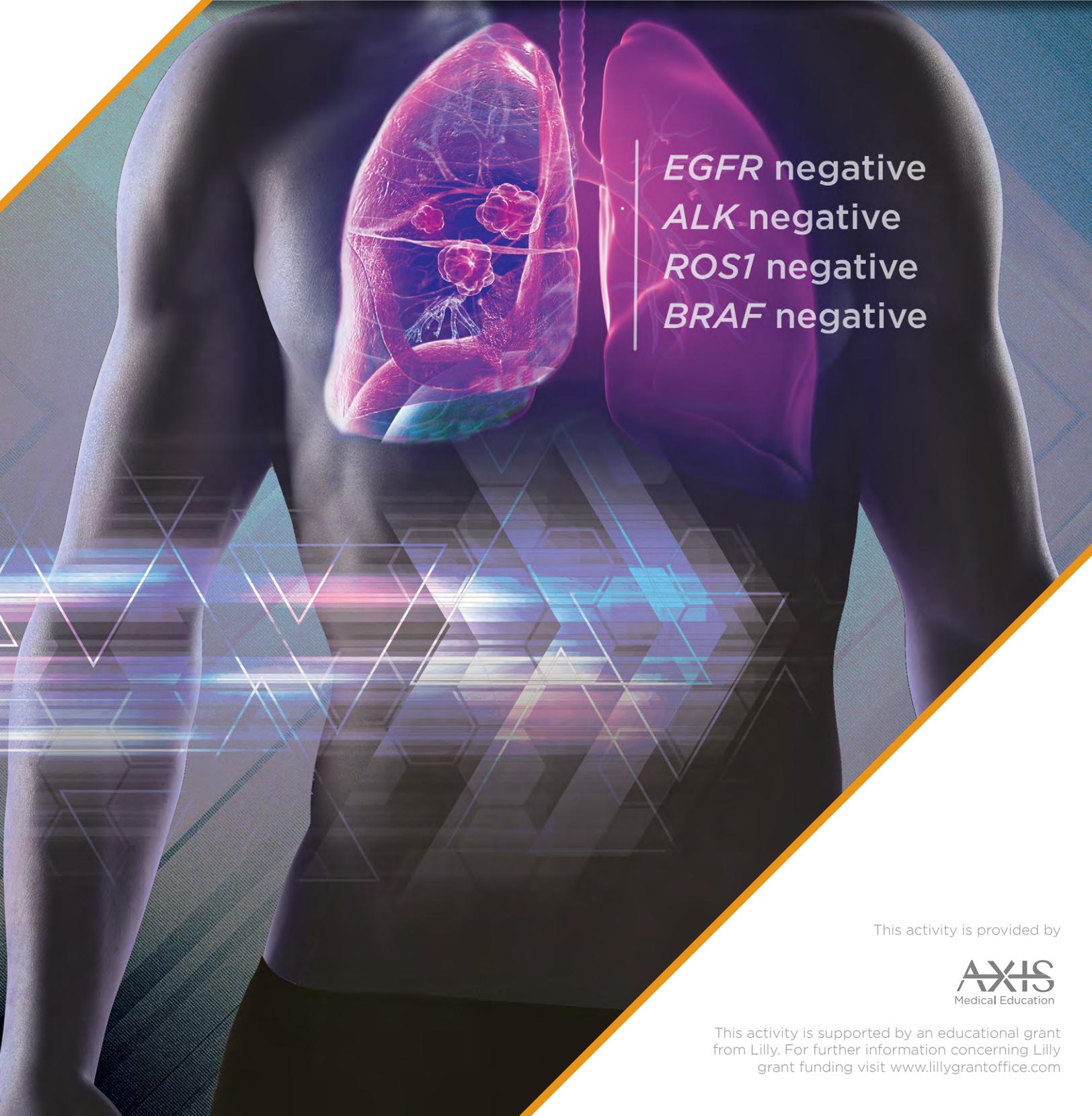


## Distilling Modern Medical Approaches in Advanced NSCLC:

Precision, Performance, and Parallels With Patients

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

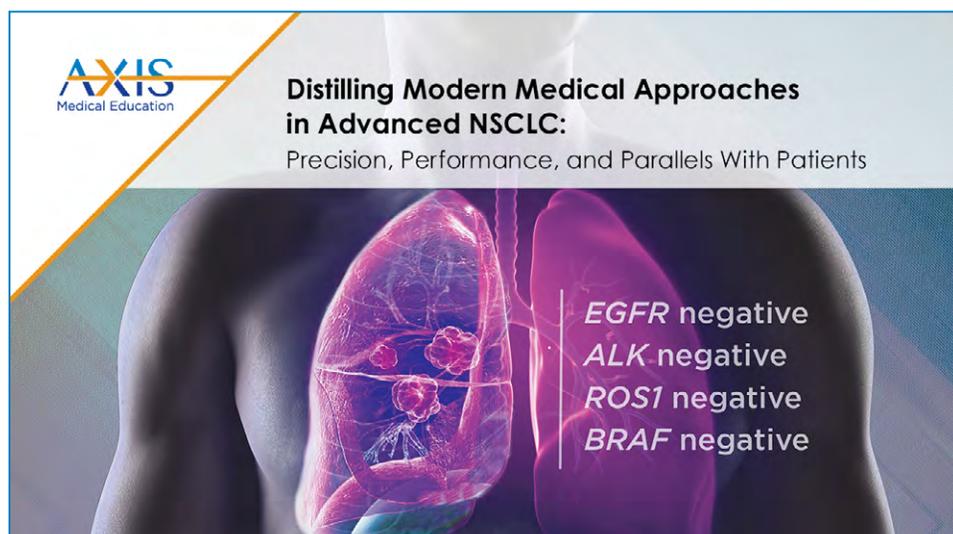


*EGFR* negative  
*ALK* negative  
*ROS1* negative  
*BRAF* negative

This activity is provided by

# 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.



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## Disclosure of Conflicts of Interest

**Joshua Bauml, MD**, reported a financial interest/relationship or affiliation in the form of *Research grant*: Takeda Oncology; Bayer HealthCare, Inc; Janssen Oncology; AstraZeneca Pharmaceuticals LP; Merck & Co, Inc; Incyte Corp; Carevive; and Novartis Pharmaceuticals Corp. *Received income in any amount from*: Bristol-Myers Squibb Co; AstraZeneca Pharmaceuticals LP; Celgene Corp; Merck & Co, Inc; Janssen Oncology; Genentech, Inc; Guardant Health, Inc; Boehringer Ingelheim; and Takeda Oncology.

**Robert Mocharnuk, MD** reported a financial interest/relationship or affiliation in the form of *Common stock*: Merck.



▶ Here is our financial disclosure information.

## MH

- 53-year-old woman presents with cough and SOB
  - 65 PY smoking history, no other medical comorbidities
- CT scan reveals a right-side pleural effusion, mediastinal lymphadenopathy and a 4-cm RML mass
- PET confirms CT findings and also reveals a solitary liver metastasis
- MRI of brain is negative for metastases
- Bronchoscopic biopsy results positive for adenocarcinoma of the lung

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PY, pack-year; RML, right middle lobe; SOB, shortness of breath.

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▶ 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.

## Key Clinical Information

- 30% of tumor cells stain for PD-L1 using the DAKO 22C3 assay
- DNA-and-RNA–based next-generation sequencing assay identified no targetable molecular alterations

PD-L1, programmed cell death protein ligand 1.

AXIS  
Medical Education

▶ 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.

## Rationale for First-Line Treatment Choice

Drug	Trial	Indication	Rationale for MH
Pembrolizumab	KEYNOTE-024	as a single agent for the first-line treatment of patients with <b>PD-L1-expressing</b> (TPS ≥50%) metastatic NSCLC with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations	30% of tumor cells stain for PD-L1 using the DAKO 22C3 assay
	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 <b>express PD-L1 (TPS ≥1%)</b> as determined by an FDA-approved test, with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations	No difference in survival between the two arms in patients with PD-L1 TPS 1% to 49% (exploratory endpoint)
	KEYNOTE-021 KEYNOTE-189	in combination with pemetrexed and platinum chemotherapy as first-line treatment of patients with metastatic <b>nonsquamous</b> NSCLC with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations	<b>Preferred category 1 recommendation in NCCN Guidelines®</b>
	KEYNOTE-407	in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of patients with metastatic <b>squamous</b> NSCLC	Bronchoscopic biopsy positive for lung adenocarcinoma
Atezolizumab	IMpower150	in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic <b>nonsquamous</b> NSCLC with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations	Category 1 recommendation in NCCN Guidelines®

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, 2019.



### ▶ Robert Mocharnuk, MD:

Thank you. Let's go through some of the treatment options appropriate for this patient.

### Joshua Bauml, MD:

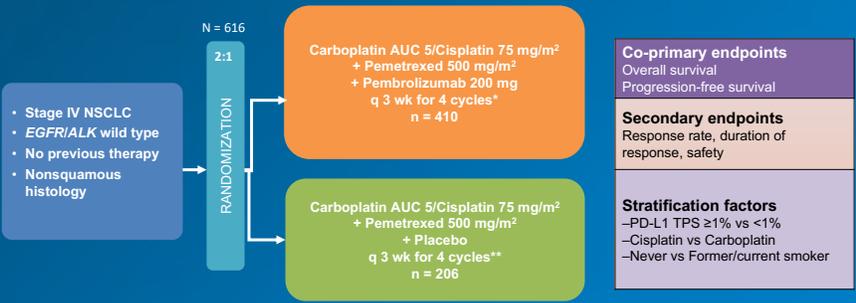
There has been an onslaught of new trials in metastatic non-small cell lung cancer, and we have multiple options that we can consider. KEYNOTE-024 looked at patients who had PD-L1 expression of over 50%. So, that doesn't apply here.

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®.

# KEYNOTE-189: Platinum/Pemetrexed +/- Pembrolizumab

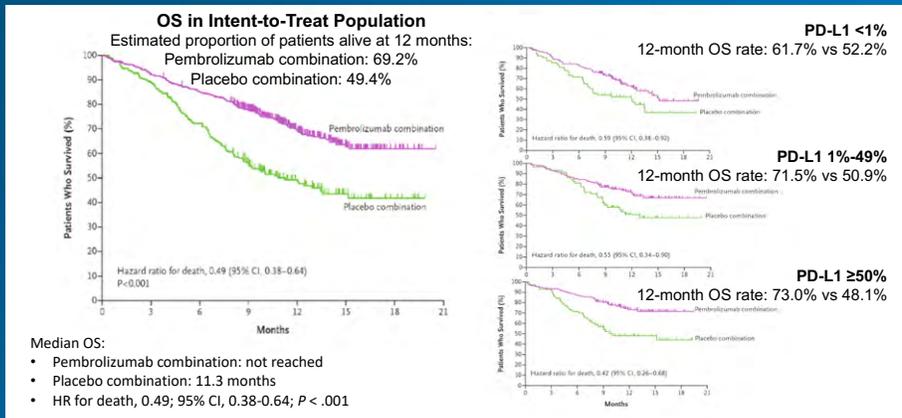


\*Followed by pembrolizumab 200 mg with pemetrexed 500 mg/m<sup>2</sup> q3wk until disease progression.  
 \*\*Followed by placebo with pemetrexed 500 mg/m<sup>2</sup> q3wk until disease progression.  
 AUC: area under the curve; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.  
 Gandhi et al. *N Engl J Med*. 2018;378:2078-2092.



► 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.

## KEYNOTE-189: Overall Survival



OS, overall survival; PD-L1, programmed cell death protein ligand 1.  
 Adapted from Gandhi et al. *N Engl J Med*. 2018;378:2078-2092.



► 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

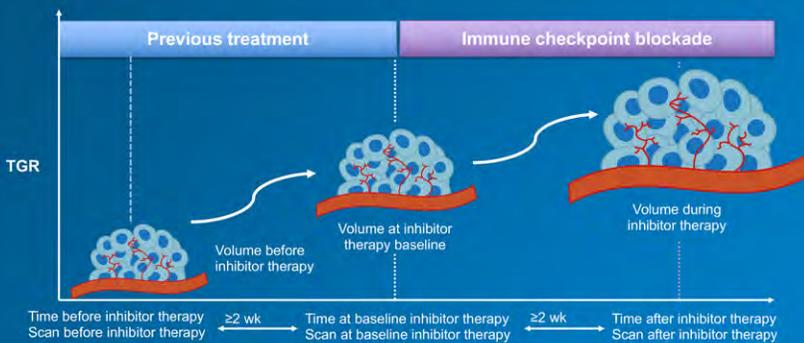
- Patient begins treatment with carboplatin/pemetrexed/pembrolizumab
- After 2 cycles, she presents to clinic with worsening abdominal pain
- CT scan reveals PD in the liver and new bilateral adrenal metastases
- She tells you she heard that sometimes immunotherapy can make cancer bigger before it gets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

CT, computed tomography; PD, progressive disease.

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► 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



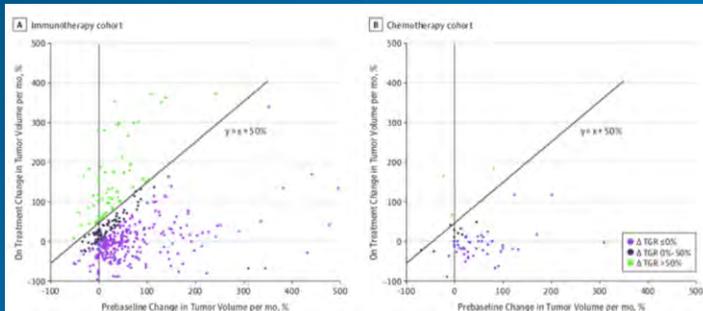
TGR, tumor growth rate.  
Adapted from Ferrara et al. *JAMA Oncol*. 2018;4:1543-1552.

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► 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.

## Hyperprogression on Immunotherapy

Multicenter retrospective study of 406 patients  
Hyperprogression 13.8% on immunotherapy, 5.1% on chemotherapy



Adapted from Ferrara et al. JAMA Oncol. 2018;4:1543-1552.

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► 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 pseudoprogession. So if you have disease that is progressing on immunotherapy, it's really best to regard that as hyperprogression and change your treatment accordingly.

## Back to MH

- Now, you discuss subsequent therapy options with MH

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

## NCCN Guidelines<sup>®</sup> Subsequent Therapy Options for Advanced/Metastatic NSCLC Without Targetable Activating Mutations

### Systemic immune checkpoint inhibitors (preferred)\*:

- Nivolumab (category 1)
- Pembrolizumab (category 1; PD-L1 expression levels  $\geq 1\%$ )
- Atezolizumab (category 1)

### Other systemic therapy (if not previously given):

- Docetaxel
- Pemetrexed (nonsquamous)
- Gemcitabine
- Ramucirumab + docetaxel

However, if progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended

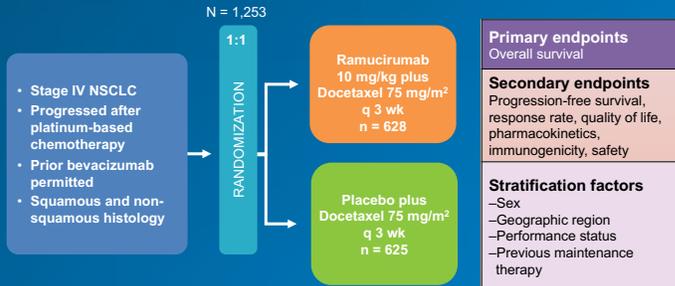
NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand 1.  
\*The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in EGFR+/ALK+ NSCLC.  
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- ▶ **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.

## REVEL: Docetaxel + Ramucirumab

Ramucirumab is a VEGFR-2 monoclonal antibody  
VEGFR blockade inhibits angiogenesis



NSCLC, non-small cell lung cancer; OS, overall survival; VEGFR, vascular endothelial growth factor receptor. Garon et al. *Lancet* 2014;384:665-673.

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- ▶ 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

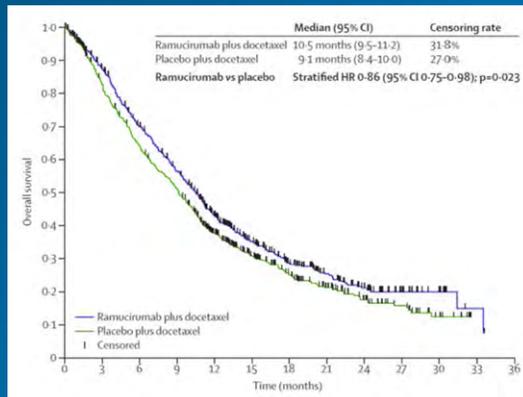
Treatment-Emergent Adverse Event	Ramucirumab + docetaxel (n = 627)		Placebo + docetaxel (n = 618)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	98%	79%	95%	71%
Fatigue	55%	14%	49%	10%
Diarrhea	32%	5%	27%	3%
Nausea	27%	1%	27%	1%
Stomatitis	23%	4%	13%	2%
Neuropathy	23%	3%	20%	2%
Neutropenia	55%	49%	45%	39%
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.

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- ▶ 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.

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- ▶ 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.

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- ▶ **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.



► 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.



► 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.

## Case Conclusion

- Remember, disease progressed rapidly (after 2 cycles) on initial platinum-based therapy (chemotherapy in combination with immune checkpoint inhibitor)
- Patient begins treatment with ramucirumab/docetaxel
  - REVEL exploratory analysis in patients with aggressive or refractory disease: patients with <9 months since start of first-line therapy had longer survival and better outcomes with ramucirumab plus docetaxel versus placebo plus docetaxel

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▶ 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.

## Summary

- Chemoimmunotherapy or immunotherapy is the current standard of care for patients with NSCLC without a molecular target
- There may be a detrimental association of immunotherapy with disease hyperprogression in a subset of patients with NSCLC
- The addition of ramucirumab to docetaxel was associated with an improvement in outcomes over docetaxel alone
- This benefit may be amplified among patients with rapid progression
  - These data were seen prior to the era of immunotherapy

NSCLC, non-small cell lung cancer.

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▶ **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.



## Distilling Modern Medical Approaches in Advanced NSCLC:

Precision, Performance, and Parallels With Patients

A 3D medical illustration of human lungs, rendered in a translucent pinkish-purple color. Several small, dark, irregular masses representing tumors are visible on the surface of the lungs. The background is a dark, textured blue.

*EGFR* negative  
*ALK* negative  
*ROS1* negative  
*BRAF* negative

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

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