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

Case by Case: Optimizing Dual Immune Checkpoint Inhibitor Combination Therapies in Advanced Driver-Negative Non–Small Cell Lung Cancer

Announcer:
Welcome to CME on ReachMD. This activity, titled "Case by Case: Optimizing Dual Immune Checkpoint Inhibitor Combination Therapies in Advanced Driver-Negative Non–Small Cell Lung Cancer" is provided by TotalCME LLC.

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Chapter 1

Dr. Forde:
Hello, this is CME on ReachMD, and I'm Dr. Patrick Forde.

Dr. Naidoo:
And I'm Dr. Jarushka Naidoo.

Dr. Forde:
Today I'm going to review a case and discuss treatment options for patients with advanced squamous non-small cell lung cancer, or NSCLC, and PD-L1 expression less than 1%.

Let's start our discussion by looking at a case. So this is a 63-year-old woman who presented to the emergency department with vague complaints of dry cough and shortness of breath, and she had recently had 8-pound weight loss, fairly typical past medical and family history. Her mom had passed away at the age of 70 from lung cancer. She herself was a former smoker of 30-pack-years, however, had quit smoking 15 years previously. On physical exam, her weight was 110 pounds. She had good performance status. And diagnostic workup, including a CT of the chest and abdomen, showed a 3-cm nodule in the left upper lobe of the lung, enlarged left hilar lymph nodes, and metastasis to the liver. Her brain scan was negative for metastasis. She had a biopsy performed, which was consistent with squamous cell carcinoma, and this was stage IV disease due to the liver metastasis. PD-L1 expression was negative, and NGS was performed that showed no actionable mutations. So what treatment options should we consider in this case?

So first of all, I'm going to review some of the clinical trials. The KEYNOTE-407 trial was one of the seminal studies in this setting. This was a study which enrolled patients with newly diagnosed stage IV non-small cell lung cancer with squamous histology. All patients had to have a sample available for PD-1 expression, no symptomatic brain metastasis or pneumonitis, and they were stratified by PD-L1 status, choice of taxane between paclitaxel and nabpaclitaxel, and geographic region, and randomized to control arm of chemotherapy, carboplatin plus taxane plus placebo or chemotherapy plus pembrolizumab. Patients could receive maintenance pembrolizumab or placebo. And in the control arm, there was crossover permitted at the time of progression to pembrolizumab.

This study showed a significant improvement in both overall survival and progression-free survival. You see the curves here, hazard ratio for overall survival favoring the pembrolizumab arm of 0.71. And in 5 years, here you see an improvement from 9.7% of patients

being alive on the control arm to 18.4% of patients in the investigational arm.

We can now break down the 5-year results by PD-L1 status. And here, you'll see some changes among the different strata. In the PD-L1 intermediate and high group, you see quite a significant difference in PD-L1 influencing the benefit from treatment, particular improvement favoring the pembrolizumab arm. However, in the PD-L1-negative disease, very little difference at 5 years, 10% of patients being alive in the pembrolizumab-containing arm, 13% in the control arm.

And there has been a meta-analysis performed, which I'll mention briefly here. this looked at patients with PD-L1-negative, newly diagnosed, non-small cell lung cancer, and compared pembrolizumab plus chemotherapy versus chemotherapy alone. And something which stands out here, again, is more modest benefit in patients with squamous differentiation, a hazard ratio to favor in pembrolizumab in nonsquamous at 0.52, whereas in squamous it's 0.81 and not statistically significant.

Let's look at some of the dual checkpoint inhibitor studies in this setting. First of all, CheckMate 227, this enrolled patients with newly diagnosed stage IV non-small cell lung cancer of both histologies, patients with EGFR and ALK alterations were excluded, and it was stratified by histology. There were two separate groups in this study that looked at either PD-L1-positive disease in 1% or greater, comparing either nivo/ipi or nivo to chemo, or in part 1B, PD-L1-negative disease less than 1% again, a similar comparison nivo/ipi versus chemo, or nivo/chemo versus chemo. And the key analysis here was overall survival in patients with PD-L1-positive disease.

And here we have 6-year follow-up presented last year by Dr. Ramalingam. This showed a significant benefit favoring nivo/ipi over chemo, hazard ratio of 0.65. And at 6 years, 16% of patients were alive in the nivo/ipi arm, versus only 5% of patients in the control arm of chemo alone. In an exploratory analysis by histology, again, a significant impact in the squamous group with 6-year overall survival of 18% versus 4% in the control arm.

And here we see those curves in part one of CheckMate 227, again here showing a significant benefit, particularly in those with squamous histology and PD-L1-negative disease, 22% survival at 4 years versus only 5% in the control arm.

Moving on to CheckMate 9LA. So this was a slightly different design, similar enrollment, population, and stratification. However, this study included chemotherapy for just two cycles with nivolumab plus ipilimumab, continued maintenance nivo/ipi after chemo versus chemo times four cycles with optional maintenance pemetrexed in the non-squamous group. The primary endpoint of this study was overall survival.

We now have 5-year data on this study, again showing a significant benefit in the full randomized population, going from 11% in the chemotherapy arm to 18% survival in the nivo/ipi plus chemo arm, hazard ratio 0.73. And when we look by histology again, we see this difference falling out for squamous disease, a hazard ratio in non-squamous of 0.77 favoring nivo/ipi plus chemo, and a hazard ratio of 0.63 favoring nivo/ipi plus chemo in the squamous group. And quite a significant difference at 5 years, going from 7% of patients alive at 5 years with squamous disease in the chemo arm versus 18% in the chemo/ipi/nivo arm.

We also have some other studies more recently published in this setting, particularly the POSEIDON study. This took the approach of giving four cycles of chemo with durvalumab and tremelimumab, and comparing this to chemotherapy up to six cycles. Patients in the durvalumab/tremelimumab arm could have maintenance durvalumab until progression, and one further dose of tremelimumab after concurrent chemotherapy plus immune checkpoint inhibitor.

And here we see the results from this study at 4 years, again, a significant benefit in progression-free and overall survival favoring the combination therapy arm. And however, we don't see quite the same difference by histology here, however, a trend in favor of the durvalumab/tremelimumab chemotherapy arm in the squamous population and also in the PD-L1-negative disease. It has raised to 0.77 in PD-L1-negative.

Finally, the EMPOWER-Lung 3 study. This looked at the combination of chemotherapy plus the anti-PD-1 antibody, cemiplimab, compared to chemotherapy plus placebo. And we have 2-year follow-up on this study from EMPOWER-Lung 3, again, showing a significant benefit of the overall population for patients who received cemiplimab plus chemotherapy. In squamous histology in particular, you see it has a hazard ratio 0.61. PD-L1-negative disease, not quite a significant benefit here, hazard ratio 0.94.

So perhaps in these chemotherapy plus PD-1 studies, you don't quite see the same benefit falling out for both squamous and PD-L1-negative disease. And we see this outlined here in a table looking at overall survival in PFS by histology.

So I'll take it back to discussion now with Dr. Naidoo. And perhaps Dr. Naidoo, what are your thoughts on the relevance of these data to clinical practice in the current situation?

Dr. Naidoo:
Yeah, I think PD-L1-negative squamous is one of the clinically trickier groups to treat. We know that these patients tend to do poorly and

sometimes trying to treat them in terms of performance status and things like that can be more challenging.

I think the data would suggest that in a patient who can tolerate treatment is otherwise fit, that trying to give some CTLA4 does appear to be associated with the best outcomes. So in these patients, if the patient is fit and well, I try to give the CheckMate 9LA regimen and see where I go from there. But understanding that chemoimmunotherapy certainly does appear to benefit these patients, particularly when the PD-L1 is negative. So if I can't give a four-drug combination, I would certainly try to give three and give KEYNOTE 407.

How did you treat this patient?

Dr. Forde:
Yeah, so this patient we actually treated with the CheckMate 9LA regimen which is two cycles of platinum doublet chemotherapy with ipilimumab/nivolumab. And she had quite a nice response to treatment, initial partial response which has now been sustained for over 3 years.

So I think so, as you mentioned for patients who have squamous histology, we have relatively limited options compared to non-squamous, particularly with the advent of KRAS-directed therapies for non-squamous disease. So my own feeling for squamous is that probably we want to give the most effective regimen up front taking into account the specifics of patient situation, performance status, comorbidities, particularly because we do see more autoimmune side effects when we add CTLA4 blockade. But in this case, this particular patient had a very good result. And similar to yourself, for those patients who have PD-L1-negative or squamous histology, or indeed both, those are the patients that tend to prioritize for combination checkpoint blockade in particular.

Just to mention briefly, in terms of toxicities, we should be on the lookout with CTLA4, what are the particular things you think of when we add CTLA4 to PD-1 blockade?

Dr. Naidoo:
Yeah I think, you know, this is a great point, obviously an area I'm particularly interested in. I think when we add the CTLA4, we have to be mindful to explain to patients and the care team about some of the toxicities that we should be mindful of. The most common for CTLA4 being colitis, hypophysitis, and skin rash; those would be the three most common. But then, of course, when you combine the two some high-grade and rare toxicities need to be mentioned, things like myocarditis, pneumonitis, and even type 1 diabetes can occur. And those are rare but potentially fatal toxicities.

I think the other toxicities we see, maybe not as severe, but can become chronic or common, is inflammatory arthritis, particularly in older patients, that can happen in 5 to 10% of patients. So really broadly explaining that inflammation of any organ system in the body can occur, and some of these rare and severe ones, particularly when we give PD-1/CTLA4 combination.

Dr. Forde:
Great. Well, I think that's very helpful. And I think something to keep in mind when we see our patients. This option of CTLA4/PD-1 blockade in combination with chemotherapy could be a good option for patients with squamous or PD-L1-negative disease or both.

So I think with that, our time is up. And I hope you all found the information presented in this episode helpful in your practice, and thanks for listening.

Chapter 2

Dr. Forde:
This is CME on ReachMD, and I'm Dr. Patrick Forde.

Dr. Naidoo:
And I'm Dr. Jarushka Naidoo.

Dr. Forde:
And today I'm going to review a case and discuss treatment options for patients with advanced PD-L1-low or PD-L1-negative, non-small cell lung cancer and no actionable mutations. And let's start our discussion by looking at a case.

So this is a 73-year-old man who presents with shortness of breath on exertion and weight loss of 10 pounds. He has a past medical history of a coronary artery bypass graft 15 years ago, well-controlled hypertension and dyslipidemia, and also COPD. And he's a former smoker, 30-pack-year with 15 years ago. Physical exam shows a weight of 180 pounds. Good performance status. And unfortunately, CT of chest and abdomen shows multiple bilateral lung metastases measuring up to 2 cm with enlarged mediastinal adenopathy and bilateral adrenal metastasis. An MRI scan of the brain shows no brain metastasis. He has a biopsy performed which is consistent with TTF-1 positive adenocarcinoma, metastatic stage IV. PD-L1 expression is performed and is negative in the tumor, and NGS shows no actionable mutations. So what treatment options could we consider in this case?

So first of all, I'm going to review one of the seminal studies in this setting. This was the KEYNOTE-189 trial. This enrolled patients with untreated stage IV, non-squamous, non-small cell lung cancer, without EGFR or ALK alterations. Patients could not have symptomatic brain metastasis or a history of pneumonitis requiring steroids. They were stratified by PD-L1 status. Platinum compound cisplatin or carboplatin, and history of smoking to a control arm of carboplatin, pemetrexed plus placebo followed by maintenance placebo plus pemetrexed maintenance which was optional, or chemotherapy plus pembrolizumab followed by maintenance pembrolizumab plus pemetrexed, which was optional. In the control arm, patients who had disease progression could cross over to pembrolizumab at that time if they fulfilled eligibility for the study.

We have follow-up from this trial showing that it met all the primary endpoints, a significant improvement for both progression-free survival, a hazard ratio of 0.52 and overall survival, a hazard ratio of 0.49. And also a significantly improved response rate in the pembrolizumab-containing arm.

We also have 5-year outcomes from KEYNOTE-189 at this point in the intention-to-treat population. At 5 years in the control arm, 11.3% of patients were alive, whereas in the investigational arm, 19.4% were alive. This was despite an effective crossover rate of 57% in the chemotherapy arm at the time of progression. So a hazard ratio for overall survival of 0.6.

Looking at one of the subgroups which might be relevant for this patient. This is the PD-L1-negative group, significant hazard ratio favoring chemotherapy plus pembrolizumab, 0.55. At 5 years, we see about a 4% difference in overall survival, 5.3% of patients being alive in the chemotherapy arm versus 9.6% in the pembrolizumab-containing arm.

There has been a meta-analysis – or pooled analysis performed looking at pembrolizumab plus chemotherapy versus chemo alone in PD-L1-negative cancers. Here we see the results of this pooled analysis. Again, at 36 months, we see an improvement overall for those patients who received pembrolizumab, going from 13.8% in the control to 24.9% survival at 3 years in the pembrolizumab-containing group. Most of this benefit is concentrated in the non-squamous disease. You'll see here in this forest plot, a hazard ratio of 0.52 in non-squamous disease. However, only 0.81 in squamous disease.

Moving on to some combination immune checkpoint studies. So CheckMate 227 was one of the first in this setting. Here we're going to concentrate on part 1b of the study. This looked at patients who received either nivolumab plus chemotherapy or nivo/ipi, and compared this to chemotherapy alone.

Here we see the results that 6-years from CheckMate 227, 6-year overall survival in tumors with negative PD-L1 expression. You see nivo/ipi here appears to be conferring benefit. You see survival at 6-years of 16% with nivo/ipi, 10% with nivo plus chemo, and just 5% with chemotherapy alone. And here we see in non-squamous histology, relevant to this patient, we see that there's a quite significant 4-year survival benefit for those patients that got nivo/ipi, 25% of them are alive at 4 years, versus only 12% in the control arm.

There have been several other studies in this setting, CheckMate 9LA looked at a short course of platinum doublet chemotherapy, two cycles plus nivo/ipi compared to standard platinum doublet, four cycles of chemo with optional maintenance pemetrexed for non-squamous disease. Primary endpoint of the study was overall survival.

And here we see the updated overall survival at 5 years from this study. A sustained benefit for the ipilimumab/nivolumab, plus chemotherapy arm, hazard ratio 0.73. And at 5 years, approximately 7% more patients are alive in that arm of the study. When we break this down by histology, we see a benefit in both groups. In the non-squamous group, we see a hazard ratio of 0.77 favoring the nivo/ipi-containing arm. And in 5 years, 19% of patients being alive in that arm versus 12% in the control. And here we see breakdown by PD-L1 status. And these are small groups, so we have to treat them with some caution; however, in the PD-L1-negative group, a very significant benefit here, in terms of patients having a sustained response, where we see in PD-L1-negative patients, 25% of patients have a sustained response if they received nivo/ipi plus chemo at 5 years versus 0% in the chemotherapy alone arm.

Moving on to a more recent trial, POSEIDON. The key comparison here is durvalumab plus tremelimumab plus chemotherapy compared to chemotherapy alone. And here we see the updated results for progression-free survival and overall survival from POSEIDON. Median progression-free survival was significantly improved with the addition of durvalumab/tremelimumab to chemotherapy, hazard ratio 0.72. And overall survival at 4 years also significantly favors durvalumab plus tremelimumab. A hazard ratio of 0.77 for that arm. When we break it down by histology and PD-L1 status, significant benefits both in PD-L1-negative disease and also in non-squamous histology, both relevant for this patient.

Finally, the EMPOWER-Lung 3 trial. Quite a similar design to KEYNOTE 189. Chemotherapy plus placebo or chemotherapy plus the anti-PD-1 antibody cemiplimab for patients with both squamous and non-squamous histology. Here's the 2-year overall survival from this study, favoring the cemiplimab-containing arm, but a significant difference there. When we break this down by PD-L1 status and histology, we see a significant benefit for non-squamous disease, you'll see in the forest plot. However, in PD-L1-negative disease here,

not quite so much benefit, 0.94 hazard ratio. And here's a summary table, looking at that breakdown, you'll see highlighted in red here, PD-L1-negative, non-squamous disease.

So we'll go back to our discussion at this point. And Dr. Naidoo, what are your thoughts on management of this patient with non-squamous disease and PD-L1-negative status, good performance status?

Dr. Naidoo:
Yeah, I think sort of this discussion mirrors a little bit the discussion that we have for squamous. I think, PD-L1-negative disease again this time, non-squamous, is associated with a slightly poorer outcome. And so for these patients, if they have a good performance status, I would definitely be wanting to give them a combination approach and maximize what that combination would be. So here, I think CheckMate 9LA or CheckMate 227, incorporating the CTLA4 are very reasonable options, as well as the KEYNOTE-189 regimen, when we know that there isn't a molecular driver.

In this instance, what did you choose for the patient?

Dr. Forde:
So in this case, we ended up choosing the CheckMate 9LA regimen again. This was a patient with a relatively distant smoking history; however, quite a heavy smoker in the past. No molecular alterations that were targetable. And we discussed one of the differences between these regimens, as well as the relatively more limited chemotherapy in CheckMate 9LA, which is two cycles of platinum doublet chemotherapy versus in KEYNOTE-189 four cycles plus or minus maintenance pemetrexed for a patient with non-squamous disease.

So we decided to go with the CheckMate 9LA regimen. The patient did have a nice response to therapy, did have some moderate toxicity, had low grade colitis, which led to some dose interruptions. However, ultimately had a sustained response to treatment, and is now over 4 years out on this regimen.

So I think what the long-term follow-up of some of these combination immune checkpoint studies suggest is that you can have these long durations of response, which can provide benefit for some patients.

Another element we did with this patient was that when they had toxicity, we were able to hold the CTLA4 component of the regimen and then retreat with PD-1 alone, which is an option in some of these studies as well. I think it can be a good option, because we know that a lot of the immune toxicity, particularly elements like colitis, are driven mainly by the CTLA4 component.

What has been your experience with this regimen in general? CTLA4/PD-1, either with or without chemotherapy?

Dr. Naidoo:
Yeah like you, I would be a big fan of this regimen, I think, across the board, and particularly for these difficult-to-treat subsets like the PD-L1-negative subset, the outcomes look the best. So my experience has been relatively good. However, I would say that with a four-drug combination to start with, the patient needs to have a good performance status going in. So this might limit my ability to give this as a universal approach, since many patients might have a compromised performance status when they start.

One element you brought up there, I think is interesting to talk through, is factoring in the smoking status into the decision-making, and the sort of push/pull between smoking status and maybe the biomarker of tumor mutational burden that had been used some years ago. Do you factor that into your decision-making here, and how so?

Dr. Forde:
Yeah, I think it's one of a number of kind of softer factors I think I bring into these things. I think the key elements are probably the histology in terms of the platinum doublet choice, the prognosis, and also the PD-L1 status. I think it's very relevant. things like tumor mutational burden, smoking status, I think higher tumor mutational burden, heavy smoking status, they make me more comfortable perhaps with PD-L1 or with single-agent anti-PD-1 if it's high PD-L1 disease, or with a non-CTLA4 regimens.

The other thing sometimes we look are the STK11 and KEAP1 status, which there's some emerging data suggesting that those tumors containing one of those mutations, particularly in combination. STK11, KRAS, may predict less sensitivity to PD-1 based therapy without CTLA4. So those are also factors which can influence my choice to a degree.

Dr. Naidoo:
Sounds good.

Dr. Forde:
So I think with that, our time is up. I hope you found the information presented in this episode helpful to you in the practice, and thanks for listening.

Chapter 3:

Dr. Forde:
This is CME on ReachMD, and I'm Dr. Patrick Forde.

Dr. Naidoo:
And I'm Dr. Jarishka Naidoo.

Dr. Forde:
Today, I'm going to review a case and discuss treatment options for patients with advanced non-small cell lung cancer with a PD-L1 expression level between 1 and 49% and no actionable mutations. So let's start our discussion by looking at a case.

This is a 58-year-old female who presents with an incidental finding of bilateral lung lesions when undergoing a preoperative CT for hernia repair. She feels well without symptoms, very mild past medical history of hypertension, currently on a thiazide diuretic. She's a distant past smoker, 10-pack-year history. Stopped smoking 25 years ago. Current weight is 120 pounds. Good performance status. CT is completed of abdomen, which shows, in addition to lung lesions, also a right adrenal metastasis and bone windows in the CT, unfortunately, suggest bone metastasis. MRI brain is negative for brain metastasis. She has a biopsy performed which is consistent with adenocarcinoma. There is a proportion of lung adenocarcinomas which are TTF-1 negative, which is the case here. However, it's CDX2 positive. And this is a marker which can suggest intestinal differentiation in lung cancer. Given her staging, she has stage IV disease. PD-L1 immunohistochemistry shows 40% expression, and next generation sequencing is negative for targetable alterations. So what treatment options should we consider in this case?

So here we see some of the results for this patient population broken down by PD-L1 expression in particular. Some of them have more granular detail than others. we'll see here in CheckMate 227, patients that got combination ipilimumab/nivolumab had a response rate of 36%, median overall survival of 17 months, median duration of response of almost 25 months. CheckMate 9LA, which was combination ipilimumab/nivolumab plus two cycles of chemo, a high response rate in this study, 87% duration of response in just under 12 months, and a median overall survival of almost 16 months.

In KEYNOTE-021, a small study, again, very high response rate adding pembrolizumab to chemotherapy. Much larger trial, KEYNOTE-189, which led to the approval of chemotherapy plus pembrolizumab for non-squamous lung cancer in the PD-L1, 1 to 49 group here, we see a response rate of 50% duration of response, median 13.6 months, and a median overall survival at 21.8 months. In the larger study, KEYNOTE-407 which looked at all patients with PD-L1, 1 to 100% expression, when we break it down into the 1 to 49 group, we see a response rate of 54.4%, median overall survival here at 18 months.

And finally, some of the other regimens, atezolizumab, plus bevacizumab plus chemotherapy, this was the IMpower150, we see a response rate 55% and a median duration of response here of 10.8 months. Chemotherapy plus cemiplimab from the EMPOWER-Lung 3 trial, a response rate in this group of 43%, duration of response just under 17 months, median overall survival of 23 months.

And finally one of the more recent studies, POSEIDON, durvalumab/tremelimumab plus chemotherapy response rate of 38.8%, median overall survival of 14 months.

So I think the take-home message here is that we're seeing not quite the same populations in all trials, but results coming in around that range of survival of about 18 months on average, response rates between 36 and 61% are the highest results we've seen so far.

We have 5-year follow-up from KEYNOTE-189. On the left of your screen here you'll see the intention-to-treat population. Significant benefit for those patients who received pembrolizumab. At 5 years, we see 11.3% of patients alive in the control arm versus 19.4 in the investigational arm. When we look at the PD-L1, 1 to 49% group, we see a significant benefit for pembrolizumab plus chemotherapy, hazard ratio of 0.65, 7.7% of patients alive in the control arm, and this is 19.8 in the chemotherapy/pembrolizumab arm.

Looking, so in more depth that CheckMate 9LA, so here we see in particular group with 1 to 49% expression, significant hazard ratio favoring chemotherapy plus ipilimumab/nivolumab, 0.61. When we look at the breakdown in terms of response, this group did quite well. Response rate of 39.4% in that subgroup and median duration response of 10 months, which is significantly longer than chemotherapy at 5.6.

In the EMPOWER-Lung 3 trial looking at cemiplimab plus chemotherapy, we again see benefit for the addition of anti-PD-1 to chemo. When we break it down by non-squamous histology, a significant hazard ratio here favoring cemiplimab addition. And in the 1 to 49 group, we see quite impressive results here, hazard ratio of 0.5 favoring cemiplimab plus chemotherapy. And here's a more detailed breakdown of these results. You'll see highlighted in red, the non-squamous PD-L1, 1 to 49% group, again, significant hazard ratio, as mentioned, for overall survival of 0.48.

To talk a little bit about the POSEIDON study, one of the more recently approved regimens. So this looks at the combination of durvalumab plus tremelimumab plus chemotherapy versus chemo alone. The overall population here you'll see a hazard ratio of 0.86 favoring durvalumab plus tremelimumab. However, not statistically significant. On the right of your screen, however, you'll see the population which led to approval. This was durvalumab/tremelimumab plus chemotherapy compared to chemo alone, and a significant hazard ratio favoring durvalumab/tremelimumab plus chemo.

But when we look at this forest plot at the different subgroups within this trial, here we focus on the 1% and above PD-L1 expression, significant benefit for durvalumab and tremelimumab, hazard ratio of 0.76. And also focusing on the non-squamous population, hazard ratio of 0.7 which also significantly showed a benefit. So dual immunotherapy is an option for this group.

Here we look at the CheckMate 227, study, the part 1 of the study, which was nivolumab plus ipilimumab versus chemotherapy in patients with PD-L1-positive disease, and here we see a significant benefit favoring nivolumab plus ipilimumab compared to chemotherapy alone. At now long-term follow-up in this trial, we see so in this population, a hazard ratio versus chemotherapy of 0.78. When we focus in on the PD-L1-positive and non-squamous histology, again, we see benefit here. Hazard ratio 0.81 favoring nivo/ipi. And at 4-year follow-up, we see 32% patients alive with nivolumab plus ipilimumab, versus 23% with chemotherapy alone.

There has been a pooled analysis performed by the FDA looking at this 1 to 49% PD-L1 expression group. You'll see here the analysis mainly looked at chemotherapy plus immunotherapy compared to immunotherapy alone. The suggestion here being that patients overall likely derive benefit from the addition of immunotherapy to chemotherapy compared to IO alone here. A median survival with immunotherapy alone for this group of 14.5 months versus 21.4 months in the chemo/IO group, hazard ratio of 0.68. There are particular subgroups, I think, for whom this may not be the best choice, particularly more frail or elderly patients. But in general, I think our standard of care for patients with PD-L1, 1 to 49 group is the combination of chemotherapy plus immunotherapy.

So in summary, I would say there's no clear role for single-agent immunotherapy for 1 to 49% outside of specific subgroups as mentioned, and both immunotherapy plus chemo, for example, anti-PD-1 plus chemo, or four-drug regimens may be used in this population.

So we'll now discuss a little bit further, and I'll go back to Dr. Naidoo for her thoughts on her management of patients with PD-L1 1 to 49% expressing tumors, particularly with non-squamous disease.

Dr. Naidoo:
Thanks, Patrick. Yeah. I think this is obviously the most common group of patients that we see clinically. And in this circumstance, the regimen that I use most often would be the KEYNOTE-189 regimen. I found this very easy to give really, from both a practical and a toxicity standpoint, most patients tolerate it without incident. I think some of the open questions really are around the maintenance portion. How long to continue it for? At what point do we feel comfortable to sort of de-escalate that? And then, as you mentioned in your discussion, what to do with those patients who don't fit neatly, maybe the performance status 2 patients and others, maybe see what you think your interpretation of the IPSOS trial here. Would we ever feel comfortable to modify this? I think as best as possible, I do try to give KEYNOTE-189.

Dr. Forde:
Yeah, and I agree. I think that's my more common regimen as well, for this population. I think it's got good efficacy data. The choice of monotherapy, I think, so very select patients, I think some of those patients who are frailer, who we're particularly concerned perhaps, about chemotherapy toxicity. The patients who I tend to look at dual checkpoint blockade is the population tend to be those on the lower PD-L1 score, perhaps in the 1 to 10% range. Or again, as we've discussed in some of the other cases, those patients who perhaps have some softer characteristics of their tumor which might suggest resistance to PD-1. And some of those can be things like co-mutation status with KRAS and STK11, perhaps those patients with relatively lower tumor mutational burden, patients with mucinous disease, I found, sometimes can be quite resistant. Their tumors can be to treat to PD-1-based treatment. Or sometimes patients who, despite having nonsmoking status or light ex-smoking status, may not have targetable alterations. And we sometimes see this particularly in this case where it was a TTF-1 negative intestinal type tumor, those are tumors where we relatively rarely see targetable mutations, even If the patient is a nonsmoker, and that's a population where sometimes I will also look at the combination immune checkpoint. Without a whole lot of data, particularly, but with a concern that perhaps PD-1 chemotherapy won't do quite so well.

In terms of looking forward with these regimens, how do you see the landscape changing in terms of this 1 to 49 group? It is the most common group, as we've said previously. Are there new therapies coming along that you think may be interesting?

Dr. Naidoo:
I think that the 1 to 49 group is probably the group that is likely to stay the most stable in terms of the landscape and how it is evolving. We are seeing some data of maybe novel combinations in the PD-L1-high population, greater than 50% adding something on to maybe

a pembrolizumab alone. An we've seen some combination approaches that appear to be interesting. As you mentioned in KRAS, maybe combining immunotherapy with a G12C inhibitor might change what we do there. And quite a lot of studies focusing on the negative population that sort of do the worst, and, could we elevate that? Having said that, I think we're coming on nearly 5 years of establishment of some of these regimens. So I think it will actually take quite a lot to move some of these combination approaches off their perch. And now that we have so many choices, I would say that maybe there will be more data that will add another choice, but may not necessarily move the dial away from some of these, which we have gained a lot of clinical experience of giving, and we know gives a lot of benefit.

Do you see anything coming and tipping the scales here?

Dr. Forde:
No, I think you've summarized it very well. So I think we have good options for these patients. Obviously, we always want to make further progress, but I think this is a relatively established treatment paradigm here, and I don't see it changing in the very near future.

So with that, our time is up. And I hope you found the information presented in the episode helpful to you and your practice. And thank you all for listening.

Chapter 4

Dr. Naidoo:
This is CME on ReachMD. And I'm Dr. Jarushka Naidoo.

Dr. Forde:
And I'm Dr. Patrick Forde.

Dr. Naidoo:
Today, I'm going to review a case and discuss the treatment options for patients with advanced non-small cell lung cancer and co-mutations in either or both KEAP1 and STK11. Let's start our discussion by looking at a case.

This is a 72-year-old female who presents to her general practitioner with a 9-cm lung mass invading the mediastinum and with liver metastases on CT that represent biopsy-proven adenocarcinoma, T4, N2, M1c, stage IV disease. The patient's tumor has a PD-L1 score of less than 1% and her ECOG performance status is 1. Molecular testing results reveal the presence of a KRAS G12C mutation, KEAP1 alteration, and a TP53 mutation. What is the most appropriate treatment? Is it either A: Chemoimmunotherapy; B: Anti-PD-1 immunotherapy alone; 3: A KRAS G12C targeting agent; or 4: Chemotherapy alone.

So with that, I'm going to review the clinical data on the first-line immunotherapy options in patients with advanced non-small cell lung cancer and co-mutations, and either KEAP1 or STK11. The systemic treatment options for patients with KRAS-mutant non-small cell lung cancer are recommended to follow the guidelines for first-line systemic therapy for patients with non-small cell lung cancer that does not harbor an actionable driver mutation. So some of the first-line treatment options, as with those who do not have an oncogenic driver, would be based on PD-L1 status. And as Dr. Forde has already gone through, these options could be chemoimmunotherapy with a three-drug combination, chemoimmunotherapy with a four-drug combination incorporating a CTLA4 agent, dual immunotherapy without chemotherapy, or immunotherapy alone.

Our subsequent treatment options are then guided by prior therapy, histology, performance status and other related supported care factors. If a patient's non-small cell lung cancer harbors the KRAS G12C mutation in the second-line setting, there are now several approved targeted therapy options. And in the case of progressive disease, once again, performance status and prior therapy would guide what we do next.

So thinking a little bit about our case in which we see an activating KRAS mutation as well as relevant co-alterations, we see that patients with KRAS-mutated non-small cell lung cancer do respond to frontline immunotherapy-based therapy.

Here we see an FDA analysis of the first-line trial outcomes according to KRAS mutation status that was presented at the ASCO meeting in 2022. And we see here that in over 800 patients who received immunotherapy with chemotherapy with KRAS wild-type disease, the response rate was 51%. In patients with KRAS-mutant lung cancer in 555 patients, this was 46%. And in those with KRAS G12C-mutant disease, representing 157 patients, this was 47%. Similarly, we see here the median overall survival in patients treated with immunotherapy and chemotherapy based on their KRAS status. And we see that KRAS wild-type disease here, had the poorest overall survival of 18.7%. But broadly, the patients with KRAS-mutant lung cancer, whether it be G12C or non-G12C, appear to have an overall survival benefit from the immunotherapy and chemo combination with a median overall survival of 22.4 months and 20.8 months, respectively.

Taking a deeper dive into the survival outcomes of these relevant co-mutation subsets in patients treated with the combination of

ipilimumab and nivolumab, we see very similar trends. We see here that the median overall survival in patients who have KRAS-mutant lung cancer, STK11-altered or KEAP1-mutant non-small cell lung cancer, all appear to benefit from the immunotherapy combination, and that actually adding the CTLA4, in this instance, appears to confer some greater degree of survival outcome, particularly for the STK11 or KRAS-mutant non-small cell lung cancers.

So what about the impact of these additional mutations, or co-mutations in driver-negative non-small cell lung cancer? So those who do not have a KRAS mutation, but do have say, KEAP1 or STK11 on its own. We've seen several subgroup analyzes as some of the major phase 3 studies recently discussed by Dr. Forde. Here we can take a look at the POSEIDON study and the CheckMate 9LA study, both incorporating a CTLA4 agent into their treatment paradigm. We see here in the POSEIDON study, that patients whose non-small cell lung cancers harbored a KEAP1 alteration appeared to be associated with a greater benefit in median overall survival when they were treated with durvalumab/tremelimumab chemotherapy, as opposed to chemotherapy alone or durvalumab with chemotherapy. And we see here, the median overall survival of the four-drug combination was 13.7 months in the KEAP1-mutant population, as opposed to 8.1 months with durva alone, or 8.7 months with chemotherapy alone. This trend was not appreciated in the KEAP1 wild-type population, where the survival outcomes all appeared to be similar, ranging from 12.2 to 14 months.

Taking a similar look at the KEAP1-mutant subgroup analysis of CheckMate 9LA, we see a very similar trend in that those patients treated with ipi/nivo plus chemotherapy had a median overall survival of 13.2 months, while chemotherapy alone had a median overall survival of just 5 months. So really, the KEAP1 mutations, in this instance, are prognostic and to some degree may be predictive of benefit when we add the CTLA4.

What about STK11? A similar analysis, subgroup analysis in both POSEIDON and CheckMate 9LA was done in those patients with STK11-mutant non-small cell lung cancer. And again, a very similar trend. In POSEIDON, a median overall survival of 15 months, the best with the four-drug combination, incorporating tremelimumab. But this trend not seen in the STK11 wild-type population. Again with CheckMate 9LA, the median overall survival with ipi/nivo/chemo in the STK11-mutant population, the best at 13.8 months, and not the same trend seen in STK11 wild-type with a median overall survival of 17.8 months versus 13.9 months.

How does this work out for patients treated with immunotherapy alone? Really, I think some of the data is mixed with regard to STK11 and KEAP1 from various subgroup analyses. This is a subgroup analysis published by Tony Mok in the Annals of Oncology based on KEYNOTE-042, assessing pembrolizumab alone. And here, what we see is that we do see some benefit for pembrolizumab monotherapy in both the STK11 and KEAP1-altered non-small cell lung cancers.

So really, all together, the data is somewhat mixed. I do feel that both STK11 and KEAP1 appear to be prognostic. There is a trend that appears consistent across many of these studies that this subgroup of the population may benefit from the addition of some CTLA4, and therefore, taking all of this into consideration, this is a nice schematic from a recent publication in the JTO that really explains how we should interpret these molecular alterations as a continuum with PD-L1 expression, and take both KEAP1 and STK11 into consideration, as well as other alterations such as p53 to selecting whether patients should get PD-1 or PD-L1 monotherapy, if their PD-L1 is high, and on a scale of PD-L1-negative disease, as well as concurrent mutations in KRAS, STK11, or KEAP1 in the negative population, who may benefit from the most combination approach incorporating PD-1 chemo with or without CTLA4.

So in summary, patients with lung cancer will have a mutation in KRAS and no other known driver alterations should be treated with frontline chemoimmunotherapy depending on their PD-L1 status. There is emerging evidence that certain molecular alterations, such as STK11 and KEAP1 may impact the efficacy of anti-PD-1-based treatments; however, we do need some prospective, randomized data to try to guide our treatment options in the future.

So with this, I think good to open up for a little bit of discussion on how to treat this patient and others. Obviously an emerging area in which we're learning new data every day. So Patrick, in your practice, do you use STK11, KEAP1, and p53, in your treatment decision-making? And do you have universal access to this testing in order to incorporate it in your treatment decision-making?

Dr. Forde:
Yeah, I think a great discussion of what's a complex area at the moment. The common driver alterations that we test for, not everyone is testing for STK11, KEAP1. I think even though it's been an emerging kind of area over the last few years. On our particular panel at my institution, we do test for STK11 and KEAP1. So we do have those data available to us. I think one of the interesting things we find is that some of these also tend to be associated with lower PD-L1 expression particularly STK11. So I think that can also play into our decision-making. I think we've discussed in some of the earlier cases about use of combination CTLA4/PD-1 blockade. And frequently when we see a PD-L1-low tumor, we're thinking of that combination of regimen for PD-L1-negative disease. And I think the addition of something like an STK11 alteration, or KEAP1 alteration, will push us even further in that direction, mainly because of the accumulated kind of subgroup data, which you've discussed, and analysis across multiple trials where we're seeing this emerging trend, and not quite

prospectively proven. So I think a lower level of evidence and some of the other things we've discussed, including PD-L1 status.

But something I do factor into my decision-making process when seeing patients with non-squamous disease, most of these alterations are seen in non-squamous if they have one of these alterations. Particularly, I like that diagram you presented from Dr. Ricciuti and Dr. Garassino. I think that's a good summary of kind of the average decision-making process here for these patients.

What are your thoughts on availability of testing for these alterations? And also whether you factor it into your decision-making?

Dr. Naidoo:
Yeah, I think certainly in different jurisdictions around the world, the availability of some of these testing results may be variable. So certainly here, we do have a broad next generation sequencing panel available but really only the actionable alterations that would change our treatment decision-making are generally reported. So some of these rarer alterations may not be reported as standard, but can be requested from our relevant pathology departments. So I see some variability, I would say, across this continent and others, as to what might be reported but I have requested to have this added onto all of our standard reporting, just to have the information to be able to make an informed decision. But definitely, I think we would see differences across the world here.

So in this instance, I chose to give the patient a combination with a CTLA4 four-drug. What treatment would you have chosen in this instance?

Dr. Forde:
Yeah, I think I probably would have looked assuming the treatment were available and reimbursed, I think I would have chosen that likely for this patient as well. and I think so, as we've discussed previously, there are kind of multiple things that go into that decision - comorbidities, performance status, along with these things such as PD-L1 status and mutations, but I think that's a very reasonable choice. And how did this patient do in terms of long-term outcome?

Dr. Naidoo:
The patient had a short-lived response to treatment and then we had the performance status declined, unfortunately, and we weren't able to get to second-line therapy. And I think that's another point that you've made before, that we should try to give our best treatment upfront. We never quite know if we're going to get to second line. So unfortunately, this patient didn't do well in the end. And it does emphasize that we need more for these patients, and enrolling on future studies will hopefully help that.

With that, our time is up. I hope you found the information presented in this episode helpful to you in your practice. And thank you for listening.

Chapter 5

Dr. Naidoo:
This is CME on ReachMD, and I'm Dr. Jarushka Naidoo.

Dr. Forde:
And I'm Dr. Patrick Forde.

Dr. Naidoo:
Today, I'm going to review a case and discuss treatment options for patients with stage III non-small cell lung cancer following progression on maintenance durvalumab. Let's start our discussion by looking at a case.

A 65-year-old male is undergoing treatment with stage III, unresectable, squamous non-small cell lung cancer T4, N2, M0. The tumoral PD-L1 score is 50% and there are no actionable genomic alterations. The patient commences consolidation durvalumab after concurrent chemotherapy and radiation. And within 6 months, his therapy develops progressive disease in the bones on his first restaging CT. What is the appropriate next treatment? Is it A: Docetaxel; B: Carboplatin, paclitaxel, and pembrolizumab; C: Ipilimumab and Nivolumab; or D: Ipilimumab, nivolumab, carboplatin, and paclitaxel.

Next, I'm going to discuss treatment options for patients with stage III non-small cell lung cancer following progression on maintenance durvalumab. So to recap from here, I might take us through the PACIFIC trial which is the regimen that the patient received, after which they developed progression. So in the last 5 years, this has represented a new standard of care for patients with stage III unresectable non-small cell lung cancer. Patients with stage III unresectable disease in this trial were randomized to receive either durvalumab at a dose of 10 mg/kg every 2 weeks for up to 12 months, or placebo. This study randomized patients between 1 to 42 days post concurrent chemoradiation and the co-primary endpoints were both overall survival and progression-free survival. We see here that this study met both of its co-primary endpoints with a statistically significant benefit in overall survival with a hazard ratio of 0.72 and a statistically significant benefit in progression-free survival with the hazard ratio of 0.55 and resulted in two back-to-back New England Journal of

Medicine publications. One of the controversial topics in the area of stage III unresectable disease is the role of PD-L1 score and PD-L1 testing. In these patients, we see that in some jurisdictions in the world, we can treat with maintenance durvalumab regardless of the PD-L1 status. However, in others approval of this treatment is contingent on the PD-L1 score being greater than 1%. And this therefore leads to some differences across the world.

In terms of this patient's particular course, we see that this patient developed progressive disease through their treatment. How does tumor resistance occur at the time of anti-PD-1? We see here a number of emerging definitions for acquired resistance in the context of immunotherapy, particularly in clinical cases such as this. There are two published sets of definitions for resistance, or acquired resistance, after anti-PD-1. The first comes from the Society for Immunotherapy in Cancer, in which patients may be separated into those who develop primary resistance, where they develop progressive disease after less than 6 weeks of drug exposure, or their best response is either progressive disease or stable disease of less than 6 months. In this consensus definition, acquired or secondary resistance requires patients to have had drug exposure for longer than 6 months and sustained an initial either complete or partial response to immunotherapy or stable disease lasting for more than 6 months. Based on this definition, our case would have developed primary resistance to immunotherapy.

The ESMO definition of acquired resistance is somewhat modified compared to the Society for Immunotherapy in Cancer definitions. In this modification, the authors suggest that grouping both PD-1 monotherapy and IO/IO combinations is appropriate when thinking about acquired resistance. The authors also assert that patients need to have sustained an objective response to immunotherapy which means have had either a complete or partial response to immunotherapy in order to be defined as having acquired resistance. They also suggest that patients need to have progressed within 6 months of their last immunotherapy in order to be defined as having acquired resistance. Using both these definitions based on our case, the patient would have developed primary resistance to immunotherapy.

So what data do we have to guide our treatment decisions after a patient has developed progression on immunotherapy or primary resistance, such as this case? In the case of PACIFIC, so far, there has been some limited data annotating the follow-up treatment regimens for those who did progress after treatment on PACIFIC. We see here in the PACIFIC trial that 231 patients did receive some subsequent therapy after progression on durvalumab. We see here that the majority of these patients received cytotoxic chemotherapy at 33%, 20% of those patients received radiotherapy, and 12% were re-challenged with a further immunotherapy, 11% of patients received some other form of systemic therapy.

At the time of immunotherapy rechallenge, we see that 12%, or 4 patients would have completed a full 12 months of additional immunotherapy. And unfortunately, this is the only data really to guide us after the treatment with the PACIFIC regimen.

Are there any other regimens that can guide us as to how these patients might do at the time of progression? There are some early lessons from the neoadjuvant studies, such as CheckMate 816. We see here in patients treated with upfront or neoadjuvant chemoimmunotherapy, that patterns of recurrence may be different after treatment, with a large proportion of patients developing local, regional recurrence, as opposed to distant recurrence, and a smaller population of patients developing progression in the brain.

In 5-year follow-up from some of the early neoadjuvant studies in nivolumab alone, we see that in total, there have been seven recurrences, and three of four of these developed local recurrence and are still alive after definitive therapy.

Therefore, taking this all together in consideration, we see that the patterns of relapse in patients who develop progressive disease after initial treatment with immunotherapy may be different. And in our case, the patient did develop progressive disease in the bones, necessitating a change in systemic therapy. Therefore, in this case, the patient was switched to standard docetaxel-based chemotherapy, and had a short-lived response to treatment.

So with that, I'd like to open up to discussion. Obviously a very controversial topic, the topic of primary resistance and what to do next. So I might invite Dr. Forde to share with us some thoughts on what he would do in this case.

Dr. Forde:
Yeah. Thanks very much Jarushka. That was an excellent summary of what's a complex topic. We don't have a whole lot of data to guide us in what to do in these scenario. I think your approach is probably what I would have done in the same scenario. I think it’s a tough one. These kind of things that I tend to factor into these decisions are how close to the previous chemotherapy the progression happens, whether that chemotherapy was sensitizing weekly chemotherapy, for example, like carboplatin, paclitaxel, or whether it was systemic dose platinum, a doublet. And I think also the extent of the progression is relevant. You know very extensive progression, CNS progression, these are things that are probably less likely to do well unfortunately. There are scenarios in the future, I think, where we may have more data, particularly as we're seeing more data recently on subgroups within the PACIFIC population who may do more poorly, particularly your own data with EGFR mutant patients and the recent update from ASCO on the LAURA. So I suspect we'll be

changing our plan for some of these patients in the future in terms of consolidation immunotherapy versus other treatments.

But for the time being, I think switching either to platinum doublet plus IO if they're quite some time out from initial chemoradiation, I think is a reasonable choice particularly if they've finished the maintenance durvalumab and they're on surveillance, and then have a recurrence.

Another scenario which sometimes arises is where they have an oligomet – some metastatic recurrence, and that's a scenario where, I think further radiation, or even in rare cases, surgery, local therapy, can be very beneficial. Is that a scenario you sometimes employ as well?

Dr. Naidoo:
Yes. I think certainly, if it's an isolated lesion or less than three, I think there's, good rationale to try to treat along an oligometastatic paradigm, and whatever makes sense in terms of the safety for the patient for the choice of local therapy, whether it be surgery or radiation. That's definitely something we would consider doing.

What's your opinion on the definitions for primary and acquired resistance? And do you actually use those in your daily practice to guide your decisions?

Dr. Forde:
Yeah, I think, to a degree. I think they're largely relevant, to be honest, for clinical trials at the moment. Many of the prospective phase 3 trials are using this as a kind of a stratification variable, particularly in the second-line setting. So if you're looking at a novel combination in a phase 3 trial after a prior platinum doublet and immunotherapy, then many of the phase 3 trials are now stratified by acquired versus primary resistance. The definition is kind of variable. You know, we did a study called HUDSON, where we looked retrospectively. This was a large study in the second line post PD-1 and chemo. And in that trial, we came up with a kind of cut-point of 4 months on prior immunotherapy as being kind of a differentiation between acquired and primary resistance. So I think something in that 4- to 6-month range kind of is where I look for either the patient's tumor not being responsive to immunotherapy or being responsive.

What are your thoughts on that kind of whole area of acquired versus primary?

Dr. Naidoo:
I think it's a debated area. I think having some kind of a standard definition would be useful to be able to rigorously assess these patients. I think the primary resistance definition is intuitive and sort of easy to see, like in our case. And I think acquired resistance in the patients who's had response is also intuitive and easy to make sense of. I think the stable disease patients are where there is a lot of discussion and a lack of understanding about how to approach those, what stable disease really means in the context of immunotherapy. So I think a lot of work, I think to understand that a little bit more. But watch this space.

Okay, so I think that brings us to the conclusion of our discussion today. Our time is up. I hope you found the information presented on this episode helpful to you in your practice. And thank you for listening.

Chapter 6

Dr. Naidoo:
This is CME on ReachMD, and I'm Dr. Jarushka Naidoo.

Dr. Forde:
And I'm Dr. Patrick Forde.

Dr. Naidoo
Today, I'm going to review a case and discuss the treatment options for patients with advanced non-small cell lung cancer and brain metastases. Let's start our discussion by looking at a case. This is a 57-year-old female who was incidentally found to have a 4-cm lung mass and multiple lung nodules on a CT scan of the chest, abdomen, and pelvis. A staging MRI of the brain identifies three brain metastases, and the patient is asymptomatic from these. The patient's tumor or PD-L1 score is 60% and her ECOG performance status is 1. Molecular testing results do not reveal the presence of any actionable genomic driver alteration.

What is the optimal next step? Is it, A: Stereotactic radiosurgery followed by systemic therapy with pembrolizumab alone? Is it B: Stereotactic radiosurgery followed by combination immunotherapy? Is it C: Combination immunotherapy with carboplatin pemetrexed and pembrolizumab? Is it D: Pembrolizumab alone? Or is it E, carboplatin pemetrexed with ipilimumab and nivolumab, the CheckMate 9LA regimen?

From here, I'm going to discuss treatment options for patients with advanced non-small cell lung cancer and brain metastases. Brain metastases are an area of unmet clinical need in patients with non-small cell lung cancer. We see that a large proportion of patients

with lung cancer have brain metastases at baseline, incorporating about 30% of the non-small cell lung cancer population. But our clinical decisions are based on clinical trials that do not necessarily assess a CNS endpoint, with only 4% of prospective clinical trials in lung cancer incorporating a CNS related endpoint. We also see here that in order for patients with brain metastases to take part in clinical trials in lung cancer and others, most of these patients need to have stable or treated brain metastases, and that approximately 20% of clinical trials in this space strictly exclude patients whose lung cancer has metastasized to the brain. So what data do we have to guide our decisions in patients in the first-line setting with non-small cell lung cancer?

Thankfully, there are several subgroup and pooled analyses that aim to generate specific data in this subset of the population. The first was a pooled analysis of patients from the KEYNOTE-021, 189, and 407 population comparing chemoimmunotherapy with chemotherapy alone in patients with brain metastasis. And we see here that the pembrolizumab and chemotherapy combinations are associated with an improvement in median overall survival, with a 2-year OS of 42% in patients with brain metastases, a median of 18.8 months, compared to just 7.6 months with chemotherapy alone. We see very similar trends in patients treated with PD-1/CTLA4 combinations.

Importantly, these two studies, CheckMate 9LA and CheckMate 227, the brain met subgroup analyses only include patients who had treated brain metastases. And in this subset of the population, the 2-year overall survival in CheckMate 9LA was 35% in patients who had brain mets with a median overall survival of 19.3 months, compared to 6.8 months for chemotherapy alone. In CheckMate 227, a similar trend was seen with a 2-year overall survival of 43%. And we see here the intracranial progression-free survival, again, favoring the combination approach with 13.5 month intracranial PFS in the CheckMate 9LA regimen, compared to just 4.6 months in those treated with chemotherapy alone.

Taking a deeper dive into CheckMate 227, we have now seen some updated data published in the Journal of Thoracic Oncology by Martin Reck and colleagues, assessing the 5-year overall survival and intracranial progression-free survival in patients with baseline brain metastases treated with ipi/nivo. Again, similar trends. We see that given combination immunotherapy appears to help these patients with a median overall survival of 17.4 months, compared to 13.7 months in those with baseline brain metastases.

With CheckMate 9LA, updated data again in the JTO, this time, 3-year overall survival and progression-free survival of patients with baseline brain metastases, again favors the combination approach, with a median overall survival of 19.3 months compared to 6.8 months. So really giving a combination does appear to help these patients.

What about those who are eligible for PD-1 monotherapy? In two separate studies, the role of PD-1 monotherapy in PD-L1-high non-small cell lung cancer was evaluated. The first was in a phase 2 study presented by Sarah Goldberg and colleagues and published in The Lancet Oncology in 2020. And this specific study focused on brain metastases, patients with a PD-L1-positive non-small cell lung cancer who had disease in the brain, had an intracranial response rate of 30%.

Separately, the Atezo-Brain study aimed to evaluate the role of combination chemotherapy with atezolizumab in patients with untreated brain metastases. In this study, the intracranial objective response rate was 42% with a 2-year overall survival rate of 28%. We also saw a trend towards an improvement in overall survival with the greater the PD-L1 score.

There are several ongoing phase 2 and 3 clinical trials in patients with lung cancer and untreated or asymptomatic brain mets similar to the patient in our case. Several of these studies are evaluating different immunotherapy agents, such as cemiplimab alone, chemoimmunotherapy combinations with anti-TIGIT compounds, and even together with VEGF, pembrolizumab with bevacizumab, or serplulimab plus bevacizumab, which we know may have improved intracranial outcomes.

We need to, of course, also evaluate the optimum timing of radiation in the context of patients with untreated or asymptomatic brain mets. And similarly, there are several ongoing studies aiming to evaluate the role of concurrent or sequential stereotactic radiosurgery in the context of immunotherapy. We see a table here of several of these studies that are exploring the timing of radiation, as well as some newer radiation approaches, such as tumor-treating fields and focused ultrasound, and we await some of these results.

So with that, I'd like to open up the discussion in this case. In this case, the patient was treated with upfront immunotherapy alone, sustained a good response to immunotherapy, and did not necessitate the need of stereotactic radiosurgery in this case, as she sustained a response intracranially.

Interested to hear what you would do, Patrick, in this case.

Dr. Forde:
Yeah, I think these are very interesting situations. You know the anti-PD-1 or PD-L1 antibodies are quite large molecules, so we don't necessarily expect them to penetrate into the brain, but we do see these intracranial responses. And I think part of the assumption here is that you're having immune activation and perhaps migration of immune cells into the brain leading to tumor regression. I have had

several patients over the years with benefit in the brain from immunotherapy. And I think the analysis you presented, they definitely support that for a patient who has a tumor likely to be sensitive to immunotherapy particularly if they have brain metastasis, they should be treated with some combination of immune checkpoint blockade, be that PD-1 alone, if it's a PD-L1-high tumor, PD-1 plus chemo, or combination immune checkpoints, CTLA4, PD-1 plus or minus chemo, depending on the scenario.

Are there particular scenarios where you choose between, for example, in this case patients who are asymptomatic, treating them with immunotherapy, as opposed to doing radiation first or immunotherapy first? What's your decision-making process there?

Dr. Naidoo:
So I suppose I factor in the symptoms. So in this case, the patient was asymptomatic. There was no edema associated with these metastases, and, her PD-L1 score was high, so I opted for the immunotherapy first, really because she was asymptomatic, and to try to avoid corticosteroids. So I was able to do that in this instance. I think it becomes a little bit trickier if there is edema or if the patient is symptomatic and we feel that they might benefit from radiation and then the tapering of the steroids.

So how do you do that in the context of giving immunotherapy? Do you usually taper and then only start your immunotherapy after the steroids are at a lower dose? I know there's different comfort levels in relation to that.

Dr. Forde:
Yeah, I think so like yourself, I prefer to avoid steroids around the time of commencement of immunotherapy where possible. You know, however, sometimes it's unavoidable. I don't have a strong feeling if the patient has to be treated with steroids, if, for example, they need upfront radiation. I will commence the immunotherapy while still on steroids for that indication. I think if it's a different scenario, if we're treating someone for an ultra-immune event due to immunotherapy, in general, in that case, you want to have the patient tapered off or very close to tapered off steroids before we commence immunotherapy.

In this scenario, we're essentially treating or preventing edema, so I don't have so many concerns there about starting steroids apart from the concern about perhaps reducing the efficacy of the immunotherapy.

And I think so another scenario where we're seeing probably increased use in lung cancer is use of stereotactic radiation in place of whole-brain radiation. And I think in many cases, in those scenarios, the duration of steroids can be somewhat shorter, and our concern about impactful edema causing significant problems is probably a little bit less than where the patient has had whole-brain radiation.

Dr. Naidoo:
Yeah, no, I think those are excellent points, how do you see the landscape changing for patients with brain mets? Are there any particular combinations or agents you think are ones to watch in the context of brain metastases?

Dr. Forde:
Yeah, I think there are scenarios expanding. Now, we obviously have three main classes of treatment for lung cancer - chemotherapy, immunotherapy, and targeted therapy. And so historically, over the past 5 to 10 years, targeted therapy and immunotherapy have been quite separate in many of the molecular subgroups we've used targeted therapy for, they're not particularly sensitive to new therapy. However, that may be changing, I think. I think with the advent of KRAS inhibitors, in particular we saw some very nice data from ASCO this year on combination KRAS G12C inhibitor with pembrolizumab. And I'd be interested to see the CNS activity of that regimen in particular. So I think potentially, as the management of subgroups like KRAS expands, perhaps even to the first-line setting, eventually, with targeted therapies, you could envisage scenarios where combination small molecule plus immunotherapy, in those scenarios could be very effective in the brain.

Dr. Naidoo:
Yeah, great thoughts there and definitely an area of focus. Okay, with that, our time is up. I hope you found the information presented in this episode helpful in your practice. And thank you for listening.

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