

The selective ERK inhibitor BVD-523 is active in models of MAPK pathway-dependent cancers, including those with intrinsic and acquired drug resistance

Ursula Germann¹, Brinley Furey², Jeff Roix³, William Markland², Russell Hoover², Alex Aronov², Michael Hale⁴, Guanjing Chen⁵, Gabriel Martinez-Botella⁶, Rossitza Alargova⁷, Bin Fan⁸, David Sorrell⁹, Kay Meshaw¹⁰, Paul Shapiro¹¹, Michael J. Wick¹², Cyril Benes¹³, Mathew Garnett¹⁴, Gary DeCrescenzo¹⁵, Mark Namchuk¹⁶, Saurabh Saha¹⁵, **Dean J. Welsch**¹⁵.

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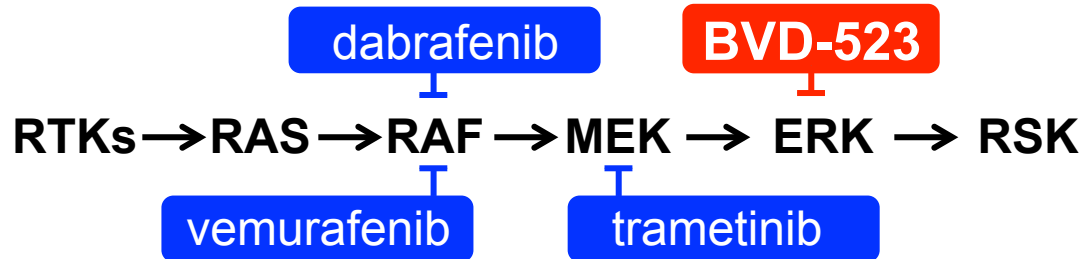
Disclosure Information

AACR Annual Meeting 2015
Dr. Dean J. Welsch

I have the following financial relationship to disclose:
Employee of BioMed Valley Discoveries

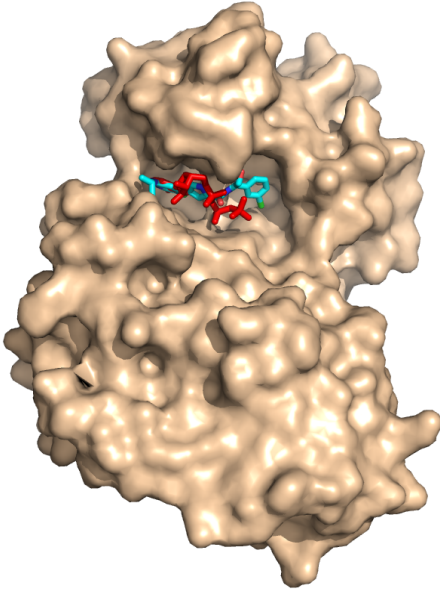
I will not discuss off label use and/or investigational use in my presentation

Mechanistic Background & Therapeutic Opportunity



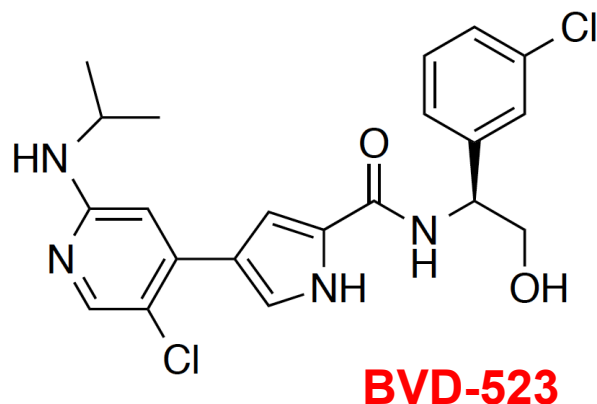
- MAPK pathway mutations causally drive many cancers
- 3 MAPK drugs are approved but limited by intrinsic and acquired resistance
- ERK inhibition has the potential to overcome or avoid resistance from upstream mutations

BVD-523 Executive Summary



- Highly potent, selective and reversible ATP-competitive ERK1 and ERK2 inhibitor
- Tumor growth regression in BRAF- and KRAS-mutant xenograft models
- Single agent inhibition of a patient-derived xenograft cross-resistant to BRAFi and MEKi
- **Phase 1 dose escalation completed with expansion cohorts in progress**

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



Highly potent

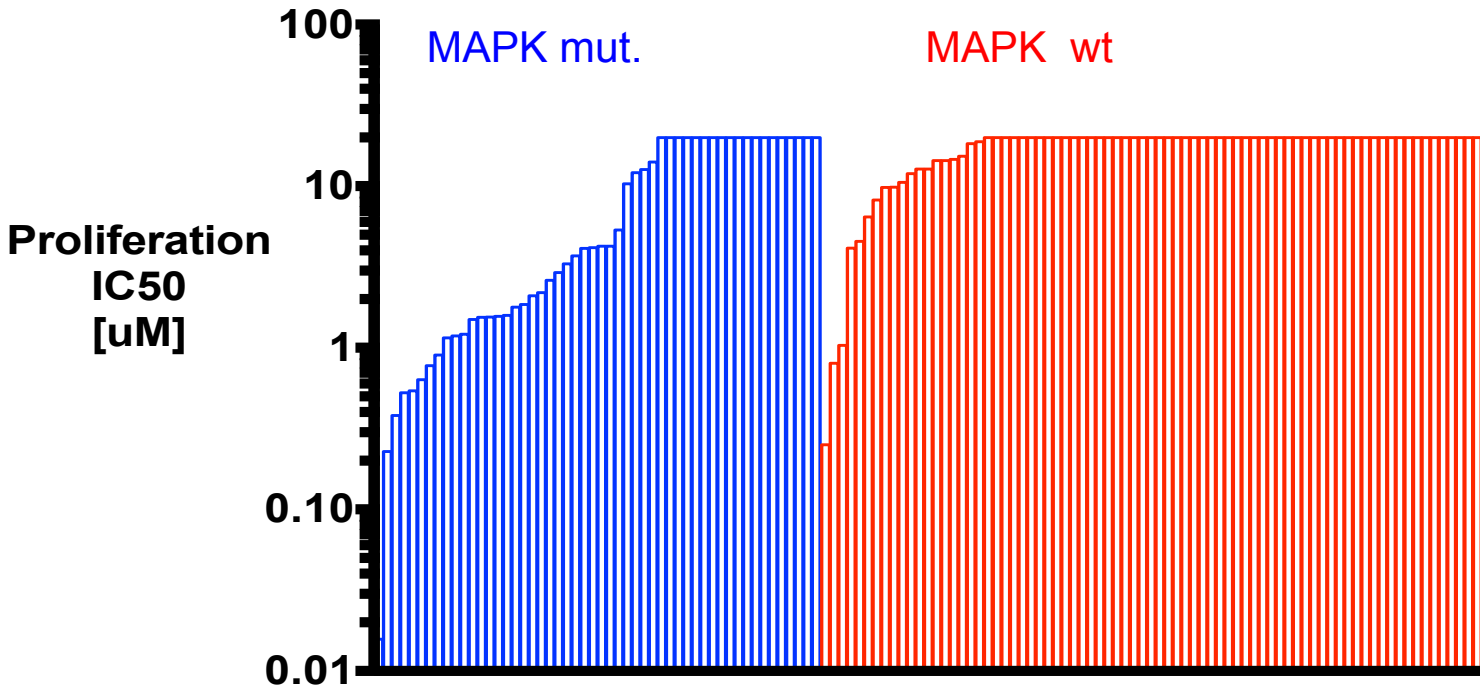
- ERK1 $K_i < 300$ pM
- ERK2 $K_i = 40$ pM

Highly selective

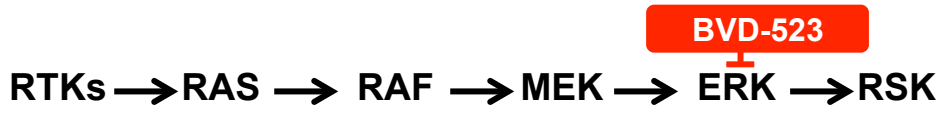
- $\geq 1,000$ -fold vs CDK1, CDK2, CDK5, CDK6, GSK3b
- $\geq 10,000$ -fold vs 70 other kinases

BVD-523 Preferential Activity in Cells with MAPK Pathway Mutations

MGH/Wellcome Genomics of Drug Sensitivity in Cancer Panel

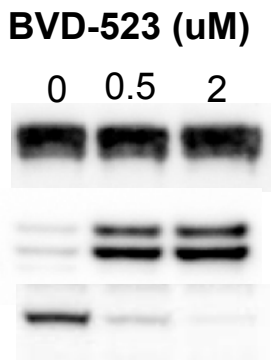


BVD-523 Mechanism of Action and Enzyme Binding



Mechanism of Action

RKO
(BRAF V600E)
Colorectal
Cancer
Cell Line



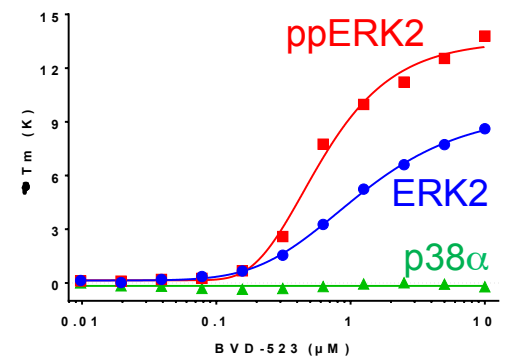
MEK1/2
p*S217/S221

ERK1/2
p*T202/Y204

RSK1/2
p*T359/S363

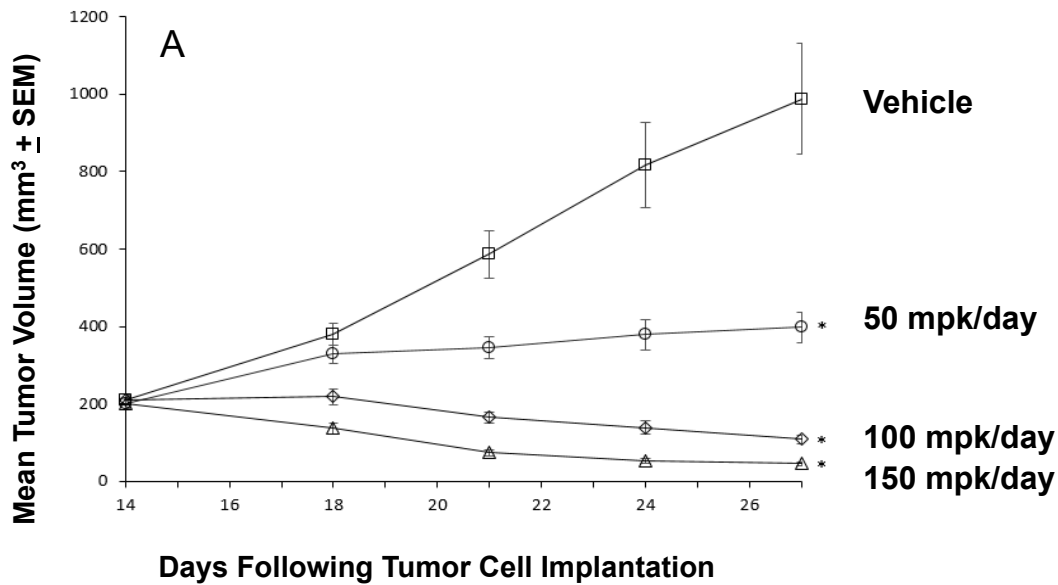
Enzyme: BVD-523 Binding

Differential
Scanning
Fluorimetry



BVD-523 Anti-tumor Activity in Multiple In Vivo Cancer Models

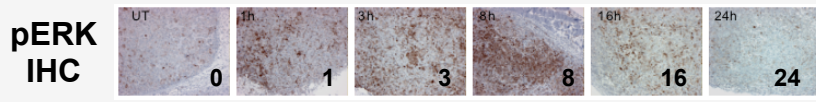
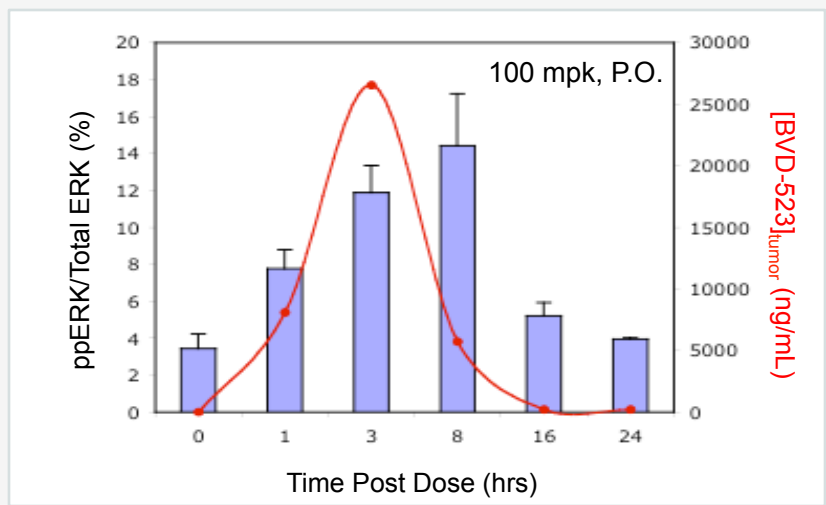
BVD-523 Tumor Growth Inhibition in Colo205 Xenograft



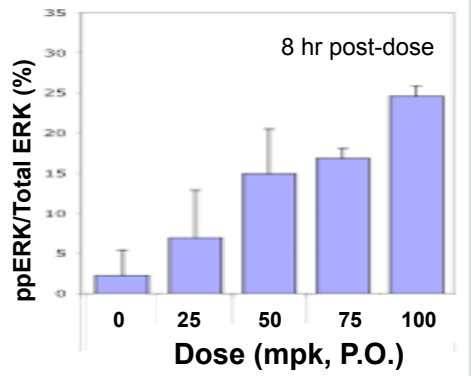
- **Single agent activity in xenografts with**
 - BRAF mutation (Colo205 CRC, A375 Mel)
 - RAS mutation (MiaPaCa2 Panc)
- **At least additive with other MAPK inhibitors**

Response Correlates with Tumor PK and Dose

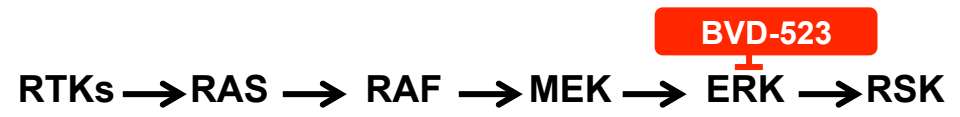
pERK Levels Correlate with Tumor PK - Timecourse



pERK Levels Correlate with Tumor PK-Dose



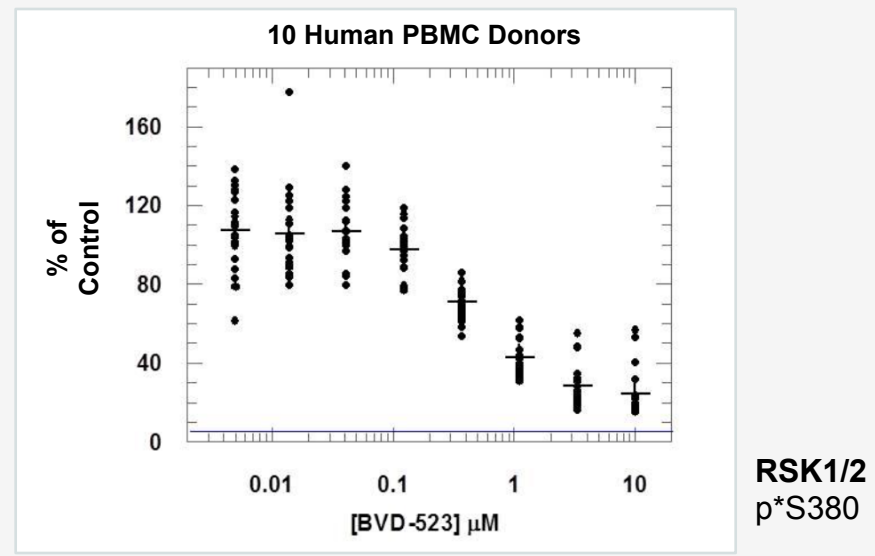
RSK1/2 Phosphorylation as a BVD-523 Activity Clinical Biomarker



RSK1/2 is a substrate for ERK phosphorylation



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



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

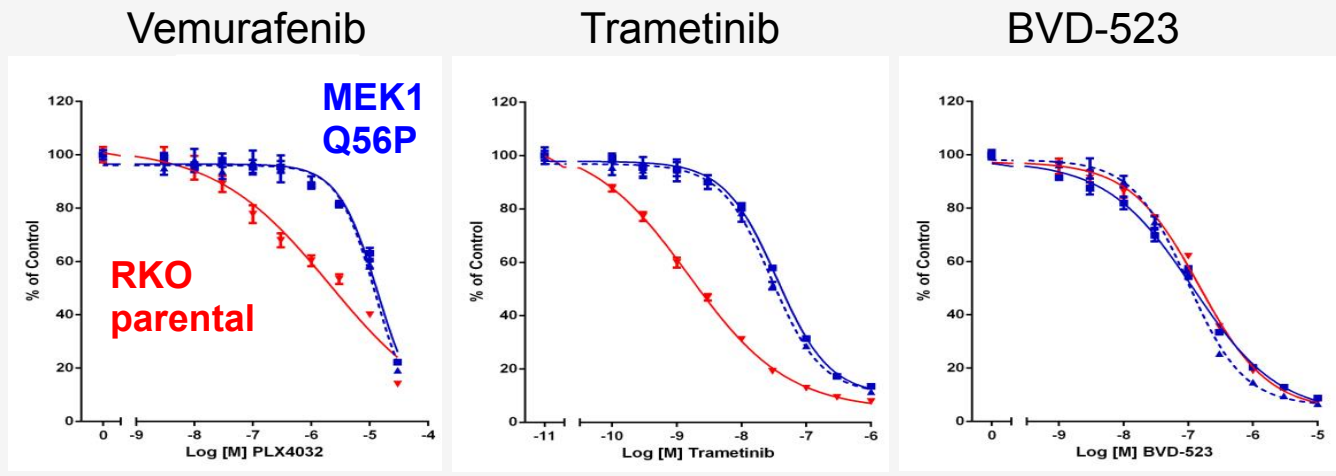
BVD-523 inhibits ERK activity following oral dosing in canine GLP tox study

Dose (mg/kg, BID)	ERK Inhibition (%)	BVD-523 Conc. (uM)
Vehicle	0	0
2	53	0.23
5	64	0.92
15	94	3.2

- **Human and canine whole blood ERK activity assays established**
- **BVD-523 demonstrated significant ERK inhibition with chronic oral dosing in canine GLP toxicity study at tolerated doses, exposures**
- **ERK activity assay supporting clinical studies**

BVD-523 Effective in Models of Acquired Resistance to BRAF and MEK Inhibitors

BVD-523 potency retained in cells cross-resistant to BRAFi & MEKi



BVD-523 sensitivity retained in A375 cells cultured to acquire resistance to BRAFi + MEKi combination

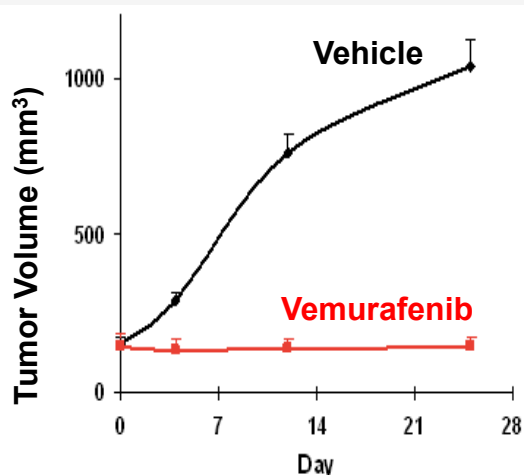
Cell Line	Proliferation IC ₅₀ (nM)			
	Dabrafenib	Trametinib	BVD-523	Paclitaxel
Parental	2.1	0.2	129	1.9
BRAFi + MEKi-Resistant	17.9	2.7	323	4.7
Fold Increase	8.5	13.5	2.5	2.5

BVD-523 Effective in Xenografts Derived from a Patient Who Progressed on BRAF Inhibitor

BVD-523 sensitivity in patient-derived xenograft model

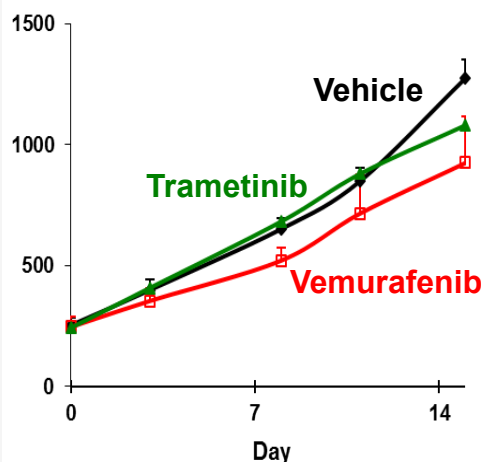
Baseline

Intrinsic BRAFi Sensitivity

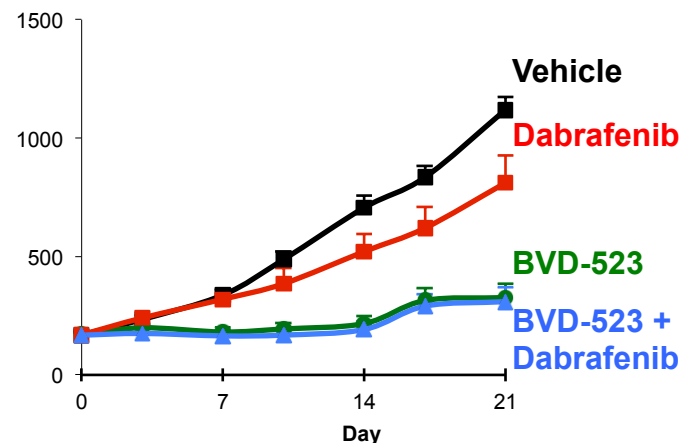


Post-Progression

BRAFi & MEKi Insensitivity



ERKi Sensitivity



Tumors that escape BRAFi and MEKi may remain sensitive to ERKi

BVD-523 IND Enabling Studies – Summary of Findings

Safety Pharmacology

- No significant interaction in in vitro screens against 65 receptors, transporters, and ion channels
- Exhibited no significant genetic toxicology risks in reverse mutation and micronucleus assays
- Inhibits the hERG current (IC₅₀ 3.4 uM)
- Dog Purkinje fiber assays revealed no significant effects up to 10 ug/mL

Metabolism

- Recombinant human CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 capable of metabolizing BVD-523
- Metabolism predominantly via oxidation and dealkylation
- Metabolic profile of BVD-523 across mouse, rat, dog, and human liver microsomes and hepatocytes very similar (monkey was unique in its metabolic profile)
- Rat & dog identified as appropriate species for toxicological evaluation

GLP Toxicity Studies

- No CV findings observed following 28 days of dosing with BVD-523
- 28-day studies, with reversal arms, conducted at doses ranging from 25-100 mg/kg/day and 4-30 mg/kg/day in rat and dog, respectively

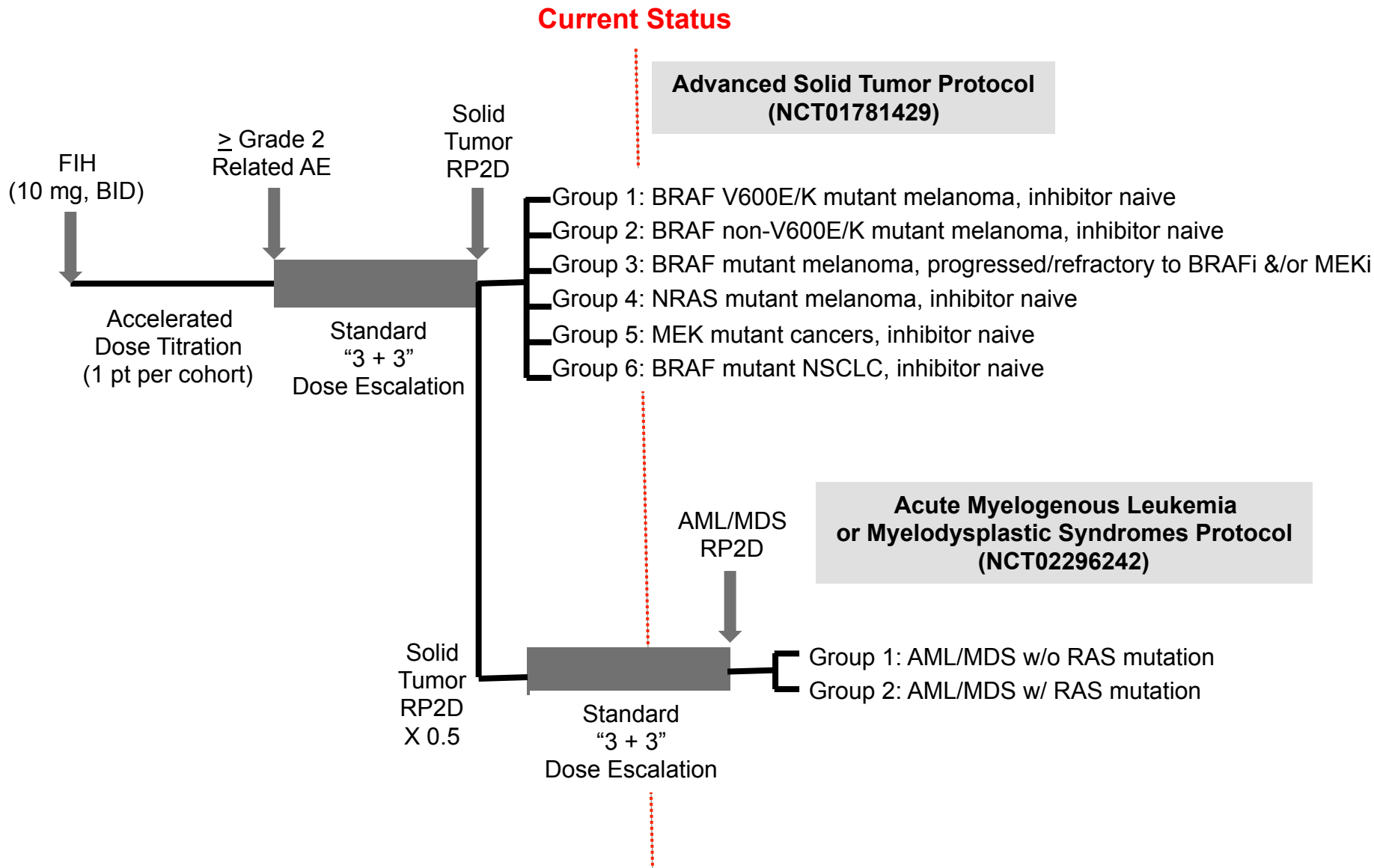
Target Tissue Toxicities

- Findings are dose-dependent, and at least partially reversible
- Rat: tissue mineralization, skin lesions/rash
- Dog: gastrointestinal
- All toxicities consistent with MAPK pathway inhibitors, further demonstrating the exquisite selectivity of BVD-523

Starting Dose Justification

- Rat identified as most sensitive species
- Supported first-in-human starting dose of 10 mg, BID

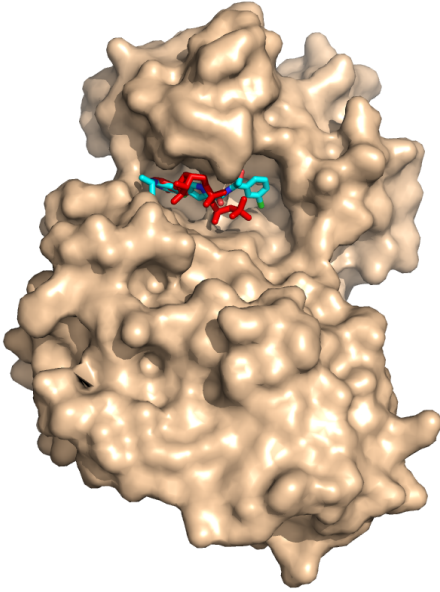
BVD-523 Clinical Development Plan – Ongoing Studies



Possible Protocols

- BVD-523 + BRAFi, MEKi, or BRAFi & MEKi
- BVD-523 + BRAFi, MEKi, or BRAFi & MEKi after acquired resistance
- BVD-523 + non-MAPK pathway targeted agents
- BVD-523 + immune response modulators
- BVD-523 + chemotherapeutics
- BVD-523 + ???

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