2008-2018

Ten Years of Advancements in GIST Research, Therapy & Survival

Dr. Michael Heinrich, M.D.
GSI Annual Summit Conference
September 2018
Overview

• Advances in GIST biology/pathology
• Update on front-line imatinib
• Adjuvant therapy and mutation status
• Current treatment approaches for imatinib-resistant GIST
• The next generation of GIST treatments
Not all GISTs are the Same

- GIST represent a collection of cancers linked by a common histology and presumed shared cell of origin (ICC)
- Most GIST are driven by a mutant kinase
- The type of underlying mutation(s) in a given patient’s GIST significantly impacts treatment response and potential mechanisms of acquired resistance
Molecular Classification of GIST 2008
Molecular Classification of GIST 2018
Molecular Classification of GIST 2018
“No subgroup left behind”
Precision Therapy of NTRK3-Translocated GIST

Shi et al., Journal of Translational Medicine, 2016
Real Estate: “location, location, location”
GIST: “mutation, mutation, mutation”
Front-line Therapy of Advanced Disease
• With a median follow-up of 34 months, median survival has not been reached

Phase 3 Front-line Imatinib for Treatment of Advanced/Metastatic GIST

A: Heinrich et al. JAMA Oncology 2017
B: Casali, et. al, Journal of Clinical Oncology 2017
Phase 3 Studies of Front-line Imatinib for Advanced GIST

S0033 (US-Canada)
- 10 year estimate of overall survival: 23%
- 10 year estimate of PFS: 7%

EORTC, Italy, Australia
- 10 year estimate of overall survival: ~20%
- 10 year estimate of PFS: ~9%

S0033: Heinrich et al. JAMA Oncology 2017
EORTC: Casali, et. al, Journal of Clinical Oncology 2017
Dosing Recommendations for KIT-mutant GIST from Phase 3 Studies

- Exon 11 (59.6%)
- Exon 9 (9.1%)
- Exon 13 (1.9%)
- Exon 17 (0.8%)

- Imatinib 400 mg
- Imatinib 800 mg
Adjuvant Therapy
1 Yr vs 3 Yrs of Adjuvant Imatinib: SSGXVIII

- Pts with resection of primary GIST and high risk of recurrence

- Primary endpoint
  - RFS

- Secondary endpoints
  - AEs and OS
  - High risk of recurrence: the “rule of 10”

Joensuu. ASCO. 2011 (abstr LBA 1).
SSGXVIII: Intention to Treat Analysis

A

Median follow up 90 months

Recurrence-Free Survival (%)

Time Since Random Assignment (years)

3 years of imatinib
1 year of imatinib
HR, 0.60; 95% CI, 0.44 to 0.81
P < .001

C

Overall Survival (%)

Time Since Random Assignment (years)

3 years of imatinib
1 year of imatinib
HR, 0.60; 95% CI, 0.37 to 0.97
P = .036

Joensuu et al., JCO 2016
Genotyping and Patient Selection for Adjuvant Imatinib Therapy

Recommendations

- Treat patients with KIT exon11-mutant GIST
- Consider high-dose imatinib for patients with KIT exon 9-mutant GIST
- No adjuvant therapy for patients with KIT/PDGFRA WT GIST
- No adjuvant therapy for patients with PDGFRA D842V-mutant GIST

Joensuu et al., JCO 2016
Management of Imatinib-resistant Disease
Sunitinib in Patients With Imatinib-Refractory GIST: Time to Tumor Progression

Phase III Trial of Regorafenib in Advanced GIST

- Primary endpoint: PFS
- Secondary endpoints: OS, TTP, RR, and DOR

Pts with metastatic or unresectable GIST after progression on imatinib and sunitinib

Phase III Trial of Regorafenib in Advanced GIST

PFS 4.9 months
0.9 months

HR 0.27, 95% CI 0.19–0.39; p<0.0001

Demetri et al., The Lancet 2013 381, 295-302 DOI: (10.1016/S0140-6736(12)61857-1)
First line:

IMATINIB

Second line:

SUNITINIB

Third line:

REGORAFENIB

Heinrich et al. JAMA (2017)


Demetri et al. Lancet (2013)
Treatment of Imatinib-resistant GIST: The Next Generation
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. To date, all approved TKIs used for the treatment of GIST are competitive ATP inhibitors. To date, all approved TKIs used for the treatment of GIST bind to the inactive kinase structure. 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/PDGFRα

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
Concept 3

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

- Exon 8
- Exon 9
- Exon 11
- Exon 13

Protein Domains

- Ligand binding
- JM
- ATP binding
- Activation Loop
- Membrane

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: Red
- SU: Green
- REG: Yellow

- NR: Not reported

Legend:
- Red: Resistant
- Intermediate
- Green: Sensitive
- Yellow: Not reported
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
Clinical activity of Avapritinib (BLU-285) in advanced GIST

Michael Heinrich, Robin Jones, Margaret von Mehren, Patrick Schoffski, Sebastian Bauer, Olivier Mir, Philippe Cassier, Ferry Eskens, Hongliang Shi, Terri Alvarez-Diez, Oleg Schmidt-Kittler, Mary Ellen Healy, Beni Wolf, Suzanne George

1Oregon Health & Sciences University, Oregon, USA; 2Royal Marsden Hospital/Institute of Cancer Research, London, UK; 3Fox Chase Cancer Center, Pennsylvania, USA; 4Leuven Cancer Institute, Leuven, Belgium; 5University of Essen, Essen, Germany; 6Institut Gustave Roussy, Paris, France; 7Centre Leon Berard, Lyon, France; 8Erasmus MC Cancer Institute, Rotterdam, Netherlands; 9Blueprint Medicines Corporation, Massachusetts, USA; 10Dana-Farber Cancer Institute, Massachusetts, USA

CTOS 2017  Presented by: Dr. Michael Heinrich
Avapritinib is a potent type 1 KIT/PDGFRα inhibitor that binds to the active conformation of the kinase.

Imatinib
Activation loop open

Avapritinib
Activation loop open

Avapritinib
Avapritinib: highly potent and selective targeting of KIT/PDGFRα mutants

- High kinome selectivity*
- Binds active conformation

*Image reproduced courtesy of CSTI (www.cellsignal.com)
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)
Demography and baseline patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients, N=116</th>
</tr>
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<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>62 (25–85)</td>
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</table>

<table>
<thead>
<tr>
<th>GIST subtype*</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>KIT mutant</td>
<td>76 (66)</td>
</tr>
<tr>
<td>PDGFRα D842 mutant</td>
<td>37 (32)</td>
</tr>
<tr>
<td>PDGFRα Exon 14 (N659K) mutant</td>
<td>2 (2)</td>
</tr>
<tr>
<td>KIT &amp; PDGFRα WT</td>
<td>1 (1)</td>
</tr>
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</table>

| Metastatic disease          | 107 (92)            |

<table>
<thead>
<tr>
<th>Largest target lesion size (cm)</th>
<th>n (%)</th>
<th>PDGFRα</th>
<th>KIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>27 (23)</td>
<td>1 (0–6)</td>
<td>4 (2–11)</td>
</tr>
<tr>
<td>&gt;5–≤10</td>
<td>42 (36)</td>
<td>11 (28)</td>
<td>67 (87)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>46 (40)</td>
<td>8 (21)</td>
<td>64 (83)</td>
</tr>
<tr>
<td>pending</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. prior kinase inhibitors</th>
<th>PDGFRα</th>
<th>KIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>1 (0–6)</td>
<td>4 (2–11)</td>
</tr>
<tr>
<td>≥3</td>
<td>11 (28)</td>
<td>67 (87)</td>
</tr>
<tr>
<td>Prior regorafenib</td>
<td>8 (21)</td>
<td>64 (83)</td>
</tr>
</tbody>
</table>

* Data are preliminary and based on a cut off date of 11 Oct 2017
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
Prolonged PFS in heavily pre-treated KIT-mutant GIST (central radiology review)

- No approved therapies beyond third-line regorafenib
  - ORR ~0% with imatinib re-treatment in ≥third-line

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

**Best response (N=30)* | Choi Criteria n (%) | RECIST 1.1 n (%)**
--- | --- | ---
PR | 16 (53) | 5 (17)^
SD | 7 (23) | 18 (60)
DCR (PR+SD) | 23 (77) | 23 (77)
PD | 7 (23) | 7 (23)

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


Remarkable activity in PDGFRα D842-mutant GIST (central radiology review)

N=31 patients across all dose levels

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

Mutation status*

PD
SD
PR
CR

31 of 31 (100%) patients with tumor shrinkage

* per archival tumor and ctDNA

PDGFRα D842-mutation is in the activation loop!
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>
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</table>

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

- ORR ~0% with currently approved agents³,⁴

Avapritinib has potent, clinically important activity in GIST

• Remarkable response rates and prolonged PFS in PDGFRα-driven GIST may support expedited path for FDA approval
• Response rate and prolonged PFS in heavily pretreated KIT-driven indicated important activity in patients with drug-resistant KIT-mutant GIST
• Based on these encouraging data:
  – Second-line expansion cohort has been added and is enrolling
  – Phase 3 randomized study comparing avapritinib to regorafenib in third-line GIST has started (first patient, May 2018)
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.
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

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.
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 \( \geq 100 \text{ mg/d} \) 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).

\( \text{mPFS is not reached} \)

All patients treated at \( \geq 100 \text{mg daily (N=49)} \)

All patients treated at <100mg daily (N=4)

mPFS is 15.2 weeks (CI 4.4 to 24)

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>49</th>
<th>45</th>
<th>32</th>
<th>21</th>
<th>19</th>
<th>18</th>
<th>15</th>
<th>9</th>
<th>8</th>
<th>8</th>
<th>5</th>
<th>2</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 100 \text{mg} )</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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\( \text{Time (weeks)} \)
A Phase 3, INter Ventional, Double-Blind Study to Assess Safety and Efficacy of DCC-2618 In Patients with Advanced c-KIT/PDGFRα Gastrointestinal Stromal TumorS WHO HAVE RECEIVED PRIOR TREATMENT WITH Imatinib, Sunitinib, and Regorafenib

invictus Study - Phase 3 Trial Design

Primary endpoint PFS
invictus

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 the pivotal Phase 3 trial in second-line GIST, we will 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.
Avapritinib and DCC-2618 Clinical Studies

- Avapritinib and DCC-2618 are novel potent KIT inhibitors with unprecedented activity against KIT exon 17 mutations.

- Both drugs appear safe and tolerable and have moved from dose-escalation to dose-expansion phase and more recently to open or planned phase 3 studies.

- Currently there are two open phase 3 studies:
  - regorafenib vs. avapritinib (third- or fourth-line).
  - DCC-2618 vs. placebo (fourth-line or later).

- Coming soon: phase 3 of DCC-2618 vs. sunitinib (second-line).

- Contact my study nurse (Tracy) at walkertr@ohsu.edu or 503-346-1183 if you are interested in being considered for any of these studies.
Summary

- In the past 10 years, there have been tremendous advances in our understanding of GIST biology and pathology
- “Mutation, mutation, mutation”
- Exciting new drugs are being developed and seem poised to transform our treatment of imatinib-resistant GIST
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 avapritinib and DCC-2618 studies