State of the Art- GU Cancers
2016

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Disclosures

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Consultant: Medivation, Pfizer
Speakers Bureau: Genentech
Prostate Cancer

Are we close to Personalized Medicine in Prostate Cancer?
**Germ Line vs. Somatic Mutations**

**Somatic mutations**
- Occur in *nongermline* tissues
- Cannot be inherited

**Germline mutations**
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

**Nonheritable**
- Mutation in tumor only (for example, breast)

**Heritable**
- Mutation in egg or sperm
- All cells affected in offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
Inherited Mutations in Prostate Cancer

Pritchard NEJM 2016
Synthetic Lethality

Iglehart NEJM 2009
Olaparib in Metastatic Prostate Cancer

N=50; 16/49 patients had a PSA response; 16 patients had mutations in the DNA repair genes; 14/16 (88%) had a response to olaparib

Mateo, NEJM 2015
Predictive Biomarker

A  Radiologic Progression–free Survival

B  Overall Survival

C  Changes in PSA during Treatment

D  Changes in CTC Count during Treatment
Clinical Disease States

Hormone Sensitive

Newly diagnosed Localized disease

Non-metastatic, Biochemical relapse

Metastatic Hormone-naïve

ADT

ADT/Docetaxel

Castration Resistant

Non-metastatic

Metastatic, Asymptomatic (chemotherapy naïve)

Metastatic, Symptomatic (chemotherapy naïve)

Metastatic, Post docetaxel

Sip T
Abiraterone
Enzalutamide

Abiraterone
Enzalutamide
Docetaxel
Radium 223

Abiraterone
Enzalutamide
Cabazitaxel
Radium 223

Armstrong, Oncologist 2009
Androgen Receptor

Nakazawa Horm Can 2014
ARV-7 Confers Resistance

Antonarkis NEJM 2014
ARV-7 and Taxane

Antonarkis, Jama Oncol 2015
Bladder Cancer

Are not all the same
Checkpoint Inhibitors crowd the disease states
Molecular Classification

- **Intrinsic subtype**
  - Claudin-low/cluster IV
  - Basal/cluster III
  - p53-like/cluster II
  - Luminal/cluster I

- **Histology**
  - Sarcomatoid?*
  - Squamous
  - Infiltrated
  - Papillary

- **Chemosensitivity**
  - Intermediate?
  - High
  - Low
  - High

*The presence of sarcomatoid features has not been directly linked to high levels of EMT biomarkers. Abbreviations: EMT, epithelial-to-mesenchymal transition; MIBC, muscle-invasive bladder cancer.

Aine, Eur Urology 2015; Choi Nat Rev 2014
Prognostic Gene signature-Predictive after NAC

N=60 patients; NAC DD MVAC+B X 4 cycles; pT0=38%; <pT1=53%
TUR/Cyst- for GEP- 38/23

McConkey Eur Urol 2016
DNA repair genes

N=46 patients
DD GC Neoadjuvant chemo followed by cystectomy
26 patients-<T2; 20 patients->T2
34/46- sequencing; 29 Gene panel
26%- deleterious gene alteration ; 8/9(89%) were responders

Iyer, ASCO 2016
IMvigor 210: Atezolizumab

- Single-arm phase II study with 2 cohorts\(^1\)

- Pts with inoperable advanced or metastatic UC, predominantly TCC histology, evaluable tumor tissue for PD-L1 testing (N = 429)

  - Cohort 1\(^2\)
    - Previously untreated, cisplatin ineligible (n = 119)
    - Atezolizumab 1200 mg IV Q3W until PD

  - Cohort 2\(^3,4\)
    - Prior platinum treatment (n = 310)
    - Atezolizumab 1200 mg IV Q3W until loss of benefit

- Cohort 2 study
  - Primary endpoints: confirmed ORR by RECIST v1.1 (per central review), ORR per immune-modified RECIST (per investigator)
  - Secondary endpoints: DoR, PFS, OS, safety

# IMvigor 210 (Cohort 1&2): Response

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>COHORT-2-</th>
<th></th>
<th></th>
<th></th>
<th>All Pts*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC0 (n = 103)</td>
<td>IC1 (n = 107)</td>
<td>IC2/3 (n = 100)</td>
<td>All Pts* (n = 310)</td>
<td></td>
</tr>
<tr>
<td>ORR† (confirmed IRF)</td>
<td>9</td>
<td>11</td>
<td>28</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>CR (confirmed IRF)</td>
<td>2</td>
<td>4</td>
<td>15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Reduced tumor burden %</td>
<td>30 (n = 84)</td>
<td>45 (n = 88)</td>
<td>61 (n = 87)</td>
<td>46 (n = 259)</td>
<td></td>
</tr>
</tbody>
</table>

### COHORT 1-

| ORR | 21 | 23 | 28 | 24 |
| CR  | 8  | 6  | 6  | 7  |
| Reduced tumor burden % | 63 | 51 | 65 | 59 |

# Single Agent CPI in UC

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Ab</th>
<th>Target</th>
<th>Setting</th>
<th>N</th>
<th>RR PR/CR/SD</th>
<th>12 mon OS</th>
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</thead>
<tbody>
<tr>
<td>Balar 2016</td>
<td>Atezolizumab</td>
<td>IgG1</td>
<td>PDL1</td>
<td>First line</td>
<td>119</td>
<td>24/7/17</td>
<td>57%</td>
</tr>
<tr>
<td>Dreicer 2015</td>
<td>Atezolizumab</td>
<td>IgG1</td>
<td>PDL1</td>
<td>Post Platinum</td>
<td>310</td>
<td>16/7</td>
<td></td>
</tr>
<tr>
<td>Sharma 2016</td>
<td>Nivolumab</td>
<td>IgG4</td>
<td>PD1</td>
<td>Post platinum</td>
<td>78</td>
<td>24/6/28</td>
<td>45</td>
</tr>
<tr>
<td>Plimack 2015</td>
<td>Pembrolizumab</td>
<td>IgG4</td>
<td>PD1</td>
<td>Post platinum</td>
<td>29</td>
<td>17/10/10</td>
<td>52</td>
</tr>
<tr>
<td>Apollo 2016</td>
<td>Avelumab</td>
<td>IgG1</td>
<td>PDL1</td>
<td>Post platinum</td>
<td>44</td>
<td>16/2/39</td>
<td>54</td>
</tr>
<tr>
<td>Massard 2016</td>
<td>Durvalumab</td>
<td>IgG1</td>
<td>PDL1</td>
<td>Post platinum</td>
<td>42</td>
<td>44/5/14</td>
<td>NA</td>
</tr>
</tbody>
</table>
Trials of PD-1 Inhibitors in Bladder Cancer

Muscle-invasive bladder cancer

- Neoadjuvant: Atezolizumab + pembrolizumab + RT
- Adjuvant: Pembrolizumab

Trimodality

Metastatic urothelial cancer

- Cisplatin eligible: Durvalumab + tremelimumab*
- Cisplatin ineligible: Pembrolizumab

Maintenance

Avelumab*

Platinum refractory

- Pembrolizumab vs chemo*

- Atezolizumab vs chemo*

*Phase III
RENAL CELL CARCINOMA

Not so clear choices
mRCC- 2016

**FIRST LINE**
- Sunitinib
- Pazopanib
- HD IL2

**SECOND LINE**
- Axitinib
- Nivolumab
- Cabozantinib
- Lenvatinib + Everolimus
- Everolimus
mRCC- Second line- Embarrassment of Riches- Lack of Biomarker

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Cabozantinib</th>
<th>Lenvatinib+Ever</th>
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</thead>
<tbody>
<tr>
<td>ORR(%)</td>
<td>25</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>PFS(mos)</td>
<td>4.6</td>
<td>7.4</td>
<td>12.8</td>
</tr>
<tr>
<td>OS(mos)</td>
<td>25</td>
<td>21.4</td>
<td>25.5</td>
</tr>
</tbody>
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NIVOLUMAB(20) CABOZANTINIB(16) LENVAT+EVERO(15) AXITINIB (16)

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

Example Evidence Block |
| E = Efficacy of Regimen/Agent |
| S = Safety of Regimen/Agent |
| Q = Quality of Evidence |
| C = Consistency of Evidence |
| A = Affordability of Regimen/Agent |

Quality of Evidence

AXITINIB (16) NIVOLUMAB(20) CABOZANTINIB(16) LENVAT+EVERO(15)
QUESTIONS?