CME/MOC

Chair's Take: Everything You Need to Know About Biomarkers, Immunotherapies, Combinations, and Other Emerging Approaches for Lung Cancer

PeerView

Chair

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What's Inside

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Activity Information

Media: Enduring Material
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Activity Description
In this activity, Suresh S. Ramalingam, MD, FACP, FASCO, provides a brief recap of the latest practice-changing data informing the use of an expanding arsenal of immune checkpoint inhibitors and combinations in NSCLC, as well as the evolving evidence on immunotherapies, transcription inhibitors, and other novel treatment approaches in SCLC.

Target Audience
This activity has been designed to meet the educational needs of oncologists and other clinicians involved in the management of lung cancer.

Educational Objectives
Upon completion of this activity, participants should be better able to:
- Assess the efficacy/safety profiles and clinical roles of approved and investigational immunotherapies, combinations, and other novel therapies in lung cancer, including NSCLC and SCLC
- Evaluate the roles of predictive biomarkers (PD-L1, TMB) and other relevant disease-, and treatment-related factors as well as patient needs and preferences that should be taken into consideration as part of individualized treatment planning and selection for patients with lung cancer
- Describe key new research directions and clinical trials evaluating cancer immunotherapy biomarkers, rational immunotherapy-based treatment strategies, and other emerging therapies in different subtypes and settings of NSCLC and SCLC to refine, expand, and maximize the use of optimal therapies throughout the disease continuum
- Educate patients with lung cancer and their caregivers about cancer immunotherapies and other treatment options to help them become well-informed participants in their care
- Implement individualized, evidence-based, patient-centric treatment plans for patients with lung cancer

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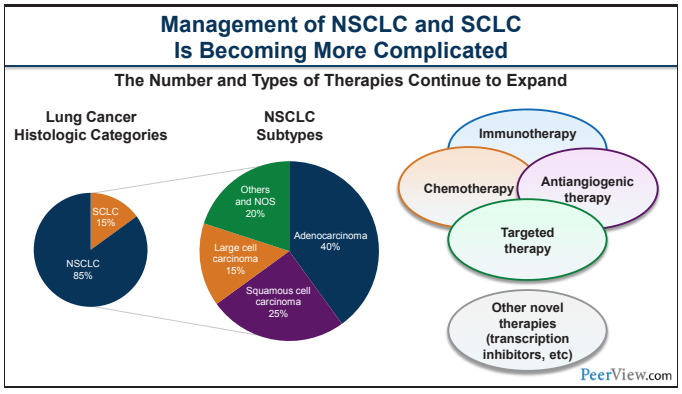
Chair's Take: Everything You Need to Know About Biomarkers, Immunotherapies, Combinations, and Other Emerging Approaches for Lung Cancer

Dr. Ramalingam: Hello. Welcome to this program, "Everything You Need to Know About Biomarkers, Immunotherapy, Combinations, and Other Emerging Approaches for Lung Cancer." I'm Dr. Suresh Ramalingam from the Winship Cancer Institute of Emory University. Today, I would like to discuss with you some of the key updates and advances in lung cancer that were reported at the ASCO 2020 Meeting that concluded recently.



Lung cancer has become a disease where individualized therapies are a reality now. Not too long ago, we were just using chemotherapy for lung cancers, and we used chemotherapy for small cell lung cancer. We used chemotherapy for non–small cell lung cancer.

Over a period of 5 to 10 years in the 2000s, we learned the importance of the histological subtype of lung cancer and slowly ventured into molecular testing for lung cancer, specifically looking at driver mutations, and using that information to make treatment decisions.

So, it was important for us to know that non–small cell lung cancer was defined by the specific histological subtype. We wanted to know whether the patient had adenocarcinoma, squamous cell carcinoma, or large-cell carcinoma, not just non–small cell lung cancer.

And for patients with non–small cell lung cancer, the nonsquamous histology, molecular testing is now considered an important first step as part of the diagnostic workup. This sets the stage for subsequent treatment options for that particular individual patient.

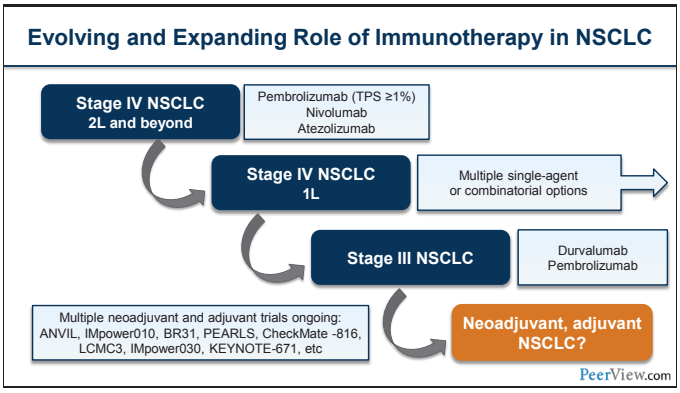
So, we highly recommend the use of molecular testing at the time of diagnosis for a patient with stage IV non–small cell lung cancer with nonsquamous histology, particularly adenocarcinoma.

In squamous cell histology, we're making treatment decisions based on PD-L1 expression level. Sometimes, rarely, patients with squamous cell may have never smoked cigarettes during their lifetime, and for those patients, we do recommend molecular testing because it could represent a mixed-histology tumor, and there may be a possibility that that patient harbors a driver mutation.

For patients who don't have driver mutations, we now move toward immunotherapy as a frontline treatment option. So, we have targeted therapy, chemotherapy, immunotherapy, and some of the other targeted agents, like antiangiogenic therapy, that are also available in our routine clinical practice.

Clearly, the outcomes for lung cancer patients have continued to improve—dramatically in some instances, and modestly in many instances.

How do we take advantage of these technological and research advances to make the best decisions for our patients? To do that, we will review some of the key data that help us put perspective and additional information in the treatment algorithms that are utilized for patients.



And when you look back at how immunotherapy has moved into the treatment landscape for non–small cell lung cancer, it can be described as nothing less than dramatic.

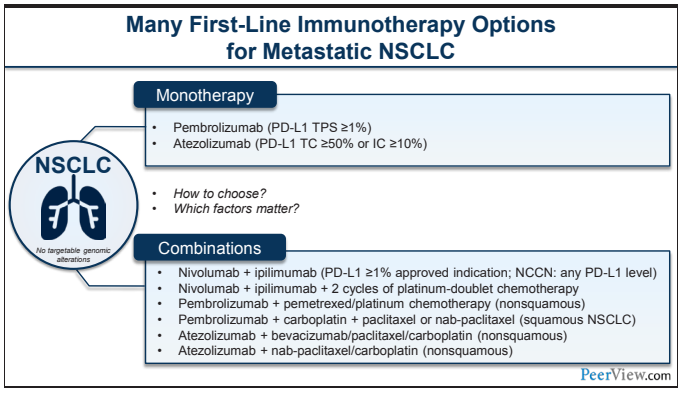
Just about 6 or 7 years ago, we were using PD-1/PD-L1 inhibitors in late lines of therapy as part of clinical trials. Clearly, early on in the course of those phase 1/phase 2 clinical trials, we saw strong activity in a subgroup of patients. And that led to randomized trials—larger trials in the salvage therapy setting for patients with non–small cell lung cancer.

So, once patients had received platinum-based chemotherapy and had undergone disease progression, we used immunotherapy in that setting. And every one of the agents tested, when compared with the standard of care at that time, docetaxel, showed superiority in overall survival. And about a third of the patients seemed to have 3-year, 4-year survival durations, which was very exciting. So, the immune checkpoint inhibitors became available as part of the second-line landscape for patients with non–small cell lung cancer.

And then studies were undertaken to move them into the first-line setting. And a lot of the first-line development focused on patients stratified based on PD-L1 expression—a high PD-L1-expressing tumor versus a low-expressing tumor versus a PD-L1-negative patient population.

And various strategies have been developed for these patients. We now have drugs approved for PD-L1–high patients: pembrolizumab and atezolizumab. And when we say PD-L1 high, we're talking about an expression level of greater than 50%.

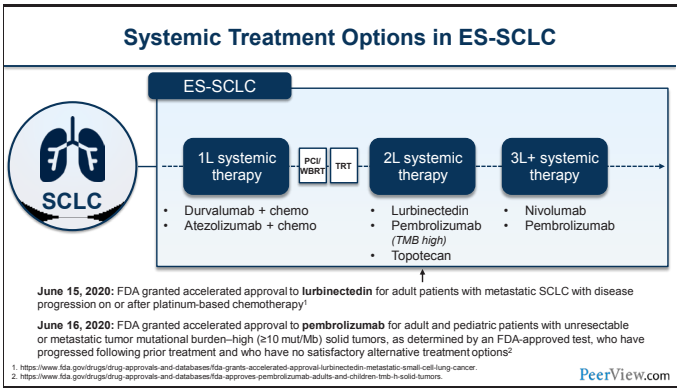
We have combination approaches that have been approved for patients with lower PD-L1 expression, which is less than 49%. And more recently, we have had approval of combination immunotherapy approaches: ipilimumab and nivolumab. So, all of these are going to help us make decisions for our patients as we move forward with treatment of non–small cell lung cancer.



So, in the frontline setting, the standard of care at this point for the high-PD-L1–expressing tumors is monotherapy in most instances. Occasionally, we will give a combination of chemotherapy plus PD-1/PD-L1 inhibition. We'll talk about that.

When you talk about lower-PD-L1–expressing tumors, there are a number of combinations: chemotherapy plus pembrolizumab, chemotherapy plus bevacizumab and atezolizumab, and more recently, ipilimumab and nivolumab are approved. The combination of ipilimumab and nivolumab is also approved in combination with chemotherapy for frontline treatment.

So, a number of different combination approaches are used. The chemotherapy backbone for these patients depends on the specific histological subset if one were to choose the chemotherapy plus immunotherapy approach.



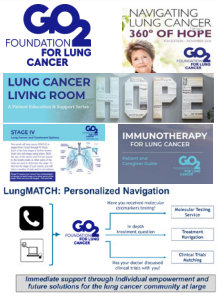
In small cell lung cancer, for a long time, we did not experience much progress. Chemotherapy continued to be the standard of care. But more recently, we have had two immune checkpoint inhibitors approved in combination with chemotherapy in the frontline setting.

The addition of either atezolizumab or durvalumab to a chemotherapy platform in small cell lung cancer patients yields an improvement in overall survival, with a hazard ratio of approximately 0.75 and a median improvement in overall survival by approximately 2 months.

While these are modest advances, they represent the first step forward in the treatment of extensive-stage small cell lung cancer in a very long time. So, we will talk about some of the developments in small cell lung cancer, as well, as we go through this presentation.

Patient/Caregiver Education and Engagement in Care Decisions Is Increasing in Importance

- Considering patient preferences, goals, and values is of increasing importance in lung cancer, because the complexity of the treatment landscape is growing, resulting in more options and the need for more individualized approaches to treatment selection and planning that, in addition to considering the evidence and best practice recommendations, should take into account the needs and preferences of the patients with lung cancer and their caregivers
  - Patient/caregiver education & support → Better informed participants in shared decision-making with their clinical team
- **GO_2 Foundation for Lung Cancer** is partnering with us in this educational series: world's leading patient education, advocacy, and research organization exclusively focused on lung cancer
- Patient-focused free programs, educational materials, and support services comprise the foundation of GO_2 resources that educate, support, empower, and provide hope to those living with lung cancer



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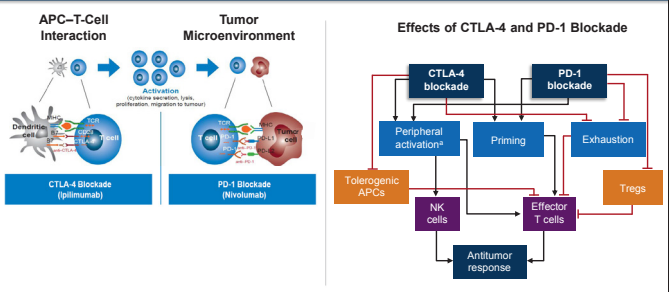
Combining CTLA-4 and PD-1 Axis Inhibitors[1]



[a] NK cells do not express CTLA-4 and are not expected to be activated by CTLA-4 blockade.
1. Rotte A. *J Exp Clin Cancer Res.* 2019;13:38:255.

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As these key advances in lung cancer have happened, it has become critically important to include the patient perspective as we make decisions. We need to take into consideration the specific patient characteristics, patient comorbid conditions, and patient expectations. What is the patient really looking for with regard to a specific treatment approach that's being chosen?

And to do this, it's important that we work together with our patient community, and from that standpoint, we're excited to have on board as a partner in this program, GO_2 Foundation for Lung Cancer. They're a leading voice for advocacy and patient support in the lung cancer journey. They also support research, and they have participated or supported a lot of clinical trials that are being done nationally to develop individualized treatment options for lung cancer.

So, it's a partnership effort between the research community, the physicians and caregivers, and our patient community that will help us deliver effective therapies for our patients.

Selected Highlights From ASCO 2020

What's New and Interesting in Advanced NSCLC?

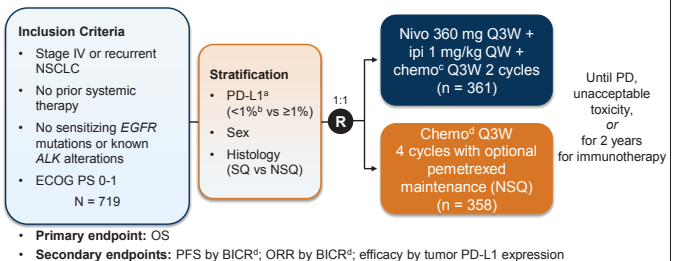
So, now I'm going to switch gears and talk about what we've learned from the recently concluded ASCO 2020 Virtual Scientific Program. We are in extraordinary times, dealing with the pandemic, but we all know that cancer doesn't wait. Cancer needs to be managed, and our research and our patient care continue on without hopefully much of an interruption for a majority of patients. So, these important research advances provide us with timely insights into evolving treatment paradigms in lung cancer.

The first concept I'm going to talk about is the combination of CTLA-4 and PD-1 inhibition, ipilimumab and nivolumab being the combination that's FDA approved. The rationale for using this combination is based on both preclinical and clinical evidence.

In the preclinical setting, we've seen evidence that when we block PD-1 or PD-L1, CTLA-4, another checkpoint, is upregulated. So, when we do combined blockade of CTLA-4 and PD-1, there is a more potent T-cell response against the tumor. After all, our whole purpose of immunotherapy in the context of PD-1 is to reverse T-cell exhaustion and maximize antitumor immunity mediated by cytotoxic CD8 T-cells.

We've also seen the combination of ipilimumab and nivolumab prove to be effective in the treatment of other cancers, like melanoma and renal cell cancer.

CheckMate -9LA: Nivo + Ipi + Platinum Doublet Chemo in 1L Treatment of Stage IV/Recurrent NSCLC[1]



- **Primary endpoint:** OS
- **Secondary endpoints:** PFS by BICR[e]; ORR by BICR[e]; efficacy by tumor PD-L1 expression

Interim database lock: October 3, 2019; minimum follow-up: 8.1 mo for OS and 6.5 mo for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 mo for OS and 12.2 mo for all other endpoints.
[a] Determined by the PD-L1 IHC 28-8 pharmDx assay. [b] Patients unevaluable for PD-L1 were stratified to PD-L1 <1% and capped to 10% of all randomized patients.
[c] NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin. [d] Hierarchically statistically tested.
1. Reck M et al. 2020 American Society of Clinical Oncology Annual Meeting (ASCO 2020). Abstract 9501.

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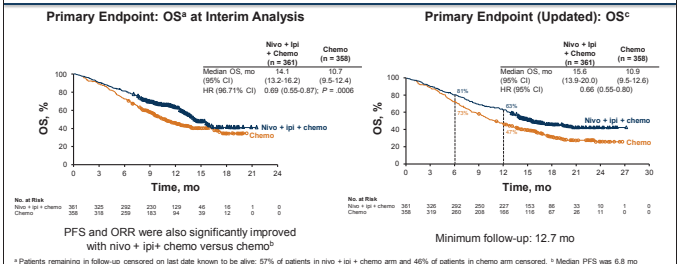
So, based on these lines of evidence and early evidence that this combination worked effectively for non–small cell lung cancer, there have been phase 3 trials conducted. I'm going to talk about two specific trials that were reported at the ASCO 2020 meeting.

The first one is a trial called the CheckMate -9LA trial. In this clinical trial, patients with advanced-stage non–small cell lung cancer who were not previously treated with other treatments—in other words, first-line therapy patients—were randomized to treatment with platinum-based chemotherapy alone or two cycles of platinum-based chemotherapy in addition to ipilimumab and nivolumab.

So, in the experimental arm, patients got histology-based chemotherapy for two cycles. They also received ipilimumab and nivolumab. And once those two cycles were completed, they were continued on with nivolumab and ipilimumab.

This trial was reported recently, and the results have led to the FDA approval. So, let's review the data that led to the FDA approval of this two cycles of chemotherapy plus ipilimumab/nivolumab regimen in the frontline setting.

CheckMate -9LA: Primary Endpoint Results[1]



PFS and ORR were also significantly improved with nivo + ipi+ chemo versus chemo[b]

Minimum follow-up: 12.7 mo

[a] Patients remaining in follow-up censored on last date known to be alive; 57% of patients in nivo + ipi + chemo arm and 46% of patients in chemo arm censored. [b] Median PFS was 6.8 mo vs 5.0 mo, respectively, HR = 0.70 (97.48% CI, 0.57-0.86; P = .0001), and ORR was 38% vs 25%, respectively. P = .0003. [c] Patients remaining in follow-up censored on last date known to be alive; 47% of patients in nivo + ipi + chemo arm and 32% in chemo arm censored. Subsequent systemic therapy received by 31% of patients in nivo + ipi + chemo arm and 40% in chemo arm; subsequent immunotherapy received by 5% and 30%, and subsequent chemo by 29% and 22%, respectively. Among patients with BICR-confirmed disease progression on study, subsequent systemic therapy received by 40% in nivo + ipi + chemo arm and 44% in chemo arm; subsequent immunotherapy received by 7% and 34%, and subsequent chemo by 38% and 24%, respectively.

1. Reck M et al. ASCO 2020. Abstract 9501.

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The primary endpoint for this clinical trial was overall survival. And what we saw in the presentation made by Dr. Reck from Germany is that the chemotherapy plus ipilimumab plus nivolumab regimen resulted in a very robust improvement in overall survival, with a hazard ratio of approximately 0.66. There was almost a 5-month improvement in median overall survival. This benefit was seen both for squamous cell histology and for nonsquamous histology. We also saw improvement in response rate with the chemotherapy plus ipilimumab/nivolumab combination.

CheckMate -9LA: Results Summary[1]

- Met its primary endpoint of OS at the pre-planned interim analysis (HR = 0.69; *P* = .0006)
- Clinically meaningful improvement of all efficacy endpoints was observed and increased with longer follow-up
  - With a minimum follow-up of 12 months, OS benefit was further improved (HR = 0.66)
- Magnitude of benefit with nivo + ipi + 2 cycles of chemo vs chemo was consistent across histologies and all PD-L1 expression levels, including PD-L1 <1% and 1%-49% populations
- No new safety signals were observed for nivo + ipi + 2 cycles of chemo
- Demonstrated that nivo + ipi with a limited course of chemo should be considered as a new 1L treatment option for advanced NSCLC

1. Reck M et al. ASCO 2020. Abstract 9501.

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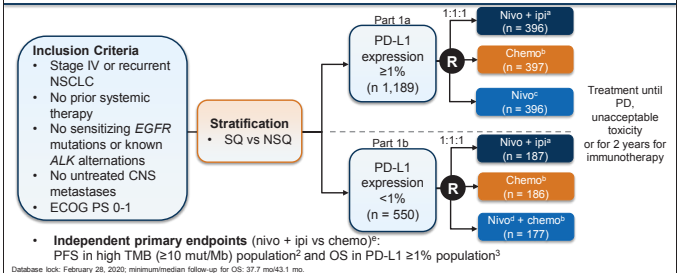
So, the trial met its primary endpoint of overall survival, with a hazard ratio of 0.69 and a *P* value of .0006. And this result was clinically meaningful for our patients. We also saw that the combination was tolerated well. The survival curves separated early and stayed separated throughout. So, this trial has now led to the approval of this combination approach.

One point I want to make also is that this trial included both PD-L1–positive and –negative patients. So, if one were to choose the chemotherapy plus ipilimumab plus nivolumab regimen, it is effective in both PD-L1–positive and –negative patients. I'll come back to talk about where I think this might help in our patient management in a few minutes.

CheckMate -227 Part 1 3-Year Update: Nivo + Ipi vs Platinum Doublet Chemo as 1L Treatment for Advanced NSCLC[1-3]



Database lock: February 28, 2020; minimum/median follow-up for OS: 37.7 mo/43.1 mo.
[a] Nivo (3 mg/kg Q2W) + ipi (1 mg/kg Q6W). [b] NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemo or nivo + pemetrexed maintenance following nivo + chemo; SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin Q3W for ≤4 cycles. [c] Nivo (240 mg Q2W). [d] Nivo (360 mg Q3W).
[e] Both endpoints were met; results were previously reported.
1. Ramalingam SS et al. ASCO 2020. Abstract 9500. 2. Hellmann MD et al. *N Engl J Med.* 2018;378:2093-2104.
3. Hellmann MD et al. *N Engl J Med.* 2019;381:2020-2031.

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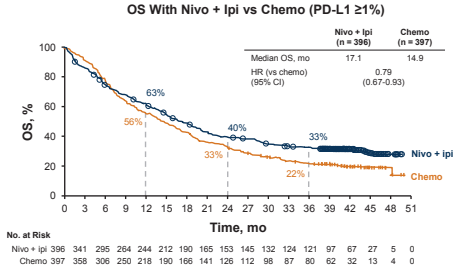
The second abstract I want to talk about is the CheckMate -227 trial. This trial is already familiar to this audience. This was a trial that evaluated the combination of ipilimumab plus nivolumab and compared it to either chemotherapy alone or nivolumab alone in the PD-1 ≥1% population, and in the PD-L1 less than 1% population, the combination of ipilimumab and nivolumab was compared with either chemotherapy alone or chemotherapy plus nivolumab.

We already learned from the publication in *The New England Journal of Medicine* several months ago that the combination of ipilimumab and nivolumab resulted in improved overall survival. The primary endpoint was for the patient population of [PD-L1 expression] ≥1%.

CheckMate -227 Part 1 3-Year Update: OS in PD-L1 ≥1%[1]



1. Ramalingam SS et al. ASCO 2020. Abstract 9500.

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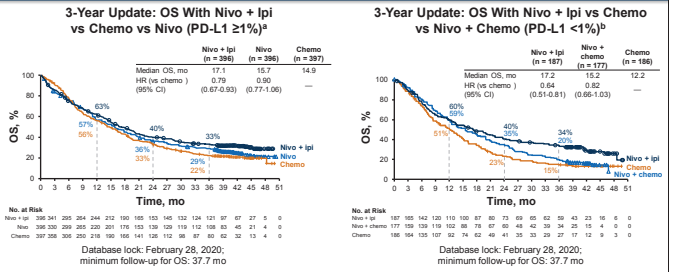
At the ASCO meeting [2020], I had the privilege of reporting the long-term follow-up of this trial. At the time of this report, the median follow-up was about 3 and a half years for patients on the trial. We saw that the 3-year overall survival rate with nivolumab plus ipilimumab was 34%.

CheckMate -227 Part 1 3-Year Update: OS in PD-L1 ≥1% and PD-L1 <1%[1]



[a] Dosages were nivo (3 mg/kg Q2W) + ipi (1 mg/kg Q6W) and nivo (240 mg Q2W). Among patients alive at 3 y, subsequent systemic therapy received by 35% in nivo + ipi arm, 45% in nivo arm, and 76% in chemo arm; subsequent immunotherapies received by 13%, 21%, and 71%; subsequent chemo received by 28%, 33%, and 30%, respectively. [b] Dosages were nivo (3 mg/kg Q2W) + ipi (1 mg/kg Q6W) and nivo (360 mg Q3W) + chemo. Among patients alive at 3 y, subsequent systemic therapy received by 49% in nivo + ipi arm, 38% in nivo + chemo arm, and 78% in chemo arm; subsequent immunotherapies received by 12%, 12%, and 74%; subsequent chemo received by 46%, 35%, and 33%, respectively.

1. Ramalingam SS et al. ASCO 2020. Abstract 9500.

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Other IO/IO Studies From ASCO 2020

CCTG BR.34

- A randomized trial of durvalumab and tremelimumab (DT) ± platinum-based chemo in patients with metastatic squamous or nonsquamous NSCLC[1]
  - Addition of chemo to 1L DT did not improve OS in advanced NSCLC
  - Chemo + DT improved ORR and PFS and was associated with greater toxicity
  - No differential effects were seen by PD-L1 TPS or bTMB

CITYSCAPE

- Primary analysis of a randomized, double-blind, phase 2 study of the anti-TIGIT antibody tiragolumab + atezolizumab vs placebo + atezolizumab as 1L treatment in patients with PD-L1–selected NSCLC[2]
  - Combination showed improvement in ORR and PFS in the ITT population
  - Longer follow-up: treatment benefit remained consistent with primary analysis, with greater magnitude of improvement in PD-L1 ≥50% subgroup
  - Well tolerated, with similar safety profile to placebo + atezolizumab

1. Leighl NB et al. ASCO 2020. Abstract 9502. 2. Rodriguez-Abreu D et al. ASCO 2020. Abstract 9503.

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This was similar for patients with PD-L1 ≥1% and for patients with PD-L1 <1%.

CheckMate -227 Part 1 3-Year Update: Results Summary[1]

- With 3-year minimum follow-up, 1L nivo + ipi continued to provide durable and long-term efficacy benefits vs chemo for patients with advanced NSCLC regardless of PD-L1 expression
  - 3-year OS rates: 33% vs 22% (PD-L1 ≥1%); 34% vs 15% (PD-L1 <1%)
  - Over one-third of all responders[a] remained in response after 3 years with nivo + ipi vs <5% with chemo
- The combination of nivo + ipi continued to provide improved efficacy compared with nivo monotherapy and nivo + chemo in patients with PD-L1 ≥1% and PD-L1 <1%, respectively[b]
- Among patients with PD-L1 ≥1%, 70% of responders at 6 months[c] in nivo + ipi arm were alive 3 years later vs 39% in chemo arm; similar findings were observed in patients with PD-L1 <1% (exploratory post-landmark OS analysis)
- No new safety signals were identified for nivo + ipi with extended follow-up
- This dual immunotherapy regimen is a novel chemo-sparing 1L treatment option for advanced NSCLC

[a] Including all patients who had CR or PR as best overall response based on all data from study follow-up. [b] Descriptive analyses. [c] Including only patients who were in response according to assessment at the 6-month timepoint after randomization.

1. Ramalingam SS et al. ASCO 2020. Abstract 9500.

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One of the other features of the combination of ipilimumab and nivolumab is the duration of response. For patients treated with ipilimumab and nivolumab, the median duration of response was almost 2 years in the PD-L1 ≥1% group and 18 months in the PD-L1 <1% group.

When you compare it in the chemotherapy group, the median duration of response was only about 6 months. So, this suggests that the response you achieve with a combination immunotherapy approach is sustained and durable, and hopefully this is going to lead to improvement at the tail end of the curve, which means improved long-term outcomes for patients with non–small cell lung cancer.

The combination was tolerated well, and most of the autoimmune adverse events were noted in the first 6 months of therapy. Once patients got beyond the 6-month point, the treatments did not result in any additional toxicity in a substantial manner. So, overall, this trial showed to us, again, that the ipilimumab–nivolumab combination was associated with durable long-term benefits.

What else did we learn about immunotherapies in lung cancer? The National Cancer Institute of Canada (NCIC) group evaluated the combination of durvalumab and tremelimumab. This is another PD-L1 and CTLA-4 blockade combination. This was compared with just the immunotherapy combination plus chemotherapy versus immunotherapy combination alone for frontline treatment.

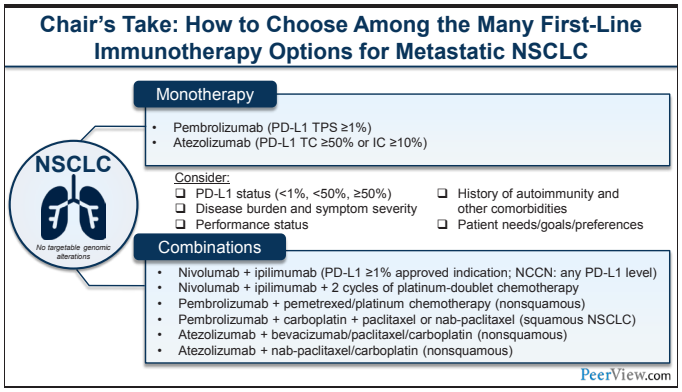
They showed that the addition of two cycles of chemotherapy to durvalumab and tremelimumab did not show an improvement in overall survival. This was a smaller randomized trial. The main question here is the durvalumab–tremelimumab regimen has not been an approved regimen. It was an experimental backbone. So, this study doesn't change in any way how we approach our frontline therapy patients.

What about advances coming down the road? We all know that immunotherapy-based combination approaches are of high interest to broaden the patient population that benefits from immune checkpoint inhibition.

The trial that I found very interesting at ASCO 2020 was the trial known as CITYSCAPE, where the combination included blocking PD-L1 and another checkpoint called TIGIT. A monoclonal antibody against TIGIT was combined with atezolizumab in frontline treatment of non–small cell lung cancer. The comparator group got atezolizumab therapy.

This was a randomized phase 2 trial, and the signal appears to be that, for patients with high PD-L1 expression, ≥50%, the combination of the anti-TIGIT antibody and anti–PD-L1 antibody, atezolizumab, was associated with favorable outcomes.

The benefit of the combination was not that pronounced, and, in fact, was relatively minimal in the PD-L1 less than 50% group. So, I anticipate that these results will lead to larger definitive trials in an enriched patient population to see if a combination immunotherapy blockade approach will result in improved outcomes for patients with advanced-stage lung cancer.



So, going back and wrapping this all up, when I have a patient in my clinic with stage IV non–small cell lung cancer, what is my treatment algorithm?

Well, this is what I do. First of all, I strongly recommend NGS profiling for every patient with nonsquamous non–small cell lung cancer. And I suggest that we wait until results are back as much as possible before we start treatment.

If the patient is really sick and has to be started on some therapy, I would just start with chemotherapy alone, not chemotherapy with immunotherapy for the first cycle. Once the NGS results are back, if they have a targetable driver mutation, they should get targeted therapy. And I want to remind our audience that there are seven FDA-approved targeted therapy approaches for various targets in non–small cell lung cancer. So, that's important.

For patients who don't have a driver mutation, we look at PD-L1 expression. For those with PD-L1 expression greater than 50%, I prefer use of immune checkpoint inhibition alone.

If the patient is very symptomatic and has bulky disease and their performance status is declining rapidly, in that situation, I would add chemotherapy to pembrolizumab or atezolizumab.

For patients with less than 50% PD-L1 expression or negative PD-L1, until now, chemotherapy plus pembrolizumab or chemotherapy plus bevacizumab plus atezolizumab has remained our frontline approach. Now, with the FDA approval of ipilimumab and nivolumab, that's another effective approach.

With ipilimumab and nivolumab, the case to be made for their consideration is the durability of response and the ability to spare patients from chemotherapy so you have an additional line of therapy. When patients progress on ipilimumab plus nivolumab, you can go to a platinum doublet, particularly in the PD-L1–negative group of patients—the hazard ratio for ipilimumab plus nivolumab is 0.62—so that approach merits our consideration.

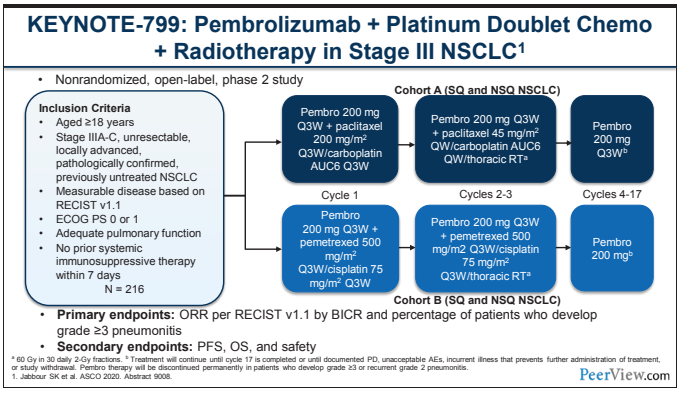
If you're going to select ipilimumab plus nivolumab, and if the patient has very bulky or symptomatic disease, then one should consider the CheckMate -9LA approach of giving two cycles of chemotherapy.

Now, these are for patients with good performance status. Obviously, we have to take into consideration the patient's specific comorbid conditions, whether they have prior autoimmune conditions, whether there are any other competing causes of mortality for that patient that would affect our decision to go with a full-court press approach.

Regardless, the key is tailoring these exciting approaches to the patient sitting in front of us so we can get the best outcomes for our patients.

What about stage III disease? Well, these are patients that have involvement of the mediastinal nodes, are contralateral, have nodal involvement, or have direct invasion of the tumor into a major organ. Now, a part of stage III patients are surgically resectable. For the remainder of stage III, we use concurrent chemoradiotherapy as the standard approach.

More recently, based on the PACIFIC trial, durvalumab has been approved as consolidation therapy after completion of chemoradiation. So, the current standard of care for stage III unresectable disease is platinum-based chemotherapy with concomitant radiation, and for patients who achieve benefit with that approach, to go on to receive 1 year of consolidation durvalumab. With that approach, we've seen improvement in overall survival and a 3-year survival rate of approximately 55%.



What is the role of some of the other checkpoint inhibitors in this space? We learned about the KEYNOTE-799 trial at ASCO 2020 this year. In this trial, pembrolizumab was given with concurrent chemoradiation and platinum-based chemotherapy for stage III disease. Patients were surgically unresectable. Patients with both squamous and nonsquamous histology were included in this study. Pembrolizumab was administered at its usual dose.

KEYNOTE-799: Results Summary[1]

- Pembro + cCRT shows promising antitumor activity in patients with unresectable, locally advanced stage III NSCLC in phase 2 study
  - ORR in both cohorts exceeded 50%
    - Cohort A: 67.0% (58.9%-74.3%)
    - Cohort B: 56.6% (44.4%-68.2%)
  - Estimated response duration was ≥6 months for most patients with a response
- Incidence of AEs among patients who received pembro + cCRT was consistent with the established toxicity profiles for cCRT for stage III NSCLC and pembro monotherapy
  - Incidence of grade ≥3 pneumonitis was 8.0% in cohort A and 5.5% in cohort B
  - Observed rates of grade ≥3 pneumonitis were within the expected range for immunotherapy combined with CCRT

1. Jabbour SK et al. ASCO 2020. Abstract 9008.

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What we were encouraged by is the safety was very good. There was no additional toxicity with adding pembrolizumab to platinum-based chemotherapy and radiation. The response rates were approximately 65% in the nonsquamous group and approximately 57% in the squamous group of patients, suggesting that the combination is active.

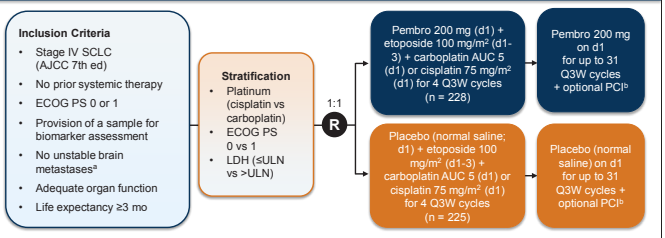
Now, there will be definitive trials. We've seen the value of pembrolizumab in another randomized phase 2 study in the consolidation setting. So, this study shows us that pembrolizumab is potentially active in the stage III setting and merits further investigation.

Selected Highlights From ASCO 2020

What's New and Interesting in SCLC?

Now, let's switch gears and talk about small cell lung cancer. I started off this session talking about the key advances in small cell lung cancer recently. We saw that durvalumab and atezolizumab are approved in the frontline setting.

KEYNOTE-604: Pembrolizumab or Placebo + Etoposide and Platinum Chemo as 1L Therapy for ES-SCLC[1]



- **Dual primary endpoints:** PFS per RECIST v1.1 by BICR and OS
- **Secondary endpoints:** ORR and DOR per RECIST v1.1 by BICR and safety

[a] All brain-targeted treatment completed ≥14 d before starting study, no new or enlarging brain lesions, and neurologically stable without steroids for ≥7 d before starting study. [b] Participants with CR or PR after cycle 4 could receive up to 25 Gy of PCI in 10 fractions at investigator's discretion; PCI was to begin within 2-4 wk and no later than 6 wk after last dose of cycle 4; study treatment could continue during PCI.

1. Rudin CM et al. ASCO 2020. Abstract 9001.

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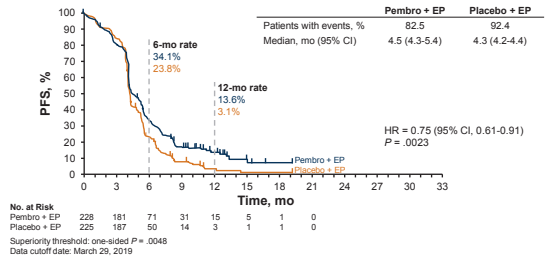
At ASCO [2020], we learned about a phase 3 trial that involved adding pembrolizumab to chemotherapy for frontline therapy. The results were reported by Dr. Charlie Rudin from Memorial Sloan Kettering Cancer Center.

This was designed in a very similar manner to the other trials that led to the approval of durvalumab and atezolizumab. So, patients with extensive-stage small cell lung cancer that had not received any prior chemotherapy were randomized to cisplatin or carboplatin with etoposide in combination with pembrolizumab or placebo.

KEYNOTE-604: PFS, ITT (IA2)[1]



Superiority threshold: one-sided *P* = .0048. Data cutoff date: March 29, 2019.
1. Rudin CM et al. ASCO 2020. Abstract 9001.

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The trial met its PFS endpoint. The median PFS was improved with the addition of pembrolizumab to chemotherapy; the hazard ratio was 0.75, and the *P* value was statistically significant.

KEYNOTE-604: Results Summary[1]

- Adding pembro to EP as 1L therapy for ES-SCLC significantly improved PFS (HR = 0.75; *P* = .0023; significance threshold *P* = .0048)
- The HR for OS favored pembro + EP, but the significance threshold was missed (HR = 0.80; *P* = .0164; significance threshold *P* = .0128)
- Pembro + EP provided durable responses in a subset of participants
- Pembro + EP safety profile was as expected and manageable
- Data support the benefit of pembro and the value of immunotherapy in SCLC

1. Rudin CM et al. ASCO 2020. Abstract 9001.

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The median overall survival, however, favored pembrolizumab but did not meet statistical significance. The hazard ratio was 0.8. The safety profile was good, and the responses were durable for a subset of the patients.

So, even though, statistically, the trial did not meet the overall survival endpoint, in my view, the results with pembrolizumab and chemotherapy are not very different from what we have seen with chemotherapy plus durvalumab or chemotherapy plus atezolizumab.

Phase 2 ECOG-ACRIN EA5161: Etoposide and Platinum Chemo ± Nivo as 1L Therapy for ES-SCLC[1]

- Patients who initiated study therapy:
  - Nivolumab + chemo significantly improved PFS vs chemo, with HR = 0.68 (95% CI, 0.48-1.00; *P* = .047); mPFS 5.5 vs 4.7 mo
  - OS improved with nivolumab + chemo vs chemo, with HR = 0.73 (95% CI, 0.49-1.11; *P* = .14); mOS 11.3 vs 9.3 mo
- ITT population:
  - Nivolumab + chemo significantly improved PFS vs chemo alone, with HR = 0.65 (95% CI, 0.46-0.91; *P* = .012); mPFS 5.5 vs 4.6 mo
  - OS improved with nivolumab + chemo vs chemo, with HR = 0.67 (95% CI, 0.46-0.98; *P* = .038); mOS 11.3 vs 8.5 mo
- Combination of nivolumab + chemo was well tolerated with manageable toxicities

1. Leal TA et al. ASCO 2020. Abstract 9000.

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We also saw the results from another trial conducted by ECOG-ACRIN, which was a randomized phase 2 study where nivolumab was given in combination with chemotherapy for first-line therapy. In this trial, patients received either chemotherapy alone or chemotherapy plus nivolumab, and then nivolumab was continued as maintenance.

The hazard ratio for PFS in this trial was approximately 0.66, and interestingly, even the overall survival hazard ratio was 0.66. This was only a randomized phase 2 trial with 150 patients, but the efficacy endpoint favored the nivolumab plus chemotherapy approach, both in terms of PFS and overall survival.

So, when you put the whole landscape of chemotherapy plus immunotherapy trials together, now we're beginning to see some improvement in longer-term survival. The 2-year overall survival rate with the chemotherapy plus immunotherapy approach across these trials is approximately 22%-23%. This is an improvement over what we had with chemotherapy alone.

The median overall survival we're seeing now is on the order of about 11 to 12 months with the addition of chemoimmunotherapy. With chemotherapy alone, the median overall survival is still in the 8-to-10-months ballpark. So, this, I think, is an important step forward for the treatment of patients with extensive-stage small cell lung cancer.

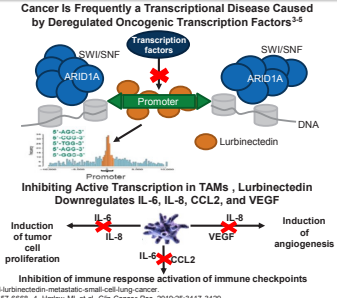
So, in frontline treatment, when we select patients, we do not use PD-L1 expression level to select who should get chemotherapy plus pembrolizumab, chemotherapy plus atezolizumab, or chemotherapy plus durvalumab. It's given regardless of PD-L1 expression.

Clearly, we need to develop biomarkers to help select therapy for those patients with small cell lung cancer that benefit from immune checkpoint inhibition.

Now, I also want to remind folks that pembrolizumab and nivolumab are approved in small cell lung cancer in the third-line setting.

Lurbinectedin in SCLC

- Topotecan was the only FDA approved therapy for patients with platinum-sensitive SCLC in the 2L setting
- Lurbinectedin now approved for adult patients with mSCLC with disease progression on or after platinum-based chemotherapy[1]
  - Selective inhibitor of oncogenic transcription programs on which SCLC is dependent
  - Demonstrated safety and efficacy in a phase 2 basket trial[2]
  - Results awaited from phase 3 ATLANTIS trial



1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-lurbinectedin-metastatic-small-cell-lung-cancer.
2. Trigo J et al. *Lancet Oncol*. 2020;21:645-654. 3. Harlow ML et al. *Cancer Res*. 2016;76:6657-6668. 4. Harlow ML et al. *Clin Cancer Res*. 2019;25:3417-3429.
5. Belgiovine C et al. *Br J Cancer*. 2017;117:628-638.

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Now, after first-line therapy for extensive-stage small cell lung cancer, we've had very limited second-line options. That has been a major challenge to the field. Topotecan has been the only FDA-approved agent, but there are limitations with topotecan.

We know that it doesn't extend survival. It's only active for patients with chemosensitive disease, which means only patients who benefit from frontline chemotherapy have some evidence of benefit with topotecan. It is also associated with a high level of myelosuppression.

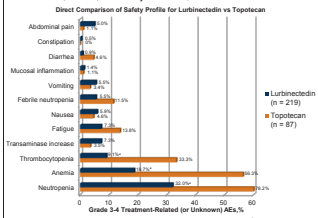
So, for all these reasons, physicians have used topotecan with a great degree of reluctance in the second-line setting, and there have been a number of ongoing efforts to develop effective options in the second-line setting.

One promising drug that I want to talk about today is lurbinectedin. Lurbinectedin is an inhibitor of transcription programs. This drug has now been studied in the second-line setting of small cell lung cancer. There have been a couple of trials.

What we have seen with lurbinectedin is that in the second-line setting, the objective response rate is approximately 35%. In the chemosensitive patient population, the response rates can be as high as 45%, and in the chemotherapy-refractory patients, the response rate can be approximately 25%. Now, these are data from single-arm phase 2 clinical trials, but these results are interesting enough, and those have led to additional evaluation.

CORAIL and Phase 2 Basket Trial Results: Pooled Safety Analysis of Single-Agent Lurbinectedin vs Topotecan[1]

- Lurbinectedin has a predictable and manageable safety profile; most common AEs were grade 1/2 fatigue, nausea, and vomiting
- TRAEs (L/T): dose reductions, 22.9%/48.3%; delays, 25.8%/52.9%; grade ≥3 SAEs, 15.0%/32.2%; discontinuations, 3.2%/5.7%, deaths, 1.3%/1.5%; G-CSF use, 23.8%/70.1%; and transfusions, 15.9%/52.9%
- Significant safety advantage observed when lurbinectedin was compared with topotecan in CORAIL in terms of hematologic toxicities; with the limitations of indirect comparisons, in the pooled safety analysis, fewer lurbinectedin-treated patients had severe hematological toxicities, SAEs, dose adjustments, treatment discontinuations, and use of supportive treatments than topotecan-treated patients



Treatment-Related (or Unknown) AE	Topotecan, % (n = 87)	Lurbinectedin, % (n = 219)
AEs of any grade	98.9	91.8
Grade ≥3	89.7	47.9
Grade ≥4	59.8	19.2
SAEs any grade	32.2	20.5
Grade ≥3 SAE	32.2	18.7
Dose delays because of AEs	52.9	25.6
Dose reductions because of AEs	48.3	16.4
Discontinuation	6.9	4.6
Deaths because of AEs	1.1	1.4
Supportive treatment		
G-CSF (secondary prophylaxis or therapeutic)[a]	70.1	24.7
RBC transfusions[b]	52.9	18.3
Platelet transfusions[b]	14.9	3.2
EPO[b]	6.9	1.8

[a] Statistically significant lower incidence of severe AEs for lurbinectedin. [b] Statistical significant lower frequency of supportive treatments.
1. Leary A et al. ASCO 2020. Abstract 3635.

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At ASCO [2020], we saw a pooled analysis that looked at efficacy and safety of single-agent lurbinectedin and compared it with a comparable set of patients treated with topotecan.

And in this trial, we saw that lurbinectedin had a safety profile that was manageable. Grade 1 and 2 nausea, fatigue, and vomiting are some of the common side effects we've seen with lurbinectedin in these clinical trials. With appropriate supportive care, treatment can be continued.

Thank You!

So, hopefully that has been useful to you. We hope to continue to bring you these advances in lung cancer through various meetings such as this. I want to thank you for joining me today, and I wish you the very best.

Narrator: This activity is jointly provided by Medical Learning Institute, Inc., GO_2 Foundation for Lung Cancer, and PVI, PeerView Institute for Medical Education.

CME/MOC

Chair's Take: Everything You Need to Know About Biomarkers, Immunotherapies, Combinations, and Other Emerging Approaches for Lung Cancer

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