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KOL INSIGHT

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Interview NSCLC4

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Highlights

In my practice, these are probably less than 20% of patients, more like 15% of patients, who will have a molecular driver that can be treated, so the majority will not have something that we can treat, they may have KRAS, or may have something against which there are no approved drugs. So, then the decision as to what regimen to use for Stage IV disease will be based on the PD-L1 expression. If PD-L1 expression is high, meaning more than 50%, I discuss with the patient whether we should use single-agent immunotherapy with pembrolizumab, or a combination of chemotherapy plus pembrolizumab, and I'm saying specifically pembrolizumab because this is the most commonly used checkpoint inhibitor for lung cancer in the first line.

So, we had a discussion several years ago with this reflexive system, it's difficult for the pathologists to know what stage the patient has, because they have the biopsy but they don't have the staging information. So, we decided that all patients with NSCLC will get tested regardless of the stage, but all patients with non-squamous histology, so we don't reflexively test squamous cell. The big academic institutions test both squamous and non-squamous, and many of the smaller groups they test only Stage IV disease. So, the practice kind of varies.

…there are several regimens that are approved, they have not been compared head-to-head, so we're kind of looking across trials, and the activity looks very similar. The four-drug Tecentriq + Avastin + CarboTaxol is used very uncommonly, and I've not used it because it's four drugs, and four drugs that have toxicity, and it's not just that Avastin adds to the toxicity, you have to use full-dose CarboTaxol, which is again a tough regimen to give. For the non-squamous patients, carboplatin + Alimta + Keytruda was the first one that was approved, we got a lot of opportunities to develop experience, to see what toxicities there are, confirm that it is active, which I think for two years, if not more than that, was the only thing that we could give in first line with chemotherapy. So, when the data came out for Tecentriq, and it was possible to use it, the numbers looked very similar, so I didn't have any incentive to switch, I have good experience with Keytruda. So, it will be tough given the dominance of Keytruda for such a long time, you have to have some differentiating feature to make use of another agent. I don't think that Tecentriq is less effective than Keytruda, I also don't think that it's more effective…I think that Tecentriq – this is for a small set of patients who cannot get Alimta because of either kidney problems or pleural effusion, so they're a minority of patients who otherwise would be good candidates for chemo + immunotherapy but simply can't get Alimta, and that's specifically for the non-squamous ones, but it's a small number.

…we're definitely not going to see a huge change, or a huge shift from Keytruda to nivo or Tecentriq, or ipi/nivo, but looking at the details of these trials gives us now more information on how to more specifically choose treatment. So, Tecentriq monotherapy is based on [IMpower]110, the numbers there look good but it's a slightly different way of scoring, you score both the tumor cells and surrounding inflammatory cells, so we don't know – several years ago, there was a comparison that there isn't that great a correlation of PD-L1 based on the Merck assay, versus PD-L1 – this immune cell and tumor cell score for atezo. SP[142] is another test, so you have to then ask your pathologist, do the PD-L1, the tumor proportion score for pembro, Keytruda, but then can you also do the testing for atezo, and most pathologists would not be eager to do something that they will say is a very similar test twice. So, the only way this could happen is if we saw a huge improvement in efficacy with atezo by itself, but we did not see that…to me the reason to consider ipi/nivo will be for a patient who I would offer them chemo + Keytruda, but they say I don't want chemotherapy, and for the very small number of patients who are well enough

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to get chemo + Keytruda but cannot get Alimta because of renal problems, because if they are too sick to get chemo, they are too sick to get ipi/nivo.

…I'm curious to see what the actual [CheckMate-]9LA results will be, but if there is going to be a dent in the Keytruda dominance, it may come from that trial.

I think in contrast with PD-L1, with TMB we still don't know what actually we should be measuring, is it the number of genes, and not even where to put the cut-off, it's what genes, are these the genes that should be expected to provide more nuance versus just the total number of genes with mutations? So, I believe that TMB has potential and may become a biomarker that will be clinically useful, but it's not there.

The resistance to osimertinib…you can get C797S in up to 20%, we don't have any drugs against it… In another 15% to 20% to 25% there is a MET involvement, usually MET amplification, and you can use crizotinib, or another MET inhibitor…I haven't had any problems with payers, as soon as you show them that there's a MET abnormality, the crizotinib gets covered.

For TAK-788, numerically I think the side effects were a little bit better, and I expect that one of these two drugs probably will get approval because it's a very well-defined subset of patients, we have no targeted treatments, and the activity we have seen so far, response rates in the kind of 50% range, it's not as high a response rate that we have seen with activating mutations [that have response rates] in the 70s, but to me this is still an indication that these are active drugs... But between TAK-788 and pozio[tinib], it's difficult to say, maybe I'm leaning more towards TAK-788.

…this is one of the most exciting developments outside of immunotherapy, KRAS was found as an oncogene around 35 years ago and every single trial has been negative… We have more information with AMG510, the Amgen drug, more clinical information, we have a little bit of clinical information with the Mirati drug… KRAS is a kind of more complicated driver than let's say EGFR and ALK, but there are usually additional mutations on top of KRAS, so it's not surprising that the activity for both drugs was lower in terms of response rates than what we see with ALK and EGFR… To me, this is not evidence that the drug is not effective, it's just what the target is… So, for both drugs, these are first-in-human trials, so they had to be studied as monotherapy, but the future I think will be in combinations either with immunotherapy, or combinations with other targeted drugs based on the traditional mutations. So, I'm very optimistic about both drugs, and I don't think we have enough data to say one is better than the other.

The ones that you should follow are the RET inhibitors, it's 1–2% of lung cancer, but again based on the number of lung cancer patients, there are patients with these mutations. There are two drugs, one is I think Loxo/Eli Lilly [selpercatinib], and the other one is Blueprint's BLU-667. They're really neck and neck, advancing with every presentation of data – it's very similar designs. They are not 100% specific inhibitors, but they're much more active against RET than anything else. So, the toxicities are quite tolerable, and just looking at numbers, maybe the Loxo compound is a little bit better, but they're both highly effective, both in first line and subsequent lines.

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About the Author

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Please can you start the interview by summarizing your clinical experience with immunotherapies and targeted therapies for your NSCLC patients?

Yes, this will also help put some of my answers in perspective. I'm a medical oncologist, and I see patients with solid tumors, but I have an interest in lung cancer, so I see probably about 260 patients with lung cancer per year, so it's a significant proportion. As you know, as medical oncologists we don't diagnose cancer, so patients have to be diagnosed with lung cancer to get referred to me, and I see maybe about two thirds of my patients with advanced Stage IV disease, and one third is with stages I, II, and III. As part of the diagnosis, with most places, including us, there's an expectation that there will be a molecular analysis of the tumor. At our place and many others, this molecular analysis is done reflexively, meaning it's ordered by the pathologist as soon as they diagnose lung cancer, so before I see the patient. And when I see a newly diagnosed patient with advanced lung cancer, I will have not only the information on the type of cancer, but most of the time I will have information on the molecular composition of the tumor, and as part of the biomarkers for immunotherapies I will also have the level of expression of PD-L1.

So, with this information, once I see a patient with lung cancer, the decision to treat is based on the desires of the patient, but if a patient wants to be treated then we look at the presence of any genomic abnormalities that we can target, like EGFR, ALK, ROS-1, and BRAF abnormalities against which there are approved drugs, and regardless of what the other results of the testing will be, if there is a molecular driver that we can target, this is by far the most important criterion that we use to choose treatment. So, if it's any of these, the patient will get a prescription for an oral targeted drug.

In my practice, these are probably less than 20% of patients, more like 15% of patients, who will have a molecular driver that can be treated, so the majority will not have something that we can treat, they may have KRAS, or may have something against which there are no approved drugs. So, then the decision as to what regimen to use for Stage IV disease will be based on the PD-L1 expression. If PD-L1 expression is high, meaning more than 50%, I discuss with the patient whether we should use single-agent immunotherapy with pembrolizumab, or a combination of chemotherapy plus pembrolizumab, and I'm saying specifically pembrolizumab because this is the most commonly used checkpoint inhibitor for lung cancer in the first line.

So, for the high expressors, more than 50% expression of PD-L1, in my practice probably about a third of these patients will get chemo plus immunotherapy, and two thirds will get immunotherapy by itself. These are the patients who are candidates for immunotherapy.

Maybe up to 20% of patients, 15–20%, will not be candidates for immunotherapy because of autoimmune conditions, or high-dose steroids, so these are the patients who will get chemotherapy alone.

For less than 50% PD-L1 expression – again, all these patients do not have a molecular driver – for less than 50% expression PD-L1, whether it's less than 1% or all the way to 49%, my default regimen is chemo plus immunotherapy, and again this would be chemotherapy with pembrolizumab. Maybe 5%, less than 10%, so 5% will get immunotherapy alone, these are the patients that either could not tolerate chemotherapy or don't want chemotherapy, so they get only the immunotherapy drug, and about 20% again will get chemotherapy alone, because of contraindications for the combined regimens. This is in the first-line setting.

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I want to talk a little bit more about the molecular testing. So, what is the standard panel that you look at, is the molecular testing done internally for the most part, or is it done through a third party like Foundation Medicine for example?

So, at our place and many of the big places it's done internally. So, we have an internal panel, which as of this month is still only 50 genes that are analyzed for mutations, so it's a very limited NGS for specific genes that are cancer-related, and we do FISH analysis for ALK and ROS-1. Because we have this internal panel, it's kind of more complicated for us to be sending out biopsies. So, in lung cancer, in our place probably 10% at the most are sent out, and when we send out tissue, we send it out to Foundation, that's usually the vendor that we use. We are using more and more liquid biopsies, meaning molecular analysis for a limited set of genes. This is something that we do more in the second-line setting, not so much upfront.

Next month, our panel will be expanded to 170 genes, and we'll include not only mutations, but will include amplifications and translocations as well. So, right now we're missing a lot of the rearrangements of the translocations, I can see a mutation, but I would not be able to see it at fusion, for example.

Can you talk a little bit about when molecular testing is done? Is it all lung cancer patients, even patients that are earlier stage such as locally advanced, or even earlier than that, or is it mainly just the patients with metastatic disease?

So, we had a discussion several years ago with this reflexive system, it's difficult for the pathologists to know what stage the patient has, because they have the biopsy but they don't have the staging information. So, we decided that all patients with NSCLC will get tested regardless of the stage, but all patients with non-squamous histology, so we don't reflexively test squamous cell. The big academic institutions test both squamous and non-squamous, and many of the smaller groups they test only Stage IV disease. So, the practice kind of varies.

And for squamous patients, is it done on a case-by-case basis?

Yes, for the squamous it's on a case-by-case basis, and it is still based on some clinical suspicion as well, maybe this is not a true squamous cell, either a squamous cell in a never-smoker, or squamous cell in a kind of light former smoker, or it was squamous but the pathologists couldn't exclude that there is a non-squamous component. So, I would say that currently, because there are no approved drugs in squamous cell, I test less than 20% of my squamous patients.

I was also wondering, aside from the primary panel of genes that you are testing for, is there a secondary panel that you test in patients who have already progressed or relapsed? Is there a second set of genes that you might look for then?

In the current practice, if you don't identify a target driver upfront, the chance that in the later lines you will find the driver decreases. So, we test patients in later lines mostly for clinical trials. If, on the other hand, the patient had a driver upfront, so they had an EGFR mutation, these are the patients I would definitely test second line or third line, looking for the mechanism of resistance, is it another EGFR mutation, or is it a MET amplification, or now HER2 – so trying to find another specific mutation that I can

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target, and we definitely test also any ALK rearranged tumor. So, upfront and then looking for resistance mutations. We haven't started yet to look for a new driver.

Could you walk me through your thought process when you're prescribing immunotherapies in the first-line setting for non-squamous patients without actionable mutations? Specifically, there are four different immunotherapy-based regimens that can be used (Keytruda monotherapy; Keytruda + Alimta + cis/carboplatin; Tecentriq + carboplatin + paclitaxel + Avastin, the four-drug combo; and Tecentriq + Abraxane + carboplatin). Out of those four, how often would you say you are prescribing those in the first line, and what goes into that decision-making process?

You're right, there are several regimens that are approved, they have not been compared head-to-head, so we're kind of looking across trials, and the activity looks very similar. The four-drug Tecentriq + Avastin + CarboTaxol is used very uncommonly, and I've not used it because it's four drugs, and four drugs that have toxicity, and it's not just that Avastin adds to the toxicity, you have to use full-dose CarboTaxol, which is again a tough regimen to give. For the non-squamous patients, carboplatin + Alimta + Keytruda was the first one that was approved, we got a lot of opportunities to develop experience, to see what toxicities there are, confirm that it is active, which I think for two years, if not more than that, was the only thing that we could give in first line with chemotherapy.

So, when the data came out for Tecentriq, and it was possible to use it, the numbers looked very similar, so I didn't have any incentive to switch, I have good experience with Keytruda. So, it will be tough given the dominance of Keytruda for such a long time, you have to have some differentiating feature to make use of another agent. I don't think that Tecentriq is less effective than Keytruda, I also don't think that it's more effective, so if I'm used to one regimen, why should I change? The reason to change would be if there were data showing that maybe in a subset I can get a different response, or what we oncologists don't want to see, is the payers telling us – well, this is a patient on our program, and you have to use this regimen rather than another regimen, but this hasn't happened yet.

Carboplatin + Alimta + Keytruda, this is the approved combination, so for non-squamous patients I'm stuck with carbo + Alimta + Keytruda.

I think that Tecentriq – this is for a small set of patients who cannot get Alimta because of either kidney problems or pleural effusion, so they're a minority of patients who otherwise would be good candidates for chemo + immunotherapy but simply can't get Alimta, and that's specifically for the non-squamous ones, but it's a small number.

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What are your thoughts on the I-O regimens that are being reviewed currently by the FDA, or are going to be in the near future? So, Tecentriq monotherapy for high PD-L1 expressors based on IMpower110, the combination of Opdivo and Yervoy for PD-L1 expressors based on CheckMate-227, and the combination of Opdivo, Yervoy, paclitaxel, and cis/carboplatin based on CheckMate-9LA. What is your perception on whether these regimens are going to displace any of the current standards going forward, if approved?

It's not going to be easy, we're definitely not going to see a huge change, or a huge shift from Keytruda to nivo or Tecentriq, or ipi/nivo, but looking at the details of these trials gives us now more information on how to more specifically choose treatment. So, Tecentriq monotherapy is based on [IMpower]110, the numbers there look good but it's a slightly different way of scoring, you score both the tumor cells and surrounding inflammatory cells, so we don't know – several years ago, there was a comparison that there isn't that great a correlation of PD-L1 based on the Merck assay, versus PD-L1 – this immune cell and tumor cell score for atezo. SP[142] is another test, so you have to then ask your pathologist, do the PD-L1, the tumor proportion score for pembro, Keytruda, but then can you also do the testing for atezo, and most pathologists would not be eager to do something that they will say is a very similar test twice. So, the only way this could happen is if we saw a huge improvement in efficacy with atezo by itself, but we did not see that. Compared to the high expressors with Keytruda, my recollection is that maybe numerically, some of the efficacy parameters were better, but not by much. So, it was not enough of an incentive, and it has a kind of direct competitor, Keytruda by itself, so they're not competing with chemo + Keytruda.

This is different than the two BMS trials, where you have non-biomarker selected patients, meaning non-high biomarker selected patients, and for the [CheckMate-]227 part one that we saw, it is a chemo-free combination. This is the main selling point, your patients will not need to get the side effects from chemo, but they will still have the side effects from the combination. So, when 227 was initially reporting as a press release, oh, this is a positive trial, we had to see the actual results. And when the results came, you have this comparison of ipi/nivo compared to chemo, you have then the not so statistically valid comparison to chemo + nivo, and the results with ipi/nivo were not kind of remarkably better than what we've seen with chemo + Keytruda. With chemo + Keytruda, there is still the question of, well, does it really work in patients with <1% PD-L1, so the PFS there was not statistically significant. So, maybe in 227, we would see good results with ipi/nivo in the patients that benefit less from chemo + Keytruda, specifically in the <1% expressors, and it wasn't such a clinically significant difference. Actually, in my analysis of the data, ipi/nivo was better than chemo + Keytruda for the high expressors, but again this is based on the response rates, and again, not by much, and these are all across-trial comparisons.

So, to me the reason to consider ipi/nivo will be for a patient who I would offer them chemo + Keytruda, but they say I don't want chemotherapy, and for the very small number of patients who are well enough to get chemo + Keytruda but cannot get Alimta because of renal problems, because if they are too sick to get chemo, they are too sick to get ipi/nivo.

So, based on 227, it may be attractive on paper, but as oncologists we are very comfortable with chemotherapy, we became already comfortable with chemo + single-agent immunotherapy. The discontinuation rate for ipi/nivo was something that had to be respected, it was 18%, so I did not see what was presented in 227 as something that would make me change my practice. Yes, there will be 2–3% of patients that I will try ipi/nivo in, but it will not make a change.

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[CheckMate-]9LA was a different approach, you're still using chemo but for a shorter duration, fewer cycles, so it was not so scientifically attractive, but in a practical sense for me this was a good design, so this was a trial design with a clinician in mind. It was reported that it was positive, so were there actual numbers, have you seen the actual numbers?

The numerical data have not been released at this time.

Yes, it's only the press release, right. So, similar to 227, I would like to see the actual numbers. If the actual numbers show kind of what we hope to see, you're getting chemotherapies with two immunotherapies, I mean if there is a difference in the response rates across trials, so 9LA compared to chemo + Keytruda, if I see a response rate better by about 10% or more, I would say this makes sense. If we see similar response rates, but maybe the PFS is longer – remember in 227, I didn't dwell on it, but if you're an optimist you will see this elevation of the tail of the survival, and flattening of the survival, it's not a huge number but it looks almost flat. If you look closely at the [KEYNOTE-]189 or [KEYNOTE-]407 trials, I mean, there is also a flattening of the tail, of the curve, so I'm not that convinced that combining ipi/nivo makes the benefit more durable, but maybe it does.

So, to summarize, of the three trials, I'm probably most optimistic about 9LA, and it may be because I haven't seen the results, but the trial has the potential to be better, I'm not sure that combining chemo + immunotherapy forever is needed, in this trial it was two cycles [of chemotherapy]. So, I'm curious to see what the actual 9LA results will be, but if there is going to be a dent in the Keytruda dominance, it may come from that trial.

Also, as we were talking about CheckMate-227 a little bit, as you know, the TMB (tumor mutational burden) biomarker was used in the earlier data releases, but more recently there was a fallout with the TMB biomarker. So, based on that, and other data that you have seen, do you think that TMB might still have a potential utility in NSCLC, or do you think it's really kind of the end for TMB?

I was part of the believers, there is consensus, PD-L1 is not a great – not even a good biomarker, but we still use it because it's part of the approval. TMB makes a lot of sense, not maybe at the deep scientific level, but superficially it makes a lot of sense. So, when the first three points of 227 came up, it's an excellent marker, see, based on PD-L1 you don't see a difference, based on TMB you do see a difference, and then kind of the disappointing follow-up, and the actual data came.

I think in contrast with PD-L1, with TMB we still don't know what actually we should be measuring, is it the number of genes, and not even where to put the cut-off, it's what genes, are these the genes that should be expected to provide more nuance versus just the total number of genes with mutations? So, I believe that TMB has potential and may become a biomarker that will be clinically useful, but it's not there.

Another problem with TMB, at least in the current shape, is that it requires more than 200 genes, and some of the panels are with 400 genes to calculate TMB, so you have four genes or five genes that you need to know the results, because there are targeted drugs. Then you have to test an additional several hundred genes to get to the number, and this uses a significant amount of tissue. So, even if the TMB is established as a good predictor, we have to find an easier way to measure it. But I still believe that it may turn out to be a biomarker, maybe not for ipi/nivo, but it makes a lot of sense.

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If one of your patients fails treatment with a PD-1/PD-L1 inhibitor regimen, what would the next line of therapy be? What about patients that fail chemotherapy plus immunotherapy? What are their options after that?

So, this is the largest unmet need if we look at all patients, because we go to chemotherapy. Depending on whether the patient was squamous or non-squamous cell, it is usually single-agent chemotherapy. I use a lot of docetaxel, or docetaxel + ramucirumab, so docetaxel + Cyramza. What I've heard from national surveys is that it's used in somewhere between 15–20% of patients, even though it's an approved regimen, but docetaxel is not an easy drug to use in its full dose, which is what the package insert says. But I believe that there is some additional benefit from getting the VEGF receptor antibody.

It is approved for both squamous and non-squamous, so if a patient can tolerate docetaxel, I usually combine it with ramucirumab. Otherwise, it's single-agent docetaxel, single-agent gemcitabine, or even single-agent Taxol, or I look for a clinical trial since many trials are specifically now trying to find a treatment that works better in previously treated patients.

I was anticipating your next question, and that is what proportion of patients will be treated in second line, and in my practice it's the majority, more than 90% of my first-line patients will get to second line.

For previously treated patients that are going to go on to receive a PD-1 or PD-L1 inhibitor, what agent do you prescribe most often, and what goes into that decision?

So, this is a small group, but I don't know, in my practice probably 10–15 – I think it would be less than 20%, but maybe 10–15% of patients, and these are the patients who didn't get immunotherapy first line because they had some transient contraindications, but if they had say an autoimmune condition, it doesn't change for us in second line. But if they had to have brain radiation and so they were on steroids when their first-line chemo was given, this would be the patient that I wouldn't have given immunotherapy first line, but I will offer it in second line.

My second-line use is mostly Tecentriq, it's again not that scientific, it's based on the initial approvals where you had to have PD-L1 results in order to give pembro, and in this case most of the time patients will get the Keytruda first line. While for Tecentriq in second line there is no requirement for PD-L1 testing, it's every three weeks, so it's a regimen that we're used to. You may ask, well, then why don't you use nivolumab, that's every four weeks? So, depending on the patient's characteristics, I mean how far they live, are they sick, are they not sick, nivolumab has this advantage that I can give it either every four weeks, or every two weeks. So, Tecentriq is my most commonly used second-line drug, followed by nivo and very little pembro.

What kind of a role do PD-1/PD-L1 inhibitors play in the treatment of patients that have addressable mutations such as ALK rearrangement or EGFR mutation-positive NSCLC currently?

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I mean, the current dogma based on mostly retrospective analysis is that immunotherapy is less effective in tumors with drivers than chemotherapy. It's not that it doesn't work, it's just that it's less effective in the trials where they were comparing it to chemotherapy, and most of the data then came from second-line trials. So, right now I try to exhaust any targeted options, followed by at least one round of chemotherapy by itself before I must consider immunotherapy.

The exception is the CarboTaxol + Avastin + Tecentriq, the four-drug combination they advertised it as, this is the immunotherapy regimen that has activity in patients with mutations, more so than the arm without it. I mean, it's based on a very limited number of patients who were with mutations, but the data is data. So, I've had one patient who progressed on an EGFR inhibitor – he was not a candidate for another targeted drug – that I offered CarboTaxol + Avastin + Tecentriq. So, it's a way to offer immunotherapy to these patients, but these are small numbers. So, still most of these patients will not get immunotherapy.

Moving on to the more targeted therapies, in patients with sensitizing EGFR mutations, could you describe your typical approach? Do you typically use Tagrisso in the first line, or earlier-generation EGFR inhibitors like Tarceva and Iressa?

No, my practice is kind of representative of what's happening, Tagrisso is the only one that we use first line.

How often do you re-biopsy after progression to check for signatures associated with EGFR inhibitor resistance? If you come across those, where do you go from there?

The guidelines are to biopsy patients on progression with EGFR and osimertinib, to make sure that you're not missing transformation to small cell. For any other reason, a liquid biopsy will be sufficient. So, I'm doing somewhat of a mixture, maybe half of the patients I will biopsy, and half of the patients I will send for a liquid biopsy.

The resistance to osimertinib is kind of more diverse than the resistance to the earlier generations. With the earlier generations, you'll get T790M in about 50%, here you will not get T790M, or if you get it it's in combination, so it's not a player. But you can get C797S in up to 20%, we don't have any drugs against it – this is an EGFR mutation, we don't have any drugs against it, but there is active research to find something that works for C797S.

In another 15% to 20% to 25% there is a MET involvement, usually MET amplification, and you can use crizotinib, or another MET inhibitor.

Most of the time you'll find something that you kind of see this is the mechanism, but you cannot use it for a treatment decision, at least for now. But the paradigm is that you have to biopsy on progression, EGFR mutant.

I see, so do you treat patients that come up with MET amplification with crizotinib, Xalkori?

That's correct, and I haven't had any problems with payers, as soon as you show them that there's a MET abnormality, the crizotinib gets covered.

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Have you encountered any patients with an EGFR exon 20 insertion mutation? How are these patients typically treated?

I follow what we've seen in retrospective, and also some single-arm trials, these patients are not expected to respond to the current three generations of inhibitors. So, these are patients that I actively look for trials for them, which in the first line I think there is no trial, so the trials are after first-line progression. So, currently when I see an exon 20 insertion, I start chemotherapy.

What is your perception of the inhibitors being developed for these patients, such as TAK-788 and poziotinib?

I mean, these are the two that are most advanced, so pozio[tinib] has activity, as you know it's a repurposing of an older drug, it's quite toxic, but the activity is there. For TAK-788, numerically I think the side effects were a little bit better, and I expect that one of these two drugs probably will get approval because it's a very well-defined subset of patients, we have no targeted treatments, and the activity we have seen so far, response rates in the kind of 50% range, it's not as high a response rate that we have seen with activating mutations [that have response rates] in the 70s, but to me this is still an indication that these are active drugs. Exon 20 is part of most panels used for testing EGFR, so you already have the information. It's a small number of patients, I mean, it's a small percentage, but given the number of lung cancer patients, it's a sizable minority. But between TAK-788 and pozio[tinib], it's difficult to say, maybe I'm leaning more towards TAK-788.

Because of the toxicity and side effects?

Yes, correct. And, as you know, both drugs are not only against EGFR exon 20, but against HER-2 exon 20, so this adds a few percent of patients, but not by much.

Can you tell me about your clinical experience with ALK inhibitors and how you decide what to prescribe in the first line and in subsequent lines?

So, ALK is straightforward, the current first-line regimen is alectinib by a huge margin. I don't think anybody's still using crizotinib. Both ceritinib and brigatinib have first-line data, but alectinib is kind of the established one. It's also less toxic than these two. So, you have a drug that's active. Once a patient progresses on alectinib, most of us, including me, the practice is to do a liquid biopsy to look for resistance, and I think most of the panels – we use Guardant360 as the liquid biopsy panel – they have a very nice table of mutations associated with resistance, in which ones of the second and third – second-generation ALK inhibitors are more likely to work. The only one that you have evidence for activity after two ALK inhibitors is lorlatinib, Lorbrena. So, I usually reserve lorlatinib as third or fourth line, and my current sequence is alectinib – based on the mutation – but the typical one is alectinib followed by brigatinib, and then lorlatinib. Then, I will circle back to something like ceritinib. Yes, I mean we have five drugs, so even though these are rare patients, I try to expose to all the drugs before we go to chemotherapy, including crizotinib.

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Do you ever use any of these drugs on ROS-1 patients, or do you stick to entrectinib for that?

Because crizotinib was the first one approved, I mean, I probably have more patients with ROS-1 on crizotinib rather than entrectinib, but again these are very rare patients.

Have you ever encountered a patient with an NTRK gene fusion in your practice?

So, I had a patient, not with lung cancer, a patient who was referred with a mammary secretory type of tumor, and we sent them to Boston for a clinical trial.

I see, it's a very rare mutation.

Yes, and because my practice is in lung cancer, these are rare there.

There are two drugs approved for NTRK mutant patients, Vitrakvi and Rozlytrek, do you have any impressions on those two, and which one is better for the NTRK gene fusion?

I mean, they were both highly active. They were both kind of not pure NTRK inhibitors, the Ignyta compound [Rozlytrek] having a kind of broader spectrum of activity, which for some targeted agents – well, it's maybe a negative because you have more side effects. There wasn't a huge difference in the toxicities. I'm maybe favoring a little more the Loxo drug [Vitrakvi].

With some results out for the KRAS inhibitors now, what is your perception of that class of drugs, Amgen's AMG510 and Mirati's MRTX849?

So, this is one of the most exciting developments outside of immunotherapy, KRAS was found as an oncogene around 35 years ago and every single trial has been negative. Targeting both upstream of KRAS and downstream of KRAS, whether it's a farnesyltransferase inhibitor, or MEK inhibitor, so when several years ago the report came out, and Shokat's group was able to find a way to block at least one of the subtypes of KRAS mutations, the G12C, it sounded very exciting, and five years later we have clinical results. We have more information with AMG510, the Amgen drug, more clinical information, we have a little bit of clinical information with the Mirati drug, but maybe slightly more preclinical with its kind of predecessor – a closely related Mirati drug. They're both not for all KRAS, they're both for the G12C-specific subtypes, which is more common in lung, rarely seen in pancreas where you have a lot of KRAS, less common in colorectal where again you have a lot of KRAS mutations. So, for both drugs, we saw clear evidence for activity in lung cancer.

KRAS is a kind of more complicated driver than let's say EGFR and ALK, but there are usually additional mutations on top of KRAS, so it's not surprising that the activity for both drugs was lower in terms of response rates than what we see with ALK and EGFR. I mean, the response rate to the Amgen drug was like 54%, but if you look at the actual individual subjects in the trial, some of those were non-confirmed responses, and some non-confirmed are never going to be confirmed because one progressed, one died, so the actual response rate is probably in the 40% range rather than in the 50%. To me, this is not evidence

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that the drug is not effective, it's just what the target is, and this also provides an explanation as to why the activity in colorectal cancer was much lower for both drugs. I strongly believe that the drug binds, so it's not that the drug doesn't reach. If you think of colorectal cancer, EGFR works differently than in lung, BRAF inhibitors don't work in colorectal, they work in melanoma, so it's the context. So, for both drugs, these are first-in-human trials, so they had to be studied as monotherapy, but the future I think will be in combinations either with immunotherapy, or combinations with other targeted drugs based on the traditional mutations. So, I'm very optimistic about both drugs, and I don't think we have enough data to say one is better than the other.

What is your perception of the inhibitors being developed for MET exon 14 skipping mutations, such as capmatinib and tepotinib?

They're both very active drugs, and I've treated patients with exon 14 skipping with crizotinib because it's the one that you can get off-label. It's a small subset, but it's a subset where this is a driver, and there is good activity, kind of durable activity with an inhibitor. And, again, the data that we have seen, in first line, in second line – whichever drug gets approved first will probably be the one that we'll use, because I haven't kind of seen any signals that one is much less toxic than the other. It's a mutation that's included basically in all panels.

Does the efficacy for capmatinib and tepotinib in your eyes look better than it would for Xalkori in these patients?

I think the numbers are better, again, they have not been compared head-to-head, but what we've seen, I think they're more active than crizotinib. My point was that between capmatinib and tepotinib I couldn't tell which one is better, but compared to crizotinib I think they're better.

In the current landscape, what are the biggest unmet needs that remain or are currently not being addressed?

It is by far effective treatments for patients previously treated with immunotherapy, and there is nothing that looks like "this is going to be the winner". There are dozens of trials that are looking at very early combinations. Then, if we accept this is the largest unmet need, then the next one will be for these very small subsets of patients with EGFR mutant lung cancer progressing on osimertinib, what do we do there? Getting the KRAS inhibitor to market, yes, it's exciting, but these are all Phase I studies.

Are there any reimbursement or pricing issues that affect patient access currently? Have you faced any restrictions in terms of prescribing any I-O or targeted therapies to your NSCLC patients?

Maybe almost two years ago I had a patient with high PD-L1, and the payer said no, either you give them Keytruda, or chemotherapy, but not the combination. Maybe now they would not do that, but at that time that was the response. Otherwise, with immunotherapy I haven't had any issues.

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With the targeted drugs I had a problem with alectinib; even though it was not a formal step therapy, they wanted ceritinib or crizotinib and using alectinib in the second line. So, we appealed, and they denied it, we appealed a second time, and then they approved it.

I haven't had issues with EGFR inhibitors, osimertinib is by far the most commonly used.

Are there any important topics pertaining to the treatment of non-small cell lung cancer or early candidates that we haven't talked about, that you would be happy to discuss?

The ones that you should follow are the RET inhibitors, it's 1–2% of lung cancer, but again based on the number of lung cancer patients, there are patients with these mutations. There are two drugs, one is I think Loxo/Eli Lilly [selpercatinib], and the other one is Blueprint's BLU-667. They're really neck and neck, advancing with every presentation of data – it's very similar designs. They are not 100% specific inhibitors, but they're much more active against RET than anything else. So, the toxicities are quite tolerable, and just looking at numbers, maybe the Loxo compound is a little bit better, but they're both highly effective, both in first line and subsequent lines.

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