Case Presentation – Non-Small Cell Lung Cancer

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Disclosures

- Speaker: MSD, BMS, Roche / Genentech, AstraZeneca
- Advisory boards: AstraZeneca, Roche / Genentech
- Research support: Merck, BMS, Astellas, Boehringher Ingelheim, Eli Lilly, AstraZeneca

History

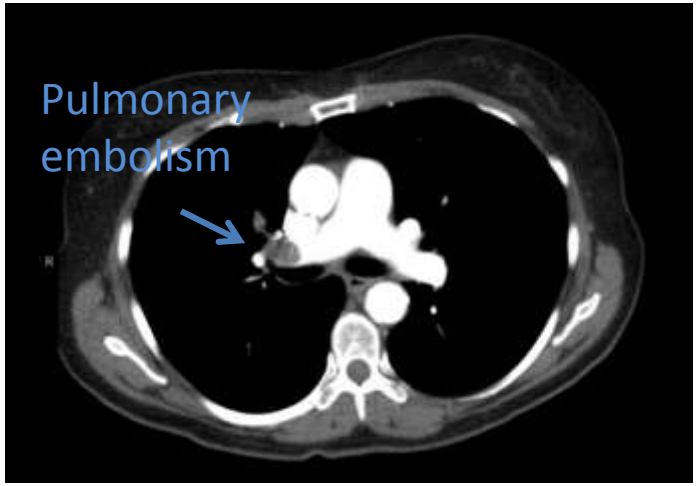
HPI: 75-year-old lady with an episode of hemoptysis in 01/2013. Denies any cough, shortness of breath or chest pains. No weight loss. Performance status 1.

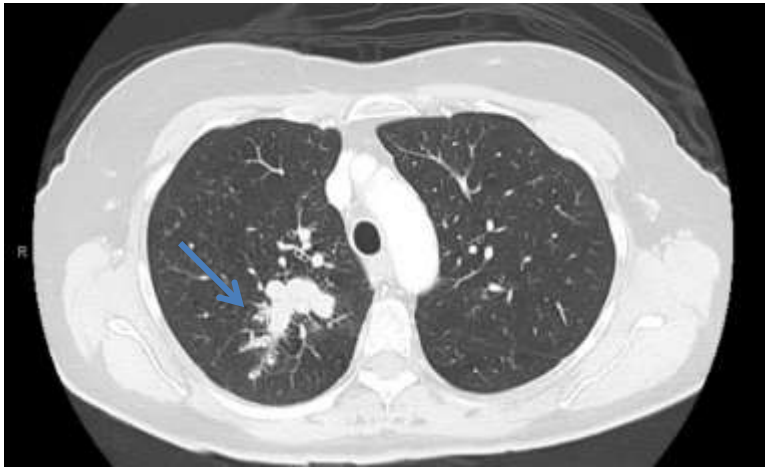
PMH: Diabetes, hypertension, dyslipidemia.

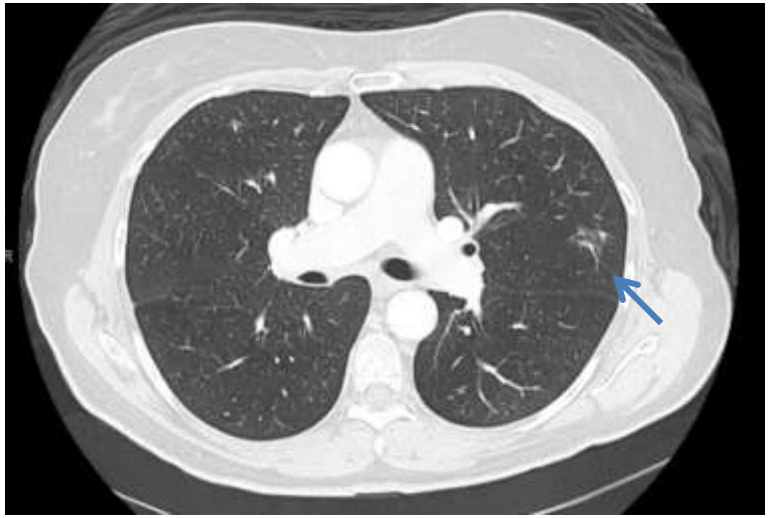
SH: Smoked 1 pack cigarettes/day from age 20-65.

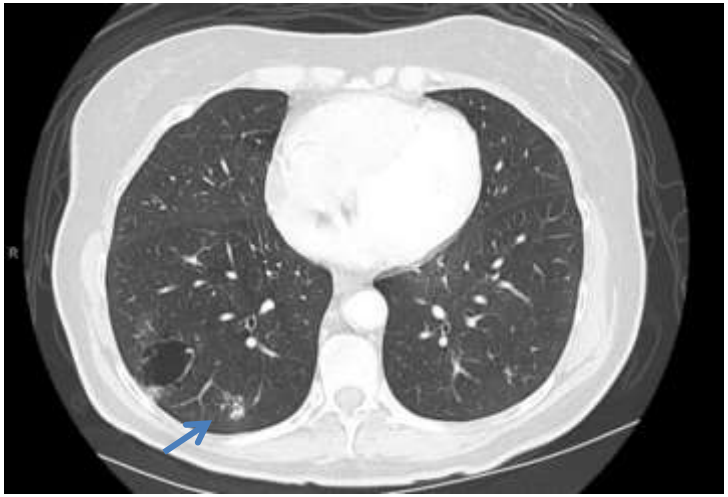
Physical Examination

Unremarkable


Pulmonary
embolism







History

The patient was initiated on enoxaparin and CT-guided biopsies of the right upper lobe and right lower lobe were obtained with a diagnosis of adenocarcinoma of the lung, multifocal.

MRI of the brain and CT abdomen and pelvis were negative.

What biomarkers would you request?

A. None, since the patient is a former smoker and unlikely to have a targetable alteration
B. K-RAS mutation and if negative, EGFR and ALK
C. EGFR, ALK, ROS, PD-L1 by immunohistochemistry
D. PD-L1 by immunohistochemistry only

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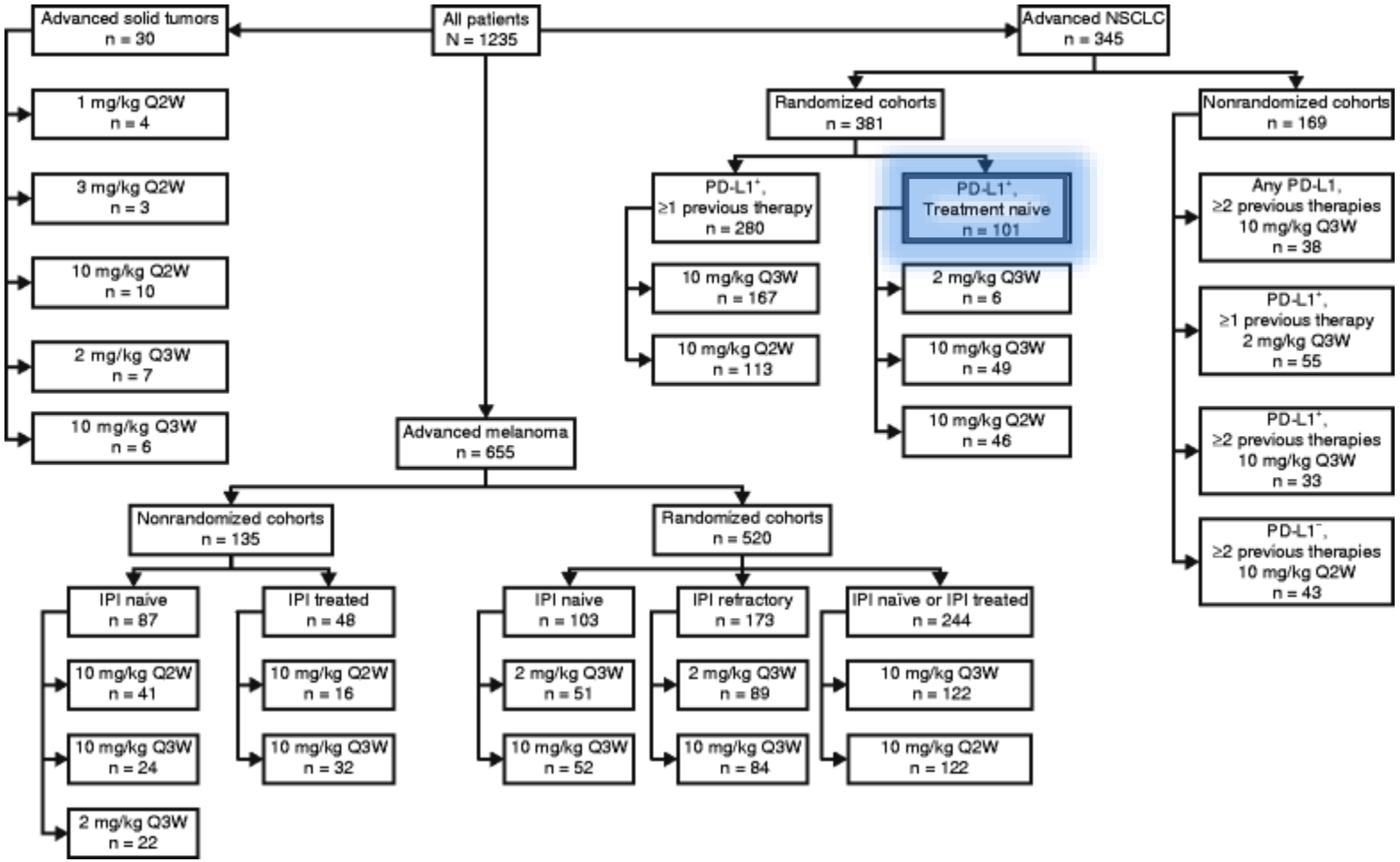
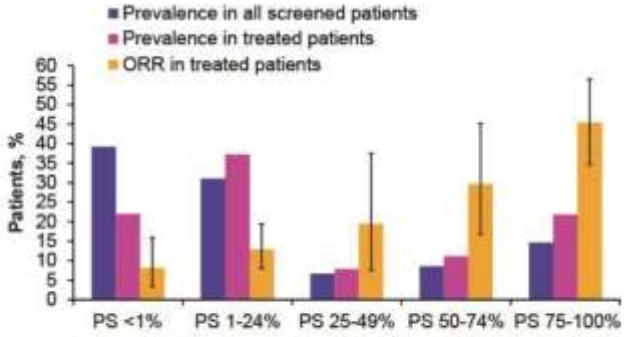
Phase I - Keynote 001
Pembrolizumab in NSCLC



Khoja *et al. Journal for ImmunoTherapy of Cancer* 2015 **3**:36

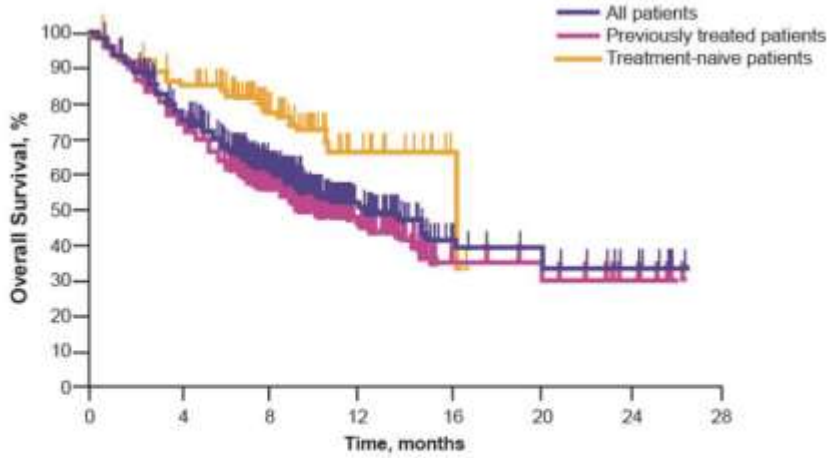
Phase I - Keynote 001
Pembrolizumab in NSCLC



All screened patients, n (%)	323 (39.2)	255 (31.0)	55 (6.7)	71 (8.6)	120 (14.6)
All treated patients, n (%)	87 (22.0)	147 (37.2)	27 (6.8)	39 (9.9)	72 (18.2)
ORR in treated patients, n (%) [95% CI]	7 (8.1) [3.3-15.9]	19 (12.9) [8.0-19.4]	6 (19.4) [7.5-37.5]	13 (29.6) [16.8-45.2]	39 (45.4) [34.6-56.5]

Median duration of response:

10.4 months (1.0 - 10.4) in previously treated patients
23.3 months (1.0 to 23.3) in previously untreated patients



n at risk

All patients	495	368	209	67	18	14	7	0
Previously treated patients	394	284	165	52	16	14	7	0
Treatment-naive patients	101	84	44	15	2	0	0	0

Garon EB et al. N Engl J Med 2015;372:2018-2028.

PD-L1 - Antibodies

	Pembrolizumab Merck	Nivolumab Bristol-Myers Squibb	MPDL3280A Roche/Genentech	MEDI4736 AstraZeneca
PD-L1 Assay	• Prototype or clinical trial IHC assay (22C3 Ab)[1,2]	• Dako automated IHC assay (28-8 Ab)[3,4]	• Central laboratory IHC assay[6] • Ventana PD-L1 (**SP142**)	• Ventana automated IHC (BenchMark ULTRA using Ventana PD-L1 (**SP263**) clone)[8,9]
Sample Source and Collection	• Surface expression of PD-L1 on tumour specimen[1,2]	• Surface expression of PD-L1 on tumour cells[3,4]	• Surface expression of PD-L1 on TILs or tumour cells[6,7]	• Surface expression of PD-L1 on tumour cells[8,9]
	• Ph I: Fresh or archival tissue[1,2]	• Archival or fresh tissue[3,4]	• Archival or fresh tissue[6]	• Unknown
Definition of Positivity†	**IHC Staining:** • Strong vs weak expression[1,2] • PD-L1 expression required for NSCLC for enrollment[1] • Note that one arm of KEYNOTE 001 trial requires PD-L1⁻ tumours[1] **Tumour PD-L1 expression:**[1,2] • ≥50% PD-L1⁺ cut-off: 32% (41/129) • 1–49% PD-L1⁺ cut-off: 36% (46/129)	**IHC Staining:** • Strong vs weak expression[3,4] • Patients not restricted by PD-L1 status in 2nd- & 3rd-line • Ph III 1st-line trial in PD-L1+[5] **Tumour PD-L1 expression:** • 5% PD-L1⁺ cut-off: 59% (10/17)[3] • 5% PD-L1⁺ cut-off: 49% (33/68)[4]	**IHC Staining Intensity (TC: 0, 1, 2, 3):** • IHC 3 (≥50% PD-L1⁺)[6,7] • IHC 2,3 (≥5% PD-L1⁺)[6,7] • IHC 1,2,3 (≥1% PD-L1⁺)[6,7] • IHC 0,1,2,3 (all patients with evaluable status)[6,7] • PD-L1 expression required for NSCLC for enrolment in Ph II trials[6] **IC: TIL PD-L1 expression:**[6] • IHC 3 (≥10% PD-L1⁺): 11% (6/53) • PD-L1 low (IHC 1, 0): 62% (33/53)	**IHC Staining Intensity:** • Not presented to date[8–10] **Tumour PD-L1 expression (all doses):**[8] • PD-L1⁺: 34% (20/58) • PD-L1⁻: 50% (29/58)

Evaluation of Multiple anti-PD-L1 Assays

- 500 samples tested
- Distribution by stage: I (38%), II (39%), III (20%), and IV (<1%)
- Distribution by histology: nonsquamous (54%) and squamous (43%) cancers
- Linear correlation (Spearman correlation)
  - 0.911 for Ventana SP263 vs Dako 22C3;
  - 0.935 for Ventana SP263 vs Dako 28-8;
  - 0.954 for Dako 28-8 vs Dako 22C3.

Ratcliffe et al. AACR 2016

Blueprint Study

2-phased study to gain sufficient data and rigor

Phase 1 study:

- Feasibility on small cohort stained at Dako and Ventana

Phase 2 study:

- Larger, statistically powered study that will be designed based on data from pilot phase study

Agent	Nivolumab	Pembrolizumab	Durvalumab	Atezolizumab
Diagnostic Platform	Dako (now approved)		Ventana (currently IUO)	
IUO Antibody	28-8	22C3	SP 263	SP 142
Cut-off(s) tested	1%, 5% or 10% (TC[1])	TC[1] ≥50% (and 1% any stroma)	≥ 25% TC[1]	TC[1] or IC[2] 1%, 5%,10%

Hirsch et al. AACR 2016

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Similar Performance

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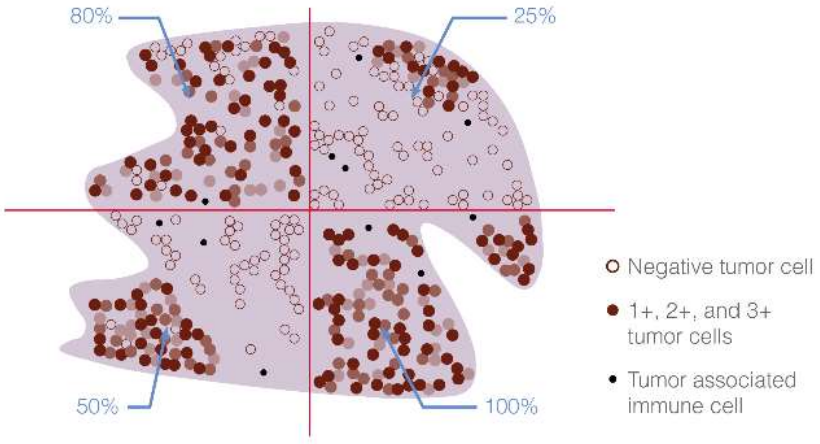
Hirsch et al. AACR 2016

Principles PD-L1 IHC – 22C3

Principle 1: Evaluate acceptability	Principle 2: Score PD-L1 staining	Principle 3: Calculate Tumor Proportion Score	Principle 4: Report results
Verify that the sample has ≥ 100 viable tumor cells for evaluation	Evaluate tumor cells for membrane staining at any intensity level: weak (1+), moderate (2+), strong (3+)	Calculate the PD-L1 expression level using the Tumor Proportion Score formula	Report the numerical TPS and expression level to the treating oncologist

Calculate the Tumor Proportion Score using this simple formula:

$$\text{Tumor Proportion Score} = \frac{\text{Number of PD-L1 stained tumor cells}}{\text{Total number of tumor cells (stained and unstained)}}$$

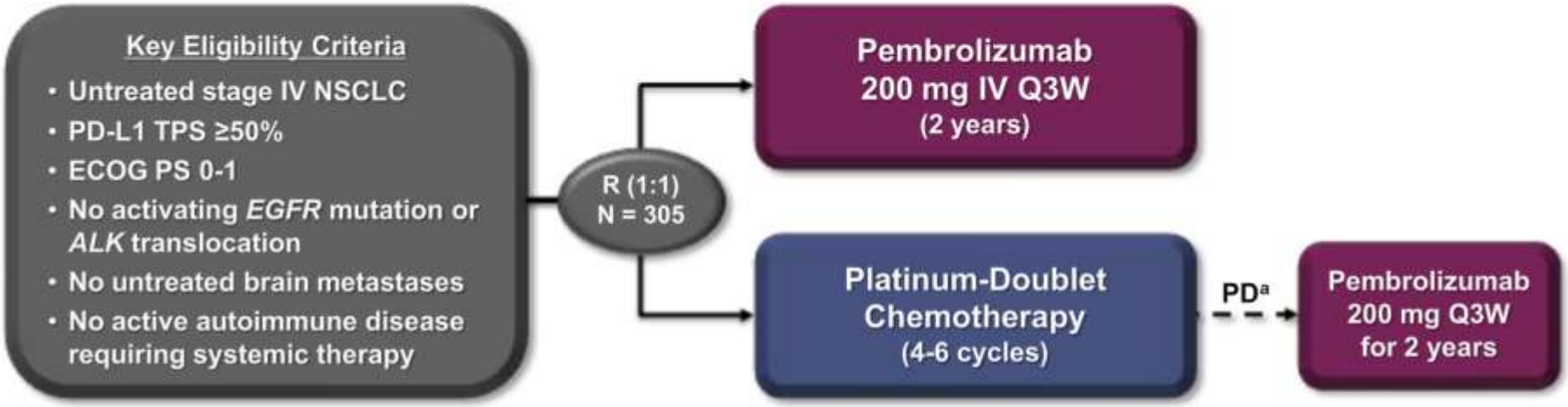


Region 1	80%
Region 2	25%
Region 3	50%
Region 4	100%
Total	255%
Tumor proportion score (255/4)	**≥ 60%**

Dako

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR

*To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Reck et al. ESMO 2016; NEJM 2016

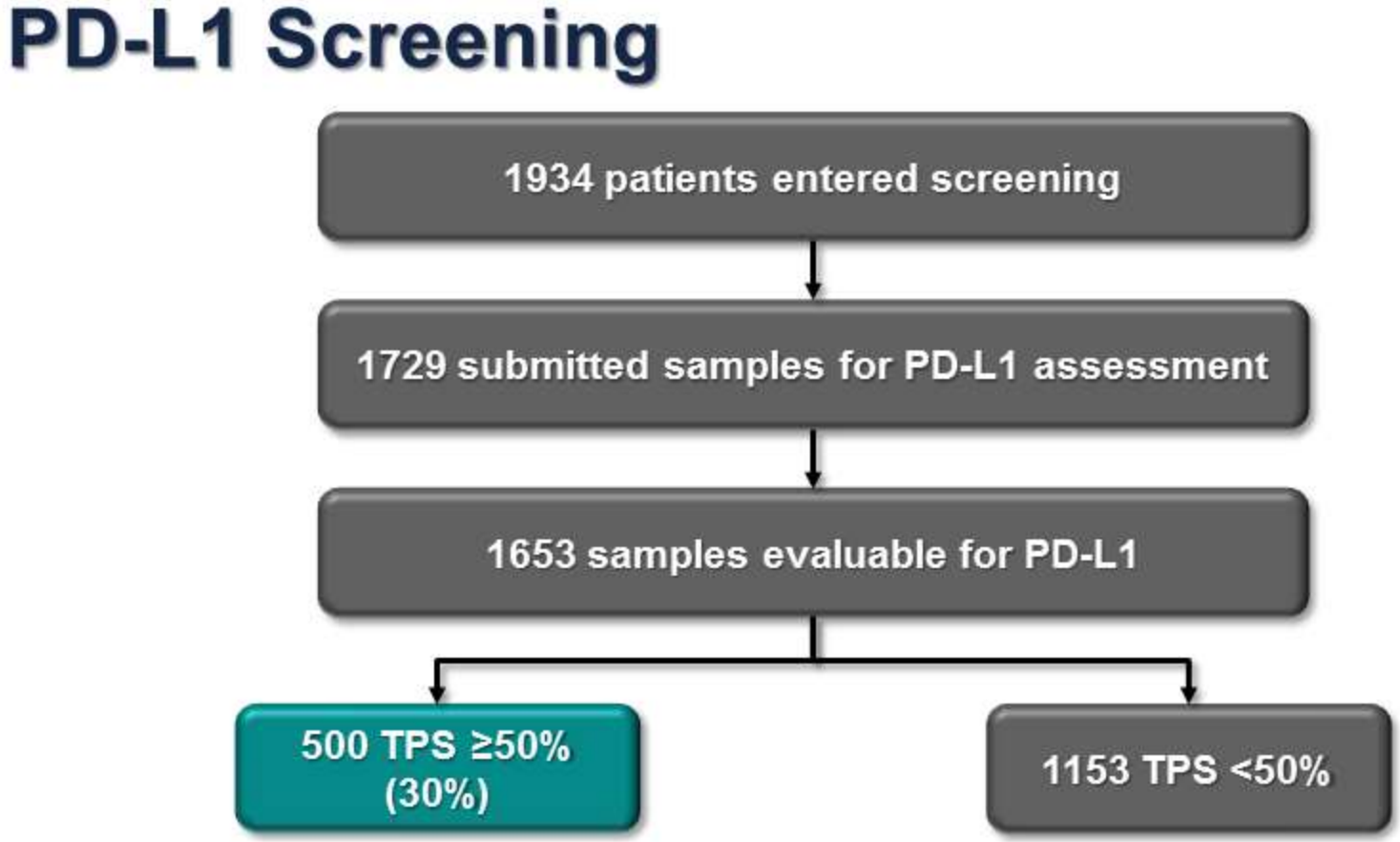
Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Statistical Considerations

- Planned sample size: ~300 patients
- Overall alpha for study: strictly controlled at one-sided 2.5%
  - Analysis plan specified 2 interim analyses and a final OS analysis
- Second interim analysis (IA2): primary PFS and interim OS
  - To occur after ~175 PFS events and ~110 OS events
  - Alpha allocated: one-sided 2.0% (97% power to detect a HR for PFS of 0.55)
  - If PFS superiority for pembro demonstrated, OS would be tested for superiority
- Data cutoff date for IA2: May 9, 2016
  - 189 PFS and 108 OS events had occurred
  - Median follow-up: 11.2 months (range, 6.3-19.7)

Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab



Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Baseline Characteristics

	Pembrolizumab N = 154	Chemotherapy N = 151
Median age (range), y	64.5 (33-90)	66.0 (38-85)
Men, n (%)	92 (60)	95 (63)
Enrolled in east Asia	21 (14)	19 (13)
ECOG PS 1, n (%)	99 (64)	98 (65)
Squamous histology, n (%)	29 (19)	27 (18)
Smoking status,[a] n (%)		
Current	34 (22)	31 (21)
Former	115 (75)	101 (67)
Never	5 (3)	19 (13)
Brain metastases, n (%)	18 (12)	10 (7)

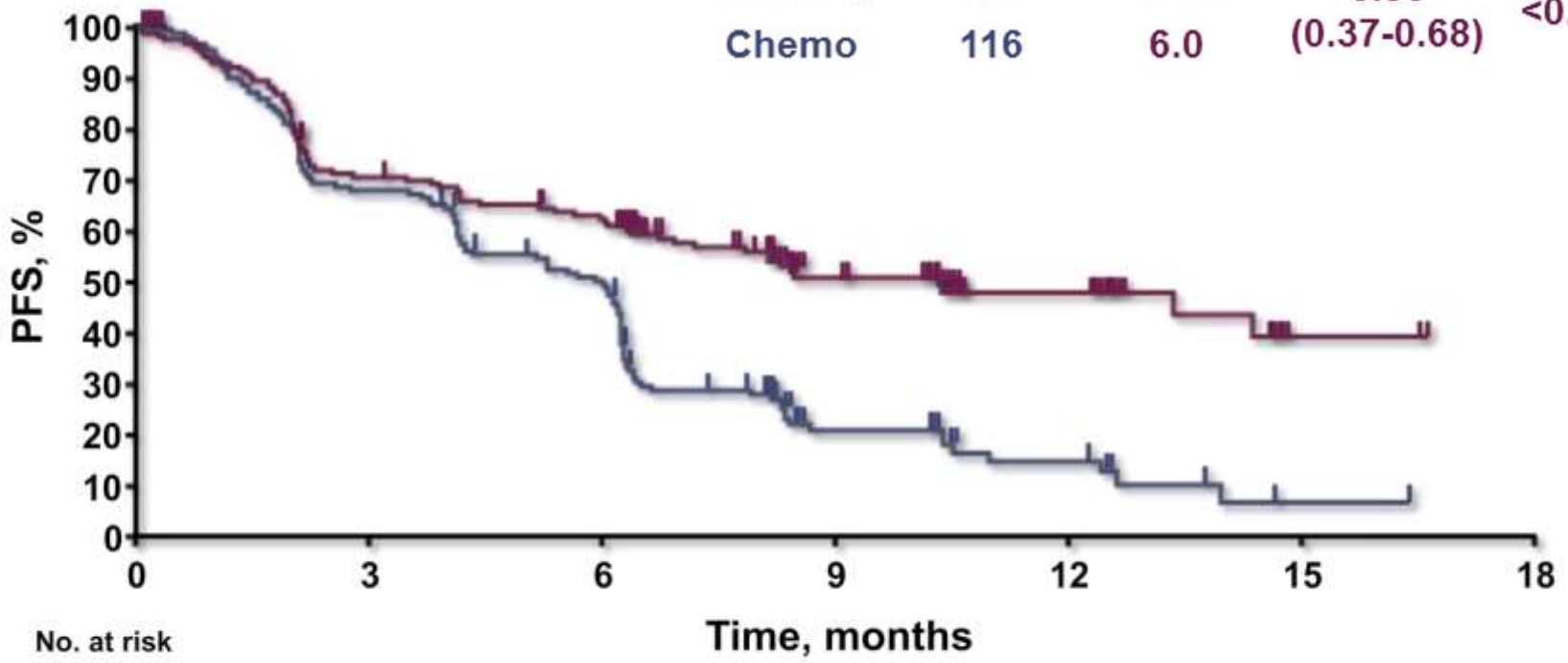
[a]As defined and reported by the patient.
Data cut-off: May 9, 2016.

Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



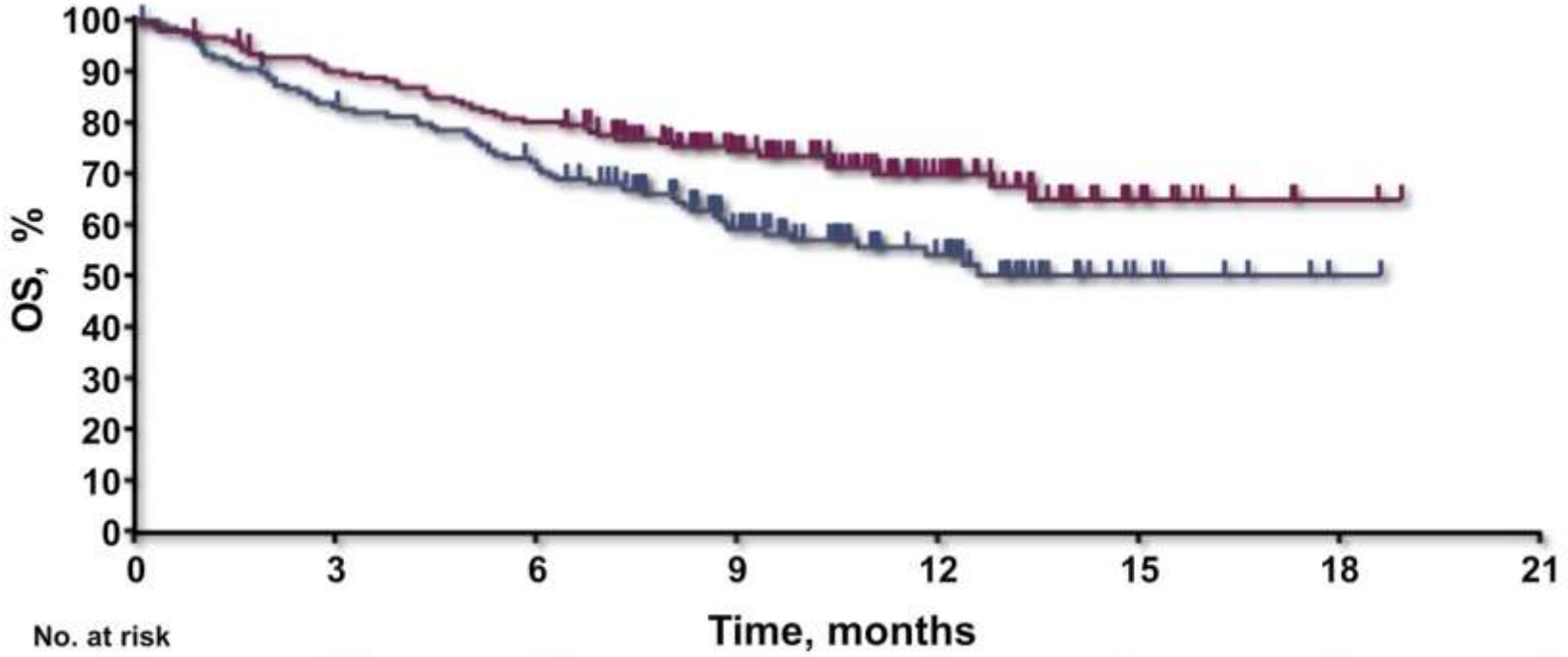
Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



Data cut-off: May 9, 2016.

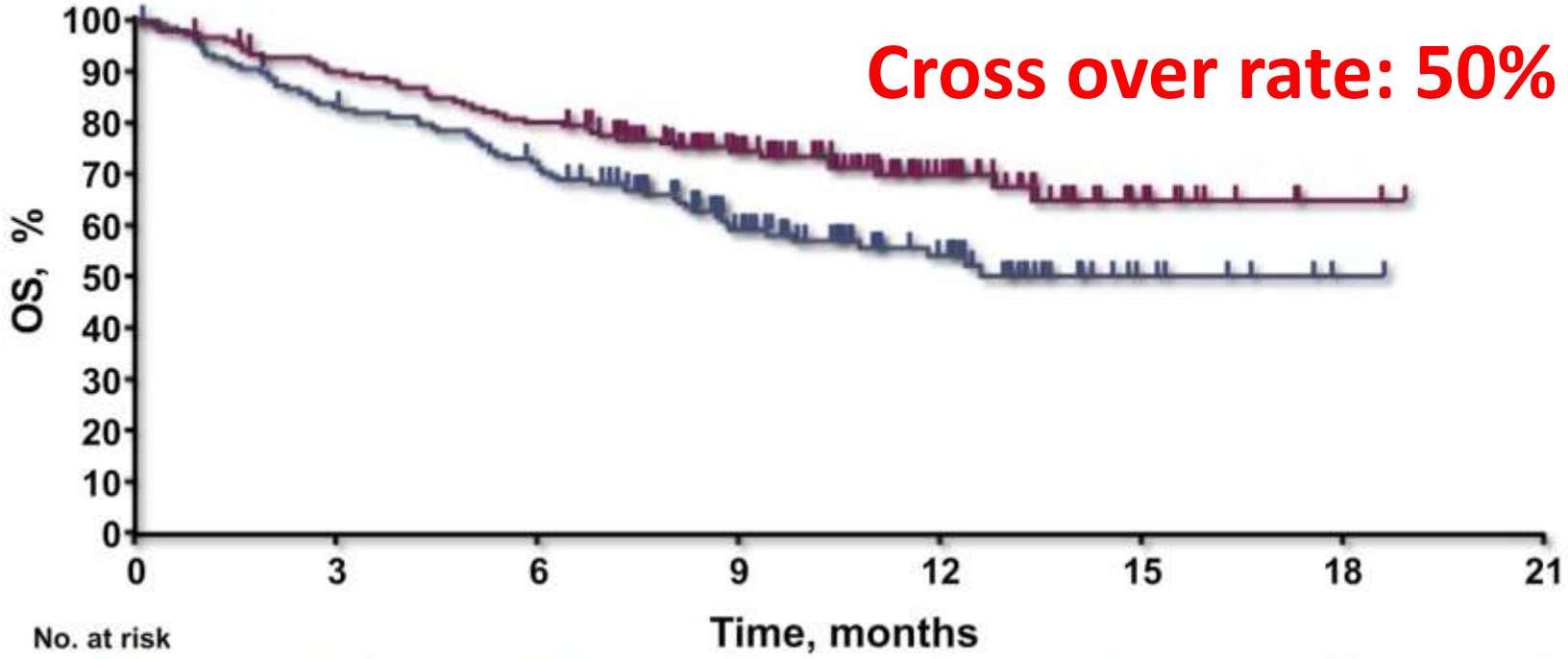
Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		

Cross over rate: 50%

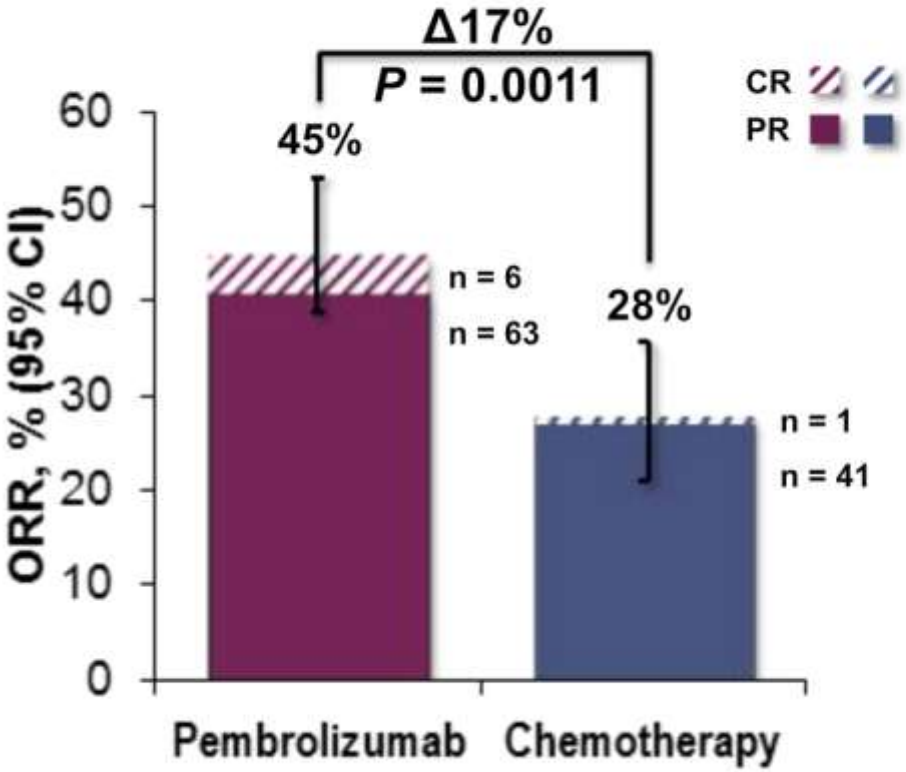


Data cut-off: May 9, 2016.

Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Confirmed Objective Response Rate

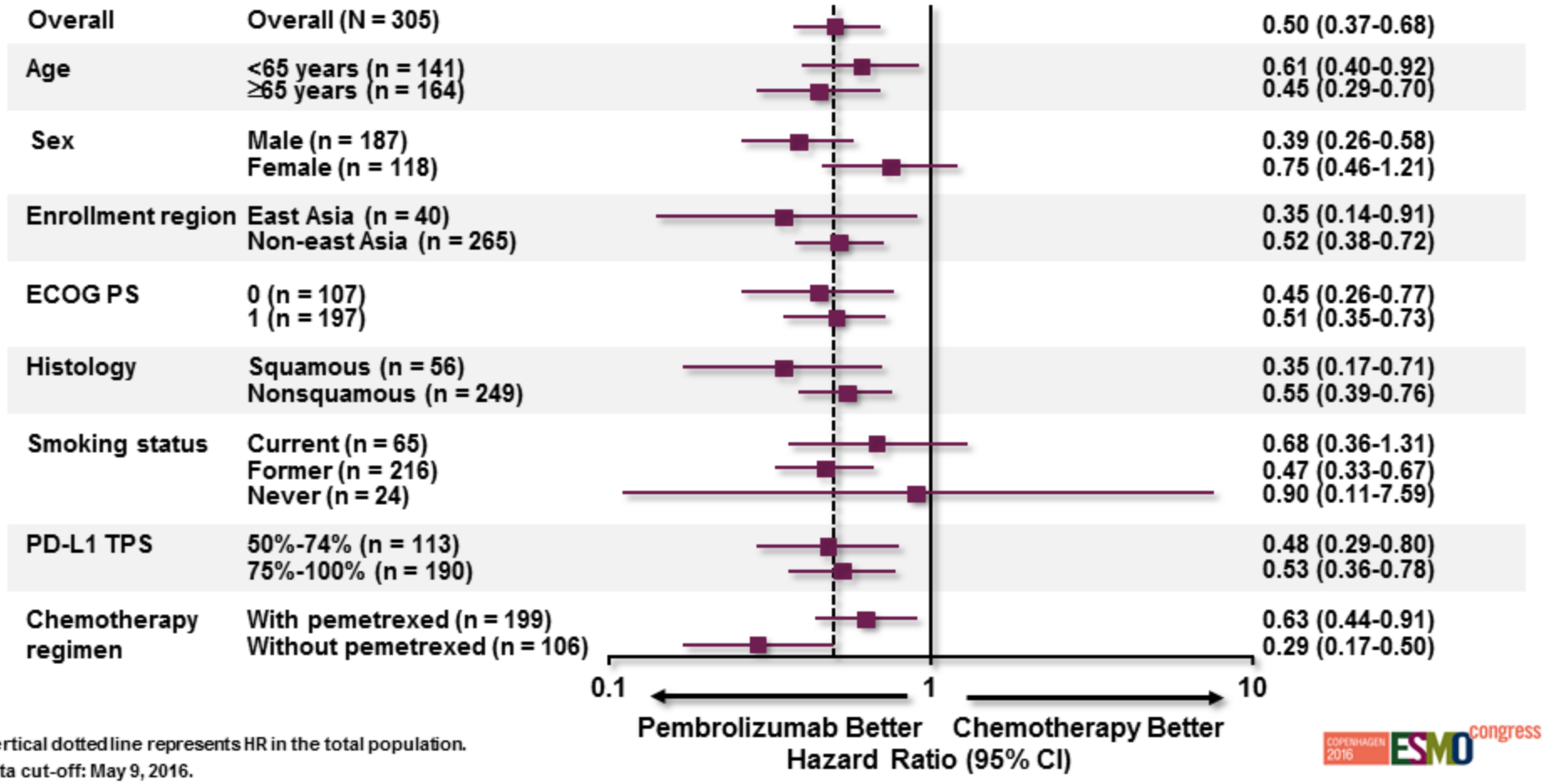


Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Progression-Free Survival in Subgroups



Vertical dotted line represents HR in the total population.
Data cut-off: May 9, 2016.

Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Exposure and AE Summary

	Pembrolizumab N = 154	Chemotherapy N = 150
Exposure, median (range)	7.0 mo (1 d-18.7 mo)	3.5 mo (1 d-16.8 mo)
Treatment-related AEs, n (%)	113 (73)	135 (90)
Grade 3-4	40 (26)	77 (51)
Serious	33 (21)	31 (21)
Led to discontinuation	11 (7)	16 (11)
Led to death	1 (<1)	3 (2)

Data cut-off: May 9, 2016.

Reck et al. ESMO 2016; NEJM 2016

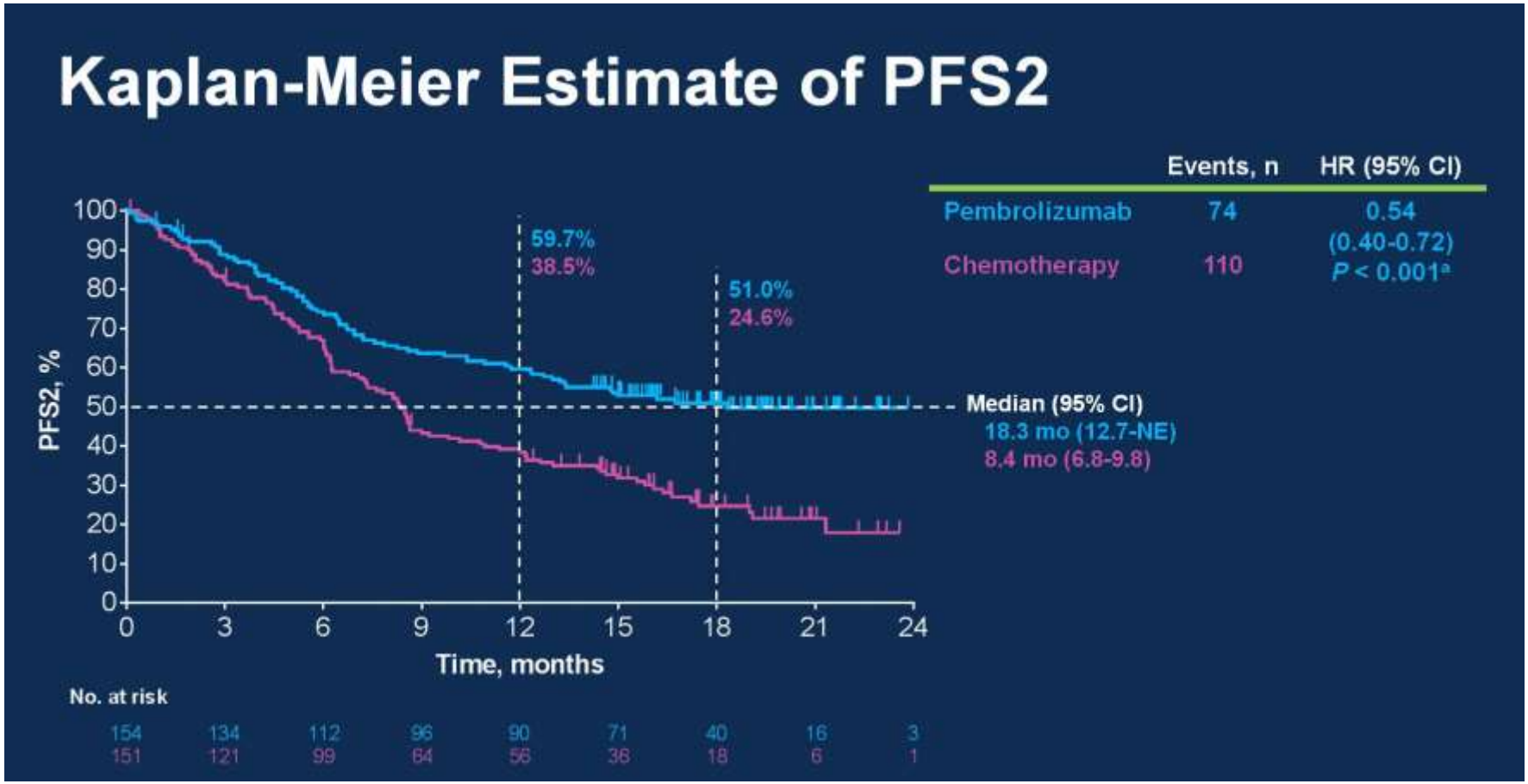
Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Progression-Free Survival In the Second Line: PFS2

- As first defined by the EMA in 2012[1]: time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever occurs first

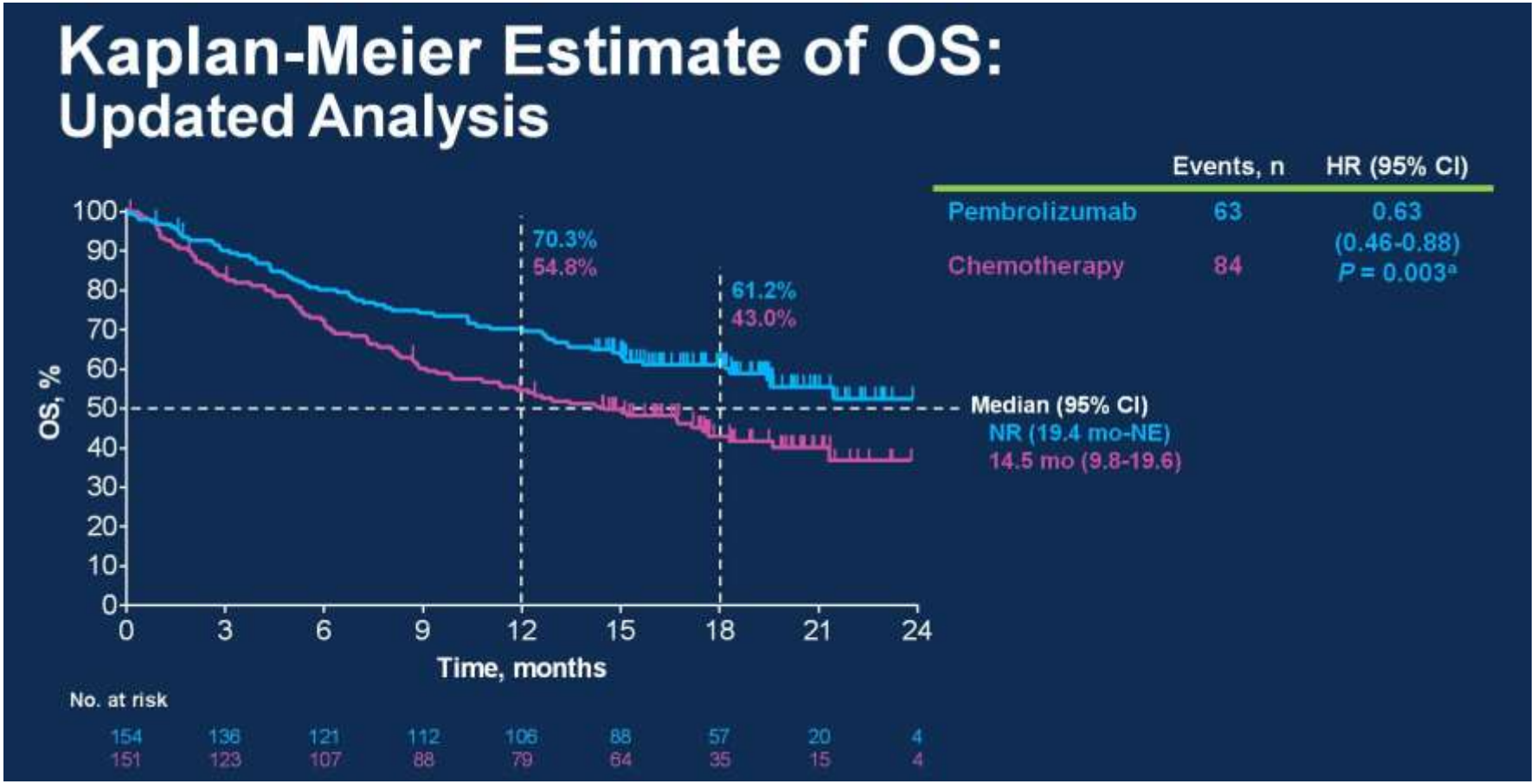
Brahmer et al., ASCO 2017

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab



Brahmer et al., ASCO 2017

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab



Brahmer et al., ASCO 2017

History

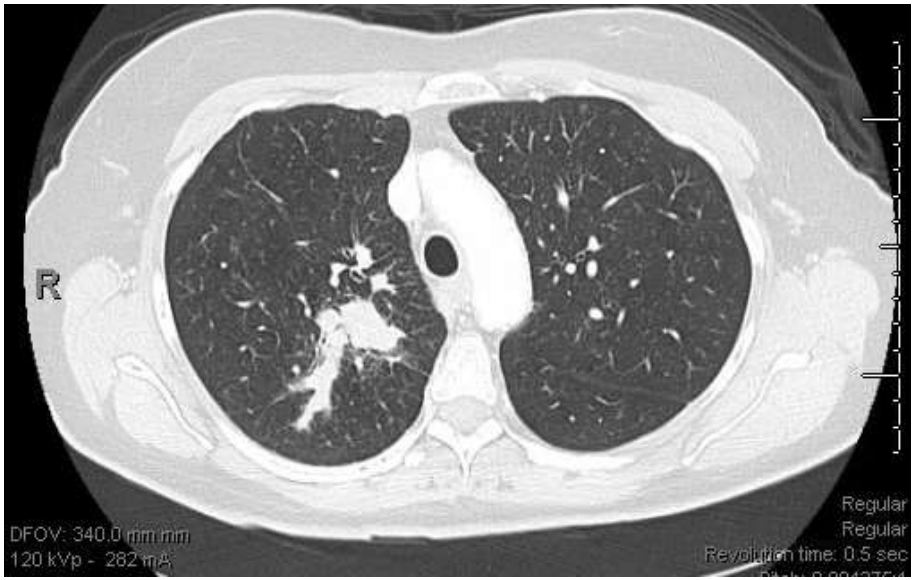
A comprehensive 50-gene panel was ordered, as well as FISH for ALK, ROS, RET and MET and PD-L1 IHC.

The tumor was positive for a G13C mutation in codon 13, exon 2 of the KRAS gene

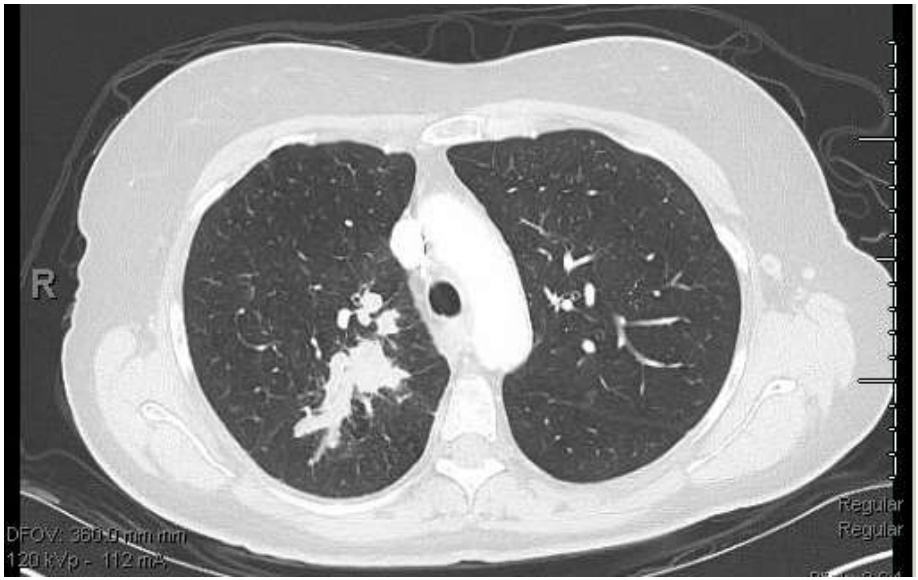
PD-L1 expression: TPS = 35%

History

The patient received 4 cycles of carboplatin and pemetrexed. She experienced significant fatigue and her hemoglobin dropped to 7 mg/dL. She required 2 blood transfusions during treatment.



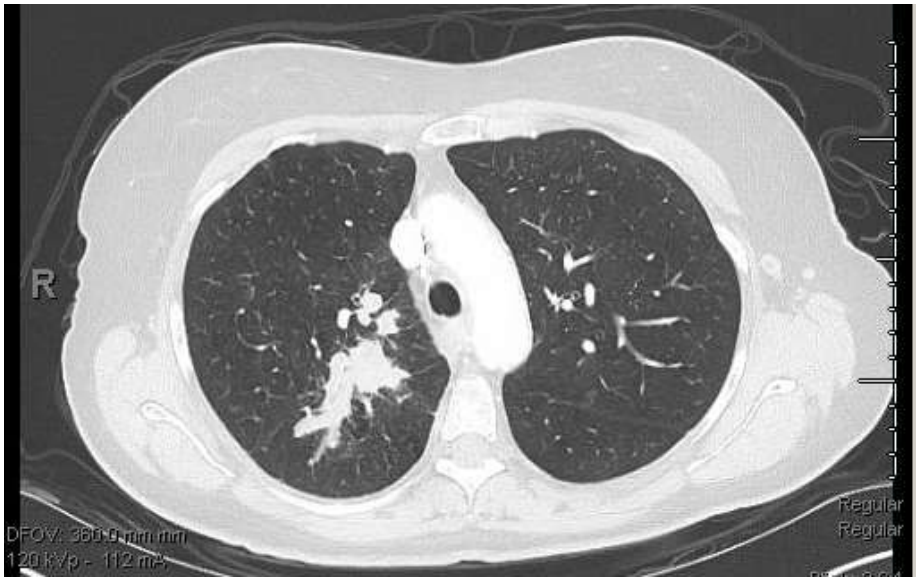
April 2013



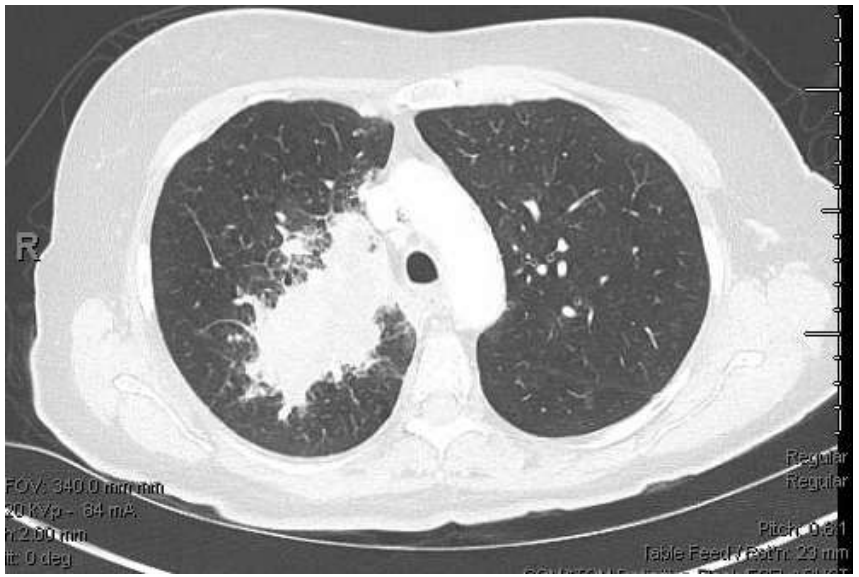
August 2013

History

The patient was placed on a treatment break. She continued to develop slow disease progression, but over the course of 18 months had improved energy levels. In Feb/2015 she had worsening cough and shortness of breath.



August 2013



March 2015

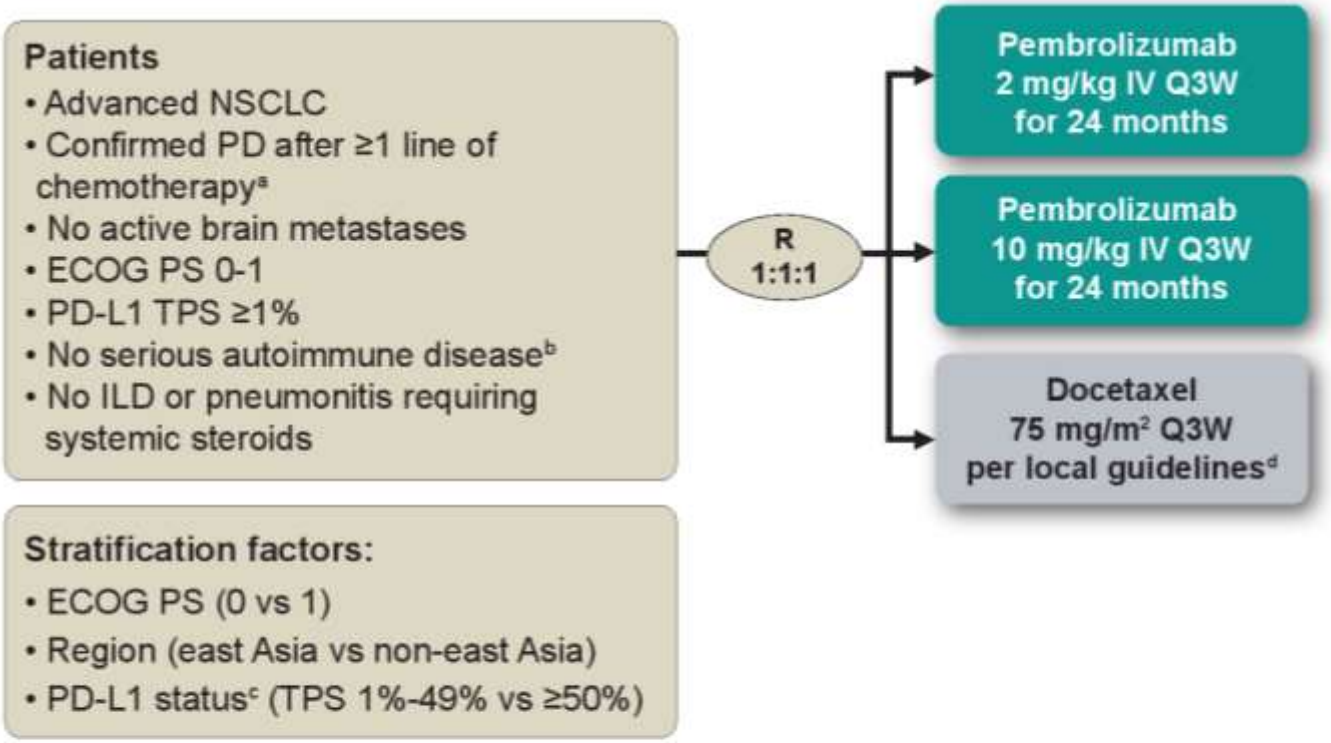
What treatment would you recommend?

A. Radiation therapy to the dominant mass
B. Docetaxel +/- nintedanib
C. Docetaxel +/- ramucirumab
D. Pembrolizumab
E. Resume carboplatin and pemetrexed

What treatment would you recommend?

A. Radiation therapy to the dominant mass
B. Docetaxel +/- nintedanib
C. Docetaxel +/- ramucirumab
D. Pembrolizumab
E. Resume carboplatin and pemetrexed

Phase II/III - Keynote 010
Pembrolizumab vs. Docetaxel in NSCLC



[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an EGFR sensitizing mutation or an ALK translocation.

[b]No active or documented history of any autoimmune disease or syndrome that required systemic steroids or immunosuppressive agents, excluding patients with vitiligo, resolved childhood asthma/atopy, or those that required inhaled steroids or local steroid injections.

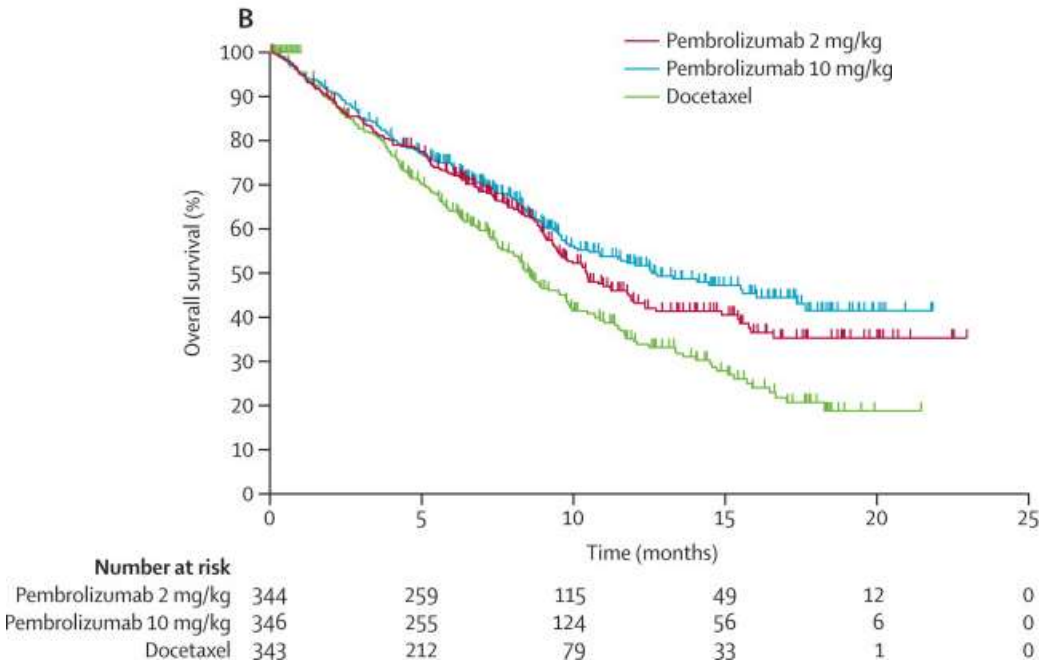
[c]Based on results from KEYNOTE-0013 and added after 441 patients enrolled to ensure equal distribution of TPS ≥50% and 1%-49% in subsequently enrolled patients.

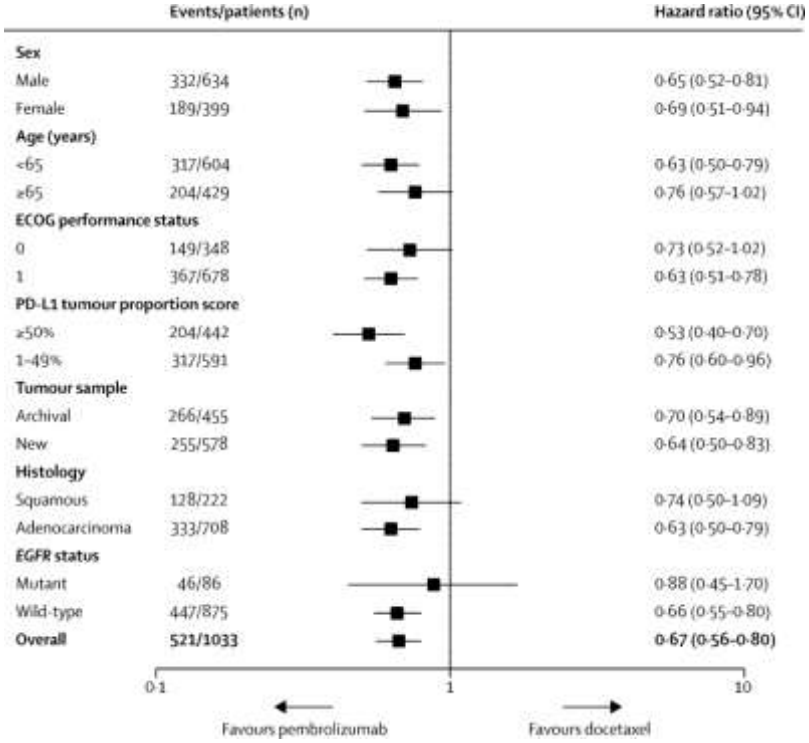
[d]Patients received the maximum number of cycles permitted by the local regulatory authority.

ECOG PS = Eastern Cooperative Oncology Group performance status; ILD = interstitial lung disease; PD = progressive disease; R = randomized.

Herbst et al. Lancet 2015

Phase II/III - Keynote 010
Pembrolizumab vs. Docetaxel in NSCLC





Median overall survival:

Docetaxel: 8.5 months
Pembrolizumab 2 mg/kg: 10.4 months (HR=0.71, 95% CI 0.58-0.88; p=0.0008)
Pembrolizumab 10 mg/kg: 12.7 months (HR=0.61, 95% CI 0.49-0.75; p<0.0001)

Herbst et al. Lancet 2015

Phase II/III - Keynote 010
Pembrolizumab vs. Docetaxel in NSCLC – TPS 1-49%

Figure 2. Kaplan-Meier estimates of OS in the PD-L1 TPS 1%-49% stratum.

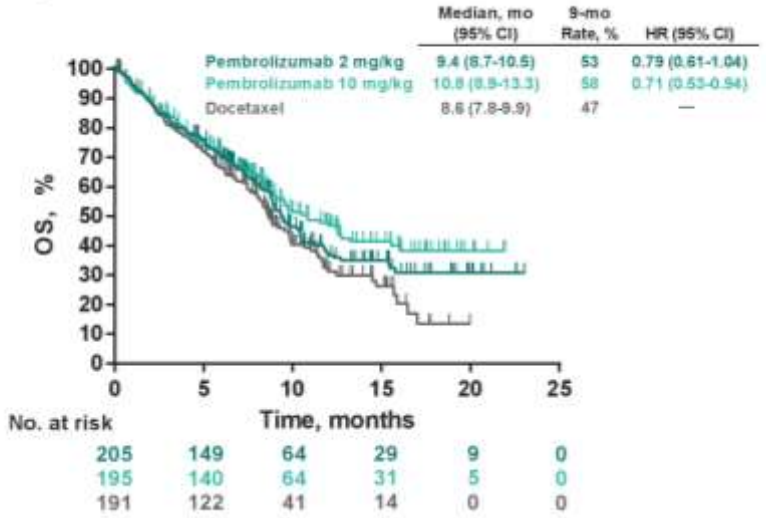


Table 2. ORR and DOR per RECIST v1.1 by independent central review in the PD-L1 TPS 1%-49% Stratum

	Pembrolizumab 2 mg/kg n = 205	Pembrolizumab 10 mg/kg n = 195	Docetaxel n = 191
ORR, % (95% CI)	10 (6-15)	10 (6-15)	10 (6-16)
DOR, median (range), wk	46 (9+ to 87+)	45 (13+ to 74+)	26 (6+ to 31)
Ongoing response,* %	65	65	35

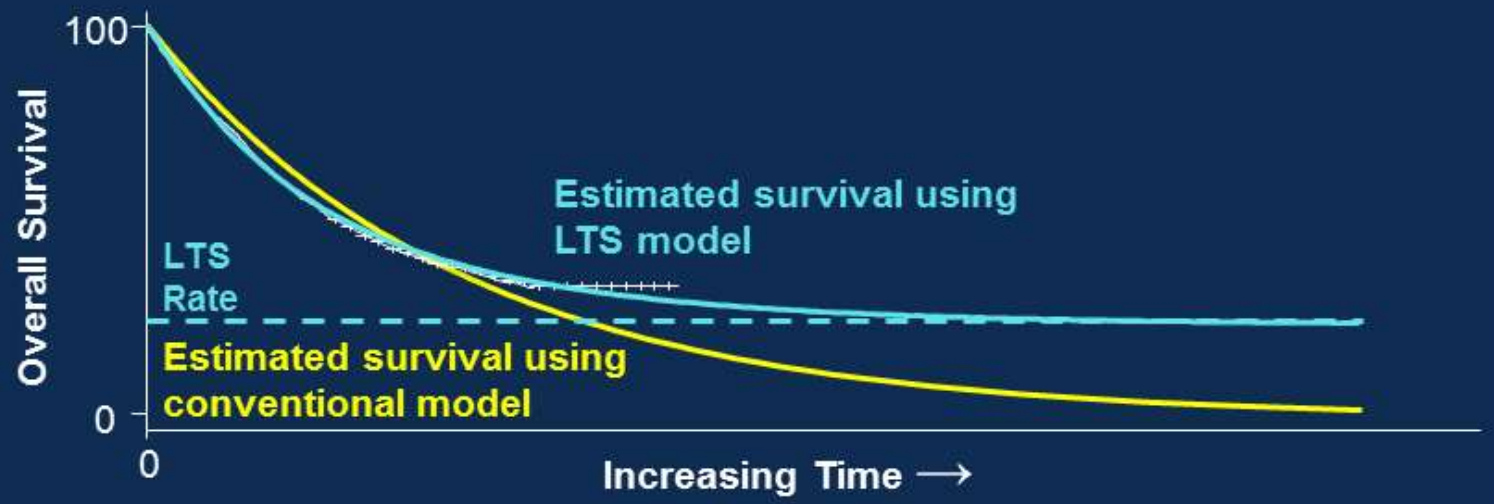
*Responders who are alive, progression free, did not initiate new anticancer therapy, and were not lost to follow-up

Garon et al. ASCO 2016

Long-Term Survival (LTS) Model

Hellmann, ASCO-SITC, Feb 2017

Why LTS Model?

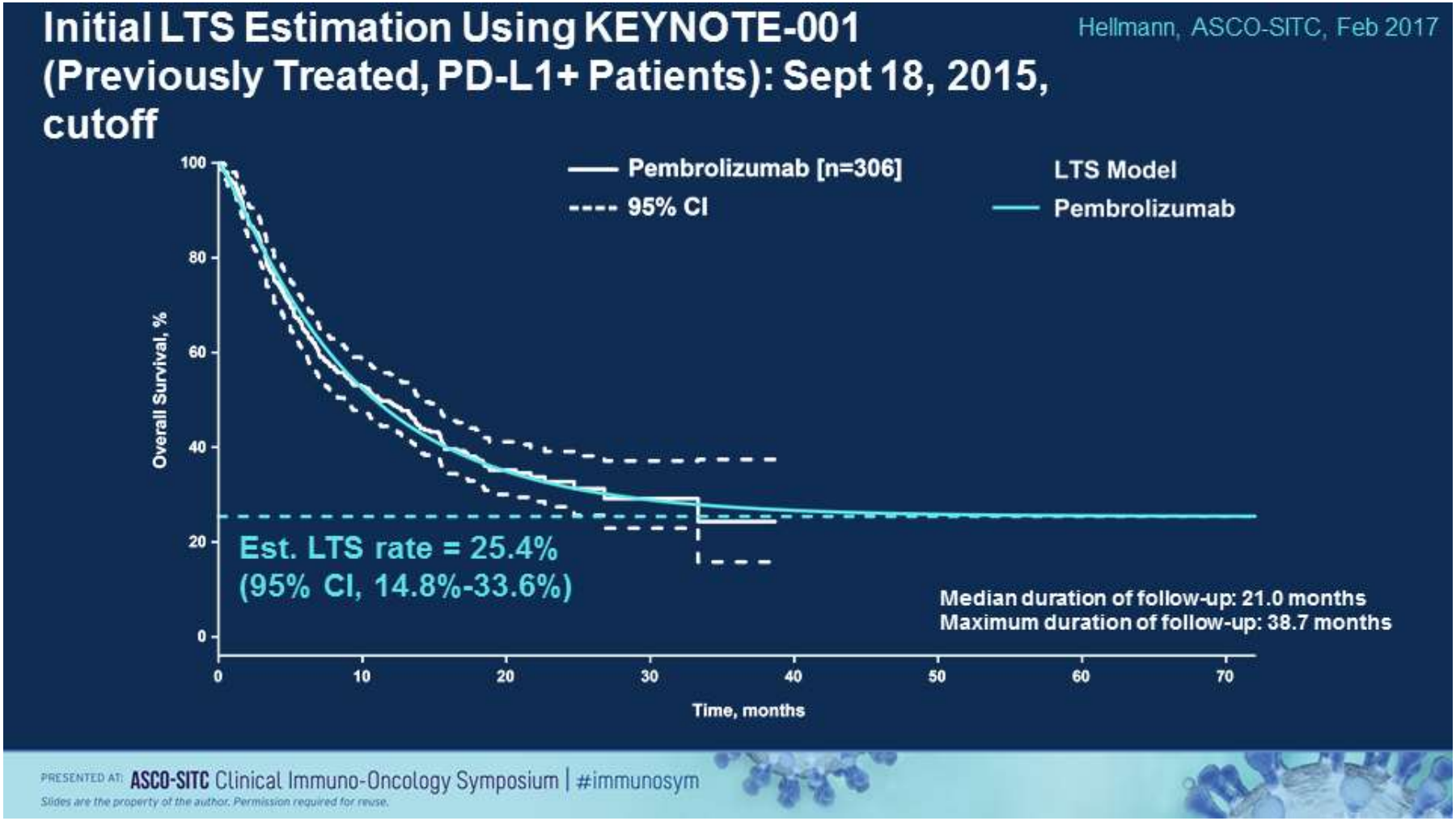


Conventional parametric models assume that LTS = 0

LTS models permit potential for LTS to be other than 0; risk of progression is not constant

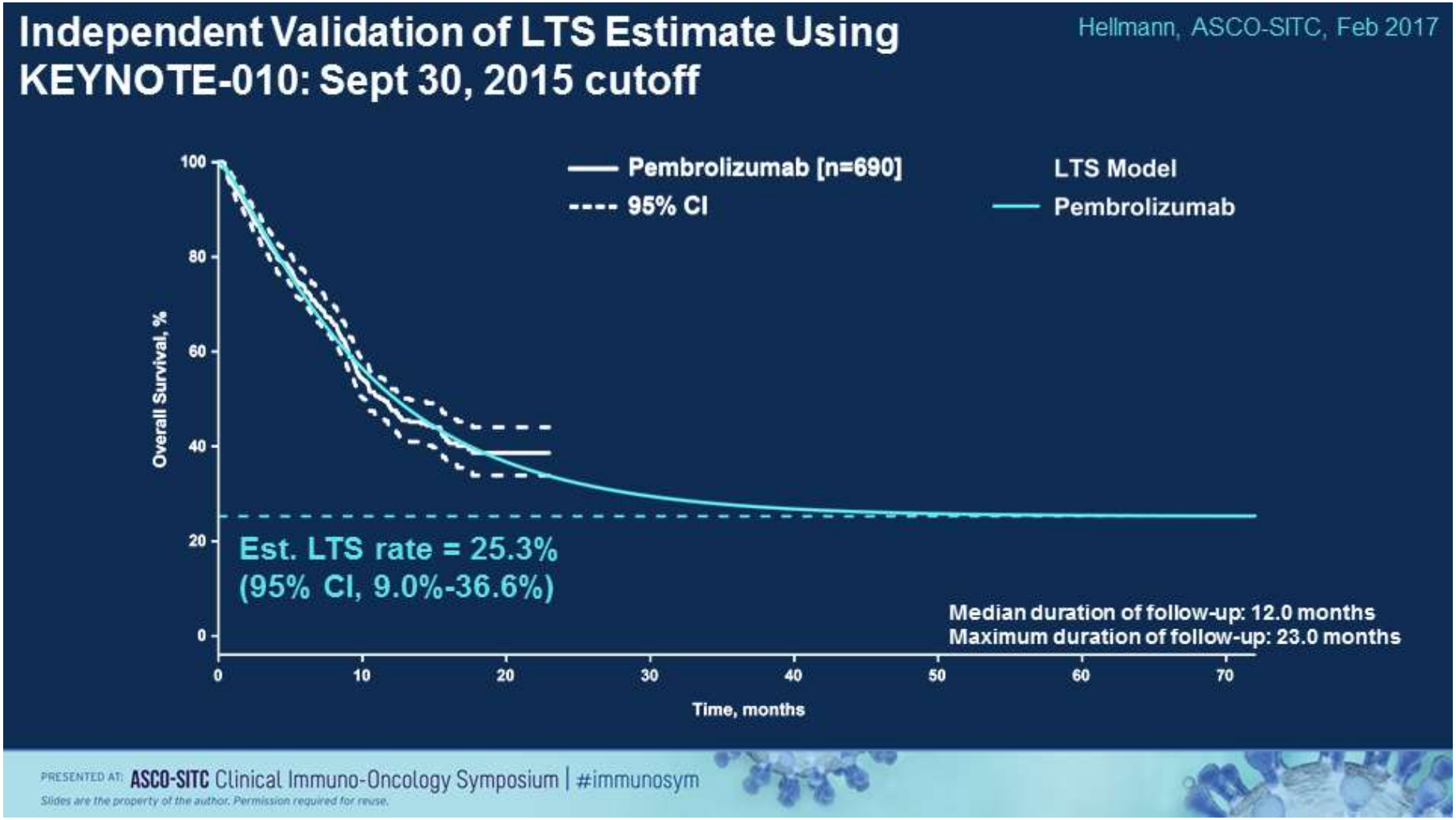
Hellman et al. ASCO-SITC 2017

Long-Term Survival (LTS) Model



Hellman et al. ASCO-SITC 2017

Long-Term Survival (LTS) Model



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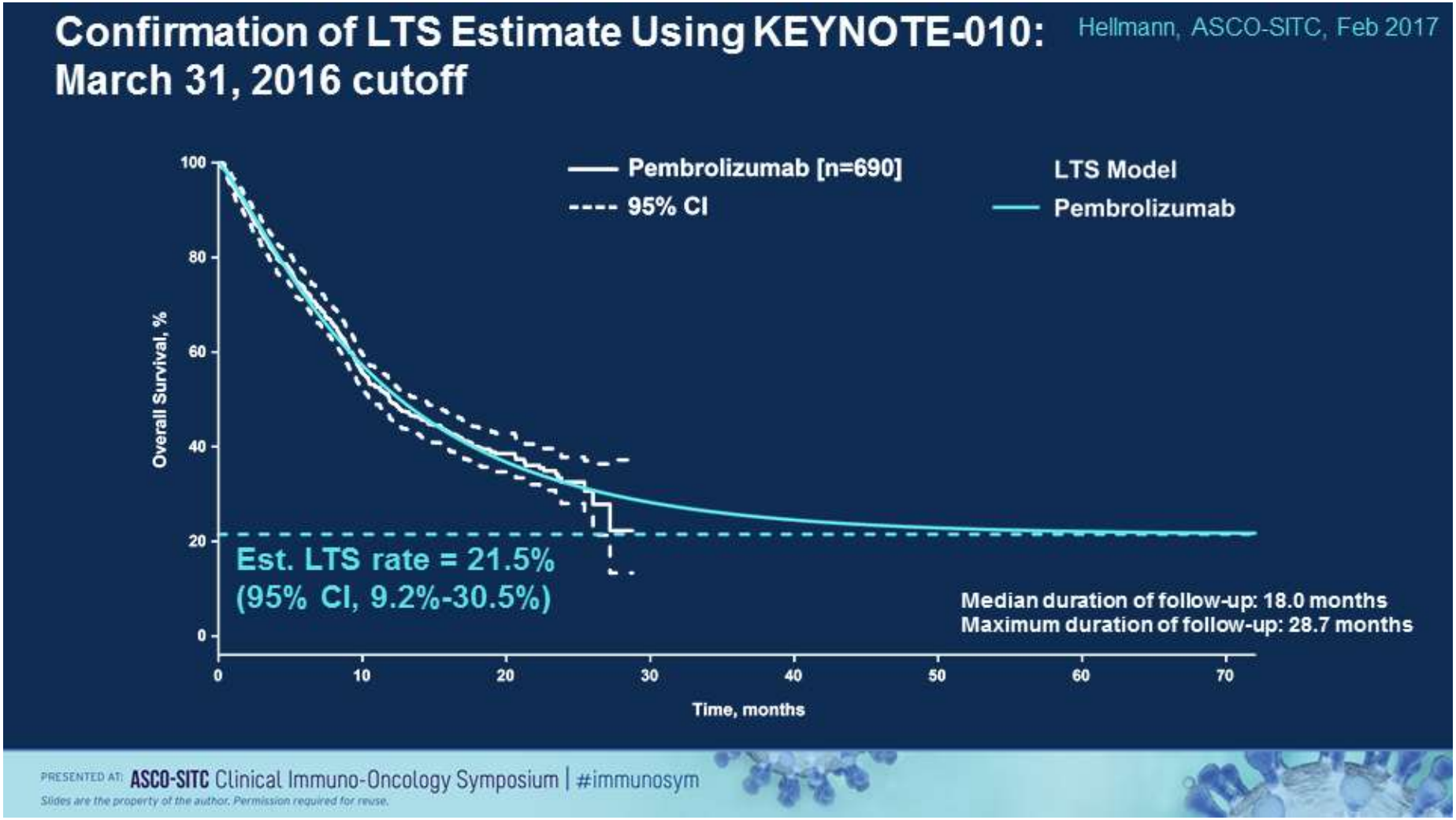
Long-Term Survival (LTS) Model



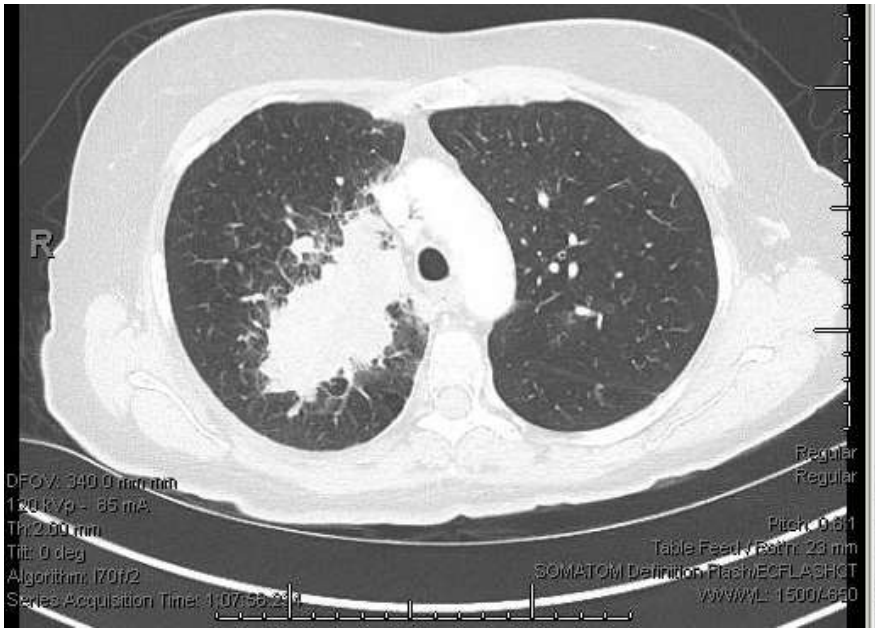
Hellman et al. ASCO-SITC 2017

History

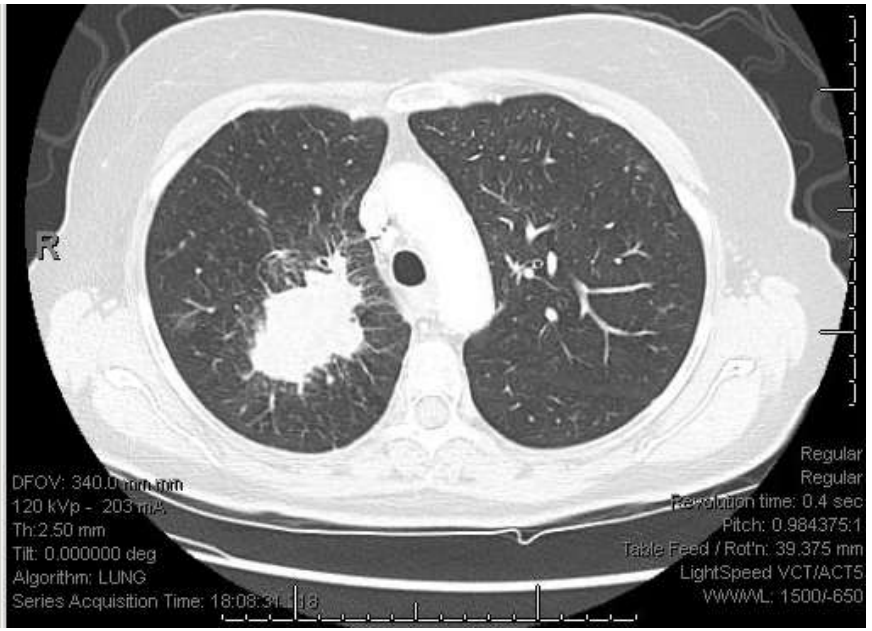
The patient was enrolled on clinical trial KEYNOTE-010, and was randomized to pembrolizumab 10 mg/kg every 3 weeks.

History

Repeat scans after 3 cycles of treatment demonstrates shrinkage of lung mass.



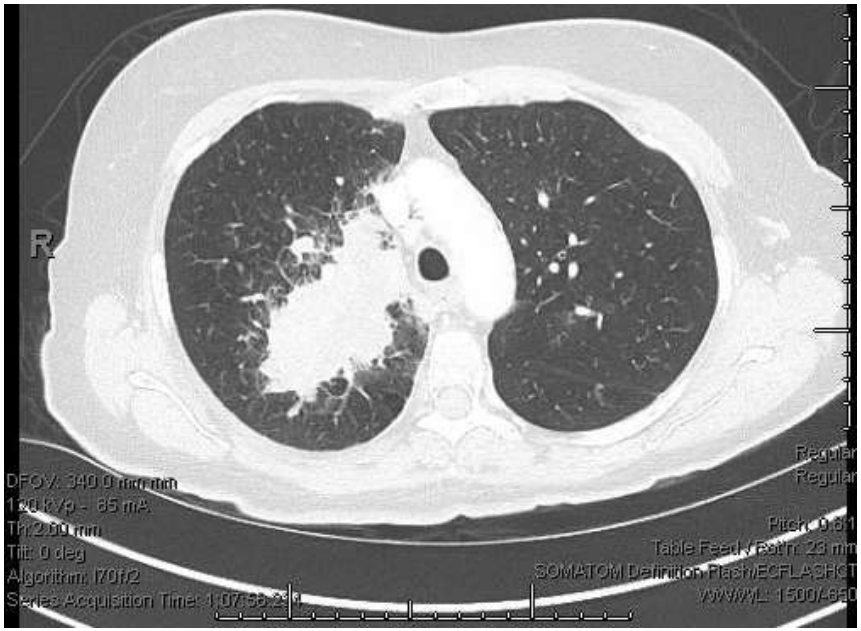
March 2015



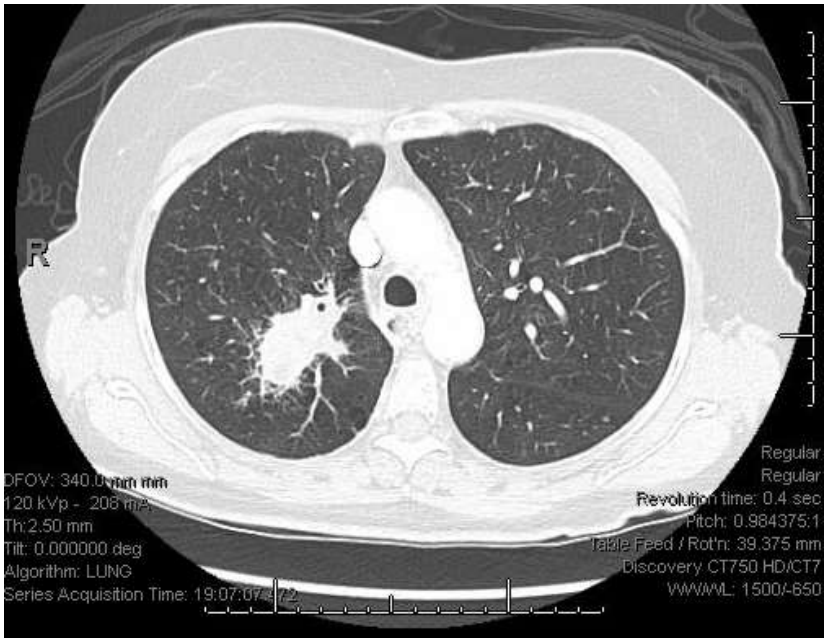
May 2015

History

Patient remained on pembrolizumab for 24 months with no major side effects. Cough has resolved. PS 0.



March 2015



March 2017

Summary

- PD-L1 expression evaluation by an approved test is part of standard of care assessment of newly diagnosed NSCLC, specially if EGFR and ALK wild-type
- Pembrolizumab is the standard of care first-line treatment for patients with PD-L1 TPS ≥ 50% assessed with 22C3 ab and no EGFR or ALK mutations
    - Improvements in PFS, OS, RR and quality of life
    - More favorable side effect profile
- In immunotherapy-naïve patients progressing after platinum-based treatment, pembrolizumab is a standard of care if PD-L1 TPS ≥ 1% assessed with 22C3 ab
    - Improvements in OS
    - More favorable side effect profile

Dica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