Statistical Issues And Challenges With Immunotherapies:

Introduction (i.e. the Perspective of Clinical Oncologists)

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Bordeaux (FRA), January 25th, 2019

Disclosures

- Advisory Boards / Honoraria / Speakers' fee / Consultant for:
  - MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis, Roche
- Research Support / Grants from:
  - A.I.R.C. (Associazione Italiana Ricerca sul Cancro)
  - I.A.S.L.C. (International Association for the Study of Lung Cancer)
  - L.I.L.T. (Lega Italiana per la Lotta contro i Tumori)
  - Fondazione *Cariverona*
  - Astra-Zeneca
  - Roche
  - Open Innovation

LILT
LEGA ITALIANA PER LA LOTTA CONTRO I TUMORI
prevenire è vivere

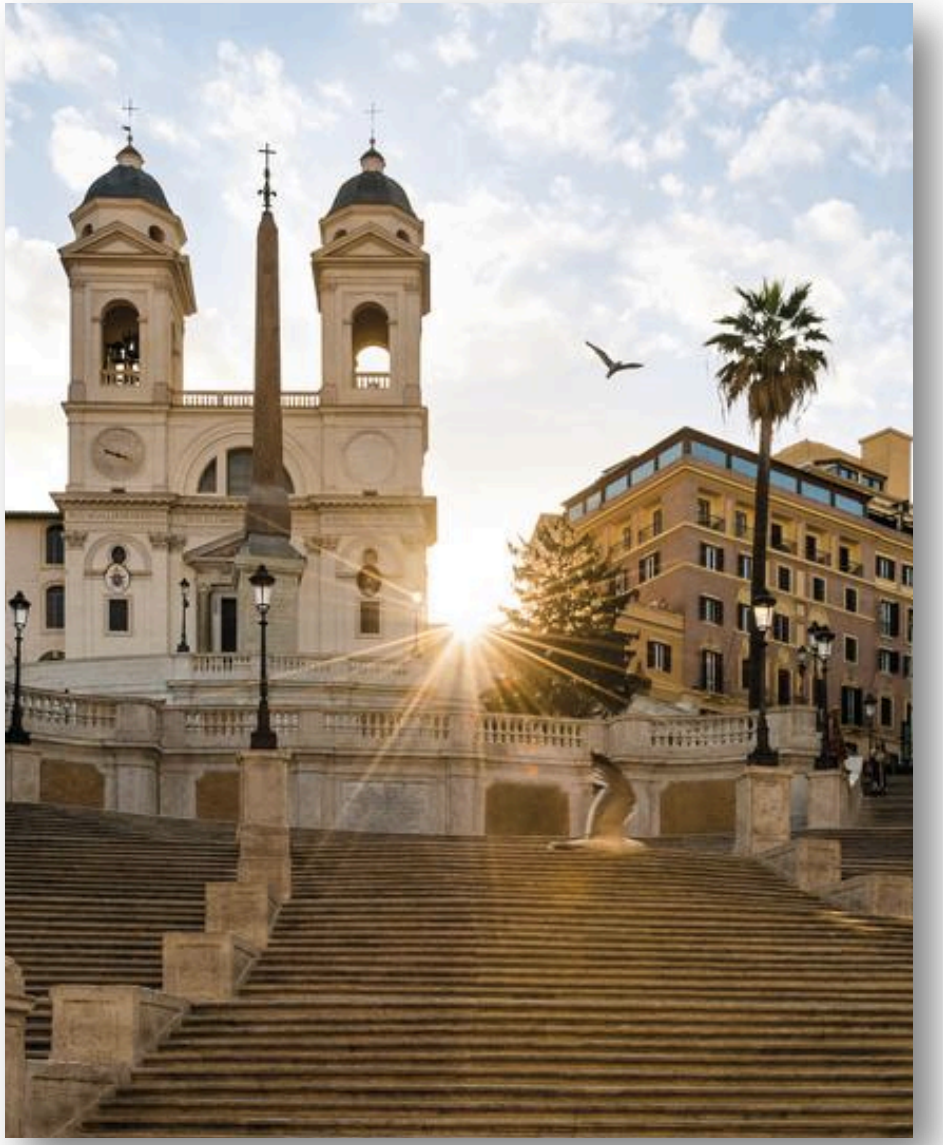
FONDAZIONE Cariverona

AIRC

IASLC
International Association for the Study of Lung Cancer

Presentation Outline

- **Impact of Immunotherapy (IO) in Medical Oncology**
- **Patients' Selection and Predictive Factors for IO**
- **Treatment End-points for IO**
- **Evidences for Real-World beyond Clinical Trials**

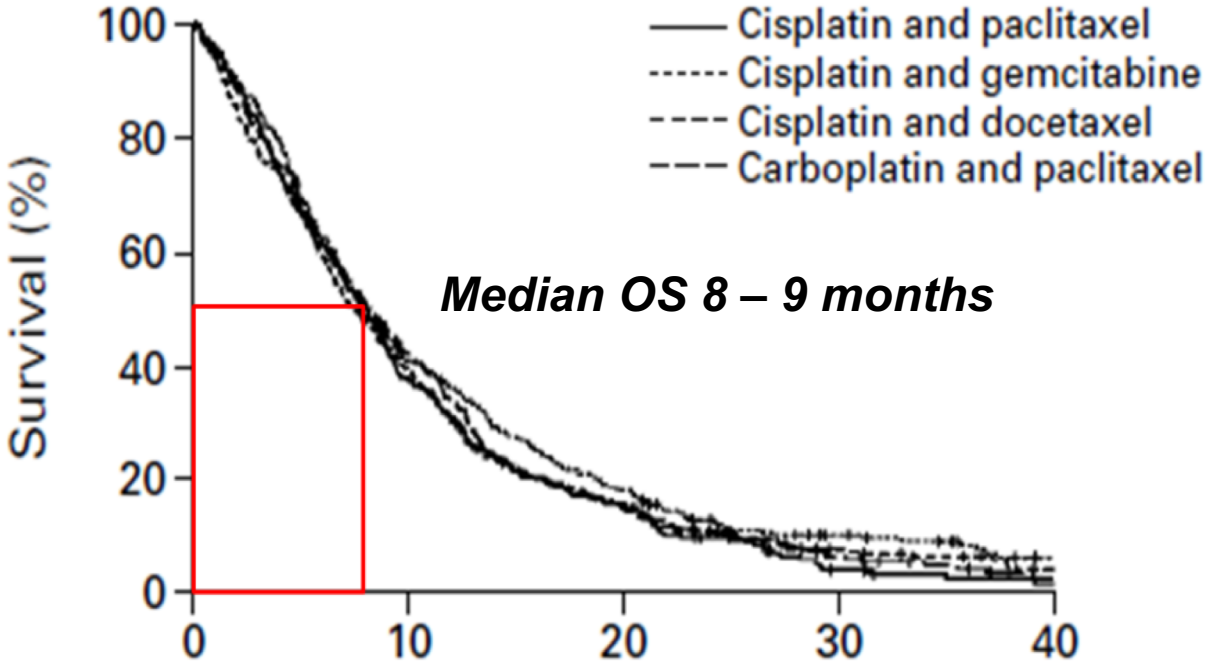


Presentation Outline

- **Impact of Immunotherapy (IO) in Medical Oncology**
- Patients' Selection and Predictive Factors for IO
- Treatment End-points for IO
- Evidences for Real-World beyond Clinical Trials

Lung Cancer Prognosis in last century (Stage III-IV)

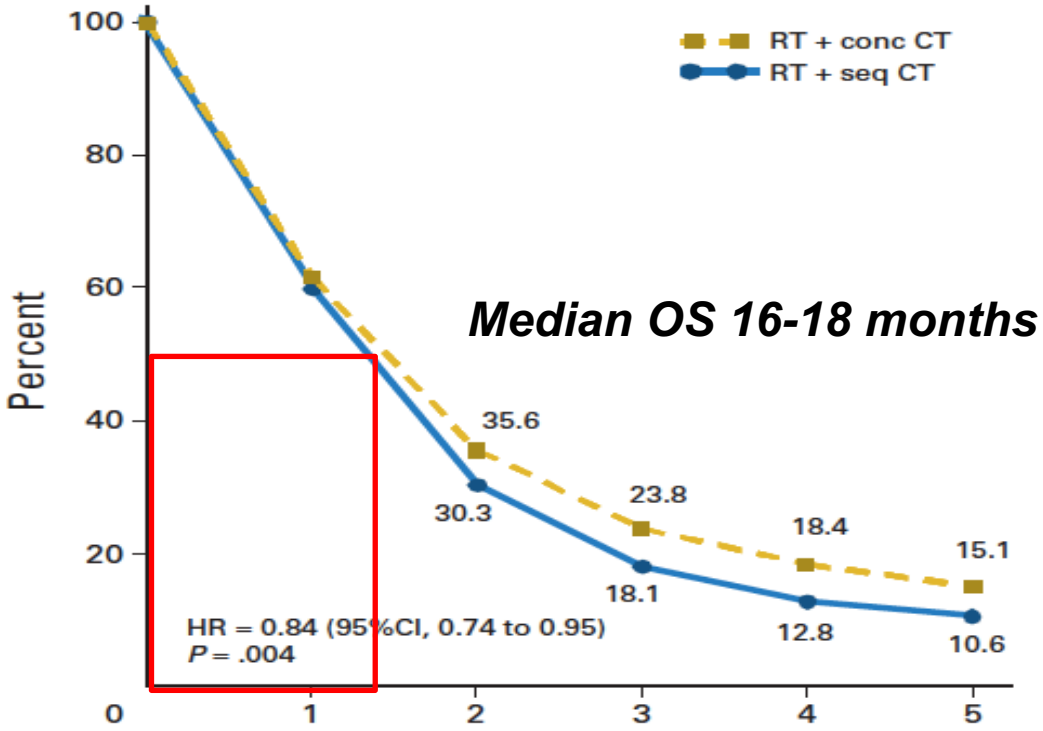
- **Stage IV Non-'*something-else-disease*' (NSCLC)**
- **Chemo Doublets reaching a '*plateu*'**
- **If fit, 100% of patients received chemotherapy**
- **ORR ranging from 15 to 30%**



2-trs OS <10%; 4-yrs OS <5%

Schiller J et al, NEJM 2002

- **Stage III (Locally Advanced)**
- **IPD Meta-Analysis [N=1,205]**
- **25% Grade 3-4 AEs**
- **ORR ranging from 15 to 45%**



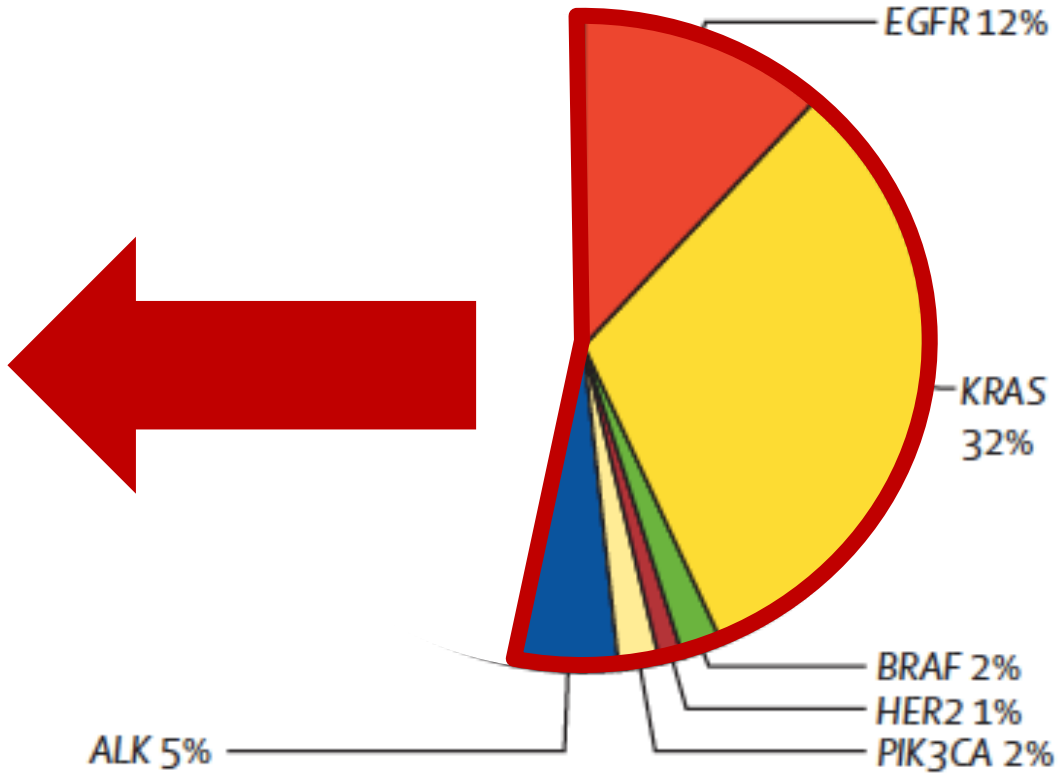
2-trs OS 30%; 4-yrs OS <20%

Auperin E et al, J Clin Oncol 2010

Advanced NSCLC in >2016: '*Operative*' Classification according to Molecular Biology

ONCOGENE Addiction ['Stupid' Disease]
Single Dominant Driver
Small Mutational Load (**LOW** Tumor Mutation Burden)
Targeted TKIs COULD work Immunotherapy MAY NOT
Resistance, late, same/other pathway
Traditional Intermediate End-points MAY work as surrogate

IFCT (France) [N=13,425 pts]



Barlesi F et al, Lancet 2016

Adapted from G. Sledge, ASCO 2011

Advanced NSCLC in >2016: '*Operative*' Classification according to Molecular Biology

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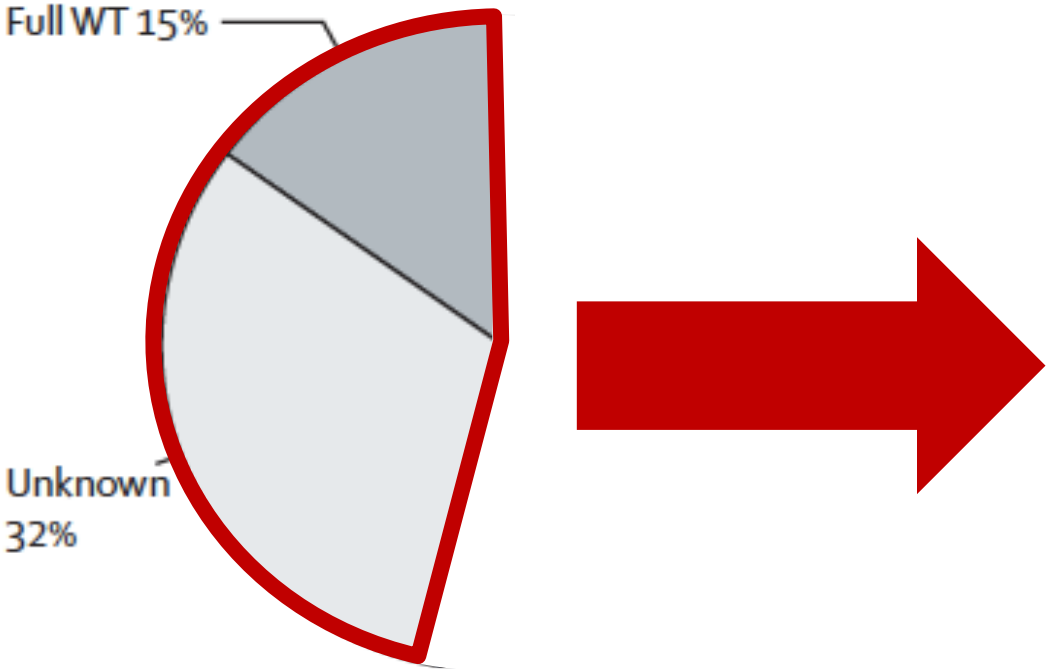


Barlesi F et al, Lancet 2016

NON-ONCOGENE Addiction ['Smart' Disease]
Multiple Drivers & Passengers
Large Mutational load (**HIGH** Tumor Mutation Burden)
(Un)Targeted TKIs are NOT effective Immunotherapy MAY effective
Resistance common, early
Traditional Intermediate End-points does NOT correlate with efficacy

Adapted from G. Sledge, ASCO 2011

The Evolving View of Lung NSCLC

The Immune System: an '*Ideal*' anti-cancer Weapon

Why I-O May Work

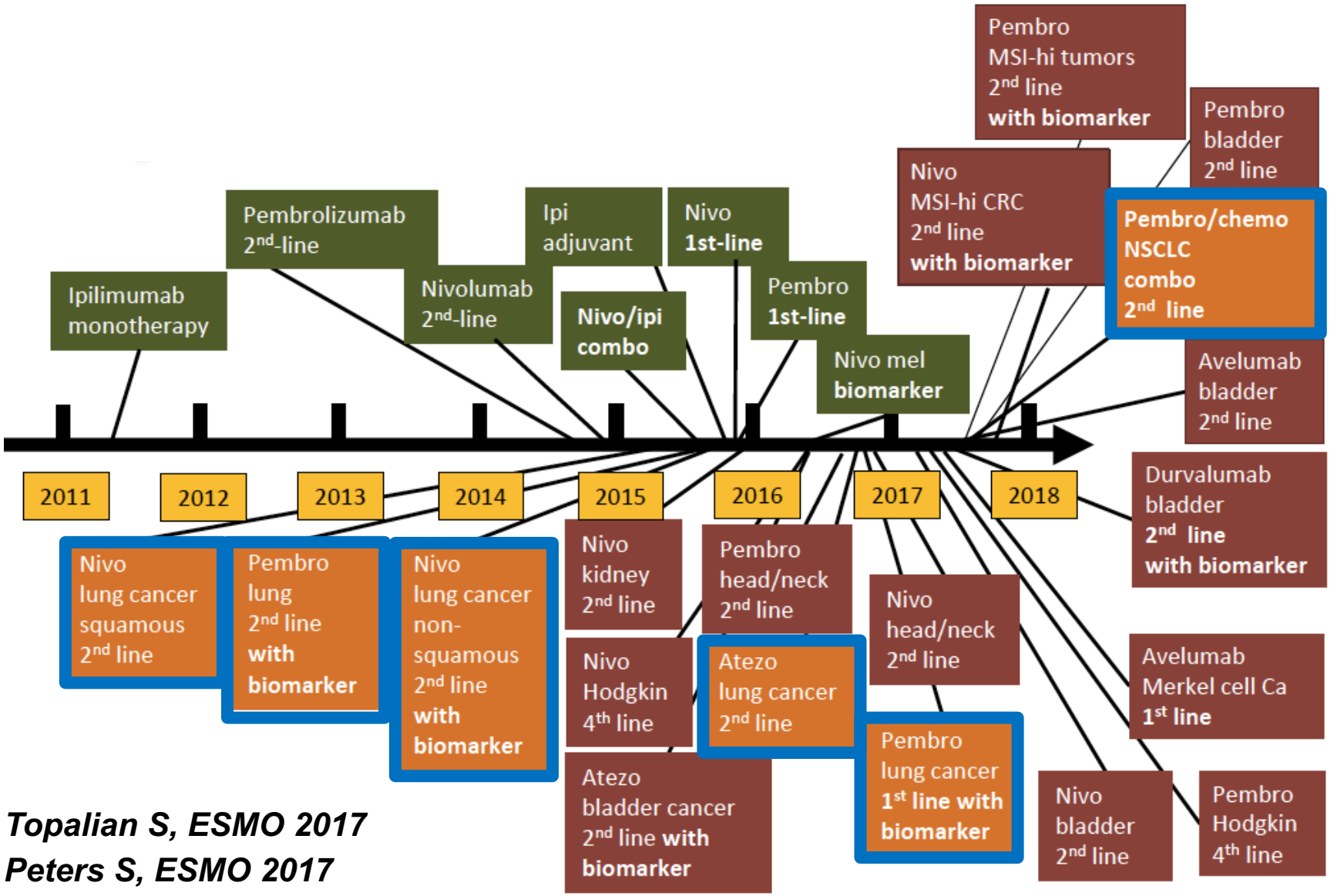
- **Diverse Attack**
  - T-Cells, antibodies, NKs, etc….
- **Precise Targeting**
  - Can distinguish minute chemical alterations
- **Recall**
  - After effective priming immunity can last for a lifetime

Hurdles

- **The wall of cancer's defence againts immune attack:**
  - Regulatory immune cells
  - Suppressive cytokines
  - Immune checkpoint

Modified - Topalian S, ASCO 2015

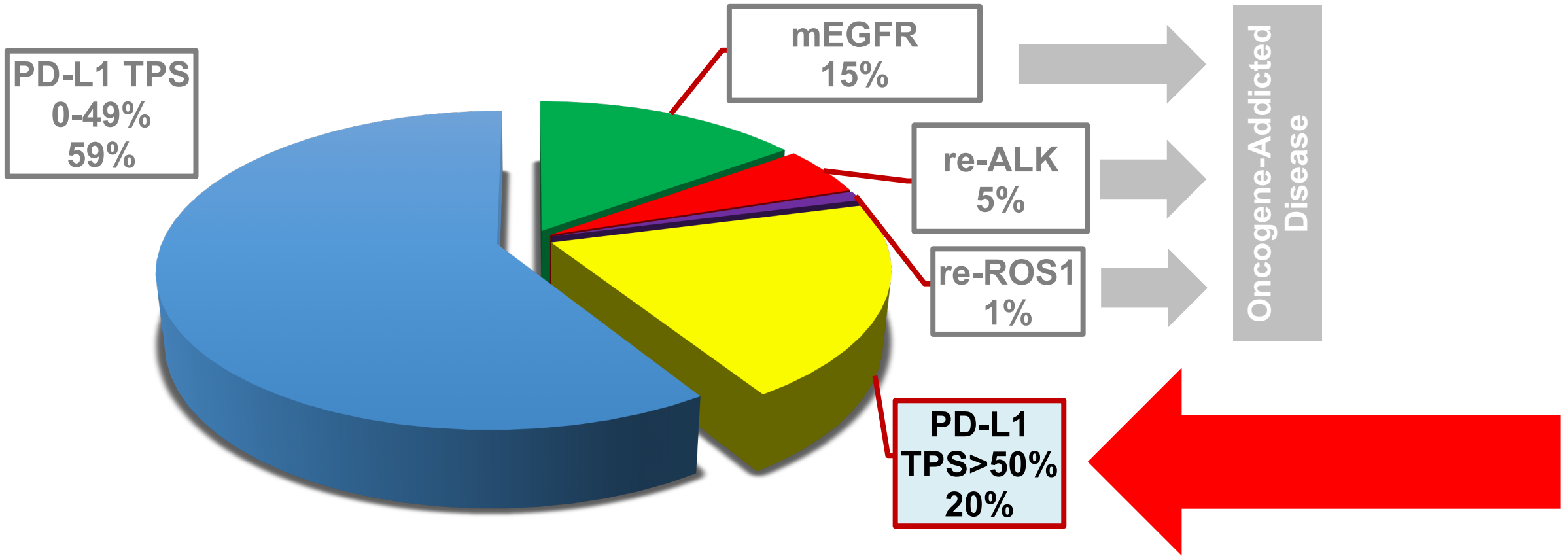
FDA approvals for Immune Checkpoint (IC) Inhibitors



AGENT	TARGET
Ipilimumab	CTLA-4
Tremelimumab	CTLA-4
Nivolumab*	PD-1
Pembrolizumab*	PD-1
Atezolizumab	PD-L1
Durvalumab	PD-L1
Avelumab	PD-L1

Topalian S, ESMO 2017
Peters S, ESMO 2017

NSCLC: Treatment Choices are Driven by Biomarkers



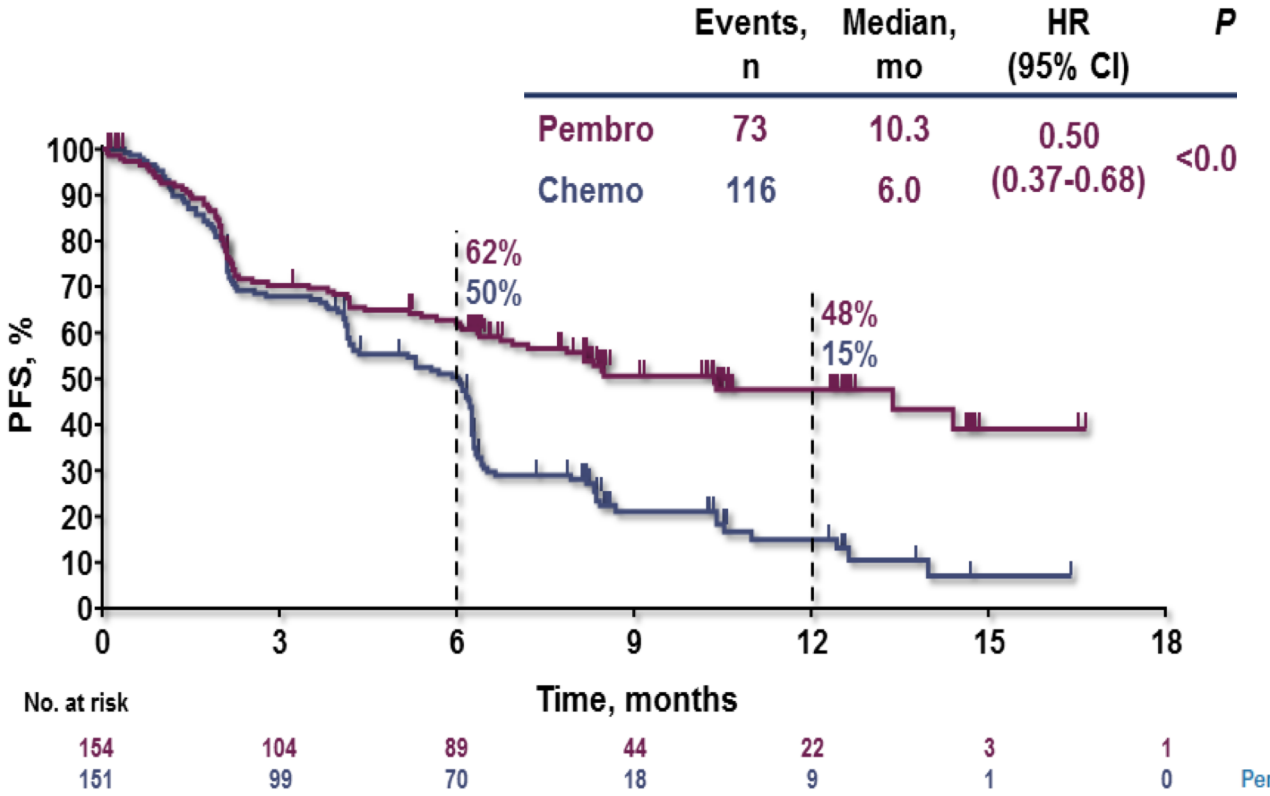
Suggested Median Time-to-report by Guidelines: <3-4 wks
'Real-World' Median Time from diagnosis to 1-line therapy: 30-34 days*

**Gobbini E et al, Lung Cancer 2017*

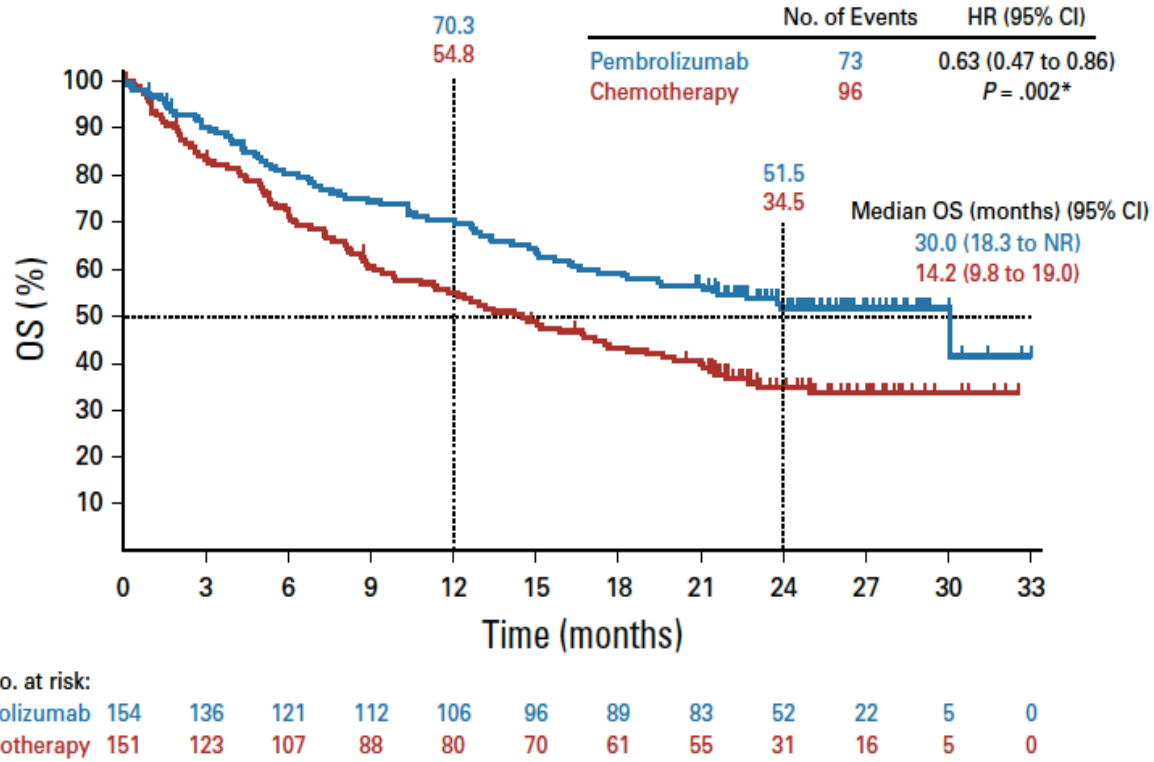
Head-to-Head Pembrolizumab Better than Chemo (PD-L1 ≥50%)

1934 Screened Patients, 500 (30%) PD-L1 TPS ≥50%, 61.5% Men, 18.5% Squamous, 90.5% C/F Smokers

PFS



(Updated) OS



Censoring rate (55% of pts with event)

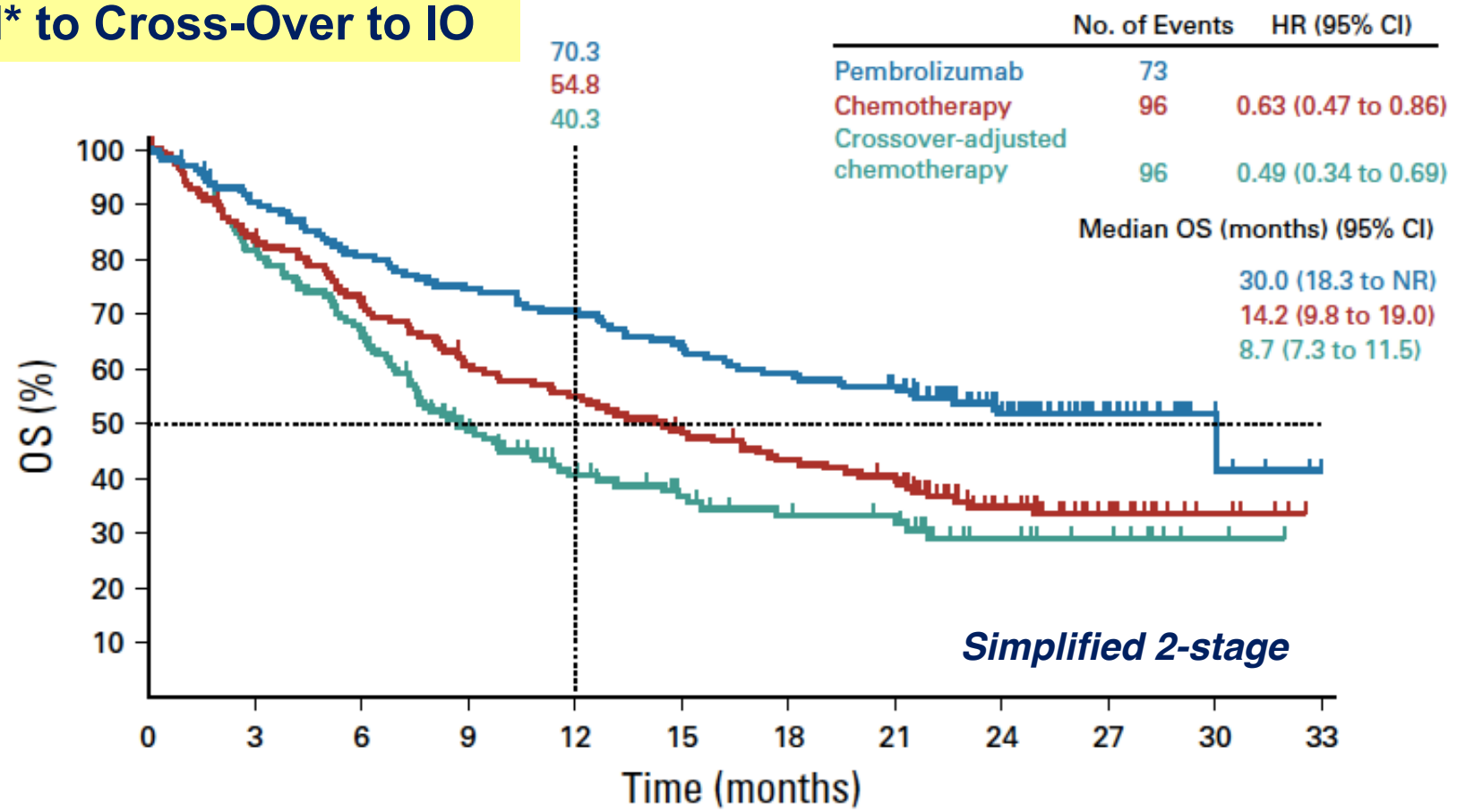
Reck M et al, ESMO 2016 & NEJM 2016

Reck M et al, J Clin Oncol 2019

Head-to-Head Pembrolizumab Better than Chemo (PD-L1 ≥50%)

(Updated) OS Udjusted* to Cross-Over to IO

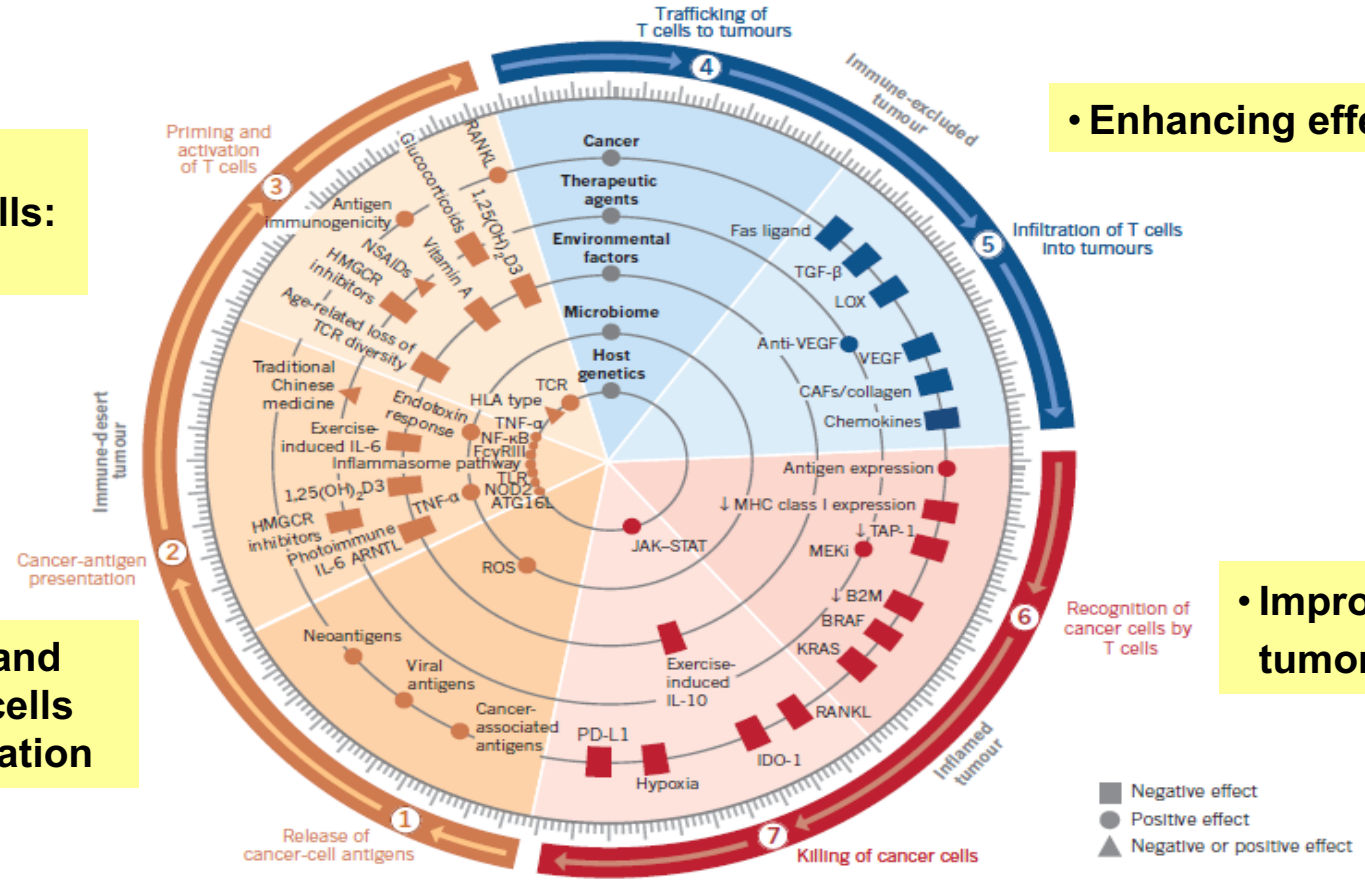
*Three statistical methods were applied:
- Simplified 2-stage
- Rank-preserving structural failure time (RPSFT)
- Inverse probability of censoring weighting (IPCW) methods



Reck M et al, J Clin Oncol 2019

Chemotherapy Enhances Anti-Cancer Immune Response: Rational Partner for Immunotherapy

- Increasing T-cell penetrance in the tumor
- Enhancing effector T-cell function
- Eliminating immunosuppressive cells: T-regulatory cells
- Improving recognition of tumor antigens by T-cell
- Enhancing maturation and activation of dendritic cells toward antigen presentation
- Inducing immunogenic cell death
- Eliminating immunosuppressive cells: T-regs, myeloid-derived suppressor cells, M2 macrophages



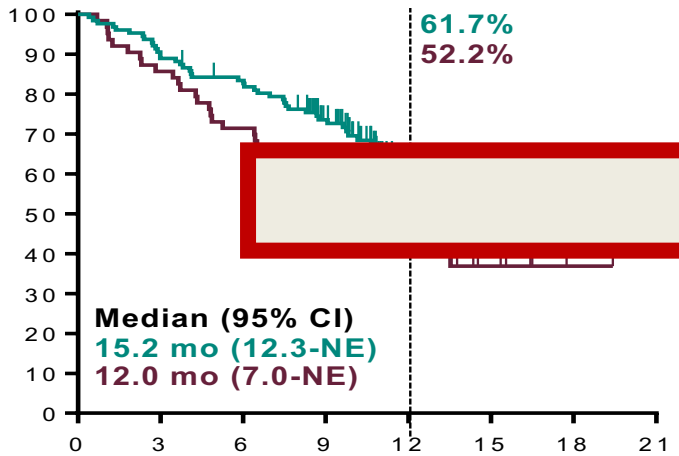
Pembro + Chemo Better than Chemo (regardless of PD-L1)

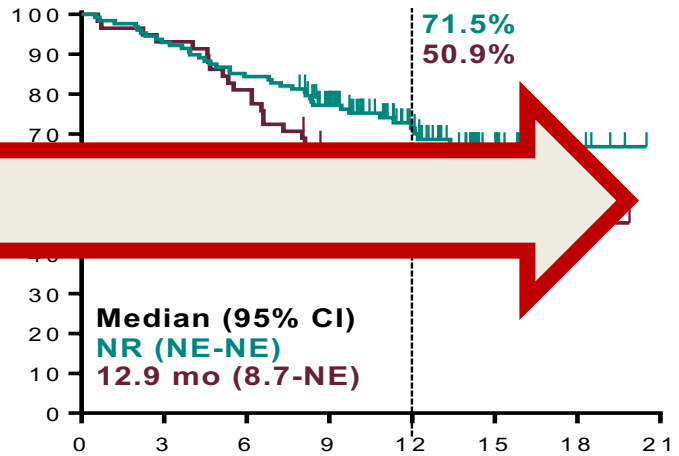
PDL1 [TPS] <1%

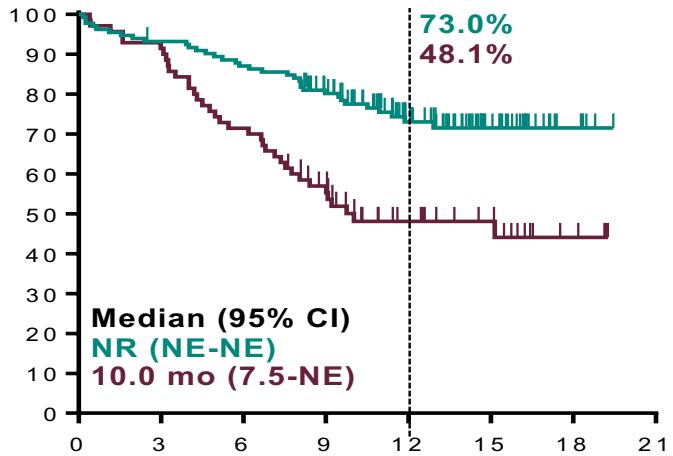
PDL1 [TPS] 1-49%

PDL1 [TPS] ≥50%

KN 189 [Non-Squamous]

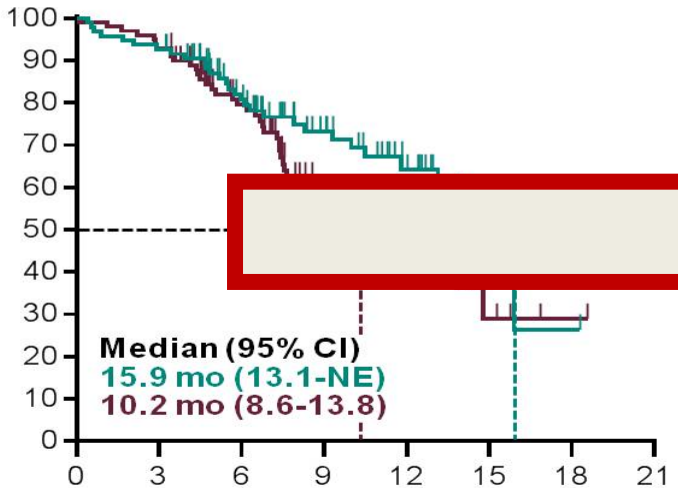


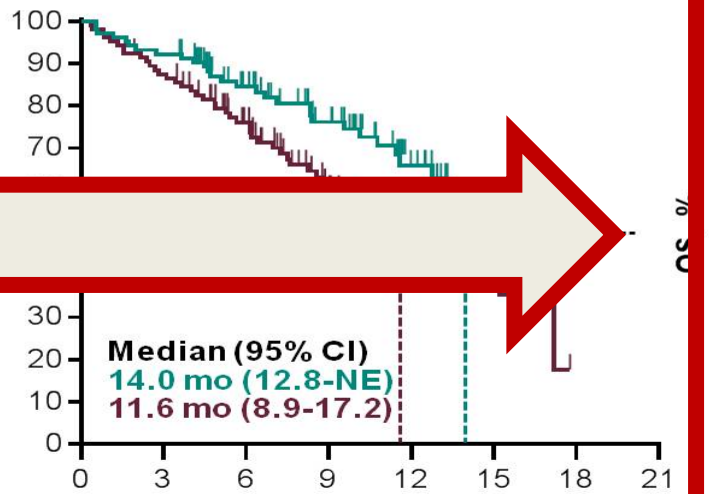


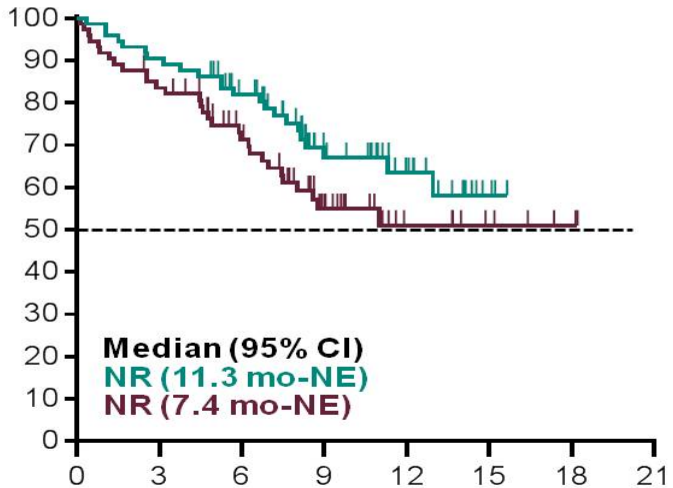


Gandhi L et al, AACR 2018, NEJM 2018

KN 407 [Squamous]

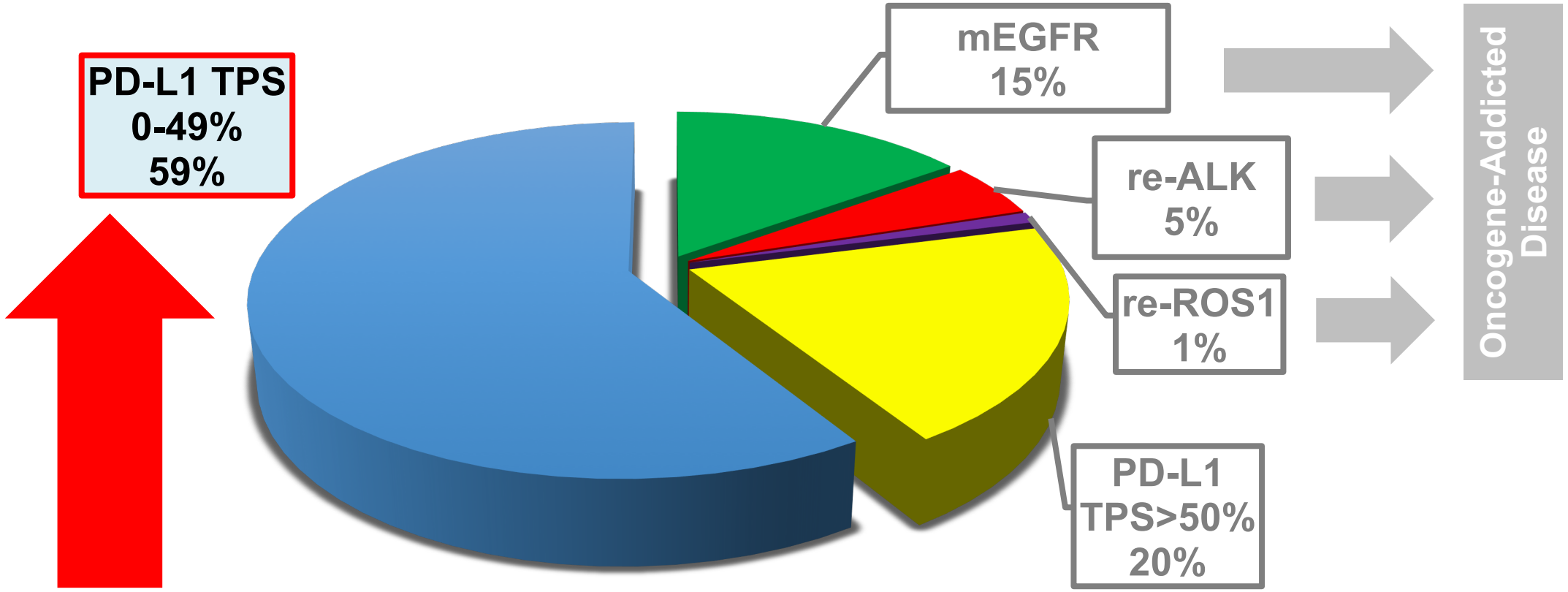






Paz-Ares L et al,ASCO 2018, NEJM 2018

NSCLC: Treatment Choices are Driven by Biomarkers



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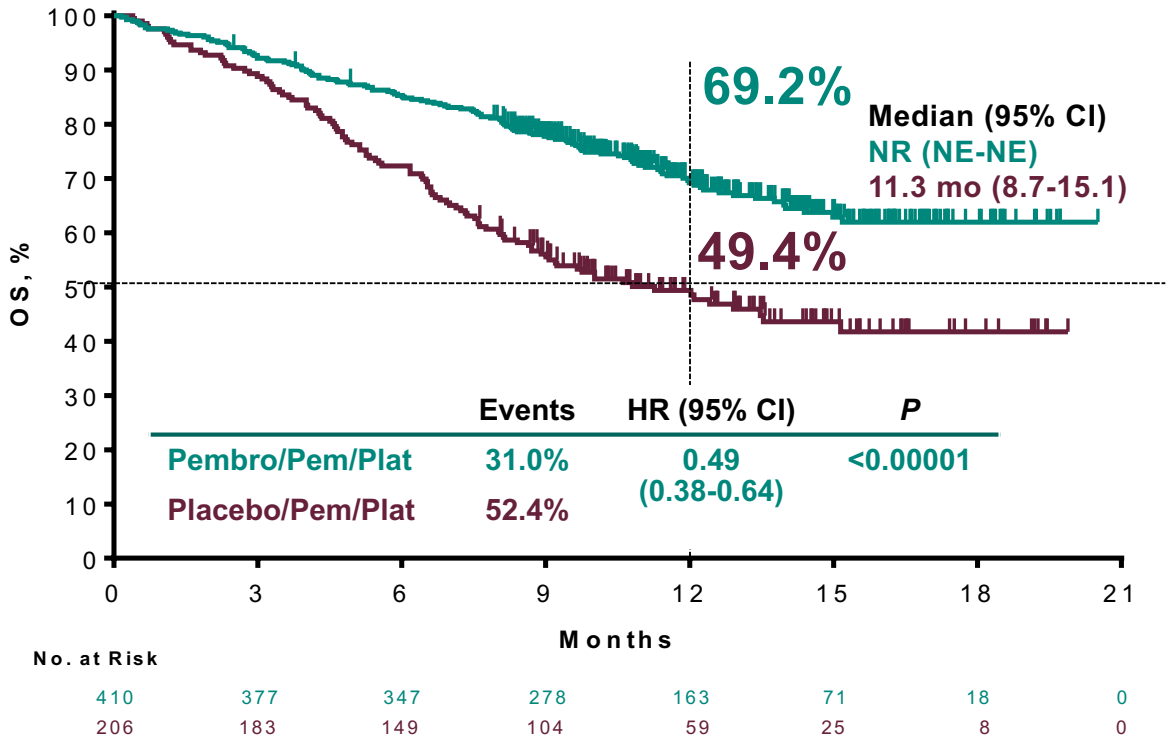

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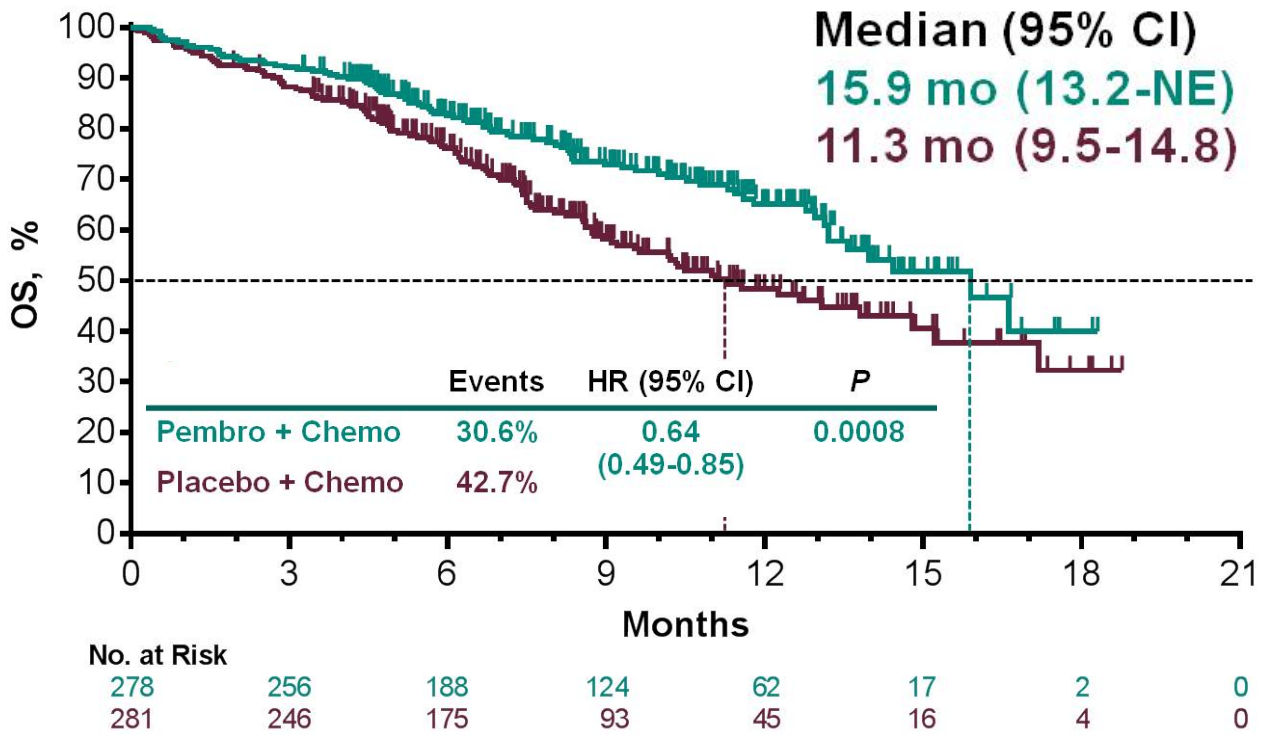

Censoring rate: 38% of pts with OS event

Censoring rate: 59% of pts with PFS event

Gandhi L et al, AACR 2018, NEJM 2018

Paz-Ares L et al,ASCO 2018, NEJM 2018

Pembro + Chemo Better than Chemo (regardless of Histology & PD-L1)

PDL1 [TPS] <1% | **PDL1 [TPS] 1-49%** | **PDL1 [TPS] ≥50%**

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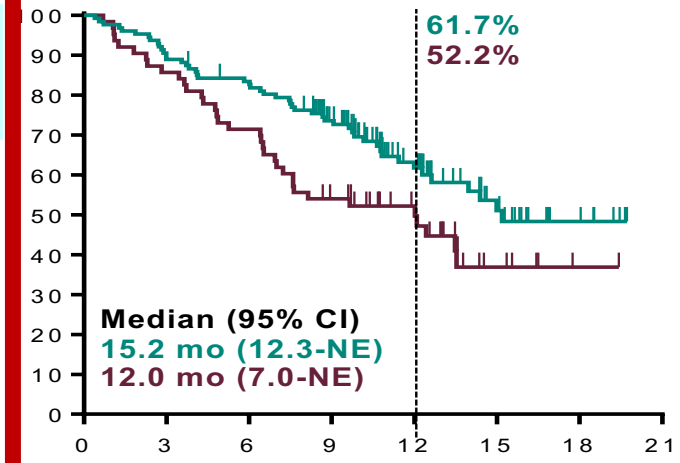

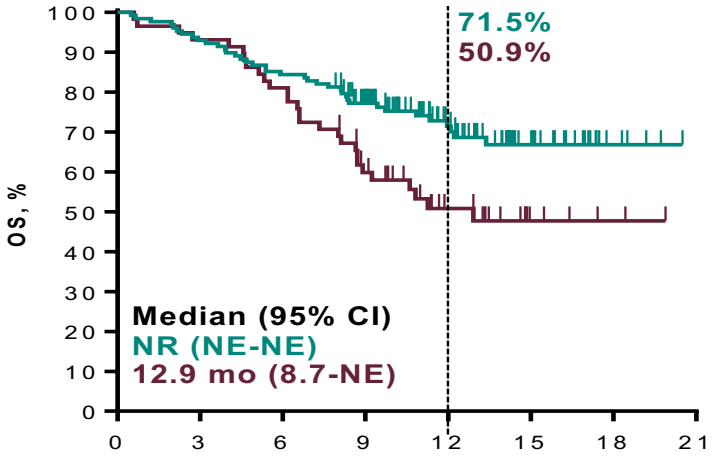

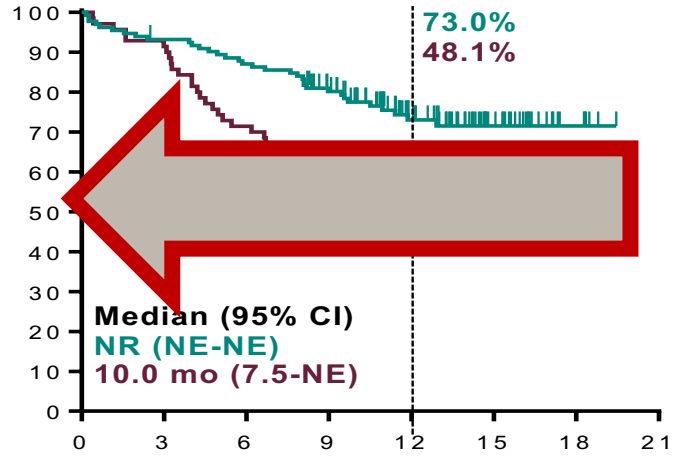

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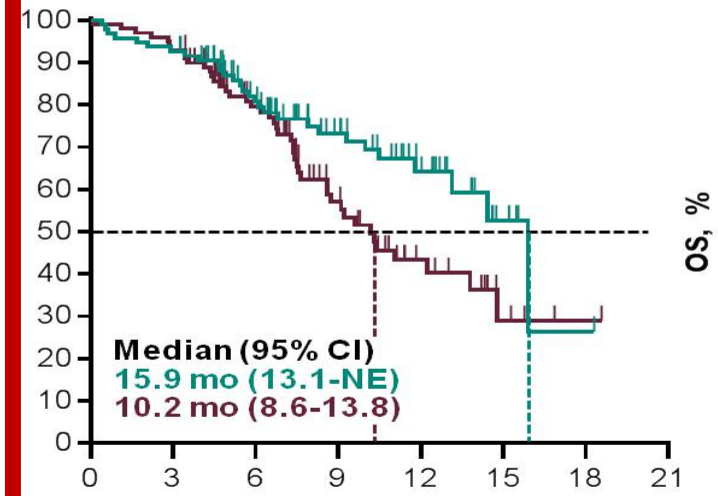
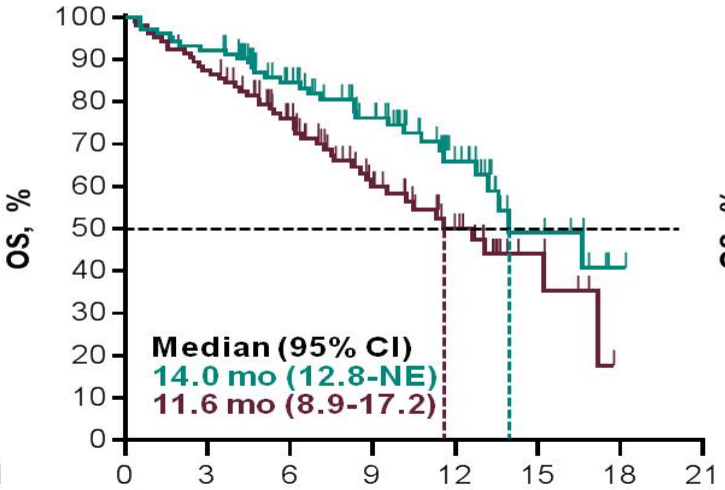
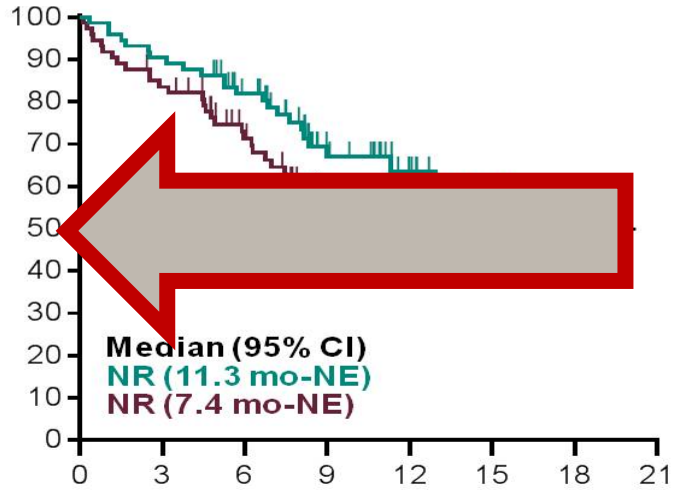
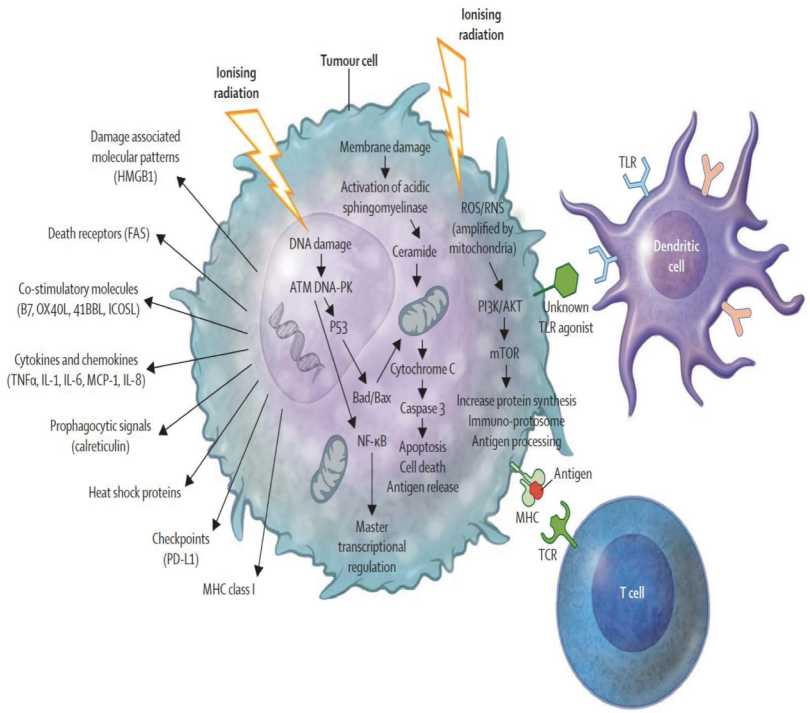






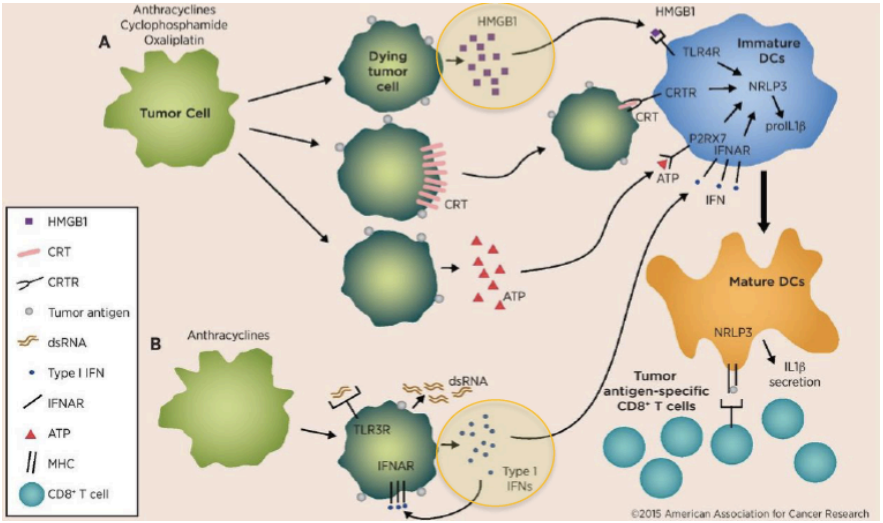
Paz-Ares L et al,ASCO 2018, NEJM 2018

RT induce Immunogenic Tumor Death and PD-L1 expression



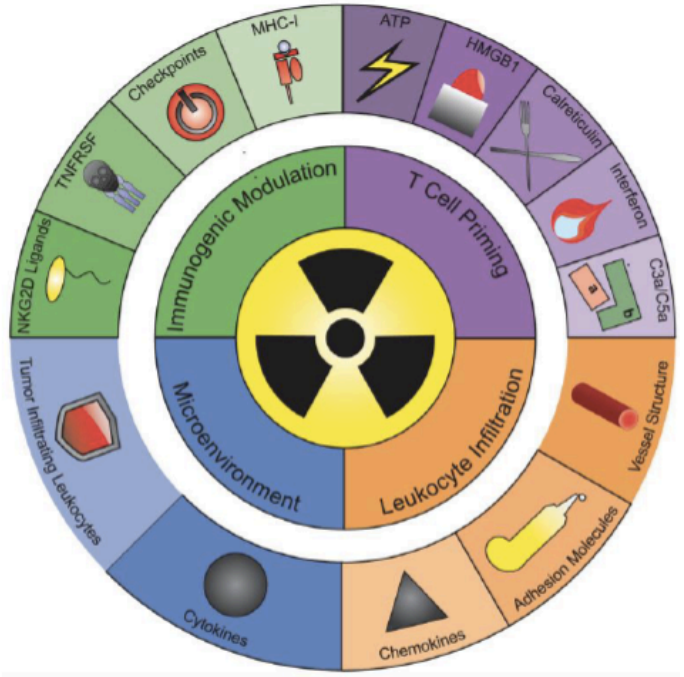
- RT DNA and membrane damage activates transcription factors and signalling pathways
- That modulates the immunophenotype and immunogenicity of tumour cells

Sarabi et al, Lancet Oncol 2015



- RT induced Damage-associated molecularpatterns (DAMPs mediate robust immunomodulation and de facto underlie the immunogenicity of cancer cell death
- Chemotherepeutics results in variable level of DAMPs with consequent activation of a therapeutically relevant anticancer immune response

Mitchell L et al, Ann Oncol 2015

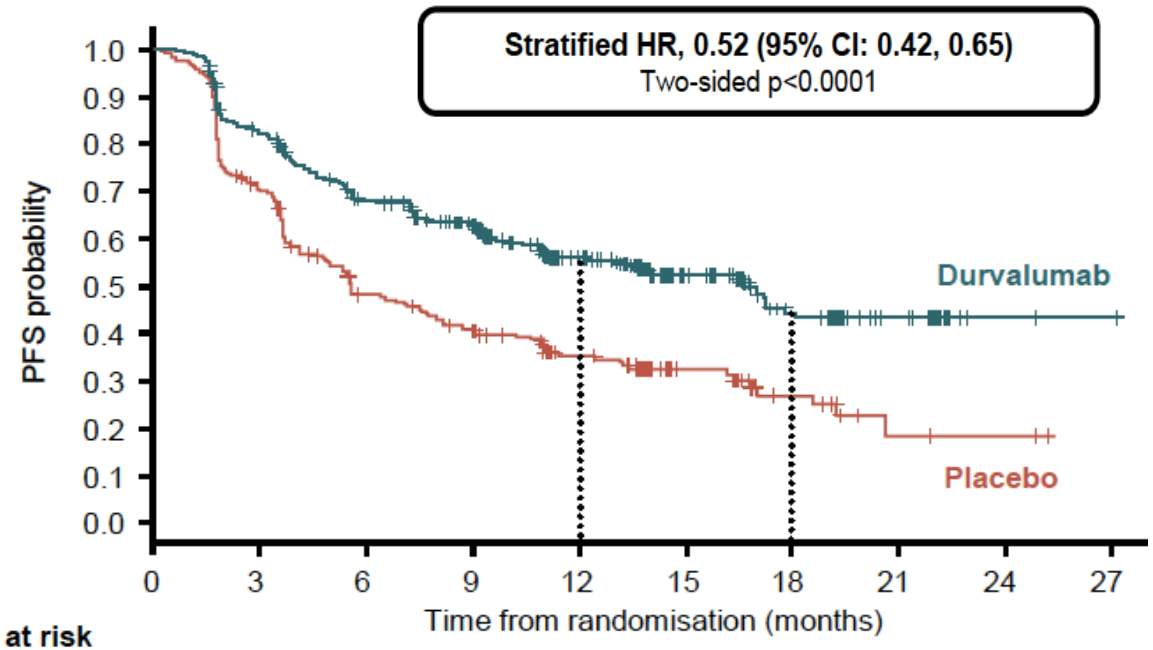


- RT initiates production of IFN/STING
- Activates Pro-Death Signaling in tumor cells
- Induced PD-L1 expression
- Initiates realeas of tumor antigens
- Generates Chemotactic Signals recruiting Myeloid cell polulations

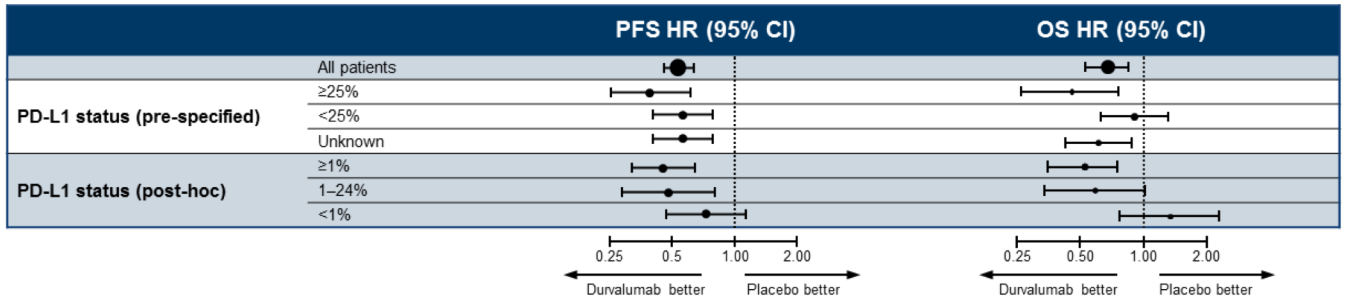
Walle et al, Ther Adv Med Oncol, 2018

Durvalumab after Concurrent CT-RT improves Prognosis

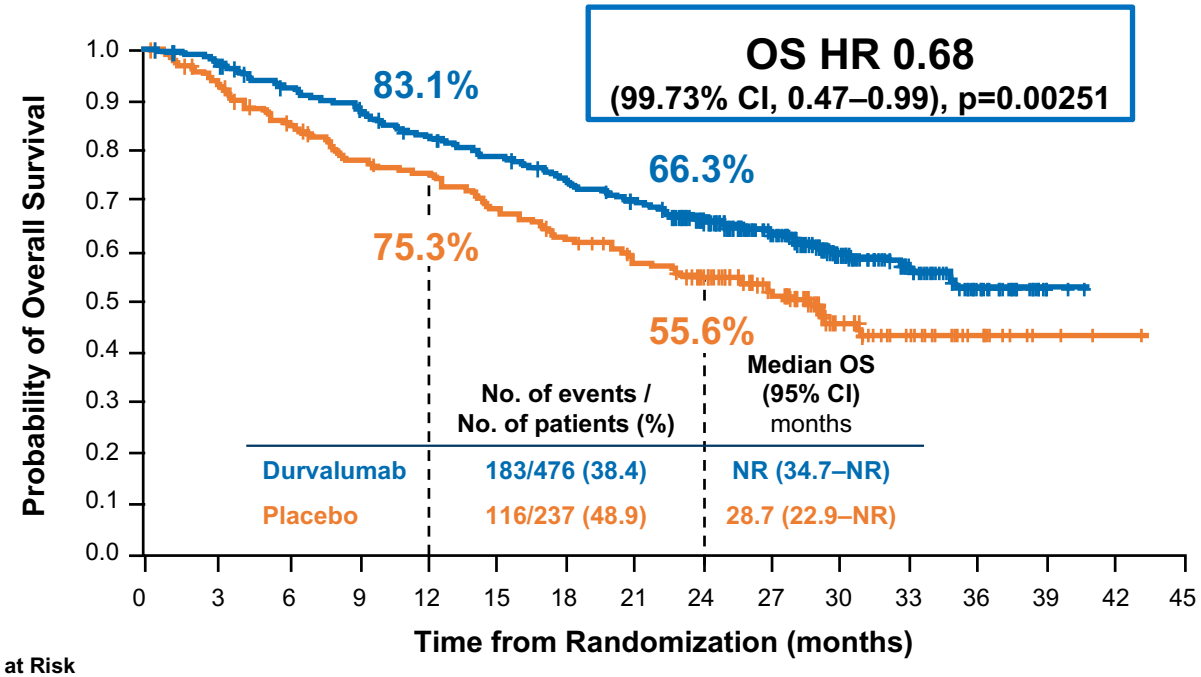
PFS



No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0



OS



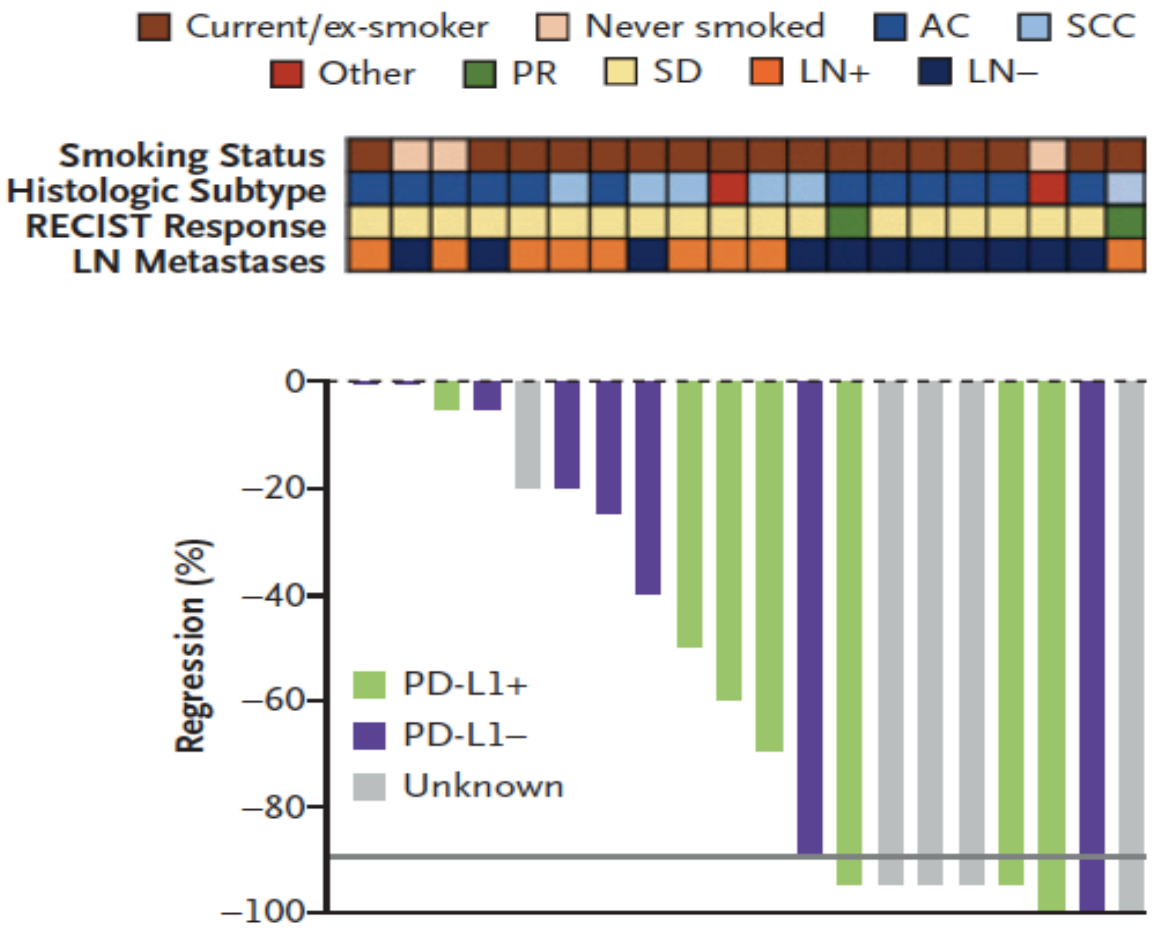
No. at Risk																	
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Regulatory Approval is Pending (PD-L1>1%)

Antonia S et al, WCLC 2018, NEJM 2018

IO: Unexpected Activity in Neoadjuvant Treatment of NSCLC

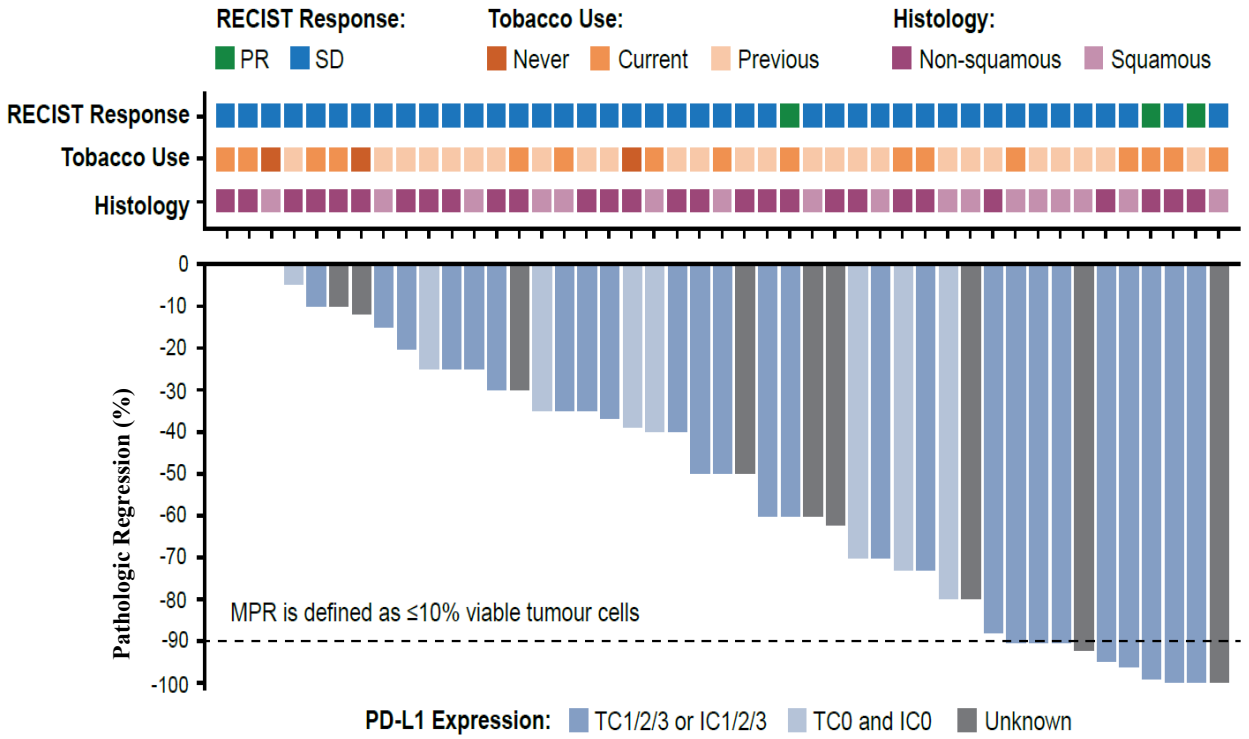
NIVOLUMAB
[26 pts, Stage I-IIIA]



Forde PM et al, NEJM 2018

ATEZOLIZUMAB
[43 pts, Stage I-IIIA]

Major Pathological Response (≤10% Viable Tumour Cells)

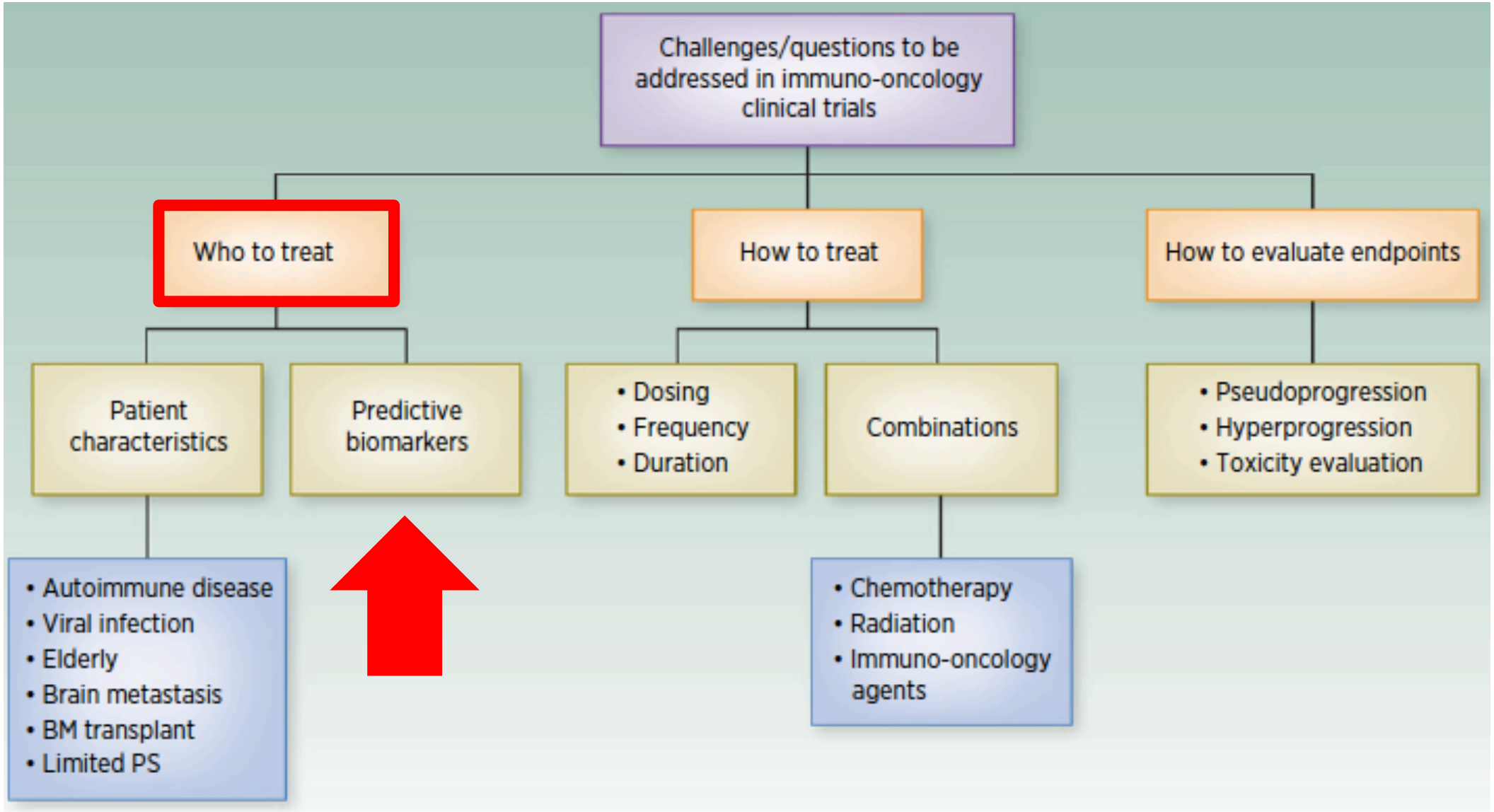


Rusch V et al, WCLC 2018

Presentation Outline

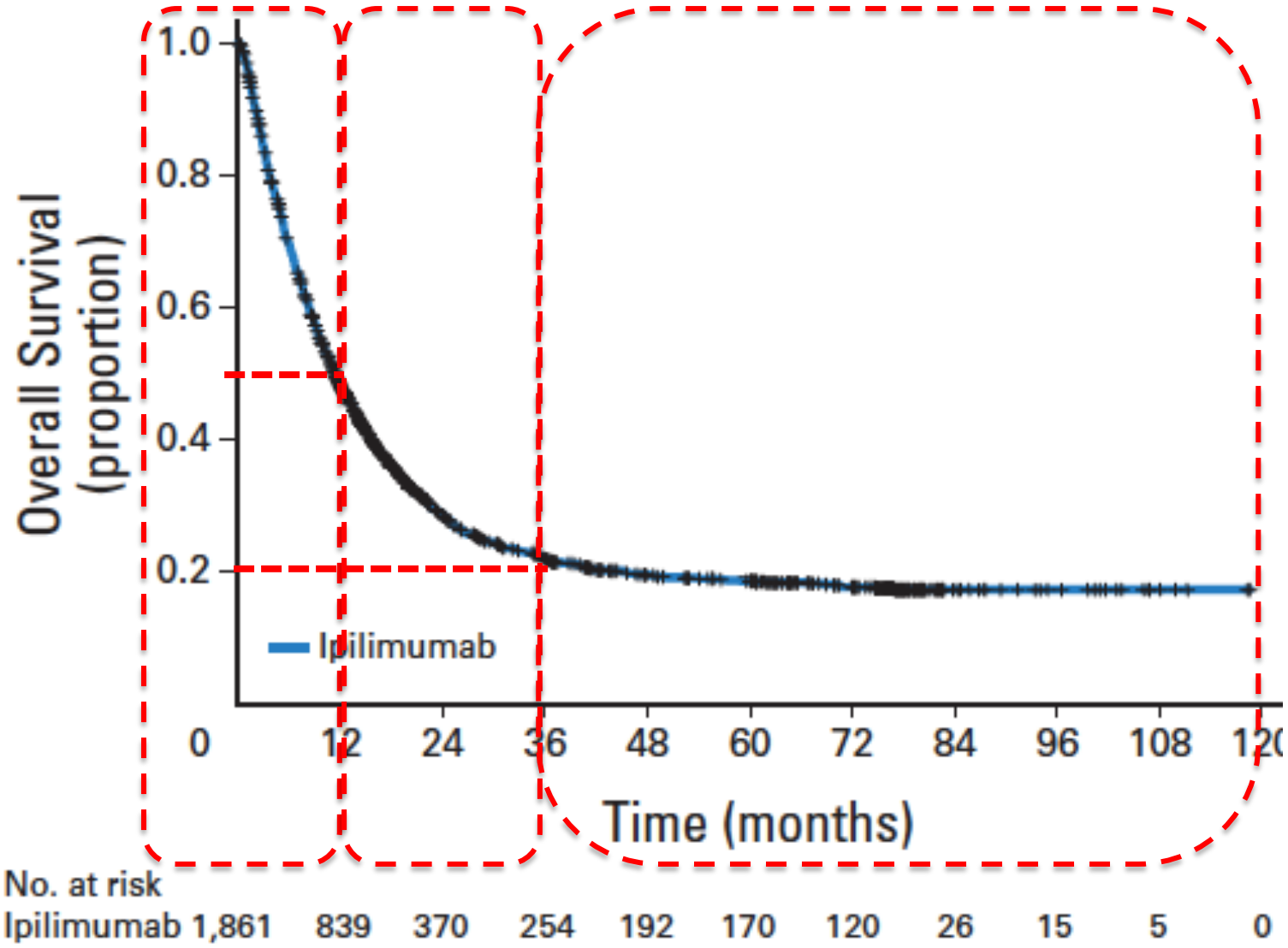
- Impact of Immunotherapy (IO) in Medical Oncology
- **Patients' Selection and Predictive Factors for IO**
- Treatment End-points for IO
- Evidences for Real-World beyond Clinical Trials

Challenges to address in IO Clinical Trials



Baik CS et al, Clin Cancer Res 2017

Efficacy *'Plateaus'* of Immunotherapy: Advanced Melanoma



	Death Rate
@1yr	50%
@3yrs	80%

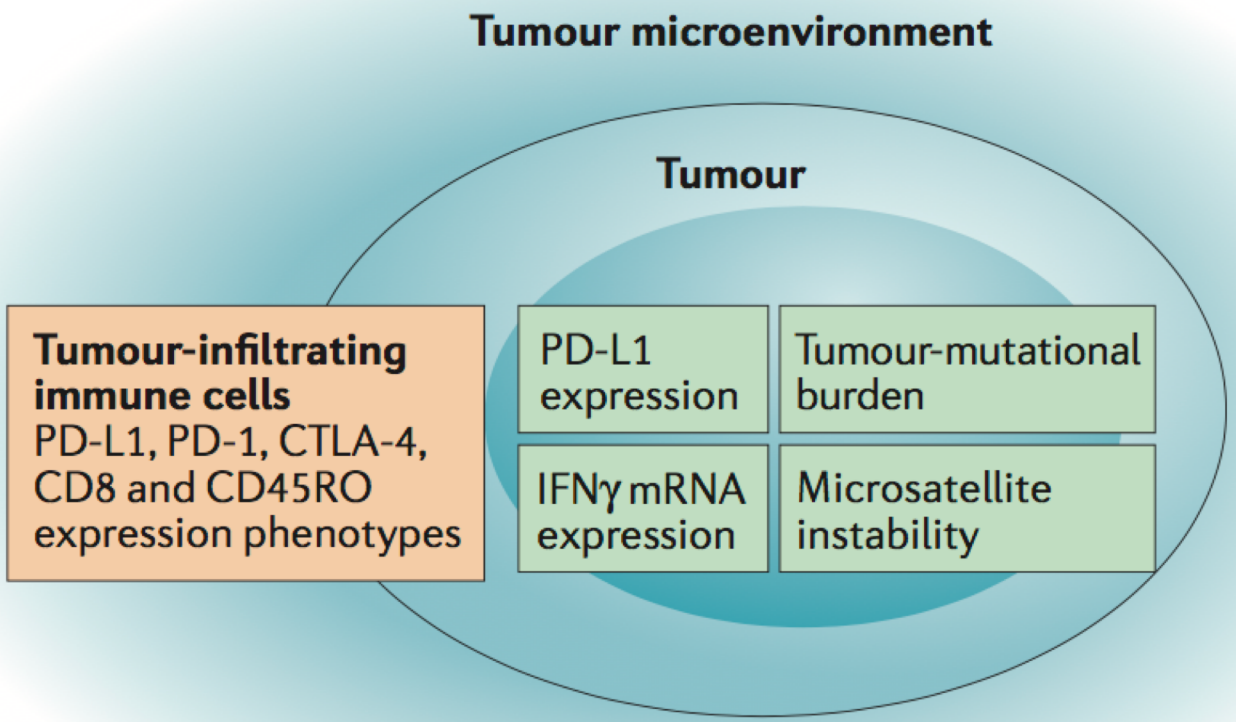
- 20% Of Patients overcome 3 yrs, no (very few) additional deaths in 10 years!
- Are we dealing with <u>CURED</u> patients?

A treatment selection factor is (clearly) required!

Schadendorf D et al, JCO 2015

Biomarkers for Immunotherapy

Current (and Validated) Option for Clinical Practice:
- **PD-L1 (IHC) on Tumor Tissue**



Unmeet Medical Need:
- **Validated Biomarkers in Tissue and Blood**

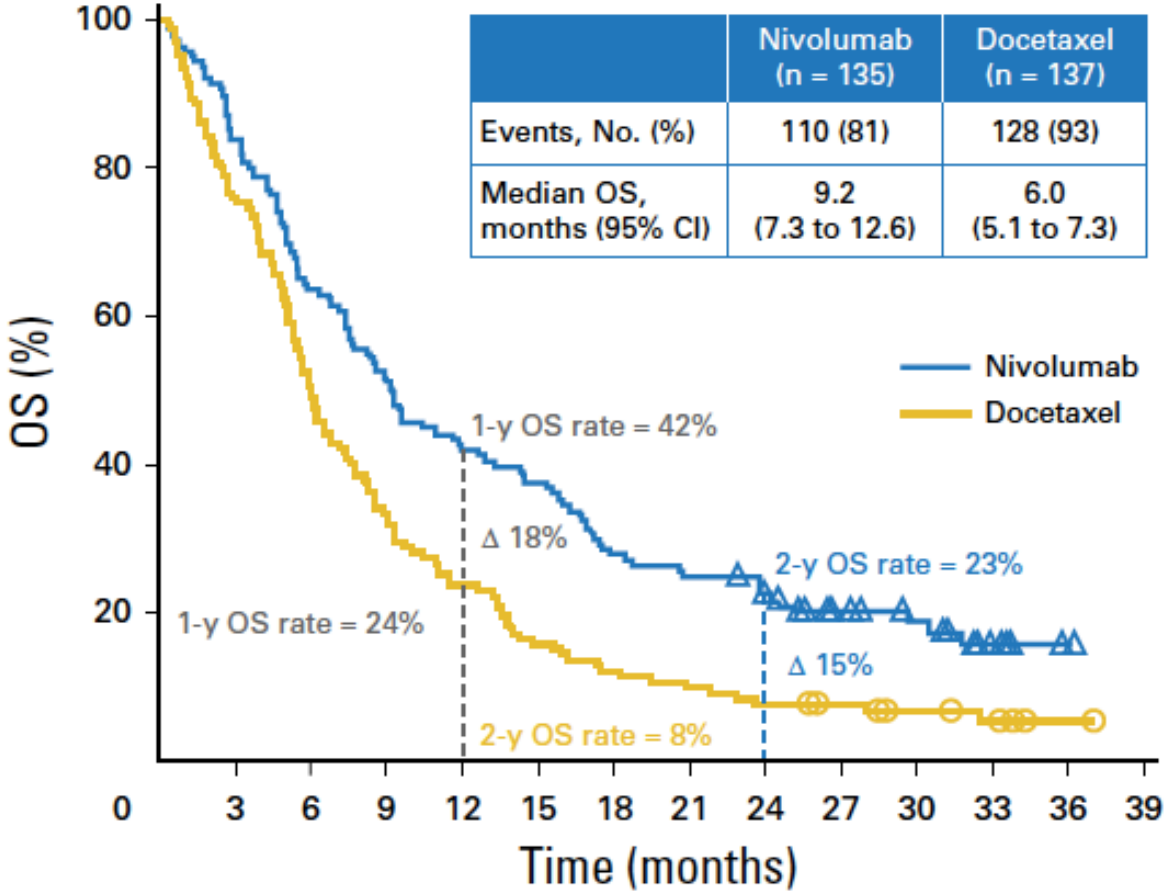
Potential Utility of Liquid Biopsy in Immunotherapy:
- **Diagnostic**
- **Prognostic**
- **Predictive of Response**
- **Monitoring**
- **Mechanisms if Resistance**

Current tools:
- **Calculation of circulating TMB**
- **Detection of bPDL1**
- **Alellic Fraction Variation Dynamic**

Nishino A et al, NRCO, 2017

Pts Unselected for PD-L1: Second Line Nivolumab

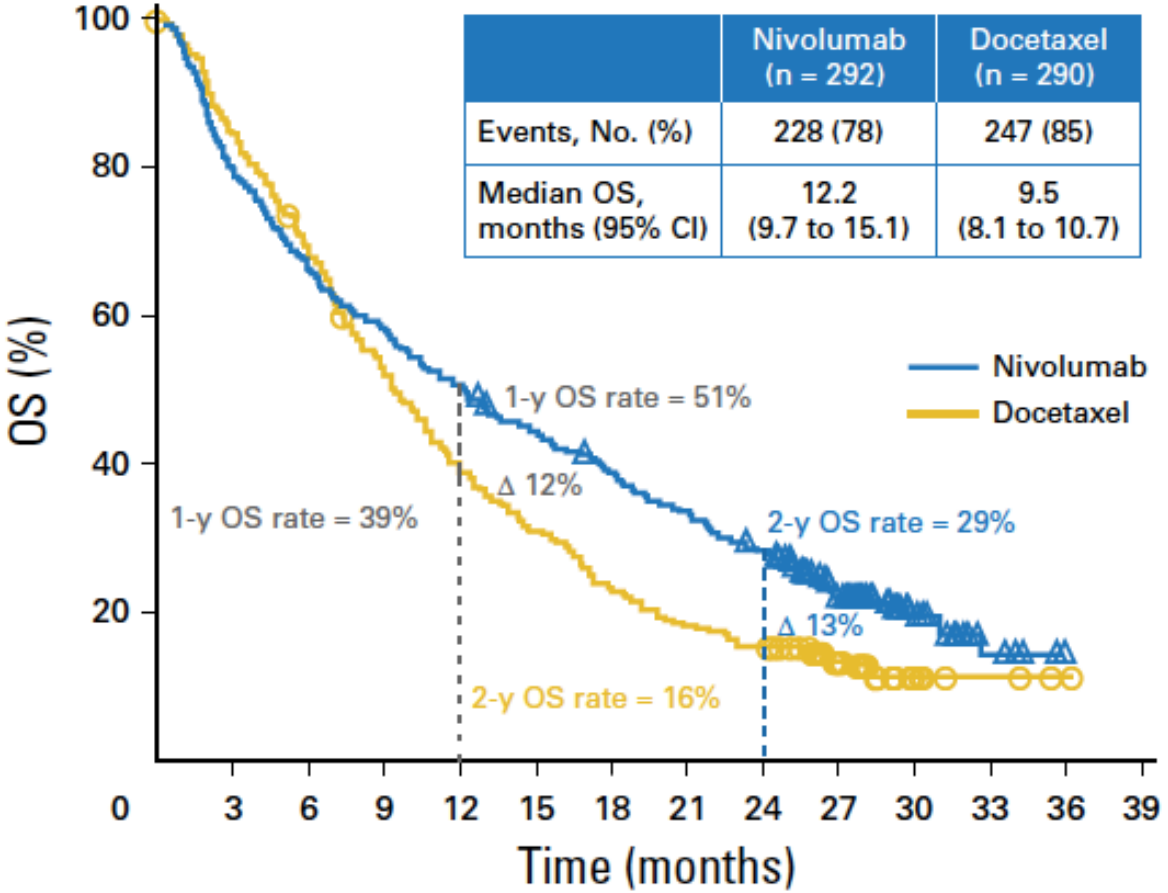
	Nivolumab (n = 135)	Docetaxel (n = 137)
Events, No. (%)	110 (81)	128 (93)
Median OS, months (95% CI)	9.2 (7.3 to 12.6)	6.0 (5.1 to 7.3)



No. at risk:

Nivolumab	135	113	86	69	57	51	38	34	29	19	14	7	1	0
Docetaxel	137	104	69	46	33	22	17	14	11	9	6	4	1	0

	Nivolumab (n = 292)	Docetaxel (n = 290)
Events, No. (%)	228 (78)	247 (85)
Median OS, months (95% CI)	12.2 (9.7 to 15.1)	9.5 (8.1 to 10.7)



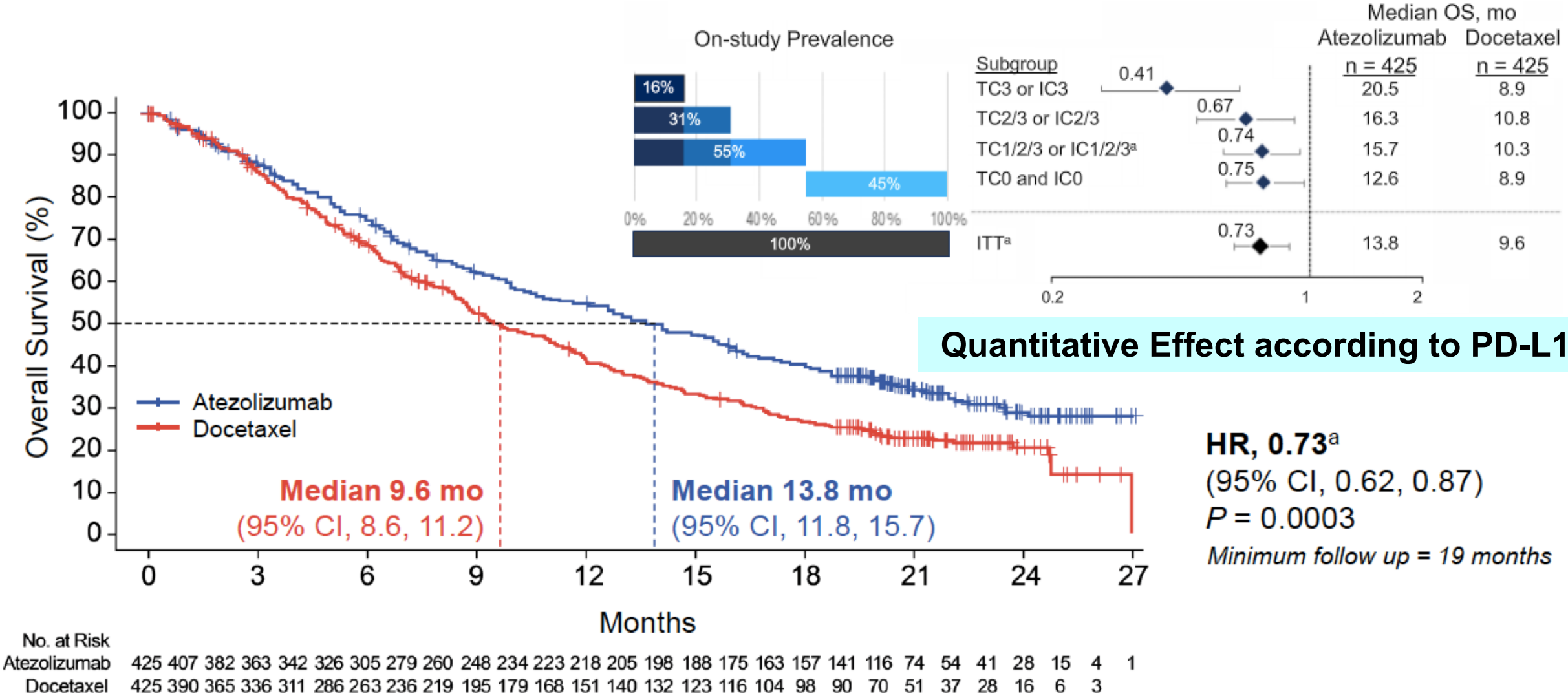
No. at risk:

Nivolumab	292	233	194	171	148	128	112	97	81	46	18	6	0	0
Docetaxel	290	243	194	150	111	89	66	53	45	25	6	3	1	0

A treatment selection factor is (clearly) required!

Horn L et al, J Clin Oncol 2017

OAK [Phase III]: Atezolizumab *vs.* Docetaxel



Quantitative Effect according to PD-L1

HR, 0.73[a]
(95% CI, 0.62, 0.87)
P = 0.0003
Minimum follow up = 19 months

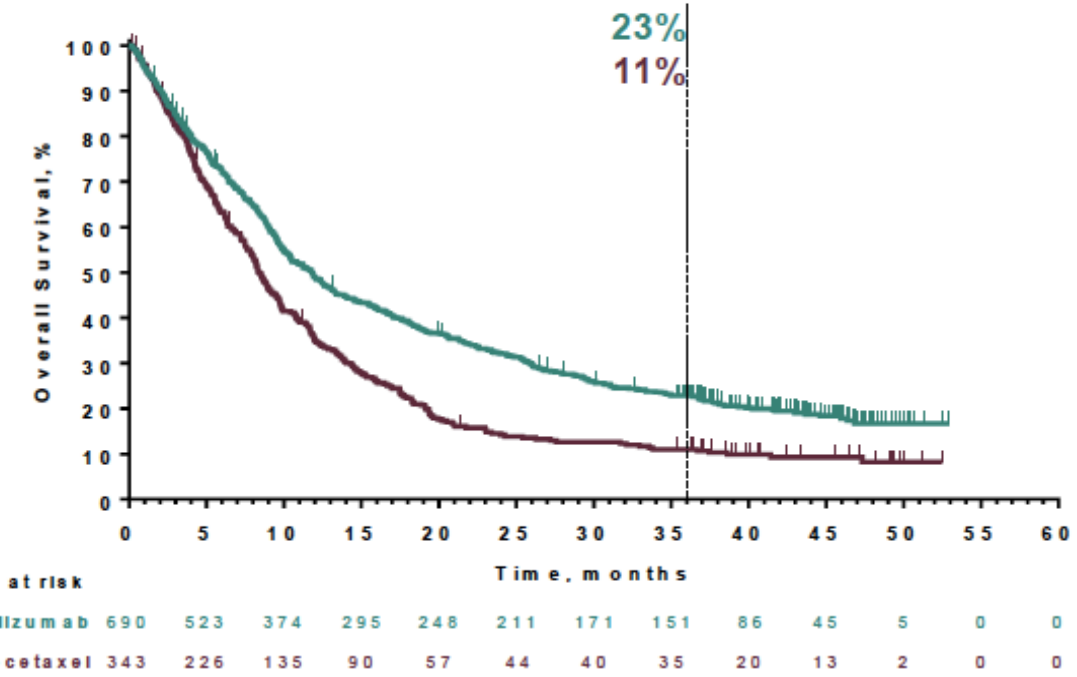
A treatment selection factor is (clearly) required!

Rittmeyer A et al, Lancet 2017

PD-L1 Positive Pts: Second Line PEMBRO [TPS ≥1 & 50%]

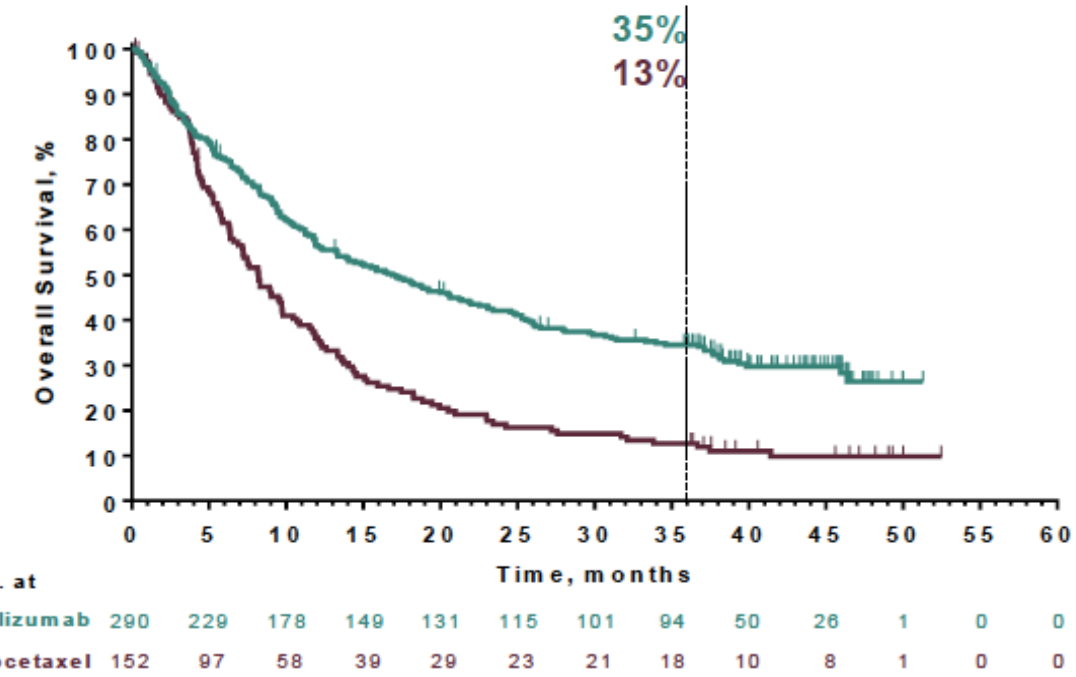
PD-L1 TPS ≥1%

	n	Events, n (%)	Median OS, mo (95% CI)	HR (95% CI)
Pembrolizumab	690	548 (79)	11.8 (10.4–13.1)	0.69 (0.60–0.80) *P*<0.00001
Docetaxel	343	295 (86)	8.4 (7.6–9.5)	



PD-L1 TPS ≥50%

	n	Events, n (%)	Median OS, mo (95% CI)	HR (95% CI)
Pembrolizumab	290	199 (69)	16.9 (12.3–21.4)	0.53 (0.42–0.66) *P*<0.00001
Docetaxel	152	127 (84)	8.2 (6.4–9.8)	

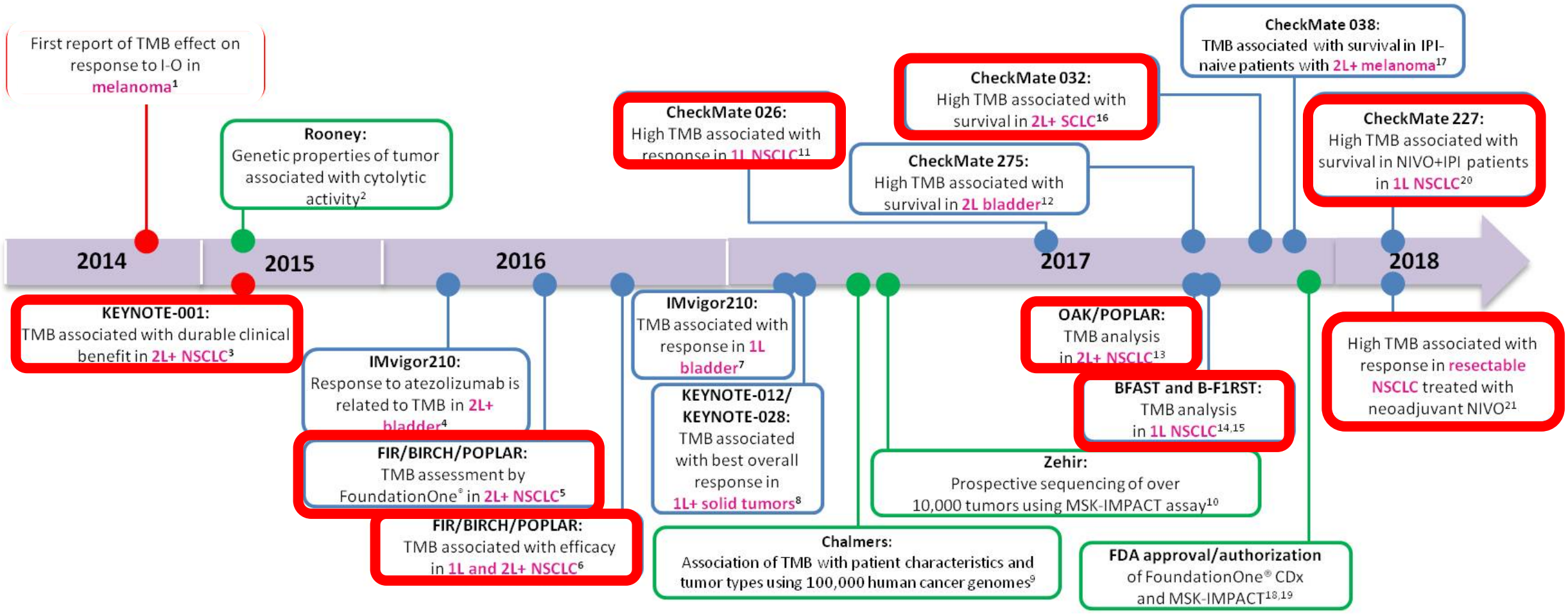


A treatment selection factor is (clearly) required!....beyond PD-L1

Herbst R et al, ESMO 2018

TMB as Biomarker in Lung Cancer: 'Evolutionary Road'

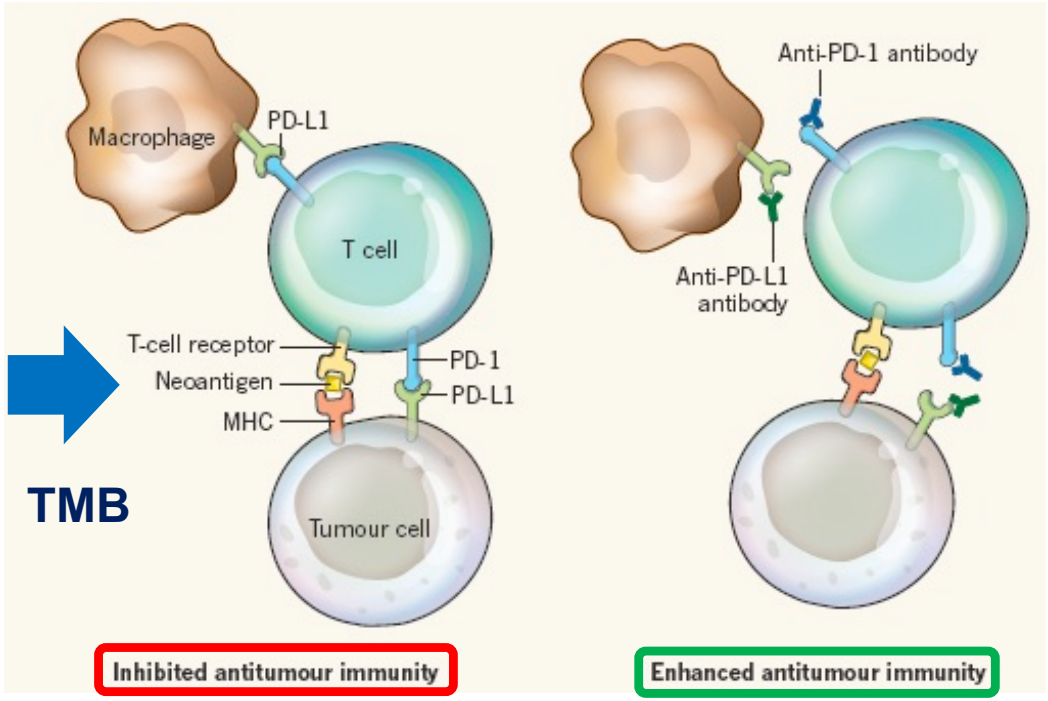
TMB as a Biomarker for I-O Therapies: LUNG CANCER

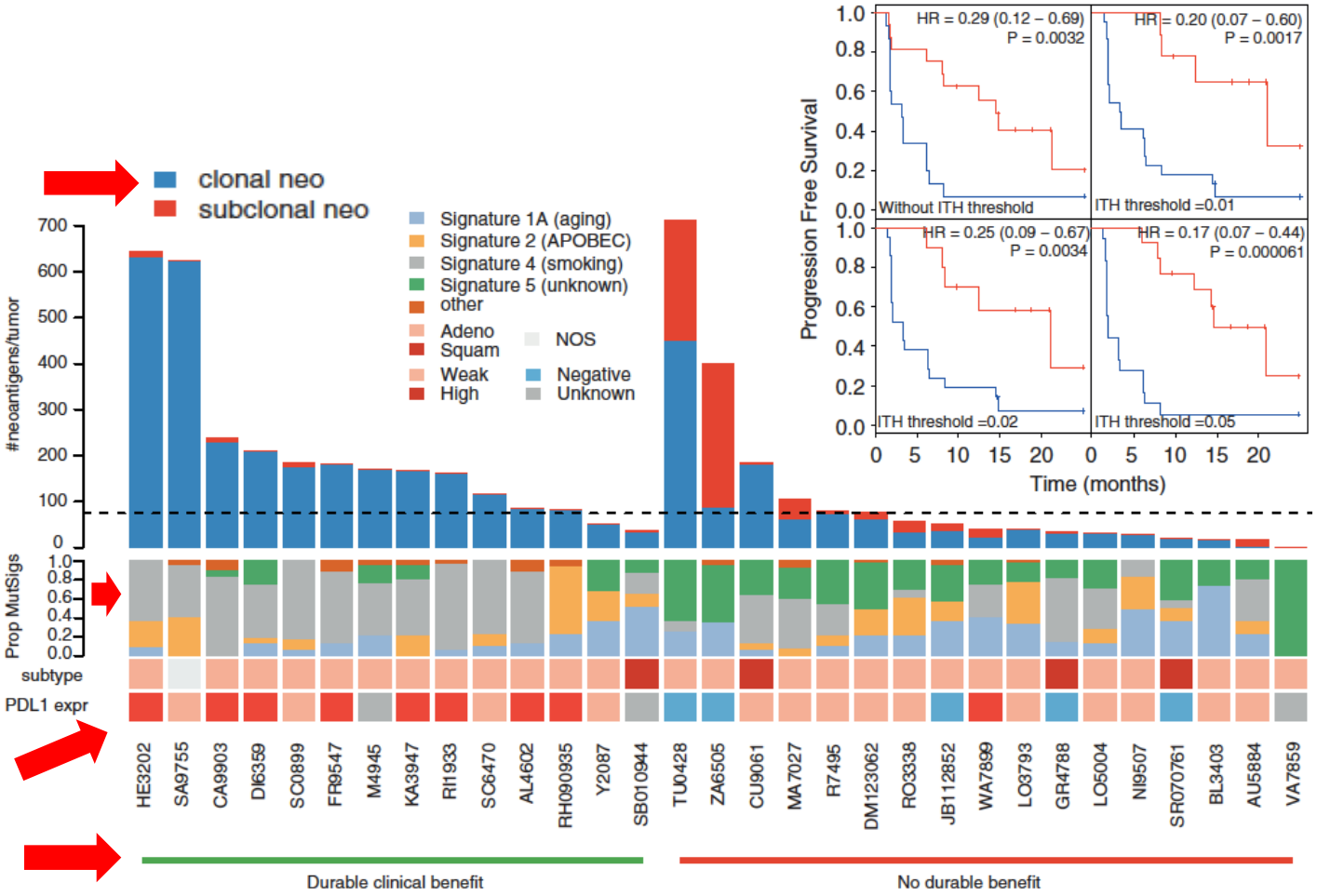


Chan T, ASCO 2018

Neoantigen Intratumor Heterogeneity (ITH) & Clonal Neoantigens

Tumor Mutational Burden (TMB) & Antitumor Immunity



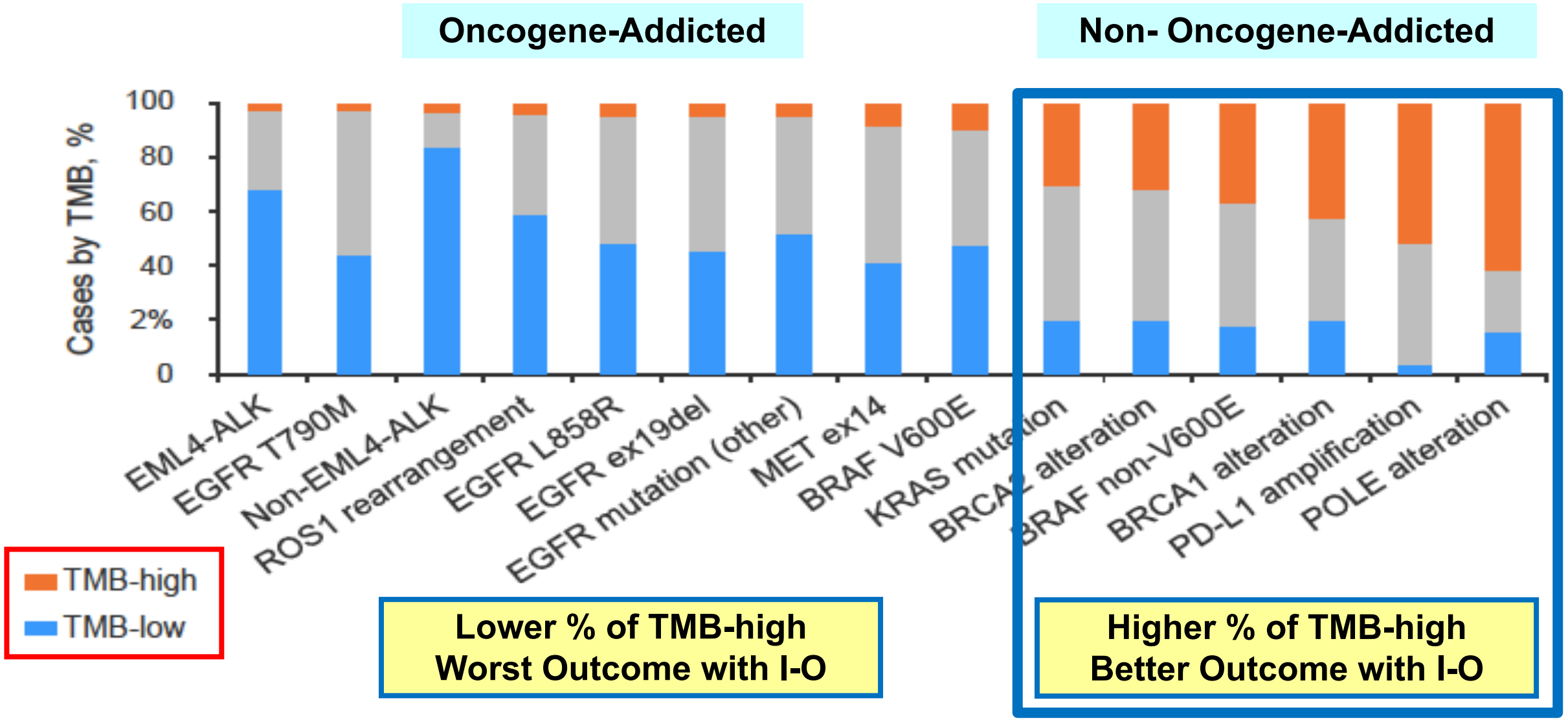


Sensitivity to PD-1 blockade enhanced in tumors enriched for clonal neoantigens.

Wolchok JD, Chan T, Nature 2014

McGranahan et al, Science 2016

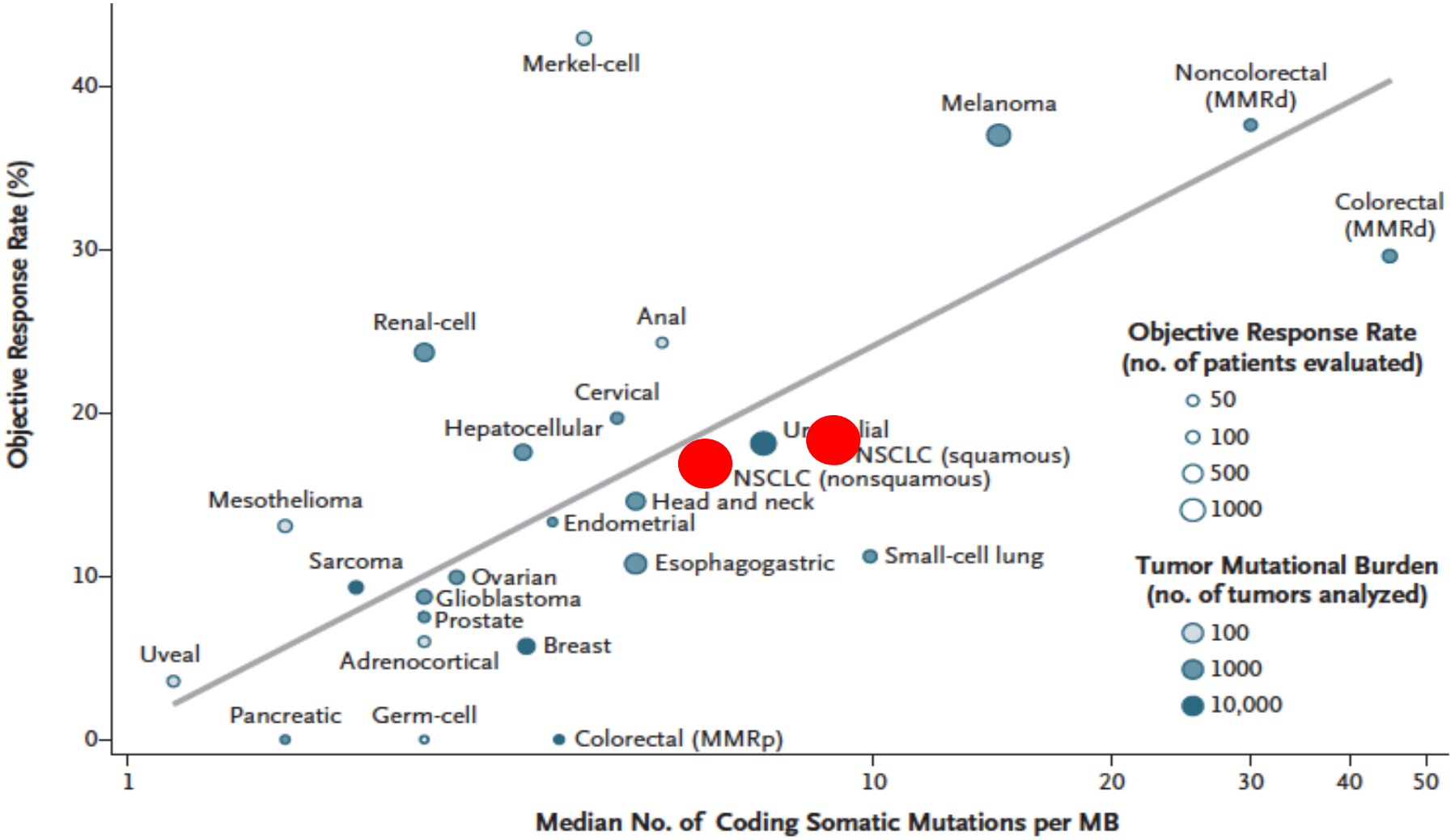
TMB according to Oncogene- Addiction



Spigel D et al, ASCO 2016

TMB as a Predictive Biomarker for I-O Therapies

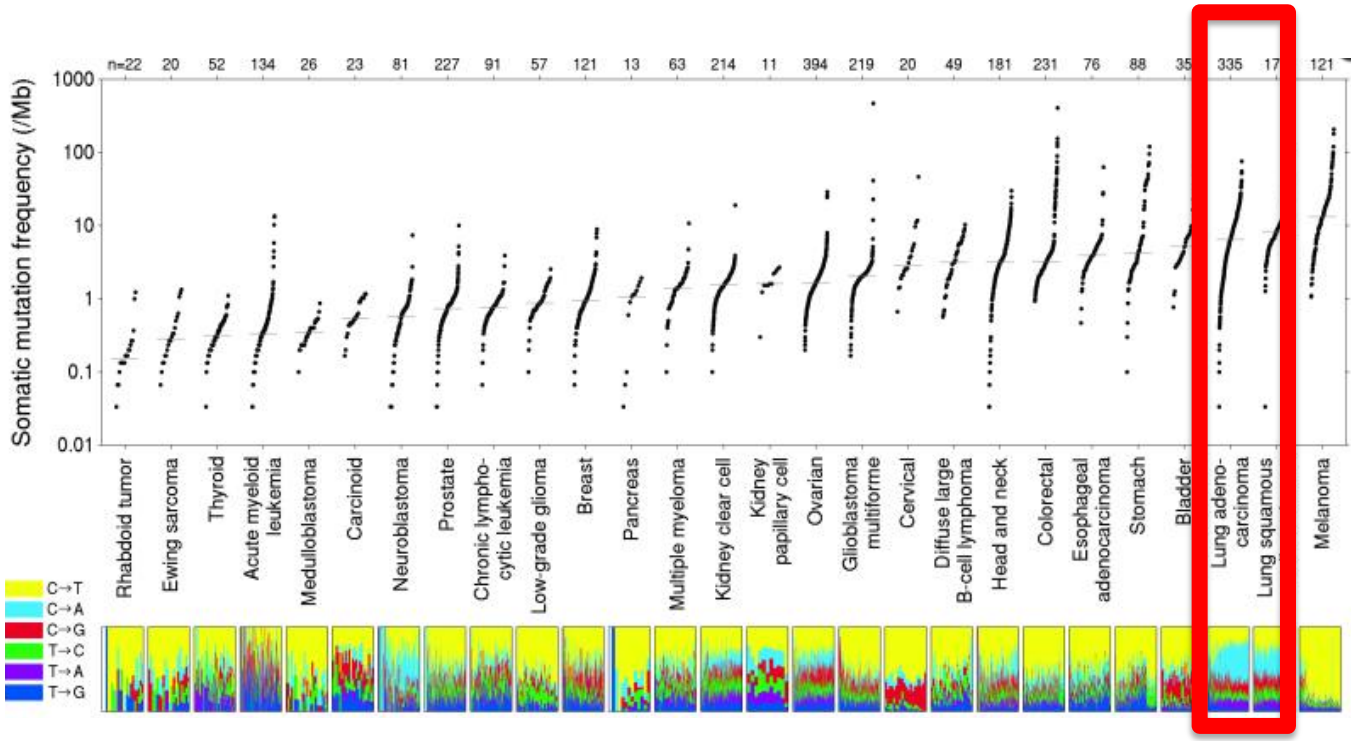
Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PDL1 Therapy in 27 Tumor Types.



Yarchoan, M et al, NEJM 2017

Tumor Mutational Burden (TMB) According to Disease

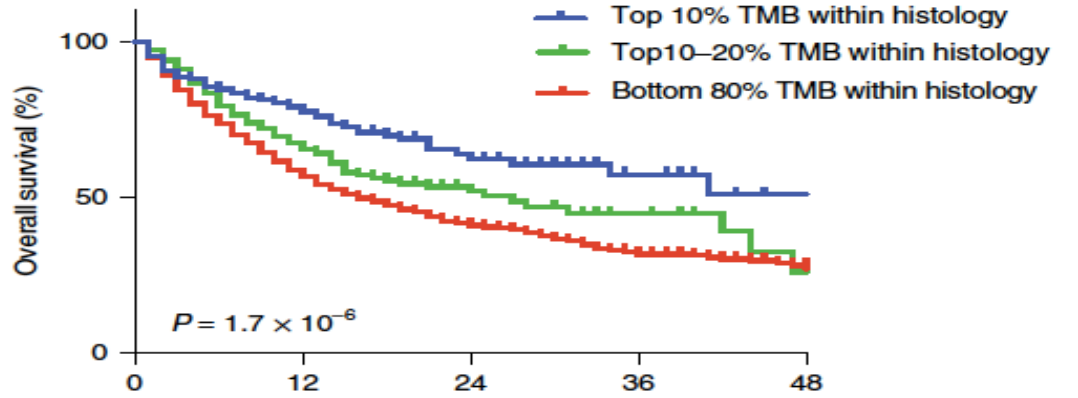
(Non-oncogene-addicted) NSCLC has High Somatic mutation frequencies (high TMB)



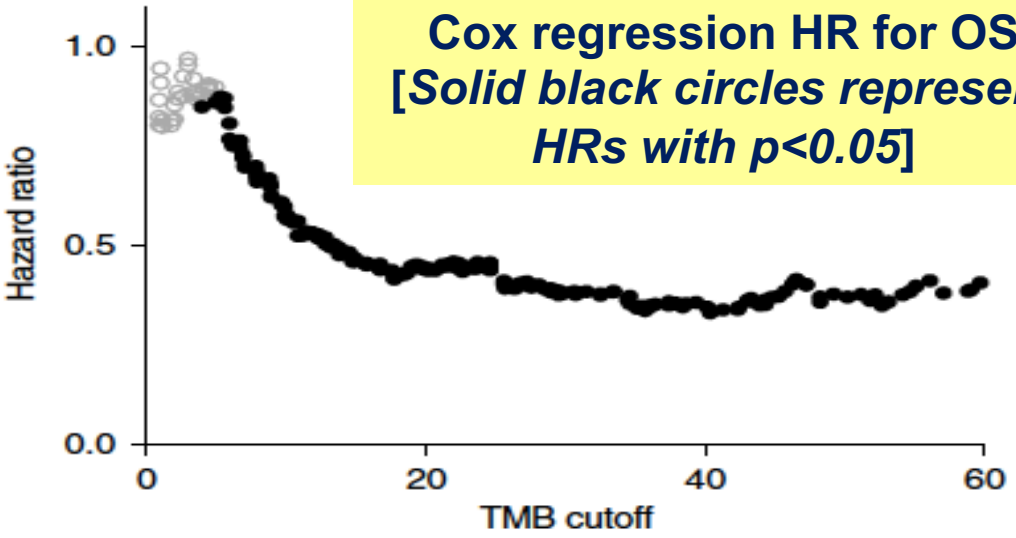
Somatic mutation frequencies observed in exomes from 3,083 tumour/normal pairs.

Lawrence M et al, Nature 2013

Effect of TMB on OS after ICI treatment [1,662 patients]



Cox regression HR for OS [*Solid black circles represent HRs with p<0.05*]

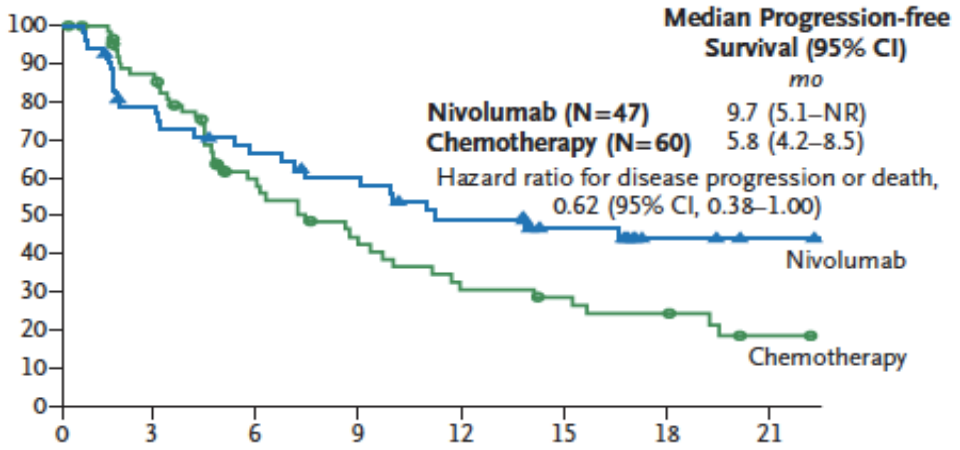


Samstein et al, Nature Gen 2019

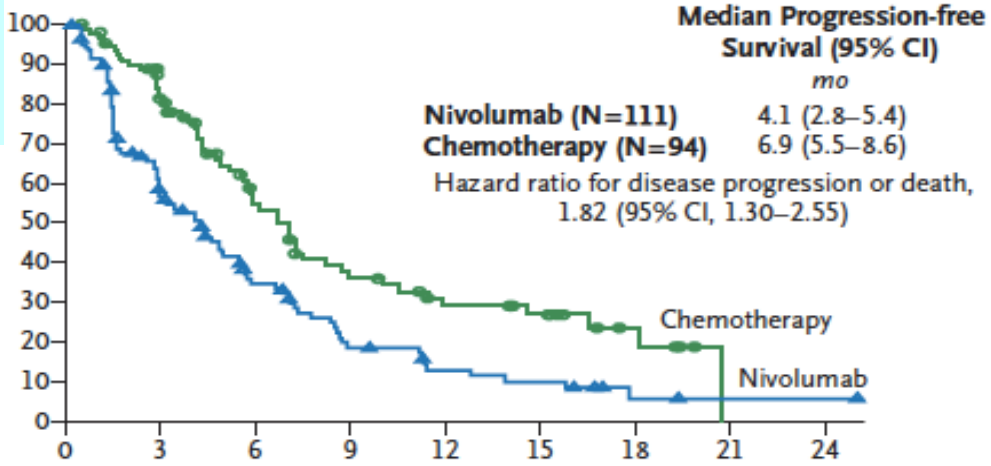
TMB IS predictor for PFS benefit of I-O vs. Chemo

CM 026: NIVO *vs.* Chemo
TMB by WGS [21,522 genes]

High TMB



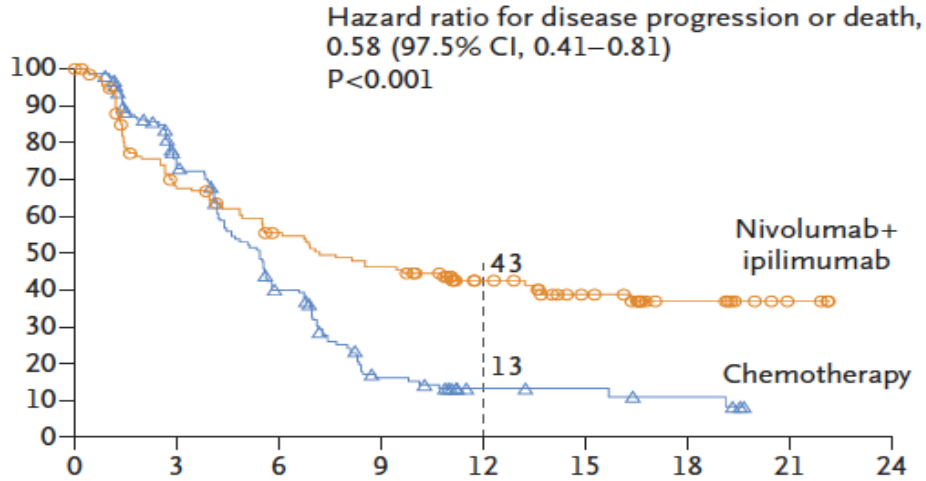
Low Medium TMB



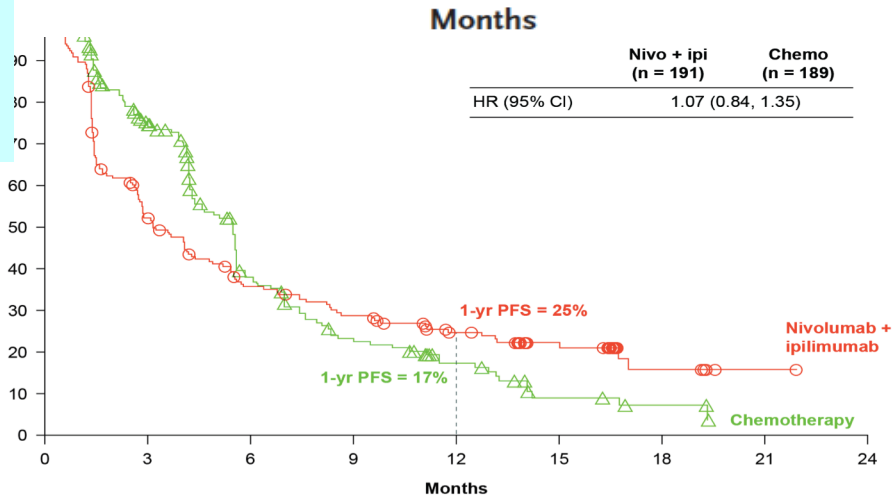
Carbone D et al, NEJM 2017

CM 227: NIVO + IPI *vs.* Chemo
TMB by NGS [324 genes]

High TMB



Low Medium TMB

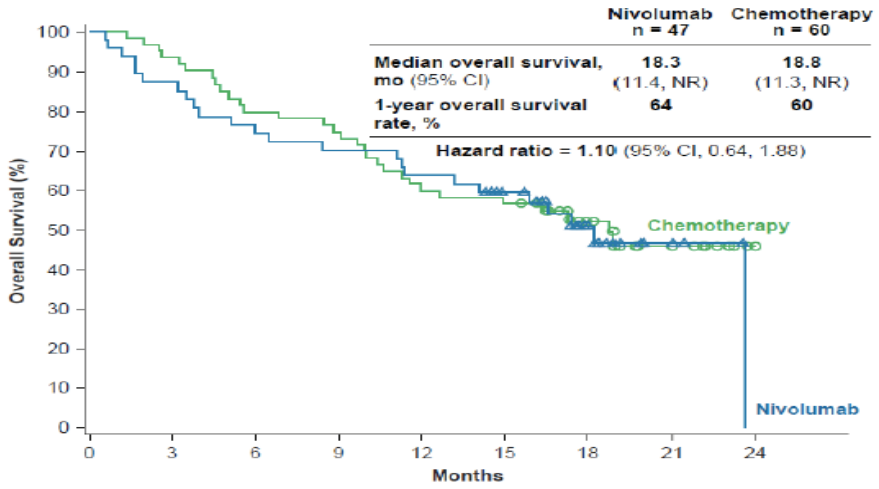


Helmann J et al, NEJM 2018

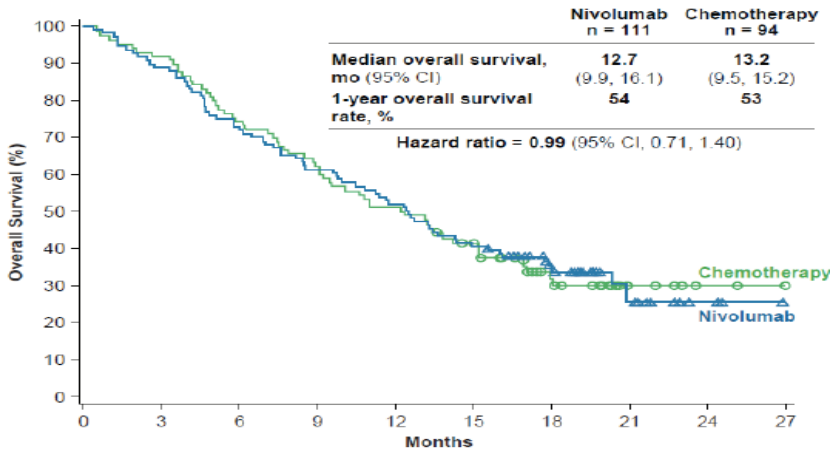
TMB IS NOT predictor for OS benefit of I-O vs. Chemo

CM 026: NIVO *vs.* Chemo
TMB by WGS [21,522 genes]

High TMB

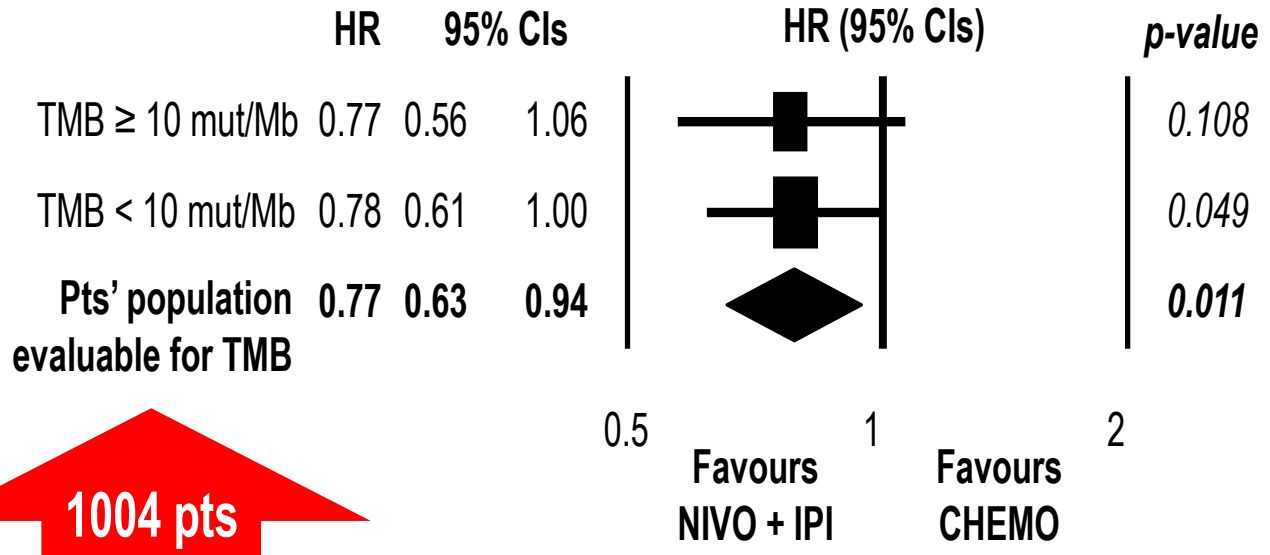


Low Medium TMB



312 pts (57.6%)

CM 227: NIVO + IPI *vs.* Chemo
TMB by NGS [324 genes]



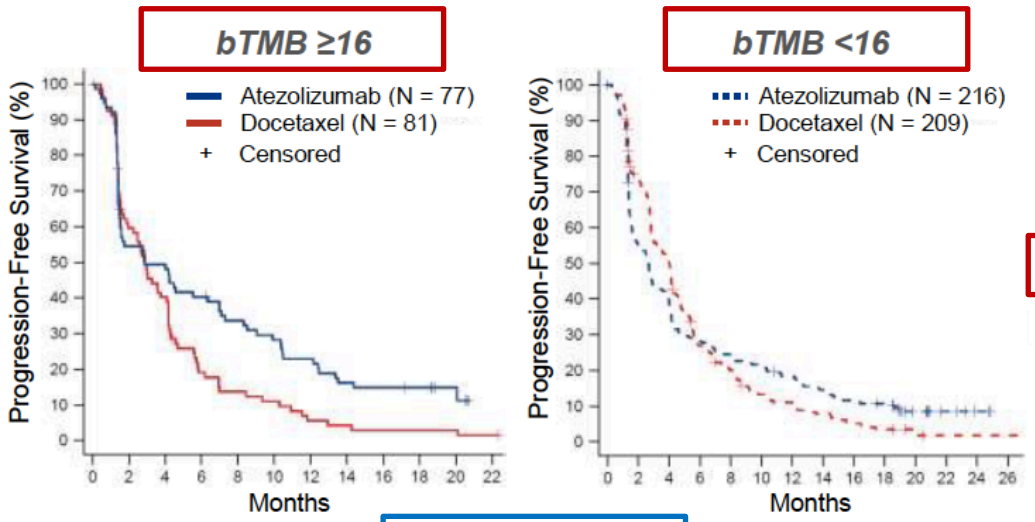
1004 pts (54.7%)

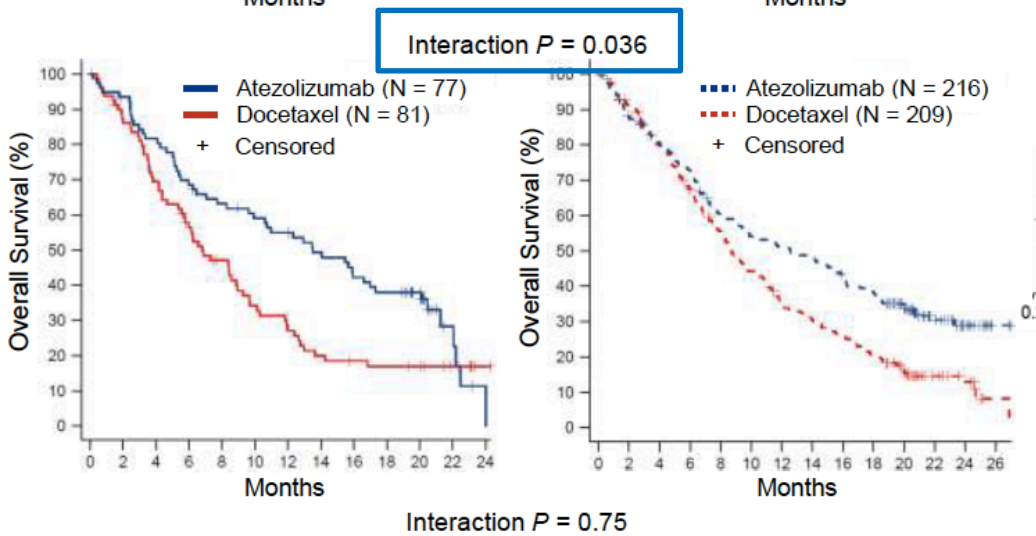
NB: data derived from press release on BMS website and cumulated according to a Random Effect Model [Heterogeneity p=0.95]

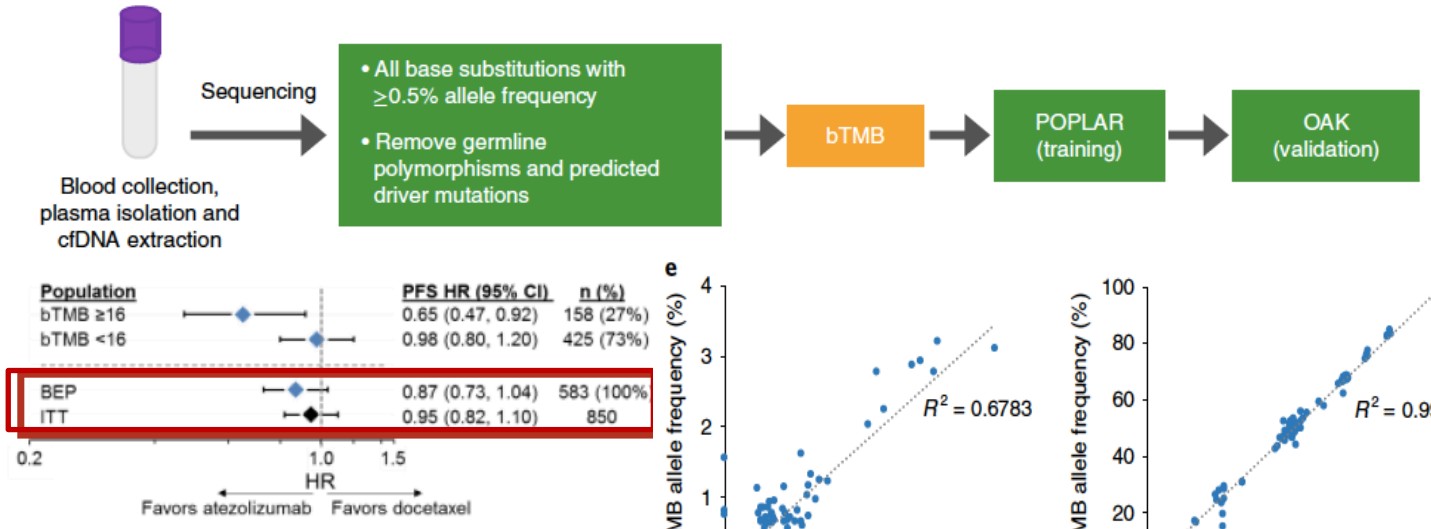
Carbone D et al, NEJM 2017

CM 227 Press release [October 19th, 2018]: Updated analysis for OS

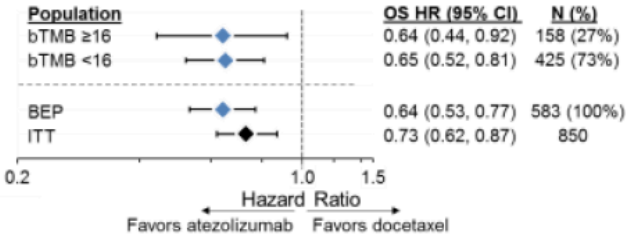
bTMB (Blood/Tissue) as a predictor of benefit of Atezolizumab

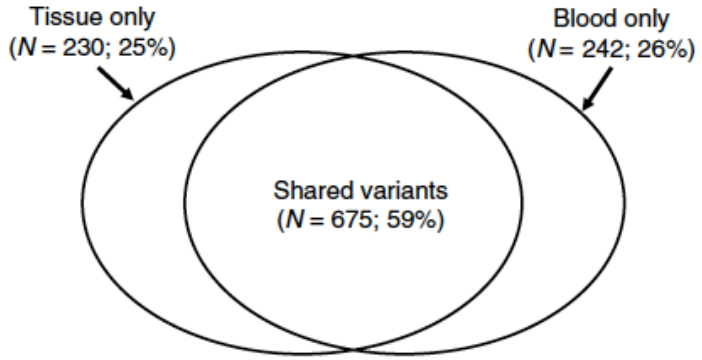






- **Training Set: POPLAR, Validation Set: OAK**

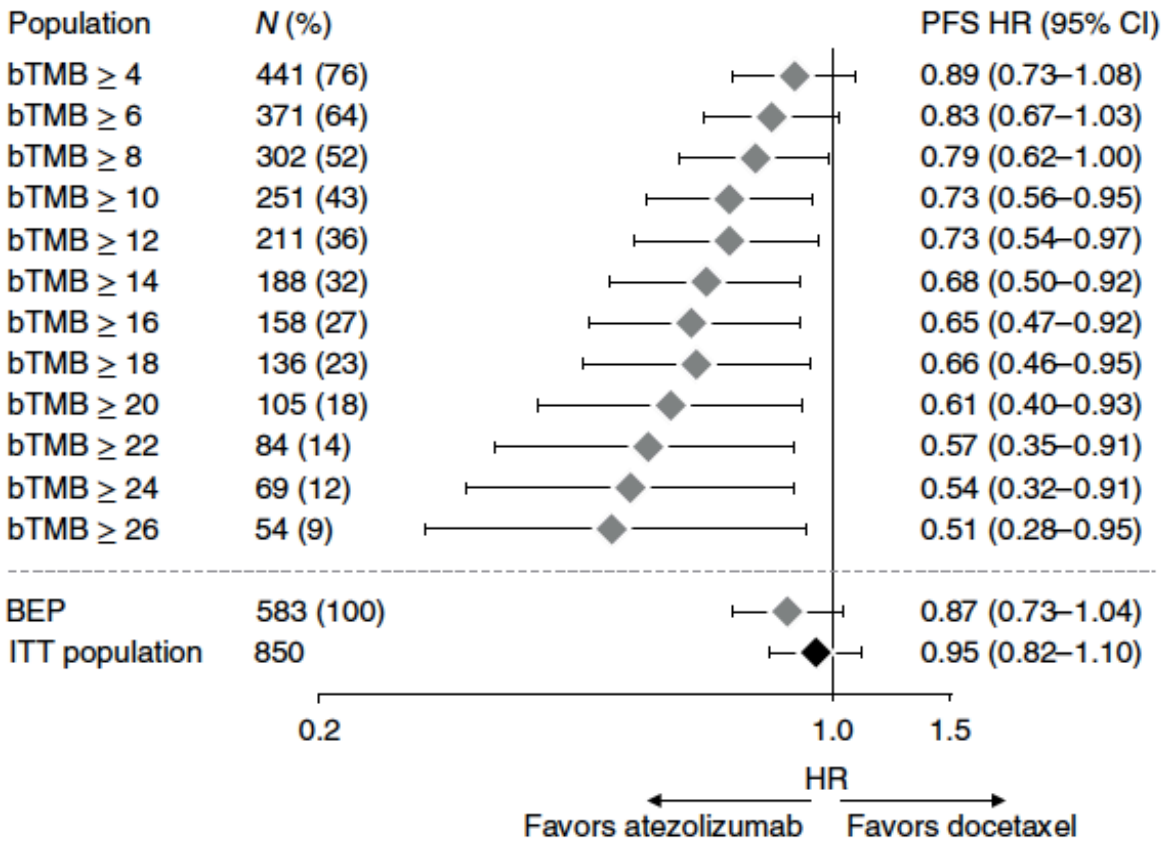




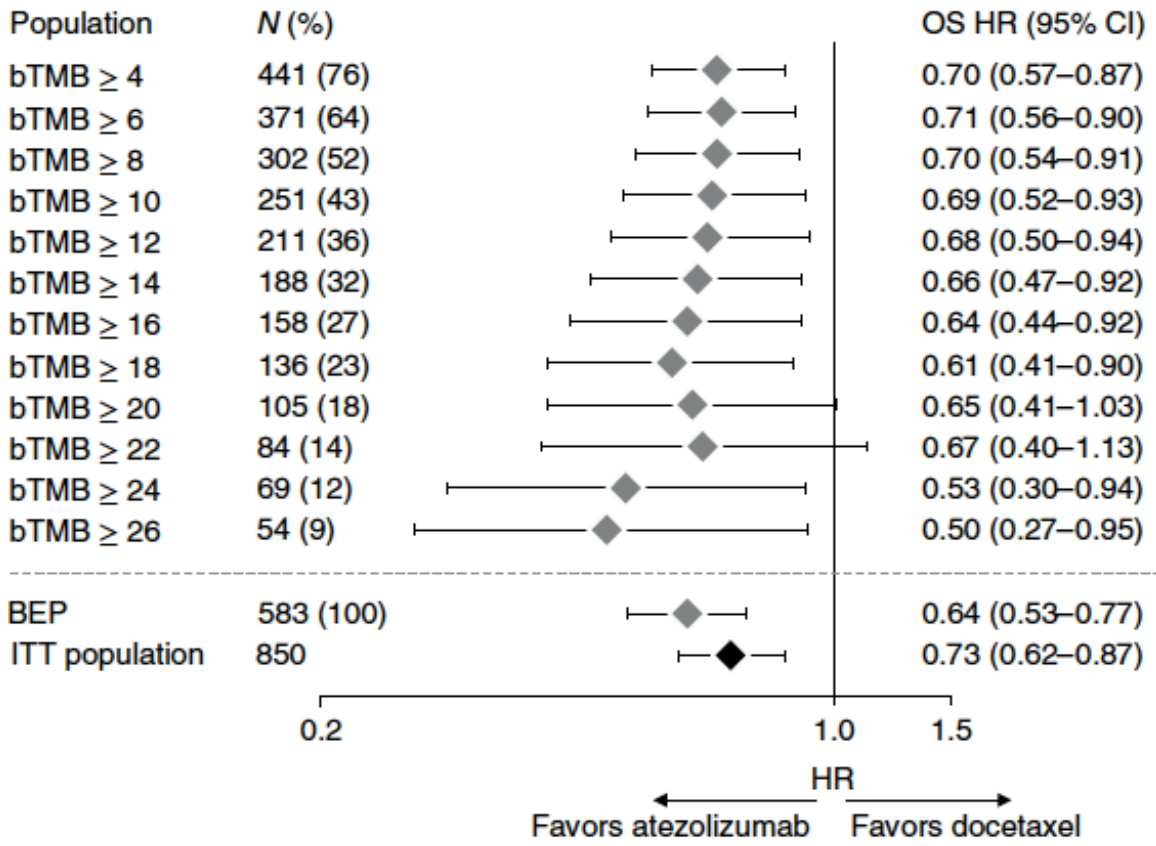
Gandara D et al, Nature Med 2018

bTMB (Blood/Tissue) as a predictor of benefit of Atezolizumab

Progression Free Survival (PFS)



Overall Survival (OS)

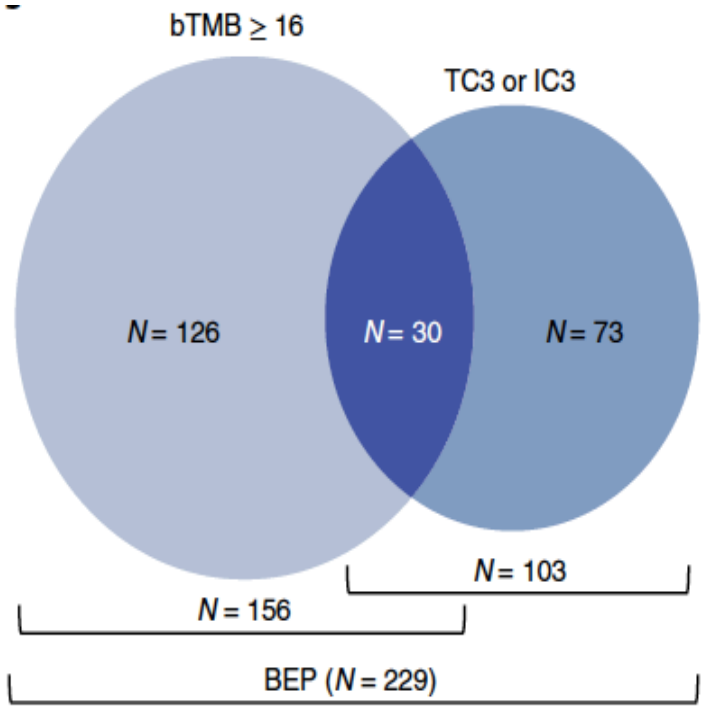


- **The higher the value, the higher the benefit……which cut-off?**

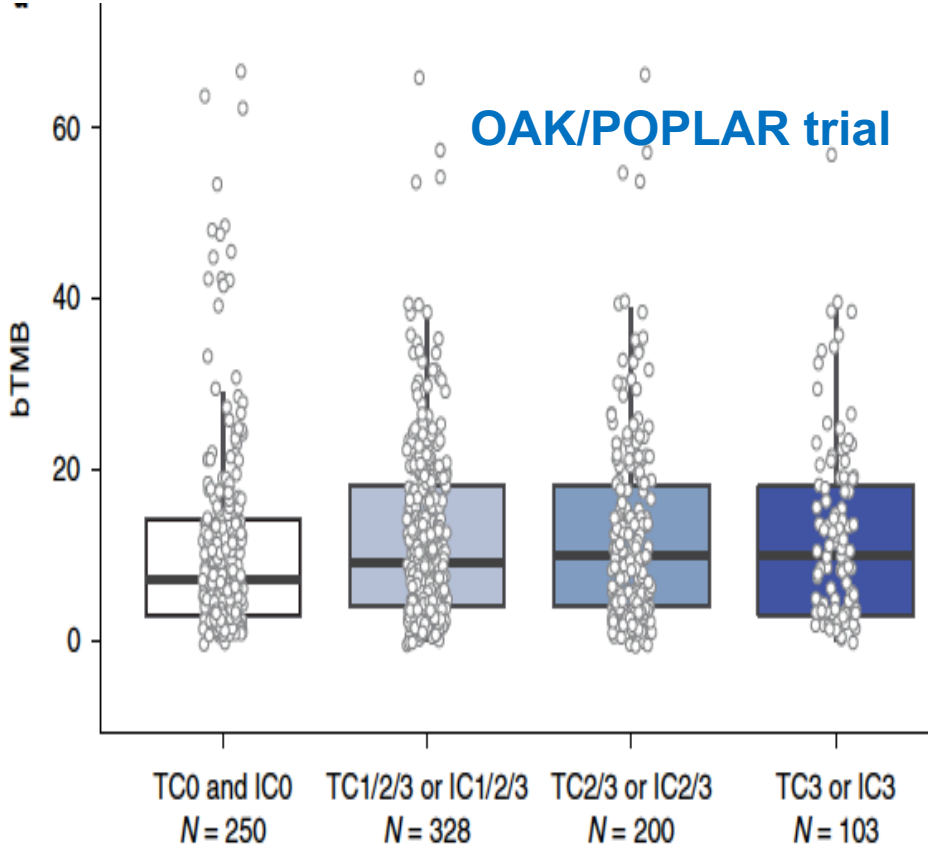
Gandara D et al, Nature Med 2018

TMB is independent from PD-L1 (over)espression

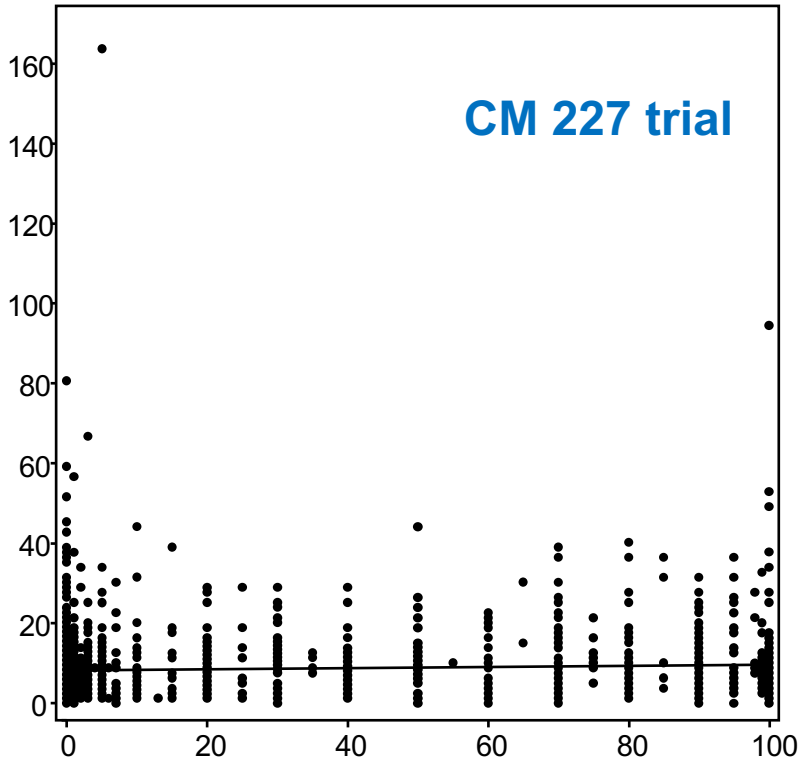
High TMB dos not overlap with PD-L1 overexpression



Categorical PD-L1 (0-3) IHC Staining



Continuous PD-L1 (%) IHC Staining



Gandara D et al, Nature Med 2018

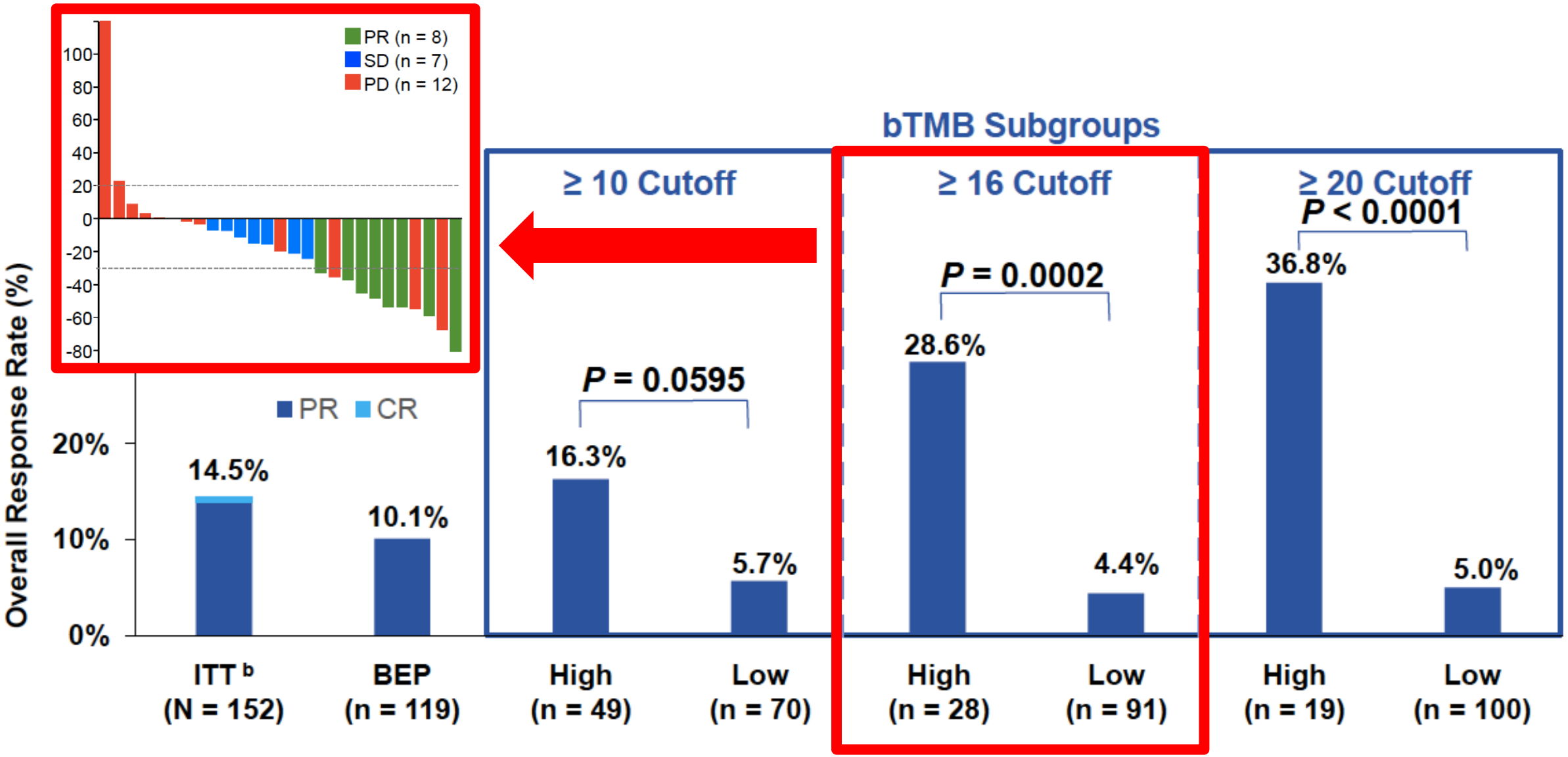
Helmann J et al, NEJM 2018

Feasibility of TMB (tissue/blood) & Positivity Rate

CM 227

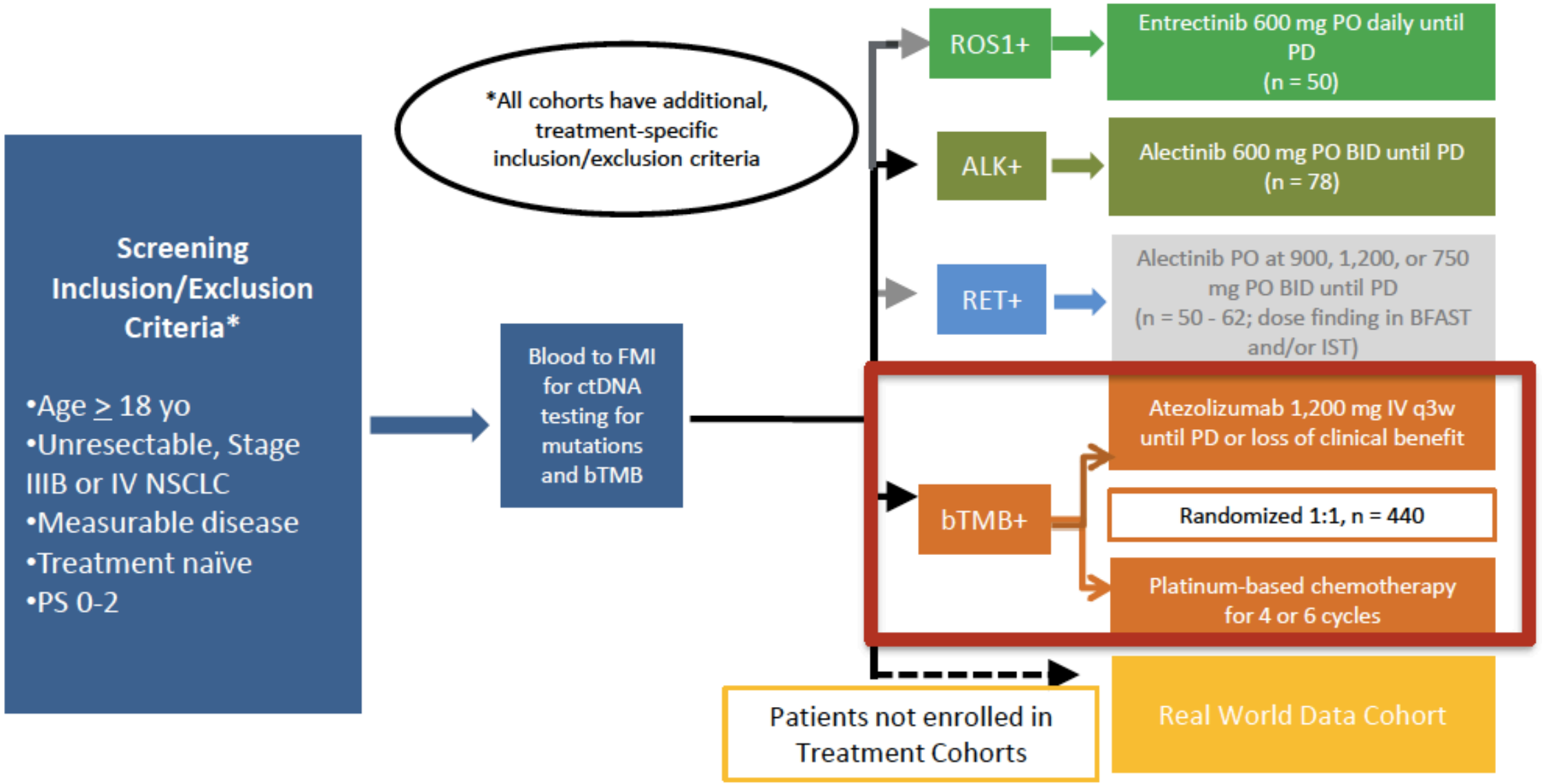
	POPLAR	OAK	B-F1RST
Samples	273	850	152
Evaluable	211 (77.2%)	642 (75.5%)	119 (78%)
Positivity (bTMB)	30%	27%	18%

B-F1RST: Prospective Evaluation of bTMB as Biomarker



Kim ES et al, ESMO 2018

bFAST: Randomized Prospective Validation Ongoing

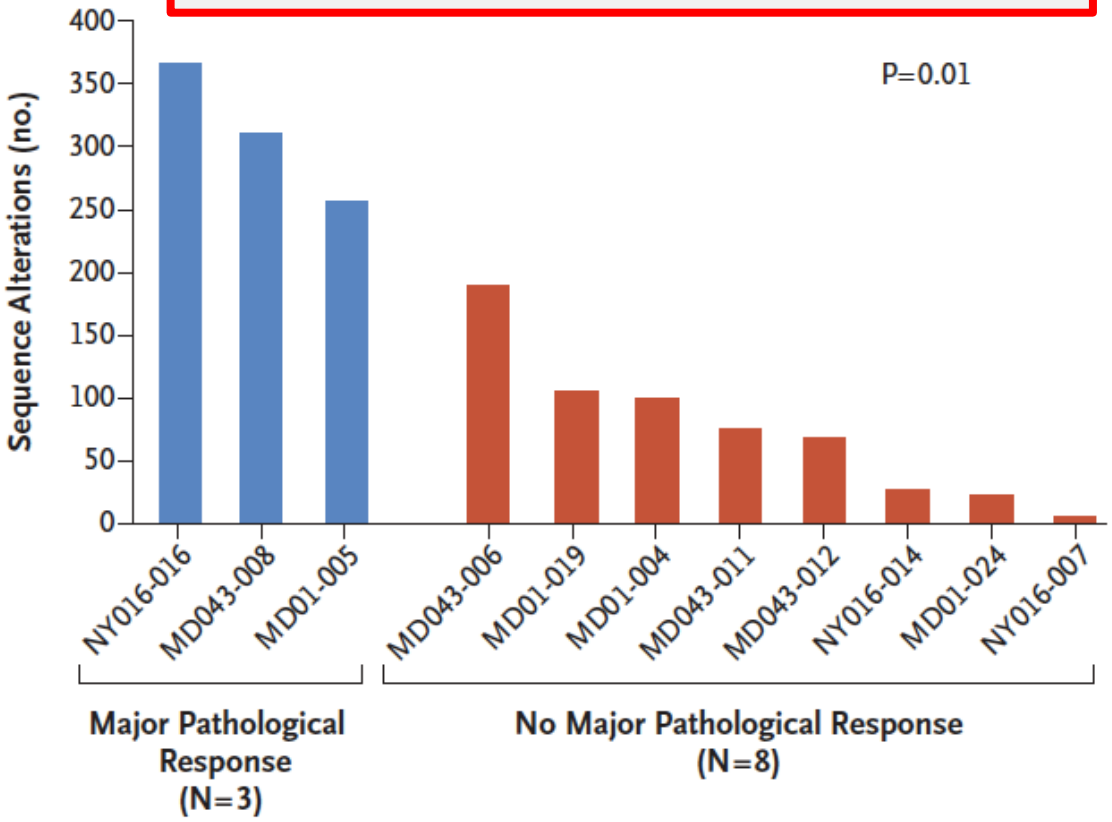


Besse B, ESMO 2018

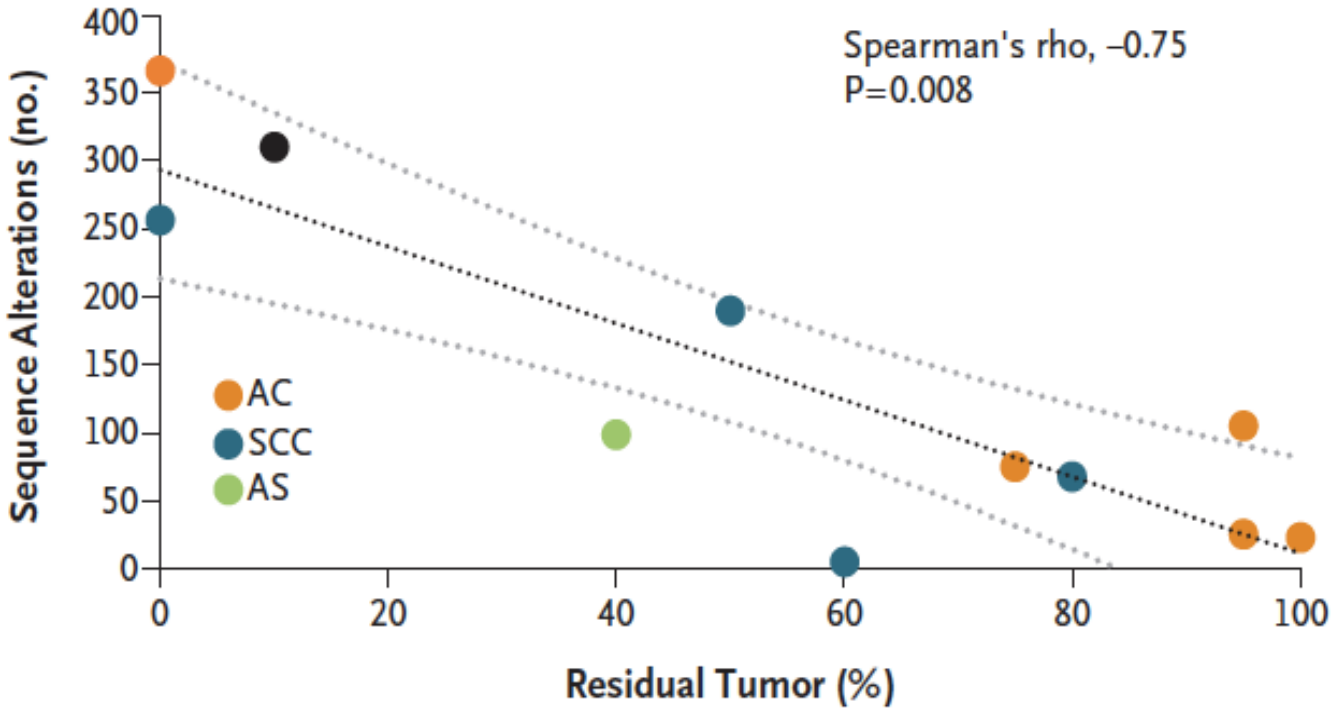
Neoadjuvant Nivolumab in Resectable Stage I-IIIA

Association between Mutational Burden and Pathological Response to PD-1 Blockade

No. Of Sequence Alterations in Pretreatment Tumor



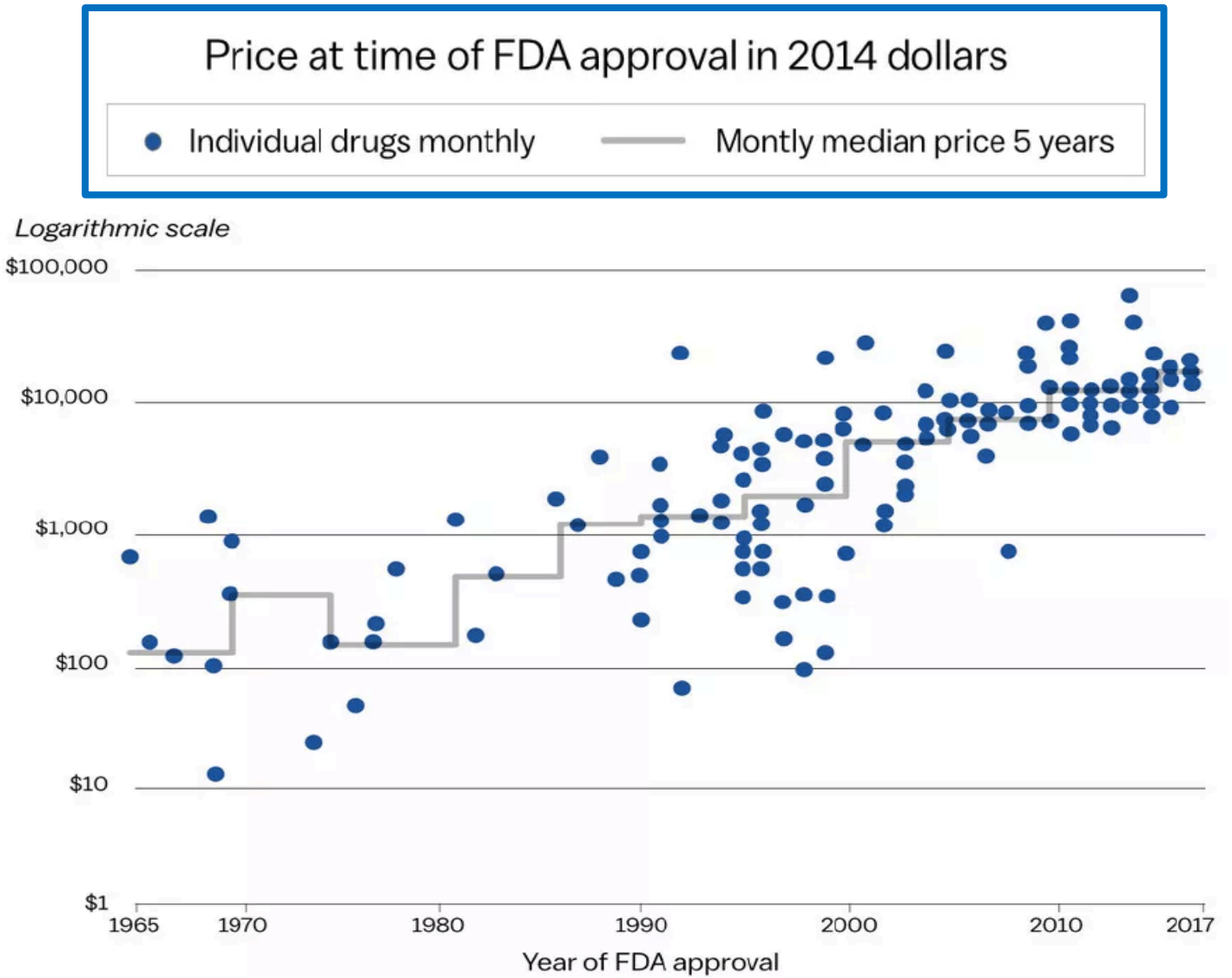
Correlation between No. Of Sequence Alterations and Percentage Of Residual Tumor



Forde PM et al, NEJM 2018

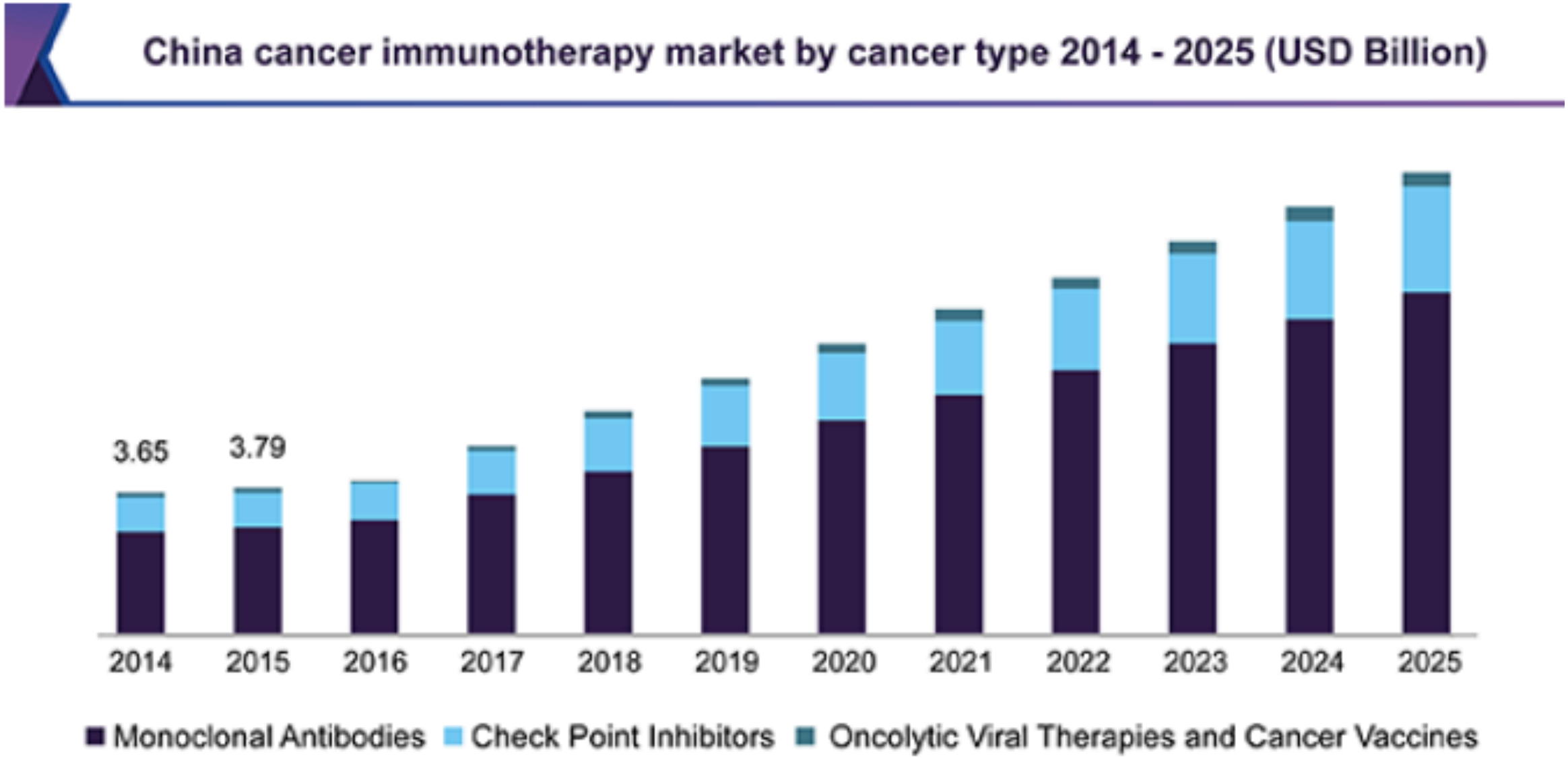
Why we need that? The Cost of Cancer is Soaring

- **The average cost of cancer drugs today is 4 times the median household income in US**
  - **Getting a cancer immunotherapy treatment costs more than a house in many cities in the US, more than putting a few kids through private college.**
  - **The average cost of cancer drugs has increased from $50,000 per patient in the mid-1990s to $250,000today.**
  - **That's four times the median US household annual income.**



Source: Peter Back, MSKCC, NYC

Cancer IO Market Analysis By Product

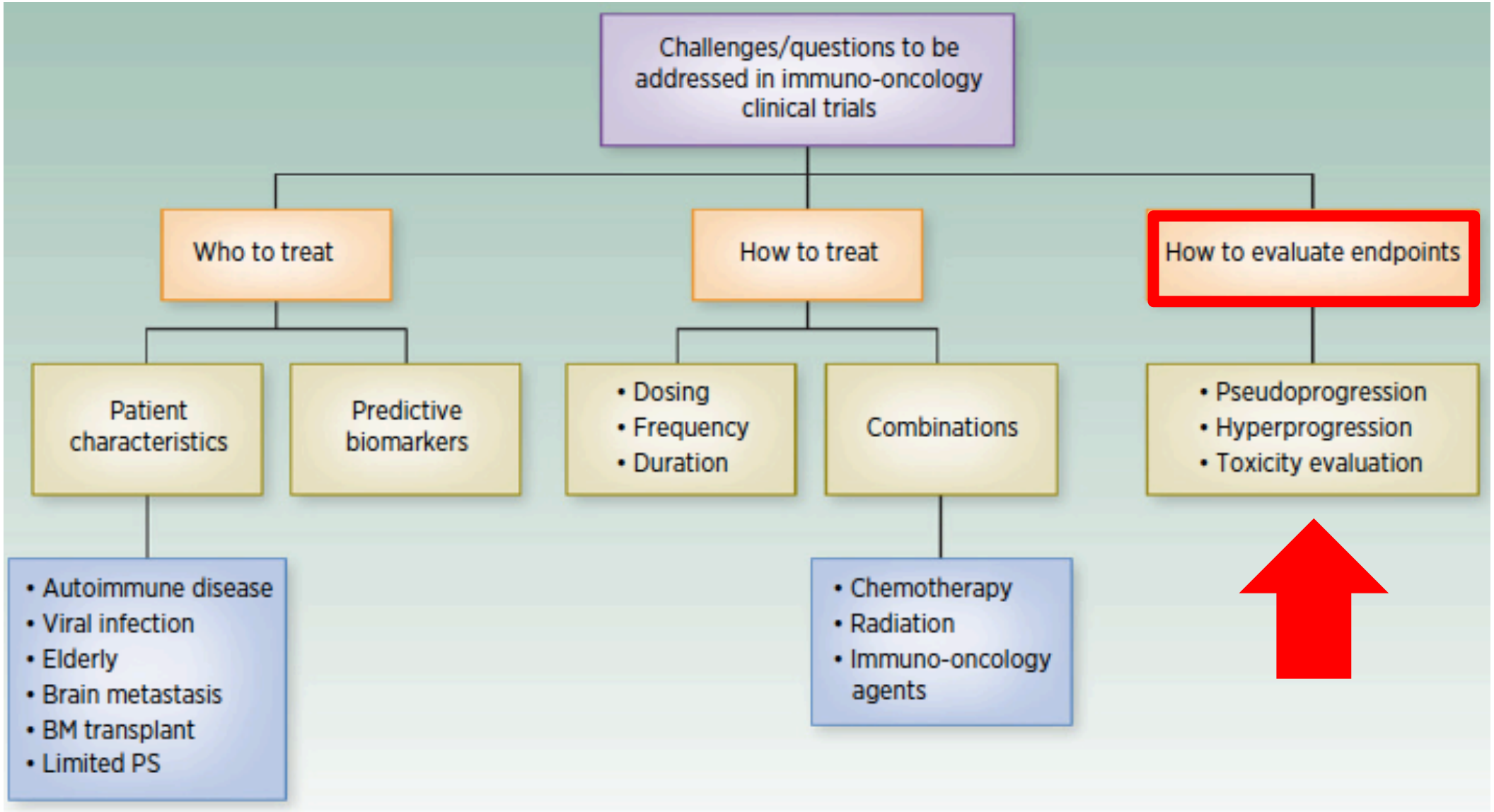


Source: https://www.grandviewresearch.com/industry-analysis/cancer-immunotherapy-market

Presentation Outline

- Impact of Immunotherapy (IO) in Medical Oncology
- Patients' Selection and Predictive Factors for IO
- **Treatment End-points for IO**
- Evidences for Real-World beyond Clinical Trials

Challenges to address in IO Clinical Trials

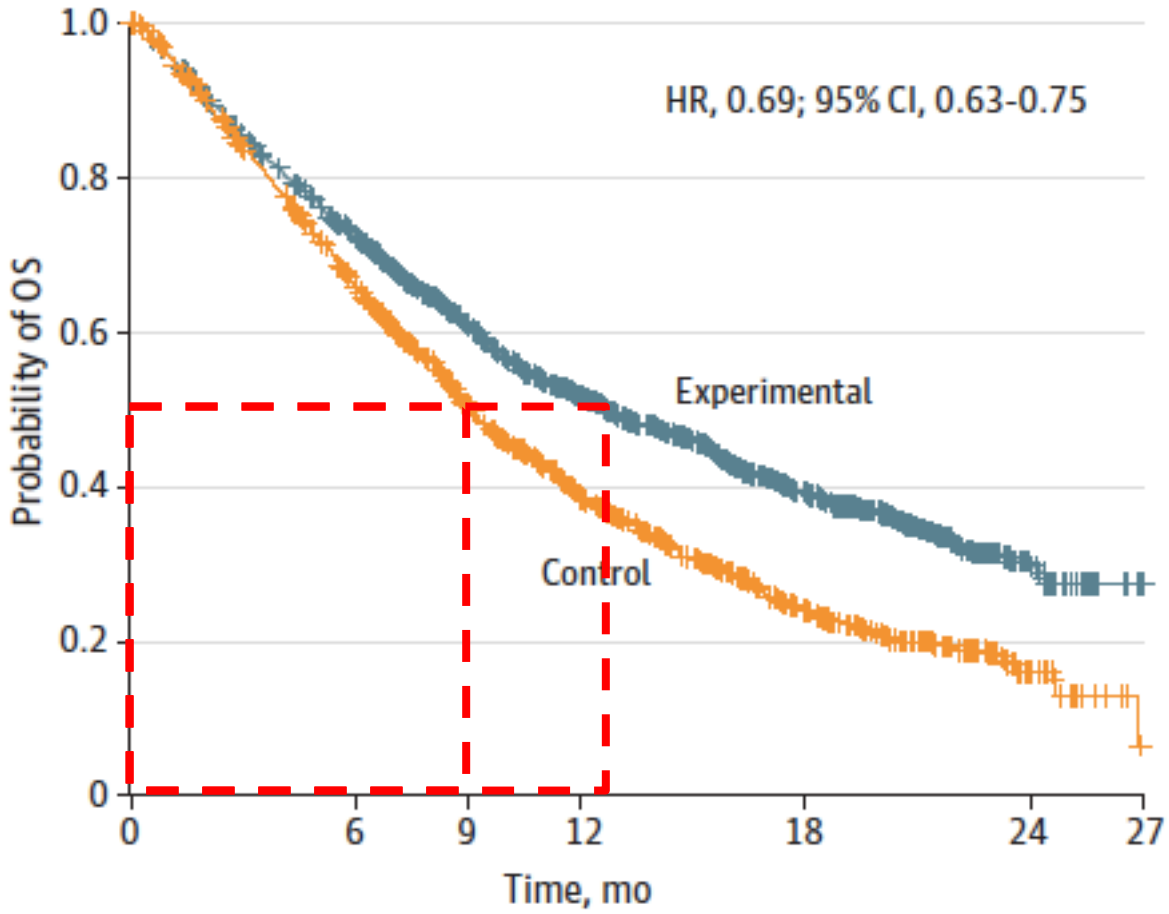


Baik CS et al, Clin Cancer Res 2017

Pretreated NSCLC: Immunotherapy is the new Benchmark

Individual Level Estimation (>3,200 pts), FDA-Driven Analysis

OS



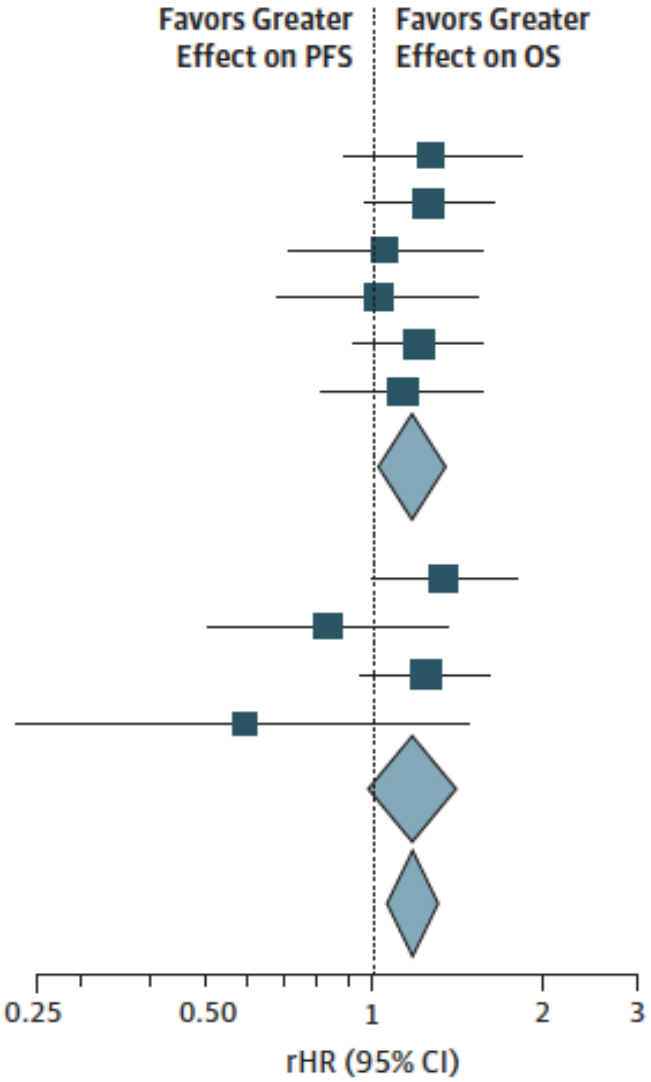
- **Moderate Association between OS at 12 and 9 months and OS HR**
- **No correlation between OS and intermediate end-points (PFS and ORR)**
- **Although 12months-OS has the strongest association it is likely to be not optimal for future trials, which will have:**
  - **Immunotherapy as control arm**
  - **Biomarker-enrichment strategies**
  - **Enrolled patients with longer survival**

- **Benchmark of Control Arm for Future RCTs:**
  - **Median OS: 12 months**
  - **1yr OS: 50%**
  - **PFS and ORR not primary**

Blumenthal GM et al [FDA Group] JAMA-Onc 2018

IO: PFS does not correlate with OS

Study	rHR (95% CI)
Nivolumab	
Ferris et al,[8] 2016 (Checkmate 141)	1.27 (0.89-1.83)
Borghaei et al,[9] 2015 (Checkmate 057)	1.26 (0.97-1.64)
Brahmer et al,[10] 2015 (Checkmate 017)	1.05 (0.71-1.56)
Robert et al,[11] 2015 (Checkmate 066)	1.02 (0.68-1.54)
Motzer et al,[12] 2015 (Checkmate 025)	1.21 (0.93-1.56)
Carbone et al,[13] 2017 (Checkmate 026)	1.13 (0.81-1.57)
Overall	**1.18 (1.03-1.34)**
Pembrolizumab	
Bellmunt et al,[14] 2017 (Keynote 045)	1.34 (1.00-1.80)
Reck et al,[15] 2016 (Keynote 024)	0.83 (0.51-1.36)
Herbst et al,[16] 2016 (Keynote 010)	1.24 (0.95-1.62)
Langer et al,[17] 2016 (Keynote 021)	0.59 (0.23-1.49)
Overall	**1.18 (0.98-1.41)**
Overall	**1.18 (1.06-1.31)**



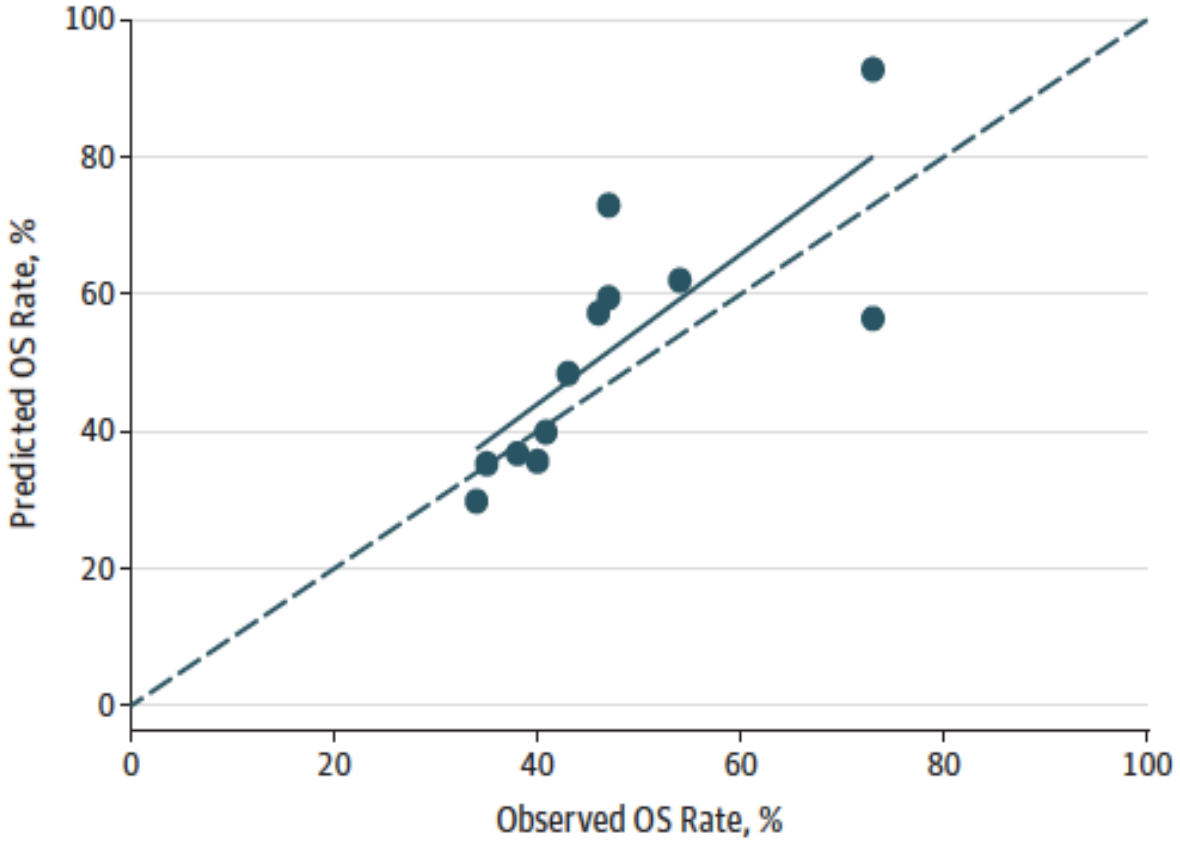
- **No significant correlation between OS and PFS (medians and gains in medians)**
- **Greatet Effects of treatment in OS than PFS.**
- **Traditional Response Evaluation Criteria in Solid Tumors (ORR and PFS) cannot capture the benefit of PD-1 inhibitors in patients with solid tumors.**
- **OS should remain the gold standard.**

Gyawali B et al, JAMA Network 2019

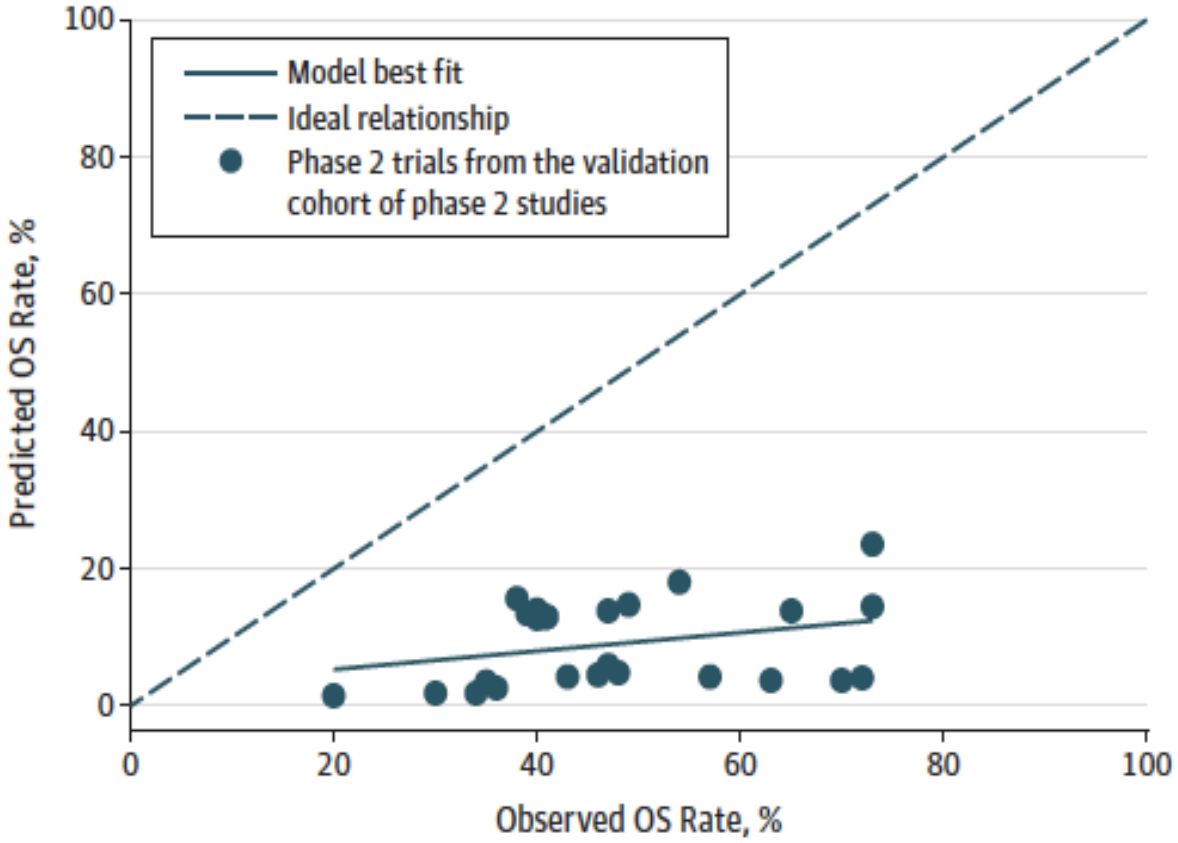
IO: Which (Best) End-point for Phase II Studies?

Observed vs Predicted 12-Month Overall Survival (OS) Rate

12-mo OS rate predicted by 6-mo PFS rate



12-mo OS rate predicted by ORR

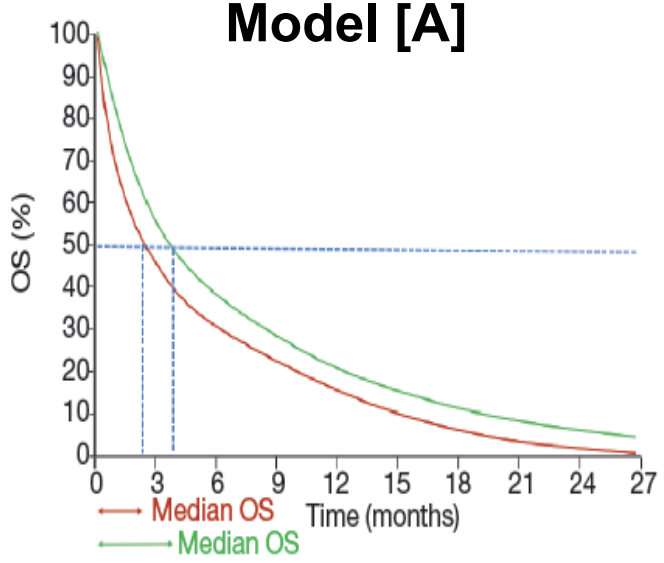


Gyawali B et al, JAMA Network 2019

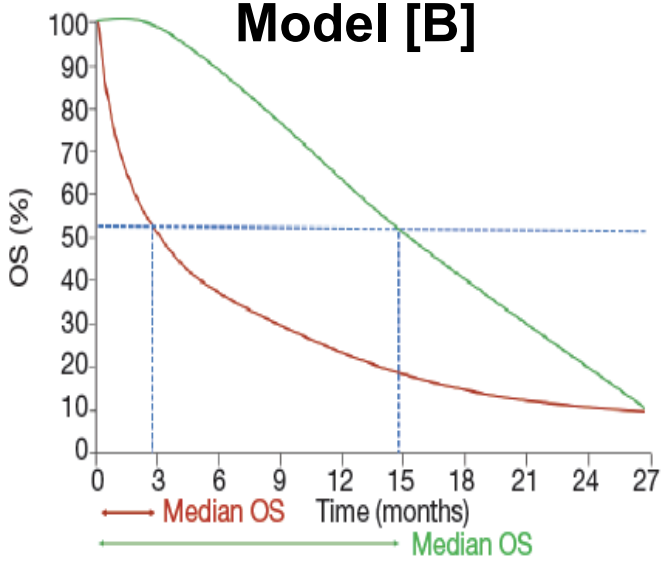
Expected Survival Modeling according to Drugs' Features

Typical survival curves (Kaplan-Meier model) observed in clinical trials

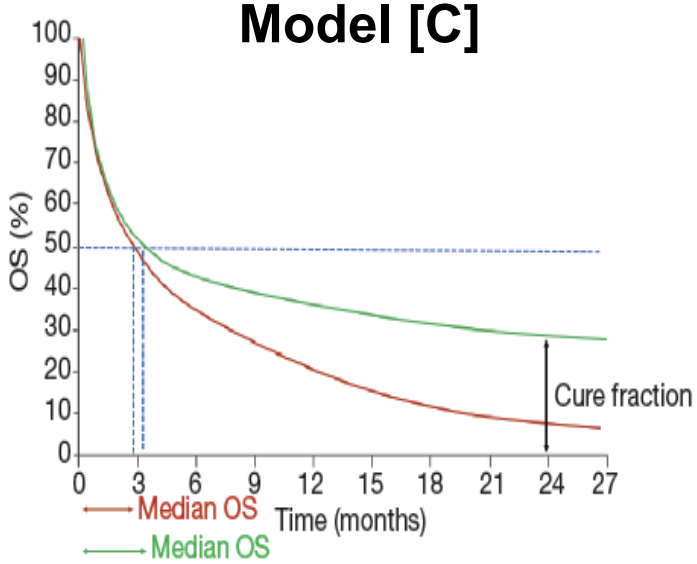
Model [A]



Model [B]



Model [C]



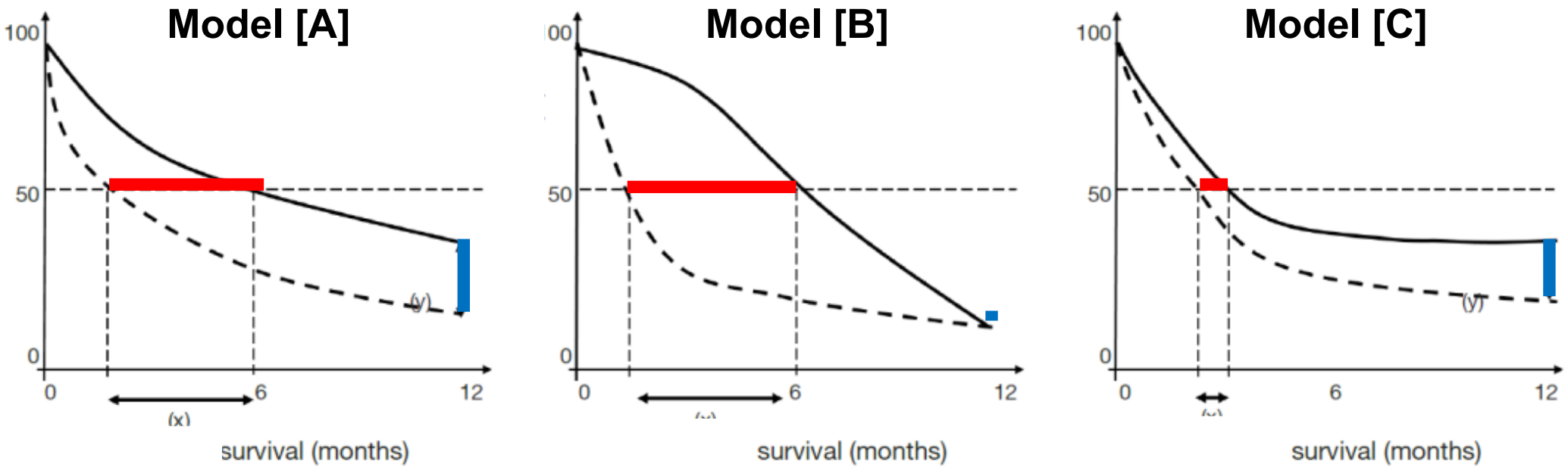
Proportional Hazard Model	**YES**	**NO**	**NO**
Delayed Effect	**YES**	**NO**	**YES**
Long Term Survival	**YES**	**NO**	**YES**

Ferrara R et al, J Thorac Disease 2018

Expected Survival Modeling according to Drugs' Features

Typical survival curves (Kaplan-Meier model) observed in clinical trials

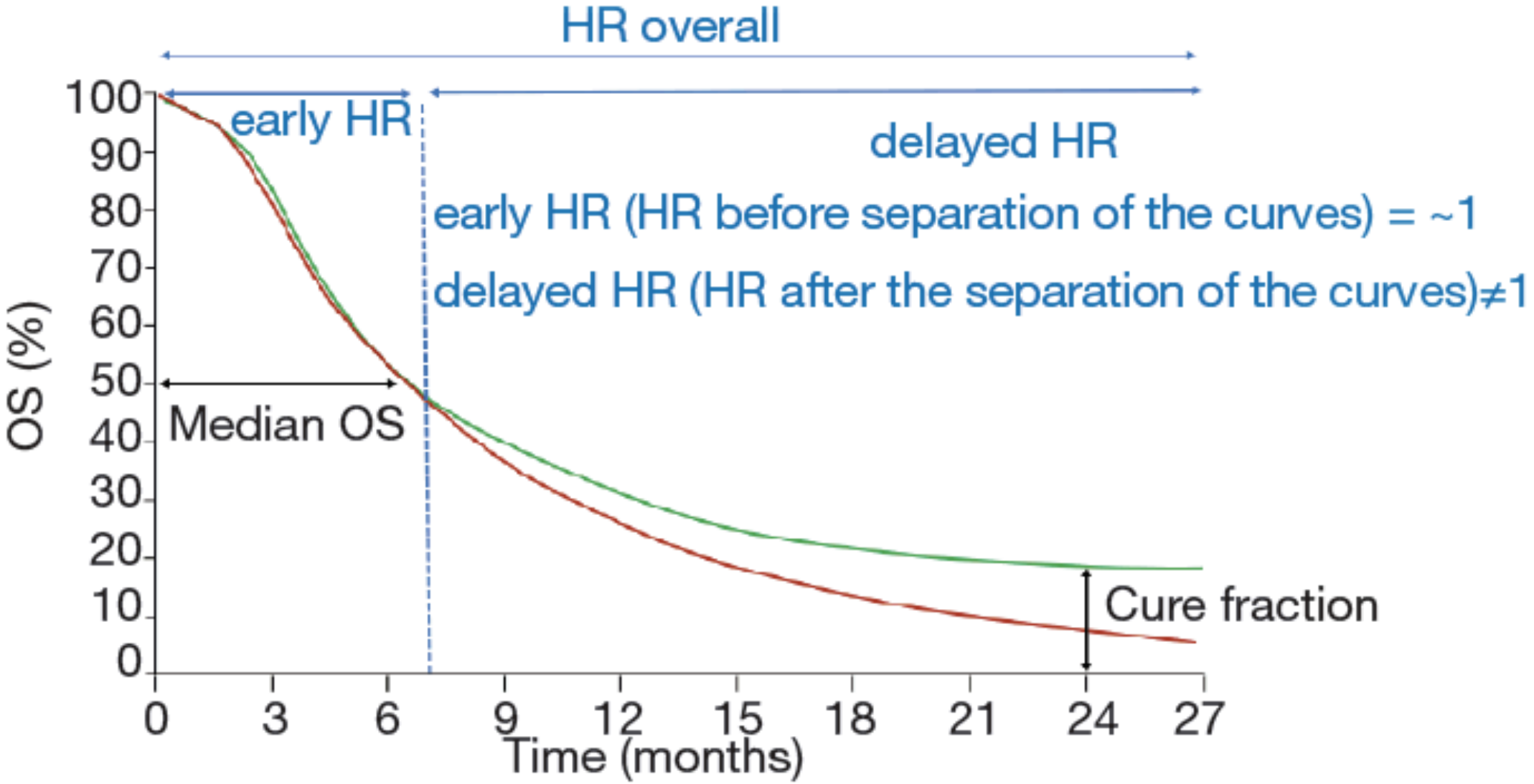
(x) difference in median survival;
(y) 12-month difference in survival rate.



Early Stop for Futility	**YES**	**YES**	**NO**
Correlation with late benefit	**YES**	**NO**	**NO**

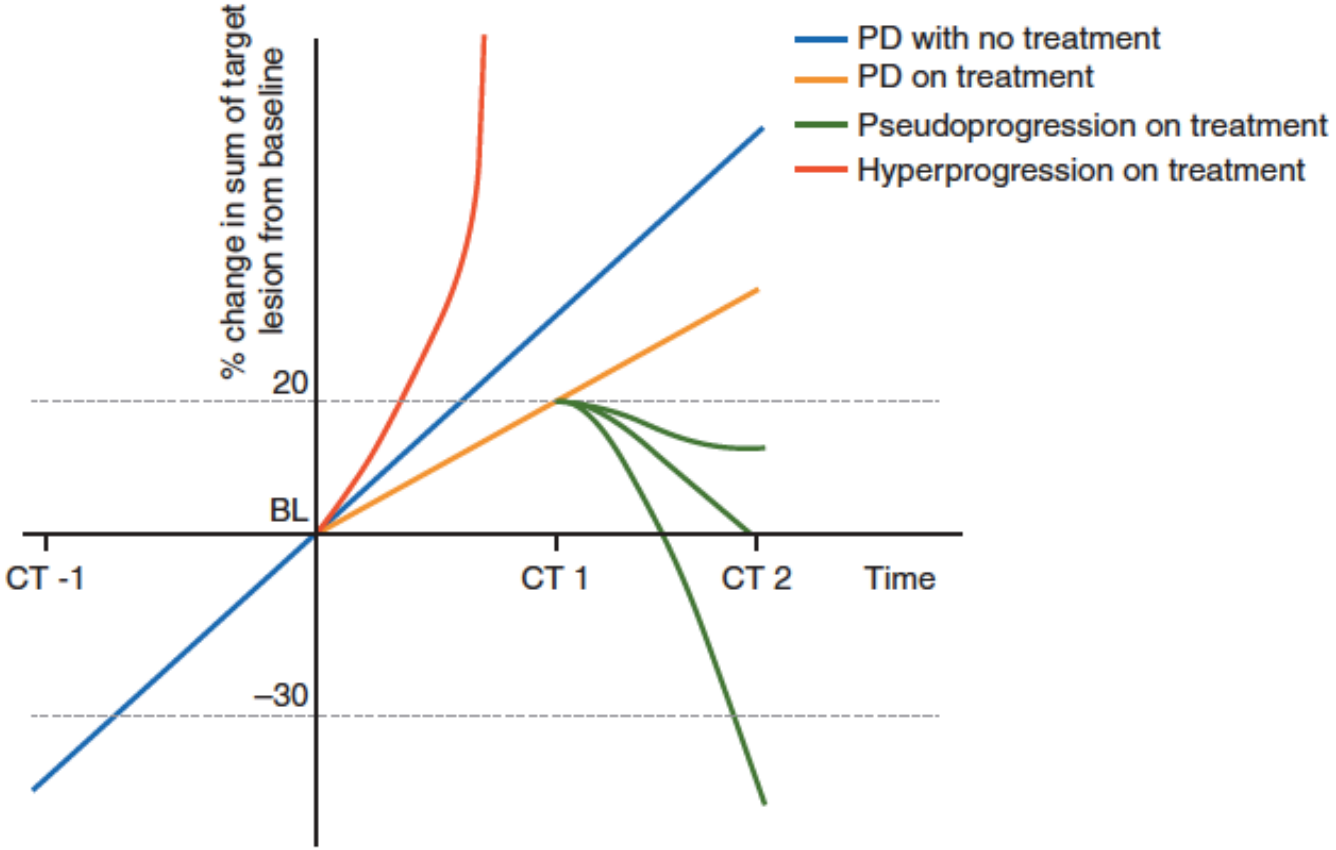
Pilotto S et al, TLCR 2015

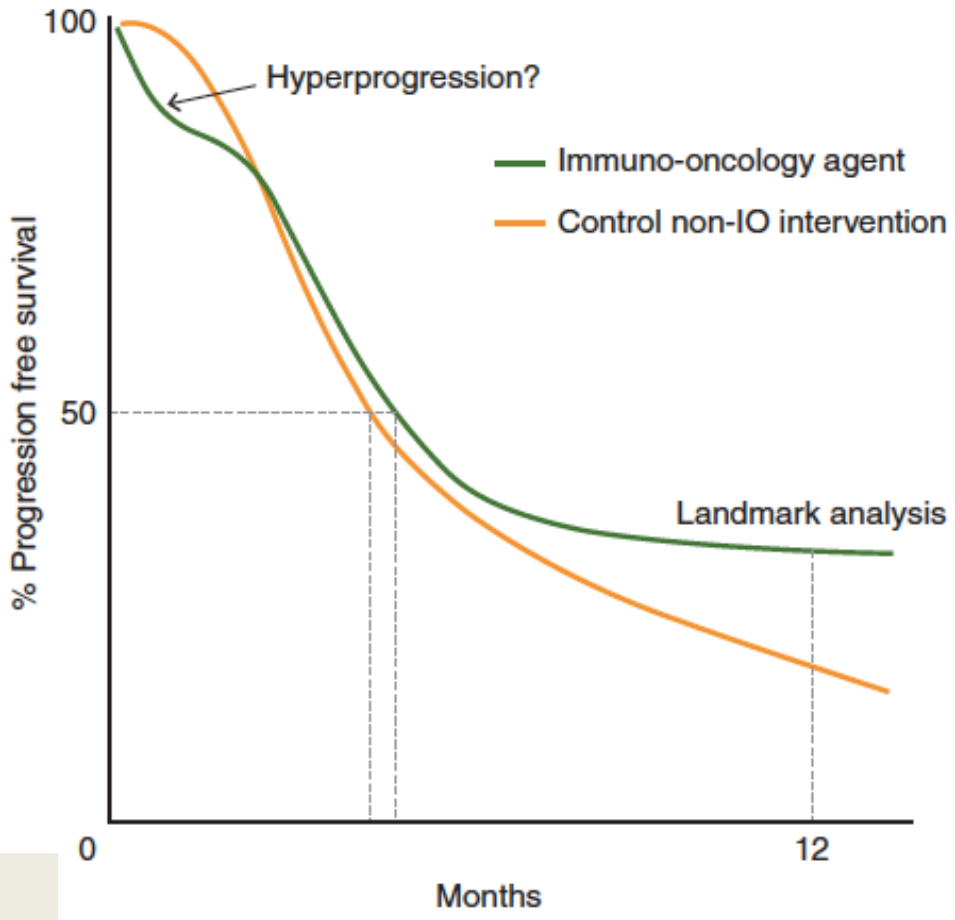
IO: '*Intercepting*' Lower HR overtime



Ferrara R et al, J Thorac Disease 2018

Pseudoprogression, Hyperprogression, and Deconvolution of the survival curves IOs

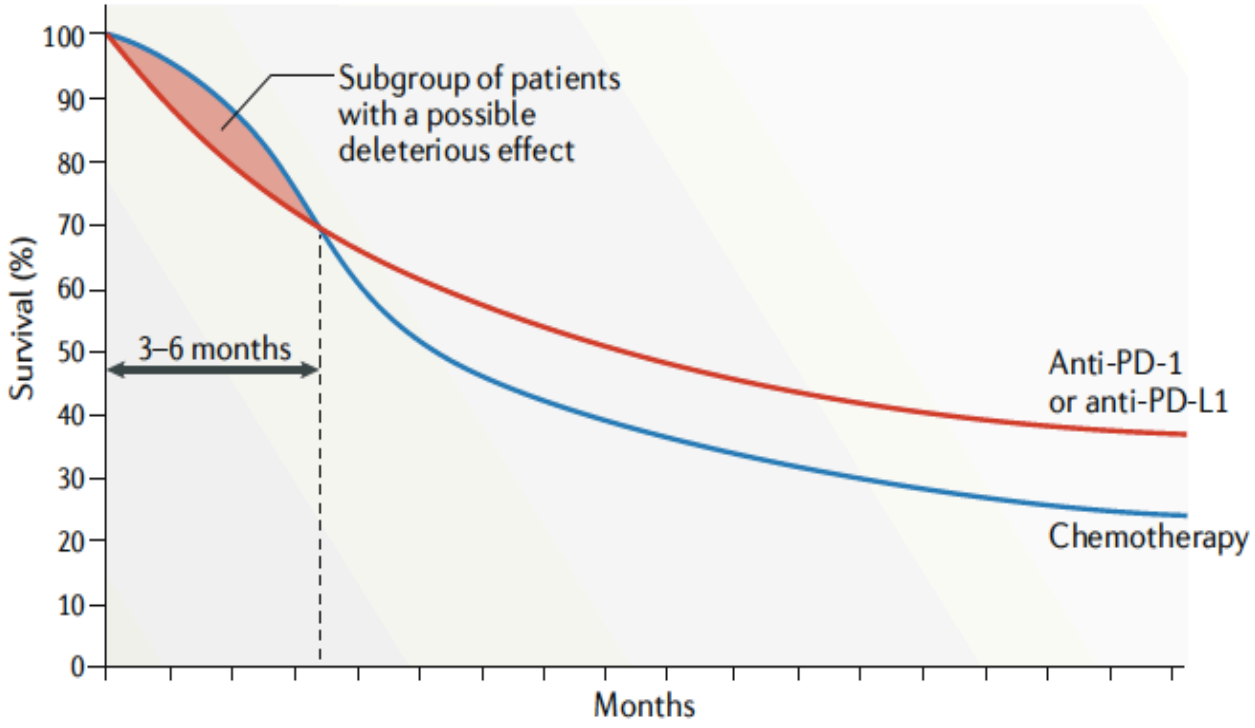




Methodology for the Development of Innovative Cancer Therapies (MDICT) Task Force

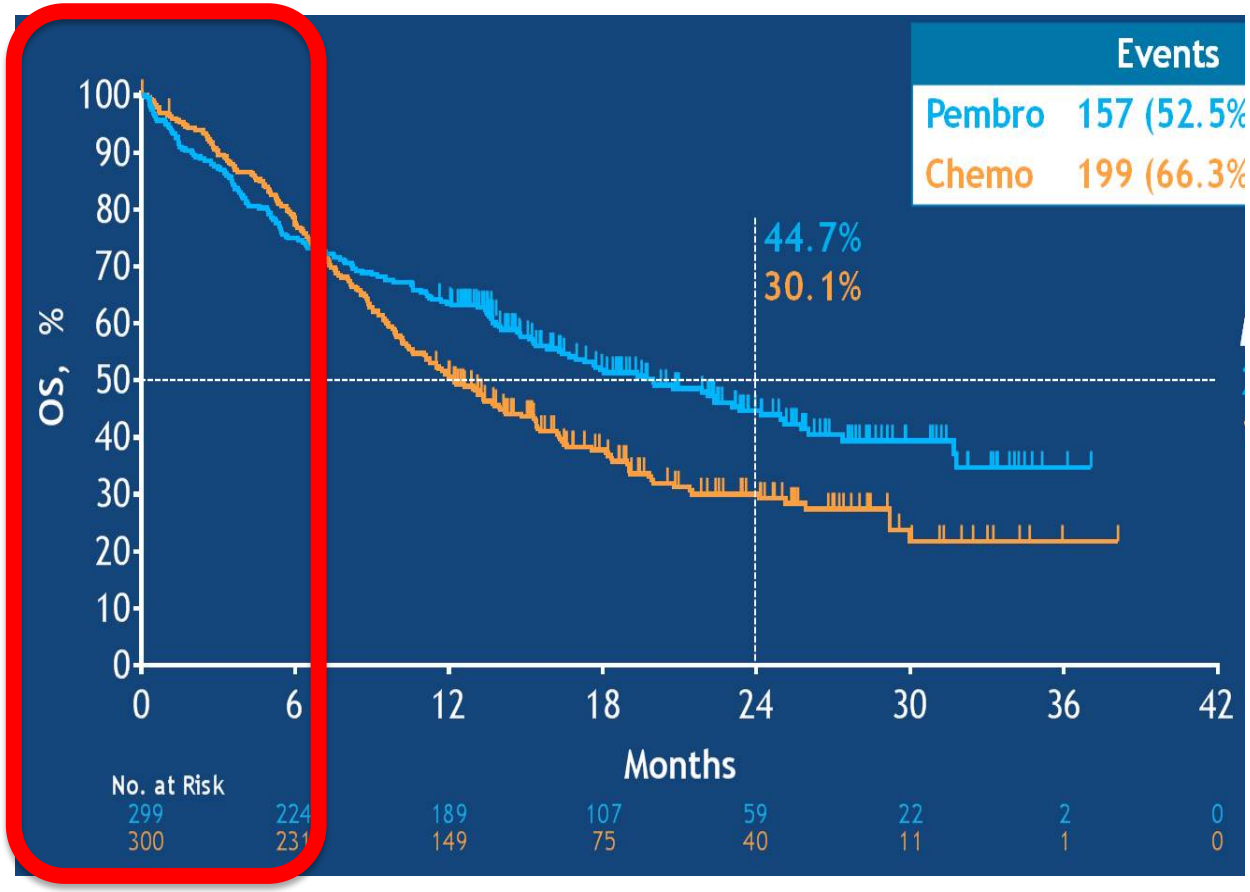
Smoragiewicz M et al, Ann Oncol 2018

Crossing survival curves in clinical trials



Chiampiat S et al, Nat Rev Clin Oncol 2018

Keynote 042

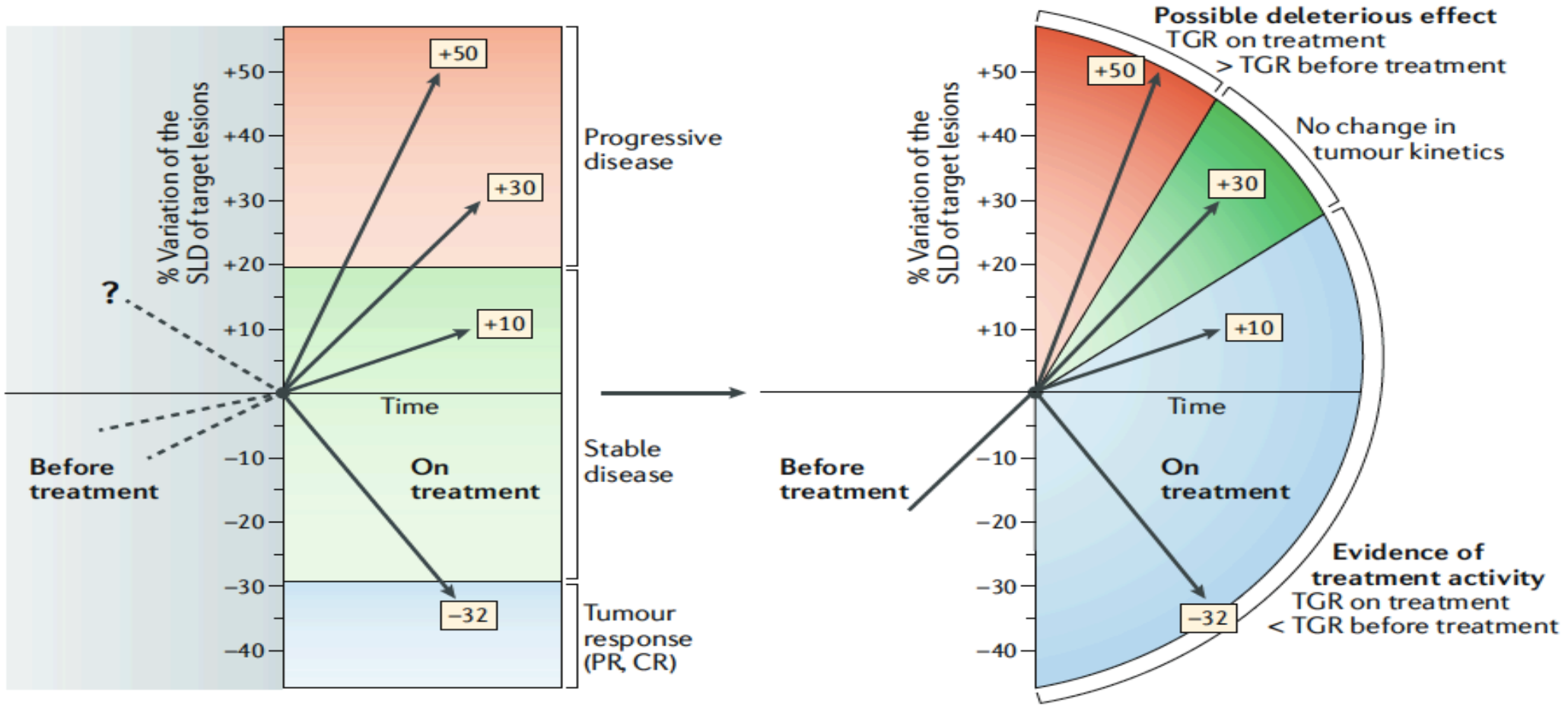


Lopes G et al, ASCO 2018

Crossing survival curves in clinical trials

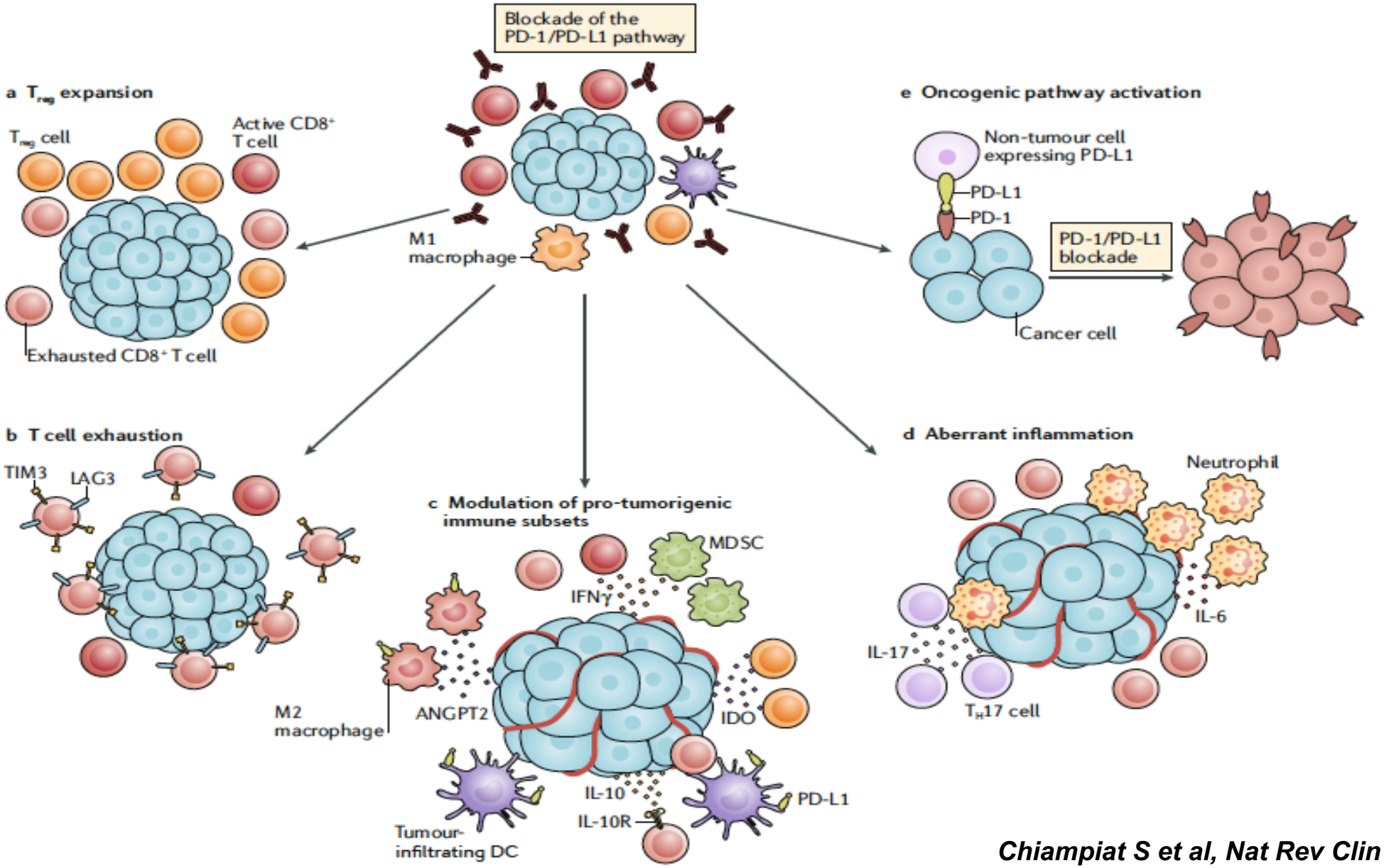
Evaluation using RECIST v1.1

Evaluation Integrating Pre-treatment Tumour Kinetics



Chiampiat S et al, Nat Rev Clin Oncol 2018

Biological Hypotheses for IO-related Hyperprogressive disease



Chiampiat S et al, Nat Rev Clin Oncol 2018

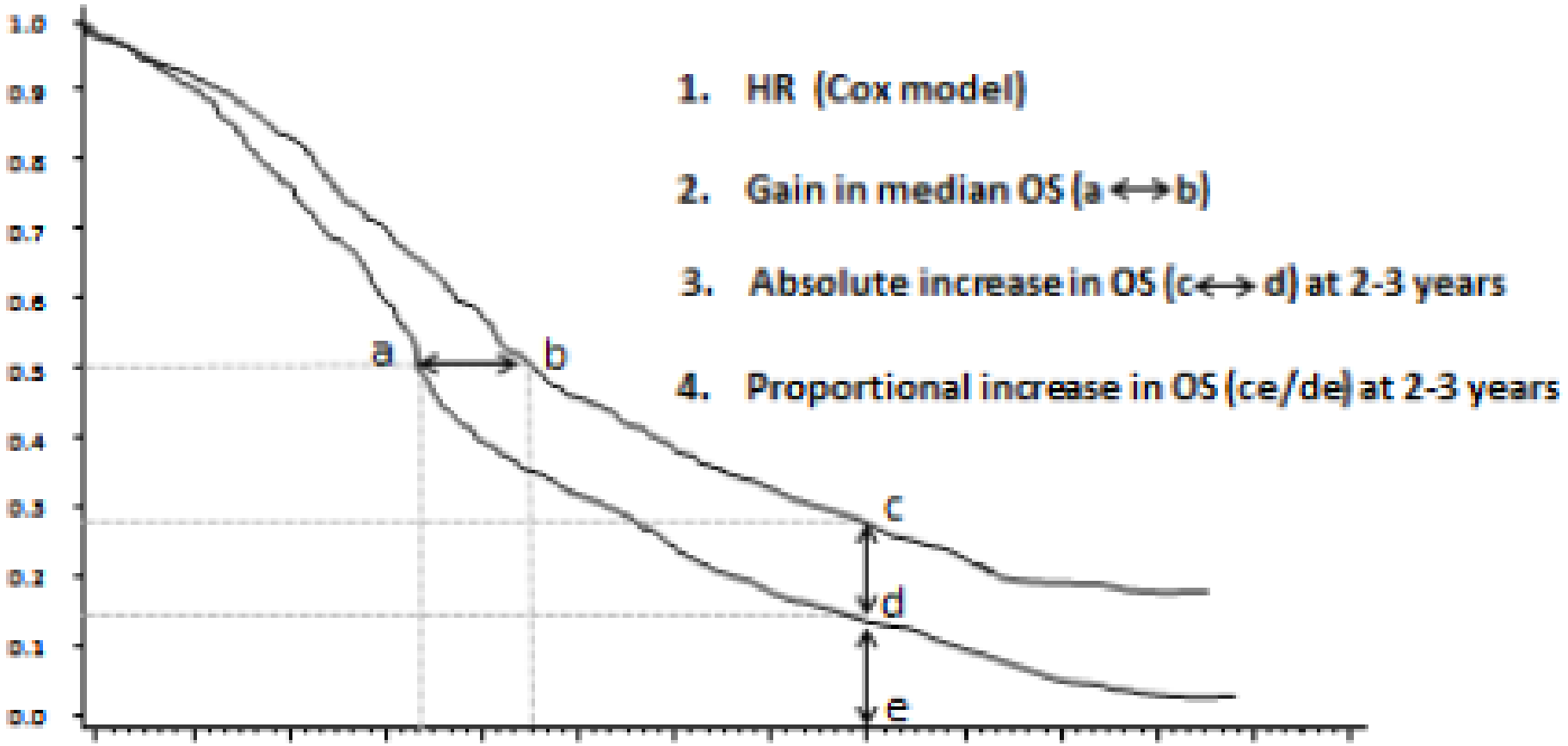
Questions & Recommendation of the MDICT task force

Question	Recommendations
What are the relevant data required to justify a combination immunotherapy clinical trial?	A robust hypothesis, with evidence of efficacy and pharmacodynamic effects in pre-clinical studies Evidence of single agent activity, or compelling pre-clinical data
What are the optimal end points and designs for combination immunotherapy clinical trials?	Evaluation of pharmacodynamic biomarkers is critical in early phase combination trials and should be incorporated into trial objectives and go/no-go decisions Trial designs: • Master protocols (basket, umbrella, and platform designs) can significantly enhance efficiencies in evaluating multiple IO combination • Sequencing designs based on a pre-emptive strategy could be considered Efficacy end points should remain response based, with definitions for response, pseudoprogression, and hyperprogression. iRECIST should be used as secondary or exploratory end point Blood based biomarkers should be prospectively evaluated
Hyperprogression: a real entity?	Protocols should capture at least one additional tumour measurement before baseline to determine tumour growth kinetics, and consider an early CT scan (at 4 weeks for example)
How to optimize efficiency and minimize redundancy?	Well-conceived master protocols are strongly encouraged Not re-testing a failed combination of in-class agents unless there is a compelling rationale Proposals of IO combinations should also have a landscape analysis to prevent duplication

Smoragiewicz M et al, Ann Oncol 2018

Clinically Meaningful Outcome (mCMO) as a Threshold

To establish the concept of minimum *clinically meaningful outcome (mCMO)* of treatment in advanced solid tumors, to establish its threshold and evaluate how many superiority trials of new antineoplastic agents pass this threshold.

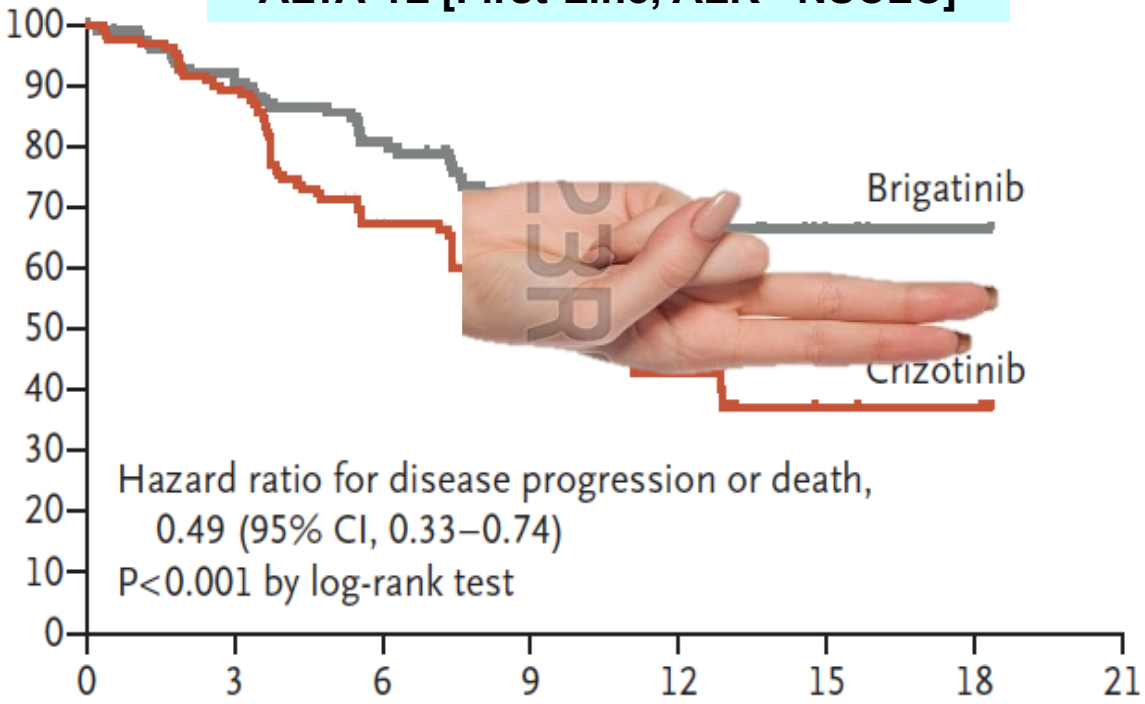


Sobrero A et al, CCR 2014

Clinical Meaningful Benefit as a Target!

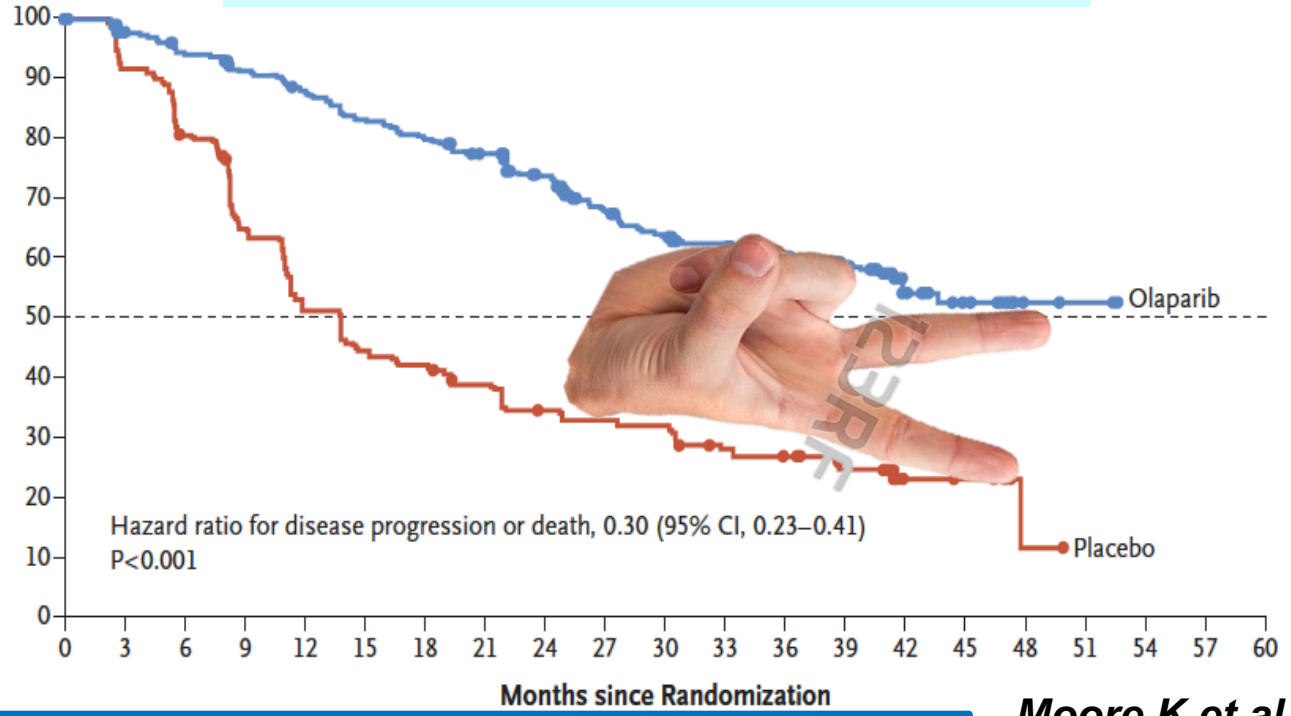
NEJM ('90s) The 'Two-Fingers' Rule: Clinically Data should be considered Meaningful if '*at least*' two fingers separates curves!

ALTA-1L [First-Line, ALK+ NSCLC]



Camidge R et al, NEJM 2018

SOLO-1 [Maintenance, BRCA1/2m OC]



Moore K et al, NEJM 2018

The Biomarker-Based Methodology is leading to the Re-discovery of Clinically Relevant Benefits

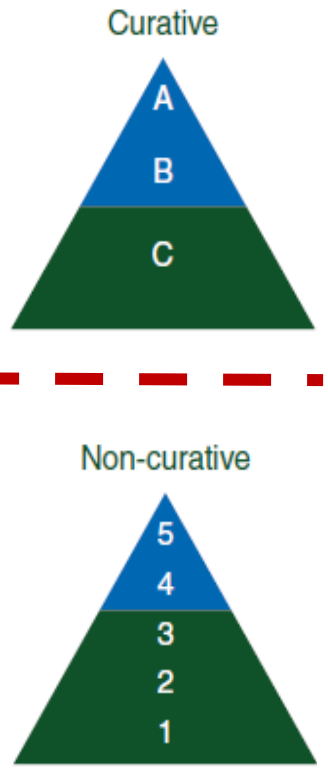
ESMO & ASCO are aiming to add Quantity to Quality

MCBS: Magnitude of Clinical Benefit Score

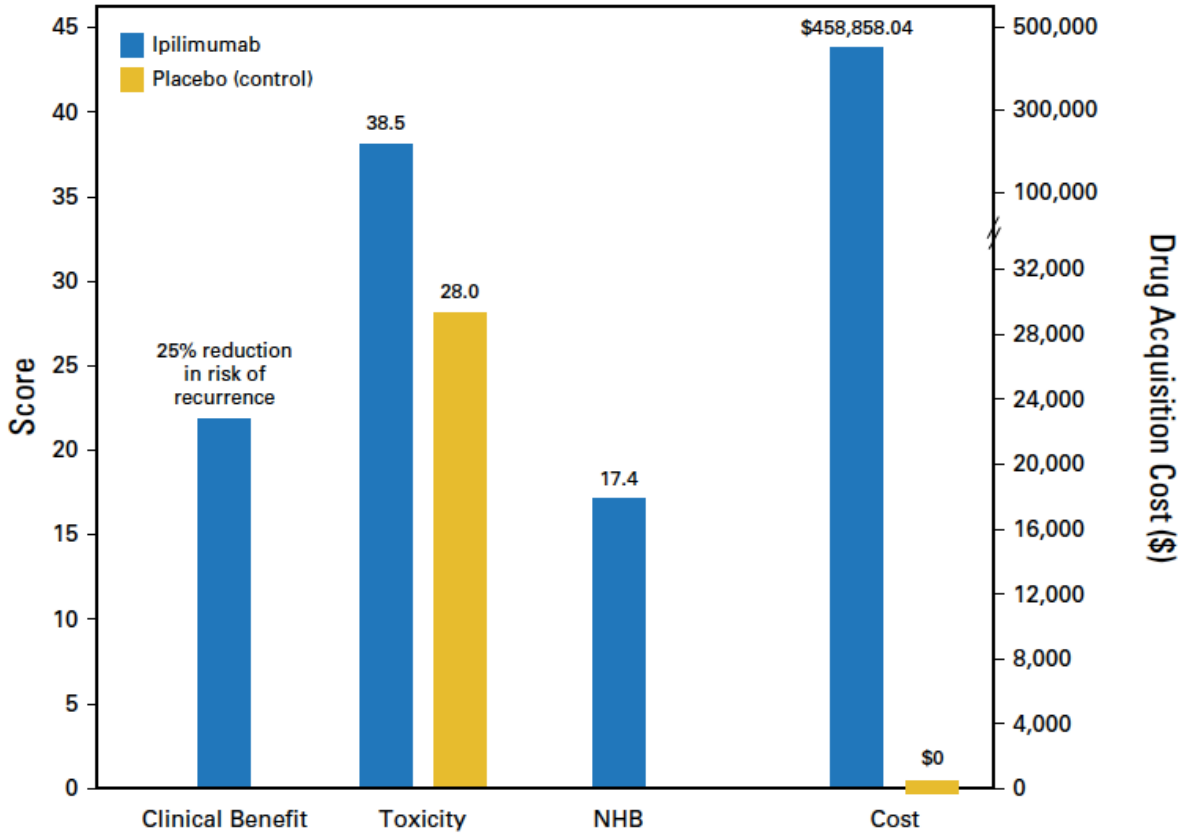
Table 2. Maximal preliminary scores

Treatments with curative intent (form 1)
>5% improvement of survival at ≥3-year follow-up
Improvements in DFS alone HR <0.60 (primary end point) in studies without mature survival data

Treatments with non-curative intent (form 2)
Primary outcome OS (form 2a)
Control ≤12 months
HR ≤0.65 *AND* gain ≥3 months *OR*
Increase *in* 2-year survival alone ≥10%
Control >12 months
HR ≤0.70 *AND* gain ≥5 months *OR*
Increase *in* 3-year survival alone ≥10%
Primary outcome PFS (form 2b)
Control ≤6 months
HR ≤0.65 *AND* gain ≥1.5 months
Control >6 months
HR ≤0.65 *AND* gain ≥3 months



NHB: Net Health Benefit (NHB)



Cherny NI, et al, Ann Oncol 2015

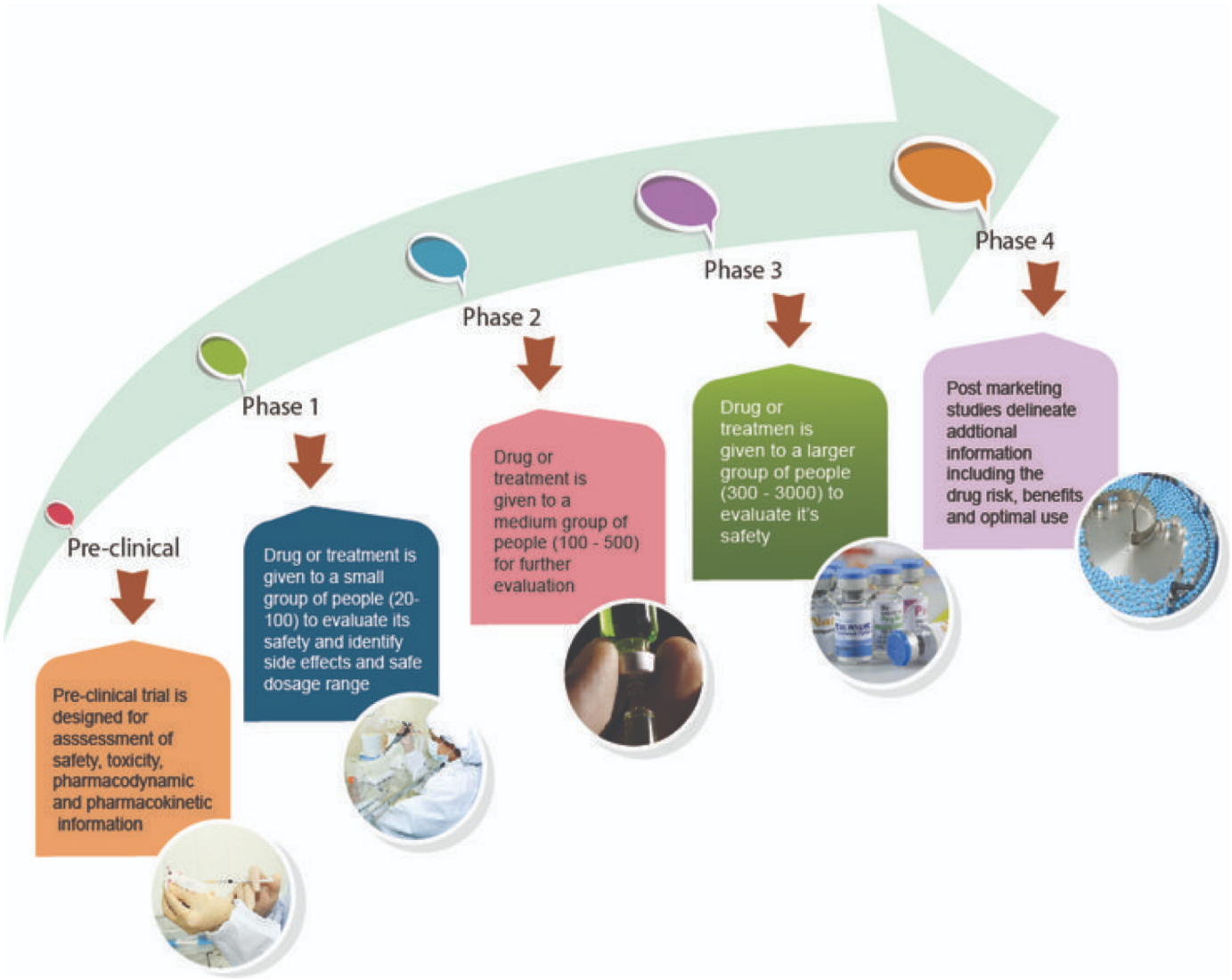
Schnipper LE, et al, JCO 2016

Presentation Outline

- Impact of Immunotherapy (IO) in Medical Oncology
- Patients' Selection and Predictive Factors for IO
- Treatment End-points for IO
- **Evidences for Real-World beyond Clinical Trials**

What do we assess in clinical trials?

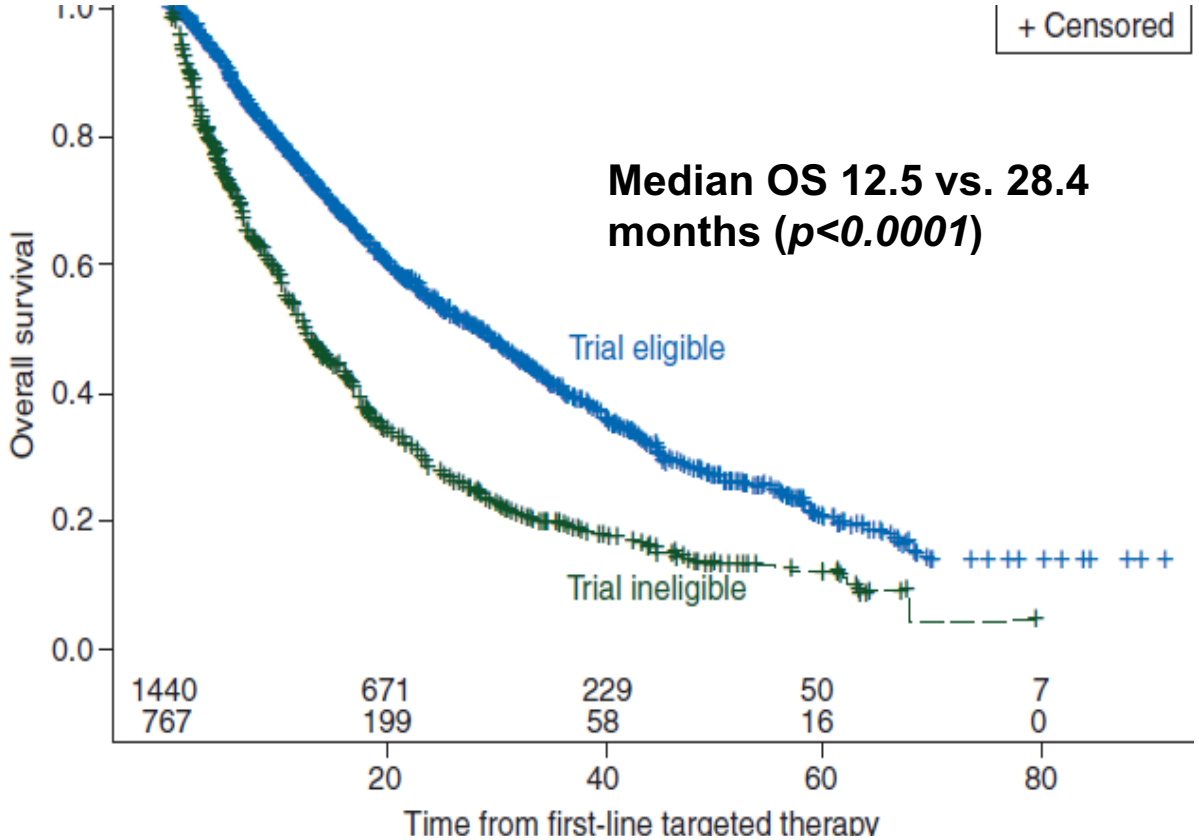
- **Activity:**
  - ability of the treatment to induce modifications of the disease thanks to which it is assumed that the patient may have a benefit **[Phase II]**
- **Efficacy:**
  - ability of the treatment to induce a clinical benefit in patients who are administered ***in an experimental context*** **[Phase III]**
- **Effectiveness:**
  - ability of a treatment to be effective in a ***non-experimental, concrete and coincident with the clinical practice*** **[are Phase IV, 'Real World' Data]**



Source: www.pinterest.it/excaliburhealth

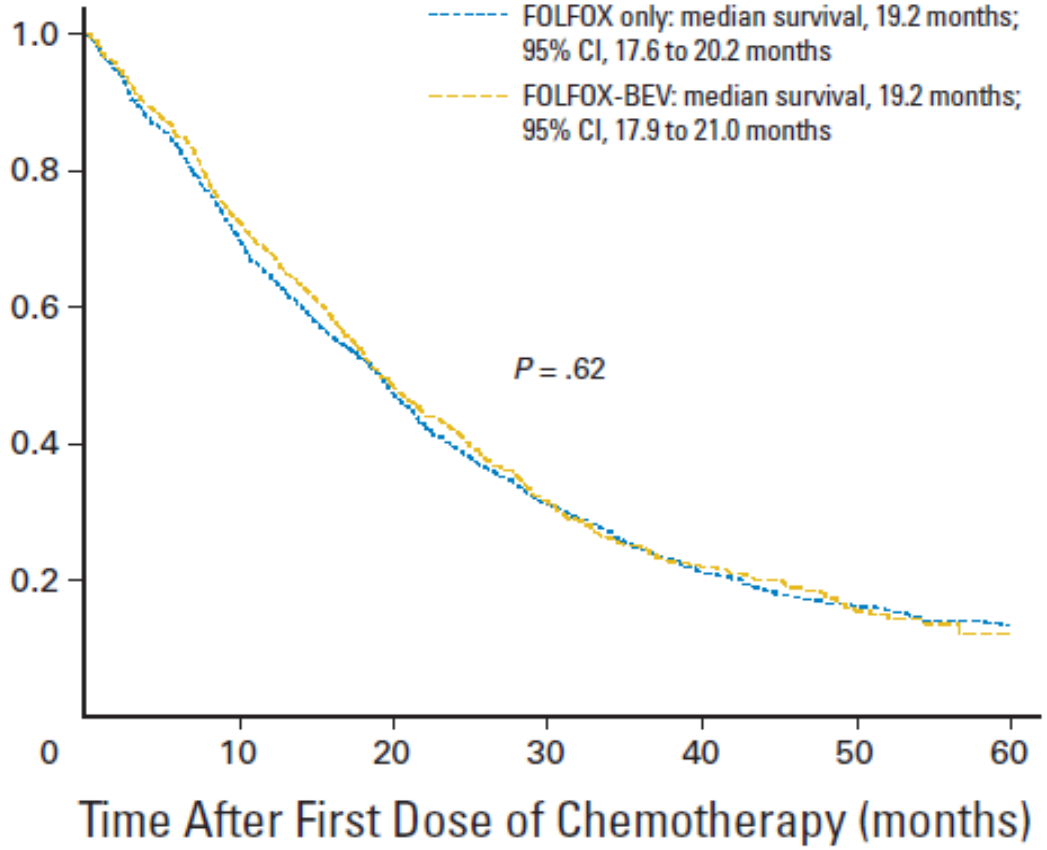
Targeted Therapy Performance in the 'Real World'

Trials' *Ineligible* Pts vs. *Eligible* (all receiving targeted agents)



Deng DY et al, Ann Oncol 2014

Addition of Bevacizumab to FOLFOX, '*Registry*' Context



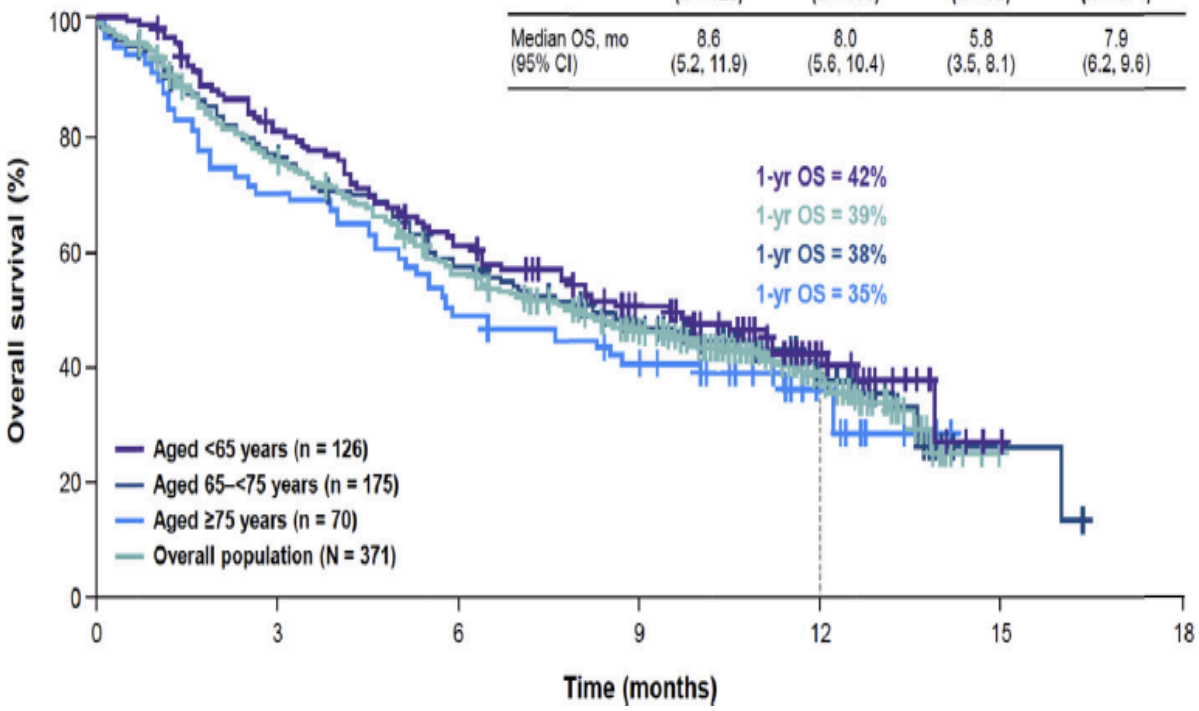
Meyerhardt T et al, JCO 2012

Take Home message(s)

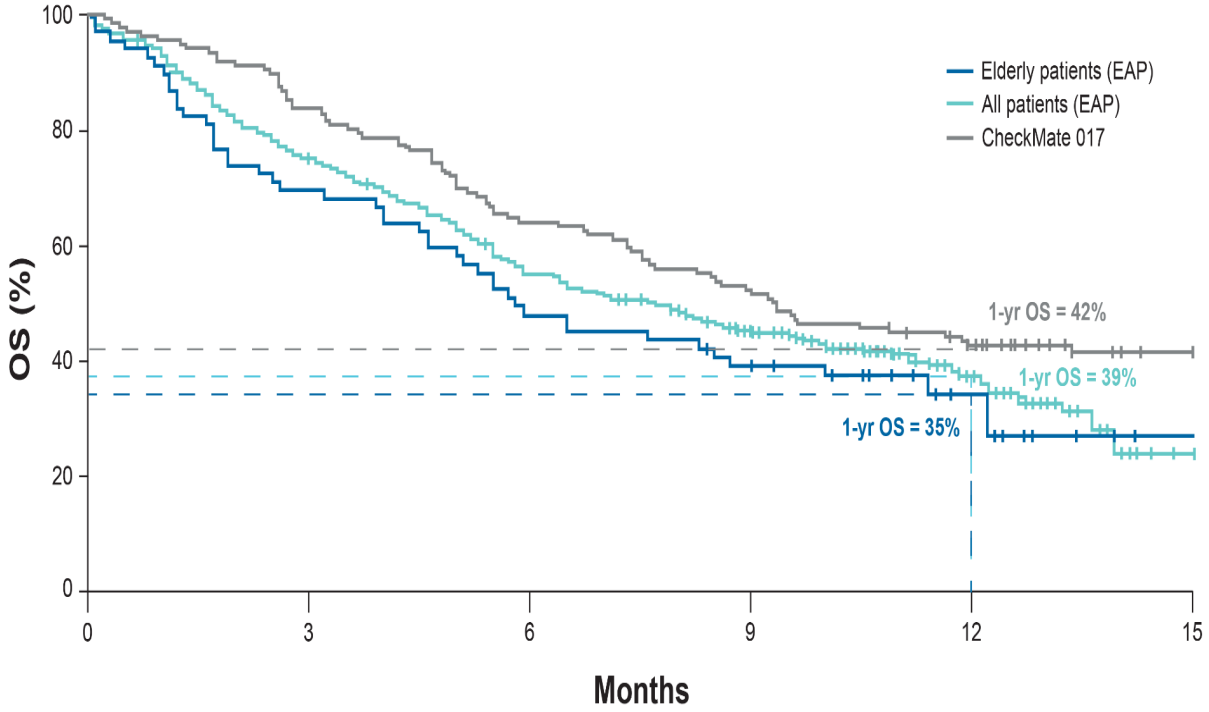
[Nivolumab]: Overall Survival [EAP *vs.* CM 017]

Real World Data ITA-EAP [Nivolumab]

	Aged <65 years (n = 126)	Aged 65–<75 years (n = 175)	Aged ≥75 years (n = 70)	Overall population (N = 371)
Median OS, mo (95% CI)	8.6 (5.2, 11.9)	8.0 (5.6, 10.4)	5.8 (3.5, 8.1)	7.9 (6.2, 9.6)

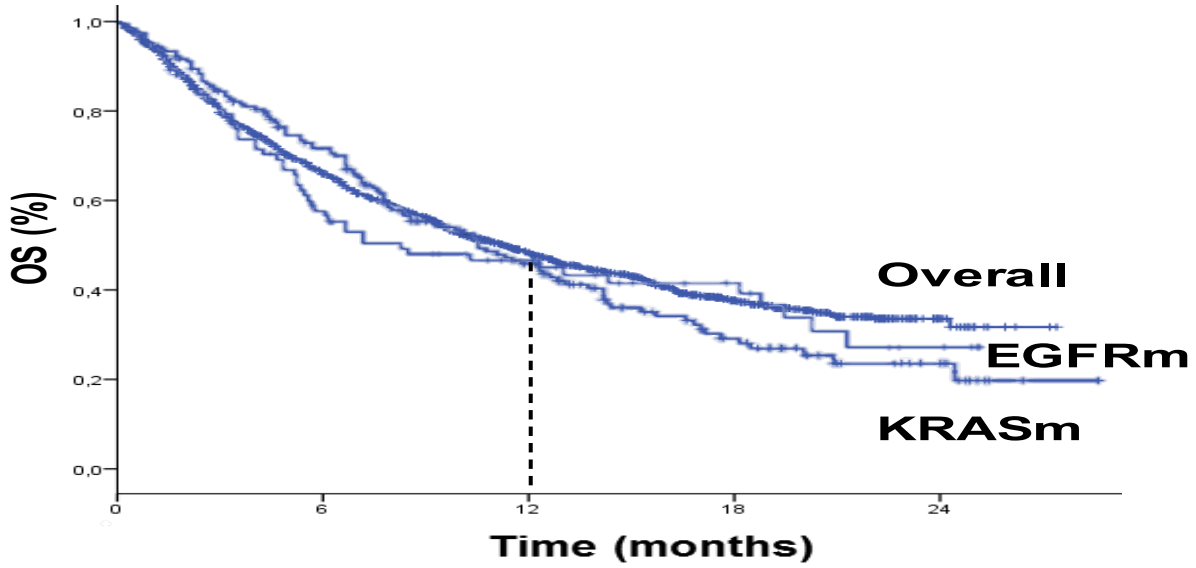


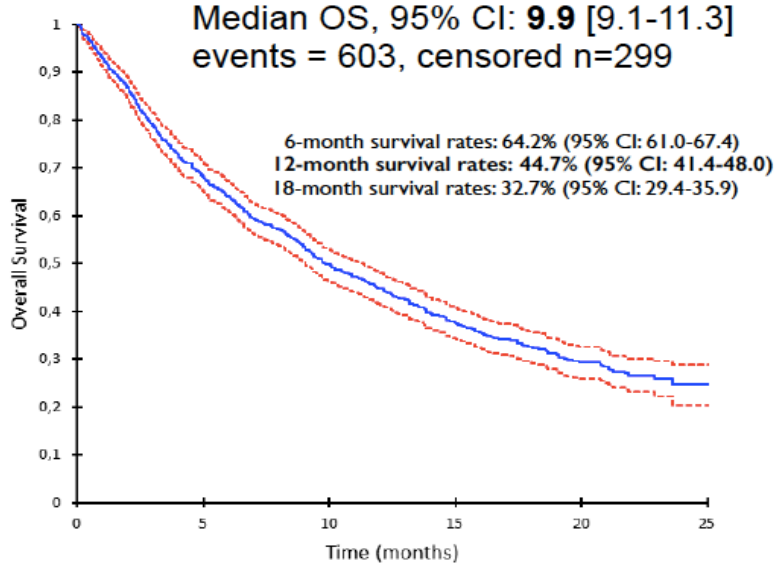
EAP (Overall & Elderly) *vs.* CM017



Grossi F et al, Eur J Cancer 2018

RWD: NON-Sq. ITA & FRA-EAP [Nivolumab]





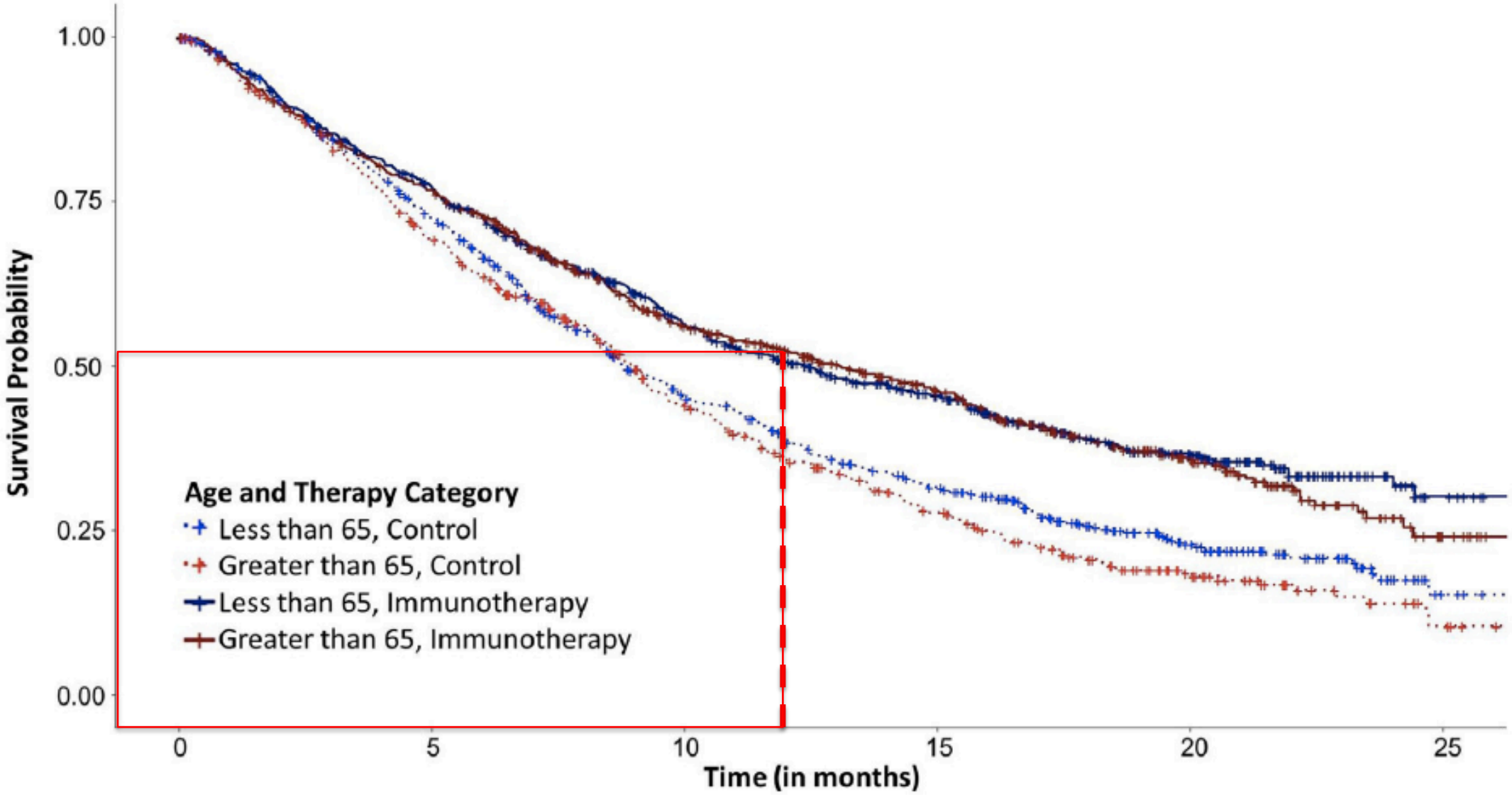
	*KRAS*m (n = 206)	*EGFR*m (n = 102)	Never smokers (N = 305)	Never smokers *EGFR*m (N = 51)	All patients (N = 1588)
ORR (%)	20	9	9	2	18
DCR (%)	47	30	42	22	44
Median OS, months (95% CI)	11.2 (9.3, 13.1)	8.1 (2.1, 14.1)	10.4 (8.6, 12.2)	5.6 (3.3, 7.9)	11.3 (10.2, 12.4)

Overall Similar & Consistent Data with Registration Trials

Ardizzoni A et al, WCLC 2017; Grossi F et al, WCLC 2017; Garassino M et al, WCLC 2017

Girard N et al, WCLC 2017

FDA Analysis: IO as a new Standard for Elderly NSCLC Pts



Marur S et al, Semin Oncol 2018

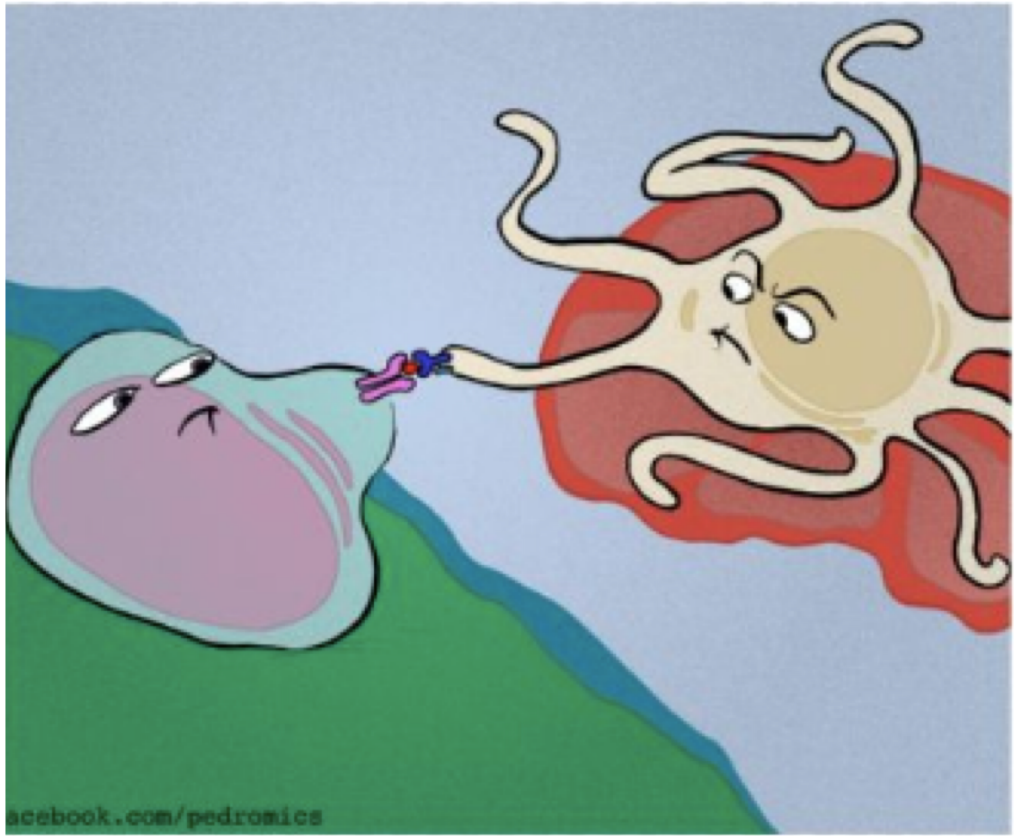
CONCLUSIONS - 1

- **Immunotherapy has significantly revolutioned treatment opportunity (particularly) for (the majority) of (non-oncogene addicted) lung cancer patients**
  - **Head-to-head comparisons have '*displaced*' 2nd line chemo**
  - **Head-to-head comparisons have '*displaced*' 1st line chemo (in pts with PD-L1>50%)**
  - **Almost all pts (regardless of PD-L1) will receive the combination of chemotherapy and Immunotherapy**
- **Nevertheless, long-term survival is expected for few patients, thus the maximization of the benefit is pursued by investigating new potential biomarkers for clinical practice**
  - **Tumor Mutational Burden has conflicting results, prospective predictive validation is ongoing**

CONCLUSIONS - 2

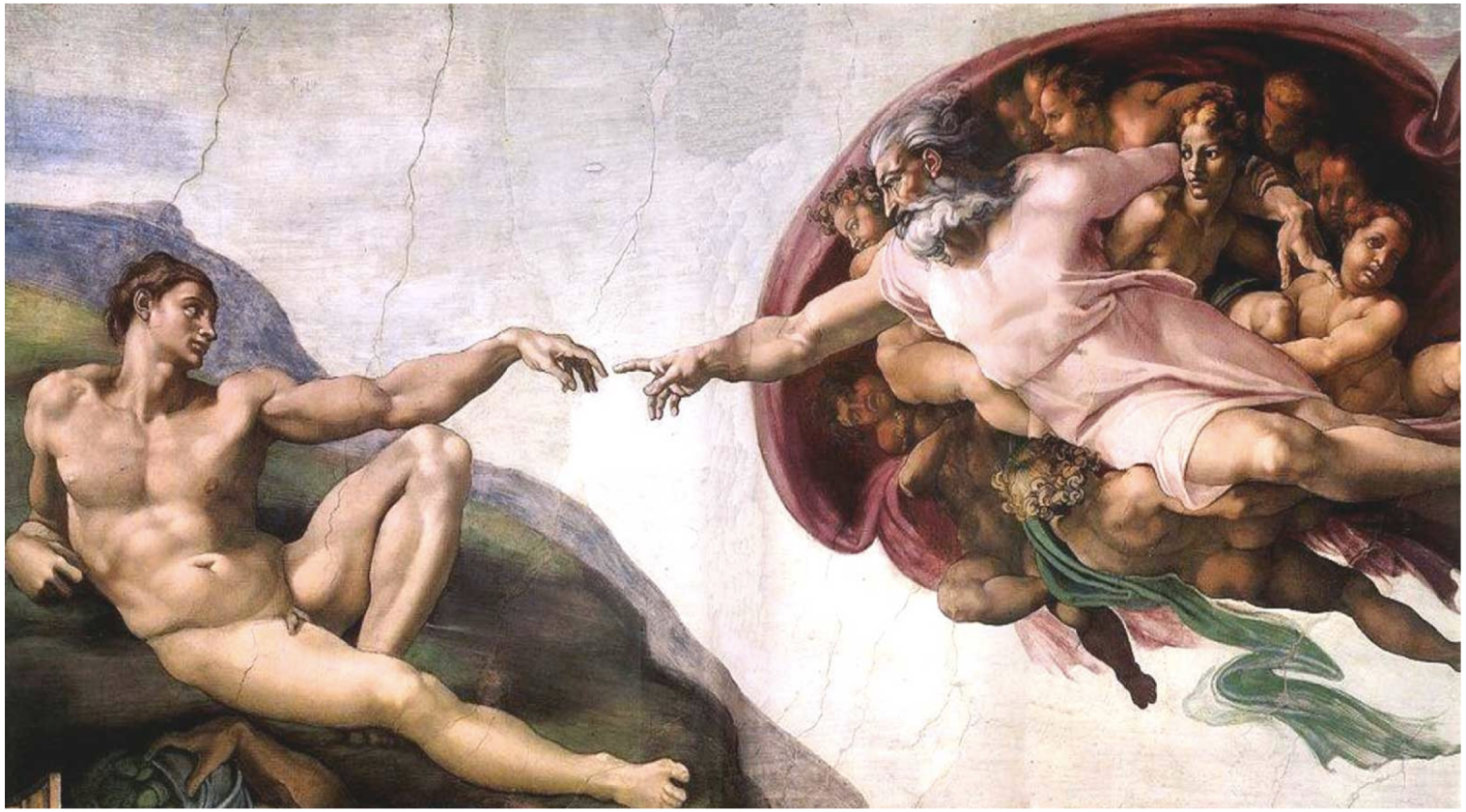
- **Traditional end-points are becoming useless (ex. ORR for Phase IIs, or PFS for Phase IIIs), and new models (for potential surrogates and intermediate end-points) are currently under investigation for improving the best way to intercept the benefit of IO**
- **Deriving the benefit of IO in clinical trials to clinical practice in the 'Real World' represents a challenge to date, although expanded-access data with IO do not significantly appear to differ from RCTs data**
- **In order to rapidly continue to impact upon patients' prognosis:**
  - **Innovative Trials for Precision Medicine are needed**
  - **Partneship between Pharma/Acamedia/Government is CRUCIAL!**

Presentation of The Antigen



The Cystein Chapel

Presentation of Adamo



The Sistina's Chapel

Modified from Botticelli A, AIOM 2018