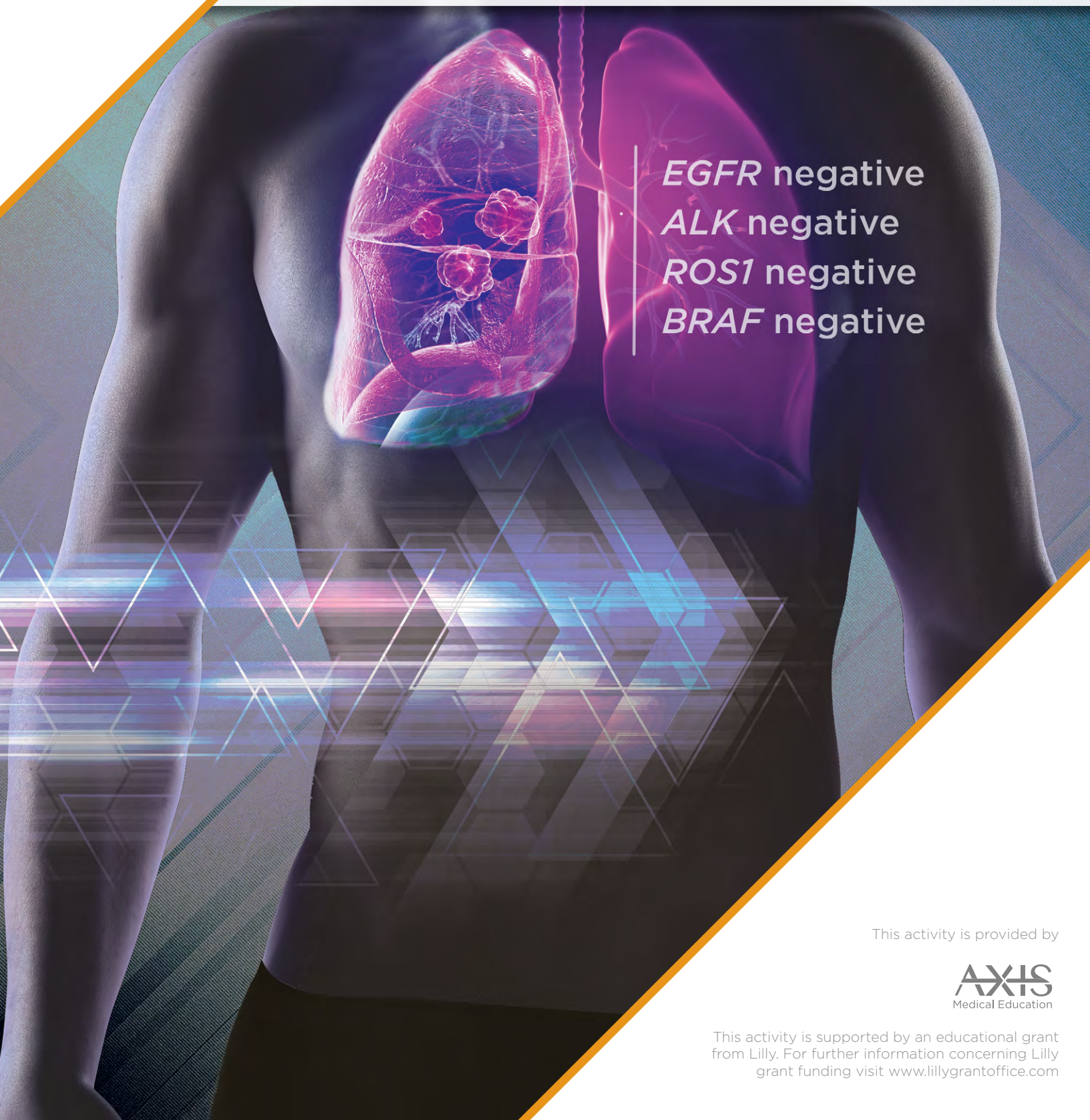
AXIS Medical Education

Distilling Modern Medical Approaches in Advanced NSCLC:

Precision, Performance, and Parallels With Patients

This transcript has been edited for style and clarity and includes all slides from the presentation.



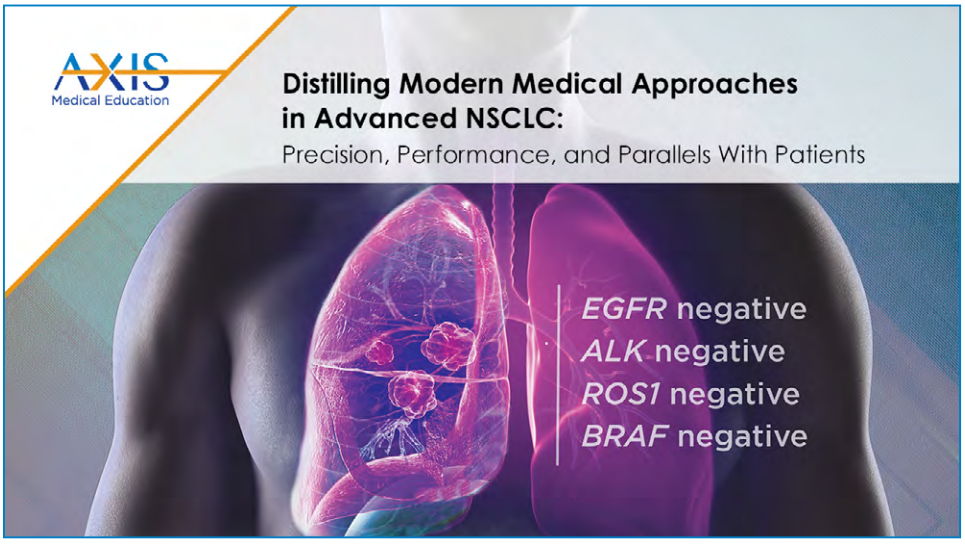
This activity is provided by

AXIS Medical Education

This activity is supported by an educational grant from Lilly. For further information concerning Lilly grant funding visit www.lillygrantoffice.com

Distilling Modern Medical Approaches in Advanced NSCLC: Precision, Performance, and Parallels With Patients

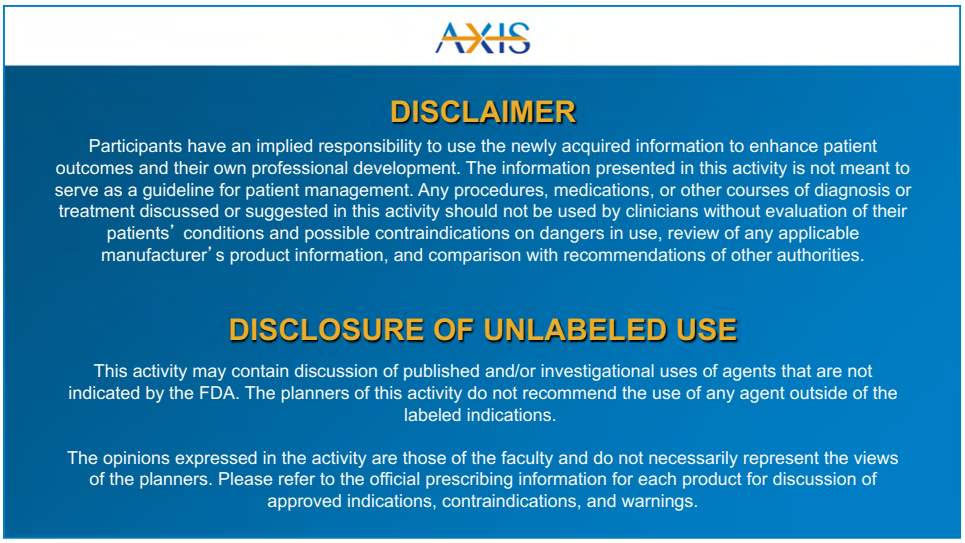
Joshua Bauml, MD



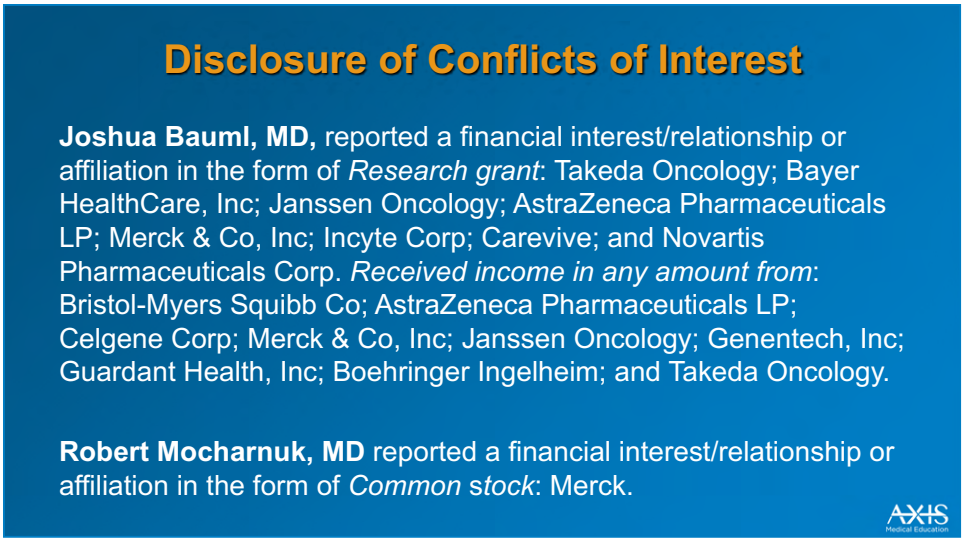
Robert Mocharnuk, MD: Hello, and welcome to this educational activity, Distilling Modern Medical Approaches in Advanced Non–Small Cell Lung Cancer: Precision, Performance, and Parallels With Patients.

I am Dr. Robert Mocharnuk, Emeritus Professor of Clinical Medicine. And I am joined today by Dr. Joshua Bauml, Assistant Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, Pennsylvania.

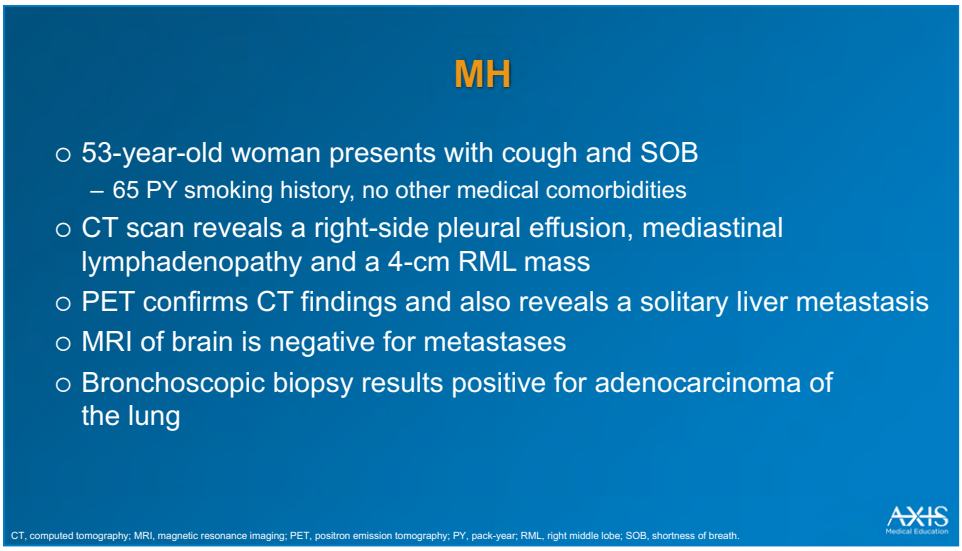
Through case studies, we will discuss and evaluate available treatment options and guideline recommendations for patients with advanced non–small cell lung cancer without targetable activating mutations after progression on initial platinum-based therapy. We will also consider available data on treatment strategies for non–small cell lung cancer that progresses rapidly on front-line therapy.



- Here is a disclaimer and disclosure indicating that we may be discussing off-label uses of approved agents or agents that are currently in development.

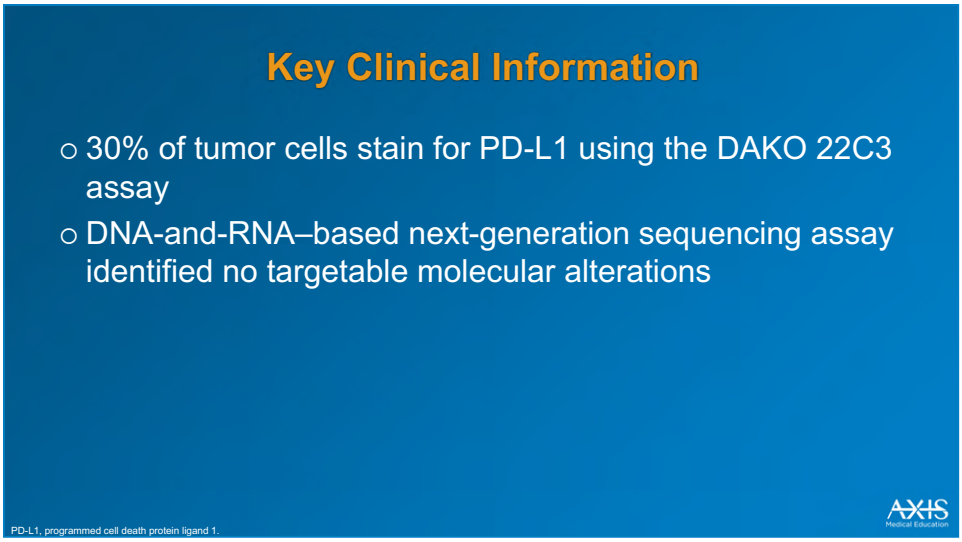


- Here is our financial disclosure information.

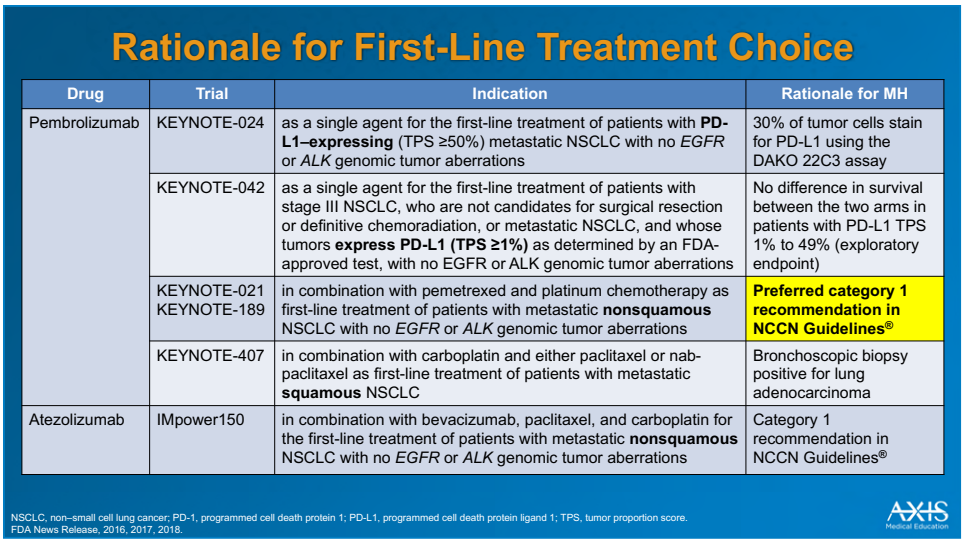


So let's begin with the case presentation. Dr. Bauml, can you tell us about this first patient?

Joshua Bauml, MD:
So our first case is a 53-year-old woman who presented with cough and shortness of breath. She has a 65-pack-year smoking history and no other medical comorbidities. A CT scan reveals a right-sided pleural effusion, mediastinal lymphadenopathy, and a 4-cm right middle lobe mass. A PET scan confirms these findings and reveals a solitary liver metastasis. Brain MRI is negative for metastases. Bronchoscopic biopsy reveals an adenocarcinoma of the lung.



Now, when we have a new diagnosis of adenocarcinoma of the lung, we need to make sure we get a comprehensive assessment of the relevant biomarkers. So in this case, we find out that this patient has 30% tumor stain for PD-L1 using the 22C3 assay. A comprehensive next-generation sequencing assay, evaluating both mutations and translocations, does not reveal a targetable alteration.



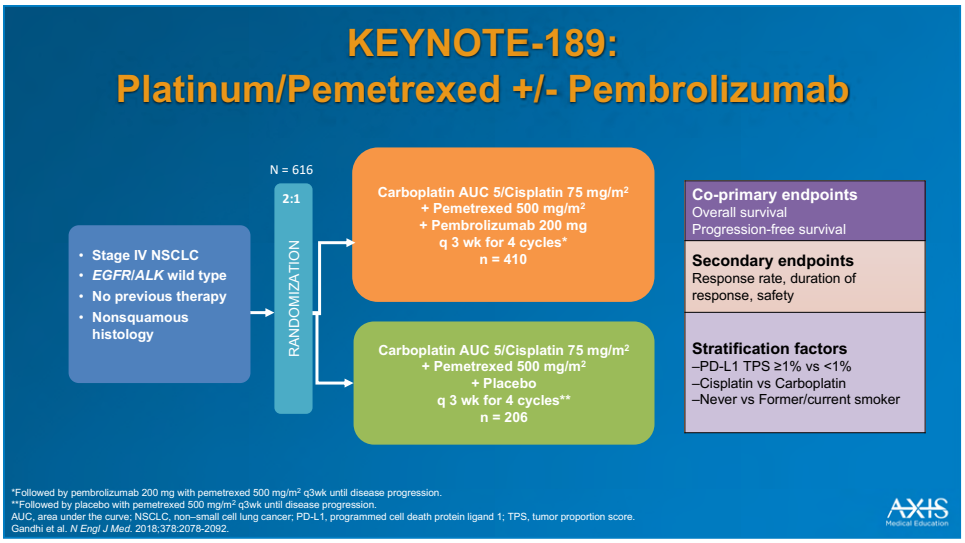
Robert Mocharnuk, MD: Thank you. Let's go through some of the treatment options appropriate for this patient.

Joshua Bauml, MD: There has been an onslaught of new trials in metastatic non–small cell lung cancer, and we have multiple options that we can consider. KEYNOTE-024 looked at patients who had PD-L1 expression of over 50%. So, that doesn't apply here.

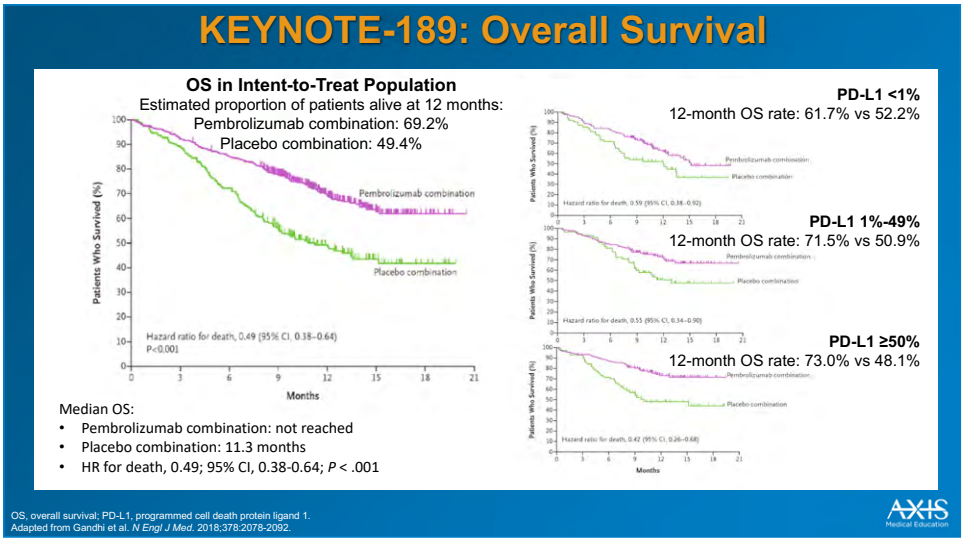
KEYNOTE-042 compared pembrolizumab to platinum doublet chemotherapy among patients who had PD-L1 greater than 1%. They showed an improvement in outcomes with pembrolizumab; however, most of that benefit was driven by patients who had greater than 50% staining. Indeed, for patients who had staining of 1% to 49%, there was no benefit for pembrolizumab.

What many of us would use in this circumstance is based on results of KEYNOTE-189 and KEYNOTE-021 G, which looked at adenocarcinoma of the lung, and it randomized patients to either carboplatin/pemetrexed or carboplatin/pemetrexed/pembrolizumab. In this study, what they found was that regardless of PD-L1 expression, the addition of pembrolizumab was associated with an improvement in overall survival.

Another approach that is approved in this setting is the IMpower150 regimen, which combines carboplatin, paclitaxel, bevacizumab, and atezolizumab regardless of PD-L1 staining. But given the taxane component here, myself and many of my colleagues tend to prefer the KEYNOTE-189 regimen, and that led to its status as the preferred Category 1 recommendation in the NCCN Guidelines®.



So, just taking a look at KEYNOTE-189 in greater detail, you can see some key points that need to be emphasized. First, patients were required to not have an *EGFR* mutation or an *ALK* translocation. These patients were excluded. Patients needed to have nonsquamous histology, and they were randomized to platinum pemetrexed with or without the pembrolizumab, and that was administered every 3 weeks.



So taking a look at the overall survival data, here you can see very nicely that in the intention-to-treat analysis, there was an early and wide separation between the triplet regimen and the placebo-containing arm. And that the benefit is seen regardless of PD-L1 status. So this becomes a rather straightforward first-line option for patients with nonsquamous metastatic non–small cell lung cancer.

Back to MH

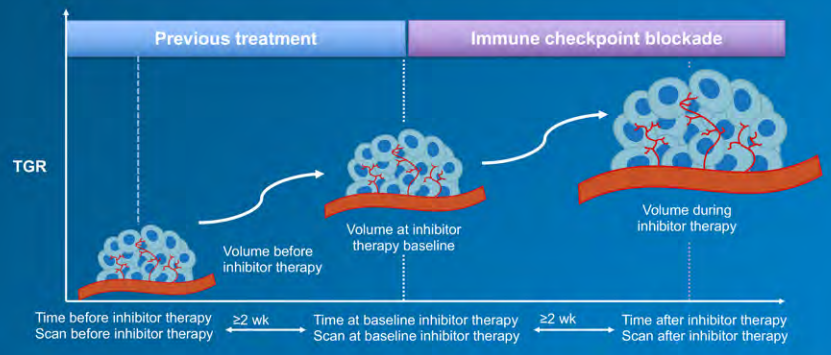
- Patient begins treatment with carboplatin/pemetrexed/pembrolizumab
- After 2 cycles, she presents to clinic with worsening abdominal pain
- CT scan reveals PD in the liver and new bilateral adrenal metastases
- She tells you she heard that sometimes immunotherapy can make cancer bigger before it gets smaller

CT, computed tomography; PD, progressive disease.

AXIS Medical Education

- So back to this patient—she begins treatment with carboplatin, pemetrexed, and pembrolizumab. After 2 cycles, she presents to the clinic with worsening abdominal pain. Imaging reveals progression in her liver, now new bilateral adrenal metastases. And she has told you that, you know, she hears sometimes immunotherapy can make cancer bigger before it gets smaller, so should we just ride it out, doc?

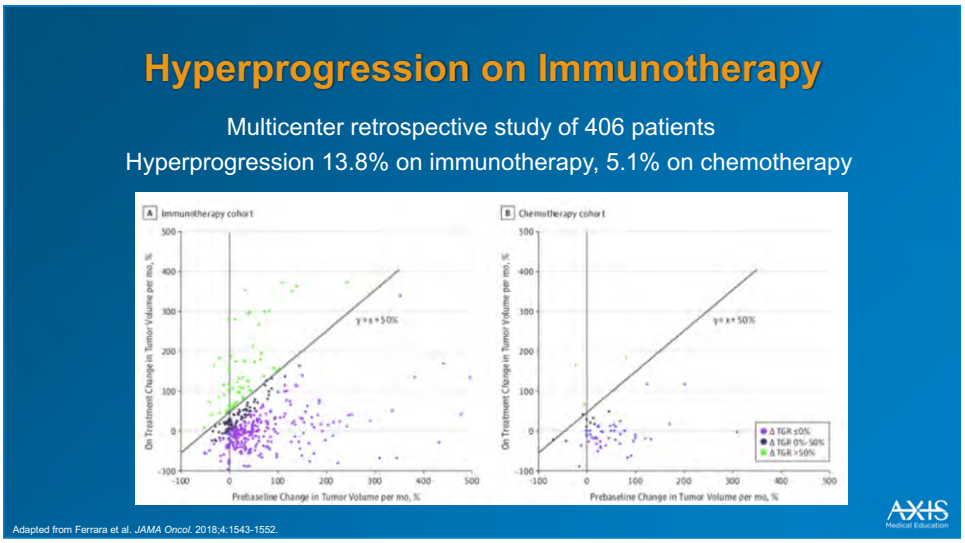
Hyperprogression on Immunotherapy



TGR, tumor growth rate.
Adapted from Ferrara et al. *JAMA Oncol.* 2018;4:1543-1552.

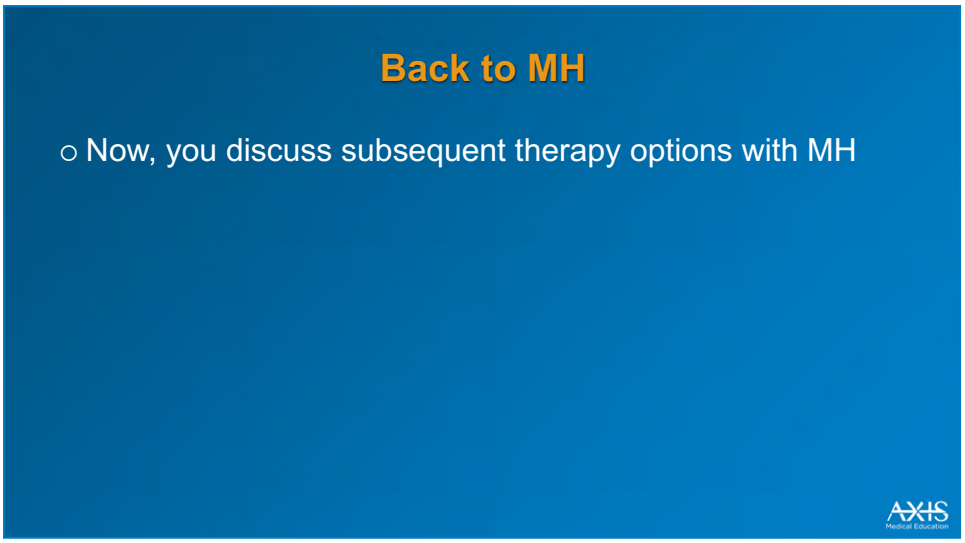
AXIS Medical Education

- This is the concept of pseudoprogression that she's referring to, but there's another more concerning concept, which is this item of hyperprogression, which is that in some patients who are treated with the immunotherapy, their cancer can actually speed up its growth. And it's unclear why this happens—whether it's directly related to the immunotherapy—but it has been repeatedly seen in multiple trials.

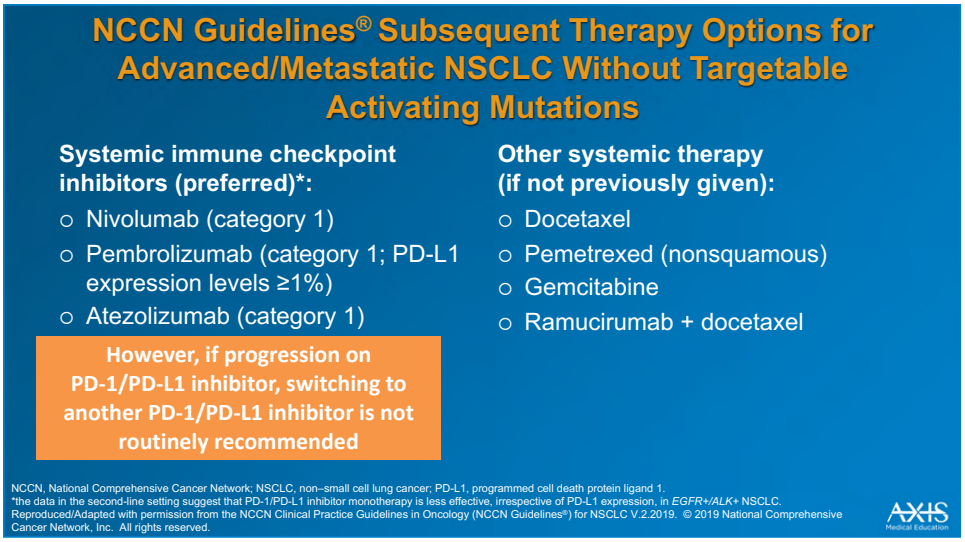


- There was a recent retrospective analysis that was done by a group in Europe. And what they were able to show was that up to 13.8% of patients on immunotherapy have hyperprogression, and this was measured as growth that occurred at a faster rate than would be expected from their prior progression. Interestingly, they also saw some hyperprogression in patients who were receiving cytotoxic chemotherapy, which implies there may be more to this story than just immunotherapy.

  At this point, we don't have good biomarkers to predict who is actually going to have this. But, the key point to remember is that hyperprogression happens, unfortunately, more frequently than pseudoprogression. So if you have disease that is progressing on immunotherapy, it's really best to regard that as hyperprogression and change your treatment accordingly.

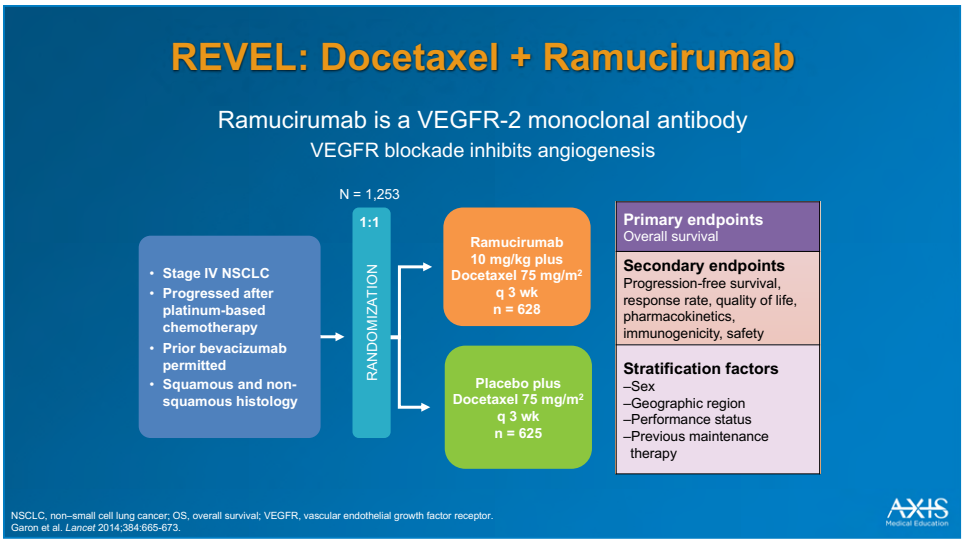


Robert Mocharnuk, MD: What are the treatment options for this patient who experienced disease progression on combination carboplatin, pemetrexed, and pembrolizumab?



Joshua Bauml, MD: When we give chemoimmunotherapy, we give lots of our treatments, and we sometimes use up multiple options that have been approved in the second line. So, it's important to remember that it is not currently recommended to just switch to another PD-1 or PD-L1 inhibitor.

We have never seen in a study that switching to another agent can improve outcomes in this setting. But there are other drugs that could be considered and are approved. Docetaxel, pemetrexed, gemcitabine, or ramucirumab with docetaxel. Now, of course, in this patient, she just received pemetrexed. So, giving her pemetrexed doesn't make a lot of sense either.



- The REVEL study tried to see if we could improve outcomes for patients receiving docetaxel with the addition of ramucirumab, which is a VEGFR2 monoclonal antibody. And VEGFR, obviously, blocks the development of new blood vessels.

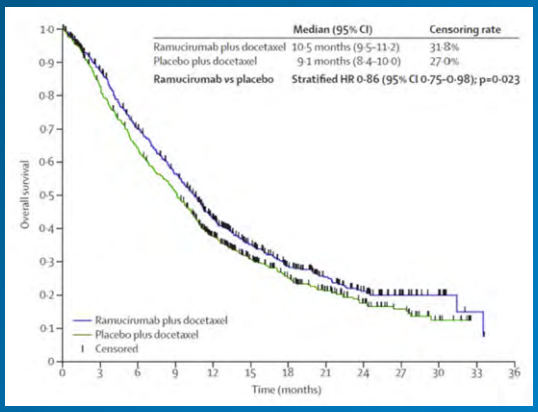
Docetaxel + Ramucirumab: Safety

Treatment-Emergent Adverse Event	Ramucirumab + docetaxel (n = 627)		Placebo + docetaxel (n = 618)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	98%	79%	95%	71%
Fatigue	55%	14%	49%	10%
Diarrhea	32%	5%	27%	3%
Nausea	27%	1%	27%	1%
Stomatitis	23%	4%	13%	2%
Neuropathy	23%	3%	20%	2%
Neutropenia	55%	49%	45%	39%
Febrile neutropenia	16%	16%	10%	10%
Bleeding or hemorrhage	29%	2%	15%	2%
Hypertension	11%	6%	5%	2%
Venous thromboembolism	3%	2%	6%	3%
Arterial thromboembolism	2%	1%	2%	1%
Proteinuria	3%	< 1%	1%	0%

Garon et al. *Lancet* 2014;384:665-673.

- So, the combination of ramucirumab with docetaxel was relatively well tolerated with no substantial increase in the rate of greater than grade 3 adverse events; 79% in the combination arm versus 71% in the placebo arm.

REVEL: Docetaxel + Ramucirumab: Overall Survival



Adapted from Garon et al. *Lancet* 2014;384:665-673.

When we look at the overall survival, we see that there is a statistically significant, if clinically modest, improvement in overall survival with the addition of ramucirumab.

Aggressive or Refractory NSCLC

- Chemorefractory or aggressive disease may be more challenging to treat
  - Common clinical scenario but difficult to clearly define
- One proposed definition of this subgroup in the second-line setting is time since start of first-line therapy
  - Short time between starting first-line therapy and second-line therapy suggests a more aggressive phenotype

NSCLC, non–small cell lung cancer.

Robert Mocharnuk, MD:
I understand there are data indicating that patients with rapidly progressing disease have benefited from treatment with ramucirumab plus docetaxel. Could you tell us a little bit about this and discuss whether this combination would be appropriate for the patient that we've been discussing?

Joshua Bauml, MD:
Trying to identify those patients most likely to benefit is really critical in this setting. So, one of the groups that was looked at in the REVEL study is patients who had either chemorefractory or otherwise aggressive disease. This is common. And just like this case that we've discussed here, they present with symptomatic or painful disease that's growing rapidly, and we need a treatment that will yield a rapid improvement in their outcomes.

So one definition of this is that if you have a short time between starting first-line therapy and needing to go to second-line therapy, this may suggest a more aggressive phenotype.

REVEL: Exploratory Subgroup Analysis of NSCLC Refractory to First-Line Chemotherapy

REVEL Refractory Disease	Ramucirumab + Docetaxel	Placebo + Docetaxel	HR (95% CI)
Histology, n (%)			
Nonsquamous	130 (73)	130 (71)	
Squamous	46 (26)	50 (27)	
Median OS, mo	8.3	6.3	0.86 (0.68-1.08)
12-mo survival rate, %	34	29	
Median PFS, mo	4.0	2.5	0.71 (0.57-0.88)
ORR, %	22.5	12.6	0.77 (0.51-1.17)
TEAEs, any grade, n (%)	173 (97)	171 (95)	

NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TEAEs, treatment-emergent adverse effects.
Reck et al. *J Clin Oncol*. 2016;34: abstract 9079. Reck et al. *Lung Cancer* 2017;112:181-187.

AXIS Medical Education

- So, what they did was an exploratory subgroup analysis of patients who had disease that was refractory to first-line chemotherapy. The benefit in overall survival was more pronounced—8.3 versus 6.3 months with a much higher overall response rate for the combination of 22.5% versus 12.6%.

REVEL: Exploratory Analysis of Patients Refractory to Prior First-Line Treatment <9 Months From Prior Therapy

REVEL study revealed significantly improved PFS, ORR, and DCR independent of histology

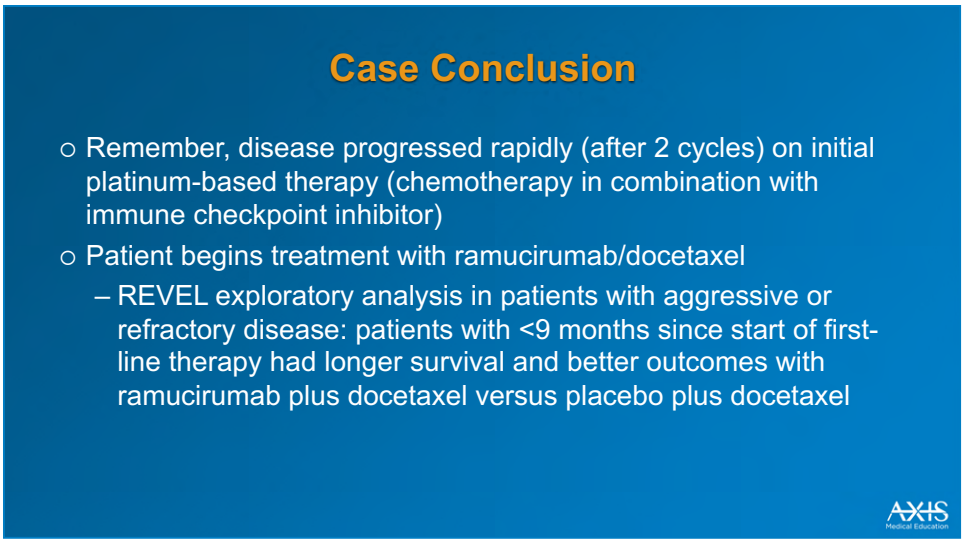
Type	Median OS, mo (ramucirumab + docetaxel)	Median OS, mo (placebo + docetaxel)
Nonsquamous NSCLC	9.7	6.9
Adenocarcinoma	9.7	7.0
Squamous NSCLC	8.9	7.2
All Histologies	9.3	7.0

Across all histologic types, patients with time since start of first-line therapy <9 months had longer survival and better outcomes with ramucirumab plus docetaxel versus placebo plus docetaxel

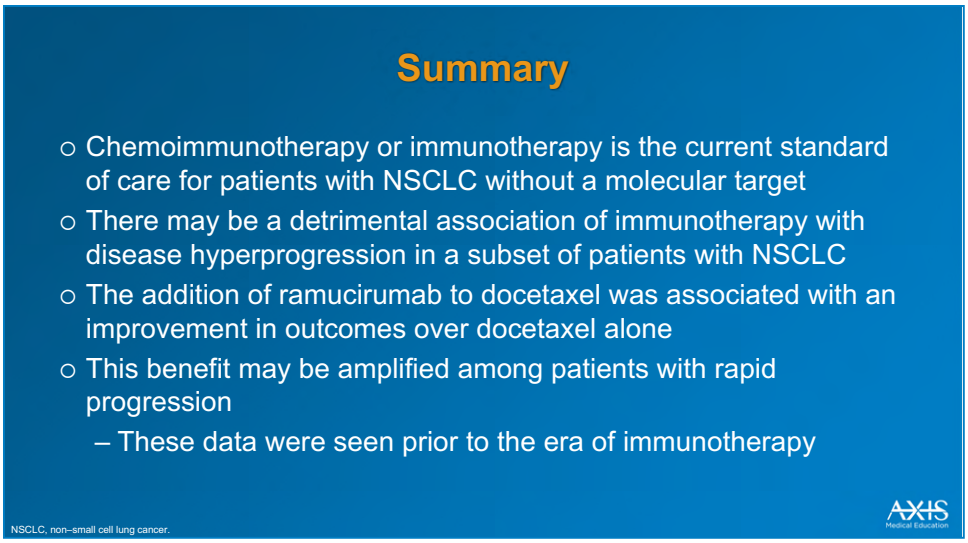
DCR, disease control rate; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
Reck et al. *J Clin Oncol*. 2016;34: abstract 9079. Reck et al. *Lung Cancer* 2017;112:181-187.

AXIS Medical Education

- Taking a look at the subgroups of nonsquamous, adeno, squamous, all histologies, if you identify patients with disease that is refractory to first-line treatment and progressed quickly, you can see that the incremental benefit of the addition of ramucirumab is more pronounced than that in the general patient population.



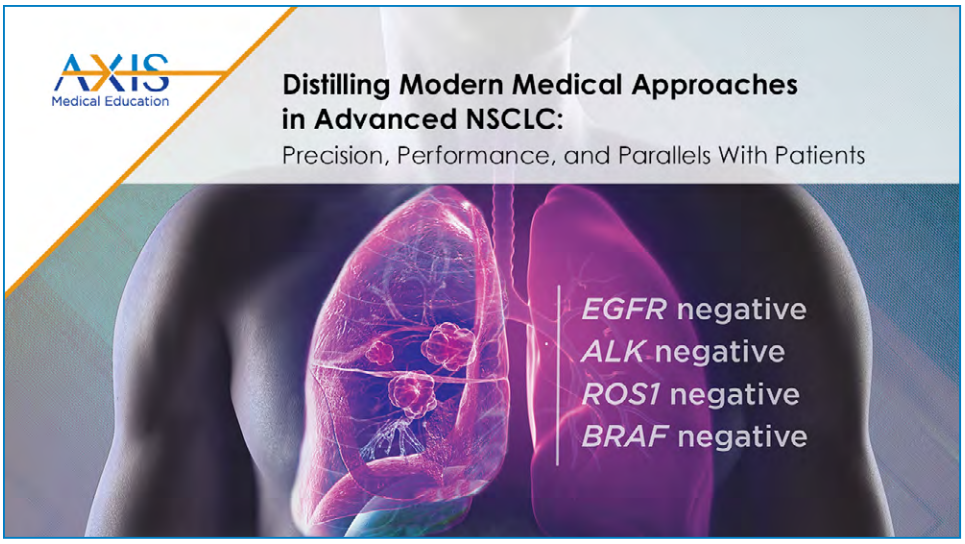
- So, in conclusion, I think it's important to remember for this case that this patient's disease progressed very rapidly, after 2 cycles. When I give chemoimmunotherapy, I don't even usually look at a scan until after 3 cycles depending upon the patient situation. So we're seeing rapid progression. And in that setting, it is possible that the addition of ramucirumab may be associated with a particularly pronounced benefit.



Robert Mocharnuk, MD: Interesting data. Well that concludes our discussion today. Dr. Bauml, would you review key take-aways from today's discussion for the audience?

Joshua Bauml, MD: Chemoimmunotherapy or immunotherapy still remains the standard of care for the first-line management of non–small cell lung cancer without a molecular target. There may be a detrimental association of immunotherapy with hyperprogression for patients who experience that. So it's really important to monitor our patients on immunotherapy closely and, for scientists to continue working in a translational fashion to help identify patients who may experience hyperprogression and those who are most likely to benefit from immunotherapy.

For those patients who with disease progressing, the addition of ramucirumab was associated with an improvement over docetaxel alone in second-line management, and this benefit may be amplified among patients with rapid progression. It is important to remember, though, that all of these data were seen prior to immunotherapy. We don't know how the REVEL outcomes would play out in the setting of prior immunotherapy, although I think that's an important area for future research.



Robert Mocharnuk, MD: Thank you, Dr. Bauml, and thank you for your participation in this activity.

REFERENCES

Ettinger DS, Wood DE, Aisner W, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 3.2019. © 2019 National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

FDA News Release. October 24, 2016. Pembrolizumab (Keytruda) checkpoint inhibitor. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm526430.htm.

FDA News Release. May 10, 2017. Pembrolizumab (Keytruda). https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm558048.htm.

FDA News Release. August 20, 2018. FDA grants regular approval for pembrolizumab in combination with chemotherapy for first-line treatment of metastatic nonsquamous NSCLC. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm617471.htm?utm_campaign=Oncology%20Pembrolizumab%208%2F20%2F2018%20&utm_medium=email&utm_source=Eloqua&elqTrackId=863601bda2b24a2b8502899dc6cdb179&elq=bccbf54bd0334203886812c8676b5c66&elqaid=4707&elqat=1&elqCampaignId=3746.

FDA News Release. October 30, 2018. FDA approves pembrolizumab in combination with chemotherapy for first-line treatment of metastatic squamous NSCLC. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm624659.htm.

FDA News Release. December 6, 2018. FDA approves atezolizumab with chemotherapy and bevacizumab for first-line treatment of metastatic non-squamous NSCLC. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm627874.htm.

FDA News Release. April 11, 2019. FDA expands pembrolizumab indication for first-line treatment of NSCLC (TPS ≥1%). https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm635857.htm.

Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive disease in patients with advanced non–small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. *JAMA Oncol*. 2018;4:1543-1552.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.

Garon EB, Clyleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014;384:665-673.

Reck M, Paz-Ares LG, Bidoli P, et al. Exploratory subgroup analysis of patients (Pts) refractory to first-line (1L) chemotherapy from REVEL, a randomized phase III study of docetaxel (DOC) with ramucirumab (RAM) or placebo (PBO) for second-line (2L) treatment of stage IV non-small-cell lung cancer (NSCLC). *J Clin Oncol*. 2016;34: abstract 9079.

Reck M, Paz-Ares, Bidoli P, et al. Outcomes in patients with aggressive or refractory disease from REVEL: a randomized phase III study of docetaxel with ramucirumab or placebo for second-line treatment of stage IV non-small-cell lung cancer. *Lung Cancer* 2017;112:181-187.

About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

To learn more and to see our current educational offerings, visit us online at www.AXISMedEd.com.

AXIS
Medical Education