THE EFFECT OF CAPMATINIB FOR THE TREATMENT OF MET AMPLIFIED NON SMALL CELL LUNG CANCER

Dr.R. DINESHKUMAR*[1], CHRISTINA PONNACHEN[2], BIVISHYA R[2], JORMY JOHN[2]

[1]Assistant Professor, [2]Doctor of Pharmacy Students
Department of Pharmacy Practice,
The Erode College of Pharmacy and Research Institute, Erode, Tamilnadu, India.

ABSTRACT

PRINCIPLE:
To assess the effect of capmatinib, a potent selective inhibitor of MET receptor among patients with non-small cell cancer (NSCLC) with MET dysregulation among patients with non–small-cell lung cancer (NSCLC), MET amplifications occur in 1 to 6%.

METHODS:
A multiple-cohort, phase 2 study was conducted evaluating capmatinib in patients with *MET*-dysregulated advanced NSCLC. Patients were assigned to cohorts on the basis of previous lines of therapy and *MET* status (*MET* exon 14 skipping mutation or *MET* amplification according to gene copy number in tumour tissue). Patients received capmatinib (400-mg tablet) twice daily.
The primary goal was to find the safety and efficacy of the drug, also to evaluate antitumour activity.

RESULTS:
The total date was collected and among patients with NSCLC with MET dysregulation, overall response showed improved survival within these patients. The most frequently reported adverse events were peripheral edema (in 51%) and nausea (in 45%); these events were mostly of grade 1 or 2.

CONCLUSION:
From the collected, we have concluded that capmatinib showed substantial antitumour activity in NSCLC with MET dysregulation. Low-grade peripheral edema and nausea were the main toxic effect.

KEYWORDS: Capmatinib, Non small cell lung cancer, MET amplication.

INTRODUCTION

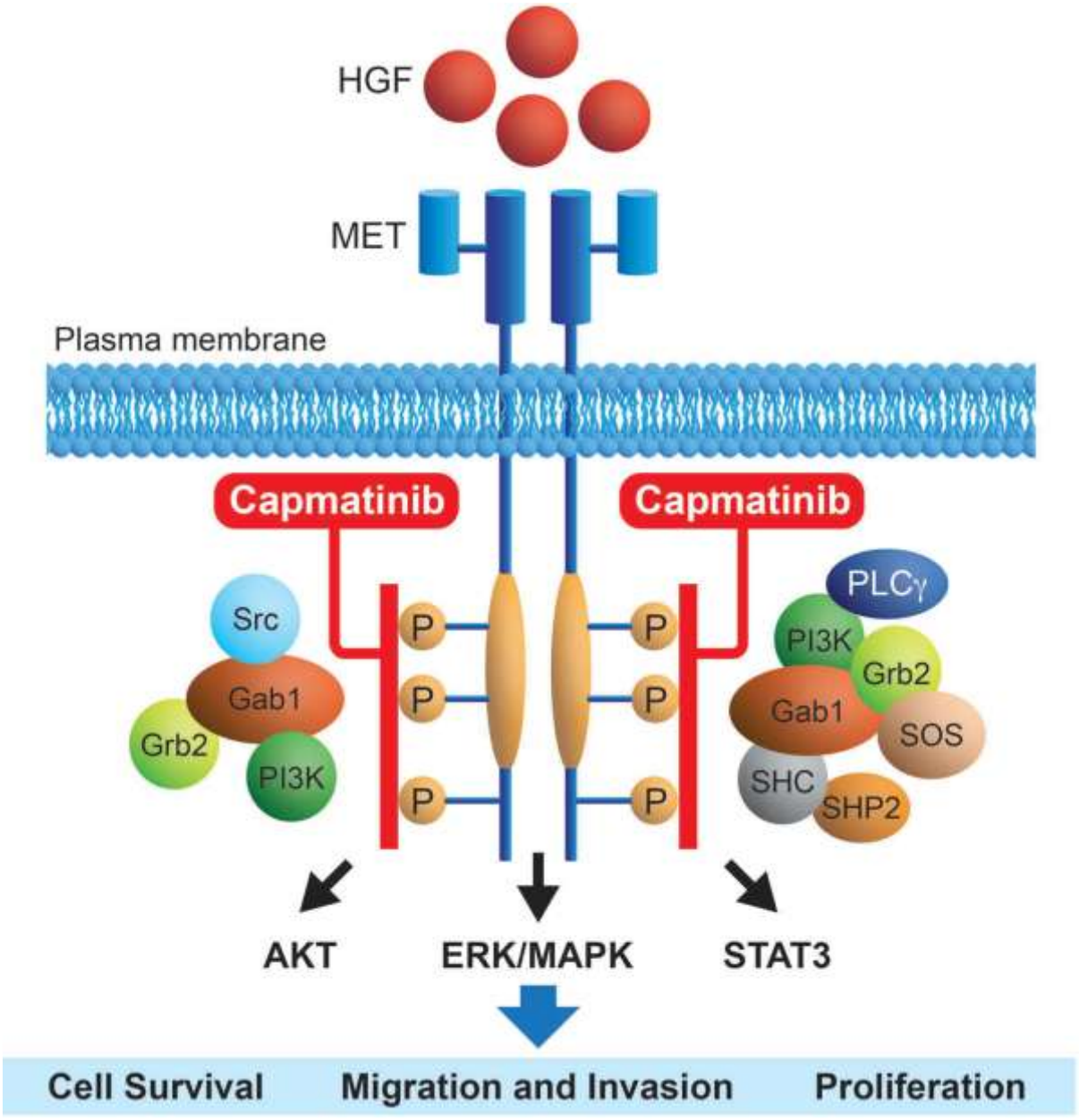
Worldwide, Lung cancer is expected to affect over 2.5 million people worldwide in 2020, with over 1.9 million deaths. NSCLC (non-small cell lung cancer) accounts for over 85% of all lung cancer cases. The most common type of lung cancer, non–small cell lung cancer (NSCLC), is usually very serious, with about a third of patients presenting with advanced stage III or IV illness and a very dismal prognosis.[1,2]

Adenocarcinoma, large-cell carcinoma, squamous cell carcinoma, and NSCLC not otherwise described are the most prevalent histological subtypes of NSCLC..[3,4] Patients with advanced lung cancer with non-squamous histology or squamous histology with clinical features that indicate a higher probability of a driver mutation, patients with advanced lung cancer with non-squamous histology or squamous histology with clinical features that indicate a higher probability of a driver mutation should be routinely tested GFR mutations, ALK translocations, ROS1 rearrangements, and BRAF mutations, because valid and approved targeted therapies are available for these patients.[5,6] Curative treatment of NSCLC remains a challenge because more than 60% of cases are diagnosed at a locally advanced or metastatic stage (III or IV), when surgical resection may no longer be a viable option.[6,7] Activation of the MET pathway is associated with many cancers and can be caused by overexpression, gene amplification, and *MET* exon 14 skipping mutations, which can come from point mutations or from insertions or deletions.[1,7] The shorter exon 14–spliced protein has increased stability, which increases MET signaling.[8] *MET* exon 14 skipping mutations occur in approximately 3 to 4% of patients with non–small-cell lung cancer (NSCLC),typically in the absence of other driver mutations and are associated with a poor prognosis. [7,9] *MET* amplification occurs in 1 to 6% of patients with NSCLC.[10,11]. These drugs include nonselective type 1a inhibitors (e.g., crizotinib) and selective type 1b inhibitors (e.g., tepotinib, savolitinib, and capmatinib).[12,13,14]

Capmatinib preclinical development

Capmatinib is highly selective for MET compared with other kinases, as demonstrated by testing over large panels of kinases in biochemical and binding assays[15,16]. Using a selectivity screening platform of 442 kinases and disease-associated variants, capmatinib bound to only nine kinases (including wild-type MET and two MET variants: MET M1250T and Y1235D). Additionally, binding affinities of capmatinib for both wild-type and the two variants of MET were several magnitudes higher than

those for other kinases, which corroborates the selectivity for MET binding[7]. Capmatinib effectively inhibits MET downstream signalling and consequently hinders tumor growth and progression [17]. Cancer cell growth in MET-dependent cancer cell lines was blocked by capmatinib treatment, and hepatocyte growth factor-stimulated cell migration was decreased by capmatinib in a concentration-dependent manner1[8]. MET signalling is known to mediate cell resistance to apoptosis.[1,12] Treatment with capmatinib induced apoptosis in MET-dependent cell lines, as shown by increased levels of fragmented DNA and by poly (ADP-ribose) polymerase activation[1,3]. In MET-dependent tumor cell lines, capmatinib inhibited the phosphorylation of downstream effectors of the MET pathway, such as ERK1/2, AKT, FAK, GAB1, and STAT3/5, and inhibited tumor cell proliferation and migration. Capmatinib has also demonstrated *in vivo* activity against MET-driven tumors in preclinical models.[6] MET inhibition by capmatinib was dose dependent and this was sustained over time[4,5,6]. Furthermore, capmatinib treatment demonstrated anti-tumor activity in xenograft models, with tumor regression shown in some of these models [6,7] including in tumors. This included the regression of tumors in a patient-derived xenograft model with *MET*ex14.



We report the results of the GEOMETRYmono-1 study, which investigated the activity of capmatinib in patients with advanced NSCLC with a *MET* exon 14 skipping mutation or *MET* amplification. The study included patients who had received treatment previously and patients who had not.[8,9]

METHODS

A prospective, international, open label, multiple-cohort, phase 2 study was done to evaluate the safety and efficacy of capmatinib in patients with advanced NSCLC with a *MET* exon 14 skipping mutation or *MET* amplification. The study aims to assess the antitumor activity and side-effect profile of 400 mg of capmatinib given orally once daily until disease progression, consent withdrawal, or adverse events leading to discontinuation.

Eligible patients were adults (≥18 years of age) with stage IIIB or IV NSCLC with any histologic features, without an activating epidermal growth factor receptor mutation or anaplastic lymphoma kinase fusion, and with at least one measurable lesion, defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. *MET* status was determined by a central Laboratory. Patients were assigned to cohorts on the basis of *MET* status and previous lines of therapy. In cohorts of patients with a *MET* exon 14 skipping mutation, enrolment was allowed regardless of concurrent *MET* amplification; however, no concurrent *MET* exon 14 skipping mutation was permitted in cohorts of patients with *MET* amplification.

The study included five cohorts (with cohorts 1 and 5 having sub cohorts) for the assessment of efficacy on the basis of prespecified statistical hypotheses; two expansion cohorts (6 and 7) were added to generate supportive clinical evidence. Patients with brain metastases who had had no increase in glucocorticoid dose within the 2 weeks before enrolment were eligible for enrolment if their condition was judged by the investigator to be neurologically stable. Oral capmatinib at a dose of 400 mg twice daily was administered under fasting conditions in cohorts 1 through 5 and was administered without fasting restrictions in cohorts 6 and 7.

RESULTS

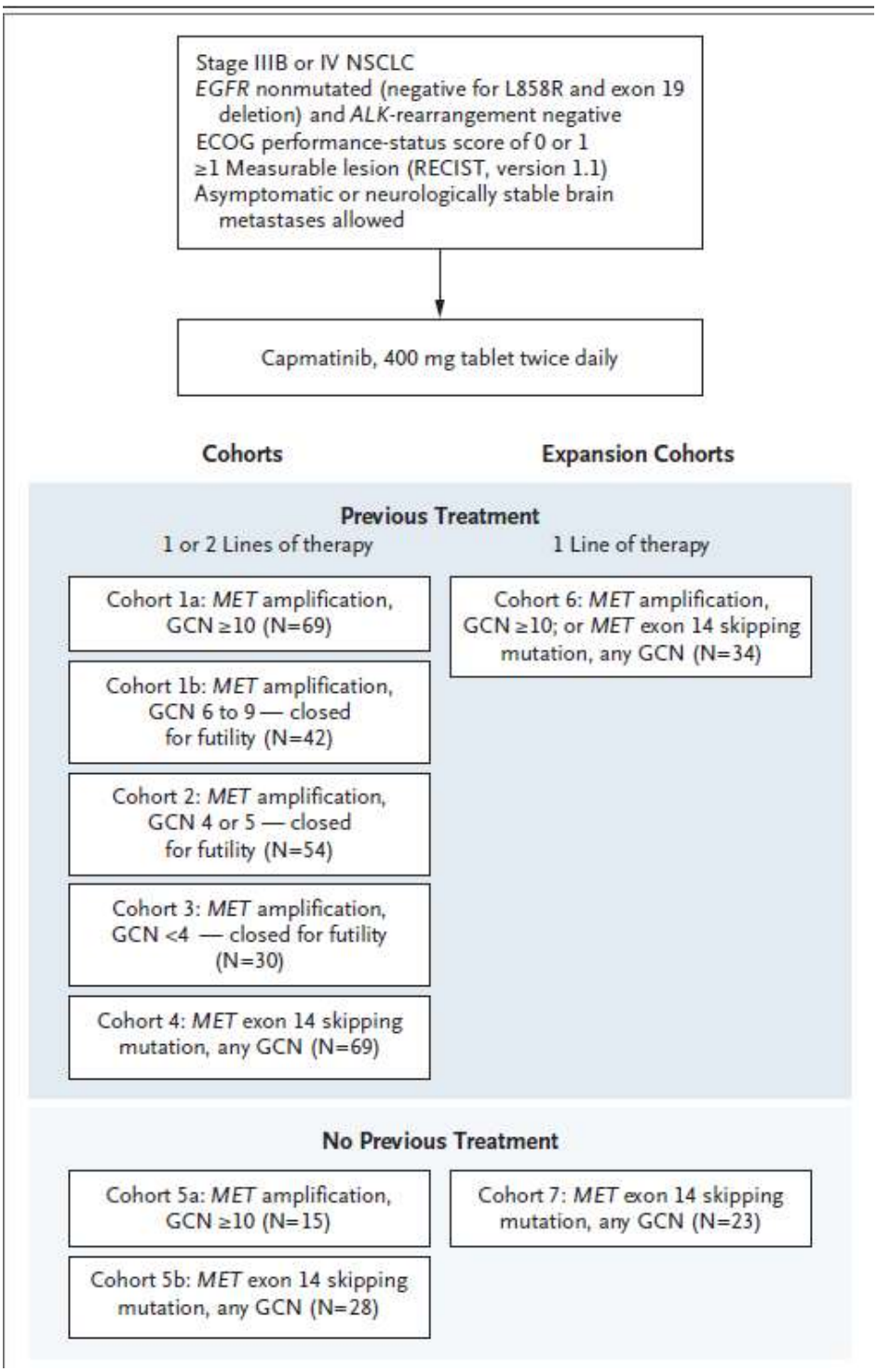
A total of 364 patients with advanced NSCLC were enrolled in the study. Across cohorts 1 through 5, a total of 97 patients had a MET exon 14 skipping mutation and 210 had MET amplification. The characteristics of these patients at baseline are described in Table1. Previously treated patients who were enrolled in cohorts 1 through 4 had received one or two lines of therapy previously, and patients in cohorts 5a and 5b had not received treatment previously. The median age of the patients was slightly higher in cohorts involving patients with a MET exon 14 skipping mutation
(71 years) than in most of the cohorts involving patients with MET amplification (60 to 70 years). Patients with a MET exon 14 skipping mutation were more likely to be women and were more likely to have never smoked than were patients with MET amplification. Cohort 6 comprised 34 patients: 3 patients with MET-amplified NSCLC with a gene copy number of at least 10 and 31 patients with NSCLC with a MET exon 14 skipping mutation who had received one previous line of therapy. As of the data-cut off point (December 15, 2020), a total of 23 patients, all of whom had NSCLC with a MET exon 14 skipping mutation and had not received treatment previously, had been enrolled in cohort 7; no efficacy data were available for this cohort.

EFFICACY

Among patients with advanced NSCLC with MET amplification, the primary end point of overall response, as assessed by the independent review committee, was observed in 12% of those (95% CI, 4 to 26) who had tumor tissue with a gene copy number of 6 to 9, in 9% of those (95% CI, 3 to 20) who had tumor tissue with a gene copy number of 4 or 5, and in 7% of those (95% CI, 1 to 22) who had tumor tissue with a gene copy number of less than 4. Therefore, these cohorts were closed for futility at the interim analysis. The median progression-free survival, as assessed by the independent review committee, was as follows: among patients who had tumor tissue with a gene copy number of 6 to 9, the median progression-free survival was 2.7 months (95% CI, 1.4 to 3.1); among those who had tumor tissue with a gene copy number of 4or 5, it was 2.7 months (95% CI, 1.4 to 4.1); and among those who had tumor tissue with a gene copy number of less than 4, it was 3.6 months (95% CI, 2,2 to 4.2). Capmatinib showed activity in patients who had tumor tissue with a gene copy number of at least 10; however, the overall response was lower than the prespecified threshold for clinically relevant activity. Among patients who had NSCLC with MET amplification and tumor tissue with a gene copy number of at least 10, a total of 66 previously treated patients (96%; cohort 1a) and all 15 patients who had not received treatment previously (cohort 5a) had discontinued treatment as of the data-cut-off date (Table S5). Discontinuation was due primarily to progressive disease. Results regarding the 3 patients who had NSCLC with MET amplification and tumor tissue with a gene copy number of at least 10 who had been enrolled in cohort 6.

Safety profile of capmatinib

The safety of capmatinib as a single agent in advanced NSCLC was assessed in the multiple cohort phase 2 trail. Most treatment-related adverse events (AEs) were grade 1 or 2 in these trials [43,44]. The most frequent AEs (≥20%) in the phase 1 study were nausea, peripheral edema, vomiting, decreased appetite, fatigue, and increased blood creatinine levels. Study-drug related AEs in ≥ 10% of patients were nausea, vomiting, peripheral edema, fatigue, decreased appetite, and diarrhea. Both peripheral edema and gastrointestinal toxicity seem to occur as AEs associated with the MET inhibitor class [48]. Indeed, gastrointestinal AEs are among the most common side effects observed with tyrosine kinase inhibitors, and several management strategies have been developed and applied across different types of cancer with diverse drugs. Death from causes other than advanced NSCLC occurred during treatment in 13 patients (4%). The reported causes were atrial fibrillation, hepatitis, pneumonia, organizing pneumonia, bacterial pneumonia, pneumonitis, respiratory distress, sepsis, septic shock, sudden death, and assisted suicide (in 1 patient each) and cardiac arrest (in 2 patients). Only one death (from pneumonitis) was suspected to be related to capmatinib. Nevertheless, awareness of all possible AEs and close monitoring and management, according to the clinical practice protocols in place at the different institutions, can make a difference in improving patient tolerability.



DISCUSSIONS

Standard therapy, including immunotherapies, have a dismal prognosis for patients with malignancies that contain a MET exon 14 skipping mutation. [2,4,5] Despite the fact that numerous testing approaches are capable of detecting MET gene changes, the complexity and diversity of METex4 mutations resulting to constitutive activation of MET necessitates testing methods with great sensitivity.[6,7.] Early, broad molecular testing is recommended to select the optimal treatment for each patient [6]. Upfront, multiplex molecular profiling (including NGS) could avoid testing delays and tissue shortages associated with sequential testing and facilitate early, appropriate upfront targeted treatment. Most patients with NSCLC are diagnosed with advanced metastatic disease Many of these individuals may have difficult-to-biopsy tumours, tiny samples, and biopsies with low tumour material. Multiple gene changes can be detected with NGS from a single sample, avoiding tissue depletion. Furthermore, modelling analysis of newly diagnosed patients with metastatic NSCLC demonstrated that NGS was associated with the same (versus hotspot panel) or shorter (versus exclusionary and sequential testing) time-to-test results, with lower testing costs than sequential, exclusionary, and hotspot panel testing. Prior to the approval of additional MET inhibitors, crizotinib was recommended for patients with *MET*ex14; crizotinib is indicated for the treatment of patients with advanced NSCLC harbouring *ALK* translocations or *ROS1* rearrangements. Data from the PROFILE 1001 clinical trial showed that the ORR with crizotinib treatment in patients with *MET*ex14 was 32.3%. However,

one important aspect to consider is the poor blood–brain barrier penetration of crizotinib, which may limit its effectiveness in patients with brain metastases.[8,9,10]
Capmatinib's efficacy is significant because these patients are typically elderly[3,5] and thus more difficult to treat due to a higher risk of adverse consequences from first-line multidrug regimens.
Capmatinib is a potent MET-selective TKI that is approved for the treatment of NSCLCs that harbour MET exon 14 skipping.[11,12,13]
Several other METS TKIs have also exhibited robust clinical activity in MET-altered NSCLC.MET TKIs are divided into several classes on the basis of receptor binding mechanics. Type I inhibitors (e.g., capmatinib and crizotinib) bind the receptor in its active conformation whereas type II inhibitors target the receptor's inactive state. Type I binding relies on critical interactions with the MET receptor hinge region and sticking interactions between the TKI and the Y1230 residue in the kinase activation loop.

Capmatinib led to clinically meaningful antitumor activity in patients with NSCLC with a *MET* exon 14 skipping mutation who had not received treatment previously (overall response in 68% of the patients and disease control in 96%).[14,15] Although these efficacy results need confirmation in a larger population, the results are similar to those reported with effective, established targeted therapies for NSCLC.30-32 Expansion cohort 7 (which includes patients with NSCLC with a *MET* exon 14 skipping mutation who had not received treatment previously) is ongoing.
The antitumor activity and duration of response that we observed showed up to be independent of the type of MET mutation leading to MET exon 14 skipping and independent of the co-occurrence of MET amplification, implying that off-target resistance mechanisms may play a role based on the available data. Molecular characterization of larger cohorts involving patients with tumour with a *MET* exon 14 skipping mutation might elucidate such mechanisms. These observations support the need for broad molecular profiling before the decision point regarding first-line therapy. Regarding intrinsic resistance, a recent preliminary analysis of patients with *MET*ex14 NSCLC who were treated with MET inhibitors demonstrated that the absence of either MET protein expression or the activation of the RAS pathway at baseline had negative predictive value for treatment response, with no responses reported in patients with either undetectable MET protein expression (by mass spectroscopy; $n = 6$) or a concordant RAS pathway mutation.[16,17,18]
Capmatinib's known safety profile was validated in our study. 17 The majority of side effects were grade 1 or 2, predictable, and reversible with dose adjustment. Peripheral oedema, nausea, vomiting, and an elevation in blood creatinine level were the most commonly reported side effects of capmatinib treatment. Peripheral oedema and gastrointestinal toxic effects are known side effects of MET inhibitors.[19,20]
The reversible increase in the creatinine level was probably due to inhibition of renal transporters multidrug and toxic extrusion protein
1 and 2-K (MATE1 and MATE2-K), because capmatinib is an inhibitor of these transporters (unpublished data). Approximately 10 to 40% of the serum creatinine is cleared by means of active tubular secretion by renal transporters such as MATE and organic anion transporter, in addition to renal glomerular filtration.

CONCLUSION

The discovery of novel relevant targets remains a top priority, inspired by the major breakthrough of targeted medicines in treating lung malignancies. Available evidence has demonstrated that patients with *MET*ex14 benefited from MET-targeted therapy with capmatinib, with preliminary evidence of activity against brain metastases in patients with NSCLC. These results, therefore, support the inclusion of *MET*ex14 testing in clinical panels to ensure that the benefit of this medicine that has been recently approved by the US FDA is extended to the appropriate patients. Currently, *MET*ex14 has the best predictive value for response to MET inhibitors, including capmatinib. Capmatinib therapy showed efficacy in patients with NSCLC with a *MET* exon 14 skipping mutation. These results and the safety profile, involving mainly low-grade and reversible adverse events, suggest that capmatinib may be a new therapeutic option in patients with advanced NSCLC with a *MET* exon 14 skipping mutation.

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