2020 Target Therapy Forum

EGFR Session

Choice of Frontline EGFR Therapies

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Dr. Jared Weiss: Associate professor of medicine at UNC Lineberger Comprehensive Cancer Center. And vice-president here at Cancer GRACE. I'm privileged to be joined from by my colleague, Dr. Piotrowska from Harvard University, MGH hospital. Unfortunately we're not in Boston, in her hometown, but rather virtually from our own offices and living room. Nonetheless, this is our breakout session on Epidermal Growth Factor Receptor or EGFR. So if that's not where you meant to be, I invite you to switch to the appropriate breakout room. But if not then let's move forward. Here are my disclosures. I didn't work on any of the agents I'm going to be discussing with you here, although I have done work with each of the relevant companies. So let's just start by reminding ourselves of the basics of what is EGFR? As I mentioned in my first talk today, the very nature of cancer are mutations. Mutations are changes in the instructions or DNA of a cell that convert it from a useful, healthy, specialized cell into a more general misbehaving cell, a cancer cell. EGFR is a particularly common and important change in lung cancer.

It is the most important driving mutation in about 15% of adenocarcinoma of the lung. It was the first of our changes to be actionable and we care about it so deeply because it actually matters. We can clinically action it for improvements in cancer control probably survival and certainly quality of life. Here's a summary of what I want to talk about today. I'll briefly look into some history because it's helps us to understand how we got to where we are, looking at the first-generation drugs to gefitinib and erlotinib. I'll take a brief look at what I personally considered the last generation of drugs, afatnib and dacomitinib, the so-called second generation drugs, moving on out to third generation drug or osimertinib. There are some new challenges that have added to first-generation drugs. They're not something that I'm advocating doing, but I think they're relevant to talk about because of ongoing studies utilizing similarly themed strategy is to add to osimertinib.

And finally, I'll end briefly on the rarer but critical to those who have them Exon 20 insertions. There are other changes in EGFR that are a bit beyond the scope of our talk today, which will mostly focus on the classical activating mutations in Exon 19 and 21. So I showed this slide before, but I just want to reiterate here a reminder that when we when we're not matched to mutation or targeted therapy is worthless, but the real reason I'm showing this slide, the aha moment that when you compare a first-generation EGF RTK like gefitinib or erlotinib to chemotherapy, they win. In case doing this once wasn't enough, we've probably done this about 15 times now in some fashion, as a field and every time the same answer emerges, which is that targeted therapy, beats chemotherapy for progression-free survival. But with one or two possible exceptions really doesn't tend to make a difference for survival. The latter is probably true, not because targeted therapies don't add to survival. They absolutely clearly do. It's more that there isn't clearly a sequence effect.

So if you have perfect crossover, meaning you get TKI first and then chemo later or chemo first, then TKI later, it's not clear that the order matters that much, at least from a survival perspective, I would argue they do from a human perspective. So there were two second generation TKIs, they're a bit more potent against the classical targets and start to get at some of the resistance changes. I'm showing you here data from the Lux Lung 7 study to progression-free survival curve, which means that it takes down every time a patient's cancer grows or a patient dies. And when you can see here is that the blue curve with afatnib is just above the red curve with gefitinib, PFS or cancer control is better with the second generation drug. At the right, you can see why I don't use these in my practice. The toxicity is also substantially enhanced, maybe enhanced is the one word we sometimes use backwards words in oncology, like progression, which is also a bad thing, but at any rate, a lot more classical EGFR side effects like diarrhea and rash.

Same thing really emerges with dacomitinib where again, progression-free survival is improved, but it's not clear not given the absence of survival advantage and the adverse effect profile that this really, that the human math really adds up here. Now as is covered elsewhere, at the time of resistance, at the time that the cancer grows, there's going to be a resistance change. The cancer is going to have learned its way around treatment. And this is going to be the subject of the next very important talk. But for now, I'll remind you that when you give a first-generation drug like gefitinib and erlotinib, 60% of the time, the resistance that emerges is from a single nameable change that happens to be called T790M. And multiple drugs were developed to inhibit T790M. I'll save you some of that history, because it's less clinically relevant and less relevant for understanding our current story. And in summary, say that osimertinib was the winner here.

Osimertinib is more potent against the classical EGFR mutations, and it's also very active against the T790M resistance change. And that was where it was first studied in the 60% of patients who after gefitinib or erlotinib would develop this change. Randomized study was done comparing the then standard of care chemotherapy, to osimertinib. And what we see here is that while chemo certainly works and I'm focusing on the top curve right now, that's a curve at least as good as what we see in patients without EGFR mutation, osimertinib works far, far better. I'll show you the toxicity profile a bit later, but for now suffice to say it is dramatically superior to chemotherapy. And so based on the curve shown on top osimertinib, it became the standard of care after progression on gefitinib or erlotinib when the resistance change was T790M. Something interesting and exciting, also emerged from this data, which is to say that this drug crosses into the brand.

What you see at bottom is that the PFS curve is every bit as good in patients with brain Mets as without, and of course, if it was better in second line, we asked the question we normally ask for good second line drugs. Well, if they're so great, they're what about bringing it forward to frontline? And in this case, you could have made arguments either way that maybe we need to save the drug for resistance changes, but you could have also said, what about the 40% who develop other resistance changes? What about preventing that resistance upfront? Could that be better? And of course, critically for quality of life. What about the superior toxicity profile? The top left is the key slide here. This is the total population showing that when you compare starting with osimertinib to starting with a standard TKI, your PFS is better nearly doubled. And I would know essentially additive for the 60% of the population that would have emerged with T790M as the resistance strategy.

But when you consider that 40% would have emerged with some other modality, that 19 months becomes all the more impressive. And column B at the far upper, right. We see the PFS in patients with brain mets. Similarly. Excellent. Again, a similar curve, I'm sorry. In patients with brain mets. Yes. Bottom left patients without brain mets, still good. And here we see two themes that are very important in the survival curves. The first is that compared to historic curves that I showed you earlier, standard TKIs are looking better than before. This is because of next generation therapies like subsequent erlotinib, better chemo, perhaps studies and also that the osimertinib looks yet better. And this really to me put the nail in the coffin for first-generation TKIs in countries that have the resources to afford osimertinib and in my practice outside of a clinical trial this is the clear standard frontline drug, and I really have no temptation to do anything different.

Of course, if you speak to patients many emphasized quality of life over duration of life, I would argue both matter. And in the case of osimertinib, we really don't need to decide between them. This is the comparison of the toxicity profile of osimertinib versus standard First-Generation EGFR TKIs. This is not the comparison to chemo, but rather to the targeted therapy that was already pretty wonderful compared to chemo we're doing yet better. And so for those who like beer, this is great taste and less filling. Again, the clear standard in my practice, at least outside of a clinical trial. Now there are new strategies that have been evaluated in frontline with earlier generation drugs. While some of these may have compendia listing or approval, I'm not advocating for their use so much as wanting to show the principle because these are being evaluated in combination with osimertinib. And so I want to give a little sneak preview of what we know so far. So you're looking here at a Japanese study of erlotinib versus erlotinib plus bevacizumab.

And at first glance, this looks exciting and I'll admit that I was excited when we first started seeing data on this combination, what's exciting here is a big PFS advantage, a hazard ratio of 0.60 with the winning curve in goal being erlotinib and bevacizumab. But with additional follow-up and look at additional measures, the advantage here seems to shrink. So PFS2 is a measure that the European regulatory agency really likes. It looks at the time from initiation of first-line drug to the time of progression or death on second line drug. And so it tries to look at how long lived the effect is and how important it is to go first. And what we see is that when we look at this longer measure, the advantage starts to shrink the hazard ratio is smaller and we lose statistical significance. And when we fast forward to the very objective and perhaps key endpoint of survival, the advantage disappears our hazard ratio is one, with no survival advantage at all.

I would further note that at least one other study of this combination didn't even show a PFS advantage. And so I'm very interested to see what this looks like in combination with osimertinib. I would note before moving on from here, that there is a positive study with first-generation drugs in combination with the VEGF receptor blocker, remnisirimab. And I'm also excited to see that in combination with Osi, the other novel not-so novel perhaps combination to talk about is adding chemo to TKI upfront. You're looking here at a study of frontline gefitinib versus gefitinib plus chemotherapy. And this study, honestly I'm not sure what to think about this, whether to be excited or disappointed. I'm excited because as you see the addition of chemo to gefitinib upfront improves progression-free survival at top and bottom as well, survival. I'm glad to have any advanced possible for patients, but the human advantage of a chemo free regimen cannot be understated.

And listening to patients I hear frequently the desire to avoid the side effects of chemo and beyond the side effects and arbitrary age rate of chemotherapy, I can't say I'd love it

either. But as well, chemotherapy beyond the side effects, it also medicalized the life of a patient. If I can give a single agent oral drug, as opposed to the need for an infusion like bevacizumab ramucirumab, or chemotherapy, the patient is out spending their time in a more normal fashion and in my office less often. And I think for some people that difference of medicalization versus de-medicalization can be very important. Exon 20 insertion is extremely important for those who have it. And I apologized to speak about it only briefly. It's not just because of its rarity, but because there's a limited amount of data out there. I think Jackson, had his own breakout session, but if he's watching, I'll also apologize for the busy-ness of my slide.

Over the 13 years we've known each other, he's been encouraging me to not show slides this busy and for 13 years I've mostly ignored that even though he's clearly right, you're looking here at waterfall plots. Waterfall plot. Every patient is represented as a bar that either goes up or down and up means percentage growth of their cancers down means percentage shrinkage and the dotted lines are the 30% shrinkage that we arbitrarily call response. There's absolutely no regression discontinuity between 29 and 31%. What I mean is that being just above or below 30 is not a magic cliff. But we had to set the bar somewhere to compare one drug to another. What you see from all of these waterfall plots is that there were multiple active agents against Exon 20 insertion. It is no longer an unarguable target. I want to highlight three of these that I'm particularly excited about. So looking at osimertinib at the top right. This is data that we just saw at ASCO.

Some of you may recognize the speaker, that's exciting because this drug is commercially available. If your patient does not have access to a clinical trial or ability to travel for a clinical trial, you can write osimertinib off-label tomorrow or rather your doctor can. And in fact, I just had one very fascinating patient I've had the privilege of getting to know for a long time with Exon 20 insertion did very well on multiple chemotherapy regimens for years. And then reach a point where she had leptomeningeal disease, which is infiltration of the cancer to the fluid filled space in the brain. This is an awful condition that contracts quality of life, but in parallel with Dr. Piotrowska ‘s presentation at ASCO, there was another one showing even superior brain activity of osimertinib at a double dose. And so with what can we lose approach? We tried this and it has resulted in a dramatic improvement in quality of life driven by neurologic improvement, and the ongoing survival of this wonderful human being who's benefiting from it.

And so in the real world, this does actually work and is accessible. I would also highlight that both Mobocertinib and Amivantanab. I practiced those for a few minutes before these talk and probably still butchered them have FDA fast track designation. Poziotinib is also active but the side effect profile is a little less impressive than what I would like to

see. I would like to thank you all for your kind attention. And as I promised in my first talk and with pictures of the kids. Top left, I really like this picture because it's sort of reflective of a time in my daughter's life. They just graduated kindergarten, excuse me preschool and are now on a virtual kindergarten. It's a time in their life, and also I think in all of our lives with the masks on there. And at bottom right, my adorable daughter, Charlotte if you've heard daddy, daddy, daddy at all in the background, with apologies, that's her.