Case: 71-Year-Old Woman With Stage IV Metastatic Adenocarcinoma of the Lung

A 71-year-old Caucasian woman with SLE and intermittent hemoptysis is diagnosed with stage IV metastatic adenocarcinoma of the lung with bilateral pulmonary nodules, 2 liver metastases, and a left adrenal metastasis. She does not have any brain metastases. A diagnostic biopsy is performed on the LLL lung and is sent for molecular profiling (NGS and IHC). Profiling shows that she is negative for *EGFR, ALK, ROS1, MET* exon 14 skip, *RET, NTRK, HER2, KRAS*, and *BRAF* mutations. IHC shows that she is PD-L1 positive, with 5% expression. She proceeds to receive frontline carboplatin-pemetrexed therapy. She declines the pembrolizumab because she is told that her SLE could get worse on this agent. After 4 cycles, she has stable disease and is planning to start maintenance pemetrexed.

How long would you administer pemetrexed therapy?

A) 6 months

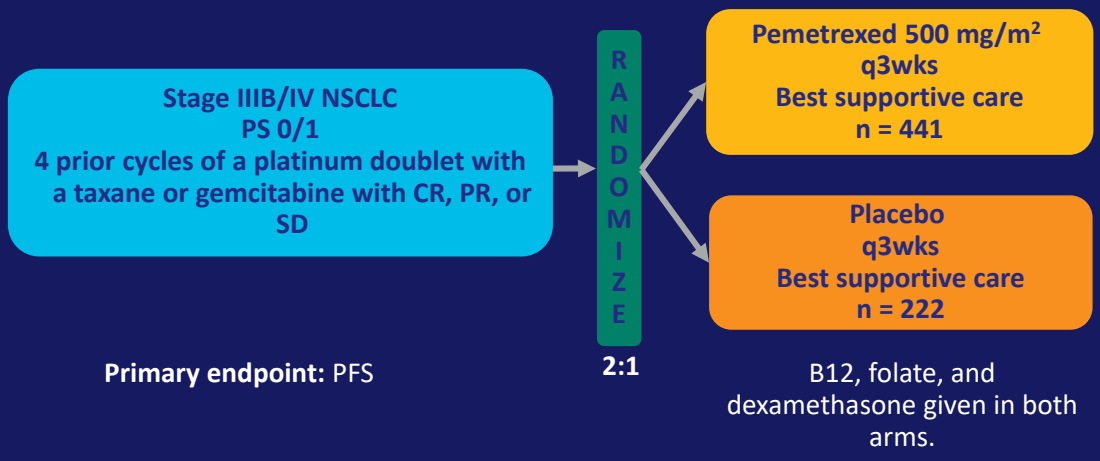
B) 1 year

C) Up to 35 treatments

D) Until disease progression or unacceptable toxicity

E) Unknown

JMEN: Phase 3 Trial of Maintenance Pemetrexed in Advanced NSCLC



Primary endpoint: PFS

B12, folate, and dexamethasone given in both arms.

Ciuleanu T, et al. *Lancet.* 2009;374:1432-40.

JMEN: Efficacy of Maintenance Pemetrexed vs Placebo in Nonprogressing Patients With Advanced NSCLC

	Median PFS, months (95% CI; independent review)		HR		Median OS, months (95% CI)		HR	
	Pem	PBO	(95% CI)	*P* Value	Pem	PBO	(95% CI)	*P* Value
Overall population	4.0 (3.1-4.4)	2.0 (1.5-2.8)	0.60 (0.49-0.73)	< .0001	13.4 (11.9-15.9)	10.6 (8.7-12.0)	0.79 (0.65-0.95)	.012

- Grade 3/4 toxic effects were higher with pemetrexed than placebo (16% vs 4%, *P* < .001), including fatigue (5% vs < 1%) and neutropenia (3% vs 0%)

Ciuleanu T, et al. *Lancet.* 2009;374:1432-40.

JMEN: Efficacy of Maintenance Pemetrexed by Histologic Groups

	Median PFS[a], months			CR + PR + SD[b]			Median OS, months		
	Pem	PBO	*P* Value	Pem	PBO	*P* Value	Pem	PBO	*P* Value
Nonsquamous (n = 481)	4.4	1.8	< .0001	58%	33%	< .0001	15.5	10.3	.002
Adenocarcinoma (n = 328)	4.6	2.7	< .0001	61%	33%	< .0001	16.8	11.5	.026
Large cell (n = 20)	4.5	1.5	.125	46%	33%	.670	8.4	7.9	.964
Other (n = 133)	4.1	1.6	.0003	51%	32%	.041	11.3	7.7	.025
Squamous (n = 182)	2.4	2.5	.896	35%	35%	> .999	9.9	10.8	.678

[a]Independent review.
[b]DCR (CR + PR + SD) was significantly improved with pemetrexed vs placebo in the ITT population (49% vs 29%, *P* < .0001) by independent review.

Ciuleanu T, et al. *Lancet.* 2009;374:1432-40.

Case (cont.)

The patient receives pemetrexed for 2 additional cycles of therapy, but then experiences disease progression with new bone metastases and new pulmonary nodules. She is now symptomatic with pain. Her hemoptysis has resolved completely. She receives palliative radiation to the painful bone metastases but would like to know her options for therapy.

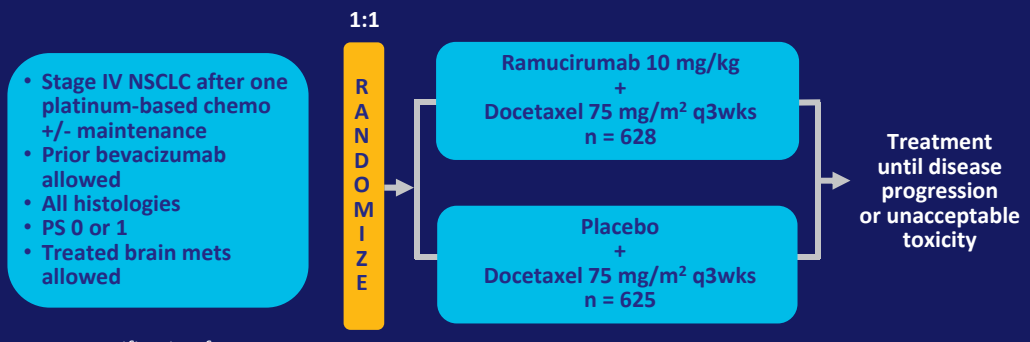
Which treatment would you switch to?

A) Carboplatin-pemetrexed-pembrolizumab
B) Erlotinib
C) Carboplatin-paclitaxel-bevacizumab-atezolizumab
D) Docetaxel-ramucirumab
E) Crizotinib

Case: Discussion

- Factors that affect second-line treatment decisions in patients
  - Tumor burden
  - Rate of disease progression
  - Efficacy/safety of treatments
  - Patient preferences
  - Comorbidities

Phase 3 REVEL: Study Design



Stratification factors:
- ECOG PS 0 vs 1
- Gender
- Prior maintenance
- East Asia vs ROW

Primary endpoint: OS
Secondary endpoints: PFS, ORR, safety, patient-reported outcomes

Garon EB, et al. *Lancet*. 2014;384:665-73.

Tumor Response by RECIST v1.1:

ITT Population, Investigator Assessment

	RAM + DOC n = 628	PBO + DOC n = 625	*P* Value
Response, n (%)			
CR	3 (0.5)	2 (0.3)	
PR	141 (22.5)	83 (13.3)	
SD	258 (41.1)	244 (39.0)	
PD	128 (20.4)	206 (33.0)	
Unknown/ not assessed	98 (15.6)	90 (14.4)	
ORR (CR + PR), % (95% CI)	22.9 (19.7-26.4)	13.6 (11.0-16.5)	< .001
DCR (CR + PR + SD), % (95% CI)	64.0 (60.1-67.8)	52.6 (48.6-56.6)	< .001

Garon EB, et al. *Lancet*. 2014;384:665-73.

REVEL: PFS and OS

	Median PFS, months (95% CI; ITT population)		Censoring Rate		Stratified HR (95% CI)	*P* Value
	RAM + DOC	PBO + DOC	RAM + DOC	PBO + DOC		
Overall population	4.5 (4.2-5.4)	3.0 (2.8-3.9)	11%	6.7%	0.76 (0.68-0.86)	< .0001

	Median OS, months (95% CI; ITT population)		Censoring Rate		Stratified HR (95% CI)	*P* Value
	RAM + DOC	PBO + DOC	RAM + DOC	PBO + DOC		
Overall population	10.5 (9.5-11.2)	9.1 (8.4-10.0)	31.8%	27.0%	0.86 (0.75-0.98)	.023

Garon EB, et al. *Lancet*. 2014;384:665-73.

OS by Histology

	Median OS, months (95% CI; ITT population)		Censoring Rate			
	RAM + DOC	PBO + DOC	RAM + DOC	PBO + DOC	HR (95% CI)	*P* Value
Nonsquamous	11.1 (9.9-12.3)	9.7 (8.5-10.6)	35.5%	29.3%	0.83 (0.71-0.98)	.020
Squamous	9.5 (8.0-10.8)	8.2 (6.3-9.4)	21.7%	19.9%	0.88 (0.70-1.13)	.319

Garon EB, et al. *Lancet*. 2014;384:665-73.

Phase 3 Results: Safety

- Common grade 3 or worse AEs:
  - Neutropenia (49% in the ramucirumab group vs 40% in the control group)
  - Febrile neutropenia (16% vs 10%)
  - Fatigue (14% vs 10%)
  - Leucopenia (14% vs 12%)
  - Hypertension (6% vs 2%)
- Risk: increased risk of hemorrhage, including severe and sometimes fatal hemorrhagic events

Garon EB, et al. *Lancet*. 2014;384:665-73; prescribing information.

REVEL: Summary

- REVEL met its primary endpoint of OS improvement
- Ramucirumab-docetaxel showed statistically significant improvement in PFS and ORR compared with placebo-docetaxel
- OS and PFS improvements were consistent in most major subgroups, including squamous and nonsquamous histology
- The addition of ramucirumab to docetaxel did not result in an increase of serious AEs and AEs leading to death; safety profile was as expected for an anti-VEGFR agent in combination with docetaxel
- Ramucirumab with docetaxel was FDA approved for platinum-refractory NSCLC in December 2014
- Exploratory analysis suggests that patients with rapid progression may benefit the most from ramucirumab-docetaxel

Guideline Recommendations—January 2019

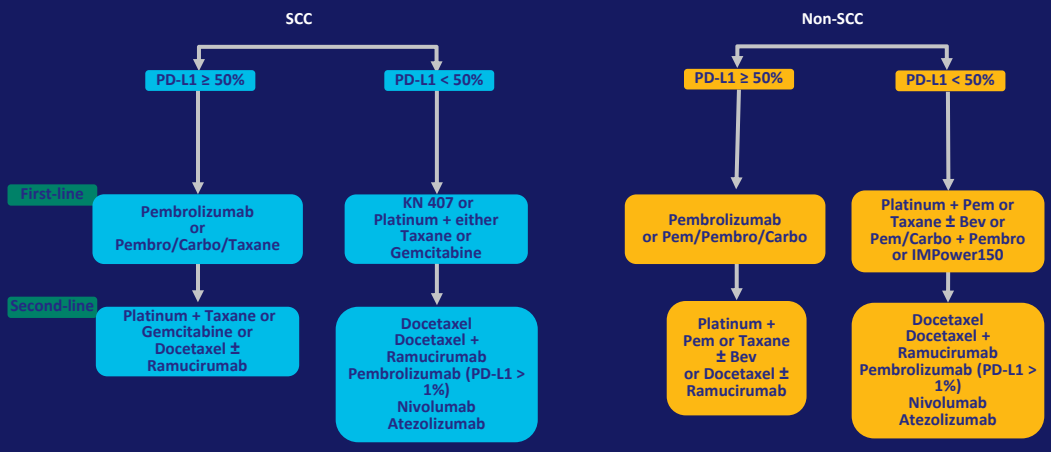
- NCCN guidelines recommend:
  - Platinum-based doublet therapy for patients who progress after first-line therapy with pembrolizumab
  - Docetaxel (with or without ramucirumab), pemetrexed (nonsquamous only), or gemcitabine for patients who progress after first-line therapy with PD-L1/PD-1 inhibitors/chemotherapy

NCCN guidelines. NSCLC v3.2019.

Case (cont.)

- What if she had SCC and SLE and progressed after first-line carboplatin-paclitaxel?
  - What are the treatment options?
    - Docetaxel
    - Gemcitabine
    - Ramucirumab-docetaxel
  - If she did not have significant SLE:
    - Nivolumab
    - Nivolumab-ipilimumab
    - Atezolizumab
    - Pembrolizumab
  - Benefits and limitations of each option

First- and Second-Line Treatment of Metastatic NSCLC Without a Driver Mutation



NCCN guidelines. NSCLC v3.2019.

Case: 59-Year-Old Man With Stage IV Metastatic Non-SCC NSCLC

A 59-year-old Caucasian man is diagnosed with stage IV metastatic non-SCC NSCLC with bilateral pulmonary nodules, mediastinal lymph nodes, 2 T-spine bone metastases, and bilateral adrenal metastases. His brain MRI is clear. A diagnostic biopsy is performed on a mediastinal lymph node and is sent for molecular profiling (NGS and IHC). Profiling shows that he is negative for *EGFR, ALK, ROS1, MET* exon 14 skip, *RET, NTRK, HER2*, and *BRAF* mutations, but he is positive for a *KRAS* G12C mutation. IHC shows that he is PD-L1 positive, with 20% expression. He is treated with carboplatin-pemetrexed-pembrolizumab. After 2 cycles, he achieves a PR, and after 4 cycles, he has stable disease.

What would you recommend for this patient?

A) Pemetrexed-pembrolizumab maintenance
B) Nab-paclitaxel maintenance
C) Docetaxel-ramucirumab
D) Nivolumab
E) Nivolumab-ipilimumab

KEYNOTE-189

- KEYNOTE-189 randomized chemo-naïve patients with metastatic non-SCC NSCLC to carboplatin-pemetrexed-pembrolizumab vs carboplatin-pemetrexed alone for 4 cycles then pemetrexed-pembrolizumab or pemetrexed maintenance therapy
- Carboplatin-pemetrexed-pembrolizumab improved:
  - Median OS (NR vs 11.3 months; HR, 0.49; $P < .00001$)
  - Median PFS (8.8 vs 4.9 months; HR, 0.52; $P < .00001$)
  - ORR (47.6% vs 18.9%; $P < .0001$)
- Survival benefit was seen in all subgroups and all PD-L1 expression subgroups
- Patients with metastatic non-SCC NSCLC who are WT for mutations and PD-L1 IHC < 50% should receive platinum-pemetrexed-pembrolizumab as standard of care
- Patients with metastatic non-SCC NSCLC who are PD-L1 IHC ≥ 50% can receive either pembrolizumab or platinum-pemetrexed-pembrolizumab as standard of care
  - Decisions should be based on patient's symptom severity, as patients with high PD-L1 have high response rates to the triplet therapy
- AEs that occurred more frequently in pembrolizumab combination group were diarrhea and rash; grade 3 AE that occurred more frequently in pembrolizumab combination group was febrile neutropenia
- Risk: immune-related adverse reactions (pneumonitis, colitis, hepatitis, nephritis, endocrinopathies)

Gandhi L, et al. *N Engl J Med.* 2018;378:2078-92; prescribing information.

Case: Discussion

- Other frontline therapy options for non-SCC NSCLC
- Frontline options for SCC NSCLC

IMPower150

- 1,202 patients randomized to one of 3 arms:
  - Chemotherapy + atezolizumab (A)
  - Chemotherapy + atezolizumab + bevacizumab (B)
  - Chemotherapy + bevacizumab (C)
- PFS between arms B and C showed:
  - Combination of atezolizumab, bevacizumab, and chemotherapy was superior to bevacizumab and chemotherapy alone
  - Median PFS of 8.3 vs 6.8 months (HR, 0.62; 95% CI, 0.52-0.74; *P* < .0001) in the ITT-WT population
  - Patients with EGFR mutations or ALK rearrangements were excluded from the primary analysis and analyzed separately
  - PD-L1–negative patients were included
  - OS was improved in arm B (19.2 months) vs C (14.7 months) (HR, 0.78; 95% CI, 0.64-0.96; *P* = .016) in the ITT-WT
- Most common grade 3 or 4 AEs were neutropenia, decreased neutrophil count, febrile neutropenia, and hypertension; treatment-related serious AEs were noted in 25.4% of patients in arm B and 19.3% of those in arm C
- Risk: immune-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies)

Socinski MA, et al. *N Engl J Med.* 2018;378:2288-301; Socinski MA, et al. *J Clin Oncol.* 2018;36:abstr 9002.

Keynote-407

- KEYNOTE-407 randomized 560 chemo-naïve patients with metastatic SCC NSCLC to carboplatin-taxane-pembrolizumab vs carboplatin-taxane alone for 4 cycles then pembrolizumab or placebo maintenance for up to 31 cycles; an optional crossover was allowed at time of disease progression
- Patients stratified by choice of taxane, PD-L1 (TPS < 1% vs ≥ 1%), and site (East Asia vs other)
- Chemo + pembrolizumab vs chemo alone:
  - Improved median OS (15.9 vs 11.3 months; HR, 0.64; *P* < .001)
  - Median PFS (6.4 vs 4.8 months; HR, 0.56; *P* < .001)
  - Response rates (58.4% vs 38%; *P* = .0004)
  - Duration of response (7.7 vs 4.8 months)
- Survival benefit was seen in all subgroups and all PD-L1 expression subgroups
- AEs of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab combination group and 68.2% in the chemo alone group
- Standard of care:
  - SCC NSCLC patients with < 50% PD-L1 IHC expression: carboplatin-taxane (paclitaxel or nab-paclitaxel)-pembrolizumab
  - SCC NSCLC patients with ≥ 50% PD-L1 IHC expression: pembrolizumab alone or platinum-taxane (paclitaxel or nab-paclitaxel) with pembrolizumab
  - Patients who have a contraindication to immunotherapy should receive a platinum-doublet

Paz-Ares LG, et al. *N Engl J Med*. 2018;379:2040-51.

Case (cont.)

The patient receives 6 cycles of pemetrexed-pembrolizumab maintenance therapy and experiences disease progression with 2 new bone metastases and a liver lesion.

- What factors affect second-line treatment decisions?
  - Treatment history
  - Tumor burden
  - Rate of disease progression
  - Patient preferences
  - Efficacy/safety of treatments

Case: Discussion

What are the treatment options?

1) Docetaxel
2) Gemcitabine
3) Ramucirumab-docetaxel
4) Nivolumab
5) Nivolumab-ipilimumab
6) Afatinib

Guideline Recommendations—January 2019

- NCCN guidelines recommend:
  - Platinum-based doublet therapy for patients who progress after first-line therapy with pembrolizumab
  - Docetaxel (with or without ramucirumab), pemetrexed (nonsquamous only), or gemcitabine for patients who progress after first-line therapy with PD-L1/PD-1 inhibitors/chemotherapy

NCCN guidelines. NSCLC v3.2019.

Case (cont.)

What if the patient had rapidly progressed on frontline carboplatin-pemetrexed-pembrolizumab?

What second-line therapy would you recommend for this patient?

A) Nivolumab-ipilimumab

B) Nab-paclitaxel

C) Docetaxel-ramucirumab

D) Gemcitabine

E) Vinorelbine

REVEL: Exploratory Analysis in Patients With Rapid Progression on First-Line Therapy

- REVEL was not powered for subgroup analyses
- Exploratory analysis of efficacy endpoints for patients refractory to frontline therapy
- Sensitivity analyses on other subgroups of patients with aggressive or rapidly progressing disease from ITT population included patients with all histologies or only adenocarcinoma histology who remained on first-line therapy for ≤ 4, ≤ 8, and ≤ 12 weeks from initiation of frontline therapy

Reck M, et al. *Lung Cancer*. 2017;112:181-7.

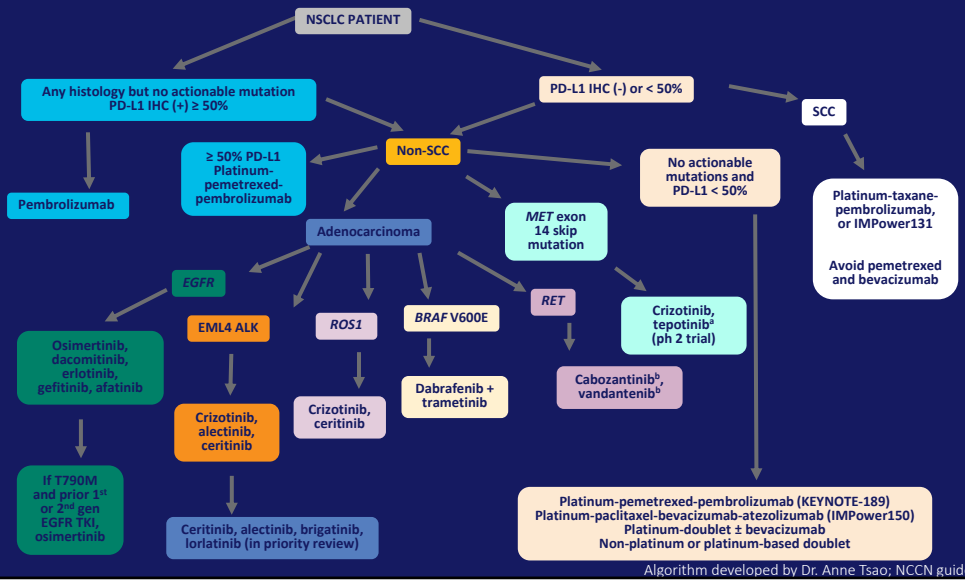
REVEL: Efficacy in Patients With Rapid Progression—ITT Population

	Duration of First-Line Therapy					
	≤ 4 Weeks		≤ 8 Weeks		≤ 12 Weeks	
ITT Population	RAM + DOC (n = 33)	PBO + DOC (n = 24)	RAM + DOC (n = 112)	PBO + DOC (n = 88)	RAM + DOC (n = 244)	PBO + DOC (n = 204)
Median OS, mo	8.8	3.2	8.6	6.9	9.2	7.2
HR[a] (95% CI)	0.40 (0.22-0.73)		0.83 (0.61-1.15)		0.85 (0.68-1.05)	
12-mo survival, %	34	13	33	26	34	30
18-mo survival, %	27	NE	19	19	21	18
Median PFS, mo	2.9	1.4	3.3	2.5	4.1	2.8
HR[a] (95% CI)	0.44 (0.25-0.78)		0.85 (0.64-1.14)		0.75 (0.61-0.91)	
ORR[b], % (95% CI)	24.2	0.0	23.2	11.4	26.2	11.8
DCR[b], % (95% CI)	51.5	20.8	51.8	45.5	58.2	46.6

[a]Unstratified; [b]CR + PR + SD.

Reck M, et al. *Lung Cancer*. 2017;112:181-7.

Frontline Histology and Molecular Profiling, Jan 2019



[a]Investigational.
[b]Off-label.

Algorithm developed by Dr. Anne Tsao; NCCN guidelines. NSCLC v3.2019.

To receive credit, click the "Advance to Post-Test" button for access to the evaluation, attestation, and post-test.

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Abbreviations/Acronyms

AE = adverse event
ALK = anaplastic lymphoma kinase
CR = complete response
DCR = disease control rate
ECOG = Eastern Cooperative Oncology Group
EGFR = epidermal growth factor receptor
EML4 = echinoderm microtubule-associated protein-like 4
FDA = Food and Drug Administration
IHC = immunohistochemistry
ITT = intention-to-treat
IQR = interquartile range
LLL = left lower lobe
NCCN = National Comprehensive Cancer Network
NGS = next-generation sequencing
NSCLC = non–small cell lung cancer
ORR = objective response rate
OS = overall survival
PBO = placebo
PD = progressive disease
PD-L1 = programmed cell death ligand-1
PFS = progression-free survival
PR = partial response
PS = performance status
RECIST = Response Evaluation Criteria in Solid Tumors
RLL = right lower lobe
ROW = rest of the world
SCC = squamous cell carcinoma
SD = stable disease
SLE = systemic lupus erythematosus
TPS = tumor proportion score
VEGFR = vascular endothelial growth factor receptor
WT = wild type