**Report from the European Society for Medical Oncology Congress**

**Lung cancer**

**TREATING EGFR-POSITIVE NON-SMALL CELL LUNG CANCER AFTER PROGRESSION**

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**TRIAL SUMMARY:** Chemotherapy with and without gefitinib after progression on gefitinib

Mok T, et al. Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) after progression on first-line gefitinib: The phase III, randomized IMPRESS study. ESMO 2014 Abstract LBA2_PR.

Most patients (pts) with EGFR mutation-positive non-small-cell lung cancer (NSCLC) respond to first-line EGFR tyrosine kinase inhibitors (TKI), but later acquire resistance. The Phase III, double-blind IRESSA Mutation Positive Multicentre Treatment Beyond Progression Study (IMPRESS; NCT01544179) evaluated the efficacy/safety of continuing gefitinib plus cisplatin/pemetrexed (cis/pem) (G) vs placebo plus cis/pem (P) in pts with acquired resistance to first-line gefitinib. The study included adult pts who were chemotherapy-naive, had locally advanced/metastatic NSCLC with an activating EGFR mutation, and had prior disease progression on first-line gefitinib from 71 centres (Europe/Asia Pacific). Pts were randomized to G or P (gefitinib 250 mg/day or placebo; plus cis 75 mg/m² and pem 500 mg/m²). The primary endpoint was progression-free survival (PFS).

**COMMENTARY:** EGFR tyrosine kinase inhibitors (E-TKIs) are the standard first-line treatment for patients with metastatic NSCLC whose tumours harbour an EGFR mutation. These agents demonstrated higher response rates, better quality of life (QOL) and longer PFS compared to standard chemotherapy. Unfortunately, acquired resistance almost inevitably appears in responding patients after a median duration of response of about 10 months.

Very little data exist regarding the optimal management of patients with acquired resistance, and practice currently changes according to physician preferences and availability. The options are to 1) continue E-TKIs beyond progression until a “clinical” progression occurs (supported by results of the ASPIRATION study, also reported in ESMO 2014); 2) switch to chemotherapy; 3) use second- or third-generation E-TKIs (if a clinical trial is available); and 4) combine chemotherapy with an E-TKI. Arguments to support the last option include potential heterogeneity within the tumour, where some clones are TKI-resistant while others are still sensitive, as well as some retrospective data indicating possible disease flare after discontinuation of E-TKI.

The IMPRESS study is the first randomized placebo-controlled trial to address this question. It compares continuation of gefitinib in addition to cis/pem vs placebo plus cis/pem. IMPRESS is the first and only randomized phase III study to confirm that continuation of gefitinib in addition to cis/pem would be of no clinical benefit for pts with acquired resistance to gefitinib. The standard of care should remain doublet chemotherapy alone.
immature (accounting for only a third of the events), but suggested a detrimental effect for the gefitinib-chemotherapy combination (14.3 vs 17.2 months, HR=1.62, p=0.029). Treatment-related serious adverse events and mortality were comparable.

A weakness of the IMPRESS study was lack of stratification factors for randomization, resulting in slightly unbalanced groups, with patients in the study arm being older, having more brain metastases (33% vs 23%) and achieving slightly lower response to first-line gefitinib (68% vs 76%). Poststudy treatments were also unbalanced in favour of the placebo arm. However, posthoc analyses adjusting for these covariates showed similar PFS and detrimental OS results.

The main message from IMPRESS is that combination E-TKI and chemotherapy should not be used after progression on gefitinib (and we can apply these results for erlotinib as well). In addition to resolving one of the more debated clinical issues in patients with EGFR-mutated tumours, this study also confirms that the choice of chemotherapy after progression on E-TKI should be platinum-based doublet (and not single-agent chemotherapy), with ORR of 34%, which is the response seen in first-line settings as well.

**IN BRIEF**

**Already known**
- Most patients with EGFR mutation-positive non-small cell lung cancer (NSCLC) respond to first-line EGFR tyrosine kinase inhibitors (TKI), but later acquire resistance. Chemotherapy is considered the standard of care following the development of resistance.

**What this study showed**
- This study showed that there was no progression-free survival, overall response rate or overall survival (OS) advantage in continuing gefitinib alongside doublet (cisplatin/pemetrexed) chemotherapy after resistance develops to first-line gefitinib. Shorter OS suggests a detrimental effect in the study arm.

**Next steps**
- The standard of care should remain doublet chemotherapy alone in patients with acquired resistance to gefitinib.