ESMO Briefing

Paolo Paoletti, MD
President, GSK Oncology
Since ASCO

- Promacta/Revolade® study in aplastic anaemia published in New England Journal of Medicine
- Withdrawal of Tykerb/Tyverb® FDA application for dual blockade
- EU approval for Votrient® in advanced soft tissue sarcoma
- Dabrafenib monotherapy submissions in US and EU
- Trametinib monotherapy submission in US
- Submission of PMA for companion diagnostic by bioMerieux
Our Growth

GSK
Oncology in H1 2012 was £375m +22% CER
Key ESMO Highlights

• Combination Dabrafenib+Trametinib
  – Randomised, open-label data for dabrafenib alone vs combination in pts with BRAF V600 mutation-positive metastatic melanoma

• Votrient®
  – Results of the COMPARZ trial
  – Results of HRQoL data from PALETTE
  – Quality of life (QoL) in renal cell carcinoma patients in a randomised double blind cross-over patient preference study of pazopanib versus sunitinib

• Tykerb/Tyverb®
  – Results from CEREBEL (Tykerb/Tyverb plus capecitabine vs. Trastuzumab plus capecitabine)

• PRAME
  – Immunogenicity and safety of the PRAME cancer immunotherapeutic in metastatic melanoma: phase I/II dose escalation study
Dabrafenib+Trametinib Phase II Randomised Data: Study 113220

Dr. Georgina Long, BSc, PhD, MBBS, FRACP
Westmead Hospital and the Melanoma Institute
Australia
Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffery R. Infante, M.D., Adil Daud, M.D., Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D., Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D., Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris, III, M.D., Gerald Felchick, M.D., Alain Algazi, M.D., Karl Lewis, M.D., Georgina V. Long, M.D., Ph.D., Igor Ruzanov, M.D., M.S.C.I., Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shandra Little, M.P.H., Peng Sun, Ph.D., Alicia Allred, Ph.D., Danielle Ouellet, Ph.D., Kevin R. Kim, M.D., Kiran Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

September 29, 2012 | DOI: 10.1056/NEJMoa1210093
Randomised Phase II study of BRAF inhibitor dabrafenib vs combination with MEK inhibitor trametinib in BRAF V600 mutant metastatic melanoma

Rationale for Combination

BRAFi (dabrafenib)
- PFS 5.1 mo; RR 53%\(^1\)

MEKi (trametinib)
- OS HR 0.54 vs chemo
- PFS 4.8 mo; RR 22%\(^2\)

Preclinical BRAFi + MEKi
- Delays BRAFi resistance
- Hyperproliferative skin AE


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Part C Randomised Phase II Study Design

- BRAF V600E/K metastatic melanoma
- No prior BRAFi or MEKi
- Up to 1 prior treatment
- Treated and stable brain mets

N=162

Monotherapy D 150mg BID*
N=54

Combination D+T 150/1
N=54

Combination D+T 150/2
N=54

*cross over to Combination D+T 150/2 after progression allowed

Objectives
- PFS, ORR, duration of response, incidence rate of cuSCC and safety
- OS

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## Confirmed Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Mono D (N=54)</th>
<th>Combination D+T 150/1 (N=54)*</th>
<th>Combination D+T 150/2 (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>PR</td>
<td>27 (50)</td>
<td>24 (44)</td>
<td>36 (67)</td>
</tr>
<tr>
<td>SD</td>
<td>22 (41)</td>
<td>24 (44)</td>
<td>13 (24)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Response Rate</strong> †</td>
<td>29 (54%)</td>
<td>27 (50%)</td>
<td>41 (76%)</td>
</tr>
<tr>
<td><strong>Duration of Response Months (95% CI)</strong></td>
<td>5.6 (4.5, 7.4)</td>
<td>9.5 (7.4, NA)</td>
<td>10.5 (7.4, 14.9)</td>
</tr>
</tbody>
</table>

*1 patient in 150/1 group was not evaluable*
Progression-Free Survival

Med (mos) HR (95% CI), P-Value 12 mo. PFS rate

Mono D 5.8 0.56 (0.37, 0.87), 0.006 9%
150/1 9.2 0.39 (0.25, 0.62), <0.0001 26%
150/2 9.4

PFS rate

9%
26%
41%

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Overall Survival

12 mo. OS

Median HR, P-Value

12 mo. OS rate

- Mono D NR
  - Median 150/1 NR 0.98, NS
  - Median 150/2 NR 0.67, NS

- 70%
- 68%
- 79%

Med follow up time 14 mo

43/54 (80%) Monotherapy D crossed to 150/2

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### MEKi and BRAFi Associated Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy D (n=53)</th>
<th>Combination D+T 150/1 (n=54)</th>
<th>Combination D+T 150/2 (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>16 (30)</td>
<td>2 (4)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>8 (15)</td>
<td>4 (7)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>16 (30)</td>
<td>3 (6)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Squamous cell carcinoma/keratoacanthoma</td>
<td>10 (19)</td>
<td>1 (2)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.004</td>
<td>0.09</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>5 (9)</td>
<td>4 (7)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Rash/Skin toxicities*</td>
<td>36 (68)</td>
<td>31 (57)</td>
<td>36 (65)</td>
</tr>
<tr>
<td>Acneiform rash</td>
<td>2 (4)</td>
<td>6 (11)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Peripheral Oedema</td>
<td>4 (8)</td>
<td>9 (17)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>↓Ejection Fraction</td>
<td></td>
<td>2 (4)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Chorioretinopathy</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*Skin toxicities include multiple terms
No cases of RVO

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<table>
<thead>
<tr>
<th></th>
<th>Monotherapy D (n=53*)</th>
<th>Combination D+T 150/1 (n=54)</th>
<th>Combination D+T 150/2 (n=55*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia†</td>
<td>12 (23)</td>
<td>34 (63)</td>
<td>37 (67)</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (17)</td>
<td>22 (41)</td>
<td>28 (51)</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>3 (6)</td>
<td>8 (15)</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (34)</td>
<td>25 (46)</td>
<td>25 (45)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (26)</td>
<td>22 (41)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9 (17)</td>
<td>11 (20)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (11)</td>
<td>15 (28)</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (17)</td>
<td>18 (33)</td>
<td>18 (33)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (23)</td>
<td>8 (15)</td>
<td>17 (31)</td>
</tr>
</tbody>
</table>

† pyrexia = temperature ≥ 38.5 degrees Celsius
*Mono D (n=53) - 1 patient in this arm received Combination D+T 150/2 (n=55) due to a dispensing error
Conclusions

- This is the 1st kinase-kinase combination to:
  - Show enhanced anti-tumour activity over the single agent
  - Reduce specific oncogenic toxicities, with biological rationale

- Combined dabrafenib and trametinib prolongs PFS and ORR over dabrafenib alone in BRAF^{V600} metastatic melanoma:
  - Med PFS 9.4 mo vs 5.8 mo; HR 0.39; p<0.0001
  - ORR 76% vs 54%; p=0.026

- Combined dabrafenib and trametinib safety profile was tolerable and manageable:
  - ↓cuSCC events
  - ↑pyrexia, neutropenia and GI toxicities

- Two phase III studies (COMBI-d and COMBI-v) are ongoing
Study Objectives

Primary

• To evaluate and compare PFS in patients treated with pazopanib to those treated with sunitinib

Secondary

• Overall survival (OS)
• Objective response rate (ORR)
• Safety
• Patient-reported outcomes
Study Design

Key Eligibility Criteria
- Advanced/metastatic RCC
- Clear-cell histology
- No prior systemic therapy
- Measurable disease (RECIST 1.0)
- KPS $\geq 70$
- Adequate organ function

Stratification Factors
- KPS 70/80 vs 90/100
- Prior nephrectomy
- Baseline LDH $>1.5$ vs $\leq 1.5 \times$ ULN

Pazopanib
800 mg qd continuous dosing
Dose reductions to 600 mg or 400 mg

Randomized 1:1

Sunitinib
50 mg qd
4 wk on/2 wk off
Dose reductions to 37.5 mg or 25 mg
Statistical Analysis Plan

- PFS non-inferiority demonstrated if upper bound of 95% CI for HR<1.25
  - Cox proportional hazard analysis adjusted for stratification factors
  - By independent review
- 631 PFS events needed for 80% power
- Planned enrollment of 1100 patients
Primary Endpoint: Progression-free Survival (independent review)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>557</td>
<td>8.4 mo (8.3, 10.9)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553</td>
<td>9.5 mo (8.3, 11.1)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 1.047 (0.898, 1.220)
Primary Endpoint: Progression-free Survival (independent and investigator review)

Independent HR (95% CI) = 1.047 (0.898, 1.220)
Investigator HR (95% CI) = 0.998 (0.863, 1.154)
<table>
<thead>
<tr>
<th>Best overall response, %</th>
<th>Pazopanib (n = 557)</th>
<th>Sunitinib (n = 553)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>Stable disease</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

**Objective Response Rate, %**

<table>
<thead>
<tr>
<th></th>
<th>31</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>26.9, 34.5</td>
<td>21.2, 28.4</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>0.032</td>
<td></td>
</tr>
</tbody>
</table>
### Interim Analysis of Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>557</td>
<td>28.4 mos (26.2, 35.6)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553</td>
<td>29.3 mos (25.3, 32.5)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.908 (0.762, 1.082)
P-value = 0.275
## Most Common Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event a</th>
<th>All Grs</th>
<th>All Grs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event b</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55</td>
<td>63</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>ALT increased</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>Taste Alteration</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>34</td>
</tr>
</tbody>
</table>

a AE ≥30% in either arm  
b2% of patients in pazopanib arm and 3% of patients in sunitinib arm had grade 5 adverse events.
Relative Risk in Adverse Events

AE occurrence $\geq 10\%$ in either arm; 95% CI for RR does not cross 1

- Hair color change
- Weight decreased
- Serum ALT increased
- Alopecia
- Upper abdominal pain
- Serum AST increased
- Fatigue *
- Rash *
- Pain in extremity
- Constipation
- Taste Alteration *
- LDH increased
- Serum creatinine increased
- Serum AST increased
- Peripheral edema
- Hand-foot syndrome *
- Dyspepsia *
- Pyrexia
- Leukopenia
- Hypothyroidism
- Epistaxis
- Serum TSH increased
- Mucositis *
- Neutropenia
- Anemia
- Thrombocytopenia

0.1 Favors pazopanib 1 Favors sunitinib 10
## Quality of Life Results (first 6 months)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Domain Name</th>
<th>Treatment difference in mean change vs sunitinib&lt;sup&gt;1&lt;/sup&gt;</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACIT-F</td>
<td>Fatigue/Total score</td>
<td>2.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FKS1-19</td>
<td>Kidney Symptom Index/Total score</td>
<td>1.41</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>0.78</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>Emotional</td>
<td>-0.05</td>
<td>0.409</td>
</tr>
<tr>
<td></td>
<td>Treatment Side Effects</td>
<td>0.31</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Functional Well Being</td>
<td>0.31</td>
<td>0.098</td>
</tr>
<tr>
<td>Cancer Treatment Satisfaction Questionnaire</td>
<td>Expectations of Therapy</td>
<td>1.41</td>
<td>0.284</td>
</tr>
<tr>
<td></td>
<td>Feelings about Side Effects</td>
<td>8.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Satisfaction with Therapy</td>
<td>3.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supplemental Quality of Life Questionnaire</td>
<td>Three items on Mouth and Throat Soreness (MTS), Hand soreness (H) and Foot soreness (F)</td>
<td>-0.505</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.204</td>
<td>0.0016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.267</td>
<td>0.0008</td>
</tr>
<tr>
<td></td>
<td>Two items on limitations due to MTS and F</td>
<td>0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.65</td>
<td>0.014</td>
</tr>
</tbody>
</table>

<sup>1</sup> **Yellow Font**: favors pazopanib. **Blue Font**: favors sunitinib. P-value <0.05 is statistically significant.
Conclusions

• This phase III trial demonstrates non-inferiority of pazopanib relative to sunitinib for progression-free survival

• Pazopanib efficacy is further supported by similar response rates and overall survival

• The differentiated safety profile of pazopanib includes:
  – Lower incidence of hand-foot syndrome, fatigue, and mucositis
  – Higher incidence of liver function test abnormalities

• Improved tolerability supported by better QoL scores for patients receiving pazopanib
Questions?