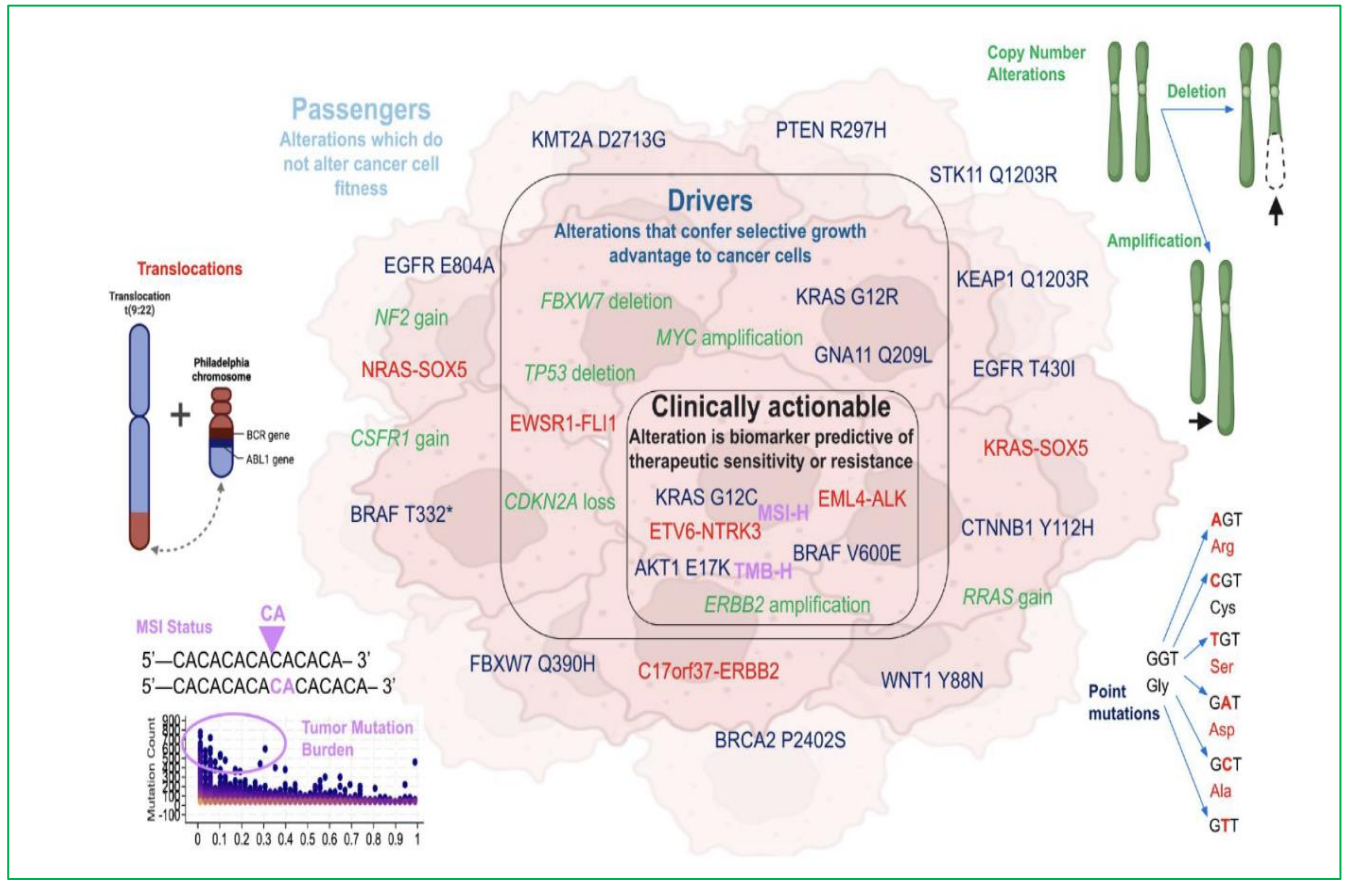
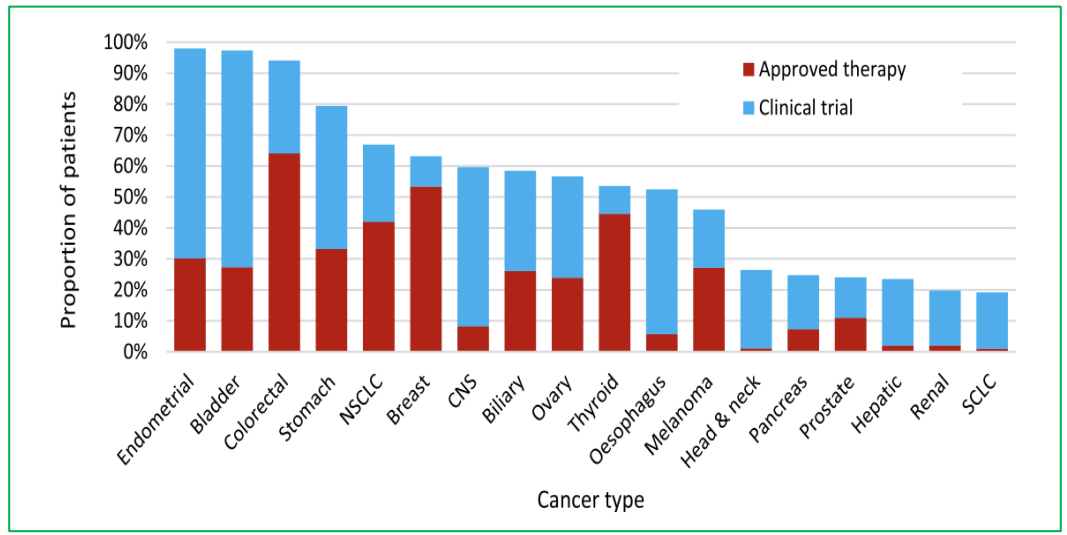

Passengers
Alterations which do not alter cancer cell fitness
KMT2A D2713G
PTEN R297H
STK11 Q1203R
Drivers
Alterations that confer selective growth advantage to cancer cells
EGFR E804A
FBXW7 deletion
KRAS G12R
KEAP1 Q1203R
NF2 gain
MYC amplification
GNA11 Q209L
NRAS-SOX5
TP53 deletion
EGFR T430I
Clinically actionable
Alteration is biomarker predictive of therapeutic sensitivity or resistance
EWSR1-FLI1
CSFR1 gain
KRAS-SOX5
CDKN2A loss
KRAS G12C
MSI-H
EML4-ALK
BRAF T332*
ETV6-NTRK3
CTNNB1 Y112H
BRAF V600E
AKT1 E17K
TMB-H
RRAS gain
ERBB2 amplification
FBXW7 Q390H
C17orf37-ERBB2
WNT1 Y88N
BRCA2 P2402S
Translocations
Translocation t(9:22)
Philadelphia chromosome
BCR gene
ABL1 gene
MSI Status
CA
5'—CACACACACACACA– 3'
5'—CACACACACACACA– 3'
Tumor Mutation Burden
Mutation Count
Copy Number Alterations
Deletion
Amplification
Point mutations
GGT
Gly
AGT
Arg
CGT
Cys
TGT
Ser
GAT
Asp
GCT
Ala
GTT


Proportion of patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Approved therapy
Clinical trial
Endometrial
Bladder
Colorectal
Stomach
NSCLC
Breast
CNS
Biliary
Ovary
Thyroid
Oesophagus
Melanoma
Head & neck
Pancreas
Prostate
Hepatic
Renal
SCLC
Cancer type

Beyond EGFR, ALK, ROS in NonSmall Cell Lung Cancer (NSCLC)

Pr Jaafar BENNOUNA

- ✓ Hôpital Foch, Suresnes
- ✓ Medical Oncology

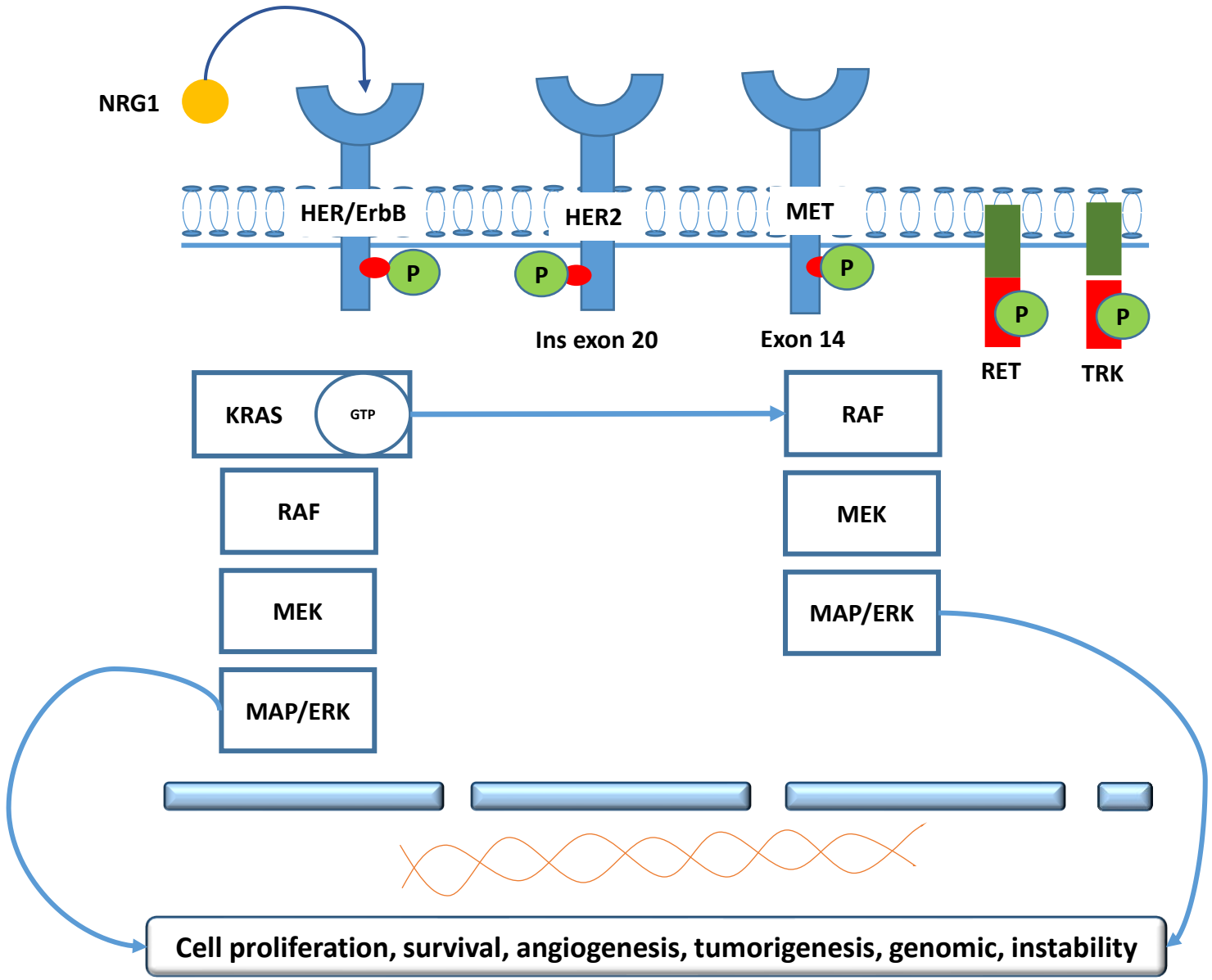
DISCLOSURE INFORMATION

Advisory board: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, F. Hoffmann–La Roche Ltd, MSD, Novartis

Research: Amgen, AstraZeneca, Medimmune, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, F. Hoffmann–La Roche Ltd, Innate Pharma, Merck,MSD, Novartis, Sanofi-Aventis, Daiichi

Honorarium: AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, F. Hoffmann–La Roche Ltd, Merck, MSD, Novartis, Daiichi

NSCLC. Biomarkers beyond EGFR, ALK, and ROS



		RoW	ASIA
1	Met Exon 14	3 %	3 %
2	HER2 Ins exon 20	2.3 %	2.3 %
3	BRAF V600E	2.1 %	2.1 %
4	RET	1.7 %	1.7 %
5	NTRK	0.23%	0.23%
6	NRG1	< 1 %	< 1 %

Tan AC. et al. J Clin Oncol 2022

Prevalence of oncogenic somatic driver alterations

in lung cancer in never smoker

Key points

Rarity

Extreme rarity

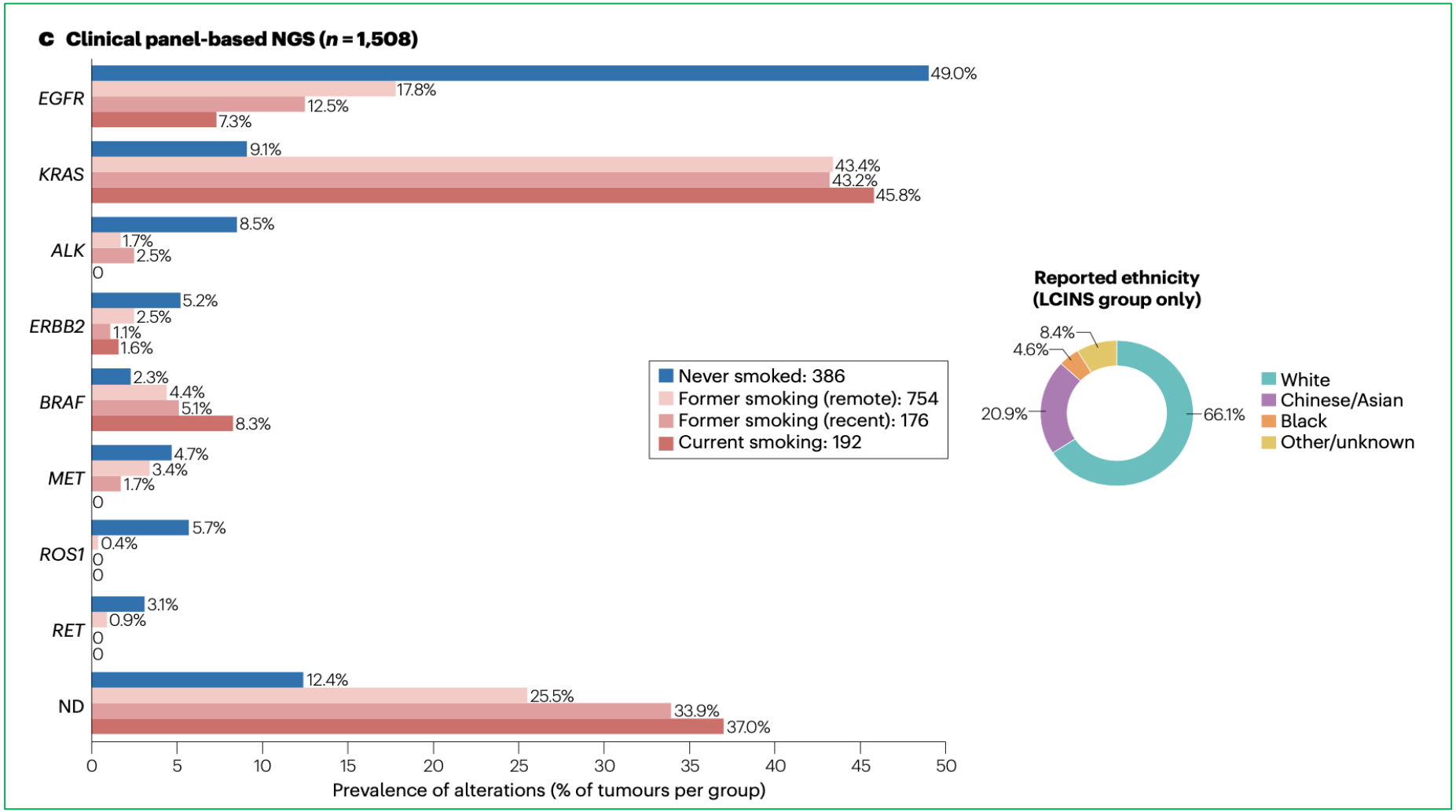
Oncogenic addiction

Anatomopathological clinical features

non-smoker: **yes !** or no

TKI efficacy

Agnostic therapy +/-



LoPiccolo J, et al. Nat Rev Clin Oncol 2024

Anatomopathological and clinical characteristics (one trend)

Met exon 14 skipping mutation[1,2]

- Nonsquamous histology : 2.4 %
- Squamous histology (1.3 %)
- **Sarcomatoïd histology**(12 %)
- **Median age : 73 years**
- female (60 %)
- ± smokers (?)

HER2 mutation[3]

- Woman
- Nonsmoker
- Adenocarcinoma
- Brain metastases
- Pejorative pronostic

BRAFV600E[4]

- Woman
- Never smoker
- **20-30 %,non smoker**
- Pejorative prognostic
- +/- less brain metastasis
- Agressive histology (i.e micropapillary)

BRAF nonV600[4]

- Almost exclusively in male gender
- **Smoking history**
- Relatively longer DFS
- Positive prognostic
- +/- more brain metastatsis
- HighTMB, sensitivity to immunotherapy

RET fusion[5]

- Young
- Non smoker
- Poorly differenciated nonsquamous
  - ➢ solid or lepidic. or papillary

NRG fusion [6]

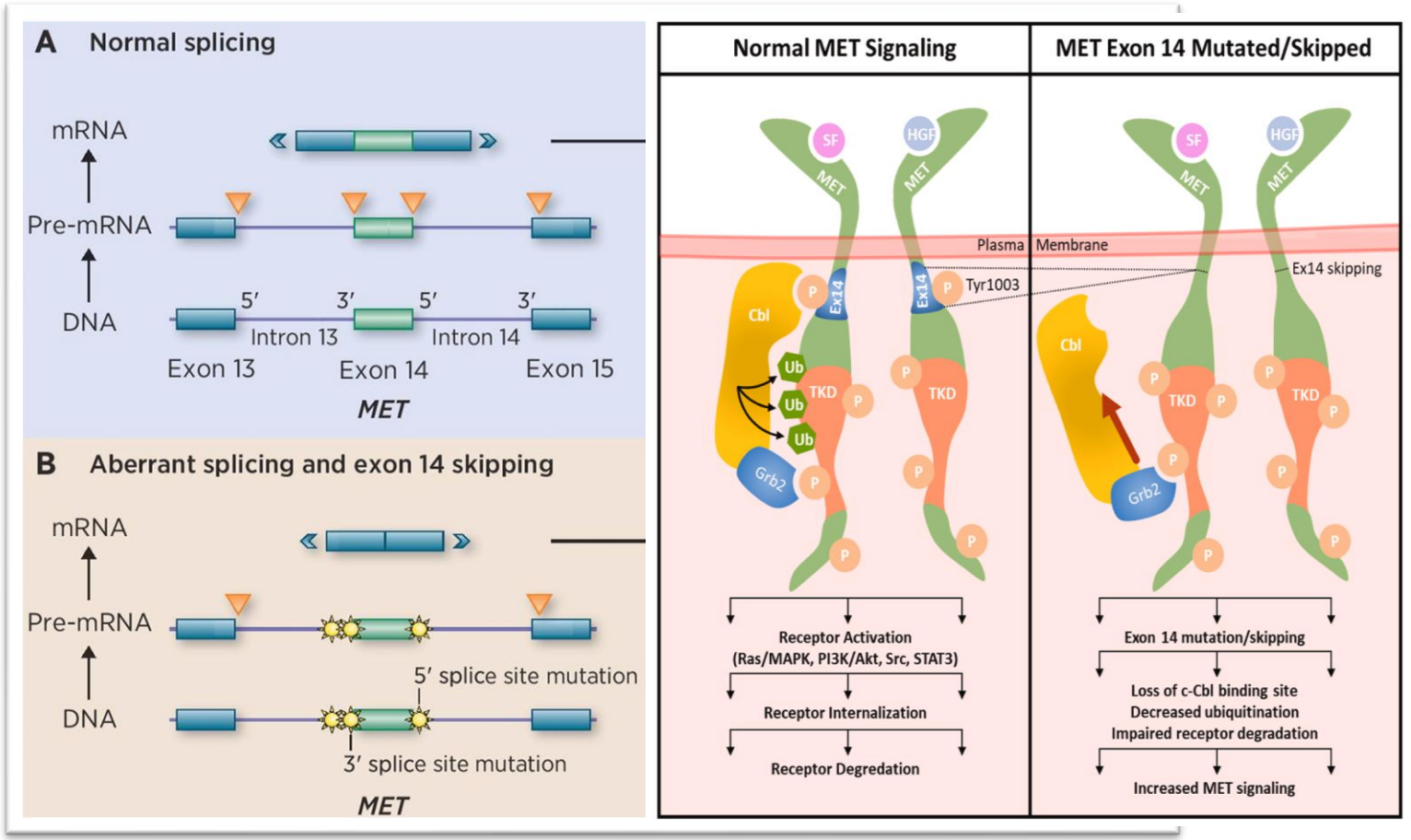
- Never smoker (57%)
- Mucinous adenocarcinoma (57%)
- Nonmetastatic (71%)
- **Heterogeneous**

NTRK fusion [7]

- Never smoker
- Adenocarcinoma
- Also neuro-endocrine
- Also squamous

1. Schrock AB. et al. J Thorac Oncol 2016 ; 2. Mazieres J, et al. Clin Lung Cancer 2023; 3. Arcilla ME, et al. Clin Cancer Res 2012; 4. Puri M, et al. Front Oncol 2023; Hess LM, et al. BMC Cancer 2021; 6. Drilon A, et al. J Clin Oncol 2021; 7. Farago AF, et al. JCO Prec Oncol 2028

Met exon 14 skipping Mutation



- **nonsquamous histology**[1,2] **:** 2.4 %
- Squamous histology (1.3 %)
- **Sarcomatoïd histology**(12 %)

Median age [1] : 73 years; female (60 %)

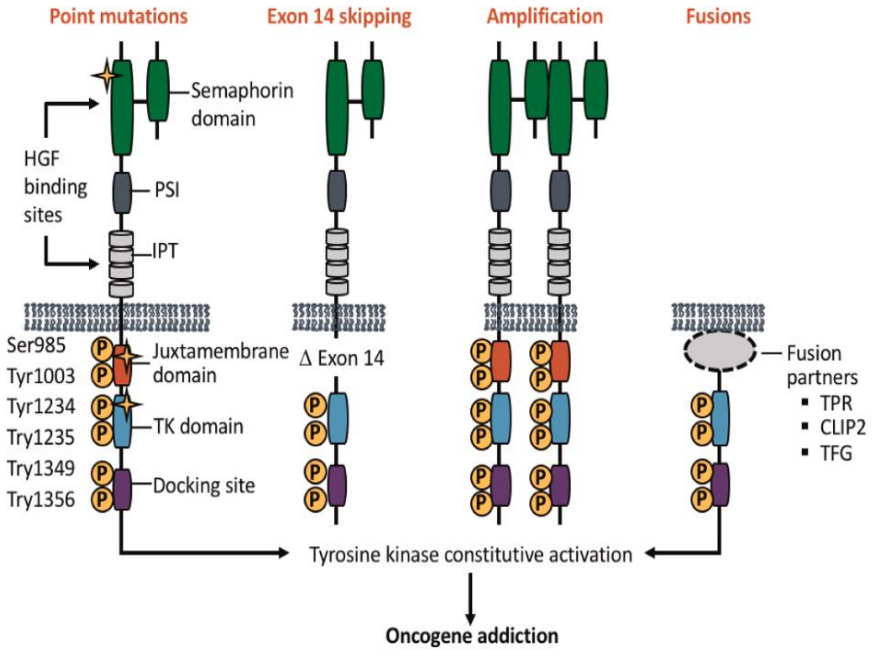
± smokers (?)

Met exon 14 skipping [3]

- aberrant splicing due to mutations in the splice junctions of MET exon14

1. Schrock AB. et al. J Thorac Oncol 2016 ; 2. Mazieres J, et al. Clin Lung Cancer 2023; 3. Drillon A, et al. Clin Cancer Res 2015; 4. Coleman L, et al. Lung Cancer 2022

Met exon 14 skipping Mutation and…

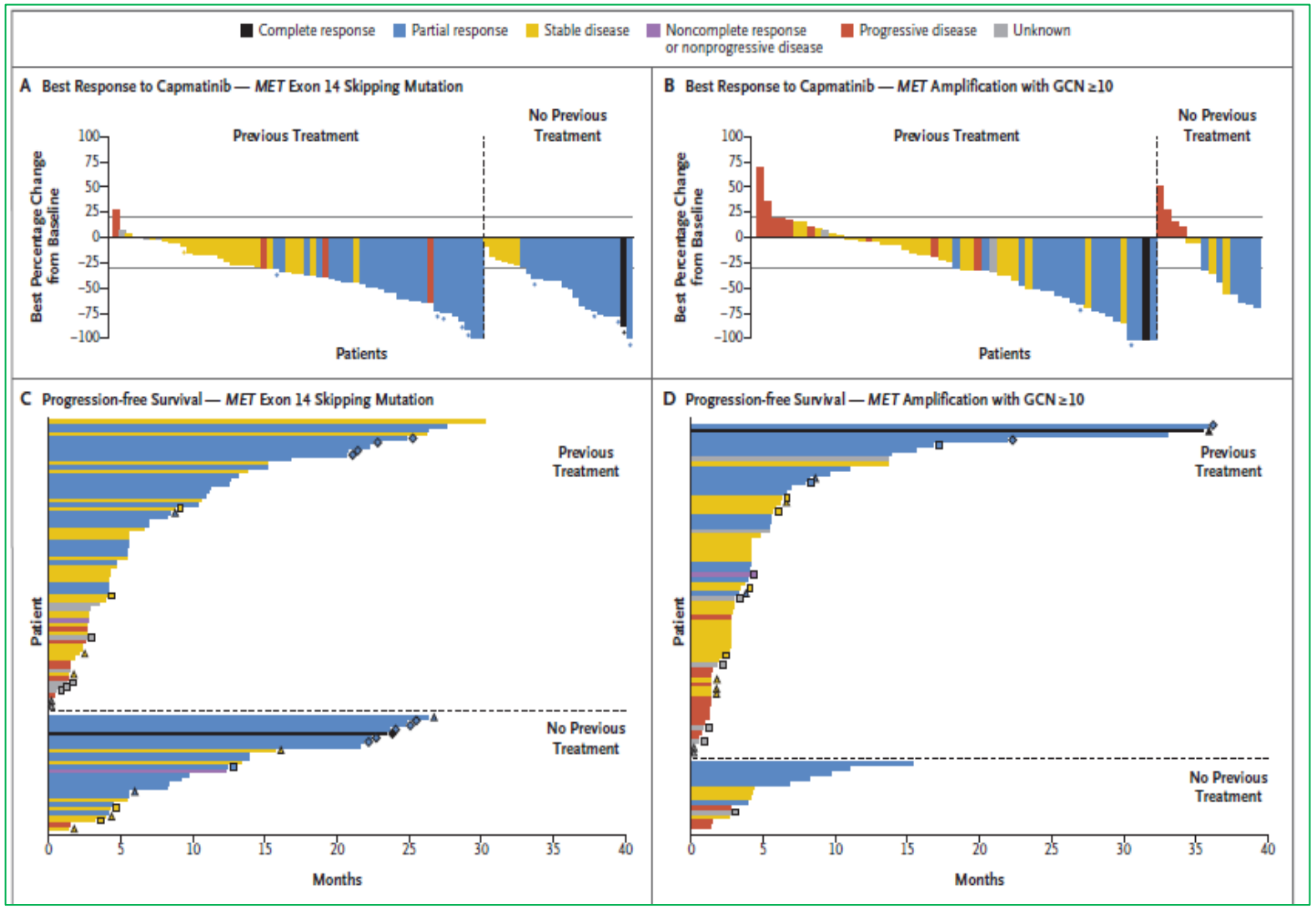


- **IHC** = protein overexpression
- **Amplification** : increase in the number of copies of a gene with a ratio gene to centromere increased (≠ polysomy)
- Met amplification : co-occurrence with EGFR mutation as a mechanism of resistance

1. Coleman L, et al. Lung Cancer 2022

Capmatinib and Met exon 14 Mutation

GEOMETRY mono-1 (trial)



n = 364

Patients with exon 14 mutation

- **Pretreated. n=69**
  - ORR = 41 %, DoR 9.7 months
  - PFS = 5.4 months
- **Non Pretreated. n=28**
  - ORR = 68 %, DoR 12.6 months
  - PFS =12.4 mois

Patients with MET amplification

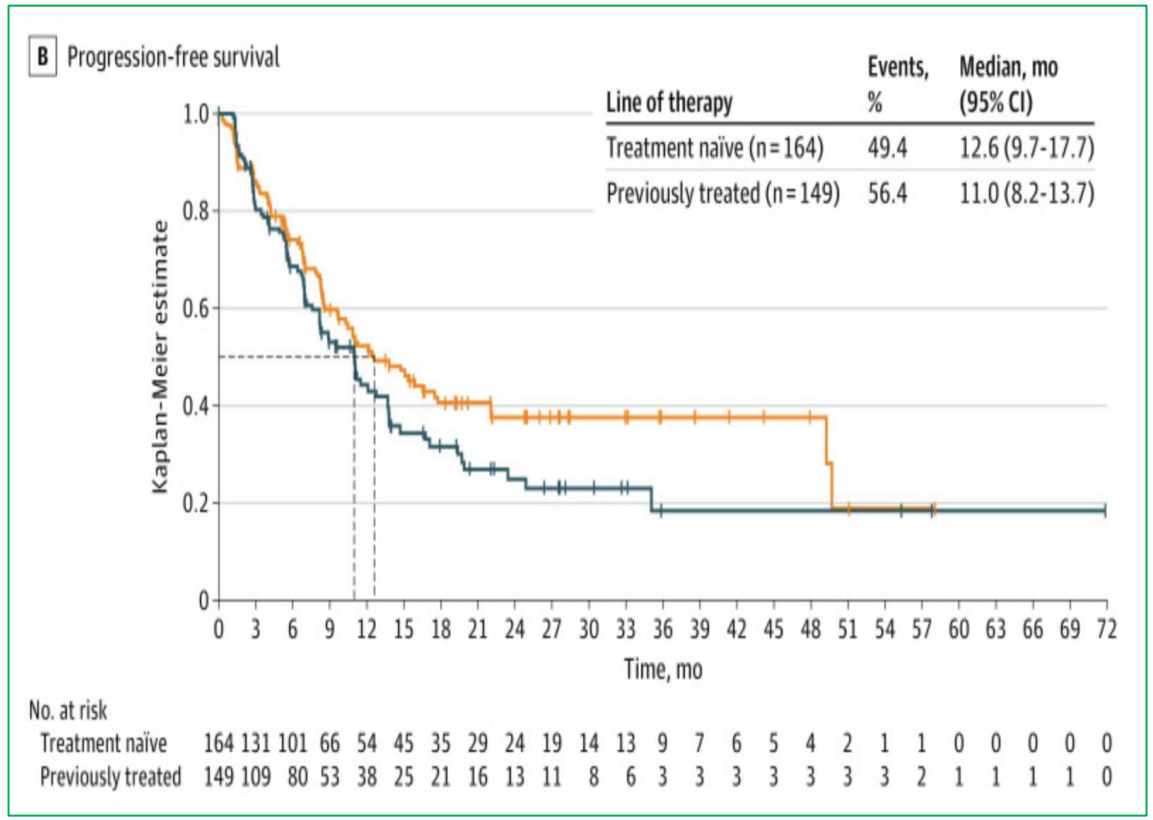
- **Pretreated. n=41**
  - ORR = 29 % if GCN ≥ 10
  - ORR = 12 % if GCN < 10
- **Non Pre-treated. n=68**
  - ORR = 40 % if GCN ≥ 10
  - ORR = 7 % if GCN < 10

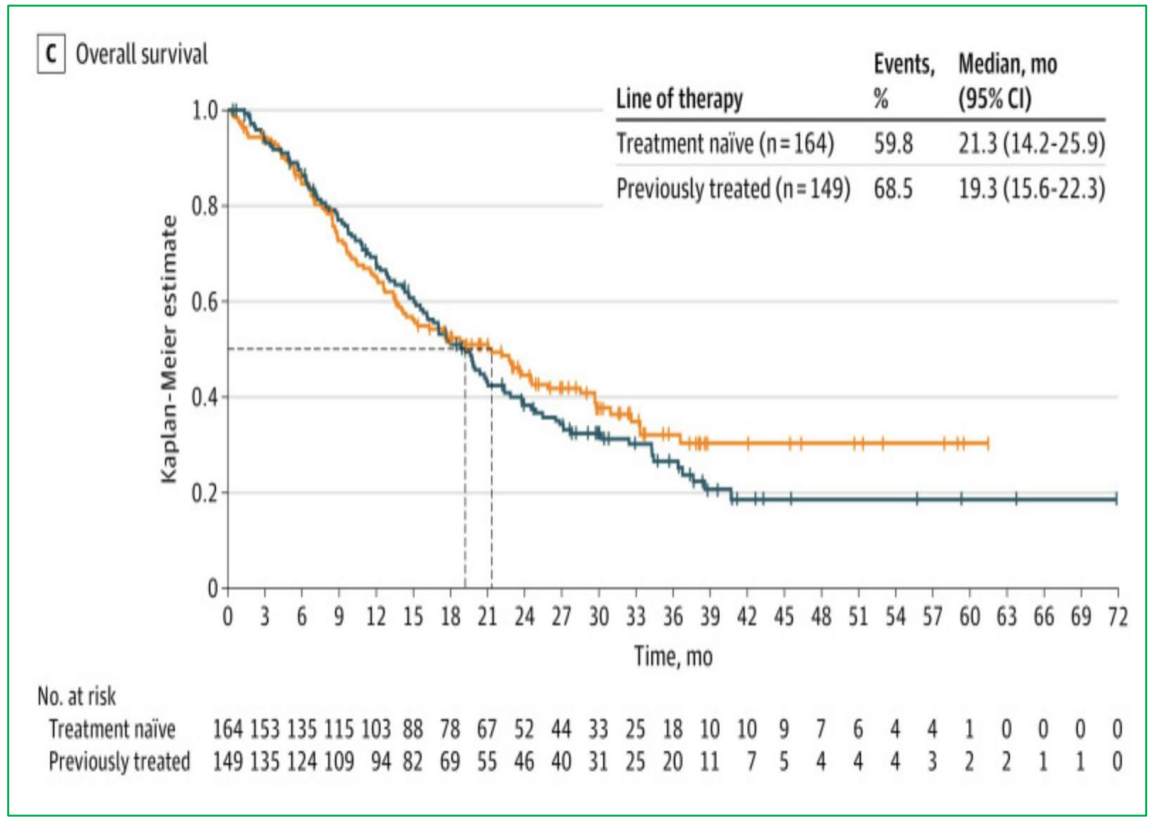
Wolf J. et al. N Engl J Med 2021

Long-term follow-up of the vision phase 2 trial (Tepotinib)

*MET*ex14-skipping advanced/metastatic NSCLC

- Treatment naive (n=164) : ORR 57.3 %; DCR 78.7 % and DoR 46.4 months
- Previously treated (n=149) : ORR 45 %; DCR 73.8 % and DoR 12.6 months





Paik PK, et al. N Engl J Med 2021; Mazieres J. et al. JAMA Oncol 2023

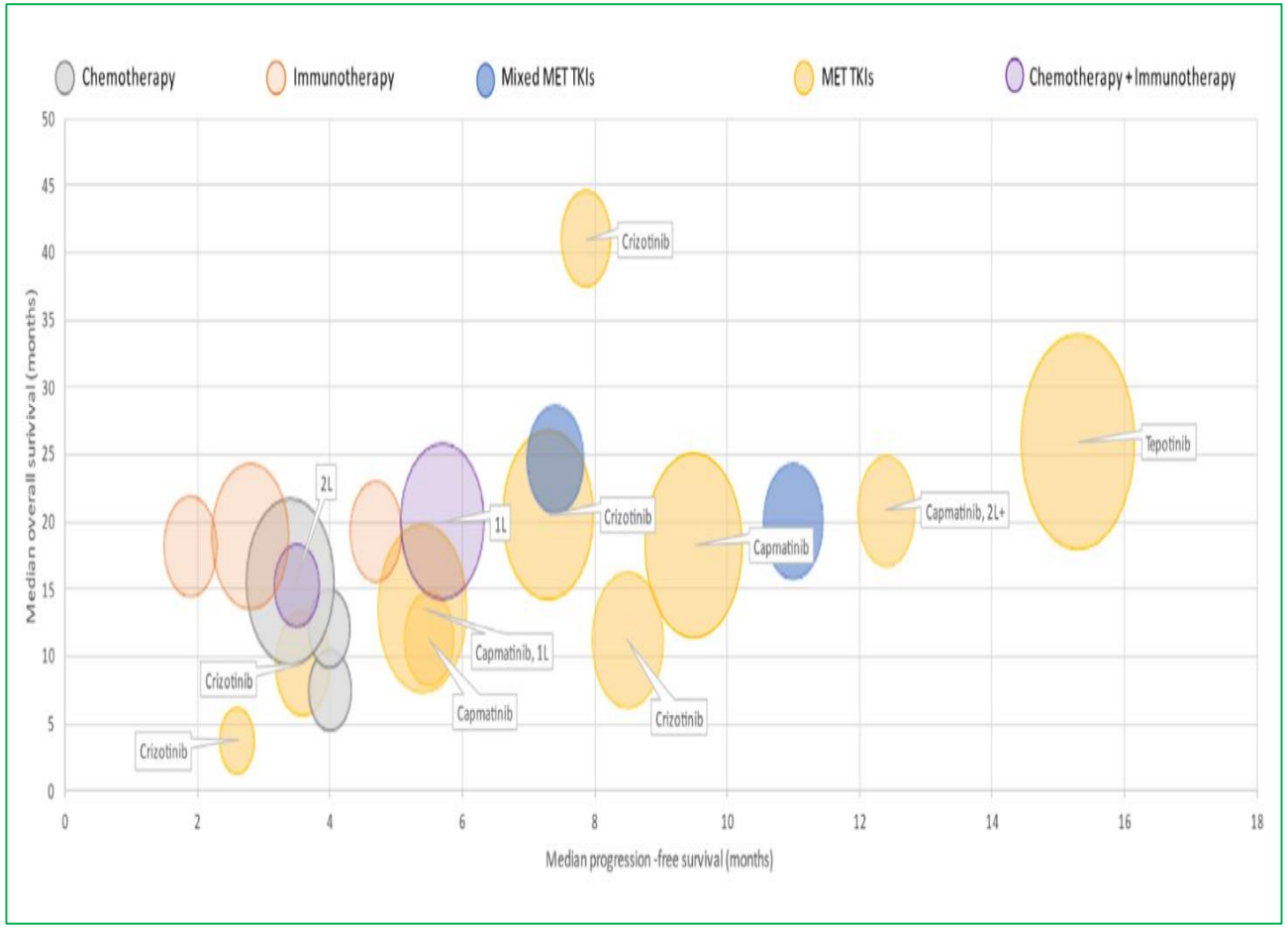
Trials with in MET-exon 14 mutation NSCLC

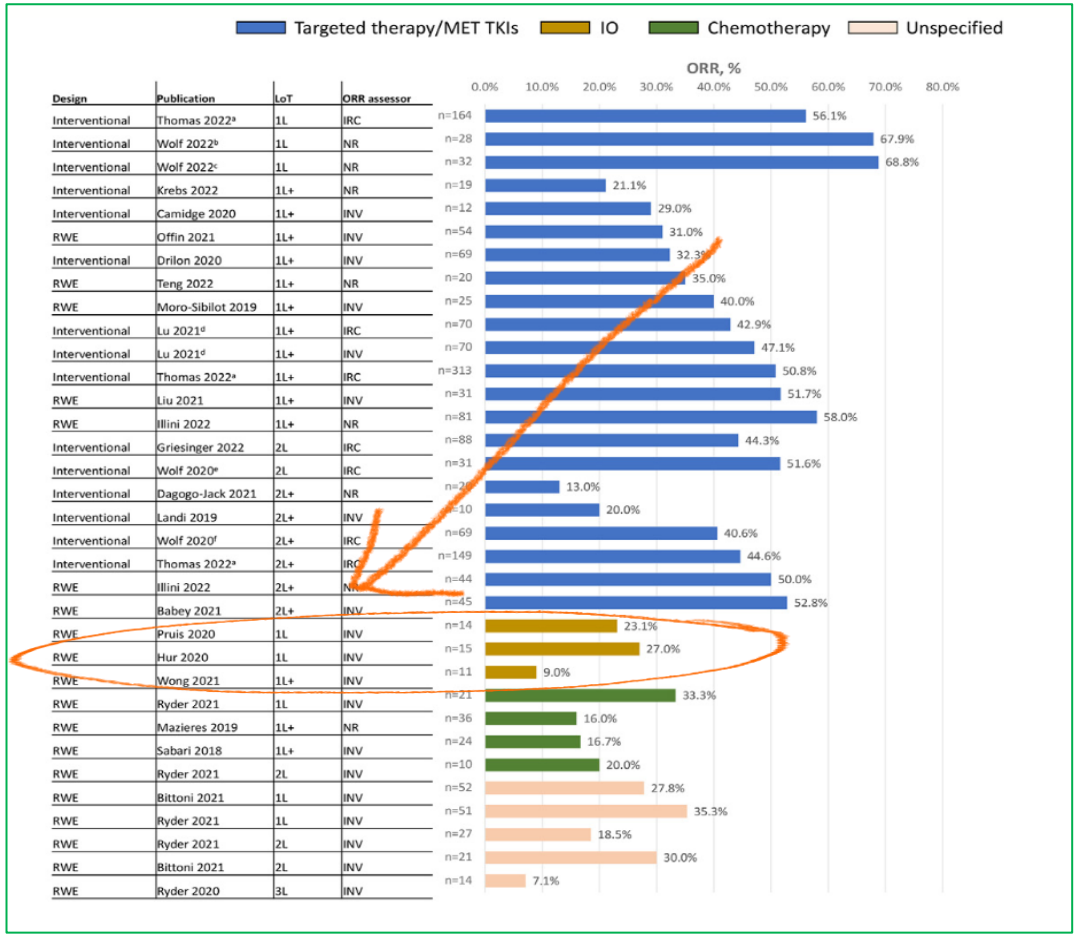
Trials	Drug	Line	n	ORR (%)	DoR (months)	PFS (months)	OS (months)
Drilon A [1] (PROFILE 1001)	Crizotinib	≥ 1	69	32	9.1	7.3	20.5
Moro-sibilot D (ACSE) [2]	Crizotinib	≥ 2	25	12	-	3.6	9.5
Wolf J [3,4, 5] **GEOMETRY Mono-1**	Capmatinib	1 (cohort 5b)	28	67.9	12.6	12.4	20.8
		1 (cohort 7 expansion)	32	68.8	16.59	12.45	NR
		2/3 (cohort 4)	69	40.6	9.7	5.4	13.6
		2L (cohort 6 expansion)	31	51.6	8.4	6.9	NE
Paik PJ [6] (VISION)	Tepotinib	1	164	57.3	46.4	12.6	21.3
Mazieres J [7] (VISION update)		> 1	149	45	12.6	11.0	19.3
Lu S [8,9] *	Savolitinib	1	28	46.4	NR	6.9	10.9
		> 1	42	47.6	NR	6.9	19.4
Yu, Y (GLORY) [10]	Gumarontinib	1	44	71	15.0	11.7	NE
		> 1	35	60	8.2	7.6	16.2
Leighl N [11]	Amivantamab	1	16	56			
		1 No prior METi	28	46	11.2	5.4	15.8
		> 1 with prior METi	53	21			

*The treatment-naive subgroup comprised a greater fraction of patients with pulmonary sarcomatoid carcinoma (46% versus 29% in the pretreated patients, median OS 10.6 months for PSC) and median age was higher (74.5 y versus 67.7 y in the pretreated patients).

1. Drilon A. et al. Nat Med 2020; 2. Moro-Sibilot D, et al. Ann Oncol 2019; 3. Wolf J, et al. N Engl J Med 2021; 4. Wolf J, et al. ASCO 2021 ; 5. Wolf J, et al. ELCC 2022; 6. Paik PK, et al. N Engl J Med 2021; 7. Mazieres J. et al. JAMA Oncol 2023; 8. Lu S, et al. Lancet Resp Med 2021 ; 9. Lu S, et al. JTO Clin Res Rep 2022; 10. Yu Y, et al. Lancet 2023. Leighl N, et al. IASLC 2023

Trials with in MET-exon 14 mutation NSCLC





Design	Publication	LoT	ORR assessor		
Interventional	Thomas 2022[a]	1L	IRC	n=164	56.1%
Interventional	Wolf 2022[b]	1L	NR	n=28	67.9%
Interventional	Wolf 2022[c]	1L	NR	n=32	68.8%
Interventional	Krebs 2022	1L+	NR	n=19	21.1%
Interventional	Camidge 2020	1L+	INV	n=12	29.0%
RWE	Offin 2021	1L+	INV	n=54	31.0%
Interventional	Drilon 2020	1L+	INV	n=69	32.3%
RWE	Teng 2022	1L+	NR	n=20	35.0%
RWE	Moro-Sibilot 2019	1L+	INV	n=25	40.0%
Interventional	Lu 2021[d]	1L+	IRC	n=70	42.9%
Interventional	Lu 2021[d]	1L+	INV	n=70	47.1%
Interventional	Thomas 2022[a]	1L+	IRC	n=313	50.8%
RWE	Liu 2021	1L+	INV	n=31	51.7%
RWE	Illini 2022	1L+	NR	n=81	58.0%
Interventional	Griesinger 2022	2L	IRC	n=88	44.3%
Interventional	Wolf 2020[e]	2L	IRC	n=31	51.6%
Interventional	Dagogo-Jack 2021	2L+	NR	n=20	13.0%
Interventional	Landi 2019	2L+	INV	n=10	20.0%
Interventional	Wolf 2020[f]	2L+	IRC	n=69	40.6%
Interventional	Thomas 2022[a]	2L+	IRC	n=149	44.6%
RWE	Illini 2022	2L+	NR	n=44	50.0%
RWE	Babey 2021	2L+	INV	n=45	52.8%
RWE	Pruis 2020	1L	INV	n=14	23.1%
RWE	Hur 2020	1L	INV	n=15	27.0%
RWE	Wong 2021	1L+	INV	n=11	9.0%
RWE	Ryder 2021	1L	INV	n=21	33.3%
RWE	Mazieres 2019	1L+	NR	n=36	16.0%
RWE	Sabari 2018	1L+	INV	n=24	16.7%
RWE	Ryder 2021	2L	INV	n=10	20.0%
RWE	Bittoni 2021	1L	INV	n=52	27.8%
RWE	Ryder 2021	1L	INV	n=51	35.3%
RWE	Ryder 2021	2L	INV	n=27	18.5%
RWE	Bittoni 2021	2L	INV	n=21	30.0%
RWE	Ryder 2020	3L	INV	n=14	7.1%

1.Mazières J, et al. Clin Lung Cancer 2023

Safety of MET TKIs in METex14 skipping NSCLC

	Tepotinib[21] N = 152% All-grade / ≥3 (Unless Stated)	Capmatinib[27] N = 151[a]% All-grade / ≥3 (Unless Stated)	Savolitinib[32] N = 70% All-grade / ≥3 (Unless Stated)	Crizotinib[36] N = 69% All-grade / ≥3 (Unless Stated)
AEs	98	97/66	100/64	
TRAEs	89/28	88/46	100/46	94/29
TRAEs Leading to Dose Reduction	33/NR	NR	NR	38/NR
TRAEs Leading to Discontinuation	11/NR	12/8	14/NR	7/NR
Serious TRAEs	15/NR	15/13	24/14	NR
Deaths (Related or Potentially Related to Treatment)	Respiratory failure and dyspnea	Pneumonitis	Tumor lysis syndrome	Interstitial lung disease
Most Frequently Reported TRAEs in ≥ 10% of Patients				
TRAEs Presented in Original Publication	TRAEs in >5% Patients/Treatment	TRAEs in >10% Patients in Any Cohort	All-cause AEs in >25% Patients	TRAEs in >10% Patients
Peripheral Edema	63/7	50/11	54/9	51/1[b,c]
Nausea	26/1	36/1	46/0	41/0
Diarrhea	22/1	9/0	NR	39/0
Increased Creatinine	18/1	19/0	NR	NR
Hypoalbuminemia	16/2	NR	23/0	NR
Increased Amylase	11/3	8/4	NR	NR
Increased Lipase	9/3	9/7	NR	NR
Decreased Appetite	8/1	13/1	20/0	19/0
Fatigue	7/1	13/3	NR	23/0
Increased AST	7/2	6/3	37/13	17/4[b,d]
Increased ALT	7/3	11/7	39/10	17/4[b,d]
Vomiting	6/0	17/1	26/0	29/0
Vision Disorders	NR	NR	NR	45/0[b]
Constipation	NR	NR	NR	20/1
Bradycardia	NR	NR	NR	16/1[b]
Pyrexia	NR	NR	14/1	NR
Anemia	NR	NR	14/1	NR
Dysgeusia	NR	NR	NR	14/0
Hypokalemia	NR	NR	10/3	NR
Neuropathy	NR	NR	NR	10/0[b]

1.Cortot A, et al. Clin Lung Cancer 2022

HER2 : nonsquamous NSCLC

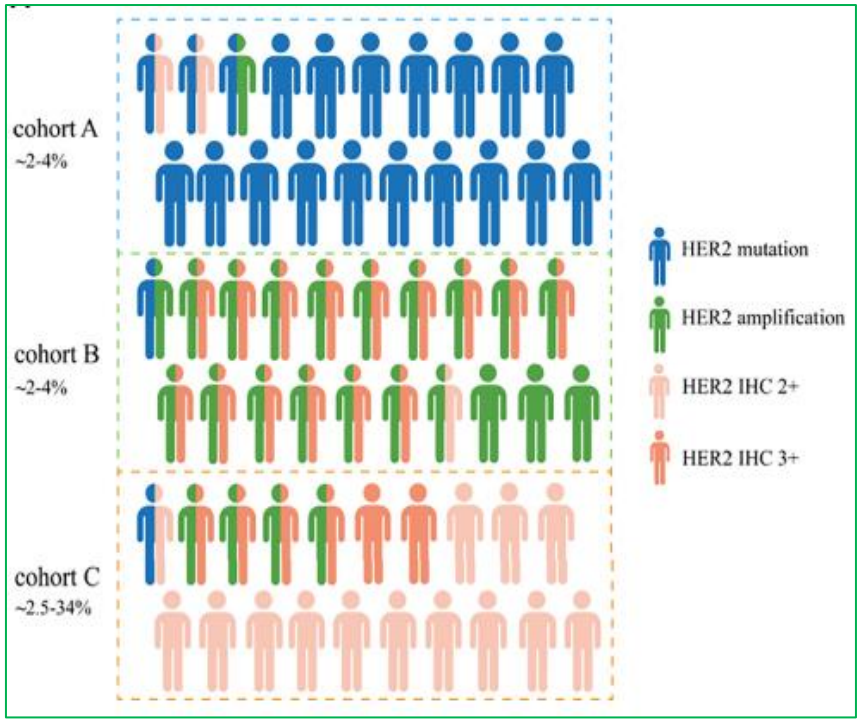
HER2 Amplification

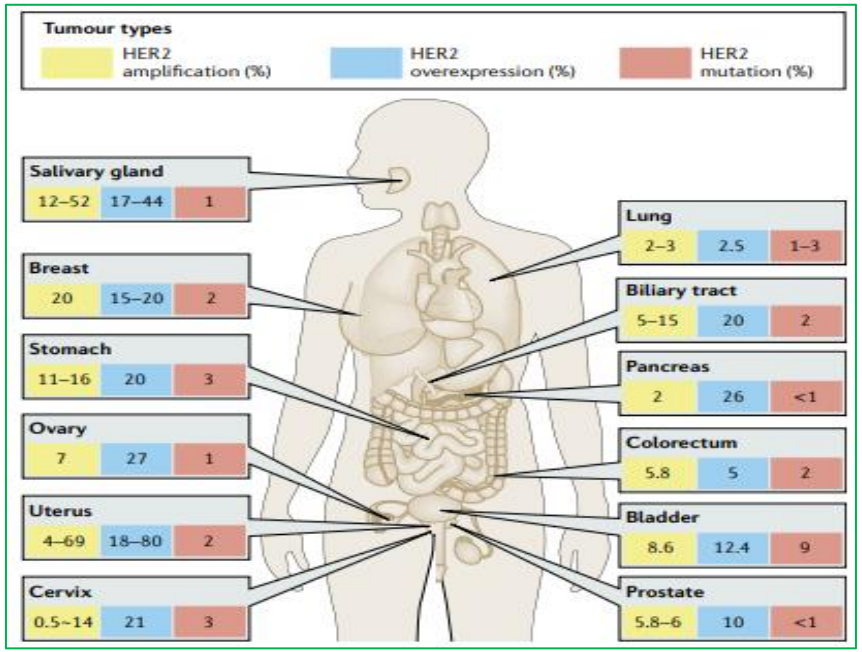
- **Ratio HER2/CEP17 ≥ 2.0 (FISH)**
- **Clinic** : male, smoker (for *de novo* alterations*)*
- Fréquence : 3 % *de novo* (10 % EGFR TKI-resistance)

HER2 overexpression (protein)

- **Clinic** : male, smoker (for de novo alterations*)*
- Frequence : 2 - 20 %
- Positivity criteria (IHC)
  - score 2 + (low to moderate membrane staining, > 10 % of tumor cells)
  - Score 3 + (intense membrane staining > 10 % of tumor cells)

- No correlation between amplification and surexpression
- Amplification et mutation almost mututally exclusive





Yu X, et al. Front Oncol 2022 ; Oh DY, et al. Nat Rev Clin Oncol 2019

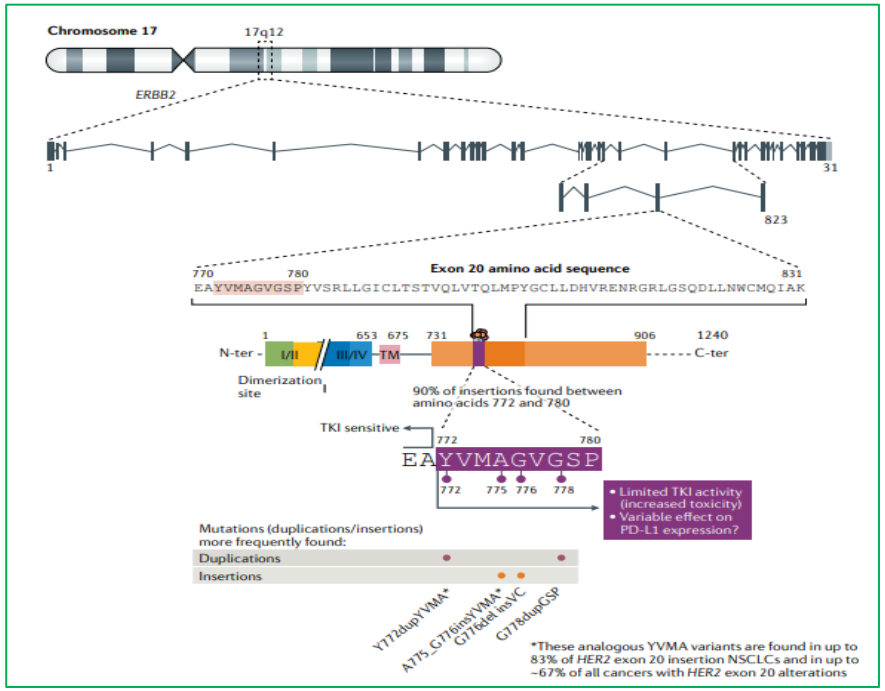
HER2 : nonsquamous NSCLC

HER2

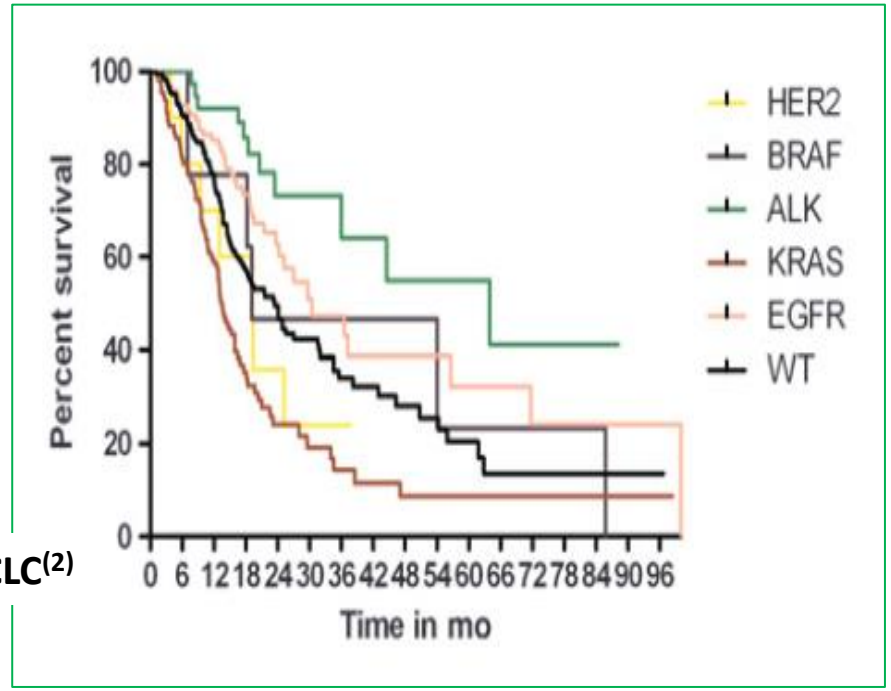
- No specific ligands

Mutations HER2 (duplications ou insertions) [1]

- **Clinic:** Woman, nonsmoker, adenocarcinoma, brain metastases
- Mutually exclusive (KRAS, BRAF, EGFR, ALK, etc)
- Exons 772 – 780 (90 %)
- Dup/ins of 4 aa (codon 775): YVMA (more frequent)
- Fréquence : 2 – 4 %



Cohort of patients with nonsquamous NSCLC[2]



1. Arcilla ME, et al. Clin Cancer Res 2012 ; 2. Oh DY, et al. Nat Rev Clin Oncol 2019

Trials with Tyrosine Kinase Inhibitors in HER2 exon 20 mutation NSCLC

Trials	TKI-anti-HER2	HER2 alterations	n	ORR (%)	DoR (months)	PFS (months)	OS (months)
Wang J [1]	Pyrotinib	Mutation	15	53.3	7.2	6.4	-
Zhou C [2]	Pyrotinib	Mutation	60	31.7	6.9	6.9	14.4
Song Z [3]	Pyrotinib	Mutation	78	19.2	-	5.6	10.5
Song Z [4]*	Pyrotinib	Amplification	27	22.2	7.2	6.3	12.5
Elamin YY [5]	Poziotinib	Mutation	30	27	5.0	5.5	15
Le X[6] (ZENITH 20)	Poziotinib	Mutation	90	27.8	5.5	5.1	-
Smit EF [6] (ETOP NICHE)	Afatinib	Mutation	13	7.7	-	3.7	13.1
Lai V [7] (retrospective)	Afatinib	Mutation	27	13	6	3.0	-
Gandhi L (PUMA-NER – 420)	Neratinib +/- Temsirolimus	Mutation	60	0 8.8		3 4.1	10 15.8

*48.1 % pre-treated with TKI-anti-EGFR ; 44.4 % with AGA (EGFR, ALK, MET, KRAS)

1. Wang J, et al. Ann Oncol 2019; 2. Zhou C, et al. J Clin Oncol 2020 ; 3. Song Z, et al. BMS Med 2022 ; 3. Song Z, et al. 4. Clin cancer Res 2022; 5. Elamin YY, et al. J Clin Oncol 2022 ; 6. Le X, et al. J Clin Oncol 2022 ; 6. Smit ET, et al. ASCO 2017; 7. Lai V, et al. Eur J Cancer 2019. 8. Gandhi L, et al. IASLC 2017.

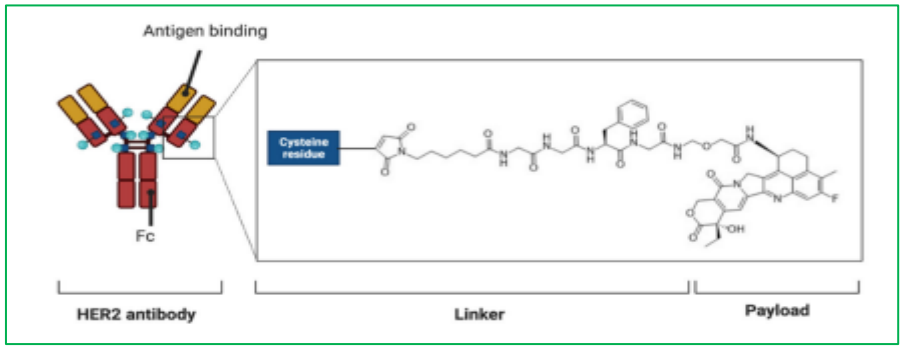
Trials including traztuzumab or T-DM1 in HER2 exon 20 mutation NSCLC

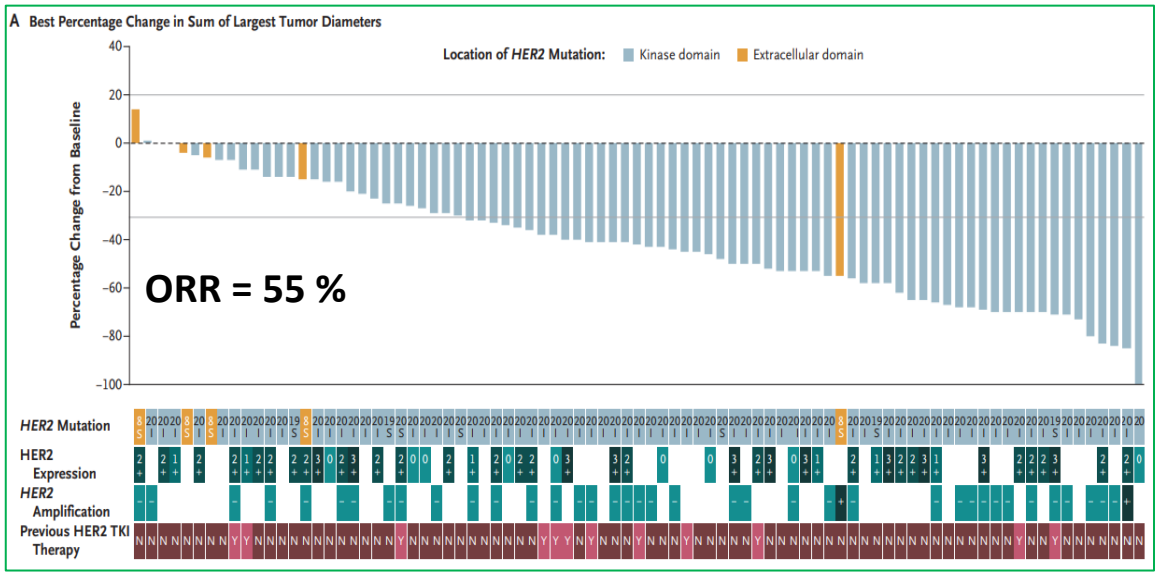
Trials	TKI-anti-HER2	HER2 alterations	n	ORR (%)	PFS (months)	OS (months)
Kinoshita I [1]	Traztuzumab	HER2 IHC 2/3+ or mutation	10	0	5.2	-
Lara PN [2]	Traztuzumab +/- Docetaxel	HER2 IHC 2/3+	13	0		5.7
Langer C [3]	Traztuzumab + Gem + CisP	HER2 IHC 1 + or ELISA	21	38	9	
Zinner RG[4]	Traztuzumab + Pacl + Carbo	HER2 IHC ≥ 1 +	56	24.5	3.3	10.1
Gatzemeir U[5]	Gem + CisP +/- Traztuzumab	HER2 IHC 2/3+ or HER2/CEPratio ≥ 2 or ELISA	101	Control arm: 41 (50, HER2 3+) Traztuzumab: 36 (83, HER2 +)	Control arm: 7.0 Traztuzumab: 6.1	Control arm: NR Traztuzumab: 12.2
Li BT [6]	T-DM1	Mutation	18	44	5	-
Peters S [7]	T-DM1	HER2 IHC 2+ HER2 IHC 3+	29 20	0 20	2,6 2,7	12,2 15,3
Van Berge Henegouwen JM [8]	Pertu + Traztu (zumab)	Mutation	24	8.3	4	10
Mazieres J [9]	Pertu + Traztu (zumab) + docetaxel	Mutation	45	29	6.8	17.6

1. Kinoshita I, et al. ESMO 2018; 2. Lara PN, et al. Lung Cancer 2004 ; 3. Langer C, et al. Lung Cancer 2004; 4. Zinner RG, et al. Lung Cancer 2004 ; 5. Gatzemeir U , et al. Ann Oncol 2004; 6. Li BT, et al. J Clin Oncol 2018. 7. Peters S, et al. Clin Cancer Res 2018; 8. Van Berge Henegouwen JM, et al. Eur J Cancer 2022; 9. *Mazieres J, et al. J Clin Oncol 2022*

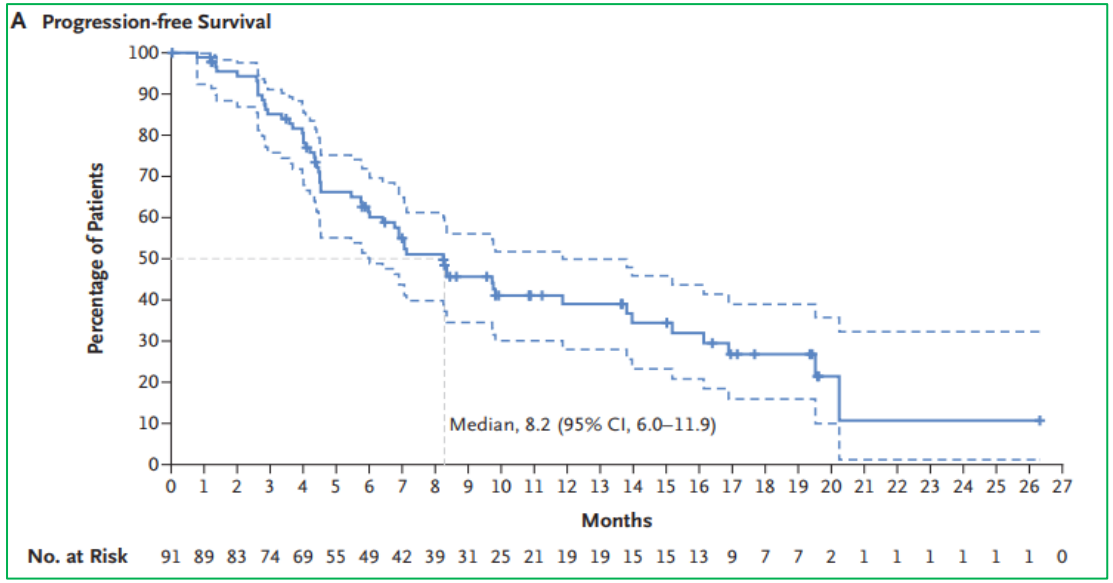
Nonsquamous NSCLC with HER2 mutation: DESTINY-Lung01

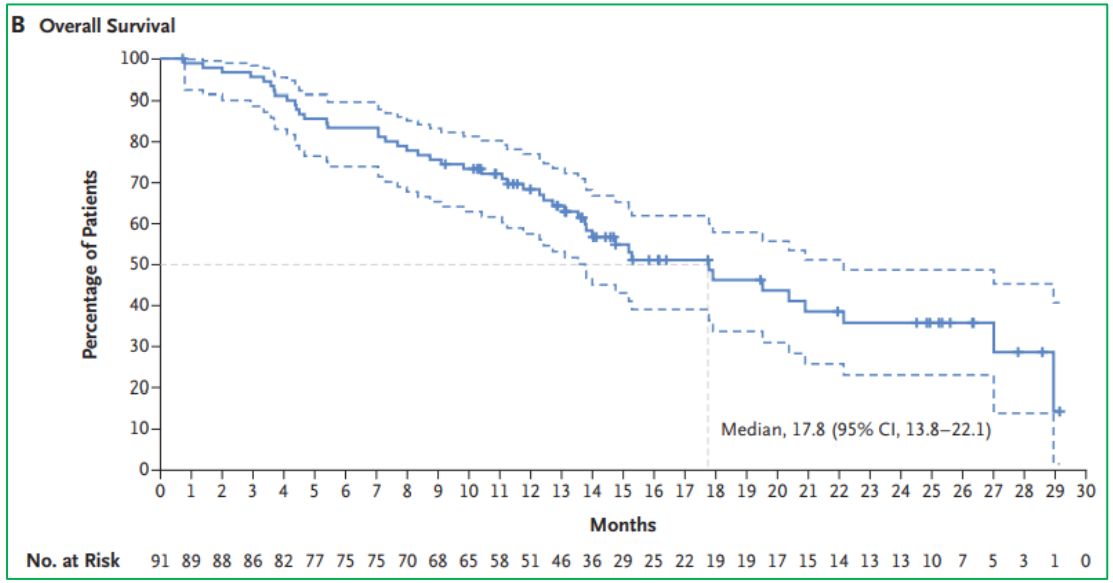
(after failure to standard treatment)





Median Duration of response 9.3 mois

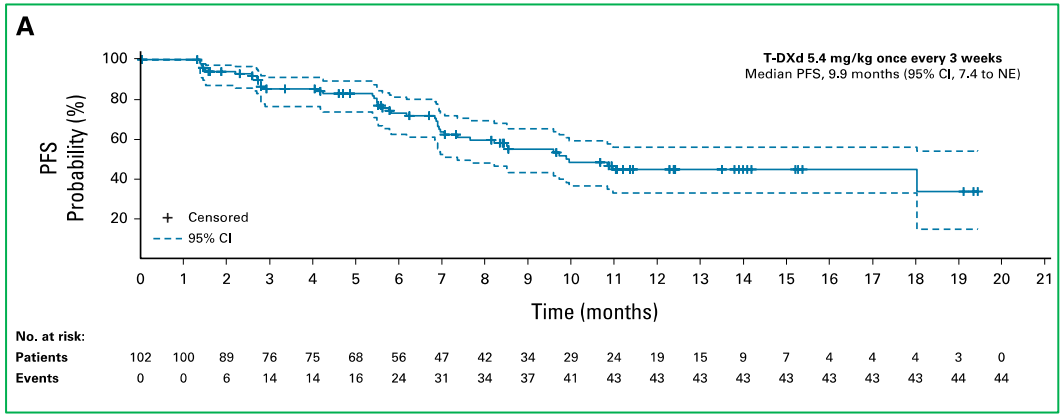




Li BT. et al. et al. N Engl J Med 2021

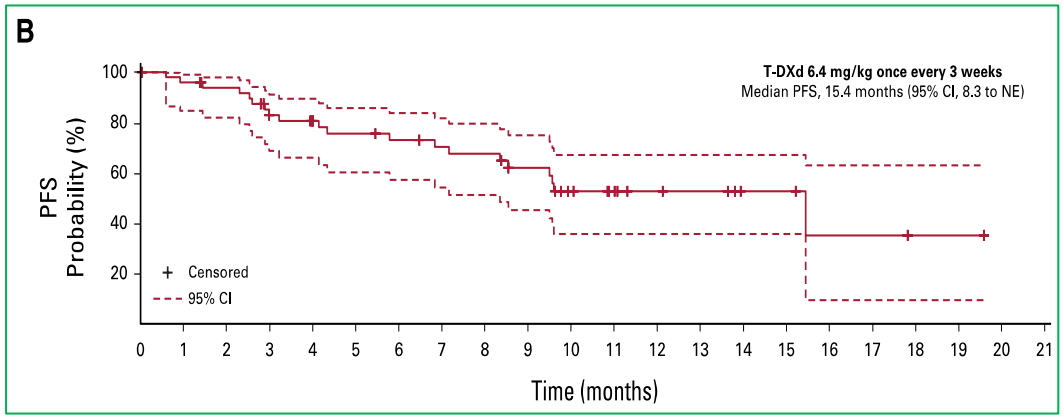
Nonsquamous NSCLC with HER2 mutation: DESTINY-Lung02

Traztuzumab-Deruxtecan	5.4 mg/kg d1 - d21 n=102	6.4 mg/kg d1 – d21 n=50
Median age (y.)	59.4 (31 – 84)	61.3 (28 – 86)
Femme (n, %)	65 (63.7 %)	34 (68 %)
Non-smokers (n, %)	55 (53.9)	29 (58)
Brain metastases (n, %)	35 (34.3)	22 (44.0)
Previous lines	2 (1 – 12)	2 (1 – 7)



OS : 19.5 months (95%CI, 13.6 – NE)

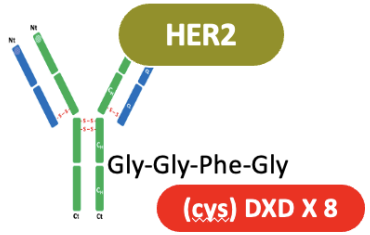
Response Assessment by BICR	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
Best confirmed overall response, No. (%)		
CR	1 (1.0)	2 (4.0)
PR	49 (48.0)	26 (52.0)
SD	45 (44.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Nonevaluable[a]	3 (2.9)	2 (4.0)
DCR, No. (%)	95 (93.1)	46 (92.0)
95% CI	86.4 to 97.2	80.8 to 97.8
DoR, months, median (95% CI)	16.8 (6.4 to NE)	NE (8.3 to NE)
TTIR, months, median (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Follow-up, months, median (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)



OS : NR (95%CI, 12.1 – NE)

Goto K, et al. J Clin Oncol 2023

Nonsquamous NSCLC with HER2 mutation : DESTINY-Lung02



Traztuzumab-Deruxtecan

TABLE 3. Most Common (≥20% of patients) Treatment-Emergent Adverse Events in Patients With Human Epidermal Growth Factor Receptor 2–Mutant Metastatic Non–Small-Cell Lung Cancer Treated With T-DXd

	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)		T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50),[a] No. (%)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	68 (67.3)	4 (4.0)	41 (82.0)	3 (6.0)
Neutropenia[b]	43 (42.6)	19 (18.8)	28 (56.0)	18 (36.0)
Fatigue[b]	45 (44.6)	8 (7.9)	25 (50.0)	5 (10.0)
Decreased appetite	40 (39.6)	2 (2.0)	25 (50.0)	2 (4.0)
Anemia[b]	37 (36.6)	11 (10.9)	26 (52.0)	8 (16.0)
Vomiting	32 (31.7)	3 (3.0)	22 (44.0)	1 (2.0)
Constipation	37 (36.6)	1 (1.0)	16 (32.0)	0
Leukopenia[b]	29 (28.7)	5 (5.0)	17 (34.0)	8 (16.0)
Thrombocytopenia[b]	28 (27.7)	6 (5.9)	14 (28.0)	5 (10.0)
Diarrhea	23 (22.8)	1 (1.0)	18 (36.0)	2 (4.0)
Alopecia	22 (21.8)	0	17 (34.0)	0
Transaminases increased[b]	22 (21.8)	3 (3.0)	10 (20.0)	0

TABLE 4. Overall Safety Summary and Adjudicated Drug-Related ILD

Type of AE	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50),[a] No. (%)
Any-grade TEAEs	101 (100.0)	50 (100.0)
Drug-related	97 (96.0)	50 (100.0)
Grade ≥ 3 TEAEs	53 (52.5)	33 (66.0)
Drug-related	39 (38.6)	29 (58.0)
Serious TEAEs	37 (36.6)	20 (40.0)
Drug-related	14 (13.9)	12 (24.0)
TEAEs associated with drug discontinuation	15 (14.9)	13 (26.0)
Drug-related	14 (13.9)	10 (20.0)
TEAEs associated with dose reduction	18 (17.8)	16 (32.0)
Drug-related	17 (16.8)	16 (32.0)
TEAEs associated with drug interruption	45 (44.6)	31 (62.0)
Drug-related	27 (26.7)	24 (48.0)
TEAEs associated with an outcome of death	6 (5.9)[b]	2 (4.0)[c]
Drug-related	1 (1.0)	1 (2.0)
Adjudicated drug-related ILD[d]		
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)
Total (95% CI)	13 (12.9) (7.0 to 21.0)	14 (28.0) (16.2 to 42.5)

Goto K, et al. J Clin Oncol 2023

DESTINY-Lung02: Drug-Related Interstitial Lung Disease

ILD, n (%)	T-DXd 5.4 mg/kg (n = 101)	T-DXd 6.4 mg/kg (n = 50)
Any grade	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)
Median time to onset, d (range)	88.0 (40-421)	83.5 (36-386)

Goto K, et al. J Clin Oncol 2023

BRAF mutation

- RAF
  - Rapidly Accelerated Fibrosarcoma
- Serine threonine kinase
- 300 distinct BRAF mutations
  - V600
  - nonV600

- **Melanoma** (40 – 60 %)
  - V600E, V600K
- **Papillary thyroid carcinoma** (45 %)
  - V600E
- **Colorectal carcinoma** (5-15 %)
  - V600E
- **Ovarian tumors** (35 %)
  - V600E
- **Gliomas** (60 – 80 %, pilocytic astrocytomas)
  - K1AA1549-BRAF fusion, V600E, BRAFFins598T
- **Nonsquamous NSCLC** (1 – 3 %)
  - V600E, G469A
- **Biliary tract cancer** (5 – 7 %)
  - V600E
- **Pancreatic cancer** (2 – 3 %)
  - V600E
- **Hepatocellular carcinoma** (> 1%)

Incidence

BRAF mutation

all human cancers

≈

8 %

Pakneshan S. et al. Pathology 2013; Davies H, et al. Nature 2002

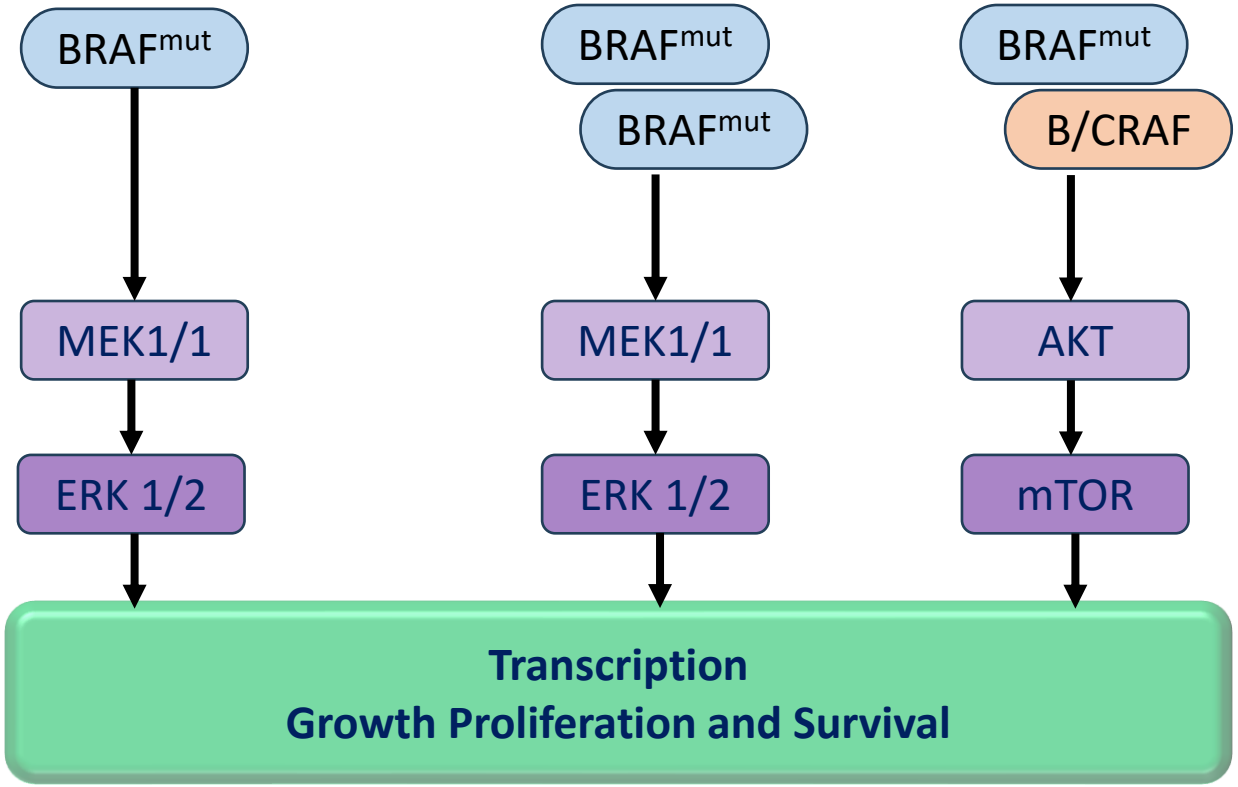
RAF : Rapidly Accelerated Fibrosarcoma

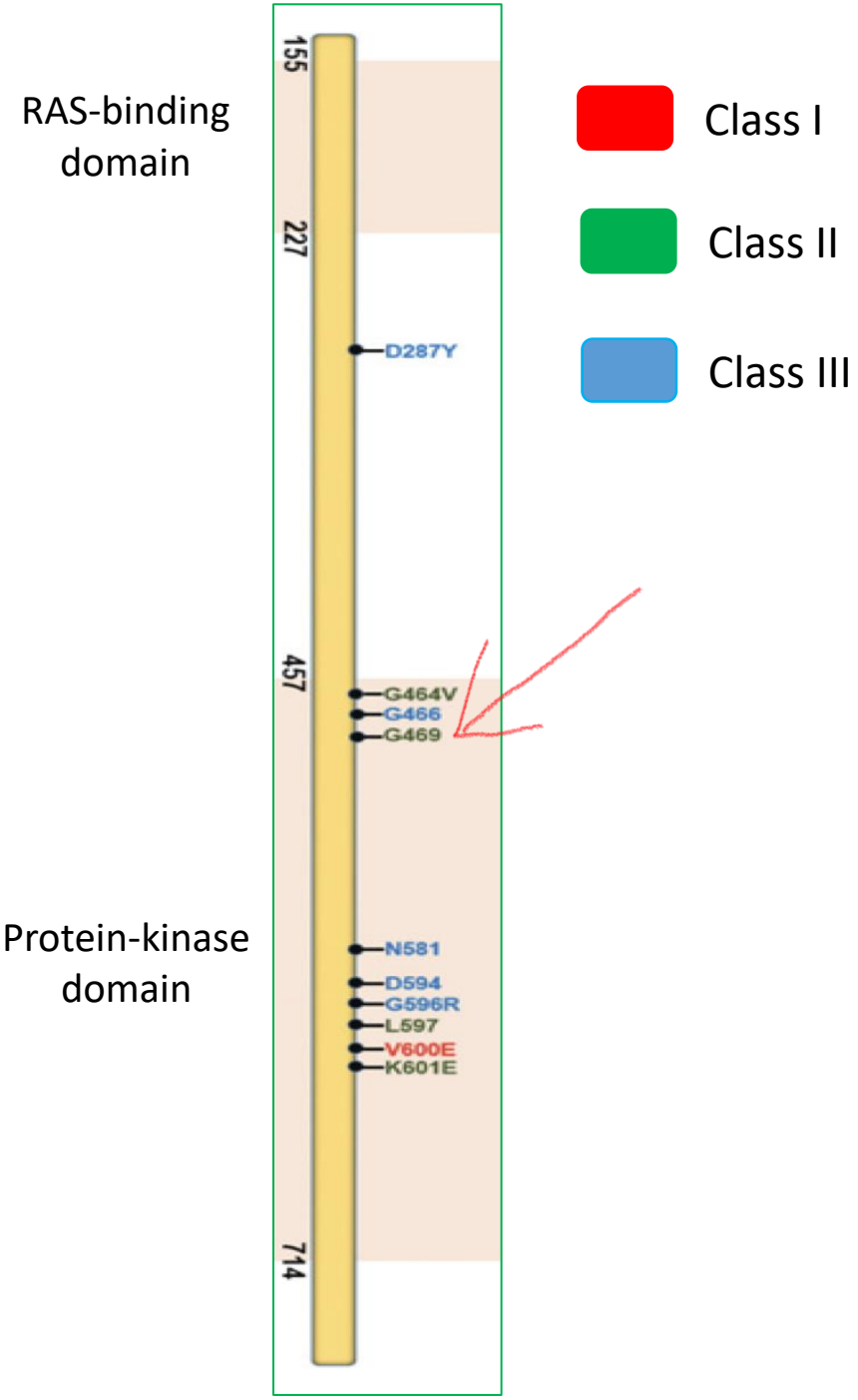
Classification of BRAF mutations

Class I
- **RAS independant monomers**
- **V600 E/K/D/R**

Class II
- **RAS independant dimers**
- **Non V600**

Class III
- **RAS dependant dimers**
- **Impaired kinase activity through CRAF**





Dagogo-Jack I, et al. Clin Cancer Res 2019, Puri M, et al. Front Oncol 2023

TKI targeting BRAF V600E mutation

Vemurafenib, Trametinib, Encorafenib

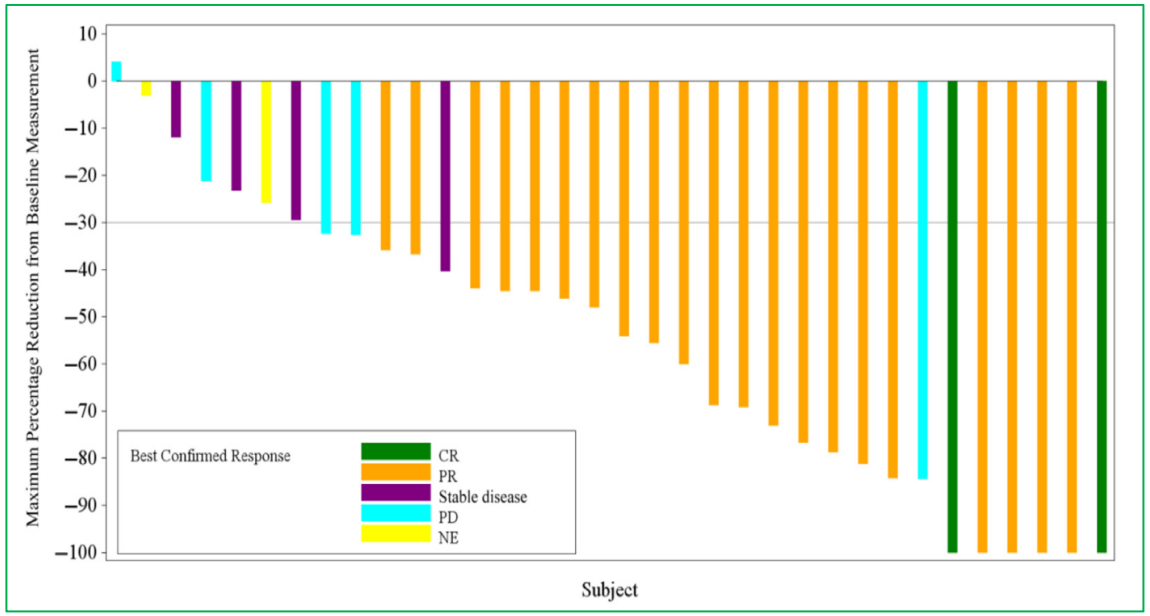
Dabrafenib, Binimetinib

Trials	BRAF-TKI	n	Lines of treatment	ORR (%)	PFS (months)	OS (months)
VE Basket Trial [1]	Vemurafenib	62	54 pretreated	37	6.1	15.4
Phase 2			8 naive	37.5	12.9	NR
EURAF [2]	Vemurafenib	24				
Retrospective	Dabrafenib	9	Pretreated and naive	54 %	5	10.8
	Sorafenib	1				
Mazieres J[3]	Vemurafenib	101 V600	Pretreated	44.9	5.2	10
Phase 2		17 non-V600		0	1.8	5.2
Planchard D[4,5]						
Cohorte A	Dabrafebinib	84	78 Pretreated, 6 naive	33, NA	5.5, NA	12.7, NA
Cohorte B	Dabrafenib +Trametinib	57	Pretreated	68	10.2	18.2
Cohorte C	Dabrafenib +Trametinib	36	Naive	64	10.8	17.3
IFCT BLaDE [6]	Dabrafenib +Trametinib	119	≥ L2	73.8	10.4	19.7
retrospective		44	naive	82.9	18.2	24.1

1. Subbiah V. et al. JCO Precis Oncol 2019; 2. Gautshi O, et al. J Thorac Oncol 2015; 3. Mazières J. et al. Ann Oncol 2020; 4. Planchard D. et al. Lancet Oncol 2016; 5. and J Thorac Oncol 2021; 6. Swalduz A, et al. ASCO 2022

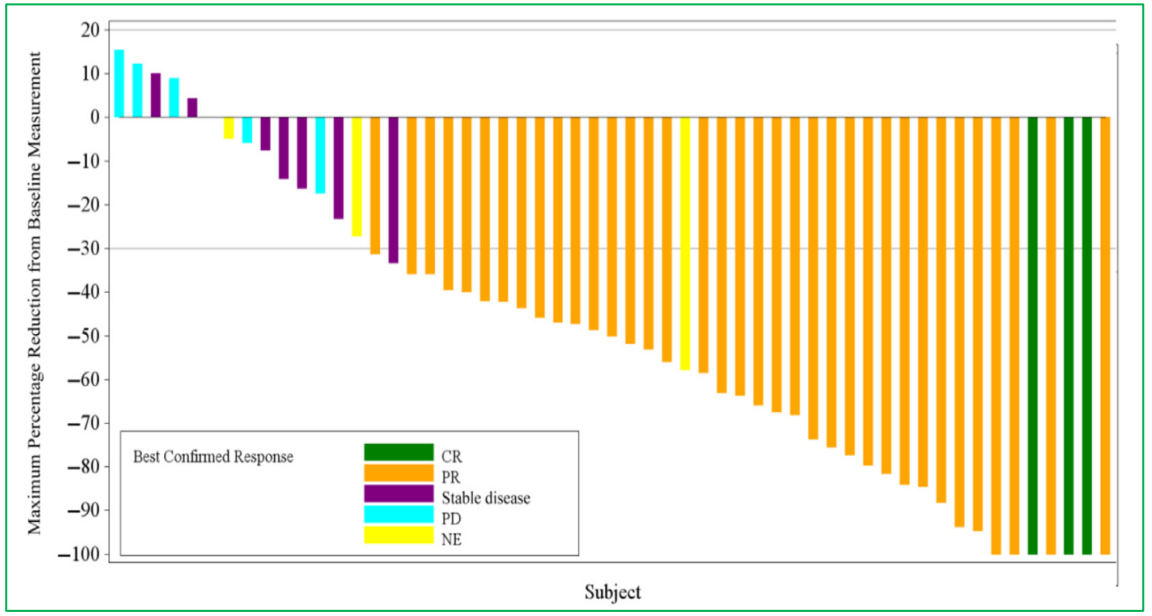
Phase 2 : Dabrafenib + Trametinib in BRAFV600E mutant NSCLC

Treatment naive (n=36)



ORR (%) 63.9 ; DCR (%) 75

Pre-treated (n=57)



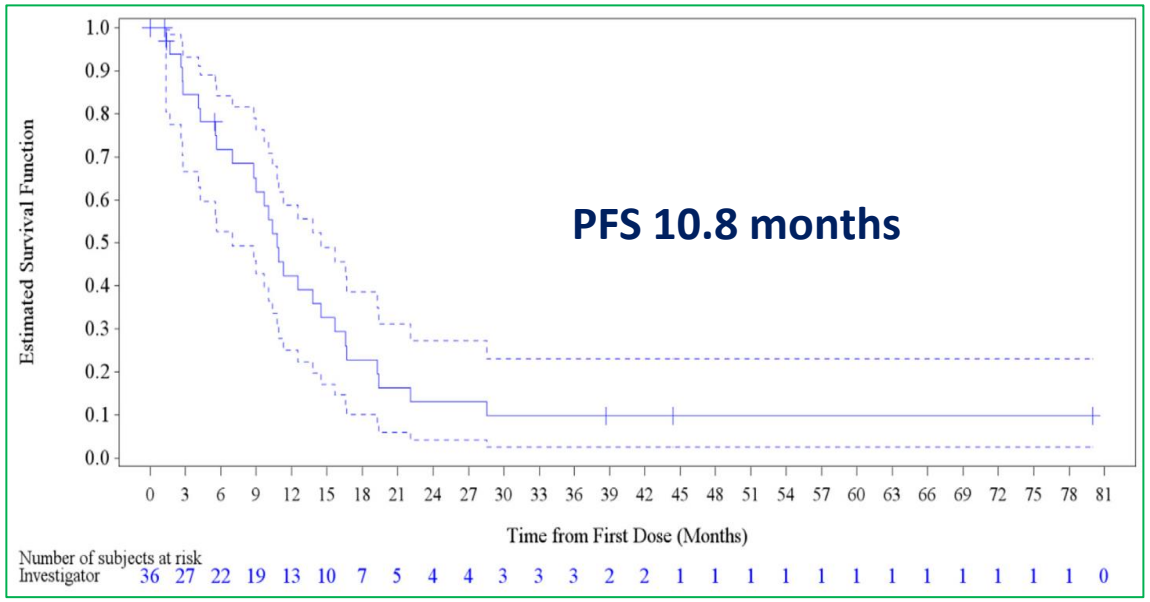
ORR (%) 68.4 ; DCR (%) 80.7

Planchard D, et al. Lancet Oncol 2016; Planchard D, et al. J Thorac Oncol 2021

Phase 2 : Dabrafenib + Trametinib

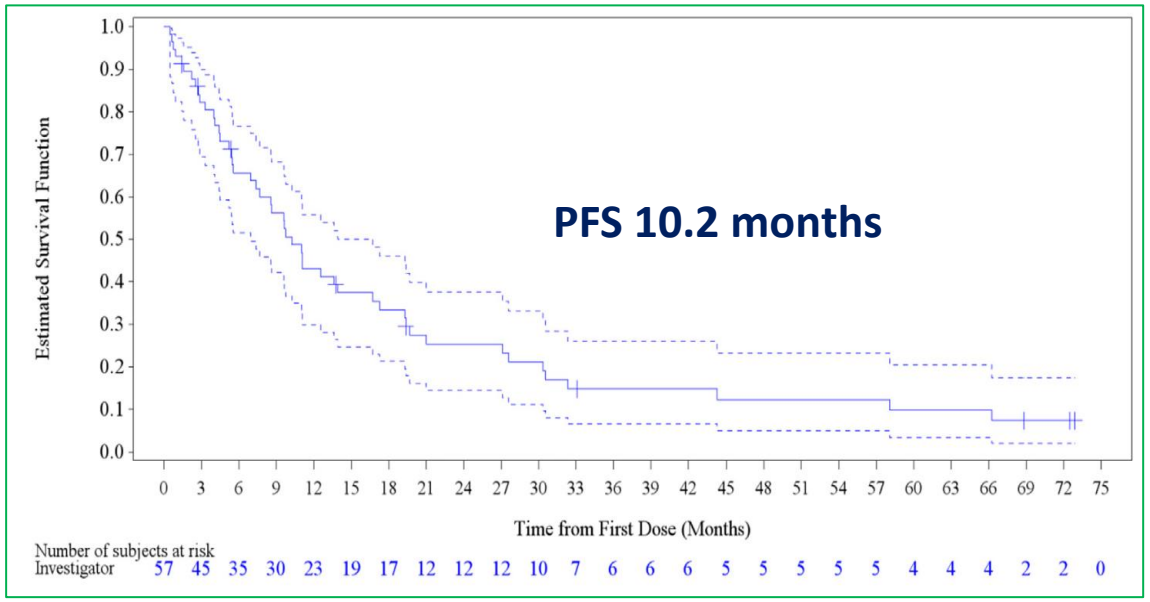
BRAFV600E mutant nonsquamous NSCLC

Treatment naive (n=36)



OS 17.3 months ; DoR 10.2 months

Pre-treated (n=57)



OS 18.2 months ; DoR 9.8 months

Planchard D, et al. Lancet Oncol 2016; Planchard D, et al. J Thorac Oncol 2021

Phase 2 : Dabrafenib + Trametinib (Toxicities)

BRAFV600E mutant nonsquamous NSCLC

Any grade

- pyrexia (56%)
- nausea (51%), vomiting (41%)
- Fatigue (29 %)
- Arthralgia (27 %)
- Chills (27 %)
- Headache (20 %)
- dry skin (39%), rash (29 %)
- peripheral edema (38%)
- diarrhea (37%)
- decreased appetite (33%)
- cough (31%)

Grade ≥ 3

- **Hypertension (10 %)**
- **Hyponatremia (9 %)**
- **Neutropenia (8 %)**, anemia (4 %)
- Pyrexia (6%)
- Dyspnea (8 %)
- increased AST (3 %), ALT (6 %)
- Fatigue (3 %)
- Vomiting (3 %)
- Diarrhea (2 %)
- Rash (2 %), Dry skin (1 %)
- Arthralgia (1 %)
- Headache (1 %)

Skin toxicities of Dabrafenib

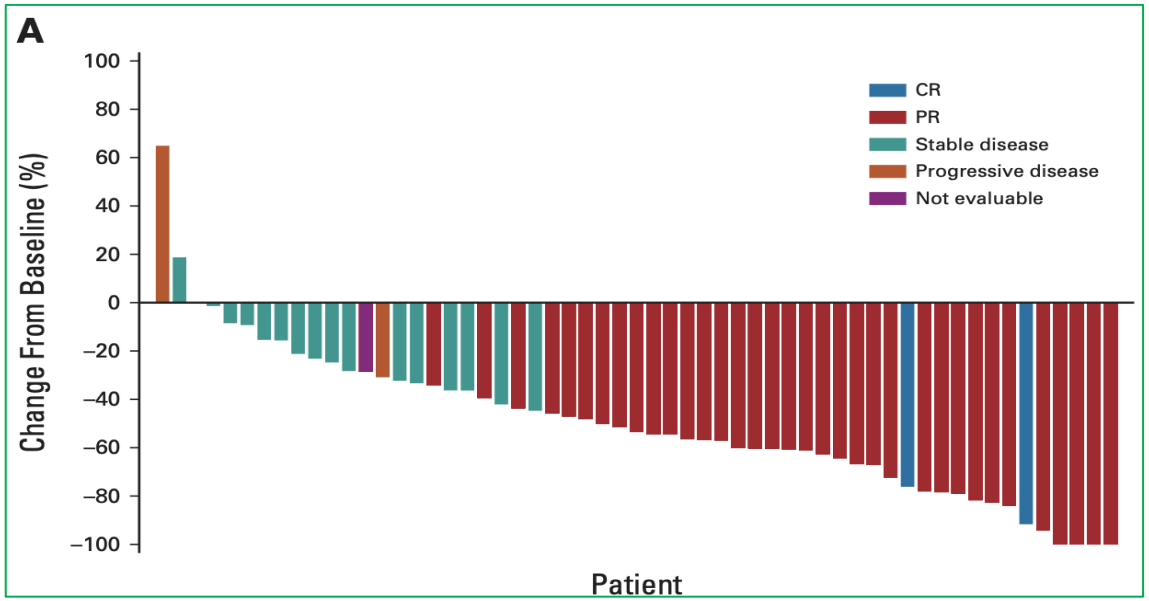
- Plantar-Palmar hyperkeratosis
- Papilloma
- Squamous Cell Carcinoma
- Keratoacanthoma
- Basal Cell Carcinoma

Planchard D, et al. J Thorac Oncol 2021

Phase 2 : Encorafenib + Binimetinib

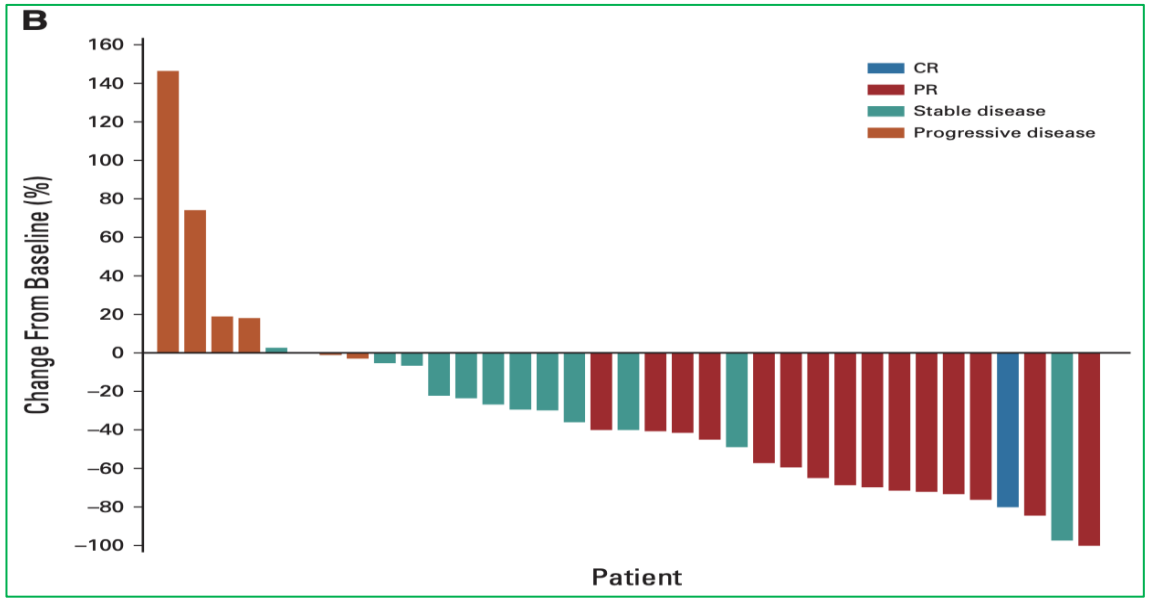
BRAFV600E mutant nonsquamous NSCLC

Treatment naive (n=59)



ORR (%) 75 ; DCR (%) 83

Pre-treated (n=39)



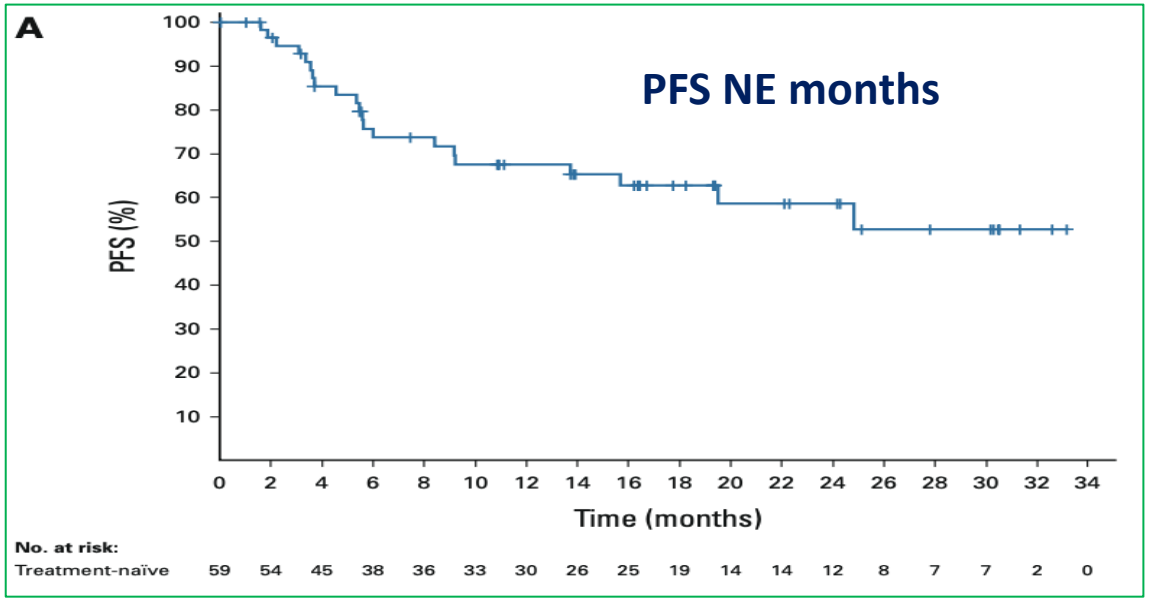
ORR (%) 46 ; DCR (%) 79

Riely GJ, et al. J Clin Oncol 2023

Phase 2 : Encorafenib + Binimetinib

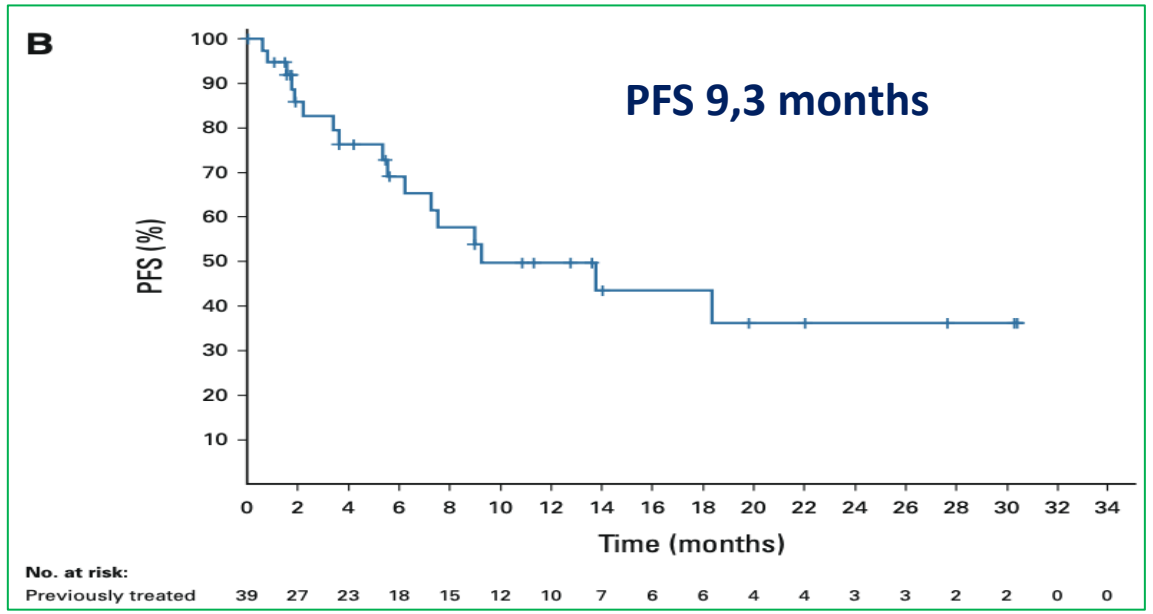
BRAFV600E mutant nonsquamous NSCLC

Treatment naive (n=59)



DoR (months) NE

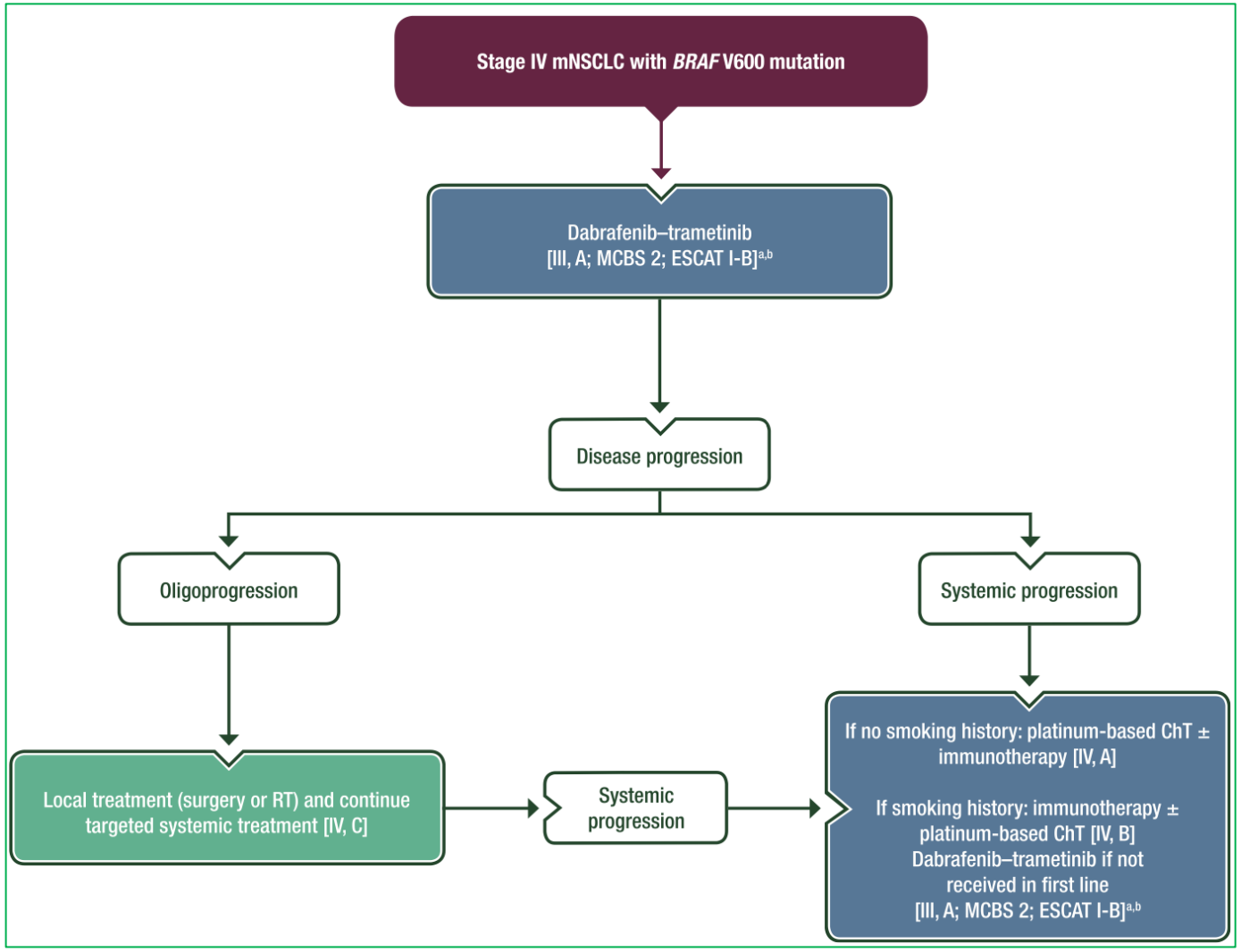
Pre-treated (n=39)



DoR (months) 16.7

Riely GJ, et al. J Clin Oncol 2023

ESMO Guidelines



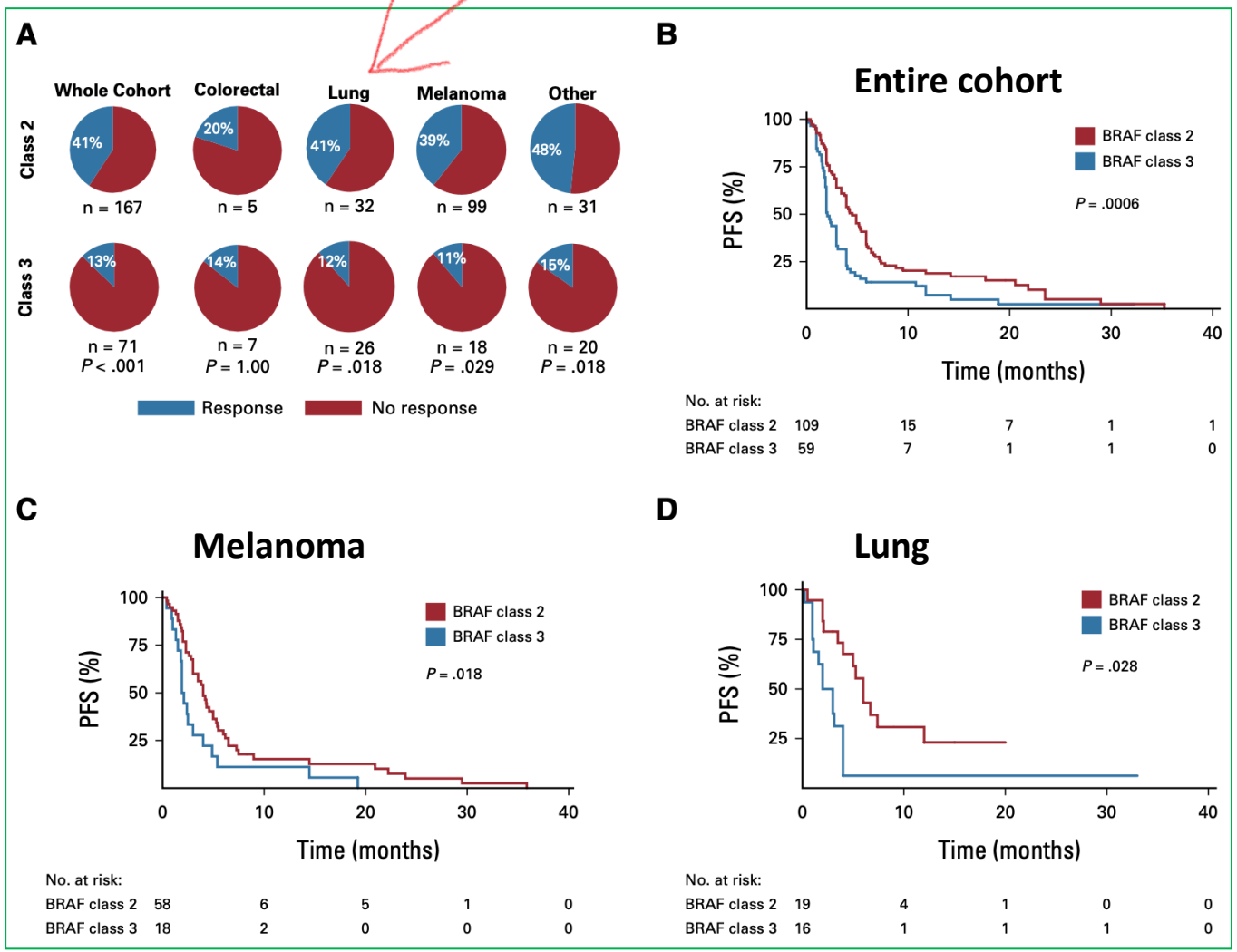
BRAF - MEK inhibition using dabrafenib – trametinib is recommended [III, A; ESMO-MCBS v1.1 score: 2; ESCAT: I-B].

If patients have received BRAF - MEK inhibition in the first-line setting, they may be offered platinum-based ChT with or without immunotherapy in the second-line setting, **if they do not have a smoking history** [IV, A].

For patients with a smoking history, immunotherapy with or without ChT should be considered as per the ESMO CPG on non-oncogene-addicted mNSCLC [IV, B]

Hendricks LE, et al. Ann Oncol 2023

Clinical Activity of MAP Kinase–Targeted Therapies in Patients with Non–V600 BRAF-Mutant Tumors



BRAF Class	Mutation	
2	L597V/S/R/Q/P/K[a]	L525R
	K601E/N[a]	L485W/F
	A598V/T599insV[a]	V600_K601del[a]
	T599I/dup/V600insT[a]	V600_K601D/E/N[a]
	G464V/E[b]	V600_K602delinsDT[a]
	N486_P490del	V600_W604delinsDQTDG[a]
	G469V/S/R/L/A/T170delinsAK[b]	BRAF fusions
3	D594N/G/F[a]	F595L[a]
	G466E/V/A[b]	T470R
	N581S/T/I[b]	Q524L
	G596V/R[a]	
	G469E[b]	
	S467L[b]	

Dankner M, et al. JCO Precis Oncol 2022

RET fusions

Why the clinician should know it ?

Phase 1/2 Libretto-001

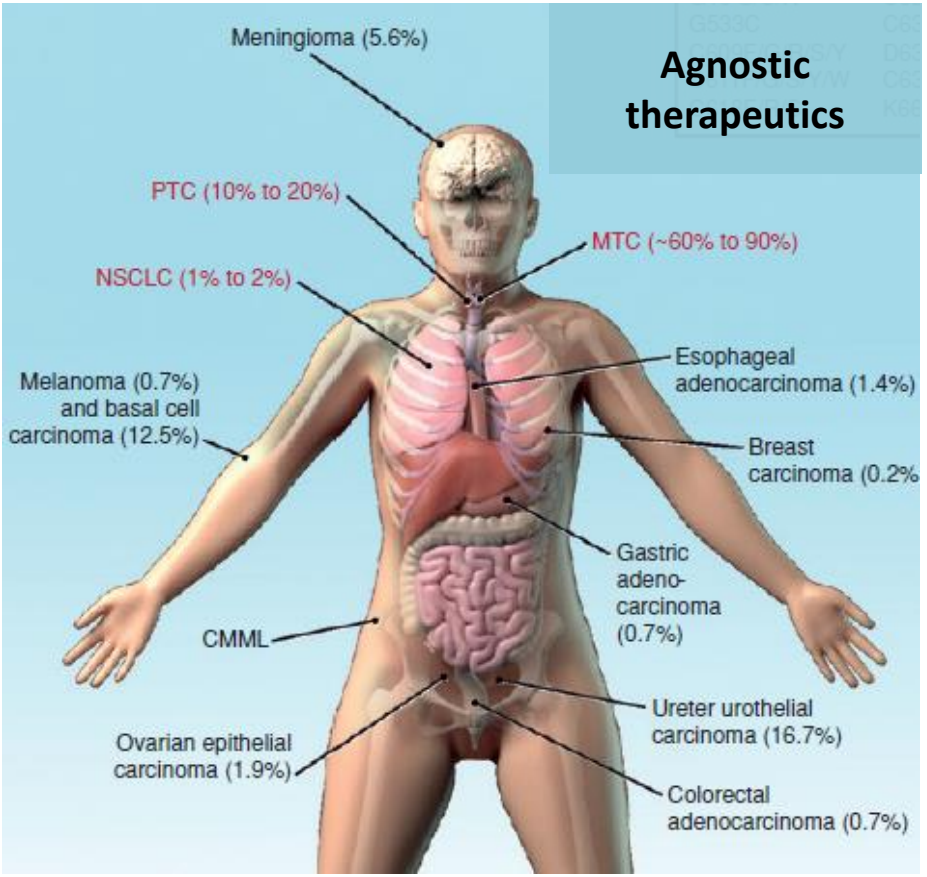
Selpercatinib (1)

NSCLC

Pralsetinib (2)

- **ORR > 60 %**
- **Median PFS > 16 months**

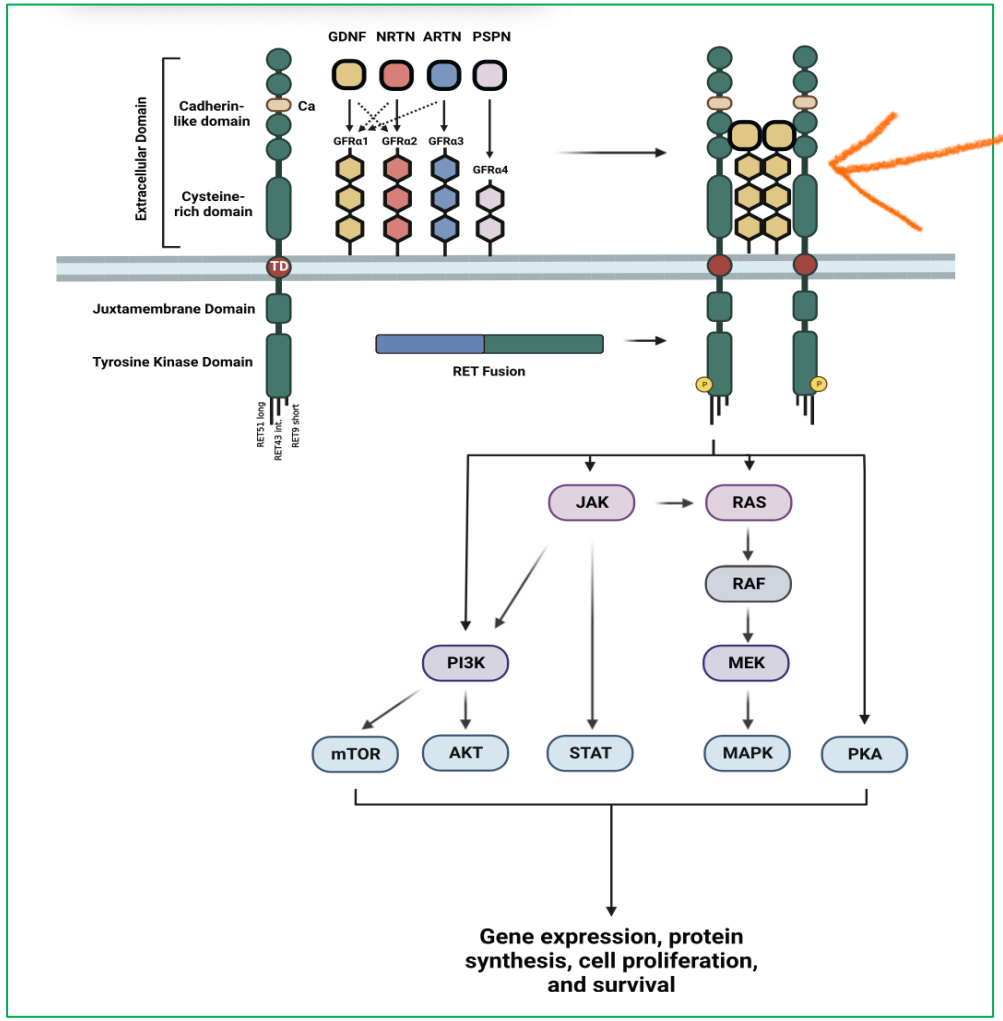
Phase 1/2 Arrows



- A rare event: 1 - 2 % of NSCLC, Young, non smoker
- Poorly differenciated nonsquamous histology, PD-L1 0
  - ➢ solid. ou lepidic. or papillary histology

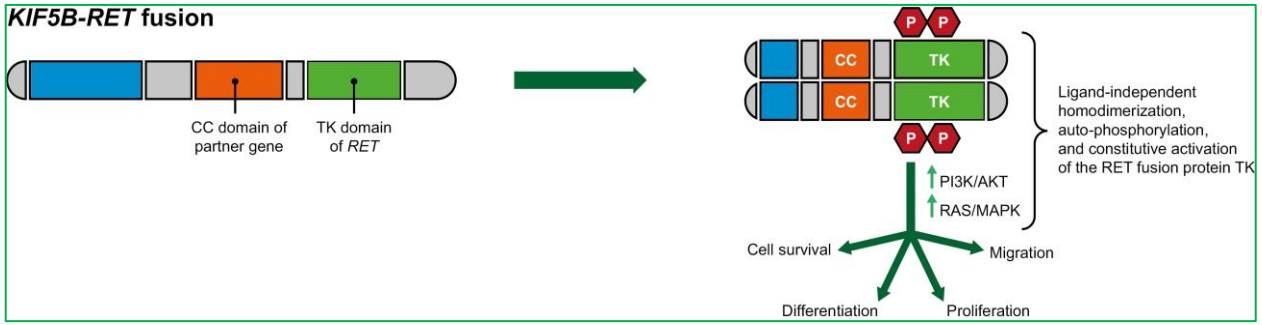
1. Drillon A. et al. N Engl J Med 2020 ; 2. Gainor JF. et al. Lancet Oncol 2021

RET fusion



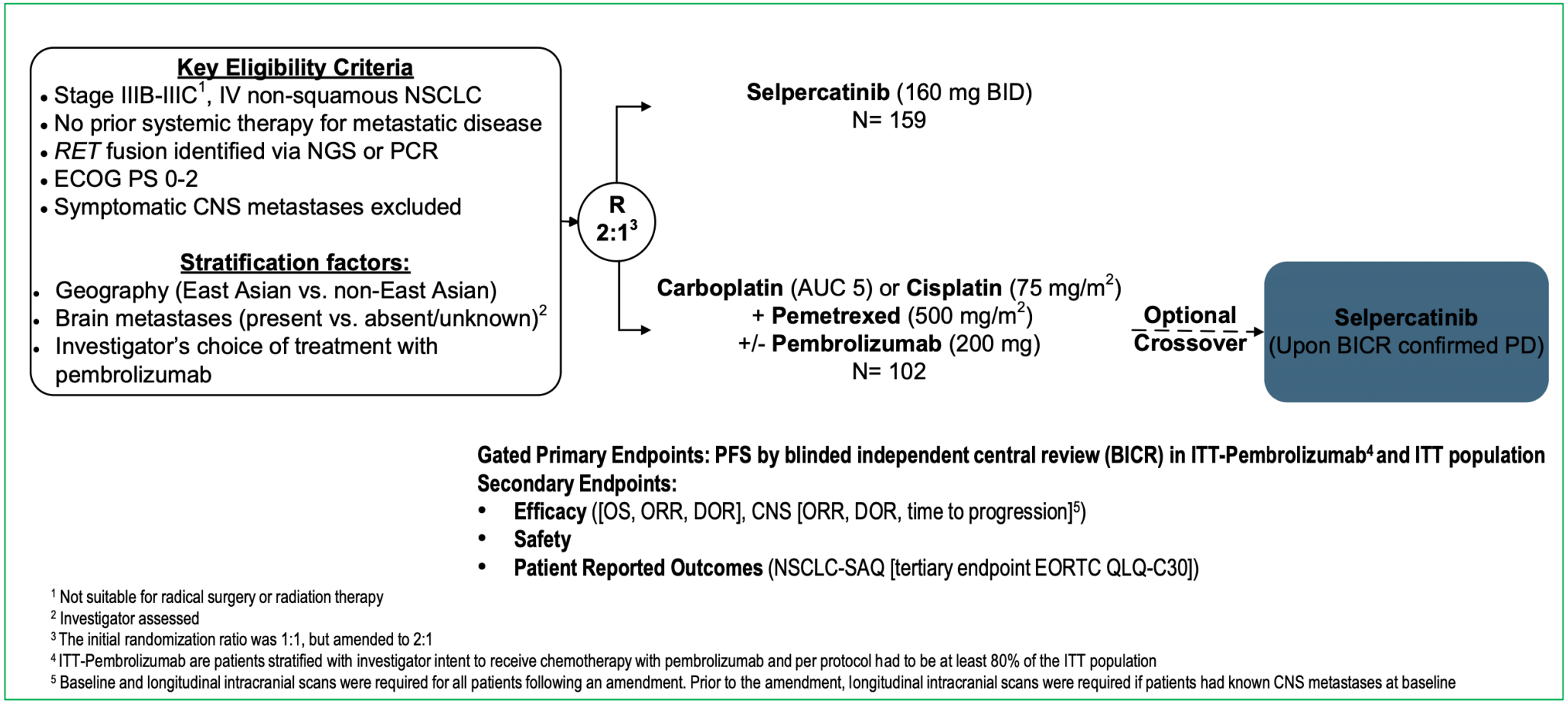
Hetero-dimeric complex

- GDNF family ligands : GDNF, NRTN, ARTN, PSPN
- GFRα family co-receptors : GFR α1 - 4



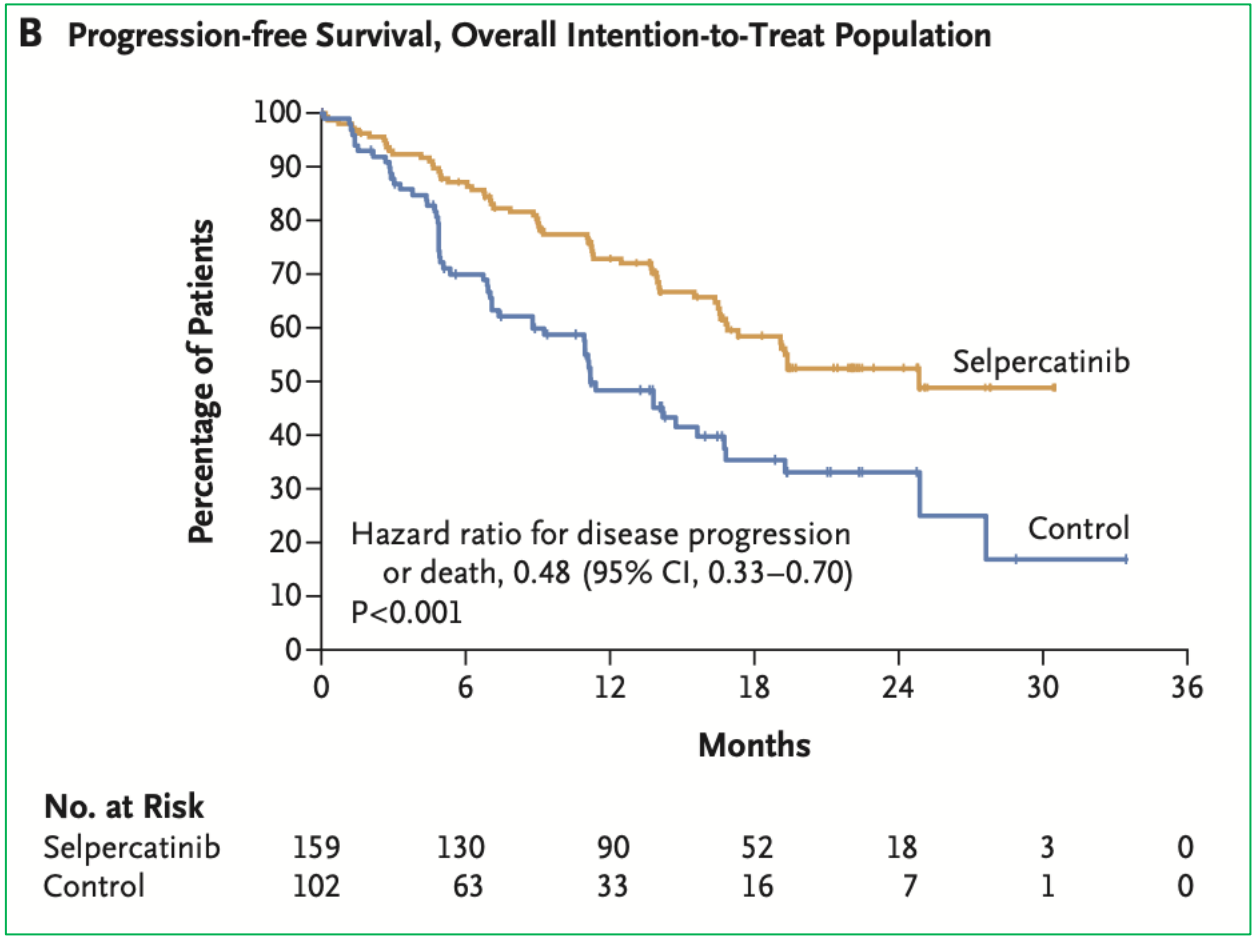
1. Nardo M, et al. Cell Reports Med 2023; Novello S, et al. Oncologist 2023

LIBRETTO-431
Randomized phase 3 trial



1. Zhou C, et al. N Engl J Med; Loong HH, ESMO 2023

LIBRETTO-431
Randomized phase 3 trial



	Selpercatinib	Control
n	159	102
PFS (month)	24.8	11.2
ORR (%)	84	63
- CR	12 (8)	5 (5)
- PR	121 (76)	59 (58)
- SD	17 (11)	26 (25)
- PD	2 (1)	7(7)
- NE	7 (4)	5 (5)
DoR (month)	24.2	12.0

1. Zhou C, et al. N Engl J Med

LIBRETTO-431

Randomized phase 3 trial

Table 1. Common side effects occurring with selpercatinib and pralsetinib

	Selpercatinib	Pralsetinib
Most common adverse events	• fatigue • hypertension • constipation • diarrhea • nausea • edema • dry mouth • abdominal pain • rash • headache	• fatigue • hypertension • constipation • diarrhea • musculoskeletal pain
Most common grade 3 or 4 laboratory abnormalities	• decreased lymphocytes • increased ALT • increased AST • decreased sodium • decreased calcium	• decreased lymphocytes • decreased neutrophils • decreased hemoglobin • increased ALT • increased AST • decreased sodium • decreased phosphate • decreased calcium • decreased platelets • increased alkaline phosphatase

Table 3. Adverse Events That Occurred during Treatment (Safety Population).*

Event	Selpercatinib (N=158)		Control (N=98)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	158 (100)	111 (70)	97 (99)	56 (57)
AST increase	97 (61)	20 (13)	39 (40)	1 (1)
ALT increase	95 (60)	35 (22)	39 (40)	3 (3)
Hypertension	76 (48)	32 (20)	7 (7)	3 (3)
Diarrhea	70 (44)	2 (1)	24 (24)	2 (2)
Edema	65 (41)	4 (3)	27 (28)	0
Dry mouth	62 (39)	0	6 (6)	0
Blood bilirubin increase	59 (37)	2 (1)	1 (1)	0
Rash	52 (33)	3 (2)	29 (30)	1 (1)
Fatigue	51 (32)	5 (3)	49 (50)	5 (5)
Thrombocytopenia	42 (27)	5 (3)	28 (29)	7 (7)
Abdominal pain	40 (25)	1 (1)	19 (19)	2 (2)
Leukopenia	40 (25)	2 (1)	32 (33)	7 (7)
Blood creatinine increase	39 (25)	2 (1)	17 (17)	1 (1)
Neutropenia	36 (23)	3 (2)	44 (45)	27 (28)
Constipation	34 (22)	0	39 (40)	1 (1)
QT prolongation on ECG	32 (20)	14 (9)	1 (1)	0
Decreased appetite	27 (17)	0	33 (34)	2 (2)
Pyrexia	21 (13)	1 (1)	23 (23)	0
Nausea	20 (13)	0	43 (44)	1 (1)
Vomiting	20 (13)	0	23 (23)	1 (1)
Anemia	18 (11)	2 (1)	58 (59)	10 (10)
Pruritus	16 (10)	0	22 (22)	0

1. Nardo M, et al. Cell Reports Med 2023 ; 2. Zhou C, et al. N Engl J Med

NRG fusion

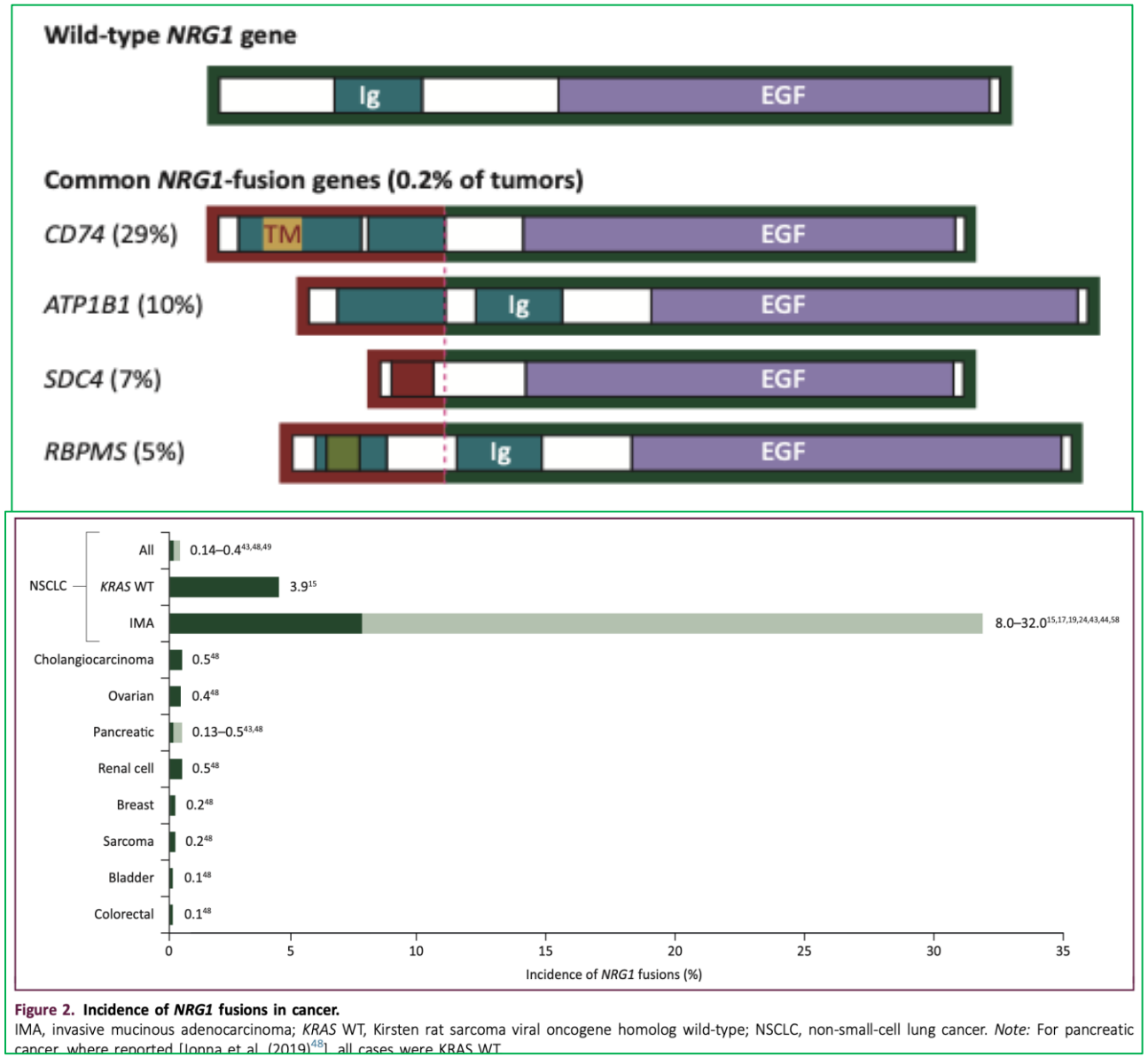
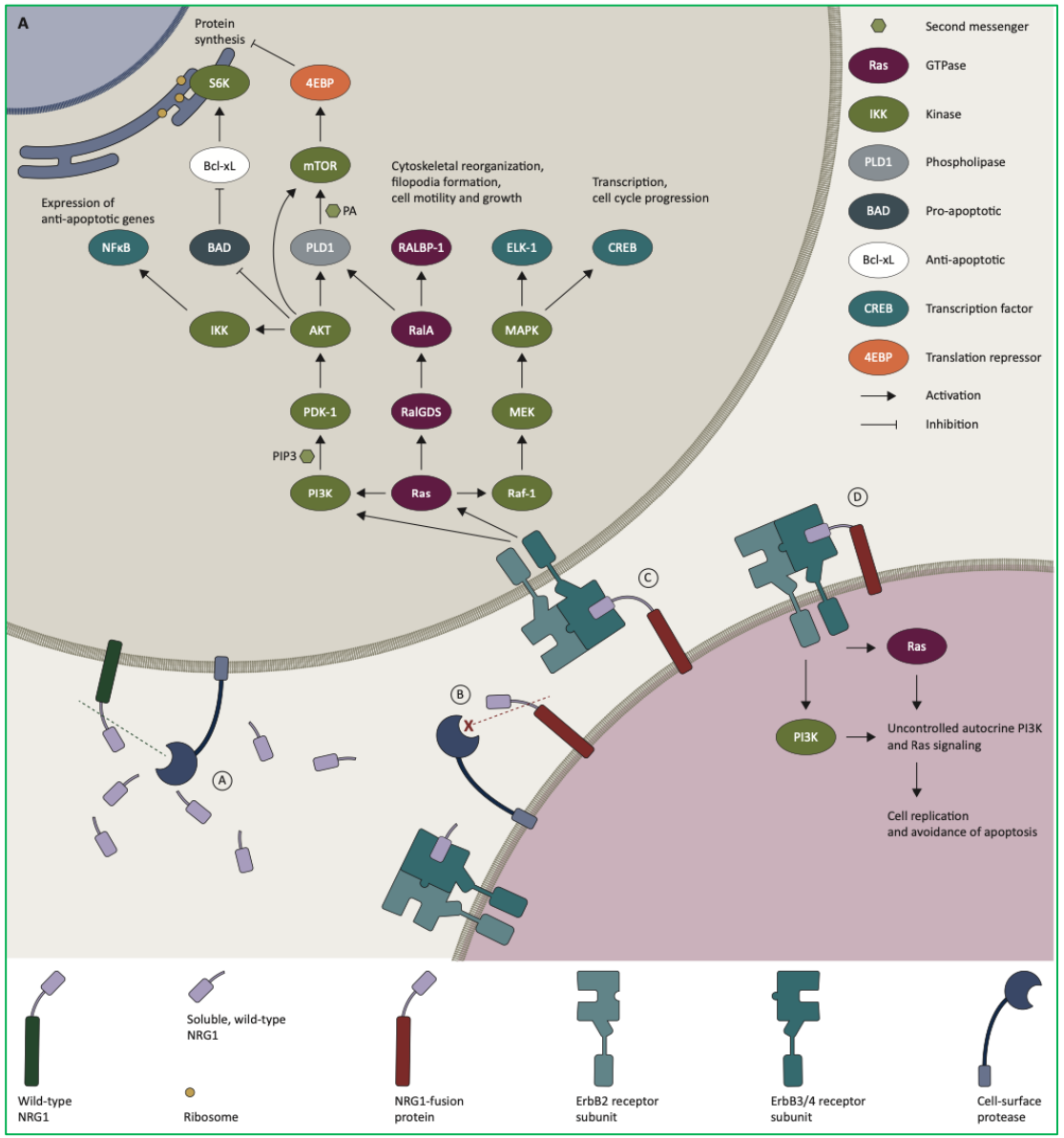


Figure 2. Incidence of *NRG1* fusions in cancer.
IMA, invasive mucinous adenocarcinoma; *KRAS* WT, Kirsten rat sarcoma viral oncogene homolog wild-type; NSCLC, non-small-cell lung cancer. *Note:* For pancreatic cancer, where reported [Jonna et al. (2019)[48]], all cases were KRAS WT.



Laskin J, et al. Ann Oncol 2020

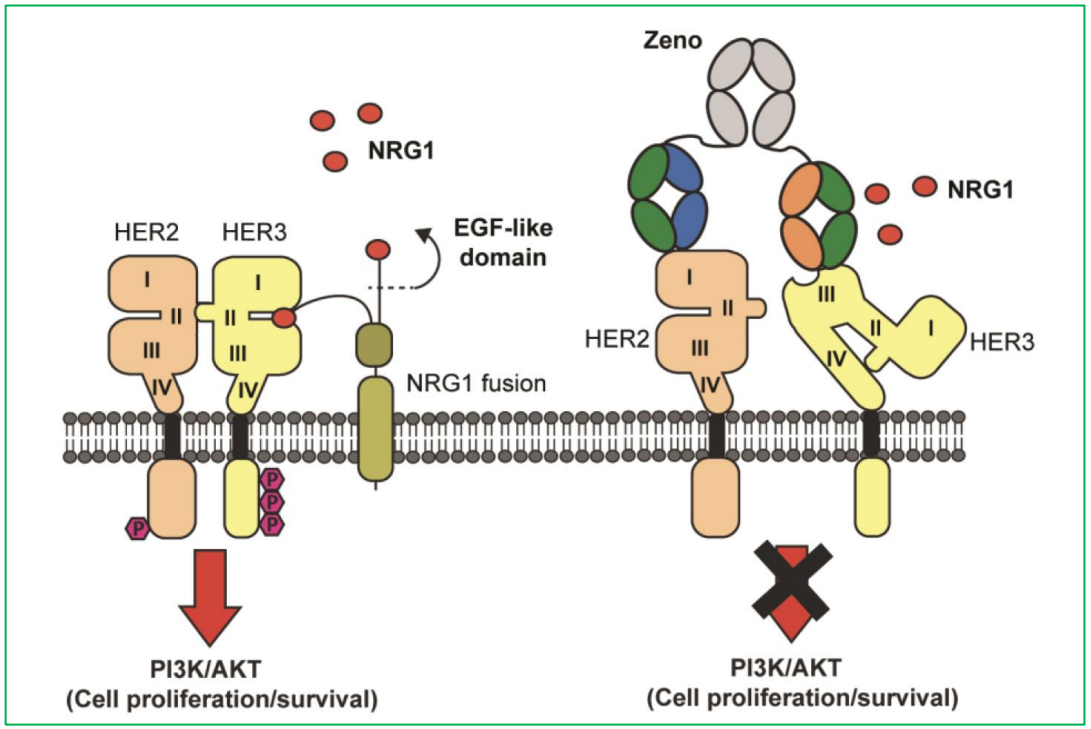
Afatinib, clinical cases in patients with NRG1 fusion NSCLC

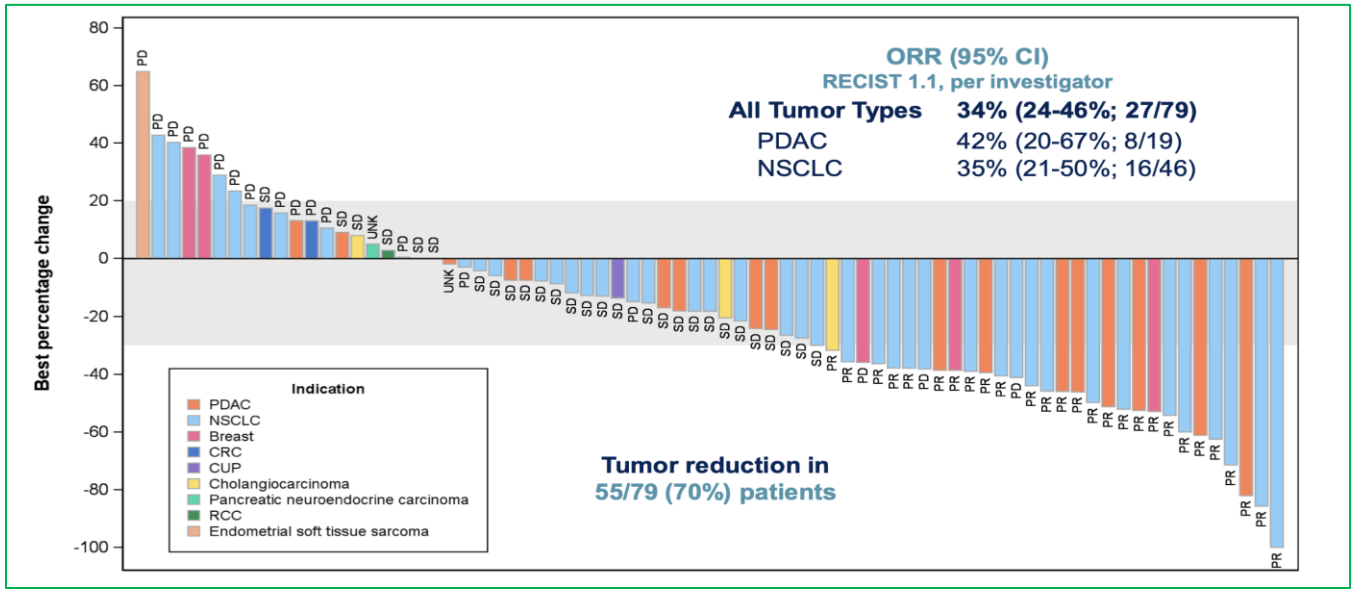
Trials	Tumor type	NRG1 fusion partner	Response	DoR (months)
Gay ND [1]	Lung adenocarcinoma	SLC3A2	PR	12
	IMA	CD74	PR	10
Jones MR [2]	Lung adenocarcinoma	SDC4	PR	12
Cheema PK [3]	IMA	CD74	PR	6.5
Drilon A [4]	IMA	CD74	SD	3
	IMA	CD74	PD	-
	IMA	SDC4	PD	-

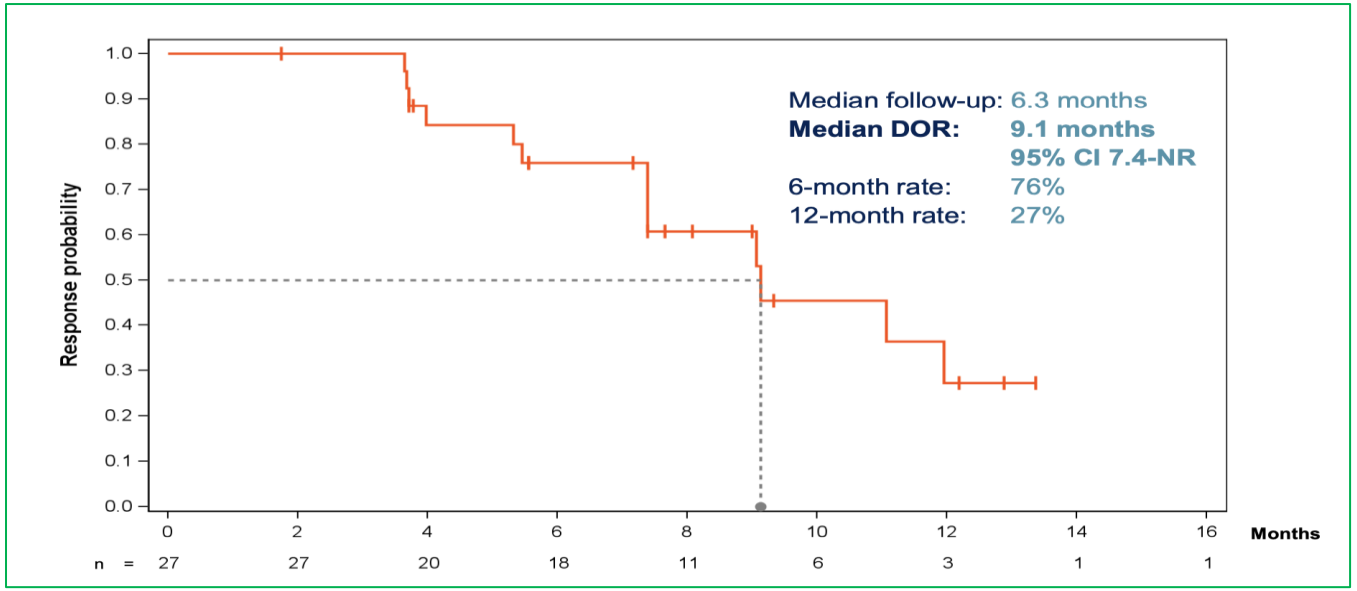
IMA : Invasive Mucinous Adenocarcinoma

1. *Gay ND, et al. J Thorac Onco 2017; 2. Jones MR, et al. Ann Oncol 2017 ; 3. Cheema PK, et al. J Thorac Oncol 2017; 4. Drilon a, et al. Cancer Discov 2018; 5. Jones MR, et al. Clin Cancer Res 2019*

NRG fusion – Zenocutuzumab (anti-HER2/HER3)

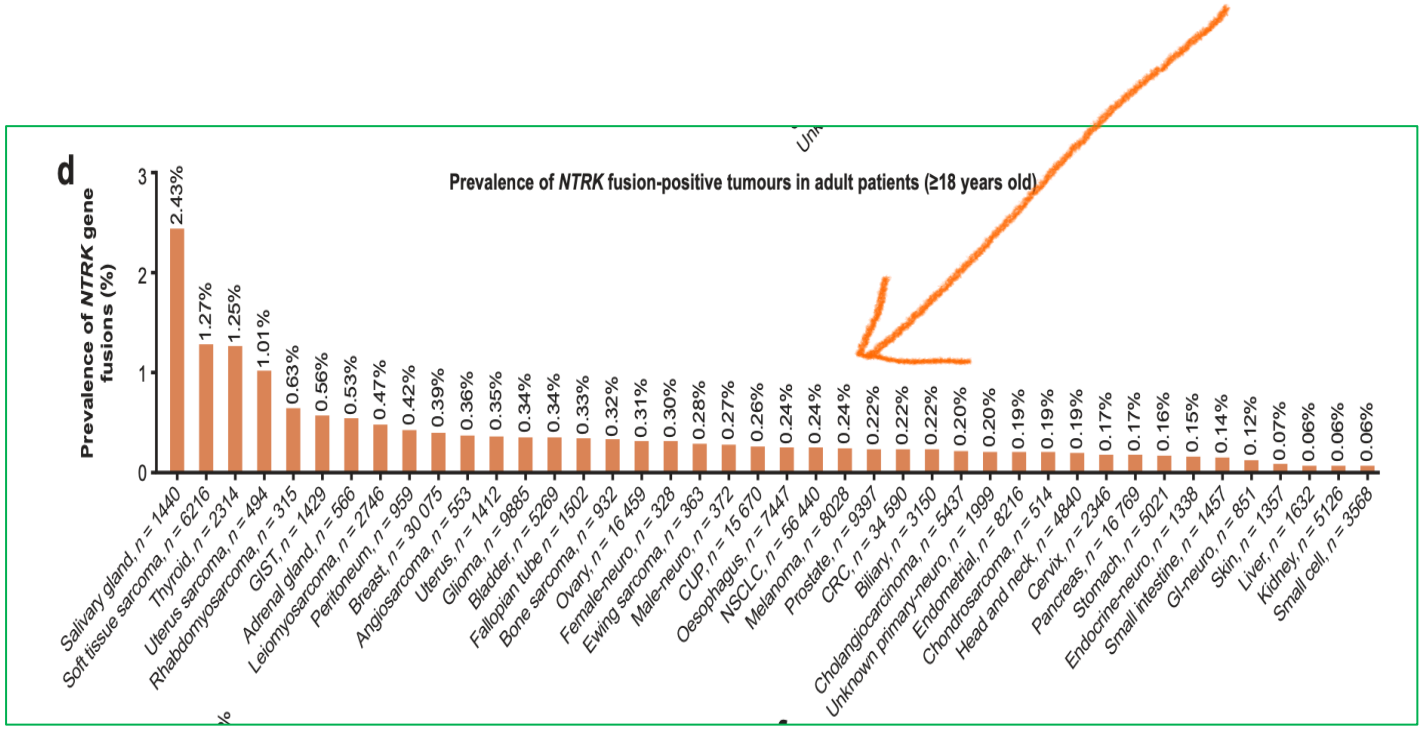


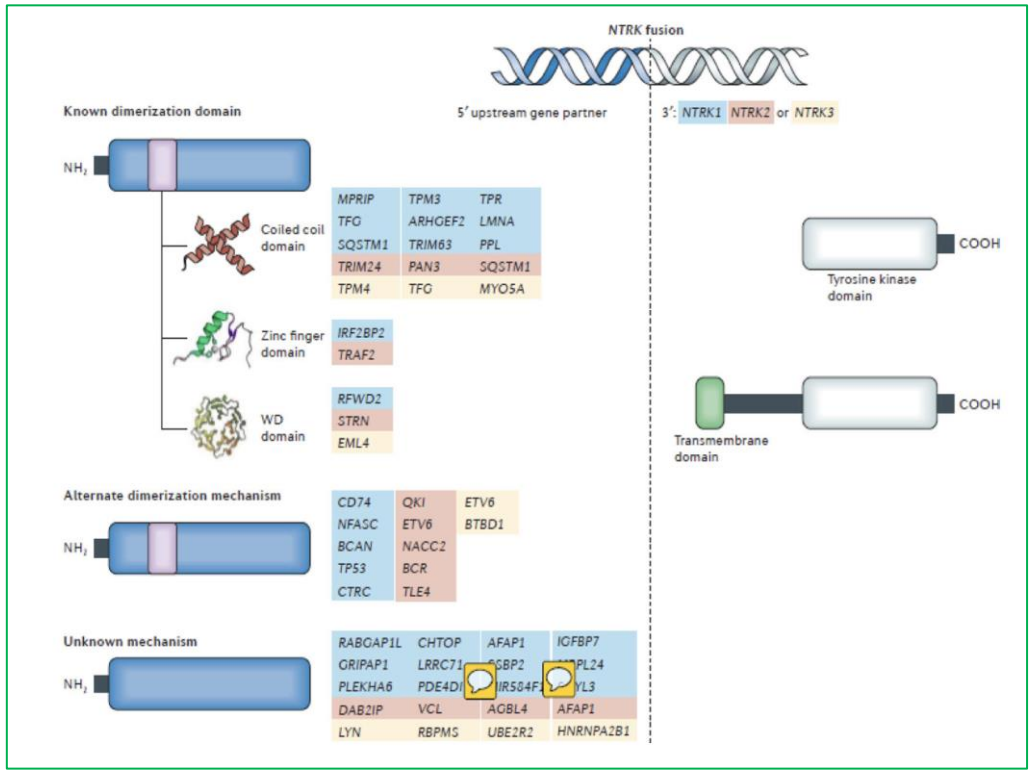




1. Gerlach J, et al. AACR 2021 ; 2. Schram A, et al. ASCO 2022

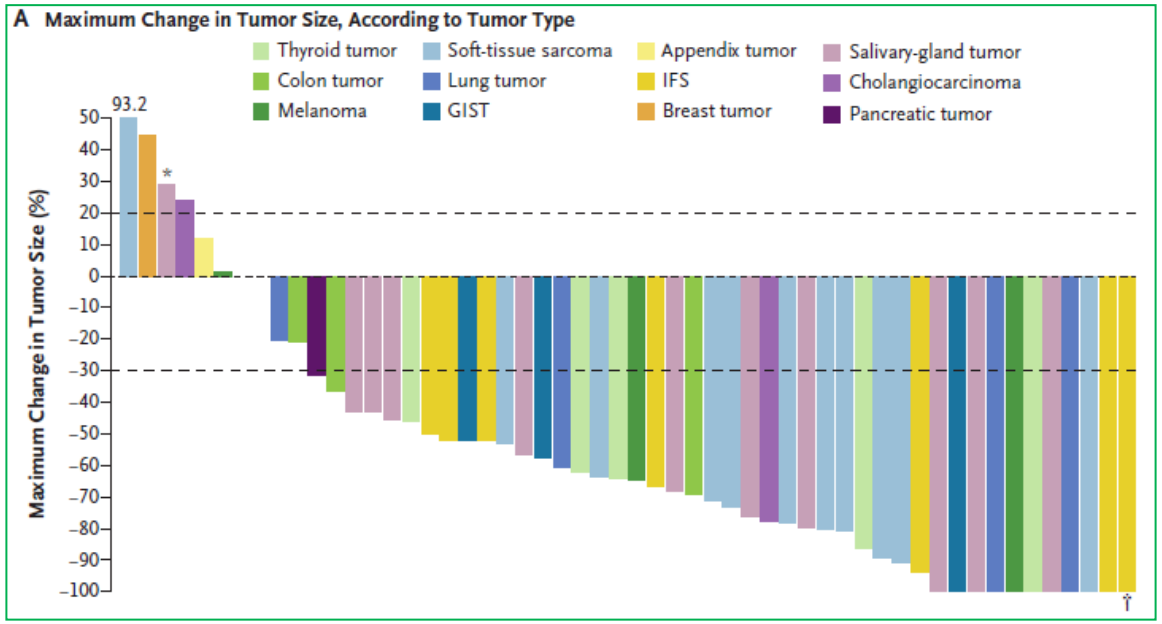
TRK fusion



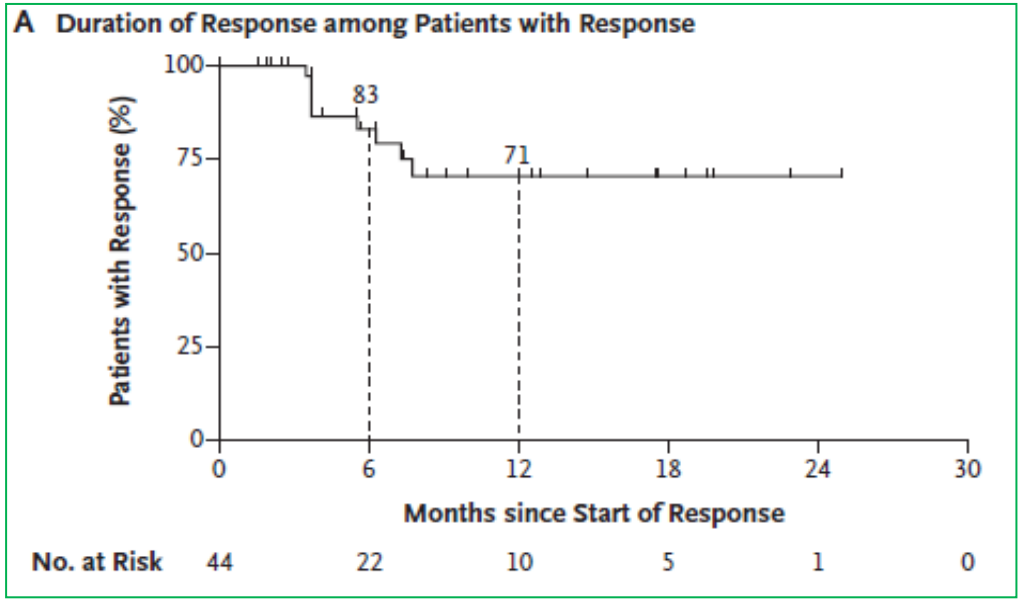


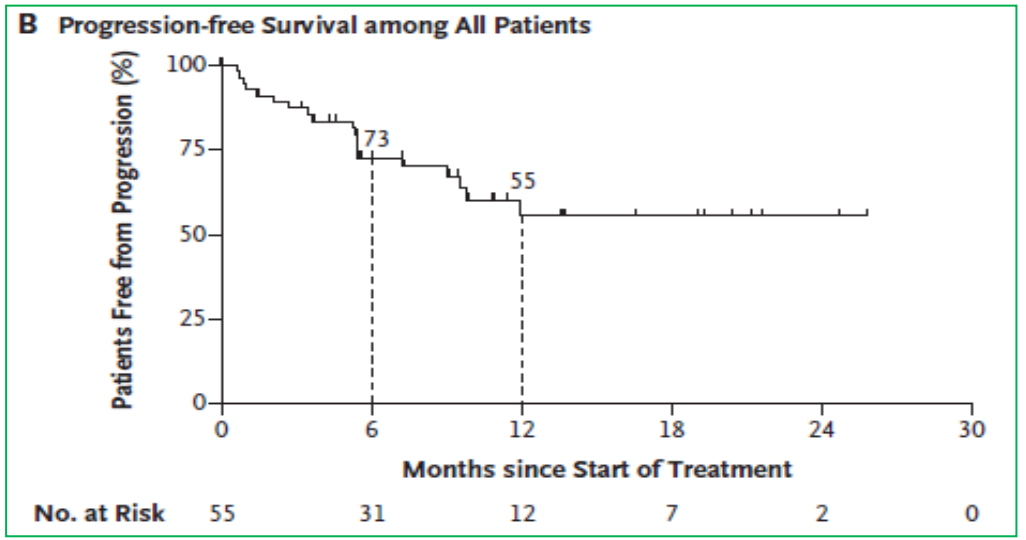
1. Westphalen CB, et al. npj Prec Oncol 2021; 2. Cocco E, et al. Nat Rev Clin Oncol 2018

Larotrectinib in cancers with TRK fusion



Agnostic therapy to the primary tumor



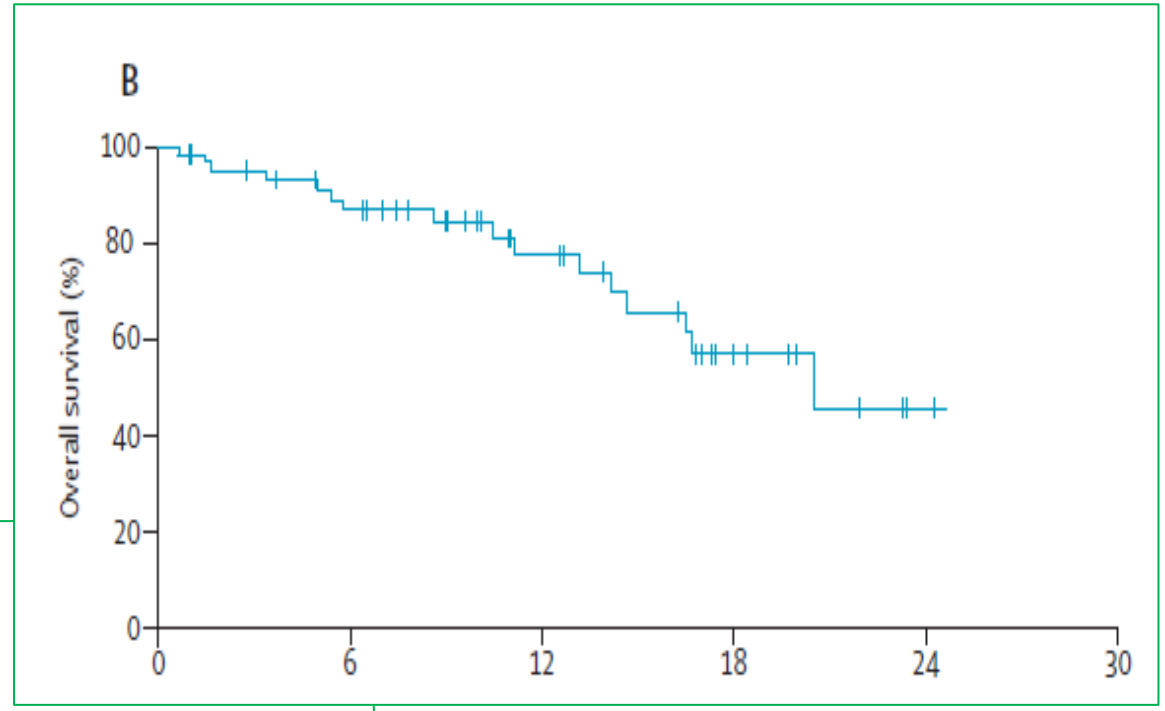


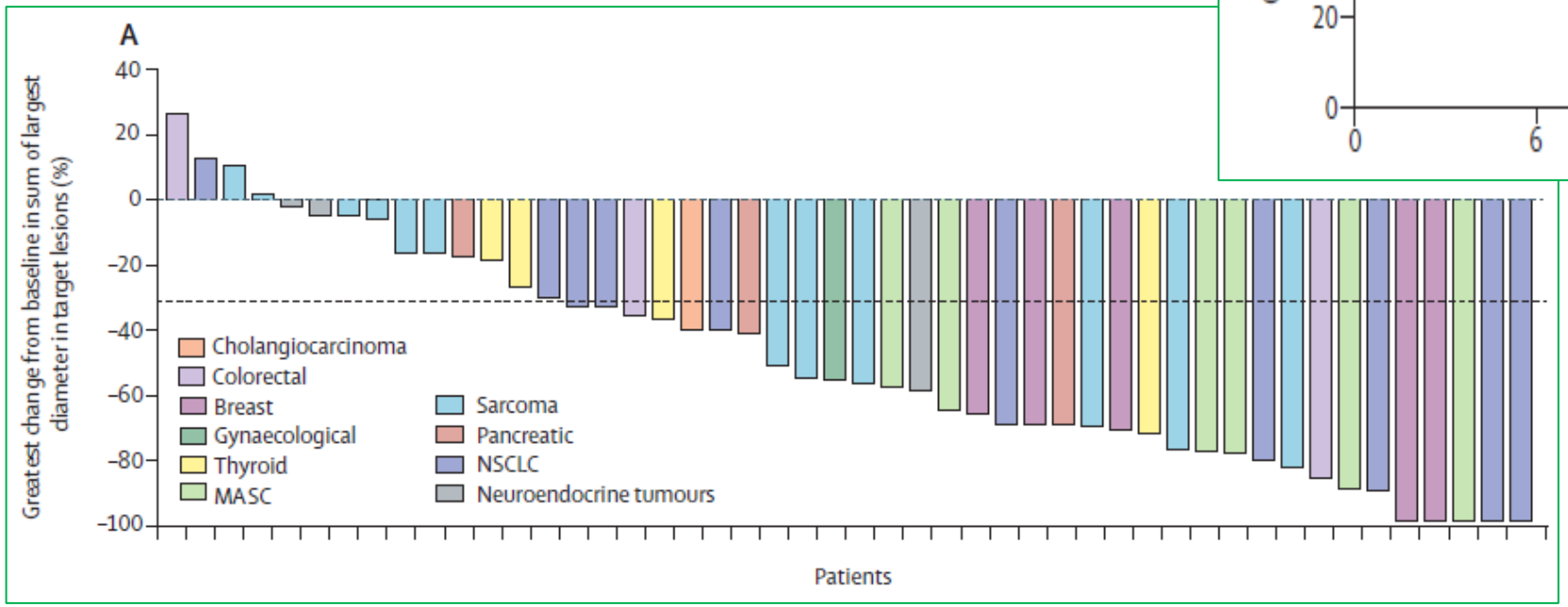
Drilon A. et al. N Engl J Med 2018.

Entrectinib in cancers with TRK fusion

3 phase 1/2 studies (ALKA 372-001. STARTRK 1. et 2)

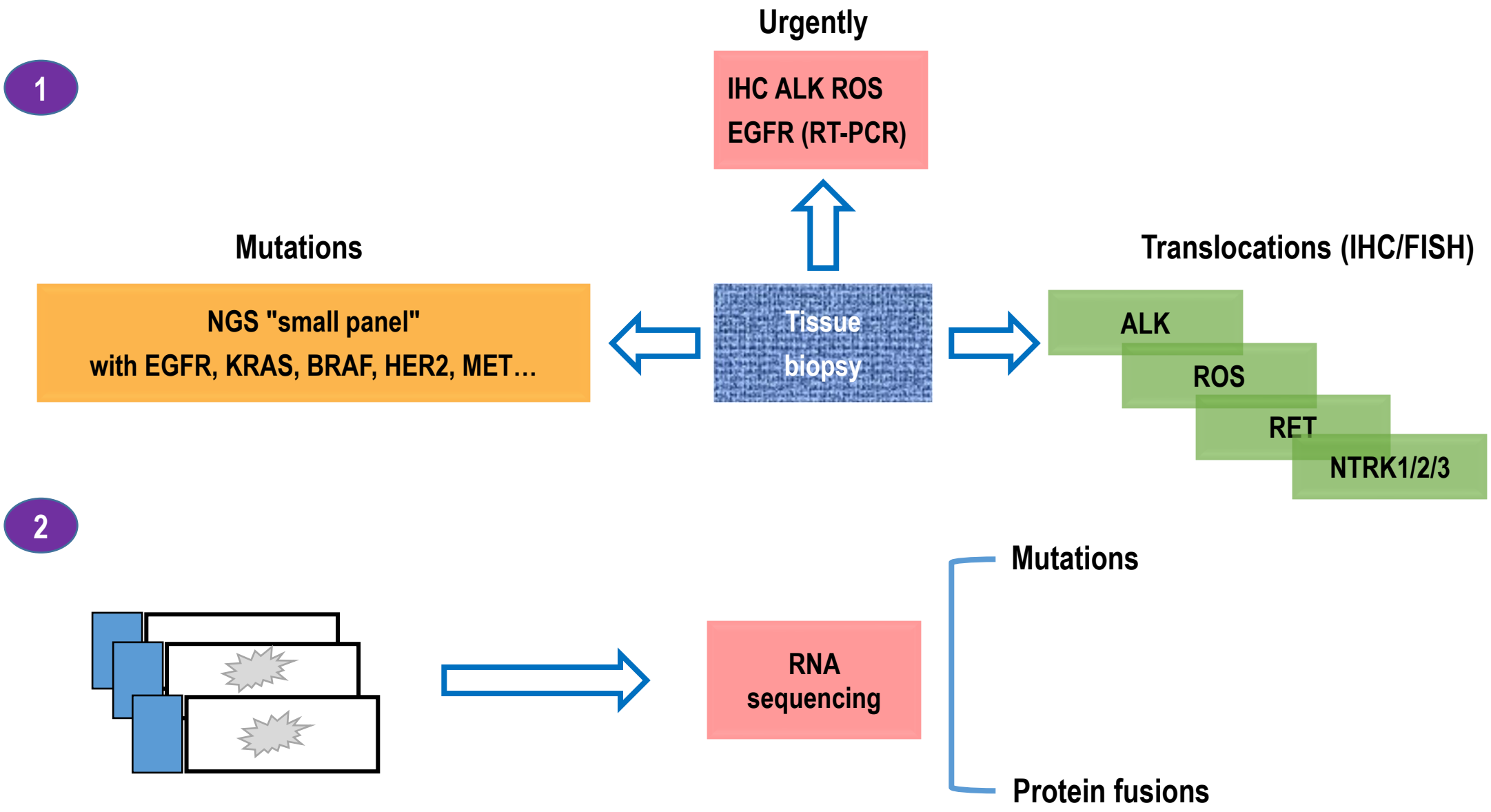
- N=54
- ORR = 57 %
- Median DoR = 10 months
- Médian PFS = 11 months
- Médian OS = 21 months





Doebele RC. et al. Lancet Oncol 2019

Strategies for biomarkers identification



Targeted therapies and NSCLC

Met Exon 14	**3%**	Crizotinib, Savolitinib, **Capmatinib**. **Tepotinib** Capmatinib or Tepotinib After first-line with platinum-based chemotherapy Immunotherapy
HER 2	**2%**	Docetaxel-pertuzumab-traztuzumab. **traztuzumab-deruxtecan** After first-line with platinum-based chemotherapy
BRAF V600	**1%**	Trametinib + dabrafenib or Encorafenib + binimetinib If smoker, immunotherapy in first-line
RET	**1%**	Pralsetinib. **Selpercatinib** After first-line with platinum-based chemotherapy
NTRK	**0.2 %**	Entrectinib. Larotrectinib After first-line with platinum-based chemotherapy

Thank you for your attention !

Hôpital FOCH. Suresnes