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Immunotherapy For Lung Cancer

Rachel E. Sanborn, M.D.
Co-Director, Thoracic Oncology Program
Phase I Clinical Trials Program
Providence Cancer Center
October 13, 2016

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Case Presentation

- 45 y.o. man, heavy tobacco history
- Stage IVB, T4N2M1b poorly differentiated squamous cell lung cancer
  - Right hilar primary, mediastinal adenopathy, multiple liver mets
- Diagnosed on workup for hemoptysis, weight loss
- August 2014

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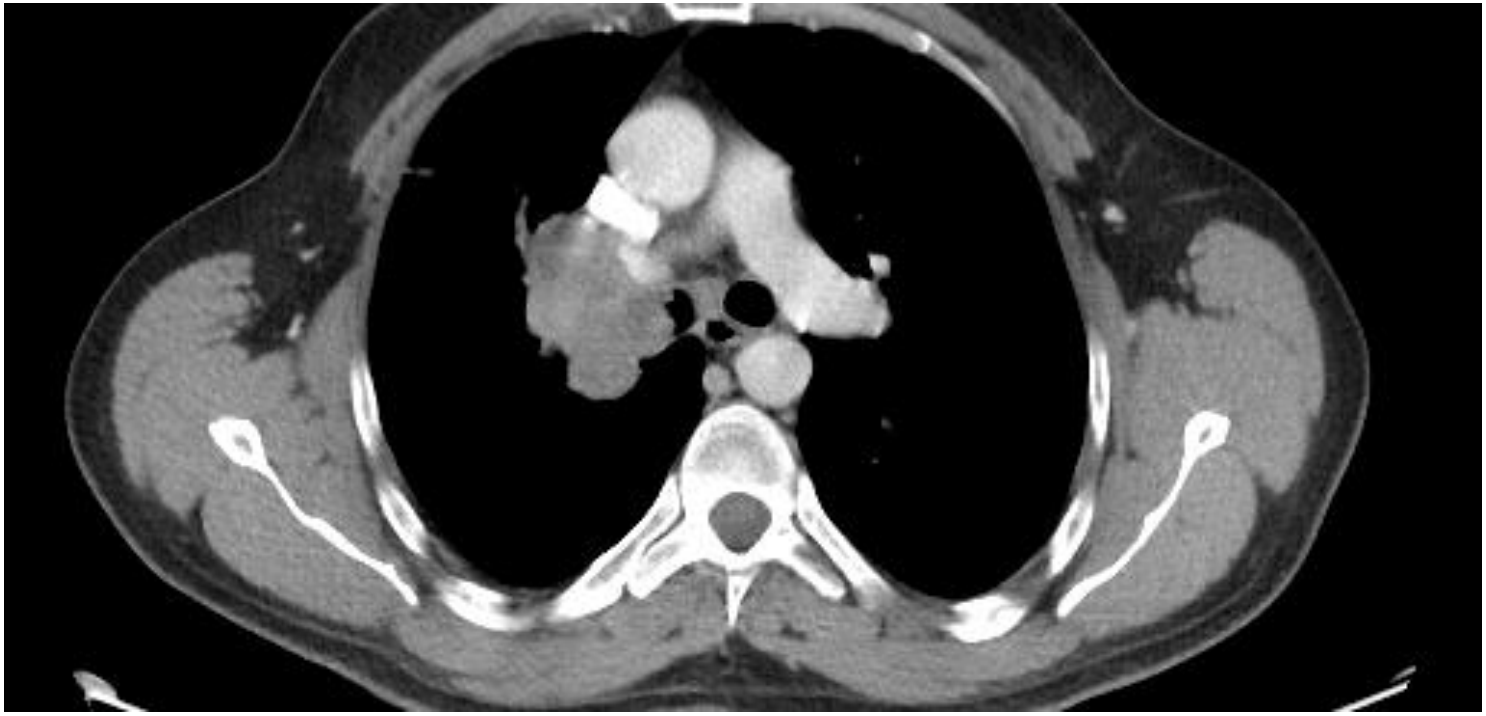
August 2014 Presenting Tumor



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Case Presentation, Continued

- Palliative radiation right hilar mass (September 2014)
- Carboplatin/Paclitaxel
  - Severe infusion reaction
- Carboplatin/Gemcitabine x4 cycles (Through 12-17-14)
- Progressive disease

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Immunotherapy for Squamous NSCLC

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

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Stage IIIB/IV squamous NSCLC

1 Line Platinum chemo

ECOG 0-1

Tissue available for biomarker analysis (Archival or recent)

Treated stable brain mets allowed

352 Patients enrolled:

272 Randomized

Nivolumab
3 mg/kg q2 weeks
(137 Pts)

Docetaxel
75 mg/m2 q3 weeks
(137 Pts)

Randomization stratified:
Prior paclitaxel, geography
(US/Canada; Europe; ROW)

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Brahmer et al, NEJM 2015

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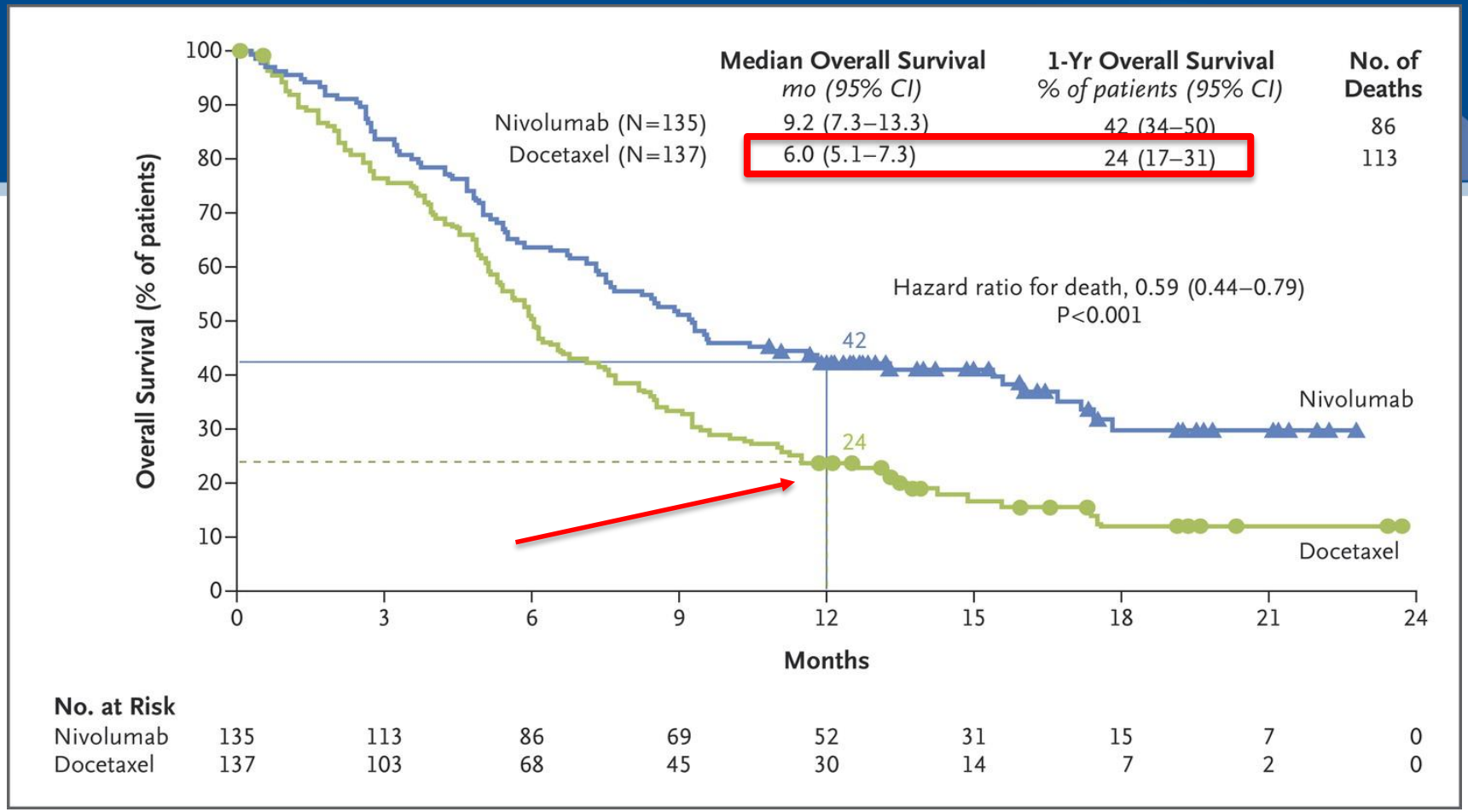
Kaplan–Meier Curves for Overall Survival.



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Brahmer J et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504627

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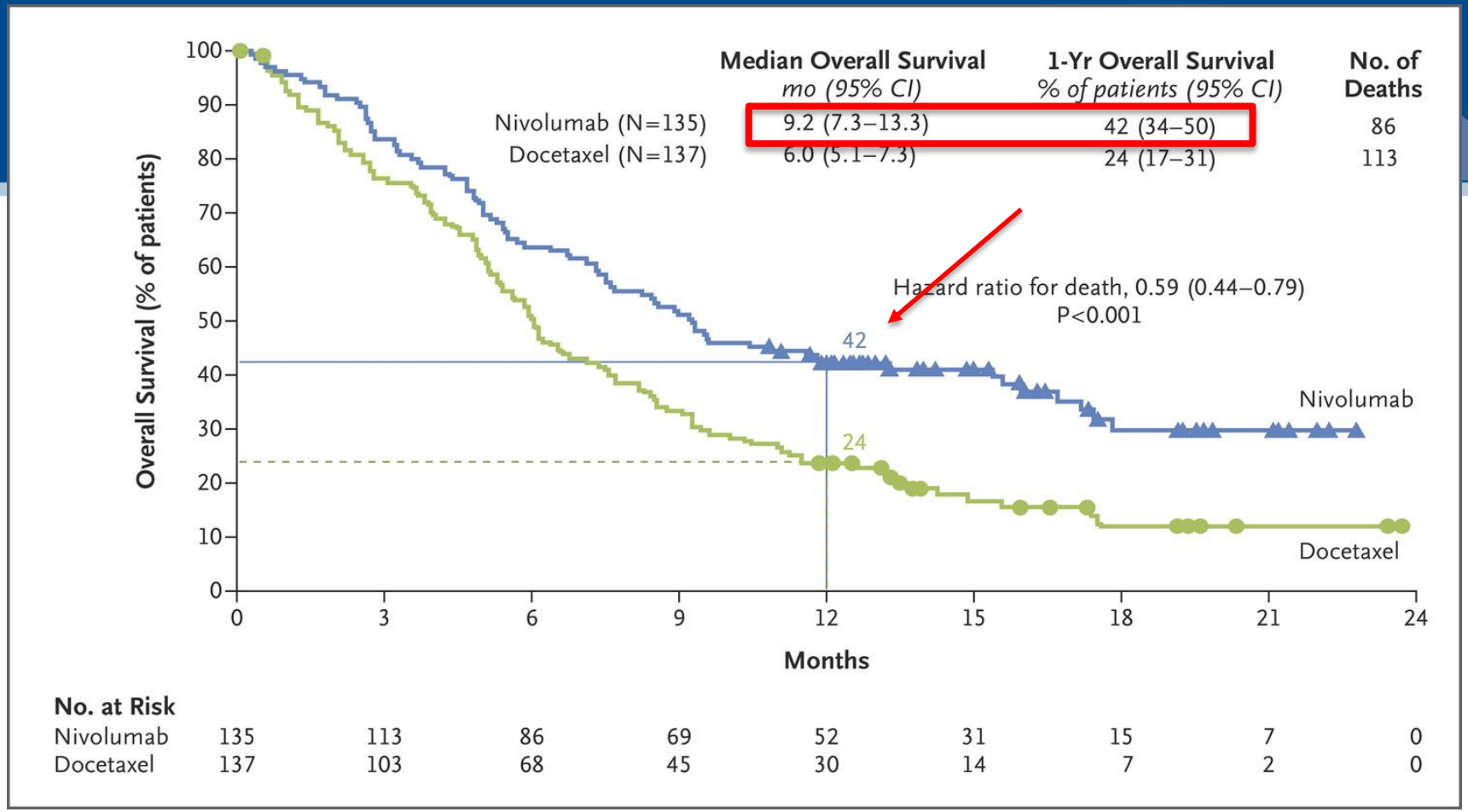
Kaplan–Meier Curves for Overall Survival.



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Brahmer J et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504627

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Patients

- Expected squamous demographics
- Median age 63 (Range 39-85)
- 76% Male
- 76% ECOG 1
- 92% Current/former smokers

Brahmer et al, NEJM 2015

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Response

- Confirmed RR
  - Nivolumab: 20%
  - Docetaxel: 9%
- Median Time to Response
  - 2.2 vs 2.1 months
- Median Duration of Response
  - 8.4 months (Doc) vs Not reached (Nivo)

Brahmer et al, NEJM 2015

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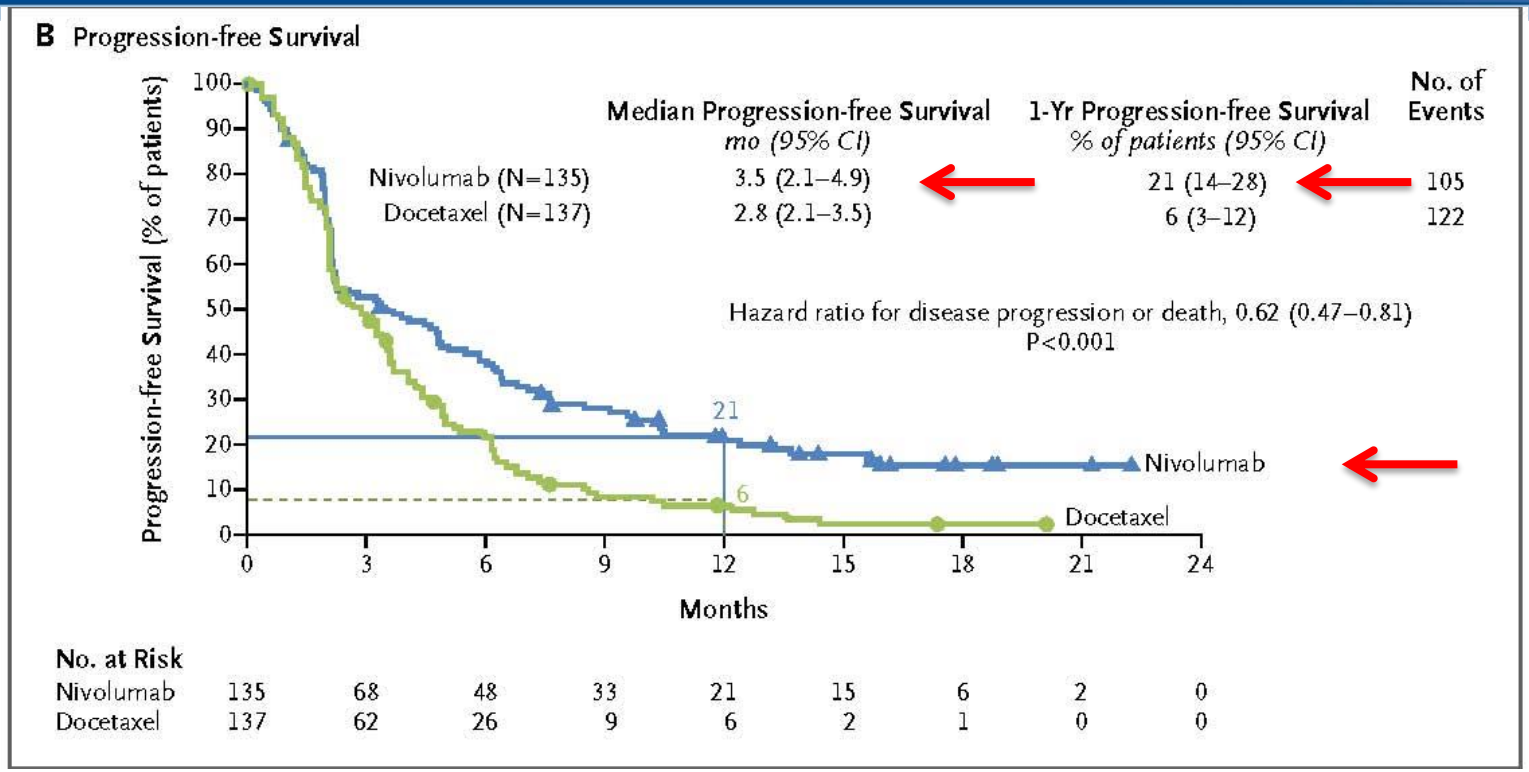
Progression-Free Survival



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Brahmer J et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504627

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PD-L1 Expression

- 83% with quantifiable PD-L1 expression (IHC, Dako)
- Expression levels: 1%, 5%, 10%
  (in a section containing ≥ 100 tumor cells)
- NO relation (prognostic or predictive) to efficacy

Brahmer et al, NEJM 2015

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Toxicity

- Grade 3/4
  - Docetaxel: 55%
  - Nivolumab: 7%
- Grade 5
  - Docetaxel: 2%
  - Nivolumab: 0
- Nivo most frequent: Fatigue, anorexia, asthenia
- Doc most frequent: Neutropenia, fatigue, alopecia, nausea

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Brahmer et al, NEJM 2015

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“Special” SAEs with Nivo

- Hypothyroidism (4%)
- Pneumonitis (5%)

- More pts with AEs continued treatment with Nivo than Doc

Brahmer et al, NEJM 2015

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Immunotherapy for NSCLC

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

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Study Design

- International Phase I trial
- NSCLC enrolled into expansion cohorts
- ECOG 0-1

- Dose ranges:
  - 2 mg/kg q3 weeks
  - 10 mg/kg q3 weeks
  - 10 mg/kg q2 weeks

Garon et al, NEJM 2015

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Survival

- Median PFS: 3.7 mo
- Previously Treated PFS: 3 mo
- Previously Untreated PFS: 6 mo

- Median OS: 12 mo
- Previously Treated OS: 9.3 mo
- Previously Untreated OS: 16.2 mo

Garon et al, NEJM 2015

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PD-L1 Testing

- Positive by IHC (Dako): ≥ 1% cells within tumor nests
- PD-L1 deterioration noted in samples > 6 months old

Garon et al, NEJM 2015

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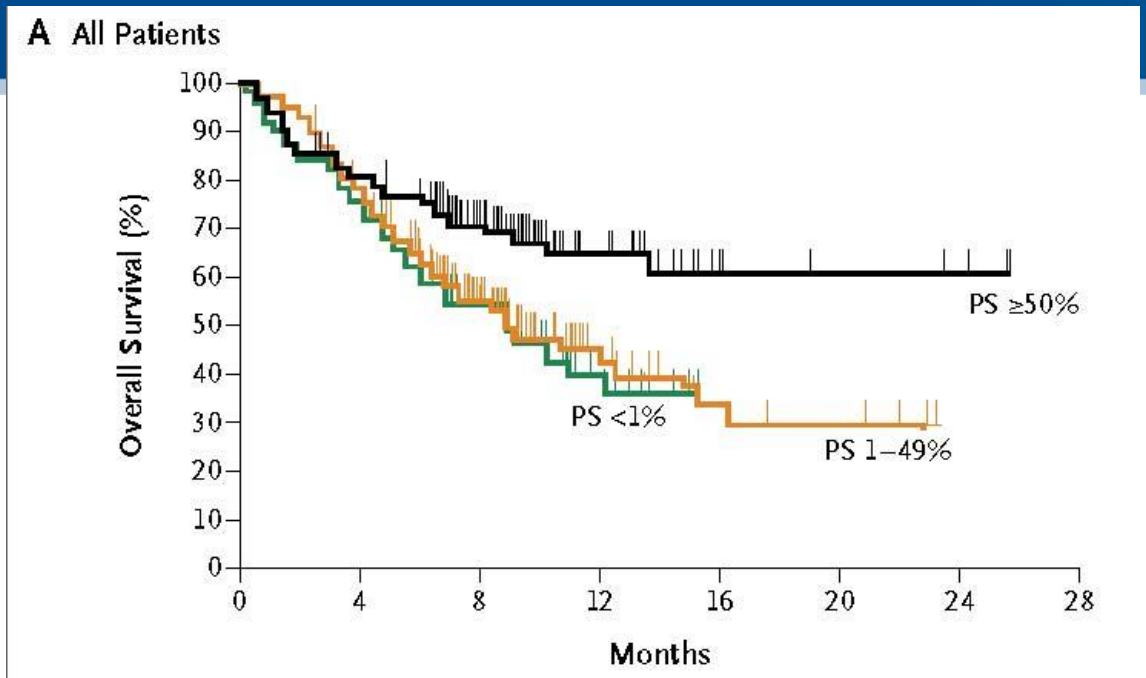
OS: All PD-L1 Positive: Not Reached



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

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AEs

- Grade 3 or higher: 9.5%
  - Immune-related in ≥ 2%:
  - Infusion reactions 3%
  - Hypothyroidism 6.9%
  - Pneumonitis 3.6% (1 Grade 5)

Garon et al, NEJM 2015

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Conclusions

- PD-L1 expression ≥ 50% associated with:
- Higher RR
- Longer PFS, OS

- Magnitude of benefit exceeds standard chemo expectations

Garon et al, NEJM 2015

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Caveats

- Pts with < 1% expression still responded
- The test is imperfect for predicting benefit, but SELECTIVE in finding those with the most benefit

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Original Article

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

Hossein Borghaei, D.O., Luis Paz-Ares, M.D., Leora Horn, M.D., David R. Spigel, M.D., Martin Steins, M.D., Ph.D., Neal E. Ready, M.D., Ph.D., Laura Q. Chow, M.D., Everett E. Vokes, M.D., Enriqueta Felip, M.D., Esther Holgado, M.D., Fabrice Barlesi, M.D., Ph.D., Martin Kohlhäufl, M.D., Ph.D., Oscar Arrieta, M.D., Marco Angelo Burgio, M.D., Jérôme Fayette, M.D., Ph.D., Hervé Lena, M.D., Elena Poddubskaya, M.D., David E. Gerber, M.D., Scott N. Gettinger, M.D., Charles M. Rudin, M.D., Ph.D., Naiyer Rizvi, M.D., Lucio Crinò, M.D., George R. Blumenschein, Jr., M.D., Scott J. Antonia, M.D., Ph.D., Cécile Dorange, M.S., Christopher T. Harbison, Ph.D., Friedrich Graf Finckenstein, M.D., and Julie R. Brahmer, M.D.

N Engl J Med
Volume 373(17):1627-1639
October 22, 2015

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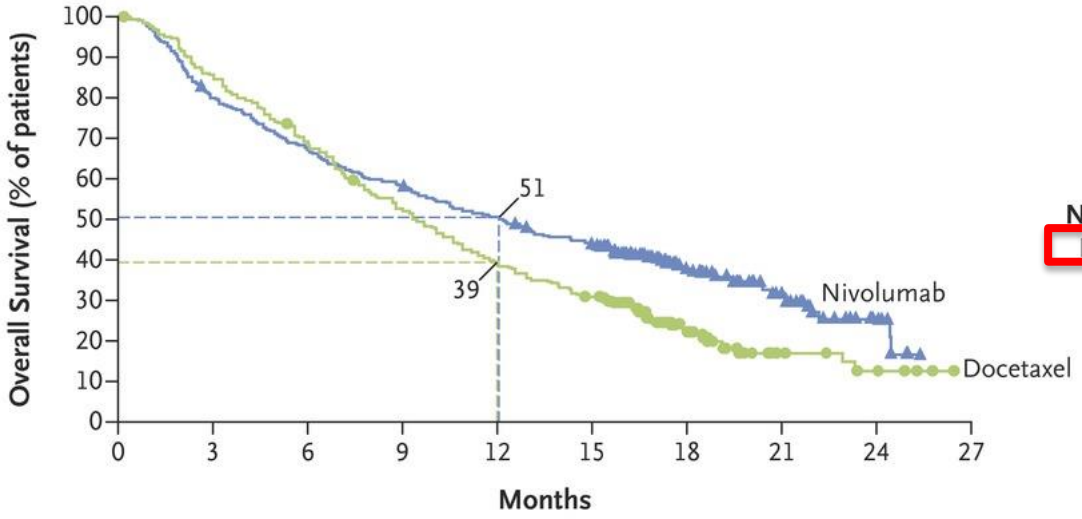
Overall Survival, Duration of Response, and Progression-free Survival.

A Overall Survival



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

No. at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Borghaei H et al. N Engl J Med 2015;373:1627-1639

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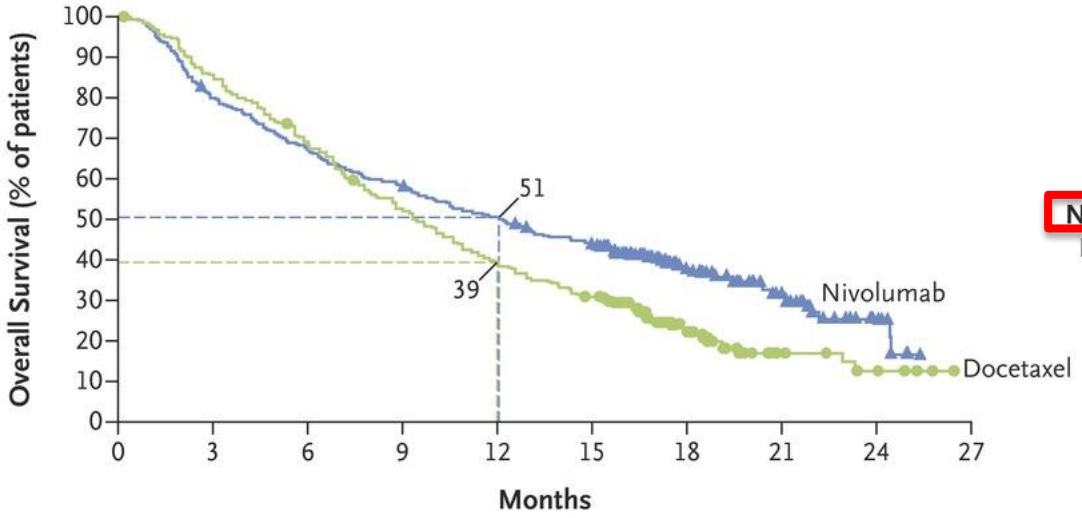
Overall Survival, Duration of Response, and Progression-free Survival.

A Overall Survival



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Nivolumab vs Docetaxel, Survival

- PFS
  - Nivolumab: 2.3 mo
  - Docetaxel: 4.2 mo
  - PFS curves separated after ~7 months
- Median OS
  - Nivolumab: 12.2 mo
    - 1-Y OS 51%
  - Docetaxel: 9.4 mo
    - 1-Y OS 39%

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Paz-Ares et al, PASCO 2015

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Immunotherapy in NSCLC is Real

- Nivolumab approved for previously-treated NSCLC
- Pembrolizumab approved for PD-L1 positive NSCLC
- What will combination immunotherapy show?

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Case Presentation

- Enrolled in combination I-O study, anti-PDL1/anti-CTLA4
- Cycle 1 Day 1 1-22-15

- Fungating scalp met
  - Palliative radiation April 2015

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Case Presentation, Events

- Eye redness/irritation
- Treatment held Cycle 6 Day 15
- Optho eval, uveitis ruled out; Grade 1 episcleritis
- Hospitalized 10-29-15, new insulin-dependent diabetes (Grade 3)
  - Glucose 683
- Grade 2 pneumonitis

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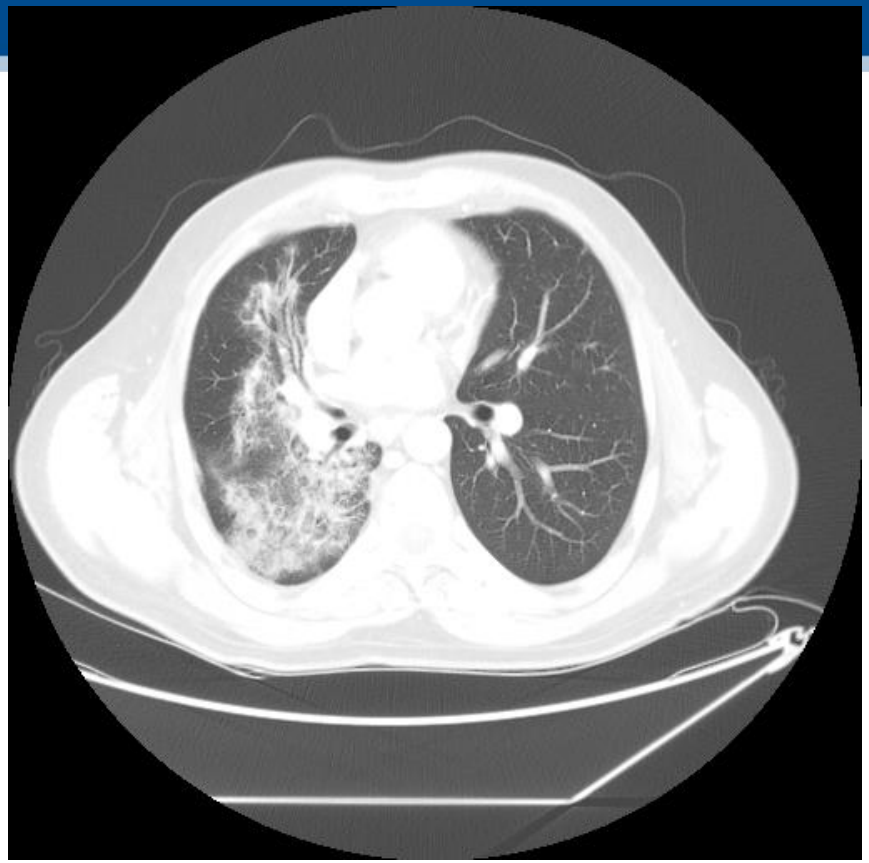
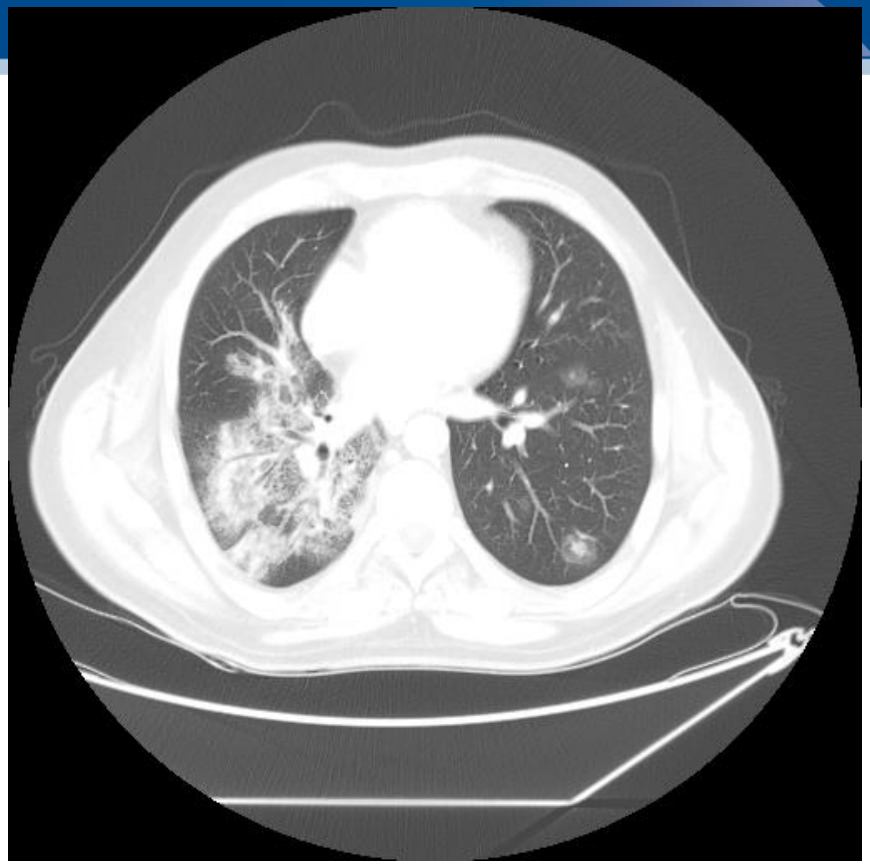
October 2015 Pneumonitis





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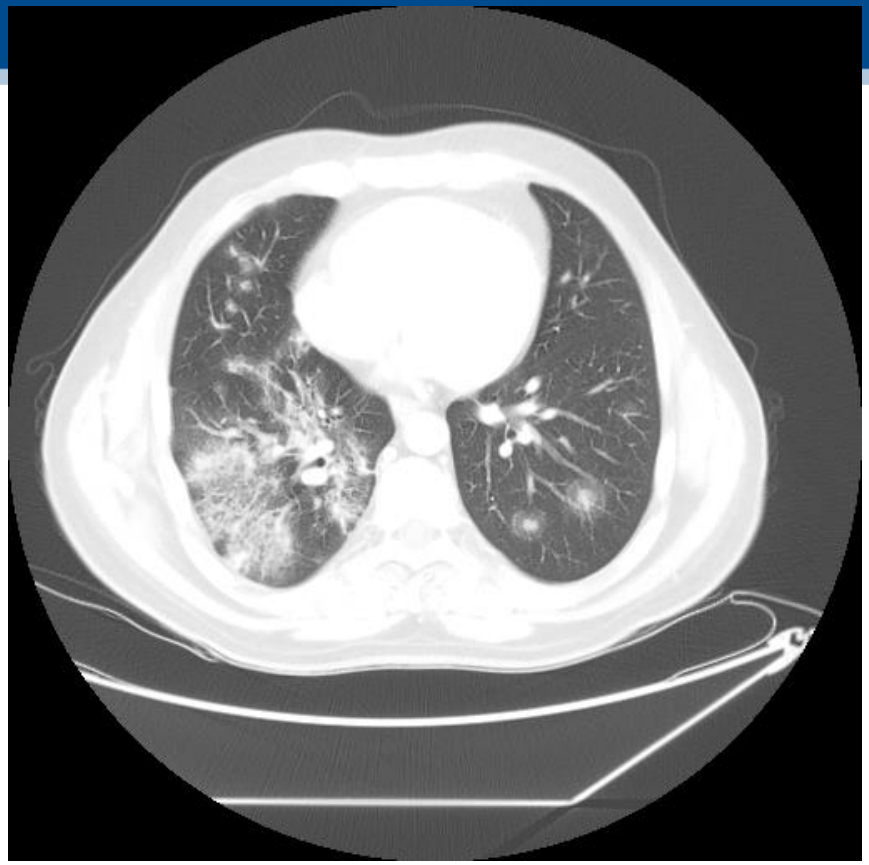
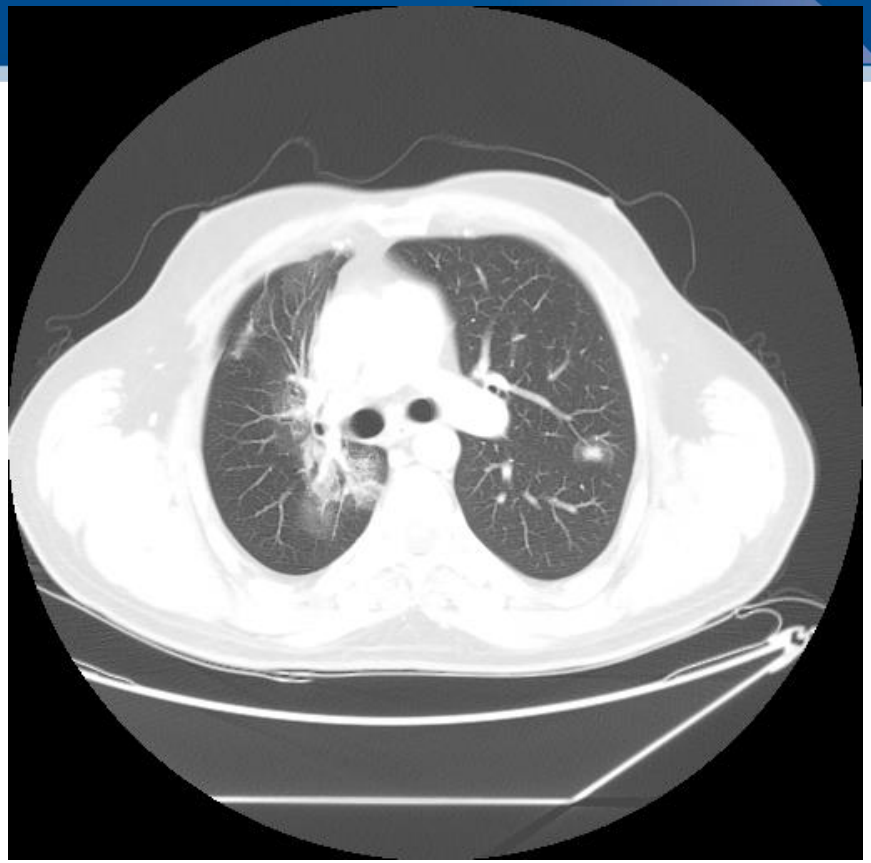
October 2015 Pneumonitis





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Case Presentation

- Diabetes/Pneumonitis
- Pulmonary evaluation, bronchoscopy: Unrevealing
- Prolonged steroid taper

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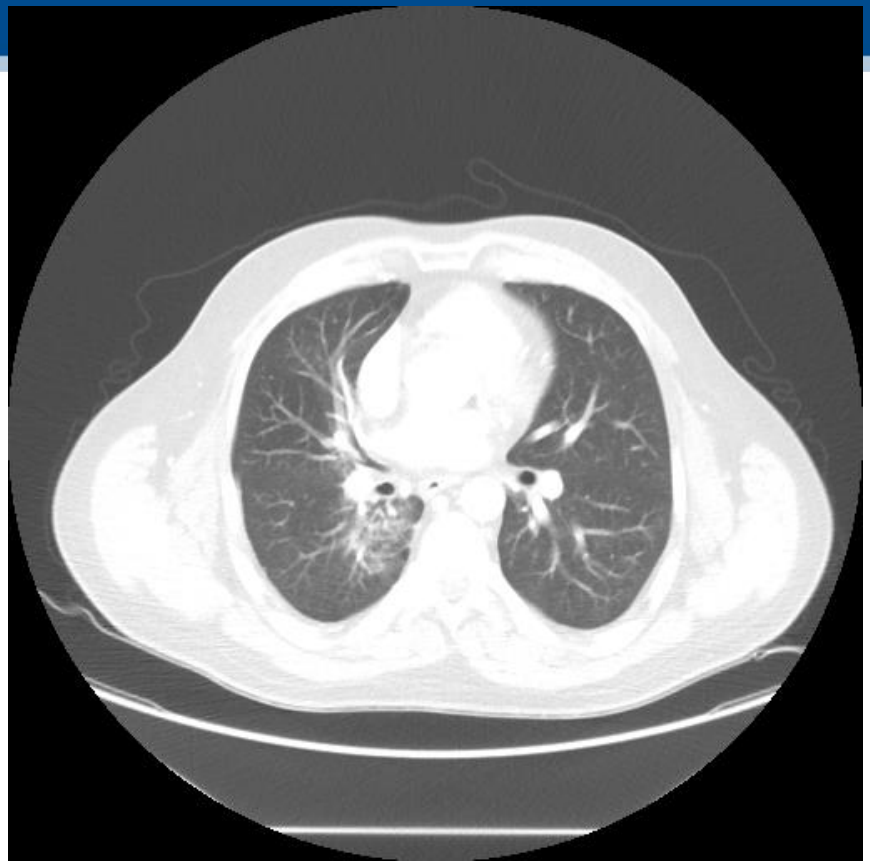
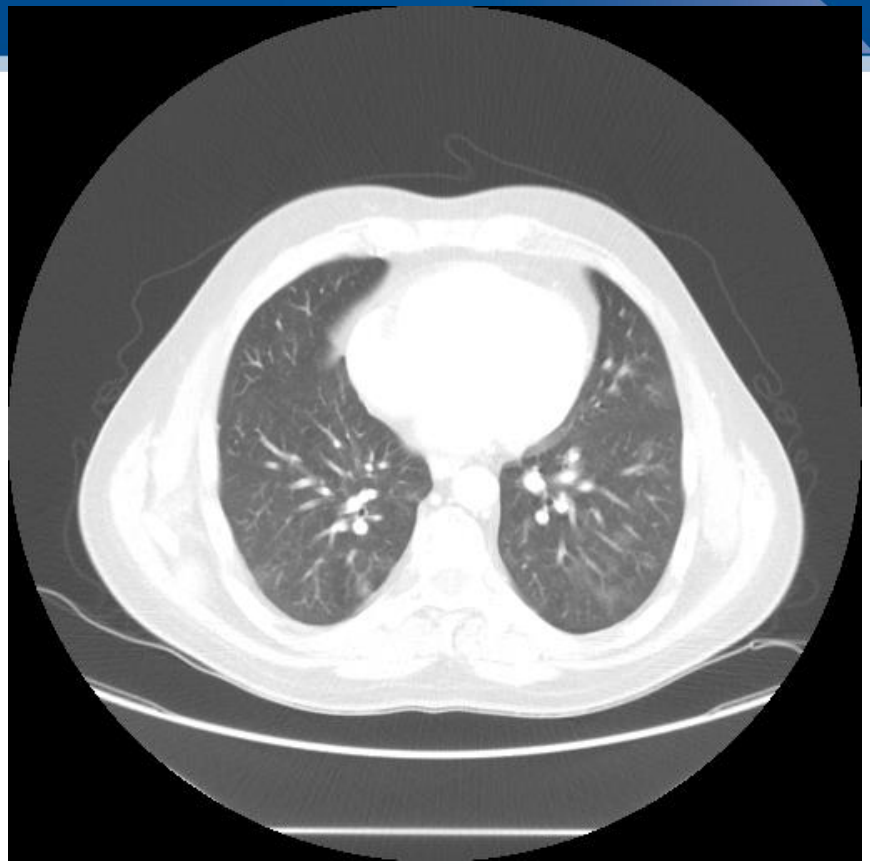
December 2015 Recovery from Pneumonitis





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Case Presentation

- Diabetes/Pneumonitis
- Pulmonary evaluation, bronchoscopy: Unrevealing
- Prolonged steroid taper
- Single dose anti-PDL1 rechallenge 1-11-16
- Incidental recurrence pneumonitis
  - 2-16-16
- Transient hypoxia
- Restarted prednisone taper

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February 2016, Recurrent Pneumonitis

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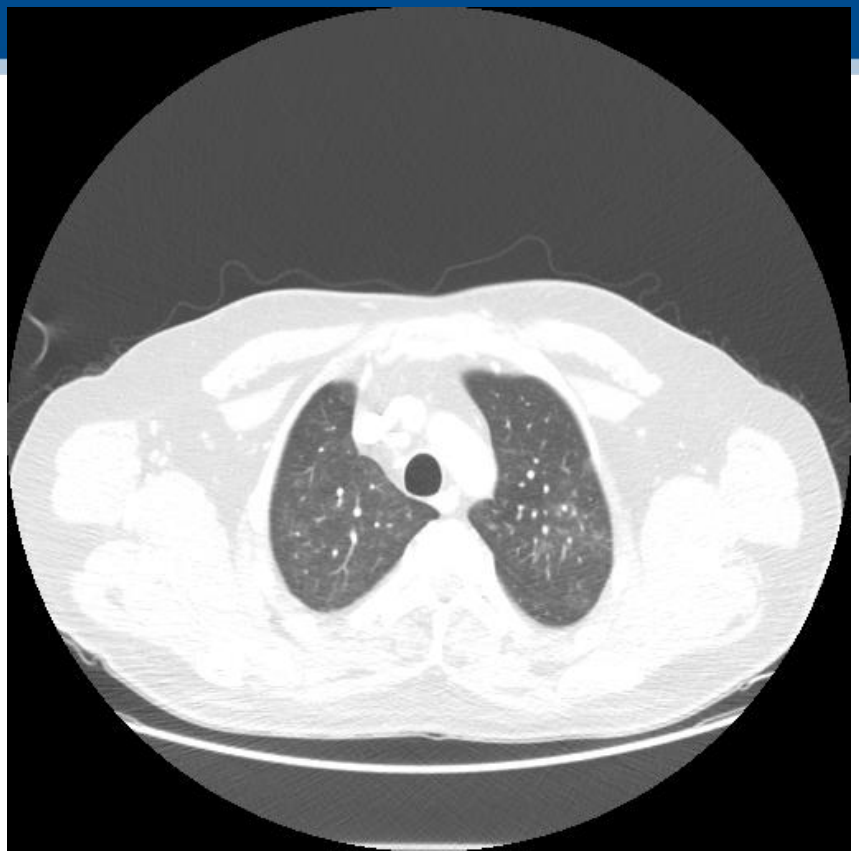
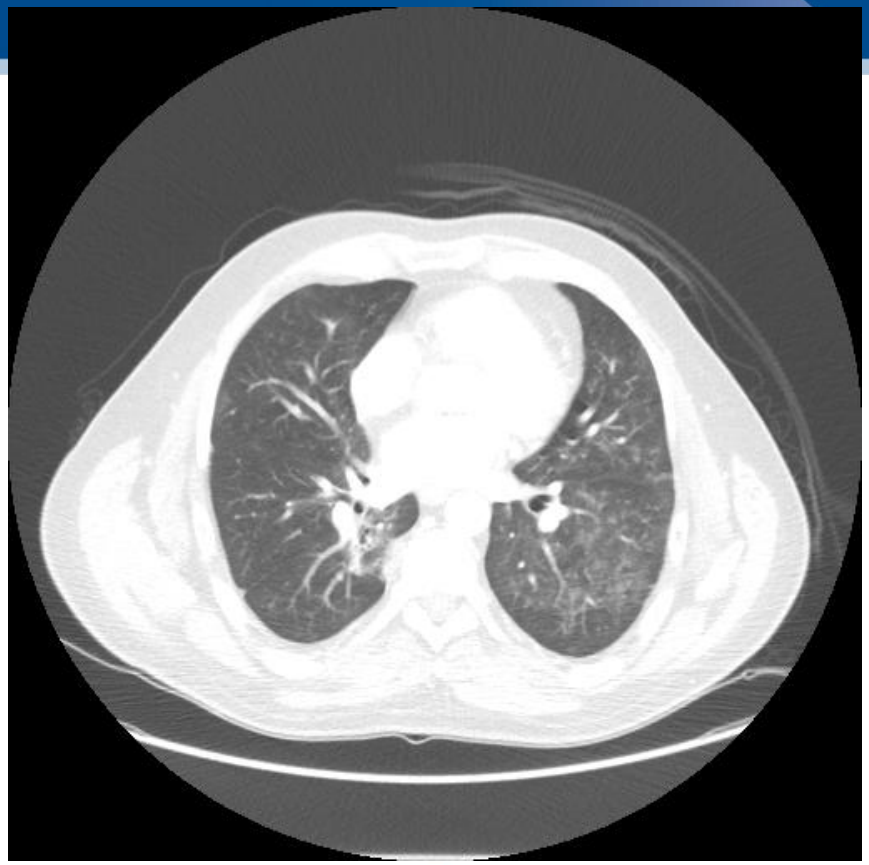
April 2016, Improvement of Pneumonitis





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Case Presentation—The Story Continues

- Follow up CT 6-11-16
- Recurrent pneumonitis (No hypoxia)
- Completed prednisone taper 7-23-16

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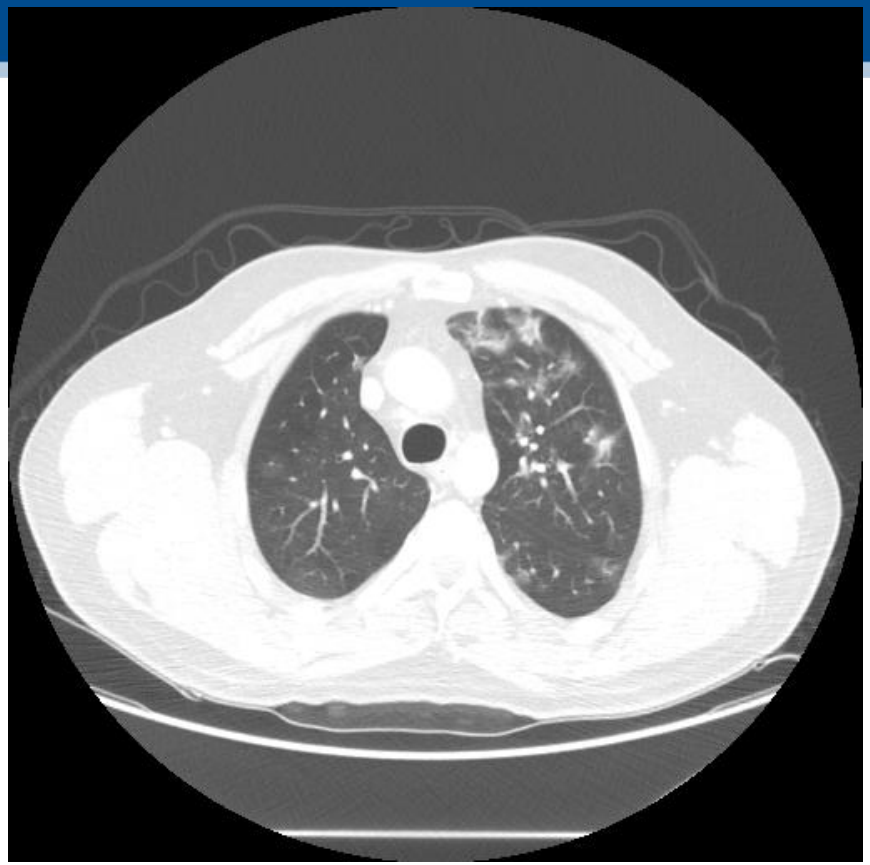
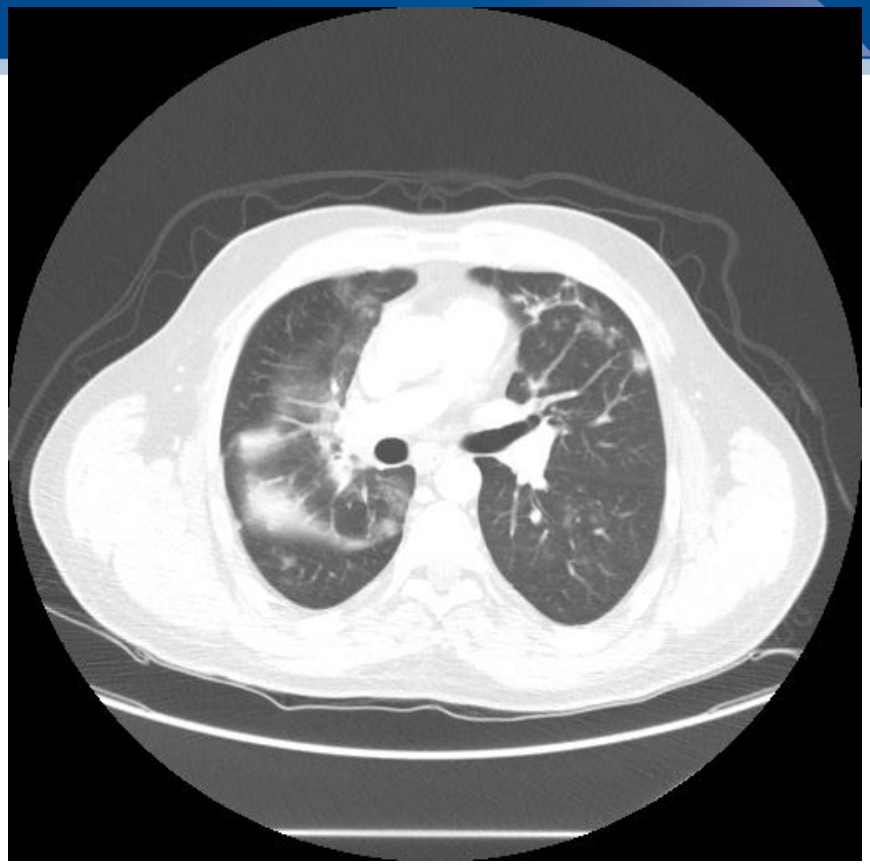
June 2016 Pneumonitis Recurrence





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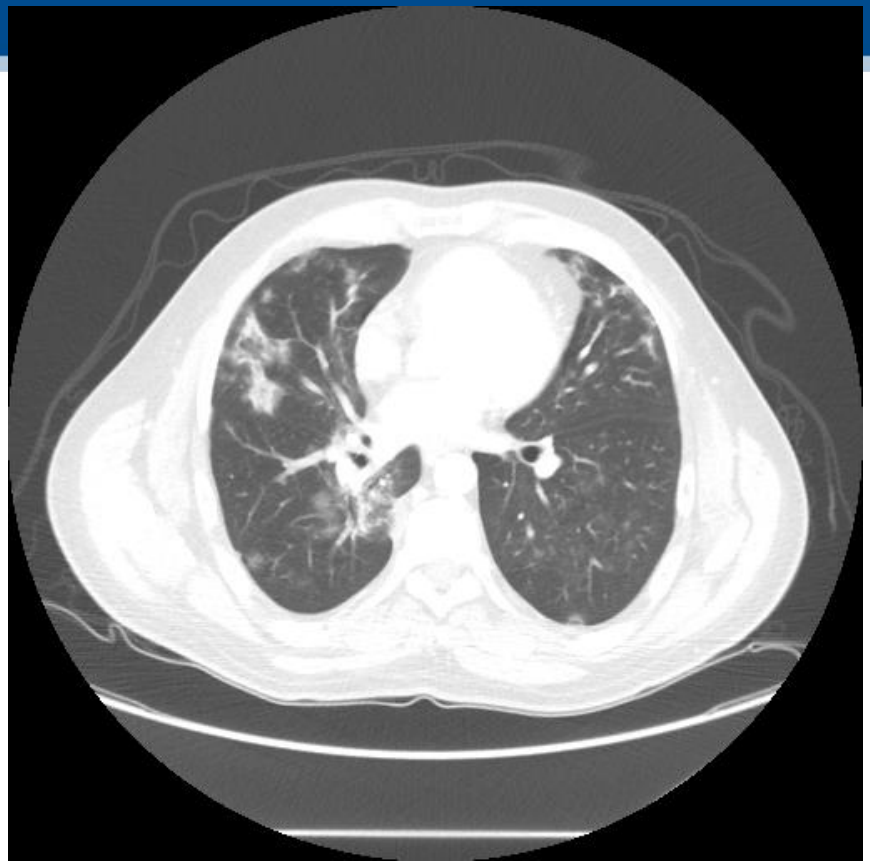
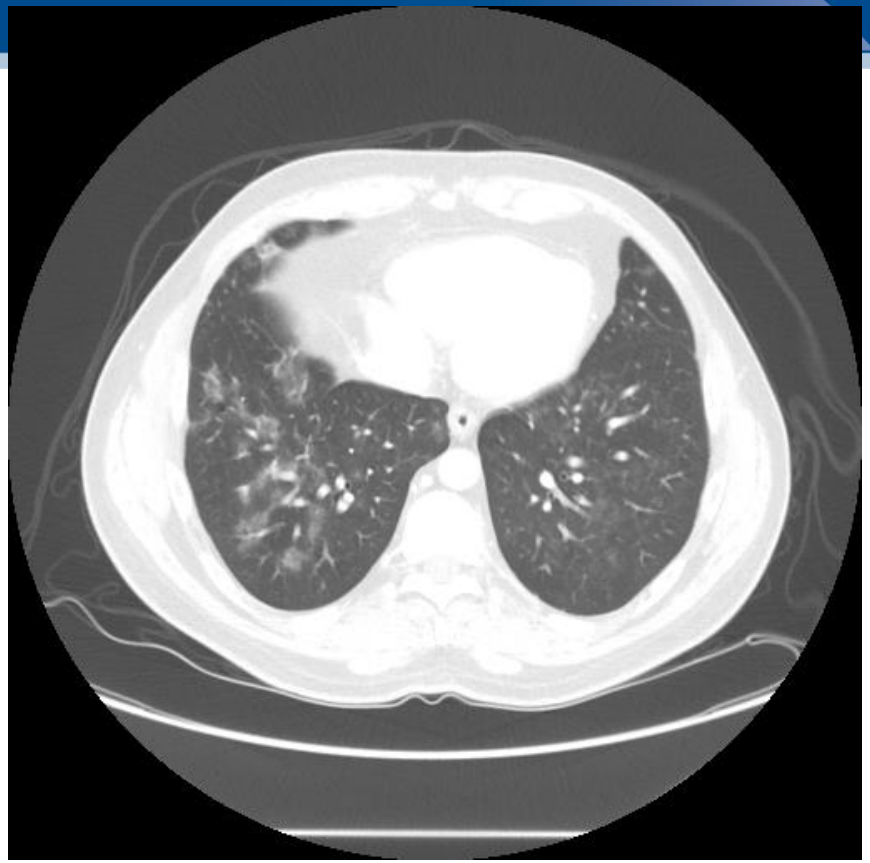
June 2016 Pneumonitis Recurrence





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Case Presentation—A Chronic Issue

- Steroid taper complete August 2016
- Resolution of pneumonitis

- September 2016: No progression (Yet)

- Pneumonitis is tumor-type agnostic*
- Pneumonitis is more frequent anti-CTLA-4*

Naidoo J, et al. J Clin Oncol, epub ahead of print 10-10-16

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Whither Now Immunotherapy?

- Nivo plus Chemo, First Line*
  - Nivo/Platinum Doublet
  - More toxicities with combo
  - Varying control with different chemotherapy (?)

- More to come
  - Multiple agents, multiple trials pending

*Rizvi et al. J Clin Oncol 2016

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A Future Without Chemo?

- Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer
  - Reck et al.
  - NEJM, Published ahead of print

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KEYNOTE-024 Study

- PD-L1 strong (≥ 50 %) tumor cells
  - Dako IHC
- Randomized phase III
- Pembrolizumab 200 mg fixed dose q3 week
- Vs Physician's Choice Platinum-doublet chemo

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KEYNOTE-024

- 1934 patients screened
- 500 eligible (30.2%)
- 154 pts pembrolizumab
- 151 pts chemotherapy
  - Crossover allowed at progression
  - 43.7% crossed to pembro

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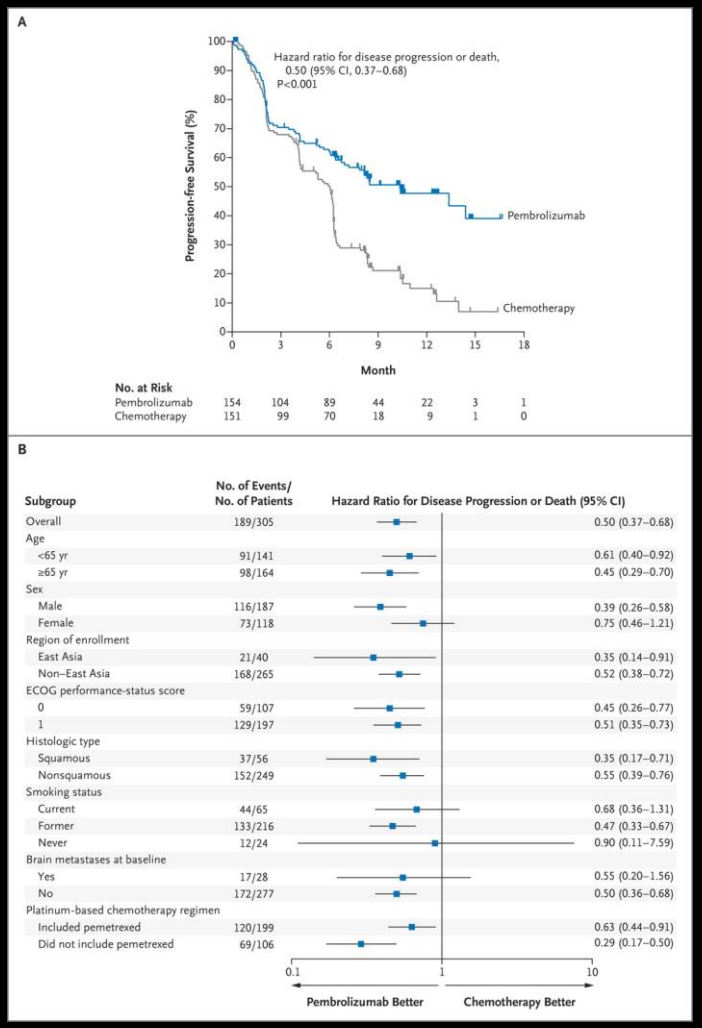
Progression-free Survival in the Intention-to-Treat Population.

Pembro
PFS:
10.3 mo

Chemo
PFS:
6 mo

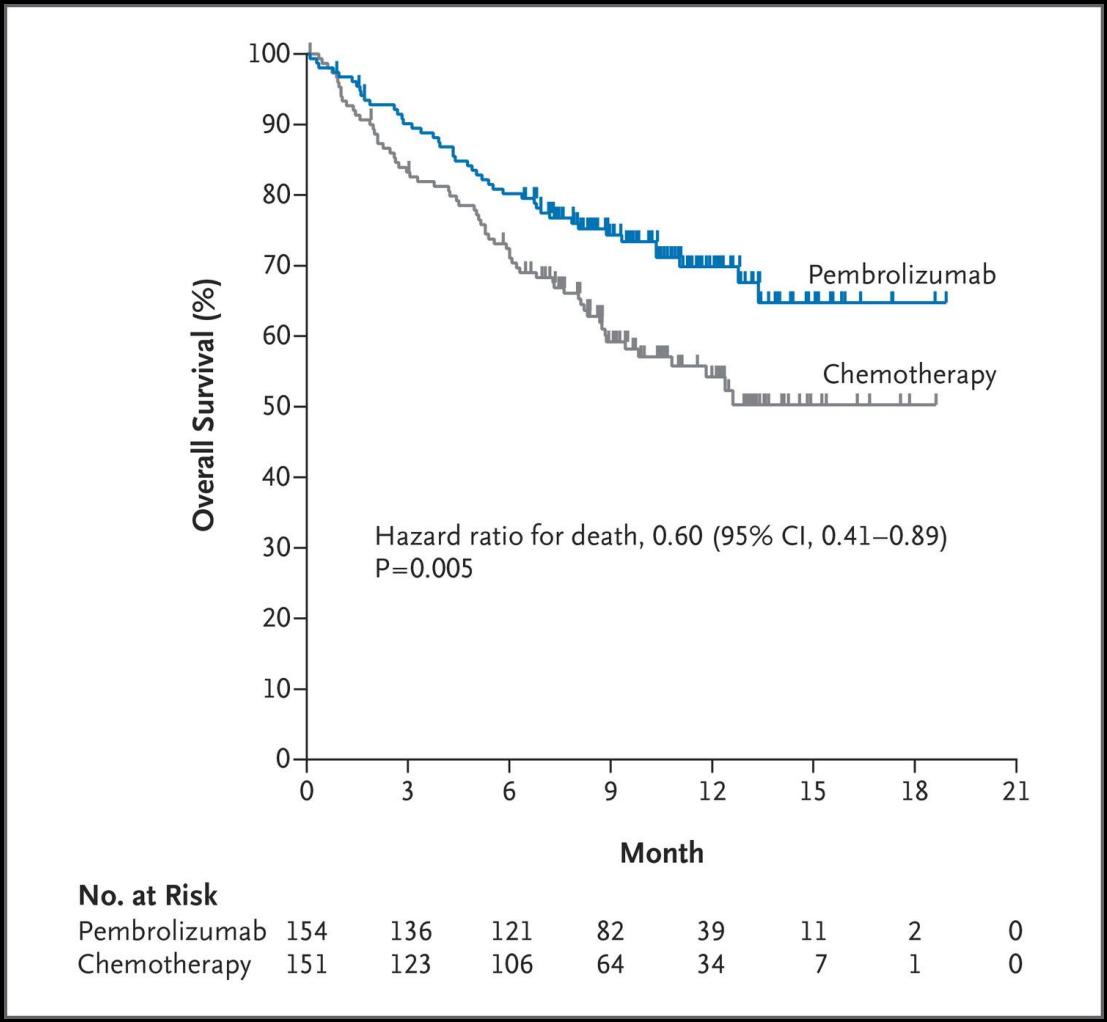


Reck M et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1606774

The NEW ENGLAND JOURNAL of MEDICINE

Overall Survival in the Intention-to-Treat Population.

OS: Not reached in either arm



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A Future Without Chemo?

- Pembrolizumab VS Chemo, First Line
  - POSITIVE (for PD-L1 high tumors)
- Nivolumab Press Release
  - NEGATIVE (for unselected tumors)

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A Future Without Chemo?

- Too Soon
- Chemo will likely always have a place

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Case Study Question

- Who would be considered eligible for anti-PD1 therapy?
  - A. 63 y.o. man with COPD, newly-diagnosed stage IV adenocarcinoma of lung with KRAS mutation
  - B. 54 y.o. woman with history of heavy tobacco use, ulcerative colitis on treatment, stage IV squamous cell lung cancer progressive after platinum-doublet chemotherapy
  - C. 84 y.o. man with stage IV NSCLC “NOS”, progressive after prior platinum doublet

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Case Study, Considerations

- Eligible for anti-PD1 therapy?
  - A. Approved only after prior therapy
  - B. Active autoimmune disease requiring ongoing therapy, with potential for life-threatening complications, considered a relative contraindication
  - C. Age and “NOS” histology are not contraindications to treatment

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Pneumonitis Diagnosis and Management

- Steps in diagnosis/treatment of symptomatic pneumonitis?
  - A. Clinical evaluation, including ambulatory pulse oximetry
  - B. High-res CT
  - C. Steroids, Prednisone equivalent 1-2 mg/kg/day
  - D. Pulmonary consultation
  - E. All of the above

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Pneumonitis Diagnosis and Management

- Steps in diagnosis/treatment of symptomatic pneumonitis?
  - A. Clinical evaluation, including ambulatory pulse oximetry
  - B. High-res CT
  - C. Steroids, Prednisone equivalent 1-2 mg/kg/day
  - D. Pulmonary consultation
  - **E. All of the above**

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