pistonbio

new medicine for cancer

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Pipeline

Program	Mechanism	Target Indication	Rights Status	IP	Stage
Mosperafenib (lead asset)	BRAF V600E inhibitor	2L+ BRAF V600E CRC	Non-binding terms agreed with Roche	Roche IP	Phase Ia/b completed N=92
PST-102	Extended half-life TLR7/8 agonist	2L+ NSCLC	100% owned	Composition of matter	Pre-IND / FDA feedback received
PST-101	Extended half-life A2A antagonist	Cancer-related apathy	100% owned	Composition of matter	FDA-aligned Phase 2

Mosperafenib Targets BRAF Dimer-Mediated Resistance

- BREAKWATER established encorafenib-based combination therapy as first-line standard of care for BRAF V600E CRC.
- Encorafenib inhibits mutant BRAF, but tumors can reactivate MAPK signaling through RAF dimers.
- Mosperafenib was designed to address this limitation by preventing RAF dimer-mediated signaling.
- This provides a mechanistic rationale for activity even in patients previously treated with encorafenib.

Phase 2 Strategy: Post-Encorafenib BRAF V600E CRC

CURRENT CLINICAL REALITY

Post-Encorafenib Vacuum

2L+ Unmet Need:

FOLFIRI + bevacizumab is standard of care after encorafenib + cetuximab in 1L. Limited established targeted options after encorafenib progression.

PISTON BIO STRATEGY

Defensible Add-On Regimen

Triplet Combination:

Add Mosperafenib to FOLFIRI + bevacizumab.

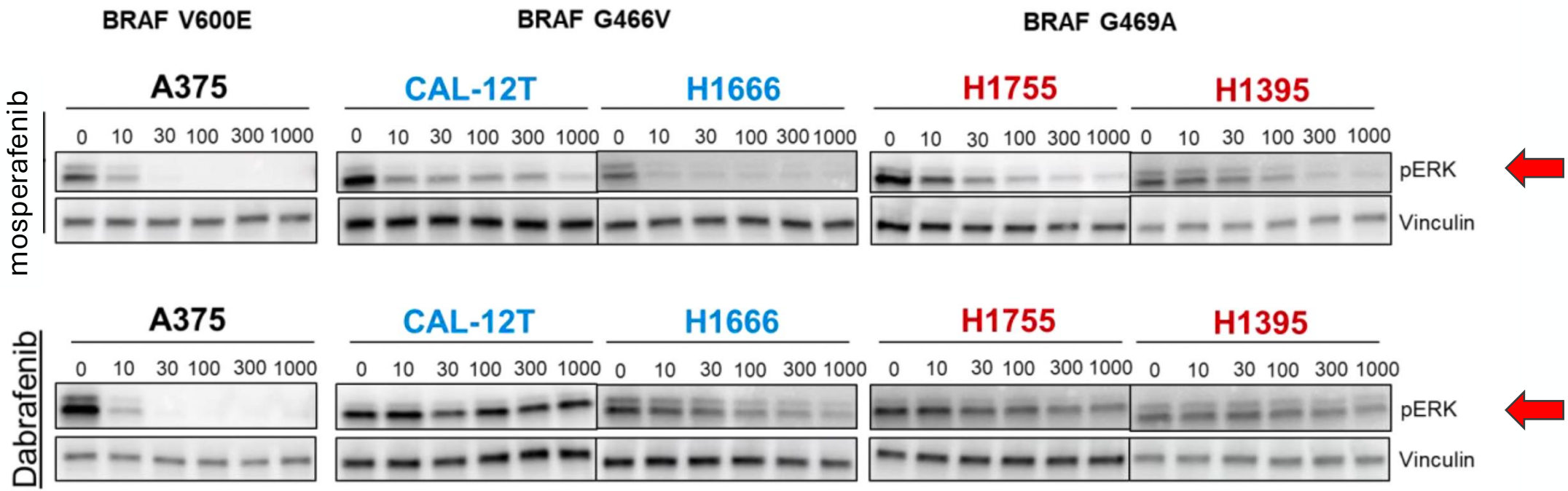
Mechanistic Rationale:

Target RAF dimer-mediated MAPK reactivation following encorafenib progression.

Target Patient Cohort:

Irinotecan-eligible 2L+ BRAF V600E CRC patients with prior encorafenib exposure.

Superior BRAF Dimer Blockade by Mosperafenib vs First-Gen BRAFi

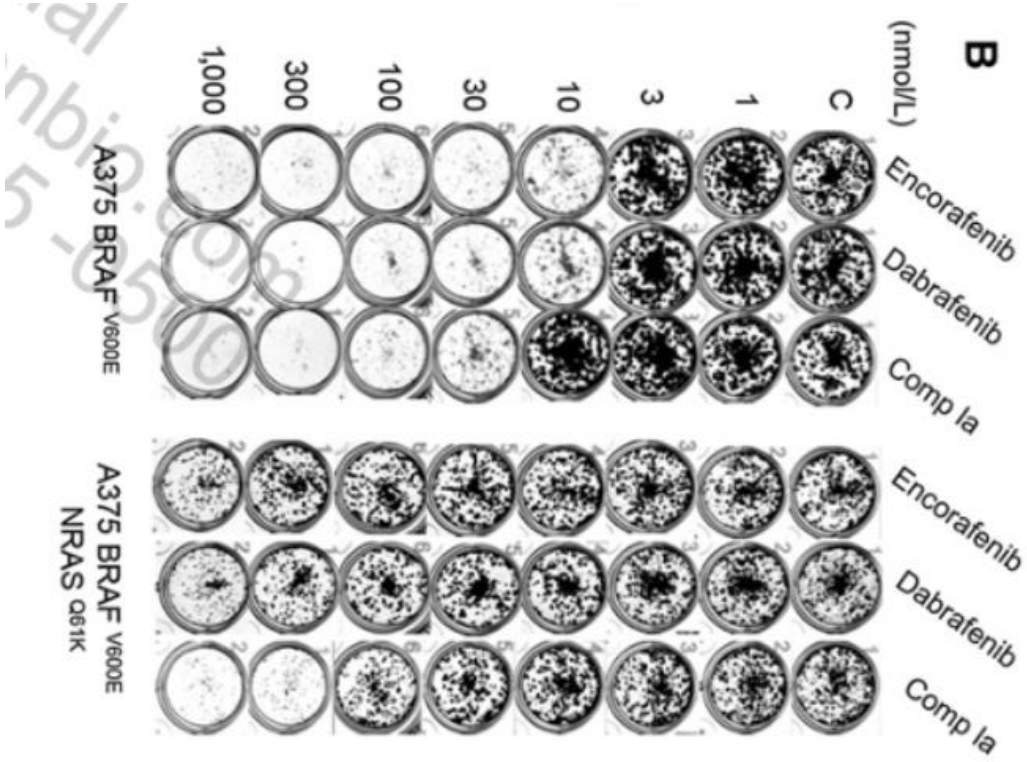


Dark bands indicate sigaling (cancer growth).

Mosperafenib blocks both BRAF monomers (A375 cells) and dimers (CAL-12T, H1666, H1755, and H1395 cells).

Dabrafenib blocks monomers (A375) only.

Mosperafenib Prevents Dimer-Driven Cancer Growth; First-Gen Doesn't



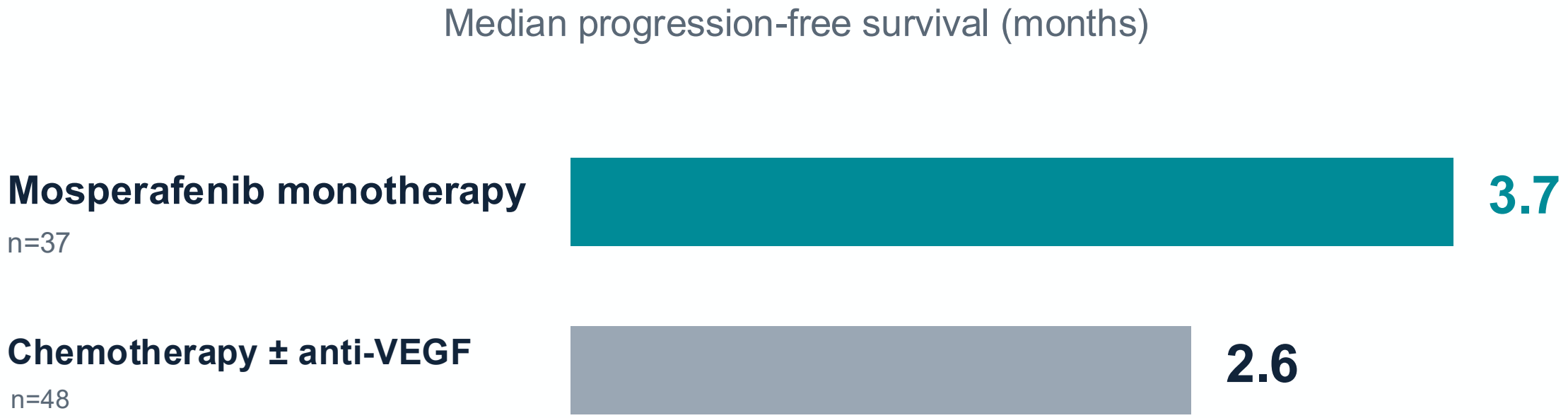
Dark wells indicate cancer cell growth.

Mosperafenib (Compound Ia) inhibits growth when BRAF is either a monomer (top) or dimer (bottom).

First-gen BRAF inhibitors allow growth in dimer-driven cells (bottom).

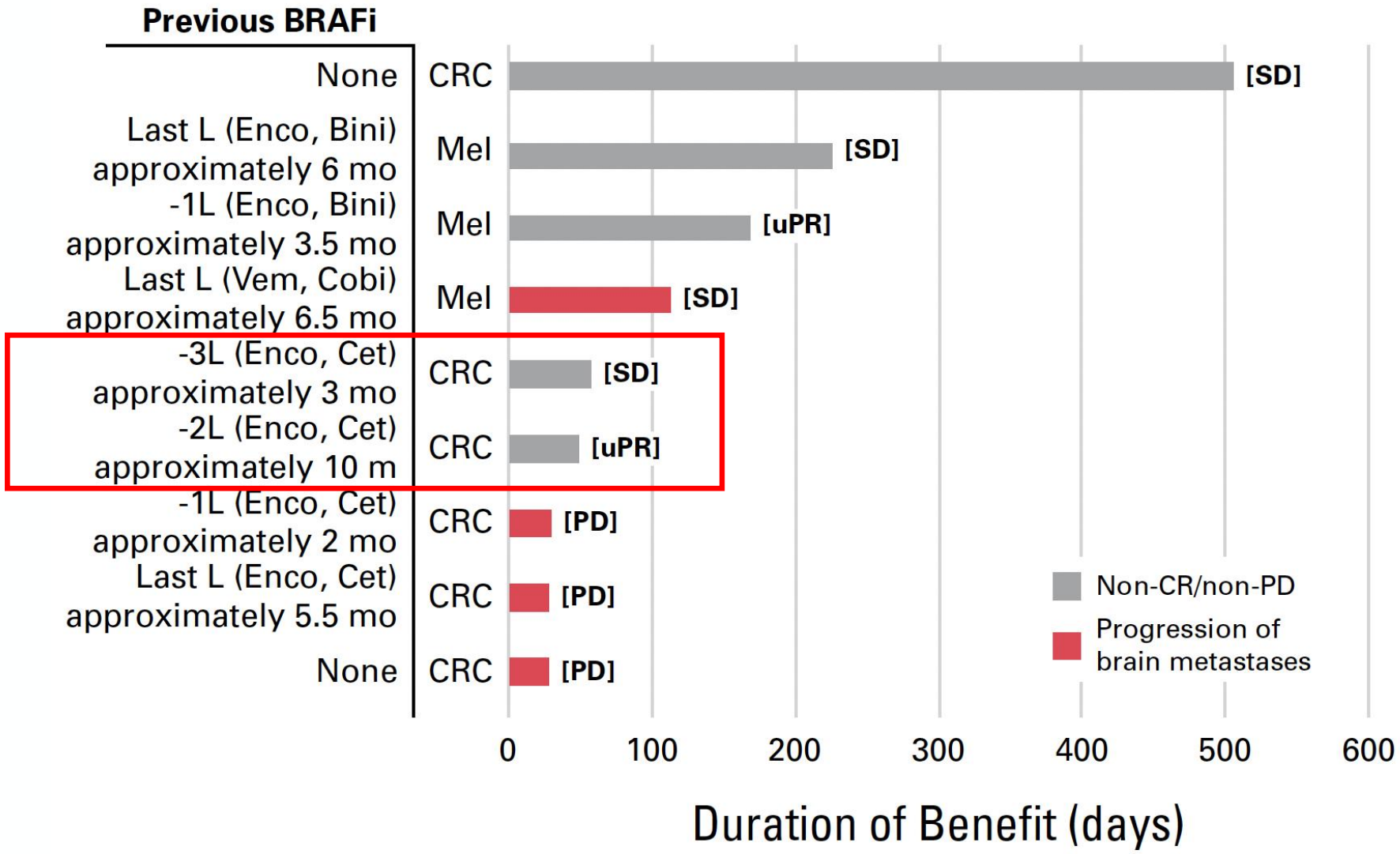
CLINICAL EFFICACY

Mosperafenib Monotherapy Beats SOC in BRAF-resistant V600E CRC



Potential triplet PFS: 6.3 months:
3.7 months (mosperafenib mono) + 2.6 months (chemotherapy ± anti-VEGF)

Mosperafenib Mono Controls CNS Mets in BRAF-Resistant V600E CRC



CLINICAL BENCHMARKING

Mosperafenib More Efficacious than First-Gen in BRAF-Naïve V600E CRC

BRAF dimers form in real-time and limit the efficacy of BRAF inhibitors in BRAF-naïve patients; mosperafenib performance in this setting predicts efficacy in the post-BRAF population.

Agent	ORR	Median PFS	DCR
Mosperafenib (N=26)	**19% (5/26)**	**7.3 mo**	**96.1% (25/26)**
Encorafenib (N=18)	0% (0/18)	4.0 mo	66.7% (12/18)
Vemurafenib (N=21)	5% (1/21)	—	—
Dabrafenib (N=9)	11% (1/9)	—	—

PHASE 1 DATA

RP2D is Established (1200 mg po TID)

Target Saturation at RP2D

PK Modeling: Predicted exposure above the ERK IC_{90} for >75% of the dosing interval at 1200 mg TID.

Low Risk of Drug Interactions

Non-CYP Metabolism: Eliminates typical CYP3A interaction risks.

TOLERABILITY THRESHOLDS

Mosperafenib Dimer Blockade Minimizes Cutaneous Toxicity vs 1st Gen

Toxicity Parameter	Mosperafenib (N=80)	Encorafenib 300mg	Vemurafenib 960mg
Discontinuation from TRAEs	**2.5% – 3.8%**	10% – 13%	10% – 15%
Keratoacanthoma / cuSCC	**0.0% KA (1 cuSCC)**	7.3%	11.8%
Skin Hyperkeratosis	**1.3%**	39.6%	29.0%
Palmar-Plantar Erythema (PPE)	**0.0%**	51.6%	Notable
Severe Arthralgia	**10.0% (0% Gr3+)**	50.5%	47.3%

Phase 2 Study Design

TARGET POPULATION

2L+ BRAF V600E CRC

FOLFIRI-naïve, relapsed on/after encorafenib + cetuximab

Stratified by baseline ctDNA and liver mets.

TOTAL N

100 Patients

10-pt safety/PK lead-in followed by 90-pt (1:1) randomization: FOLFIRI + bevacizumab ± mosperafenib (1200 mg TID).

PRIMARY ENDPOINT

BICR-Assessed ORR

Progression-free survival (PFS) key secondary.

90 randomized patients provide 77% power to detect a threefold increase in ORR (10% vs. 30%; one-sided $\alpha = 0.05$).