Clovis Oncology: CO-1686 (Phase I/II/NSCLC) is Wild-Type EGFR Sparing and Appears to Be More Selective vs. AstraZeneca's AZD9291

As we head into ESMO this weekend, we conducted an analysis of the pre-clinical data on AZD9291, the closest competitor to Clovis' CO-1686 in lung cancer patients with the T790M resistance mutation. **A key question for investors is how active is AZD9291 against T790M vs. wild-type EGFR.** Based on our preliminary analysis of available pre-clinical data, AZD9291 does not spare wild-type EGFR as selectively compared to CO-1686. While there is less data to make a comparison on the relative potency at T790M, the drug does have activity based on preclinical data, but activity could be impacted by dose limiting side effects. We expect to get a better sense of the competitive landscape this weekend at ESMO, when we will get our first glimpse at the AZD9291 phase 1 clincal data.

AZD9291 Wild-Type EGFR Activity May Be Dose Limiting. Based on our preliminary analysis of the AZD9291 pre-clinical data, we believe that the compound has the potential to show dose limiting toxicity associated with wild-type EGFR inhibition. In pre-clinical mouse lung xenograft models, AZD9291 had 78% tumor growth inhibition in wild-type cells which is similar to Iressa (gefitinib) which had 62% tumor growth inhibition in wild-type cells (see figure 1 on page 2). Given that Iressa is associated with known GI toxicity and skin rash, due to wild-type EGFR inhibition, similar side effects could be dose limiting and potentially limit the therapeutic window of AZD9291, while CO-1668 is already showing decent potency (3/4 PR in T790M mutations) without toxicity issues so far and is still in the dose escalation phase which bodes well from an efficacy perspective.

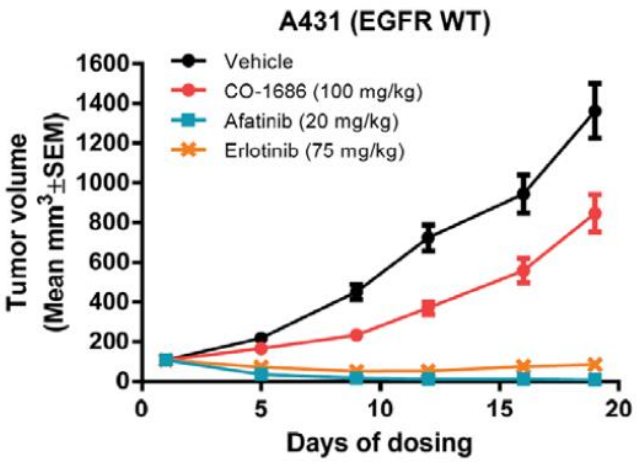
CO-1686 is Wild-Type EGFR Sparing and More Selective. We believe CO-1686 could potentially be more selective than AZD9291 as the drug targets activating EGFR mutations and the T790M resistance mutation, but spares wild-type EGFR at anticipated therapeutic doses. In a recently published analysis, CO-1686 had almost no activity against wild-type EGFR compared to existing earlier generation tyrosine kinase inhibitors such as Tarceva (erlotinib) and Gilotrif (afatinib).This difference in selectivity may drive CO-1686 to have a better toxicity profile compared to AZD9291, which could lead to a better therapeutic window.

Figure 1. AZD-9291and EGFR TKI Efficacy in Mouse Lung Xenograft Models

Model/ Mutation status	NCI-H1975 (T790M/L858R)	PC-9 (Ex19del)	A431 (wild type)
First Generation			
Gefitinib (Astrazeneca)	8% @ 100mkd (n=1)	183% @ 6.25mkd (n=4)	62% @ 6.25mkd (n=3)
Second Generation			
Afatinib (Boehringer Ingelheim)	16% @ 7.5mkd (n=3)	254% @ 7.5mkd (n=2)	107% @ 7.5mkd (n=1)
Competitor B	75% @ 15mkd (n=1)	266% @ 15mkd (n=1)	138% @ 15mkd (n=1)
Third Generation			
AZD9291 (Astrazeneca)	132% @ 5mkd (n=13)	250% @ 5mkd (n=6)	78% @ 5mkd (n=10)

Source: Citi Research and Astra Zeneca

Figure 2. . CO-1686 Efficacy in Mouse Lung Xenograft Models



Source: Citi Research and Medical Literature

CO-1686 Market Opportunity Attractive. We model only 50% penetration into the T790M mutation population as 2nd-line therapy and factor in competition. We assume a 65% probability of success in this indication given the current data, and the drug's mechanism of action. We model approval in 2017 and global probability adjusted peak sales of $517M in 2033.

Source: Citigroup/Werber, September 26, 2013
Oncology Indication: Lung
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