ALK Positive Summit - 1 August 2020

Prepared on behalf of Alk Positive Lung Cancer (UK)

The following summarises some interesting learning points from the presentations relevant to our treatments, the progress that has been made in ALK+ and NSCLC treatment and the excellent US research giving us hope for the future:

1. The molecular testing guideline on diagnosis in the US in 2013 was to test for EGFR and ALK mutations, with PDL as the standard bio marker test.

2. In 2018, the US changed its guideline to testing for 8 mutations: EGFR ALK ROS1 BRAF RET HER2 KRAS MET. This can be deduced from Next Generation Sequencing (NGS) and FISH testing. NGS is not used routinely in the UK and is not the standard in the US either, although many are pushing for it.

3. Each of these genetic mutations gives the potential for more targeted treatment options, that may potentially give us better responses and longer lives. So, for example, the first generation TKI Crizotinib is really a MET drug that is also used for ALK. Lorlatinib, the inventor who spoke at the Summit told us, was developed for ALK and ROS1. There was much comparison data about TKI cell potency. For example, the data indicated that Alectinib was likely to be very poor against ROS1, but Lorlatinib is potentially great.

4. There are three variants of EM4-ALK: V1, V2, V3a/b. V3a/b tends to do worse on things like response to Alectinib. But it was not apparent at present how this knowledge would meaningfully inform treatment. There are also other variants, but these three are the vast majority. Some reports show the variant but some (e.g. NGS) do not.

5. Although in the US some patients are treated through TKI after TKI, the standard approach is currently Alectinib then Lorlatinib.

6. Alectinib appears in studies to be the most effective ALK TKI and there are more studies on it. Lorlatinib has the added benefit of even less likely toxicity generally and the ability to penetrate the blood brain barrier. Weight gain and changes in cognitive function were noted as side effects of Lorlatinib.

7. Lorlatinib was developed originally to improve and overcome Crizotinib resistances and it took 8 years to get to FDA approval, which was apparently quick.

8. Almost all tumours develop resistance to ALK+ drugs. One of the research areas is why we eventually develop resistance to our drugs and the TKI stops working. In some cases, we develop ALK mutations, which mean we acquire resistance. In around 40-60% cases of resistance depending on the TKI, there are no ALK mutations and so chemo/radio/immunotherapy are considered, if there is no other mutation that can be treated with a TKI e.g. EGFR.

9. Best TKI sequencing was considered and is the subject of research. A biopsy (tissue or liquid) can be performed after progression on a TKI and testing can then label all the mutations after progression, and analyse in the lab to see what the next best drug may be, so the oncologist can take a view. For example, the research presented was that the three most common Alectinib

resistant ALK-mutations were G1202R, I1171X and V1180L. Brigatinib is active against I1171X and V1180L but not G1202R (which Lorlatinib is active against). So arguably if you develop ALK resistance mutation I1171X or V1180 on Alectinib - which is 15-20% of patients in a study - the next step could then be Brigatinib before Lorlatinib.

10. After developing resistance to Lorlatinib, there are likely to be more complex mutations to consider than the mutations that may happen after progression on an older TKI. In the US, the labs can even run tests to predict that a drug might work again e.g. in a unique case, it was decided after mutation testing to go back to Crizotinib after a long gap, and that gave the patient to another 9 months, even though she had Crizotinib at the beginning of her treatment regime, and had undergone chemo then lorlatinib and other treatment since.

11. Options after Lorlatinib other than chemotherapy or radiotherapy appear still limited. ALK patients in some studies seem to have a statistically better run on chemo than those NSCLC with some other oncogenetic mutations, such as EGFR. ALK patients tend to respond poorly to immunotherapy and much worse than the 20-30% overall of NSCLC patients who respond to current immunotherapies.

There is nevertheless much hope for the future. There is TPX-0131 in development, which would be a 4th generation TKI, at present in studies to secure approval for first human trials, as well as the hint there may be others in development. But big pharmaceuticals will not give information away that easily it seems!

There are also exciting trials and research in the US, including:

1. Developing a therapeutic vaccine for ALK+ lung cancer, which is already tested in mice and going to phase 1 in human trials.

2. Understanding how ALK+ NSCLC escapes surveillance and developing strategies to overcome the immune system including T cell therapy.

3. Using an approved drug as a “complement inhibitor” to boost the immune systems cancer fighting ability - for example Eculuiziumab; also there’s a phase 1 trial.

4. Studies on the development of sensitivity and resistance to ALK TKI therapy. “Clusterin” seems to be a bad-guy target here.

5. Phase 3 trial of using Lorlatinib as a first line treatment.

6. Examining MET amplification in ALK Phase 1b/2 trial of combination therapies using Lorlatinib and Crizotinib or Capmatinib where there is amplification of MET and Lorlatinib and either MEKi or SHP2 where there is not.