

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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MET as a Drug Target



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H&O Could you describe MET?

RS MET is a receptor tyrosine kinase that is located on the cell surface and is activated by the binding of its ligand, hepatocyte growth factor (HGF; previously known as scatter factor). MET activates a variety of signaling pathways within the cell, and in normal circumstances is involved in embryonic development and wound healing. However, in cancer cells, MET can be aberrantly active and cause abnormal signaling, which leads to tumor growth, angiogenesis, and metastasis.

H&O What causes aberrant MET activity in cancer cells?

RS There are many different causes of MET activation in cancer cells. *MET* can be overexpressed or its ligand HGF can be hyperactive. *MET* also can be mutated, which is common in hereditary papillary renal cell carcinoma; activating mutations in the tyrosine kinase domain can lead to sporadic papillary renal cell carcinoma. Other activating mutations are possible as well. More recently, a chromosomal translocation involving *MET* has been described in which it fuses with another gene. Finally, MET sometimes has very rapid signaling that does not get degraded properly, causing hyperactivity. The fact that there are so many different causes of MET activation can be problematic for developing a biomarker test and applying targeted therapeutics.

H&O Are there any cancers in which MET is more commonly mutated or amplified?

RS Many cancers can have *MET* mutations. For example, it is very commonly mutated in papillary renal cell carcinoma. It also can be amplified in lung cancer, but the mutation typically is not in the tyrosine kinase domain. Gastroesophageal cancer, as an example, is another disease in which *MET* expression is amplified. Small-molecule inhibitors of multiple tyrosine kinases that also inhibit MET have been approved by the US Food and Drug Administration (FDA) for the treatment of medullary thyroid cancer and certain types of non-small cell lung cancer (NSCLC).

H&O What is the difference between class I and class II MET inhibitors?

RS This is how the inhibitors originally were defined, based on molecular structure, how the agents bind to the various pockets of the tyrosine kinase domain, and how they act on the MET receptor. Personally, I do not consider these drug groupings to be beneficial clinically. My view is that if the inhibitor is effective, the class it belongs to does not matter.

H&O Could you provide some details on cabozantinib (Cometriq, Exelixis)?

RS Cabozantinib inhibits MET along with the vascular endothelial growth factor receptor and other receptor

tyrosine kinases. The inhibitor is not specific to one molecule and can inhibit several different pathways. This drug was FDA approved in 2012 for the treatment of medullary thyroid carcinomas. Our group performed the original phase 1 clinical trial with colleagues at the MD Anderson Cancer Center. The phase 3 trial that led to FDA approval, published by Elisei and colleagues, found that cabozantinib improved progression-free survival and reduced tumor size. It seems to be relatively well tolerated, although there are some side effects.

This drug is currently being investigated for a wide variety of other cancers, including glioblastoma and prostate cancer. Though cabozantinib does not exclusively inhibit MET, these studies show the proof of concept that MET inhibition may be effective for cancer treatment.

H&O Could you provide some details on the tyrosine kinase inhibitor crizotinib (Xalkori, Pfizer)?

RS Like cabozantinib, crizotinib is an oral tyrosine kinase inhibitor. The original phase 1 clinical trial, performed by our group in collaboration with others, investigated crizotinib specifically as a MET inhibitor. However, subsequent study revealed that the drug also has activity against other tyrosine kinases, including anaplastic lymphoma kinase (ALK).

In 2011, crizotinib was approved by the FDA for treatment of patients with NSCLC who have a chromosomal rearrangement resulting in a fusion of *EML4* and *ALK*. However, ongoing studies are still investigating crizotinib in patients with other biomarkers. More recent work has found that crizotinib may be effective in patients with NSCLC who have a *ROS1* translocation. Furthermore, our group is still examining crizotinib inhibition of MET activity in patients with *MET* mutations or amplifications. Hopefully, the inhibitor will show activity in these cases as well.

H&O Could you describe these clinical trials using crizotinib specifically for MET inhibition?

RS We are still investigating this topic within our phase 1 program, which started almost a decade ago. This is one of the longest running phase 1 clinical trials at the University of Chicago.

H&O Are any other promising MET inhibitors currently in clinical trials?

RS There are several ongoing anti-MET clinical trials for many types of cancer, and some are specifically targeting patients with *MET* mutations or amplifications. I am quite optimistic that inhibition of MET is a promising direction for future therapies.

Cabozantinib and crizotinib are still being used in various clinical trials for other indications. There are also promising drugs that work, unlike tyrosine kinase inhibitors, as antibodies against MET. For example, ABT-700 is currently in a phase 1 clinical trial for patients with advanced solid tumors who have overexpression or amplification of *MET* (NCT01472016). There are also antibodies targeted against MET's ligand HGF, including a randomized phase 3 trial of rilotumumab for patients with gastric cancer (NCT02137343).

One study that looked very promising initially involved the use of onartuzumab, a MET antibody; however, the subsequent trials came back negative. This study examined protein expression (using immunohistochemistry) as a biomarker for patient selection. We believe that the study was unsuccessful because of the biomarker analysis; therefore, in the future we must develop better patient selection strategies using appropriate biomarkers and analysis.

H&O Are there differences between inhibiting MET with kinase inhibitors vs antibodies?

RS From a scientific perspective, it is very interesting to know that antibodies work differently than small-molecule inhibitors such as tyrosine kinase inhibitors. But at the same time, a lot of the information we get is through in vitro cell culture and in vivo mouse modeling. This information does not always carry over into clinical trials. Therefore, from a clinical perspective it does not matter to me whether we use the kinase inhibitor or the antibody, as long as it works.

H&O Are there any strategies for using MET inhibitors in combination with other therapies?

RS I think that future studies using MET inhibitors in combination with traditional therapies will be very important. These drugs could potentially be combined with cytotoxic therapies or radiation. They could also be used in an adjuvant setting, such as after surgical resections of early-stage disease.

It may be beneficial to determine whether any pathways for MET can synergize, in which case targeting both pathways might allow us to develop more effective therapeutics. Most recently, we have found that the protein RON, which is also a receptor tyrosine kinase, may be important in diseases such as NSCLC. RON is a family member of MET that synergizes very elegantly with the MET receptor tyrosine kinase. Perhaps a therapeutic strategy for MET and RON inhibition together would be more effective than MET inhibition alone. I think we need more preclinical studies on how combination therapies can be used, because this is a promising potential therapeutic area.

H&O Could MET inhibitors be used in patients whose disease has become resistant to other therapies?

RS There are mechanisms of resistance to other drugs that involve overexpression or amplification of *MET*, for example, cytotoxic therapies with cisplatin or endothelial growth factor receptor inhibition. *MET* inhibitors could prove useful in these situations, but clinical trials are needed to examine this hypothesis. One must also consider whether the resistance is exclusively from *MET* activity or whether other molecules are involved, such as the oncogene *KRAS*. There are a lot of questions that we want to ask about future therapeutic strategies, but I am a little cautious about this issue. I think we need a specific signal that guides physicians to determine that a therapy will be effective in a specific subtype of cancer and in patients with the proper biomarker.

H&O What are some of the challenges associated with using MET as a drug target?

RS It is very clear that *MET* inhibition is effective for treating cancer, but these drugs may only work in a subset of patients. I think the biggest hurdle is choosing the right patient for the right drug, and that is true for any precision medicine. At the same time, it is possible that this process has become like searching for a needle in a haystack. It may be problematic if a drug will only work in a very small subset of patients with a very specific type of *MET* mutation. Defining those specific patients within the patient population and developing a drug that they can tolerate is an additional hurdle.

Another major problem is defining proper biomarkers and analyses. There are many underlying causes of aberrant *MET* activity, and different analyses are associated with each. For example, amplification of *MET* requires a fluorescence in situ hybridization analysis. Mutations in *MET* must be defined as functional or nonfunctional before a biomarker can be determined. For degradation of the pathway, a good biomarker still has not been identified.

The third hurdle is determining whether the drug only affects the *MET* pathway or if it also affects something else. If the drug is nonspecific, then we must also

define which pathway is the more predominant one that will affect carcinogenesis or pathogenesis of the cancer. Though these are major challenges, I am optimistic that *MET* pathway inhibition could be effective in the future for patients with cancer.

H&O Would you consider MET to be a validated drug target?

RS I think that *MET* is still being validated. We have yet to adequately categorize cancers into various subtypes, but there are some hints of a signal in certain cancer subtypes with certain *MET* mutations. There are definitely a lot of cancers in which *MET* is aberrantly active, and I think the difficulty will be in defining the biomarkers and ensuring that *MET* is the main target of inhibition.

H&O What is your opinion on the future of MET as a drug target?

RS I am a strong believer in *MET* as a drug target. As with any drug, we have to find the correct patient population with the least toxicity. I believe that we are seeing strong signals against *MET* with our current therapeutics. These drugs may not be beneficial for everyone, but they will be for those with the correct biomarkers. I think this is a great way to do precision medicine. *MET* inhibition is one of the first examples, given that research on it began more than a decade ago.

Suggested Readings

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