Proffered Paper & Poster Discussion – Developmental Therapeutics

Abstracts No. 125O & 126O

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Disclosure slide

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  • MSD

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  • Bayer, BMS, MSD, Novartis, Roche
Abstracts 125O & 126O

• 125O – Hollebecque et al.
  • First-in-human study of oral S 49076, a MET/AXL/FGFR inhibitor in advanced solid tumors

• 126O – Li et al.
  • A phase 1 study evaluating the safety, efficacy, pharmacokinetics of AL3810 (lucitanib) in advanced solid tumors
Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

• S 49076 is an ATP-competitive tyrosine kinase inhibitor with specific activity on MET, AXL and FGFR 1/2/3

IC50 values in radiometric assays on various mutant isoforms

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Examples of tumors where these mutations have been detected</th>
<th>IC50 (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>MET&lt;sup&gt;D1248N&lt;/sup&gt;</td>
<td>Germline renal papillary carcinoma</td>
<td>8</td>
</tr>
<tr>
<td>MET&lt;sup&gt;Y1248C&lt;/sup&gt;</td>
<td>Renal cell carcinoma</td>
<td>16</td>
</tr>
<tr>
<td>MET&lt;sup&gt;D1248H&lt;/sup&gt;</td>
<td>Somatic papillary renal cell carcinoma</td>
<td>11</td>
</tr>
<tr>
<td>MET&lt;sup&gt;Y1248D&lt;/sup&gt;</td>
<td>Head and neck squamous cell carcinoma</td>
<td>17</td>
</tr>
<tr>
<td>MET&lt;sup&gt;Y1248H&lt;/sup&gt;</td>
<td>Renal cell carcinoma, non-small-cell lung carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>MET&lt;sup&gt;M1268T&lt;/sup&gt;</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>AXL</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>MER</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>FGFR1</td>
<td>—</td>
<td>18</td>
</tr>
<tr>
<td>FGFR1&lt;sup&gt;V561M&lt;/sup&gt;</td>
<td>Squamous cell lung cancer</td>
<td>23</td>
</tr>
<tr>
<td>FGFR2</td>
<td>—</td>
<td>17</td>
</tr>
<tr>
<td>FGFR2&lt;sup&gt;N549H&lt;/sup&gt;</td>
<td>Endometrial carcinoma</td>
<td>19</td>
</tr>
<tr>
<td>FGFR3</td>
<td>—</td>
<td>15</td>
</tr>
</tbody>
</table>

Appleman LJ. JCO 2011
Burbridge et al. Mol Cancer Ther 2013
MET, AXL and FGFR TKI: S 49076

- S 49076 inhibits tumour growth in xenografts expressing activated MET, AXL or FGFR
- S 49076 is highly active in a bevacizumab-resistant model

**U87-MG glioblastoma - HGF-MET autocrine loop**

- Untreated
- S 49076 (mg/kg)
  - 6.25
  - 12.5
  - 25
  - 50

**RXF 1220 renal carcinoma - highly activated MET & AXL**

- Untreated
- S 49076 (mg/kg)
  - 37.5
  - 75

**SNU-16 gastric carcinoma - constitutively active FGFR2**

- Untreated
- S49076 (mg/kg)
  - 75 (once daily)
  - 100 (once daily)
  - 37.5 (twice daily)
  - 50 (twice daily)

**LS-174T colon carcinoma - acquired resistance to bevacizumab**

- Untreated
- Bevacizumab weeks 1 - 2
- Bevacizumab weeks 1 - 5
- Bevacizumab weeks 3 - 5

Paris, March 4-6, 2013

www.tatcongress.org

Presented by Depil S. TAT 2013
Patient Population:
• All-comers, regardless of MET amplification status
  • Majority mCRC, also lung, mesothelioma, uveal melanoma
  • 45% patients are of other primaries

Trial Design:
• Classic 3+3 design investigating 2 dosing strategies with expansion once recommended dose determined
Dose escalation – RD*

**Arm QD**

- 15 mg QD 0 DLT (n=3)
- 22.5 mg QD 0 DLT (n=3)
- 30 mg QD 0 DLT (n=6)
- 45 mg QD 0 DLT (n=3)
- 67.5 mg QD 0 DLT (n=4)
- 180 mg QD 0 DLT (n=6)
- 270 mg QD 0 DLT (n=3)
- 405 mg QD 0 DLT (n=4)
- 600 mg QD 2 DLT (n=3)
- 900 mg QD 2 DLT (n=6) G4 Neutropenia/Thrombocytopenia G1 dizziness

**Arm BID**

- 7.5 mg BID 0 DLT (n=3)
- 15 mg BID 0 DLT (n=3)
- 30 mg BID 0 DLT (n=3)
- 60 mg BID 0 DLT (n=3)
- 120 mg BID 0 DLT (n=3)
- 180 mg BID 0 DLT (n=3)
- 225 mg BID 1 DLT (n=7)
- 285 mg BID 1 DLT (n=7) G3 Hallucination/Cerebellar syndrome G2 Asymptomatic EF

- **MTD QD**
  - 760 mg QD G2 Asymptomatic EF

- **MTD BID**
  - 285 mg BID G2 Asymptomatic EF

**Recommended dose at 600mg QD**
Currently the expansion cohort is ongoing (n=2)

**Amendment:** modification of dose escalation procedure to avoid exposure of subtherapeutic doses

« Continous B.i.D » schedule has not been selected for expansion part

* Recommended dose
Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

• Safety and toxicity profile is what one expects from this class of agent
  • Hypoalbuminaemia }
  • Peripheral oedema } in 50% of patients at RD;
  • with only 1/28 patients >/= G3

• 10 patients had G2 “decrease in EF” which were all asymptomatic and reversible
- Majority of clinical benefit is SD
- Apparent efficacy over a large range of doses
- ? A larger proportion of patients on BID dosing had tumour shrinkage
- ? Should we revisit the dosing schedule
Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

<table>
<thead>
<tr>
<th>IHC</th>
<th>MET</th>
<th>AXL</th>
<th>FGFR1</th>
<th>FGFR2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All</td>
<td>RD</td>
<td>All</td>
<td>RD</td>
</tr>
<tr>
<td>2+</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3+</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th>FISH amplification</th>
<th>MET</th>
<th>AXL</th>
<th>FGFR1</th>
<th>FGFR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All n= 27, RD n=11</td>
<td>0</td>
<td>Not performed</td>
<td>2 Confirmed by CGH</td>
<td>1</td>
</tr>
</tbody>
</table>

- About 70% of total patients had either IHC/FISH testing (close to 80% at RD)
- Small numbers of IHC/FISH +ve patients → no obvious association with response
- At present, no obvious biomarker
Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

• Possible future directions:
  • Concentrate on malignancies in which all MET, AXL and FGFR have shown resistance mechanisms
    • EGFR-resistant NSCLC
    • BRAF V600E mutated melanoma (and not uveal melanoma)
    • Chemotherapy resistant AML
  
  • Concentrate on malignancies where VEGF inhibitors are considered standard-of-care as MET, AXL/ and FGFRs are important in angiogenesis
  
  • Combination approach to standard-of-care treatments to postpone acquired resistance
Abs. 126O | AL3810 (Lucitanib) –VEGFR, FGFR, PDGFR inhibitor

- Non-selective FGFR inhibitor with equipotency against FGFR1 and VEGFR1-3

Non selective FGFR inhibitors = mostly FGFR1-VEGFR inhibitors

<table>
<thead>
<tr>
<th>Compound/IC50 (nM)</th>
<th>FGFR-1</th>
<th>VEGFR-1</th>
<th>VEGFR-2</th>
<th>VEGFR-3</th>
<th>PDGFRα</th>
<th>PDGFRβ</th>
<th>Other</th>
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<tbody>
<tr>
<td>E-3810</td>
<td>22</td>
<td>7</td>
<td>25</td>
<td>10</td>
<td>175</td>
<td>525</td>
<td>FGFR-2 70, FGFR3 238, FGFR4 &gt;1000, c- Kit 456</td>
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<tr>
<td>Dovitinib</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>8</td>
<td>unk</td>
<td>12</td>
<td>FGFR-2 40, FGFR-3 9, FLT3 2, c-Kit 1</td>
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<tr>
<td>Brivanib</td>
<td>148</td>
<td>380</td>
<td>25</td>
<td>10</td>
<td>unk</td>
<td>&gt;6000</td>
<td>FGFR2 202, FGFR3 503, FGFR4 2003 Flt3, Src, Lyn</td>
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<tr>
<td>Sunitinib</td>
<td>320</td>
<td>9</td>
<td>19</td>
<td>4</td>
<td>46</td>
<td>41</td>
<td>C- Kit 104</td>
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<tr>
<td>Sorafenib</td>
<td>154</td>
<td>6</td>
<td>16</td>
<td>10</td>
<td>744</td>
<td>&gt;1000</td>
<td>C-Raf 0.006, B- Raf 0.22</td>
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<td>Pazopanib</td>
<td>720</td>
<td>10</td>
<td>7-47</td>
<td>30</td>
<td>unk</td>
<td>70-84</td>
<td>C-Met 6</td>
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<tr>
<td>Axitinib</td>
<td>218</td>
<td>1.2</td>
<td>0.25</td>
<td>0.29</td>
<td>unk</td>
<td>0.29</td>
<td>C- Kit 2</td>
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<tr>
<td>Vandetanib</td>
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<td>1800</td>
<td>40</td>
<td>110</td>
<td>unk</td>
<td>1100</td>
<td>EGF- R 500</td>
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<td>BIBF 1120</td>
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<td>34</td>
<td>21</td>
<td>13</td>
<td>59</td>
<td>65</td>
<td>FLT3 26, Src 156</td>
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<td>Cediranib</td>
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<td>5</td>
<td>1</td>
<td>3</td>
<td>unk</td>
<td>5</td>
<td>C-Kit 2</td>
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<tr>
<td>Motesanib</td>
<td>unk</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>unk</td>
<td>84</td>
<td>C-Kit 8</td>
</tr>
</tbody>
</table>

Soria JC; Presented at TAT 2014
Abs. 126O | AL3810 (Lucitanib) –VEGFR, FGFR, PDGFR inhibitor

- Classical 3+3 design – extension at 10mg/d → RD
- Variety of tumour types; some heavily pre-treated with >/= 5 lines of treatment

<table>
<thead>
<tr>
<th>Escalation</th>
<th>Dose level</th>
<th>Dose mg/day</th>
<th>Patients treated</th>
<th>Dose-limiting toxicity (DLT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>3</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>3 + 2</td>
<td>G3 Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G3 Blood bilirubin increase</td>
<td></td>
</tr>
<tr>
<td>Extension</td>
<td>1</td>
<td>10</td>
<td>9</td>
<td>G3 Cellulitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G3 Bile duct obstruction</td>
</tr>
</tbody>
</table>
Abs. 126O | AL3810 (Lucitanib) – VEGFR, FGFR, PDGFR inhibitor

- AEs are more reflective of anti-VEGF component
- Responses predominantly SDs
- No correlative studies on potential biomarkers
AL3810 | E3810 – Lucitanib – VEGFR, FGFR and PDGFR inhibitor

Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors

J.-C. Soria1*, F. DeBraud2, R. Bahleda1, B. Adamo3, F. Andre1, R. Dientsmann3,4, A. Delmonte2, R. Cereda5,6,7, J. Isaacson5,6,7, J. Litten5,6,7, A. Allen5,6,7, F. Dubois8, C. Saba8, R. Robert8, M. D'Incalci8, M. Zucchetti9, M. G. Camboni5,6,7† & J. Tabernero3

1 Department of Drug Development, Gustave-Roussy Cancer Campus, Villejuif, France; 2 European Institute of Oncology, Milan, Italy; 3 Vall d’Hebron Institute of Oncology (VHIO), Vall d’Hebron University Hospitals, Universitat Autònoma de Barcelona, Barcelona, Spain; 4 Sage Bionetworks, Fred Hutchinson Cancer Research Center, Seattle; 5 Clovis Oncology, Inc., San Francisco; 6 Clovis Oncology, Inc., Boulder, USA; 7 Clovis Oncology, Inc., Milan, Italy; 8 Institut de Recherche Internationale Servier, Suresnes, France; 9 Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa, Milan, Italy

• 76 patients; 42% patients had >/= 3 lines of prior chemotherapy
• Classical 3+3 design from 5mg up to 30mg/day
• **Dose expansion phase** at RD to obtain preliminary efficacy evidence on tumours which may harbour FGF-aberrant pathways or considered angiogenesis sensitive

Soria JC et al. 2014
AL3810 | E3810 – Lucitanib – VEGFR, FGFR and PDGFR inhibitor

Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors

J.-C. Soria¹, F. DeBraud², R. Bahleda¹, B. Adamo³, F. Andre¹, R. Dientsmann³,⁴, A. Delmonte², R. Cerda⁵,⁶,⁷, J. Isaacson⁵,⁶,⁷, J. Litten⁵,⁶,⁷, A. Allen⁵,⁶,⁷, F. Dubois⁸, C. Saba⁸, R. Robert⁸, M. D’incalci⁹, M. Zucchetti⁹, M. G. Camboni⁵,⁶,⁷‡ & J. Tabernero³

¹Department of Drug Development, Gustave-Roussy Cancer Campus, Villejuif, France; ²European Institute of Oncology, Milan, Italy; ³Vall d’Hebron Institute of Oncology (VHO), Vall d’Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; ⁴Sage Bionetworks, Fred Hutchinson Cancer Research Center, Seattle; ⁵Clovis Oncology, Inc., San Francisco; ⁶Clovis Oncology, Inc., Boulder, USA; ⁷Clovis Oncology, Inc., Milan, Italy; ⁸Istituto di Ricerca Farmacologica Mario Negri, Via La Masa, Milan, Italy

- MTD 30mg/d, Initial RD 20mg/d; then adjust to 15mg/d as pts cannot be sustained on multiple cycles
- Presumably East Asians/Chinese population is a minority or absent.
Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors

Tumor response to treatment (RECIST) in 58 assessable patients with measurable lesions and time on treatment (days).

- All 12 FGFR aberrant breast patients had treatment benefit (50% SD, 50% PR)

A single-arm, open-label, phase 2 study to assess the efficacy and safety of lucitanib given orally as a single agent to patients with advanced/metastatic lung cancer and FGF, VEGF, or PDGF-related genetic alterations.

**BACKGROUND**
- Lung cancer is the leading cause of cancer-related mortality, accounting for approximately 18% of cancer-related deaths worldwide.
- The recent discovery of genetic changes that drive tumor growth has accelerated the development of targeted therapies.
- Genetic changes associated with tumor growth and metastasis include abnormalities related to fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) signaling.
- Alterations in the FGF, VEGF, and PDGF pathways are common and have been described across many lung cancer histologies, with incidence varying from 1% to 10%, depending on the subtype.

**OBJECTIVES**
- **PRIMARY**: Evaluate the ORR of lucitanib in patients with advanced/metastatic lung cancer and FGF, VEGF, or PDGF genetic alterations.
- **SECONDARY**: Evaluate the clinical benefit rate (CBR), progression-free survival (PFS), duration of the response (DR), and overall survival (OS).

**STUDY DESIGN**
- Patients with advanced/metastatic lung cancer and FGF, VEGF, or PDGF genetic alterations (n = 60).
- 10 mg daily of lucitanib.
- Objective response rate.

**患者背景**
- 本研究为一项单臂、开放标签的2期研究，旨在评估拉替尼布在具有FGF、VEGF或PDGF相关基因突变的晚期非小细胞肺癌患者中的疗效和安全性。
- **背景**
  - 非小细胞肺癌是导致癌症死亡的主要原因，占全世界癌症死亡人数的18%。
  - 近期的遗传变化研究揭示了驱动肿瘤生长的机制，加速了靶向治疗的开发。
  - FGF、VEGF和PDGF通路的异常在多种肺癌亚型中被发现，其发生率从1%到10%不等，具体取决于亚型。

**目的与具体活动**
- **主要目的**：评估拉替尼布在具有FGF、VEGF或PDGF相关基因突变的晚期非小细胞肺癌患者中的客观缓解率。
- **次要目的**：评估临床获益率（CBR）、无进展生存期（PFS）、反应持续时间（DR）和总生存期（OS）。

**研究方案**
- 患者选择：具有FGF、VEGF或PDGF相关基因突变的晚期非小细胞肺癌患者（n=60）。
- 拉替尼布剂量：10 mg每日。
- 主要终点指标：客观缓解率。
Abs. 126O | AL3810 (Lucitanib) –VEGFR, FGFR, PDGFR inhibitor

Direction:
• Future trials need to be biomarker driven

Challenge:
• Identify a robust biomarker
  • Definition of FGFR pathway amplification varies between trials in methods used and threshold copy number
  • No consensus → difficulties for cross trial comparison

Future Directions:
• Correlate PK/PD differences between ethnicities of patients across trials
• Asian to take leadership roles in niche Asian FGFR related tumours
  • e.g. Hepatocellular Ca, Gastric Ca
Challenges of Targeting FGFR as a whole

- Target FGFR pathway as oncogenic driver
- Reverse resistance to targeted agents
- Target angiogenesis

Which is the optimal setting?

- Enrich for patients harboring the specific oncogenic alteration
- After PD to another targeted agent?
- After PD to another antiangiogenic agent?

Challenges

- Molecular screening
- Avoid resistance to anti-FGFR agents
- How to combine anti-FGFR and other targeted agents?
- FGF activation as selection criteria?

Unsolved questions

- Selective vs. nonselective anti-FGFR
- Feasibility of combinations
- Long-term safety of FGFR inhibition

Dieci MV, Areedos M, Andre F, Soria JC; Cancer Discovery 2013