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Advanced/Metastatic NSCLC Treatment:
Advancements for Patients Without Targetable Activating Mutations

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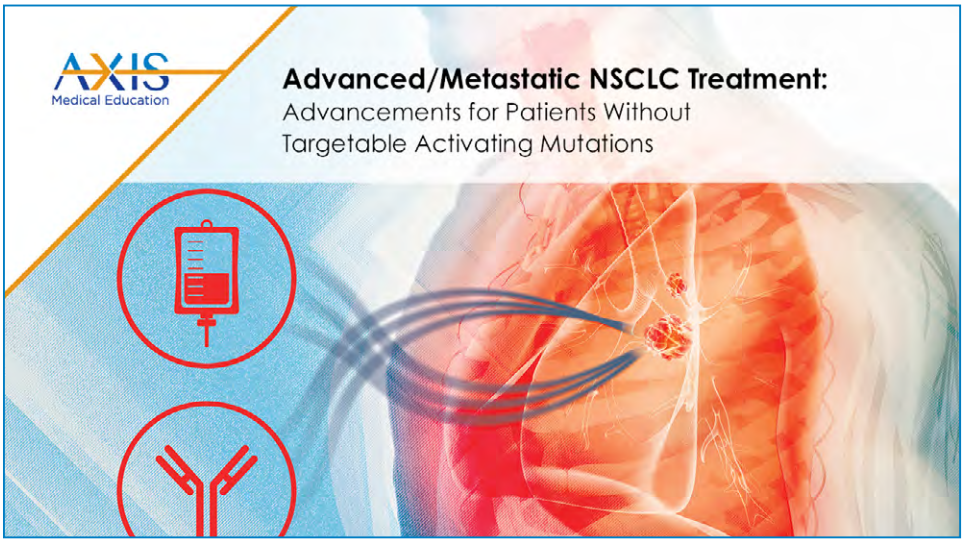
Advanced/Metastatic NSCLC Treatment: Advancements for Patients Without Targetable Activating Mutations

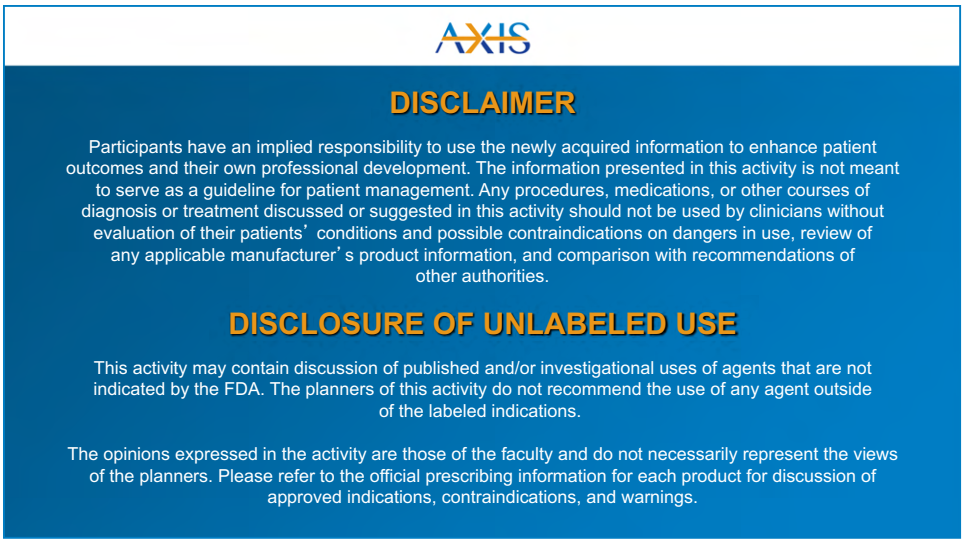
Karen L. Reckamp, MS, MD | Mark A. Socinski, MD | Helena Yu, MD



Karen L. Reckamp, MS, MD:

Hello, and welcome to this educational activity, Advanced/Metastatic NSCLC Treatment: Advancements for Patients Without Targetable Activating Mutations.

I am Dr. Karen Reckamp, Professor of Medicine at the City of Hope Comprehensive Cancer Center, in Duarte, California. I am joined today by Dr. Mark Socinski, Executive Medical Director at the Advent Health Cancer Institute in Orlando, Florida; and Dr. Helena Yu, Assistant Attending Physician at Memorial Sloan Kettering Cancer Center in New York, New York.



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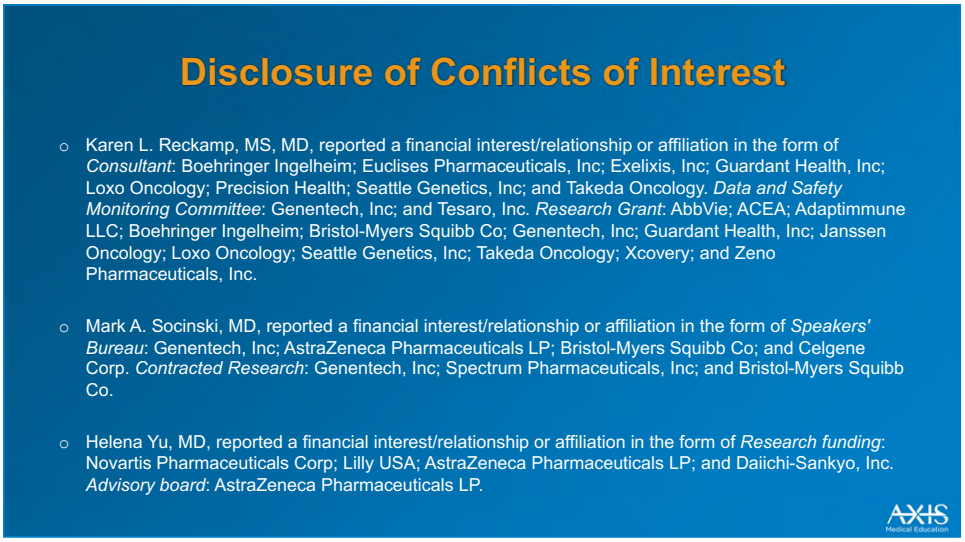

- Here is our financial disclosure information for you to review.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Identify first-line therapy options for patients with advanced non–small cell lung cancer without targetable activating mutations based on clinical trial data and guideline recommendations, including platinum-based chemotherapy, and single-agent immune checkpoint inhibitor or in combination with chemotherapy
- Integrate recommended subsequent chemotherapy and immunotherapy options for the treatment of patients with advanced non–small cell lung cancer without targetable activating mutations
- Analyze recent clinical trial results supporting the use of chemotherapy and immunotherapy combination regimens for patients with advanced NSCLC without targetable activating mutations
- Discuss how emerging immunotherapies and chemotherapy combination regimens may be incorporated into future clinical practice

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Here are the learning objectives for this activity. Through case examples, we will evaluate the most recent clinical data and provide evidence-based updates and expert insights on first-line treatment of advanced non–small cell lung cancer without targetable activating mutations. We will also discuss how we discern the best treatment approach and use of chemotherapy and immunotherapy for these patients. So let's discuss our first case.

Approved First-Line Therapy: PD-1/PD-L1 Inhibitors

PD-1/PD-L1 Inhibitor	Trial	Indication	Appropriate for Patient	Rationale for Patient
Pembrolizumab (PD-1)	KEYNOTE-024	as a single agent for the first-line treatment of patients with **PD-L1–expressing (TPS ≥50%)** metastatic NSCLC with no *EGFR* or *ALK* genomic tumor aberrations	X	PD-L1, 0%
	KEYNOTE-042	as a single agent for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors **express PD-L1 (TPS ≥1%)** as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations	X	PD-L1, 0%
	KEYNOTE-021 KEYNOTE-189	in combination with pemetrexed and platinum chemotherapy as first-line treatment of patients with metastatic **nonsquamous** NSCLC with no EGFR or ALK genomic tumor aberrations	X	Squamous cell carcinoma
	KEYNOTE-407	in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of patients with metastatic **squamous** NSCLC	✓	Stage IV squamous cell carcinoma PD-L1, 0%
Atezolizumab (PD-L1)	IMpower150	in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic **nonsquamous** NSCLC with no EGFR or ALK genomic tumor aberrations	X	Squamous cell carcinoma

PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.
FDA News Release, 2016, 2017, 2018, 2019.

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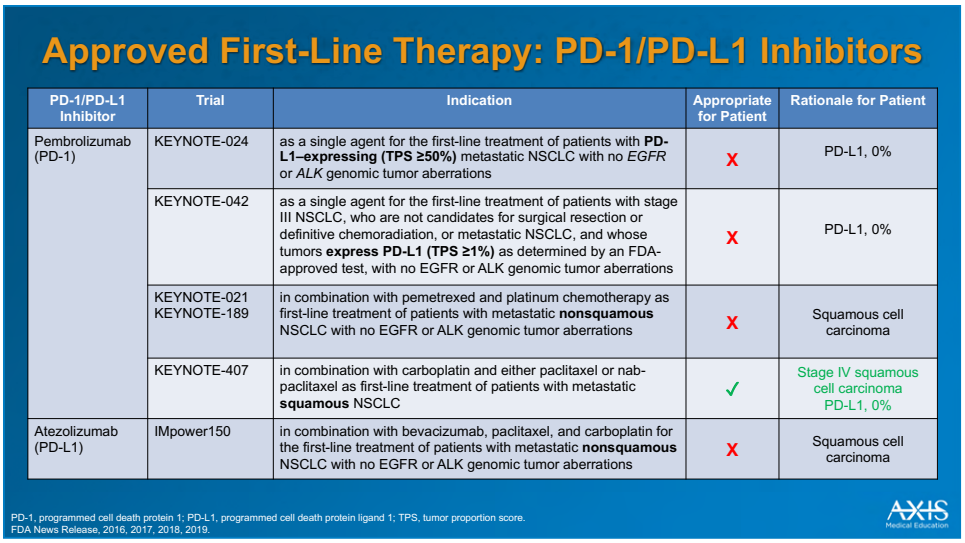
We have a 60-year-old woman who is diagnosed with stage IV squamous cell carcinoma of the lung, with metastatic disease to the left adrenal gland, and at least 3 hepatic metastases measuring greater than 2 cm. Other findings include a PD-L1 [programmed cell death protein ligand 1] tumor expression of 0% and a tumor mutational burden of 2 mutations per megabyte. Dr. Socinski, how would you treat this patient?

Mark A. Socinski, MD: This is a relatively young patient with lung cancer, so we're going to assume her performance status is excellent. We have confidence in her histologic diagnosis being squamous cell. Most of us would choose a platinum doublet; and in squamous, my first choice is a platinum plus a taxane. We can debate what the best taxane may be in that setting.



Then, based on the results of the recent KEYNOTE-407 trial, which grafted pembrolizumab onto that backbone and demonstrated a very positive survival advantage in this population—that would be my recommendation. What we've done in the past couple years is take all of our platinum-based doublets that we all used as standard therapy in the first-line setting and we would sequence to second-line immunotherapy. All of the original immunotherapy agents were approved after platinum failure.

What we've done is take second-line therapy, graft it onto the first-line therapy, and all of these trials have been positive, and some of them wildly positive. So, that's changed the standard of care—grafting these things together. In a patient like this, that would be my go-to recommendation, assuming there are no obvious contraindications to immunotherapy.

Reckamp: Can you talk a little bit about the rationale for combining chemotherapy and immunotherapy?

Socinski: Much of it remains a mystery. One of the lessons that we learned from KEYNOTE-024 is that there might be something magical about giving immunotherapy up-front.

If you look at KEYNOTE-024, which gave patients with greater than 50% PD-L1 expression pembrolizumab versus chemotherapy, I probably would've bet that if those patients on chemotherapy transitioned to pembrolizumab in second line, that their survival time would've increased if they got pembrolizumab, but it didn't.

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Atezolizumab (PD-L1)	IMpower150	in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic **nonsquamous** NSCLC with no EGFR or ALK genomic tumor aberrations	X	Squamous cell carcinoma

PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.
FDA News Release, 2016, 2017, 2018, 2019.

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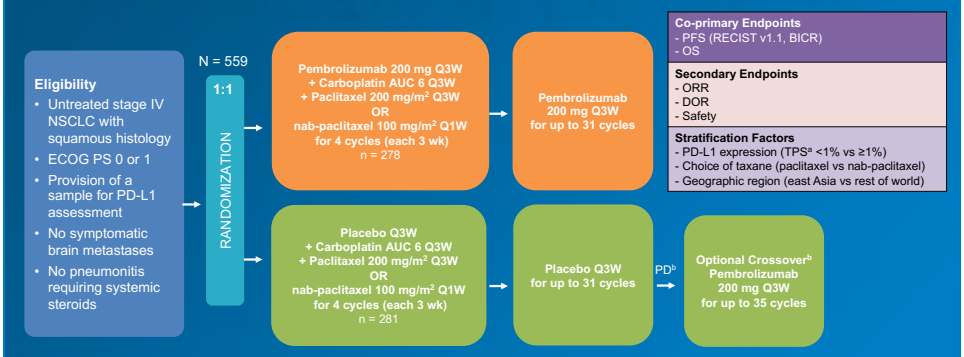
So is there something magical about early on in the course of the disease, is the immune system more on? And when you're using it with chemotherapy, is there an advantage if you see cytotoxic cell death and other immunologic mechanisms that may enhance the effect of immunotherapy in that setting?

Those were all theoretical sorts of reasons. The clinical data are incontrovertible. I mean, all of these trials, particularly KEYNOTE-407, was a striking benefit in the combination arms.

Reckamp: Can you tell us a little bit about the KEYNOTE-407 trial?

KEYNOTE-407: Carboplatin/Taxane +/- Pembrolizumab



[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
[b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met. Taxane choice up to treating physician.
BICR, blinded independent central radiologic review; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; PD-L1, programmed cell death protein ligand 1; Q3W, every 3 weeks; TPS, tumor proportion score.
Paz-Ares et al. *N Engl J Med*. 2018;379:2040-2051.

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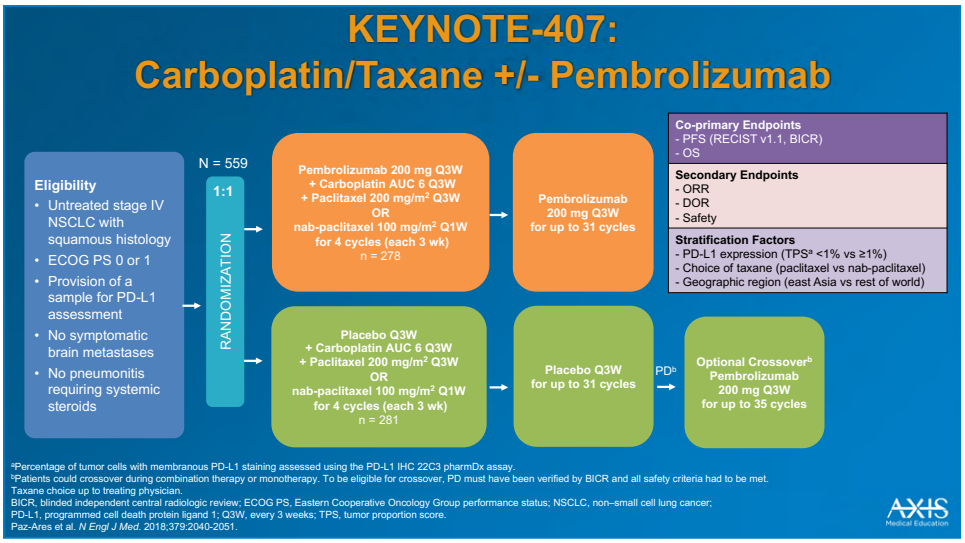
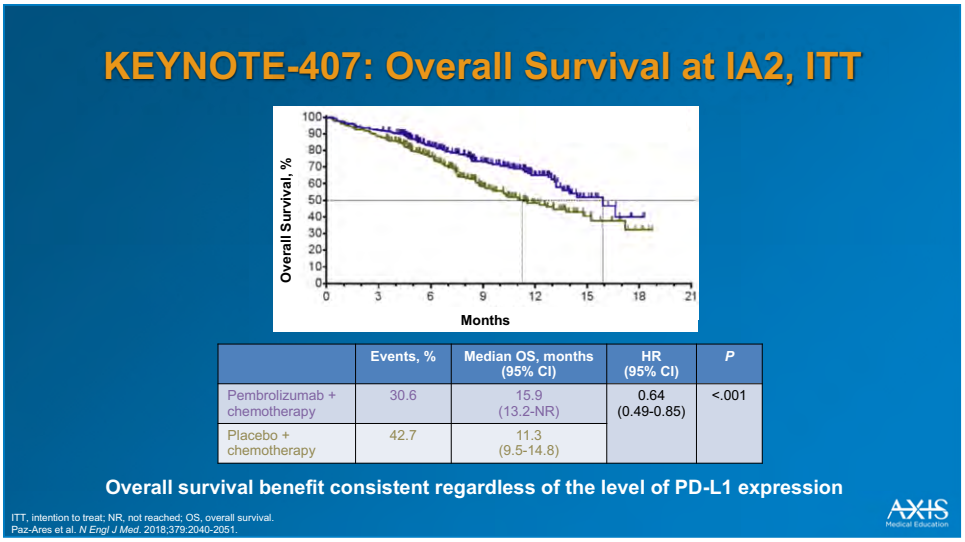
Socinski:

Yes. KEYNOTE-407 was a randomized phase 3 trial. Patients had to have untreated stage IV disease with squamous histology, good performance status, and a sample for PD-L1 assessment. No symptomatic brain metastases were allowed, and there were the usual contraindications for immunotherapy; specifically, no pneumonitis that required systemic steroids.

The randomization, the control arm, was a standard carboplatin, physician's choice of either solvent-based paclitaxel or nab-paclitaxel. It was a 60-40 split; 60% with solvent-based and 40% with nab-paclitaxel. They got 4 cycles. The investigational arm simply grafted pembrolizumab onto that at standard doses and schedule. There was a maintenance phase for those who didn't have disease progression, either placebo or pembrolizumab.



- Patients on the control arm were allowed to cross over at the time of disease progression. Primary endpoints were both progression-free survival as well as overall survival. And stratification factors were PD-L1 expression status, choice of the taxane, as well as geographic region.



	Events, %	Median OS, months (95% CI)	HR (95% CI)	*P*
Pembrolizumab + chemotherapy	30.6	15.9 (13.2-NR)	0.64 (0.49-0.85)	<.001
Placebo + chemotherapy	42.7	11.3 (9.5-14.8)		

- As you see on the Kaplan-Meier curve, these curves separate by about 3 months, and the hazard ratio for overall survival is 0.64. Obviously, both statistically significant as well as clinically significant when you look at these curves. The median survival for the control arm was 11.3 months, which is typically what we see with platinum-based doublets. And then, nearly 16 months, 15.9 months for the investigational arm of this trial. So, a pretty impressively positive trial.

KEYNOTE-407: Adverse Events

Event (any Grade)	Pembrolizumab Combination (N = 278)	Placebo Combination (N = 280)
Any event	273 (98.2%)	274 (97.9%)
Event leading to discontinuation of all treatment components	37 (13.3%)	18 (6.4%)
Event leading to discontinuation of any treatment component	65 (23.4%)	33 (11.8%)
Event leading to death	23 (8.3%)	18 (6.4%)
Attributed to a trial regimen by an investigator	10 (3.6%)	6 (2.1%)
Select events occurring in ≥15% of patients in either group		
Anemia	148 (53.2%)	145 (51.8%)
Alopecia	128 (46.0%)	102 (36.4%)
Neutropenia	105 (37.8%)	92 (32.9%)
Nausea	99 (35.6%)	90 (32.1%)
Thrombocytopenia	85 (30.6%)	65 (23.2%)
Diarrhea	83 (29.9%)	65 (23.2%)
Decreased appetite	68 (24.5%)	82 (29.3%)
Constipation	64 (23.0%)	61 (21.8%)

Paz-Ares et al. *N Engl J Med*. 2018;379:2040-2051.

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Toxicity is shown on the slide here. I commented earlier that we've grafted our former second-line standard therapies with the 3 immunotherapies onto our chemotherapy backbones. And the take-home message is that if you give immunotherapy with our standard chemotherapy regimens, it really doesn't change the toxicity of the chemotherapy. And chemotherapy doesn't seem to change the toxicity of the immunotherapy.

You have to be prepared to deal with more toxicity because you're giving a greater number of drugs. But there's nothing really unusual from the chemotherapy point of view or nothing really unusual from the immunotherapy point of view. You just have to manage them together.

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	KEYNOTE-042	as a single agent for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors **express PD-L1 (TPS ≥1%)** as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations • Nonsquamous OS HR in TPS ≥1%: 0.86	✓	Stage IV nonsquamous cell carcinoma PD-L1 50%
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Atezolizumab (PD-L1)	IMpower150	in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic **nonsquamous** NSCLC with no EGFR or ALK genomic tumor aberrations	✓	Stage IV nonsquamous cell carcinoma

NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.
FDA News Release, 2016, 2017, 2018, 2019.

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Reckamp:
Thank you, Dr. Socinski. And Dr. Yu, do you agree or have anything else to add to this scenario?

Helena Yu, MD: Mark really comprehensively went over KEYNOTE-407, so I don't have a whole lot to add. I would just say that in some ways, I do find squamous cell lung cancer a little bit more challenging to treat. There are fewer options, and we'll go over some of the options for adenocarcinoma so to counterpoint. And just to note that the survival, both the progression-free survival as well as the overall survival, are numerically lower than those with adenocarcinoma. There is less ability to pick out or have predictive markers to figure out who really responds. That's a challenge.

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NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.
FDA News Release, 2016, 2017, 2018, 2019.

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Socinski: What we know about the squamous population, they tend to be a little older, they tend to be much more male dominated. It's a more smoking-related disease than the nonsquamous population. You tend to have more comorbidities, so your observations about the overall survival experience for this group of patients isn't as good as we see in the nonsquamous population. It could be because of all of those factors.

Yu: In adenocarcinoma, there are some emerging, genomic biomarkers that can help us figure out what the best treatment is. We have yet to find that in squamous cell.

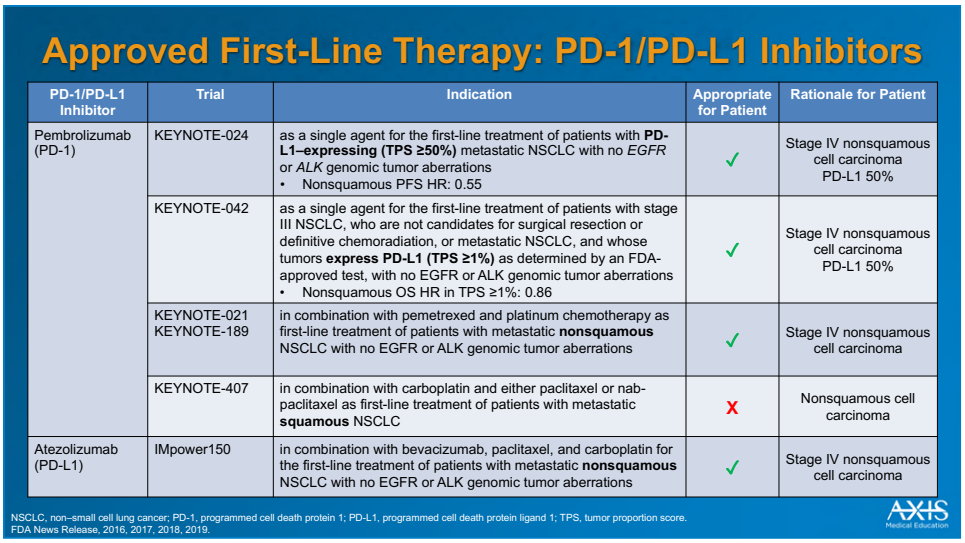
Socinski: We're still waiting.

Reckamp: And is there anything that makes you choose the solvent-based paclitaxel versus nab-paclitaxel in your patients?

Yu: I tend to agree with Mark, where I do end up choosing the nab-paclitaxel more frequently, although not always. In terms of patient tolerability and some of the toxicities, including neuropathy, it's a little bit easier to tolerate for patients.

Socinski: Now we had at World Lung, last year in Toronto, a retrospective, I believe it was an unplanned analysis, although it was a stratification factor, where they looked at the survival based on what taxane you received, solvent-based versus nab-paclitaxel.

There was a little bit of a trend in favor of nab-paclitaxel for overall survival compared to solvent-based paclitaxel. To your point, most of the people that I talk to think that there's a toxicity advantage, although there's also an inconvenience disadvantage because it's a weekly infusion.



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NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.
FDA News Release, 2016, 2017, 2018, 2019.

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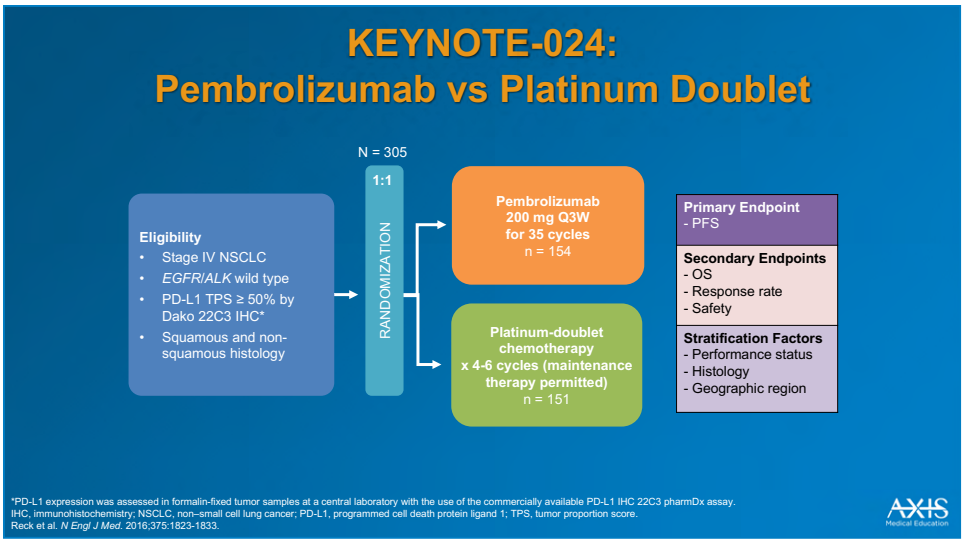
You can probably play it both ways; however, I find myself using the nab approach more often than not.

Reckamp: I agree. I mean, these data from the KEYNOTE-407 are pretty straightforward to help you decide whether to use chemotherapy and immunotherapy for squamous cell non–small cell lung cancer. So, we want better therapies. We still have a ways to go with squamous cell and definitely for targeted therapy. But for this case, we all agree.

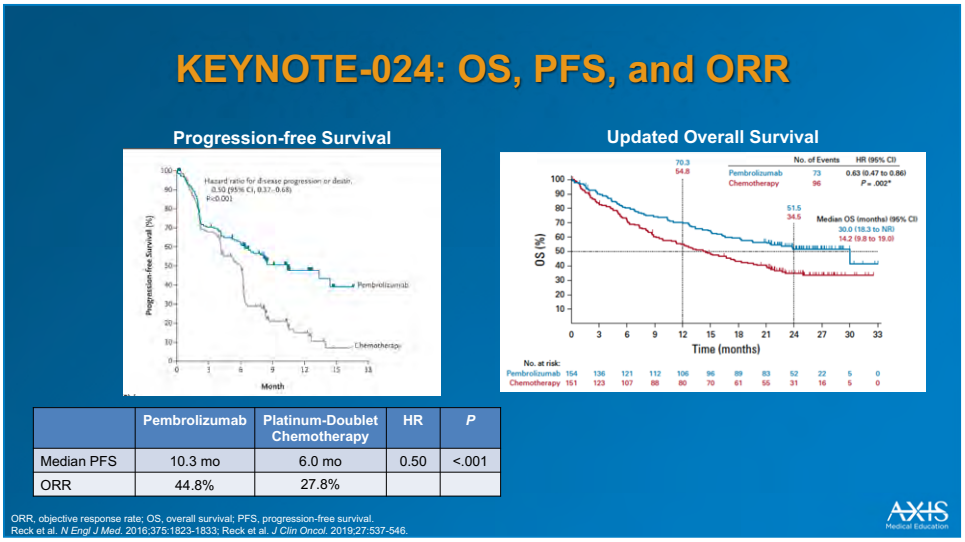
Now we'll discuss case two. This is a 66-year-old man with a newly diagnosed stage IV adenocarcinoma of the lung. Additional findings show PD-L1 is 50%. The patient has no evidence of a targetable actionable mutation. Dr. Yu, which treatment would you select for this patient and why?



Yu:

For this patient, there are a few more options we can explore, so there are a few other studies that we could go over. Personally, and most of us would likely agree, I would choose single-agent pembrolizumab for this patient. And that's really based primarily on this KEYNOTE-024 study.

As you can see on the slide, the study schema, KEYNOTE-024 took patients that had stage IV non–small cell lung cancer, both squamous and nonsquamous histology, specifically *EGFR* and *ALK* wild type because they had more appropriate treatments. Then they took patients with PD-L1 expression greater than 50% and randomized them to platinum doublet chemotherapy appropriate to their histology versus pembrolizumab.



	Pembrolizumab	Platinum-Doublet Chemotherapy	HR	*P*
Median PFS	10.3 mo	6.0 mo	0.50	<.001
ORR	44.8%	27.8%		

You can see that both the progression-free survival and the overall survival results significantly favored the pembrolizumab monotherapy for these patients.

KEYNOTE-024: Adverse Events

Treatment-related Adverse Event (any Grade)	Pembrolizumab Group (N=154)	Chemotherapy Group (N=150)
Any event	113 (73.4%)	135 (90.0%)
Serious	33 (21.4%)	31 (20.7%)
Led to discontinuation	11 (7.1%)	16 (10.7%)
Led to death	1 (0.6%)	3 (2.0%)
Select events occurring in 10% of patients in either group		
Nausea	15 (9.7%)	65 (43.3%)
Anemia	8 (5.2%)	66 (44.0%)
Fatigue	16 (10.4%)	43 (28.7%)
Decreased appetite	14 (9.1%)	39 (26.0%)
Diarrhea	22 (14.3%)	20 (13.3%)
Neutropenia	1 (0.6%)	34 (22.7%)
Vomiting	4 (2.6%)	30 (20.0%)
Pyrexia	16 (10.4%)	8 (5.3%)
Constipation	6 (3.9%)	17 (11.3%)
Stomatitis	4 (2.6%)	18 (12.0%)
Immune-mediated (any)	45 (29.2%)	7 (4.7%)

Reck et al. *N Engl J Med*. 2016;375:1823-1833.

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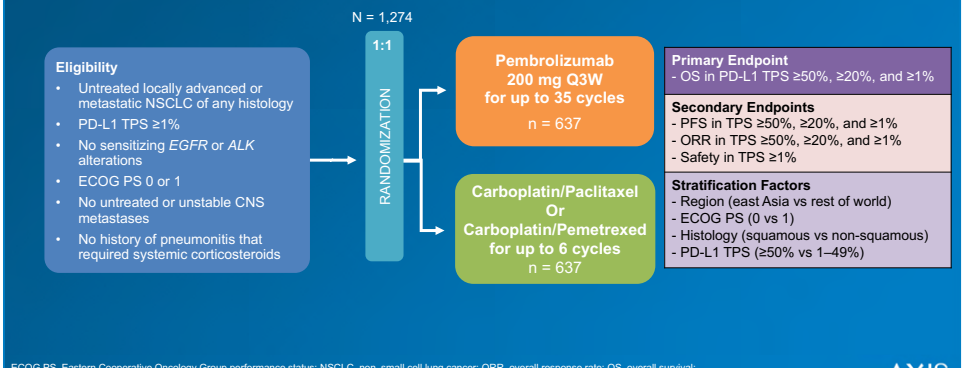
- The toxicity, as Mark mentioned earlier, there are clear toxicities that are attributed to both immunotherapy and chemo, so we really saw no surprises here in terms of toxicity.

KEYNOTE-042: Pembrolizumab vs Platinum Doublet



ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PS, performance status; TPS, tumor proportion score.
Lopes et al. *J Clin Oncol*. 2018;36: abstract LBA4; Mok et al. *Lancet* 2019;393:1819-1830.

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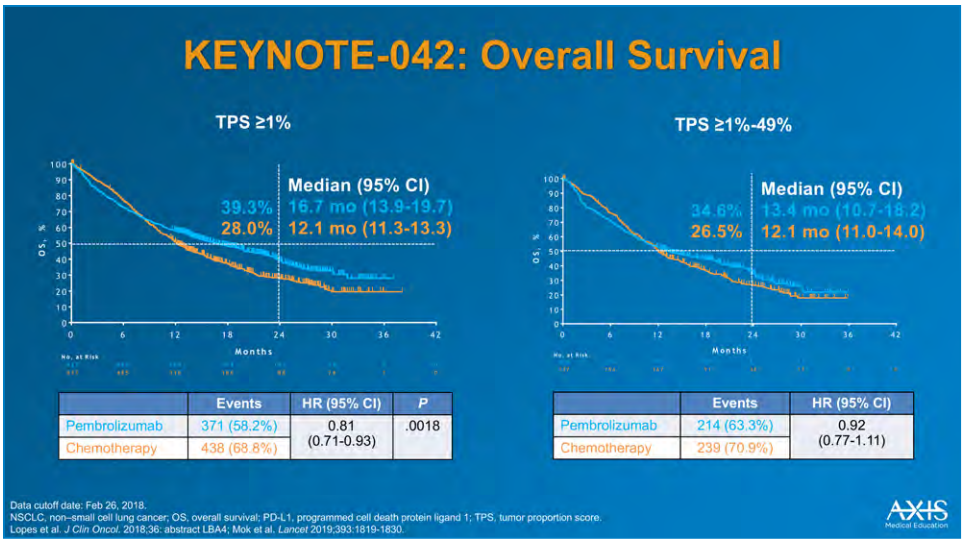
- That study really most closely mirrors this patient. Since that study came out, there are more data suggesting that we could use single-agent pembrolizumab for more patients. That is based on the KEYNOTE-042 study. So exactly same treatment arms, but this time really looked at patients who had PD-L1 expression greater than or equal to 1% and gave them either pembrolizumab or a platinum-doublet chemotherapy.



- Again, it did show in the prespecified greater than 1%, greater or equal to 1%, PD-L1 expression did show an improvement with the pembrolizumab compared to chemotherapy. However, many think that that was primarily driven by the patients with PD-L1 expression greater than 50%. The data were less convincing when they showed us the subset of patients with 1% to 49% PD-L1 expression.

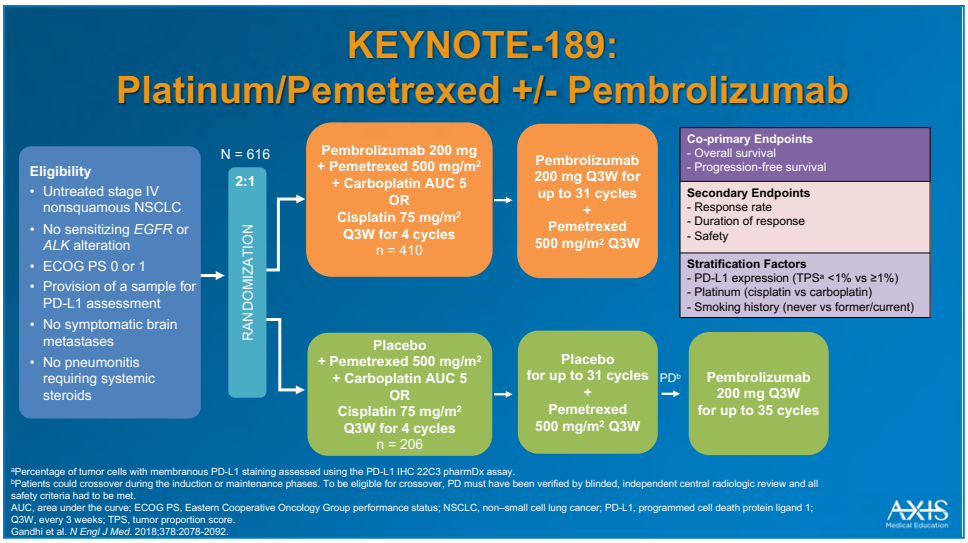
KEYNOTE-042: Adverse Events

Adverse Event	Pembrolizumab (N = 636)	Chemotherapy (N = 615)
Treatment-related	399 (62.7%)	553 (89.9%)
Grade 3-5	113 (62.7%)	252 (41.0%)
Led to death	13 (2.0%)	14 (2.3%)
Led to discontinuation	57 (9.0%)	58 (9.4%)
Immune mediated adverse events and infusion reactions*	177 (27.8%)	44 (7.2%)
Grade 3-5	51 (8.0%)	9 (1.5%)
Led to death	1 (0.2%) Pneumonitis	0

*Based on a list of terms specified by the sponsor and considered regardless of attribution to treatment or immune relatedness by the investigator.
Lopes et al. J Clin Oncol. 2018;36: abstract LBA4.

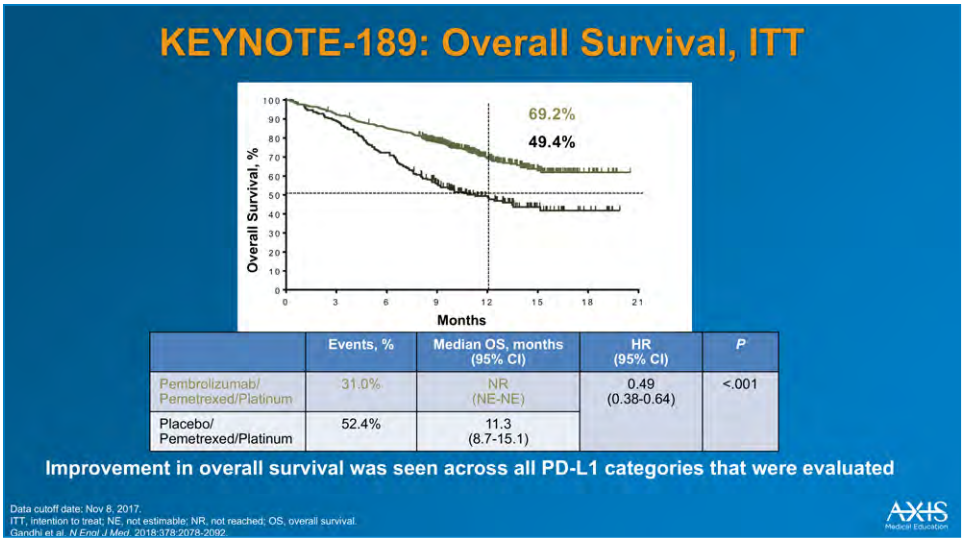
- Again, here you see the toxicity. Very similar to that of KEYNOTE-024.

  The final, or 2 other studies to think about are the chemotherapy/immunotherapy combination studies.



- All of us are familiar with KEYNOTE-189, which is the study that specifically took patients—the difference here being nonsquamous adenocarcinoma lung cancer patients—and then randomized them to receive platinum, either carboplatin or cisplatin, with pemetrexed, with or without pembrolizumab.

  The primary endpoints of this study were overall survival as well as progression-free survival. As you can see from the study schema, patients received both, in the control arm, received pemetrexed maintenance. And the patients in the study arm received pembrolizumab and pemetrexed maintenance until disease progression or intolerance.



	Events, %	Median OS, months (95% CI)	HR (95% CI)	P
Pembrolizumab/ Pemetrexed/Platinum	31.0%	NR (NE-NE)	0.49 (0.38-0.64)	<.001
Placebo/ Pemetrexed/Platinum	52.4%	11.3 (8.7-15.1)		

- As you can see here from the Kaplan-Meier curves, there was a commanding benefit to the addition of pembrolizumab to the platinum-doublet chemotherapy, with a hazard ratio of 0.49, so quite significant. Again, both statistically and, of course, clinically significant for our patients.

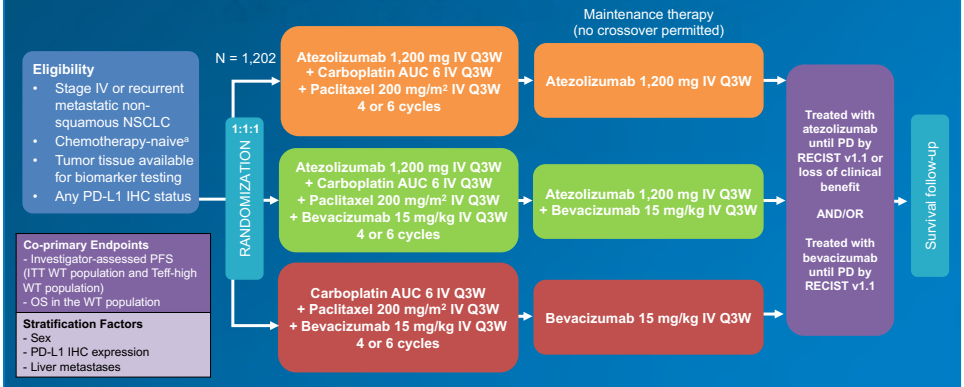
KEYNOTE-189: Summary of Adverse Events

Adverse Event	Pembrolizumab/Pemetrexed/ Platinum (N = 405)	Placebo/Pemetrexed/ Platinum (N = 202)
All cause	404 (99.8%)	200 (99.0%)
Grade 3-5	272 (67.2%)	133 (65.8%)
Led to death	27 (6.7%)	12 (5.9%)
Led to discontinuation		
All treatment[a]	56 (13.8%)	16 (7.9%)
Any treatment	112 (27.7%)	30 (14.9%)
Immune mediated	92 (22.7%)	24 (11.9%)
Grade 3-5	36 (8.9%)	9 (4.5%)
Led to death	3 (0.7%)	0

[a]Includes patients who discontinued pembrolizumab or placebo, pemetrexed, and carboplatin for an adverse event at any time and patients who discontinued pembrolizumab or placebo and pemetrexed for an adverse event after completing 4 cycles of platinum.
Data cutoff date: Nov 8, 2017.
Gandhi et al. *N Engl J Med.* 2018;378:2078-2092.

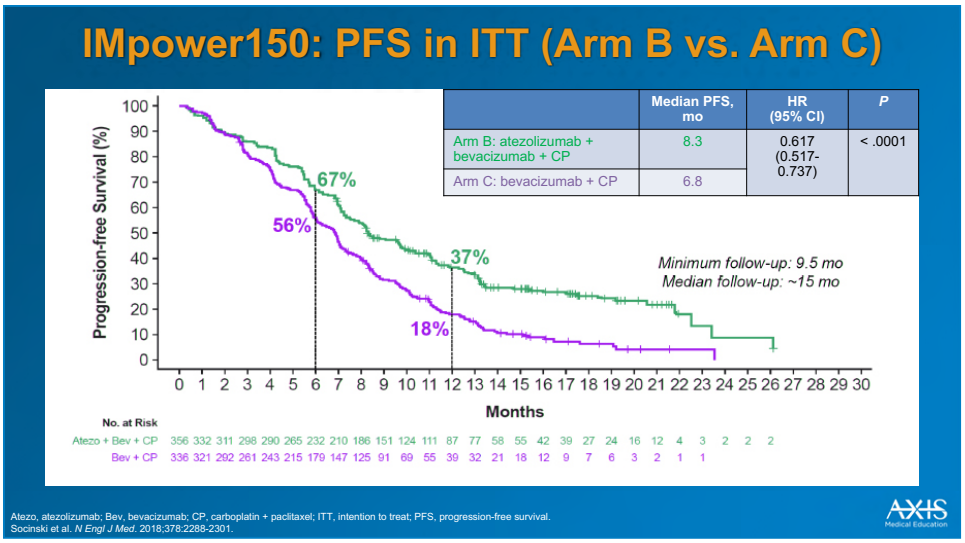
- Mirroring some of the other chemotherapy/ immunotherapy combination studies, we saw expected side effects, including, of course, more immune-related toxicities with the addition of pembrolizumab.

IMpower150: Carboplatin/Paclitaxel +/- Atezolizumab +/- Bevacizumab

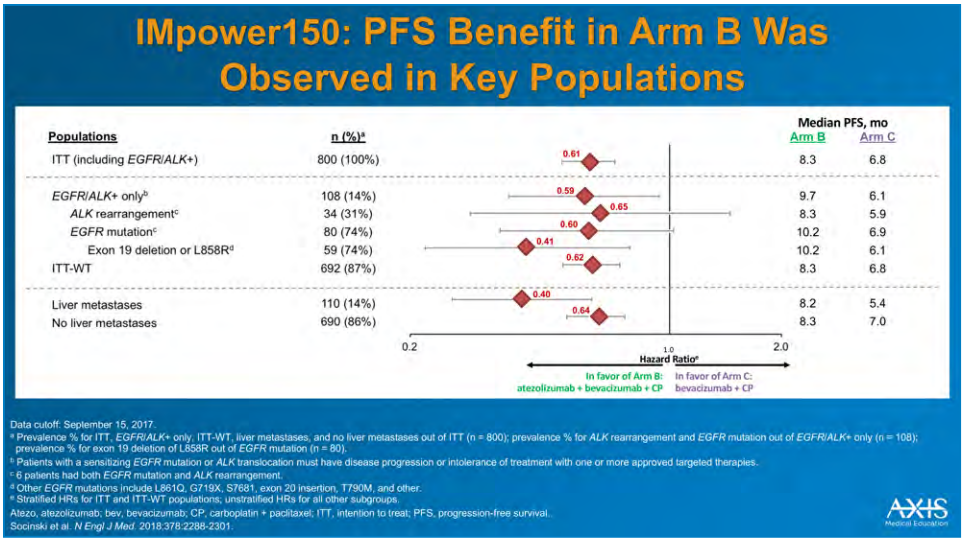


[a]Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more targeted therapies.
AUC, area under the curve; IHC, immunohistochemistry; ITT, intention to treat; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death protein ligand 1; PS, performance status; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitor.
Socinski et al. *N Engl J Med.* 2018;378:2288-2301.

- And finally, the other counterpoint not to omit, especially since my colleague here presented and published these data, is the IMpower150 data. It was a very large study with multiple arms. For our patient, this case really focused on the arms that included the carboplatin/paclitaxel/ bevacizumab versus that same trio of chemotherapy and bevacizumab with the addition of atezolizumab so we are looking at cohorts B and C of that study.



- You can see here that there is a clear improvement in progression-free survival with the addition of atezolizumab to that trio of bevacizumab plus a platinum-doublet chemotherapy.



- There was a clear benefit in all of the different subgroups that were looked at. Not relevant to this case, but unique to IMpower150 is they did include patients who were *EGFR* and *ALK* positive and did show both an overall survival and progression-free survival benefit in that subgroup, which is unique, and we might talk about further.

IMpower150: Adverse Events

Adverse Event	ABCP Group (N = 393)	BCP Group (N = 394)
Treatment-related adverse events*	371 (94.4%)	376 (95.4%)
Grade 3-4 adverse events	242 (61.6%)	230 (58.4%)
Treatment-related serious adverse events*	100 (25.4%)	76 (19.3%)
Immune-related adverse events	77.4%	–
Adverse events leading to withdrawal from any treatment*	128 (32.6%)	58 (14.7%)
Treatment-related deaths	11 (2.8%)	9 (2.3%)

*Incidence of treatment-related adverse events, serious treatment-related adverse events and adverse events leading to withdrawal from any treatment are for any treatment.
ABCP, atezolizumab/bevacizumab/carboplatin/paclitaxel; BCP, bevacizumab plus carboplatin plus paclitaxel.
Socinski et al. *N Engl J Med*. 2018;378:2288-2301.

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- And then, giving 4 drugs together compared to 3 drugs, we did see increased toxicity with this combination, which is one of the reasons why for this patient, we wouldn't choose this regimen.

Approved First-Line Therapy: PD-1/PD-L1 Inhibitors

PD-1/PD-L1 Inhibitor	Trial	Indication	Appropriate for Patient	Rationale for Patient
Pembrolizumab (PD-1)	KEYNOTE-024	as a single agent for the first-line treatment of patients with **PD-L1–expressing (TPS ≥50%)** metastatic NSCLC with no *EGFR* or *ALK* genomic tumor aberrations • Nonsquamous PFS HR: 0.55	✓	Stage IV nonsquamous cell carcinoma PD-L1 50%
	KEYNOTE-042	as a single agent for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors **express PD-L1 (TPS ≥1%)** as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations • Nonsquamous OS HR in TPS ≥1%: 0.86	✓	Stage IV nonsquamous cell carcinoma PD-L1 50%
	KEYNOTE-021 KEYNOTE-189	in combination with pemetrexed and platinum chemotherapy as first-line treatment of patients with metastatic **nonsquamous** NSCLC with no EGFR or ALK genomic tumor aberrations	✓	Stage IV nonsquamous cell carcinoma
	KEYNOTE-407	in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of patients with metastatic **squamous** NSCLC	x	Nonsquamous cell carcinoma
Atezolizumab (PD-L1)	IMpower150	in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic **nonsquamous** NSCLC with no EGFR or ALK genomic tumor aberrations	✓	Stage IV nonsquamous cell carcinoma

NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.
FDA News Release, 2016, 2017, 2018, 2019.

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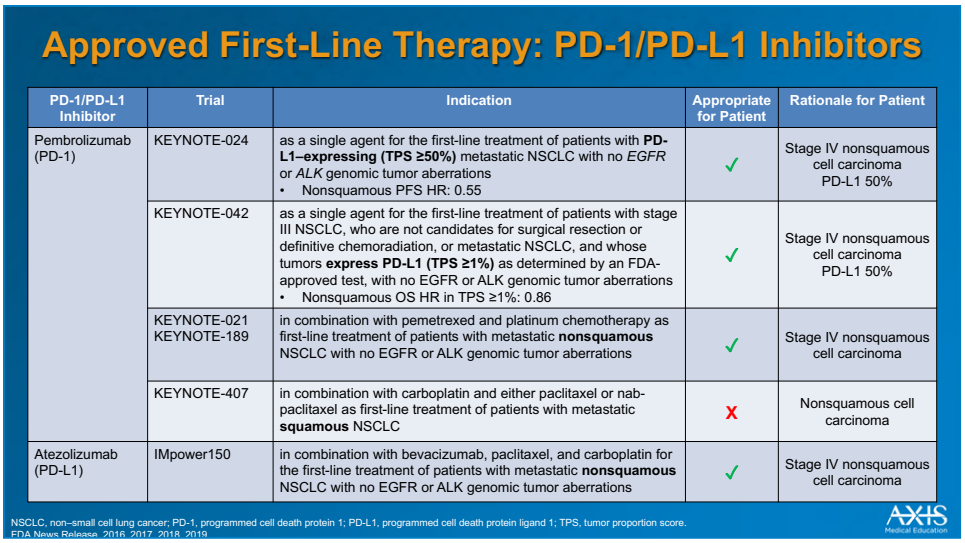
- In conclusion, and I'm interested to hear what my colleagues say, is if we want the best, most effective treatments for our patients, but we also want to consider toxicity. I would need a real reason to escalate treatment or add additional treatments to what I already know is effective. KEYNOTE-024 clearly showed us that pembrolizumab monotherapy would be a good choice for this patient, and I don't have great confidence that adding the chemotherapy in this particular situation would be additive to the degree that would be worth added toxicity.

Reckamp: Dr. Socinski?

Socinski: I agree with all the comments that were made. KEYNOTE-024 actually changed the landscape and did allow patients with high expression of PD-L1 to have a very effective treatment that's very nontoxic.

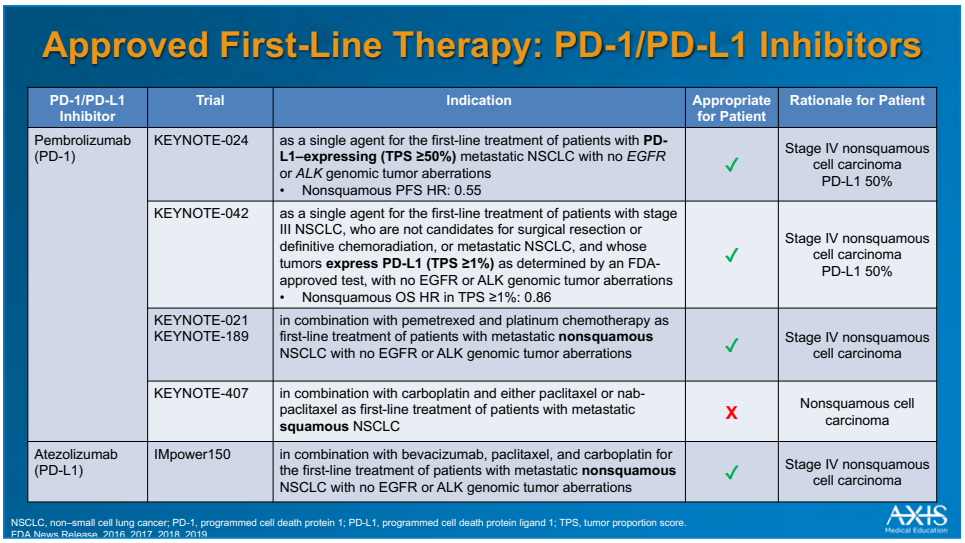


However, I have several patients with 90% PD-L1 expression and a high volume of disease who are quite symptomatic. If you combine a chemotherapy with pembrolizumab in that setting, you at least improve the response rates. One of the questions we have out there in practice is does adding chemo in that population actually improve outcomes such as progression-free survival as well as overall survival relative to pembrolizumab alone. We don't have the answer to that question yet.

However, in highly symptomatic patients with very bulky disease, I will give them chemoimmunotherapy rather than immunotherapy alone.

In terms of KEYNOTE-042, one of the things I would advise the audience to do is to look at the Kaplan-Meier curves. There's always an early disadvantage in overall survival that you don't see on the chemotherapy curves. I do not, in my practice, advocate using immuno-monotherapy in patients with less than 50% PD-L1 expression and certainly not the negative populations.

KEYNOTE-189 was, again, a very impressively positive trial. One of the issues in practice is who are the patients that are going to benefit from the IMpower150 regimen. Before we leave KEYNOTE-189, I do want to note that we have a similar trial, IMpower132, that was carbo/pemetrexed plus or minus atezolizumab, which was a negative trial. So you could argue that we have one positive and one negative trial, and we can debate as to why that may be.

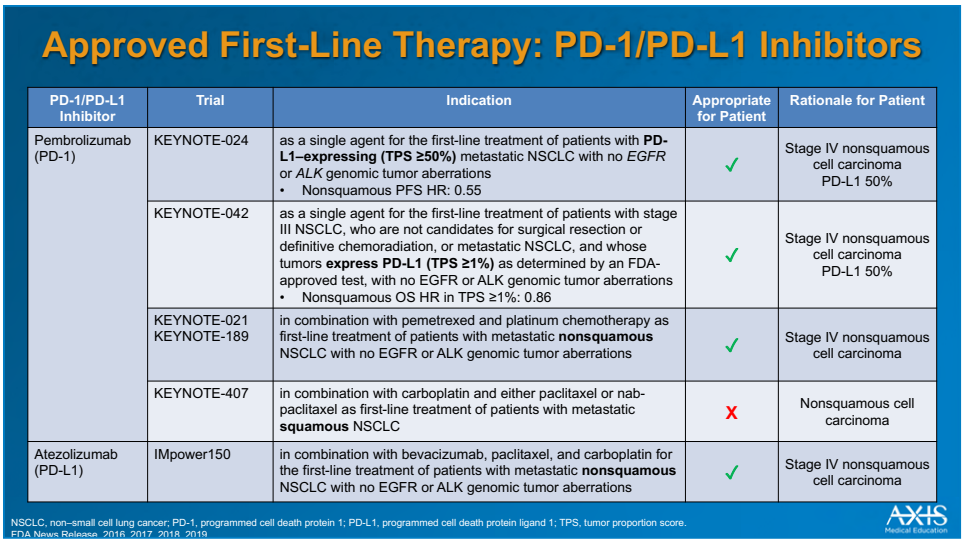


Regarding IMpower150, 4 drugs can be demanding on the patient as well as the resources that you may have. I do think it plays a role. This interplay and the reason we did the trial was that VEGF does have an immunosuppressive aspect to multiple levels of the cancer immunity cycle. Targeting VEGF is a valid strategy, in general, and seems to improve outcomes if you use it in combination with anti–PD-1 or anti–PD-L1 agents.

It's not going to get the majority of play in that setting, but I do think in select patients, where you might want to be more aggressive in that they're optimal candidates for a drug such as bevacizumab, then I would consider the 150 regimen. And you pointed out in the *EGFR/ALK* space, there may be a niche for it.

The liver space, the liver metastasis story, is in evolution. Both immunotherapy as well as the anti-VEGF therapy, and perhaps maybe the combination, is best for patients with liver metastases. But, that's still debatable.

Reckamp: So I would agree. You two have both given us a lot to think about with all the trials that are out there, especially for our patients with nonsquamous, non–small cell lung cancer. I would like to just also note, because we're talking about our patients with *EGFR* and *ALK*, as we can move toward treating patients without potentially testing PD-L1, it's incredibly important to still make sure we have our molecular testing, and that patients are truly wild-type before they go on to receive chemoimmunotherapy or immunotherapy alone.



The toxicity with first-line EGFR TKIs may be significantly higher if you use immunotherapy first. So, making sure that that testing is done, even if there's a slight delay in starting therapy, because we have so many options for our patients, they still might not be the right options.

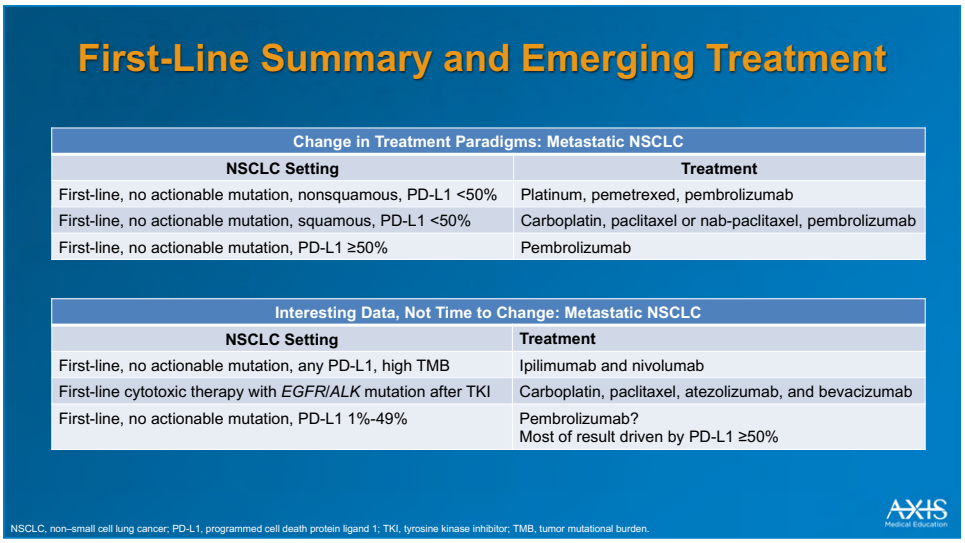
Socinski: And I would advocate being more comprehensive in your testing going beyond even what the NCCN may call out at this particular point—things such as *RET* fusions or *MET* exon 14 are very important to identify. This is, generally, not a population that we think it's a big bang out of immunotherapy, there's nothing distinguishing about chemo and that crowd. But, obviously, to use the growing number of targeted therapies we have, you've got to make the molecular diagnosis.

Reckamp: Right.

Yu: Absolutely. The real point to make is even though these studies have really advanced how we treat people without mutations—the response rates, the progression-free survival, the survival we see with our targeted therapies—far surpasses that.

Socinski: Yes.

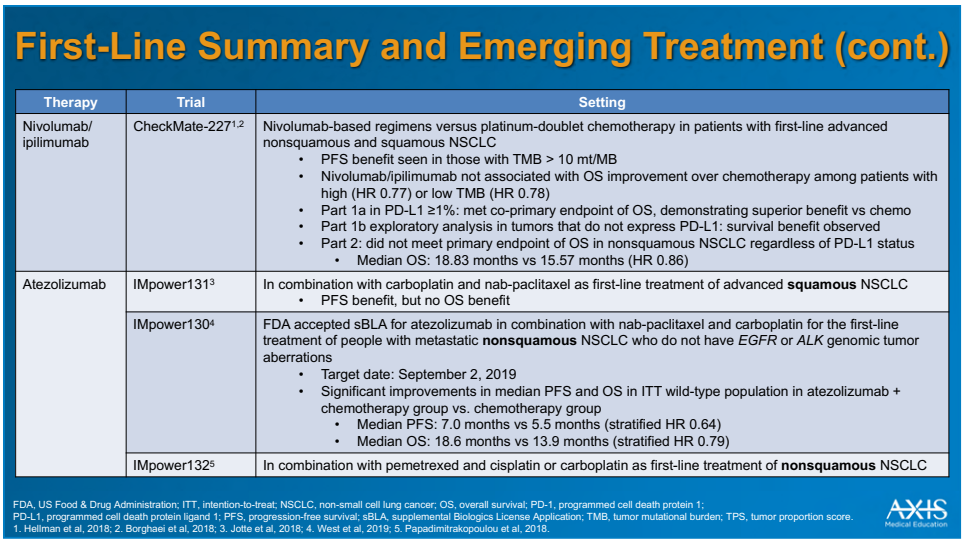
Yu: To Karen's point, not only are we withholding or leaving to later some really valuable treatment, but also that sequence of starting with immunotherapy and sequencing quickly with one of the targeted therapies can potentially harm patients. So it's not only not omission, it's also potential harm. All the more really important.



Reckamp:

Right. So next I'd like to summarize where we are and where we're going in the future with first-line treatment for non–small cell lung cancer. As we've heard, for patients without actionable mutations, nonsquamous, PD-L1 less than 50%, the combination of platinum/pemetrexed/pembrolizumab is still our first choice for those patients. First-line, no actionable mutation, squamous cell PD-L1 less than 50%, again, the KEYNOTE-407 study; carboplatin, either paclitaxel or nab-paclitaxel with pembrolizumab. And for those without an actionable mutation who have PD-L1 greater than 50%, pembrolizumab alone is a very reasonable choice. There may be sometimes where you might want to use chemotherapy with pembrolizumab; but generally, pembrolizumab regardless of histology.

Some interesting data that are out there that we're still learning how we might implement these therapies, and things to watch out for. So, I'll talk about the IMpower150. We had just talked about this. First-line cytotoxic therapy for patients with *EGFR* and *ALK* after they've received their tyrosine kinase inhibitor; importantly that they've already received their therapy. But the IMpower150 study was the first study to allow those patients into the trial and show a benefit to that combination with bevacizumab, atezolizumab, and carboplatin and paclitaxel. And really the only trial we have that included these patients.



Then thinking about patients and other ways of testing for patients. So, in the front-line setting, we're also looking at other markers where we can test patients and understand benefit of immunotherapy for patients. In the CheckMate 227 study, nivolumab and ipilimumab were investigated versus chemotherapy.

This study looked at PD-L1 as the primary marker but also presented data using high tissue tumor mutational burden and showed that patients with high tumor mutational burden had potentially higher benefit with the combination immunotherapy ipilimumab and nivolumab. Subsequently, there's been a press release showing that the study was positive in patients with PD-L1 positivity. And we await that data to help us guide how we might treat our patients with combination immunotherapy.

And then back to the data from the KEYNOTE-042 study—the patients without actionable mutation and PD-L1 expression 1% to 49%. We all agree that most patients who benefited were patients with greater than 50% PD-L1 expression. The 1% to 49% subset unplanned analysis does not show significant benefit for these patients. It's still an area where we would generally give combination chemotherapy with pembrolizumab.

First-Line Summary and Emerging Treatment (cont.)

Therapy	Trial	Setting
Nivolumab/ ipilimumab	CheckMate-227[1,2]	Nivolumab-based regimens versus platinum-doublet chemotherapy in patients with first-line advanced nonsquamous and squamous NSCLC • PFS benefit seen in those with TMB > 10 mt/MB • Nivolumab/ipilimumab not associated with OS improvement over chemotherapy among patients with high (HR 0.77) or low TMB (HR 0.78) • Part 1a in PD-L1 ≥1%: met co-primary endpoint of OS, demonstrating superior benefit vs chemo • Part 1b exploratory analysis in tumors that do not express PD-L1: survival benefit observed • Part 2: did not meet primary endpoint of OS in nonsquamous NSCLC regardless of PD-L1 status • Median OS: 18.83 months vs 15.57 months (HR 0.86)
Atezolizumab	IMpower131[3]	In combination with carboplatin and nab-paclitaxel as first-line treatment of advanced **squamous** NSCLC • PFS benefit, but no OS benefit

	IMpower130[4]	FDA accepted sBLA for atezolizumab in combination with nab-paclitaxel and carboplatin for the first-line treatment of people with metastatic **nonsquamous** NSCLC who do not have *EGFR* or *ALK* genomic tumor aberrations
		• Target date: September 2, 2019
		• Significant improvements in median PFS and OS in ITT wild-type population in atezolizumab + chemotherapy group vs. chemotherapy group
		  • Median PFS: 7.0 months vs 5.5 months (stratified HR 0.64)
		  • Median OS: 18.6 months vs 13.9 months (stratified HR 0.79)

	IMpower132[5]	In combination with pemetrexed and cisplatin or carboplatin as first-line treatment of **nonsquamous** NSCLC

FDA, US Food & Drug Administration; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; sBLA, supplemental Biologics License Application; TMB, tumor mutational burden; TPS, tumor proportion score.
1. Hellman et al, 2018; 2. Borghaei et al, 2018; 3. Jotte et al, 2018; 4. West et al, 2019; 5. Papadimitrakopoulou et al, 2018.

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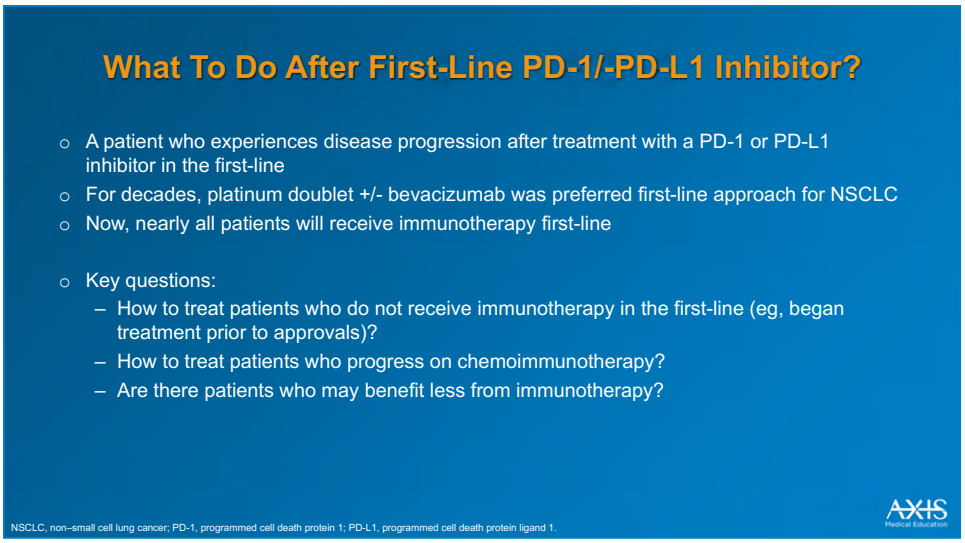
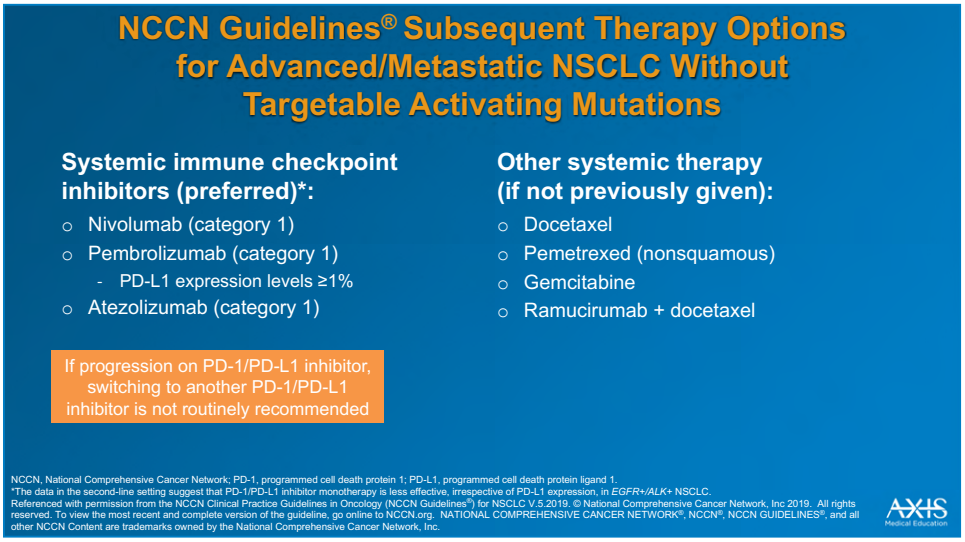
- Other emerging areas are looking at blood-based markers, especially blood tumor mutational burden. And this comes from data that was presented this spring at AACR by Dr. Peters. The MYSTIC trial looked at combination immunotherapy with tremelimumab and durvalumab. With that combination, study results were negative overall. When they looked back at blood tumor mutational burden at the highest levels of greater than 16 or greater than 20 mutations per megabase, those patients seemed to have a benefit with combination immunotherapy. These are things to watch out for and things that we may start to look for to help us understand how to treat patients beyond using PD-L1.

  There was a European approval for the IMpower130 study looking at first-line metastatic nonsquamous non–small cell lung cancer with carboplatin/nab-paclitaxel. The IMpower131 and 132 were not positive studies with overall survival. And again, as to Dr. Socinski's comment earlier, not all of these studies are showing the same benefit.



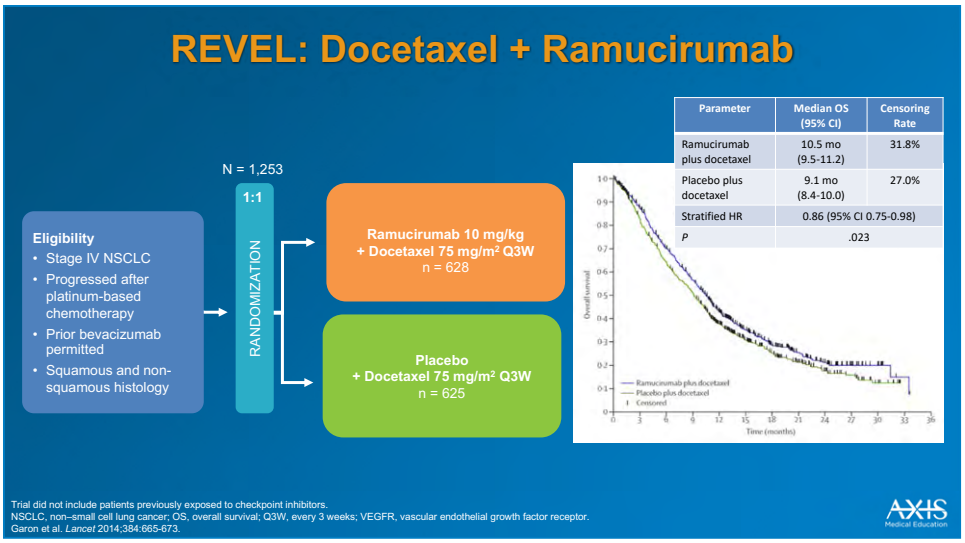
- What you would do for a patient who has disease progression after a PD-1 or PD-L1 inhibitor with or without chemotherapy in the first-line setting? As Dr. Socinski mentioned earlier, for decades we've been using platinum-based doublets with or without bevacizumab. Now we have jumped forward, and we're giving patients immunotherapy or combination immunotherapy with chemotherapy.

  So we'd like to think about how to treat patients who don't receive immunotherapy in the front-line. Not many of those patients are left, but maybe they began treatment prior to the approvals. How do we treat patients who have disease progression on chemoimmunotherapy? And then, whether there might be patients who will benefit less from immunotherapy that you might think they might not be the right patients to treat with immunotherapy. Dr. Socinski, we'll start with you.



- **Socinski:**

  For those patients who have received the regimens we've been talking about—chemoimmunotherapy regimens here—we've essentially taken our first-line regimens/second-line regimens and combined them. So what we used to do as third line, which was typically docetaxel with or without ramucirumab depending upon if there were any contraindications in this setting, has moved up to historically where docetaxel started, which was second line. That's my go-to regimen. In the majority of patients, I tend to use ramucirumab.



- Because we know from the REVEL trial that we did see the triple benefit—overall response, progression-free survival, and overall survival—although, you know, not in very modest improvements in the survival outcomes.

Approved Second-Line Therapies

Drug	FDA Approval Date	Trial	Indication
Nivolumab (PD-1)	March 2015	CheckMate-017	Metastatic **squamous** NSCLC that progresses on or after platinum-based chemotherapy
	October 2015	CheckMate-057	Metastatic **nonsquamous** NSCLC that progresses on or after platinum-based chemotherapy
Pembrolizumab (PD-1)	October 2015 (accelerated) October 2016 (regular)	KEYNOTE-001 KEYNOTE-010	Metastatic NSCLC that **expresses PD-L1** (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy
Atezolizumab (PD-L1)	October 2016	OAK POPLAR	Metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy
Ramucirumab (VEGFR-2 inhibitor)	December 2014	REVEL	In combination with docetaxel for the treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy

FDA, US Food & Drug Administration; NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score; VEGFR, vascular endothelial growth factor receptor.
FDA News Release 2015, 2016.

- For those patients who might not have gotten immunotherapy first line—maybe because they were treated a while ago, or someone missed the boat—then immunotherapy is our standard second-line therapy. We had all 3 agents that were compared to docetaxel, all of which clearly beat docetaxel in the second-line setting. So that's what I would do in that setting. It really comes down to where we find ourselves using more docetaxel. This is an area to try to figure out what further immunologic strategies could be employed for those patients who have run through anti–PD-1/anti–PD-L1 agents. I don't know that we know that much about resistance mechanisms or what direction to go in in this setting, although that would be very helpful to design subsequent trials.

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FDA News Release 2015, 2016.

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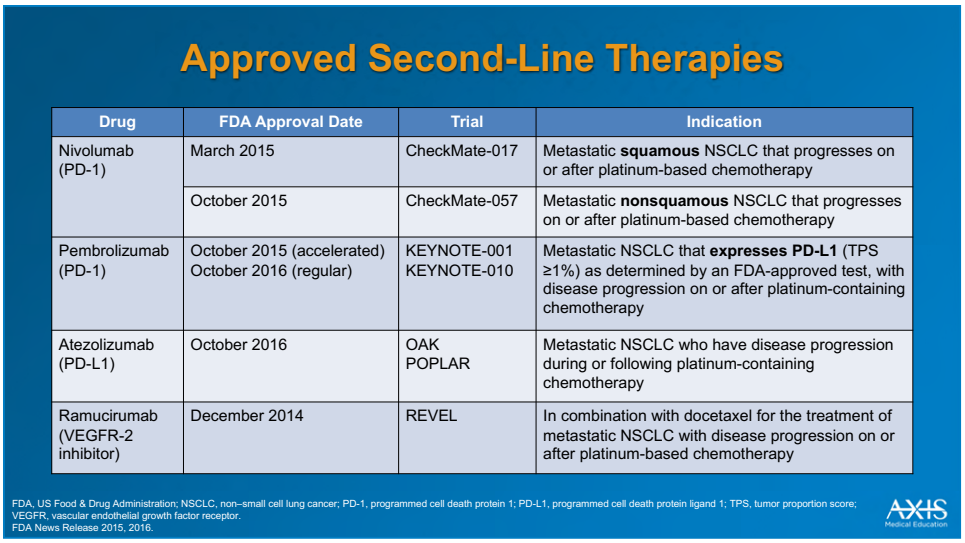
Right now, in standard practice, we're back to docetaxel second line. Usually I give it with ramucirumab; sometimes there's a contraindication.

Reckamp: Dr. Yu.

Yu: Just to echo what Mark is saying, it's such a black box as to what to do after this new first-line standard of care; even the REVEL study that was done prior to the era of immunotherapy. So, do those results stand up after first-line immunotherapy? With targeted therapies, we know acquired resistance, figuring out the mechanism, and then addressing that has been the key to progress. We're really not there yet with immunotherapy in terms of figuring out why people become resistant, can we re-harness that immune response? We're trying a lot of different combination immunotherapies a little bit blindly.

Finally, certain people really benefit from immunotherapy, but there is a subset that don't. There are really intriguing data at ASCO this year about certain genomic subsets that might not respond. So thinking about *KEAP1* mutants or a *STK11*, which comprise 25% of lung adenocarcinomas—they really did not seem to benefit. So there are emerging data to help us pick the best treatments for our patients.

Socinski: I want to ask my colleagues a question that I thought of when you said the REVEL trial was done before the era of immunotherapy. Every once in a while, I hear anecdotal things that maybe chemotherapy works better after you've been exposed to immunotherapy. Does that resonate with either one of you?



Reckamp:

There are some data on second progression-free survival, and that has some support to show that maybe there's a longer progression-free survival indicating that maybe you are getting better benefit. Again, as you mentioned from the first, the KEYNOTE-024 study, these patients went on to receive other therapies; but getting immunotherapy first was the important thing. So, actually it's hypothetical, but we're changing the milieu of the tumor microenvironment in a way and the immune system in a way that potentially can help other therapies to work better. But that's based more on anecdotes and small subset analyses than primary data at this time.

We've discussed a lot of topics—first-line therapy squamous cell, first-line therapy nonsquamous cell non–small cell lung cancer and the large number of amount of data that has really been presented over the past year/year and a half that have changed how we treat non–small cell lung cancer. And we can see, even in the next 6 to 12 months, we'll probably get more data that may make us think about how we're choosing and treating our patients.

I'd like to thank both Dr. Socinski, Dr. Yu for discussing these cases with me today and for your participation in this activity. Thank you.

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