TREATMENT OPTIONS FOR *BRAF*-MUTANT NSCLC

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Conquering Thoracic Cancers Worldwide

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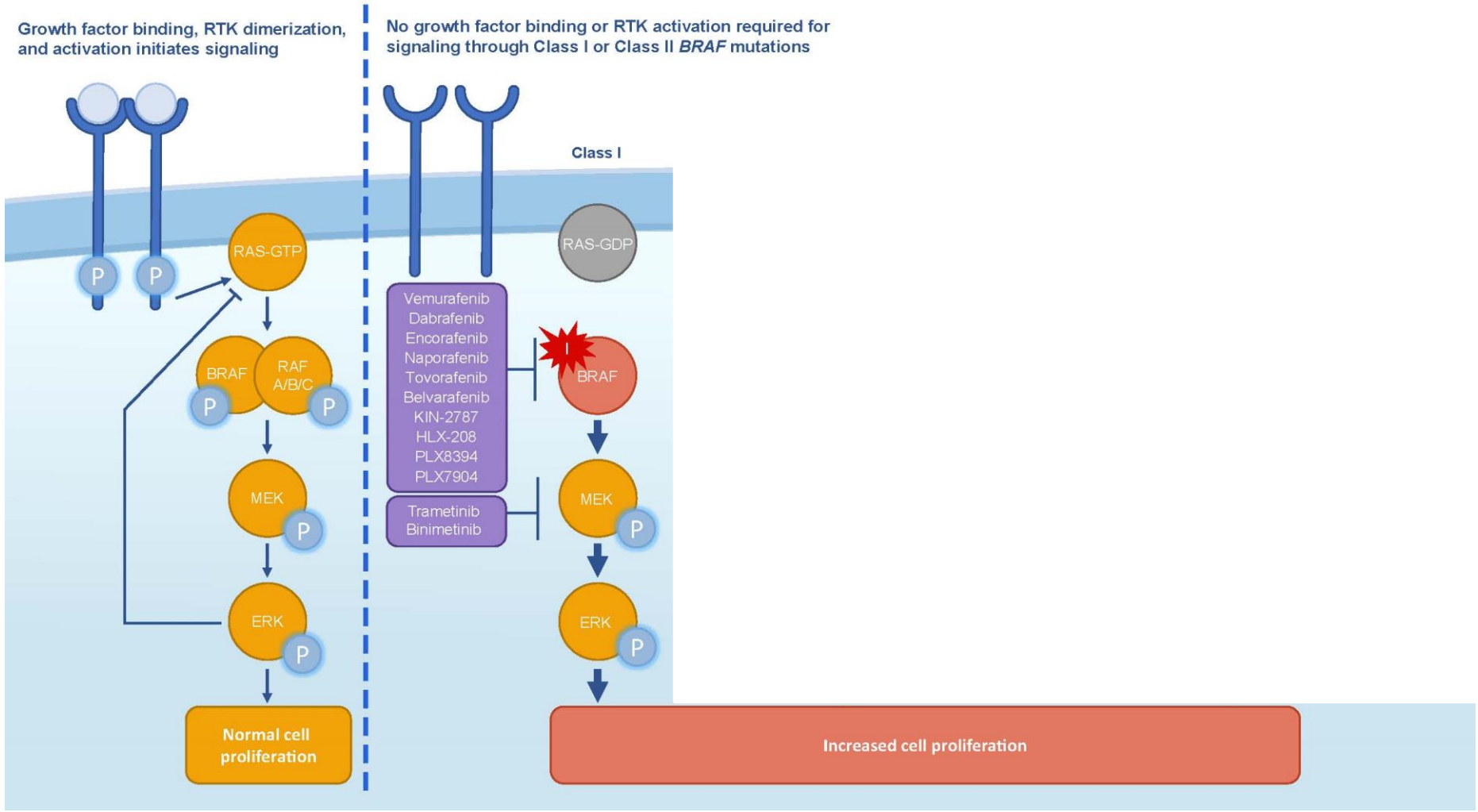
BRAF mutations can be classified into three groups



Adapted from Planchard, Sanborn, Negrao, Vaishnavi, Smit. Accepted for publication - *NPJ Precision Oncology*

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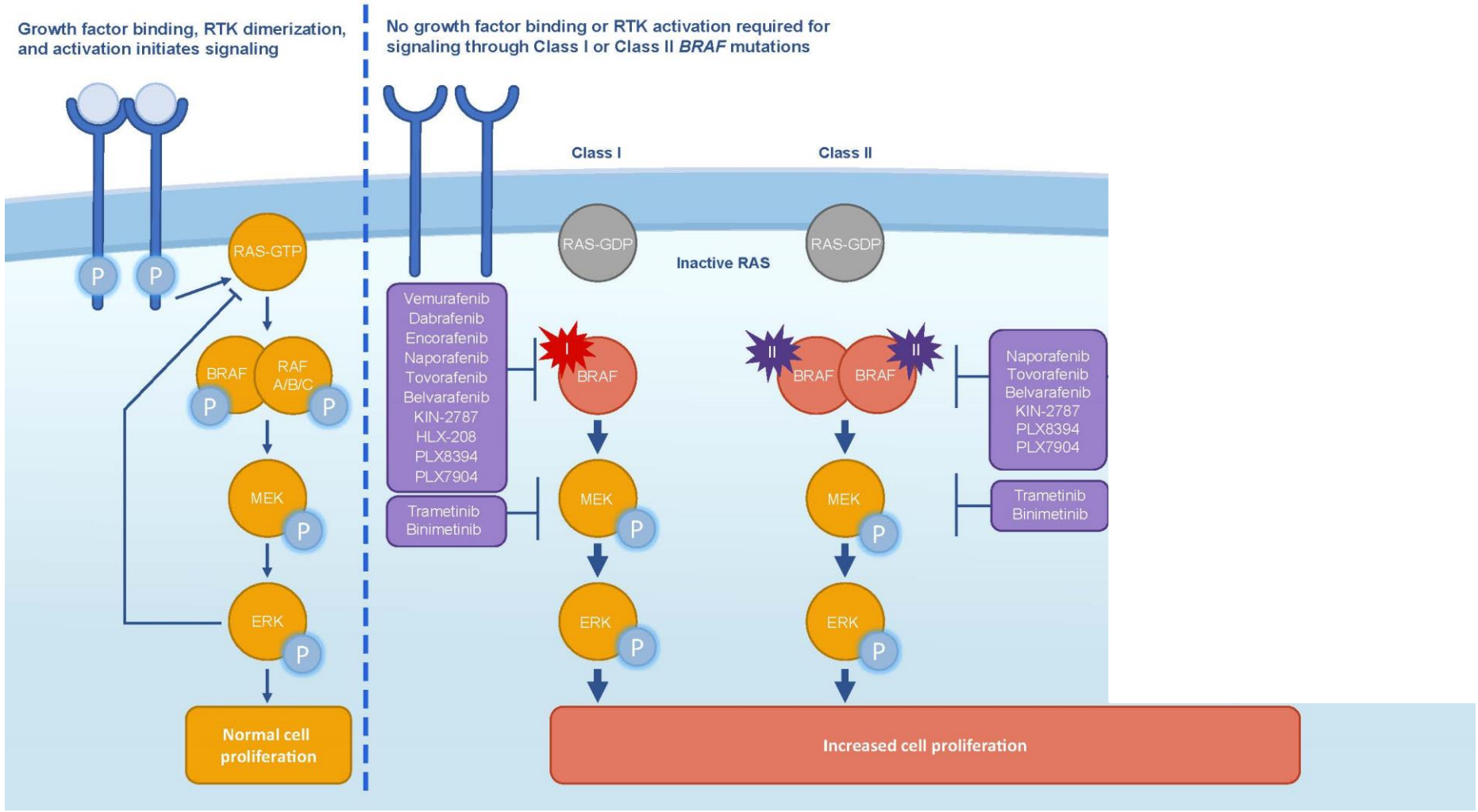

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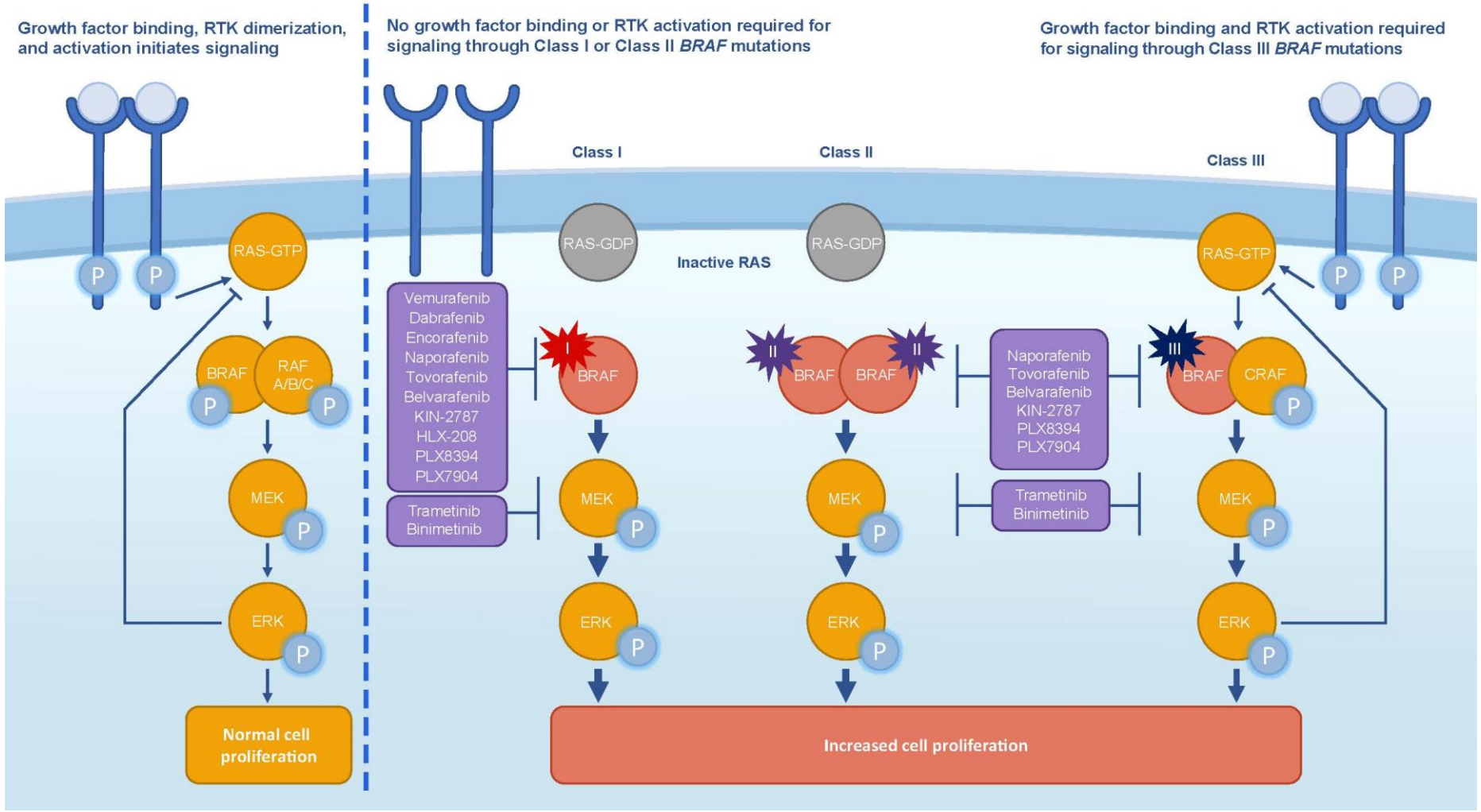

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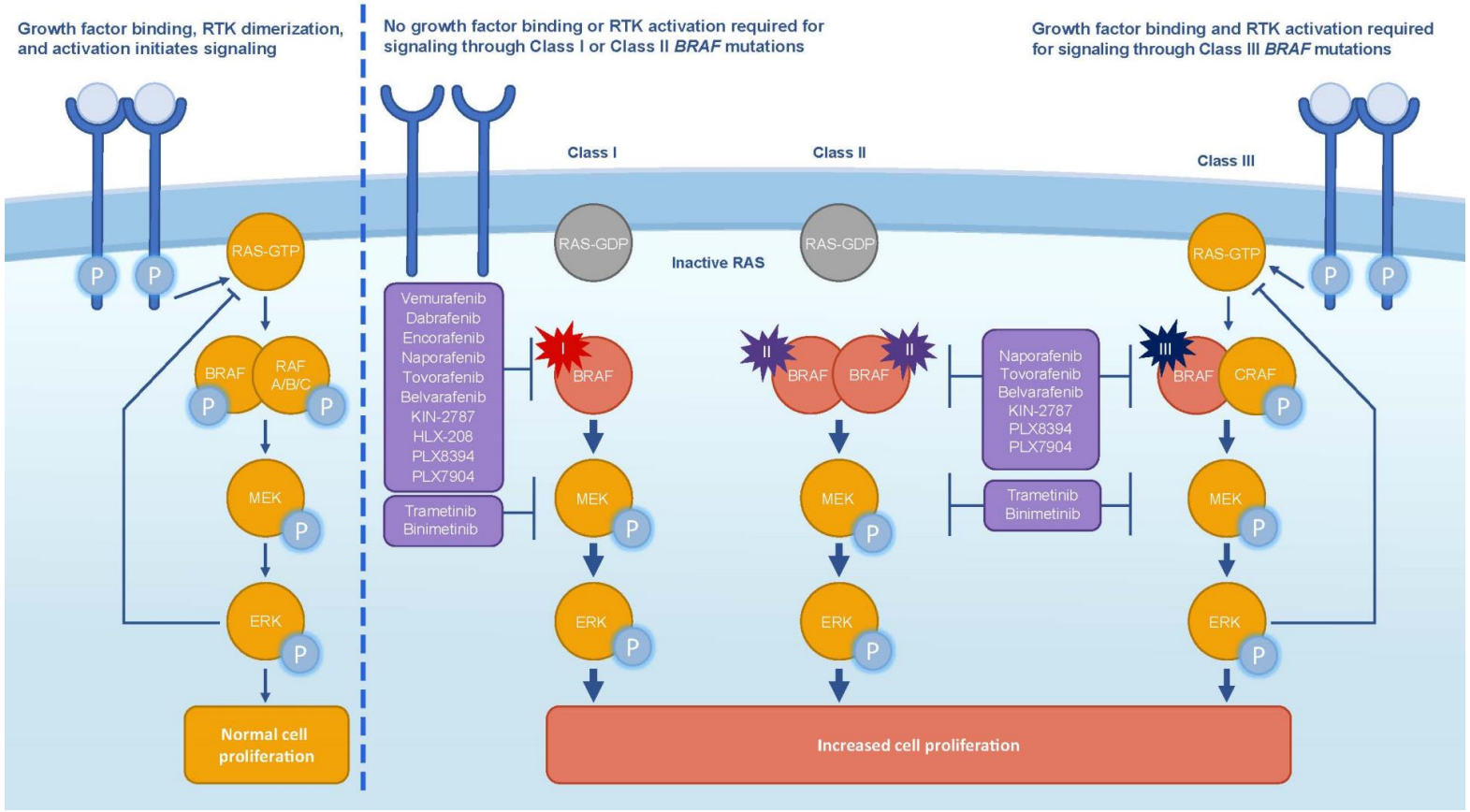
There are several topics for discussion



Class 1

- BRAF+MEKi
- Sequencing options
- Mechanisms of resistance
- Novel therapies
- Treatment of stage I-III disease

Class 2

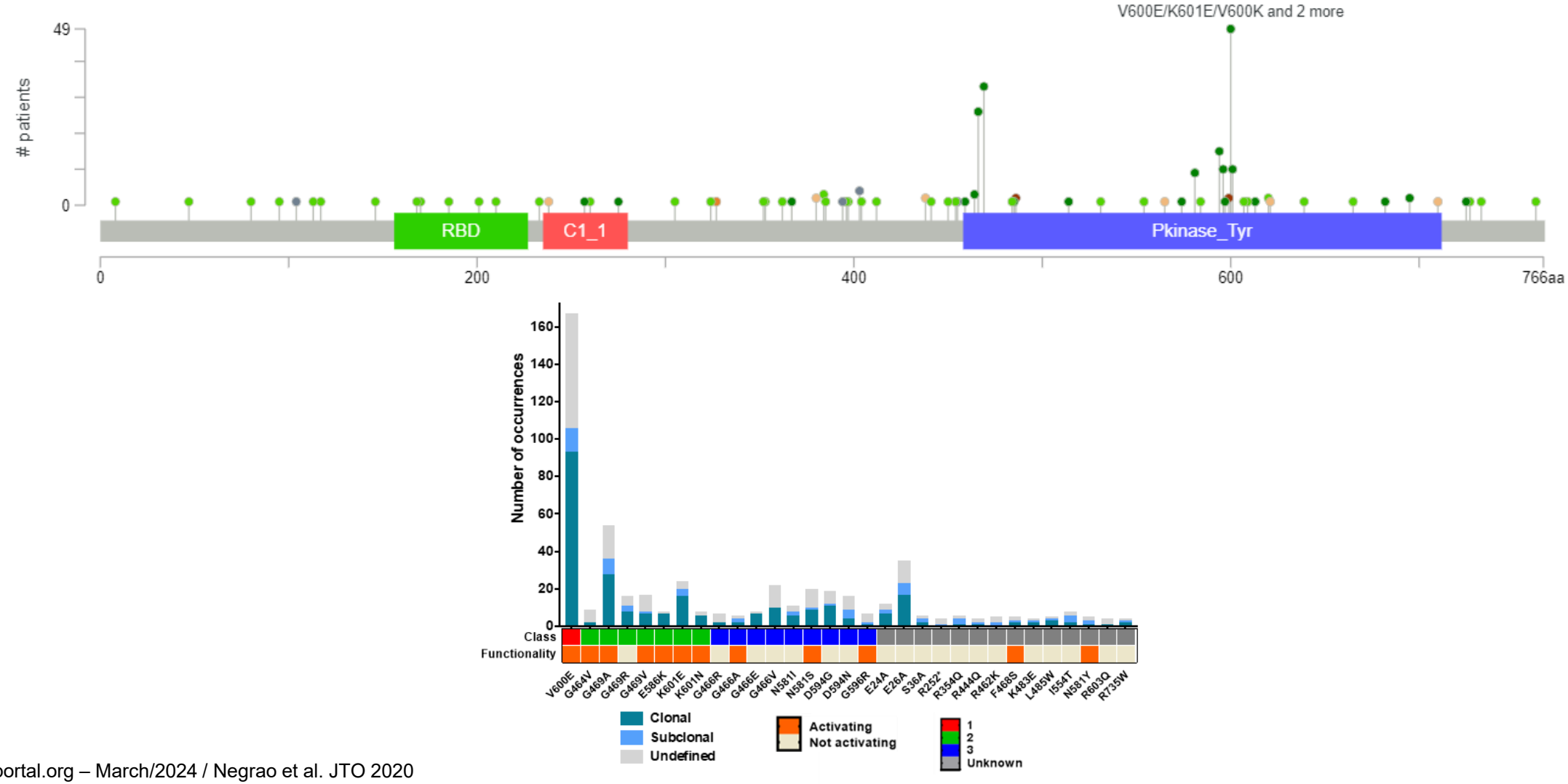
- BRAF+MEKi efficacy
- Novel therapies

Class 3

- Treatment options
- Novel therapies

Adapted from Planchard, Sanborn, Negrao, Vaishnavi, Smit. Accepted for publication - *NPJ Precision Oncology*

V600X are the most prevalent *BRAF* mutations in NSCLC



cbioportal.org – March/2024 / Negrao et al. JTO 2020

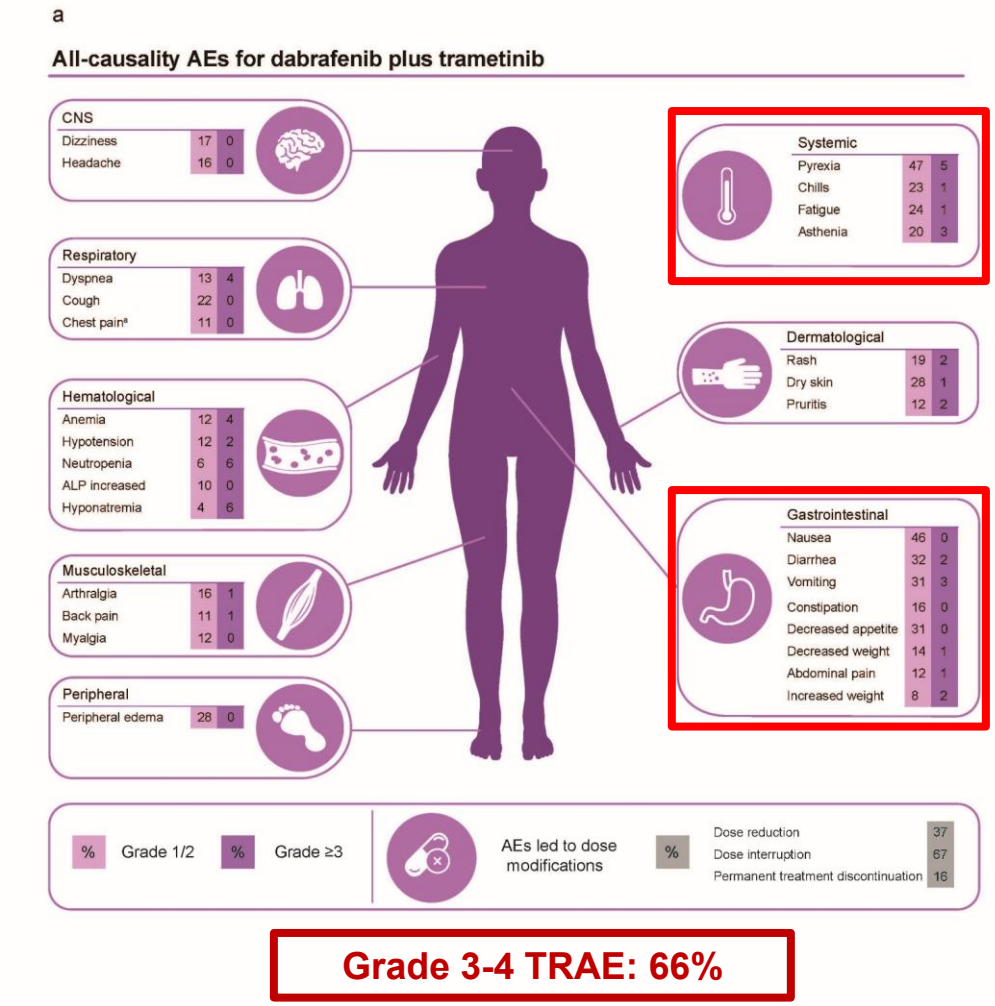
BRAF+MEK inhibitor combos are effective for treatment of *BRAF* V600E NSCLC

	Encorafenib+Binimetinib		Dabrafenib+Trametinib	
	Naïve (N=59)	Prior tx (N=39)	Naïve (N=36)	Prior tx (N=57)
ORR	75%	46%	64%	68%
DOR	NR	16.7 mo	10.2 mo	9.8 mo
PFS	NR	9.3 mo	10.8 mo	10.2 mo
OS	NA	NA	17.3 mo	18.2 mo

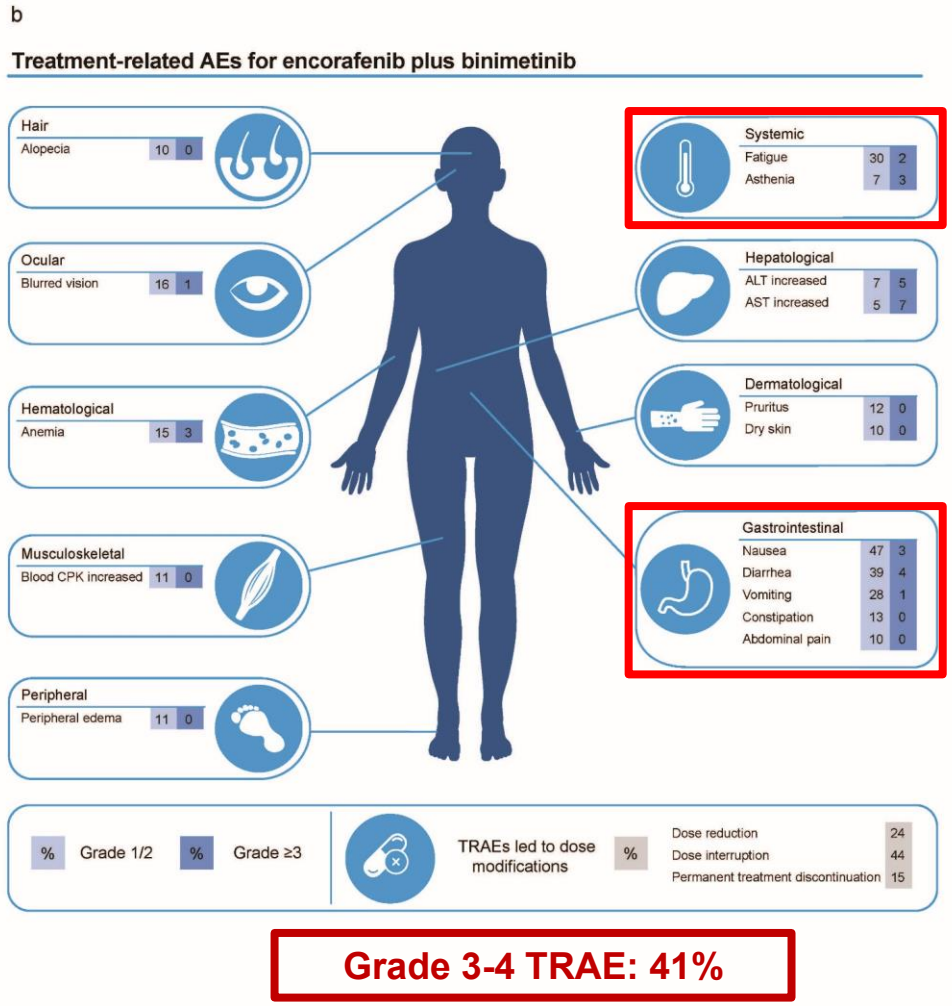
Brain mets underrepresented in both trials – PHAROS: 8/98; D+T - tx-naïve: 2/36; prior tx: 1/57
PHAROS: prior ICI: 59% / ICI post-PD: 17% for tx naïve vs 26% for prior tx
D+T trial: prior ICI – none / ICI post-PD: ~25%

Adapted from Riely et al. JCO 2023, Planchard et al. JTO 2021

Side effect profile differs for D+T and E+B



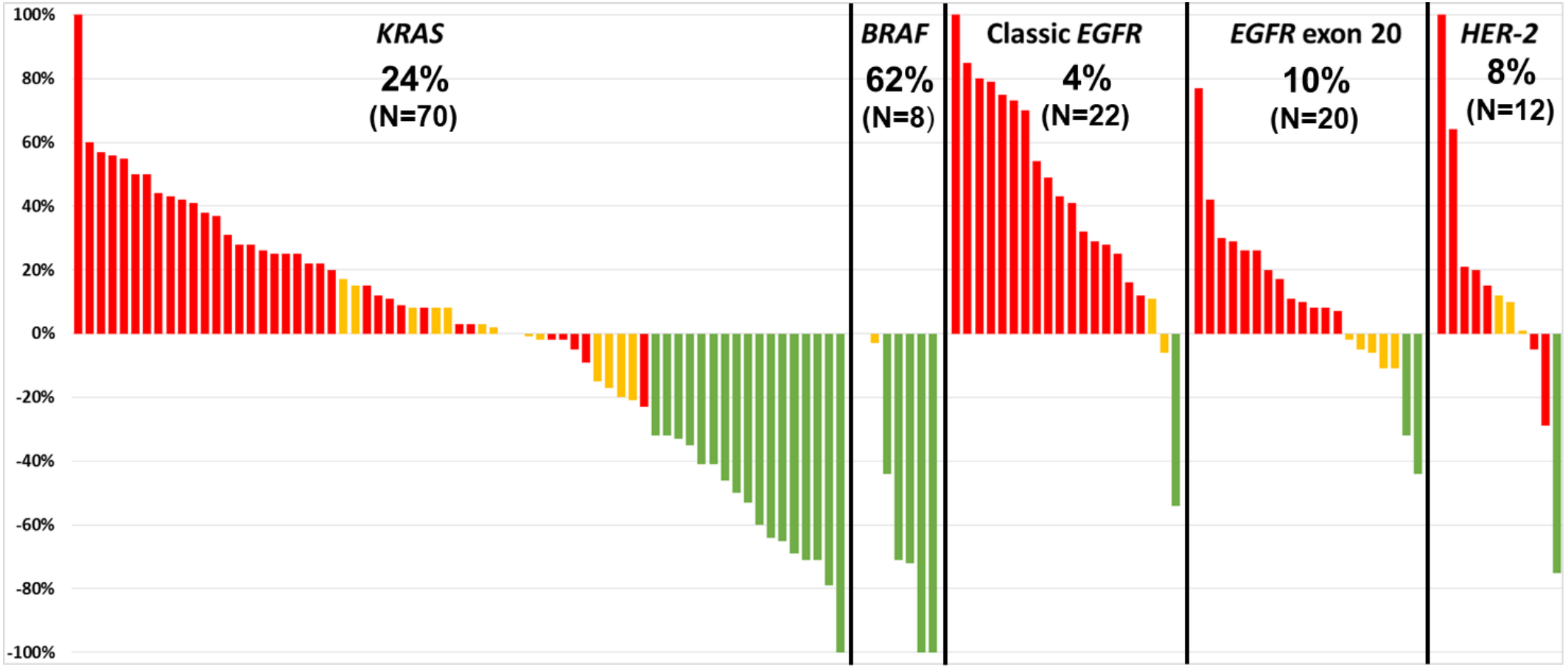
Grade 3-4 TRAE: 66%



Grade 3-4 TRAE: 41%

Planchard et al. JTO 2021; Riely et al. JCO 2023; Planchard, Sanborn, Negrao, Vaishnavi, Smit. Accepted for publication - *NPJ Precision Oncology*

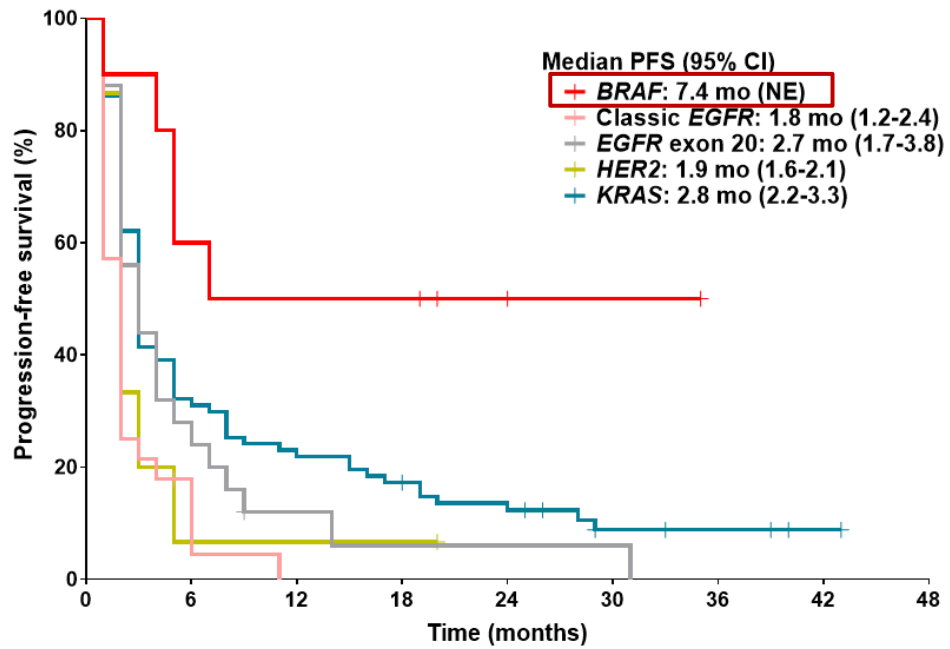
BRAF-mutant NSCLC patients may have more favorable clinical outcomes to PD-1/PD-L1 inhibitor therapy…



Negrao et al. WCLC 2019

BRAF-mutant NSCLC patients may have more favorable clinical outcomes to PD-1/PD-L1 inhibitor therapy…

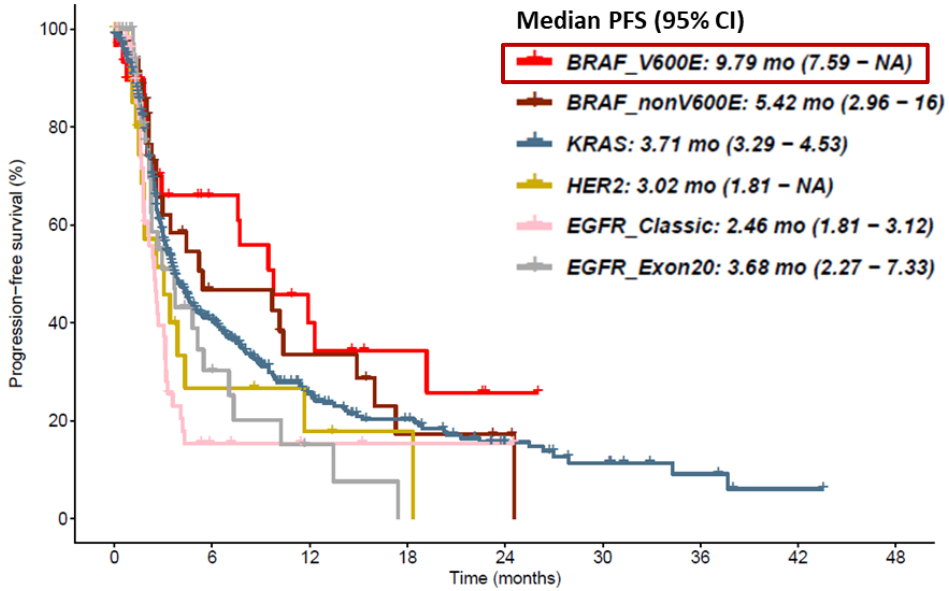
A



Number at risk

BRAF	10	6	5	3	1	1	0	0	0
Classic *EGFR*	28	2	0	0	0	0	0	0	0
EGFR Exon 20	25	7	2	1	1	1	0	0	0
HER2	15	1	1	1	0	0	0	0	0
KRAS	87	27	20	15	9	4	2	1	0

B



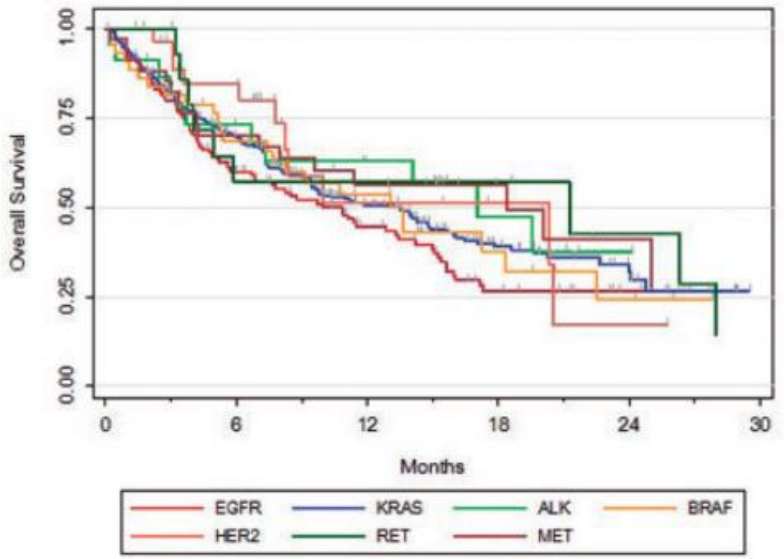
Number at risk

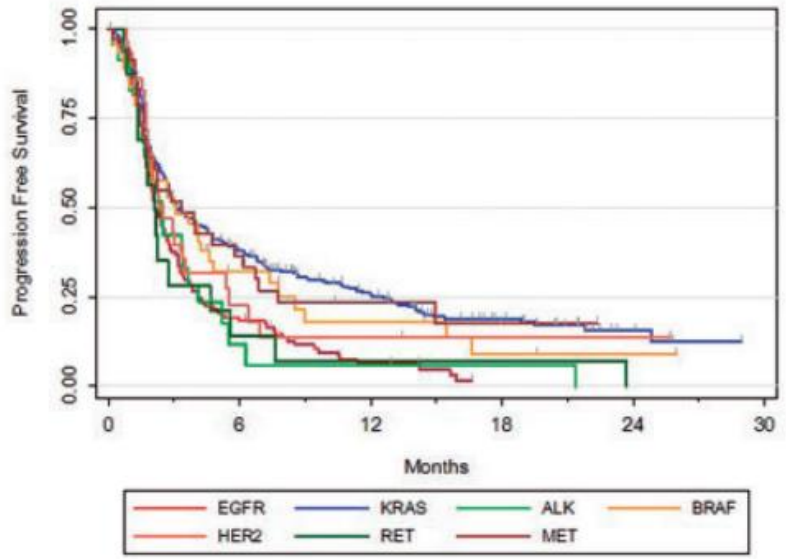
BRAF V600E	30	13	7	4	1	0	0	0	0
BRAF non-V600E	36	11	7	3	2	0	0	0	0
Classic *EGFR*	54	4	2	1	1	0	0	0	0
EGFR Exon 20	37	7	2	0	0	0	0	0	0
HER2	21	4	2	1	0	0	0	0	0
KRAS	529	138	53	33	17	9	4	1	0

Negrao et al. JITC 2021

… or maybe not

Oncogenic driver subgroups *n*=543

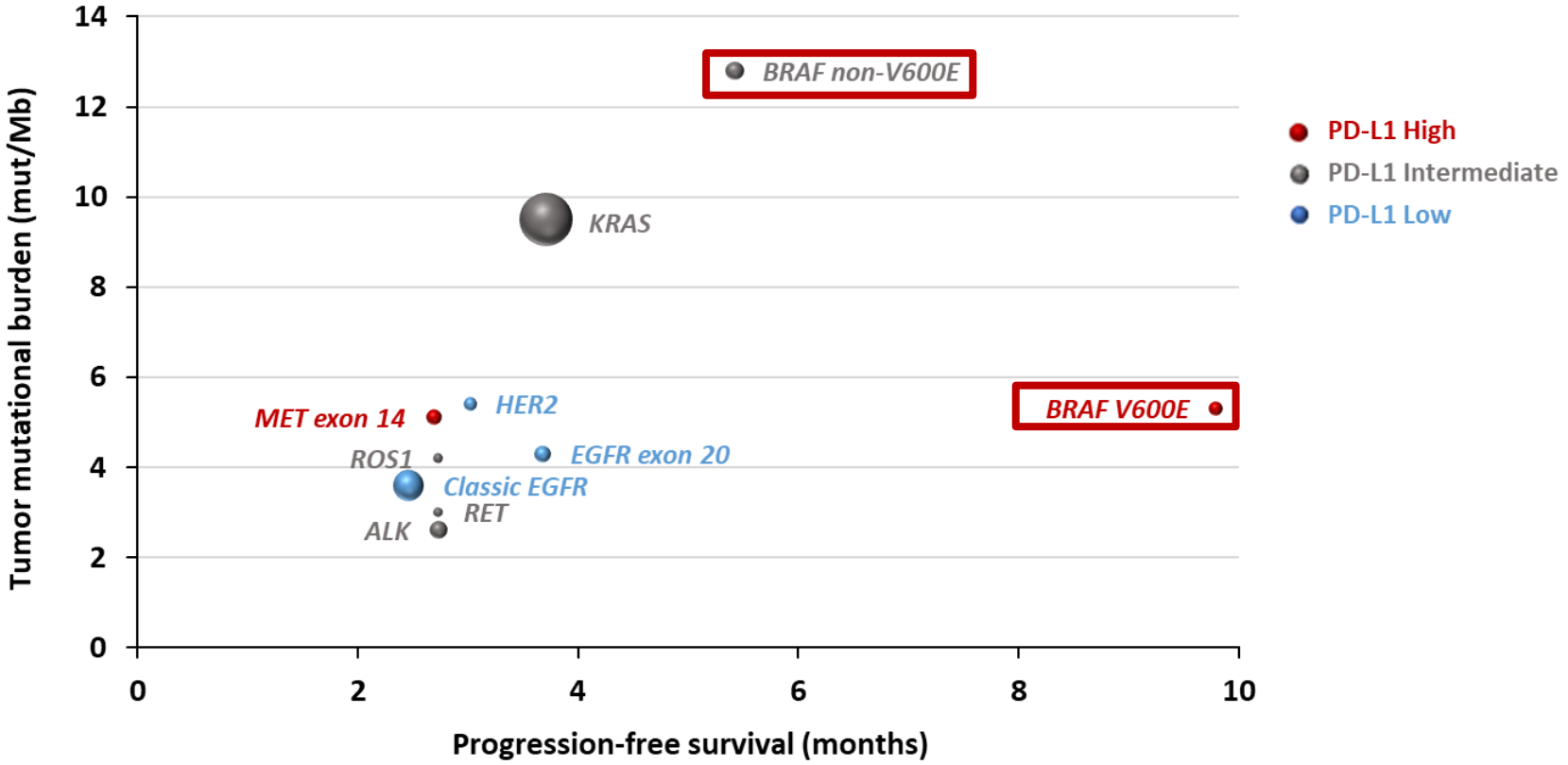




	EVT/*N*	Median PFS [95% CI] (months)	6-month PFS [95% CI]	12-month PFS [95% CI]
KRAS	208/271	3.2 [2.7; 4.5]	37.9 [32.1; 49.8]	25.6 [20.2; 31.3]
EGFR	117/125	2.1 [1.8; 2.7]	18.4 [12.1; 25.6]	6.4 [2.7; 12.1]
BRAF	34/43	3.1 [1.8; 4.6]	32.1 [18.3; 46.6]	18.0 [7.2; 32.7]
HER2	23/29	2.5 [1.8; 3.5]	22.7 [8.9; 40.2]	13.6 [3.6; 30.1]
MET	26/36	3.4 [1.7; 6.2]	36.5 [20.7; 52.4]	23.4 [10.6; 39.0]
ALK	21/23	2.5 [1.5; 3.7]	11.8 [2.2; 30.2]	5.9 [0.4; 23.0]
ROS1	–	–	–	–
RET	15/16	2.1 [1.3; 4.7]	14.1 [2.3; 35.9]	7.0 [0.4; 27.1]

Mazieres et al. Annals of Oncology 2019

BRAF-mutant NSCLC patients can have favorable TMB and PD-L1 expression profile for PD-1/PD-L1 inhibitor therapy



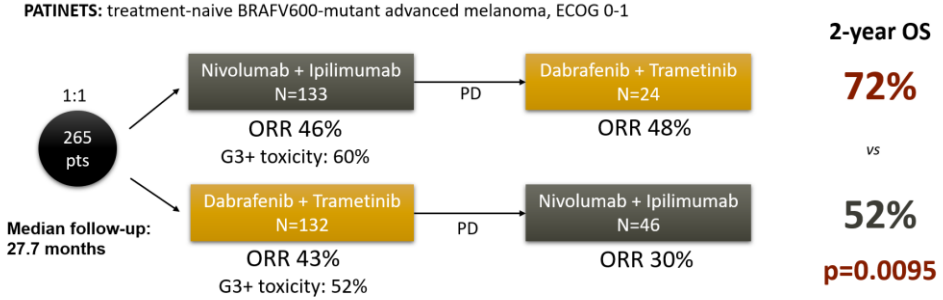
Negrao et al. JITC 2021

Melanoma trials suggest frontline anti-PD-1+CTLA-4 combo is superior to BRAF+MEK inhibitor combo

DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): A phase III trial—ECOG-ACRIN EA6134

AIM: to compare the efficacy and toxicity of the sequence of nivolumab/ipilimumab followed by dabrafenib/trametinib to the converse sequence

PATINETS: treatment-naive BRAFV600-mutant advanced melanoma, ECOG 0-1



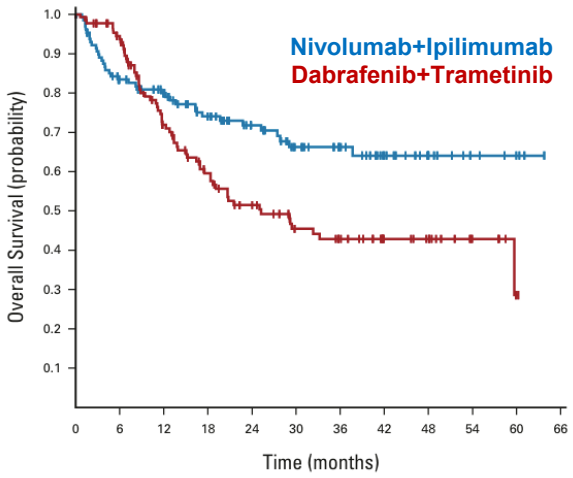
2-year OS

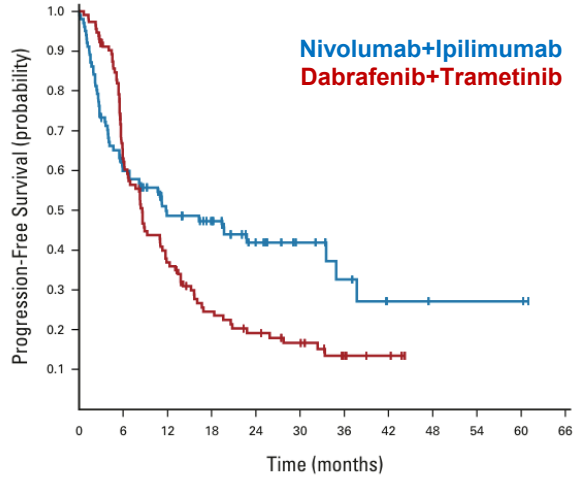
72%

vs

52%

p=0.0095





No. at risk:	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66
A/C	133	99	87	71	55	42	33	23	15	6	3
B/D	132	115	78	60	47	35	30	18	15	6	1

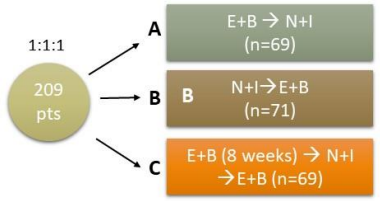
No. at risk:	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66
A	101	57	40	32	19	12	7	3	2	2	2
B	113	66	38	23	17	13	6	3	0	0	0

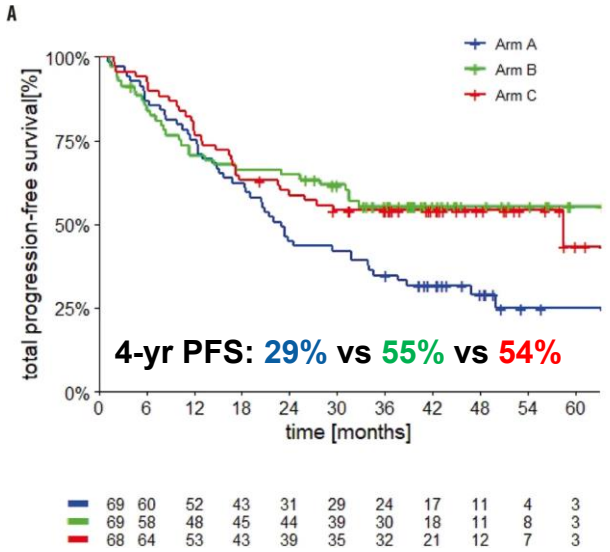
2021 ESMO congress

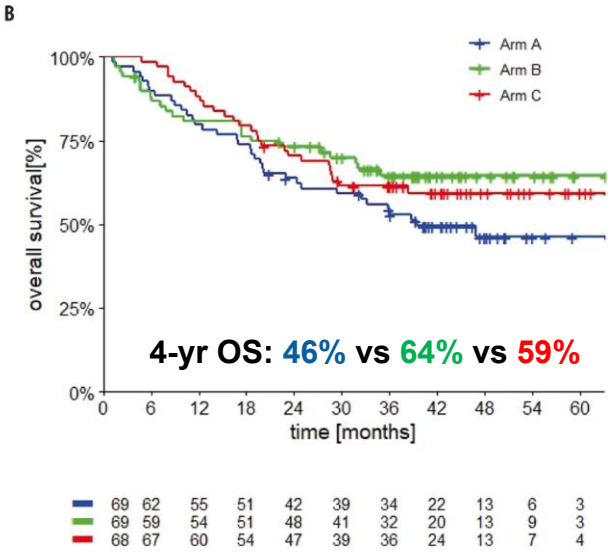
SECOMBIT: The best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma: A phase II randomized study

Population:
- metastatic BRAFV600-mutated melanoma
- treatment naïve
- ECOG PS 0 or 1

Primary endpoint:
- overall survival







	69	60	52	43	31	29	24	17	11	4	3
	69	58	48	45	44	39	30	18	11	8	3
	68	64	53	43	39	35	32	21	12	7	3

	69	62	55	51	42	39	34	22	13	6	3
	69	59	54	51	48	41	32	20	13	9	3
	68	67	60	54	47	39	36	24	13	7	4

Atkins et al. ASCO Plenary Series 2021 and JCO 2022 / Ascierto et al. ESMO 2021 and Nature Communications 2024

Launch of a multi-institution collaborative effort to determine the optimal treatment sequence for *BRAF* V600E NSCLC patients

Multi-institution project
DFCI – Ricciuti / Di Federico
MSKCC – Offin / Chen
Gustave Roussy – Aldea
Bologna – Ardizzoni
Yale – Stockhammer
Detroit – Rous
UChicago – Garassino / Tawhani

Aim: determine best treatment sequence in BRAF V600E NSCLC

Primary endpoint: OS

Population:
- Advanced NSCLC
- BRAF V600X

Interest and support are welcome for this important effort

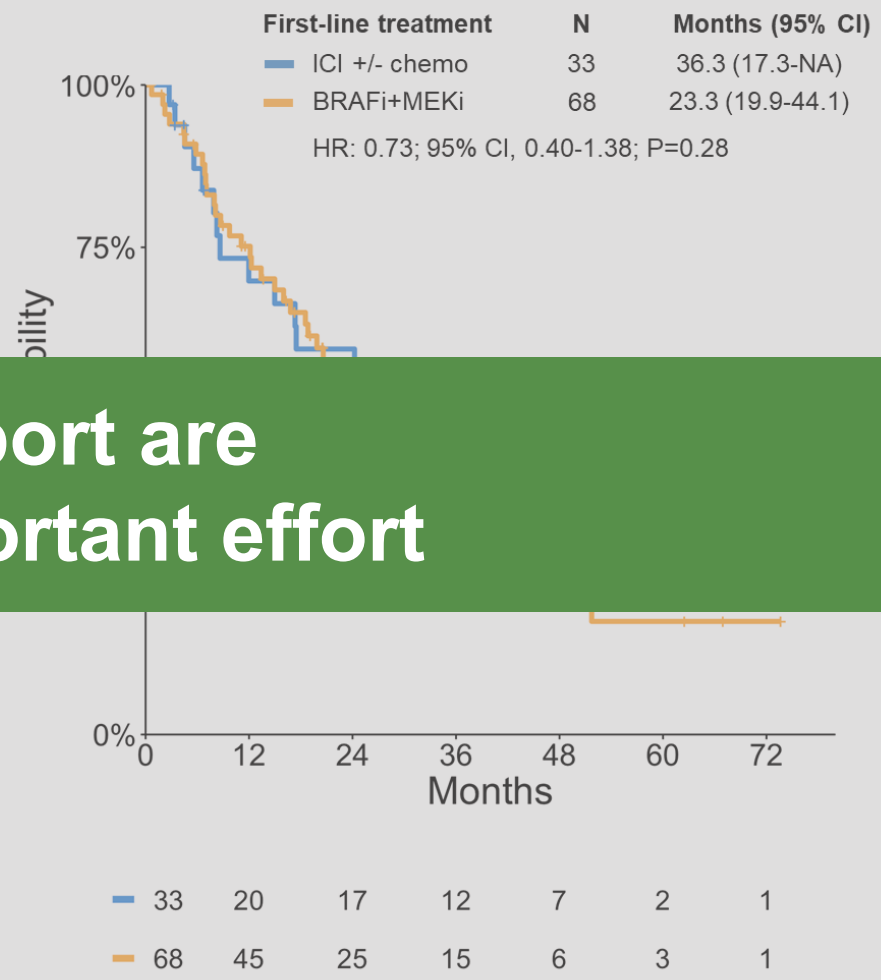
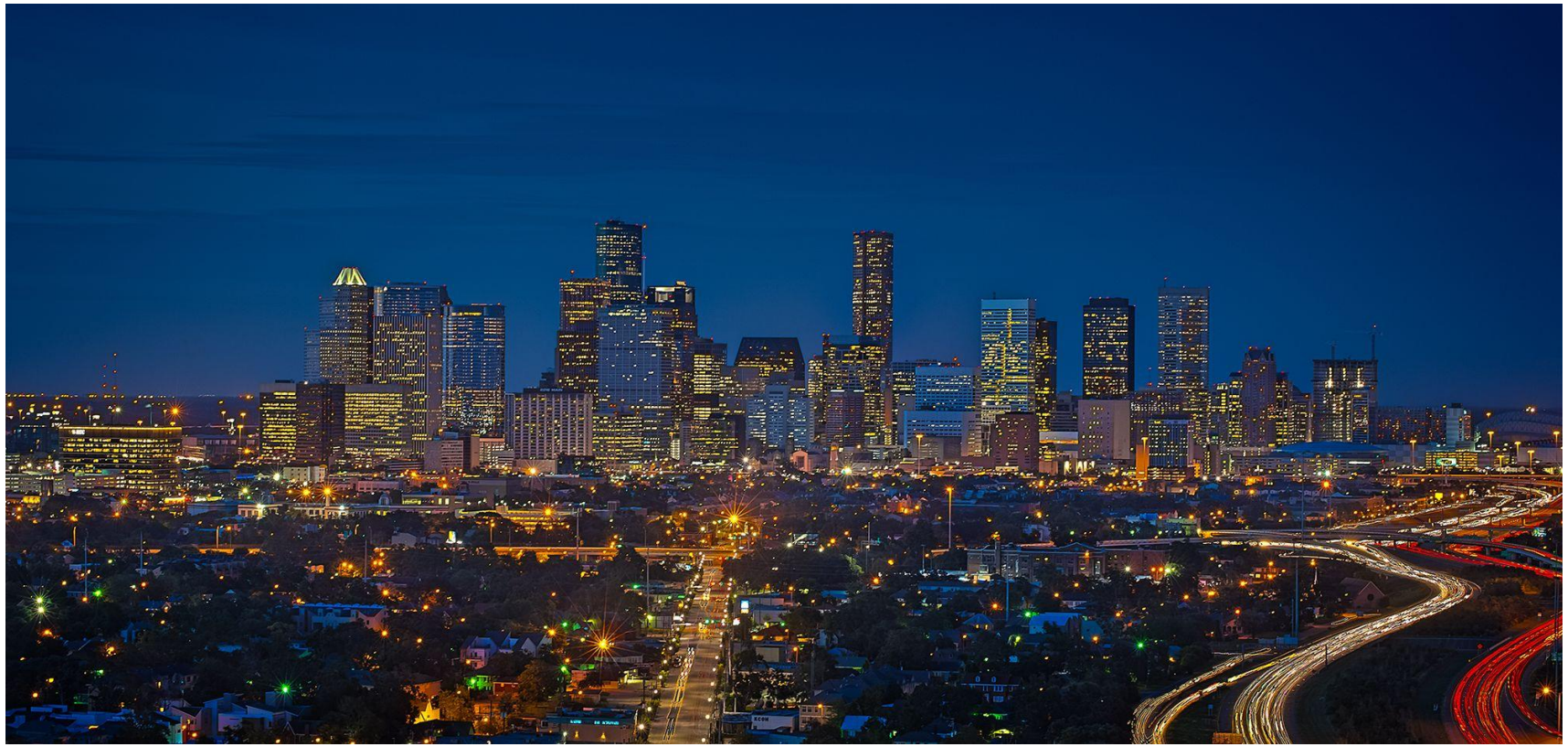


Figure courtesy of Biagio Ricciuti

Conclusions

- *BRAF* mutations are categorized into three classes based on their functional properties
- *BRAF* V600X are the most prevalent mutations
- BRAF+MEK inhibitors: effective for frontline and salvage therapy with distinctions in safety profile
- Role of ICI remains subject of further investigation – PD-L1 and/or TMB high status may favor ICI therapy over BRAF+MEK inhibitor combo
- Multi-institution efforts collaborations are key in this disease space
  - Necessary to answer relevant clinical questions since *BRAF* V600X mutations are uncommon drivers in NSCLC
  - May facilitate clinical trial development - particularly in the frontline setting

Thank you for your time and attention!



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