Evolution of Systemic Therapy for Urothelial Carcinoma

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Disclosures

• Advisory Board
  – Astellas

• Honoraria
  – Astellas, Janssen, sanofi, Pfizer, Novartis, Roche, Merck, AstraZeneca

• Clinical Trial Participation
  – Astellas, Janssen, sanofi, Pfizer, Novartis, Roche, Merck, AstraZeneca
  • All funds paid to Alberta Health Services
Outline

• Review changes in systemic therapy of UC
  – Where does chemotherapy fit and what’s the emerging role of immuno-oncology
    • First line metastatic disease
    • Second line metastatic disease
    • Adjuvant therapy
    • Neoadjuvant Therapy

• PET imaging in UC – what role

• Trials on the horizon
## Cancer Mortality - 2015

**Men:** ~1650 deaths  
**Women:** ~675 deaths

### Figure 3.2: Percent distribution of estimated cancer deaths, by sex, Canada, 2015

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Percentage</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>26.6%</td>
<td>~10,860</td>
</tr>
<tr>
<td>Colorectal</td>
<td>12.4%</td>
<td>~5,190</td>
</tr>
<tr>
<td>Prostate</td>
<td>10.1%</td>
<td>~4,170</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5.6%</td>
<td>~2,320</td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td><strong>4.0%</strong></td>
<td>~660</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3.9%</td>
<td>~1,590</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3.8%</td>
<td>~1,520</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3.5%</td>
<td>~1,340</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.1%</td>
<td>~1,220</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>3.0%</td>
<td>~1,170</td>
</tr>
<tr>
<td>Kidney</td>
<td>2.7%</td>
<td>~1,040</td>
</tr>
<tr>
<td>Liver</td>
<td>2.1%</td>
<td>~830</td>
</tr>
<tr>
<td>Oral</td>
<td>2.0%</td>
<td>~790</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.8%</td>
<td>~740</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.8%</td>
<td>~740</td>
</tr>
<tr>
<td>Larynx</td>
<td>0.8%</td>
<td>~350</td>
</tr>
<tr>
<td>Breast</td>
<td>0.1%</td>
<td>~40</td>
</tr>
<tr>
<td>All other cancers</td>
<td>12.5%</td>
<td>~5,190</td>
</tr>
</tbody>
</table>

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CNS = central nervous system  
*Note:* The complete definition of the specific cancers listed here can be found in Table A10.  
*Analysis by:* Surveillance and Epidemiology Division, CCDC, Public Health Agency of Canada  
*Data source:* Canadian Vital Statistics Death database at Statistics Canada
First Line Metastatic Disease

• Platinum based combination chemotherapy
  – Cisplatin wherever possible; carboplatin if not possible
• Cisplatin/gemcitabine combination most commonly used
  – Cisplatin Day 1 every 21 d x 6 cycles
  – Gemcitabine D 1, 8
• Patients intolerant of cisplatin may receive carboplatin; more myelosuppressive
First Line Chemotherapy

- Cisplatin based combination regimen will yield a median OS of ~ 12 months in all comers fit for cisplatin
- Carboplatin regimens are inferior; 8-10 months mOS
- Other combinations can be used
  - MVAC, ddMVAC, CMV
  - No real advantage in the metastatic setting so cis/gem is the de facto standard
Second Line Chemotherapy

• There is no true standard of care in 2nd line
  – Clinical trials should be our SOC
• Taxanes are generally accepted as good options, either alone or combination
• All second line options have ~15-20% response rate, PFS of 3-4 months and survivals of 6-9 months
  – For those patients fit enough to even qualify
High Rate of Mutations Detected in UC

Prevalence of somatic mutations across human cancer types

Red horizontal lines represent the median numbers of mutations in the respective cancer types

Cancer antigen presentation is an important step in the cancer immunity cycle

Immuno-Oncology (I-O)
Mechanism of Action of Checkpoint Inhibitors

I-O agents in mUC

• PD-L1/PD-1 pathway has been most targeted
• Atezolizumab now approved in US
• Other agents are nipping at atezo’s heels based on data
  – Pembrolizumab, nivolumab, durvalumab
• Combinations still under investigation
GO29293 Phase II (IMvigor 210): Study design and objectives

- Locally advanced/metastatic transitional cell carcinoma of the urothelium
- ECOG PS 0–1
- FFPE tissue specimen for PD-L1 analysis by IHC (central laboratory)a
- No autoimmune disease or corticosteroid use
  N=429

**Cohort 1: no prior chemotherapy and ineligible for cisplatin-based chemotherapy**
Atezolizumab 1,200mg IV q3w until PD
(n=119; ≥30 with IHC 2/3)

**Cohort 2: PD during or following >1 platinum-containing regimen**
CrCl ≥30 mL/min
Atezolizumab 1,200mg IV q3w
(n=310)

For duration of clinical benefit*

- Patients were not excluded on the basis of PD-L1 status
- Dose interruptions were allowed for toxicity, but dose reductions were not permitted
- Patients could continue treatment after RECIST v1.1 PD if pre-specified clinical benefit criteria were met

NCT02108652 Clinicaltrials.gov/NCT02108652
GO29293 Phase II (IMvigor 210): Cohort 1
Overall survival (median and landmark 12-month OS)

With a median follow-up of 14.4 months, the event rate is 47%.

Atezolizumab compares favorably with historic data from cisplatin-ineligible patients, both from clinical trials and real-world studies.

OS, overall survival; mOS, median overall survival; mo, month; CI, confidence interval; NE, not estimable.

Range, 0.2 to 20.1 mo. Data cutoff: March 14, 2016.

2. Galsky ECC 2015 [poster 115]
Balar A, et al. ASCO 2016 (Abstract LBA4500)