Editorial

Exploiting *MET* dysregulation in *EGFR*-addicted non-small-cell lung carcinoma: a further step toward personalized medicine

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Patients affected by non-small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) activating mutations derive a dramatic and essential clinical benefit from *EGFR* tyrosine kinase inhibitors (TKIs) therapy in terms of activity, efficacy and quality of life (1,2). Nevertheless, besides the important therapeutic impact of these targeted agents, *EGFR*-addicted diseases typically develop resistance under the selective pressure of TKIs, usually within 1 year of treatment. In 50–60% of patients, such acquired resistance to first- and second-generation *EGFR* TKIs is related to the acquisition of *EGFR* T790M mutation, a second-site 'on-target' point mutation which affects the adenosine triphosphate (ATP) binding pocket of *EGFR* tyrosine-kinase domain. In this regard, osimertinib, a third-generation *EGFR* inhibitor with prominent activity against both T790M resistance mutation and the standard activating EGFR mutations, represents a very active treatment for patients with *EGFR* T790M-dependent NSCLC who experienced disease progression after first-line *EGFR* TKIs therapy, as demonstrated in AURA1-2-3 studies (3-5). While the *EGFR* T790M-driven disease still mirrors the typical oncogene-addicted NSCLC, with the majority of tumors dramatically responding to osimertinib and deriving a significant delay in tumor progression, *T790M* negative patients represent a heterogeneous population whereas tumors with extremely different clinical and biological findings co-exist and where platinum-based chemotherapy remains the only available worldwide approved treatment option. For these reasons, such clinical scenario represents a challenging issue for physicians in clinical practice.

MET gene amplification is the second most important mechanism (5–20% of patients) of acquired resistance to *EGFR* TKIs and in a half of cases concurrently occurs with T790M EGFR mutation (6). MET-dependent resistance is triggered by the activation of common downstream pathways to *EGFR* receptor, directly by the homodimer formation or indirectly by trans-activating other tyrosine kinase receptors. This way *EGFR* signaling becomes redundant and, as preclinical studies suggest, targeting both receptors by adding an anti-MET agent to *EGFR* TKIs is required to obtain an effective antitumor activity (7). A series of anti-MET-agents, including TKIs or monoclonal antibodies (MoAbs), have been developed and tested in NSCLC patients. The outcomes of EGFR mutated population included in anti-MET trials are reported in *Table 1* (8-12).

Wu *et al.* recently published a phase 1b/2 study (13), in which the combination of the *MET* inhibitor capmatinib and the *EGFR* inhibitor gefitinib appears safe and active in patients with T790M-negative acquired resistance to prior *EGFR* TKI therapy carrying MET-dysregulation (amplification or overexpression). Different doses of capmatinib plus gefitinib (250 mg) were examined in

Table 1 Other phase II and III trials evaluating anti-MET in EGFR-mutated non-small cell lung cancer

Agent	Trial	Population	EGFR status	MET abnormalities	Setting	Arms	N	Primary endpoint	ORR (OR)	Median (ms)	HR [95% CI]
Capmatinib	Phase II	NSCLC	Mutated	IHC MET-positive (2+ or 3+ in ≥50% of TC) or MET amplification by FISH (GCN ≥4)	Acquired resistance to EGFR-TKIs	Capmatinib + Gefitinib	61	ORR	29%	–	–
		NSCLC	Mutated	MET amplification by FISH (GCN ≥6)	Acquired resistance to EGFR-TKIs	Capmatinib + Gefitinib	36	ORR	47%	–	–
		NSCLC	Mutated	IHC MET-positive (2+ or 3+ in ≥50% of TC)	Acquired resistance to EGFR-TKIs	Capmatinib + Gefitinib	25	ORR	32%	–	–
Emibetuzumab	NCT01900652 (8); phase II	NSCLC	Mutated (27% T790M+)	IHC MET-positive (2+ or 3+ in ≥10% of TC)	Pretreated	Emibetuzumab; Erlotinib + Emibetuzumab	28; 83	ORR	4.3%; 3.0%	–	–
		NSCLC	Mutated (27% T790M+)	High IHC; MET-positive (2+ or 3+ in ≥60% of TC)	Pretreated	Emibetuzumab; Erlotinib + Emibetuzumab	21; 53	ORR	4.8%; 3.8%	–	–
Onartuzumab	Phase II (9)	NSCLC	Mutated	Unselected	2–3 lines	Erlotinib + Placebo; Erlotinib + Onartuzumab;	6; 7	OS*	–	NR; NR	2.2
		NSCLC	Mutated	IHC MET-positive (2+ or 3+ in ≥60% of TC)	2–3 lines	Erlotinib + Placebo; Erlotinib + Onartuzumab;	2; 7	OS*	–	NR; NR	4.81E7
	METLung (10); phase III	NSCLC	Mutated	IHC MET-positive (2+ or 3+ in ≥60% of TC)	2–3 lines	Erlotinib + Onartuzumab; Erlotinib + Placebo	28; 57	OS	–	12.6; NE	4.68 [0.97–22.63]
Tivantinib	MARQUEE (11); phase III	Non-squamous	Mutated 109/1,048 (10.4%)	Unselected	Pretreated	Erlotinib + Tivantinib; Erlotinib + Placebo	56; 53	PFS	–	13; 7.5	0.49 [0.31–0.77]

Table 1 (*Continued*)

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Agent	Trial	Population	EGFR status	MET abnormalities	Setting	Arms	N	Primary endpoint	ORR (OR)	Median (ms)	HR [95% CI]
Tepotinib	Phase II (12)	NSCLC	EGFR mutated; No T79M	MET-positive (2+ or 3+ or MET amplification by ISH (GCN ≥5 and/ or MET/CEP ≥2)	Resistance to prior EGFR TKI	Tepotinib + Gefitinib; Carboplatin/cisplatin + pemetrexed	31; 24	PFS	–	4.9; 4.4	0.71 [0.36–1.39]
		NSCLC	EGFR mutated; No T79M	High IHC 3+	Resistance to prior EGFR TKI	Tepotinib + Gefitinib; Carboplatin/cisplatin + pemetrexed	19; 15	PFS	–	8.3; 4.4	0.35 [0.17–0.74]
		NSCLC	EGFR mutated; No T79M	MET amplification by ISH [GCN ≥5 and/or MET/ CEP ≥2]	Resistance to prior EGFR TKI	Tepotinib + Gefitinib; Carboplatin/cisplatin + pemetrexed	12; 7	PFS	–	21.2; 4.4	0.17 [0.05–0.57]

*, the primary endpoint of the study was PFS, but only the OS outcome were reported for EGFR mutated population. CEP, chromosome enumeration probes; FISH, Fluorescence In situ hybridization; IHC, immunohistochemistry; ISH, in situ hybridization; GCN, gene copy number; ms, months; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

the phase 1b part of the trial, in which 61 patients were enrolled. In the phase II of the trial, 100 patients received the combination of gefitinib (250 mg per day) plus capmatinib at the dose identified in the phase I part of the study (400 mg twice daily), and an overall response rate of 29% was achieved. Combining both phases, overall response rate was 27%, with a generally well-tolerable safety profile of the combination. With regard to predictors of activity, a higher response rate (47%) was observed in patients whose tumors harbor *MET* amplification with a gene copy number (GCN) ≥6; the ORR was 32% in patients with immunohistochemistry (IHC) score 3+ tumors, which was comparable with the observed activity in patients with IHC 2+ and GCN ≥5 tumors. A trend towards a longer progression-free survival (PFS) was seen in patients with tumors with a GCN ≥6 (5.49 months) or IHC2+/GCN ≥5 (7.29 months). Thus, the biomarker analysis prioritizes MET fluorescence in situ hybridization (FISH) analysis (with a cut-off of GCN ≥6) in comparison with MET IHC staining to identify tumors more likely to be shrank with the combination of capmatinib plus gefitinib.

These results, generate the hypothesis that a therapeutic strategy including the concurrent inhibition of *MET* and *EGFR* signaling could be conceivable for T790M negative NSCLC patients with *MET* induced acquired resistance to EGFR TKIs, who are currently candidate to receive platinum-based chemotherapy as standard treatment. In addition, these promising early data deserve to be preferentially investigated than those emerging from the addition of check-point inhibitors, whose efficacy appear to be limited in the oncogene-addicted disease, at least for now (14). With regard to chemotherapy, in the IMPRESS trial (15), non-squamous NSCLC patients who had progressed on first-line gefitinib were randomized to up to 6 cycles of cisplatin-pemetrexed chemotherapy together with continuation of the gefitinib or placebo. Patients who received chemotherapy alone achieved an ORR of 34% and a median PFS of 5.4 months, which were even lower in the plasma T790M negative population (ORR of 32% and PFS 4.6 months). Thus, although considering the bias of an indirect comparison, the activity of capmatinib and gefitinib seems to be at least comparable with chemotherapy in patients with acquired resistance to EGFR TKIs, and the hypothesis that this combination would better work in patients with *MET* amplification or overexpression is suggested.

Conversely to other studies including combination of targeted agents which were early stopped for unacceptable

toxicity [*ex*. erlotinib plus tivantinib (16) and dacomitinib plus crizotinib (17)], the combination of capmatinib and gefitinib appears to be safe. The most common study drug—related any-grade and grade 3/4 adverse events were nausea (28%) and increased lipase and amylase levels (both 6%), respectively. Peripheral edema (all grades) was believed to be drug related and occurred in 22% of patients; that may be a potential drug-class effect since it has been peculiarly reported for other MET inhibitors as well.

Overall, the majority of trials investigating *MET* inhibition (either with TKIs or MoAbs) were prospectively conducted in non-*EGFR*-addicted disease, thus trying to interfere with a *MET* pathway dysregulation different from that emerging as an acquired mechanism of resistance in EGFR mutant NSCLC progressing during TKIs. Two phase III trials (MARQUEE and MET-Lung) were negative, although a signal of efficacy of tivantinib in combination with erlotinib (in comparison with erlotinib alone) is showed in the subgroup analysis performed in *EGFR* mutant patients of the MARQUEE trial (11). In this retrospective analysis, PFS was significantly longer in patients receiving the combination of TKIs, with a HR of 0.49 (95% CI, 0.31–0.77), with a trend towards a longer OS as well (HR 0.68; 95% CI, 0.43–1.08). In this subgroup analysis, 14% and less than 4% of patients showed *MET* overexpression or amplification, respectively, in the combination arm. All patients enrolled had received 1 or 2 prior line of chemotherapy regimens and no EGFR-TKIs therapy. The most common adverse events of any grade were diarrhea, rash, and asthenia, which occurred at similar rates in the experimental arm (39.3%, 30.4%, 35.7%, respectively) and in the control group (43.4%, 30.4%, 39.6%, respectively). A higher rate of both febrile neutropenia (3.6%) and neutropenia (14.3%) of grade ≥3 was observed in patients receiving erlotinib and tivantinib.

In the trial of Wu *et al.*, while patients were selected for acquired resistance to TKI according to the well-defined acquired resistance criteria (18), the definition of *MET* dysregulation, one of the key inclusion criteria, was amended overtime. Indeed, patients were sequentially required to have: (I) GCN ≥5 or 50% of tumor cells with IHC 2+/3+; (II) 50% of tumor cells with IHC 3+ or IHC 2+ plus MET GCN ≥5; and finally 50% of tumor cells with IHC 3+ or MET GCN ≥4. Furthermore, in the early phase of enrollment *MET* dysregulation was assessed also in local laboratories, while finally, the central evaluation becomes mandatory.

Actually, the lack of a standard definition of c-Met dysregulation (as observed in this trial) suggests that several mechanisms, including amplification, rearrangements, protein overexpression and mutations are responsible for *MET* activation and probably determine different type and level of activation, which may induce different responses to specific therapeutic approaches. In addition to the biological issues, diagnostic tests and molecular biomarkers for patients' selection have never been established or validated. Wu *et al.* had considered to evaluate *MET* abnormalities in terms of gene amplification by FISH and expression by IHC. Although the use of each technique is hampered by specific limitations, both assays deal with a continuous variable, and the selection of the cut-off points remains a crucial issue for the best selection of patients, since the ORR of capmatinib plus gefitinib increase directly and quantitatively with the rising of the cut-off considered. In particular, the evaluation of *MET* amplification by FISH was affected in first instance by the imperfect correlation between *MET* amplification and c-Met overexpression, which underline the potential influence of other mechanisms affecting gene expression (19). In addition, FISH cannot identify *MET* dysregulation arising from alterations other than *MET* amplification and it is technically limited by the small number of cells that can be feasibly assessed, resulting in a possible underestimation of true amplification of *MET* in heterogeneous tumors. This is particularly relevant for the assessment of tumors harboring small numbers of *MET*-amplified clones with the potential to expand under the selective pressure imposed by continued *EGFR* TKI therapy.

Even the IHC evaluation of *MET* expression required technical adjustments, such as careful sample handling, the inclusion of adequate controls, and the interpretation by experienced pathologists. Bypassing the technical issues, even in this case, *MET* levels cannot directly reflect the receptor activity, which is influenced also by the cross-interaction of MET with others TK receptors. Furthermore, tumors with similar levels of c-Met expression may differ in their sensitivity to c-Met inhibitors, depending on whether c-Met overexpression drives tumorigenesis, or is a bystander/passenger alteration.

A possible way of resolution of some (but not all) limitations related to *MET* IHC evaluation consists of the direct detection of phospho-c-Met- residues, which may be a more accurate indicator of *MET* activation than total MET-expression by IHC (20). Significant MET pathway inhibition was induced in 5 patients included in the trial, whose pre- and post-dose tumor samples were assessed for p-MET expression. Unfortunately, clinical outcome of the patients evaluated in this exploratory analysis were not

reported by the authors and thus the two methods were not comparable for their predictive value.

Another interesting field of application of *MET* inhibition could be the landscape of acquired resistance to the third-generation *EGFR* TKI osimertinib. Biomarker analysis performed on liquid biopsies in the FLAURA study demonstrated *MET* amplification as the most frequent mechanism of resistance to first-line osimertinib (15% of evaluable patients) (21). A relevant role was attributed to *MET* amplification also in the acquired resistance to second-line osimertinib, as showed in a similar biomarker analysis of AURA3 study, in which *MET* amplification was the second cause of resistance (19% of cases) after the loss of T790M EGFR mutation, detected in 49% of treated patients (22). Nevertheless, also the activity of the combination of *MET* inhibitors with third-generation EGFR TKIs seems to be promising. A response rate of 40% was recently reported for combinations of osimertinib and the MET-TKIS savolitinib in the phase Ib TATTON trial (23), including a cohort of patients with *MET* amplification assessed by FISH irrespective to T790M status. The targeting of both *MET* and *EGFR* pathway seems to be active also in treatment-naive patients unselected for *MET* status, considering the 47% of response observed with the combination of capmatinib plus the EGFR 3th generation TKI nazartinib in a phase Ib/II study (24).

All these perspectives encourage further studies focused on anti-MET agents in different contexts of lung cancer. Probably, in the forthcoming future, considering the potential role of molecular *MET* testing as a predictor of efficacy of anti-MET therapy (25), it would be included in the routine panel of targetable molecular alteration of NSCLC. Before to move to such important step, the standardization of MET evaluation assays with the crucial definition of reliable (and reproducible) cut-offs is absolutely required to clearly identify those *MET* dysregulated NSCLC patients who would best benefit from *MET*-targeted therapy.

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Footnote

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