

Anti-tumor activity of tepotinib

Anti-VEGF therapy sensitizes EGFR/MET co-altered NSCLC cells

Determinants of immune evasion in MET driven lung cancer

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T-cell recruitment tumor lysis via a novel c-MET/CD3 bispecific antibody

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MET exon 14 skipping mutations in lung cancer Your resource for the latest research into the MET alteration.



Liquid biopsy to detect MET exon 14 skipping (METex14) and *MET* amplification in patients with advanced NSCLC: Biomarker analysis from *VISION* study

The VISION study is a phase 2 trial looking at a targeted treatment called tepotinib. Tepotinib is a MET inhibitor that has shown efficacy in patients with a variety of MET alterations, including MET exon 14 skipping, MET amplification, and MET overexpression.

This is the "biomarker analysis" portion of the VISION study, meaning they specifically looked at biological aspects of 151 patients enrolled in the trial (i.e. blood pressure, heart rate, lab values from blood tests, etc). They included patients who had either a tissue and/or a liquid biopsy (i.e. blood samples) to detect certain types of MET alterations and a gene sequencing

continued on p2 \blacktriangleright



In this edition

Anti-tumor activity of tepotinib	3 T- C-
The effect of savolitinib plus osimertinib	3 Mi
Synergism of PARP inhibitor and MET	3 Ge
Anti-VEGF therapy sensitizes	4 Mi
The novel bi-specific antibody CKD-702	4 JN do
Determinants of immune evasion	4 A sk
Inhibition of c-MET upregulates PD-L1	5

T-cell recruitment tumor lysis via a novel5 c-MET/CD3 bispecific antibody
MET mediates entrectinib resistance5 in ROS1 gene fusion positive NSCLC
Genomic and clinical characteristics6 of MET exon14 alterations
MET exon 14 skipping mutations in lung cancer6
JNJ-61186372 mediates EGFR and cMet
A novel functional analysis of MET exon 14

This study suggests that a less invasive technique (blood sample) can be used to effectively detect MET alterations.

continued from p1

Biomarker analysis from VISION study

panel called Guardant360, which can detect a variety of alterations. A total of 3.6% of patients had MET exon 14 skipping and 4.9% of patients had MET amplification. The median age of patients with MET exon 14 skipping in the study was 72 years, 47% were male, and 46% were never smokers. The study also included patients with brain metastases.

This specific analysis showed that patients with MET exon 14 skipping or amplification often had other alterations in addition to their MET alteration that was driving the cancer. Patients with MET exon skipping also had alterations in *EGFR* (7.4%), *CDK4* (6.4%), *BRAF* (5.3%) and *CDK6* (4.8%), *GNAS* (5.3%), and *TP53* (55.9%).Patients with MET amplification had alterations in *CDK6* (60.5%), *BRAF* (43.4%), *EGFR* (28.9%), *MYC* (21.9%), *CCNE1* (19.9%), and *TP53* (79.7%). Some patients had both MET exon 14 skipping and MET amplification (13.3%).

This study suggests that a less invasive technique (blood sample) can be used to effectively detect MET alterations. Objective response rate (ORR) was similar between patients who had a liquid biopsy versus tissue biopsy. Overall, tepotinib is a promising targeted therapy with durable clinical activity in patients with MET exon 14 skipping NSCLC confirmed via liquid and/or tissue biopsy, including patients with brain metastases.

READ FULL ABSTRACT

Anti-tumor activity of tepotinib in orthotopic models of lung cancer patient-derived brain metastases with *MET* amplification

This study looked at how mice that were given a lung metastasis with a MET alteration in the brain orthotopically (meaning it was transferred from a human to a mouse in its normally occurring place in the body – in this case, the brain) responded to different treatments. This study looked at the efficacy of a variety of MET inhibitors (tepotinib, capmatinib, savolitinib, and crizotinib) in mice with lung cancer-based brain metastasis with MET alterations.

Only 2 mice (out of 21) had MET alterations, and both were specifically MET amplifications. As a result, these were the only 2 mice whose tumors shrunk in response to tepotinib. Tumor regression (decrease in size, indicating response to treatment) in one of these tumors was observed with all of the MET inhibitors (tepotinib, capmatinib, savolitinib, and crizotinib). The other mouse with a MET amplified tumor had growth inhibition (slowing growth but not a decrease in tumor size) when treated with savolitinib and crizotinib, and tumor regression with tepotinib and capmatinib.

Overall, this study concluded that tepotinib was effective in the two mice with MET amplification and therefore may be a viable option for patients with MET amplification and lung-based brain metastasis.

READ FULL ABSTRACT

The effect of savolitinib plus osimertinib on ctDNA clearance in patients with EGFR mutation positive (EGFRm) *MET*- amplified NSCLC in the TATTON study

This study involves patients who have both MET amplification and an EGFR mutation. MET amplification can actually contribute to resistance of medications used to target EGFR mutations in lung cancer (i.e. osimertinib). So, the theory is that if we can inhibit MET in these patients with both alterations, we may be able to decrease the resistance to EGFR inhibitors. This can be determined by combining osimertinib (an EGFR inhibitor) and savolitinib (a MET inhibitor).

This study looked at ctDNA ("circulating tumor" DNA – essentially tumor found in the bloodstream) clearance to determine response to the medications, as ctDNA has shown to be correlated with progression-free survival (PFS – how long patients are on treatment with no progression of disease). This was a phase 1 trial, meaning they focused on determining the appropriate dose for patients. ctDNA clearance was similar between the two doses of savolitinib (300mg and 600mg), suggesting the lower dose is just as effective.

READ FULL ABSTRACT

Synergism of PARP inhibitor and MET inhibitor in multiple cancer types with intrinsic and acquired PARP inhibitor resistances

This study focused on a variety of malignancies and analyzed the impact of combining two medications in cell lines with acquired resistance to a specific medication. They discovered that cells with PARP inhibitor resistance also harbored MET alterations. Therefore, by combining a MET inhibitor and PARP inhibitor, it is hypothesized that we can overcome PARP inhibitor resistance. This is also referred to as "synergism," meaning the combined efforts of two medications can overcome a physiologic obstacle.

This study used breast, ovarian, and liver cancer cell lines that had developed PARP inhibitor resistance to test this hypothesis of synergism. They confirmed that many of these cells with PARP inhibitor resistance also had MET activations. This study showed that combining PARP inhibitors and MET inhibitors were moderately to strongly synergistic in a variety of cancer types.

Of note, this study has not provided detail on results in lung cancer cell lines, but verbally stated during the live session at the AACR 2020 annual meeting that they have seen synergism with PARP inhibitors and MET inhibitors in lung cancer cells. Moreover, the study did not provide specifics on BRCA1 vs BRCA2 or which types of MET alterations were discovered in these cell lines.

Anti-VEGF therapy sensitizes EGFR/MET co-altered NSCLC cells to TKIs via inhibiting the VEGF/ERK/MET pathway

This study observed combining multiple therapies in lung cancer cell lines that had MET amplification and EGFR exon 19 deletion. They showed that combining a VEGF inhibitor (bevacizumab) with a MET inhibitor (crizotinib) and EGFR inhibitor (gefitinib) in patients with EGFR exon 19 deletion and MET amplification resulted in stronger inhibition of tumor growth than a MET inhibitor or EGFR inhibitor either alone, or in combination.

READ FULL ABSTRACT

The novel bi-specific antibody CKD-702 is a potential agent for NSCLC patients with aberrant cMET and EGFR signaling

This study looked at a type of drug called a "bispecific antibody," which is a type of immunotherapy. It is an artificial protein that specifically binds to MET and EGFR and therefore prevents other molecules from binding to these proteins that would typically promote tumor growth. This bispecific antibody also promotes degradation (breakdown) of MET and EGFR receptors, thus preventing the ability of other molecules to bind to the receptors and promote tumor growth.

Using this bispecific antibody in lung cancer cell lines and mouse models with both a MET alteration (amplification and exon 14 skipping) and EGFR mutation (L858R, T790M, and exon 19 deletion) resulted in decreased tumor size. Another promising result in this study was that the bispecific antibody showed limited skin rash toxicity, a plus for EGFR patients. Overall, this study showed that this bispecific antibody may potentially be used for the treatment of patients with lung cancer who harbor both a MET amplification / exon 14 skipping mutation *and* EGFR L858R, T790M, or exon 19 deletion mutation. They are currently piloting a phase I trial of CKD-702 in humans in Korea.

<u>READ FULL ABSTRACT</u> <u>VIEW POSTER</u>

Determinants of immune evasion in MET driven lung cancer

This study looked at CD73 (a protein that helps create an anti-inflammatory molecule) expression in lung cancer cell lines and its role in regulating immune pathways to determine if it could be a viable drug target.

They found that there is a strong correlation between MET and CD73 expression. Specifically, tumors with MET amplification or MET exon 14 skipping had increased levels of CD73. CD73 was also correlated with high levels of CD8+, another important immune system regulator. They are currently looking at the role of CD73 as a predictive marker of response to immune checkpoint inhibitors.

Overall, this study showed that tumors with MET amplification or MET exon 14 skipping had high levels of CD73, which may be a way in which these tumor cells are able to evade the body's immune system, and therefore may be a target for immunotherapy. They are working on putting together a study looking at the role of CD73-specific immunotherapy in humans.

READ FULL ABSTRACT VIEW POSTER

Inhibition of c-MET upregulates PD-L1 related immune escape in lung adenocarcinoma

This study focused on determining ways to make MET inhibitors more effective in lung cancer by combining with another therapy that focused on PD-L1 inhibition. PD-L1 stands for programmed death-ligand 1, which plays a role in the immune response.

This study exposed lung cancer cells to a MET inhibitor called tivantinib. When these cells were exposed to tivatinib, their levels of PD-L1 increased, which caused the cells to become more resistant to T-cell killing. Inhibition of MET led to the stabilization of PD-L1. These findings suggest a potential crosstalk between MET inhibition and immune escape, and therefore provides a rationale for combining MET inhibitors with immune checkpoint inhibitors in NSCLC.

READ FULL ABSTRACT

T-cell recruitment tumor lysis via a novel c-MET/CD3 bispecific antibody

This study looked at a bispecific antibody called BS001 that targets both MET and CD3. CD3 is a protein in an immune pathway that helps target cells for destruction. These bispecific antibodies not only can target multiple molecules, but can also recruit immune cells to the tumor to target it for destruction. BS001 showed potent immune-mediated tumor cell killing *in vitro* in addition to MET inhibition.

BS001 inhibited tumor growth in mouse models with MET overexpression. Additionally, when BS001 was combined with a PD-L1 inhibitor (atezolizumab) in vivo, there was an increase in tumor inhibition compared to either of the therapies alone. BS001 may be an effective treatment option for patients with lung cancer harboring MET overexpression.

READ FULL ABSTRACT

VIEW POSTER

MET mediates entrectinib resistance in ROS1 gene fusion positive NSCLC

ROS1 gene fusion is a major driver in the formation of cancer, responsible for approximately 1% of all NSCLC. There are currently two FDAapproved medications for patients with ROS1 gene fusions – crizotinib (targets both MET and ROS1) and entrectinib (targets ROS1), with others showing efficacy in clinical trials. ROS1 patients inevitably experience progression.

This study looked at a patient-derived entrectinib-resistant NSCLC cell line with ROS1 fusion and identified three key concepts:

- 1. MET-mediated bypass signaling as an acquired resistance mechanism to entrectinib
- 2. Upregulation of MET signaling is accomplished via MET amplification in entrectinib-resistant cells
- 3. Resistance may be overcome by crizotinib (dual MET/ROS1 inhibitor)

This illustrates that MET status should be determined in patients with ROS1 positive lung cancer who experience disease progression on entrectinib or another ROS1 inhibitor that does not also inhibit MET. Once determining MET status, we can better determine ways to overcome drug resistance in these patients.

READ FULL ABSTRACT

Genomic and clinical characteristics of MET exon14 alterations in 26,391 Chinese cancer patients

This study looked at the prevalence of MET exon 14 skipping in Chinese lung cancer patients. They found that compared to the Western population, the frequency of MET exon 14 skipping was much lower in Chinese lung cancer patients. A small portion of these patients also had increased PD-L1 expression, indicating an option for immunotherapy. In the portion of patients who received crizotinib, the median PFS was 7 months and the longest PFS was 17 months.

READ FULL ABSTRACT

MET exon 14 skipping mutations in lung cancer: Screening, functional and clinical impact

This study's analysis of pulmonary cell lines revealed that MET exon 14 skipping leads to a change within the CBL binding site (an area of the protein that helps target it for degradation) and also creates resistance to apoptosis (cell killing). Additionally, they found that there was a high rate of alterations in the PI3K pathways (another pathway involved in cell growth) in cell lines with MET exon 14 skipping, indicating a potential mechanism of resistance to MET inhibitors (such as capmatinib). The researchers found that this MET resistance was overcome by a PI3K inhibitor called GDC0941.

READ FULL ABSTRACT

JNJ-61186372, an Fc enhanced EGFR/cMet bispecific antibody, mediates EGFR and cMet downmodulation and therapeutic efficacy preclinically through monocyte / macrophage mediated trogocytosis

EGFR inhibitors are often used in patients with lung cancer who are harboring EGFR mutations. However, resistance often develops over time, through additional alterations either within EGFR or other pathways and proteins in the body (such as MET). JNJ-61186372, also known as amivantamab, is an Fc-enhanced bispecific antibody that inhibits both EGFR and MET (of note, "Fc" represents a protein found on the surface of a variety of immune cells that contributes to the protective function of the immune system).

This study demonstrated potent anti-tumor activity of amivantamab in mouse models with EGFR-mutated (specific mutation not provided) lung cancer that did not respond to an EGFR inhibitor (due to resistance via mechanisms like MET amplification), but only modest anti-growth effects in vitro. When immune cells were added to the Petri dish, it actually enhanced amivantamab's inhibition of EGFR and MET, and also demonstrated dose-dependent tumor killing.

They also discovered that monocytes and macrophages (large white blood cells that kill other cells and boost immune response) are necessary for amivantamab to be effective. Overall, this study supports the continued clinical development of amivantamab in patients with both an EGFR mutation and MET alteration (such as amplification).

READ FULL ABSTRACT

A novel functional analysis of MET exon 14 skipping mutation in regulation of tumor cell invasion and metastasis

This study performed an array of experiments to determine the role of MET exon 14 skipping in NSCLC. They determined that MET 14 exon skipping impaired receptor degradation (breakdown of the receptors), which led to overactivity of MET signaling. They also identified that MET exon 14 skipping significantly increases tumor cell migration and invasion capacity *in vitro* as well as metastasis *in vivo* compared to wild-type MET (MET without an alteration).

Analysis also revealed a large number of cell signaling pathways that were remarkably activated in MET exon 14 skipping models (vs MET wild-type with no alteration). Inhibition of the PI3K pathway (another cell signaling pathway that promotes cell growth) decreased MET exon 14 skipping activity. They found that MET inhibitors like capmatinib and MGCD516 remarkably inhibited MET exon 14 skipping signaling and inhibited cell invasion *in vitro* and metastasis *in vivo*. In conclusion, these data demonstrate that MET exon 14 skipping plays a critical role in enhancing cell movement and metastasis, at least partially via the PI3K pathway, and blockade of MET exon 14 skipping signaling using MET inhibitors might be therapeutic options for MET exon 14 skipping-mutated NSCLC patients and might yield additional synergistic (combination of medications) treatment strategies.

READ FULL ABSTRACT

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MET Crusaders is a community of Lung Cancer patients and care givers collaborating with advocates and medical professionals collectively dedicated to helping patients with the MET alteration live normal lives.