Best Practices for *BRAF*-Mutant Lung Cancer

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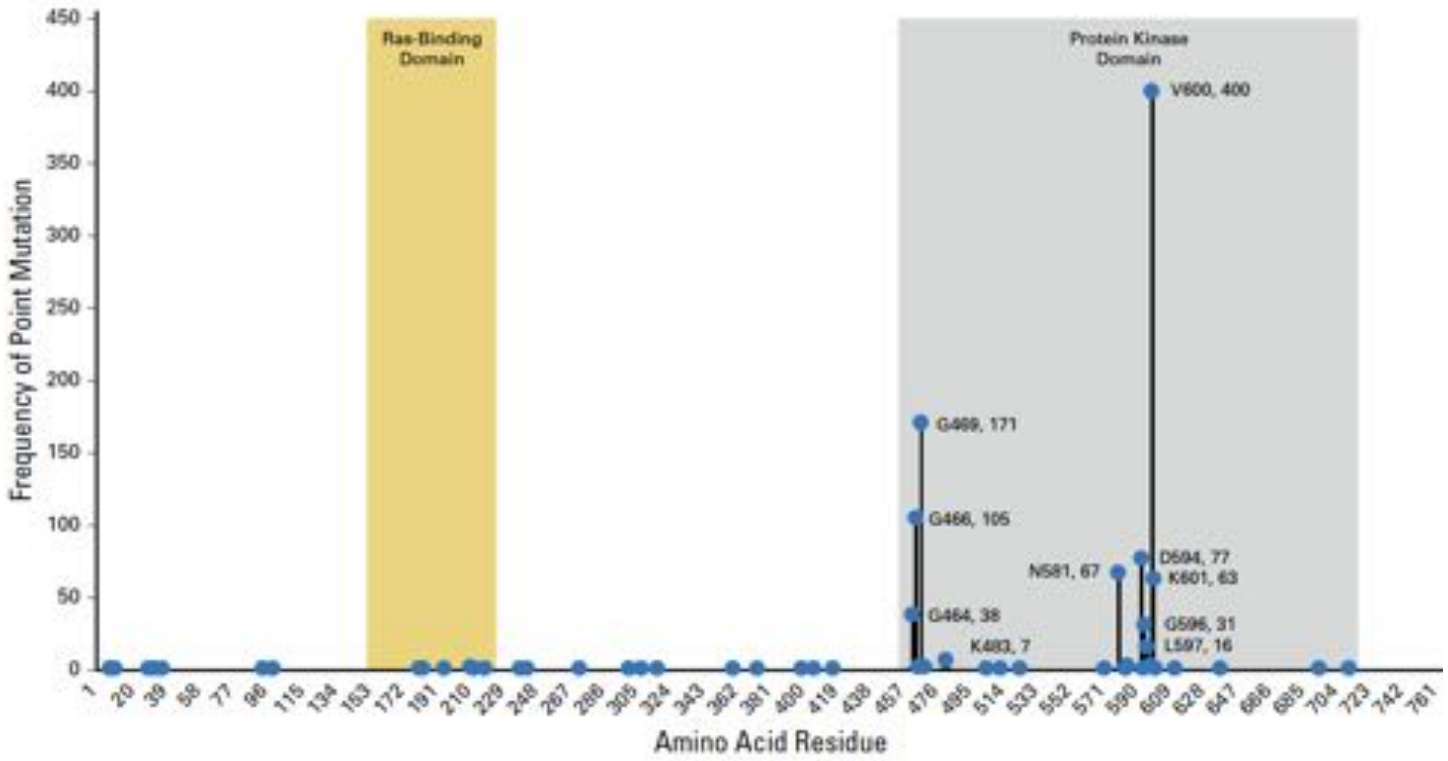
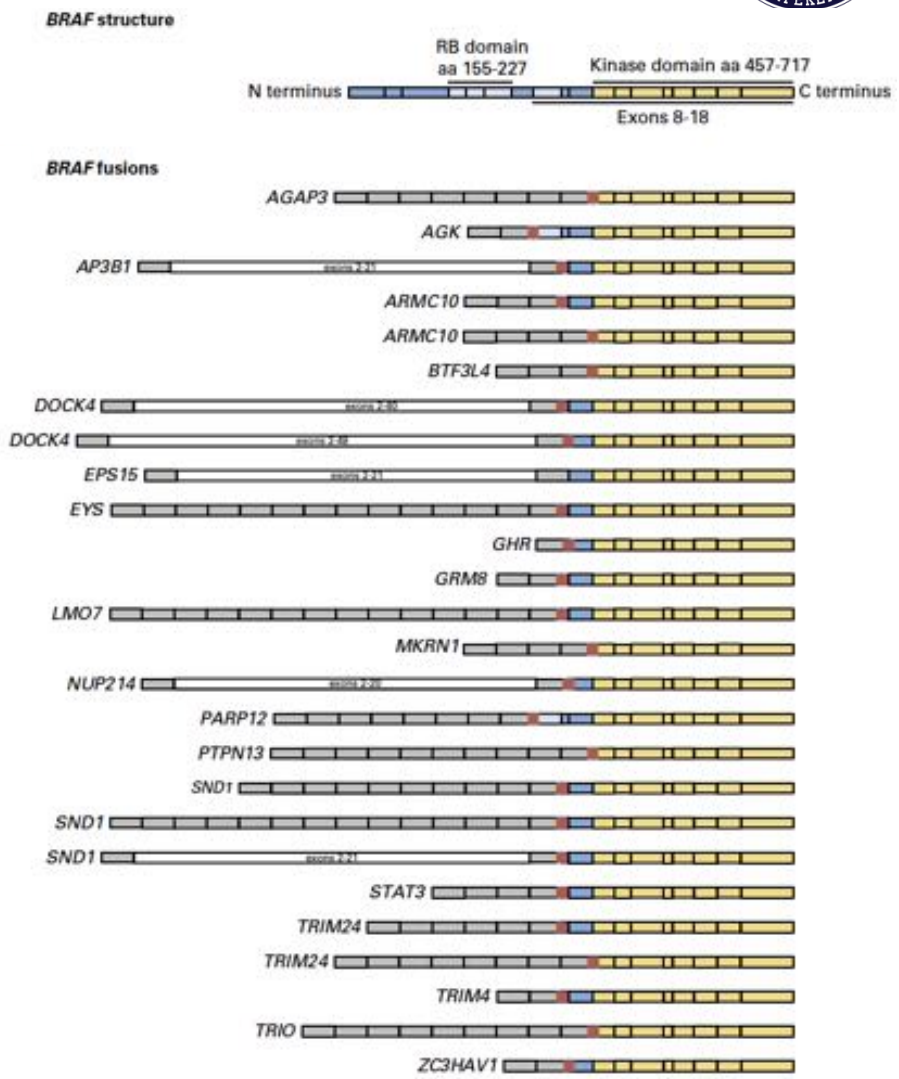
BRAF Alterations in Lung Cancer

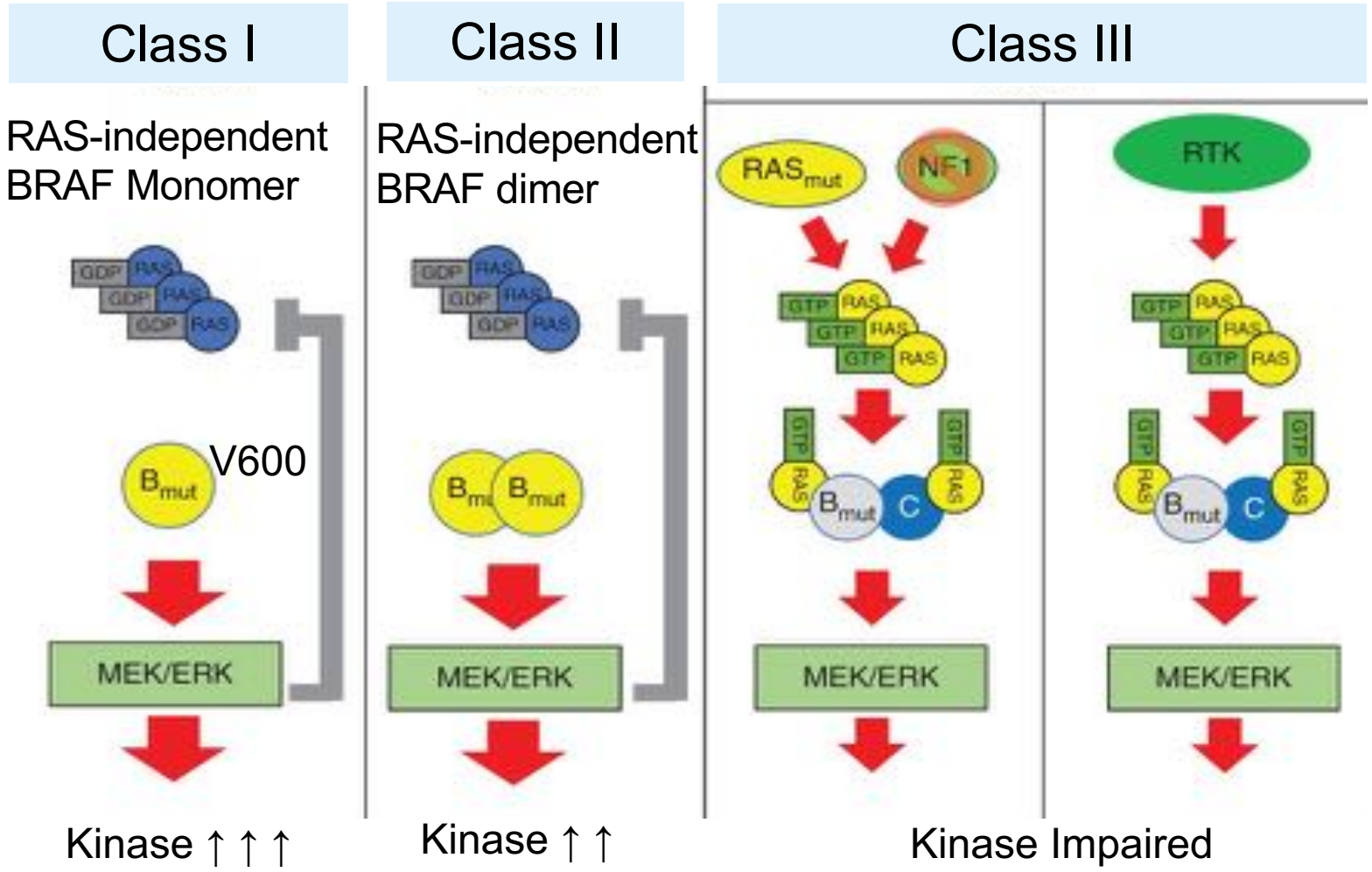
- ***BRAF* alterations** are present in 4-5% of NSCLC
- **V600** mutations comprise ~ 40% of BRAF alterations
- ***BRAF* fusions** (de novo, acquired) in <1% of NSCLC



Sheikine JCO Precision Oncology 2018



Mechanisms of RAF Activation and Signalling



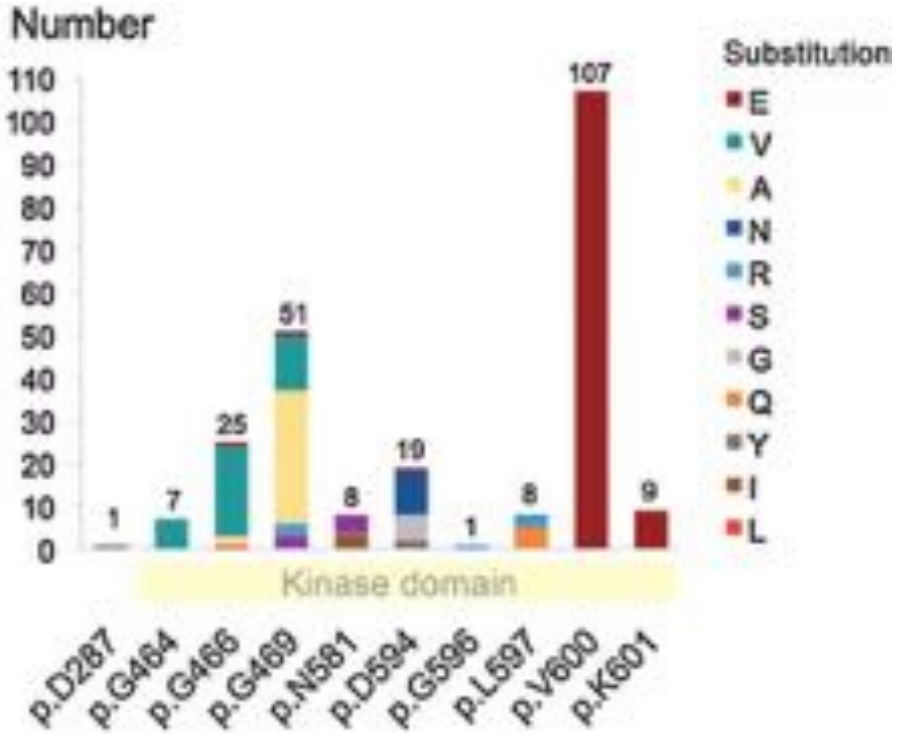
Class III
RAS-dependent
- RTK activation
- NF1 inactivation
- *KRAS* mutation

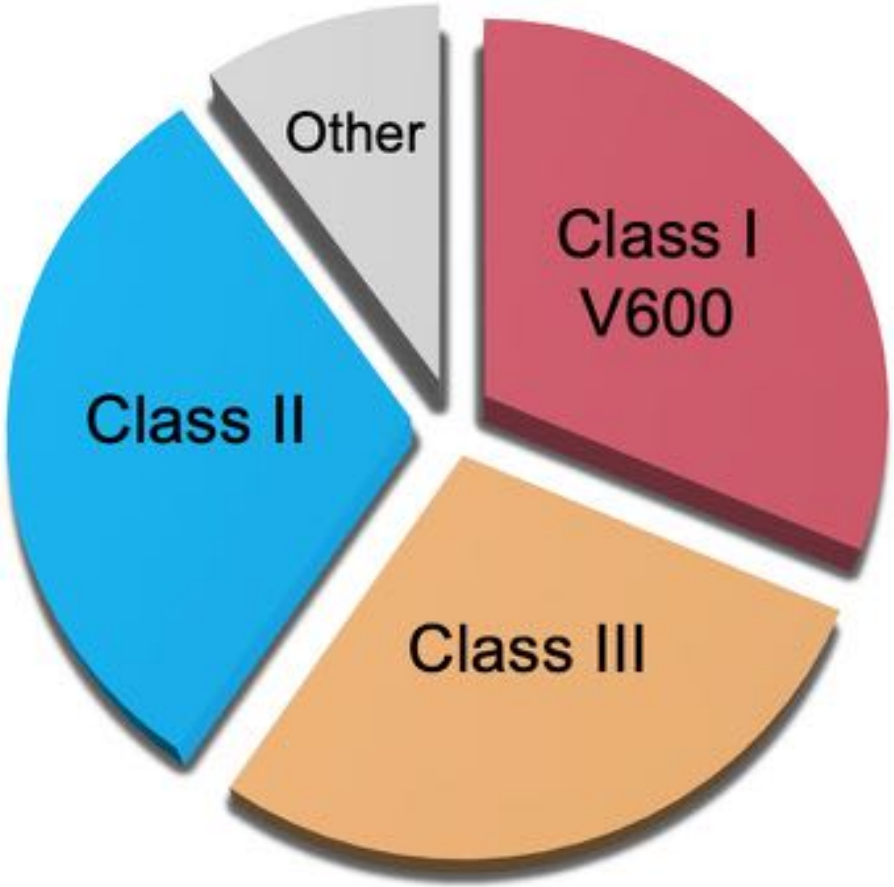
BRAF-CRAF heterodimer

Adapted from Yaeger Cancer Discovery 2019

Class I-III BRAF Alterations in Lung Cancer

Class	BRAF Alteration
Class I	V600
Class II	K601E, L597V/Q/R, G469V/S/R/E/A, G464V, *BRAF* fusions
Class III	G596R, D594Y/N/G/E, N581Y/S/I, G466V/L/E/A, D287Y

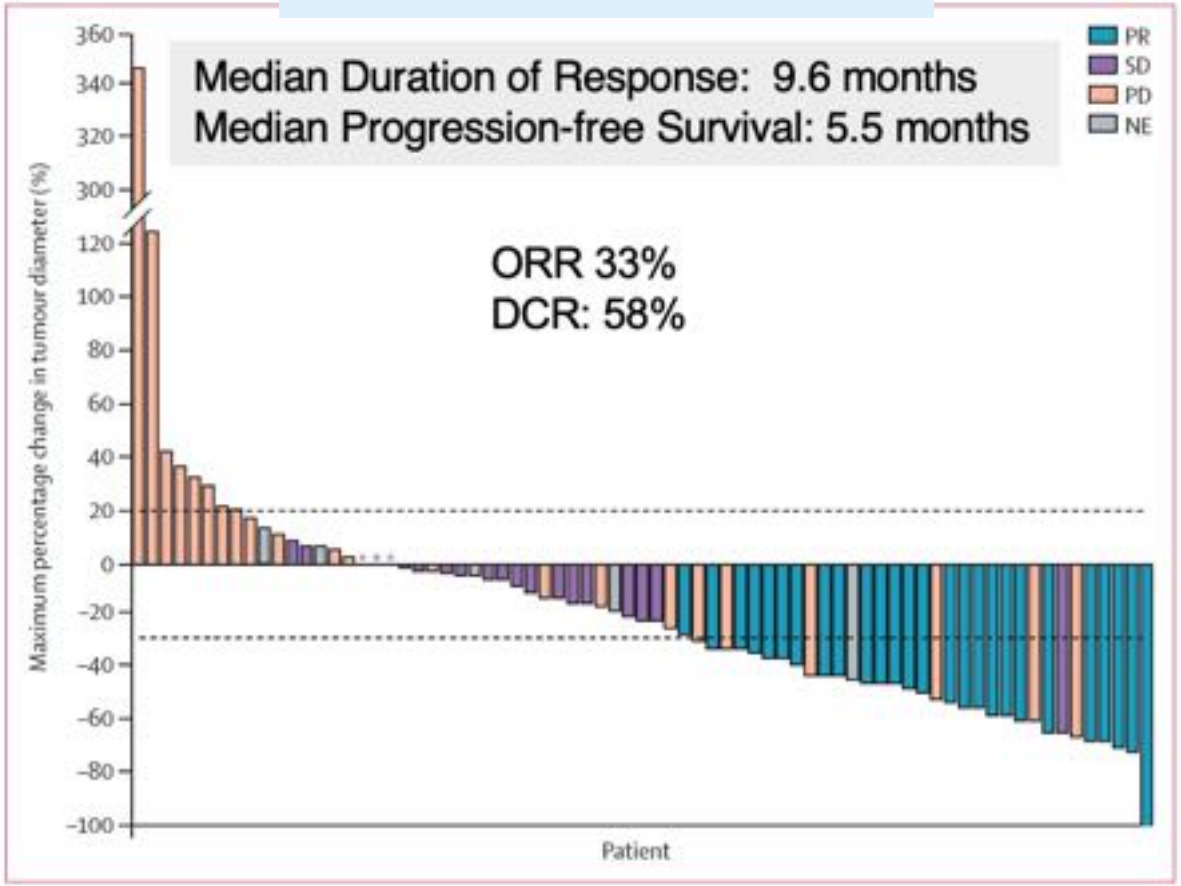




Dagogo-Jack Clinical Cancer Research 2019

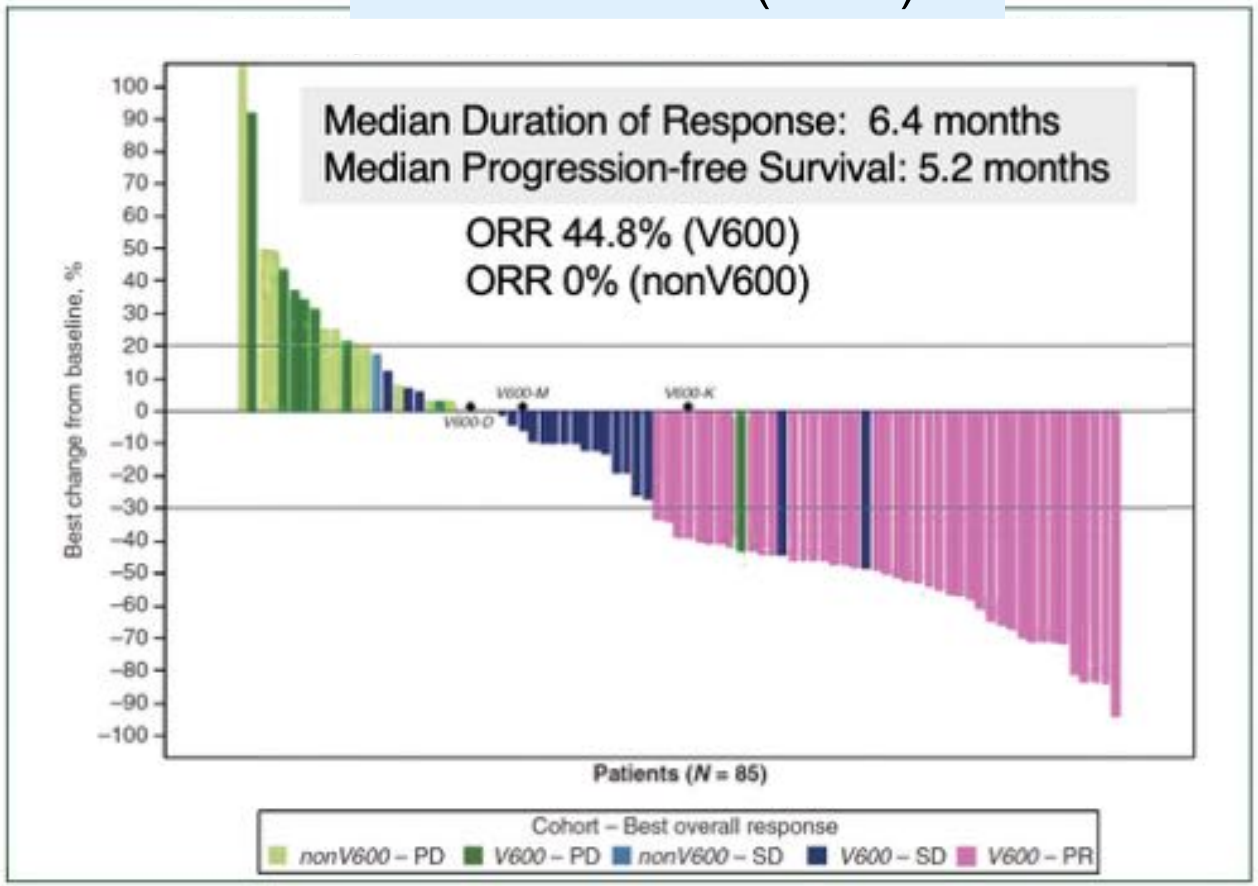
BRAF Monomer Inhibitors in Class I BRAFmut NSCLC

Dabrafenib



Planchard Lancet 2016

Vemurafenib (AcSe)

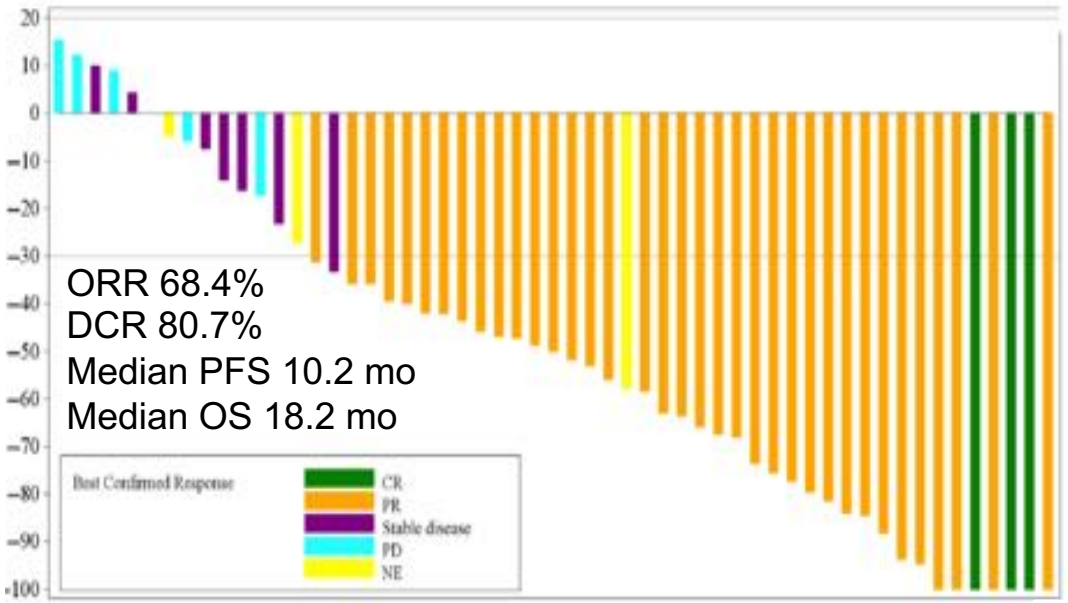


Mazieres Annals of Oncology 2020

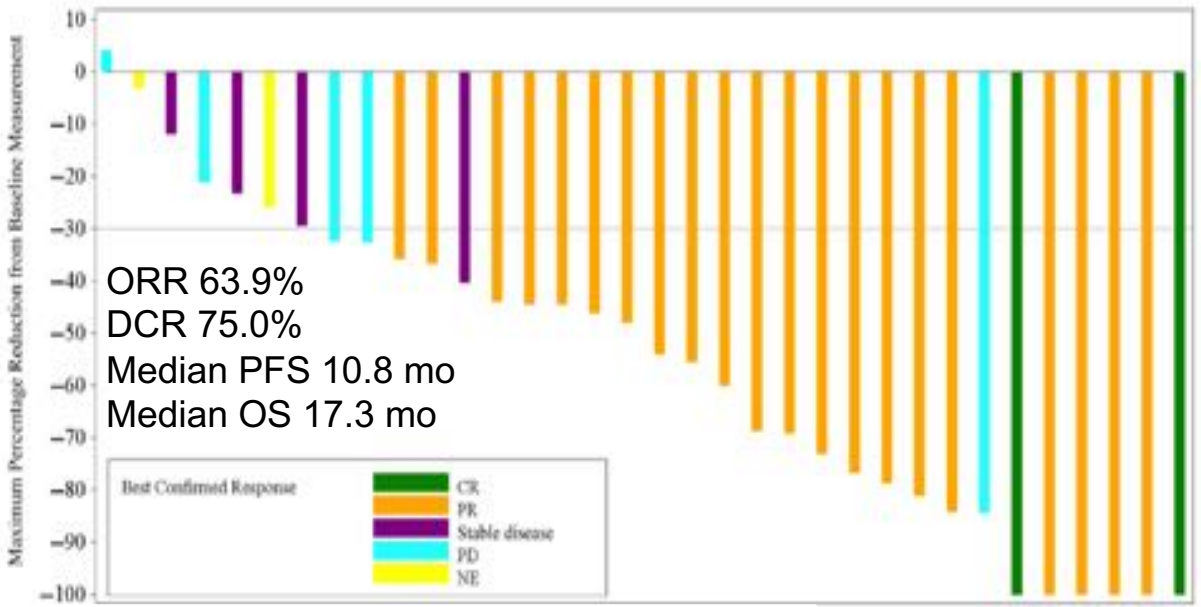
Dabrafenib+Trametinib in Class I BRAFmut NSCLC

Maximum Percentage Reduction from Baseline

Best Response Pretreated



Best Response Treatment Naive

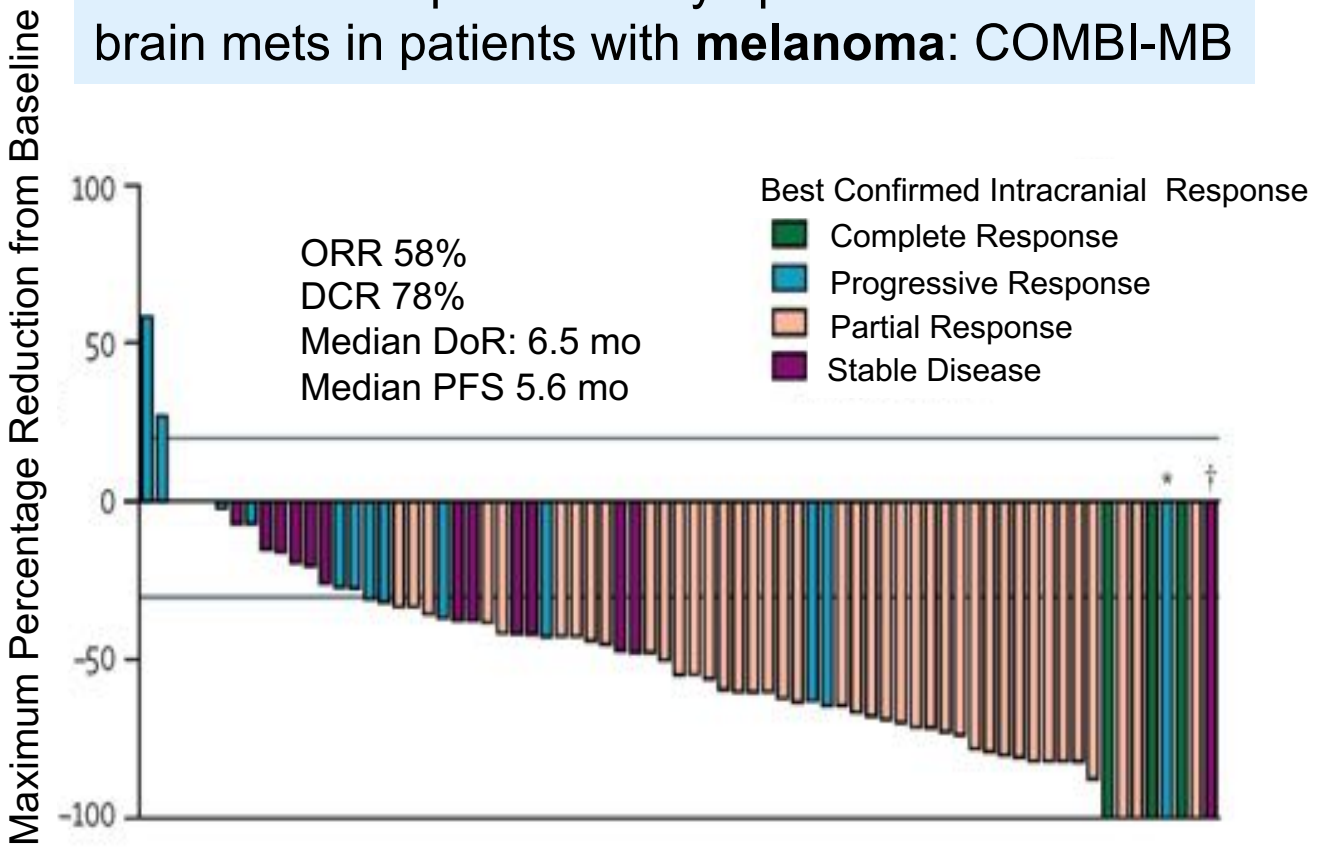


Pooled cohort dose reduction of Trametinib: 32%
Pooled cohort dose reduction of Dabrafenib: 48%
Note: Only 1 pt with brain mets (asymptomatic)

Planchard JTO 2021

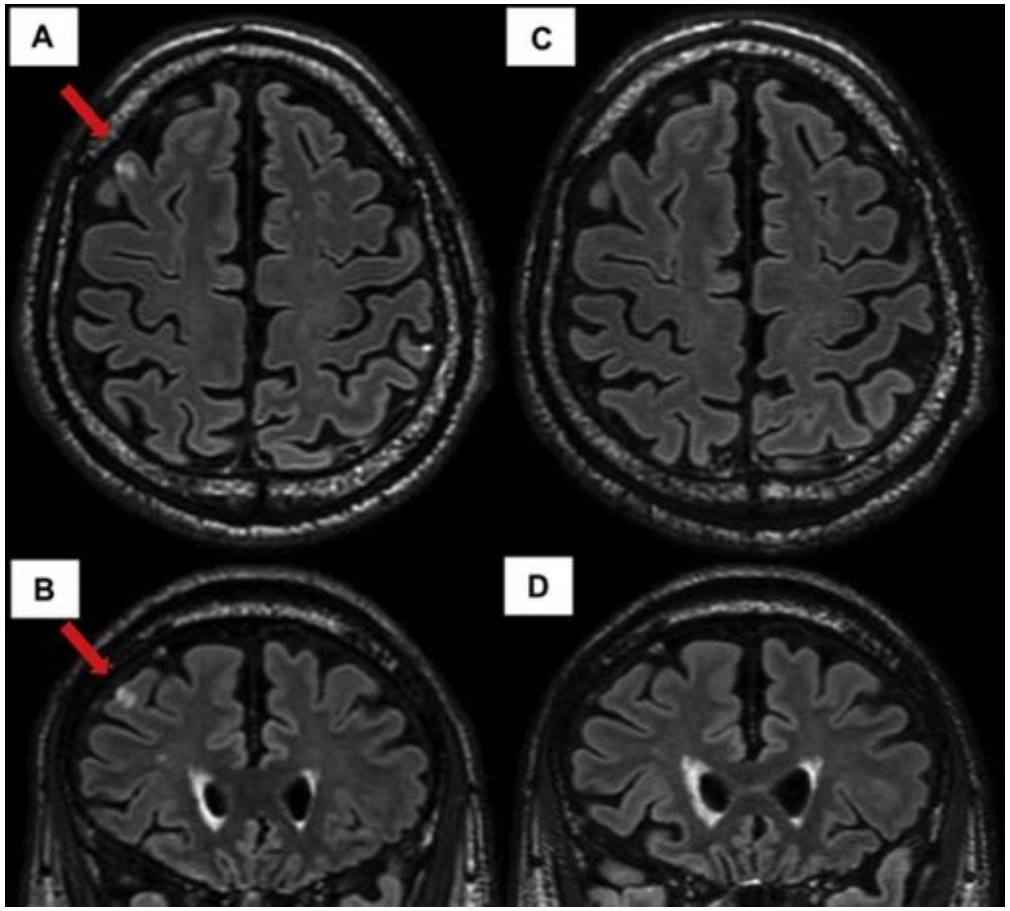
CNS Activity of Dabrafenib+Trametinib in Class I BRAFmut

Intracranial response in asymptomatic untreated brain mets in patients with **melanoma**: COMBI-MB



Davies Lancet Oncology 2017, Yamamoto JTO 2018

NSCLC: Resolution of frontal met and stable LMD after 6 weeks on Dabrafenib/Trametinib



Tolerability of D+T in Class I BRAFmut NSCLC

Dabrafenib + Trametinib

	Grade 1–2	Grade 3	Grade 4	Grade 5
Pyrexia	25 (44%)	1 (2%)	0	0
Nausea	23 (40%)	0	0	0
Vomiting	20 (35%)	0	0	0
Diarrhoea	18 (32%)	1 (2%)	0	0
Decreased appetite	17 (30%)	0	0	0
Asthenia	16 (28%)	2 (4%)	0	0
Dry skin	14 (25%)	1 (2%)	0	0
Peripheral oedema	13 (23%)	0	0	0
Chills	12 (21%)	1 (2%)	0	0
Cough	12 (21%)	0	0	0
Rash	11 (19%)	1 (2%)	0	0
Arthralgia	11 (19%)	0	0	0
Constipation	10 (18%)	0	0	0
Fatigue	9 (16%)	1 (2%)	0	0
Blood alkaline phosphatase increased	9 (16%)	0	0	0
Dyspnoea	8 (14%)	2 (4%)	0	0
Pruritus	8 (14%)	1 (2%)	0	0
Dizziness	8 (14%)	0	0	0
Anaemia	7 (12%)	2 (4%)	1 (2%)	0
Weight decreased	7 (12%)	1 (2%)	0	0
Upper abdominal pain	7 (12%)	0	0	0
Hypotension	7 (12%)	0	0	0
Neutropenia	6 (11%)	5 (9%)	0	0
Chest pain	6 (11%)	0	0	0
Dysgeusia	6 (11%)	0	0	0
Headache	6 (11%)	0	0	0
Muscle spasms	6 (11%)	0	0	0
Myalgia	6 (11%)	0	0	0
Productive cough	6 (11%)	0	0	0
Vertigo	6 (11%)	0	0	0

<u>BRAF+MEK vs BRAF Monotherapy</u>

Nausea 40% vs 27%

Pyrexia: 46% vs 35%

Diarrhea 34% vs 16%

Vomiting 34% vs 20%

Peripheral Edema 13% vs <10%

Squamous Carcinoma 4% vs 12%

<u>With dabrafenib+trametinib, AEs led to</u>:

Discontinuation in 12%

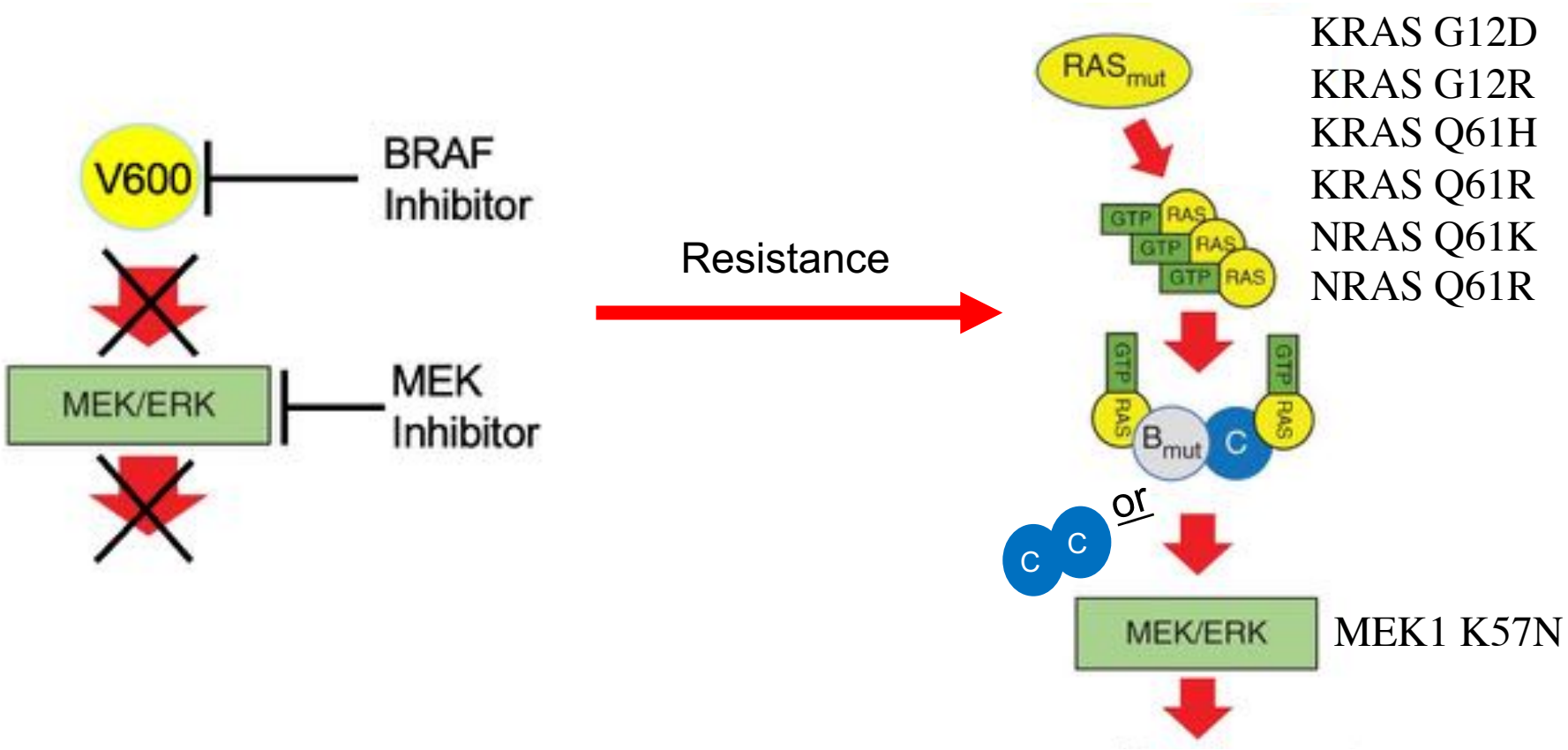
Dose Interruption/Delay in 61%

	Grade 1–2	Grade 3	Grade 4	Grade 5
Pyrexia	28 (33%)	2 (2%)	0	0
Asthenia	21 (25%)	3 (4%)	1 (1%)	0
Hyperkeratosis	24 (29%)	1 (1%)	0	0
Decreased appetite	23 (27%)	1 (1%)	0	0
Nausea	22 (26%)	1 (1%)	0	0
Cough	22 (26%)	0	0	0
Fatigue	21 (25%)	1 (1%)	0	0
Skin papilloma	22 (26%)	0	0	0
Dry skin	19 (23%)	0	0	0
Alopecia	18 (21%)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	15 (18%)	2 (2%)	0	0
Rash	16 (19%)	1 (1%)	0	0
Vomiting	16 (19%)	1 (1%)	0	0
Dyspnoea	14 (17%)	2 (2%)	0	0
Headache	13 (15%)	2 (2%)	0	0
Arthralgia	13 (15%)	1 (1%)	0	0
Diarrhoea	13 (15%)	1 (1%)	0	0
Pain in extremity	14 (17%)	0	0	0
Chills	12 (14%)	1 (1%)	0	0
Weight decreased	13 (15%)	0	0	0
Pruritus	12 (14%)	0	0	0
Myalgia	11 (13%)	0	0	0
Papule	11 (13%)	0	0	0
Squamous-cell carcinoma	0	10 (12%)	0	0
Back pain	10 (12%)	0	0	0
Anaemia	7 (8%)	2 (2%)	0	0
Constipation	8 (10%)	1 (1%)	0	0
Melanocytic naevus	9 (11%)	0	0	0
Seborrhoeic keratosis	9 (11%)	0	0	0
Actinic keratosis	8 (10%)	0	0	0
Dysphonia	8 (10%)	0	0	0
Nasopharyngitis	8 (10%)	0	0	0

Dabrafenib

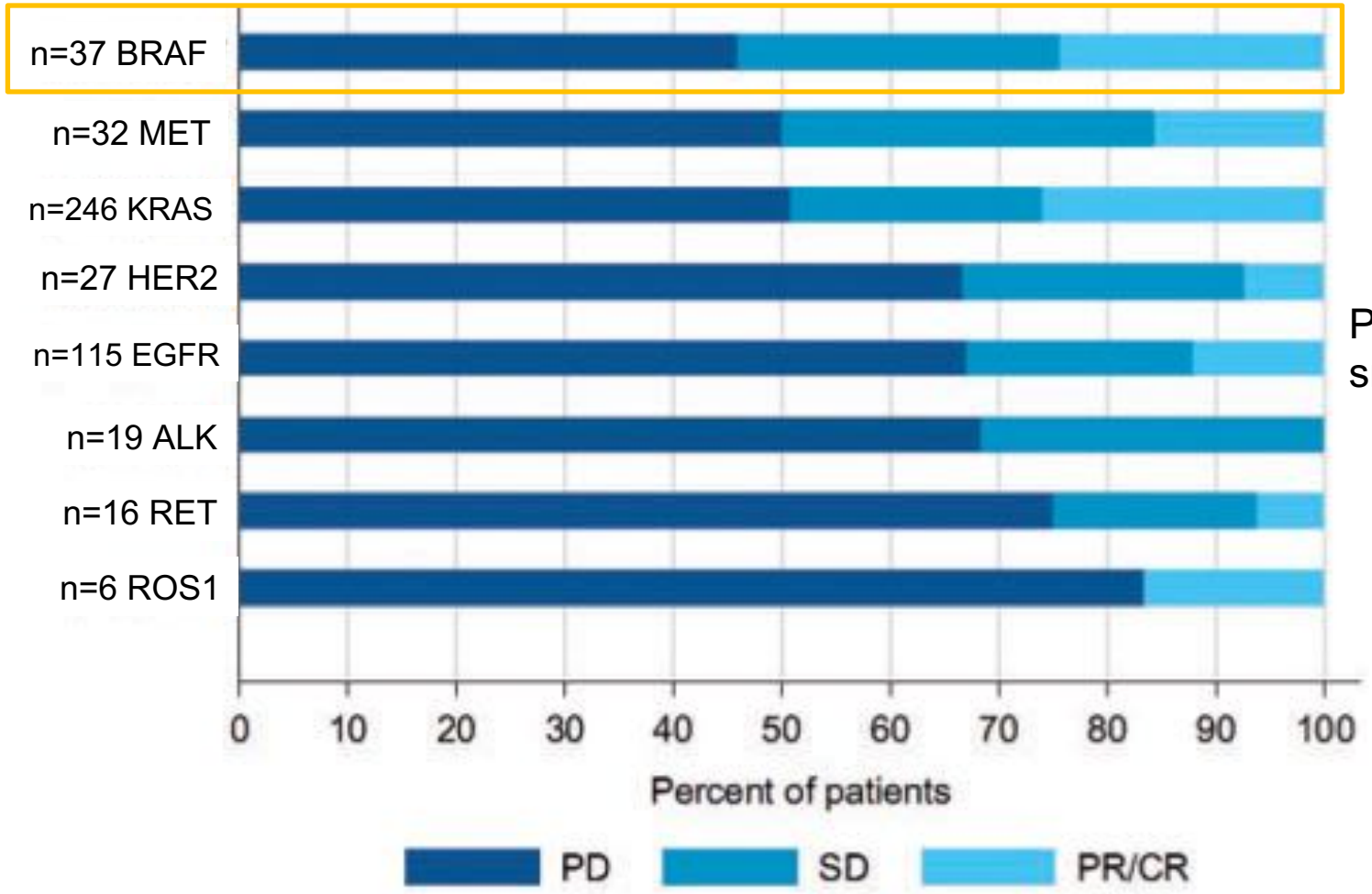
Planchard Lancet 2016

Resistance to Dabrafenib+Trametinib in BRAFmut NSCLC



Ortiz Cuaran CCR 2020, Sheikine JCO Precision Oncology 2018, Facchinetti Eur J Cancer 2020, Abravanel JTO 2018, Yaeger Cancer Discovery 2019

PD(L)1 Inhibitor Monotherapy in BRAFmut NSCLC

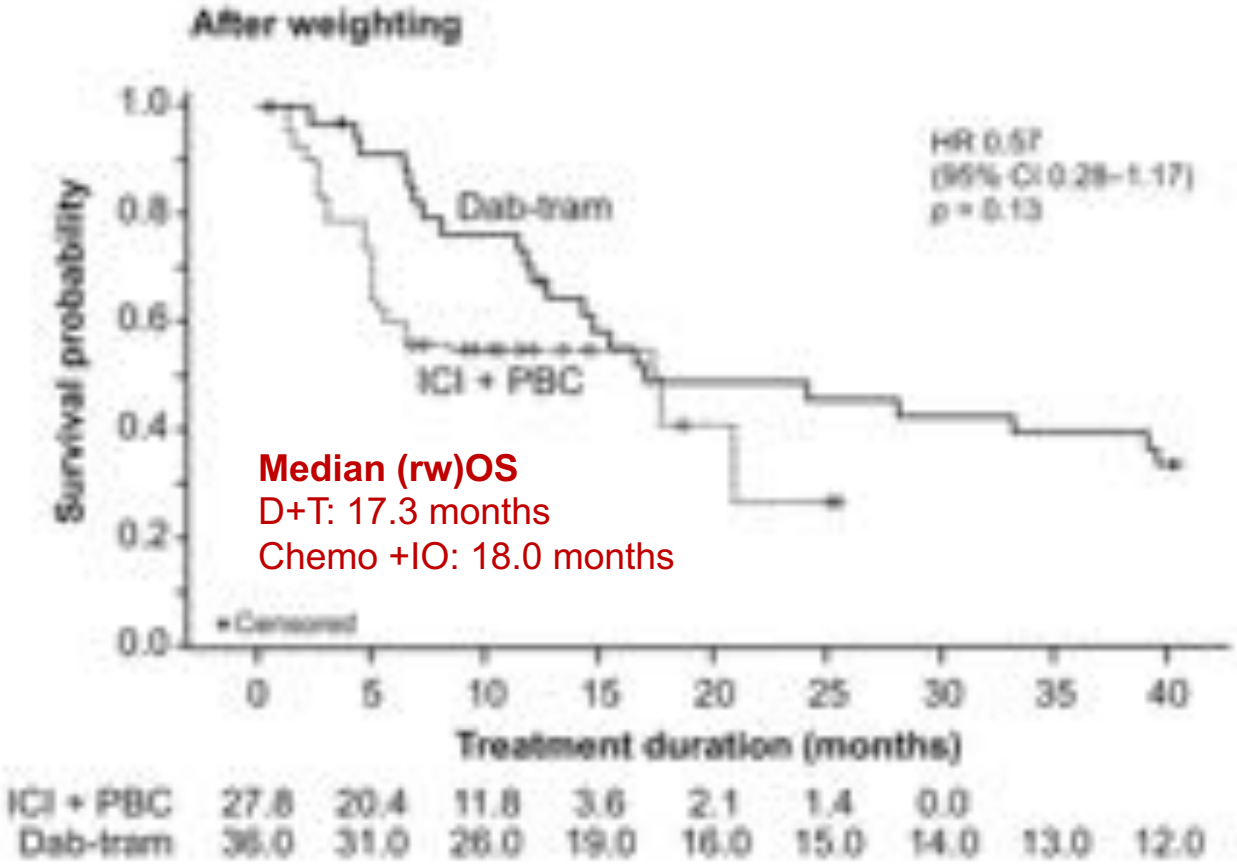


PFS longer in pts with smoking history vs never-smokers (4.1 vs 1.9 months, *p*= 0.03).

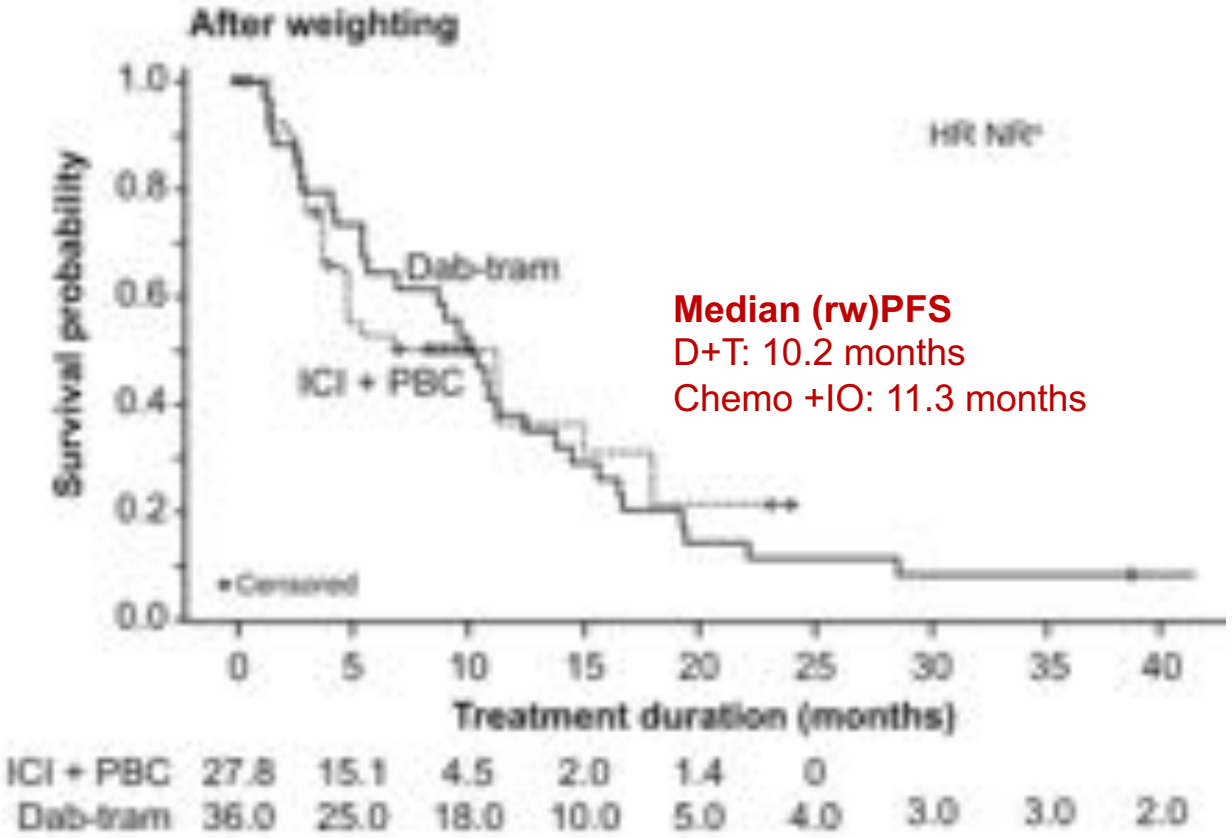
Mazieres Annals of Oncology 2019

Chemo+IO vs D+T in 1st Line for Class I BRAFmut NSCLC

Overall Survival

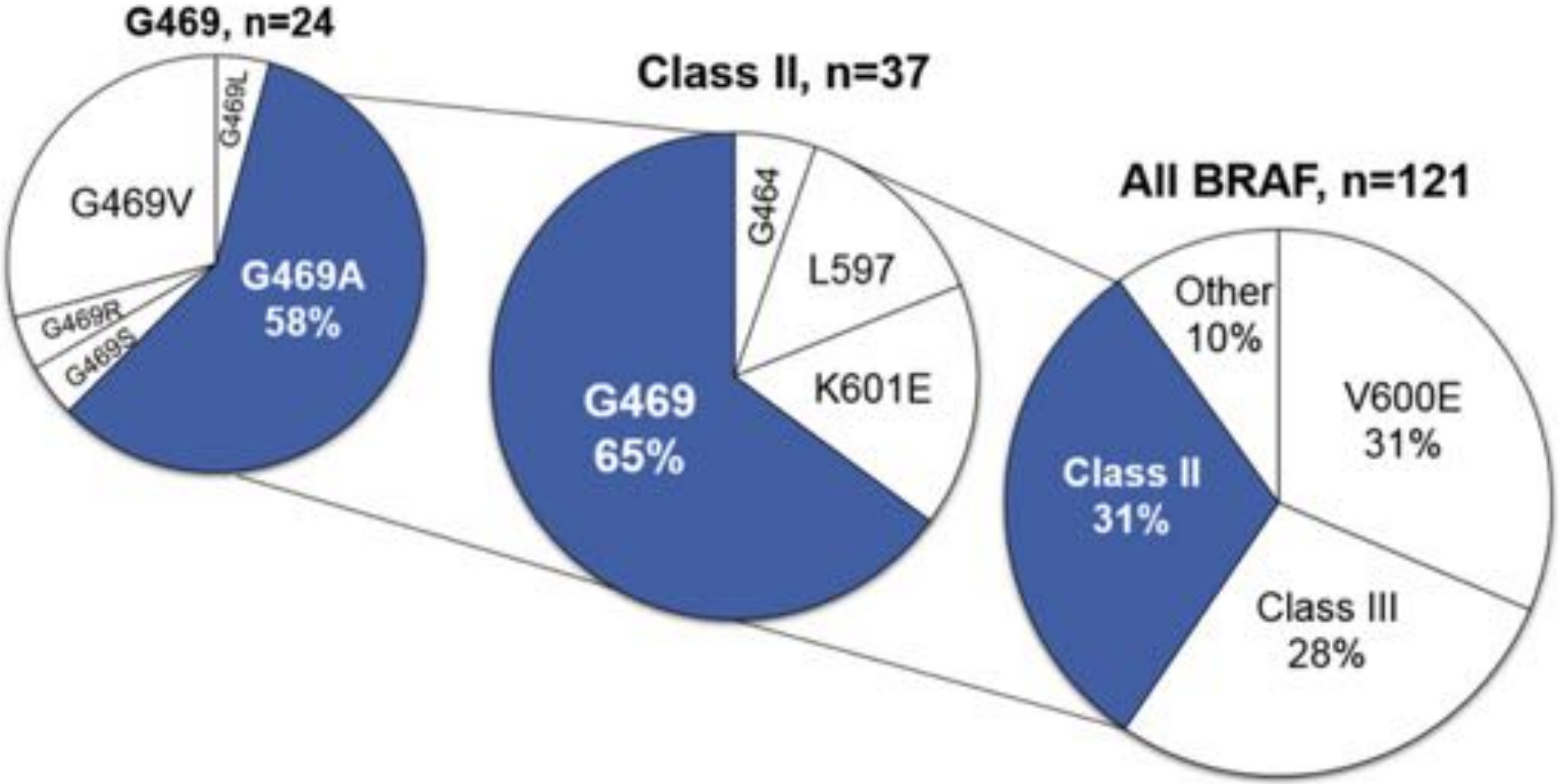


Progression-Free Survival



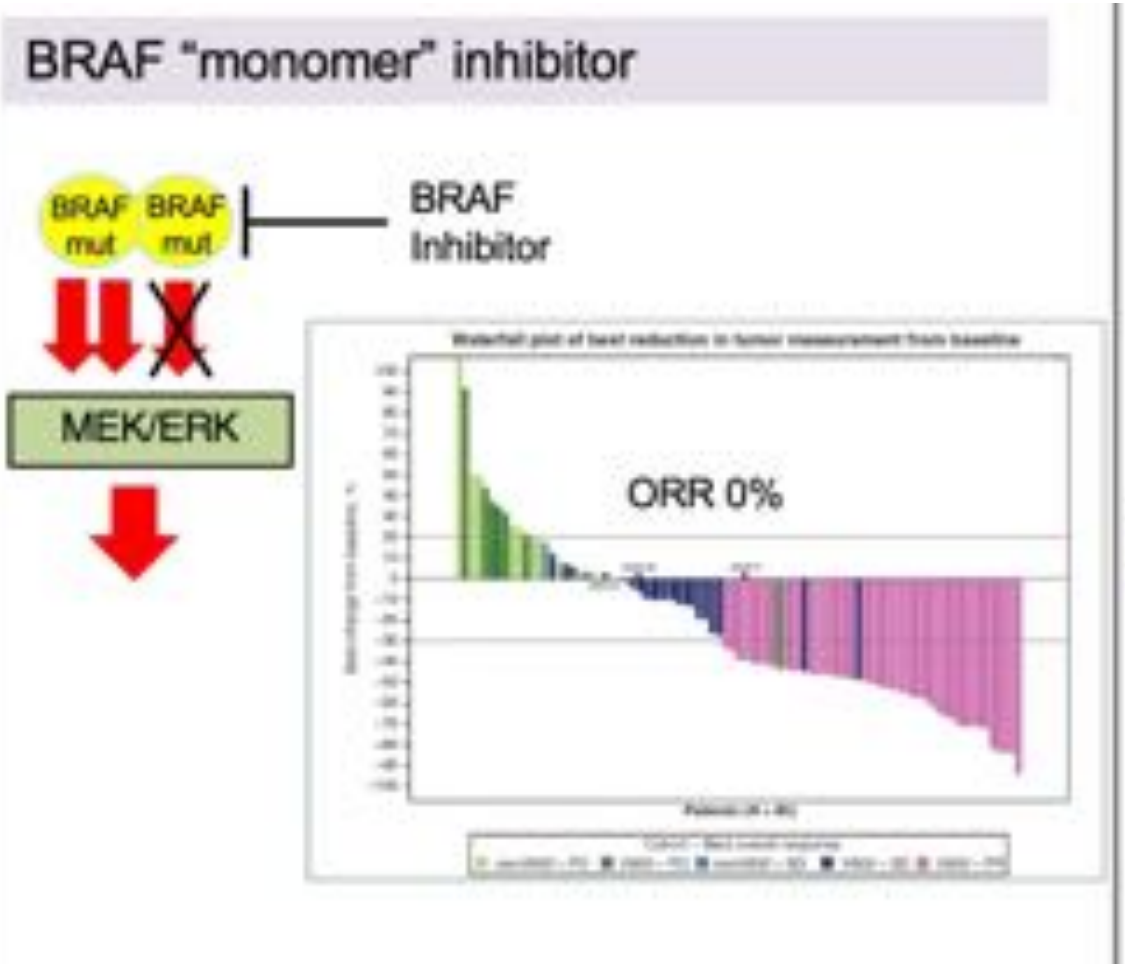
Johnson JTO CRR 2022

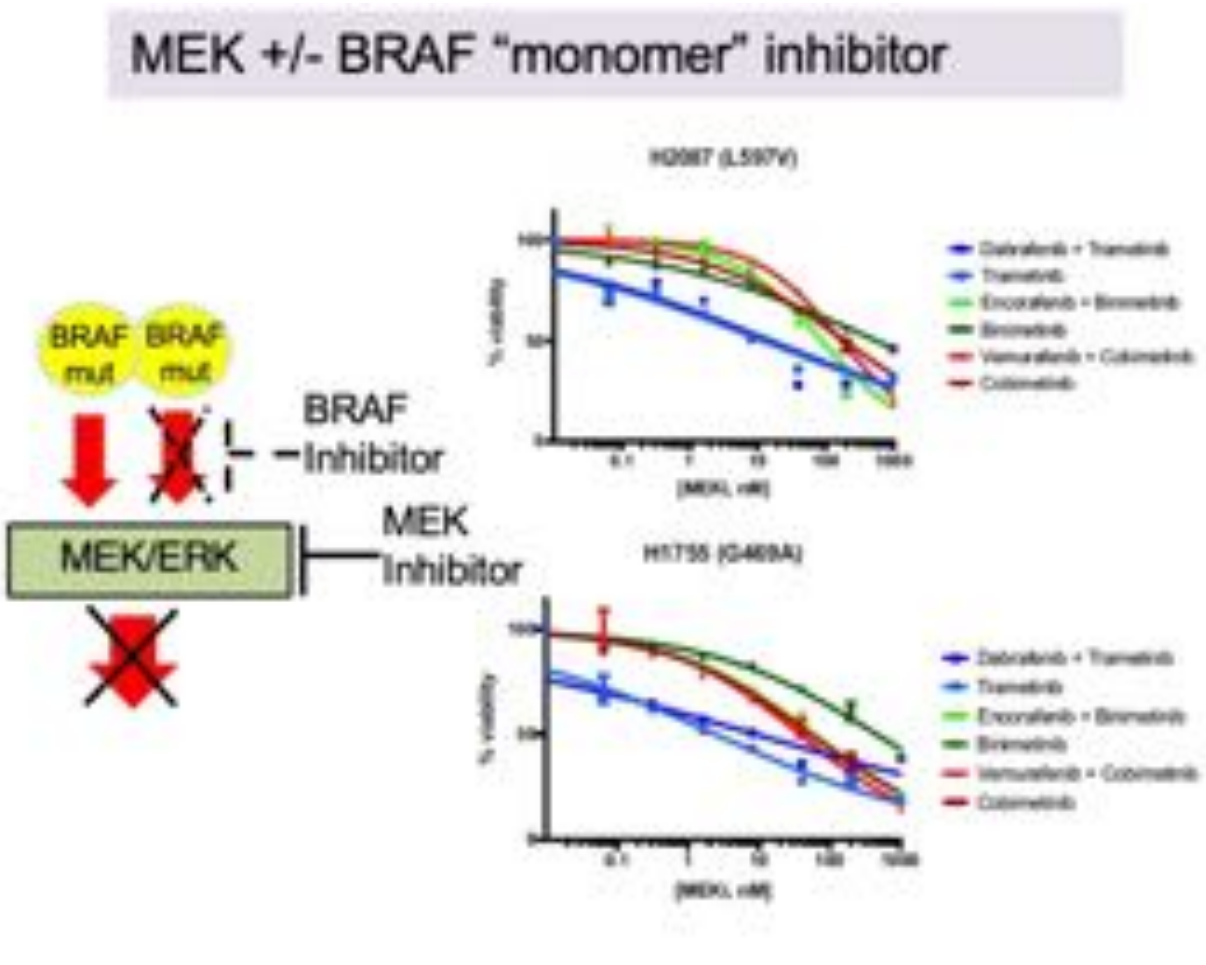
Spectrum of Class II BRAF Mutations in NSCLC



Dagogo-Jack JTO 2020

BRAF/MEK Inhibitors in Class II BRAFmut NSCLC



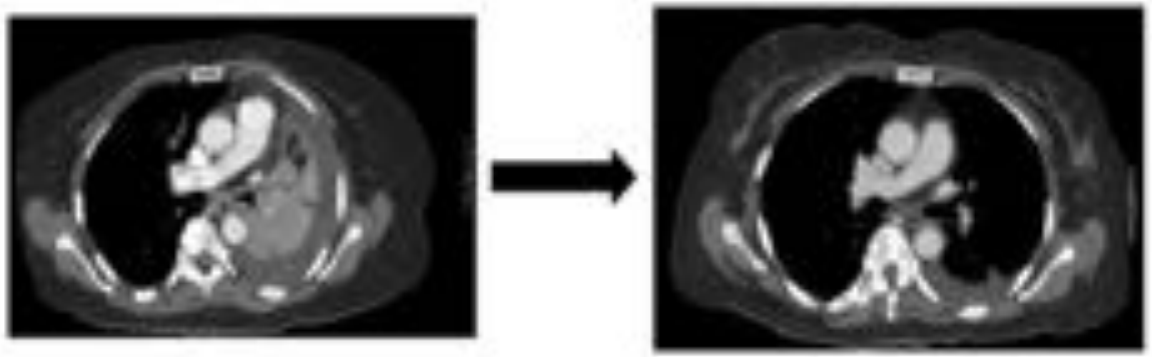


Mazieres Annals of Oncology 2020

Negrao JTO 2020

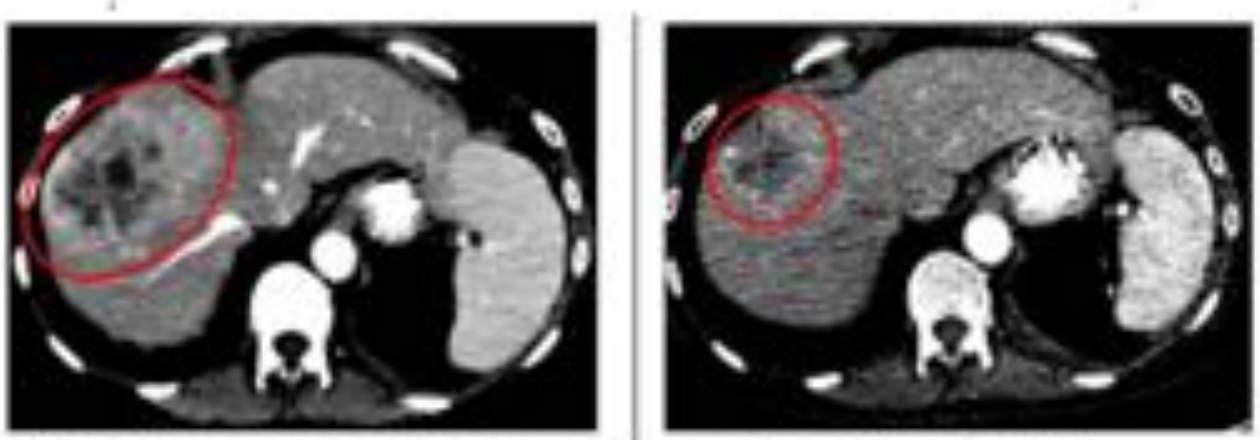
BRAF/MEK Inhibitors in Class II *BRAF*^{mut} NSCLC

Response to Dabrafenib/Trametinib in a Patient with NSCLC Harboring *BRAF* L597R mutation



Patient had ongoing response at 12 months.

Response to Dabrafenib/Trametinib in a Patient with *BRAF* G469A-mutant NSCLC



Patient experienced disease progression after 6 months.

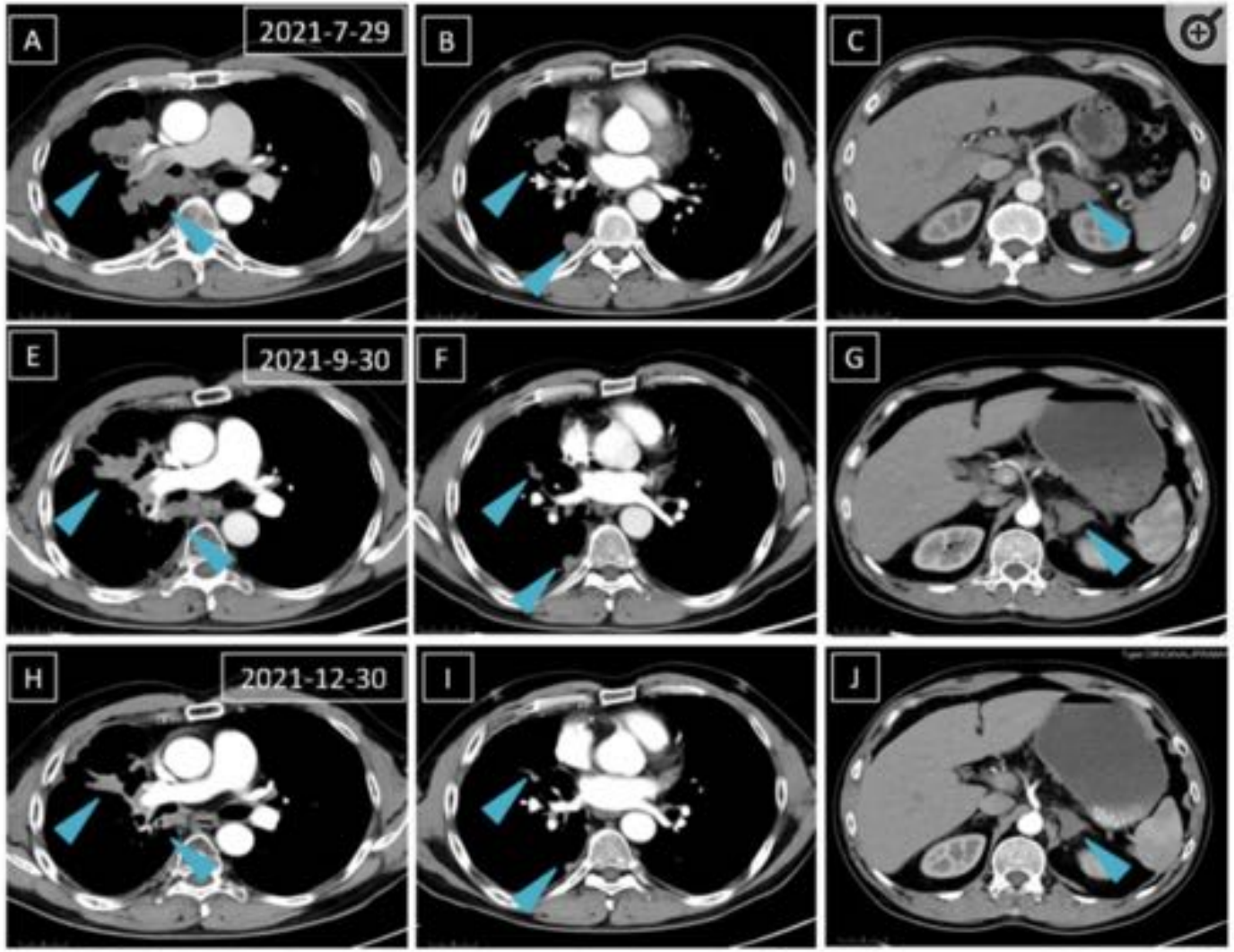
Negrao JTO 2020, Dagogo-Jack JTO 2020

Trametinib in NSCLC with De Novo SDN1-BRAF Fusion

Baseline

1 Month

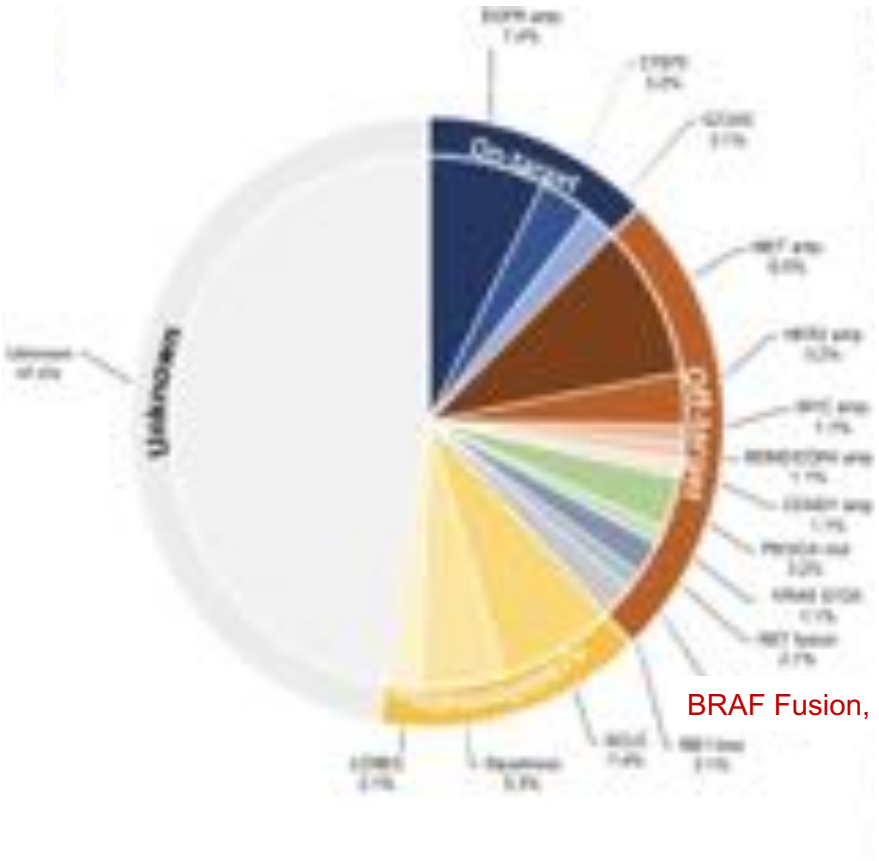
4 Months



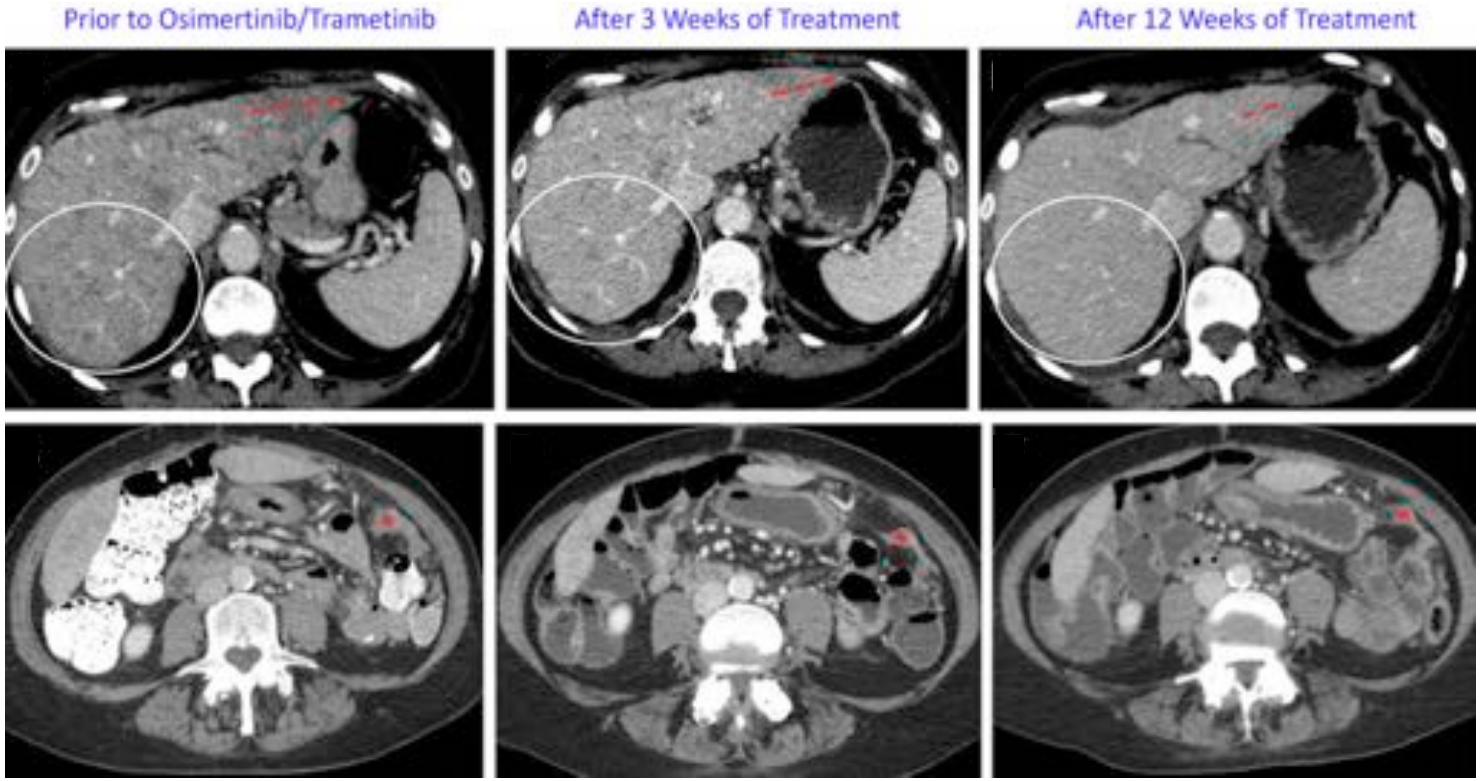
Yu Frontiers in Oncology 2022

Trametinib in EGFR+ NSCLC with Acquired BRAF Fusion

1st Line Osimertinib Resistance



Osimertinib + Trametinib in EGFR+ NSCLC with *AGK-BRAF*



Note: BRAF monomer inhibitors (e.g., dabrafenib) are ineffective

Choudhury JTO 2022, Dagogo-Jack JTO 2019

Conclusions (and Additional Thoughts)

- Dabrafenib + Trametinib has comparable activity in the 1st line setting vs post-chemo. Intracranial activity is anticipated based on melanoma studies. There's space for better tolerated combinations.
- Some patients with *BRAF* mutations benefit from immunotherapy. In the absence of prospective head-to-head data, I use clinical and tumor characteristics to guide 1st line treatment choice for class I *BRAF*-mutant NSCLC.
- Dabrafenib + Trametinib has activity against some class II *BRAF* mutations (e.g., G469 and L597). We need prospective studies for class II *BRAF*-mutant NSCLC.
- *BRAF* fusions (de novo and acquired) are sensitive to MEK inhibition, at least in case reports. Efficacy is being explored in phase II studies for EGFR+ NSCLC.