Roma, 02 Dicembre 2019

Post-ESMO : from Barcellona to Real-World

Tumori Toracici: Il punto di vista dell'esperto

Antonio Passaro MD PhD
Division Of Thoracic Oncology
European Institute of Oncology, IRCCS, Milan, Italy
Email **antonio.passaro@ieo.it** Twitter: **@APassaroMD**

Disclosure

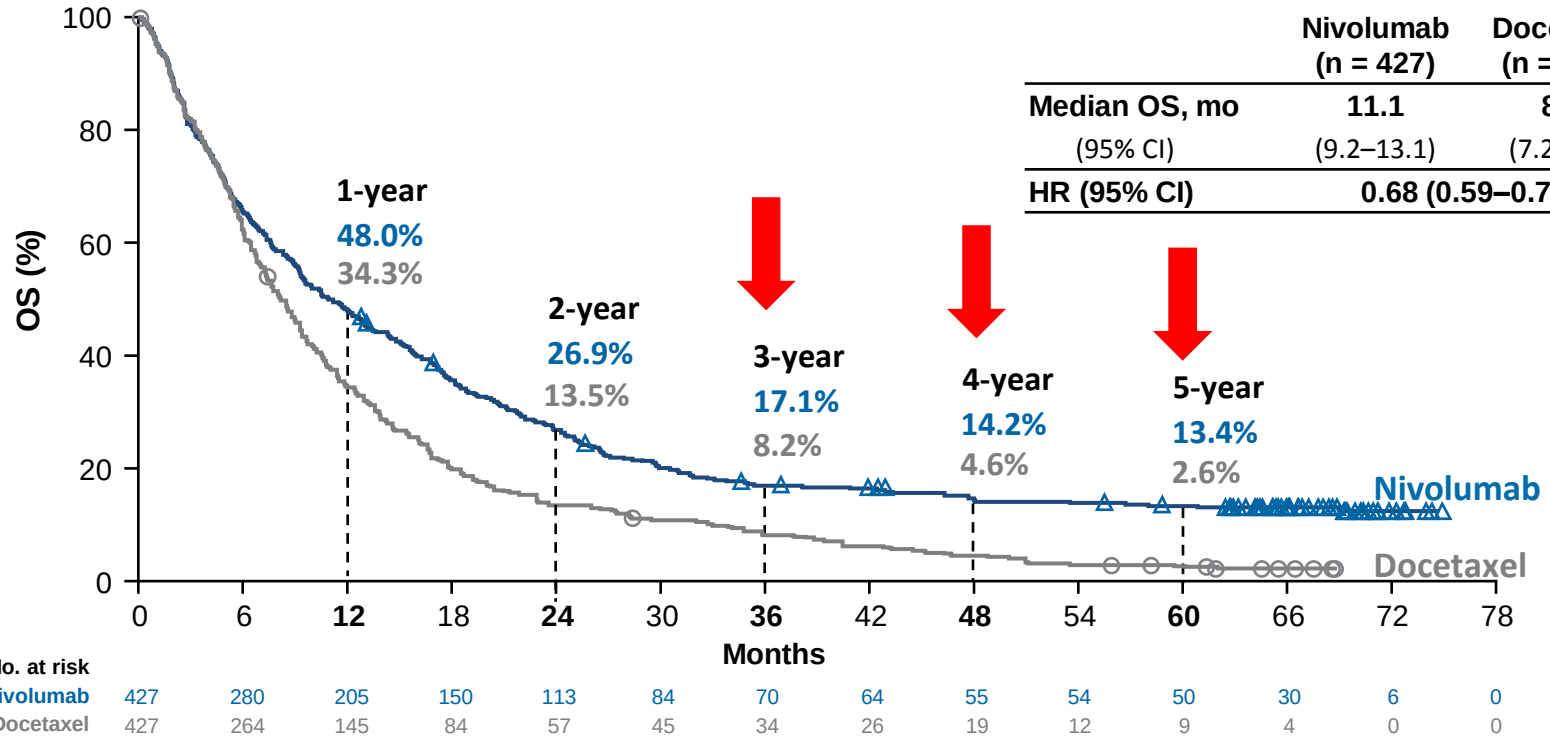
Advisory Boards/Honoraria/Speakers' fee/Consultant for:

- AstraZeneca
- Bristol-Myers Squibb
- Dako / Agilent
- Roche Genentech
- Merck Sharp & Dohme

5-Year Pooled OS: Nivolumab vs Docetaxel

From PFS to long-term survival

Gettinger, WCLC19



	Nivolumab (n = 427)	Docetaxel (n = 427)
Median OS, mo	**11.1**	**8.1**
(95% CI)	(9.2–13.1)	(7.2–9.2)
HR (95% CI)	**0.68 (0.59–0.78)**	

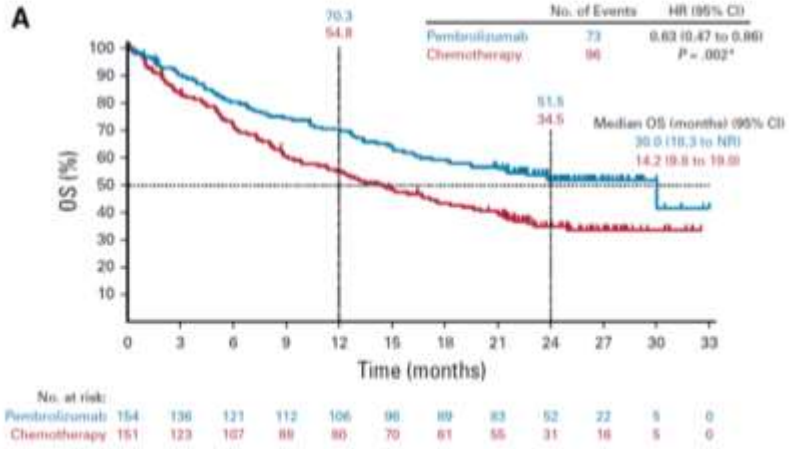
- 5-year OS rate (nivolumab vs docetaxel): 12.3% vs 3.6% (CheckMate 017; SQ); 14.0% vs 2.1% (CheckMate 057; NSQ)

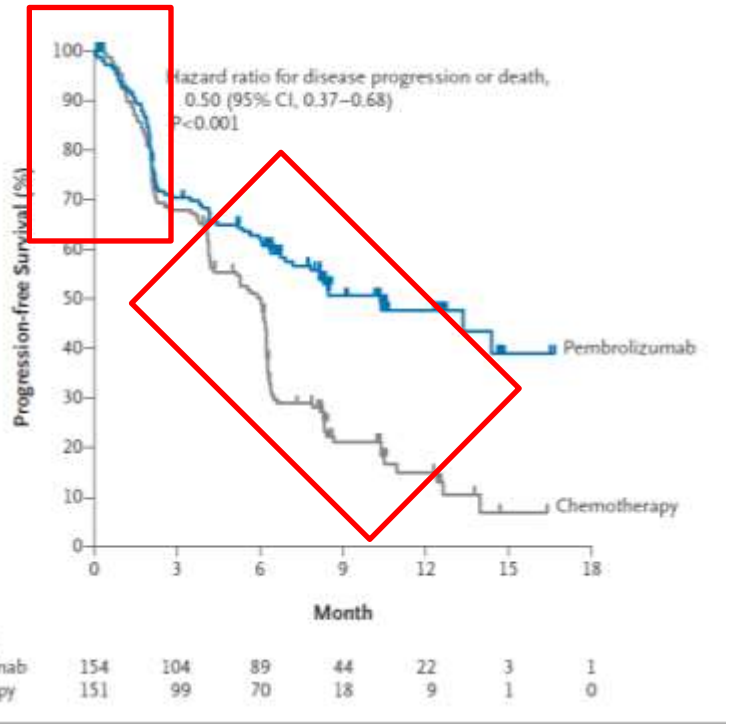
[a]Minimum follow-up for OS: 62.6 months (CheckMate 017), 62.7 months (CheckMate 057).

PD-L1 ≥ 50% 1° line: what have we learnt? KN-024

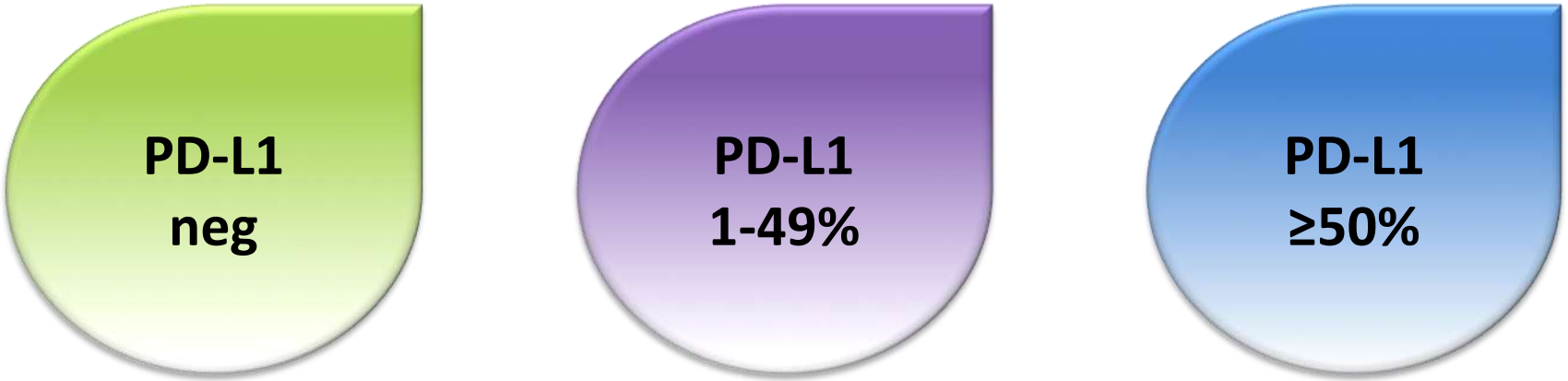
- ✓ **Responses** ≈ 45%
- ✓ **mPFS** ≈ 10.3 months
- ✓ **mOS** = 30.0 months

Benefit seen across most subgroups





Looking for a wide spectrum of activity



CM-227

Regardless PD-L1/TMB

IMpower 110

TC/IC 1/2/3

Options for Non-Oncogene addicted NSCLC with PD-L1 ≥50%

	Trial	Type	Drugs	M OS mo	HR	1yS	2yS	3yS
SINGLE AGENT	KN 024	NSCLC	Pembrolizumab	26.3	0.65	51.7%	43.7%	41.0%
	KN 042	NSCLC	Pembrolizumab	20.0	0.69	-	44.7%	-
	IM 110	NSCLC	Atezolizumab	20.2	0.59	64.9%	-	-
COMBO	KN 189	NSq	Pembro+ P/Pem	NR	0.59	73%	51.9%	-
	KN 407	Sq	Pembro+ Carbo/Pac	NR	0.64	-	-	-
	IM 150	NSq	Atezo+ Carbo/Pac+Beva	25.2	0.70	-	-	-
	IM 130	NSq	Atezo+ Carbo/nab Pac	17.3	0.84	-	-	-
	IM 131	Sq	Atezo+ Carbo/nab Pac	23.4	0.48	-	-	-
	CM 227	NSCLC	Nivolumab+LD Ipilimumab	21.2	0.70	67%	48%	-

Single Immuno agent vs Combo in PD-L1 ≥50%

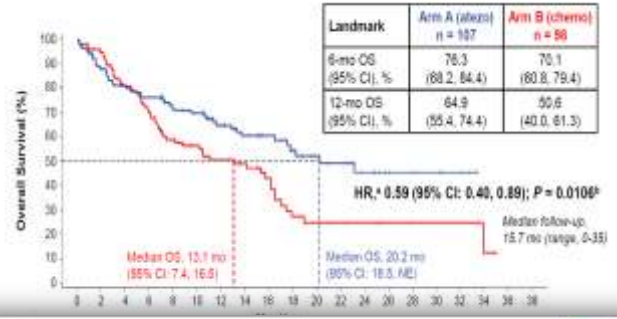
	KN 024	KN 189 (TPS≥50%)
ORR	45%	61.4%
DOR	NR	11.2%
Median PFS	10.3	11.2
HR	0.50	0.36
Median OS	30.0	NR
HR	0.63	0.59
2yOS	51.5%	51.9%

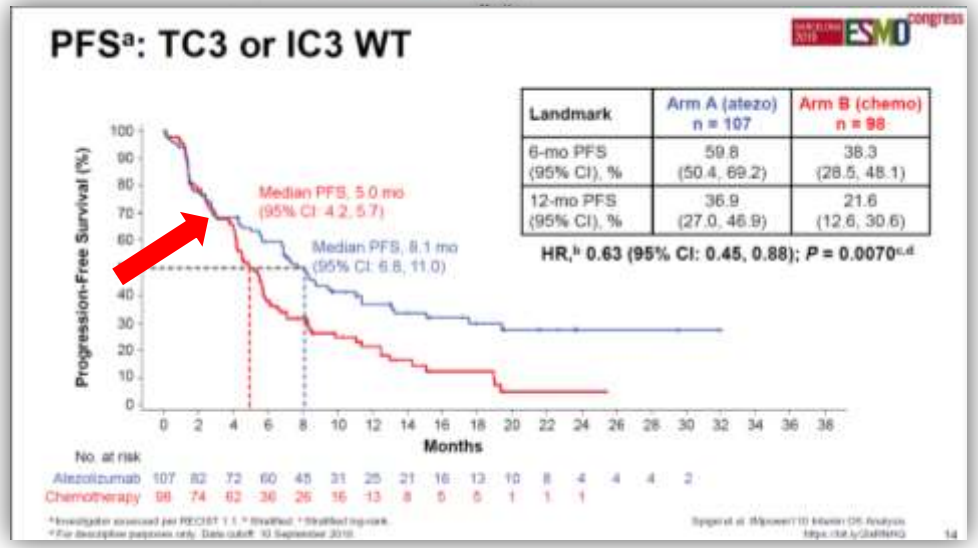
	KN 024	KN 189 (TPS≥50%)
All TRAEs	76.6%	99.8%
Grade 3-5 TRAEs	31.2	67.2
Discontinuation Rate	13.6%	27.7%
Lead to Death	1.3%	6.7%

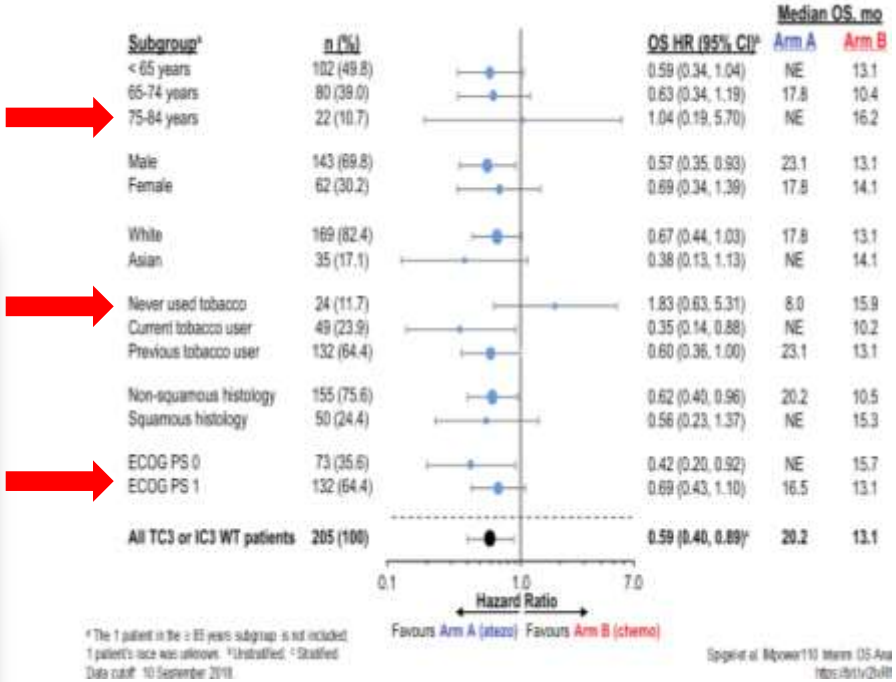
WHO ARE THE PATIENTS CANDIDATE TO IMMUNO/CHEMO COMBO?

- ✓ Never smokers
- ✓ Women
- ✓ Brain/Liver Mets
- ✓ High cancer related Symptoms
- ✓ Bulky disease

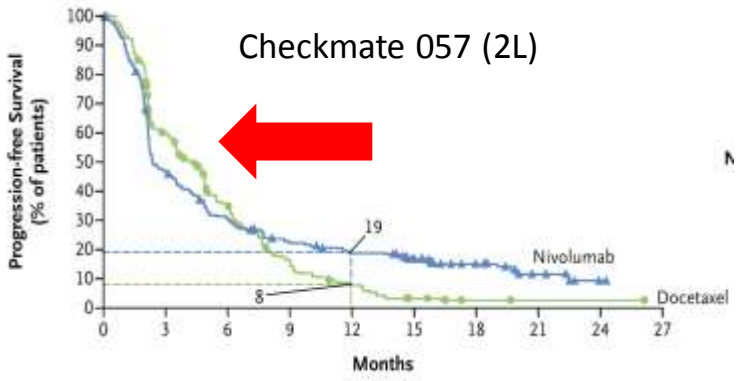
Impower 110: survival analysis

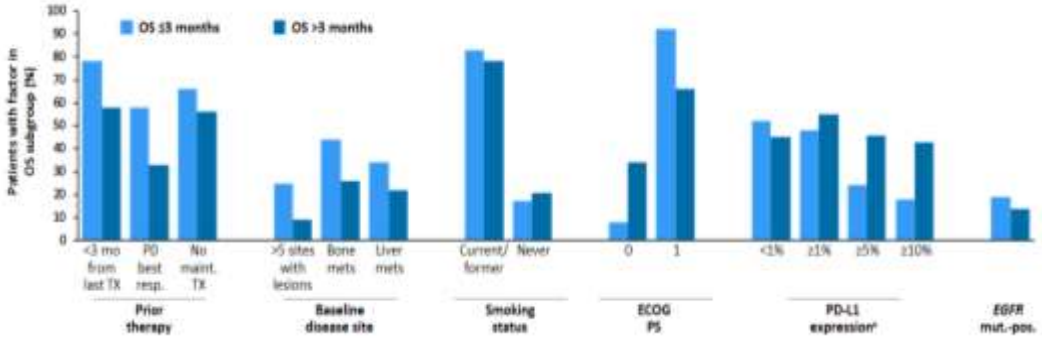


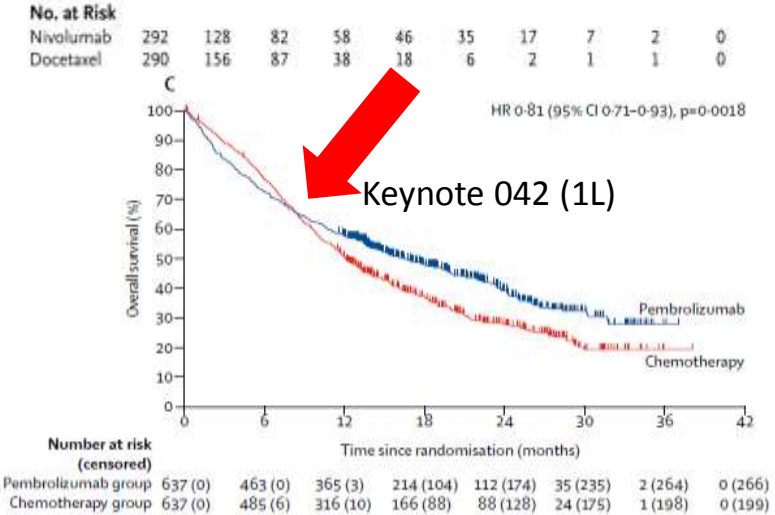


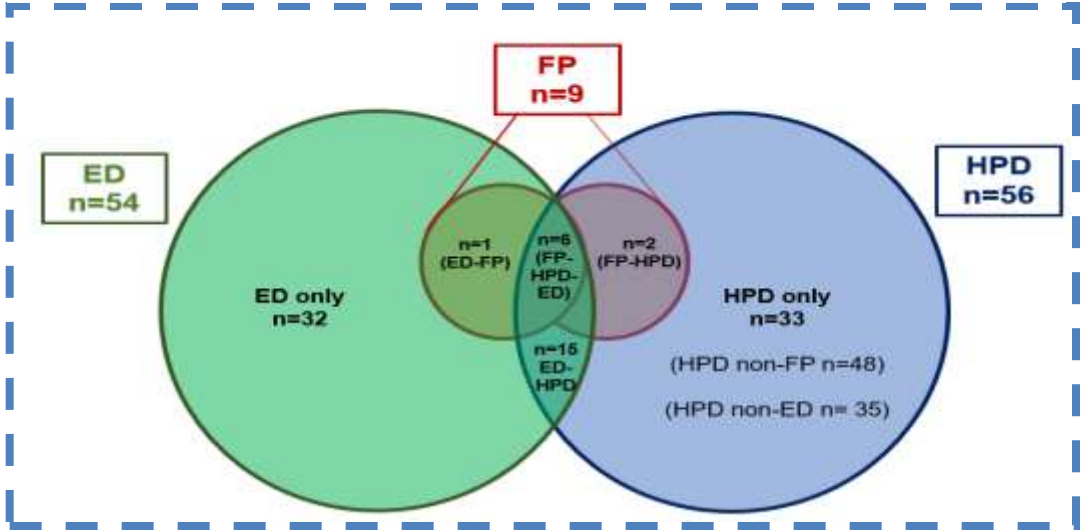


Immuno Single Agent Benefit limitations

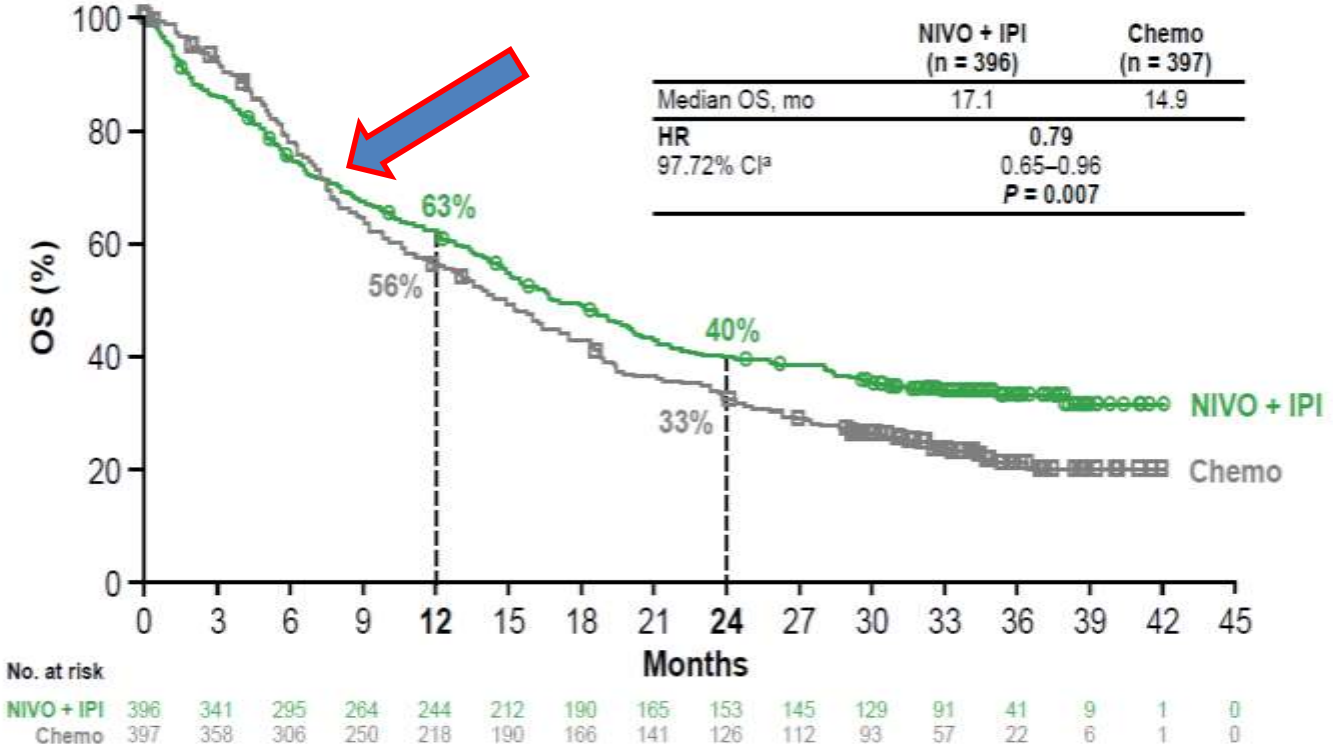








CM227: Primary Endpoint: OS N+I vs CTx in pts with PD-L1 ≥ 1%



	NIVO + IPI (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	14.9
HR	**0.79**	
97.72% CI[a]	0.65–0.96	
	***P* = 0.007**	

Minimum follow-up for primary endpoint: 29.3 months.
NIVO + IPI dosage was NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm and 54% of patients in the chemo

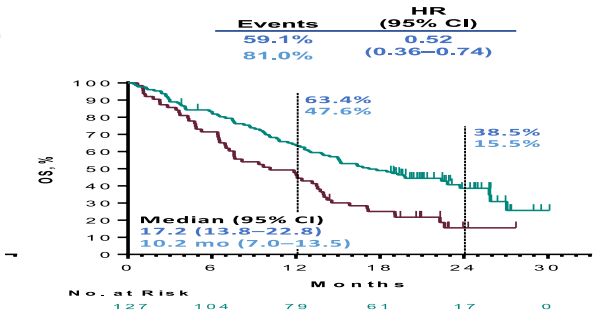
Options for Non Oncogene addicted NSCLC with PD-L1 1-49%

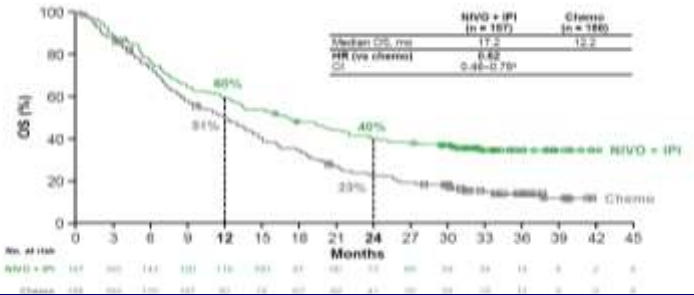
	Trial	Type	Drugs	M OS mo	HR	1yS	2yS	3yS
COMBO	KN 189	NSq	Pembro+ P/Pem	21.8	0.62	71.7%	44.3%	-
	KN 407	Sq	Pembro+ Carbo/Pac	14.0	0.57	-	-	-
	IM 150	NSq	Atezo+ Carbo/Pac+Beva	20.3	0.80	-	-	-
	IM 130	NSq	Atezo+ Carbo/nab Pac	23.7	0.70	-	-	-
	IM 131	Sq	Atezo+ Carbo/nab Pac	12.8	1.08	-	-	-
	CM 227	NSCLC	Nivolumab+LD Ipilimumab	15.1	0.94	-	-	-

Options for Non Oncogene addicted NSCLC with PD-L1 < 1%

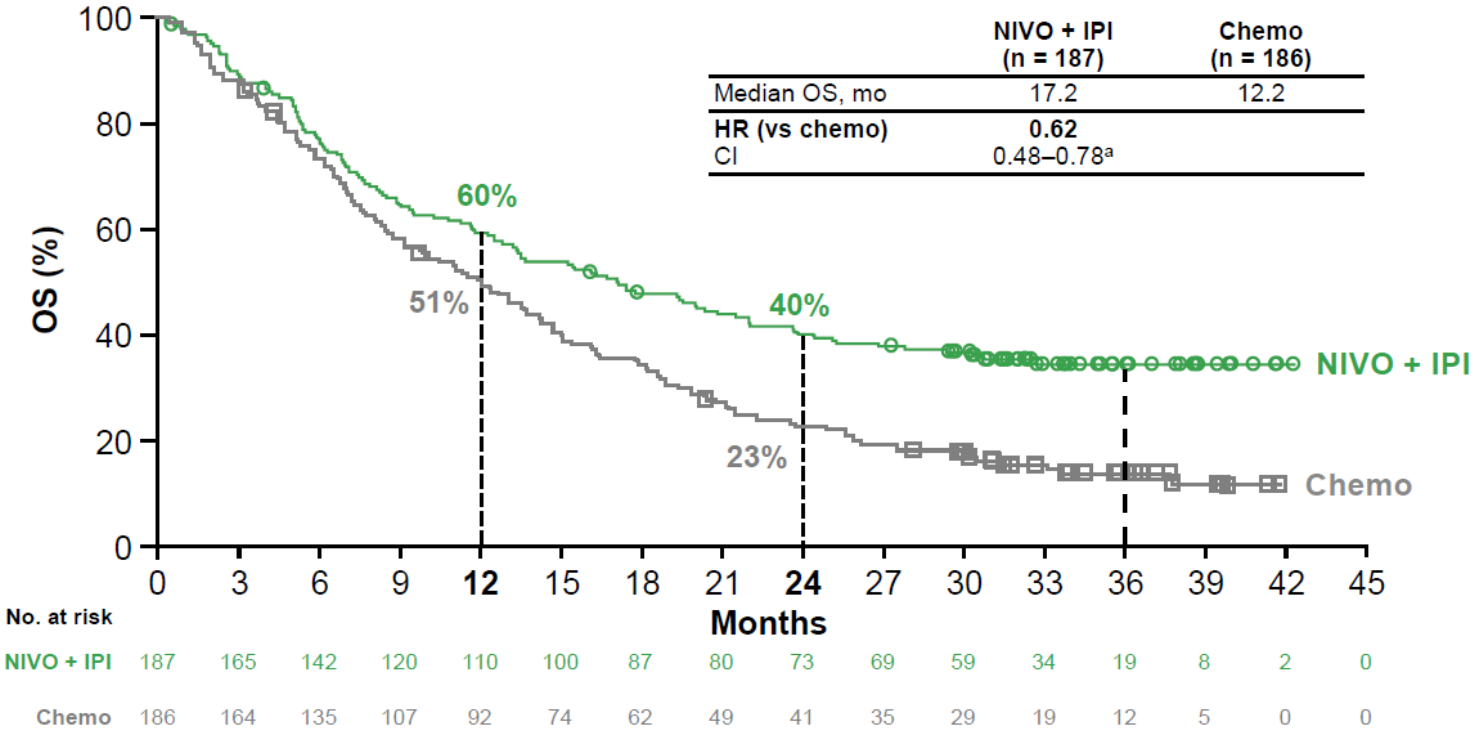
	Trial	Type	Drugs	M OS mo	HR	1yS	2yS	3yS
COMBO	KN 189	NSq	Pembro+ P/Pem	17.2	0.52	63.4%	38.5%	-
	KN 407	Sq	Pembro+ Carbo/Pac	15.9	0.61	-	-	-
	IM 150	NSq	Atezo+ Carbo/Pac+Beva	17.1	0.82	-	-	-
	IM 130	NSq	Atezo+ Carbo/nab Pac	15.2	0.81	-	-	-
	IM 131	Sq	Atezo+ Carbo/nab Pac	14.0	0.87	-	-	-
	CM 227	NSCLC	Nivolumab+LD Ipilimumab	17.2	0.62	60%	40%	-

EMA





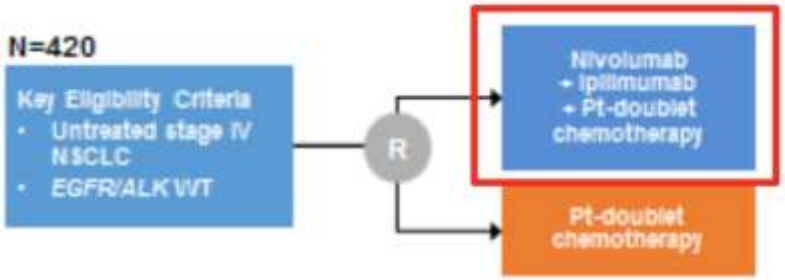
OS with Nivo + Ipi vs Chemo in PD-L1 < 1%



Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% of patients in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively.
[a]95% CI.

Looking to the future of combinations

Checkmate 9LA



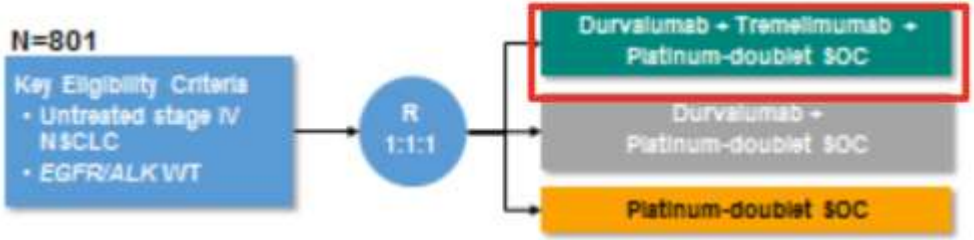
Primary endpoints: OS

Press Release

CheckMate -9LA, a Phase 3 Trial Evaluating Opdivo (nivolumab) Plus Low-Dose Yervoy (ipilimumab) Combined with Chemotherapy, Meets Primary Endpoint Demonstrating Superior Overall Survival Compared to Chemotherapy Alone in First-Line Lung Cancer

Study evaluated Opdivo plus low-dose Yervoy given concomitantly with two cycles of chemotherapy vs. chemotherapy alone for the first-line treatment of advanced non-small cell lung cancer

POSEIDON



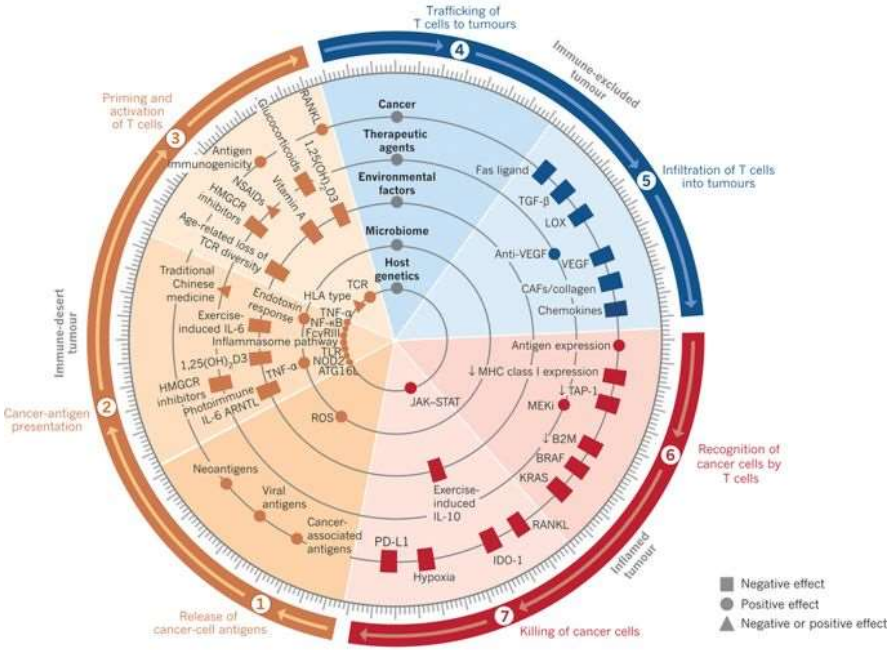
Primary endpoints: PFS

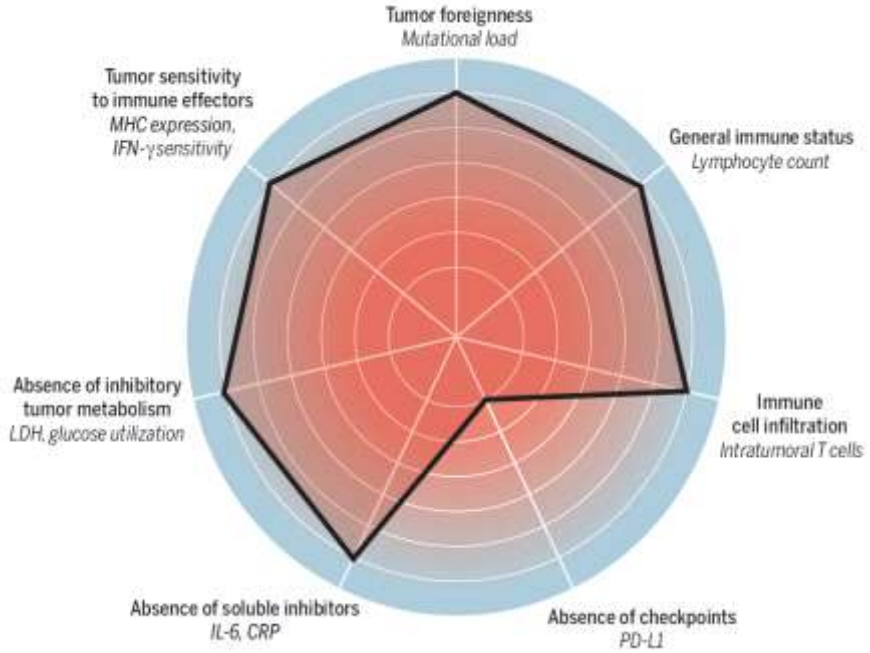
Imfinzi and Imfinzi plus tremelimumab delayed disease progression in Phase III POSEIDON trial for 1st-line treatment of Stage IV non-small cell lung cancer

This announcement contains inside information

POSEIDON included both non-squamous and squamous patients and a broad choice of standard chemotherapy options

The Immune Response & the Cancer Immunogram





- Numerous factors determine effectiveness of a tumour-directed immune response
- Some cancers are NOT immunogenic; there is no immune response
- How does the tumour EVADE an immune response, assuming there is one?
- Inhibitory immune checkpoints are one important mechanism

Blank CU et al. Science 2016
Chen DS et al. Nature. 2017

Consideration about TMB by F Cecere

Considerations:

- TMB threshold of 175 muts by WES and 10 muts/mb is a consistent threshold 

- Higher TMB levels associated with improved clinical outcomes for pembrolizumab monotherapy in patients with PD-L1 positive tumors 

- PD-L1 1-49% and TMB high may be benefit from pembrolizumab monotherapy 

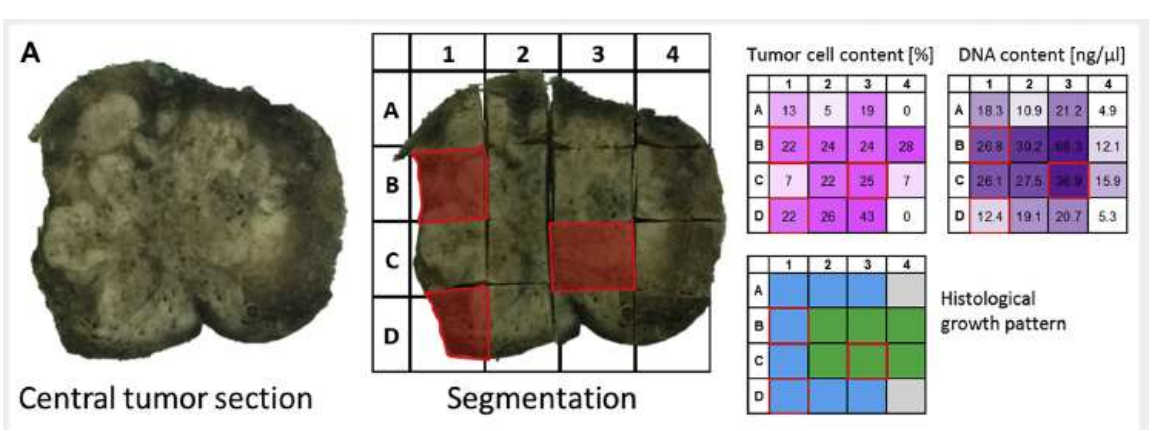
- Pembrolizumab and chemo active in both TMB high and low 

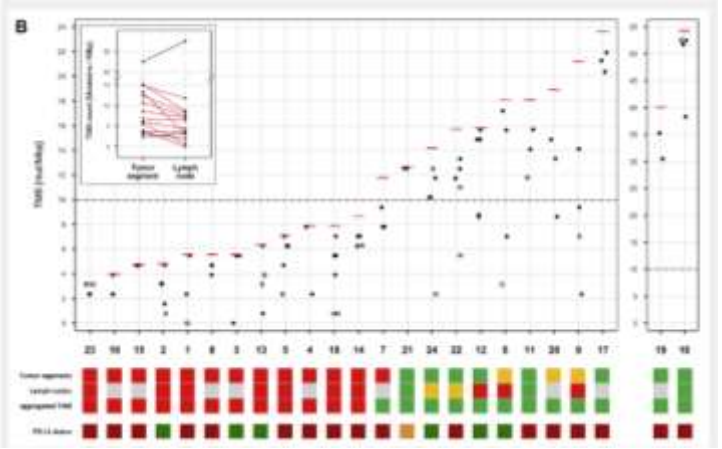
Questions: *Harmonization needed to define TMB* 

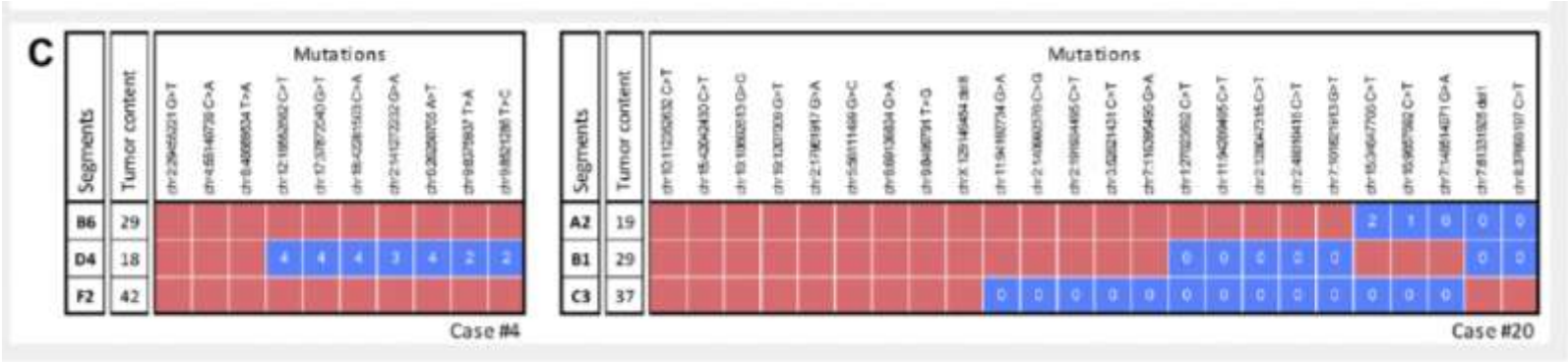
Why we consider the failure of TMB in NSCLC?

- Is the impact of TMB in PD-L1 high pos clinically relevant? **NO**
- Is there a role of TMB in combo-treatment? **NO**
  Combo treatments: chemo + IO / anti PD1 + anti CTLA4
- Is TMB able to indentify fast-progressor or poor prognosis patient pupulation? **NO!**

The spatial and temporal heterogenty is the key





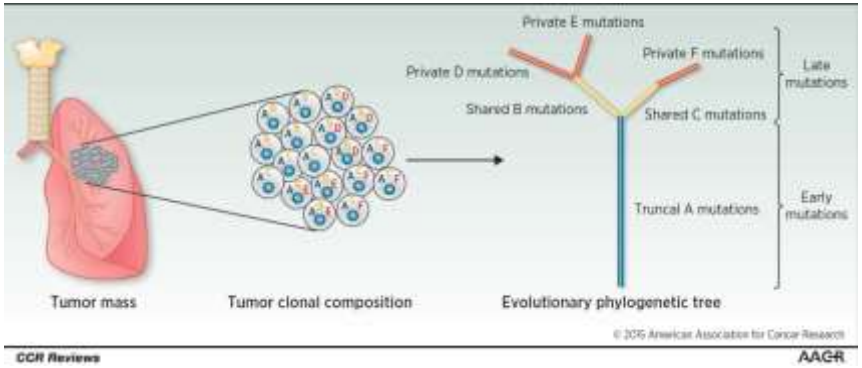


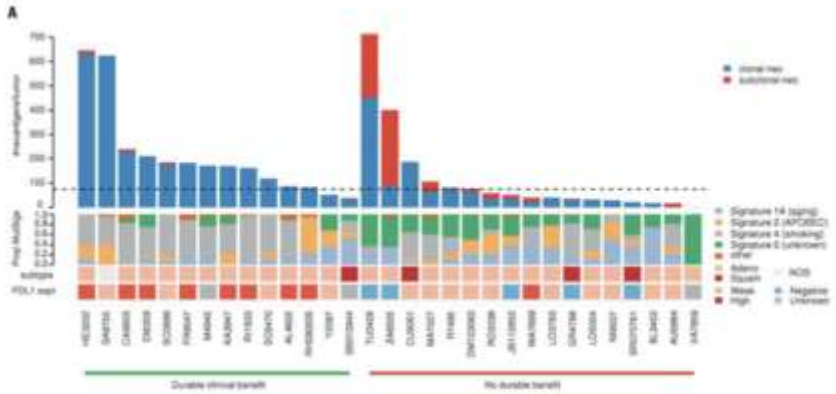
Quality and not quantity

TUMOR IMMUNOLOGY

Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

- Survival is related to clonal neoantigen burden
- CD8+ TILs react to clonal neoantigens
- Cytotoxic chemotherapy (& target therapies) induce only subclonal neoantigens





Two different oncological moods

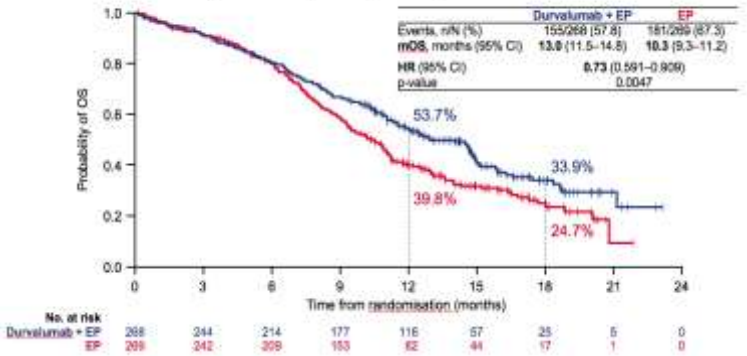
1) We've been stopped for about 20 years ... 3 months are enough for now

2) Only 3 months in SCLC? Yes, but I don’t think that these results are really pratice changing

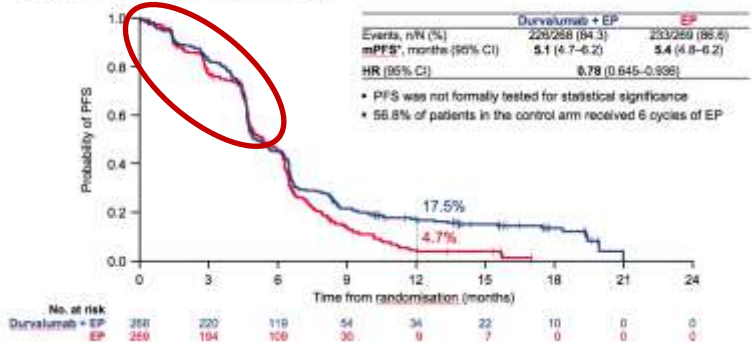
Outcomes IO in SCLC: IMpower133 vs CASPIAN

	IMpower 133		CASPIAN	
	Atezolizumab (pts n 201)	Placebo (pts n 202)	Durvalumab (pts n 268)	Placebo (pts n 269)
Overall Survival				
HR	0.76		0.73	
median	12.3	10.3	13.0	10.3
12 mos	**52%**	39%	**54%**	40%
Progression-free survival				
HR	0.77		0.78	
median	**5.2**	4.3	**5.1**	5.4
12 mos	12.6%	5.4%	17.5%	4.7%
Response				
ORR	**60.2%**	64.4%	**67.9%**	57.6%
DoR mos	**4.2**	3.9	**5.1**	5.1
AEs				
G3- G4	**67.7%**	63.3%	**61.5%**	62.4%
Discontinuation	**12.1%**	3.1%	**9.4%**	9.4%

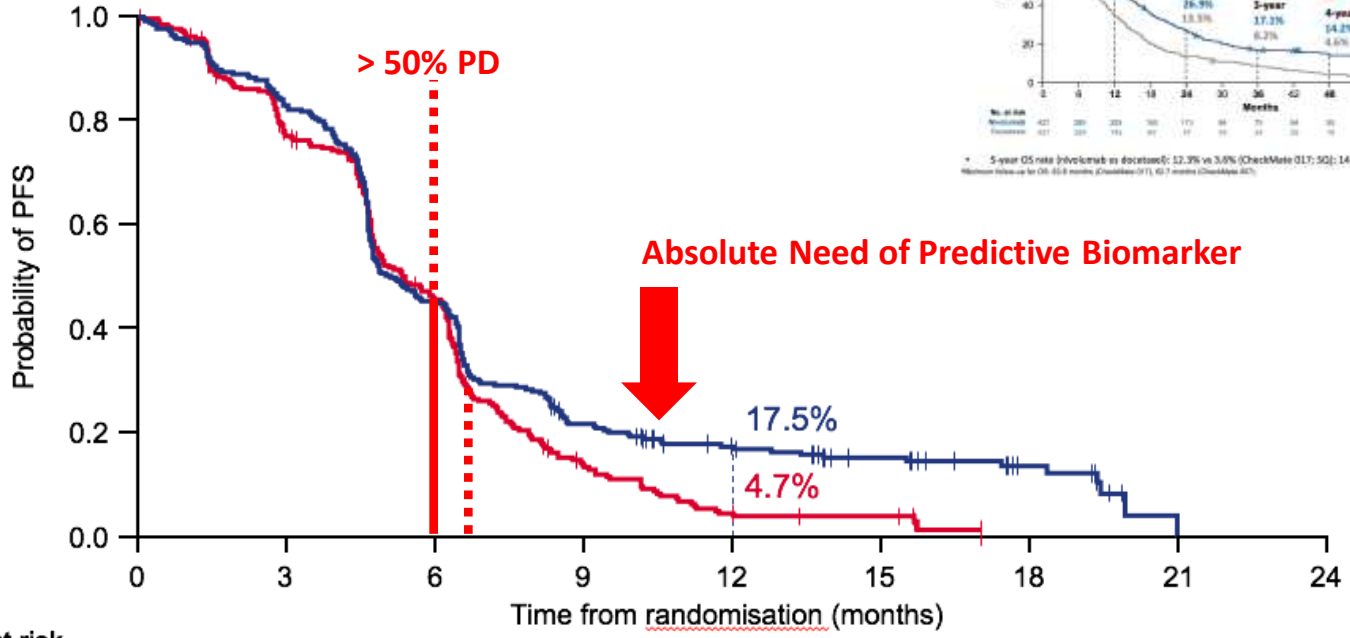
Overall Survival (Primary Endpoint)



Progression-free Survival

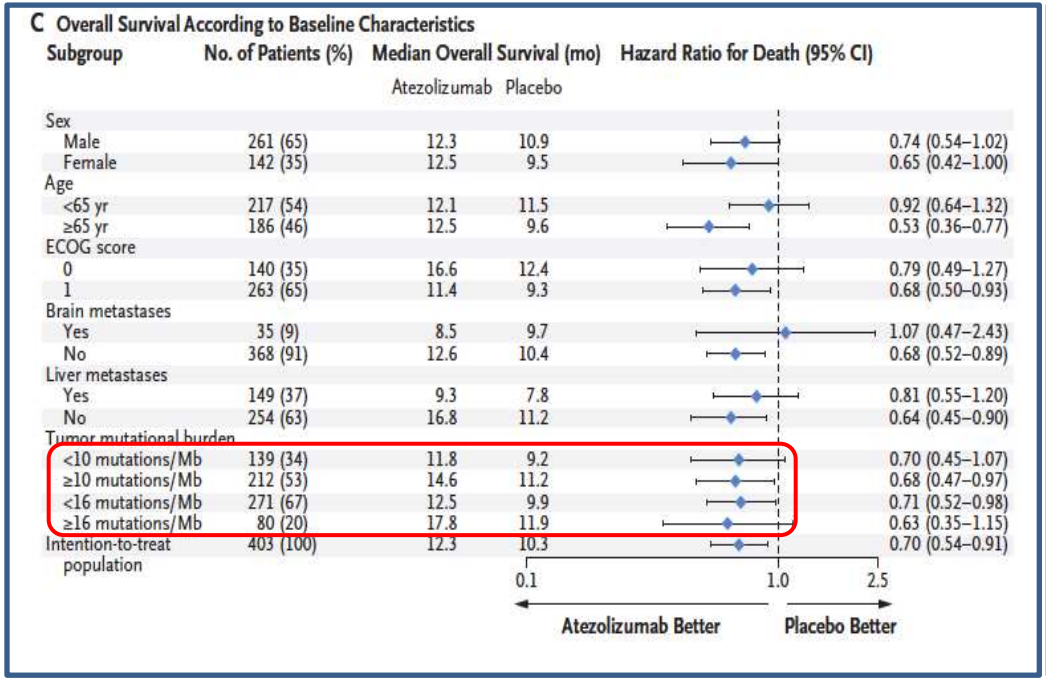


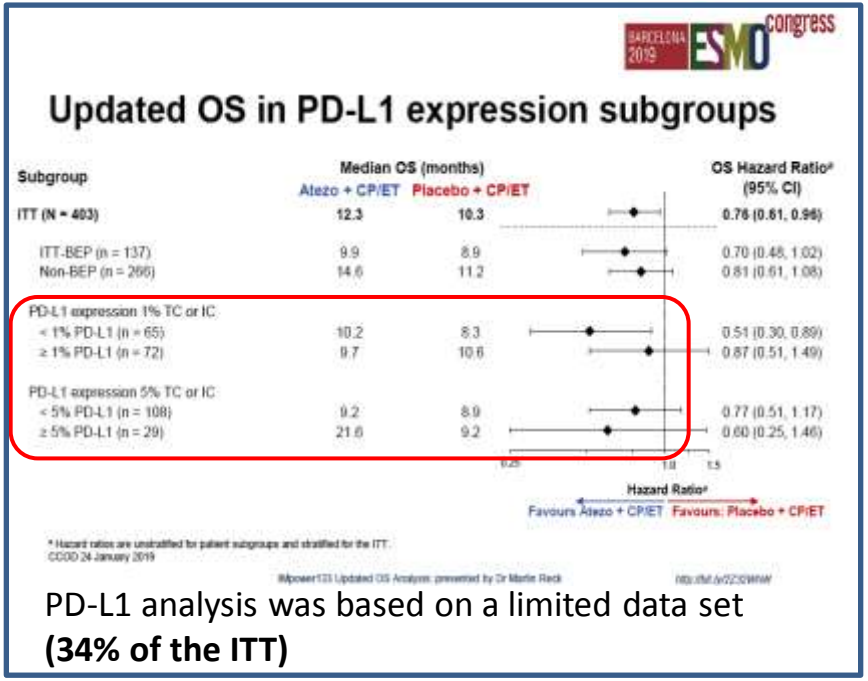
Progression-free Survival



No. at risk									
Durvalumab + EP	268	220	119	54	34	22	10	0	0
EP	269	194	109	30	9	7	0	0	0

IMpower 133: biomarkers





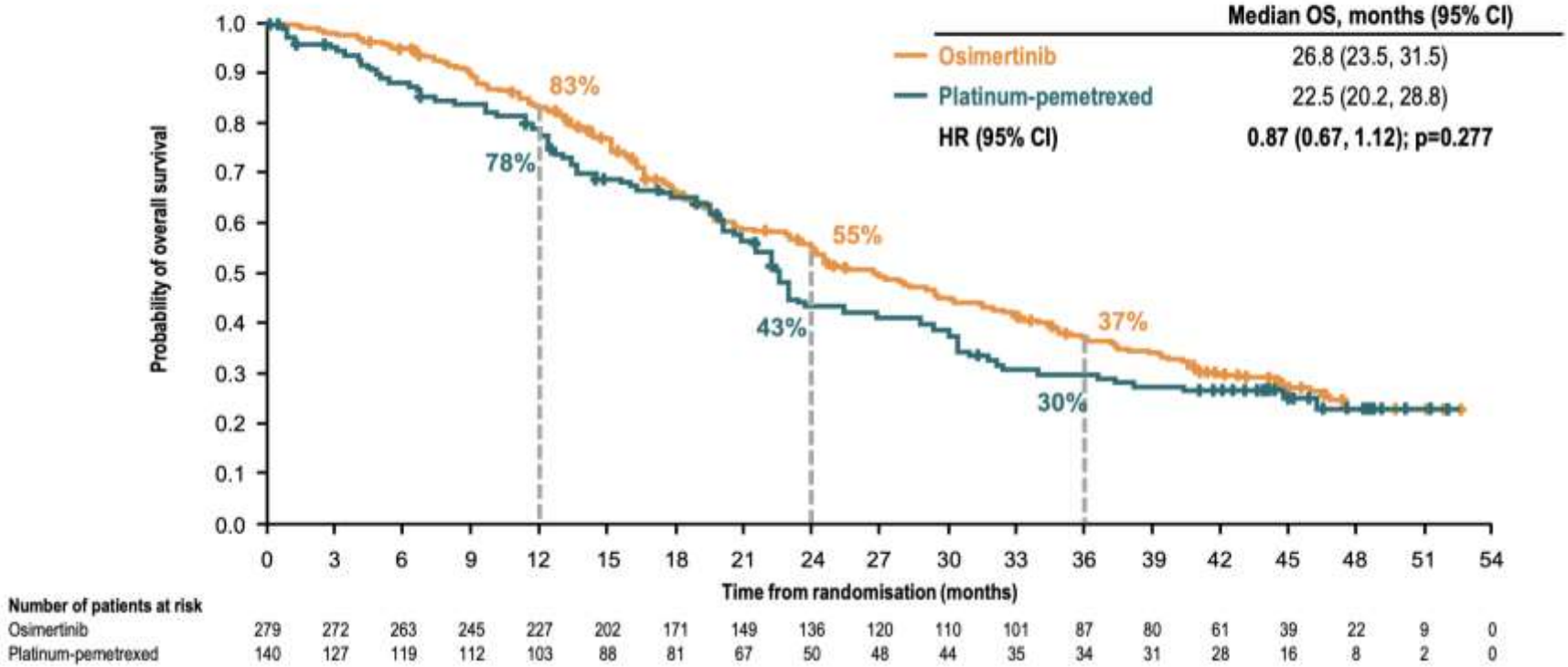
PD-L1 analysis was based on a limited data set **(34% of the ITT)**

Exploratory biomarker analyses that included both PD-L1 IHC and bTMB are not usefull to stratify patients

Horn, NEJM 2018; Reck ESMO 2019

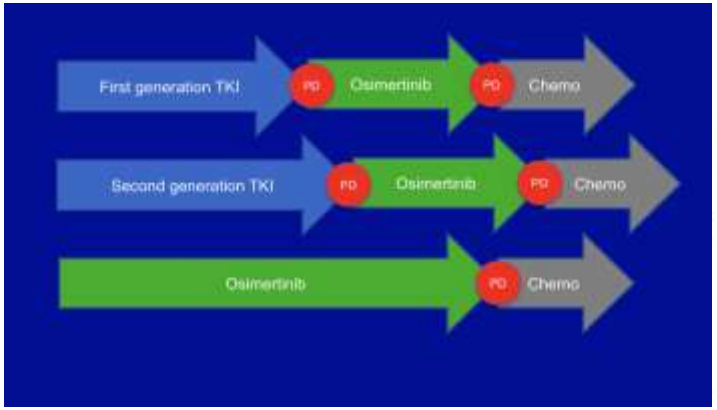
3° Gen EGFR TKIs **upfront** or TKIs **sequence**?

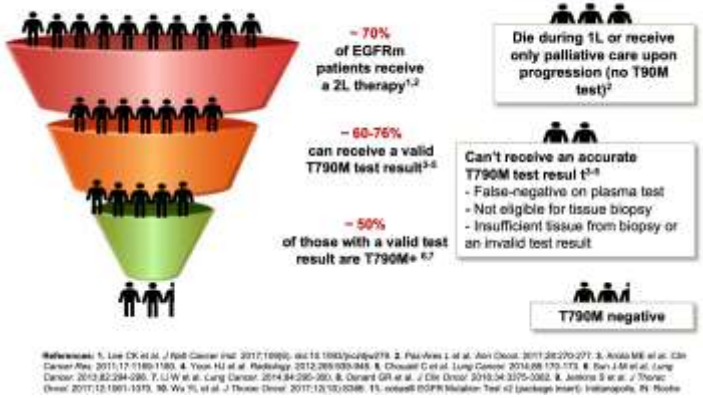
AURA3 overall survival



From a conceptualized sequential therapy to a dramatic reality

By T Mok





References: 1. Lee CK et al. J Natl Cancer Inst. 2017;109(6). doi:10.1093/jnci/djw279. 2. Paz-Ares L et al. Ann Oncol. 2017;28:270-277. 3. Kosaka MB et al. Clin Cancer Res. 2011;17:1189-1195. 4. Yoon HJ et al. Radiology. 2012;265:930-948. 5. Chouaid C et al. Lung Cancer. 2014;86:170-173. 6. Ban J-M et al. Lung Cancer. 2013;82:294-298. 7. Li W et al. Lung Cancer. 2014;84:295-300. 8. Oxnard GR et al. J Clin Oncol. 2016;34:3375-3382. 9. Jenkins S et al. J Thorac Oncol. 2017;12:1661-1673. 10. Wu YL et al. J Thorac Oncol. 2017;12:1021-1028. 11. cobas® EGFR Mutation Test v2 [package insert]. Indianapolis, IN: Roche

Subsequent treatment issues

Among RCT,

- 47-82% (first generation TKIs) and 58-78% (second generation TKIs) received second line
- The majority of patients received CT (except H2H trials)
- At that time T790M was not routine and third generation EGFR TKIs were not available

In Real World Data, the proportion of patients receiving second line treatment can be lower

- German study 70 % received second line *(Roeper, J. et al JTO 2018 Abst 5494-5495)*
- US study 38% received second line *(Chiang et al. , JTO 2018; Abstr 5410-5411)*
- US Flatiron Electronic Health record database 44% received second line *(Li Y et al. PLoS ONE 2019)*

Theoretically, 50% of patients treated with first and second generation TKIs will be T790M + and eligible to receive osimertinib

- Real-World EGFR T790M Testing (plasma sample, cytology or tissue biopsy) in Japan: only 30% T790M+ *(Seto T et al. Oncol Ther 2018)*

FLAURA: final overall survival data

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years old
- WHO performance status 0/1
- Exon 19 deletion/L858R (enrollment by local or central *EGFR* testing)
- No prior systemic anticancer/ EGFR-TKI therapy
- Stable CNS metastases were allowed

Stratification by **mutation status** (exon 19 deletion/ L858R) and **race** (Asian/non-Asian)

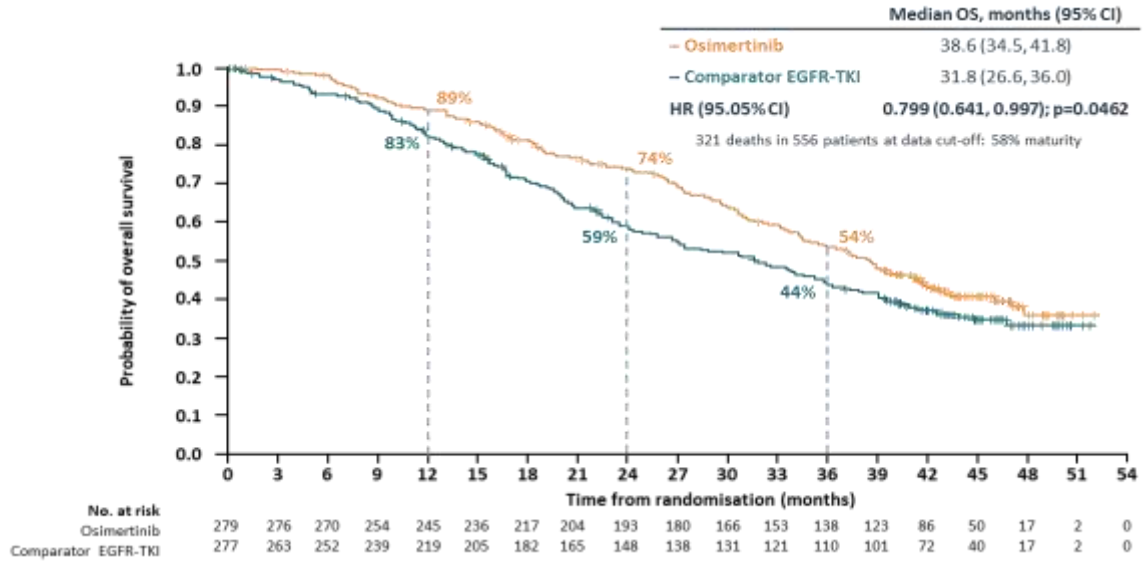
R 1:1

Osimertinib (80 mg po qd) (n=279)

Comparator EGFR-TKI: Gefitinib (250 mg po qd) or **Erlotinib** (150 mg po qd) (n=277)

RECIST v1.1 assessment every 6 weeks until objective progressive disease
Following the primary PFS analysis, progression events per RECIST 1.1 were no longer collected centrally

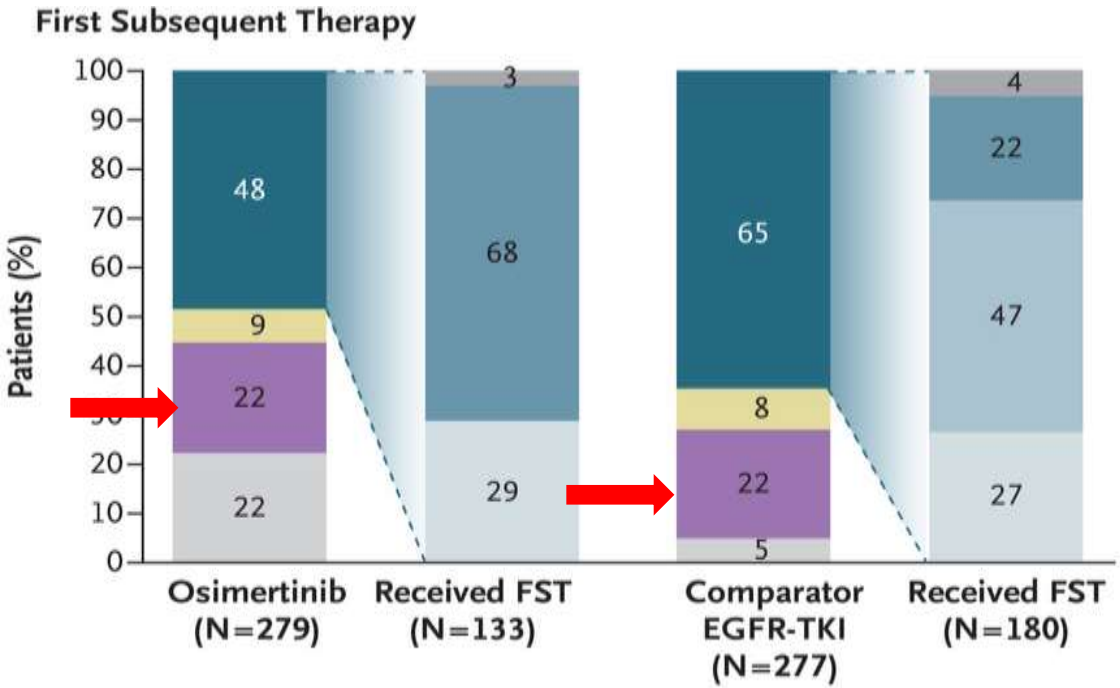
Crossover was allowed for patients in the **comparator** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity



FLAURA Study Outcomes

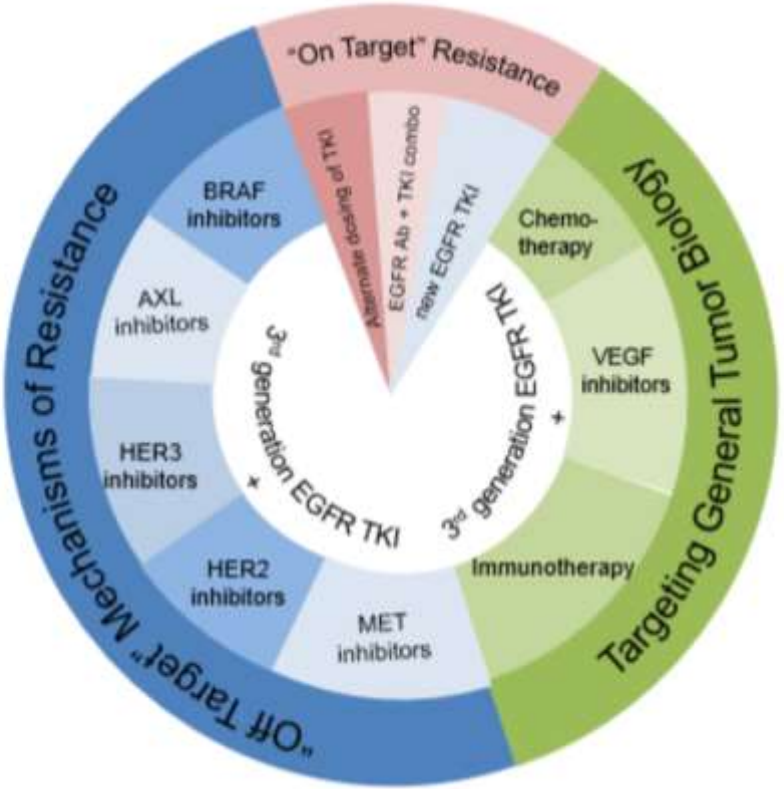
- Clinically meaningful ?
  - Yes !
    - Median OS improvement of almost 7 months
    - 28% vs. 9% of patients receiving study therapy at 36 months
- Consistent across subgroups ?
  - Yes but magnitude of benefit varies in subgroups
- Change clinical practice ?
  - Not in US (already changed)
  - Should dissuade EGFR TKI sequencing

Post-progression treatment



SS Ramalingam et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1913662

What do we do next to avoid or treat acquired resistance?



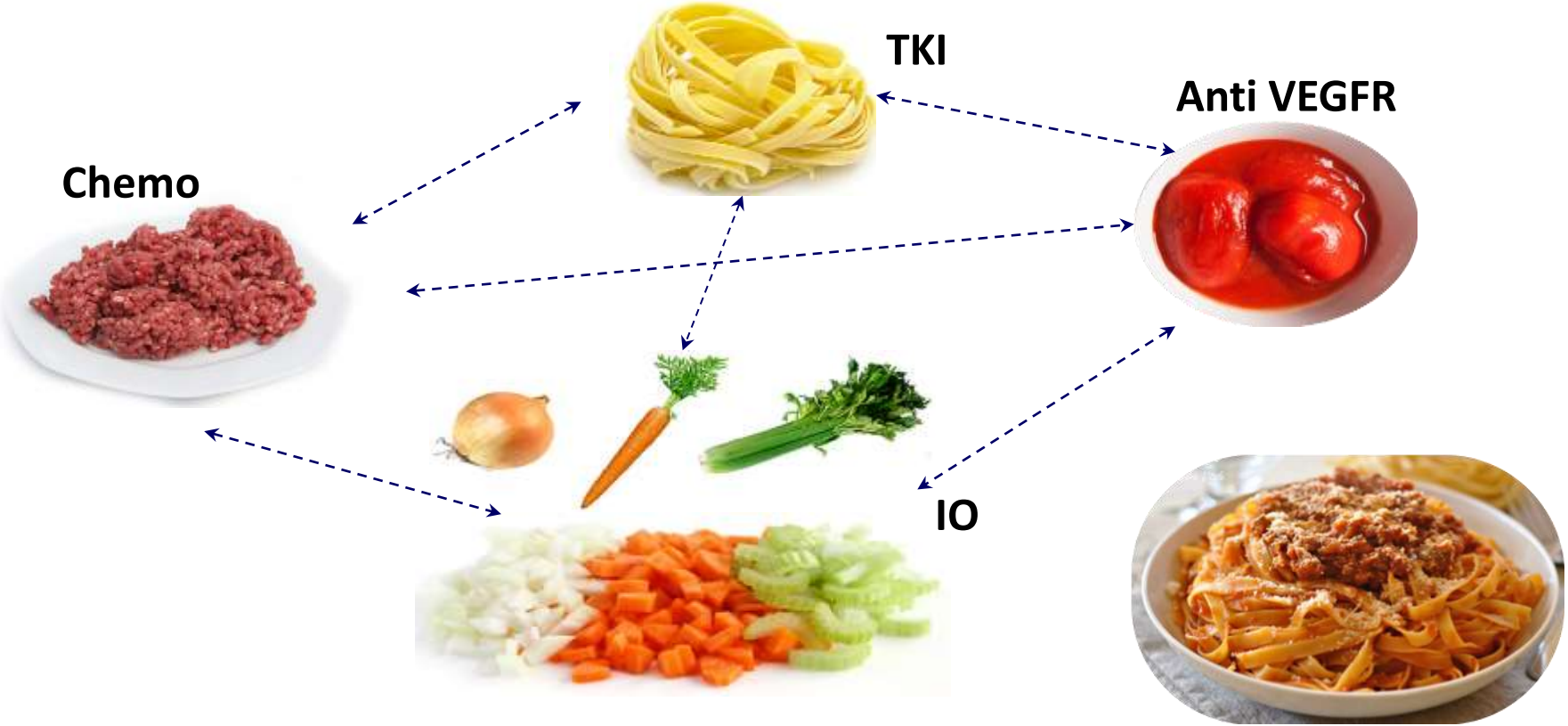
Arbour and Riely, *Cancer* 2018

What can we do after osimertinib?

1. CLINICAL TRIALS
2. CTx + Atezo + Beva
3. Standard Chemo

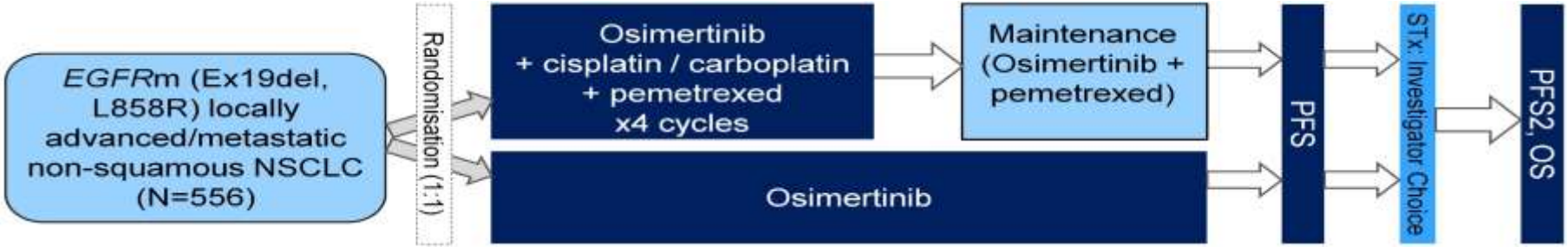
Improving the outcome over 3° Gen TKI

Looking for the ideal combination



Study design: randomised phase

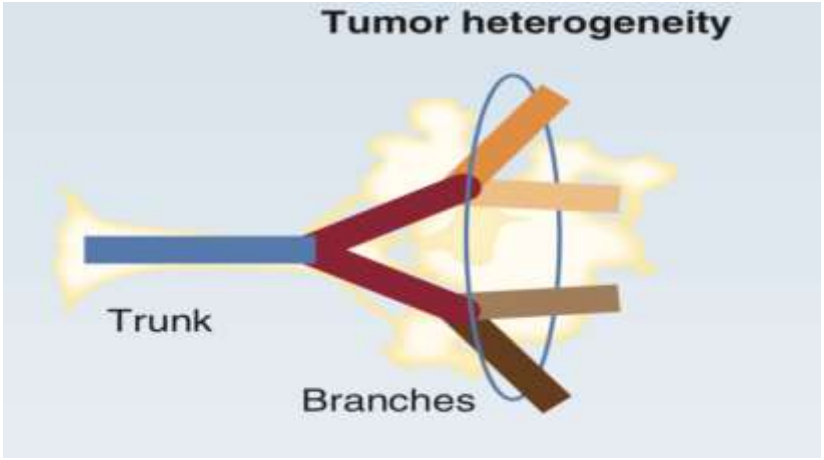
Osimertinib plus platinum/pemetrexed in newly-diagnosed advanced *EGFR*m-positive NSCLC

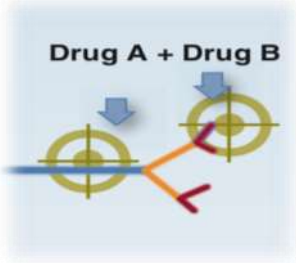


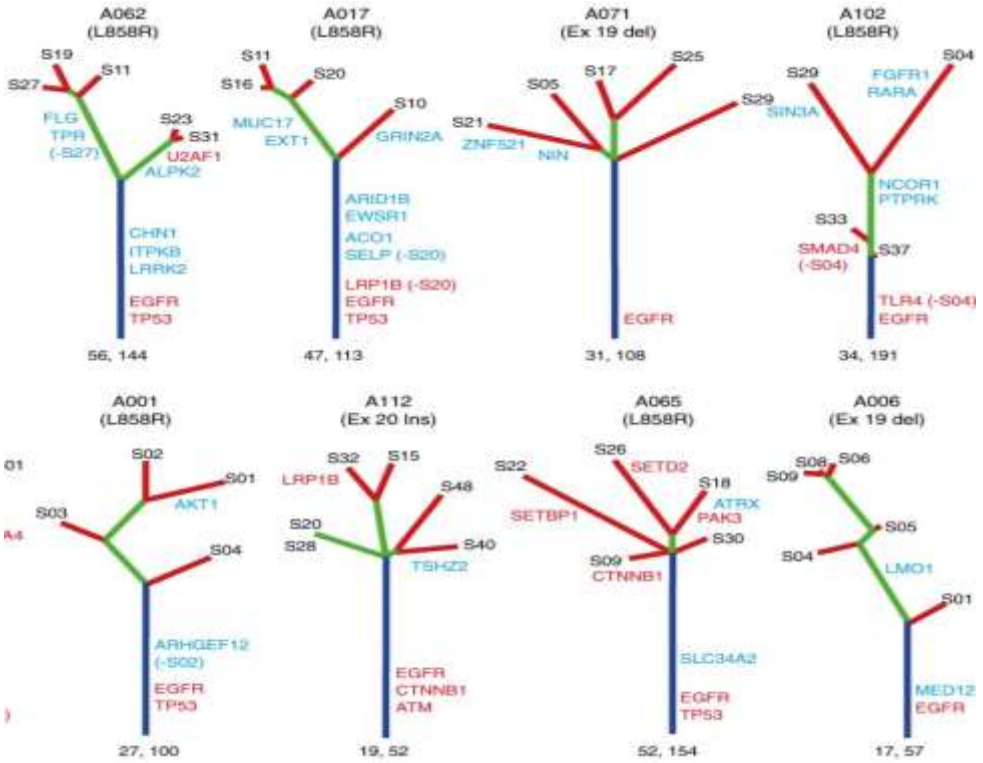
- Osimertinib given at a dose of 80 mg QD during induction and maintenance
- The osimertinib dose can be reduced to 40 mg QD for management of AEs; chemotherapy dose interruption/reduction is to be prioritised over reduction/interruption of osimertinib
- Randomisation will be stratified by race, WHO PS (0 vs 1), and tissue *EGFR* mutation test at enrolment
- Planned to involve approximately 248 sites in 27 countries

Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death on a subsequent treatment; QD, once daily; STx, subsequent treatment; vs, versus; WHO, World Health Organization

Understading how to target the clonal evolution

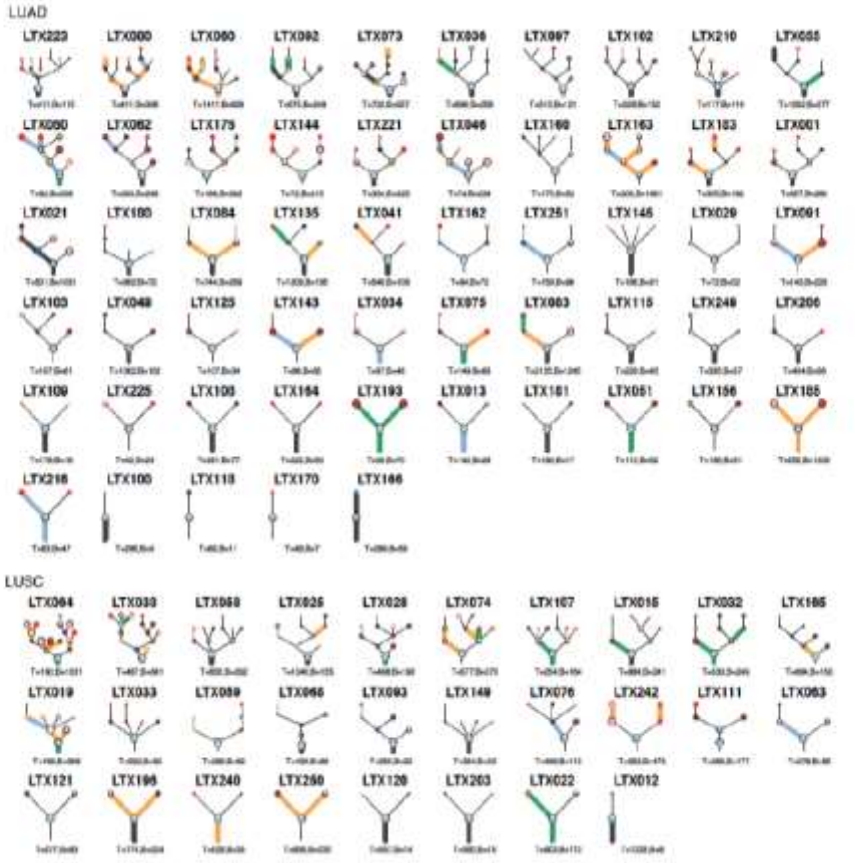






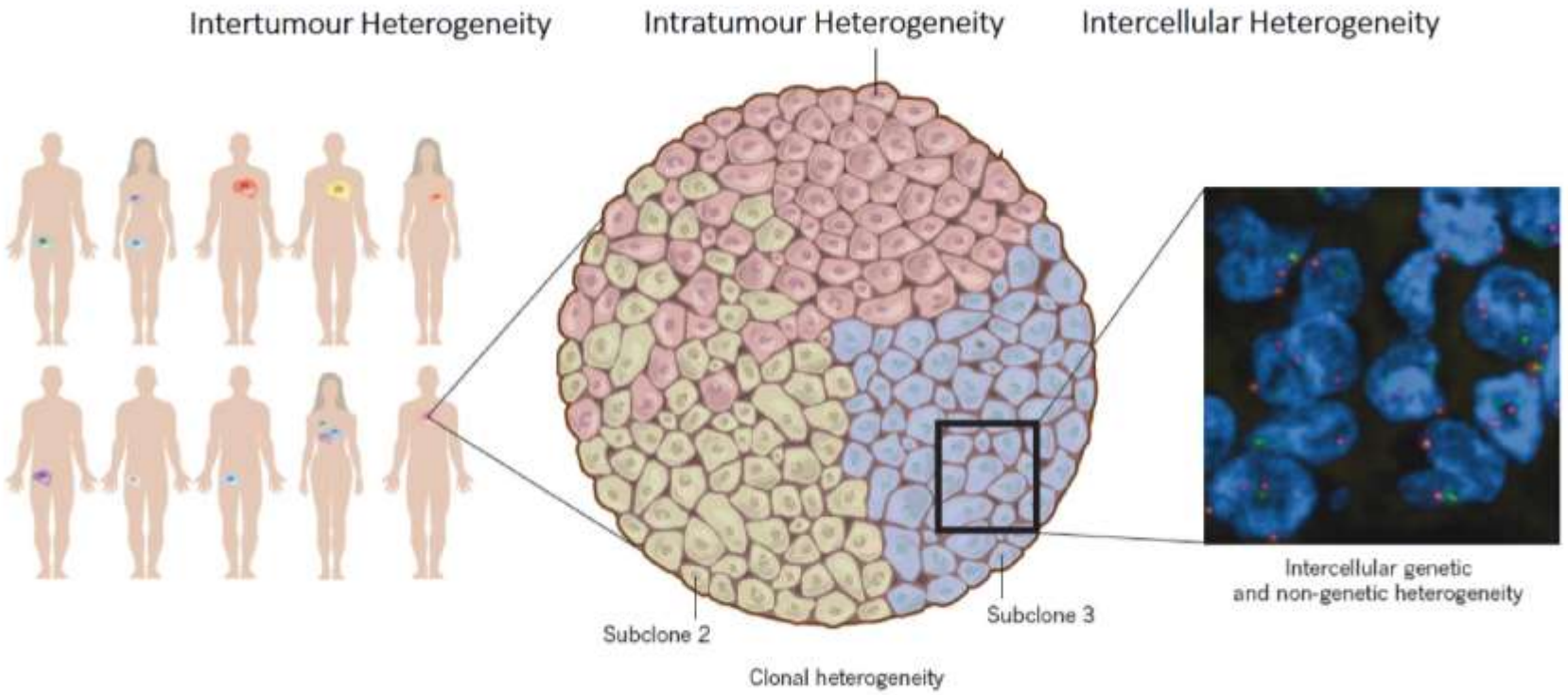
100 Patients with Lung Cancer: 100 different evolutionary Cancer Histories

Swanton, ESMO19



Implications for Therapy and Outcome

Swanton, ESMO19



- Intervene earlier in the disease course when Diversity is low to achieve cures?

Burrell et al. Nature (2013)