

# MEK inhibition in KRAS-mutant NSCLC did not improve survival

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MEK inhibitor selumetinib in combination with docetaxel does not improve progression free or overall survival in individuals with KRAS-mutant non-small-cell lung cancer (NSCLC), according to data presented at the ESMO 2016 Congress in Copenhagen.

"KRAS-mutant lung cancer is the largest genomically defined subset of lung cancer where we do not have effective targeted therapies," said principal investigator Dr Pasi Jänne, from the Dana-Farber Cancer Institute in Boston, US.

Selumetinib inhibits an effector protein immediately downstream from KRAS, which was thought to turn off KRAS-mediated signalling in KRAS-mutant cancers.

An earlier phase II trial in KRAS-mutant NSCLC had shown significant improvements in progression-free survival and objective response rate in patients treated with selumetinib plus docetaxel compared to docetaxel alone.

In the phase III, double-blind, randomized SELECT-1 trial, 510 patients with KRAS-mutant [non-small-cell lung cancer](#) were randomized either to oral selumetinib (75mg, twice daily) plus intravenous docetaxel (75mg/m<sup>2</sup> on day 1 of a 21 day-cycle), or docetaxel plus placebo.

At data cut-off, median progression-free survival was not significantly different between the selumetinib arm and placebo arm (3.9 months vs.

2.8 months, HR 0.93,  $p=0.44$ ), nor was there a significant difference in median overall survival (8.7 months vs. 7.9 months, HR 1.05,  $p=0.64$ ).

There was a trend towards a higher objective response rate in the selumetinib group compared to the placebo group (20.1% vs. 13.7%, OR 1.61,  $p=0.051$ ).

Serious adverse events occurred more frequently in patients treated with the selumetinib plus docetaxel combination compared to placebo (49% vs. 32%), as did adverse events leading to hospitalisation (46% vs. 30%).

"The results of the phase III trial demonstrate that the addition of selumetinib to docetaxel, in patients with advanced KRAS mutant [lung cancer](#), does not provide clinical benefit in terms of improving progression free or overall survival," Jänne said.

"Hence it is not a treatment approach that should be adapted moving forward, and there remains a desperate need and an opportunity to develop new treatments for this subset of NSCLC patients."

Commenting on the study, Dr Alex Adjei, director of the Early Cancer Therapeutics Program and Global Oncology at the Mayo Clinic in Rochester, US, said "Dr Jänne and colleagues should be congratulated for performing a well-designed genotype-driven trial, however the preclinical rationale for studying this combination specifically in KRAS mutant NSCLC was weak, at best."

"Selumetinib and other MEK inhibitors are not effective in KRAS mutant NSCLC cell lines and, while there are preclinical data that demonstrate cytotoxic synergy between selumetinib and other MEK inhibitors combined with docetaxel in a number of tumor types, including NSCLC, such synergy is independent of KRAS status," Adjei said.

"A randomized phase II trial of the combination of another MEK inhibitor, trametinib and docetaxel failed to show any difference in efficacy between KRAS mutant and wild-type NSCLC. Furthermore, the phase II study on which this phase III trial design was based had a very small sample size and historically, such small randomized phase II studies have led to negative phase III trials," concluded Adjei.

**More information:** "Selumetinib in combination with docetaxel as second-line treatment for patients with KRAS-mutant advanced NSCLC: Results from the phase III SELECT-1 trial" will be presented by Prof Pasi Jänne during the Proffered Paper session, NSCLC, metastatic 2 on Monday, 10 October 2016, 09:15 to 10:15 CEST in Room Vienna.

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