Advances in Cancer Immunotherapy
Lung Cancer

10/14/16

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An NCI-Designated Cancer Center

Disclosures

- Advisory board: Ariad Pharmaceuticals
- Honoraria: Merck & Co., Inc

- Discussion will include non-FDA labeled use of drugs

Total Incidence and Mortality

	Common Types of Cancer	Estimated New Cases 2016	Estimated Deaths 2016
1.	Breast Cancer (Female)	246,660	40,450
2.	**Lung and Bronchus Cancer**	**224,390**	**158,080**
3.	Prostate Cancer	180,890	26,120
4.	Colon and Rectum Cancer	134,490	49,190
5.	Bladder Cancer	76,960	16,390
6.	Melanoma of the Skin	76,380	10,130
7.	Non-Hodgkin Lymphoma	72,580	20,150
8.	Thyroid Cancer	64,300	1,980
9.	Kidney and Renal Pelvis Cancer	62,700	14,240
10.	Leukemia	60,140	24,400

Lung and bronchus cancer represents 13.3% of all new cancer cases in the U.S.

13.3%

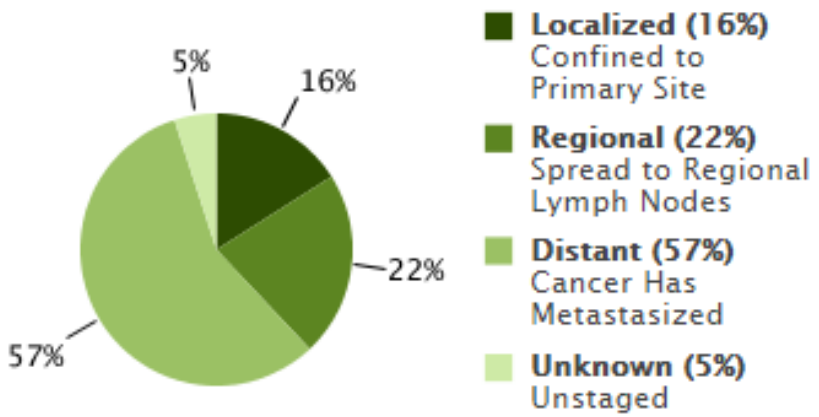
In 2016, it is estimated that there will be 224,390 new cases of lung and bronchus cancer and an estimated 158,080 people will die of this disease.

NCI SEER Database 2016. http://seer.cancer.gov/statfacts/html/lungb.html

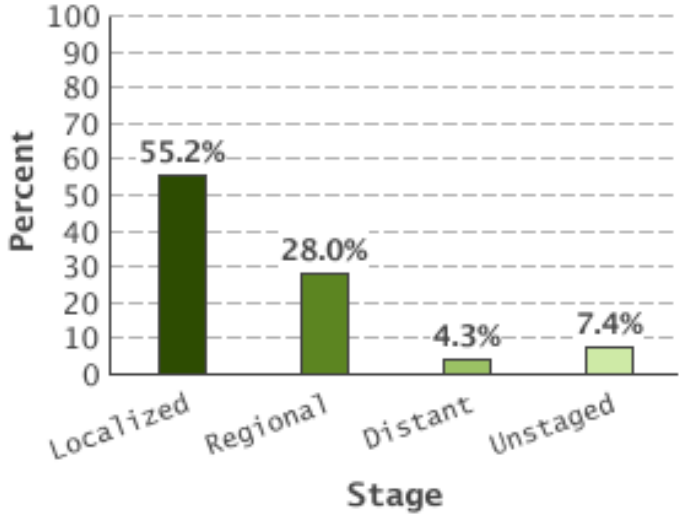
Poor Survival

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Lung and Bronchus Cancer

Percent of Cases by Stage



5-Year Relative Survival



SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

NCI SEER Database 2014. http://seer.cancer.gov/statfacts/html/lungb.html

Next Generation Chemotherapy 2002

The New England Journal of Medicine

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP

- ECOG 1594
- 4 platinum-doublet chemotherapies have equivalent PFS and OS
- mOS = 7.9 months
- <u>Carboplatin and paclitaxel</u> preferred regimen

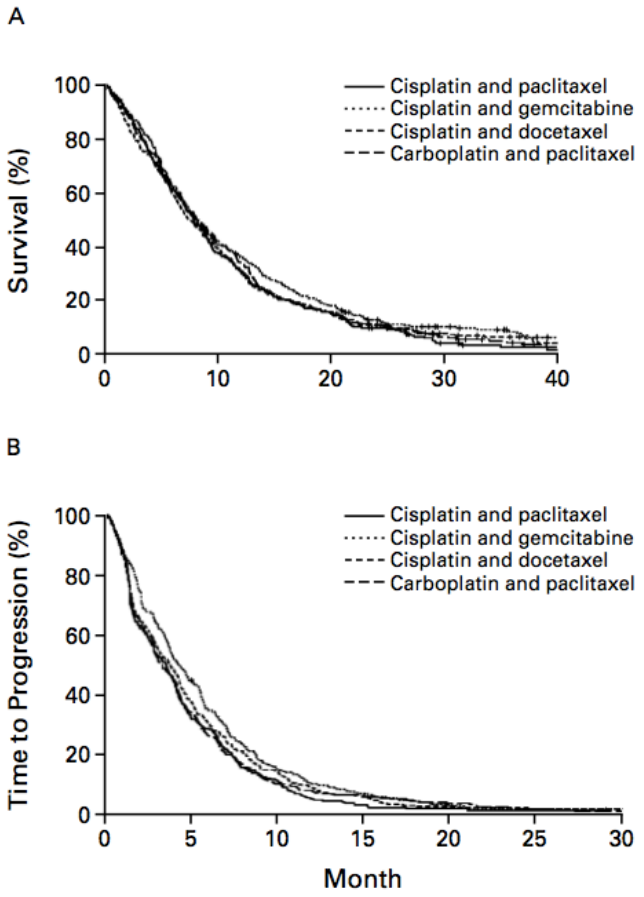


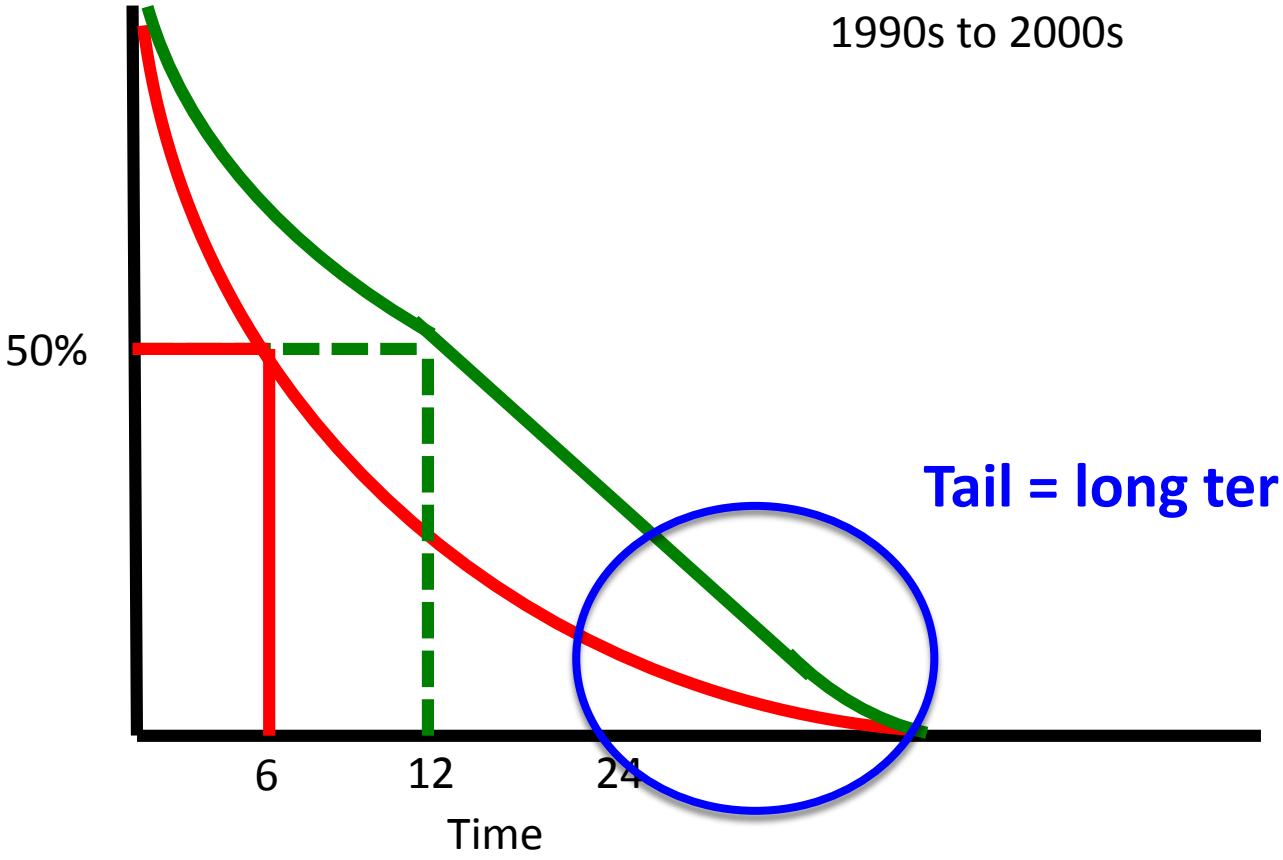
Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and the Time to Progression of Disease (Panel B) in the Study Patients, According to the Assigned Treatment.

Schiller JH, et al. NEJM 2002

Survival Curves

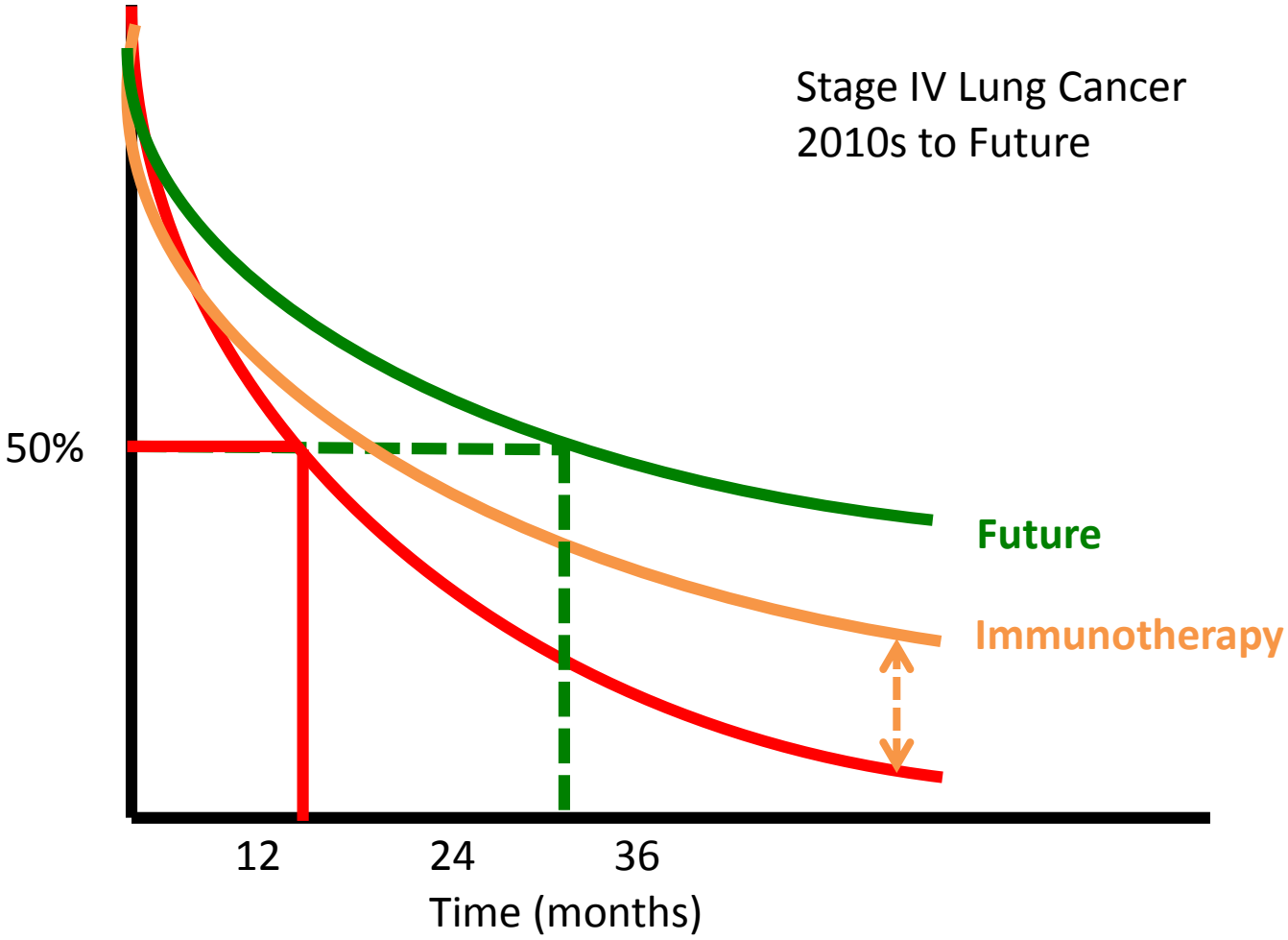
Clinical Trials Goal: Improve Survival

Stage IV Lung Cancer
1990s to 2000s



Tail = long term survivors

Lung Cancer 2016+



Outline

- Immunotherapy in Lung Cancer
  - Notable Clinical Trials
  - Managing side effects
  - PDL1 expression
  - Future directions
  - *ESMO 2016 Update*

Drug Development

Anti PD-1 Drugs:	Trial Names:
• Nivolumab (Opdivo®)	CHECKMATE
• Pembrolizumab (Keytruda®)	KEYNOTE
• Pidilizumab (CT-011)	
Anti PD-L1 Drugs:	
• Atezolizumab (MPDL3280A)	Trees (Birch, Fir, Oak); IMpower
• Durvalumab (MEDI4736)	ATLANTIC, PACIFIC, ARCTIC, NEPTUNE
• BMS935559 (MDX-1105)	
• Avelumab (MSB0010718C)	JAVELIN
Anti CTLA4 Drugs:	
• Ipilimumab (Yervoy®)	
• Tremelimumab	

Nivolumab Phase I

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

18% RR (14 of 76) for patients with NSCLC

Nivolumab Trials

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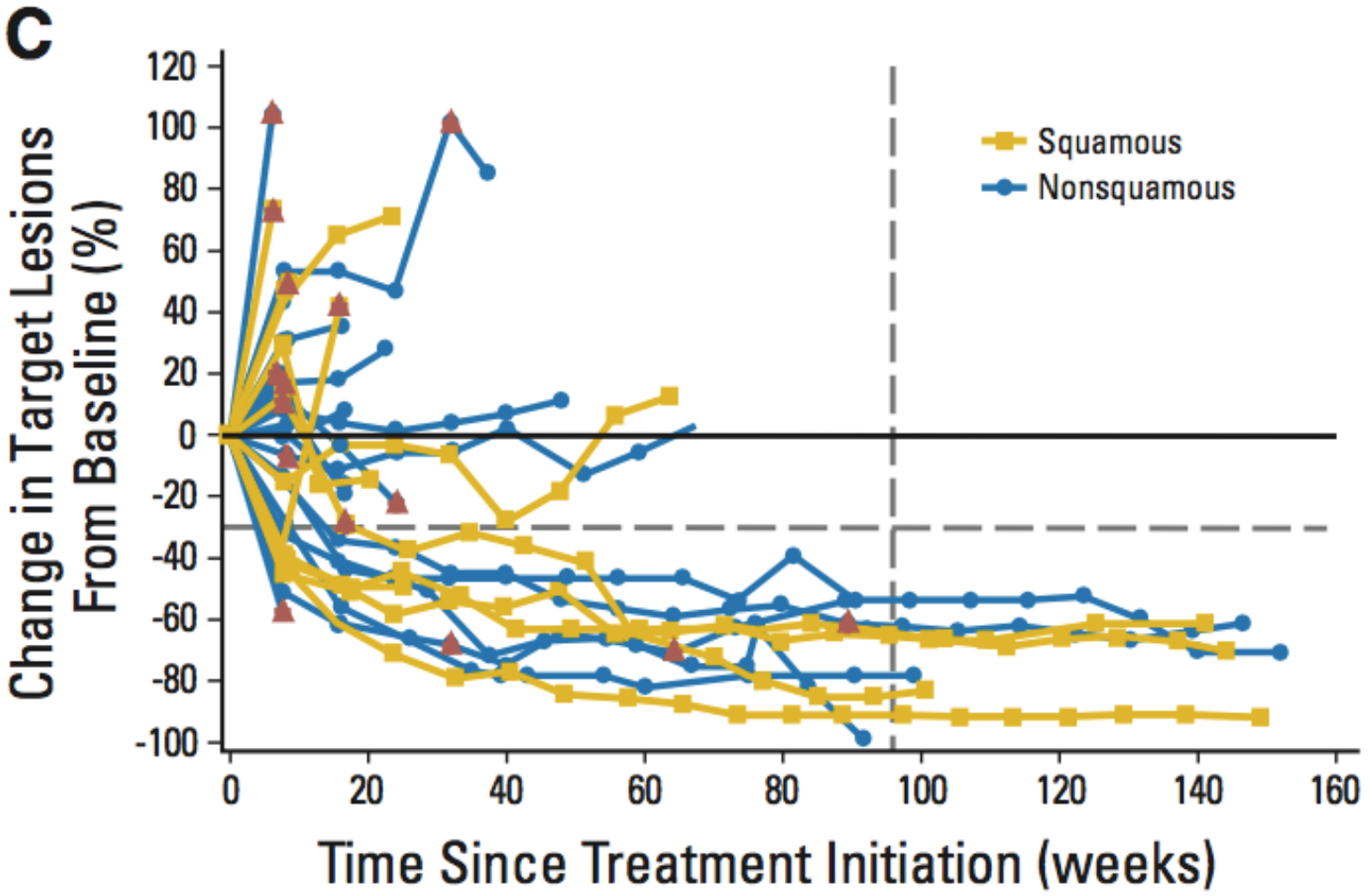
Early Phase

- 001
  - Multiple solid tumors, NSCLC expansion cohort
  - Median duration of response 17 months
  - NEJM 2012 (Topalian), J Clin Oncol 2015 (Gettinger)
- 063
  - Single arm phase II, nivolumab monotherapy for SCC
  - ≥ 2 prior chemotherapies (platinum doublet, docetaxel)
  - 14.5% RR (17 of 117)
  - March 2015, Lancet Oncology (Rizvi)

Checkmate 001



Gettinger SN. *J Clin Oncol.* 2015;33(18):2004

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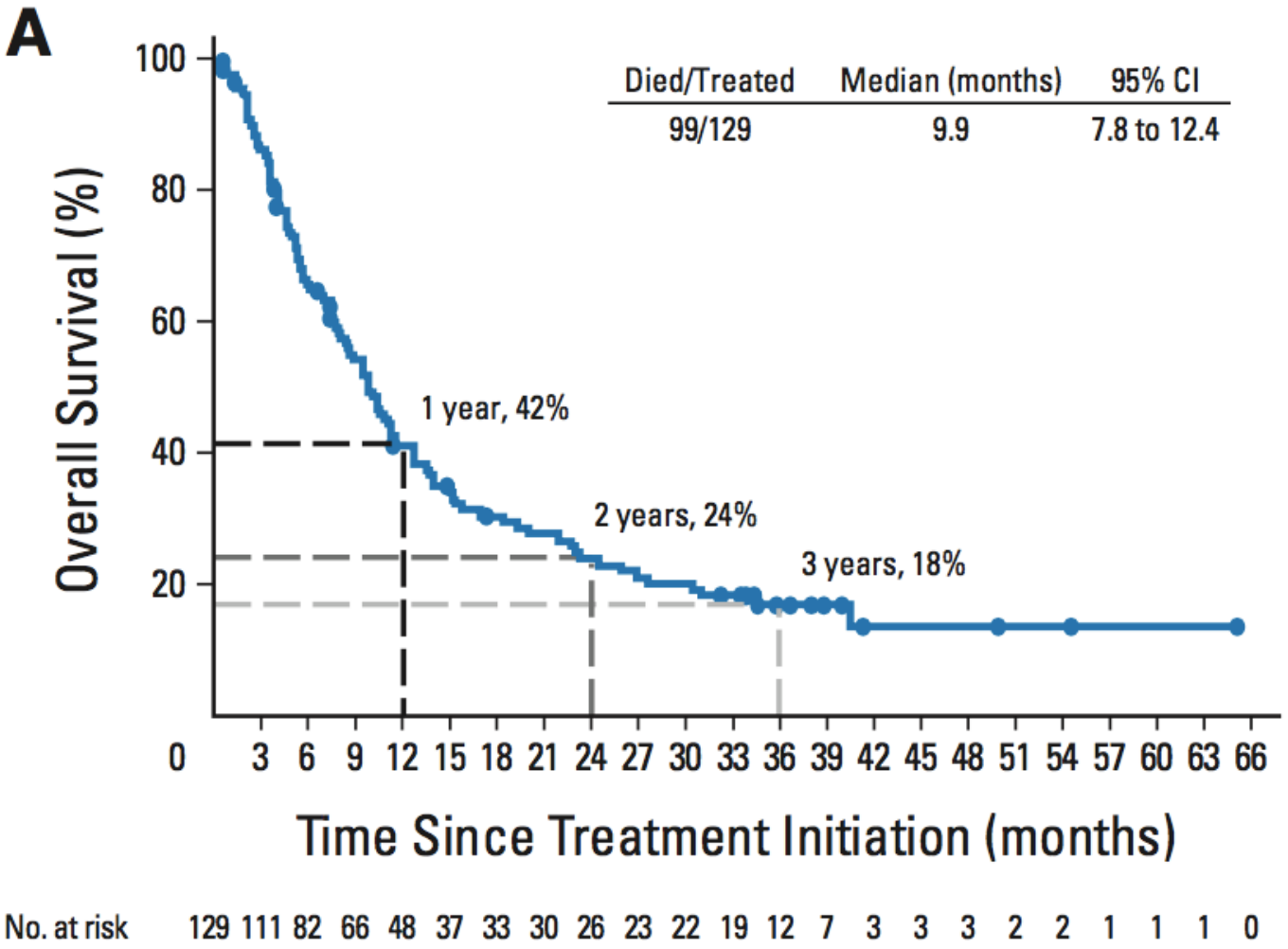
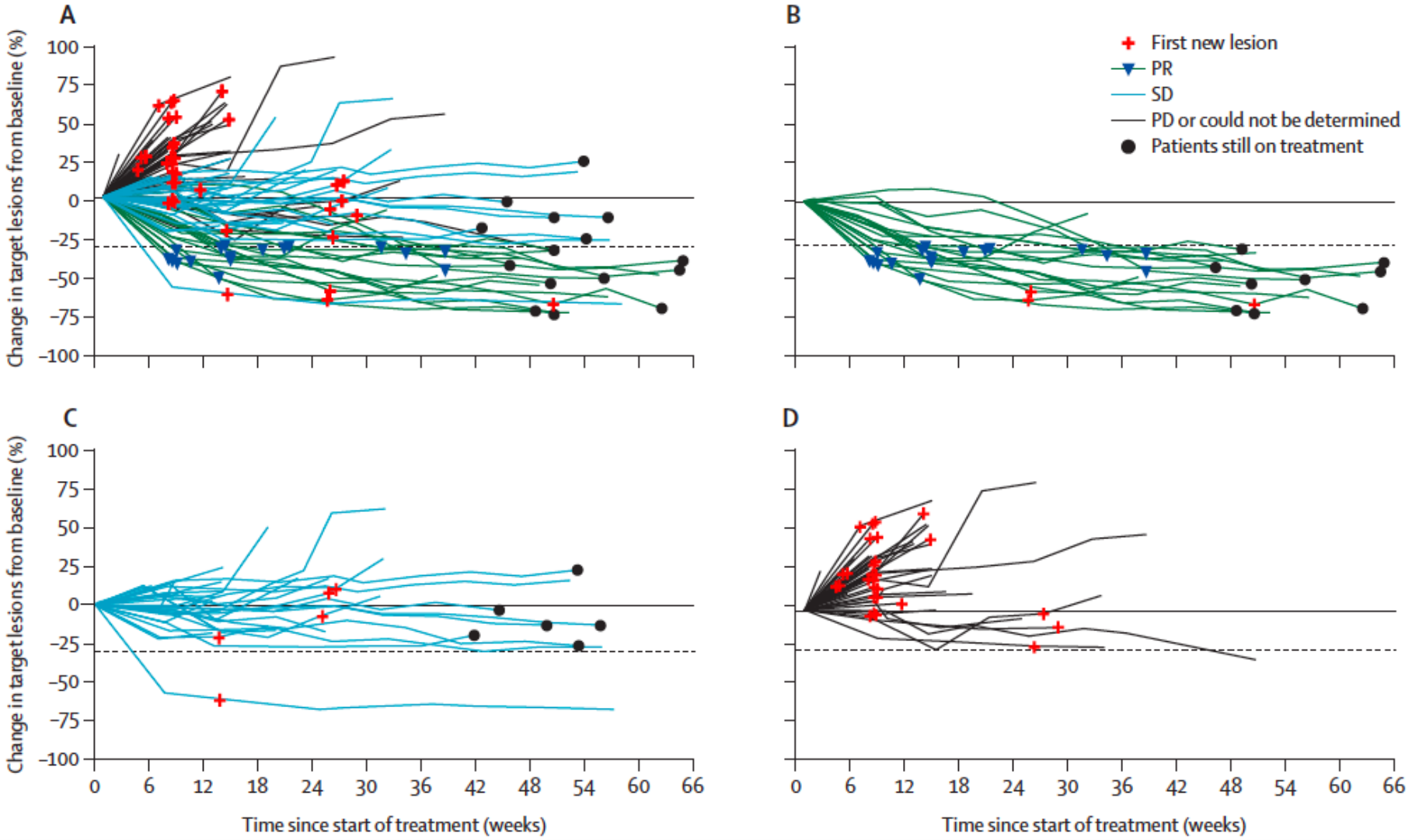


Gettinger SN. *J Clin Oncol.* 2015;33(18):2004

Checkmate 063



Lancet Oncology 2015; 16: 257, Figure 2

Checkmate, Ph III - Results

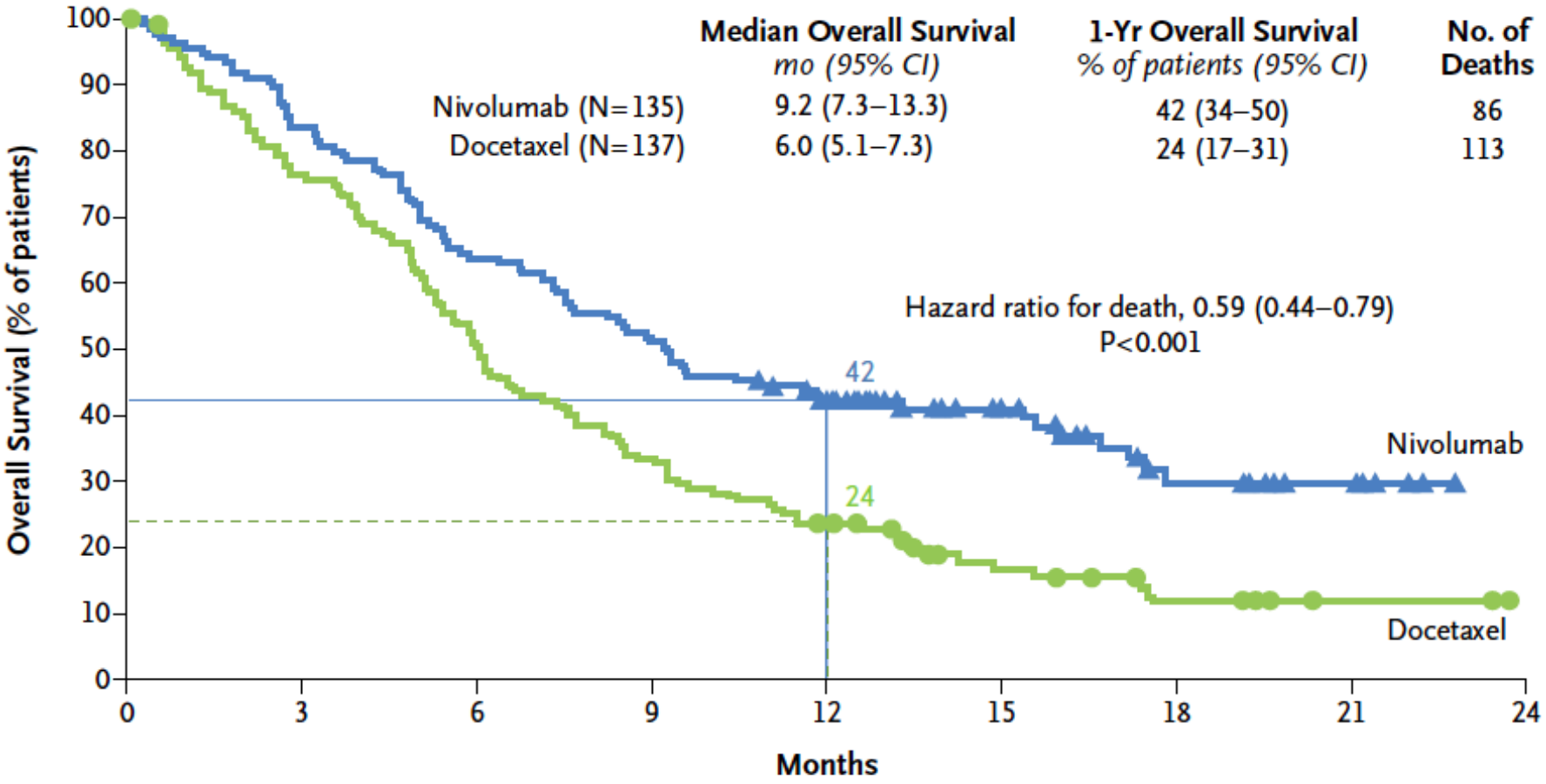
Checkmate 017

- **SCC**
- Nivo vs. docetaxel
- ORR
  - 20% vs. 9%
  - P=0.0083
- Median DOR
  - NR vs. 8.4 mo
- Median OS
  - 9.2 mo vs. 6.0 mo
  - HR 0.59, p=0.00025

Checkmate 057

- **Non-Squamous**
- Nivo vs. docetaxel
- ORR
  - 19% vs 12%
  - HR 1.72, p=0.0246
- Median DOR
  - 17.2 mo vs. 5.6 mo
- Median OS
  - 12.2 mo vs. 9.4 mo
  - HR 0.73, p=0.0015

Checkmate 017



Brahmer et al. *N Engl J Med* 2015; 373:123-135

Checkmate 017 Toxicity

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

* Safety analyses included all the patients who received at least one dose of study drug. No treatment-related deaths occurred in patients treated with nivolumab. Treatment-related deaths were reported in three patients treated with docetaxel (one death each from interstitial lung disease, pulmonary hemorrhage, and sepsis).

Brahmer et al. *N Engl J Med* 2015; 373:123-135

Pembro, Atezo

Pembrolizumab (MK-3475)

- Keynote 001
  - 495 pts with NSCLC
  - ORR 19.4%
  - ORR of 45.2% with PDL1>50% (more later)
- Keynote 010
  - Phase III

Garon et al, NEJM 2015;372:21

Atezolizumab (MPDL3280A)

- BIRCH (ESMO 2015)
  - 667 pts
  - PDL1 (2+/3+)
  - ORR 17-27%
  - Increasing PDL1 associated with higher RR
- FIR (ASCO 2015)
  - Similar results, 138 pts
- POPLAR (ASCO 2015)
  - Phase II vs. docetaxel
  - Improved OS, 12.6 mo vs. 9.7
- OAK (ESMO 2016)
  - Phase III vs. docetaxel
  - Improves OS

Besse B, et al. ESMO 2015, abst:16LBA
Spigel D, et al. ASCO 2015, abst:8028
Fehrenbacher , et al. *Lancet* 2016
Barlesi F, et al. ESMO 2016; abst:LBA44

Keynote 001 Adverse Events

Table 1. Adverse Events in 495 Patients in the Treated Population.*

Adverse Event	Any Grade	Grade 3–5
	no. of patients (%)	
Fatigue	96 (19.4)	4 (0.8)
Pruritus	53 (10.7)	0
Decreased appetite	52 (10.5)	5 (1.0)
Rash	48 (9.7)	1 (0.2)
Arthralgia	45 (9.1)	2 (0.4)
Diarrhea	40 (8.1)	3 (0.6)
Nausea	37 (7.5)	4 (0.8)
Hypothyroidism	34 (6.9)	1 (0.2)
Asthenia	24 (4.8)	5 (1.0)
Anemia	21 (4.2)	0
Dyspnea	21 (4.2)	19 (3.8)
Pyrexia	21 (4.2)	3 (0.6)
Decreased weight	19 (3.8)	2 (0.4)
Dry skin	18 (3.6)	0
Pneumonitis†	18 (3.6)	9 (1.8)
Elevation in aspartate aminotransferase	15 (3.0)	3 (0.6)
Vomiting	14 (2.8)	3 (0.6)
Dermatitis acneiform	13 (2.6)	0
Myalgia	13 (2.6)	0
Cough	12 (2.4)	0
Elevation in alanine aminotransferase	11 (2.2)	2 (0.4)
Chills	10 (2.0)	0
Constipation	10 (2.0)	2 (0.4)
Infusion-related reaction	15 (3.0)	1 (0.2)

* Listed are events that were considered to be related to treatment by the investigator and were reported in at least 2% of patients.
† Included among patients with pneumonitis is one patient with grade 5 interstitial lung disease.

Garon et al, NEJM 2015;372:21

Keynote 010

- Phase II/III randomized trial
- 2nd line after platinum doublet
- PDL1 expression ≥ 1%
- 1:1:1 randomization:
  - Pembrolizumab 2 mg/kg q3 weeks
  - Pembrolizumab 10 mg/kg q3 weeks
  - Docetaxel 75 mg/kg q3 weeks

Herbst RS, et al. *Lancet* 2016;387:1540-50

Keynote 010

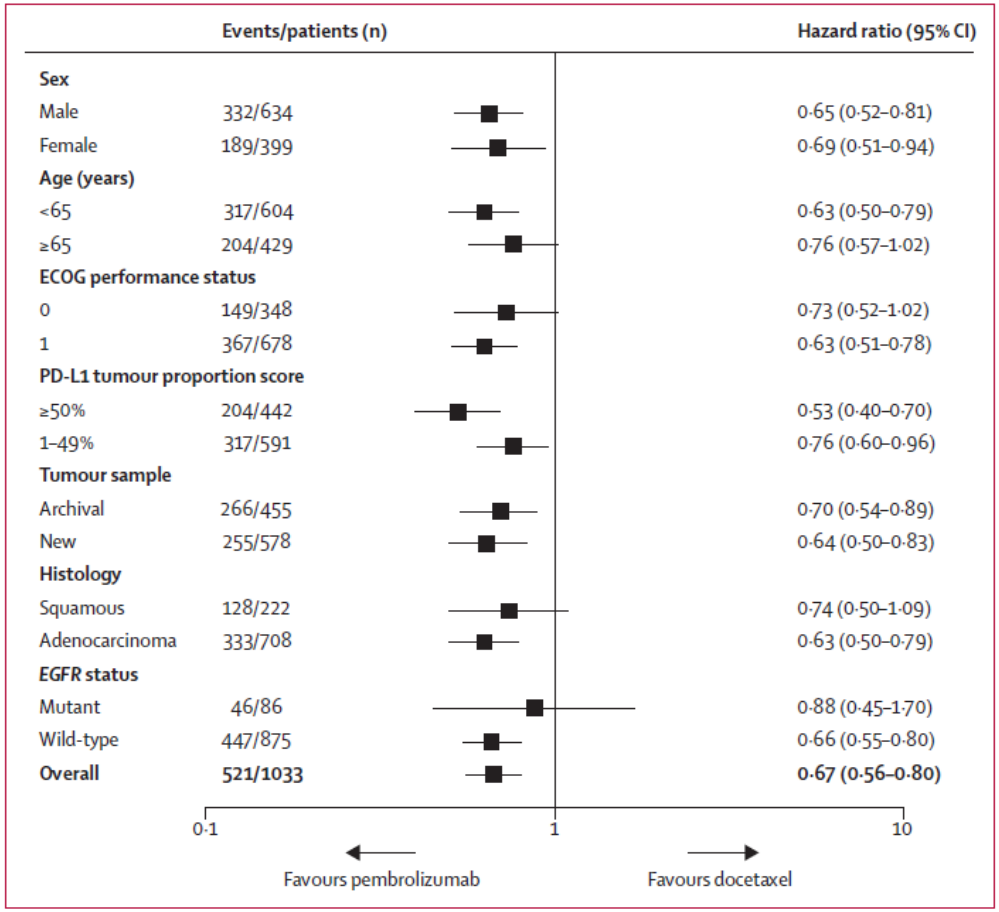
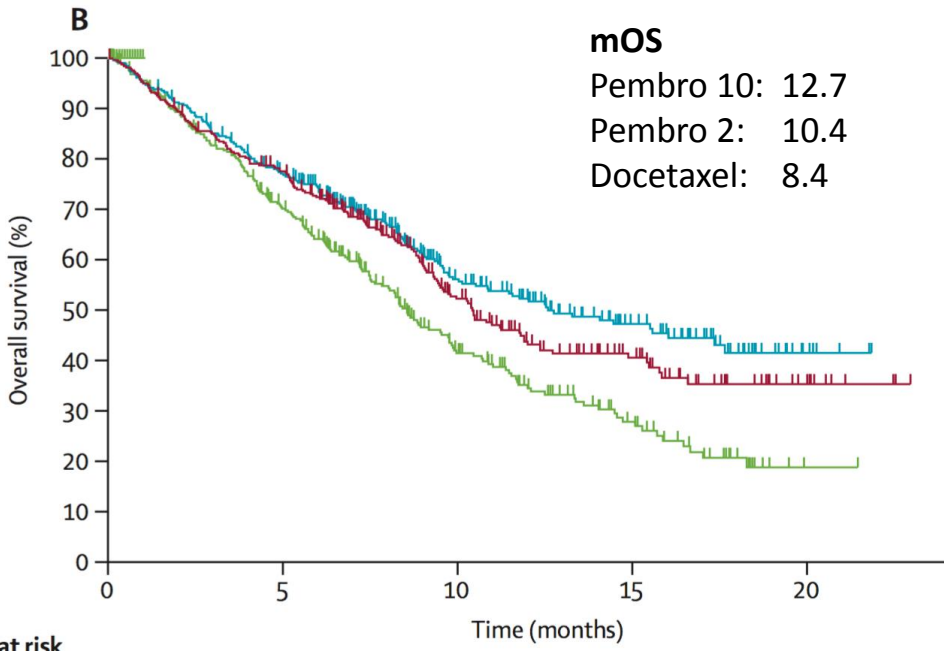


Figure 3: **Subgroup analysis of overall survival**
Shows the comparison of the pooled pembrolizumab doses versus docetaxel. ECOG=Eastern Cooperative Oncology Group.

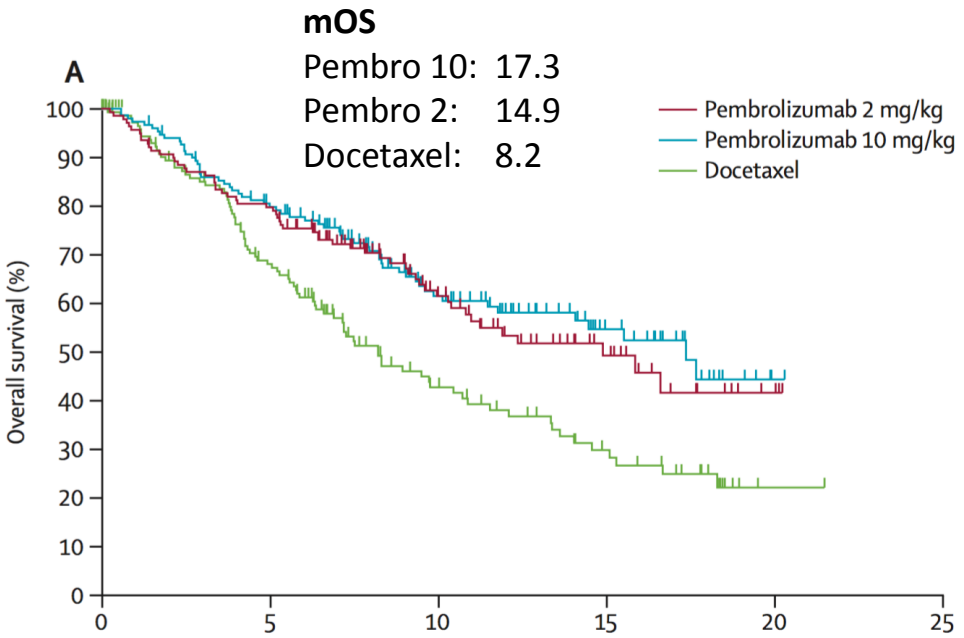
Herbst RS, et al. *Lancet* 2016;387:1540-50

Keynote 010

All patients (PD-L1 ≥ 1%)



PD-L1 ≥ 50%



Herbst RS, et al. *Lancet* 2016;387:1540-50

FDA Approvals

- **Nivolumab** ~~3 mg/kg~~ 240 mg every 2 weeks
  - March 4, 2015
    - Squamous NSCLC (Checkmate 063 and 017)
  - October 9, 2015
    - Non-Squamous NSCLC (Checkmate 057)
  - September 2016
    - Dose modification to 240 mg q2 weeks

- **Pembrolizumab** 2mg/kg every 3 weeks
  - October 2, 2015
    - NSCLC (any histology), PDL1 positive (Keynote 001)

Outline

- Immunotherapy in Lung Cancer
  - Notable Clinical Trials
  - Managing side effects
  - PDL1 expression
  - Future directions

Immunotherapy toxicity

- Treatment
  - Grade 3-4 toxicity* (life-threatening)
    - Permanently discontinue
    - Initiate prednisone 1-2 mg/kg day
    - Taper over 1 month
  - Grade 2-3 toxicity (requiring intervention/hospitalization)
    - Hold immunotherapy until Grade 0-1
    - Steroids as above
  - Other grade 1 toxicity
    - Observe

  - *For grade 3 nephritis, pneumonitis, hypophysitis, Type I diabetes, LFT elevations, permanently discontinue

Immunotherapy toxicity (melanoma)

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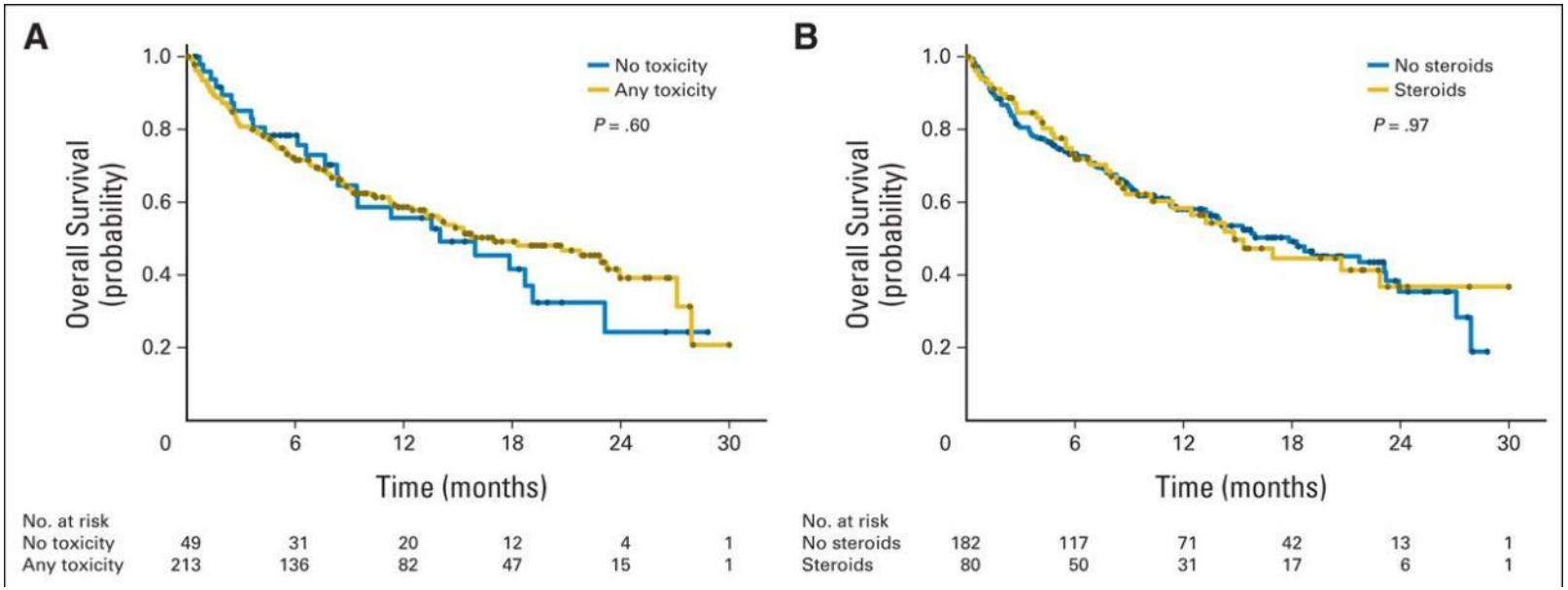
OS by immune toxicity

OS by steroids received

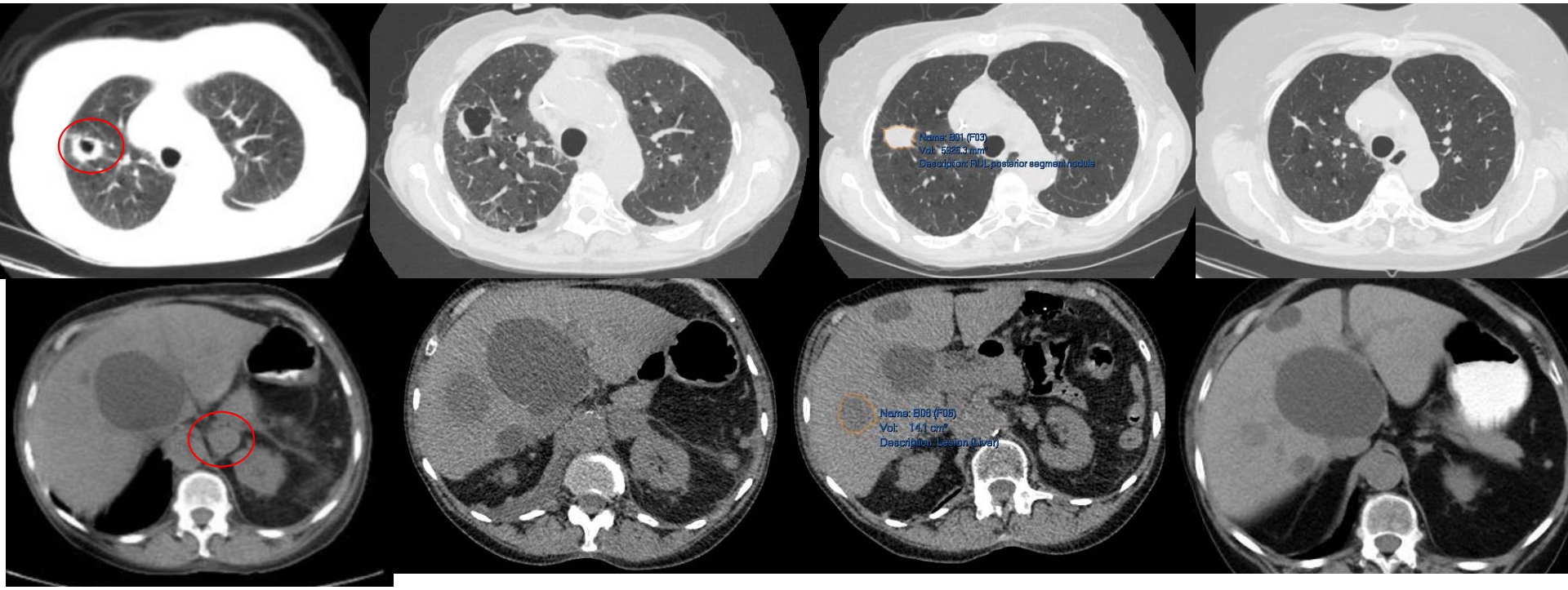


Horvat et al. JCO 2015;33:3193-3198

Case #1

- 66 yo F former 15 pk-yr smoker, presented with weight loss, dyspnea, cough. Mediastinal lymphadenopathy with bilateral lung nodules, liver and adrenal metastases
- Stage IV lung adenocarcinoma
  - EGFR, ALK, ROS1 wild-type
- Treatments:
  - Carboplatin/pemetrexed x 6 cycles
  - Maintenance pemetrexed x 4 months
  - Docetaxel, 11 months
  - Gemcitabine, 4 months
- Started Nivolumab

Baseline | 2 months | 4 months | 10 months



Nivolumab started

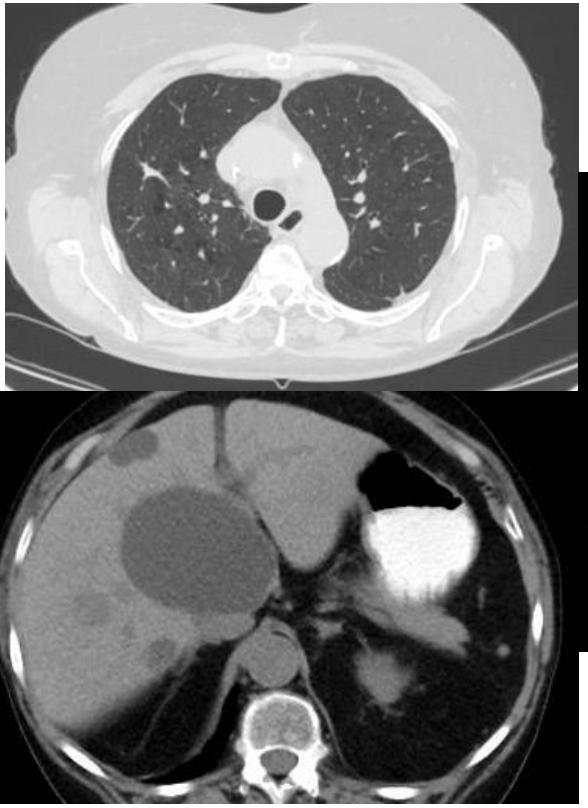
"Progression"

Nivolumab continued

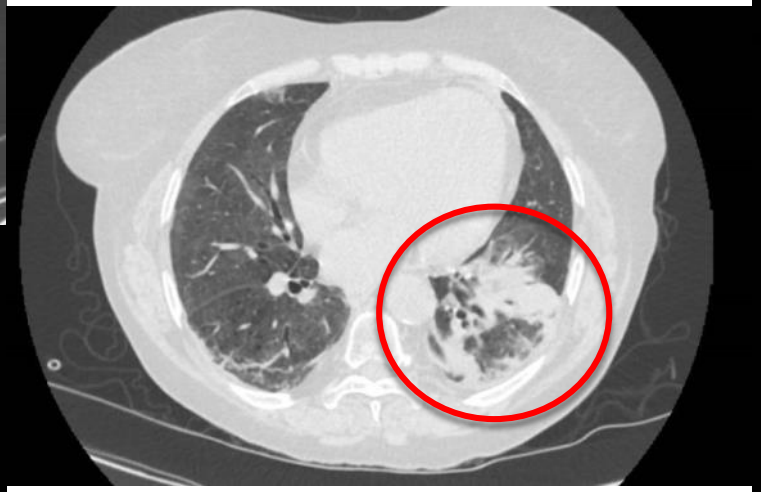
Developed uveitis, grade 2
Topical steroids

7 Months
Uveitis + cataracts, held nivo 1 month, prednisone 1 mg/kg

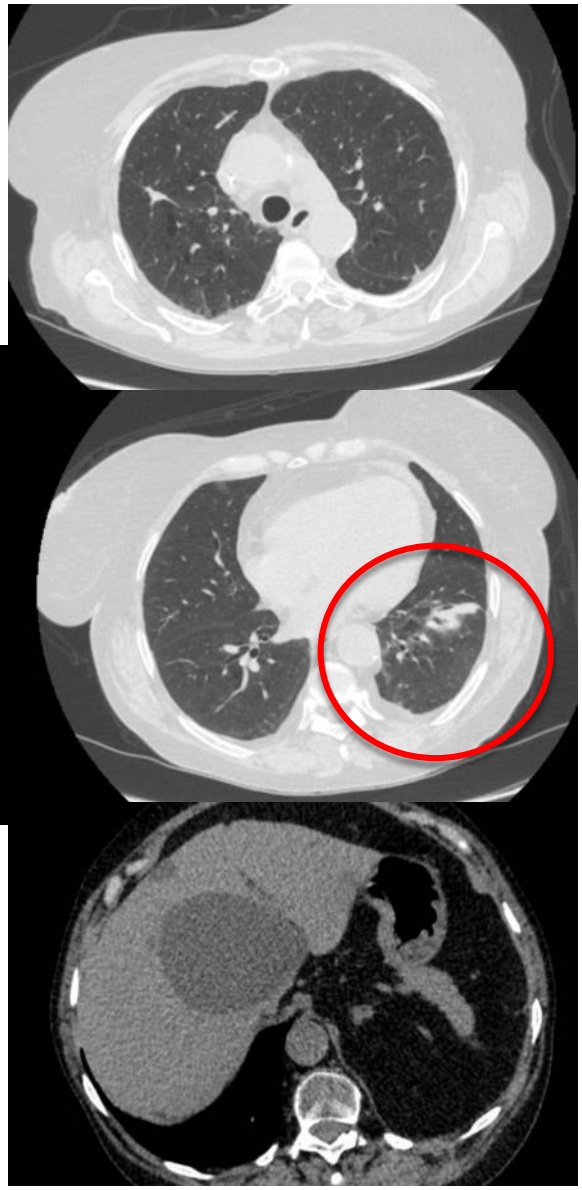
10 months



12 months



14 months



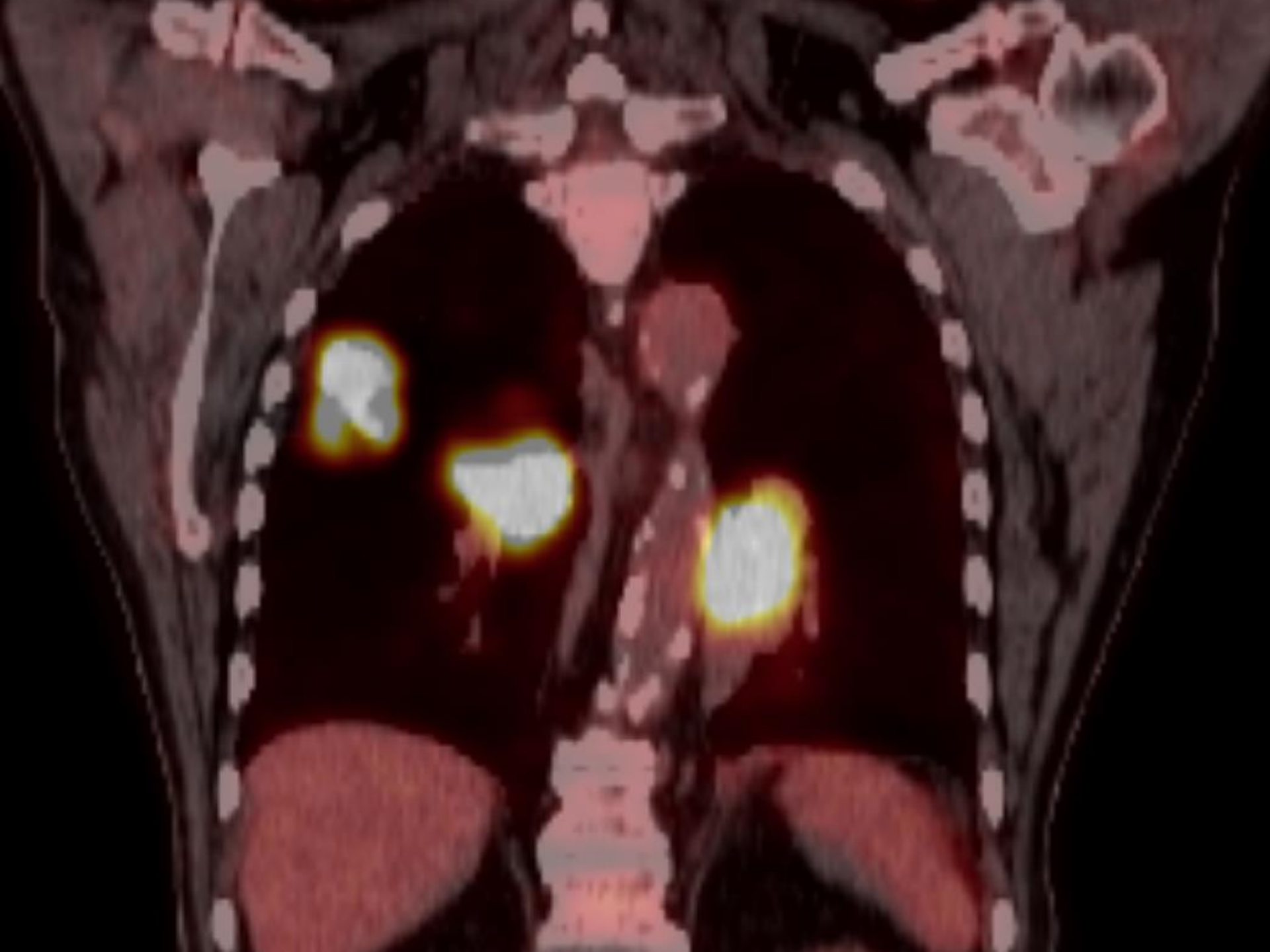
Pneumonitis requiring O2 and hospitalization

- Bronchoscopy: lymphocyte predominate, negative for infectious etiology
- Prednisone 1 mg/kg
- Discharged w/o oxygen

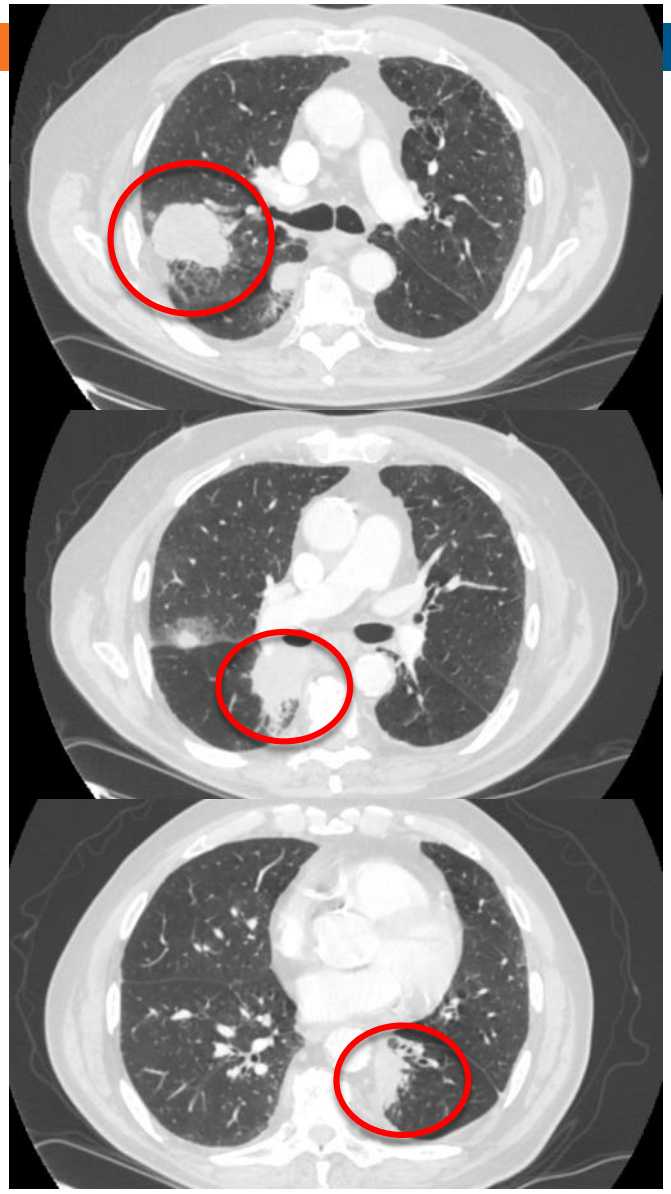
Stable disease
Resolution of pneumonitis

Case #2

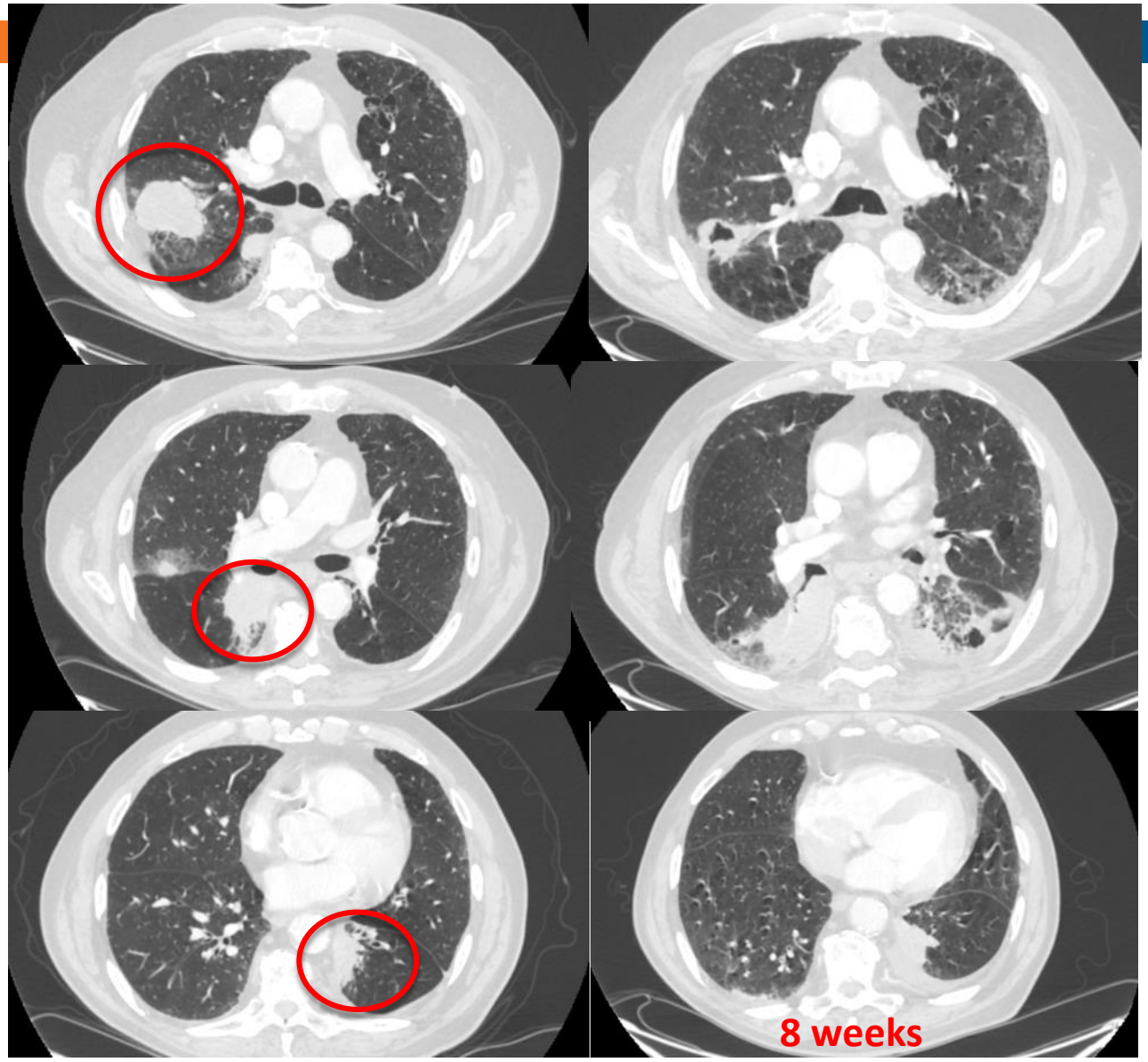
- 79 yo M former 35 pk-yr smoker with COPD, CAD, PE, presented with worsening dry cough and dyspnea. CXR showed lung mass. CT and PET imaging with bilateral lung masses and right hilar lymphadenopathy.
- Stage IV lung squamous cell carcinoma
- Treatment course:
  - Carboplatin/gemcitabine x 4 cycles, responsive disease
  - Progression 2 months later
- Started Nivolumab 3 mg/kg
  - 6 months after diagnosis



Case #2: Nivolumab



Case #2: Nivolumab



8 Weeks

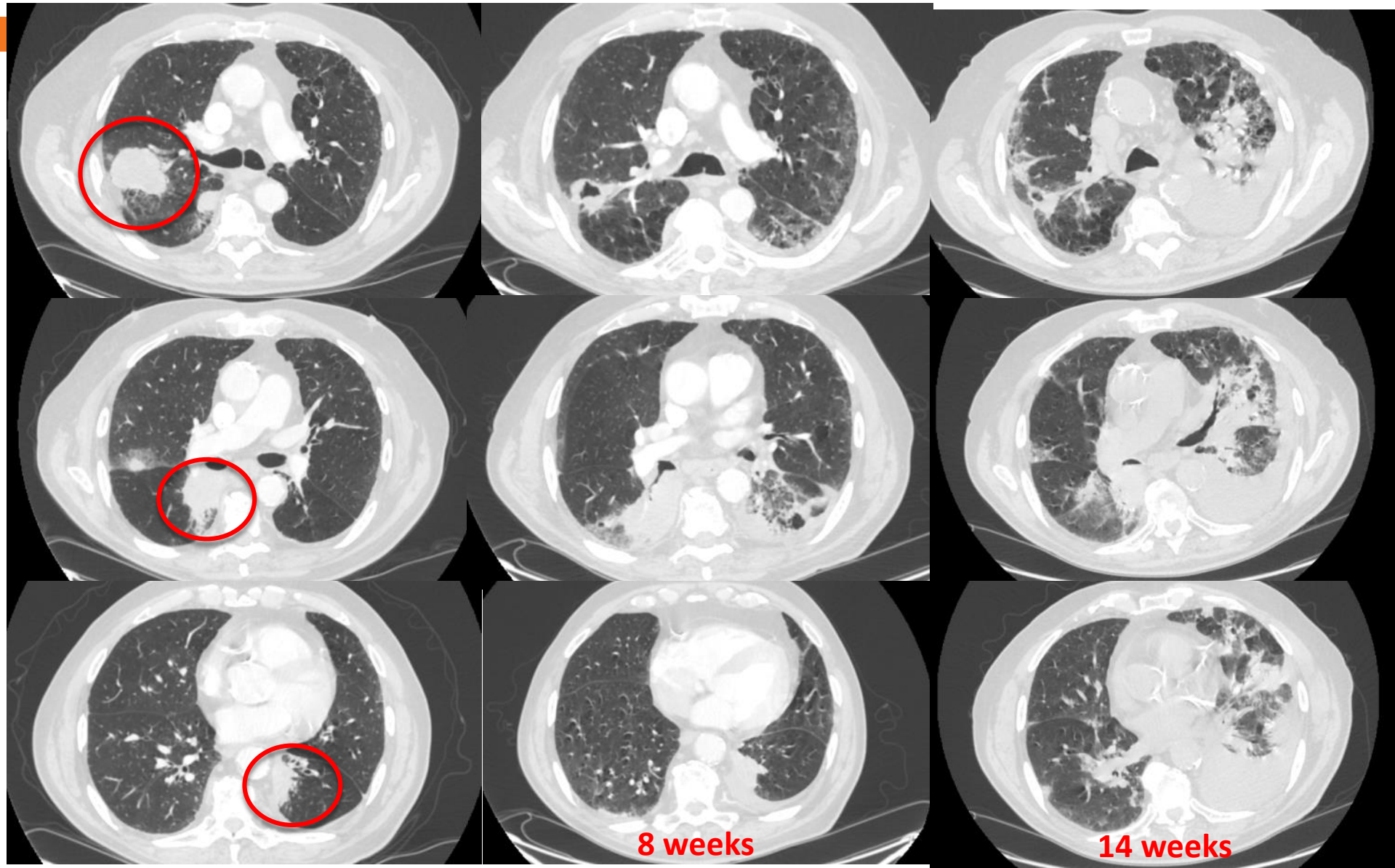
No complaints

Cough improved.

Increased light-moderate physical activity

SpO2: 92%/RA (baseline COPD)

Case #2: Nivolumab



Case #2 - Pneumonitis

- Week 14
  - Patient reports increased dyspnea on exertion
  - Remains active, but more limited
  - SpO2: 85%/RA, corrected to 92%/2L O2 while ambulating
  - methylprednisolone 125mg IV,
  - Prednisone 1 mg/kg daily, arranged for home O2.
- Week 15 (~11 months after diagnosis)
  - Resolution of dyspnea, increased appetite
  - Not wearing O2
  - 92% on RA
  - Initiated slow prednisone taper over 4 weeks

Outline

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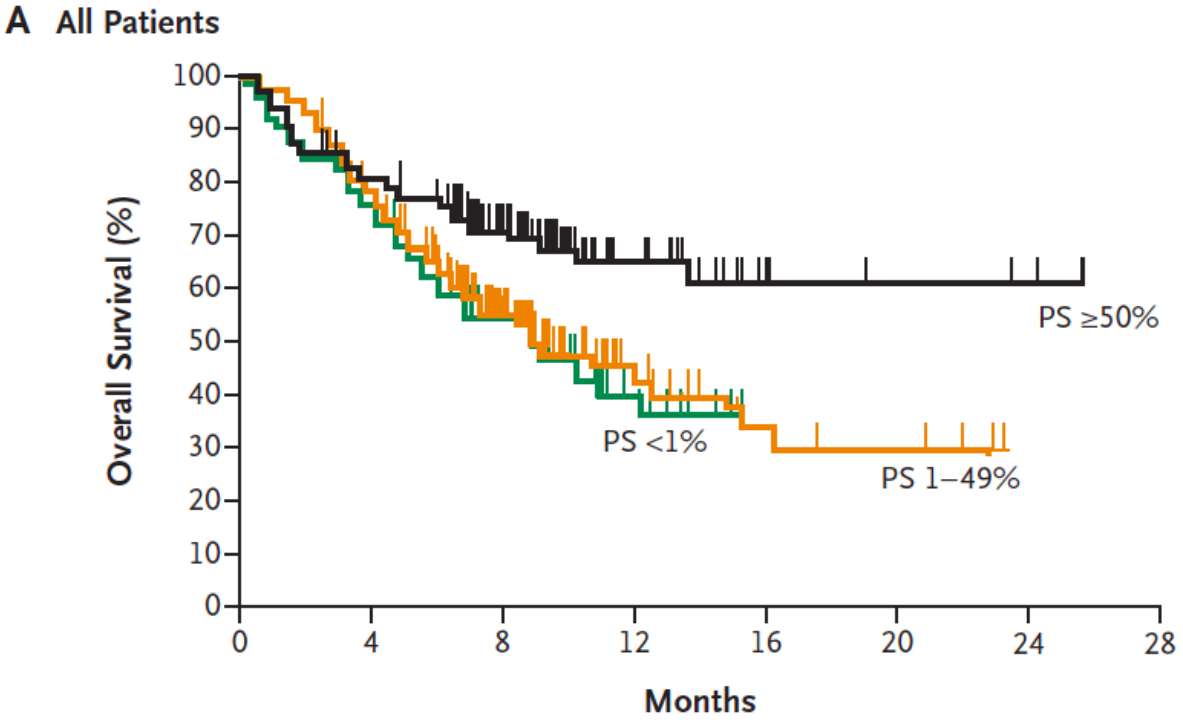
  - PDL1 expression
  - Future directions

PDL1 Expression

Keynote 001: 356 patients, Pembrolizumab



No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

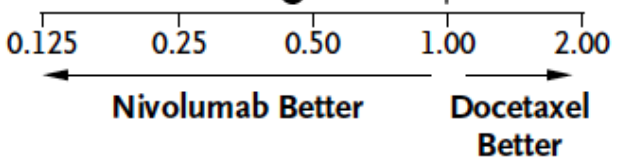
Garon et al, NEJM 2015

PDL1 Expression

CHECKMATE 017 (SCC):

C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)

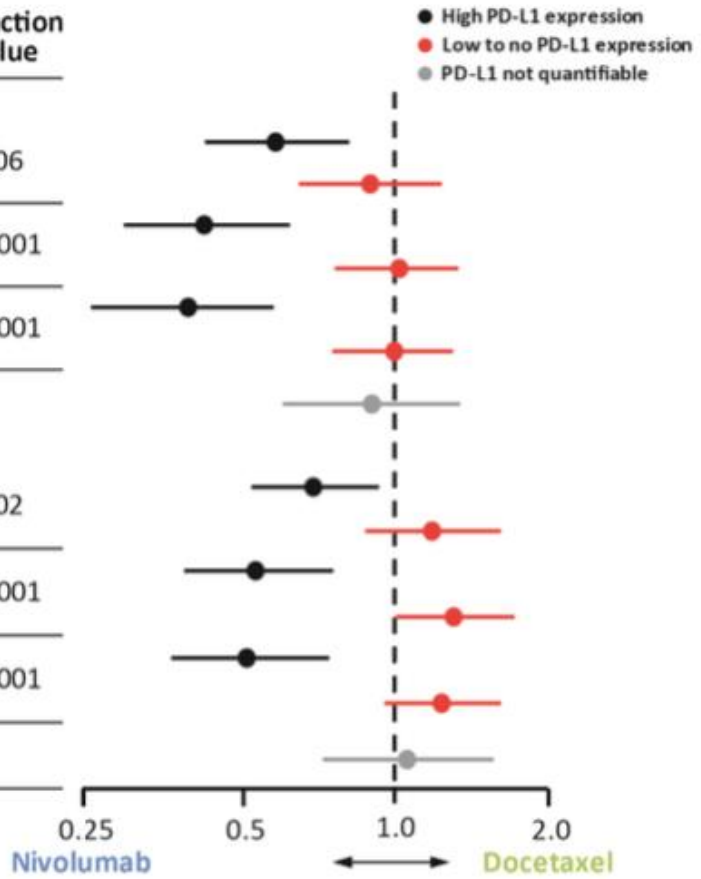


Brahmer et al. *N Engl J Med* 2015; 373:123-135

PDL1 Expression: Checkmate 057 (non-squamous)

Figure S7. Plot of Overall Survival and Progression-free Survival Hazard Ratios by PD-L1 Expression at Baseline.

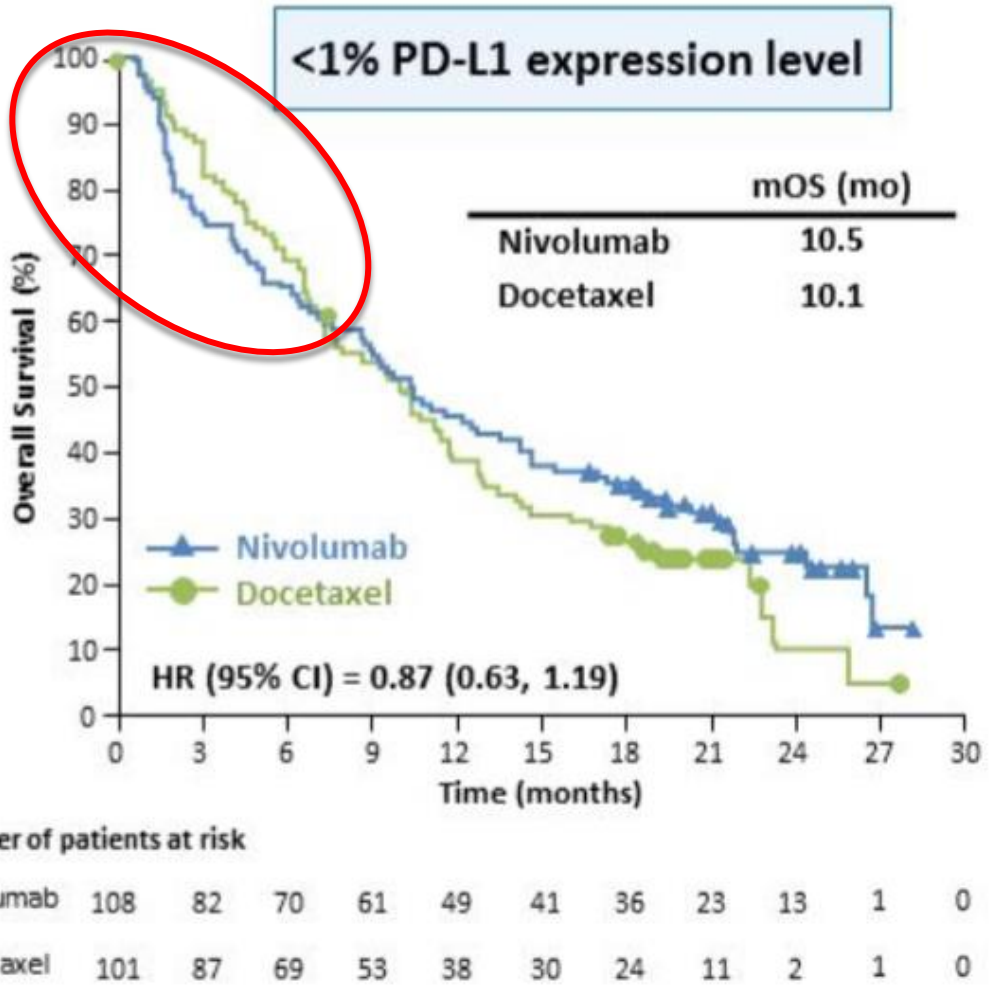
PD-L1 expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.06
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	<0.001
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	<0.001
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.02
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	<0.001
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	



Borghaei H, et al. NEJM 2015; 373:1627-1639

PDL1 Expression

Who are these patients who may be better served by 2nd line docetaxel?



Borghaei H, et al. NEJM 2015; 373:1627-1639

Toxicity

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

* Safety analyses included all the patients who received at least one dose of study drug. No treatment-related deaths occurred in patients treated with nivolumab. Treatment-related deaths were reported in three patients treated with docetaxel (one death each from interstitial lung disease, pulmonary hemorrhage, and sepsis).

Brahmer et al. *N Engl J Med* 2015; 373:123-135

Immunotherapy

- Immunology and checkpoint regulation
- Notable Clinical Trials
- PDL1 expression
- **Future directions**
- ***ESMO 2016 updates***

First line PD-1 vs. chemo

University of Virginia Health System | UVA Cancer Center
An NCI-Designated Cancer Center

KEYNOTE 024

- Pembrolizumab vs. chemo
- PDL1 ≥ 50%
- **PFS** 10.3 mo vs. 6 mo, (HR 0.50, p<0.001)
- **RR** 44.8% vs. 27.8%
- **OS** significant, medians not reached

Reck M, et al. ESMO 2016, abst: LBA8
Reck M, et al. NEJM 2016

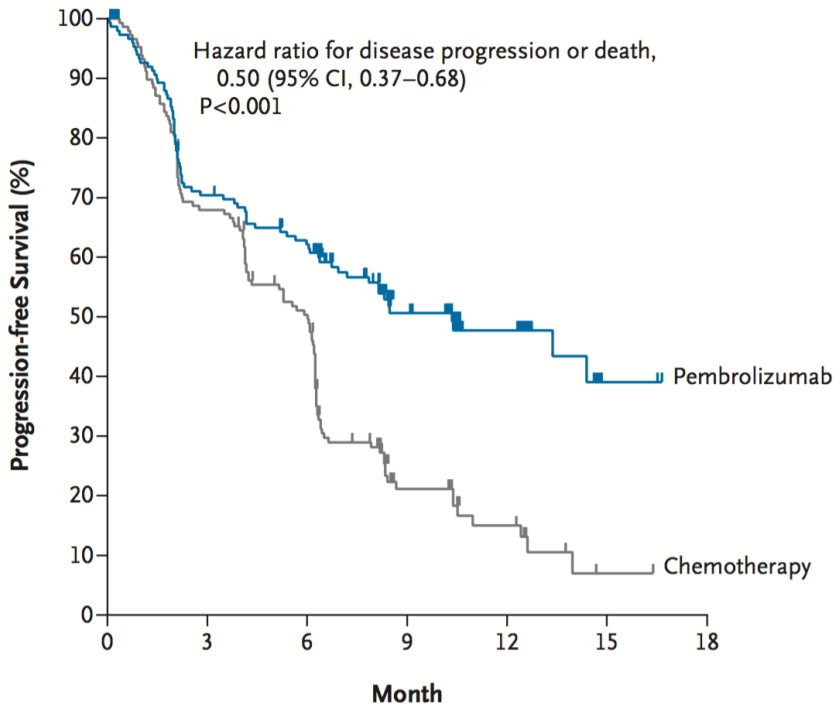
Checkmate 026

- Nivolumab vs. chemo
- PDL1 ≥ 5%
- **PFS** 4.2 vs 5.9 mo (HR 1.15, p=0.25)

Socinski M, et al. ESMO 2016, abst: LBA7

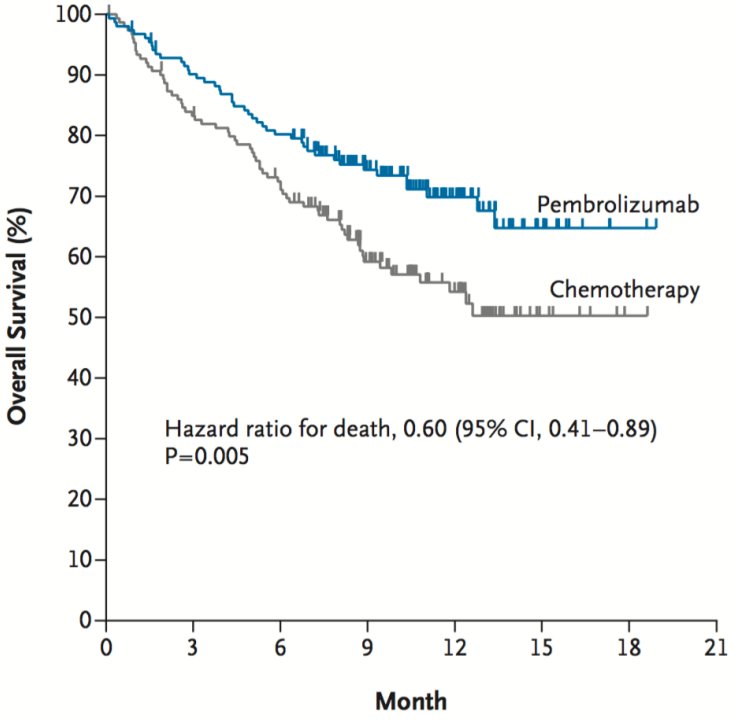
Keynote 024 PFS, OS

PFS



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

OS

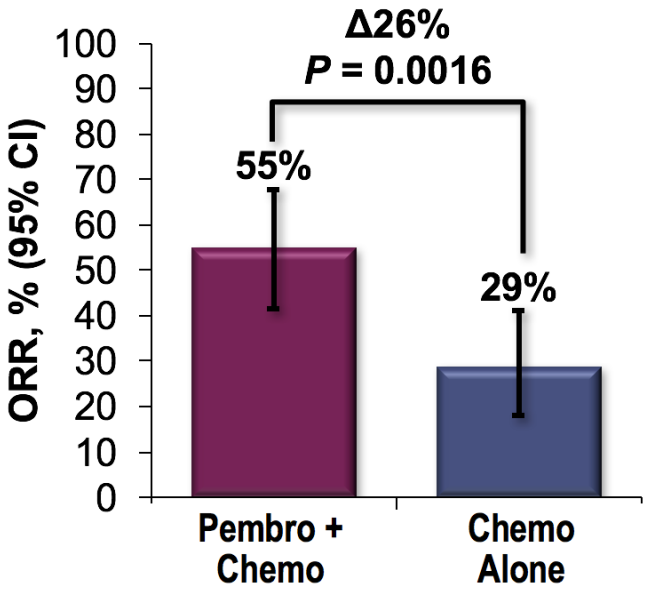


No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

Reck M, et al. NEJM 2016

Pembro + Chemo Keynote 021, G

Confirmed Objective Response Rate
(RECIST v1.1 by Blinded, Independent Central Review)



Data cut-off: August 8, 2016.

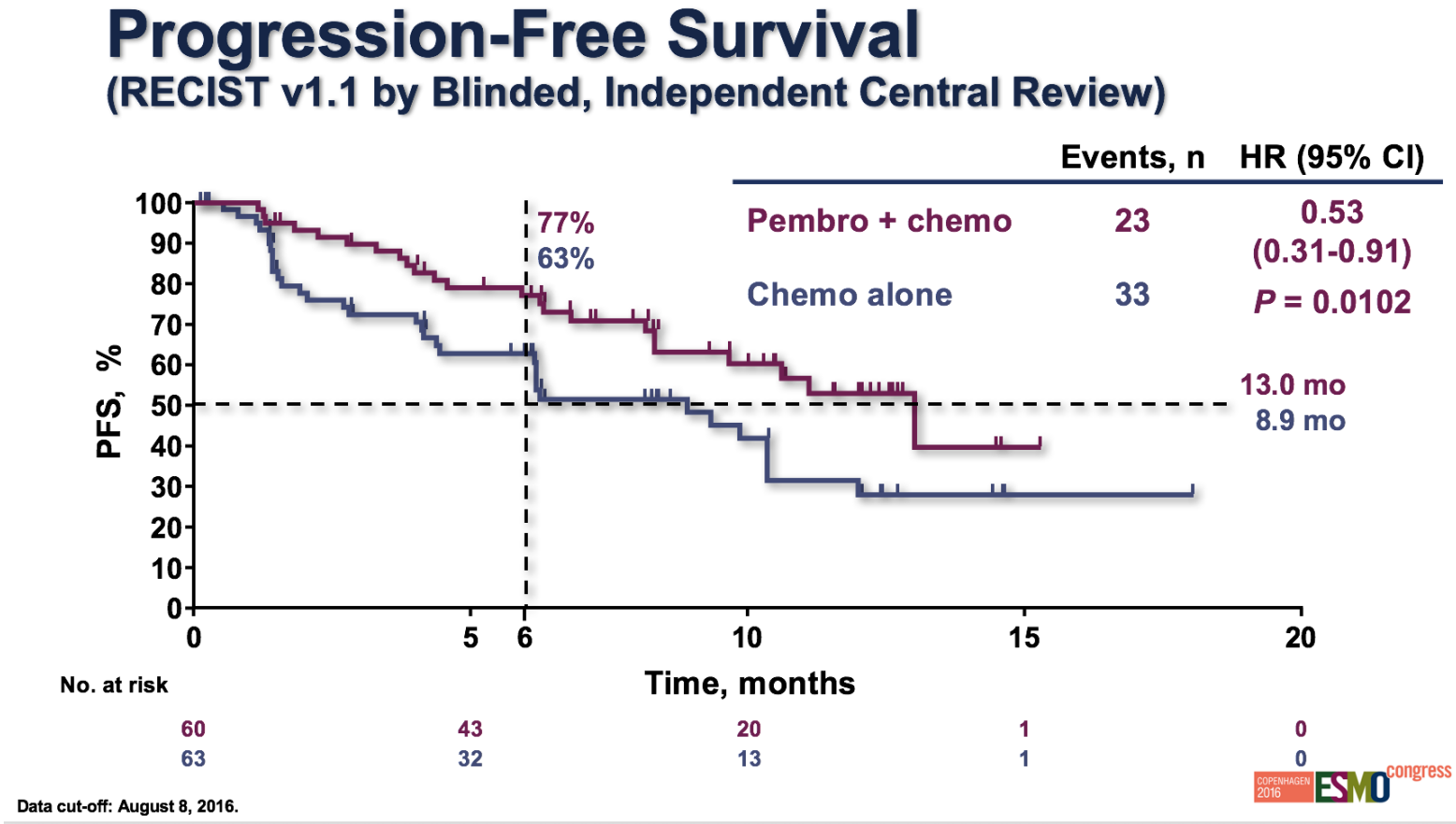
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response,[a] n (%)	29 (88)	14 (78)

DOR = duration of response; TTR = time to response.
[a]Alive without subsequent disease progression.

COPENHAGEN 2016 ESMO congress

Langer CJ, et al. *Lancet Oncology* 2016, epub ahead of print

Keynote 021, PFS

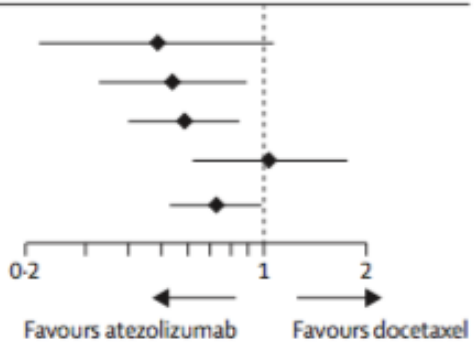


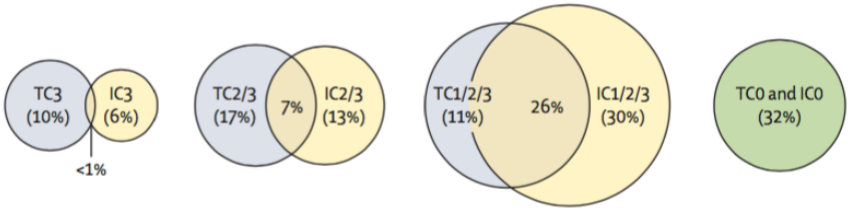
Langer CJ, et al. *Lancet Oncology* 2016, epub ahead of print

POPLAR, Phase II

B

	n (%)	HR*	95% CI	p value	Median overall survival (months [95% CI])	
					Atezolizumab (n=144)	Docetaxel (n=143)
TC3 or IC3	47 (16%)	0·49	0·22–1·07	0·068	15·5 (9·8–NE)	11·1 (6·7–14·4)
TC2/3 or IC2/3	105 (37%)	0·54	0·33–0·89	0·014	15·1 (8·4–NE)	7·4 (6·0–12·5)
TC1/2/3 or IC1/2/3	195 (68%)	0·59	0·40–0·85	0·005	15·5 (11·0–NE)	9·2 (7·3–12·8)
TC0 and IC0	92 (32%)	1·04	0·62–1·75	0·871	9·7 (6·7–12·0)	9·7 (8·6–12·0)
Intention to treat	287	0·73	0·53–0·99	0·040	12·6 (9·7–16·4)	9·7 (8·6–12·0)





PD-L1 tumour cell scoring		PD-L1 tumour-infiltrating immune cell scoring	
Score	Percentage of PD-L1-expressing cells	Score	Percentage of PD-L1-expressing cells
TC3	≥50%	IC3	≥10%
TC2	≥5% and <50%	IC2	≥5% and <10%
TC1	≥1% and <5%	IC1	≥1% and <5%
TC0	<1%	IC0	<1%

Overall prevalence	
Subgroup	Proportion
TC3 or IC3	16%
TC2/3 or IC2/3	37%
TC1/2/3 or IC1/2/3	68%
TC0 and IC0	32%

Fehrenbacher , et al. *Lancet* 2016, epub ahead of print

OAK, Phase III

	OS					
	Atezo		Doc		HRa (95% CI)	P Value
	n	Median, mo	n	Median, mo		
ITT	425	13.8	425	9.6	0.73 (0.62, 0.87)	0.0003b
TC1/2/3 or IC1/2/3	241	15.7	222	10.3	0.74 (0.58, 0.93)	0.0102b
TC2/3 or IC2/3	129	16.3	136	10.8	0.67 (0.49, 0.90)	0.0080
TC3 or IC3	72	20.5	65	8.9	0.41 (0.27, 0.64)	<0.0001
TC0 and IC0	180	12.6	199	8.9	0.75 (0.59, 0.96)	0.0215
Squamous	112	8.9	110	7.7	0.73 (0.54, 0.98)	0.0383
Nonsquamous	313	15.6	315	11.2	0.73 (0.60, 0.89)	0.0015

TC, tumor cell; IC, tumor infiltrating immune cells. PD-L1 expression was centrally evaluated with the VENTANA SP142 IHC assay
aStratified for ITT and TC1/2/3 or IC1/2/3, unstratified for other subgroups.
bFormally tested with alpha control

Barlesi F, et al. ESMO 2016; abst:LBA44_PR

Possible roles for immunotherapy

- Use as first line single agent
  - Keynote 024
- Combination with chemotherapy (1st and 2nd+ line chemo)
  - Keynote 189, IMpower studies
- Maintenance after chemotherapy
- Adjuvant for stage I-III
  - ANVIL (part of ALCHEMIST trials program)
  - PACIFIC: durvalumab (MEDI4736) – Stage III
  - HCRN 14-179: after concurrent chemoRT
- Combination immunotherapy
  - CTLA4 + PD-1
    - Lung-MAP
    - Checkmate 012
    - Keynote 021, Cohorts D, H
    - Checkmate 227, Phase III vs. chemo 1st line
    - NEPTUNE, Medimune + tremelimumab vs. chemo
  - PD-1 plus others (LAG3, etc.)
- Immunotherapy + targeted therapy (EGFR, etc.)
  - Keynote 021
  - Checkmate 370
  - AZD9291 + durvalumab for T790M+

Key Questions

- Increased antigen load = increased efficacy?
  - Concurrent with chemotherapy
  - Concurrent with radiotherapy
- Effects of prior chemotherapy?
  - Certain chemotherapy agents may be deleterious to tumor infiltrating lymphocytes or promote Treg
- Effects of corticosteroids when given with chemotherapy

Summary

- Nivolumab
  - FDA approved for the treatment of 2nd line or greater SCC-NSCLC based on CHECKMATE 017 and CHECKMATE 063 and for NS-NSCLC based on CHECKMATE 057.
    - Improved OS vs. docetaxel
- Pembrolizumab
  - FDA Approved based on KEYNOTE 001 and KEYNOTE 010
    - Improved OS vs. docetaxel
  - KEYNOTE 024: Improved OS vs. chemotherapy for PDL1 ≥ 50%
- Atezolizumab
  - FDA breakthrough designation
    - OS benefit compared to docetaxel from Ph II POPLAR and Ph III OAK studies
- SAEs are usually mild and less frequent than with chemotherapy
- PDL1 expression seems to play a role, but there may be differences between drugs, assays, histology that need to be further explored.
- Many areas of active research, including clinical trials at UVA

University of Virginia Lung Cancer Clinical Trial Program

July 2016

For more information or to speak with Ryan D. Gentzler MD, MS or Richard D Hall MD, MS, please call **Leslie Greenhowe at (434) 924-4246** M-F 8:00am to 4:30pm

Trial Name	Indication	Description	Treatment Arms
Stage IV Trials			
HCRN 13-175 NCT 02382406	1st line stage IV NSCLC (SCC and adenocarcinoma)	***Currently on hold re-opening to phase II soon*** **Single arm** phase II study of carboplatin, nab-paclitaxel, and pembrolizumab	Carboplatin day 1, nab-paclitaxel days 1, 8, and 15, and pembrolizumab day 1, repeat cycle every 21 days for 4 cycles followed by pembrolizumab maintenance.
KEYNOTE 189 NCT 02578680	1st line stage IV non-squamous NSCLC	Randomized, double-blind, placebo controlled phase III study of platinum and pemetrexed +/- pembrolizumab	Platinum (either cisplatin or carboplatin) + pemetrexed 500mg/m2 +/- pembrolizumab 200mg IV day 1, repeat every 21 days for up to 4 cycles followed by pembro +/- pemetrexed maintenance
LUN 288 NCT 02443337	2nd line stage IV lung SCC	**Single arm** phase II study of necitumumab (anti-EGFR antibody) + LY3023414 (PI3K inhibitor) Prior platinum doublet chemotherapy required Prior immunotherapy (anti-PD-1 or anti-PD-L1) allowed	Necitumumab 800mg IV days 1 and 8 LY3023414 200mg po BID days 1-21 continuously Repeat cycle every 21 days
Lung MAP (S1400) NCT 02154490	2nd line or greater stage IV lung SCC	Multi arm master protocol study in second line SCC. Prior platinum doublet chemotherapy required Recent significant protocol changes	Arm 1400B: Single agent PI3KCA inhibitor Arm 1400C: Single agent palbociclib Arm 1400D: Single agent FGFR inhibitor Arm 1400I: Nivolumab vs Nivolumab + Ipilimumab
X-396 CLI 101 NCT 01625234	1st, 2nd, and 3rd line *ALK* rearranged NSCLC	Phase II multi arm study of single agent X-396 in *ALK*-rearranged NSCLC	Arm I: ALK TKI naïve Arm II: Prior crizotinib Arm III: Prior crizotinib and 2nd gen TKI Arm IV: CNS metastasis Arm V: Leptomeningeal disease
Stage III, Unresectable Trial			
HCRN 14-179 NCT 02343952	1st line inoperable stage IIIA or IIIB NSCLC	Single arm phase II study of pembrolizumab 200mg IV every 3 weeks **after** completion of concurrent chemo + XRT.	Pembrolizumab 200mg IV every 3 weeks Need to be screened 28-56 days **after** completion of chemoRT
AbbVie M14-360 NCT 02412371	1st line stage III NSCLC	Phase I and II study of carboplatin/paclitaxel +/- veliparib concurrent with radiation, currently in phase I (single arm 3+3 dose finding study, all patients receive veliparib)	Phase I: carboplatin and paclitaxel + veliparib (to determine MTD) concurrent with radiation
Stage IB-IIIA, Adjuvant Trials			
ALCHEMIST NCT 02194738 NCT 02193282 NCT 02201992	Adjuvant stage IB-IIIA lung adenocarcinoma after surgery	Adjuvant erlotinib or crizotinib for up to 2 years (can receive standard chemo elsewhere) for *EGFR* mutation or *ALK* rearrangements.	A081105 (*EGFR* mutation positive): Randomized 1:1 to erlotinib 150mg po once daily or placebo E4512 (*ALK* rearranged): Randomized 1:1 to crizotinib 250mg po BID or placebo
ANVIL NCT 02595944	Adjuvant stage IB-IIIA NSCLC (SCC and adenocarcinoma)	Part of ALCHEMIST trial program Randomized phase III study of adjuvant nivolumab or observation for resected NSCLC (can receive standard chemo elsewhere)	Nivolumab 240mg IV every 2 weeks for 1 year or observation
Extensive Stage Small Cell Lung Cancer (SCLC)			
TRINITY NCT 02674568	3rd line SCLC	Single arm phase II study of antibody-drug conjugate rovalpituzumab-tesirine (Rova-T) after 2 prior lines of therapy (one of which must be platinum doublet)	Single arm of Rova-T IV Q6 weeks x 2 treatments

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