ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

Luis E. Raez MD FACP FCCP
Vice-President Florida Society Clinical Oncology (FLASCO)
Chief of Hematology/Oncology &
Medical Director
Memorial Cancer Institute
Clinical Professor of Medicine
Florida International University

AMERICAN ACADEMY OF EMERGENCY MEDICINE

ACCC
Association of Community Cancer Centers

sitc
Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Disclosures

- **Research Support:**

• Genentech/Roche	Pfizer
• MSD	NantOmics
• BMS	Lilly Oncology
• Boheringer Ingelheim	Novartis
• Astra-Zeneca	

- **Speakers Bureau/Stocks:** None

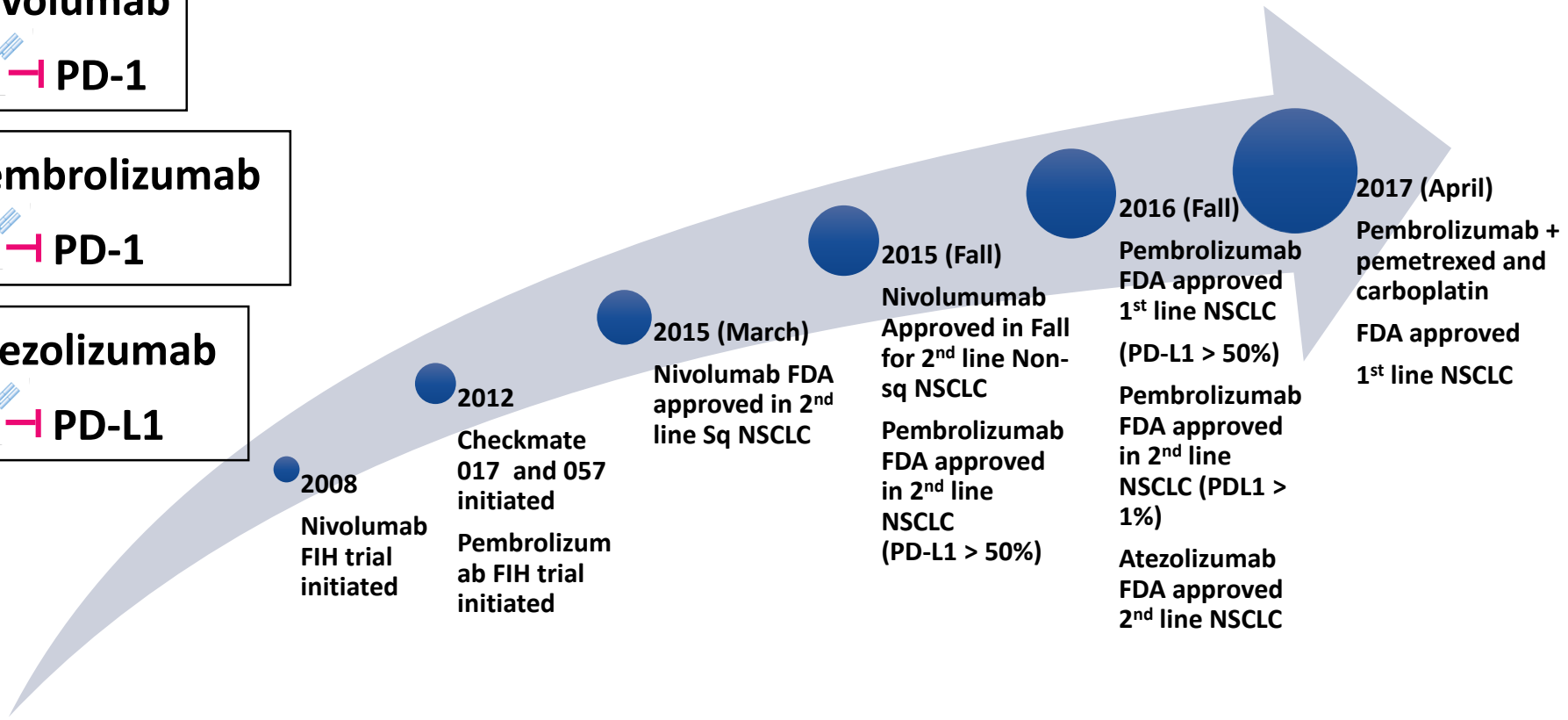
ADVANCES IN Cancer IMMUNOTHERAPY™

Immune checkpoint inhibitors in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

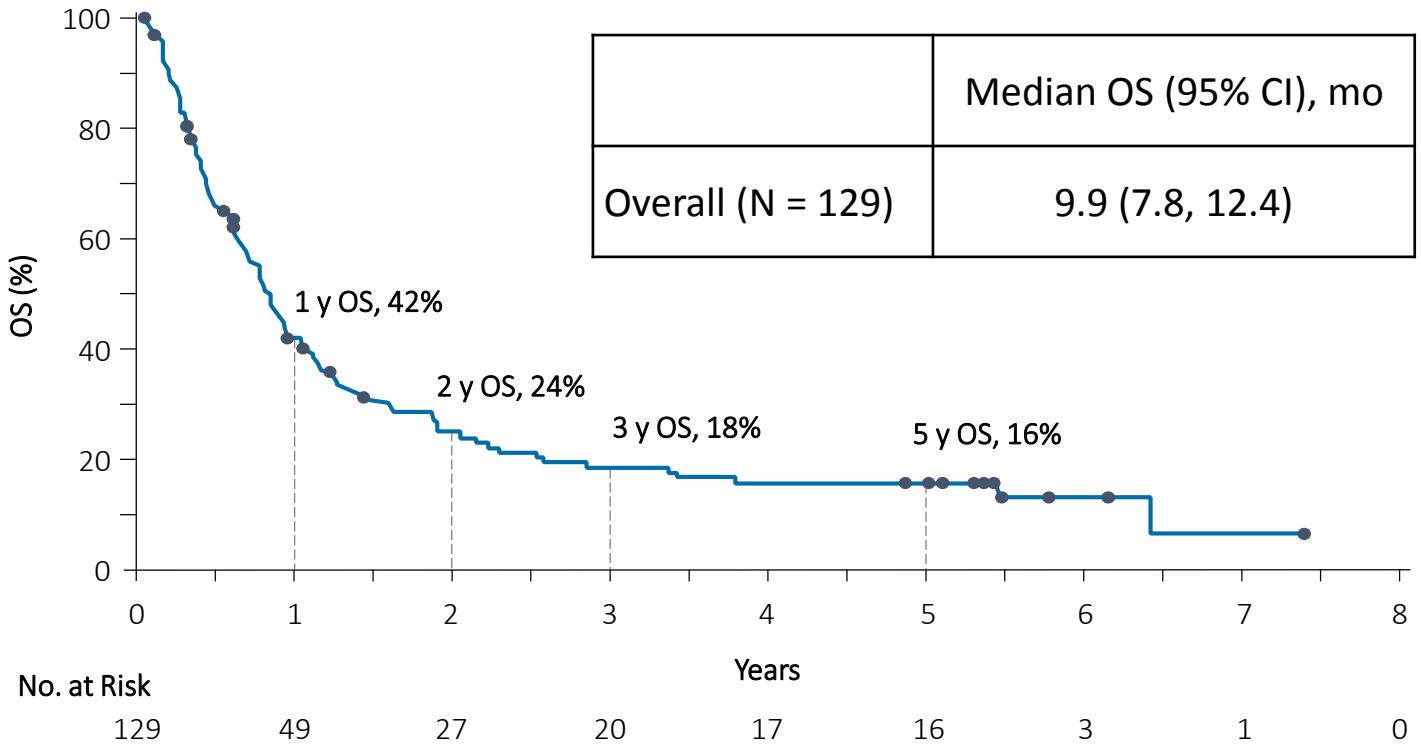
Atezolizumab
PD-L1



ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

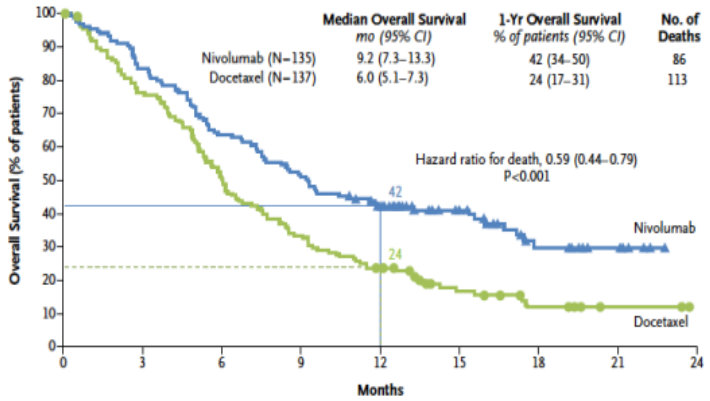


	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

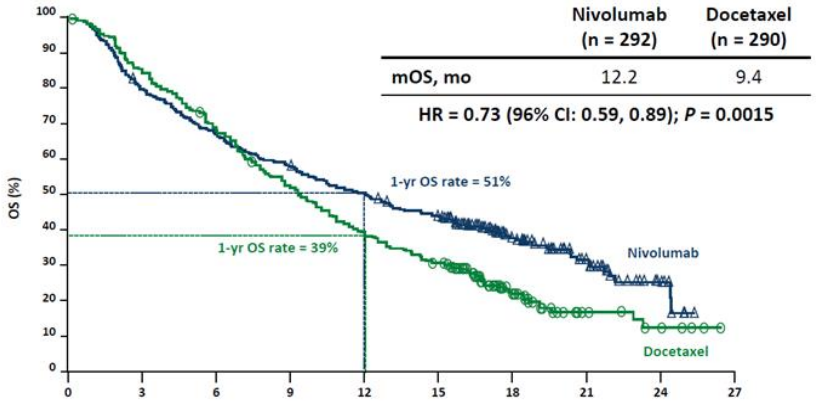
Brahmer et al, AACR 2017

PD1/PD-L1 Inhibitors increase *Overall Survival* in 2L Advanced NSCLC

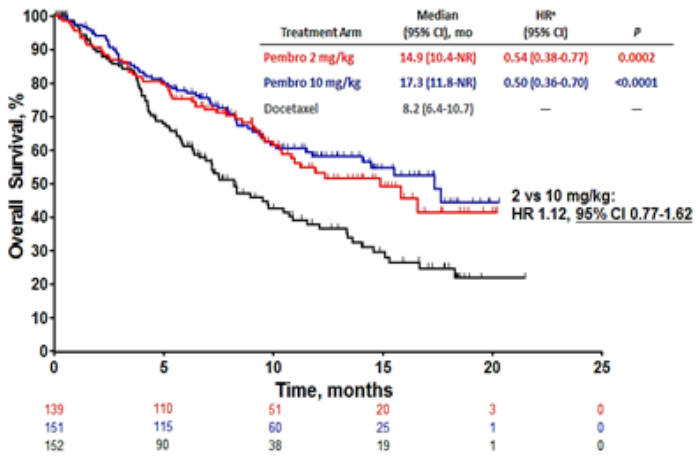
CHECKMATE 017



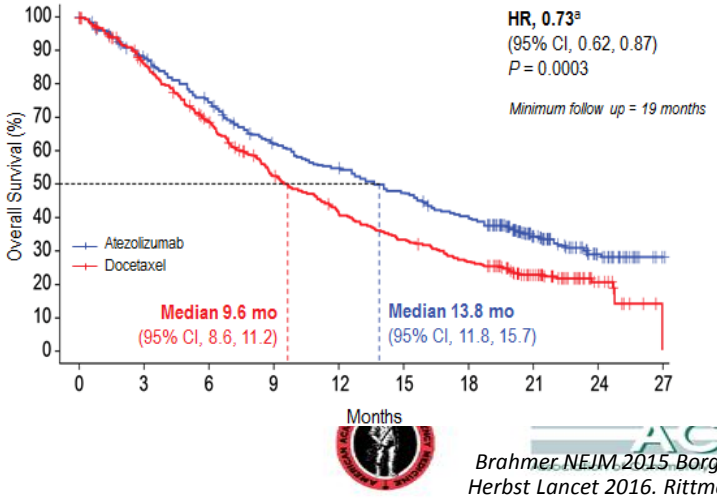
CHECKMATE 057



KEYNOTE 010 (TPS ≥ 1%)

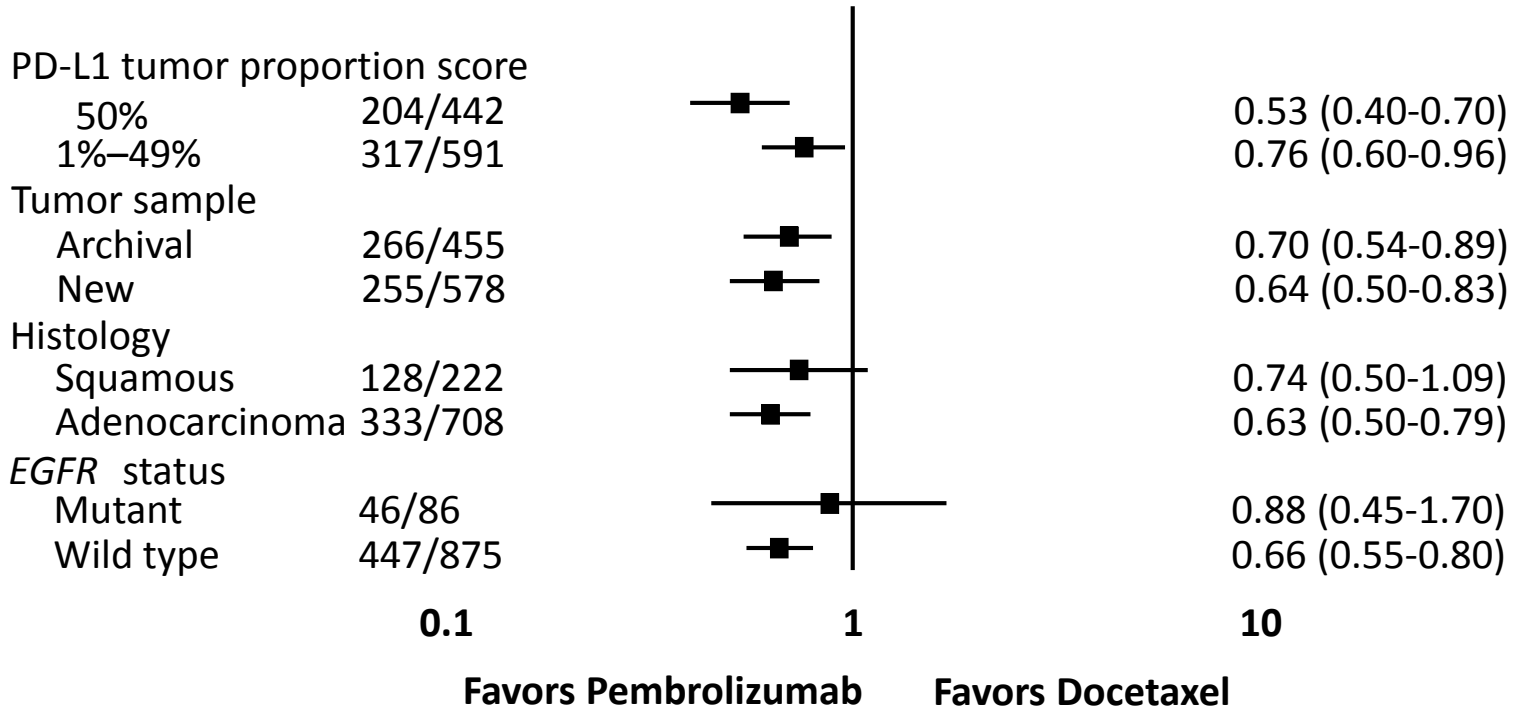


OAK



Brahmer NEJM 2015 Borghaei, NEJM 2015
Herbst Lancet 2016. Rittmeyer Lancet 2017

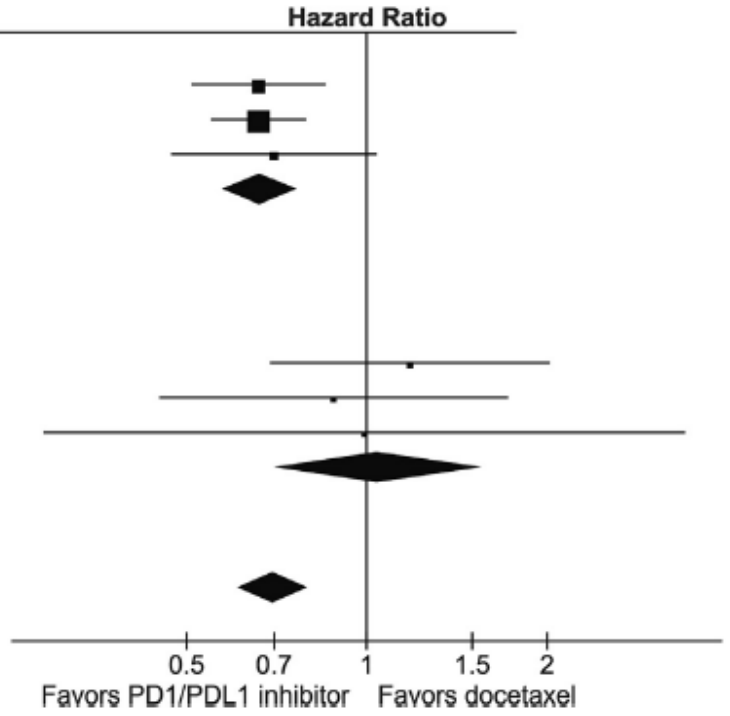
KEYNOTE 010: Pembrolizumab approval > 2nd line (PD-L1 > 1%)



Herbst et al, Lancet 2015

EGFRm PD-(L)-1 meta-analysis

Study	Weight	Hazard Ratio [95% CI]
EGFR wild-type		
Checkmate 057	26.0%	0.66 [0.51, 0.86]
Keynote 010	52.0%	0.66 [0.55, 0.80]
POPLAR	11.0%	0.70 [0.47, 1.04]
Subtotal (95% CI)	**89.0%**	**0.66 [0.58, 0.76]**
EGFR mutant		
Checkmate 057	6.0%	1.18 [0.69, 2.00]
Keynote 010	3.8%	0.88 [0.45, 1.70]
POPLAR	1.1%	0.99 [0.29, 3.40]
Subtotal (95% CI)	**11.0%**	**1.05 [0.70, 1.55]**
Total (95% CI)	**100.0%**	**0.70 [0.61, 0.80]**



CK Lee et al., *JTO* 2016

ADVANCES IN Cancer IMMUNOTHERAPY™

Toxicities in 2/3L Randomized trials

	Atezolizumab OAK	Nivolumab SQ: CM 017 (updated OS; 2L)	Nivolumab NSQ:CM 057 (updated OS; 2/3L)	Keynote 010
Related Grade 3-5 AEs	15%	8%	11%	13-16%
Discontinuation due to related AEs	5%	6%	6%	4-5%
Pneumonitis AEs	1%	5%	3%	4-5%

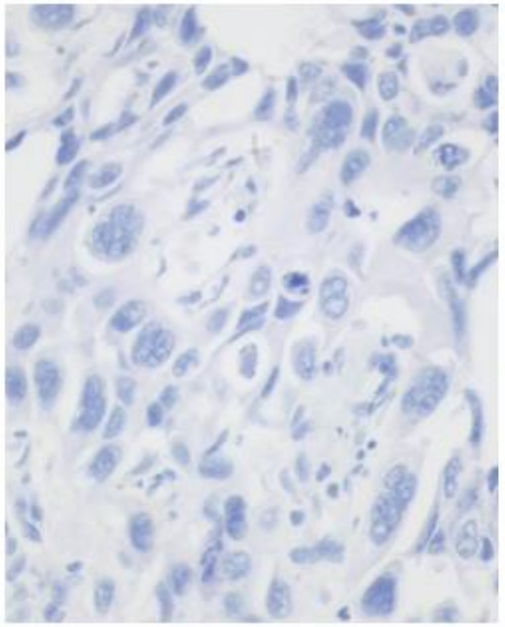
Rittmeyer, et al., *Lancet* 2017
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015
Herbst, et al., *Lancet* 2015

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

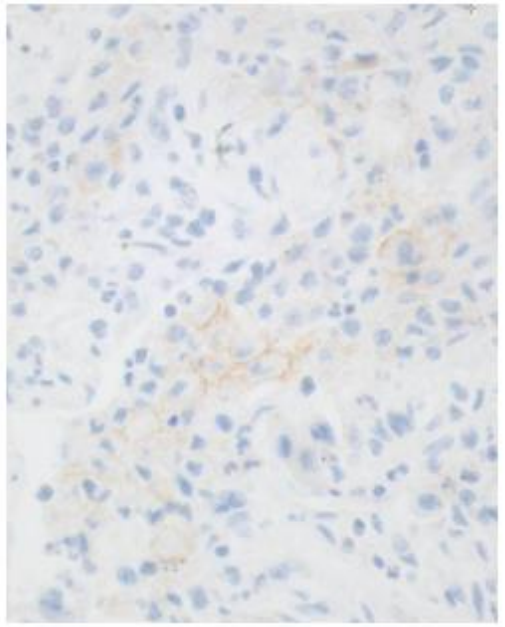
ADVANCES IN Cancer IMMUNOTHERAPY™

PD-L1 selection to bridge the gap?



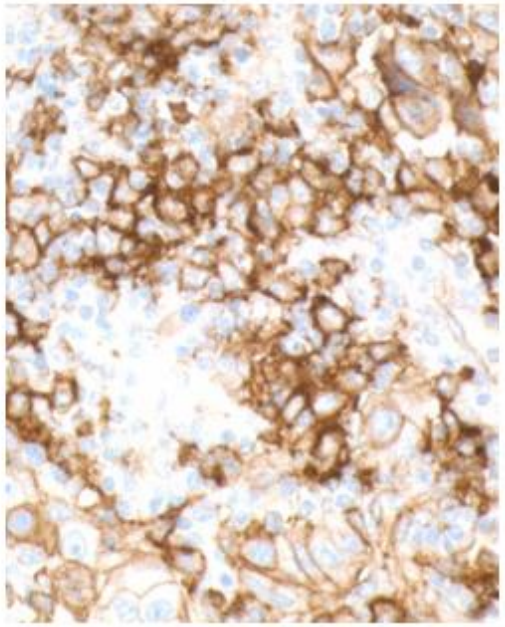
PD-L1 = 0% positive

Negative



PD-L1 = 2% positive

Weak Positive (1%-49%)



PD-L1 = 100% positive

Strong Positive (50%-100%)

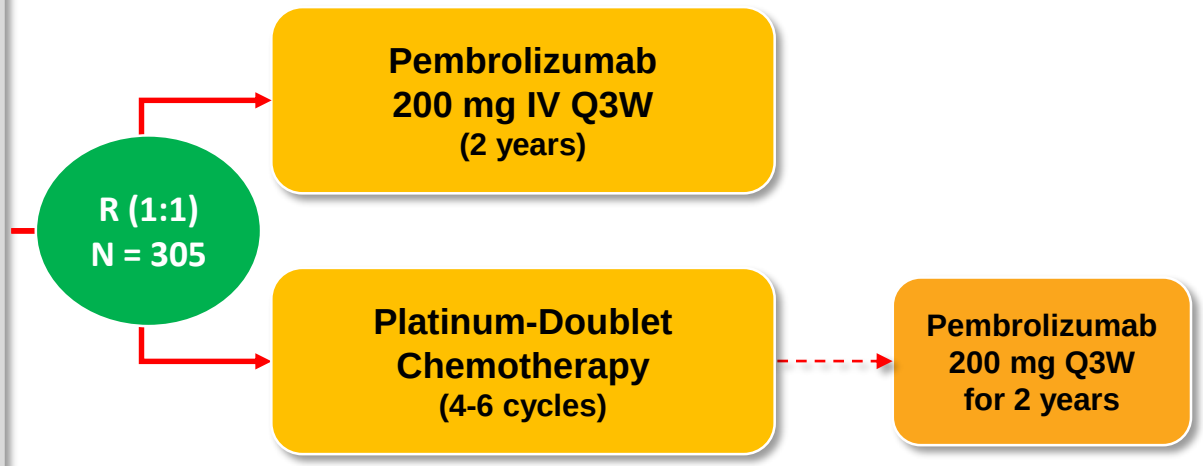
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

KEYNOTE-024 Study Design (NCT02142738)

Key Eligibility Criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy



[a]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.

Key End Points

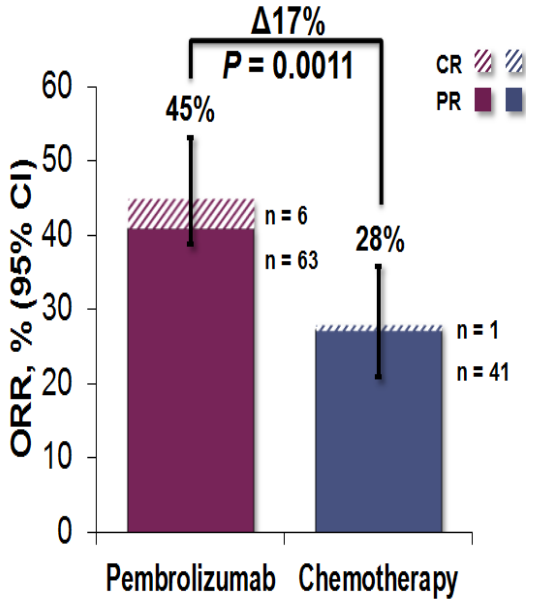
Primary: PFS (RECIST v1.1 per blinded, independent central review)

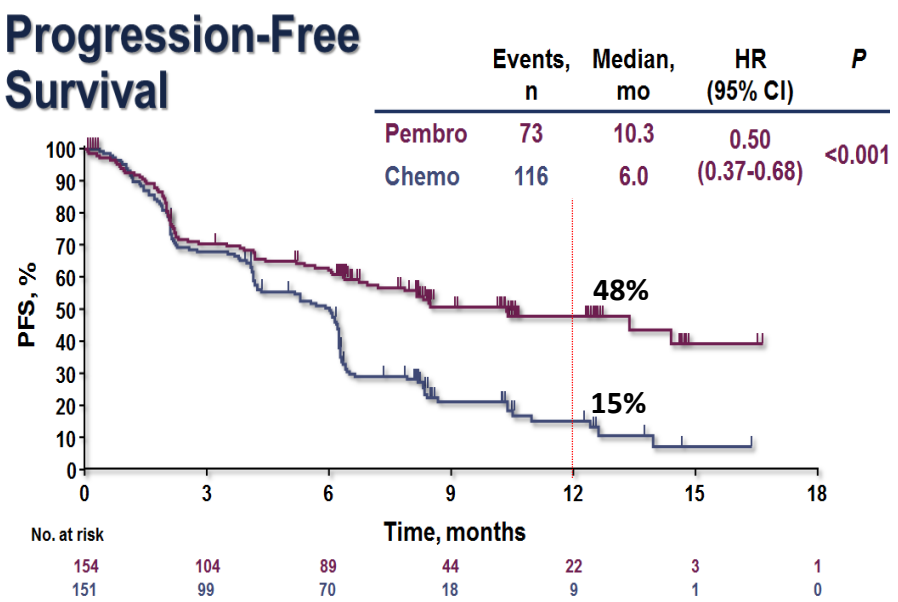
Secondary: OS, ORR, safety

Exploratory: DOR

Reck M et al, ESMO 2016, NEJM 2016

KEYNOTE-024 Efficacy





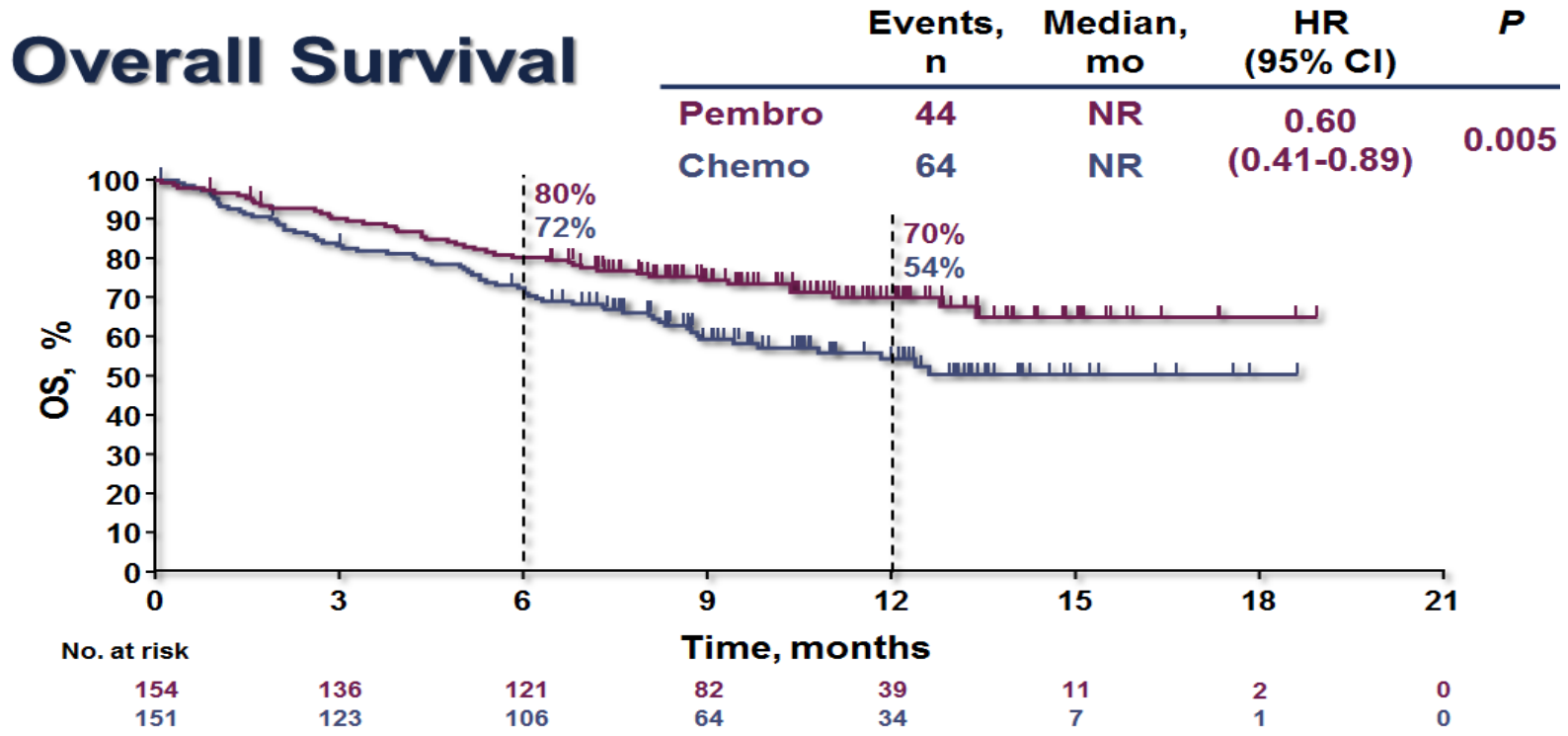
***Imaging every 9 weeks**

Clear and strong signal of activity

- ORR is improved, with a control arm that performs as expected (based on other phase III trials)
- 45% ORR is the one of best RRs ever reported in 1st line setting (and with monotherapy!)
- Time to Response is identical between Pembro and Chemo
- PFS is improved by 4.3 months (HR of 0.50)
- Improvement of PFS in all subgroups (except female/never smokers => lower mutational load ?)
- Strongest signal of PFS benefit observed in SqCC (HR of 0.35)

Reck M et al, ESMO 2016, NEJM 2016

KEYNOTE-024
Overall Survival



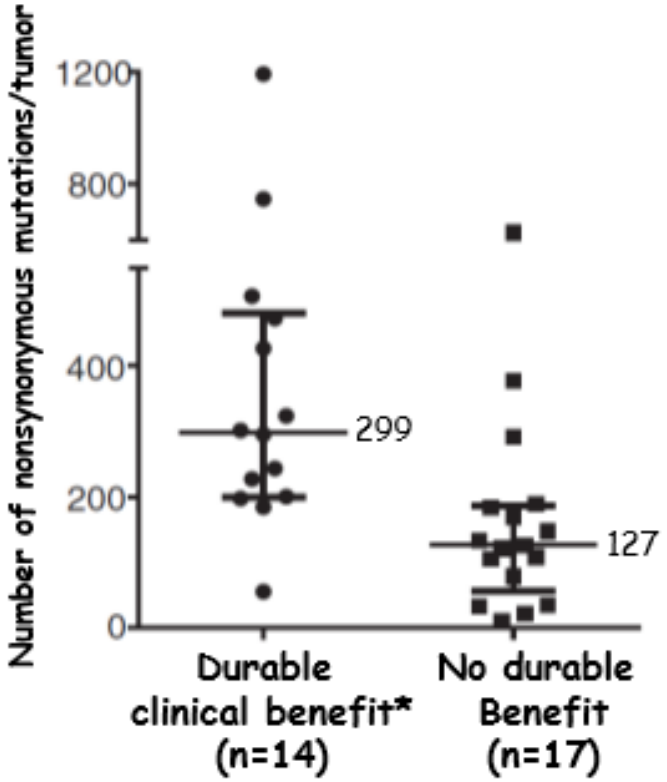
Survival benefit

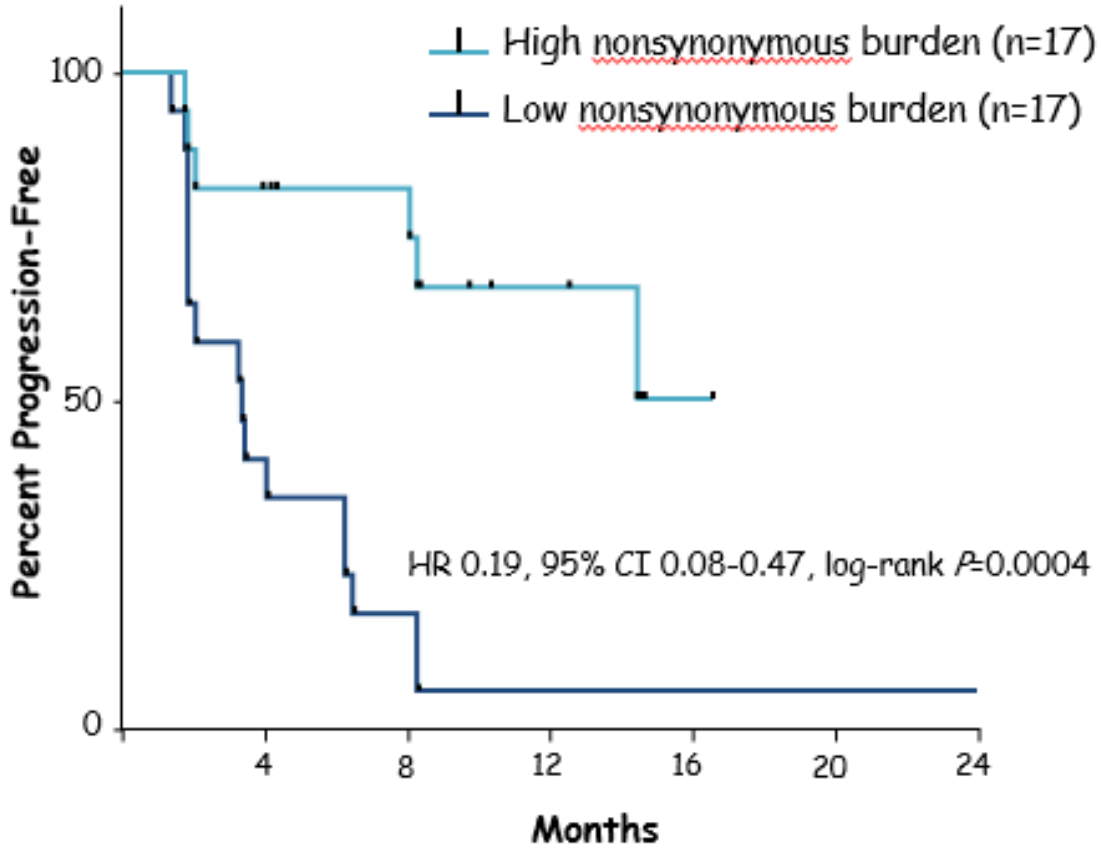
- Estimated rate of OS @ 12 months: 70% (Pembro) vs 54% (CT)
- HR for death: 0.60
- Despite cross-over in 50% of patients on the control arm

Reck M et al, ESMO 2016, NEJM 2016

ADVANCES IN Cancer IMMUNOTHERAPY™

Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC



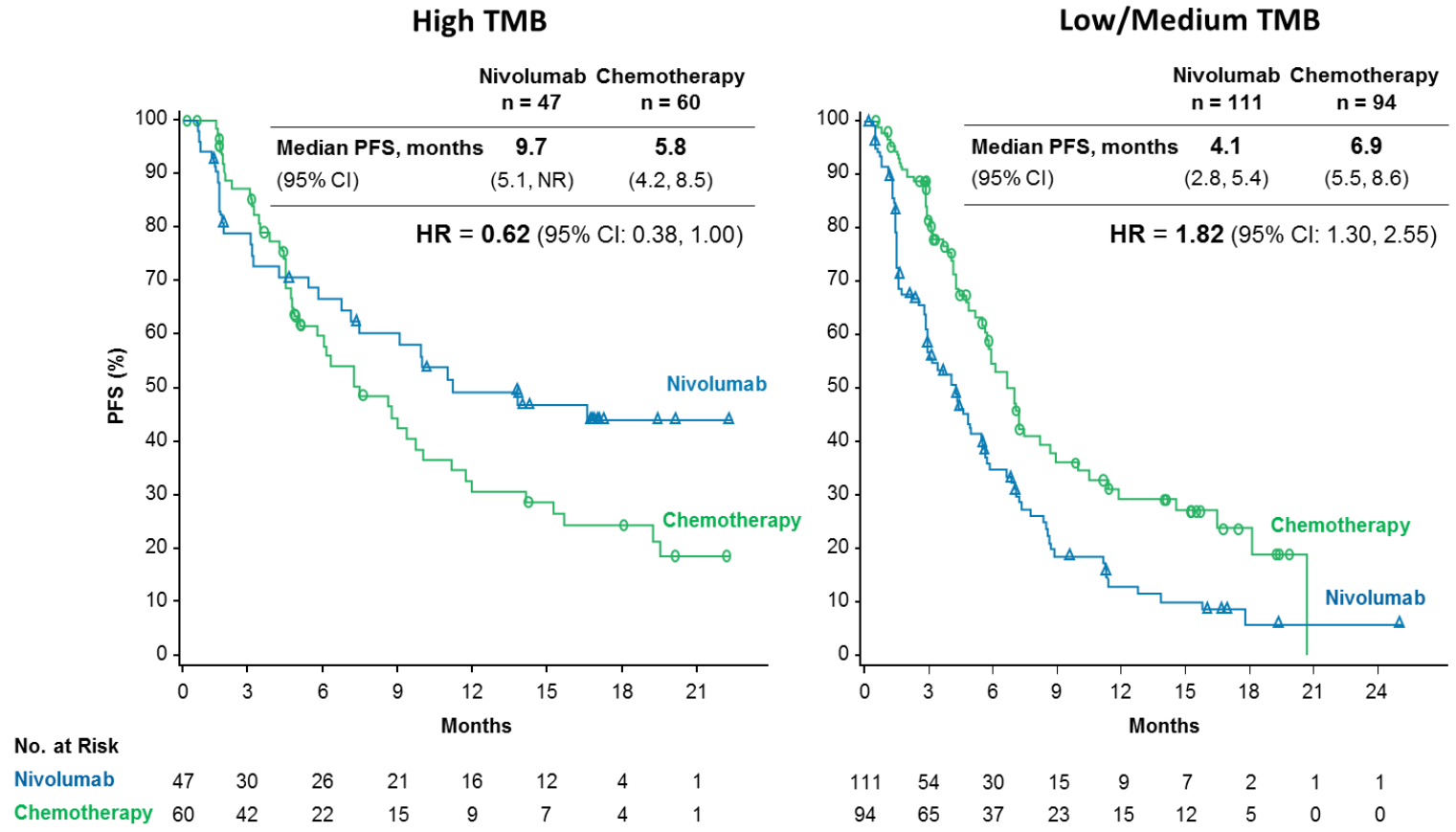


***Partial or stable response lasting > 6 mo**

Rizvi N et al, Science, 2015

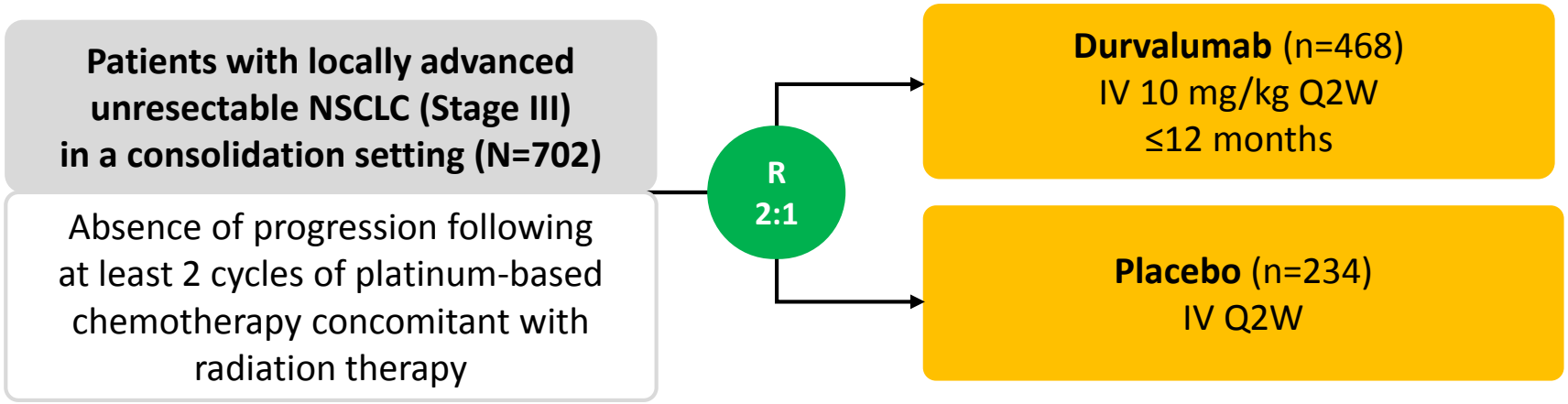
CheckMate 026 Subgroup: Nivolumab in First-line NSCLC

PFS by Tumor Mutational Burden



Peters, et al., AACR 2017

PACIFIC (NCT02125461):
Phase 3, randomized, double-blind, placebo-controlled trial



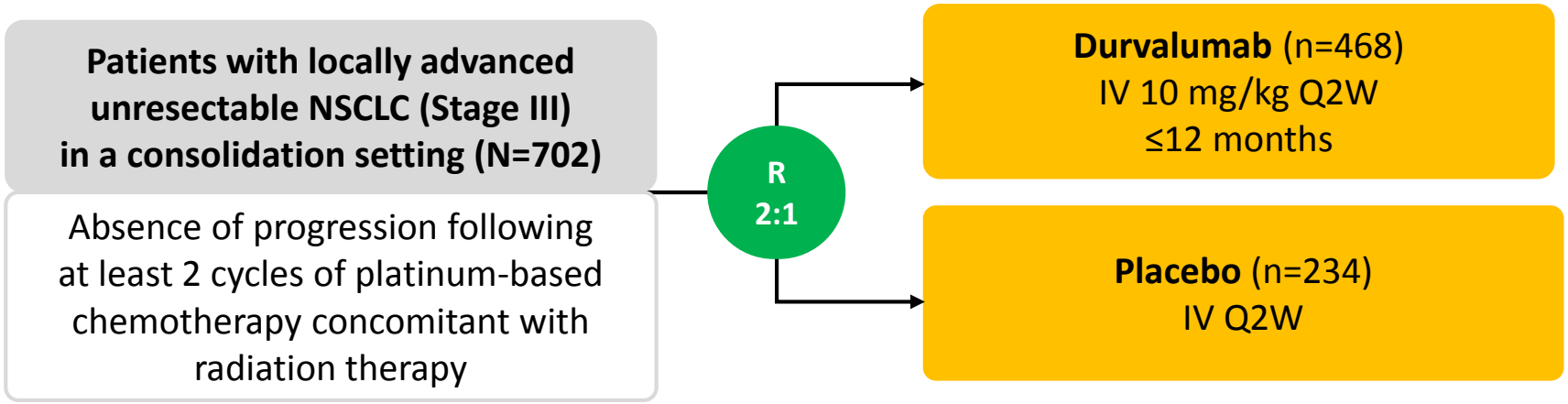
Primary endpoints: PFS, OS

Secondary endpoints: ORR, DoR, DSR, Safety/tolerability, PK, immunogenicity, QoL

Estimated completion: 2017
First patient dosed[4]: Q2 14
Last patient commenced dosing: Q2 16

DoR = duration of response; DSR = deep sustained response;
NSCLC = non-small cell lung cancer; ORR = objective response rate;
OS = overall survival; PFS = progression-free survival;
PK = pharmacokinetics; Q2W = every 2 weeks; QoL = quality of life.

PACIFIC (NCT02125461):
Phase 3, randomized, double-blind, placebo-controlled trial



Results: Durvalumab significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer

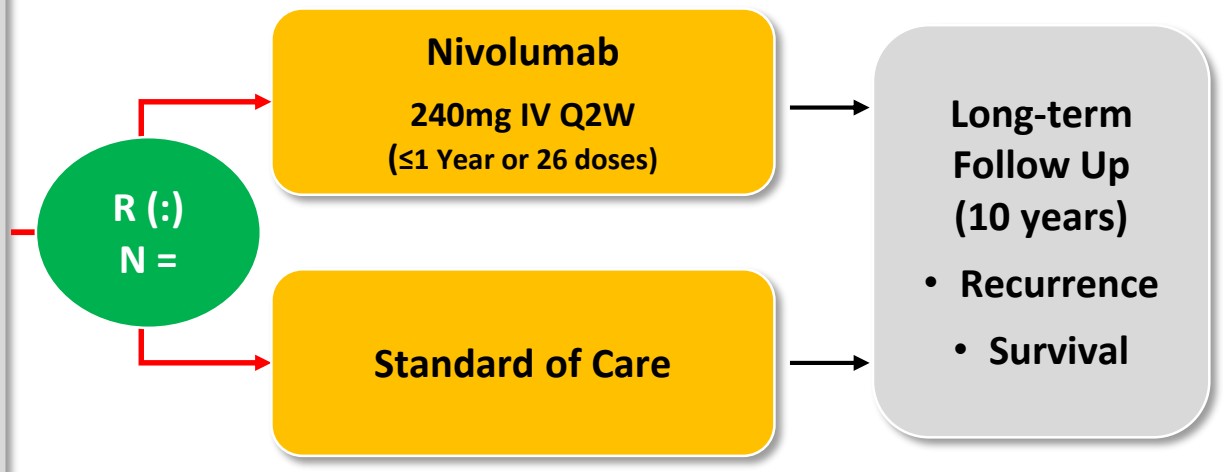
EA5142: ANVIL – Adjuvant Nivolumab in Resected NSCLC

Key Eligibility Criteria

- **Patient registered to ALCHEMIST screening trial (A151216)**
- **EGFR/ALK wildtype (if non-squamous)**
- **No contraindication to nivolumab**

Stratification

- **Stage IB (≥4cm)/IIA vs IIB/IIIA**
- **Squamous vs. non-squamous***
- **No prior adjuvant treatment vs. chemotherapy vs. chemotherapy + radiation**
- **PD-L1 positive** (≥1%) vs. Negative (<1%)**

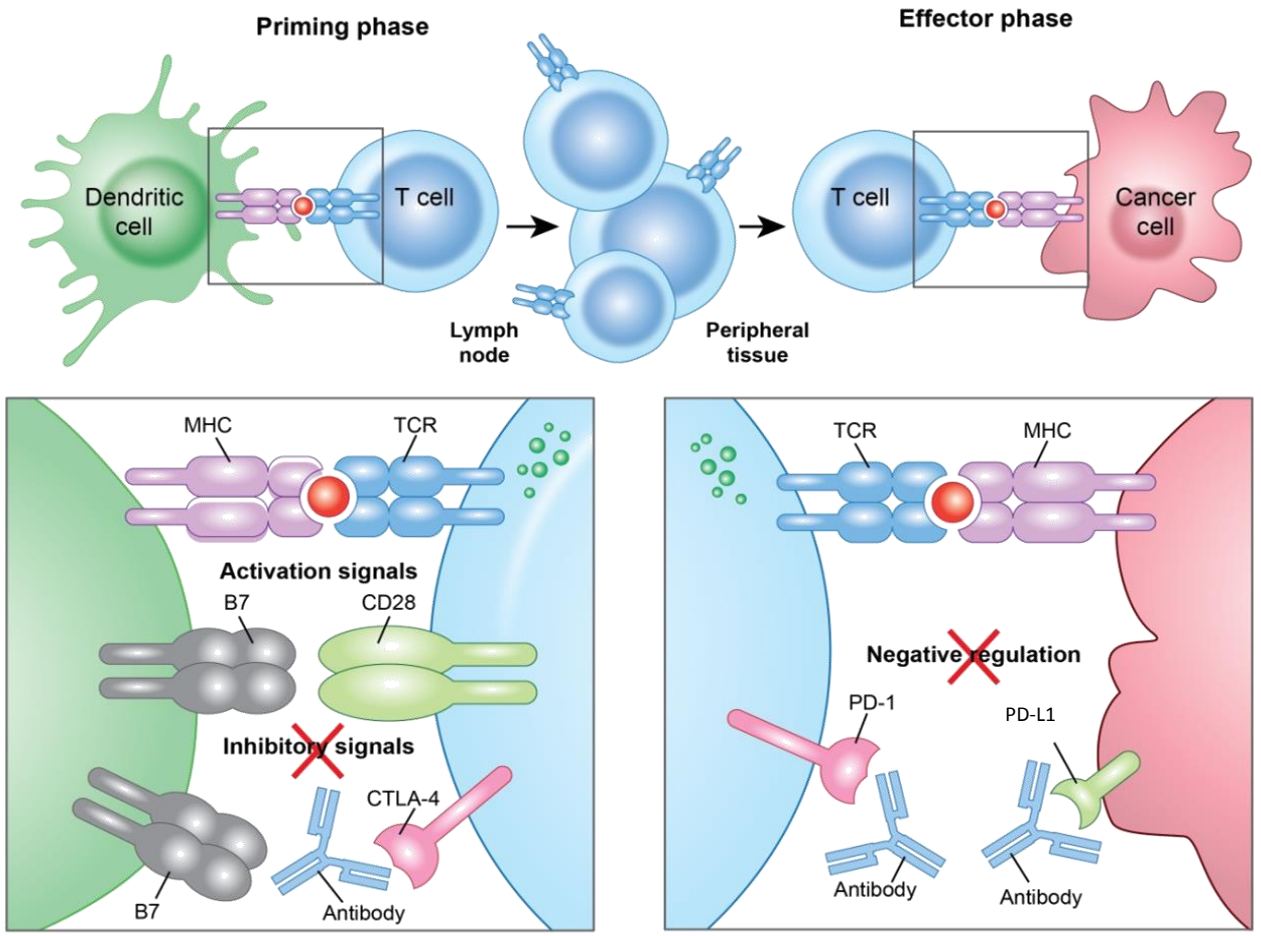


Primary endpoints: DFS and OS in all patients

*Adenosquamous grouped as non-squamous
**PD-L1+ defined as ≥ 1% by IHC
Accrual Goal = 714 patients

ADVANCES IN Cancer IMMUNOTHERAPY™

Combination Immune checkpoint blockade

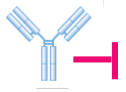


Ribas A, NEJM, 2012

CheckMate 012: Combination Immunotherapy

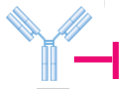
Ipilimumab/Nivolumab potential first line therapy?

Ipilimumab:

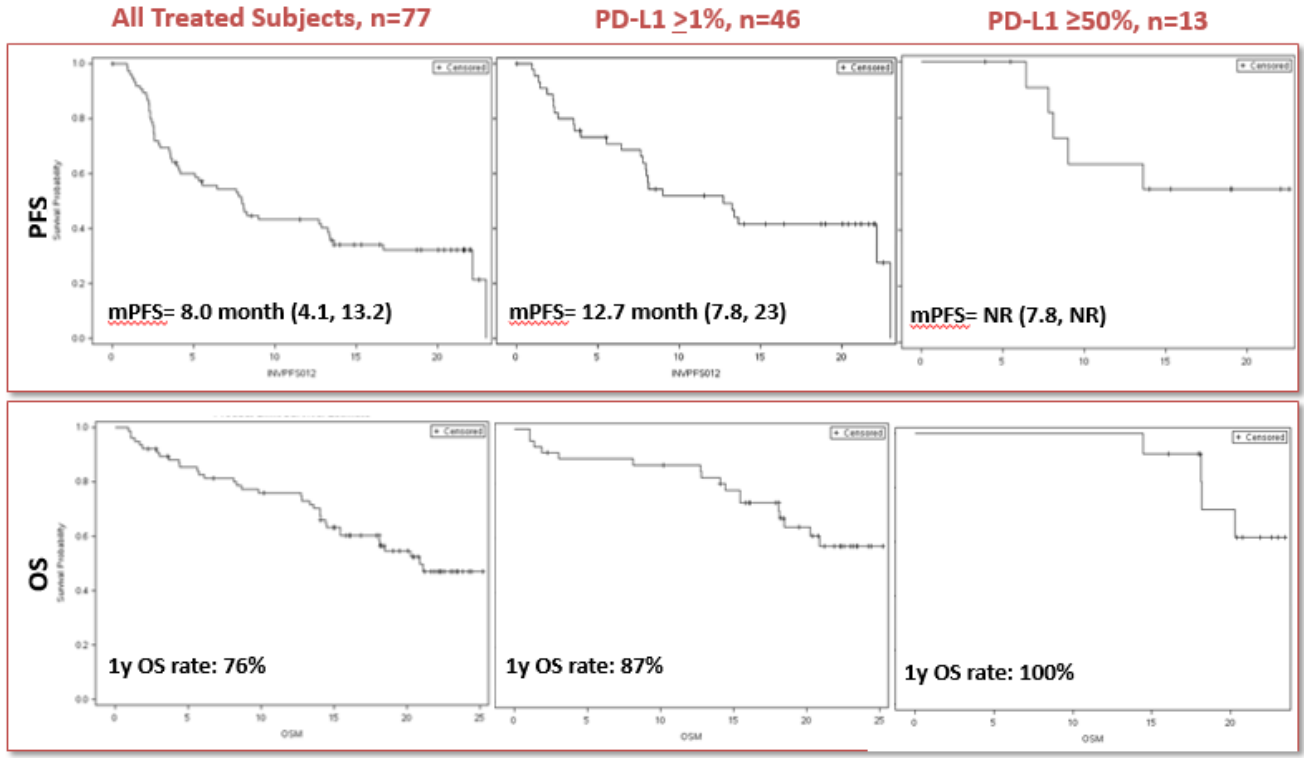


CTLA-4

Nivolumab:



PD-1



Goldman, et al, ASCO, 2017

KEYNOTE 021: Cohort G

Key Eligibility Criteria

- Untreated stage IIIB or IV nonsquamous NSCLC
- No activating EGFR mutation/ALK translocation
- Provision of a sample for PD-L1 assessment[a]
- ECOG PS 0-1
- No untreated brain mets
- No ILD or pneumonitis requiring systemic steroids

R (1:1)[a]
N = 123

Pembrolizumab 200 mg Q3W for 2 years
+
Carboplatin AUC 5 mg/mL/min
+ **Pemetrexed** 500 mg/m2 Q3W for 4 cycles[b]

Carboplatin AUC 5 mg/mL/min
+ **Pemetrexed** 500 mg/m2 Q3W for 4 cycles[b]

PD

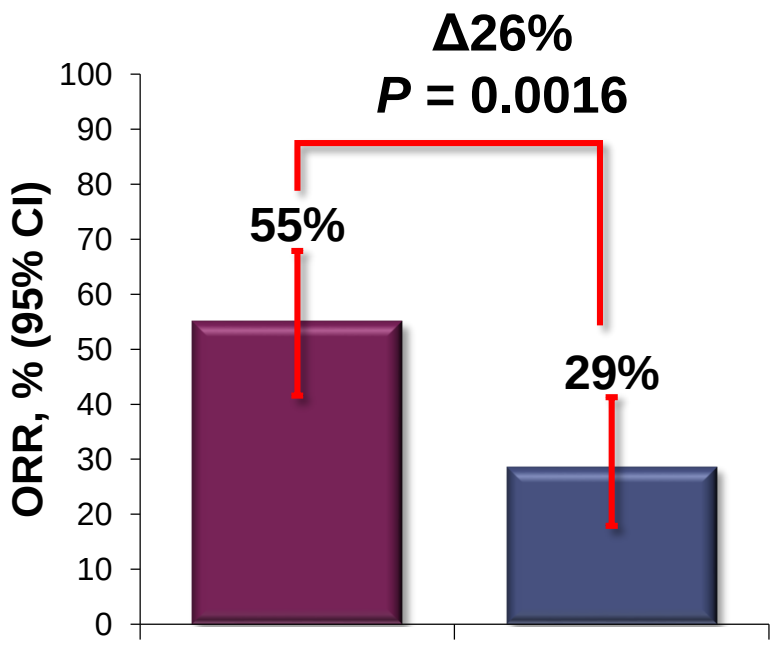
Pembrolizumab 200 mg Q3W for 2 years

Primary Endpoints: ORR (RECIST v1.1 per blinded, independent central review)
Secondary Endpoints: PFS, OS, safety, relationship between antitumor activity and PD-L1 TPS

Langer, et al Lancet Oncology 2016

Confirmed Objective Response Rate

(RECIST v1.1 by Blinded, Independent Central Review)



Data cut-off: August 8, 2016.

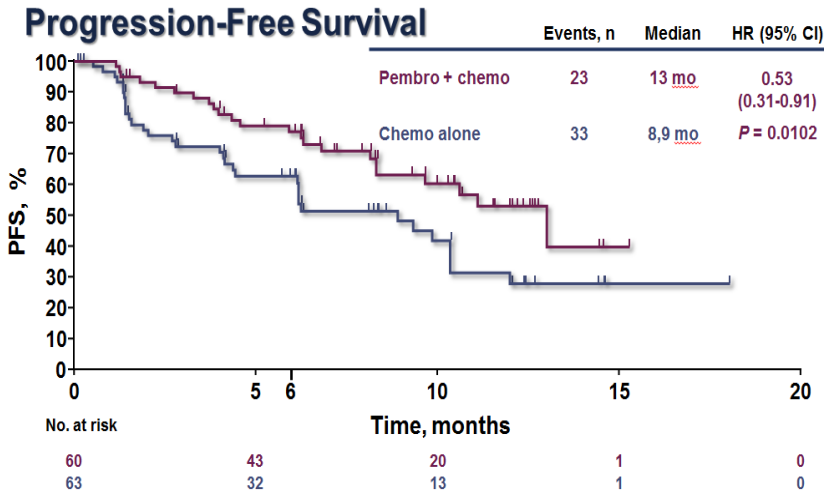
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response, [a] n (%)	29 (88)	14 (78)

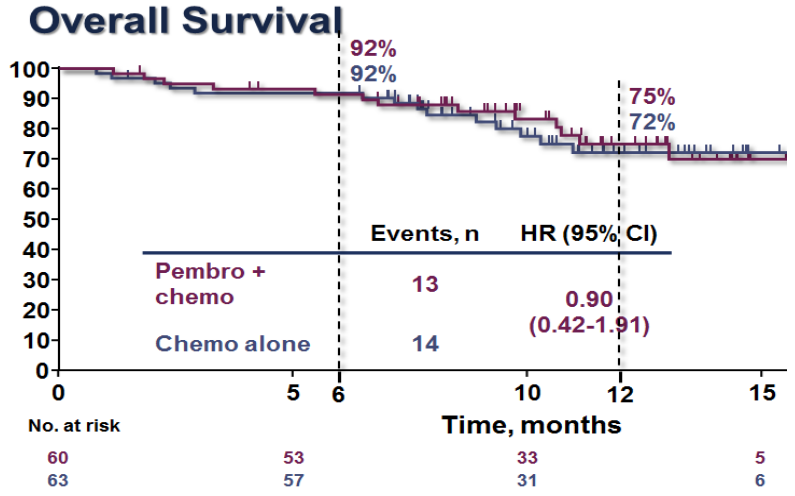
DOR = duration of response; TTR = time to response.

[a]Alive without subsequent disease progression.

Langer, et al Lancet Oncology 2016

PFS and OS Survival data



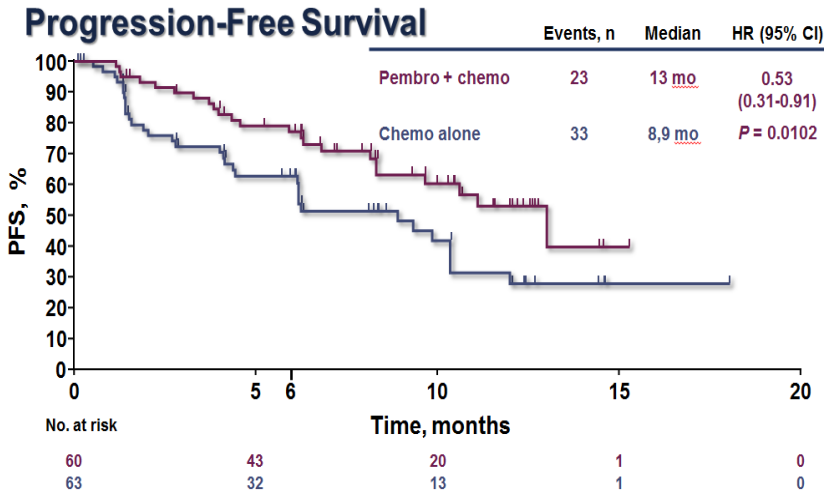


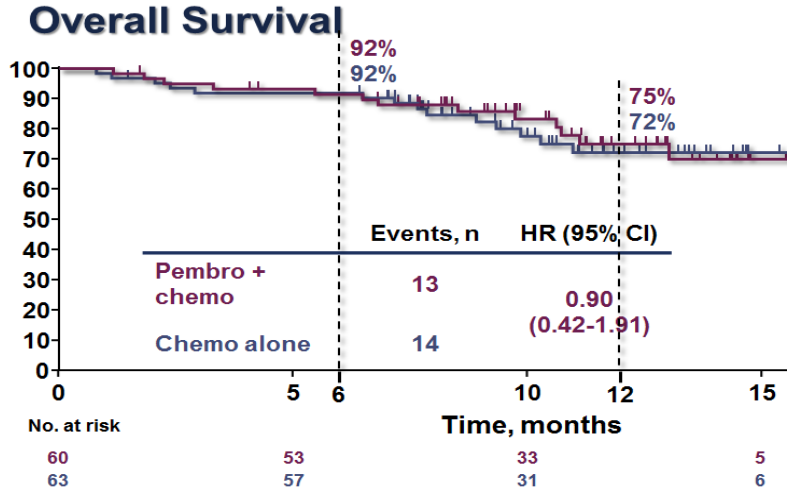
Clear PFS benefit and no OS advantage

- Median PFS improved by 4.1 months
- PFS HR is 0.53
- No difference for OS (crossover; immature data……..)
- Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
- In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others)

Langer, et al Lancet Oncology 2016

PFS and OS Survival data





Clear PFS benefit and no OS advantage

- Median PFS improved by 4.1 months
- PFS HR is 0.53
- No difference for OS (crossover; immature data……..)
- Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
- In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others)

Updated (ASCO ‘17):

- RR: 57% vs 30.5%
- PFS HR has dropped to 0.5 from 0.53, Median now NR vs 8.9
- OS HR has dropped to 0.69 from 0.9 with dip in p value from 0.37 to 0.13 (1yr OS 76% vs 69%)

Langer, et al Lancet Oncology 2016,
Papadimitrikopolou, ASCO 2017

Study Design

Keynote A Clinical Trial for Non-Small Cell Lung Cancer 189

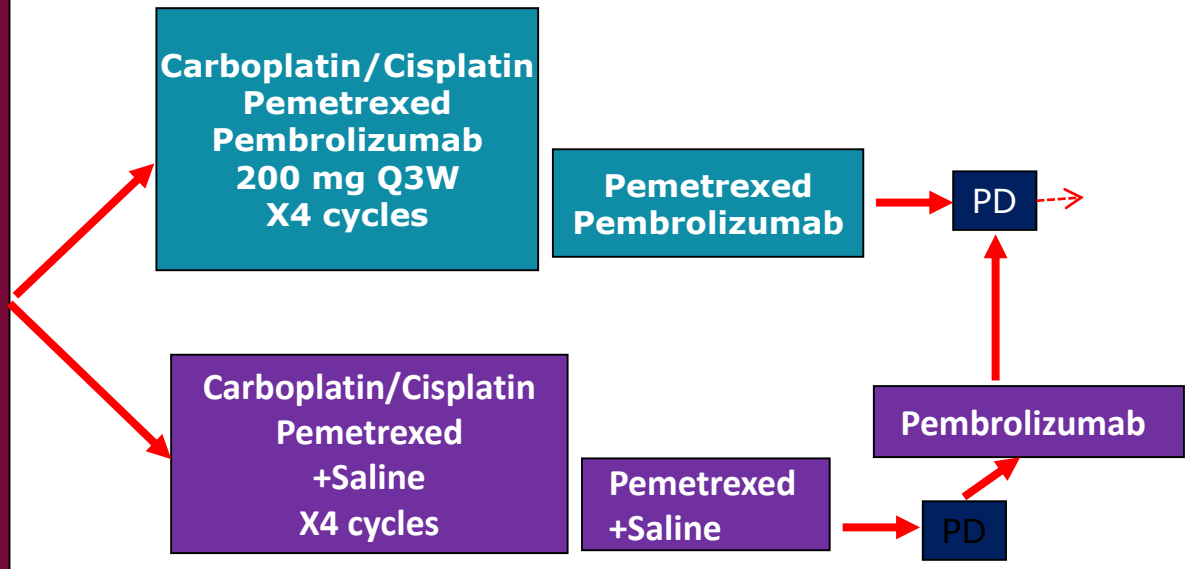
Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

Stratify:
- PDL1 prop score: ≥1%, <1%
- Smoking status
- cisplatin vs carboplatin

RANDOMIZATION

2:1

N=570



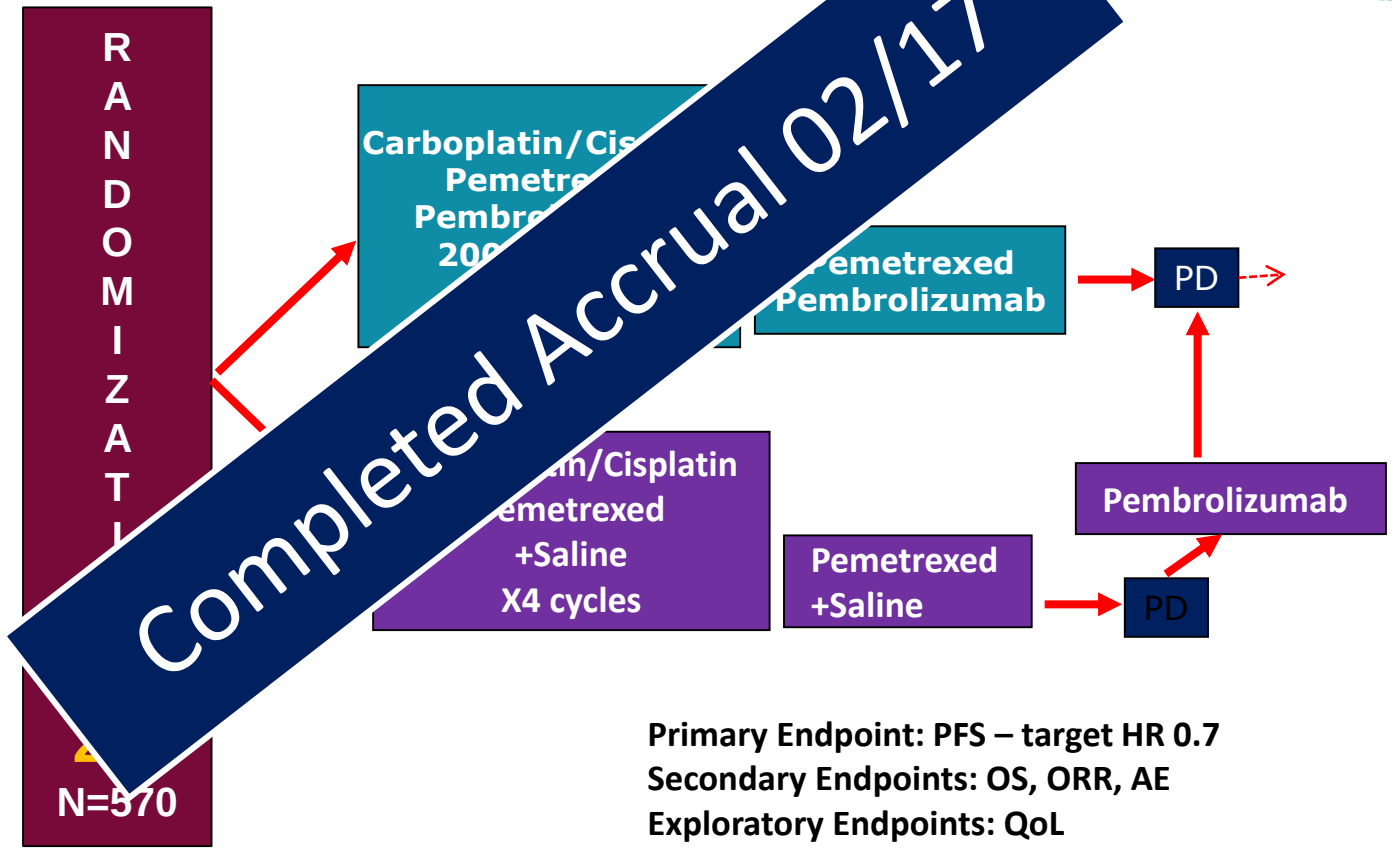
Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

Study Design

Keynote A Clinical Trial for Non-Small Cell Lung Cancer 189

Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

Stratify:
- PDL1 prop score: ≥1%, <1%
- Smoking status
- cisplatin vs carboplatin



Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

ADVANCES IN Cancer IMMUNOTHERAPY™

Phase 3 first-line combination trials in advanced NSCLC (all PD-L1 unselected)

Treatment	N*	Arms			Primary endpoint
Checkmate 227[1]	1980	Nivolumab, ipilimumab	Nivolumab	Plt-doublet chemotherapy	OS
MYSTIC[2]	1092	Durvalumab, tremelimumab	Durvalumab	SOC Plt-based chemotherapy	PFS
NEPTUNE[3]	800	Durvalumab, tremelimumab	SOC Plt-based chemotherapy	-	OS
IMpower 130[4]	550	Atezolizumab, nab-paclitaxel/carboplatin	nab-paclitaxel/carboplatin	-	PFS
IMpower 150[5]	1200	Atezolizumab, paclitaxel/carboplatin, bevacizumab	Atezolizumab, paclitaxel/carboplatin	Paclitaxel/ carboplatin, bevacizumab	PFS
IMpower 131[6]	1200	Atezolizumab, nab-paclitaxel/carboplatin	Atezolizumab, paclitaxel/carboplatin	Nab-paclitaxel/carboplatin	PFS

*Estimated enrolment

Plt, platinum; SOC, standard of care

1. NCT02477826; 2. NCT02453282; 3. NCT02542293; 4. NCT02367781; 5. NCT02366143; 6. NCT02367794

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Case Study #1

A 58-year-old female never smoker with bilateral lung mets, biopsy shows adenocarcinoma, EGFR mutation (L858R) and PD-L1 is 90% positive (22C3 assay). What do you recommend?

1. Erlotinib 150 mg po qd
2. Pembrolizumab
3. Pembrolizumab + pemetrexed and carboplatin combination

ACCC Association of Community Cancer Centers

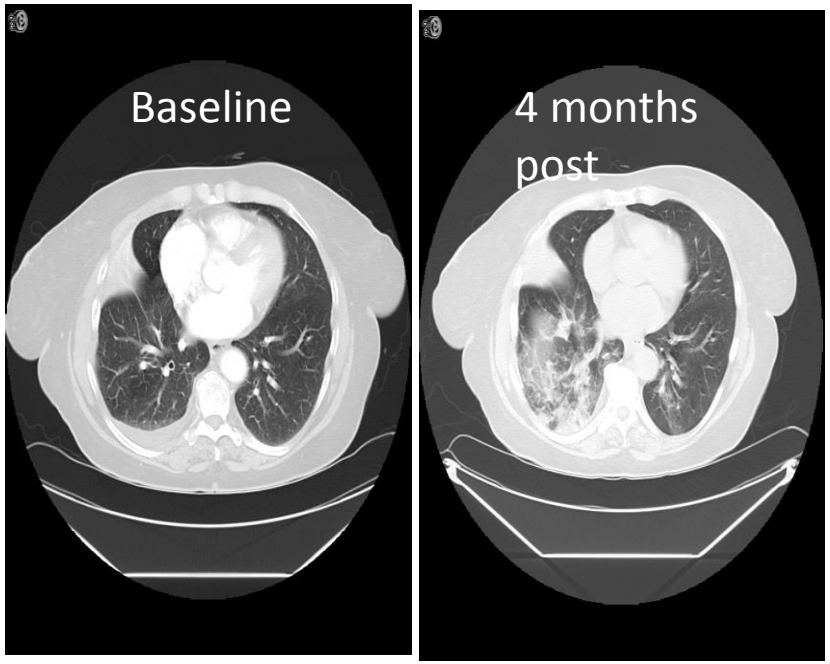
sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Case Study #2

A 70-year-old female ex-smoker with NSCLC with treatment response to anti-PD-1 antibody presents with increasing cough, SOB and new decline in O2 sat to 82%. What is your management recommendation ?

1. Continue anti-PD-1 antibody
2. Continue anti-PD-1 with dose reduction
3. Hold anti-PD-1 for 2 weeks
4. Discontinue anti-PD-1 and start prednisone 40 mg po qd
5. Discontinue anti-PD-1 and admit for IV steroids



ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer