



# Reflex Testing Guidelines for Immunotherapy in Non-Small Cell Lung Cancer

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# Disclosures

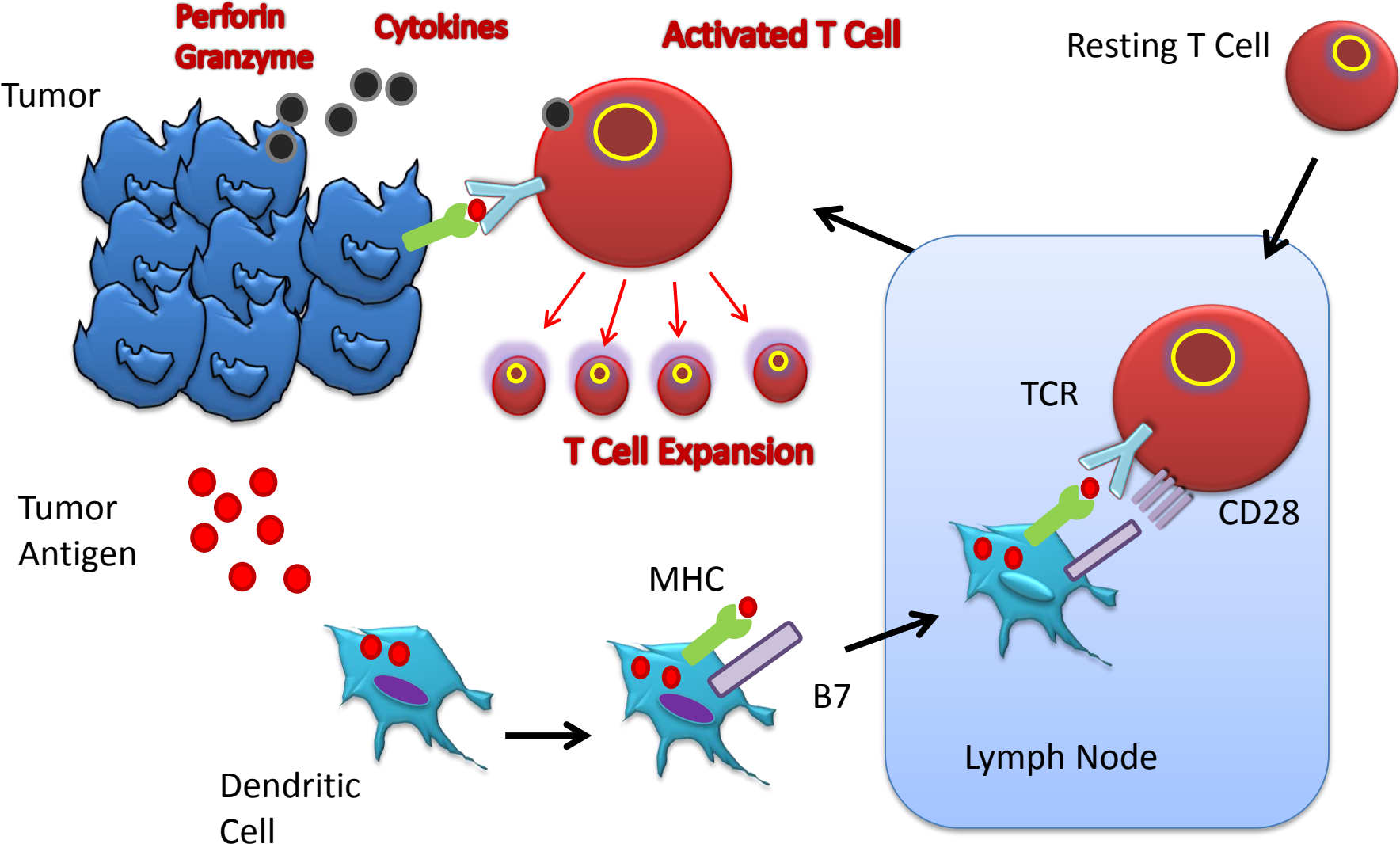
- I have no actual or potential conflicts of interest in relation to this presentation.

# Objectives

- To provide background on the immune process and how immune checkpoints work
- Review key clinical trials in non-small cell lung cancer (NSCLC) that utilize PD-L1 and PD-1 inhibitors and role of PD-L1 expression
- Use and timing of PD-L1 testing
- Other potentially useful biomarkers in development for checkpoint inhibitors
- PD-L1 liquid biopsies

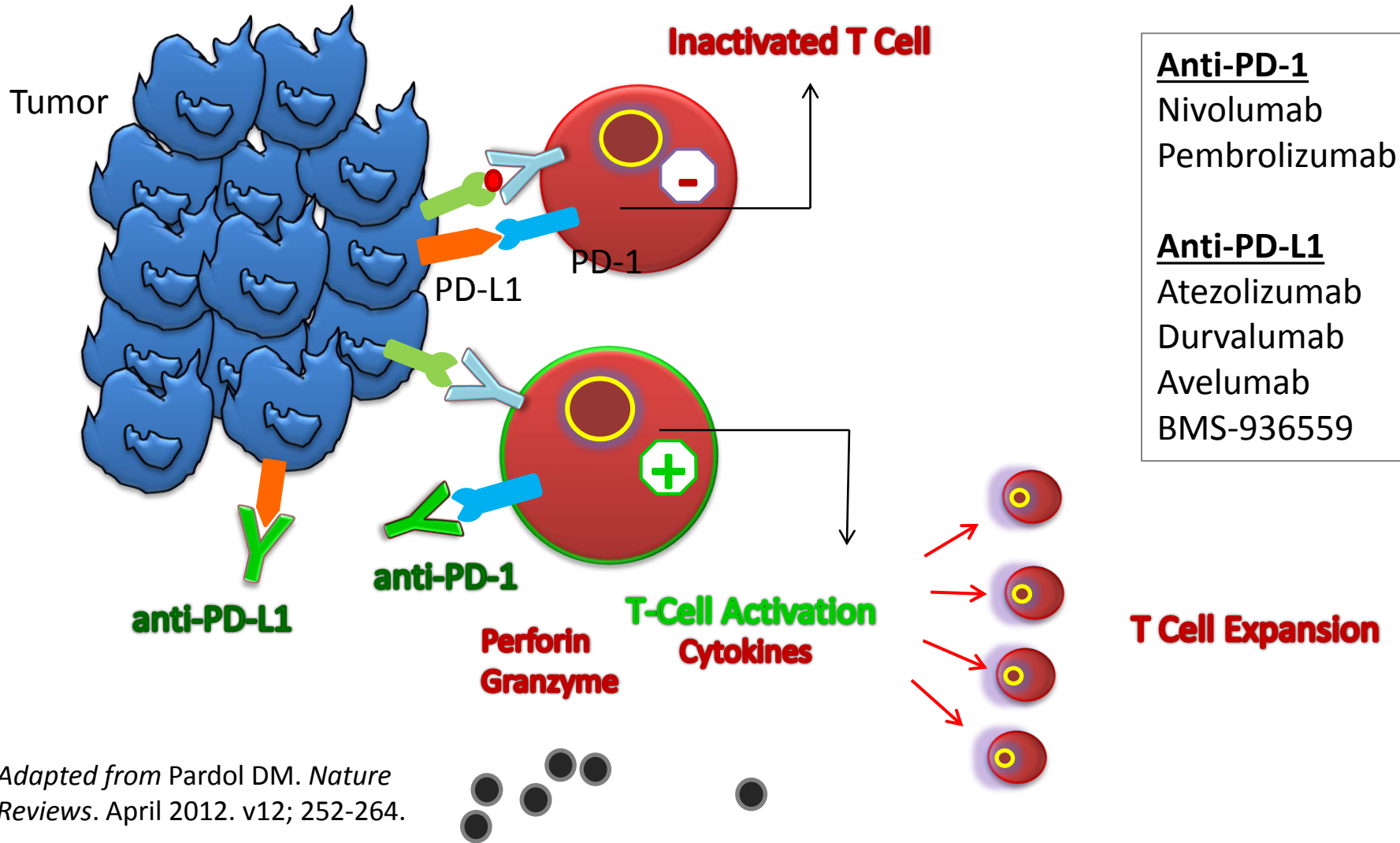


# Immune System Processes



Adapted from Pardoll DM. *Nature Reviews*. April 2012. v12; 252-264.

# Immune Check Points (PD-1/PD-L1)



Adapted from Pardoll DM. *Nature Reviews*. April 2012. v12; 252-264.



# Immunotherapy in NSCLC: 2<sup>nd</sup> Line Therapy



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# CheckMate 017- Phase III randomized study

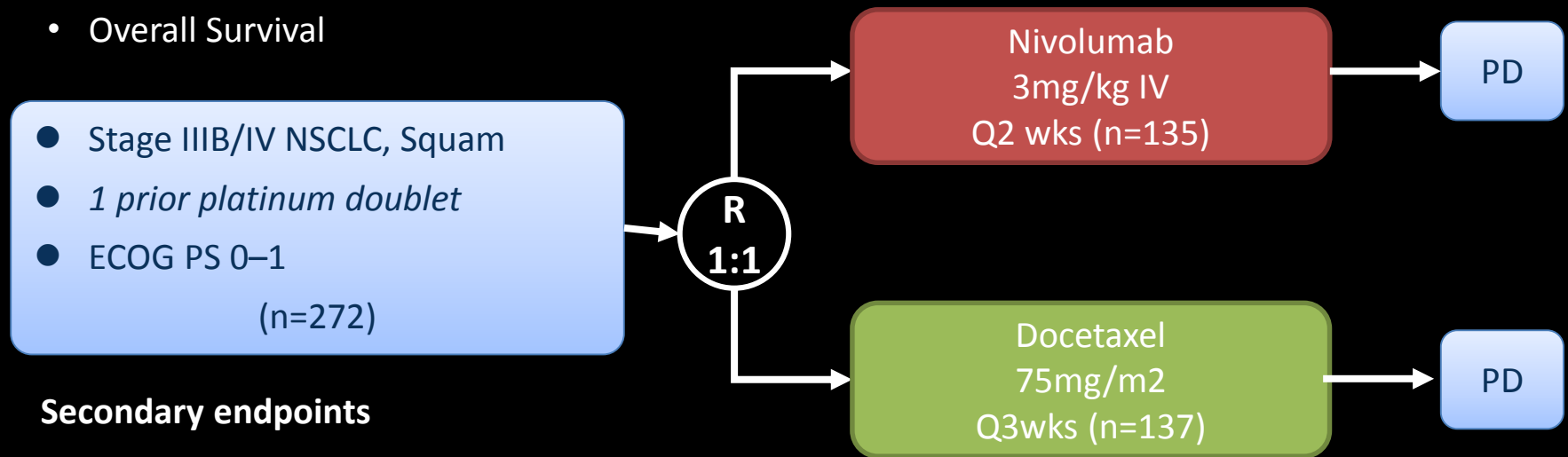
## Primary endpoint

- Overall Survival

- Stage IIIB/IV NSCLC, Squam
  - 1 prior platinum doublet
  - ECOG PS 0–1
- (n=272)

## Secondary endpoints

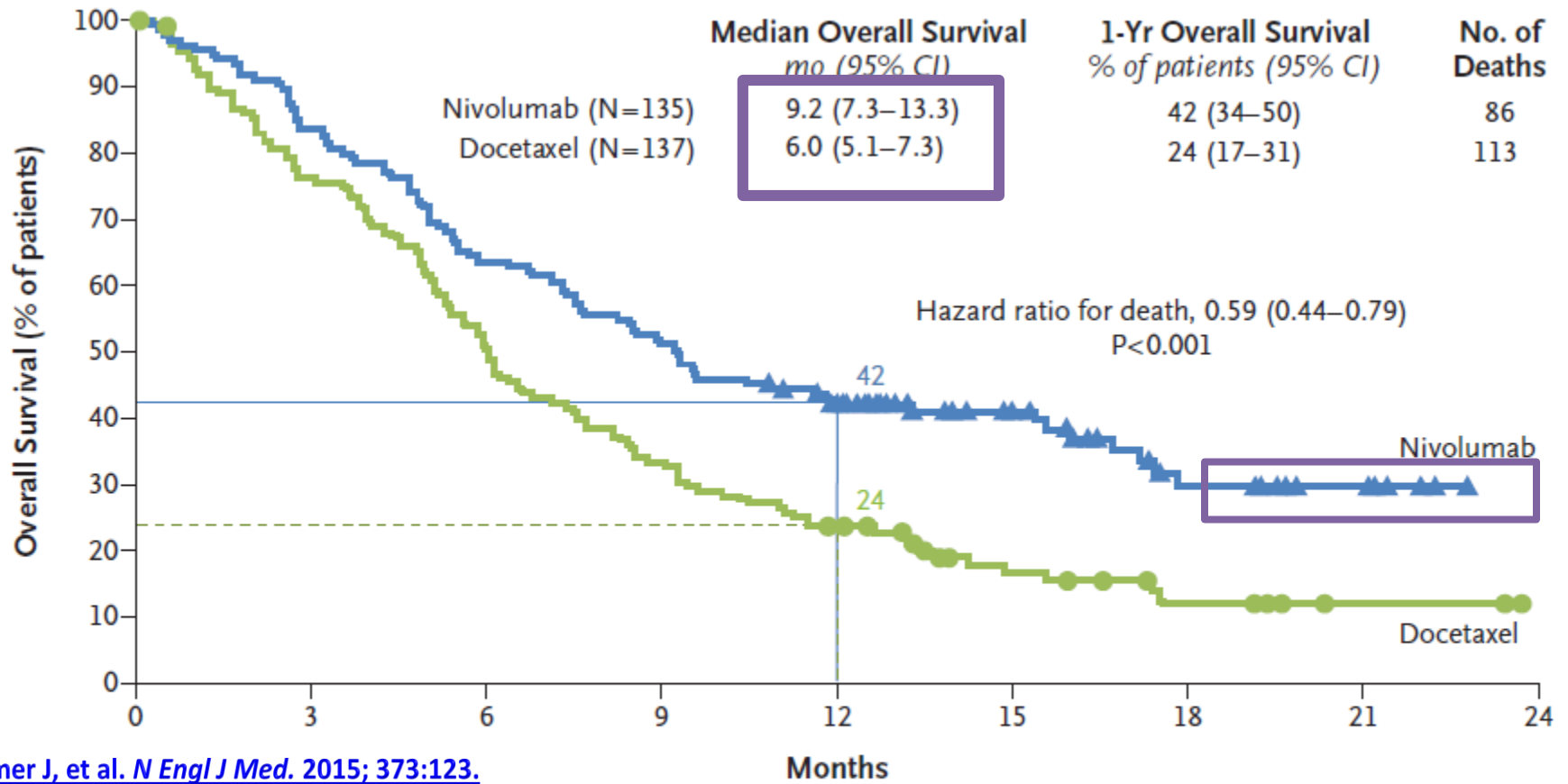
- Overall Response Rate
- Progression Free Survival
- Safety
- QoL



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



# CheckMate 017- Overall Survival



[Brahmer J, et al. N Engl J Med. 2015; 373:123.](#)

## No. at Risk

	0	3	6	9	12	15	18	21	24
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

# CheckMate 057- Phase III randomized study

- Stage IIIB/IV NSCLC, Non-Squam
  - *Pre-treatment tumor sample required for PD-L1*
  - *1 prior platinum doublet*
  - *Prior maintenance therapy allowed*
  - *Prior TKI therapy allowed for known ALK/EGFR mutation*
  - ECOG PS 0–1
- (n=582)

## Primary endpoint

- Overall Survival

R  
1:1

Nivolumab  
3mg/kg IV  
Q2 wks (n=292)

PD

Docetaxel  
75mg/m<sup>2</sup>  
Q3wks (n=290)

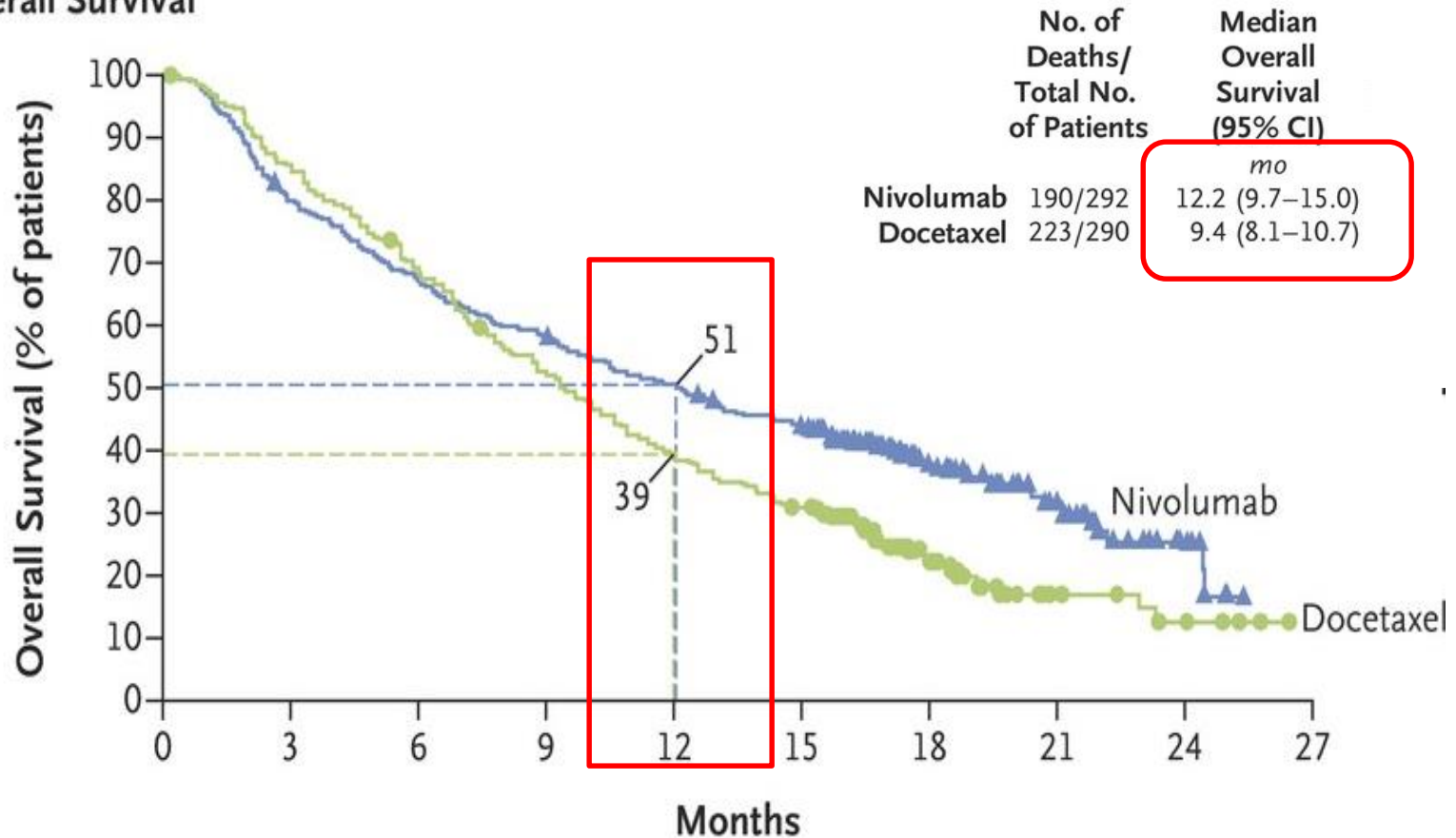
PD

## Secondary endpoints

- Overall Response Rate
- Progression Free Survival
- Safety
- Efficacy by tumor PD-L1
- QoL

# CheckMate 057- Overall Survival

## A Overall Survival



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

# Nivolumab and PD-L1

- In CHECKMATE 017 (Squamous), PD-L1 positivity at any cutoff was not significantly prognostic nor predictive of benefit.
- In CHECKMATE 057, PD-L1 positivity at  $\geq 5\%$  strongly correlated with objective response (34% vs 14% for PD-L1 negative) as well as predicted an OS benefit compared with docetaxel.
- In all studies a significant proportion of PD-L1 negative patients benefitted from treatment (*FDA did not specify any PD-L1 threshold and does not require testing*).

# KEYNOTE-010: Pembro v. Docetaxel (Phase 2/3)

## Key entry criteria

- Eligible pts with locally adv or metastatic NSCLC
- PD-L1 TPS  $\geq$  1
- ECOG PS 0-1
- No brain metastasis

(N=1034)

R

Pembrolizumab 2 mg/kg  
Q3wks, for 24wks  
(N=345)

Pembrolizumab 10 mg/kg  
Q3wks, for 24wks  
(N=346)

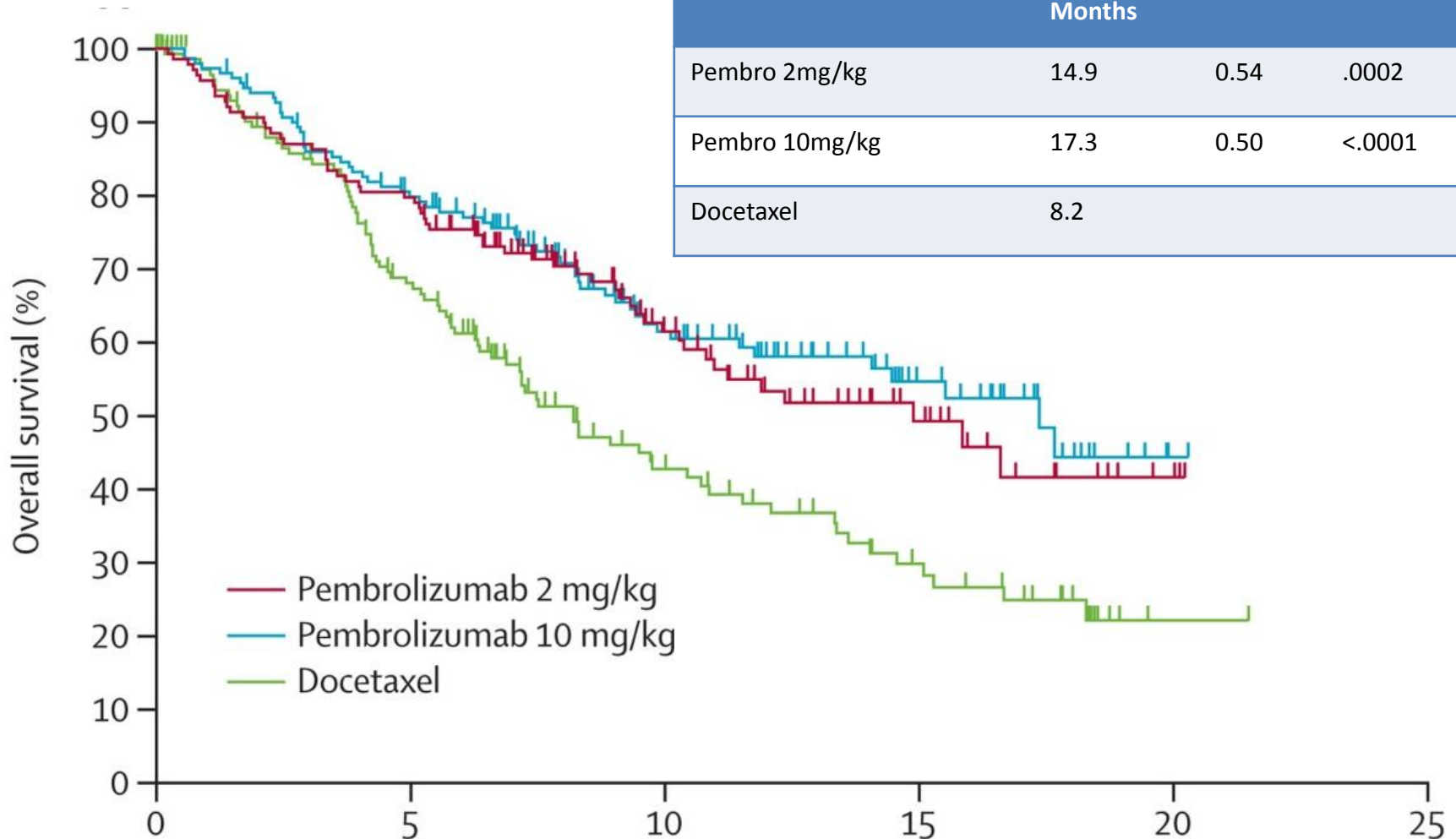
Docetaxel 75mg/m<sup>2</sup>  
q3wks  
(N=343)

## Endpoints

- Primary
    - PFS, OS
  - Secondary
    - ORR, DoR, Safety
- (both PD-L1 TPS  $\geq$  1% and  $\geq$  50%)

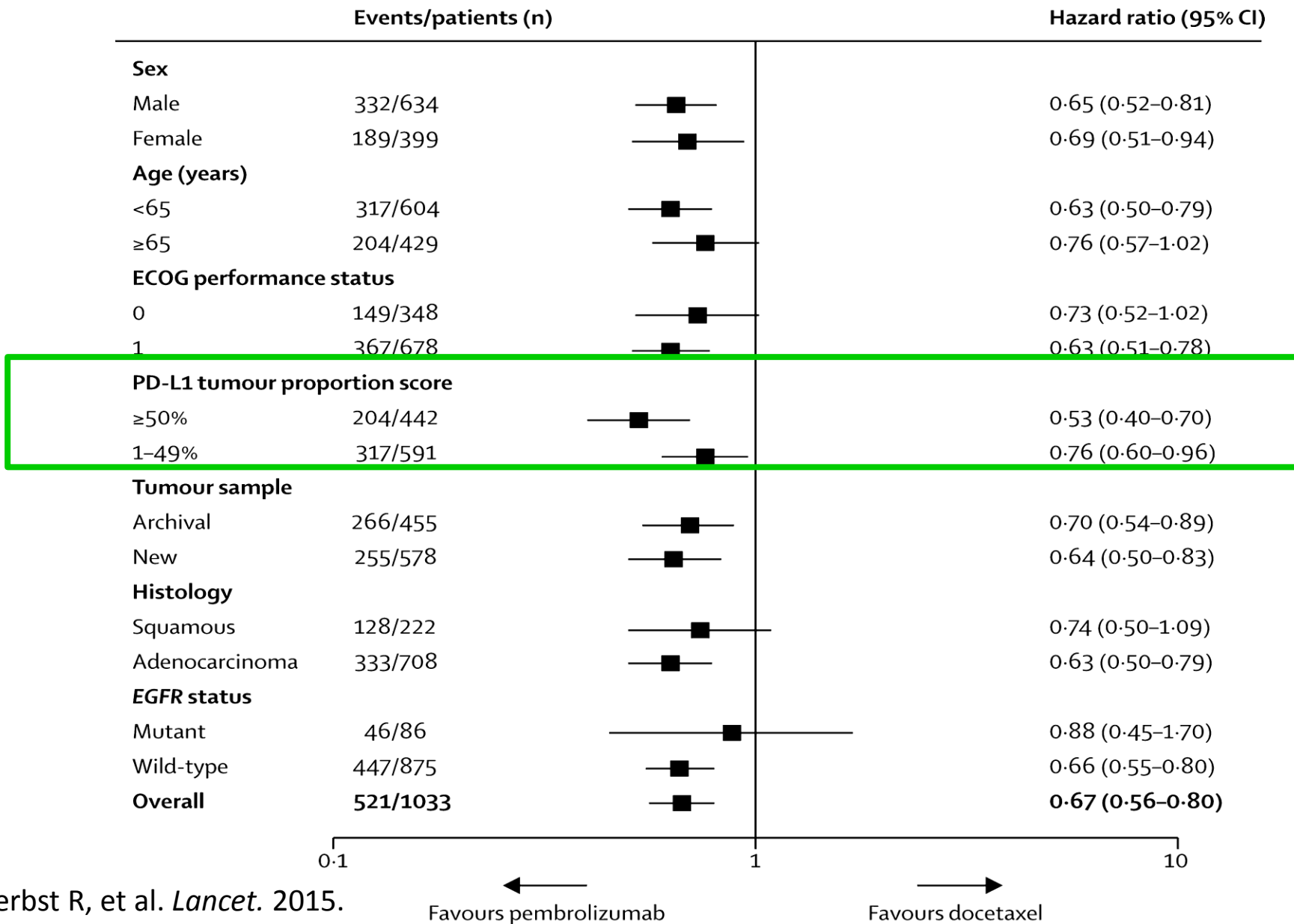
# KEYNOTE-010: Pembro v. Docetaxel

PD-L1 TPS  $\geq 50$



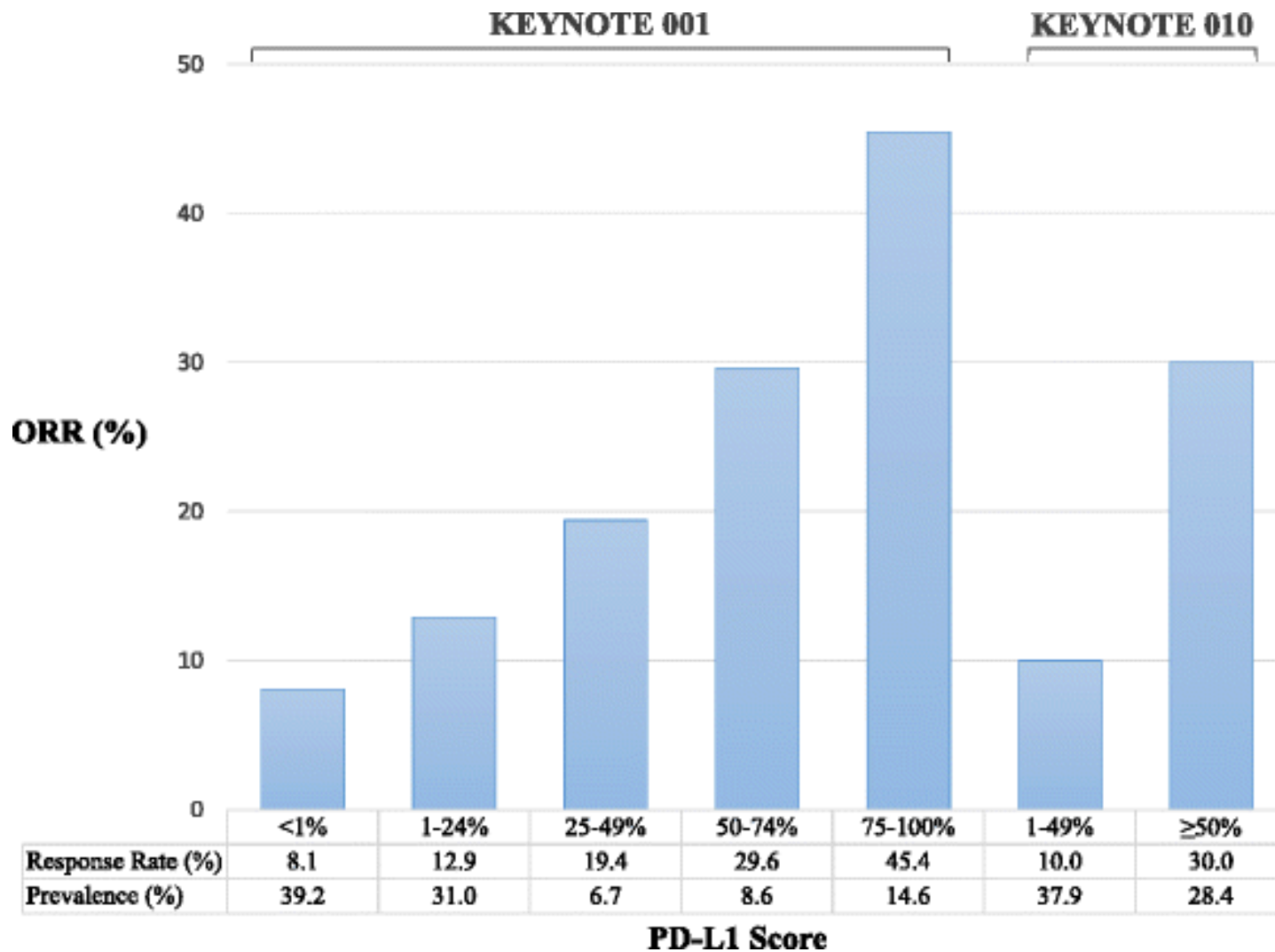


# KEYNOTE-010: Pembro v. Docetaxel



# Pembro and PD-L1

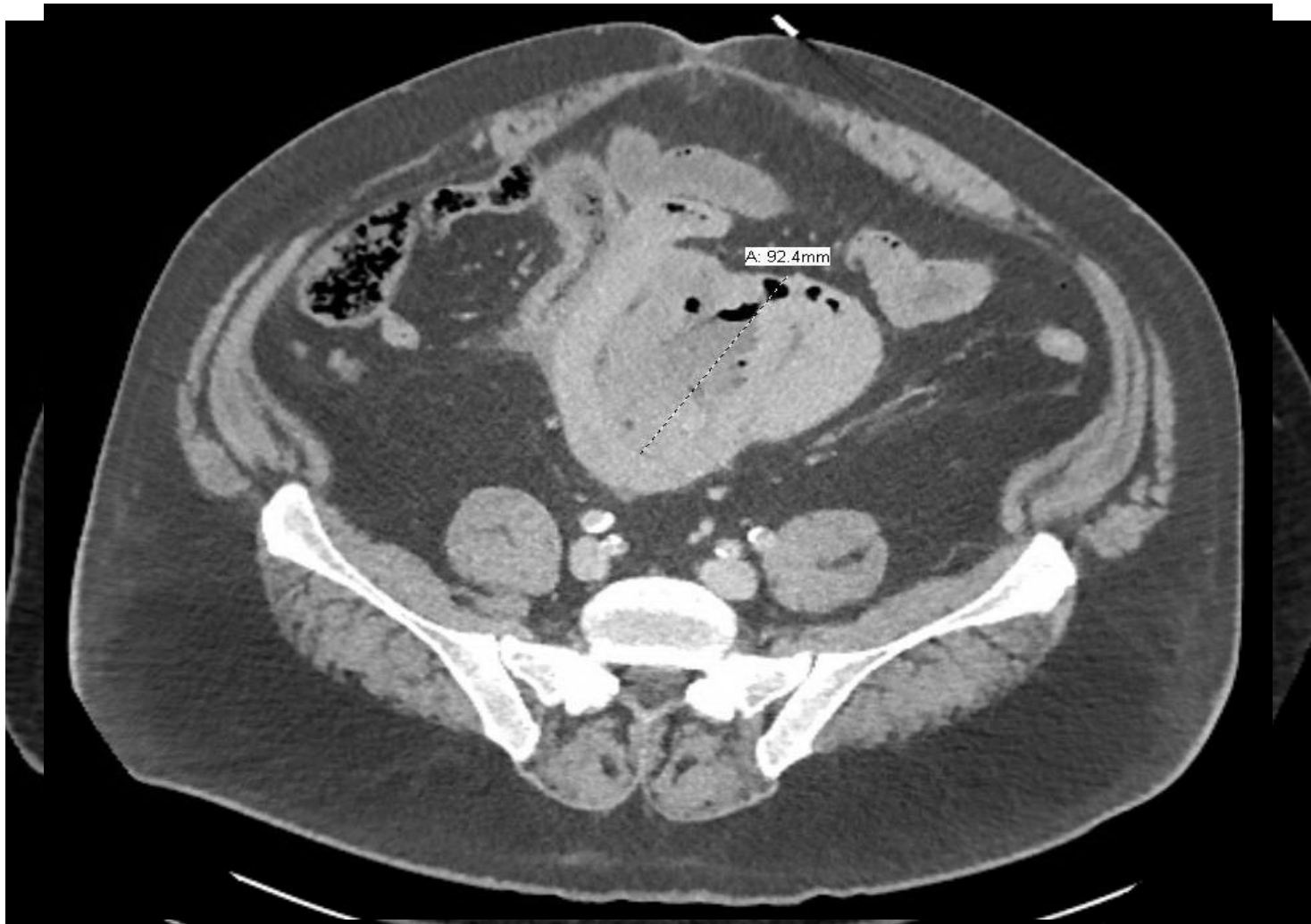
- In KEYNOTE 001, PD-L1 PS  $\geq$  50% had PFS and OS that were considerably longer.
- Duration of response was no different between the other groups (PS <1% or 1% - 49%).
- KEYNOTE 010, patients with higher PS were more likely to have an objective response.
- Responses were still observed in 10% of those with PS 1-49%.



Grigg C, et al. *J Immunother Cancer*. 2016.

# Case Z

- 54-year-old male that presented to medical attention with small bowel perforation secondary to mass in the central abdomen and mesenteric masses.
- He underwent surgical repair of bowel perforation.
- Dx: Metastatic – Adenocarcinoma lung primary by IHC.



*Right lower pulmonary primary and multiple enlarged mediastinal lymph nodes (right subcarinal 1.1 cm, right hilar 1.8 cm, right paratracheal 1.2 cm). Malignant right pleural effusion, metastatic involvement of multiple nodal regions (including left supraclavicular, mediastinal, mesenteric, & retroperitoneal regions), left adrenal metastasis, and small bowel mesentery with surrounding fat stranding.*

# Case Z

- Carboplatin and pemetrexed for two cycles that was poorly tolerated
  - Complicated course with HCAP requiring admission
  - Intractable nausea and vomiting with second course
  - CT scan with progression
- Nivolumab: every 2 weeks, started April 2016



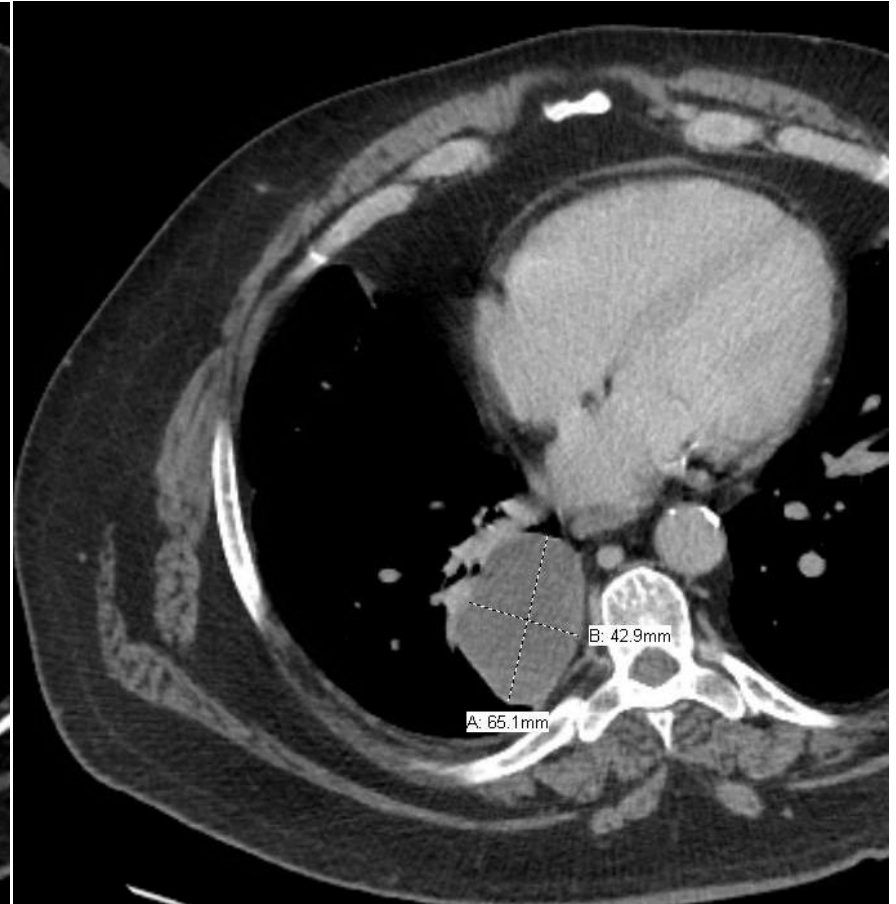
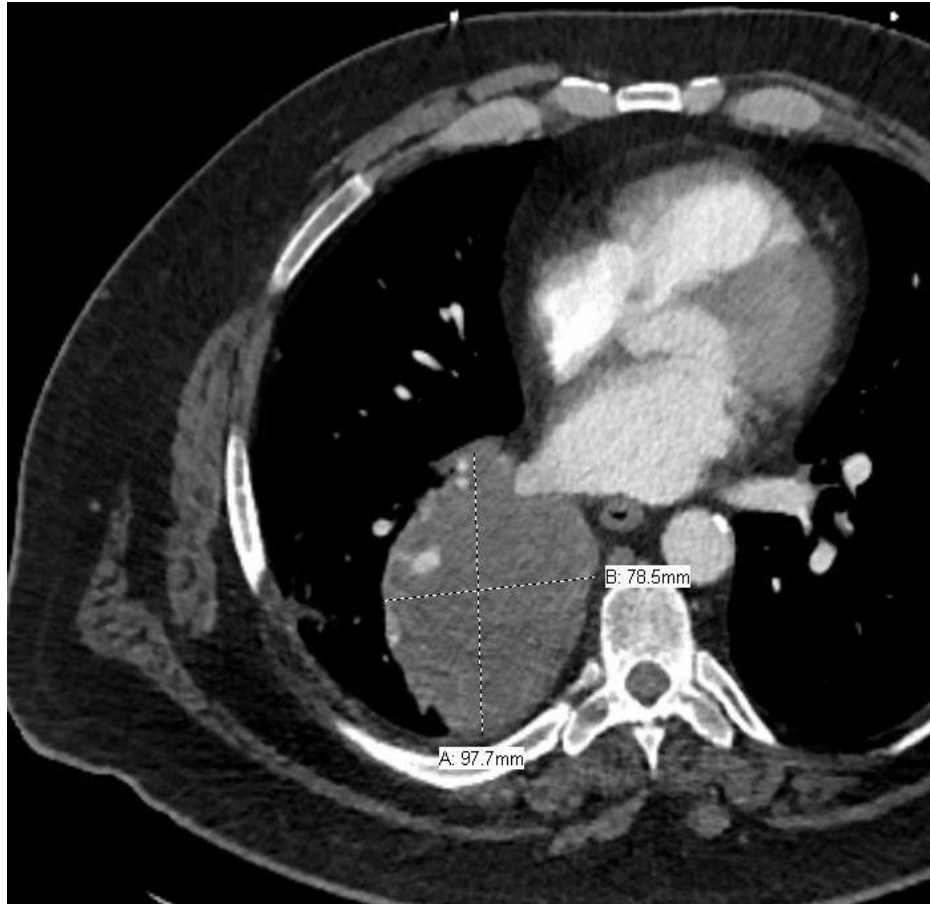
# Case Z

Test Name	In Range	Out of Range	Reference Range
PD-L1 Lung (Pembrolizumab), IHC			
PD-L1 Lung (Pembrolizumab), IHC			
Paraffin Block Number:	SL15-2271A17		
Primary Tumor Site:	BOWEL		
Collection Site:	BOWEL		
Tumor Type:	NOT GIVEN		
Stage:	NOT GIVEN		
Grade:	NOT GIVEN		
Oncologist Name:	NOT GIVEN		
Oncologist NPI:	NOT GIVEN		
Pathologist Name:	NOT GIVEN		
Pathologist NPI:	NOT GIVEN		
Quest Internal Number:	2015-11261		
Tumor Proportion Score	100		
Interpretation	POSITIVE		

This specimen was examined by a pathologist and showed sufficient viable tumor cells for testing. Positive and negative protein expression controls worked as expected.

This test was performed on formalin-fixed paraffin embedded tissue sections by immunohistochemistry using the FDA-approved PD-L1 IHC 22C3 pharmDx (IM) kit and Dako automated Link 48 platform. This test detects PD-L1 expression in non-small cell lung carcinoma. Interpretation was based on scoring guidelines published by manufacturer of the kit. PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining. The specimen should be considered PD-L1 positive if TPS greater than or equal to 50% of the viable tumor cells exhibit membrane staining at any intensity. PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA (pembrolizumab).

# Case Z



# Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

Louis Fehrenbacher, Alexander Spira, Marcus Ballinger, Marcin Kowanetz, Johan Vansteenkiste, Julien Mazieres, Keunchil Park, David Smith, Angel Artal-Cortes, Conrad Lewanski, Fadi Braiteh, Daniel Waterkamp, Pei He, Wei Zou, Daniel S Chen, Jing Yi, Alan Sandler, Achim Rittmeyer, for the POPLAR Study Group\*

- 287 patients with previously treated advanced or metastatic NSCLC
- Randomized Atezolizumab to docetaxel
- Results:
  - Overall survival 12.6 months vs 9.7 months; HR 0.73,  $p = 0.04$
  - Median duration 14.3 months vs 7.2 months
- Enrollment stratified by PD-L1 expression w/ IHC assay (Ventana SP142)
- PD-L1 positivity was categorized according to the expressing cell type or immune cell and then scored along a gradient
  - <1%, 1–4%, 5–49%, and  $\geq 50\%$
- Tx w/ Atezolizumab favored in all but the least PD-L1 positive tumors

# Atezolizumab and PD-L1

- Regardless of PD-L1 expression levels and including patients with PD-L1 expression of  $<1\%$  = improvement in OS vs. Docetaxel.
- OS was 59% greater among patients in the highest tertile of PD-L1 expression.
- Those with no expression still had a significant 25% improvement in OS.

# Companion PD-L1 Assays in Development for PD-1/PD-L1 Inhibitors

Drug	Drug target	Companion antibody clone	Developer	Definition of positive test
<i>Nivolumab</i>	PD-1	28-8	Dako Bristol-Meyers Squibb	≥5 % membranous staining of tumor cells (minimum 100 cells evaluated)
				<b>“Complementary in 2<sup>nd</sup> line”</b>
<i>Pembrolizumab</i>	PD-1	22C3	Dako Merck	≥1% <sup>a</sup> membranous staining of tumor cells or immune cells that are intercalating or at the tumor interface
				<b>“Companion diagnostic”</b>
<i>Atezolizumab (MPDL3280A)</i>	PD-L1	SP142	Ventana Genentech/Roche	Each specimen assigned a score based on both tumor and immune cell PD-L1: TC3/IC3 PD-L1 ≥ 50 % TC2/IC2 PD-L1 5-49 % TC1/IC1 PD-L1 1-4 % TC0/IC0 PD-L1 < 1 %
				<b>“Complementary in 2<sup>nd</sup> line”</b>
<i>Durvalumab (MEDI4736)</i>	PD-L1	SP263	Ventana MedImmune/AstraZeneca	≥25 % membranous staining of tumor cells

<sup>a</sup>The FDA indication in NSCLC for pembrolizumab requires PS ≥50 %

Grigg C, et al. *J Immunother Cancer*. 2016.

# Immunotherapy in NSCLC: 1st Line Therapy



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ORIGINAL ARTICLE

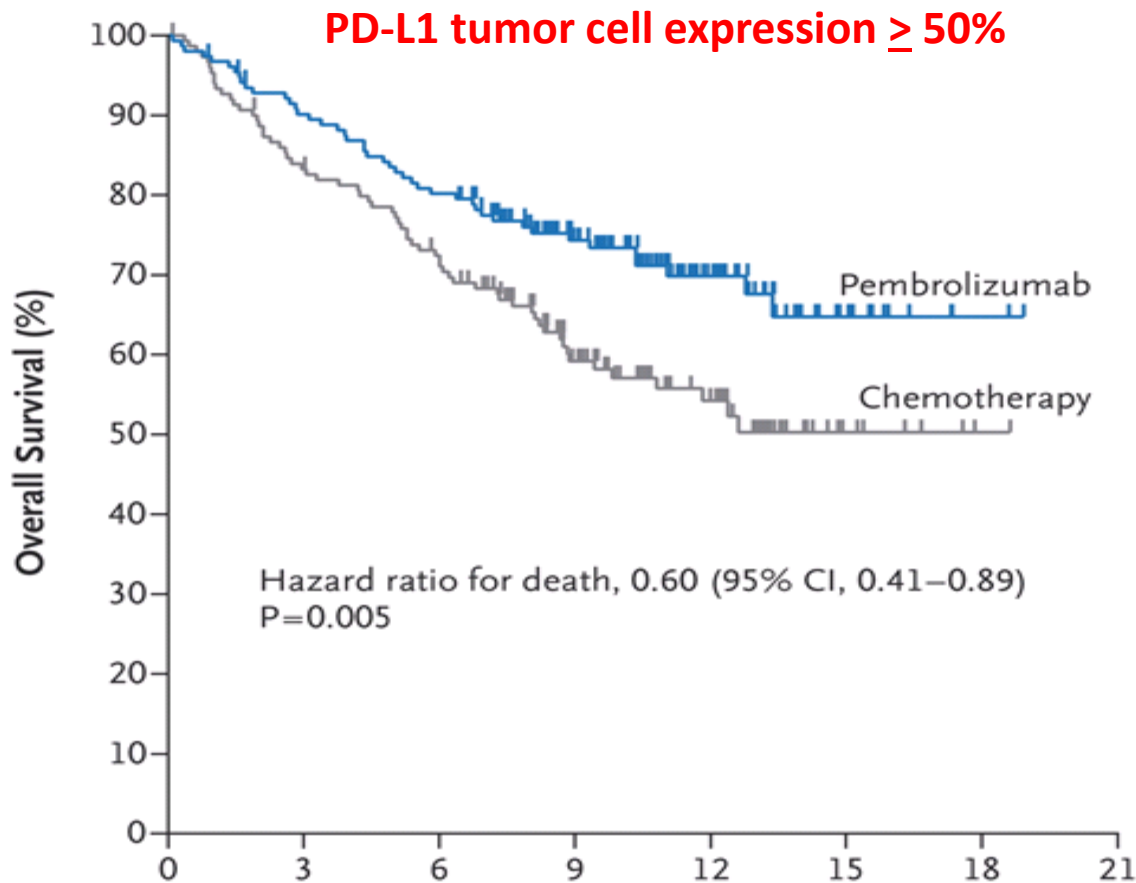
## Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators\*

N Engl J Med 2016; 375:1823-1833 | November 10, 2016 | DOI: 10.1056/NEJMoa1606774

- 305 patients with untreated advanced NSCLC
- **PD-L1 expression on at least 50% of tumor cells**
- Treatment to receive either pembrolizumab (at a fixed dose of 200 mg every 3 weeks) or the investigator's choice of platinum-based chemotherapy
- Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression

# Overall Survival in the Intention-to-Treat Population



- Median progression-free survival 10.3 vs. 6.0 months
- Response rate 44.8% vs. 27.8%
- Median duration of response was longer (not reached) vs. 6.3 months

Reck M, et al. *N Engl J Med.* 2016;375:1823-1833.

# Testing for PD-L1 in NSCLC?

- **When:** “first line” reflexive testing

frontline approval of Pembrolizumab requires that we test at diagnosis

- **What to test:** accessible tissue

- Archival
- Fresh
- KEYNOTE 001: archival tissue over 6 months led to unreliable testing \*concern over deterioration of PD-L1 protein. Fresh tumor biopsies were required for PD-L1 staining by IHC
- KEYNOTE 010: confirmed that archival tissue can be used

- **How often to test:** Unclear

# Testing for PD-L1 in NSCLC?

- **Where to test:**

- Primary
- Metastases
- Case series suggest a reasonable concordance between both synchronous (same time but different location) and metachronous (different time) specimen in the range of 75–90%
- PD-L1 expression is also affected by concurrent or prior treatments, including radiation or chemotherapy, which may have been administered after a biopsy was obtained

# Case X

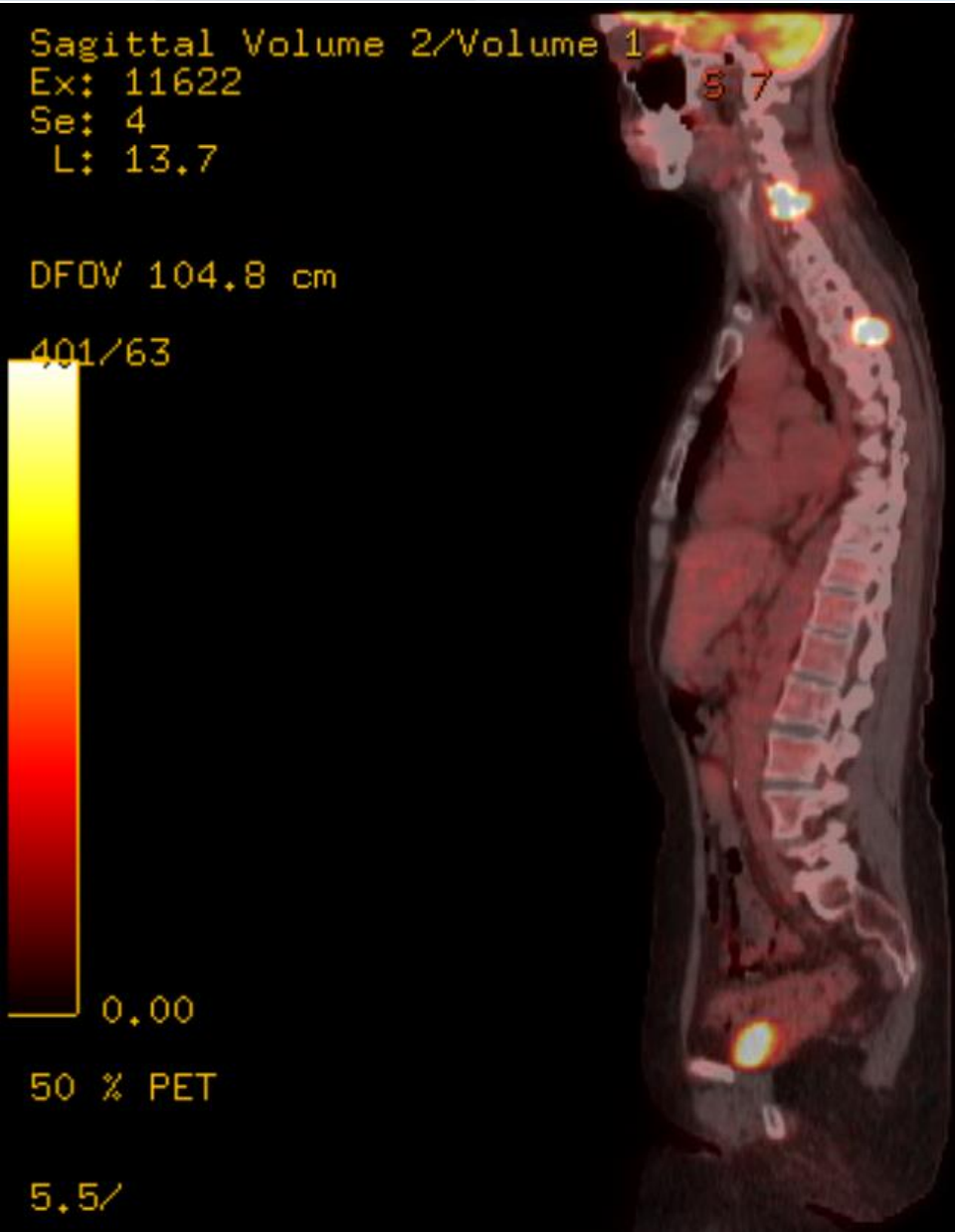
- 59-year-old female with recurrent URI. CT revealed a nodular density in LUL.
- Underwent LUL lobectomy with removal of 4.5 cm tumor - T2N0M0, non-small cell carcinoma with giant cell features.
- Negative for ALK, EGFR, ROS-1 mutations, and PD-L1 negative expression.



# Case X

- 3 months later evaluated for progressive neck pain and MRI showed a foramina stenosis at C5-6 that failed conservative management.
- She was taken to OR for neurosurgery for continued progressive neck pain and intraoperative found the facet complex completely replaced with soft tissue that resulted in pathologic fracture.
- Pathology: consistent with similar primary NSCLC with giant cell features.





**PD-L1 22C3 pharmDx by Immunohistochemistry with Interpretation, pembrolizumab (KEYTRUDA)**

ARUP test code 2013284

PDL1 22C3 by IHC Result

See Note

Unlike in non-small cell lung cancer, the predictive value of PD-L1 22C3 biomarker testing in other tumor types is uncertain and represents off-label use of this test. This result has been reviewed and approved by Georgios Deftereos, M.D. Controls performed as expected.

**INTERPRETIVE INFORMATION:** PD-L1 22C3 pharmDx by Immunohistochemistry with Interpretation, pembrolizumab (KEYTRUDA)

PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. In the clinical setting of first-line therapy (treatment-naive patients), the specimen is considered PD-L1 positive if the TPS is equal to or greater than 50 percent. In the setting of second-line therapy, the specimen is considered positive if the TPS is equal to or greater than 1 percent.

PD-L1 22C3 by IHC with Interpretation is a qualitative immunohistochemical assay using monoclonal mouse Anti-PD-L1 Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue using EnVision FLEX visualization system on Autostainer Link 48. The specimen submitted for testing should contain at least 100 viable tumor cells to be considered adequate for evaluation. This assay is indicated as an aid in identifying NSCLC patients for treatment with pembrolizumab (KEYTRUDA).

This assay is validated and FDA-approved for lung cancer specimens only. For all other specimen types, results should be interpreted with caution and within the appropriate clinical context. The use of this assay on decalcified tissues has not been validated and is not recommended.

For more information, please refer to practice guidelines published by the National Comprehensive Cancer Network (NCCN) at [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines\\_h0ja\\_ver.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines_h0ja_ver.asp).

*addendum issued - ADPL*

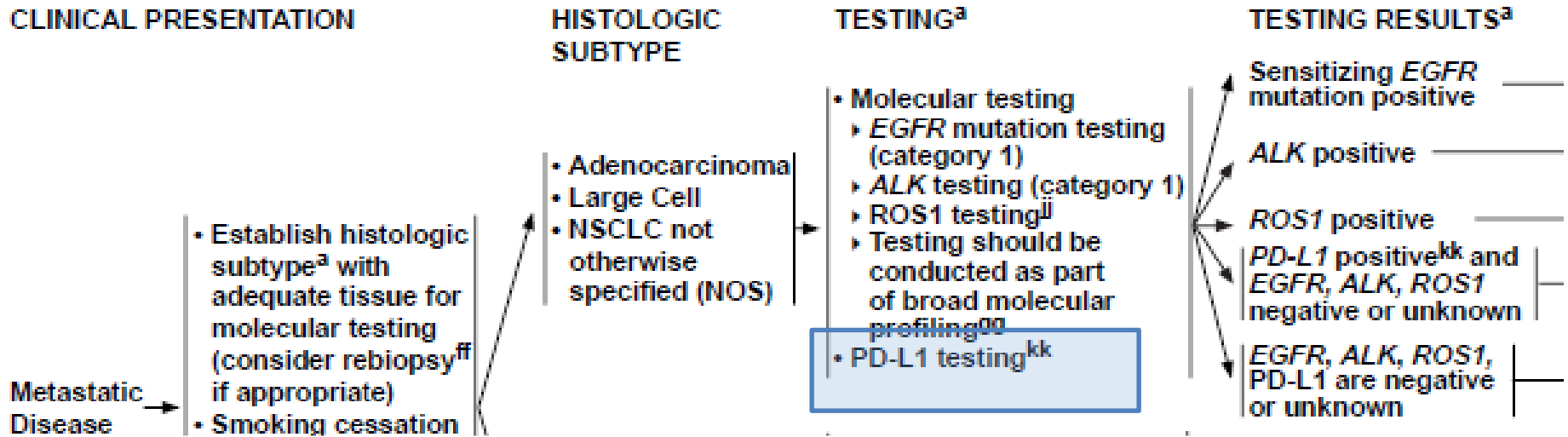
Tumor Proportion Score

50-60%

Adequacy of Specimen

Adequate

# NCCN Guidelines Version 3.2017 Non-Small Cell Lung Cancer



# PD-L1 Testing in Blood?

- PD-L1 detection by immunohistochemistry on tumor or immune cells is standard.
- PD-L1 expression is controversial in predicting which patient might benefit from therapy (low positive predictive value).
  - Significant number of patients with PD-L1 positive tumor do not respond.
  - PD-L1 expression is not necessary for achieving objective responses in some patients.
  - PD-L1 is a dynamic biomarker and is currently being measured as a one-time “snapshot.”

# Ready for prime time?

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## Biocept Launches Liquid Biopsy Immuno-Oncology PD-L1 Test

New test uses patient's blood sample to profile and monitor for PD-L1 expression, an important biomarker in immuno-oncology treatment decision making

Test developed in collaboration with renowned pathologist David Rimm, MD, PhD, of Yale University School of Medicine

# Checkpoint Immunotherapy Biomarkers

Evaluation	Brief Description	Clinical outcome correlations
PD-L1	IHC assessment (% of PD-L1 + tumor and/or immune cells)	Associated improvement in response to treatment
Mutational Burden	Next generation exome sequencing for non-synonymous somatic mutations	Improved response in high mutational count
Multiplex IHC	Assessment of a number of protein markers on tumor and immune cells and their relationship with one another	Improved outcomes in those displaying interaction of PD-1 + and PD-L1 + cells.
Immune gene signatures	Assessment of tumor gene expression profiles and its microenvironment	Positive associations with t-cell inflamed profile, or interferon gamma

# Genomic “Immuno-Biomarkers”

- High mutational load and number of mutations per exome have been correlated with improved OS.
- Neoantigen load in patients correlates with tobacco carcinogen-related mutagenesis, higher neoantigen burden, and DNA repair pathway mutations.
- DNA mismatch repair (MMR) gene deficiency associated with a heavy mutational burden.
- Mutations in enzymes involved in DNA replication and repair like POLE and POLD1.

# Closing

- There have been rapid and significant advances as related to tumor immunotherapy treatment in NSCLC.
- Improvements in clinical outcomes with emerging research discoveries.
- Challenges:
  - Develop an ability to predict who will respond; fewer than 25-50% of patients have a clinical benefit while on anti-PD-1 or anti-PD-L1 therapies.
  - Patients whose disease is PD-L1-negative by immunohistochemistry can still achieve clinical benefit with anti-PD-1 or anti-PD-L1.
  - Liquid biopsies for CTC or other soluble factors need to be fully validated in randomized prospective clinical trials.






Now this is not the end. It is not even the  
beginning of the end. But it is, perhaps, the end  
of the beginning.

(Winston Churchill)

# Questions?



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Thank you for participating in the ICLIO e-Course. Presentation slides and archived recording will be available at [acc-iclio.org](http://acc-iclio.org).



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