Editorial

Cetuximab in advanced non-small cell lung cancer (NSCLC): the showdown?

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Nowadays, epidermal growth factor receptor (EGFR) is an important therapeutic target in non-small-cell lung cancer (NSCLC). Monoclonal antibodies (mAbs) targeting the extra-cellular domain of EGFR together with small molecule tyrosine kinase inhibitors (TKIs) have been exploited pharmacologically to block EGFR activation. While the EGFR-TKIs erlotinib and gefitinib are established treatment options for patients with advanced NSCLC, above all in patients with activating EGFR mutations (exon 19 deletion and mutation L858R in exon 21), the role of cetuximab (mAb) was recently clarified. Cetuximab (marketed as Erbitux) is a chimeric human/murine monoclonal immunoglobulin G1 antibody, that inhibits the receptor function, mediates antibody-dependent cell-mediated cytotoxicity and receptor downregulation, leading to a mitigation of EGFR activity. Several phase II trials have evaluated if cetuximab in combination with different first-line chemotherapy regimens could enhance synergic effect. First, the promising efficacy results of the addiction of cetuximab to cisplatin plus vinorelbine as first-line treatment in the phase II Lung Cancer Cetuximab Study [LUCAS; overall response rate (ORR): 35% *vs.* 28%] (1) led to the FLEX (First-Line Erbitux in Lung Cancer) phase III trial (2,3). In this landmark phase III trial, the combination with cetuximab significantly improved overall survival (OS, primary endpoint) compared with chemotherapy alone (cisplatin plus vinorelbine) in 1,125 chemo-naïve patients with advanced EGFR-positive NSCLC (median OS: 11.3 versus 10.1 months, respectively; HR: 0.871, P=0.044). This small but significant survival benefit was seen in all histological subgroups. Progression-free survival (PFS) time was similar, showing a median 4.8 months in both groups (HR: 0.943, P=0.39) (2). As expected with an anti-EGFR antibody, acne-like skin rash, diarrhoea, and infusion-related reactions were more common in patients given cetuximab plus chemotherapy. Interestingly, early-onset acne-like rash of any grade was associated with better outcome: median survival of 15.0 *vs.* 8.8 months (HR: 0.63, P<0.001) (3).

Another phase II trial, SWOG S0342, evaluated concurrent and sequential administration of cetuximab with a standard chemotherapy (carboplatin plus paclitaxel) regimen in untreated patients with advanced NSCLC (4). Both arms meet the predefined efficacy end point of median OS time of ≥10 months; RR and PFS were similar, as well as grade 3 rash, whereas sensory neuropathy was higher in the concurrent arm. The concurrent regimen was chosen in subsequent phase III trial BMS-099 (Bristol-Myers Squibb 099), testing the addition of cetuximab to carboplatin plus paclitaxel in 676 chemo-naïve patients with advanced NSCLC, without restrictions based on histology or EGFR expression (5). Although BMS-099 did not meet its primary end point (PFS, 4.4 *vs.* 4.24 months; HR: 0.902, P=0.24), there were some similarities with the FLEX trial. Both studies reported a statistically significant benefit in ORR with the addition of cetuximab to platinum-based chemotherapy (36% *vs.* 29% in FLEX; 25.7% *vs.* 17.2% in BMS), and failed to show any improvement in PFS. However, the difference in OS was similar in both studies (approximately 1.3-month increase in median OS and 11% to 13% reduction in the death risk), although BMS099 lacked power to detect a difference of this magnitude with statistical significance (5).

Cetuximab added to a platinum agent (mostly carboplatin)

plus gemcitabine in chemo-naïve patients with advanced NSCLC, regardless of EGFR expression, resulted in a higher RR (27.7% *vs.* 18.2%) and longer PFS (median 5.09 *vs.* 4.21 months) compared to chemotherapy alone, in another phase II trial (6). To better understand the real impact of cetuximab-based treatment in first-line setting, a metanalysis including 2018 patients from four randomized trials, was performed. The survival benefit of chemotherapy plus cetuximab compared to chemotherapy alone [regardless of the chemotherapy protocol used: cisplatin plus vinorelbine (1-3), platin plus paclitaxel (5), and platin plus gemcitabine (6)] was confirmed in chemo-naïve patients with advanced NSCLC (7). Despite these positive results—in biomarker unselected population—both the FDA and the EMEA rejected the licensing of cetuximab in combination with chemotherapy for first-line therapy of advanced NSCLC in consideration of the small OS benefit of the addition of cetuximab to chemotherapy, which should be weighed against its side effects, the weekly administration, and costs.

The identification of a biomarker predictive of a treatment benefit associated with the addition of cetuximab to first-line chemotherapy for NSCLC would enable a personalised approach to care. To pursue this possibility, retrospective analyses of FLEX and BMS-099 investigated a panel of candidate pretreatment molecular markers (KRAS mutational status, EGFR mutational status, and EGFR copy number) in tumours, but none of these have a predictive role in clinical benefit (8,9). Interestingly, tumour EGFR expression levels seemed to be associated with clinical outcome in FLEX study patients (10). In a further prospective analysis of this study, Pirker *et al.* collected tumour EGFR expression data to generate an immunohistochemistry score (H score), to provide a more detailed assessment of EGFR protein expression, and to evaluate its role as predictive biomarker of survival benefit. The H score takes into account the percentage of cells (0-100%) in each intensity category (0-3+) and computes a final score, on a continuous scale between 0 and 300.

High EGFR expression according to a tumour IHC score of 200 or more seems to be the only effective pre-treatment biomarker so far identified for the prediction of clinical benefit from chemotherapy plus cetuximab in the first-line treatment of advanced NSCLC (10).

Although the predictive role of EGFR expression levels seems to emerge from this analysis, FDA and EMA rejected the approval of cetuximab in high score EGFR expression NSCLC due the fact that the data come from a subgroup analysis. They required a confirmatory prospective trial that the pharmaceutical company has decided not to run.

Most patients receiving front-line cytotoxic therapy for advanced NSCLC experience progressive disease. Several single agents are approved for use in advanced, second-line NSCLC, including pemetrexed, docetaxel, and erlotinib. However, in patients who become refractory to front-line chemotherapy, no new treatment has shown significant survival benefit in unselected patient populations for the past decade outside of single-agent therapy. Based on promising safety and efficacy results of combined regimen (cetuximab plus docetaxel) in a phase II trial (11), the SELECT study evaluated if the addition of cetuximab to standard chemotherapy might improve outcome in patients with pretreated advanced NSCLC (12). In this open-label phase III trial, Kim and colleagues randomized 938 patients with metastatic, unresectable, or locally advanced NSCLC to four arms of treatment: 605 patients received pemetrexed (301 patients with cetuximab and 304 alone) and 333 received docetaxel (167 in combination with cetuximab and 166 alone). The initial primary analysis was a comparison of the ORR between chemotherapy alone or combined with weekly cetuximab. However during the trial, the primary endpoint was changed to compare PFS with cetuximab plus pemetrexed versus pemetrexed alone, on an intention-to-treat basis, after data publication of phase III trial, in which pemetrexed showed a clinically equivalent efficacy outcomes to docetaxel, with fewer side-effects (13). The addition of cetuximab to pemetrexed did not improve PFS (2.9 *vs.* 2.8 months, respectively; HR: 1.03, P=0.76), nor there were improvements in any of the other assessed efficacy or quality-of-life measures, including OS (6.9 *vs.* 7.8 months, respectively; HR 1.01, P=0.86). Data from pre-specified efficacy subgroup analyses by EGFR status and histology (squamous *vs.* non-squamous) confirmed any improvement in outcome. There were no significant differences between the two treatment groups in median PFS or in OS, when assessed by EGFR staining intensity (positive: EGFR 1+, 2+, 3+/negative: EGFR undetectable) and H-score (low H-score: <200/high H-score: ≥200). More and worse adverse events (AEs) were recorded with cetuximab plus pemetrexed, mainly due to skin-related toxic effects (grade 3-4 acneiform rash: 11% *vs.* 0%), gastrointestinal symptoms (grade 1-2 diarrhoea: 27% *vs.* 13%; grade 1-2 mucositis oral: 18% *vs.* 7%), and hypomagnesaemia (grade 1-2: 19% *vs.* 6%).

These disappointing results confirmed the ineffectiveness of the combination of cetuximab and pemetrexed, already reported in a single arm phase II study (14), suggesting that the addition of cetuximab in an unselected patient

population in this setting is unlikely to result in significantly superior outcomes to single-agent therapy alone.

Nowadays, cetuximab failed to demonstrate a great and clinically significantly survival benefit when combined with chemotherapy regimens (mono- or poly-chemotherapy), regardless line setting (first- or second line). Furthermore, the data reported by Kim and colleagues (12) highlighted that the use of cetuximab in unselected patients not only did not improve outcomes, but also worsened toxic effects. So the identification of NSCLC patients that might potentially benefit from treatment with this monoclonal antibody is needful, but not yet clarified. The use of EGFR staining intensity and H-score, for selection of patients need to be confirmed in prospective trials but pharmaceutical company decided to stop the cetuximab clinical development in NSCLC.

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References

1. Rosell R, Robinet G, Szczesna A, et al. Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. Ann Oncol 2008;19:362-9.
2. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-31.
3. Gatzemeier U, von Pawel J, Vynnychenko I, et al. First-cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study. Lancet Oncol 2011;12:30-7.
4. Herbst RS, Kelly K, Chansky K, et al. Phase II selection design trial of concurrent chemotherapy and cetuximab versus chemotherapy followed by cetuximab in advanced-stage non-small-cell lung cancer: Southwest Oncology Group study S0342. J Clin Oncol 2010;28:4747-54.
5. Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol 2010;28:911-7.
6. Butts CA, Bodkin D, Middleman EL, et al. Randomized phase II study of gemcitabine plus cisplatin or carboplatin [corrected], with or without cetuximab, as first-line therapy for patients with advanced or metastatic non small-cell lung cancer. J Clin Oncol 2007;25:5777-84.
7. Thatcher N, Linchy TJ. Cetuximab plus platinum-based chemotherapy as 1st-line treatment in patients with nonsmall cell lung cancer (NSCLC): A meta-analysis of randomized phase II/III trials. WCLC 2009;4:S5-968; [abstr A3.7].
8. O'Byrne KJ, Gatzemeier U, Bondarenko I, et al. Molecular biomarkers in non-small-cell lung cancer: a retrospective analysis of data from the phase 3 FLEX study. Lancet Oncol 2011;12:795-805.
9. Khambata-Ford S, Harbison CT, Hart LL, et al. Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2010;28:918-27.
10. Pirker R, Pereira JR, von Pawel J, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol 2012;13:33-42.
11. Kim ES, Mauer AM, William WN Jr, et al. A phase 2 study of cetuximab in combination with docetaxel in chemotherapy-refractory/resistant patients with advanced nonsmall cell lung cancer. Cancer 2009;115:1713-22.
12. Kim ES, Neubauer M, Cohn A, et al. Docetaxel or pemetrexed with or without cetuximab in recurrent or progressive non-small-cell lung cancer after platinum-based therapy: a phase 3, open-label, randomised trial. Lancet Oncol 2013;14:1326-36.
13. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
14. Jalal S, Waterhouse D, Edelman MJ, et al. Pemetrexed plus cetuximab in patients with recurrent non-small cell lung cancer (NSCLC): a phase I/II study from the Hoosier Oncology Group. J Thorac Oncol 2009;4:1420-4.

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