Editorial

Is more the better?—cetuximab in non-small cell lung cancer patients

Teresa Moran

Medical Oncology Department, Catalan Institute of Oncology, Badalona Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona (UAB), Badalona, Spain

Correspondence to: Teresa Moran. Medical Oncology Department, Catalan Institute of Oncology, Badalona Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona (UAB), Carretera Canyet s/n, 08916 Badalona, Spain. Email: mmoran@iconcologia.net.

Provenance: This is an invited Editorial commissioned by the Section Editor Hengrui Liang (Nanshan Clinical Medicine School, Guangzhou Medical University, Guangzhou, China)

Comment on: Herbst RS, Redman MW, Kim ES, *et al.* Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study. Lancet Oncol 2018;19:101-14.

Submitted Apr 07, 2018. Accepted for publication Apr 16, 2018.
doi: 10.21037/tlcr.2018.04.14
View this article at: http://dx.doi.org/10.21037/tlcr.2018.04.14

Lung cancer treatment has experienced a major change in the last decades with the identification of differential molecular traits to guide the therapeutic decisions. This strategy has led to classify patients in lung cancer subsets with differential prognosis and treatment approaches. However, there is still a substantial proportion of patients in whom no molecular marker is found and upfront chemotherapy still remains their best option.

EGFR protein is expressed in most non-small cell lung cancer (NSCLC) tumors and targeting EGFR, beyond treatment selection based on the presence of an *EGFR* mutation, has been a field of interest in lung cancer (1).

Several clinical trials have been carried out to try to elucidate the benefit of adding cetuximab to chemotherapy in lung cancer. Furthermore, efforts have been made to identify a molecular marker able to predict the benefit of adding cetuximab to chemotherapy in these patients. Cumulative data has been mixed. Different phase II/III trials have demonstrated encouraging results when cetuximab is added to chemotherapy. Phase II SO342 trial included cetuximab concurrently or as maintenance with a carboplatin and paclitaxel based chemotherapy (2). Phase II SO536 trial, restricted to non-squamous histologies, contained cetuximab plus bevacizumab concurrently with the same chemotherapy schedule, followed by cetuximab and bevacizumab as maintenance therapy (3). Both trials met their objectives in terms of efficacy and safety. In contrast, the phase III BMS099 trial comparing the addition of cetuximab to a carboplatin and paclitaxel-based chemotherapy versus chemotherapy alone failed to demonstrate any benefit regarding any efficacy endpoint (4). All these trials included unselected population based on EGFR expression or other biomarkers.

Both the BMS099 and SO536 trials did not find any correlation of efficacy according to retrospective biomarker evaluation that included *KRAS* and *EGFR* mutations and EGFR expression by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) (3,5). The reasons for these negative biomarkers analyses could be explained by the effect of cetuximab in biomarker-negative patients, the retrospective nature of these analyses, the fact that no biomarkers were selected for randomization, the small population and a potential real negative interaction between cetuximab and chemotherapy. Conversely, the SO342 trial found that patients whose tumors were EGFR FISH positive had greater survival and response than those whose tumors were negative (6).

In addition, cetuximab has been combined with other platinum-based chemotherapies, such as cisplatin and vinorelbine in the FLEX trial, where patients were included according to EGFR expression evaluated by IHC (7). All patients with at least one positively stained tumor cell were eligible for the trial. This phase III randomized trial demonstrated a statistically significant benefit in terms of overall survival (OS) and response rate (RR) with no differences in terms of progression-free survival (PFS). The benefit was similar across different subgroups. However, the magnitude of the clinical gain was so modest that

cetuximab has not obtained the regulatory approval for this combination, neither based on the initial FLEX trial results, nor in the results based on the subgroups analyses considering an immunoscore. This subsequent analysis considered both the percentage and the intensity of the stained cells, and showed the higher the immunoscore the greater the benefit of cetuximab.

The provocative results of the SO342 trial paved the way to the initiation of the SO819 trial.

In the *Lancet Oncology* 2018, Herbst *et al.* have recently published the results of the SO819 trial, an open-label, phase III, randomized study of carboplatin and paclitaxel with or without bevacizumab plus cetuximab or control arm without cetuximab (8). Overall, 1,313 patients were assigned to the control arm (n=657) or experimental arm (n=656). Based on a subgroup focused multiple hypothesis design, the study sought to evaluate if PFS in patients who were EGFR FISH-positive and OS in the entire population were improved by the addition of cetuximab (co-primary endpoints). As secondary endpoints, the study evaluated the differences in OS in EGFR FISH-positive patients and the PFS differences the entire population. Bevacizumab could be prescribed according to general guidelines of the antiangiogenic drugs such as non-squamous histology, no prior history of hemorrhagic condition, thromboembolic disease, anticoagulant therapy and cavitary lesions among others. The study failed to demonstrate both the primary objective and the secondary endpoints, based on the hypothesis of the synergy of chemotherapy and anti-EGFR antibodies. Overall, patients who were treated with cetuximab experienced a higher rate of adverse events that can be anticipated according to the specific toxicity profile of the antibody. However, based on the positive results of the SQUIRE trial testing the efficacy of necitumumab, another anti EGFR antibody, in combination with cisplatin and gemcitabine as first line in squamous NSCLC patients, the SO819 was amended (9). A prespecified analysis of OS and PFS analysis, focused exclusively in squamous cell NSCLC and stratified by EGFR FISH, was included and showed a significant longer OS, with no differences in PFS or RR in this subgroup of patients. Cetuximab has demonstrated a significant benefit in terms of RR, PFS and OS in other tumors when combined to chemotherapy (10). The SO819 trial results are intriguing and more typically seen in current trials involving immunotherapeutic agents that might elicit a delayed treatment effect (11). This effect has not been previously described in other chemotherapy combinations including cetuximab.

According to these results one might wonder if cetuximab in addition to chemotherapy in EGFR positive squamous NSCLC patients can be recommended. Further, the costs in terms of quality of life, toxicity and economic cost should be considered. In case one might agree with a straightforward implementation of cetuximab in lung cancer patients, some additional questions still arise. Should testing of EGFR FISH be recommended for therapy selection? If so, which technique should be used? Are the results by FISH or IHC consistent? Are both techniques easy to implement in the laboratories?

The clinical benefit of cetuximab is not seen broadly across all patient types, but in more restricted subsets, mainly represented by the squamous EGFR FISH positive NSCLC patients. OS results of the SO819 trial are in line with these of the SQUIRE trial. But, data derived from the SQUIRE trial have been obtained on the basis of a prospective, phase III, randomized clinical trial, in contrast the subgroup analysis in the SO819 study (8,9). So far, it appears that the robustness of the efficacy data of the SO819 trial are not sufficient to recommend the inclusion of cetuximab as an immediate change in the standard of care of this subgroup of patients. Likewise, the expected but increased rate of adverse events that these patients presented with the addition of cetuximab to the chemotherapy, as well as the weekly schedule, are facts that need to be balanced when considering such recommendation. According to the overall results, we can consider that the SO819 trial generates the hypothesis of testing such combination in a defined subgroup of patients. Given that the results of the SQUIRE trial have led to the approval of an anti- EGFR in patients with squamous-NSCLC (9), we will learn in the near future about the interest in continuing the clinical development of cetuximab in lung cancer treatment.

Currently, both FISH and IHC has been used to evaluate EGFR expression (5-7,9) Retrospective, as well as prospective data, do not support the use of one technique over the other. In addition, the implementation of such techniques seems easy in clinic today. Other biomarkers using similar procedures have been rapidly incorporated in the last years in the diagnostic algorithm of several cancers, including lung cancer, and represent nowadays an everyday routine (12). Neither the economic cost, nor the difficulty of the techniques should represent a problem.

According to the S0819 trial, patients with EGFR FISH positive and squamous histology represent the 8% of the patients included (8). This means that the potential target population most likely to benefit from the FISH analysis

and subsequent cetuximab treatment, if positive, represents a population comparable with *ALK* positive, *ROS1* positive or *BRAF*-mutant lung cancer, in which great efforts have been made to identify the particular underlying molecular alteration to select the corresponding targeted therapy (12). So, it seems fair to try to implement the EGFR expression analysis in a subgroup of patients less likely to harbor any targetable alteration, especially if PDL1 expression does not permit the use of upfront immunotherapy and standard chemotherapy will remain as first treatment choice. On the other hand, the potential benefit of cetuximab would need to be carefully evaluated to fit in the upcoming strategies of lung cancer treatment, which involve the combination of immunotherapy and chemotherapy as first line therapy (13).

The potential benefit of cetuximab would need to be further explored in a confirmatory prospective study to finally place it in the current scenario of the lung cancer biomarker selection and molecular-based treatment.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. López-Malpartida AV, Ludeña MD, Varela G, et al. Differential ErbB receptor expression and intracellular signaling activity in lung adenocarcinomas and squamous cell carcinomas. Lung Cancer 2009;65:25-33.
2. 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.
3. Kim ES, Moon J, Herbst RS, et al. Phase II trial of carboplatin, paclitaxel, cetuximab, and bevacizumab followed by cetuximab and bevacizumab in advanced nonsquamous non-small-cell lung cancer: SWOG S0536. J Thorac Oncol 2013;8:1519-28.
4. 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.
5. 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.
6. Hirsch FR, Herbst RS, Olsen C, et al. Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy. J Clin Oncol 2008;26:3351-7.
7. 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.
8. Herbst RS, Redman MW, Kim ES, et al. Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study. Lancet Oncol 2018;19:101-14.
9. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol 2015;16:763-74.
10. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.
11. Alexander BM, Schoenfeld JD, Trippa L. Hazards of Hazard Ratios - Deviations from Model Assumptions in Immunotherapy. N Engl J Med 2018;378:1158-9.
12. Kristina Gregory N, Miranda Hughes O, Aisner DL, et al. Farber/Brigham and Women's Cancer Center NCCN Guidelines Version 3.2018 Non-Small Cell Lung Cancer NCCN Evidence Blocks TM. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf
13. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-508.

Cite this article as: Moran T. Is more the better?—cetuximab in non-small cell lung cancer patients. Transl Lung Cancer Res 2018;7(Suppl 3):S195-S197. doi: 10.21037/tlcr.2018.04.14

