Systemic therapy and a new paradigm in Urothelial Bladder Cancer – on the cusp of a sea change?

Andrea Necchi
Department of Medical Oncology
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Treasurer – EORTC GU Cancers Group
Disclosures

- Consultant and advisory role, GlaxoSmithKline (GSK)
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- Research funding, Amgen
- Research funding, MerckSharp&Dohme (MSD)
- Consultant and advisory role, Celgene
- Treasurer of the EORTC-GU Cancers Group
- Member of the EAU-YAU Bladder Cancer Working Group
- Member of the ESMO Faculty – Genitourinary Cancers
Bladder Cancer Treatment Paradigm (US & EU)

Cystoscopy, TURBT+/-biopsy, histology (for diagnosis) and imaging (for staging) esp. CT scan

NMIBC
- TURBT
  - SOC
  - Cystectomy
  - Chemo (neoadjuvant / adjuvant)
  - RT
  - Metastatic
    - Chemo
    - RT

MIBC
- BCG Refractory
- BCG
- Lower risk
- Higher risk
- mitomycin (or anthracyclines in JPN)
- BCG
- Failures treated as metastatic
- GC/MVAC
- GC/MVAC Refractory
- 1st line
- 2nd line...
- Various combos esp. platinum-based + paclitaxel

Metastatic
- Cis-eligible: GC/MVAC
- Cis-ineligible: Gem/carbo
- Clinical Trial

Gemcitabine (US/EU)
Valrubicin (US/EU)
Epirubicin (US/EU)
Taxane
Carboplatin
Vinflunine (EU)
Reduction in tumor diameters

Time (DD)EMVAC CEG TCG Mod. MVAC

CR (15-25%)

CR+PR (40-60%)

SD

Long-lasting Response (5-10%)

Progression

Relapse

PD

Unresectable to metastatic UC

• Rational delivery of conventional chemotherapeutic options
• Molecularly-driven patient selection
• Future directions (immunotherapy revolution beyond the corner)
First-line chemotherapy: 
Overall Survival for MVAC vs Gem/Cis

**GC** 13.8 months (12.3-15.8)

**MVAC** 14.8 months (13.2-16.8)

HR: 1.04 (0.82-1.32)

von der Maase H et al, J Clin Oncol 2000
First-line chemotherapy: 
**Accelerated MVAC vs. standard MVAC**

P = 0.121

Sternberg CN et al, J Clin Oncol 2001; Eur J Cancer 2006
First-line chemotherapy:
*The addition of Paclitaxel to Gem/Cis*

ORR: 55.5% vs 43.6%
Median PFS (mos): 8.3 (PCG) vs 7.6 (CG)
Median OS (mos): 15.8 (PCG) vs 12.7 (CG)

Bellmunt J et al, J Clin Oncol 2012
Approximating 50%
Galsky MD et al. ASCO 2013

Cisplatin ineligibility

Table 4. Proposed Working Group Eligibility Criteria for Clinical Trials Enrolling Patients With Metastatic Urothelial Carcinoma “Unfit” for Cisplatin-Based Chemotherapy

<table>
<thead>
<tr>
<th>Eligibility Criteria (at least one of the following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO or ECOG PS of 2 or Karnofsky PS of 60%-70%</td>
</tr>
<tr>
<td>Creatinine clearance (calculated or measured) &lt; 60 mL/min</td>
</tr>
<tr>
<td>CTCAE v4 grade ≥ 2 audiometric hearing loss</td>
</tr>
<tr>
<td>CTCAE v4 grade ≥ 2 peripheral neuropathy</td>
</tr>
<tr>
<td>NYHA Class III heart failure</td>
</tr>
</tbody>
</table>

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status.
Outcome of different populations treated with different chemotherapy

<table>
<thead>
<tr>
<th>GEM/CIS +/-PAC</th>
<th>VIN + GEM or CARBO</th>
<th>CARBO + GEM or VINBLAST METHOTREX</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 0/1 GFR-good</td>
<td>PS 0/1 GFR-poor</td>
<td>PS2 or GFR-poor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RR %</th>
<th>PFS months</th>
<th>OS months</th>
<th>RR %</th>
<th>PFS months</th>
<th>OS months</th>
<th>RR %</th>
<th>PFS months</th>
<th>OS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-43</td>
<td>7.6-8.3</td>
<td>12.7-15.8</td>
<td>54 -43</td>
<td>5.9-6.1</td>
<td>12.8-14</td>
<td>41-30</td>
<td>4.2-5.8</td>
<td>8.3-9.3</td>
</tr>
</tbody>
</table>

Pending publication

JASINT-2: Randomized phase III study comparing vinflunine-gemcitabine and gemcitabine carboplatin combinations in patients ineligible to cisplatin with advanced or metastatic urothelial carcinoma.

Study Scheme

Pts with renal function impairment, PS 0-1

D1

Arm A (VG)
- Vinflunine* 280 or 250 mg/m²
- Gemcitabine 750 mg/m² or 1000 mg/m²**

1:1

Arm B (GC)
- Gemcitabine 1000 mg/m²
- Carboplatin AUC 4.5

D8

Arm A (VG)
- Gemcitabine 750 mg/m² or 1000 mg/m²**

Treatment until progression (every 6 weeks staging) or unacceptable toxicities

Post treatment follow-up
- Every: 6 weeks up to PD
- 3 months after PD

Assessment q 6 weeks (2 cycles) 1 Cycle = 21 days

* Starting dose of drug depending on calculated creatinine clearance (Cockcroft-Gault formula) randomization value.
** Beyond cycle 1, if no toxicity of Grade > 2 occurs in cycle 1.
Role of primary tumor location on survival in first-line therapy for advanced UC (EORTC 30987 Study)

Bellmunt J, Semin Oncol 2012

Gem-Platinum vs Gem-Platinum-Taxane in the first-line setting of UC: A Systematic review and Meta-analysis

Table 3 – Efficacy outcomes according to the combination chemotherapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GEM-CDDP</th>
<th>GEM-CBDCA</th>
<th>GEM-CDDP-taxane</th>
<th>GEM-CBDCA-taxane</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>13.47 (38--65.3)</td>
<td>13.45 (24--67)</td>
<td>5.55 (40--81)</td>
<td>2.55 (43--68)</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>12.73 (3.5--8.5)</td>
<td>9.75 (4.6--9.4)</td>
<td>5.83 (7.4--10)</td>
<td>1.74 (7.4--7.4)</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>14.13 (8.5--18)</td>
<td>13.10 (3.3--20)</td>
<td>5.15.8 (14--22)</td>
<td>2.12 (11--14.7)</td>
</tr>
<tr>
<td>1-yr OS (%)</td>
<td>6.53 (28--82)</td>
<td>5.42 (26--58.5)</td>
<td>3.68 (61.4--73.3)</td>
<td>2.52 (46--58.5)</td>
</tr>
</tbody>
</table>

CBDCA = carboplatin; CDDP = cisplatin; GEM = gemcitabine; OS = overall survival; PFS = progression-free survival; RR = response-rate.

<table>
<thead>
<tr>
<th>Previous perioperative therapy counted as first-line therapy</th>
<th>N</th>
<th>RR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly paclitaxel</td>
<td>31</td>
<td>10</td>
<td>2.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Paclitaxel q21d</td>
<td>14</td>
<td>7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>47</td>
<td>27.7</td>
<td>6.0</td>
<td>10.8</td>
</tr>
<tr>
<td>Eribulin</td>
<td>48</td>
<td>27</td>
<td>4.1</td>
<td>10.4</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>40</td>
<td>5</td>
<td>2.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>42</td>
<td>11.9</td>
<td>2.7</td>
<td>8.0</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>47</td>
<td>27.7</td>
<td>2.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>18</td>
<td>6</td>
<td>1.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>56</td>
<td>20</td>
<td>2.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>NA</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>12</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>30</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>30</td>
<td>11</td>
<td>4.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>35</td>
<td>22.5</td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>Topotecan</td>
<td>NA</td>
<td>9.1</td>
<td>1.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Paclitaxel+gemcitabine</td>
<td>41</td>
<td>60</td>
<td></td>
<td>14.4</td>
</tr>
<tr>
<td>Ifosfamide+gemcitabine</td>
<td>34</td>
<td>21</td>
<td>4.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Carboplatin+paclitaxel</td>
<td>44</td>
<td>16</td>
<td>4.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Gemcitabine+Ifosfamide</td>
<td>23</td>
<td>22</td>
<td>3.5</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Second-line phase III trial: Vinflunine + BSC vs. BSC
Bellmunt J, J Clin Oncol 2009

>2 months, maintained at > 3.5 yr FUP

Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study selection</th>
<th>ORR</th>
<th>Probability % (95%CI)</th>
<th>PFS</th>
<th>Median PFS (95%CI)</th>
<th>OS</th>
<th>Median OS (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent chemotherapy</td>
<td>22</td>
<td>14.2 (11.1-17.9)</td>
<td>18</td>
<td>2.65 (2.22-3.07)</td>
<td>20</td>
<td>6.98 (6.19-7.78)</td>
</tr>
<tr>
<td>Vinflunine</td>
<td>3</td>
<td>11.7 (6.2-20.9)</td>
<td>3</td>
<td>2.92 (2.56-3.29)</td>
<td>3</td>
<td>7.20 (6.30-8.10)</td>
</tr>
<tr>
<td>Paclitaxel or docetaxel</td>
<td>5</td>
<td>10.5 (6.9-15.8)</td>
<td>3</td>
<td>2.15 (1.36-2.94)</td>
<td>4</td>
<td>7.36 (6.16-8.55)</td>
</tr>
<tr>
<td>Doublet chemotherapy</td>
<td>24</td>
<td>31.9 (27.3-36.9)</td>
<td>15</td>
<td>4.76 (3.70-5.62)</td>
<td>23</td>
<td>8.50 (7.35-9.64)</td>
</tr>
<tr>
<td>Doublet with cisplatin</td>
<td>2</td>
<td>40.4 (28.5-53.5)</td>
<td>1</td>
<td>6.20 (3.95-8.45)</td>
<td>2</td>
<td>10.39 (7.53-13.26)</td>
</tr>
<tr>
<td>Doublet without cisplatin</td>
<td>22</td>
<td>30.9 (26.1-36.3)</td>
<td>14</td>
<td>4.66 (3.55-5.77)</td>
<td>21</td>
<td>8.35 (7.15-9.55)</td>
</tr>
<tr>
<td>Doublet with carboplatin</td>
<td>4</td>
<td>25.4 (17.9-34.7)</td>
<td>4</td>
<td>3.88 (3.15-4.62)</td>
<td>4</td>
<td>8.14 (5.76-10.52)</td>
</tr>
</tbody>
</table>

High rate of mutations detected in bladder cancer

- High mutational complexity rates due to tobacco/environmental carcinogen exposure.
- Potential for many neo-antigens to be seen as foreign by host immune system, leading to increased activity of immunotherapy.
- Mutational load could be a response biomarker.

A Phase 2, Two-arm Multicenter, Open-Label Study to Determine the Efficacy and the Safety of Two Different Dose Regimens of a pan-FGFR Tyrosine Kinase Inhibitor JNJ-42756493 in Subjects with Metastatic or Surgically Unresectable Urothelial Cancer with FGFR Genomic Alterations

“...Tumors must have at least 1 of the following translocations: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or
One of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C”

BGJ-398 in FGFR3-mutated UBC

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Tumor</th>
<th>Schedule (125 mg/day)</th>
<th>Best Overall Response (% tumor change)</th>
<th>Duration on Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>86 ♂</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>PR (-48%)</td>
<td>5 cycles</td>
</tr>
<tr>
<td>62 ♂</td>
<td>FGFR3-mutated</td>
<td>3 weeks on/ 1 week off</td>
<td>PR (-45%)</td>
<td>9+ cycles</td>
</tr>
<tr>
<td>53 ♂</td>
<td>FGFR3-mutated</td>
<td>3 weeks on/ 1 week off</td>
<td>SD (-28%)</td>
<td>4 cycles</td>
</tr>
<tr>
<td>77 ♂</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>SD (-27%)</td>
<td>4 cycles</td>
</tr>
<tr>
<td>52 ♂</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>SD (+11.4%)</td>
<td>3 cycles</td>
</tr>
<tr>
<td>80 ♂</td>
<td>FGFR1-amplified</td>
<td>3 weeks on/ 1 week off</td>
<td>PD</td>
<td>&lt; 2 weeks</td>
</tr>
</tbody>
</table>

In FGFR3-mutated urothelial carcinoma
- Overall response rate 40% (2/5)
- Disease control rate 100% (5/5)

Sequist LV, AACR 2014

JNJ-42756493 at ≥6mg dose in UBC with FGFR aberrations

Bahleda R, ASCO 2014
Rationale for the development of immunotherapy in early stage urothelial bladder carcinoma

*The Cancer Immunity Circle*

Chen DS & Mellman I. Immunity 2013
PD-L1 IHC staining in urothelial bladder cancer

Tumor cells

Tumor + inflammatory cells
Phase Ia Study PCD4989g: Clinical Activity of Atezolizumab in mUC Cohort

Presented by Petrylak et al. ASCO 2015

- Median DOR not reached (range, 0+ to 43 mo) in any IHC subgroup
- Median overall survival
  - Not reached in IC2/3 (median survival follow up 14 months)
  - 7.6 months in IC0/1 (median survival follow up 12 months)

SLD, sum of longest diameters. \( ^a \)Change in SLD > 100%. \( ^b \)Seven patients without post-baseline tumor assessments not included. Asterisks denote 9 CR patients, 6 of whom have been confirmed by data cutoff date (Dec 2, 2014) and 7 of whom had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.
Atezolizumab: two studies in first-line/second-line UC are under way

**IMvigor 210/GO29293 (phase II)**

- **Patients with disease progression following or during platinum-containing treatment for MIBC or mUBC (n=300 [100 PD-L1+])**
- **Treatment-naive and cisplatin-ineligible MIBC or mUBC (n=100 [33 PD-L1+])**
- **Primary endpoint:** ORR in IHC 2/3→1/2/3→ITT
- **Secondary endpoints:** DoR, PFS, OS
- **FPI:** May 2014

**IMvigor 211/GO29294 (phase III)**

- **Patients with previously treated relapsed UBC (n=767 [230 PD-L1+])**
- **Primary endpoint:** OS in IHC 2/3→1/2/3→ITT
- **Secondary endpoints:** PFS, ORR, DoR
- **FPI:** Q4 2014

http://www.clinicaltrials.gov/ct2/show/NCT02108652
FPI=first patient in; ITT=intent-to-treat
Atezolizumab in Patients with Locally-Advanced or Metastatic Urothelial Carcinoma (mUC): Results from a Pivotal Multicenter Phase II Study (IMvigor 210)

Jonathan E. Rosenberg, 1 Daniel P. Petrylak, 2 Oyewale Abidoye, 3 Michiel S. van der Heijden, 4 Jean Hoffman-Censits, 5 Andrea Necchi, 6 Peter H. O’Donnell, 7 Ani Balmanoukian, 8 Yohann Loriot, 9 Margitta Retz, 10 Jose Luis Perez-Gracia, 11 Nancy A. Dawson, 12 Arjun V. Balar, 13 Matthew D. Galsky, 14 Mark T. Fleming, 15 Thomas Powles, 16 Na Cui, 3 Sanjeev Mariathasan, 3 Gregg D. Fine, 3 Robert Dreicer 17

1 Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2 Yale Cancer Center, New Haven, CT, USA; Genentech, Inc., South San Francisco, CA, USA; 4 Netherlands Cancer Institute, Amsterdam, Netherlands; 5 Thomas Jefferson University Hospital, Philadelphia, PA, USA; 6 Istituto Nazionale dei Tumori, Milan, Italy; 7 University of Chicago, Chicago, IL, USA; 8 The Angeles Clinic and Research Institute, Los Angeles, CA, USA; 9 Gustave Roussy, Villejuif, France; 10 Urologische Klinik und Poliklinik, Technische Universität München, Munich, Germany; 11 Clínica Universidad de Navarra, Pamplona, Spain; 12 Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; 13 Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA; 14 Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 15 Virginia Oncology Associates, Norfolk, VA, USA; 16 Barts Cancer Institute, Queen Mary University of London, London, UK; 17 Division of Hematology/Oncology, University of Virginia, Charlottesville VA USA
Atezolizumab (MPDL3280A): A Humanized Anti-PDL1 Antibody

- Signaling through programmed death-ligand 1 (PD-L1), which is expressed in many cancers including mUC, can inhibit antitumor immune responses
  - Atezolizumab can enhance T-cell priming and reinvigorate suppressed immune cells by inhibiting binding of PD-L1 to PD-1 and B7.1
  - By leaving the PD-L2/PD-1 interaction intact, atezolizumab has the potential to preserve peripheral immune homeostasis\(^1,2\)


Rosenberg JE et al, ECC2015
**IMvigor 210: PD-L1 IHC**

**PD-L1 Immune Cell Expression and Prevalence**

**IHC Status of Treated Patients in IMvigor 210 Study (N = 311)**

- IMvigor 210 enrolled an all-comer population
- VENTANA PD-L1 (SP142) CDx Assay was used to prospectively measure tumor-infiltrating immune cell (IC) PD-L1 expression based on 3 IHC scoring levels

Rosenberg JE et al, ECC2015
**IMvigor 210: Efficacy**

Changes in Target Lesions by PD-L1 Subgroup

![Graph showing changes in target lesions by PD-L1 status with percentages and ORR values.]

- **IC2/3**: 51/85 (60%) **ORR**: 27%
- **IC1**: 38/88 (43%) **ORR**: 10%
- **IC0**: 27/85 (32%) **ORR**: 9%

111/258 (43%) patients with tumor assessments had SLD reduction.
IMvigor 210: Efficacy

Preliminary Analyses of Overall Survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>IC2/3 n = 100</th>
<th>IC0/1 n = 211</th>
<th>All N = 311</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (7.6, NE)</td>
<td>6.7 (5.7, 8.0)</td>
<td>7.9 (6.7, NE)</td>
</tr>
</tbody>
</table>

Median follow up: 7 mo (range, 0-11 mo)

NR, not reached; NE, not estimable. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.
KEYNOTE-012: study design

- Recurrent or metastatic cancer of the renal pelvis, ureter, bladder, or urethra
- Transitional or non-transitional cell histology
- ECOG PS 0/1
- No systemic steroid therapy
- No autoimmune disease
- No active brain metastases
- PD-L1+ tumour

Pembro 10 mg/kg IV q2w (n=33)

CR

Discontinuation permitted

Discontinue

PR or SD

Treat for 24 months or until progression or intolerable toxicity

Confirmed PD

Screening for PD-L1

PD-L1 positivity was defined as any staining in the stroma or in ≥1% of tumour cells, using a prototype IHC assay and the 22C3 antibody clone

61 of 95 (64.2%) patients screened were found to be PD-L1 positive

Response assessment: performed every 8 weeks per RECIST v1.1

At the discretion of the investigator, patients who received pembrolizumab for ≥24 weeks and for ≥2 treatments beyond confirmed complete response may discontinue therapy. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy was received. If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. Plimack, et al. ASCO 2015. https://clinicaltrials.gov/show/NCT01848834
KEYNOTE-012: maximum percent change from baseline in target lesions

64% experienced a decrease in target lesions

Analysis includes patients with measurable disease per central review at baseline who received ≥1 pembrolizumab dose and had ≥1 post-baseline tumour assessment (n=25)
RECIST v1.1, Central Review
Analysis cutoff date: March 23, 2015
Plimack, et al. ASCO 2015
KEYNOTE-012: treatment exposure and response duration

- Median follow-up duration: 15 (0.6–20) months
- Median time to response: 9 (7.7–55.9) weeks
- Response duration: 8.1 to 64.1+ weeks
- 3 patients remain on therapy

Time, weeks

RECIST v1.1, Central Review
Analysis cutoff date: March 23, 2015
Plimack, et al. ASCO 2015
## Summary: pembrolizumab and atezolizumab in UC

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab KEYNOTE-012 (phase Ib)¹</th>
<th>Atezolizumab PCD4989g (phase Ia)²</th>
<th>Atezolizumab IMvigor 210 (phase II)³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
</tr>
<tr>
<td><strong>Number of evaluable patients</strong></td>
<td>29</td>
<td>87 (IC2/3 = 46)</td>
<td>311 (IC2/3 = 100)</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>PD-L1+*</td>
<td>All comers**</td>
<td>All comers**</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>q2wk</td>
<td>q3wk</td>
<td>q3wk</td>
</tr>
<tr>
<td><strong>Grade 3–4 toxicity</strong></td>
<td>15%</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>28%</td>
<td>IC2/3 = 50%</td>
<td>IC2/3 = 27%</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>13 months</td>
<td>IC2/3 = NR (1 to 20+ months)</td>
<td>IC2/3 = NR (7.6, NE)</td>
</tr>
<tr>
<td><strong>12-month OS rate</strong></td>
<td>53%</td>
<td>57%</td>
<td>–</td>
</tr>
</tbody>
</table>

*Defined as any staining in the stroma or in ≥1% of tumour cells

**IHC status defined as IC3: ≥10% of IC expressing PD-L1; IC2: ≥5% but <10% of IC expressing PD-L1; IC1: ≥1% but <5% of IC expressing PD-L1; IC0: <1% of IC expressing PD-L1 (SP142 IHC assay)

1. Plimack, et al. ASCO 2015
Urothelial Bladder Cancer: Next Development Steps in I-O

Biomarker-driven approach

• P53 53%
• FGFR3 19%
• RAS 4%
• PI3KCA 25%
• FGFR1 12%

Potential 2nd gen I-O combos

• Pan-FGFR inh/aPD1-PD-L1
• Parp Inh/aPD1-PD-L1
• Rad223/Atezolizumab
• aPD1-PD-L1/aCTLA4
• .....  

Non-biomarker-driven approach

• Improving frequency of sustained responses
• Improving responses in PD-L1 negative cohort

Sharma P & Allison JP, Science 2015
A myriad of next generation I-O trials with mono- or combination therapy are underway in almost all clinical settings.

**Non-muscle Invasive**
- Pembrolizumab
- Everolimus +intravesical GEM (NCT01259063)

**BCG Refractory**
- Pembrolizumab+RT (NCT02560636)
- **PURE01**: Pembrolizumab>Cystectomy (EudraCT: 2015-002055-10)
- **MIRTOS**: Atezolizumab>Cystectomy

**Muscle Invasive**
- pembrolizumab +RT (NCT03060867)

**1L Metastatic cis-eligible**
- **Phase II**: KEYNOTE-052, Pembrolizumab (NCT02335424)
- **Phase III**: MEDI4736 vs MEDI4736+Tremelimumab vs ChemoTx (DANUBE, NCT02516241)

**1L Metastatic cis-ineligible**
- **Phase III**: KEYNOTE-045, Pembrolizumab (NCT02256436)
- **Phase III**: Atezolizumab (GO29294), NCT02302807

**2L Metastatic**
- **Phase III**: Pembrolizumab (AMBASSADOR)
- **Phase III**: Nivolumab (CA209-274)

**3L Metastatic**
- **Phase III**: Avelumab (EudraCT: 2015-003262-86)

**NEOADJUVANT**
- Pembrolizumab+RT (NCT02560636)
- **PURE01**: Pembrolizumab>Cystectomy (EudraCT: 2015-002055-10)
- **MIRTOS**: Atezolizumab>Cystectomy

**ADJUVANT**
- **Phase III**: Atezolizumab (NCT02450331)
- **Phase III**: Pembrolizumab (AMBASSADOR)
- **Phase III**: Avelumab (EudraCT 2015-003262-86)
- **Phase III**: Nivolumab (CA209-274)

**MAINTENANCE Tx**
- **Phase III**: Avelumab (EudraCT 2015-003262-86)
- **Phase II**: Regorafenib (NCT02459119)

**REFRACTORY**
- Atezo+Bevacizumab
- Atezo+Rad223
- AD4547/MEDI4736
- AZD8166/MEDI4736
- Olaparib/MEDI4736
- Weex/MEDI4736
- Olaparib/MEDI4736/Tremelimumab Etc.

**Sources:** http://ClinicalTrials.gov; http://www.bcan.org
Durvalumab (MEDI4736): phase III study of first-line durvalumab with or without tremelimumab vs SOC CT in patients With unresectable stage IV UBC

Key eligibility
- First-line histologically or cytologically confirmed unresectable stage IV UBC
- Eligible or ineligible for cisplatin-based CT
- Cisplatin ineligible defined as meeting 1 of the below criteria:
  - Creatinine clearance <60 mL/min; CTCAE grade ≥2 audiometric hearing loss; CTCAE grade 2 peripheral neuropathy; NY Heart Association class III heart failure
- Tumor PDEL1 status (IHC confirmed by reference laboratory) is required prior to randomisation
  \[ N = 525 \]

- Primary endpoint: PFS of combination therapy vs SOC CT
- Secondary endpoint: PFS in PD-L1-negative patients, OS, safety and tolerability, ORR, functional assessment of cancer therapy- bladder cancer (FACT-BL), immunogenicity, pharmacokinetics
- Study start date: October 2015
- Estimated study completion date: August 2019
- Estimated primary completion date: November 2017

https://clinicaltrials.gov/ct2/NCT02516241
Patients with histologically-confirmed transitional-cell carcinoma (T2-T4a) of the bladder

3x3 weekly cycles of MK-3475 200 mg

CyStectomy

Post-cystectomy management according to local guidelines. Study visits at +4, +12, +24 weeks after surgery

Survival data collected until 2-years post-cystectomy

Collection of 50 mL blood aliquots and FFPE archival tissue from the TURB

Collection of 50 mL blood aliquots before cystectomy and FFPE archival tissue from cystectomy

Primary Endpoint: Pathological complete response rate in T2-T4a NoMo UBC

Study sponsor: Fondazione IRCCS Istituto Nazionale dei Tumori
Principal Investigator: A. Necchi
Inclusion criteria:
- Failure of ≥1 prior chemotherapy regimen
- Adequate organ function
- Measurable disease
- TCC histology
- Availability of sufficient archival tumor tissue for analyses

Industry-sponsored NGS or Ion Ampliseq™ Comprehensive Cancer Panel (+ customized additional analyses)

Primary Endpoint (descriptive):
Overall survival (benchmark of 6 months)
[Global and according to study arm]
Bladder Cancer White Paper EU action recommendations

- **Education** and **information** for patients and broad public, including policy makers
- **Prevention**: smoking cessation and occupational cancer
- **More research funding and centralised data** to better understand the risk factors and the disease
- **Early diagnosis**: screening programme for high-risk groups
- **Money and resources** should always be readily available but austerity measures
- **Training urologists** when cancer manifested long after initial exposure
- **Access** to novel technological solutions

Group consensus document launch in December 2015 in EU Parliament

**Opportunity** for the community to **contribute** and further **cascade** the initiative