New Drugs to Treat GIST: An update on ongoing clinical studies

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New Agents in GIST

• Avapritinib (BLU-285) and DCC-2618
• Both are novel potent and specific KIT inhibitors that were rationally designed to inhibit TKI-resistance mutations associated with drug-resistant GIST
• Both have completed phase 1 dose escalation dose expansion studies for advanced GIST
Avapritinib (BLU-285) is a potent type 1 KIT/PDGFRα inhibitor that binds to the active conformation of the kinase.
NAVIGATOR
Avapritinib Phase 1 Study Design

Key objectives
• Part 1: MTD, safety, pharmacokinetics, ctDNA analyses, anti-tumor activity
• Part 2: response rate, duration of response, safety

Part 1
Dose escalation *completed*

- Advanced GIST
- MTD
- 3+3 design with enrichment
- Dose levels: 30, 60, 90, 135, 200, 300, 400 and 600 mg QD
- MTD determined to be 400 mg PO QD

Part 2
Dose expansion *enrolling*

- PDGFRα D842V-mutant GIST (n=50)
- Unresectable GIST after imatinib and ≥1 other TKI (n=50)
Avapritinib phase 1-2 Study

Tumor reduction across multiple KIT genotypes (central radiology review)

N=30 patients 300 mg (RP2D) – 400 mg (MTD)

20 of 30 (67%) patients with tumor shrinkage

* ctDNA results pending; ^ per archival tumor and ctDNA

Heinrich et al, CTOS 2017
Prolonged PFS in heavily pre-treated KIT-mutant GIST (central radiology review)

- 35 of 64 patients remain on therapy
- No approved therapies beyond third-line regorafenib
  - ORR ~0% with imatinib re-treatment in ≥third-line

<table>
<thead>
<tr>
<th>Best response (N=30)*</th>
<th>Choi Criteria n (%)</th>
<th>RECIST 1.1 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>16 (53)^</td>
<td>5 (17)^</td>
</tr>
<tr>
<td>SD</td>
<td>7 (23)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>DCR (PR+SD)</td>
<td>23 (77)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>PD</td>
<td>7 (23)</td>
<td>7 (23)</td>
</tr>
</tbody>
</table>

* 300 RP2D–400 MTD mg; ^ 2 pending confirmation

Median PFS 11.5 months, 95% CI (9.3, NE)
PFS at 6 months 69%


Heinrich et al, CTOS 2017
Remarkable activity in PDGFRα D842-mutant GIST (central radiology review)

Avapritinib phase 1-2 Study

N=31 patients across all dose levels

Maximum reduction: sum of diameter change from baseline (%)

31 of 31 (100%) patients with tumor shrinkage

* per archival tumor and ctDNA

Heinrich et al, CTOS 2017
Avapritinib phase 1-2 Study

High response rate and prolonged PFS in PDGFRα D842-mutant GIST (central radiology review)

<table>
<thead>
<tr>
<th>Best response (N=31)*</th>
<th>Choi Criteria n (%)</th>
<th>RECIST 1.1 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (3)^</td>
<td>1 (3)^</td>
</tr>
<tr>
<td>PR</td>
<td>30 (97)^†</td>
<td>21 (68)^†</td>
</tr>
<tr>
<td>CR+PR</td>
<td>31 (100)</td>
<td>22 (71)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>9 (29)</td>
</tr>
<tr>
<td>DCR (PR+SD)</td>
<td>31 (100)</td>
<td>31 (100)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* All dose levels included
^ PR from C3 to C13, CR at C16, CR pending confirmation
† 3 pending confirmation

- 30 of 37 remain on therapy
- ORR ~0% with currently approved agents^3,4

Median PFS not reached
PFS at 12 months 78%
Approved agents are ineffective^3,4
median PFS ~3 months


Heinrich et al, CTOS 2017
Phase 1 NAVIGATOR clinical trial now enrolling patients with 2L GIST

Design
- Open-label, Phase 1 clinical trial
- All enrolled patients receive avapritinib

Eligibility
- Aged 18 years or older
- Metastatic and/or unresectable GIST
- Have received Gleevec® (imatinib) or are intolerant to imatinib

More Information
- Website: www.NavigatorStudy.com
- Email: studydirector@blueprintmedicines.com

Key endpoints: overall response rate, duration of response, safety

Part 1 complete
- Open-label dose escalation (3+3)
- avapritinib 300 mg once daily

Part 2 ongoing
- PDGFRα D842V (n= ~50) fully enrolled
- 3L+ GIST (n= ~100) fully enrolled
- 2L GIST (n= ~50) enrolling
Phase 3 VOYAGER is now enrolling patients with 3L and 4L GIST

**Design**
- Open-label, randomized, Phase 3 clinical trial
- Patients randomized to receive either avapritinib or Stivarga® (regorafenib)
- Patients assigned to receive regorafenib may cross over to receive avapritinib following confirmed disease progression

**Eligibility**
- Aged 18 years or older
- Metastatic and/or unresectable GIST
- Have received Gleevec® (imatinib) and 1 or 2 other tyrosine kinase inhibitors

**More Information**
- Website: www.VoyagerTrial.com
- Email: studydirector@blueprintmedicines.com

**Primary endpoint:** progression free survival

- **Avapritinib (n= 230)**
  - 300 mg once daily

- **Stivarga® (regorafenib) (n= 230)**
  - 160 mg once daily for 3 out of every 4 weeks
Pharmacokinetic-driven phase I study of DCC-2618 a pan-KIT and PDGFR inhibitor in patients (pts) with gastrointestinal stromal tumor (GIST) and other solid tumors

RATIONALE FOR DCC-2618 STUDY

- Activity regardless whether primary mutation is in KIT Exon 9, Exon 11, or Exon 17
  - IC$_{50}$ for KIT Exon 11 deletion 3 nM, IC$_{50}$ PDGFRA D842V 60 nM
- Broad activity in secondary KIT mutations across Exons 13, 14, 17, and 18
  - Active metabolite DP-5439 possesses comparable activity across all mutations
- KIT T670I and V654A secondary mutations are the least sensitive to DCC-2618
Waterfall Plot of KIT/PDGFRα GIST Patients (Best Response Per RECIST, N=37)

DCC-2618 Dose Assigned
- <100mg daily
- >=100mg daily

# Patients dosed at 150mg QD (RP2D)

PD = Progressive disease, SD = Stable disease, PR = Partial response

*66% increase in tumor size; #Patients treated at RP2D
DCC-2618: Progression-Free Survival
Patients treated at $\geq100$ mg/d compared to $<100$ mg/d

- Despite small sample size results suggest that doses of 40 or 60 mg/d are insufficient
- The fact that 30 mg BID is an insufficient dose is supported by improvement in disease control in a patient with PD after 24 weeks following dose escalation (not shown)
A Phase 3, INTERVENTIONAL, Double-Blind Study to Assess Safety and Efficacy of DCC-2618 IN Patients with Advanced c-KIT/PDGFRA Gastrointestinal Stromal TUMORS Who Have Received Prior Treatment with Imatinib, Sunitinib, and Regorafenib
The countries that will be involved in invictus are:

- North America: US, Canada
- Europe: Belgium, Finland, France, Germany, Italy, Netherlands, Poland, Spain, UK
- Australia
- Singapore
Planned *intrigue* Study

Phase 3 Pivotal Trial of DCC-2618 versus sunitinib

FPI 2H 2018
The primary endpoint in this pivotal Phase 3 trial in second-line GIST will most likely be a clinically meaningful improvement in median PFS in patients treated with DCC-2618 compared to sunitinib.

Median PFS will be determined by independent radiologic review of CT scans, as assessed by RECIST.

In this pivotal Phase 3 trial in second-line GIST, we expect to enroll patients who have progressed on or are intolerant to imatinib, comparing DCC-2618 against sunitinib.

The design for this trial has not yet been finalized.
Summary of Clinical Development of New Agents in GIST

• Avapritinib will be tested in a phase 3 randomized, open-label study vs. third-line regorafenib (VOYAGER, now open at a few sites, the rest to be opened by November, 2018)
• Based on the phase 1-2 data, Blueprint Medicines is seeking approval of avapritinib for treatment of D842V-mutant GIST
• DCC-2618 is currently being tested in a phase 3 randomized, double-blind, placebo-controlled study of treatment of advanced GIST in the fourth-line or later (invictus, open now, projected to complete enrollment by November 2018)
• DCC-2618 will also be tested in a randomized phase 3 study vs. sunitinib for second-line treatment of advanced GIST (intrigue, opening soon)
Avapritinib  
Treatment emergent adverse events ≥20%

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Any AE</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>65 (56)</td>
<td>41 (35)</td>
<td>17 (15)</td>
<td>7 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62 (53)</td>
<td>23 (20)</td>
<td>31 (27)</td>
<td>8 (7)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Periorbital edema</td>
<td>50 (43)</td>
<td>42 (36)</td>
<td>8 (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>48 (41)</td>
<td>36 (31)</td>
<td>9 (8)</td>
<td>3 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>39 (34)</td>
<td>28 (24)</td>
<td>9 (8)</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>36 (31)</td>
<td>7 (6)</td>
<td>10 (9)</td>
<td>17 (15)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (31)</td>
<td>26 (22)</td>
<td>8 (7)</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cognitive Effects*</td>
<td>35 (30)</td>
<td>20 (17)</td>
<td>10 (9)</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>35 (30)</td>
<td>29 (25)</td>
<td>6 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>33 (28)</td>
<td>24 (21)</td>
<td>6 (5)</td>
<td>3 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>27 (23)</td>
<td>21 (18)</td>
<td>6 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>25 (22)</td>
<td>18 (16)</td>
<td>6 (5)</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>25 (22)</td>
<td>24 (21)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Consists of multiple similar AEs that have been aggregated into a single category. 42% of patients at 400 mg (MTD), 18% of patients at 300 mg (RP2D).

- 39 (34%) patients had grade ≥3 treatment-related AEs: anemia (9%), fatigue (7%), hypophosphatemia (4%), nausea (4%), cognitive effects (3%)

- 67 patients on treatment; 49 discontinued: PD n=40, AEs n=6, withdrew consent n=3
DCC-2618
Favorable Tolerability Profile

Treatment-emergent Adverse Events in ≥ (10%) GIST Patients (n=100) @ 150 mg QD

- Well tolerated up to 400 mg per day
- MTD not reached
- 3 DLTs:
  - Reversible plasma enzyme elevations: lipase (2) and CPK (1)
  - Deemed not clinically significant
- 150 mg QD dose for Phase 1 Expansion and 4th Line GIST Phase 3 Trial

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>GRADE 1/2</th>
<th>GRADE 3/4</th>
<th>TOTAL (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>39</td>
<td>0</td>
<td>39 (39%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>0</td>
<td>39 (39%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>35</td>
<td>0</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>29</td>
<td>0</td>
<td>29 (29%)</td>
</tr>
<tr>
<td>Hand-Foot-Skin reaction</td>
<td>26</td>
<td>1</td>
<td>27 (27%)</td>
</tr>
<tr>
<td>Rash</td>
<td>21</td>
<td>0</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>10</td>
<td>10</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19</td>
<td>0</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18</td>
<td>0</td>
<td>18 (18%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>2</td>
<td>18 (18%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>2</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>2</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15</td>
<td>0</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>13</td>
<td>0</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>0</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>0</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>3</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>1</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>11</td>
<td>0</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11</td>
<td>0</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>10</td>
<td>0</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>10</td>
<td>0</td>
<td>10 (10%)</td>
</tr>
</tbody>
</table>

Note: Data presented at AACR Annual Meeting on April 16, 2018 based on cutoff as of March 18, 2018.
DCC-2618 BACKGROUND

• DCC-2618 is a *KIT* and *PDGFRA* inhibitor resilient to gain-of-function and drug resistance mutations
  • Potency independent of ATP concentration

• DCC-2618 was designed to potently inhibit a broad range of mutations in *KIT* and *PDGFRA* kinases

• Gastrointestinal stromal tumor (GIST) is an important disease to achieve proof-of-concept in the FIH study due to the multiplicity and heterogeneity of resistance mutations within *KIT*
JM-Inhibited Inactive Kinase

Snapshot 1. The rightmost green residue from the inhibitory JMD switch occupies the #3 position in the kinase vertical spine (the other three spine residues are shown in yellow).

In this conformation, KIT kinase is in its OFF state. Note that the ‘DFG’ phenylalanine amino acid (green) is in the left-most position, blocking the ATP pocket.
Activated Kinase Structure

Snapshot 2. The rightmost green residue from the inhibitory JMD switch has been moved out of the #3 position in the kinase vertical spine (the other three spine residues are shown in yellow).

In this conformation, KIT kinase is in its ON state. Note that the ‘DFG’ phenylalanine amino acid (green) is now in the #3 position in the vertical spine.
Switch Pocket Inhibitor Locks Kinase Into Inactive Conformation

Snapshot 5. Switch Pocket Inhibitor binds to mutant KIT, with part of the inhibitor structure (blue) occupying the #3 position of the spine. This binding mode provides a biomimetic surrogate for the deleted inhibitory switch of mutant KIT.

The ‘DFG’ phenylalanine residue (green) is forced to occupy the out/inhibited conformation.
Background

• Inhibitors of KIT/PDGFRA (TKIs) such as imatinib and sunitinib have transformed the medical treatment of advanced GIST
• However, disease control in the metastatic setting is limited by the development of drug-resistant clones
• Concept 1: To date, all approved TKIs used for the treatment of GIST are competitive ATP inhibitors
• Concept 2: To date, all approved TKIs used for the treatment of GIST bind to the inactive kinase structure
• Concept 3: Drug-resistance is commonly due to the development of acquired mutations in the disease causing mutant kinase (e.g. KIT)
Concept 1: ATP is the battery pack for KIT/PDGFRA

Imatinib and other current GIST drugs bind into the KIT battery pack space (competitive ATP inhibitors)
Concept 2: To date, all approved GIST kinase inhibitors bind to the inactive conformation

Adapted from Gajiwala K. S. et.al. PNAS 2009;106:1542-1547
KIT activation loop mutations prevent Imatinib from binding to KIT/PDGFRα
Imatinib and Sunitinib (and Regorafenib) Only Inhibit the Inactive Form of KIT

Adapted from Gajiwala K. S. et.al. PNAS 2009;106:1542-1547
Concept 3

Drug-resistance is commonly due to the development of acquired mutations in the disease causing mutant kinase (e.g. KIT)
First line:

![Chemical structure of IMATINIB]

IMATINIB

Second line:

![Chemical structure of SUNITINIB]

SUNITINIB

Third line:

![Chemical structure of REGORAFENIB]

REGORAFENIB

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Heinrich et al. JAMA (2017)


George et al. JCO (2012)
Primary Mutations
- Exon 13
- Exon 9
- Exon 11
- Exon 17

Protein Domains
- Ligand binding
- JM
- ATP binding

Secondary Mutations
- Exon 13
- V654A
- Exon 14
- T670I
- Exon 17
- D816A/G/H/V
- D820A/E/G/Y
- N822H/K
- Y823D
- A829P

Drug Sensitivity
- IM
- SU
- REG

Exon 8
- Activation Loop

Exon 9
- Membrane

Exon 11
- JM

Exon 13
- ATP binding

Exon 14
- V654A

Exon 18
- Activation Loop
Activation Loop Mutations Force KIT/PDGFRα into the Active Conformation

Inactive conformation
Activation loop closed confirmation
Type II inhibitors active

Active conformation
Activation loop open confirmation
Type II inhibitors inactive