PATHOLOGY AND MOLECULAR PATHOLOGY CLINICAL APPLICATION

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DISCLOSURE OF INTERESTS

Nothing to disclose
THE MOLECULAR BIOMARKERS AND PATHWAYS INVOLVED IN BLADDER CANCER

Molecularly and clinico-pathologically heterogeneous diseases

✓ An increased understanding of the molecular pathology of bladder cancer has led to the identification of specific molecular subtypes

✓ Utility of identification of specific molecular subtypes:
  a. to predict clinical outcomes
  b. to predict treatment responsiveness to personalized therapies
Future Treatment Paradigm

Kamoun et al. Eur Urol 2019

[Image of the table and diagram]
FGFR3 IN BLADDER CANCER

Non-Responders to CPI in “Immune desert” with High FGFR3 Expressions

10–20% of MIBC

Rosenberg J et al. ASCO 2016
Kamoun et al. Eur Urol 2019
ERDAFITINIB: TYROSINE KINASE INHIBITOR OF FGFR1–4

In this open-label, phase 2 study, we enrolled patients who had locally advanced and unresectable or metastatic urothelial carcinoma with prespecified *FGFR* alterations.

### Table 2. Antitumor Activity of Erdafitinib in the 99 Patients in the Selected-Regimen Group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Rate of Response (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>percent</td>
</tr>
<tr>
<td>Response per investigator assessment — no. of patients†</td>
<td>40</td>
<td>40 (31–50)</td>
</tr>
<tr>
<td>Any objective response</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Complete response</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Partial response</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Stable disease</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Median time to response — mo</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Median duration of response (95% CI) — mo</td>
<td>5.6 (4.2–7.2)</td>
<td></td>
</tr>
<tr>
<td>Response per independent radiologic assessment — no. of patients†</td>
<td>34</td>
<td>34 (25–44)</td>
</tr>
<tr>
<td>Objective response</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Complete response</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Partial response</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>

Loriot Y et al, N Engl J Med 2019
MOLECULAR SUBTYPE: 
LUMINAL SUBTYPE AND IMMUNOTHERAPY RESPONSE

Kamoun et al. Eur Urol 2019


**LUMINAL UNSTABLE**

- **LumU**: limited benefit from NAC $\rightarrow$ checkpoint inhibition AND NAC impact on OS
- Basal tumors $\rightarrow$ NAC impact on OS
- **STROMA-RICH**: worst outcome regardless of NAC treatment $\rightarrow$ novel therapies needed
- **Ne-LIKE**: NAC impact on OS

Kamoun et al. Eur Urol 2019
NA-CT: Predictive biomarker
Impact of Molecular Subtypes – APOBEC mutational signature

APOBEC3A and APOBEC3B:
✓ upregulated
✓ correlated with TMB
✓ Correlated with response

Kamoun et al. Eur Urol 2019
Marianthasan S et al. Nature 2018 (IMvigor210)
MOLECULAR SUBTYPE: BASAL SUBTYPE AND IMMUNOTHERAPY RESPONSE

Neoadjuvant Pembrolizumab (PURE01) in MIBC with variant histologies

## Future Treatment Paradigm

### FGFR3 Inhibitors

- **% of MIBC**: 24%
- **Class Name**: Luminal papillary (LumP), Luminal non-specified (LumNS), Luminal unstable (LumU), Stroma-rich, Basal/squamous (BaSq), Neuroendocrine-like (NE-like)
- **Differentiation**: Urothelial / luminal
- **Oncogenic mechanisms**: FGFR3 + PPARγ + CDKN2A-
- **Mutations**: FGFR3 (40%), KDM6A (38%)
- **Stromal infiltrate**: Fibroblasts
- **Immune infiltrate**: Papillary morphology (59%), Micropapillary variant (36%)
- **Clinical**: T2 stage + (<50 yrs), Older patients + (80+)
- **Median overall survival (yr)**: 4, 1.8, 2.9, 3.8
- **FGFR3 Inhibitors**

### RT/CT

- **Cell cycle +**
- **TP53 (76%), ERCC2 (22%) TMB +, APOBEC +**
- **Smooth muscle Fibroblasts Myofibroblasts**
- **B cells**
- **Histology**: Papillary morphology (59%), Micropapillary variant (36%)
- **TP53 (61%), RB1 (25%)**
- **TP53 (94%) RB1 (39%)**
- **Fibroblasts Myofibroblasts**
- **CD8 T cells NK cells**
- **Histology**: Papillary morphology (59%), Micropapillary variant (36%)
- **Clinical**: T2 stage + (<50 yrs), Older patients + (80+)
- **Median overall survival (yr)**: 4, 1.8, 2.9, 3.8
- **RT/CT**

### Anti-EGFR

- **EGFR +**
- **Smooth muscle Fibroblasts Myofibroblasts**
- **B cells**
- **Histology**: Papillary morphology (59%), Micropapillary variant (36%)
- **Clinical**: T2 stage + (<50 yrs), Older patients + (80+)
- **Median overall survival (yr)**: 4, 1.8, 2.9, 3.8
- **Antigen**

### Immuno-checkpoint inhibitors

- **TP53-, RB1-, Cell cycle +**
- **TP53 (61%), RB1 (25%)**
- **TP53 (94%) RB1 (39%)**
- **Neuroendocrine differentiation (72%)**
- **Squamous differentiation (42%)**
- **Women + T3/T4 stage +**

*94% of these tumors present either RB1 mutation or deletion*
BISCAY: PHASE IB MULTI-DRUG BIOMARKER-DIRECTED UMBRELLA STUDY IN MUC

Study design

- **Biomarker**
  - FGFR1,2,3 mutations/fusions
  - ATM, BRCA1/2, HRR gene
  - RICTOR, TSC1, TSC2 (partial selection*)
  - No biomarker selection

- **Drug(s)**
  - AZD4547
  - AZD4547 + durvalumab
  - Olaparib + durvalumab
  - Vistusertib + durvalumab
  - Durvalumab
Advances in the treatment of bladder cancer are lacking compared to those in other malignancies.

Two main subtypes can be distinguished:
- luminal and basal type

There is still no agreement regarding how many subgroups can be established and defined.

The identification of molecularly-defined subtypes may enable the implementation of tailored therapies and better patient management.