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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 ...wever, reliable ...to become more fle...approval for the ne...al that com...erlotinib versus e...cuss several points as...

Keywords

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, the -MET positive ival formalin NFIRM anti-total ME mab [8,9]. This 84 equivoc on resectio been tested, which sh g 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 [illegible] the results presente[illegible]., a lot of variation[illegible] preclinical evide[illegible] in patients with [illegible] that the c-MET and[illegible]wed that c-MET can[illegible]scription (TGF-β a[illegible]y 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.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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Refer

1. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039-43
PubMed | Web of Science ® | Google Scholar

2. Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci USA 2007;104:20932-7
PubMed | Web of Science ® | Google Scholar

3. Guo B, Cen H, Tan X, et al. 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. PLoS One 2014;9:e99399
PubMed | Web of Science ® | Google Scholar

4. Tsuta K, Kozu Y, Mimae T, et al. c-MET/phospho-MET protein expression and MET gene copy number in non-small cell lung carcinomas. J Thorac Oncol 2012;7:331-9
PubMed | Web of Science ® | Google Scholar

5. Kubo T, Yamamoto H, Lockwood WW, et al. MET gene amplification or EGFR mutation activate MET in lung cancers untreated with EGFR tyrosine kinase inhibitors. Int J Cancer 2009;124:1778-84
PubMed | Web of Science ® | Google Scholar

6. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of Onartuzumab in combination with Erlotinib in patients with advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2013;31:4105-14
PubMed | Web of Science ® | Google Scholar

7. Spigel ... the MetLu... (MetMAb) in ... received stand... 2;13:500-4

8. Koeppen H, Yu W, Zha J, et al. 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. Clin Cancer Res 2014;20:4488-98
PubMed | Web of Science ® | Google Scholar

9. Merchant M, Ma X, Maun HR, et al. Monovalent antibody design and mechanism of action of onartuzumab, a MET antagonist with anti-tumor activity as a therapeutic agent. Proc Natl Acad Sci USA 2013;110:E2987-96
PubMed | Web of Science ® | Google Scholar

10. Yano S, Takeuchi S, Nakagawa T, et al. Ligand-triggered resistance to molecular targeted drugs in lung cancer: roles of hepatocyte growth factor and epidermal growth factor receptor ligands. Cancer Sci 2012;103:1189-94
PubMed | Web of Science ® | Google Scholar

11. Yano S, Wang W, Li Q, et al. Hepatocyte growth factor induces gefitinib resistance of lung adenocarcinoma with epidermal growth factor receptor-activating mutations. Cancer Res 2008;68:9479-87
PubMed | Web of Science ® | Google Scholar

12. De Bacco F, Luraghi P, Medico E, et al. Induction of MET by ionizing radiation and its role in radioresistance and invasive growth of cancer. J Natl Cancer Inst 2011;103:645-61
PubMed | Google Scholar

13. Spigel DR, Edelman MJ, O'Byrne K, et al. Onartuzumab plus erlotinib versus erlotinib in prev e 3 rando l trial. J Clin Oncol
G

14. Reznik factor recept 139-50
PubMed | Google Scholar

15. Guo A, Villén J, Kornhauser J, et al. Signaling networks assembled by oncogenic EGFR and c-Met. Proc Natl Acad Sci USA 2008;105:692-7

PubMed | Web of Science ® | Google Scholar

16. Breindel JL, Haskins JW, Cowell EP, et al. EGF Receptor activates MET through MAP kinases to enhance non-small cell lung carcinoma invasion and brain metastasis. Cancer Res 2013;73(16):5053-65

PubMed | Google Scholar

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