Editorial

Blocking both epidermal growth factor receptor and mesenchymal-to-epithelial transition pathways in *EGFR*-mutated lung cancer

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Although most of epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) is sensitive to EGFR tyrosine kinase inhibitor (TKI), the tumor becomes resistant to the drug after around 1 year. *EGFR* T790M secondary mutation occupies more than 50% of the resistant mechanisms. Mesenchymal-to-epithelial transition (*MET*) amplification is approximately 20% among non-T790M resistance (1). MET inhibitors include MET selective and non-selective TKIs and anti-MET antibodies such as onartuzumab and emibetuzumab. In the treatment of advanced NSCLC, non-selective TKIs such as tivantinib, cabozantinib, foretinib, crizotinib and glesatinib and selective TKIs such as tepotinib and capmatinib have been developed (2). Although substantial MET expression and *MET* amplification are observed even in treatment-naïve NSCLC (1), MET inhibitor monotherapy has not been useful in molecularly unselected NSCLC patients. It is actually effective if the progression of NSCLC depends on MET signals such as MET exon 14 skipping mutations (3).

The reports of MET inhibitor plus EGFR-TKI for the treatment of advanced NSCLC are summarized in *Table 1*. A randomized phase II study comparing erlotinib plus onartuzumab with erlotinib alone in MET-positive NSCLC, which was determined using immunohistochemistry (IHC), showed improved progression-free survival (PFS) and overall survival (OS) (9). However, the combination in phase III study (METLung) did not show its efficacy (10). Non-selective MET-TKI plus EGFR-TKI have been also investigated. A randomized phase II study of erlotinib with tivantinib showed improved PFS [hazard ratio (HR) 0.18] among patients with *KRAS* mutations compared with erlotinib monotherapy on exploratory analysis (4). A subsequent phase III study (MARQUEE) demonstrated increased PFS but did not improve OS in the overall nonsquamous NSCLC population (6). Another phase III study in Asian nonsquamous NSCLC patients with wild type-*EGFR* was prematurely terminated due to the increased interstitial lung disease incidence: 14 (9.2%, 3 deaths) in the erlotinib plus tivantinib group and 6 (4.0%, 0 death) in erlotinib plus placebo group (5). The combination group significantly prolonged PFS (HR 0.719) but OS was similar (HR 0.891). Previously treated *EGFR*-mutant NSCLC patients in the MARQUEE study were further analyzed (7). The subanalysis showed that erlotinib plus tivantinib had significantly better median PFS (13.0 *vs.* 7.5 months for erlotinib monotherapy, HR 0.49) and non-significantly better median OS (25.5 *vs.* 20.3 months for erlotinib monotherapy, HR 0.68). In 45 *EGFR* mutation-positive patients who progressed while on EGFR-TKI, the median PFS was only 2.7 months although it was longer in MET high group (4.1 *vs.* 1.4 months in MET low group) (8). Thus, combination of tivantinib with erlotinib might be effective in previously treated *EGFR*-mutant and MET-positive NSCLC patients.

Crizotinib blocks not only ALK and ROS1 signal pathways but also MET pathway (2). Thus, the combination of crizotinib and EGFR-TKI (erlotinib or dacomitinib) was investigated in phase I studies (*Table 1*). Crizotinib (300 mg/day) plus erlotinib (100 mg/day), both doses of which were less

Table 1 A combination of MET inhibitor with EGFR-TKI in NSCLC

Study phase (study name)	MET-inhibitor	EGFR-TKI	Response rate	Median PFS	Median OS	EGFR status	Note	First author
Phase 2	Tivantinib *vs.* Placebo	Erlotinib	10% *vs.* 7%	3.8 *vs.* 2.3 months	8.5 *vs.* 6.9 months	All (n=84 *vs.* 83); mutant (n=6 *vs.* 11)	Better PFS in KRAS mutant	Sequist (4)
Phase 3 (ATTENTION)	Tivantinib *vs.* Placebo	Erlotinib	8.4% *vs.* 6.5%	2.9 *vs.* 2.0 months	12.7 *vs.* 11.1 months	All wild (n=154 *vs.* 153)	ILD developed in 14 patients (9.2%, 3 deaths) *vs.* 6 patients (4.0%, 0 deaths)	Yoshioka (5)
Phase 3 (MARQUEE)	Tivantinib *vs.* Placebo	Erlotinib	10.3% *vs.* 6.5%	3.6 *vs.* 1.9 months	8.5 *vs.* 7.8 months	All (n=526 *vs.* 522)	Improved PFS	Scagliotti (6)
Phase 3 subanalysis (MARQUEE)	Tivantinib *vs.* Placebo	Erlotinib	61% *vs.* 43%	13.0 *vs.* 7.5 months	25.5 *vs.* 20.3 months	Mutant (n=56 *vs.* 53)	Improved PFS	Scagliotti (7)
Phase 2	Tivantinib *vs.* Placebo	Erlotinib	6.7% (3/45)	2.7 months	18.0 months	All mutant (n=45)	Just after PD on EGFR-TKI	Azuma (8)
Phase 2	Onartuzumab *vs.* Placebo	Erlotinib	5.8% *vs.* 4.4%	2.2 *vs.* 2.6 months	8.9 *vs.* 7.4 months	All (n=69 *vs.* 68) [mutant (n=7 *vs.* 6)]	Improved PFS and OS in the MET-positive	Spigel (9)
Phase 3 (METLung)	Onartuzumab *vs.* Placebo	Erlotinib	8.4% *vs.* 9.6%	2.7 *vs.* 2.6 months; HR 0.99	6.8 *vs.* 9.1 months; HR 1.27	All (n=250 *vs.* 249); mutant (n=28 *vs.* 29)	In mutant, PFS: NE *vs.* 8.5 mo (HR1.15); OS: 12.6 mo *vs.* NE (HR4.68)	Spigel (10)
Phase 1	Crizotinib	Dacomitinib	1.5%	2.1–3.0 months	NA	Mutant (n=18)	Grade 3/4: 43%	Jänne (11)
Phase 1	Crizotinib	Erlotinib	8% (2/25)	NA	NA	Mutant (n=2)	2 PR with EGFR ex19 del mutant	Ou (12)
Phase 2	Tepotinib	Gefitinib	28% (5/18)	–	NA	Mutant (n=18)	–	Wu (13)
Phase 2 (INSIGHT)	Tepotinib	Gefitinib	–	–	target n=156	Mutant/T790M–/MET+	*vs.* CDDP+PEM (on going)	Wu
Phase 1b/2	Capmatinib	Gefitinib	27% (47% with MET amp in p2)	5.5 months in p2	NA	All mutant: n=61 in p1b and n=100 in p2	–	Wu (14)
A case	Crizotinib	Osimertinib	PR	3 months	NA	L858R+T790M+MET mutant	–	Kang (15)
A case	Crizotinib	Osimertinib	SD	6 months	NA	L858R+MET amp	–	York (16)
A case	Crizotinib	Osimertinib	SD	6 months	NA	L858R+T790M+MET amp	–	Deng (17)

amp, amplification; del, deletion; ex, exon; HR, hazard ratio; ILD, interstitial lung disease; NA, not available; NE, not evaluable; OS, overall survival; p, phase; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

than those approved for single-agent use, was feasible and response was observed in two of 25 patients (12). Both responders had tumors harboring *EGFR* exon 19 mutation. A phase I study of the combination of crizotinib with second-generation EGFR-TKI, dacomitinib, in NSCLC patients after failure of at least one prior chemotherapy regimen or EGFR-TKI was also reported (11). Only one patient among 33 escalation cohort and 37 expansion cohort achieved objective response. The responding tumor had *EGFR* exon 19 deletion with T790M mutation and without *MET* amplification. In the study overall, 66 patients (94%) had at least one treatment-related adverse events and 27 (39%) and three (4%) patients had grade 3 and 4 treatment-related adverse events, respectively. The combination was considered to be ineffective and toxic.

How about the combination of MET-selective TKI (capmatinib or tepotinib) with EGFR-TKI? Recently, Wu *et al*. reported capmatinib plus gefitinib was effective even after failure of EGFR inhibitor therapy in patients with *EGFR*-mutated and *MET* amplified NSCLC (14). In the phase Ib portion (n=61), the response rate was 23% regardless of MET status although five patients had *EGFR* T790M mutation. The patients with *EGFR* T790M mutation were excluded in the phase II portion. Response was observed in 29 of 100 patients (29%) regardless of MET status; of the responders, 25 of 29 (86%) had received an EGFR-TKI as their last prior therapy. The response rate was 47% in 36 patients whose tumor had high MET gene copy number (≥6). The combination seems to be a promising strategy in such EGFR-TKI resistant patients.

Another MET-selective inhibitor, tepotinib, plus gefitinib were also investigated in the 18 Asian patients with MET-positive (IHC 3+ or 2+) and *EGFR*-mutant NSCLC (13). Partial response was observed in 5 patients and 4 of the 5 responders had high MET-positive (IHC 3+) tumors. Now, tepotinib plus gefitinib are compared with cisplatin plus pemetrexed in advanced NSCLC patients, with acquired resistance to first-line EGFR-TKIs (INSIGHT study, NCT01982955). According to the eligibility criteria on the protocol, the tumor should harbor EGFR-activating mutation without T790M and MET-dysregulated (IHC 2+ or 3+, amplification, or increased gene copy number). The recruitment was already finished on December 12, 2017 and the estimated study completion date was October 16, 2018. Thus, we are looking forward to seeing the results.

Meanwhile, 40% of the samples with *MET* amplification harbored *EGFR* T790M mutation in EGFR-TKI resistant tumors (1). Inhibition of both MET and *EGFR* T790M, using MET inhibitor and osimertinib, seems to be attractive strategy. Three patients with *EGFR* mutation and *MET* amplification were successfully treated with the combination of crizotinib with osimertinib (15-17). Two of three patients had harboring *EGFR* L858R and T790M mutations with *MET* amplification (15-17). Nowadays, the standard 1st line treatment for *EGFR*-mutated NSCLC is 3rd generation EGFR-TKI, osimertinib. The resistance mechanisms on progression after 1st line usage of osimertinib have been reported. *MET* amplification was identified in T790M-preserved (5/19) and T790M-loss (1/21) cases (18). Seven of 32 osimertinib-resistant tumors (22%) developed MET amplification (19). In FLAURA study, *MET* amplification in plasma samples was observed in 15% (14/19) on progression after treatment with 1st line osimertinib (20). Suppressing *MET* amplification by MET inhibitor combining with osimertinib on 1st line treatment for *EGFR*-mutant advanced NSCLC may more effective, compared with osimertinib monotherapy.

Wu *et al*. firstly documented that combining selective MET-TKI with EGFR-TKI had substantial effects in *EGFR*-mutated and MET-dysregulated NSCLC on progression after 1st line EGFR-TKI treatment (14). Subsequent randomized studies are warranted. Further, clinical trials of MET-TKI plus EGFR-TKI may be also expected in 1st line treatment in *EGFR*-mutant NSCLC patients.

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Footnote

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