Current Issues in Checkpoint Immunotherapy for NSCLC: A Perspective from January 2018

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Disclosures

- **Research Grants: AstraZeneca/Medi, BMS, Clovis, Genentech, JNJ, Lilly, Merck, Novartis**
- **Consultant: Ariad, AstraZeneca, Bayer, Boehringer-Ingelheim, Celgene, Clovis, Genentech, Guardant Health, Eli Lilly, Liquid Genomics, Merck, Mirati, Novartis, Peregrine, Pfizer, Roche Diagnostics, Synta, Trovogene**

Current Issues in Checkpoint Immunotherapy for NSCLC: A Perspective from January 2018

- Overview of Immunotherapy trial results in advanced NSCLC
  - 1st line
  - 2nd line
- Selection of Patients most likely & least likely to Benefit:
  - Clinical Factors (Smoking status, Histology, PS)
  - Predictive Biomarkers
    - PD-L1 Assay
    - Tumor Mutational Burden (TMB)
    - Other biomarkers in development
- Judging Clinical Efficacy
  - Best endpoint: ORR, PFS, OS, LTS (long term survivors)?
  - QOL/Symptom Control

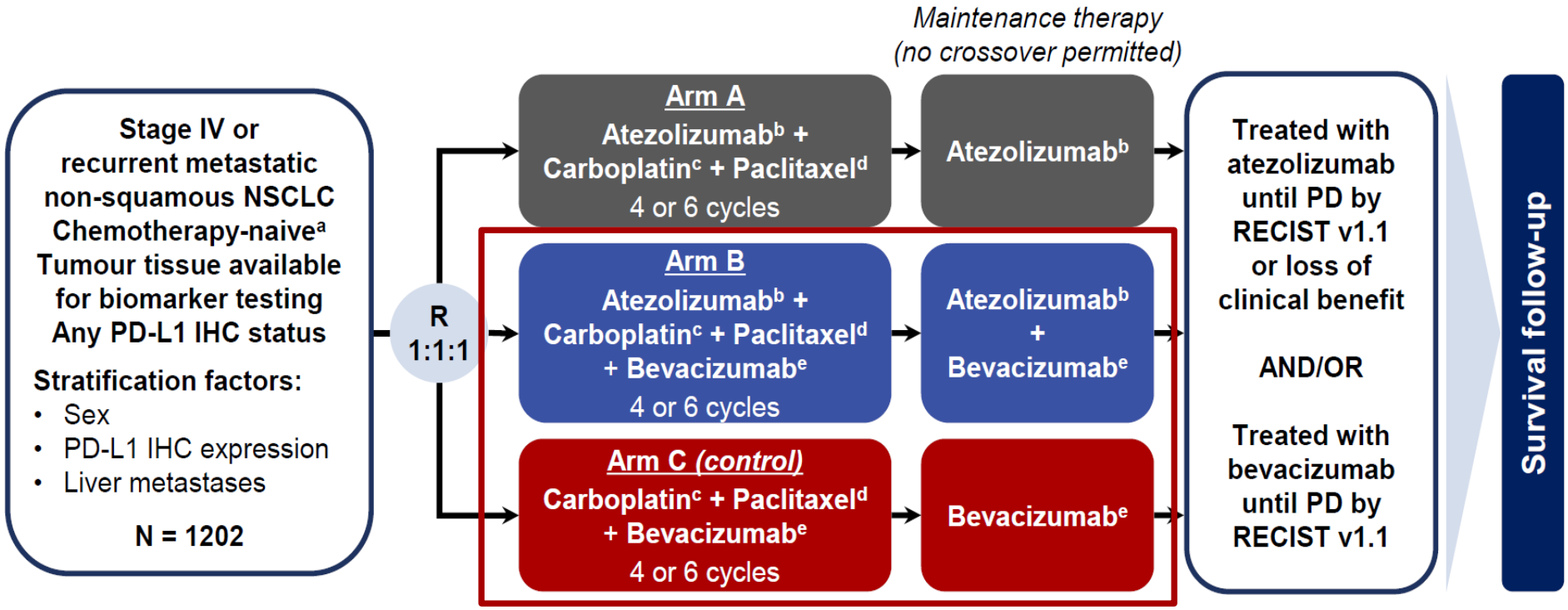
Assumptions for this Presentation

- The clinical efficacy of currently available PD-1/PD-L1 agents is similar
- Differences in trial outcomes between currently available PD-1/PD-L1 agents are largely related to variable patient characteristics and/or trial designs
- Histologic subtype of NSCLC is important in assessing efficacy of PD-1/PD-L1 agents
- Clinical outcomes by various PD-L1 IHC assays is similar (accounting for differences in pre-determined cutpoints)

Key Clinical Trials of Checkpoint Immunotherapy in Advanced NSCLC

Study	Drug	PDL1 Selection	Line of therapy	Control	Primary Endpoint	HR-Primary Endpoint	FDA Approval
K024	Pembro	>50%	1st	Plat Chemo	PFS	0.50	Yes
K021G (Ph II)	Pembro-Chemo	None	1st	Plat Chemo	ORR	NR (0.53)	Yes (Accel)
CM026	Nivo	>5%	1st	Plat Chemo	PFS	1.15	No
CM017	Nivo	None	2nd	Docetaxel	OS	0.62	Yes
CM057	Nivo	None	2nd-3rd	Docetaxel	OS	0.75	Yes
K010	Pembro	>1%	2nd-3rd	Docetaxel	OS & PFS	0.61	Yes
OAK	Atezo	None	2nd-3rd	Docetaxel	OS	0.73	Yes
IMpower 150	Atezo-Chemo-Bev	None	1st	Pac-Carbo	PFS	0.62	Not Yet

Impower 150: Atezolizumab-Platinum Chemotherapy-Bevacizumab



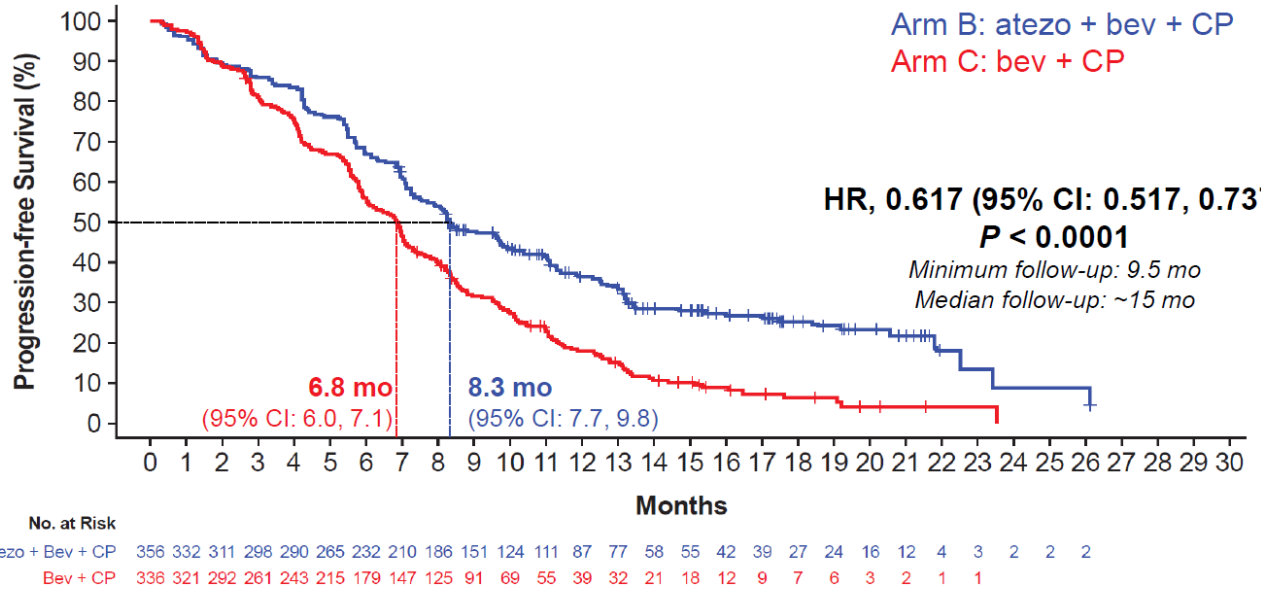
The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Reck M, et al. IMpower150 PFS analysis.

Impower 150: Atezolizumab-Platinum Chemotherapy-Bevacizumab

INV-assessed PFS in ITT-WT (Arm B vs Arm C)



INV, investigator.
Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

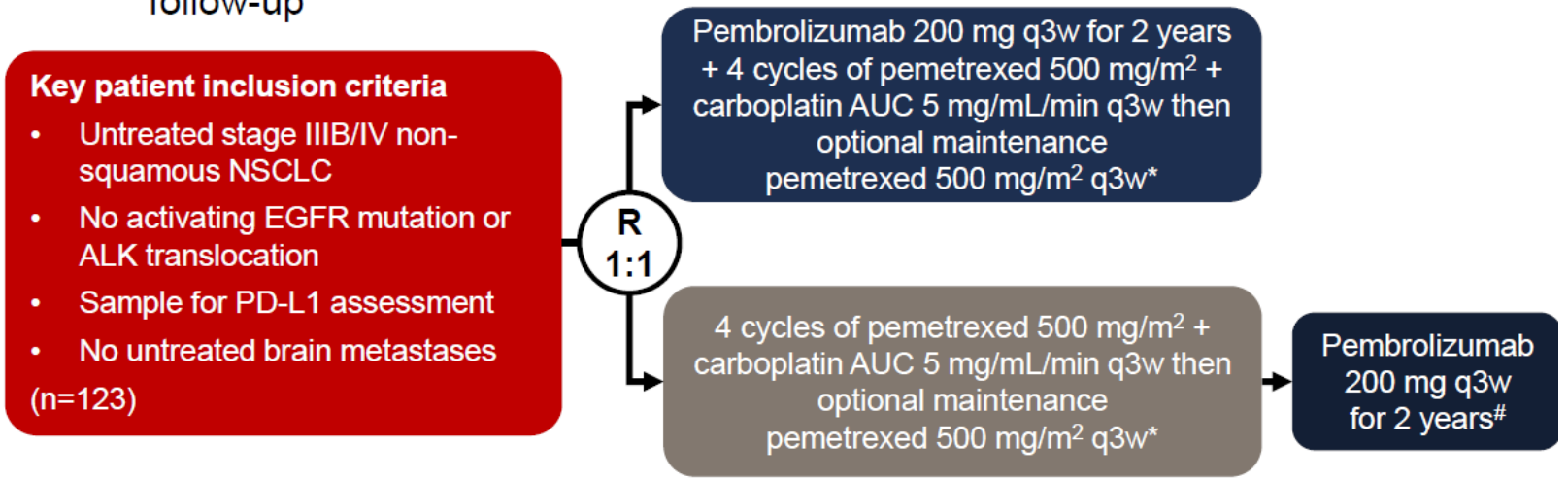
But

	Arm C: bev + CP (n = 336)	Arm A: atezo + CP (n = 348)
Median PFS, mo (95% CI)	6.3 (5.6, 7.0)	6.8 (6.0, 7.1)
PFS HR (95% CI)	**0.936 (0.787, 1.112)**	
Median OS, mo (95% CI)	14.4 (12.8, 17.1)	17.9 (15.0, 21.0)
OS HR[a] (95% CI)	0.884 (0.709, 1.101)	

KEYNOTE-021 Cohort G: Phase II trial of Pemetrexed/Carboplatin + Pembrolizumab vs Pemetrexed/Carboplatin alone

Objective

- To assess the efficacy and safety of pembrolizumab added to 1L carboplatin + pemetrexed in cohort G of KEYNOTE-021 after an additional 5 months of follow-up



Primary endpoint

- ORR per RECIST v1.1 by BICR

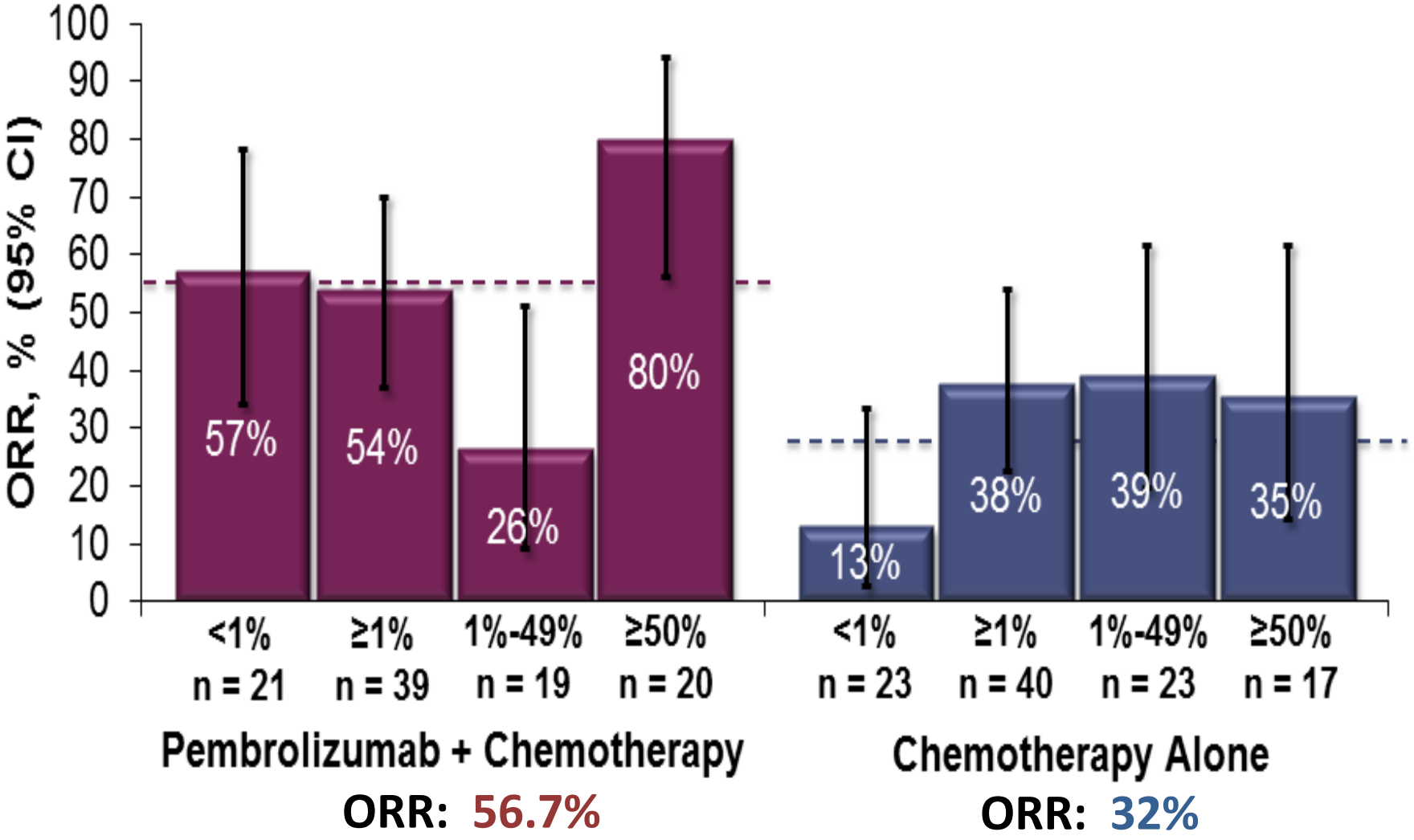
Secondary endpoints

- PFS, OS, DoR, safety

*Treatment continued until PD, intolerable toxicity, physician decision or patient withdrawal; patients in both arms could receive indefinite maintenance with pemetrexed; #patients with radiologic disease progression could crossover if protocol-specified safety criteria met

Langer et al: Lancet Oncol 2017

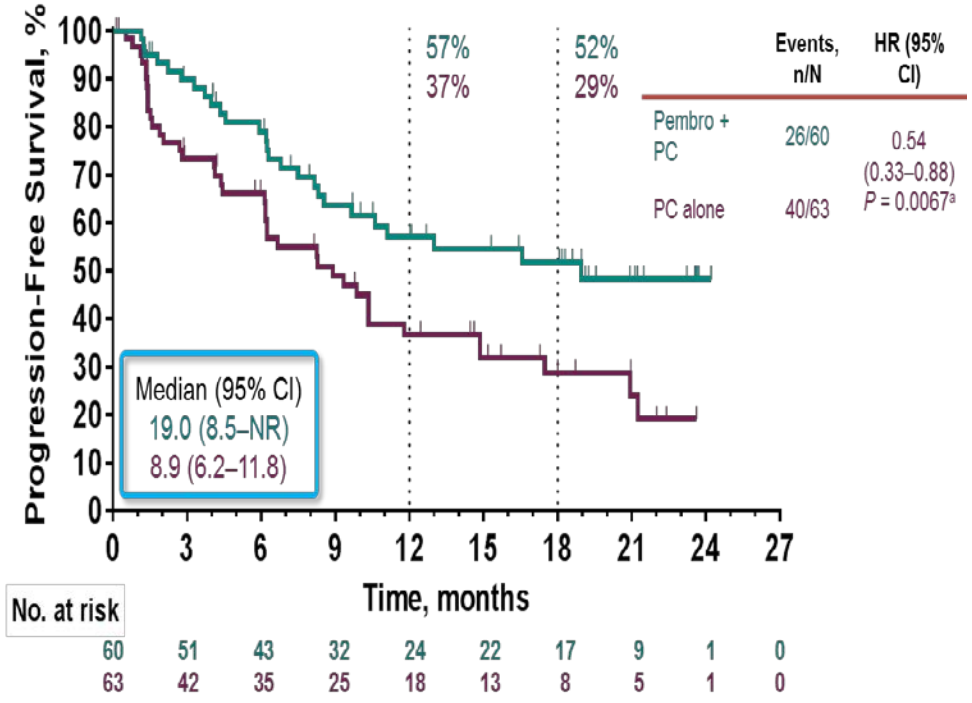
KEYNOTE-021 Cohort G: Pemetrexed/Carboplatin + Pembrolizumab vs Pemetrexed/Carboplatin alone: Overall Response Rate (ORR)



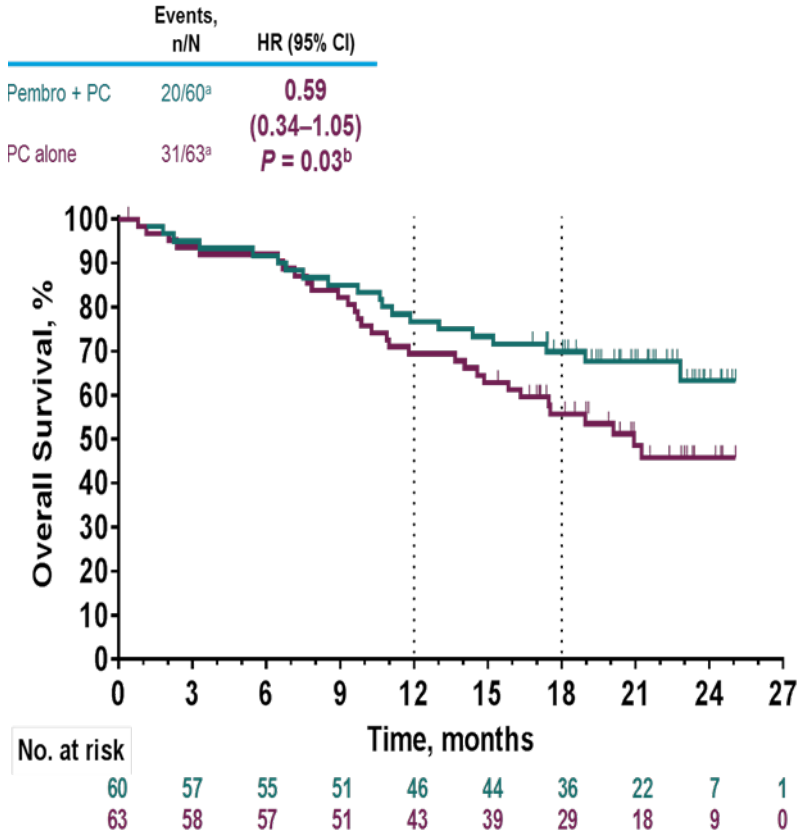
Langer et al: Lancet Oncol 2017

KEYNOTE-021 Cohort G: Pemetrexed/Carboplatin + Pembrolizumab vs. Pemetrexed/Carboplatin Alone

PFS: ESMO 2017[3]



OS: ESMO 2017[3]



1. Langer C et al. Presented at: ESMO 2016 Congress; October 2016; Copenhagen, Denmark. Abstract LBA46_PR. 2. Langer CJ et al. *Lancet Oncol.* 2016;17:1497-1508. 3. Borghaei H et al. Presented at: ESMO 2017 Congress; October 2017; Madrid, Spain. Abstract LBA49.

Outcomes in KN021G compared to data from Trials with Nivolumab-Platinum Chemotherapy

	KEYNOTE-021		CheckMate 012
	CarboPem	CarboPem +Pembro	Doublet + Nivo
ORR [%]	31.7	56.7	46
mPFS [months]	8.9	19	4.8-7.1
mOS [months]	20.9	NR	19.2

KEYNOTE-189: Study Design

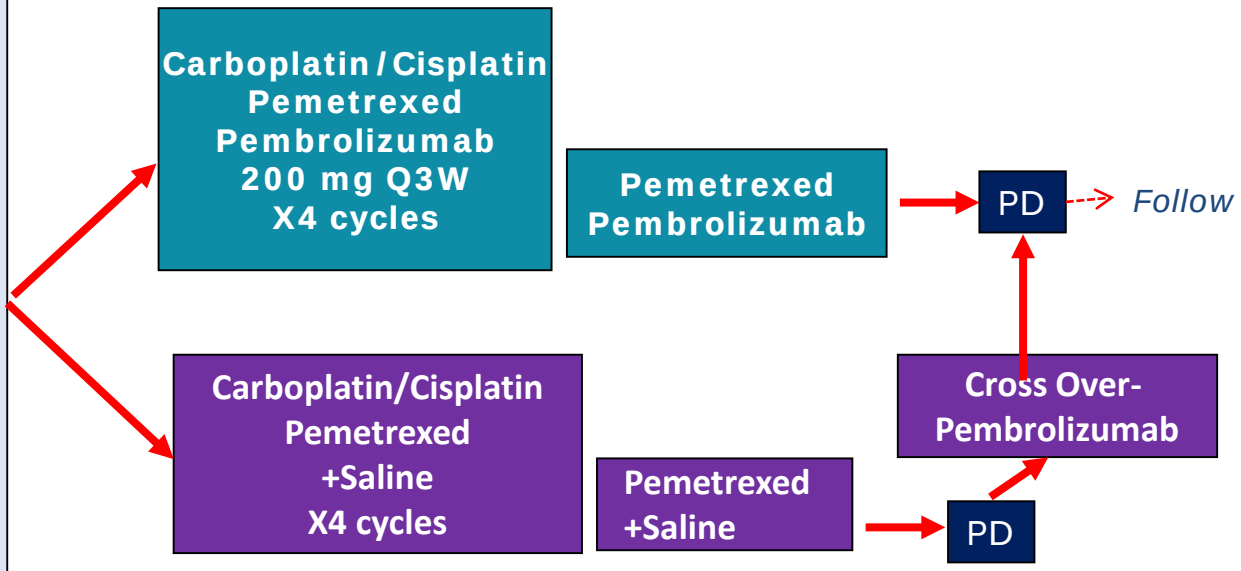
Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

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

RANDOMIZATION

2:1

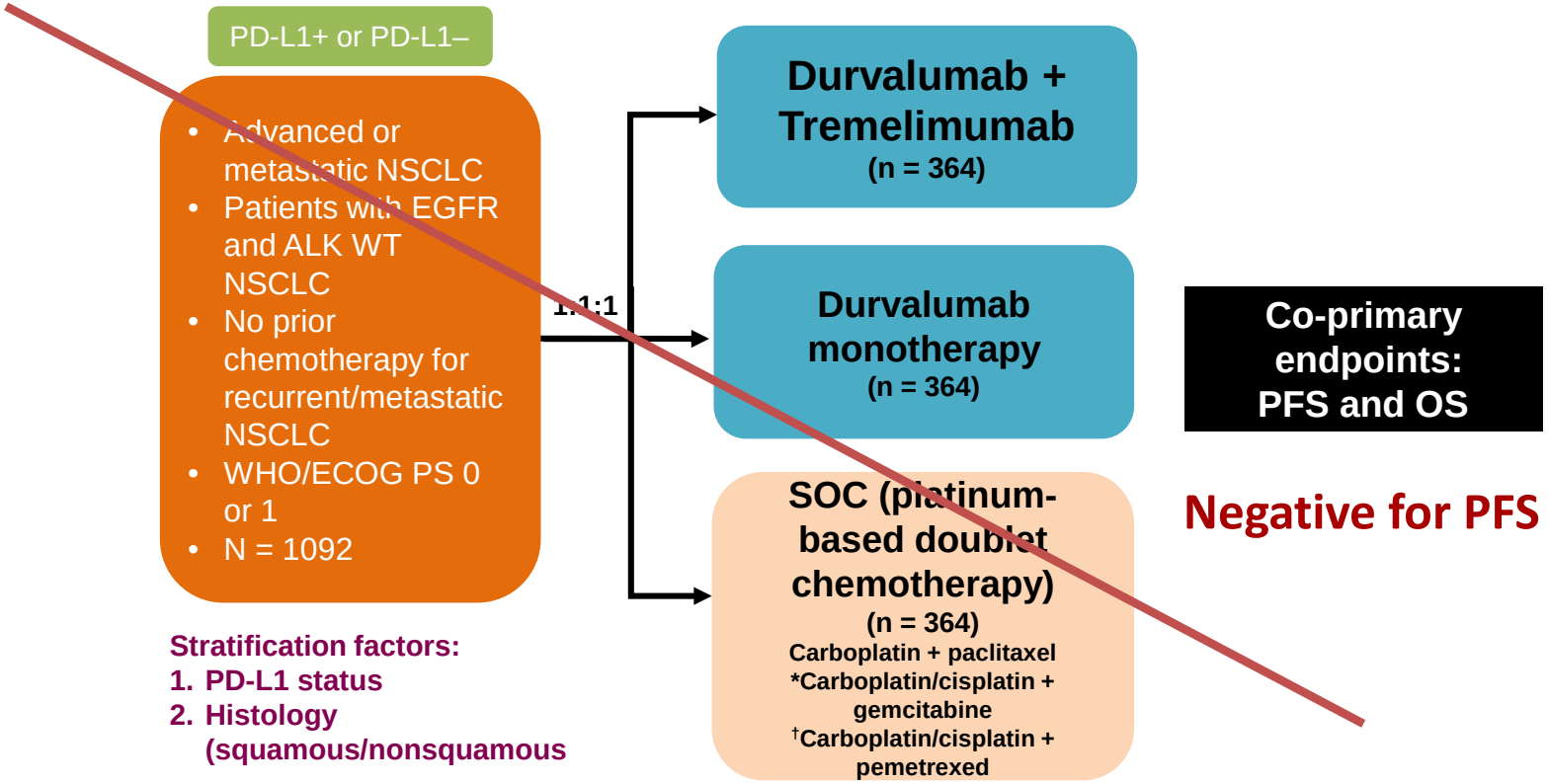
N=570



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

MYSTIC: Durvalumab +/- Tremilumumab vs Platinum Chemotherapy

Phase III, randomized, open-label, global, multicenter first-line study



*Squamous NSCLC only.
†Nonsquamous NSCLC only.

D419AC00001: ClinicalTrials.gov. Available at: http://www.clinicaltrials.gov/ct2/show/NCT02453282;
Rizvi N, et al. Poster presented at SiTC 2015. Poster 181.

Durvalumab is an investigational drug and is not approved for use in any country.

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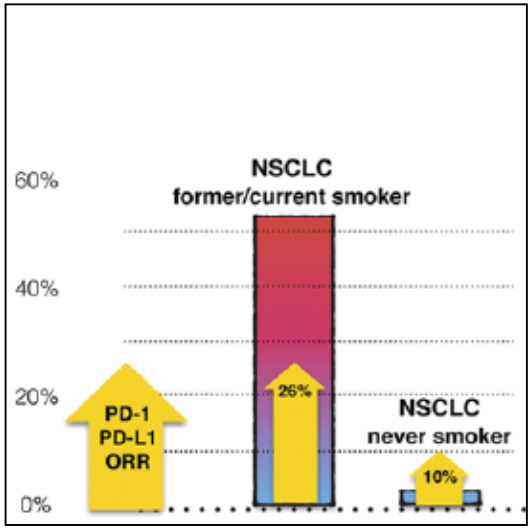
Clinical Selection Factors for Immunotherapy Efficacy in NSCLC

- **Smoking Status**
- **Histology**
- **Performance Status (PS)**

Efficacy by Smoking Status

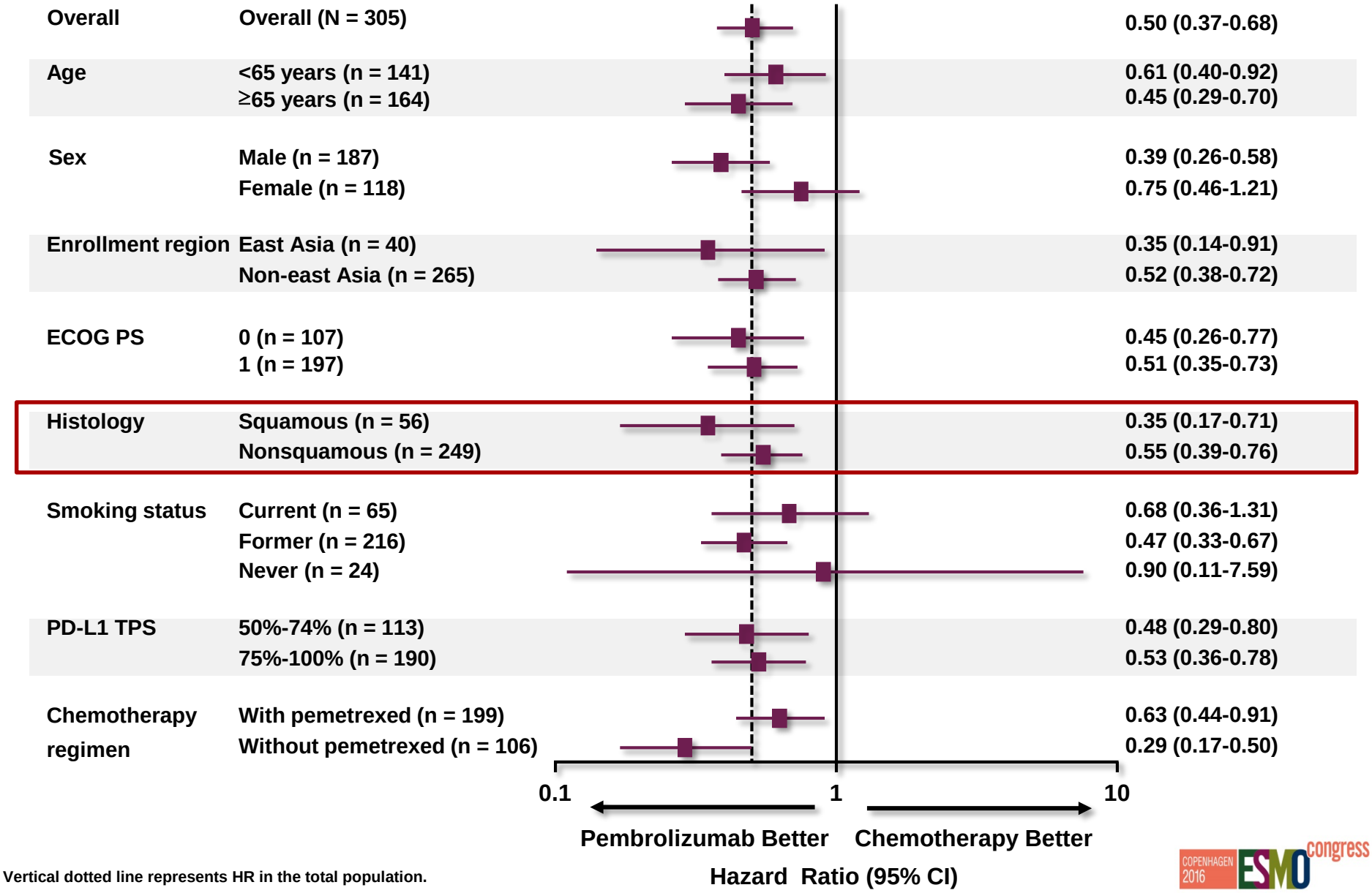


Champiat et al: OncoImmunology 2014

CheckMate 057: OS in Predefined Subgroups

	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)

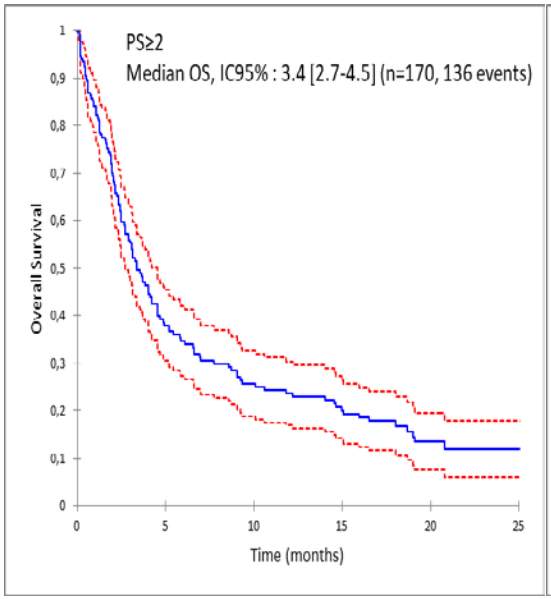
KeyNote 024 of Pembrolizumab vs Chemotherapy in 1st line therapy: PFS in Subgroups

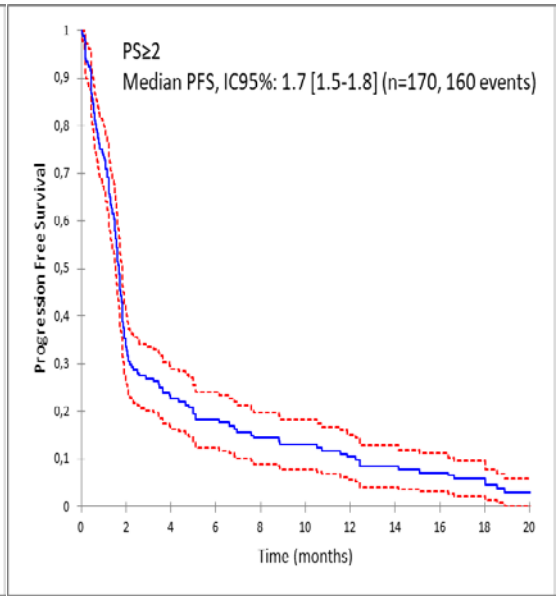


Vertical dotted line represents HR in the total population.
Data cut-off: May 9, 2016.

Patients with PS2 in the French Nivolumab Expanded Access Program

Best response In PS 2 patients %, 95%CI	Total (n=121)
Objective response	12% [6.5%-18.3%]
Stable Disease	31% [23.1%-39.7%]
Progression	56% [47.4%-65.0%]





	Univariate analysis			Multivariate analysis (n=889)		
Characteristic	HR	95% CI	p	HR	95% CI	p
PS ≥2 (vs 0/1)	2.24	1.85-2.72	<0.0001	2.21	1.82-2.69	<0.0001

Adapted from Girard N et al, WCLC 2017

Data from the French Nivolumab EAP (n=902)
PS2 patients, n=121

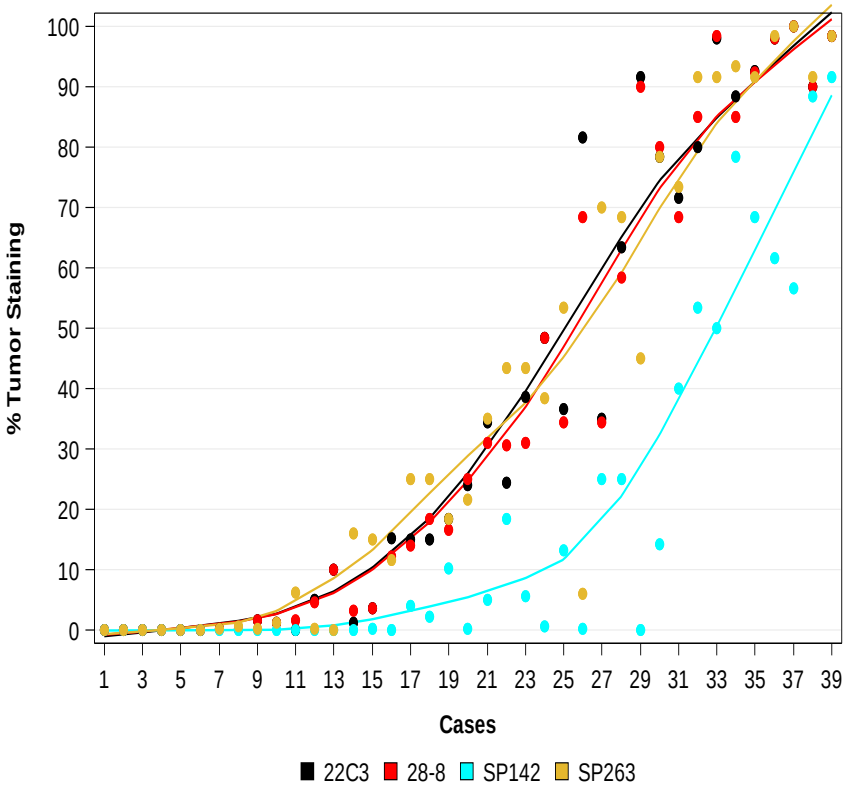
PD-L1 Assay Systems in the Blueprint Project

Assay primary antibody clone	28-8(Dako)		22C3(Dako)		SP142(Ventana)	SP263(Ventana)
PD-1/PD-L1 Agent	Nivolumab (BMS)		Pembrolizumab (Merck)		Atezolizumab (Genentech)	Durvalumab (AstraZeneca)
Interpretative Scoring	Tumor cell membrane		Tumor cell membrane		-Tumor cell membrane -Infiltrating immune cells	Tumor cell membrane
Instrument and Detection Systems Required	EnVision Flex-Autostainer Link 48		EnVision Flex-Autostainer Link 48		OptiView Detection & Amplification-Benchmark ULTRA	OptiView Detection-Benchmark ULTRA
Cut Point	1st line 5%	2nd line 1%-5%	1st line 50%	2nd line* 1%; 50%	2nd line 1%; 5%, 10%	NR

Adapted from Hirsch et al. J Thorac Oncol. 2017 Feb;12(2):208-222

PD-L1 Analytical Evaluation Results: Mean Tumor Proportion Score (TPS) per case based on three readers

- Analytical comparison of % tumor cell staining (Tumor Proportion Score), by case, for each assay
- Data points represent the mean score from three pathologists for each assay on each case
- Superimposed lines / points indicate identical TPS values
- No clinical diagnostic cut-off applied
- **Conclusion:** 3 of 4 assays are analytically similar for tumor cell staining (SP142 is outlier)



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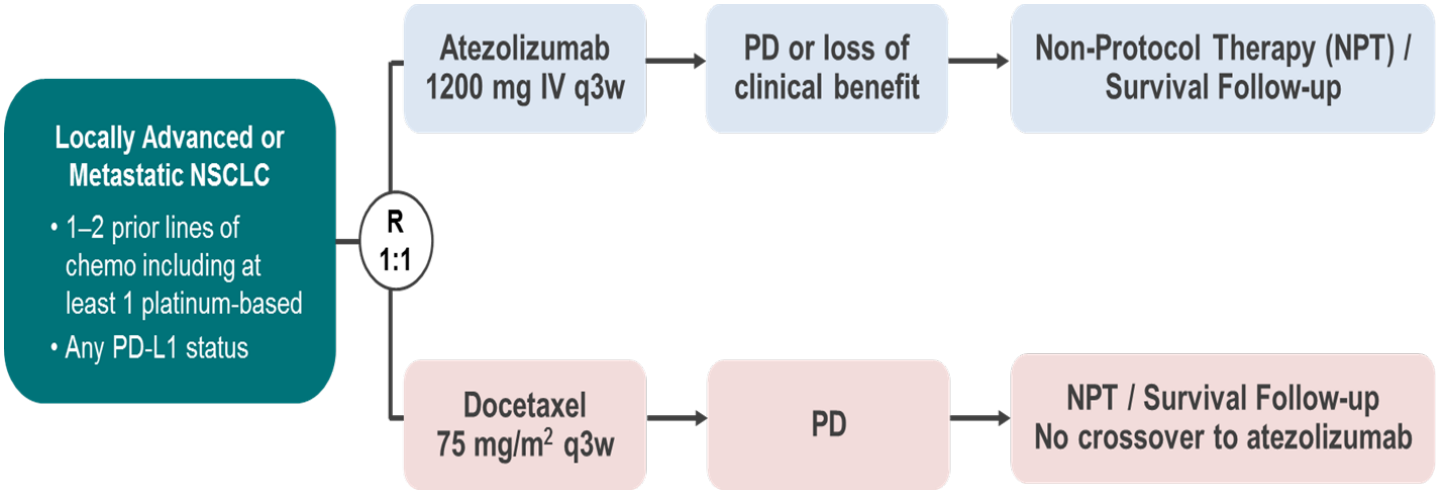
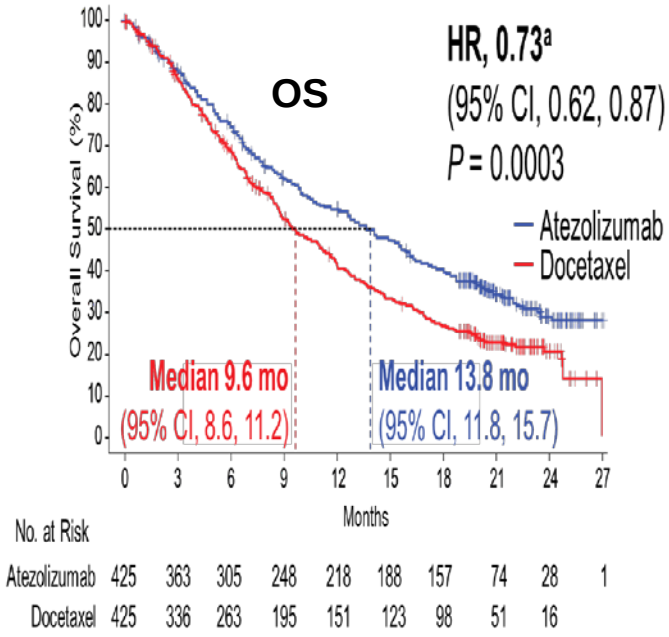
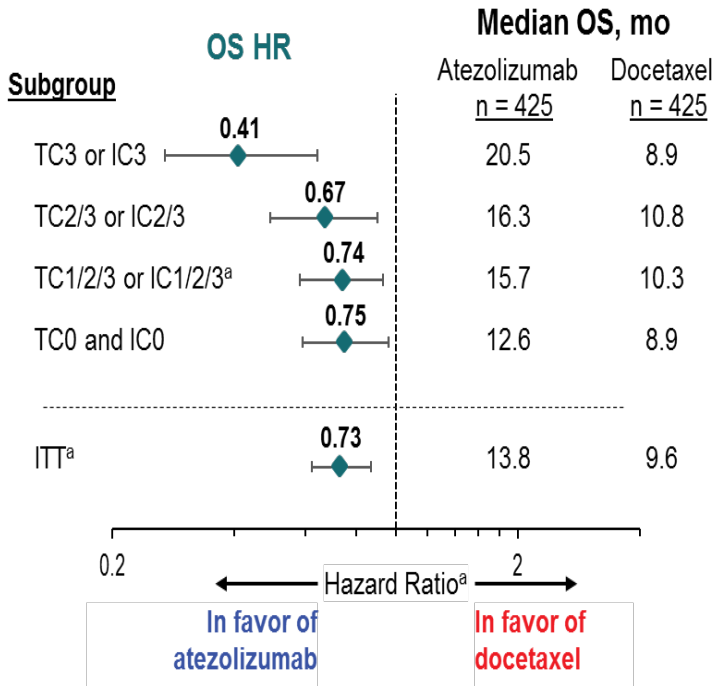
Comparison of PD-L1 assays (Dako 22C3 vs Ventana SP142) in OAK Trial



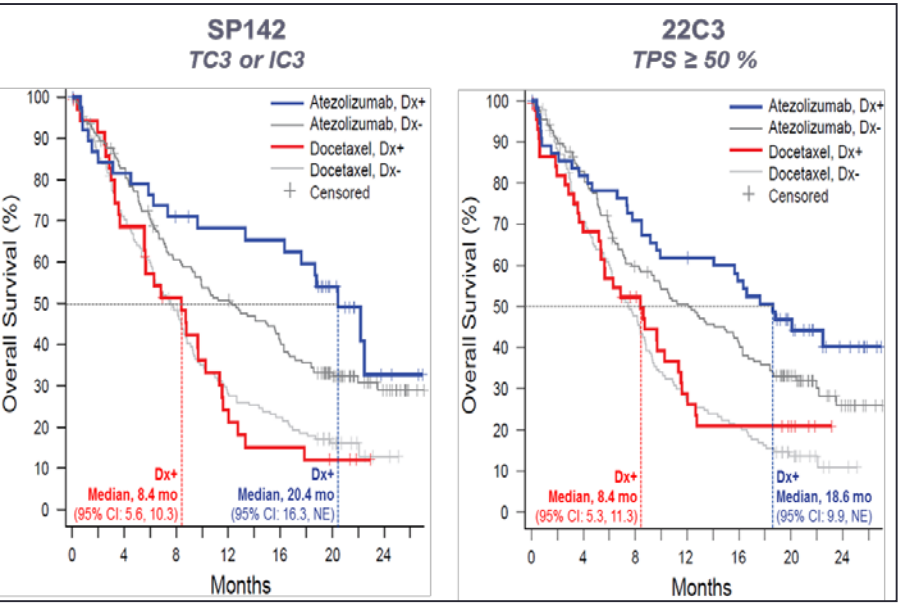




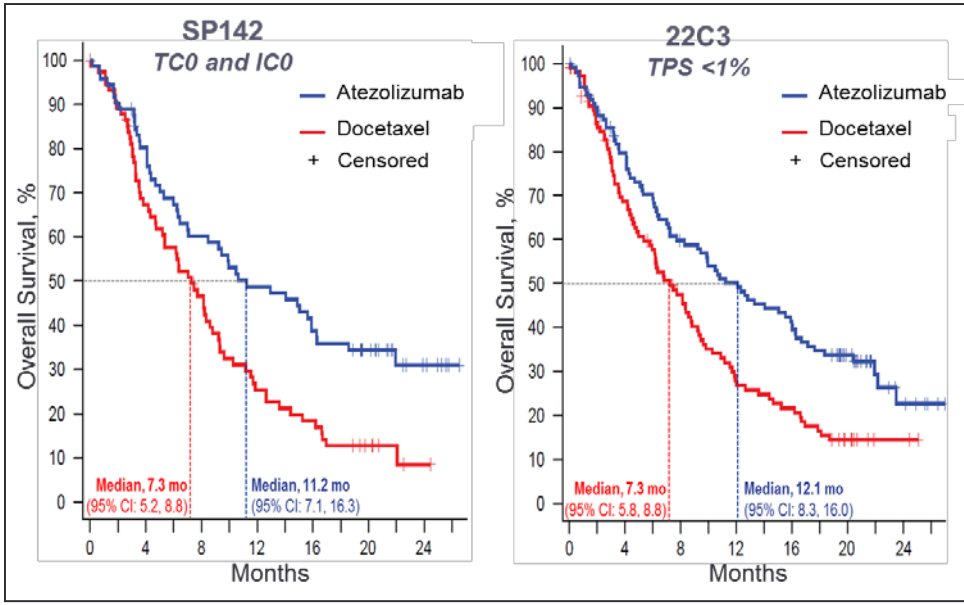
Gadgeel S et al. ESMO 2017 Abstract 1296O.

Comparison of PD-L1 assays (Dako 22C3 vs Ventana SP142) in OAK Trial

OS in PD-L1-High Subgroups



OS in PD-L1-Negative Subgroups

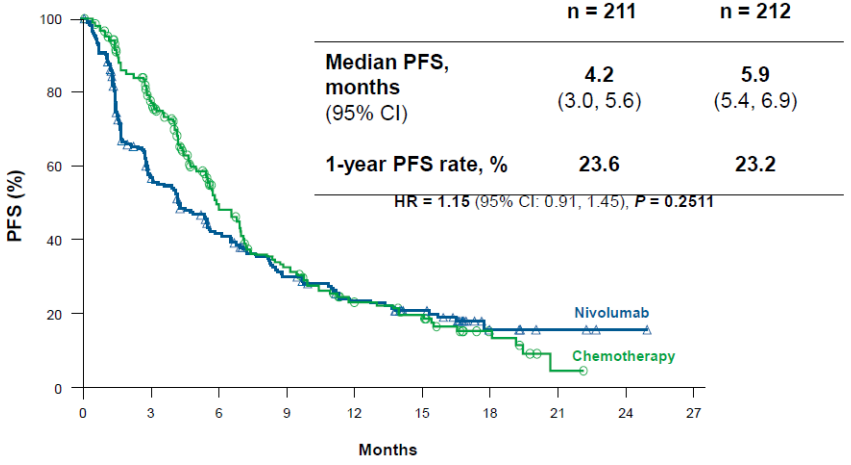


Each assay identifies cohorts with improved OS, both in the PD-L1 High and PD-L1 Negative subgroups

- Dx+, TC3 or IC3 (SP142) or TPS ≥50% (22C3); Dx–, not TC3 or IC3 (SP142) or TPS <50% (22C3)
- Gadgeel S et al. Presented at: ESMO 2017 Congress; September 2017; Madrid, Spain. Abstract 1296O.

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC: Biomarker Analysis

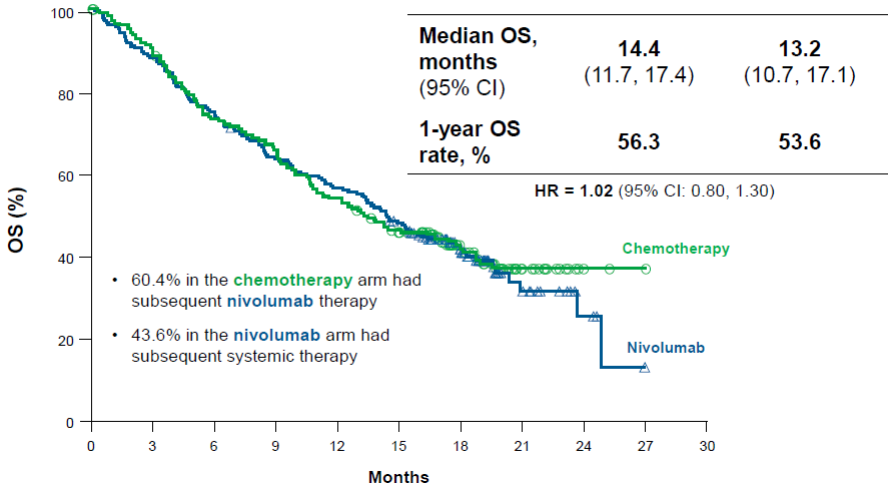
Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)



	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	4.2 (3.0, 5.6)	5.9 (5.4, 6.9)
1-year PFS rate, %	23.6	23.2

HR = 1.15 (95% CI: 0.91, 1.45), *P* = 0.2511

OS (≥5% PD-L1+)



	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	14.4 (11.7, 17.4)	13.2 (10.7, 17.1)
1-year OS rate, %	56.3	53.6

HR = 1.02 (95% CI: 0.80, 1.30)

	Nivolumab	Chemotherapy
ORR, % (95% CI)	26.1 (20.3, 32.5)	33.5 (27.2, 40.3)

Summary of CHECKMATE 026

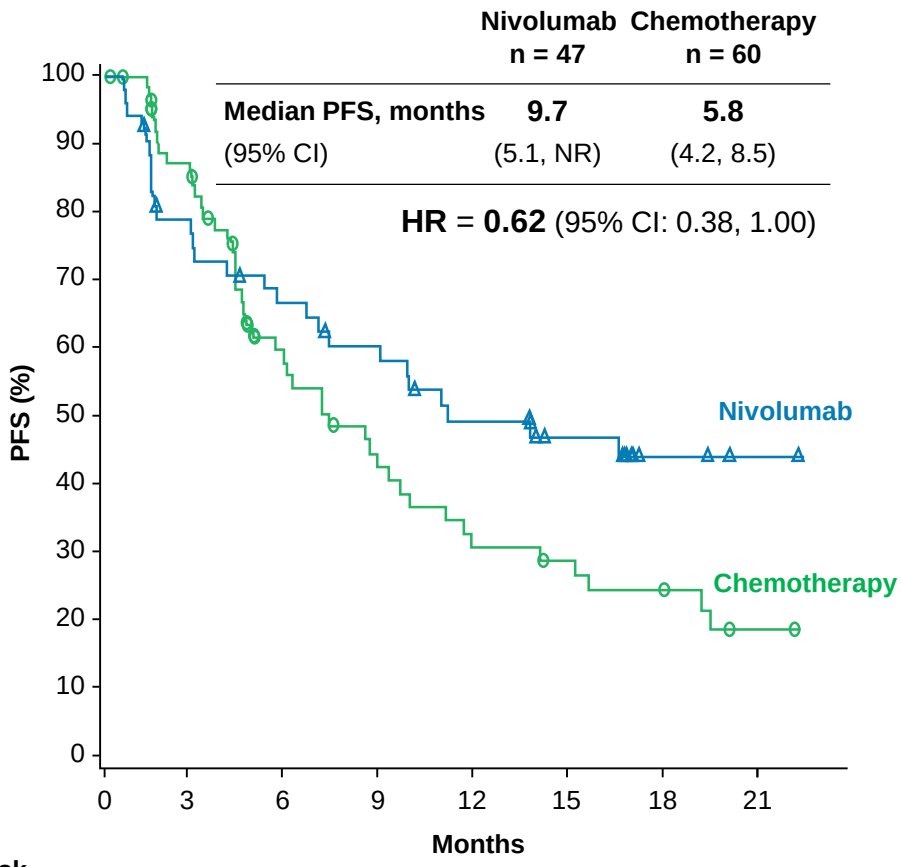
This trial was negative for the primary endpoint of improved PFS in NSCLC with PD-L1+ at 5% level (this is ~50% of the total NSCLC population)

Carbone et al: NEJM 2017

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC:

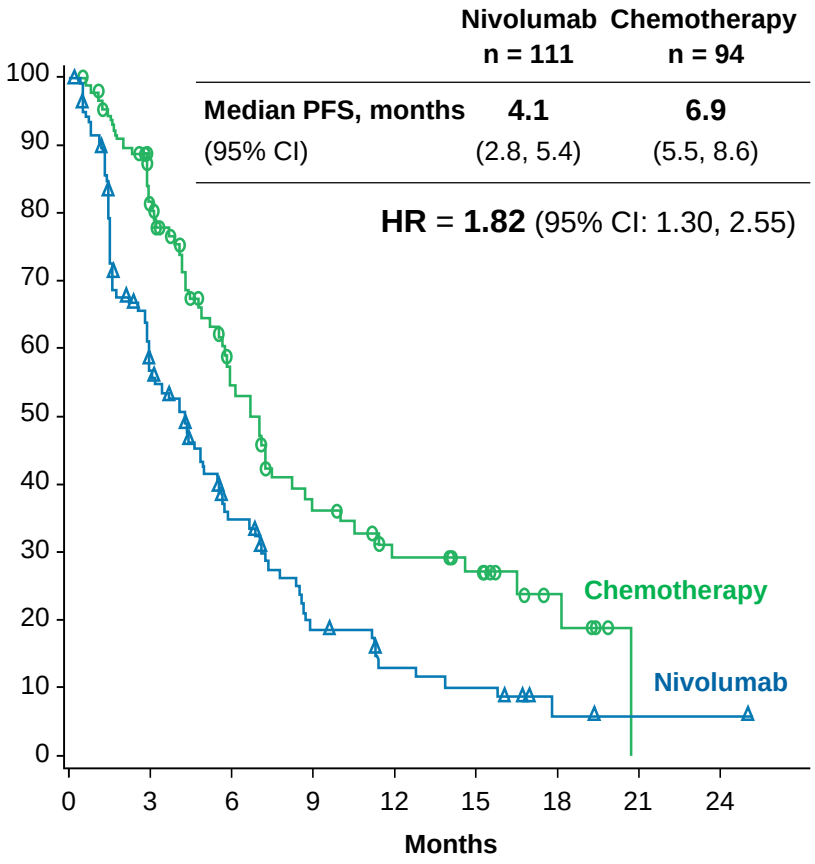
PFS by Tumor Mutation Burden Subgroup

High TMB



No. at Risk								
Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

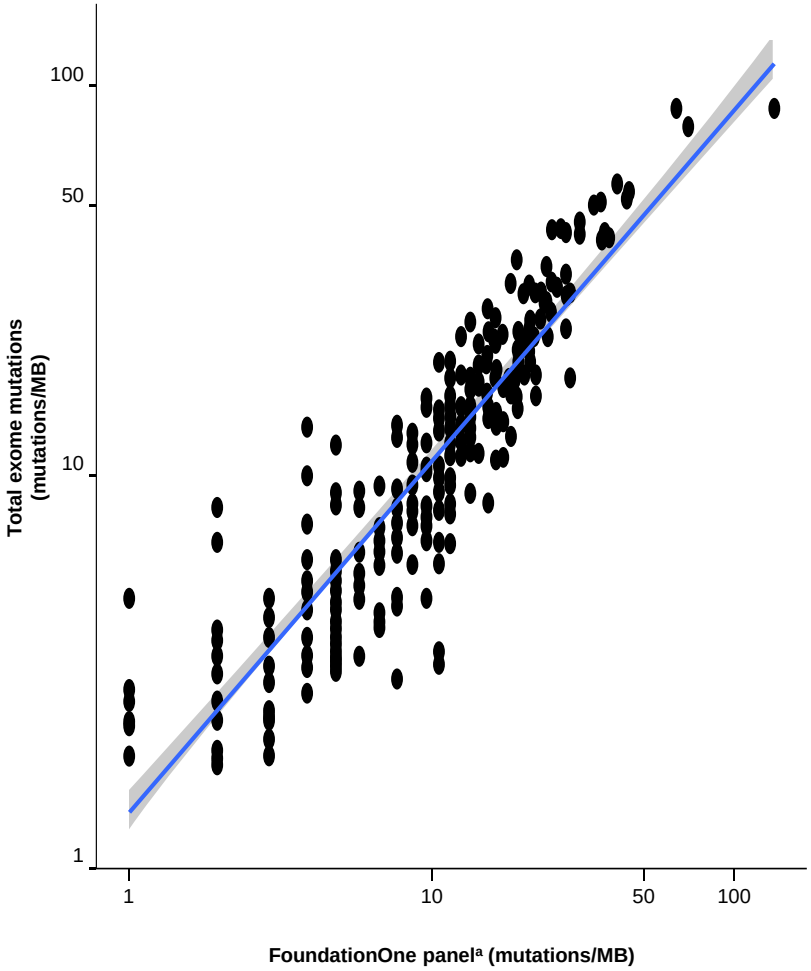
Low/medium TMB



Nivolumab	111	54	30	15	9	7	2	1	1
Chemotherapy	94	65	37	23	15	12	5	0	0

Carbone et al: NEJM 2017

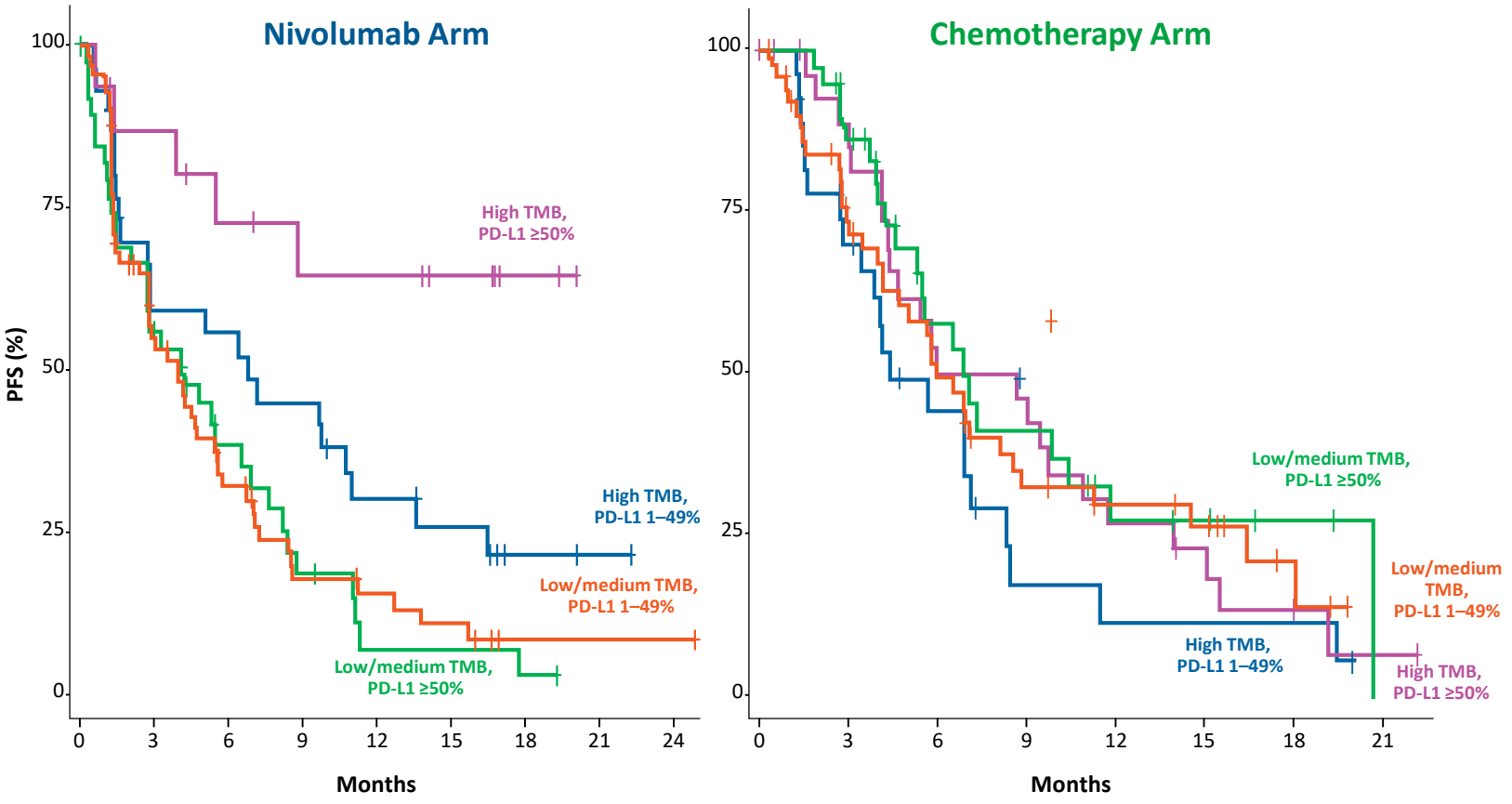
CheckMate 026 TMB Analysis:
Nivolumab vs Platinum Chemotherapy in 1st line NSCLC
Total Exome Mutations vs Genes in Foundation One Panel[a]



[a]Based on in silico analysis filtering on 315 genes in FoundationOne comprehensive genomic profile (Foundation Medicine, Inc, Cambridge, MA, USA)[1]

1. Frampton GM, et al. *Nat Biotechnol* 2013;31:1023–1031

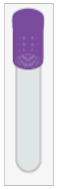
CM 026: PFS by TMB Subgroup and PD-L1 Expression



Peters et al, AACR 2017
Carbone et al, NEJM 2017

Tumor mutational burden in blood (bTMB) and Atezolizumab efficacy in 2nd-Line+ NSCLC (POPLAR & OAK Trials)

bTMB Computational Methodology and Study Design



Blood collection, plasma isolation & cfDNA extraction

Sequencing

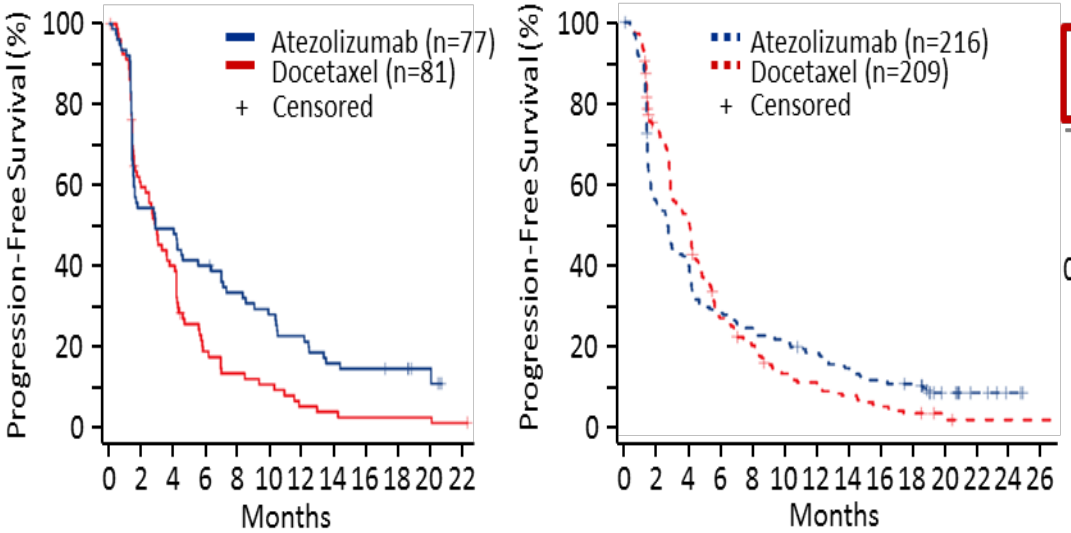
- All base substitutions at ≥0.5% allele frequency
- Remove germline polymorphisms & predicted driver mutations

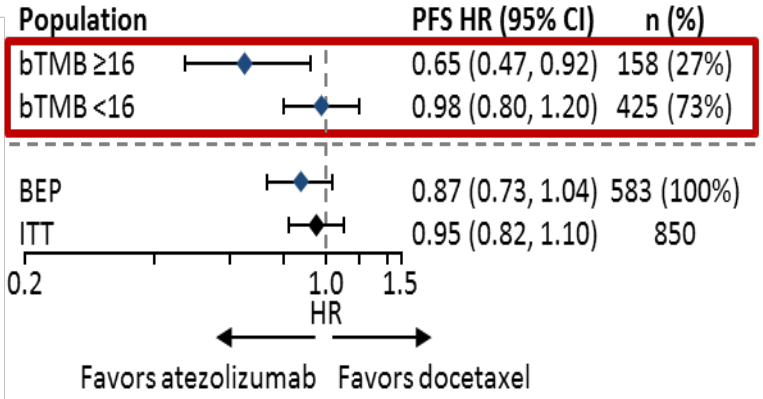
bTMB Score

POPLAR (training)
211/273 biomarker-evaluable

OAK (validation)
583/797 biomarker-evaluable

OAK Study





Gandara DR, et al. ESMO 2017. Abstr 1295O.

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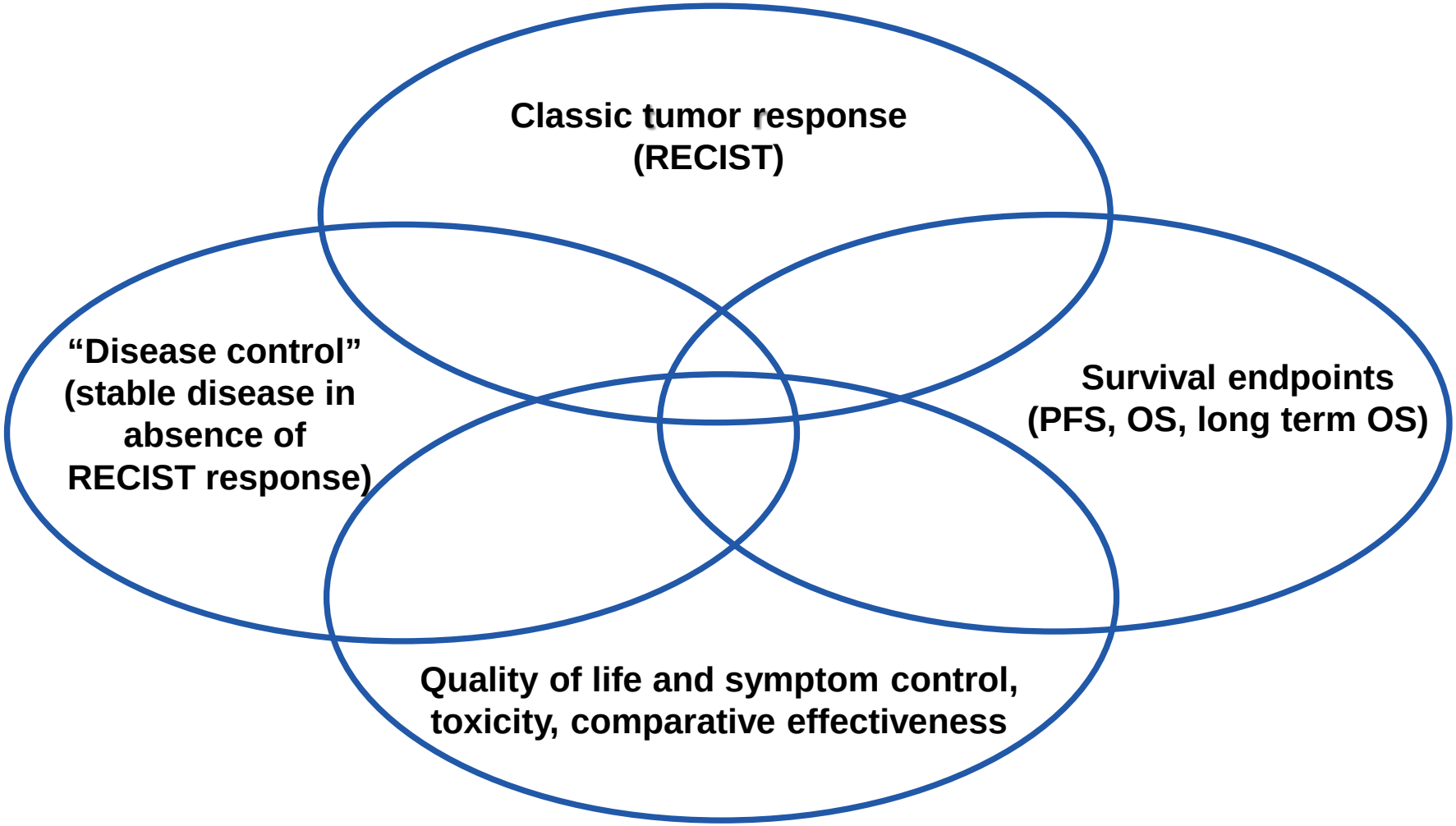
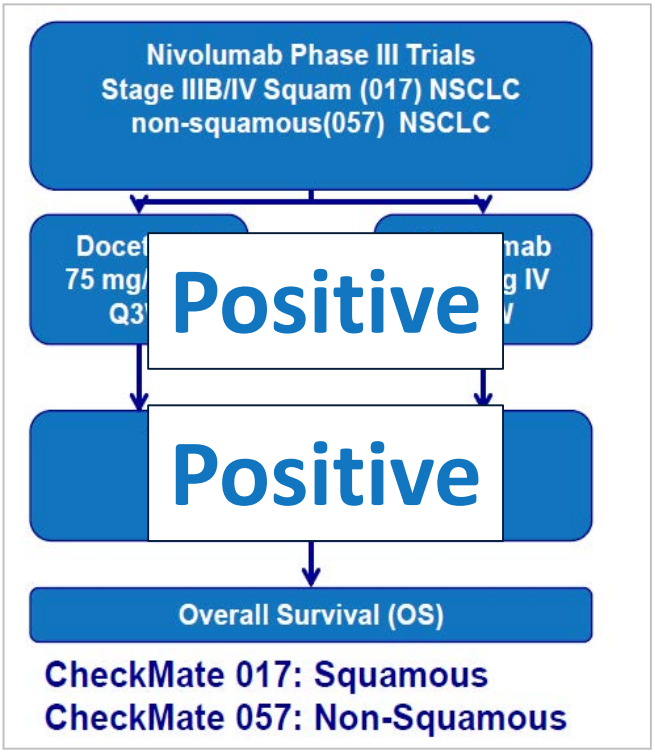
Measuring "Clinical Benefit" From Therapeutic Interventions: a Four-Dimensional Model



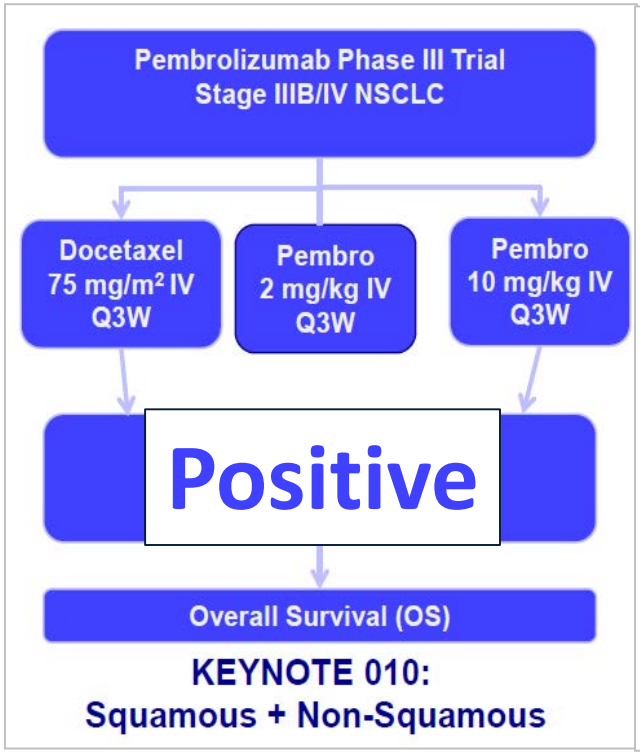
OS, overall survival; PFS, progression-free survival
Adapted from Gandara D, et al. IASLC WCLC 2009

Phase 3 Trials of Anti-PD-1/PD-L1 Therapy vs. Docetaxel in Second Line+ Advanced/Metastatic NSCLC

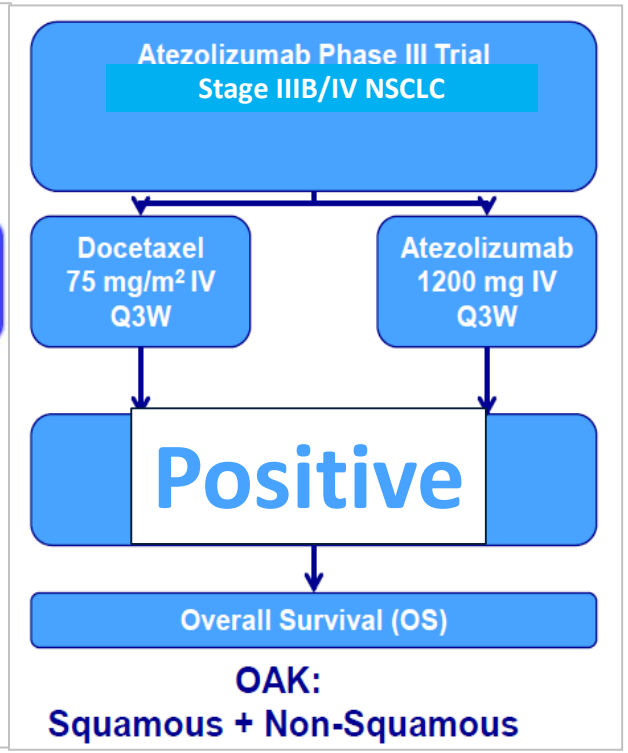
Nivolumab "All Comers" Strategy: (PD-L1+ and PD-L1-)[1,2]



Pembrolizumab Marker Positive Strategy: PD-L1+[3]



Atezolizumab Marker Positive Strategy: PD-L1+ (TC+ITL)[4]



IV, intravenous; Pembro, pembrolizumab; Q2W, every 2 weeks; Q3W, every 3 weeks

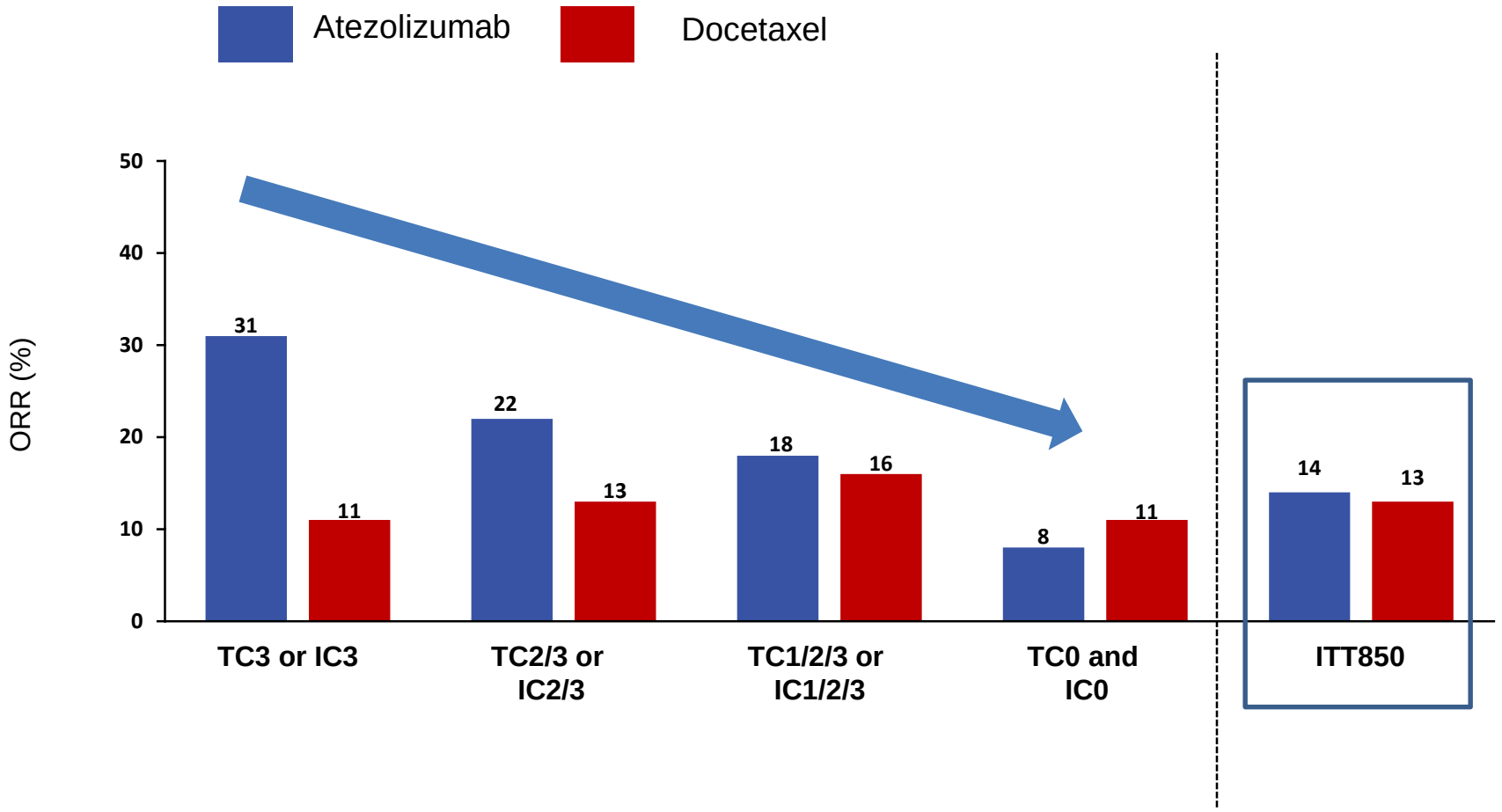
1. Brahmer J et al. *N Engl J Med.* 2015;373:123-135. 2. Borghaei H et al. *N Engl J Med*. 2015;373:1627-1639.
3. Herbst RS et al. *Lancet.* 2016;387:1540-1550. 4. Rittmeyer A, Gandara DR, et al. *Lancet*. 2017;389:255-265.

Response Rates of PD-1/PD-L1 Agents in 2nd-Line+ Phase III Trials

STUDY	ORR
CheckMate 017 (SQ)	20%
CheckMate 057 (Non-SQ)	19%
KEYNOTE 010	18%
OAK	15%

Response rates of PD-1/PD-L1 agents in 2nd line+ therapy of NSCLC are not impressive

OAK TRIAL: OVERALL RESPONSE RATE BY PD-L1 STATUS



Confirmed investigator-assessed ORR per RECIST v1.1.
DOR, duration of response; NE, not estimable; ORR, objective response rate.
TC, tumor cells; IC, tumor-infiltrating immune cells.

Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

mPFS from PD-1/PD-L1 Agents in 2nd-Line+ Phase III Trials

Trial	ORR	mPFS (mos)
CheckMate 017 (SQ)	20%	3.5
CheckMate 057 (Non-SQ)	19%	2.3 (4 -Docetaxel)
KEYNOTE 010	18%	4
OAK	15%	2.8 (4 -Docetaxel

mPFS of PD-1/PD-L1 agents in 2nd line+ therapy of NSCLC are not impressive, And are sometimes misleading

mOS from PD-1/PD-L1 Agents in 2nd-Line+ Phase III Trials

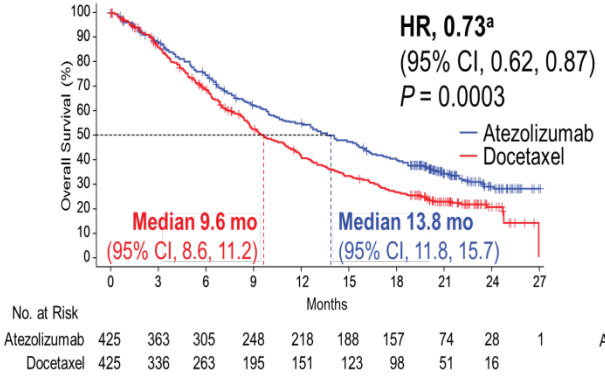
Trial	ORR	mPFS (mos)	mOS (mos)
CheckMate 017 (SQ)	20%	3.5	9.2
CheckMate 057 (Non-SQ)	19%	2.3	12.2
KEYNOTE 010	18%	4	12.7
OAK	15%	2.8	13.8

It is in OS that PD-1/PD-L1 agents are most promising

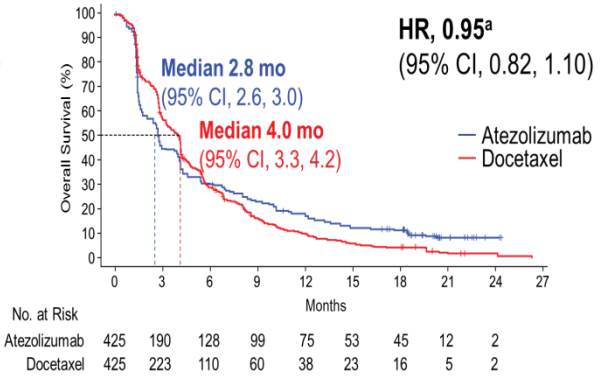
Discordance of OS from ORR and PFS in the OAK trial of Atezolizumab vs Docetaxel in 2nd line+ NSCLC

- **RECIST v1.1-based endpoints such as ORR and PFS underestimate the potential OS benefit of checkpoint immunotherapy (CIT)**
  - **Hypothesis: CIT may alters tumor biology such that survival benefit extends beyond radiographic progression, termed post progression prolongation of survival (PPPS),[1] an effect particularly relevant to PD-L1 inhibitors such as atezolizumab due to inhibition of PD-L1:PD-1 and PD-L1:B7.1 interactions**
  - **Discordance between OS and ORR/PFS was seen in Ph III OAK study of atezolizumab vs docetaxel , which demonstrated OS benefit but no improvement in ORR/PFS[2]**

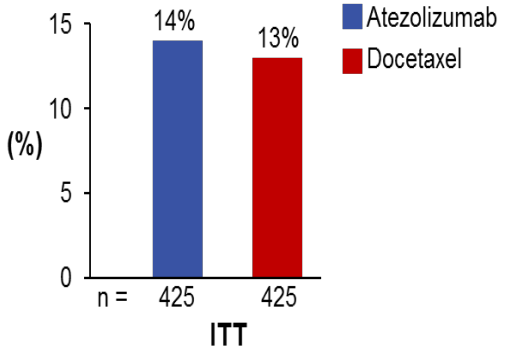
OS



PFS



ORR



- **Similar discordance was previously observed in the Ph II POPLAR study**

[a]Stratified HRs. ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Gandara D et al. JAMA Onc 2016. 2. Rittmeyer A et al. Lancet 2017. 3. Mazieres J et al. ASCO 2016.

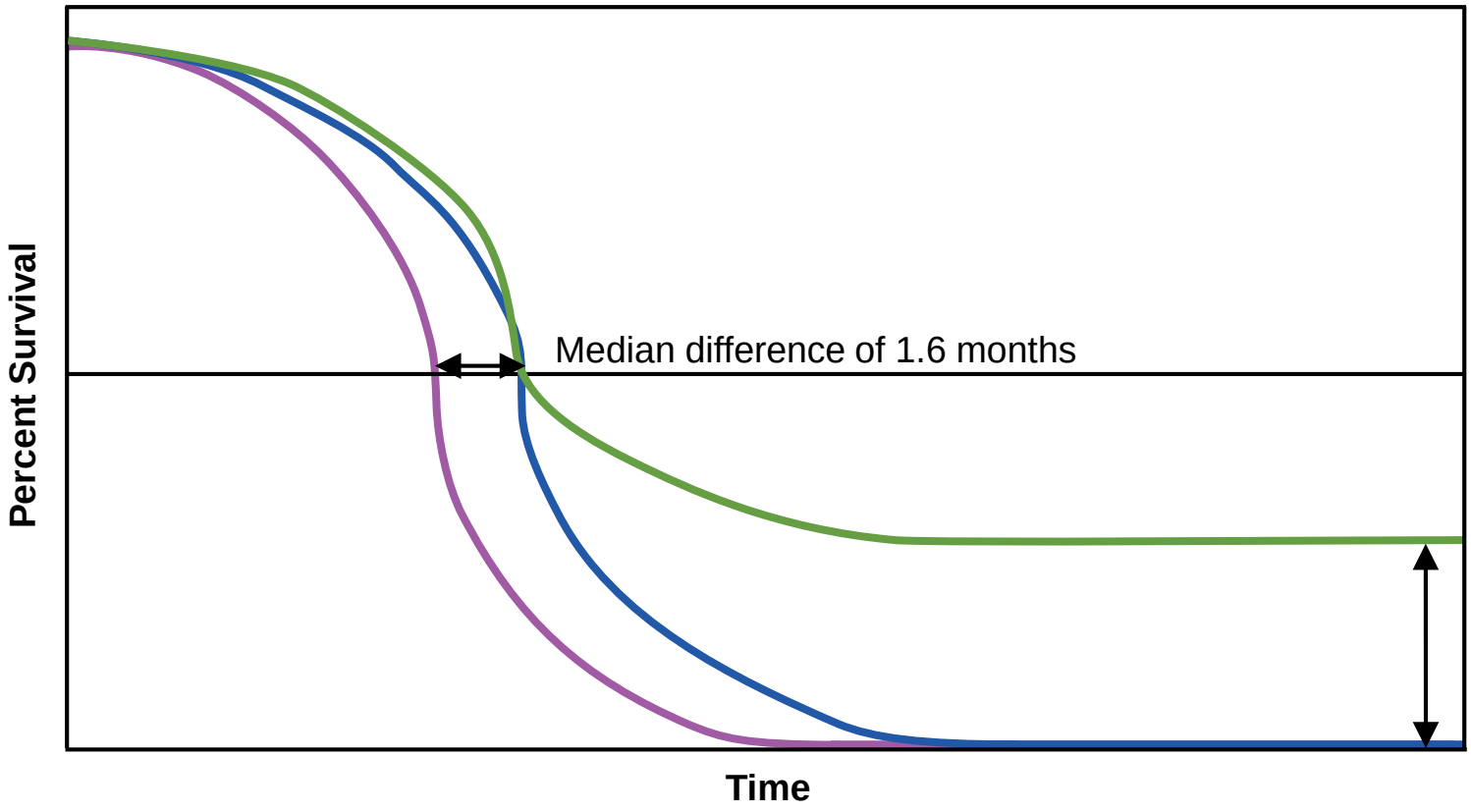
Gandara DR et al. OAK: Atezolizumab treatment beyond disease progression.

PD-1/PD-L1 Agents in 2nd-Line+ Phase III Trials

Trial	ORR	mPFS (mos)	mOS (mos)
CheckMate 017 (SQ)	20%	3.5	9.2 (HR 0.62)
CheckMate 057 (Non-SQ)	19%	2.3	12.2 (HR 0.75)
KEYNOTE 010	18%	4	12.7 (HR 0.61)
OAK	15%	2.8	13.8 (HR 0.73)

HR is a more appropriate way of expressing the KM curve

Measuring Survival Endpoints by the Median: Misinterpreting the Kaplan-Meier Curve



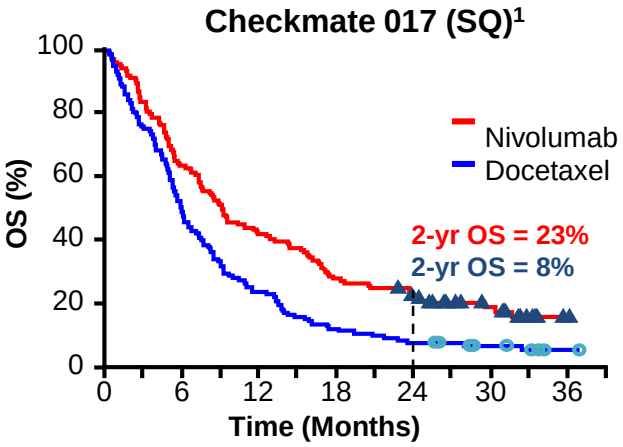
Gandara D, et al. UCDCC 2015

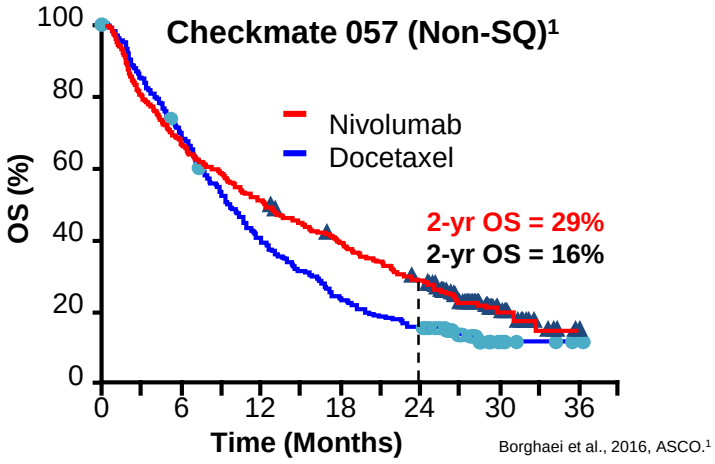
PD-1/PD-L1 Agents in 2nd-Line+ Phase III Trials

Trial	ORR	mPFS (mos)	mOS (mos)	2 yr OS
CheckMate 017 (SQ)	20%	3.5	9.2 (HR 0.62)	23%
CheckMate 057 (Non-SQ)	19%	2.3	12.2 (HR 0.75)	29%
KEYNOTE 010	18%	4	12.7 (HR 0.61)	29.5%
OAK	15%	2.8	13.8 (HR 0.73)	31%

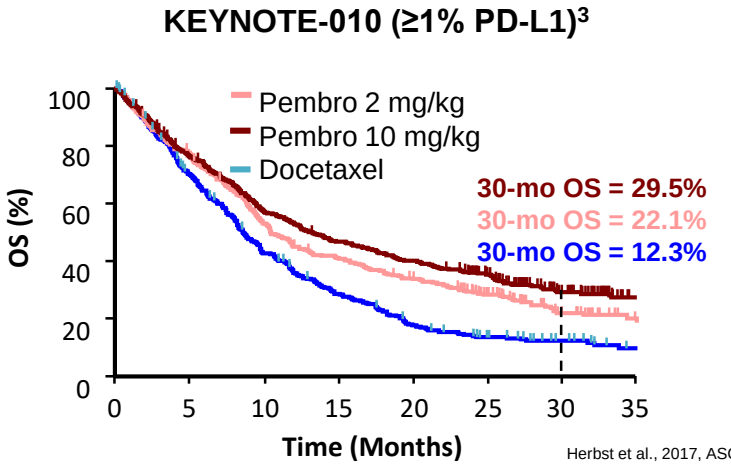
Long term OS with PD-1/PD-L1 agents in 2nd line+ therapy offers the potential for "Cure"

Consistent Benefit in OS in 2nd line+ Phase III Trials

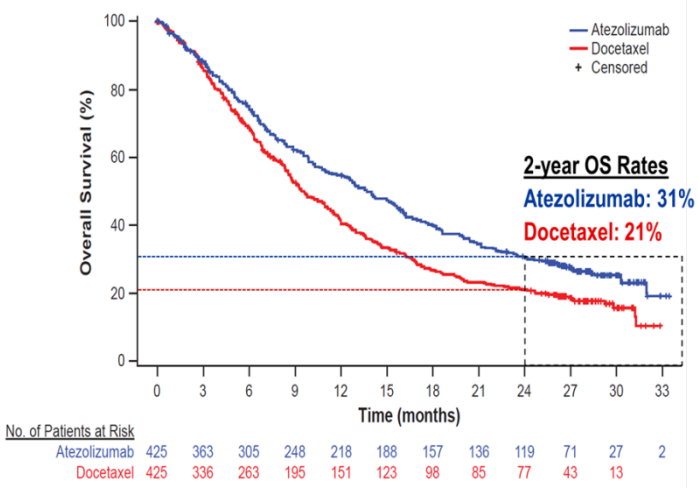




Borghaei et al., 2016, ASCO.[1]

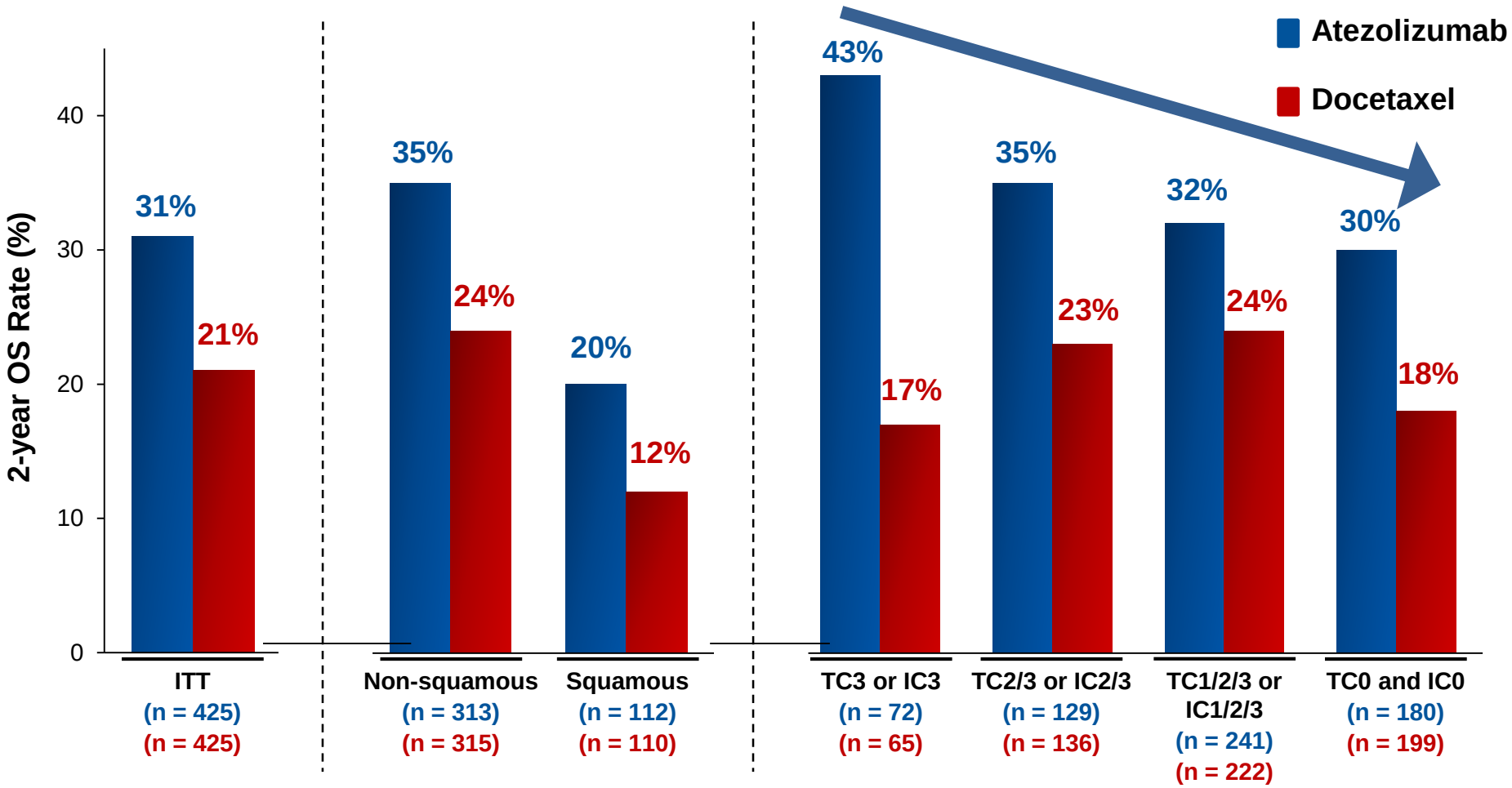


Herbst et al., 2017, ASCO.[3]



Satouchi, et al. WCLC 2017

Long-term survival benefit at 2 years by histology and PD-L1 expression subgroups in OAK Trial



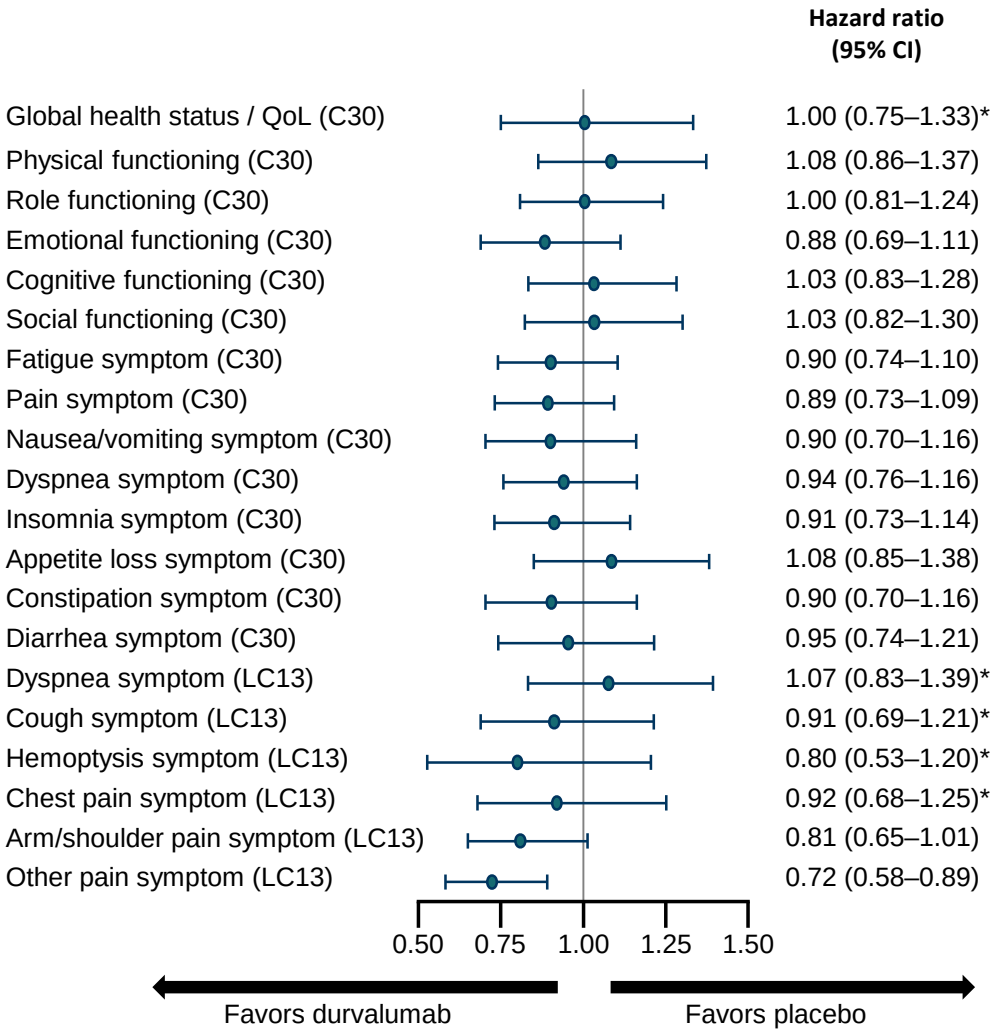
•IC, tumor-infiltrating immune cells; TC, tumor cells. Data cutoff: 23 January, 2017.
•TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+.

Satouchi, et al. WCLC 2017

Current Issues in the Clinical Application of Checkpoint Immunotherapy (IO)

- Selection of Patients most likely & least likely to Benefit by Predictive Biomarkers
  - PD-L1 Assay
  - Tumor Mutational Burden (TMB)
- Judging Clinical Efficacy
  - Best endpoint: ORR, PFS, OS, LTS (long term survivors)?
  - QOL/Symptom Control
- Recognition & Management of Immune-related Adverse Events
  - Guidelines
  - Clinical Judgement

PACIFIC: Chemo-RT +/- Durvalumab
Time to Deterioration in Function and Symptoms



- No differences between Durvalumab and placebo in time to deterioration for functioning or most symptoms

*Figures in brackets denote 99% CI. 'Other pain' refers to anything other than chest pain and arm/shoulder pain
CI, confidence interval; QoL, quality of life; TTD, time to deterioration

Current Issues in Checkpoint Immunotherapy for NSCLC: A Perspective from January 2018

- Overview of Immunotherapy trial results in advanced NSCLC
  - 1st line
  - 2nd line
- Selection of Patients most likely & least likely to Benefit:
  - Clinical Factors (Smoking status, Histology, PS)
  - Predictive Biomarkers
    - PD-L1 Assay
    - Tumor Mutational Burden (TMB)
    - Other biomarkers in development
- Judging Clinical Efficacy
  - Best endpoint: ORR, PFS, OS, LTS (long term survivors)?
  - QOL/Symptom Control