ALK – Is there a role for more potent ALK inhibitors in crizotinib-resistant patients?

LEERINK SWANN

- Underlying mechanisms* for crizotinib resistance – YES
  - ALK – dependent: secondary mutations in ALK genes → suitable for more potent ALK
  - ALK – independent: activation in alternative signaling pathways (EGFR, c-Met, KIT, K-Ras, or HSP90) → requires a combination therapy
- Pre-clinical and clinical evidence
  - Evidence 1** – ORR of 81% in 26 ALK-positive NSCLC patients who received LDK378 and prior crizotinib treatment
  - Evidence 2*** – 22-36% of 18 crizotinib-resistant NSCLC patients (EML4-ALK positive) developed multiple mutations in ALK gene. However, the rest of the mutations were associated with other signaling pathways. A combination with EGFR or KIT inhibitor could overcome crizotinib resistance.
  - Evidence 3**** – In an EML4-ALK positive NSCLC cell model, a gatekeeper mutation (L1196M) was developed after high-dose crizotinib. Structurally different ALK inhibitors (NVP-TAE684 and AP26133) were highly active against such crizotinib-resistant cells.

Source: *Front Oncol (2012) 2:17; **2012 ASCO #3007; ***Sci Trans Med (2012) 4:120; ****PNAS (2011) 108:7535