



Oncogene alterations in non-small cell lung cancer—have we *MET* a new target?

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Non-small cell lung cancers (NSCLCs) represent over 80% of all malignant lung tumours and are one of the leading causes of cancer death worldwide (1). First-line treatment of advanced or metastatic NSCLCs has changed dramatically during the last two decades, and novel treatment options such as immunotherapies (e.g., checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4), and tyrosine kinase inhibitors (TKIs) have demonstrated significant benefit for several NSCLC patients sparing them from the toxic effects of chemotherapy (2). Amongst the targetable molecular alterations that have been identified in NSCLC (e.g., EGFR, ALK, ROS, RET, c-MET), c-MET [a hepatocyte growth factor (HGF) receptor tyrosine kinase] alterations (e.g., c-MET exon 14 skipping mutations, c-MET gene amplifications, protein overexpression) have been identified to be one of the frequently altered oncogenic drivers in NSCLCs. Of note, c-MET exon 14 skipping mutations are found in up to 4% of all NSCLC patients (3).

Several lines of research have provided compelling evidence that c-MET exon 14 skipping mutations were associated with older age (median age 73 years), certain histologic subtypes (e.g., acinar, solid), and high c-MET immunohistochemical expression. Moreover, amongst NSCLC patients with c-MET exon 14 skipping mutations, two thirds were female, and approximately one third of patients had been identified to be never-smokers. In addition, tumour mutational burden (TMB) has been demonstrated to be low since half of the patients which commonly present with stage I disease (4,5) suggesting that c-MET exon 14 skipping mutations is an early onset

in NSCLC development, and the stepwise addition of c-MET amplification and/or overexpression may contribute to a more aggressive clinical phenotype (4,5). Several experimental studies have provided compelling evidence that c-MET is involved in the regulation of the immune response by upregulating inhibitory molecules (e.g., PD-L1) and down-regulating of immune stimulators (e.g., CD137, CD252, CD70, etc.). In addition, c-MET was found to be implicated in the regulation of the inflamed tumour microenvironment (TME) and thereby contributing to an increased immune escape of tumour cells from T cell killing. Moreover, evidence has been provided that c-MET represents a key resistance mechanism following treatment of epidermal growth factor receptor mutations (EGFRmut) with TKIs (2).

Four oral c-MET TKIs are currently FDA- and EMA-approved for the treatment of NSCLC patients harbouring c-MET exon 14 skipping mutations (e.g., tepotinib, capmatinib, savolitinib, and crizotinib) (*Table 1*). These c-MET TKIs have shown to be very potent and highly selective against c-MET and belong to the type I inhibitors. Type I c-MET TKIs are regarded to be ATP-competitive and can interact with the activation loop of c-MET and thereby preventing the dysregulation of the c-MET/HGF pathway which is known to be involved in the proliferation, survival, and invasion of malignant cells. By contrast, type Ia inhibitors (e.g., crizotinib) are thought to interact with tyrosine [1,230], the hinge and glycine [1,163], while type Ib inhibitors (e.g., capmatinib, tepotinib, and savolitinib) do not interact with G1163, but have a much stronger

Table 1 Characteristics of oral c-MET inhibitors used for NSCLC patients in the clinic

Inhibitor	Approval	Pivotal Trial	Outcome	Reference
Tepotinib (Tepmetko [®])	FDA, EMA, Japan	VISION (phase II, N=337): NCT02864992	ORR =44.9%; mPFS =8.5 months	Paik <i>et al.</i> 2020 (6)
Capmatinib (Tabrecta [®])	FDA, EMA	GEOMETRY mono-1 (phase II, N=364): NCT02414139	ORR =68.8%; mPFS =12.5 months	Wolff <i>et al.</i> 2020 (7)
Savolitinib (Orpathys [®])	China	Phase II (N=76); NCT02897479	ORR =42.9%	Lu <i>et al.</i> 2021 (8)
Crizotinib (Xalkori [®])	FDA, EMA (for ALK- and ROS1-positive NSCLC); c-MET: off-label use	PROFILE 1001 (Phase I, N=69/596 with c-MET mutations); NCT 00585195	ORR = 32%	Drilon <i>et al.</i> 2020 (9)

ORR, overall response rate; mPFS, medium progression free survival.

interaction with Y1230 and the hinge. This results in a significantly greater specificity for c-MET and much lower off-target interactions (3).

C-MET exon 14 skipping alterations (e.g., point mutations, deletions, insertions, and complex mutations) lead to a decreased degradation of the c-MET receptor, resulting in the activation of c-MET signaling and tumorigenesis (10). Furthermore, impaired c-MET receptor degradation is known to be an important mechanism for ligand-independent aberrant c-MET signaling (11). Interestingly, in NSCLCs almost all of the c-MET exon 14 skipping mutations can delete tyrosine-1003 (the c-cbl binding site) located in the juxtamembrane domain (12,13). This leads to c-MET ubiquitination abrogation, increased c-MET protein stability, and impaired c-MET degradation which then, in turn, induces ligand-independent c-MET activation (11,12).

In particular, the FDA- and EMA-approved molecules tepotinib and capmatinib have been shown in clinical trials to exert a very high c-MET exon 14 skipping mutation inhibitory efficacy and, therefore, represent a novel therapeutic option for the treatment of NSCLC patients harbouring c-MET alterations. However, the precise role of these molecules as a new treatment option is still not fully defined and further larger studies are clearly needed (14).

Several resistance mechanisms for c-MET inhibitors have been identified in preclinical studies (15). On-target acquired mechanisms of resistance (e.g., mutations at histidine-1094, glycine-1163, lysine-1195, aspartic acid-1228, tyrosine-1230, and high c-MET amplification levels) are found in approximately one third of patients, whereas resistance due to off-target mechanisms (e.g., K-RAS mutations and amplifications in K-RAS, EGFR, HER3, PI3K, and B-RAF) have been documented in

45% of patients (2,15). In the remaining proportion of patients (25%) the underlying resistance mechanism is still unknown.

Shen *et al.* (16) demonstrated for the first time that c-MYC alterations can confer resistance to currently available c-MET inhibitors in c-MET-driven cancers. Using c-MET-amplified patient-derived xenograft mouse models (NSCLC, gastric cancer), Shen *et al.* could show that c-MYC inhibitors can overcome the intrinsic or acquired resistance to c-MET inhibitors due to c-MYC amplification. The authors concluded that combining c-MYC and c-MET inhibitors, if confirmed in clinical trials, may be a novel and interesting new approach to overcome c-MYC-mediated resistance to c-MET inhibitors.

Several lines of support for this conclusion came from a case report from Choi *et al.* in this journal (17). The authors reported an 82-year-old male NSCLC patient with an intense staining for c-MET (gene copy number: 13.5 as judged by immunohistochemistry). The patient was treated with capmatinib (2×400 mg/day). However, he progressed rapidly, and re-biopsy of a new lesion was performed which revealed a c-MYC amplification (gene copy number: 5). The patient then received chemotherapy (second- and third-line including stereotactic radio-therapy) without any tumour response. He died due to tumor progression shortly thereafter. Following capmatinib treatment, patient-derived cells from the re-biopsy were cultured and used for *in vitro* studies. Interestingly and in line with the study provided by Shen *et al.* (16) the authors could show that the observed primary capmatinib resistance was, at least in part, associated with a concurrent c-MYC amplification, and an investigational c-MYC inhibitor (ICX-101) was found to overcome the observed capmatinib resistance *in vitro*. This case report, therefore, adds further weight to

Table 2 Selected inhibitors of c-MYC

Compound	IC ₅₀ value	Development phase
ICX-101	NS	Preclinical
IIA6B17	50 µM	Preclinical
MYCMI-6	1.6 µM	Preclinical
Mycro3	40 µM	Preclinical
Omomyc (OMO-103)	0.4–3 µM	Phase I/II (NCT04808362)
OTX-2002	0.3–1.5 µM	FDA clearance for phase I/II (NCT05497453)

NS, note stated.

the conclusion that c-MYC amplification may be a novel resistance mechanism for c-MET inhibitor resistance in c-MET amplified cancers which provides further evidence that co-treatment of c-MET and c-MYC inhibitors could be of potential benefit for these patients if confirmed in larger clinical trials.

It should be noted that the prevalence of pan-MYC amplifications in c-MET-driven NSCLCs is still far from being conclusive, however, a study published by Castiglione *et al.* (18) provided the first evidence that c-MYC alterations are more pronounced in NSCLCs harbouring c-MET amplifications (but not c-MET exon 14 skipping mutations) suggesting that c-MYC amplification is a key resistance mechanism following treatment with c-MET inhibitors in c-MET amplified NSCLCs.

The oncogene c-MYC (62 kD, 439 amino acids) is known to play an important role in carcinogenesis and tumour promotion. It exerts several important domains in its intracellular part which can serve as binding sites for many and diverse binding partners which are then, in turn, responsible for the c-MYC dependent downstream signaling cascades. C-MYC acts as a transcription factor which is altered in over 70% of all malignant human tumours (19). Of note, blockage of c-MYC has been shown to result in significant tumour shrinkage in mice which was associated with only mild and fully reversible side effects, adding weight to the proposal that c-MYC can be a promising therapeutic option for cancer treatment strategies (20).

A huge body of evidence has demonstrated that c-MYC controls many cellular signal transduction cascades by interacting with more than 15% of all human genes. It is widely accepted that c-MYC is involved in the global control of gene expression, cell proliferation, cell differentiation, cell cycle, metabolism, and apoptosis (19). In

addition, c-MYC is also implicated in both, carcinogenesis and tumour maintenance. It should be noted that no drug (e.g., antibodies, small molecules) inhibiting c-MYC has been approved for clinical use yet, however, studies over the last 20 years have demonstrated problems that may limit the development of c-MYC inhibitors, and new strategies have been identified to pave the way for the development of potent and highly selective c-MYC inhibitors with favourable pharmacokinetic properties, although these are still in very early stage of development (21).

Some decades ago, c-MYC was considered to be a difficult therapeutic target, due to possible serious side effects resulting from inactivating a master regulator oncogene which is known to be critical for the normal cell survival and proliferation, however, this was not reported in several *in vivo* studies so far.

Omomyc (OMO-103) (90 amino acid) has been developed as a c-MYC mini-mutant with a short half-life time that contains the bHLH-LZ domain and interacts with c-MYC for binding to DNA displacing the MYC/MAX heterodimers and thereby inhibits the target gene transcription (22). Co-treatment with OMO-103 and paclitaxel was found to inhibit tumour growth of human NSCLC xenografts in mice (23). A dose-escalation phase I/II study with OMO-103 started in 2021, and OMO-103 is currently the only direct c-MYC inhibitor which is evaluated clinically in patients with advanced solid cancers including NSCLCs, colorectal carcinomas and triple-negative breast cancers (NCT04808362) (Table 2).

To date, with OMO-103 only one selective and potent inhibitor that directly target c-MYC has entered the clinic. Reduced selectivity for c-MYC (low potency) and a quick turn-over have been considered to be the most likely mechanisms for these observations and may be the reason why many other inhibitors failed preclinically.

Over the last twenty years, however, c-MYC has been considered to have a “bad name” for drug developers and has been considered to be “undruggable”, however, due to the recently published preclinical research it now has become one of the most attractive targets for cancer treatment (19). Despite the current challenges to inhibit c-MYC and the issues in terms of translating the current *in vitro* results to meaningful early clinical trials, several small molecule c-MYC inhibitors are now on the edge of starting clinical evaluation in phase I/II studies. Some of these small molecules are able to inhibit all MYC family members (i.e., c-, N, and L-MYC), and it can be expected that the future evaluation of these new pan-MYC inhibitors will have a

greater efficacy in the clinic.

Overall, the combined treatment with small molecule c-MYC inhibitors, c-MET inhibitors, and possibly checkpoint inhibitors are warranted in future clinical trials. Major progress has been achieved so far, but additional studies are still warranted to better clarify the molecular background of c-MYC inhibition which will pave the way to bring MYC inhibitors to clinical practice.

In this regard the observation reported by Choi *et al.* (17) in this journal that capmatinib resistance due to c-MYC amplification can be overcome by c-MYC inhibition appears to be a novel finding that, if confirmed in larger clinical trials, may have significant clinical implications.

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