Food and Drug Administration

Center for Drug Evaluation and Research
Oncologic Drugs Advisory Committee

Questions for Discussion

Background

A randomized controlled unblinded trial was conducted in 571 patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy comparing Alimta with docetaxel. The primary objectives were 1) to show Alimta's superiority to docetaxel for overall survival and 2) to show Alimta's non-inferiority to docetaxel for overall survival if there was failure to show superiority. The efficacy results are summarized in the following Table.

	ITT[a]		RT[b]	
	Alimta	Docetaxel	Alimta	Docetaxel
Resp Rate (%) (95% CI)			9.1 (5.9, 13.2)	8.8 (5.7, 12.8)
P-val (Fisher)[c]			.999	
Resp Duration (median)[d]			4.6	5.3
PFS (median)[d]	2.9	2.9	2.9	3.0
HR (95% CI) p-val (Wald)[c]	.97 (.82,1.16) .759		.98 (.82,1.17) .821	
TTP (median)[d]	3.4	3.5	3.1	3.5
HR (95% CI) p-val (Wald)[c]	.97 (.80, 1,17) .721		1.01 (.83, 1.22) .951	
OS (median)[d]	8.3	7.9	8.4	8.0
HR (95% CI) p-val (log rank)[c]	.99 (.82, 1.20) .930		.97 (.80, 1.18) .765	

[a]Intent to Treat
[b]Randomized and Treated
[c]All p-values two-sided
[d]Months

The FDA believes Alimta non-inferiority for overall survival can not be demonstrated for two reasons. First, there is only one small historical study (total 104 patients) from which to estimate the survival effect of docetaxel, resulting in inability to estimate the docetaxel effect with precision, to evaluate interstudy variability and to assess constancy. A meta-analysis of multiple historical studies is ordinarily required for a

Discussion Questions Continued

non-inferiority analysis. Second, in the Alimta versus docetaxel study comparison of survival effect is confounded by the 32% crossover rate of Alimta patients to docetaxel after tumor progression and the greater number of docetaxel patients who did not receive any post study chemotherapy.

In the Alimta versus docetaxel study the Alimta 9.1% tumor response rate provides evidence of some Alimta anticancer activity and the similarity of Alimta and docetaxel in PFS and TTP provides some support for Alimta efficacy. If these were taken as surrogate effects reasonably likely to predict benefit and if Alimta had a documented safety advantage over docetaxel, accelerated approval could be a possibility.

Questions

1. Do you believe Alimta has a more favorable toxicity profile than docetaxel?

2. If the answer is yes, does the more favorable Alimta toxicity profile with supporting efficacy data on tumor response and PFS outweigh the uncertainty regarding loss of docetaxel survival effect by using Alimta?

3. Given the potential confounding effects of cross-over, and problems in estimating the control effect, is there a convincing effect on survival to warrant regular approval?