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A first-in-human, phase 1a/1b, open-label, dose-escalation and expansion study to investigate the safety, pharmacokinetics, and antitumor activity of the RAF dimer inhibitor BGB-3245 in patients with advanced or refractory tumors

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Disclosure Information

Alison Schram, MD

I have the following relevant financial relationships to disclose:

Employee of: Memorial Sloan Kettering Cancer Center New York, NY, USA

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Targeting BRAF: Limitations of 1st Generation Inhibitors

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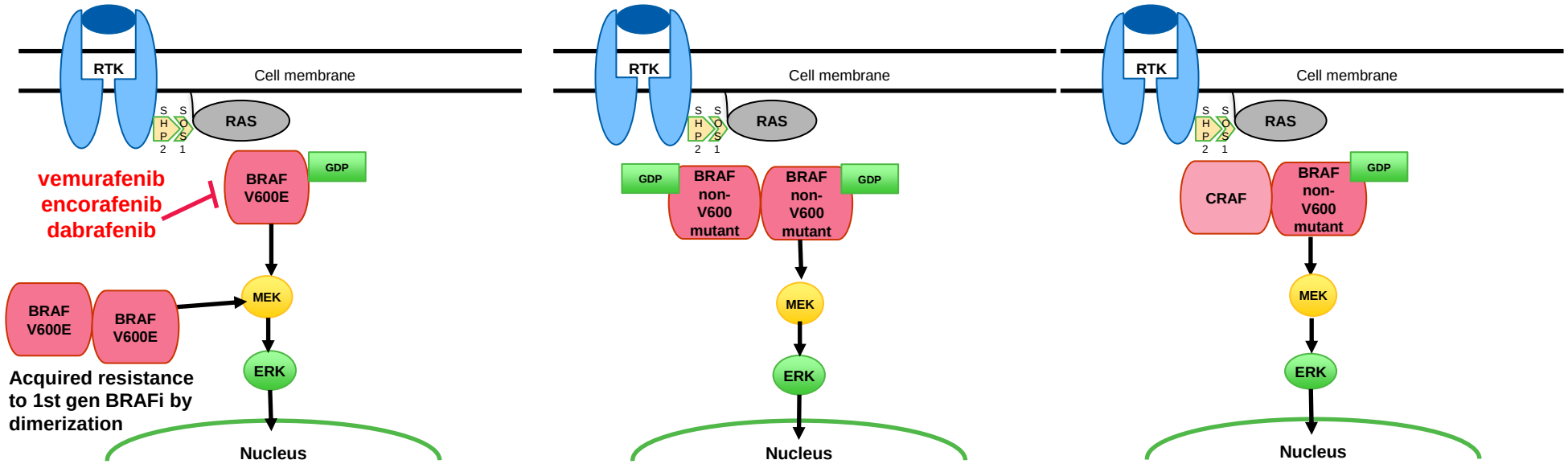
BRAF Class I
- V600 mutant
- Kinase activated
- BRAF monomers
- RAS-independent

BRAF Class II
- Non-V600 Mutant
- Kinase activated
- BRAF dimers
- RAS-independent

BRAF Class III
- Non-V600 mutant
- Kinase impaired
- BRAF heterodimers
- RAS-dependent



- Limitations of 1st generation BRAF inhibitors:
  - Inhibition of only Class I mutations, ineffective in BRAF Class II/III mutations, splice variants, fusions, and N-terminal deletions
  - Development of acquired resistance mediated by RAF dimer signaling
  - Ineffective in RAS-driven tumors
  - Paradoxical pathway activation leading to the development of keratoacanthomas and cutaneous squamous cell carcinomas

Yao et al. Cancer Cell 2015; Yao et al., Nature 2017

BGB-3245: Next-Generation RAF Dimer Inhibitor

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- V600 mutant
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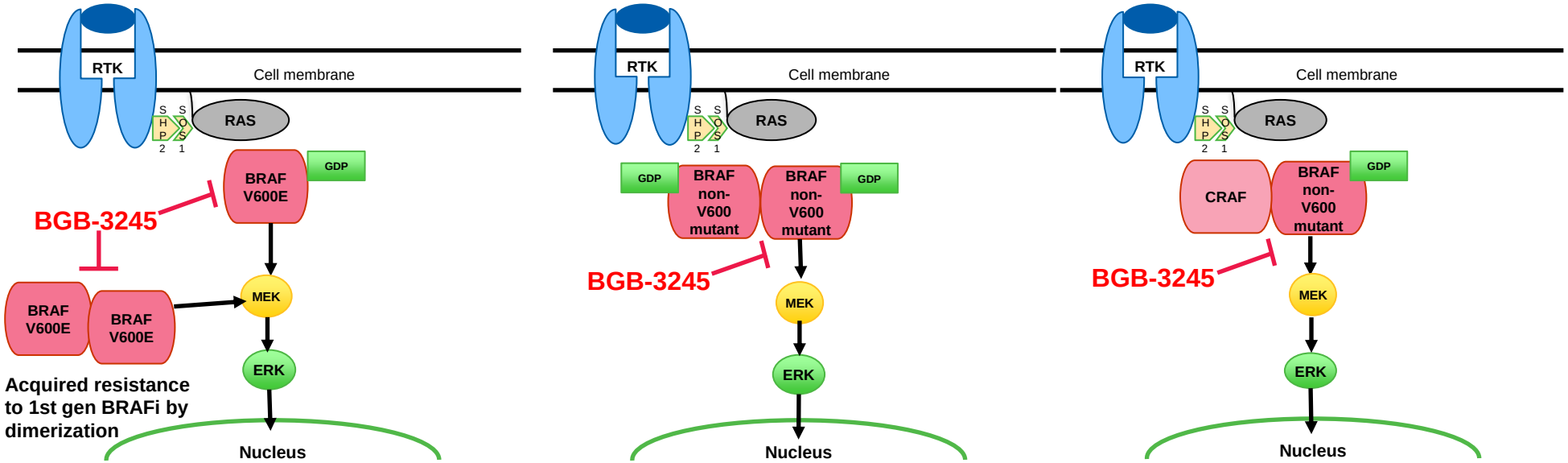

- Inhibits all RAF isoforms with nanomolar potency, blocking monomer and dimer-mediated signaling
- Minimal paradoxical pathway activation at therapeutically relevant exposures
- Achieves potent inhibition in preclinical models with BRAF/MEKi-resistance mutations, BRAF Class II/III mutations, fusions, and splice isoforms at clinically achievable concentrations
- Potential to target KRAS/NRAS mutations via vertical pathway combinations

Yao et al. Cancer Cell 2015; Yao et al., Nature 2017

BGB-3245 Exhibits Activity Against a Broad Spectrum of BRAF Class I/II/III Mutations and Fusions

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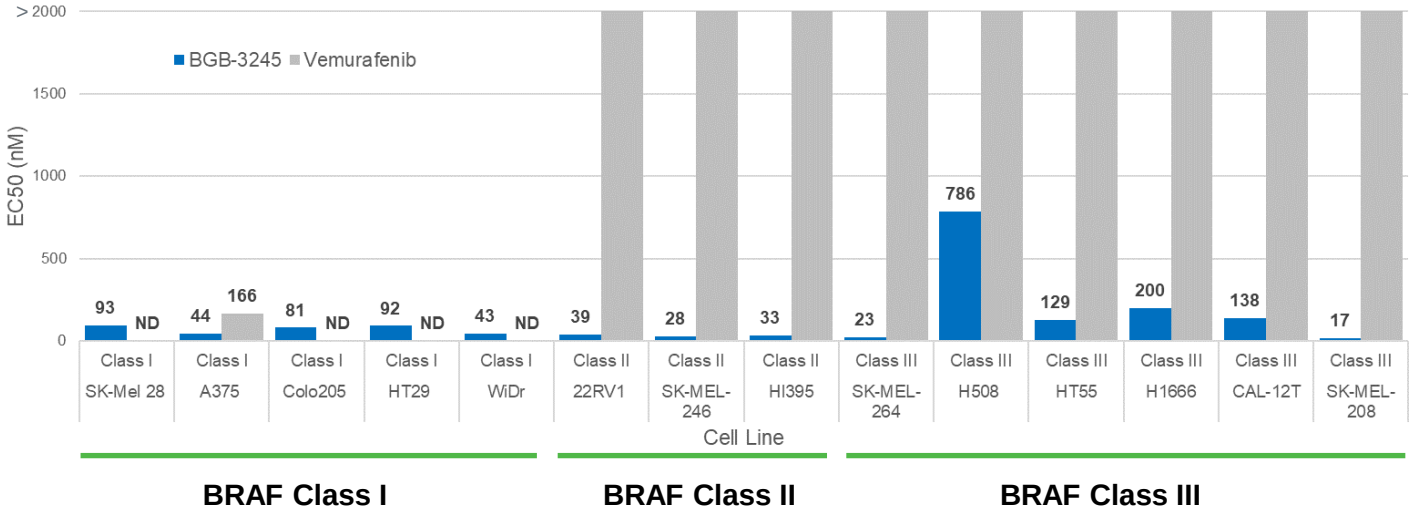
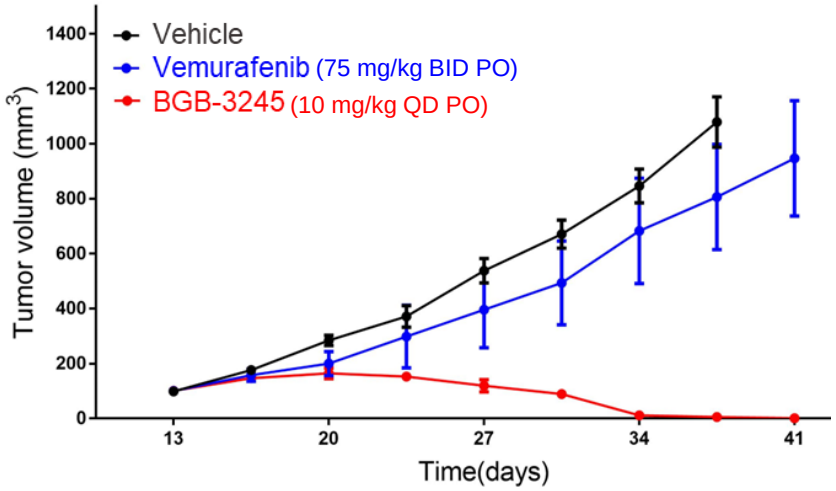
Cell Proliferation Inhibition in Cancer Models



BGB-3245 Inhibits a Melanoma PDX with AGK-BRAF Fusion *In Vivo*



BGB-3245 is Active Against BRAFi Resistance Mutations

	Proliferation IC_{50} [nM]*		Ratio
	BRAF V600E (VE)	BRAF V600E/L514V (VELV)	VELV/VE
Vemurafenib	52.5	1222.4	23
BGB-3245	24.5	20.9	0.85

Source: Data generated from the lab of Neal Rosen, M.D., Ph.D. and reported in *Cancer Cell*, 28 (3) 2015; *Cancer Discov; 8(9); 1–12.* 2018; & *ACCELERATE ped Strategy Forum* 2022
* Cell line data from A375 cells

BGB-3245 Phase 1a/b Study Design

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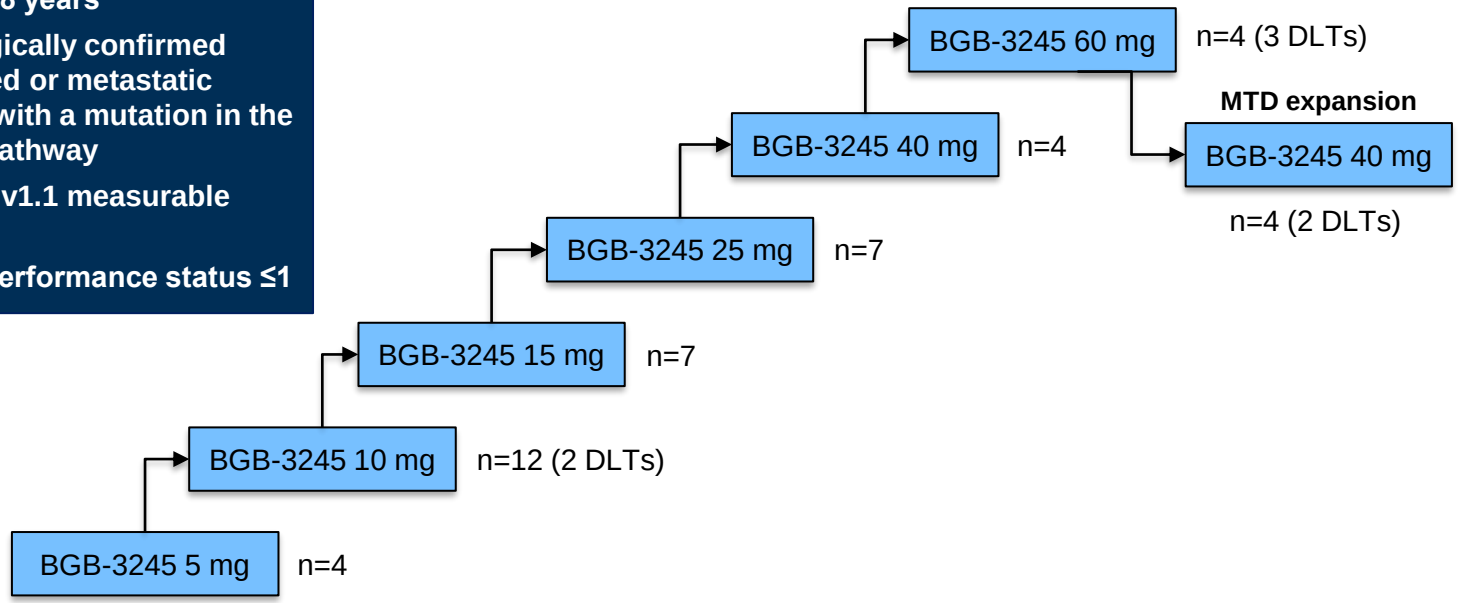
Eligible patients:
- Aged ≥18 years
- Histologically confirmed advanced or metastatic tumors with a mutation in the MAPK pathway
- RECIST v1.1 measurable disease
- ECOG performance status ≤1



RP2D Determination

Phase 1b Expansion in pts with advanced solid tumors that have:
- BRAF V600 mutations after prior BRAF +/- MEK inhibitors
- BRAF Class II mutation or BRAF fusion
- Cutaneous melanoma with NRAS mutation

Enrollment | **Phase 1a (mTPI-2 design)** | **Phase 1b**

Primary endpoints:
- Safety and tolerability, MTD/RP2D

Secondary endpoints:
- PK and preliminary antitumor activity

Exploratory endpoints:
- Tumor and liquid biomarkers

Primary endpoints:
- RP2D and ORR

Secondary endpoints:
- PFS, DCR, DOR, CBR, safety and tolerability and PK

Exploratory endpoints:
- Tumor and liquid biomarkers

Note: BRAF: v-RAF murine sarcoma viral oncogene homolog B; CBR: clinical benefit rate; DCR: disease control rate; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; MAPK: mitogen-activated protein kinase; MEK: mitogen-activated protein kinase kinase; MTD: maximum tolerated dose; ORR: objective response rate (evaluable pts must have at least one post-baseline scan); PK: pharmacokinetics; RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: randomized phase 2 dose

Baseline Characteristics

Characteristic	Overall, n (%)
Patients enrolled	42 (100)
Still on Treatment	9 (21)
Sex	
Male	23 (55)
Female	19 (45)
Age	
Mean	59
Median (Range)	60 (31-83)
Cancer stage at entry	
III	3 (7)
IV	39 (93)
Prior systemic cancer regimens	
Median (Range)	3 (1-9)
ECOG status at entry	
0	24 (57)
1	18 (43)

Characteristic	Overall, n (%)
Primary Tumor	
Melanoma	12 (29)
NSCLC	5 (12)
Colorectal cancer	4 (10)
Pancreatic cancer	3 (7)
Ovarian cancer	3 (7)
Cholangiocarcinoma	3 (7)
Thyroid cancer	2 (5)
Other*	10 (24)
Mutation Status	
RAS	**11 (26)**
KRAS	6 (14)
NRAS	4 (10)
HRAS	1 (2)
BRAF	**31 (74)**
V600E	18 (43)
BRAF Fusions	8 (19)
Class II	5 (12)

Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Data as of September 1, 2022.
* Appendiceal cancer (1), leiomyosarcoma (1), chondrosarcoma (1), endometrial cancer (1), prostate cancer (1), testicular cancer (1), breast cancer (1), HNSCC (1), astrocytoma (1), GIST (1).

Preliminary BGB-3245 Clinical PK

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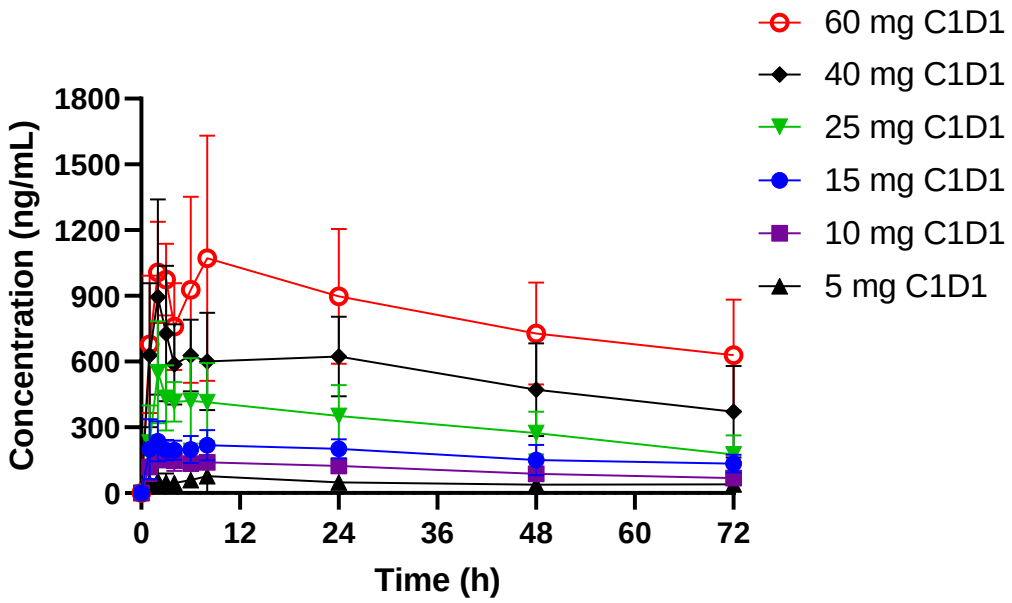
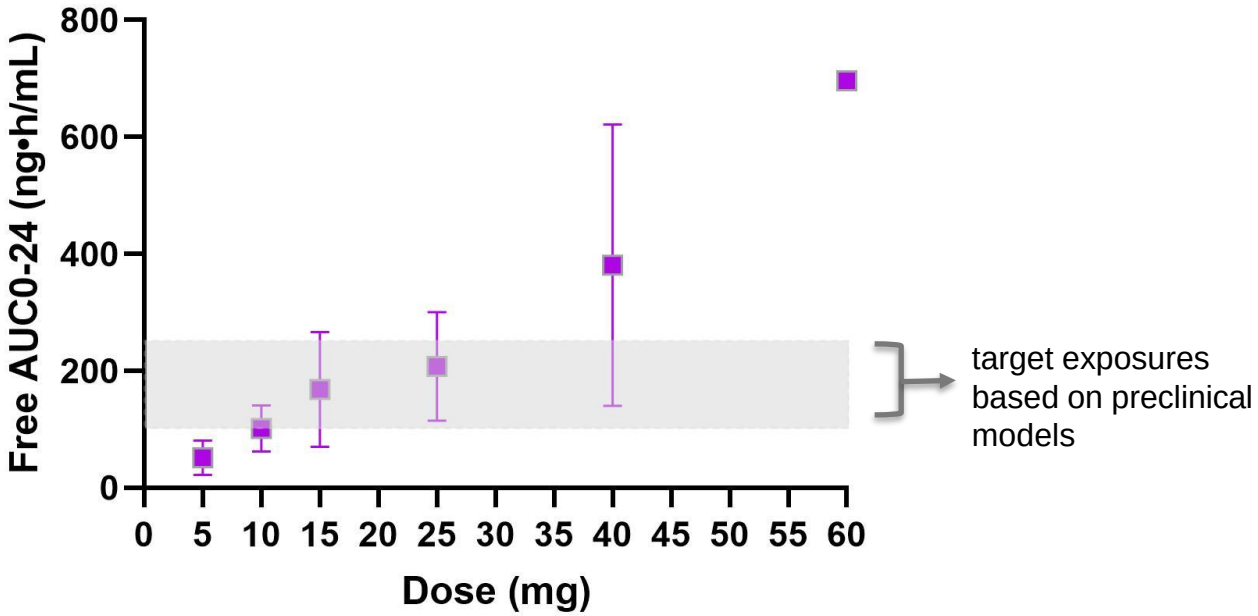
BGB-3245 Exposure at Cycle 1 Day 1



Free BGB-3245 Exposure (AUC_{0-24}) at Cycle 2 Day 1

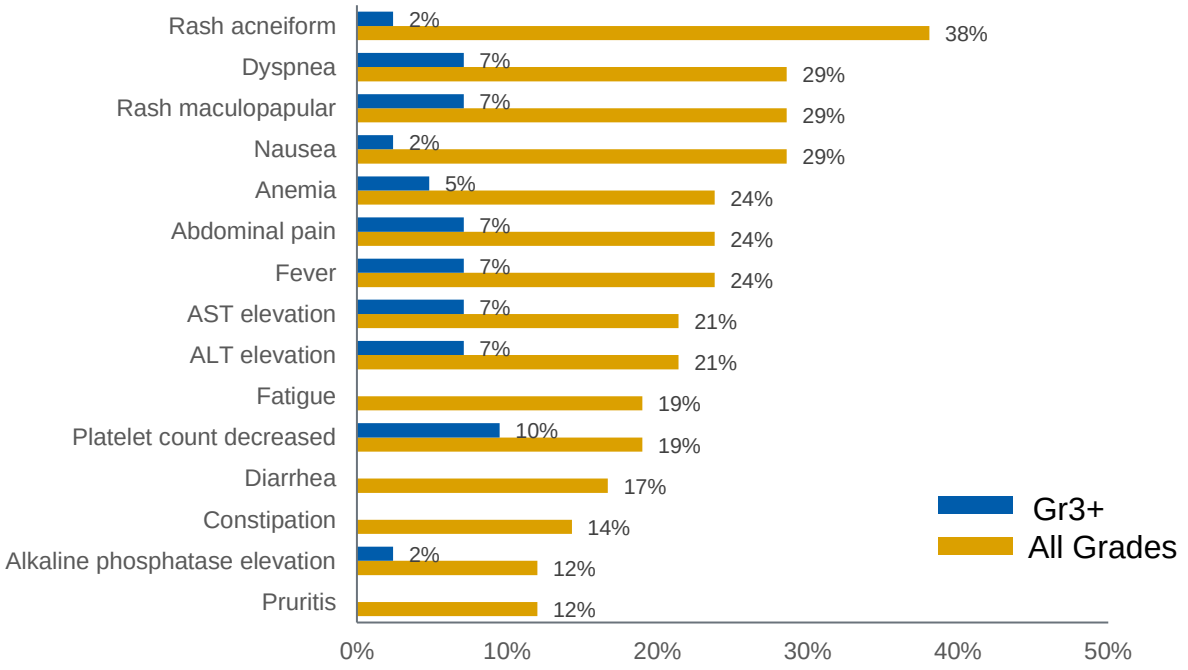


- Median T_{max} was ~ 2 hours at Cycle 1 Day 1
- Exposures, C_{max} and $AUC_{8h,}$ were generally dose proportional from 5 mg QD to 60 mg QD
- Long terminal half-life(1), with significant accumulation observed at steady state
- Free exposure range of BGB-3245 at clinical dose ≥ 25 mg QD corresponds to that leading to significant tumor growth inhibition in preclinical tumor models

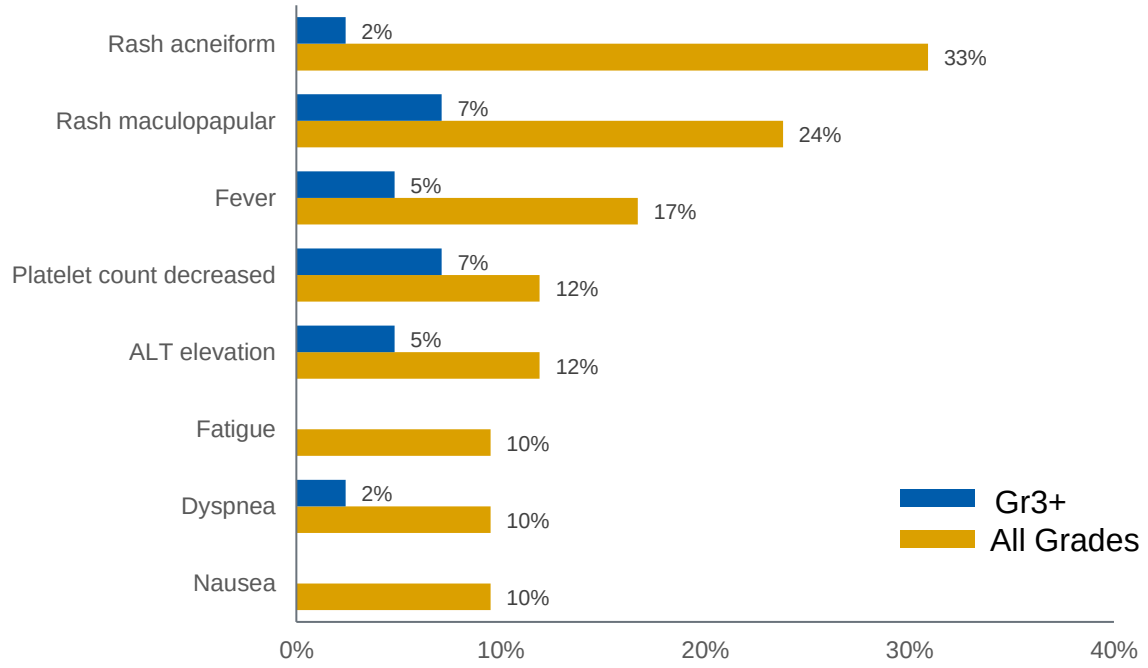
Note: Clinical PK data as of August 19, 2022.
(1) Could not be accurately determined due to insufficient sampling in the terminal elimination phase at C1D1.
Note: Only 1 participant PK data is available in 60 mg cohort at C2D1 and shown in graph. AUC0-24 h was estimated using C2D1 pre-dose as concentration for 24-h post-dose timepoint.

Adverse Events and Disposition (N=42)

Treatment Emergent AEs (≥10% of all events)



Treatment Related AEs (≥10% of all events)



Treatment Modification	Overall, n (%)
Dose Interruption	25 (60)
Dose Reduction	5 (12)
Drug Discontinuation	33 (79)
Due to disease progression or death	25 (60)
Due to AE	8 (19)

- Safety was manageable
- AE findings consistent with MAPK inhibitors
- 40 mg was determined to be MTD

Anti-Tumor Activity

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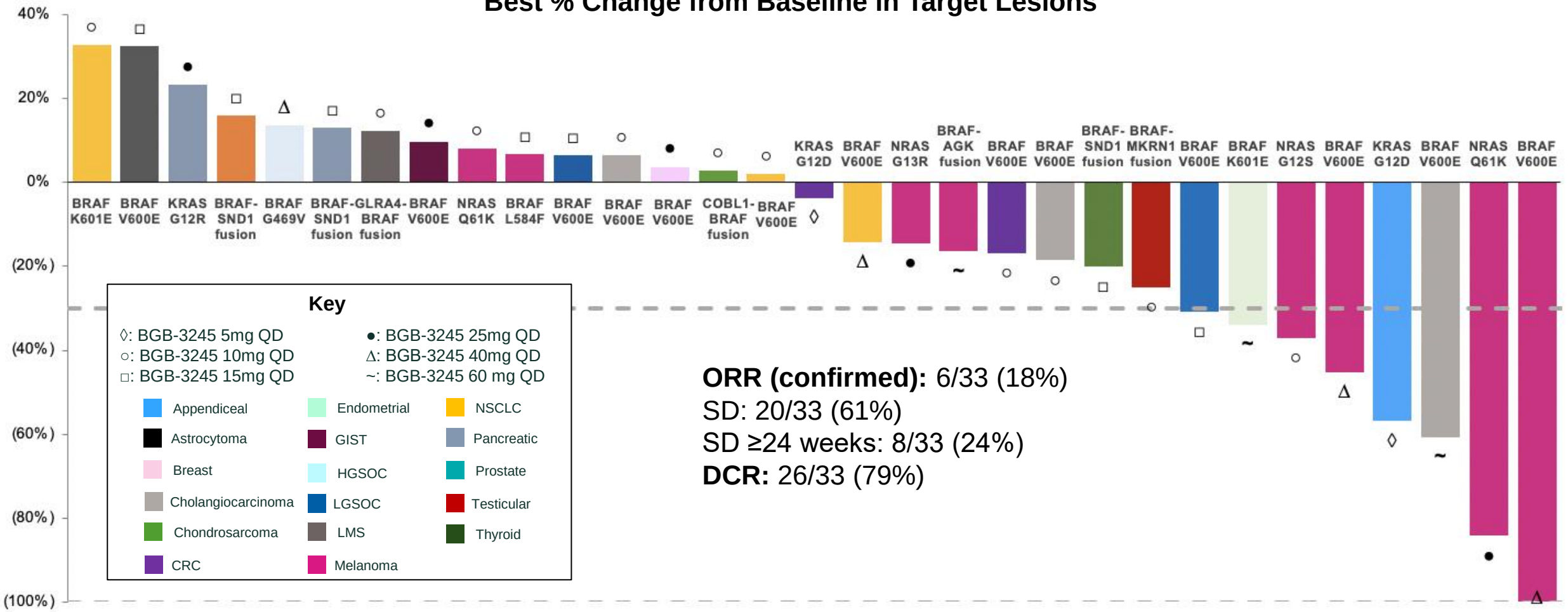
Best % Change from Baseline in Target Lesions



ORR (confirmed): 6/33 (18%)
SD: 20/33 (61%)
SD ≥24 weeks: 8/33 (24%)
DCR: 26/33 (79%)

Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Data as of September 1, 2022.
Note: Follow up scans on two patients indicated new lesions with progressive disease (PD) recorded as their best objective response. These follow-up scans did not measure target lesion and therefore are not included in the waterfall plot.
Note: CRC: colorectal cancer; GIST: gastrointestinal stromal tumor; HGSOC: high grade serous ovarian cancer; LMS: leiomyosarcoma; LGSOC: low-grade serous ovarian cancer; NSCLC: non-small cell lung cancer.

Time on Treatment

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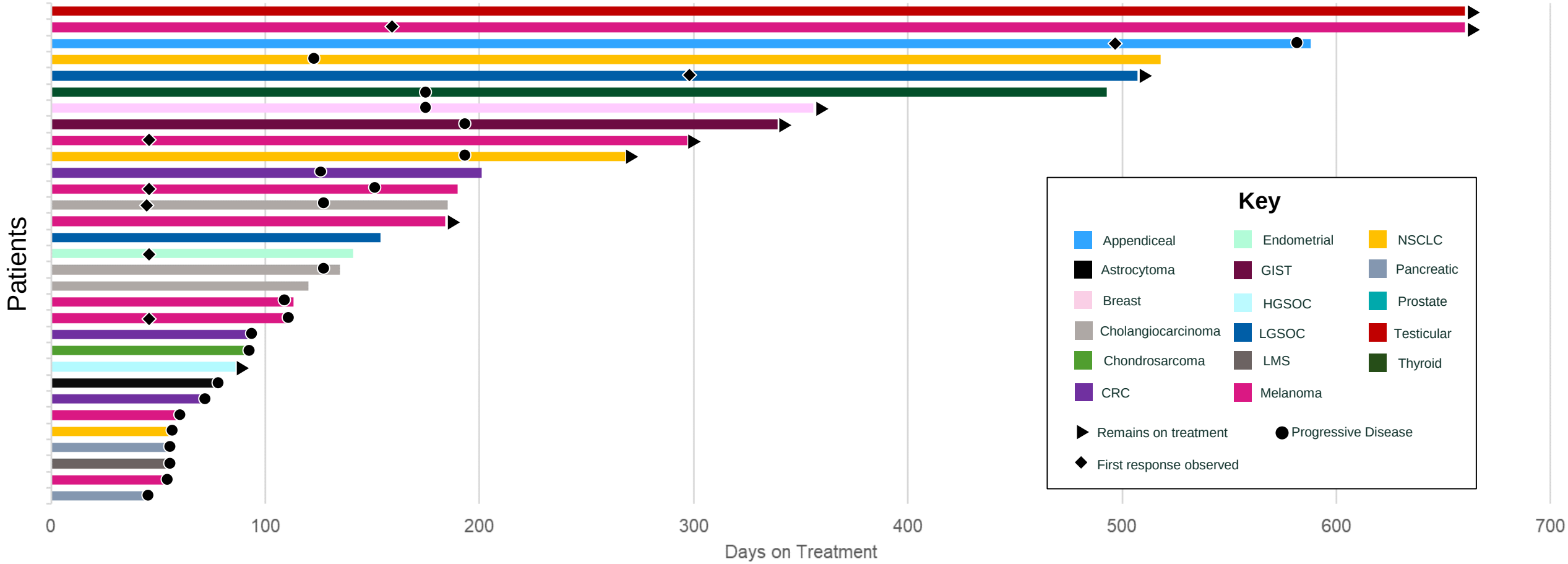

- As of data cut (September 1, 2022), median time on treatment: 154 days (range: 54 – 660 days)
- 9 patients remain on treatment

Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Data as of September 1, 2022.

Anti-Tumor Activity in BRAF V600E Patients with Prior BRAF/MEKi Treatment and NRASmut Melanoma Patients

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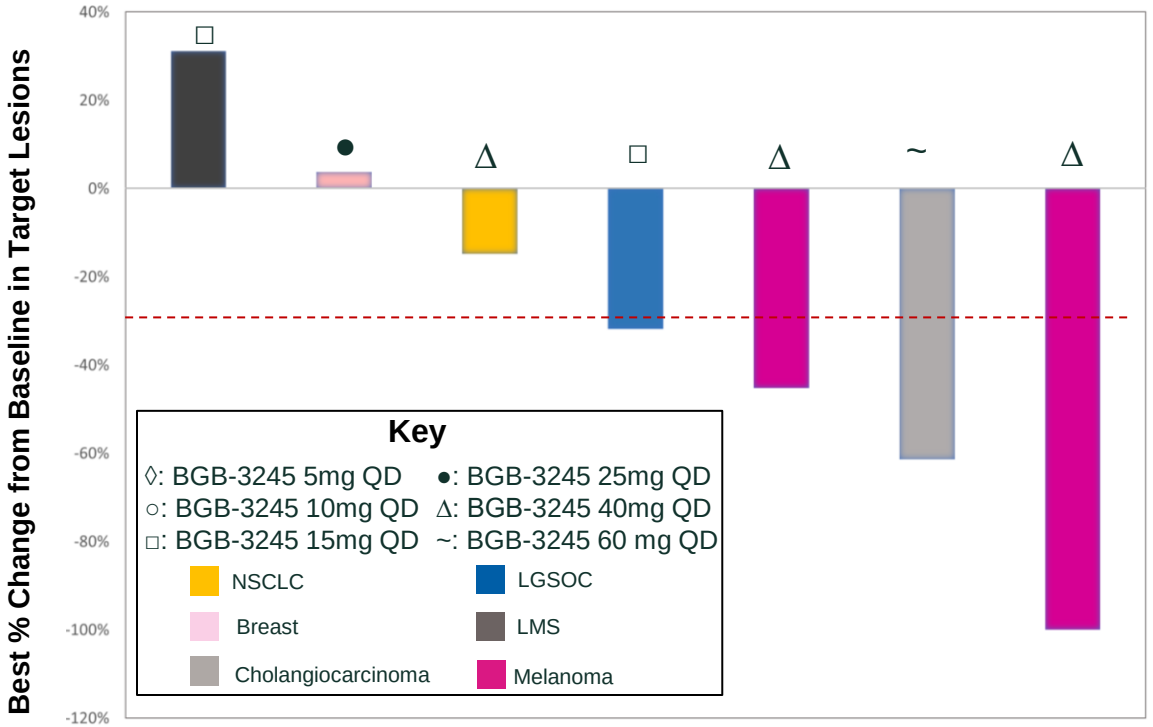
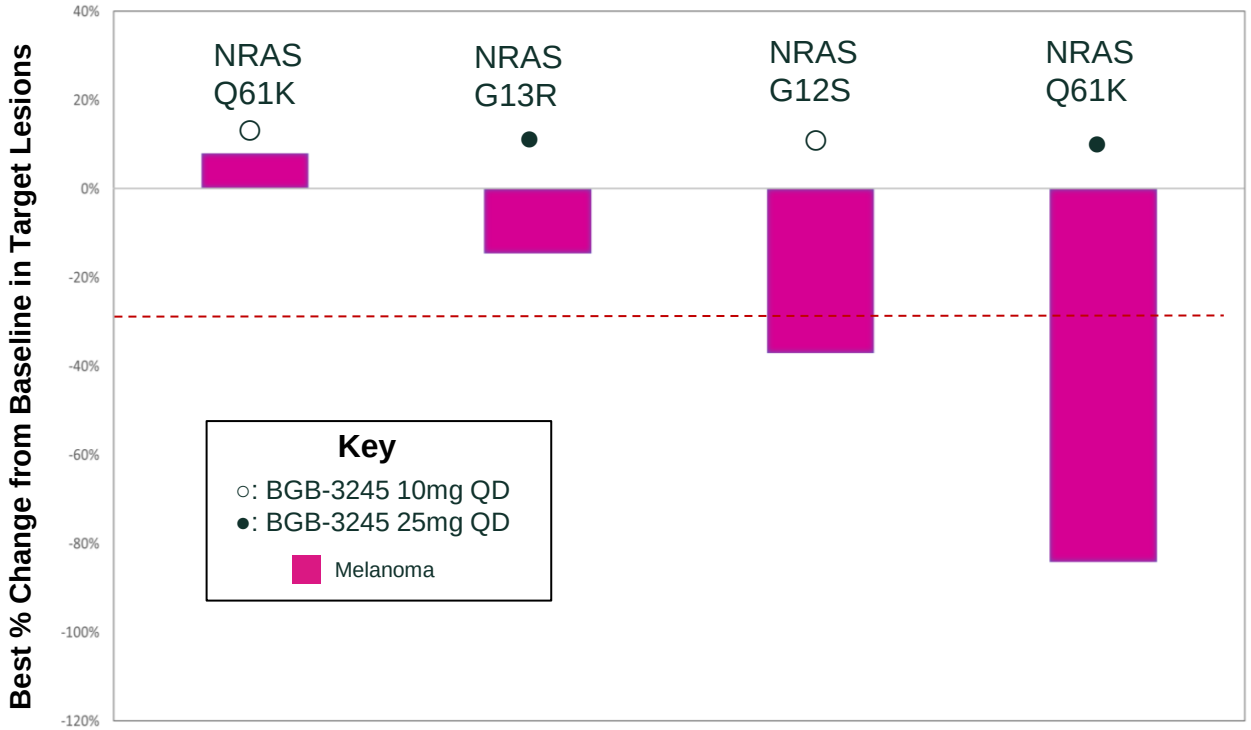
BRAF V600E Patients with Prior BRAF/MEKi Treatment



NRAS Mutated Melanoma Patients



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Note: Follow up scans on two patients indicated new lesions with progressive disease (PD) recorded as their best objective response. These follow-up scans did not measure target lesion and therefore are not included in the waterfall plot.
Note: LMS: leiomyosarcoma; LGSOC: low-grade serous ovarian cancer; NSCLC: non-small cell lung cancer.

57F with Melanoma
BRAF V600E+, Progressed on Prior BRAF/MEKi

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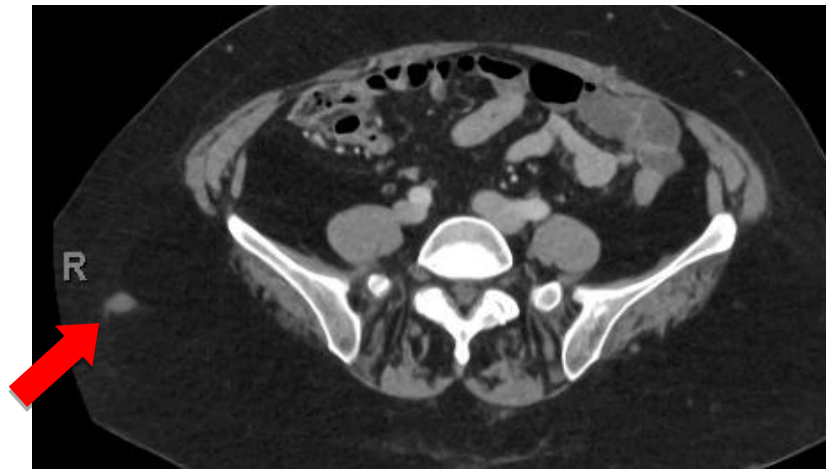
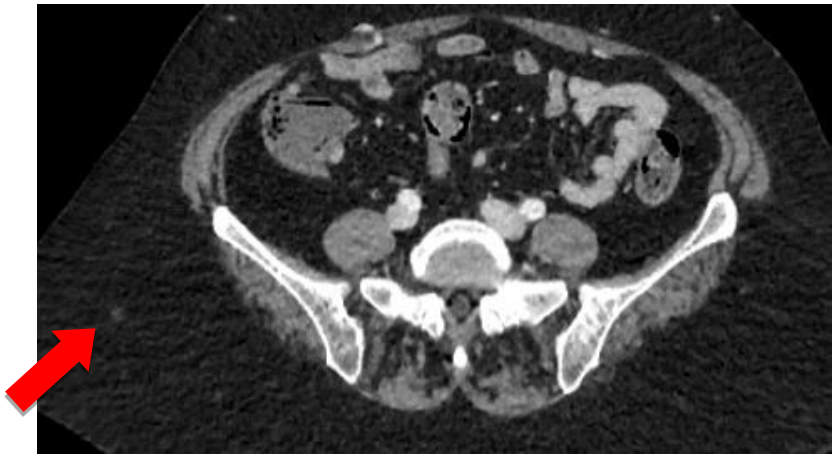
- Prior therapies:
  - Surgery with adjuvant nivolumab → metastasis
  - Dabrafenib + trametinib (BOR: SD)
  - Ipilimumab + nivolumab (BOR: PD)
  - Stereotactic radiosurgery to brain lesion
- Initiated BGB-3245 40mg QD in Nov 2021
- Symptomatic relief with PR observed at the week 8 scan
- Disease progression noted in Oct 2022 after the data cut

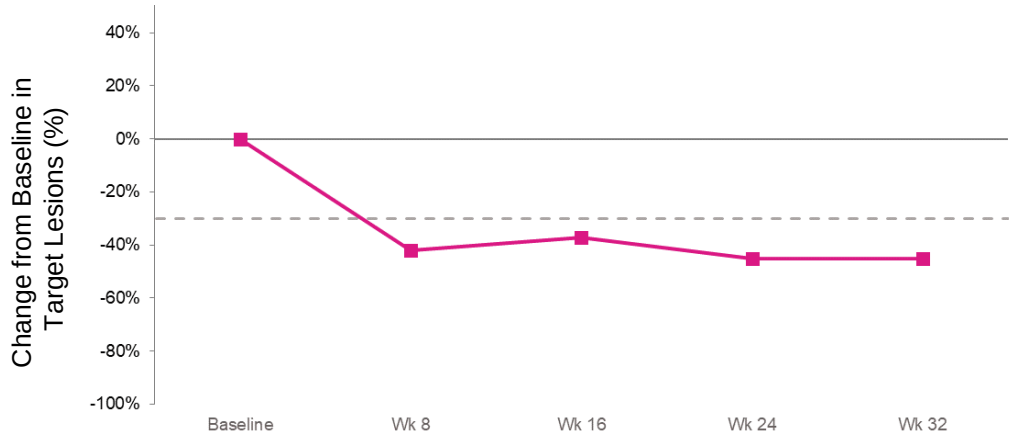


Baseline Scan



14 months into treatment

Tumor Response by Week



67M with Melanoma
NRAS G12S

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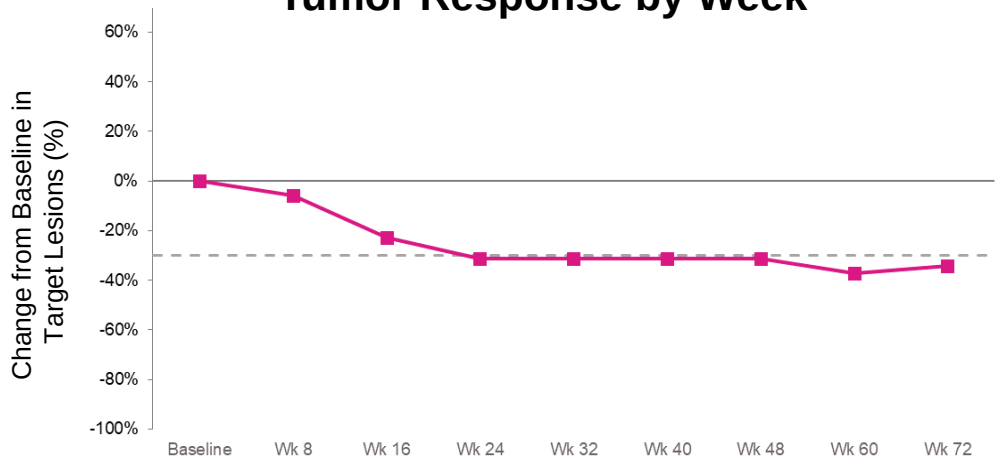
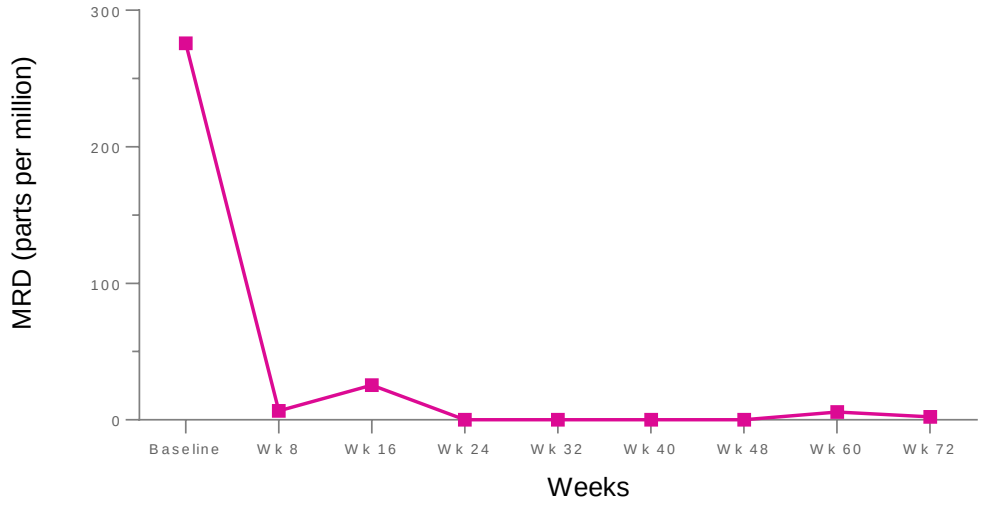
- Prior therapies:
  - Resection of 2 lesions and multiple lymph nodes
  - Adjuvant pembrolizumab
  - Pembrolizumab + ipilimumab for recurrent metastases (BOR: PD)
  - Investigational bispecific IL-2v immunotherapy (BOR: PD)
- Initiated BGB-3245 10 mg QD in Nov 2020, escalated to 25 mg QD in Nov 2021
- PR observed in Apr 2021, durable and ongoing
- CtDNA analysis showed a marked reduction in the molecular residual disease (MRD) and NRAS G12S allelic fraction, correlating with clinical response
- Patient remains on trial

Tumor Response by Week



Longitudinal ctDNA Analysis



Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Data as of March 2023.

34M with Testicular Cancer
MKRN1-BRAF Fusion+

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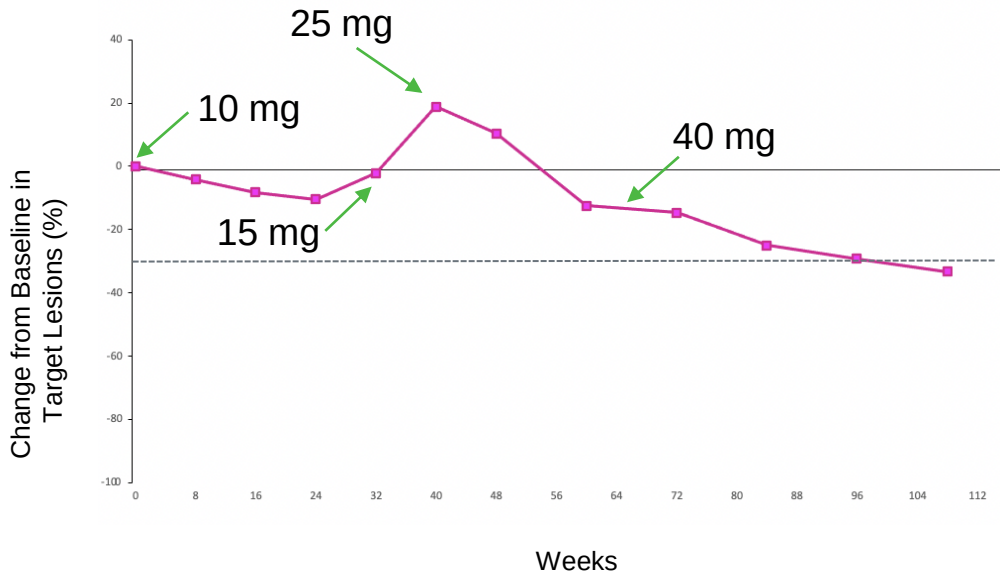
- Prior therapies:
  - Right orchiectomy
  - Carboplatin and paclitaxel (BOR: stable disease)
- POD in aortocaval and subcarinal lymph nodes
- Initiated BGB-3245 10mg QD in Oct 2020
- Initially had SD/PD but continued due to clinical benefit and dose escalated sequentially up to 40mg QD in Feb 2022, with significant tumor shrinkage at this dose
- Patient remains ongoing with symptomatic relief

Tumor Response by Week



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Conclusions and Next Steps

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- BGB-3245 has a manageable safety profile
- Encouraging antitumor activity was observed in the heavily pretreated heterogeneous patients
  - ORR (confirmed): 6/33, 18%; CBR: 14/33, 42%; DCR: 26/33 (79%)
- Efficacy in patients with tumors harboring BRAF V600E progressed on prior BRAF/MEK inhibitors, BRAF Class II mutations, BRAF fusions, and NRAS mutations
- These data support ongoing investigation of BGB-3245 in defined cohorts
  - BRAF V600 tumors progressed after prior BRAF and/or MEK inhibitors
  - Solid tumors with BRAF Class II mutations and BRAF fusions
  - NRAS mutant melanoma
- Evaluation of BGB-3245 in combination with the MEK inhibitor, mirdametinib, in MAPK-altered advanced solid tumors has been initiated (NCT05580770)

Thank You

- Patients, families and caregivers