Current Issues in Checkpoint Immunotherapy for NSCLC: A Perspective from February 2020

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Disclosures

- **Institutional Research Grants: Astex, Roche-Genentech, Merck**

- **Consultant/Advisory Board: AstraZeneca, Celgene, CellMax, FujiFilm, Roche-Genentech, Guardant Health, Inivata, IO Biotech, Lilly, Merck, Oncocyte, Samsung Bioepis**

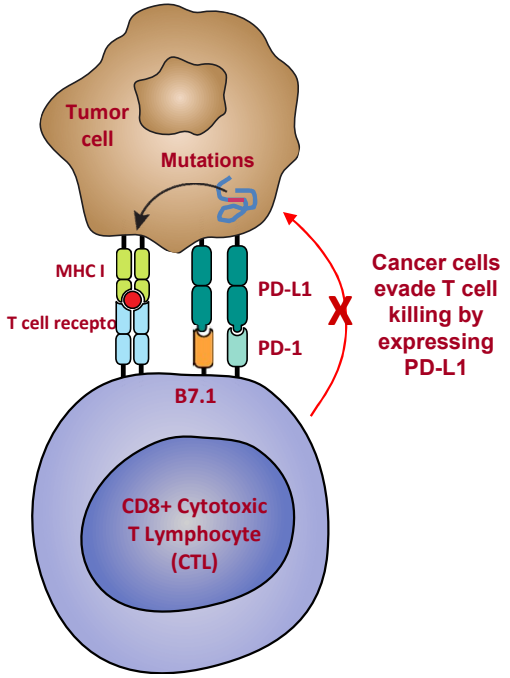
Current Issues in Checkpoint Immunotherapy (CPI) for NSCLC: A Perspective from February 2020

- Overview: Evolving Role of CPI in advanced (Stage IV) NSCLC
- Predictive Biomarkers
    - PD-L1 Assay
    - Tumor Mutational Burden (TMB)
    - Other biomarkers in development
- Clinical trial results in advanced NSCLC
  - 2nd line CPI Monotherapy –Updates on Long Term Survival
  - 1st line (CPI monotherapy, CPI-Chemotherapy)
- Stage III Unresectable NSCLC: Platinum Chemotherapy/RT → Consolidation CPI (PACIFIC)

Checkpoint Immunotherapy for Advanced NSCLC

- Cancer cells have mutations that make them recognizable by the immune system (neo-antigens)
- Theoretically, the higher the mutational burden of neoantigens (e.g. through smoking), the greater the immune recognition
- Cancer cells can evade immune surveillance by expressing proteins such as PD-L1 (serves as a predictive biomarker)
- Inhibiting PD-L1/PD-1 interaction can restore anti-tumor T-cell activity, leading to immune-mediated response
- Multiple Phase III trials of PD(L)-1 agents in advanced NSCLC
  - Some positive, some negative
  - Many variables to consider
- Predictive biomarkers:

  PD-L1 IHC, TMB (tumor mutational burden)



Major PD-1/PD-L1 antagonists

√ • Nivolumab (anti-PD-1)
√ • Pembrolizumab (anti-PD-1)
√ • Atezolizumab (MPDL3280A, anti-PD-L1)
√ • Durvalumab (MEDI-4736, anti-PD-L1)
• Avelumab (anti-PD-L1)

Compartmental Treatment Algorithm for Advanced NSCLC: As of January 2020

Patients With Advanced Stage NSCLC (PS 0-1)

	Non-Squamous			Squamous	
	Oncogene-Driven	PD-L1+	PD-L1-	PD-L1+	PD-L1-
1st Line	TKI (Targeted therapy) EGFR, ALK, ROS1, BRAF TKIs	Pembro ± Chemo or Atezo-Bev-Chemo	Pembro-Chemo or Atezo-Bev-Chemo	Pembro ± Chemo or Atezo-Chemo	Pembro-Chemo or Atezo-Chemo
1st Line Maintenance	EGFR, ALK, ROS1, BRAF TKIs	Pembro-Pem or Atezo-Bev	Pembro-Pem or Atezo-Bev	Pembro or Atezo	Pembro or Atezo
2nd Line	Next-Gen TKIs	Nivo or Pembro or Atezo	Nivo or Pembro or Atezo	Nivo or Pembro or Atezo	Nivo or Pembro or Atezo
		Docetaxel (± Anti-angiogenic)	Docetaxel (± Anti-angiogenic)	Docetaxel (± Anti-angiogenic)	Docetaxel (± Anti-angiogenic)
		Chemo	Chemo	Chemo	Chemo
2nd-3rd Line	3rd-GEN TKI or Chemo doublet	Chemo	Chemo	Chemo	Chemo
				Afatinib	Afatinib

Adapted from Gandara et al. *Clin Lung Cancer*. 2017; 18:1

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Immune Phenotype as potential Predictive Biomarkers for benefit from Checkpoint Immunotherapy

Tumor Neo-antigenicity

- Biomarkers indicative of hypermutation & neoantigens

Examples:

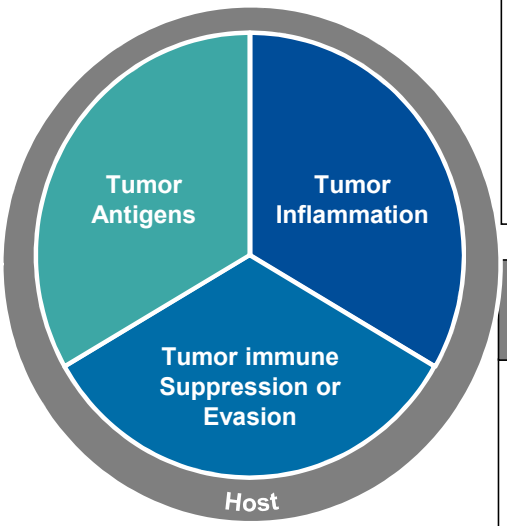
–TMB, MSI-high, neoantigen load

Tumor Microenvironment (Inflammation)

- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype

Examples:

–PD-L1, inflammatory signatures



Tumor Immune Suppression/Evasion

- Biomarkers that identify tumor immune system suppression or evasion beyond PD-1/CTLA-4

Examples:

–Tregs, MDSCs, IDO, LAG-3

–STK11 and KEAP1

Host Environment (e.g. Microbiome)

- Biomarkers that characterize the host environment, beyond tumor microenvironment

Examples:

–Microbiome, germline genetics

Adapted from Blank CU, et al. *Science* 2016;352:658–660

Predictive Biomarkers for Checkpoint Immunotherapy (CPI)

Note: cannot be equated to a discrete variable like driver mutations (Present or Absent)

PD-L1 & TMB are dynamic & continuous variables across a context-specific range

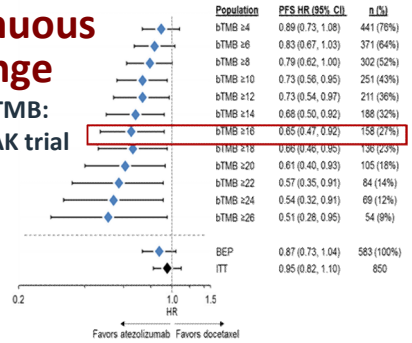
- **Which Biomarker(s)?**
  - PD-L1 IHC
  - TMB
  - PD-L1 IHC + TMB
  - PD-L1 + TMB + Other
  - Multitude of Others

- TMB Assessment
  - WES vs Neo-antigen Load vs NGS
    - Optimal Cutpoints for each
    - Tumor-type specific vs Agnostic
  - Tissue vs Blood

- **Which Analytic Algorithm for Analysis?**
  - Across a Continuous Range
  - As a Binary Variable

Continuous Range

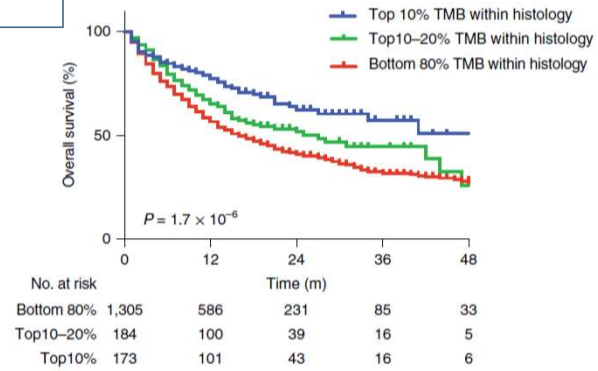
Blood TMB:
PFS in OAK trial



Gandara et al: NatMed 2018

As a Binary Variable

TMB highest 10-20% across Tumor Types



Samstein et al: NatGen 2018

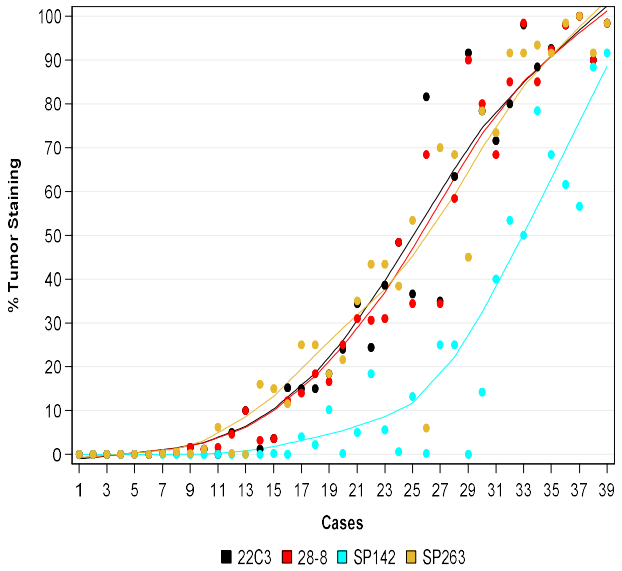
- **What is the context?** (Biomarker for which type of CPI regimen)
  - NSCLC (Squamous or Non-Squamous) vs SCLC
  - CTLA-4 vs PD-1/PD-L1 vs PD-1/PD-L1 + CTLA-4
  - PD-1/PD-L1 + Platinum Chemotherapy

→ **Chemotherapy likely "agnostic" to immuno-biomarker . "Dilutes out predictive value**

Gandara: Lung Cancer Summit. ESMO19

Analytical Validation of PD-L1 Assay Systems: The Blueprint Project

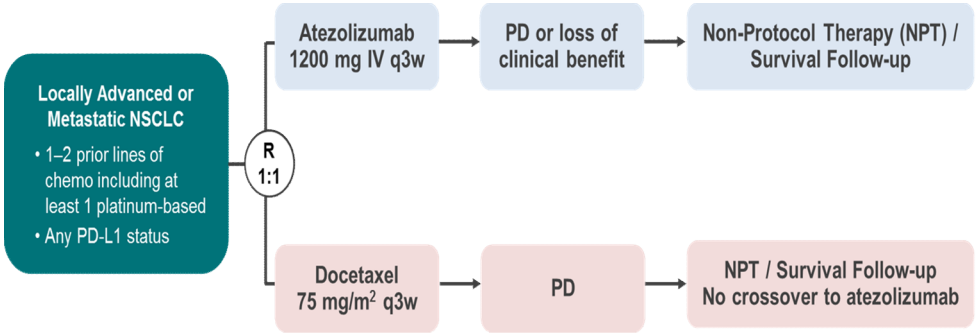
Assay primary antibody clone	28-8(Dako)		22C3(Dako)		SP142(Ventana)	SP263(Ventana)
PD-1/PD-L1 Agent	Nivolumab (BMS)		Pembrolizumab (Merck)		Atezolizumab (Genentech)	Durvalumab (AstraZeneca)
Interpretative Scoring	Tumor cell membrane		Tumor cell membrane		-Tumor cell membrane -Infiltrating immune cells	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



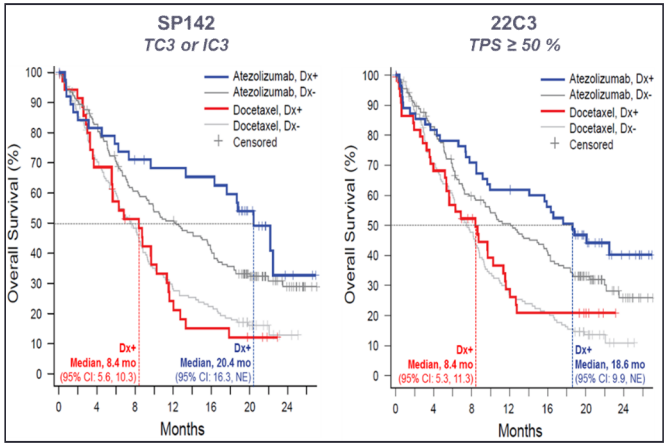
- Analytical comparison of % tumor cell staining (Tumor Proportion Score), by case, for each assay
- Data points represent the mean score from three pathologists for each assay on each case
- **Conclusion:** 3 of 4 assays are analytically similar for tumor cell staining (SP142 is outlier)

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

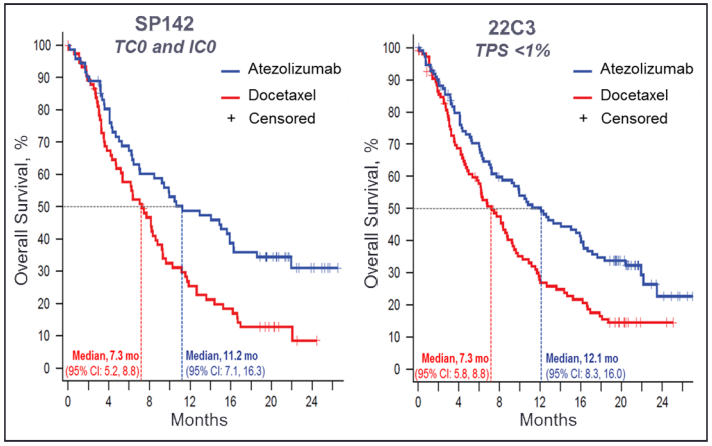
Comparison of PD-L1 assays (Dako 22C3 vs Ventana SP142) in OAK Trial Specimens



OS in PD-L1-High Subgroups

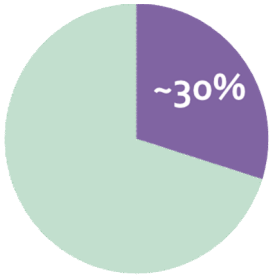


OS in PD-L1-Negative Subgroups



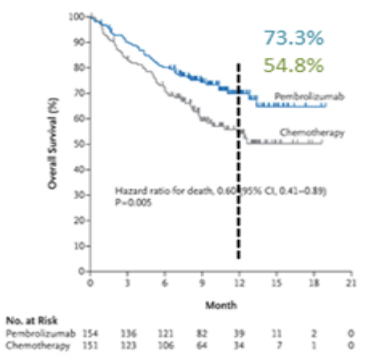
Gadgeel S et al. ESMO 2017 Abstract 1296O.

PD-L1 ≥50% distinguishes a Patient Subset with Substantial Benefit from CPI Monotherapy (KN024) as well as CPI + Chemotherapy (KN189)



PD-L1 ≥50%
EGFR/ALK WT

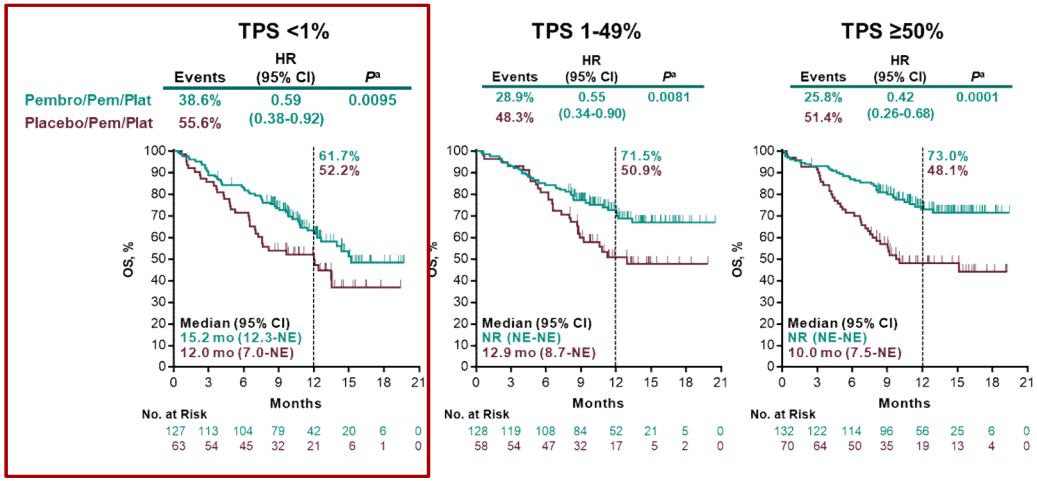
KeyNote 24: Pembro Monotherapy (OS by TPS ≥50%)



OS: HR 0.60 [95% CI 0.41-0.89]
p=0.005

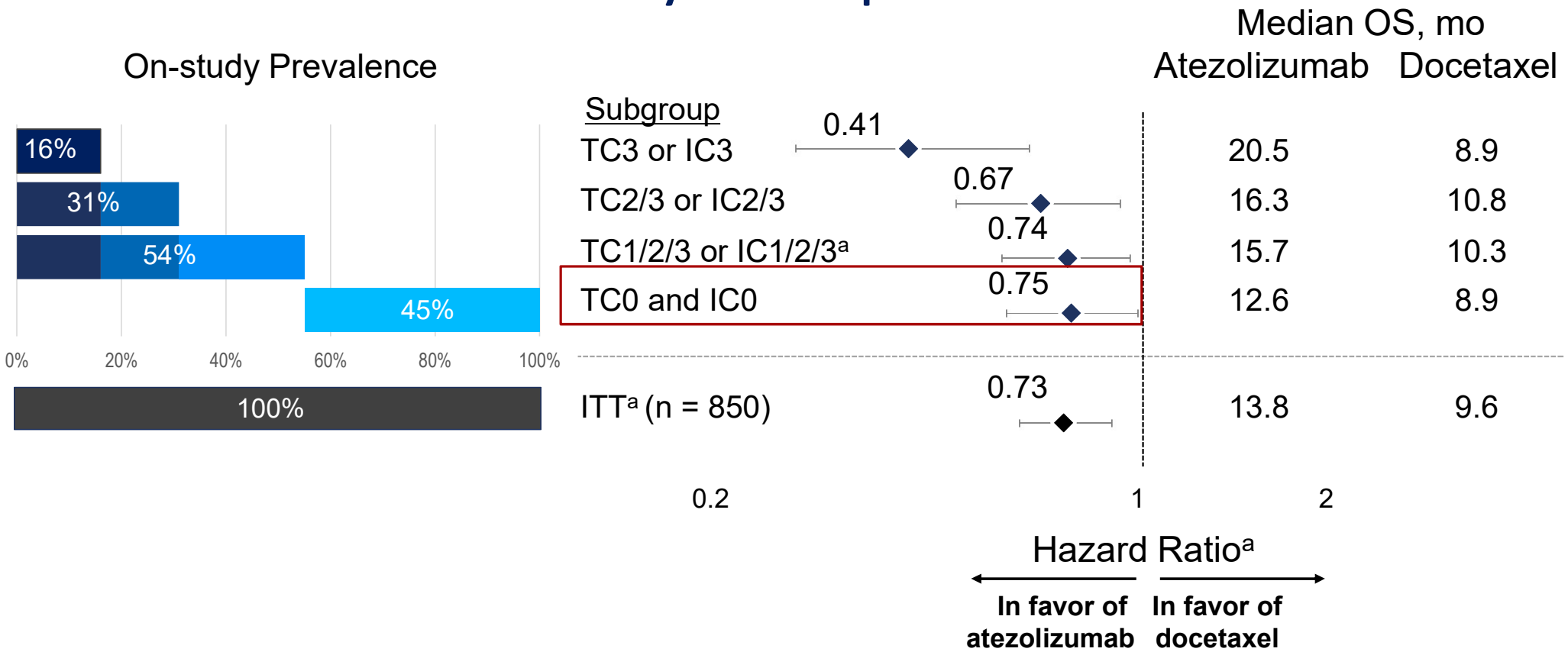
Reck et al. NEJM 2016; 275:1823-1833

KeyNote 189: Pembro-Chemo (OS by PD-L1 TPS)



Gandhi et al. NEJM 2016

OAK (Atezolizumab vs Docetaxel in 2nd line+ Advanced NSCLC: OS by PD-L1 Expression

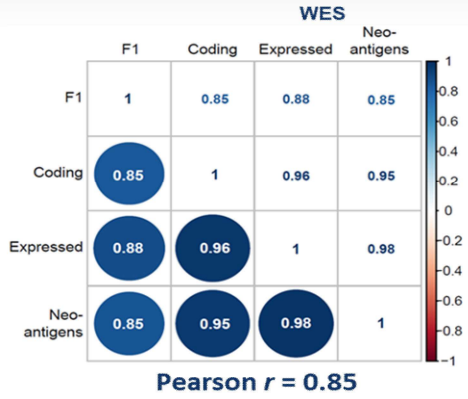


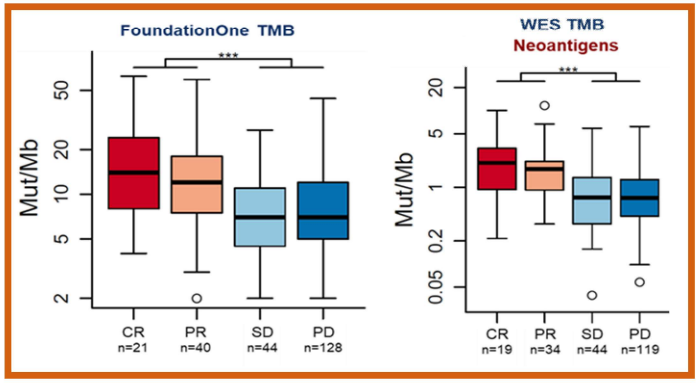
[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for other subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

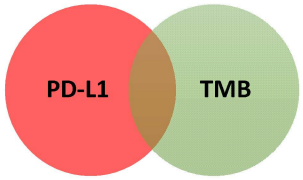
Rittmeyer. Gandara et al. Lancet. 2017;389:255-265

Tumor Mutational Burden (TMB) as a Candidate Predictive Biomarker for Cancer Immunotherapy

- **Somatic mutations in cancers are multifactorial** (including DNA repair defects, carcinogens & enzymatic alterations in DNA polymerases)
- These mutations produce **neoantigens** that induce anti-tumor immune responses
- **TMB is an emerging predictive biomarker** for cancer checkpoint immunotherapy (CIT)
- TMB can be estimated using whole-exome sequencing (WES) or comprehensive genomic profiling by NGS (e.g., FoundationOne & FACT in blood[bTMB]) . MSK-IMPACT. Guardant OMNI[1-8]
  - Studies show that TMB either by WES or CGP correlate with each other & with efficacy of CPI therapy in multiple cancer types[1-3]
- **Predicted neoantigen load (NAL),** a component of TMB most closely linked to immune response, correlates with F1 TMB[4,5,7]
- **TMB identifies a distinct patient population** not currently captured by PD-L1 IHC or other immune biomarkers[5,6]





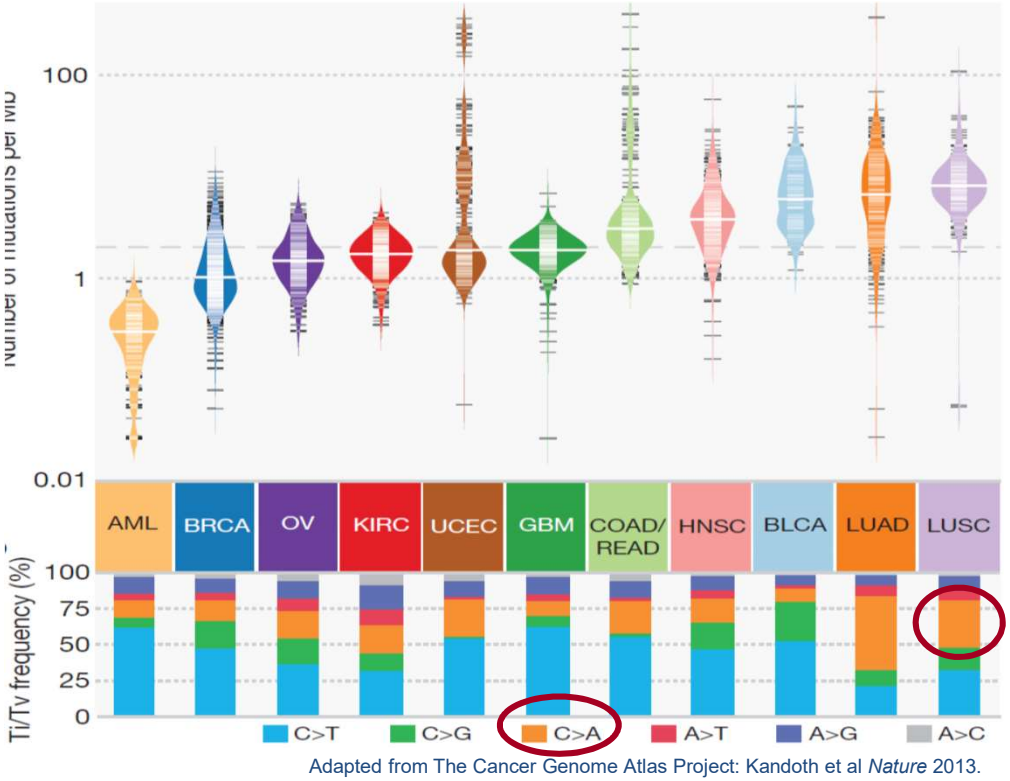


From Gandara, LeGrand et al: ASCO 2018

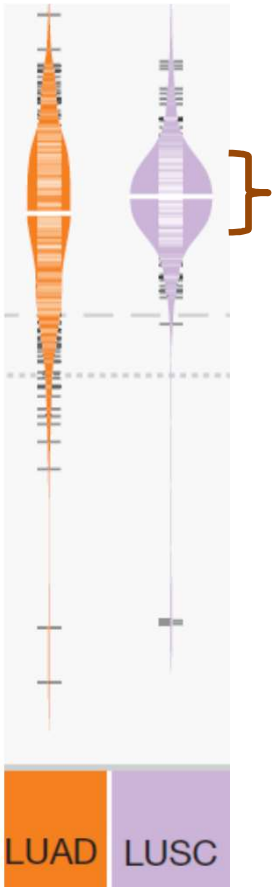
IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.

1. Yarchoan M, et al. *N Engl J Med.* 2017; 2. Chalmers ZR, et al. *Genome Med.* 2017; 3. Goodman AM, et al. *Mol Cancer Ther.* 2017; 4. Efremova M, et al. *Front Immunol.* 2017; 5. Topalian SL, et al. *Nat Rev Cancer.* 2016; 6. Kowanetz M, et al. WCLC 2017. 7. Mariathansan, et al. Nature 2018. 8. Rizvi et al: ESMO IO 2018.

Magnitude of Genomic Derangement ("Mutational Load") in Various Cancers & Subtypes

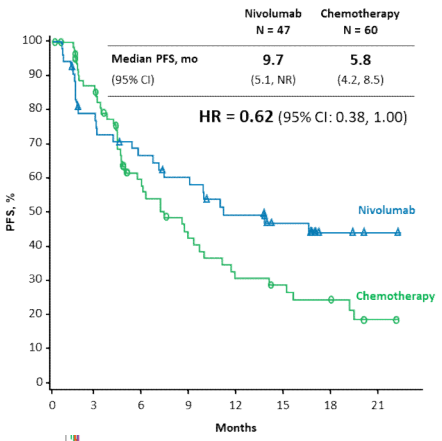


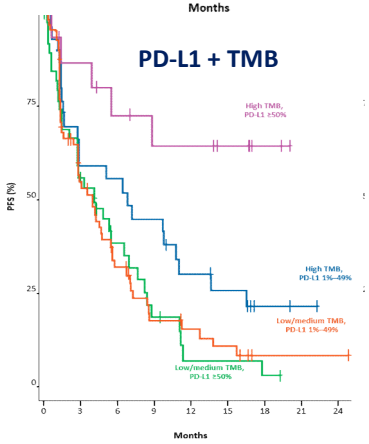
Adapted from The Cancer Genome Atlas Project: Kandoth et al *Nature* 2013.



High Tissue TMB is associated with increased efficacy of Checkpoint Inhibitor Monotherapy

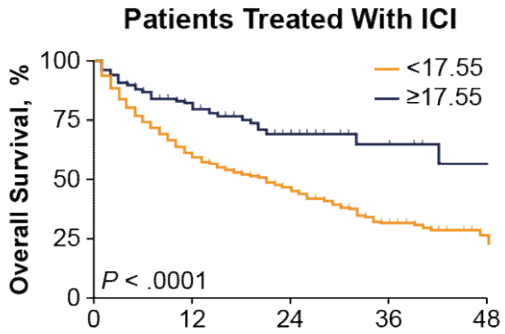
WES: CM-026 NSCLC (Nivo -high TMB)

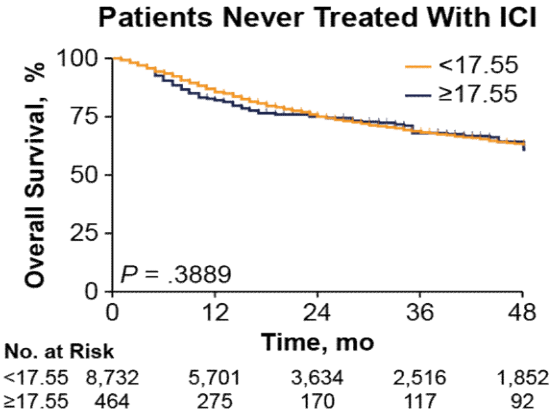




Carbone et al: NEJM 2017

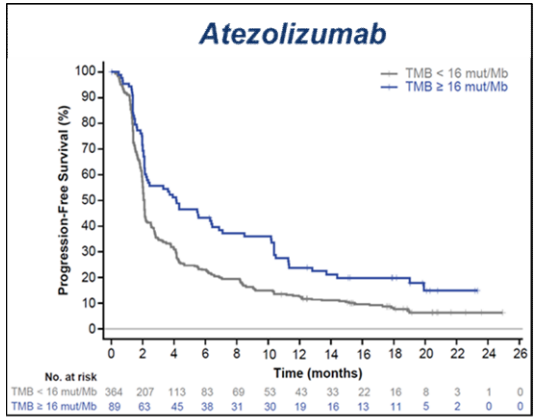
NGS -IMPACT: Multiple Tumor Types

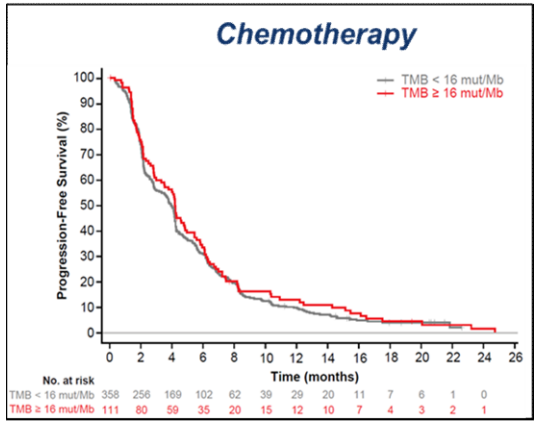




Samstein et al: NatGen 2019

NGS Foundation-One: Multiple Tumor Types

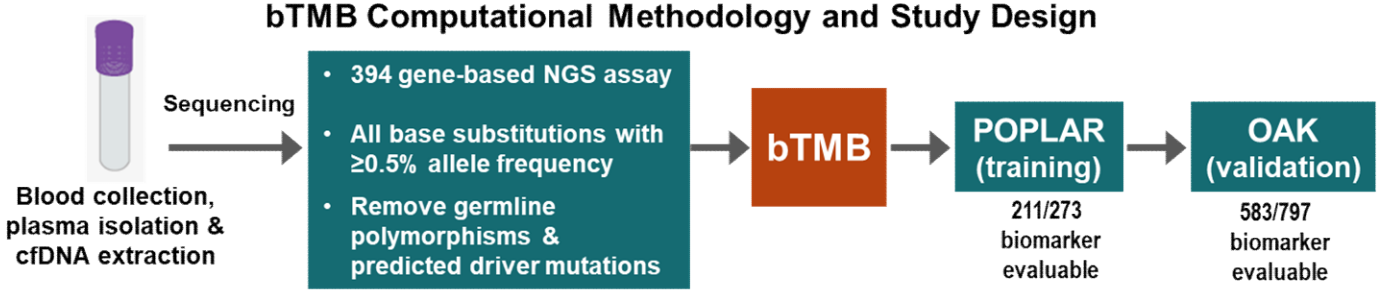


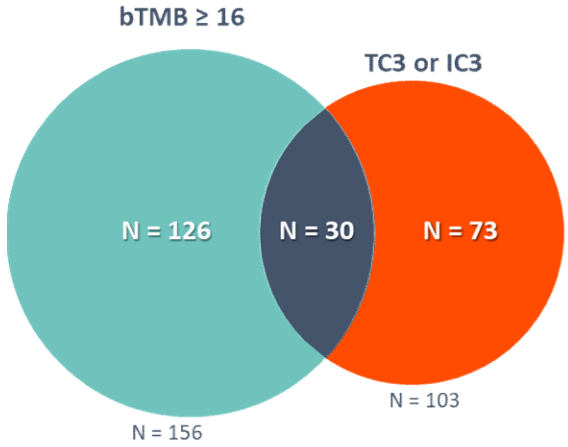


Gandara, Legrand et al: ASCO 2018

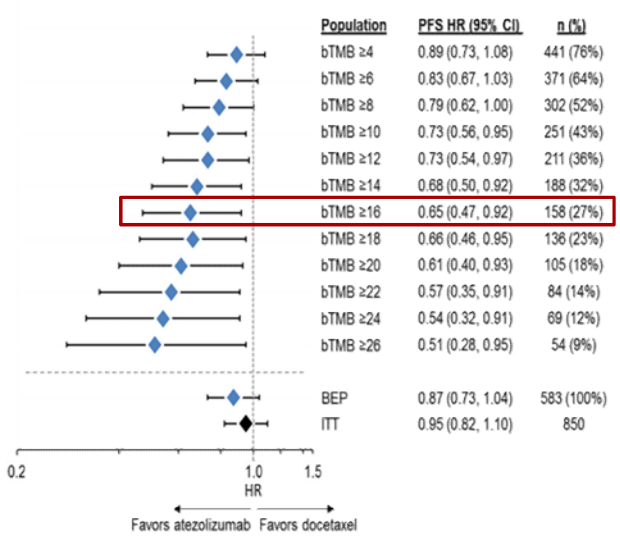
Analytical & Clinical Validation of Tumor Mutational Burden in Blood (bTMB) in association with Atezolizumab efficacy in advanced NSCLC (POPLAR & OAK Trials)

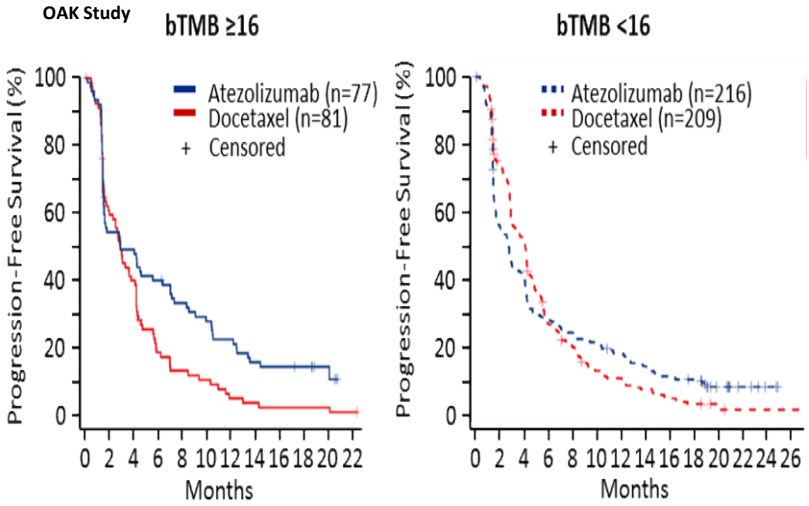
bTMB Computational Methodology and Study Design





Progression-Free Survival – OAK



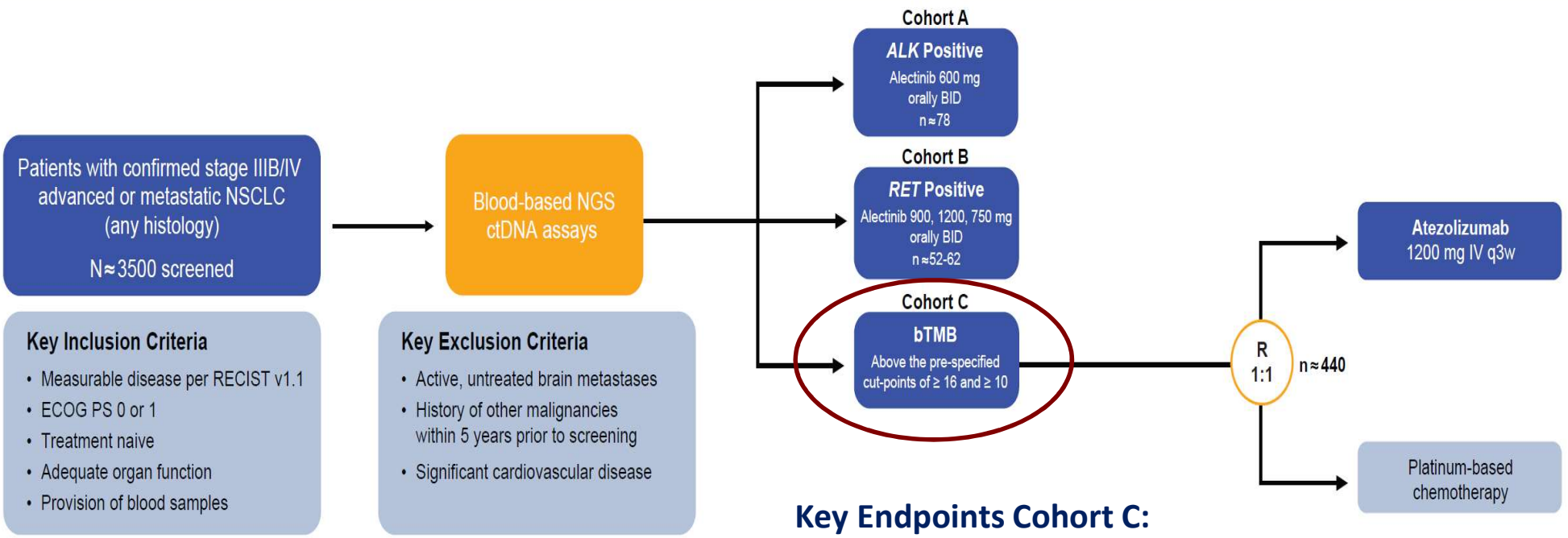


BEP (N = 229)

	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

Gandara DR, et al. Nature Med 2018.

BFAST (Blood First Assay Screening Trial): Phase II/III in Advanced Treatment-naïve Advanced NSCLC



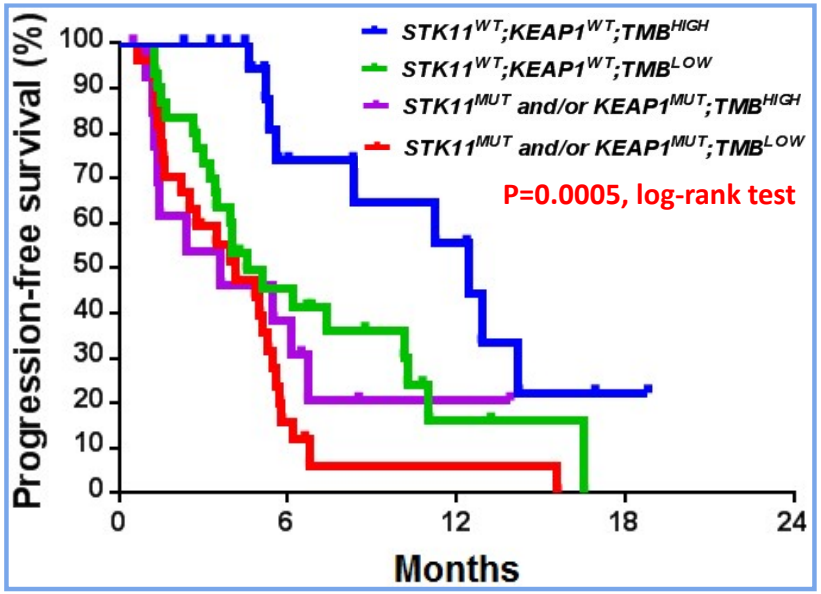
Key Endpoints Cohort C:

- Primary = PFS by Investigators
- (hierarchical testing, bTMB>16 first, then bTMB >10)
- Secondary = PFS by IRF, OS, ORR, PRO

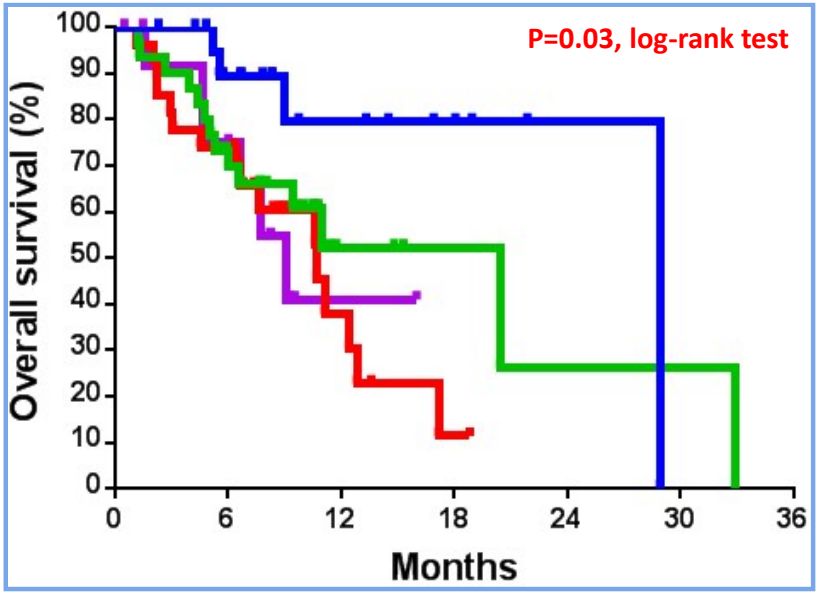
Accrual Completed 9/2019

Integration of *STK11* and *KEAP1* genomic alterations with TMB and other biomarkers: Moving towards a composite panel?

Group	PFS
$STK11^{WT}$;$KEAP1^{WT}$;TMB^{HIGH}	12.4m
$STK11^{WT}$;$KEAP1^{WT}$;TMB^{LOW}	4.5m
$STK11^{MUT}$ and/or $KEAP1^{MUT}$;TMB^{HIGH}	4.1m
$STK11^{MUT}$ and/or $KEAP1^{MUT}$;TMB^{LOW}	3.6m



Group	OS
$STK11^{WT}$;$KEAP1^{WT}$;TMB^{HIGH}	28.9m
$STK11^{WT}$;$KEAP1^{WT}$;TMB^{LOW}	20.4m
$STK11^{MUT}$ and/or $KEAP1^{MUT}$;TMB^{HIGH}	10.7m
$STK11^{MUT}$ and/or $KEAP1^{MUT}$;TMB^{LOW}	9.1m



Skoulidis: ASCO 2019.

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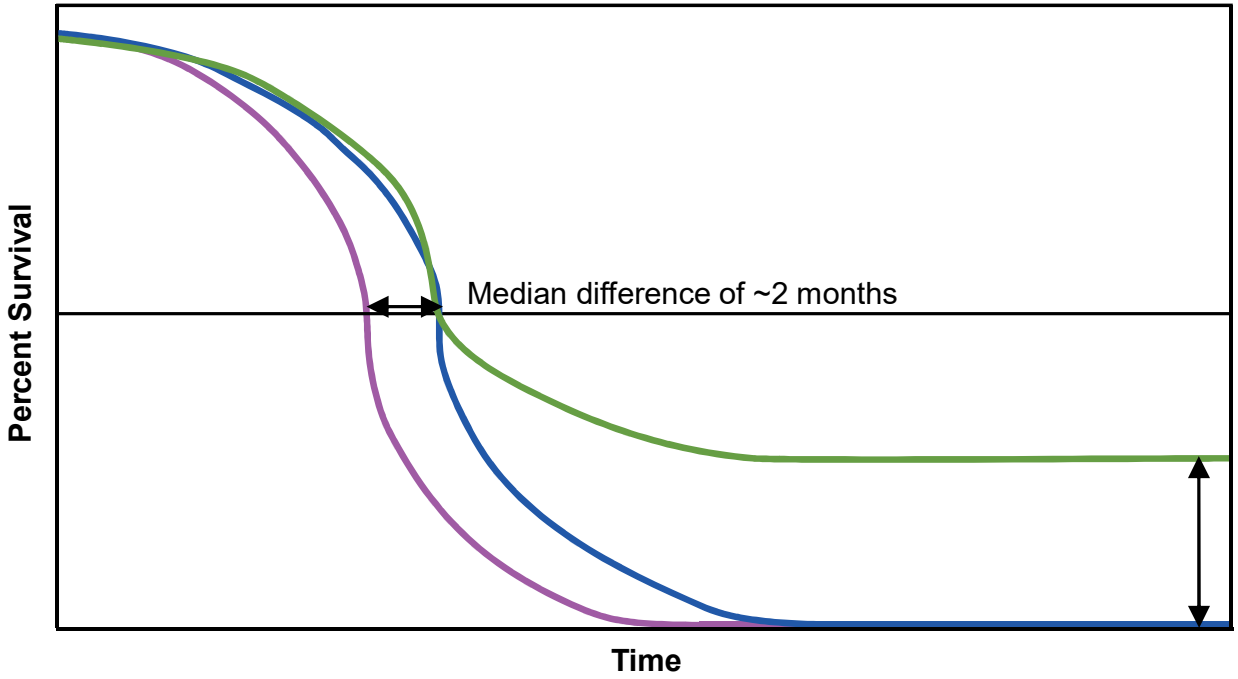
Key 2nd+ Phase III Trials of Checkpoint Immunotherapy in Advanced NSCLC							
Study	Drug	PDL1 Selection	Line of therapy	Control	Primary Endpoint	HR-Primary Endpoint	FDA Approval
CM017 (SQ)	Nivo	None	2nd	Docetaxel	OS	0.62	Yes
CM057 (Non-SQ)	Nivo	None	2nd-3rd	Docetaxel	OS	0.75	Yes
K010	Pembro	>1%	2nd-3rd	Docetaxel	OS & PFS	0.61	Yes
OAK	Atezo	None	2nd-3rd	Docetaxel	OS	0.73	Yes

Trial	ORR	mPFS (mos)	mOS (mos)	2 yr OS
CheckMate 017 (SQ)	20%	3.5	9.2	23%
CheckMate 057 (Non-SQ)	19%	2.3	12.2	29%
KEYNOTE 010	18%	4	12.7	30%
OAK	15%	2.8	13.8	31%

Gandara:
Best of ASCO Central Europe 2019

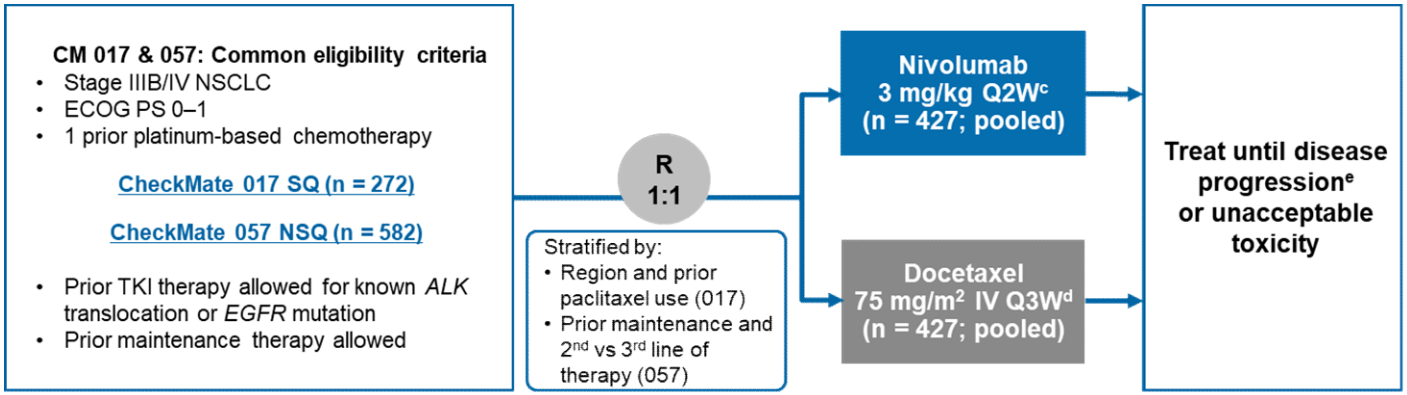
Extending the Tail of the Kaplan-Meier Curve: Potential for "Cure"

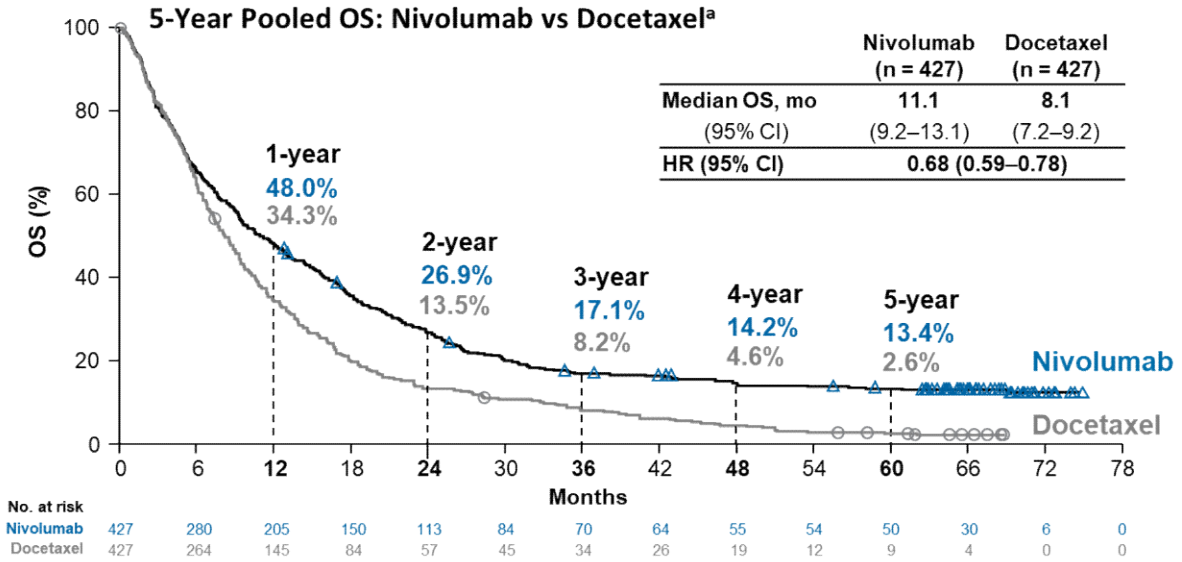


The "tail: of the OS curve for long term survival is the most important aspect of PD-1/PD-L1 therapy

Gandara D, et al. UCDCC 2015

Long Term (5 year) OS in CheckMate 017 & 057

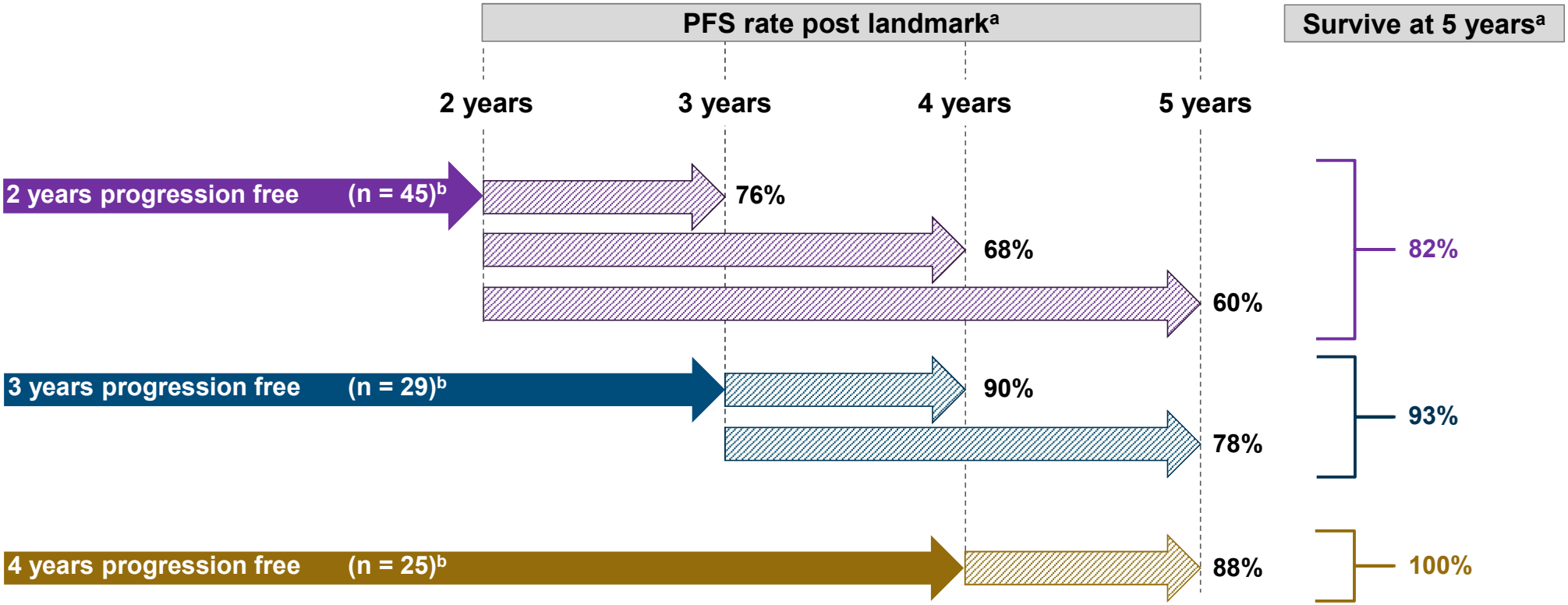




Trial	Nivo	Doc
CM017	12.3%	3.6%
CM057	14%	2.1%

Gettinger et al: WCLC 2019

PFS and OS Landmark Analyses by PFS at 2, 3, and 4 Years

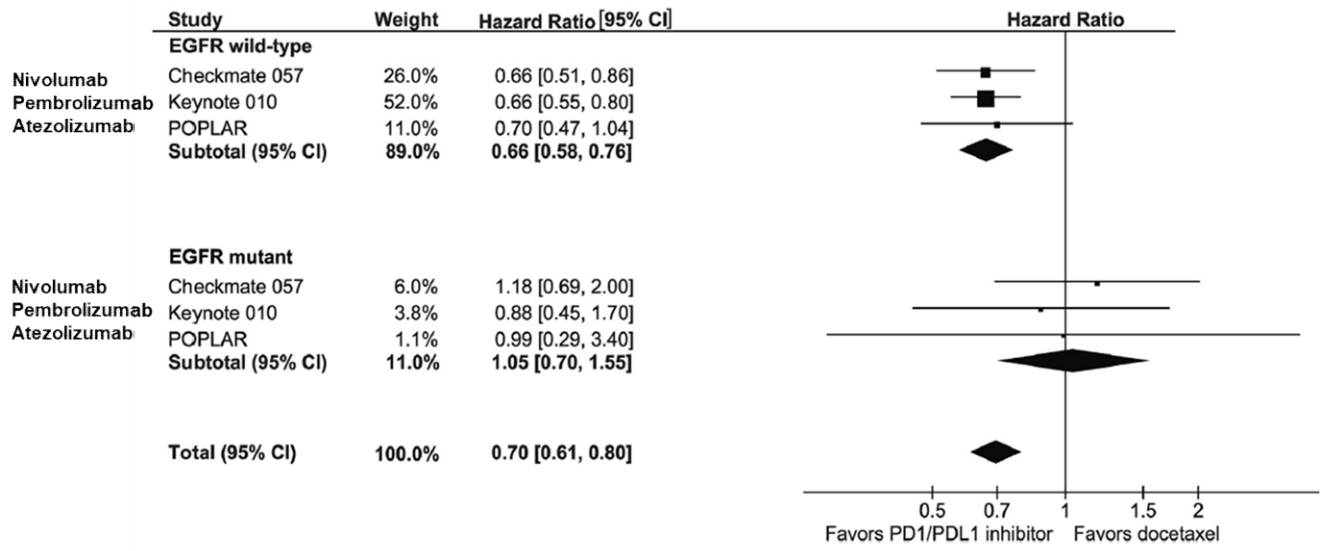


- There were 4, 1, and 0 patients who had PFS ≥ 2, 3, and 4 years, respectively, in the docetaxel arm; none of these patients survived ≥ 5 years

Gettinger et al: WCLC 2019

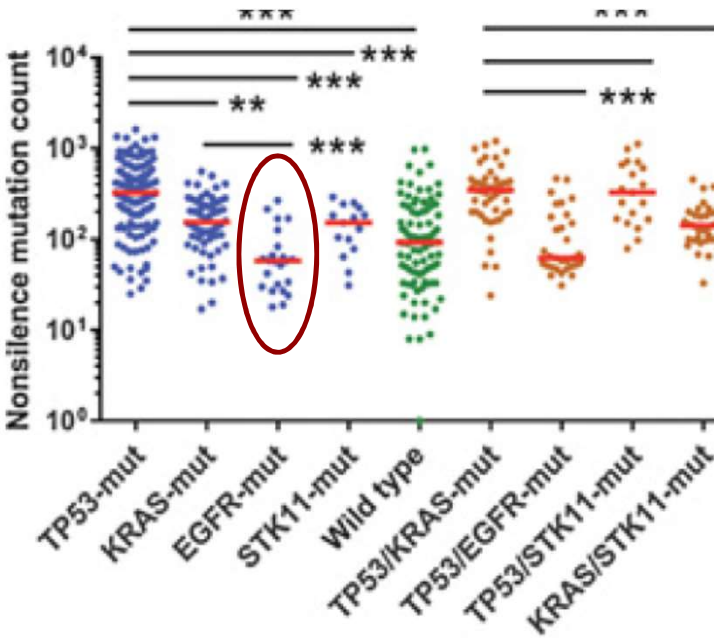
Oncogene-driven NSCLC: Efficacy of PD1/PD-L1 inhibitors is poor and TMB is low

PD-(L)1 Inhibitors in EGFR-mutated NSCLC



Lee CK, et al. J Thorac Oncol 2016

TMB is low in EGFR-mutated cancers



Dong, Wu et al CCR 2017

Clinical Trial Results of 1st line Checkpoint Immunotherapy in Advanced NSCLC							
Study	Drug (vs Chemo)	PDL1 Selection	Line of Therapy	Control	Primary Endpoint	HR-Primary Endpoint	Result
KN024	Pembro	≥50%	1st	Plat Chemo	PFS	0.50	Positive
CM026	Nivo	≥5%	1st	Plat Chemo	PFS	1.15	Negative
MYSTIC	Durva or Durva-Tremi	≥25%	1st	Plat Chemo	PFS & OS	NR	Negative
KN189 (Non-SQ)	Pembro-Chemo	≥1%	1st	Plat Chemo	PFS	0.52	Positive
KN042	Pembro	≥1%	1st	Plat Chemot	OS	0.81 for OS 0.69 for 50%	Positive
KN047 (SQ)	Pembro-Chemo	None	1st	Plat-Nab Paclitax	PFS & OS	0.64 for OS	Positive
Impower 150 (Non-SQ)	Atezo +Bev/ Pac/Carbo	None	1st	Bev/Pac Carbo	PFS OS	0.71	Positive
Impower 131 (SQ)	Atezo + Nab/Carbo	None	1st	Pac/ Carbo	PFS OS	0.71 (PFS)	Positive
CM227	Nivo or Nivo-Ipi	<1% & TMB≥10	1st	Plat Chemo	PFS & OS	0.58 (in H-TMB)	Positive
IMpower 110	Atezo	≥1%	1st	Plat Chemo	OS in TC3/IC3	0.59	Positive

New ⇨

1st Line Trials

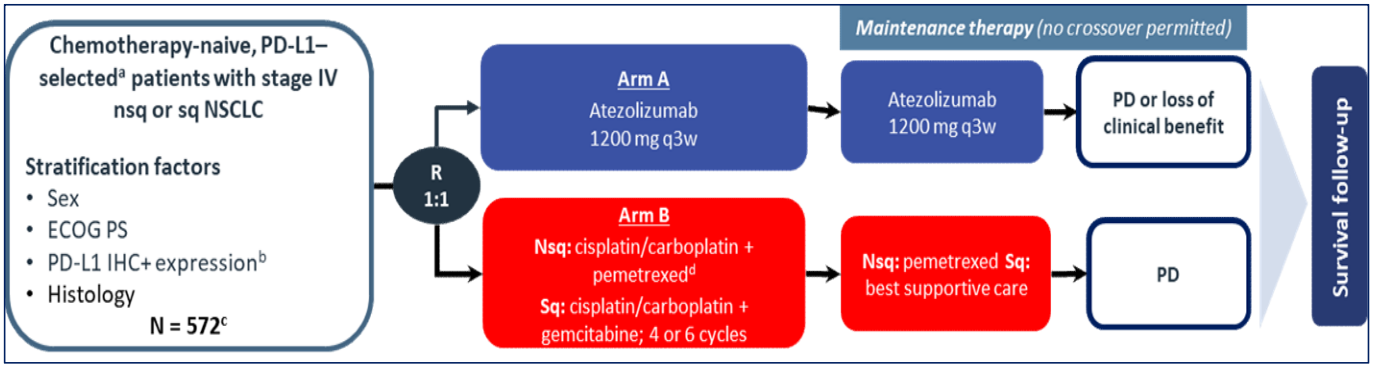
Test Regimen
CPI Monotherapy
CPI+Chemo
CPI+Chemo+Bev
CPI + CTLA4

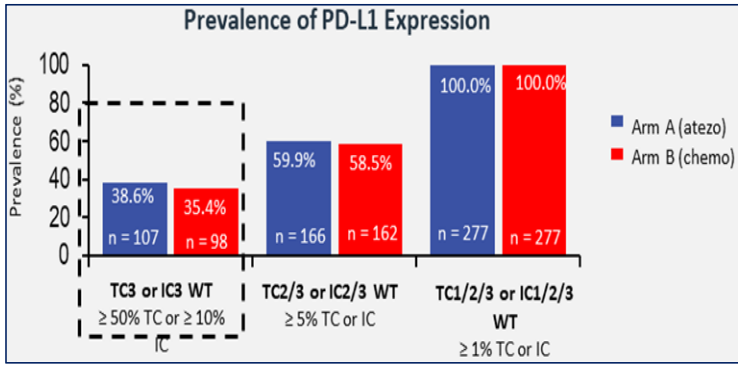
Biomarker
None
PD-L1
TMB

Histology
All
Squamous
Non-Squamous

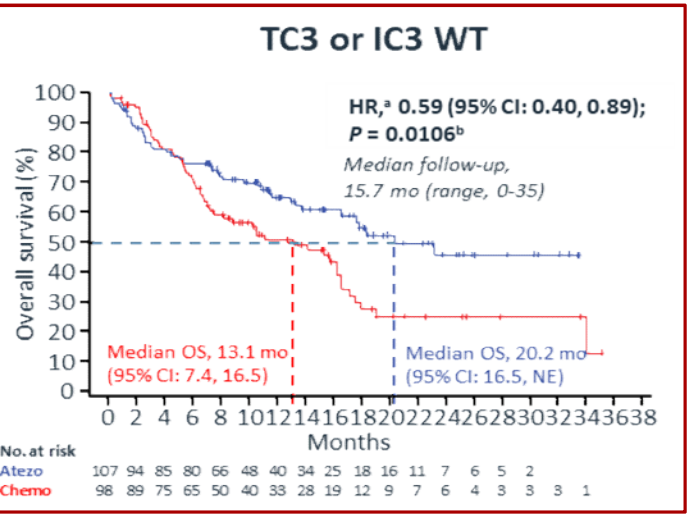
1 Endpoint
PFS
OS
Both

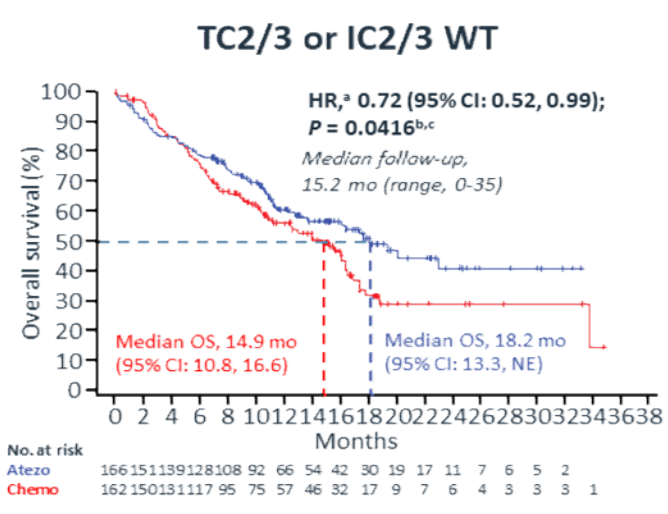
IMpower110: Atezo vs Platinum Chemotherapy - Overall survival

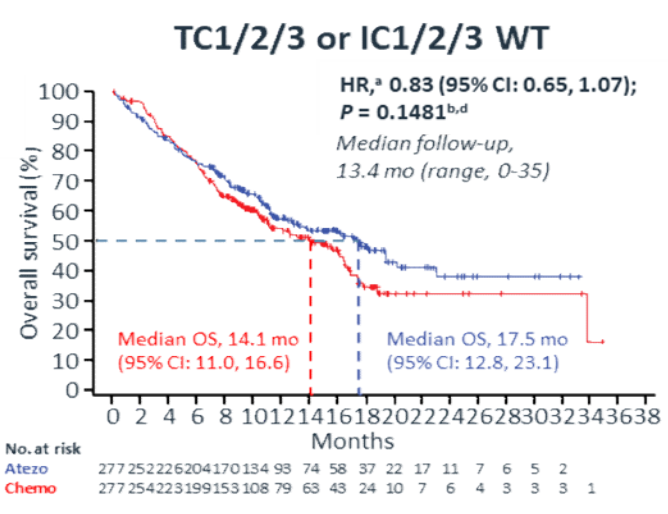




Primary Endpoint: OS in PD-L1 ≥50% (TC3/IC3)

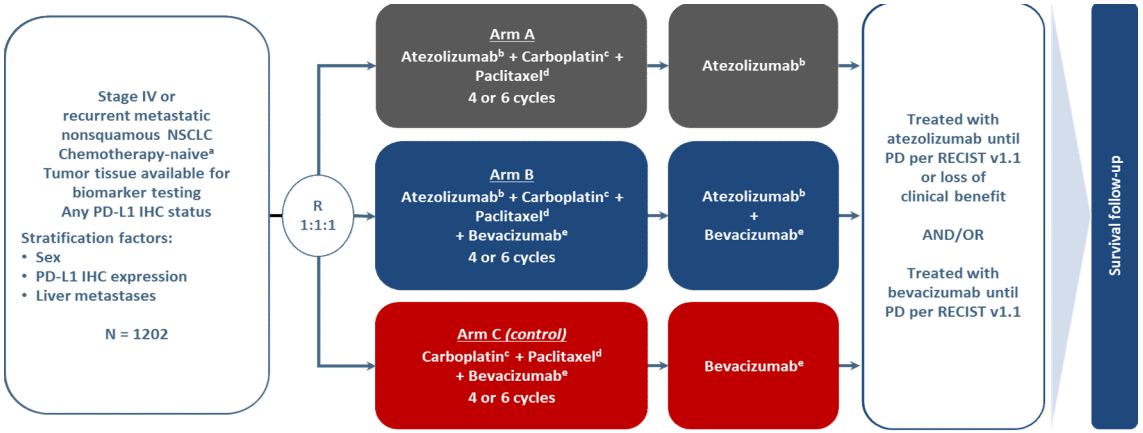




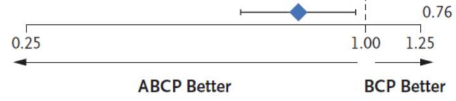


Spigel D, et al. ESMO 2019. Abstract LBA78.

IMpower150: Phase 3 study of Atezolizumab + Chemo ± Bevacizumab vs Chemo + Bevacizumab in 1st-line Non-Squamous NSCLC



Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)
Teff subgroups (in the WT population)				
High gene-signature expression	284 (43)	11.3	6.8	0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0	0.76 (0.60–0.96)



Socinski et al: NEJM 2018

Predictive Biomarkers for Checkpoint Immunotherapy (CPI):

Note: cannot be equated to a discrete variable like driver mutations (Present or Absent)
Instead, a variety of dynamic & continuous variables across a context-specific range

- **Which Biomarker(s)?**
  - PD-L1 IHC
  - TMB
  - PD-L1 IHC + TMB
  - PD-L1 + TMB + Other
  - Multitude of Others

→

- TMB Assessment
  - WES vs Neo-antigen Load vs NGS
    - Continuous vs Binary algorithm
    - Optimal Cutpoints for each
    - Tumor-type specific vs Agnostic
  - Tissue vs Blood

- **What is the context?** (Biomarker for which type of CPI regimen)
  - NSCLC (Squamous or Non-Squamous) vs SCLC
  - CTLA-4 vs PD-1/PD-L1 vs PD-1/PD-L1 + CTLA-4
  - PD-1/PD-L1 + Platinum Chemotherapy →

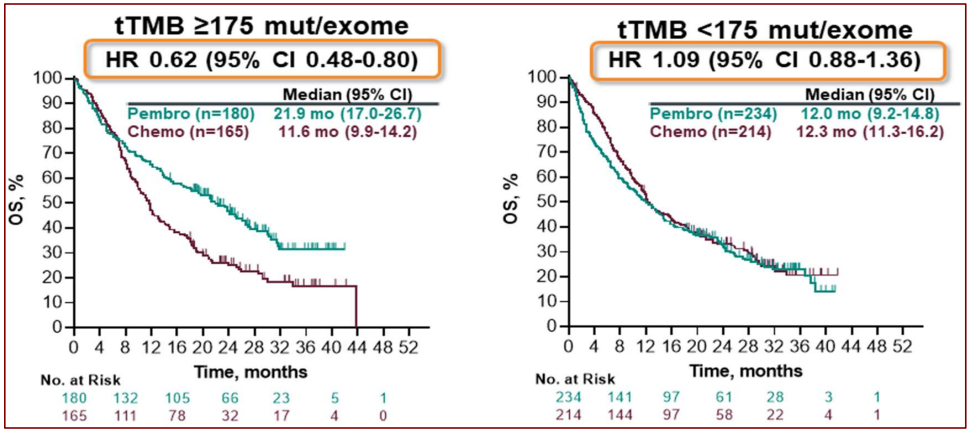
Chemotherapy likely "agnostic" to immuno-biomarker .
"Dilutes out predictive value

Gandara: Lung Cancer Summit. ESMO19

Summary of tTMB in CPI Monotherapy vs CPI + Chemo (or Ipi) Trials: Including New Data from WCLC & ESMO 2019

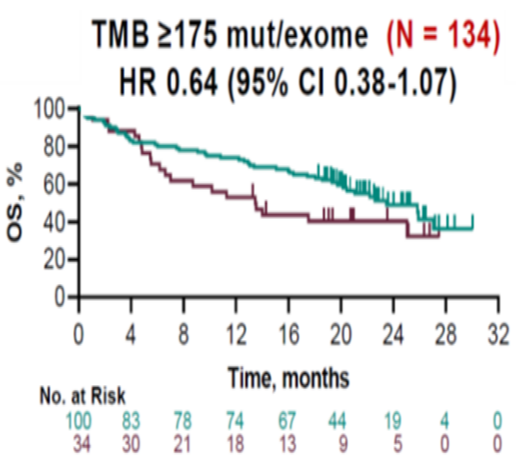
Phase III TrialS	Mono- or Combination	PFS	OS
KN-010	Pembro Mono	√	√
KN-042	Pembro Mono	√	√
KN-189	Pembro + Chemo	No	No
KN-047	Pembro + Chemo	No	No
CM 227	Nivo + Ipi	√	No
S1400i (LUNG MAP)	Nivo + Ipi	√	√

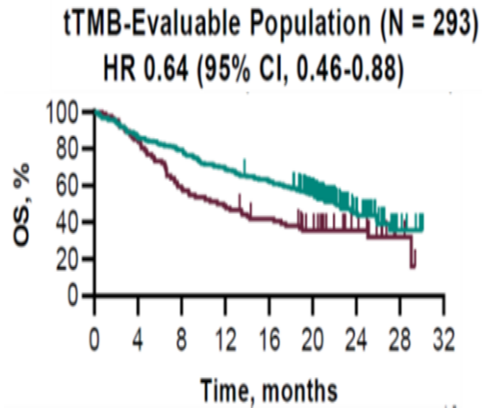
KN-042: Pembro vs Chemo: tTMB by WES



Herbst: ESMO 2019

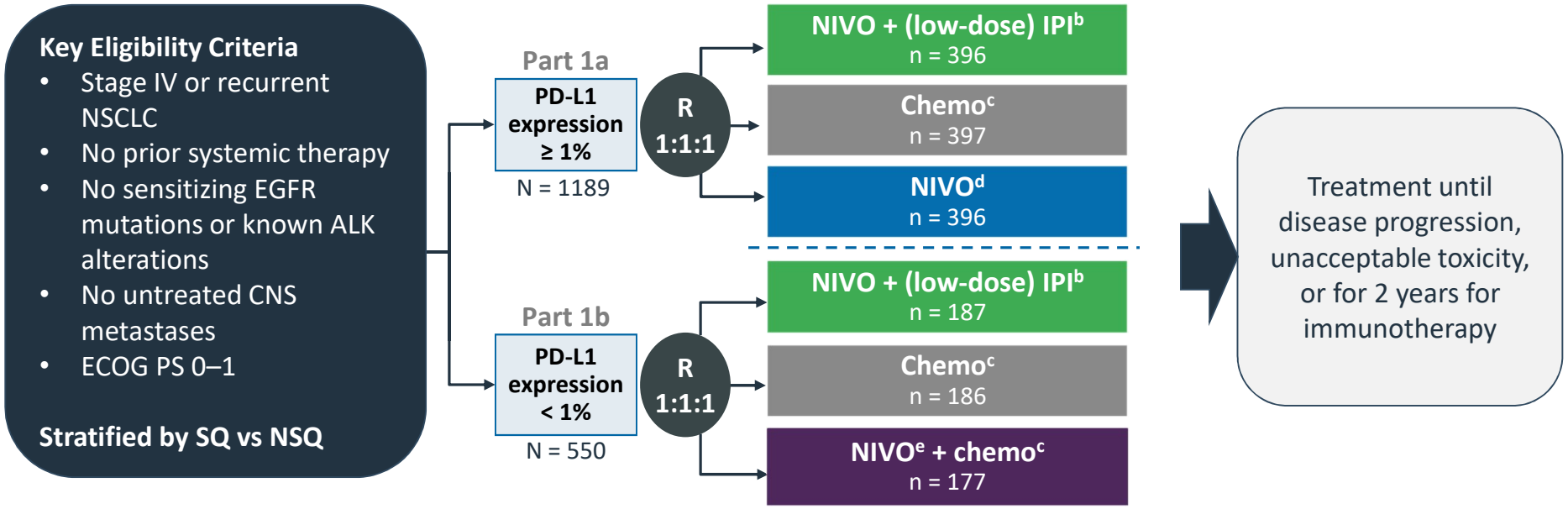
KN-189: Pembro+Chemo vs Chemo (Non-Squamous): tTMB by WES





Garissino: ESMO 2019

CheckMate 227: Part 1 final analysis of nivolumab + low-dose ipilimumab vs platinum-doublet chemotherapy in 1L advanced NSCLC



Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population[f]
- **OS in PD-L1 ≥ 1% population[g]**

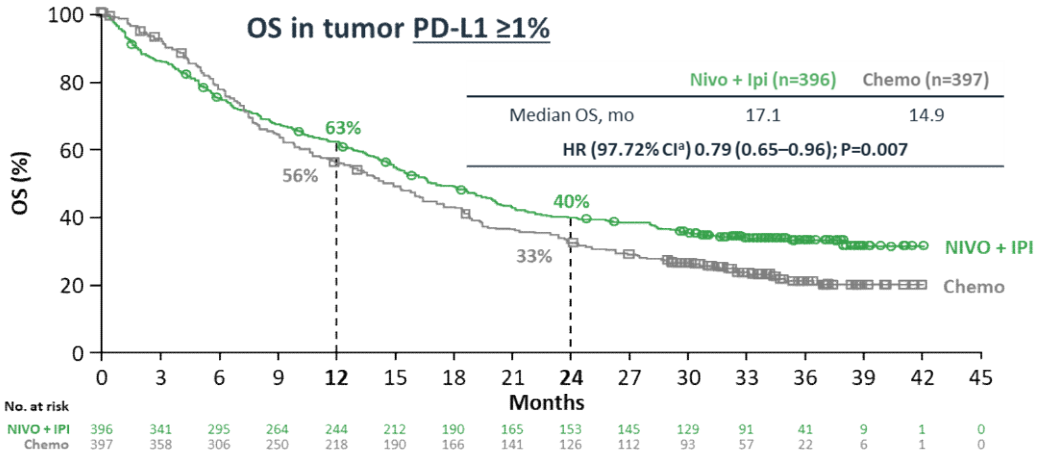
Secondary endpoints (PD-L1 hierarchy):
- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

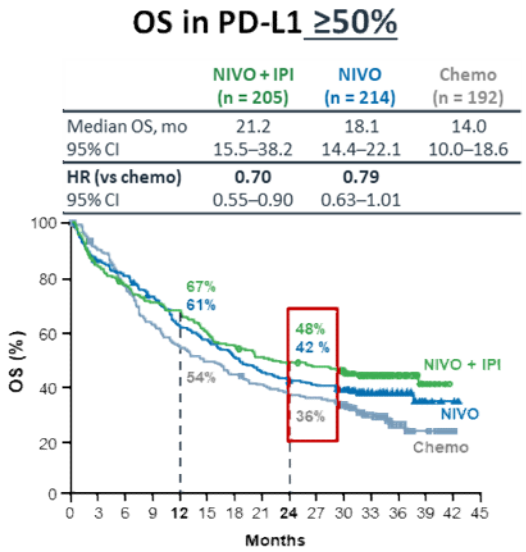
Database lock: July 2, 2019; **minimum follow-up for primary endpoint: 29.3 months**

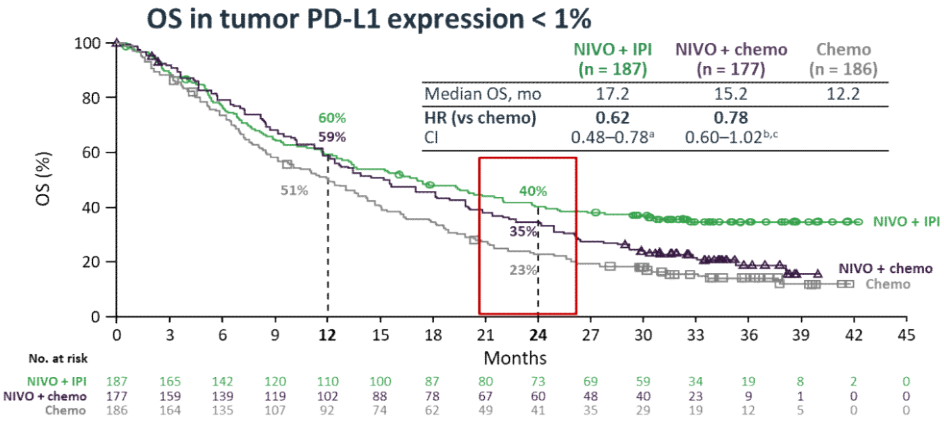
[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

Peters S, et al. ESMO 2019. Abstract LBA4_PR

CheckMate 227: Part 1 final analysis of nivolumab + low-dose ipilimumab vs platinum-doublet chemotherapy in 1L advanced NSCLC





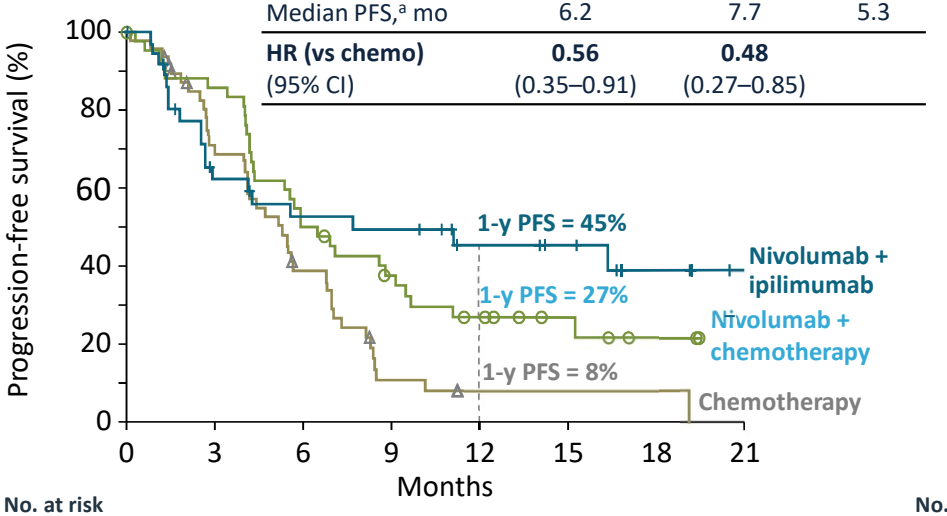


Peters S, et al. ESMO 2019. Abstract LBA4_PR

CheckMate 227: Nivolumab +/- Ipilimumab vs Chemotherapy
Progression-free survival by Tumor Mutation Burden and PD-L1 expression

TMB ≥10 mut/Mb and <1% tumor PD-L1 expression

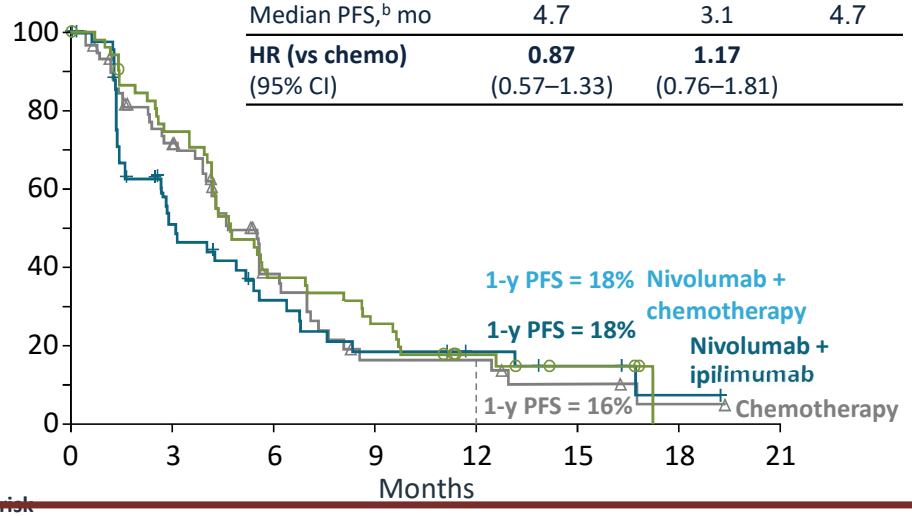
	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo) (95% CI)	**0.56** (0.35–0.91)	**0.48** (0.27–0.85)	



No. at risk								
Nivo + chemo	43	36	21	14	9	5	2	0
Nivo + ipi	38	20	16	15	10	8	4	1
Chemo	48	30	16	4	1	1	1	0

TMB <10 mut/Mb and <1% tumor PD-L1 expression

	Nivo + chemo (n = 54)	Nivo + ipi (n = 52)	Chemo (n = 59)
Median PFS,[b] mo	4.7	3.1	4.7
HR (vs chemo) (95% CI)	**0.87** (0.57–1.33)	**1.17** (0.76–1.81)	



No. at risk								
Nivo + chemo	54	38	19	13	6	3	0	0
Nivo + ipi	52	22	12	7	5	3	1	0
Chemo	59	39	16	6	6	3	1	0

Exploratory analysis. Chemo, chemotherapy; mut, mutations; ipi, ipilimumab; nivo, nivolumab; TMB, tumor mutation burden.

[a]95% CI: nivo + chemo (4.3–9.1 mo), nivo + ipi (2.7–NR mo), chemo (4.0–6.8 mo); [b]95% CI: nivo + chemo (4.2–6.9 mo), nivo + ipi (1.6–5.4 mo), chemo (3.9–6.2 mo).

Borghaei H, et al. ASCO 2018. Abstract 9001.

MYSTIC: 1L durvalumab ± tremelimumab vs chemotherapy in metastatic NSCLC – bTMB

Stage IV NSCLC
All-comers population
(i.e. irrespective of PD-L1 status)
EGFR–/ALK–
ECOG PS 0/1
Immunotherapy- and CT-naïve
N=1118 randomized

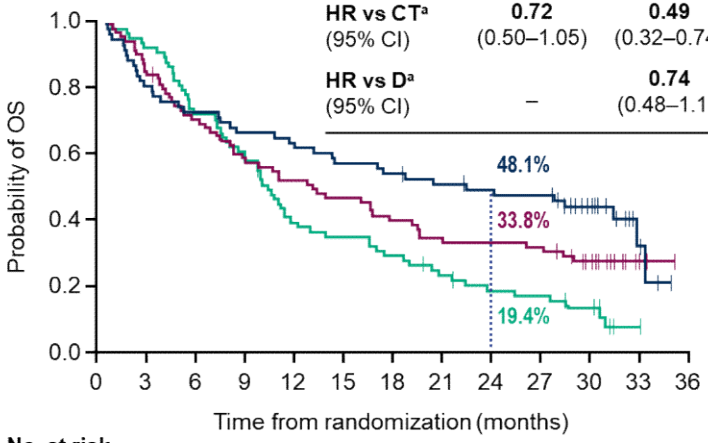
1:1:1 R
Stratified by PD-L1 TC (<25% vs ≥25%*) and histology

- **Durvalumab (n=374)** — 20 mg/kg q4w until disease progression
- **Durvalumab + tremelimumab (n=372)** — D 20 mg/kg q4w until disease progression + T 1 mg/kg q4w for up to 4 doses
- **Platinum-based CT (n=372)**

Primary endpoints
(PD-L1 TC ≥25%*)
OS (D vs CT)
OS (D+T vs CT)
PFS (D+T vs CT)
Key exploratory endpoints
OS by bTMB and tTMB

bTMB ≥20 mut/Mb

	D (n=77)	D+T (n=64)	CT (n=70)
mOS, months (95% CI)	**12.6** (7.8–18.6)	**21.9** (11.4–32.8)	**10.0** (8.1–11.7)
HR vs CT[a] (95% CI)	**0.72** (0.50–1.05)	**0.49** (0.32–0.74)	–
HR vs D[a] (95% CI)	–	**0.74** (0.48–1.11)	–

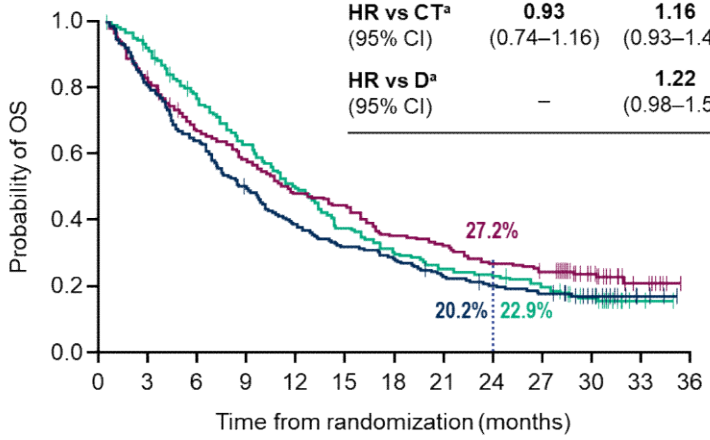


No. at risk

D	77	64	53	44	39	35	30	25	25	23	10	1	0
D+T	64	50	47	43	40	37	35	32	29	29	14	2	0
CT	70	65	51	41	27	25	21	16	12	11	6	0	0

bTMB <20 mut/Mb

	D (n=209)	D+T (n=204)	CT (n=185)
mOS, months (95% CI)	**11.0** (8.9–14.9)	**8.5** (6.7–9.8)	**11.6** (9.6–13.1)
HR vs CT[a] (95% CI)	**0.93** (0.74–1.16)	**1.16** (0.93–1.45)	–
HR vs D[a] (95% CI)	–	**1.22** (0.98–1.52)	–



D	209	167	134	114	98	86	72	63	55	49	21	8	0
D+T	204	161	129	98	75	65	55	45	39	35	18	4	0
CT	185	162	135	110	89	68	53	45	41	34	17	1	0

Rizvi NA, et al. ASCO 2019. Abstract 9016.

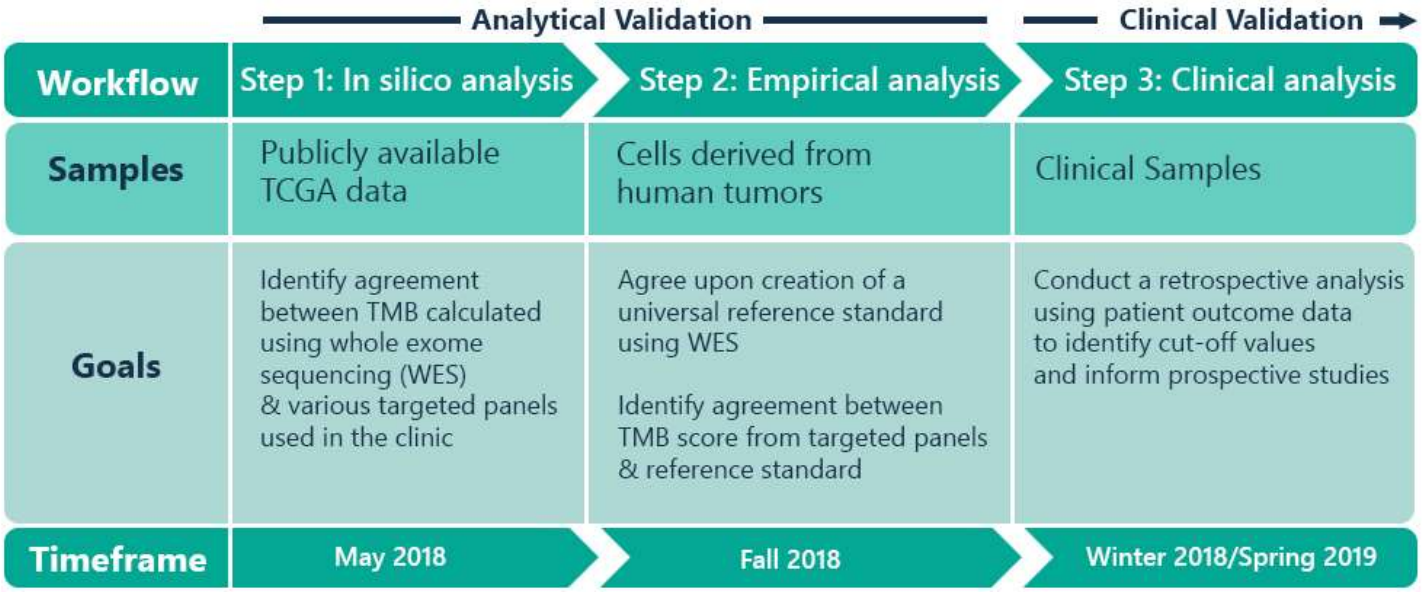
Friends of Cancer Research (FOCR) TMB Harmonization Effort

Friends of Cancer Research has convened a multi-stakeholder working group to align on and publish universal best practices for defining TMB, analytic validation, and alignment against reference standards.

Participants:

- Seven test developers
- Six pharma companies
- FDA
- NCI
- Academia

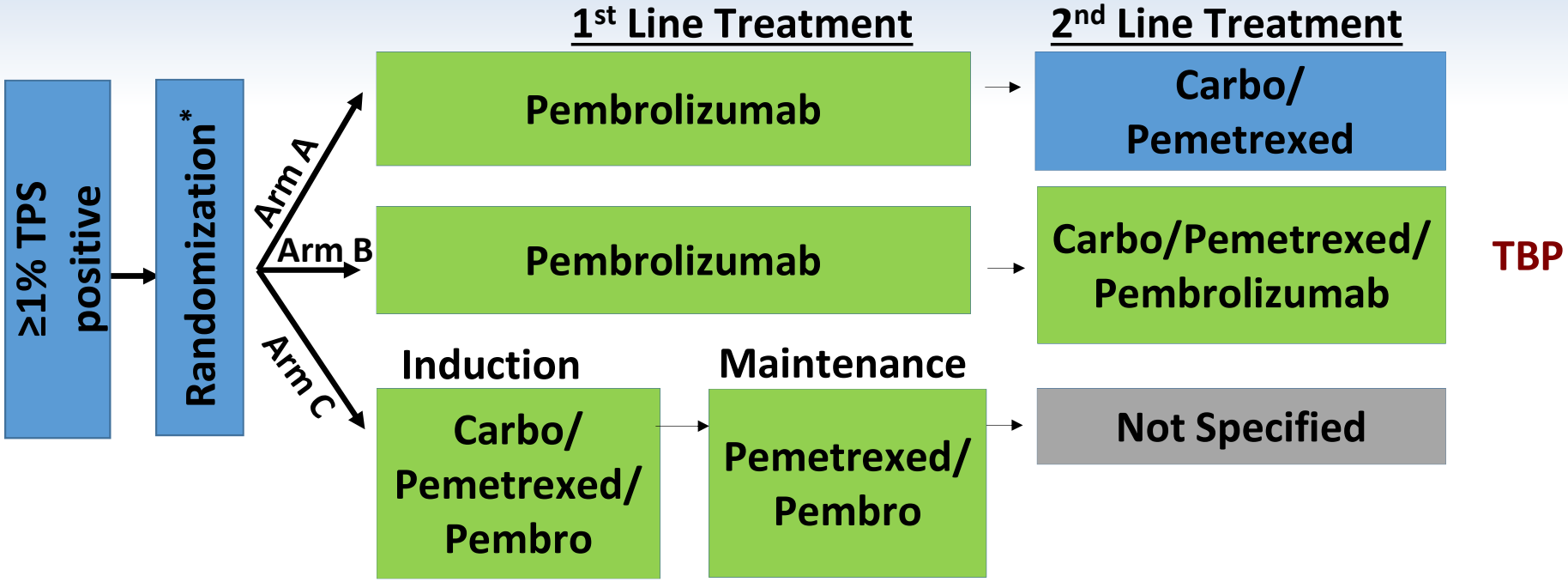
TMB Workflow



https://www.focr.org/tmb

Perspective: *INSIGNA: ECOG/SWOG Advanced Non-squamous Trial*

PIs: H. Borghaei and A. Chiang

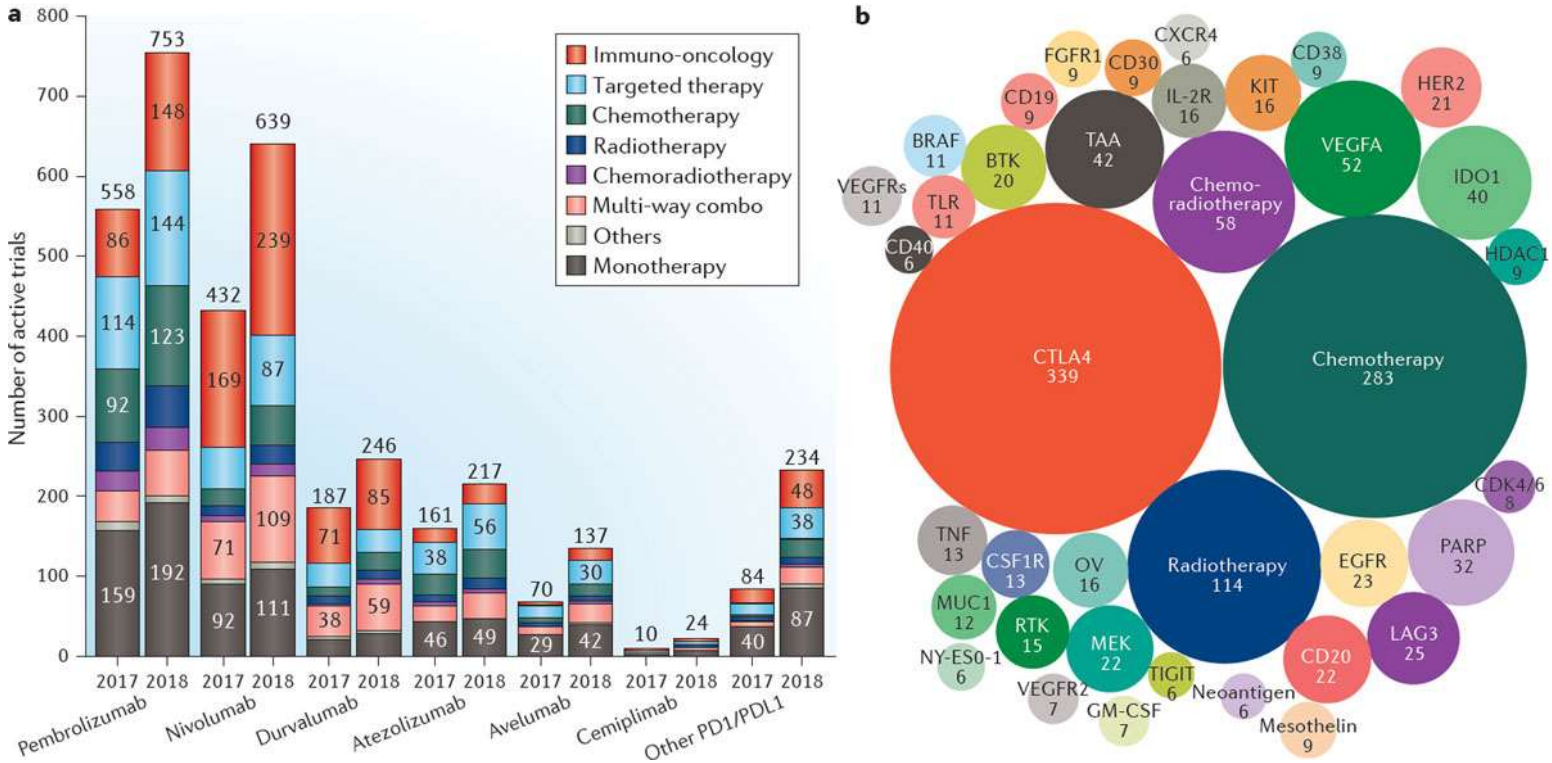


Primary Endpoint: Overall Survival

Integrated Biomarker Objectives:

- To establish a ***predictive* immuno-*signature*** for clinical benefit (OS) with chemo combined with pembrolizumab versus pembrolizumab alone in patients with PD-L1 expressing tumors (≥1%, 1-49%, ≥50%)
- To establish a ***prognostic* immuno-*signature*** associated with better outcome (OS) to 1st line treatment with pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50% TPS).

Unmet Need for Predictive Biomarkers in Clinical Trials of Checkpoint Immunotherapy



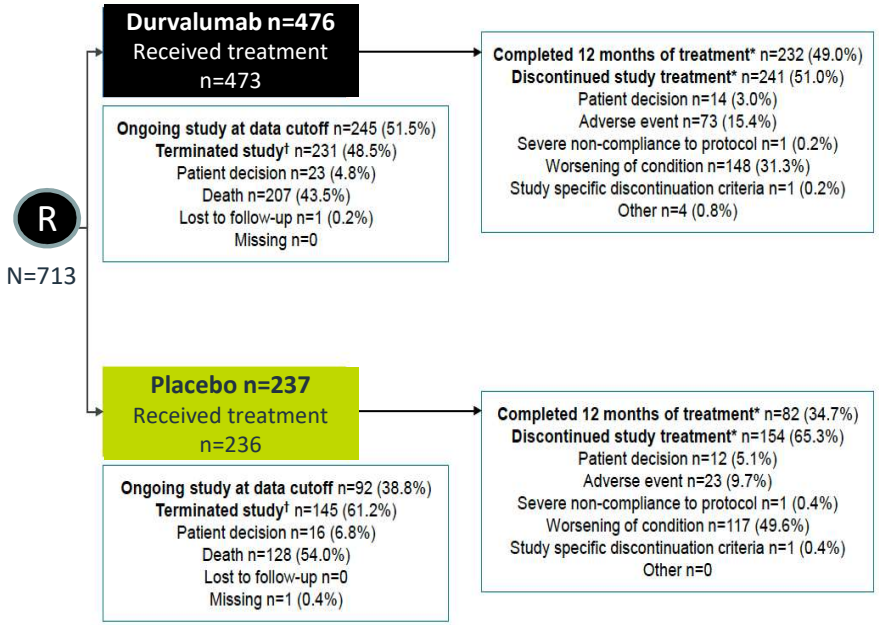
Over 2,250 clinical trials ongoing as of January 2019
requiring 380,900 patients
~750 trials in NSCLC

Tang: Nat RD 2018

Current Issues in Checkpoint Immunotherapy (CPI) for NSCLC: A Perspective from February 2020

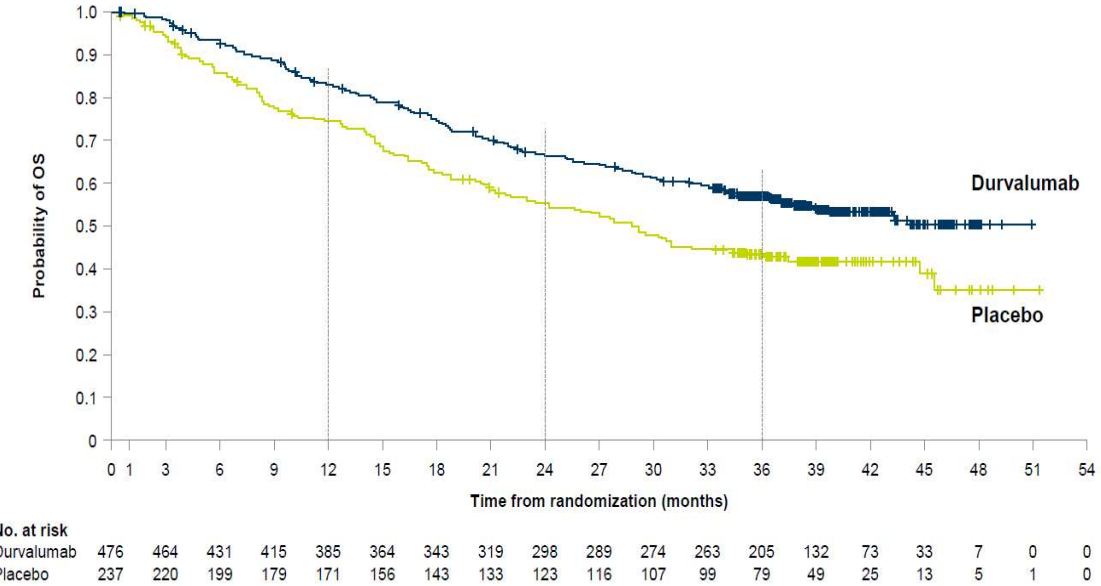
- Overview: Evolving Role of CPI in advanced (Stage IV) NSCLC
- Predictive Biomarkers
    - PD-L1 Assay
    - Tumor Mutational Burden (TMB)
    - Other biomarkers in development
- Clinical trial results in advanced NSCLC
  - 2nd line CPI Monotherapy –Updates on Long Term Survival
  - 1st line (CPI monotherapy, CPI-Chemotherapy)
- Stage III Unresectable NSCLC: Platinum Chemotherapy/RT → Consolidation CPI (PACIFIC)

PACIFIC: Durvalumab versus placebo after Concurrent Chemo-RT in unresectable, stage III NSCLC — 3-year OS update



	No. of events, n/N (%)	Median OS, mo (95% CI)	12-month OS, % (95% CI)	24-month OS, % (95% CI)	36-month OS, % (95% CI)
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86)[a]

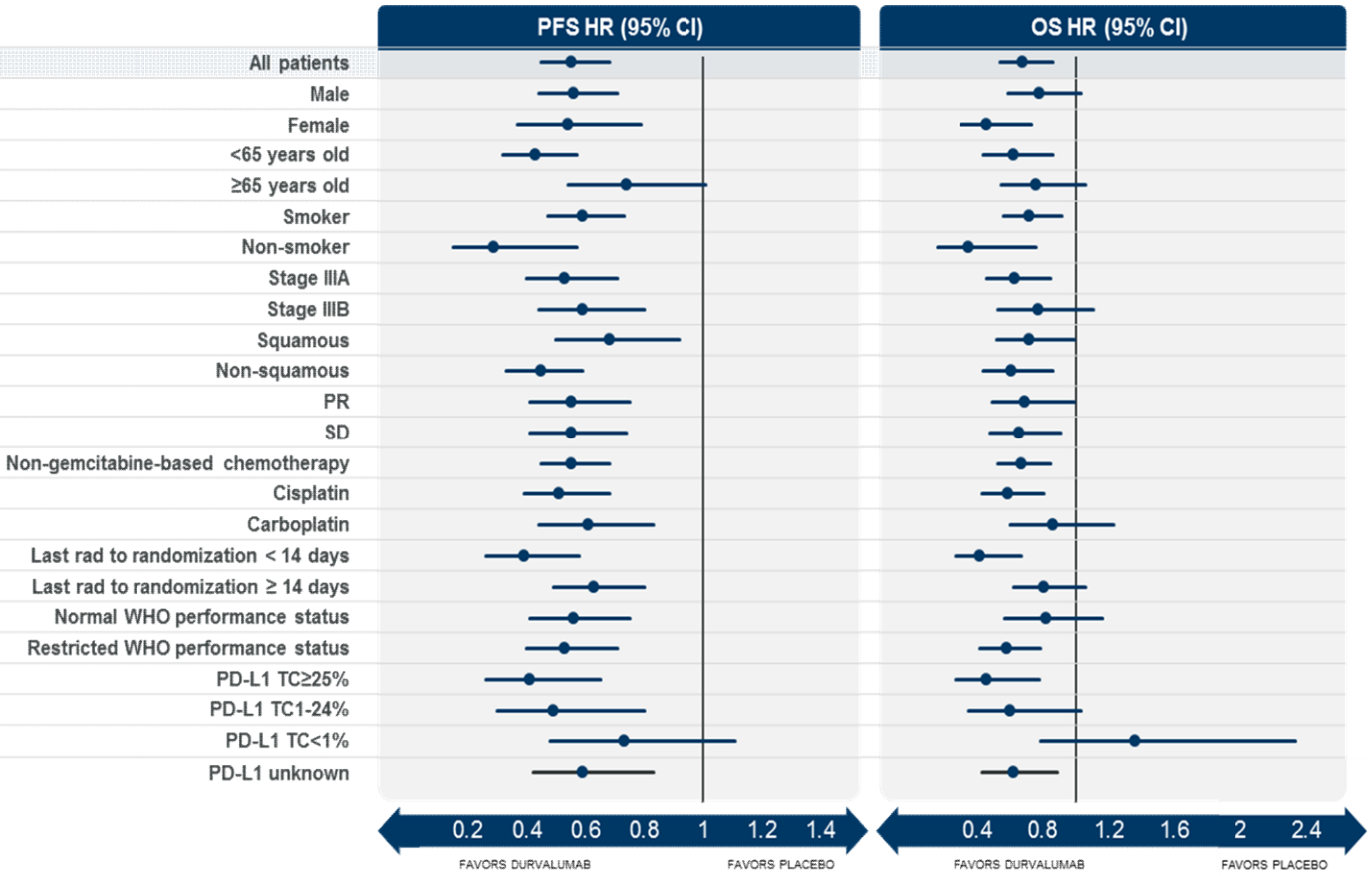


[a]Stratified hazard ratio for death from the primary analysis, 0.68 (95% CI, 0.53–0.87)

Gray JE, et al. ASCO 2019. Abstract 8526.

How do we apply the PACIFIC data in Clinical Practice?

Progression-free and Overall Survival by Subgroup (ITT)



Gray JE, et al. ASCO 2019. Abstract 8526.

Practical Applications (Selection vs De-Selection)

- Both IIIA (unresectable) & IIIB
- All Histologies of NSCLC
- Smokers/Non-Smokers

- What chemotherapy?
  - Cisplatin preferred over low dose weekly Carbo
- What Radiotherapy regimen?
  - 60-66Gy standard fx
- EGFR-mutated NSCLC
  - Unclear
- PD-L1 <1%
  - Unclear