Activity of ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with BRAF and NRAS Mutant Melanoma

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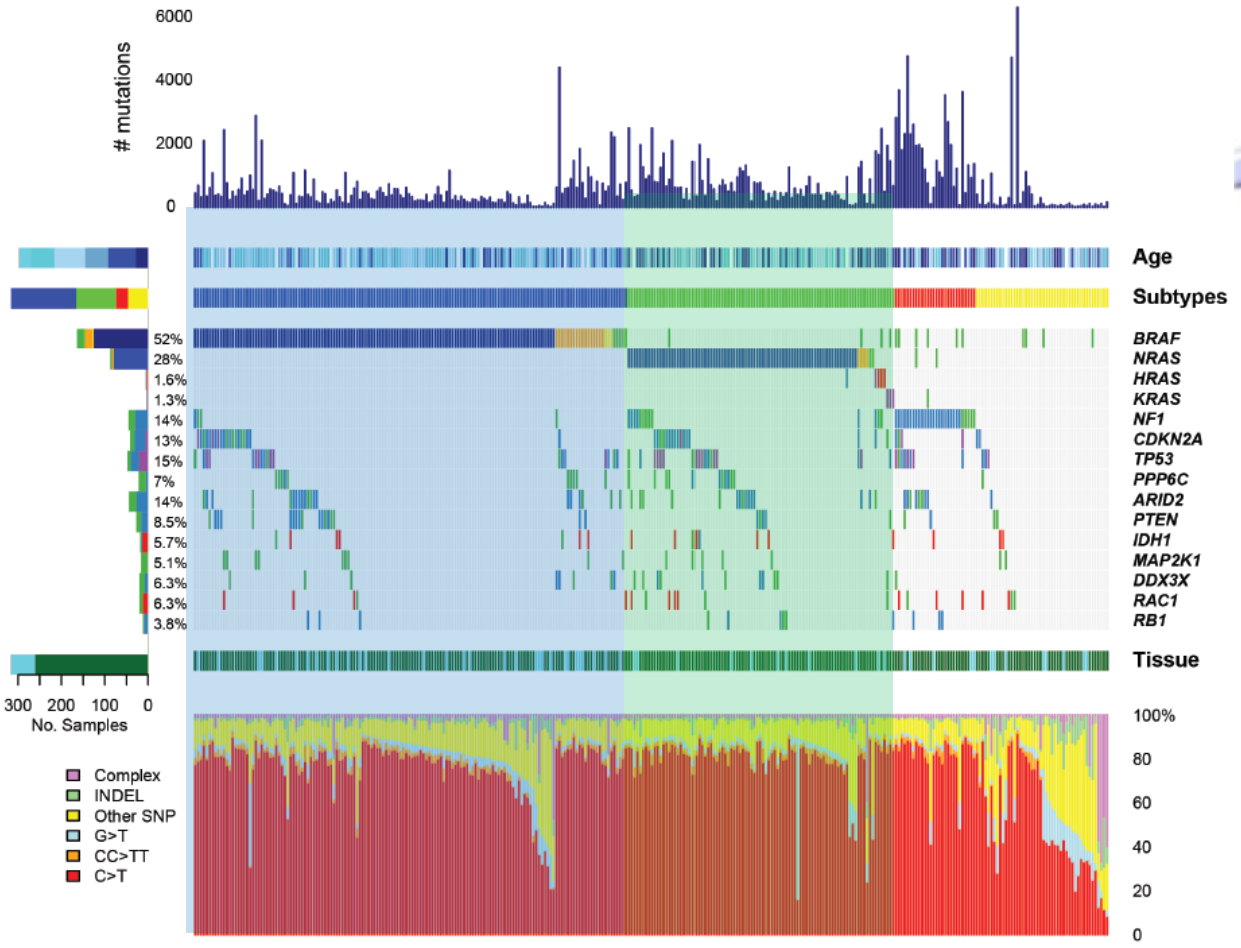
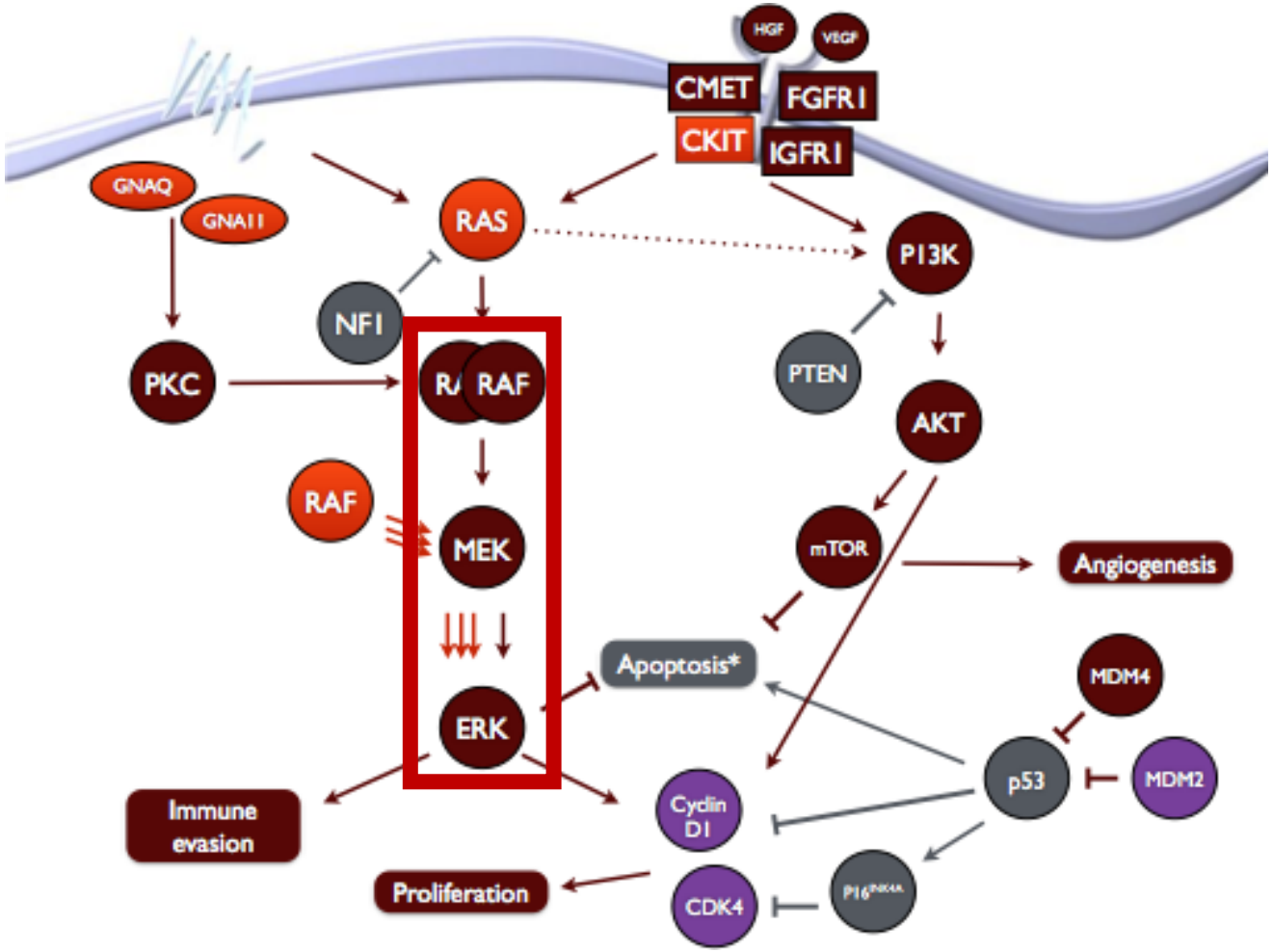
Disclosures

- Advisory Board/Consulting:
  - Novartis
  - Biodesix
  - Amgen
  - Takeda
- Research Sponsorship:
  - Biodesix
  - Exosome Diagnostics
  - Amgen
  - Merck
  - Bristol Myers Squibb
  - Prometheus

I will discuss the investigational use of:
Ulixertinib

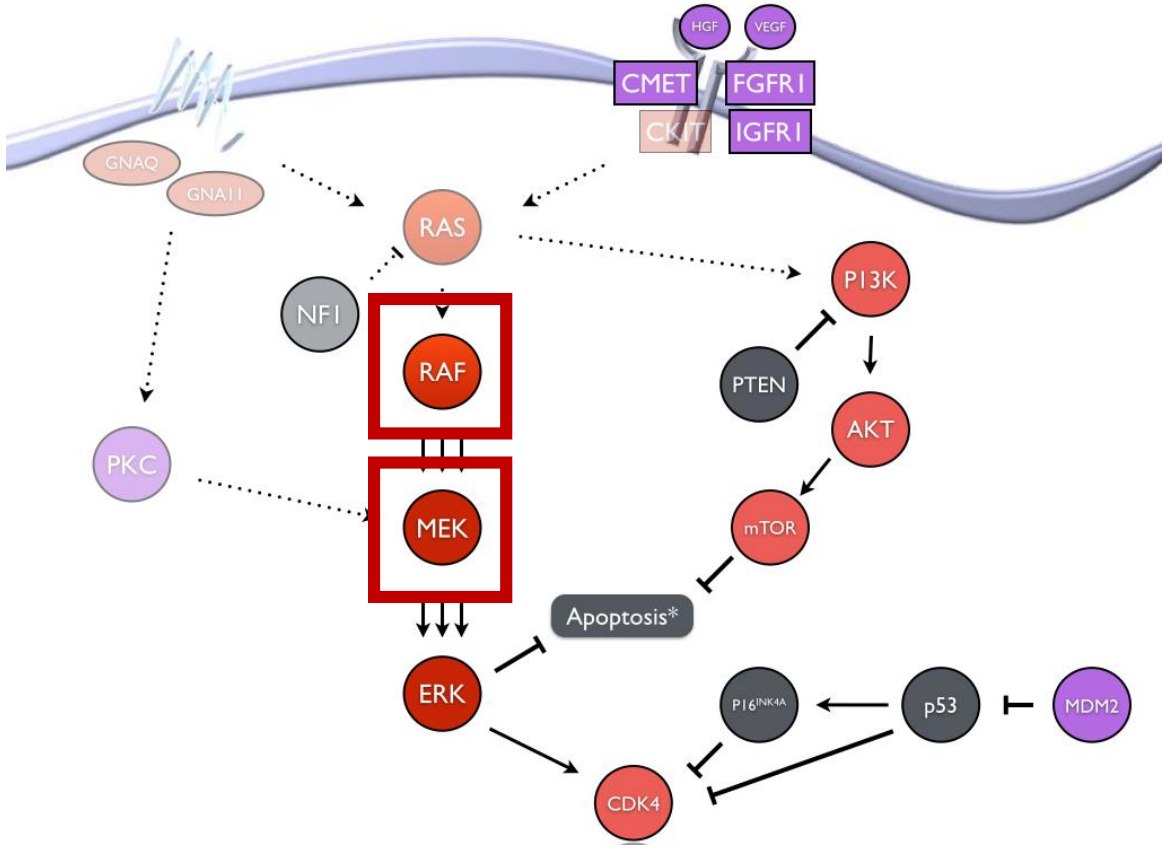
Melanoma is a genetic disease with two major subtypes

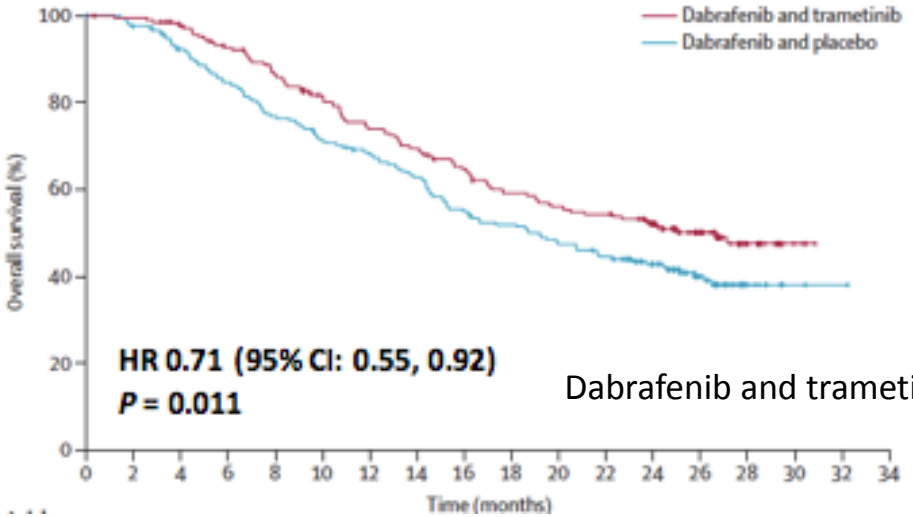




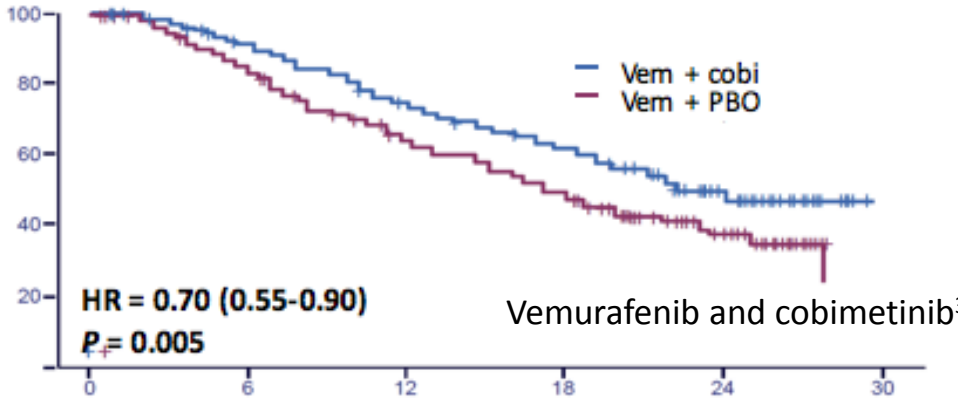
Melanoma TCGA. Cell 2015

Dual BRAF plus MEK inhibition is the standard therapy for BRAF mutant melanoma…but most patient progress





Dabrafenib and trametinib[1,2]

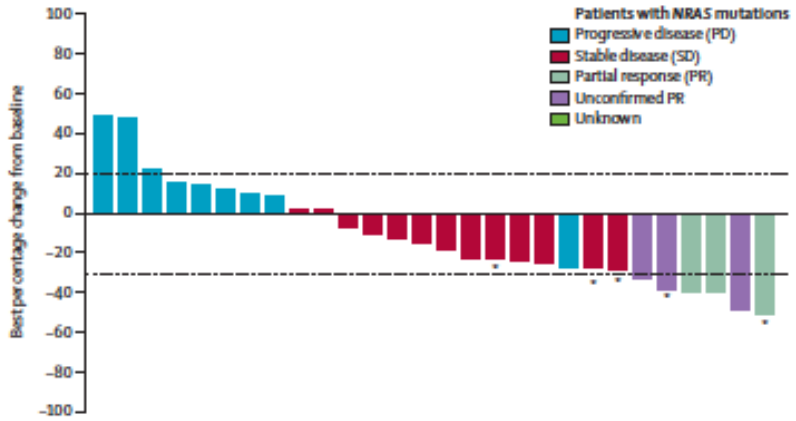


Vemurafenib and cobimetinib[3]

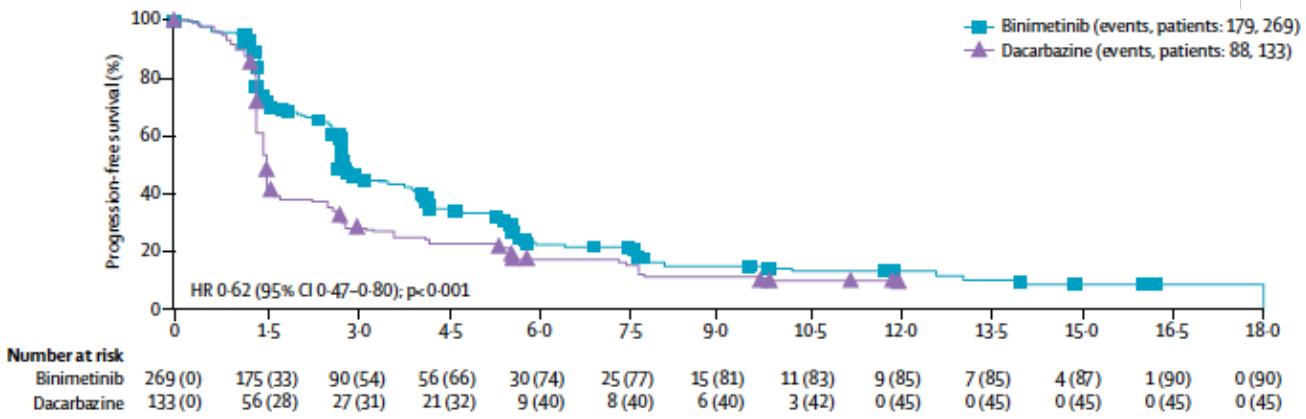
Encorafenib and binimetnib[4] (data not shown)

1. Long et al. Lancet 2015
2. Robert et al. NEJM 2015
3. Larkin et al. NEJM 2015
4. Dummer et al. Soc Melanoma Res 2016 (Presented by Flaherty)

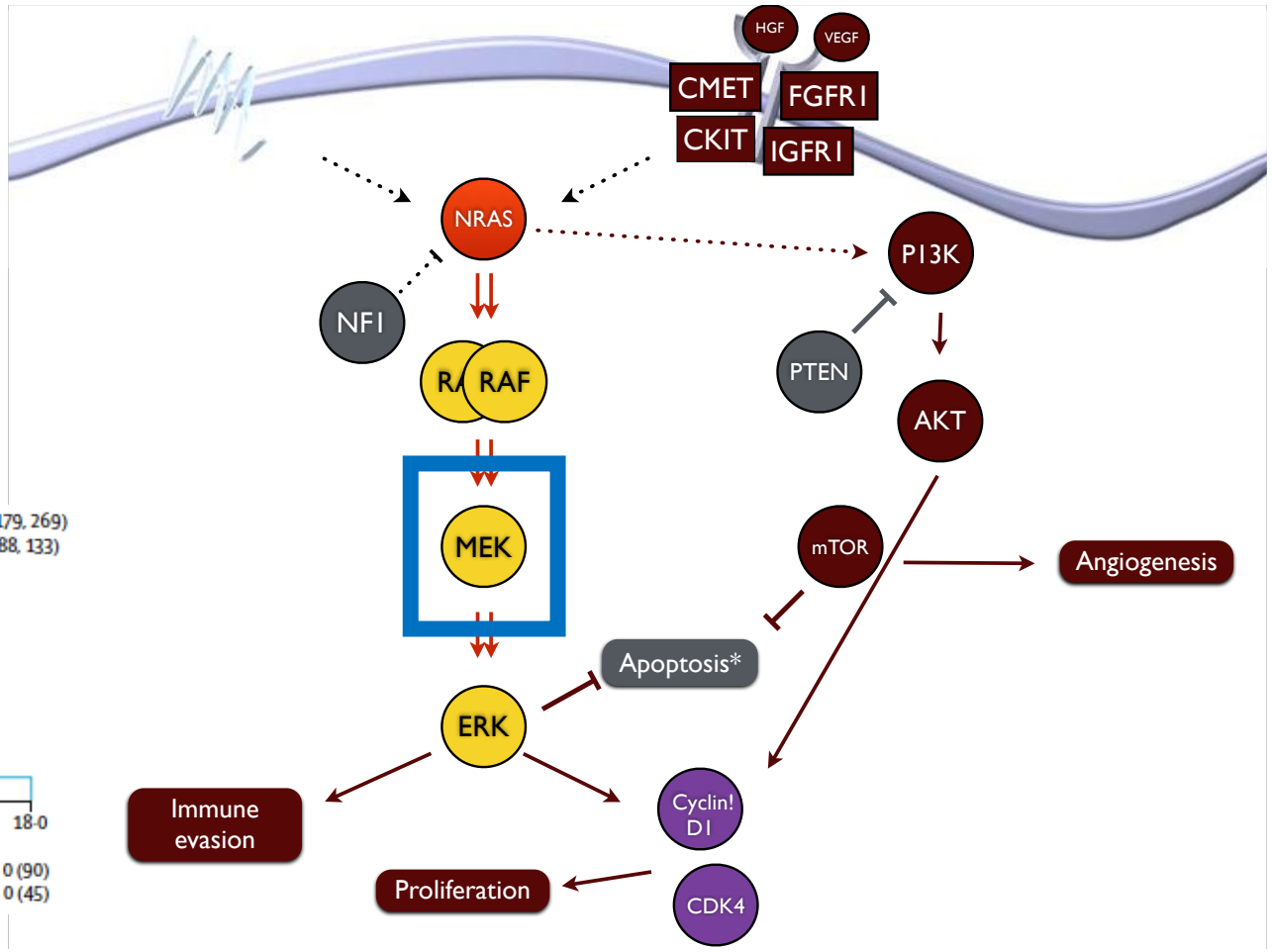
Targeting NRAS has been more challenging



Single-agent MEK inhibitors are active…[1]



MEK inhibitors are only a little better than chemo[2]



1. Ascierto et al. Lancet Oncol 2013
2. Dummer et al. Lancet Oncol 2017

The development of effective treatment for:

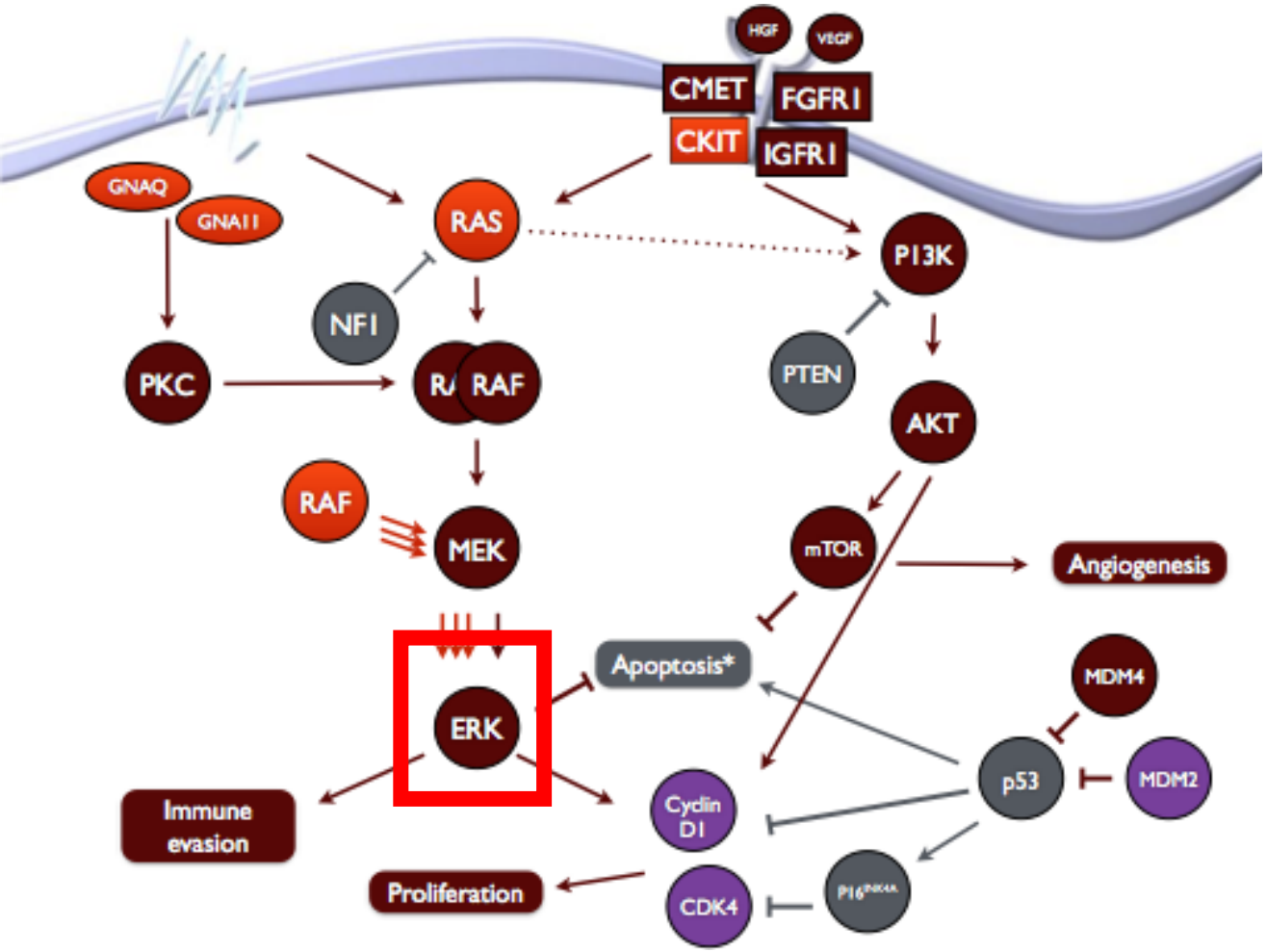
1. BRAF mutant melanoma following progression on a BRAF/MEK inhibitor regimen

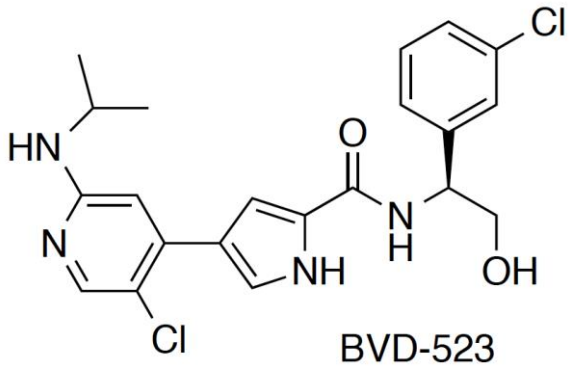
AND

2. NRAS mutant melanoma

is sorely needed

Ulixertinib (BVD-523) is a potent inhibitor of ERK1/2





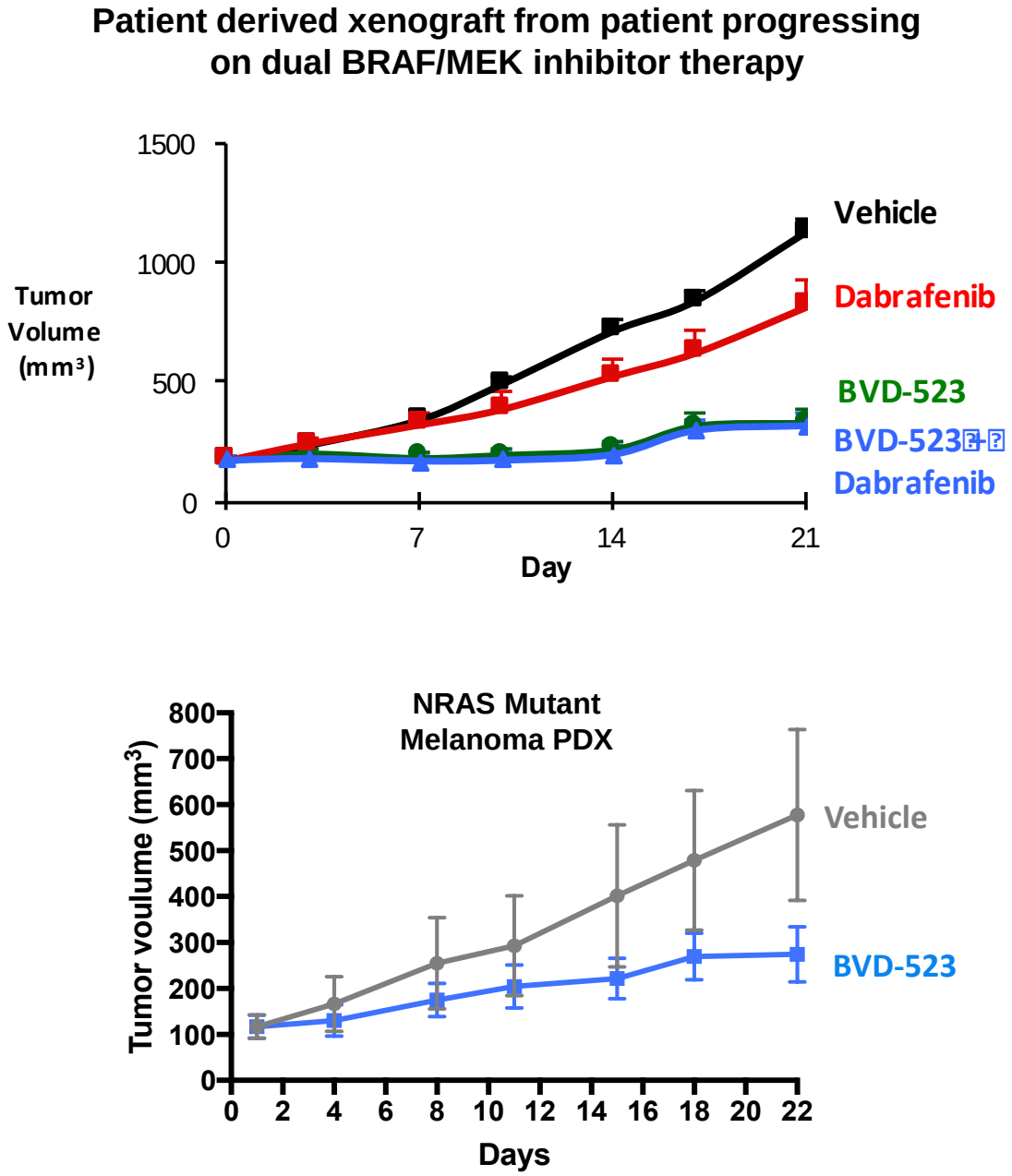
BVD-523

Highly potent

- ERK1 K_i < 300 pM
- ERK2 K_i = 40 pM

Highly selective

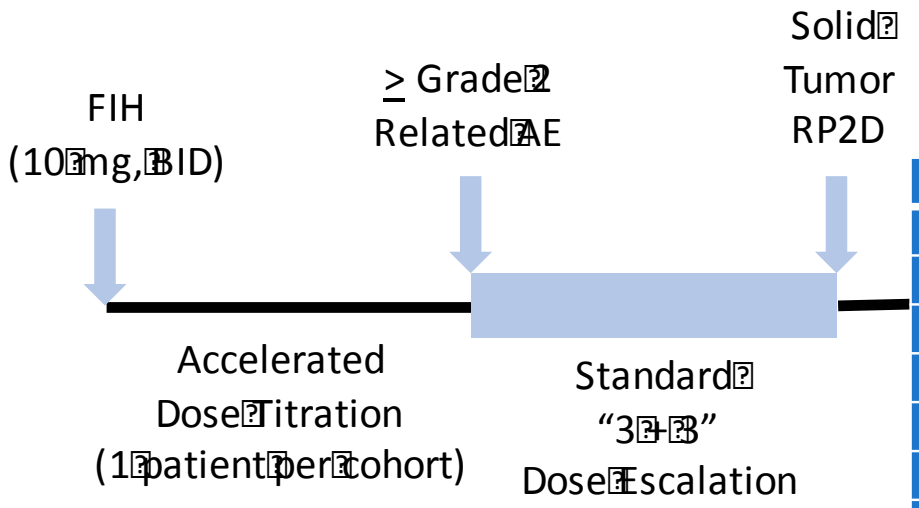
- ≥ 1,000-fold vs CDK1, CDK2, CDK5, CDK6, GSK3b
- ≥ 10,000-fold vs 70 other kinases



Ulixertinib has preclinical activity in both BRAF/MEK dual inhibitor resistant melanoma *and* NRAS mutant melanoma

NCT01781429:

Phase I trial of ulixertinib in patients with advanced solid tumors[1]



Advanced Solid Tumor Protocol (NCT01781429)

Dose-limiting Toxicities in Cycle 1 (21 days)

Dose (mg, BID)	DLT Frequency (%)	DLT Description
10	0/1	
20	0/1	
40	0/1	
75	0/1	
150	0/1	
300	0/4	
600		
750		to cycle 2 dosing
900		ine G3

* Intermedia

Mutation status	Dose Escalation	Dose Expansion
BRAF mt, no prior BRAFi	1	1
BRAF mt, prior BRAFi +/- MEKi	6	21
NRAS mt	0	22
Other/unknown	1	0

Recommended Phase II Dose:
600 mg BID

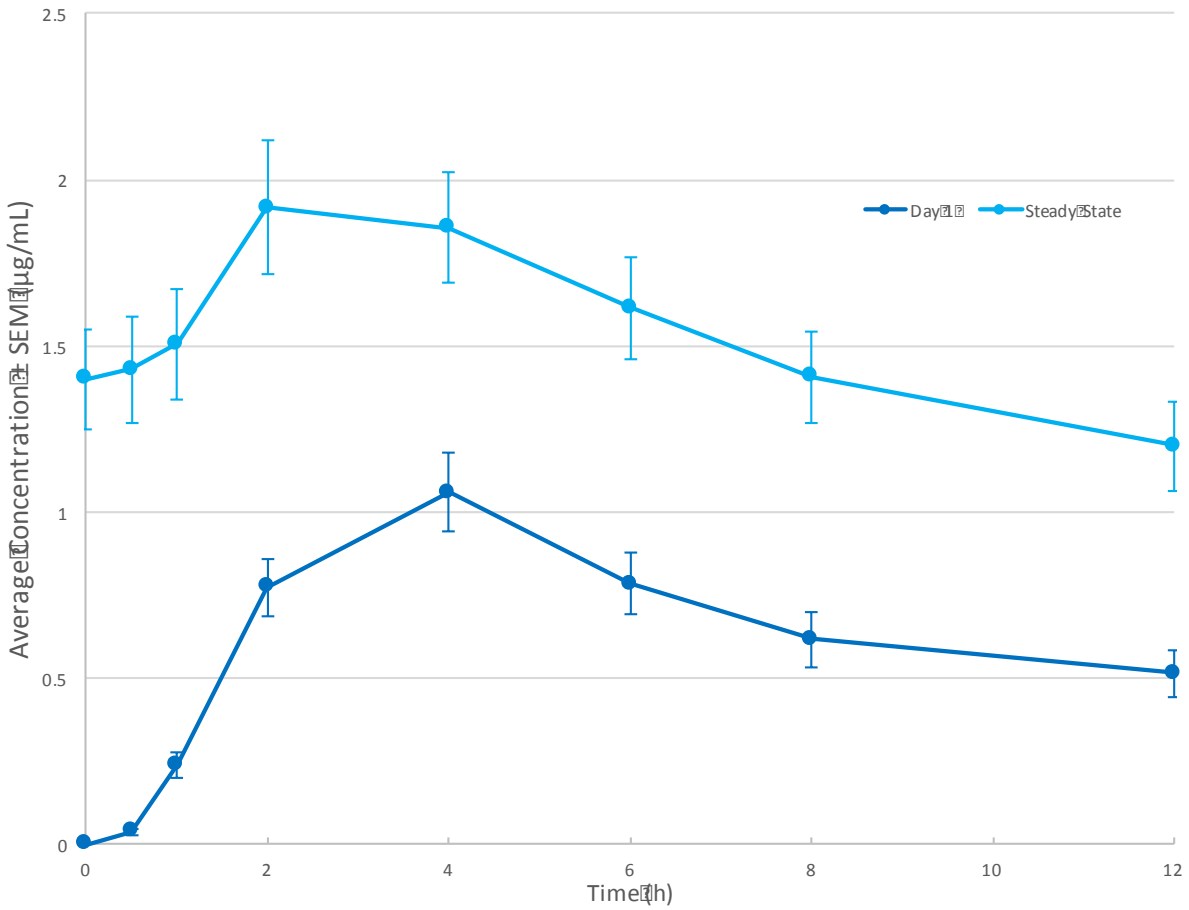
52 patients with metastatic melanoma treated

Infante et al. ASCO 2015; manuscript in preparation

Melanoma patient characteristics

	Dose Escalation (8 patients)	Dose Expansion (44 patients)
Age (median)	63.5	59
Gender		
Male	6	27
Female	2	17
Pre-treatment LDH		
Elevated	2	24
Not-elevated	1	18
Prior immune therapy	6	40
Mutation Status		
BRAF	7	22
NRAS	0	22
Unknown	1	

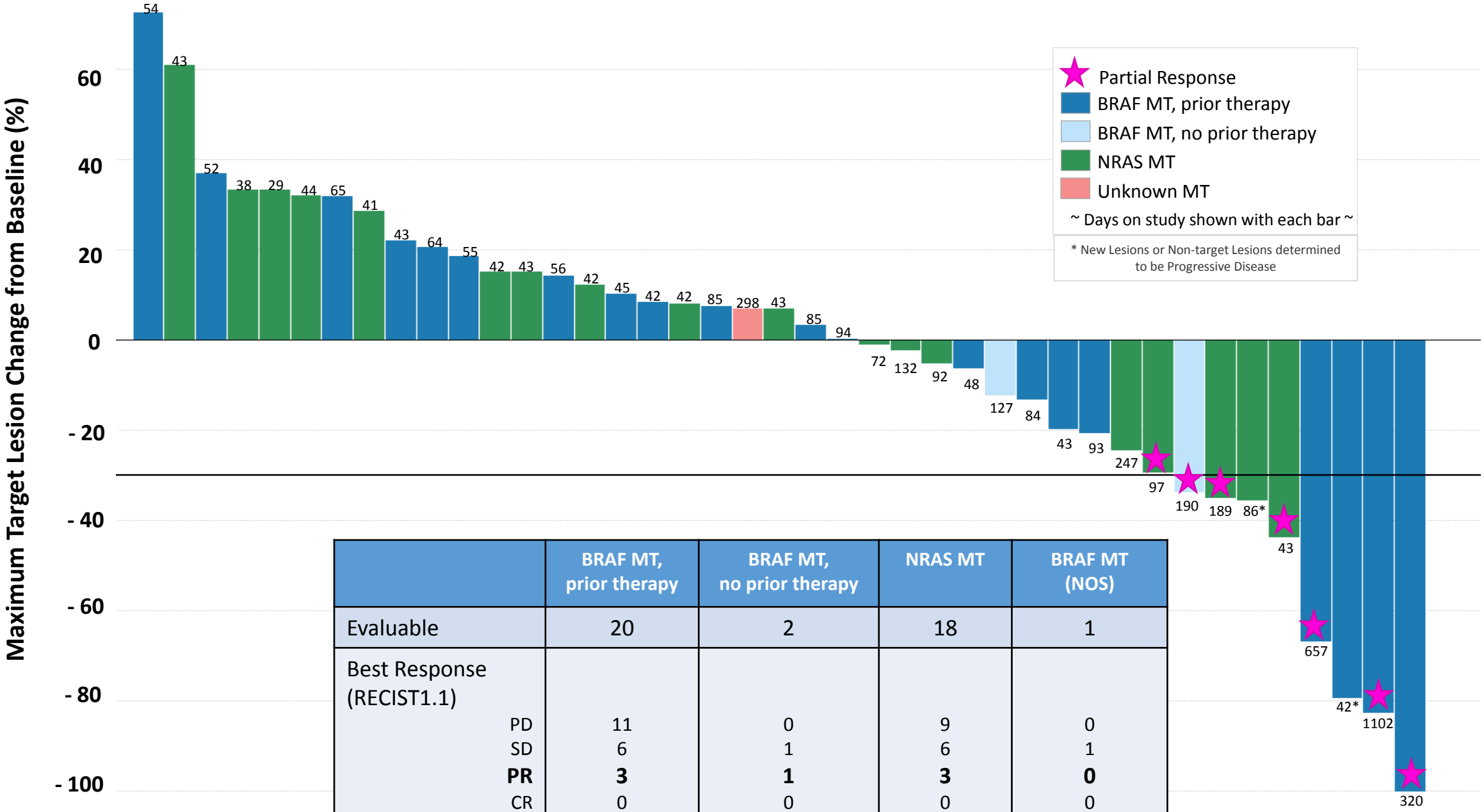
BVD-523 Plasma Concentrations in Melanoma Patients Dosed at 600 mg, BID



	Day 1 Average ± SEM N=39	Steady State Average ± SEM N=28
T_{max} (hours)	3.87 ± 0.38	2.82 ± 0.41
C_{max} (µg/mL)	1.21 ± 0.11	2.18 ± 1.87
AUC (µg*hr/mL)	7.83 ± 0.81	18.63 ± 1.71

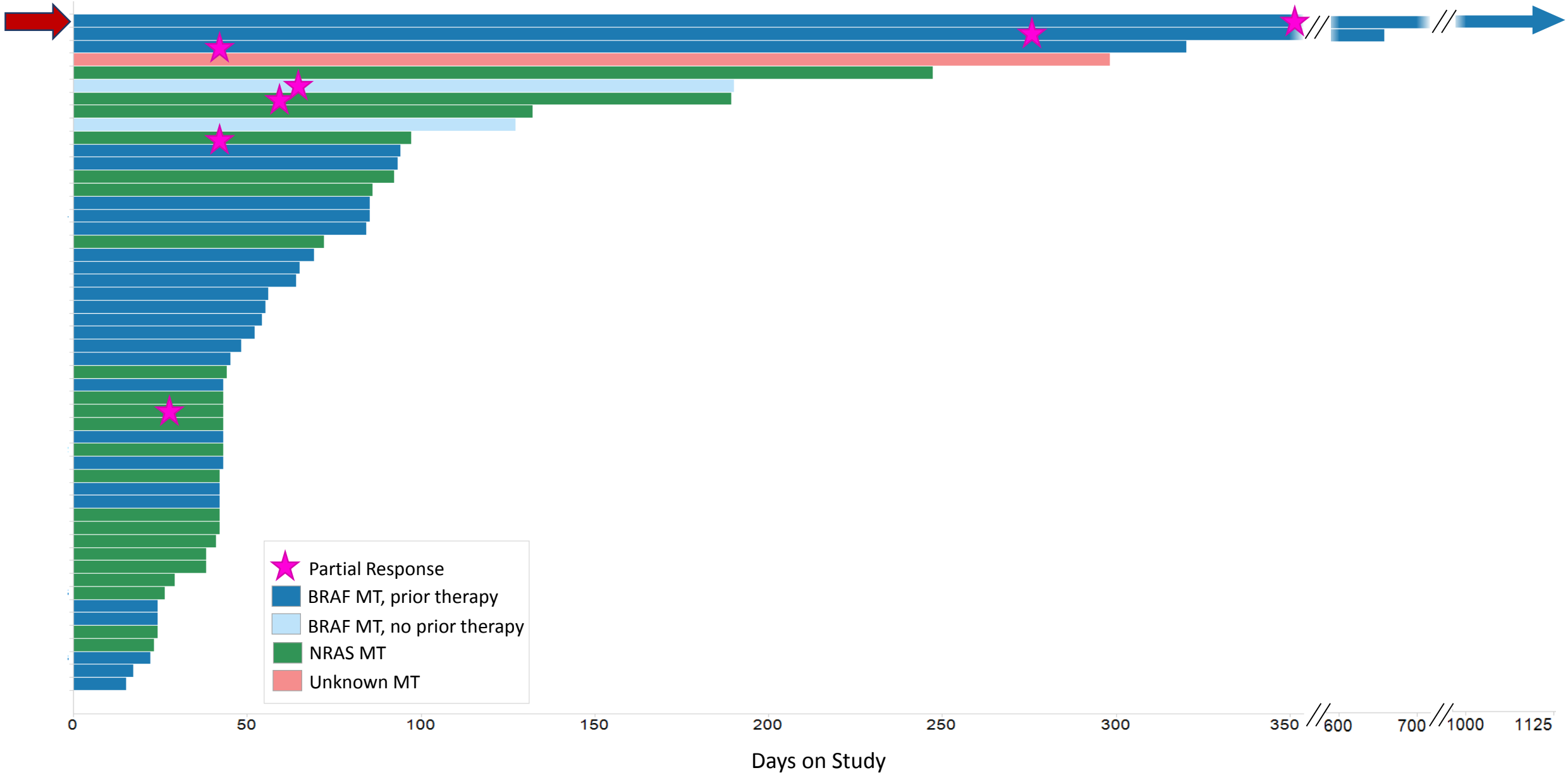
- Patients dosed at RP2D (600 mg, BID) had steady state plasma concentrations ranging from 2-5µM
- Blood based pRSK assay demonstrated near complete inhibition at plasma concentrations seen at 600 mg, BID

BVD-523 Demonstrates Efficacy in NRAS and BRAF Mutant Melanoma

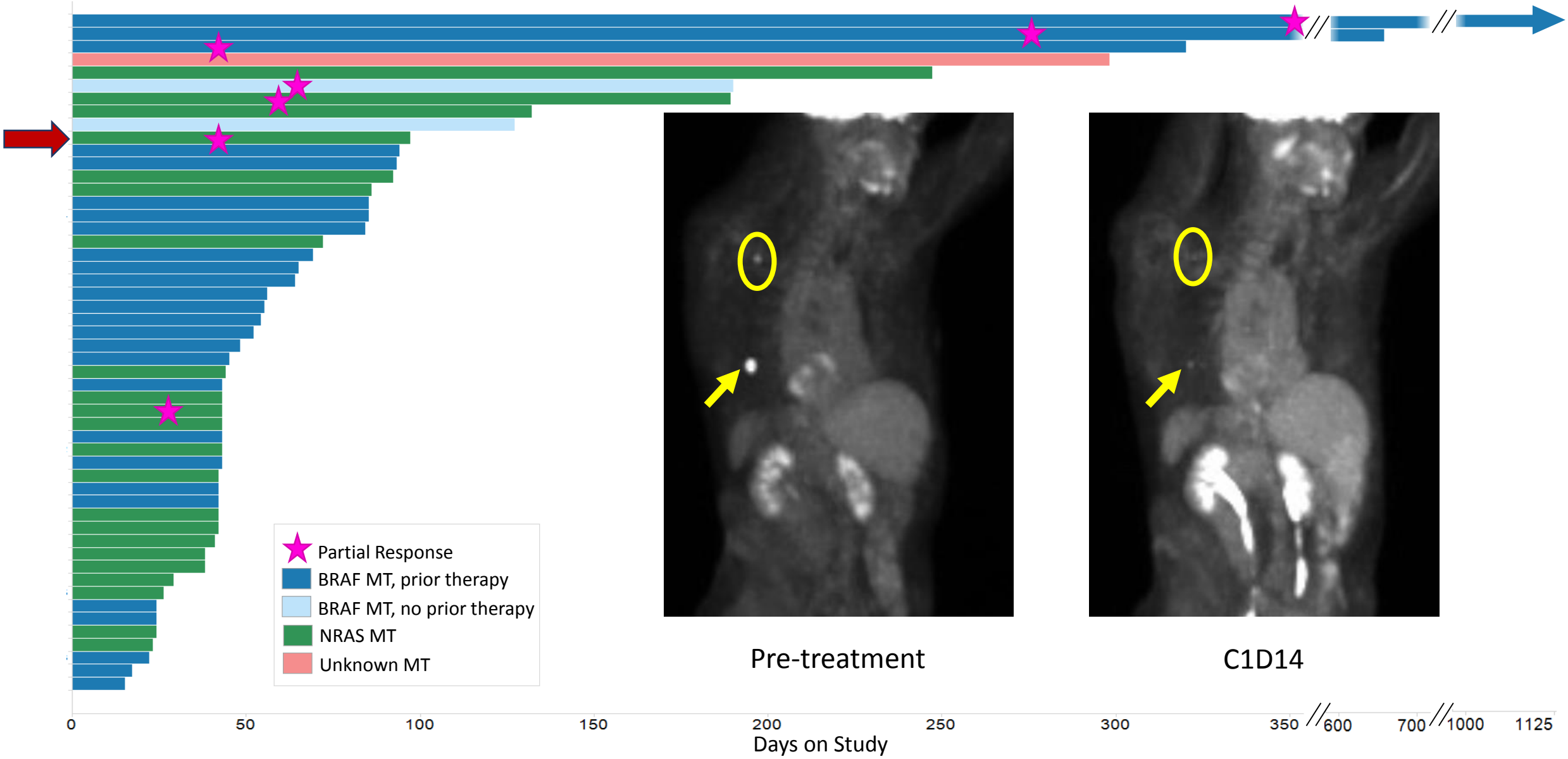


	BRAF MT, prior therapy	BRAF MT, no prior therapy	NRAS MT	BRAF MT (NOS)
Evaluable	20	2	18	1
Best Response (RECIST1.1)				
PD	11	0	9	0
SD	6	1	6	1
PR	**3**	**1**	**3**	**0**
CR	0	0	0	0

Time on Study: Example of Durable Responses to BVD-523



Time on Study: Example of Durable Responses to BVD-523



Most common related adverse events of ulixertinib (≥ 20%*)

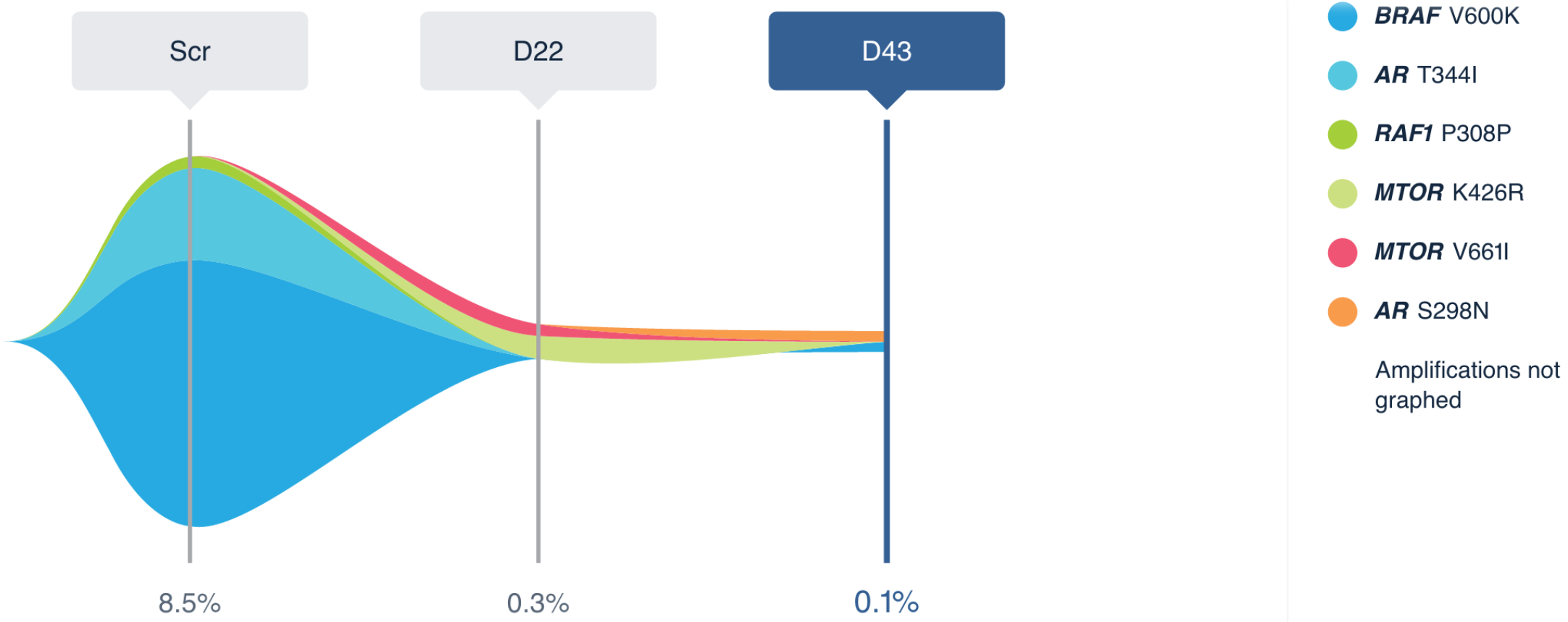
	All Patients (N=52)	
	All Grade (%)	Grade 3/4^
Rash (not acneiform)	30 (58)	7 (13)
Diarrhea	29 (56)	3 (6)
Fatigue	21 (40)	2 (4)
Rash, acneiform	16 (31)	1 (2)
Reduced appetite	14 (27)	0
Ophthalmologic	11 (21)	0
Anemia	8 (15)	3 (6)

*or > 1 Grade 3/4 toxicity

^no Grade 4, treatment related events have occurred

Updated through 01Mar17

Treatment with ulixertinib is associated with changes in ctDNA clonality in a patient with BRAFi/MEKi naïve, BRAFV600K mutant melanoma



Conclusions

- Ulixertinib is a novel ERK1/2 inhibitor that is well tolerated at the maximum tolerated dose of 600 mg BID
- The major toxicities of ulixertinib were rash, diarrhea, and fatigue; no grade 4 or 5 treatment related toxicities were seen.
- Ulixertinib resulted in responses in patients with NRAS mutant melanoma (17%)
- BRAF mutant melanoma following BRAF +/- MEK inhibitor (15%)
  - **Received FDA Fast-Track Designation as single agent**
- Likely, the optimal use of in NRAS and BRAF mutant melanoma may be in combination with other targeted agents such as BRAF inhibitors and/or CDK4/6 inhibitors, as well as with immunotherapy.

Thank You to the patients and their families

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Manish R. Patel

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Amita Patnaik
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Dean Welsch