New approaches in RET and MET in NSCLC

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The era of precision medicine has resulted in the identification of several genomic alterations that can be targeted with novel therapies. In lung adenocarcinomas, a histology that accounts for nearly 50% of all cases of lung cancer, a few genomic targets have been linked with effective targeted therapies. For patients with advanced--stage lung adenocarcinomas, molecular testing is now a standard part of diagnostic workup; for patients that have specific driver molecular events, targeted therapies have resulted in substantial improvement in efficacy without excessive toxicity.

RET NSCLC

The rearranged during transfection activating gene (RET) was originally identified in 1985[1]. It encodes the transmembrane RET kinase; RET is activated when the glial cell line-derived neurotrophic factor family ligands binds to the RET coreceptor, glycosyl-phosphatidylinositol–anchored coreceptor (GFR-a)[2]. This leads to a signaling cascade that triggers the activation of downstream signals including MAPK and PI3K-AKT pathways and promotes cancer initiation and progression[3]. In normal cells, RET kinase signaling is well--controlled. In cells with activating alterations of the RET gene, aberrant signaling leads to uncontrolled cell growth that eventually results in malignant transformation[4]. RET is activated by two major mechanisms in cancer: RET fusions and RET point mutations. In RET fusions, owing to aberrant DNA repair processes, the RET gene is fused to another unrelated gene. Recurrent rearrangements between *RET* and various fusion partners (coiled-coil domain containing 6 [*CCDC6*], kinesin family member 5B [*KIF5B*], nuclear receptor coactivator 4 [*NCOA4*]) have been identified in 1 to 2 percent of adenocarcinomas[5]. In addition to RET fusions, activating RET point mutations can also lead to constitutive ligand independent RET signaling.

RET gene fusions have been reported in 1% to 2% of NSCLC and in 10% to 20% of sporadic

papillary thyroid cancer[6]. Other cancer types like breast cancer, colorectal cancer, and pancreatic cancer are also known to harbor activating RET fusions at a lower frequency (<1%). In addition, approximately 60% sporadic medullary thyroid cancer (MTC) and greater than 90% of hereditary MTC harbor an activating intracellular or extracellular RET mutation. The characteristics and outcomes of patients with RET fusion–positive NSCLC were presented by Gautschi et al. from the Global Multicenter RET Registry (GLORY)[5], the largest and international registry of 165 patients identified by a global network of thoracic oncologists. RET rearrangements were identified by reverse transcriptase–polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), or next-generation sequencing (NGS). The median age of patients was 61 years (range, 29–89), and most patients were never-smokers (63%), with lung adenocarcinomas (98%). Most patients had the advanced-stage disease (stage III-IV) (91%). The most frequent rearrangements were KIF5B-RET (72%) and CCDC6-RET (23%). NCOA4 (2%), EPHA4 (1%), and PICALM (1%) were uncommon partners. It is not known whether there are any biological differences in downstream signaling based on the RET fusion partner. Most patients were from the United States and Europe (86%) with a modest representation of Asian patients (16%). As such, it is very important to screen patients with NSCLC for RET rearrangements at the time of diagnosis, because there are no specific clinical features of this subset of NSCLC, clinical selection cannot be used to determine whether a given patient should be screened for RET. Multiple methods have been used for RET analysis: NGS, FISH, immunohistochemistry, and RT-PCR. NGS is currently the most sensitive method for RET analysis[7].

When the first reports of RET fusions in NSCLC emerged in 2012 clinical trials were launched with multikinase inhibitors such as cabozantinib[8], vandetanib[9], Lenvatinib[10], and sunitinib[5] that also inhibit RET. These agents have revealed modest anti-RET activity with an increased off-target toxicity profile that required often dose interruption, reduction, or treatment cessation. The increased toxicity is due to stronger inhibition of other targets such as VEGFR and EGFR inhibition and unfavourable pharmacokinetic profile for use in this setting. However, the emergence of a new generation of highly selective RET inhibitors has revealed robust clinical results with favourable toxicity profiles.

The RET inhibitor selpercatinib, has recently received approval in first line treatment from EMA. In the multicohort, open-label, phase I/II LIBRETTO-001 study, among 39 treatment-naïve patients with *RET* fusion-positive NSCLC, the overall response rate with selpercatinib was 85 percent, with 90 percent of responses lasting at least six months[11]. Among 105 patients previously treated with platinum chemotherapy, the overall response rate was 64%, with 63 % of responses lasting at least 12.1 months, and with a median duration of response of 18 months. Concerning the sub-group of patients with brain metastasis in the LIBRETTO-001 study, among the 105 patients with *RET* fusion-positive NSCLC, all previously treated with platinum-based chemotherapy, 80 patients had brain metastases, and 22 had measurable CNS metastases at baseline, as assessed by independent review committee[12]. No patients received RT to the brain within two months prior to study entry. Responses in intracranial lesions were observed in 82% of the patients with measurable disease, including 23% with complete responses; median duration of response had not been reached at a median follow-up of 9.5 months. In all 80 patients, median

intracranial PFS was 13.7 months. Among all patients with *RET* fusion-positive NSCLC, 58% had grade 3 to 4 toxicities, with the most frequent being hypertension (14%), an increased aspartate aminotransferase level (10%), hyponatremia (6%), and lymphopenia (6%). Fatal adverse events occurred in 4%, and were due to sepsis, cardiac arrest, multiple organ dysfunction syndrome, pneumonia, and respiratory failure. These events were deemed by the investigators to be unrelated to selpercatinib.

Another highly selective RET inhibitor is pralsetinib. ARROW a multicohort, open-label study of 114 patients with metastatic *RET* fusion-positive NSCLC, among 27 patients with treatment-naïve disease, the overall response rate was 70%, with 58% of responses lasting at least six months and median duration of response of 9 months[13]. Among 87 patients previously treated with platinum chemotherapy, the overall response rate was 61 percent, the median duration of response had not been achieved, and approximately 80 percent of responses lasted at least six months. Serious adverse reactions occurred in 45 percent of patients. Grade 3 to 4 events occurring in at least 2 percent included hypertension (14%), pneumonia (8%), diarrhea (3%), and fatigue (2%). Fatal adverse events occurred in 5% of patients and occurred due to pneumonia and sepsis. Pralsetinib also showed activity among patients with brain metastases, with intracranial response rate of 80 % (7 of 9 patients) in those with baseline measurable intracranial metastases in an early-phase clinical study[14].

MET NSCLC

Mesenchymal-epithelial transition (MET) oncogene is a multifaceted receptor tyrosine kinase that has been under intensive preclinical investigation for over 25 years. A deregulated MET pathway is commonly involved in tumorigenesis, tumor invasion, metastasis, and tumor progression. Diverse oncogenic alterations, including mutations, MET amplification, MET overexpression, chromosomal rearrangements, and fusions, cause dysregulation of the HGF/MET axis and lead to a wide range of human cancers.[15]. Increasing evidence implicates MET also as a common mechanism of resistance to targeted therapies (epidermal growth factor receptor [EGFR] and vascular EGFR [VEGFR] inhibitors). Thus, these diverse oncogenic alterations may function as a primary oncogenic driver or a mechanism of acquired resistance to another oncogenic pathway treated with targeted therapy (described in patients with ALK, ROS1, KRAS and EGFR alterations).

In the last decade, several MET inhibitors, including monoclonal antibodies, bispecific antibodies (bsAb), antibody-drug conjugate (ADC) and small molecules, have been developed and are in various phases of clinical evaluation. Despite the failure of some clinical trials, investigators have observed certain benefits with MET inhibitors in a selected MET-altered population[15].

The process of identifying patients with MET--dependent cancers is complex. From a diagnostic perspective, clinically meaningful cut-off points need to be standardized for continuous variables including the level of MET amplification or MET expression before these features can be used to guide treatment-related decision making.

Assays such as NGS should be considered for the detection of these alterations in both tumour biopsy and plasma samples and ideally in both DNA and RNA. The effective detection of MET-dependent cancers is crucial given that MET-directed targeted therapy is active in many of these cancers. Importantly, the level of activity of these therapies can be modulated by the type

of alteration identified and the degree of oncogenic addiction to MET signalling[16].

On the path to finding the right biomarkers for MET inhibitors, the first breakthrough was in MET exon 14 skipping mutations.

MET exon 14 skipping mutation reported in 3–4% of NSCLC cases is believed to be an independent driver mutation in NSCLC and is usually mutually exclusive from other drivers (e.g., EGFR, anaplastic lymphoma kinase [ALK], c-ros oncogene 1 [ROS1]) and associated with a poor prognosis.

Broad molecular testing with NGS is the current gold standard for METex14 skipping detection. RNA-based testing identifies a higher rate of METex14 skipping alterations compared with DNA-based testing. Not all PCR-based assays that include MET will detect all known METex14 skipping variants. FISH and IHC are currently used to detect MET amplification and overexpression, respectively.

When it comes to clinicopathologic features most studies show that patients with METex14 NSCLC are older with equal sex distribution with a relatively high incidence in nonadenocarcinoma pathology. A higher proportion of those with MET exon 14 skipping have a history of smoking compared with those harboring other drivers, such as ALK, ROS1 or RET fusions, although never-smokers still make up a substantial proportion of patients with MET exon 14 skipping alterations.[17].

Small molecule MET tyrosine kinase inhibitors (TKIs) (crizotinib, capmatinib, tepotinib, and savolitinib) have become the new standard of care in NSCLC, specifcally with MET exon 14 skipping mutations showing objective response rate ranging from 25% to 68% and median progression-free survival at 7.6-13.8 months.[16].

Crizotinib is a multitargeted small-molecule tyrosine kinase inhibitor (TKI) specifically targeted to ALK, ROS1 and MET. The efficacy of crizotinib against tumors with MET exon 14 skipping alterations or MET amplification has not been reported in a large population. Drilon et al. conducted the phase I PROFILE 1001 study (n=69) and reported the efficacy of crizotinib (median progression free survival (PFS) 7.3 months; objective response rate [ORR] 32%) in patients with advanced stage NSCLC harboring MET exon 14. Today MET inhibition with crizotinib remains a treatment option for NSCLCs with MET exon 14 alterations.[18].

The need for durable clinical activity, better control of resistance mutations and better central nervous system penetration makes highly potent and selective MET inhibitors of ME receptor such as tepotinib, capmatinib or savolitinib attractive options.

Tepotinib is a selective MET inhibitor that disrupts the MET signal transduction pathway and exhibits potential antineoplastic activity. Phase 2 VISION study, published in NEJM in 2020 evaluated the efficacy and safety profile of tepotinib in patients with advanced NSCLC with MET alterations[19].

Study concluded that among patients with advanced NSCLC with a confirmed MET exon 14 skipping mutation, the use of tepotinib was associated with response rates from 46 to 50% by independent review and 56 to 62% by investigator assessment. The onset of response was mostly within 6 weeks after the initiation of therapy, with a median duration of response as long as 15.7 months. The main toxic effect of grade 3 or higher mas peripheral edema[19].

In a recent update Tepotinib has continued to demonstrate durable clinical activity in MET exon 14 (METex14) skipping non–small cell lung cancer (NSCLC) with a manageable safety profile and few treatment discontinuations. Meaningful clinical activity was observed across age groups, including in patients ≥80 years, and also effective

regardless of whether prior therapies were received. These two aspects are very relevant in clinical practice due to the advanced age of patients with METex14 skipping NSCLC and the potential concerns regarding sequencing of tepotinib. Intracranial disease control was achieved in most evaluable patients, indicating that tepotinib may be beneficial for intracranial disease control[20].

Capmatinib, a highly potent and selective inhibitor of the MET receptor, has shown in vitro and in vivo activity in cancer models with various types of MET activation. GEOMETRY investigated the activity of capmatinib in patients with advanced NSCLC with a MET exon 14 skipping mutation or MET amplification.

In the GEOMETRY mono-1 phase 2 trial of capmatinib, the response rate by independent review was 41% (95% CI, 29 to 53), with a median duration of progression-free survival of 5.4 months (95% CI, 4.2 to 7.0) among 69 patients with pretreated disease; among 28 patients who had not received previous treatment, the response rate was 68% (95% CI, 48 to 84), with a median duration of progression-free survival of 9.7 months (95% CI, 5.5 to 13.9) and activity seen in patients with brain metastases.1

Thus, capmatinib showed substantial antitumor activity in patients with advanced NSCLC with a MET exon 14 skipping mutation, particularly in those not treated previously. The efficacy in MET-amplified advanced NSCLC was higher in tumors with a high gene copy number than in those with a low gene copy number. Low-grade peripheral edema and nausea were the main toxic effects.[21].

Savolitinib is a highly selective oral MET inhibitor, which has been used in various malignancies including gastric and papillary renal cell carcinoma and NSCLC. The Phase Ib TATTON study in patients with advanced EGFRmutant NSCLC with MET amplification reported an ORR of 44% (95% CI, 22–69) in the 18 patients who received the combination of savolitinib and osimertinib. Other ongoing trials evaluating this combination include SAVANNAH (NCT03778229) and ORCHARD (NCT03944772).A phase II study evaluating the safety and efficacy of savolitinib in METex14 showed an ORR of 49.2% (95% CI, 36.1–62.3) with a disease control rate of 93.4% and a duration of response of 6.9 months (95% CI, 4.9–12.5). The median PFS was reported to be 6.8 months (95% CI, 4.2–9.6). With respect to safety, grade 3 and higher adverse events occurred in 41.4% of the patients, resulting in treatment discontinuation in 14.3%. The common adverse events noted were edema, nausea, hypoalbuminemia, deranged liver functions, hypersensitivity, and vomiting.[22].

Despite the advances in this field of target therapy for METex14 NSCLC co-occurring genetic alterations are frequent and their potential impact to therapeutic sensitivities has not yet been fully described.

METex14 mutations frequently co-occur with other potential driver oncogenes with differing patterns of clonal dominance observed among the drivers.

Obtaining a full understanding of co-occurring alterations with METex14 could be crucial in providing novel insights to increase understanding of treatment sensitivity and resistance in METex14 NSCLC, and thus, guide future therapeutic strategy development.

Co-occuring genetic alterations with an oncogene driver can associate with clinical response or resistance. METamp was found as the most frequent co-occuring alterations in METex14 NSCLC, at approximately 8%.[16].

This is associated with high METex14 variant allele frequency (VAF) and potential targeted therapy benefit, whereas MET kinase domain secon-

dary mutations are associated with targeted therapy resistance. When METex14 co-occurs with EGFR and ERBB2 mutations, METex14 most commonly serves as a nondominant subclone and is a potential mediator of EGFR TKI resistance. Emerging novel resistance mechanisms to MET TKI, such as RET fusion were also found, which warrant future translational and therapeutic studies to overcome resistance[16].

As mentioned above MET alterations are also found to be an important mechanism of acquired resistance to another oncogenic pathway treated with targeted therapy as in patients with ALK, ROS1, KRAS and EGFR alterations.

The combination of MET TKI and EGFR TKI may be a potential solution for MET-driven EGFR TKI resistance.

Trials such as INSIGHT[23] and TATTON[24] evidenced the clinical benefits of tepotinib plus gefitinib and osimertinib plus savolitinib, respectively, in patients with NSCLC. Based on these results the combination of tepotinib plus osimertinib is now being investigated in patients with EGFRm NSCLC with MET amplification in INSIGHT 2[25].

Inicial analysis of INSIGHT 2 has been recently published showing promising activity in these patientes. ORR was 54,5% in patients with ≥ 9months´ follow-up and 45,8% in patients with ≥ 3months´ follow-up. The study data indicate that FISH MET GCN of ≥ 5 and/or MET/CEP7 ratio of ≥ 2 in TBx samples define a METamp-positive population with an original sensitizing EGFR mutation that derives clinical benefit from the combination of tepotinib plus osimertinib. The safety profile of the combination was consistent with the known safety profiles of tepotinib and osimertinib.[25]

Due to groundbreaking developments and continuous progress, the treatment of advanced and metastatic NSCLC has become an exciting field, including in RET and MET patients. However, in order to fully impact the clinical outcome in lung cancer, a number of questions remain to be further addressed. These include optimal patient selection, predictive biomarker development, better strategies of single agent or in combination with other targeted agents, and resistance mechanisms. With concerted efforts in translational and clinical development of the RET and MET targeting agents to continue, certainly stronger impact on lung cancer clinical outcome will be achieved as happened in other known and more familiar oncogenic alterations.

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