Update on Lux Lung 7: Afatinib versus Gefitinib for first-line treatment of advanced/metastatic EGFR positive non-small cell lung cancer

By Dr. Parneet K. Cheema, HBSc, MD, MBiotech, FRCPC, Medical Oncologist, Sunnybrook Odette Cancer Centre

Introduction

• An EGFR TKI is the recommended first-line treatment for patients with advanced EGFR positive NSCLC.1
• Gefitinib and erlotinib are first generation EGFR TKIs that have shown to improve progression-free survival (PFS) and overall response (ORR) compared to platinum doublet.2
• Afatinib, an irreversible ErbB family blocker, is a second generation EGFR TKI that has shown to improve PFS and ORR and, in a pooled analysis, improved overall survival (OS) compared to first-line platinum doublet.3
• Lux Lung 7 is the first prospective randomised trial comparing a first and second generation EGFR TKI as first-line systemic therapy for EGFR positive NSCLC.5

Study design

• Randomized, phase IIb, afatinib 40 mg po OD versus gefitinib 250 mg po OD in treatment naïve advanced EGFR positive (common mutations) NSCLC.
• Co-primary endpoints were PFS, time to treatment failure (time to discontinuation by all cause) (TTF), and OS.

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Results (from primary analysis)

• Afatinib significantly improved PFS compared to gefitinib (median 11.0 mos with afatinib vs 10.9 mos with gefitinib; HR 0.73, p=0.017) and improved ORR (70% versus 58%; p=0.0083).
• PFS/ORR by genotype
  ▪ Deletion 19: PFS: HR 0.76, p=0.107, ORR: 73% vs 66%
  ▪ L858R: PFS: HR 0.71, p=0.85, ORR: 66% vs 42%
• PFS with afatinib was consistent across pre-defined clinical subgroups, including age, sex and race.
• There was a significant improvement in median TTF (13.7 mos with afatinib vs 11.5 mos with gefitinib; HR 0.73, p=0.0073).
• Toxicity: Afatinib was associated with increased grade 3/4 diarrhea, rash, paronychia, stomatitis and fatigue, whereas gefitinib had increased rates of transaminitis. Dose reductions due to adverse events (AEs) occurred in 42% of patients with afatinib; gefitinib has a fixed dose and, thus, is not able to directly compare effect of AEs leading to dose reductions. However, despite the difference in AEs, the rate of discontinuation was low at 6% in both arms.
• Dose reductions of afatinib due to AEs did not impact the PFS.
• Patients who were dose reduced (<40 mg po OD): PFS 12.8 mos
• Patients who were maintained full dose: PFS 11 mos, HR 1.34
• Despite increased toxicity with afatinib, PROs were similar with afatinib and gefitinib.

ESMO 2016 update – Mature OS data

• Update with a median follow-up of 42.6 mos.
• Previously reported PFS, TTF and ORR were maintained with further follow-up.
• There was a numerical trend of improved median OS with afatinib that did not reach statistical significance and this trend was also found among the two common genotypes.
• Median OS of afatinib vs gefitinib: 27.9 vs 24.3 mos; HR 0.86, p=0.258
• Deletion 19: 30.7 vs 26.4 mos; HR 0.83
• L858R: 25.0 vs 21.2 mos; HR 0.91
• Sub analysis showed no difference in median OS with afatinib according to age including patients who were ≥75.
• Subsequent therapies: 14 and 15% of patients received a third generation EGFR TKi in the afatinib and gefitinib arms, respectively.

Impact on practice

Lux Lung 7 is currently the only reported prospective head-to-head comparison of EGFR TKIs as first-line therapy for advanced EGFR-positive NSCLC. This update confirms the improvement of PFS and ORR with afatinib compared to gefitinib. The PFS advantage with afatinib becomes more pronounced over time, with separation of PFS curve after one year. The delayed benefit of afatinib is hypothesized to be due to delayed onset of resistance mechanisms. Although OS was not significantly different between the arms, there was a consistent trend of ~3-month improvement in OS with afatinib across both common genotypes. Gefitinib and afatinib both remain valid options for patients with EGFR-positive NSCLC. The clinical benefits of afatinib need to be weighed with the increased toxicity seen with afatinib and, thus, performance status, comorbidities and compliance need to be factored into the selection of EGFR TKI. However, the discontinuation rate with afatinib was low, indicating that toxicity was manageable. To optimize therapy with afatinib at the Sunnybrook Odette Cancer Centre, Toronto, we have undertaken a multidisciplinary proactive call back protocol to manage our patients on afatinib.

References

5. Paz-Ares L, et al. Afatinib (A) vs gefitinib (G) in patients (pts) with EGFR mutation-positive (EGFRm+) non-small-cell lung cancer (NSCLC): overall survival (OS) data from the phase IIb trial LUX-Lung 7 (LL7). Abstract #LB4A43, ESMO 2016, Copenhagen, Denmark.