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Long-term efficacy of immune checkpoint inhibitors in non-small cell lung cancer patients harboring \textit{MET} exon 14 skipping mutations

Drugs: Pembrolizumab, Nivolumab, Atezolizumab

Objective:

• To investigate the characteristics of patients with NSCLCs harboring MET exon 14 mutations and their response to immune checkpoint inhibitors (ICI) in Japan

Design:

• Single-site, retrospective NSCLC study looking at patient cases from 2010-2019 at the Saitama Cancer Center in Japan
• Sought to determine efficacy of ICI in MET exon 14 skipping mutation positive NSCLC patients
• Results analyzed according to tumor proportion scores (TPS) of Programmed Cell Death Ligand 1 (PD-L1, predictor of ICI effectiveness)

Population:

• 1954 NSCLC patients were screened
• 68 (3.5%) confirmed positive for MET exon 14 skipping mutation
• Median age was 73 years; 63.2% males, 52.9% former smokers
• Tumor histology: 85.3% adenocarcinoma, 7.4% squamous cell carcinoma, 5.9% pleomorphic carcinoma
• Tumor staging: 55.9% stage I/II, 35.2% recurrent/metastatic disease
• Splice site mutations: 54.4% Donor splice-site mutations, 2.9% acceptor splice-site mutations, 2.9% EGFR mutations
• 24 patients were assessed for PD-L1 expression
• 7 patients received ICIs, 5 of whom were assessed for PD-L1 expression
• Of these seven given ICI monotherapy:
  – 4 had strong PD-L1 expression (>50%) and were treated with pembrolizumab
  – 1 had intermediate PD-L1 expression (1-49%) and was treated with nivolumab after first-line platinum doublet
  – 2 with weak PD-L1 expression (unknown) received either atezolizumab or nivolumab after first-line platinum doublet

Effectiveness Results:

• Responses: Objective Response Rate 42.9%
  – 3 with Partial Response
  – 3 with Progressive Disease
  – 1 Not Evaluated
• Median progression-free survival (PFS) 24.7 months, median Overall Survival (OS) not assessed due to insufficient number of events
  – Patients with Progressive Disease died
  – Patients with Donor splice-site mutations benefited from ICI for > 1 year
  – Patients with Acceptor splice-site mutations had no benefit from ICI

Safety Results

• No severe immune-related adverse events in this study

Strengths

• The study suggests that those with MET exon 14 skipping mutation may benefit from ICI
• Specifically, MET exon 14 skipping mutated patients with Donor splice-site mutations demonstrated long-term response to ICI treatment
• First research to discuss MET exon 14 skipping mutation and ICI effects

Weaknesses

• Single-center, retrospective study with small sample size introduces issues around patient population selection; additionally few patients included had different numbers of treatment lines
• Non-controlled trial limits comparison to other potential therapies
• Not enough samples to also assess tumor mutation burden (TMB)
• No patients received molecular agents targeting MET exon 14 skipping mutations which are first-line

Conclusion

• ICI is a potential treatment option for NSCLC patients harboring MET exon 14 skipping mutations and high PD-L1 expression, especially those with Donor splice-site mutations
• Larger, prospective, controlled trials are needed to further evaluate these potential benefits

LINK TO ARTICLE
Crizotinib in Patients With MET-Amplified NSCLC

Drug: Crizotinib | NCT 00585195

Objective:
• To determine the safety and effectiveness of tepotinib, a selective MET inhibitor, in patients with MET exon 14-altered non-small cell lung cancer (NSCLC).

Design:
• Multicenter, open-label, non-controlled sub-analysis of PROFILE 1001, an ongoing phase 1 study evaluating use of crizotinib in heavily pre-treated patients with ROS1-mutated NSCLC
• Patients were confirmed to have MET amplification per MET/CEP7 ratio ≥1.8 by local testing (such as Fluorescence In-Situ Hybridization (FISH))

Population:
• Advanced or metastatic NSCLC with MET-amplification: 38 patients included
• Median age 66.5 years, 44.7% female
• Tumor histology: 96.8% adenocarcinoma, 5.3% squamous
• Former smokers: 84.2%
• Prior treatments: 18.4% of patients previously untreated; 81.6% of patients with 1 or more prior therapy

Effectiveness Results:
• Objective response rate (ORR) 28.9% (5.3% complete response, 23.7% partial response, 28.9% stable disease, 21.2% disease progression, 13.2% early death, 7.9% indeterminate)
• Median duration of response (DOR) 5.2 months
• Median progression-free survival (PFS) 5.1 months
• Median overall survival 11 months
• Clinically meaning results seen in patients with high MET amplification (MET/CEP7 ratio ≥4), with median ORR 38%, median DOR 5.2 months, median PFS 6.7 months
• Patients previously treated with erlotinib had EGFR-activating mutations and did not respond to crizotinib; other known mutation drivers of cancer were found in the low- and medium-amplification groups

Safety Results:
• Common adverse effects: similar to those reported previously for patients with ALK- and ROS1-rearranged NSCLC
• Adverse effects associated with dose reductions (n=9): elevated liver enzymes, bradycardia, diarrhea, dizziness, prolonged QTc interval, decreased neutrophil count, vomiting
• Adverse effects leading to discontinuations (n=4): interstitial lung disease, cardiac failure, elevated liver enzymes

Strengths:
• Outcomes are further broken down by level of MET amplification. This provides clearer definition of what MET amplification testing parameters should be (MET/CEP7 ratio) to identify what specific MET amplified patient populations would benefit from crizotinib treatment

Weaknesses:
• Non-controlled trial: limits comparisons to other potential therapies and could introduce bias as investigators know what patients are receiving
• Small sample size: overall response rates may not be clinically meaningful because of non-significantly different statistical differences
• Some patients with high MET amplification still had no objective response, suggesting that MET/CEP7 ratios are not guaranteed to predict responses
• MET activation is associated with programmed death ligand 1 (PD-L1) expression, but because this study was started many years ago, this information is not available for all patients

Conclusion:
• Crizotinib is a possible treatment option in patients with high MET amplification (MET/CEP7 ratio ≥4) and no other cancer-causing mutations, who are either newly diagnosed or have been previously treated
• Data confirm the need to identify different diagnostic tests to determine the level of MET expression and identify other cancer-causing mutations, in order to identify the patients who would benefit most from crizotinib treatment

LINK TO ARTICLE
**MET exon 14 skipping mutation positive non-small cell lung cancer: Response to systemic therapy**

**Drugs:** Crizotinib, platinums, immunotherapy

**Objective:**
- To analyze prevalence, biology, and patient responses in those treated with systemic therapy who harbor METex14 mutated NSCLC and to determine if treatment response predictions can be made based off of molecular signatures or co-mutations.

**Design:**
- Retrospective analysis of 1934 patients with NSCLC treated with systemic therapy

**Population:**
- 41 patients identified with METex14 skipping mutation
  - 33 patients treated with crizotinib (24), platinum-based (11), or immunotherapy (14)
- Median age of 77 years
- Histology: adenocarcinoma (83%), squamous cell carcinoma (12%), sarcomatoid (5%)
- Co-mutations: none (59%), TP53 (22%), BRCA2 (7%)
- Presence of brain metastases: at diagnosis (5%), during course of disease (7%)

**Effectiveness:**
- Crizotinib (n=24): partial response (21%), stable disease (33%), not evaluable (21%); disease control rate = 68%
- Platinum-based therapy (n=11): partial response (9%), stable disease (64%), not evaluable (9%); disease control rate = 80%
- Immunotherapy (n=14): partial response (7%), stable disease (43%), not evaluable (29%); disease control rate = 70%
- Median overall survival: 15.4 months

**Safety:**
- 5 patients stopped crizotinib due to extreme fatigue, hepatotoxicity and cardiotoxicity

**Strengths:**
- Data collected was from real life application of each treatment rather than in controlled clinical trial setting

**Weaknesses:**
- Small cohort of patients along with limitations of data analyzed retrospectively rather than data collected from a prospective study should be considered

**Conclusion:**
- Modest response seen in the three systemic treatments. Correlation between co-mutations and treatment response was not established in this study.

[LINK TO ARTICLE]
Dramatic intracranial response to tepotinib in a patient with lung adenocarcinoma harboring MET exon 14 skipping mutation

Drug: Tepotinib

Objective:
- To report a case of a significant response to tepotinib in a patient with METex14 NSCLC with symptomatic brain metastases

Population:
- 75-year-old female with METex14 NSCLC with brain metastases
- Received tepotinib 500mg once daily

Efficacy Results:
- Headache and loss of appetite quickly disappeared 10 days after starting tepotinib
- Brain MRI demonstrated that all lesions were too small to measure after being on tepotinib for 23 days
- Received tepotinib for 2 months without progression

Safety Results:
- Nausea

Strengths:
- Showed that a patient with multiple symptomatic brain metastases was able to quickly and dramatically respond to tepotinib

Weaknesses:
- Demonstrated safety and efficacy of tepotinib in only one patient
- Need a larger study to better understand the role of tepotinib in METex14 NSCLC with multiple symptomatic brain metastases
- No further information (ie grade, severity, management) provided for adverse effect experienced while on tepotinib

Conclusion:
- Tepotinib demonstrated rapid antitumor activity and provided symptomatic relief in a patient with METex14 NSCLC with brain metastases

Responses to crizotinib and cabozantinib in patient with lung adenocarcinoma harboring mesenchymal-epithelial transition factor exon 14 skipping mutation

Drugs: Crizotinib, Cabozantinib

Objective:
- Limited data are available on the responses to crizotinib and cabozantinib in MET-altered NSCLC, especially in sequence.

Design:
- Case report of single patient

Report:
- 77 year old woman diagnosed with lung adenocarcinoma metastatic to bones and adrenal gland
- MET exon 14 skipping mutation identified
- First-line crizotinib 250mg twice daily initiated
  - Partial response after 2 months
  - Progression after 8 months
- Second-line cabozantinib 60mg PO daily initiated
  - Grade 2 hand foot syndrome, prompting dose reduction to 40mg daily
  - Partial response after 2 months
  - Ongoing response at time of publication, >4 months
- Overall survival >12 months at time of publication

Conclusion:
- Although other studies have validated the effectiveness of crizotinib for MET exon 14-altered NSCLC, the effectiveness of cabozantinib in this population is less well-established. This patient experienced a favorable response to second-line cabozantinib (a type II inhibitor), suggesting this may be an option after progression on type 1 inhibitors like crizotinib.
A Phase 2 Study of Capmatinib in Patients With MET-Altered Lung Cancer Previously Treated With a MET Inhibitor

Drug: Capmatinib | NCT ID: NCT02750215

Objective:
- To observe the objective response rate in patients treated with capmatinib who were previously treated with a MET inhibitor.

Design:
- Open-label, investigator-initiated, single-institution, single-arm phase 2 trial
- 20 patients given 400 mg capmatinib twice daily in 21-day cycles

Population:
- Stage IIIb-V NSCLC with MET amplification or METex14 skipping with past MET TKI treatment
- Median age 70 years
- Tumor histology: adenocarcinoma (80%); squamous (10%); sarcomatoid or poorly differentiated (10%)
- MET alteration: amplification (25%); METex14 skipping (75%)
- Number of prior lines of therapy: 1 (45%); 2 (15%); ≥3 (40%)

Effectiveness Results:
- Disease control rate (DCR): 80% [objective response (10%) + stable disease (70%)]
- Median progression-free survival: 5.5 months
- Median overall survival: 11.3 months

Safety Results:
- Common adverse effects: Grade 1 and 2 lower extremity swelling (65%), Fatigue (35%), muscle pain (20%)
- Serious adverse effects (grade ≥3): pancreas lipase enzyme elevation (15%), pancreas amylase enzyme elevation (10%), inflammation of lungs (10%), liver injury (5%)

Strengths:
- Including patients who all were treated with crizotinib helps look into that treatment’s resistance mechanism with more precision

Weaknesses:
- Small cohort of patients along with the lack of tumor biopsy makes it difficult to analyze resistance mechanisms

Conclusion:
- More data is needed to elucidate resistance mechanisms of TKI therapies along with what therapies are appropriate after resistance takes place. Current data shows that capmatinib’s highly selective properties make it a better first-line option in MET altered NSCLC.

LINK TO ARTICLE
The Clinical Impact of Capmatinib in the Treatment of Advanced Non-Small Cell Lung Cancer with MET Exon 14 Skipping Mutation or Gene Amplification

Drug: Capmatinib

Objective:
• To determine the safety and effectiveness of tepotinib, a selective MET inhibitor, in patients with MET exon 14-altered non-small cell lung cancer (NSCLC).

Design:
• Multicenter, open-label, non controlled phase 2 study
• Results analyzed according to liquid biopsy or tissue biopsy used to confirm MET mutation

Population:
• Advanced or metastatic NSCLC with MET exon 14 skipping mutation
• Median age 74 years
• Tumor histology: 90% adenocarcinoma; 7% squamous
• Presence of brain metastases: 11%
• Prior treatments: 43% of patients previously untreated; 33% of patients with 1 prior therapy; 23% with 2 or more prior therapies

Effectiveness Results:
• Objective response rate 46% (all partial responses, no complete responses)
• Median duration of response 11.1 months
• Median progression-free survival 8.5 months
• Median overall survival 17.1 months

Safety Results:
• Common adverse effects: lower extremity swelling (63%), nausea (26%), diarrhea (22%)
• Serious adverse effects (grade ≥3): lower extremity swelling (7%), pancreas inflammation (3%), fluid in the lungs (3%)

Strengths:
• Patients included in the trial are representative of the broader population of patients who have MET-altered NSCLC

Weaknesses:
• Non-controlled trial: this limits comparisons to other potential therapies and could introduce bias because investigators know what patients are receiving.

Conclusion:
• Tepotinib yielded durable responses in a large portion of patients with MET exon 14-mutated NSCLC. Side effects were comparable to other MET-directed therapies and typically manageable.

LINK TO ARTICLE
Efficacy and Safety of Anti-PD-1 Immunotherapy in Patients With NSCLC With *BRAF*, *HER2*, or *MET* Mutations or *RET* Translocation: GFPC 01-2018

Drugs: Pembrolizumab, Nivolumab

Objective:

- To evaluate the efficacy and safety of immune checkpoint inhibitors (ICIs) in patients harboring *BRAF*, *HER2*, *MET*, or RET-translocated advanced NSCLC

Design:

- Retrospective, multicentered study aimed to evaluate ICI-treatment duration, progression-free survival (PFS), objective response rate, duration of response, and overall survival (OS)
- 107 total patients; 84 receiving nivolumab and 18 receiving pembrolizumab

Population:

- Metastatic NSCLC with *BRAF*, *HER2*, or *MET* mutations or RET translocations treated with anti-PD-1 therapy
- Median age of 65.5 years old
- Tumor histology: 94% adenocarcinoma, 3% squamous cell carcinoma, 2% large cell carcinoma
- Metastatic sites: 30% bone, 23% lung, 23% brain

Effectiveness:

- Partial response seen in 31.3% of total patients with a response rate of 36% seen in MET NSCLC patients
- Median duration of response: 15.4 months
- Median progression-free survival: 4.7 months
- Median overall survival: 16.2 months

Safety:

- 26% of patients experienced adverse events including colitis, pneumonitis, hypophysitis nephritis, hepatitis and anemia

Strengths:

- Study conducted with more patients in each subgroup than typically seen. This makes the data gathered more impactful when it's drawn from a larger cohort of patients

Weaknesses:

- Majority of patients PD-1L status was unknown
- Many patients received various treatments after ICI therapy was complete which impacts data analysis as not all patients received the same treatments

Conclusion:

- Response in patients with MET altered NSCLC treated with ICI therapy appeared to be higher in comparison with similar studies. Larger studies are still needed to better understand the role of ICI therapy in rarer cancer subtypes.

LINK TO ARTICLE
Intracranial Activity of Gefitinib and Capmatinib in a Patient with Previously Treated Non–Small Cell Lung Cancer Harboring a Concurrent EGFR Mutation and MET Amplification

Drugs: Gefitinib, Capmatinib

Objective:
• To provide an update on a case report of a patient with EGFR-mutated and MET-amplified advanced NSCLC with brain metastases and subsequent safety and efficacy of the combination of gefitinib and capmatinib.

Design:
• Case report

Population:
• 73-year-old male with EGFR-mutated and MET-amplified advanced NSCLC with brain metastases
  – Progressed on erlotinib plus MET inhibitor (was receiving through study/trial)
• Patient received combination of gefitinib 250mg once daily plus capmatinib 400mg twice daily

Efficacy Results:
• Significant improvement in gait and energy within weeks of starting combination therapy
• ECOG performance status improvement from 3 to 0
• Repeat scans after 6 weeks on dual therapy showed significant intracranial response
• Patient continued to receive combination therapy for more than 19 months with continued intracranial response

Safety Results:
• Grade 2 peripheral edema
• Transient grade 3 transaminase elevations
  – Decreased dose of capmatinib to 300mg twice daily

Strengths:
• Demonstrated ability of EGFR-mutated/MET-amplified NSCLC to respond to second-line EGFR/MET inhibitors, specifically those with CNS progression

Weaknesses:
• Demonstrated safety and efficacy of this combination in only one patient with brain metastases
• Need a larger study to better understand the role of gefitinib plus capmatinib in this setting

Conclusion:
• Utilizing a MET inhibitor with documented CNS penetration such as capmatinib combined with gefitinib produced a significant durable response in a patient with EGFR-mutated/MET-amplified NSCLC with brain metastases with manageable toxicity

LINK TO ARTICLE
Activity and bioavailability of tepotinib for leptomeningeal metastasis of NSCLC with MET exon 14 skipping mutation

Drug: Tepotinib

Objective:
- To determine how much tepotinib is present in cerebrospinal fluid (CSF) to better understand its ability to penetrate the blood brain barrier (BBB) and target leptomeningeal metastases.

Design:
- Case report

Population:
- 56-year-old male with METex14 NSCLC and leptomeningeal metastases
  - ECOG performance status = 4 (low)
- Received second line tepotinib 500mg once daily (first line cisplatin and pemetrexed)

Efficacy Results:
- After 14 days on tepotinib, performance status improved from 4 to 1
- Tepotinib concentrations demonstrated high rate of penetration into the brain
- Brain MRI after 14 days showed diminished leptomeningeal metastases
- After 5 months on tepotinib, patient’s disease progressed with new liver metastases

Safety Results:
- Side effects included grade 2 edema and low albumin

Strengths:
- First report of leptomeningeal metastases successfully treated with tepotinib
- Demonstrates ability for a patient with low performance status to tolerate tepotinib
- Provides data on levels of tepotinib in CSF

Weaknesses:
- Demonstrated efficacy and safety in only one patient with leptomeningeal metastases
- Need a larger study to better understand tepotinib’s activity in leptomeningeal metastases

Conclusion:
- Tepotinib was safe and effective in a patient with METex14 NSCLC and leptomeningeal metastases and was able to achieve high CSF concentrations allowing for antitumor response

LINK TO ARTICLE
Patient with *EGFR*-mutant lung cancer harboring \textit{de novo} \textit{MET} amplification successfully treated with gefitinib combined with crizotinib

**Drugs:** Gefitinib, Crizotinib

**Objective:**
- To report a case of a patient with metastatic NSCLC harboring an EGFR exon 19 deletion and \textit{de novo} MET amplification who was treated with combination gefitinib and crizotinib

**Design:**
- Case report

**Population:**
- One patient with stage IV NSCLC with pleural effusion, mediastinal lymph node metastasis, and rib bone metastasis, initially treated with gefitinib alone. After the patient reported increased chest pain, a CT scan showed that the lesion had increased, so crizotinib was added.

**Efficacy Results:**
- Response deemed a complete recovery at the time of last follow-up, which was 4 months after the addition of crizotinib

**Safety Results:**
- “First-degree” rash, not further described

**Strengths:**
- Compares this case to other published case reports of patients with \textit{EGFR}-mutant lung cancer harboring \textit{de novo} MET amplification

**Weaknesses:**
- Results are demonstrated in only one patient in this case report, larger studies are needed to confirm response rates in patients with concomitant EGFRex19del and MET amplification
- Status of the reported MET amplification (low, high, or any other quantification) not provided
- This report does not discuss other existing literature around resistance mechanisms of EGFR mutated lung cancers, or other trials such as one that investigated the safety and efficacy of capmatinib plus gefitinib in patients with EGFR-mutated, MET-dysregulated (amplified/overexpressing) NSCLC who experienced disease progression while receiving EGFR-TKI treatment (NCT01610336)

**Conclusion:**
- This case report demonstrates the possibility of treatment with concomitant gefitinib and crizotinib in a patient with concomitant EGFRex19del and \textit{de novo} MET amplification
- Other studies have already demonstrated treatment possibilities for patients with \textit{EGFR} mutations and \textit{de novo} MET amplifications, and additional, larger, randomized studies are needed for further confirm these findings
Regulation of immune microenvironment may enable MET-altered NSCLC patients to benefit from immune checkpoint inhibitors

Drug: immune checkpoint inhibitors
(pembrolizumab, nivolumab, avelumab, atezolizumab, ipilimumab, durvalumab, etc)

Objective:
• To describe the activity of immune checkpoint inhibitors in MET-altered lung cancer and evaluate aspects of the immune microenvironment that could help explain this response.

Design:
• Letter to the editor (not peer reviewed)
• Retrospective study utilizing data from the cBioPortal and TISIDB databases

Population:
• 5718 patients with non-small cell lung cancer (NSCLC)
• 1311 patients receiving immune therapy for a disease other than NSCLC

Results – Immune Microenvironment:
• MET-altered NSCLC more likely to have other mutations than unaltered NSCLC
  – More likely to have MUC17 mutation and less likely to have KRAS mutation
• MET-altered NSCLC had higher copy number variation than MET-unaltered NSCLC
• Increased MET copy number alteration was associated with higher numbers of tumor-infiltrating lymphocytes (TILs)

Results – Survival:
• Overall survival not significantly different between MET-altered NSCLC and unaltered NSCLC general populations.
• In patients receiving immune therapy for NSCLC, MET alteration was associated with longer survival.
• Among patients receiving immune therapy for other cancers, MET was also associated with improved survival.

Strengths:
• Using a large database allows for larger numbers of patients to be included in the analysis

Weaknesses:
• Not peer-reviewed
• Retrospective analysis of database data can introduce many confounding factors and biases
• The characteristics of the patients included in the study are not described. Notably, the type of MET alteration, the number and type of prior therapies, and the disease burden and location would be helpful in interpreting the survival data.

Conclusion:
• The authors speculate that MET alteration causes an immunogenic tumor microenvironment, which may explain the positive response to immune therapy in MET-altered NSCLC
• Results should be interpreted as hypothesis-generating. This study does not prove MET impacts on the tumor microenvironment and it should not be used to recommend immune therapy in MET-altered NSCLC, but it supports ongoing research in this area.

LINK TO ARTICLE
ADDITIONAL READING

In the construction of the MET Crusader newsletter, the research team searches content from across the Internet. In that process, they come across articles that don't reasonably fit our criteria but are still significant. The following are the articles found in preparation of this newsletter.

Preclinical Readings

- Anlotinib suppresses metastasis and multidrug resistance via dual blockade of MET/ABCB1 in colorectal carcinoma cells, Journal of Cancer, February 16, 2021

Additional Readings

- Narrative review: mesenchymal-epithelial transition inhibitors—meeting their target, Translational Lung Cancer Research, January 2021
- Targeted Therapy Approaches for MET Abnormalities in Non-Small Cell Lung Cancer, DOI.org, February 3, 2021
- Current and future treatment options for MET exon 14 skipping alterations in non-small cell lung cancer, Therapeutic Advances in Medical Oncology, 2021
- The role of MET in chemotherapy resistance, Oncogene, February 1, 2021
- Targeted Therapy in Advanced and Metastatic Non-Small Cell Lung Cancer, An Update on Treatment of the Most Important Actionable Oncogenic Driver Alterations, Cancers, February 10, 2021
- Detection of MET Exon 14 Skipping Alterations in Lung Cancer Clinical Samples Using a PCR-Based Approach, Methods in Molecular Biology, 2021
- Detection of Non-Small Lung Cell Carcinoma-Associated Genetic Alterations Using a NanoString Gene Expression Platform Approach, Lung Cancer Methods and Protocols, Methods in Molecular Biology, 2021
- Capmatinib for patients with non-small cell lung cancer with MET exon 14 skipping mutations- A review of preclinical and clinical studies, Cancer Treatment Reviews 95, 2021
- Novel Therapies for Metastatic Non-Small Cell Lung Cancer with MET Exon 14 Alterations: A Spotlight on Capmatinib, Lung Cancer Targets and Therapies, March 18, 2021
- Novel Emerging Molecular Targets in Non-Small Cell Lung Cancer, International Journal of Molecular Sciences, March 5, 2021
MET Clinical Trials

Below is a list of clinical trials involving MET alterations on ClinicalTrials.gov. This list is a summary snapshot of emerging therapeutic strategies, details of these trials can be found at ClinicalTrials.gov. Recruitment for clinical trials is constantly changing, and many eligibility criteria are typically required in order to participate. The treatments being studied in the clinical trials listed here are meant for reference only and do not replace medical advice. Always have a discussion with your oncologist if you have questions about clinical trial participation.

This list was last updated on December 1, 2020.

TKI TRIALS

| NIH Identifier: NCT04084717 | Link: [https://clinicaltrials.gov/ct2/show/NCT04084717](https://clinicaltrials.gov/ct2/show/NCT04084717) | Title: Study of Crizotinib for ROS1 and MET Activated Lung Cancer | Status: Recruiting | Drug: Crizotinib | Phase: P2 | Countries: Canada |
| NIH Identifier: NCT03693339 | Link: [https://clinicaltrials.gov/ct2/show/NCT03693339](https://clinicaltrials.gov/ct2/show/NCT03693339) | Title: Capmatinib in Patients With Non-small Cell Lung Cancer Harboring cMET exon14 Skipping Mutation | Status: Recruiting | Drug: Capmatinib | Phase: P2 | Countries: Republic of Korea |
| NIH Identifier: NCT03993873 | Link: [https://clinicaltrials.gov/ct2/show/NCT03993873](https://clinicaltrials.gov/ct2/show/NCT03993873) | Title: Phase 1 Study of TPX-0022, a MET/CSF1R/SRC Inhibitor, in Patients With Advanced Solid Tumors Harboring Genetic Alterations in MET | Status: Recruiting | Drug: TPX-0022 | Phase: P1 | Countries: US, Republic of Korea |
| NIH Identifier: NCT02864992 | Link: [https://clinicaltrials.gov/ct2/show/NCT02864992](https://clinicaltrials.gov/ct2/show/NCT02864992) | Title: Tepotinib Phase II in Non-small Cell Lung Cancer (NSCLC) Harboring MET Alterations (VISION) | Status: Recruiting | Drug: Tepotinib | Phase: P2 | Countries: US, Austria, Belgium, France, Germany, Israel, Italy, Japan, Republic of Korea, Netherland, Poland, Spain, Switzerland, Taiwan, Israel, Italy, Japan, Republic of Korea, Netherland, Poland, Spain, Switzerland, Taiwan, |
| NIH Identifier: NCT03175224 | Link: [https://clinicaltrials.gov/ct2/show/NCT03175224](https://clinicaltrials.gov/ct2/show/NCT03175224) | Title: APL-101 Study of Subjects With NSCLC With c-Met EXON 14 Skip Mutations and c-Met Dysregulation Advanced Solid Tumors (SPARTA) | Status: Recruiting | Drug: APL-101 | Phase: P2 | Countries: US, Australia, Canada, Italy, Puerto Rico, Singapore, Spain, Taiwan, Ukraine, United Kingdom |
| NIH Identifier: NCT02920996 | Link: [https://clinicaltrials.gov/ct2/show/NCT02920996](https://clinicaltrials.gov/ct2/show/NCT02920996) | Title: Merestinib In Non-Small Cell Lung Cancer And Solid Tumors | Status: Active, Not Recruiting | Drug: Merestinib | Phase: P2 | Countries: US |
| NIH Identifier: NCT02750215 | Link: [https://clinicaltrials.gov/ct2/show/NCT02750215](https://clinicaltrials.gov/ct2/show/NCT02750215) | Title: A Study of Capmatinib (INC280) in NSCLC Patients With MET Exon 14 Alterations Who Have Received Prior MET Inhibitor | Status: Active, Not Recruiting | Drug: Capmatinib | Phase: P2 | Countries: US |
| NIH Identifier: NCT02414139 | Link: [https://clinicaltrials.gov/ct2/show/NCT02414139](https://clinicaltrials.gov/ct2/show/NCT02414139) | Title: Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer (Geometry Mono-1) | Status: Recruiting | Drug: Capmatinib | Phase: P2 | Countries: US, Argentina, Austria, Belgium, Brazil, Canada, France, Germany, Israel, Italy, Japan, Republic of Korea, Lebanon, Mexico, Netherlands, Norway, Poland, Russia, Singapore, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom |
| NIH Identifier: NCT01639508 | Link: [https://clinicaltrials.gov/ct2/show/NCT01639508](https://clinicaltrials.gov/ct2/show/NCT01639508) | Title: Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity | Status: Recruiting | Drug: Cabozantinib | Phase: P2 | Countries: US |
| NIH Identifier: NCT02197111 | Link: [https://clinicaltrials.gov/ct2/show/NCT02197111](https://clinicaltrials.gov/ct2/show/NCT02197111) | Title: Phase 1/1b Study of MGCD516 in Patients with Advanced Cancer | Status: Active, Not Recruiting | Drug: MGCD516 | Phase: P1 | Countries: US, Republic of Korea |
| NIH Identifier: NCT04270591 | Link: [https://clinicaltrials.gov/ct2/show/NCT04270591](https://clinicaltrials.gov/ct2/show/NCT04270591) | Title: Assess the Anti-tumor Activity and Safety of Glumetinib in Patient with Advanced c-MET-positive Non-Small Cell Lung Cancer | Status: Recruiting | Drug: Glumetinib | Phase: P1/P2 | Countries: US, China |
UMBRELLA TRIALS

NIH Identifier: NCT03574402
Link: https://clinicaltrials.gov/ct2/show/NCT03574402
Title: Phase II Umbrella Study Directed by Next Generation Sequencing (TRUMP)
Status: Recruiting
Trial Name: Umbrella (TRUMP)
Phase: P2
Countries: China

NIH Identifier: NCT02693535
Link: https://clinicaltrials.gov/ct2/show/NCT02693535
Title: TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer (TAPUR)
Status: Recruiting
Trial Name: TAPUR
Phase: P2
Countries: US

NIH Identifier: NCT02664935
Link: https://clinicaltrials.gov/ct2/show/NCT02664935
Title: National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer
Status: Recruiting
Trial Name: Matrix
Phase: P2
Countries: United Kingdom

IMMUNOTHERAPY TRIALS

NIH Identifier: NCT02323126
Link: https://clinicaltrials.gov/ct2/show/NCT02323126
Title: Study of Efficacy and Safety of Nivolumab in Combination with EGF816 and of Nivolumab in Combination With INC280 in Patients With Previously Treated Non-small Cell Lung Cancer (EGF816)
Status: Active, Not Recruiting
Drug: Nivolumab + EGF816 + Capmatinib
Phase: P2
Countries: US, Australia, France, Germany, Italy, Netherlands, Singapore, Spain, Switzerland

NIH Identifier: NCT04310007
Link: https://clinicaltrials.gov/ct2/show/NCT04310007
Title: Testing the Addition of the Pill Chemotherapy, Cabozantinib, to the Standard Immune Therapy Nivolumab Compared to Standard Chemotherapy for Non-small Cell Lung Cancer
Status: Recruiting
Drug: Cabozantinib + Nivolumab
Phase: P2
Countries: US

NIH Identifier: NCT03666143
Link: https://clinicaltrials.gov/ct2/show/NCT03666143
Title: A Phase 1b Study to Assess Sitravatinib in Combination with Tislelizumab in Patients With Advanced Solid Tumors.
Status: Recruiting
Drug: Sitravatinib + Tislelizumab
Phase: P1
Countries: Australia, China

NIH Identifier: NCT04139317
Link: https://clinicaltrials.gov/ct2/show/NCT04139317
Title: Safety and Efficacy of Capmatinib (INC280) Plus Pembrolizumab vs Pembrolizumab Alone in NSCLC With PD-L1e 50%
Status: Recruiting
Drug: Capmatinib + Pembrolizumab
Phase: P2
Countries: US, Australia, Belgium, Czechia, France, Germany, Hong Kong, India, Italy, Japan, Malaysia, Spain, Taiwan, Thailand
### EGFR + MET TRIALS

<table>
<thead>
<tr>
<th>NIH Identifier</th>
<th>Link</th>
<th>Title</th>
<th>Status</th>
<th>Drug</th>
<th>Phase</th>
<th>Countries</th>
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<tbody>
<tr>
<td>NCT03944772</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT03944772">Link</a></td>
<td>A Study of Tepotinib Plus Osimertinib in Osimertinib Relapsed Metastatic Non-Small Cell Lung Cancer (INSIGHT 2)</td>
<td>Recruiting</td>
<td>Tepotinib + Osimertinib</td>
<td>P2</td>
<td>US, Denmark, Japan, Republic of Korea, Netherlands, Norway, Spain, Sweden</td>
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<tr>
<td>NCT03940703</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT03940703">Link</a></td>
<td>Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Participants with Advanced Non-Small Cell Lung Cancer (CHRYSALIS)</td>
<td>Recruiting</td>
<td>JNJ-61186372</td>
<td>P1</td>
<td>US, Australia, Canada, France, Germany, Hong Kong, Japan, Republic of Korea, Malaysia, Netherlands, Russia, Singapore, Spain, Taiwan, Thailand, Vietnam</td>
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<tr>
<td>NCT02609776</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT02609776">Link</a></td>
<td>Osimertinib Plus Salvotinib in EGFRm+/MET+ NSCLC Following Prior Osimertinib (SAVANNAH)</td>
<td>Recruiting</td>
<td>Osimertinib + Salvotinib</td>
<td>P2</td>
<td>US, Brazil, Canada, Chile, Denmark, France, India, Israel, Italy, Japan, Republic of Korea, Spain, Taiwan, Vietnam</td>
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<tr>
<td>NCT03778229</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT03778229">Link</a></td>
<td>A Study Comparing Salvotinib Plus Osimertinib vs Salvotinib Plus Placebo in Patients with EGFRm+ and MET Amplified Advanced NSCLC (CoC)</td>
<td>Recruiting</td>
<td>Osimertinib + Salvotinib</td>
<td>P2</td>
<td>US, Argentina, Brazil, Chile, India, Republic of Korea, Taiwan, Thailand, Vietnam</td>
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### ANTIBODY-ADC TRIALS

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<tr>
<th>NIH Identifier</th>
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<th>Drug</th>
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<tbody>
<tr>
<td>NCT03539536</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT03539536">Link</a></td>
<td>A Study of Telisotuzumab Vedotin (ABBV-399) in Subjects with Previously Treated c-Met+ Non-Small Cell Lung Cancer</td>
<td>Recruiting</td>
<td>ABBV-399</td>
<td>P2</td>
<td>US, Australia, Belgium, Canada, China, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Republic of Korea, Romania, Russia, Spain, Taiwan, Turkey, United Kingdom</td>
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<tr>
<td>NCT04077099</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT04077099">Link</a></td>
<td>REGN5093 in Patients With MET-Altered Advanced Non-Small Cell Lung Cancer</td>
<td>Recruiting</td>
<td>REGN5093</td>
<td>P1, P2</td>
<td>US, Republic of Korea</td>
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<tr>
<td>NCT02648724</td>
<td><a href="https://www.clinicaltrials.gov/ct2/show/NCT02648724">Link</a></td>
<td>Sym015 (Anti-MET) in Patients With Advanced Solid Tumor Malignancies</td>
<td>Active, Not Recruiting</td>
<td>Sym015</td>
<td>P1, P2</td>
<td>US, Denmark, Hong Kong, Republic of Korea, Spain, Taiwan</td>
</tr>
</tbody>
</table>
The MET Crusader newsletter is written for the benefit of MET patients, caregivers, clinicians and researchers. It contains an outlined summary of MET related abstracts, posters and articles. The outline summaries provide key metrics and improve readability. The summaries are not intended to replace the abstracts, posters and articles. Where possible, links are provided to the source materials. Where links are not possible, a reference is made to help locate the source documents. If you need help in finding a document contact us.

Where possible, the outlined summaries contain the NIH ID that links to the actual clinical trial. This helps our community in the evaluation of clinical trials. The drug under trial is also provided.

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Your comments and suggestions are always welcome.