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Editorial

Onartuzumab in lung cancer: the fall of Icarus?

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Abstract

The development of targeted therapies has led to a revolution in non-small-cell lung cancer, and opened up possibilities for improved personalized medicine. With the constant findings of new targets, a lot of inhibitors are being developed. However, reliable biomarkers are urgently needed. The design of clinical trials needs to become more flexible in order to obtain the best results and gain the US FDA/EMEA approval for the new drugs. A recent example of a failed trial is the Phase III MetLung trial that compared the effects of the c-MET monovalent antibody onartuzumab with erlotinib versus erlotinib alone in late-stage non-small-cell lung cancer. Here, we discuss several points as to why this trial could have failed.

Keywords:

c-MET | non-small-cell lung cancer | ornatuzumab | Phase I | trial design

During the last decade, there has been a revolution in non-small-cell lung cancer (NSCLC) with the development of targeted therapies. The best known example being the inhibition of EGFR-activating mutations by tyrosine kinase inhibitors (TKIs), for example, erlotinib or gefitinib. Unfortunately, after a few months, these patients show signs of resistance. One of the resistance mechanisms against EGFR-TKIs is c-MET amplification, which occurs in approximately 10–20% of patients with acquired resistance [1,2].

Despite its fame as a resistance mechanism, the receptor also plays a role in TKI-naïve patients. In this population, c-MET overexpression can be found in 14–69% of patients [3] and de novo c-MET amplification in about 5% [4,5].

A number of targeted therapies against c-MET have been developed and several are in clinical trials. One of these inhibitors is the c-MET monovalent antibody onartuzumab of Genentech, which has received a lot of attention lately due to the failed Phase III trial in late-stage NSCLC in combination with erlotinib. Although the overall results of the randomized Phase II trial of onartuzumab in combination with erlotinib in advanced NSCLC were negative, analysis showed that the subgroup of c-MET immunohistochemistry (IHC)-positive patients showed both improved progression-free survival (1.5 vs 2.9 months; $p = 0.04$) and overall survival (7.4 vs 8.9 months; $p = 0.002$) [6]. On the basis of these results, a randomized Phase III trial was initiated in c-MET IHC-positive patients [7], which was stopped prematurely due to the lack of clinically meaningful efficacy.

What arguments can explain the failure of this Phase III trial?

First, there is a biomarker problem. In this study, patients were defined as c-MET positive or negative, based on protein expression with an IHC assay on archival formalin-fixed paraffin-embedded tissue with the accompanying assay (CONFIRM anti-total MET SP44, Ventana) [8], focusing on a different epitope than onartuzumab [8,9]. This accompanying diagnostic has been tested extensively for intrarun (84/84 equivocal in five different runs) and interrun (147/150 equivocal) variations on resection sections or tissue blocks. Also, the specificity and accuracy have been tested, which showed that there was no cross-reactivity for RON and that the scoring of the IHC was in accordance with the mRNA levels of c-MET. In terms of fixation, the pathologist

can be guided by the internal controls of the tissue (endothelium = 1+ staining intensity, bronchial epithelium = 2+ intensity), but the use of semi-quantitative controls is recommended [8]. About 50% of the screened patients could be enrolled in the trial. However, the scoring criteria can greatly influence the number of selected patients. As reported, the choice of biomarker was made based on a comparison between FISH and IHC in the Phase II study (on a small number of 66 patients). It should be noted that, as for IHC, the cutoff value for FISH can make a big difference. In the Phase II study, a MET/CEP7 ratio of 2 or a total copy number of 5 was used as a cutoff, whereas other studies (e.g., crizotinib in c-MET-amplified NSCLC) showed the best response in patients with a ratio of 5 or more. Should we focus more on HGF, the ligand of c-MET? As HGF is produced by the tumor microenvironment or can even be produced by the tumor cells themselves, it can also evoke the activation of c-MET and even resistance against gefitinib [10,11]. The great number of selected patients might have obscured beneficial results in the actual group of patients that could benefit from treatment with onartuzumab.

The second comment that can be made is the fact that the c-MET status is determined on archival tissue of patients treated with one or two lines of chemotherapy. As resection/biopsy is done at the time of initial diagnosis, the level of c-MET expression may change during treatment, as has been reported for radiotherapy [12], raising the question if archival formalin-fixed paraffin-embedded material is a good estimate for the level of c-MET expression after one or more lines of treatment. Another problem that arises with the use of archival tissue is that the quality of the tissue will vary between different sites, due to differences in fixation time and procedure. Since fixation can have a big effect on the performance of an IHC assay, this again might influence the results.

Third, given the known success of erlotinib in EGFR-mutated patients, it is remarkable that only 28 patients with sensitizing mutations were included. Looking at the results presented at the American Society of Clinical Oncology 2014 by Spigel et al., a lot of variation can be seen in the patient group, which raises questions about the preclinical evidence supporting the combination therapy of erlotinib and onartuzumab in patients with wild-type EGFR [13]. There are several papers in literature suggesting that the c-MET and EGFR pathways are closely linked. Among others, Reznik et al. showed that c-MET can activate the EGFR pathway through the upregulation of ligand transcription (TGF-β and EGF) [14,15]. However, Breindel et al. showed that EGFR directly activates c-MET, but that c-MET needs the HER3 receptor to activate EGFR [16]. There is no

doubt that there exists a connection between both pathways, the only question is if EGFR is as strongly activated by c-MET as c-MET is activated by EGFR. In fact, the dual inhibition of c-MET and EGFR might have no real impact. Nevertheless, the results seen in the Phase II trial might be biased since the c-MET-positive arm contained a higher population of EGFR-mutant NSCLC patients in the erlotinib + onartuzumab arm (20%) in comparison with 7% EGFR-mutant patients in the erlotinib + placebo arm. This would mean that the real potential target population should present with both an EGFR mutation and c-MET positivity. At the American Society of Clinical Oncology 2014, data from the Phase III trial were presented but submolecular analysis was still ongoing.

Although this clinical trial may have failed, it gives rise to a lot of new questions and encourages the discussion of which c-MET biomarker to use for optimal patient selection. Should we really quit choosing c-MET IHC as a biomarker? Or do we need to change the IHC cutoffs? Is it ethical to include a large number of patients in a Phase III study (490 patients) when we have evidence of lack of efficacy in the Phase II study? Must we be more cautious with the design of clinical studies? In oncology, history continues to demonstrate that matching the right patient (with the appropriate biomarker) with the appropriate drug is the winning team [13]. Maybe we should, like Icarus, fly low to avoid falling down and try to reach our destination.

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Related Research Data

Biomarker Analyses from a Placebo-Controlled Phase II Study Evaluating Erlotinib ± Onartuzumab in Advanced Non–Small Cell Lung Cancer: MET Expression Levels Are Predictive of Patient Benefit

Source: Clinical Cancer Research

MET gene amplification or EGFR mutation activate MET in lung cancers untreated with EGFR tyrosine kinase inhibitors

Source: International Journal of Cancer

MET Amplification Leads to Gefitinib Resistance in Lung Cancer by Activating ERBB3 Signaling

Source: Science

Prognostic Value of MET Gene Copy Number and Protein Expression in Patients with Surgically Resected Non-Small Cell Lung Cancer: A Meta-Analysis of Published Literatures

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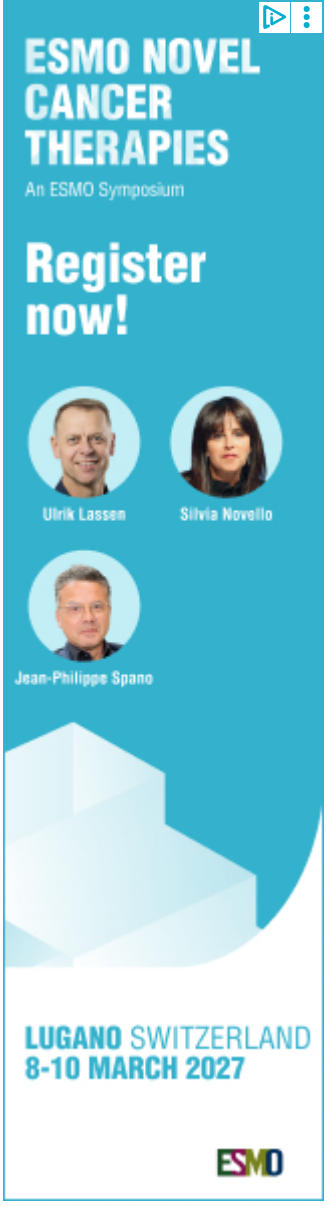
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