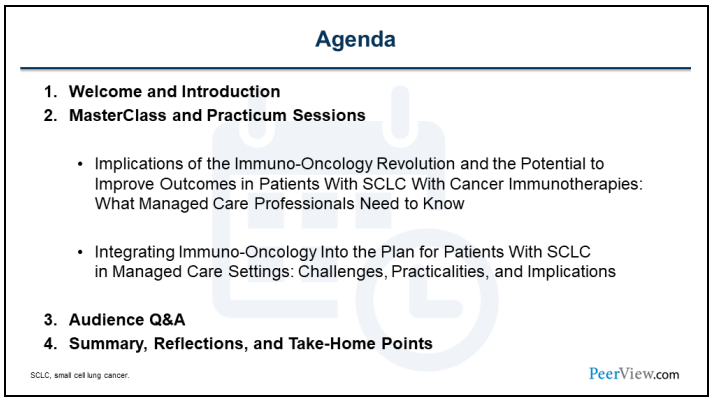
Implications of the Immuno-Oncology Revolution and the Potential to Improve Outcomes in Patients With SCLC With Cancer Immunotherapies: *What Managed Care Professionals Need to Know*

Slide 1



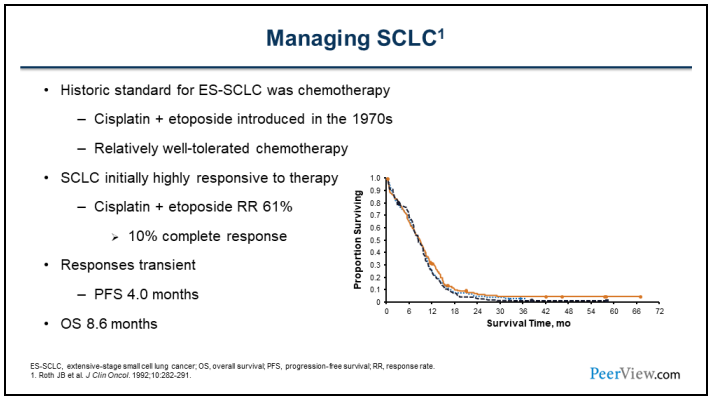
Dr. Shah: Thank you for joining us. It's a really exciting time in small cell lung cancer; we have a significant amount of innovation for immunotherapy in the treatment arsenal for small cell lung cancer. This discussion is on the implications for patients, providers, pharmacies, and, of course, in the managed care setting for our faculty.

Today's faculty is Dr. Stephen Liu from Lombardi Comprehensive Cancer Center at Georgetown University, and then me, Bhavesh Shah. I'm from Boston Medical Center.

In regards to the agenda today, we have several topics. Dr. Liu will focus on how we have transitioned from chemotherapy and radiation to innovative therapies such as immunotherapy—really shifting the treatment paradigm for small cell lung cancer.

Then my goal is to talk about the implications from a health system, provider, patient, and managed care setting perspective. I'll be taking on the second part of the lecture, and then we have summary, reflections, and take-home points. With that being said, Dr. Liu can begin the first part of the presentation.

Slide 2



Dr. Liu: Thanks, Bhavesh, and thanks for joining us today. Small cell lung cancer is not a rare disease, but it is an uncommon subtype of lung cancer, accounting for about 13% of new lung cancer diagnoses. This is a cancer that spreads very quickly, and there is very little role for surgery in the treatment of small cell lung cancer. Most patients unfortunately are metastatic or in extensive stage at the time of diagnosis; even those picked up at an earlier stage are very likely to recur and spread to distant organs.

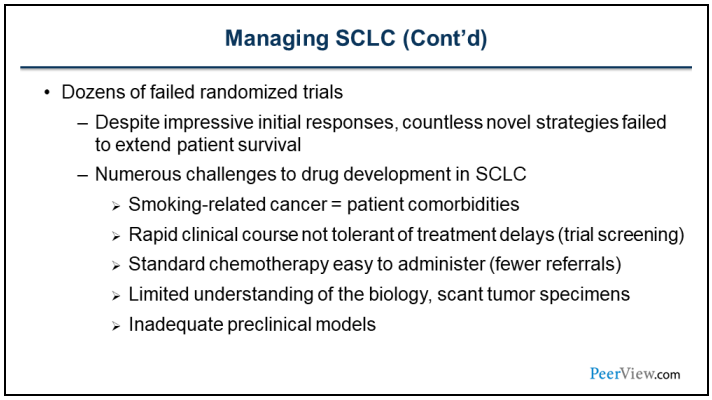
The treatment for this, the backbone of therapy, is chemotherapy. It's not particularly new chemotherapy. We use platinum/etoposide that was first introduced for small cell lung cancer in the 1970s. It's a relatively well-tolerated chemotherapy. I think at first blush, it seems like a good treatment. The response rates are high, about 60%. They're relatively rapid, and about 10% of patients will have a complete response.

But in reality, this is not a very good treatment for cancer. The relapse rates are just as high. The responses that you see, even complete responses, are transient, with a progression-free survival (PFS) of about 4 months. Remember, that's measured from the time you start treatment, so most patients will progress either during chemotherapy or shortly after chemotherapy.

If you look at the Kaplan–Meier curves in Slide 2 from the original platinum/etoposide studies, you can see the vast majority of patients are not surviving even to a year.

This is a standard treatment for small cell lung cancer, and despite these poor outcomes, this has been our standard since the 1970s, 1980s. We have not been able to improve on a platinum/etoposide backbone.

Slide 3



It's not for lack of trying. There have been dozens of randomized phase 3 trials that have simply failed to improve survival. For a compound to get to the phase 3 setting, it needs to show tremendous progress, with a lot of investment. We have gone all the way to the finish line for many of these studies and simply not improved outcomes.

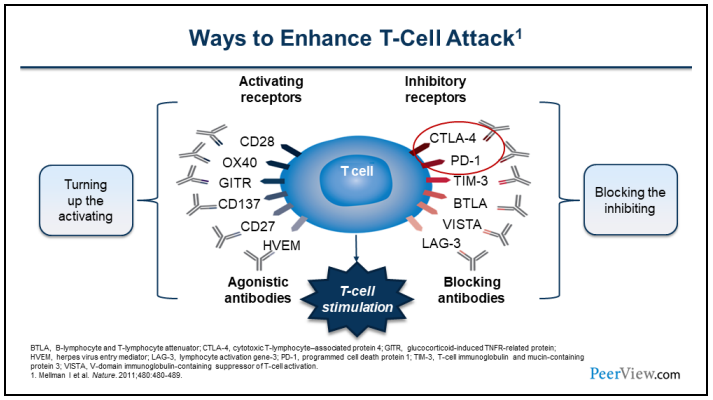
There are a lot of challenges to drug development for small cell lung cancer. This is a smoking-related cancer, and so patients often have smoking-related comorbidities and may be too ill for certain types of therapy.

It is a relatively rapid course, with patients typically noting symptoms only for a few months before diagnosis. This is a cancer that moves quickly, and so screening is very difficult to do.

Standard chemotherapy is fairly easy to administer, and so centers with specific specialties and research in this area, such as our two centers, may not get referrals because the chemotherapy may be started at an outside hospital or at a smaller practice. Frankly, there's a limited understanding of the biology for small cell lung cancer, in part due to the scant tumor specimens available for study.

In addition, the preclinical models on which we base a lot of our therapies simply are flawed and may not reflect human biology as much as we'd like. This is particularly true for small cell lung cancer. It's really hindered progress.

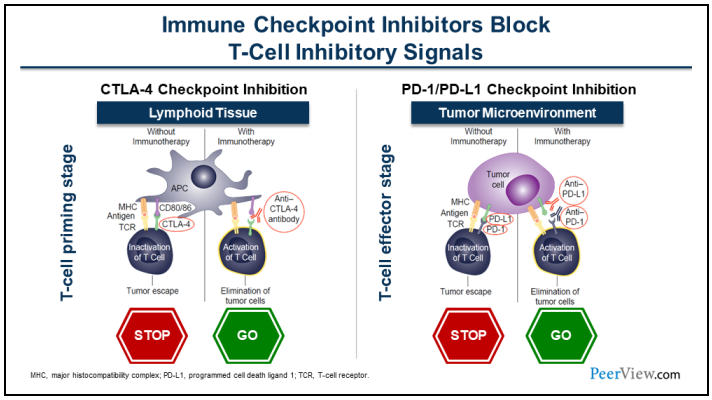
Slide 4



Where we finally saw advances was in the development of immunotherapy. Going in, there was a lot of rationale as to why immunotherapy could work. The early signal was that immunotherapy seemed to be more effective for carcinogen-related cancers, and small cell lung cancer is very closely related to smoking.

In addition, we know that small cell lung cancer has a high rate of somatic mutations, and a high mutational burden or mutational load also seemed to correlate to response to immunotherapy. Going in, we thought we were going to see response. We thought this was going to be an active drug class for small cell lung cancer.

Slide 5



Now that we've got some decades behind us, we can say that there is some activity, but I think it's somewhat modest. The two classes in which we've seen the most activity in solid tumors have been targeting the programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) pathways, with antibodies targeting either ligand or receptor, and the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) pathway.

Dr. Shah: Stephen, I had a question. We are in interesting times. Coronavirus disease 2019 (COVID-19) has definitely changed the way we practice things, and if you've attended a conference recently, it's been pretty much all virtual.

I came across this interesting paper from the COVID Cancer Consortium that was presented at the American Association for Cancer Research Annual Meeting 2020 (AACR 2020) that talked about higher mortality for patients who had cancer and had malignancy, and of course, especially higher for patients who had lung cancer.

I wanted to know, from your perspective, if you've actually seen that in your practice, or if you have any guidance for providers who have seen this data—basically, patients having COVID, on a PD-1/PD-L1 or CTLA-4 checkpoint inhibitor, and having lung cancer. Are those patients at increased risk of higher mortality versus patients who are not on that therapy?

Dr. Liu: The mortality risk that we've seen in lung cancer has been higher than with other cancers, and it has been consistent. In both of the consortium papers that you mentioned—the international TERAVOLT study, reports from Memorial Hospital when New York was really hit hard—the numbers have been high, but they've been consistent. Patients with lung cancer do seem to be at greater risk.

Because this is something we're living through now, we're constantly asking ourselves if there are ways that we can modify our practice to better protect our patients—maybe not from infection, but from complications related to that infection.

Certainly, reducing the risk of an infection is something that we've both done, and I know Boston was really hit hard at times. We're keeping patients out of the hospital and out of waiting rooms, and maintaining distance strategies within our cancer center to be sure that patients who may be carriers or may be infected are not spreading that infection to other patients, caregivers, faculty, and staff, as well.

In addition to reducing the risk of exposure, we wanted to ask ourselves, were there ways that we can modify our treatment strategies? When we saw complications related to COVID—and you and I have both seen these patients—it seems like an overwhelming immune response, right? It seems like a cytokine release syndrome in which patients get quite ill. There was initially some concern and some preclinical rationale as to why immunotherapy could exaggerate that, could make that worse. That was certainly a concern here.

Data have shown differently, but initially, we were worried. I'm not sure if you had the same concerns. Your area was hit among the highest in the country. Did you have similar concerns about the use of immunotherapy?

Dr. Shah: That's a great question, Stephen. We were definitely concerned, and we were looking for guidance. The European Society of Medical Oncology (ESMO) had put together guidance. The National Comprehensive Cancer Network (NCCN) had put together guidance. We were really in the initial stages.

The other thing I would say is that I think the COVID that we were treating before was much different than the COVID we're treating now, when we have more treatments that are approved for COVID, and we know how to manage COVID better.

There are probably differences in management that's also leading to some of the mortality that we had seen in lung cancer and other malignancies. We definitely need more fresh data about COVID and malignancy to really make decisions on how to manage patients appropriately.

We have a clinical trial with etoposide in our institution, which is an investigator-initiated study specifically in patients with COVID when we know that there is a cytokine release syndrome and this acute respiratory distress syndrome

(ARDS) that happens in severe COVID patients.

What we identified in our autopsy series is that basically this was a hemophagocytic lymphohistiocytosis (HLH) type of picture. It was confirmed from these SARS-CoV-2 autopsies that we did. We initiated this study, and it'll be interesting to see the results. But obviously, it's too early to say anything.

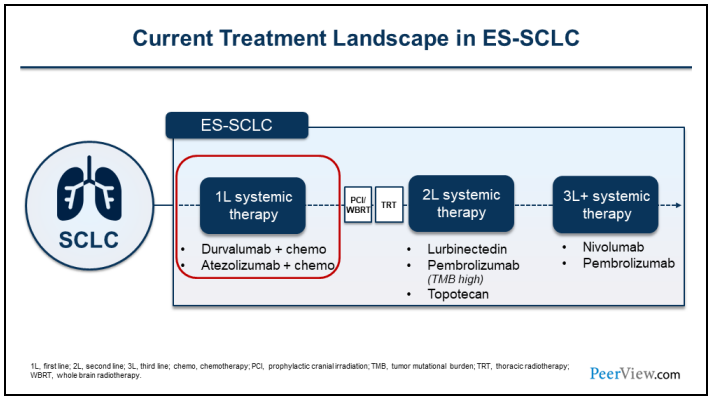
Dr. Liu: What we've seen so far from these data—and you're right, these data need to be looked at in a special way—is that targeted therapy did not seem to confer greater risk of mortality with COVID infections. Fortunately for us, out of the most recent data set from Memorial, the use of immunotherapy, either immediately before infection or up to a year before, didn't really seem to predict mortality either. Based on those data, we do feel it's safe to use those modalities in the setting of the pandemic.

There was some increased risk in some of the registries, like the TERAVOLT study, with recent use of cytotoxic chemotherapy. But again, the early mortality numbers may not be totally reflective of the current state of things, especially in the United States, and so those data will continue to emerge.

Our general strategy in lung cancer has been to not compromise care. If patients need a specific therapy for their cancer that is far and away better than another treatment, we should use that to not trade the potential risk of COVID complications for the very real and current risk of their cancer.

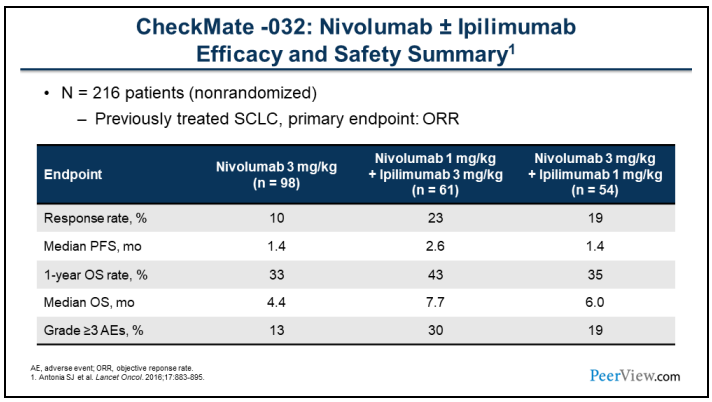
When we look at immunotherapy in lung cancer, again, the main pathways we're engaging are PD-1/PD-L1 and CTLA-4, which is slightly different but along comparable pathways, with both having an effect on T-cell inhibitory signals. CTLA-4 is a bit more on the priming stage in lymphoid tissue; the PD-1/PD-L1 interaction is more in the tumor microenvironment targeting the T-cell effectors. But these have really changed oncology in general and small cell lung cancer.

Slide 6



Our current landscape in small cell lung cancer for the first time in many decades looks different, where we're implementing immunotherapy in the first-line setting. In the second-line setting, we have some immunotherapy options in the use of lurbinectedin, which was recently approved. In the third-line setting, we also have immunotherapy drugs approved. Let’s go through how immunotherapy has been working in small cell lung cancer in its relatively short journey.

Slide 7



CheckMate -032: Nivolumab ± Ipilimumab Efficacy and Safety Summary[1]

- N = 216 patients (nonrandomized)
  - Previously treated SCLC, primary endpoint: ORR

Endpoint	Nivolumab 3 mg/kg (n = 98)	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n = 61)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 54)
Response rate, %	10	23	19
Median PFS, mo	1.4	2.6	1.4
1-year OS rate, %	33	43	35
Median OS, mo	4.4	7.7	6.0
Grade ≥3 AEs, %	13	30	19

AE, adverse event; ORR, objective reponse rate.
1. Antonia SJ et al. *Lancer Oncol*. 2016;17:883-895.

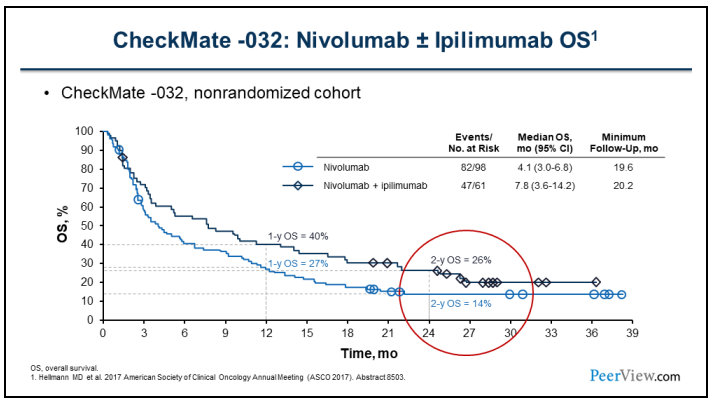
PeerView.com

Our first large experience with immunotherapy in small cell lung cancer was the CheckMate -032 study. This was a nonrandomized trial for patients with previously treated small cell lung cancer, in many cases, very heavily pretreated.

These were very select patients, and they received nivolumab alone or nivolumab with ipilimumab at various doses and schedules. Somewhere around 10% to 20% of patients responded. The progression-free survivals were modest, but the survival rates were impressive.

The median PFS in this study for nivolumab alone, for example, was 1.4 months. That's not very impressive. It's really the first scan; but the 1-year survival rate of 33% tells us that some patients are getting substantial benefit from these agents.

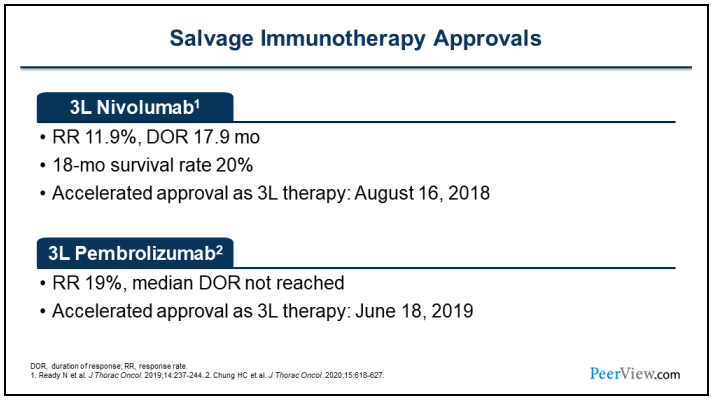
Slide 8



It's important to point out that this was a nonrandomized trial, and it's not valid to compare nivolumab versus nivolumab and ipilimumab. What we draw from this study is that some patients receiving these checkpoint inhibitors are still alive 1 and 2 years later, which is really not something we'd expect with standard cytotoxic therapy.

If we look at the 2-year survival rate in Slide 8, for example, between 14% and 26% of heavily pretreated small cell lung cancer patients were still alive at 2 years. I wish that number were 80% or 90%, but really, with standard therapy, that number would be much closer to 0.

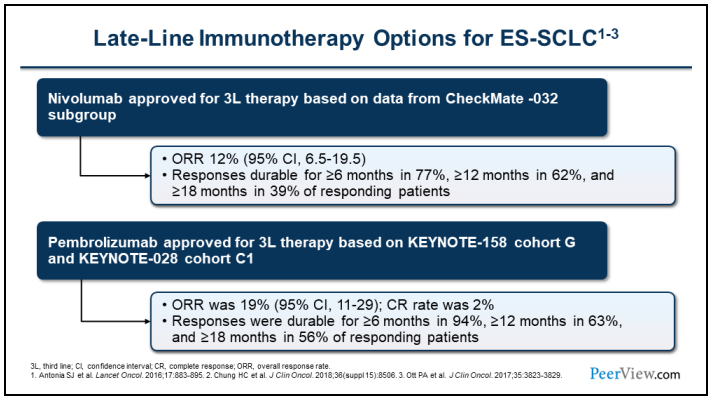
Slide 9



These data directly led to the approval of both nivolumab and pembrolizumab monotherapy in the third-line setting. Nivolumab was approved based on CheckMate -032, with a response rate of 12%. Not everyone responds; a minority of patients respond, but those who do respond do quite well. These responses are fairly durable, with about 40% of the responses still ongoing at 18 months.

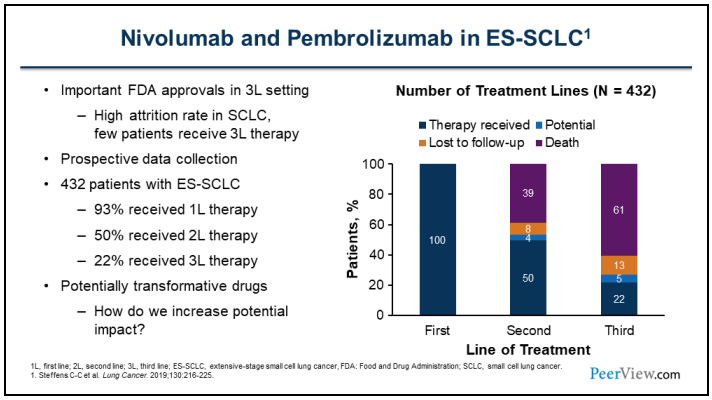
Pembrolizumab is also approved in the third-line setting. It has a modest response rate—19%—but the responses are durable. It's not that everyone responds. Most people don't. But those who do respond can do quite well, and in the third-line setting, we really had no significant options.

Slide 10



These were important approvals. We had nothing available in the third-line setting, so to have any drugs approved as a third line for small cell lung cancer was really filling an unmet need. There's a subset of patients who get tremendous benefit. In fact, these are potentially transformative drugs. But in the third-line setting, unfortunately, there's quite a bit of attrition for small cell lung cancer.

Slide 11

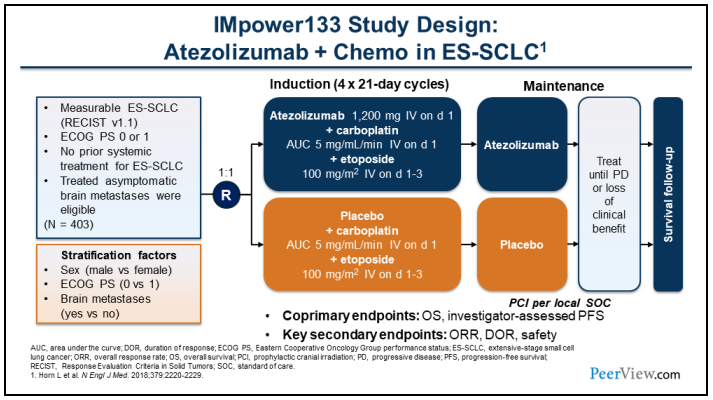


Slide 11 displays some data out of Germany looking at patients with small cell lung cancer who received therapy. Of all those who received treatment, only about 1 in 5 get any third-line therapy. Are these attrition numbers in line with what you're seeing at your center?

Dr. Shah: I think somewhat. I think for the first line definitely, but I think the second and third lines actually were probably much lower than what the literature shows. It really speaks to the healthcare disparities that we see in our patient population that we serve. We'll talk about that a little bit later in my side of the lecture.

Dr. Liu: I agree that this is sort of a best-case scenario. But this is a cancer that moves fast, and generally, most patients are only going to get one shot at treatment. Yet, when we look at immunotherapy, when we think of the tail of that curve from Slide 8, you've got some people who are alive 2 years later for heavily pretreated small cell lung cancer. These are potentially transformative agents, and yet it would be a shame to deprive that patient who would get that long-term benefit and live for many years of the opportunity to get these agents. If you reserve them for third-line use, most patients won't get the opportunity.

Slide 12



How do we increase the effect of immunotherapy? We try to move it up. The trials that have changed the paradigm for small cell lung cancer have been the first-line studies. The first trial to release reports in September 2018 was the IMpower133 trial.

This was a randomized, double-blind, phase 3 placebo-controlled trial for patients with untreated extensive-stage small cell lung cancer. It included patients with brain metastases if they were treated, and a good performance status of 0 to 1.

All patients here received standard carboplatin to achieve an area under the curve (AUC) of 5 mg/mL/min on day 1, and etoposide 100 mg/m^2 days 1 through 3 for 4 cycles, and a 1:1 randomization of concurrent atezolizumab at a flat dose of 1,200 mg or placebo given on day 1. After the completion of 4 cycles of therapy, patients would then continue atezolizumab or placebo until progression or loss of benefit. The primary endpoints here were overall survival (OS) and PFS.

Dr. Shah: I have a lot of questions here, Stephen. You were involved in the trial design, so why was cisplatin not allowed in this clinical trial? And we could talk about this a little bit later, but how was supportive care in terms of growth factor support allowed in the clinical trial?

One last question. The patients who were included had asymptomatic brain metastasis or were they treated brain metastases?

Dr. Liu: Only treated brain metastases.

Dr. Shah: Okay. My question always is, was there a difference between patients who received immunotherapy and had brain metastases versus patients who didn't receive immunotherapy? It would be interesting if you had seen any differences there.

Dr. Liu: Sure. Lots of great questions. Let me take the platinum first. We know in our practice that we consider cisplatin and carboplatin fairly equivalent in terms of efficacy. There was an impression early on by many, myself included, that cisplatin probably had higher response rates, but maybe no difference in survival.

But we now know from large single-patient meta-analyses, like the COCIS meta-analysis, that not only is there no difference in OS or PFS, there is no difference in response rate. This is a very sensitive drug to chemotherapy, but response is not the endpoint we're looking for. Response rate, PFS. We've had many drugs that have improved response rate and that have improved PFS that just never translated into a survival benefit.

When we look at the history of small cell lung cancer in trials, this is really where drugs went to fail, where at every American Society of Clinical Oncology (ASCO) meeting, we would see a failed phase 3, a negative trial. As we were designing this trial, one thing that we noticed when we looked at these studies is that often there were subsets of patients in whom there were stronger signals.

What we wanted to try to do with this trial—really trying to get the first positive trial in 40 years—was have a trial with a very homogeneous patient population, so we wanted to eliminate as many variables as we could—control for everything and have the only variable be the immunotherapy. That will really tell us, is this drug working or not?

There are many other questions that we can ask, but first we needed a win. First we needed to show that there truly was an effect. Then we could further refine it and adapt it based on our clinical practice.

When we look at cisplatin or carboplatin, practice patterns in the United States, and really in the world, tell us most are using carboplatin. We didn't want to have to stratify for choice of platinum, and we didn't want differences in the outcomes to be reflective of platinum choice, so we made a choice, and majority rules here. We went with carboplatin.

If we had allowed cisplatin, a small concern that we potentially had—it turns out this is probably not true, but let's say we gave cisplatin and then cycled to someone who had nephritis, an elevation in creatinine. We may attribute that to cisplatin, which we know is more nephrotoxic, but you wouldn't be able to say for sure that it wasn't due to an immune-mediated nephritis.

Based on that, you would have to hold treatment, whether it's atezolizumab or placebo. What if that was one of those patients who was really going to make the difference, who was really going to show that response? We wouldn't want to withhold that, because it would only take a few patients to turn a positive trial to a negative trial. To make it clean, we kept carboplatin.

In practice, would I feel comfortable substituting cisplatin? I really don't see any difference there. But the study was carboplatin alone and did not allow the choice. Based on that, some institutions chose not to participate, but we wanted to keep a very clean study.

Same with brain metastases. We know in practice that if someone has asymptomatic brain metastases, we won't pause for radiation. This is a disease that won't wait. We'll start with chemotherapy, often get a response in the brain, and do radiation later.

Asymptomatic brain metastases—should we have included them? We wanted to, because that would reflect our practice. But again, that's more heterogeneity, and what I would consider an asymptomatic brain metastasis, or what you may consider, might be different from someone in another country, maybe someone who doesn't have access to magnetic resonance imaging (MRI) is using computed tomography (CT) to screen things. Keeping in mind this is a phase 3 global trial, we wanted to account for some differences in practice and take out any variables as low risk as we could.

It meant that it would take longer to accrue, but we would rather do that than risk it with different variables, so only treated brain metastases, only carboplatin, and only 4 cycles. No options for 4 to 6. Again, we were trying to keep it clean, no variables.

The question is an interesting one. Do patients with brain metastases fare differently? I suspect that they would have, but this study did stratify for presence of brain metastases, so they were evenly distributed. We didn't really see any differences in patients who did or didn’t have brain metastases in the study.

It was a minority of patients though. That's not truly reflective of our own practice, in part because when I had the study open, if I had someone with many asymptomatic brain metastases, for that person to qualify for this trial, I would

have to do radiation and then begin treatment. Often I don't accept that type of delay.

If I had seen that patient in my practice during that time, I wouldn't enroll them on the trial. I would simply treat them with standard-of-care chemotherapy at the time because I thought the wait would be detrimental to their health, a little too risky. That's reflected in the patient population, in whom the incidence of brain metastases in this study was actually quite low.

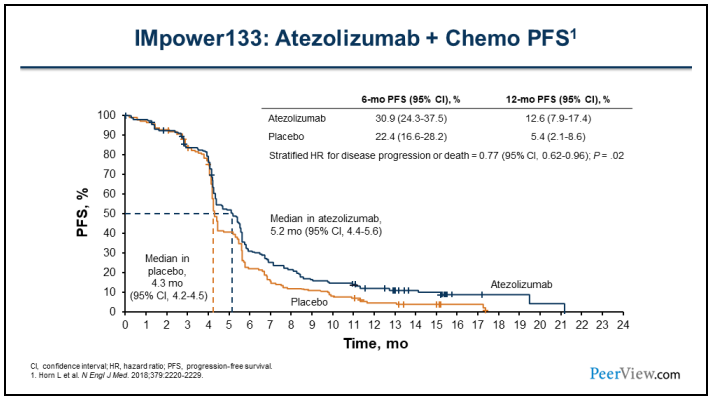
Dr. Shah: One of the interesting things that I had noticed was even though you would anticipate that carboplatin would have more neutropenia versus cisplatin, when we look at the grade 3/4 neutropenia versus the CASPIAN trial, there was actually no difference. It's an interesting perspective.

Dr. Liu: Yeah, it really is. When we look at historic rates of febrile neutropenia, they were lower in this study than we would have predicted from previous trials, and that may have to do with better overall care.

To answer your question about the use of growth factor, it was not permitted with cycle 1 of this study. Secondary prophylaxis was permitted, but not primary. Part of it is because we're moving quickly with this. We didn't have safety data for this combination before the trial started, so this is one of the few studies that is actually a phase 1/3 trial, to gather some safety data on the first patients before we finished accrual. We needed to capture those rates, and you're right, while neutropenia was common, febrile neutropenia was quite rare.

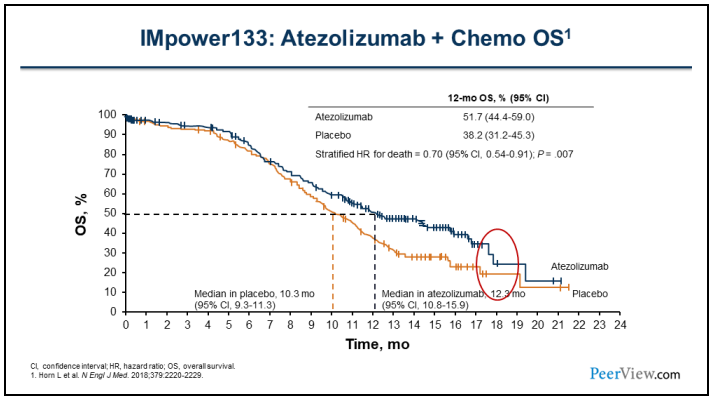
In this study looking at the effect of adding atezolizumab, a PD-L1 antibody, to chemotherapy, the primary endpoints here were PFS and OS.

Slide 13



This was a positive trial—the first in over 4 decades—meeting both of its primary endpoints, showing an improvement in PFS, with a hazard ratio of 0.77.

Slide 14

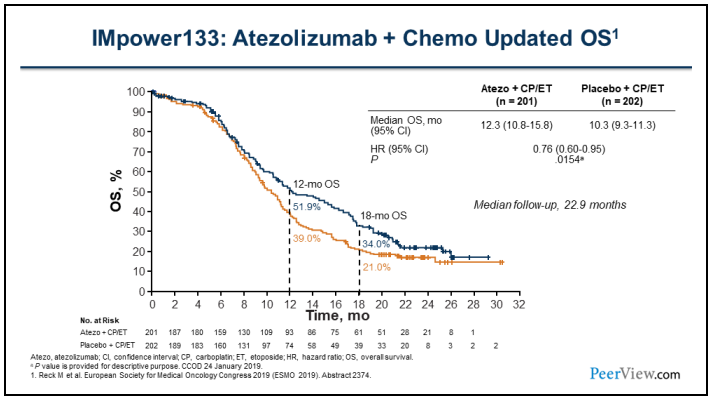


Importantly, there was an improvement in OS. The median was improved from 10.3 months to 12.3 months, the 1-year survival rate from 38% to 52%, and a hazard ratio for death of 0.70, or a 30% reduction in the risk of death.

When we see these survival curves, I appreciate that I'm not showing you a hazard ratio of 0.1, that I'm not showing you a 90% 2-year survival. But remember the context—this is a disease that we've had no advances in since the 1970s and one in which we have tried and tried again to improve survival and have consistently failed. To have any effect on survival really is a victory, and there's a clear improvement here.

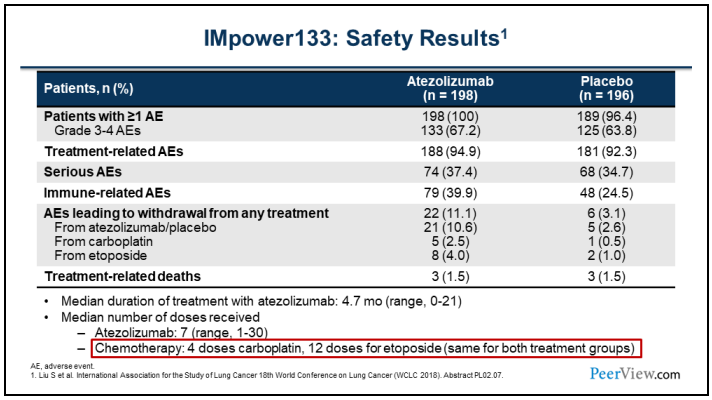
When we look at these survival curves, many were quick to point out that toward around 18 months, they seemed to come together. This graph in Slide 14 from the original publication had a median follow-up of only about 13 to 14 months.

Slide 15



With more follow-up, as was presented at the ESMO Congress in 2019, we saw that at 18 months there's a clear separation. In fact, the difference between the atezolizumab and placebo arms in terms of survival at 18 months really is the same as at 12 months, so we see a consistent benefit over time. We'll continue to follow these patients to really look at the long-term effect.

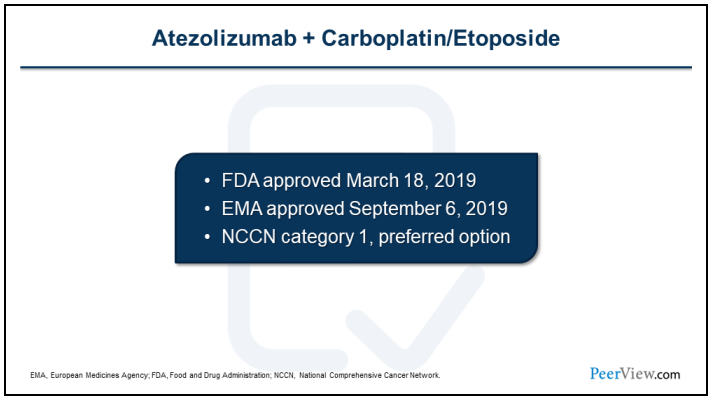
Slide 16



Importantly, the addition of atezolizumab improved PFS and improved OS, but didn't significantly worsen toxicity. While the rates of grade 3 or 4 adverse events were quite high, they were similar between the two arms and were primarily chemotherapy toxicities. As you mentioned, Bhavesh, neutropenia, leukopenia, and even thrombocytopenia are often paper toxicities that don't have a lot of clinical effect—things that we expect with chemotherapy that we have gotten used to managing in treating lung cancer, and are often things that resolve on their own.

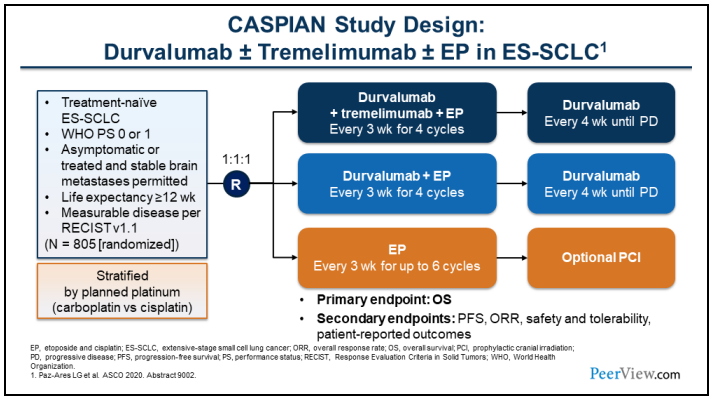
The febrile neutropenia rate was quite low, and the surrogate, for tolerance of atezolizumab, we look at delivery of chemotherapy. Patients receive a median of 4 doses of carboplatin and 12 doses of etoposide or four full cycles, which tells us that the addition of atezolizumab improves outcomes without sacrificing our ability to deliver 4 full cycles of chemotherapy.

Slide 17



Based on the survival rates, the efficacy, and the favorable safety profile, atezolizumab was approved as part of first-line treatment for extensive-stage small cell lung cancer in March 2019. It has since been approved by the European Medicines Agency (EMA) and several other regulatory authorities across the world and remains an NCCN category 1, preferred option.

Slide 18



We waited over 40 years to see some improvement in the frontline setting for survival. We waited less than a year for the second improvement, which was the CASPIAN study. There is a slightly different design here. This trial was an open-label, three-arm study looking at standard chemotherapy. Here, investigators had the choice of cisplatin or carboplatin, had the choice of 4 to 6 cycles, and had the option for prophylactic cranial irradiation.

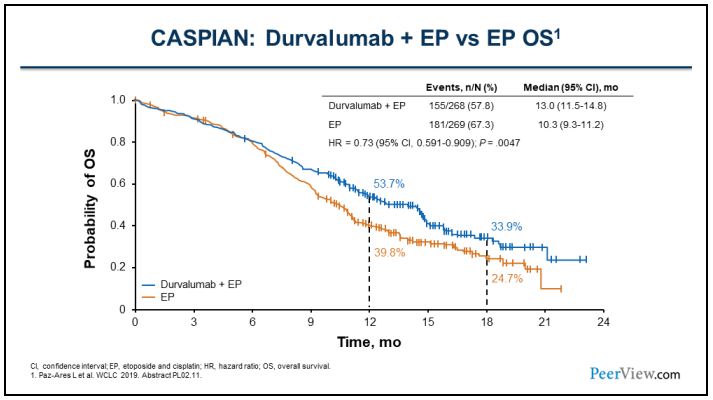
There was 1:1:1 randomization of standard chemotherapy. The first experimental arm was the addition of the PD-L1 antibody durvalumab to chemotherapy. Again, it was investigator's choice of platinum, but in this arm, it was limited to 4 cycles, and no prophylactic cranial irradiation (PCI) was permitted. The final randomization was to a combination of durvalumab with tremelimumab—an anti-CTLA-4 antibody—also with chemotherapy for only 4 cycles, and no PCI was permitted.

In both of the experimental arms, the maintenance treatment was durvalumab—so tremelimumab was not given as maintenance—and that was given every month, whereas in the chemotherapy arm, it was observation alone, and the primary endpoint here was OS. There were some slight differences in study design here.

Dr. Shah: The slight differences are that they're allowing cisplatin and in regards to the brain metastases, correct?

Dr. Liu: Correct. There are some slight differences here, as you mentioned. You had a choice of cisplatin or carboplatin. In the control arm, you could go up to 6 cycles. The use of PCI in these different arms was a little different, and asymptomatic untreated brain metastases were permitted in this study, which is different from the IMpower133 trial. When I look at the study design overall, there are more variables here, which we were worried would cloud interpretation of the study.

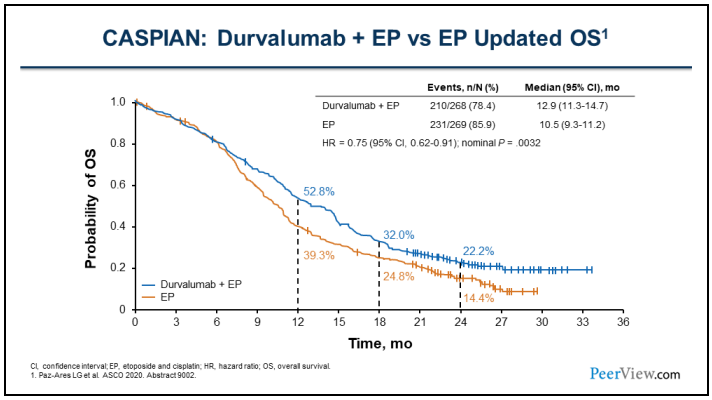
Slide 19



But when we saw the results, we were quite assured this was a positive trial that improved survival and looked strikingly similar to what we saw with atezolizumab. In Slide 19, we see the Kaplan–Meier curves for the addition of durvalumab to chemotherapy. We see an improvement in survival. There is a hazard ratio here of 0.73, and improvement in the 1-year survival rate from 39.8% to 53.7%.

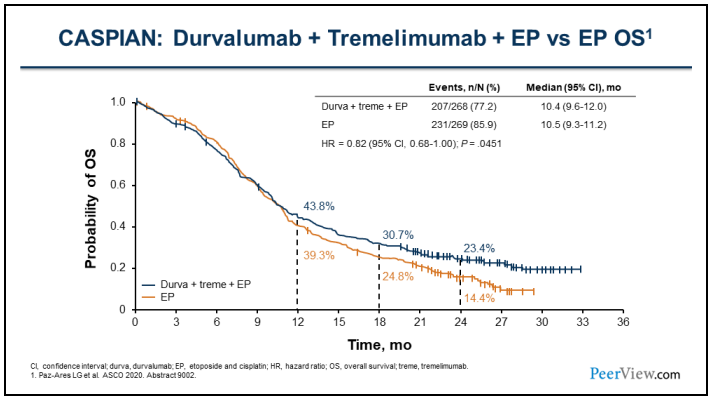
The addition of durvalumab improved survival, and despite all of these small differences in study design, these survival curves almost overlap with atezolizumab. In my mind, these two studies really reinforce each other, showing that when you add a PD-L1 antibody to platinum/etoposide, you see a modest but significant improvement in survival.

Slide 20



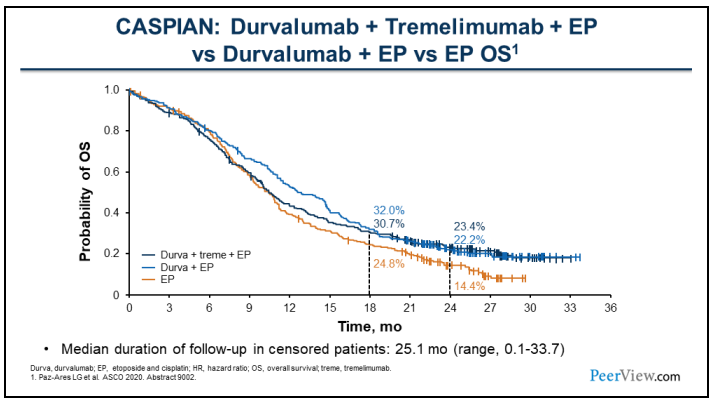
With more follow-up, that OS benefit has persisted. Slide 20 displays more recent data from ASCO 2020, showing a hazard ratio here of 0.75, and a separation of those curves is maintained at 12, 18, and 24 months.

Slide 21



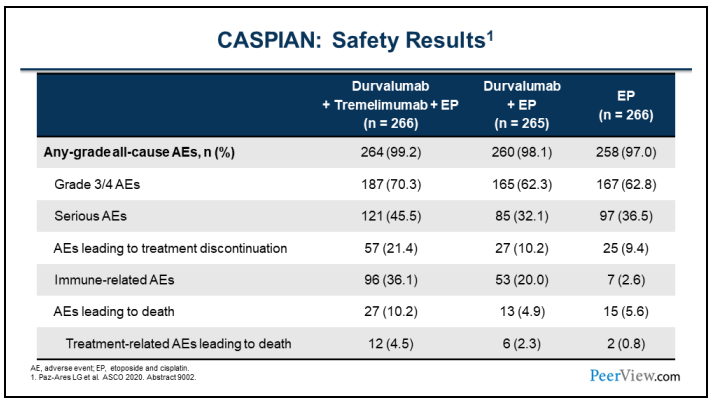
This study did have a third arm looking at durvalumab with tremelimumab during induction followed by durvalumab maintenance. As we learned at ASCO 2020, that arm was not positive. The addition of durvalumab plus tremelimumab did not improve survival compared with chemotherapy alone. The hazard ratio here is 0.82, with a nonsignificant *P* value. Although the curves do separate as they go further out, they largely overlap.

Slide 22



If we look at these three curves together in Slide 22, you see durvalumab in dark blue, which is clearly superior to chemotherapy in orange, whereas the durvalumab-plus-tremelimumab arm really falls behind in the beginning and only catches up to durvalumab after about 18 months.

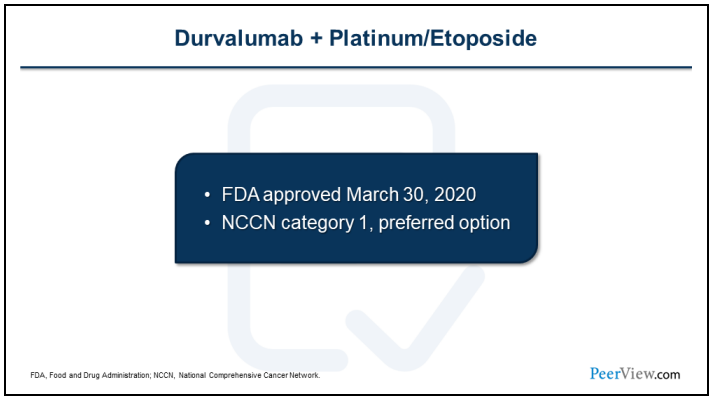
Slide 23



We both know the addition of CTLA-4 inhibitors in this population adds toxicity. If you look at serious adverse events with durvalumab/tremelimumab, it's about 45.5% compared with only 32% with durvalumab, which was comparable with chemotherapy alone.

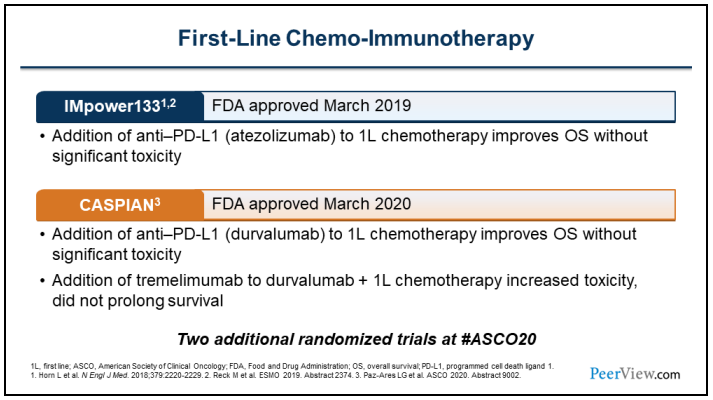
For adverse events leading to discontinuation of treatment, durvalumab/chemotherapy numbers were pretty similar to chemotherapy alone, but you double that when you add durvalumab/tremelimumab. Twenty percent, over 1 in 5, patients stopped therapy because of adverse events with durvalumab/tremelimumab. Clearly, it is a more toxic regimen, and that toxicity simply didn't pay off in terms of improving survival.

Slide 24



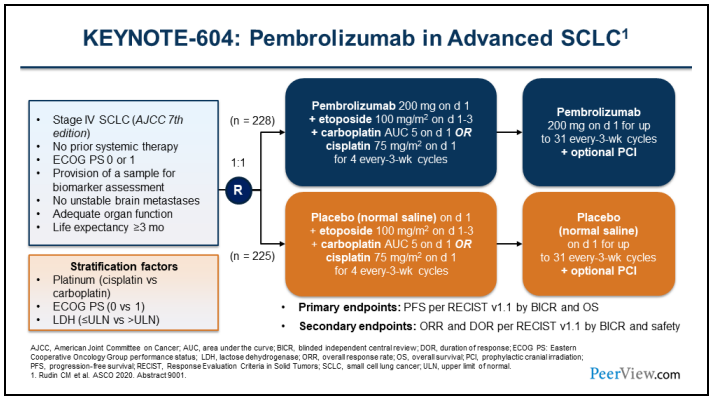
What we're left with after the results from CASPIAN is an approval for the addition of durvalumab to platinum/etoposide chemotherapy. That was approved in March 2020. Tremelimumab is not an approved agent in this setting. This is also an NCCN category 1, preferred option.

Slide 25



As of today, our standard of care has changed. For patients with extensive-stage small cell lung cancer, chemotherapy alone is no longer a preferred treatment. It is chemotherapy—platinum/etoposide—with durvalumab or with atezolizumab. Both are Food and Drug Administration (FDA) approved, and both show a very comparable improvement in OS.

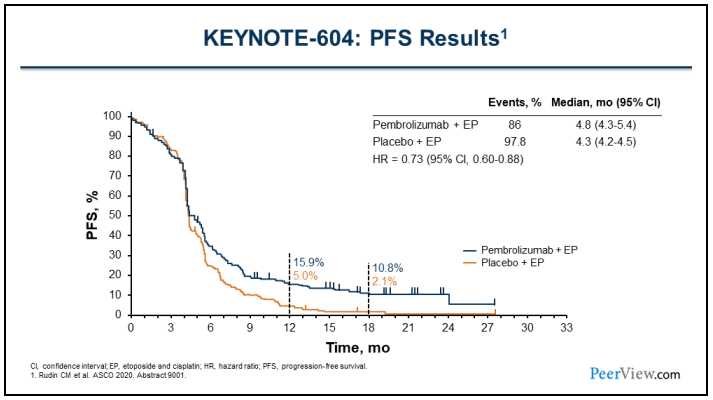
Slide 26



However, there were questions that were also asked. What about the other immunotherapy drugs that we use in lung cancer and in small cell lung cancer? We saw two other randomized trials at ASCO 2020 that were highly anticipated.

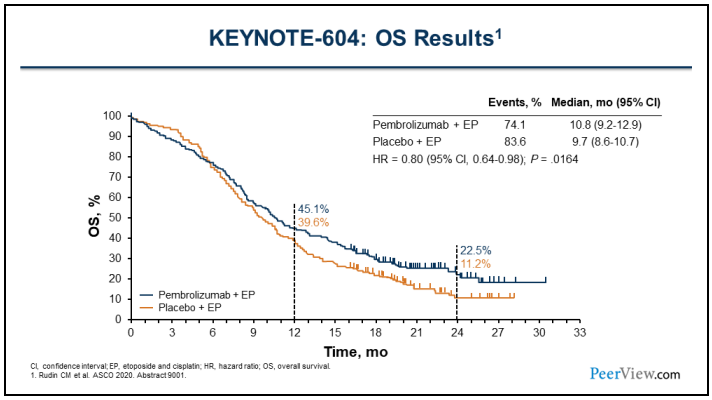
The first was KEYNOTE-604, which looked at pembrolizumab. Pembrolizumab is a drug that has taken market share in non–small cell lung cancer. It's a very active anti–PD-1 antibody. KEYNOTE-604 looked at the addition of pembrolizumab to chemotherapy in a very straightforward design. Patients received choice of platinum with etoposide and were randomized 1:1 to receive concurrent pembrolizumab followed by pembrolizumab or placebo maintenance. The dual primary endpoints were PFS and OS.

Slide 27



Charlie Rudin presented the data in Slide 27 at ASCO. What we saw was a modest improvement in PFS with a hazard ratio here of 0.73.

Slide 28



However, the study did not improve OS, which was somewhat of a surprise. Although the hazard ratio was 0.80, it did not cross the predetermined threshold for statistical significance. The KEYNOTE-604 study was negative for survival. Pembrolizumab improved PFS, but did not improve OS, which, to us, was a bit of a surprise.

Dr. Shah: I have a question here, Stephen. Based on these results, would that change your practice in using pembrolizumab for second-line therapy because of these first-line results?

Dr. Liu: That's a good question. I understand what you're saying. I want to be sure that the audience doesn't misinterpret. If someone had progressed on immunotherapy in the first-line setting, progressed on durvalumab or atezolizumab, I wouldn't use pembrolizumab in a second- or third-line setting. Again, that is second-line approval, only for microsatellite instability (MSI)–high. I wouldn't use immunotherapy after progressing on a PD-L1 inhibitor. To me, those are pretty lateral moves. I don't know if you agree with that.

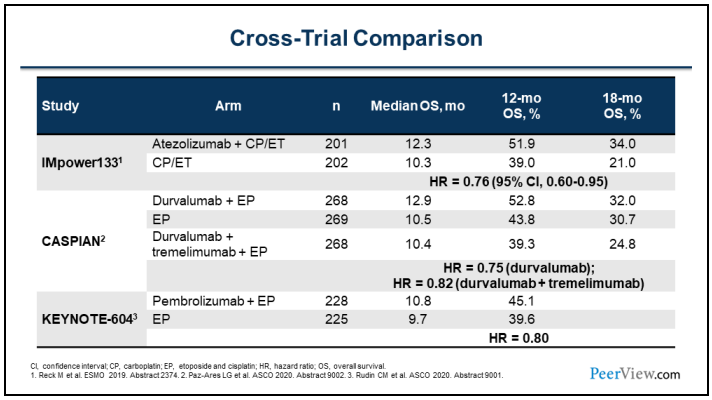
Dr. Shah: Absolutely.

Dr. Liu: But, if someone had not received immunotherapy as part of their frontline treatment, would I still consider pembrolizumab in the second- or third-line setting based on the negative KEYNOTE-604? I would. It is clearly an active drug. The study did not meet its survival endpoint, but there was a trend. The survival curves looked comparable, and the degree of benefit was comparable. I suspect this is more of a statistical, trial design failure than an actual failure of biologic activity.

When you add these checkpoint inhibitors, you see some modest activity. This study was negative, and in my mind, should not lead to approval and wouldn't change my standard of care. However, it's still an active drug.

In fact, if you showed me that a pembrolizumab combination outperformed pembrolizumab with chemotherapy, I would still accept pembrolizumab/chemotherapy as a control arm. I still think that's a reasonable comparison. I'm not using that. It doesn't change my standard of care. I certainly wouldn't explore off-label use when I have drugs that are approved in the phase 3 setting, but I think it's still an active drug, and I'm very comfortable using it in the second- or third-line setting for patients who hadn't previously received immunotherapy.

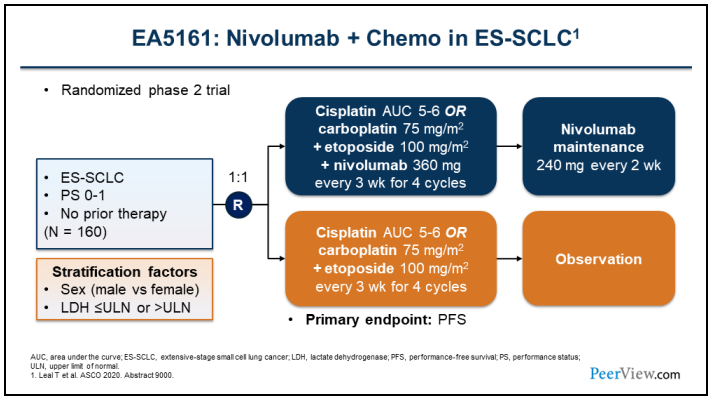
Slide 29



In fact, if you'll allow me to commit a faux pas here and show a cross-trial comparison—which is absolutely not statistically valid—what you'll see in Slide 29 is that the results are pretty comparable. The median survival numbers between the atezolizumab and the durvalumab and even the pembrolizumab arm were comparable. There is a comparable effect when we add a PD-1/PD-L1 inhibitor, and while the numbers are a little bit lower for KEYNOTE-604, I still think there's an effect there.

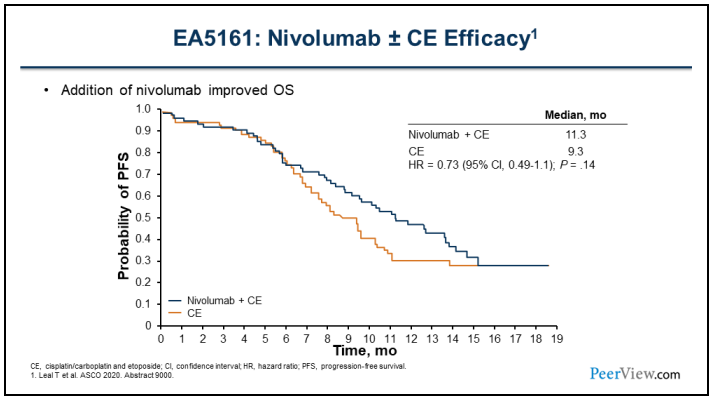
One question I get asked, is it really the difference in PD-1 or PD-L1? The two positive trials were durvalumab and atezolizumab, which are both PD-L1 inhibitors. The negative trial was pembrolizumab, which is a PD-1 inhibitor. Is it really something about targeting PD-L1? It is possible. The expression patterns are actually quite different in small cell versus non–small cell.

Slide 30



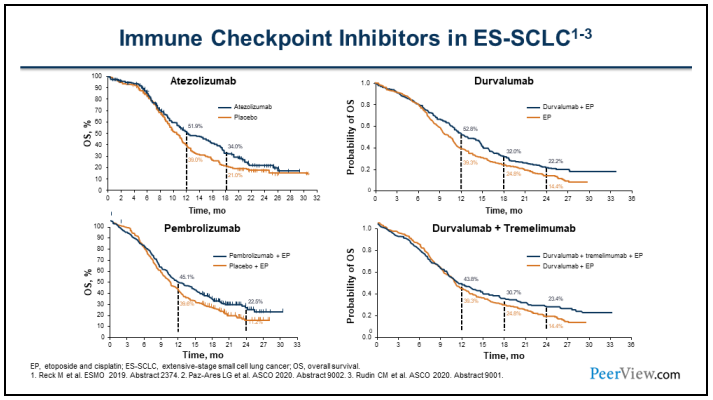
However, we also saw at ASCO 2020 a trial led by Dr. Ticiana Leal—the EA5161 study—that looked at nivolumab, which is another PD-1 inhibitor that is also approved for small cell lung cancer. This trial took patients receiving any platinum plus etoposide and randomized to receive nivolumab or not, followed by nivolumab maintenance or observation. This is an open-label randomized phase 2 trial showing a survival benefit.

Slide 31



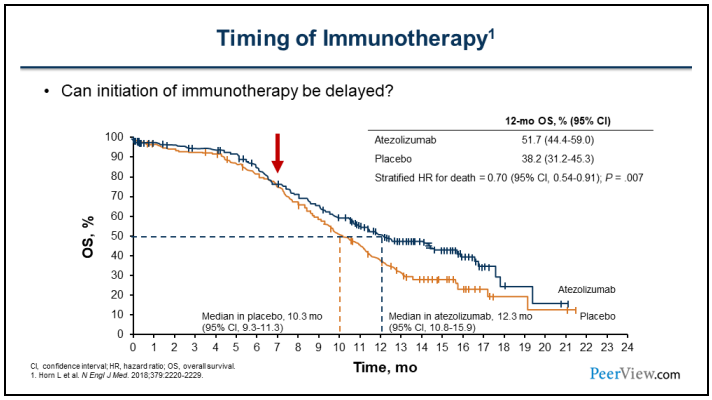
The addition of nivolumab improved PFS and improved OS, and it was to the same degree. It was a hazard ratio of 0.73. The curves in Slide 31, again, look very similar to what we saw with atezolizumab and durvalumab. To me, the immunotherapy drugs have this consistent effect. They're producing a similar effect. In a world where we don't have randomized phase 3 trials showing a survival benefit, I might consider the use of nivolumab, but here I wouldn't consider off-label use. I see some effect. It's an active drug. Our standards, though, are those determined by the randomized phase 3 trials and the FDA approvals of durvalumab and atezolizumab.

Slide 32



When we look at these Kaplan–Meier curves all together in Slide 32, we do see fairly consistent benefit, with the addition of a checkpoint inhibitor to chemotherapy improving outcomes.

Slide 33



Probably the most frequent question I get asked is, can the initiation of immunotherapy be delayed? Do we need to give it up front, or can we wait until longer?

Part of the reason this comes up is because when you look closely at those Kaplan–Meier curves from IMpower133 in Slide 33, from CASPIAN, and even from the nivolumab studies, they don't really split until after about 6 months. A lot of the questions I get asked are, can we finish the chemotherapy and then use immunotherapy later? It's active, but do we need to give it up front?

One of the reasons I get asked this question a lot is because patients present often very fulminantly, and, at least in my institution, are often hospitalized at the time of diagnosis. It's not uncommon for us to start chemotherapy as an inpatient. Is that true at your institution, as well, Bhavesh?

Dr. Shah: Yeah, absolutely. Many of the patients who present with small cell lung cancer have second primary cancers (SPC), spinal cord compression, or some type of oncologic emergency where they need to be started on the inpatient side. My question was going to be, does your institution administer immunotherapy with the first cycle or not?

This also fuels the fact that you can probably put that immunotherapy off for the next cycle, or when the patient is outpatient, because there is this cost that is incurred by the institution when it's not covered by the diagnosis-related group (DRG), and unfortunately the patients may have to end up paying for that. That’s a question that arises frequently about immunotherapy, especially because we have this in the frontline.

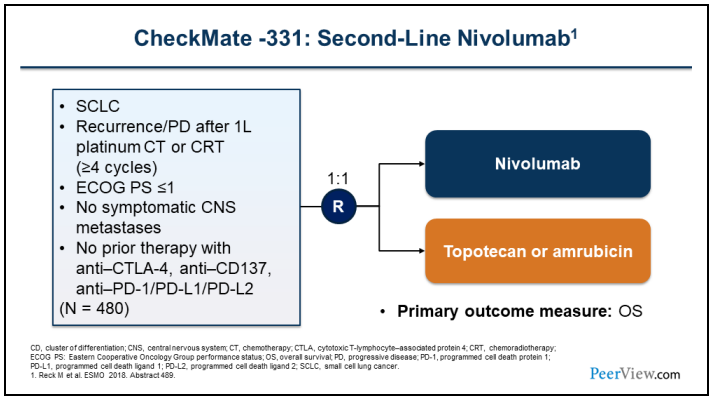
Dr. Liu: I know that every institution's policies are a little different, but the use of atezolizumab in the inpatient setting would not be approved by our own internal committee, primarily because of cost. That's not a decision that I would ever fight. If someone is admitted inpatient and I'm worried about the patient incurring that cost, I don't need to give the atezolizumab with the first cycle.

In the outpatient setting, I do. But in the inpatient setting, if I'm giving chemotherapy for someone who's presumably quite ill because they are an inpatient, I'll finish that first cycle of chemotherapy, and if they improve to the point where they can be discharged, I'll then continue the immunotherapy with subsequent cycles and not wait until progression or until they complete chemotherapy. I do want to give it concurrently as the trials did, but I feel comfortable waiting until cycle 2 if the circumstances are necessary.

That's a very relevant question because the medicines certainly do have their own cost, but I wouldn't want to wait. I wouldn't want to save it. That's a strategy that often doesn't work out as we planned, and in fact, in small cell, we have some of that data.

First, we know there's a lot of attrition, that a significant number of patients won't make it to second line. Even fewer will make it to third line, so if I'm saving that drug in my pocket and I promise that I'm going to use that drug at progression, that is a promise that more often than not I won't be able to keep.

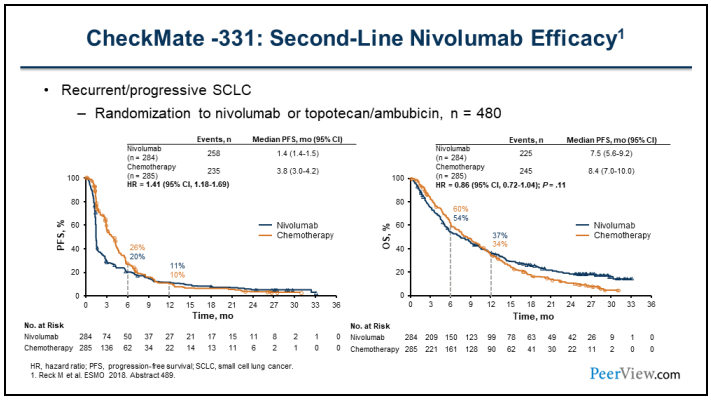
Slide 34



If we look at immunotherapy in the second-line setting, the results are, surprisingly, somewhat disappointing. The CheckMate -331 study was a randomized phase 3 trial for patients with relapsed small cell lung cancer who had already received platinum looking at second-line topotecan, or amrubicin in parts of the world where that was approved, versus nivolumab monotherapy. Here we have an active immunotherapy drug compared with topotecan.

Topotecan sort of has a lousy reputation. It is the FDA-approved drug in the second-line setting, but it doesn't have a great schedule—days 1 through 5. It is a fairly toxic treatment, and I think a lot of investigators, at least at our institution, don't like giving topotecan because of the toxicity associated with it.

Slide 35

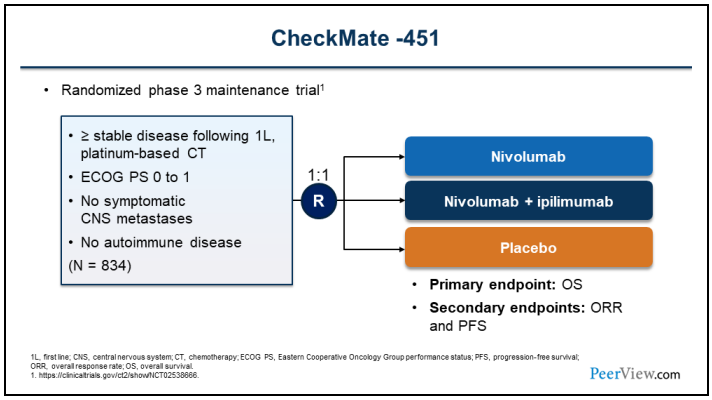


Despite the low bar of topotecan, nivolumab was not better. This was somewhat of a surprise, but there was no difference in OS. The 1-year survival rate was almost identical between nivolumab and topotecan, and PFS strongly favored chemotherapy. Here, that immediate drop before the 3-month mark that you see in that Kaplan–Meier curve for PFS in Slide 35—that very scary drop straight down—was the nivolumab arm.

In an unselected population in a second-line setting, nivolumab was not superior to topotecan, and was not approved in the second-line setting based on this.

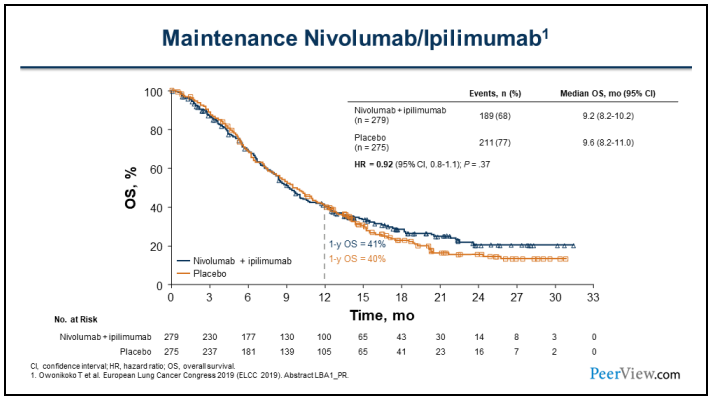
This was somewhat surprising to us, but we also realized that when small cell lung cancer relapses, it is different. Small cell lung cancer is responsive to almost any cytotoxic agent you give. It's unique in that you can get a response with many different agents, but the responses are fairly transient. When they relapse, they're different. They don't respond to as many treatments. When they come back, they're a much more difficult cancer to treat, so maybe waiting until relapse was a little too late.

Slide 36



What about maintenance treatment? What if we complete induction chemotherapy, don't wait until progression, and immediately give those patients immunotherapy? This was the CheckMate -451 study, in which after chemotherapy, patients who had not progressed received nivolumab alone, nivolumab plus ipilimumab, or placebo.

Slide 37



Interestingly enough, the addition of nivolumab/ipilimumab as maintenance did not have an effect on survival compared with placebo, so waiting until the maintenance setting for immunotherapy was no better than not giving immunotherapy at all. These data were quite surprising to me; I'm not sure if you expected it to be something different. I certainly did.

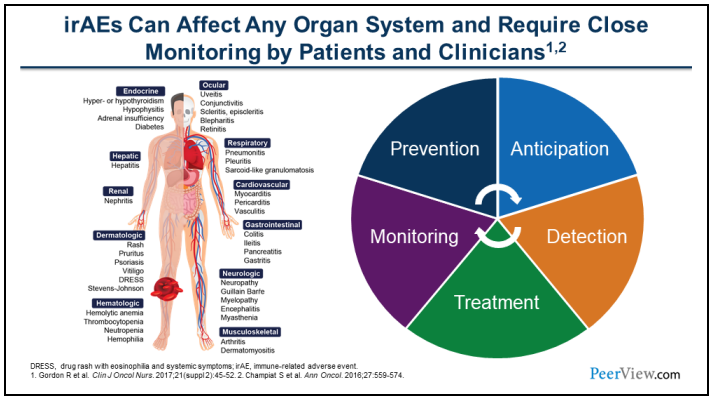
Dr. Shah: No, I definitely anticipated the same as you did.

Dr. Liu: It tells us that when we add immunotherapy—atezolizumab or durvalumab—to first-line chemotherapy, we improve survival. If you wait until completing chemotherapy and then just deliver nivolumab/ipilimumab alone, that has no effect on survival compared with placebo.

It's hard to explain it. There are certainly plenty of theories. We could work out reasons as to why that might be the case, but in clinical practice, waiting until the end of chemotherapy to start immunotherapy is not a proven strategy. It's not an approved strategy, and in my opinion, not a recommended one. The only strategy that's improved survival is the concurrent use of a first-line PD-L1 inhibitor—atezolizumab or durvalumab—with chemotherapy.

I'm very comfortable with cycle 2, if someone's admitted for cycle 1, but I wouldn't wait until completion of cycle 4, and I certainly wouldn't wait until progression, when it's no better than chemotherapy.

Slide 38



We see a clear benefit here, but we know these drugs can also induce some risk, and immune-related adverse events can occur with this. Overall it's a very well-tolerated regimen and generally patients feel better with chemotherapy because of the high response rates, but because many of their symptoms are related to the cancer itself, immune-related adverse events can occur.

These are of the utmost importance, not just in small cell lung cancer, but oncology in general. Bhavesh, I think you and I have both worked on different strategies to try to educate our patients, our colleagues, and patient caregivers about recognition of these immune-related adverse events, because the bad outcomes that I see when I'm reviewing cases, reviewing charts, are primarily due to slow recognition or slow action.

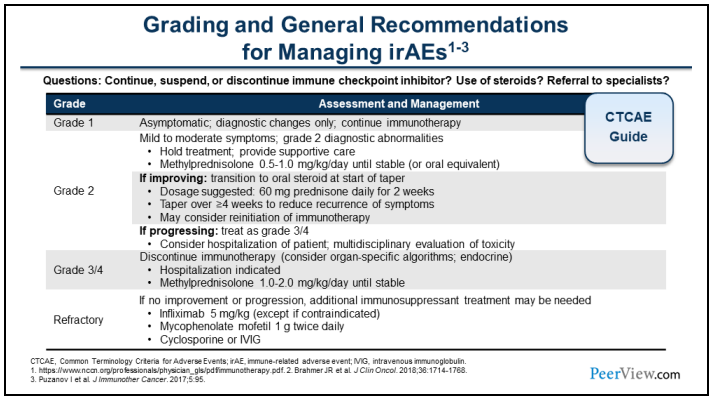
Dr. Shah: Absolutely. When you have those prominent grade 1 or 2 events, if you're not identifying those and in a timely fashion, they could be escalated to a much higher grade. We noticed in both the clinical trials that the majority of the immune-related adverse events were basically hypothyroidism or hyperthyroidism. We really need to be on top of that.

There was one patient in one of the immunotherapy trials with hepatic toxicity, so there is definitely a need for some long-term monitoring, some short-term monitoring, and education for all the stakeholders who are involved in managing the patient that is really important.

Dr. Liu: What I tell patients is that with chemotherapy, we have a list of expected toxicities. With targeted therapy toxicities, and when patients may notice something completely unrelated, we'll say it's probably not related.

But the default for immunotherapy is that anything new could be considered related because our immune system can target any part of our body. For anything new that happens, my default is I think it's going to be related unless I can find an alternate explanation. Really, head to toe, as this chart suggests, any organ can be affected with immune-related toxicity, and we've seen them all.

Slide 39



The management for the immune-related toxicities really is immune suppression. This is not like chemotherapy or targeted therapy, where it's dose reduction. That's not an effective strategy. It's really stopping the therapy if needed and immune suppression, escalating those based on severity.

The event that we worry about the most when we're dealing with lung cancer is largely pneumonitis. Pneumonitis can go from 0 to 60 overnight, so if a patient is newly hypoxic, has a new cough, or has new shortness of breath, that's something that we have taught our trainees, our nurses, and our support staff that we've got to take any new complaint very seriously. Those patients are getting CT scans, even going through the emergency room if we need to.

New hypoxia, you're getting a CT scan. We're staying late to see it, and if it shows pneumonitis, you're getting admitted to the hospital. These are our patients who can decompensate very quickly. We have to have a healthy respect for the immune-related adverse events. I'm not sure if you have a similar strategy at your institution, as well.

Dr. Shah: Absolutely. Pneumonitis is definitely a concerning aspect. A very small percentage of patients can have that, but we inform our patients that if there are changes from their baseline pulmonary function status that they need to come to the clinic right away and not wait until their appointment next month.

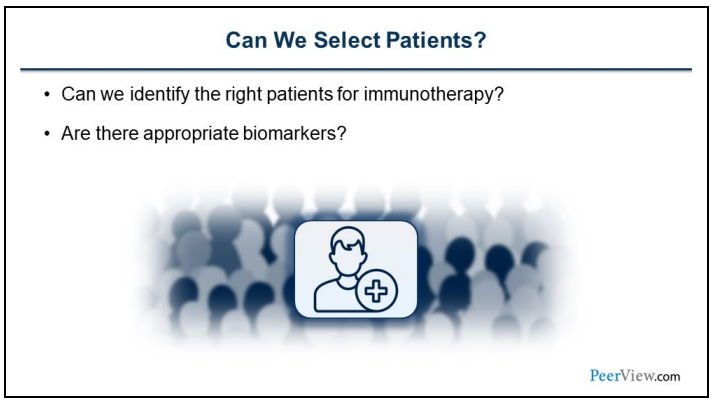
Dr. Liu: Fortunately, as you mentioned, they are rare, and I try not to scare patients off from the use of immunotherapy. I say, “These are rare,” but it's important they know about that, so when they're feeling more short of breath or if they're having notable diarrhea, for example, that they're not waiting 3 weeks to tell us, that they're calling overnight, that they're taking these seriously.

We've also had many efforts at both of our institutions to educate our colleagues in primary care, in emergency rooms, and in other specialties to recognize these as possible toxicities because the time course can be quite variable. Although most will occur within the first 3 to 6 months, we can see new toxicities potentially years later.

It may be important for our anesthesia colleagues to understand that this patient may be at risk for adrenal insufficiency or an adrenal crisis, and that these are toxicities that can affect really any part of medical care. As we see more and more of these drugs used, those toxicities are going to become more and more pervasive in our day-to-day medical routines.

Managing toxicities is clearly an important thing. Overall, we see the addition of atezolizumab and durvalumab to chemotherapy as safe. We don't see a significant increase in toxicities. We see an improvement in survival. That's where we are now.

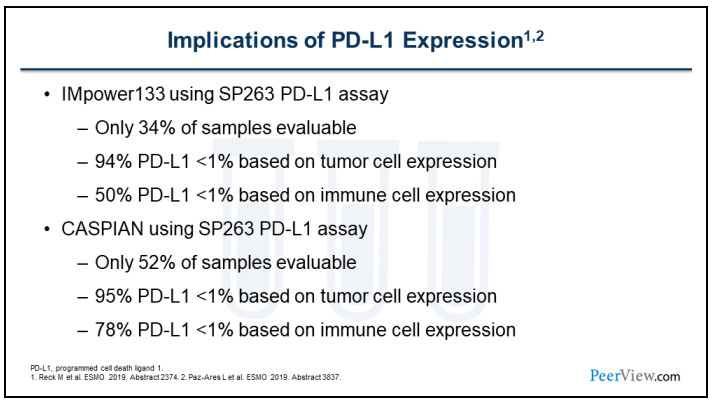
Slide 40



But where do we want to be? What we want is a bigger therapeutic window. What we want is a larger degree of benefit. To do that, we need to identify who is getting that benefit. We see a tail to this curve. We see a subset of patients who are living for years, certainly living longer than they otherwise would with chemotherapy. We can increase the effect if we can prospectively identify who those patients are.

As with any study that's showing improvement, we want a biomarker that's going to help identify those people more likely to benefit from this strategy so we can ensure they get that treatment. For others, we can direct them toward a clinical trial or try to better understand the biology of why they're not getting that benefit so we can overcome that.

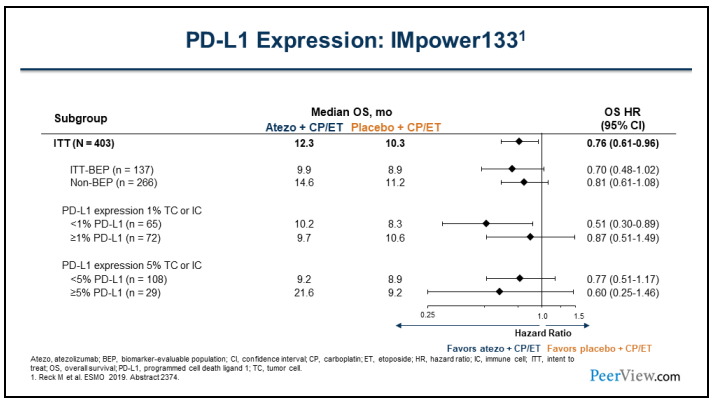
Slide 41



Biomarkers for immunotherapy are not perfect—far from it. In non–small cell lung cancer, the best biomarker we have is PD-L1 expression by immunohistochemistry (IHC), so we looked at that in these two randomized trials, IMpower133 and CASPIAN. Again, these trials reinforce each other. They show very similar things.

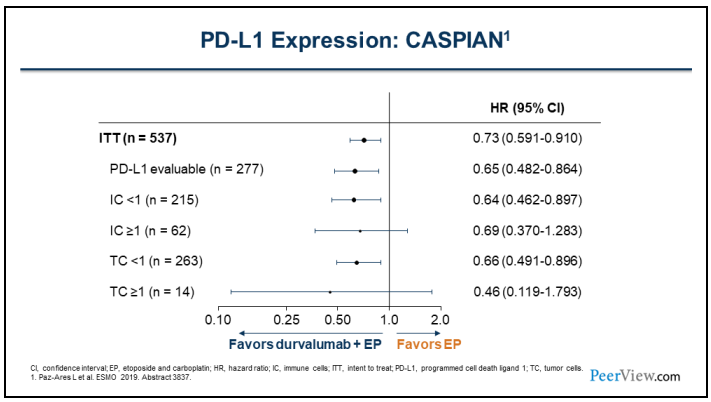
First, generally, PD-L1 is negative in small cell lung cancer if you look at the tumor. We do see expression of PD-L1, but primarily on the microenvironment or in surrounding lymphocytes. Even in this trial, which was under the best circumstances, most patients did not have samples that were evaluable for a simple PD-L1 IHC, which, again, shows that tissue specimens are very scant and difficult to come by.

Slide 42



When PD-L1 was explored, whatever cutoff you used, whether you were above or below, it wasn't useful in discriminating who gets that benefit. All patients seemed to derive benefit, high or low, from atezolizumab.

Slide 43



Or from CASPIAN.

Slide 44

PD-L1 Expression: KEYNOTE-604[1]

- Randomized phase 3 trial for 1L ES-SCLC
  - Platinum + etoposide + pembrolizumab/placebo
    - PFS benefit achieved, did not achieve OS endpoint
    - PD-L1 evaluable in majority of patients (~80%)
    - Higher rates of PD-L1 positivity than other trials

PD-L1 CPS	Pembrolizumab + EP (n = 228)	Placebo + EP (n = 225)
<1	97 (42.5)	78 (34.7)
≥1	88 (38.6)	97 (43.1)
Unknown	43 (18.9)	50 (22.2)

CPS, combined positive score; EP, etoposide and cisplatin; ES-SCLC, extensive-stage small cell lung cancer; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; OS, overall survival.
1. Rudin CM et al. *J Clin Oncol*. 2020;38:2369-2379.

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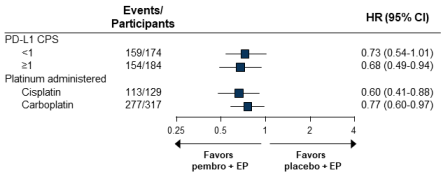
We even saw the same thing with pembrolizumab.

Slide 45

PD-L1 Expression: KEYNOTE-604[1] (Cont'd)

- PD-L1 expression (CPS, 22C3) did not correlate with survival benefit from pembrolizumab in ES-SCLC



CI, confidence interval; CPS, combined positive score; EP, etoposide and carboplatin; ES-SCLC, extensive stage small cell lung cancer; HR, hazard ratio; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab.
1. Rudin CM et al. *J Clin Oncol*. 2020;38:2369-2379.

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The subsets based on PD-L1 expression using the Dako 22C3 clone didn't help predict patients. There is no utility in patient selection.

Slide 46

Blood TMB[1,2]

- Blood TMB in IMpower133
  - Blood collected for TMB at study entry
  - Predictive role for PFS with second-line atezolizumab in NSCLC
    - OAK, POPLAR
  - Prespecified cutoffs of 10 and 16 mutations/Mb

NSCLC, non–small cell lung cancer; PFS, progression-free survival; TMB, tumor mutational burden.
1. Liu S et al. WCLC 2018. Abstract PL02.07. 2. Gandara DR et al. *Nat Med*. 2018;24:1441-1448.

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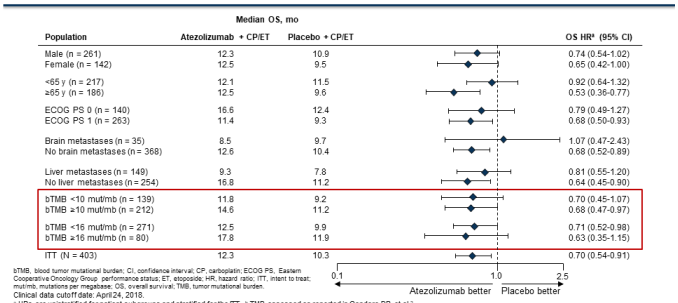
The other biomarker we often use in non–small cell lung cancer is tumor mutational burden (TMB). It's not a perfect biomarker either; in fact, it has a questionable role even in non–small cell lung cancer.

Slide 47

Blood TMB: IMpower133[1]



bTMB, blood tumor mutational burden; CI, confidence interval; CP, carboplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, etoposide; HR, hazard ratio; ITT, intent to treat; mut/mb, mutations per megabase; OS, overall survival; TMB, tumor mutational burden.
Clinical data cutoff date: April 24, 2018.
[a] HRs are unstratified for patient subgroups and stratified for the ITT. [b] TMB assessed as reported in Gandara DR et al.[2]
1. Liu S et al. WCLC 2018. Abstract PL02.07. 2. Gandara DR et al. *Nat Med*. 2018;24:1441-1448.

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But in small cell lung cancer, we looked at blood-based TMB in the IMpower133 regimen and tissue TMB in the CASPIAN regimen, and again, whatever cutoff you used, whether you're above or below, outcomes were better with immunotherapy. For PD-L1 expression, for TMB, there is no utility in patient selection. There is still a subset of patients getting benefit from immunotherapy. Clearly, that subset exists; we just don't have the tools to identify who those patients are.

Slide 48

SCLC Subtypes

- Biologic subtypes can be established by differential expression of four key transcription regulators
  - ASCL1 (achaete-scute homologue 1)
  - NeuroD1 (neurogenic differentiation factor 1)
  - YAP1 (yes-associated protein)
  - POU2F3 (POU class 2 homeobox 3)

SCLC, small cell lung cancer.

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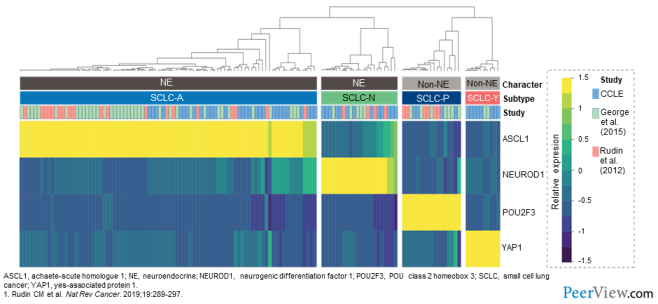
There's a lot of work being done now to try to advance biomarker work, and some of that work, primarily by Dr. Charlie Rudin at Memorial, is looking at transcription regulator expression as different biologic subsets—looking at things like ASCL1, NeuroD1, YAP1, and POU2F3—based on their expression of certain transcriptional regulators.

Slide 49

Distinct SCLC Subsets[1]



ASCL1, achaete-scute homologue 1; NE, neuroendocrine; NEUROD1, neurogenic differentiation factor 1; POU2F3, POU class 2 homeobox 3; SCLC, small cell lung cancer; YAP1, yes-associated protein 1.
1. Rudin CM et al. *Nat Rev Cancer*. 2019;19:289-297.

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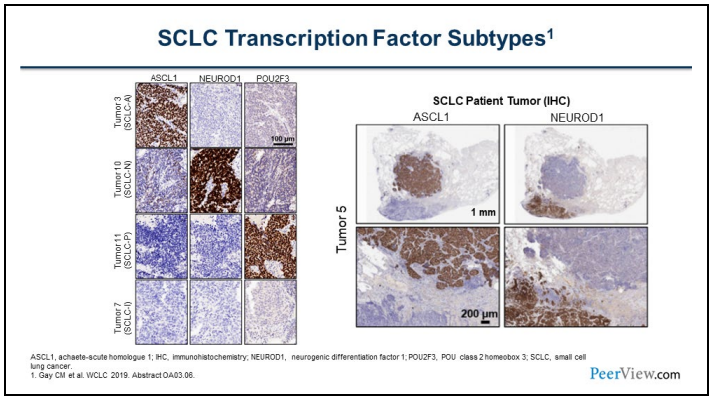
We know that this represents some slightly different biology, and importantly, these can be tested with IHC. We don't need large tissue specimens for next-generation sequencing.

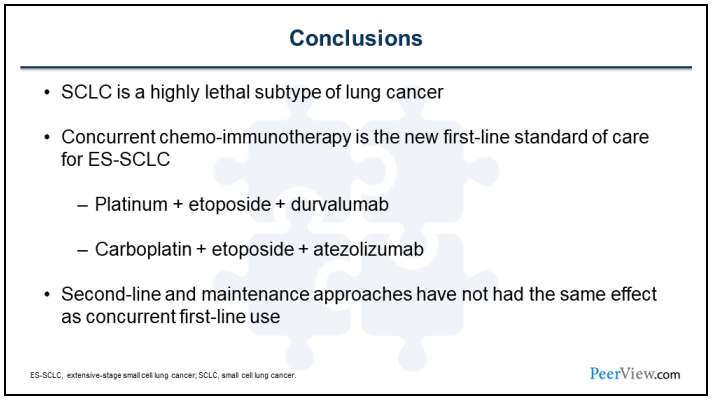
Slide 50



We can do IHC and identify these different subsets. If there is one subset, like the YAP1 subset, potentially that subset could derive most of the benefit from immunotherapy. Maybe the other subsets are not getting that benefit. That could be used to help direct therapy where it's supposed to go, and improve that signal of benefit delivering treatment where it's most needed.

We're quite a ways from validating that and showing that is the case. There are a lot of challenges with that, including the fact that one tumor specimen can be positive for multiple subsets at once. It's not as clean as the driver mutation status we see in non–small cell lung cancer, but it clearly is a start.

Slide 51

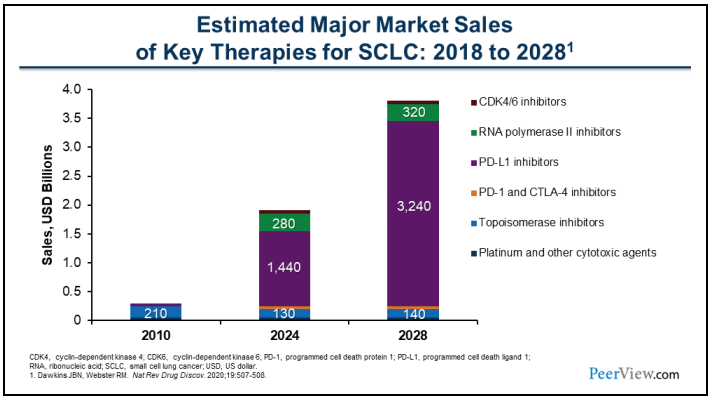


What we've talked about so far is that small cell lung cancer is a very lethal cancer. It remains disproportionately lethal, but the addition of atezolizumab to carboplatin/etoposide and the addition of durvalumab to platinum/etoposide improves survival. These regimens represent our current standards of care.

Second-line approaches, maintenance approaches, have not had the same effect. The best treatment we have, the only intervention that improves survival, is really that concurrent first-line use.

Integrating Immuno-Oncology Into the Plan for Patients With SCLC in Managed Care Settings: Challenges, Practicalities, and Implications

Slide 52



Dr. Shah: Dr. Liu discussed about all these amazing studies and innovation with immunotherapy. My objective, the second half of this lecture, is to talk about how to integrate these from a managed care perspective, and the challenges and the practicalities from a health system, managed care perspective. Hopefully I can share some of that.

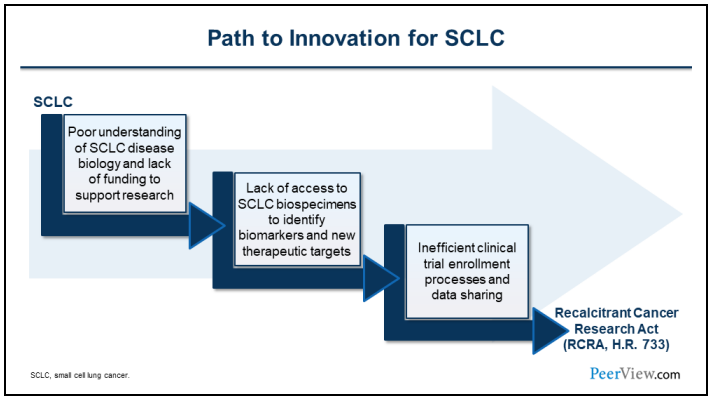
As I was looking at the market, I came across this article that was published in *Nature Reviews Drug Discovery* just recently, which was done by a life science company from London. They were evaluating the small cell lung cancer market.

They identified that between 2018 and 2028, we would see an increase in therapies across global markets—the United States, EU5, and Japan—to about $3.8 billion in expenditure because of the innovation. About 85% of that is forecasted to be due to PD-1 inhibitors.

This is a really interesting analysis, and I thought it was nice that they actually broke it down in terms of the different therapies that are being considered for this analysis across the globe.

It's an interesting perspective from a life science company, if you wanted to follow that. It also tells you, from a managed care perspective, that immunotherapy is definitely here to stay, and there's more innovation coming in small cell lung cancer.

Slide 53

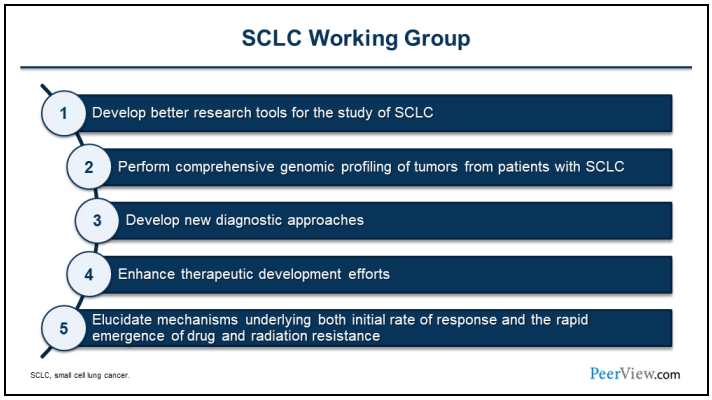


One of the other questions I had as I was preparing for this lecture was why was small cell lung cancer so behind on the path to innovation? I did some digging and identified that for 20, 30 years—I've been practicing for over 20 years, so I know—there's been poor understanding of the disease biology.

Of course, there's lack of funding and lack of access to biospecimens. We know that there are all these repositories and access to biomarkers for non–small cell lung cancer, unlike small cell, and there was not really a great collaboration between international working groups and local working groups in designing clinical trials specifically around small cell lung cancer.

In 2012, Congress passed a regulation called the Recalcitrant Research Act, which basically forced the National Cancer Institute (NCI) to identify two recalcitrant tumors—one was pancreatic, and one was small cell lung cancer—and focus efforts to identify ways to improve these diseases. If you looked at the 5-year OS, it was less than 20% for pancreatic cancer, and in small cell lung cancer, it was actually 8%, so there was significant room for improvement in this malignancy.

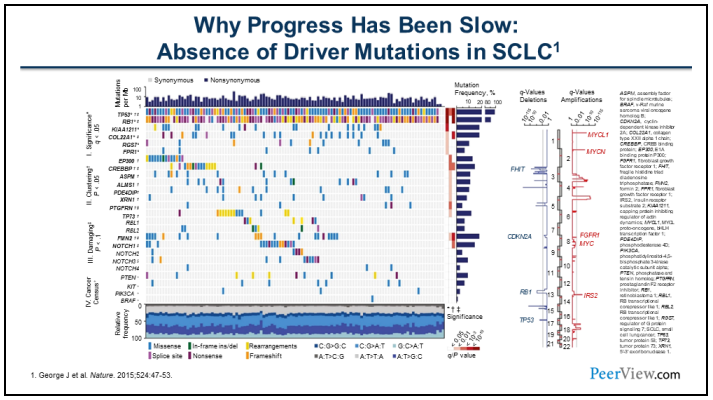
Slide 54



Basically, a group of about 50 experts came together, and they put together five recommendations for the NCI to focus research around (Slide 54). Develop better research tools to study small cell lung cancer; develop comprehensive genomic profiling, just like we have done for non–small cell lung cancer; and develop new diagnostic approaches.

We know that small cell lung cancer is a highly responsive malignancy to chemotherapy, but there was this really fast emergence of resistance to chemotherapy and radiation, so the group recommended looking at the underlying mechanism behind that.

Slide 55



If we look at the progress specifically in some of these recommendations, as we know, there is not too much in regards to driver mutations in small cell lung cancer, so obviously, we don't have many targets or any targets in small cell lung cancer, like we have in non–small cell lung cancer.

I wanted to know, Stephen, if you have anything to add to that. That's an interesting perspective, right?

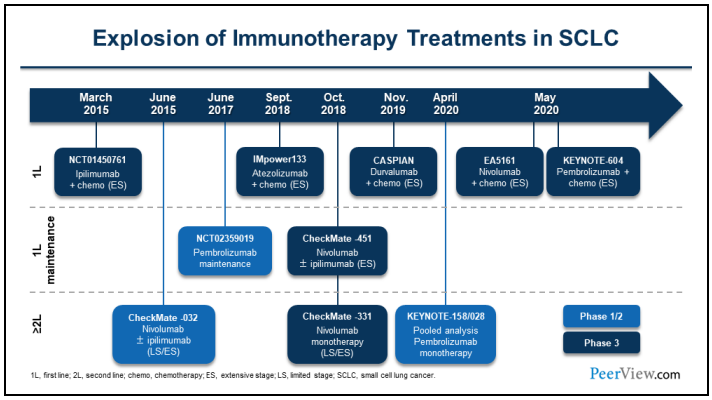
Dr. Liu: Yeah. I think there are a lot of reasons that you could explain it. One reason is that small cell lung cancer moves very quickly. For non-small cell, if we have a patient who presents, we get a biopsy, there's not enough tissue for all these in-depth analyses, we'll send that patient back for another biopsy, because it dramatically changes our treatment plan. It's so important to know.

It's partly the rebiopsy and those large biopsy specimens that led to a lot of advances, but small cell moves very quickly. Patients often can't wait for rebiopsy. It's usually a central tumor, so it's diagnosed by bronchoscopy or fine needle aspirate. We'll have a few cells, enough to make a diagnosis of small cell, but not enough to do any meaningful work. Because the chemotherapy is old, comfortable, familiar chemotherapy, we're very quick to just reach for it.

Then you get that initial response, and you get a good response. When it comes back, it's a little different, but we've been having trouble understanding that initial, de novo small cell, really studying it more, and I think that's really led to a lot of the inequities in care that you mentioned.

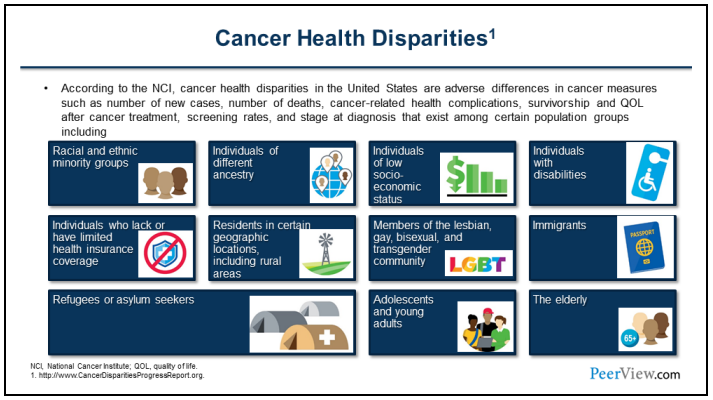
Dr. Shah: Thank you for sharing that.

Slide 56



We know there's an explosion of immunotherapy, and as you can see in Slide 56, there are at least 10 randomized controlled trials that are either ongoing or completed in this arena. There's a huge amount of innovation that came through because of all these initiatives that were initiated a while back.

Slide 57



As we talk about managed care, I think one of the most important aspects to talk about is cancer-related healthcare disparities. We live in times when we've really identified these—especially COVID has brought light to a lot of these disparities.

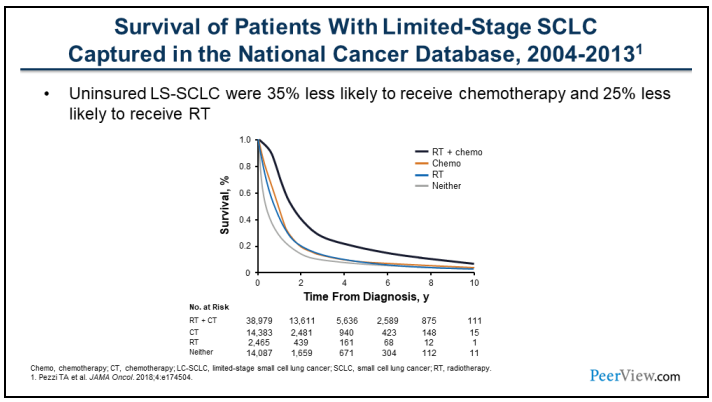
We know that African Americans and patients who are of Hispanic descent are affected by these healthcare disparities and by COVID, and the AACR recently released a report that talks about these disparities and highlights them in every single malignancy. Looking at the population that we have, it's so broad, and there's such a variety of shouldering of cancer that happens between these different varieties of populations.

For example, in the AACR report, we identified that about 100% of African American patients are 100% likely to be at risk of dying versus their white counterparts.

Patients who have lung cancer in Kentucky are three and a half times more likely to die of lung cancer versus patients who are diagnosed with lung cancer in Utah. And patients who are bisexual have about a 70% higher incidence of malignancy versus patients who are heterosexual.

There are huge disparities in burdening of cancer across our patient population. One of the things we talked about is that even having a specific insurance can be disadvantageous, where we know commercial patients actually fare better versus patients who have Medicare and Medicaid because of access issues. There are a lot of things that we need to do around cancer health disparities, and I think this fits nicely into a managed care setting, too.

Slide 58



I wanted to pull the small cell lung cancer disparities in Slide 58. There was a very large database from 2004 to 2013 that revealed that patients who were uninsured were 35% less likely to receive chemotherapy and 25% less likely to receive radiation, and we know the combination approach is the more beneficial that these patients can have.

It was really bringing out the fact that these patients are not getting the care that is standard of care for this specific disease. Dr. Liu, I wanted to know if you see this across the practices that you've been in contact with, if you've seen this in your practice with this patient population.

Dr. Liu: I think we all have, and it's something we don't talk enough about. We know from many studies, including the ones that you've mentioned, that the disparities in care directly affect outcome. It's not surprising, but it's also not acceptable. We really need to try to relieve a lot of these barriers, and we can.

Where I see it affecting patients is really every step of the way, whether it's slower to get diagnosis, whether it's not being able to come in for a biopsy or bronchoscopy. Maybe it’s because you don't have transportation to get there or maybe because you don't have the ability to take a day off work to get this bronchoscopy because you can't afford to miss a single paycheck.

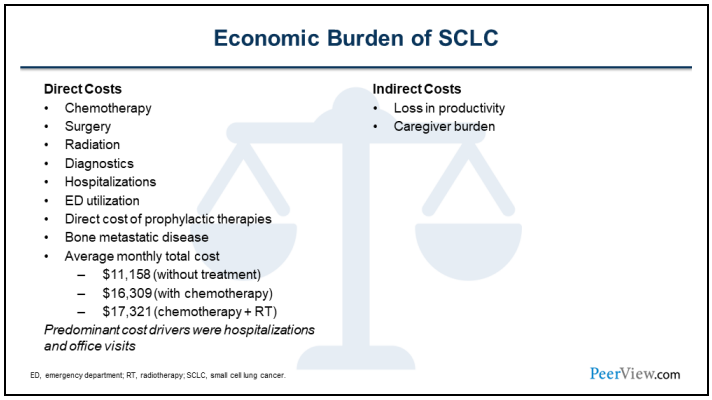
As institutions, it's our responsibility to identify what these barriers are and do everything we can to eliminate them. It's hard work, but it is important work. We can't allow the income level or where you live determine your outcomes for cancer. I mean, that's just not acceptable in this day and age. We do see it in the District of Columbia (DC) area. We have parts of DC that are underserved, where there are different barriers to care that we're working hard to try to eliminate. I know you see this in Boston, as well. You must.

Dr. Shah: Absolutely. We started the journey on the social determinants of health a long time ago, and we actually have a process in place where we know that food insecurities, housing insecurities, these things also drive how a patient fares in their malignancy.

If a patient is identified in our system as having food insecurity, they could get a prescription, and they could go to our food pantry, and they could get food for their entire family. We actually do about 600 prescriptions a week for patients with food insecurities. Similar to that, we've developed this housing insecurity intervention, too.

Like you said, everybody needs to play a role in supporting these types of disparities in patients with malignancy.

Slide 59



When we talk about the economic burden of small cell lung cancer, we know that this is an aggressive cancer. There haven't been a lot of resources that have been dedicated to really understanding what the total cost of care impact is of this malignancy.

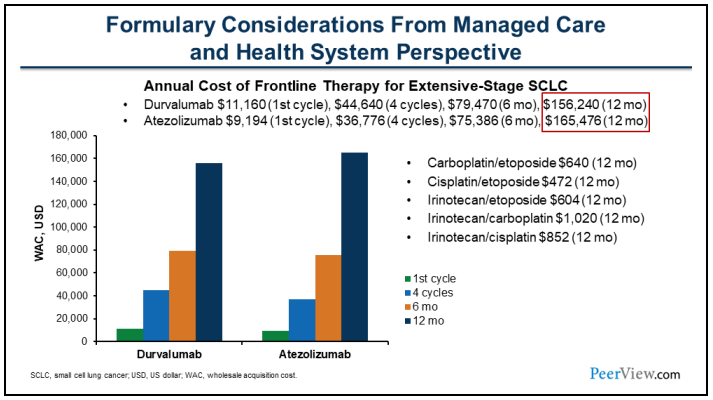
In Slide 59, I wanted to highlight the fact that there are indirect costs and there are direct costs. Direct cost is related to hospitalizations, the drug, the radiation, the surgery, and the diagnostics. All of those things are taken together, and we have very little information in terms of what happens to these patients with chemotherapy versus what happens to those patients now when we're adding immunotherapy to their regimen.

We wanted to highlight the fact that there needs to be some partnership between pharma and payers to develop some models that can help us, because we know that as we are looking at moving away from a fee-for-service model to a value-based environment in the United States, these are the things that are going to help us in terms of adopting these innovative therapies and understanding the total cost of care. We are all getting into those Oncology Care Model (OCM), Accountable Care Organization (ACO) models in which value is more important than volume.

As I was talking about the cost, from a formulary perspective, as a payer and a provider, you're looking at cost of each therapy that you're utilizing.

Not only do we look at the cost of the therapy, but we also look at whether this therapy is going to increase the number of admissions. Is it going to increase emergency department (ED) utilization? All of these things need to be factored in, not just the cost.

Slide 60

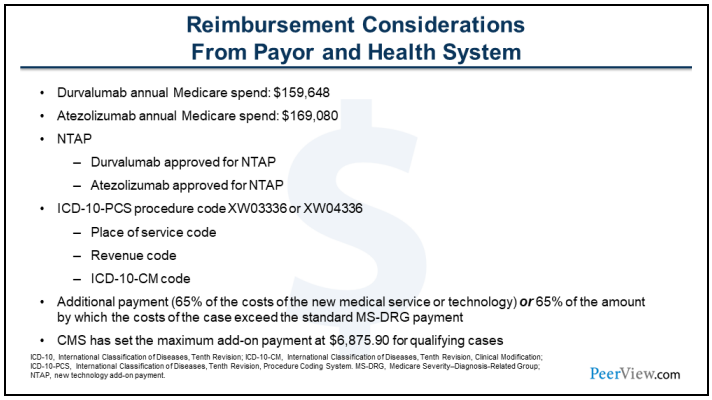


Sometimes it's deceiving, what we see in terms of the pricing. I wanted give this example of something that a lot of times providers may not be aware of. In Slide 60, durvalumab looks like it's more costly for the first cycle or the first 4 cycles, whereas atezolizumab looks like it's less costly for 4 cycles.

But as you look beyond that, based on the dose and the frequency, it looks like it actually costs more for a health system to use atezolizumab versus durvalumab. I think it's important to look at this from an annual, overall global perspective.

This is important to healthcare providers and payers who are paying for these therapies that, if I can save $10,000 on a patient with small cell lung cancer every year, of course I'm going to prefer that therapy over another. It's important for even pharma to be aware of these differences that drive some of these formulary changes in health systems and payers.

Slide 61



The other aspect is reimbursement considerations. Of course, payers have a fee schedule. Health systems observe that fee schedule. Then who's the biggest payer? Medicare is the biggest payer, right?

If I'm looking at Medicare patients and I'm looking to see, “Oh, wow, I'm spending $10,000 more,” that means that that patient is sharing that $10,000 and cost sharing 20% of that. That's another perspective that providers and payers may consider as they're using these therapies—how much is it going to cost the patient? Can I use something that's less costly to the patient?

The other thing that also drives some of this decision is having a new technology assessment payment. This is something new that came about. We talked about how some of these patients are going to be in the hospital, admitted to the hospital, starting their therapy in the hospital.

This new technology assessment payment basically provides some reimbursement for using immunotherapy in the hospital from Medicare. But that's the key. It's just from Medicare, not from Medicaid, not from commercial payers. I think we need to understand that.

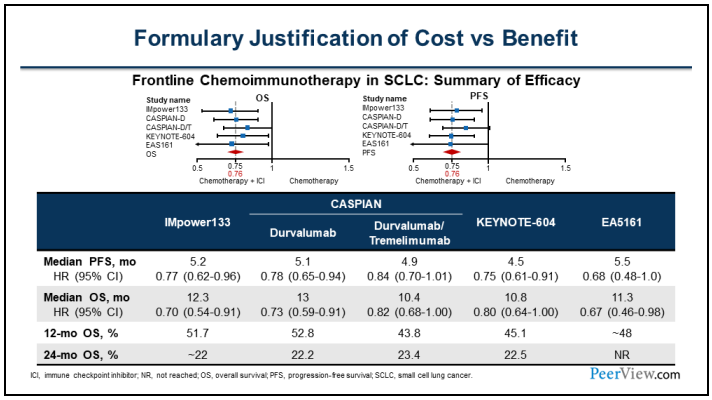
There's also a limitation in the reimbursement. It’s not like you get fully reimbursed based on the acquisition cost. That would be great. If I was getting reimbursed 100% of what I was spending, I would have no problem using immunotherapy in the hospital for any patient.

The other limitation is that this is only for small cell lung cancer. Of course, we know that these drugs are approved for other indications. You will not get reimbursed for new technology add-on payment (NTAP) for other indications in the inpatient side.

There's a very complex way of coding and billing, which is really the biggest hurdle that a lot of institutions have. You have to have this secondary procedure code on top of the DRG, and then you have to have the specific service code and a revenue code, and then this International Classification of Diseases–10 (ICD-10) DRG code that's tied to that.

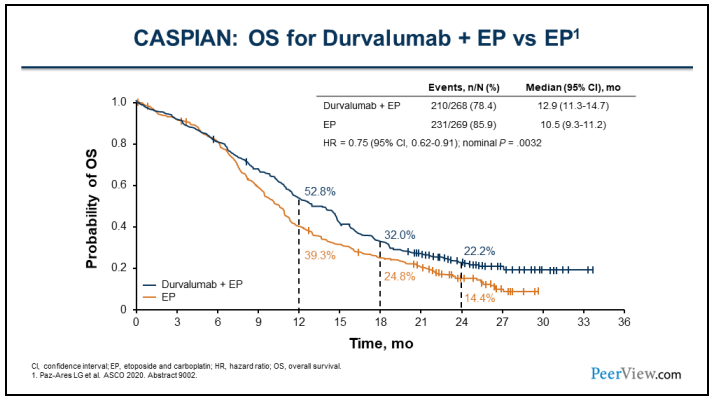
You can imagine this is not something that your finance department is really well versed on for every single NTAP. It is definitely a complexity in managing this drug in the inpatient side. But if you have the resources and have appropriate guidance, I think you can definitely get some type of payment from the payers that do pay for it.

Slide 62



We're going to do a faux pas. I'm going to do the same thing with a cross-trial comparison, part two. As you can see in Slide 62, there's an equivalency in these regimens, and then even if you look at it compared with chemotherapy, like you said, it's not groundbreaking, significantly. You have a 6-month difference in OS.

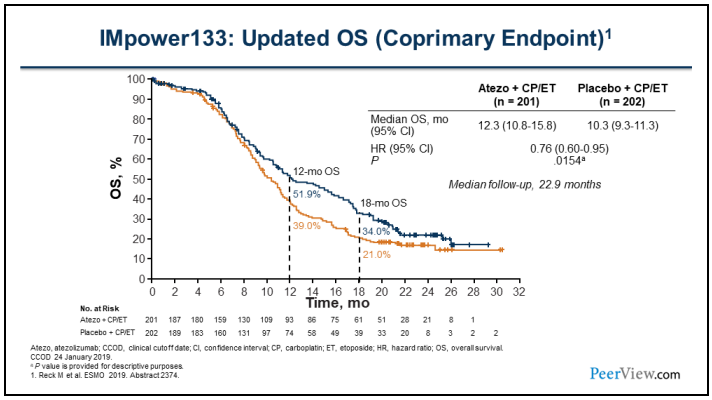
Slide 63



How do you justify the cost to the benefit that you've seen in these diseases? Sometimes a lot of systems and payers are just looking at the OS, but not looking at the OS over time. That is the key to immunotherapy, and I think payers need to really focus on going a little bit beyond the OS, PFS, the median OS that you see at that time point.

Look at having a difference in double the number of patients actually having a survival benefit, which we haven't seen in small cell lung cancer. We know that immunotherapy can benefit some of these patients. It would not be justifiable not to offer this just based on the cost.

Slide 64



Looking at it from a cost-effective perspective, it makes sense to see that from both of the immunotherapies that have been currently approved. I wanted to see if you had any perspective on that.

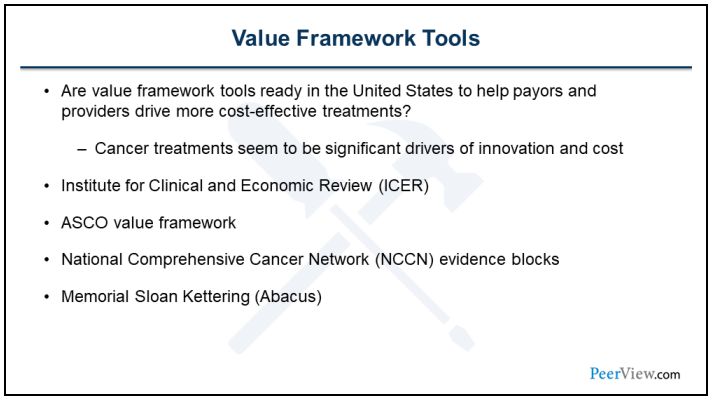
Dr. Liu: Yeah, I couldn't agree more. We're used to looking at medians, and for cytotoxic agents, for tyrosine kinase inhibitors (TKIs), I think there can still be some value in that. But for immunotherapy, the benefit is delayed. It's shouldered by a subset, and I think the real value for immunotherapy is landmark survival.

How many patients are alive 2, 3 years later? With immunotherapy in particular, these survival curves did not cross, but sometimes the curves cross, in which case your assumptions for hazard ratio go out the window, and the number is sort of meaningless.

For me, the value of immunotherapy, it's not response rate, it's not a better PFS. It's whether more people are alive years later with the addition of immunotherapy. For both of these drugs, we see that is the case. Look toward the right end of those survival curves for the benefit from immunotherapy.

Dr. Shah: I would love to see the 5-year survival, like we say in melanoma, long term. That'd be really interesting when that comes out.

Slide 65



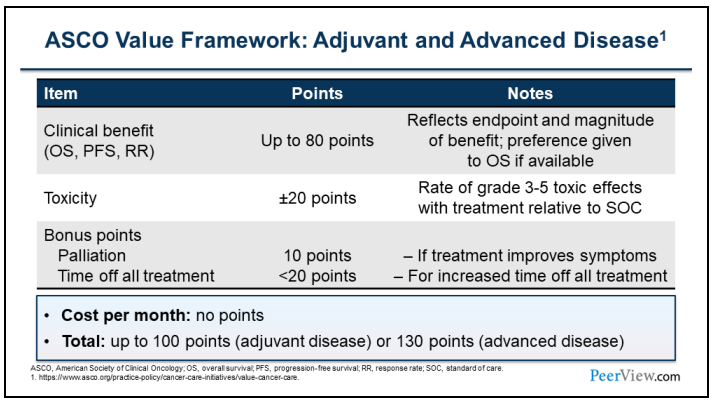
We have these value-based frameworks that are out there. The thought is that this would help providers and payers in terms of deciding, "Here's a value-based tool to identify more cost-effective therapies." I listed a couple of them on Slide 65. I'm not going to go into detail for all of them, but I want to point out some of the things that I've noticed.

The Institute for Clinical and Economic Review (ICER) always has their analysis done, and especially in oncology. They did one on immunotherapy for PD-L1 in lung cancer, and their analysis said that immunotherapies are overpriced and they need to reduce their price by 68% for them to have the quality-adjusted life year that's $150,000.

Nothing happens based on that. There is obviously no oncology input. There's no long-term data that actually goes into that. It's hard to utilize some of the guidance from ICER from a payer perspective and from a provider perspective and in these value-based tools.

NCCN has these evidence blocks, and Memorial Sloan Kettering has a tool that the provider can adjust the price based on the innovation of the therapy.

Slide 66

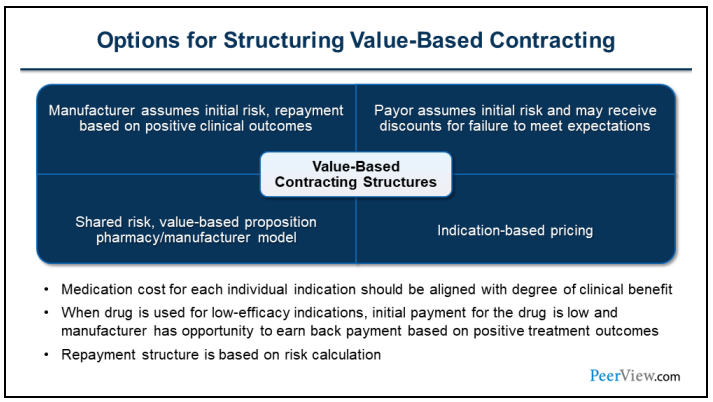


Going to ASCO, which is more oncology oriented. They take into account OS, overall response rate, and PFS. They provide a structured amount of points that you get for the benefit, and they have it broken down by adjuvant versus metastatic. Then, there are points that get taken out for toxicity.

One of the limitations is that it doesn't incorporate cost into it. I'm maybe simplifying it too much, but there is a lot of time that goes into calculating a score. It's not really something that you can use while you're seeing a patient. "Let me look at the value-based score from ASCO on this specific regimen." Because innovation is so rapid, not all of the regimens are in that framework to incorporate in the model.

There's a lot of work that needs to happen in regards to these models, but I think it's a start. I don't think that we should stop doing this. I think that we will probably eventually come up with a model that fits everybody and that can be used by payers and providers to say, "This is more cost-effective, and this is not more cost-effective from a toxicity perspective, from a survival perspective, from a quality-of-life perspective." I think we will probably get to that one day.

Slide 67

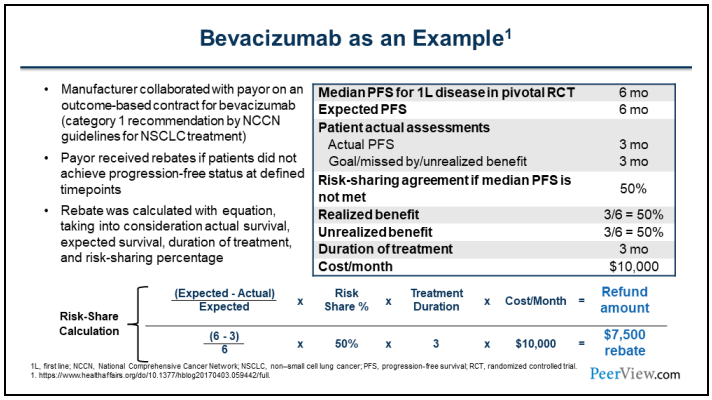


The other subject I wanted to introduce is value-based contracting. This has been something that we heard about for a lot of these rare-disease drugs coming out. Payers are announcing that they're doing value-based contracting with many of the manufacturers. Of course, a lot of the contracts are never publicized, but there are different models.

One is that the manufacturer takes the risk, and if they don't achieve that outcome, then they have to repay the payer or the provider. The second model is that the payer assumes the risk, and then they receive the discount if the product doesn't achieve the expected outcome.

The last one is basically a shared model, where they're both sharing the risk. This is probably the most appealing model because it makes sense that if you're taking risk, it should be both-sided, right? It shouldn't be one-sided risk.

Slide 68



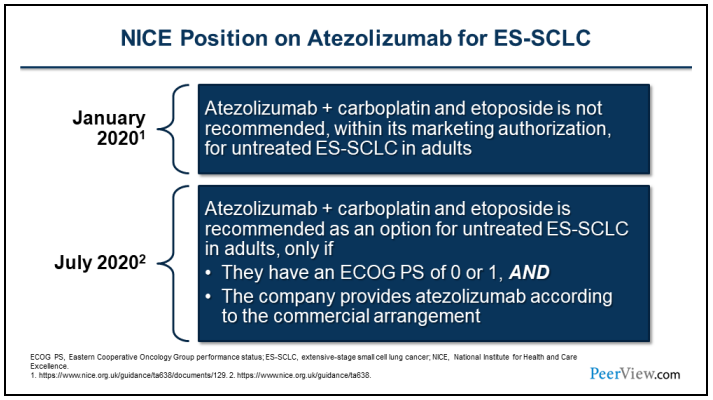
I wanted to talk about one of the most publicized models that I've come across in Slide 68. Bevacizumab has an outcome-based contract with this health plan in Michigan.

It's a very large health plan, with over a million members. They have a risk-based contract in which we know how much bevacizumab costs, and the equation that they're using is publicized, but of course, not the actual rebate or the risk that they're incurring.

Let's say we anticipate based on lung cancer trials that there's a 6-month median PFS, and this patient only achieved 3 months. There's that risk in which there's a rebate that goes to the payer if that member doesn't achieve that median PFS.

It's really innovative and interesting, and, believe it or not, this is ongoing. There's a data aggregator that's like a middleman that actually gets the radiographic scans and assesses for progression and response to validate that for the contract. So very, very innovative, and I'm glad that it was publicized because we don't see a lot of these great outcome-based contracts that are out there.

Slide 69



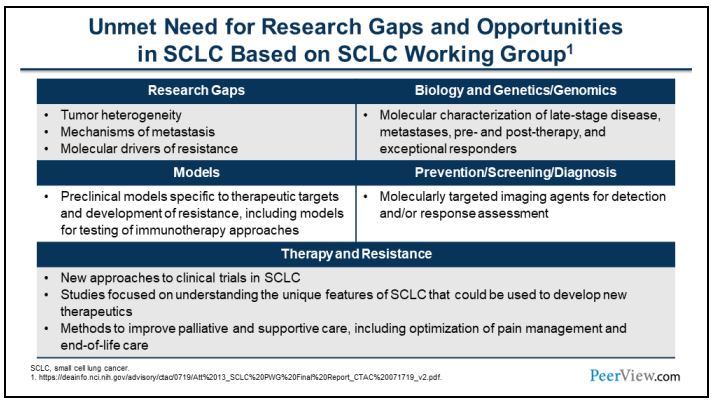
Based on the cost of a lot of the immunotherapies and the degree of benefit, of course we're going to see pushback from many of the authorities. We've seen this with the National Institute for Health and Care Excellence (NICE).

In January 2020, they basically said they would not recommend atezolizumab for extensive-disease small cell lung cancer. But then in July, things changed when they said, "Okay, we see a benefit in the Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1."

They negotiated an aggressive pricing for the drug to put the drug on formulary for the entire healthcare system in the United Kingdom.

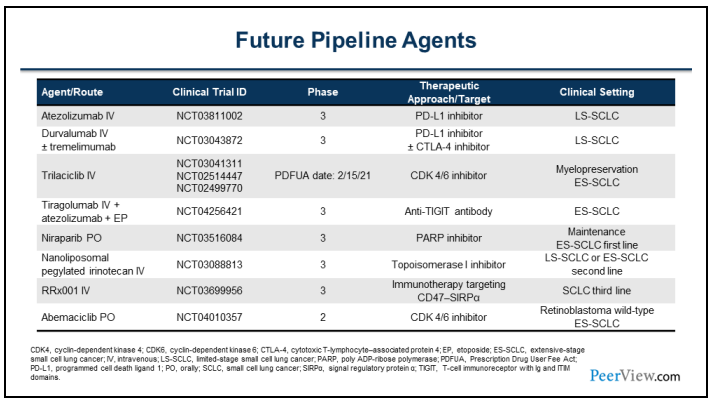
This is one of the more extreme models that you have, in which the government is negotiating the value-based or outcome-based contract versus we could start doing this ourselves. There's a precedence of having some type of model that we can sustain this innovation.

Slide 70



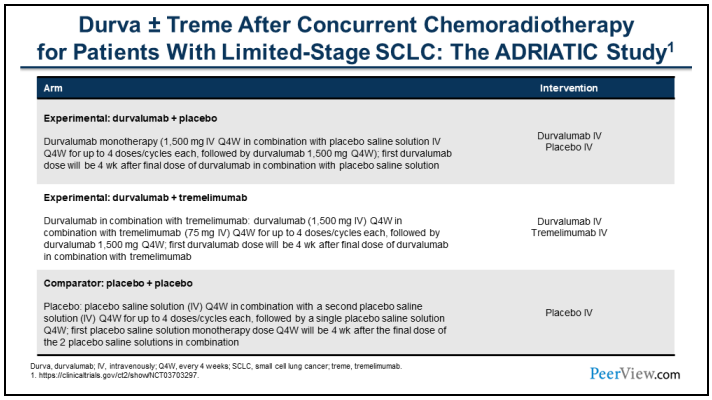
What happened when the Small Cell Lung Cancer Working Group met in 2019? They basically are guiding the NCI in terms of what needs to be focused on. Here are the recommendations from them in terms of where we need to focus and where the funding should go for the types of projects that NCI should be sponsoring.

Slide 71



It's taking us to the next step, and that's why I wanted to focus on the future pipeline of agents. We know that there is this push for these agents to more limited-stage small cell lung cancer—durvalumab and atezolizumab. Atezolizumab is being studied in the limited-stage small cell lung cancer, phase 3, randomized controlled trials that are being done in that setting.

Slide 72

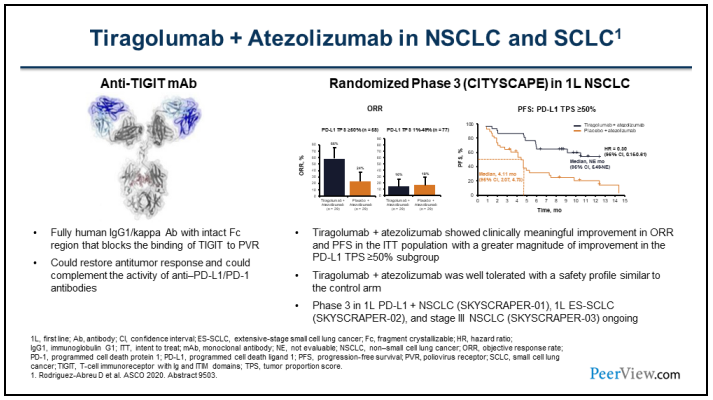


If you have any comments about the ADRIATIC study, Stephen, here's the opportunity for that.

Dr. Liu: Both the ADRIATIC and the NRG-LU005 studies, looking at durvalumab and atezolizumab for limited-stage, are going to be very important studies because we know that these drugs are active in small cell for a limited-stage patient with potentially curable cancer. But we really, really need better outcomes.

This is combining what we saw in IMpower133 and in CASPIAN with what we saw in PACIFIC—when you use immunotherapy after chemoradiation, we see an improvement in outcomes. That interplay is really setting it up for success in small cell. I expect both of these trials to yield positive results and make a difference here.

Slide 73



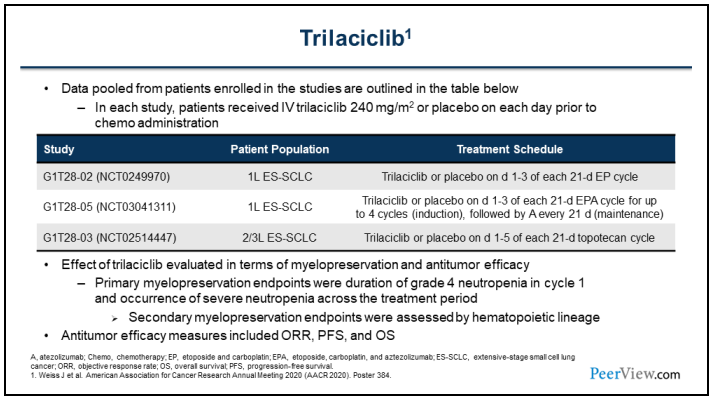
Dr. Shah: The next molecule I wanted to bring up in the pipeline is tiragolumab. We saw some preliminary results in phase 2 in non–small cell lung cancer in which there was a significant benefit, and even for patients who may be refractory to PD-1.

It's an interesting combination. It's being studied in phase 3 in small cell with atezolizumab and tiragolumab, and also in non–small cell lung cancer. If you have any perspective into this molecule, I would love to hear that, too.

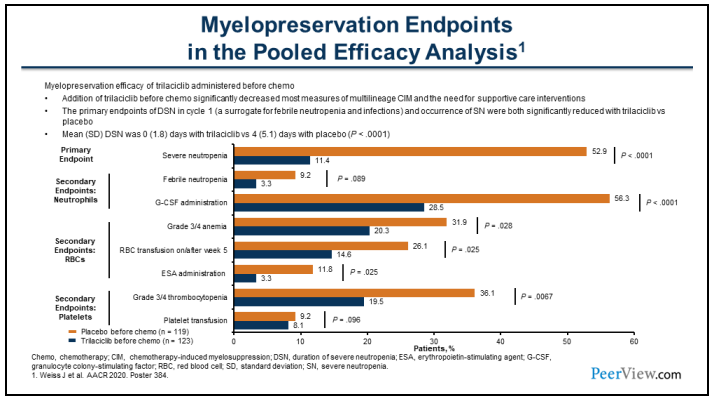
Dr. Liu: What you're referring to is the CITYSCAPE study that looked at the addition of tiragolumab to atezolizumab. We saw that it had a substantial benefit in that subset of patients who were PD-L1–high, which is probably because T-cell immunoreceptor with Ig and ITIM domains (TIGIT) seems to be coexpressed with PD-L1. That subset of patients seems to be deriving what could be substantial benefit, expanding the role of atezolizumab and immunotherapy in those patients, both for non–small cell and small cell.

In the SKYSCRAPER trial, we'll see carboplatin, etoposide, and atezolizumab with or without tiragolumab. We're starting to look forward to seeing those results, hopefully further improving outcomes.

Slide 74



Slide 75



Dr. Shah: That's great. Trilaciclib is this interesting molecule that is a CD4/6 inhibitor, which we usually see being used in patients with breast cancer.

This is being used as a myeloprotective agent, when you're basically trying myelosuppression. It's really interesting, and I wanted to get your perspective in terms of how this would fit into the small cell lung cancer treatment algorithm, because it all depends on how we currently utilize granulocyte colony-stimulating factor (G-CSF) prophylaxis and if there is any benefit to having this also added to it.

As you can see, there was some benefit in the degree and duration of severe neutropenia in these patients. Growth factor support has always been controversial in small cell lung cancer, and now adding another agent to growth factor support, I wanted to know what your perspective was with that.

Dr. Liu: Supportive care is important, and we know that the chemotherapy regimen we use, the platinum/etoposide regimen, carboplatin plus etoposide, is myelosuppressive. I see value in avoiding neutropenic fevers. I see value in avoiding delays in treatment.

When we look at the IMpower133 regimen, maybe we're a little surprised that a lot of toxicities didn't seem to have clinical effect. While you saw high rates—about 23% of patients developing grade 3 or higher neutropenia—the febrile neutropenia rate was only 3%. It was pretty small, and that's without growth factor use.

Reducing neutropenia and leukopenia—in my mind, I'm not sure the value of that. If that is largely a paper toxicity and it's not having a clinical effect, I'm not sure reducing that will improve outcomes.

The exception to that would be if it's important to preserve those lymphocytes, for example, to get your immune response. If the likelihood of an immune-mediated antitumor response or long-term benefit is predicated on preventing those cells from being damaged, then maybe there is a role for

myelopreservation there.

For me, if the drug were completely free, I probably have no objections to using it, but I still need to be convinced of the true value of adding that type of support in this setting.

Dr. Shah: I have to agree. As I had mentioned, growth factor support is such a controversial aspect in small cell lung cancer as it is. If you look at the NCCN guidelines, the recommendation is to use it for patients with curative intent and febrile neutropenia incidence of greater than 20%.

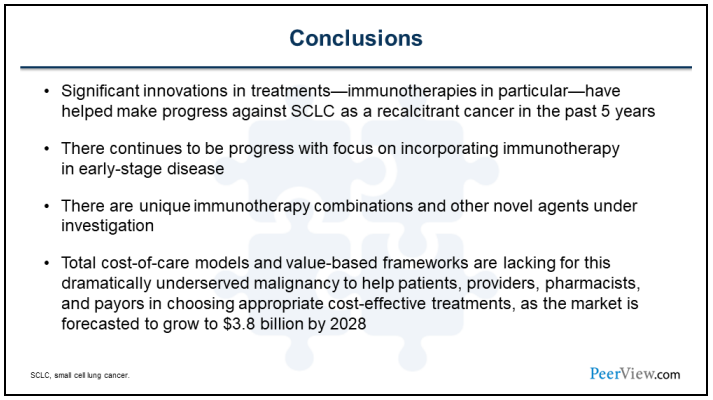
In small cell lung cancer, we don't use it in our practice. We use dose reduction and there's nothing in the literature that I'm aware of that talks about having a relative dose intensity of 85% that's going to have better OS for patients with small cell lung cancer.

We're hard-pressed to add more cost to immunotherapy and other agents that we may be using in small cell lung regimens.

Dr. Liu: We follow the same procedures at our institution. We're very liberal with dose reduction should we need that. That's a very chemosensitive tumor, and in fact, if you look at the platinum/etoposide regimens throughout history, the doses in all of these studies are all a little different, which just shows that it probably doesn't matter specifically which exact dose you're giving. I find that to be generally a better strategy.

Secondary prevention I would handle maybe a little differently. In the setting of no neutropenic fevers, I'm pretty comfortable with just modifying the dose.

Slide 76

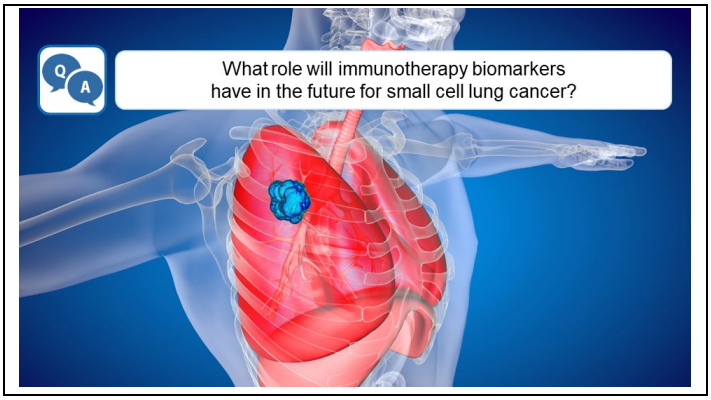


Dr. Shah: In conclusion, there's been significant innovation in small cell lung cancer for a tumor that's recalcitrant. In the past 5 years, we've seen a change in the treatment paradigm. There continues to be focus on incorporating immunotherapy in earlier stages of the disease.

We're also looking at unique combinations of immunotherapy that are under investigation. We'll see utilization of these drugs beyond resistance in small cell lung cancer. That brings us back to the managed care perspective—how we're going to need to understand the total cost of care models, the value-based framework for these types of agents, and how do we adopt this innovation with the significant costs that we're going to be seeing, and create access for patients?

We saw that there was a huge disparity in patients across various different patient populations. As payers and manufacturers, we really need to work hard on developing these models further because, as you saw, there's a forecast of this continued growth of $3.8 billion over the next 10 years in the small cell lung cancer space. We're really looking toward a lot of innovation in this space.

Slide 77



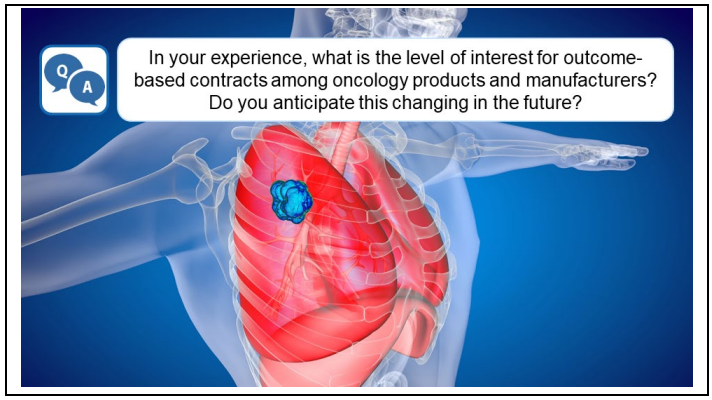
It's time for a few questions. This is for you, Stephen—how do you see immunotherapy biomarkers playing a role in the future in small cell lung cancer?

Dr. Liu: It's something we have to keep working toward. That's our goal. We know that a subset of patients is really carrying the benefit, and we can increase value if we can identify who those patients are to make sure they do receive that. I could certainly envision a future when we would limit the use of certain medications, like immunotherapy, based on biomarkers to when they are going to provide benefit.

We think of positive biomarkers. We're going to start seeing negative biomarkers; when we see a certain mutation or certain set of biomarkers that predict a patient won't derive benefit, we can avoid delivering that drug, avoid the added costs, the risk for toxicities, and explore alternate strategies. Both positive and negative predictors of benefit would be incorporated in the near future for small cell.

It's been challenging, and you hit on some of the challenges. They're things that we must rise up and combat. Those are definitely coming, hopefully sooner rather than later.

Slide 78



Dr. Shah: Thank you, Stephen. I'll take this next question. In your experience, what is the level of interest for outcome-based contracts among oncology products and manufacturers? Do you anticipate this changing in the future?

Absolutely. We've seen quite a few oncology product contracts. It's challenging to do contracts, especially with immunotherapy, when you're looking at long-term survival. It’s definitely harder to do, but as Stephen had mentioned, there may be biomarkers. There may be patients who will lose responses early.

There are ways you can be innovative and do these types of contracts. We've started to see this, especially on our payer side, with some manufacturers that are dabbling in these outcome-based contracts, more than value-based contracts.

This concludes our presentation for today. Thanks to Dr. Liu for all his insights and expertise and for sharing all the data on small cell lung cancer.