1921 UN SECOLO DI STORIA DAVANTI A NOI 2021 — UNIVERSITÀ CATTOLICA del Sacro Cuore

Comprehensive Cancer Center

Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Modern Radiation Oncology: multidisciplinarity in the era of OMICS and AI guided oncology

32° RESIDENTIAL COURSE

SESSION 7: OMICS and AI in LUNG cancer

AIRO MRO .ART

Omics Driven Systemic Treatments

Emilio Bria

U.O.S.D. Oncologia Toraco-Polmonare
Comprehensive Cancer Center,
Fondazione Policlinico Universitario Agostino Gemelli IRCCS,
Università Cattolica del Sacro Cuore, Roma
emilio.bria@unicatt.it

Roma, 18 Ottobre 2022

Disclosures

- Advisory Boards / Speakers' fee:
  - *MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis, Roche*
- Research Support / Grants from:
  - *Università Cattolica del Sacro Cuore (UCSC), Fondazione Policlinico Universitario Agostino Gemelli IRCCS, 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), A.I.O.M. (Associazione Italiana di Oncologia Medica), Fondazione Cariverona, Fondazione Roche, AZ Open Innovation*
- Travels / Hospitality:
  - *Roche, Astra-Zeneca, BMS, MSD.*

UNIVERSITÀ CATTOLICA del Sacro Cuore

AIRC

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Aiom
Associazione Italiana di Oncologia Medica

IASLC

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

Fondazione Roche

AstraZeneca
openinnovation

FONDAZIONE Cariverona

(Gen)-Omic Profiling and (Lung) Cancer

Why Doing Tumor Genomic Profiling?

Therapeutic information:

- characteristics of tumors / biomarkers that predict **response** to therapies
- characteristics of tumors / biomarkers that predict **resistance** to therapies

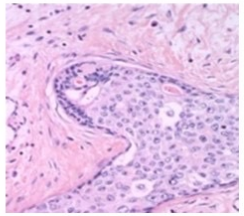
Prognostic information

Diagnostic information

Characterizing the tumor to find vulnerabilities – and then targeting or exploiting those vulnerabilities

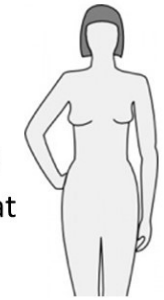
Types of Genomic Profiling

- Profiling DNA vs RNA
- Massively parallel sequencing (NGS) vs hotspot profiling
- Scope of profiling:
  - Whole genome sequencing (WGS)
  - Whole exome sequencing (WES) – 20,000 genes (1% of genome)
  - Multigene Panel – tens to hundreds of genes
  - Single-gene testing



Somatic (Tumor) Genetics
(Test *tumor cells* in tumor biopsy sample or "liquid biopsy" blood tests)

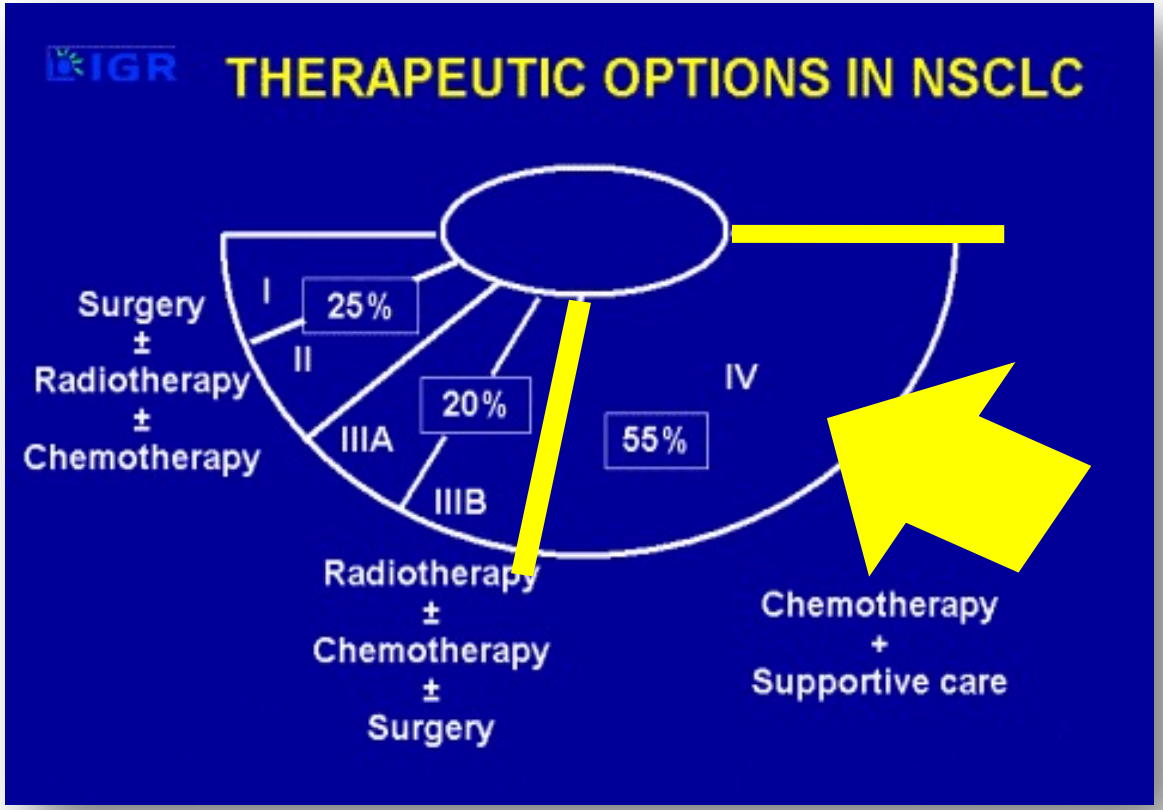
Germline Genetics
(Blood test looking at *normal cells)*



Modified from Wangle N, ASCO 2022

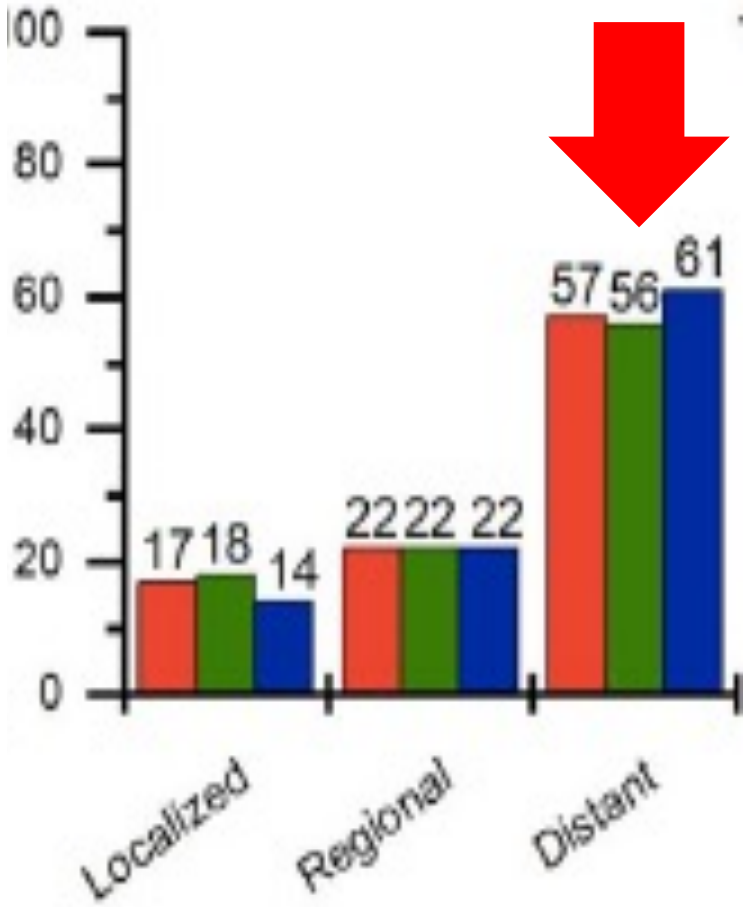
NSCLC: Presentation according to Stage

NSCLC Clinical Presentation according to stage [2003]



Le Chevalier T, Lecture at ASCO 2003

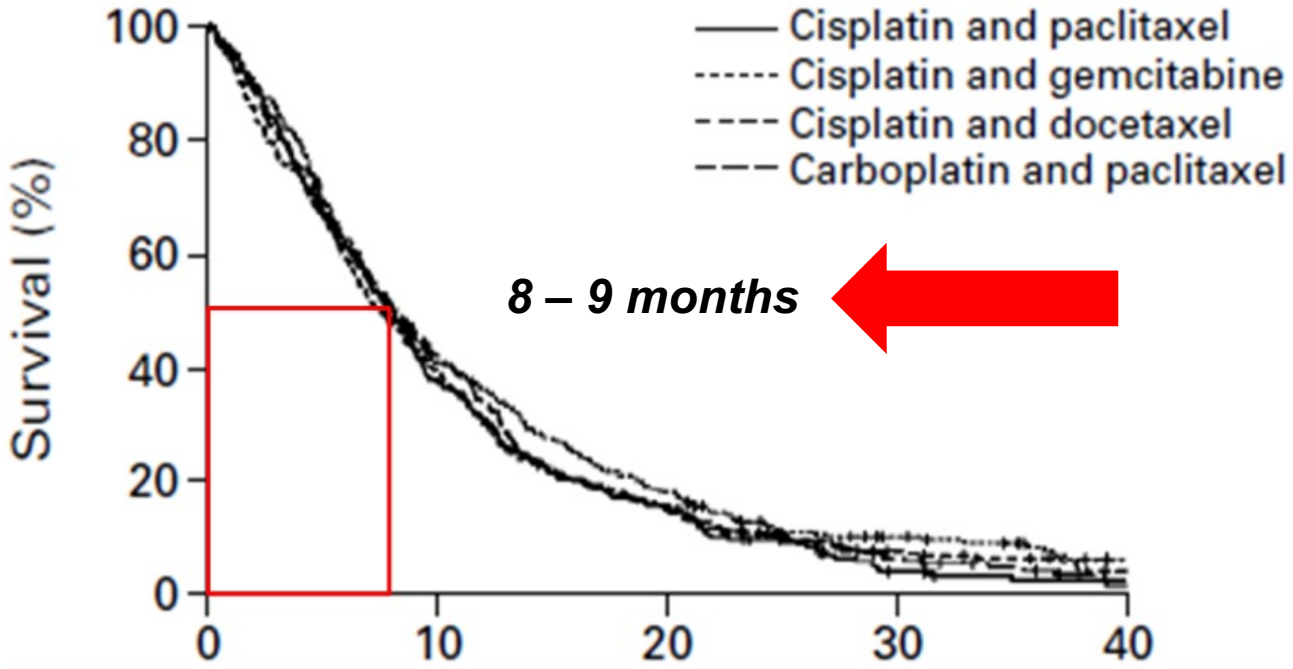
NSCLC Clinical Presentation according to stage [2021]



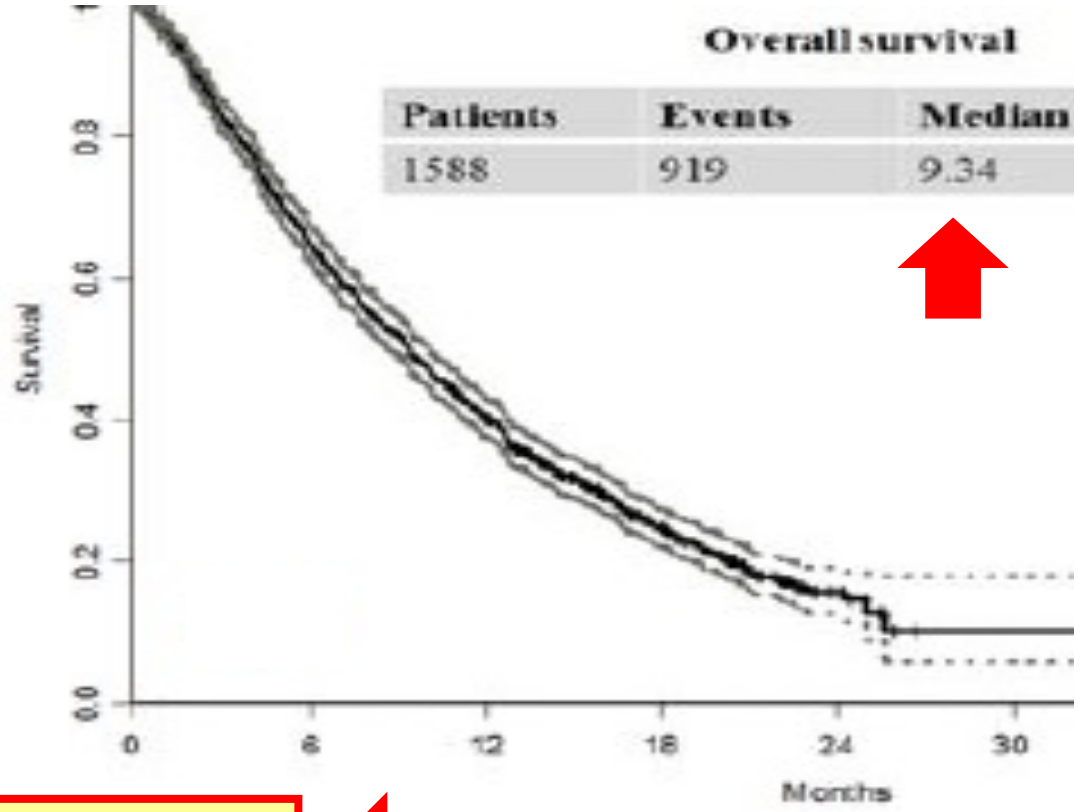
Siegel RL et al, CA CA CANCER J CLIN 2021

NSCLC Prognosis in late 90s

- Prognosis in Clinical Trials
- 'Modern' Chemo Doublets reaching a '*plateu*'
- If fit, 100% of patients received chemotherapy



- Italian RWD (38 Centers)
- 88.8% of pts do receiving first-line



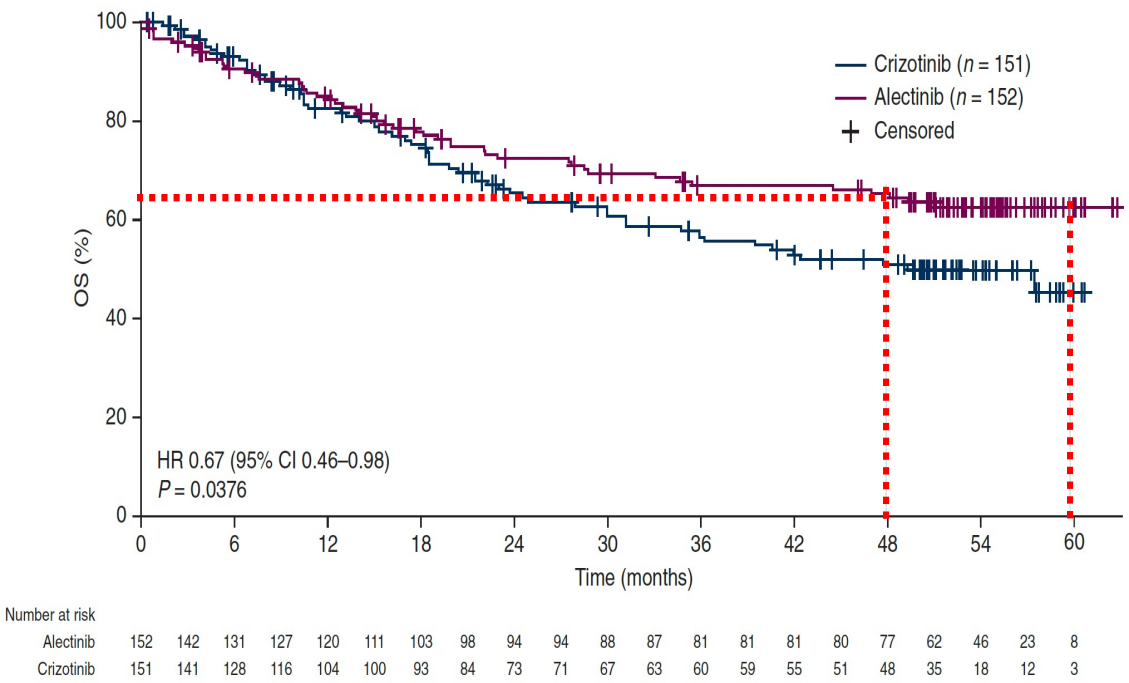
2-trs OS <10%; 4-yrs OS <5%

Schiller J et al, NEJM 2002

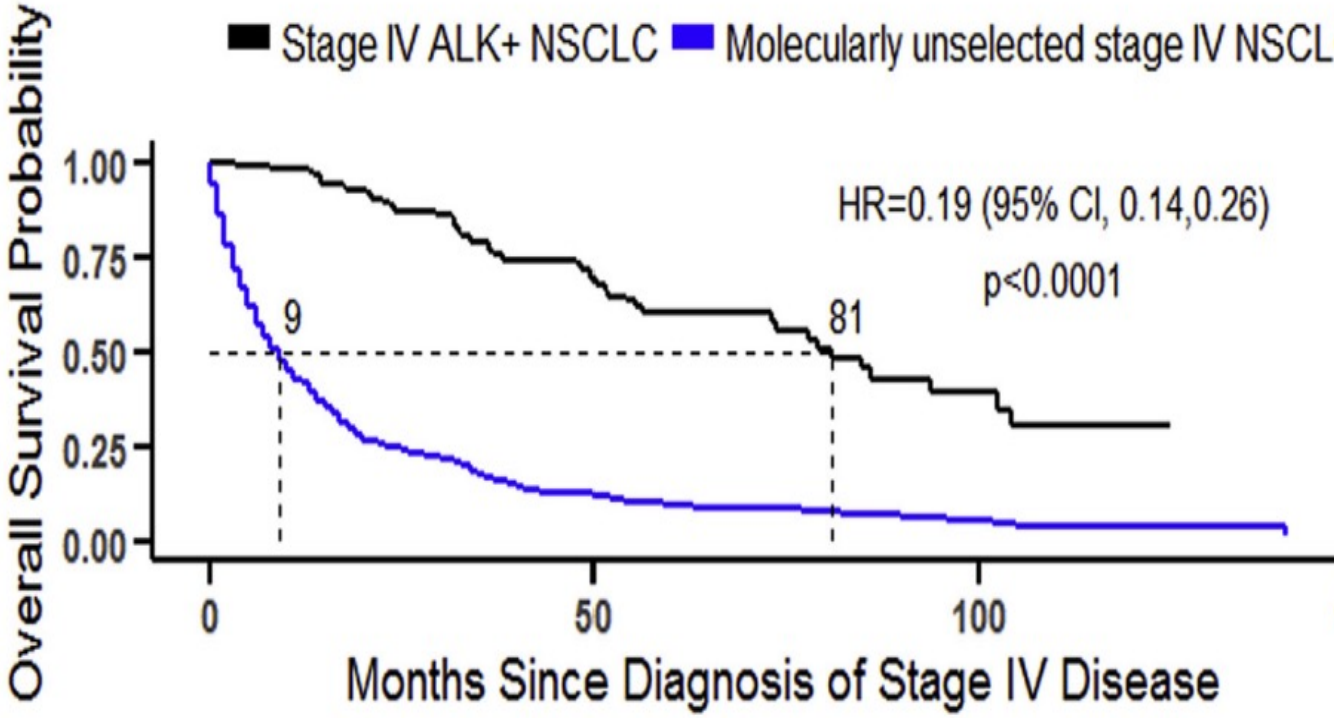
Stanley KE et al, JNCI 1980

ALK-Driven NSCLC Prognosis Receiving in 2022: OS

ALEX (Alectinib vs. Crizotinib) Trial



RWD Colorado University 2004 - 2017



ALK-addicted NSCLC receiving Alectinib or TKIs: Estimated OS @5yrs: 60%

Mok T et al, Ann Oncol 2020

Pacheco JM et al, JTO 2019

The Evolving View of NSCLC

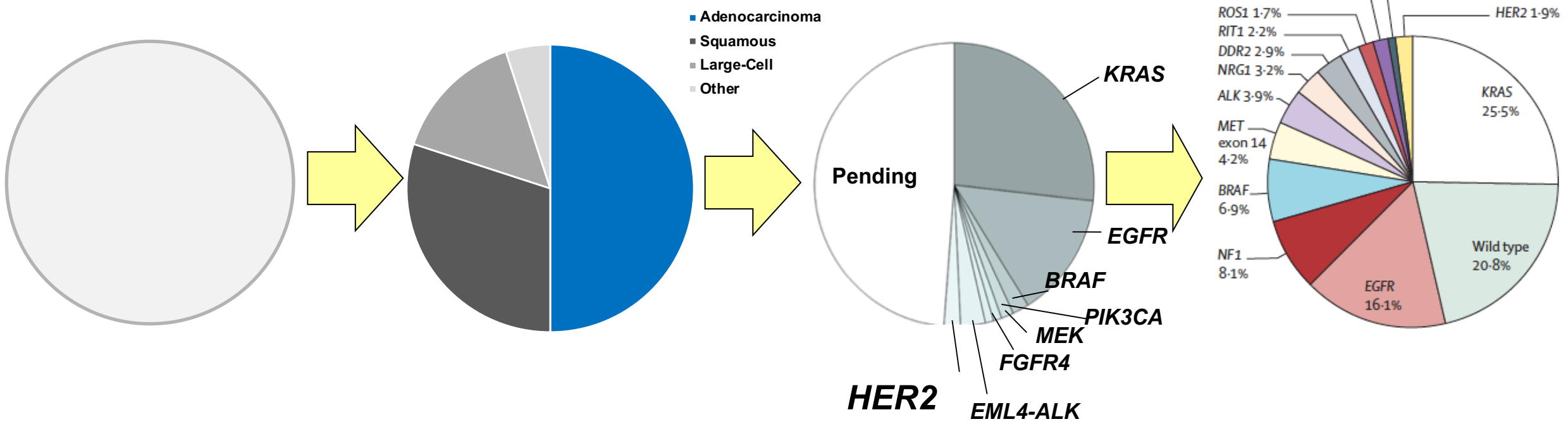
[NSCLC IS a Heterogenous Disease]

1995

2007

2009

2016



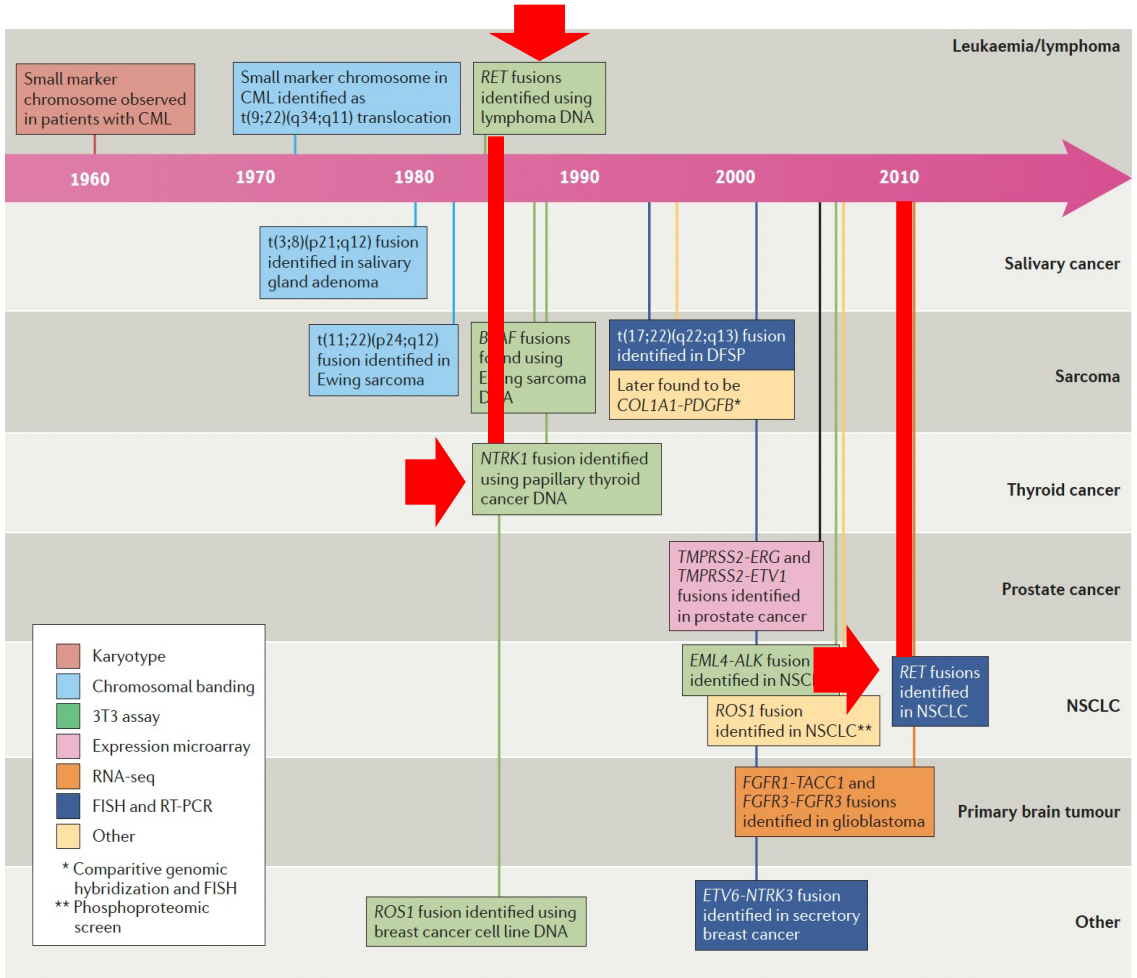
Tumor Morphology

Tumor Histology

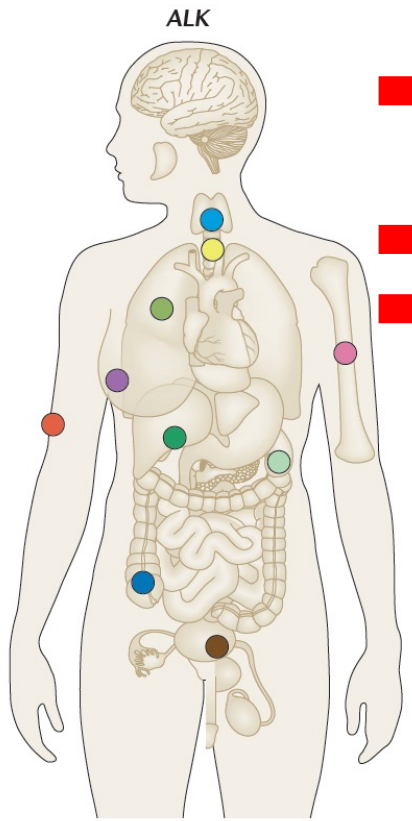
Tumor Genomics

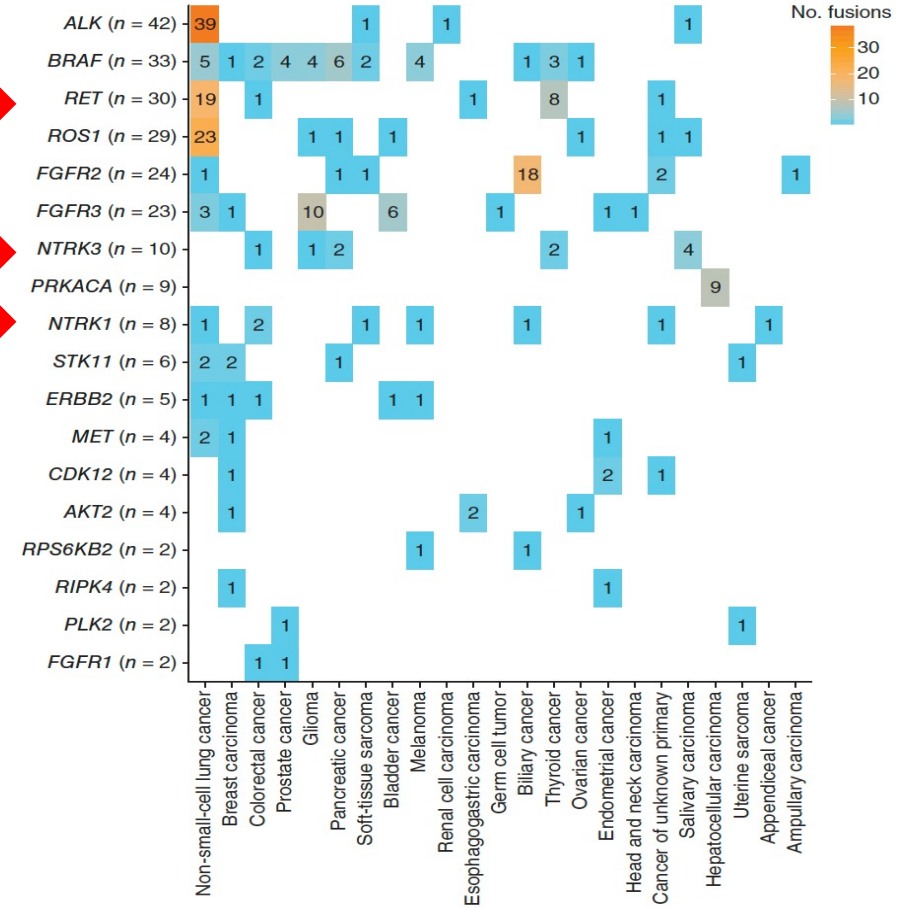
Gene Fusions as Pathogenic Oncological Events

Discovery of Oncogenic fusions: Timeline



Massive Paralle Sequencing [MSKCC], 15% (1,597/11,369) of pts harbor genomic rearrangements; of these 35% (268 fusions) involved kinase genes

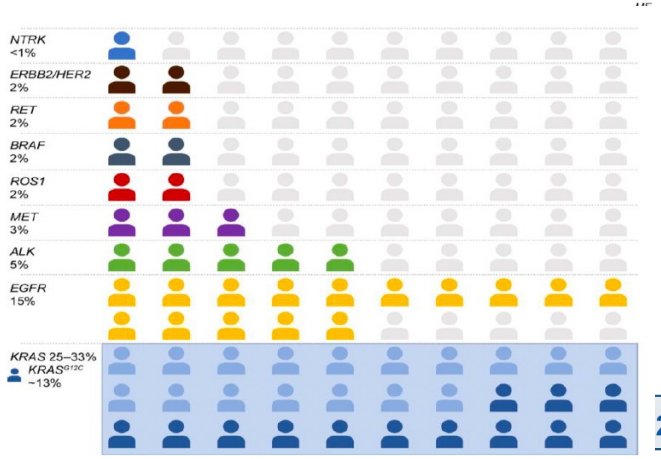


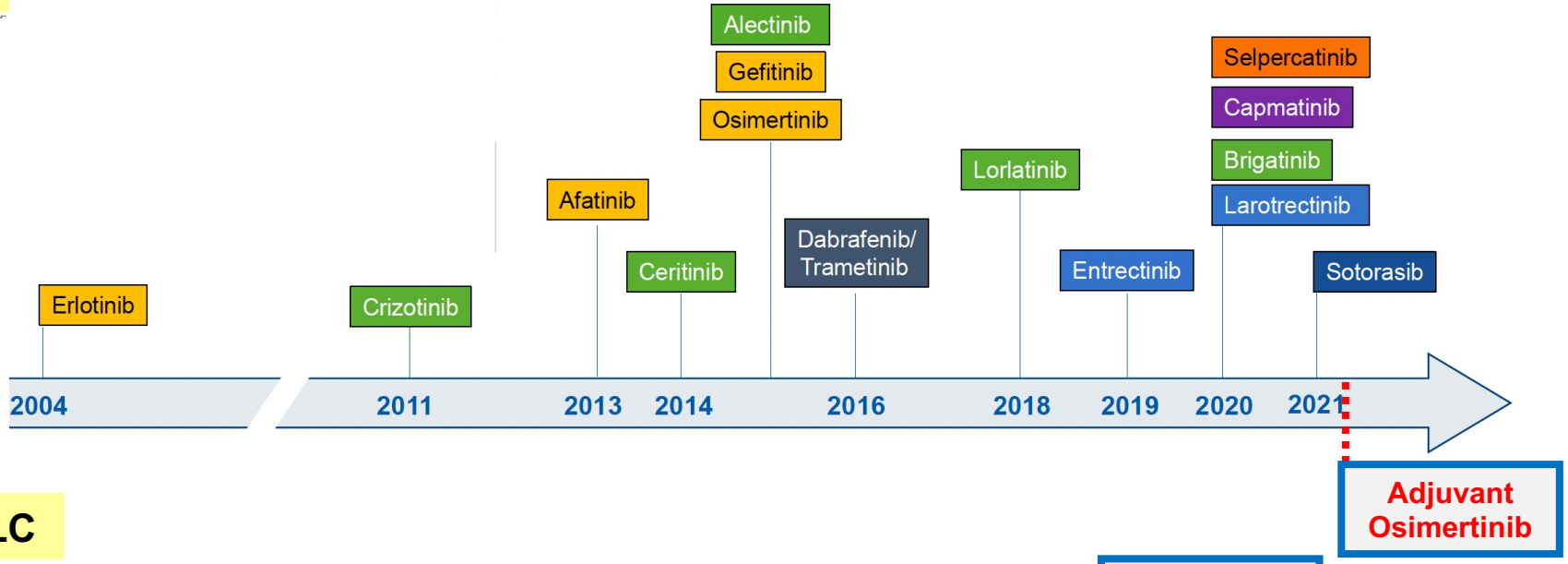


Schram A et al, Nat Rev Clin Oncol 2017

Treatment NSCLC Evolution Overtime: '*Plethora*' of Targeted Agents, regardless of the Stage!

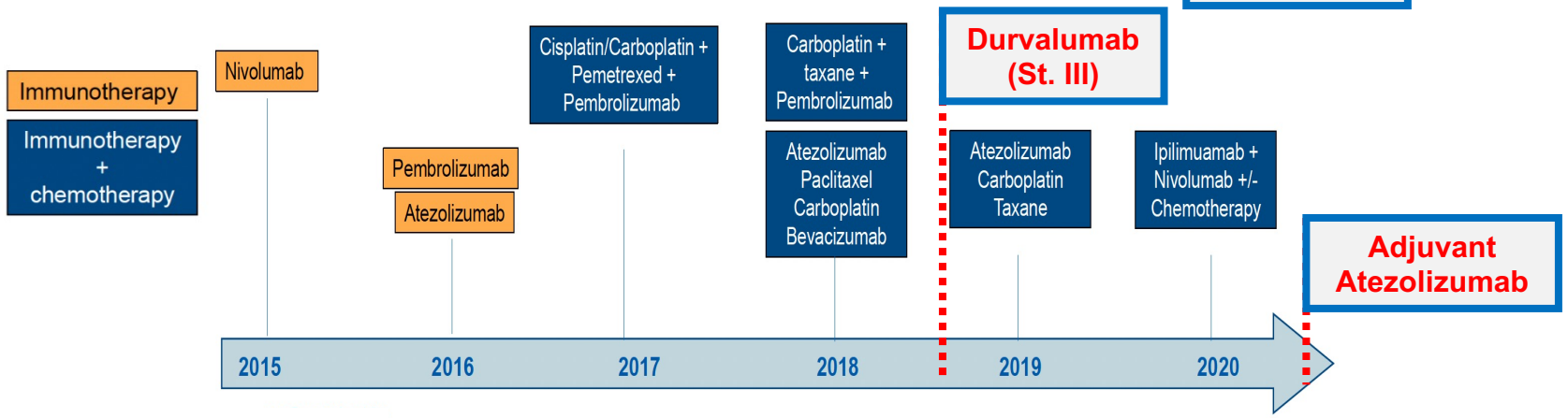
Oncogene-Addicted NSCLC





Non-Oncogene-Addicted NSCLC

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



Modified from Curioni A, ELCC 2022

The Evolving View of NSCLC: '*Operative*' Classification

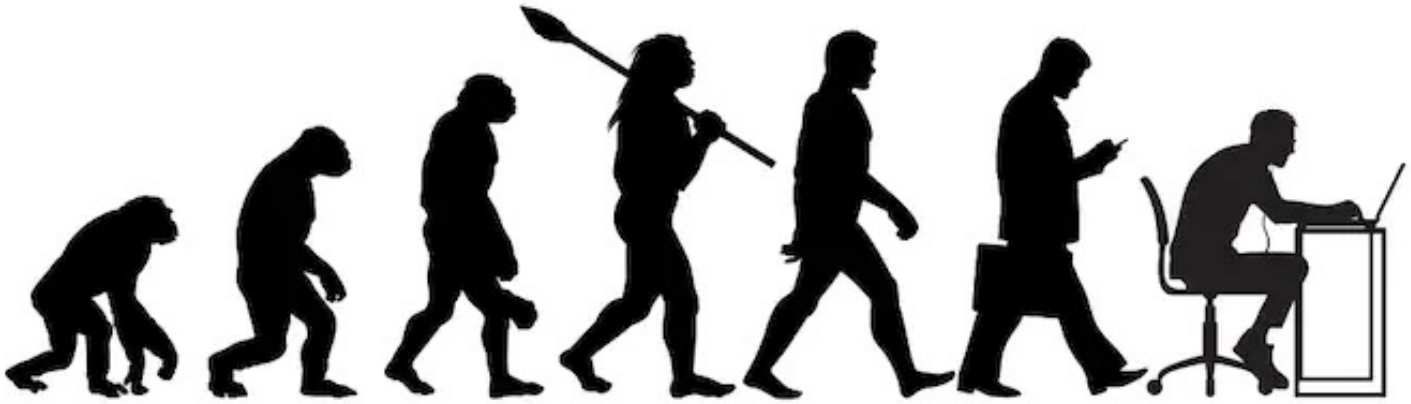
30% of pts **70% of pts**

Characteristics	Oncogene Addicted Disease	Non-Oncogene Addicted Disease
Number of Drivers	Single (Dominant) Driver	Multiple Drivers and Passengers
Mutational Load Tumor Mutational Burden (TMB)	Small LOW TMB	Large HIGH TMB
Efficacy of Targeted Therapy (TKIs)	Yes, proven	No, still unproven
Efficacy of Immunotherapy	No, still unproven	Yes, proven
Early Resistance Rate	Low (≤20% at first evaluation)	High (≥50% at first evaluation)
Late Acquired Resistance (same/other pathways)	Always, proven	Few Late Acquired Resistance, unproven (long-term survivors, cured patients?)
Traditional Intermediate End-points Surrogacy (in absence of cross-over)	Yes	No

Molecular Biology Behind is crucial for the overall understanding of the clinical behavior of tumors

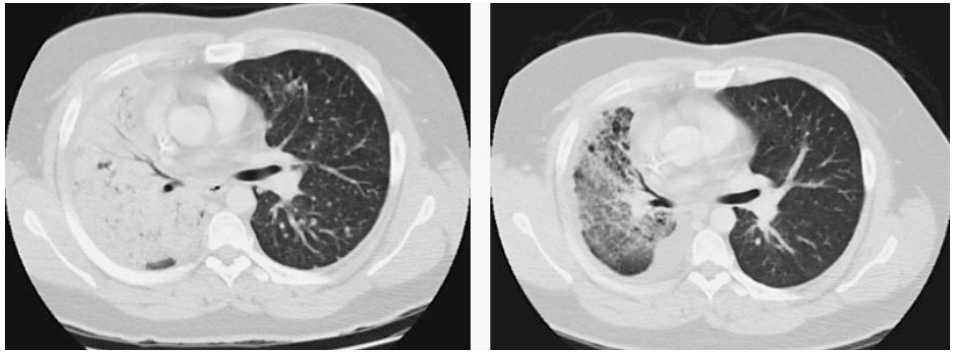
Ferrara MG et al, Cancers 2020

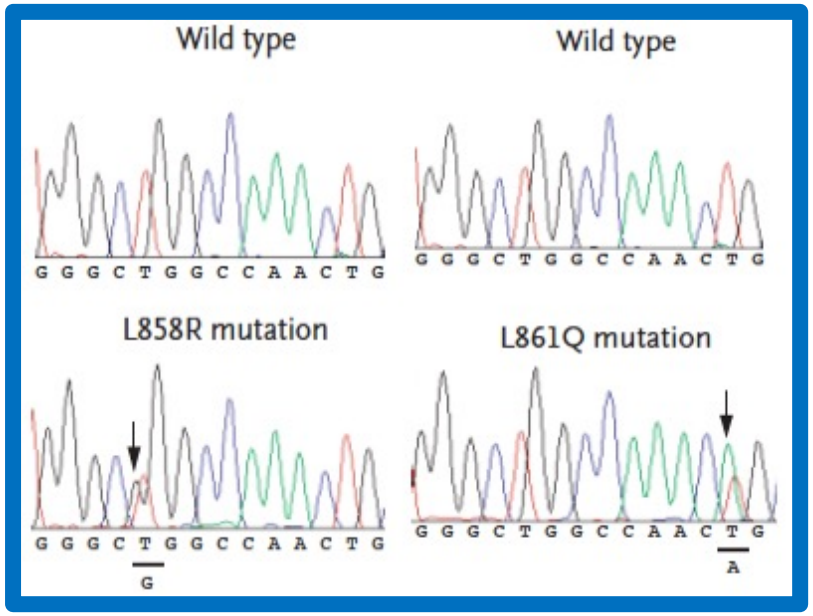
The Evolving View of NSCLC



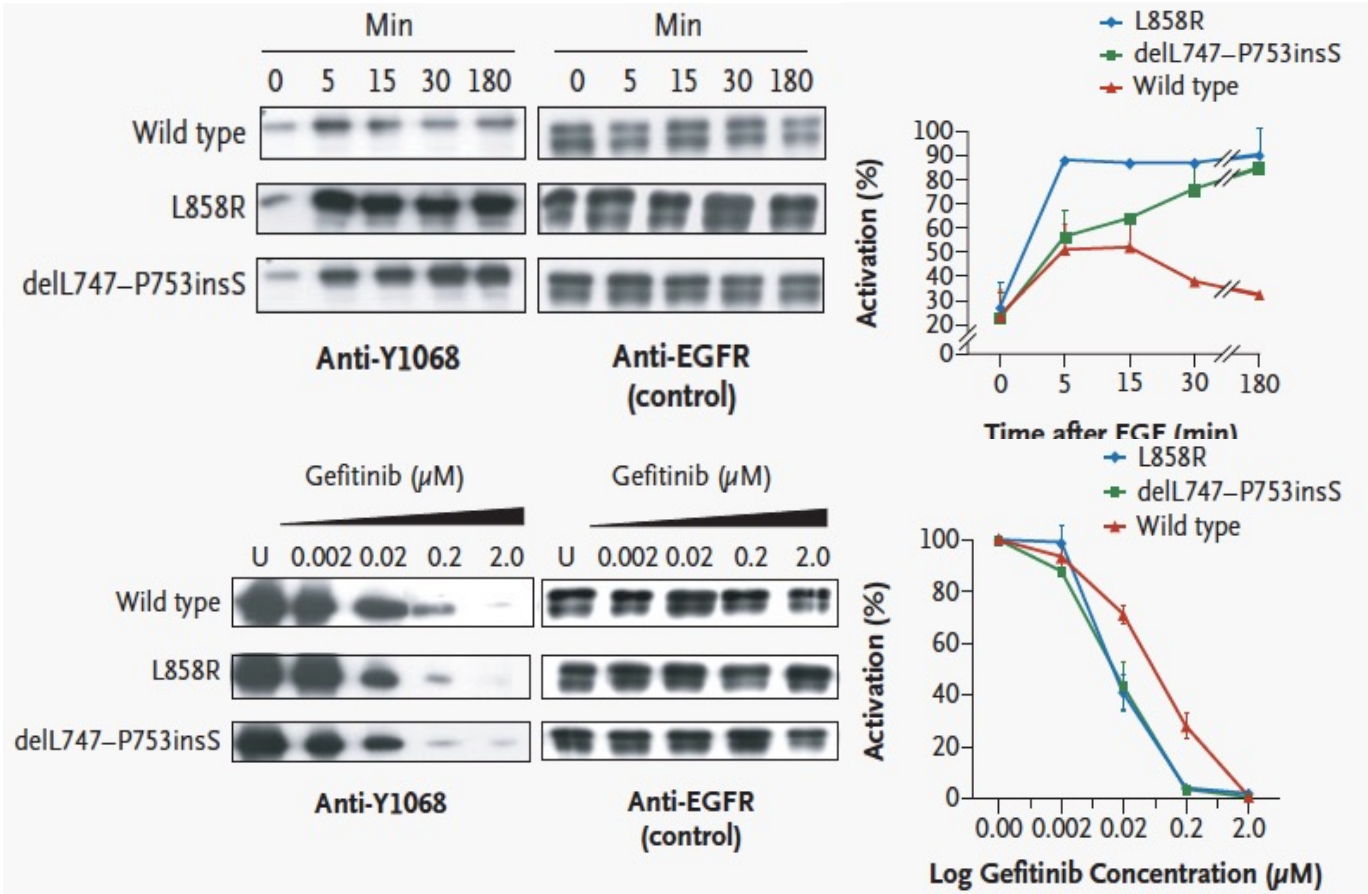
Revolution	Focused on:	Research Strategy:	Trials' Approach:	FINAL Regulatory Approval based upon:
#1 Oncogene Addiction	Tumor	• Identification of Targets/Drivers which leads Tumor progression	• Biomarker-driven with Genomics • Patients' Superselection	• Phase IIIs (*EGFR*, *ALK*) • Phase I/IIs (*ROS1*) • Phase IIs (*BRAF*)
#2 Immune-Dependence	Patient	• Unlock Immune-Response against Tumor	• (Mainly) Unselected Patients' Samples • Immune-dependence evaluated	• Phase IIIs

Mining the Genome of Exceptional Responders





Mutations in the *EGFR* Gene in Gefitinib-Responsive Tumors



Enhanced EGF–Dependent Activation of Mutant EGFR and Increased Sensitivity of Mutant EGFR to Gefitinib

Lynch T et al, NEJM 2005

'The Lazarus Response' and Oncogene Addicted NSCLC

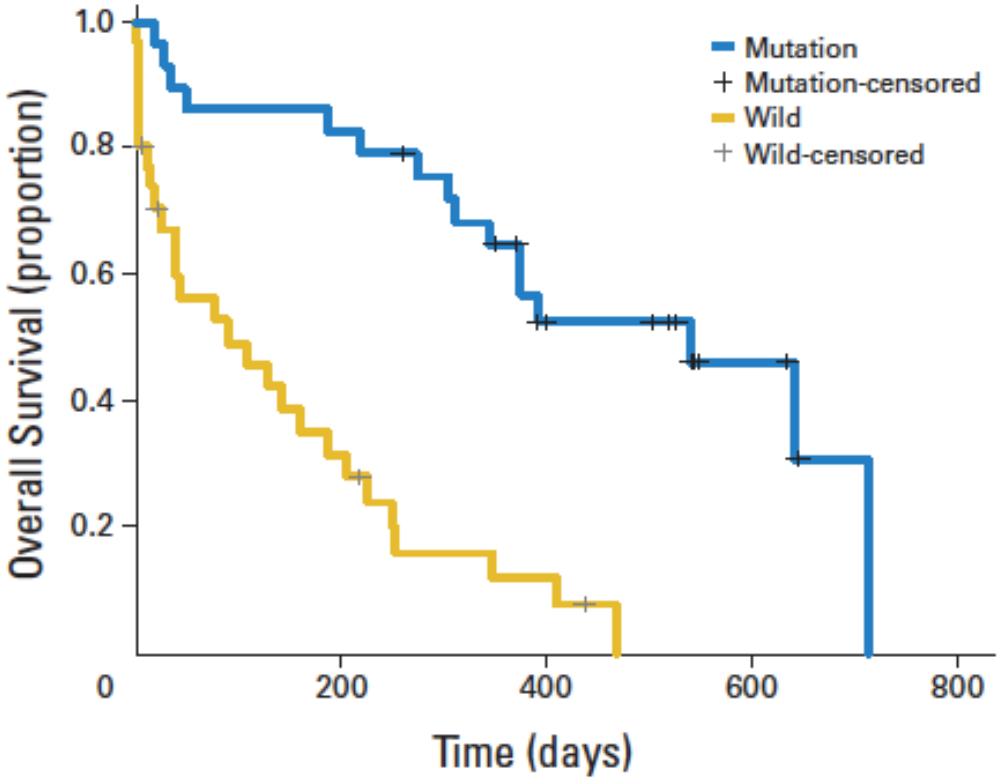
"Four days? Boy, time sure flies when you're dead!"

Parameter	Trial		
	Lilenbaum[24]	Hesketh[25]	Inoue[14]
Performance status	2	2	2-4
Mutation status	Unselected	Unselected	Purely selected
EGFr mutation positive, %	0	NA	100
No. of patients	52	81	30
OR, %	4	8	66
PFS, months	1.9	2.1	6.5
OS, months	6.6	5	17.8

Abbreviations: EGFr, epidermal growth factor recepto; TKI, tyrosine kinase inhibitor; OR, overall response rate; PFS, progress on-free survival; OS, overall survival.

Langer C, J Clin Oncol 2009

Multicenter Phase II Study, Poor ECOG PS (2-4), 30 patients

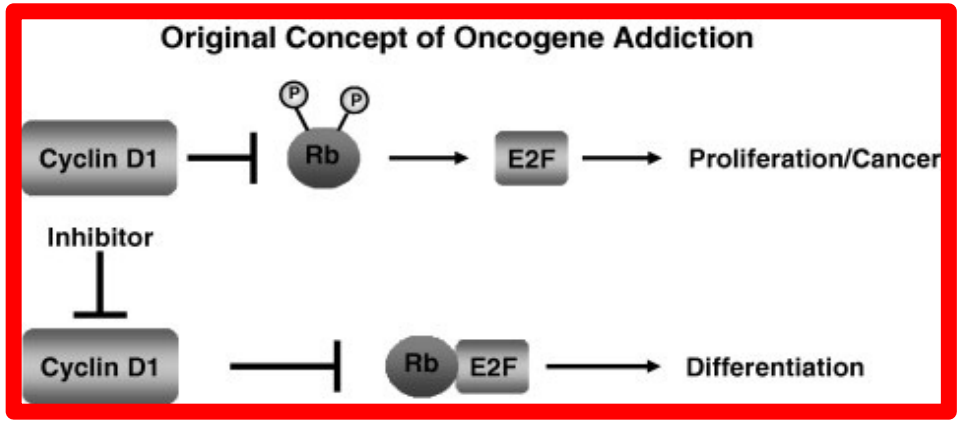


Inoue A et al, J Clin Oncol 2009

REVOLUTION #1: Oncogene Addiction

Biological Relevance

- Cancer cells contain multiple genetic and epigenetic abnormalities. ***A series of 'Featured Cells' needed a very high level of (a predominat) oncogene to survive.***
  - *Targeting cyclin D1 was enough to arrest the growth of cancer cells overexpressing the protein (that's why addiction)*

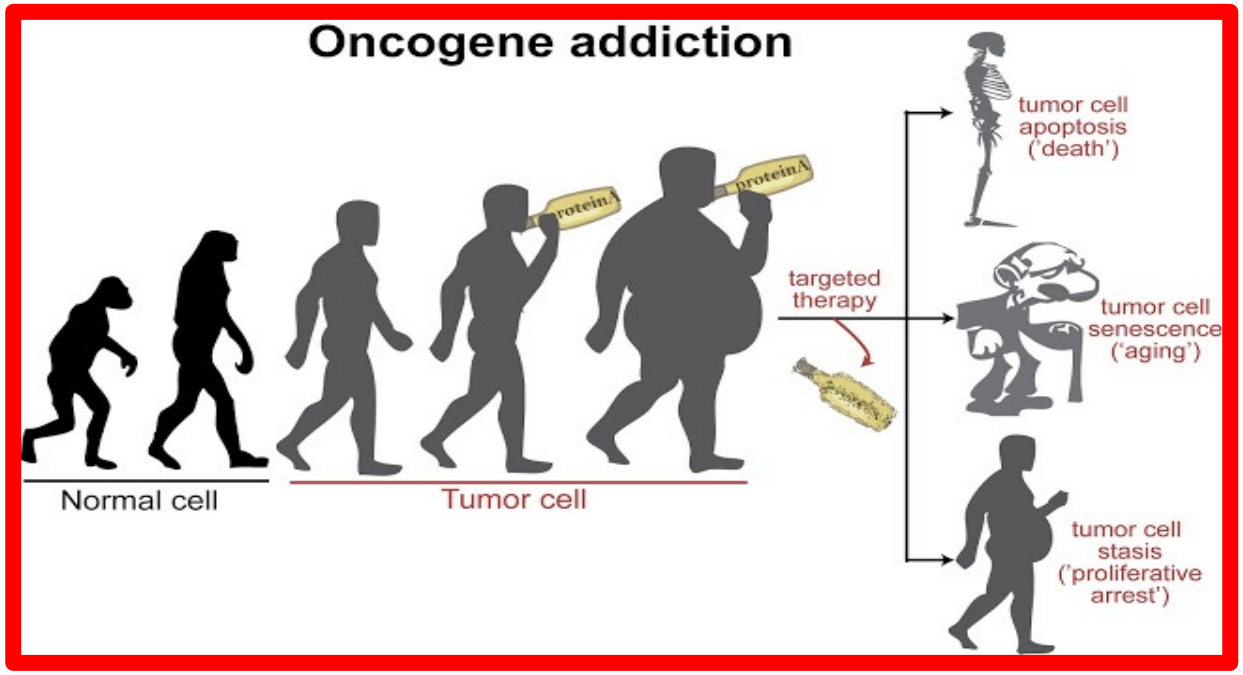


Bernard Weinstein, Columbia University, 1999

Garben K et al, JNCI 2007

Alonzo MM et al, Cancer Letter 2008

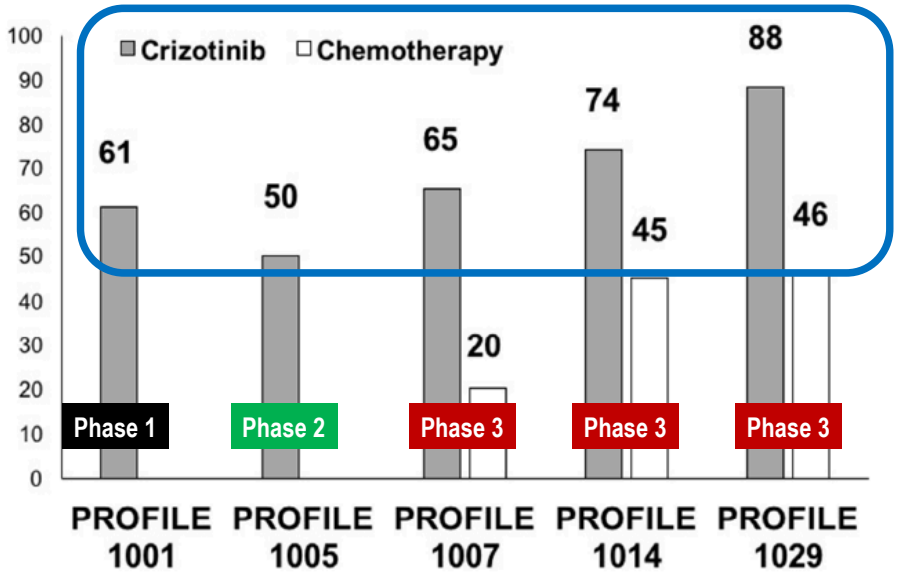
Treatment Opportunities



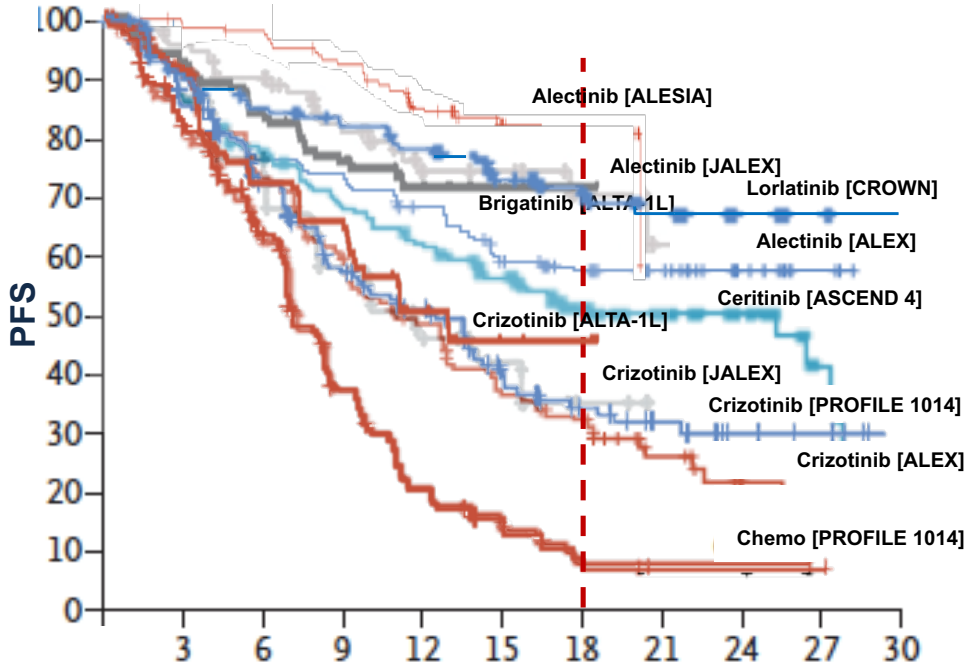
Thus, despite this complexity, tumor growth and survival can often be impaired by the inactivation of a single oncogene (Oncogene Addiction), which, if identified, may represent the rationale for molecular targeted therapy (the Achilles Heel).

ALK De-addiction: Crizotinib Activity across Studies and PFS Improvement due to Newer Upcoming TKIs Overtime

Consistent Activity of Crizotinib (ORR) Across Developmental Phases (from Phase 1 to 3)



Clinical Progress Overtime of *ALK*-Deaddiction



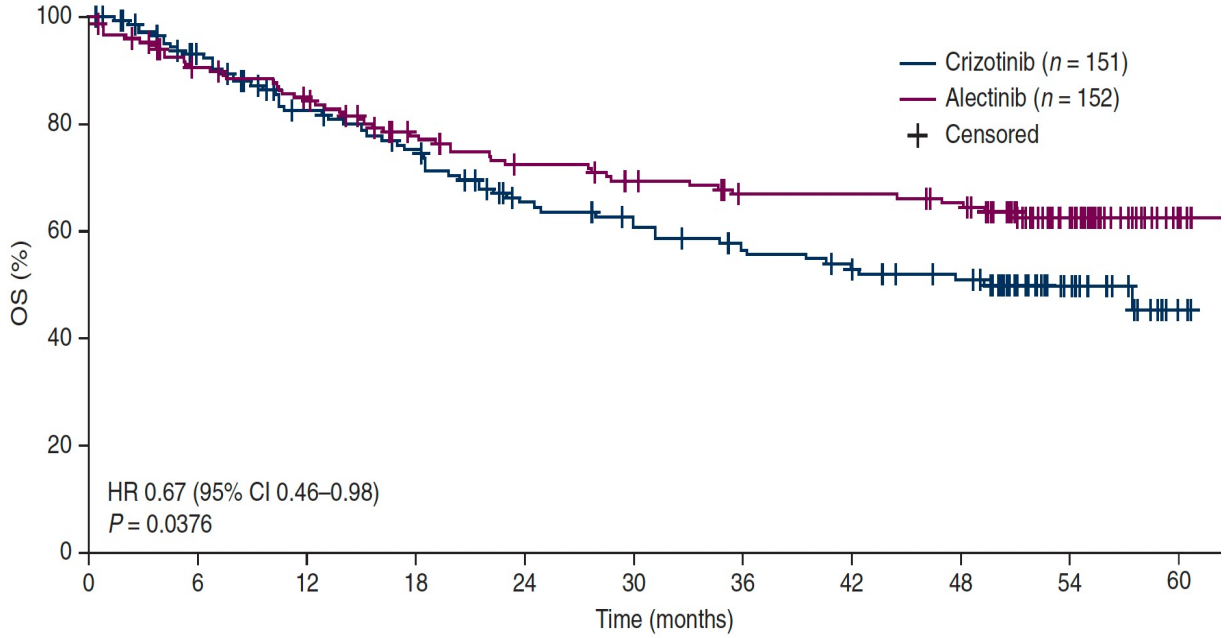
Average PFS (%) at 18 months	
57-78%	Alectinib Brigatinib Lorlatinib
50%	Ceritinib
30-45%	Crizotinib
<10%	Best Chemotherapy

Caccese M et al, Exp Opinion Pharm 2016

NB: PFS K-M Curves from PROFILE 1014, ASCEND 4, JALEX, ALEX, ALTA-1L, ALESIA, CROWN

ALK De-Addiction: OS Data with Alectinib in RCTs

ALEX: Survival Update

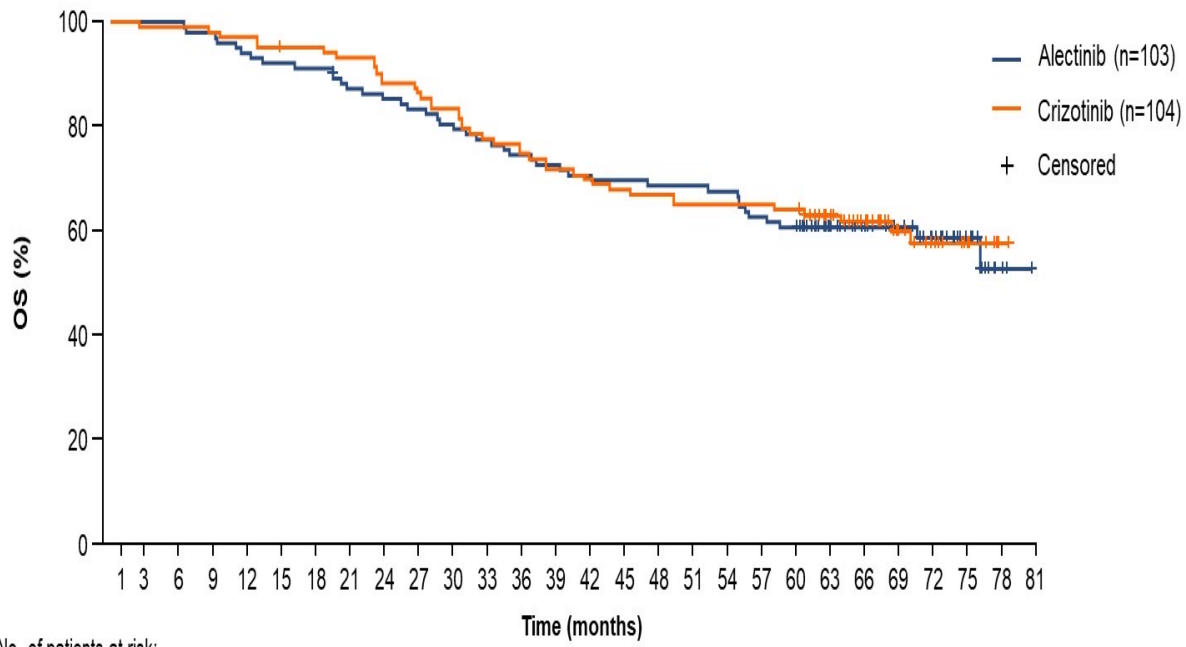


Number at risk

Alectinib	152	142	131	127	120	111	103	98	94	94	88	87	81	81	81	80	77	62	46	23	8
Crizotinib	151	141	128	116	104	100	93	84	73	71	67	63	60	59	55	51	48	35	18	12	3

Mok T et al, Ann Oncol 2020

J-ALEX: Final OS



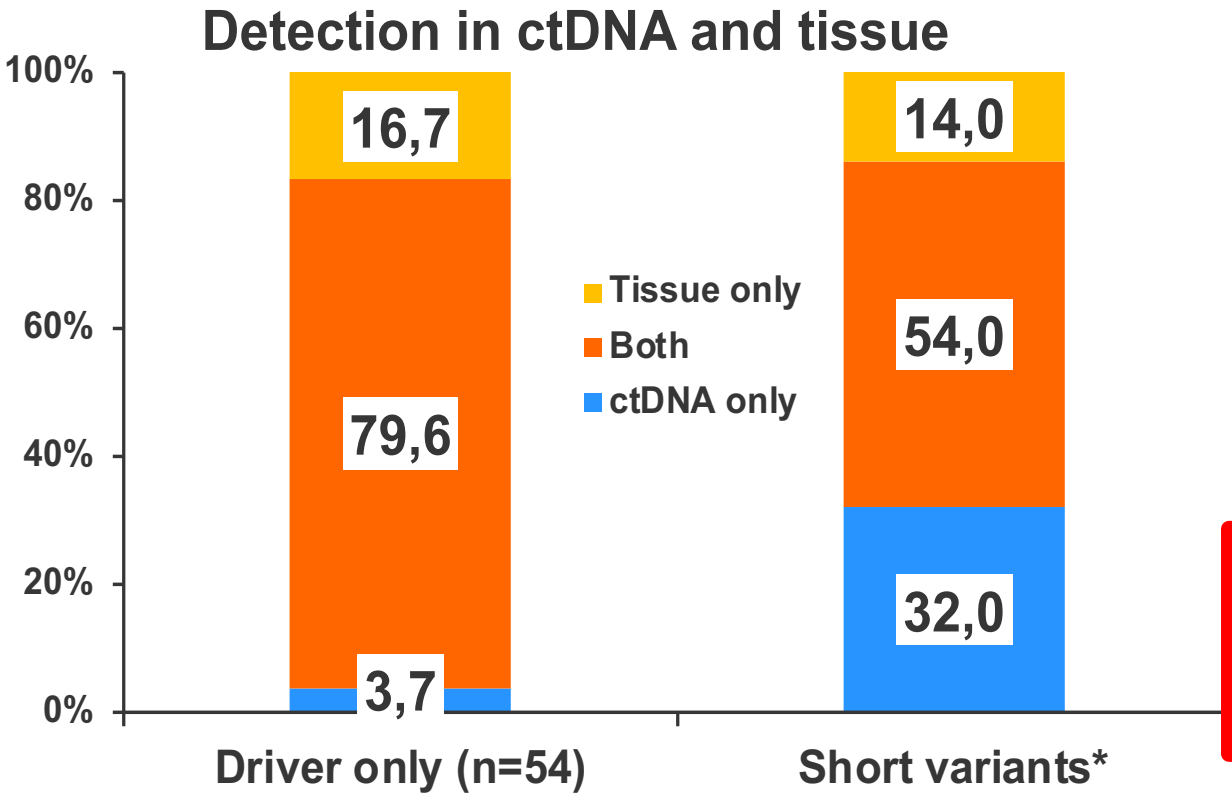
No. of patients at risk:

Crizotinib	104	103	103	102	101	98	98	96	91	88	86	80	77	74	72	70	69	67	67	67	66	54	42	27	20	10	2
Alectinib	103	103	103	101	97	95	94	89	87	85	82	79	76	74	72	71	70	70	69	64	62	48	40	31	23	13	3

Yoshioka H et al, ASCO 2021

Is ctDNA as RELIABLE & AFFORDABLE as Tissue in Depicting the Molecolar Portrait of NSCLC?

LUNGMAP Master Protocol: Concordance Between Plasma ctDNA (*FoundationONE CDx*) and Tissue Molecular Analysis (*FoundationACT*)



Mack PC et al, WCLC 2020

VALUE (multi-centre, prospective trial, 6 Canadian cancer centres - NCT03576937): cfDNA profiling *Guardant360TMassay* vs. Standard – Markov's MODEL

Actionable mutations present, n (%)	
By tumour tissue (TT) alone	77 (53%)
EGFR/ALK	58 (40%)
Other	19 (13%)
By liquid biopsy + TT	100 (68%)
EGFR/ALK	68 (47%)
Other	32 (22%)

Testing strategy	Cost (CAD$)	QALY	Incremental cost (CAD$)
Liquid biopsy + Tumour tissue biopsy	1,305,524	7.17	Reference
Tumour tissue biopsy alone	1,342,740	7.10	37,216

Eziels DA et al, WCLC 2021

Relationship between Blood Biomarkers and Activity: BFAST

- Unresectable, stage IIIB or IV NSCLC
- *ALK*+ by centralised blood screening only
- Treatment naïve
- ECOG PS 0–2

→ **Alectinib 600mg BID** →

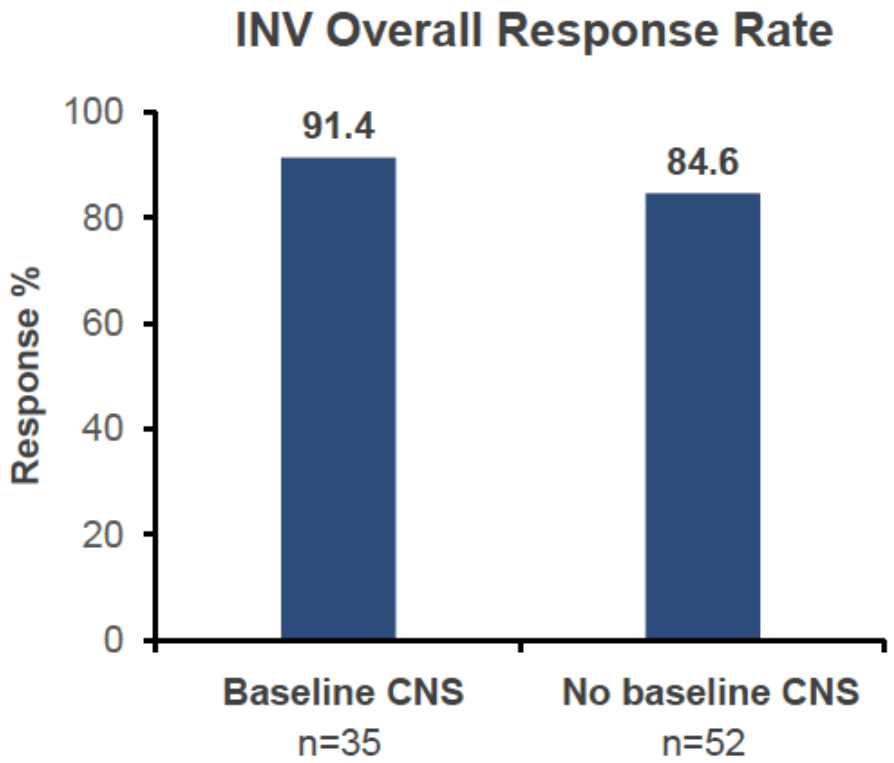
Until PD, toxicity, withdrawal or death

Primary endpoint
Confirmed ORR by investigator

Exploratory endpoint
Confirmed ORR by investigator for patients with baseline CNS metastases

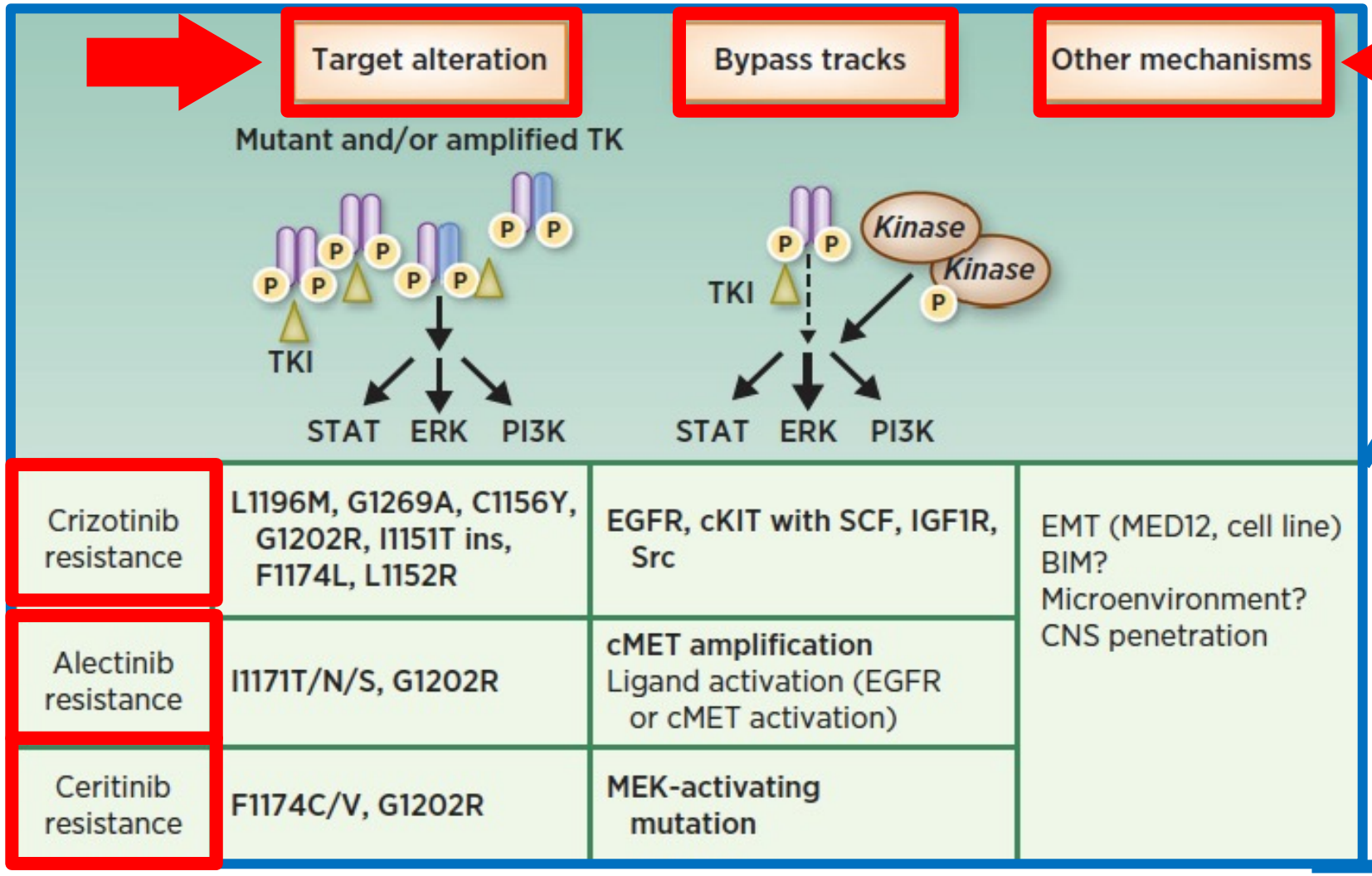
- 83.9% — N=73 ***EML4***
- 3.4% — N=3 **Not identified**
- 2.3% — N=2 ***CLIP4***
- 1.4% — N=1 ***ERCC8*** ***DCTN1*** ***STRN*** ***ETV6*** ***AAK1*** ***TMEM178*** ***KIF5B*** ***PGM2*** ***EPS8***

- The **5.4%** (119 of 2219) prevalence of *ALK* in the screening population is close to the expected rate of 5%[1]
- 38/87 (43.7%) patients had a ***TP53*** mutation
- **Median bTMB** at baseline was **two mutations** (range: 0 to 21)
  - 3/87 (3.4%) patients had bTMB ≥ 16 mutations



Gadgeel S et al, ESMO 2019

Resistance to Targeted Therapies: Mechanisms



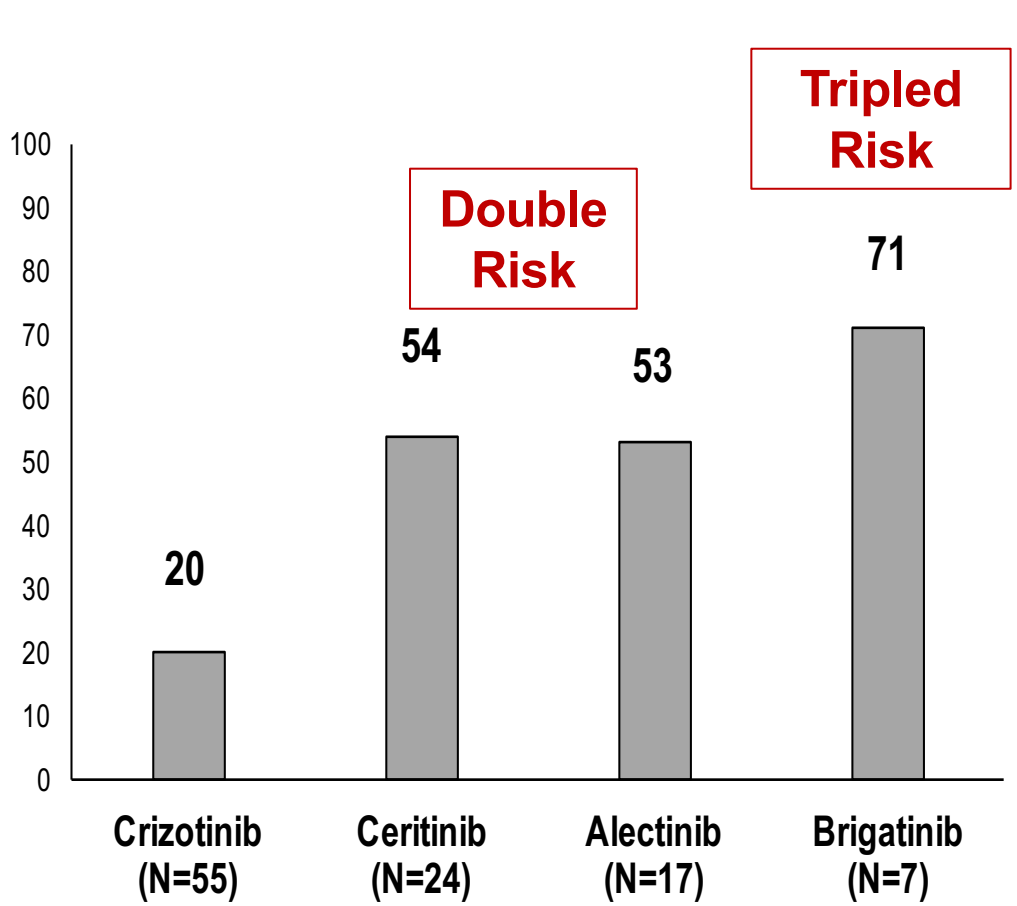
	Target alteration	Bypass tracks	Other mechanisms
Crizotinib resistance	L1196M, G1269A, C1156Y, G1202R, I1151T ins, F1174L, L1152R	EGFR, cKIT with SCF, IGF1R, Src	EMT (MED12, cell line) BIM? Microenvironment? CNS penetration
Alectinib resistance	I1171T/N/S, G1202R	cMET amplification Ligand activation (EGFR or cMET activation)	
Ceritinib resistance	F1174C/V, G1202R	MEK-activating mutation	

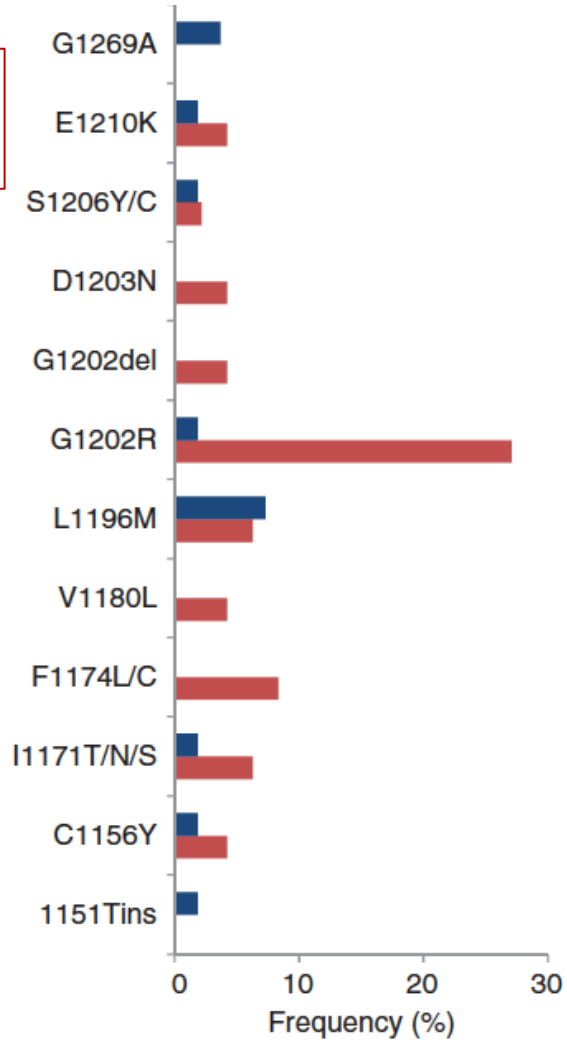
- EGFR activation
- MAPK pathway reactivation
- c-KIT amplification and SCF overexpression
- SRC activation
- IGF-1R activation
- Ligand-mediated HER2/3 activation
- Protein kinase C activation
- Small cell transformation (rare)

Katayama R et al Clin Cancer Res 2016
Modifed from Gainor JF, ASCO 2017

ALK-Resistance Mutations (%) are differentaly expressed according to TKI

TKI Selective Pressure Significantly Influences Mechanism of Resistance





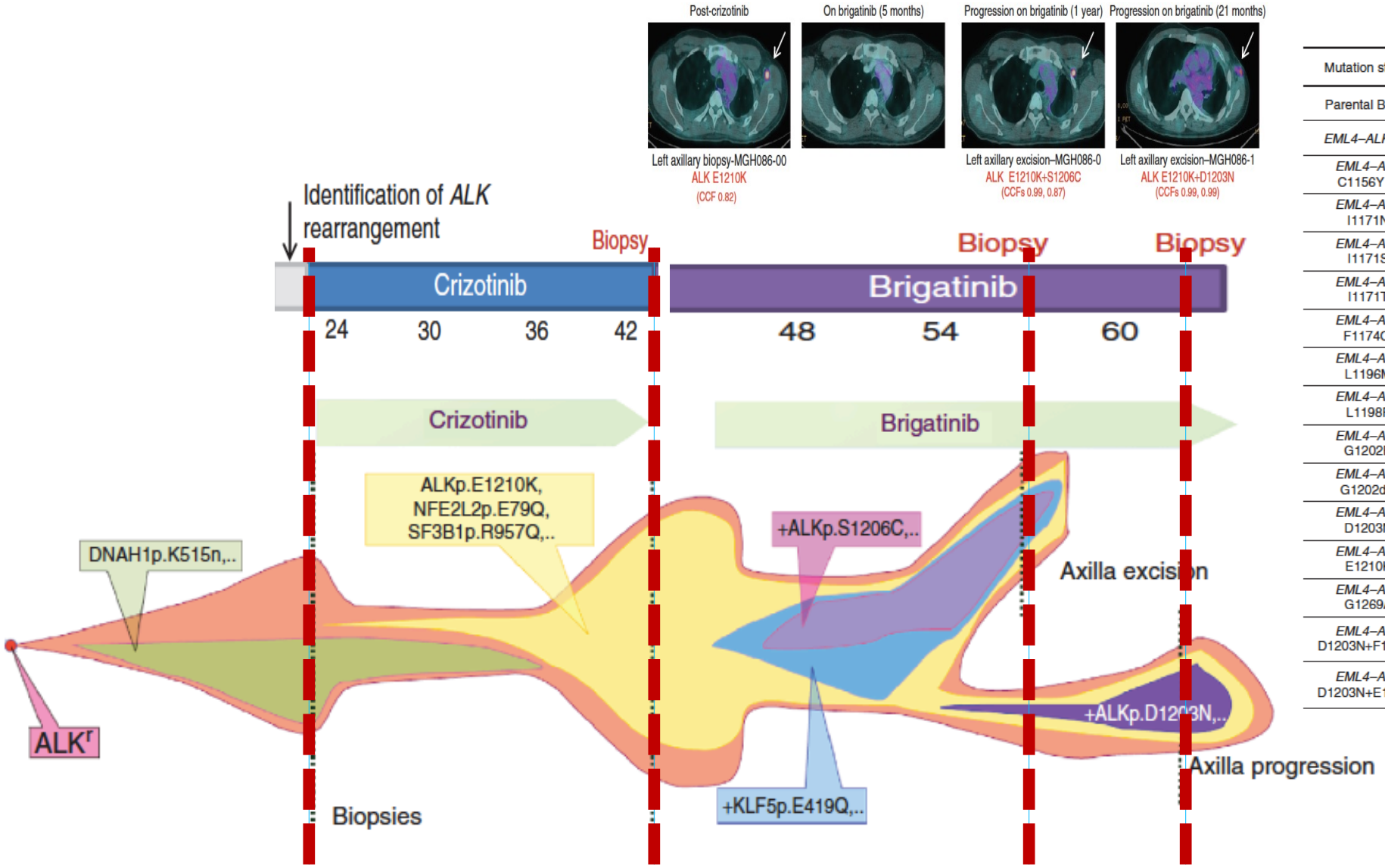
ALK resistance mutations[a]	Crizotinib (*N* = 55)	Ceritinib (*N* = 24)	Alectinib (*N* = 17)	Brigatinib (*N* = 7)
1151Tins	2%	0%	0%	0%
C1156Y	2%	8%	0%	0%
I1171T/N/S	2%	4%	12%	0%
F1174L/C	0%	17%	0%	0%
V1180L	0%	4%	6%	0%
L1196M	7%	8%	6%	0%
G1202R	2%	21%	29%	43%
G1202del	0%	8%	0%	0%
D1203N	0%	4%	0%	14%
S1206Y/C	2%	0%	0%	14%
E1210K	2%	0%	0%	29%
G1269A	4%	0%	0%	0%
ALK mutations[b]	**20%**	**54%**	**53%**	**71%**

Post crizotinib

Post 2nd gen. ALK inhibitor

Gainor JD et al, Cancer Discovery 2016

Monitoring Patient' Molecular Mechanisms of Resistance to ALK-TKIs



Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

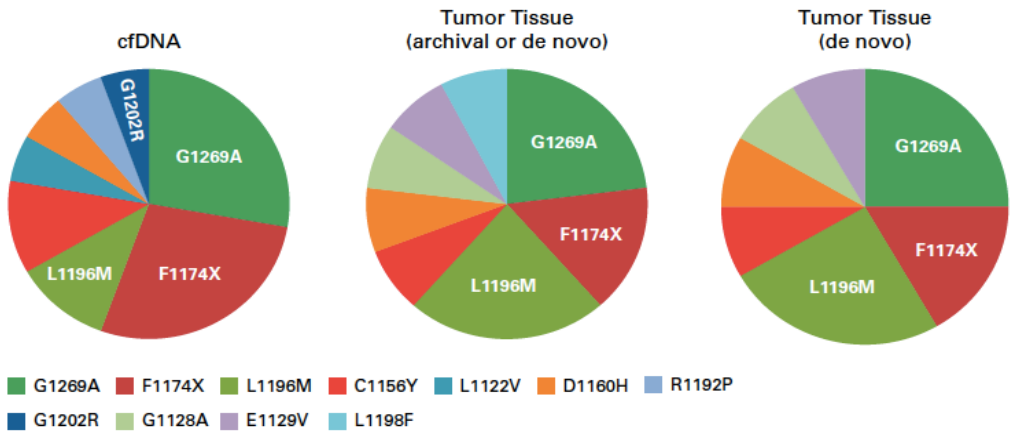
$IC_{50} > 50 < 200$ nmol/L

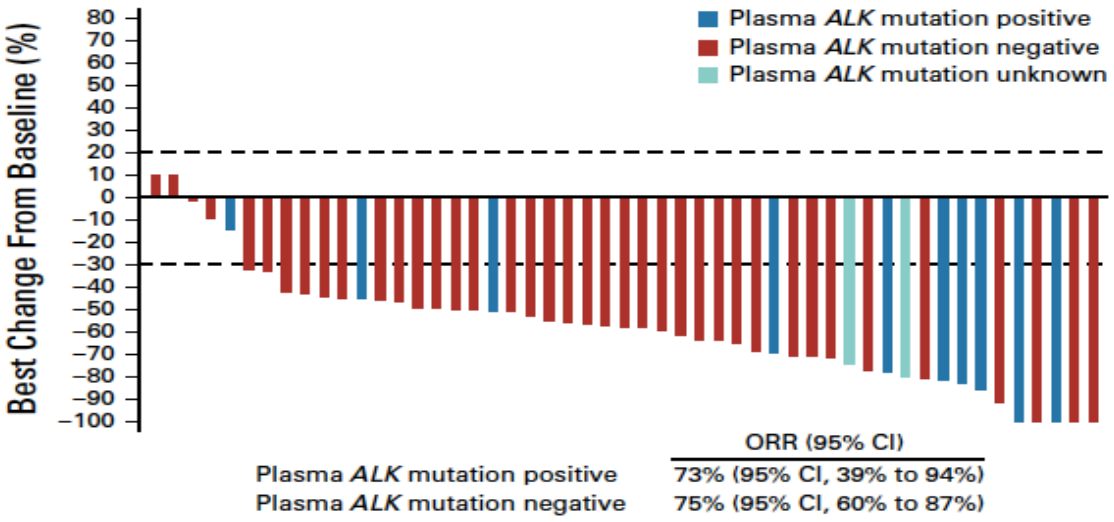
$IC_{50} \geq 200$ nmol/L

Gainor J et al, Cancer Discovery 2016

EML4-ALK Variants may influence following resistance mechanism

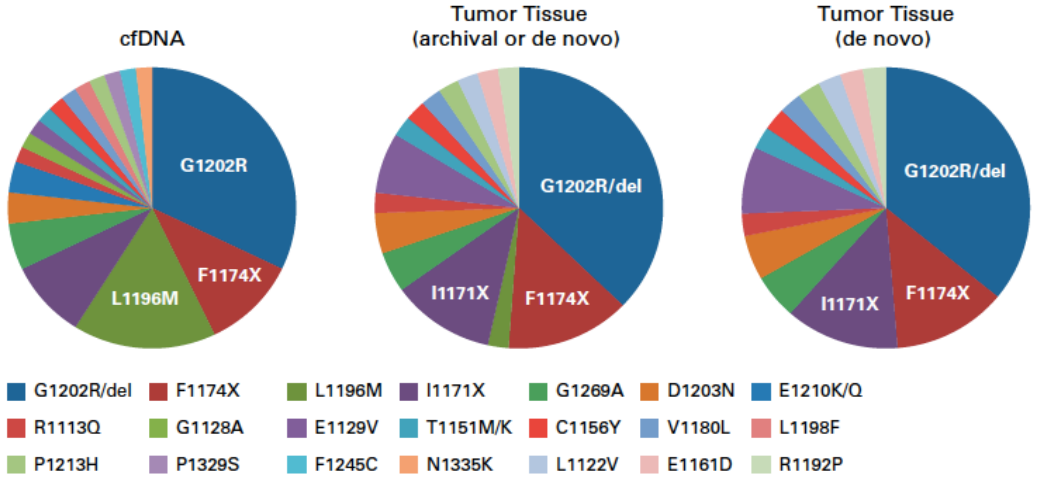
Prior Crizotinib

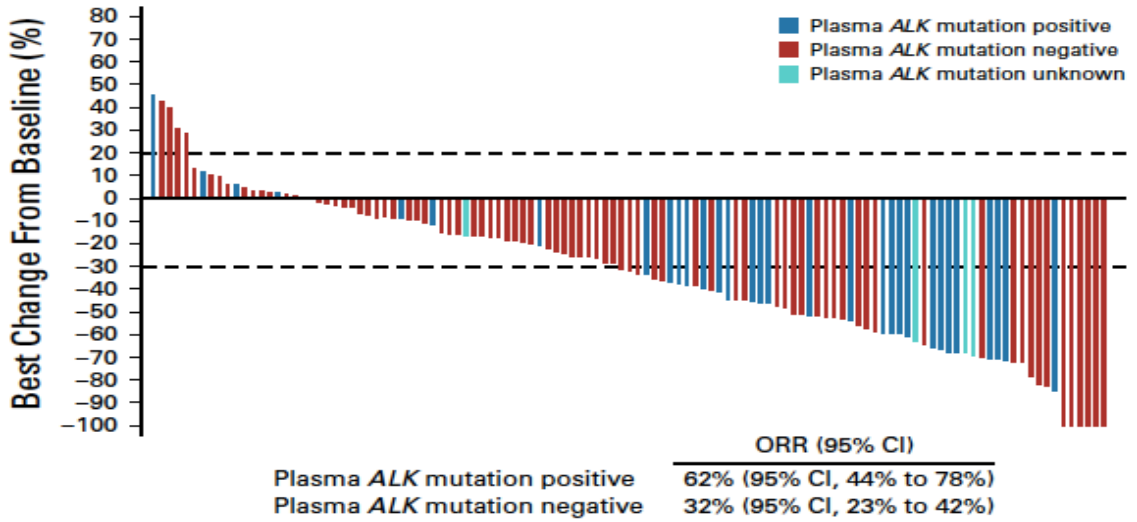




	ORR (95% CI)
Plasma *ALK* mutation positive	73% (95% CI, 39% to 94%)
Plasma *ALK* mutation negative	75% (95% CI, 60% to 87%)

Prior Second-Generation TKI(s)



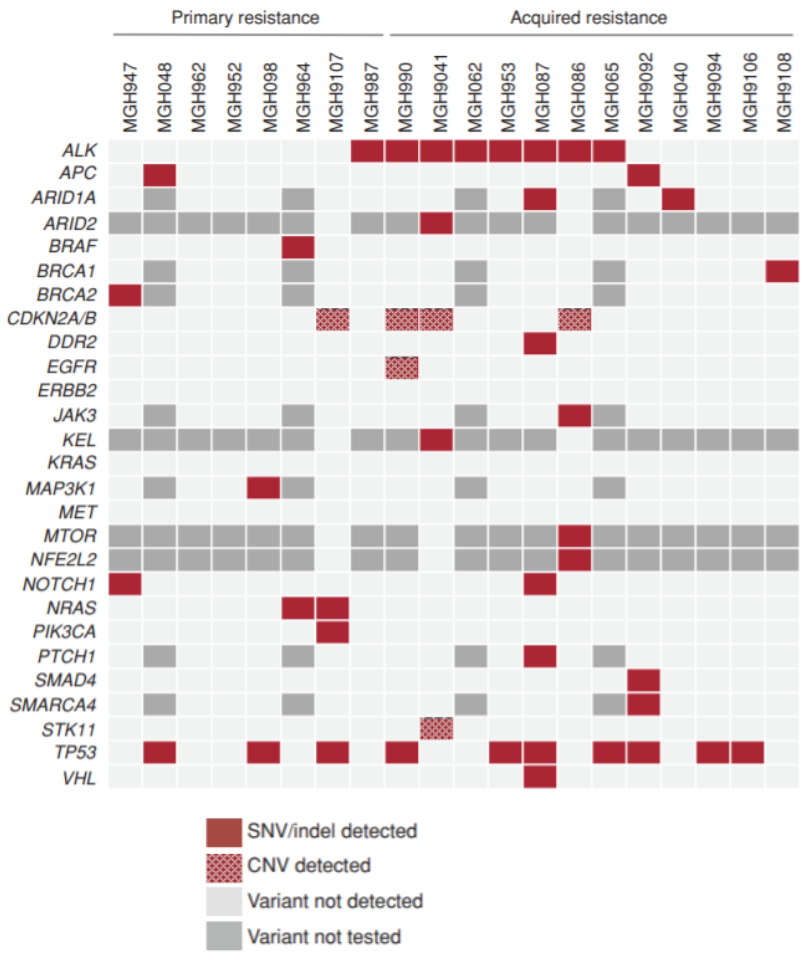


	ORR (95% CI)
Plasma *ALK* mutation positive	62% (95% CI, 44% to 78%)
Plasma *ALK* mutation negative	32% (95% CI, 23% to 42%)

Shaw A et al, J Clin Oncol 2019

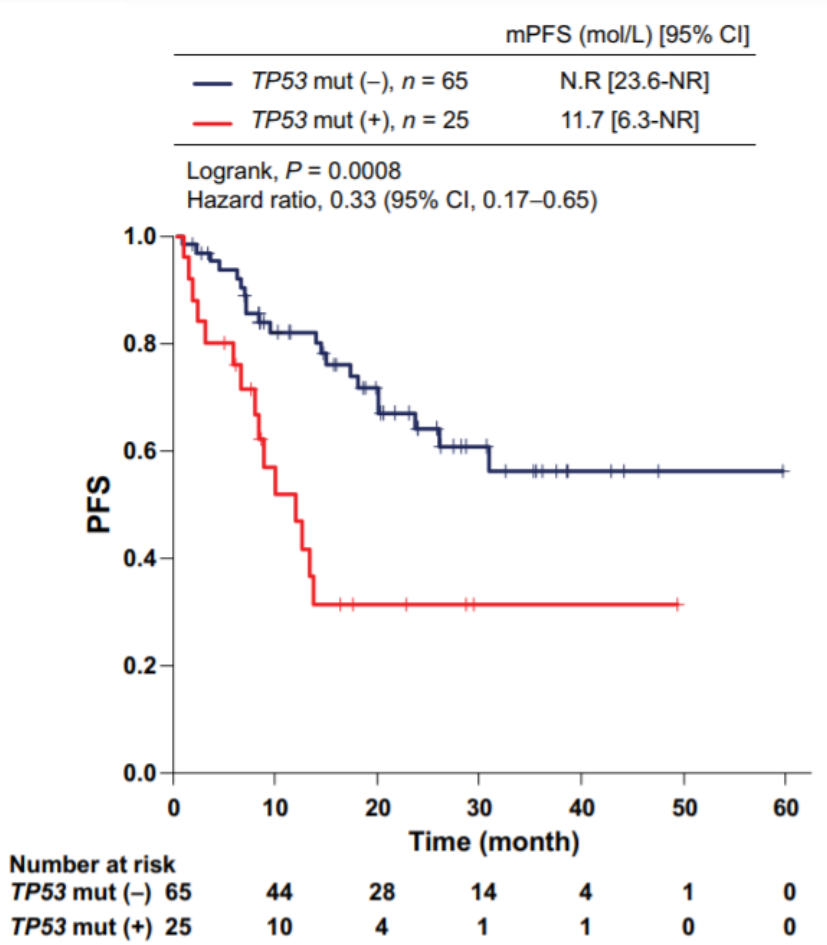
Predictors of Resistance to TKIs in ALK-addicted NSCLC Pts

Genomics of Lorlatinib-Resistant ALK+ NSCLC



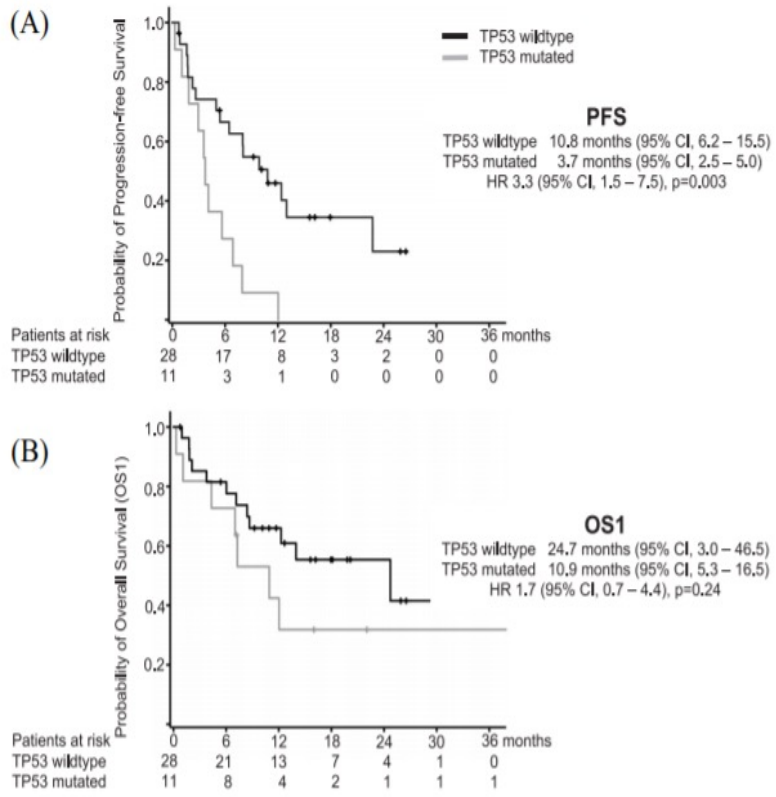
Yoda et al, Cancer Disc 2018

Lorlatinib EAP – Japan (125 patients)



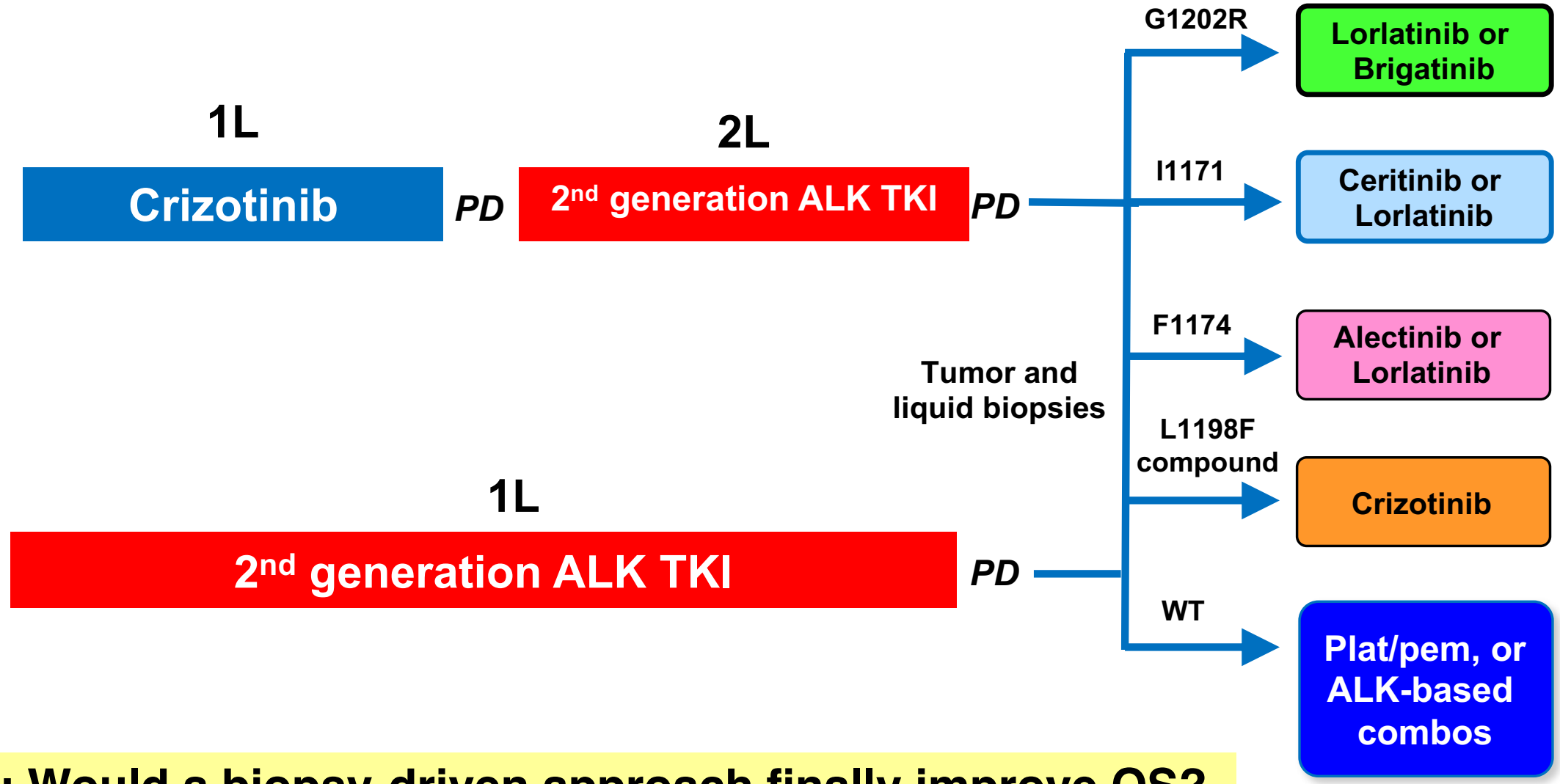
Tanimoto et al, Clin 2021

Lorlatinib EAP – Germany (37 patients)



Frost et al. Ther Adv Med Onc 2021

Treatment Tailoring upon PD & Resistance: ALK Master Protocol

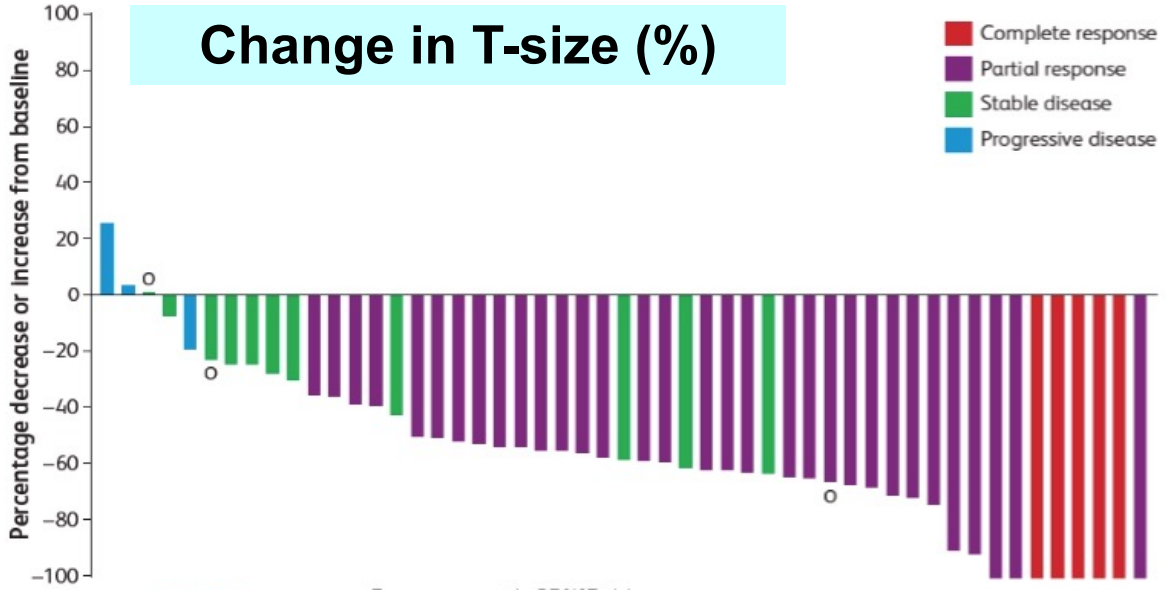


AIM: Would a biopsy-driven approach finally improve OS?

Shaw A, WCLC 2017

ROS1: Updated Evidences with Crizo

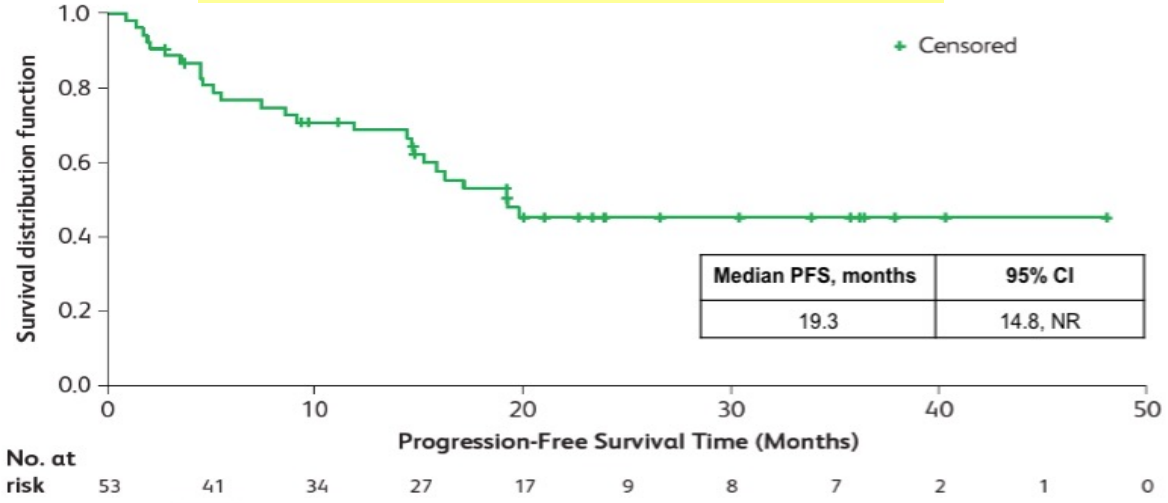
Change in T-size (%)



ORR (%)

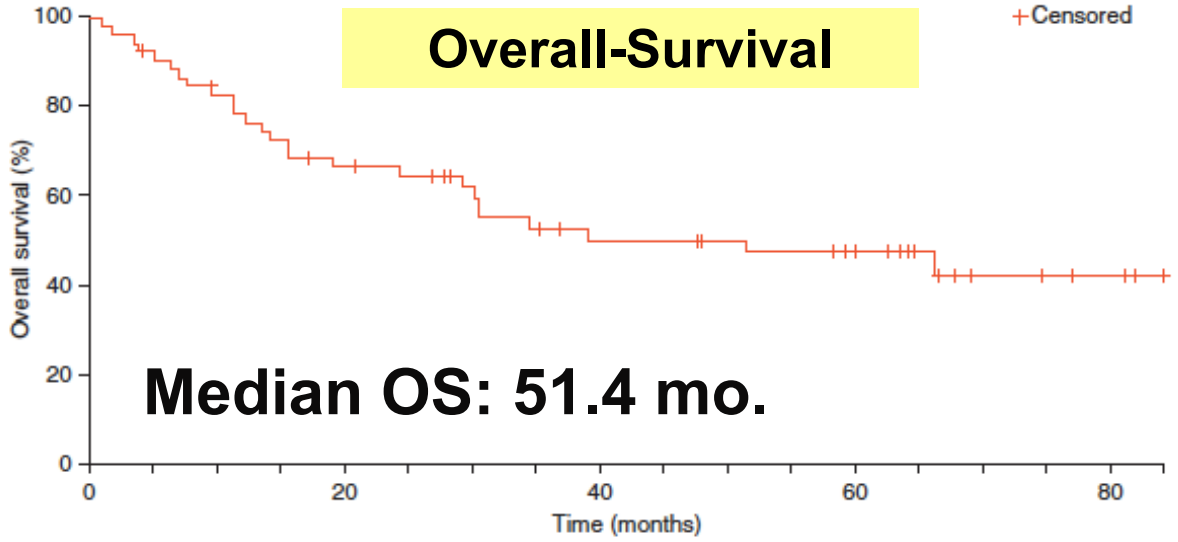
Objective response rate	
By derived investigator assessment, % (95% CI)	69.8 (55.7, 81.7)
Complete response, n	5
Partial response, n	32
Stable disease (≥ 6 weeks), n	11
Progressive disease, n	3
Median time to first tumor response, weeks (range)	7.9 (4.3–32.0)
Median duration of response, months (95% CI)	NR (15.2, NR)
Survival probability, % (95% CI)	
6-month	90.6 (78.8, 96.0)
12-month	79.0 (65.3, 87.8)

Progression-Free-Survival



Median PFS, months	95% CI
19.3	14.8, NR

Overall-Survival



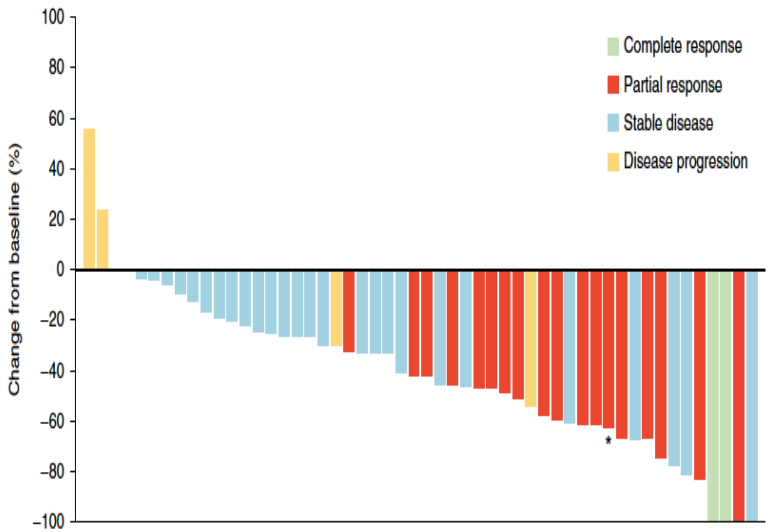
Median OS: 51.4 mo.

Shaw A et al, Ann Oncol 2019

Phase 1 Exp/2 Results: *METex14 De-addiction*

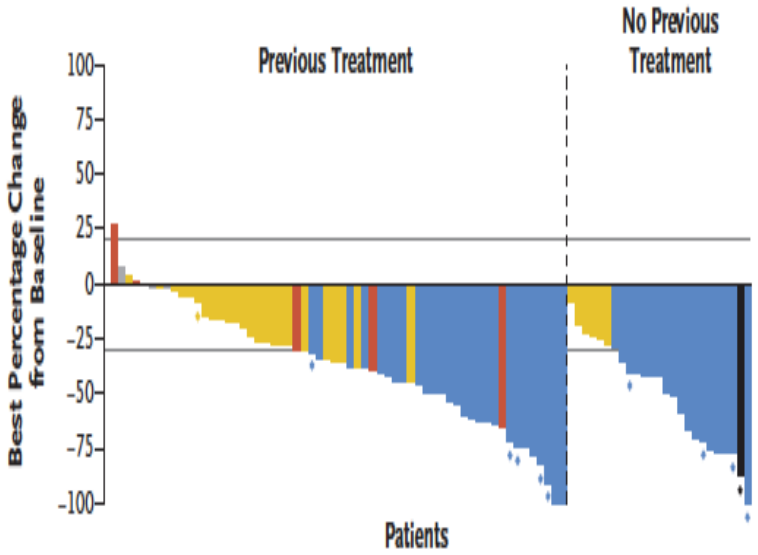
METex14 Mut [2.4%]

CRIZOTINIB



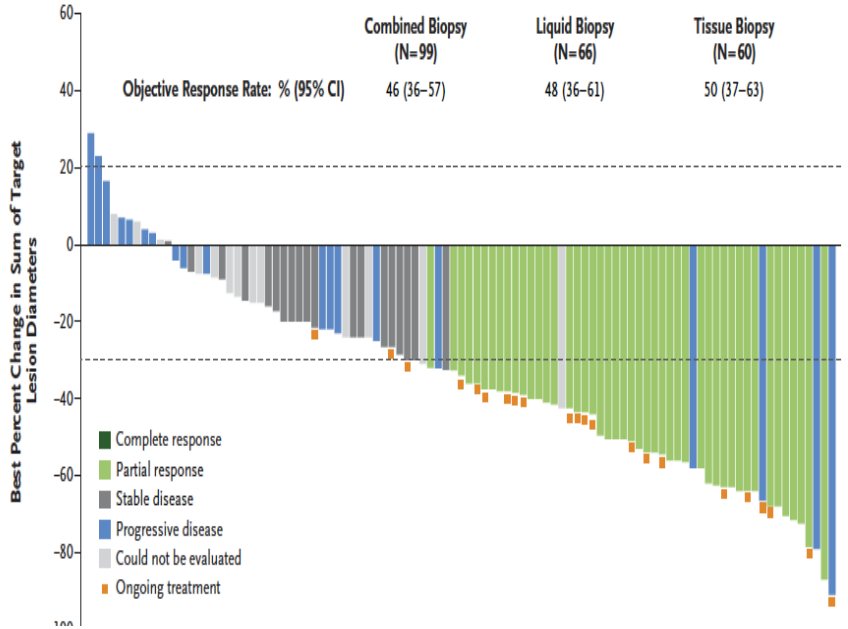
Drilon A et al, Nat Med 2020

CAPMATINIB



Wolf J et al, NEJM 2020

TEPOTINIB

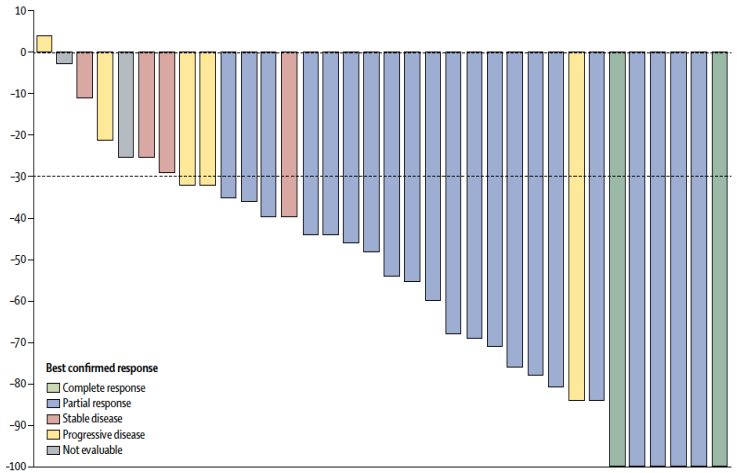


Paik PK et al, NEJM 2020

Key Results of De-Addiction in NSCLC [*BRAF & KRAS^{G12C}*]

BRAF Mutation [4-5%] :
Dabrafenib + Trametinib

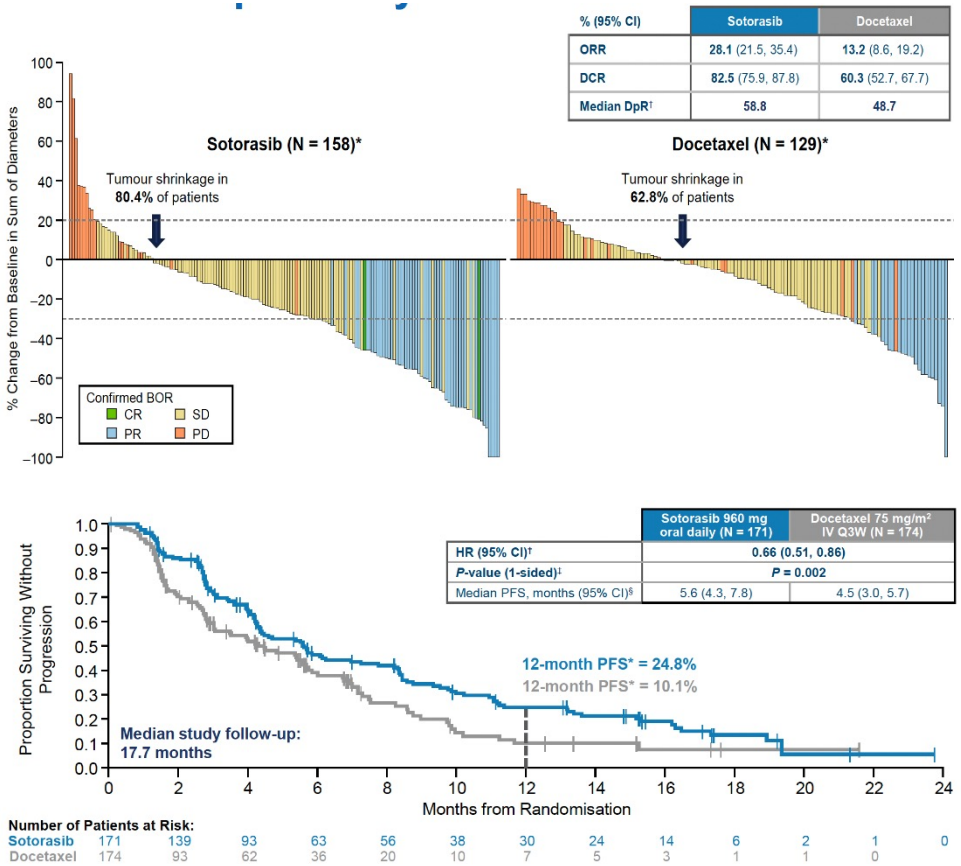
ORR 64.0%
[95% CI 46–69]



Planchard D et al, Lancet Oncol 2017

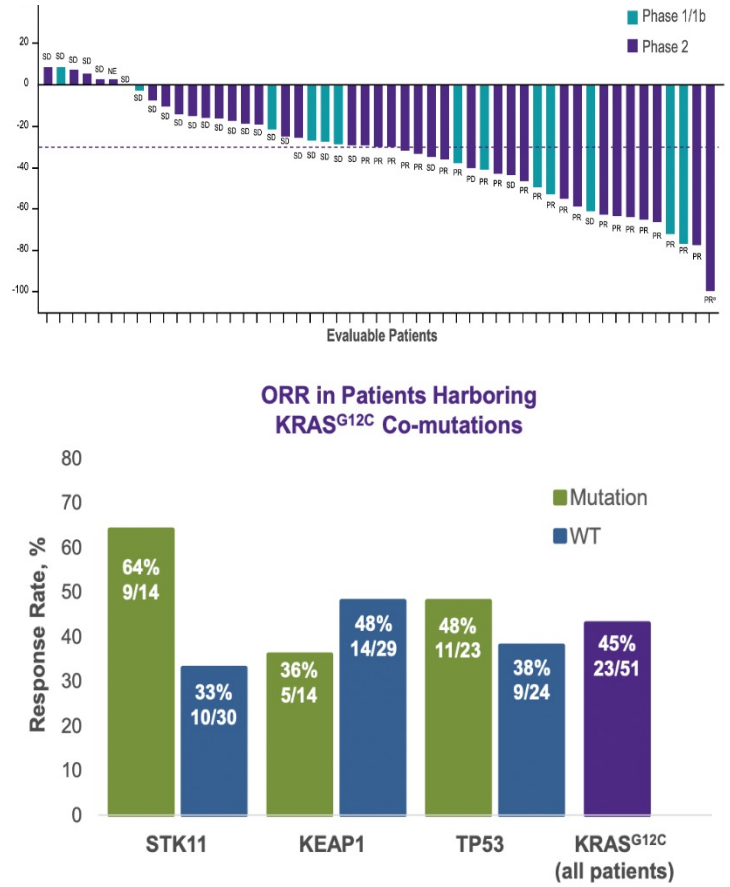
KRAS G12C Mut. [12%]

Sotorasib [AMG 510]



Johnson M et al, ESMO 2022

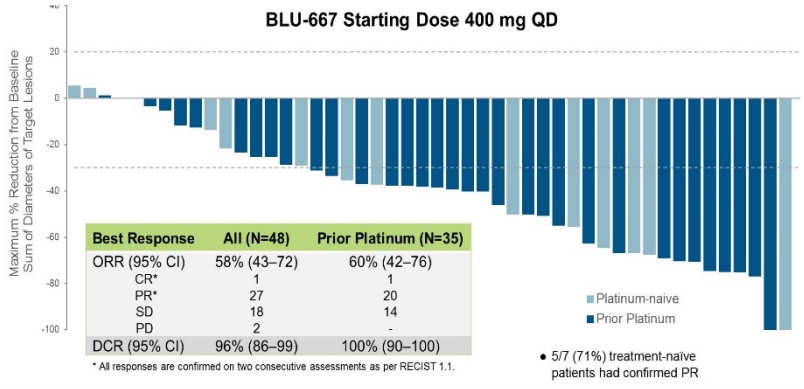
Adagrasib [MRTX849]



Riely G et al, ELCC 2021

'*Rare*' [<3%] Genomic Drivers WITH Ongoing Phase III

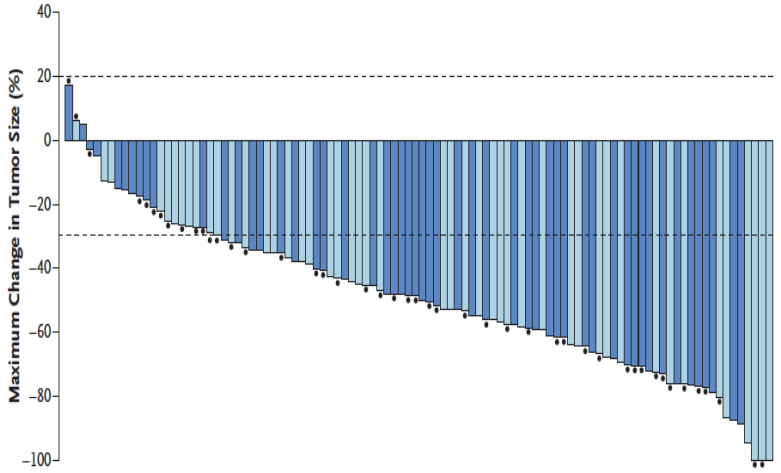
RET Fusions [1.5-2%]: Pralsetinib & Selpercatinib



Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

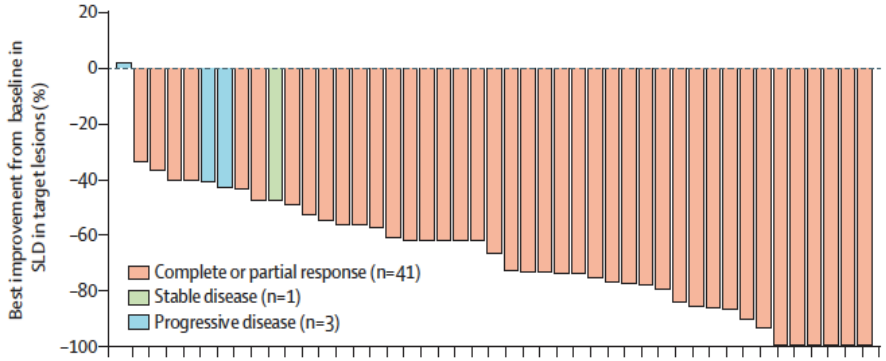
* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

Gainor J et al, ASCO 2019

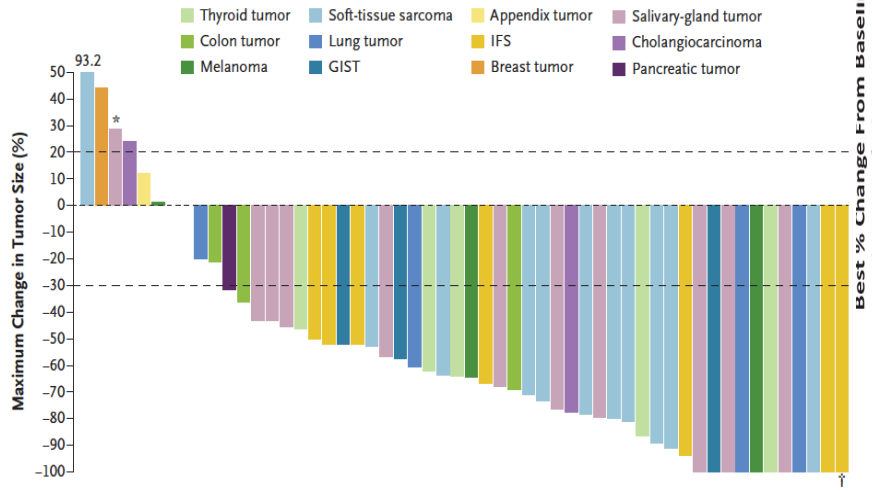


Drilon A et al, NEJM 2020

NTRK Copy Number Alt. [2-3%] : Entrectinib & Larotrectinib



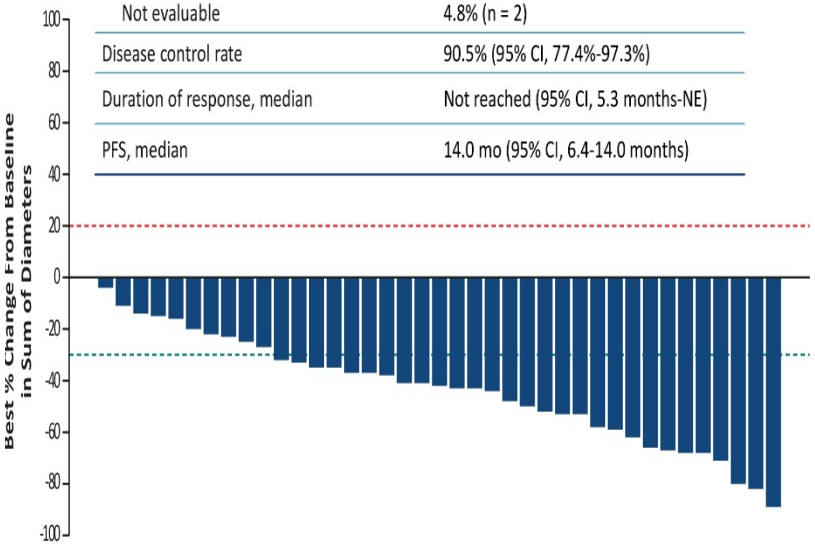
Drilon A et al, Lancet Oncol 2019



Drilon A et al, N Engl J Med 2018

HER2. Mut [1-3%]: Trastuzumab Deruxtecan

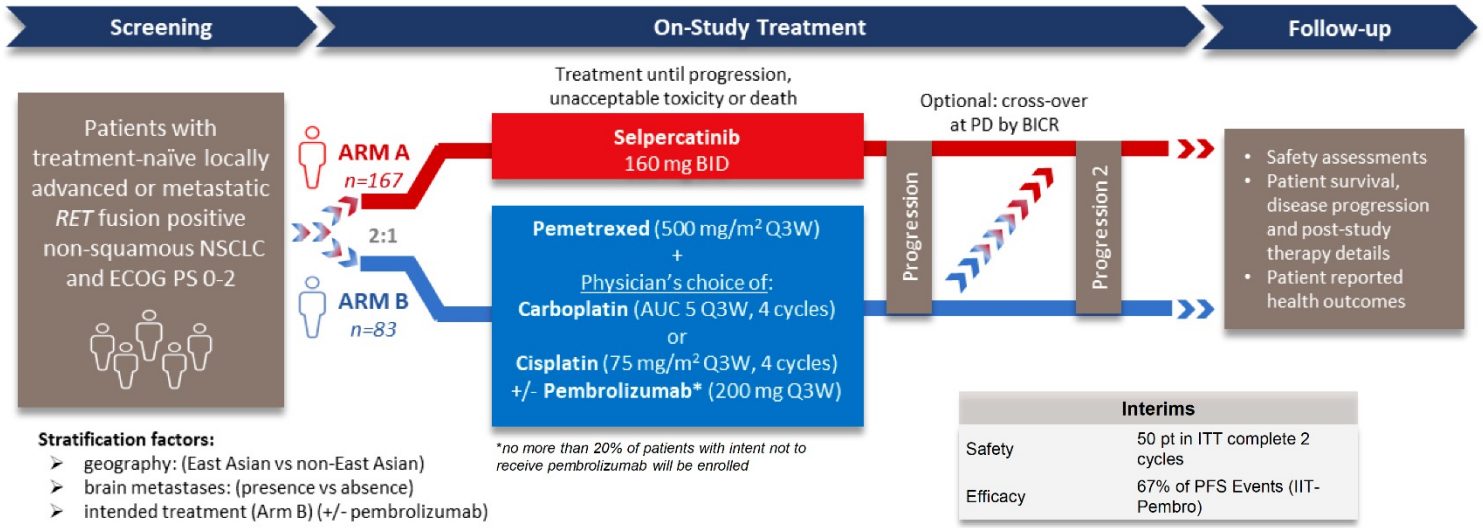
	Patients (N = 42)
Confirmed ORR by ICR	61.9% (n = 26) (95% CI, 45.6%-76.4%)
CR	2.4% (n = 1)
PR	59.5% (n = 25)
SD	28.6% (n = 12)
PD	4.8% (n = 2)
Not evaluable	4.8% (n = 2)
Disease control rate	90.5% (95% CI, 77.4%-97.3%)
Duration of response, median	Not reached (95% CI, 5.3 months-NE)
PFS, median	14.0 mo (95% CI, 6.4-14.0 months)



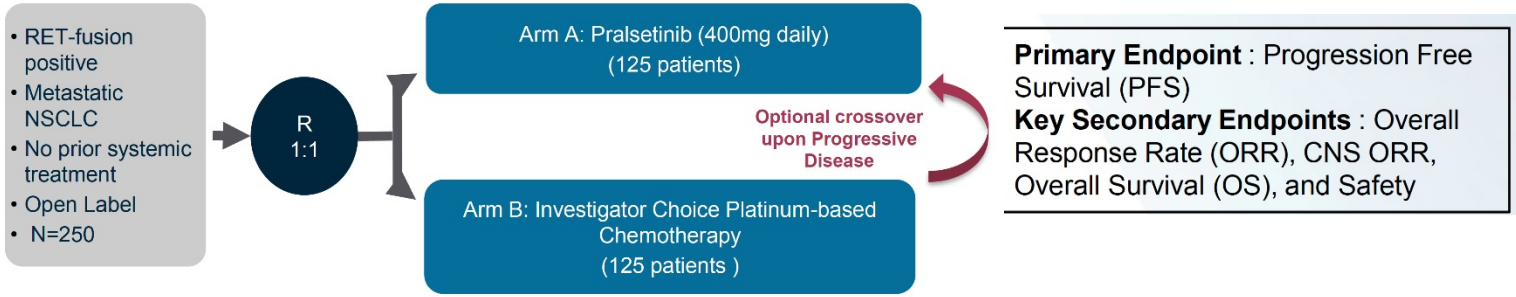
Le R et al, NEJM 2022

Ongoing Randomized Ph.III, First Line

LIBRETTO-431



AcceleRET



- Investigator's choice includes:
  - **(1) Non-Squamous histology:** Carboplatin or cisplatin / pemetrexed (with opt. pemetrexed maintenance)
    - Investigator's choice as above with pembrolizumab
  - **(2) Squamous histology:** carboplatin or cisplatin / gemcitabine

Courtesy of Garassino M, ELCC 2022

EGFR De-addiction: Osimertinib Does Improve Outcome After Adjuvant Chemo for Resected NSCLC

ADAURA Trial

Key patient inclusion criteria
- Completely resected stage IB, II, IIIA NSCLC
- With or without adjuvant chemotherapy
- Confirmed EGFR mutation (Ex19del/L858R)
- WHO PS 0–1

(n=682)

R 1:1

Osimertinib 80 mg QD (n=339) → PD/3 years/ discontinuation

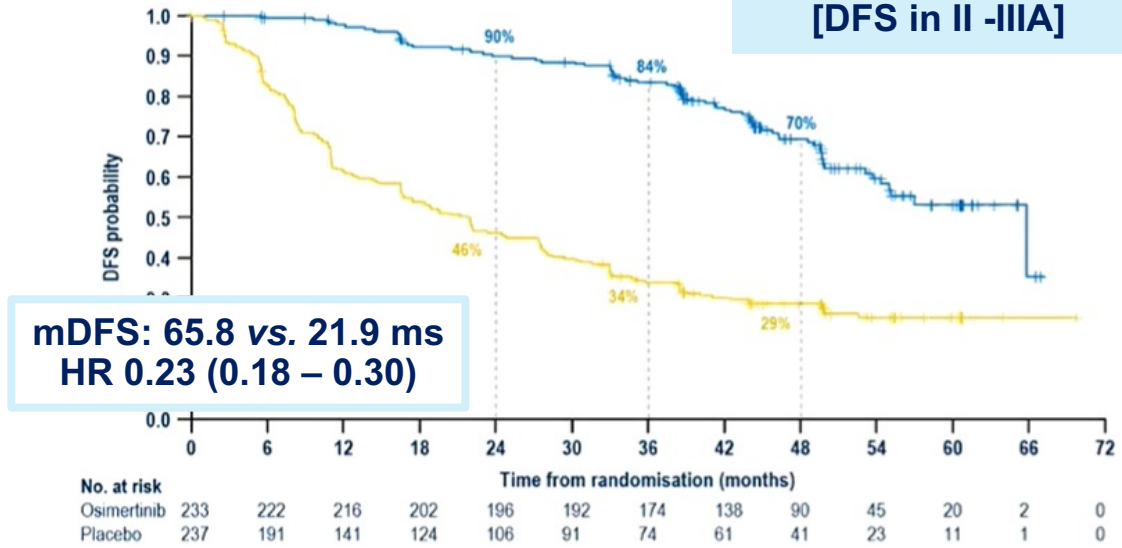
Placebo QD (n=343) → PD/3 years/ discontinuation

Stratification
- Stage (IB vs. II vs. IIIA)
- EGFRm (Ex19del vs. L858R)
- Race (Asian vs. non-Asian)

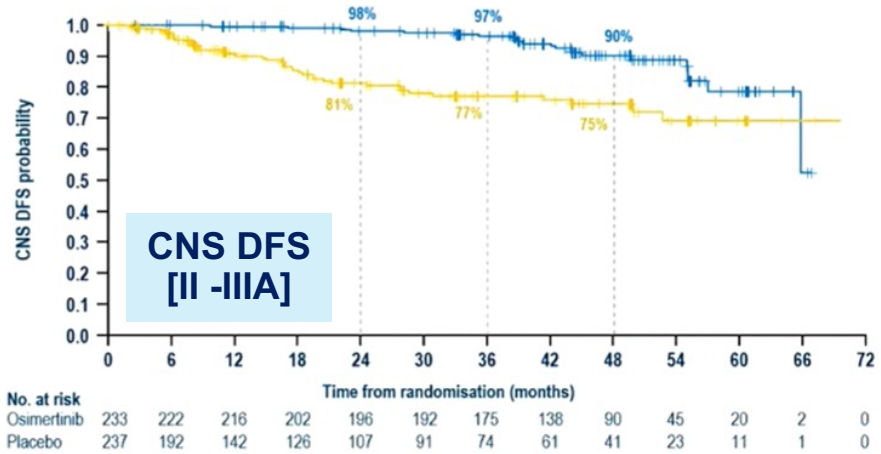
Primary endpoint
- DFS in stage II/IIIA patients (investigator assessment)

Secondary endpoints
- DFS in overall population, DFS at 2, 3, 4, and 5 years, OS, safety, HRQoL

PRIMARY ENDPOINT [DFS in II -IIIA]

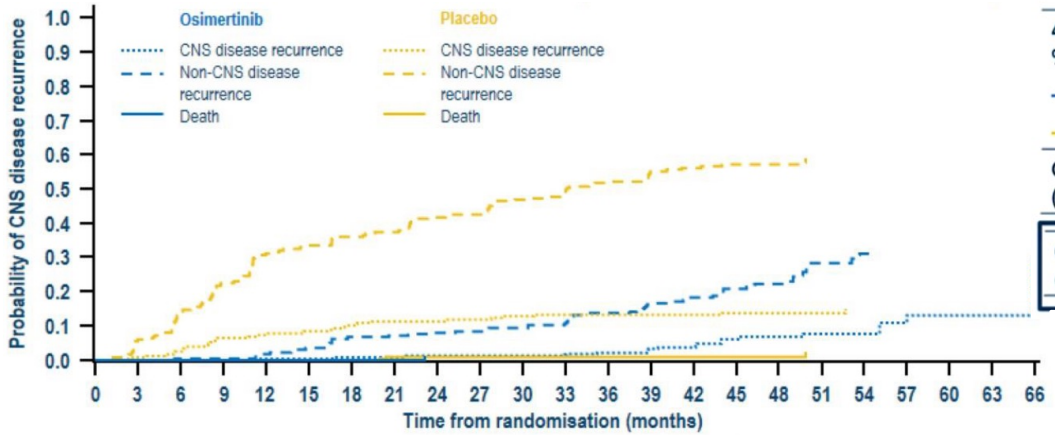


mDFS: 65.8 *vs.* 21.9 ms
HR 0.23 (0.18 – 0.30)



CNS DFS [II -IIIA]

mCNS DFS: NR *vs.* NR
HR 0.24 (0.14 – 0.42)



	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (70, 87)	74 (64, 82)	65 (54, 74)
– Placebo	59 (48, 68)	42 (33, 51)	14 (8, 22)
Overall HR (95% CI)	0.41 (0.23, 0.69)	0.34 (0.23, 0.52)	0.20 (0.14, 0.29)
Overall HR (95% CI)	0.44 (0.25, 0.76)	0.33 (0.21, 0.50)	0.22 (0.15, 0.31)

Benefit was highly consistent on restaging AJCC 8th ed.

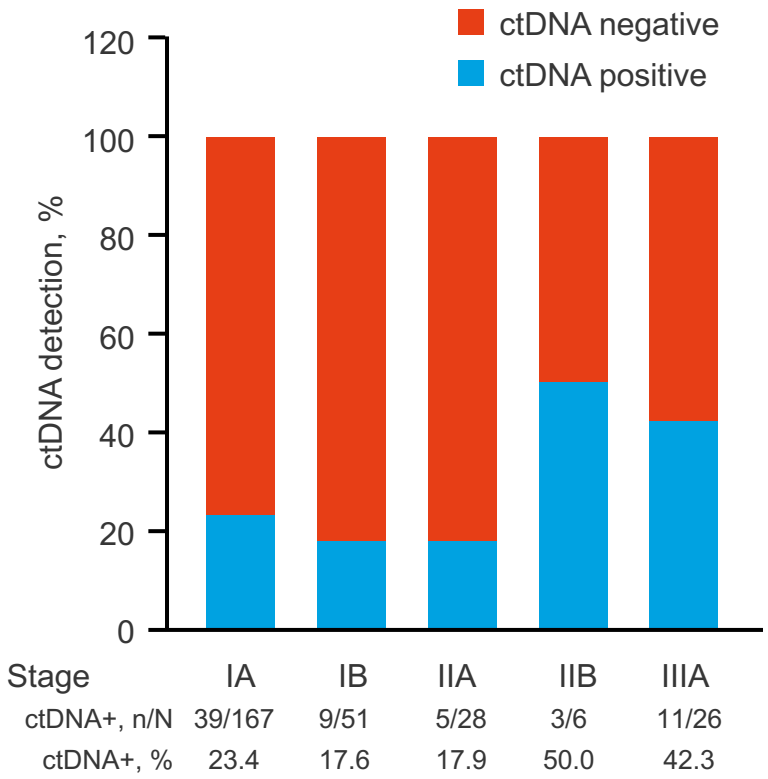
Estimated probability of CNS recurrence at 36 ms
2% osimertinib *vs.* 13% placebo

Tsuboi M et al, ESMO Congress 2022

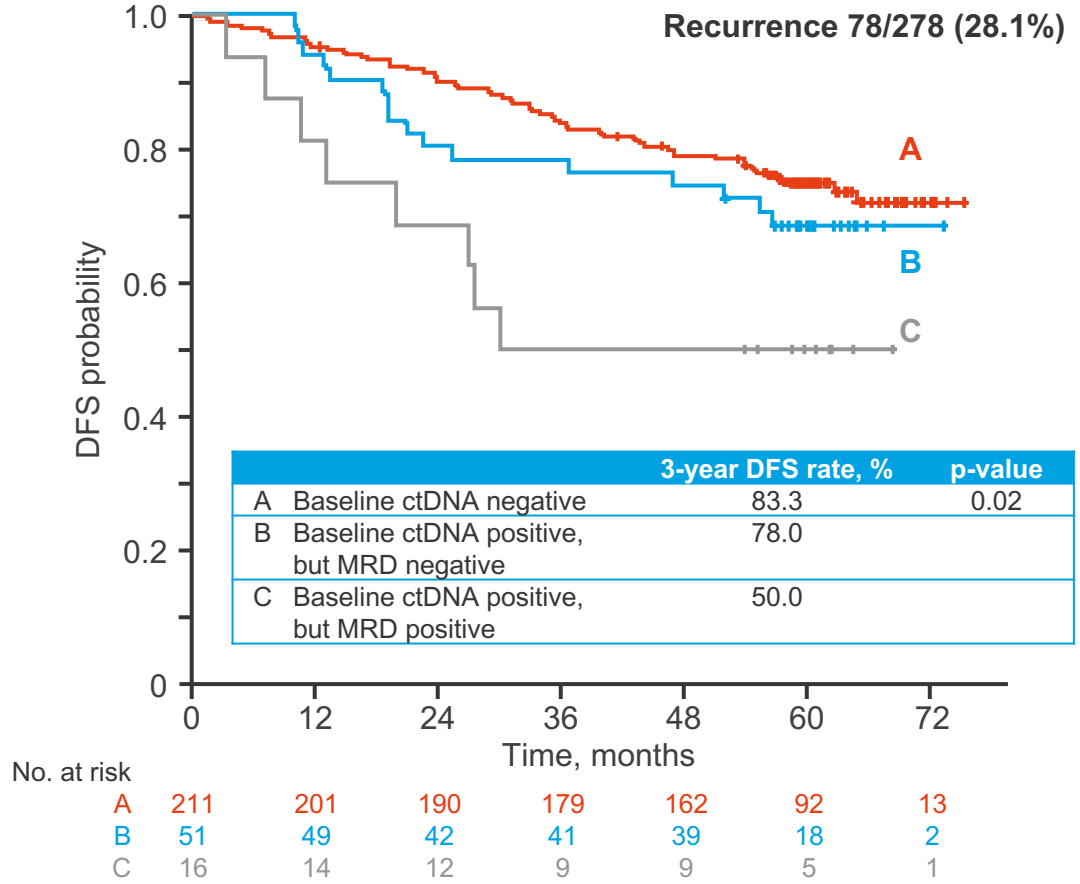
933MO: Longitudinal monitoring of circulating tumor DNA from plasma in patients with curative resected stage IA-IIIA EGFR mutant non-small cell lung cancer – Ahn M-J, et al

- **Key results**

Baseline ctDNA detection rate



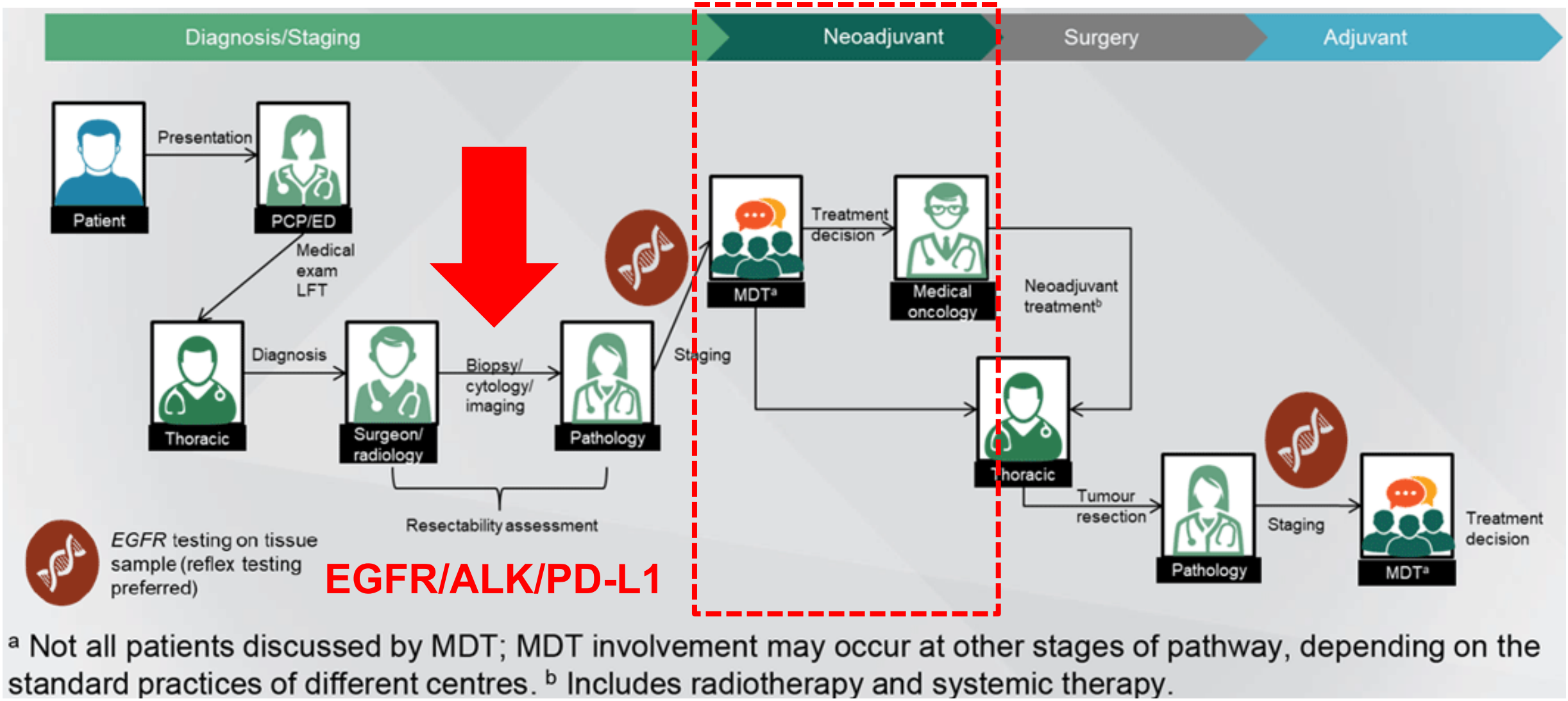
DFS by ctDNA status



		3-year DFS rate, %	p-value
A	Baseline ctDNA negative	83.3	0.02
B	Baseline ctDNA positive, but MRD negative	78.0	
C	Baseline ctDNA positive, but MRD positive	50.0	

Ahn M-J, et al. Ann Oncol 2022;33(suppl):Abstr 933MO

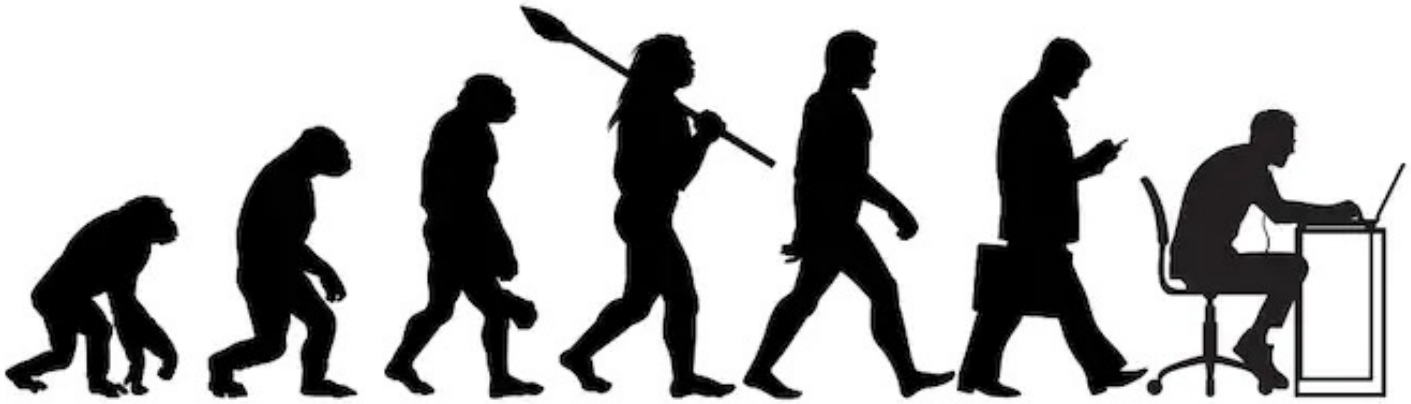
MDT in the Management of Early-Stage NSCLC



[a] Not all patients discussed by MDT; MDT involvement may occur at other stages of pathway, depending on the standard practices of different centres. [b] Includes radiotherapy and systemic therapy.

Source: Ramalingham S et al; www.peervoice.com/ESR910

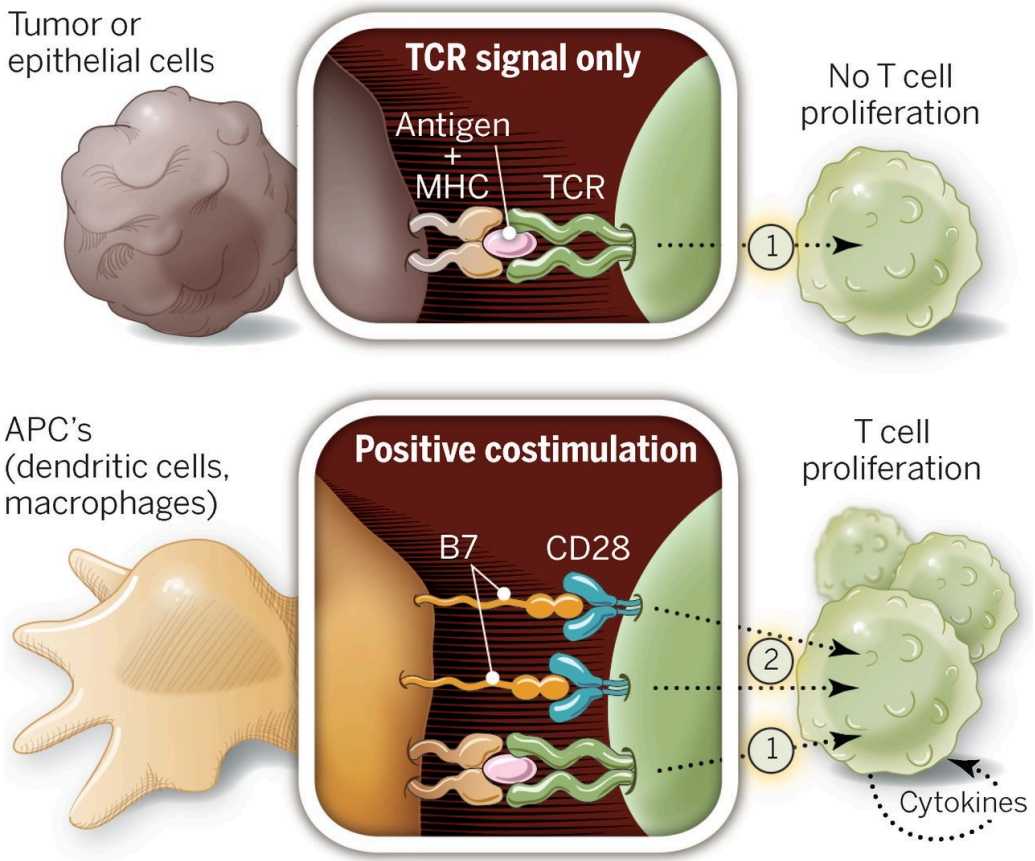
The Evolving View of NSCLC



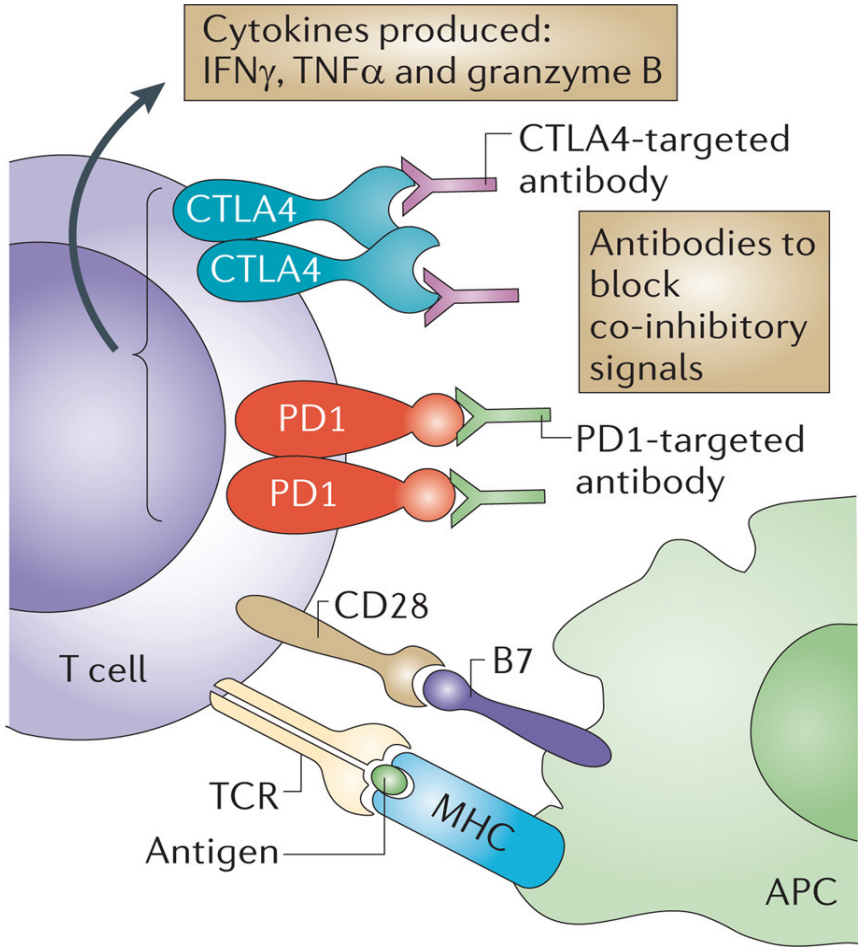
Revolution	Focused on:	Research Strategy:	Trials' Approach:	FINAL Regulatory Approval based upon:
#1 Oncogene Addiction	Tumor	• Identification of Targets/Drivers which leads Tumor progression	• Biomarker-driven with Genomics • Patients' Superselection	• Phase IIIs (*EGFR*, *ALK*) • Phase I/IIs (*ROS1*) • Phase IIs (*BRAF*)
#2 Immune-Dependence	Patient	• Unlock Immune-Response against Tumor	• (Mainly) Unselected Patients' Samples • Immune-dependence evaluated	• Phase IIIs

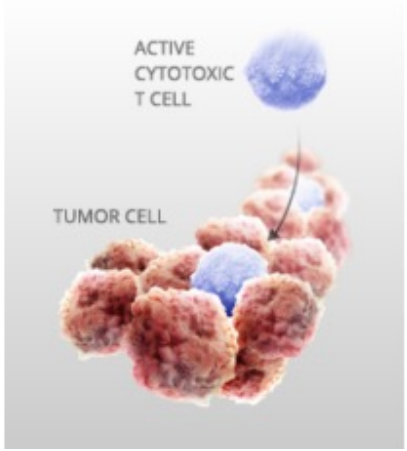
Anti-Cancer Immunity

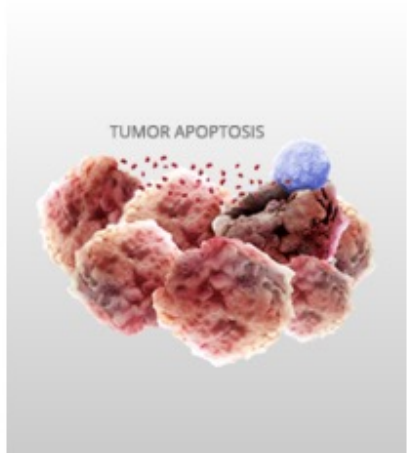
T-Cell Activations Requires (*at least…*) 2 Triggers



Immune Checkpoint Blockade Turns T-cell response On against tumor



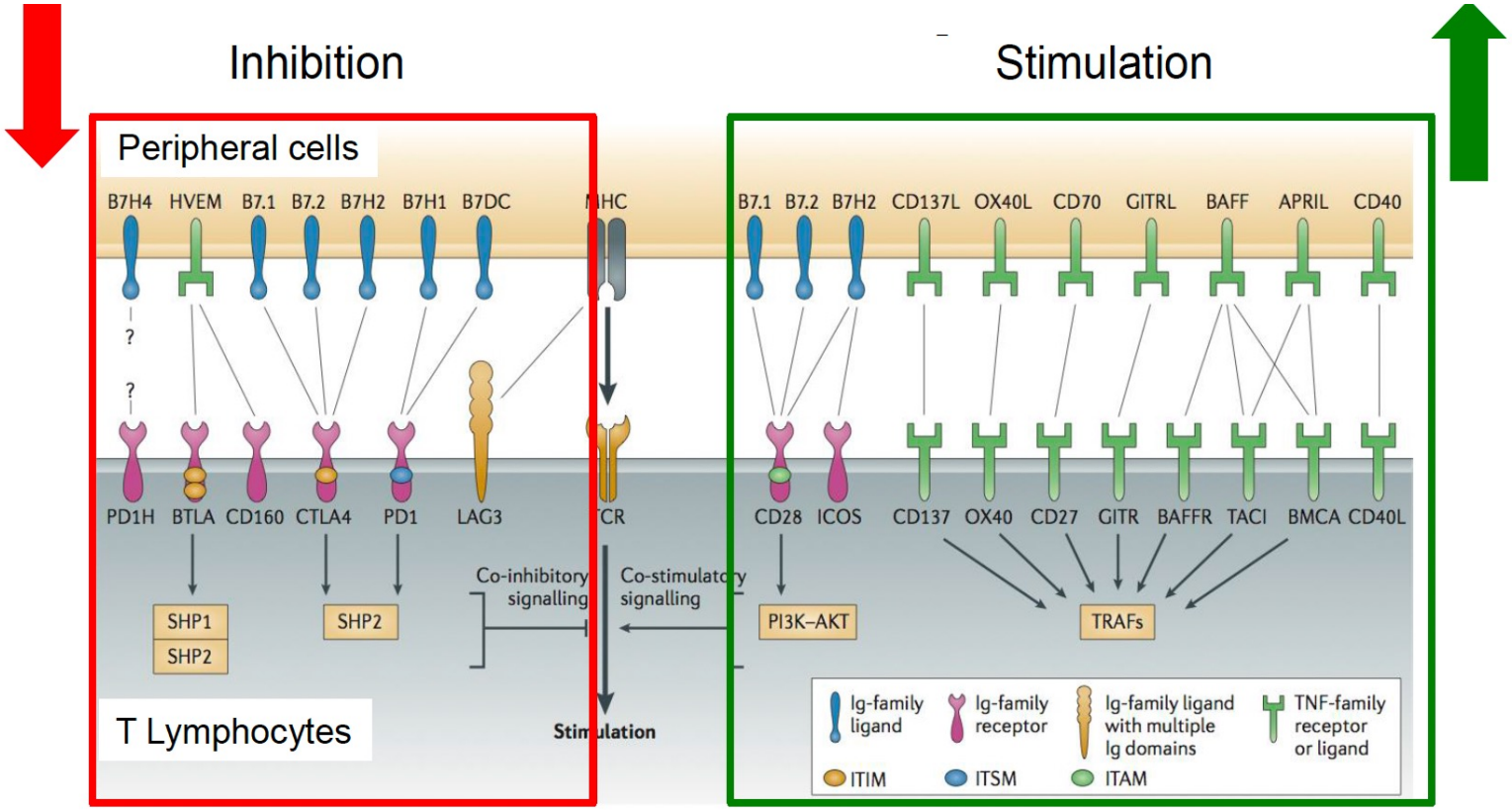




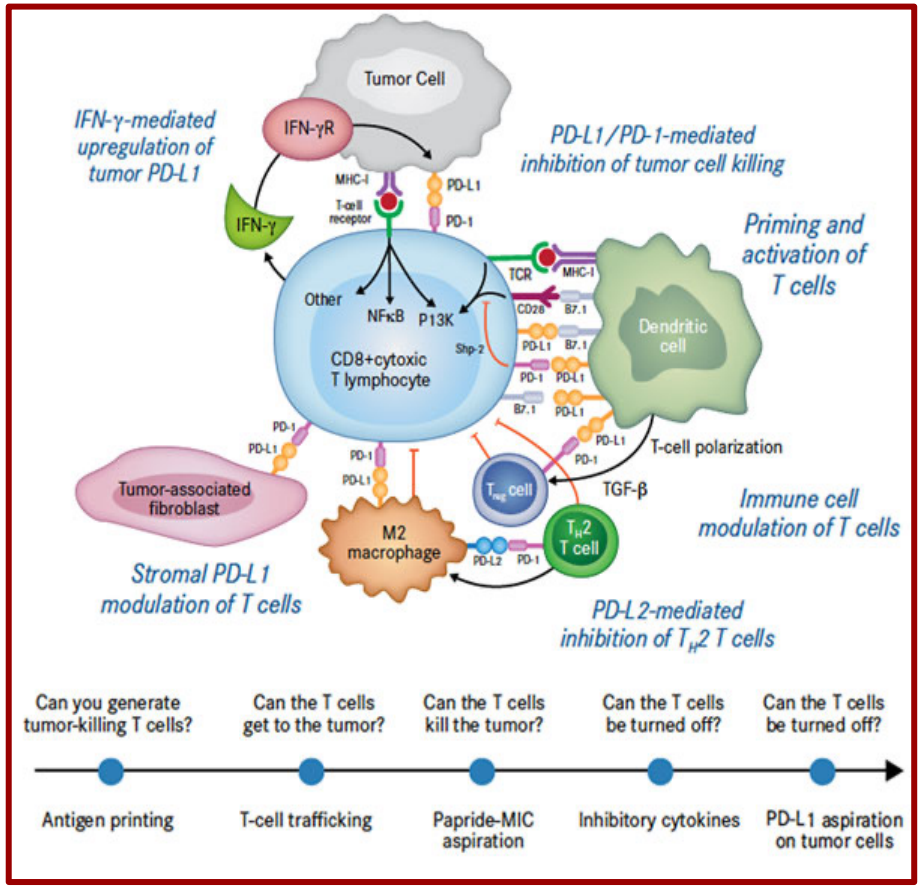
Sharma P et al, Science 2015

Sharma P et al, Nat Rev Cancer 2011

Fine-Tuning of the Immune Response: Immune Checkpoints



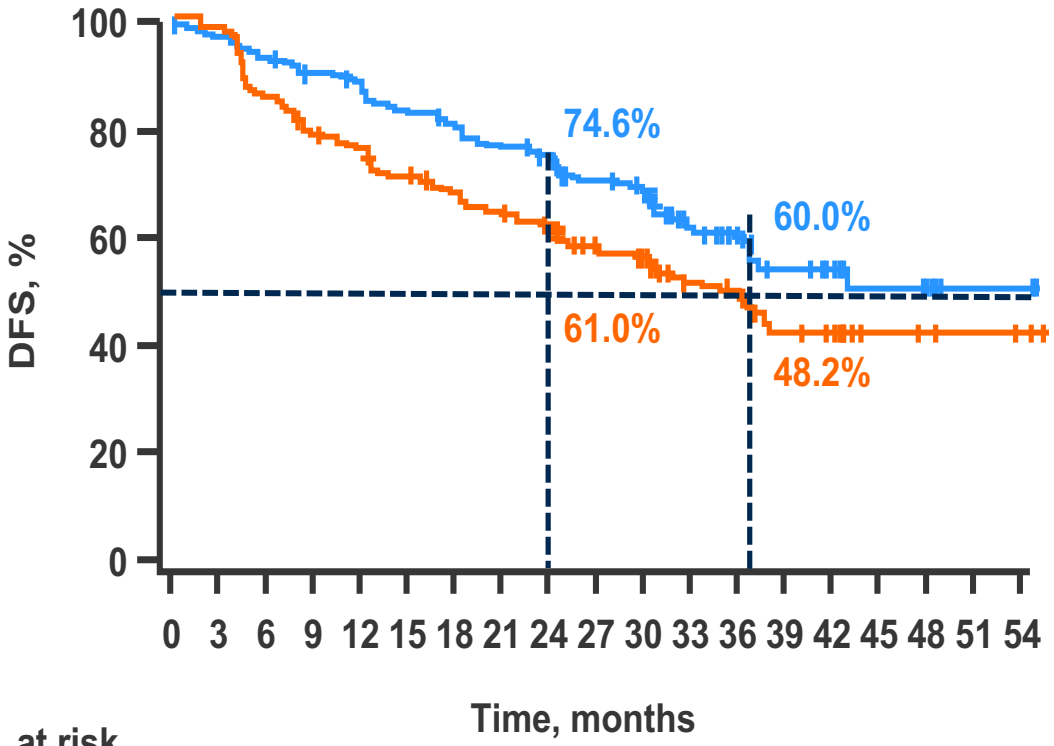
PD-1/PD-L1-Driven Immune-Dependency



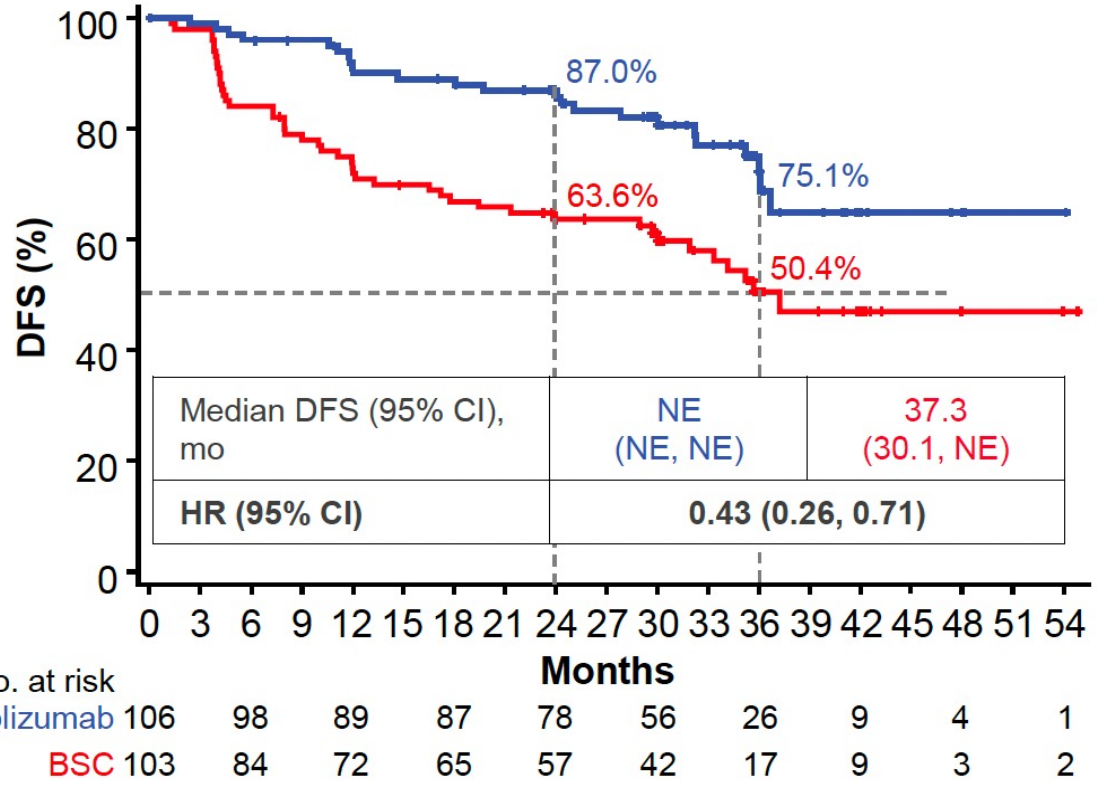
Yao S et al, Nat Rev Drug Disc 2013

IMpower 010: Adjuvant ATEZO *vs.* BSC (FDA/EMA Approvals)

FDA Approval:
Stage II-IIIA, PD-L1 ≥1%



EMA Approval:
Stage II-IIIA, PD-L1 ≥50%, *EGFR/ALK* neg.

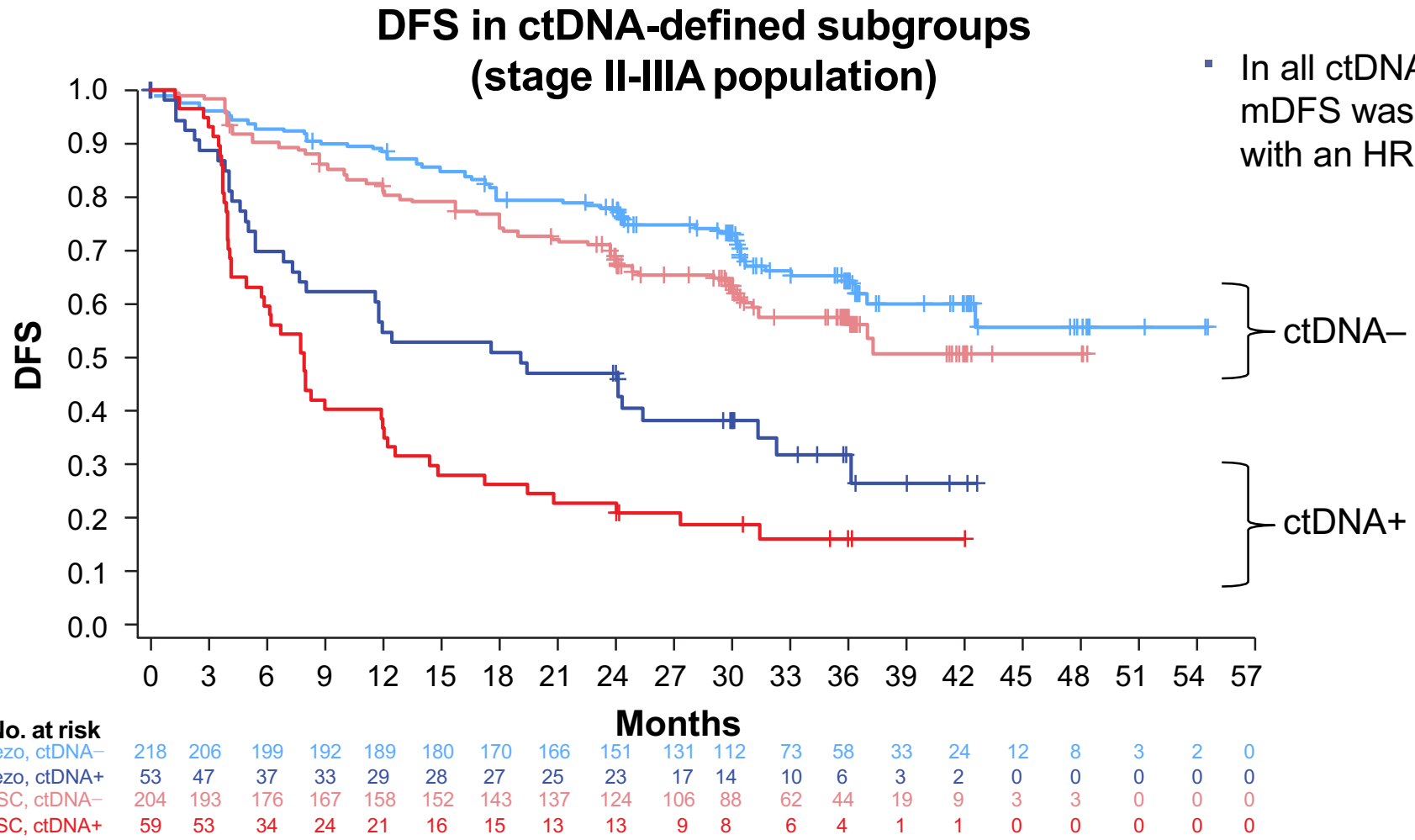


OS (interim analysis), next WCLC, PL03.09!!!

Wakalee H et al, ASCO 2021; Felip E et al, Lancet Oncol 2021

Felip E, et al, ELCC 2022

IMpower 010: Adjuvant Atezolizumab *vs.* BSC



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

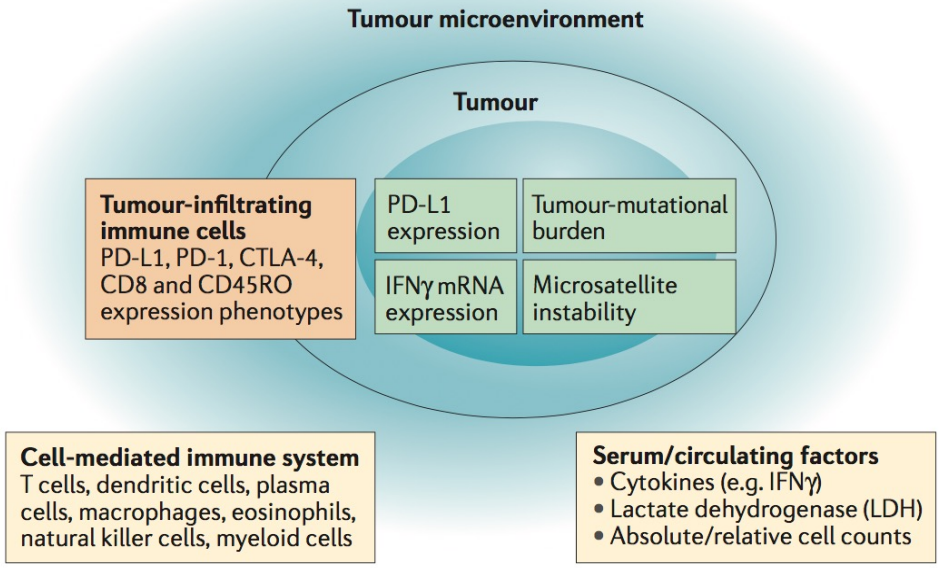
ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Zhou C et al, ESMO-IO 2021

Potential 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**

Nishino A et al, NRCO, 2017

Select the right patient for ICIs efficacy/toxicity/resistance

Tumor cells
PDL- 1 expression
TMB
Specific mutated gene pathways
- INF-γ
- KRAS
- STK11

Tumor microenvironment
PDL- 1 expression
- Immune cells with specific phenotypes
- CD8+, CD4+ T-cells, FOXP3 T-cells
- TAMs, myeloid cells

Diversity of TCR repertoires:
- TILs, TCR clonality

Circulating factors
ct-DNA
Cytokines
Inflammatory factors
Soluble proteins
Pheripheral blood cells:
- CD8+, CD 4+ T-cells, FOXP3 T-cells

Host-related markers
Gender
Age
Intestinal microbiota
Specific mutations
Microbiome
Epigenetics

Potential Utility of Liquid Biopsy in Immunotherapy:

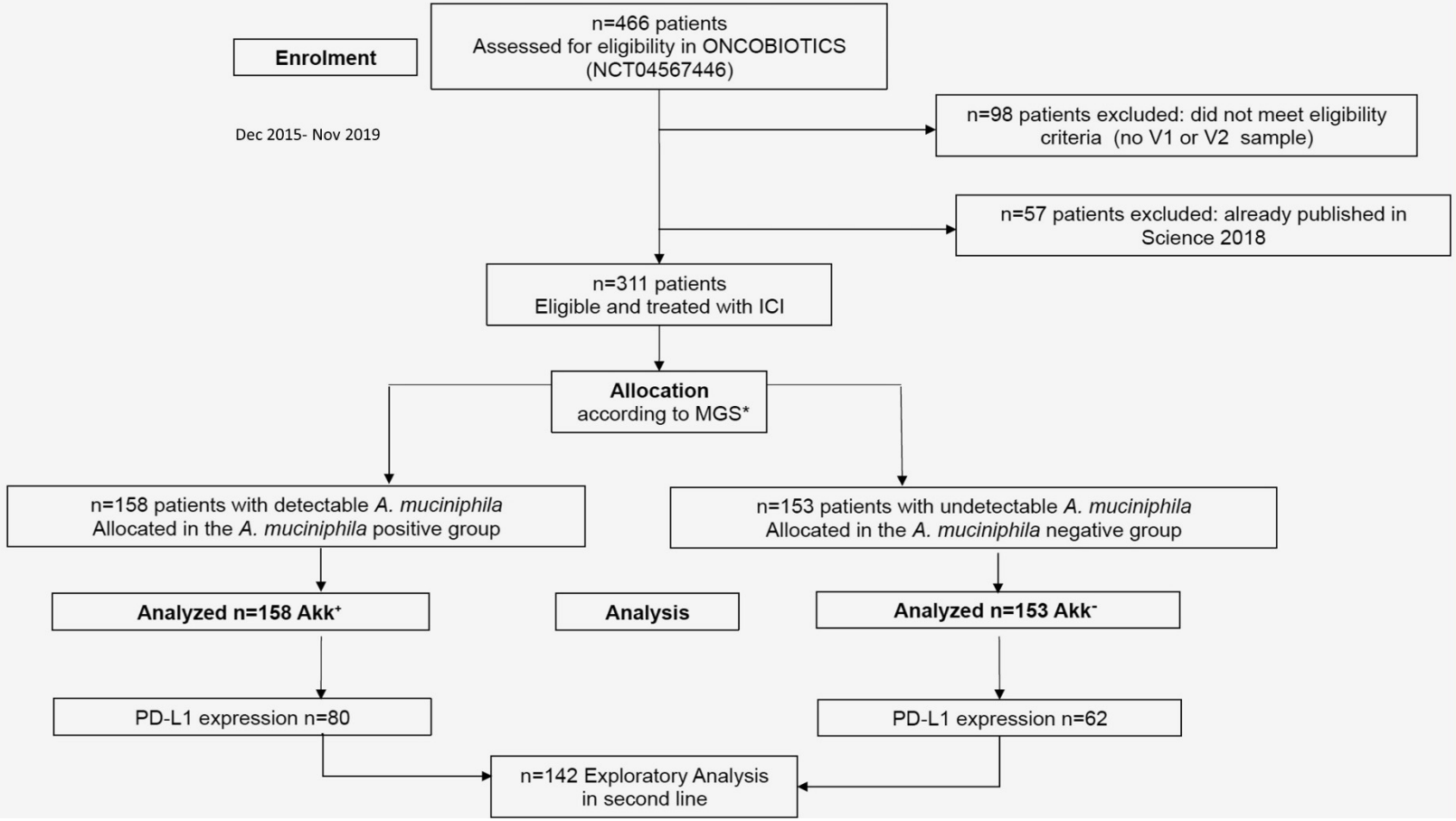
- **Diagnostic**
- **Prognostic**
- **Predictive of Response**
- **Monitoring**
- **Mechanisms if Resistance**

Current tools:

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

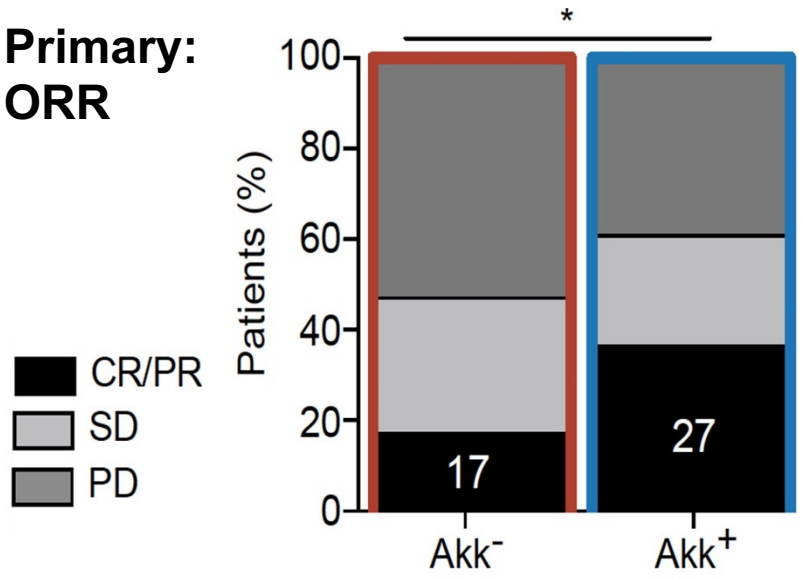
Provencio M, WCLC 2020

Prognostic/Predictive *Akkermansia* & ATB: Phase II Trial

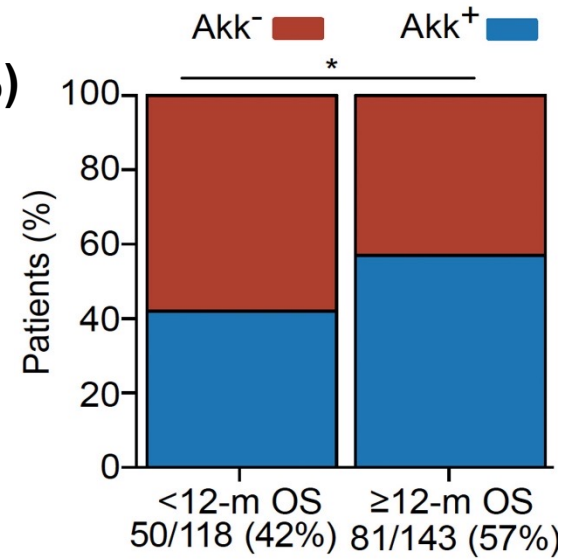


- **Primary end-point was investigator-assessed objective response rate (ORR).**
- **We considered that a meaningful clinical difference would correlate to a 10% ORR increase in the Akk-Pos group compared to the Akk-Neg group. At least 292 patients equally divided in each group would be required for a power at 80% and a two-sided alpha level of 5%.**

Primary: ORR

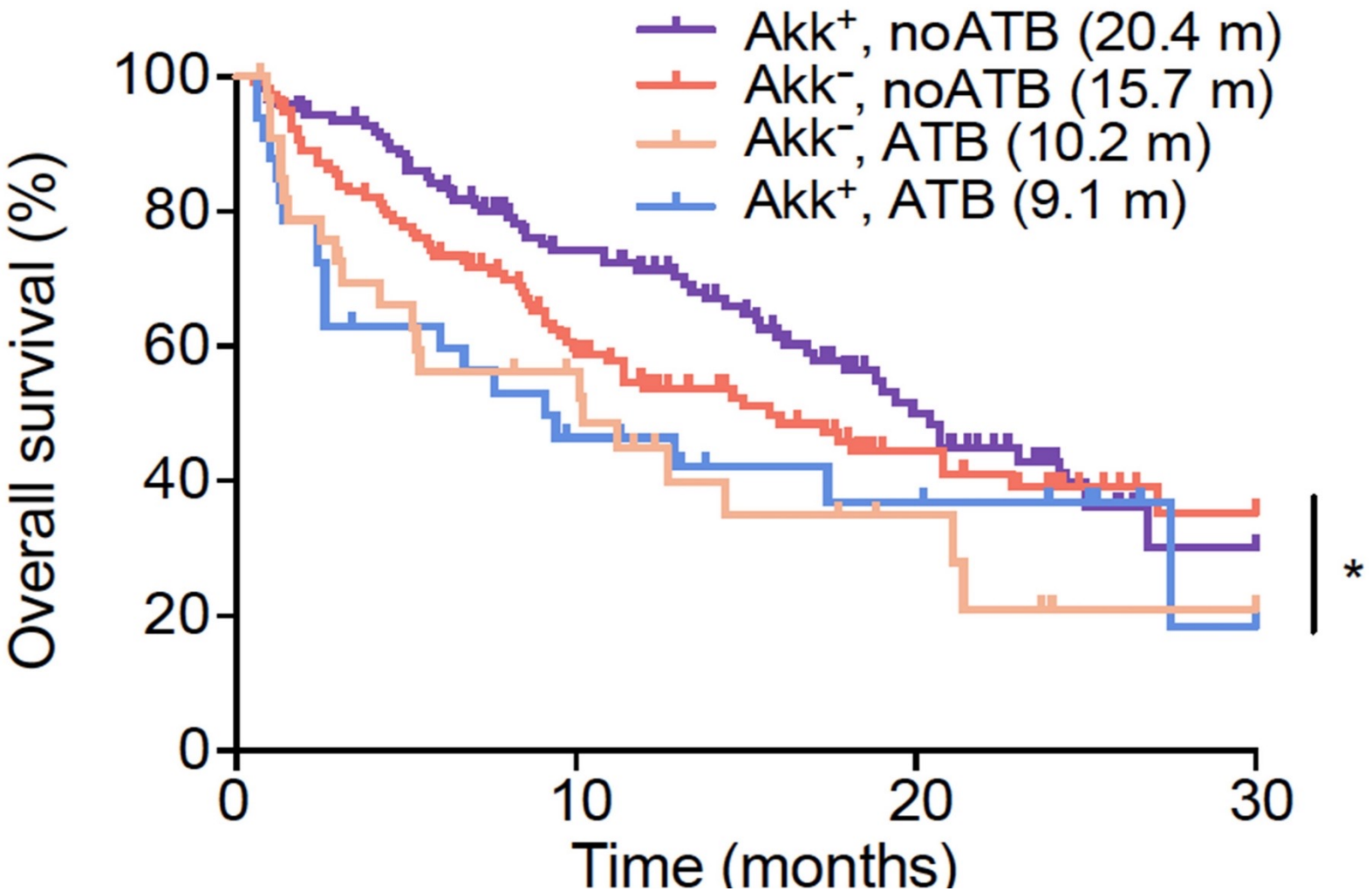


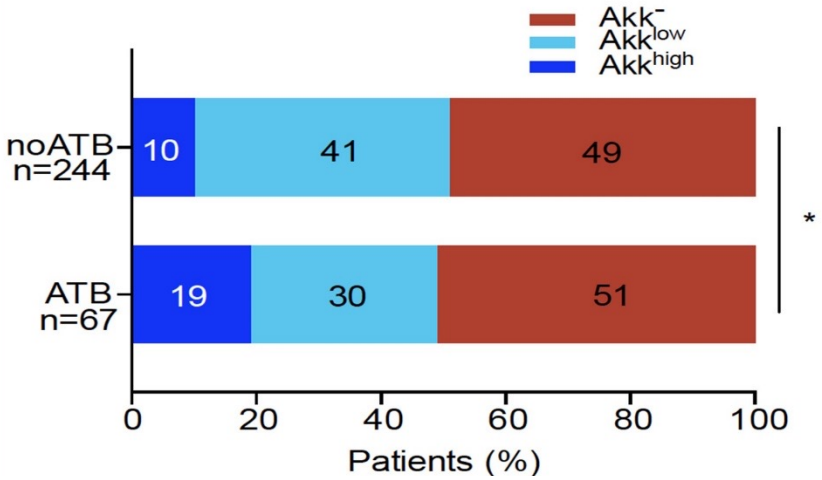
Secondary: OS (1mo. %)

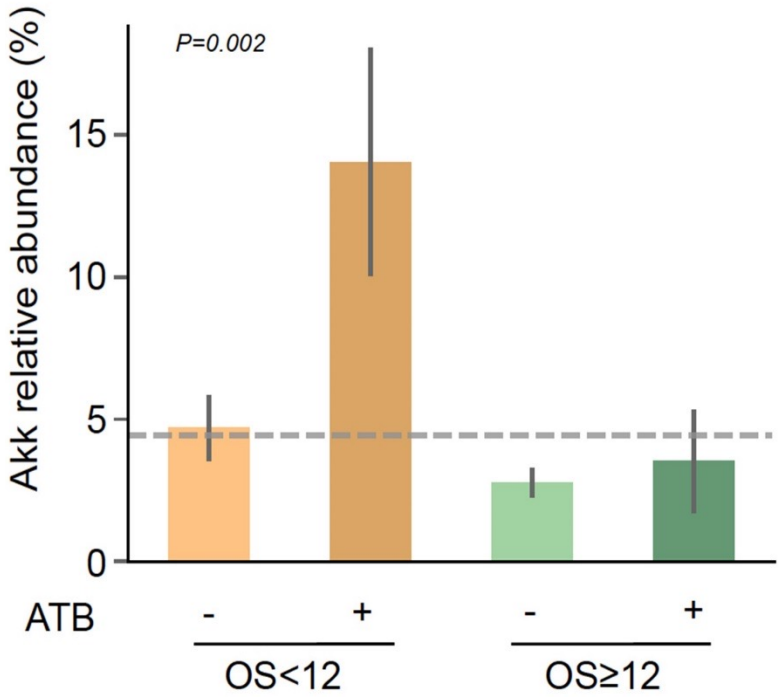


Derosa L et al, ASCO 2021, Nat Med 2022

Prognostic/Predictive *Akkermansia* & ATB: Phase II Trial



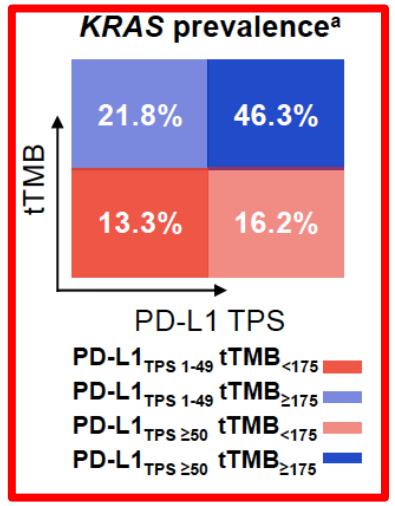


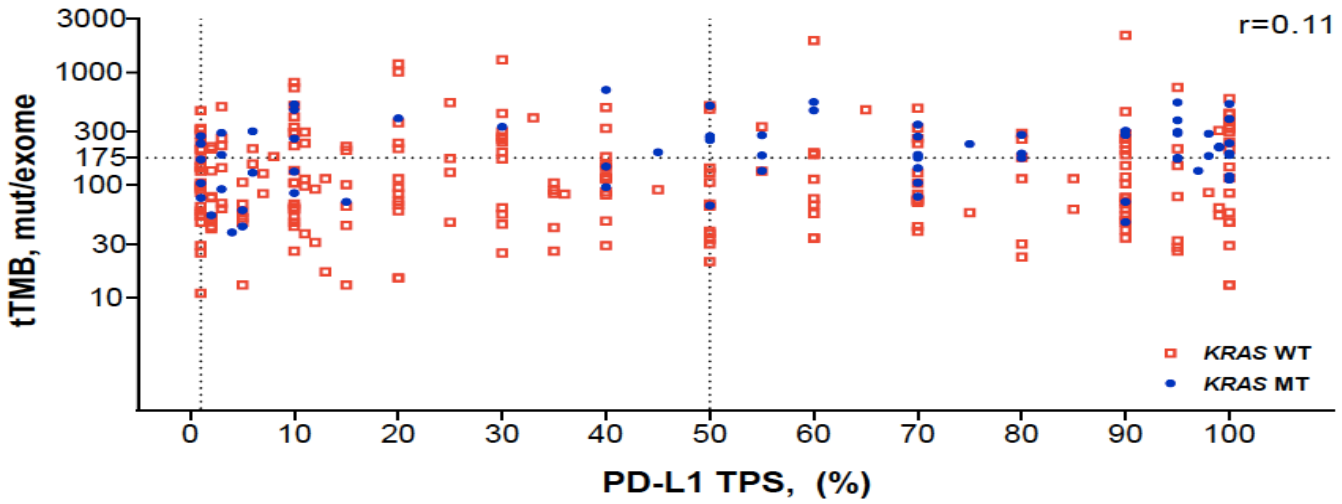


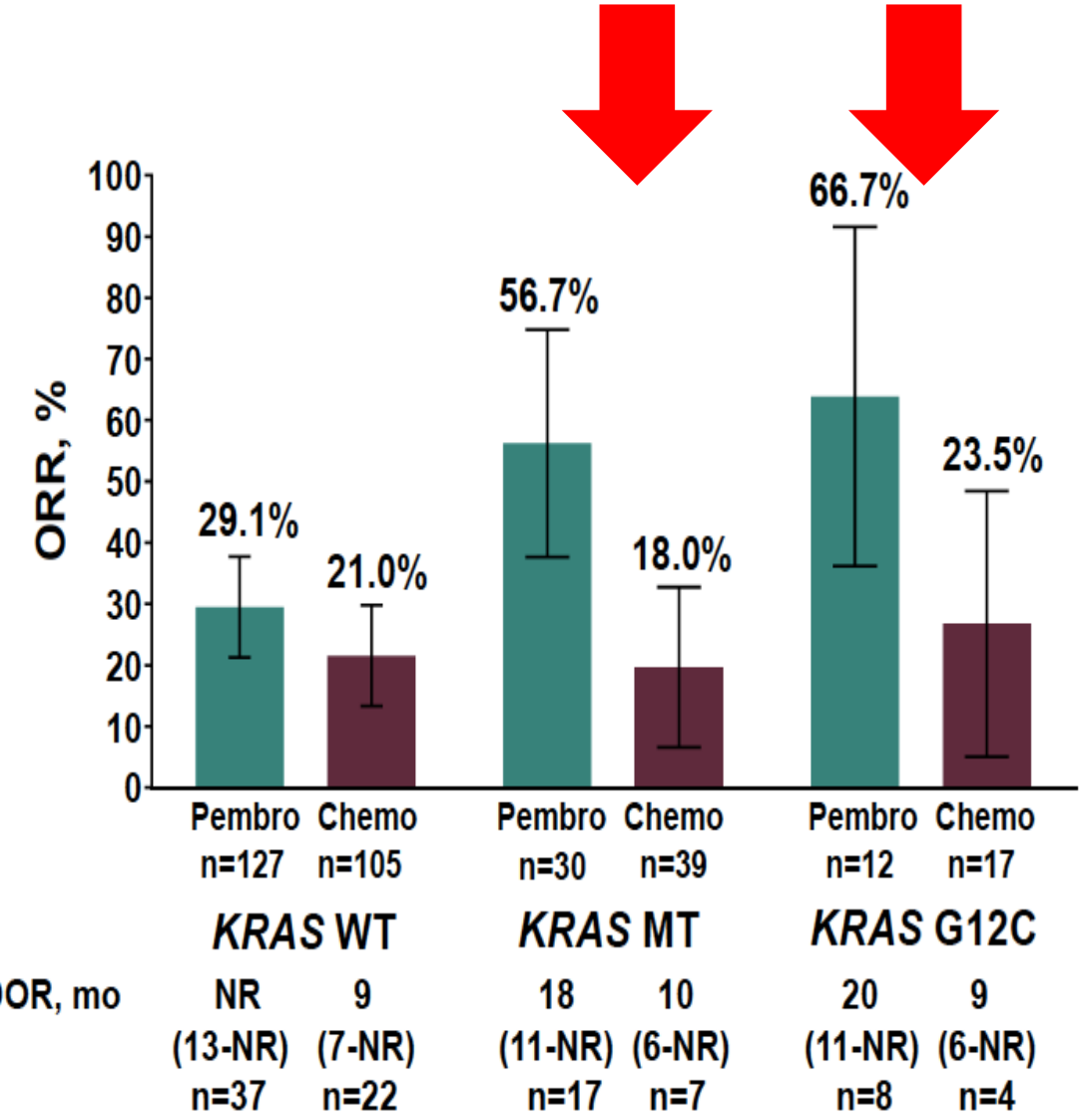
Derosa L et al, ASCO 2021, Nat Med 2022

PD-L1, tTMB, *KRAS* [Upfront PEMBRO - KN 042]

Characteristic (%)	*KRAS*[a] Nonsquamous (N = 301)	Total Nonsquamous (N = 783)
Age y, median (IQR)	62 (56-68)	63 (56-69)
Male	65.1	64.2
ECOG PS 1	66.1	67.7
Former/current smoker	74.4	72.7
PD-L1 TPS		
1-49%	53.2	51.6
≥50%	46.8	48.4





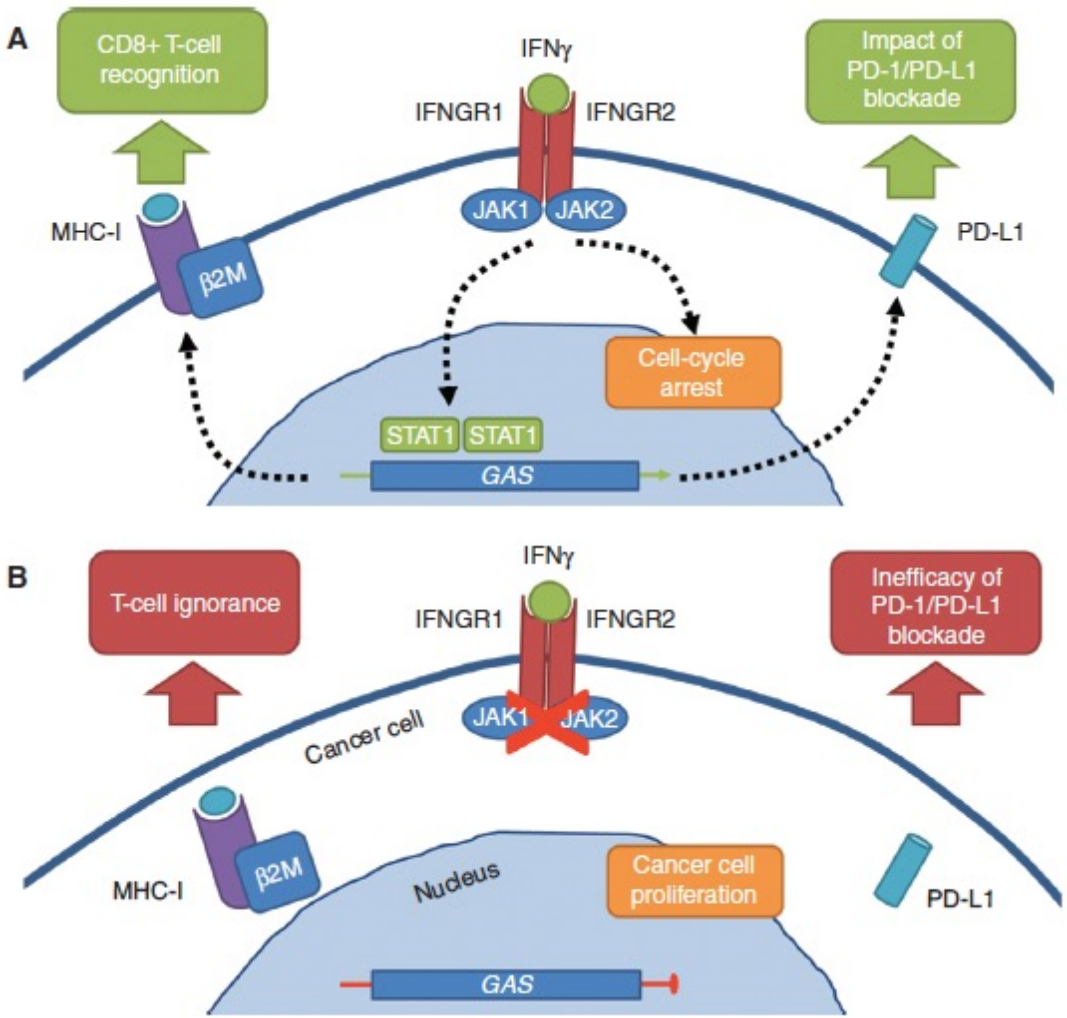


- **Prevalence of KRAS mutations was higher among patients with higher vs lower levels of PD-L1 expression and tTMB**

Lopes G et al, ESMO-IO 2019

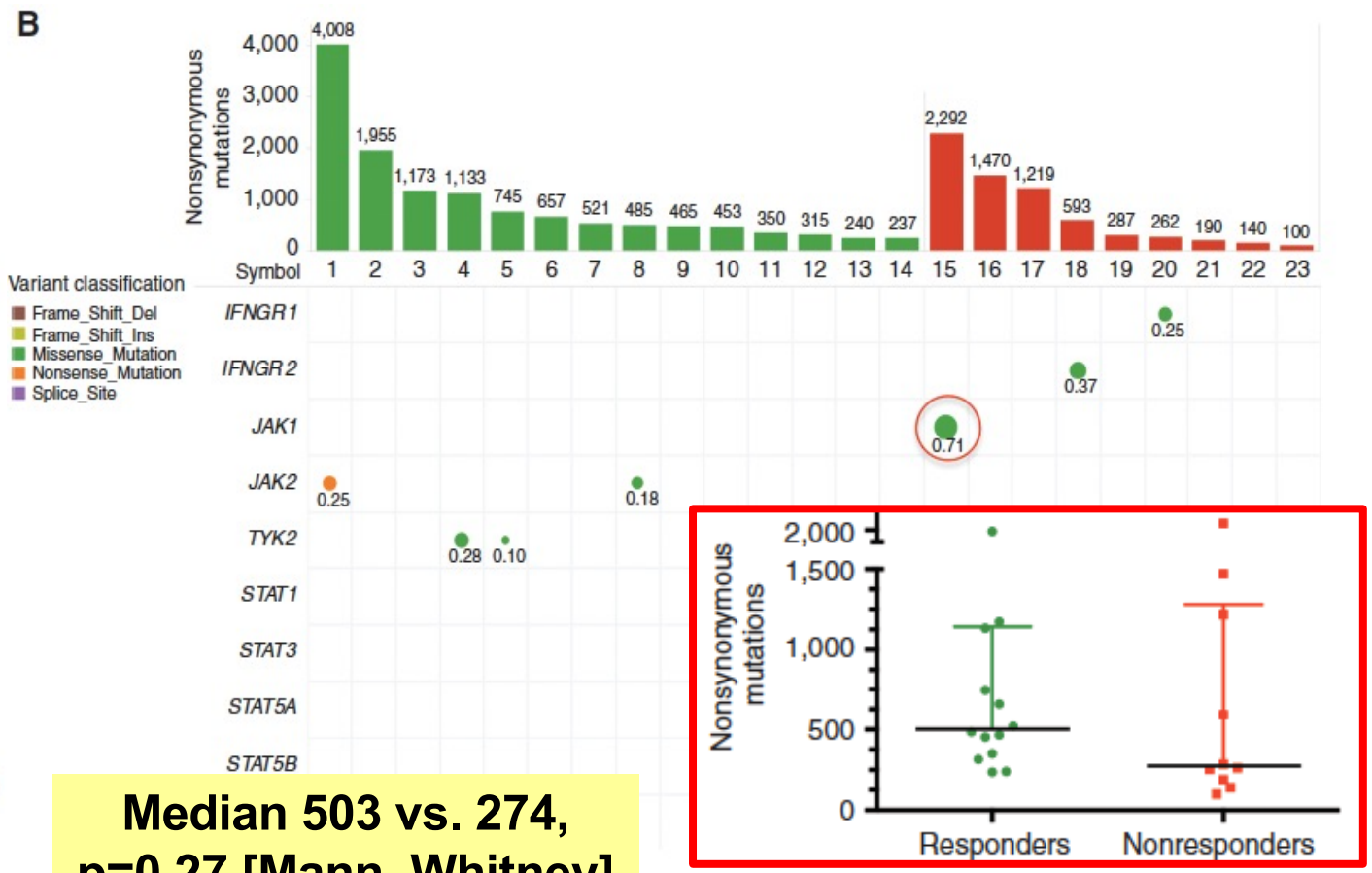
IFN/JAK Escape Pathway as Primary Resistance to I-O

Impact of *JAK* mutations on IFNγ signaling



Marabelle A et al, Cancer Disc 2017

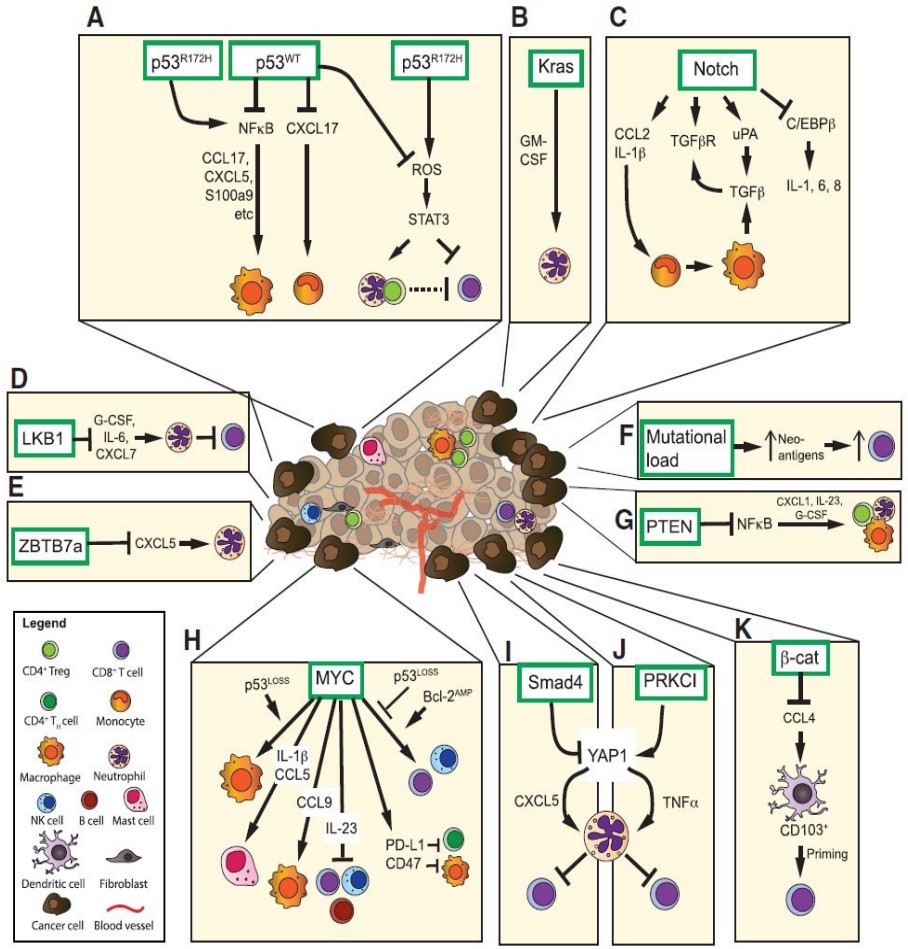
Mutational Load & Mutations in the IFN signaling [MM]



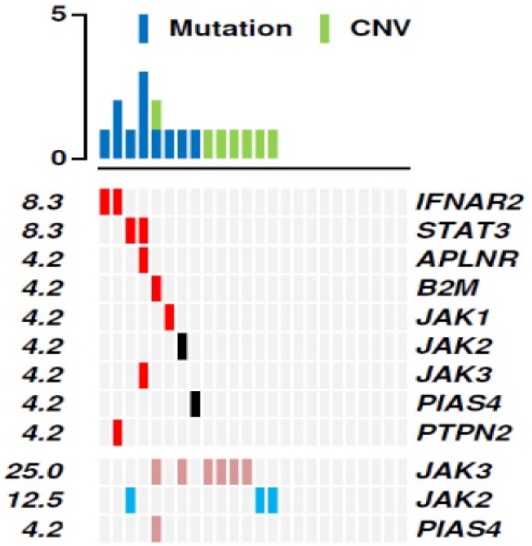
Median 503 vs. 274, p=0.27 [Mann–Whitney]

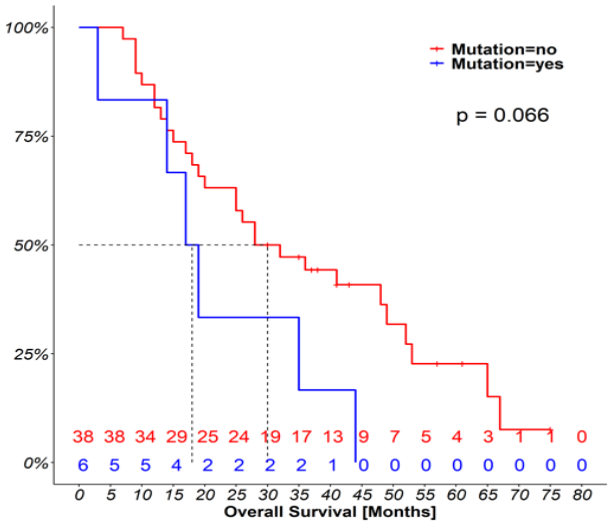
Shin DS et al, Cancer Discovery 2017

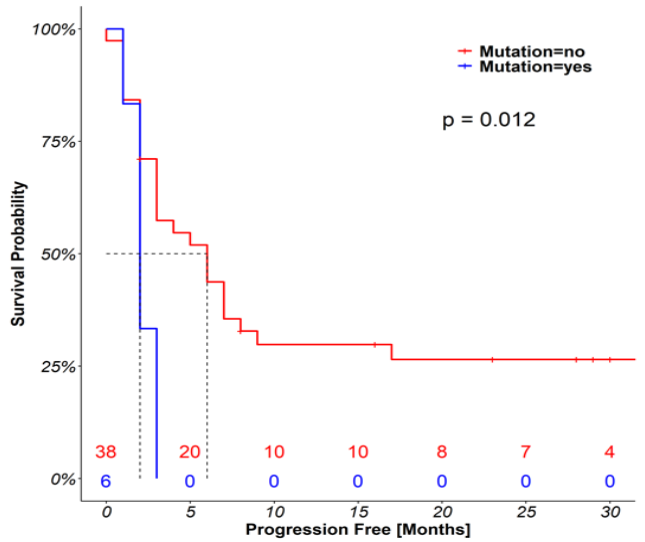
Immunephenotype, Microenvironment & …Genomics



PRINCIPE Study: Customized Genomic Signature Predicts Resistance to Nivolumab



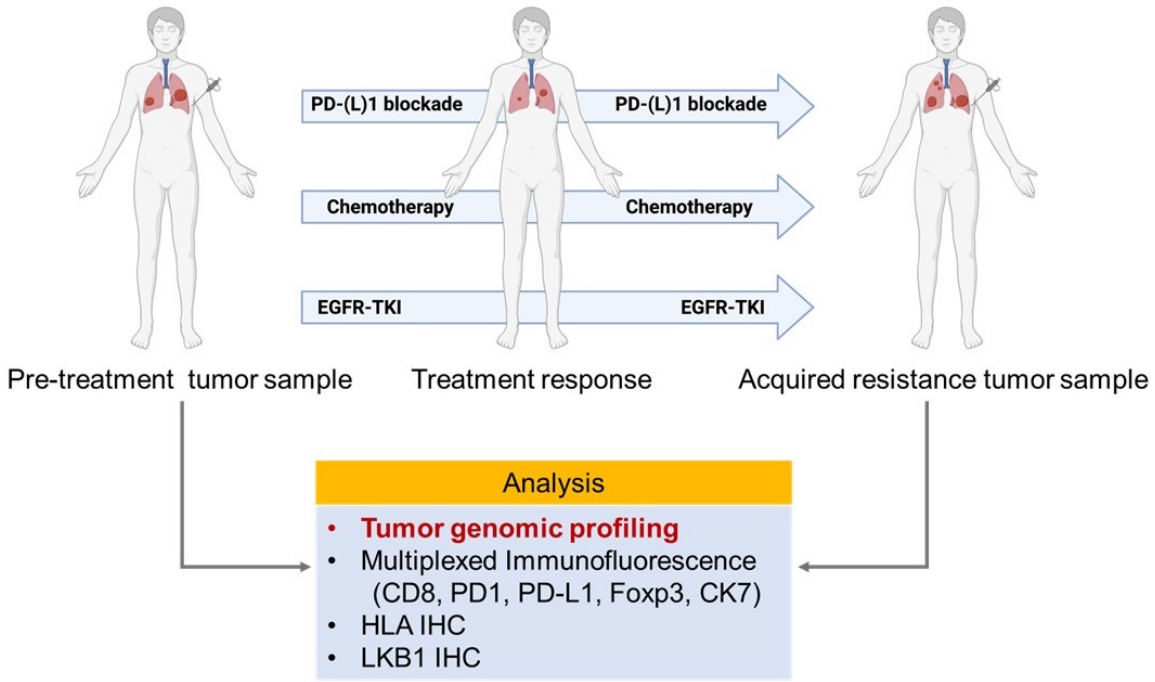


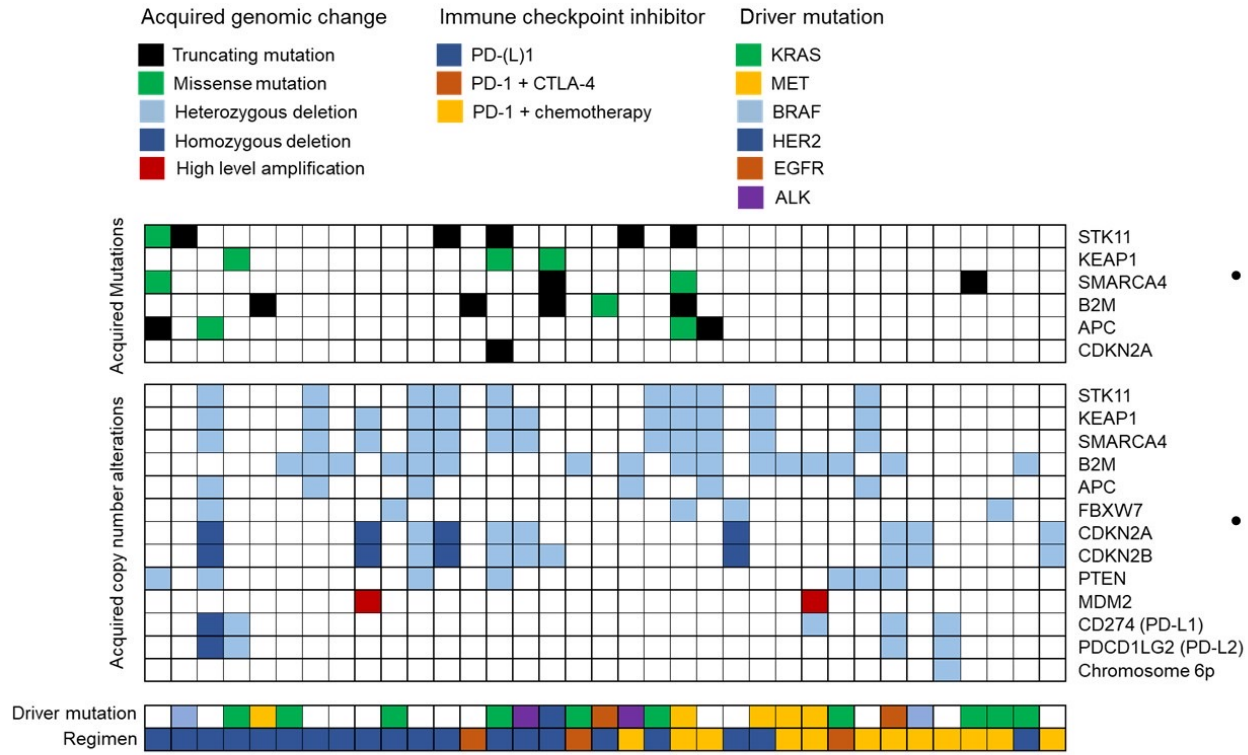


Wellenstein MD, Cell 2018

Pilotto S et al, WCLC 2018 & Submitted

Genomic Correlates of Acquired Resistance to ICI



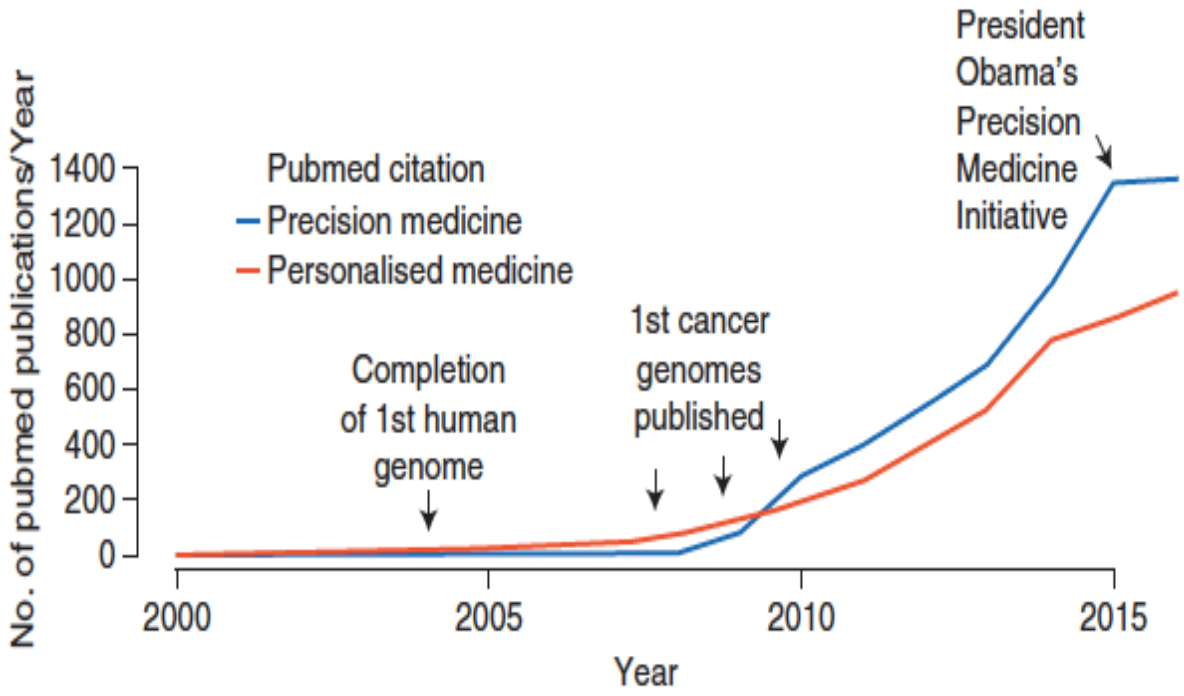


- Acquired loss-of function mutations in *STK11* and *B2M* were detected in 9.1% (6/66) and 7.5% (5/66) of patients at the time of acquired resistance
- No such mutations identified in chemotherapy or EGFR TKI comparison arms

Ricciuti B et al, ASCO 2022

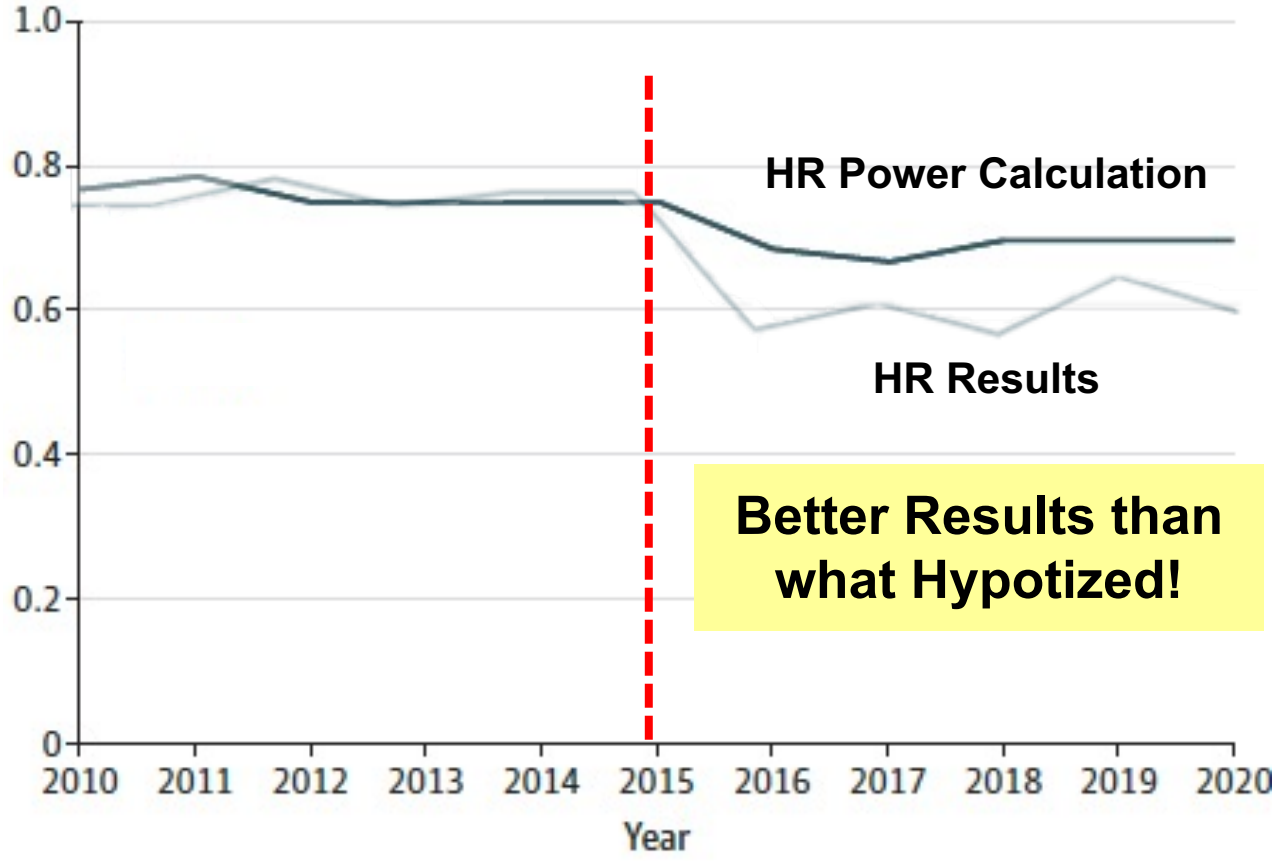
NSCLC and Impact of Precision Medicine

Lung Cancer represents a model of the impact of Precision Medicine (*when a diagnostic testing is employed for selecting optimal therapies on the basis of the patient's genetic/molecular features*) upon patients' prognosis



Yates LR, et al, Ann Oncol 2018

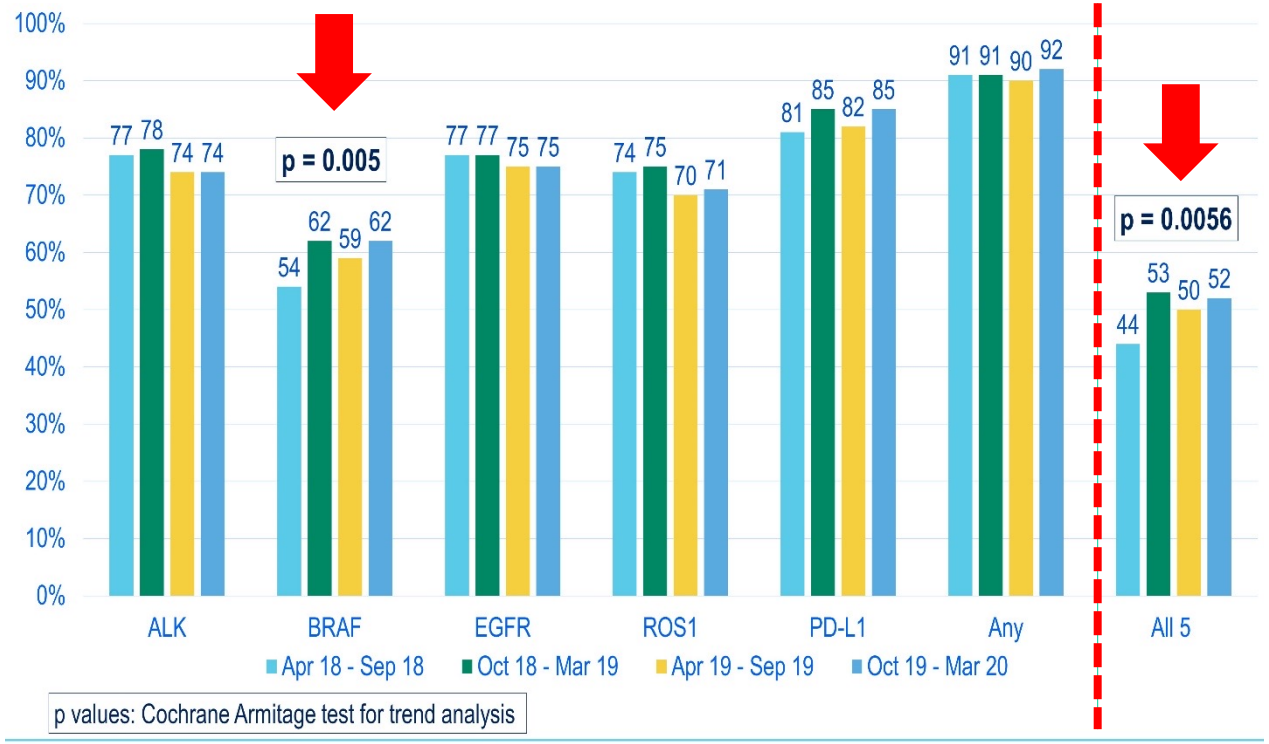
Temporal Trends in Effect Size [Power Calculation and Results], Positive Superiority Trials for RCTs of Breast, CRC, & NSCLC [*7 Major Journals, 1995-2020*]

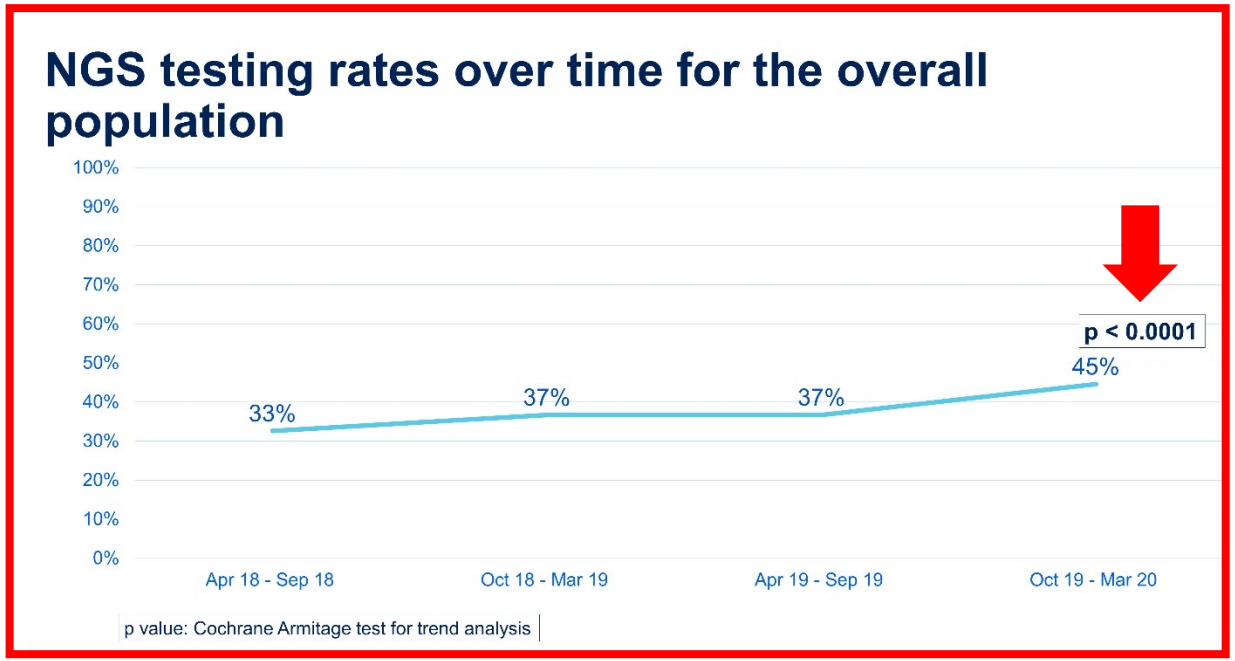


Del Paggio J et al, JAMA Onc 2021

Oncogene-Addicted NSCLC is becoming 'Bigger' (>50%)

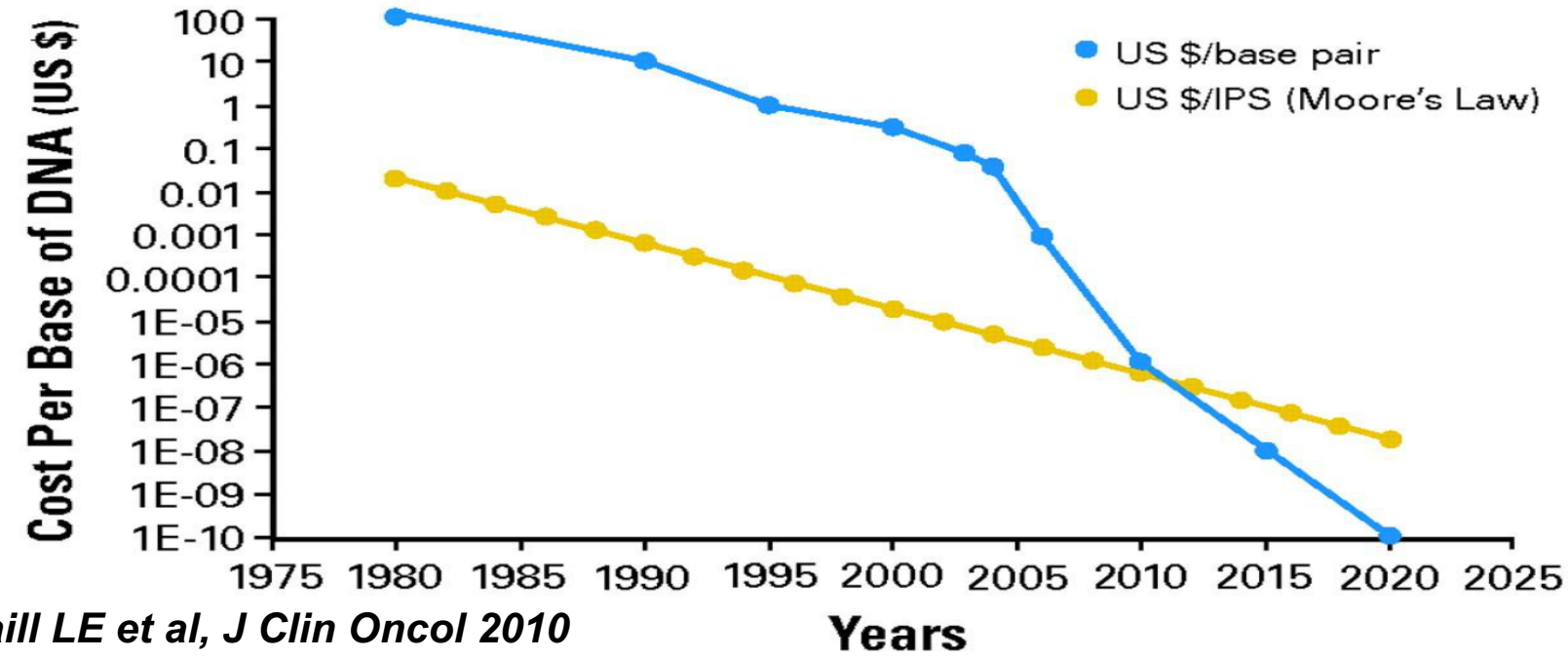
Modest Improvement in Testing for all 5 biomarkers (Apr. 2018 – Mar. 2020)





Robert NJ et al, ASCO 2021

Cost of Sequencing Overtime: Provocative Question…

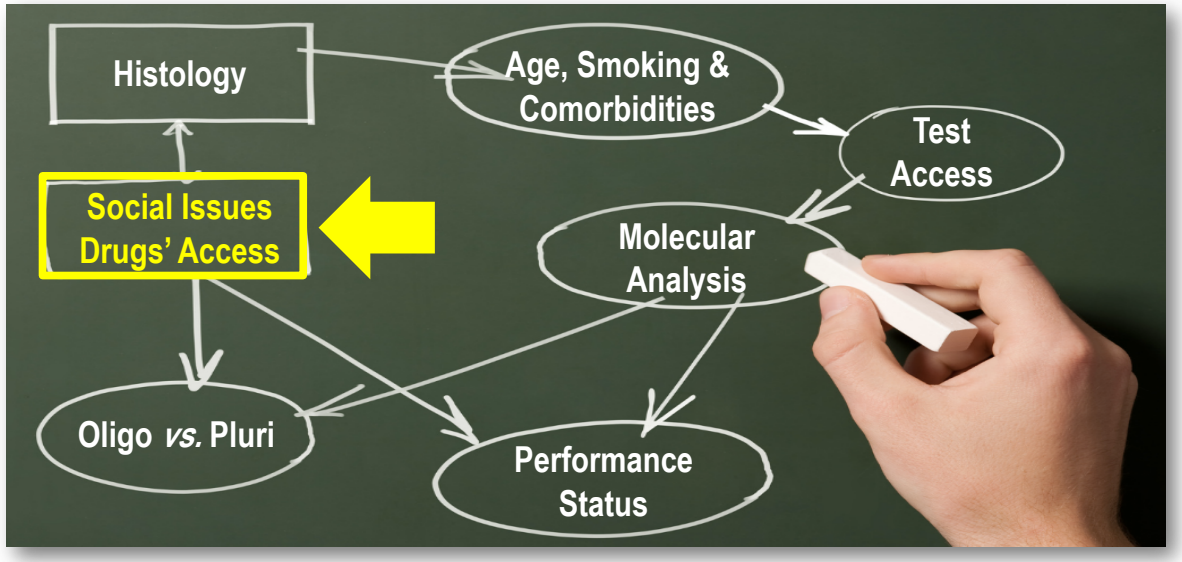


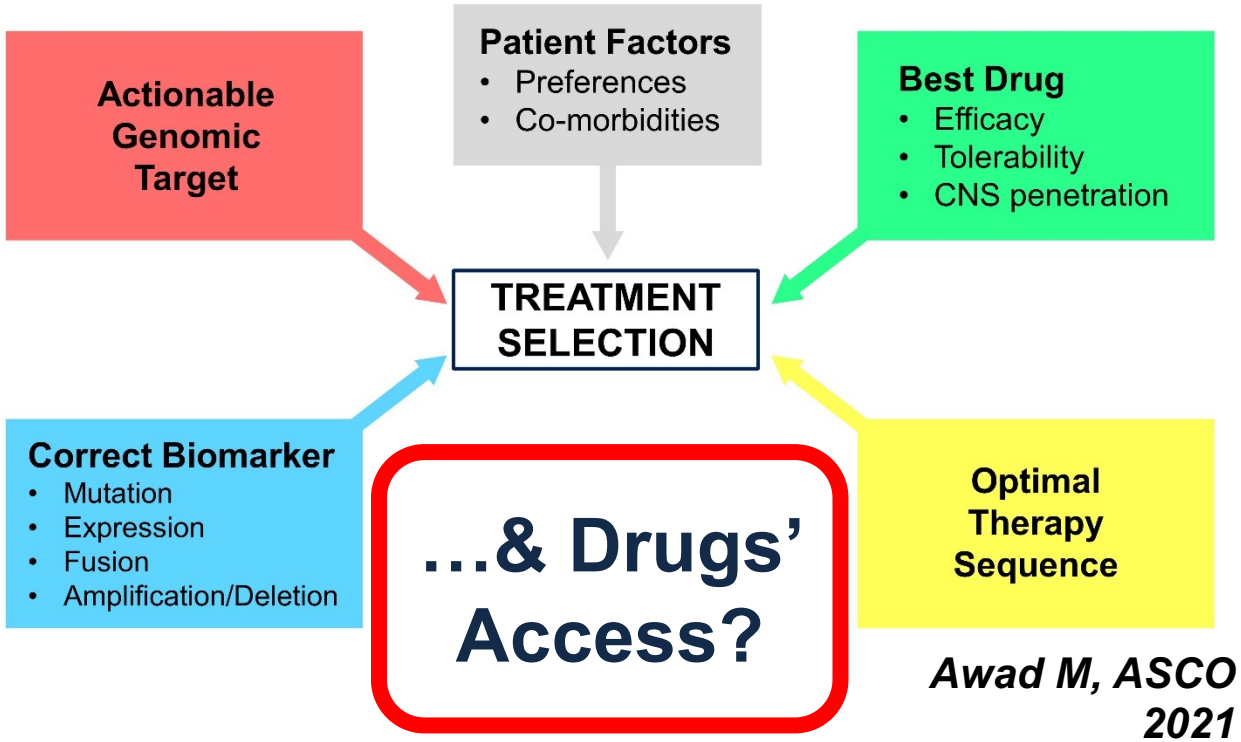
MacConaill LE et al, J Clin Oncol 2010

Test	Setting	N. of examines genes/expression pathways	Potential Benefit of the Biomarker/Classifier	Cost Range (Euros)
Genomic Testing (ex. Oncotype Dx)	Early Hormone-sensitive Post-menopausal EBC	15-24	Exclusion of adjuvant Chemo addition to HT (for '*non-inferiority*' over HT alone)	2800-3500
NGS DNA/RNA Testing (Gene Panels)	Advanced NSCLC	150-500	Predictor of activity/efficacy of 9 targeted therapies (including EAPs), changing prognosis from <12 months to > 5yrs in featured case	650-1700

Choosing Targeted Therapy in NSCLC

MedOncs Use Omics to Select Therapies in Clinical Practice





Awad M, ASCO 2021

2021 Presidential Address: Equity: Every Patient. Every Day. Everywhere

Pierce JL, JCO 2021