Individualized management of urogenital tumors
The impact of ACCC

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National & Kapodistrian University of Athens
Individualized anti-cancer therapy

• One treatment FITS all
• Solid tumors = Polyclonal populations
• One treatment DOES NOT FIT all
Outcomes at 5 years after neoadjuvant chemotherapy and/or cystectomy in patients with muscle invasive bladder cancer*

Data are derived from the Southwest Oncology Group (SWOG) trial 8710


Advantages of individualized anti-cancer therapy

• Increased efficacy
• Increased tolerance
• Avoidance of unnecessary toxicity
• Favorable pharmacoeconomics
Targeted therapies in urogenital cancer

**VEGF/VEGFR targeting**
- Sorafenib
- Sunitinib
- Bevacizumab
- Pazopanib
- Axitinib
- Cabozantinib
- Lenvatinib

**mTOR inhibitors**
- Everolimus
- Temsirolimus

**Checkpoint inhibitors**
- Nivolumab
- Pembrolizumab
- Atezolizumab
- Avelumab
- Durvalumab

mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Evolution in the first-line treatment of mRCC

Median survival before and after the introduction of targeted agents (TKIs)\(^1-11\)

**Before** | **After**
---|---
**PFS** | 3–6 | 6–15* |
**OS** | 13–22 | 18–32* |

*With targeted agents as first-line mRCC therapy primarily in favourable/intermediate risk patients

Immunotherapy for RCC: targeting the PD-1/PD-L1 Pathway

PD-1 receptor (T lymphocytes) + PD-L1 ligand (tumor cells) → Blocking PD-1/PD-L1 signaling can enhance the immune response

Suppression of immune response to tumor

PD-1, programmed cell-death protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2.

PD-L1 is Expressed in a Range of Tumor Types

Examples of Tumor Types with Strong PD-L1 Staining (≥10% of cells):

CheckMate 214: Study Design

**Co-primary endpoints:** ORR, PFS, and OS in patients with IMDC-defined poor-/intermediate--risk RCC

**Co-secondary endpoints:** ORR, PFS, and OS in ITT patients; AE incidence rate

Patients (ITT, N = 1096)
- Treatment-naive, advanced or metastatic clear-cell RCC

Treatment
- 3 mg/kg nivolumab i.v. + 1 mg/kg ipilimumab i.v. q3w (four doses), then 3 mg/kg nivolumab i.v. q2w
- 50 mg sunitinib p.o. q.d. for 4 weeks (6-week cycles)

# CheckMate 214: Exploratory Endpoint Antitumor Activity by Tumor PD-L1 Expression Level

<table>
<thead>
<tr>
<th>IMDC-defined poor/intermediate risk</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-L1 &lt; 1%</strong></td>
<td><strong>PD-L1 ≥ 1%</strong></td>
</tr>
<tr>
<td>NIVO + IPI (n = 284)</td>
<td>SUN (n = 278)</td>
</tr>
<tr>
<td>ORR, a % (95% CI)</td>
<td>ORR, a % (95% CI)</td>
</tr>
<tr>
<td>37 (32–43)</td>
<td>28 (23–34)</td>
</tr>
<tr>
<td>p = 0.0252</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>BOR, a % CR</td>
<td>BOR, a % CR</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>p = 0.8799</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

**PFS IMDC-defined poor/intermediate risk**

<table>
<thead>
<tr>
<th>PD-L1 &lt; 1% (n = 562)</th>
<th>PD-L1 ≥ 1% (n = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months (95% CI)</strong></td>
<td></td>
</tr>
<tr>
<td>NIVO + IPI</td>
<td>11.0 (8.1–14.9)</td>
</tr>
<tr>
<td>SUN</td>
<td>10.4 (7.5–13.8)</td>
</tr>
<tr>
<td>HR (95% CI) 1.00 (0.74–1.36)</td>
<td>p = 0.9670</td>
</tr>
<tr>
<td>HR (95% CI) 0.48 (0.28–0.82)</td>
<td>p = 0.0003</td>
</tr>
</tbody>
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a IRRC assessed.

Combinations May Only Be Needed in PD-L1 Negative Tumors

- Addition of CTLA-4 inhibition may only lead to toxicity in pts with PD-L1-high tumors
- No data yet in bladder cancer

PDL1 Testing (IC 2/3 vs 1/2) Loses Ability to Enrich for Response Across Atezolizumab Studies

![Graph showing response rates for PDL1 'high' (IC 2/3) and PDL1 'low' (IC 0/1) across different phases of studies.]

- **Phase I**
  - Petrylak ASCO 15
  - PDL1 "high" (IC 2/3) 50%
  - PDL1 "low" (IC 0/1) 10%

- **Phase II Post Platinum**
  - Dreicer ASCO 16
  - PDL1 "high" (IC 2/3) 30%
  - PDL1 "low" (IC 0/1) 20%

- **Phase II First line**
  - Balar ASCO 16
  - PDL1 "high" (IC 2/3) 50%
  - PDL1 "low" (IC 0/1) 15%

Plimack E. ASCO 2016
## Phase I Data: Assays for Measurement of PD-L1 Expression in Advanced Urothelial Cancer

<table>
<thead>
<tr>
<th>Detection antibody</th>
<th>Atezolizumab¹</th>
<th>Nivolumab²</th>
<th>Pembrolizumab³</th>
<th>Durvalumab⁴</th>
<th>Avelumab⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP142</td>
<td>28-8</td>
<td>22C3</td>
<td></td>
<td>SP263</td>
<td>73-10</td>
</tr>
<tr>
<td>Ventana</td>
<td>Dako</td>
<td>Dako</td>
<td>Ventana</td>
<td>Dako</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>TC</td>
<td>TC</td>
<td>IC and TC</td>
<td>IC and TC</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cut-off definitions for urothelial cancer</th>
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<tbody>
<tr>
<td>PD-L1+ (IHC 2/3) as ≥5% of ICs PD-L1+</td>
</tr>
<tr>
<td>PD-L1+ ≥1% TC expression</td>
</tr>
<tr>
<td>PD-L1+ ≥1% TC staining</td>
</tr>
<tr>
<td>PD-L1+ as ≥25% of ICs and TCs with membrane PD-L1 staining</td>
</tr>
<tr>
<td>PD-L1+ as ≥5% TC staining or ≥10% IC staining</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated PD-L1 prevalence in urothelial cancer trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>~32%¹</td>
</tr>
<tr>
<td>~37%²</td>
</tr>
<tr>
<td>~62%³</td>
</tr>
<tr>
<td>~65%⁴</td>
</tr>
<tr>
<td>~36%⁵</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1+ ORR (phase I trials)</th>
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<tbody>
<tr>
<td>50.0</td>
</tr>
<tr>
<td>24.0</td>
</tr>
<tr>
<td>29.0</td>
</tr>
<tr>
<td>46.0</td>
</tr>
<tr>
<td>53.8</td>
</tr>
</tbody>
</table>

Antigenicity Is a Major Component of Tumor Immunogenicity

Downregulation and disruption of antigen-presenting machinery reduces immunogenicity

Total Mutations

Predicted Neoantigens

Neoantigens Per Tumor Correlates With Mutation Burden

Tumor Mutational Load Varies Across and Within Tumor Types


Molecular characterization of urothelial cancer

IMvigor210: PD-L1 IC and TC Scores Associated With Basal Phenotype

Gene Signatures in the Tumor Microenvironment

IMvigor210: TCGA Subtype in metastatic urothelial cancer

- IMvigor 210 subtypes have distinct tumor-immune landscapes that reflect responsiveness to atezolizumab

TIL, tumor-infiltrating lymphocyte. "High myeloid, inflammatory, activated stromal/fibroblast markers

Response by TCGA Molecular Subtype

Atezolizumab 1\textsuperscript{st}-line\textsuperscript{1}

Atezolizumab 2\textsuperscript{nd}-line\textsuperscript{2}

Response by TCGA Molecular Subtype

Nivolumab 2nd-line

Molecular characterization of urothelial cancer

FGFR3 activation can occur by mutation, overexpression or gene fusion

- **Ligand independent dimerization**
- **Overexpression**
- **Fusion/translocation**

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di Martino et al. Advances in Urology 2012
FGFR

- FGF signaling promotes oncogenesis, tumor neoangiogenesis and drug resistance\(^1\)

- FGF signaling alterations, particularly those involved in FGFR3 and FGFR1 pathway, are implicated in bladder tumors\(^2\)

- Important molecular alteration in bladder cancer\(^3\)

Significance in resistance to chemotherapy

Soria et al: Safety and Activity of the Pan–Fibroblast Growth Factor Receptor (FGFR) Inhibitor Erdafitinib in Phase 1 Study Patients with Advanced Urothelial Carcinoma (UC)

Antitumor Efficacy

- Responses were observed at the 9 mg QD and 10 mg intermittent levels (as of 06 Jun 2016)
  - 11 PR out of 24 FGFR+ pts, ORR of 45.8% (95% CI 25.6%, 67.2%)
    - 9 mg QD: 7 PR of 11 pts, ORR of 63.6%
    - 10 mg intermittent: 4 PR of 13 pts, ORR of 30.8%
- Median duration of response: 7.2 mo (1.6+ to 15.3 mo), (95% CI 3.3 to 15.3 mo)
- Median PFS: 5.1 mo (95% CI 2.8 to 5.9 mo)
  - 6-mo PFS of 24% and 12-mo PFS of 12%

No responses were noted in 36 patients with unknown or no known FGFR alterations.
Metastatic urothelial cell carcinoma case study

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

Images courtesy of Jason Luke, MD, and Geoff Shapiro, MD, Dana-Farber Cancer Institute
Response to everolimus on MSKCC IRB protocol 08-123.

- 73 year old women with metastatic bladder cancer with progression after platinum-based treatment.
- Achieved a complete response to everolimus (mTORC1 inhibitor) on MSKCC protocol 08-123.
- The patient remains on drug with no evidence of disease > 48 months after starting treatment.
- This patient was one of only 2 of 45 patients who responded to drug.

Why did this patient respond so dramatically to mTORC1 inhibition?
First Cancer Genome at MSKCC

- 17,000+ somatic mutations
- 140 NS coding mutations

Iyer et al., Science, 2012
Moving to personalized medicine

- Cancers emerge from genomic errors
- Sequencing technology is now at the bedside

- Clinical computational biology:
  - Computational algorithms to analyze and interpret genomic data from patient samples are available
How this translates to daily clinical practice?
An opportunity for genomic “media”

- Can we visually represent an exome to enable clinical interpretation?
- Can we make complex genomic data approachable for busy clinicians (and patients)?
- Can we place these data in a useful portion of the medical record?
- Do we need to include expression analysis, mutational burden, nanostring when deciding for Immunotherapy?
Contents of a Report

Summary of genomic alterations and therapeutic implications

<table>
<thead>
<tr>
<th>Patient and ordering physician information</th>
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</thead>
<tbody>
<tr>
<td>Summary of results and genomic alterations identified</td>
</tr>
<tr>
<td>Targeted therapies and clinical trials that may be relevant based on genomic alterations identified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Tumor Type: LUNG ADENOCARCINOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Table content]</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>THERAPEUTIC IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomic Alterations Detected</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>ALK EML4ALK fusion (Variant Safe)</td>
</tr>
</tbody>
</table>

*Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs. However, the agents listed in this report may have varied clinical outcomes in the patient’s tumor type. The therapeutic agents listed in this report are ranked in order of potential or projected efficacy for this patient, not as prioritized by level of evidence for the patient’s tumor type.*
Analysis Pipeline

Informatics Review

Content Creation

Expert Opinion

Online Databases

QC control/Lab Director Approval

ICE
Clinical Interpretation Needs

Clinical Sequencing Pipeline Development

Clinical Genomics Data Interpretation

Data Representation for Clinicians

Genomic media in clinical cancer medicine

◆ A field in its infancy
◆ Needs standardization
◆ Needs best practices
◆ Needs prospective testing in the clinic
◆ Needs regulatory evaluation
Impact of Athens Comprehensive Cancer Center (ACCC)

Athens City Comprehensive Cancer Center

Aims:

A. to improve the health of Athens citizens
B. Efficient “translation” of research results into the clinics
C. New approaches derived from recent cancer research
## Professors/Researchers from International Partner Organisations for ACCC networking:

### DKFZ (Heidelberg, Germany)

<table>
<thead>
<tr>
<th>JP No.</th>
<th>Joint Project Title</th>
<th>Start Month</th>
<th>End Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Data Integration</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Biobanking and Omics Technology</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>Multiple Myeloma (MM)</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>Paediatric Cancers</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Colorectal Cancer (CRC)</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Gynaecological (breast and ovarian) cancer</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>Head and neck cancer (HNSCC)</td>
<td>1</td>
<td>36</td>
</tr>
</tbody>
</table>