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The Evolving Role of MET TKIs in NSCLC

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Chapter 1

Dr. Patel:
How do you test for biomarkers in patients with metastatic non-small cell lung cancer? This is CME on ReachMD, and I’m Dr. Jyoti Patel. MET alterations are known driver oncogenes in non-small lung cancer. Since the identification of MET is a potential therapeutic target, extensive clinical trials have been performed, and we’re very interested in understanding the role of MET in non-small cell lung cancer.

So MET encodes a c-MET protein, which belongs to a receptor tyrosine kinase family. MET plays a role in promoting tumor invasion, angiogenesis, and metastasis, and we see MET alterations in all of non-small cell lung cancer, adenocarcinoma and squamous. And these mainly include MET exon 14 skipping mutations, which occur in 2% to 4% of people with non-small cell lung cancer; MET amplification, which can occur in about 1% to 2% of people with lung cancer; and MET overexpression which occurs in about a quarter of people; and then finally, very uncommonly, we’ll see MET fusions. Of all of these, probably secondary MET amplification is the most common type of EGFR resistance bypass, and that occurs in about almost 15% of people with EGFR-acquired resistance mutations.

So we know that MET exon 14 and MET amplification are treatable driver genes for non-small cell lung cancer. When you have MET exon 14 mutations, you essentially have loss of regulation of MET signaling, and so you have increased cellular survival.

Sometimes, we’ll see elevation of MET gene copy number, and that’s MET amplification, and that essentially means that this is another mechanism of oncogene activation and has sort of cemented both of these targets as good targets for therapeutics.

How we detect MET alterations has really gained a lot of attention recently. We primarily use assays that combine DNA-based next-generation sequencing as well as RNA next-generation sequencing. And this increases our sensitivity and detection. You can use FISH for MET amplification, but that’s not used very commonly. How we define MET amplification changes from study, but I think most of us feel that a gene copy number of greater than 5 is certainly reasonable.

And then finally, we can use IHC to look for MET overexpression, and that has varied significantly amongst trials, and I would say is not such a standard approach to detecting MET amplifications or MET exon 14.

So we prioritize tissue testing, but often we will do it in concert or in parallel with blood testing, and we’re able to pick up MET exon 14 mutations in blood. It’s less common to catch gene copy number but that can also be done.

So sort of our approach to testing, when we meet a new patient, is that I do blood and tissue simultaneously, knowing that sometimes blood will return more quickly and may have an answer, but a negative blood test does not mean that that mutation doesn’t exist, and so

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I do tissue testing. And reasonable times for results for tissue testing are changing these days, but generally, we'd hope they'd be back in a couple of weeks. So less than 2 weeks.

It's important that we coordinate tissue stewardship amongst disciplines, so perhaps an interventional pulmonologist may meet your patient first, they do tissue acquisition, and, hopefully, that's enough for things beyond histology that can help us with PDL testing and NGS testing. And that process going from interventional pulmonary to pathology and then ordering the testing either by the medical oncologist or reflex testing has happened in some institutions and that decreases the amount of turnaround time.

It's important that, as patients start these highly active TKIs, that we think about sort of next steps. And that's an area that has also grown in patients with other driver mutations such as EGFR and ALK, as I mentioned. And so, often we'll start a patient on a TKI, but then when someone has resistance, it may be reasonable then to re-biopsy to understand the mechanism of resistance. And so, particularly with EGFR, we know that a MET amplification is a common bypass track and so we'd want to assess for that before we use one of these TKIs.

When we think about using a MET TKI as frontline therapy for someone with a MET exon 14 mutation, we're now starting to understand resistance mechanisms. These are largely things that are investigational, but we do know that agents that are bispecifics or MET-targeting bispecifics have efficacy, as do chemotherapy and immunotherapy. So we use this testing to inform subsequent therapies.

In short, the field is evolving quickly. We know that testing both tissue and blood improves delivery and appropriate therapy to patients. Essentially, it shortens time to get patients to the right and most active therapies.

Thank you for tuning in.

In Chapter 2, we'll be discussing the role of MET inhibitors in MET-positive non-small cell lung cancer. Stay tuned.

Chapter 2

Dr. Patel:
Welcome back. I'm Dr. Jyoti Patel. In this chapter, we'll look at the role of MET inhibitors in MET-positive non-small cell lung cancer.

There are multiple ways in which to target MET. I think 3 main categories are the MET TKIs [tyrosine kinase inhibitors], monoclonal antibodies, and antibody-drug conjugates [ADCs]. I'd first like to focus on the TKIs. Those are farthest along in development and the ones that are FDA-approved for treating this particular subtype of lung cancer. So when we think about MET TKIs, we think about 3 types, type 1, 2, and 3. Type 1 drugs are the ones that have been most developed. The two type 1B TKIs that are approved in the United States are capmatinib and tepotinib. And these tend to have a much higher binding selectivity than type 1 TKIs, such as crizotinib in particular. The data that we have for these type 1B MET TKIs is pretty robust with both of these drugs.

GEOMERY is a trial that looked at the efficacy of capmatinib in patients with MET alterations. GEOMETRY was a multicenter, open-label, phase 2 study of capmatinib in patients with advanced or metastatic non-small cell lung cancer. In this study, patients received capmatinib, and this led to a response rate of over 60% and progression-free survival of almost 12 and a half months and median overall survival of almost 21 months in patients who were receiving capmatinib in the frontline setting.

The phase 2 study, called VISION, this looked at the efficacy and safety of tepotinib in patients with MET exon 14. Again, this was a very effective drug studied in over 300 patients. The overall response rate in the overall population was over 50% with greater than 90% of patients having at least stable or responsive disease. Progression-free survival was 11 and a half months, and median overall survival was 19.6 months.

So the outcomes of these trials were quite similar. What we know is that treatment-naïve patients have a higher response rate, as one would expect, in both of these trials. And if we look at that, that's somewhere around 60%. In the second-line setting, the number drops to about 40%. Generally, these trials showed that these drugs were well tolerated with low rates of discontinuation.

These studies primarily focused on MET exon 14, which is much more common. However, we also know that MET amplification is a targetable driver of MET TKIs, and GEOMETRY included patients who had MET amplification. Capmatinib, in this study, or in this setting, had a response rate of about 12% and shorter PFS in patients with low copy number, but a response rate of almost 40% in patients who had a gene copy number of greater than 10%. Tepotinib, similarly, in patients who had a higher gene copy number had a response rate of about 42% in the VISION study.

Generally, these drugs, as I said, tend to be pretty well tolerated. There are consistent side effects. The most common adverse event is peripheral edema, and this can happen in a third to two-thirds of patients, and grade 3 peripheral edema can occur in about 10% of patients. Management of this adverse event is difficult. It tends to be more non-pharmacologic, so that means like elevation of the feet, compression stockings, massage. Sometimes we use diuretics with sort of mixed efficacy. Importantly, often medication dose reduction

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needs to be used as well. We tend not to want to do dose interruption for patients, but generally, again, if we can get patients moving, often get them into physical therapy and lymphedema clinic, this can be quite helpful. Other toxicities that tend to be lower grade include some nausea, hypoalbuminemia, some LFT [liver function test] abnormalities. But by and large, these drugs tend to be very well tolerated.

Importantly, both drugs have demonstrated consistent CNS [central nervous system] activity. So for a patient who's identified with a MET exon 14 mutation at the time of diagnosis, they have low or small-volume or asymptomatic CNS metastasis, it's not unreasonable to use either tepotinib or capmatinib up front and follow closely to see if one can avoid CNS radiation. Again, the response rate in the frontline setting tends to be higher than that in the second-line setting.

Remember, the first MET TKI that was studied was crizotinib. This is a type 1A MET inhibitor. We know crizotinib has minimal CNS activity, and so, again, because of the higher response rate because of the CNS activity, one would choose an approved 1B TKI such as tepotinib or capmatinib because of the response rate of approximately 60%. So good correlation between systemic and CNS disease.

There are a number of other MET inhibitors, TKIs that are approved around the world and are undergoing clinical trials now, such as savolitinib, for example. And so we sort of await more mature studies.

We know that, often, MET alterations are more common in older patients, often patients who have less reserve. And so we have some data about how these patients do from the trials. We know that in GEOMETRY, for example, the average age was 71 years, so certainly representative. And the response rate was a little bit lower, 35% in patients who were greater than 80 years old, compared to almost 50% in younger patients. More importantly, though, than that difference in response rate, I think, is really understanding how to manage toxicity for these patients. Certainly, the peripheral edema can be quite cumbersome for an older patient. Understanding, again, how to manage with diuretics, leg elevation, those become crucial for this subset of patients.

We know that many patients who receive MET TKIs, unfortunately, will develop resistance, and so we've also been able to look at on-target resistance. Sometimes sequential use of structurally distinct MET TKIs can be considered. More recently, I think, we've been switching over to antibody drugs and ADCs. An antibody that is approved as amivantamab, that's a fully human bispecific antibody that targets both eGFR and MET. And we know that in the CHRYSALIS study, the response rate for amivantamab in patients with MET exon 14 mutations was 33% and the response rate was 45.5% in patients who were treatment naïve and who hadn't received prior TKIs. The toxicities that we see with amivantamab are often rash, infusion reactions, and paronychia, as well as edema.

That's an approved drug. There are other antibody-drug conjugates that certainly are of interest. One such drug that is further along in testing is Teliso-V [telisotuzumab vedotin]. This is an antibody-drug conjugate that targets MET. In clinical trials, we've seen a response rate of about 30%.

So much to learn as these drugs continue to be studied in these populations. Sequencing of these agents will certainly be important.

So to sum up, patients with MET exon 14 mutation should likely get an approved 1B TKI, so either tepotinib or capmatinib, with careful AE [adverse event] management. We see robust response rates as well as CNS responses for these patients.

Thank you for joining me today. In Chapter 3, we'll be discussing the potential roles of MET inhibition in other subsets of patients with non-small cell lung cancer.

Chapter 3

Dr. Lopes:
Welcome back. I'm Dr. Gilberto Lopes, and in this chapter, in the next 10 minutes or so, we will be discussing the use of MET inhibition in other subsets of patients with non-small cell lung cancer, but I'll actually start by discussing what we see today for MET inhibition resistance as well.

We do have 3 agents that are primarily used when we treat patients with MET exon 14 mutations, and these are crizotinib, which was initially developed as a MET inhibitor even though today we think of it more as an ALK inhibitor, as well as capmatinib and tepotinib. We do know that all these agents have response rates of about 30% to 50%, and we also know that the duration of response with these agents is around 9 months or so with median progression-free survivals of about 7 to 10 months as well. We also know that the adverse event profile of these medications can be slightly different with more of the GI and fatigue in patients receiving crizotinib, and peripheral edema being one of the main issues when we talk about patients who receive capmatinib and tepotinib.

When we do get these agents, however, we can develop acquired resistance and, of course, some patients will have primary resistance. Even though, when we look at the waterfall plots in clinical trials, we see that most patients do have at least some shrinkage of disease, there's a few patients who have no responses at all, and most patients eventually do actuate, develop resistance. And the

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mechanisms for these can be both MET related and MET unrelated.

When we talk about the MET-related resistance, we can have secondary mutations or we can have amplifications or even disappearance of MET, and of course, a different metabolic pathway becoming activated. So, for instance, people have shown that KRAS can become activated, eGFR, HER2. So there's a number of potential mechanisms that are not MET related. And what do we do? We're trying to develop new agents that hopefully will be able to overcome resistance in this setting.

Some of these agents can be MET inhibitors, so when we do develop resistance, for instance, on a type 1A or a type 1B MET inhibitor, we could use a type 2 or type 3. And what we're talking here is that type 1A are inhibitors that will be ATP competitors and they will bind to that ATP binding pocket. Type 1A is mostly crizotinib, and type 1B includes capmatinib and tepotinib. And there's slight differences in which of the codons it actually interacts with for the specific MET receptor. We have type 2, which are ATP competitors, but they bind to the inactive state of the molecule, and we have type 3, which are allosteric inhibitors. And that class is represented by tivantinib, and type 2 are represented by cabozantinib and glesatinib for instance, and these are drugs that are under development for their MET activity.

When we really talk about emerging uses of MET inhibitors as well, we have to talk about amplification, and this is still emerging. We still do not have specific approvals for the use of these agents in patients with amplification.

We have doubts in terms of what exactly constitutes amplification. If you measure it by FISH or if you measure it by NGS, then usually you do need a consensus. We don't quite have a consensus on what that number would be that would make you consider it a MET-amplified tumor. Usually, a number between 5 and 10 is what we think will be what eventually becomes what is approved. And we do have NCCN classifying these as emerging targets, so MET amplification is not yet an approval indication, but already it is something that we believe we will be using and it's something that you can use on a patient-by-patient basis in an off-label way.

We also have to talk a little bit about MET inhibition in the setting of different metabolic pathways. And here, where we most actually develop is MET as a secondary driver in patients with eGFR mutations. We have a number of examples in terms of case reports and of course, now, well-done competitive and prospective studies showing that if we do MET inhibition, we do see responses and we do see better overall survival in patients that had eGFR mutations and then developed an acquired resistance to osimertinib. We know that the most common mutation that we see in patients getting osimertinib in the first line would be the C797 mutations, which are usually seen in about 8% of patients that receive osimertinib as a first-line, but MET mechanism simplification as well as mutations and others can actually happen in about 10% to 20% of patients depending on the study we are discussing. And we have seen a number of different trials looking at combinations of eGFR inhibitors and MET inhibitors, usually tyrosine kinase inhibitors, that show that we do see responses in patients that had failure of osimertinib or eGFR TKIs alone.

We also see that amivantamab, which is MET and eGFR monoclonal antibody – so up to now, we've talked mostly about tyrosine kinase inhibitors, but we also have MET inhibitors that are monoclonal antibodies. And amivantamab is a great example of a molecule that blocks MET and eGFR and has since shown responses and better survival when we actually combine this agent with a different eGFR inhibitor as well, not just in the metastatic refractory setting, but also in first line, showing that combination of amivantamab with an oral tyrosine kinase GFR inhibitor also leads to better progression-free survival than osimertinib alone.

So we clearly know that MET can be an important secondary driver change, and we do know that this can have implication in the way we treat patients who do not have primary alterations de novo, so in the beginning of the disease, but who do develop changes. So this is an interesting discussion because it helps us expand on what we have learned about MET inhibition in patients with specific MET changes in the first line, also helping us develop treatments for patients with eGFR mutations and probably other types of alterations as we start to move from first-line into the refractory setting.

Thanks for your attention. In Chapter 4, we're going to be reviewing a case of a patient who has metastatic non-small cell lung cancer and the MET exon 14 skipping mutation. Stay tuned.

Chapter 4

Dr. Lopes:
Welcome back. I'm Dr. Gilberto Lopes, and in this chapter, I'm going to be reviewing a case of a patient with metastatic non-small cell lung cancer. This is an 87-year-old woman with a newly diagnosed stage 4 lung adenocarcinoma. Patient has an Eastern Cooperative Oncology Group performance status of 1, PD-L1 tumor proportion score was 20%, and patient was found to have a MET exon 14 skipping mutation.

This is a typical case that we see for patients with MET exon 14 skipping mutations. We usually have about 3% to 4% of patients with non-small cell lung cancer, especially adenocarcinoma, maybe 1% to 2% of patients have squamous cell carcinomas, and up to 10% or

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more of patients that actually have sarcomatoid features can have MET exon 14 skipping mutations. So these are important because there's different subtypes. We get used to expecting these mutations only in nonsmokers with adenocarcinoma, but this is a particular change that we can see in smokers as well.

One of the main challenges for us is to make sure that we do get next-generation sequencing. We have too many potential targets today that drive the disease that we can actually do specific treatments for, so if we do target-by-target testing, we usually run out of materials. So we absolutely want to do NGS. And in most academic centers, we do both liquid biopsies as well as tumor.

So some of the other challenges would be to define what exactly our goal of therapy is for the patient. For most patients with known-driver lung cancer, we usually want to imagine that chemotherapy and immunotherapy could actually, at least for some patients, lead to long-term survival, even 5-year survival as we have seen in many clinical trials today. For patients with alterations, we want to give the best treatment with the best results and the least amount of side effects as we would have. And for MET exon 14 mutation, it's no different. So this is certainly a patient that we would consider a tyrosine kinase inhibitor as the initial treatment.

We have different types of tyrosine kinase inhibitors when we treat patients with MET exon 14 mutations. We do have type 1, which are ATP competitors. You think about crizotinib as a type 1A that interacts more with the G1163 codon.

We also have type 1B. Also, ATP competitors, capmatinib, tepotinib, and savolitinib, and some of these are approved; some are not.

We also have type 2 inhibitors, which are ATP competitors, but they bind to the inactive state of the molecule, and they are, for instance, cabozantinib, merestinib, and glesatinib are some of these examples. None of them are fully approved for this indication but are potentially useful if you have a patient with resistant disease.

And finally, we have type 3, allosteric inhibition, and that the only example we have today in development is dovitinib. And most of these will have preclinical activity for most of the subtypes of MET mutations we have. When we do use crizotinib, capmatinib, or tepotinib, which are the agents that we use the most, we do expect to see between 30% and 50% response rates, we expect durations of response of around 9 months, and we expect progression-free survivals of about 7 to 8 months or so.

We really don't have a lot of guidance to select among these 3 main options: crizotinib, capmatinib, and tepotinib. We do know that crizotinib, even though we think of it as an ALK inhibitor, was actually initially developed as a MET inhibitor. And when ALK fusions were found, we knew that these agents were active. We knew that crizotinib was an agent that was active in ALK as well as it's a multi-target kinase inhibitor, versus capmatinib and tepotinib, which are more of specific inhibitors. And when we do look at the IC50, so when you look in the lab before we come to clinic, even though IC50 with crizotinib are less than the 50 nanomolar that we usually consider active, we do see IC50s are even lower with capmatinib and tepotinib by even 1 degree of significance. So we can use any of these 3 agents.

The adverse events, the side effects, are actually part of what would help us select these agents, as well. We would look at the potential side effects that we see with any of these class of drugs. So with crizotinib, we have been using this drug for decades, and GI adverse events are usually what we see. We can see diarrhea in about 30% to 40% of patients, vomiting up to a third, edema, and unusually for other types of treatments that we give, you can also have vision disorder that you can see in up to 30% of patients as well. Elevated transaminases, fatigue, anemia, those are all things that we can see with crizotinib, but usually are not a big issue.

When we think about grade 3 or more, we're really not seeing a lot of issues except for maybe transaminase elevation, which you can see in maybe 10% of patients and can be managed by dose reduction. With capmatinib, tepotinib, and even savolitinib, peripheral edema seems to be what truly bothers patients on these agents. We can see that up to 40%, or even a little more, of patients can have, and some of these adverse events can reach grade 3 or 4 for about 10% of patients. Using diuretics is the main way of actually treating these patients and, of course, dose reductions as appropriate can be very useful as well.

So when would we consider other treatments? When would we consider chemo? Can we consider immunotherapy for patients with MET exon 14 skipping mutations? And here, the question is not quite clear. We do tend to prefer using a specific tyrosine kinase inhibitor in the first-line setting. Patients have excellent responses and do have duration of responses that seem to be longer. At least across trial comparison, we can see that patients that get specific-dosing kinase inhibitors, and that's, today, the recommendation of most academic centers and by NCCN as well. But we do know that patients can and do respond to chemotherapy. What we're not 100% sure is if immunotherapy, as single agent, would be a good idea.

We do know that immunotherapy alone only has between 15% and 20% responses when we use them in patients with exon 14 skip mutations, so this is not something that we would usually suggest as a single agent. We do often use chemotherapy with immunotherapy for patients beyond the use of tyrosine kinase inhibitors because we have seen that some patients do respond, and some patients can have long durations of responses as well. It's not as much as we see for patients who do not have specific driver

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mutations, but it's not as bad as we see with ALK inhibitors, for instance, with ALK fusion patients that we really don't see a lot of benefit from immunotherapy at all.

Finally, when we do talk about what you could use – so could you use capmatinib or tepotinib if you use crizotinib? So it's unlikely that switching from a type 1A to a type 1B drug – so if you had crizotinib first, it's unlikely that getting tepotinib or capmatinib you would see a response. But maybe when we switch to a type 2 or type 3 drug, you might see some responses. So those agents might become an option beyond what we usually do. So my, and what most academic centers tend to do is that we usually use one of the new MET-specific tyrosine kinase inhibitors, and if that fails, we go into chemotherapy and immunotherapy, and if that fails, we often would try one of the other MET inhibitors, and these are MET inhibitors that we just discussed that would not be type 1A or type 1B. So type 1 crizotinib, type 1B capmatinib/tepotinib. So type 2 are multikinase inhibitors such as cabozantinib, and we hope that we will have new agents in the near future, such as tivantinib, which is a Type 3. So we would potentially use those agents if patients do not have a response or if they have a response and they progress on the more specific or first-line MET inhibitors.

Thank you for tuning in. I hope that this case review will be useful to you in your practice.

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