BridgeBio Oncology

Fourth quarter 2022
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BridgeBio Executive Summary

• BridgeBio Oncology is advancing 3 lead programs targeting the two most prominent oncogenes in human cancer (KRAS & PIK3CA): 1) Dual KRAS<sup>G12C</sup>, 2) PI3Kα:RAS breaker, and 3) pan-KRAS.

• **Dual KRAS**<sup>G12C</sup> inhibitor program has selected a Development Candidate (BBO-8520).
  - BBO-8520 is a highly potent dual inhibitor of KRAS<sup>G12C</sup> with 30-300x higher potency than sotorasib in vitro and in vivo including differentiated activity in a PDX model.
  - Complete inhibition of the active and most prominent KRAS<sup>G12C</sup> form should lead to deeper and longer lasting responses in patients.
  - BBO-8520’s IND-filling is projected for 2023.

• **PI3Kα:RAS breaker** is highly differentiated in that it is a) tumor selective, b) targets both mutant and wild-type PIK3CA, and c) does not induce hyperglycemia
  - Our compounds demonstrate robust efficacy in multiple mouse xenograft models including those with HER2/HER3 dependency, KRAS mutation and PIK3CA helical mutation
  - Our latest molecules produce dose-responsive pharmacodynamic data and display promising drug-like properties.
  - Biomarker data shows that Her2/Her3 dependency, PIK3CA helical mutations and KRAS<sup>G12X</sup> mutations may be sensitive tumor types.
  - Development Candidate selection in 2023, and IND-filling in 2024

• **pan-KRAS** program targets KRAS<sup>G12D</sup> and KRAS<sup>G12V</sup> mutations present in a large percentage of colorectal, pancreatic and NSCLC tumors.
  - The Team has achieved in vivo target engagement and has identified leads with promising oral bioavailability.
  - The Team projects Development Candidate selection in the 2023.
BBIO pipeline attacks Ras mutant tumors from multiple angles

BBIO oncology programs address the 2 most mutated oncogenes in human cancer and potentially enable tolerable and simultaneous inhibition of the MAPK and PI3K signaling pathways.

- **G12C**
  - >25K patients
  - CRC, NSCLC, PC
  - Dual G12C inhibitor
  - PIK3CA:RAS Breaker

- **G12D**
  - >50K patients
  - CRC, NSCLC, PC
  - Pan-KRAS inhibitor
  - PIK3CA:RAS Breaker

- **G12V**
  - >50K patients
  - CRC, NSCLC, PC
  - Pan-KRAS Inhibitor
  - PIK3CA:RAS Breaker

- **PI3KCA**
  - >20K patients
  - BC, CRC, Endometrial
  - PIK3CA:RAS Breaker

Novel First-In-Class PI3Kα breaker has the potential to address PI3KCA helical mutations, half of KRAS\(^{G12X}\) mutations and nearly all HER family driven cancers.
We have a world class oncology team and strategic partners driving forward our targeted pipeline

Frank McCormick  
Chairman of Oncology  

Richard Scheller  
Chairman of R&D  

Eli Wallace  
CSO, Oncology  

Pedro Beltran  
SVP, Oncology  

- Partnership with the National RAS Initiative, including 60 of the world’s foremost academic RAS researchers  
- Cutting edge RAS structural biology expertise  
- Home to Sierra: the world’s 3rd fastest computing system  
- Enables multi-microsecond molecular dynamics simulations of protein complexes, and highly efficient in silico docking simulations
BridgeBio is progressing multiple approaches against KRAS

- **Dual KRAS\textsuperscript{G12C} inhibitor** program has selected a Development Candidate (BBO-8520) with projected IND-filing 2023
  - Inhibits both KRASG12C GTP (active) and GDP (inactive) states; directly binds KRAS
  - Differentiates from KRASG12C GDP (inactive)-only inhibitors

- **PI3K\(\alpha\):RAS breaker** is highly differentiated in that it is a) tumor selective, b) targets both mutant and wild-type PIK3CA, and c) does not induce hyperglycemia
  - Projected Development Candidate selection in 2023
    - Blocks specific interaction between RAS and PI3Ka
    - RAS driver agnostic
    - Blocks PI3Ka / AKT effector signaling

- **pan-KRAS** program targets multiple KRAS mutants including KRAS\textsuperscript{G12D} and KRAS\textsuperscript{G12V}
  - Projected Development Candidate selection in the 2023
    - Potent pan-KRAS inhibitor
    - Directly binds KRAS
BBO-8520: A KRAS\textsuperscript{G12C} Dual Inhibitor

- PI3Kα:RAS Breaker
- Pan-KRAS program
Mutant KRAS is the most common oncogene in cancer – KRAS$^{\text{G12C}}$

- Lung cancer is the second most common cancer in the US with greater than 235K new cases and 130K deaths a year

- **KRAS$^{\text{G12C}}$ mutant found in ~15% of all NSCLC (~35K pts/yr)**

- Other common human cancers with KRAS mutations are colorectal and pancreatic adenocarcinomas with a combined 168K new cases a year in the US

- **KRAS$^{\text{G12D/G12V}}$ mutant found in 70% of pancreatic cancers (~43K pts/yr) and 25% of colorectal cancers (~53K pts/yr)**
**KRAS^{G12C}-GDP inhibitors do not directly inhibit the active form of KRAS^{G12C} allowing for the emergence of resistance**

Shokat’s discovery led to an explosion of KRAS^{G12C}-GDP inhibitors; led by sotorasib, these will change the treatment paradigm for people with KRAS^{G12C}-driven cancers.
Efficacy of KRAS\textsuperscript{G12C}-GDP inhibitors in the clinic is clearly suboptimal when compared to other driver-targeted therapies in the pathway

<table>
<thead>
<tr>
<th>KRAS\textsuperscript{G12C}-GDP inhibitors</th>
<th>RTK targeted agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Sotorasib, Adagrasib, GDC-6036]</td>
<td>[Selpercatinib, Alectinib, Osimertinib, Capmatinib]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sotorasib</th>
<th>Adagrasib</th>
<th>GDC-6036</th>
<th>Selpercatinib</th>
<th>Alectinib</th>
<th>Osimertinib</th>
<th>Capmatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>2L+ KRAS G12C NSCLC</td>
<td></td>
<td></td>
<td></td>
<td>2L+ RET Fusion+ NSCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>41%</td>
<td>43%</td>
<td>46%</td>
<td>64%</td>
<td>79%</td>
<td>77%</td>
<td>68%</td>
</tr>
<tr>
<td>mPFS (mo.)</td>
<td>6.3</td>
<td>6.5</td>
<td>{\textit{tbd}}</td>
<td>{\textit{tbd}}</td>
<td>25.7</td>
<td>18.9</td>
<td>12.4</td>
</tr>
</tbody>
</table>

Phase 3 CODEBREAK 200 – PFS 5.6 months; ORR 28%

OrR, objective response rate; PFS, progression-free survival
Sources: Sotorasib data from registrational Ph2 CODEBREAK 100 & Ph3 CODEBREAK 200 results presented at 2022 EMSO meeting; Adagrasib data from KRYSTAL-1 results presented at 2022 ASCO Meeting; GDC-6036 data from 2022 WCLC meeting; Analog data taken from product labels
Alterations associated with clinical resistance to KRAS$^{\text{G12C}}$-GDP inhibitors

**BBO-8520**

<table>
<thead>
<tr>
<th>KRAS$^{\text{G12C}}$ amplification</th>
<th>Independent RTK activation</th>
<th>2$^\text{ry}$ in cis KRAS mutations</th>
<th>2$^\text{ry}$ KRAS mutation &amp; lineage plasticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>New KRAS$^{\text{G12C}}$ is GTP-bound</td>
<td>2$^\text{ry}$ mut BBIO IC$_{50}$</td>
<td>2$^\text{ry}$ mut BBIO IC$_{50}$</td>
<td>Non-NSCLC Transition</td>
</tr>
<tr>
<td>Fast adaptation</td>
<td>CRC Tx</td>
<td>ORR</td>
<td>G12Ci</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G12Ci + EGFRi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Y96D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R68</td>
</tr>
</tbody>
</table>

BBIO’s dual KRAS$^{\text{G12C}}$ inhibitor can address 3 of the 4 most prevalent mechanisms of resistance to current clinical KRAS$^{\text{G12C}}$ inactive inhibitors.
A compound that inhibits both GTP (active) and GDP (inactive) forms of KRAS^G12C will be superior to one that only inhibits the latter.

**GDPi does not achieve complete inhibition of “active” KRAS^G12C**

<table>
<thead>
<tr>
<th>Drug (h)</th>
<th>KRAS-GTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDPi</td>
<td>0 4 24 48 72</td>
</tr>
</tbody>
</table>

**Growth factors render GDPi completely inactive**

<table>
<thead>
<tr>
<th>Drug (h)</th>
<th>KRAS-GTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTPi</td>
<td>0 4 24 48 72</td>
</tr>
</tbody>
</table>

**KRAS^G12C prefers the GTP state: GTP levels are 10x GDP levels**

- A mechanism of resistance was not identified for most NSCLC patients that became refractory to sotorasib**
- Among patients with identified resistance mechanisms to sotorasib, the majority were driven by RTK re-activation**

We believe efficacy of targeting of KRAS^G12C can be improved by targeting the oncogenic active GTP form.

*Ryan et al. Cell Reports 2022; **Li BT, et al. Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 102-102*
BBO-8520 completely modifies both GTP (active) and GDP (inactive) forms of KRAS<sup>G12C</sup> and is exceptionally potent

<table>
<thead>
<tr>
<th>% modified</th>
<th>KRAS&lt;sup&gt;G12C&lt;/sup&gt; GTP (active)</th>
<th>15’</th>
<th>100</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60’</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>KRAS&lt;sup&gt;G12C&lt;/sup&gt; GDP (inactive)</td>
<td>15’</td>
<td>91</td>
<td>80</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60’</td>
<td>100</td>
<td>82</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>KRAS&lt;sup&gt;G12C&lt;/sup&gt; : RAF1 Effector Binding IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>33</td>
<td>&gt;100,000</td>
<td>20,000</td>
<td>4,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H358 pERK IC&lt;sub&gt;50&lt;/sub&gt; @ 30’ (nM)</td>
<td>4</td>
<td>50</td>
<td>310</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H358 kinact/Ki (M*s)-1</td>
<td>43,000</td>
<td>776</td>
<td>1064</td>
<td>27,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- High degree of protein modification supports high affinity binding to GTP state
- Potent inhibition of effector binding and oncogenic signaling
- Superior kinact/Ki
Cysteine proteome selectivity and mechanism of action

Global cysteine proteomics shows high degree of selectivity for G12C

31P NMR peak shifts suggest that BBO-8520 stabilizes State 1 of active GTP-bound KRAS, which disrupts effector protein binding

p=0.000072

γ1 population increases from < 5% to > 85% upon binding
Targeting KRAS$^{G12C}$-GTP activity allows for rapid signal inhibition and overcomes RTK drive.

Rapid and complete inhibition of KRAS$^{G12C}$-GTP

GFs abundantly present in human tissues render GDP inhibitors inactive

<table>
<thead>
<tr>
<th>Compound</th>
<th>MALDI-TOF% GTP, 5min</th>
<th>Time (min) to IC$_{50}$</th>
<th>% of AMG510 Time to IC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG510</td>
<td>0</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>MRTX849</td>
<td>0</td>
<td>26</td>
<td>118</td>
</tr>
<tr>
<td>BBO-8520</td>
<td>94</td>
<td>3.0</td>
<td>14</td>
</tr>
</tbody>
</table>
Cellular data support hypothesis that targeting the GTP form yields greater potency and deeper responses.

10x increased potency is observed in viability assays.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H358</td>
<td>MIAPaCa-2</td>
</tr>
<tr>
<td>AMG510</td>
<td>2</td>
</tr>
<tr>
<td>BBO-8520</td>
<td>0.2</td>
</tr>
</tbody>
</table>

H358 Clonogenic Assay suggests GTPi may reduce development of resistance.

BBO-8520 retains single-digit nM activity against reported GDP-inhibitor active-site mutants, including G12C/R68S, G12C/Y96D, G12C/G13D, G12C/Q61H, and G12C/A59G.
BBO-8520 exhibits strong efficacy in KRAS\textsuperscript{G12C} models

**High Potency**
- MIA PaCa-2
  - Vehicle and BBO-8520 at 0.1 mg/kg, 0.3 mg/kg, and 3.0 mg/kg

**Deep Efficacy**
- H358
  - Vehicle, BBO-8520 at 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, and 10 mg/kg

**Differentiated**
- LUN055 (PDX) - NSCLC
  - Vehicle, AMG510 at 100 mg/kg, and BBO-8520 at 30 mg/kg

\textbf{10/10 CRs at 10 mg/kg}

- **ED_{50}**
  - Vehicle 0.13 mg/kg
  - BBO-8520 0.61 mg/kg

- **ED_{90}**
  - Vehicle 0.40 mg/kg
  - BBO-8520 1.6 mg/kg

- **EC_{50}**
  - Vehicle 4.6 nM
  - BBO-8520 14 nM

- **EC_{90}**
  - Vehicle 9.9 nM
  - BBO-8520 34 nM

**BBO-8520 is efficacious in cell line and PDX models with high potency, deep efficacy, and differentiated activity**

<table>
<thead>
<tr>
<th>Group (n=10)</th>
<th>TGI</th>
<th>Regression</th>
<th>FF AUC\textsubscript{0-24} (ng·hr/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBO-8520</td>
<td>100%</td>
<td>23% (7/10)</td>
<td>59</td>
</tr>
<tr>
<td>AMG510</td>
<td>71%</td>
<td>-</td>
<td>1563</td>
</tr>
</tbody>
</table>
BBO-8520: G12C Dual Inhibitor Development Candidate

- BBO-8520 is a potential “first-in-class” direct KRAS$^{G_{12C}}$ dual inhibitor
  - Completely modifies both GTP (active) and GDP (inactive) forms of KRAS$^{G_{12C}}$
  - Exceptionally potent and selective with superior kinact/Ki
  - Binding stabilizes GTP-bound KRAS$^{G_{12C}}$ in state 1 which cannot bind effectors
  - Overcomes RTK drive
  - Strong efficacy in KRAS$^{G_{12C}}$ models
- IND projected 2023
- Therapeutic opportunity in KRAS$^{G_{12C}}$ mutant NSCLC, CRC and other GI tumors in both GDP-KRAS$^{G_{12C}}$ inhibitor naïve and experienced patients
PI3Kα:RAS Breaker is a novel, potent and differentiated therapeutic approach that can deliver efficacy in multiple common tumor genotypes as monotherapy or in combination

- First-in-class molecular mechanism targeting the second most mutated oncogene in human cancer
- Molecular mechanism provides tumor selectivity and prevents well-known target liability (hyperglycemia)
- Proven activity in common tumor genotypes (KRAS\textsuperscript{G12x}, PIK3CA helical and HER2/HER3)
- Differentiated activity from Her2 and KRAS approved inhibitors (tucatinib, sotorasib, etc)

KYSE-410 CDX esophageal carcinoma - HER2\textsuperscript{amp} KRAS\textsuperscript{G12C}

Tucatinib is a HER2 inhibitor, sotorasib is a KRAS-G12C inhibitor, alpelisib is a PI3Kα inhibitor. All groups dosed PO, QD, *p<0.05 RM ANOVA vs vehicle
Inhibiting the 2nd most mutated oncogene (PIK3CA) in human cancer has been limited by side effects of glucose metabolism

Solar-1 study – Hyperglycemia & Efficacy*

- High rate of dose modifications and interruptions (>30%) does not allow effective target coverage
- Adverse events are not conducive to combination studies
- Increased insulin secretion leads to increased pathway signaling and resistance

- Dose interruptions occurred in 66% versus 21% in placebo
- Dose reductions due to adverse events occurred in 55% versus 4.5% in placebo
- The most common adverse reactions were hyperglycemia (65%), diarrhea (58%), and rash (52%)

*Adapted from Rugo et al. Annals of Oncology 2020
Inhibiting PI3Kα activity by preventing its interaction with RAS provides a “tumor selective” mechanism that spares glucose metabolism

- PI3Kα kinase inhibitors block normal cell signaling resulting in dose-limiting hyperglycemia and insulin-driven resistance
- Inhibiting PI3Kα:RAS PPI with a “PI3Kα Breaker” should avoid hyperglycemia and insulin-driven resistance by specifically targeting tumor cells and may provide multiple therapeutic opportunities
- Mice with mutations in the RBD that impair the PI3Kα:RAS interaction block oncogene-driven NSCLC tumor growth in vivo and have no effect on glucose metabolism*

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**Normal Cells**

- RTK
- PI3K
- AKT (PI3Kα)
- Glucose metabolism, survival

**Tumor Cells**

- RTK
- RAS
- PI3K
- AKT (PI3Kα)
- BBO Breaker
- Survival & proliferation

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PPI, protein-protein interactions; RBD, RAS-binding domain

*Gupta et al. Cell 2007; Castellano et al. Cancer Cell 2013; Murillo et al., Cell Reports 2018
BridgeBio has designed potent and selective PI3Kα:RAS breakers

- PI3Kα:RAS breakers selectively bind to PI3Kα
- By ITC and SPR we observe
  - RAS binds to PI3Kα with ~10 μM affinity
  - Breakers binding to PI3Kα blocks its interaction with RAS
  - No binding affinity to RAS
- PI3Kα:RAS breakers do not affect kinase activity of PI3Kα

<table>
<thead>
<tr>
<th>BBO</th>
<th>Alpelisib</th>
</tr>
</thead>
<tbody>
<tr>
<td>pAKT (IC50, nM)</td>
<td>34</td>
</tr>
<tr>
<td>Cell Viability (nM)</td>
<td>67</td>
</tr>
</tbody>
</table>
One third of all cancer cell lines depend on PI3Kα:RAS interaction for activation of AKT signaling

- 105/282 (37%) of screened cell lines are responders
- Responders include:
  - 29/50 (58%) KRAS$^{G12X}$ mutant
  - 18/19 (94%) PIKCA helical mutant
  - 16/21 (76%) HER2 amp

PIK3CA helical mutants are highly sensitive

$pAKT (IC_{50} \text{ nM})$

100nM = “Responder” threshold

Mutations Responders vs Non-Responders

mutation

<table>
<thead>
<tr>
<th>mutation</th>
<th>Mut</th>
<th>WT</th>
</tr>
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<tbody>
<tr>
<td>pAKT nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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</table>
BBO is orally bioavailable and achieves near complete inhibition of signaling in tumors at 100 mg/kg without risk of hyperglycemia.

**BBO Dose Ranging Mouse PK**

- IV 3 mg/kg
- PO 100 mg/kg
- PO 7 mg/kg
- PO 30 mg/kg

**BBO Dose Response PD**

Full target inhibition achieved at 100 mg/kg

**BT474 CDX**

(4 hours post BBO or alpelisib dose)

- % pAKT: BBO
- % pAKT: alpelisib
- PK

**Blood Glucose (mg/dL)**

- Vehicle
- Alpelisib, 50 mg/kg
- BBO, 300 mg/kg

**Insulin (ng/mL)**

- Vehicle
- Alpelisib
- BBO

Unlike alpelisib, Breaker MOA does not affect glucose metabolism.

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1. One-way ANOVA with Dunnett’s test vs vehicle; *p<0.01, **p<0.001
2. Top: One-way ANOVA with Dunnett’s test vs vehicle, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, Bottom: One-way ANOVA with Tukey’s multiple comparisons test vs all other groups : *p<0.0001
**PI3Kα breakers are efficacious in xenograft models**

**KYSE-410 CDX**
- KRAS<sup>G12C</sup>
- HER2<sup>amp</sup>

**GP2d CDX**
- KRAS<sup>G12D</sup>
- PIK3CA<sup>H1047L</sup>

**SNU-601 CDX**
- KRAS<sup>G12D</sup>
- PIK3CA<sup>E542K</sup>

**SNU-16 CDX**
- KRAS<sup>G12D</sup>

**Efficacy is observed in models with KRAS<sup>G12X</sup> mutations, with or without PIK3CA mutation**

All groups dosed PO, QD, *p<0.0005 RM ANOVA vs vehicle
BridgeBio has designed potent and selective PI3Kα:RAS breakers

- Potential first-in-class opportunity
  - Novel mechanism of action: PI3Kα breakers selectively block RAS activation of PI3Kα
  - Exhibits potent inhibition of AKT activation in KRAS<sup>G12x</sup>, PIK3CA helical mutations and HER family driven populations
  - Potent efficacy in multiple models without hyperglycemia
- Development candidate projected 2023
- Multiple opportunities as monotherapy and in combination in large patient populations
Agenda

- BBO-8520: A KRASG12C Dual Inhibitor
- PI3Kα:RAS Breaker
- Pan-KRAS program
Mutant KRAS is the most common oncogene in cancer – pan KRAS

- Lung cancer is the second most common cancer in the US with greater than 235K new cases and 130K deaths a year

- KRAS$^{G12C}$ mutant found in ~15% of all NSCLC (~35K pts/yr)

- Other common human cancers with KRAS mutations are colorectal and pancreatic adenocarcinomas with a combined 168K new cases a year in the US

- KRAS$^{G12D/G12V}$ mutant found in 70% of pancreatic cancers (~43K pts/yr) and 25% of colorectal cancers (~53K pts/yr)

Figure from: Moore, Rosenberg, McCormick, Malek Nat Rev Drug Disc 2020
Pan-KRAS program: current lead molecules

- Recent progress has identified molecules with the right potency and bioavailability

<table>
<thead>
<tr>
<th>PPI: KRAS/RAF1 effector IC_{50} (nM)</th>
<th>BBO-a</th>
<th>BBO-b</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12D</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>G12V</td>
<td>430</td>
<td>270</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pERK: HTRF IC_{50} (nM)</th>
<th>BBO-a</th>
<th>BBO-b</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP2D (G12D) @ 1h</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>SW620 (G12V) @ 4 h</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mouse PK (IV ER % / PO %F)</th>
<th>BBO-a</th>
<th>BBO-b</th>
</tr>
</thead>
<tbody>
<tr>
<td>64 / 6.9 (10 mpk)</td>
<td></td>
<td>44 / 34 (10 mpk)</td>
</tr>
</tbody>
</table>
Potent inhibitory activity against multiple KRAS-mutant models *in vitro*

<table>
<thead>
<tr>
<th>KRAS variant</th>
<th>BBO-b EC(_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pERK</td>
</tr>
<tr>
<td>G12D</td>
<td>6.7</td>
</tr>
<tr>
<td>G12V</td>
<td>2.7</td>
</tr>
<tr>
<td>G12C</td>
<td>11.0</td>
</tr>
<tr>
<td>G12S</td>
<td>126</td>
</tr>
<tr>
<td>G13D</td>
<td>37.1</td>
</tr>
<tr>
<td>G12A</td>
<td>406</td>
</tr>
<tr>
<td>BRAF(^{V600E})</td>
<td>&gt;10 uM</td>
</tr>
</tbody>
</table>

We have identified leads with strong *in vivo* target engagement which are progressing into efficacy studies.
Pan-KRAS: Lead optimization progressing towards a development candidate

- Potent activity against multiple KRAS mutants
- Selective for KRAS over H- and NRAS
- Potent PD and good mouse oral bioavailability
- Development candidate projected 2023
BridgeBio is progressing multiple approaches against KRAS

- **Dual KRAS\(^{G12c}\) inhibitor** program has selected a Development Candidate (BBO-8520) with projected IND-filing 2023

- **PI3K\(\alpha\):RAS breaker** is highly differentiated in that it is a) tumor selective, b) targets both mutant and wild-type PIK3CA, and c) does not induce hyperglycemia

- Projected Development Candidate selection in 2023

- **pan-KRAS** program targets multiple KRAS mutants including KRAS\(^{G12D}\) and KRAS\(^{G12V}\)

- Projected Development Candidate selection in the 2023