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EDWIN YAU: We're going to focus mostly on metastatic lung cancer, and some updates, and some of the new FDA approvals. And just nothing to disclose. And just a couple survey questions to start with. So for those that see lung cancer, what's your preference for molecular testing in newly diagnosed metastatic non small cell lung cancer? Is it a broad panel testing for finding that you're including genes without FDA approved therapies, would you get it in all adenocarcinomas or only in nonsmokers? Or would you do more limited testing, restricted to FDA approved drugs in all cases, or in nonsmokers only?

And then, a second survey question. A preferred first line treatment, as first line treatment in treatment naive metastatic non squamous, non small cell lung cancers, without driver mutations, with a PDL1 low or intermediate, between 1 and 50% and eligible for checkpoint inhibitors. So would you give pembro monotherapy? Would you give platinum plus pembro, plus pemetrexed? Or would give atezo/bev/paclitaxel and carbo. And this is-- I understand there's a lot of caveats here. My dad, as a kid, always made me pick my favorite. So this is a pick your favorite type of survey.

OK, so this here, nothing like KEYNOTE-189, which was the platinum pemetrexed-pembro trial. But some updates for today. Basically, just two larger points. One is, basically, I'm going to focus just on immunotherapies and targeted therapies in metastatic lung cancer, and similar of the new approved agents in some of the new trials. And a big take home point is that as we develop better means of identifying the correct targets in patients, and as we develop better drugs, it seems like what is especially true in target therapies, moving the best drugs with the best targets upfront and giving those therapies first is what seems to be most effective.

So lung cancer, still a leading cause of cancer mortality, both men and women. And we talk about lung cancer and the broad histologies. Today we'll focus on the 15% that are small cell lung cancers. And the rest are non small cell lung cancers. And within non small cell lung cancer, we have predominantly adenocarcinomas, and then second is squamous cell carcinomas. And today, mostly, we'll be talking about small cell lung cancer and adenocarcinoma. So less stuff on squamous. And here's the brief outline.

So we'll start with immunotherapy updates in a non small cell and small cell lung cancer. Then we'll talk about some of the newer targeted treatments, either FDA approved or coming down the pipeline. And I think at this point, I probably don't have to introduce checkpoint inhibitors. Just that PD1 inhibition in lung cancer has been very successful. And we came later in the game, compared to melanoma. So it seems like the CTLA checkpoint is a little bit less useful in lung cancer, although we're still having ongoing studies or still waiting for a number of studies to read out. But so far, PD1 inhibition of the immunotherapy checkpoint has been very successful.

And, of course, like everybody else, what we're most interested is the long tail of the curve. And we had a five-year overall survival data from the nivo phase I trials, presented last year, with a 16% five-year overall survival. And this year at ASCO, they updated the five-year overall survival from KEYNOTE-01, which was the phase I, humongous phase I-B. And here, they showed that in all comers, for frontline pembro treatment, we have a five-year overall survival around 23%.

And this was even better in PDL1 high, so PDL1 greater than 50%, the five-year overall survival and frontline treatment was almost 30% here. And in previous treated, about 25%. So we are seeing long-term survivals as compared to the 5% prior to checkpoint inhibitors. And so, of course, because of this, many approvals. And for this year, three approvals-- or two approvals. I'll talk about nivo as well. But two in small cell. And then one somewhat controversial approval on first line pembro in PDL1 positive.

So as of today, our frontline options with immunotherapy eligible patients with metastatic non small cell lung cancer, from KEYNOTE-024, and confirmed with KEYNOTE-042, we know that pembro is definitely superior to chemo in PDL1 high patients, so PDL1 greater than 50% on the tumor. And in red is-- the 042 trial was discussed last year at ASCO. And the paper came out in *Lancet* this year.

And it was FDA approved this year. And that's for PDL1 greater than 1% now. And 189 was pembrolizumab added to platinum pemetrexed versus chemo alone. And then Power 150 was the four drug ABCP with atezolizumab and chemo, and bevacizumab, which outperformed the chemotherapy as well. And then for the squamous cells, based on KEYNOTE-407, we had the approval of pembro plus carbo with either nab-paclitaxel or paclitaxel in advanced squamous cell lung cancer.

And so this is a lot of hand-waving. We don't know exactly why chemo combinations with PD1 inhibition works so well in lung cancer. It works, so, several hypotheses. I don't think anything has come out as a slam dunk. Some postulate that with the chemo and killing tumor cells, that there's more antigen presentation. And others postulate that perhaps we're reducing levels of inhibitory immunotherapy cells. And that's sort of my favorite speculation at this point.

But regardless, so far, the overall story in lung cancer has been the success of chemo I/O combos. And just some updates on the two big chemo I/O combos in non squamous and non small cell lung cancer. And so KEYNOTE-189, this year we finally got the median overall survival. It wasn't reached when it was approved. But ASCO, the median overall survival of 22 months with pembro compared to 10.7 months with chemo alone. And that chemo alone arm is sort of what everyone looks at. It kind of underperformed in this population. And why that is, we don't exactly know. But clear hazard ratio and clear benefits.

And then IMpower 150, which was the four drug cocktail, a little bit more toxic, with the addition of paxol and bevacizumab, but they did some extra subset analysis that they presented at ASCO this year, and this was one of their pre-specified subset analysis, was looking at patients with baseline liver mets. And it did seem that the four drug cocktail did outperform either chemo plus atezo alone or chemo plus bevacizumab. Both seemed to favor the four drug cocktail.

And whether or not we remain to-- we're still waiting on one of that one in the main arms from IMpower 150 to read out. That's the chemo plus the atezo arm without the bevacizumab. Based on the study in the liver, it didn't seem like that arm did very well. So we still await the overall results of the arm, Arm A, in IMpower 150, to see if bevacizumab is really needed or not. And here, they may have much better performing chemo with bevacizumab arm compared to 189. And of course, patients that are eligible to get bevacizumab are going to be a little bit healthier overall. So this is probably a healthier population than 189. But still, significant hazard ratio with the addition of atezo.

And then this year, the FDA approved pembrolizumab monotherapy in PDL1 greater than 1%, based on the KEYNOTE 042 trial, which was overall a positive trial, but sort of the approval, the patients that they extended approval to, somewhat negative. It was positive because the overall specified endpoint after a lot of modifications was overall survival in PDL1 greater than 50%, greater than 20%, and greater than 1%. And it did meet all those end points on the bottom.

You can look at the overall survival curves of pembro versus chemo. And in greater than 50%, greater than 20%, and greater than 1%, were all positive with significant hazard ratios. Some criticisms about the trial. So 042, unlike 024, which is the trial that led to approval of pembro in PDL1 high patients, crossover was not allowed in this study. And this study was driven mostly by the PDL1 high population.

Over three quarters of the patients were PDL1 greater than 50%. And when they excluded the greater than 50%, their hazard ratio crossed 1. And there was no improvement. Although, their argument was that this was the overall end point, and adverse events favored pembro, with significantly less grade 3 to 5. Similar mortality, 2% in each arm, with some extra immunotherapy adverse events, of course, in the pembro only arm.

So in any case-- and another criticism of the study is that not all of those-- so you could get either carbo-taxol or carbo-pemetrexed as the chemo. And for those that their plan to get pemetrexed maintenance, only about 75% of those patients actually got pemetrexed maintenance. So perhaps not the most optimal chemotherapy. And also this trial was a mostly Asian and South American trial, whereas 024 was a mostly European and North American trial, so how much are we going to extrapolate to the North American population as well.

There's a lot of caveats with this approval in the PDL1 between 1 to 50%. Clearly, though, this does confirm KEYNOTE-024, that in the PDL1 high patients, in my mind, pembrolizumab as a monotherapy is a viable option. And we await the longer term follow up with KEYNOTE-189 to kind of see how the tail of those curves look when comparing 024 and 189, and trying to decide whether to add chemo in those patients that are going to have a good response with pembro alone.

And this is just showing the KEYNOTE-189 data again with the different PDL1 groups. And even in the negative patients, a clear overall survival difference. And also in this middle tier, with a PFS also approved, except for in the PDL1 negative patients. So in my mind, in this intermediate range, if you're not eligible for chemotherapy, you wouldn't have been eligible for the 042 trial. It is ECOG 0 and 1. You had to be eligible for chemo. So whether we can extrapolate those patients, where we're a little bit worried about them, whether we want to give chemo, and we really would like to just give pembrolizumab monotherapy, we're extrapolating a little bit, although retrospective studies suggest that probably they performed just as well.

So I think if chemo is definitely not an option in a frail patient perhaps, but in general, I tend to favor the combination in this middle range, especially if they have bulkier disease. We recognize from all of these curves that PDL1 is a continuum, and that the more you have, more likely the more benefit you have from pembrolizumab. So there's probably a difference between a score of 25% versus a score of 1%. So if you're 25%, and you really don't want chemo, perhaps.

And as far as picking between these two, I think in the-- between all these choices in the PDL1 high population, again, it's a discussion with the patient about chemo with immunotherapy versus immunotherapy alone. And the jury is still out on which one will ultimately be better. And as far as picking between the two chemos, in IMpower 150 regimen, you have to tolerate bevacizumab. And you get some-- pemetrexed is much more favorable for the patient, toxicity profile wise. And so I consider this regimen here in younger, healthier patients, who maybe have liver mets, especially, and some other genomic characteristics. But in general, like the audience, we mostly favor the 189 regimen.

OK, so moving onto small cell lung cancer. So these were the recent approvals of checkpoint inhibitors in small cell lung cancer, with nivolumab and pembrolizumab monotherapy being approved in the third line setting, so meaning platinum doublet and then some other treatment before nivolumab or pembrolizumab. We know that the second line nivo trial failed. And we know that the chemo ipi trial failed. We know the ipi and the nivo maintenance trials failed. But the IMpower 133, the combination of atezolizumab to carboplatin and etoposide in the first line was positive.

And these are all kind of modest incremental approvals. We'll talk first about the third line approvals. The nivolumab, this is based on CheckMate-032. And overall response rate in the 12% range. But a good duration of response. But again, with a big range. And as you can see, the long duration response is again restricted to these very few patients that ultimately respond to checkpoint inhibitors.

And the same for pembro. So they combined the analysis of 028 and 158. 028 was restricted to PDL1 positive, so PDL1 greater than 1% patients in small cell lung cancer. And 158, you can have PDL1 negative or PDL1 positive. And the combined analysis showed a good overall response rate in the 20% range. And it's even better-- in the 028 population, the response was over 30%.

And it's sort of difficult to cross compare small trials. But if we're looking at the ipi-nivo trial, where they compared the nivolumab monotherapy versus in ipi-nivo in two different concentrations, one with more ipi and less nivo, the other with less ipi and more nivo, we had response rates in the 10% on the nivolumab monotherapy. About 20% with the lower ipi and the higher nivo. And then closer to 25% on the higher ipi dose.

That regimen is a bit more toxic. And so I think the combined data of the pembrolizumab favors this in the third line setting, based on toxicity profile and on the response rates. But again, the second line pembro trial and the maintenance pembro trial are still-- they looked favorable in their early reports. But we're still waiting to see if they meet their end points. So for now monotherapy of pembro and nivo approved in the third line.

And then we had the approval this of atezolizumab carboplatin and etoposide as the new standard of care in an extensive stage small cell lung cancer. And this is approved for the first line setting, based on meeting the overall survival endpoint. But it was modest. We're talking about bevacizumab versus chemo days, where we had a hazard ratio of 0.7, improvement in overall survival about two months. So significant, but definitely incremental only. But also without a lot of addition of extra side effects.

The trial design was limited to only carboplatin and carboplatin and etoposide for four to six cycles. Patients were not allowed to get consolidation thoracic radiation, which in some small studies had shown improvements in PFS. And PCI was very limited in both arms. About 10% of all patients got PCI. And for the atezolizumab group, you went on to get maintenance atezolizumab.

At World Lung this year, they also released early results from the CASPIAN trial. Similar trial design to the atezolizumab plus carboplatin-etoposide, but with nivolumab as the PD1 inhibitor. Here, they allowed cisplatin as well. And about 25% of patients got cisplatin instead of carboplatin. You can also get the platinum doublet for up to six cycles. But you can also stop at four cycles. And again, you're allowed to get consolidation radiation here, but no PCI radiation in the durva arm.

And they did also meet their overall survival. And encouraging that both curves look similar. So I think there's definitely effect with checkpoint inhibitor plus chemo in small cell lung cancer. But the effect is incremental. And so on the right is the CASPIAN trial results, with similar improvements-- about three months, hazard ratios are similar at 0.7. And they both exhibit this-- the lines don't separate until after the chemo is done. And so whether that's a maintenance effect or not remains to be determined. And again, finding biomarkers to identify those people that are responding will be important.

And here's the comparison between the two. And the overall response, no difference in the 133 trial. And significantly different in the CASPIAN trial. Whether this was the difference of cis or not remains to be teased out. And the adverse events, the scoring on the placebo arm seems to be a little bit off here, in terms of that difference. So whether that's a real difference remains to be seen. So we await the publication of the CASPIAN. But this approval should also be coming down the line, and so we'll have to look carefully at the published results to determine distinguish between the two in choosing for our patients.

And then as I'm mostly focusing on metastatic lung cancer, but just one slide on the neoadjuvant, I think we're going to see more and more of this. I think the field in general, we're moving to pushing immunotherapy into the neoadjuvant setting. We know that in mice models, the neoadjuvant setting is much more effective than the adjuvant setting, although we await read out of all the adjuvant trials. But so far, neoadjuvant immunotherapy therapy has been gaining more momentum. And in ACR last year, the results of the Stand Up to Cancer nivolumab prior to surgery, with 20% major path responses.

And now, there is presentation of more and more patients on this regimen with chemo plus nivo. And they're getting major path responses. After 41 patients, in the 70% to 80%, whether its intention to treat or not. But 74% in the intention to treat arm of less than 10% residual tumor. So this is potentially going to be practice changing. And their overall survival rate, the PFS's are excellent as well. And so we're opening a number of neoadjuvant trials at Roswell as well, with an ALLIANCE trial coming up. And so I think this is definitely a lot of momentum towards neoadjuvant immunotherapy, and probably given all the data in the metastatic setting, chemo plus immunotherapy.

Moving on to targeted treatments, and you know we know from lots of sequencing now that we have different molecular profiles in the adenocarcinomas, squamous cells, large cell neuroendocrine and small cell. And so for target therapy so far, we're talking mostly about adenocarcinomas. And some recent updates, World Lung looked at results from the MYSTIC trial and looking at genotypes. And it does look like there's going to be mutations here that affect our response to immunotherapy therapy.

And so we've know for a long time that LKB1, STK11, LKB1 mutant patients, they tend to be PDL1 negative. They do very poorly with both pemetrexed and with immunotherapy therapy. If you look at the KEYNOTE-189 stratified by STK11-- sorry, LKB1 loss, there's almost no benefit of the pembrolizumab for those patients.

And some updates from Dr. Grigsby at World Lung, that [INAUDIBLE] 1A might be a potential [INAUDIBLE]. These patients looked like they responded better to combine tremelimumab, which is CTLA4 plus PD1. So I think the NCCN, of course, favors broad molecular profiling. We know that most of our patients get small IBIS FNA samples or tissues at a minimum. We're finding more and more targets. And so this favors-- economically favors getting broad sequencing upfront in all of our patients, not just our nonsmokers.

These SDK11 mutants, these KEAP1 mutants that seem resistant to immunotherapy therapy, they are found more predominantly in smokers, whereas the pure driver mutations, we still find mostly in nonsmokers with targetable treatments. But with all the new targets being identified, and better drugs being developed, it's easier to just get all your testing upfront with our limited tissue samples.

And so this is sort of how I think about lung adenocarcinomas. And based on a lot of sequencing from foundation, this is our Roswell patient cohort. But basically, you get this pattern of overlapping MAP kinase alterations. So the lung cancer cells only need to get one of these pathways to get the MAP K signal they need to become oncogenic. Too much and they [INAUDIBLE].

So they're all mutually exclusive. So these what we've seen with EGFR and ALK. And then the two I'll talk about today, ROS and RET, these are all our non-smoking, predominantly younger patients, often female, especially ROS and RET fusions. And then we have our MAP K alterations related more to smoking. And at Roswell, we have a lot of KRAS mutant cancers with our Buffalo population and our higher than average smoking prevalence rates. And then with other MAP kinase mutations thrown in there as well.

There is a group that doesn't have any. We're still trying to figure out-- they seem to-- they seem to activate MAP K still. And so we're just collating and adding extra mutations as well. And then we know that we have tumor suppressors as well. And these SDK11s are found exclusive of the non-smoking driver patients. So these are patients and smoking patients, who we expect should have a lot of antigens, should respond to PD1, but they don't.

So here's the recently approved targeted treatments in non small cell lung cancer, with just one this year, entrectinib for ROS1 positive tumors. Afatinib and dacomitinib are second generation EGFR TKIs. They're irreversible. They're very toxic, but also superior in terms of PFS to first generation EGFR TKIs. But with the FLAURA trial reading out, with the approval of osimertinib and with the toxicity profile. And then I'll just present one figure from ESMO that I think clinches that osimertinib for the most part, as our go-to first line TKI, the caveat with afatinib being approved in addition to the common Exon 19 deletions and L858R mutations.

Also for the rarer or sensitive EGFR mutations, afatinib is the one that is the only one approved based on LUX-Lung8. Last year we had the presentation of lorlatinib as effective option, second, third line. And we're waiting to see how first line lorlatinib compares to first line brigatinib and alectinib, which are the second generation ALK inhibitors with CNS penetration. And then, with the approval of entrectinib positive drugs. And this represents around 1% of non small cell lung cancer.

So this was just presented at ESMO. This is the overall survival from FLAURA, looking at osimertinib versus first generation TKIs. And this is the first trial to show one TKI superior to over the others, in terms of overall survival. So all the EGFR TKIs, all the approvals have come with PFS improvements over chemo or PFS improvements over first line TKIs, never overall survival, until this osimertinib American study. And they showed a significant improvement in median overall survival, around seven months.

This was in spite of crossover. And we know that most of our lung cancer patients, they don't make it to second line therapy. And so on this study, about 30% of patients in both arms made it to second line treatment, which is what we sort of expect for this population. So EGFR TKIs are great, but once they progress, it's a difficult cancer to control. And of those 30%, most of the patients that got second line, got second line-- about 50% of them got second line osimertinib for T790M.

And so despite by crossover, we had overall survival improvement. So with the toxicities of the other TKIs, the overall survival, I think osimertinib is sort of the clear winner so far. It doesn't target the wild type EGFR, so you have a very good safety profile. And because of the adverse effect, the limited adverse effects, and with the data coming out last year about combinations with first generation TKIs of chemo, or VEGF inhibitors improving PFS again, they're running the chemo plus osimertinib frontline treatment. And so we await the results from that trial. But that trial is ongoing.

I think based on knowing that these EGFR mutant tumors, they do respond to chemo, all the approvals of TKIs came with PFS only. And some retrospective studies suggest that patients that got EGFR TKIs, if they get chemo at any point in their treatment, they certainly do better than not. Granted, a lot of caveats with that analysis. But I suspect that chemo plus osimertinib will play a role and because of how tolerable that whole regimen is as well. So we'll await the results of that.

And so for the remainder of the time, I'll talk about RET and ROS1 fusions. These are both fusions that we find in young, non-smoking, predominantly female patients, about 1% to 2% for both. And again, once you find one of these, you're not going to find one of the other mutations. And for ROS1, we know that crizotinib is very effective. And from all these TKI studies, we do know that. And whether we need to keep running trials versus chemo with PFS as the end point, debatable. But we all like to see now these waterfalls with lots of good responses. And we like to see waterfalls that are more like the Canadian side of the falls, less like the American side.

So crizotinib, clearly very effective in ROS1, but it doesn't penetrate the CNS. And most patients that progress, progress in the CNS with ROS1. And so that led to the design of entrectinib, which is an entrec ALK ROS1 inhibitor. It's has a higher affinity for ROS1 than crizotinib does. And it penetrates the blood brain barrier. It doesn't get pumped out like crizotinib did.

And this was the waterfall plot again, excellent overall response rate, above 70%, with great CNS penetration, and 73% of those with CNS still responded with the overall CNS response. So this is the response in the CNS of imaging of 55%. And excellent progression free survival. So based on this entrectinib, FDA approved this year for first line treatment for ROS1 fusion, non small cell lung cancer. And if we're extrapolating on the stories from ALK and from EGFR, seems like we should give our best treatment upfront in terms of the best outcome for our patients.

And coming down the road, not FDA approved yet, but presented this year are the selective RET inhibitor. So RET again, RET fusion, for many years, we've been using multi-- repurposing multi kinase inhibitors, so a variety of them-- cabozantinib, lenvatinib now have an overall response rate of around 25%. So not clearly winners that we want to see, versus the selective RET inhibitors. So these are designed to selectively inhibit RET and selpercatinib also LOXO-292.

And these were the results presented at World Lung. Again, great waterfall, big overall response rate. Good PFS. And not a lot of toxicity. And at ASCO, the initial data for pralsetinib was also presented. This is BLU-667. So these are the two selective RET inhibitors in development. A little hard to distinguish between it at this point. They both look like they're very active. They both look like they have great CNS activity. And they look both very tolerable, with hypertension being the biggest signal so far coming out for both of these trials.

Initially, LOXO-292 had a little bit lower rate, but with the larger cohort, looks like it's caught up. So it remains to be seen how we're going to differentiate between these two, but these two approvals are probably coming down the line. And they're running the-- these are all registration trials. And they are going to run the comparisons with chemo. Although, at this point, in 2019, a little hard to put the patients on the chemo only arms now.

Just wanted to end with the other exciting news in target therapy, is these KRAS G12C inhibitors. And so KRAS has been a drug target for a long time. The oncogenic form a KRAS is constitutive active. And it's a GTPase. And so it's been a difficult drug to target. Because the affinity of KRAS to GDP is so high, compared to other kinases that use ATP. And the molecule's very smooth, that there's nowhere to stick an inhibitor in.

But with Kevan Shokat at UCSF, discovering that G12C mutation, it opens up this extra pocket away from the binding site. And so with fancy chemistry, they can slip a scaffold in the ship to pocket that's opened by this mutation. And then they can use it to lock the mutant KRAS into its inactive GDP bound state. So we're not trying to kick out GDP here. We're locking it in an inactive state.

And G12C is the mutation because it makes the biggest pocket. And it has the highest affinity for GDP out of all of the KRAS codon 12 and 13 mutations. And so this is why this one is making it to the clinic first, the G12C. They are trying to figure out ways for the other mutations. G12C is the most common mutation in KRAS for non small cell lung cancers. About 40% of all KRAS mutations are G12C, and so that represents around 13% of all non small cell lung cancer. In the Buffalo area, because of our high rates of KRAS, it's more like 25% of our population. So quite significant, as much as the EGFR population.

And because this targets the mutant, just like osimertinib, we were hoping that this drug is relatively tolerable, since it only hits the mutant KRAS, leaving the-- sparing the wild type. And so, so far, no big safety signals. And they presented at ASCO and at World Lung. Just the initial cohort of Amgen is the first company that has the G12 inhibitor in patients. There's two others following behind. And we are participating in this trial, as well, in the early phase group at Roswell.

And so far, some promising response. And no big safety issues identified yet. And so we have further drugs in this area coming through. And then behind these are the next, will be the G12D, I think, is the next to high affinity to GDP coming down. And eventually, hopefully, we'll have a pan-G12 inhibitor.

So these are exciting. We already know that they're probably going to develop resistance and already trying to figure out ways. But in general, the overall story from osimertinib and from ALK is trying to hit the mutant target as hard as we can. So osimertinib was designed against the gatekeeper mutations in EGFR that allowed them to escape first generation TKIs.

And similar to the lorlatinib as well, targeting all the gatekeepers. And we know that once we can inhibit EGFR really well, like with osimertinib, we're finding less mutations in EGFR, and all switching to bypass mechanisms to escape resistance. So similar stories here. We try to find the best drug to inhibit the mutant as hard as we can. And that seems to be giving us the best outcome so far.

We'll end a little bit early. Just one question to recap. And this is for the small cell lung cancer approval. So for a small cell lung cancer patient, who's progressed on platinum and one other therapy, which of the following is not FDA approved? Atezolizumab, carboplatin, etoposide, nivolumab, pembrolizumab or topotecan?

So again, this is third line. So this is after chemo, plus another agent, and this IMpower 133 was designed for first line treatment. So this is approved for first line only, whereas all of these are approved for third line. So the correct answer is the atezo combination.

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