Integrating Immunotherapy into Urologic Oncology: The New Urothelial Cancer Paradigm

**Immunotherapy in Urothelial Cancer: Where are We Now & Where are We Going?**

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NYU Langone Medical Center
New York, NY

**Bladder Cancer Therapeutic Landscape**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta/T1/Tis</td>
<td>Non-Muscle Invasive Bladder Cancer (NMIBC) TURBT/Intravesical BCG Normal Urothelium</td>
</tr>
<tr>
<td>T2-T4</td>
<td>Muscle-Invasive Bladder Cancer (MIBC) Radical cystectomy, 15% 1-year survival, neoadjuvant Gem/Cis</td>
</tr>
<tr>
<td>First-Line Metastatic</td>
<td>Gem/Cis or MVAC in 90% 1-year survival, neoadjuvant or Neo-adjuvant of Citotragile (50%)</td>
</tr>
<tr>
<td>Second-Line Metastatic</td>
<td>Avelumab, Atezolizumab, Durvalumab, Nivolumab, Pembrolizumab ORR 15%–19.6% mOS: 7.9–11.4 mo Taxanes, gemcitabine, pemetrexed, vinflunine (EU) ORR: 10% mOS: 7–9 mo</td>
</tr>
</tbody>
</table>

**Cisplatin in Muscle-Invasive and Metastatic Urothelial Cancer**

- Cisplatin improves survival (including some cures), however 50–70% of patients ineligible due to comorbidities
  - PS and Renal Dysfunction
  - Neuropathy/Hearing Loss
  - Heart Failure
- Cisplatin-eligible
  - Gem/Carbo (if chemo eligible)
  - Outcomes are very poor
- 20–40% or more never treated

**Data from:**
- Funt SA, Rosenberg J. Nat Rev Clin Oncol. 2017

[Image of bladder cancer therapeutic landscape]

[Image of cisplatin in muscle-invasive and metastatic urothelial cancer]
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Somatic Mutational Burden is High in UBC

- High mutational complexity rates linked to tobacco/environmental carcinogen exposure.¹
- Potential for many "neoantigens" to be seen as foreign by host immune system.²


Chen and Mellman. Immunity. 2013


Anti-PD-1/PD-L1: Unleash Cytotoxic CD8+ T-cells

A separate therapy uses antibodies that bind PD-L1 on the tumour cell.

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**IMVigor210: Phase II Atezolizumab in Metastatic UC**

- Co-primary endpoints:
  - 1L confirmed ORR by RECIST v1.1 and central IRF
  - ORR by investigator-assessed modified RECIST

- Key secondary endpoints: DOR, PFS, OS, safety.

**Efficacy: Atezolizumab in 2nd-line mUC**

- Median time to first response was 2.1 mo.
- Ranges: 1.4 to 3.3 mo.
- 5 PR-to-CR and 2 SD-to-PR conversions observed with longer follow-up.

**KEYNOTE-045 Study Design (NCT02256436)**

- Key Eligibility Criteria:
  - Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
  - Transformed cell predominant
  - PD after 1-2 lines of platinum-based chemotherapy or recurrence within 12 mo of perioperative platinum-based therapy
  - ECOG PS 0-2
  - Provision of tumor sample for biomarker assessment

- Stratification Factors:
  - ECOG PS (0 vs 1)
  - Hemoglobin level (<10 vs ≥10 g/dL)
  - Liver metastases (yes vs no)
  - Time from last chemotherapy dose (<3 vs ≥3 mo)

- Key End Points:
  - Pembrolizumab 200 mg IV Q3W for 2 years
  - Paclitaxel 175 mg/m² Q3W
  - Docetaxel 75 mg/m² Q3W
  - Vinflunine 320 mg/m² Q3W
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**KEYNOTE-045**
Overall Survival: Update

![Graph showing survival rates](image)

**Confirmed Objective Response and Overall Survival Rates**

<table>
<thead>
<tr>
<th>Total Population</th>
<th>Carboplatin Group (N=270)</th>
<th>Carboplatin Group (N=272)</th>
<th>Carboplatin Group (N=74)</th>
<th>Carboplatin Group (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Overall Survival (95% CI)</strong></td>
<td>10.3 months (8.0-11.8)</td>
<td>7.4 months (6.1-8.3)</td>
<td>9.4 months (5.0-12.3)</td>
<td>10.4 months (4.0-17.4)</td>
</tr>
<tr>
<td><strong>Objective Response Rate (95% CI)</strong></td>
<td>21.1% (16.4-26.5)</td>
<td>11.4% (7.9-15.8)</td>
<td>21.6% (13.9-31.7)</td>
<td>8.7% (2.5-15.9)</td>
</tr>
</tbody>
</table>

**Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Antibody (Study)</th>
<th>N</th>
<th>DCR</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum-pretreated</td>
<td>Atezolizumab (IMpower 210, Cohort 2)</td>
<td>310</td>
<td>15%</td>
<td>7.9 months</td>
</tr>
<tr>
<td></td>
<td>Nivolumab (CheckMate 275)</td>
<td>265</td>
<td>20%</td>
<td>8.74 months</td>
</tr>
<tr>
<td></td>
<td>Durvalumab (Study 1108)</td>
<td>191</td>
<td>18%</td>
<td>18.2 months</td>
</tr>
<tr>
<td></td>
<td>Avelumab (JAVELIN Solid Tumor)</td>
<td>242</td>
<td>16%</td>
<td>7.7 months</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>KEYNOTE-045 (Ph 3)</td>
<td>270</td>
<td>21%</td>
<td>10.3 months</td>
</tr>
</tbody>
</table>

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**First-line Atezolizumab in mUC: IMvigor210 Study: Cohort 1**

- IMvigor210
  - Inoperable locally advanced or metastatic urothelial carcinoma
  - Predominantly UC histology
  - Tumor tissue evaluable for PD-L1 testing

Cohort 1–specific inclusion criteria
- No prior treatment for mUC (>12 mo since perioperative chemo)
- ECOG PS 0–2
- Cisplatin ineligible based on ≥1 of the following:
  - CrCl <60 mL/min
  - ECOG PS 2
  - ≥grade 2 neuropathy or hearing loss
- NYHA class III CHF

**Primary endpoints**
- Confirmed ORR: RECIST v1.1

**Key secondary endpoints**
- DOR, PFS, OS, safety

**Cohort 1 (N=119):**
- 1L cisplatin ineligible

**Cohort 2:**
- Platinum-treated mUC

- Atezolizumab 1200 mg IV q3w until RECIST v1.1 progression

**Frontline Therapy for Cisplatin-ineligible mUC: Old versus New Paradigm**

- GC (n=119)
- M-CAVI (n=119)

- ORR: 36% CR rate: 4%

- ORR: 23% CR rate: 9%

**KEYNOTE-052: Pembrolizumab as 1st-Line Therapy for Cisplatin-Ineligible Advanced Urothelial Cancer**

- Patients (N = 350)
  - Advanced urothelial cancer
  - No prior chemotherapy for metastatic disease
  - ECOG PS 0–2
  - Ineligible for cisplatin based on ≥1 of the following:
    - CrCl <60 mL/min
    - ECOG PS 2
    - ≥grade 2 neuropathy or hearing loss
    - NYHA class III CHF

- Pembrolizumab 200 mg Q3W

- Primary Endpoints:
  - ORR in all patients
  - ORR in patients with PD-L1–positive tumors

- Secondary Endpoints:
  - DOR, PFS, OS, and ORR in all patients, PD-L1–positive and PD-L1–high expressing patients, safety and tolerability
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Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 370</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>74 (34-94)</td>
</tr>
<tr>
<td>≥80 years</td>
<td>107 (29)</td>
</tr>
<tr>
<td>Men</td>
<td>286 (77)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>80 (22)</td>
</tr>
<tr>
<td>1</td>
<td>134 (36)</td>
</tr>
<tr>
<td>2</td>
<td>155 (42)</td>
</tr>
<tr>
<td>Primary tumor location</td>
<td></td>
</tr>
<tr>
<td>Upper tract</td>
<td>69 (19)</td>
</tr>
<tr>
<td>Lower tract</td>
<td>300 (81)</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>77 (21)</td>
</tr>
<tr>
<td>Metastases location</td>
<td></td>
</tr>
<tr>
<td>Lymph node only</td>
<td>51 (14)</td>
</tr>
<tr>
<td>Visceral disease</td>
<td>315 (85)</td>
</tr>
<tr>
<td>Reasons for cisplatin ineligibility</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>183 (50)</td>
</tr>
<tr>
<td>ECOG performance status 2</td>
<td>34 (9)</td>
</tr>
<tr>
<td>ECOG performance status 2 and renal dysfunction</td>
<td>34 (9)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>33 (9)</td>
</tr>
</tbody>
</table>

Data cutoff: Mar 9, 2017.

KEYNOTE-052: Confirmed Objective Response Rate

<table>
<thead>
<tr>
<th>Total Population (N=370)</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>108</td>
<td>29% (25-34)</td>
</tr>
<tr>
<td>Complete response</td>
<td>27</td>
<td>7 (5-10)</td>
</tr>
<tr>
<td>Partial response</td>
<td>81</td>
<td>22 (18-27)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>67</td>
<td>18 (14-22)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>155</td>
<td>42 (37-47)</td>
</tr>
</tbody>
</table>

With longer follow-up:
- 5% increase in ORR
- 10 additional complete responses
- 9 additional partial responses

KN052 vs IMVigor 210 Cohort 1: Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Atezolizumab IMVIGOR 210 Cohort 1 (Balar Lancet 2017)</th>
<th>Pembrolizumab KEYNOTE 052 (Balar Lancet Onc 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>23%</td>
<td>29%</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>28% (IC 23-33)</td>
<td>51% (CPS ≥10%)</td>
</tr>
<tr>
<td>Visceral</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Liver</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>Prior Perioperative Tx Survival</td>
<td>38%</td>
<td>NR</td>
</tr>
<tr>
<td>15/15 months (median)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>57% 12 months OS Rate</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
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### Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma

**7 US FDA Approvals May 2016-May 2017**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Antibody</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line (cisplatin-ineligible)</td>
<td>Atezolizumab</td>
<td>Accelerated approval granted in April 2017</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Accelerated approval granted in May 2017</td>
</tr>
<tr>
<td>Platinum-pretreated</td>
<td>Atezolizumab</td>
<td>Accelerated approval granted in May 2016. In May 2017, the subsequent phase 3 IMvigor211 trial did not meet primary endpoint of overall survival</td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Accelerated approval granted in February 2017</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>Accelerated approval granted in May 2017</td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td>Accelerated approval granted in May 2017</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Full approval granted in May 2017</td>
</tr>
</tbody>
</table>

### Immune Checkpoint Inhibitors in mUC: A Clinical Perspective

- Administration: intravenous over 30-60 minutes, no premedications required
- Dosing Schedules Variable
  - Q2, Q3 and Q4 weeks dosing
- Anti PD-1 vs Anti PD-L1
- Disease monitoring
  - Scans should be repeated every 8-10 weeks
  - Responses tend to be early (1st or 2nd scan)
  - Pseudoprogression is uncommon (mUC < Renal), and diagnosed clinically
  - Progression on imaging is thus most likely real
  - Consider pseudoprogression if clinical improvement (pain, appetite, energy) and stable to improved labs

### IMVigor 210 Cohort 2: Treatment Beyond Progression

- 220 patients with RECIST confirmed PD of 310 total patients included in analysis
- 4% ORR in 137 patients received post-PD Tx with avelumab
- None of the 4% were initial responders
- Pre-PD responders maintain decrease in SLDs with continued treatment
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**Immune Checkpoint Inhibitors in mUC**

- 1st line vs 2nd line: Unanswered questions
  - Ideal patient population
  - Sequencing
    - Who should receive chemotherapy vs immunotherapy first?
    - Chemotherapy-eligible patients now have an option
  - Minority respond to single agent PD-1 axis inhibition
  - Outcomes appear binary
  - Focus on novel combinations to improve engagement of immune system in single-agent IO refractory patients

**Enhancing Anti-Tumor Immunity Beyond PD-1/L1 Blockade**

- Multiple strategies either novel agents or combinations must be considered
- Tumor-protective mechanisms are varied
- Rational combinations will be required to increase the proportion of bladder cancers responsive to immunotherapy

**Possible combinations with immune checkpoint inhibitors**

- Other immune checkpoint inhibitors
- Chemotherapy
- Radiation
- Anti-angiogenic therapy
- Targeted therapy

**Novel Combinations in Metastatic Bladder Cancer**

- "Immune" Stimulating/Synergizing Combinations
  - CTLA-4
  - VEGF
  - IDO
  - FGFR3
  - Radiation/Chemo

- DNA Damage Repair
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CheckMate 032: Study Design
Open-label, multicenter, phase III study (NCT01928394)
- Pretreated patients with locally advanced or metastatic urothelial carcinoma
- Nivolumab 3 mg/kg IV Q2W (N=78)
- Nivolumab + Ipilimumab 3 mg/kg (Nivo 3 + Ipi 3) IV Q3W for 4 cycles (N=104)
- Nivolumab 1 mg/kg + Ipilimumab 1 mg/kg (Nivo 1 + Ipi 1) IV Q3W for 4 cycles (N=104)

- Treatment beyond progression was permitted if treatment was tolerated and prespecified clinical benefit was noted
- Tumor measurements: CT or MRI every 6 weeks (±1 week) from first dose for the first 24 weeks, then every 12 weeks (±1 week)


Anti–CTLA-4 and Anti–PD-1: CheckMate 032: Antitumor Activity

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>NIVO 1 + IPI 3 (n = 26)</th>
<th>NIVO 3 + IPI 1 (n = 104)</th>
<th>NIVO Monotherapy (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, %</td>
<td>38.5</td>
<td>26.0</td>
<td>24.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>20.2-55.2</td>
<td>17.9-35.5</td>
<td>15.3-35.4</td>
</tr>
<tr>
<td>Best overall response, %</td>
<td>Complete response 3.8 2.9 6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial response 34.6 23.1 17.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable disease 19.2 25.0 28.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progressive disease 26.9 41.3 38.5</td>
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</tr>
</tbody>
</table>


PD-L1 plus CTLA-4 in Metastatic Bladder Cancer
- First-line
  - DANUBE: Phase III Durvalumab +/- Tremelimumab vs Platinum-chemotherapy
  - CHECKMATE 901: Phase III Nivo/Ipi vs Platinum-chemotherapy
- Second-line
  - Durvalumab plus Tremelimumab (D4190C00010 – UBC Expansion Cohort)
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**Novel Combinations in Metastatic Bladder Cancer**

- CTLA-4
- VEGF
- IDO
- Radiation/Chemom
- DNA Damage Repair
- FGFR3

**VEGF as a Cancer Target: Angiogenesis**

- VEGF/R signaling induces proliferation of mature endothelial cells and promotes tumor neovasculature
- VEGF over-expression associated with poor prognosis in UC
- Blockade of VEGF-mediated angiogenesis with bevacizumab is active in mUC
  - Two phase II trials of chemotherapy + Bev promising compared to historical controls1,2
  - CALGB 90601 Phase III Gem/Cis ± bevacizumab completed

**VEGF as a Cancer Target: Tumor Immune Microenvironment**

- ↑VEGF shown to alter tumor immune recognition by inhibiting dendritic cell maturation/antigen presentation, and increasing tumor levels of T-Regs and MDSCs1-4
- VEGF blockade normalizes vasculature → T-cell trafficking
- Phase I Bevacizumab + Ipilimumab (anti-CTLA-4) in Adv Melanoma5
  - Promoted T-cell and dendritic cell trafficking in tumors
  - Induced peripheral memory T-cell expansion

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A Phase II Trial of First-Line Atezolizumab +/- Bevacizumab in Cisplatin-Ineligible mUC

- Metastatic UC
- Cisplatin-ineligible
  - ECOG PS ≤ 2
  - CrCl > 60 cc/min
  - Grade 1 ≤ PN
  - Grade 1 ≤ HL
  - Solitary kidney
  - eGFR > 30 cc/min

Randomized

Atezolizumab + Bevacizumab Q3 Wks

Excessive Toxicity or Progressive Disease

Atezolizumab Q3 Wks

3 weeks = 1 cycle Response assessment every 3 cycles

PI: Balar (NYU); HCRN GU15-215

Other VEGF(R) Combinations

- Cabozantinib plus Nivolumab or Ipilimumab
  - Phase I data showing tolerability in GU Cancers (Apolo, et al. ASCO 2017)
- Axitinib plus Pembrolizumab
  - 70% ORR in RCC (Phase I)
  - RP3 on-going
- Pazopanib plus PD-1 combinations
  - Too toxic (liver)
- Optimal partners/sequence unknown

Novel Combinations in Metastatic Bladder Cancer

- “Immune” Stimulating/Synergizing Combinations
- Targeted Therapy Combinations – Exploratory

CTLA-4, VEGF, IDO, FGFR3, Radiation/Chemotherapy, DNA Damage Repair
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IDO (indoleamine 2,3 – dioxygenase)

- IDO-1
  - IFN-γ-induced catalytic enzyme of tryptophan degradation to kynurenine
  - Tryptophan/kynurenine ratio is immunosuppressive to effector T-cells
- Several agents in testing
  - Epacadostat
  - Indoximod
  - BMS986205
  - PF-0684003
- Epacadostat + PD-1: active/well-tolerated
  - 35% ORR in phase I ECHO-202/KEYNOTE-037
  - Phase III in first-line cisplatin ineligible and second-line cisplatin (platinum-refractory/relapsed) planned

Novel Combinations in Metastatic Bladder Cancer

“Immune” Stimulating/Synergizing Combinations

- CTLA-4
- VEGF
- IDO
- Radiation/Chemo
- FGFR3
- DNA Damage Repair

Targeted Therapy Combinations – Exploratory

Muscle Invasive Bladder Cancer: Platform for Testing Chemoradiation added to PD-1 Blockade

- Chemoradiation is a standard in non-surgical candidates or those refusing radical cystectomy
- Radiation → Immunogenic cell death
  - Radiation may enhance T-cell priming/Type 1 IFN → convert non-infamed tumors and enable response to PD-1 blockade
  - Best chemotherapy to pair is radiosensitizing at low-doses to minimize systemic toxicity
  - Gemcitabine highly radiosensitizing at < 5% of systemic dose
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PACIFIC: Immunotherapy after ChemoRT in Stage III NSCLC

- Patients with stage III, locally advanced, chemotherapy-naive NSCLC who have not progressed following definitive platinum-based CRT (O1 united)
- Age 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Tumor tissue was collected
- Arm: concurrent" +
- Arm: concurrent"

PACIFIC: Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Durvalumab</th>
<th>Placebo</th>
<th>HR/RR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>16.8 mon</td>
<td>5.8 mon</td>
<td>0.52</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PFS at 1 year</td>
<td>47%</td>
<td>21%</td>
<td>1.77</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Metastasis at 1 year</td>
<td>23.2 mon</td>
<td>14.6 mon</td>
<td>0.52</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ORR</td>
<td>28%</td>
<td>16%</td>
<td>1.78</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

PI: Balar (NYU); NCT02621151

Phase II Trial of Pembrolizumab, Gemcitabine and Hypofractionated RT as Bladder Sparing Treatment for MIBC

- N=54 (safety lead-in = 8)
- Primary Endpoint: BDFS
- Participating Sites: 4

PL: Balar (NYU), NCT02621151
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Novel Combinations in Metastatic Bladder Cancer

- Targeted Therapy Combinations – Exploratory
  - FGFR3
    - Luminal 1 tumors (TCGA) least likely to respond to SA PD-1
    - Enriched with FGFR3 activating alterations and “cold” phenotype
    - FGFR3 plus PD-1/L1 in phase I
  - DNA – Damage Repair Deficiency
    - Associated with higher mutational burden → neoantigens
    - PARPi may increase mutational burden and synergize with PD-1 blockade
    - PARPi plus PD-1/L1 in phase I


Immunotherapy in UC - Conclusions

- Pace of progress in urothelial carcinoma treatment is unprecedented
- Immunotherapy is a well tolerated and active treatment for our patients
- Reliable predictive biomarkers for clinical decision-making are lacking
- Several other novel therapies and combinations are in clinical development
  - Checkpoint inhibitors
  - Angiogenesis inhibitors
  - Targeted Therapy
  - Radiation/Chemotherapy