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Phase 1B Study of Vemurafenib in Combination with the MEK inhibitor, GDC-0973, in Patients with Unresectable or Metastatic *BRAF^{V600}*-Mutated Melanoma (BRIM7)

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Disclosures

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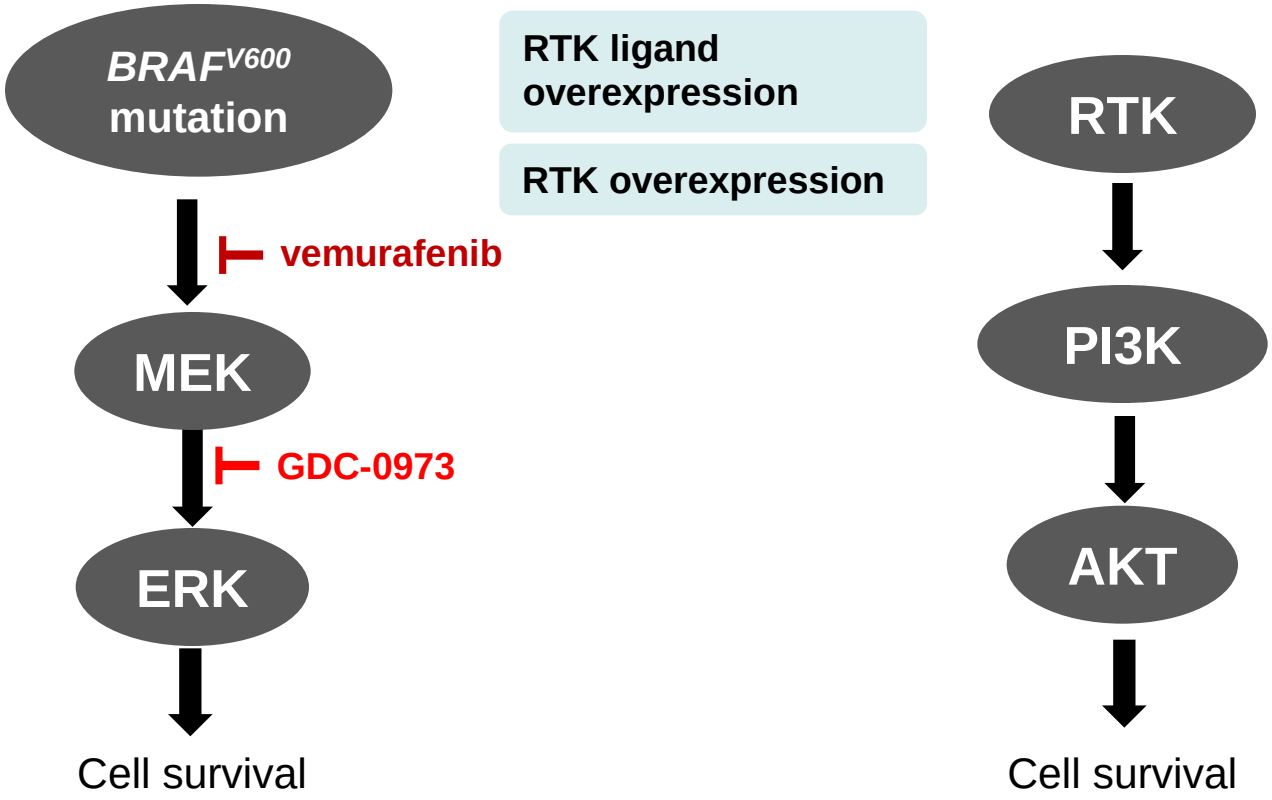
Acquired resistance to BRAF inhibition

MEK-dependent resistance

- NRAS mutations
- *BRAF*^{V600} mutation truncation / amplification
- COT overexpression
- MEK mutations

MEK-independent resistance

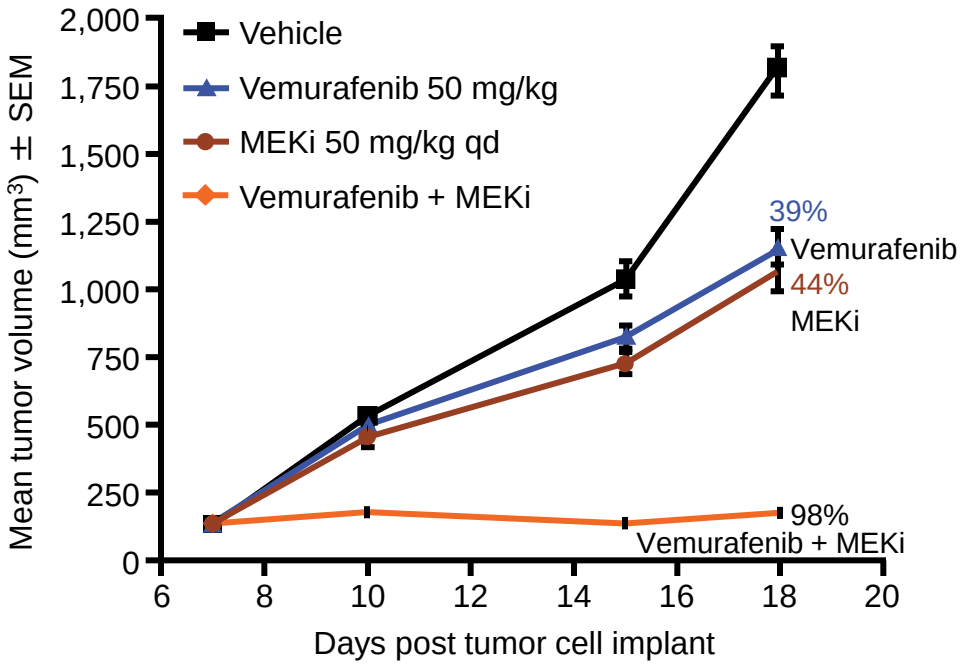
- RTK ligand overexpression
- RTK overexpression



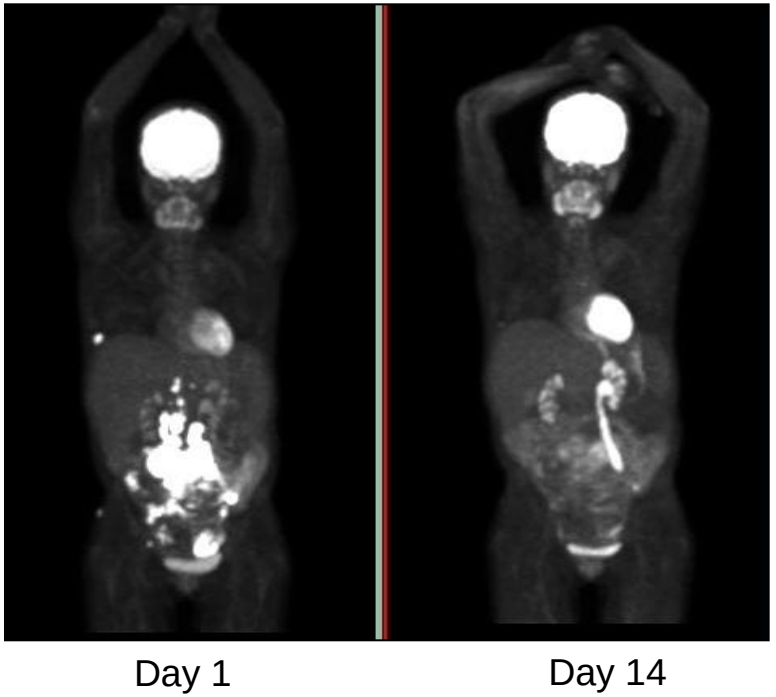
Corcoran RB, et al. Sci Signal 2010 23;3:ra84; Villanueva J et al. Cancer Cell 2010; Nazarian R et al. Nature 2010; Su F et al. Cancer Res 2011; Wagle N et al. J Clin Oncol 2011; Johannessen CM et al. Nature 2010; Poulikakos PI et al. Nature 2011

Combined BRAF & MEK inhibition:
Preclinical data & PET scan response

- Preclinical data support combined inhibition of BRAF and MEK:
  - Prevents the emergence of resistance
  - Overcomes acquired resistance



In vivo combination of vemurafenib and MEK inhibition in the vemurafenib-resistant A375 melanoma xenograft model overcomes acquired resistance (KRAS^{K117N} mutation)



PET scan response in a patient after progression on vemurafenib and after treatment with vemurafenib + GDC-0973

Paraiso KH et al. Br J Cancer 2010; Su F et al. Cancer Res 2012

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GDC-0973 & BRIM7 study objectives

GDC-0973*:

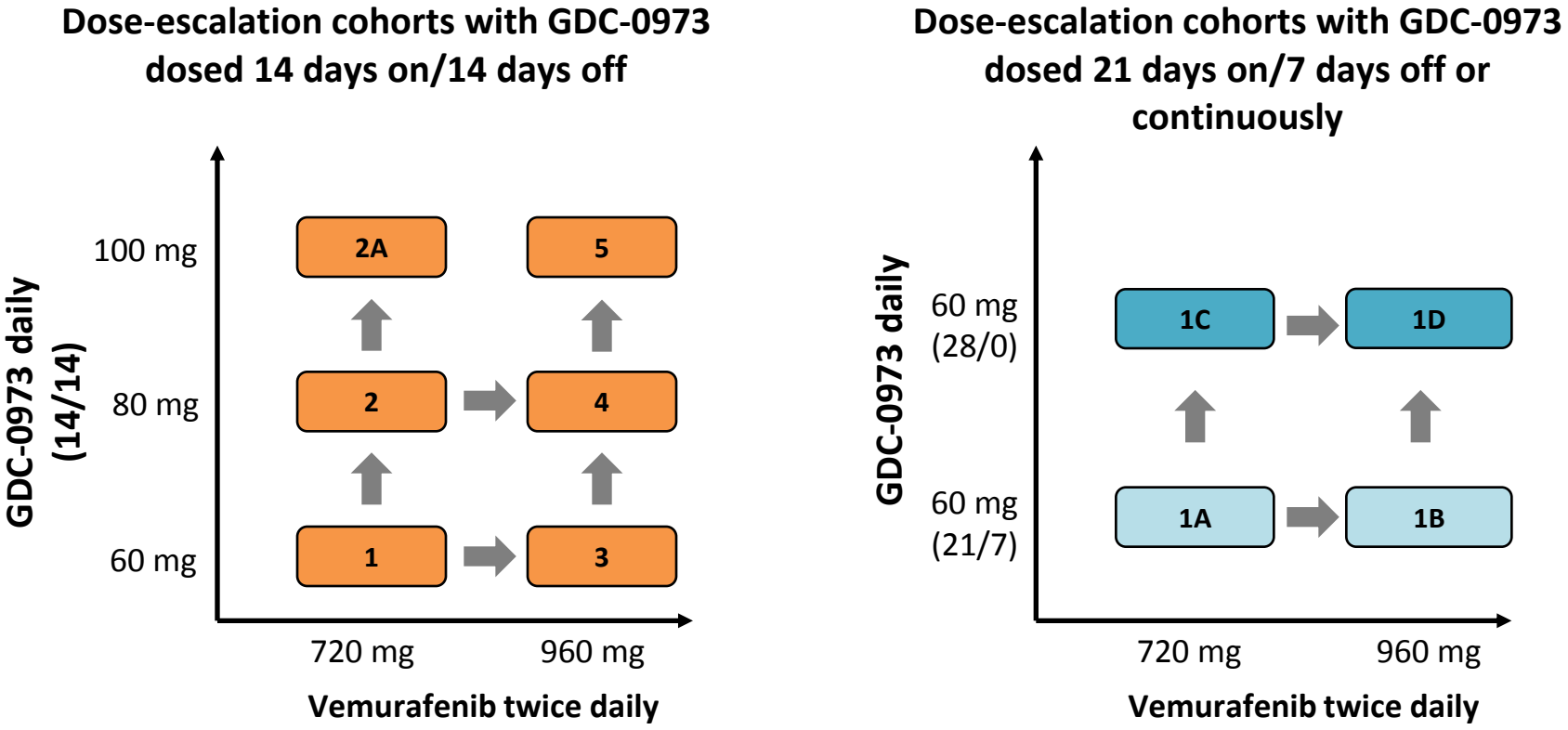
- Orally available, potent and highly selective small-molecule inhibitor of both MEK 1 and MEK 2
- GDC-0973 monotherapy Phase I study:
  - 14 day on/14 day off schedule MTD = 100mg
  - 21 day on/7 day off schedule MTD = 60mg
  - Common AEs: diarrhea, rash, edema, fatigue, nausea
  - Encouraging single-agent activity in *BRAF^{V600}* melanoma
    - 7 responders out of 12 melanoma patients
    - 6 responders were BRAF^{V600E} mutation-positive (1 pt unknown mutation status)
    - Median time on GDC-0973 treatment: 9.3 months (range 1.4 - 23 + months).

BRIM7 Objectives:

- To evaluate the safety and tolerability of vemurafenib + GDC-0973
- To identify the dose-limiting toxicities (DLTs) that determine the maximum tolerated dose (MTD) of vemurafenib + GDC-0973
- To identify a Phase II/III dose and schedule for vemurafenib + GDC-0973

*GDC-0973 is being developed by Genentech, a member of the Roche Group, under a collaboration agreement with Exelixis

BRIM7 study design: Dose-escalation and expansion stages



- **Dose escalation stage:** 10 cohorts, 3–6 patients/cohort
- **Expansion stage:** up to 20 BRAFi-naïve and vemurafenib-progressing patients, respectively

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Key inclusion and exclusion criteria

- Patients with either unresectable Stage IIIc or Stage IV metastatic melanoma
- Measurable disease (RECIST version 1.1)
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
- Adequate hematologic, liver and renal function
- Patients had either:
  - no prior exposure to BRAF inhibitor therapy, OR
  - progressed on vemurafenib immediately prior to enrollment in this study
- Patients were excluded if they had:
  - Ocular pathology or risk factors that predispose to retinal vein occlusion
  - QTc > 450ms
  - Active CNS metastasis. Patients treated with stereotactic RT or surgery are eligible if stable for ≥ 3 weeks

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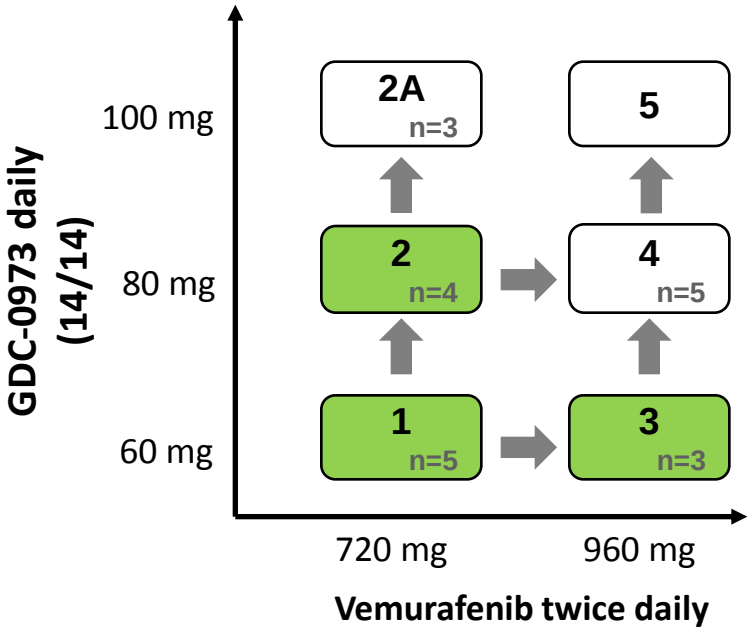
BRIM7 Study: Patient characteristics

(6 July 2012)

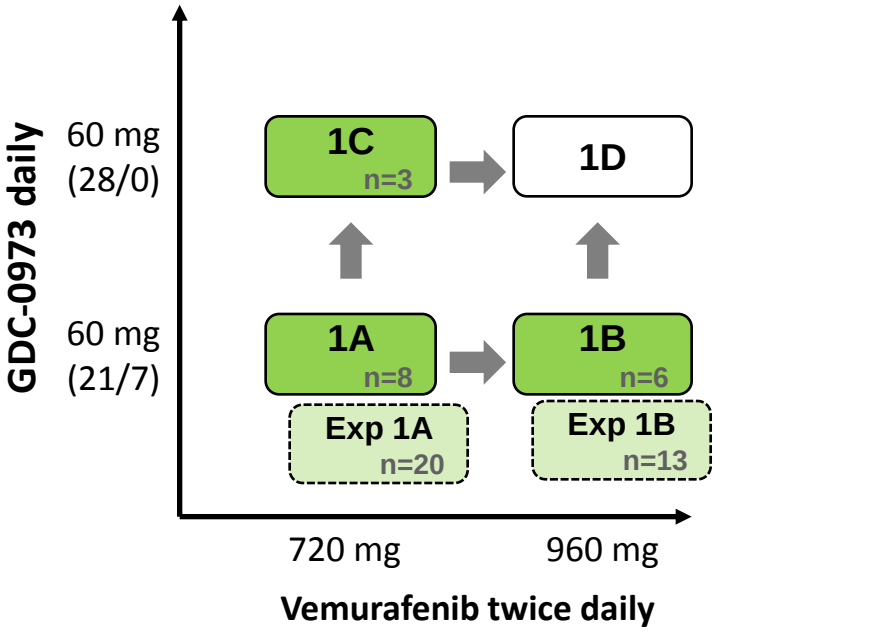
Treated patients (n=70)	
Median age, years (range)	57.5 years (19–76)
Gender, n (%) Male Female	 49 (70.0) 21 (30.0)
ECOG performance status, n (%) PS 0 PS 1	 35 (50.0) 35 (50.0)
Elevated LDH at baseline, n (%)	44 (63.0)
Melanoma stage at enrollment, n (%) Unresectable stage IIIc Stage IV, M1a Stage IV, M1b Stage IV, M1c	 6 (8.6) 2 (2.9) 10 (14.3) 52 (74.3)
Vemurafenib progressors, n (%)	38 (54.3)
Median treatment cycles	3 cycles (1 – 13)

BRIM7 Results: Cohort Assignment and Dose-limiting toxicity (6 July 2012)

Dose-escalation cohorts with GDC-0973 dosed 14 days on/14 days off



Dose-escalation cohorts with GDC-0973 dosed 21 days on/7 days off or continuously



- As of 6 July 2012, **6 out of 10 dose cohorts** have met the protocol-specified criteria to be declared safe (cohorts shown in green in figures below)
- **One DLT observed in Cohort 1B:** Gr 3 QT interval prolongation, related to vemurafenib

BRIM-7 Results: AEs attributed to either vemurafenib or GDC-0973 in all patients* (6 July 2012)

Most common AEs attributed to either vemurafenib or GDC-0973				
n=70	Grade 3 or 4		Total	
	n	%	n	%
Total number of patients with AEs	20	28.6	67	95.7
Non-acneiform rash[a]	5	7.1	37	52.9
Diarrhea	4	5.7	36	51.4
Photosensitivity / Sunburn	0	0	22	31.4
Fatigue	1	1.4	21	30.0
Nausea	1	1.4	20	28.6
Selected AEs attributed to either vemurafenib or GDC-0973				
Creatine phosphokinase elevation	3	4.3	14	20.0
Liver function test elevation[b]	3	4.3	14	20.0
Arthralgia	1	1.4	9	12.9
Serous chorioretinopathy[c]	0	0	3	4.3
Cutaneous squamous cell carcinoma, KA	1	1.4	1	1.4

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*Includes all patients reporting each of AE general terms, even for zero incidence.
[a]Non-acneiform rash includes MedDRA terms rash, rash generalised, rash maculo-papular, rash macular, rash papular, rash erythematous, erythema, rash pruritic, dermatitis, skin exfoliation, dermatitis exfoliative, lividity
[b]LFT elevation includes MedDRA terms alkaline phosphatase increased, bilirubin increased, hyperbilirubinaemia, AST & ALT increased, transaminases increased, and gamma-glutamyltransferase increased.
[c] Serous chorioretinopathy includes MedDRA terms chorioretinal disorder, chorioretinopathy, 1 pt with blurred vision later diagnosed as serous choreoretinopathy.

BRIM-7: AEs leading to dose interruptions, reductions and permanent discontinuations (6 July 2012)

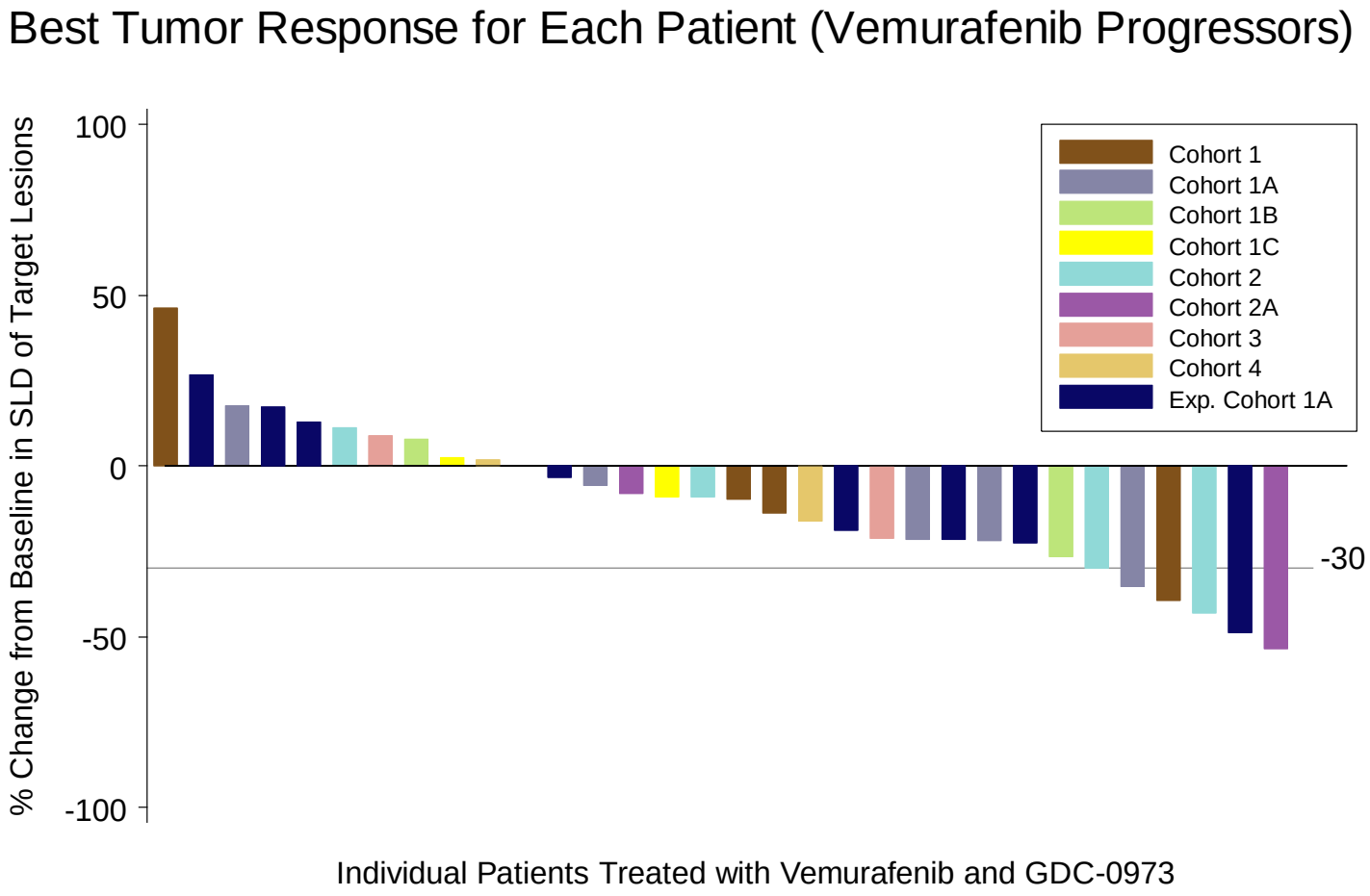
All pts (n=70)	Vemurafenib	GDC-0973	Vem and GDC-0973
Temporary interruption	17 (24.3%)	15 (21.4%)	13 (18.6%)
Dose reduction	3 (4.3%)	2 (2.9%)	2 (2.9%)
Permanent discontinuation due to AE	1 (1.4%)	0 (0%)	0 (0%)

Most common reasons for temporary interruption of vem: Rash 8pts, LFT abnormalities 3pts and arthralgia 3pts
Most common reasons for temporary interruption of GDC-0973: Rash 5pts and diarrhea 3pts

Reasons for primary dose reduction interruption of vem: LFT abnormality 1pt, central serous retinopathy 1pt and rash 1pt
Reasons for primary dose reduction interruption of GDC-0973: Central serous retinopathy 1pt and rash 1pt

Reason for discontinuation of vemurafenib: QT interval prolongation 1pt

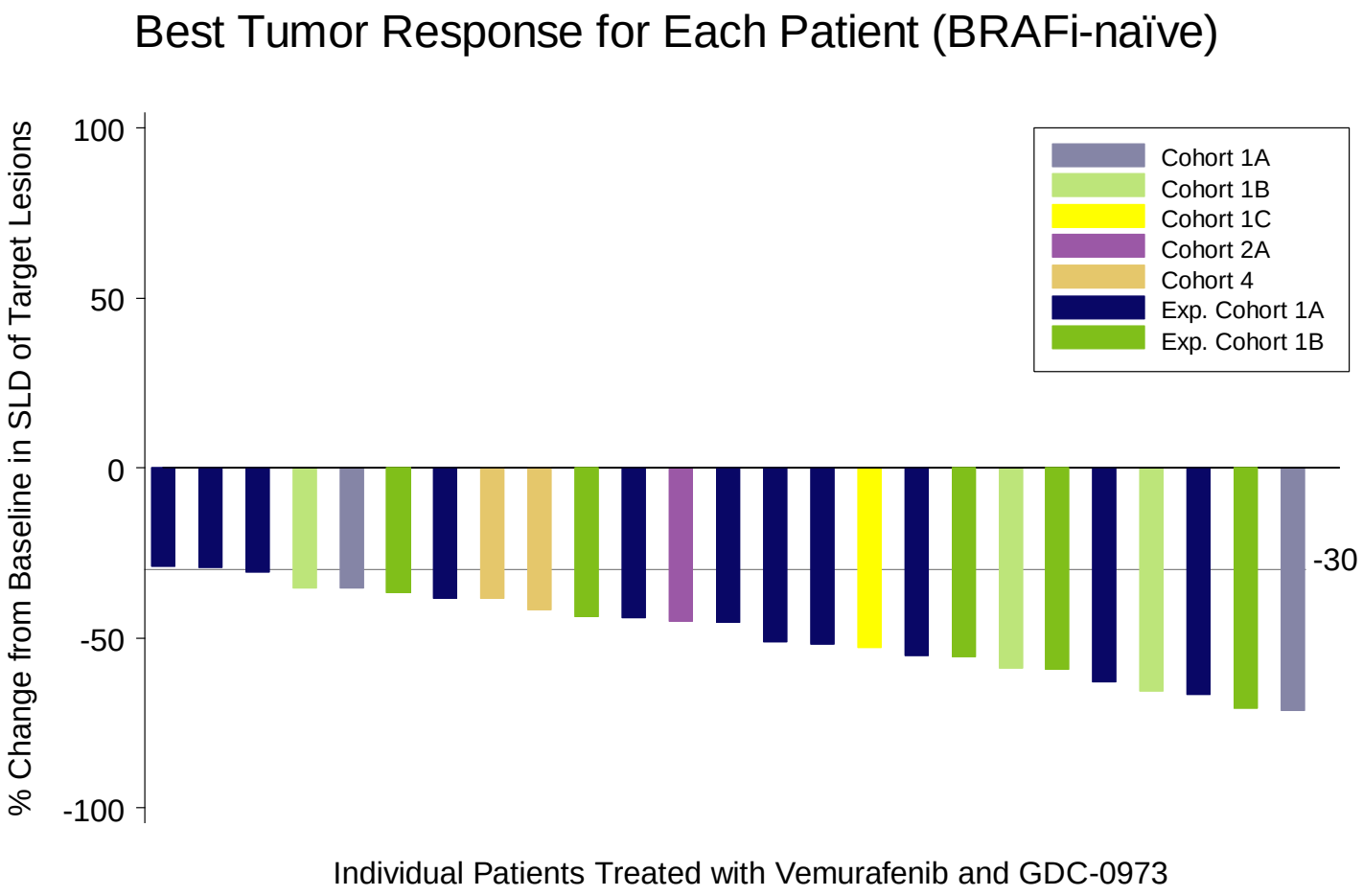
BRIM7 Results: Change in tumor size from baseline to best response in patients who progressed on prior vemurafenib



SLD, sum of longest diameters

n=32 evaluable patients

BRIM7 Results: Change in tumor size from baseline to best response in BRAFi-naïve patients



SLD, sum of longest diameters

n=25 evaluable patients

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BRIM7: Conclusions

- GDC-0973 in combination with vemurafenib can be delivered safely at the respective single-agent MTDs:
  - vemurafenib 960 mg BID, and
  - GDC-0973 60 mg QD 21 days on / 7 days off
- Adverse events were tolerable and manageable
- Preliminary anti-tumor activity in vemurafenib-naïve patients is encouraging
- Phase 3 study of vemurafenib + GDC-0973 is being initiated

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