Systemic therapy in the treatment of bladder cancer

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Bladder Cancer - Objectives

- Describe the epidemiology and staging of bladder cancer
- Describe the evidence for the use of neoadjuvant and adjuvant chemotherapy with surgery in the treatment of localized bladder cancer
- Describe the evidence for the use of chemotherapy, anti-PD1/PDL1 therapy and FGFR inhibitors in metastatic bladder cancer
## Bladder Cancer - Epidemiology

### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>191,930</td>
<td>21%</td>
<td>Breast</td>
<td>276,480</td>
<td>30%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,300</td>
<td>13%</td>
<td>Lung &amp; bronchus</td>
<td>112,520</td>
<td>12%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>78,300</td>
<td>9%</td>
<td>Colon &amp; rectum</td>
<td>69,650</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>62,100</td>
<td>7%</td>
<td>Uterine corpus</td>
<td>66,620</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>60,190</td>
<td>7%</td>
<td>Thyroid</td>
<td>40,170</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>45,520</td>
<td>5%</td>
<td>Melanoma of the skin</td>
<td>40,160</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>42,380</td>
<td>5%</td>
<td>Non-Hodgkin lymphoma</td>
<td>34,860</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>38,380</td>
<td>4%</td>
<td>Kidney &amp; renal pelvis</td>
<td>28,230</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35,470</td>
<td>4%</td>
<td>Pancreas</td>
<td>27,200</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>30,400</td>
<td>3%</td>
<td>Leukemia</td>
<td>25,060</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>893,660</strong></td>
<td><strong>100%</strong></td>
<td><strong>All Sites</strong></td>
<td><strong>912,930</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>72,500</td>
<td>23%</td>
<td>Lung &amp; bronchus</td>
<td>63,220</td>
<td>22%</td>
</tr>
<tr>
<td>Prostate</td>
<td>33,330</td>
<td>10%</td>
<td>Breast</td>
<td>42,170</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>28,630</td>
<td>9%</td>
<td>Colon &amp; rectum</td>
<td>24,570</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>24,640</td>
<td>8%</td>
<td>Pancreas</td>
<td>22,410</td>
<td>8%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>20,020</td>
<td>6%</td>
<td>Ovary</td>
<td>13,940</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,420</td>
<td>4%</td>
<td>Uterine corpus</td>
<td>12,590</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>13,100</td>
<td>4%</td>
<td>Liver &amp; intrahepatic bile duct</td>
<td>10,140</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>13,050</td>
<td>4%</td>
<td>Leukemia</td>
<td>9,680</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,460</td>
<td>4%</td>
<td>Non-Hodgkin lymphoma</td>
<td>8,480</td>
<td>3%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>10,190</td>
<td>3%</td>
<td>Brain &amp; other nervous system</td>
<td>7,830</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>321,160</strong></td>
<td><strong>100%</strong></td>
<td><strong>All Sites</strong></td>
<td><strong>285,360</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

- 62,100 new cases/year
- 13,050 deaths/year
- Lower incidence and risk in women
- Slight decrease in incidence over time
Risks - Bladder cancer

• Tobacco
  ➢ ~ 50% of bladder cancer deaths are due to tobacco use
• Occupational exposures
  – Benzene, aniline dyes, polycyclic hydrocarbons
  – Painters, metal workers, firemen
• Diet
  Carcinogens in water (e.g. arsenic)
  Coffee
  Fluid intake → increased is possibly protective
  Fruits and vegetables → increased is possibly protective
• Chronic inflammation/cystitis
  – Schistosomiasis, indwelling urinary catheters, bladder stones
• Cyclophosphamide
• Prior urothelial carcinoma of the upper tract
• Lynch syndrome
Pathology

• Urothelial carcinoma
  – Majority of cases (~90%)
  – Some element of differentiation to other subtypes is present in 20-50% (Squamous, adenocarcinoma – not pure histology)
  – Micropapillary variant

• Depth of invasion is the most important element in pathologic staging of localized disease
  – Implications for treatment and prognosis

• Treatment paradigm based on invasion
  – Ta, CIS, T1 → non-muscle invasive (~70% of cases)
  – ≥T2 → Muscle invasive
  – Metastatic
Systemic therapy in localized bladder cancer

Neoadjuvant therapy

Advantages
- Early therapy of micrometastatic disease
- Performance status is clearly better prior to cystectomy – better tolerance
- Randomized trial data indicate an OS benefit

Disadvantages
- Delay of potentially curative therapy (cystectomy)

Adjuvant therapy

Advantages
- Better staging and risk assessment

Disadvantages
- Evidence for benefit of adjuvant therapy is not robust
Perioperative Chemotherapy

- SWOG-8710: Neoadjuvant MVAC + Surgery vs. Surgery
- N = 317
- Patients with T2-T4, N0
- 3 cycles of neoadjuvant MVAC (methotrexate, vinblastine, adriamycin, cisplatin)

Median OS 46 vs. 77 months (HR 0.78; 95% CI 0.58-1.04, p=0.06)
SWOG 8710: Complete Responses Matter

- Improved pCR rate with MVAC: 38% vs. 15%
- No clear benefit unless pCR is achieved
- No accurate way to identify patients with ‘platinum-sensitive’ tumors prior to therapy
  - ERCC2, FANCC, ATM, RB1?

Allen E, et al. Ca Discovery 2014
Support for neoadjuvant chemotherapy

**Advanced Bladder Cancer (ABC) meta-analysis**

- Muscle invasive bladder cancer (T2-4N0)
- Analyzed 3055 patients from 11 randomized trials
- Intervention included cystectomy or radiotherapy
- Platinum **combination chemotherapy** had significant survival benefit (HR= 0.86 (95% CI 0.77 to 0.95, P = 0.003))
  - 5% absolute benefit at 5 years (95% CI 1% to 7%)
  - Overall survival increased from 45% to 50%.
  - All clinical subgroups benefited (cT2-T4)
  - Single agent platinum alone is not recommended (no statistically significant benefit)
- Most common regimens: ddMVAC or gemcitabine + cisplatin

Update 2008 – Cochrane Library*
Problems with Adjuvant Chemotherapy Studies

- Split results in the existing studies
- Small under-powered studies
- Serious methodological flaws
- Early stopping of patient entry
- Confusing statistical analyses
- Reporting of questionable results

Support for Adjuvant Chemotherapy

**Advanced Bladder Cancer (ABC) meta-analysis**

- Analyzed 945 patients from 9 randomized trials

- Most with T3-4 or N1

- Platinum combination chemotherapy had statistically significant survival benefit (HR= 0.77, 95% CI 0.59-0.99, p = 0.049)
  - Effect most pronounced in studies where patients had node positive disease

- “However, the impact of trials that stopped early, of patients not receiving allocated treatments or not receiving salvage chemotherapy is less clear.”

Bladder sparing - chemoradiotherapy

- Best performed by teams experienced with this approach
  - Complete TURBT is critical
- Ideal candidate: small tumor size (<5 cm), T2 disease, no hydronephrosis, unifocal disease (i.e. no diffuse CIS)
- Neoadjuvant chemotherapy is not recommended (based on small randomized studies)
  - Benefit of adjuvant chemo unclear
- Concurrent radiation with platinum chemotherapy or mitomycin/5-FU
- Re-evaluation with cystoscopy and biopsy:
  - If residual tumor consider cystectomy
- Poor prognosis if patients have hydronephrosis or lack CR after induction
- Outcomes
  - Outcomes similar compared to cystectomy in select patients
  - 50-60% long-term survival (comparable to cystectomy).
  - Bladder function retained in 75-80% of patients

Shipley, J Clin Oncol. 1998;16:3576
Efstathiou, J Clin Oncol. 2009;27:4055
Conclusion for localized disease

- Meta-analysis supports the use of neoadjuvant chemotherapy prior to cystectomy. NCCN recommends neoadjuvant therapy for appropriate patients.
- Meta-analysis suggests benefit for adjuvant chemotherapy after cystectomy but is limited by the number of randomized studies. NCCN recommends adjuvant therapy (category 2B) if ≥T3 or N+.
- Bladder sparing chemoradiotherapy is an alternative approach, with evidence suggesting similar outcomes to cystectomy in highly selected patients treated by experienced teams.
Metastatic Disease

- Sites of metastasis
  - Lungs
  - Pelvic and abdominal lymph nodes
  - Liver
  - Bone
  - CNS

- Median overall survival likely 24+ months since the approval of immune checkpoint inhibitors

- Metastatic disease has variable prognosis
  - Poor performance status, bone and liver metastasis decrease median survival significantly
Chemotherapy for metastatic disease

- No good randomized studies performed to compare multi-agent chemotherapy to supportive care
- Cisplatin is the most active drug
  - Carboplatin is inferior
  - Meta-analysis of RCTs comparing carboplatin vs. cisplatin regimens
  - Advanced disease, only 4 studies (N=286 patients)

<table>
<thead>
<tr>
<th>Response*</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response</td>
<td>1.34</td>
<td>1.04 – 1.71</td>
<td>0.02</td>
</tr>
<tr>
<td>Complete Response</td>
<td>3.54</td>
<td>1.48 – 8.49</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Cisplatin compared to carboplatin

- Patients unable to tolerate cisplatin (GFR < 50-60, PS 2)
  - Options: split dose gemcitabine + cisplatin, gemcitabine + carboplatin, anti-PD1/PDL1 drugs (PDL1+ only)

Loehrer J Clin Oncol. 1992 ;10:1066
Bajorin J Clin Oncol 17: 3173.
The MVAC Story

- Methotrexate, vinblastine, doxorubicin, cisplatin
- Survival advantage (12.5 months) over single agent cisplatin (8.2 months)
  - Response rate 39% vs. 12%
  - Toxic death rate 3%
- MVAC superior to CISCA (cisplatin, cytoxan, doxorubicin)
- CMV (cisplatin, methotrexate, vinblastine) less toxic than MVAC, but no randomized study

MVAC vs. dose dense/accelerated MVAC - metastatic

- Dose dense MVAC
  - Same dose as day 1&2 of MVAC, but given every 2 weeks
  - GCSF support
- Overall response rate 62 vs. 50% (p=0.06)
- CR 21% vs. 9% (p=0.009)
- PFS 9.1 vs. 8.2 months (p=0.037)
- Overall survival equivalent
- Standard MVAC more toxic

ddMVAC is recommended over MVAC by NCCN.
MVAC vs. Gemcitabine/cisplatin – metastatic

- \( N = 405 \)
- Median OS 14 vs. 15.2 months
- Less grade 3-5 hematologic toxicity in patients receiving GC

- No bone or visceral metastases: Med OS 18.4 vs. 10.3 months
  5-year survival 20.9% vs. 6.8%.
- Karnofsky 80-100: Med OS 16 vs. 8.3 months.
Bladder cancer – Second line and beyond

Immune checkpoint inhibitors (CPI)
- Multiple agents approved now: pembrolizumab, atezolizumab, nivolumab, durvalumab, avelumab

Antibody drug conjugates: Enfortumab vedotin

FGFR inhibitors
- Erdafitinib approved; other approvals likely in the future

Multiple chemotherapeutics have activity
- Docetaxel, paclitaxel, pemetrexed, others
### Response Rates to Chemo Post-Platinum are Low

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>Patients</th>
<th>RR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witte²¹</td>
<td>Ifosfamide</td>
<td>56</td>
<td>20</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>McCaffrey²²</td>
<td>Docetaxel</td>
<td>30</td>
<td>13</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Lorusso³³</td>
<td>Gemcitabine</td>
<td>31</td>
<td>23</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vaughn⁴⁴</td>
<td>Paclitaxel</td>
<td>31</td>
<td>10</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Sweeney⁵⁵</td>
<td>Pemetrexed</td>
<td>47</td>
<td>28</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Galsky⁶⁶</td>
<td>Pemetrexed</td>
<td>13</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bambury⁷⁷</td>
<td>Pemetrexed</td>
<td>129</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Dreicer⁸⁸</td>
<td>Ixabepilone</td>
<td>45</td>
<td>12</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Bellmunt⁹⁹</td>
<td>Vinflunine</td>
<td>253</td>
<td>9</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Dreicer¹⁰¹⁰</td>
<td>Sorafenib</td>
<td>22</td>
<td>0</td>
<td>2</td>
<td>7</td>
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<tr>
<td>Wulfing¹¹¹¹</td>
<td>Lapatinib</td>
<td>59</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Gallagher¹²¹²</td>
<td>Sunitinib</td>
<td>77</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Ko¹³¹³</td>
<td>Nab-paclitaxel</td>
<td>48</td>
<td>28</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>


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Slide courtesy of Noah Hahn from ASCO 2015 Discussion
### Checkpoint Inhibitors Approved for Platinum-Treated Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>N</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>PFS (mos)</th>
<th>OS (mos)</th>
<th>1yr Sur (%)</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>PDL1</td>
<td>310</td>
<td>15</td>
<td>6</td>
<td>2.1</td>
<td>7.9</td>
<td>36</td>
<td>2016</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD1</td>
<td>27</td>
<td>26</td>
<td>11</td>
<td>2</td>
<td>13</td>
<td>50</td>
<td>2017</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD1</td>
<td>265</td>
<td>20</td>
<td>2</td>
<td>2</td>
<td>8.7</td>
<td></td>
<td>2017</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PDL1</td>
<td>191</td>
<td>18</td>
<td>4</td>
<td></td>
<td>18.2</td>
<td></td>
<td>2017</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PDL1</td>
<td>161</td>
<td>17</td>
<td>6</td>
<td>3</td>
<td>13.7</td>
<td>51</td>
<td>2017</td>
</tr>
</tbody>
</table>

Summary: All CPI inhibitors active in Post platinum disease; ORR-15-26%; Small fraction with CR; Pembrolizumab demonstrating superior OS to chemotherapy.
Key Eligibility Criteria
• mUC with progression during or following platinum-based chemotherapy
  – ≤ 2 prior lines of therapy
• Measurable disease per RECIST v1.1
• ECOG PS 0-1
• Evaluable sample for PD-L1 testing
• TCC histology as primary component (N = 931)

Stratification Factors
• No. of risk factors (0 vs. 1/2/3)
• Liver metastases (yes vs. no)
• PD-L1 status (0/1 vs. 2/3)
• Chemotherapy (vinflunine vs. taxanes)

Primary endpoint
– OS, tested hierarchically in pre-specified populations

Additional endpoints
– Efficacy: RECIST v1.1 ORR, PFS and DOR
– Safety
– PROs: EORTC QLQ-C30

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. *ClinicalTrials.gov, NCT02302807. † Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. & Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.
Overall Survival: IC2/3 Population

<table>
<thead>
<tr>
<th></th>
<th>Events/ Patients</th>
<th>Median OS (95% CI)</th>
<th>12-mo OS Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>72/116</td>
<td>11.1 mo (8.6, 15.5)</td>
<td>46% (37, 56)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>88/118</td>
<td>10.6 mo (8.4, 12.2)</td>
<td>41% (32, 50)</td>
</tr>
</tbody>
</table>

HR = 0.87 (95% CI: 0.63, 1.21)  
*P* = 0.41

Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

HR = 0.85 (95% CI: 0.73, 0.99)
P = 0.038

KEYNOTE-045: Phase 3 Post-Platinum Trial Design

Key Eligibility Criteria
- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1–2 lines of platinum-based chemotherapy or recurrence <12 months after perioperative platinum-based therapy
- ECOG performance status 0–2
- Provision of tumor sample for biomarker assessment

Stratification Factors
- ECOG performance status (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 months)

N = 270
- Pembrolizumab 200 mg IV Q3W

N = 542
- R (1:1)

N = 272
- Paclitaxel 175 mg/m² Q3W
- Docetaxel 75 mg/m² Q3W
- Vinflunine 320 mg/m² Q3W

- Dual primary end points: OS and PFS³
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review
- Both unselected and biomarker-selected patients

³In total ITT population and in patients with combined positive score ≥10%.

KEYNOTE-045: Pembrolizumab vs Chemo

- Median OS (pembro vs. chemo): 10.3 mos vs. 7.4 mos (P=0.002)
- Median PFS: 2.1 mos vs. 3.3 mos (P=NS)
  - 18 mos PFS: 16.8% vs. 3.5%
- Response rate: 21.1% vs. 11% (P=0.001)
Overall Survival: CPS ≥10%

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>0.57 (0.37-0.88)</td>
<td>0.0048</td>
</tr>
<tr>
<td>Chemo</td>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OS, %

Time, months

No. at risk

74  60  51  42  35  31  18  12  7  3  0  0  0
90  76  51  36  28  24  16  8  4  1  0  0  0

Median (95% CI)

8.0 mo (5.0-12.3)
5.2 mo (4.0-7.4)

Data cutoff date: Sep 7, 2016.
Confirmed Objective Response Rate

**Total Population**

- **Pembrolizumab** (N = 270): ORR = 21.1%
  - CR: 7.0%
  - PR: 14.1%
- **Chemotherapy** (N = 272): ORR = 11.4%
  - CR: 3.3%
  - PR: 8.1%

**CPS ≥10% Population**

- **Pembrolizumab** (N = 74): ORR = 21.6%
  - CR: 6.8%
  - PR: 14.9%
- **Chemotherapy** (N = 90): ORR = 6.7%
  - CR: 2.2%
  - PR: 4.4%

Δ9.6%  
P = 0.0011

No alpha allocated to the comparison of ORR in the CPS ≥10% population.  
Assessed per RECIST v1.1 by blinded, independent central review.  
Data cutoff date: Sep 7, 2016.
### Checkpoint Inhibitors with Regulatory Approval in Cisplatin Ineligible Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumb ImVigor 210</td>
<td>119</td>
<td>24</td>
<td>7</td>
<td>2.7</td>
<td>14.8</td>
</tr>
<tr>
<td>Pembrolizumab Key Note 052</td>
<td>370</td>
<td>29</td>
<td>7</td>
<td></td>
<td>6 mos OS: 67%</td>
</tr>
</tbody>
</table>

- **Carboplatin/Gemcitabine:**
  - ORR 36%; PFS-5.8 mos; OS-9.3 mos

• In two ongoing trials, low PD-L1 expressing patients receiving pembrolizumab (KEYNOTE-361) or atezolizumab (IMVIGOR-130) monotherapy were found to have inferior survival to cisplatin or carboplatin
• Label now restricted to mandate PD-L1 testing for patients planning to receive monotherapy with either agent in the first-line who are cisplatin-ineligible
• If ineligible for any platinum chemo, PD-L1 testing is not mandated
• Label does not change for previously platinum-treated patients
JAVELIN Bladder 100 study design (NCT02603432)

All endpoints measured post randomization (after chemotherapy)

- CR, PR, or SD with standard 1st-line chemotherapy (4-6 cycles)
  - Cisplatin + gemcitabine or
  - Carboplatin + gemcitabine
- Unresectable locally advanced or metastatic UC

Avelumab
10 mg/kg IV Q2W + BSC*
N=350

Until PD, unacceptable toxicity, or withdrawal

BSC alone*
N=350

Primary endpoint
- OS

Primary analysis populations
- All randomized patients
- PD-L1+ population

Secondary endpoints
- PFS and objective response per RECIST 1.1
- Safety and tolerability
- PROs

Stratification
- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; CR, complete response; IV, intravenous; PR, partial response; PRO, patient reported outcome; Q2W, every 2 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Presented at: 2020 ASCO Annual Meeting
Presented by: Thomas Powles, MD

Every day, we turn cancer patients into cancer survivors.
OS in the overall population

Median OS (95% CI), months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab + BSC</td>
<td>21.4</td>
<td>(18.9, 26.1)</td>
</tr>
<tr>
<td>BSC alone</td>
<td>14.3</td>
<td>(12.9, 17.9)</td>
</tr>
</tbody>
</table>

Stratified HR 0.69 (95% CI, 0.56, 0.86) P<0.001

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)
OS in the PD-L1+ population

Presented By Thomas Powles at TBD

<table>
<thead>
<tr>
<th>Median OS (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab + BSC</td>
</tr>
<tr>
<td>NE (20.3, NE)</td>
</tr>
<tr>
<td>BSC alone</td>
</tr>
<tr>
<td>17.1 (13.5, 23.7)</td>
</tr>
</tbody>
</table>

Stratified HR 0.56 (95% CI, 0.40, 0.79)
P<0.001

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). NE, not estimable
## Confirmed objective response

Response to maintenance therapy post randomization

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th></th>
<th>PD-L1+ population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avelumab + BSC</td>
<td>BSC alone</td>
<td>Avelumab + BSC</td>
<td>BSC alone</td>
</tr>
<tr>
<td></td>
<td>(N=350)</td>
<td>(N=350)</td>
<td>(N=189)</td>
<td>(N=169)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>9.7 (6.8, 13.3)</td>
<td>1.4 (0.5, 3.3)</td>
<td>13.8 (9.2, 19.5)</td>
<td>1.2 (0.1, 4.2)</td>
</tr>
<tr>
<td>Stratified odds ratio (95% CI)</td>
<td>7.464 (2.824, 24.445)</td>
<td></td>
<td>12.699 (3.160, 114.115)</td>
<td></td>
</tr>
</tbody>
</table>

### Best overall response, %

<table>
<thead>
<tr>
<th>Response</th>
<th>Overall population</th>
<th></th>
<th>PD-L1+ population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>6.0</td>
<td>0.9</td>
<td>9.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Partial response</td>
<td>3.7</td>
<td>0.6</td>
<td>4.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12.6</td>
<td>13.1</td>
<td>10.1</td>
<td>13.6</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>18.9</td>
<td>12.9</td>
<td>20.1</td>
<td>13.0</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>37.1</td>
<td>48.3</td>
<td>31.2</td>
<td>48.5</td>
</tr>
<tr>
<td>Not evaluable*</td>
<td>21.7</td>
<td>24.3</td>
<td>24.9</td>
<td>23.7</td>
</tr>
</tbody>
</table>

### Disease control, %

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th></th>
<th>PD-L1+ population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41.1</td>
<td>27.4</td>
<td>43.9</td>
<td>27.8</td>
</tr>
</tbody>
</table>

---

**PD, progressive disease**

Objective response was assessed by independent radiology review; in patients with a CR after chemotherapy, best overall response was not evaluable if no evidence of disease at baseline was maintained after randomization, or PD if disease progression occurred after randomization.

*Reasons for not evaluable included no evidence of disease at baseline; no post-baseline assessments; SD <6 weeks after randomization; PD>12 weeks after randomization; new anticancer therapy started before first post-baseline assessment; or all post-baseline assessments have objective response of not evaluable.

*Patients with a best overall response of CR, PR, SD, or non-CR/non-PD.
Enfortumab Vedotin

- Enfortumab vedotin: antibody-drug conjugate targeting Nectin-4

- Nectin-4 is a transmembrane cell adhesion molecule that is highly expressed (>90%) on urothelial carcinomas

- Accelerated FDA approval in 12/2019 → post-platinum chemo and anti-PD1/PDL1
EV-101: Phase 1 Study of Enfortumab Vedotin Monotherapy (NCT02091999)

- The data presented here are updated results from all patients with mUC treated with 1.25 mg/kg\(^1\)

**Part A (closed to accrual)**
Dose-escalation/-expansion adaptive trial design utilizing a Continual Reassessment Method to determine RP2D
- Cohort 1: 0.5 mg/kg
- Cohort 2: 0.75 mg/kg
- Cohort 3: 1 mg/kg
- Cohort 4: 1.25 mg/kg
Nectin-4 expressing tumors, including mUC

**Part B (enrolling)**
Dose expansion: 3 cohorts
- Cohort 1: mUC with severe renal insufficiency (0.75 mg/kg escalating to 1.25 mg/kg)
- Cohort 2: NSCLC (1.25 mg/kg)
- Cohort 3: Ovarian cancer (1.25 mg/kg)
*Only Cohort 1 is actively recruiting*

**Part C (closed to accrual)**
Dose expansion: 1 cohort
- CPI-treated mUC patients (1.25 mg/kg)

Radiographic Responses

### Table 1: Best Confirmed Overall Response in Patients With mUC Treated With Enfortumab Vedotin 1.25 mg/kg

<table>
<thead>
<tr>
<th>Response</th>
<th>Overall mUC, No. (%)</th>
<th>Investigator Review</th>
<th>Central Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>112</td>
<td>89</td>
<td>74</td>
</tr>
<tr>
<td>Confirmed CR</td>
<td>5 (5)</td>
<td>3 (5)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>43 (38)</td>
<td>35 (39)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>SD</td>
<td>32 (29)</td>
<td>28 (32)</td>
<td>27 (37)</td>
</tr>
<tr>
<td><strong>Confirmed ORR, % (95% CI)</strong></td>
<td>43 (33.6 to 52.6)</td>
<td>43 (32.3 to 53.6)</td>
<td>45 (33.0 to 56.6)</td>
</tr>
<tr>
<td><strong>DCR, % (95% CI)</strong></td>
<td>71 (62.1 to 79.6)</td>
<td>74 (63.8 to 82.9)</td>
<td>81 (70.3 to 89.3)</td>
</tr>
<tr>
<td>Median DoR, months (95% CI)</td>
<td>7.4 (5.6 to 9.6)</td>
<td>7.3 (4.2 to 9.6)</td>
<td>7.5 (5.8 to NR)</td>
</tr>
</tbody>
</table>

**NOTE:** ORR = CR + PR + SD; DCR = CR + PR + SD.

**Abbreviations:** CR, complete response; DCR, disease control rate; DOR, duration of response; mUC, metastatic urothelial carcinoma; NR, not reached; ORR, objective response rate; PD-(L)1, programmed death-1 receptor/programmed death-ligand-1; PR, partial response; SD, stable disease.

*Parts A and C.

*Part C only.

*The 95% CI was based on the Clopper-Pearson method.
Progression Free Survival

No Disease
Progression or Death (%)

Events | No. of Patients | Median (95% CI)
--- | --- | ---
94 | 112 | 5.4 (5.06 to 6.28)

No. at risk:
1.25 mg 112 83 71 45 32 24 17 12 5 1 0 0 0

Rosenberg, et al. JCO 2019
Rosenberg, et al. 2018 ASCO Annual Meeting
Overall Survival

Number at risk:

- 1.25 mg
  - 112
  - 102
  - 94
  - 81
  - 69
  - 62
  - 53
  - 39
  - 21
  - 10
  - 5
  - 4
  - 2
  - 2
  - 1
  - 0

Number of events and patients at risk over time:

- Events: 72
- No. of Patients: 112
- Median (95% CI): 12.3 (9.33 to 15.31)
## ORR Forest Plot

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/ No. of Patients</th>
<th>% (95% CI)</th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>55/125</td>
<td>44 (35.1 to 53.2)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75</td>
<td>43/91</td>
<td>47 (36.7 to 58)</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>12/34</td>
<td>35 (19.7 to 53.5)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>24/40</td>
<td>60 (43.3 to 75.1)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>31/85</td>
<td>36 (26.3 to 47.6)</td>
<td></td>
</tr>
<tr>
<td>Bellmunt risk score†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>37/72</td>
<td>51 (39.3 to 63.3)</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>17/52</td>
<td>33 (20.3 to 47.1)</td>
<td></td>
</tr>
<tr>
<td>Primary tumor sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper tract</td>
<td>17/44</td>
<td>39 (24.4 to 54.5)</td>
<td></td>
</tr>
<tr>
<td>Bladder/other</td>
<td>38/81</td>
<td>47 (35.7 to 58.3)</td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19/50</td>
<td>38 (24.7 to 52.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>36/75</td>
<td>48 (36.3 to 59.8)</td>
<td></td>
</tr>
<tr>
<td>No. of prior therapies in metastatic UC setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>29/62</td>
<td>47 (34 to 59.9)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>26/63</td>
<td>41 (29 to 54.4)</td>
<td></td>
</tr>
<tr>
<td>Best response to prior anti-PD-1/L1‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder</td>
<td>14/25</td>
<td>56 (34.9 to 75.6)</td>
<td></td>
</tr>
<tr>
<td>Nonresponder</td>
<td>41/100</td>
<td>41 (31.3 to 51.3)</td>
<td></td>
</tr>
<tr>
<td>PD-L1 expression§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPS &lt; 10</td>
<td>37/78</td>
<td>47 (36 to 59.1)</td>
<td></td>
</tr>
<tr>
<td>CPS ≥ 10</td>
<td>15/42</td>
<td>36 (21.6 to 52)</td>
<td></td>
</tr>
</tbody>
</table>
## Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>125 (100)</td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse events</td>
<td>117 (94)</td>
<td></td>
</tr>
<tr>
<td>Grade ≥ 3 treatment-related adverse events</td>
<td>68 (54)</td>
<td></td>
</tr>
<tr>
<td>Treatment-related serious adverse events</td>
<td>24 (19)</td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse events resulting in treatment discontinuation</td>
<td>15 (12)</td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse events leading to death*</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>62 (50)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>61 (49)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>55 (44)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>50 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>50 (40)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>49 (39)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40 (32)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>27 (22)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>28 (22)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>28 (22)</td>
<td>0</td>
</tr>
</tbody>
</table>
Phase 2 BLC2001 Study Design

Erdafitinib: FGFR 1/2/3 inhibitor

Patients
- Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR
- Chemo-naïve: cisplatin ineligible per protocol criteria
- Prior immunotherapy was allowed

Regimen 3a:
- 8 mg QD with PD Uptitrion to 9 mg QD
  - n = 99

Primary end point
- ORR

Secondary end points
- PFS, DoR, OS, safety, predictive biomarker evaluation, and PK

Primary hypothesis:
- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

Abbreviations: DoR, duration of response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, daily; TRAEs, treatment-related adverse events.
Most Patients Receiving 8 mg QD Erdafitinib Had Tumor Shrinkage

Siefker-Radtke, et al. 2018 ASCO Annual Meeting
Loriot, et al. NEJM 2019
Progression-Free Survival ~6 Months
Overall Survival > 1 Year

Median PFS = 5.5 months (95% CI, 4.2-6.0)
Progression/death events = 77

Median OS = 13.8 months (95% CI, 9.8-NE)
Survival events = 40

No. at risk 99, 63, 35, 16, 6, 1, 0
No. at risk 99, 87, 70, 42, 22, 4, 0

Abbreviation: NE, not estimable.

Siefker-Radtke, et al. 2018 ASCO Annual Meeting
Loriot, et al. NEJM 2019
### Most Common Treatment-Related AEs (TRAEs)

<table>
<thead>
<tr>
<th>Reported in &gt;20% of patients</th>
<th>8 mg continuous dose (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with TRAEs, n (%)</td>
<td>Any grade</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>72 (73)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>54 (55)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>43 (43)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 (37)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>35 (35)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>32 (32)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 (25)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (21)</td>
</tr>
</tbody>
</table>

Most were grade 1 or 2

There were no grade 4 or 5 TRAEs

Serious TRAEs were reported in 9 patients (9%); none was reported in more than 1 patient

---

Siefker-Radtke, et al. 2018 ASCO Annual Meeting
Loriot, et al. NEJM 2019
Bladder Cancer - Conclusions

- Chemotherapy plays no role in patients with less than T2 disease
  - Muscle needs to be in TURBT specimen to establish T2 disease
- Patients with extensive CIS, hydronephrosis or bulky disease are NOT chemo-radiotherapy candidates
- For neoadjuvant therapy, CISPLATIN based regimens are the only drugs with data to support them (ddMVAC, Gem/Cis)
- Gemcitabine/cisplatin is the standard first line option for metastatic urothelial CA
- Immune checkpoint inhibitors, enfortuamb and erdafitinib are standard ≥2nd line treatment metastatic urothelial CA
Thank You!

- Michael Schweizer
- 206-606-6252
- schweize@uw.edu