JADPRO CE

Regional Lectures

Clinical Advances and Case Studies in Immune Checkpoint Inhibitors in Oncology

Non–Small Cell Lung Cancer

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Faculty Financial Disclosures

- Ms. Hoffner has received consulting fees/honoraria from Abbott, Array BioPharma, and Merck.
- Ms. Zitella has served on the advisory board for Array Biopharma and has equity interests/stock options in Kite Pharma.
- Dr. Lewis has nothing to disclose.

Planning Committee Financial Disclosures

- Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has served as a consultant for Pfizer and Eisai.
- Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has nothing to disclose.
- Annenberg Center for Health Sciences at Eisenhower
  - John Bayliss, VP, Business Development, spouse is an employee of Amgen, Inc.; Charles Willis, Director, Continuing Education, consults for Pfizer Inc.; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.
- Alana Brody, Lynn Rubin, and Patti McLafferty (Harborside Medical Education) have nothing to disclose.
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Learning Objectives

- Differentiate between early and late adverse effects associated with immunotherapeutic agents.
- Recognize the differences between immunotherapeutic agents and chemotherapeutic agents: mechanisms of action, adverse effects, and toxicity management.
- Summarize data on currently available immunotherapeutic agents as they relate to durable treatment responses.
- Explain the utility of biomarker testing in selecting patients for immunotherapy and in predicting clinical outcomes.

Cancer of the Lung and Bronchus

- 13.2% of all new cancer cases
- 25.9% of all cancer deaths
- 222,500 estimated new cases in the United States in 2017
- Rates for new lung and bronchus cancer cases have been falling on average 2.0% each year over the past 10 years
  - Death rates falling on average 2.5% each year over 2005–2014

Approved Immunotherapies

- **3/4/15:** Nivolumab for squamous NSCLC with progression on or after platinum-containing chemotherapy
- **10/2/15:** Pembrolizumab for PD-L1+ NSCLC progressed beyond platinum-containing chemotherapy
- **10/9/15:** Nivolumab for NSCLC (squamous *and* nonsquamous) with progression on or after platinum-containing chemotherapy
- **10/18/16:** Atezolizumab for the treatment of metastatic NSCLC that has progressed during or after first-line chemotherapy with a platinum-based drug

NSCLC = non–small cell lung cancer.

Approved Immunotherapies (cont.)

- **10/24/16:** Pembrolizumab for the first-line treatment of patients with metastatic NSCLC whose tumors overexpress PD-L1
- **5/10/17:** Pembrolizumab in combination with pemetrexed and carboplatin for the treatment of previously untreated metastatic NSCLC
- **2/16/18:** Durvalumab for the treatment of patients with stage III NSCLC whose tumors are unresectable and whose cancer has not progressed after treatment with chemotherapy and radiation
- **3/6/18:** Nivolumab approved at Q4 week dosing schedule

PACIFIC

- Phase 3 study comparing durvalumab as consolidation therapy with placebo in patients with stage III, locally advanced, unresectable NSCLC that had not yet progressed after platinum-based chemoradiotherapy
- Progression-free survival was significantly longer with durvalumab than with placebo
  - 12 month PFS: 55.9% vs. 35.3%
  - 18 month PFS: 44.2% vs. 27%
- Grade 3 or 4 events:
  - 29.9% durvalumab arm
  - 26.1% placebo arm
  - Most common event of grade 3 or 4 was pneumonia

Antonia, S.J. et al. (2017). Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. NEJM, 377(20).

PACIFIC (cont.)

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)

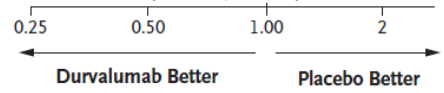


Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

Progression-free survival was defined according to RECIST, version 1.1, and assessed by means of blinded independent central review. The hazard ratio and 95% confidence interval were not calculated for the complete response because this subgroup had less than 20 events. EGFR denotes epidermal growth factor receptor, and PD-L1 programmed death ligand 1.

Antonia, S.J. et al. (2017). Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. NEJM, 377(20).

OAK

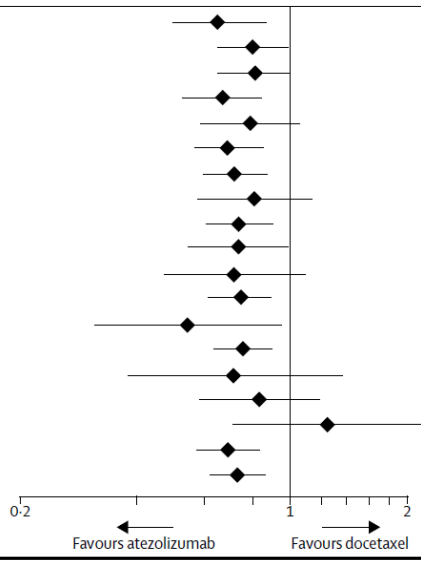
- Phase III study comparing atezolizumab vs. docetaxel in patients previously treated with one or two cytotoxic chemotherapy regimens for stage IIIB or IV squamous or nonsquamous NSCLC
- Clinically relevant improvement of overall survival with atezolizumab vs. docetaxel, regardless of PD-L1 expression or histology
  - In ITT group, OS 13.8 mo with atezolizumab vs 9.6 mo with docetaxel
- Fewer patients with treatment-related grade 3 or 4 adverse events with atezolizumab vs. docetaxel

Rittmeyere, A. et al. (2017). Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer (OAK): a phase 3, open-label, multicenter randomized controlled trial. Lancet, 389, 255-65.

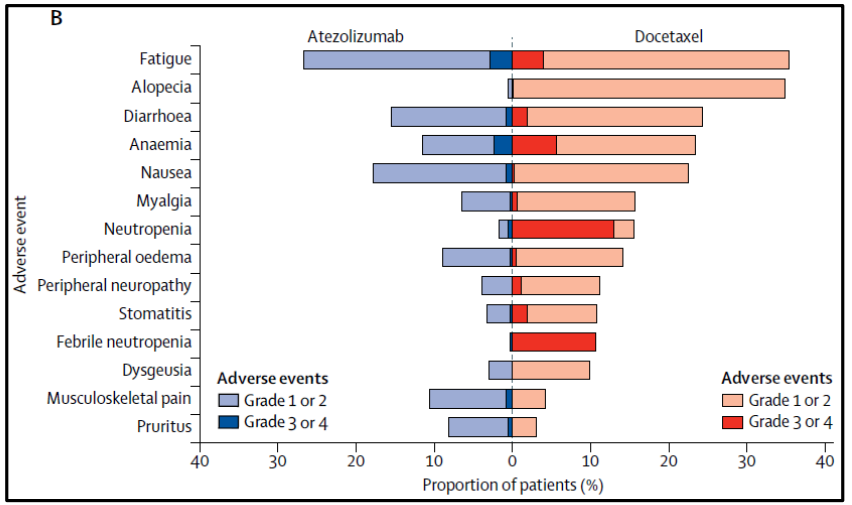
OAK (cont.)

A

	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
Female	330 (39)	16·2	11·2	0·64 (0·49–0·85)
Male	520 (61)	12·6	9·2	0·79 (0·64–0·97)
<65 years old	453 (53)	13·2	10·5	0·80 (0·64–1·00)
≥65 years old	397 (47)	14·1	9·2	0·66 (0·52–0·83)
ECOG PS 0	315 (37)	17·6	15·2	0·78 (0·58–1·04)
ECOG PS 1	535 (63)	10·6	7·6	0·68 (0·56–0·84)
1 previous therapy	640 (75)	12·8	9·1	0·71 (0·59–0·86)
2 previous therapies	210 (25)	15·2	12·0	0·80 (0·57–1·12)
Non-squamous	628 (74)	15·6	11·2	0·73 (0·60–0·89)
Squamous	222 (26)	8·9	7·7	0·73 (0·54–0·98)
Never smokers	156 (18)	16·3	12·6	0·71 (0·47–1·08)
Current or previous smokers	694 (82)	13·2	9·3	0·74 (0·61–0·88)
CNS metastases	85 (10)	20·1	11·9	0·54 (0·31–0·94)
No CNS metastases	765 (90)	13·0	9·4	0·75 (0·63–0·89)
KRAS mutant	59 (7)	17·2	10·5	0·71 (0·38–1·35)
KRAS wildtype	203 (24)	13·8	11·3	0·83 (0·58–1·18)
EGFR mutant	85 (10)	10·5	16·2	1·24 (0·71–2·18)
EGFR wildtype	628 (74)	15·3	9·5	0·69 (0·57–0·83)
ITT	**850 (100)**	**13·8**	**9·6**	**0·73 (0·62–0·87)**



Median overall survival stratified for ITT



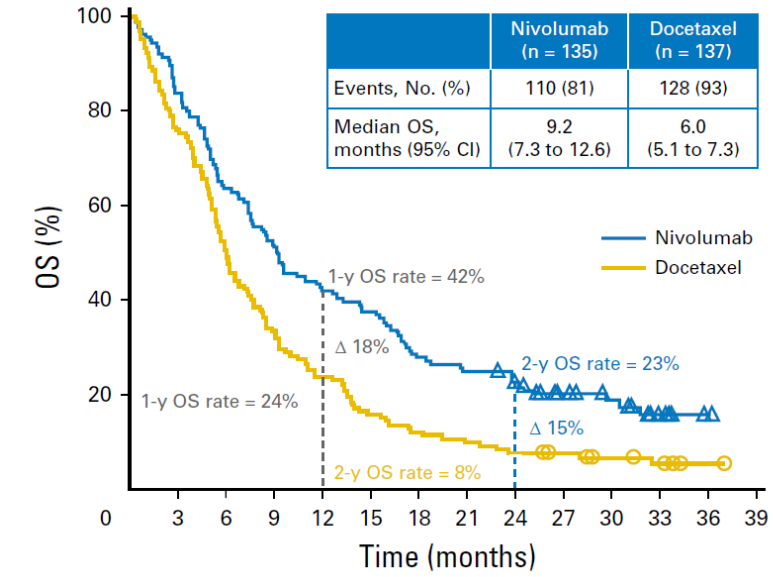
All-cause adverse events that differed by 5% or more between study groups

CheckMate 017 and 057

- Phase III trial comparing nivolumab vs. docetaxel in previously treated squamous (CheckMate 017) and nonsquamous (CheckMate 057) NSCLC patients
- 2-year overall survival outcomes
  - CheckMate 017
    - 23% nivolumab, 8% docetaxel
    - 37% confirmed responders with ongoing responses after 2 years
  - CheckMate 057
    - 29% nivolumab, 16% docetaxel
    - 34% confirmed responders with ongoing responses after 2 years
- Treatment-related adverse events lower with nivolumab than docetaxel

Horn, L. et al. (2017). Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cnacer: Two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). JCO, 35.

CheckMate 017 and 057 (cont.)

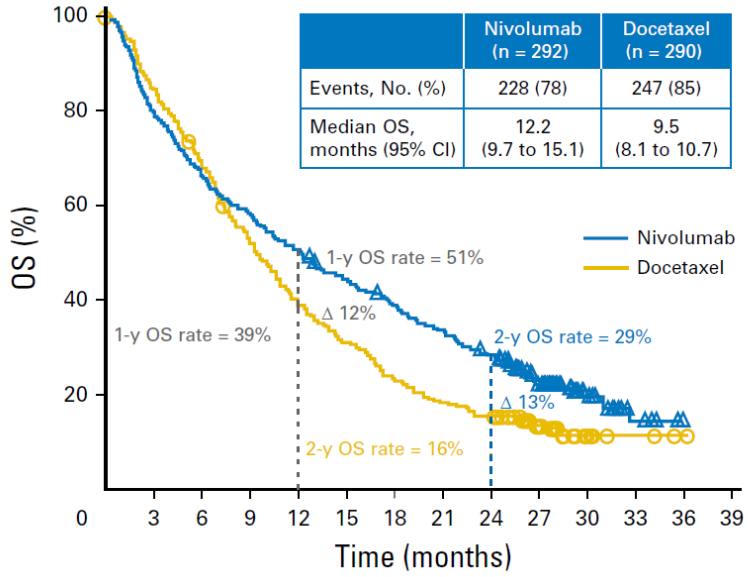


	Nivolumab (n = 135)	Docetaxel (n = 137)
Events, No. (%)	110 (81)	128 (93)
Median OS, months (95% CI)	9.2 (7.3 to 12.6)	6.0 (5.1 to 7.3)

No. at risk:

Nivolumab	135	113	86	69	57	51	38	34	29	19	14	7	1	0
Docetaxel	137	104	69	46	33	22	17	14	11	9	6	4	1	0

Squamous NSCLC



	Nivolumab (n = 292)	Docetaxel (n = 290)
Events, No. (%)	228 (78)	247 (85)
Median OS, months (95% CI)	12.2 (9.7 to 15.1)	9.5 (8.1 to 10.7)

No. at risk:

Nivolumab	292	233	194	171	148	128	112	97	81	46	18	6	0	0
Docetaxel	290	243	194	150	111	89	66	53	45	25	6	3	1	0

Nonsquamous NSCLC

Horn, L. et al. (2017). Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cnacer: Two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). JCO, 35.

CheckMate 026

- Phase III trial comparing first-line nivolumab vs. platinum-based chemotherapy in untreated PD-L1–positive NSCLC
- 432 patients with PD-L1 expression of 5% or more
  - Median PFS 4.2 mo nivolumab vs. 5.9 mo chemotherapy
  - Median OS 14.4 mo nivolumab vs. 13.2 mo chemotherapy
- Treatment-related adverse events
  - Any grade: 71% nivolumab, 92% chemotherapy
  - Grade 3/4: 18% nivolumab, 51% chemotherapy
- Nivolumab not associated with significantly longer PFS than chemo in untreated stage IV or recurrent NSCLC

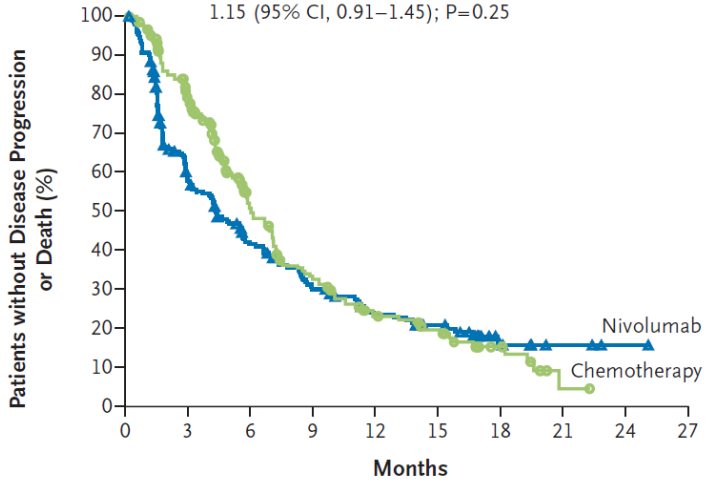
Carbone, D.P. et al. (2017). First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. NEJM, 376(25).

CheckMate 026 (cont.)

Progression-free Survival

	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate
	mo	%
Nivolumab (N=211)	4.2 (3.0–5.6)	24
Chemotherapy (N=212)	5.9 (5.4–6.9)	23

Hazard ratio for disease progression or death, 1.15 (95% CI, 0.91–1.45); P=0.25



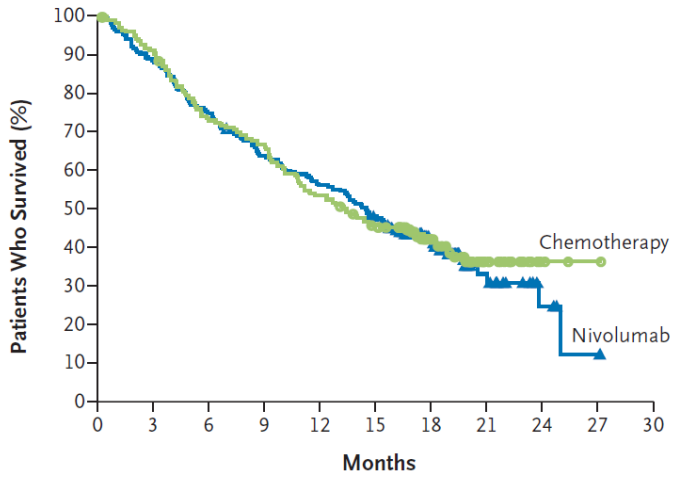
No. at Risk

Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

Overall Survival

	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate
	mo	%
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)



No. at Risk

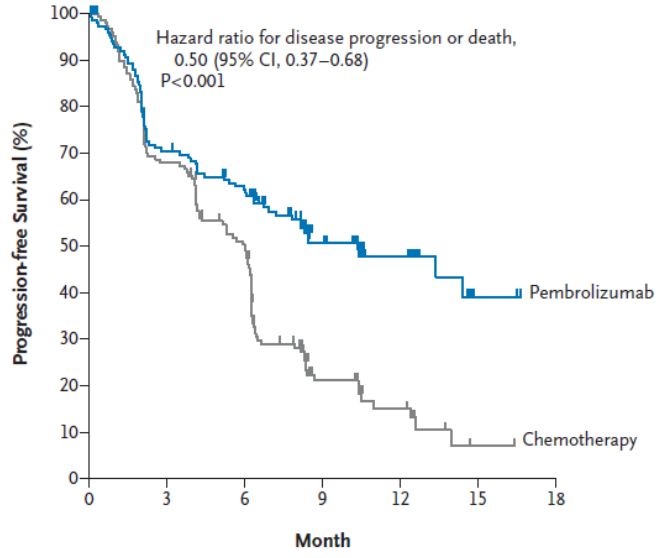
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

Carbone, D.P. et al. (2017). First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. NEJM, 376(25).

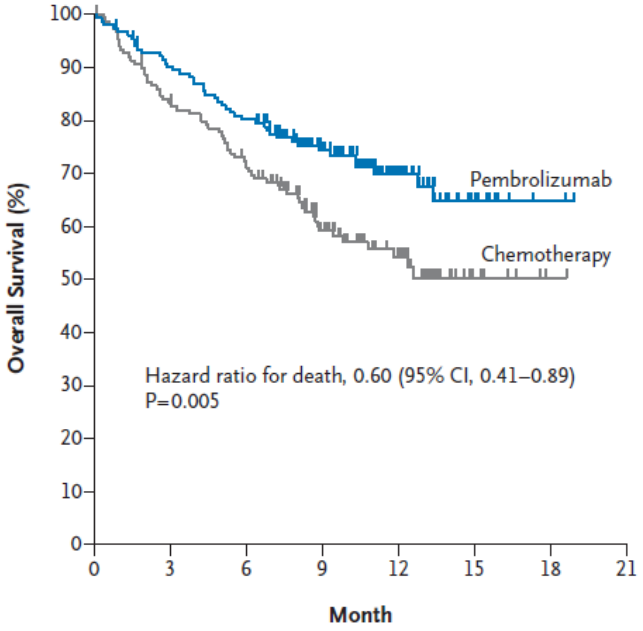
KEYNOTE-024

- Open-label, phase III trial
- Randomly assigned 305 patients who had previously untreated advanced NSCLC with
  - PD-L1 expression on at least 50% of tumor cells
  - *ALK* and *EGFR* negative
- Received either pembrolizumab (at a fixed dose of 200 mg every 3 weeks) or the investigator's choice of platinum-based chemotherapy
- Pembrolizumab associated with longer overall and progression-free survival

KEYNOTE-024 (cont.)



No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0



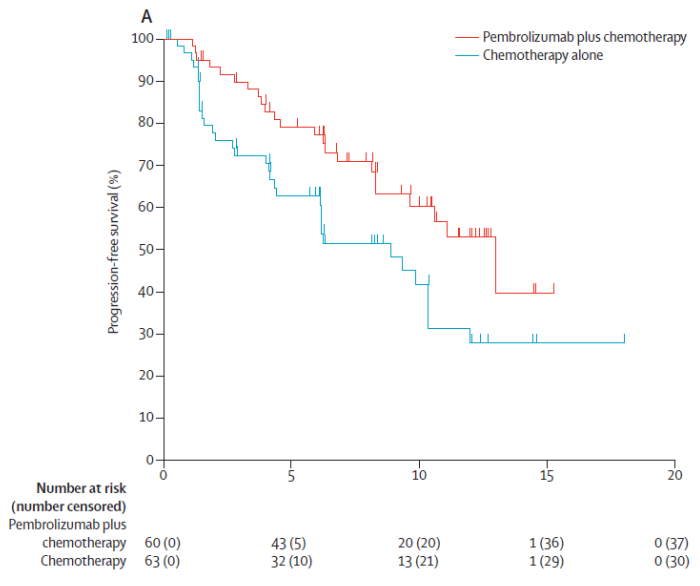
No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

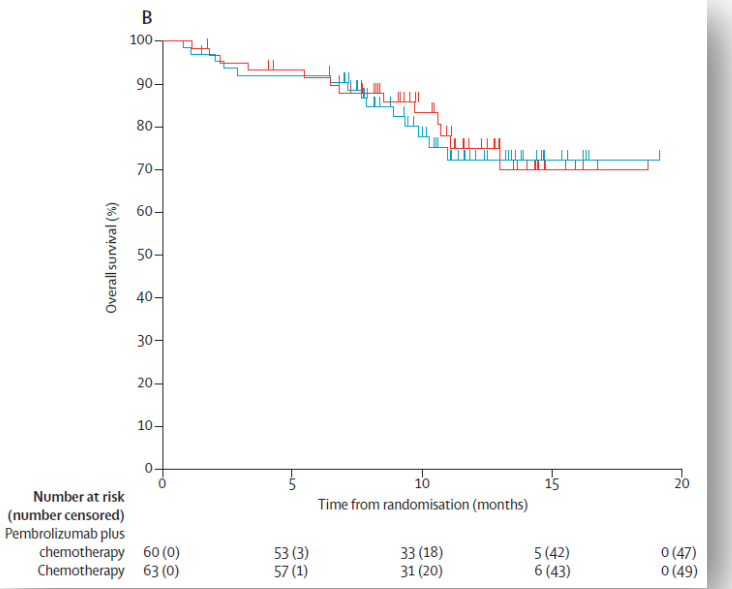
KEYNOTE-021

- Phase II randomized open-label trial
- Patients were randomized 1:1
  - Four cycles of pembrolizumab at 200 mg plus carboplatin/pemetrexed every 3 weeks followed by pembrolizumab for 24 months and pemetrexed maintenance therapy
  - Four cycles of carboplatin/pemetrexed followed by pemetrexed maintenance therapy
- Patients in the control arm (chemotherapy) could cross over to pembrolizumab monotherapy at disease progression, and 32% crossed over

Langer CJ, et al. *Lancet Oncol* 2016;17:1497-508.

KEYNOTE-021 (cont.)





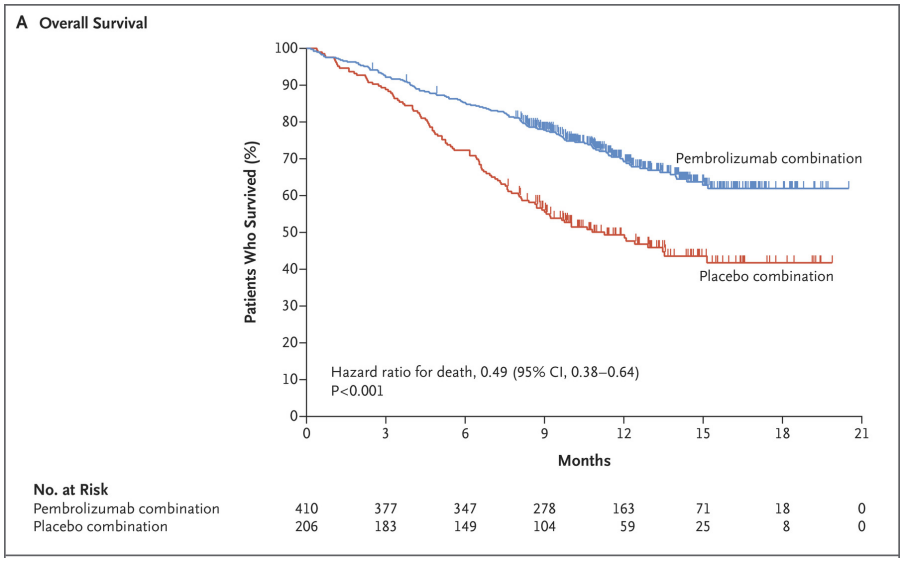
Langer CJ, et al. *Lancet Oncol* 2016;17:1497-508.

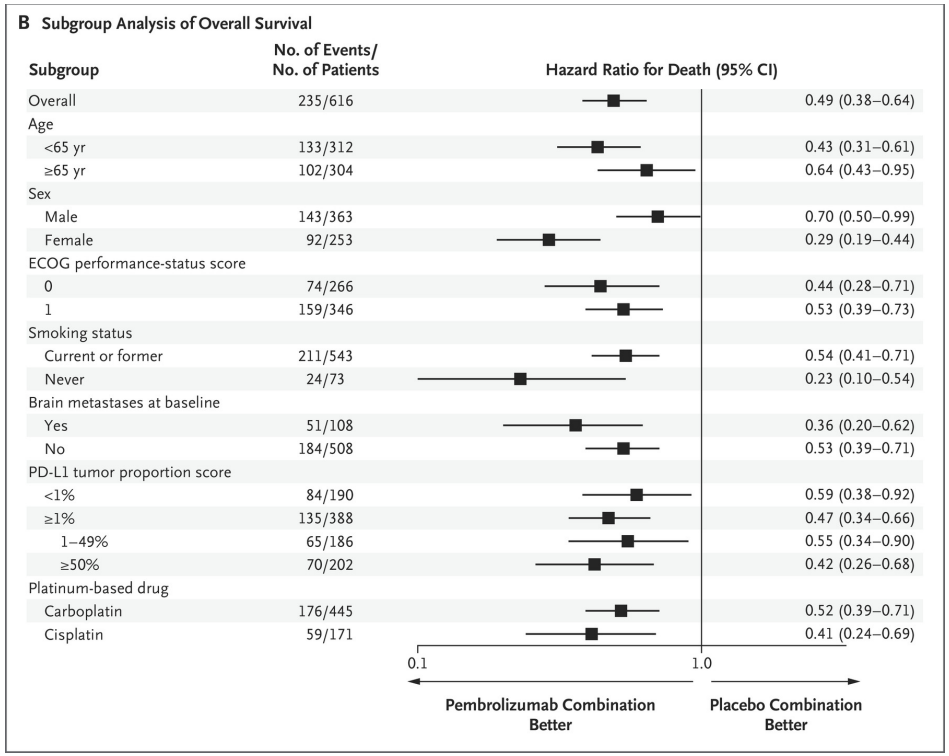
KEYNOTE-189

- Phase III randomized, double-blind trial (n = 616)
  - Patients received cisplatin or carboplatin + pemetrexed q3wk for 4 cycles followed by pemetrexed maintenance indefinitely +/- pembrolizumab/placebo for up to 2 years
  - *ALK* and *EGFR* mutations were excluded
- Median 12-month OS
  - 69.2% (pembrolizumab arm) vs. 49.4% (placebo arm)
- Grade 3/4 adverse events
  - 67.2% (pembrolizumab) vs. 65.8% (placebo)

Gandhi L, et al. *NEJM* 2018; doi: 10.1056/NEJMoa1801005. [Epub ahead of print].

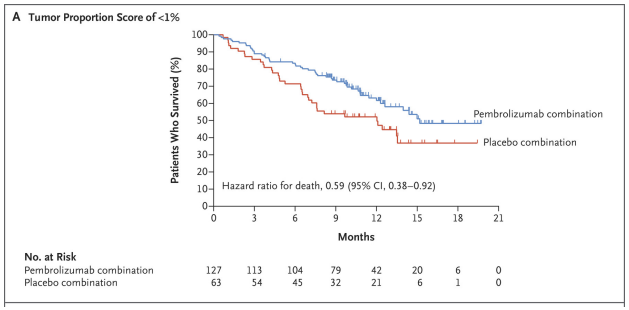
KEYNOTE-189 (cont.)

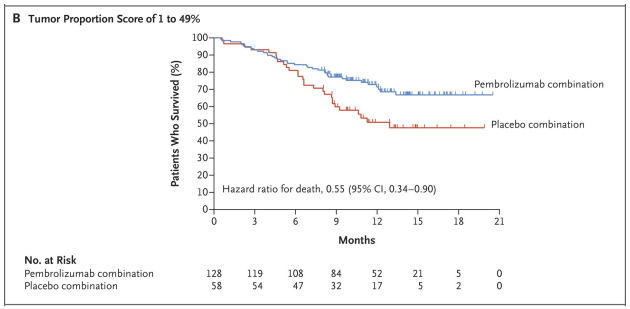


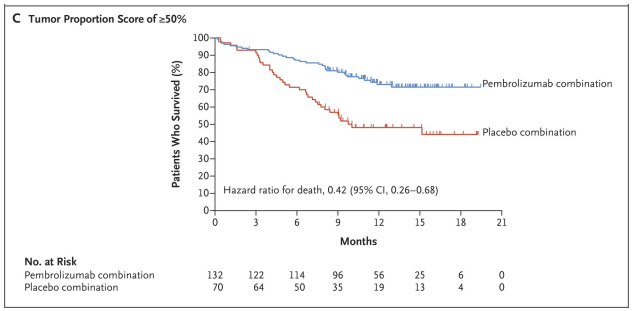


Gandhi L, et al. *NEJM* 2018; doi: 10.1056/NEJMoa1801005. [Epub ahead of print].

KEYNOTE-189 (cont.)







Gandhi L, et al. *NEJM* 2018; doi: 10.1056/NEJMoa1801005. [Epub ahead of print].

IMpower150

- 3-arm, randomized, phase III trial for first-line treatment of **non-squamous** NSCLC
  - Arm A: carboplatin + paclitaxel + atezolizumab (data not yet mature)
  - Arm B: carboplatin + paclitaxel + atezolizumab + bevacizumab
  - Arm C: carboplatin + paclitaxel + bevacizumab
  - Patients receive 4–6 cycles of platinum-based treatment then move into maintenance with atezolizumab (arms A, B) +/- bevacizumab (arms B, C)
- Co-primary endpoint of OS and PFS was met between Arms B and C

IMpower150 (cont.)

Endpoint	Number of patients	Hazard ratio	PFS Arm B (months)	PFS Arm C (months)
Overall population	800	0.61	8.3	6.8
PD-L1–negative*	237 (30%)	0.72	7.2	7.0
PD-L1 low (≤ 50%)*	140 (18%)	0.57	9.7	6.9
PD-L1 high (> 50%)*	126 (16%)	0.5	9.1	6.2
EGFR/ALK+	108 (14%)	0.59	9.7	6.1

*not all patients were evaluable for biomarker testing

IMpower131

- 3-arm, randomized, phase III trial for first-line treatment of **squamous** NSCLC
  - Arm A: carboplatin + paclitaxel + atezolizumab
  - Arm B: carboplatin + nab-paclitaxel + atezolizumab
  - Arm C: carboplatin + nab-paclitaxel
  - Patients receive 4–6 cycles of platinum-based treatment then move into maintenance with atezolizumab (arms A, B) or supportive care (arm C)
- Co-primary endpoint of OS and PFS was met between Arms B and C

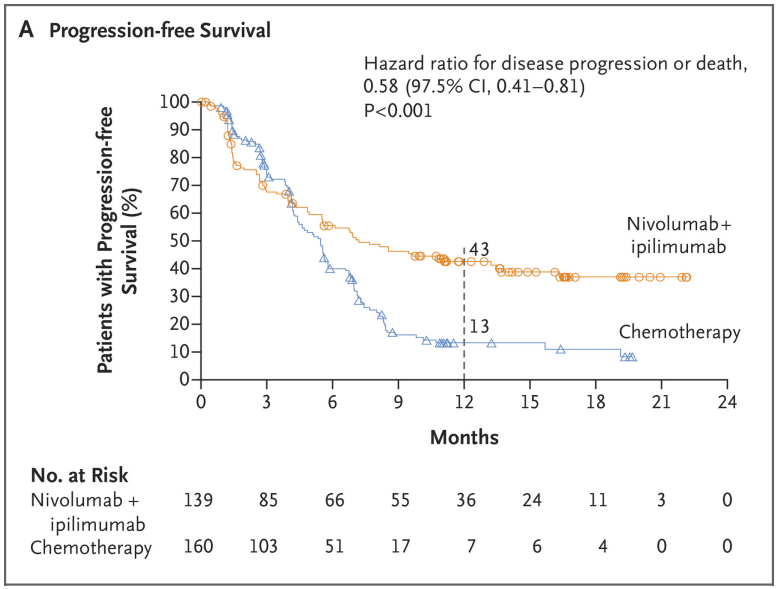
CheckMate 227

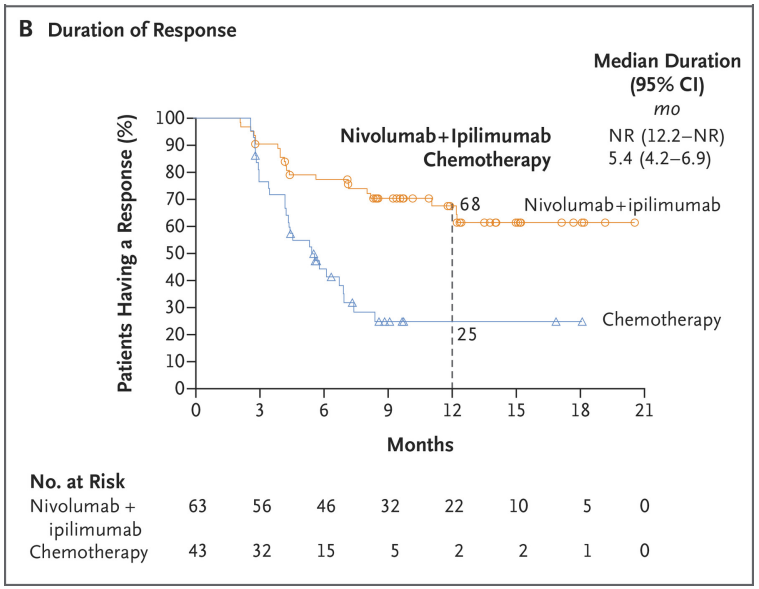
- Multi-part phase III trial with patients randomly assigned 1:1:1 to ***first-line*** nivolumab + ipilimumab, nivolumab, or platinum doublet
- PFS and OS were coprimary endpoints for patients in high TMB subgroup analysis
- Median progression-free survival
  - 7.2 (ipi/nivo) vs 5.5 months (chemo)
- Overall response rate
  - 45.3% (ipi/nivo) vs. 26.9% (chemo)

TMB = tumor mutational burden

Hellman MC, et al. *NEJM* 2018. DOI: 10.1056/NEJMoa1801946 [Epub ahead of print].

CheckMate 227 (cont.)

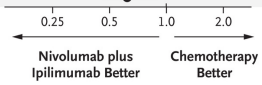


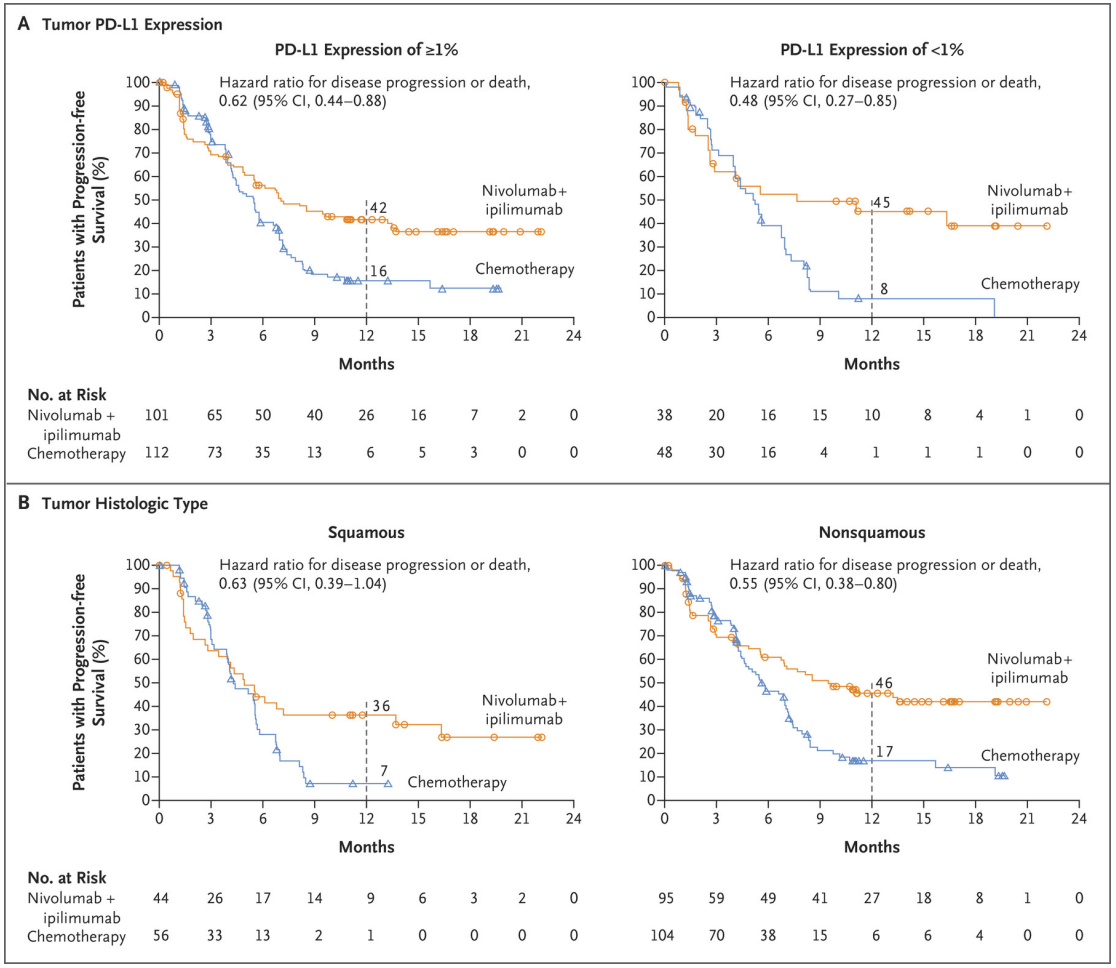


Hellman MC, et al. *NEJM* 2018. DOI: 10.1056/NEJMoa1801946 [Epub ahead of print].

CheckMate 227 (cont.)

Subgroup	Nivolumab plus Ipilimumab	Chemotherapy	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients evaluated		
Overall	139	160	0.58 (0.43–0.77)
Age			
<65 yr	73	83	0.51 (0.34–0.77)
≥65 yr	66	77	0.62 (0.40–0.97)
≥75 yr	13	14	0.42 (0.14–1.30)
Sex			
Male	98	106	0.52 (0.36–0.74)
Female	41	54	0.70 (0.41–1.20)
Region			
North America	14	16	0.46 (0.17–1.30)
Europe	77	87	0.53 (0.36–0.79)
Asia	21	32	0.34 (0.15–0.75)
Rest of world	27	25	1.20 (0.61–2.36)
ECOG performance-status score			
0	56	49	0.62 (0.38–1.02)
1	82	110	0.55 (0.38–0.80)
Tumor histologic type			
Squamous	44	56	0.63 (0.39–1.04)
Nonsquamous	95	104	0.55 (0.38–0.80)
Current or former smoker	130	146	0.57 (0.42–0.78)
PD-L1 expression level			
<1%	38	48	0.48 (0.27–0.85)
≥1%	101	112	0.62 (0.44–0.88)





Hellman MC, et al. *NEJM* 2018. DOI: 10.1056/NEJMoa1801946 [Epub ahead of print].

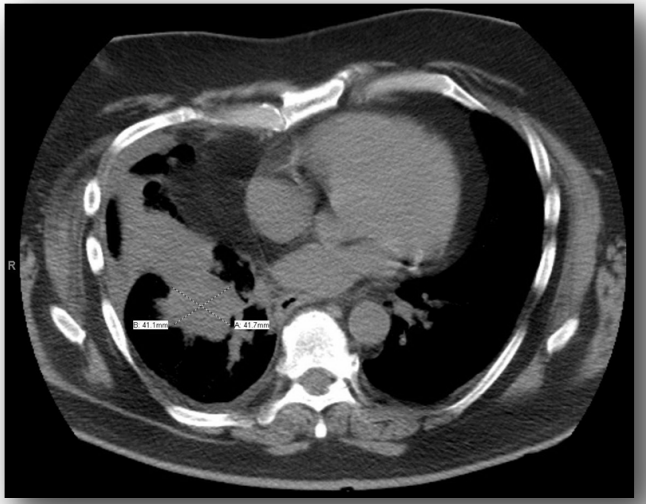
Neoadjuvant PD-1 in NSCLC

- Pilot study of two preoperative doses of nivolumab in adults with untreated, surgically resectable early (stage I, II, or IIIA) NSCLC
  - Nivolumab administered IV every 2 weeks, with surgery planned approximately 4 weeks after the first dose
- Major pathological response in 45% (9/20)
  - Responses occurred in both PD-L1–positive and PD-L1–negative tumors
- Significant correlation between pathological response and pretreatment tumor mutational burden
- Number of T-cell clones in both tumor and peripheral blood increased systemically after PD-1 blockade in 8 of 9 evaluated patients.

Forde, P.M., et al. (2018). Neoadjuvant PD-1 blockade in resectable lung cancer. NEJM, doi: 10.1056/NEJMoa1716078

Case Study: JL

- JL is a 65-year-old male, nonsmoker
- Diagnosed 6/21/2017 with stage IV adenocarcinoma of lung involving right lung, right hilar, mediastinal lymph nodes, right pleural nodularity with malignant right pleural effusion
- Molecular status
  - *ALK* rearrangement negative, *ROS1* negative, *MET* amplification negative, *RET* rearrangement negative, NGS showed no *EGFR, KRAS, BRAF*, or *HER2*/neu; PD-L1 negative



Right infrahilar mass

NGS = next-generation sequencing.

Case Study: JL (cont.)

- JL's past medical history
  - Arthritis
  - Gastroesophageal reflux disease
  - Hyperlipidemia
  - Hypertension
  - Hypothyroidism
- Meds: levothyroxine, losartan, metoprolol

- JL is started on pembrolizumab, carboplatin, and pemetrexed
  - C1D1: 7/3/17
  - C2D1: 7/24/17
  - C3D1: 8/14/17
  - C4D1: 9/4/17
- Tolerated first 4 cycles well without irAE
- Scans after C4 show 35% decrease in disease burden

Case Study: JL (cont.)

- 9/25/17: Presents for C5 (pembrolizumab/pemetrexed) complaining of increased fatigue, urinary hesitancy and dyspnea on exertion
- Pertinent laboratory findings

	9/4/17	9/25/17
Hgb (14.3–18.1 g/dL)	9.1	7.8
MCV (80–100 fL)	85	82
Sodium (133–145 mmol/L)	135	130
BUN (7–25 mg/dL)	14	16
Creatinine (0.7–1.3 mg/dL)	1.1	4.0
TSH (0.34–5.60 mIU/L)	NA	1.95

BUN = blood urea nitrogen; Hgb = hemoglobin; MCV = mean corpuscular volume; THS = thyroid-simulating hormone.

Audience Response Question

At this time, you would:

A) Recognize that C5 is too early to see any immune related adverse events, assume that changes in Hgb and Cr are related to chemotherapy toxicity and treat the patient.

B) Delay treatment by one week, bring the patient back with repeat labs to determine whether there is improvement in Hgb and Cr. Encourage home hydration.

C) Add on reticulocyte and iron studies to determine etiology of anemia; add on urinalysis and calculate FENa. Treat patient while results are pending.

D) Add on reticulocyte and iron studies to determine etiology of anemia; add on urinalysis and calculate FENa. Hold treatment while results are pending.

E) Unsure

Case Study JL: Differential Diagnoses

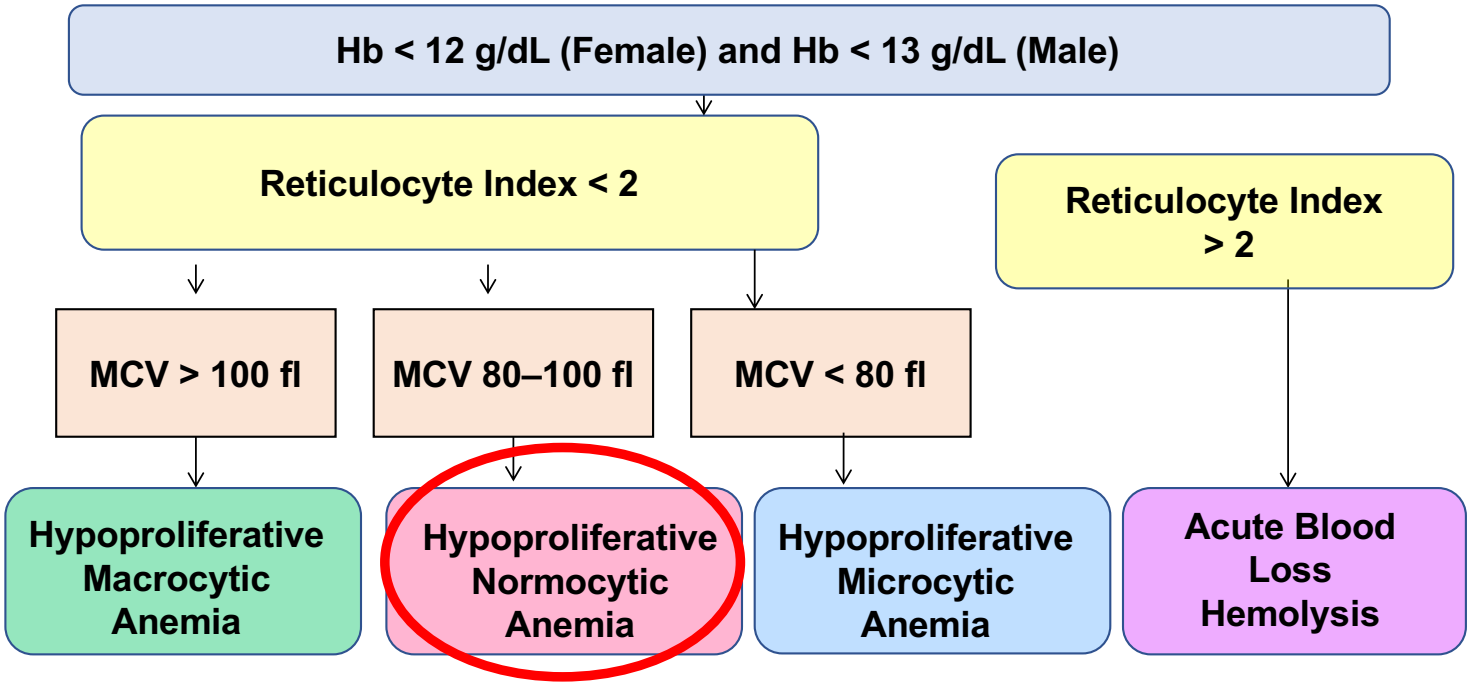
- Grade 3 anemia
  - Anemia of chronic disease
    - Secondary to lung cancer
    - Secondary to thyroid dysfunction
    - Secondary to kidney dysfunction
  - Iron deficiency anemia
    - Secondary to blood loss
    - Secondary to insufficient dietary iron
- Grade 3 creatinine increased
  - Nephritis
  - Nephrotoxicity from chemotherapy
  - Dehydration
  - Other drug injury
  - Hypertension

Case Study JL: Anemia

Add-on labs to include reticulocyte count and iron studies:

Reticulocyte count (0.5%–2.5%)	0.90%
Hgb (14.3–18.1 g/dL)	7.8
MCV (80–100 fL)	82
Iron serum (45–160 µg/dL)	30
Transferrin (203–362 mg/dL)	299
Ferritin (11–307 ng/mL)	150

Diagnostic Evaluation of Anemia Based on MCV and Reticulocyte Index



Differential Diagnosis of Anemia

MICROCYTIC ANEMIA

- Iron deficiency
- Thalassemia
- Lead toxicity
- Sideroblastic anemia
- Anemia of chronic disease (late, uncommon)

NORMOCYTIC ANEMIA

- Anemia of chronic disease (CKD, malignancy, heart failure, endocrine dysfunction)
- Blood loss
- Iron deficiency anemia (early)
- Bone marrow disorders
- Bone marrow suppression (drugs, chemotherapy, radiation)
- Low levels of hormones
  - EPO deficiency (CKD)
  - Thyroid hormone (hypothyroidism)
  - Androgens (hypogonadism)

MACROCYTIC ANEMIA

- Folate or vitamin B_{12} deficiency
- Medications (AZT, hydrea, imatinib, sunitinib, methotrexate, 6MP, capecitabine, cladribine, cytarabine)
- Alcohol abuse
- Hypothyroidism
- Certain bone marrow disorders (MDS, leukemia, pure red cell aplasia)
- Increased reticulocytes (hemolytic anemia)

☐ Decreased RBC production
■ Increased RBC destruction or loss

6MP = mercaptopurine; AZT = azidothymidine; CKD = chronic kidney disease; EPO = erythropoietin; MDS = myelodysplastic syndrome; RBC = red blood cell.

Cascio MJ, et al. *Med Clin North Am* 2017;101:263-84.

Case Study JL: Anemia

- Hypoproliferative normocytic anemia
  - No sign of early iron deficiency on labs
  - Blood pressure is well controlled
  - Kidney disease is acute, not chronic
  - Thyroid function is well preserved with replacement
- Likely related to chemotherapy
  - 12.9% incidence of grade 3 anemia with carboplatin/pemetrexed[1]

1. Xu H, et al. *Clin Epidemiol* 2016;8:61-71.

Case Study JL: Creatinine Increased

- FENa > 1%
- Urine culture: negative

	Reference and units	Result
Color urine	Yellow	Yellow
Appearance urine	Clear	Clear
Specific gravity urine	1.001-1.035	1.012
pH urine	5.0-8.0	6.0
Protein urine	Negative mg/dL	1+
Glucose urine	Negative mg/dL	50
Ketones urine	Negative mg/dL	80
Bilirubin urine	Negative	Negative
Blood urine	Negative	Small
Nitrite urine	Negative	Negative
Urobilinogen urine	< 2.0 EU/dL	< 2.0
Leukocyte esterase urine	Negative	Trace
White blood cells urine	0-5 /HPF	38
Red blood cells urine	0-3 /HPF	4
Squamous epithelial cells	Occasional/HPF	Occasional

FENa = fractional excretion of sodium;
HPF = high power field.

Nephritis

The most typical clinical presentation is a rise in creatinine with mild proteinuria and/or pyuria.

- Rare side effect estimated to occur in 2% of patients
- Incidence higher with combination therapy
- Median time to onset:
  - Ipilimumab: 2–3 months
  - PD-1/PD-L1 inhibitors: 3–10 months
- Majority of patients recover renal function with steroids
- Recovery of renal function takes weeks

Cortazar FB, et al. *Kidney Int* 2016;90:638-47; Haanen, J. B. A. G., et al. Annals of Oncology. 2017, 28(suppl_4), iv119-iv142. Hassel, J. C., et al. Cancer Treatment Reviews, 2017, 57, 36-59. Wanchoo R, et al. *Am J Nephrol* 2017;45(2):160–9.

Audience Response Question

At this time, you would:

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D) Add on reticulocyte and iron studies to determine etiology of anemia; add on urinalysis and calculate FENa. Hold treatment while results are pending.

E) Unsure

Case Study JL: Conclusion

- Grade 3 anemia related to chemotherapy
  - Recovered in time off of chemo
- Grade 3 nephritis related to pembrolizumab
  - Treated with prednisone 1 mg/kg for a month, and serial Cr was measured 2x per week
  - Renal function recovered after 4 weeks, and the steroids were tapered over 8 weeks
  - Treated with pentamidine for PCP prophylaxis, clotrimazole troches for thrush prevention and famotidine for gastritis prevention
  - Pembrolizumab discontinued
    - In the approval study, the most common adverse reaction resulting in discontinuation of pembrolizumab (≥ 2%) was acute kidney injury (3.4%)[1]

Cr = creatinine.

1. FDA Press Release, Pembrolizumab (Keytruda) 5-10-2017, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm558048.htm.