A First-in-class Phase 1 Dose-escalation Study of the Novel Oral ERK 1/2 Kinase Inhibitor BVD-523 (ulixertinib) in Patients with Advanced Solid Tumors

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PRESENTED AT: ASCO Annual '15 Meeting

Disclosures

ASCO 2015
Jeffrey R. Infante MD

I have no personal financial relationship to disclose

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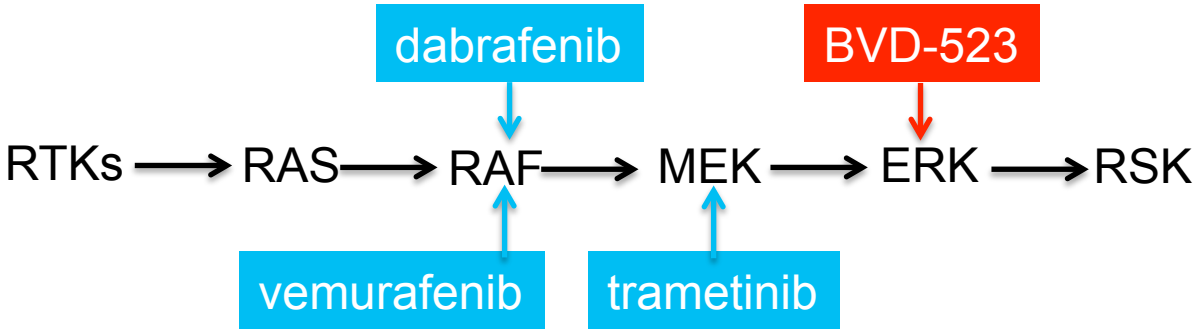
Targeting the MAPK pathway



- MAPK pathway mutations causally drive many cancers
- RAF and MEK inhibitors are approved but limited by intrinsic and acquired resistance
- ERK inhibition has the potential to overcome or avoid resistance from upstream mutations

- BVD-523 : Highly potent, selective and reversible ATP-competitive ERK1/2 inhibitor

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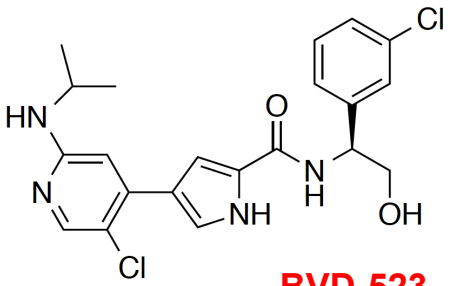
BVD-523 (ulixertinib): A Potent & Selective ERK Inhibitor



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

- Tumor growth regression in BRAF and KRAS-mutant xenograft models
- Single agent inhibition in patient-derived xenograft models cross-resistant to BRAFi and MEKi

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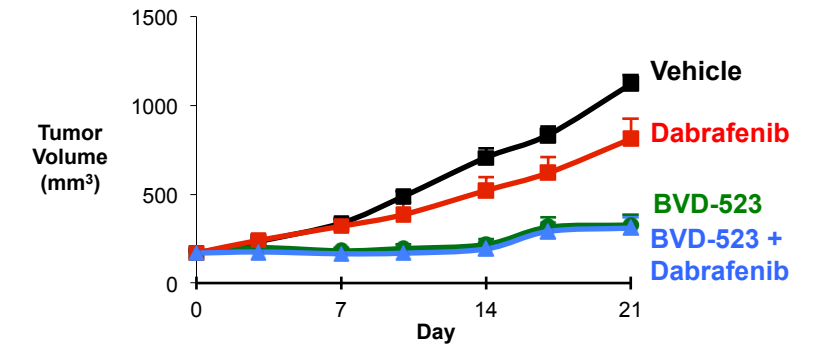
BVD-523: Patient-derived Xenografts that Progressed on BRAF and MEK Inhibitors

Post BRAFi-Progression



Tumors that escape BRAFi and MEKi may remain sensitive to ERKi

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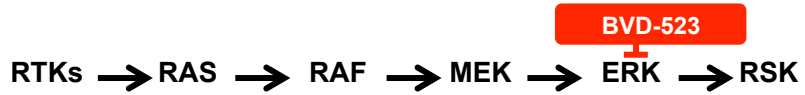
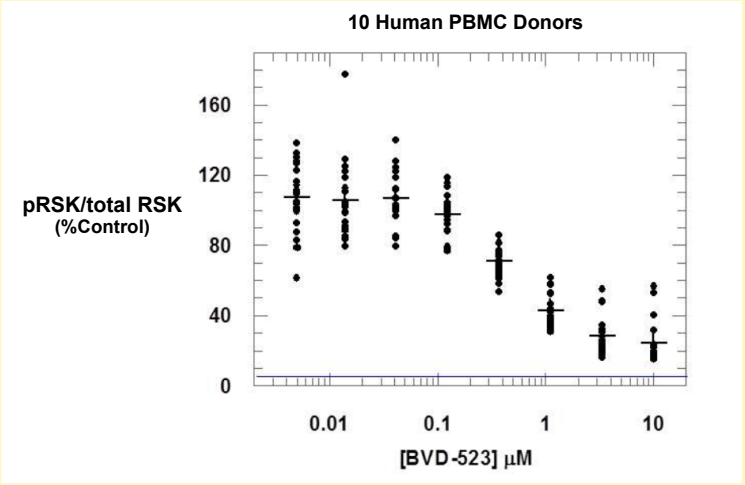
RSK1/2 Phosphorylation as a BVD-523 Activity Clinical Biomarker





EC_{50} ~450 nM (200 ng/mL)

BVD-523 inhibits RSK1/2 phosphorylation using an *ex vivo* human whole blood assay

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BVD-523: FIH Study Objectives

Primary objective: To define the safety and tolerability of BVD-523, the maximum tolerated dose (MTD), and the recommended Phase 2 Dose (RP2D).

Secondary objectives: To determine the pharmacokinetic profile of BVD-523 and selected metabolites. To investigate any preliminary clinical efficacy.

Exploratory objective(s): To evaluate pharmacodynamic marker (biomarker) measures. To investigate any preliminary clinical effects on tumor response assessed by FDG-PET as indicated.

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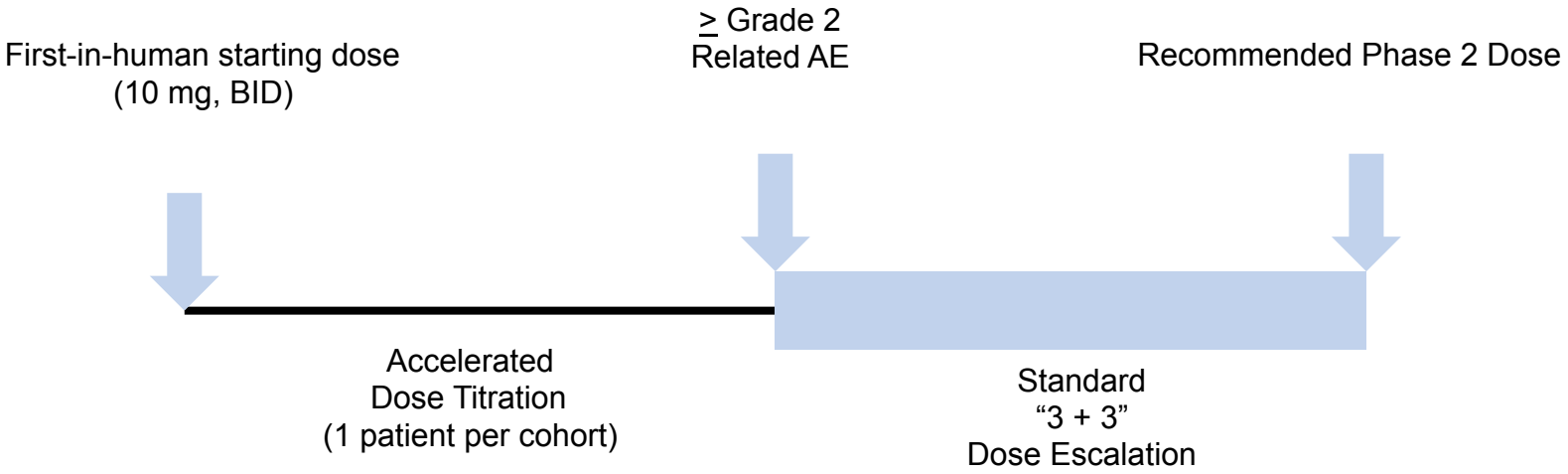
Study Design: Dose Escalation Phase



- PK collection, pre-dose through 12 hours post-dose, on Days 1 and 15
- PD collection, at pre-dose and 4 hours post-dose, on Days 1 and 15

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BVD-523: Key Eligibility

- **Inclusion Criteria**
  - Patients with metastatic or advanced-stage malignant tumor, for whom no therapy exists that would be curative
  - ECOG performance status of 0 or 1
  - Adequate renal, hepatic, bone marrow, and cardiac function

- **Exclusion Criteria**
  - A history or current evidence/risk of retinal vein occlusion or central serous retinopathy
  - Concurrent therapy with drugs known to be strong inhibitors of CYP1A2, CYP2D6, and CYP3A4, or strong inducers of CYP3A4

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BVD-523: Dose-Limiting Toxicity Criteria

- BVD-523 related toxicity in the first 21 days (Cycle 1) of treatment
  - ≥ Grade 4 hematologic toxicity > 1 day
  - Grade 3 hematologic toxicity with complications
  - ≥ Grade 3 non-hematologic toxicity (except untreated nausea, vomiting, constipation, pain and rash unless they persist with adequate treatment), including a doubling of AST/ALT in patients with grade 2 ALT/AST at baseline
  - A treatment interruption exceeding 5 days (or > 7 days for rash, despite adequate treatment) in Cycle 1 (or inability to begin Cycle 2 for ≥ 7 days) due to BVD-523-related toxicity

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BVD-523: Patient Characteristics

All Patients (n=27)	n (%)
Age (yr), median (range)	61 (33-86)
Sex	
Female	13
Male	14
ECOG Performance Status (Initial)	
0	10 (37)
1	17 (63)
Tumor Types	
Melanoma	8 (30)
BRAF mt	7
Unknown	1
Colorectal Cancer	5 (18)
Papillary Thyroid Cancer	4 (15)
Non-small Cell Lung Cancer	2 (7)
Others*	8 (30)
Prior Systemic Therapy	
0	1 (4)
1	2 (7)
2-3	11 (41)
>3	13 (48)

*2 Pancreatic, 1 Appendiceal, 1 NSGCT, 1 Ovarian, 3 Unknown

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BVD-523: Dose Escalation and DLT

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	1/7 (14)	• Rash G3
750*	2/4 (50)	• Rash G3, diarrhea G2 • Hypotension G2, elevated creatinine G2, anemia G2, delay to cycle 2 dosing
900	2/7 (29)	• Pruritis G3, elevated AST G3 • Diarrhea G3, vomiting G3, dehydration G3, elevated creatinine G3

* Intermediate dose

MTD defined as 600 mg po BID continuously

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Adverse Events Possibly Related/Related to BVD-523 in ≥ 10% of Patients

	All Patients (N=27)		
	All Grade (%)	Grade 1/2	Grade 3/4
Blood and Lymphatic			
Anemia	5 (18)	3	2
Gastrointestinal			
Constipation	3 (11)	3	
Diarrhea	14 (52)	12	2
Nausea	14 (52)	14	
Vomiting	8 (30)	7	1
General			
Peripheral Edema	5 (18)	5	
Fatigue	16 (59)	15	1
Fever	3 (11)	3	
Laboratory Values			
Increased Creatinine	5 (18)	4	1
Increased LFTs (ALT/AST)	4 (15)	1	3
Metabolism and Nutrition			
Anorexia	6 (22)	3	3
Dehydration	4 (15)	2	2
Ophthamalogical			
Blurry/Dimmed Vision	3 (11)	3	
Skin and Subcutaneous			
Erythema Multiforme	3 (11)	3	
Rash	19 (70)	17	2
Pruritis	6 (22)	6	

Analysis cut-off date of 13 March 2015

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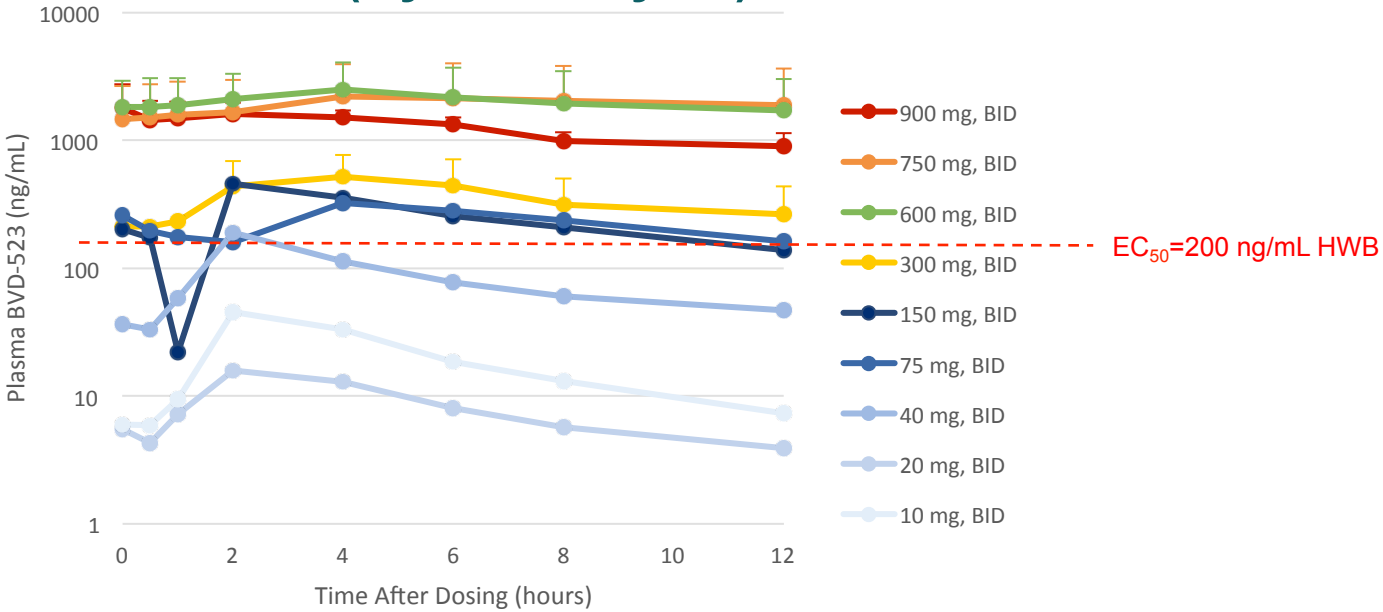
BVD-523: Pharmacokinetics (Cycle 1 Day 15)



- BVD-523 is absorbed slowly, Tmax 2 – 4 hours post dose
- Cmax and AUC generally dose related, up to 600 mg BID
- Moderate accumulation in plasma (1.3 to 4.0 fold at doses >75 mg BID)
- Moderate inter-patient variability.

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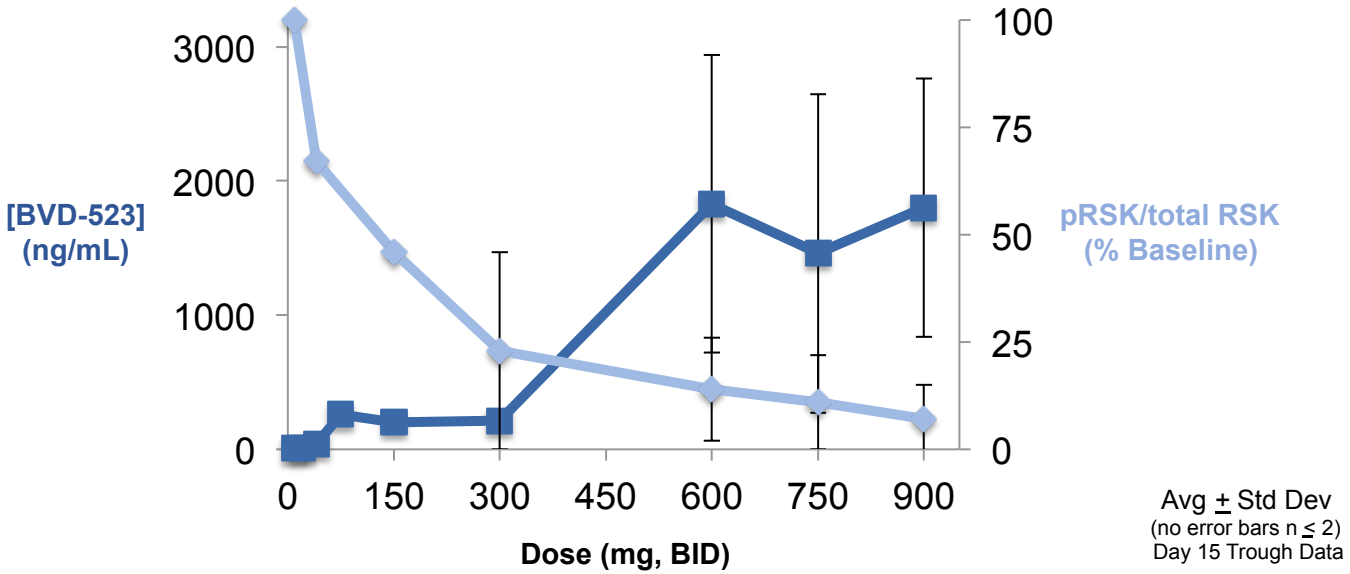
BVD-523: Pharmacodynamic inhibition of ERK substrate phosphorylation



Concentration-dependent inhibition of ERK activity in whole blood; ≥80% target inhibition at tolerated doses/exposures

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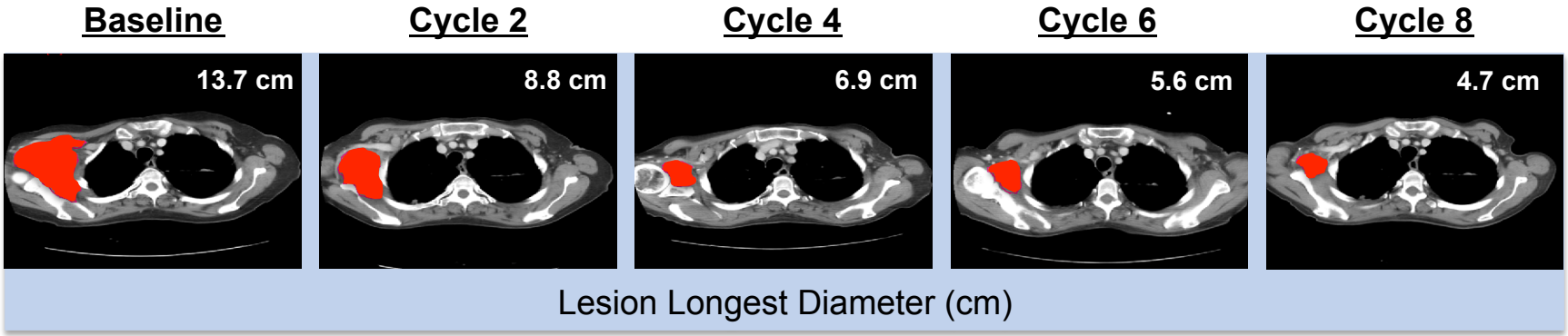
BVD-523: Pharmacodynamic / Radiographic Response

- Metabolic response observed by FDG-PET in 5/16 evaluable patients

- Patient: 61 y/o V600E BRAF mutant melanoma
  - Post-vemurafenib & dabrafenib progression
  - Confirmed CT Partial Response on BVD-523, on-study > 500 days



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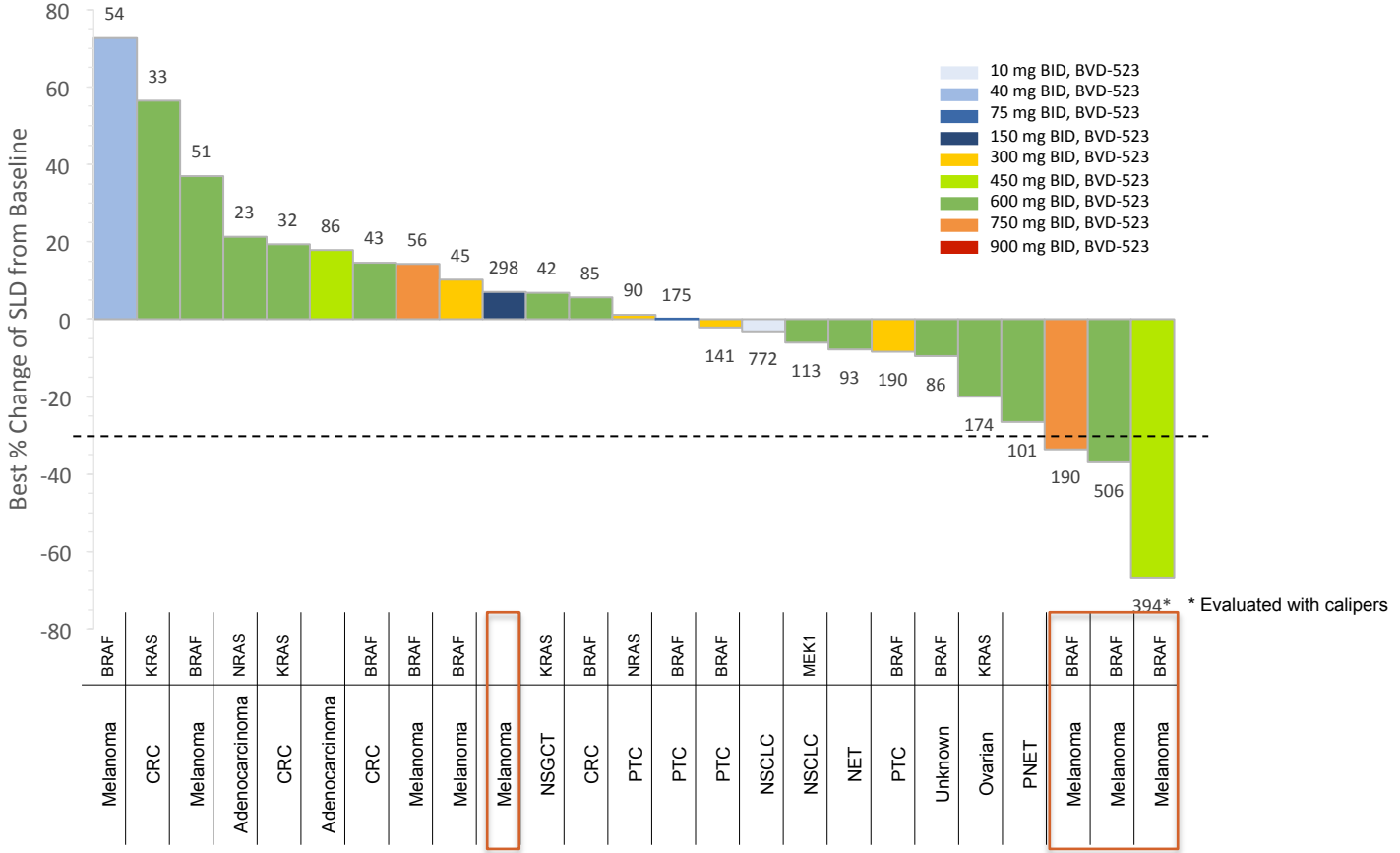
BVD-523: Radiographic Response



Note: All patients with disease measured by RECIST v1.1 who received ≥ 1 dose of study treatment and had > 1 on-treatment tumor assessment (n=25 of 27: 2 did not receive both scans of target lesions)

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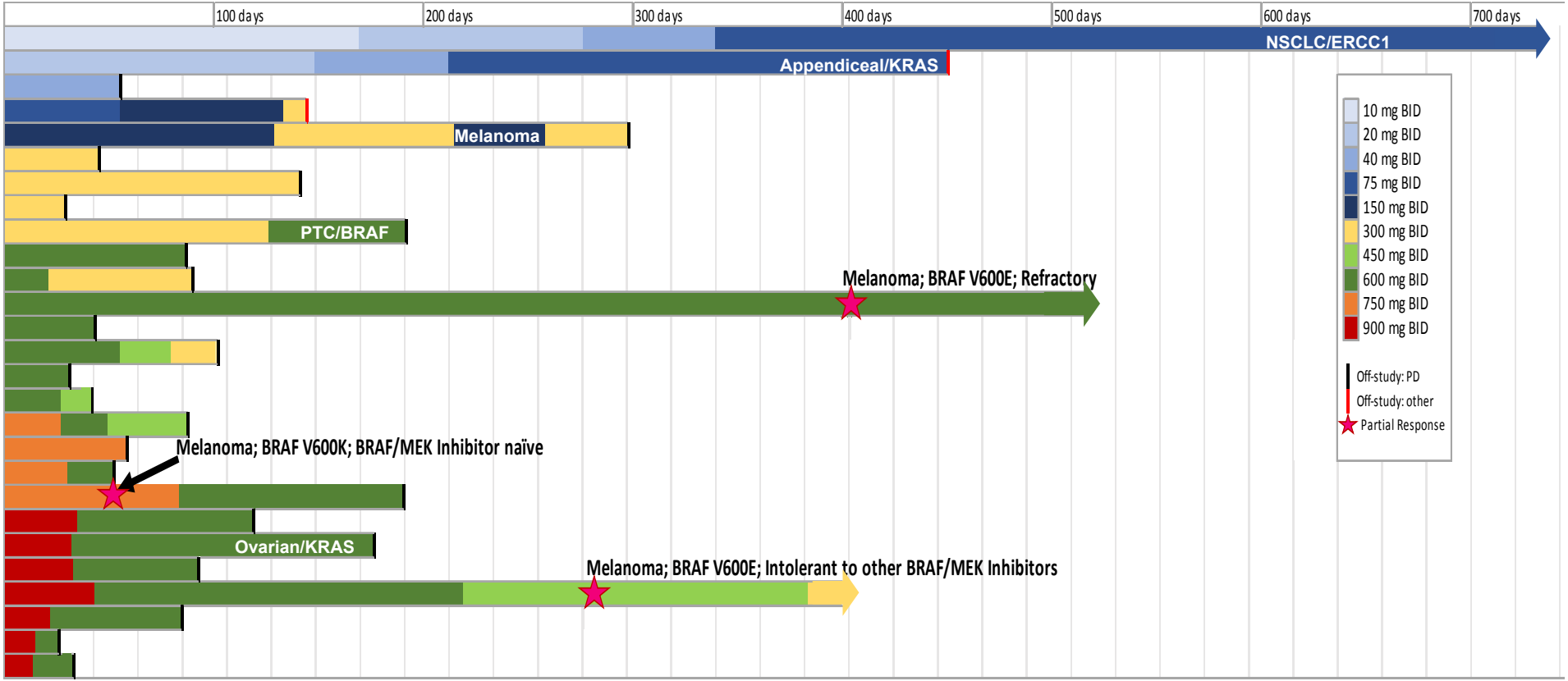
BVD-523: Duration on Study



Analysis cut-off date of 13 March 2015

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Conclusions

- BVD-523 showed manageable tolerability in 27 patients with solid tumors
- The MTD and preliminary RP2D is 600 mg BID
- PK was generally linear and dose-dependent up to 600 mg BID
- In patients' peripheral blood, phosphorylation of the ERK substrates RSK1/2 was shown to be inhibited at doses ≥75 mg BID
- 3 PR and 7 SD >3 months

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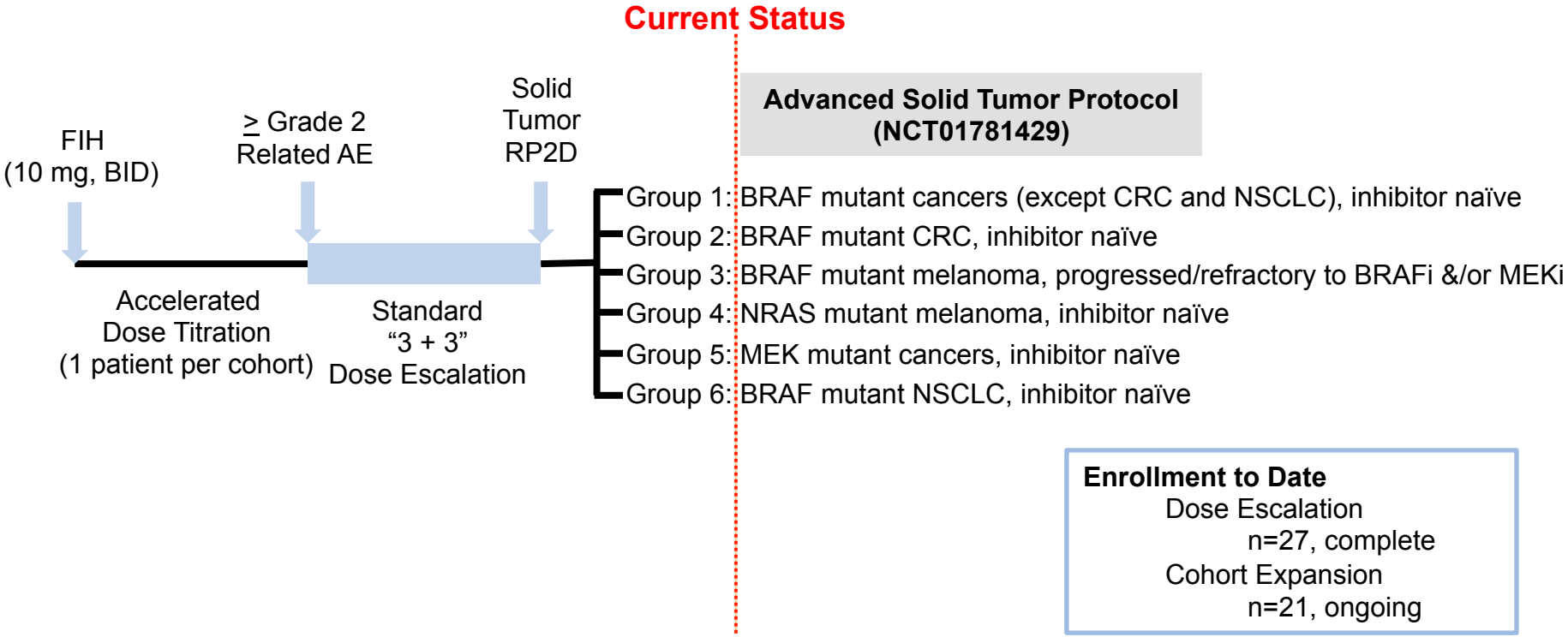
BVD-523 Clinical Program



Enrollment to Date

Dose Escalation
n=27, complete

Cohort Expansion
n=21, ongoing

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Thank You to the patients and their families

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Fighting Cancer Together.

Howard A Burris
Todd Bauer
Johanna C. Bendell
Manish R. Patel
Terri Peterson
Michael Shearer
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