MOLECULAR PATHOLOGY
Clinical Application

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DISCLOSURE OF INTEREST

- Advisory role:
  - MSD, Pfizer, BMS, Astellas, Janssen, Clovis, Bayer, Roche

- Speaker role:
  - Pfizer, MSD, Astellas, Sanofi Aventis, Janssen, Bayer, BMS, Roche, AstraZeneca

- Research funding:
  - Takeda, Pfizer, MSD
Molecular Characterization

- **TCGA (N = 412, previously: N = 131)**
  - 58 SMGs (34 not previously, 16 not in Pan-Cancer)

- Median F/U -> 17.5 m

- Included 3 of 4 with NE histology
- High expression of many neuronal differentiation and development genes
- Loss of TP53 and RB1


MSig 1 cancers with high-APOBEC and high-mutation load had an extraordinary 89% 5-year survival
Future treatment paradigm??

Framework for prospective hypothesis to be tested in clinical trials

TCGA bladder identifies multiple potential therapeutic targets

Potential therapeutic target in 69% of samples!

- PI3KCA pathway (22%)
- TSC1 mutations (8%)
- Akt overexpression (10%)
- FGFR3 mutation and fusion (16%)
- ATM-ERCC2 mutations (14%/9%)
- Her2-EGFR alterations (9% each)

c/o Lerner, et al. GU Cancer Symposium 2016
# Platinum pretreated patients - SINGLE TARGETED AGENTS

## Summary of studies

<table>
<thead>
<tr>
<th>Author, year of publ.</th>
<th>Agent</th>
<th>N (evaluable)</th>
<th>ORR (%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrylak (SWOG), 2009</td>
<td>Gefitinib</td>
<td>29</td>
<td>3</td>
<td>NR</td>
<td>1.0</td>
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<tr>
<td>Gomez-Albuin, 2007 Rosenberg, 2008</td>
<td>Bortezomib</td>
<td>19 25 (24)</td>
<td>0</td>
<td>1.4</td>
<td>3.8</td>
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<tr>
<td>Wulfing, 2009</td>
<td>Lapatinib</td>
<td>59 (34)</td>
<td>2.0</td>
<td>4.2</td>
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<tr>
<td>Dreicer, 2009</td>
<td>Sorafenib</td>
<td>27</td>
<td>2.2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Gallagher, 2010 (arm A)</td>
<td>Sunitinib 50 mg/d: 4w/2w</td>
<td>37.5 mg/d (cont)</td>
<td>50 mg/d: 4w</td>
<td>(41)</td>
<td>31</td>
</tr>
<tr>
<td>Gallagher, 2010 (arm B)</td>
<td></td>
<td></td>
<td></td>
<td>50 mg/d: 4w</td>
<td>32 (28)</td>
</tr>
<tr>
<td>Theodore, ESMO 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twardowski, 2010</td>
<td>Aflibercept</td>
<td>22</td>
<td>4.5</td>
<td>2.8</td>
<td>NR</td>
</tr>
<tr>
<td>Necchi, ASCO 2012</td>
<td>Pazopanib</td>
<td>41</td>
<td>17 (conf.)</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Pili, ASCO GU 2011</td>
<td>Pazopanib</td>
<td>16</td>
<td>0</td>
<td>1.9</td>
<td>NR</td>
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<tr>
<td>Stadler, ASCO GU 2011</td>
<td>Volasertib</td>
<td>50</td>
<td>14</td>
<td>1.4</td>
<td>NR</td>
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<tr>
<td>Milowski, ASCO GU 2011</td>
<td>Everolimus</td>
<td>37</td>
<td>5</td>
<td>3.3</td>
<td>10.3</td>
</tr>
<tr>
<td>Seront ASCO 2011</td>
<td>Everolimus</td>
<td>50</td>
<td>5</td>
<td>2.0</td>
<td>3.32</td>
</tr>
<tr>
<td>Choueiri, 2012</td>
<td>Vandetanib (cross over)</td>
<td>37</td>
<td>3</td>
<td>NR</td>
<td>5.2</td>
</tr>
<tr>
<td>Gerullis, ASCO-GU 2012</td>
<td>Temsirolimus</td>
<td>14</td>
<td>0</td>
<td>2.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>
BISCAY: Phase Ib multi-drug biomarker-directed umbrella study in patients with previously treated metastatic UC

N≈100
FGFR3

- Mutation frequency in non-invasive disease is >50% in Ta tumors
- Mutations and fusions are less frequent in advanced UC
  - Mutations 15-20%
  - Fusion 3-5% using NGS
- Is it a driver of stage IV urothelial carcinoma?

- FGFR3 activation can occur by mutation, overexpression or gene fusion
- But what is the best way to select potential responders to FGFR3 blockade?
Case Study

• 62-year-old female with metastatic urothelial carcinoma

• Treated with gemcitabine/cisplatin with CR,
• Recurrent supraclavicular disease, treated with RT to neck

• Progression after RT, treated with dose dense MVAC chemotherapy

• NGS testing found to have FGFR3 activating mutation

• Patient was started on BGJ398 phase I trial

Courtesy of Dr Joaquim Bellmunt, MD PhD
FGFR3 mutant metastatic urothelial cell carcinoma

- Patient ongoing (9+ cycles) with PR (45% tumor reduction)

Left Lung Nodule

Mediastinal Mass

Baseline

Month 8

Images courtesy of Jason Luke, MD, and Geoff Shapiro, MD, Dana-Farber Cancer Institute

Courtesy of Dr Joaquim Bellmunt, MD
Complexity of FGFR signalling in metastatic urothelial cancer

Alejo Rodriguez-Vida, Matilde Seggese, Simon Hughes, Sarah Rudman, Simon Chowdhury, Neil R. Smith, Peter Lawrence, Claire Rooney, Brian Dougherty, Donal Landers, Elaine Kilgour and Hendrik-Tobias Arkenau

Abstract

Background: Urothelial cancers (UC) are the fourth most common tumours worldwide after prostate (or breast), lung and colorectal cancer. Despite recent improvements in their management, UC remain an aggressive disease associated with a poor outcome. Following disease progression on first-line platinum-based chemotherapy, very few effective treatment options are available and none of them have shown significant improvement in overall survival. Alterations of the fibroblast growth factor receptor (FGFR) pathway including amplification, mutations and overexpression are common in UC. Preclinical data suggest that the presence of such dysregulations may confer sensitivity to FGFR inhibitors.

Materials and methods: We present here the case of a patient with a metastatic UC of the renal pelvis with lymph node metastases treated with the selective FGFR inhibitor AZD4547.

Results: To date, the patient has been on a study drug for 32 months with acceptable tolerance and maintained radiological partial response as per RECIST 1.1 criteria. Exploratory biomarker analysis showed FGFR3, FGFR1, FGFR-ligand and fibroblast growth factor receptor substrate 2 (FRS2) expression in the patient’s tumour, together with the presence of a germ-line mutation in the FGFR3 extracellular binding domain. This is not a known hotspot mutation, and the functional significance remains unclear.

Conclusions: The FGFR inhibitor AZD4547 exhibits antitumour activity in a metastatic urothelial cancer displaying FGFR1, FGFR3, FGFR-ligand and FRS2 expression. This lends support to the further exploration of FGFR inhibitors in urothelial cancer. Further studies are required to validate this hypothesis.

Keywords: Urothelial cancer, FGFR, AZD4547.

Table 2: Patient molecular screening showing complex dysregulation of the FGFR signalling pathway. FGFR1 FISH was performed by central screening laboratory (Quintiles), FGFR1 and FGFR3 protein levels were assessed by IHC and FGFR1, FGFR3 and FGFR-ligand expression assessed by NanoString. Gene variants and copy number gains were determined by next-generation sequencing analysis at Foundation Medicine.

<table>
<thead>
<tr>
<th>FGFR protein H-score</th>
<th>FGFR status (FISH)</th>
<th>FGFR pathway RNA expression (NanoString)</th>
<th>Variants detected in tumour</th>
<th>Copy number gain (copy number, exons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1: cytosol 1500/membrane 0</td>
<td>No FGFR1 amplification (FGFR1/CEP10 ratio 1.26)</td>
<td>High FGFR1 mRNA expression</td>
<td>FGFR3 (5236N)</td>
<td>MDM2 amplification (16, exons 11 of 16)</td>
</tr>
<tr>
<td>FGFR3: cytosol 1000/membrane 1</td>
<td>High FGFR3 mRNA expression</td>
<td>ARID1A N399K*218</td>
<td>PIK3R4 A291fs*6</td>
<td>MYC amplification (7, exons 5 of 8)</td>
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<tr>
<td></td>
<td>High FGF-Ligand mRNA expression</td>
<td>CHEK2 T367Y*15</td>
<td>BRCA2 Q107R</td>
<td>TTK3 amplification (7, exons 8 of 8)</td>
</tr>
<tr>
<td></td>
<td>High FRS2 mRNA expression</td>
<td>FANCD2 Q140S</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EGFR signaling pathways are upregulated in selected advanced UC

• EGFR activating mutations are frequent
• ERBB3 and ERBB4 mutations are of unclear significance
• HER2 overexpression is relatively common, but not tightly correlated with amplification
• Which, if any, EGFR pathway alteration matters?

Case Study

- 69-year-old man, former smoker

- Diagnosed with metastatic bladder UC at baseline, with bone metastases and soft tissue associated mass

- Treated with 1\(^{st}\) line gemcitabine/cisplatin x6 cycles with SD

- Rapid progression 2 months after chemotherapy. Severe bone pain refractory to radiotherapy and opioids

- NGS testing found to have HER2 amplification. Patient was started on afatinib in LUX-bladder 1 phase II trial
LUX bladder-1: Phase II open label single arm exploratory trial of oral afatinib monotherapy following platinum failure for patients with metastatic UC with HER2/HER3 deregulation.
Afatinib

The EGFR/erbB receptor family is a validated target in oncology.

Combined inhibition of EGFR, HER2 and HER4 blocks signaling from all cancer-relevant erbB receptor dimers.
Case Study

- Patient ongoing (13+ cycles) with PR (45% tumor reduction) and resolution of refractory bone pain

Soft tissue mass: 6cm diameter

Soft tissue mass: 3.5cm diameter

Treatment is ongoing nowadays with excellent tolerance
Phase III, Double-Blind, Randomized Trial That Compared Maintenance Lapatinib Versus Placebo After First-Line Chemotherapy in Patients With Human Epidermal Growth Factor Receptor 1/2–Positive Metastatic Bladder Cancer