2019
AIOM REVIEW:
FROM CHICAGO
TO VERONA

JUNE 14-15 2019

Verona,
Palazzo della Gran Guardia
Piazza Bra, 1

Aiom
Associazione Italiana di Oncologia Medica

LUNG CANCER

Poster Review

Francesco Passiglia
Dipartimento di Oncologia
Università degli Studi di Torino

Outline

- **Early Disease**

1. NEO-adjuvant chemo-immunotherapy for the treatment of STAGE IIIA resectable NSCLC: Data of patients who underwent surgical assessment

- **Locally Advanced Disease**

1. Three year OS update from the PACIFIC trial
2. Alteration in TME after CRT for locally advanced NSCLC

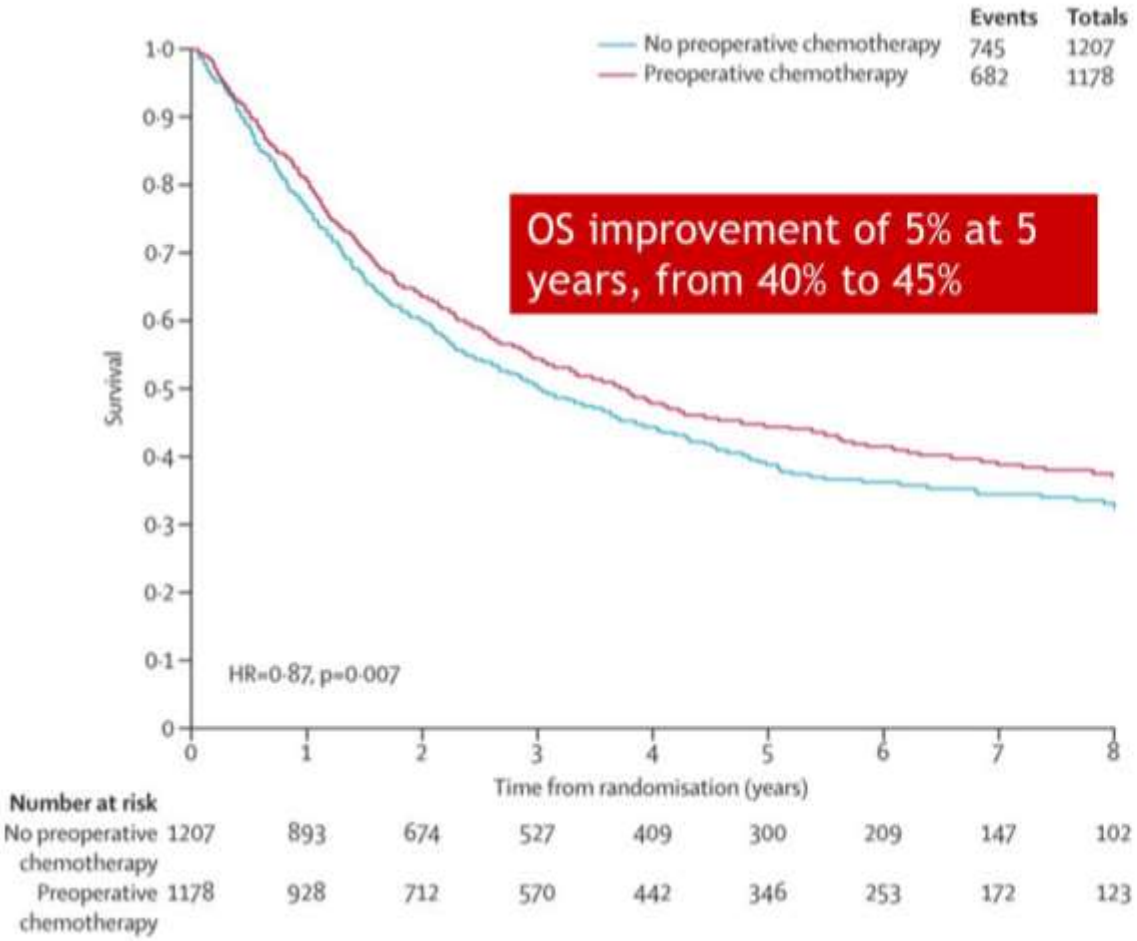
- **Advanced Disease**

1. 5-Year OS from the KEYNOTE-001 Trial
2. Updated OS from the KEYNOTE-189 Trial

- **Emerging IO Biomarkers**

1. Association of STK11/LKB1with lack of benefit from the addition of Pembro to CT in non-squamous NSCLC

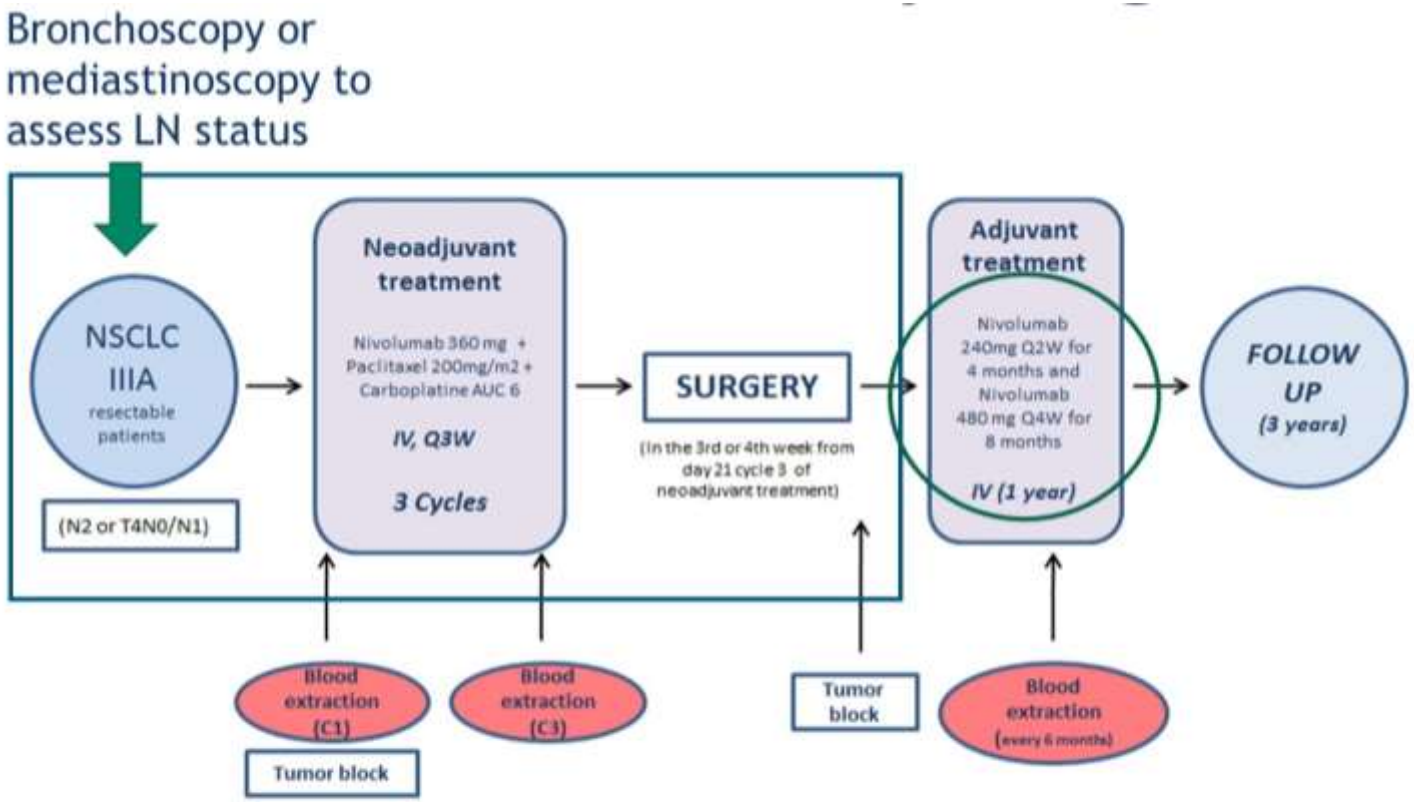
Neoadjuvant Chemotherapy for resectable NSCLC



- Meta-analysis of preoperative chemotherapy for patients with resectable NSCLC
- 15 randomized controlled trials (2385 patients)
- Significant benefit of preoperative chemotherapy on OS:
  - hazard ratio [HR] 0·87, 95% CI 0·78-0·96, p=0·007
  - 13% reduction in the relative risk of death (no evidence of a difference between trials; p=0·18

NSCLC Meta-Analysis Collaborative Group. The Lancet 2014

NADIM Study Design



A Phase II, single-arm, open-label and multicenter study of resectable stage IIIA NSCLC patients with CT + IO as a neoadjuvant treatment (46 patients).

ELIGIBILITY CRITERIA:

Patients aged ≥ 18 years.

Stage IIIA NSCLC (7th edition) and resectable tumor.

ECOG Performance Status 0-1.

Forced expiratory volume (FEV1) ≥ 1.2 liters.

Adequate hepatic, hematological and renal functions.

EGFR and ALK mutated patients are ineligible.

Primary endpoint: Progression-Free Survival at 24 months.

Secondary endpoints::

Down-staging rate, complete resection rate and response rate (RR).

Toxicity profile.

Time to progression and 3-year overall survival.

Surgical outcome and operative and post-operative complications.

To explore the expression of other biomarkers.

To determine whether PD-L1 expression is a predictive biomarker for ORR.

To determine PFS in PD-L1+ (≥ 1%) population.

Presented by Mariano Provencio-Pulla at ASCO 2019

Neoadjuvant IO + CT: Efficacy and Safety Results

Study	Stage	Drug	N. Cycles	N. Resected	MPR	G3-5 TRAEs
IO + Chemotherapy Combination						
NADIM	IIIA	Nivo + CT	3	30	86%	13%

Provencio-Pulla, ASCO 2019

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NCT02716038	IB - IIIA	Atezo + CT	4	14	50%	86% neutropenia

Provencio-Pulla, ASCO 2019

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IO + IO Combination						
NEOSTAR (Arm B)	IA-IIIA	Nivo + Ipi	3	21	33%	8%
IO Monotherapy						
NEOSTAR (Arm A)	IA-IIIA	Nivo	3	23	17%	16%
LCMC3	IB-IIIA	Atezo	2	84	19%	6%
Forde et al.	IB-IIIA	Nivo	2	20	45%	5%

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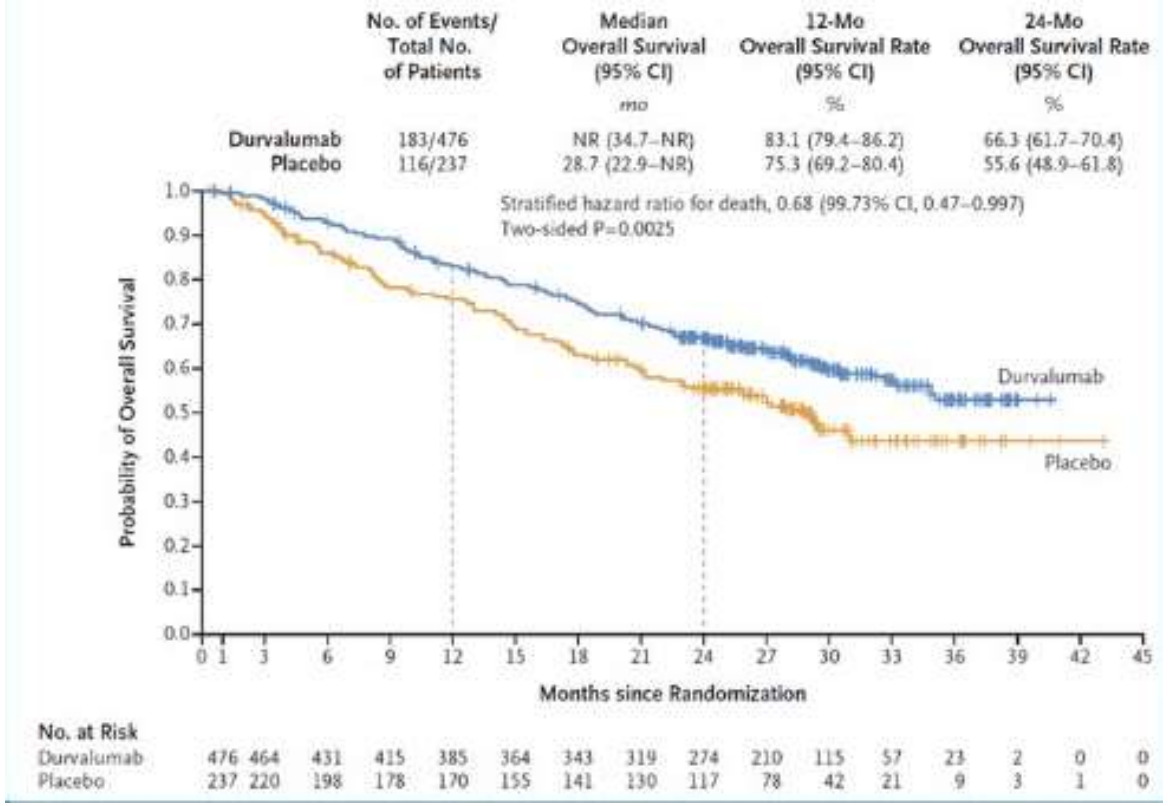
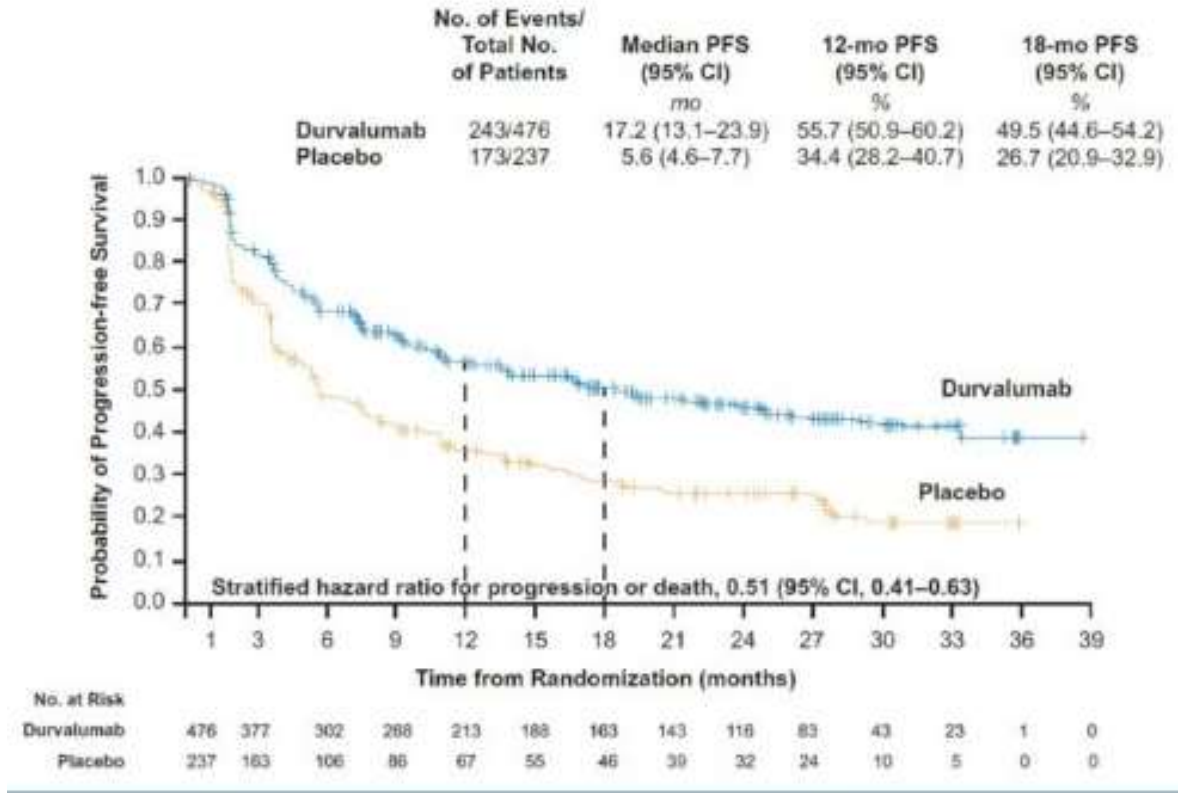
Durvalumab new standard of care in stage III NSCLC

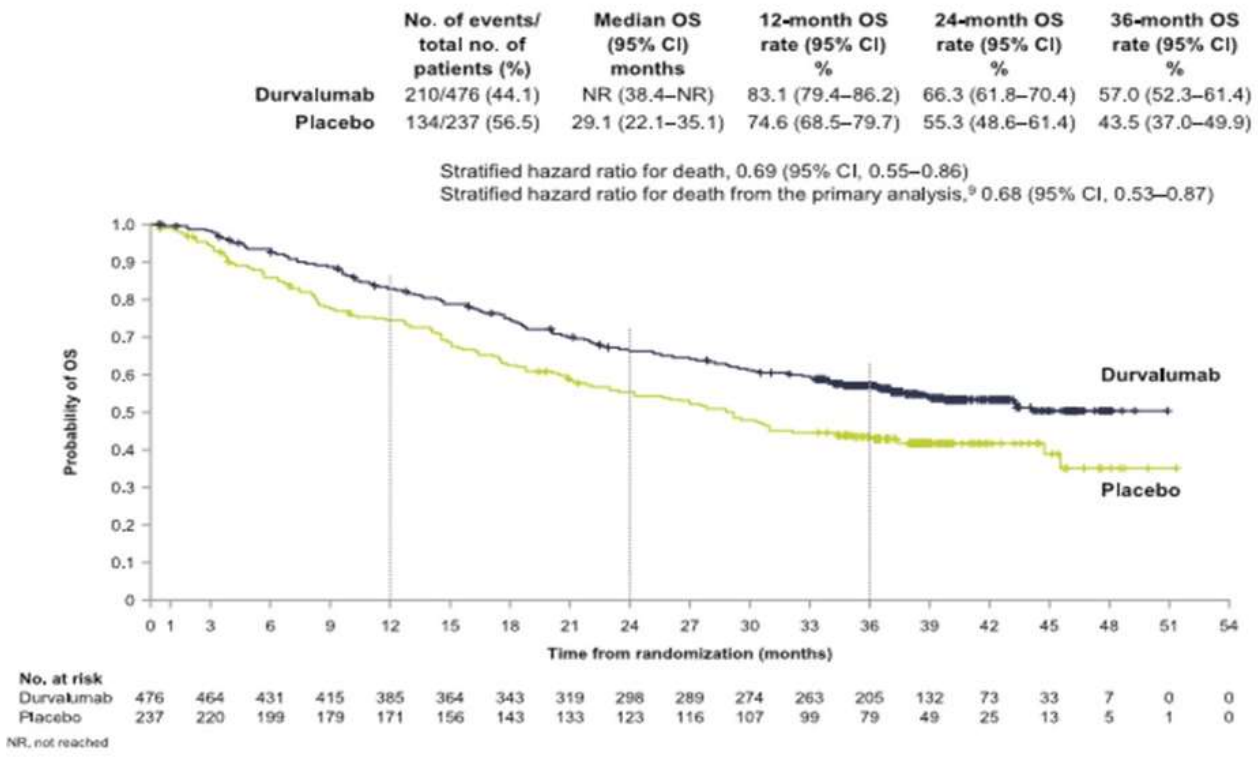




Consolidation IO after CRT significantly improves RFS and OS

Antonia NEJM 2018

PACIFIC: 3 year OS update



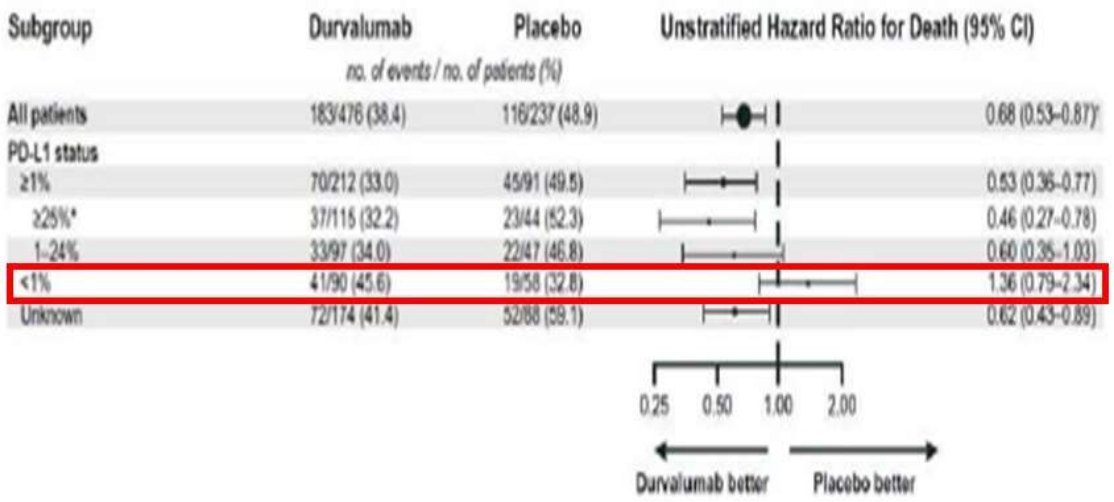
HR: 0.69 (vs 0.68 primary analysis)
31% reduction of death risk

OS rate	Durvalumab	Placebo	Delta
12-month	83.1%	74.6%	8.5%
24-month	66.3%	55.3%	11%
36-month	57%	43.5%	13.5%

Presented by E. Gray at ASCO 2019

PACIFIC: PD-L1 expression and OS

Primary exploratory analysis



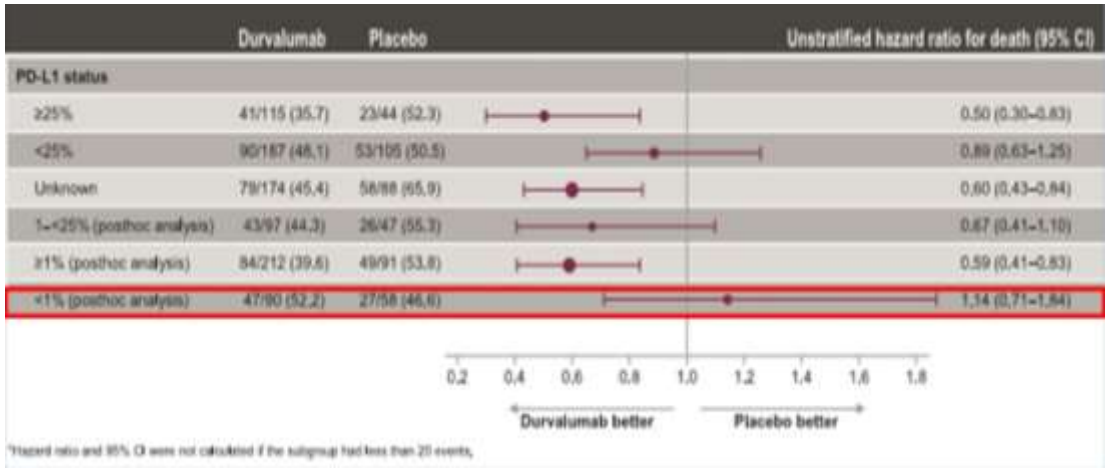
Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Death (95% CI)
	no. of events / no. of patients (%)		
All patients	183/476 (38.4)	116/237 (48.9)	0.68 (0.53–0.87)*
PD-L1 status			
≥1%	70/212 (33.0)	45/91 (49.5)	0.53 (0.36–0.77)
≥25%*	37/115 (32.2)	23/44 (52.3)	0.46 (0.27–0.78)
1–24%	33/97 (34.0)	22/47 (46.8)	0.60 (0.35–1.03)
<1%	41/90 (45.6)	19/58 (32.8)	1.36 (0.79–2.34)
Unknown	72/174 (41.4)	52/88 (59.1)	0.62 (0.43–0.89)

0.25 0.50 1.00 2.00

Durvalumab better | Placebo better

OS HR: 1.36 in PD-L1 <1%

Updated analysis at 3 years



	Durvalumab	Placebo	Unstratified hazard ratio for death (95% CI)
PD-L1 status			
≥25%	41/115 (35.7)	23/44 (52.3)	0.50 (0.30–0.83)
<25%	90/187 (48.1)	53/105 (50.5)	0.89 (0.63–1.25)
Unknown	79/174 (45.4)	58/88 (65.9)	0.60 (0.43–0.84)
1–<25% (posthoc analysis)	43/97 (44.3)	26/47 (55.3)	0.67 (0.41–1.10)
≥1% (posthoc analysis)	84/212 (39.6)	49/91 (53.8)	0.59 (0.41–0.83)
<1% (posthoc analysis)	47/90 (52.2)	27/58 (46.6)	1.14 (0.71–1.84)

0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8

Durvalumab better | Placebo better

*Hazard ratio and 95% CI were not calculated if the subgroup had less than 20 events.

OS HR: 1.14 in PD-L1 <1%

Presented by E. Gray at ASCO 2019

#8530

Alteration in tumor immune microenvironment after chemo-radiotherapy for locally advanced NSCLC

ASCO Annual Meeting (June 2, 2019)

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1) Second Department of Surgery (Chest Surgery), 2) Department of Respiratory Medicine, 3) Department of Radiology, 4) Department of Pathology and Oncology, 5) Department of Pathology, University of Occupational and Environmental Health (UOEH), Kitakyushu, Japan

ABSTRACT

Background: The consolidation treatment with durvalumab, an anti-PD-L1 antibody, after concurrent chemo-radiotherapy (cCRT) has become a new standard of care for locally advanced non-small cell lung cancer (LA-NSCLC). The rationale of the addition of anti-PD-L1 antibody is based on evidence suggesting that chemotherapy and radiotherapy may up-regulate PD-L1 expression on tumor cells. However, there has been reported clinical evidence showing up-regulation of PD-L1 expression after cCRT.

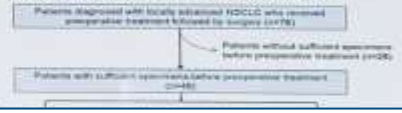
Methods: LA-NSCLC patients with paired histologic specimens for immuno-histochemical analysis of tumoral PD-L1 expression (tumor proportion score, TPS) and stromal CD8+ tumor-infiltrating lymphocyte (CD8+TIL) density before and after pre-operative treatment were included in this study. Twenty-three patients who underwent cCRT were reviewed in comparison with 11 patients who underwent chemotherapy.

Results: PD-L1 expression was significantly enhanced after cCRT (median TPS, 48 from 0; P<0.01), but not after chemotherapy (median, 7.5 from 1; P=0.62). No significant correlation between baseline TPS and TPS after cCRT (P=0.119). Stromal CD8+TIL density was significantly increased after cCRT (median, 39 from 11; P<0.01) but not after chemotherapy (median, 23 from 12; P=0.003). No significant correlation between baseline TPS and TPS after cCRT (P=0.378). Among cCRT cases, stromal CD8+TIL density after treatment was significantly higher in cases with higher pathologic response to cCRT (median, 55 versus 27; P<0.01), and higher stromal CD8+TIL density was a significant factor to predict a favorable survival after surgery (P=0.03 for recurrence-free survival; P=0.02 for overall survival).

Conclusions: PD-L1 expression was significantly upregulated after cCRT regardless of baseline PD-L1 status, which may provide a pathologic rationale for the use of anti-PD-L1 agent after cCRT to improve the prognosis. Stromal CD8+TIL density also increased after cCRT, which was correlated with pathologic response to cCRT and provided a significant prognostic impact.

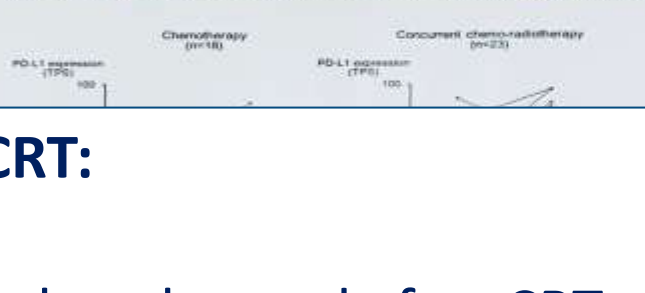
Patients

·Flow diagram of patients enrolled in the study

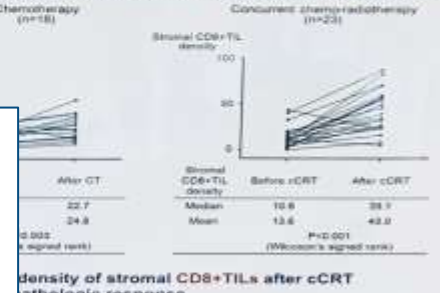


Alterations in PD-L1 expression on tumor cells and stromal CD8+TIL density

·Alteration in PD-L1 expression on tumor cells after chemotherapy or cCRT



·Alteration in density of stromal CD8+TILs after chemotherapy or cCRT

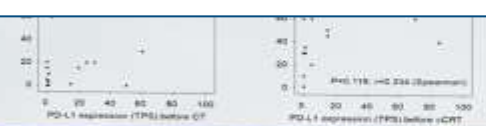


Results from 23 pts receiving CRT:

PD-L1 expression was significantly enhanced after CRT

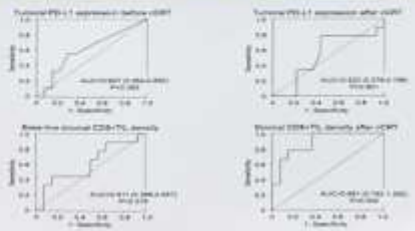
No correlation between baseline PD-L1 and PD-L1 after CRT

Stromal CD8+ TIL density was significantly increased after CRT and correlated to pathological response



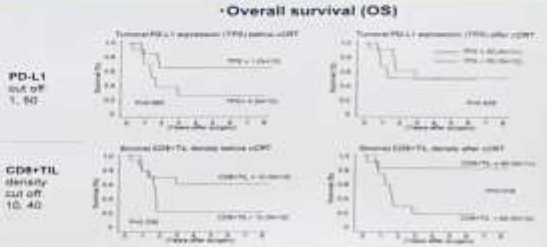
Prognosis according to PD-L1 expression on tumor cells or stromal CD8+TIL density before and after cCRT

·ROC curve for PD-L1 expression on tumor cells or density of stromal CD8+TILs to predict death or recurrence after surgery following cCRT

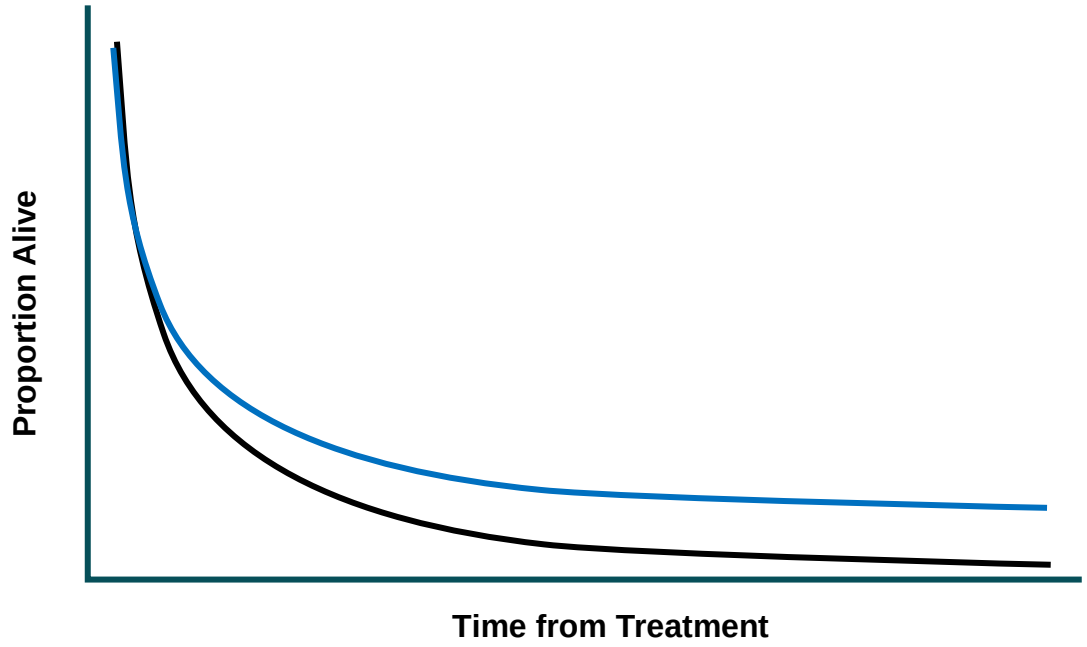


·Recurrence-free survival (RFS)

·Overall survival (OS)



Long-term Survival in advanced NSCLC
The IO Revolution



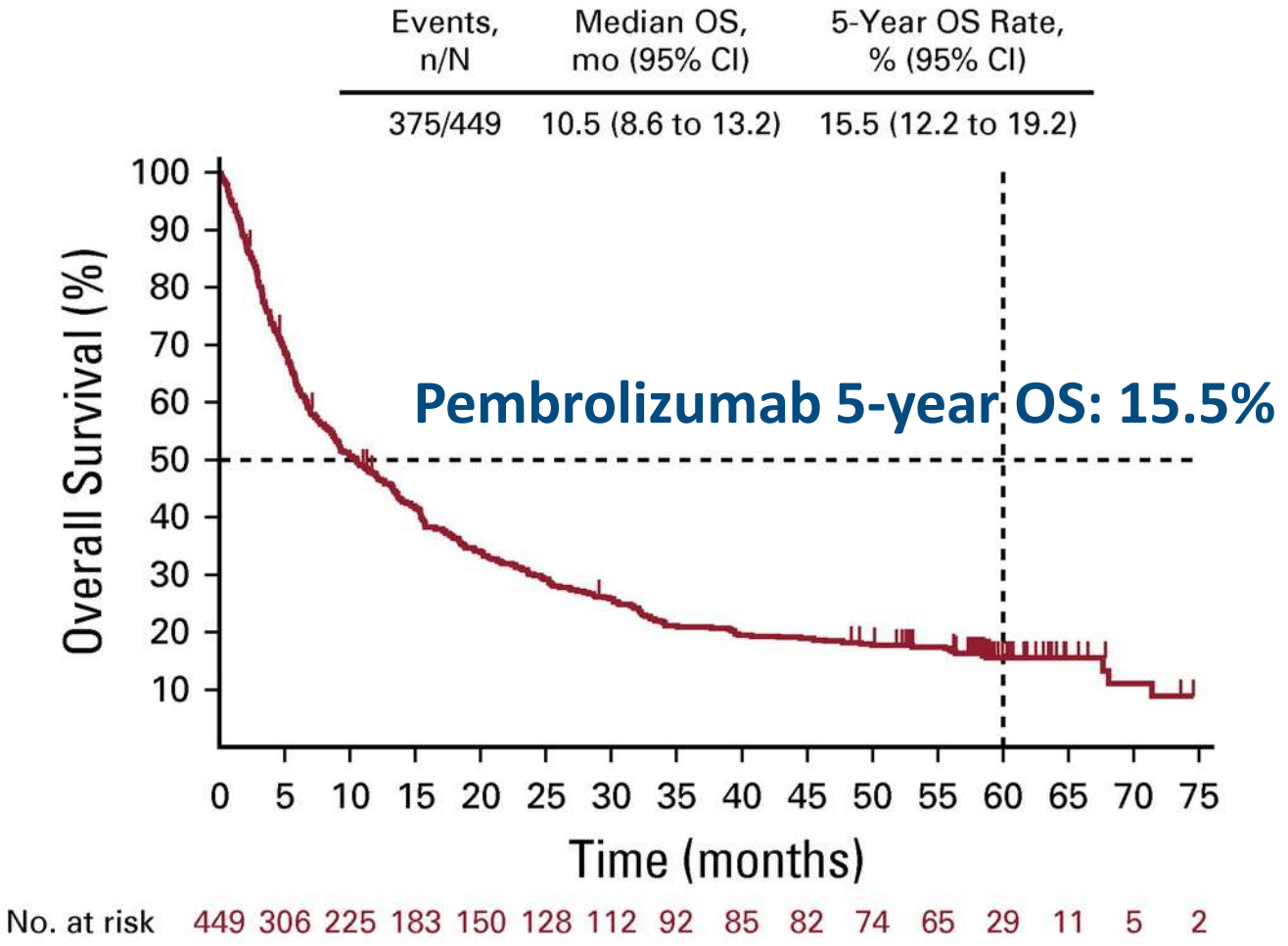
Long-term Survival

IO (pre-treated pts): 5-year OS: 16%

Chemotherapy: 5-year OS: 5.5%

Noone, SEER Cancer Statistics Review, 1975-2015. National Cancer Institute, 2018 GettInger JCO 2018

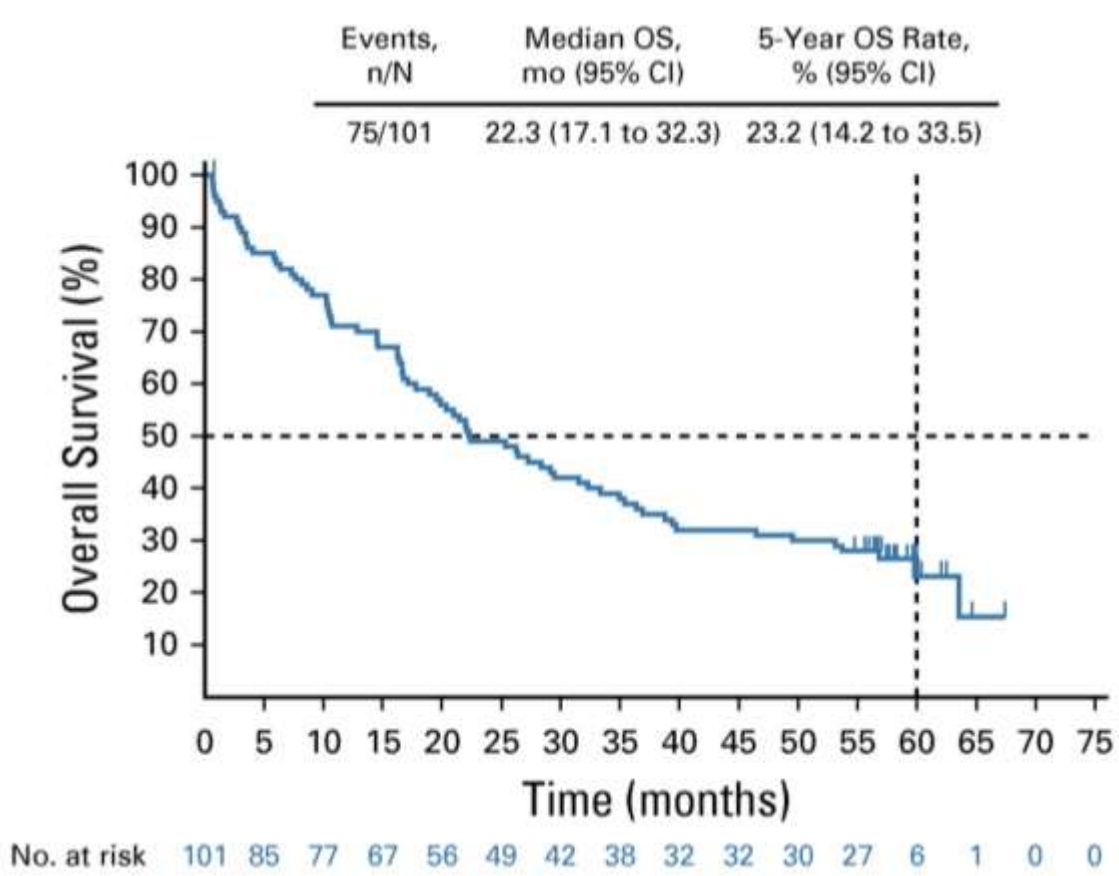
KEYNOTE-001
5-year OS in pre-treated patients



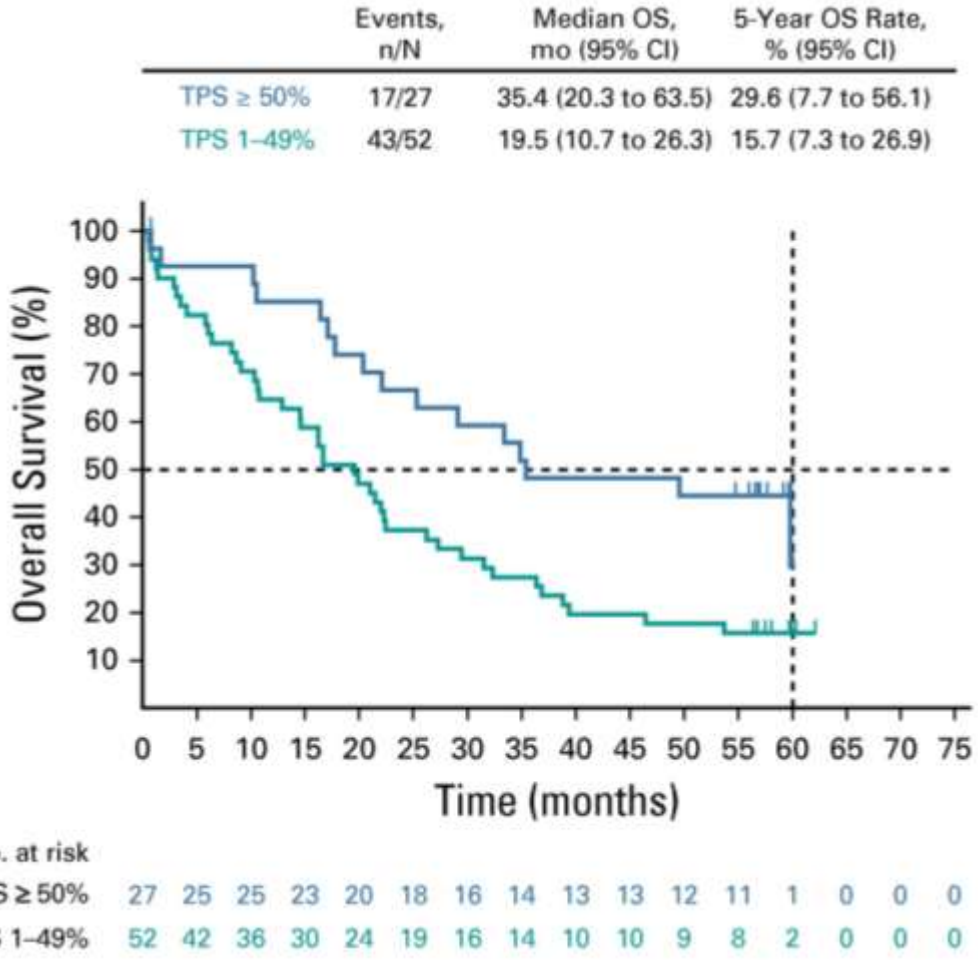
Pembrolizumab 5-year OS: 15.5%

Gainor, ASCO 2019, Gainor, JCO 2019

KEYNOTE 001
5-year OS in naive patients



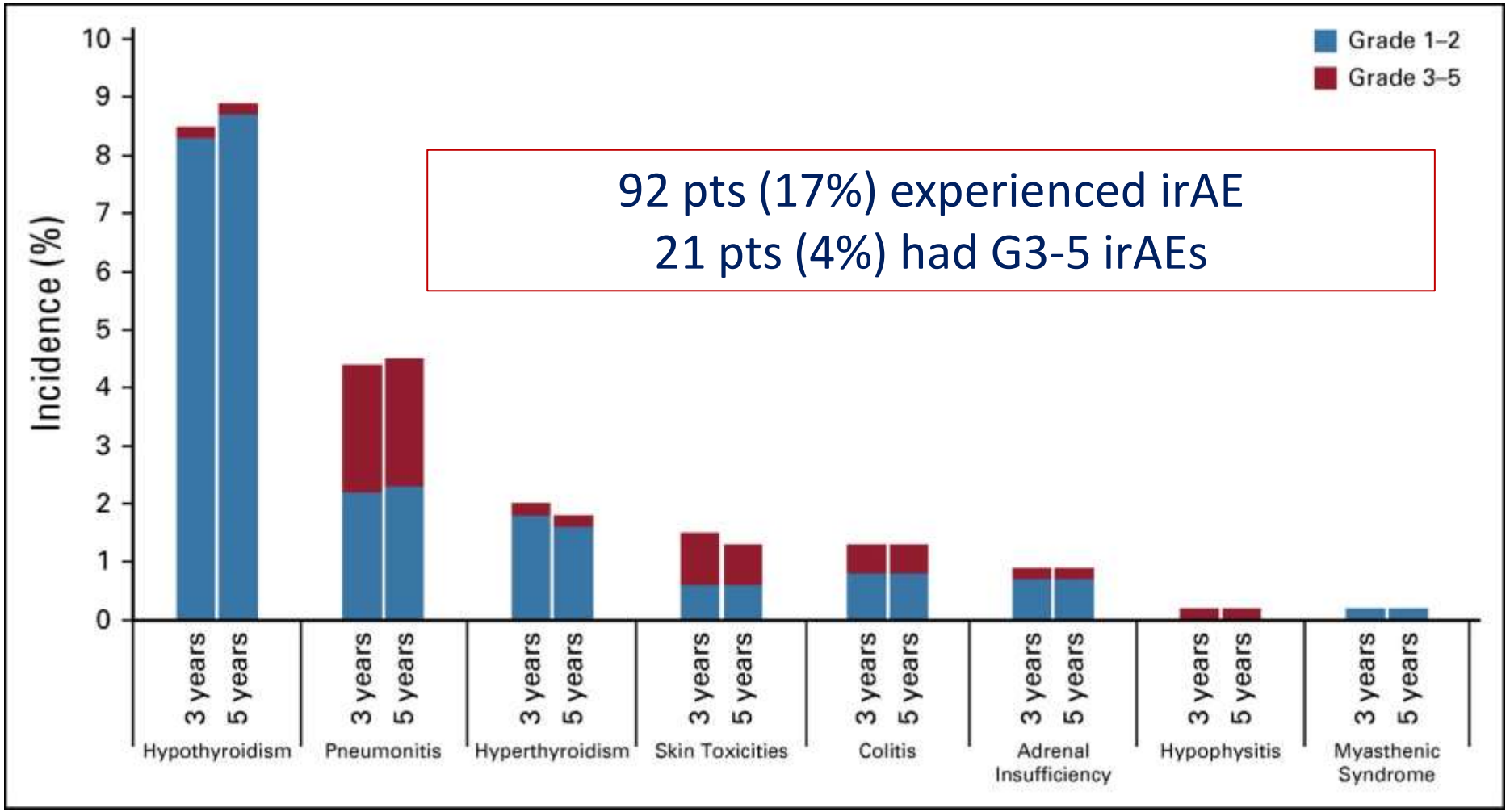
Pembrolizumab 5-year OS: 23%



Pembrolizumab 5-year OS: 29% (PD-L1>50%)

Gainor, ASCO 2019, Gainor, JCO 2019

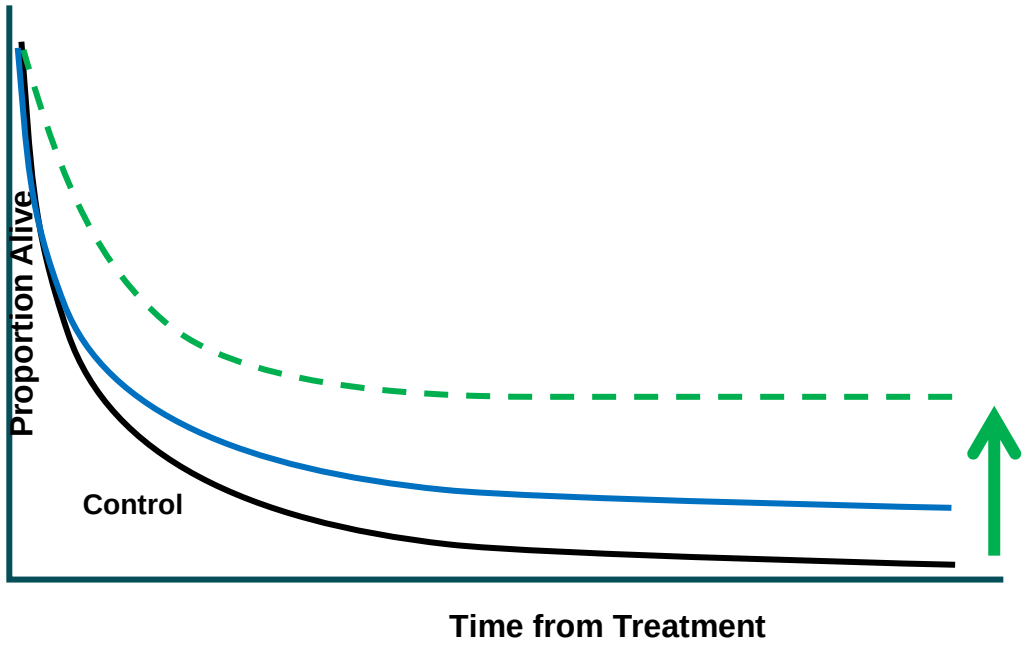
KEYNOTE-001
Long-term Tolerability



92 pts (17%) experienced irAE
21 pts (4%) had G3-5 irAEs

Garon, ASCO 2019, Garon, JCO 2019

Long-term survival in advanced NSCLC
The IO Revolution



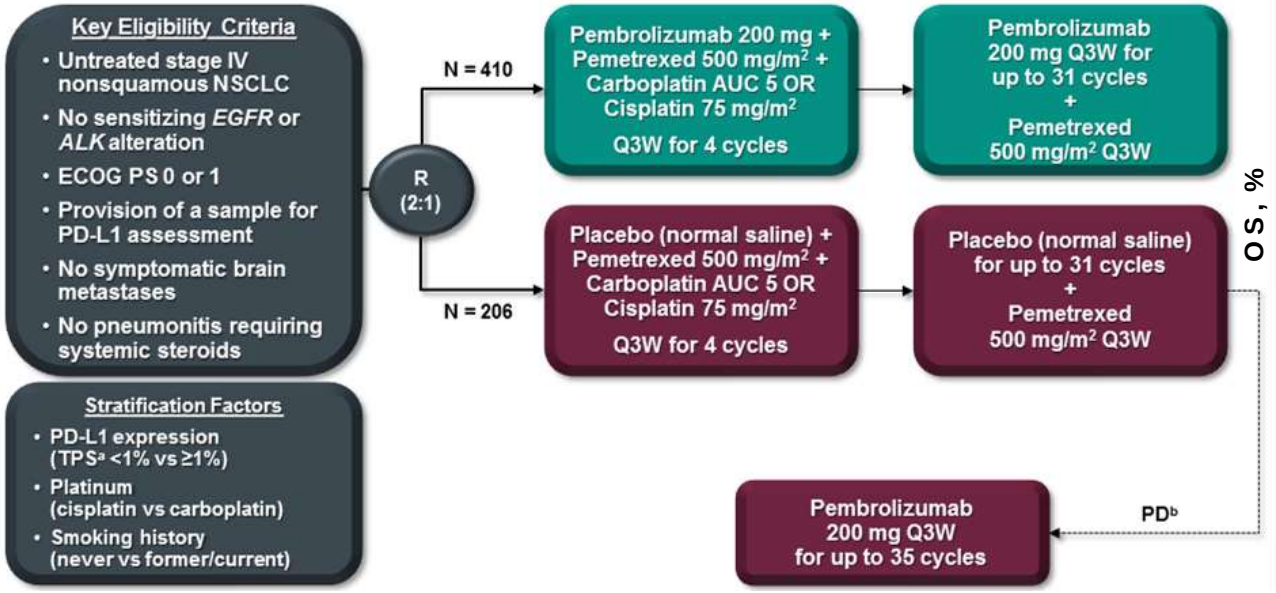
Long-term survival

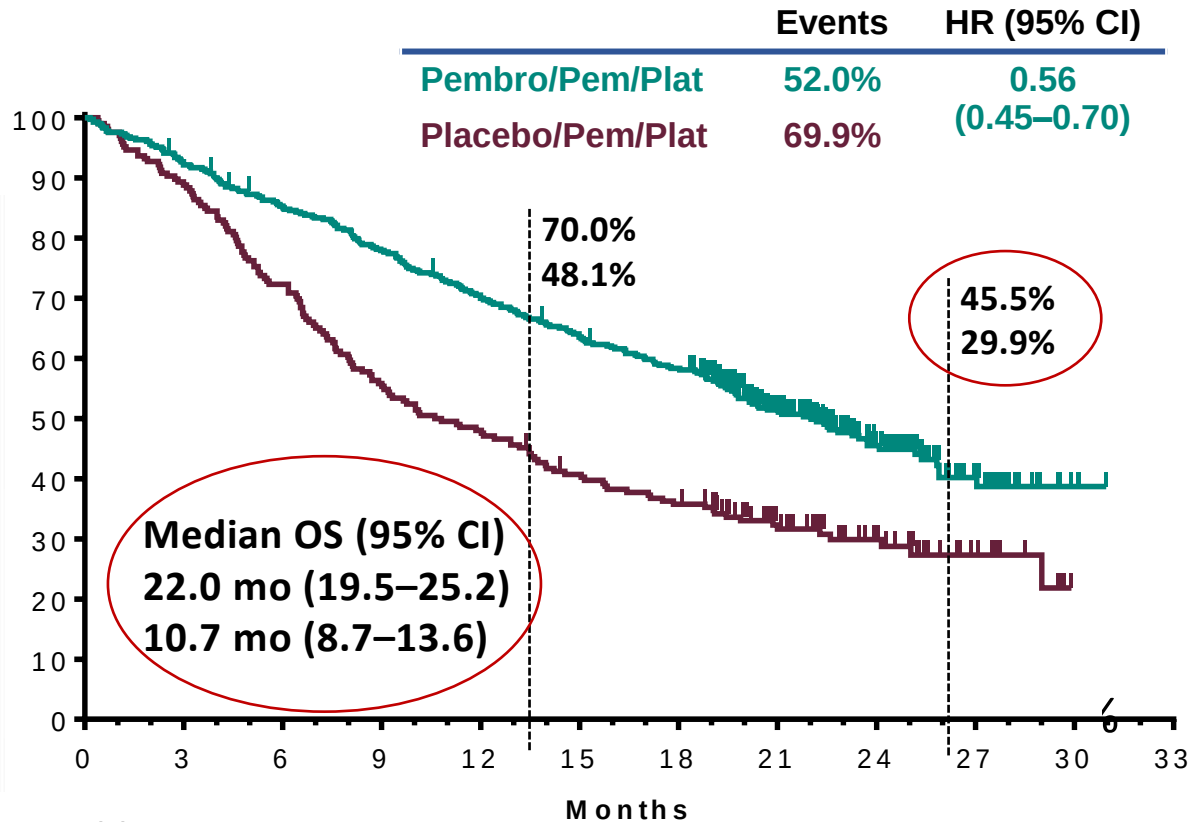
IO (Naïve PD-L1>50%): 5-year OS: 29% ?
IO (Naive): 5-year OS: 23%

IO (pre-treated pts): 5-year OS: 16%

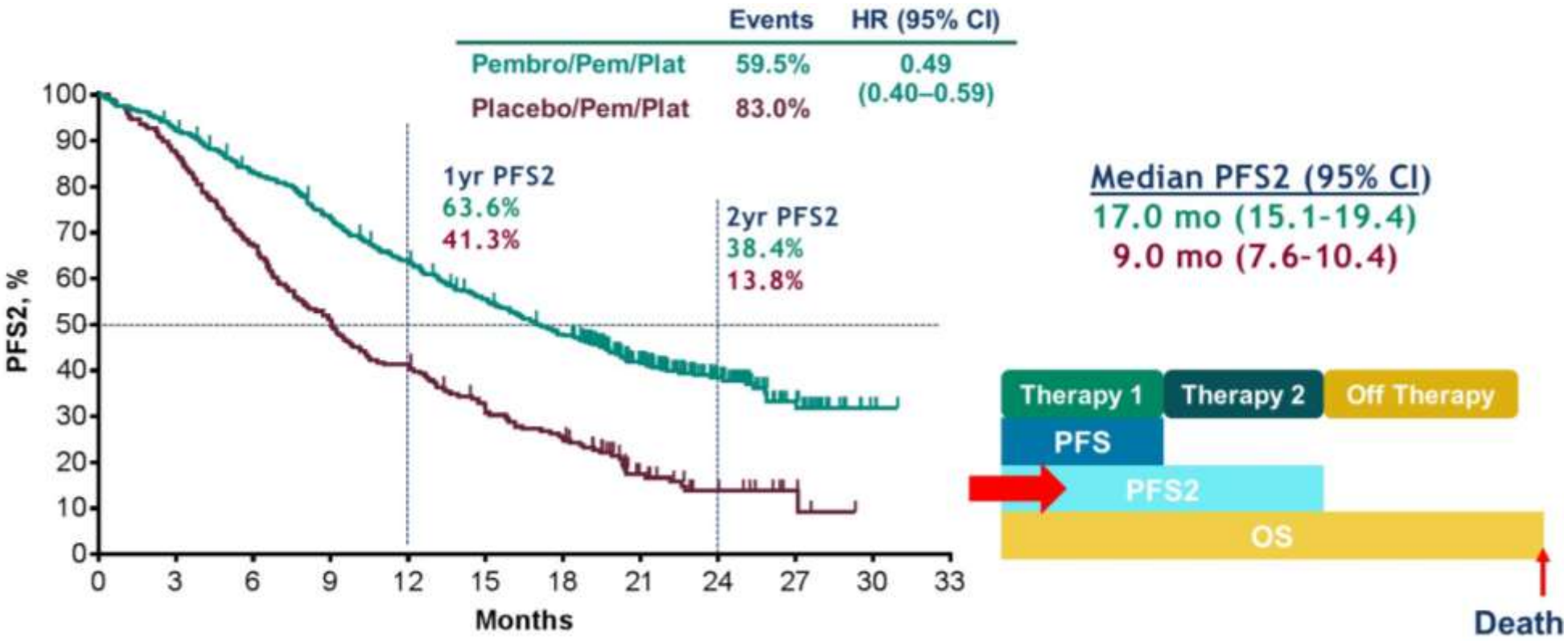
Chemotherapy: 5-year OS: 5.5%

KEYNOTE-189
Updated OS in the ITT population





KEYNOTE-189
Progression after second-line (PFS2)



Gadgeel, ASCO 2019

KEYNOTE-189
Subsequent Therapies

Participants, n (%)	Pembro/Pem/Platinum (N = 410)	Placebo/Pem/Platinum (N = 206)
Remaining on ≥1 component of allocated study therapy	58 (14.1)	7 (3.4)
Discontinued all components of allocated study therapy	352 (85.9)	199 (96.6)
Alive, no subsequent therapy	58 (14.1)	8 (3.9)
Without PD	36 (8.8)	4 (1.9)
Died without subsequent therapy	111 (27.1)	69 (33.5)
≥1 subsequent therapy	183 (44.6)	122 (59.2)
≥1 subsequent immunotherapy	55 (13.4)	111 (53.9)

Gadgeel, ASCO 2019

KEYNOTE-189
Subsequent Therapies by PD-L1 TPS

Participants, n (%)	TPS ≥50%		TPS 1-49%		TPS <1%	
	Pembro Arm (n = 132)	Placebo Arm (n = 70)	Pembro Arm (n = 128)	Placebo Arm (n = 58)	Pembro Arm (n = 127)	Placebo Arm (n = 63)
Remaining on ≥1 component of allocated study therapy	28 (21.2)	4 (5.7)	17 (13.3)	2 (3.4)	11 (8.7)	1 (1.6)
Discontinued all components of allocated study therapy	104 (78.8)	66 (94.3)	111 (86.7)	56 (96.6)	116 (91.3)	62 (98.4)
Alive, no subsequent therapy	26 (19.7)	2 (2.9)	16 (12.5)	3 (5.2)	12 (9.4)	3 (4.8)
Died without subsequent therapy	35 (26.5)	22 (31.4)	33 (25.8)	14 (24.1)	39 (30.7)	24 (38.1)
≥1 subsequent therapy	43 (32.6)	42 (60.0)	62 (48.4)	39 (67.2)	65 (51.2)	35 (55.6)
≥1 subsequent immunotherapy	11 (8.3)	37 (52.9)	21 (16.4)	34 (58.6)	15 (11.8)	34 (54.0)

Gadgeel, ASCO 2019

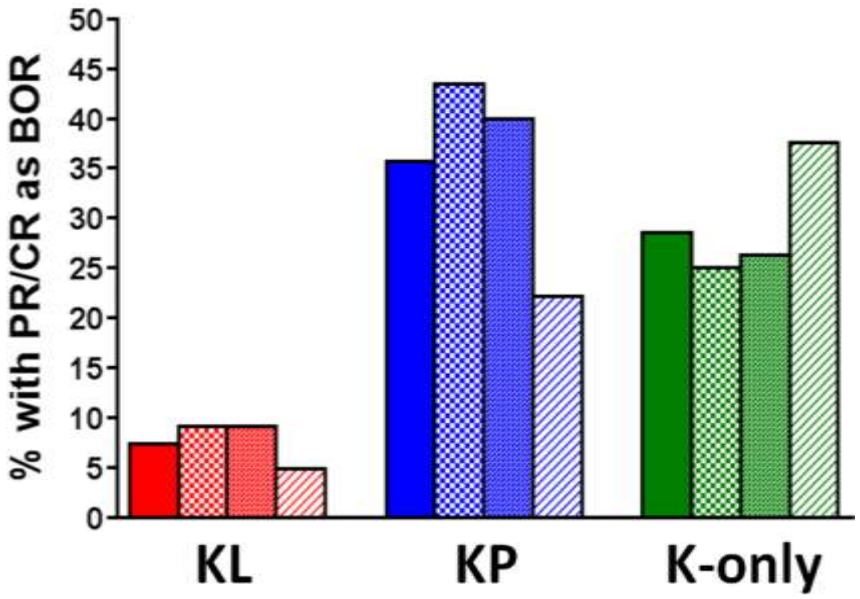
Unanswered Question

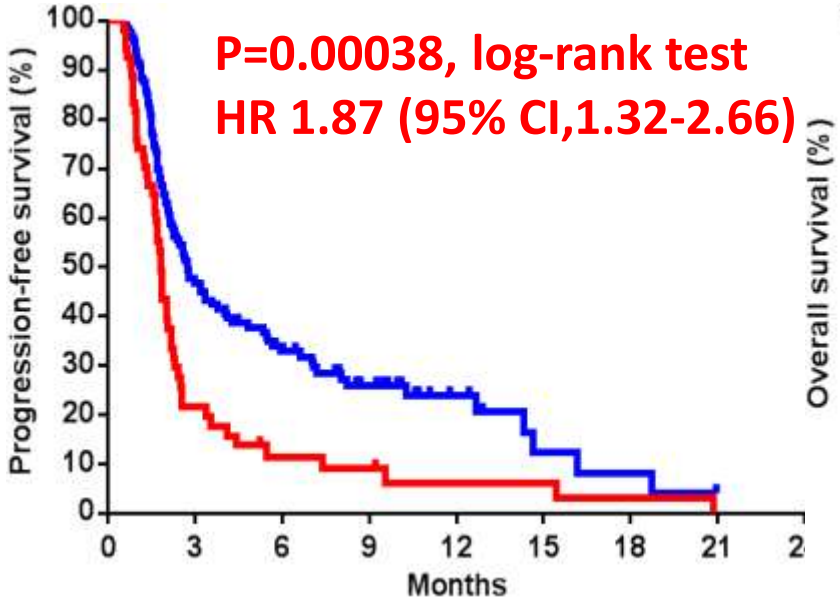
How identifying 1/3 of naive NSCLC patients who do not receive survival benefit from the addition of Pembrolizumab to Platinum Chemotherapy

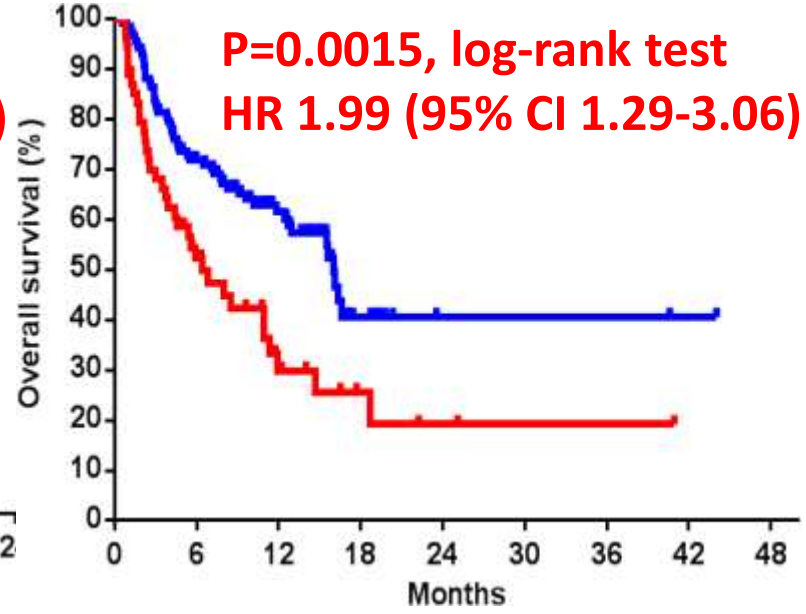
???

IO Biomarkers (beyond PD-L1) needed

STK11 mutations and PD-1 monotherapy resistance in NSCLC





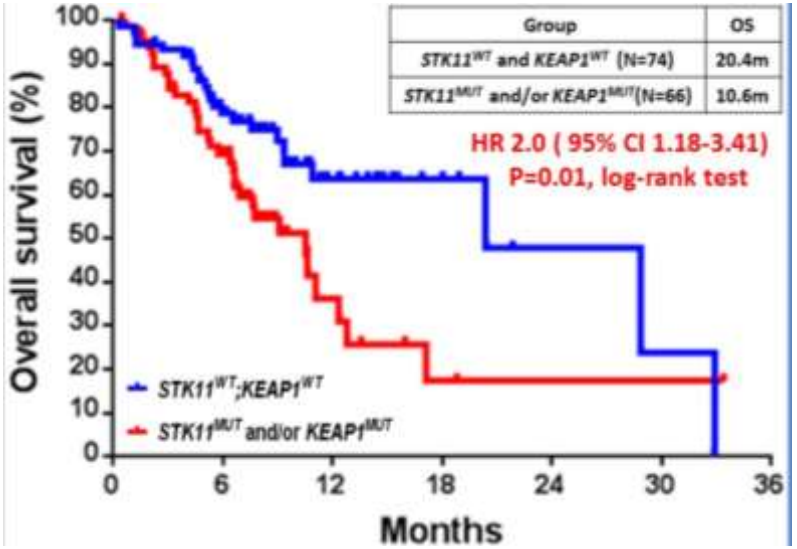


STK11 alterations are enrichied in TMB low/PD-L1 negative tumors associated with a cold TME (TILs low/ MDSC high)

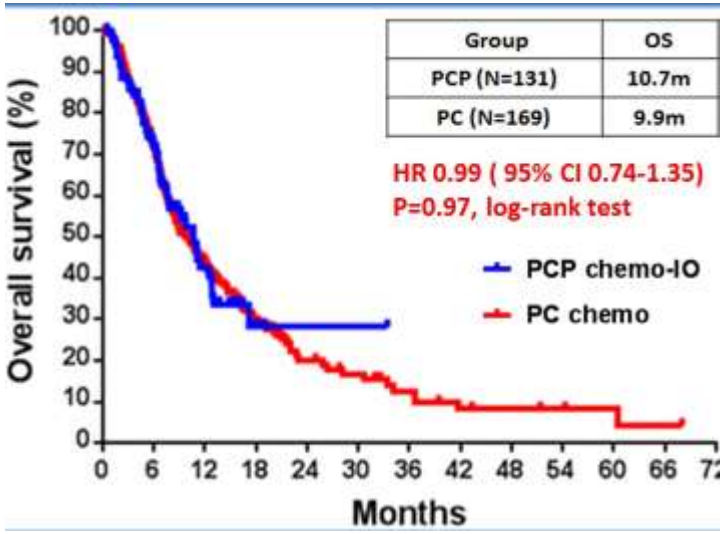
Skoulidis, Cancer Discovery 2018

Are STK11/KEAP1 alterations associated to IO+CT resistance in NSCLC ?

IO+CT in STK11 and/or KEAP MUT vs WT



IO+CT vs CT in STK11 and/or KEAP MUT



STK11/KEAP MUT identify a group of non-sq NSCLC pts with poor OS

Lack of OS benefit from addition of IO to CT in STK11/KEAP MUT NSCLC

STK11/KEAP1 MUT is a potential biomarker of IO primary resistance in advanced non-squamous NSCLC

Skoulidis, ASCO 2019

ASCO 2019 - Poster Review
Key messages

- **Early Disease**

1. Strong rationale and promising data for Neoadjuvant IO (+ CT ?)

- **Locally Advanced Disease**

1. Consolidative Durvalumab SOC in stage III NSCLC
2. All eligible pts should receive concurrent CRT starting Durvalumab < 14 days

- **Advanced Disease**

1. IO 5-year OS constitutes a milestone in lung cancer treatment
2. IO+CT SOC in naïve pts with PD-L1<50%
3. IO and IO+CT effective options in naive pts with PD-L1 >50%

- **IO Biomarkers**

1. STK11/KEAP1 MUT biomarker of primary resistance to IO and IO+CT