BRAF and NTRK Inhibitors in NSCLC

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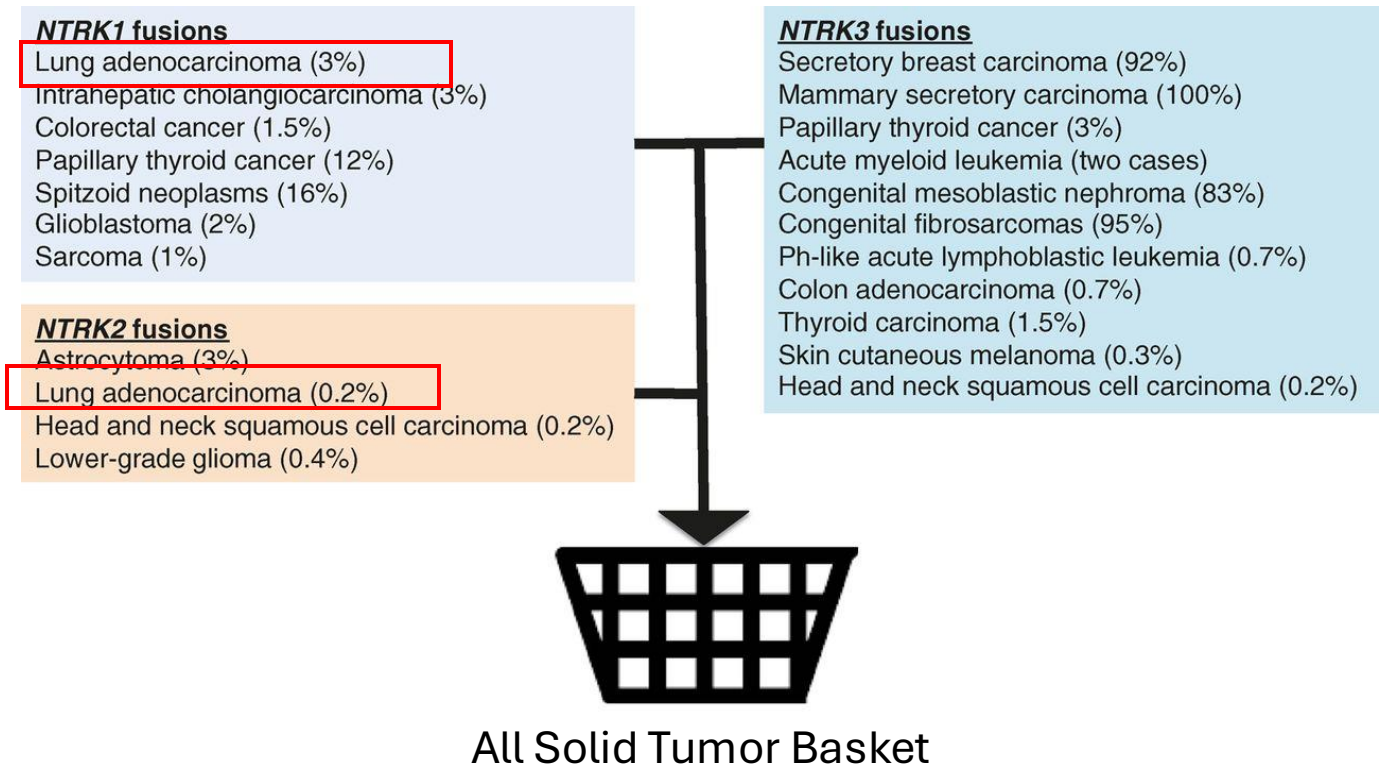
NTRK Fusions in Lung Cancer



All Solid Tumor Basket

- Intra- and Interchromosomal rearrangements juxtapose 3' TRK kinase domain fused to diverse 5' partners
- Chimeric protein leads to ligand independent constitutive activity
- Oncogene addiction regardless of tissue of origin
- NTRK1/2/3 fusions: 0.2%
  - Difference in frequencies may be attributed to testing panels (NGS, FISH), sample size and screened patient populations.

Okimoto and Bivona, Cancer Discov 2016; Kheder and Hong, Clin Cancer Res 2018; Farago et al. J Thorac Oncol 2015.

Efficacy of 1st Generation TRK Inhibitors:
Pooled Phase I/II Clinical Trials

	Overall Population				NSCLC	
	N	**ORR**	**DOR**	**CNS ORR**	**N**	**ORR**
Larotrectinib Selective inhibitor of TRK A, B and C	153	79%	35.8 mo	75%	12	75%
Entrectinib Multikinase inhibitor of TRK A, B and C, ROS1 and to a lesser degree ALK	54	57%	10.4 mo	50%	10	70%

Hong et al. Lancet Oncol 2020; Doebele et al. Lancet Oncol 2020.

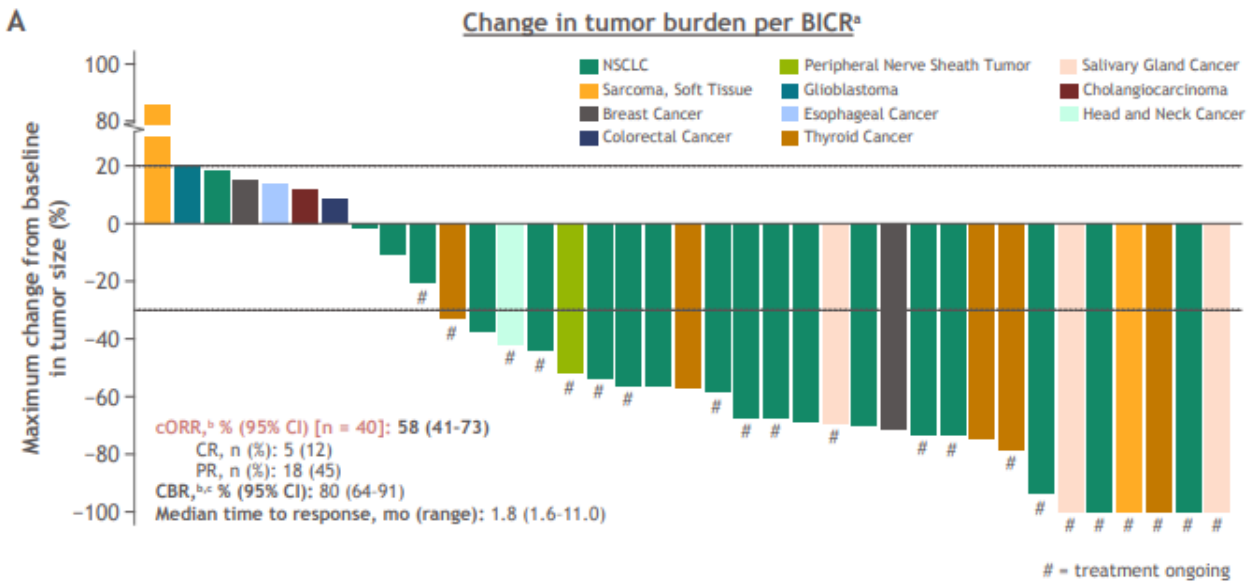
On Target Resistance → 2nd Generation TRK inhibitors

IC_{50} (±SD) TRK mutation			First generation		Second generation	
			Larotrectinib	Entrectinib	Selitrectinib	Repotrectinib
No mutation	TRKA	WT	23.5 ± 8.6	0.30 ± 0.10	3.9 ± 4.2	<0.2
	TRKB	WT	36.5 ± 20.8	0.80 ± 0.50	1.8 ± 0.9	<0.2
	TRKC	WT	49.4 ± 22.8	1.3 ± 1.0	3.0 ± 2.9	<0.2
Solvent front	TRKA	G595R	3,540 ± 1,560	987 ± 487	18.7 ± 6.4	0.2 ± 0.1
	TRKB	G639R	3,670 ± 2,080	1,690 ± 470	28.8 ± 16	2.6 ± 2.2
	TRKC	G623R	6,940 ± 1,090	1,500 ± 440	27.7 ± 6.8	2.0 ± 1.8
	TRKC	G623E	1,510 ± 680	1,470 ± 220	27.0 ± 20.4	0.40 ± 0.40
Gatekeeper	TRKA	F589L	675 ± 137	<0.2	27.8 ± 5.6	<0.2
	TRKB	F623L	5,730 ± 1,580	6.4 ± 3.7	85.4 ± 24.4	<0.2
	TRKC	F617I	4,330 ± 1,150	60.4 ± 11.7	51.8 ± 22.5	<0.2
xDFG	TRKA	G667C	1,630 ± 270	138 ± 82	118 ± 31	11.8 ± 7.3
	TRKB	G709C	3,450 ± 510	876 ± 309	341 ± 86	67.6 ± 22
	TRKC	G696C	4,360 ± 1,470	547 ±339	182 ± 51	19.5 ± 12.1
Compound mutation	TRKA	G595R F589L	>10,000	1,840 ± 250	468 ± 55	17.7 ± 7.8

Murray et al. Mol Cancer Ther 2021

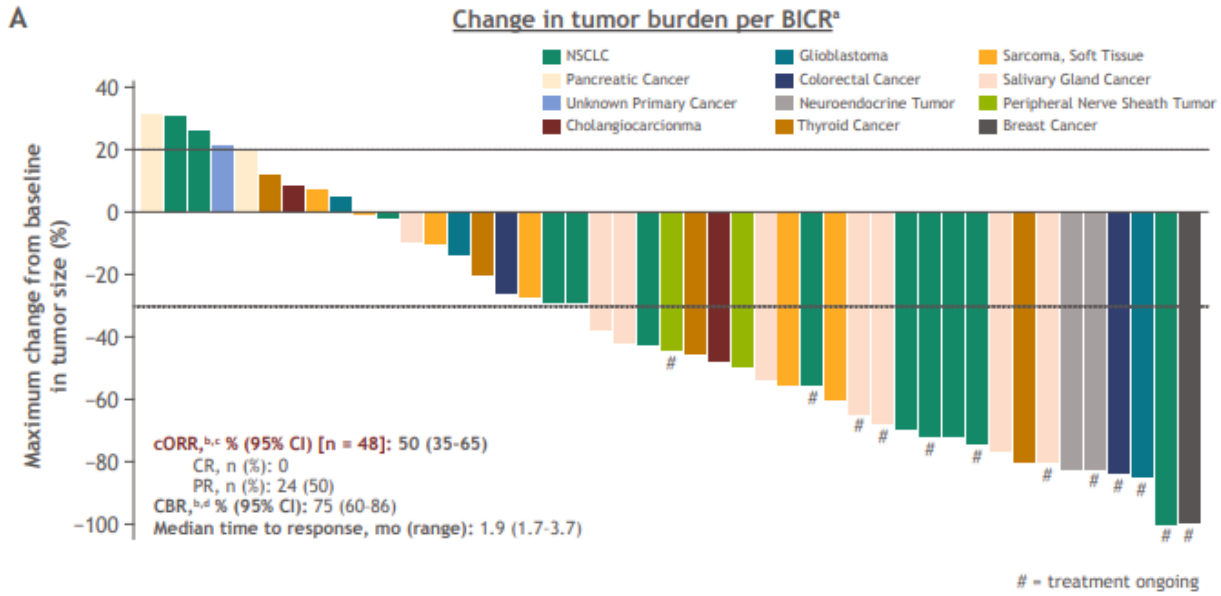
TRIDENT 1: Repotrectinib in all solid tumors including NSCLC

TKI-Naive



DOR and PFS: NE

TKI-Pretreated



DOR 9.8 mos
PFS: 7.4 mos

- FDA approved June 2024 for NTRK fusion + tumors

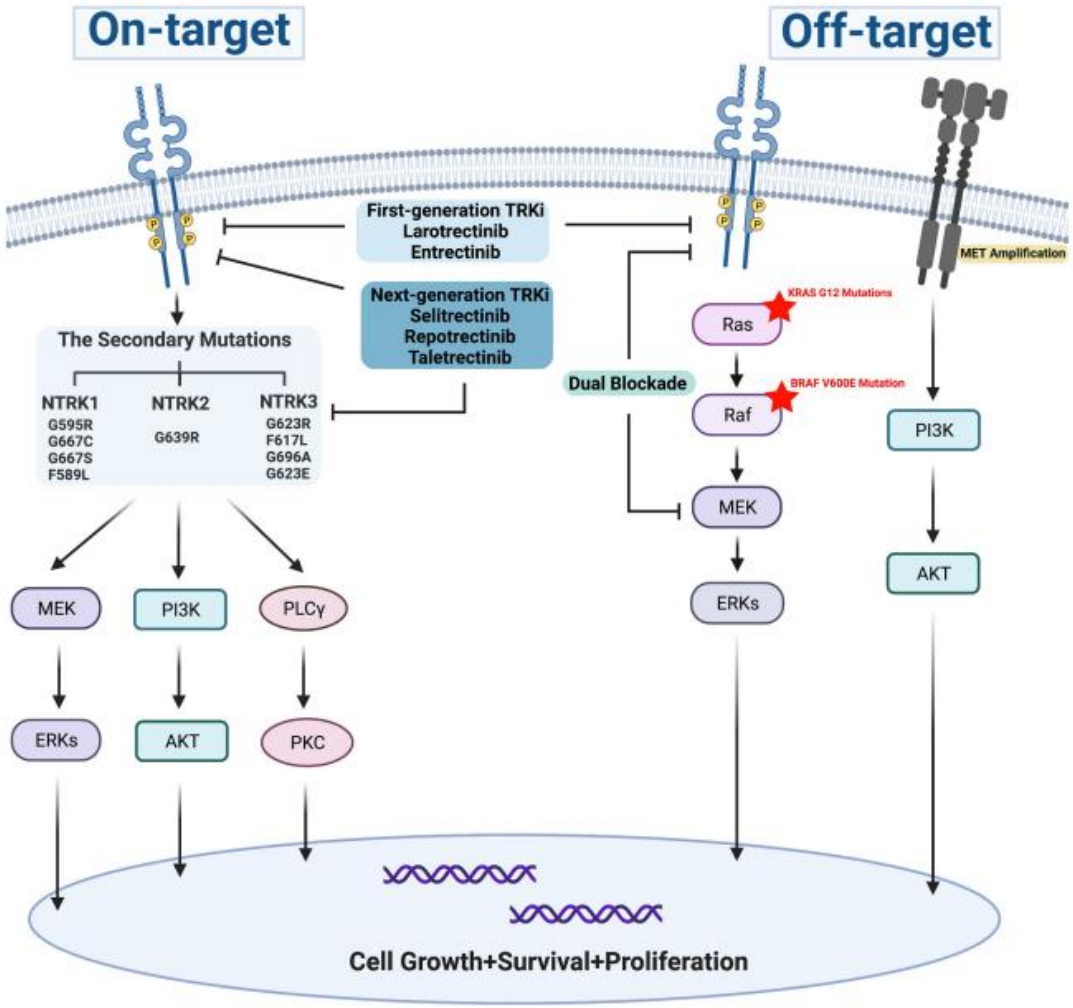
Solomon et al. ESMO 2023

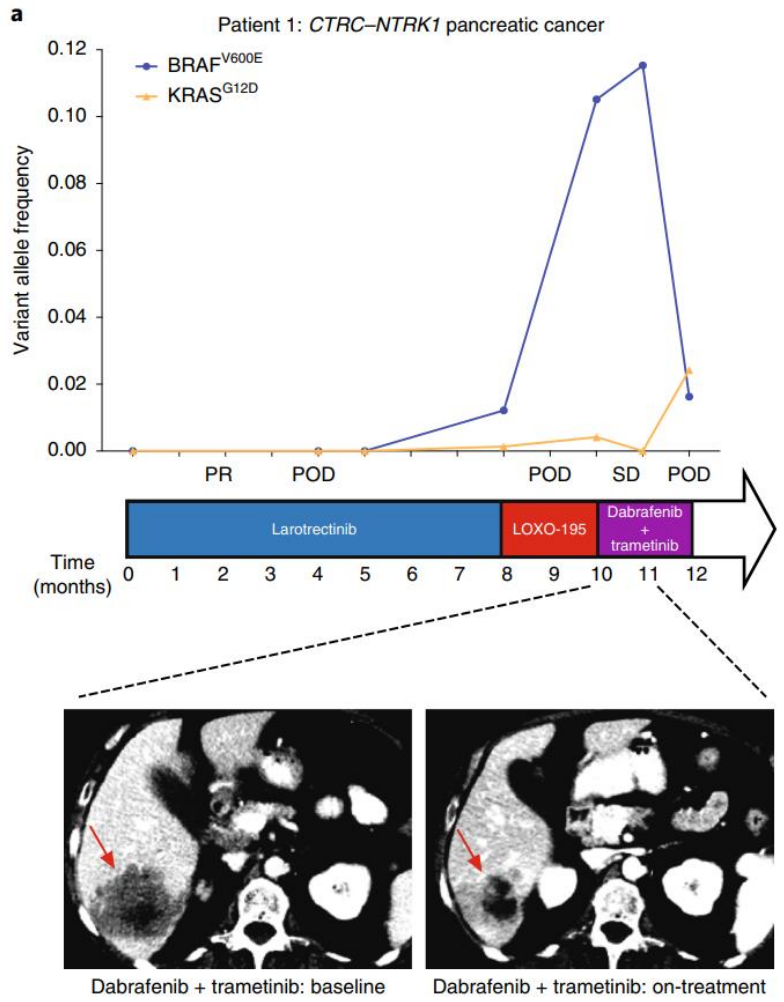
TRK TKIs and Adverse Events

- Specific CNS toxicity related to TRK inhibition, which plays a role in CNS homeostasis, most prominent with repotrectinib.
  - Majority of CNS AEs are mild to moderate with repotrectinib
  - All grade toxicities (mostly mild to moderate)
    - Dizziness (62%), paresthesia (34%), ataxia (21%), headache (20%), memory impairment (10%).
  - Grade ≥ 3 dizziness (3%), paresthesia (1%), ataxia (<1%), headache (0%), memory impairment (<1%).
  - Dose reduction (38%) and interruption (50%) most commonly in the setting of dizziness; Discontinuation (7%)

Drilon, et al. NEJM 2024.

Off-Target Resistance to 1st Generation TRK inhibitors

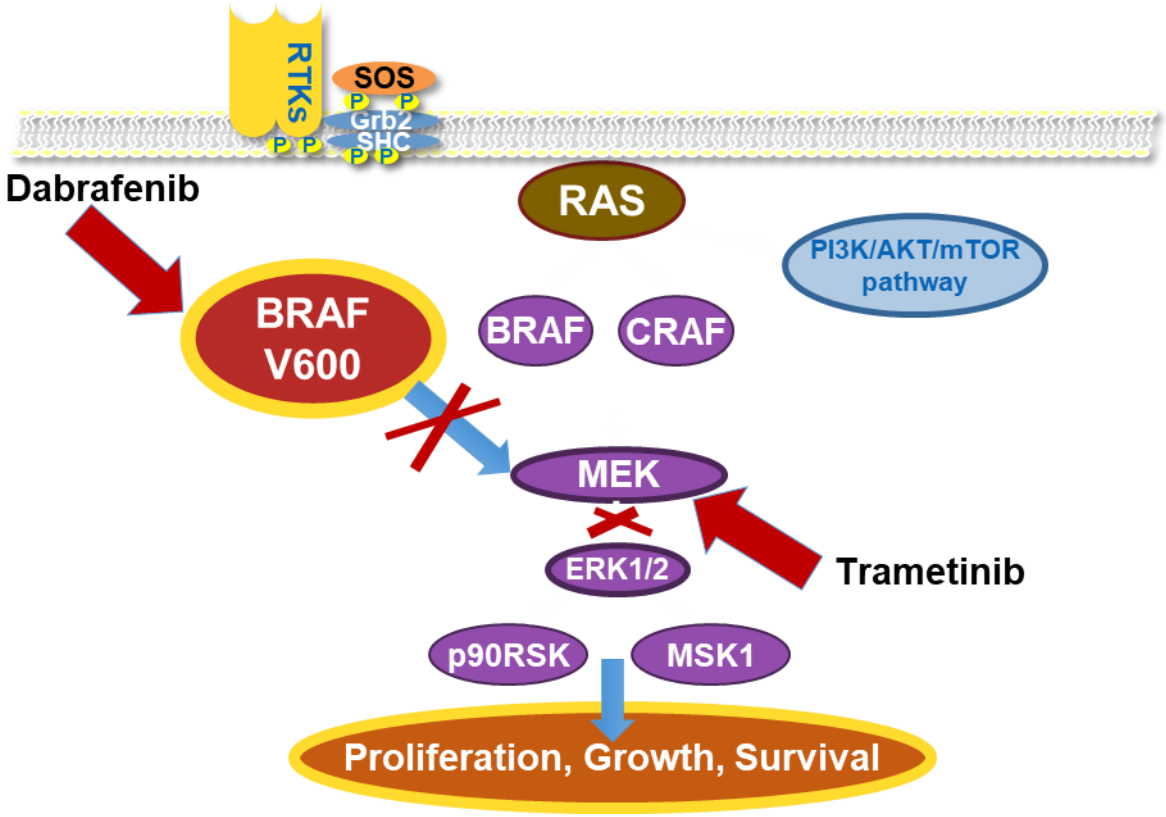




Liu et al. Front Oncol 2022; Cocco et al. Nature Medicine 2019

BRAF in Lung Cancer

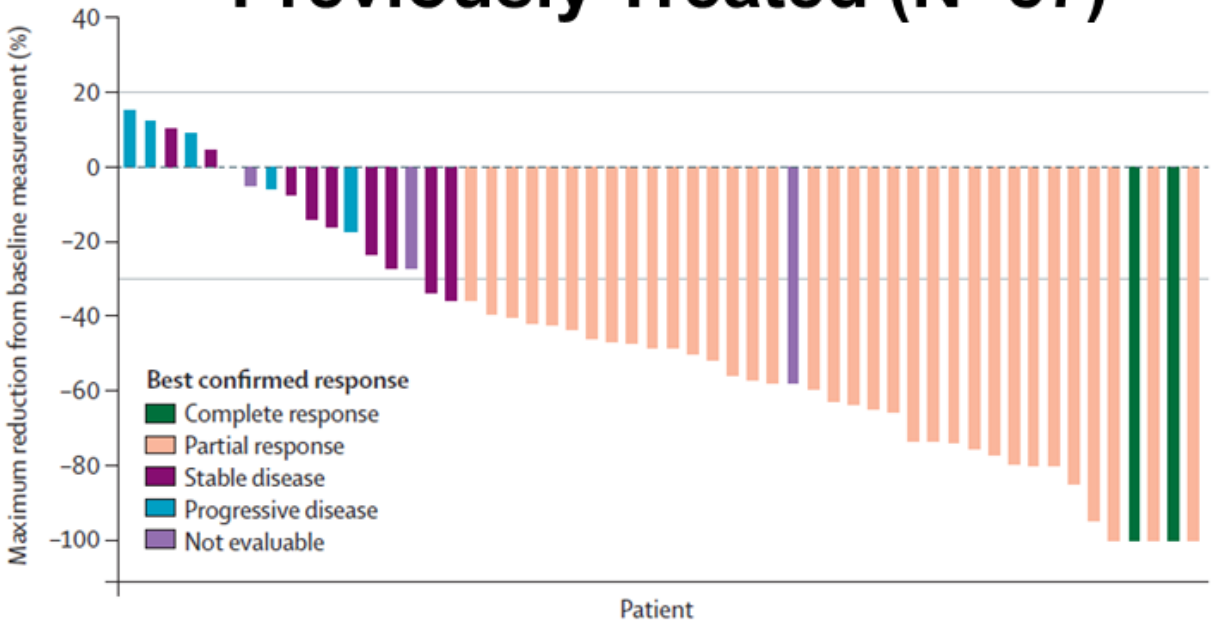
- BRAF mutations originally described in melanoma but also seen in colon, thyroid, lung cancers and other solid tumors
- 2-5% lung adenocarcinomas; 50% having V600E mutation
  - V600E – light/never smoker
  - Non V600E – smokers
- Dabrafenib and encorafenib potent BRAFi; Used in combination with MEKi
  - Blocks ERK signaling, maximizing MAPK pathway blockade and delaying the emergence of resistance mechanisms.
- MEK inhibition hinders paradoxical MAPK activation in BRAF wild-type cells preventing BRAFi induced hyperproliferative cutaneous events



Paik et al, J Clin Oncol 2011; Villaruz et al, Cancer 2015; Cardarella et al, Clin Cancer Res 2013; Tissot et al, Lung Cancer 2016.

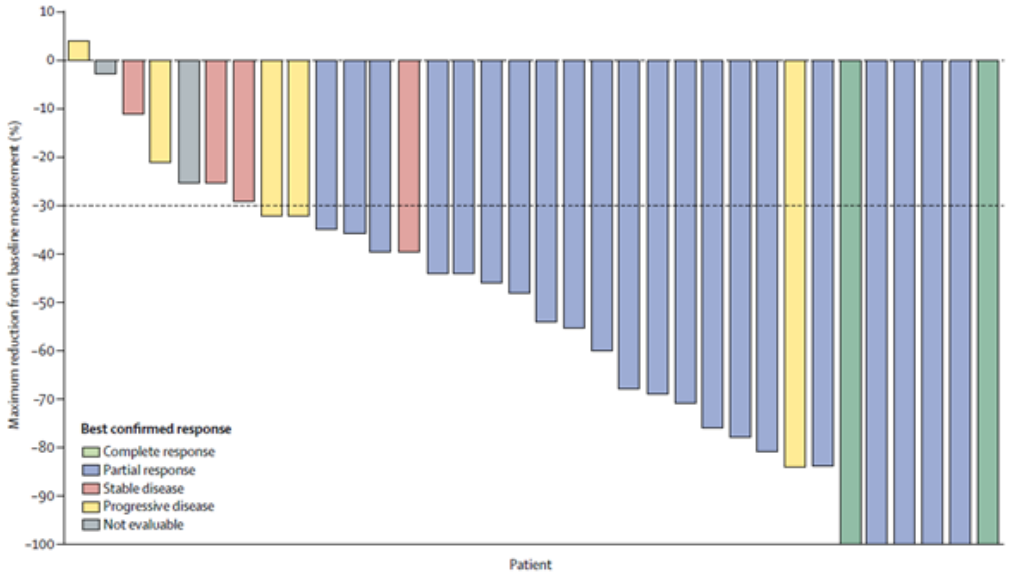
Efficacy of Dabrafenib + Trametinib

Previously Treated (N=57)



ORR 63.2% (95% CI 49-76)
DOR 9.0 mos; PFS 9.7 mos

Previously Untreated (N=36)



ORR 64% (95% CI 46-79)
DOR 10.4 mos; PFS 10.9 mos

Planchard et al, Lancet Oncol 2016; Planchard et al, Lancet Oncol 2017.

Efficacy of Encorafenib + Binimetinib: PHAROS

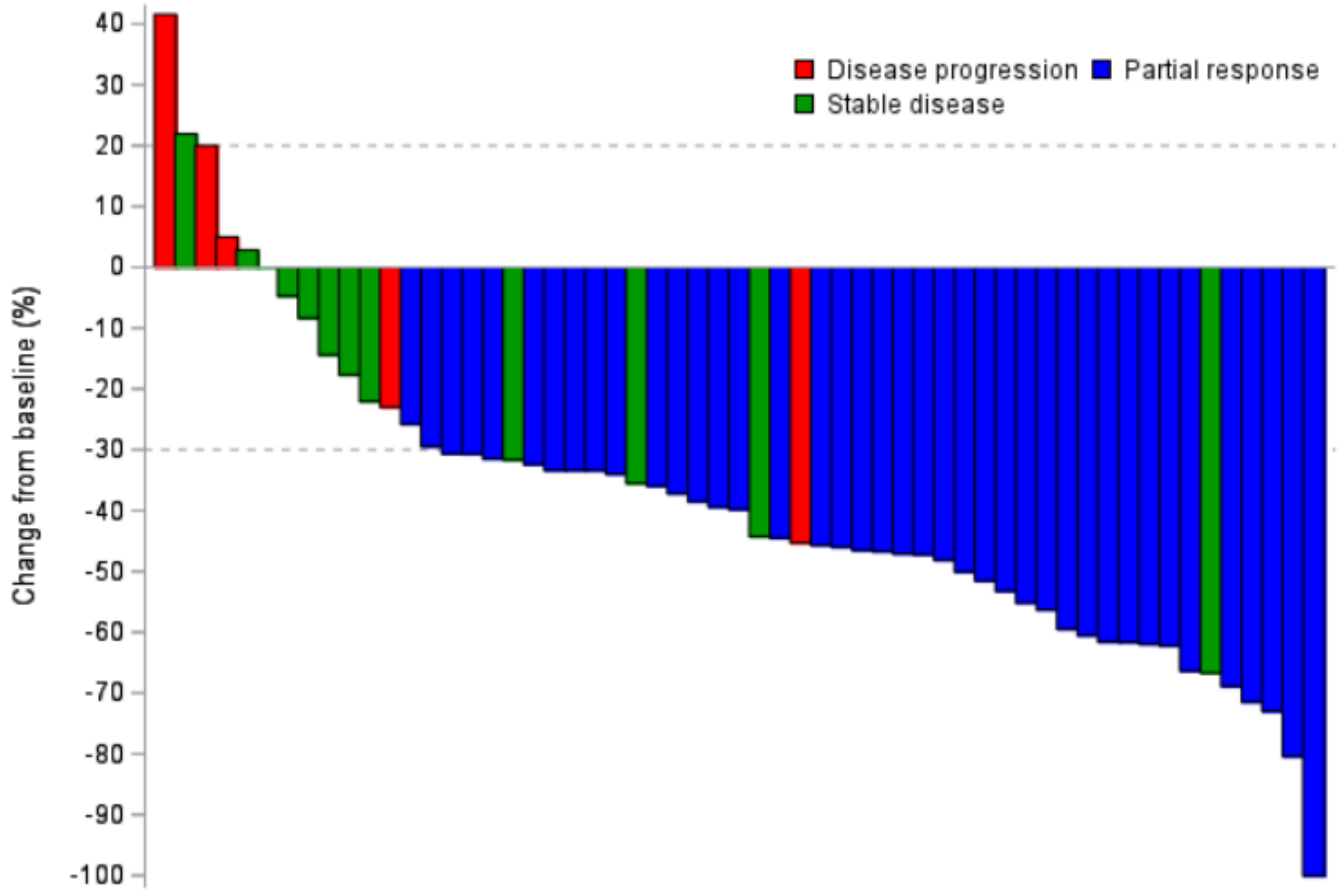
	Primary analysis (data cutoff: Sep 22, 2022)[1]		Current analysis (data cutoff: Apr 1, 2024)	
	Treatment naive	Previously treated	Treatment naive	Previously treated
Objective response rate (95% CI), %[a]	75 (62, 85)	46 (30, 63)	**75 (62, 85)**	**46 (30, 63)**
Complete response	9 (15)	4 (10)	9 (15)	4 (10)
Partial response	35 (59)	14 (36)	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)	64 (51, 76)	44 (28, 60)
Median time to response (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)	1.9 (1.1-19.1)	1.7 (1.2-7.3)
Median duration of response (95% CI), months	NE (23.1, NE)	16.7 (7.4, NE)	**40.0 (23.1, NE)**	**16.7 (7.4, NE)**

Treatment naïve
PFS 30.2 mo
OS NE

Previously treated
PFS 9.3 mo
OS 22.7 mo

Riely GK et al, ESMO 2024

Efficacy of Encorafenib + Binimetinib: IFCT-1904 ENCO-BRAF 1st line Cohort

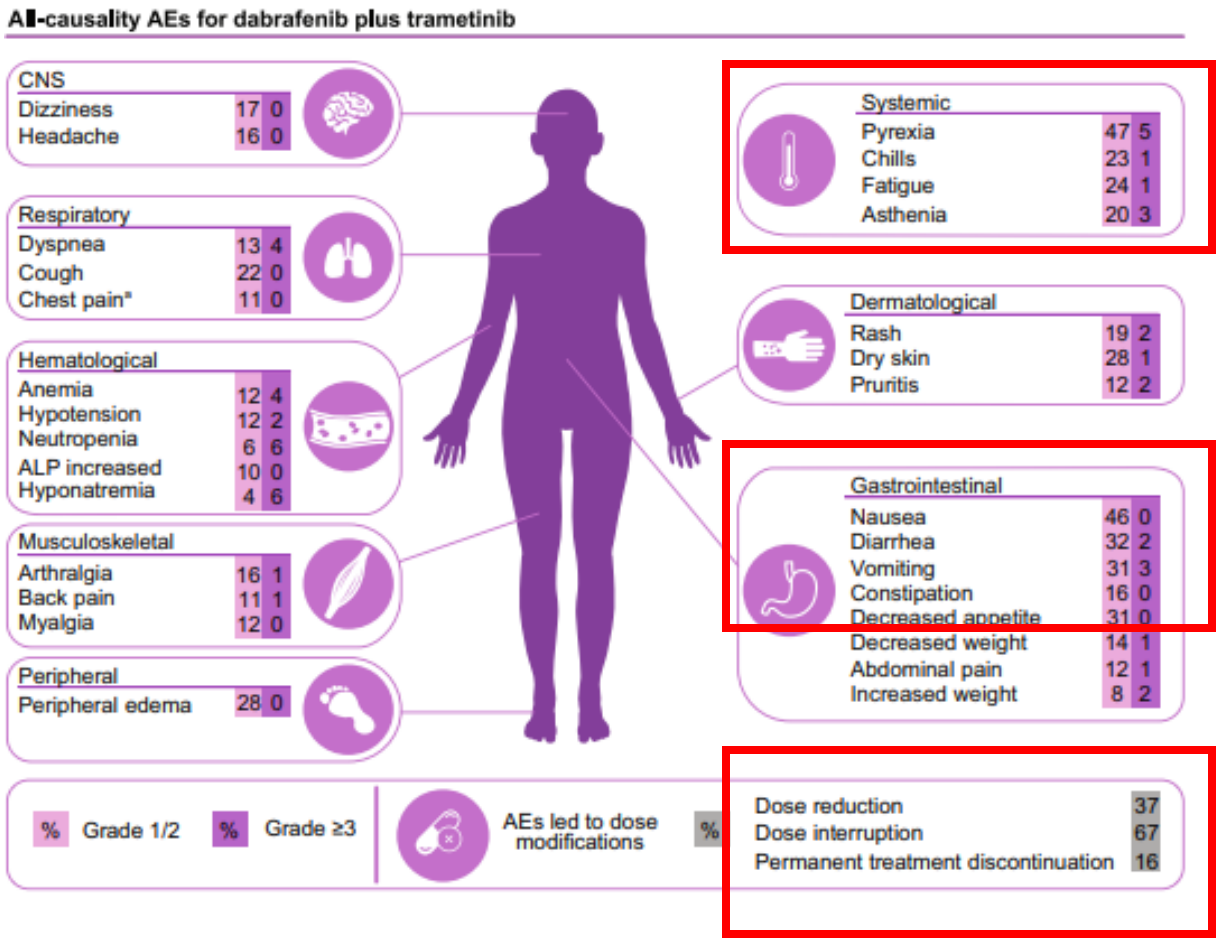


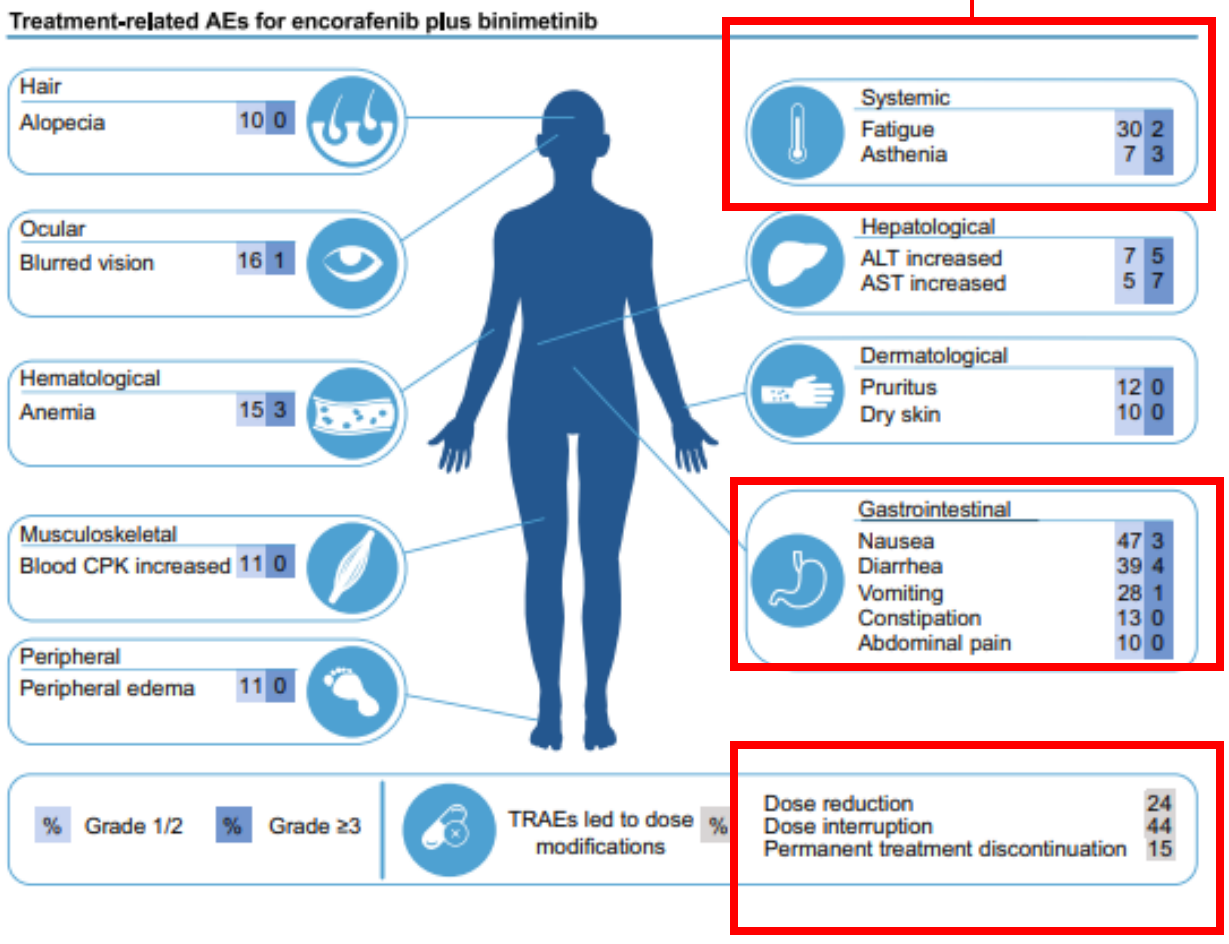
ORR 65.6%
DOR 13 mos
DCR 85.2%
PFS 10.9 mos
OS NR

Planchard D et al, ESMO 2024

BRAFi + MEKi Adverse Events

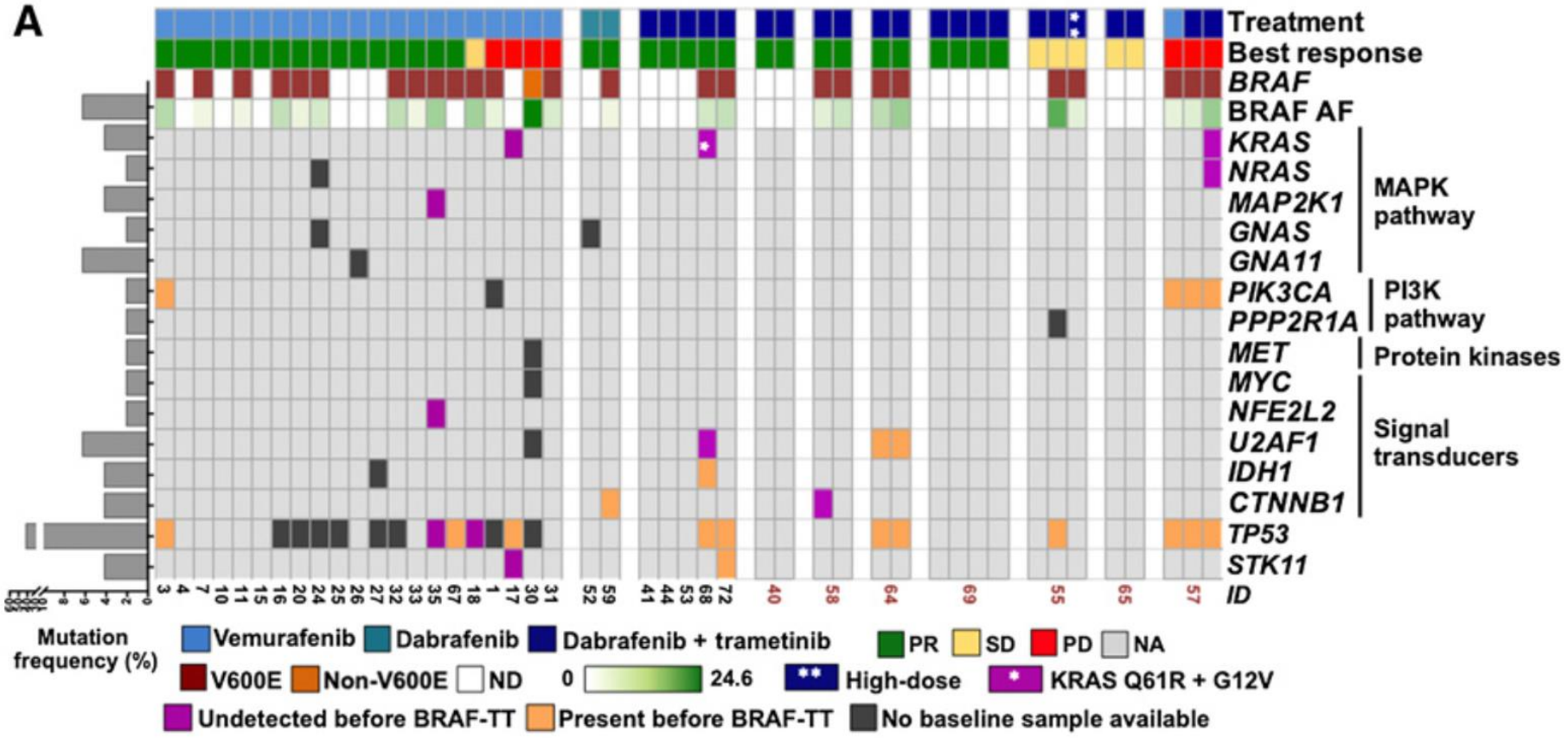
Pyrexia occurs in 22%





Planchard et al, npj Precis. Onc 2024

Acquired Resistance to BRAF targeted therapy

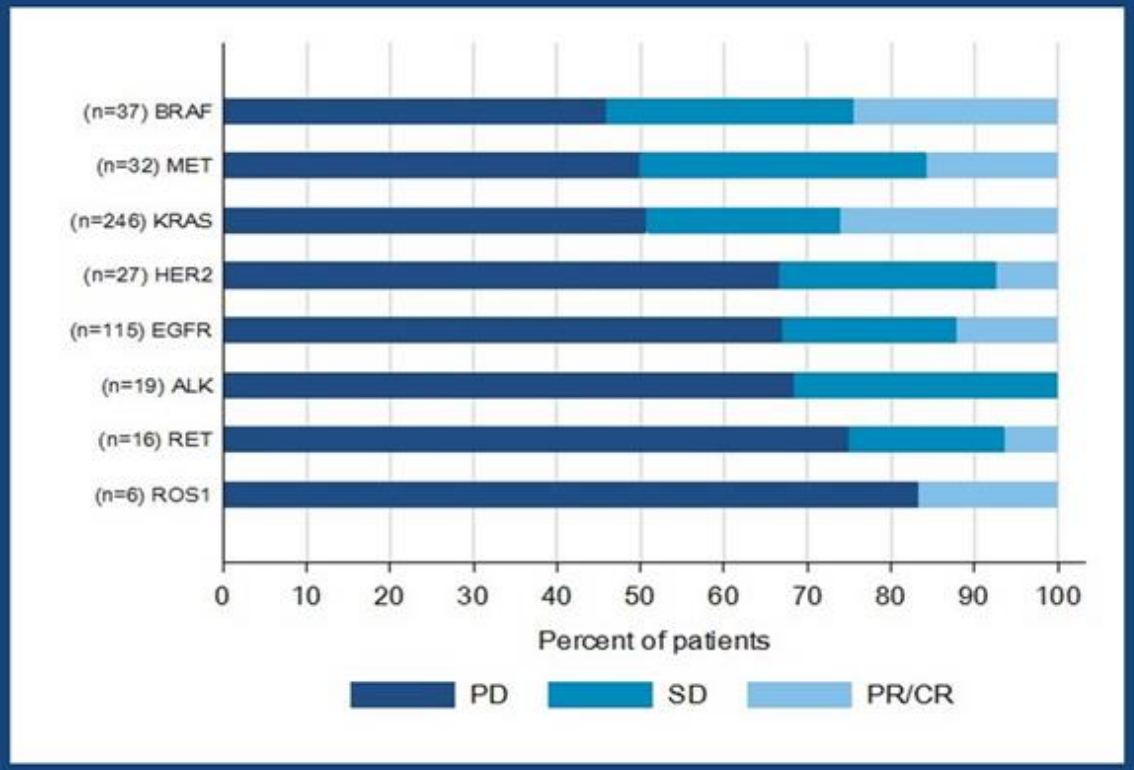


Ortiz-Cuaran et al, Clin Cancer Res 2020.

Immunotherapy in BRAF mt NSCLC

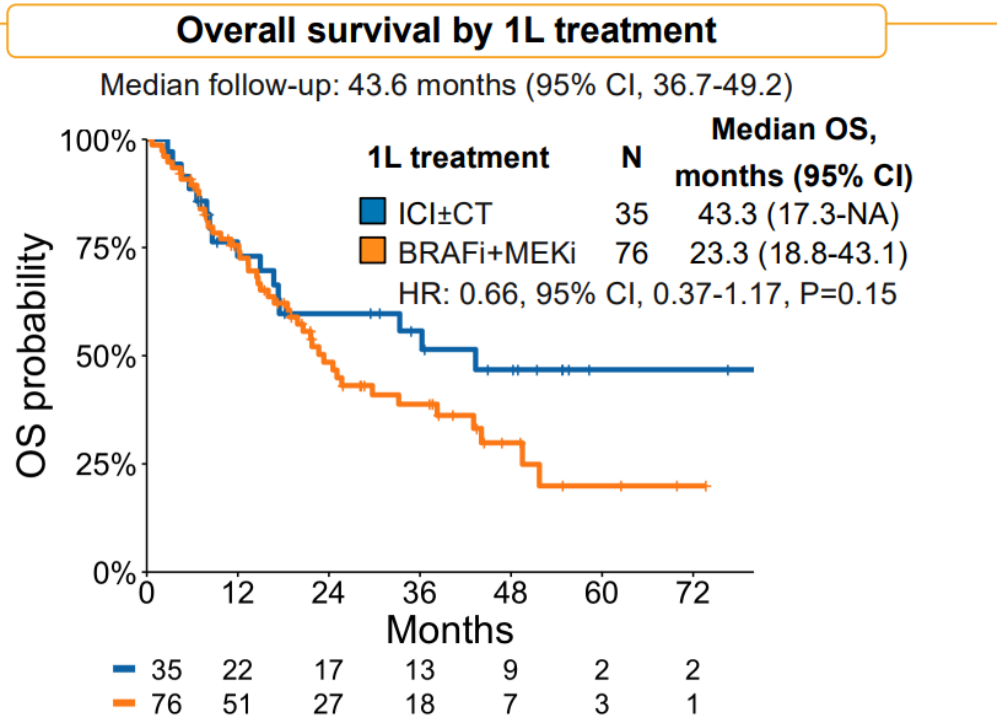
IMMUNOTARGET COHORT: Response

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%

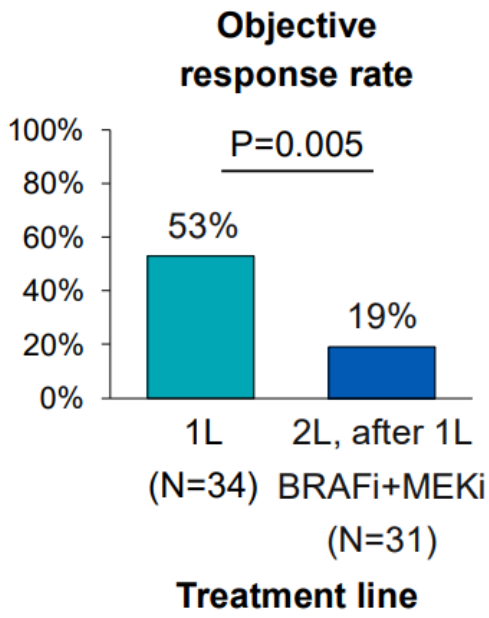


Mazieres et al, ASCO 2018; Mazieres et al, Annals of Oncology 2019.

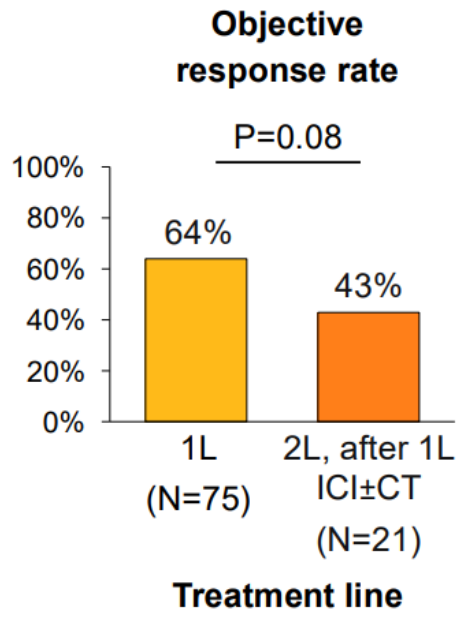
Immunotherapy +/- Chemo in BRAF mt NSCLC



Outcomes of ICI +/- Chemo by line of therapy



Outcomes of BRAKi+ MEKi by line of therapy



Safety of BRAFi+MEKi similar between administration 1st line or 2nd line after ICI± chemotherapy

Di Federico et al, ESMO 2024

Take Home Messages

- Larotrectinib, entrectinib and repotrectinib are highly effective therapies across tumor types harboring NTRK fusions.
  - Defining optimal therapy for on- and off- target resistance may be challenging given rarity of this genotype.
- Dab/Tram and Enco/Bini are highly effective 1st line therapies for patients with BRAF mt NSCLC with slightly distinct toxicity profiles
  - IO +/- chemotherapy remains a viable therapy in the treatment of these patients.