UNIVERSITÀ di VERONA
Department of ENGINEERING FOR INNOVATION MEDICINE

Il trattamento della malattia con altri bersagli molecolari

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Conflict of interests

Type of Affiliations	Sponsor
Advisory Board, Speaker's Bureau	AstraZeneca
Speaker's Bureau, Consultant, Travel fee	Takeda
Speaker's Bureau, Travel fee	Sanofi
Speaker's Bureau, Consultant	Eli Lilly
Speaker's Bureau, Research Funding	BMS
Speaker's Bureau, Research Funding	Roche
Speaker's Bureau, Advisory Board	Novartis

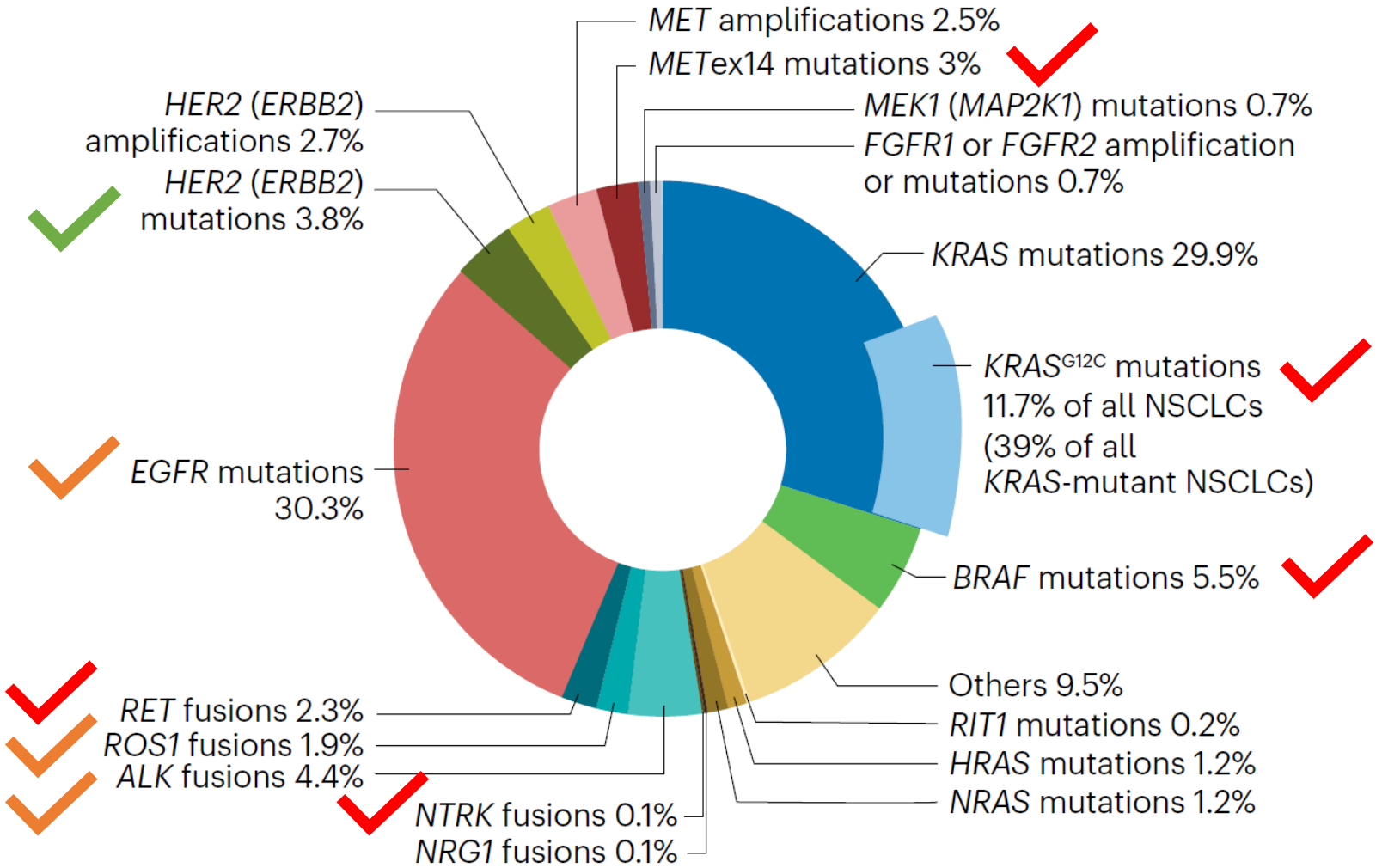
Agenda

The *historical* trio: EGFR, ALK & ROS1

The *teenager* drivers: BRAF, RET, MET, KRAS, NTRK

The *baby* driver: HER2 mutation

Small slices also make NSCLC the paradigm for personalized medicine



- ✓ EGFR mutations
- ✓ ALK fusions
- ✓ ROS1 fusions

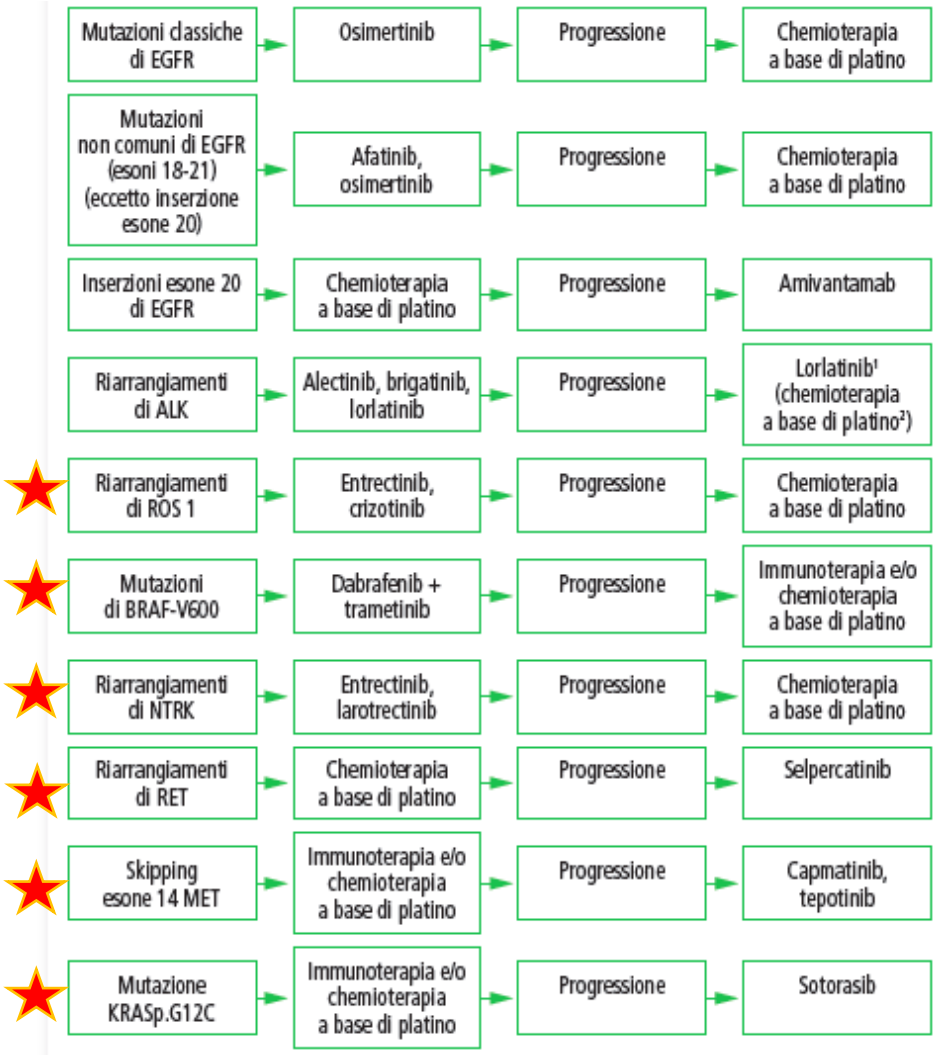
- ✓ BRAF V600 mutations
- ✓ RET fusions
- ✓ KRAS G12C mutation
- ✓ NTRK fusions
- ✓ METex14 mutations

- ✓ HER2 mutations

Otano I et al, Nature Reviews Clinical Oncology 2023

Targeted therapy in advanced OA NSCLC

State of the art



- **Treatment enrichment** in first-line (new combos and new agents)
  which strategy for which patient?
- Management of resistance (**sequencing** approach)
  new strategies and new agents

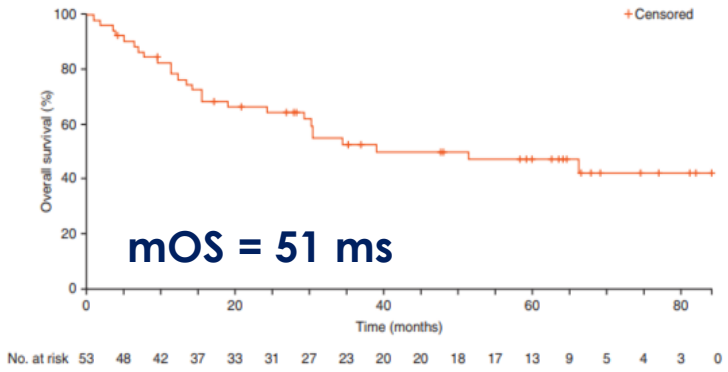
Metastatic OA NSCLC AIOM Guidelines 2024

Standard of care

Crizotinib & Entrectinib in 1st line

ROS1

PROFILE 1001: **crizotinib**

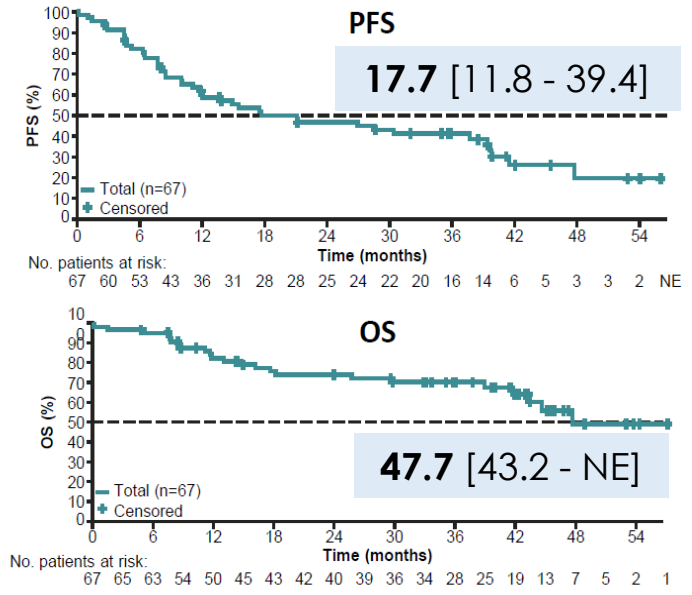


End points	*ROS1*-rearranged NSCLC (*N* = 53)
ORR, % (95% CI)[a]	72 (58–83)
CR, *n* (%)	6 (11)
PR, *n* (%)	32 (60)
SD (≥6 weeks), *n* (%)	10 (19)
PD, *n* (%)	3 (6)
Not evaluated[b]	2 (4)
Median time to first tumor response, weeks (range)[c]	7.9 (4.3–103.6)
Median duration of response, months (95% CI)[d,e]	24.7 (15.2–45.3)
Median PFS, months (95% CI)[d,f]	19.3 (15.2–39.1)

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

Integrated analysis of 3 phase I and II trials: **entrectinib**

	First-line population† (n=67)
ORR, n (%) [95% CI]	**46 (68.7)** [56.2–79.4]
CR	10 (14.9)
PR	36 (53.7)
SD	7 (10.4)
PD	5 (7.5)
Non CR / PD	6 (9.0)
Missing / unevaluable	3 (4.5)
Median DoR, months [95% CI]	**35.6** [13.9–38.8]
icORR	**61%**



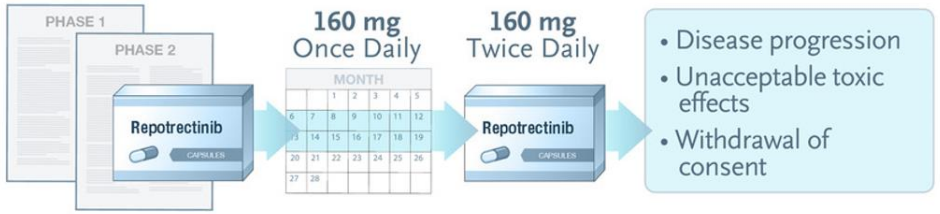
Grade ≥ 3 AEs 43% mainly dysgeusia, weight increase, constipation and diarrhea – **discontinuation 7%**

Shaw AT et al, Ann Oncol 2019
Drilon A et al, JTO Clinical and Research Reports 2022
Fan Y et al, WCLC 2022

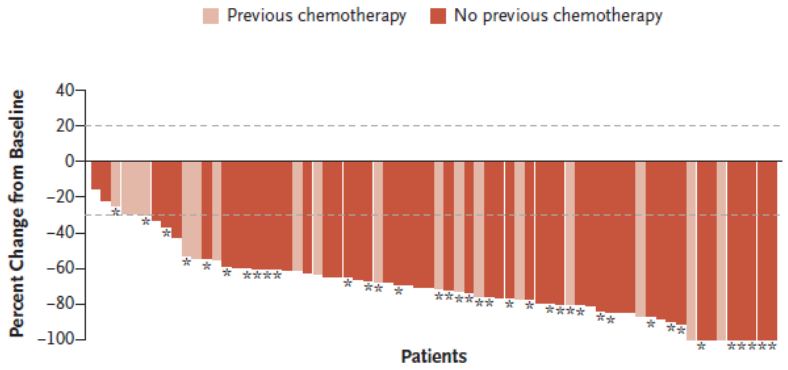
Should we escalate 1st line?

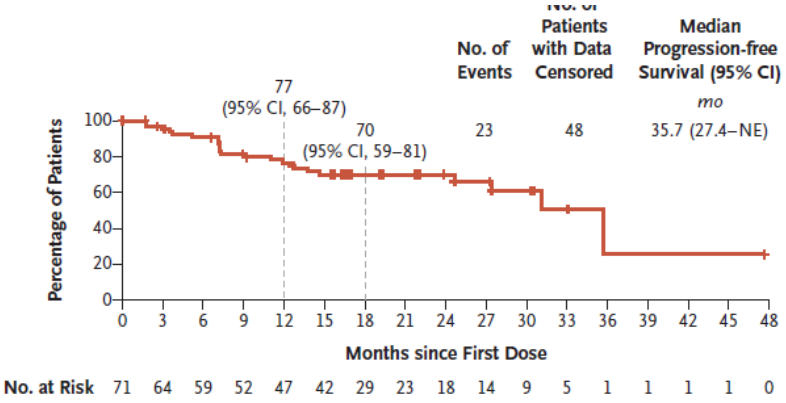
Repotrectinib [TRIDENT-1]

ROS1

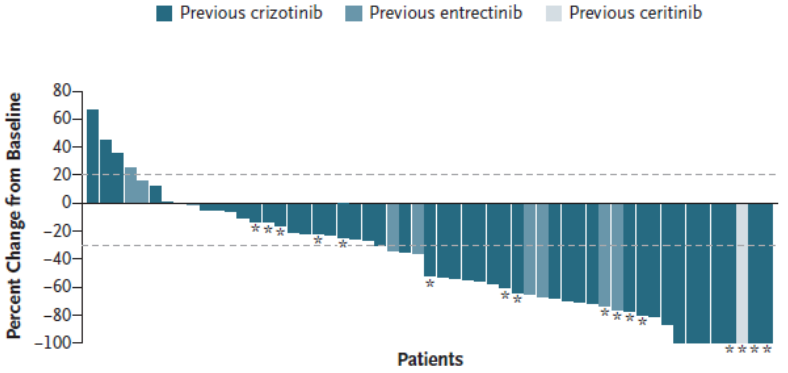


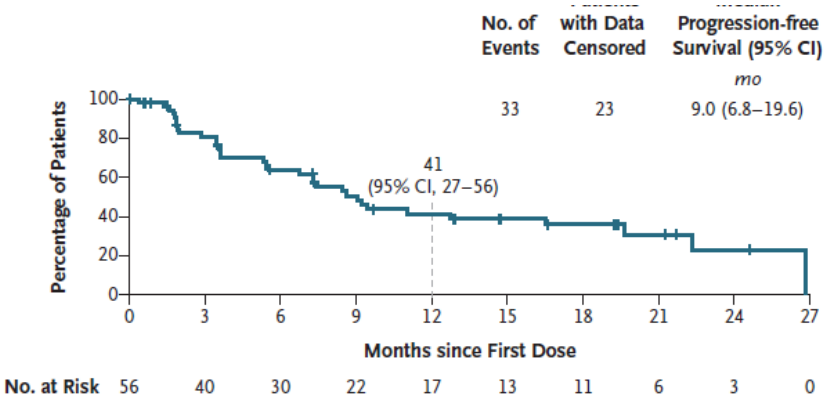
No previous TKI
ORR 79% [CR 10%]





Previous ROS1 TKI
ORR 37% [CR 5%]





Drilon A et al, NEJM 2024

New selective, brain penetrant, TRK sparing TKIs

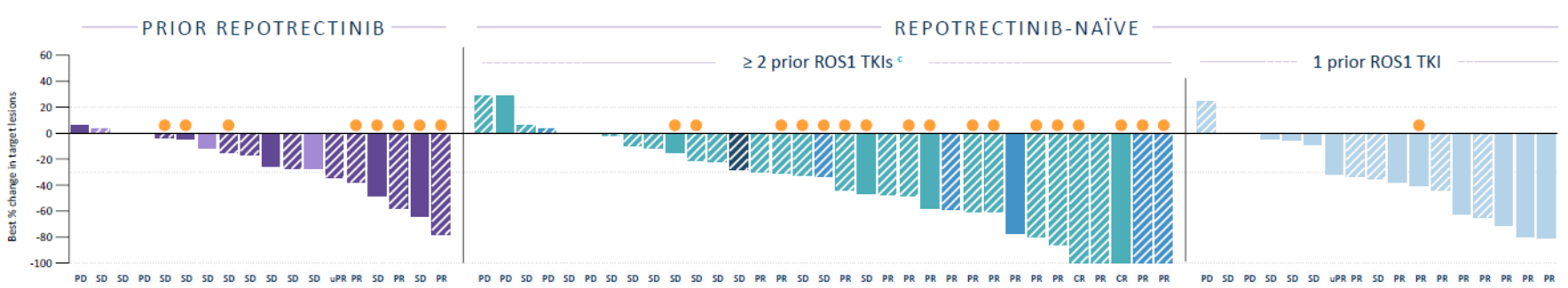
Phase 1/2 of NVL-520 in ROS1+ [ARROS-1]

ROS1

NVL 650 (zidesamtinib) was well tolerated and 100 mg QD was selected as the RP2D (Discontinuation due to TRAE: 0%) N = 104

All NSCLC Response Evaluable Patients *± chemotherapy*	Any Prior ROS1 TKI (range 1-4)				≥ 2 prior ROS1 TKIs			1 prior ROS1 TKI (crizotinib)
	All	Repotrectinib-naive	ROS1 G2032R Resistance Mutation [b]		All	Prior Lorlatinib	Repotrectinib-naive	
			Prior Repotrectinib	Repotrectinib-naive				
RECIST 1.1 ORR % (n/n) [a]	44% (31/71)	51% (27/53)	38% (3/8)	72% (13/18)	41% (21/51)	44% (17/39)	47% (17/36)	73% (8/11)
CR *	2	2	-	2	2	2	2	-

* 2 confirmed CRs ongoing with DOR 19.3+ and 26.3+ months. 5 additional CRs observed among patients without measurable disease (2 prior ROS1 TKIs [n=2], 1 prior ROS1 TKI (crizotinib [n=1], entrectinib [n=2])), all ongoing with DOR 3.6+, 3.7+, 13.8+, 13.9+, and 18.5+ months.



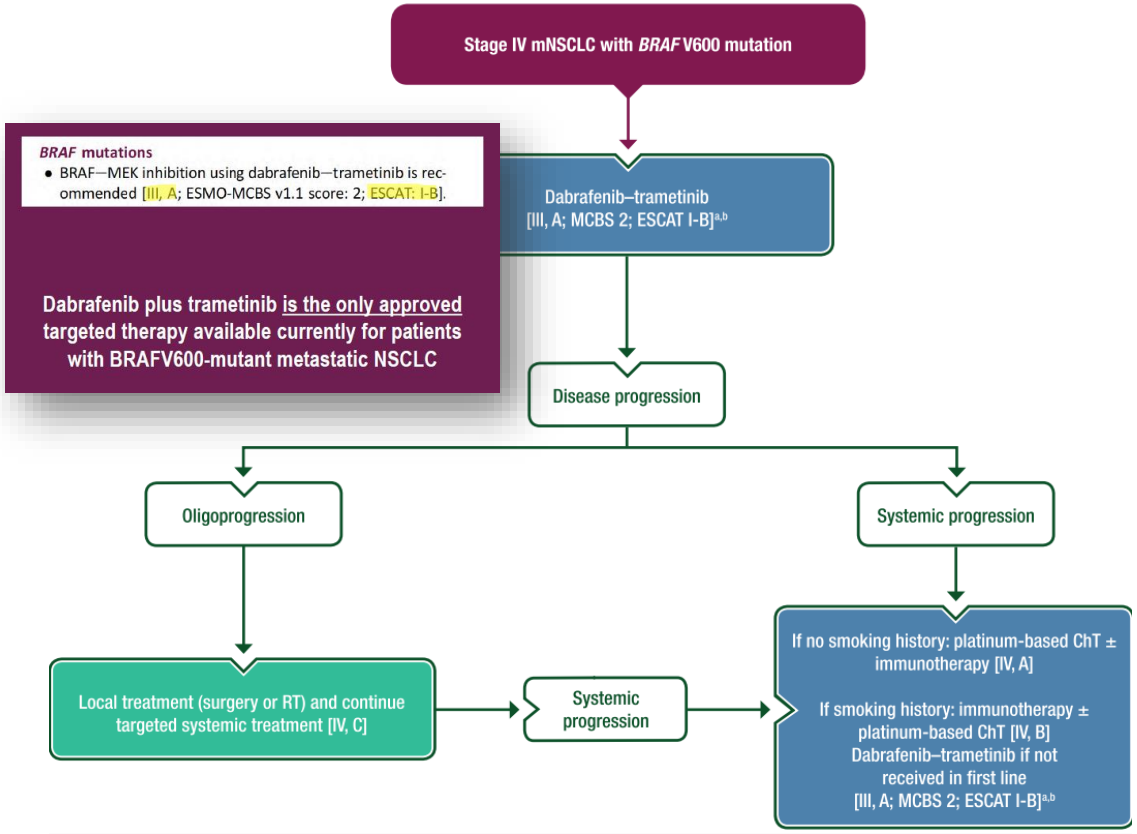
- **Durable responses** were observed in **heavily pre-treated populations** and across patient subgroups
- **Durable intracranial responses** were observed, including complete intracranial responses in patients who previously received brain penetrant TKIs
- **Room for sequencing and/or in earlier setting**

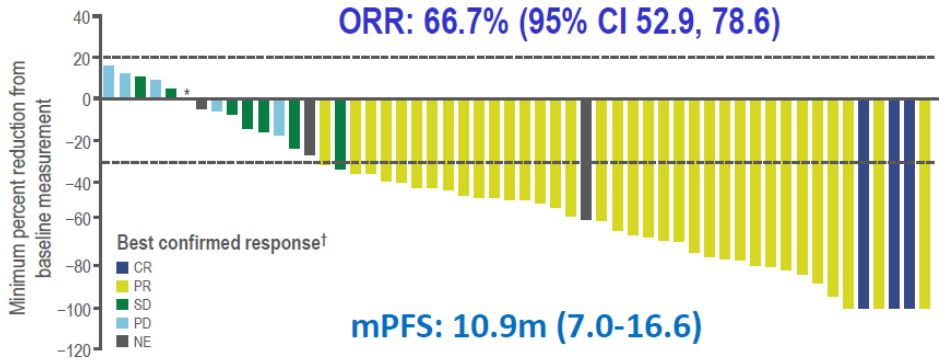
Besse B et al, ESMO 2024

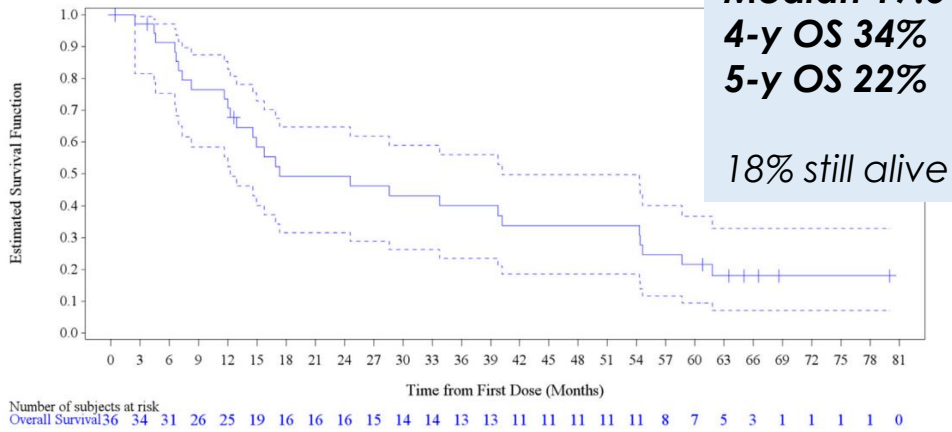
Standard of care

Dabrafenib-trametinib in 1st line [*BRAF p.V600*]

BRAF







OS in treatment-naïve:
Median 17.3 ms
4-y OS 34%
5-y OS 22%

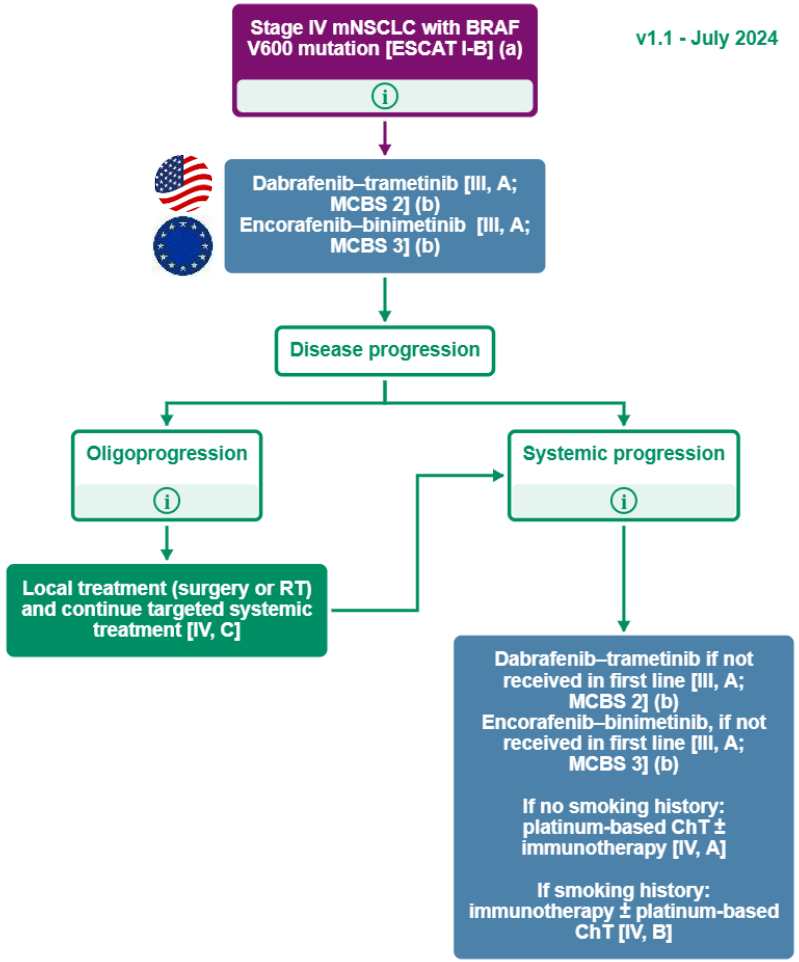
18% still alive

Planchard D, Lancet Oncol 2017
Planchard D, J Thorac Oncol 2022
Oncogene-addicted metastatic NSCLC ESMO Clinical Practice Guideline 2023

Encorafenib + binimetinib in BRAFV600Em aNSCLC

PHAROS & ENCO-BRAF

BRAF



1st line

	BRF113928 Dabrafenib + trametinib (n=36)	PHAROS Encorafenib + binimetinib (n=59)	ENCO-BRAF Encorafenib + binimetinib (n=64)
ORR	64%	75%	66%
PFS	10.8	30.2	10.9
OS	17.3	NR	NR

Different toxicity profile:

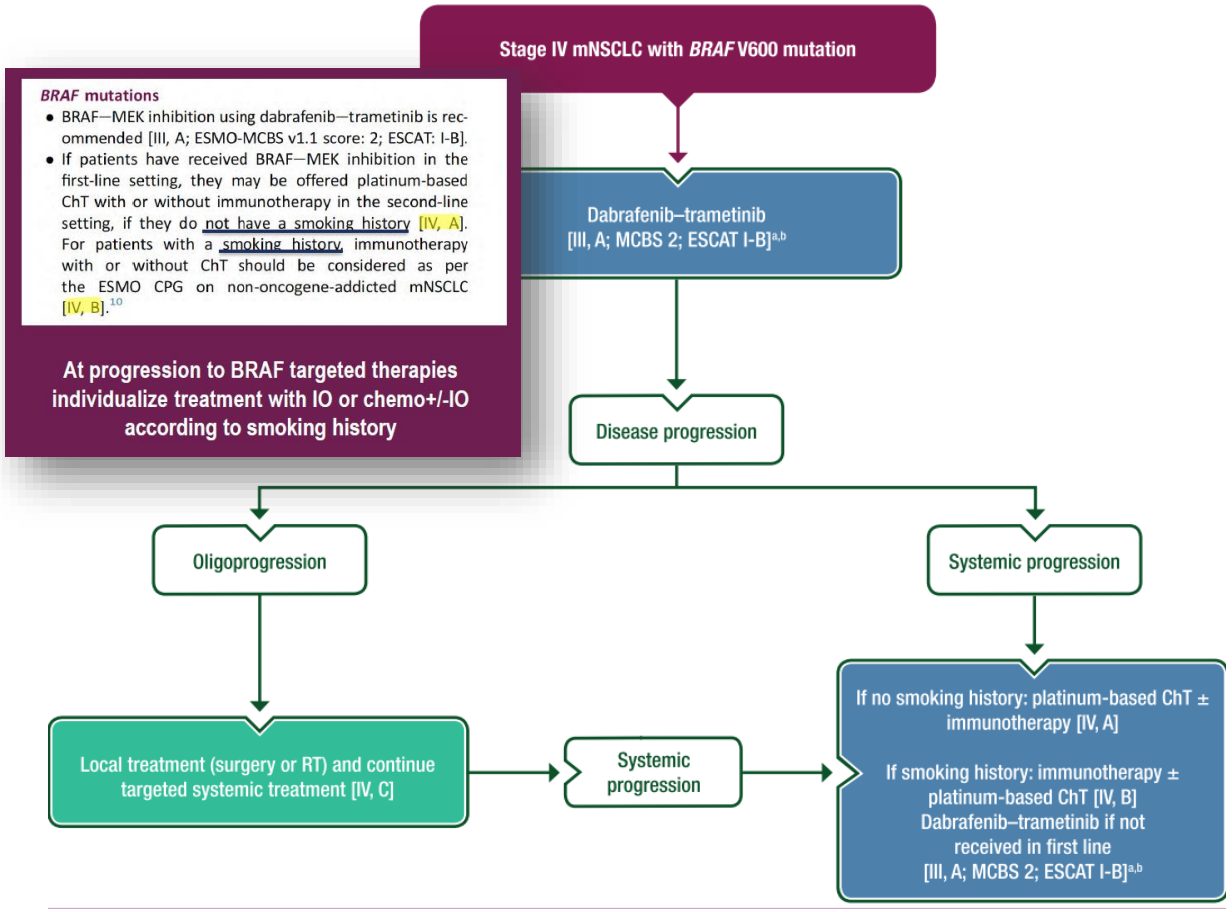
- **DT:** G≥3 64% - fever, GI, hepatological
- **EB:** G≥3 50% - fatigue, GI, hepatological

Modified from ESMO living guidelines – July 2024; Planchard D et al, ESMO 2024; Riely GJ et al, ESMO 2024

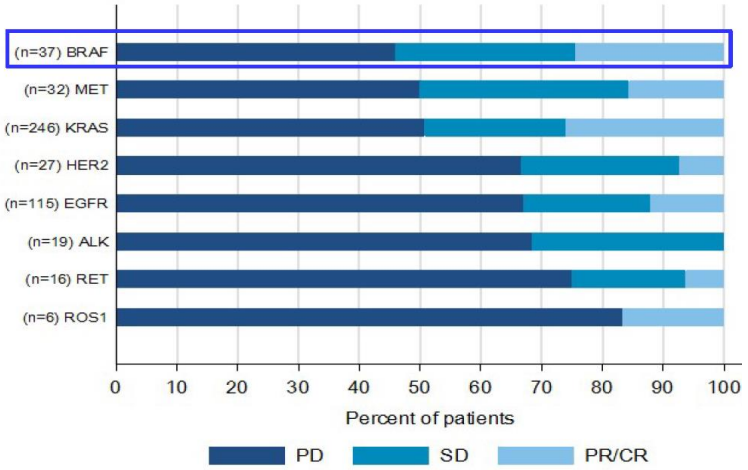
Standard of care

Impact of IO in RW [*BRAF p.V600E*]

BRAF



Driver	PD	SD	CR/PR
BRAF	46%	30%	24%
MET	50%	34%	16%
KRAS	51%	23%	26%
HER2	67%	26%	7%
EGFR	67%	21%	12%
ALK	68%	32%	0
RET	75%	19%	6%
ROS1	83%	0	17%
TOTAL	57%	24%	19%



Outcome by 1° line regimen	rwTOT
PD-(L)1 mono [N = 26]	7.6 ms
PD-(L)1 + ChT [N = 13]	17.5 ms
Pembro + platinum + pem [N = 12]	20.7

BRAF V600E: rwTOT and rwTTNT similar for PD-(L)1 mono but markedly longer for PD-(L)1+ChT *VS* other cohorts, including the driver-negative cohort

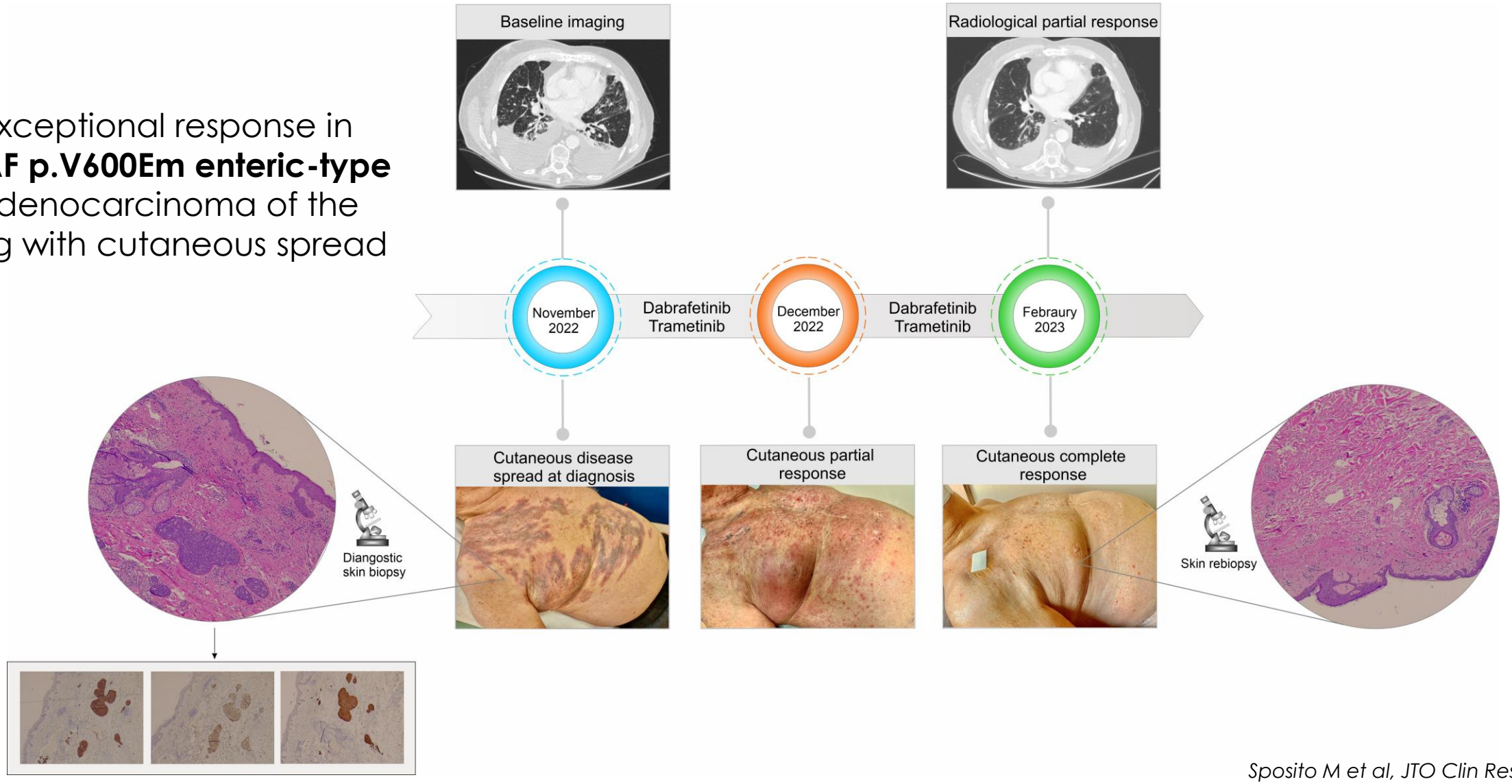
Mazieres J et al, Ann Oncol 2019; Garassino MC et al, JTO Clin Res Rep 2023; ; Oncogene-addicted metastatic NSCLC ESMO Clinical Practice Guideline 2023

Standard of care

The importance of testing our patients!

BRAF

Exceptional response in **BRAF p.V600Em enteric-type** adenocarcinoma of the lung with cutaneous spread



Sposito M et al, JTO Clin Res Rep 2023

Our comfort zone still in 2nd line

Selpercatinib & Pralsetinib

RET

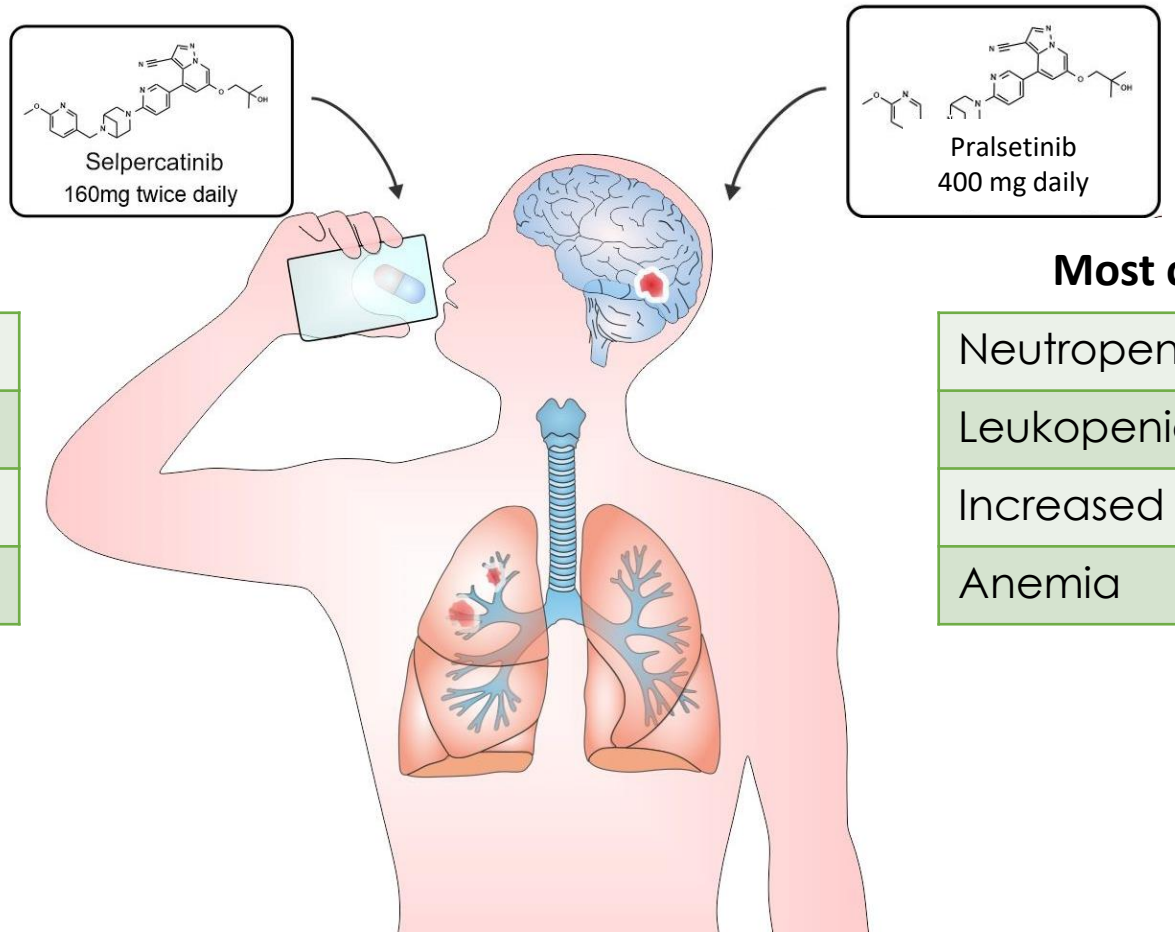
	SELPERCATINIB [LIBRETTO-001]	PRALSETINIB [ARROW]
ORR (%, N)		
Prior platinum-based chemotherapy	**61%** (n = 247)	**59%** (n = 136)
Treatment-naïve	**84%** (n = 69)	**72%** (n = 75)
DCR (%, N)		
Prior platinum-based chemotherapy	**94%** (n = 247)	**90%** (n = 136)
Treatment-naïve	**93%** (n = 69)	**91%** (n = 75)
mPFS (months, N)		
Prior platinum-based chemotherapy	**24.9** (n = 247)	**16.5** (n = 136)
Treatment-naïve	**22.0** (n = 69)	**13.0** (n = 75)
3y-OS (%, N)		
Prior platinum-based chemotherapy	**58.5%** (n = 247)	**58%** (n = 141)
Treatment-naïve	**57.1%** (n = 69)	**58%** (n = 69)
iORR (%, N)	**85%** (n = 26)	**70%** (n = 10)
Grade ≥3 TRAEs (%, N)	**38.6%** (n = 796)	**52%** (n = 281)
Discontinuation rate (%, N)	**3%** (n = 796)	**7%** (n = 281)

Updated from Belluomini L et al, Expert Rev Anticancer Ther 2022; Drilon A et al, JCO 2022; Drilon A et al, JCO 2023

Our comfort zone still in 2nd line

Selpercatinib & Pralsetinib

RET



Most common TRAEs

Dry mouth	38%
Hypertension	28%
Increased ALT/AST	28%
Diarrhea	27%

Hypersensitivity

Most common TRAEs

Neutropenia	46%
Leukopenia	38%
Increased ALT/AST	35%
Anemia	32%

Updated from Belluomini L et al, Expert Rev Anticancer Ther 2022; Drilon A et al, JCO 2022; Drilon A et al, JCO 2023

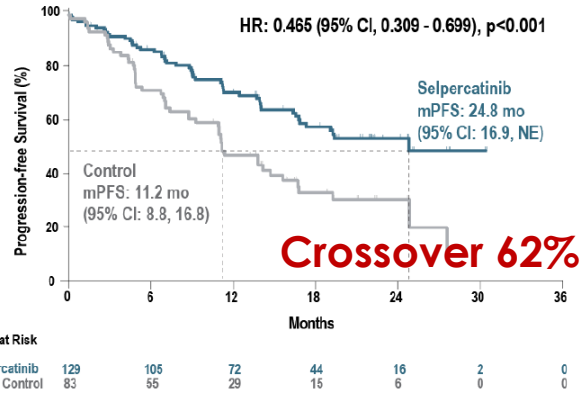
Should we escalate 1st line?

LIBRETTO-431 [selpercatinib vs CT+/-pembro]

RET

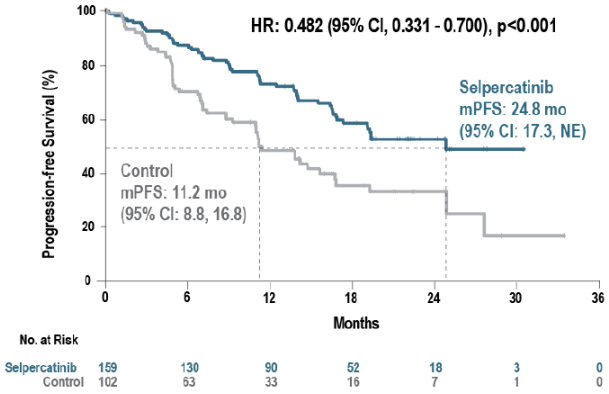
ITT-Pembrolizumab Population

(Median follow-up of ~19 mo)



ITT Population

(Median follow-up of ~18 mo)



Key Eligibility Criteria

- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

Stratification factors:

- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

20%

R 2:1[3]

Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

81%

Optional Crossover

Selpercatinib
(Upon BICR confirmed PD)

Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population

Secondary Endpoints:

- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time to progression][5])
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

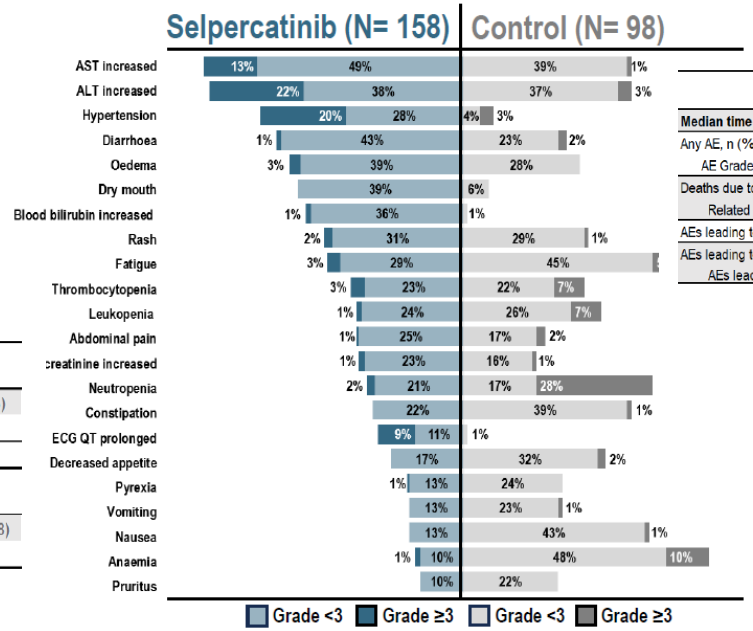
Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

Risk of CNS Progression

Without CNS Metastases at Baseline	Selpercatinib (N= 99)	Control (N= 51)
12-month CIR, % (95% CI)	1.1% (0.1, 5.2)	14.7% (5.7, 27.6)
Cause-specific HR[1] (95% CI)	0.17 (0.04, 0.69)	

With CNS Metastases at Baseline	Selpercatinib (N= 21)	Control (N= 21)
12-month CIR, % (95% CI)	25.7% (8.8, 46.7)	33.3% (14.3, 53.8)
Cause-specific HR[1] (95% CI)	0.61 (0.19, 1.92)	



	Selpercatinib N= 158	Control N= 98
Median time on treatment, months ± SD	16.7 ± 8.3	9.8 ± 7.2
Any AE, n (%)	158 (100.0)	97 (99.0)
AE Grade ≥3	111 (70.3)	56 (57.1)
Deaths due to AE, n (%)	7 (4.4)	0
Related AE (malnutrition and sudden death)	2 (1.3)	0
AEs leading to discontinuation, n (%)	16 (10.1)	2 (2.0)
AEs leading to any dose adjustment, n (%)	123 (77.8)	74 (75.5)
AEs leading to dose reduction	81 (51.3)	28 (28.6)

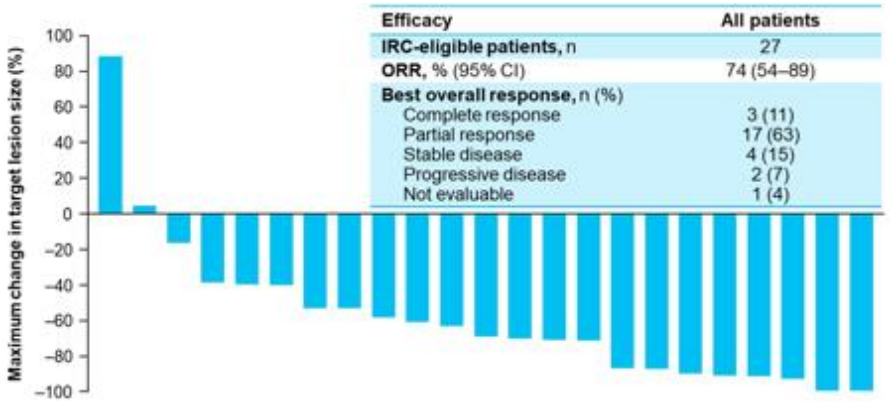
Loong HH et al, ESMO 2023 & Zhou C et al, NEJM 2023

Standard of care

Larotrectinib & Entrectinib

NTRK

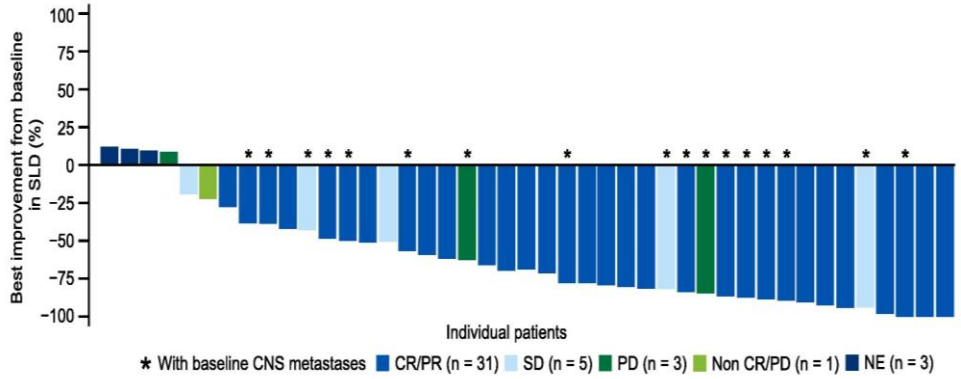
Larotrectinib (n=30)



Efficacy	All patients
IRC-eligible patients, n	27
ORR, % (95% CI)	74 (54–89)
Best overall response, n (%)	
Complete response	3 (11)
Partial response	17 (63)
Stable disease	4 (15)
Progressive disease	2 (7)
Not evaluable	1 (4)

ORR (%)	**74**
mPFS (ms)	33
2y-PFS (%)	52
mOS (ms)	39.3
2y-OS (%)	67
Grade 3 AEs (%)	17
Discontinuation (%)	0

Entrectinib (n=51)



ORR (%)	**62.7**
mPFS (ms)	28
2y-PFS (%)	52
mOS (ms)	41.5
2y-OS (%)	73
iORR (%)	64.3
Grade 3 AEs (%)	43.6
Discontinuation (%)	5.5

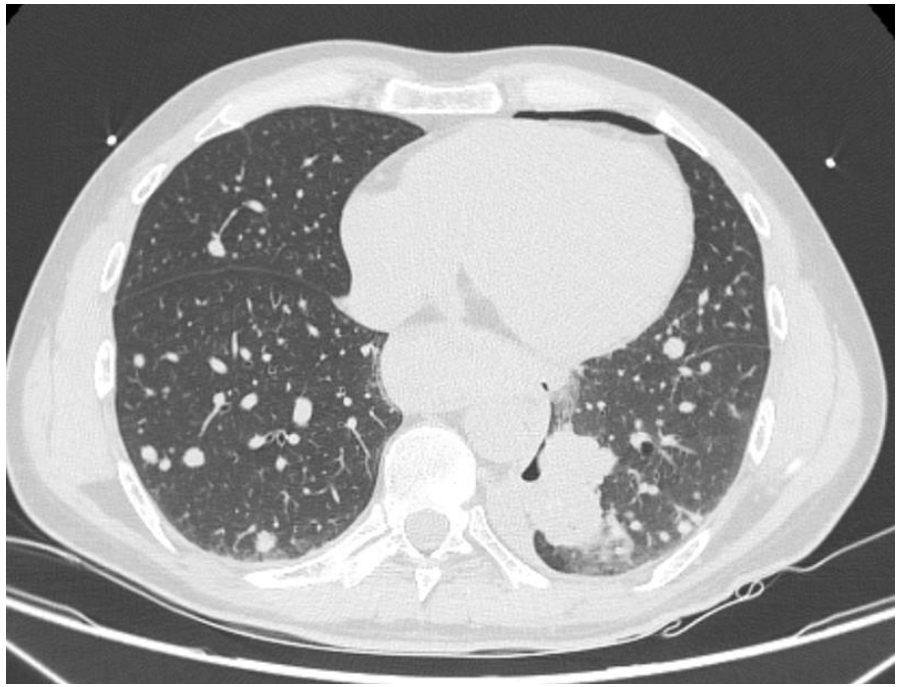
Lin J et al, ASCO 2023
Cho BC et al, Lung Cancer 2024

NTRK

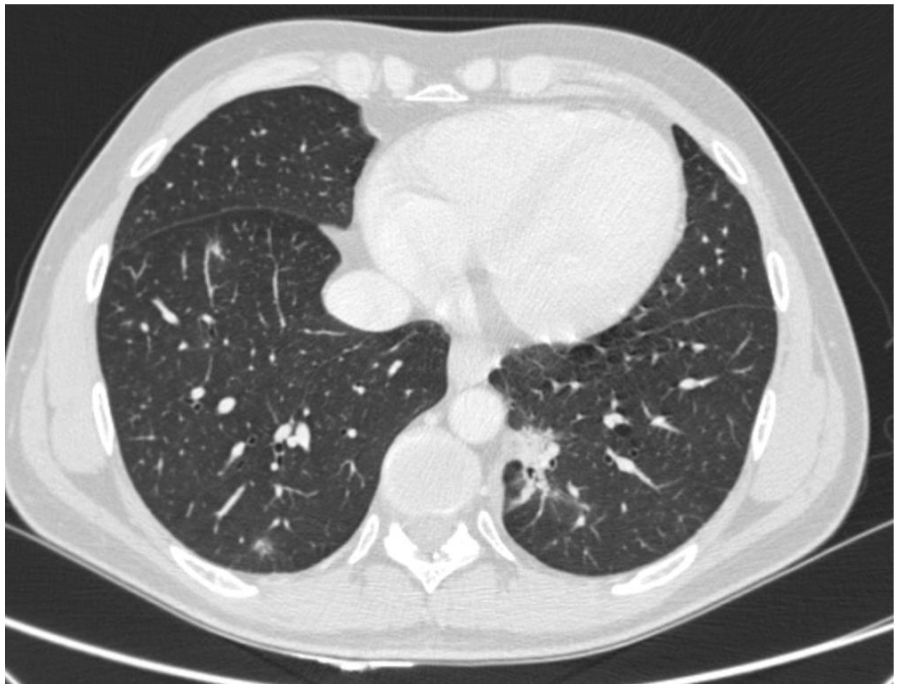
Age: 44 years
Sex: M
Never smoker

NTRK1 fusion (SQSTM1-NTRK1 fusion)

ENTRECTINIB



29 Jun 2023



30 Oct 2023

MET deregulated NSCLC

Three realities

MET ex14

***MET* exon14 mutation**
~3%

I remain the most interesting in

***MET* amplification**
~1-5%

No TREATMENT APPROVED EITHER AS PRIMARY or AS AQUIRED RESISTANCE

***MET* overexpression**
~30%

No TREATMENT APPROVED Promising ADC Teliso-V in High MET expression

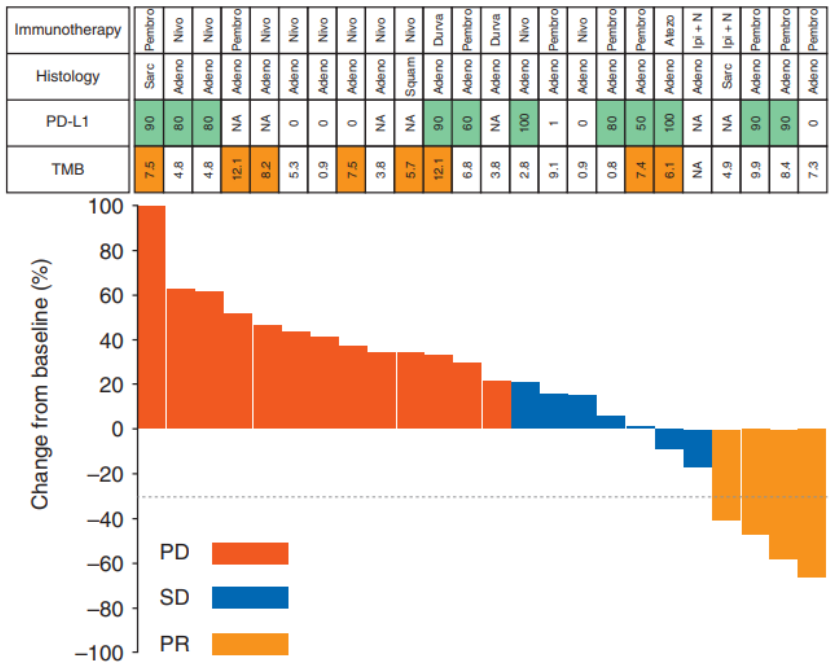
J. Remon, Lung Summit 2023

Our comfort zone still in 2nd line

Standard treatment

MET ex14

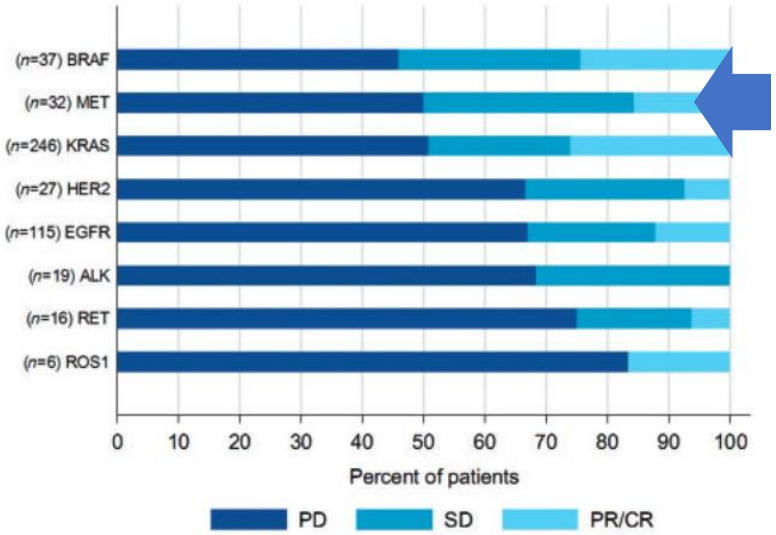
MSKCC



N = 147
ORR 17%
mPFS 1.9 ms

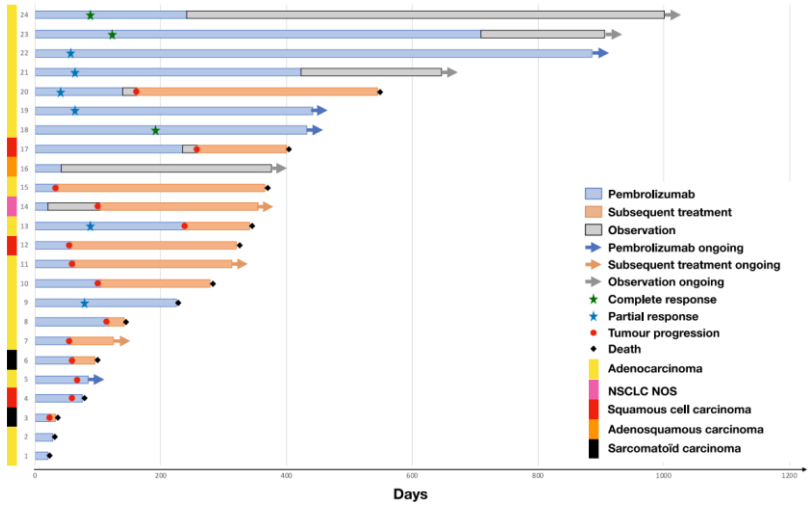
Responses not enriched in PD-L1 high nor high TMB

IMMUNOTARGET



N = 36
ORR 16%
mPFS 3.4 ms

GFPC 01-20



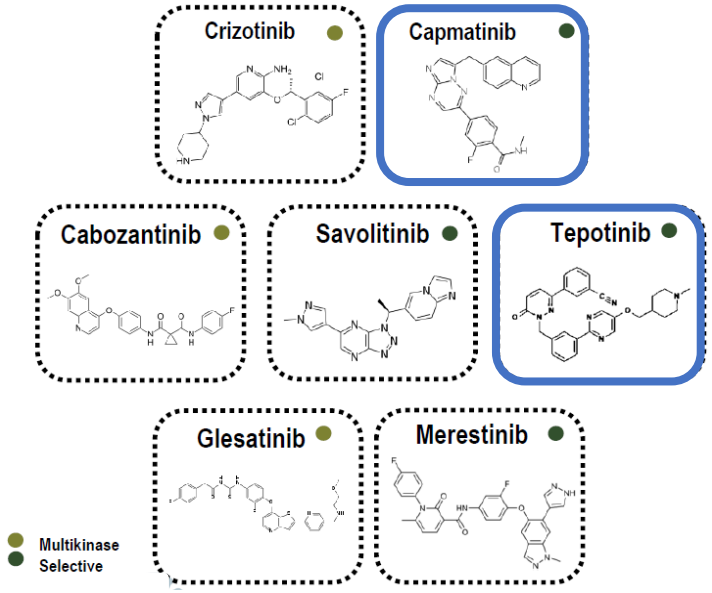
N = 30 PDL1 high
ORR 43%
mPFS 3.5 ms
mOS 12.1 ms

Sabari JK et al, Ann Oncol 2018; Mazieres J et al, Ann Oncol 2019; Guisier F et al. Clin Lung Cancer 2022

Our comfort zone still in 2nd line

Capmatinib & Tepotinib

MET ex14



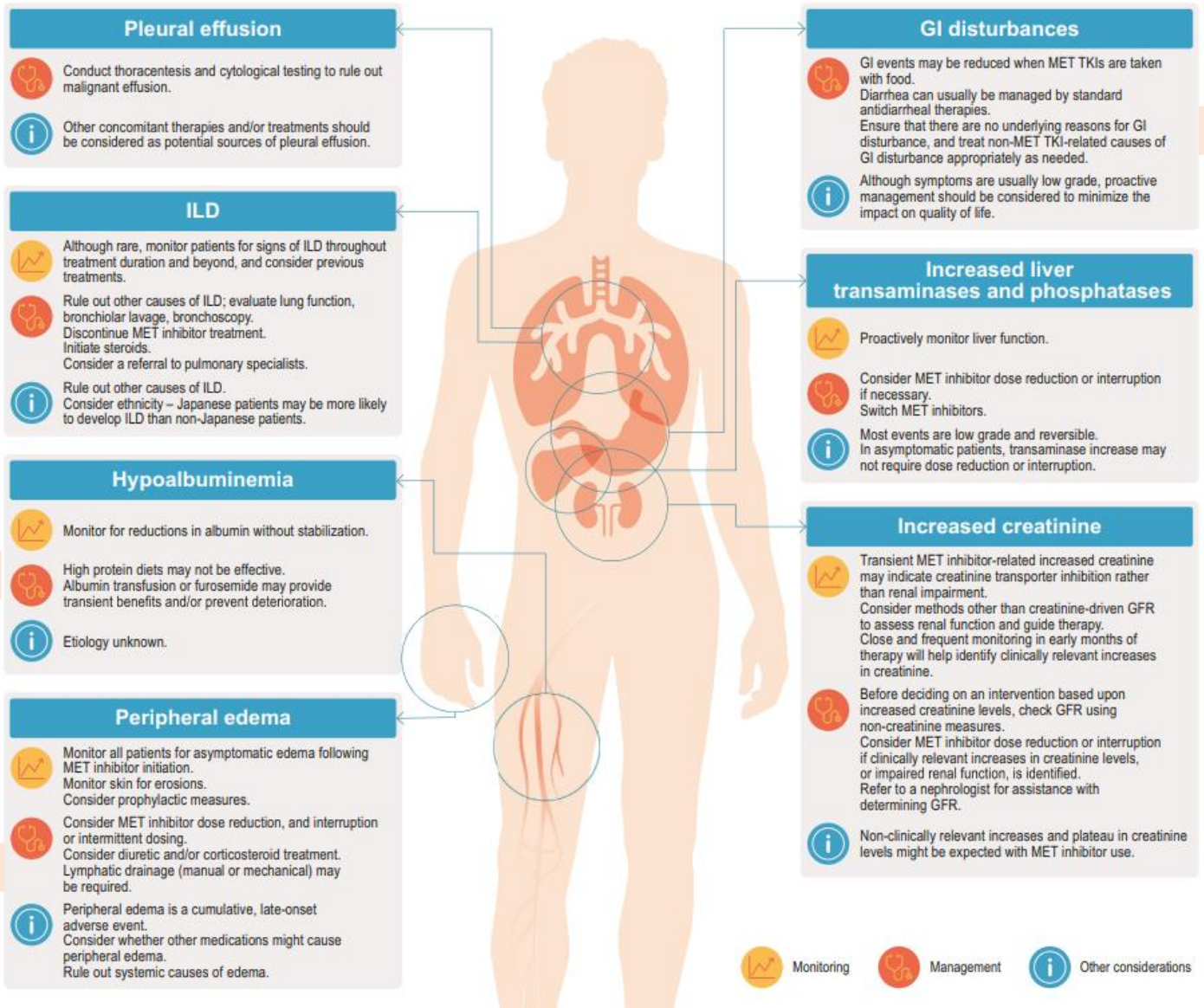
	CAPMATINIB	TEPOTINIB
	[GEOMETRY mono1]	**[VISION]**
ORR (%, N)		
Pre-treated	**44%** (n = 100)	**45%** (n = 149)
Treatment-naïve	**66.7%** (n = 60)	**57.3%** (n = 164)
mPFS (months, N)		
Pre-treated	**5.5** (n = 100)	**11** (n = 149)
Treatment-naïve	**12.3** (n = 60)	**12.6** (n = 164)
mOS (months, N)		
Pre-treated	**13.6** (n = 100)	**19.3** (n = 149)
Treatment-naïve	**20.8** (n = 60)	**21.3**(n = 164)
iORR (%, N)	54% (n = 13)	66.7% (n = 15) target
Grade ≥3 TRAEs (%, N)	**37.6%** (n = 364)	**34.8%** (n = 313)
Discontinuation (%, N)	10%	14.7%

Wolf J et al, NEJM 2020; Wolf J et al, ASCO 2021; Mazieres J et al, Jama Oncol 2023

Our comfort zone still in 2nd line

Capmatinib & Tepotinib

MET ex14



Nausea
All 26%-46%
G ≥3 1%

All 16%
G ≥3 2%

All 50%-63%
G ≥3 1%-11%

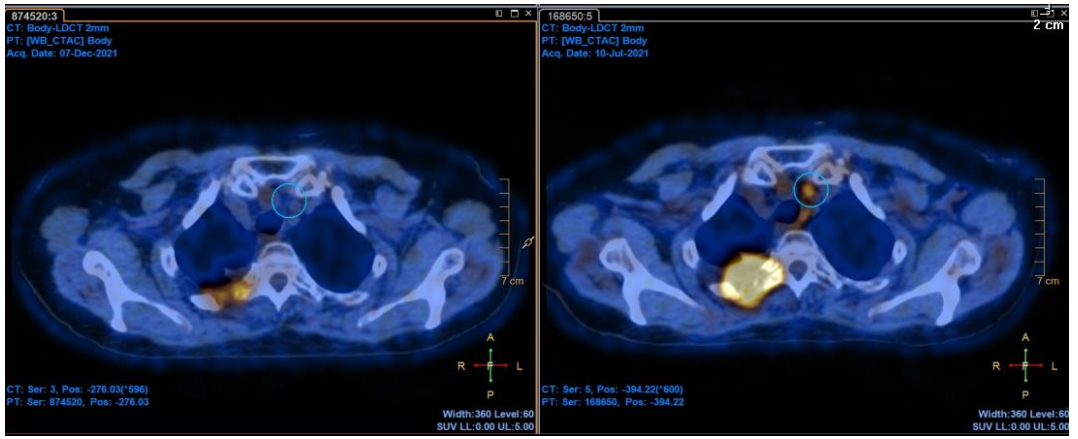
Cortot A et al, Clin Lung Cancer 2022

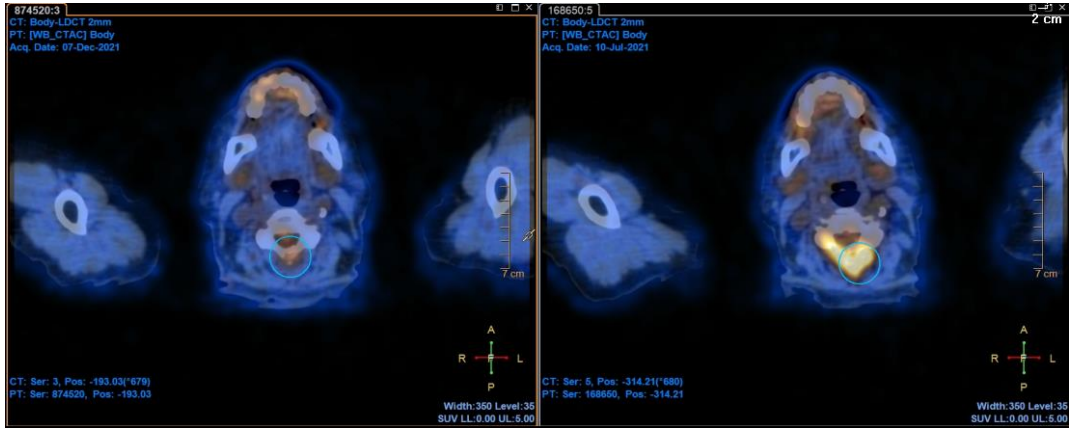
Standard of care

The importance of testing our patients!

MET ex14

- **86 yo**, female
- ECOG PS 1
- NSCLC IV stage (bone and lung) with *MET exon 14*
- Start *Capmatinib* Sep 2021
- Best response: *PR*
- Ongoing





KRAS G12C finally druggable!

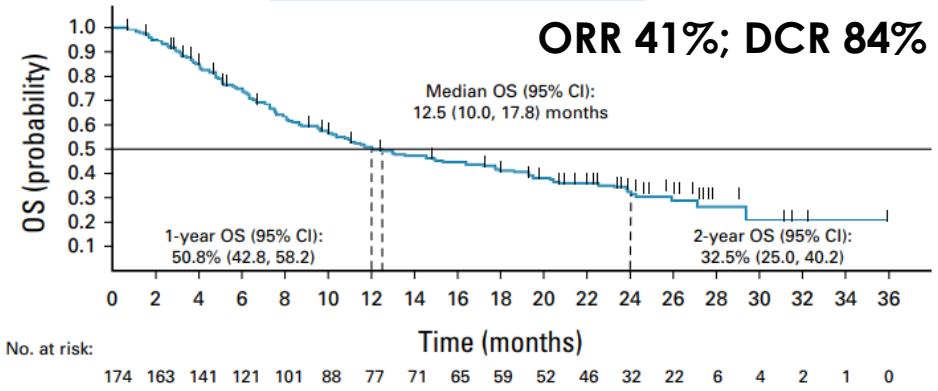
KRASp.G12C (OFF) inh

KRAS G12C

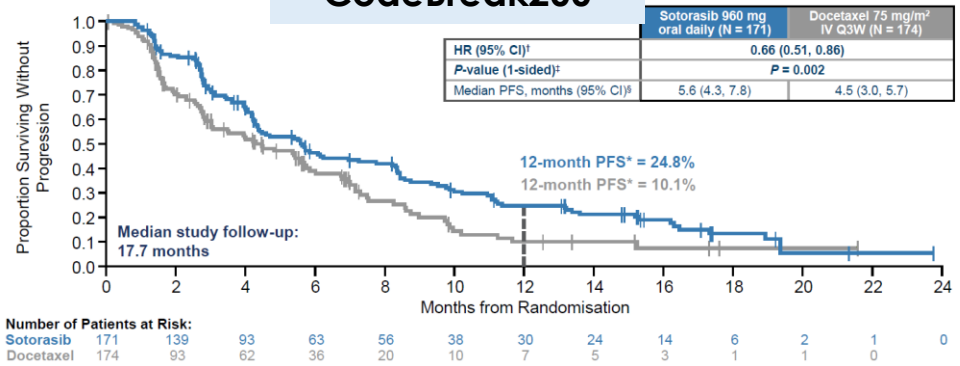
SOTORASIB

CodeBreak100

ORR 41%; DCR 84%



CodeBreak200



CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

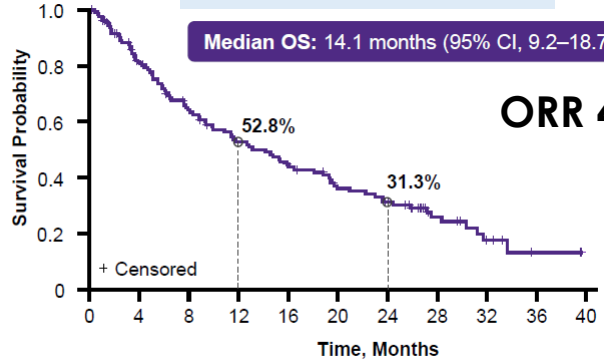
Dy GK et al, JCO 2023; De Langen AJ et al, The Lancet 2023

ADAGRASIB

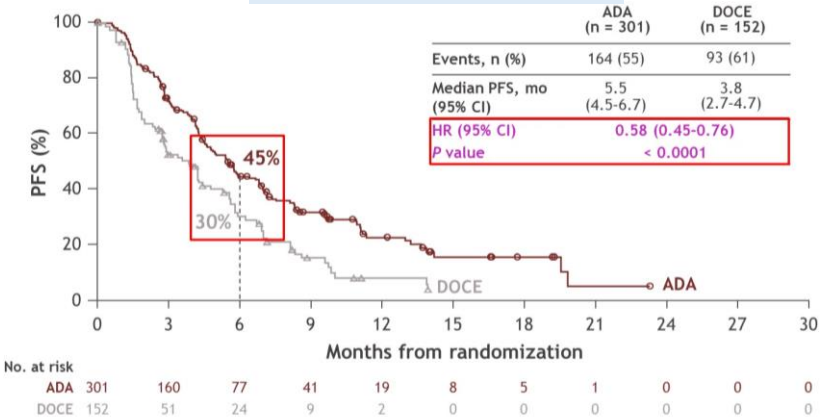
KRYSTAL-1

Median OS: 14.1 months (95% CI, 9.2–18.7)

ORR 43%; DCR 80%



KRYSTAL-12

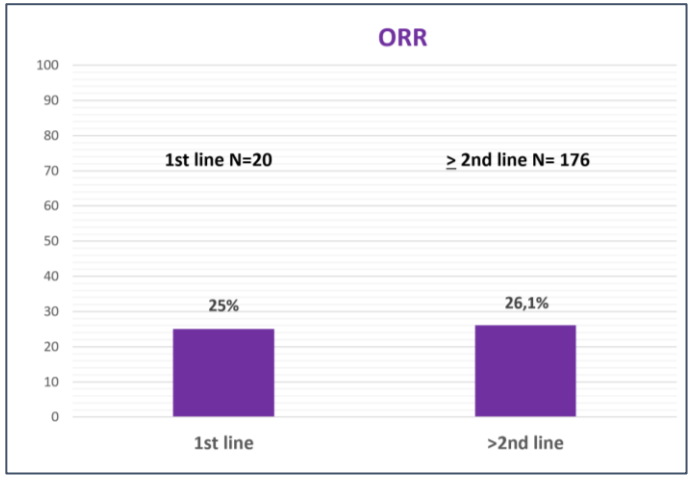


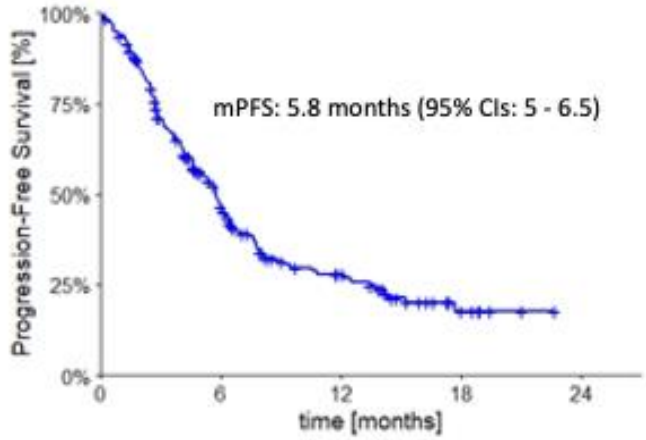
Gadgeel SM et al, WCLC 2023; Mok T et al, ASCO 2024

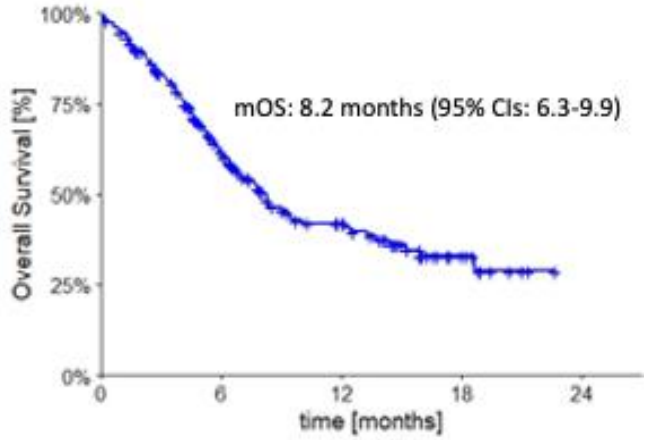
KRAS G12C finally druggable!

Italian RWE from the ATLAS registry (n=196 pts)

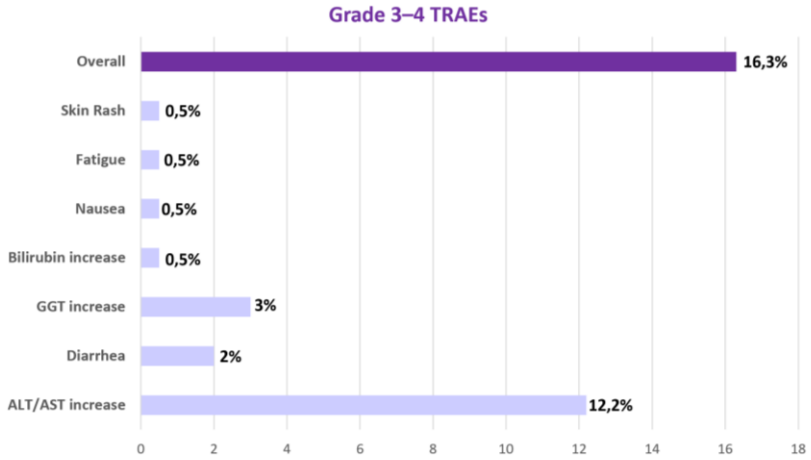
KRAS G12C







	Pts with BM (N=64)
Intracranial RR	15 (23%)
CR	2 (4%)
PR	10 (19%)
Intracranial DCR	31 (48%)
Median time to CNS response	2.9 months (IQR: 1.8-4.5)
Median duration of CNS resp	14.2 months (95% CI: 6.9-19)
Intracranial mPFS	8.6 months (95% CI: 6.0-11.2)
Prior brain radiotherapy	24 (38%)
Local CNS treatment	5 (8%)



88% treated with previous anti-PD-(L)1

Passiglia F et al, Lung Cancer 2024

KRAS G12C finally druggable!

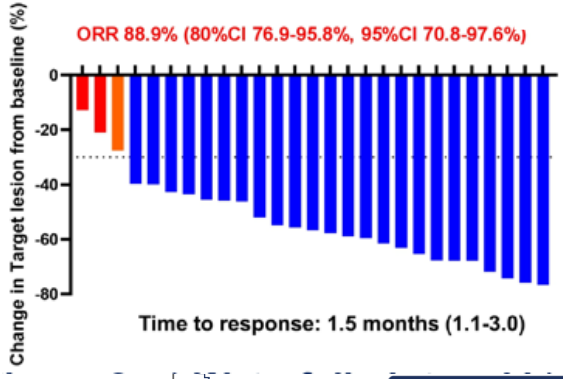
The future is likely to be in combo

KRAS G12C

- Develop improved/more potent agents
- Develop agents with different mode of action

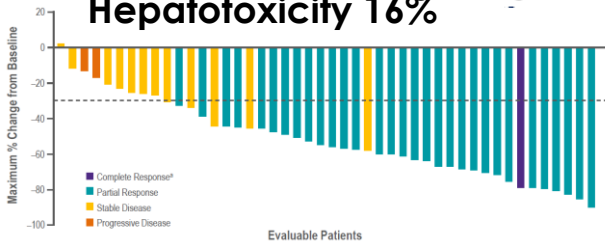
- **Combination** therapies

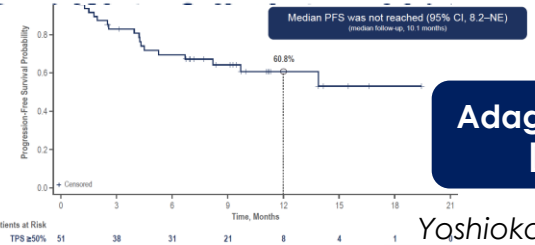
Sotorasib + ChT [SCARLET]



Time to response: 1.5 months (1.1-3.0)

ORR 63%
DCR 84%
Hepatotoxicity 16%

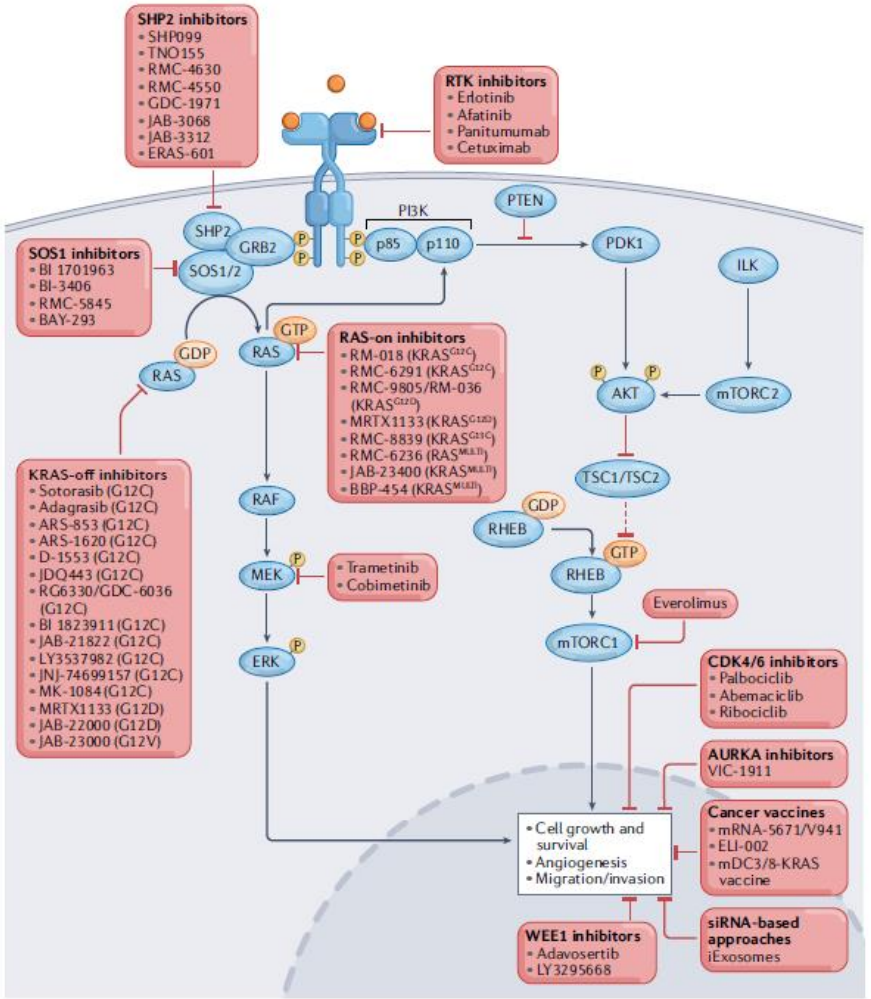




ORR did not differ by PD-L1 expression level or TP53 co-mutation

Adagrasib + pembro [KRYSTAL-7]

Yoshioka H et al, ASCO 2024
Garassino M et al. ESMO 2023

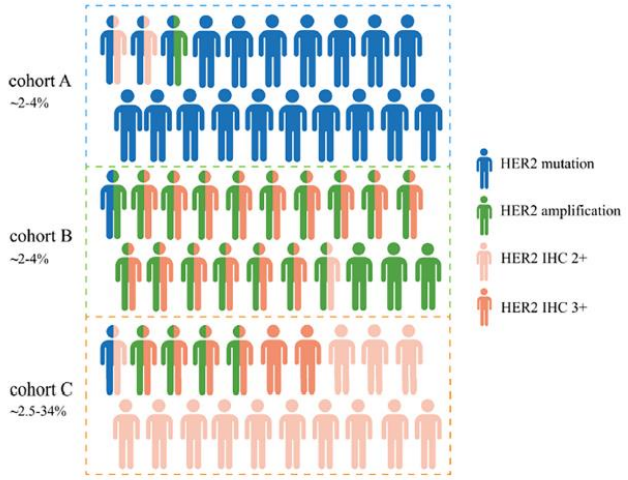


Punekar SR et al, Nature Reviews Clinical Oncology 2022

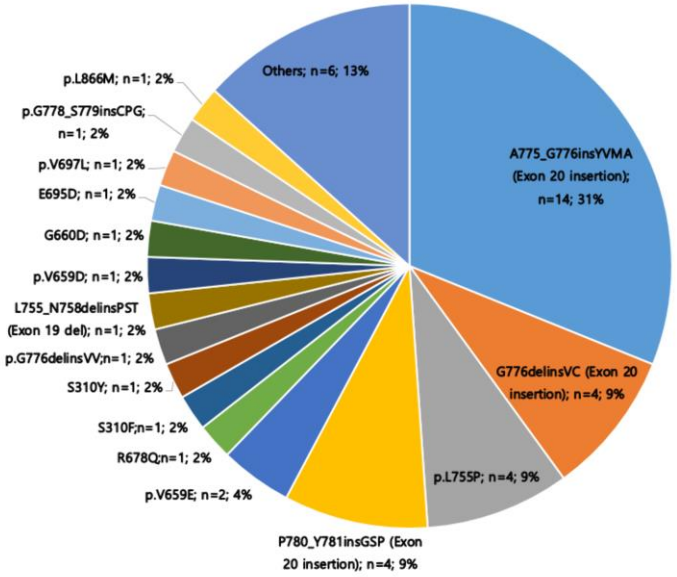
HER2 mutations

The oncogenic mechanisms

HER2



- HER2 dysregulations encompass **heterogeneous and distinct alterations**
- **Lack of correlation** between overexpression (6-35%), amplification (10-20%), and mutations
- Patients should be considered as **three distinct HER2-altered subgroups**



- **Exon 20 insertions** affecting TKD, 3-12 bp, less heterogeneous than EGFR ex20 insertions (YVMA variant ~85%)
- **Point mutations** in the TK, transmembrane and extracellular domain

Yu X et al, Front. Oncol. 2022
Han Y et al. J Thorac Oncol. 2021

The rise of a new ADC [TDX-d]

Our highly expected comfort zone

HER2

DESTINY-Lung01

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS 0 or 1
- Locally reported *HER2* mutation (cohort 2)[b]

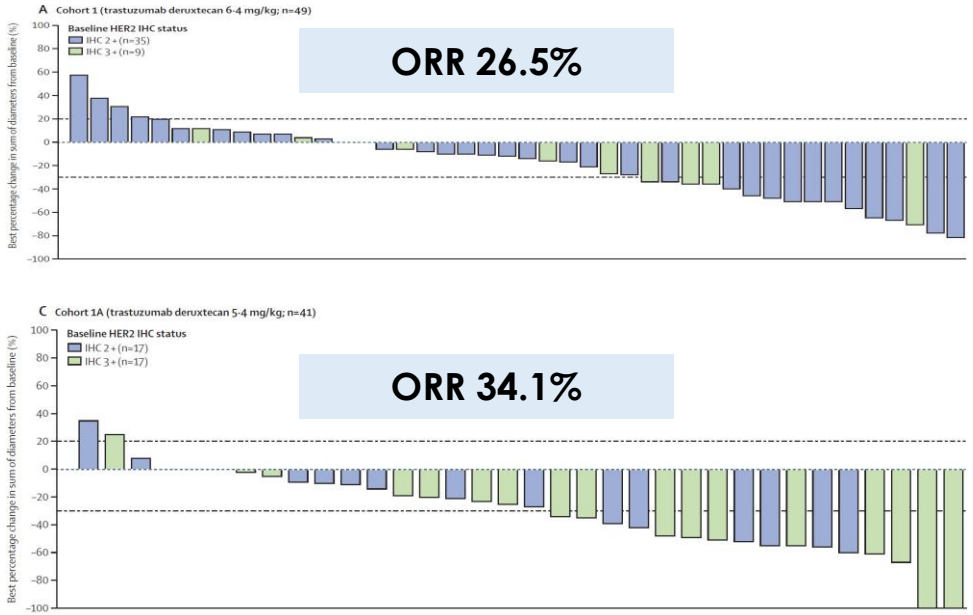
→ **Cohort 1**[c] (n = 49) **HER2 overexpressing** (IHC 3+ or IHC 2+) **T-DXd** 6.4 mg/kg Q3W

→ **Cohort 1a**[c] (n = 41) **HER2 overexpressing** (IHC 3+ or IHC 2+) **T-DXd** 5.4 mg/kg Q3W

→ **Cohort 2** (n = 42) ***HER2* mutated** **T-DXd** 6.4 mg/kg Q3W

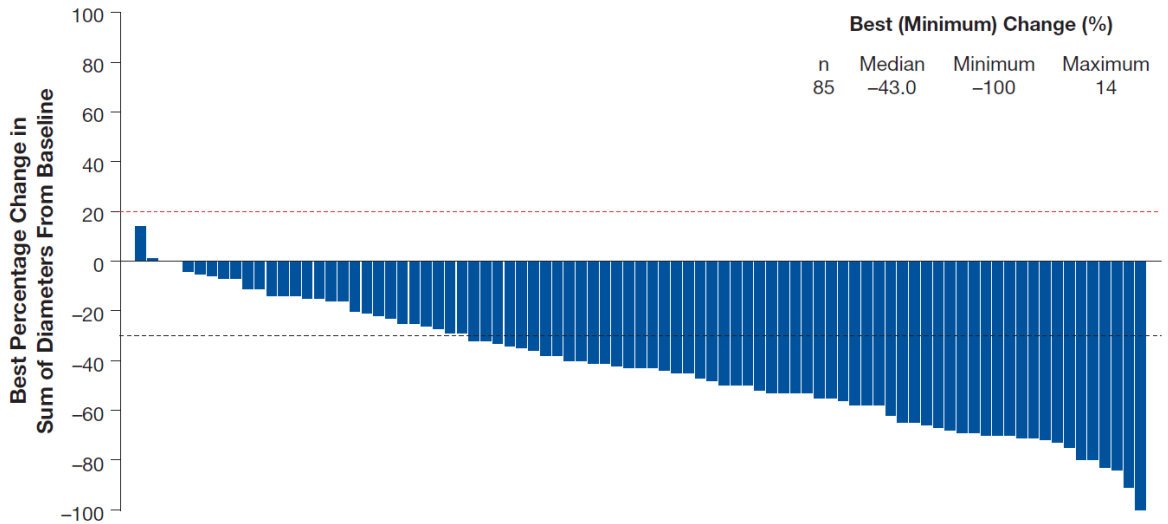
→ **Cohort 2** (n = 49) ***HER2* mutated** **T-DXd** 6.4 mg/kg Q3W

- **Primary endpoint:** Confirmed ORR by ICR[d]
- **Secondary endpoints:** DOR, PFS, OS, DCR, and safety
- **Exploratory endpoint:** biomarkers of response



ORR 26.5%

ORR 34.1%



- Confirmed **ORR by ICR 54.9%**
- Confirmed ORR by ICR **similar across subgroups:**
  - 54.5% and 55.2% in pts with/without CNS met
  - 55.7% and 53.3% in pts with ≤2/>2 prior lines

- **mPFS 8.2 ms**
- **mOS 18.6 mos**

Li BT et al. NEJM 2022, ESMO 2022; Smit E et al, Lancet Oncol 2024

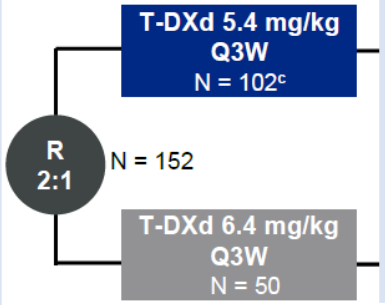
Randomized dose-finding studies

DESTINY-Lung02

HER2

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment



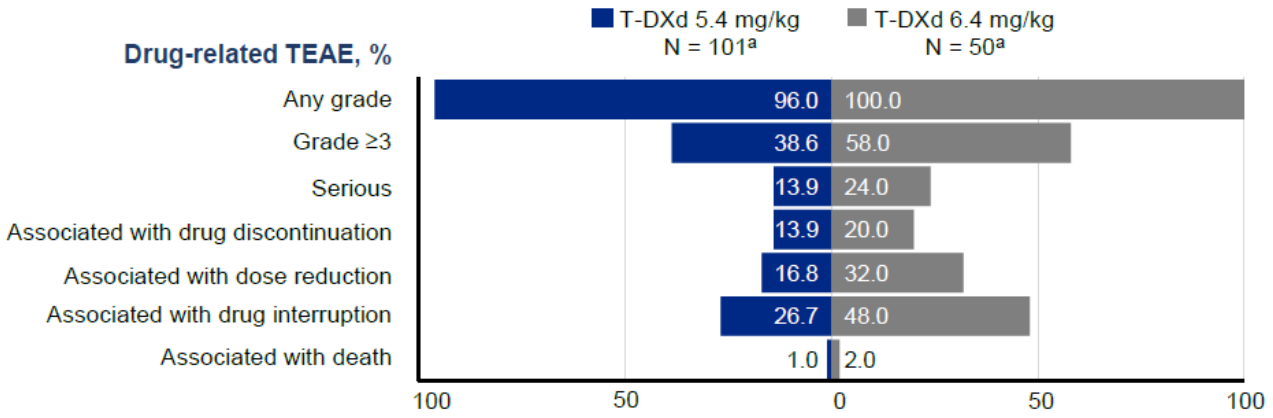
Primary Endpoint
- Confirmed ORR by BICR

Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

Overall Safety



Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

Lower incidence of drug-related G≥3 TEAEs, serious TEAEs, discontinuations, dose reductions, and interruptions & **ILD rate** were observed with the 5.4 mg/kg dose

Janne P et al, WCLC 2023
Goto K et al, JCO 2023

Moving to 1st line

Will TDX-d be enough?

HER2

DESTINY-Lung04

Phase 3 study of T-DXd as 1L treatment of NSCLC harboring *HER2* exon 19 or 20 mutations

- Metastatic or unresectable nonsquamous NSCLC
- Treatment naïve for advanced disease
- *HER2*mut exon 19/20 by central or local test
- RECIST v1.1 evaluable

1:1 R N = 264

T-DXd 5.4 mg/kg Q3W

Pembrolizumab + platinum + pemetrexed

- **Primary endpoint:** PFS by BICR
- Prespecified subgroups include *HER2* co-amplification; PD-L1 status (≥1%)

DESTINY-Lung03

- **Metastatic/unresectable nonsquamous HER2+ NSCLC[a] by central assessment**
- **Part 1: 2L/3L**
- **Part 2: previously untreated unresectable/mNSCLC**
- **ECOG PS 0 or 1**
- **RECIST v1.1 evaluable (N≈136)[b]**

Part 1 – Dose Escalation

- Arm 1A: T-DXd + durvalumab + cisplatin Q3W
- Arm 1B: T-DXd + durvalumab + carboplatin Q3W
- Arm 1C: T-DXd + durvalumab + pemetrexed Q3W
- Arm 1D: T-DXd (monotherapy)

Part 2 – Dose Expansion

- Arm 2A: T-DXd + durvalumab + cisplatin Q3W
- Arm 2B: T-DXd + durvalumab + carboplatin Q3W
- Arm 2C: T-DXd + durvalumab + pemetrexed Q3W
- Arm 2D: T-DXd + durvalumab Q3W

Primary Endpoints

- Safety

Secondary Endpoints

- Confirmed ORR
- DOR
- DCR
- PFS
- OS
- PK
- Immunogenicity

Conclusions

TT in Advanced NSCLC

TEST!

Therapy → optimize 1st line (RB ratio & multidimensional patient's selection)

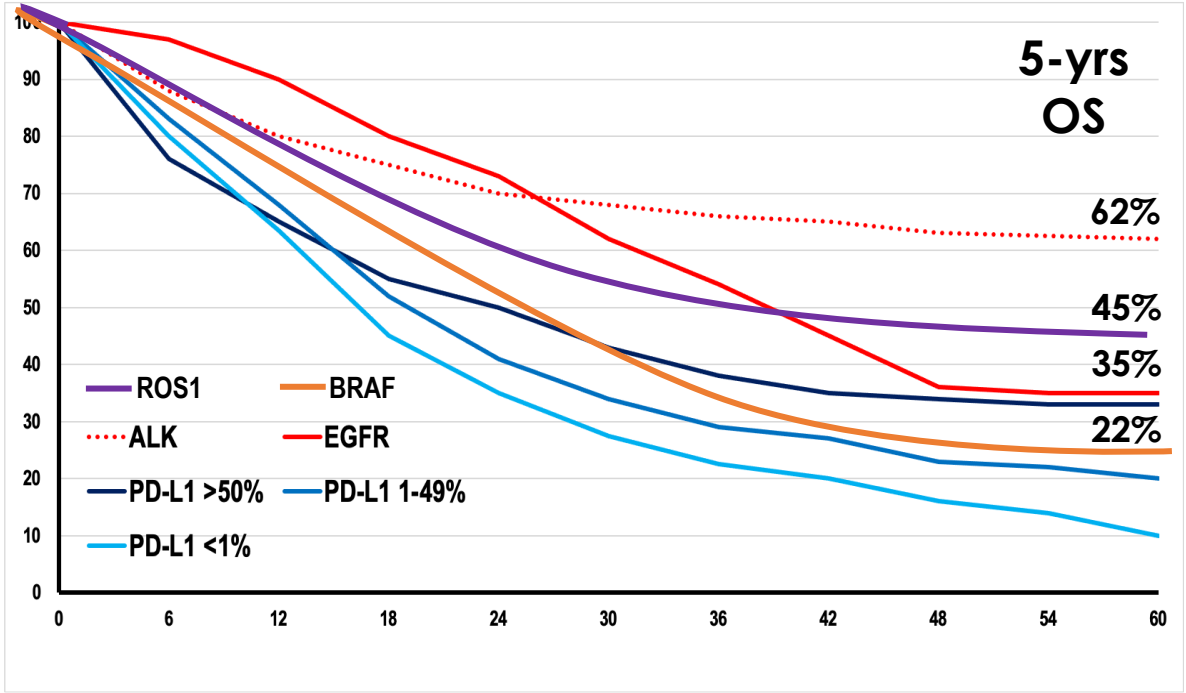
Strategy → Adequately manage 1st line to reach 2nd line if TT is there

Biology & heterogeneity → dig deep into disease details (NGS!)

Estimated prognostic horizons according to 1st line biomarkers

Long-term benefit

Addiction	Biomarker	Current Options	Data Source	Median OS (months)	Estimated OS @5 yrs
YES	***ALK+***	***Alectinib Brigatinib***	**Phase 3 Phase 3**	***N.R.***	**62%**
YES	***ROS1+***	***Crizotinib Entrectinib***	**Phase 1b Pooled Ph.1b**	***48 mo.***	**45%**
YES	***EGFR+***	***Osimertinib***	**Phase 3**	***40 mo.***	**35-40%**
YES	***BRAF+***	***Dabrafenib + Trametinib***	**Phase 2**	***18-20 mo.***	**22%**
NO	*PD-L1 >50%*	*Pembrolizumab Atezolizumab Cemiplimab*	Phase 3 Phase 3 Phase 3	*24 mo.*	30-35%
NO	*PD-L1 1-49%*	*4 Chemo + PEMBRO 2 Chemo + NIVO-IPI*	Phase 3 Phase 3	*19 mo.*	20%
NO	*PD-L1 <1%*	*4 Chemo + PEMBRO 2 Chemo + NIVO-IPI*	Phase 3 Phase 3	*16 mo.*	10%



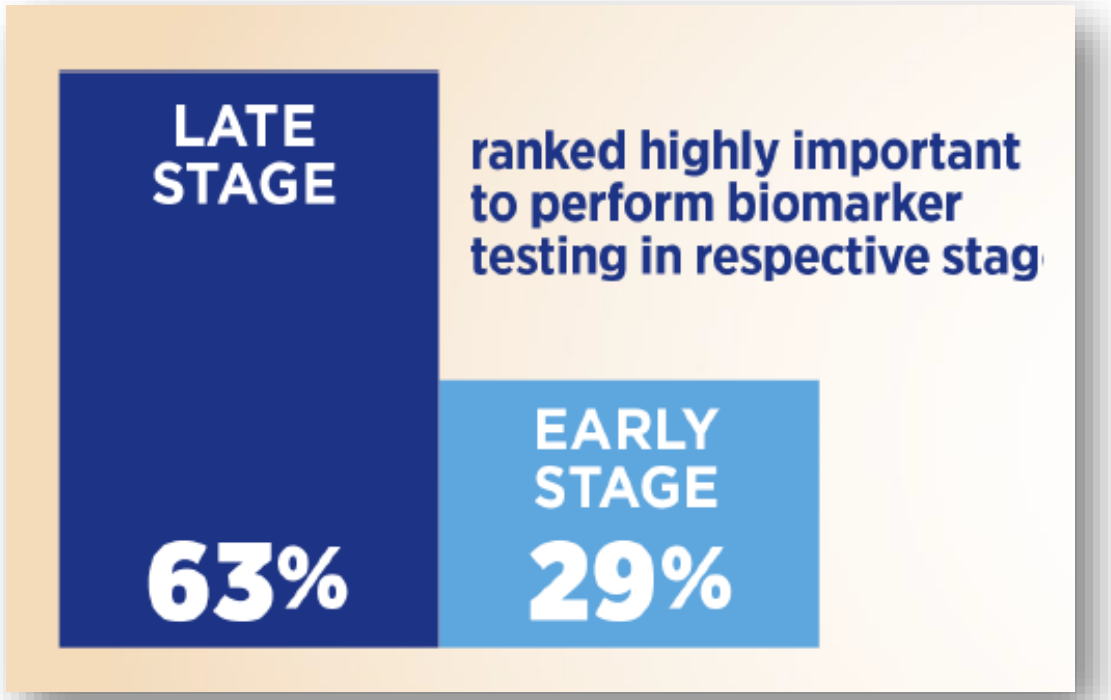
** Pending Important Limitations/Variability with regard to Histology, Data Maturity and Follow-Up*

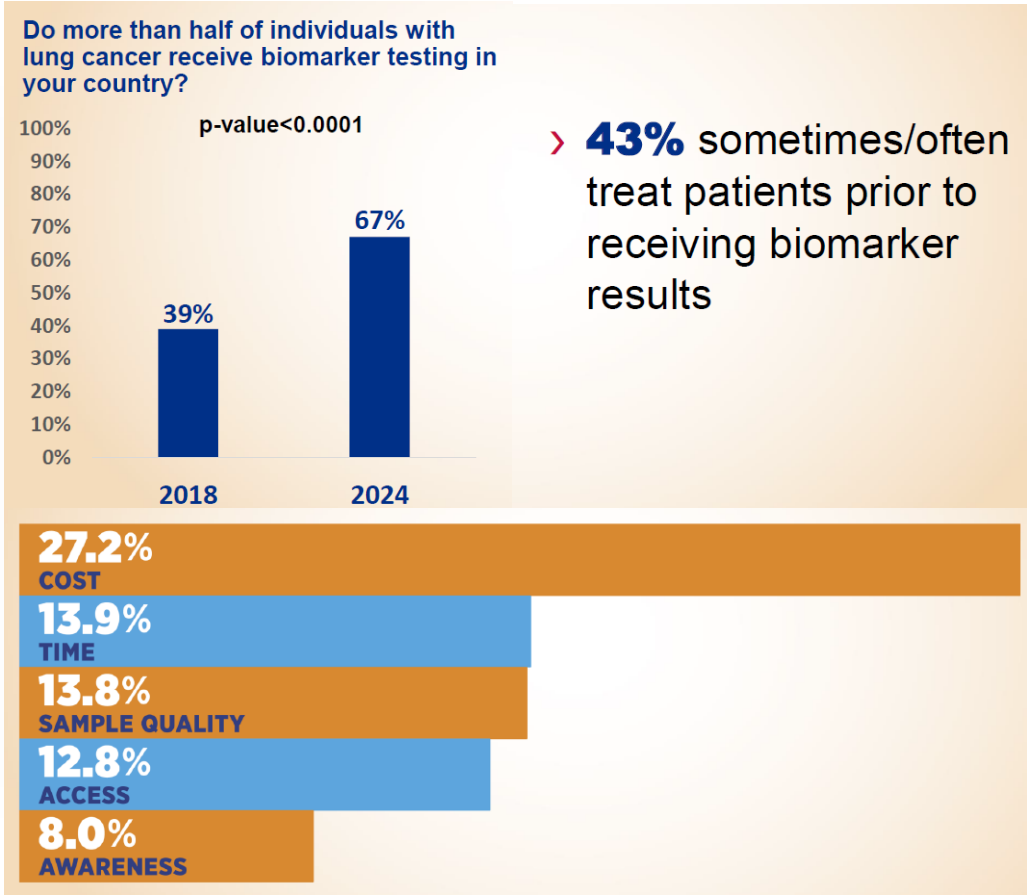
Modified from Emilio Bria

The 2024 IASLC Global Survey on Biomarker Testing

Knowledge, awareness and perception of current practice

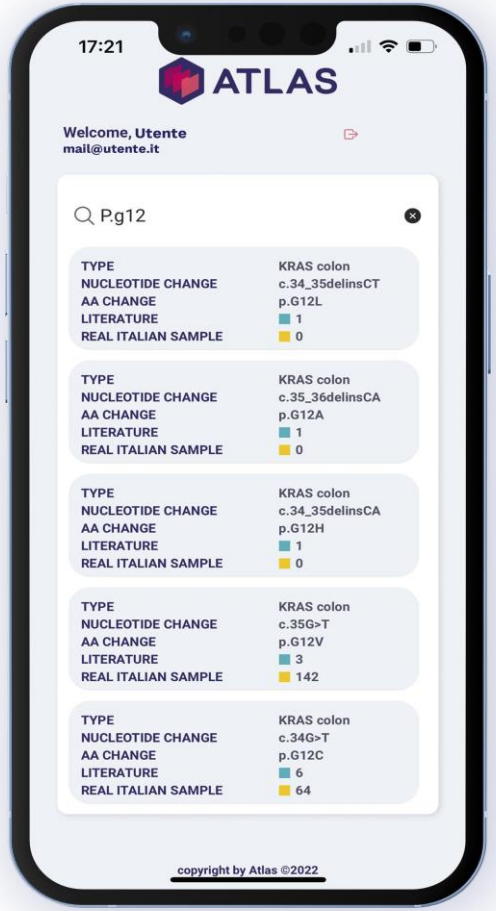
1,677 responses across 90 countries and 14 disciplines (mainly oncologists, pathologists, pneumonologists and thoracic surgeons)





Smeltzer MP et al, WCLC 2024

The value of National Platforms: ATLAS



Malapelle U et al, Eur J Cancer 2021

https://biomarkersatlas.com/