Updates in Sarcoma

Priscila Barreto Coelho

May, 2023
Learning Objective and Outline

• Describe recent updates in the diagnosis and treatment of Sarcomas
  • ASCO 2022
  • ESMO 2022
  • CTOS 2022
  • FDA approvals
INTRIGUE: A phase III, randomized, open-label study to evaluate the efficacy and safety of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib

Michael C Heinrich, Robin L Jones, Hans Gelderblom, Suzanne George, Patrick Schöffski, Margaret von Mehren, John R Zalcberg, Yoon-Koo Kang, Albiruni Abdul Razak, Jonathan Trent, Steven Attia, Axel Le Cesne, Ying Su, Julie Meade, Tao Wang, Matthew L Sherman, Rodrigo Ruiz-Soto, Jean-Yves Blay, Sebastian Bauer

January Program
Tuesday, January 25, 2022
Methods

Patients ≥18 years old with a confirmed diagnosis of GIST who progressed on or had documented intolerance to imatinib

Patients were enrolled from 122 sites across North America, South America, Europe, Australia, and Asia

Stratified by
• Mutational status:
  - KIT exon 11
  - KIT exon 9
  - KIT/PDGFRA WT
  - Other KIT/PDGFRA
• Intolerance to imatinib

Randomization
Open label

Primary endpoint:
PFS by IRR (using mRECIST v 1.1) in the KIT exon 11 ITT and AP ITT populations

Key secondary endpoints:
ORR by IRR and OS in the KIT exon 11 ITT and AP ITT populations

Other secondary endpoints:
TTR, QoL (EORTC QLQ-C30 and DLQI), DCR, safety

Data cutoff: September 1, 2021

A hierarchical testing sequence was performed for primary and key secondary endpoints; statistical testing of patients with a KIT exon 11 primary mutation preceded the AP population

The estimated 426-patient sample size was based on the assumption that the median PFS would be 9 months for ripretinib and 6 months for sunitinib according to previous studies.\(^1,2\)

AP: all patient; DCR: disease control rate; DLQI: Dermatology Life Quality Index; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life questionnaire for cancer-30 item; GIST: gastrointestinal stromal tumor; IRR: independent radiologic review; ITT: intention to treat; mRECIST: modified Response Evaluation Criteria in Solid Tumors; ORR: objective response rate; OS: overall survival; PDGFRA: platelet-derived growth factor receptor alpha; PFS: progression-free survival; QD: once daily; QoL: quality of life; TTR: time to response; WT: wild-type

Kaplan-Meier analysis of PFS by IRR

- 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)

AP, all patients; CI, confidence interval; HR, hazard ratio; IRR, independent radiologic review; ITT, intention-to-treat; PFS, progression-free survival.

Michael C. Heinrich, M.D. Head of the OHSU Knight Cancer Institute GIST

Presented by: Translational and Clinical Research Programs

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## ORR and duration of response by IRR

<table>
<thead>
<tr>
<th></th>
<th>KIT exon 11 ITT population</th>
<th>AP ITT population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ripretinib (n = 163)</td>
<td>Sunitinib (n = 164)</td>
</tr>
<tr>
<td><strong>Objective response rate, n (%)</strong></td>
<td>39 (23.9) [17.6, 31.2]</td>
<td>24 (14.6) [9.6, 21.0]</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>0 (0.0)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>39 (23.9)</td>
<td>22 (13.4)</td>
</tr>
<tr>
<td><strong>Difference in objective response rate, %</strong></td>
<td>9.3 [0.7, 17.8]</td>
<td>4.2 [-3.2, 11.5]</td>
</tr>
<tr>
<td><strong>P-value, n (%)</strong></td>
<td>0.03</td>
<td>0.27</td>
</tr>
</tbody>
</table>

- The ORR in the KIT exon 11 ITT population was higher with ripretinib vs sunitinib (nominal P = 0.03)
- The ORR in the all-patient ITT population was similar between treatment arms (nominal P = 0.27)
- Median duration of response for both populations was 16.7 months for patients randomized to ripretinib and 20.1 months for patients randomized to sunitinib

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*Confirmed complete and partial responses

| AP, all patients, CI, confidence interval, IRR, independent radiologic review, ITT, intention-to-treat, NE, not estimable, ORR, objective response rate | }
Grade 3/4 TEAEs for ripretinib vs sunitinib

- Grade 3/4 TEAEs (≥2% in either arm) with an absolute difference ≥1% were nearly all lower with ripretinib vs sunitinib
- Patients receiving sunitinib were 3 times more likely to experience Grade 3 hypertension compared with patients receiving ripretinib
- Patients receiving sunitinib were 7 times more likely to develop Grade 3 PPES vs patients receiving ripretinib

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Michael C. Heinrich, M.D. Head of the OHSU Knight Cancer Institute GIST
Presented by Translational and Clinical Research Programs

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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-plantar 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

GIST, gastrointestinal stromal tumor; ITT, intention-to-treat; ORR, objective response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse event.
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  VOYAGER phase III clinical trial

VOYAGER

3L/4L GIST R, 1:1
Avapritinib N=240
Regorafenib N=236

Primary endpoint: PFS

KIT-MUTANT GIST

SECONDARY MUTATIONS

DRUG SENSITIVITY

IM   SU   RE   AV   RI

V654
T670

Ex 13
Ex 14

Ex 9
Ex 11

Ex 17
Ex 18

D816
D820
N822
Y823
A829

Sensitive
Resistant
Background

VOYAGER phase III clinical trial

VOYAGER

3L/4L GIST R, 1:1

Avapritinib
N=240

Regorafenib
N=236

Primary endpoint: PFS

Kang YK et al, J Clin Oncol 2021
ctDNA mutations & outcomes: ATP-binding pocket (Exon 13)

Shorter mPFS and mOS in patients with ctDNA+ ATP binding pocket mutations treated with AVAPRITINIB vs. REGORAFENIB

Median PFS

- Regorafenib, 7.4 mo
- Avapritinib, 1.9 mo
- Log-rank P < 0.001

Months from Randomization: 0 3 6 9 12 15 18 21 24

- Avapritinib: 25 9 3 0
- Regorafenib: 29 21 12 7 2 0

Median OS

- Regorafenib, 11.3 mo
- Avapritinib, 8.3 mo
- Log-rank P = 0.0651

Months from Randomization: 0 3 6 9 12 15 18 21 24

- Avapritinib: 25 21 15 7 3 0
- Regorafenib: 29 29 26 15 6 0
ctDNA mutations & outcomes: Activation loop (Exon 17)

Shorter mPFS in patients with ctDNA+ Activation loop mutations (in the absence of ATP-BP mutants) treated with AVAPRITINIB v. REGORAFENIB

Median PFS

- Regorafenib, 6.7 mo
- Avapritinib, 4.7 mo
- Log-rank P < 0.03

Median OS

- Regorafenib, N.R.
- Avapritinib, 19.2 mo
- Log-rank P = 0.628

Presented by:
César Serrano, MD PhD
Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain
Conclusions

- This is the first study to address the utility of ctDNA sequencing in advanced GIST in the context of a large, international phase III clinical trial.

- Hybrid capture-based plasma sequencing detects KIT primary and secondary mutations in the majority of TKI-resistant GIST patients.

- ctDNA studies reveals important inter- and intra-patient heterogeneity of KIT secondary mutations after progression to imatinib and sunitinib.

- ctDNA sequencing correlates with outcomes in pretreated GIST. Identification of ATP binding pocket mutations in KIT negatively correlates with avapritinib activity.

- The multikinase inhibitory nature of regorafenib may be relevant for its clinical activity regardless the type of KIT secondary mutation by plasma.
Phase III assessment of topotecan & cyclophosphamide and high-dose ifosfamide in rEECur, an international randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES)

Martin G. McCabe, Laura Kirton, Maria Khan, Nicola Fenwick, Sandra J. Strauss, Claudia Maria Valverde Morales, Cristina Mata, Nathalie Gaspar, Roberto Luksch, Alessandra Longhi, Uta Dirksen, Marianne Phillips, Akmal Safwat, Hans Gelderblom, Thomas Kühne, Jukka Kanerva, Andrew J Westwood, Stefano Ferrari, Jeremy Whelan, Keith Wheatley
martin.mccabe@manchester.ac.uk
reecur@trials.bham.ac.uk
Primary outcome: EFS by treatment group

Kaplan–Meier survival estimates

<table>
<thead>
<tr>
<th>1st event</th>
<th>TC</th>
<th>IFOS</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>No event</td>
<td>6 (8%)</td>
<td>10 (14%)</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>Event</td>
<td>67 (92%)</td>
<td>63 (86%)</td>
<td>130 (89%)</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>73</td>
<td>146</td>
</tr>
</tbody>
</table>

Note very small numbers beyond ~6 months

Median survival:
TC: 3.5 months (95% CI 2.1, 5.1)
IFOS: 5.7 months (95% CI 3.8, 6.9)

6-month survival
TC: 37% (95% CI 26%, 48%)
IFOS: 47% (95% CI 35%, 58%)
Secondary outcome: OS by treatment group

Table:

<table>
<thead>
<tr>
<th>Vital status</th>
<th>TC</th>
<th>IFOS</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>16 (22%)</td>
<td>20 (27%)</td>
<td>36 (25%)</td>
</tr>
<tr>
<td>Dead</td>
<td>57 (78%)</td>
<td>53 (73%)</td>
<td>110 (75%)</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>73</td>
<td>146</td>
</tr>
</tbody>
</table>

Again, note small numbers beyond ~2 years

Median survival:
- TC: 10.5 months (95% CI 7.2, 15.0)
- IFOS: 15.4 months (95% CI 11.3, 20.9)

1-year OS:
- TC: 45% (95% CI 33%, 56%)
- IFOS: 55% (95% CI 43%, 66%)
Conclusions

- Ifosfamide is effective in the first line and relapse disease
- This is the first controlled evidence of its superiority at relapse and the authors should be commended for their efforts
- Survival outcomes highlights the urgency to find more active and less toxic agents
A phase Ib/II study of the combination of lenvatinib and eribulin in advanced liposarcoma and leiomyosarcoma (LEADER study) – Final efficacy updates

Tom Wei-Wu Chen\textsuperscript{1,2,3}, Chueh-Chuan Yen\textsuperscript{4}, Ruey-Long Hong\textsuperscript{1}, Jen-chieh Lee\textsuperscript{5}, Koping Chang\textsuperscript{5}, Chih-Wei Yu\textsuperscript{6}, San-Chi Chen\textsuperscript{4}, Mei-Lu Chen\textsuperscript{1}, Meng-Chi Hsu\textsuperscript{1}, Ting-Fang Kung\textsuperscript{8}, Ann-Lii Cheng\textsuperscript{1,2,3}

1. Department of Oncology, 5. Department of Pathology, 6. Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan
2. Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan
3. National Taiwan University Cancer Center, Taipei, Taiwan
4. Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan
**Study Design**

A multi-center single-arm study

**Key Inclusion/Exclusion criteria**

1. Advanced LPS/LMS
2. ≤ 2 lines of chemotherapy in advanced disease
3. Age ≥ 20
4. No previous eribulin or lenvatinib treatment

### Phase Ib part (n = 6)

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Lenvatinib (mg/day)</th>
<th>Eribulin (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level 11</td>
<td>18</td>
<td>1.1</td>
</tr>
<tr>
<td>Dose level 21</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td>Dose level 31</td>
<td>10</td>
<td>1.1</td>
</tr>
<tr>
<td>Dose level 12</td>
<td>18</td>
<td>0.7</td>
</tr>
<tr>
<td>Dose level 22</td>
<td>14</td>
<td>0.7</td>
</tr>
</tbody>
</table>

### Phase II (n = 24)

Lenvatinib 14mg/day
Eribulin 1.1mg/m² D1, D8

1 DLT, but 5/6 (83%) patients required multiple lenvatinib dose reductions in cycles 2 and 3
Primary endpoint: Objective response rate by RECIST 1.1

20% (6/30) (95% CI 8 - 39%)

Waterfall plot of the changes in the max diameter of target lesion(s)

<table>
<thead>
<tr>
<th>RECIST 1.1</th>
<th>PR</th>
<th>SD</th>
<th>PD*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>21</td>
<td>3</td>
</tr>
</tbody>
</table>

*Two patients had progressive non-target lesions
Indirect comparisons between lenvatinib + eribulin and eribulin single agent in advanced LPS and LMS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Late-line (%)</th>
<th>ORR (%)</th>
<th>Median PFS*</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. ASCO 2022</td>
<td>Lenvatinib + eribulin</td>
<td>30</td>
<td>64%</td>
<td>20</td>
<td>8.5 months</td>
<td>27.1 months</td>
</tr>
<tr>
<td>Schoffski et al. Lancet 2016</td>
<td>Eribulin</td>
<td>228</td>
<td>100%</td>
<td>4</td>
<td>2.6 months</td>
<td>13.5 months</td>
</tr>
</tbody>
</table>

⚠️ Caution:
(1) phase Ib/II vs randomized phase III study
(2) less patients received treatments as later-line therapy in LEADER

* if in the original article median PFS was reported in weeks, it was transformed to months by (weeks * 7/30)

Alessandro Gronchi MD; Emanuela Palmerini, MD, PhD; Vittorio Quagliuolo, MD; Javier Martin Broto, MD, PhD; Antonio Lopez Pousa, MD; Giovanni Grignani, MD; Antonella Brunello, MD; Jean-Yves Blay, MD, PhD; Oscar Tenderso, MD; Robert Díaz Beveridge, MD, Ph; Virginia Ferraresi, MD; Iwona Lugowska, MD, PhD; Sara Pizzamiglio, MSc; Paolo Verderio, PhD; Valeria Fontana, PhD, MSc; Davide M Donati, MD; Elena Palassini, MD; Roberta Sanfilippo MD, Giuseppe Bianchi, MD; Alexia Bertuzzi, MD; Carlo Morosi, MD; Sandro Pasquali, MD, PhD; Silvia Stacchiotti, MD; Silvia Bagué, MD; Jean Michel Coindre, MD; Rosalba Miceli, PhD, MSc; Angelo Paolo Dei Tos, MD; Paolo G Casali MD
ISG/GEIS/FSG/PSG – STS 1001

287 pts 2011-2016

histology-tailored chemo x 3 → Surgery + RT

MLPS: Trabectedin*
LMS: GEM + DTIC*
UPS: GEM + TXT*
Synovial Sa: HD-IFX*
MPNST: IFX + VP-16*

R

- high grade
- deeply seated
- ≥5 cm

epiADM+IFX x 3 → Surgery + RT

*Ann Oncol 2012; 23:771-776
*J Clin Oncol 2011; 29:2528-2533
*Sarcoma 2017; 2017:8685638
ISG/GEIS/FSG/PSG – STS 1001

36 pts 2017-2020 with MLPS after amendment 3

- histology-tailored chemo x 3 → Surgery + RT
  - MLPS: Trabectedin
- high grade
- deeply seated
- >5 cm

epiADM+IFX x 3 → Surgery + RT
Disease Free Survival

median FU 66 months (IQ range 37-89)

5-yr DFS: 0.86 vs 0.73

HR: 0.60; 95% CI: 0.24-1.46; log-rank p=0.26

Number at risk

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Standard</th>
<th>Tailored</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>24</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>36</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>60</td>
<td>26</td>
<td>18</td>
</tr>
</tbody>
</table>
Overall Survival

- **Standard**
- **Tailored**

**median FU 66 months (IQ range 37-89)**

**5-yr OS:** 0.88 vs 0.90

HR: 1.20; 95% CI: 0.37-3.93; log-rank p=0.77

**Number at risk**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Standard</th>
<th>Tailored</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>24</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>36</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>48</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>60</td>
<td>32</td>
<td>20</td>
</tr>
</tbody>
</table>
# Toxicity T vs S

<table>
<thead>
<tr>
<th></th>
<th>Standard N=55</th>
<th>Tailored N=42</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-tax</td>
<td>13 (23%)</td>
<td>29 (69%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G1-02</td>
<td>34 (62%)</td>
<td>13 (31%)</td>
<td></td>
</tr>
<tr>
<td>G2-04</td>
<td>8 (15%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-tax</td>
<td>34 (62%)</td>
<td>28 (67%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G1-02</td>
<td>4 (7%)</td>
<td>11 (26%)</td>
<td></td>
</tr>
<tr>
<td>G3-04</td>
<td>3 (7%)</td>
<td>3 (7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Feveri Neutropenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-tax</td>
<td>41 (74%)</td>
<td>42 (100%)</td>
<td>0.004</td>
</tr>
<tr>
<td>G1-02</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>G3-04</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-tax</td>
<td>30 (54%)</td>
<td>37 (88%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G1-02</td>
<td>21 (38%)</td>
<td>5 (12%)</td>
<td></td>
</tr>
<tr>
<td>G3-04</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ocular mucosites</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-tax</td>
<td>36 (65%)</td>
<td>42 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G1-02</td>
<td>19 (35%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>G3-04</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Liver Toxicity (ALT/AST increased)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-tax</td>
<td>42 (75%)</td>
<td>22 (53%)</td>
<td>0.025</td>
</tr>
<tr>
<td>G1-02</td>
<td>12 (22%)</td>
<td>19 (45%)</td>
<td></td>
</tr>
<tr>
<td>G3-04</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-tax</td>
<td>38 (69%)</td>
<td>25 (60%)</td>
<td>0.392</td>
</tr>
<tr>
<td>G1-02</td>
<td>17 (31%)</td>
<td>17 (40%)</td>
<td></td>
</tr>
<tr>
<td>G3-04</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Nausea/Vomiting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-tax</td>
<td>2 (40%)</td>
<td>21 (50%)</td>
<td>0.599</td>
</tr>
<tr>
<td>G1-02</td>
<td>31 (56%)</td>
<td>20 (48%)</td>
<td></td>
</tr>
<tr>
<td>G3-04</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

**Hematological toxicity**

**Liver toxicity** (mainly G1-2)

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Alexandro Gronchi MD

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2022 ASCO Annual Meeting

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Sylvester Comprehensive Cancer Center
UNIVERSITY OF MIAMI HEALTH SYSTEM

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NCC Comprehesive Cancer Center
A Cancer Center Designated by the National Cancer Institute
DeFi: A Phase 3 Trial of Nirogacestat for Progressing Desmoid Tumors (DT)

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September 10, 2022
**DeFi: Phase 3 Study of Nirogacestat vs Placebo in Adult Patients With DT**

**Trial Summary**
- Global, randomized, double-blind, placebo-controlled, Phase 3 trial comparing the efficacy, safety, and tolerability of nirogacestat vs placebo in adult patients with progressing DT
- 142 patients randomized across 37 sites in North America and Europe

**Key Endpoints**
- **Primary**: Progression-free survival
- **Secondary**: Objective response rate and patient-reported outcomes, such as pain, symptom burden, physical/role function, and overall quality of life

**Adult Eligible Patients**
- Histologically confirmed DT with progressive disease per RECIST v1.1
- Treatment-naive with DT not amenable to surgery, or
- Refractory or recurrent disease (after ≥ 1 line of therapy)

**Randomization**
- 28-day cycles
- Stratified by tumor location (intra- vs extra-abdominal)

**Primary Analysis Data Cutoff:** April 7, 2022

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*Progressive disease defined by histologically confirmed DT that has progressed ≥25% within the past 12 months by RECIST v1.1. Target tumors identified at screening by the investigator.
*Progression was determined radiographically using RECIST v1.1 or clinically by independent, blinded, central radiologic or clinical review.
*As assessed by change from baseline for BPI-SF, GODDESS-DTSS, GODDESS-DTIS, and EORTC QLQ-C30 at Cycle 10.
*Radiographic disease progression or once the required number of events have been observed and the primary progression-free survival analysis has been completed.

BID, twice daily dosing; BPI-SF, Brief Pain Inventory-Short Form; DT, desmoid tumor; DTIS, GODDESS DT Impact Scale; DTSS, GODDESS DT Symptom Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GODDESS, G2/3/4 Desmoid Tumor Research Foundation; Response Evaluation Criteria in Solid Tumors. ClinicalTrials.gov: NCT03785564. Accessed August 24, 2022.

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Nirogacestat Significantly Reduced Risk of Disease Progression

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Median (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirogacestat</td>
<td>70</td>
<td>12</td>
<td>NE (NE, NE)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>72</td>
<td>37</td>
<td>15.1 (8.4, NE)</td>
<td>0.29 (0.15, 0.55)</td>
</tr>
</tbody>
</table>

No. of Participants at Risk:

- Nirogacestat: 70, 63, 56, 52, 52, 47, 46, 44, 44, 41, 26, 26, 17, 12, 4, 4, 0
- Placebo: 72, 67, 58, 47, 45, 40, 32, 29, 27, 25, 10, 8, 6, 5, 1, 1, 0

Median follow-up time was 19.2 months for nirogacestat and 10.9 months for placebo. NE, not estimable.

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PFS Benefit With Nirogacestat Was Observed Across Prespecified Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>Nirogacestat Censored/Events</th>
<th>Placebo Censored/Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.26</td>
<td>21 / 4</td>
<td>14 / 11</td>
</tr>
<tr>
<td>Female</td>
<td>0.30</td>
<td>37 / 8</td>
<td>21 / 26</td>
</tr>
<tr>
<td><strong>APC mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.20</td>
<td>9 / 2</td>
<td>3 / 8</td>
</tr>
<tr>
<td><strong>CTNNB1 mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.28</td>
<td>37 / 6</td>
<td>21 / 21</td>
</tr>
<tr>
<td><strong>Target tumor location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>0.17</td>
<td>15 / 2</td>
<td>7 / 11</td>
</tr>
<tr>
<td>Extra-abdominal</td>
<td>0.34</td>
<td>43 / 10</td>
<td>28 / 26</td>
</tr>
<tr>
<td><strong>Focality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0.29</td>
<td>37 / 6</td>
<td>22 / 19</td>
</tr>
<tr>
<td>Multifocal</td>
<td>0.30</td>
<td>21 / 6</td>
<td>13 / 18</td>
</tr>
<tr>
<td><strong>Prior surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.31</td>
<td>26 / 5</td>
<td>21 / 23</td>
</tr>
<tr>
<td>No</td>
<td>0.33</td>
<td>32 / 7</td>
<td>14 / 14</td>
</tr>
<tr>
<td><strong>Prior chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.24</td>
<td>19 / 5</td>
<td>10 / 17</td>
</tr>
<tr>
<td>No</td>
<td>0.32</td>
<td>39 / 7</td>
<td>25 / 20</td>
</tr>
<tr>
<td><strong>Prior TKI treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.15</td>
<td>19 / 4</td>
<td>8 / 16</td>
</tr>
<tr>
<td>No</td>
<td>0.38</td>
<td>39 / 8</td>
<td>27 / 21</td>
</tr>
</tbody>
</table>

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## Objective Response Rate by Blinded Independent Central Review

<table>
<thead>
<tr>
<th></th>
<th>Nirogacestat (n=70)</th>
<th>Placebo (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate (CR+PR), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>29 (41)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Two-sided P value</td>
<td>&lt;0.001</td>
<td>(3.1, 17.3)</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>5 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>24 (34)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>35 (50)</td>
<td>55 (76)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (1)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Time to objective response, median (range), mo</strong></td>
<td>5.6 (2.6, 19.4)</td>
<td>11.1 (2.8, 16.4)</td>
</tr>
<tr>
<td><strong>Kaplan-Meier estimate of median duration of objective response (95% CI), mo</strong></td>
<td>NE (NE, NE)</td>
<td>NE (8.3, NE)</td>
</tr>
</tbody>
</table>

*Duration of objective response was defined as duration in months from the time CR or PR (whichever came first) was met until the date of progression, death, or censoring.
CR, complete response; NE, not estimable; PR, partial response.

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Nirogacestat Treatment Resulted in Substantial Reductions in Tumor Size

Nirogacestat

Placebo

Change in tumor size, %

*Patient had a complete resolution of the target lesion but still had documented non-target lesion; therefore, not a complete response.

Best percent change values are averaged between 2 blinded independent reviewers unless a reader was selected for adjudication, in which case only the adjudicated value is presented.

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# Nirogacestat Safety Profile

<table>
<thead>
<tr>
<th>Safety population, n (%)</th>
<th>Nirogacestat (n=69)</th>
<th>Placebo (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of study drug exposure, median (range), months</td>
<td>20.6 (0.3, 33.6)</td>
<td>11.4 (0.2, 32.5)</td>
</tr>
<tr>
<td>Dose intensity, median (range), mg/d</td>
<td>288.3 (169, 300)</td>
<td>300.0 (239, 300)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any TEAE</th>
<th>Grade ≥3</th>
<th>Any TEAE</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>69 (100)</td>
<td>39 (57)</td>
<td>69 (96)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>58 (84)</td>
<td>1 (16)</td>
<td>25 (35)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (54)</td>
<td>1 (1)</td>
<td>28 (39)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35 (51)</td>
<td>2 (3)</td>
<td>26 (36)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>29 (42)</td>
<td>2 (3)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Rash, maculopapular</td>
<td>22 (32)</td>
<td>4 (6)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>20 (29)</td>
<td>0</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>20 (29)</td>
<td>3 (4)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TEAEs leading to death</th>
<th>0</th>
<th>1 (1)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose reductions due to TEAEs</td>
<td>29 (42)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuations due to TEAEs</td>
<td>14 (20)²</td>
<td>1 (1)²</td>
</tr>
</tbody>
</table>

- 95% of TEAEs were Grade 1 or 2; the first onset of TEAEs in most patients occurred during Cycle 1

¹Death due to sepsis.
²TEAEs leading to discontinuations in ≥1 patient include gastrointestinal disorders (n=5 [4%]), ovarian dysfunction (n=4 [3%]), alanine aminotransferase increase (n=3 [2%]), aspartate aminotransferase increase (n=2 [1%]), and metabolism disturbances (n=1 [1%]).

TEAE, treatment-emergent adverse event.

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Summary

- DeFi represents the largest and most rigorous randomized controlled trial conducted to date in DT
  - DeFi is also the first Phase 3, randomized, controlled trial to demonstrate clinical benefit with a GSI in any indication
- Nirogacestat demonstrated rapid, sustained, and statistically significant improvements in all primary and secondary efficacy endpoints
  - 71% reduction in the risk of disease progression as compared with placebo
  - Objective response rate of 41%, including a 7% complete response rate
  - Statistically significant and clinically meaningful improvements in pain, disease-specific symptom burden, physical/role functioning, and overall quality of life (P<0.007)
- Nirogacestat exhibited a manageable safety profile, with 95% of all treatment-emergent adverse events being Grade 1 or 2
- Nirogacestat has the potential to become the standard of care for patients with DT requiring systemic treatment
UPDATED EFFICACY AND SAFETY OF ENTRECINIB IN PATIENTS WITH NTRK FUSION-POSITIVE SARCOMAS

Herbert HF Loong, MD; Laura Medina, MD; Gabriel Tinoco, MD; Ignacio Carrido-Laguna, MD, PhD; Koichi Goto, MD; Conor Steuer, MD; Stephen Y Liu, MD; Stuart Osborne, MSc; Walter Bordogna, PhD; Sebastian Heinzmann, PhD; Harald Zeuner; George Demetri, MD

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4. Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA
5. National Cancer Center Hospital East, Kashiwa, Japan
6. Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA
7. Georgetown University Medical Center, Washington, DC, USA
8. F. Hoffmann-La Roche Ltd, Basel, Switzerland
9. Dana-Farber Cancer Institute and Ludwig Center at Harvard Medical School, Boston, MA, USA
Introduction

- NTRK1/2/3 gene fusions encode constitutively active tropomyosin receptor kinase (TRK) proteins, which act as oncogenic drivers in many solid tumor types.\(^1\)
  - NTRK gene fusions occur in \(<5\%\) of sarcoma cases.\(^2,3,4\)

- Entrectinib is an oral, CNS-active, potent inhibitor of TRK proteins with proven efficacy in a range of NTRK-fp solid tumors.\(^5\)

- Entrectinib demonstrated an ORR of 56\% in a previous analysis of 16 patients with NTRK-fp sarcomas (data cut-off 31 Oct 2018).\(^6\)

We present an updated analysis (data cut-off: 31 Aug 2020) of the NTRK-fp sarcoma cohort, with more patients (N=26 vs. 16 previously) and a longer follow-up (median 22.3 months vs. 17.7 months).
The *NTRK*-fp sarcoma cohort showed a 57.7% ORR

<table>
<thead>
<tr>
<th>Response</th>
<th>n/N (%)</th>
<th>Sarcoma tumor histology</th>
</tr>
</thead>
</table>
| BICR ORR | 15/26 (57.7) | • Other sarcoma (7)  
          | (95% CI 36.9–76.7)  
          | • Spindle cell sarcoma (3)  
          |         | • GIST (2)  
          |         | • Cervical adenocarcinoma (1)  
          |         | • Endometrial stromal sarcoma (1)  
          |         | • Leiomyosarcoma (1) |
| CR       | 3/26 (11.5)   | • Other sarcoma (2)  
          |         | • GIST (1) |
| PR       | 12/26 (46.2) | • Other sarcoma (5)  
          |         | • Spindle cell sarcoma (3)  
          |         | • Cervical adenocarcinoma (1)  
          |         | • Endometrial stromal sarcoma (1)  
          |         | • GIST (1)  
          |         | • Leiomyosarcoma (1) |
| SD       | 4/26 (15.4)   | • Other sarcoma (1)  
          |         | • Angiosarcoma (1)  
          |         | • Follicular dendritic cell sarcoma (1)  
          |         | • MPNST (1) |
| PD       | 5/26 (19.2)   | • Other sarcoma (2)  
          |         | • Chondrosarcoma (1)  
          |         | • Inflammatory myofibroblastic tumor (1)  
          |         | • Leiomyosarcoma (1) |
| Missing/unevaluable | 2/26 (7.7)   | • Spindle cell sarcoma (2) |

*Enrollment cut-off: 31 Jul 2019; data cut-off: 31 Aug 2020*

Patients without matched pre/post therapy scans were excluded and patients without measurable disease at baseline were excluded. *ORR was assessed by BICR as per RECIST v1.1*; *Target lesions; Response classification based on target and non-target lesions (RECIST v1.1) and assessed by BICR.*

Presented by: Herbert HF Loong, MD

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Median overall survival was longer than previously reported in patients with NTRK-fp sarcomas.

<table>
<thead>
<tr>
<th></th>
<th>Total (N=26)</th>
<th>Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with event, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-month event-free rate, % (95% CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Enrolment cut-off: 31 Jul 2019; data cut-off: 31 Aug 2020. Median duration of survival follow-up: 22.3 months. *PFS was assessed by BICR with RECIST v1.1
Conclusions

- In this integrated analysis of entrectinib activity in patients with NTRK-fp sarcomas, with more patients and a longer follow-up than previously reported:
  - ORR was 57.7%
    - In an updated analysis (data cut-off 02 August 2021) with 6 additional patients with NTRK fusion-positive sarcomas, ORR was 59.4% (n=19/32)\(^1\)
  - Median DoR was **15.0 months**
  - Median PFS was **10.1 months** and median OS was **18.7 months**
- Entrectinib demonstrated meaningful responses **across a range of sarcoma histologies**
- One of two patients with baseline CNS metastases had an **intracranial complete response**
- Entrectinib demonstrated a **manageable safety profile**, consistent with previous reports

We would like to thank the patients, their families, and participating study centres and look forward to answering your questions

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ABI-009 (nab-sirolimus) in Advanced Malignant Perivascular Epithelioid Cell Tumors (PEComa): Preliminary Efficacy, Safety, and Mutational Status from AMPECT, an Open-label Phase 2 Registration Trial

Andrew J. Wagner, MD, PhD,1 Vinod Ravi, MD,2 Kristen N. Ganjoo, MD,3 Brian A. Van Tine, MD,4 Richard F. Riedel, MD,5 Rashmi Chugh, MD,6 Lee D. Cranmer, MD, PhD,7 E. Maria Gordon, MD,8 Jason L. Hornick, MD, PhD,9 David J. Kwiatkowski, MD, PhD,9 Heng Du, MD,9 Derta Grigorian,10 Anita N. Schmid, PhD,10 Shihe Hou, PhD,10 Katherine Harris, DrP H,10 Neil Desai, PhD,10 Mark A. Dickson, MD11

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2. MD Anderson Cancer Center, Houston, TX
3. Stanford University, Stanford, CA
4. Washington University in Saint Louis, St. Louis, Missouri
5. Duke Cancer Institute, Durham, NC
6. University of Michigan
7. Univ Washington/Fred Hutchinson Cancer Res Ctr, Seattle, WA
8. Sarcoma Oncology Center, Santa Monica, CA
9. Brigham and Women’s Hospital, Boston, MA
10. Aadi Bioscience, Pacific Palisades, CA
11. Memorial Sloan Kettering Cancer Center, New York, NY
Patients received sirolimus protein-bound particles at 100 mg/m² on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity.

ORR was 39% including 2 patients with CR.

Among responders, 67% had a response lasting >12 months and 58% had a response lasting >than 24 months.

FDA Approved
Take Home Points

- HD Ifosfamide is the confirmed best option for a relapsed Ewing’s patient if no clinical trials are available.
- Consider mutation testing analysis on all progressing GIST patients.
- Trabectedin can be considered for myxoid liposarcoma patients who need neoadjuvant chemotherapy and predicted to not tolerate standard anthracycline/Ifosfamide.
- The combination of lenvatinib and eribulin is promising, warrants confirmatory randomized trial.
- NGS should be considered in patients that will undergo systemic therapy and/or have refractory/relapse disease – possibility of NTRK-fp.
- FDA approved new drugs: Nirogacestat for DT and nab-Sirolimus for PEComa.
Thank you!

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Twitter: @PriscilaBCMD