



TUESDAY JULY 5TH, 2011

Goedenavond Canada! Good Evening Canada as the Dutch say it!

We continue to learn about the EGFR pathway and how to best inhibit it to improve efficacy and survival for our patients. Today a multitude of interesting phase 2 trials involved in this pathway were presented.

Adding dalotuzumab (MoAb against IGF-1R) to erlotinib did not improve efficacy in metastatic NSCLC. Similarly adding apricoxib (COX-2 inhibitor) to erlotinib failed to show benefit.

Nonetheless, there were some positive combinations presented. As our understanding of the EGFR pathway improves, we are seeing trials designed to best target it and emerging resistance. As cmet is recognized as an important part of this, inhibiting it makes perfect rationale. As previously presented at ASCO 2011, adding MetMab to erlotinib in advanced NSCLC looks beneficial. This benefit is restricted to those patients whose tissues were “met high” or more specifically “met diagnostic positive” as defined by met IHC expression levels of moderate +2 or high +3. A statistically and clinically significant improvement in both PFS and OS in this Met Dx+ group was seen (Figure 1). Overall survival was 12.6m vs 3.8m (MetMab/erlotinib vs erlotinib alone). We look forward to seeing this combination in a phase 3 trial.

A second recognized resistant mechanism to tyrosine kinase inhibition involves acquired T790M mutations. Afatinib as a single agent was presented in the Asian trial LUX-LUNG4. This phase 2 trial showed a RR of only 8% in PFS of approximately 4 moths in patients previously treated with erlotinib or gefitinib. Adding cetuximab (MAB to EGFR) markedly improved efficacy as presented by Dr Leora Horn from Vanderbilt. 80 pts who were EGFR mutation+ upon progression were biopsied and then treated with the combination of afatinib 40mg and cetuximab 500mg/m2. 55 of these pts were able to be evaluated for efficacy and presented today. A partial response of 35% was confirmed and 95% had clinical benefit (PR/SD). The waterfall plot is impressive (Figure 2)! This data supports that EGFR M+ NSCLC with acquired resistance continues to benefit from EGFR targeting pathways.

Final thoughts...

- 1) Dual inhibition of Met and EGFR pathways as well as vertical blockade of EGFR pathways to overcome EGFR inhibitor resistance appears promising based on these important phase 2 studies. We await with anticipation the confirmatory phase 3 trials. Until then, these combinations should not be used outside of clinical trials.
- 2) These illustrate that future advancement in lung cancer trials must follow the science and our understanding of it.

Have a good night!

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Figure 1: MetMab plus erlotinib in Met Dx+ patients

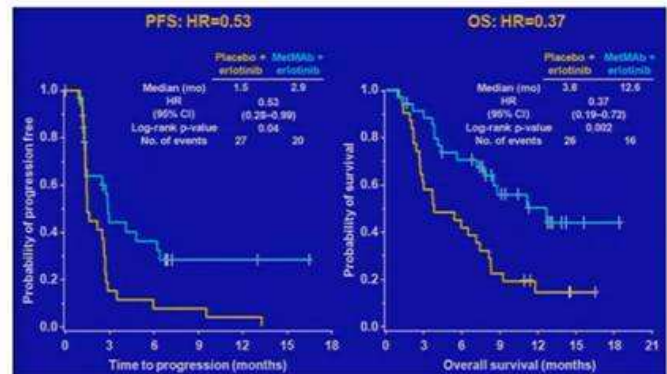


Figure 2: Tumour regression by T790M mutation status at recommended dose

