The role of necitumumab in the treatment of advanced NSCLC

L. Paz-Ares, J. E. Miziara, G. Losonczy, et al. Randomized phase 3 trial (INSPIRE) of necitumumab plus cisplatin-pemetrexed versus cisplatin-pemetrexed alone as first-line therapy in stage IV non-squamous NSCLC.

BACKGROUND

Epidermal growth factor receptor (EGFR) is expressed on the surface of the majority of cases of NSCLC irrespective of EGFR mutation status. Necitumumab is a humanized anti-EGFR antibody that competes with EGFR ligands for receptor binding. INSPIRE is a phase III study that evaluated the efficacy of necitumumab combined with chemotherapy in metastatic non-squamous cell lung cancer patients in the first-line setting.

This study randomized patients with non-squamous histology in a 1:1 fashion to receive cisplatin and pemetrexed with or without necitumumab. The primary endpoint of this study was OS with secondary endpoints including PFS, response rate (RR), toxicity and EGFR protein expression levels based on immunohistochemistry (H-score) performed on archived tumour tissue.

FINDINGS

Only 633 patients of a planned 947 patients were recruited to this study. Enrolment was stopped early secondary to safety concerns regarding increased toxicity in the necitumumab arm. No difference was observed between the 2 study arms with respect to median OS (mOS 11.3 vs 11.5 months, HR 1.01), PFS (5.6 vs 5.6 months, HR 0.96) or ORR (31.1% vs 32.1%, HR 0.96). No association was found between EGFR expression levels and efficacy (H-score <200: mOS 8.97 vs 9.72 months, HR 1.07; mPFS 4.90 vs 4.76 months, HR 0.95; ORR 27.1 vs 26.0%; H-score ≥200: mOS 15.01 vs 13.34 months, HR 1.03; mPFS 5.59 vs 5.62 months, HR 0.94; ORR 39.6 vs 39.4%). Significantly increased toxicity was seen in the necitumumab treatment arm, including skin or subcutaneous disorders (14.1 vs 0.3%), thromboembolic events (9.5 vs 6.4%), hypomagnesemia (7.6 vs 2.2%), asthenia (6.9 vs 1.9%), vomiting (6.6 vs 3.2%), dyspnea (5.3 vs 2.6%) and diarrhea (4.3 vs 2.2%). The frequency of study drug-related deaths (14.1 vs 0.3%) and thromboembolic events (9.5 vs 6.4%) were increased in the necitumumab arm versus 2.9% in the control arm.

The authors conclude that the addition of necitumumab to standard first-line chemotherapy did not improve efficacy in metastatic non-squamous cell lung cancer patients. Further, necitumumab was associated with unacceptable toxicity, including an increased risk of thromboembolic events, which led to premature termination of study enrolment.

COMMENTARY: The use of EGFR TKIs is well established in advanced NSCLC with EGFR activating mutations. The use of antibodies targeting EGFR has been evaluated as a means of preventing ligand binding and thus inhibiting EGFR signalling and tumour growth in advanced NSCLC. Several anti-EGFR antibodies have been developed and are currently undergoing evaluation in clinical trials.1-4 The role of these antibody-based therapies in advanced NSCLC remains controversial.

Cetuximab was the first anti-EGFR antibody evaluated in advanced NSCLC. The FLEX phase III study randomized 1125 patients with advanced EGFR-expressing NSCLC to receive first-line cisplatin-vinorelbine with or without cetuximab. This trial demonstrated a modest improvement in the primary endpoint, OS, associated with cetuximab treatment (mOS 11.3 vs 10.1 months, HR 0.87, p=0.04). While this difference was statistically significant, many clinicians assess the 1-month difference in OS to be clinically insignificant. The subgroup of patients with high EGFR immunohistochemistry (IHC) scores appeared to derive increased benefit in this trial (mOS 12.0 vs 9.6 months, HR 0.73, p=0.01).5 The BMS099 phase III trial randomized 676 patients with unselected advanced NSCLC to receive carboplatin plus a taxane with or without cetuximab. This trial failed to demonstrate a significant difference between treatment arms with respect to its primary endpoint of PFS.6 The use of cetuximab in advanced NSCLC remains controversial and it is not currently approved for this indication.

Necitumumab is a novel humanized monoclonal anti-EGFR antibody that has demonstrated antitumour activity in preclinical models.7 It has been evaluated in two separate phase III clinical trials combined with standard chemotherapy in the first line. The INSPIRE trial discussed above examined the addition of necitumumab to cisplatin/pemetrexed in non-squamous patients. Trial enrolment was terminated prematurely due to safety concerns regarding increased toxicity in the necitumumab treatment arm, in particular an increased risk of thromboembolic events. No significant difference was noted between the treatment and control groups with respect to OS, PFS or RR. Further, EGFR expression did not predict for clinical benefit or treatment response. The significant toxicity and lack of clinical benefit associated with the addition of necitumumab to standard first-line chemotherapy in non-squamous NSCLC preclude its use in this setting.

The SQUIRE trial followed a similar design but evaluated the addition of necitumumab to cisplatin/gemcitabine in patients with squamous cell histology. A press release from Eli Lilly has indicated that this trial has demonstrated clinical benefit in this patient population.
IN BRIEF

Already known
• Preclinical and early-phase clinical evidence suggests potential activity of necitumumab combined with standard chemotherapy in NSCLC.

What this study showed
• The addition of necitumumab to standard first-line chemotherapy in non-squamous NSCLC is associated with significantly increased toxicity and no improvement in survival outcomes.

Next steps
• The SQUIRE trial investigating necitumumab in addition to chemotherapy in squamous cell lung cancer has reportedly found clinical benefit associated with necitumumab treatment. We await the presentation of these data in order to clarify the nature of this benefit as well as significant toxicities in this patient population.

In summary, the use of necitumumab in addition to standard treatment in squamous cell histology. However, the detailed results of this trial have not been presented, so the degree of benefit remains unknown, and increased rates of thromboembolism in the necitumumab arm were seen. It is therefore difficult to ascertain the role that necitumumab might play in the treatment of NSCLC.

The use of EGFR expression as a biomarker for necitumumab activity was investigated in the INSPIRE trial and was not demonstrated to predict for clinical benefit. It remains to be seen whether EGFR expression will have utility as a predictive biomarker in the SQUIRE trial or whether other predictive biomarkers are identified.

In summary, the use of necitumumab in addition to standard first-line chemotherapy in non-squamous NSCLC is associated with significant toxicity, including an increased risk of thromboembolic events, and did not improve overall survival, progression-free survival or response rates. The results of the SQUIRE trial evaluating necitumumab in squamous cell lung carcinoma have yet to be released, and therefore benefits and potential toxicities in this population remain to be seen.

References