0020, and 41% of the PL00012 patients were stage IIIB).

Review Issues Raised by the Sponsor's Proposed Labeling:

5) Survival Claims:

- *Significantly longer Overall Survival,(Does the p=0.026 in the sponsor's table refer to median survival or 1-year Survival*
- *Higher 1-year Survival*
- *They report even higher significance when censoring for subsequent chemotherapy is performed, p=0.012.*

2) Response and TTP:

- *They report the response rate in the ITT and "eligible and evaluable population" – 13% and 20%, respectively. (26.3% were reportedly not evaluable)*
- *They report a significantly longer time to progression, p<0.001 (Both ITT and evaluable analyses presented; only 4% were not evaluable for this endpoint.)*

3) Other Benefits:

- *They report "Clinical Benefit Parameters" with significant improvement include less use of radiotherapy (p<0.01), less "disease related medications other than for pain" (p<0.01), less morphinic analgesics (p<0.001), and less non-morphinic analgesics (p<0.001).*
- *They report Quality of Life "significant trends favoring docetaxel" in emotional function (p=0.01). pain (p<0.001), and dyspnea (p<0.01).*

Additional Review Issue: The sponsor has only submitted one controlled trial for the indication of first line treatment of locally advanced or metastatic non-small cell lung carcinoma. The sponsor reports this study has demonstrated survival benefit for docetaxel when compared with best supportive care. The supportive studies are phase 2, but the sponsor has submitted two studies in second-line treatment of non-small cell lung carcinoma that they report demonstrates survival benefit associated with this stage of disease as well.

A table summarizing the sponsor's efficacy analyses is shown below. Pre-specified endpoints are enclosed in heavy crossbars, while those analyses that were not pre-specified are enclosed in dashed crossbars.

TAX 308 First Line

	TAX 100 mg	BSC	
Median Survival	**6 months**	**5.7 months**	
95% CI	**5.0, 8.0**	**4.4, 6.8**	
Log Rank			
%1-year Survival?? (*in a 1/99 statistical analysis plan*)	25	16	
95% CI	17, 32	7,25	
Log Rank	P=0.026		
Censored for further chemotx: Median Survival	6.0 months	4.6 months	
95% CI	4.7, 8.0	3.9, 6.8	
Log Rank			
Censored for further chemotx: % 1 year Survival	25%	15%	
	17, 33	6, 25	
Log Rank Test	P=0.012		
TTP **Stat Plan:** to date of last evaluation before starting antitumor therapy including radiotherapy **Study Report:** to date of last evaluation before starting surgery, immunotherapy, chemo, but excluding XRT.	**12.6 weeks**	**8.9 weeks**	
95% CI	9.9, 16.6	7.7, 9.7	
Log Rank Test	**<0.001**		
RESPONSE	13.1% CI = (7.5, 18.8)		
Duration of Response	37.1 weeks		

	CI = (30.9, 69.9)		
Stat Plan = "Tumor Related Symptoms": **Hemoptysis** **Pulmonary Cough** **Pain not related to study medication**			
Study Report = Clinical Benefit: Usage of concurrent medications for relief of cancer related symptoms Morphine Non-Morphine analgesics Tumor-related medications Anti-infective therapy Concurrent Radiotherapy Dyspnea Pain Hemoptysis Cough			
QoL - QLQ-C30	88% baseline	57% baseline	
	Worst Score	Longitudinal	Pattern Mixture
Global health status	0.09	0.16	0.13
Physical Functioning	0.08	0.14	0.22
Emotional Functioning	**0.01**	**0.01**	**0.04**
Pain	**<0.001**	**<0.001**	**<0.001**
Dyspnea	**0.03**	**<0.01**	**0.02**
QoL – QLQ LC13	<30%	<30%	

Supportive Phase 2 Studies:

There are twelve supportive phase 2 studies submitted in this application. The docetaxel dose specified in the protocol was 100 mg/m2 in 7/12, but during the course of one of the studies it was reduced to 75 mg/m^2 in a protocol amendment (June 15, 1993; TAX231). Two multicenter phase 2 studies, CHI-202 and KOR302, utilized a dose of 75 mg/m^2, and 3 studies, all conducted in Japan (TAX241, TAX284, and TAX290) utilized a dose of 60 mg/m^2. Three of the twelve studies were conducted in the United States, one of which was a multi-center trial (TAX269). Five of the twelve studies were multi-center studies – TAX 269 (USA), TAX223 (EU), TAXSI002A (EU), TAX 295 (Canada), and TAX292 (Mexico).

4. **Recommended Regulatory Action:** Both supplemental NDA submissions (SE1 011 meet criteria for filing. The sponsor will need to submit a proposed label that clearly reflects the efficacy data provided by the two phase 3 trials in second line treatment of non-small cell lung carcinoma (SE-011).

Please convey the following comments to the sponsor:

We have done a preliminary review of the proposed labeling provided in SE011 . and have noted the following deficiencies:

- The labeling for second-line treatment of non-small cell lung carcinoma should include the efficacy and safety data from both pivotal phase 3 studies. As the label currently stands, the data from TAX 317 has not been provided. Please submit an updated label that includes this information.

- The Clinical Studies section of labeling should provide the efficacy and safety data that form the basis of including 60 mg/m^2 in the recommended dose for first and second line treatment of non-small cell lung carcinoma.

- We note in your cover letter dated 6/23/99 that accompanies SE011 that you suggest that "the optimal dose range and schedule for this patient population is 60 mg/m^2 to 75 mg/m^2 administered...." This, however, is not reflected in your proposed labeling under Dosage and Administration. Please revise accordingly.

In addition, the Office of Post-Marketing Drug Risk Assessment has requested a review of the current label to address medication error reports received through the AERS and USP voluntary reporting systems. These errors appear to be related to the dilution instructions and the labeling of the vial overfill volumes. We are submitting these proposed changes for your concurrence.

/S/ 8/9/99
Donna J. Griebel, MD

/S/ 8/9/99
Julie Beitz, MD

CC:
NDA#20-449
SE1 011 and SE1 012
HFD-150/Div.File
HFD-150/D. Griebel
HFD-150/A.Staten