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

### 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

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BGB-3245: Next-Generation RAF Dimer Inhibitor

- 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

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

**Cell Proliferation Inhibition in Cancer Models**

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>BRAF Class I</th>
<th>BRAF Class II</th>
<th>BRAF Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK-Mel-28</td>
<td>93</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>A375</td>
<td>44</td>
<td>33</td>
<td>129</td>
</tr>
<tr>
<td>Colo205</td>
<td>81</td>
<td>23</td>
<td>200</td>
</tr>
<tr>
<td>HT29</td>
<td>ND</td>
<td>786</td>
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<tr>
<td>V6Dr</td>
<td>92</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>22R1V1</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>84</td>
<td></td>
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</tr>
</tbody>
</table>

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

- Vehicle
- Vemurafenib (75 mg/kg BID PO)
- BGB-3245 (10 mg/kg QD PO)

**BGB-3245 is Active Against BRAFi Resistance Mutations**

<table>
<thead>
<tr>
<th></th>
<th>Proliferation IC_{50} [nM]</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRAF V600E (VE)</td>
<td>BRAF V600E/L514V (VELV)</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>52.5</td>
<td>1222.4</td>
</tr>
<tr>
<td>BGB-3245</td>
<td>24.5</td>
<td>20.9</td>
</tr>
</tbody>
</table>

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

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

Primary endpoints:
- Safety and tolerability, MTD/RP2D

Secondary endpoints:
- PK and preliminary antitumor activity

Exploratory endpoints:
- Tumor and liquid biomarkers

Enrollment

BGB-3245 5 mg
n=4

BGB-3245 10 mg
n=12 (2 DLTs)

BGB-3245 15 mg
n=7

BGB-3245 25 mg
n=7

BGB-3245 40 mg
n=4

BGB-3245 60 mg
n=4 (3 DLTs)

MTD expansion

Phase 1a (mTPI-2 design)

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

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall, n (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary Tumor</strong></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>12 (29)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Other*</td>
<td>10 (24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mutation Status</strong></td>
<td></td>
</tr>
<tr>
<td>RAS</td>
<td>11 (26)</td>
</tr>
<tr>
<td>KRAS</td>
<td>6 (14)</td>
</tr>
<tr>
<td>NRAS</td>
<td>4 (10)</td>
</tr>
<tr>
<td>HRAS</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td></td>
</tr>
<tr>
<td>V600E</td>
<td>18 (43)</td>
</tr>
<tr>
<td>BRAF Fusions</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Class II</td>
<td>5 (12)</td>
</tr>
</tbody>
</table>

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

* Appendiceal cancer (1), leiomyosarcoma (1), chordrosarcoma (1), endometrial cancer (1), prostate cancer (1), testicular cancer (1), breast cancer (1), HNSCC (1), astrocytoma (1), GIST (1).
Preliminary BGB-3245 Clinical PK

- Median $T_{\text{max}}$ was ~ 2 hours at Cycle 1 Day 1
- Exposures, $C_{\text{max}}$ 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 $\geq 25$ 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. $AUC_{0-24}$ was estimated using C2D1 pre-dose as concentration for 24-h post-dose timepoint.
Adverse Events and Disposition (N=42)

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

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.


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**Best % Change from Baseline in Target Lesions**

**Key**

- **◊**: BGB-3245 5mg QD
- **○**: BGB-3245 10mg QD
- **□**: BGB-3245 15mg QD
- **●**: BGB-3245 25mg QD
- **∆**: BGB-3245 40mg QD
- **~**: BGB-3245 60 mg QD

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>BGB-3245 Dose (mg)</th>
<th>QD</th>
<th>ORR (confirmed)</th>
<th>SD (61%)</th>
<th>SD ≥24 weeks (24%)</th>
<th>DCR (79%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma</td>
<td>5</td>
<td>QD</td>
<td>6/33 (18%)</td>
<td>20/33</td>
<td>8/33 (24%)</td>
<td>26/33 (79%)</td>
</tr>
<tr>
<td>Breach</td>
<td>10</td>
<td>QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>15</td>
<td>QD</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chondrosarcoma</td>
<td>25</td>
<td>QD</td>
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</tr>
<tr>
<td>CRC</td>
<td>40</td>
<td>QD</td>
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<tr>
<td>GIST</td>
<td>60</td>
<td>QD</td>
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<td>Endometrial</td>
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<td>Melanoma</td>
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<td>NSCLC</td>
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<td>Pancreatic</td>
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<td>Prostate</td>
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<td>Testicular</td>
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<tr>
<td>Thryoid</td>
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</tbody>
</table>
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

BRAF V600E Patients with Prior BRAF/MEKi Treatment

NRAS Mutated Melanoma Patients

Key

<table>
<thead>
<tr>
<th>NRAS Q61K</th>
<th>NRAS G13R</th>
<th>NRAS G12S</th>
<th>NRAS Q61K</th>
</tr>
</thead>
<tbody>
<tr>
<td>○: BGB-3245 10mg QD</td>
<td>●: BGB-3245 25mg QD</td>
<td>○: BGB-3245 10mg QD</td>
<td>●: BGB-3245 25mg QD</td>
</tr>
</tbody>
</table>

Best % Change from Baseline in Target Lesions

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

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.

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

- 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

Tumor Response by Week

14 months into treatment
67M with Melanoma
NRAS G12S

- 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

Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Data as of March 2023.
34M with Testicular Cancer
MKRN1-BRAF Fusion+

- 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

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

- 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