Novedades y Claves en Cáncer de Pulmón 2021

Biomarcadores

Paloma Martín Martorell

Hospital Clínico Universitario de Valencia

Organizado por:

GECP lung cancer research

A TRATAR…

NSCLC

- TMB and advanced NSCLC
  - TMB and B-FAST (Diadzuszko R, ESMO 2021)
  - TMB in 9LA (Paz Ares L, ESMO 2021)??
  - TMB adjusted to tumoral load (Nie W, WCLC 2021)

SCLC

- HLA genotyping in CASPIAN (Garassino M, WCLC 2021)

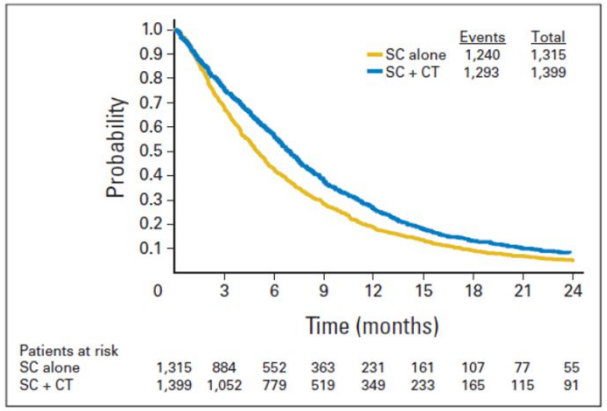
Molecular subgroups

- Ex 20 EGFR

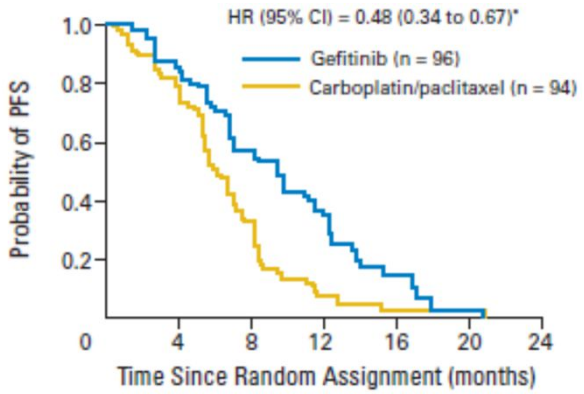
Biomarker: definition

Biomarker: “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” (National Institute of Health Biomarkers Definitions Working Group)

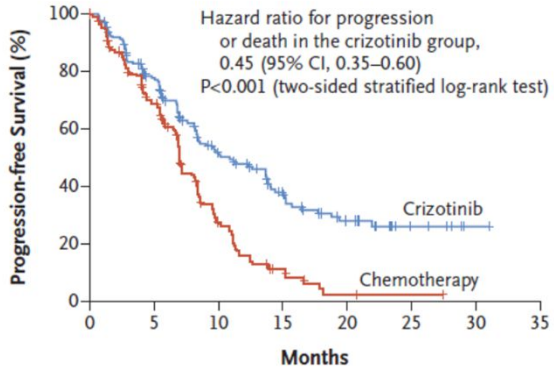
NSCLC – TMB as a biomarker



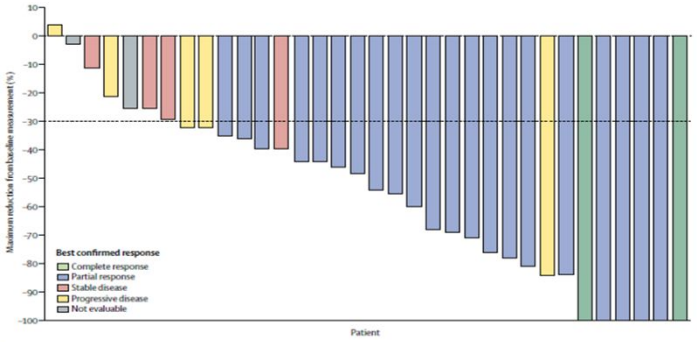
CHEMOTHERAPY



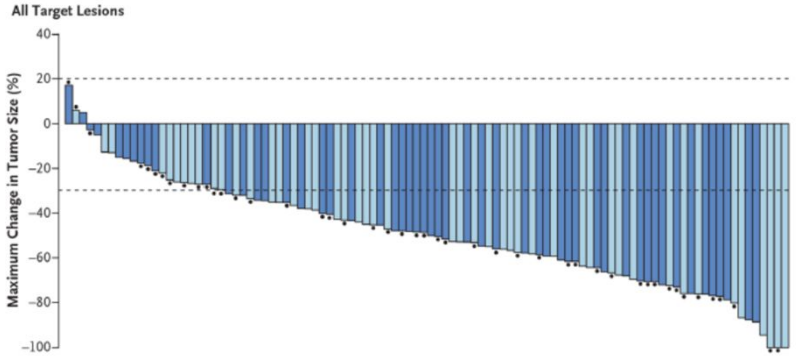
EGFR



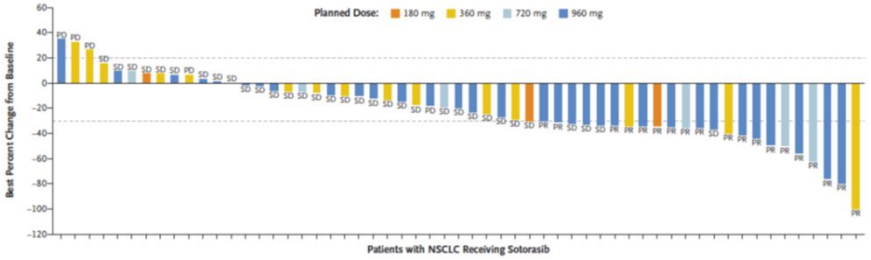
ALK



BRAF



RET



KRAS

Burdett JCO 2008, Fukuoka J Clin Oncol. 2011, Solomon NEJM 2014, Planchard Lancet 2017, Drilon NEJM 2020, Skoulidis NEJM 2021

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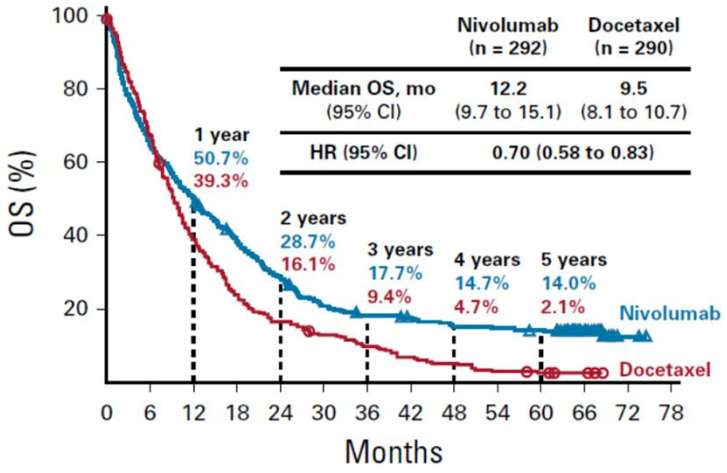
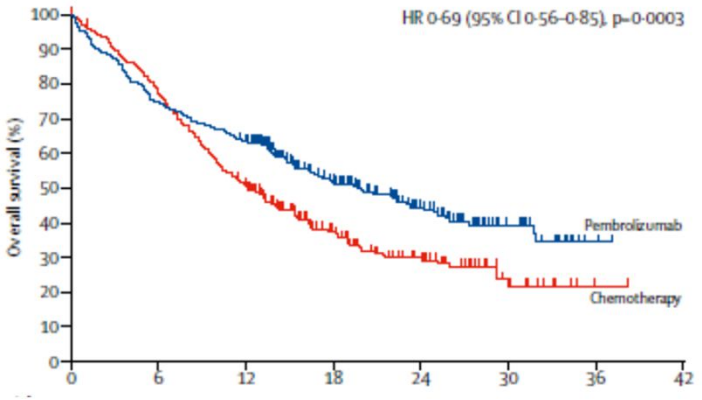
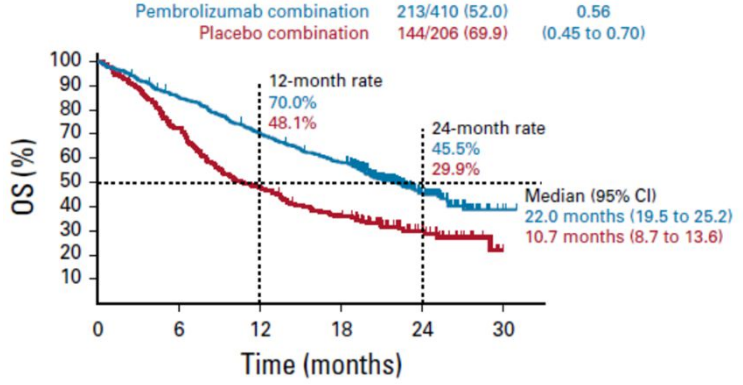


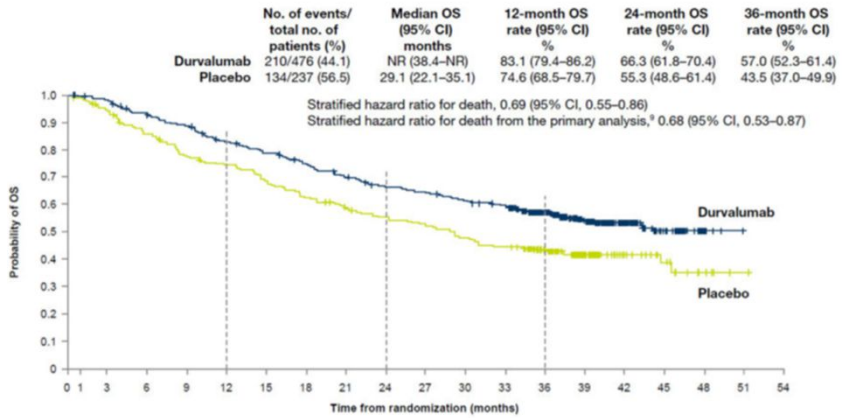
2nd L



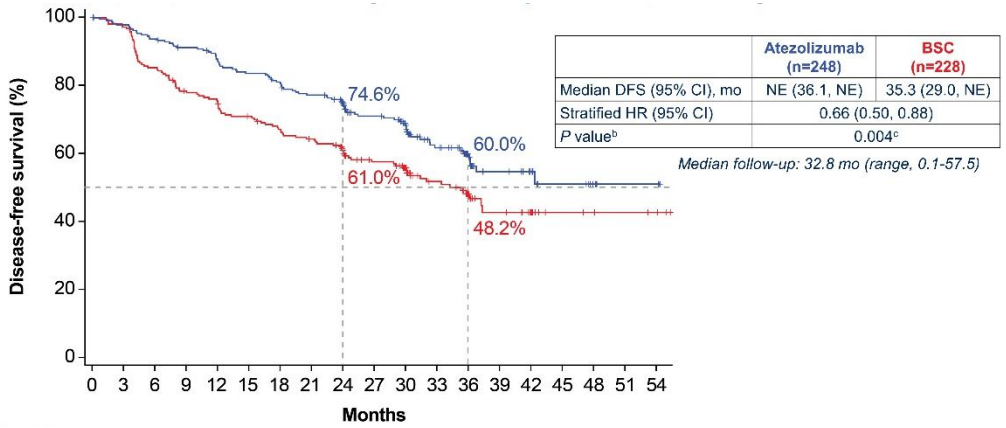
1st L Mol. selected



1st L CT/IO combination



Stage III CT/RT maintenance



Adjuvant treatment

Borghaei NEJM 2021, Mok Lancet 2019, Gadgeel JCO 2020, Gray JTO 2020, Provencio Wakelee

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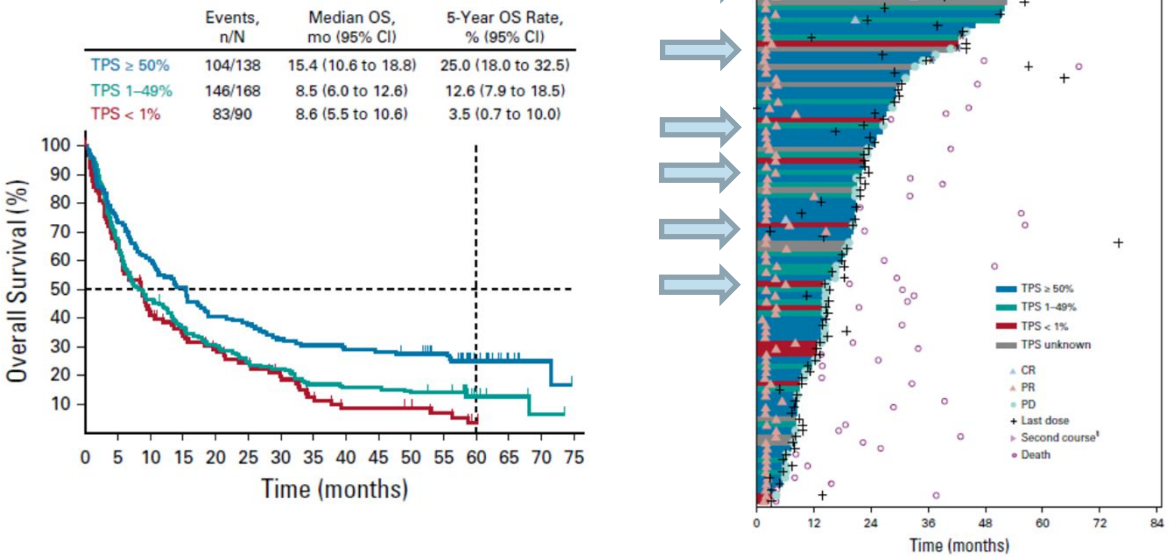
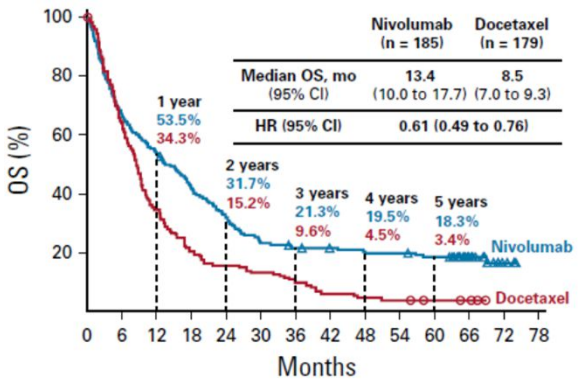
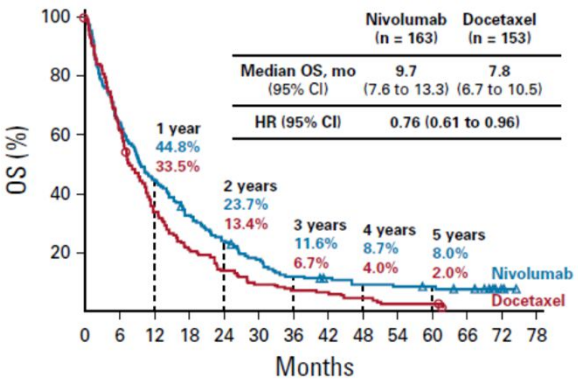


KEYNOTE 001



PD-L1 ≥1 %



PD-L1 <1 %

CHECKMATE 057

Garon JCO 2019, Borghaei JCO 2021.

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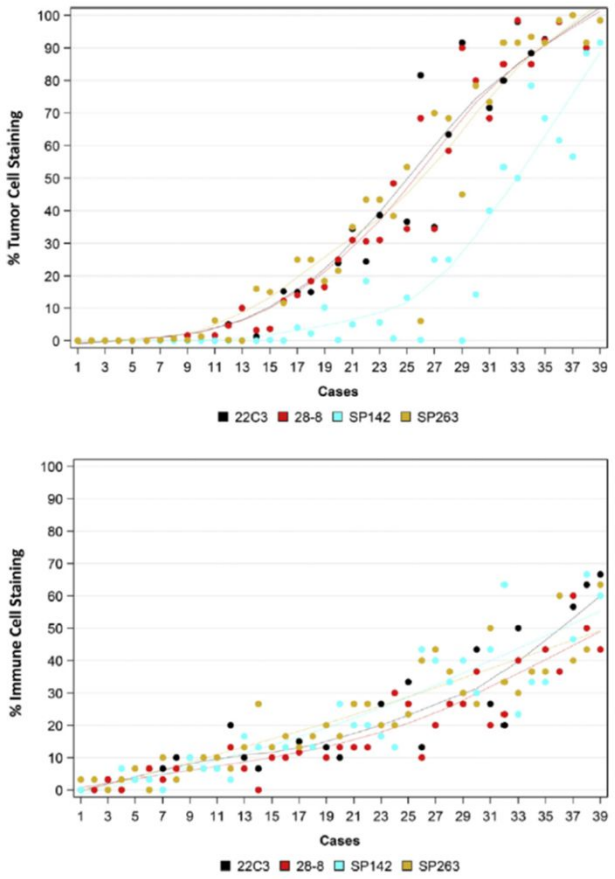

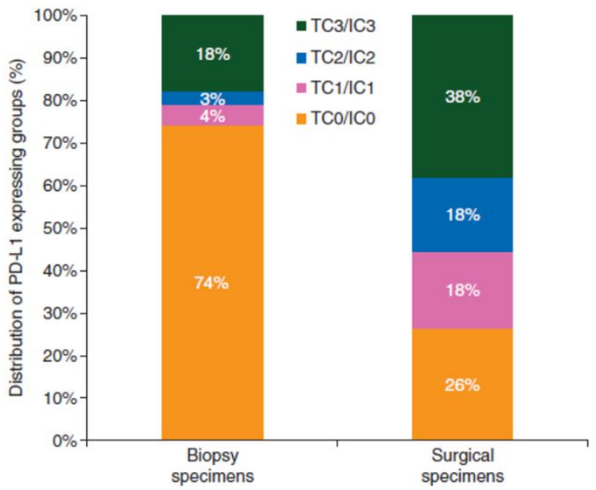

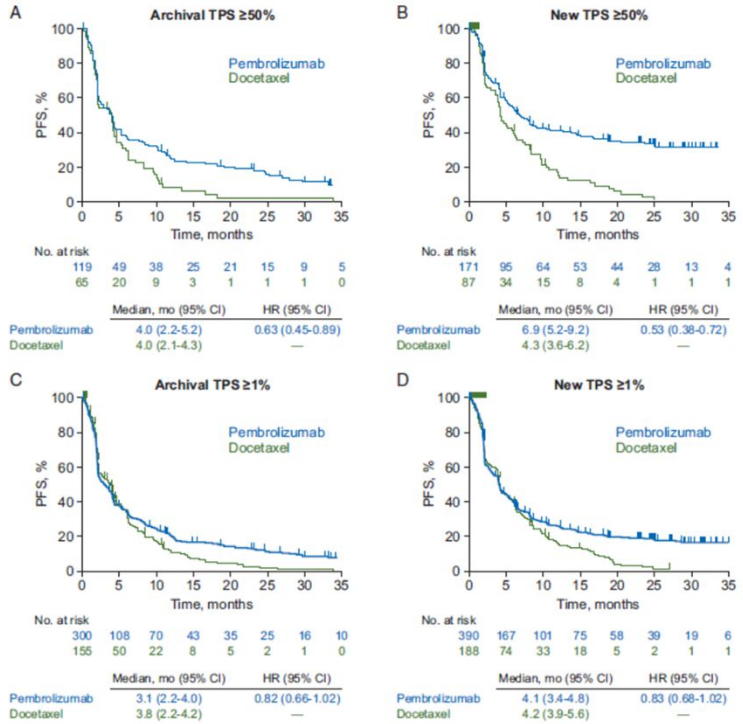

- **Amount of tissue and representability**
- **Archival vs new biopsy**
- **Expression variability according to stage**
- **Tumor staining vs tumor and ME staining**
- **Dynamic changes to previous therapy**

Hirsch JTO 2017, Illie Ann Oncol 2016, Herbst Ann Oncol 2019

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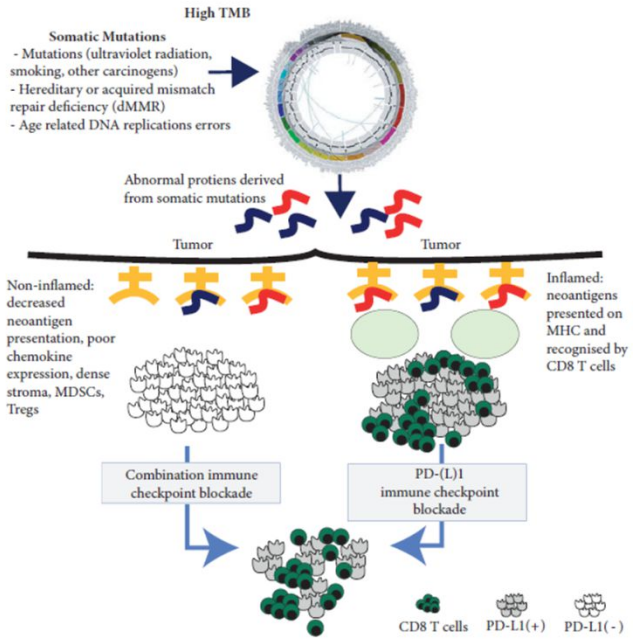
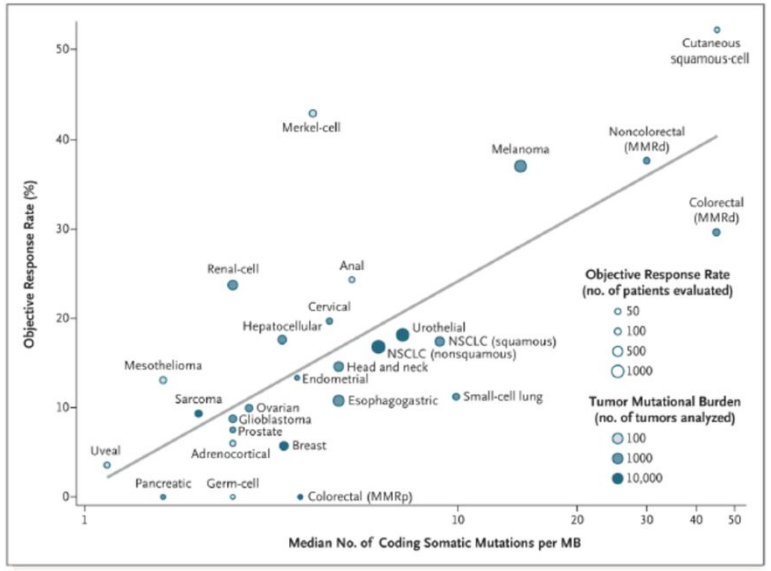
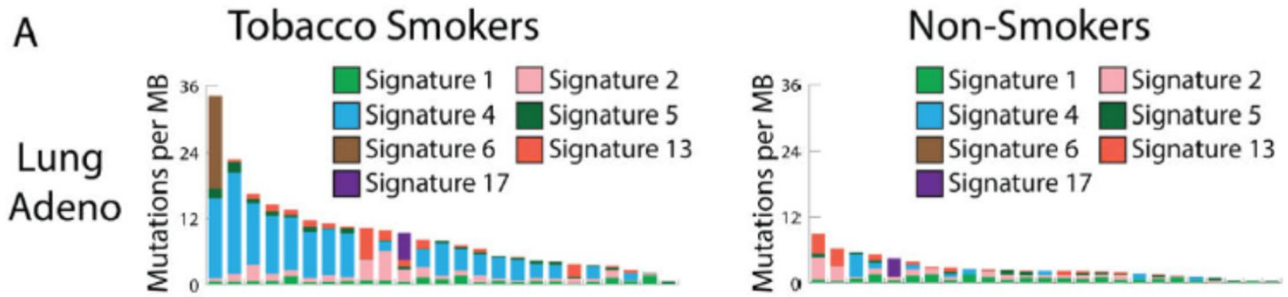
Tumor immunogenicity and TMB

Not all are created alike…

Tumor mutation may arise as a result of DNA damage from exogenous factors (tobacco smoke, ultraviolet light, DNA-damaging therapies), or from defects in DNA repairing machinery (MMR, homologous recombinantion repair, base excision repair)







Chan Ann Oncol 2019, Yarchoan NEJM 2017

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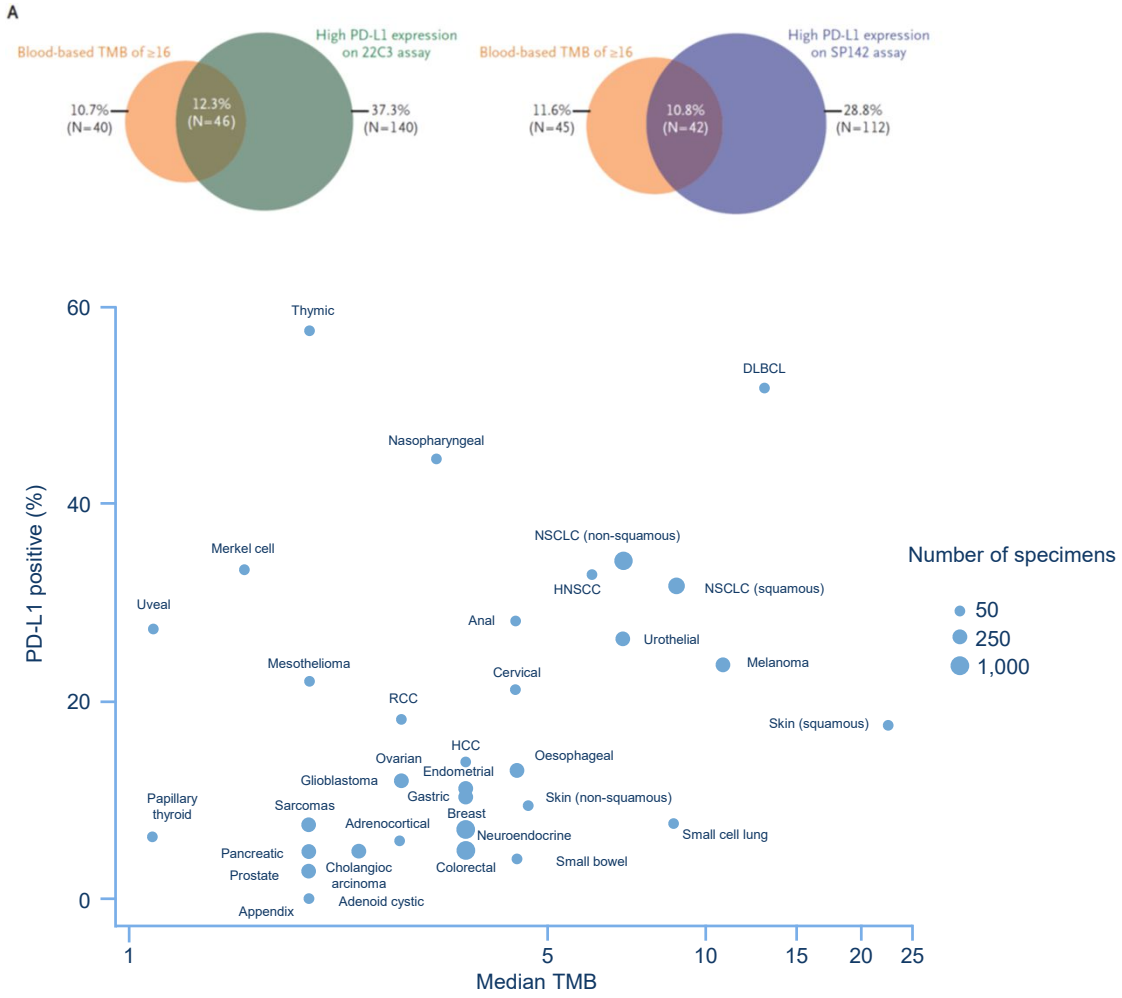
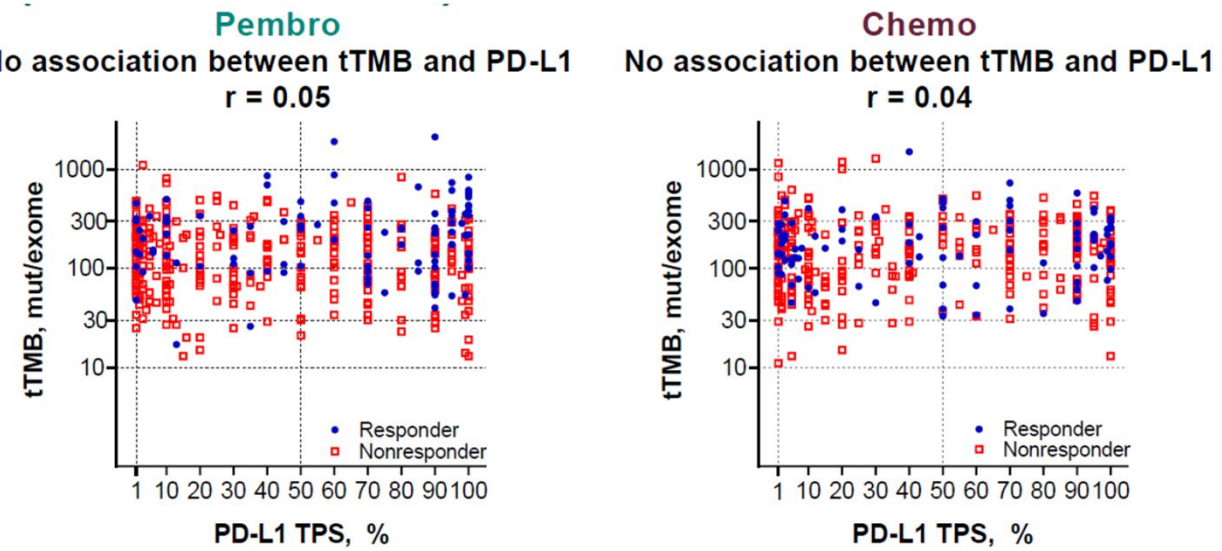
TMB and PD-L1 association





KEYNOTE 042

Herbst NEJM 2020, Herbst ESMO 2019, Yarchoan JCI Insight 2019

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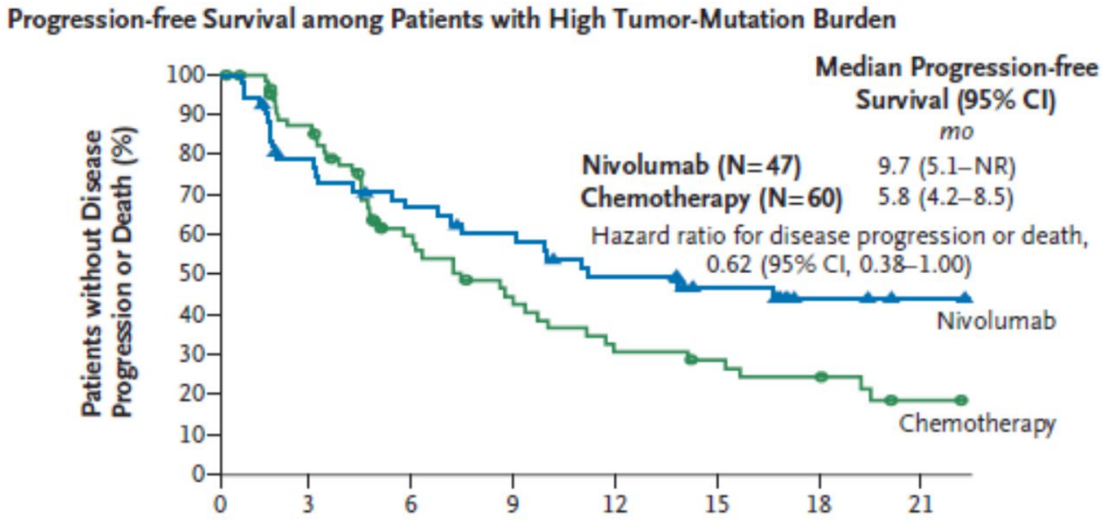
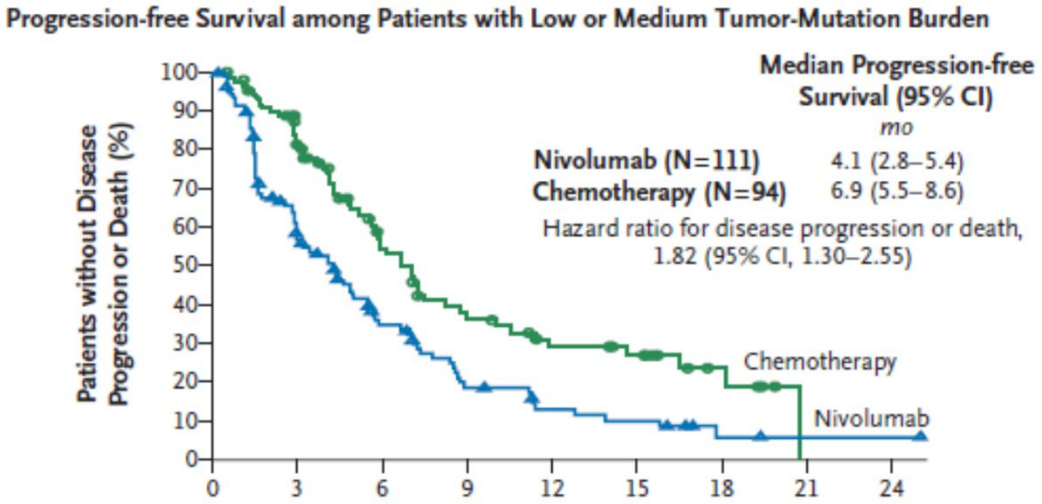
TMB predictive value in IO monotherapy

CHECKMATE 026





Carbone NEJM 2017.

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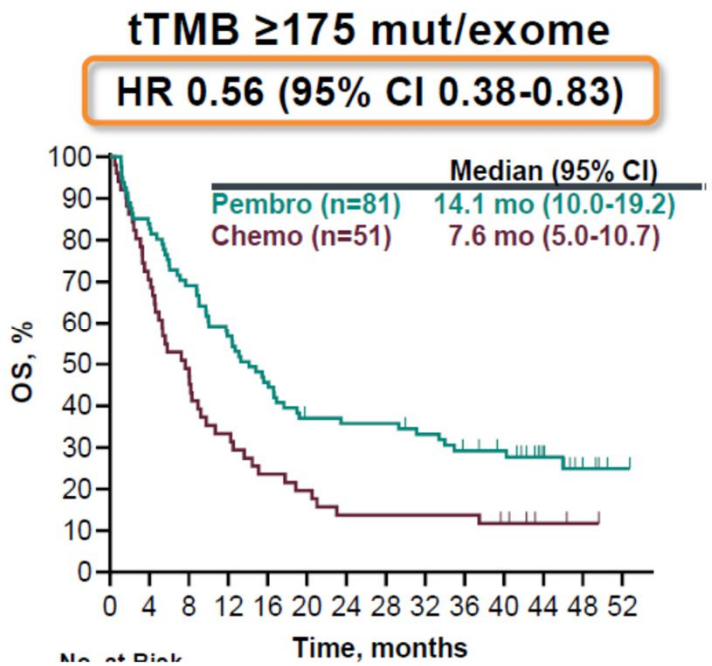
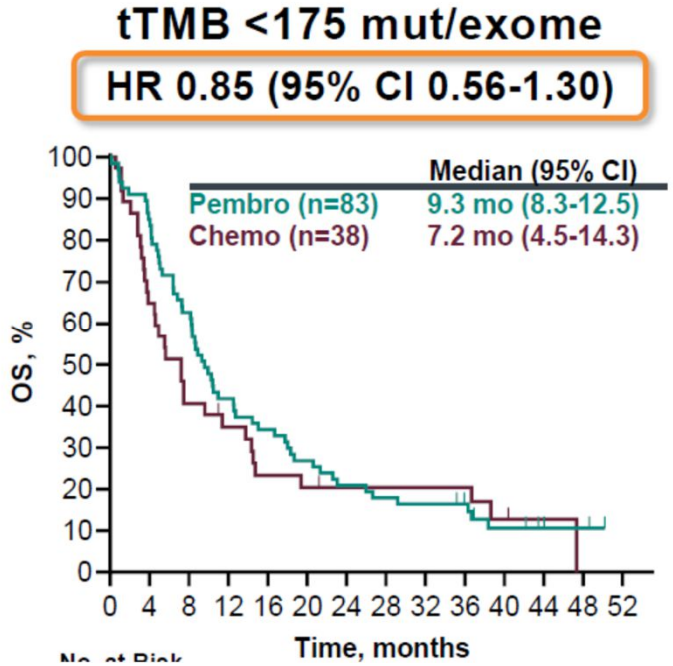
TMB: predictive value monotherapy IO

KEYNOTE 010 and KEYNOTE 042





Herbst, ESMO 2019.

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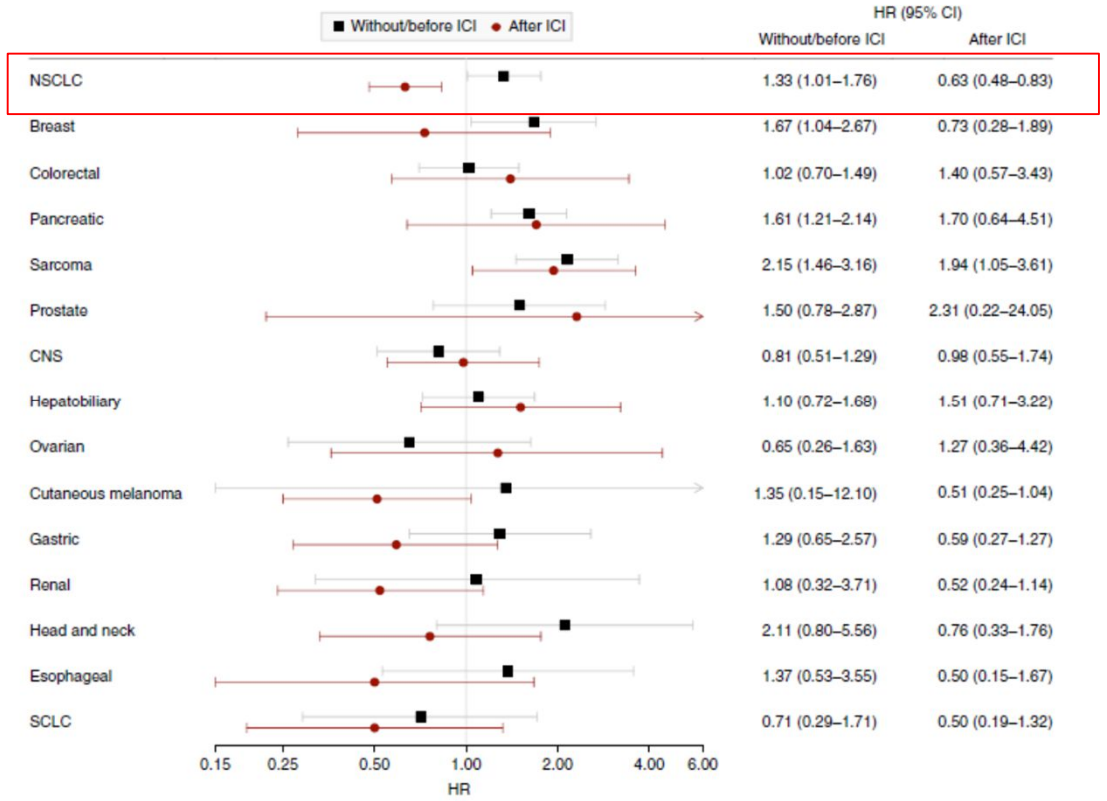
TMB: predictive vs prognostic



N= 2.084 pts, 20%

High TMB could:

Increase the likelihood of mutagenic drivers or resistance mutations

Increase the intratumoral heterogeneity under selective pressure

Represent chromosomal instability

Valero Nat Gene 2021

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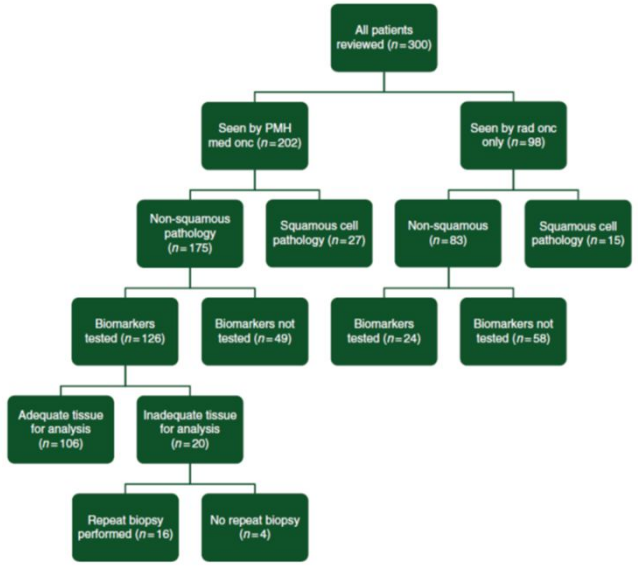
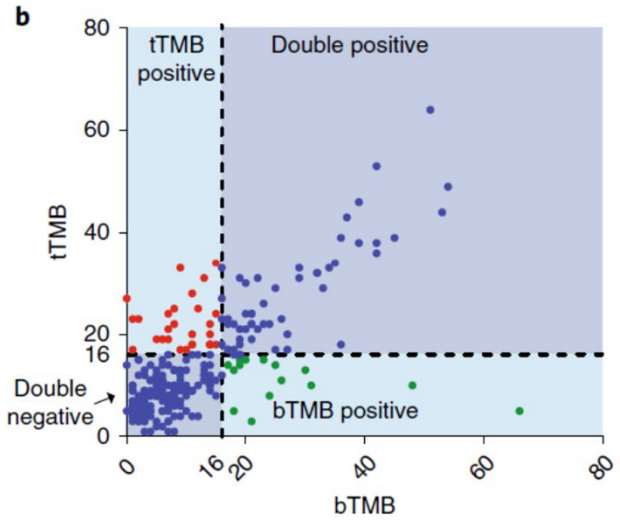
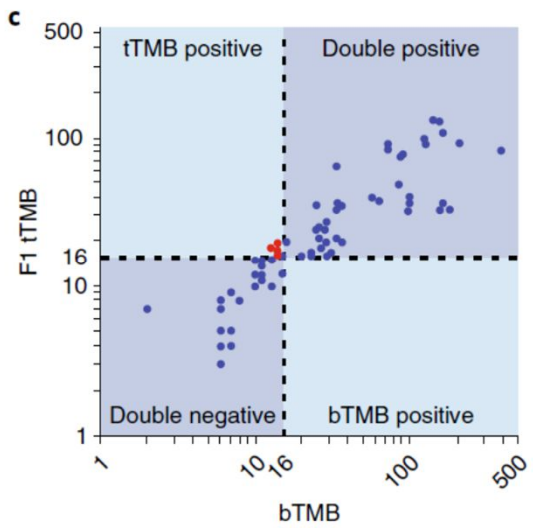
tTMB vs bTMB

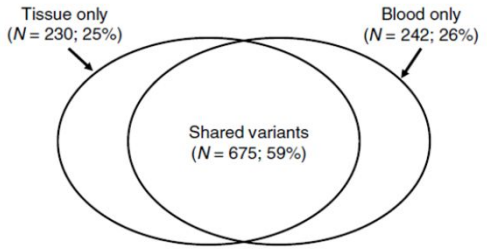
OAK and POPLAR



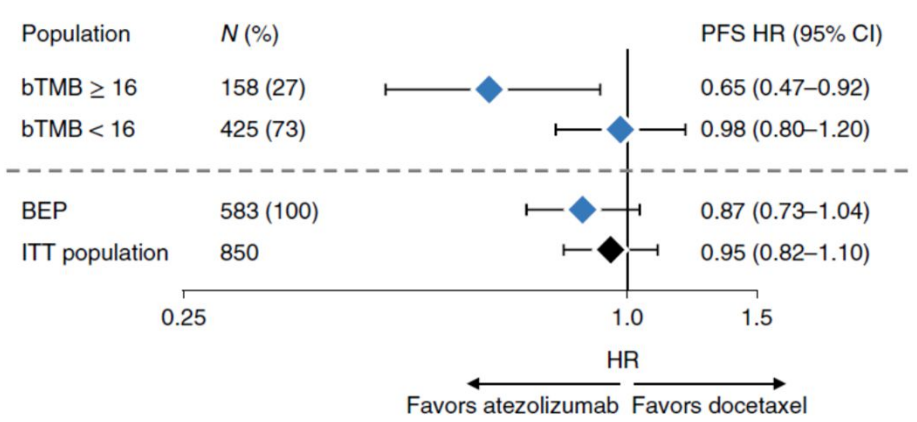




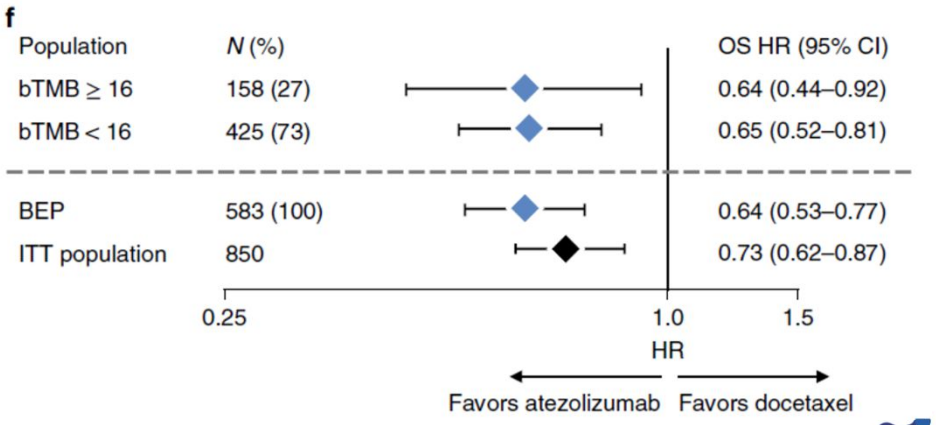
bTMB	PPA (%)	NPA (%)
≥10	100	100
≥11	94.6	92.3
≥12	89.1	92.9
≥13	94	84.2
≥14	90	89.5
≥15	85.7	90
≥16	89.1	100
≥17	90.2	89.3
≥18	92.1	83.9
≥19	94.4	81.8
≥20	97.1	82.4



PFS



OS



Lim C Ann Oncol 2015, Gandara Nat Med 2018

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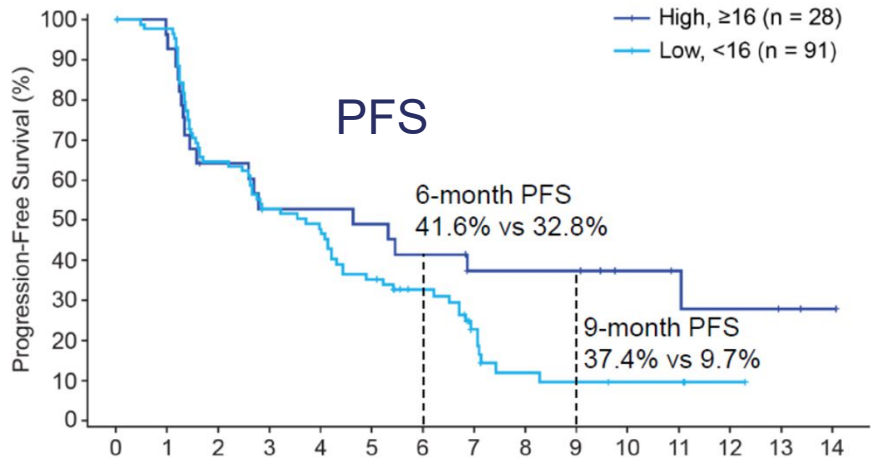
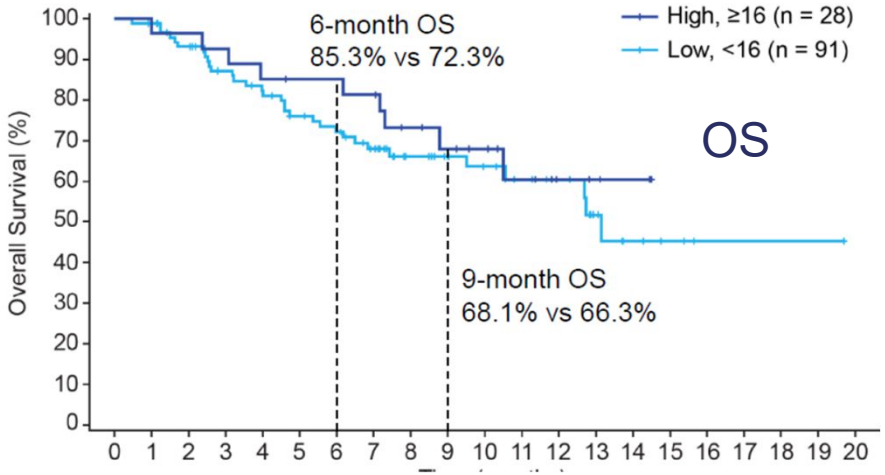
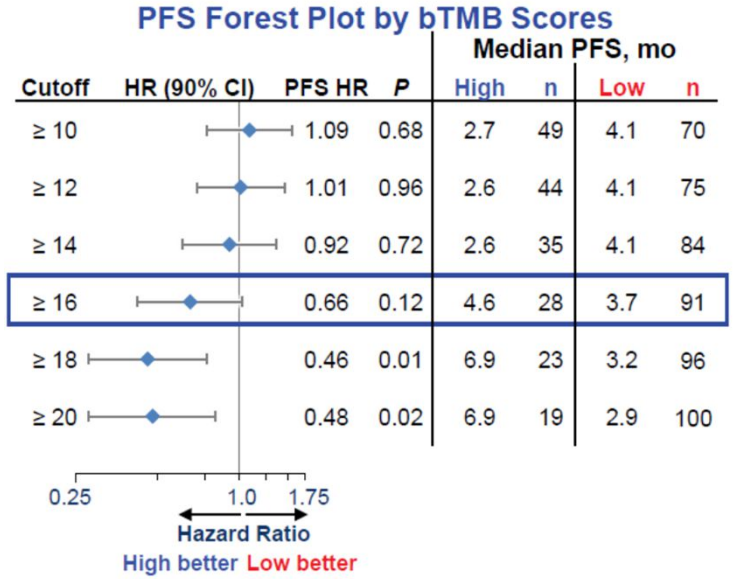
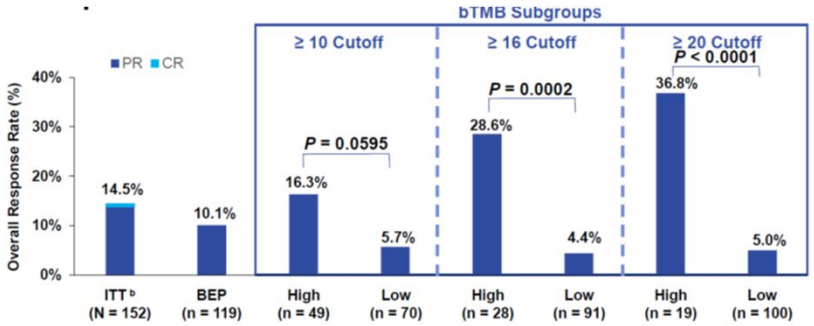




B-F1RST





BEP: 78 % (vs aprox. 40-42 % in tTMB in previous studies)

Kim ESMO 2018, Socinsky ESMO 2019

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B-FAST: prospective validation of bTMB as a biomarker (ESMO 2021)

2021 ESMO congress

Atezolizumab vs Platinum-Based Chemotherapy in Blood-Based Tumour Mutational Burden–Positive NSCLC: Results of the Blood First Assay Screening Trial (BFAST) Phase 3 Cohort C

Rafal Dziadziuszko,[1] Solange Peters,[2] Shirish M. Gadgeel,[3] Michael Mathisen,[4] Sarah M. Shagan,[4] Enriqueta Felip,[5] Alessandro Morabito,[6] Parneet Cheema,[7] Manuel Cobo Dols, [8] Zoran Andric,[9] Carlos H. Barrios,[10] Masafumi Yamaguchi,[11] Eric Dansin,[12] Pongwut Danchaivijitr,[13] Melissa Johnson,[14] Silvia Novello,[15] David R. Gandara, [16] Erica Schleifman,[4] Jin Wang,[4] Tony Mok[17]

Primary objective: PFS as assessed by the investigator in bTMB ≥16 mut/MB

BFAST Cohort C study design

Key eligibility criteria
- Unresectable, stage IIIB or IV NSCLC
- Untreated
- ECOG PS 0 or 1
- bTMB+ (bTMB ≥10[a] cutoff)
- Absence of *EGFR/ALK* genetic alteration

R 1:1

n=472[b]

Atezo 1200 mg q3w until PD or loss of clinical benefit

Platinum-based chemo q3w x 4 or 6 cycles (maintenance pemetrexed allowed for nsq NSCLC)

Stratification factors
- **ECOG PS** (0 vs 1)
- **Histology** (sq vs nsq)
- **Tissue availability**[c] (yes vs no)
- **bTMB cutoff status** (moderate [10-15] vs high [≥16])

Primary endpoints
- Investigator-assessed PFS (RECIST 1.1) in bTMB ≥16[d]

Key secondary endpoints
- OS in bTMB ≥10[a] (ITT) and bTMB ≥16[e]
- Investigator-assessed PFS (RECIST 1.1) in ITT[e]
- Confirmed investigator-assessed ORR and DOR

Dziadziuszko, ESMO 2021

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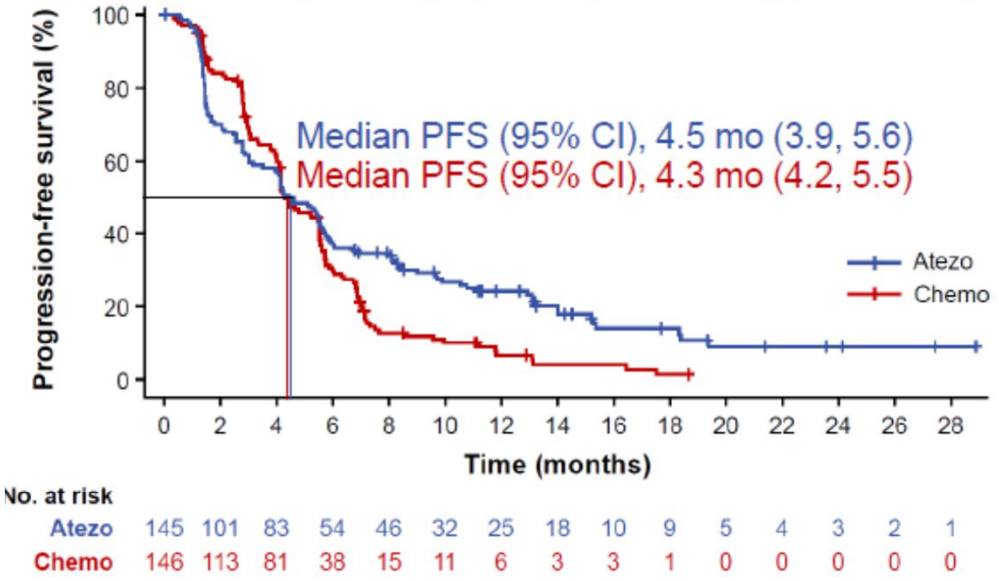
B-FAST (ESMO 2021)

PFS and OS in the bTMB ≥16 population

	Atezo (n=145)	Chemo (n=146)
PFS events, n (%)	119 (82)	124 (85)
Stratified HR (95% CI)	0.77 (0.59, 1.00); *P*=0.053	

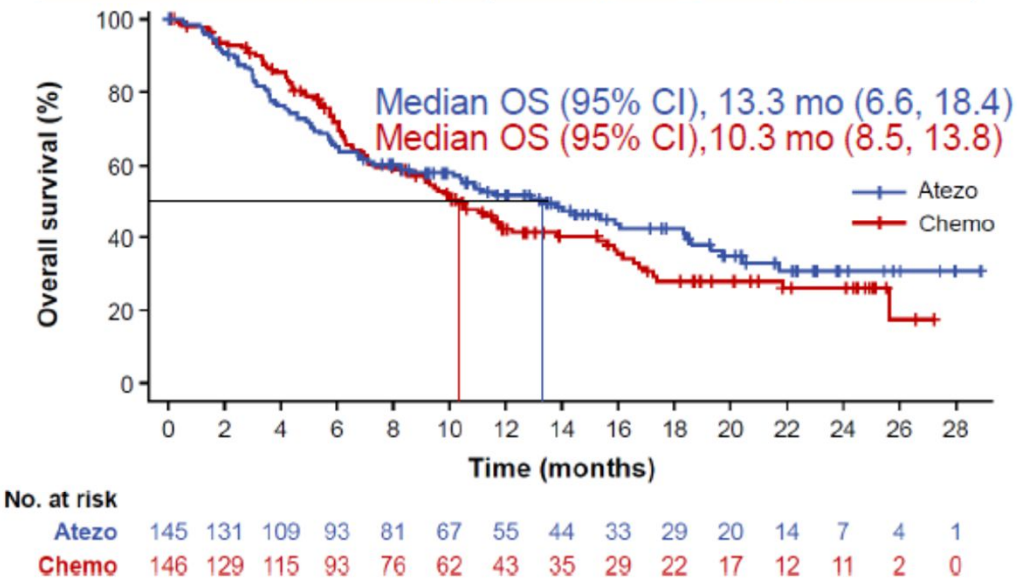


No. at risk

Atezo	145	101	83	54	46	32	25	18	10	9	5	4	3	2	1
Chemo	146	113	81	38	15	11	6	3	3	1	0	0	0	0	0

Although progression rates were initially higher in the atezo vs chemo arm, PFS benefit was seen with atezo after 4 months

	Atezo (n=145)	Chemo (n=146)
OS events, n (%)	82 (57)	88 (60)
Stratified HR (95% CI)	0.87 (0.64, 1.17); *P*=0.35[a]	



No. at risk

Atezo	145	131	109	93	81	67	55	44	33	29	20	14	7	4	1
Chemo	146	129	115	93	76	62	43	35	29	22	17	12	11	2	0

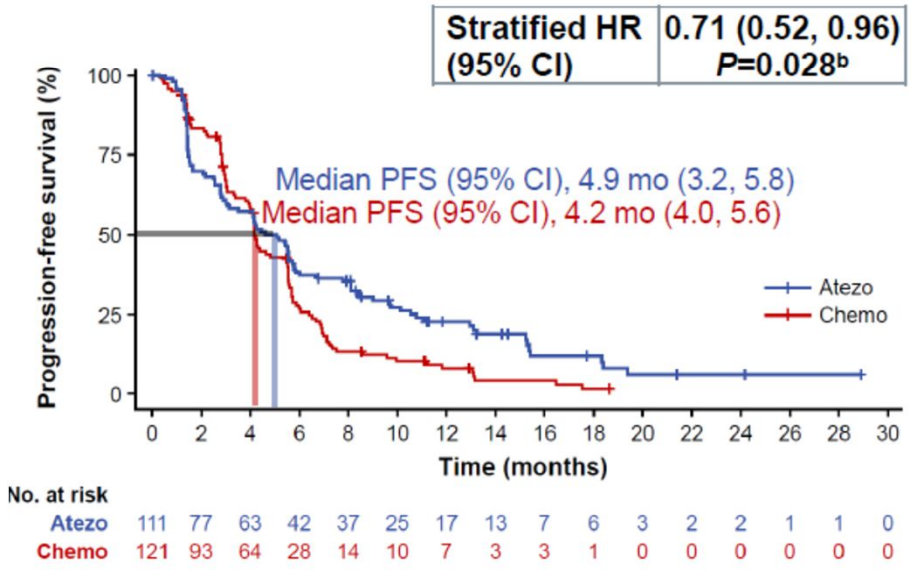
Confirmed ORR for bTMB ≥16 was 25.5% (95% CI: 18.7, 33.4) for atezo vs 17.8% (12.0, 25.0) for chemo

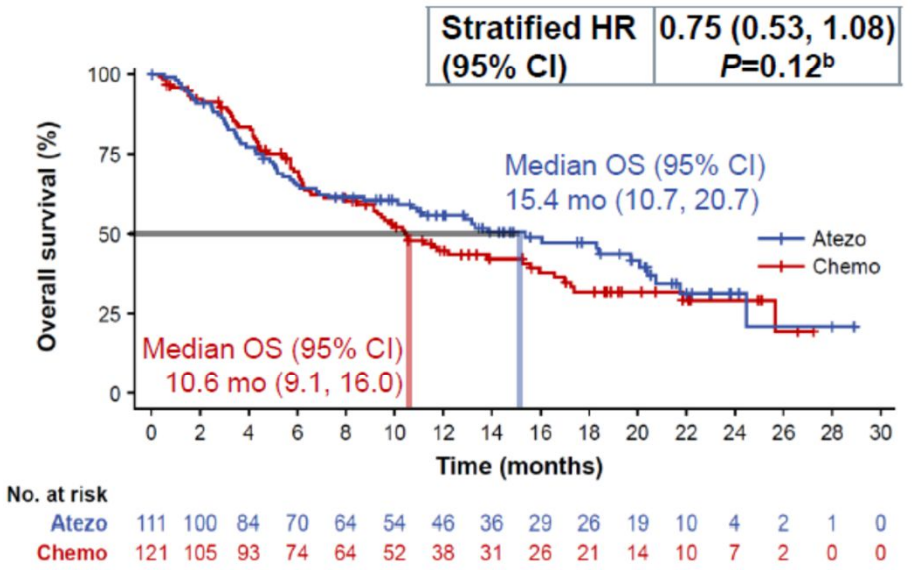
Dziadziuszko, ESMO 2021

GECP lung cancer research

B-FAST (ESMO 2021)

Exploratory analysis of PFS and OS in bTMB ≥13.6 mut/Mb[a] population by FoundationOne Liquid companion diagnostic





- The assays were highly concordant, with PPA (82.9%), PPV (89.4%), NPA (91.5%) and NPV (86.0%)

High concordance with other bTMB assays F1L CDx

Dziadziuszko, ESMO 2021

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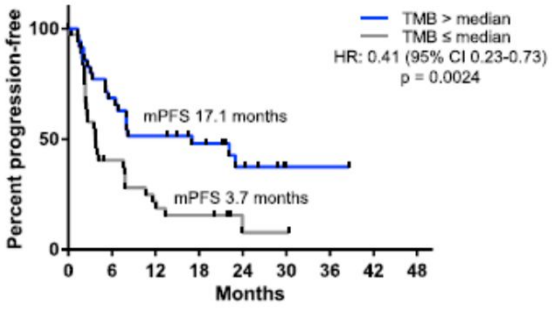
Possible explanations

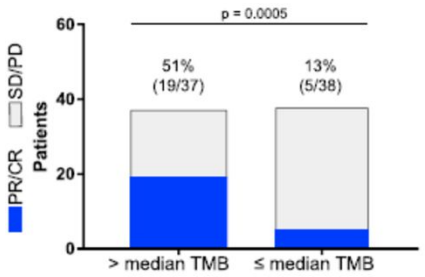
Immune response may depend on….

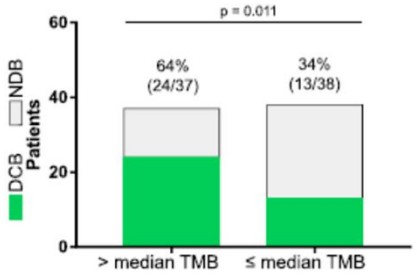
- HLA homozygosity or LOH (Agnanostou)
- CD8+ T cell infiltration
- Clonal composition (Agnanostou)
- SNVs, synonimous vs only non-synonimous mutations, indels, contribution of mutations types and mutational signatures (Samstein, Wang)
- Antigenicity of generated epitopes (Anagnostou, Samstein, Alexandrov)
- Tumor simple purity (Agnastou)
- Tumor mass load (Wei)
- Technique: WES, NGS, TMB limited panels (Samstein, Merino)

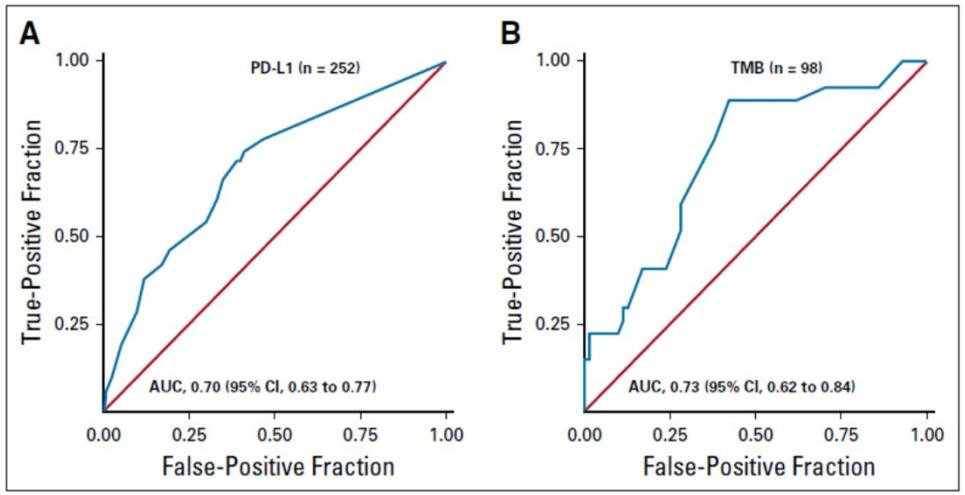
TMB: predictive value CT/IO combinations

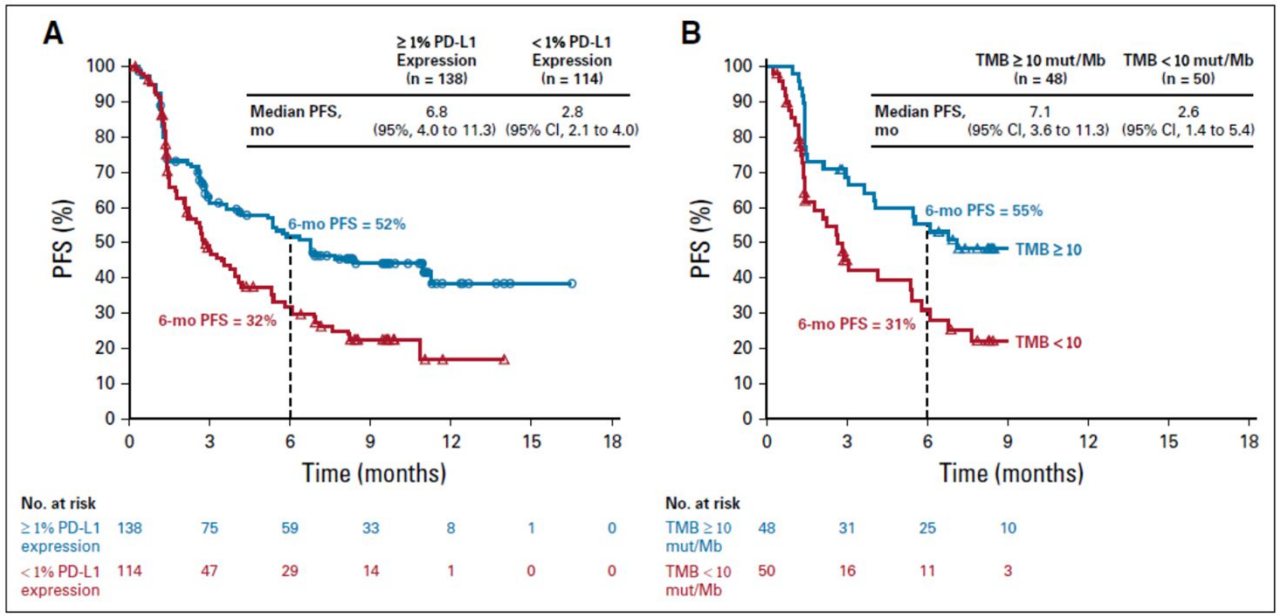
CHECKMATE 012 and CHECKMATE 568











Hellmann Cancer Cell 2018, Ready JCO 2019

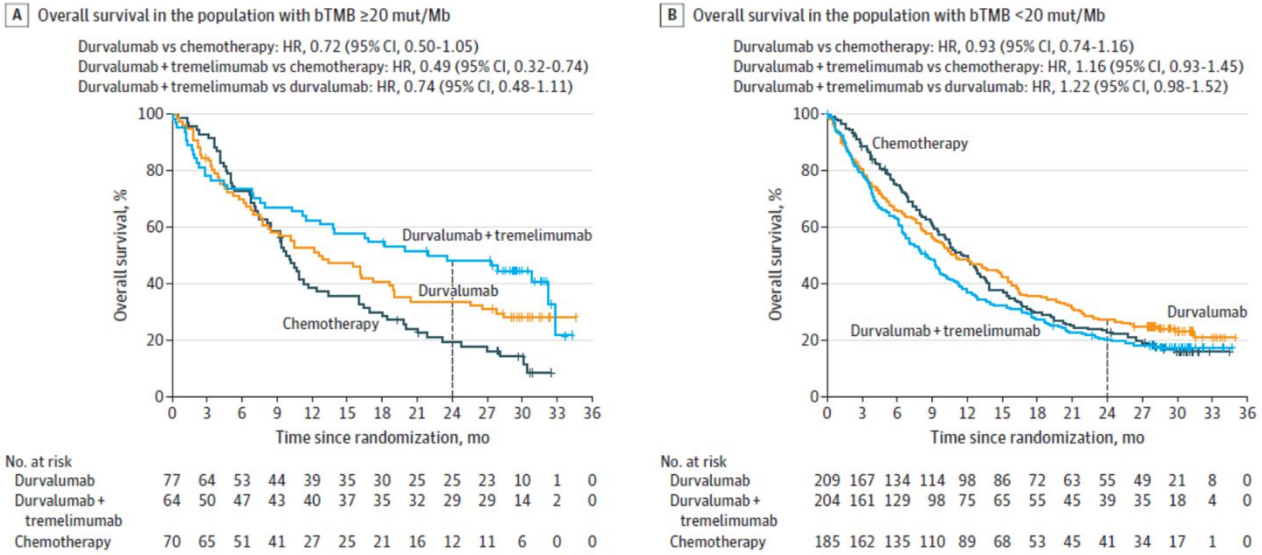
GECP lung cancer research

TMB: predictive value CT/IO combinations

MYSTIC and NEPTUNE

✓ PFS

✗ OS



21 August 2019 07:00 BST

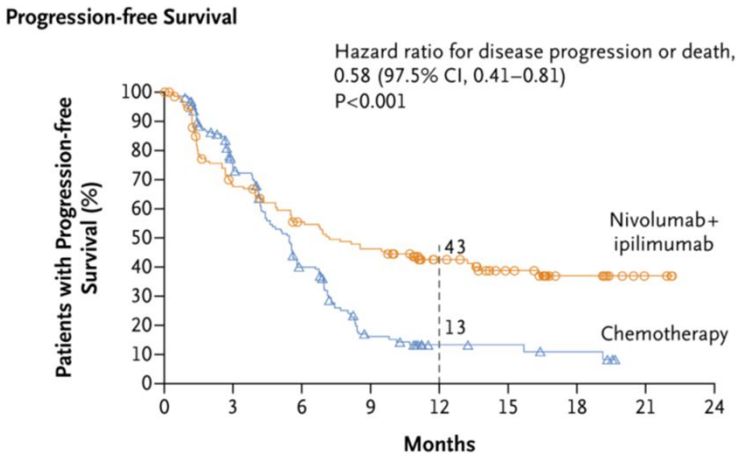
AstraZeneca today announced final overall survival (OS) results from the Phase III NEPTUNE trial, a randomised, open-label, multi-centre, global trial of *Imfinzi* (durvalumab) in combination with tremelimumab, an anti-CTLA4 antibody, vs. standard-of-care (SoC) platinum-based chemotherapy in previously-untreated Stage IV (metastatic) non-small cell lung cancer (NSCLC) patients. The trial was performed in an all-comers population, and the primary analysis population was patients with a high tumour mutational burden (TMB). TMB is a measurement of the number of mutations within the genome (DNA) of a tumour, and tumours with high levels of TMB may be more visible to the immune system.[1,2]

In the primary analysis population of patients whose blood TMB was 20 or more mutations per megabase (mut/Mb), the combination of *Imfinzi* and tremelimumab did not meet the primary endpoint of improving OS compared to SoC chemotherapy. The safety and tolerability profile for the combination of *Imfinzi* and tremelimumab was consistent with previous trials.

Rizvi JAMA 2020. https://www.astrazeneca.com/media-centre/press-releases/2019/update-on-the-phase-iii-neptune-trial-of-imfinzi-plus-tremelimumab-in-stage-iv-non-small-cell-lung-cancer-21082019.html

Organizado por:
GECP lung cancer research

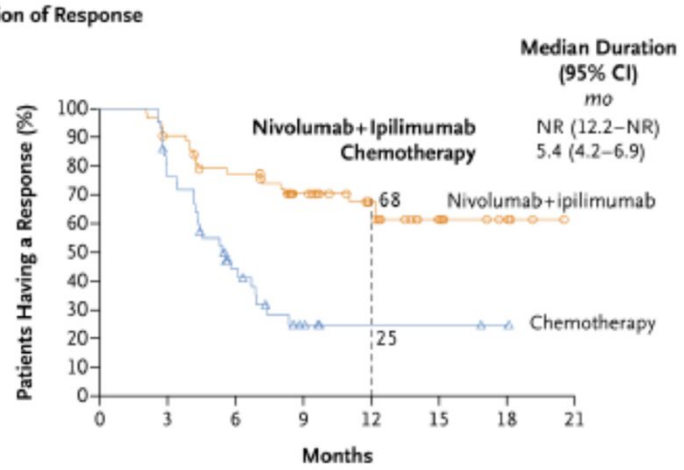
TMB: predictive value CT/IO combinations



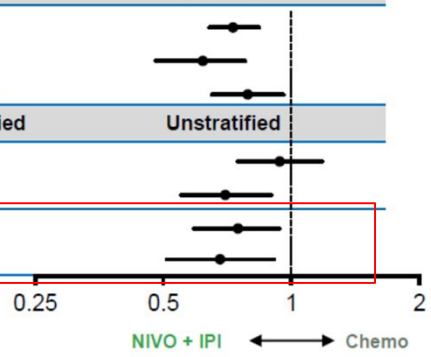
Checkmate 227

✓ PFS

✗ OS



		Median OS, months NIVO + IPI n = 583	Chemo n = 583	HR	HR (95% CI)
Randomized groups				**Stratified**	**Stratified**
PD-L1	All randomized (N = 1166)	17.1	13.9	0.73	
	PD-L1 < 1% (n = 373)	17.2	12.2	0.62	
	PD-L1 ≥ 1% (n = 793)	17.1	14.9	0.79[a]	
Additional exploratory subgroups analyses[b,c]				**Unstratified**	**Unstratified**
PD-L1	1–49% (n = 396)	15.1	15.1	0.94	
	≥ 50% (n = 397)	21.2	14.0	0.70	
TMB[d] (mut/Mb)	low, < 10 (n = 380)	16.2	12.6	0.75	
	high, ≥ 10 (n = 299)	23.0	16.4	0.68	



Hellman NEJM 2018, Hellman NEJM 2019. Peeters ESMO 2019

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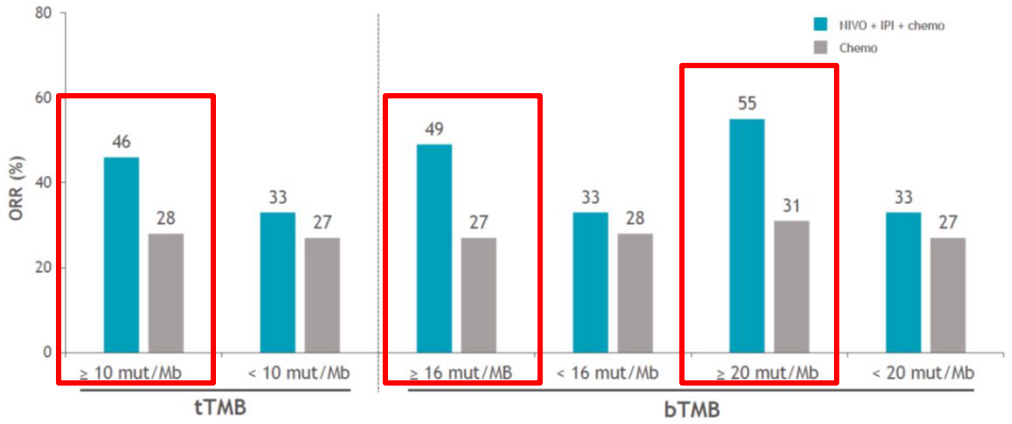
TMB: predictive value CT/IO combinations

9LA (ELCC 2021)

ORR in tTMB and bTMB subgroups



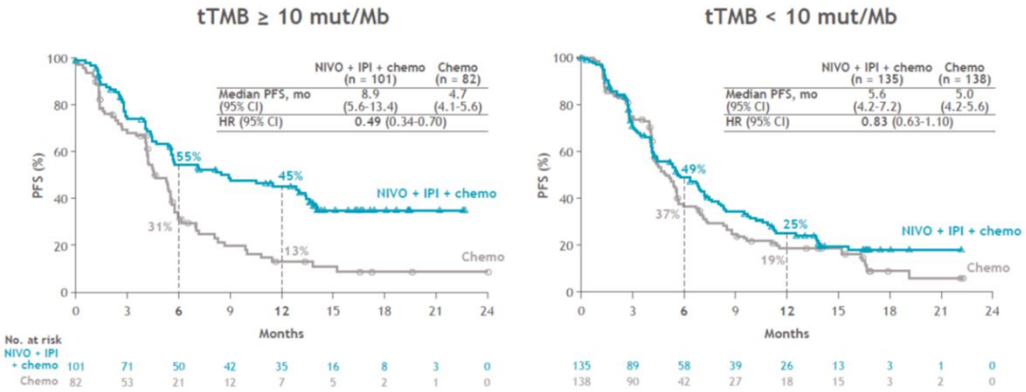
Secondary objective

✓ PFS

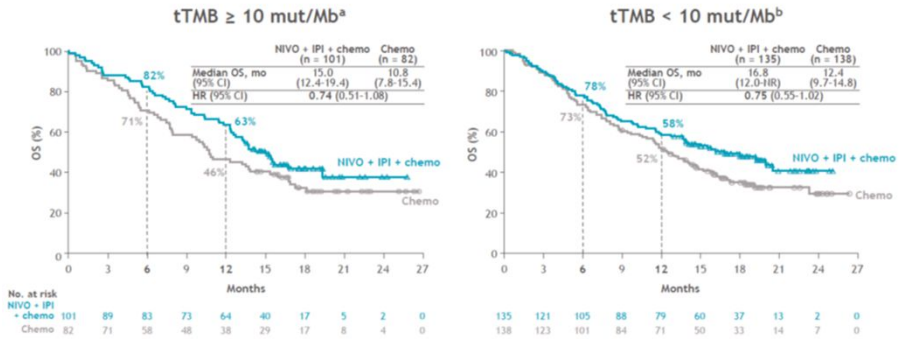
✗ OS

Foundation One CDx

PFS in tTMB subgroups



OS in tTMB subgroups



Paz Ares ELCC 2021

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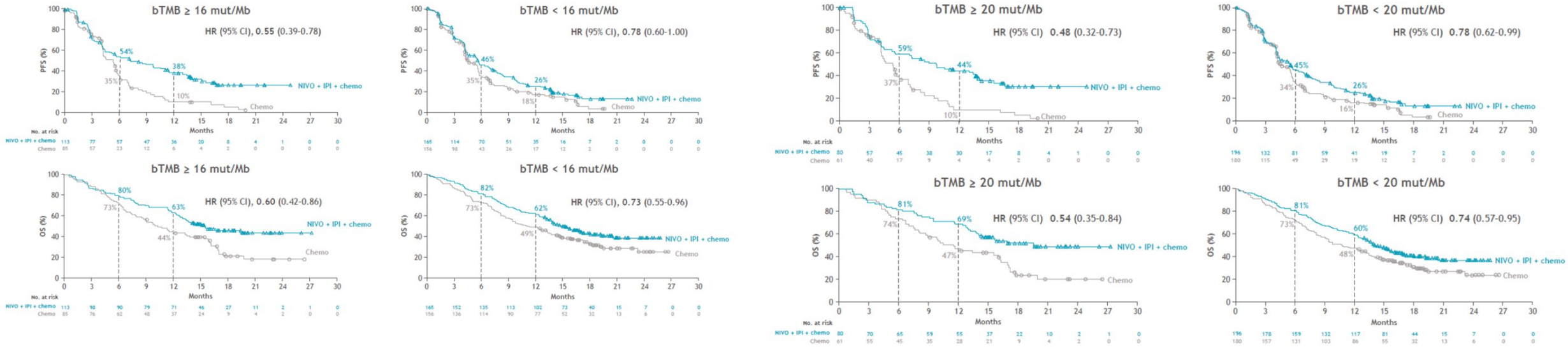
TMB: predictive value CT/IO combinations

9LA (ELCC 2021)

Guardant OMNI



bTMB ≥ 16 mut/MB discriminates w/r to PFS but not OS

bTMB ≥ 20 mut/MB does discriminate for either

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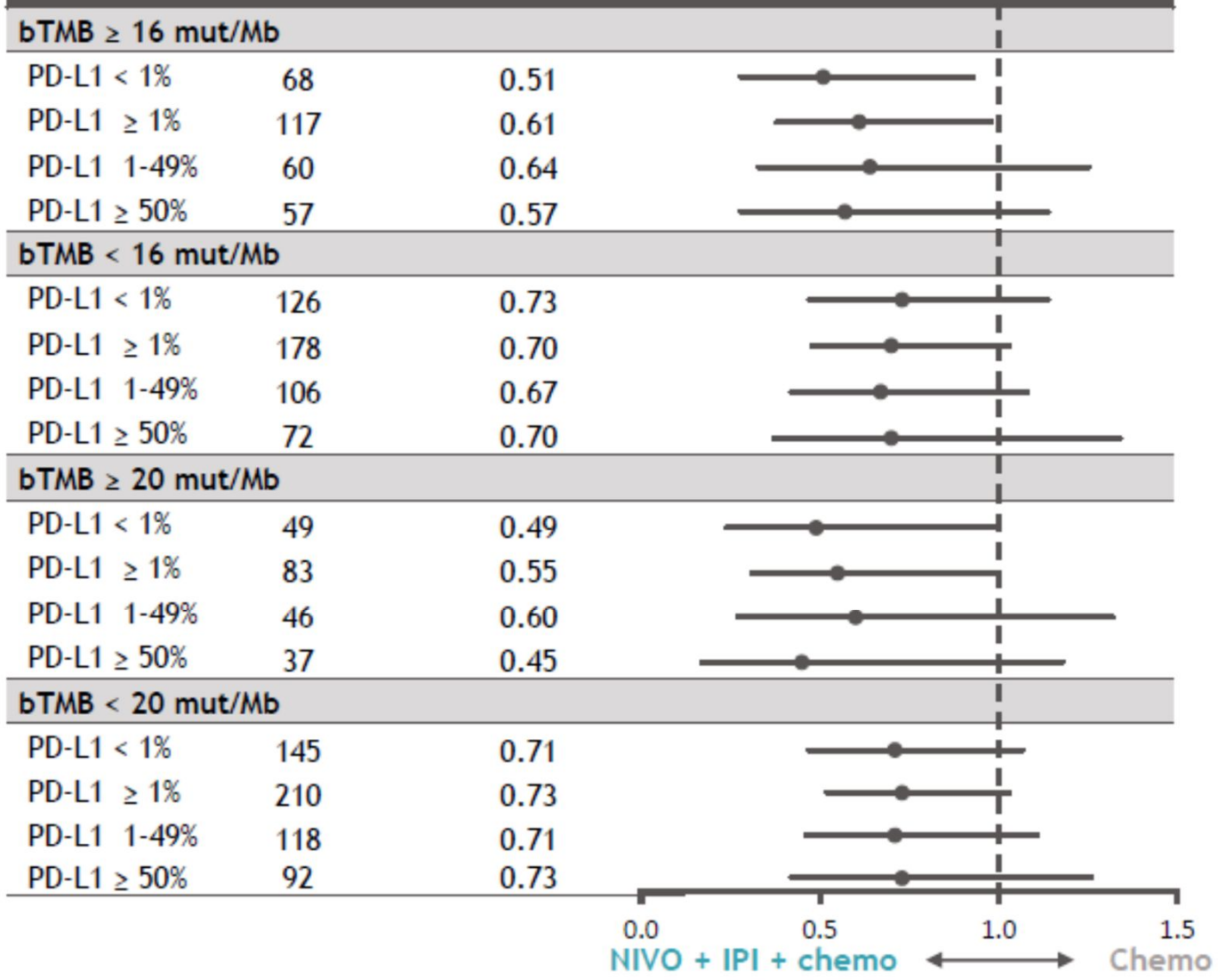
bTMB

mut/Mb	n	Unstratified OS HR	Unstratified OS HR (95% CI)
bTMB ≥ 16 mut/Mb			
PD-L1 < 1%	68	0.51	
PD-L1 ≥ 1%	117	0.61	
PD-L1 1-49%	60	0.64	
PD-L1 ≥ 50%	57	0.57	
bTMB < 16 mut/Mb			
PD-L1 < 1%	126	0.73	
PD-L1 ≥ 1%	178	0.70	
PD-L1 1-49%	106	0.67	
PD-L1 ≥ 50%	72	0.70	
bTMB ≥ 20 mut/Mb			
PD-L1 < 1%	49	0.49	
PD-L1 ≥ 1%	83	0.55	
PD-L1 1-49%	46	0.60	
PD-L1 ≥ 50%	37	0.45	
bTMB < 20 mut/Mb			
PD-L1 < 1%	145	0.71	
PD-L1 ≥ 1%	210	0.73	
PD-L1 1-49%	118	0.71	
PD-L1 ≥ 50%	92	0.73	



Paz Ares ELCC 2021

With so many uncertainties…

Metanalysis!

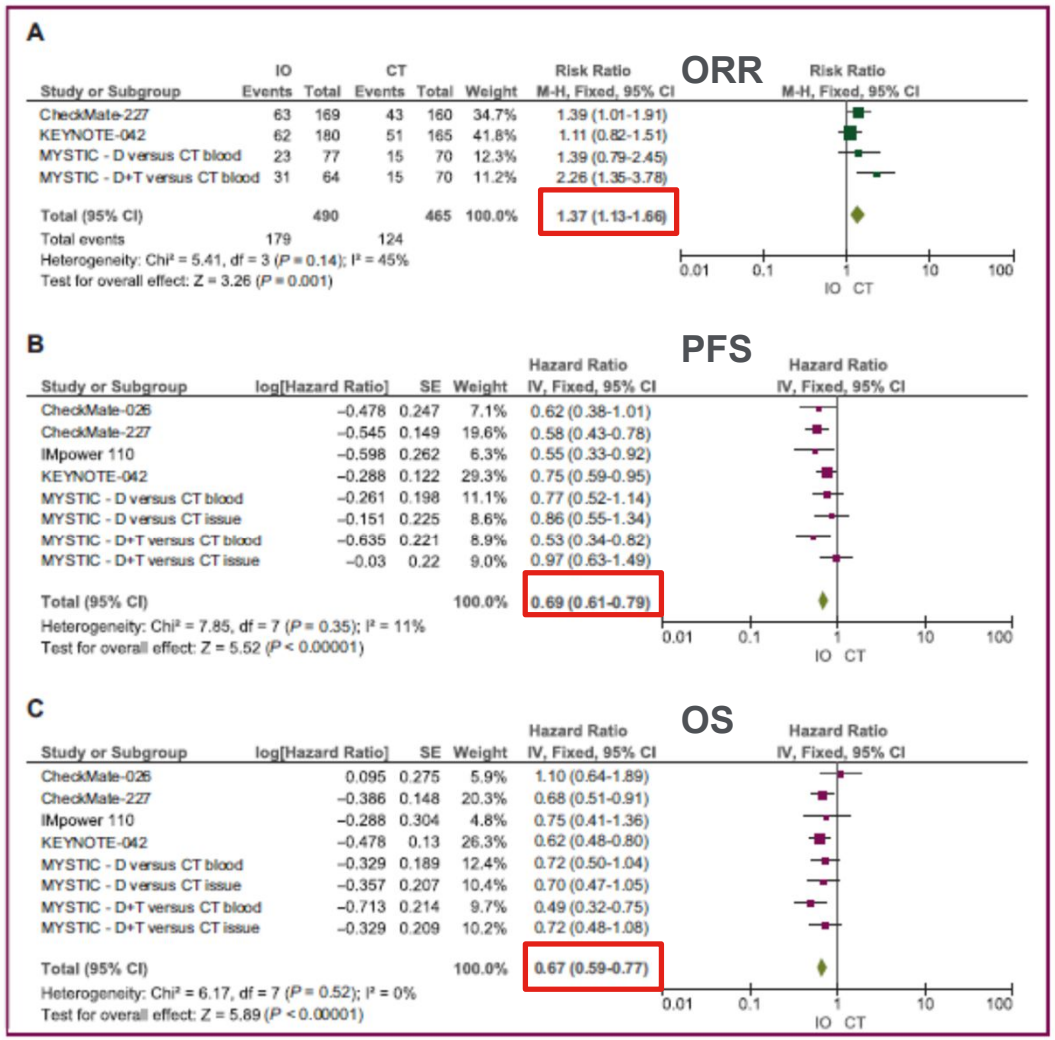


Figure 2. Meta-analysis results including forest plots of (A) RR of ORR, (B) HR of PFS and (C) OS in patients with high TMB assigned to receive first-line IO regimens versus CT.

Table 1. The main baseline characteristics of each included trial considered in this meta-analysis

Study	TMB-evaluable patients, *n* (%)	Treatment arm	Number of patients	Detection method	Threshold defined	Sample
KEYNOTE-042[28]	793/1274 (62.2)	Pembrolizumab versus CT	180 versus 165 (TMB-high); 234 versus 214 (TMB-low)	WES	175 mut/exome	Tissue
CheckMate 227 part 1[31]-2[10]	679/1166 (58.2)	Nivolumab + ipilimumab versus CT	139 versus 160 (TMB-high); 191 versus 189 (TMB-low)	NGS (FoundationOne®CDx)	10 mut/mb	Tissue
CheckMate 026[13]	312/541 (57.6)	Nivolumab versus CT	47 versus 60 (TMB-high); 111 versus 94 (TMB-low)	WES	243 missense mut	Tissue
MYSTIC[32]	315/744 (42.3)	Durvalumab + tremelimumab versus CT	60 versus 67 (TMB-high); 104 versus 84 (TMB-low)	NGS (FoundationOne®CDx)	10 mut/Mb	Tissue
MYSTIC[32]	296/746 (39.6)	Durvalumab versus CT	60 versus 67 (TMB-high); 85 versus 84 (TMB-low)	NGS (FoundationOne®CDx)	10 mut/Mb	Tissue
MYSTIC[32]	523/744 (70.2)	Durvalumab + tremelimumab versus CT	64 versus 70 (TMB-high); 204 versus 185 (TMB-low)	NGS (Guardant OMNI®)	20 mut/Mb	Blood
MYSTIC[32]	541/746 (72.5)	Durvalumab versus CT	77 versus 70 (TMB-high); 209 versus 185 (TMB-low)	NGS (Guardant OMNI®)	20 mut/Mb	Blood
IMpower110[33]	389/554 (70.2)	Atezolizumab versus CT	87 (TMB-high); 302 (TMB-low)	NGS (FoundationOne®CDx)	16 mut/Mb	Blood

CT, platinum-based chemotherapy; Mb, megabase; mut, mutations; NGS, next-generation sequencing; TMB, tumor mutational burden; WES, whole-exome sequencing.

Galvano. ESMO Open 2021

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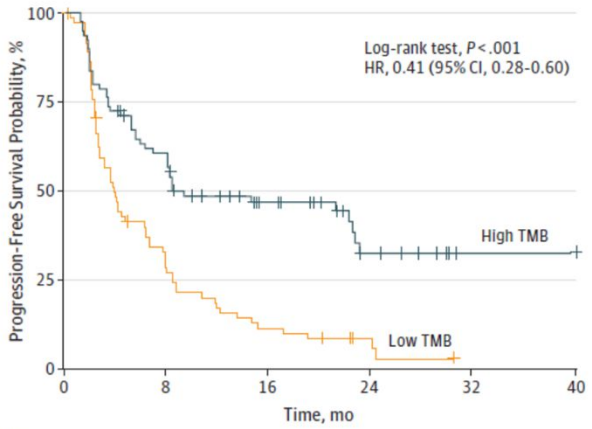
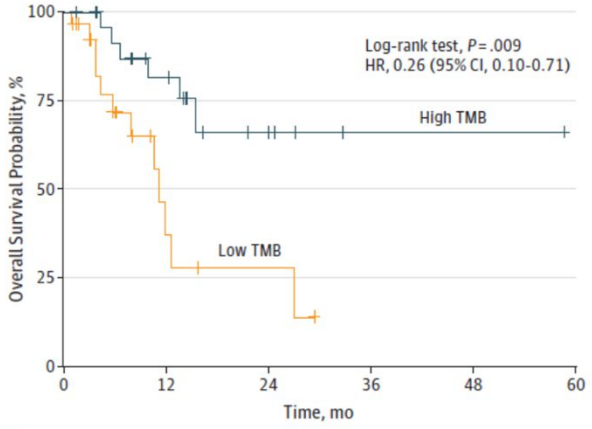
C Progression-free survival by tumor mutation burden



No. at risk

High TMB	82	43	24	10	1	0
Low TMB	76	19	8	2	0	0

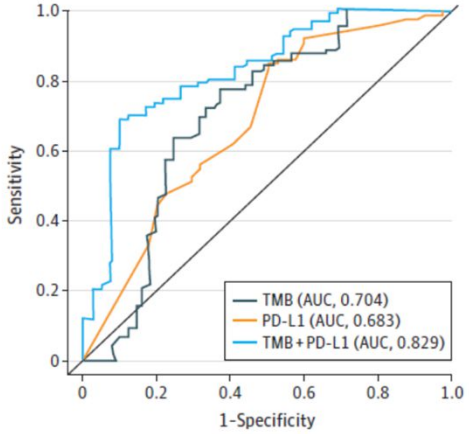
D Overall survival by tumor mutation burden



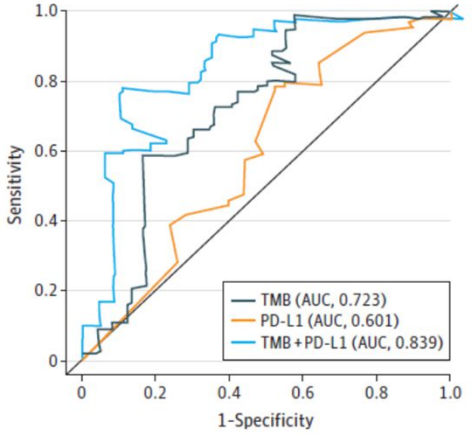
No. at risk

High TMB	26	15	5	1	1	0
Low TMB	30	4	2	0	0	0

A 1-Year progression-free survival quantified by WES



B 3-Year progression-free survival quantified by WES



Yufang, JAMA Network Open 2019

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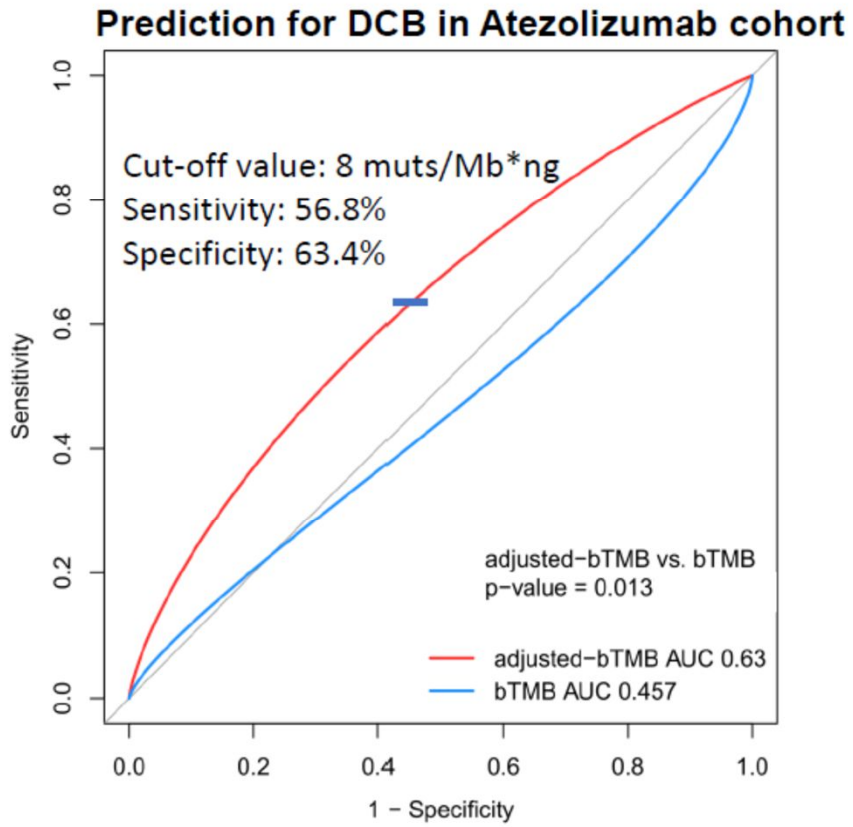
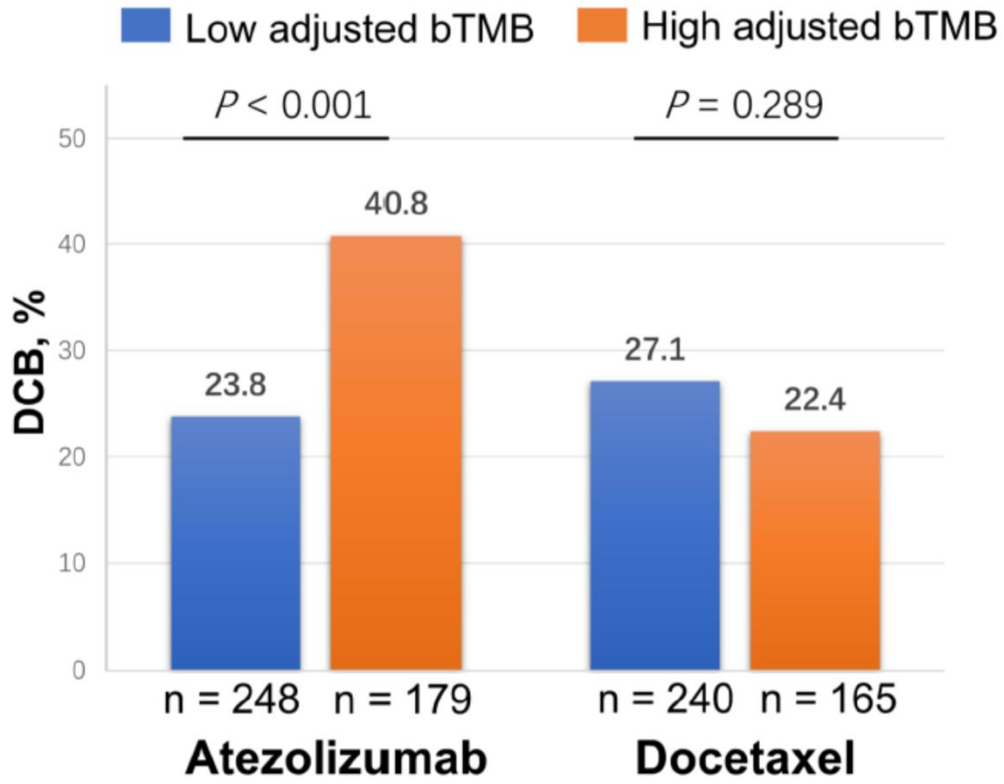
Improving TMB as a biomarker

ctDNA mass adjused bTMB and durable clinical benefit (DCB*) in OAK & POPLAR studies





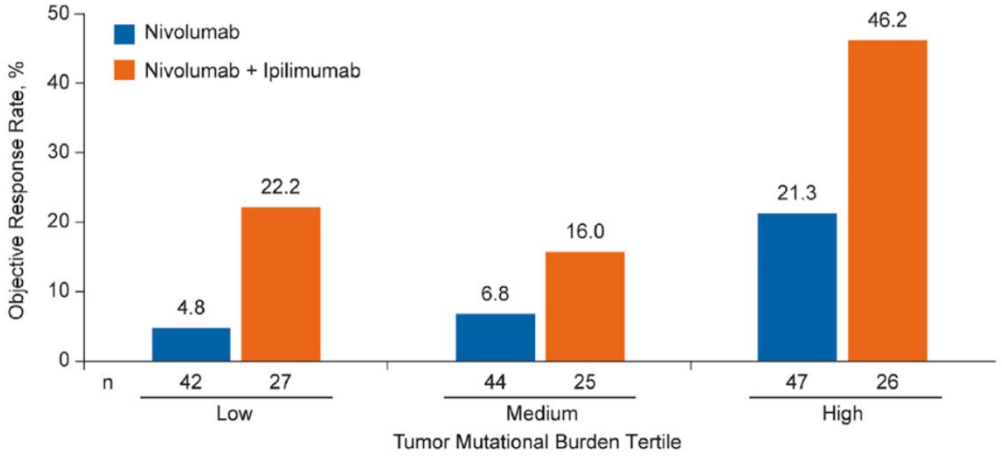
DCB defined as PFS at 6 months

Nie W, WCLC 2021

SCLC – TMB as a biomarker

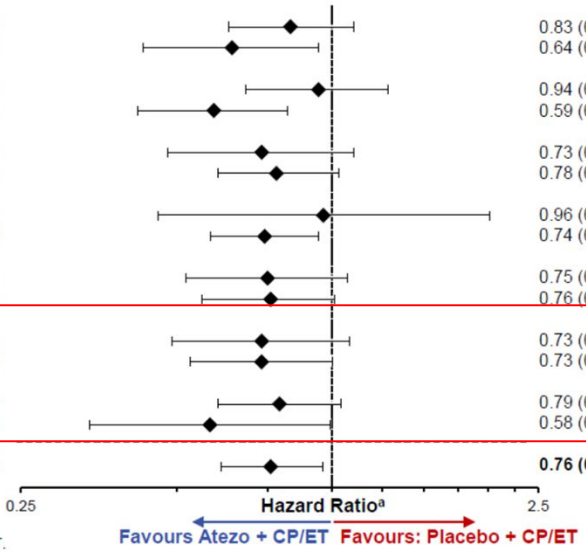
Biomarkers in SCLC

CHECKMATE 032



IMPOWER 133

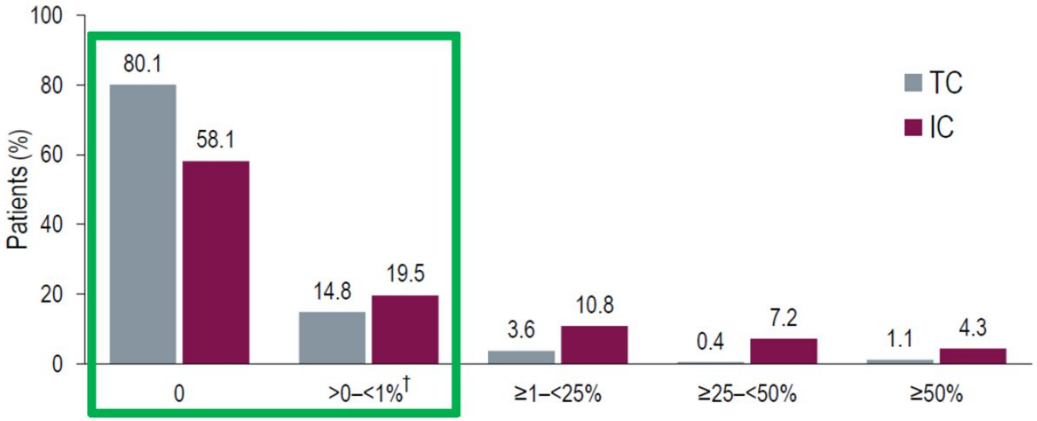
Subgroup	Median OS (months) Atezo + CP/ET	Median OS (months) Placebo + CP/ET	OS Hazard Ratio[a] (95% CI)
Male (n = 261)	12.2	10.9	0.83 (0.63, 1.10)
Female (n = 142)	13.6	9.5	0.64 (0.43, 0.94)
< 65 years (n = 217)	12.1	11.5	0.94 (0.68, 1.28)
≥ 65 years (n = 186)	14.4	9.6	0.59 (0.42, 0.82)
ECOG PS 0 (n = 140)	16.8	12.6	0.73 (0.48, 1.10)
ECOG PS 1 (n = 263)	11.3	9.3	0.78 (0.60, 1.03)
Brain metastases (n = 35)	8.5	9.7	0.96 (0.46, 2.01)
No brain metastases (n = 368)	12.6	10.4	0.74 (0.58, 0.94)
Liver metastases (n = 149)	9.3	7.8	0.75 (0.52, 1.07)
No liver metastases (n = 254)	16.3	11.2	0.76 (0.56, 1.01)
bTMB < 10 (n = 134)	11.8	9.4	0.73 (0.49, 1.08)
bTMB ≥ 10 (n = 212)	14.9	11.2	0.73 (0.53, 1.00)
bTMB < 16 (n = 266)	12.5	10.0	0.79 (0.60, 1.04)
bTMB ≥ 16 (n = 80)	17.1	11.9	0.58 (0.34, 0.99)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.61, 0.96)**

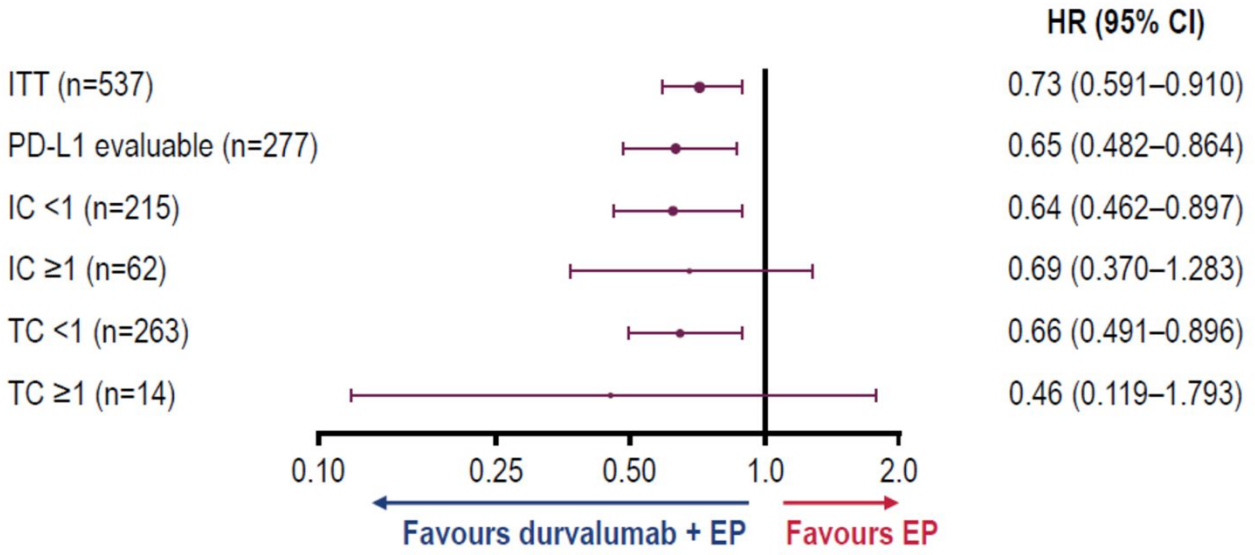


A total of 57 patients had unknown bTMB score.
bTMB, blood tumour mutational burden.
[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.
CCOD 24 January 2019

Hellman Cancer Cell 2018, Reck ESMO 2019

CASPIAN





Paz Ares ESMO 2019

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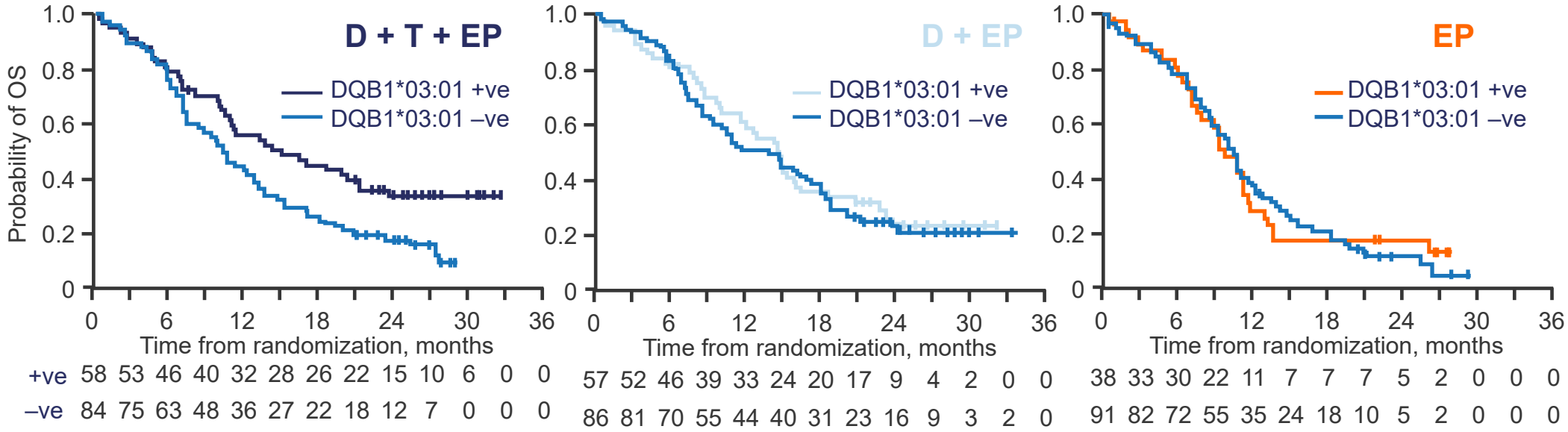
lung cancer research

MA16.06: Durvalumab ± Tremelimumab + Platinum-Etoposide in 1L ES-SCLC: Exploratory Analysis of HLA Genotype and Survival in CASPIAN – Garassino MC, et al



	D + T + EP (n=142)		D + EP (n=143)		EP (n=129)	
DQB1*03:01 status	Positive	Negative	Positive	Negative	Positive	Negative
n	58	84	57	86	38	91
mOS, mo (95%CI)	14.9 (10.4, 21.2)	10.5 (7.6, 12.9)	14.7 (11.5, 16.3)	14.3 (9.4, 17.2)	9.7 (7.7, 11.7)	10.5 (8.9, 11.3)
HR (95%CI)	0.59 (0.39, 0.88)		0.93 (0.63, 1.37)		0.94 (0.61, 1.40)	
OS <18 mo, n	32	62	37	55	31	73
OS ≥18 mo, n	26	22	20	31	7	18
Odds DQB1*03:01 present (OS ≥18 vs. <18 mo)	2.28		0.96		0.92	

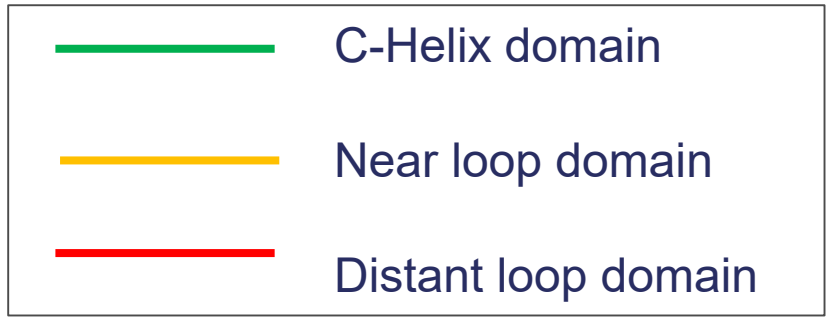
Garassino MC, et al. WCLC 2021. J Thorac Oncol 2021;16(suppl):Abstr MA16.06

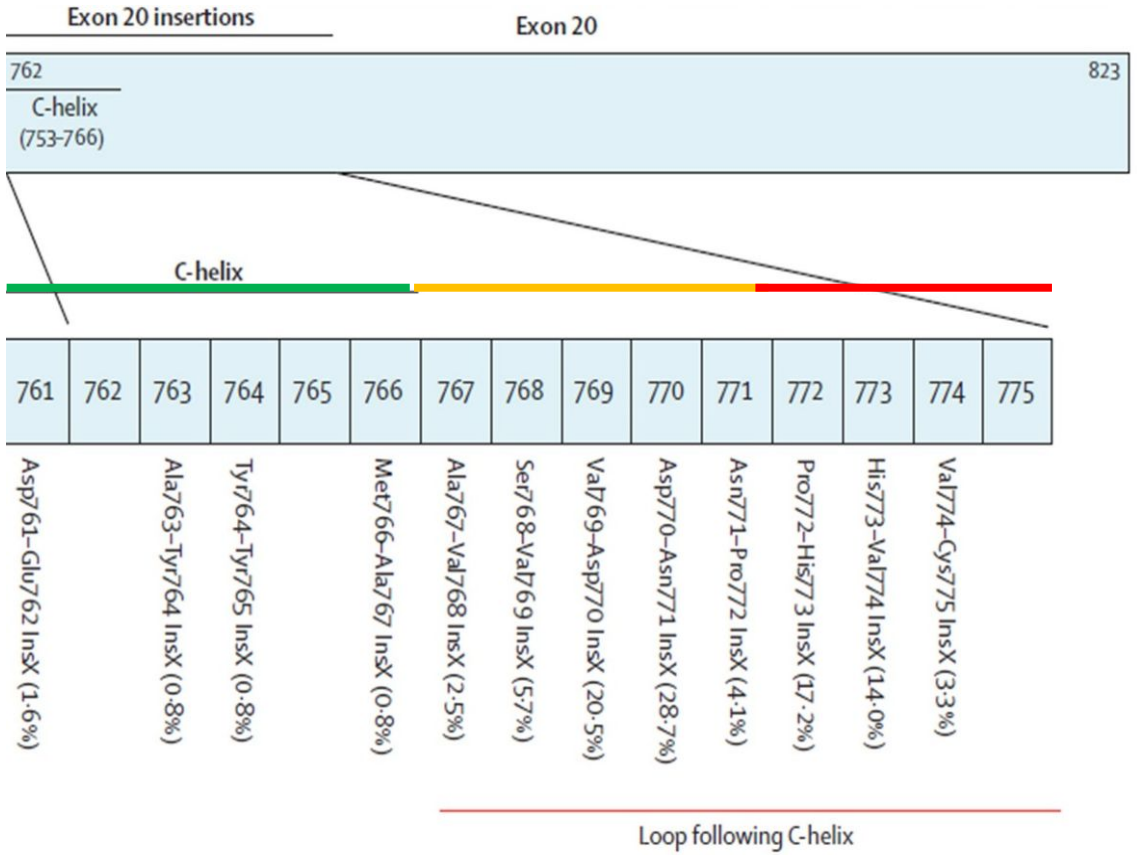
EGFR exon 20 insertions

EGFR exon 20 – response according to variants

EGFR ex 20 ins 4-10 % of all EGFR mut

- ***<30% ORR with 1st and 2nd gen TKI, PFS 3 months***
- ***50% ORR with CT/IO but PFS 4-6 months***
- ***Very limited efficacy of IO in 2nd L***

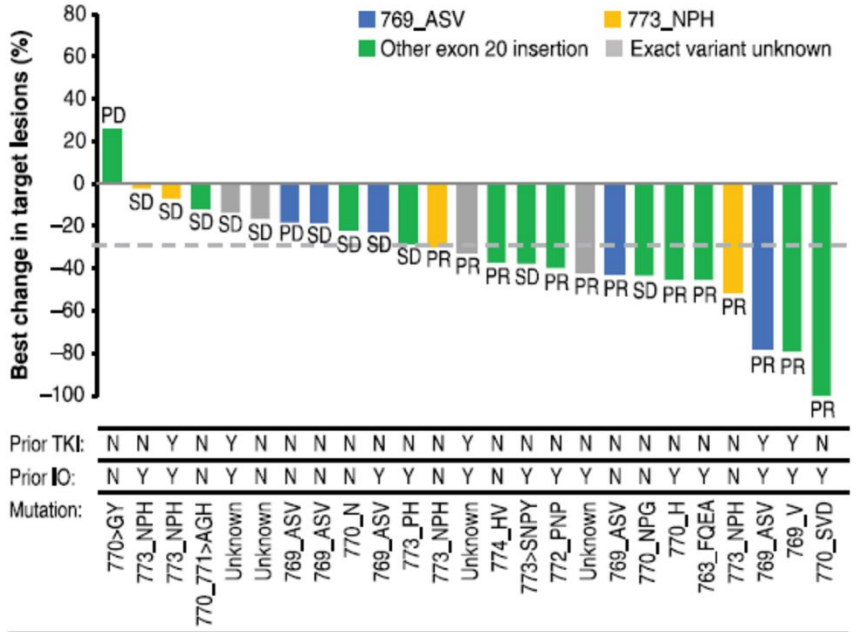




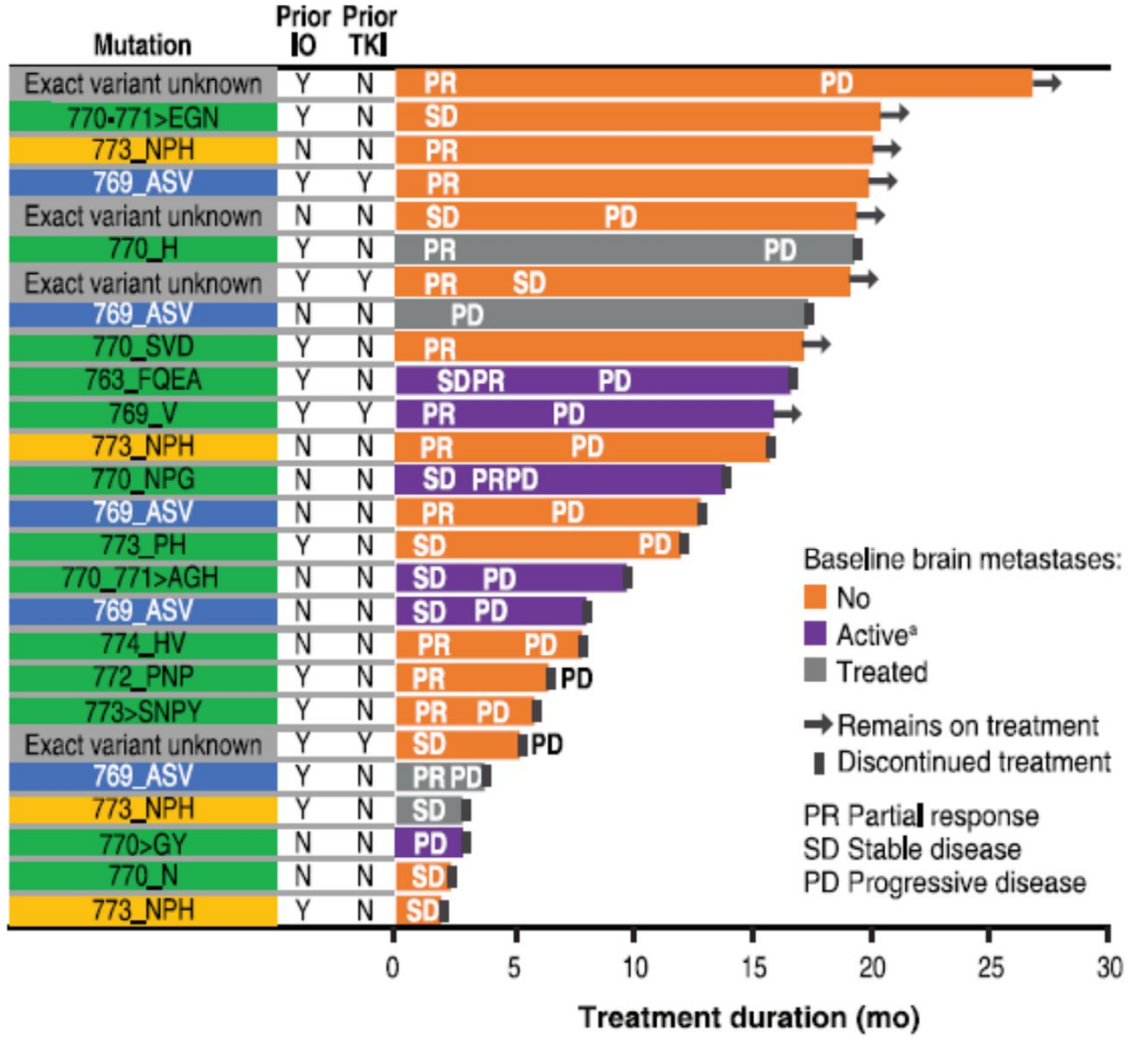
Yang ASCO 2021

EGFR exon 20 – response according to variants

Phase I/II mobocertinib in pretreated pts



EGFR exon 20 insertion variant	No. of patients	No. of confirmed responders	Confirmed ORR
769_ASV	5	2	40%
773_NPH	4	2	50%
Other exon 20 insertion	12	6	50%
Exact variant unknown	4	2	50%

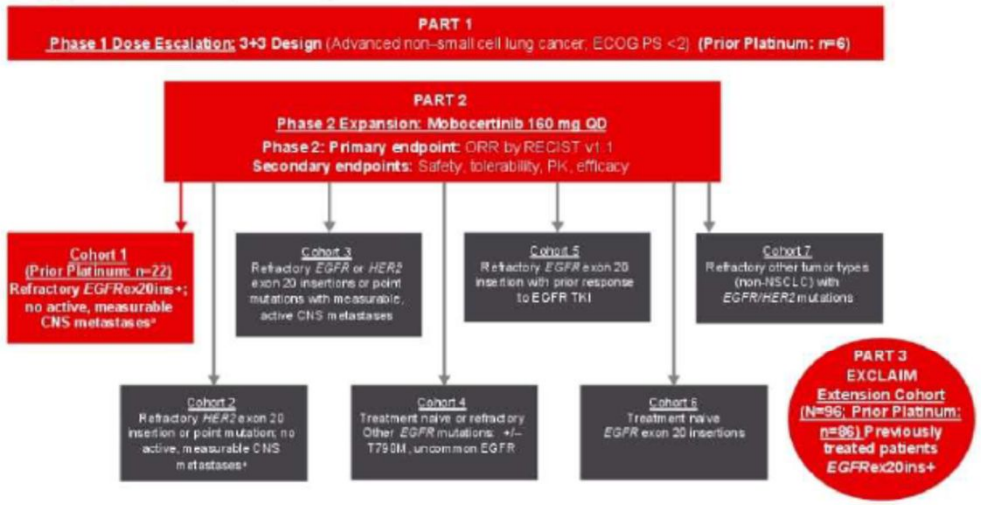


Riely Cancer Discov 2021, esmo 2020

GECP lung cancer research

Mobocertinib Ph I/II PPP and EXCLAIM

Figure 2. Study Design



Data cutoff date: November 1, 2020

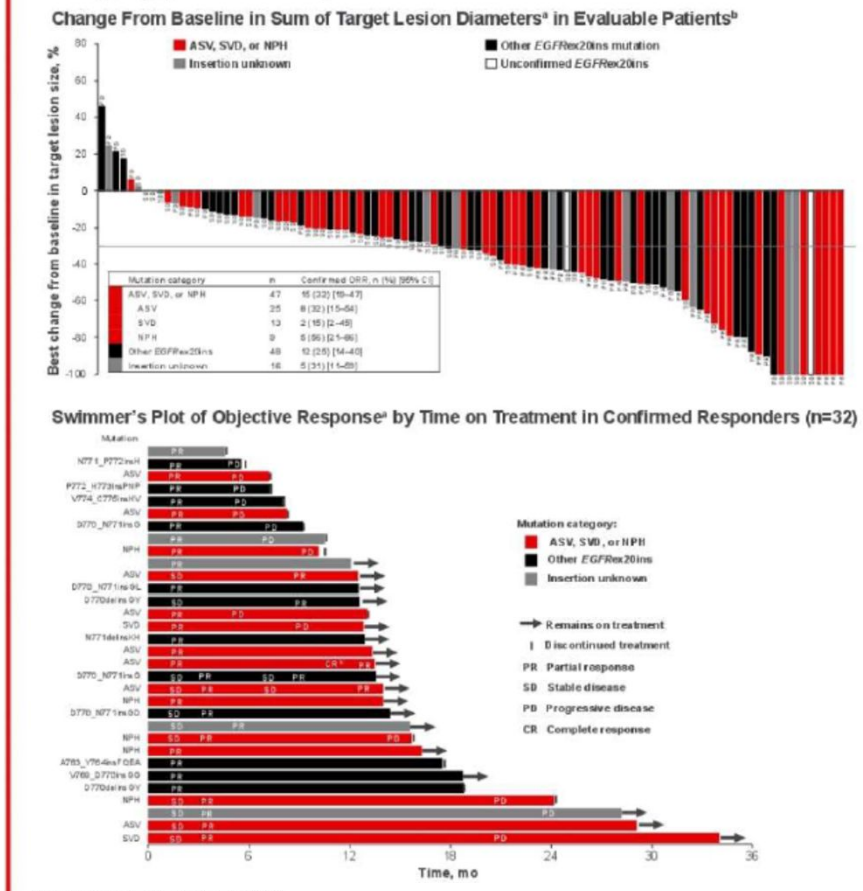
Locations: United States only for phases 1 and 2; United States, Europe, and Asia for phase 2 extension cohort

[a]Active or measurable (but not both) CNS metastases permitted

Active CNS metastases: Untreated or treated and progressing; measurable CNS metastases: ≥10 mm in longest diameter by contrast-enhanced MRI

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor gene; *HER2*, human epidermal growth factor receptor 2 gene; MRI, magnetic resonance imaging; NSCLC, non–small cell lung cancer; ORR, objective response rate; QD, once daily; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor

Figure 3. Objective Response by *EGFR*ex20ins Mutation Category (PPP Cohort)



Data cutoff date: November 1, 2020

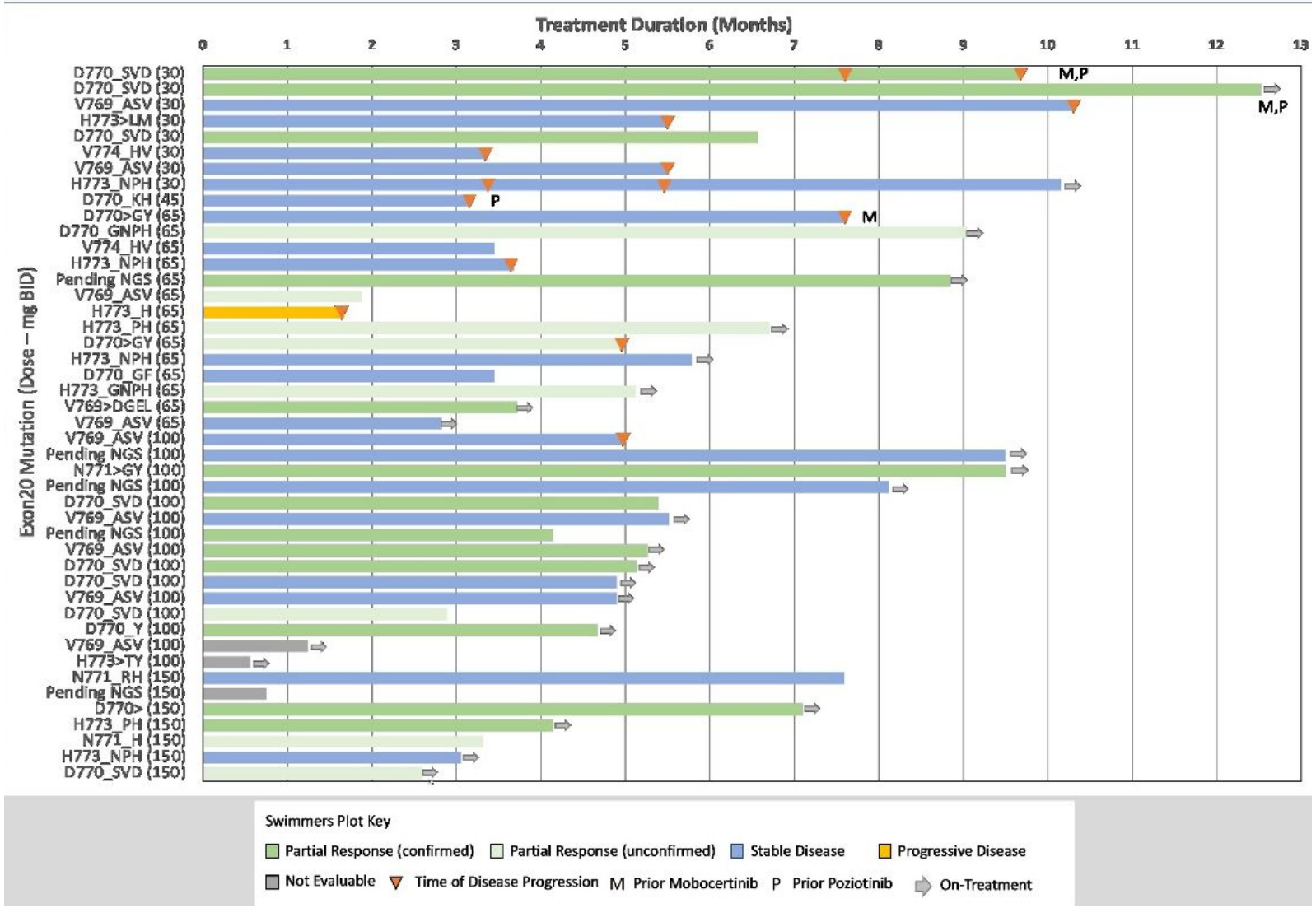
[a]Per IRC assessment; [b]101 patients had evaluable target lesions

Ramalingam ASCO 2021

Organizado por:

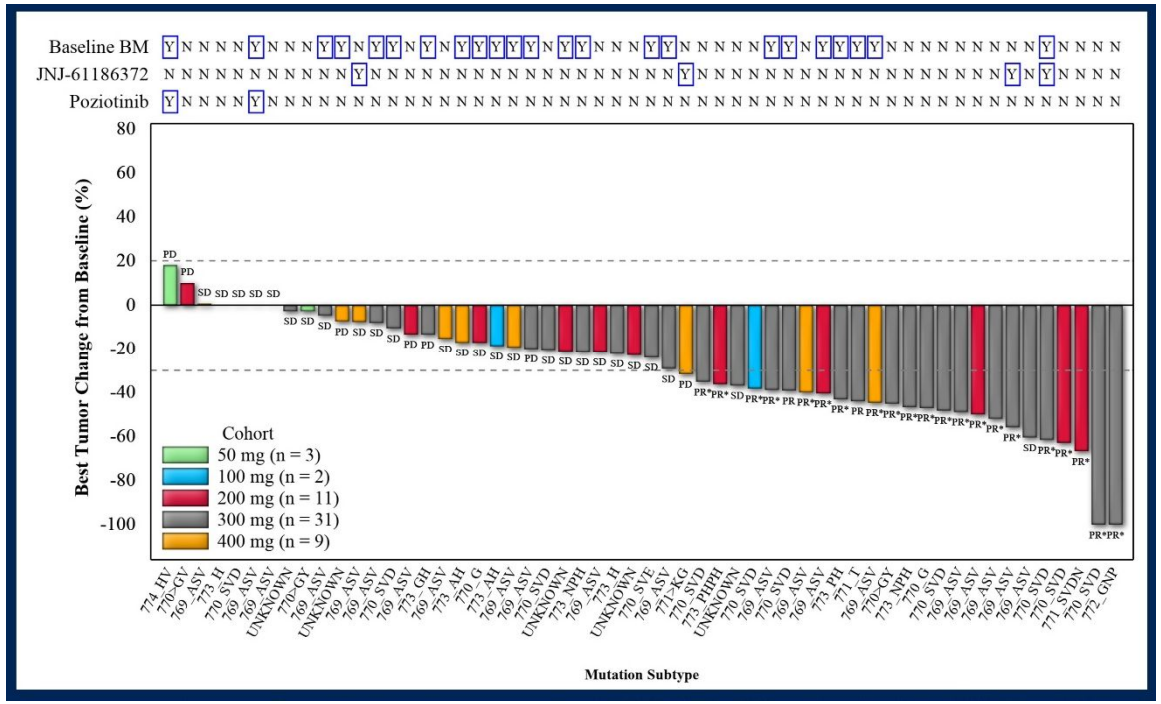
GECP lung cancer research

TAS6417 Ph I/IIa



Pietrowska ASCO 2021

WUKONG1 and WUKONG 2 – Ph I



Mutation subtypes	ORR# n (%)	DCR n (%)
V769_D770insASV (N = 20)	8 (40.0)	19 (90.0)
D770_N771insSVD (N = 10)	6 (60.0)	9 (90.0)
Other subtypes* (N = 18)	7 (38.9)	15 (83.3)
Unknown subtypes (N = 5)	0 (0.0)	4 (80.0)
All (N = 53)	21 (39.6)	46 (86.8)

Data was analyzed at dose levels with observed response (≥ 100 mg);

#: Confirmed ORR

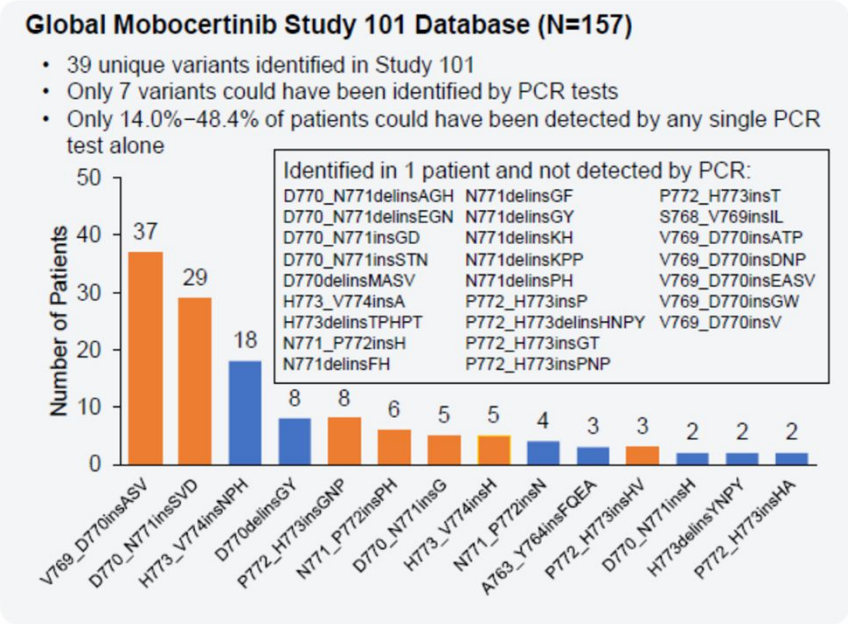
*: Other subtypes of *EGFR* Exon20 insertion include: V774_C775insHV, D770delinsDV, V769_D770insASV, H773_V774insH, H773_V774insAH, D770_N771insG, H773_V774insPHPH and N771_P772insSVDN

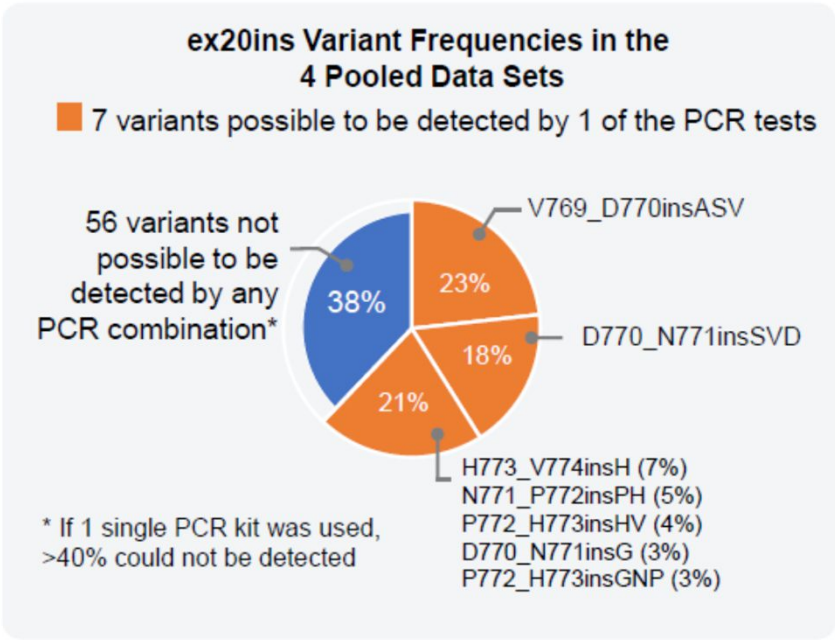
Yang ASCO 2021

Detection method: PCR vs NGS

Estimation of missed EGFR ex.20 insertions using 6 PCR platforms vs NGS

Amivantamab – FDA approved May 2021. EMA pending approval
Mobocertinib – FDA breakthrough therapy dessignation





Ou, WCLC 2021

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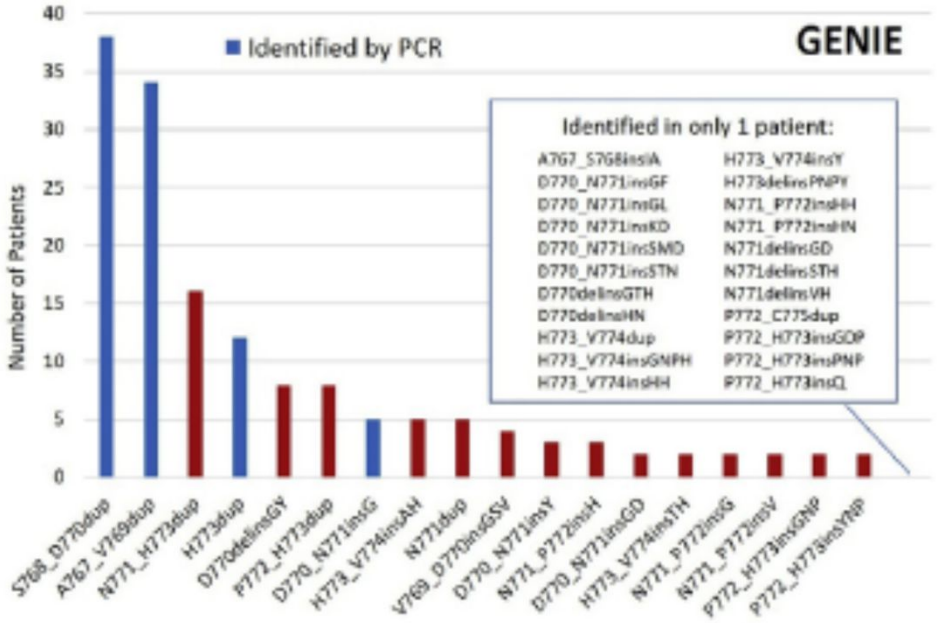
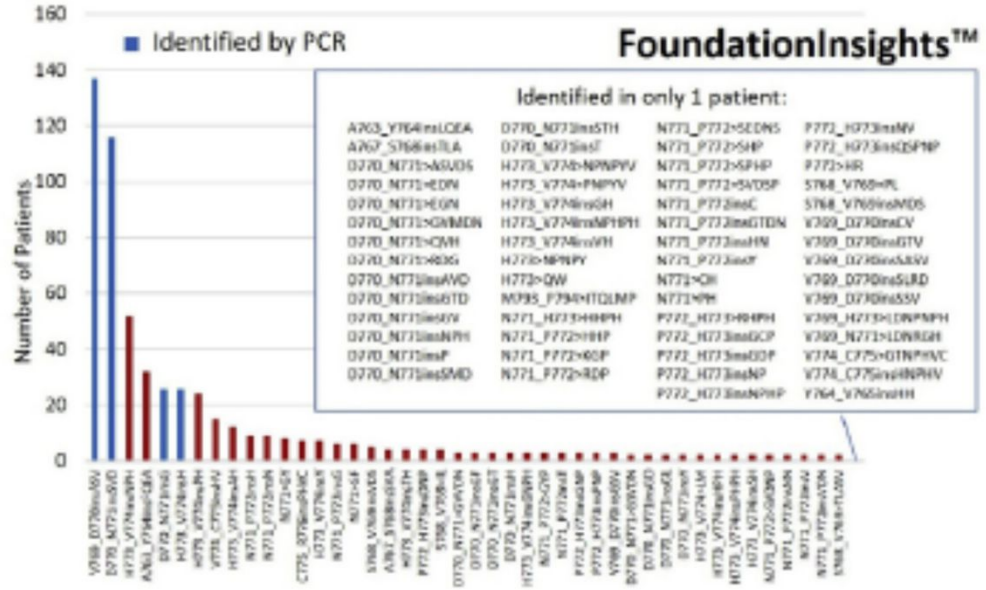
Detection method

Analysis of real-world genomic data from 2 US-based datasets: ***48-50 % PCR detection rate***





40 unique ex 20 variants identified
Only 4/9 most common variants would be identified by PCR

102 unique ex 20 variants identified
Only 4/17 most common variants would be identified by PCR

Bauml WCLC 2021

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CONCLUSIONS

NSCLC

1. TMB cannot (yet) replace PD-L1 as the main biomarker to choose immune-based monotherapy in 1st line
2. TMB does not discriminate clinical benefit in chemo-immune therapy combinations 1st line (as neither does PD-L1)

SCLC

1. No biomarkers as yet to choose candidates for chemo-immune therapy combination 1st line
2. The role of HLA genotyping is yet to be defined, but may identify a subgroup benefitting from CT/double IO combination

Molecular subgroups - ex 20 insertions

1. All ex 20 variants seem to be benefit from specific inhibition. Perhaps near loop variants show more benefit, but is to be defined in Phase III trials
2. NGS should be the preferred diagnostic tool. High heterogenity

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