CARCINOMA POLMONARE: QUALI NOVITÀ NEL 2022?

Il trattamento della malattia con alterazioni di *BRAF*, *ROS1* o *RET* e altri target emergenti

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Disclosures

Commercial Interest	Relationship(s)
AstraZeneca	Speaker’s Bureau, Consultant, Research Funding
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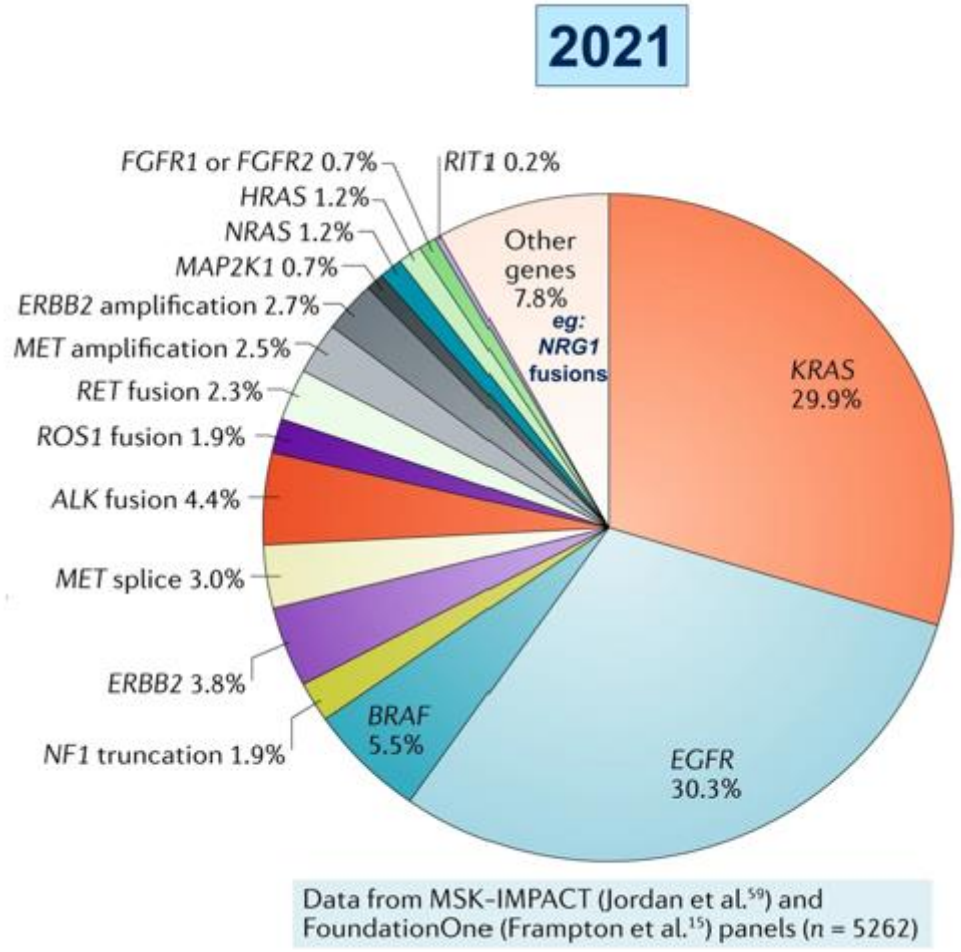
Boehringer Ingelheim	Speaker’s Bureau, Consultant
BMS	Speaker’s Bureau, Consultant, Research Funding
Roche	Advisory Board, Speaker’s Bureau, Consultant
AMGEN	Advisory Board, Consultant
Novartis	Advisory Board, Consultant

Precision Therapy for non-squamous (*for now*) NSCLC in 2021/2022



	What we absolutely need TODAY*
15%	EGFR mutations
4%	ALK rearrangements
1%	ROS1 rearrangements
4%	BRAF p.V600E mutations
<1%	NTRK 1,2,3 rearrangements

* In metastatic non-squamous NSCLC (before 1° line initiation) - in Italy

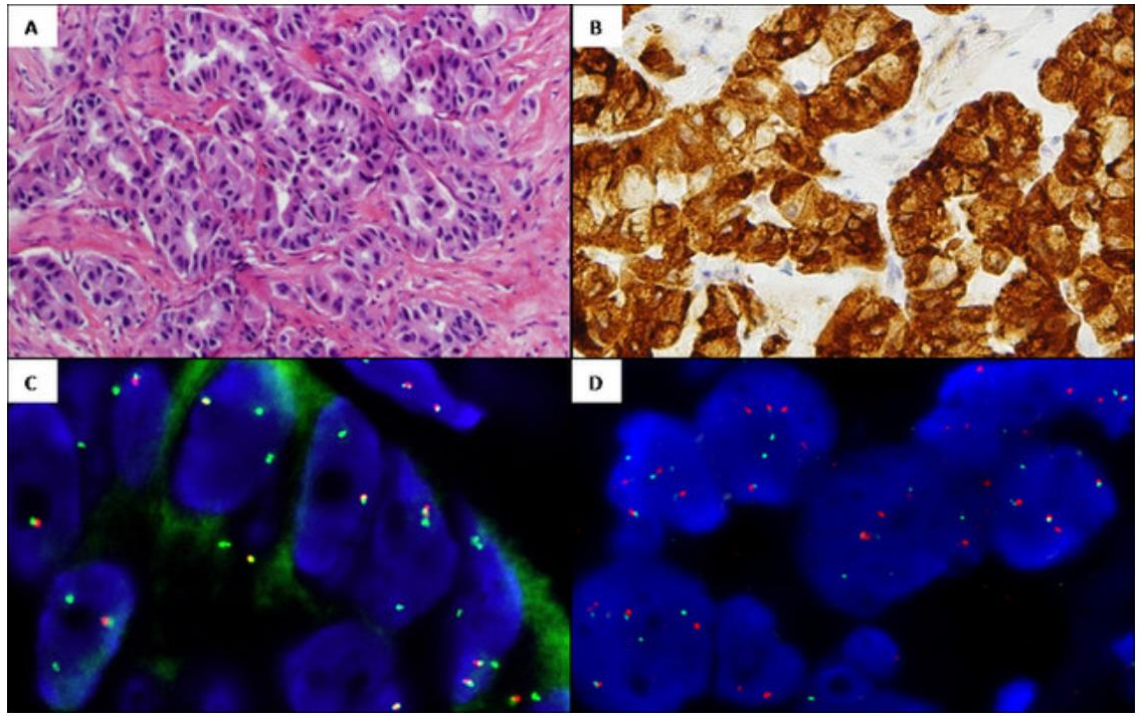
Aiom
Associazione Italiana di Oncologia Medica

proposito, in tutti i pazienti con NSCLC in stadio IIIB-IIIC (non candidati a trattamenti loco-regionali), e IV, risulta raccomandato completare la diagnosi morfologica (di cui sopra) con la caratterizzazione delle mutazioni in *EGFR* (*Epidermal Growth Factor Receptor*) e *BRAF (B-Raf proto-oncogene),* la definizione delle traslocazioni a carico di *ALK* (*Anaplastc Lymphoma Kinase*), *ROS-1* (*Proto-oncogene tyrosine-protein kinase* ROS) e *NTRK 1,2 e 3 (Neurotrophic Tyrosine Receptor Kinase)* e la valutazione dei livelli di espressione del PD-L1 (Programmed-death ligand 1) (secondo i cut – off validati dagli studi

Linee Guida AIOM – Neoplasie del Polmone 2021

ROS1 rearrangements: do not forget this rare target!

- Seen in 0.9% - 2% of lung adenocarcinoma
- Typically associated with younger age (average 50y), never/light smoking history, adenocarcinoma subtype

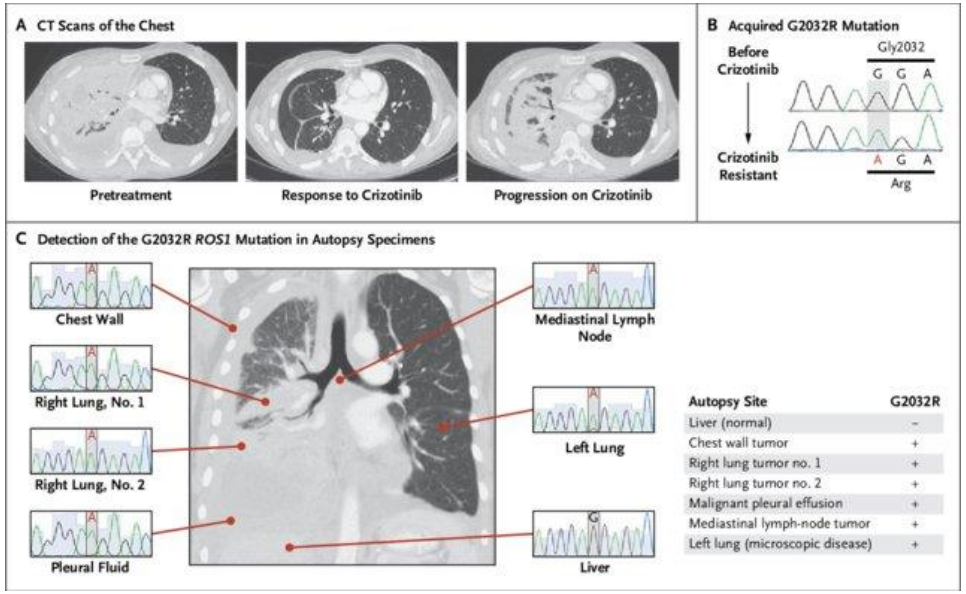


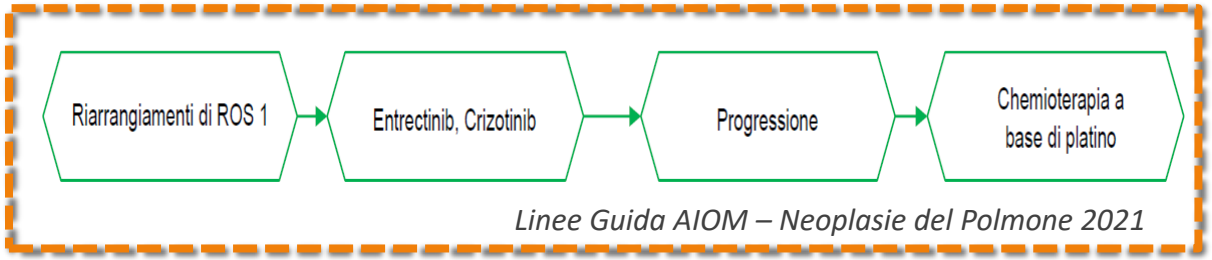
Clave S et al, Oncotarget 2016

ROS1 rearrangements: crizotinib, a (EX?) standard of care

Study	Phase	Patients, No.	ORR, %	DCR, %	mPFS, Months	mOS, Months
PROFILE 1001[12,30]	I/II	53	72	90	19.3	51.4
Phase II East Asian Study[31]	II	127	71.7	88.2	15.9	12-month rate, 83.1%
EUCROSS[32]	II	30	70	90	20	NR (12-month rate, 83%)
AcSé[33]	II	37	69.4	69.4	5.5	17.2
METROS[34]	II	26	65	85	22.8	NR
EUROS1[11]	Retrospective	30	80	86.6	9.1	NR
ROS1 Fusion Partners[35]	Retrospective	49	83.3	97.2	12.6	32.7
Pemetrexed study[36]	Retrospective	15	80	90	9.6	NA

- On-target resistance mutations (*G2032R*)
- CNS progression

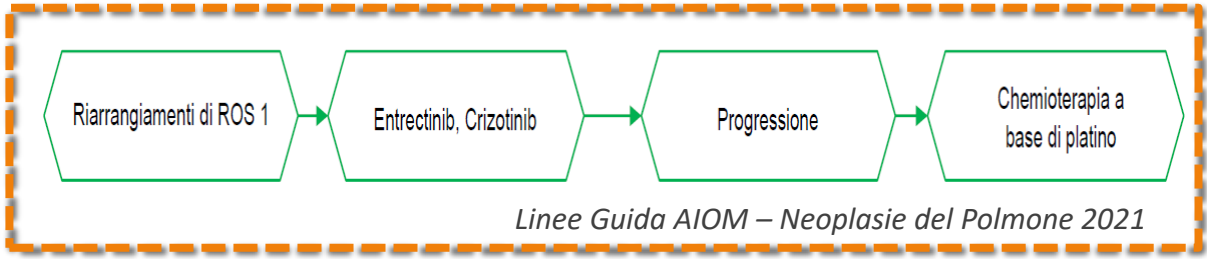




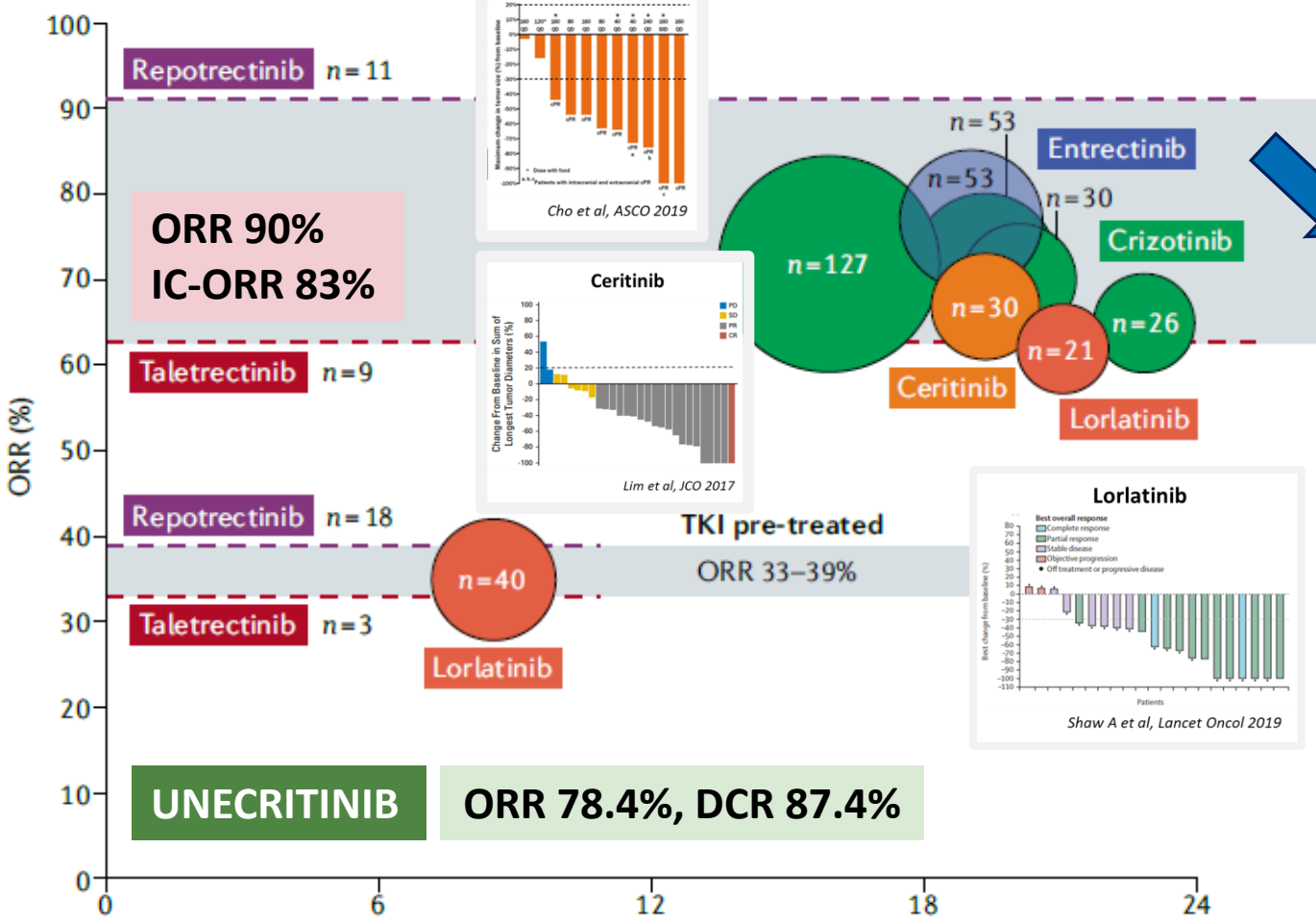
Linee Guida AIOM – Neoplasie del Polmone 2021

Almquist and Ernani, JCO Oncology Practice 2021
Awad M et al, NEJM 2013

ROS1 rearrangements: a changing (*overcrowded*) landscape



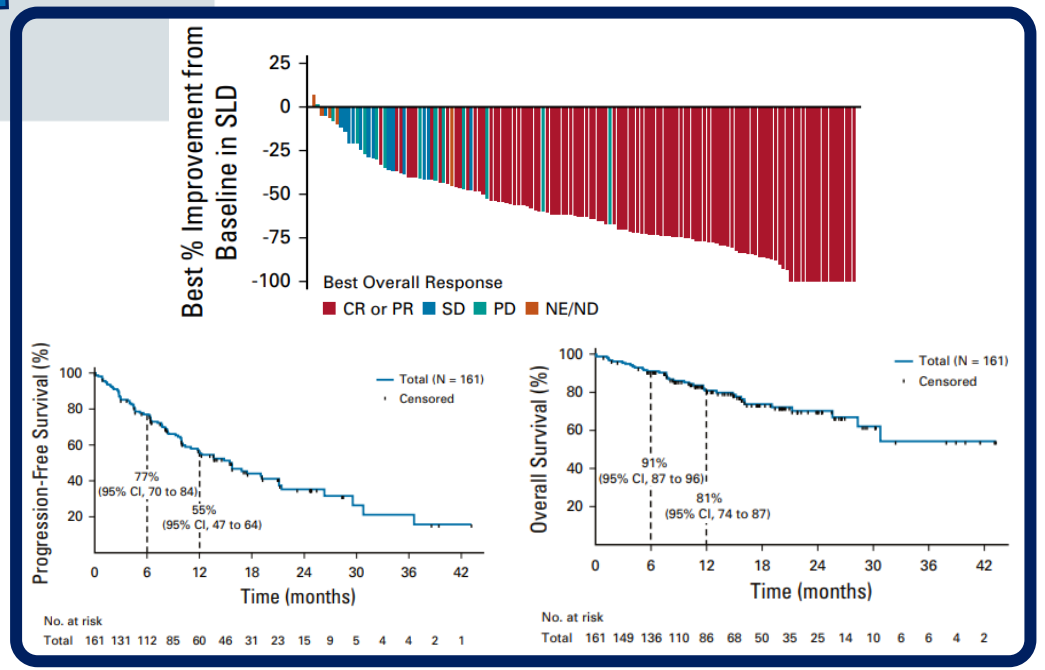
Linee Guida AIOM – Neoplasie del Polmone 2021



Cho et al, ASCO 2019

Lim et al, JCO 2017

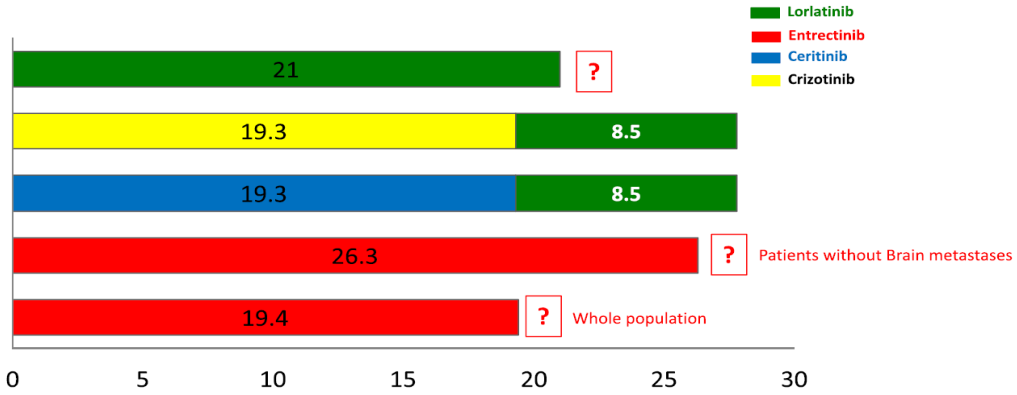
Shaw A et al, Lancet Oncol 2019



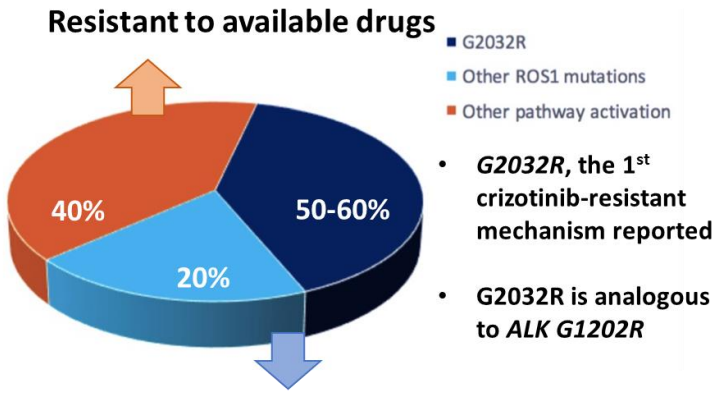
Dziadziuszko R et al, JCO 2021

Modified from Drilon A et al, NRCO 2020

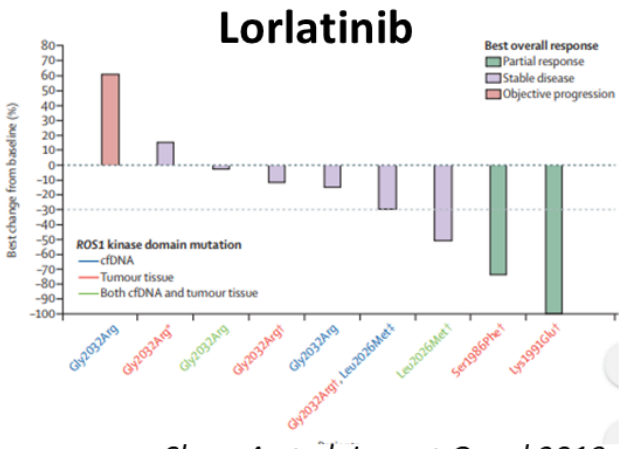
How do we best sequence?? [*yesterday, today and tomorrow*]



Modified from Remon J et al, CTR 2021



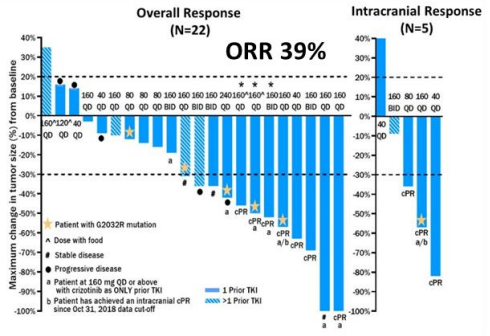
- ***G2032R*, the 1st crizotinib-resistant mechanism reported**
- **G2032R is analogous to *ALK G1202R***

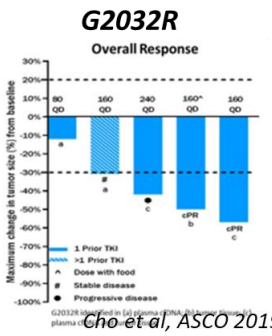


Shaw A et al, Lancet Oncol 2019

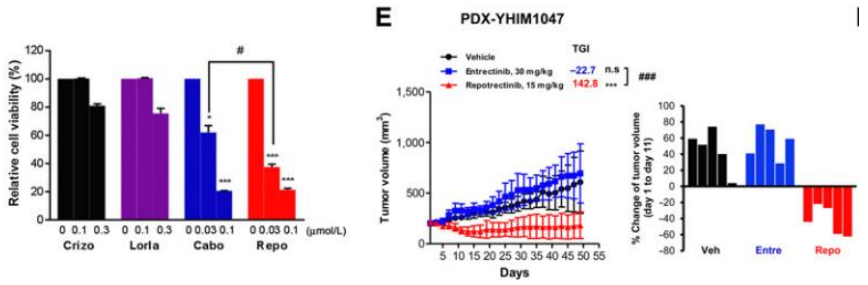
Repotrectinib showed selective and potent in vitro and in vivo activity against ROS1 G2032R

Repotrectinib





Cho et al, ASCO 2019

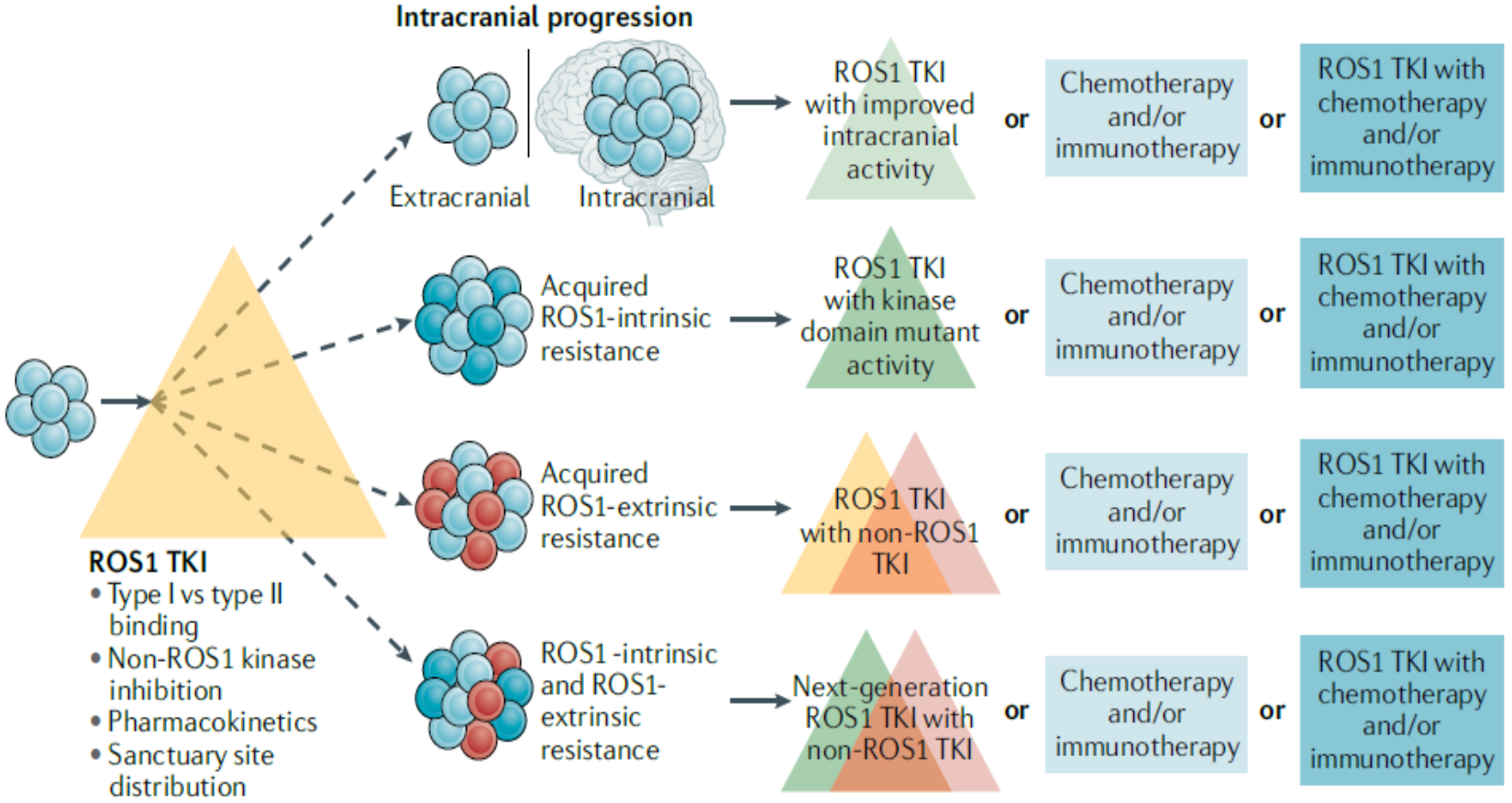


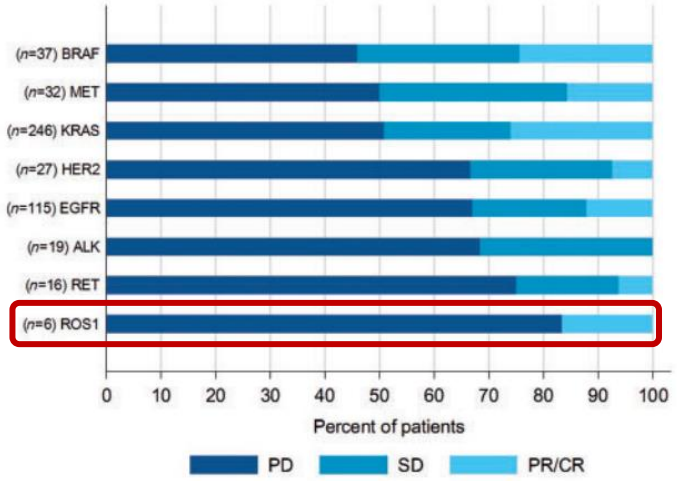
Baseline (blood/ tumor)	best response
PF-001-002 SLC34A2-ROS1, **G2032R**, **TP53**	PD
PF-001-003 EZR-ROS1, **TP53**	PD
PF-001-004 SDC4-ROS1, **G2032R**, **TP53**	PD
PF-001-005 SDC4-ROS1, **G2032R**, **TP53**	PD
PF-001-006 SDC4-ROS1, **TP53**	PD
PF-001-007 CD74-ROS1, **G2032R**	PD
PF-001-013 MTOR	PD
PF-001-016 none	SD
PF-001-022 Nil sample	SD
PF-001-017 **TP53**	SD
PF-001-021 EGFR	SD
PF-001-019 None	SD
PF-001-008 EZR-ROS1, S1861I, **TP53**	SD
PF-001-001 EGFR	PR
PF-001-011 SLC34A2-ROS1	PR
PF-001-018 LRIG3-ROS1, V2054A, **TP53**	PR
PF-001-009 intergenic-ROS1, **TP53**	PR
PF-001-020 TSC	PR
PF-001-010 none	PR
PF-001-012 nil sample	PR
PF-001-015 none	PR
PF-001-014 CD74-ROS1, **TP53**	PR

Landi L, WCLC 2019, ESMO 2019

Yun MR et al, Clin Cancer Res 2020

How do we best sequence?? [*yesterday, today and tomorrow*]

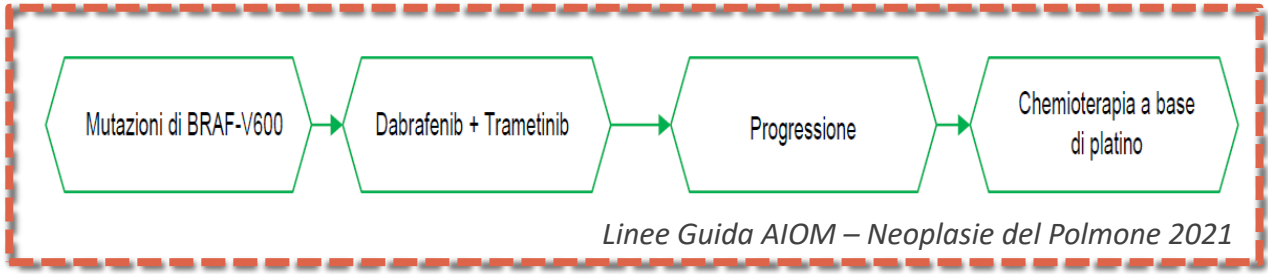




Room for IO? Not alone!
In combos? Mah!

Drilon A et al, NRCO 2020

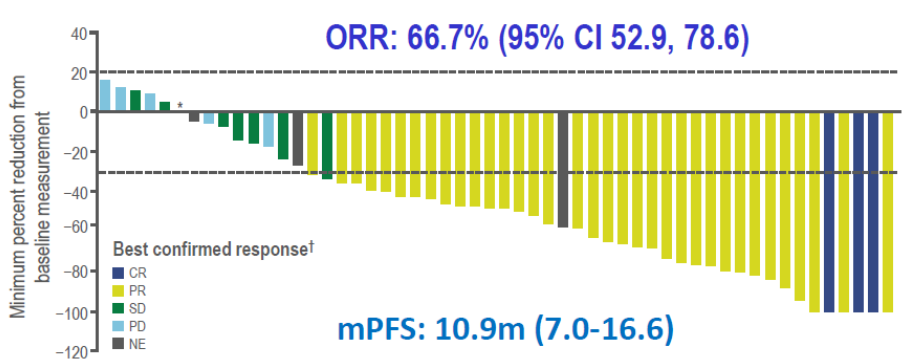
BRAF p.600E mutation: an established SoC



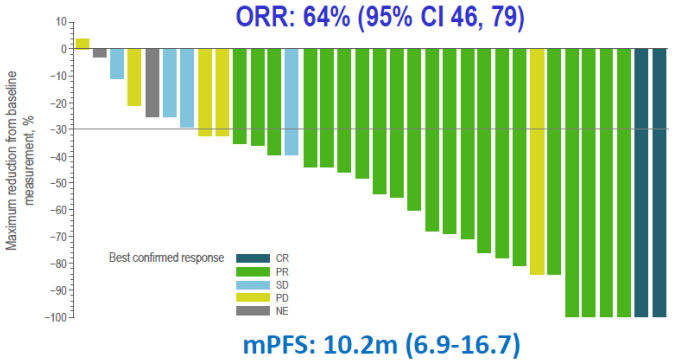
Linee Guida AIOM – Neoplasie del Polmone 2021

- BRAF mutations present in **2% - 4%** of NSCLC (½ BRAF V600E or class 1 BRAF mutations)
- V600E: mainly female (~ 60%), **current/former smokers** (never smokers ~ 30%)
- Non-V600E: mainly male and almost exclusively current/former smokers
- Potential **mechanism of resistance in EGFR-mutated NSCLC** (osi-treated 3-10%)

	Previously Treated				Treatment Naive
	VE-Basket trial **vemurafenib** (n=20)	AcSé trial **vemurafenib** (n=100)	BRF113928 **dabrafenib** (n = 78)	BRF113928 **Dabrafenib Plus Trametinib** (n = 57)	BRF113928 **Dabrafenib Plus Trametinib** (n = 36)
Male	14 (70%)	-	39 (50%)	29 (51%)	14 (39%)
Never smoker	7 (35%)	-	29 (37%)	16 (28%)	10 (28%)
ORR % (95% CI)	42 (20-67)	44.9	33 (23–45)	67 (53–79)	64 (46-79)
PFS, median (95% CI)	**7.3** (3.5-10.8)	**5.2**	**5.5** (3.4–7.3)	**10.2** (6.9–16.7)	**10.9** (7.0-16.6)
OS, median (95% CI)	NA	9.3	12.7 (7.3–16.3)	18.2 (14.3–NE)	24.6 (12.3-NE)



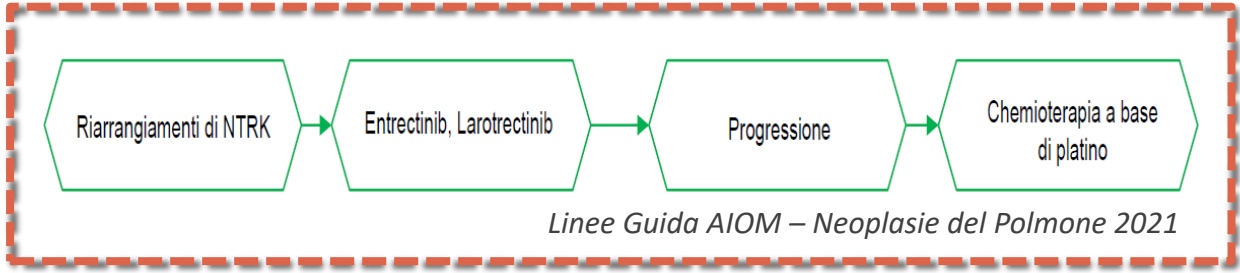
Planchard D, Lancet Oncol 2016



Planchard D, Lancet Oncol 2017

NTRK 1,2,3 rearrangements

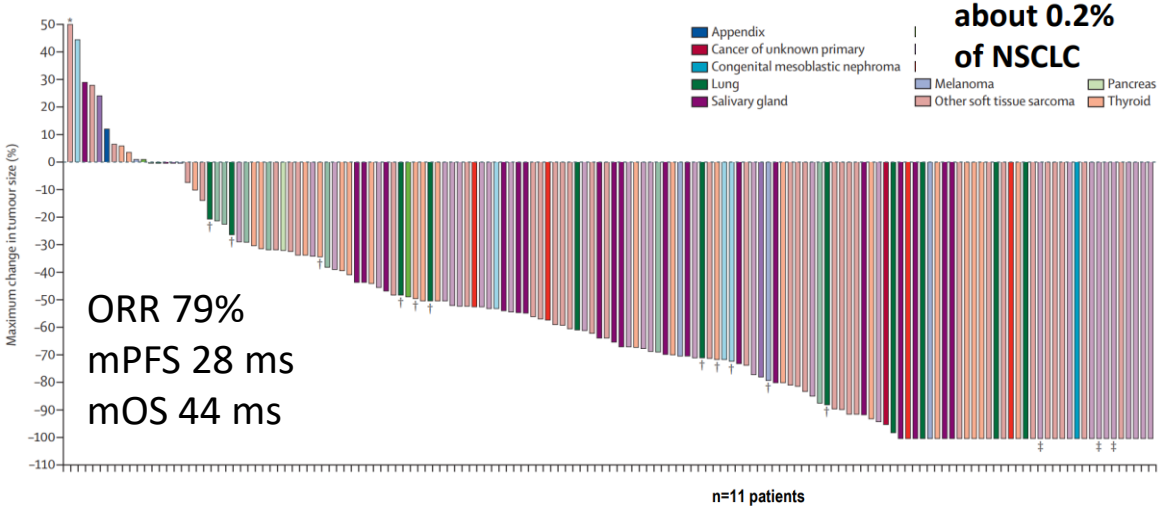
***NTRK* fusions are rare events: 0.21% across 11,116 patients with tumors of all types**

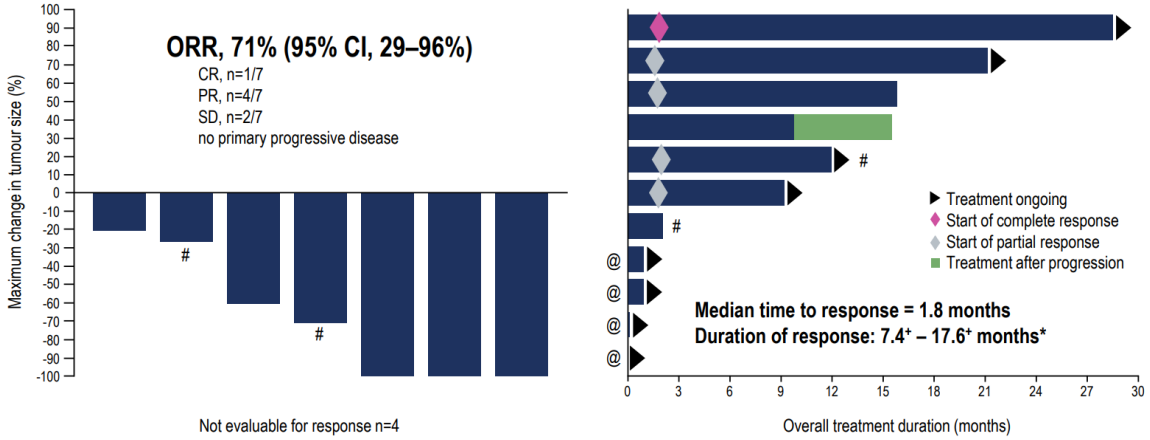


Linee Guida AIOM – Neoplasie del Polmone 2021

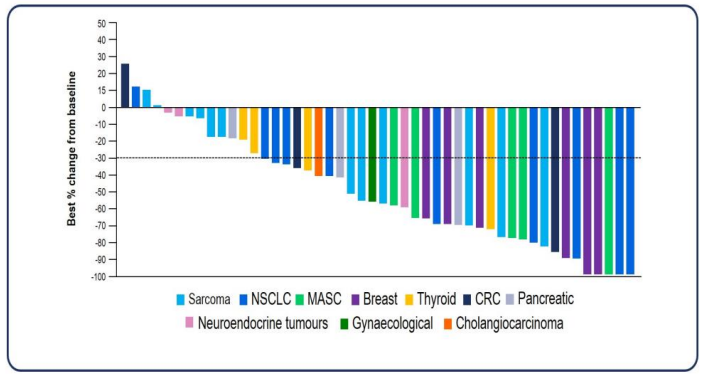
LAROTRECTINIB

Found in about 0.2% of NSCLC





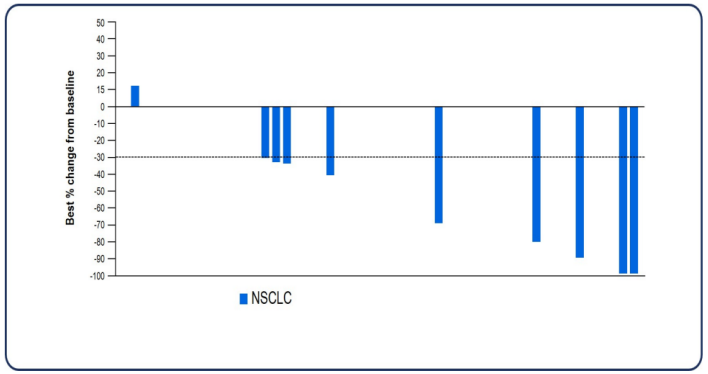
Hong D et al, Lancet Oncol 2020



Efficacy outcomes	*NTRK*+ patients (n=54)
ORR,* %	**57.4 (95% CI: 43.2–70.8)**
CR,* n (%)	4 (7.4)
Median DOR,* months	10.4 (95% CI 7.1–NR)
Median PFS,* months	11.2 (95% CI 8.0–14.9)
Median OS, months	20.9 (95% CI 14.9–NR)

NTRK+ patients ORR* 57.4%

Data cut-off date: 31 May 2018. Note: Patients (n=6) without matched pre/post therapy scans were excluded from the plot



Efficacy outcomes	*NTRK*+ NSCLC patients (n=10)
ORR,* %	**70.0 (95% CI: 34.75–93.33)**
CR,* n (%)	1 (10)
PR,* n (%)	6 (60)
SD,* n (%)	1 (10)
Median DOR,* months	NE (95% CI 10.4–NE)
Median PFS,* months	14.9 (95% CI 4.7–NE)

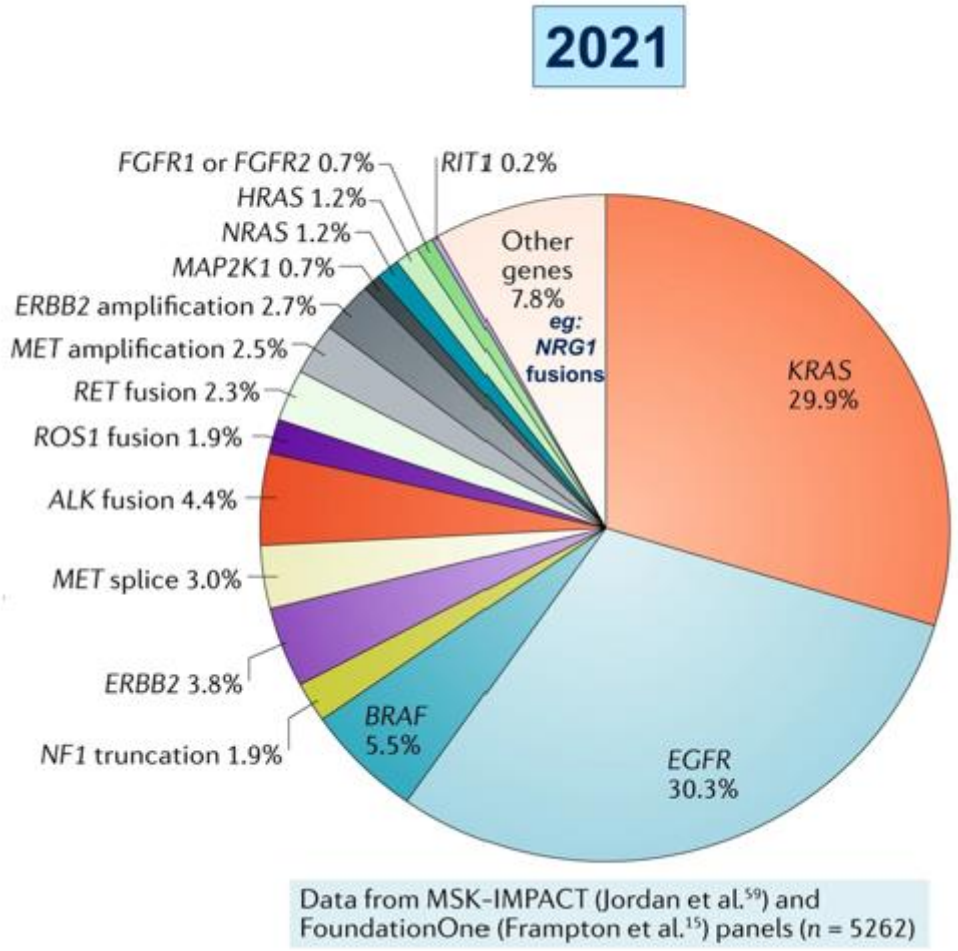
NTRK+ NSCLC patients with CNS disease at baseline (n=6)	
Intracranial response,* n (%)	**4 (66.7)**
CR	2 (33.3)
PR	2 (33.3)
SD	1 (16.7)
IE	1 (16.7)

Data cut-off date: 31 May 2018. Note: Patients (n=6) without matched pre/post therapy scans were excluded from the plot. * By blinded independent central review

Doebele RC et al, Lancet Oncol 2020

ENTRECTINIB

Precision Therapy for non-squamous (*for now*) NSCLC in 2021/2022

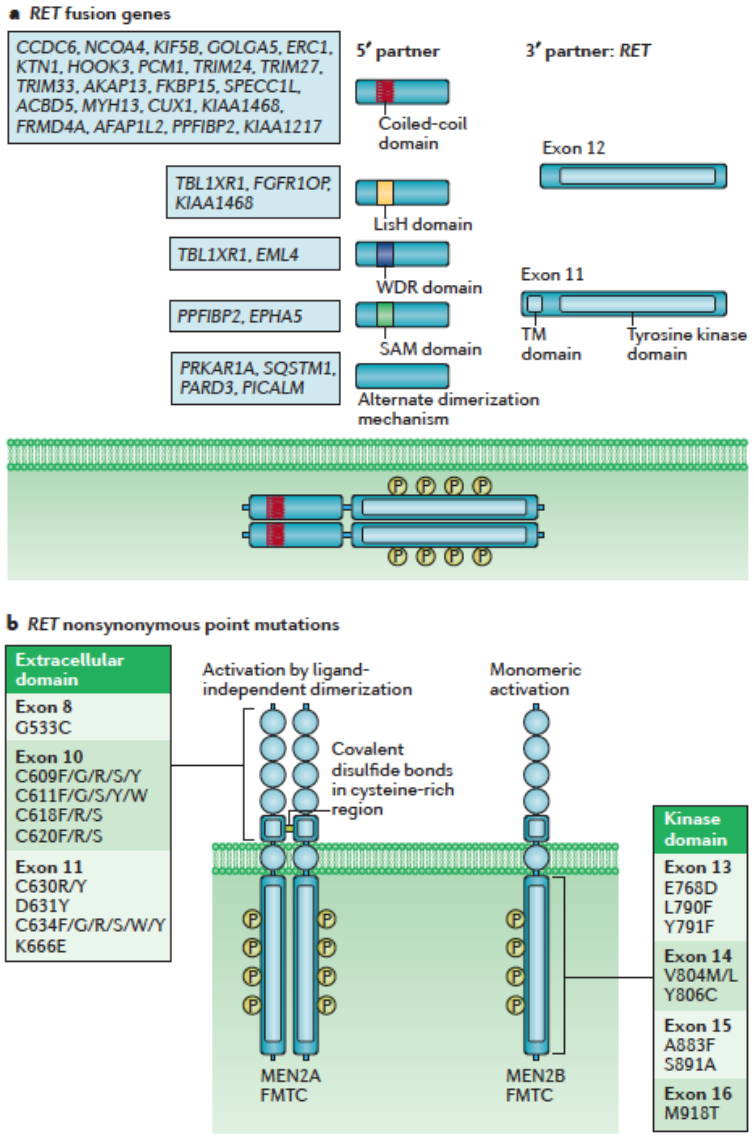


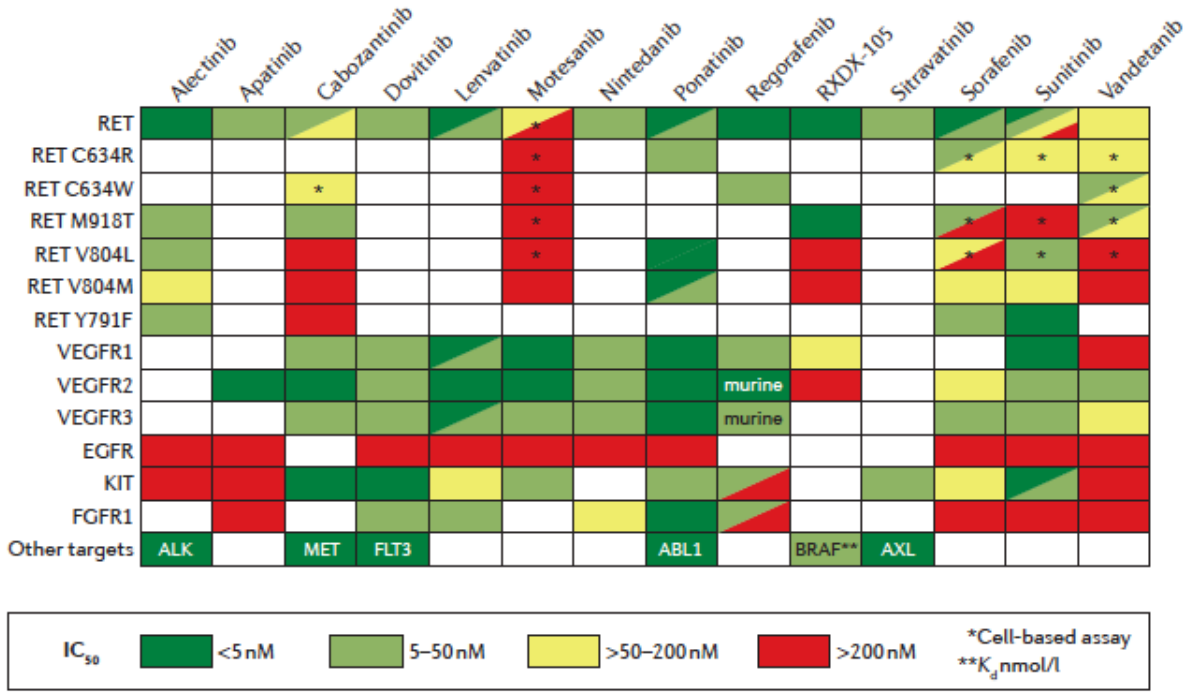
	What we absolutely need TODAY*	What we (also) need TODAY	
15%	EGFR mutations	RET rearrangements	1-2%
4%	ALK rearrangements	MET ex 14 mutations	3-4%
1%	ROS1 rearrangements	HER2 mutations	2-4%
4%	BRAF p.V600E mutations	KRAS p.G12C mutations	13%
<1%	NTRK 1,2,3 rearrangements		

***** In metastatic non-squamous NSCLC (before 1° line initiation) - in Italy

Linee Guida AIOM – Neoplasie del Polmone 2021

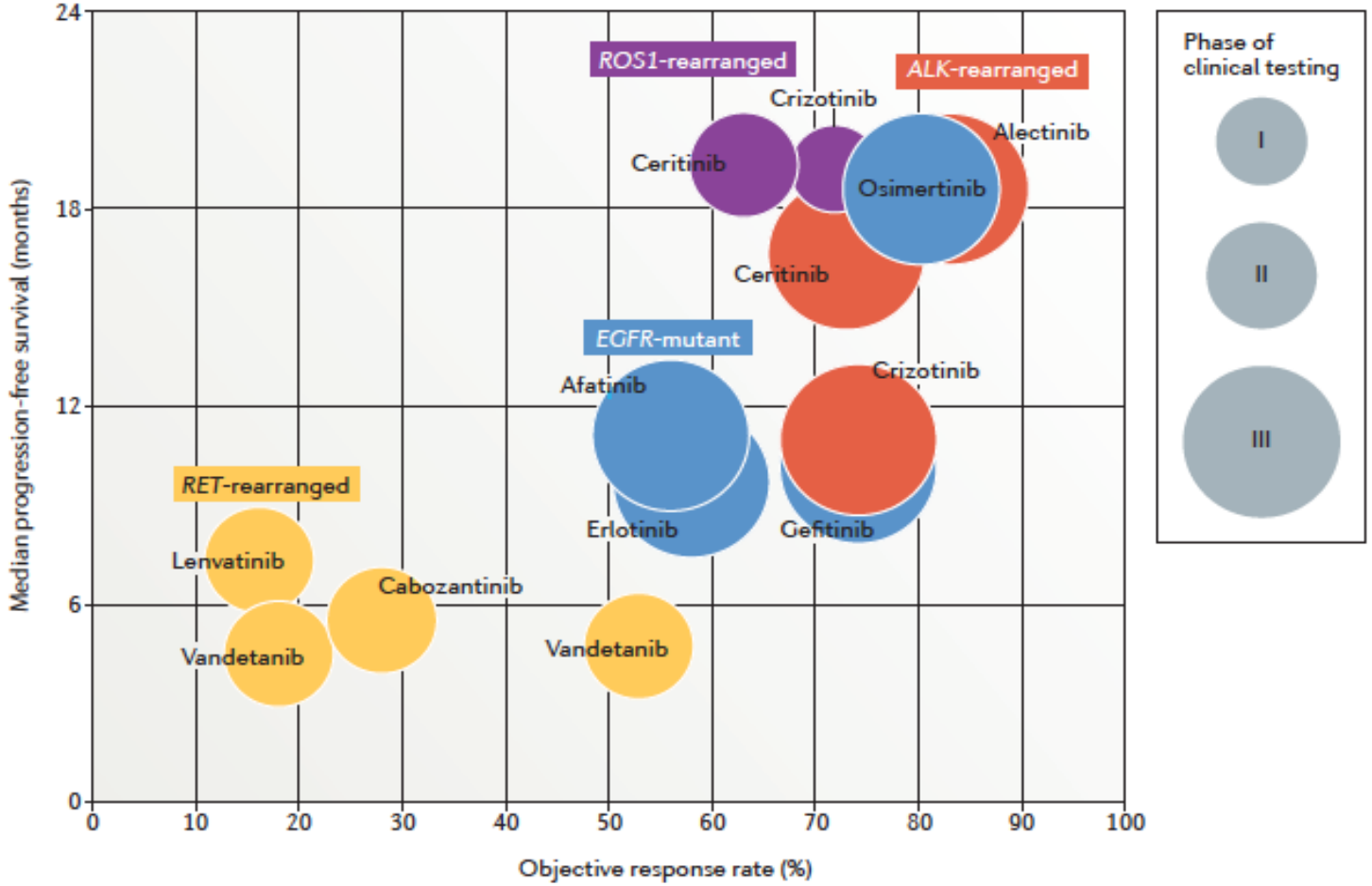
RET rearrangements: the next big target..





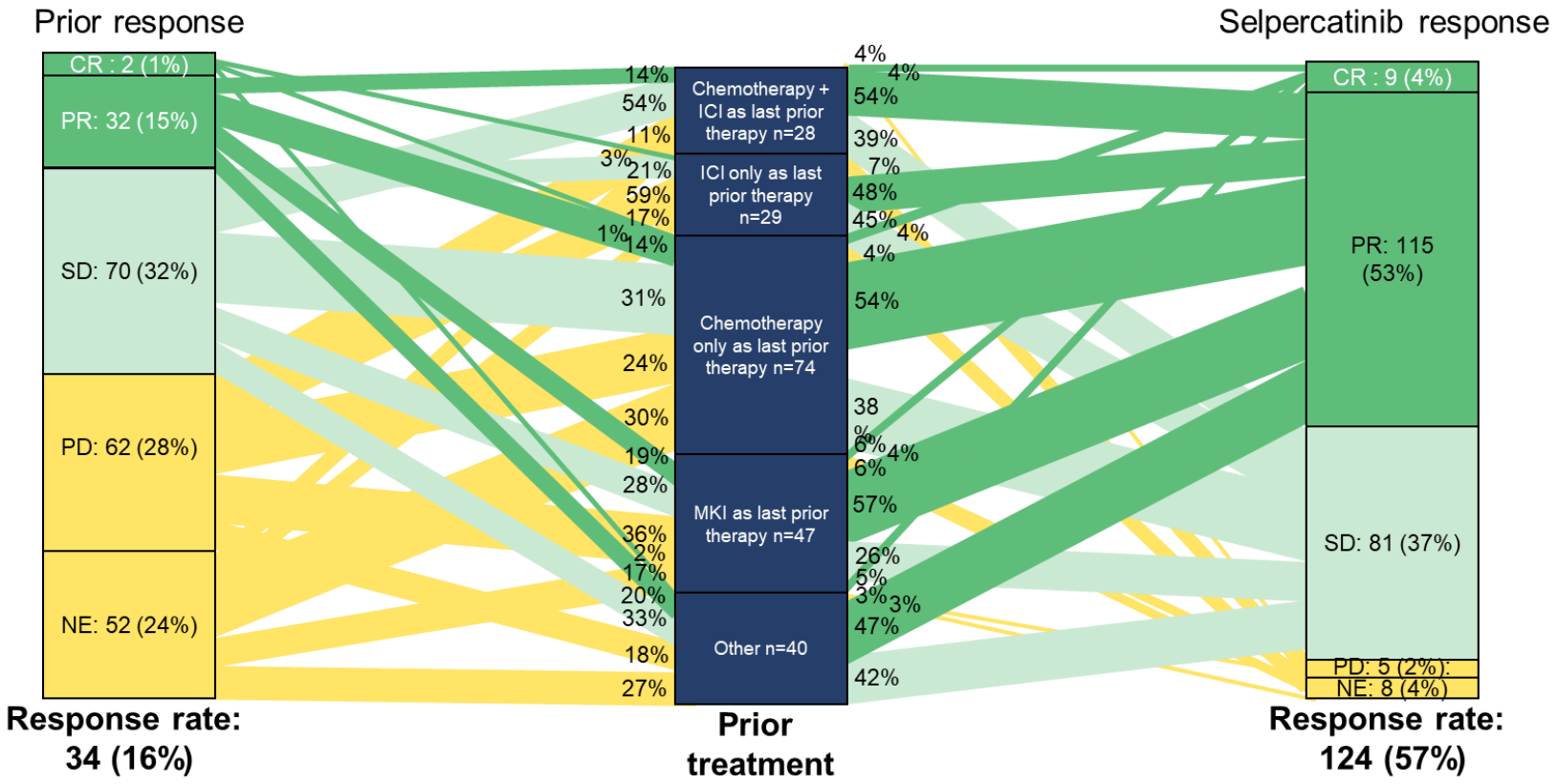
Wang R, et al. JCO 2012; Drilon A, et al. Nat Rev Clin Oncol 2018

RET rearrangements as the next big target: Are we sure??

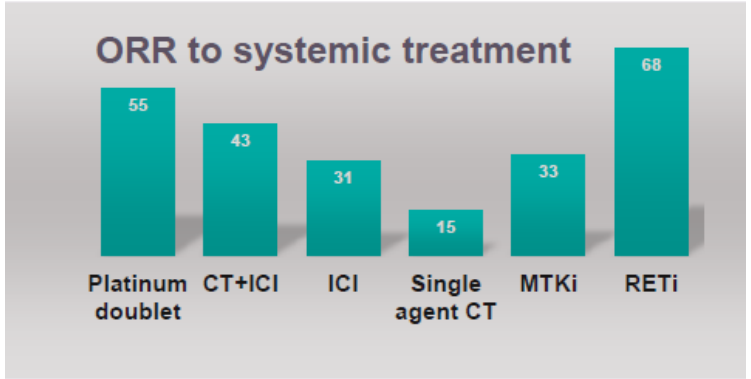


Drilon A, et al. Nat Rev Clin Oncol 2018

Systemic therapy in *RET* rearranged NSCLC



Patients' characteristics	N = 149
Median age (range)	61.9 (53-69.6)
Female sex (%)	87 (58.4)
Smoking history (%)	67 (45)
Adenocarcinoma histology (%)	138 (92.5)
Median number of lines (IQR)	2 (1-3)

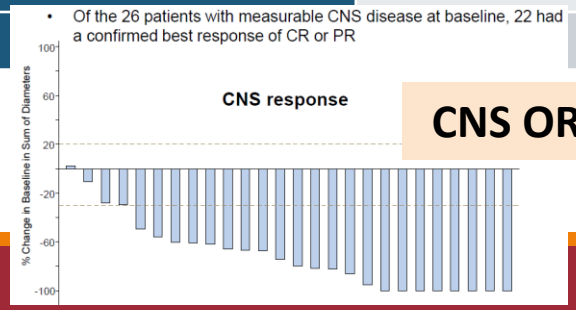


Drilon A et al, ASCO 2021

Marinello A et al, RET-MAP ELCC 2022

RET rearrangements: two guest Stars!!

	SELPERCATINIB	PRALSETINIB
	[LIBRETTO-001]	**[ARROW]**
	Drilon A. et al ELCC 2022	Curigliano G. et al ASCO 2021
ORR (%, N)		
Prior platinum-based chemotherapy	**61%** (n = 247)	**62%** (n = 126)
Treatment-naïve	**84%** (n = 68)	**88%** (n = 25) [3]
DCR (%, N)		
Prior platinum-based chemotherapy	**94%** (n = 218) [1]	**91%** (n = 126)
Treatment-naïve	**93%** (n = 48)	**96%** (n = 25) [3]
mPFS (months, N)		
Prior platinum-based chemotherapy	24.9 (n = 247)	16.5 (n = 136)
Treatment-naïve	22.0 (n = 68)	NR
Grade ≥3 TRAEs occurring in ≥ 10% of patients (%, N)	Hypertension 12.1% (n = 746) [2]	Neutropenia 19%, anemia 13%, hypertension 12% (n = 471) [4]
Discontinuation rate (%, N)	2% (n = 746) [2]	6% (n = 471) [4]

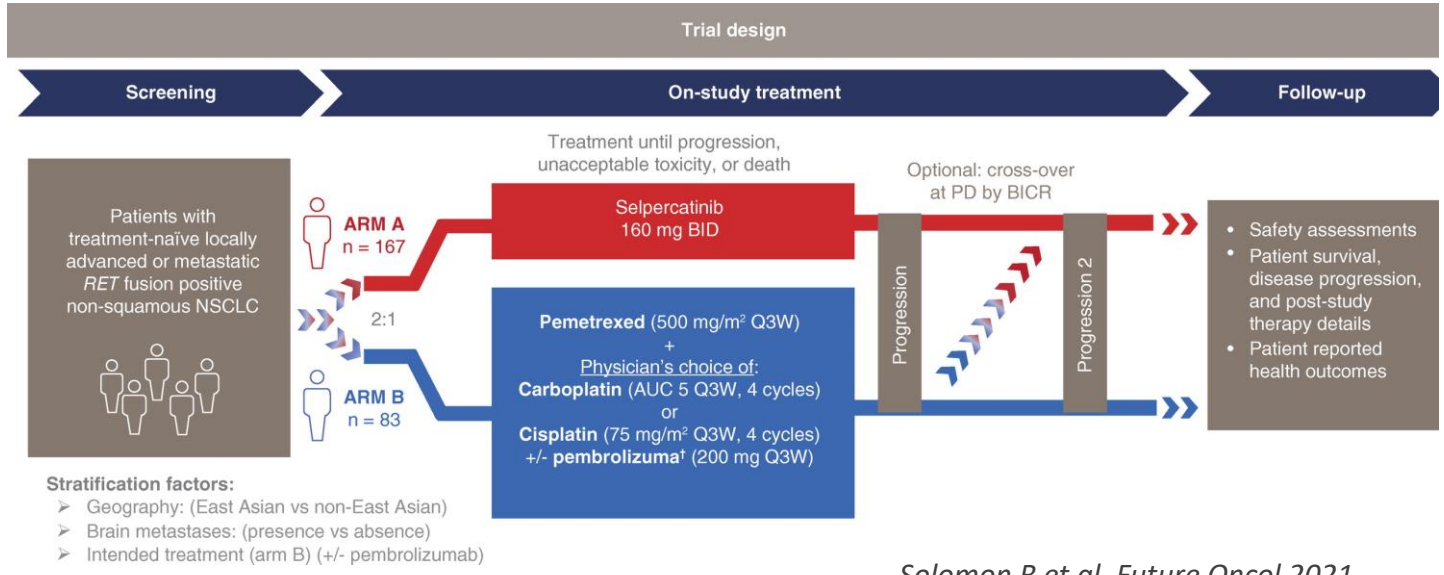


CNS ORR 85%

Belluomini L et al, SUBMITTED

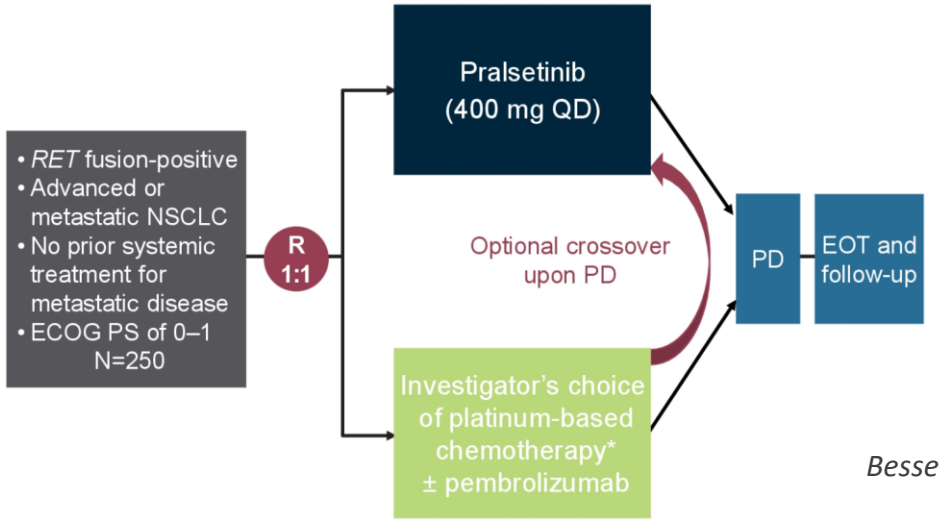
RET rearrangements: phase 3 trials are ongoing in 1st line

LIBRETTO-431



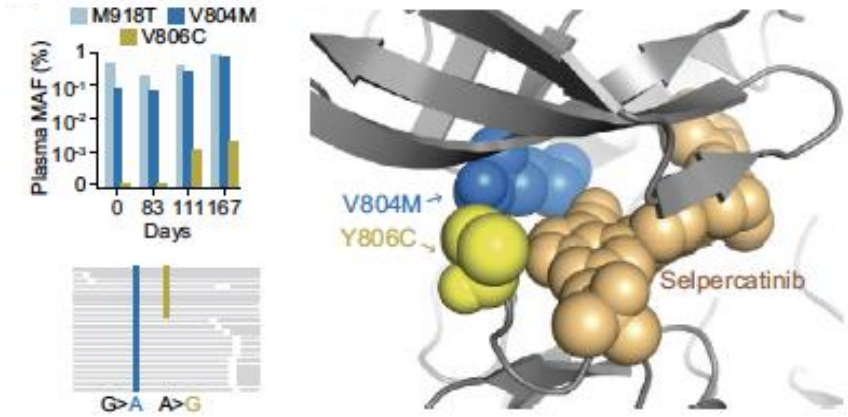
Solomon B et al, Future Oncol 2021

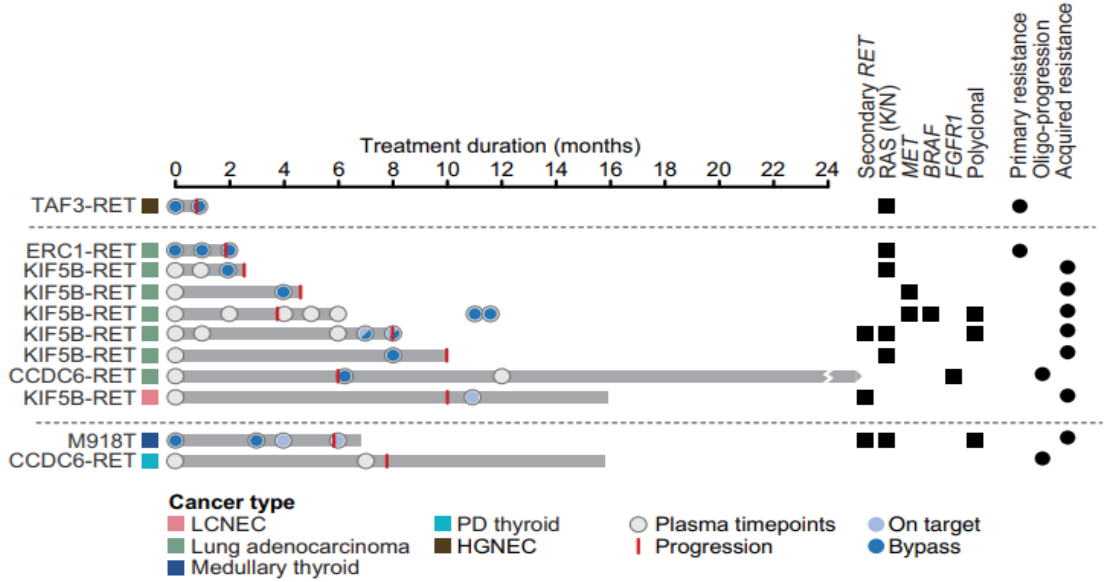
AcceleRET

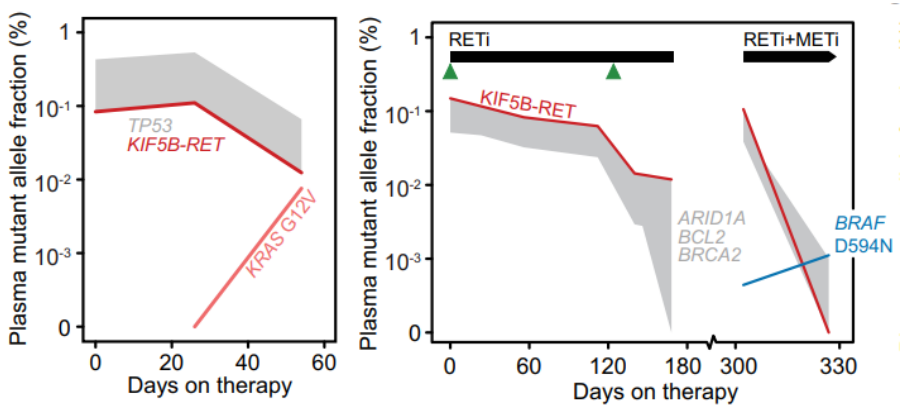


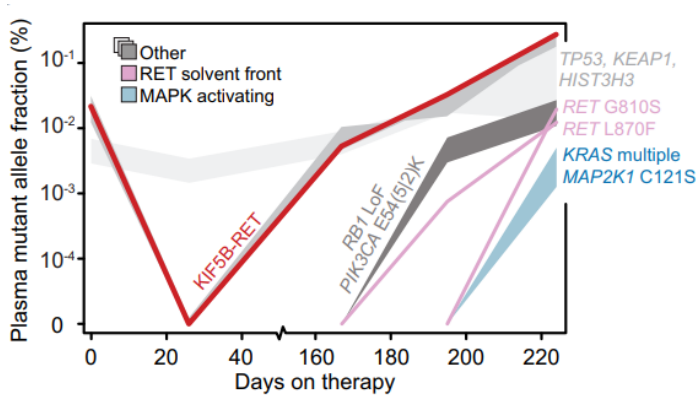
Besse B et al, ASCO 2020

Mechanisms of acquired resistance to RETi







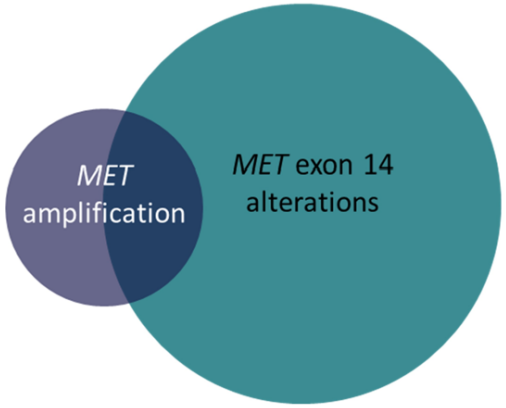


- Acquired selpercatinib resistance is driven by **MAPK pathway reactivation**, on- and off-target pathway reactivation via **secondary RET mutations** or **MET amplifications**
- Multiple distinct mechanisms are often observed in the same patient (**polyclonal resistance**)

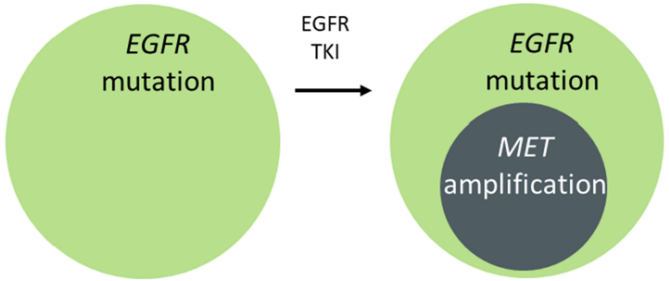
Rosen EY et al, Nature Communications 2022

MET alterations: still a diagnostic challenge but..

MET as a primary driver

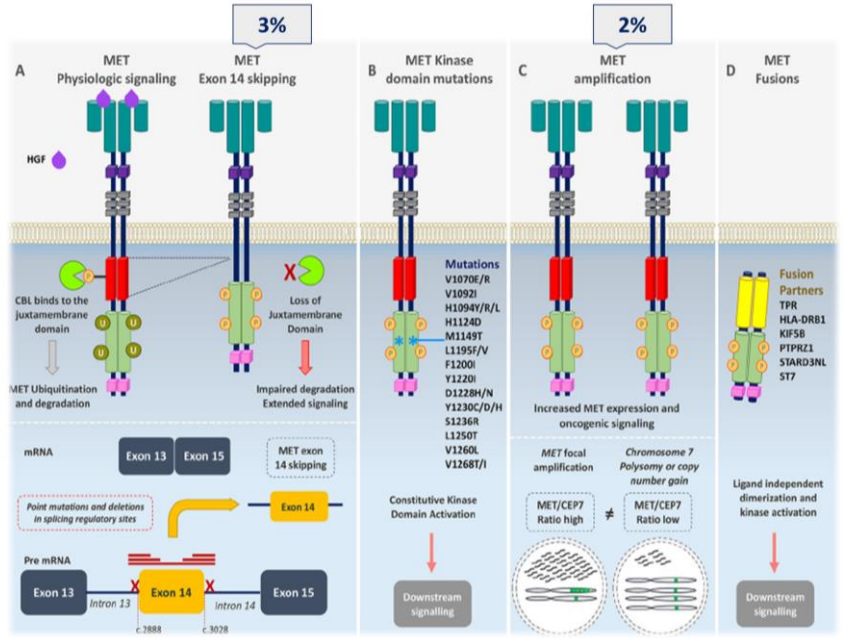


MET as a secondary/co-driver



	Lu S, ASCO 2020	Paik PK, NEJM 2020	Drilon A, Nat Med 2020	Wolf J, ASCO 2021
METex14	-RT-PCR -NGS Geneseeq Tetradecan Panel	-NGS Guardant 360 (cfDNA) -NGS Oncomine Focus Assay (tissue)	-RT-PCR -NGS, DNA or RNA-based (different panels)	-RT-PCR -NGS FoundationONE CDx

- MET exon 14 skipping mutation on tissue, blood, both
  - DNA or **RNA** NGS
  - RT-qPCR
  - Sanger sequencing



concomitant MET ex14 mutations and MET amplifications may occur

- MET amplification
  - FISH
  - NGS

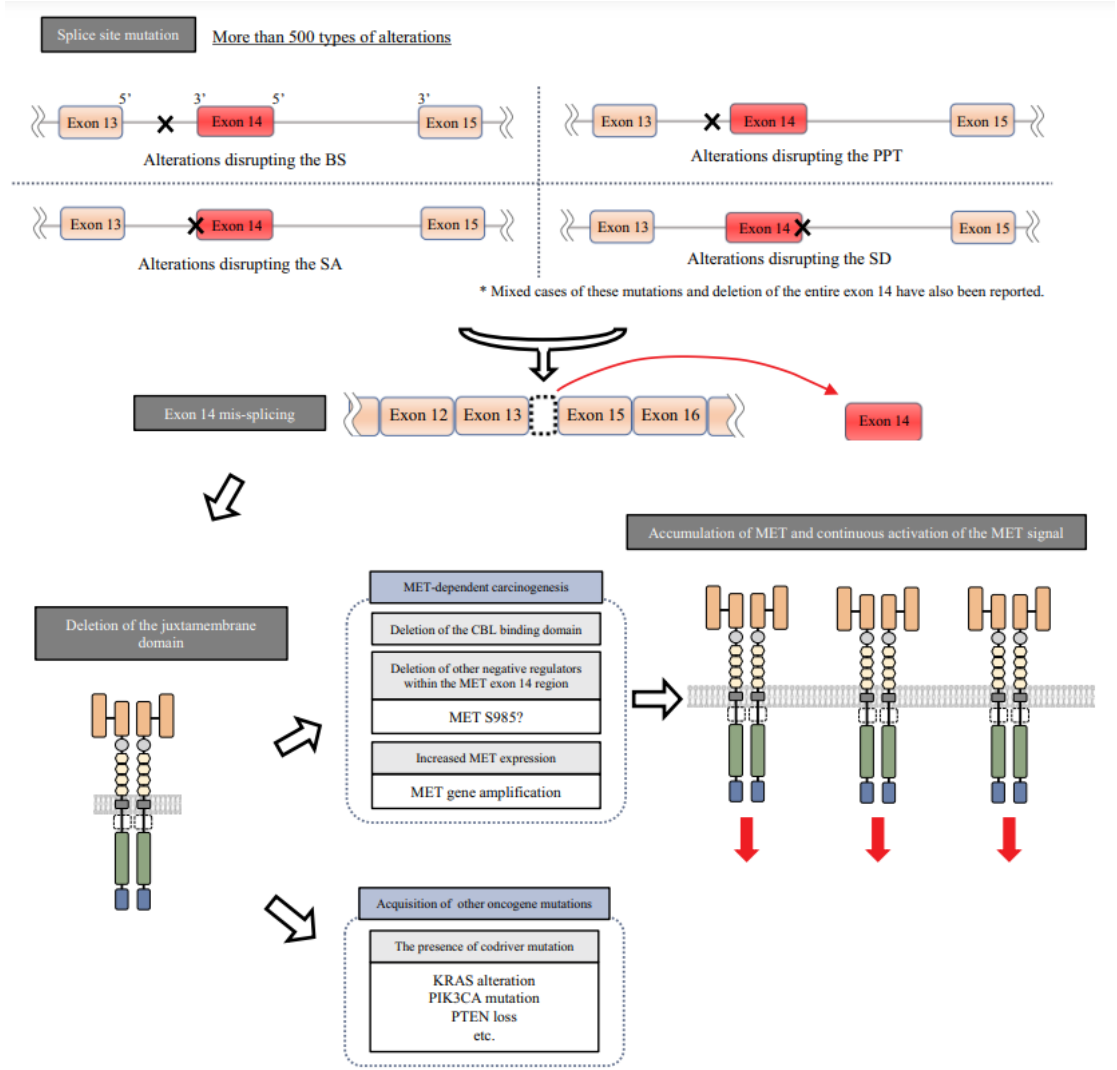
<u>Optimal copy number cut off tbd</u>

<u>Liquid biopsy: sensitivity, specificity</u>

	Le X, ASCO 2021	Camidge R, JTO 2020	Wolf J, NEJM 2020
MET ampl	-NGS Guardant 360 (cfDNA): *GCN* $\geq$*2.5*	- FISH: *MET/CEP7* $\geq$*1.8* - NGS FoundationONE CDx (tissue): *GCN* $\geq$*6*	-NGS FoundationONE CDx (tissue): *GCN* $\geq$*6*

Modified from Drilon A and Pasello G, ASCO 2021

MET exon 14 skipping mutations



Up to 4% of non-squamous NSCLCs

- older patients, more smokers
- sarcomatoid tumour
- highly heterogeneous
- up to 20% with concurrent MET amplification

Fujino et al, Lung Cancer: Targets and Therapy 2021

… we finally MET the right combo target-drugs

MET exon 14sk	N of patients	Line of treatment	RR (%)	DOR (months)	icRR (%)	PFS (months)	OS (months)	TR-AEs discontinuation
CRIZOTINIB	65	1 >1	25 36.6	9.1 (overall)	20[§]	7.3 (overall)	20.5 (overall)	7%
CAPMATINIB	63	1 2	65.6 51.6	12.6 9.7	54	10.8 6.9	20.8* 13.6*	11%
TEPOTINIB	152	1 >1	43 43	10.8 11.1	55	8.5 (overall)	17.1 (overall)	11%
SAVOLITINIB	70	1 >1	54.4 46	6.8 NR	NA	5.6 13.8	NA	14.3%

MET *de novo* amplification	N of patients	Line of treatment	RR (%)	DOR (months)	PFS (months)	OS (months)	TR-AEs discontinuation
CRIZOTINIB	21	≥1	38.1	5.2	6.7	11.4	10.5%
CAPMATINIB	84	1 >1	40 29	7.5 8.3	4.2 4.1	NA	11%
TEPOTINIB	24	1 >1	71.4 28-30	NR	4.2 (overall)	NA	0%

**Data not mature for expansion cohorts; [§] retrospective data, not reported in Profile 1001*
NR: not reached; NA: not available

Wolf J, 2021 ASCO meeting; Le X, 2021 ASCO meeting; Drilon A Nat Med2020; Camidge R JTO 2021;Lu S, 2020 ASCO meeting; Paik PK NEJM 2020; Wolf J NEJM 2020; Offin M, JCO Precis Oncol 2020

CAPMATINIB

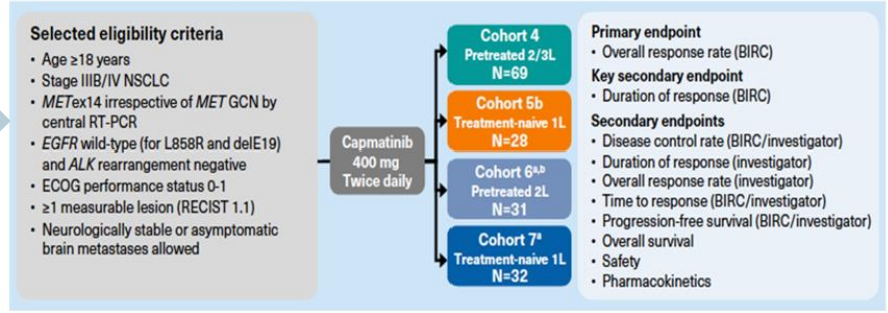
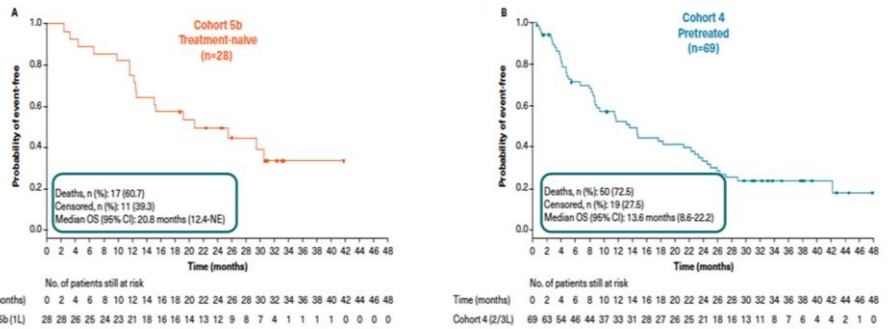
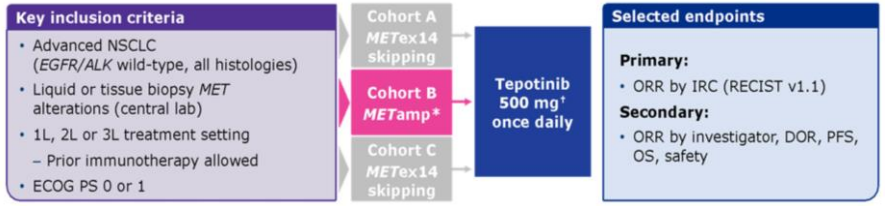


Figure 3. (A) Overall survival for treatment-naive patients with *MET*ex14 NSCLC in Cohort 5b. (B) Overall survival for pretreated (2/3L) patients with *MET*ex14 NSCLC in Cohort 4



Wolf J et al, ASCO 2021

TEPOTINIB



		Overall (n=24)	1L (n=7)	2L (n=10)	3L (n=7)
Best overall response, n (%)	PR	10 (41.7)	5 (71.4)	3 (30.0)	2 (28.6)
	SD	1 (4.2)	0	1 (10.0)	0
	PD	5 (20.8)	1 (14.3)	2 (20.0)	2 (28.6)
	NE	8 (33.3)	1 (14.3)	4 (40.0)	3 (42.9)
ORR, n (%) [95% CI]		10 (41.7) [22.1, 63.4]	5 (71.4) [29.0, 96.3]	3 (30.0) [6.7, 65.2]	2 (28.6) [3.7, 71.0]

Le X et al, ASCO 2021

MET exon 14 skipping mutations: new drug on the horizon [SCC244]

GLORY

Key patient inclusion criteria
- Locally advanced or metastatic NSCLC
- METex14 skipping mutations
- ≤2 prior systemic therapies or no prior systemic therapy
- ECOG PS 0–1

(n=73)

→ SCC244 300 mg/day q3w → PD/toxicity

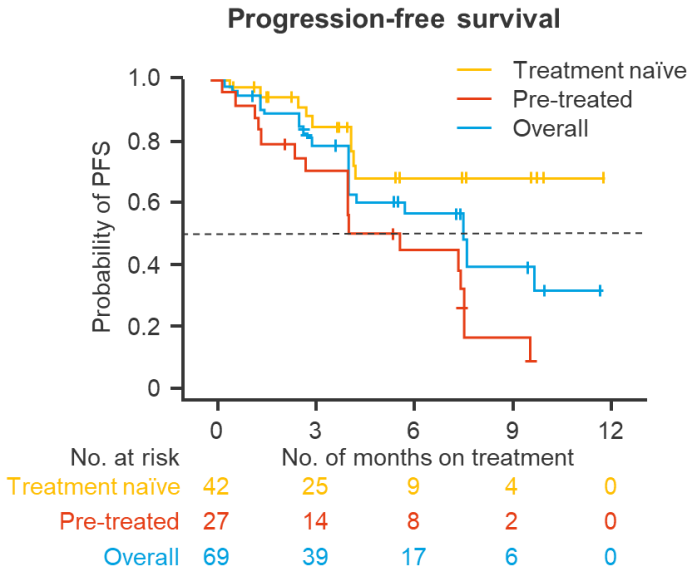
Primary endpoint
- ORR (BIRC, RECIST v1.1.)

Secondary endpoints
- DoR, DCR, TTR, PFS, OS, safety

TRAEs, n (%)	All (n=73)
Any	71 (97.3)
Grade ≥3	32 (43.8)
Serious	13 (17.8)
Led to dose interruption	18 (24.7)
Led to dose reduction	21 (28.8)
Led to discontinuation	5 (6.8)

* Mainly peripheral edema, neutropenia, headache, rash

Efficacy analysis set	Treatment-naïve (n=42)	Previously treated (n=27)	All (n=69)
ORR, % (95%CI)	66.7 (50.5, 80.4)	51.9 (31.9, 71.3)	60.9 (48.4, 72.4)
DCR, % (95%CI)	88.1 (74.4, 96.0)	74.1 (53.7, 88.9)	82.6 (71.6, 90.7)
mDoR, mo (95%CI)	NE (NE, NE)	5.1 (2.8, 8.2)	8.2 (4.8, NE)
PFS events, n (%)	9 (21.4)	17 (63.0)	26 (37.7)
mPFS, mo (95%CI)	NE (4.3, NE)	5.7 (2.8, 7.6)	7.6 (4.2, NE)



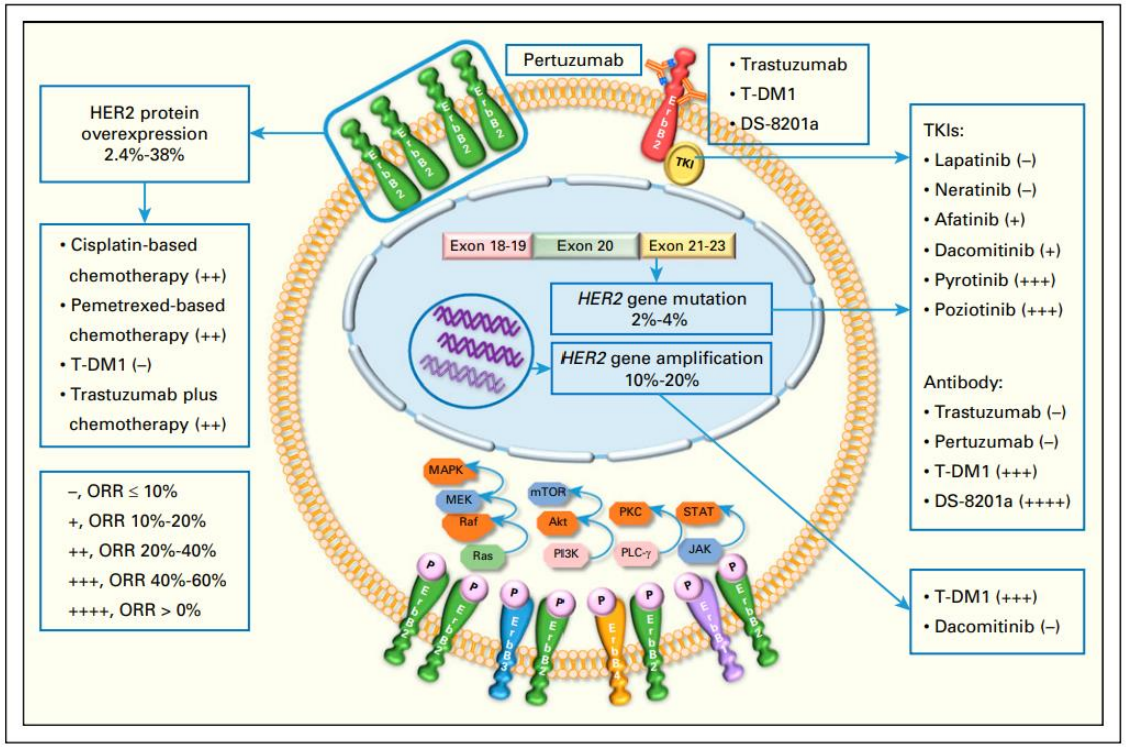
Lu S et al, AACR 2022

HER2 alterations: still a diagnostic challenge but…

Define **“HER2 positivity”** in lung cancer**:**

- **Overexpression** (2+/3+) in 23-35%, high (3+) in 4%
- **Amplification** in 10-20%, high in 7% (also in EGFR)
- **Mutations** in 2-4%, mainly insertions in exon 20-21 causing constitutive TKI activation

- *The association between amplification and overexpression is controversial*
- *Lack of standardized testing techniques and cut-offs for defining HER2 positivity in lung cancer*

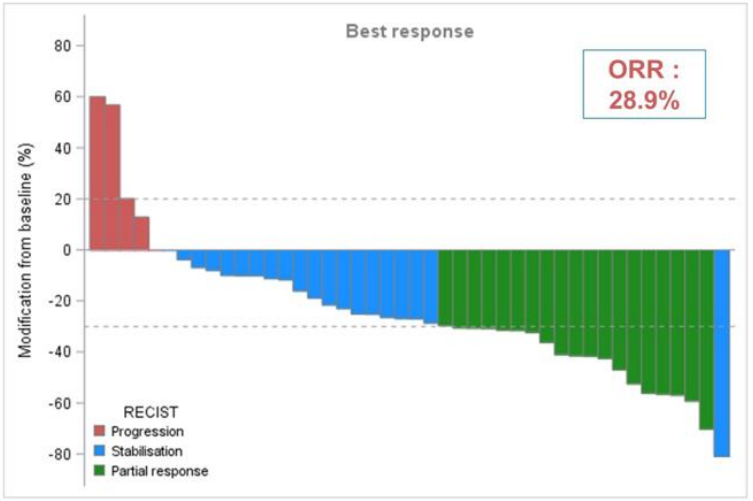


Zhao and Xia, JCO Precision Oncology 2020

Patients harbouring HER2 alterations more frequently **women, young, never smoker, and mainly adenocarcinomas**

HER2 alterations: should we just copy the example of breast?

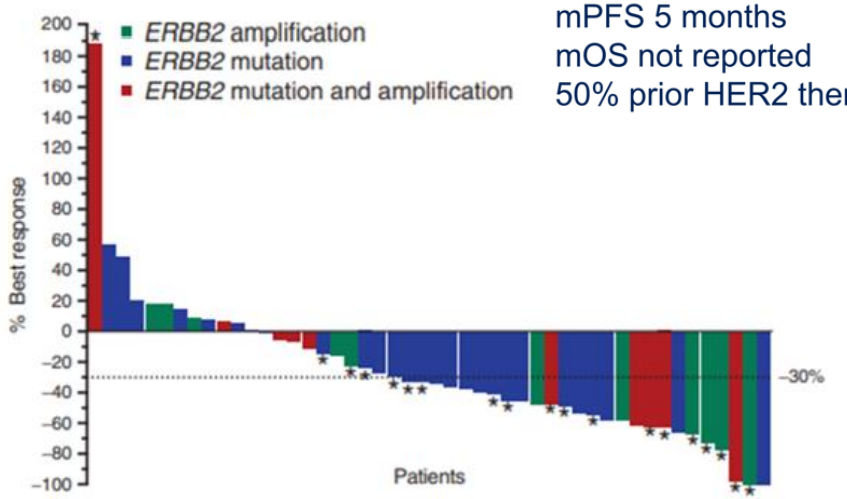
- **TKIs** bind to the tyrosine domain of activated HER2 protein → several pan-HER TKIs have been tested for NSCLC with modest results (ORR 20-30%) and relevant toxicities.
- **Chemotherapy** still a standard of care (waiting for..)
- The efficacy of the **monoclonal antibodies pertuzumab and trastuzumab** has also been studied, alone or conjugated to cytotoxic drugs such as trastuzumab emtansine (T-DM1).



Mazieres J et al, ASCO 2021

Trastuzumab/pertuzumab/docetaxel
N=46 (HER2-mutant/insertions)
ORR 29%
mPFS 6.8 months
mOS 17.6 months
TRAEs G3-4 64%

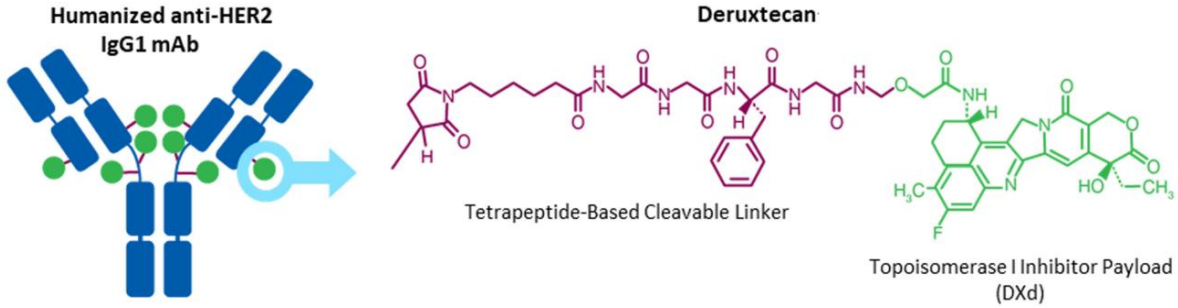
T-DM1
N=38 (HER2-mutant)
ORR 50% (95% CI 31-69%) RECIST/mPERCIST
mPFS 5 months
mOS not reported
50% prior HER2 therapy



Li, BT; et al. Cancer Discovery 2020

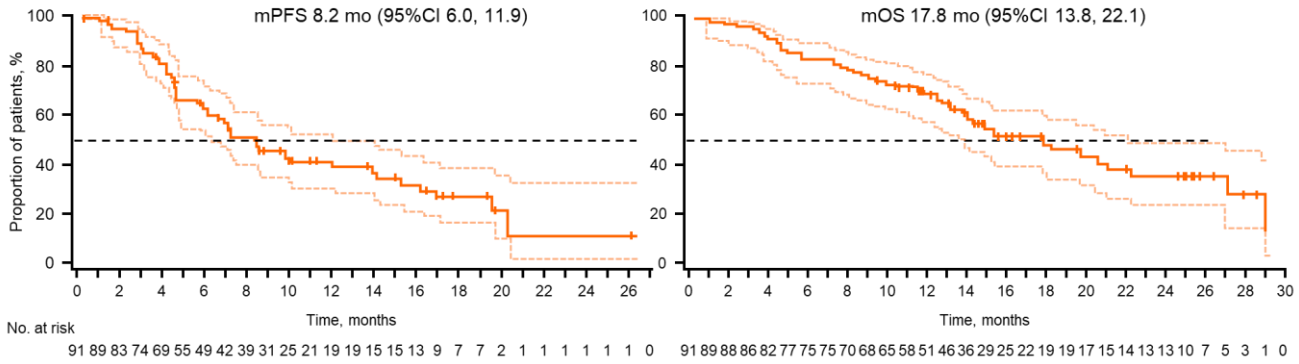
The revolution of ADC for *HER2* mutations

TRASTUZUMAB DERUXTECAN

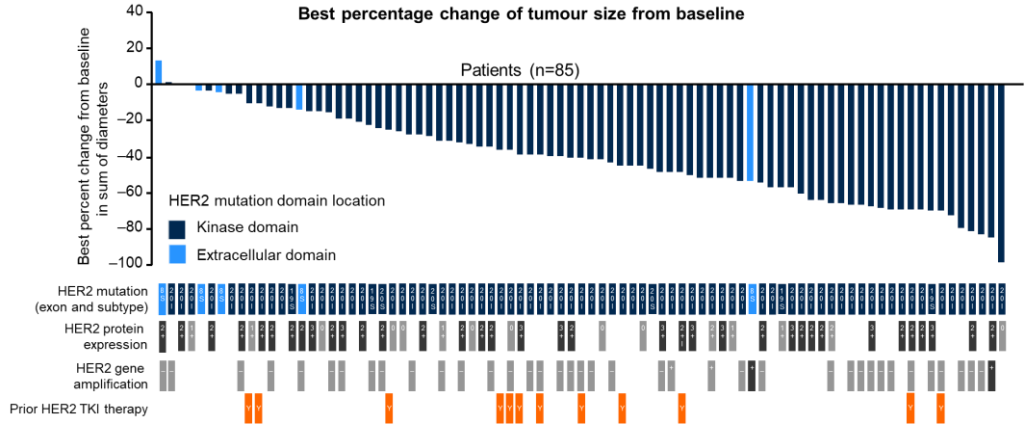


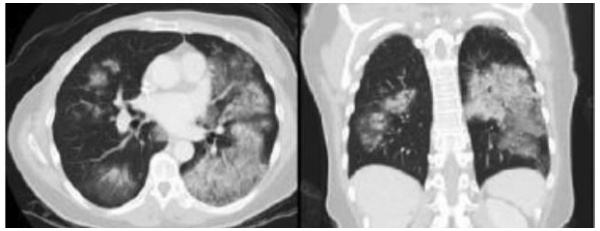
	Trastuzumab deruxtecan (n=91)
Confirmed ORR, n (%) [95%CI]	50 (54.9) [44.2, 65.4]
BOR, n (%)	
CR	1 (1.1)
PR	49 (53.8)
SD	34 (37.4)
PD	3 (3.3)
NE	4 (4.4)
DCR, n (%) [95%CI]	84 (92.3) [84.8, 96.9]
mDoR, mo (95%CI)	9.3 (5.7, 14.7)
Median follow-up, mo (range)	13.1 (0.7–29.1)

Progression-free survival



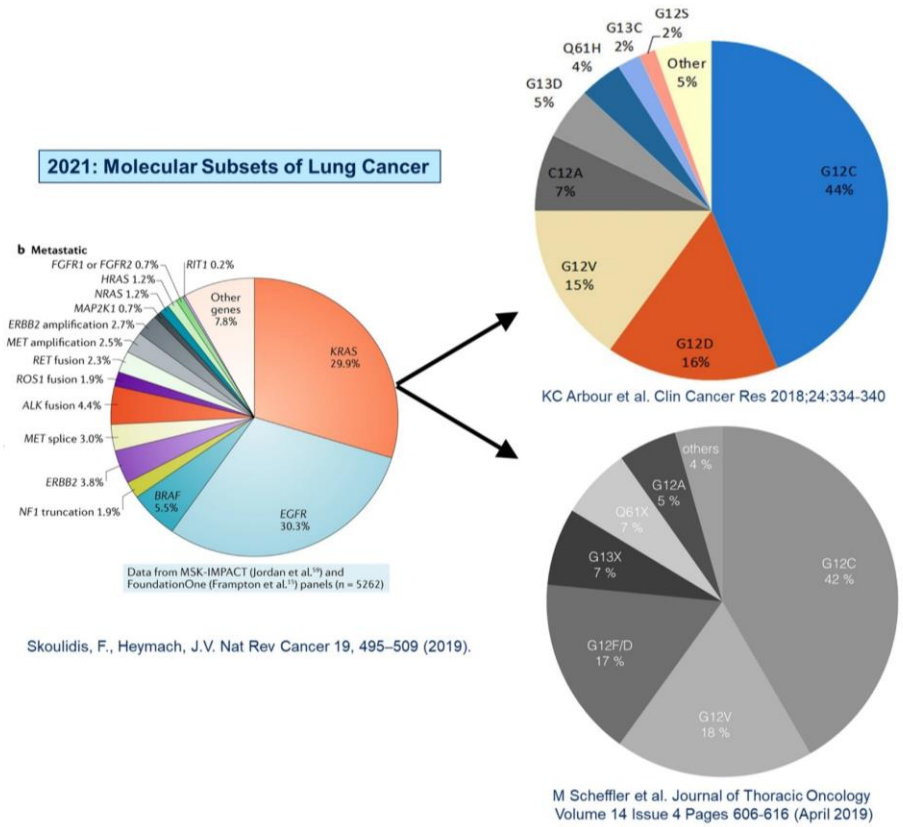
Overall survival





Li BT et al. NEJM 2022
Azar I et al. Lung Cancer: Targets and Therapy 2021

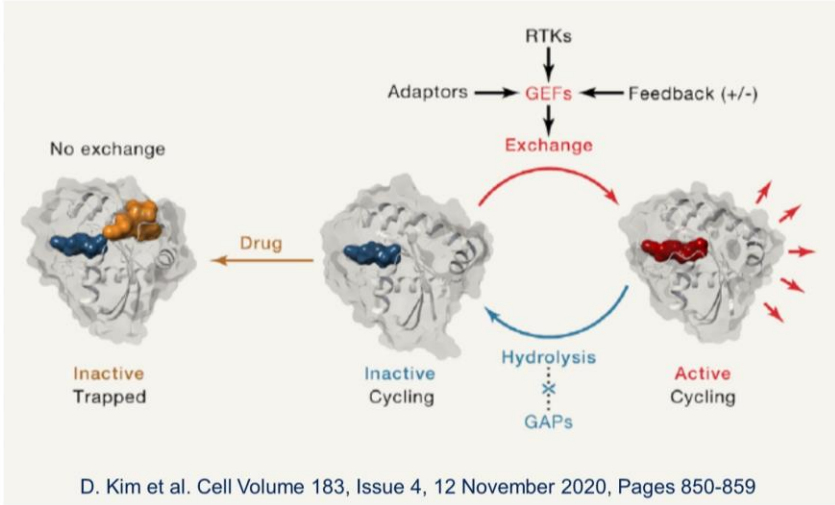
KRAS p.G12C mutations [*Drugging the 'undruggable' KRAS*]



- KRAS G12C most common KRAS variant
- 13% (1 in 8) or all lung adenocarcinomas
- Multiple KRAS G12C inhibitors being developed

KRAS G12C Inhibitors - Mechanism of Action

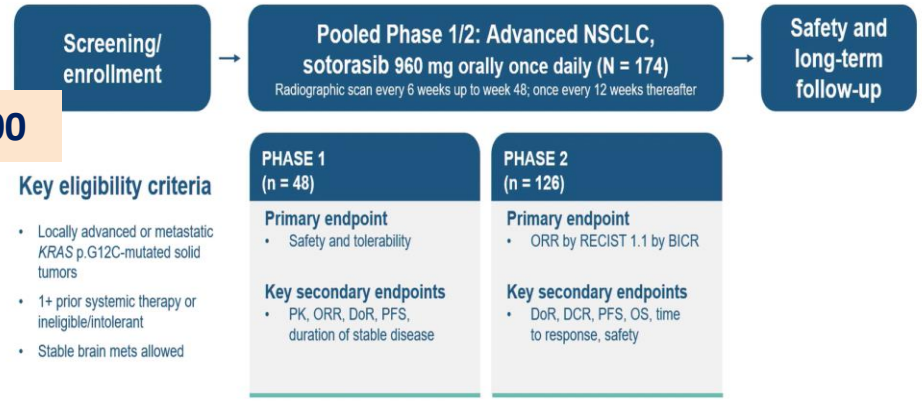
- Novel class of drugs → these are targeted therapies but they are not TKIs
- Allele-specific inhibitors targeting the Cysteine (C) residue.
- The inhibitors bind covalently to the mutant cysteine residue and occupy a pocket in the switch II region (SIIP) when KRAS G12C is in its inactive GDP-bound state (inactive-state selective drugs).



Lovly CM, ASCO 2021

The first-in-class in *KRAS p.G12C* mutations: sotorasib

CODEBREAK 100



TRAEs, %	Overall (n=174)	Onset after 1 year (n=45)
Any	70	24
Grade 2	20	9
Grade 3	20	2
Grade 4	1	0
Led to treatment modification	22	2
Led to discontinuation	6	0

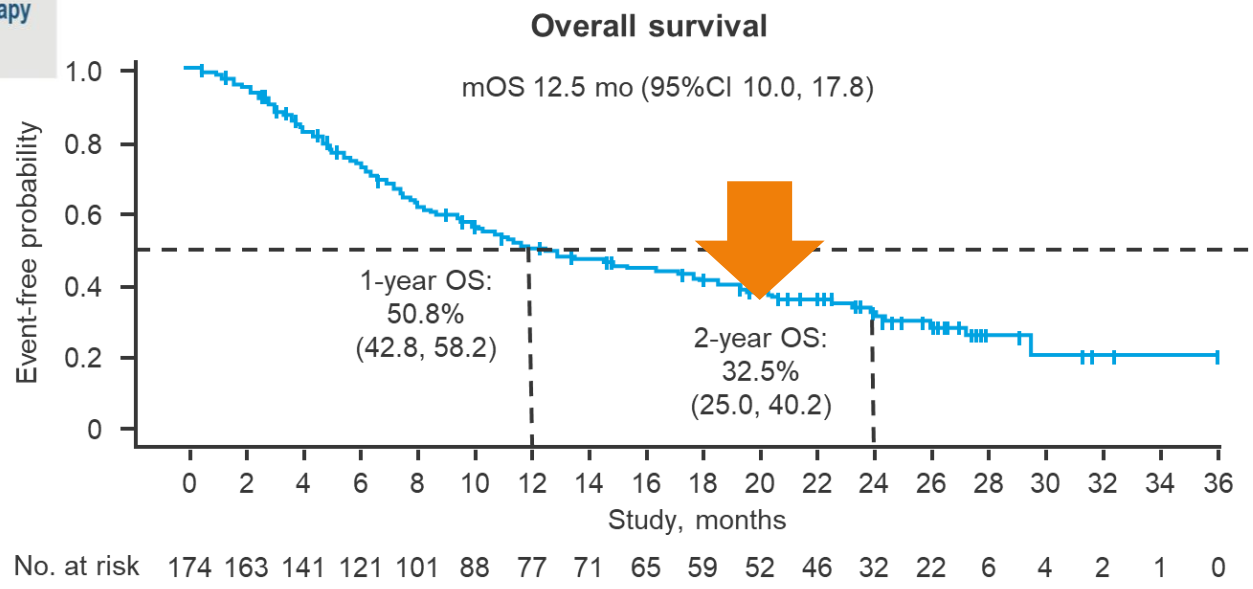
* Mainly diarrhea, ALT/AST increase, nausea and fatigue

Median Follow-up for Overall Survival: 24.9 months

Data cutoff: February 22, 2022

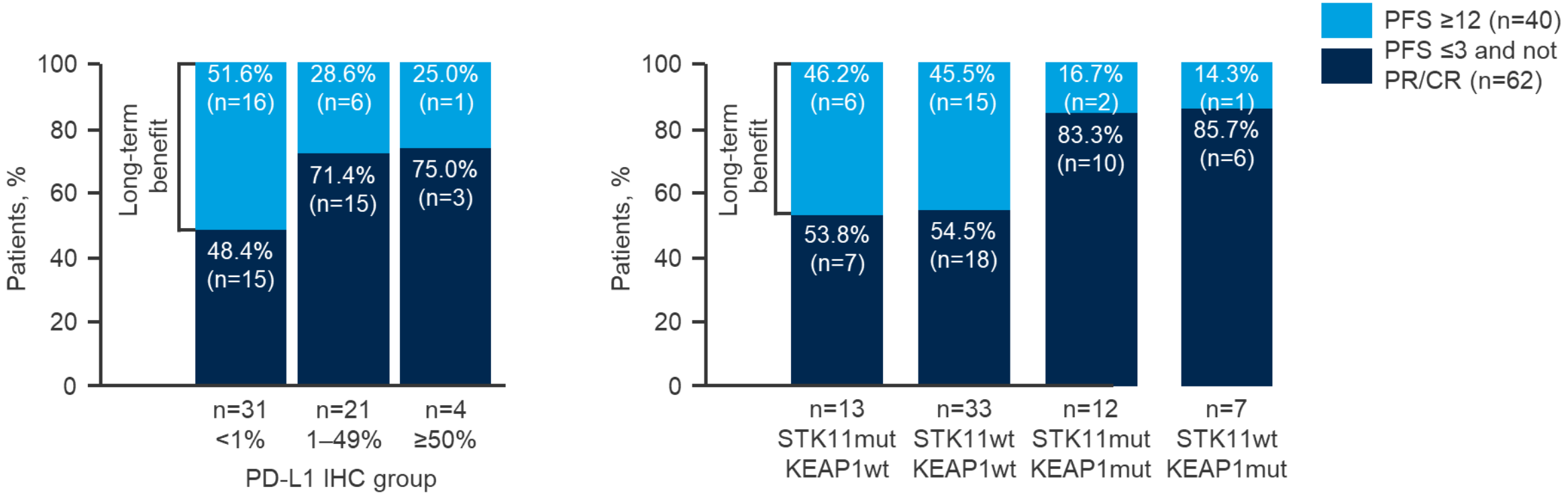
Global study with 83% of enrolled patients having received prior platinum-based chemotherapy and anti-PD-(L)1 therapy

Response	n=172
ORR, % (95%CI)	40.7 (33.3, 48.4)
BOR, n (%)	
CR	5 (2.9)
PR	65 (37.8)
SD	74 (43.0)
PD	23 (13.4)
NE	5 (2.9)
DCR, % (95%CI)	83.7 (77.3, 88.9)
mPFS, mo (95%CI)	6.3 (5.3, 8.2)
mDoR, mo (95%CI)	12.3 (7.1, 15.0)



Dy GK et al, AACR 2022

The first-in-class in *KRAS p.G12C* mutations: sotorasib



- Long-term benefit was seen regardless of PD-L1 expression, KRAS G12C allele frequency, co-mutations
- Patients with long-term benefit had lower plasma ctDNA at baseline and these levels correlated with tumor burden

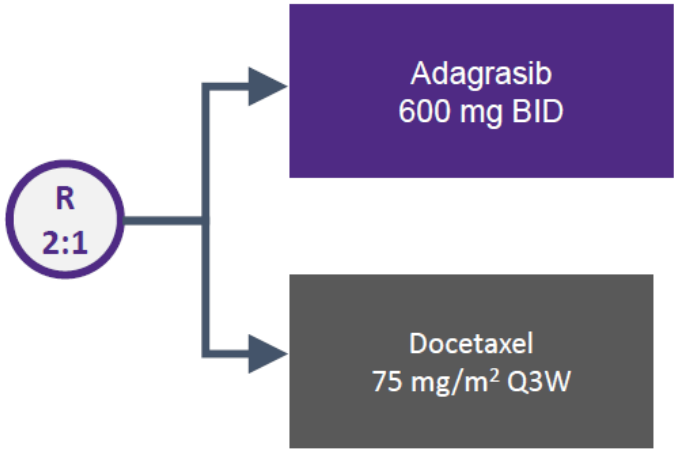
Dy GK et al, AACR 2022

KRAS p.G12C mutations: phase 3 trials are ongoing in 2nd line

KRYSTAL-12: Phase 3 Randomized, Open-Label Trial of 2L Adagrasib vs Docetaxel in Patients With Previously Treated NSCLC With KRAS^{G12C} Mutation[1,2]

Key Eligibility Criteria (n=452)

- NSCLC with KRAS^{G12C} mutation based on sponsor-approved test
- ECOG PS of 0 or 1
- No active brain metastases
- Prior treatment with platinum-based regimen and a checkpoint inhibitor
- No prior treatment with a KRAS inhibitor



Endpoints

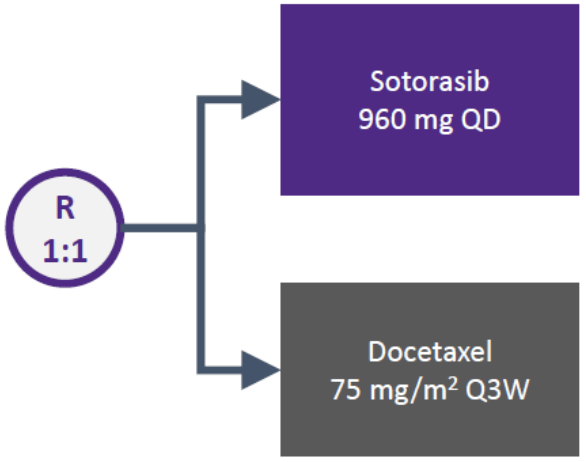
Primary: PFS, OS

Secondary: AEs, ORR, DOR, PROs, 1-year survival rate, PK

CodeBreaK 200: Phase 3 Randomized, Open-Label Trial of Sotorasib vs Docetaxel in Patients with Previously Treated Metastatic NSCLC with KRAS^{G12C} Mutation[3,4]

Key Eligibility Criteria (n=345)

- NSCLC with KRAS^{G12C} mutation confirmed through central testing
- ECOG PS of 0 or 1
- No active brain metastases
- Prior treatment with platinum-based regiment and a checkpoint inhibitor
- No prior treatment with a KRAS ^{G12C} inhibitor



Endpoints

Primary: PFS

Secondary: OS, ORR, DOR, TTR, DCR, PRO, QoL, PK

KRAS p.G12C mutations: new drug on the horizon [JDQ443]

KONTRAST-01

Key patient inclusion criteria
- Advanced solid tumors
- KRAS G12C mutation
- No prior KRAS G12C inhibitors
- ECOG PS 0–1

(n=73)

Dose escalation

JDQ443
200 mg/day,
400 mg/day,
200 mg BID,
300 mg BID

Dose expansion*

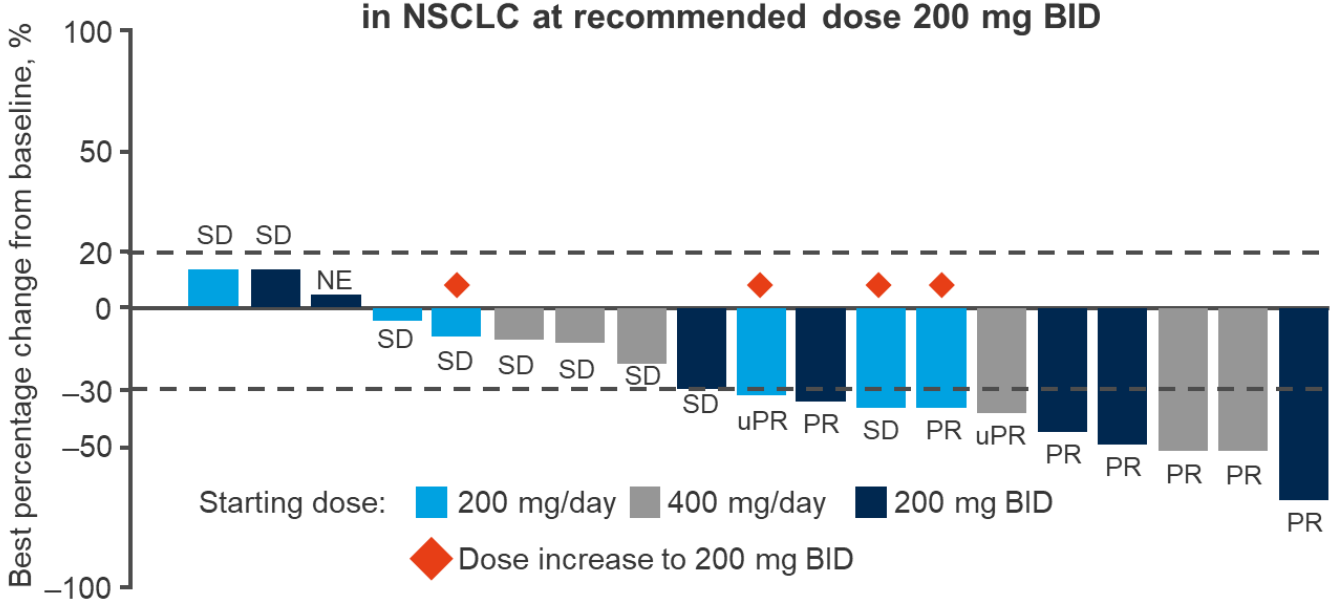
JDQ443
200 mg BID

Primary endpoint
- Safety

Secondary endpoints
- Antitumor activity, PK

Grade ≥3 TRAEs, n (%)	JDQ443 200 mg BID (n=11)	JDQ443 all patients (n=39)
Any	0	5 (12.8)
Photosensitivity reaction	0	2 (5.1)
Fatigue	0	1 (2.6)
Neutropenia	0	1 (2.6)

Confirmed ORR 57% (4/7)
in NSCLC at recommended dose 200 mg BID



BoR, n (%)	Patients with NSCLC (n=20)
PR (confirmed)	7 (35)
SD	11 (55)
PD	0
NE	2 (10)
ORR (confirmed and unconfirmed)	9 (45)
ORR (confirmed)	7 (35)

Tan DS et al, AACR 2022

How did we arrive here & where are we going?

❖ Enlarging the *family* of oncogene-addicted

- New drugs and targets on the horizon
- Understanding the *difficult* targets
- Drugging the *undruggable(s)*

❖ Deciphering resistance & Patients' selection

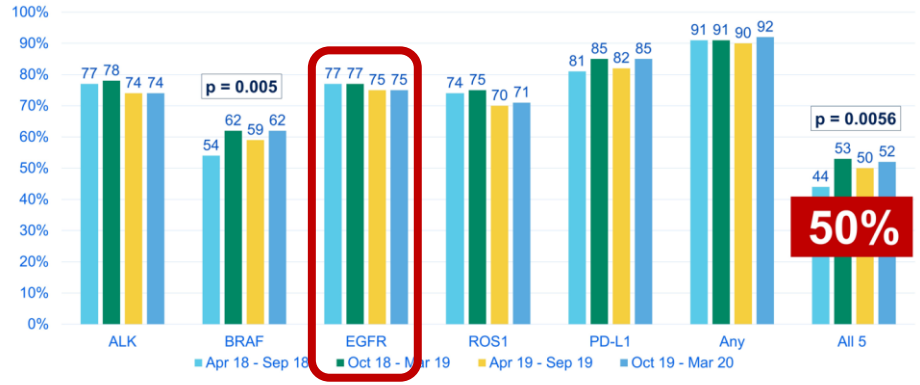
- In both oncogene-addicted and not oncogene-addicted

❖ Bring innovation as early as possible

- Oncogene-addicted vs. not?
- Neoadjuvant vs/with adjuvant? For how long? Combos?

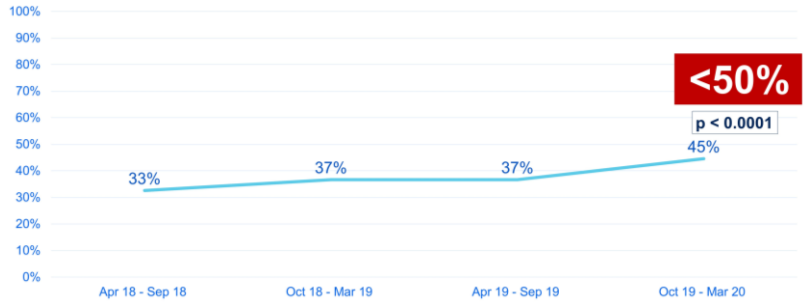
The *primum movens* is always the Test!!

Biomarkers testing rates over time



Robert NJ et al, ASCO 2021

NGS testing rates over time



EGFR mutation testing data collected in 36 Italian institutions in 2020

Malapelle U et al, CROH 2021

ATLAS

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CARCINOMA POLMONARE: QUALI NOVITÀ NEL 2022?