New Approaches to Treatment of Gastrointestinal Stromal Tumor

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Director Sarcoma Oncology
Associate Director for Clinical Research
Professor of Medical Oncology
Outline

• The GIST Basics
• Approved treatments
• New approaches
THE GIST BASICS
Coined the term **Gastrointestinal stromal tumors**

Some **smooth muscle tumors of the GI tract**
“expressed **neural crest antigens** such as S-100 protein and neuron-specific enolase”
Most common GI sarcoma

- Arises from Interstitial cell of Cajal or precursor cell
- 0.2% of all GI tumors, but 80% of GI sarcomas
- Can arise anywhere along GI tract (stomach>small intestine>others)

Most commonly diagnosed in the 40-60 year age group

- Similar male/female incidence, although some reports suggest a slightly higher incidence in men

GIST have an incidence of 14.5 per million annually and a prevalence of 129 per million

Time to Progression on Chemotherapy

![Graph showing time to progression on chemotherapy with probability on the y-axis and time to progression in months on the x-axis.](image)

Courtesy of Demetri, G
Survival correlates with Resection Status

<table>
<thead>
<tr>
<th>Status</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor, completely resected</td>
<td>96</td>
</tr>
<tr>
<td>Primary tumor, <em>incompletely</em> resected</td>
<td>26</td>
</tr>
<tr>
<td>Recurrent disease, completely resected</td>
<td>49</td>
</tr>
<tr>
<td>Recurrent disease, <em>incompletely</em> resected</td>
<td>8</td>
</tr>
<tr>
<td>Metastatic disease, completely resected</td>
<td>39</td>
</tr>
<tr>
<td>Metastatic disease, <em>incompletely</em> resected</td>
<td>11</td>
</tr>
</tbody>
</table>

Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhsa Shinomura, Yukihiko Kitamura†

279:577-580, 1998

• 5 of 6 GIST had mutations in KIT gene
• Mutant forms of KIT are constitutively active
• Proposed that GIST may originate from ICCs
• Studies in knock-in mice with KIT mutations
  – Demonstrated that constitutive KIT signaling is sufficient to induce GIST
  – Parallel with the pathology seen with familial KIT mutations, eg.
    mastocytosis
Frequency of Mutation in $KIT$ and $PDGFRA$

Tarn & Godwin, *Curr Treat Options Oncol*, 2005
Ligand-dependent Activation of Wild-type KIT

Membrane

Cytoplasm

Women’s Cancer Program
Ligand-independent Activation of Mutant KIT

In frame mutation of exon 11

Membrane
Cytoplasm
APPROVED AGENTS
Mazur and Clark recognize GIST

KIT ex.11 Mutation

1983

1998

STI-571 for 1st GIST patient

2000

FDA approves imatinib

2002

FDA approves sunitinib

2006

FDA approves regorafenib

2013

FDA approves larotrectinib

2018
Identified in a screen for tyrosine kinase inhibitors
Synthesized compound was optimized for inhibition for specific kinases
Competitively inhibits the ATP-binding site of the enzyme and leads to inhibition of phosphorylation of downstream signals
Has activity against KIT and PDGFRA mutations

Murphy EA et al. PNAS 2010; 107: 4299–4304
Ligand-independent Activation of Mutant KIT

In frame mutation of exon 11

Membrane

Cytoplasm

Imatinib
Figure 2. PET Studies with $^{18}$FFluorodeoxyglucose as the Tracer.

Before STI571 therapy (Panel A), there were multiple metastases in the liver and upper abdomen. There was also marked retention of $^{18}$Ffluorodeoxyglucose in the right renal pelvis and ureter, a finding indicative of hydronephrosis. After four weeks of treatment (Panel B), there was no abnormal uptake of tracer in the liver or right kidney.

### Response data for Imatinib

<table>
<thead>
<tr>
<th>Dose</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>NE/unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg daily</td>
<td>0-5</td>
<td>40-68.5</td>
<td>13.7-32</td>
<td>12-15.1</td>
<td>2.7-10</td>
</tr>
<tr>
<td>300 mg BID</td>
<td>2.7</td>
<td>64.9</td>
<td>17.6</td>
<td>8.1</td>
<td>6.8</td>
</tr>
<tr>
<td>400 mg BID</td>
<td>3-6</td>
<td>42-48</td>
<td>22-32</td>
<td>10-9</td>
<td>5-15</td>
</tr>
<tr>
<td>500 mg BID</td>
<td>0</td>
<td>57</td>
<td>29</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

Blanke CD et al. JCO, 2008.
### Functional Resistance: Phase III data

<table>
<thead>
<tr>
<th>Response</th>
<th>Exon 9</th>
<th>Exon 11</th>
<th>Exon 13</th>
<th>Exon 17</th>
<th>PDGFRA mutants</th>
<th>Wild type</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>5.17%</td>
<td>6.45%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.04%</td>
</tr>
<tr>
<td>PR</td>
<td>17</td>
<td>152</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>12</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>29.31%</td>
<td>61.29%</td>
<td>66.67%</td>
<td>66.67%</td>
<td>30.00%</td>
<td>23.08%</td>
<td>50.40%</td>
</tr>
<tr>
<td>NC</td>
<td>27</td>
<td>63</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>26</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>46.55%</td>
<td>25.40%</td>
<td>33.33%</td>
<td>33.33%</td>
<td>30.00%</td>
<td>50.00%</td>
<td>32.36%</td>
</tr>
<tr>
<td>PD</td>
<td>10</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>17.24%</td>
<td>3.23%</td>
<td>-</td>
<td>-</td>
<td>40.00%</td>
<td>19.23%</td>
<td>8.49%</td>
</tr>
<tr>
<td>Uneval.</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>1.72%</td>
<td>3.63%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.69%</td>
<td>3.71%</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>248</td>
<td>6</td>
<td>3</td>
<td>10</td>
<td>52</td>
<td>377</td>
</tr>
</tbody>
</table>

High Dose Imatinib improves PFS for Exon 9

Secondary Resistance: Clonal Evolution

Baseline: *KIT* exon 9 mutation

1 month on imatinib

Response in GIST followed by SECONDARY resistance

9 months on imatinib

E9 + mutation #1

E9 + mutation #2

E9 + mutation #3

Demetri et al ASCO 2013
### Sunitinib: Multi-targeted Receptor Tyrosine Kinase Inhibitor

**Enzymatic $K_i$ (µM)**

<table>
<thead>
<tr>
<th>Protein</th>
<th>PDGFR-β</th>
<th>VEGFR-2</th>
<th>VEGFR-3</th>
<th>FGFR1</th>
<th>EGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.008</td>
<td>0.009</td>
<td>0.017</td>
<td>0.83</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

**Cellular $IC_{50}$ (µM)**

<table>
<thead>
<tr>
<th>Protein</th>
<th>PDGFR-β</th>
<th>VEGFR-2</th>
<th>KIT</th>
<th>FLT3 (WT)</th>
<th>EGFR</th>
<th>MET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.008</td>
<td>0.009</td>
<td>0.01</td>
<td>0.25</td>
<td>8.9</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*Receptor phosphorylation

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Sunitinib Improves PFS & OS Compared to Placebo

Sunitinib Phase I/II: OS based on 1° Mutation

Women’s Cancer Program

Median (95% CI)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT WT (N=9)</td>
<td>29.2 months (19.8, NA)</td>
</tr>
<tr>
<td>KIT exon 9 (N=19)</td>
<td>12.7 months (7.5, NA)</td>
</tr>
<tr>
<td>KIT exon 11 (N=42)</td>
<td>12.2 months (12.2, NA)</td>
</tr>
</tbody>
</table>

KIT WT vs exon 11: P = 0.005
KIT exon 9 vs 11: P = 0.01

NA = not available; WT = wild type

Effect of secondary exon 11 Mutations

Site of Secondary Mutation

A

V654A, D816H

 progression on Sunitinib

Progression Free Survival

Heinrich et al. J Clin Oncol. 2006
Regorafenib (BAY 73-4506)

Biochemical activity

<table>
<thead>
<tr>
<th>Percent control</th>
<th>IC$_{50}$ (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>7</td>
</tr>
<tr>
<td>0.1%</td>
<td>13</td>
</tr>
<tr>
<td>0.1-1%</td>
<td>4</td>
</tr>
<tr>
<td>1-5%</td>
<td>22</td>
</tr>
<tr>
<td>5-10%</td>
<td>1.5</td>
</tr>
<tr>
<td>10-35%</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>FGFR1</td>
</tr>
</tbody>
</table>


Demetri et al. ASCO 2012
Regorafenib significantly improved PFS vs placebo (p<0.0001); primary endpoint met

Demetri et al. ASCO 2012
### Benefit of Regorafenib based upon Primary Mutation

**Progression-free survival (PFS)**

<table>
<thead>
<tr>
<th>Mutation status</th>
<th>Placebo (N=15)</th>
<th>Regorafenib (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT exon 11 mutation</td>
<td>1.1</td>
<td>5.6</td>
</tr>
<tr>
<td>KIT exon 9 mutation</td>
<td>0.9</td>
<td>5.4</td>
</tr>
</tbody>
</table>

**Phase II study of Regorafenib**

<table>
<thead>
<tr>
<th>SDH-deficient tumors (N=6)</th>
<th>PR: 33.3</th>
<th>SD: 66.7</th>
<th>PFS (median months)</th>
</tr>
</thead>
</table>

Demetri et al. ASCO 2012  
**Primary Mutations**

- **Exon 9**: 12%
  - K642E

- **Exon 11**: 70%

- **Exon 13**: 1%
  - V654A
  - T670I
  - D816A/G/H/V
  - D820A/E/G/Y
  - N822H/K
  - Y823D

- **Exon 17**: 1%
  - N822H/K, D820Y
  - A829P

**Secondary Mutations**

- **Exon 14**: T670I
- **Exon 17**: D816A/G/H/V, D820A/E/G/Y, N822H/K, Y823D, A829P

**Drug Sensitivity**

- **IM**: Resistant
- **SU**: Intermediate
- **REG**: Sensitive
- **NR**: Not reported

**Protein Domain**

- Ligand binding
- Membrane
- ATP binding
- Activation Loop

**Heinrich et al. ASCO, 2014**
Summary

Primary resistance

1L imatinib
- ORR ~60%
- PFS 19 mo

2L sunitinib
- ORR ~7%
- PFS 6 mo

Secondary resistance

3L regorafenib
- ORR ~5%
- PFS 4.8 mo

4L no approved therapy
- ORR ~0%
- PFS ≤1.8 mo*

Prevalence\(^7,8\)

<table>
<thead>
<tr>
<th>Resistance mutation</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGFRα D842V</td>
<td>~5–6%</td>
<td>Rare</td>
</tr>
<tr>
<td>KIT exon 17/18</td>
<td>~1%</td>
<td>2L ~23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3L ~90%</td>
</tr>
<tr>
<td>KIT exon 13</td>
<td>N/A</td>
<td>2L ~40%</td>
</tr>
</tbody>
</table>

Primary and secondary mutations cause therapeutic resistance
Approved agents are ineffective against PDGFRα D842V

Heinrich MC et al. ASCO 2017
NEW APPROACHES
Avapritinib (BLU-285): potent against KIT/PDGFRα GIST mutants

- High kinome selectivity
- Binds active conformation

Heinrich MC et al. ASCO 2017
**Key objectives**
- Part 1: Maximal tolerated dose, safety, pharmacokinetics, ctDNA analyses, anti-tumor activity
- Part 2: response rate, duration of response, safety

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

- Starting dose: 300 mg daily
- If treatment tolerated for 2 cycles, dose escalation to 400 mg daily allowed at the discretion of the treating MD

Heinrich MC et al. ASCO 2017
### Baseline patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients, N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>61 (25–85)</td>
</tr>
<tr>
<td><strong>GIST subtype</strong></td>
<td></td>
</tr>
<tr>
<td>KIT mutant</td>
<td>40 (56)</td>
</tr>
<tr>
<td>PDGFRα mutant</td>
<td>32 (44)</td>
</tr>
<tr>
<td><strong>Metastatic disease</strong></td>
<td>69 (96)</td>
</tr>
<tr>
<td><strong>Largest target lesion size (cm)</strong></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>18 (25)</td>
</tr>
<tr>
<td>&gt;5–≤10</td>
<td>25 (35)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>29 (40)</td>
</tr>
<tr>
<td><strong>No. prior kinase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>PDGFRα</td>
</tr>
<tr>
<td></td>
<td>1.5 (0–6)</td>
</tr>
<tr>
<td></td>
<td>10 (31)</td>
</tr>
<tr>
<td>Prior regorafenib</td>
<td>8 (25)</td>
</tr>
<tr>
<td></td>
<td>KIT</td>
</tr>
<tr>
<td></td>
<td>4 (2–11)</td>
</tr>
<tr>
<td></td>
<td>36 (90)</td>
</tr>
<tr>
<td></td>
<td>34 (85)</td>
</tr>
</tbody>
</table>

Data are preliminary and based on a cut off date of 28 April 2017
Heinrich MC et al. ASCO 2017
Response in PDGFRα D842V-mutant GIST

- Ongoing at cycle 5
- Prior imatinib and sunitinib
- Partial response, size decreased by 63%

- Ongoing at cycle 3
- Prior imatinib
- Partial response, size decreased by 85%

Heinrich MC et al. ASCO 2017
Tumor regression across all dose levels in PDGFRα D842-mutant GIST

Heinrich MC et al. ASCO 2017
High response rate and prolonged PFS in PDGFRα D842-mutant GIST

<table>
<thead>
<tr>
<th>Best response (N=25)</th>
<th>Choi Criteria n (%)</th>
<th>RECIST 1.1 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>25 (100%)</td>
<td>15* (60%)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>DCR (PR + SD)</td>
<td>25 (100%)</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Approved agents are ineffective: ORR ~0%

Heinrich MC et al. ASCO 2017
Radiographic response in heavily pre-treated KIT-mutant GIST

BLU-285 300 mg (dose escalation)

- Ongoing at cycle 12
- 6 prior TKIs; exon 11, 13, and 18 mutations
- CHOI

BLU-285 400 mg (dose expansion)

- Ongoing at cycle 4
- 5 prior TKIs; 1° exon 11 mutation; ctDNA pending
- CHOI

Heinrich MC et al. ASCO 2017
Dose-dependent tumor reduction across multiple KIT genotypes

*ctDNA results pending

**per archival tumor and ctDNA
Important clinical activity in heavily pre-treated KIT-mutant GIST

Beyond third-line regorafenib there are no approved therapies
Imatinib re-treatment in ≥third-line GIST\(^3\)
ORR ~0%

Heinrich MC et al. ASCO 2017
### Adverse events (AE) associated with BLU-285

**Safety population, N=72**

<table>
<thead>
<tr>
<th>AEs in ≥20% of patients</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>43 (60)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (53)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30 (42)</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>26 (36)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (33)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>22 (31)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Anemia</td>
<td>18 (25)</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (22)</td>
</tr>
</tbody>
</table>

Sever toxicities thought to be treatment-related:
- Fatigue [8%]
- Hypophosphatemia [6%]
- Anemia [4%]
  - Nausea, vomiting, hyperbilirubinemia [3% each])

DLT in 2 patients at 600 mg: 1 G2 hyperbilirubinemia; 1 G2 rash, hypertension, memory impairment

Cognitive effects: includes issues with concentration, memory, mood changes

Recommendations for dose interruption and consideration of dose reduction

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Heinrich MC et al. ASCO 2017
Heinrich MC et al. CTOS 2018
Voyager: Study of Avapritinib vs Regorafenib in Patients With Locally Advanced Unresectable or Metastatic GIST

- Randomized
- open label
- 1:1 ration

Avapritinib 300 mg daily continuously

Regorafenib 160 mg daily 3 weeks on, 1 week off

Continued Avapritinib 300 mg daily or discontinuation

Avapritinib 300 mg daily continuously

- Previously treated with imatinib and 1 or 2 other TKI’s
- Documented KIT/ PDGFRA mutation

Study endpoints: PFS based on independent radiology assessment
Secondary endpoints: Response rate, Overall Survival, Quality of Life, Time to tumor progression, Safety profile.
Blueprint filed a New Drug Application on 6/14/19 with U.S. Food and Drug Administration for avapritinib for the treatment of adult patients with PDGFRA Exon 18 mutant gastrointestinal stromal tumors (GIST), regardless of prior therapy, and fourth-line GIST.
Current Status

• Plans for trial in the second line setting compared with sunitinib

• Also establishing a compassionate use program at a variety of centers nation wide.
Study Design
ARO-002 was a dose-escalating study with 4 dosing cohorts to assess clinical benefit of crenolanib in patients with advanced GIST with PDGFRA D842V activating mutations.

Primary Objectives
- Response Rate

Secondary Objectives
- PFS
- Safety
- Pharmacokinetics

Study Schema
D842-related mutations and deletions in advanced GIST (N=20) → Crenolanib 200 mg QD 340 mg QD 140 mg BID 73.3 mg/m² TID → Treat until lack of clinical benefit, unacceptable toxicity, or withdrawal of consent

von Mehren et al., Proc. ASCO: 2016. abstract 11010
5/16 (31%) of patients with D842V mutated GIST derived clinical benefit from crenolanib treatment.

- 2 (13%) patients achieved a partial response.
- 3 (19%) patients achieved stable disease.

### Overall Response Rate

<table>
<thead>
<tr>
<th>Response</th>
<th># of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>2</td>
<td>13%</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>3</td>
<td>19%</td>
</tr>
<tr>
<td>Overall clinical benefit (CR+PR+SD)</td>
<td>5</td>
<td>31%</td>
</tr>
</tbody>
</table>

*Non-evaluable patients included:
- 3 patients off study prior to receiving 1 full cycle and
- 1 did not have recurrent GIST (aggressive fibromatosis).
Patient case: 62 year old female

- Patient achieved a partial remission at 140 mg BID

von Mehren et al., Proc. ASCO: 2016. abstract 11010
Current Status

- A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Trial of Crenolanib in Subjects with Advanced or Metastatic Gastrointestinal Stromal Tumors with a D842V Mutation in the PDGFRA Gene
Reprenitinib (DCC-2618) background

- Novel mechanism of action
- Preclinical broad range activity against GIST relevant KIT and PDGFRA primary and secondary mutations
- Also has activity against FLT-3, PDGFRB, KDR, TIE2 and FMS
Repretinib (DCC2618): Mechanism of Action

Type II switch control kinase inhibitor of KIT and PDGFRα
**Part 1: Dose Escalation**

- Key Objectives: MTD, recommended Phase 2 dose (RP2D), safety, tolerability, pharmacokinetics and anti-tumor activity (NCT# 02571036)
- Design: 3+3 design for Patients with advanced refractory cancers (KIT/PDGFRα mutated) with a focus on GIST
- Dose Levels tested: 20, 30, 50, 100, 150, and 200 mg BID; and 100, 150 and 250 mg QD - IPDE\(^1\) to 150mg BID permitted
- CT scans every 2 cycles
- ECOG 0-2; adequate end organ function
- MTD: not determined

**Part 2: Dose Expansion @ 150 mg QD (RP2D)**

- Various cohorts:
  - 3 GIST by line of therapy (2\(^{nd}\)-3\(^{rd}\), 4\(^{th}\), > 4\(^{th}\) line)
- Dose escalation n to 150mg BID permitted at RECIST progression
DCC-2618: PFS for doses ≥100 mg/d compared to <100 mg/d

- DCC-2618 is a potent pan-KIT and PDGFRα kinase switch control inhibitor active across a broad range of mutations.
- In non-clinical analyses, DCC-2618 showed activity against all initiation and resistance mutations tested.
- During the escalation stage of the First-In-Human Study, 150 mg QD was selected as the recommended dose for the Phase 1 expansion stage (NCT02571036).

![Graph showing progression-free survival](image)

Janku et al. ESMO, 2017
Women's Cancer Program

Waterfall Plot of KIT/PDGFRα GIST Patients, N=37

DCC-2618 Dose Assigned

- <100mg daily
- >=100mg daily

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

*66% increase in tumor size; #PR at RP2D

Janku et al. ESMO, 2017
Women’s Cancer Program

**cfDNA Pharmacodynamic Biomarker Demonstrates pan-KIT Activity**

(Best Response, N=19)

Enrolled patient population reveals broad range of KIT mutations

DCC-2618 leads to reductions in MAF in cfDNA across all exons associated with resistance

Treatment decisions were made based on disease control and not on changes in MAF

*Patient in first dose cohort, Patient represented with mixed histology

Janku et al. ESMO, 2017
### Baseline Characteristics GIST Patients at $\geq 100$ mg/d DCC-2618 (n=178)

<table>
<thead>
<tr>
<th></th>
<th>2nd Line (n=38)</th>
<th>3rd Line (n=29)</th>
<th>$\geq$ 4th Line (n=111)$^4$</th>
<th>Total (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Median (min, max)</strong></td>
<td>60 (32, 80)</td>
<td>64 (48, 82)</td>
<td>60 (27, 87)</td>
<td>61 (27, 87)</td>
</tr>
<tr>
<td><strong>ECOG PS 0-1</strong></td>
<td>38 (100%)</td>
<td>29 (100%)</td>
<td>108 (97%)</td>
<td>175 (98%)</td>
</tr>
<tr>
<td><strong>ECOG PS 2</strong></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td><strong>Primary Mutation$^1$ n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIT Exon 9</td>
<td>4 (11%)</td>
<td>8 (28%)</td>
<td>22 (20%)</td>
<td>34 (19%)</td>
</tr>
<tr>
<td>KIT Exon 11</td>
<td>31 (82%)</td>
<td>20 (69%)</td>
<td>71 (64%)</td>
<td>122 (69%)</td>
</tr>
<tr>
<td>Other KIT$^2$</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>12 (11%)$^3$</td>
<td>13 (7%)$^3$</td>
</tr>
<tr>
<td>PDGFR$\alpha$</td>
<td>3 (8%)</td>
<td>0 (%)</td>
<td>6 (5%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td><strong>Pts at RP2D (150 mg QD)</strong></td>
<td>32 (84%)</td>
<td>27 (93%)</td>
<td>83 (75%)</td>
<td>142 (80%)</td>
</tr>
</tbody>
</table>

Notes: (1) Primary mutation per local assessment; (2) KIT exon 13 (4), KIT exon 17 (5), not done (3); (3) Includes one SDH deficient patient; (4) Mean # is 4.63 (range 4-7).
### Objective Response Rate

- **2nd Line (n=38)**: 18% (7/38)
  - Disease Control Rate at 3 Months: 79%
  - Median Progression Free Survival (mPFS): 42 weeks (24, NE)
  - Censored Patients for mPFS: 58%
  - Median Treatment Duration: 48 weeks (31, NE)

- **3rd Line (n=29)**: 24% (7/29)
  - Disease Control Rate at 3 Months: 83%
  - Median Progression Free Survival (mPFS): 40 weeks (24, NE)
  - Censored Patients for mPFS: 52%
  - Median Treatment Duration: NR (36, NE)

- **≥4th Line (n=111)**: 9% (10/106)
  - Disease Control Rate at 3 Months: 66%
  - Median Progression Free Survival (mPFS): 24 weeks (16, 30)
  - Censored Patients for mPFS: 35%
  - Median Treatment Duration: 28 weeks (22, 47)

- **2nd & 3rd Line (n=67)**: 21% (14/67)
  - Disease Control Rate at 3 Months: 81%
  - Median Progression Free Survival (mPFS): 40 weeks (24, NE)
  - Censored Patients for mPFS: 55%
  - Median Treatment Duration: 52 weeks (36, NE)

### Notes
- (1) Includes 9 unconfirmed responses in 2nd line (n=1), 3rd line (n=3) and ≥4th 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.
mPFS by Line of Therapy for ≥100 mg/d DCC-2618 (n=178)

<table>
<thead>
<tr>
<th>Lines</th>
<th>N</th>
<th>mPFS</th>
<th>Number Censored</th>
<th>Active Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>38</td>
<td>42 weeks</td>
<td>22 (58%)</td>
<td>61%</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>40 weeks</td>
<td>15 (52%)</td>
<td>59%</td>
</tr>
<tr>
<td>4+</td>
<td>111</td>
<td>24 weeks</td>
<td>40 (36%)</td>
<td>44%</td>
</tr>
</tbody>
</table>

- DCC-2618 demonstrated prolonged progression free survival in a meaningful subset of patients across all lines of treatment
- Following progression, 63% (n=29) and 28% (n=13) of patients stayed on study for >8 and >16 weeks, respectively
Good Tolerability Allowed for Prolonged Treatment

2nd Line Patients (n=38)

>6 months: 17 pts (11 active)
>12 months: 3 pts (2 active)

3rd Line Patients (n=29)

>6 months: 20 pts (15 active)
>12 months: 4 pts (4 active)

Notes: (1) Includes 4 unconfirmed responses in 2nd line (n=1) and 3rd line (n=3); (2) Does not reflect 1 PR after cut off date; (3) Includes 14 patients who elected for intra-patient dose escalation.
Best Response by RECIST in 2<sup>nd</sup> & 3<sup>rd</sup> Line GIST Patients at ≥100 mg/d DCC-2618 (n=67)

2<sup>nd</sup> Line (n=38)
- 7/38 PRs<sup>(1)</sup> (18%) as of data cut off

3<sup>rd</sup> Line (n=29)
- 7/29 PRs<sup>(1)</sup> (24%) as of data cut off

2<sup>nd</sup> & 3<sup>rd</sup> Line (n=67)
- 14/67 PRs<sup>(1)</sup> (21%) as of data cut off

Notes: (1) Includes unconfirmed responses in 2<sup>nd</sup> line (n=1) and 3<sup>rd</sup> line (n=3).
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

Notes: (1) Treatment Emergent Adverse Events; (2) Palmar-plantar erythrodyssyesthesia syndrome was reported in 19 patients.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Ripretinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression Free Survival</td>
<td>4.1 weeks</td>
<td>27.6 weeks</td>
</tr>
<tr>
<td>Change in risk of disease progression or death</td>
<td></td>
<td>Decreased by 85% (HR of 0.15, p&lt;0.0001)</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>0.0%</td>
<td>9.4% (p-value=0.0504)</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>6.6 months</td>
<td>15.1 months (HR = 0.36, nominal p-value=0.0004)</td>
</tr>
<tr>
<td>Grade 3 or 4 treatment-emergent adverse events</td>
<td>44%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Based on the **positive INVICTUS data**, Deciphera expects to submit a **New Drug Application** to the U.S. Food and Drug Administration for ripretinib for the **treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib and regorafenib in the first quarter of 2020.**
Intrigue: A Phase 3, Interventional, Randomized, Multicenter, Open-Label Study of DCC-2618 vs Sunitinib in Patients with Advanced Gastrointestinal Stromal Tumors after Treatment with Imatinib

- Randomized
- open label
- 1:1 ration

Ripretinib 150 mg daily continuously

Study discontinuation for:
- disease progression,
- unacceptable toxicity
- withdrawal of consent

Sunitinib 50 mg daily 4 weeks on, 2 weeks off

- Progression on imatinib
- Documented KIT/ PDGFRA mutation

Study endpoints: PFS based on independent radiology assessment
Secondary endpoints: Response rate (RECIST and CHOI), Overall Survival, Quality of Life, Time to tumor progression, Safety profile.
Larotrectonib is an inhibitor of neurotrophic receptor tyrosine kinase proteins.

Fusions with one of the 3 NTRK proteins is found in a diversity of tumors.

Patients without response were found to not have NTRK fusions or have mutations affecting the kinase domain.

Mazur and Clark describe GIST in 1983. KIT ex.11 Mutation was described in 1998. PDGFRA Mutations were identified in 2003. NF-1 GIST mutations were described in 2005. BRAF mutations were identified in 2007. SDH mutant GIST was described in 2009. NTRK Fusion was identified in 2013. Aberrant methylation was noted in 2015.
Future Directions

• Greater use of mutational testing for selection of therapy
  • How will we incorporate new agents
  • Therapies for NF-1 and SDH deficient GIST are needed
• Evaluation of combination therapies
• Evaluation of immunotherapy: checkpoint inhibitor therapies as well as cellular therapies
Future Directions

- Enhanced methods of assessing for resistance clones

Thank you for being able to Participate!
Phase 2 Study Design

**Pediatric WT Eligibility Criteria:**
- Diagnosis ≤18 years of age or diagnosis of Carney Triad or Carney-Stratakis Dyad
- Progressed on or intolerant to sunitinib

**Adult WT Eligibility Criteria:**
- Diagnosis >18 years of age and no diagnosis of Carney Triad or Carney-Stratakis Dyad
- Progressed on or intolerant to imatinib

**Linsitinib**
(150 mg PO BID days 1-28, cycles repeated every 28 days in the absence of disease progression or unacceptable toxicity)

N=40

**Primary end point:** CR and PR

**Secondary end points:** SD ≥9 months, PFS, OS, time to progression, metabolic responses

WT= negative for mutations in KIT, PDGFRA and BRAF

http://clinicaltrials.gov/ct2/show/NCT01560260
<table>
<thead>
<tr>
<th>RECIST 1.1 Response</th>
<th>N (20)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>SD</td>
<td>17</td>
<td>85%</td>
</tr>
<tr>
<td>CR/PR/SD ≥ 9 months</td>
<td>8</td>
<td>40%</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>NA</td>
<td>1</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Best Radiographic Response**

-20 -15 -10 -5 0 5 10 15 20 25 30 35

On study for 9 months or longer
Women’s Cancer Program

PFS and OS

PFS, 9 Month Estimate: 55%
14/20 Events

OS, 9 Month Estimate: 80%
6/20 Events
Immunotherapy trials

- Nivolumab with or without Ipilimumab in Treating Patients with Metastatic Sarcoma that cannot be removed by Surgery (NCT02500797)
- Combination of MK3475 and Metronomic Cyclophosphamide in Patients with Advanced Sarcoma: Multicenter Phase II trial (PEMBROSARC), (NCT02406781)
- A Phase II study of Nivolumab plus Ipilimumab in Non-Resectable Sarcomas and Endometrial Carcinoma (NCT02982486)
Women’s Cancer Program

Clinical Trials in “Wild Type GIST”

Vandetanib
  • No responses

Guanecitadine
  • Ongoing at the NCI

Temazolamide
  • To be activated soon
Ripretinib (DCC-2816) Mechanism of Action

Think of this as a “Push-Pull” mechanism for inhibiting kinases

Switch Control Inhibitors provide micropockets to attract Switches

- Role reversal: Inhibitor functions as “pocket”, stabilizing the Ligand in the OFF state

Switch Control Inhibitors compete with Switch for the Switch pocket

- Eject/compete with Switch Ligand for Pocket
- Classical ligand antagonist concept