Editorial

The lesson learned from figitumumab clinical program and the hope for better results in squamous lung cancer

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Submitted Nov 28, 2014. Accepted for publication Dec 08, 2014.
doi: 10.3978/j.issn.2218-6751.2015.01.02
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.01.02

In recent years, therapeutic advances for patients with advanced non-small cell lung cancer (NSCLC) have been substantially limited to non-squamous histology, while the treatment of patients with squamous cell carcinoma of the lung remained unchanged during the last ten years. Patients with squamous cell carcinoma of the lung are neither eligible for treatment with pemetrexed (due to the qualitative interaction between its efficacy and histology, being the drug more effective in non-squamous tumors), nor for the monoclonal anti-vascular endothelial growth factor (VEGF) antibody bevacizumab (due to safety reasons). Furthermore, in clinical practice, no molecularly targeted agents have been specifically successful for patients with squamous tumors, because epidermal growth factor receptor (EGFR) sensitizing mutations and anaplastic lymphoma kinase (ALK) rearrangements, as well as the use of the respective inhibitors, are virtually limited to non-squamous tumours.

In this context, improvements in the treatment of patients with squamous cell carcinoma of the lung represent an unmet need, and new drugs are eagerly awaited. Overexpression of insulin-like growth factor 1 receptor (IGF-1R) is detectable in a relevant proportion of advanced NSCLCs, particularly in squamous tumors. Figitumumab is a fully human monoclonal antibody directed against IGF-1R. An initial randomized phase II trial showed activity when figitumumab was added to carboplatin plus paclitaxel, with efficacy outcomes more promising in patients with squamous cell carcinoma of the lung (1). Based on these data, a randomized phase III trial was subsequently and specifically designed in patients with advanced NSCLC with non-adenocarcinoma histology, with the primary aim of improving overall survival (2). The study randomized 681 patients, but disappointingly it was closed early by the independent Data Safety Monitoring Committee, due to negative outcome of a planned futility analysis, and because of an increased incidence of serious adverse events and treatment-related deaths in the group of patients assigned to figitumumab. Overall survival analysis did not suggest any benefit with the experimental drug, and the difference between treatment arms was even in the opposite direction: median overall survival was 8.6 months with figitumumab plus chemotherapy compared to 9.8 months with chemotherapy alone (hazard ratio 1.18; 95% confidence interval, 0.99-1.40; P=0.06). There were no significant differences in progression-free survival and objective response rate. Patients treated with figitumumab had a higher rate of serious adverse events (66% *vs.* 51%) and a higher rate of treatment-related lethal adverse events (5% *vs.* 1%). Furthermore, data from the previous randomized phase II trial were re-analyzed by the sponsor and revealed that the original analysis was incorrect and that the promising results in terms of objective response rate and progression-free survival were not confirmed (1).

In the current therapeutic landscape for patients with squamous cell carcinoma of the lung, even a modest survival benefit could be judged as a clinical achievement. For instance, the addition of necitumumab, a monoclonal antibody directed against the EGFR receptor, to first-line chemotherapy for advanced squamous NSCLC was associated with a statistically significant improvement in overall survival (3). Similarly, the addition of ramucirumab, a monoclonal antibody directed against the VEGF receptor, to second-line docetaxel was associated with an

improvement in overall survival, with subgroup analyses suggesting similar efficacy in patients with squamous and non-squamous tumors (4). For both these drugs, a prolongation of about one month and half in median overall survival was observed. Although the results of these two studies may theoretically modify future therapeutic choices, it should also not be ignored the recent position paper from the American Society of Clinical Oncology (ASCO) that invited to "raise the bar" in clinical research, by defining clinically meaningful outcomes when designing and interpreting results of clinical trials (5). Advanced squamous NSCLC was chosen as one of the settings discussed by the panel: in these patients, considering a median overall survival of 10 months achievable with current standard treatment, the experts recommended to target at least a 2.5-3 months' improvement in median overall survival, corresponding to hazard ratio ranging around 0.77-0.80. Although the magnitude of the benefit suggested by the ASCO working group as clinically meaningful is necessarily subjective, smaller benefit, even if reaching the formal threshold of statistical significance, could be probably judged as clinically not relevant. From this point of view, the phase III trial of figitumumab was well designed, because sample size was based on the hypothesis of achieving a 30% improvement with the addition of figitumumab to paclitaxel plus carboplatin, over the median survival of 10 months achievable with chemotherapy alone, corresponding to a hazard ratio 0.77. If the predicted study hypothesis had been reached, the benefit could have been considered clinically relevant. Similarly to other studies investigating the role of targeted therapies in the setting of advanced NSCLC, the figitumumab study did not include any predictive biomarker to improve treatment efficacy, even if in the study a prospective assessment of several potential markers was included. Similarly to what we have observed in recent years in adenocarcinoma, also patients with squamous tumors would benefit from new drugs clinically investigated on the basis of a better knowledge of the relevance of the targets, and consequently with a proper selection of patients, in order to obtain larger benefits in molecularly characterized subgroups. Unfortunately, this was not the case for figitumumab: the randomized phase III trial was initiated without any robust knowledge about predictive factors. Subsequently, interesting pre-clinical data have been published about the predictive role for figitumumab activity of several components of the IGF pathway, including insulin receptor substrate 2 (IRS2) and IGF-binding protein 5 (IGFBP5), and of the alteration or expression of the MYB oncogene (6). These data are probably too late for changing the story of figitumumab, because its development has been discontinued, but could help to improve the development of other IGF-1R inhibitors.

Interestingly, in the study of figitumumab, baseline IGF-1 levels were predictive of figitumumab toxicity: patients with low levels of IGF-1 appeared to be at higher risk of toxic death when treated with figitumumab. However, the practical implication of this finding appears limited. Ironically, as a matter of fact, a predictive factor of severe toxicity for a drug that did not prove any benefit in the whole study population is completely the opposite of the ideal scenario that would be a drug well tolerated in the whole population, with an optimal biomarker useful to select patients who could benefit from the treatment.

We can derive at least three relevant lessons from the negative story of figitumumab development in advanced NSCLC. Firstly, clinical results observed with figitumumab underline the relevance of randomized phase III trials to confirm the efficacy of a drug, especially if the anticipated benefit is "incremental", and not a dramatic improvement similar to the effect of targeted drugs in oncogene-addicted tumors. Secondly, the story emphasizes the risk of failure in the development of a new drug, if the process is conducted without any knowledge of predictive factors of its efficacy. Thirdly, the development of figitumumab in advanced NSCLC tells us that a relevant increase in adverse events can be completely missed in phase II trials, which are conducted in a limited number of patients. This is a relevant finding not to be forgotten, especially in the context of the recent wave of approval of new drugs often based on the evidence of a strong activity in the early phase trials. This could lead to the introduction of new drugs in clinical practice with a less solid knowledge of their toxicity profile that can necessarily derive only by their use in a wider number of patients.

At the end of the story, after the negative results of the phase III trial conducted in first-line, along with the failure of another phase III trial conducted in patients with non-adenocarcinoma NSCLC and testing figitumumab in combination with erlotinib (7), the clinical development of this anti-IGF-1R antibody in NSCLC has been sadly discontinued. Was it the wrong drug for the right target, or is the target itself (IGF-1R) not the right driver for the biology of squamous lung cancer? Most recently, relevant progress has been made in the molecular characterization of lung squamous tumors. Interestingly, a comprehensive genomic characterization of 178 lung squamous cell

carcinomas, conducted as part of The Cancer Genome Atlas, showed that this tumor type is characterized by complex genomic alterations, but in most cases a potential therapeutic target can be identified, offering new issues of investigation for the treatment of squamous cell lung cancers (8). The hope is that in the next few years, many of those potential targets will be addressed by specific drugs, reproducing also in squamous tumors the meaningful progress recently obtained in patients with lung adenocarcinoma. This will probably imply a "fragmentation" in many different sub-populations, similarly to what we are experiencing in adenocarcinoma, but it will probably help to obtain clinically relevant results.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Di Maio M, Scagliotti GV. The lesson learned from figitumumab clinical program and the hope for better results in squamous lung cancer. Transl Lung Cancer Res 2015;4(1):15-17. doi: 10.3978/j.issn.2218-6751.2015.01.02

