Gastrointestinal Stromal Tumor (GIST)
Treatment Landscape In 2022

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Sylvester Cancer Center
Outline

• Treatment PRIOR to 2020 (BC- before COVID)
  • Curable
  • Treatable

• Updates in GIST what’s happening in the 2020s AC (after COVID)
  • Newly FDA treatments
  • Updates in NCCN guidelines
  • Phase 3 clinical trials
WHERE DOES GIST START?

- Stomach (60%).
- Small intestine (30%).
- Rectum (3%).
- Colon (1–2%).
- Esophagus (<1%).
- Omentum/mesentery (rare).
Back to the Basics: Cancer and GIST 101

- **Curable**: treatment that you receive can eliminate the cancer from your body and it never comes back
  - Surgery is the cure
  - Must be done by experience surgeon in GIST

- **High risk**
  - Curable but high likelihood of recurrence
  - Additional therapy can be given to prevent if from recurring
    - Adjuvant- treatment given *after* the cure (surgery)
    - Neoadjuvant- treatment given *before* the cure (surgery)

- **Treatable**:
  - Metastatic/multifocal/unresectable/recurrent-Can’t eliminate the cancer totally from body but can control it, protect organs and you can live with it
  - First line, second line, third line- terms for treatments in the metastatic setting
Updates in Curable GIST

• Surgery still the standard- MUST be done by GIST/sarcoma surgeon
• Now upfront imatinib given neoadjuvant is recommended if unresectable, borderline resectable to resection can cause too much harm
• Every tumor should be sent for molecular testing
### Table 1. Guidelines for Risk Assessment of Primary Gastrointestinal Stromal Tumor (GIST)

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk of Progressive Disease* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastric</td>
</tr>
<tr>
<td>Mitotic Rate</td>
<td></td>
</tr>
<tr>
<td>≤5 per 50 high-power fields (HPF)</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td>&gt;2 - ≤5 cm</td>
<td>Very low (1.9%)</td>
</tr>
<tr>
<td>&gt;5 - ≤10 cm</td>
<td>Low (3.6%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>Moderate (10%)</td>
</tr>
<tr>
<td>&gt;5 per 50 HPF</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>None##</td>
</tr>
<tr>
<td>&gt;2 - ≤5 cm</td>
<td>Moderate (16%)</td>
</tr>
<tr>
<td>&gt;5 - ≤10 cm</td>
<td>High (55%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>High (86%)</td>
</tr>
</tbody>
</table>

*Defined as metastasis or tumor-related death.
## Denotes small number of cases.

3 MAIN factors to determine risk of recurrence:

1. **Size** of tumor
2. **Primary Location** of the primary tumor
3. **Mitotic index** of the tumor
Updates in Adjuvant Treatment

• MUST test for mutation status to make sure treatment will help
• Imatinib at 400 mg daily ONLY FDA approved dose
• Imatinib at 800 mg (400mg twice per day) now offered to patients if Exon 9 mutations
• ?? Should you receive Avapritinib for high risk D842V GIST???
Mutations in KIT in GIST

There are several different areas in several different genes that can cause GIST and based on the gene and location in the gene will help determine best treatment.
WHAT DOES IT MEAN TO HAVE A MUTATION?

Mutations code for **proteins**

These mutations in genes that code for proteins responsible to cell growth can cause the cell to grow and divide.
# Quick Recap of Pre-COVID FDA approved Treatments for GIST

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand Name</th>
<th>Receptor Targets</th>
<th>FDA Approval</th>
<th>Trial that led to Approval</th>
<th>Effective mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Gleevec</td>
<td>Type II kinase inhibitor ABL, KIT, PDGFRa</td>
<td>2002-1st line metastatic GIST</td>
<td>Phase 2- 80% clinical benefit rate</td>
<td>Exon 11, 9 (needs higher dose), PDGRa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2008- adjuvant for 1 year</td>
<td>Phase 3-Z9001 trial 97% vs 83% RFS placebo</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2012-adjuvant for 3 years</td>
<td>Phase 3-SGGXVIII trial improved OS 3 v 1 years</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Sutent</td>
<td>Type II kinase inhibitor VEGFR 1, 2, FLT3, KIT, PDGFR a,b</td>
<td>2006- 2nd line metastatic GIST</td>
<td>Phase 3 trial mPFS 6.3 mos. vs 1.5 mos. placebo</td>
<td>Exon 9, 11, 13</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Stivarga</td>
<td>Type II kinase inhibitor VEGFR 1, 2 RET, KIT, PDGFR-a, RET, BRAF, FGFR1</td>
<td>2013-3rd line metastatic GIST</td>
<td>GRID phase 3 trial 4.8 mos vs .9 mos placebo</td>
<td>Exon 11, 17, 9</td>
</tr>
</tbody>
</table>
## POST- COVID treatment options

### Systemic Therapy Agents and Regimens for Unresectable, Progressive or Metastatic Disease

<table>
<thead>
<tr>
<th>First-line therapy</th>
<th>Second-line therapy</th>
<th>Third-line therapy</th>
<th>Fourth-line therapy</th>
<th>Additional options after progression on approved therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Regimen</strong>&lt;br&gt;• Imatinib (category 1) for sensitive mutations or for PDGFRA exon 18 mutations (excluding the D842V mutation)&lt;br&gt;• Sunitinib&lt;sup&gt;4,5&lt;/sup&gt; (category 1)&lt;br&gt;• Dasatinib&lt;sup&gt;7&lt;/sup&gt; for patients with PDGFRA exon 18 mutations that are insensitive to imatinib (including the PDGFRA D842V mutation)</td>
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<td><strong>Preferred Regimen</strong>&lt;br&gt;• Regorafenib&lt;sup&gt;5,6&lt;/sup&gt; (category 1)</td>
<td><strong>Preferred Regimen</strong>&lt;br&gt;• Ripretinib 150 mg daily&lt;sup&gt;1,7&lt;/sup&gt; (category 1)</td>
<td>Useful in Certain Circumstances&lt;br&gt;• Avapritinib&lt;sup&gt;7,3&lt;/sup&gt;&lt;br&gt;• Cabozantinib&lt;sup&gt;10&lt;/sup&gt;&lt;br&gt;• Everolimus + TKI&lt;sup&gt;3,11&lt;/sup&gt;&lt;br&gt;• Nilotinib&lt;sup&gt;12,13&lt;/sup&gt;&lt;br&gt;• Pazopanib&lt;sup&gt;14&lt;/sup&gt;&lt;br&gt;• Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)&lt;sup&gt;1,7,15&lt;/sup&gt;&lt;br&gt;• Sorafenib&lt;sup&gt;16-18&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Preferred Regimen</strong>&lt;br&gt;• Avapritinib&lt;sup&gt;7&lt;/sup&gt; for GIST with PDGFRA exon 18 mutations that are insensitive to imatinib (including the PDGFRA D842V mutation)</td>
<td>• Dasatinib</td>
<td></td>
<td></td>
<td>Useful in Certain Circumstances&lt;br&gt;• Ripretinib 150 mg daily&lt;br&gt;• Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)&lt;sup&gt;1,7,15&lt;/sup&gt;</td>
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<td>Useful in Certain Circumstances&lt;br&gt;• NTRK gene-fusion positive GISTs only&lt;br&gt;  • Larotrectinib&lt;sup&gt;4&lt;/sup&gt;&lt;br&gt;  • Entrectinib&lt;sup&gt;5&lt;/sup&gt;</td>
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UCLA Jonsson Comprehensive Cancer Center
NCCN Guidelines 2022

UCLA Health
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<thead>
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<td><strong>Preferred Regimen</strong>&lt;br&gt; <strong>Sunitinib</strong>&lt;sup&gt;3&lt;/sup&gt; (category 1)</td>
<td><strong>Preferred Regimen</strong>&lt;br&gt; <strong>Regorafenib</strong>&lt;sup&gt;4&lt;/sup&gt; (category 1)</td>
<td><strong>Preferred Regimen</strong>&lt;br&gt; <strong>Ripretinib 150 mg daily</strong> (category 1)</td>
<td><strong>Used in Certain Circumstances</strong>&lt;br&gt; - <strong>Ipilimumab</strong>&lt;sup&gt;5&lt;/sup&gt;&lt;br&gt; - <strong>Axitinib</strong>&lt;sup&gt;6&lt;/sup&gt;&lt;br&gt; - <strong>Pazopanib</strong>&lt;sup&gt;6&lt;/sup&gt;&lt;br&gt; - <strong>Sorafenib</strong>&lt;sup&gt;7,8&lt;/sup&gt;&lt;br&gt; - <strong>Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)</strong>&lt;br&gt; - <strong>Sorafenib</strong>&lt;sup&gt;7,8&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Figure 1. Transverse Gadolinium-Enhanced T1-Weighted MRI Studies of the Upper Abdomen.
Before STI571 therapy (Panel A), multiple metastatic lesions were present in the liver. Contrast enhancement of the metastases was highly heterogeneous, with strong enhancement at the periphery. Enhancement was less intense in the central parts of the metastases, suggesting necrosis. After four weeks of treatment with STI571 (Panel B), the metastases had a cyst-like appearance. After eight months of treatment (Panel C), the metastases were smaller, and some had disappeared.

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maaret Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Terzaharttala, M.D., David Toyeson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.
Efficacy and Safety of Imatinib Mesylate in Advanced Gastrointestinal Stromal Tumors

George D. Demetri, M.D., Margaret von Mehren, M.D., Charles D. Blanke, M.D., Annick D. Van den Abbeele, M.D., Burton Eisenberg, M.D., Peter J. Roberts, M.D., Michael C. Heinrich, M.D., David A. Tuveson, M.D., Ph.D., Samuel Singer, M.D., Milos Janicek, M.D., Ph.D., Jonathan A. Fletcher, M.D., Stuart G. Silverman, M.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Beate Kiese, M.Sc., Bin Peng, M.D., Ph.D., Sasa Dimitrijevic, Ph.D., Brian J. Druker, M.D., Christopher Corless, M.D., Christopher D.M. Fletcher, M.D., and Heikki Joensuu, M.D.
<table>
<thead>
<tr>
<th>Best Response</th>
<th>400 mg (N=73)</th>
<th>600 mg (N=74)</th>
<th>Either Dose (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>36 (49.8 [37.4–61.3])</td>
<td>43 (58.1 [46.1–69.5])</td>
<td>79 (53.7 [45.3–62.0])</td>
</tr>
<tr>
<td>Stable disease</td>
<td>23 (31.5 [21.1–43.4])</td>
<td>18 (24.3 [15.1–35.7])</td>
<td>41 (27.9 [20.8–35.9])</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (16.4)</td>
<td>8 (10.8)</td>
<td>20 (13.6)</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>2 (2.7)</td>
<td>5 (6.8)</td>
<td>7 (4.8)</td>
</tr>
</tbody>
</table>
Figure 1. Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.
What is the right dose of Gleevec?

- 1640 pts with advanced GIST
Response by Mutational Status
Response by Genotype

Fig. 3 – Cumulative incidence of response observed in the three largest subgroups of kinase genotypes analyzed in this study.
Resistance to Imatinib

• 5% primary resistance
• 14% have early resistance
• Secondary /acquired resistance
  • Median of 2 years
KIT and PDGFRA mutations and correlation to protein structure

Pierotti, M. A. et al. (2011) Targeted therapy in GIST: in silico modeling for prediction of resistance
WHY DO MUTATIONS CAUSE RESISTANCE TO DRUGS?

OUTSIDE CELL

CELL MEMBRANE

INSIDE CELL

Exon 11

Gleevec

Exon 11 + Exon 17

Gleevec

MUTATIONS CAUSE SHAPE CHANGES
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<td>Useful in Certain Circumstances</td>
</tr>
<tr>
<td>Imatinib (category 1) for sensitive mutations or for PDGFRα exon 18 mutations (excluding the D842V mutation)</td>
<td>Sunitinib (category 1)</td>
<td>Sunitinib (category 1)</td>
<td>Ripretinib 150 mg daily (category 1)</td>
<td>Avascularinib</td>
</tr>
<tr>
<td>Preferred Regimen</td>
<td>Dasatinib</td>
<td>Regorafenib</td>
<td>Ripretinib</td>
<td>Uses in Certain Circumstances</td>
</tr>
<tr>
<td>Avascularinib for GIST with PDGFRα exon 18 mutations that are insensitive to imatinib (including the PDGFRα D842V mutation)</td>
<td>Dasatinib</td>
<td></td>
<td></td>
<td>Uses in Certain Circumstances</td>
</tr>
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<td>Use in Certain Circumstances</td>
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</tr>
<tr>
<td></td>
<td>Larotrectinib</td>
<td></td>
<td></td>
<td>Uses in Certain Circumstances</td>
</tr>
<tr>
<td></td>
<td>Entrectinib</td>
<td></td>
<td></td>
<td>Uses in Certain Circumstances</td>
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</tbody>
</table>
FOCUS ON:
- RIPRETINIB (QINLOCK)
- AVAPRITINIB (AYVAKIT)
Avapritinib: Type I kinase receptor inhibitor, inhibits at the activation loop PDGFRα and KIT

Type I kinase receptor inhibitor, inhibits at the activation loop
Summary

Background

Targeting of KIT and PDGFRA with imatinib revolutionised treatment in gastrointestinal stromal tumour; however, PDGFRA Asp842Val (D842V)-mutated gastrointestinal stromal tumour is highly resistant to tyrosine kinase inhibitors. We aimed to assess safety, tolerability, and antitumour activity of avapritinib, a novel KIT and PDGFRA inhibitor that potently inhibits PDGFRA D842V.
Avapritinib (AYVAKIT)- Data in PDGFRA exon 18 Mutation

• On January 9, 2020, the FDA approved Avapritinib (AYVAKIT) for adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including D842V mutations

• First therapy approved for GIST patients harboring a PDGFRA exon 18 mutation

• Efficacy was investigated in NAVIGATOR (NCT02508532), a multi-center, single-arm, open-label trial enrolling 43 patients with GIST harboring a PDGFRA exon 18 mutation, including 38 patients with PDGFRA D842V mutations

• For patients harboring a PDGFRA exon 18 mutation, the ORR was 84% (7% complete responses and 77% partial responses). For the subgroup of patients with PDGFRA D842V mutations, the ORR was 89% (8% complete responses and 82% partial responses)

• 61% of the responding patients with exon 18 mutations had a response lasting 6 months or longer (31% of patients with an ongoing response were followed for less than 6 months).

• The most common adverse reactions (incidence ≥ 20%) edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash and dizziness

• The recommended avapritinib dose is 300 mg orally once daily on an empty stomach, at least one hour before and two hours after a meal
Avapritinib

- VOYAGER Trial: An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 (Avapritinib) vs Regorafenib in Patients With Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)
- Unfortunately, study did meet it’s primary endpoint (improved PFS) which means that it do not work better than Regorafenib
- Need to further explore mutation status as to why
- Regorafenib remains standard 3rd line treatment
Ripretinib: a type 3 kinase inhibitor

Binds to both the activation switch pocket, regardless of where the mutations arise

Locks the kinases in the inactive ("off") state, inhibiting downstream signaling cancer cell proliferation
Ripretinib: INVICTUS trial Published in Lancet Oncology July 2020

Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial

Jean-Yves Blay, César Serrano, Michael C Heinrich, John Zalcberg, Sebastian Bauer, Hans Gelderblom, Patrick Schöffski, Robin L Jones, Steven Attia, Gina D’Amato, Ping Chi, Peter Reichardt, Julie Meade, Kelvin Shi, Rodrigo Ruiz-Soto, Suzanne George, Margaret von Mehren

Patients with advanced (metastatic) GIST who have progressed on Imatinib, Sunitinib and Regorafenib Could have also had another TKI
FOR DOCTORS: Improved response, stable disease, progressive free survival and overall all survival, improved QOL, compared to placebo

FOR PATIENTS: IT WORKS GREAT!!!
On May 15, 2020 FDA approved ripretinib (Qinlock) for adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors including imatinib.
Ripretinib (Qinlock)

- Dose is 150 mg (three 50 mg pills once daily) with or without food
- Common (20%) side effects include:
  - Hair loss
  - Fatigue
  - Nausea/vomiting
  - Abdominal pain
  - Constipation or diarrhea
  - Muscle pain
  - Palmar-plantar erythodysthesia syndrome

Uncommon but possible serious:
- New skin cancers
- High blood pressure
- Heart problems (cardiomyopathy)
Summary

• Now 5 FDA treatments approved for GIST patients with a handful others also shown to be effective (Pazopanib (Votrient), Dasatinib (Sprycel), Nilotinib (Tasigna), Sorafenib (Nexavaar),…

• Avapritinib and Ripretinib were developed specifically for GIST patients

• Use of GIST mutation analysis either from the tumor biopsy or liquid biopsy (ctDNA from the blood plasma) is extremely important to help decide which treatment is best
Ripretinib

**INTRIGUE Trial:**
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

Metastatic, measurable, progressed or intolerant to Imatinib

117 international locations, enrolling quickly!
Ripretinib (Qinlock)

- Dose is 150 mg (three 50 mg pills once daily) with or without food
- Common (20%) side effects include:
  - Hair loss
  - Fatigue
  - Nausea/vomiting
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Ripretinib

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Metastatic, measurable, progressed or intolerant to Imatinib
Kaplan-Meier analysis of PFS by IRR

**K/T exon 11 ITT**

- **Median PFS**
  - **Ripretinib**: 6.3 months (95% CI 6.8, 13.3)
  - **Sunitinib**: 6.1 months (95% CI 6.1, 9.1)
  - HR 0.8, 95% CI 1.00, 1.14, *P* = 0.36

**AP ITT**

- **Median PFS**
  - **Ripretinib**: 8.0 months (95% CI 6.5, 10.8)
  - **Sunitinib**: 8.3 months (95% CI 6.3, 11.0)
  - HR 1.05, 95% CI 0.92, 1.19, nominal *P* = 0.57

Ripretinib did not meet the primary endpoint of superiority in PFS over sunitinib.

However, the median PFS observed with ripretinib was comparable to the median PFS observed with sunitinib in the exon 11 ITT population (8.3 months vs 7.0 months) and AP ITT population (8.0 months vs 8.3 months).
PFS by IRR according to stratification subgroups

<table>
<thead>
<tr>
<th></th>
<th>Ripretinib (events)</th>
<th>Sunitinib (events)</th>
<th>Median ripretinib (months)</th>
<th>Median sunitinib (months)</th>
<th>Hazard ratio (95%CI)</th>
<th>Favor ripretinib</th>
<th>Favor sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>226 (146)</td>
<td>227 (130)</td>
<td>8.0</td>
<td>8.3</td>
<td>1.05 (0.82, 1.33)</td>
<td></td>
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<tr>
<td>Mutation type</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>KIT exon 11</td>
<td>163 (100)</td>
<td>164 (98)</td>
<td>8.3</td>
<td>7.0</td>
<td>0.88 (0.67, 1.17)</td>
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<tr>
<td>K/T exon 9</td>
<td>31 (27)</td>
<td>29 (14)</td>
<td>5.5</td>
<td>13.8</td>
<td>2.85 (1.48, 5.48)</td>
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<tr>
<td>KIT/PDGFRα WT</td>
<td>15 (9)</td>
<td>18 (10)</td>
<td>7.0</td>
<td>4.1</td>
<td>0.90 (0.36, 2.23)</td>
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<tr>
<td>Other KIT/PDGFRα</td>
<td>17 (10)</td>
<td>16 (8)</td>
<td>6.8</td>
<td>8.4</td>
<td>0.90 (0.35, 2.28)</td>
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<td>Inhibitor oligance</td>
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<tr>
<td>Yes</td>
<td>22 (14)</td>
<td>23 (10)</td>
<td>13.7</td>
<td>10.9</td>
<td>1.01 (0.44, 2.33)</td>
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</tr>
<tr>
<td>No</td>
<td>204 (132)</td>
<td>204 (120)</td>
<td>7.1</td>
<td>8.1</td>
<td>1.02 (0.80, 1.31)</td>
<td></td>
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</tr>
</tbody>
</table>

- Subgroup analyses of PFS based on stratification factors (KIT/PDGFRα mutation type and imatinib intolerance) revealed that PFS benefit for patients with primary KIT exon 9 mutations favored treatment with sunitinib vs ripretinib.
Conclusions

- Ripretinib did not meet the primary endpoint of superiority in PFS over sunitinib
  - However, the median PFS observed with ripretinib was comparable to the median PFS observed with sunitinib
  - The ORR was higher for patients receiving ripretinib in the KIT exon 11 ITT population compared with sunitinib
- Ripretinib had a more favorable safety profile compared with sunitinib
  - Patients receiving ripretinib were less likely to experience Grade 3/4 TEAEs including hypertension, palmar-planter erythrodysesthesia, diarrhea, and stomatitis compared with patients receiving sunitinib
  - Patients receiving ripretinib were less likely to need dose modification compared with patients receiving sunitinib
  - Patients receiving ripretinib reported better tolerability than patients receiving sunitinib
- Ripretinib may provide meaningful clinical benefit to patients with advanced GIST previously treated with imatinib
Type I kinase receptor inhibitor, inhibits at the activation loop
• Each bar is a patient
• Bars below 0 indicate GIST shrinkage!

Fig. 3. Maximal percentage change from baseline in sum of target lesion diameters in the $PDGFRA$ D842V population. CR, complete response; PD, progressive disease; PDGFRA, platelet-derived growth factor receptor A; PR, partial response; SD, stable disease.
Avapritinib is Very effective for PDGFRA D842V mutated GIST

Fig. 5. Progression-free survival in the PDGFRA D842V population, PDGFRA, platelet-derived growth factor receptor A.
Table 2
Any-cause adverse events occurring in ≥20% of patients in the safety population and the PDGFRA D842V population.

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>PDGFRA D842V population (n = 56)</th>
<th>Safety population (N = 250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>38 (68)</td>
<td>161 (64)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35 (63)</td>
<td>157 (63)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>37 (66)</td>
<td>136 (54)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>37 (66)</td>
<td>112 (45)</td>
</tr>
<tr>
<td>Periorbital oedema</td>
<td>27 (48)</td>
<td>110 (44)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (38)</td>
<td>106 (42)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23 (41)</td>
<td>101 (40)</td>
</tr>
<tr>
<td>Increased lacrimation</td>
<td>21 (38)</td>
<td>88 (35)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>23 (41)</td>
<td>81 (32)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>21 (38)</td>
<td>80 (32)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19 (34)</td>
<td>64 (26)</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (21)</td>
<td>64 (26)</td>
</tr>
<tr>
<td>Hair colour changes</td>
<td>16 (29)</td>
<td>62 (25)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (29)</td>
<td>59 (24)</td>
</tr>
<tr>
<td>Face oedema</td>
<td>13 (23)</td>
<td>57 (23)</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>16 (29)</td>
<td>54 (22)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>14 (25)</td>
<td>48 (19)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (23)</td>
<td>48 (19)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>13 (23)</td>
<td>47 (19)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>15 (27)</td>
<td>46 (18)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13 (23)</td>
<td>44 (18)</td>
</tr>
<tr>
<td>Cough</td>
<td>15 (27)</td>
<td>39 (16)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (25)</td>
<td>29 (12)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12 (21)</td>
<td>27 (11)</td>
</tr>
</tbody>
</table>

PDGFRA, platelet-derived growth factor receptor A.
Avapritinib Versus Regorafenib in Locally Advanced Unresectable or Metastatic GI Stromal Tumor: A Randomized, Open-Label Phase III Study

Yoon-Koo Kang, MD, PhD; Suzanne George, MD; Robin L. Jones, MD; Piotr Rutkowski, MD, PhD; Lin Shen, MD, PhD; Olivier Mir, MD, PhD, MPH; Shreyanskumar Patel, MD; Yongjian Zhou, MD, PhD; Margaret von Mehren, MD; Peter Hohenberger, MD; Victor Villalobos, MD, PhD; Mehdi Brahmi, MD; William D. Tap, MD; Jonathan Trent, MD, PhD; Maria A. Pantaleo, MD, PhD; Patrick Schoffski, MD; Kevin He, PhD; Paggy Hew, MS; Kate Newberry, PhD; Maria Roche, MS; Michael C. Heinrich, MD; and Sebastian Bauer, MD

VOYAGER

3L/4L GIST R, 1:1

Avapritinib N=240

Regorafenib N=236

Primary endpoint: PFS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Avapritinib (n = 240)</th>
<th>Regorafenib (n = 236)</th>
<th>Total (N = 476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of previous TKIs, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>207 (86.3)</td>
<td>201 (85.2)</td>
<td>408 (85.7)</td>
</tr>
<tr>
<td>3</td>
<td>33 (13.8)</td>
<td>35 (14.8)</td>
<td>68 (14.3)</td>
</tr>
<tr>
<td>Previous surgical resection, No. (%)^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total debulking</td>
<td>213 (88.8)</td>
<td>208 (88.1)</td>
<td>421 (88.4)</td>
</tr>
<tr>
<td>Partial debulking</td>
<td>78 (36.6)</td>
<td>90 (43.3)</td>
<td>168 (39.9)</td>
</tr>
<tr>
<td>Others</td>
<td>116 (54.5)</td>
<td>120 (57.7)</td>
<td>236 (56.1)</td>
</tr>
<tr>
<td>Baseline ctDNA, No. (%)^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDGFRA exon 18</td>
<td>11 (4.6)</td>
<td>7 (3.0)</td>
<td>18 (3.8)</td>
</tr>
<tr>
<td>PDGFRA D842V</td>
<td>7 (2.9)</td>
<td>6 (2.5)</td>
<td>13 (2.7)</td>
</tr>
<tr>
<td>PDGFRA exon 18 not D842V</td>
<td>4 (1.7)</td>
<td>1 (&lt; 1)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>KIT V654A/T670I (no PDGFRA exon 18 mutation)</td>
<td>33 (13.8)</td>
<td>34 (14.4)</td>
<td>67 (14.1)</td>
</tr>
<tr>
<td>KIT exon 17 (no PDGFRA exon 18 or KIT V654A/T670I mutations)</td>
<td>49 (20.4)</td>
<td>60 (25.4)</td>
<td>109 (22.9)</td>
</tr>
<tr>
<td>Others^c</td>
<td>80 (33.3)</td>
<td>66 (28.0)</td>
<td>146 (30.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>67 (27.9)</td>
<td>69 (29.2)</td>
<td>136 (28.6)</td>
</tr>
</tbody>
</table>
3L Treatment
Avapritinib

VOYAGER Trial: An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 (Avapritinib) vs Regorafenib in Patients With Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

Unfortunately, study did meet its primary endpoint (improved PFS) which means that it do not work better than Regorafenib

Need to further explore mutation status as to why Regorafenib remains standard 3rd line treatment
THANK YOU!!

Especially to the PATIENTS for being so PATIENT
EXTRA SLIDES
CIRCULATING TUMOR DNA (ctDNA) IN GIST

WHAT INFORMATION DO YOU GET FROM A BIOPSY VERSUS BLOOD?
Circulating tumor DNA (ctDNA) analyses of the phase III VOYAGER trial: KIT mutational landscape and outcomes in patients with advanced gastrointestinal stromal tumor (GIST)

César Serrano, Sebastian Bauer, David Gómez-Peregrina, Yoon-Koo Kang, Robin L. Jones, Piotr Rutkowski, Olivier Mir, Michael C. Heinrich, William D. Tap, Kate Newberry, Alexandra Grassian, Steve Miller, Hongliang Shi, Patrick Schoffski, Maria Pantaleo, Margaret von Mehren, Jonathan C. Trent, Suzanne George
Background

TKI-resistance is defined by KIT secondary mutations

- The main mechanism of resistance to imatinib is the emergence of heterogeneous KIT secondary mutations in ~90% patients
  - ATP binding pocket (exons 13/14)
  - Activation loop (exons 17/18)

- TKIs after imatinib resistance are effective only against subsets of KIT secondary mutations

---

![Diagram](image)

**Modified from Schaefer, DeMatteo & Serrano, ASCO Ed Book 2022**
Background  ctDNA in GIST

1. **Heterogeneity** in primary and secondary KIT mutations

![Genetic alterations affecting KIT exon 11](image)

Data obtained from COSMIC
Background  ctDNA in GIST

1. **Heterogeneity** in primary and secondary KIT mutations

Bauer, *Clin Cancer Res* 2021
Background  ctDNA in GIST

1. **Heterogeneity** in primary and secondary KIT mutations

2. ↓ **ctDNA shedding** in GIST

<table>
<thead>
<tr>
<th>Variable</th>
<th>ctDNA Mutation Positive</th>
<th>Tumor FFPE Mutation Positive</th>
<th>Detection Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 36)</td>
<td>20</td>
<td>36</td>
<td>56</td>
</tr>
<tr>
<td>Primary tumor</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic low burden and responding</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic low burden and progressive</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic high burden and responding</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Metastatic high burden and progressive</td>
<td>19</td>
<td>19</td>
<td>100</td>
</tr>
</tbody>
</table>

Arshad, JCO PO 2020
Background ctDNA in GIST

1. **Heterogeneity** in primary and secondary KIT mutations

2. ↓ ctDNA shedding in GIST

3. ctDNA has only been explored in **multiple small series**, but with **limited data from clinical trials**

- **Ph I/II PLX9486 (n=35)**
  - Association with response
- **Ph II Ponatinib (n=45)**
  - Heterogeneity of KIT muts
- **Ph I SuRe (n=14)**
  - Treatment monitoring
- **Various series**
  - Outcomes
  - Treatment guidance

Study Design and Methods

- Collection of **plasma samples** from all patients recruited in the VOYAGER phase III clinical trial:
  - Baseline
  - End of Treatment (EoT)

- **ctDNA analysis**: 74-gene panel G360 from Guardant®
  - Landscape of KIT and PDGFRA mutations in advanced GIST
  - ctDNA & outcomes*

*Cutoff date: March 9, 2020
Results: detection of KIT/PDGFRA variants at baseline

Total subjects
N=476
- KIT/PDGFRA-mutant, advanced GIST pts
- 3rd line and 4th after IM and SU

Avapritinib
N=240
ctDNA performed
n=196 (81.7%)
ctDNA detected
n=168 (85.7%)

Regorafenib
N=236
ctDNA performed
n=190 (80.5%)
ctDNA detected
n=165 (86.8%)

N = 386 (81.1%)
N = 333 (86%)

Any KIT variant detected ► n = 250 pts (75.1%)
Any PDGFRA variant detected ► n = 18 pts (5.4%)
Landscape of KIT mutations: heterogeneity (2)

- **Primary and secondary KIT mutations:** codons affected across KIT sequence

![Graph showing alteration occurrence and KIT mutations](image-url)

**KIT primary mutations**

**KIT secondary mutations**

- ATP-Binding Pocket
- Activation loop
End of Treatment: **Resistance to avapritinib (n=42)**

Enrichment in resistance mutations emerging from the **ATP binding pocket (exons 13 and 14)** in 42 patients after progression to avapritinib.
ctDNA mutations & outcomes: ctDNA negative for KIT mut

Different PFS behavior among ctDNA KIT negative patients treated with avapritinib (targeted TKI) v. regorafenib (multikinase inhibitor)

Median PFS – avapritinib

- KIT absent, 5.7 mo
- KIT present, 3.7 mo
- Log-rank P = 0.002

Median PFS – regorafenib

- KIT absent, 5.7 mo
- KIT present, 5.5 mo
- Log-rank P = 0.972