GIST et Sarcomes des tissus mous et osseux

Bruges, le 22 Juin 2016
Dose Escalating Study of Crenolanib Besylate in Advanced GIST Patients with *PDGFRA D842V* Activating Mutations

Margaret von Mehren, MD, Eric Tetzlaff, MD, Meghan Macaraeg, BS, Jeremy Davis, MS, Vartika Agarwal, MS, Abhijit Ramachandran, MS, Michael C. Heinrich, MD
Dose Escalating Study of **Crenolanib** in GIST Patients with **PDGFRA** D842V Activating Mutations

<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>

A placebo controlled randomized phase III trial with crenolanib in patients with **PDGFRA** D842V mutated GIST is being initiated. (EudraCT Number: 2015-000287-34)
### PDGFRA Exon 18 GISTs (N=71, 3 databases)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>D842V mutated (48)</th>
<th>Non-D842V mutated (23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (58.3%)</td>
<td>15 (65.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (42.9%)</td>
<td>8 (34.8%)</td>
</tr>
<tr>
<td><strong>Age in years (median:range)</strong></td>
<td>56 (23-80)</td>
<td>62 (46-87)</td>
</tr>
<tr>
<td><strong>Tumor status at registry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local disease</td>
<td>33 (68.8%)</td>
<td>15 (65.2%)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>11 (22.9%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>Metastasized</td>
<td>4 (8.3%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43 (89.6%)</td>
<td>21 (91.3%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (10.4%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td><strong>Imatinib treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (45.8%)</td>
<td>14 (60.9%)</td>
</tr>
<tr>
<td>No</td>
<td>26 (54.2%)</td>
<td>9 (39.1%)</td>
</tr>
<tr>
<td><strong>Treatment objective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neo-adjuvant</td>
<td>12 (20.8%)</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Palliative</td>
<td>5 (12.5%)</td>
<td>5 (17.4%)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>5 (12.5%)</td>
<td>6 (30.4%)</td>
</tr>
<tr>
<td>No systemic treatment</td>
<td>25 (54.2%)</td>
<td>9 (39.1%)</td>
</tr>
</tbody>
</table>

*Figure 2. Radiological responses according to Choi’s criteria in patients with measurable disease treated with imatinib.*

*Figure 3. Partial response to imatinib seen in patient with a PDGFRA D842V mutated GIST.*
**New Oncogenic RTK translocation in quadruple negative WT GIST**

<table>
<thead>
<tr>
<th>GIST classification</th>
<th>Fusion Panel results</th>
<th>SDHB IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-WT GIST</td>
<td><em>ETV6-NTRK3</em></td>
<td>Positive</td>
</tr>
<tr>
<td>Q-WT GIST</td>
<td>None detected</td>
<td>Positive</td>
</tr>
<tr>
<td>Q-WT GIST</td>
<td>None detected</td>
<td>Positive</td>
</tr>
<tr>
<td>Potential Q-WT GIST</td>
<td><em>FGR1-TACC1</em></td>
<td>Unknown</td>
</tr>
<tr>
<td>Potential Q-WT GIST</td>
<td>None detected</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
LOX-101 (anti-NTRK3) in ETV6-NTRK3 fusion GIST

- 55 yo male with GIST progressed through imatinib, sunitinib, sorafenib, nilotinib, and regorafenib
- 150mg BID 28 day cycle
- Confirmed partial response
- Currently on study in cycle 10

Baseline                     Cycle 3                   Cycle 9

PET

David Hong MDA
AACR 2016
Sarcomes des tissus mous et osseux
Efficacy of **Busulfan-Melphalan** high dose chemotherapy consolidation in localised high-risk Ewing sarcoma:

Results of EURO-E.W.I.N.G 99 R2Loc randomised trial
EURO-E.W.I.N.G 99 stratification

All newly diagnosed Ewing Sarcoma up to age 50 years

Localised disease

- Surgery after VIDE
- Histological response

- Histological response
  - <10%
  - ≥10%

- Initial tumour volume
  - <200ml
  - ≥200ml

- Localised High risk
  - R2Loc

Metastatic disease

- Pulmonary metastases
  - R2Pulm

- Other metastases
  - R3

- Initial surgery
  - Pre-op RT
  - Exclusive RT

- Standard risk
  - R1

Le Deley et al, JCO 2014
Ladenstein et al, JCO 2010
VAI: vincristine, actinomycin D, ifosfamide x 7
BuMel: Busulfan-Melphalan x 1
with stem cell rescue
Flow chart

3223 patients assessed for eligibility

591 localised high risk patients

2632 pts without localised high-risk disease

107 assigned to VAI
103 eligible for R2loc trial
4 not eligible for R2loc trial

109 assigned to Bu-Mel
101 eligible for R2loc trial
8 not eligible for R2loc trial

261 pts not included
164 patient/clinician reasons
97 for miscellaneous reasons

477 pts documented as met eligibility criteria

114 Loc-HR pts did not meet eligibility criteria

106 received assigned intervention
1 received Bu-Mel

107 in the intention-to-treat analysis

109 received assigned intervention
17 did not receive any HDT
5 received another HDT

109 in the intention-to-treat analysis

216 pts ® in the R2Loc trial
from 112 centres, 13 countries

190 pts ® in the R2Loc trial
from 112 centres, 13 countries

106 received assigned intervention
1 received Bu-Mel

107 in the intention-to-treat analysis

109 received assigned intervention
17 did not receive any HDT
5 received another HDT

109 in the intention-to-treat analysis

591 localised high risk patients

477 pts documented as met eligibility criteria

114 Loc-HR pts did not meet eligibility criteria

261 pts not included
164 patient/clinician reasons
97 for miscellaneous reasons

3223 patients assessed for eligibility
Benefit of BuMel on Event-Free Survival

ITT analysis, 103 events

BuMel, 3-y EFS= 67%
VAI, 3-y EFS=53%

HR = 0.64 (95%CI, 0.43-0.94)  
p= 0.024

Translates into better Overall Survival

ITT analysis, 88 deaths

BuMel, 3-y OS= 78%
VAI, 3-y OS=70%

HR = 0.60 (95%CI, 0.39-0.92)  
p= 0.019
No major heterogeneity of BuMel effect on EFS across subgroups
Acute toxicity analysis
EURO-E.W.I.N.G 99 stratification

All newly diagnosed EwS up to age 50 yrs

Localised tumour

- Surgery after VIDE
- Histological response
  - <10%
  - ≥10%
- Initial tumour volume
  - <200ml
  - ≥200ml

  - Standard risk
    - R1
      - Le Deley et al, JCO 2014

  - Localised High risk
    - R2Loc

Metastatic tumour

  - Pulmonary metastasis
    - R2Pulm
  - Other metastasis
    - R3

Ladenstein et al, JCO 2010
Haeusler et al, 2010
Randomization in R2 pulm

- R 2
- VIDE x 6
- Randomisation
- VAI x 1
- VAI x 7
- & Whole Lung Irradiation (WLI)
- BuMelHD x 1
No Benefit of BuMel on Overall Survival

**ITT analysis**

BuMel, 3-y EFS= 55%

VAI+WLI, 3-y EFS=51%

HR = 0.82 (95%CI, 0.58 – 1.15)

p= 0.24

No benefit on Overall Survival

BuMel, 3-y OS= 68%

VAI+WLI, 3-y OS=68%

HR = 0.96 (95%CI, 0.65 – 1.40)

p= 0.82
Regorafenib in doxorubicin-pre-treated patients with advanced soft tissue sarcomas: final analysis of a stratified double-blind placebo-controlled randomized phase II trial

Study Design

- Randomized, double-blind, placebo-controlled, multi-center phase II trial with 4 parallel cohorts in pts with refractory STS – Preliminary results presented at last ASCO meeting
- Pts were assigned in a 1:1 ratio to receive either regorafenib plus BSC or placebo plus BSC

Until unacceptable toxicity or progression. Pts receiving PBO who experience PD were offered open-label RE
Liposarcoma

Progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1 (0.9-2.3)</td>
<td>1.7 (0.9-1.8)</td>
<td>1.13</td>
<td>0.700</td>
</tr>
</tbody>
</table>

Same results observed with Pzb
Non-Adipocytic sarcoma: pooled analysis

PFS

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regorafenib</td>
<td>4.0 (2.6-5.5)</td>
<td>0.36 [0.26-0.53]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.0 (1.0-1.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OS

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regorafenib</td>
<td>13.4 (8.6-17.3)</td>
<td>0.67 [0.44-1.02]</td>
<td>0.060</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.0 (6.8-12.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Improved sarcoma management in a national network of reference centers: Analysis of the NetSarc network on 13,454 patients treated between 2010 and 2014

Jean-Yves Blay, Axel Le Cesne, Nicolas Penel, Emmanuelle Bompas, Florence Duffaud, Christine Chevreau, Maria Rios, Pierre Kerbrat, Didier Cupissol, Philippe Anract, Jean-Emmanuel Kurtz, Celeste Lebbe, Nicolas Isambert, Francois Bertucci, Antoine Thyss, Sophie Piperno-Neumann, Pascale Dubray-Longeras, Francoise Ducimetiere, Jean-Michel Coindre, Antoine Italiano from the French Sarcoma Group
Origin of patients in MDT of NetSARC

These represent an estimated 78% of sarcoma case in France in 5 years.
Relapse free survival n=13454 pts

Patients whose primary surgery was performed in Netsarc centers had R0, R1, R2 surgery in 49%, 27%, 7% vs 24%, 31%, 21% in centers outside Netsarc (p<0.000001).
Patterns of care and outcome of metastatic soft-tissue sarcoma (STS) patients (pts) according to histological subtype and treatment setting: the METASARC study

Antoine Italiano, Axel Le Cesne, Jean-Yves Blay, Isabelle Ray Coquard, Olivier Mir, Maud Toulmonde, Philippe Terrier, Dominique Ranchere-Vince, Pierre Meeus, Eberhard Stoeckle, Charles Honoré, Paul Sargos, Marie-Pierre Sunyach, Cécile Le Péchoux, Antoine Giraud, Carine Bellera, Marion Savina, Jean-Michel Coindre
Patients with advanced STS: the METASARC study

<table>
<thead>
<tr>
<th>No treatment</th>
<th>N = 2225</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>No treatment</td>
<td>625 (28%)</td>
<td>elderly</td>
</tr>
<tr>
<td>1\textsuperscript{st} line</td>
<td>1600 (72%)</td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} line</td>
<td>950</td>
<td>Lost: 41%</td>
</tr>
<tr>
<td>3\textsuperscript{rd} line</td>
<td>650</td>
<td>Lost: 32%</td>
</tr>
<tr>
<td>4\textsuperscript{th} line</td>
<td>496</td>
<td>Lost: 24%</td>
</tr>
<tr>
<td>5\textsuperscript{th} line</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>6\textsuperscript{th} line</td>
<td>134</td>
<td></td>
</tr>
</tbody>
</table>
### Impact of locoregional treatment of metastases on OS (patients treated with systemic treatment, n=1600)

<table>
<thead>
<tr>
<th>T to next tt (n=1600)</th>
<th>p</th>
<th>HR [IC95%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional tt of mets</td>
<td>&lt;.0001</td>
<td>0.485 [0.430; 0.547]</td>
</tr>
<tr>
<td>Grade: 3</td>
<td>&lt;.0001</td>
<td>1.380 [1.226; 1.554]</td>
</tr>
<tr>
<td>PolyCT in 1st line</td>
<td>0.0048</td>
<td>0.821 [0.716; 0.942]</td>
</tr>
<tr>
<td>Sex: Female</td>
<td>0.0032</td>
<td>0.837 [0.744; 0.942]</td>
</tr>
<tr>
<td>Labelled drugs</td>
<td>0.0022</td>
<td>0.728 [0.594; 0.892]</td>
</tr>
<tr>
<td>Anthracycline in 1st line</td>
<td>0.0090</td>
<td>0.828 [0.718; 0.954]</td>
</tr>
</tbody>
</table>
Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial


OS = 15 vs 8 mos

Lancet 2016 Feb 10 [Epub]

S. Hudgens (abstract 11015)
Trabectedin + olaparib: ISG phase 1b of trial

Recommended dose:
T: 1.3 mg/m2
O: 150 mg BID
Immunotherapy in Sarcoma: Where Do We Go From Here?

Breelyn A. Wilky, MD
Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine
Timeline of Immunotherapy in Sarcoma

1890s
- William Coley

1980 - 2005
- Cytokines +/- chemo
  - IL-2 (high dose)
  - IFN-α/β
  - mifamurtide

2005 - 2012
- Vaccines
  - Autologous tumor cells
  - Dendritic cells
  - GVAX

2010
- Adoptive T cell therapy – NY-ESO-1+ synovial sarcoma

2013 - today
- Checkpoint inhibitors

Wilky and Goldberg, Discov Med 2014
Abstract 1 – SARC 028 Pembrolizumab

- 11/37 with tumor regressions, UPS, dedifferentiated LPS, and synovial sarcoma
- Overall 19% ORR rate by RECIST, additional 40% of patients with best response of stable disease
  - Melanoma 33%
  - NSCLC 19%
  - >20% ORR gastric, bladder, head and neck

LMS: 0/11
LPS: 1/9
SS: 1/8
UPS: 4/9
Abstract 1 – SARC 028 Pembrolizumab

- Median F/U - 7.5 months
- 4-months PFR 44% [C.I., 22%-66%] statistically significant improvement relative to historical control PFR rate (20%)
Abstract 1 – SARC 028 Pembrolizumab

- 3 patients with partial responses

OS: 1/19
Ewing: 0/13
CS: 1/9
Abstract 2 – Phase 2 Nivolumab for uLMS

- 12 patients – small numbers
- All with progressive disease at 3 month scans
- Consistent with lack of response for LMS in SARC 028
- However one exceptional responder reported separately
Integrative assessment of expression/levels and prognostic value of PD-L1, IDO1 and Kynurenine in 328 Primary Soft Tissue Sarcomas with Genomic Complexity

Maud Toulmonde, Julien Adam, Alban Bessège, Dominique Ranchère-Vince, Valérie Velasco, Véronique Brouste, Jean-Yves Blay, Olivier Mir and Antoine Italiano, on behalf of the GSF-GETO French Sarcoma Group
PD-L1 Expression in Sarcoma

- About 20% positivity in sarcomas
- Problems with PD-L1 as biomarker (staining, transient expression, heterogeneity)
- May not be required for response
- Await analysis of responders in Tawbi trial

<table>
<thead>
<tr>
<th></th>
<th>IHC PDL1 % positive</th>
<th>IHC PD1 % positive</th>
<th>IHC PDL2 % positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>malignant cells</td>
<td>non-malignant cells</td>
<td>malignant cells</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>na</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Breeklin A. Wilky (discutant)
Results – Prognostic Factors

Potential role of Kynurénine on OS

IDO1 was more expressed in UPS than LMS (48% vs 30% p=0.01)

M. Toulmonde (abstract 11008)
Potential Predictive Biomarkers for Checkpoint Blockade

- Tumor PD-L1 expression? Most tumors, but some responders even in PD-L1 negative tumors (RCC, melanoma, squamous NSCLC)
- PD-1/PD-L1 expression on TIL (Bladder, melanoma)
- Presence of CD8+ TIL, particularly at tumor invasive margin (melanoma)
- High somatic mutation burden (MMR deficient colorectal cancer, melanoma, NSCLC)
- Low Tregs/MDSC in tumor OR peripheral blood (melanoma)
- Elevated IDO1/2 and KYN (linked to anti-CTLA4 activity in melanoma)
- And many more…

### Results – Prognostic Factors

**Potential role of IDO1/Kyn and CD8 effector cells?**

- STS with genomic complexity have heterogeneous immune infiltrates.

<table>
<thead>
<tr>
<th>Percentage</th>
<th>PD-L1+ And/or IDO1/KYN+ CD8+</th>
<th>PD-L1+ And/or IDO1/KYN+ CD8-</th>
<th>PD-L1- And IDO1/KYN- CD8+</th>
<th>PD-L1- And IDO1/KYN- CD8-</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>Adaptive resistance</td>
<td>Intrinsinc inhibition</td>
<td>Tolerance</td>
<td>Ignorance</td>
</tr>
<tr>
<td>25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Additional biomarker / immunocorrelative studies are critical for future trials to further delineate immunoactive sarcomas (Breeklin A. Wilky, discutant)

Adapted from Snolz et al. *Clin Cancer Res.*, 2013
Merci