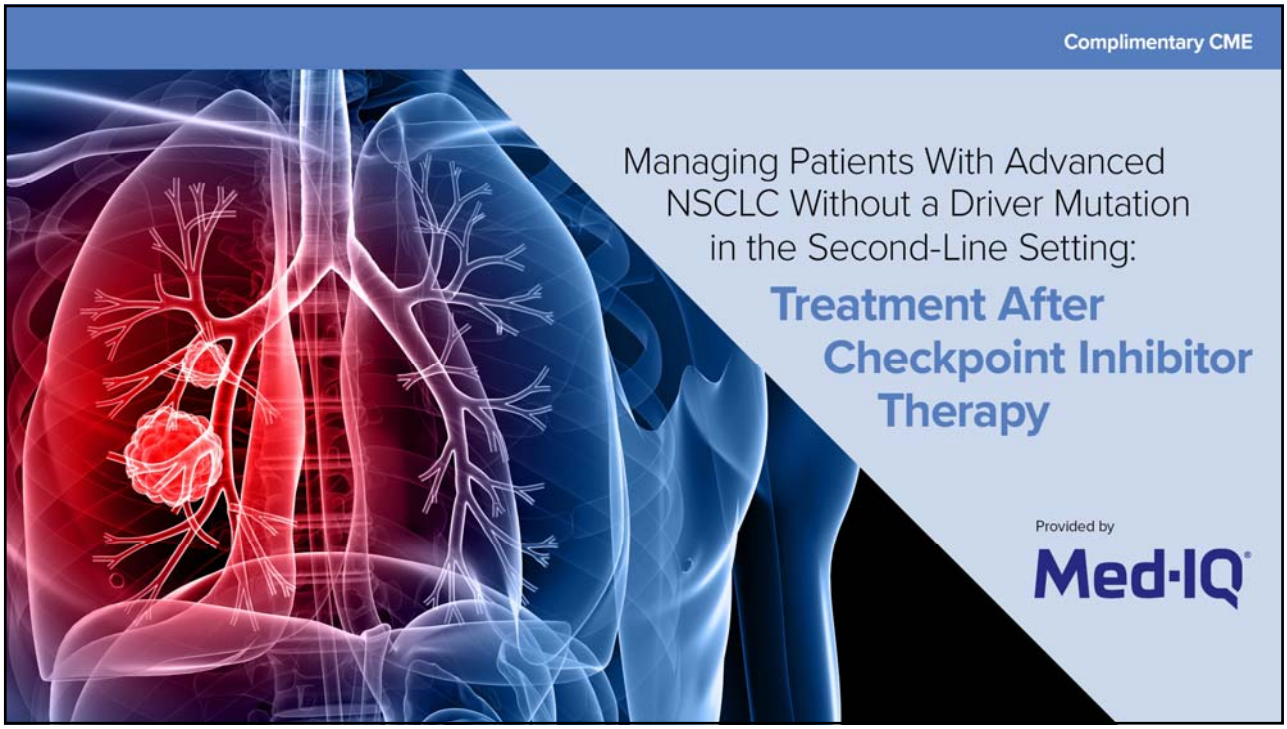


Case: 65-Year-Old Man With Stage IV Metastatic Adenocarcinoma of the Lung

A 65-year-old Caucasian man is diagnosed with stage IV metastatic adenocarcinoma of the lung with diffuse bilateral pulmonary nodules and multiple T-spine bone lesions. He does not have any brain metastases. A diagnostic biopsy is performed on the RLL lung 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, KRAS*, and *BRAF* mutations. IHC shows that he is PD-L1 positive, with 65% expression. He proceeds to frontline pembrolizumab therapy.

- How long would you administer pembrolizumab therapy?

  A) 6 months

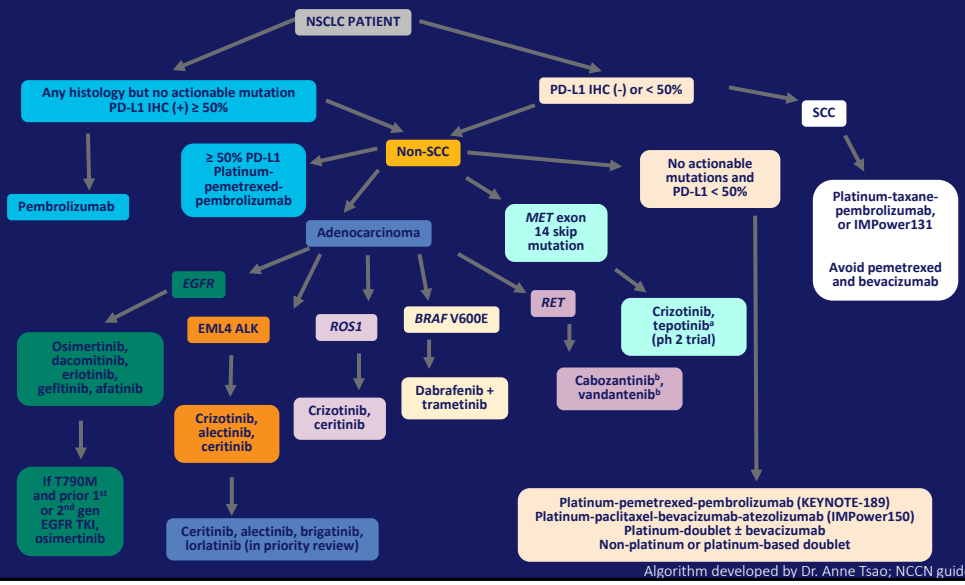
  B) 1 year

  C) Up to 35 treatments

  D) Until disease progression or unacceptable toxicity

  E) Unknown

Frontline Histology and Molecular Profiling, Jan 2019



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

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

KEYNOTE-042

- KEYNOTE-042 was a phase 3 trial that randomized patients with metastatic NSCLC (PD-L1 IHC positive) to pembrolizumab or platinum-doublet chemotherapy; patients in the pembrolizumab arm received up to 35 cycles of therapy
- Patients with PD-L1 ≥ 50% had the greatest magnitude of PFS and OS benefit
  - PD-L1 IHC ≥ 50%: median OS was 20 months vs 12.2 months (HR, 0.69; *P* = .0003)
  - PD-L1 IHC ≥ 20%: median OS was 17.7 months vs 13 months (HR, 0.77; *P* = .0020)
  - PD-L1 IHC ≥ 1%: median OS was 16.7 months vs 12.1 months (HR, 0.81; *P* = .0018)
- However, the high PD-L1 IHC group likely accounts for all of the positive results on the trial; recommendation is to give pembrolizumab alone only in those with high PD-L1 IHC expression
  - TPS ≥ 1%-49% OS was 13.4 months (95% CI, 10.7-18.2) in pembrolizumab alone vs 12.1 months (95% CI, 11.0-14.0) in chemotherapy group (HR, 0.92; 95% CI, 0.77-1.11)
- Patients with known mutations were excluded from this trial; avoid pembrolizumab monotherapy in these patients
- Grade 3-5 drug-related AEs occurred less frequently with pembrolizumab (17.8% vs 41%)

Lopes G, et al. *J Clin Oncol*. 2018;36:abstr LBA4.

Case (cont.)

The patient receives pembrolizumab and, after 2 cycles of therapy, experiences rapid disease progression. He is now symptomatic with shortness of breath and has multiple new pulmonary nodules, liver metastases, and adrenal metastases. He is also now experiencing hemoptysis.

- Which treatment would you switch to?

  A) Carboplatin-pemetrexed-pembrolizumab

  B) Carboplatin-pemetrexed

  C) Carboplatin-paclitaxel-bevacizumab-atezolizumab

  D) Docetaxel-ramucirumab

  E) Carboplatin-paclitaxel

Case: Discussion

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

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.

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.

Case (cont.)

- What if he had SCC and progressed on first-line platinum-taxane-pembrolizumab?
  - What are the treatment options?
    - Docetaxel
    - Gemcitabine
    - Ramucirumab-docetaxel
    - Nivolumab
    - Nivolumab-ipilimumab
    - Afatinib
  - Benefits and limitations of each option

KEYNOTE-407: Chemotherapy ± Pembrolizumab in Treatment-Naïve SCC NSCLC Patients

- 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 (59.4% 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: 68-Year-Old Man With Stage IV Metastatic Adenocarcinoma of the Lung

A 68-year-old Caucasian man is diagnosed with stage IV metastatic adenocarcinoma of the lung with bilateral pulmonary nodules, mediastinal lymph nodes, several T- and L-spine metastases, and 4 liver metastases. His brain MRI is clear. A diagnostic biopsy is performed on the LLL lung and is sent for molecular profiling. Profiling shows that he is negative for *EGFR*, *ALK*, *ROS1*, *MET* exon 14 skip, *RET*, *NTRK*, *HER2*, *KRAS*, and *BRAF* mutations. IHC shows that he is PD-L1 positive, with 20% expression. He is symptomatic with dyspnea on exertion. He is treated with carboplatin-pemetrexed-pembrolizumab. After 2 cycles, he has stable disease. After 4 cycles, he experiences rapid disease progression with new bone lesions and multiple new liver metastases.

- What would you recommend for this patient?

  A) Nivolumab-ipilimumab

  B) Nab-paclitaxel

  C) Docetaxel-ramucirumab

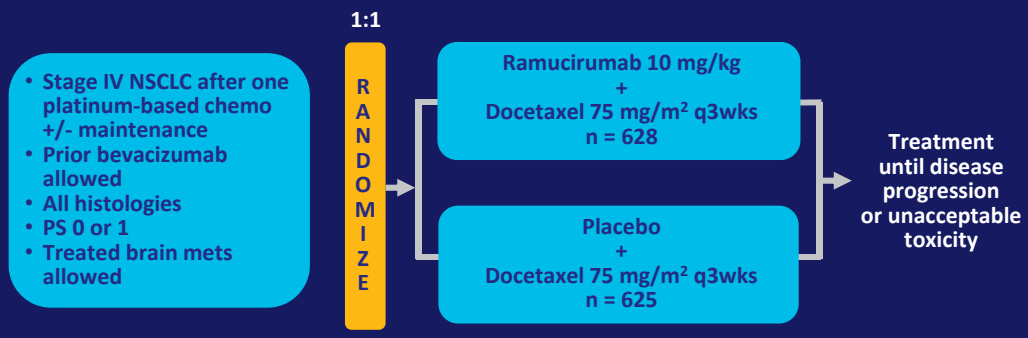
  D) Gemcitabine

  E) Vinorelbine

Case: Discussion

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

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.

Phase 3 REVEL: Results

- Median PFS (ITT population, investigator assessment): 4.5 months (IQR, 2.3-8.3; 11.1% censoring) for ramucirumab group compared to 3 months (IQR, 1.4-6.9; 6.7% censoring) for the control group (HR, 0.76; 95% CI, 0.68-0.86; *P* < .0001)
- Median OS (ITT population): 10.5 months (IQR, 5.1-21.2; 31.8% censoring) in ramucirumab group and 9.1 months (IQR, 4.2-18.0; 27% censoring) for placebo (stratified HR, 0.86; 95% CI, 0.75-0.98; *P* = .023)

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.

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: 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

ITT Population	Duration of First-Line Therapy					
	≤ 4 Weeks		≤ 8 Weeks		≤ 12 Weeks	
	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.

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

Case

- What would you recommend for this patient?
  A) Nivolumab-ipilimumab
  B) Nab-paclitaxel
  C) Docetaxel-ramucirumab
  D) Gemcitabine
  E) Vinorelbine
- Benefits and limitations of the treatment options

Optimal Sequential Therapy: Discussion

- What if the patient received first-line platinum-based chemotherapy?
  - What are the second-line treatment options?
- What if the patient received first-line atezolizumab in combination with paclitaxel and bevacizumab?
  - What are the second-line treatment options?

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

Contact Information

For CME questions, please contact Med-IQ:

Call (toll-free) 866 858 7434

E-mail info@med-iq.com

Please visit us online at www.Med-IQ.com for additional activities provided by Med-IQ.

Acknowledgment of Commercial Support

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

Med-IQ®

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