Treatment of imatinib-resistant GIST: the next generation

Dr. Michael Heinrich, M.D
OHSU Knight Cancer Institute
Disclosures/Conflict of Interest

- Consultant – Molecular MD, Novartis, Deciphera Pharmaceuticals, Blueprint Medicines
- Laboratory Research Funding – Blueprint Medicines, Deciphera Pharmaceuticals
- Equity Interest – Molecular MD
- Patents-5 patents related to diagnosis or treatment of GIST and/or KIT mutant tumors. One of these patents has been licensed to Novartis
Overview

• Development of new tyrosine kinase inhibitors for GIST
  – Background/rationale
  – Avapritinib (BLU-285)
  – Ripretinib (DCC-2618)
New TKIs for GIST: Background

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

• Concept 2: To date, all approved TKIs used for the treatment of GIST bind to the inactive kinase structure

• Concept 3: To date, all approved TKIs used for the treatment of GIST are competitive ATP inhibitors
Drug-resistance is commonly due to the development of acquired mutations in the disease causing mutant kinase (e.g. KIT)
First line:

IMATINIB

Second line:

SUNITINIB

Third line:

REGORAFENIB
Primary Mutations

Exon 13

Exon 9

Exon 11

Exon 17

Protein Domains

Ligand binding

JM

ATP binding

Activation Loop

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

Membrane

Resistant

Intermediate

Sensitive

NR

Not reported

Resistant

Intermediate

Sensitive

NR

Not reported
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
Concept 2: Imatinib and Sunitinib (and Regorafenib) only Inhibit the Inactive Form of KIT

Adapted from Gajiwala K. S. et.al. PNAS 2009;106:1542-1547
To date, all approved GIST kinase inhibitors bind to the inactive conformation.

Adapted from Gajiwala K. S. et.al. PNAS 2009;106:1542-1547
Activation Loop Mutations Force KIT/PDGFRA into the Active Conformation

Inactive conformation
Activation loop closed confirmation
Type II inhibitors active

Active conformation
Activation loop open conformation
Type II inhibitors inactive
Unlike imatinib, avapritinib binds to the active conformation

Avapritinib (Blu-285)  Imatinib
Avapritinib is Highly Active and Well-tolerated in Patients With Advanced GIST Driven by a Diverse Variety of Oncogenic Mutations in KIT and PDGFRA


Connective Tissue Oncology Society 2018 Annual Meeting
Rome, Italy • November 15, 2018

Abstract no: 3027631
Avapritinib: a highly selective and potent KIT/PDGFRA inhibitor for GIST

<table>
<thead>
<tr>
<th>GIST mutation(s)</th>
<th>Medical need by mutation</th>
<th>Avapritinib biochemical IC$_{50}$(^{1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT Exon 11 deletion</td>
<td>JM domain 1L imatinib is effective 2L sunitinib/3L regorafenib have low ORR/short PFS</td>
<td>0.6 nM</td>
</tr>
<tr>
<td>KIT Exon 11 V560G</td>
<td>ATP binding site 11 nM</td>
<td></td>
</tr>
<tr>
<td>KIT Exon 11/13</td>
<td>Activated ATP 2L/3L agents have low ORR/short PFS 28 nM</td>
<td></td>
</tr>
<tr>
<td>KIT Exon 11/14</td>
<td>Activation loop 0.1 nM</td>
<td></td>
</tr>
<tr>
<td>KIT Exon 11/17</td>
<td>PDGFRα D842V No highly effective therapy in any line 0.24 nM</td>
<td></td>
</tr>
</tbody>
</table>

**Ongoing clinical trials**

**Avapritinib kinome selectivity**

**Navigator GIST**
Phase 1 advanced GIST

**Voyager GIST**
Phase 3 trial of avapritinib vs. regorafenib in 3L and 4L GIST

KIT, KIT proto-oncogene receptor tyrosine kinase; PDGFRA, platelet-derived growth factor alpha; IC$_{50}$, concentration causing 50% inhibition; L, line; JM, juxtamembrane; ORR, objective response rate; PFS, progression-free survival.

Kinome illustrations reproduced courtesy of Cell Signaling Technology, Inc. (CSTI) (www.cellsignal.com). Blueprint Medicines is not responsible for the content of the CSTI site.

NAVIGATOR Phase 1 study design

Part 1 dose escalation

Advanced GIST (N = 46)

RP2D*

avapritinib PO QD

PDGFRα D842V (n = 33)
registration enabling – fully enrolled

≥3L (n = 116)
≥4L registration enabling – fully enrolled

2L
Ongoing (n ~50) – fully enrolled

KEY OBJECTIVES

• Determine MTD/RP2D, safety, PK and clinical activity by line of therapy and mutational status
• ORR/DOR per central radiology assessment (mRECIST 1.1) for planned NDA and MAA regulatory filings

RP2D, recommended Phase 2 dose; PO, orally; QD, once daily; MTD, maximum tolerated dose; PK, pharmacokinetics; DOR, duration of response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NDA, New Drug Application; MAA, Marketing Authorization Application.

*MTD 400 mg; RP2D 300 mg.
Demography and baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (N = 231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>62 (25, 90)</td>
</tr>
<tr>
<td>GIST mutational subtype, % (n)</td>
<td></td>
</tr>
<tr>
<td>KIT</td>
<td>72% (167)</td>
</tr>
<tr>
<td>PDGFRα D842V</td>
<td>24% (56)</td>
</tr>
<tr>
<td>PDGFRα non-D842V</td>
<td>4% (8)</td>
</tr>
<tr>
<td>Metastatic disease, % (n)</td>
<td>89% (205)</td>
</tr>
<tr>
<td>Largest target lesion size, % (n)</td>
<td></td>
</tr>
<tr>
<td>≤5 cm</td>
<td>34% (79)</td>
</tr>
<tr>
<td>&gt;5 –≤10 cm</td>
<td>40% (93)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>20% (47)</td>
</tr>
<tr>
<td>Pending</td>
<td>5% (12)</td>
</tr>
<tr>
<td>No. prior kinase inhibitors, % (n)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>PDGFRα</td>
</tr>
<tr>
<td>0</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td>1</td>
<td>17% (11)</td>
</tr>
<tr>
<td>2</td>
<td>37% (24)</td>
</tr>
<tr>
<td>3</td>
<td>19% (12)</td>
</tr>
<tr>
<td>4</td>
<td>11% (7)</td>
</tr>
<tr>
<td>≥5</td>
<td>8% (5)</td>
</tr>
</tbody>
</table>

*Similar to Phase 3 trial population (VOYAGER).
Data are preliminary and based on a cutoff date of October 15, 2018.
Side Effects

- Most AEs (adverse events) were grade 1 or 2
- No treatment-related deaths
- 8.7% (20) of patients discontinued due to related AEs
- Grade 3-4 treatment-related AEs ≥2%: anemia, fatigue, hypophosphatemia, increased bilirubin, decreased white blood count/neutropenia, and diarrhea

AE, adverse event.
98% of patients with tumor reduction

Best response by central radiology in PDGFRα D842V GIST

n = 56 patients across all dose levels

Maximum reduction – sum of diameter change from baseline, %

PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.
### ORR and DOR by central radiology in PDGFRα D842V GIST

<table>
<thead>
<tr>
<th>Best response*</th>
<th>mRECIST 1.1% (n) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>84% (47) [71.7-92.47]</td>
</tr>
<tr>
<td>CR/PR*</td>
<td>9% (5)/75% (42)</td>
</tr>
<tr>
<td>SD</td>
<td>16% (9)</td>
</tr>
<tr>
<td>CBR†</td>
<td>96% (54) [87.7-99.6]</td>
</tr>
</tbody>
</table>

CI, confidence interval; CBR, clinical benefit rate.

*4 PR pending confirmation. Patients who have had ≥1 post-baseline radiographic assessment. Response evaluable includes all doses.

†PR + SD lasting ≥4 months.
PDGFRA D842V-mutant GIST
Treatment with avapritinib

Before treatment
Best response by central radiology in ≥4L GIST

60% of patients with tumor reduction

n = 109 patients 300/400 mg
Best response by mutational profile in ≥4L GIST

<table>
<thead>
<tr>
<th>Best response*</th>
<th>V654A or T670I POSITIVE, % (n) (n = 25)</th>
<th>V654A and T670I NEGATIVE, % (n) (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>0</td>
<td>26% (22)*</td>
</tr>
<tr>
<td>CR/PR</td>
<td>0/0</td>
<td>1% (1)/ 25% (21)†</td>
</tr>
<tr>
<td>SD</td>
<td>28% (7)</td>
<td>51% (43)</td>
</tr>
<tr>
<td>CBR‡</td>
<td>8% (2)</td>
<td>49% (41)</td>
</tr>
<tr>
<td>PD</td>
<td>72% (18)</td>
<td>23% (19)</td>
</tr>
</tbody>
</table>

n = 109 patients 300/400 mg; baseline genotype per ct-DNA and tumor sequencing

CT-DNA, circulating tumor DNA.
*Patients who have had ≥1 post-baseline radiographic assessment. Response evaluable includes 300 mg and 400 mg.
† Includes 1 unconfirmed PR.
‡PR + SD lasting ≥4 months
Best response by central radiology in 3L/4L regorafenib-naïve GIST*

78% of patients with tumor reduction

KIT
Other PDGFRA

n = 23 patients 300/400 mg

PDGFRα D842V patients, n=10, and ORR 80% are not included here

*Similar to Phase 3 trial population (VOYAGER), except that PDGFRα D842V patients (ORR 80%) are not included here.
Avapritinib has important clinical activity in advanced GIST

<table>
<thead>
<tr>
<th></th>
<th>PDGFRα D842V n = 56</th>
<th>≥4L all patients n = 109</th>
<th>3L/4L regorafenib-naïve non-D842V n = 23</th>
<th>2L non-D842V n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (central radiology), % (n) [95% CI]</td>
<td>84% (47) [72-92]</td>
<td>20% (22) [13.1-29.0]</td>
<td>26% (6) [10.2-48.4]</td>
<td>25% (5) [9-49]</td>
</tr>
<tr>
<td>mDOR (central radiology), months [95% CI]</td>
<td>NE [NE, NE]</td>
<td>7.3 [7.2-NE]</td>
<td>10.2 [4.2-NE]</td>
<td>NR</td>
</tr>
<tr>
<td>CBR (central radiology), % (n) [95% CI]</td>
<td>96% (54) [88-100]</td>
<td>40% (44) [31.1-50.2]</td>
<td>70% (16) [47.1-86.8]</td>
<td>NR</td>
</tr>
<tr>
<td>mPFS (central radiology), months [95% CI]</td>
<td>NE [NE, NE]</td>
<td>3.7 [3.5-5.6]</td>
<td>8.6 [5.6-14.7]</td>
<td>NR</td>
</tr>
<tr>
<td>mPFS (investigator), months [95% CI]</td>
<td>22.8 [20.8-28.4]</td>
<td>5.5 [3.8-6.8]</td>
<td>10.2 [5.7-NE]</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Benchmarks**

- **PDGFRα D842V**
  - Approved agents:
    - ORR ~0%
    - mPFS ~3 mo
    - mOS ~15 mo

- **4L**
  - Imatinib re-treatment:
    - ORR ~0%
    - PFS 1.8 mo

- **3L**
  - Regorafenib:
    - ORR ~5%
    - PFS 4.8 mo

- **2L**
  - Sunitinib:
    - ORR ~7%
    - PFS 6 mo

NR, not reported; mPFS, median progression-free survival; mOS, median overall survival.

- ORR is not an endpoint for 2L but is early signal readout.
Avapritinib has the potential to change GIST treatment paradigms

- Phase 1 NAVIGATOR study demonstrates favorable tolerability and encouraging clinical activity across lines of therapy
  - Most AEs were grade 1 or 2, with manageable on-target toxicity
  - Important efficacy in PDGFRα D842V GIST and refractory, ≥4L GIST supports regulatory filing
  - Encouraging activity in 3L/4L regorafenib-naïve GIST indicates the potential for a favorable outcome in the ongoing randomized Phase 3 VOYAGER study
  - Mutational profiling analyses and promising 2L data provide strong rationale for genotype-selected 2L study
Acknowledgments

We would like to thank the participating patients, their families, all study co-investigators, and research coordinators at the following institutions:

• OHSU Knight Cancer Institute
• Fox Chase Cancer Center
• Royal Marsden Hospital/Institute of Cancer Research
• University of Duisburg-Essen
• Asan Medical Centre
• University Hospitals Leuven
• Erasmus MC Cancer Institute
• Vall d’Hebron Institute of Oncology
• Centre Leon Berard
• Institut Gustave Roussy
• Memorial Sloan Kettering Cancer Center
• Maria Sklodowska-Curie Institute – Oncology Center
• University of Miami Sylvester Comprehensive Cancer Center
• MD Anderson Cancer Center
• Sarcoma Oncology Centre
• Dana-Farber Cancer Institute

Editorial and medical writing support were provided by Lauren Fink, PhD, of Cello Health Communications, and were funded by Blueprint Medicines.
Ongoing and planned avapritinib clinical trials in patients with GIST

**NAVIGATOR**

- Phase 1
- Advanced GIST
- Dose Escalation
- RP2D
- 3L+ (n=100; fully enrolled)
- PDGFRα D842V (n=50)
- 2L (n=50)

- Primary endpoints: ORR, safety
- Currently enrolling expansion

**VOYAGER**

- Global Phase 3
- 3L advanced GIST
- Randomized
- Avapritinib (n=230)
- Regorafenib (n=230)

RP2D, recommended part 2 dose.
Concept 3: All approved TKIs used for the treatment of GIST are competitive ATP inhibitors
Concept 3: 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 3: Avapritinib and Imatinib bind in the ATP binding site
Concept 3: Active KIT requires ATP binding and activation loop in the correct position

$X = \text{Imatinib or other TKI}$
Strategies to inhibit KIT

• Block ATP binding
  – Class = competitive ATP inhibitors
  – Examples: imatinib, sunitinib, regorafenib, avapritinib (BLU-285)

• Prevent activation loop from moving into the kinase active position
  – Class = switch pocket inhibitor
  – Example: ripretinib (DCC-2618)
Inactive KIT Structure

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 Inhibitors like DCC-2618 Lock KIT into an Inactive Conformation

Switch pocket inhibitors represent a new class of KIT inhibitors
INITIAL RESULTS OF PHASE 1 STUDY OF DCC-2618, A BROAD-SPECTRUM KIT AND PDGFRα INHIBITOR, IN PATIENTS (PTS) WITH GASTROINTESTINAL STROMAL TUMOR (GIST) BY NUMBER OF PRIOR REGIMENS.

S George, M Heinrich, P Chi, A Abdul Razak, M von Mehren, M Gordon, K Ganjoo, N Somaiah, J Trent, J Rodon, K Shi, R Ruiz-Soto, O Rosen, F Janku

Proffered Paper Session - Sarcoma
Publication number 1603O

19 October 2018
RATIONALE FOR DCC-2618 STUDY

- Activity regardless whether primary mutation is in KIT Exon 9, Exon 11, or Exon 17
  - IC₅₀ for KIT Exon 11 deletion 3 nM, IC₅₀ 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
DCC-2618 Results Provided Encouraging Efficacy across all Lines of Treatment ≥100 mg/d (n=178)

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Objective Response Rate(^{(1)})</th>
<th>Disease Control Rate @ 3 Months</th>
<th>Median Progression Free Survival (mPFS)</th>
<th>Censored Patients for mPFS</th>
<th>Median Treatment Duration(^{(4)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(^{nd}) Line</td>
<td>18%(^{(2)}) (7/38)</td>
<td>79%</td>
<td>42 weeks (24, NE)</td>
<td>58%</td>
<td>48 weeks (31, NE)</td>
</tr>
<tr>
<td>(n=38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3(^{rd}) Line</td>
<td>24% (7/29)</td>
<td>83%</td>
<td>40 weeks (24, NE)</td>
<td>52%</td>
<td>NR (36, NE)</td>
</tr>
<tr>
<td>(n=29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4(^{th}) Line</td>
<td>9% (10/106)(^{(3)})</td>
<td>66%</td>
<td>24 weeks (16, 30)</td>
<td>35%</td>
<td>28 weeks (22, 47)</td>
</tr>
<tr>
<td>(n=111)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd &amp; 3rd Line (n=67)</td>
<td>21%(^{(2)}) (14/67)</td>
<td>81%</td>
<td>40 weeks (24, NE)</td>
<td>55%</td>
<td>52 weeks (36, NE)</td>
</tr>
</tbody>
</table>

Notes: (1) Includes 9 unconfirmed responses in 2\(^{nd}\) line (n=1), 3\(^{rd}\) line (n=3) and ≥4\(^{th}\) line (n=5); (2) Does not reflect 1 PR reported after cut off date; (3) Excludes 5 patients due to due to missing data at the time of data cut off (n=2), lack of first tumor assessment (n=1), withdrawal of consent prior to first assessment (n=1) and unrelated death at C1D4 prior to first assessment (n=1); (4) Includes 46 patients who elected for intra-patient dose escalation.
DCC-2618 – Treatment Emergent Adverse Events (TEAE) in >10% of GIST Patients at >100 mg/d (n=178)

Out of 178 patients treated with DCC-2618 at >100 mg/d

• 24 (14%) experienced dose reductions due to TEAE
• 19 (11%) experienced treatment discontinuations due to TEAE
• Clinically asymptomatic lipase elevations most frequent G3 TEAE
A Phase 3, INterVentional, Double-Blind Study to Assess Safety and Efficacy of DCC-2618 In Patients with Advanced c-KIT/PDGFRA Gastrointestinal Stromal Tumor Who Have Received Prior Treatment with Imatinib, Sunitinib, and Regorafenib

invictus Study - Phase 3 Trial Design
Enrollment completed October 2018!!

Primary endpoint PFS
The primary endpoint in this pivotal Phase 3 trial in second-line GIST will 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, patients were enrolled who progressed on or are intolerant to imatinib, comparing DCC-2618 against sunitinib.
Summary

- Avapritinib and Ripretinib are novel potent KIT inhibitors with unprecedented activity against KIT exon 17 mutations
- Avapritinib is extremely active against PDGFRA D842V mutant kinase
- Both drugs appear safe, tolerable and have promising activity and have moved from dose-escalation to dose-expansion phase to multiple phase 3 studies
- Based on results to date, we expect that both agents will be FDA-approved in 2020
GIST: 1998

**Molecular Classification**
- Unclassified 100%

**Research**
- New pathology tests to diagnose GIST developed

**Treatment**
- No known effective medical treatments for advanced disease
- Median overall survival for advanced disease 1-1.5 years
GIST: 2019

Molecular Classification

- **KIT mutant** 77.1%
- **PDGFRA mutant** 10.1%
- **SDH deficient** 10.0%
- **BRAF mutant** 1.5%
- **RAS mutant** 0.1%
- **NF1-related** 0.1%
- **RTK translocation** 0.1%
- **Unclassified** 1.0%

**Exons**
- **Exon 9**
- **Exon 11**
- **Exon 13**
- **Exon 17**
- **Exon 18**

**Drugs**
- **Imatinib**
- **Sunitinib**
- **Regorafenib**
- **Ripretinib**
- **Avapritinib**
- **Larotrectinib**
- **NTRK3-fusion**
- **Dabrafenib**
- **Vemurafenib**
- **Avapritinib**

**Gene Mutations**
- **D842V**
- **Other Exon 18**
- **Exon 14**
- **Exon 12**
- **NTRK3-fusion**
Real Estate: “location, location, location”
GIST: “mutation, mutation, mutation”
Advanced GIST: Improved Survival in the Precision Medicine Era

Overall Survival

- Pre-2000: Median 1.5 years
- 2000-2019: Median 7.3 years

Survival (%) vs Years
Available GIST Studies for 2019
OHSU Knight Cancer Institute

- Third-line avapritinib [BLU-285] vs. regorafenib, randomized phase 3 study (Voyager)
- Now open: second-line DCC-2618 vs. sunitinib (Intrigue)
- Opening later in 2019: second line avapritinib vs. sunitinib study (ctDNA mutation testing to determine patient eligibility)
- Now open: compassionate use ripretinib, expanded access avapritinib
- Contact my study nurse (Tracy) at walkertr@ohsu.edu or 503-346-1183 if you are interested in being considered for these studies
Acknowledgements

- Blueprint Medicines for sharing slides and data
- Deciphera Pharmaceuticals for sharing slides and data
- Patients, families, investigators, and study team support members who participated in the ongoing BLU-285 and DCC-2618 studies
- LRG for their support of our research over the past 10+ years
It takes a village, or a small city…