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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Biomarker Testing in NSCLC: Who, What, When?

Announcer Introduction:
Welcome to CME on ReachMD. This activity, titled "***Biomarker Testing in NSCLC: Who, What, When?"*** is Provided by Partners for Advancing Clinical Education (PACE) in partnership with Smart Patients and is supported by an educational grant from Amgen.

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Dr. Persinger:
Biomarker testing in advanced non-small cell lung cancer – breakdown non-squamous versus squamous. This is NCCN guidelines. This is where we should be going by in terms of what we are testing in patients, and so these are recommended that above should be assessed as part of the broad molecular testing by NGS to use least amount of tissue, and then even more so, the action items are remembers that order biomarker testing, preferably NGS, to identify actionable mutations in all patients with advanced non-squamous non-small cell lung cancer and then to consider in those with squamous non-small cell lung cancer. Taren, back to you.

Let's look at biopsy for biomarker testing. How do we get it? Tissue from the primary tumor or metastatic site – equally suitable. It's considered the gold standard for biomarker testing. Lung cancer biopsies are less cellular than other solid tumors. There's a need of 10 to 20% of viable cancer cells in sample for reliable results. We also need to make note that lung tumors can be heterogeneous in origin, meaning that a particular mutation may only be noted in one part of the tissue, not necessarily that other tissue that is sample. Bone biopsy potentially suboptimal due to decalcification and degradation of DNA, but new methodologies are evolving. Liquid biopsy is another option. It's where we're looking at the cell-free DNA in plasma, and that's another one that can be used. Liquid biopsy is blood sample containing cell-free DNA from multiple sources, including the DNA shed from the tumor. When do we use liquid biopsy? You can use it in a plasma-first approach or inadequate or no tissue biopsy, but if it's negative, you still need to re-biopsy for tumor tissue. You can use it as a sequential approach, meaning that tumor tissue is adequate for typing followed with cell-free DNA testing only when results from the tissue is incomplete, or complementary approach increases the rate biomarker detection. Do remember that it is resistance, and you can do it when it's resistance to TKIs as well. What are the advantages? It's minimally invasive, may overcome tumor heterogeneity, but there are limitations. Limitations is that its sensitivity is only 70-80%, specificity is near 100%, negative result is not informative and cannot assess histology of PDL1, and I think that's a big takeaway. Tumor is the only way to assess histology and PDL1.

Dr. Sims:
So, back to our case study – here's Ida. She gets molecular testing indicating that her tumor is driven by an EGFR exon 19 deletion mutation. There's the summary of her somatic alterations and associated treatment options.

Dr. Persinger:
EGFR mutations in non-small cell lung cancer – let's just get a little overview. It's more common, but not exclusively, to never and minimal smokers, East Asians, and women. Remember – more common but not exclusively. Classic mutations make a majority – that's the exon 19 deletion and an exon 21.L858R mutation. Atypical and uncommon EGFR mutations, including G719X, LA 16q, 16 1q, S7681, some are sensitive to traditional EGFR inhibitors, but more study is needed. We'll go over a little bit further later on in terms of exon 20 insertions. I will say that there are new drug approvals for this one.

When we look at biomarker-directed therapy as it relates to the EGFR classical mutation, there are first and second generations – that's the gefitinib, erlotinib, and a second generation is afatinib – and that's targeting on osimertinib, which is the first line in metastatic non-small cell lung cancer indication, remember, that has L858R or exon 19 deletion. Subsequent line of metastatic non-small cell lung

cancer – let's say a patient is started on first and second generation, they progress, you get re-biopsy, they're noted with a EGFR T790M mutation, which is a resistant strain - then you can also transition them to osimertinib.

And this was based on the FLAURA study – osimertinib versus the first generation TKIs, which demonstrated to improve PFS for patients with advanced EGFR-positive non-small cell lung cancer and CNS met, which is huge, right? Because we know most of these patients will at some point develop a brain metastasis. So, osimertinib improved overall survival and PFS in overall patients in the osimertinib line versus gefitinib or erlotinib. It is known to have good CNS penetration, it reduced the risk of progression by approximately 53% with or without baseline CNS mets, and this slide on this side just shows us that information in a graph.

So, the other indication for osimertinib is based on the phase 3 ADAURA trial in which there was an update that looked at adjuvant osimertinib for early-stage EGFR-mutated non-small cell lung cancer. This was indicated in patients with stage 1B to 3A. The graph shows us the DFS in overall population. The median DFS for osimertinib was 65.8 months versus 28.1 months in the placebo arm, the arm that didn't get any treatment that we just watched surveillance, so that's huge. So, based on this data, FDA approved in December of 2020 for adjuvant treatment of adults with stage 1B to 3A EGFR-positive deletion 19 or L585R non-small cell lung cancer following tumor resection plus or minus adjuvant chemotherapy.

So, once again, going back to the dosing and side effects of EGFR TKIs, you'll see them all listed. Osimertinib is given as 80 mg daily with or without food. Common side effects greater than 20% that were safe with all TKI or the EGFR drugs – diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue, decreased appetite. Remember, in this third generation of drug, though, we saw them less prominently as in the first and second generation, and then when we look at the grade 3 equal to side effects, we saw decreased appetite, diarrhea, QT prolongation.

Remember, I said we would talk about the exon 20 insertions – know that they are resistant to traditional EGFR inhibitors, but there are new drugs that have been approved, and so one of the drugs that have been approved is based on the CHRYSALIS study of amivantamab, and what they were looking at the best overall response by exon 20 insertion's region, and that's what this graph shows us is that they broke it down in terms of different regions based on where the exon 20 insertion was noted, and so what we see here in the helical region is where there was one patient, overall response was 100%. The near loop – that's where that exon 20 insertion was noted – we saw the overall response rate was 41%. Far loop was overall response rates with 25% and not detected by CT DNA, meaning that they couldn't identify these set patients of where the exon 20 insertion was noted. It was still noted with an overall response rate of 39%.

When we look at amivantamab's AEs, it is intravenous, it is most commonly known to cause infusion-related reactions first infusion, and in most cases, it was 93% of cases. It did not affect the ability to receive subsequent treatments. It's one of those expected things, and because of that, the first treatment is divided into 2 days. So, with that first treatment, you're going to premedicate with glucocorticoid on week 1 day 1 and day 2, and then premedicate with acetaminophen and diphenhydramine with all other doses. Again, split the doses for the first infusion over 2 days. If IRR is suspected, interrupt the drug and give supportive medication as needed. That's the biggest thing – you're more than likely are going to see that.

And to the right is the table that shows other different AEs broken down based on EGFR-related versus met-related because patients – this was not just a study that looked at EGFR mutations – patients who had a met mutation was also included, and there goes the breakdown in terms of the AEs.

The anti-tumor activity – this is the second drug of mobocertinib in previously treated EGFR exon 20 insertion-positive metastatic non-small cell lung cancer. This is an oral drug, and so there's two different cohorts – the PPP cohort platinum-based pre-treated, and the EXCLAIM cohort – and when we looked at the overall response rate and percentages, it was 28% on the PPP cohort, 25% in EXCLAIM cohort. When we looked at the median DoR – 15.8 on the PPP cohort and not noted in the EXCLAIM cohort at time of this. And then we looked further, when we looked at the median DoR in months, we saw 13.9 in the investigator assessment versus 11.2 months.

When we look at the side effects, the treatment-related adverse effects with mobocertinib in greater than 20% patients, we divide it from the ones that are pre-treated with platinum bases versus the EXCLAIM cohort, you'll see the similar side effects – diarrhea, rash, perionychia, decreased appetite, nausea, vomiting, dry skin, increased creatinine, stomatitis, and pruritis.

Dr. Sims:
Here's a new case. Ray, 63-year-old with non-small cell lung cancer with KRAS G12C mutation after first-line therapy. He has a 40 pack year smoking history and was diagnosed with metastatic lung adenocarcinoma after he presented with back pain and shortness of breath. His biomarker testing showed PD-L1 by IHC less than 1%, an NGS was KRAS G12C mutation, and he received first-line pembrolizumab plus carboplatin pemetrexed and now has disease progression.

Dr. Persinger:

So, let's look at the characteristics of KRAS mutation in non-small cell lung cancer. Communications differ among KRAS mutations. The clinical relevance of difference in KRAS mutation subtype is unknown and should be further investigated, and so this pie chart here just shows us the different KRAS mutation subtypes.

So, phase 3 CodeBreaK 200 is the trial that looked at sotorasib versus docetaxel in pre-treated advanced KRAS G12C mutation-positive non-small cell lung cancer. The primary endpoint was the PFS, and when we look at the sotorasib arm versus the docetaxel arm at 12 month, the PFS percentage was 24.8 versus 10.1 with the median PFS in months was 5.6 versus 4.5.

When we look at the TREs as it relates to sotorasib versus docetaxel, we all should be very familiar with docetaxel and its side effect, but as it compares to sotorasib, we see that diarrhea's a little bit more on the sotorasib arm and is less than the other side effects as it relates to fatigue, alopecia, nausea, and anemia. And then leading to discontinuation was 9.5 on the sotorasib arm versus docetaxel. So, again, most common grade 3 or equal to TREs with sotorasib was diarrhea, elevated ALT and AST. So, in May 2021 is when the FDA granted an accelerated approval for treatment of adults with LA or metastatic KRAS G12C-mutant non-small cell lung cancer patients that had a prior systemic therapy.

When we look at the phase 2 CRYSTAL one where we're looking at aggressive and pre-treated advanced KRAS G12C mutation-positive non-small cell lung cancer, and when we look at this drug and when we looked at the overall survival is 6 months, overall survival is 71%, and the one year overall survival was 51%. When we looked at the median overall survival in months, that was 12.6 months. The median DoR in months was 8.5, and we look at the common TREs as it relates to this drug where, again, we see the diarrhea, the nausea/vomiting, the fatigue, the ALT increase, blood creatinine increase, the AST increase, and decreased appetite. 52% of patients had a dose reduction, 61% had a dose interruption, and 7% discontinued due to TRAEs. This drug was approved for FDA-granted acceleration in December 2022. Again, these patients had to receive one or more prior systemic treatment.

ALK rearrangements – they are found in approximately 5% of patients with non-small cell lung cancer – occurs more frequently in younger patients, light or never smokers, predominantly a fusion of ALK with partner oncogenes, particularly EML4,occurs in similar subgroups as patients with EGFR mutations, but EGFR mutations and ALK rearrangements are typically mutually exclusive.

When we look at the biomarker-directed therapy for ALK rearrangement, all five are indicated, but we're going to focus on those that are most commonly seen, which are alectinib, brigatinib, and lorlatinib, and so when we look at the median PFS in these first-line therapies, we see alectinib versus crizotinib was 34.8 versus 10.9, when we look at brigatinib versus crizotinib, that's 24 months versus 11.1, and then lorlatinib is not estimated as of now versus 9.3. Again, all of these are indicated in ALK-positive patients.

Then, ALK inhibitors – when we look at the side effects focusing more on those last three of the alectinib, the brigatinib, and lorlatinib – all of these are all doses. When we look at the side effects, some of them are very overlapping. We see that in the alectinib, you have that fatigue, that constipation, that edema, myalgia, anemia. In brigatinib, you see the diarrhea, the nausea, the rash, the cough, the myalgia, headache, hypertension, vomiting, and dyspnea. When we look at the lorlatinib, one of the things that is very common to make sure that we are aware of are those cognitive effects that can happen, peripheral neuropathy, edema, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea, so those cognitive things that we are seeing a little bit more in lorlatinib. In those things that happen grade 3 or more than 2% of the time, as it relates to alectinib you're looking at the renal impairment, brigatinib I really would focus on that hypertension, lorlatinib, though it's not mentioned in here, I would also say in terms of lipidemia as well.

Let's move on to ROS-1 fusions. This is most common in younger patients, never smokers, adenocarcinoma, high grade histology frequency is 1.2 to 1.7%. Of the drugs that are indicated for this particular fusion are crizotinib/entrectinib. Listed there is their efficacies in first-line setting. ROS-1, also, you have in terms of the crizotinib, it is a twice-a-day job, it is adjusted for renal impairment. The entrectinib is a daily drug. Things that we should keep an eye on, rare but possible, the QT prolongation in the crizotinib, diarrhea, vomiting, constipation, esophagitis, and then also in entrectinib, that cognitive impairment.

Let's look at the BRAF V600E mutation – some of you are probably just like, I know that from melanoma – you are correct. Occurs predominantly in adenocarcinoma, both patients with a history of smoking and never smoking. Frequency is 1 to 2% overall. The drug that's indicated for this particular mutation is the dabrafenib and trametinib – approved for BRAF V600-positive metastatic non-small cell lung cancer. In previously untreated patients, the overall response rate was 63% with a median PFS of 10.8 and a median overall survival of 17.3. In previously treated patients, overall response rate was 68.4%, median PFS was 10.2, and a median overall survival was 18.2. Most common side effects if you're familiar with it in melanoma, pyrexia, nausea, vomiting, dry skin, peripheral edema, diarrhea, decreased appetite, and cough. Most frequent grade 3 or more – hypertension, hyponatremia, neutropenia, pyrexia, dysthymia, anemia, and increased ALT.

Let's move to MET exon 14-positive advanced non-small cell lung cancer, so we're looking at those MET inhibitors capmatinib and tepotinib. When we look at these drugs, they were both approved. Capmatinib was approved in May of 2020. Tepotinib was approved

in February of 2021. When you looked at capmatinib prior treatment versus treatment-naïve patients, the overall response rate in prior treatment was 44 versus 66.7 when they were treatment naïve, and the median PFS was 5.5 in prior treatment versus 12.3. When we look at tepotinib, the overall response rate was 44.6 in prior treatment versus 44.9, and we looked at that median PFS – 10.9 versus 8.5.

Selective MET inhibitors, when we're looking at the dose and side effects, capmatinib is a twice daily with or without food, tepotinib is daily with food. I think the biggest takeaway as it relates to MET inhibitors is that peripheral edema. That is most commonly seen and definitely you have to stay on top of that with patients.

When managing edema associated with selective MET inhibitor therapy, elevation – we know this, right? Elevation, compression stockings or sleeves, physical therapy referral, diuretics but not always effective, need to watch blood pressure, need to watch the kidney function, often not able to manage and may require dose reductions depending on patient's quality of life.

When we look at selpercatinib and pralsetinib, these are two approved selective RET inhibitors for REF fusion-positive non-small cell lung cancer, and again, we're looking at it in the terms of prior treatment, platinum-based treatment, versus treatment naïve. When we look at selpercatinib, the overall response rate is 61% versus 84% in that treatment-naïve group. Median PFS is 24.9 months versus 22 months in the treatment naïve. When we look at pralsetinib, the overall response rate is 59% versus 72%, and the median PFS is 16.5 versus 13. Selpercatinib was approved in May of 2020 followed by pralsetinib in September of 2020.

Looking at the dosing and side effects, selpercatinib is a little bit of weight-based, right? Less than 50 kg versus if they are more than 50 kg. It is oral, it is twice daily. Listed on the slides are the frequent side effects. Grade 3 is what I want to really hone in on in terms of hypertension. It's 20% diarrhea, QT prolongation and dyspnea. Pralsetinib is a once-daily oral medication. Common side effects are listed there as well. We're still looking at those labs. Hypertension is another thing that we need to keep an eye on. Pneumonia/diarrhea are less likely.

Monitoring and managing toxicity associated with RET-specific inhibitors – remember I brought up that hypertension. You want to optimize that blood pressure before starting drug. Monitoring blood pressure after week 1 and then monthly and thereafter as clinically indicated. You also want to make sure that they have a proper blood pressure at home or know how to utilize it if that's what you're instructing them to do. Hepatotoxicity is a TKI – you want to monitor those AST and ALT every 2 weeks in the first 3 months, then monthly thereafter or clinically indicated. Hemorrhagic events – advise patients about risk of bleeding with drug, and contact their healthcare provider. Good communication is a takeaway point. You've got to have that as you are starting these patients on these drugs and any other drugs.

The NTRK rearrangements and TRK fusions in cancer - so, what we need to know is that it's a normal role in neuronal development in the utero and postnatal neuronal differentiation – survival, function, expression limited to CNS. NTRK fusions – we're looking at it as the rearrangements not only just in lung cancer, but its prevalence in other cancers as well.

When we look at those inhibitors that target this drug that are NTRK or TRK fusion-positive lung cancer, there's two drugs that are out there FDA-approved. It's entrectinib and larotrectinib. Again, we're looking at that overall response rate. We see a 63.6 on the entrectinib arm and then 73% in the larotrectinib. When we look at entrectinib and we're looking at the median PFS, that's 14.9 in months, and the median overall survival is not noted as of yet. When we looked at the larotrectinib, the overall response rate is 73% as I stated, median DoR is 33.9 in months, median PFS is 35.4 months. And then to the right, just in case you were not as familiar, this is a point graph, right? So, each line represents a patient that has gained a response from the particular treatment.

The new thing – the HER2 mutations in advanced non-small cell lung cancer – its incidence is 2 to 3% of non-squamous non-small cell lung cancer, and you're correct, yes, HER2 mutations, you've heard it before in breast. In lung, it can be indicated as HER2 or ERBB2 mutation. It's different from the HER2 overexpression or amplification, so it's very important to know that, and also a fact to know is there is potentially a higher propensity for brain metastasis while in treatment for patients with HER2 mutations versus those with KRAS or EGFR mutations.

T-DXd – a HER2-targeted, ADC coupling, and anti-HER2 monoclonal antibody with trastuzumab, sequence 2, topoisomerase 1 inhibitor payload using a tumor-selective cleavable linker. Simply said, it is a different mechanism that we are not used to as in a lung cancer. You have this Herceptin conjugated molecule that's able to go to the cell, opens up, hemo is released and kind of another way of kind of killing that cell. It is FDA-approved in August of 2022 at 5.4 mg per kg for treatment of adults with unresectable or metastatic HER2-muted non-small cell lung cancer who received a prior systemic therapy so they have had to have treated before, and this was based on the phase 2 DESTINY-Lung02 where we looked at trastuzumab deruxtecan and pre-treated HER2-muted metastatic non-small cell lung cancer, and when we looked at efficacy outcome, the confirmed overall response rate by BICR was 57.7, and the median DoR was 8.7. This was approved in August of 2022 as I stated. Those who were indicated to have this had a prior systemic treatment. When we looked at the TRAEs as related to this drug were any grade of 92.1% grade 3 or greater was 31%. Associated with drug discontinuation

was 7.9, dose reduction was 9.9, and so on as listed in the table here.

Patient-specific molecular profile determines treatment course. Choose therapy directed toward each patient's specific non-small cell lung cancer genotype. Most TKRs are now recommended as first-line therapy for patients with a specific targeted mutation. For many patients diagnosed with advanced non-small cell lung cancer, the best therapeutic option may be a clinical trial.

Action item – just a takeaway – select therapy based on the results of molecular profiling and evidence from clinical trials. So, when we started out – why is biomarker testing needed? This is the reason. As you can see, there's a lot of different drivable mutation.

Now we know that the potential lack of efficacy with immune checkpoint inhibition in EGFR mutant-positive non-small cell lung cancer. There was a phase 2 study of pembrolizumab in patients with PD-L1-positive EGFR mutant-advanced non-small cell lung cancer. This is about a small study, it was 25, stopped due to futility at 11 patients. Basically, it just confirmed that we know that there's a lack of efficacy when you use immunotherapy in patients who harbor EGFR mutations that have exon 19 deletion and L858R.

Potential toxicity with sequential use of immunotherapy followed by TKI, a retrospective review of patients' records to identify severe toxicity with ICI EGFR-TKI, regardless of sequence, in patients with EGFR-mutant patients – this was a study of 126 patients – and what it shows is that in patients treated with osimertinib within 3 months of after being on an immunotherapy, they were noted with 20% developed a severe IRAE. Conversely, there were no severe IRAEs were identified if osimertinib was given upfront and then transitioned to immunotherapy. So, the takeaway point is, again, you need to know the patient's profile and treat them accordingly.

Patient-specific molecular profile determines treatment course. Why? High PD-L1 expression does not exclude the presence of a targeted mutation. Efficacy to immunotherapy potentially reduced in patients with a driver mutation. Given immunotherapy upfront in a patient with a driver mutation may increase the risk of AEs with targeted therapy later. Review molecular testing results before initiating treatment in patients with advanced non-small cell lung cancer. Even when their PD-L1 IHC results are high, you still need to get that complete molecular profile.

So, now switch gear into immunotherapy. So, the 2023 paradigm for immunotherapy in advanced non-small cell lung cancer without an actionable mutation, so you'll see this broken down – advanced non-small cell lung cancer without actionable mutation, and based on their PD-L1 score and what their treatment option could be – but we're also going to talk about the IMpower010 study design. This was looking at immunotherapy in the adjuvant setting. So, these patients received resection, patients had completed resected stage 1B to 3A, non-small cell lung cancer, they did not harbor any mutations such as EGFR because we talked about the adjuvant indication of EGFR with osimertinib, and they got adjuvant chemotherapy for 1 to 4 cycles and then they separated to atezolizumab or our standard of care. Primary endpoint was hierarchical evaluation of investigator, so we're looking at the DFS and at the 3-year, 5-year DFS.

Phase 3 CheckMate 816 was a neoadjuvant approach where it looked at nivolumab and platinum chemotherapy base for resectable stage 1B-3A. You got this upfront. That's a neoadjuvant followed by surgery and so forth, and so the co-primary endpoints were EFS BICR. The median EFS was 31.6 months with nivo and chemotherapy versus 20.8 if you didn't get that upfront. That's huge, and so surgery received and cancer percentage – nivolumab and CT was 83.2 versus just the chemotherapy median duration of surgery, and then the complete resection was 83.3 in the nivolumab chemotherapy arm versus 77.8 in the chemotherapy arm.

Summary – when to test. Initial diagnosis stage 1B to 3A resected EGFR because we talked about osimertinib indication in the adjuvant setting. Stage 2 to 3A resected PD-L1 because we talked about atezolizumab in that subset of patients. Metastatic disease comprehensive biomarker testing, or NGS panel as it's called, locally advanced receiving definitive chemoradiation, currently no indications for approval, but consideration should be done. Disease progression in EGFR can be resistant mechanisms that are targetable, T790M, small cell lung cancer transformation – we didn't talk about that – MET or HER2 resistance, clinical trials for other biomarkers, mostly informational for clinical trials, and then a disease recurrence. Try to retest, especially if there has been a long interval from definitive to therapy.

PC action plan. What is the take-home message? Order biomarker testing, preferably NGS, to identify actionable mutations in all patients with advanced non-squamous non-small cell lung cancer. Consider in squamous non-small cell lung cancer. Select therapy based on the results of molecular profiling and the evidence from clinical trials. Review molecular testing results before initiating treatment in patients with advanced non-small cell lung cancer, even when their PD-L1 IHC results shows a high expression.

Dr. Sims:
So, we have some questions. What do you think is the biggest barrier to genetic testing in a community? And how would you have us address it?

Dr. Persinger:
I think that's a great question, and I think one of it is education, right? And another thing is cost. In terms of education, I think a lot of

practitioners are not sure what would be covered, if insurance will cover a complete next-generation sequence, and especially in advanced stage, they do that single testing or a single assay, but it delays things even further, and so I think the biggest thing that we can tackle is education, educating our peers just in a format like this in different meetings and settings of the importance of next-generation sequencing, whether that's even done in-house because sometimes in a community setting, they are dependent on what that local hospital, but then also know that there are other different platforms out there that they possibly can utilize. Typically, they have some patient assistance and ways, but I think those are the big things – education and cost – because what we don't want to do is cause financial toxicity to our patients.

Dr. Sims:
Now, a leading question off of that is are you seeing both tissue and liquid biopsy testing being done upfront? Or are you only incorporating liquid biopsy testing in certain scenarios?

Dr. Persinger:
I think that's a great question, and if you heard me speak to the point of, in lung cancer, the tumor can be heterogenic, right? And so because of that and because of the NILE study and other studies that have come out, we actually do it simultaneously. When my physician partners see patients in for consult or a second opinion, if we don't have that profile upfront or if that tissue is still testing, we are automatically going liquid at the same time. So, if we have a patient that comes in for a second opinion and only tissue was done and it was not noted, we are getting liquid at that. So, our normal protocol is that we do it upfront, but we will also add it on if we have a second opinion where that may not have been done.

Dr. Sims:
And here's another question – should we do next-gen testing when people progress even though they had it done originally or initially?

Dr. Persinger:
So, that's a great question. In lung cancer, there could be some resistant strains that develop. One thing that comes to mind is that EGFR can do a transformation to MET, and so there is some benefit in doing a repeat NGS to see what could have been. I will say that it will be weighed on different cases. I'm not going to say a blanket statement that every patient that had an NGS upfront deserves a one at progression, especially if that progression is within 6 months or a year, but definitely there are cases that you can argue that an NGS repeat is needed.

Dr. Sims:
If you have NGS results with more than one targetable mutation, how do you choose which one to target?

Dr. Persinger:
Typically, you will not have that. Most of these mutations are exclusive. You can have an EGFR-mutant patient that may have gotten treatment in the past and then they kind of transition into that MET mutation, but typically you will not have an ALK and an EGFR or an EGFR and a KRAS G12C or RET fusion and EGFS. They're usually mutually exclusive.

Dr. Sims:
I want to thank you, Rasheda, for an amazing talk today.

Dr. Persinger:
Thank you so much.

Dr. Sims:
Our topic is Biomarker Testing in Non-Small Cell Lung Cancer, and our speaker today is Rasheda Persinger. She is a nurse practitioner – in fact, the lead nurse practitioner – at the Division of Medical Oncology at John Hopkins University in Washington, D.C. Welcome, Rasheda.

Dr. Persinger:
Thank you for having me.

Dr. Sims:
These are her disclosures. We'll move on to the learning objectives for this session include: summarize the most recent guideline-recommended biomarker molecular testing strategies for non-small cell lung cancer, formulate evidence-based personalized treatment plans for patients with NLC/LC based on actual biomarkers, and integrate patient education and feedback to optimize patient experiences from treatment and survivorship. And now let me turn it over to Rasheda.

Dr. Persinger:
Thank you so much, Taren. Lung cancer remains the major global health burden. Here are some facts just to remind us about it. Lung

cancer is one of the most common cancers and is the leading cause of cancer deaths in the US and worldwide. New cases in the US is over 200,000 estimated in 2023, globally 2.2 million in 2020. When we look at deaths in the US, it's around 127,000 plus estimated in 2023, but the global number was 1.8 million in 2020. Five-year US survival rates – that's what we're really going after – overall, it's 22.9%. When we break that down for metastatic disease, that's only 7% of a five-year survival rate. Non-small cell lung cancer accounts for between 80% and 85% of lung cancer. So, approximately 50% of patients with advanced non-squamous non-small cell lung cancer have a driver mutation prior to FDA-approved agent. So, you may ask, why are we even having this talk? This is why. This is a breakdown of the different driver mutations and their FDA-approved agent.

Why do we perform biomarker testing on non-small cell lung cancer? What we do know from many studies is that patients who get chemotherapy opposed to their targeted therapy, or specific to their driver mutation, have a much poorer overall outcome, and this slide just shows us in terms of overall survival. The blue line obviously are those patients who are treated appropriately with their targeted therapy versus those who are not. As you can see, the overall survival's 18.6 months in those that are treated versus 11.4 months in those who are treated with standard of care chemotherapy.

Now, I'll turn it over to Taren for our case study.

Dr. Sims:
Here's our case, Ida, who's 55. She presented to her PCP complaining of dyspnea, persistent cough, and intermittent pain on the left side of her chest, and after examination, the nurse practitioner referred her to an oncologist. She's a never smoker. However, she had childhood exposure to secondhand smoke. No palpable masses or visible lesion on physical exam, and her ECOG performance status is 1. Her diagnostic workup included a biopsy confirming adenocarcinoma of the left lung. PET imaging reveals extensive tissue involvement greater than 3 cm, and her brain MRI shows one brain metastasis at 0.5 cm. Her diagnosis is stage 4B adenocarcinoma.

Dr. Persinger:
Thank you. But are we testing? That's the big takeaway. Based on the MYLUNG consortium data, this was a study that looked at over 3,000 patients in the US Oncology Network between the years of 2018-2020, and if you broke that down in those who had adenocarcinoma within the study was 74%. So, when we look at this study, and they broke it up into terms of how many patients were being tested for single assay versus maybe just any biomarker versus all 5 biomarker versus next-generation sequence, this nice table breaks it down versus non-squamous, which will be adenocarcinoma, and overall, which includes the squamous. So, when we look down to that NGS level there, we see only 39% of patients were being tested, and if you even look for all 5 biomarkers, that's not even 100%, and I think this just speaks to the value of that it will be great the day that when patients are diagnosed with non-small cell lung cancer, especially advanced cancer, the importance of all testing being done upfront as if it was breast cancer.

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