BLADDER CANCER
Systemic treatment

Carlos Vallejos, MD. Medical Oncologist. Founding Director – Oncosalud AUNA.
Bladder Cancer: Spectrum of Disease

<table>
<thead>
<tr>
<th>Histological type (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial carcinoma</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
</tr>
</tbody>
</table>

Localized: ~ 95%

NMIBC: 70%
CIS, Ta, T1

MIBC: 30%
T2-T4

Metastatic: ~ 5%

FIRST-LINE SYSTEMIC TREATMENT FOR METASTATIC UROTHELIAL CARCINOMA OF THE BLADDER
Evolution of Systemic Therapy for Urothelial Carcinoma

1974: Doxorubicin FDA approved

1978: Cisplatin FDA approved

1989: Standard MVAC

1997: Docetaxel

2000: GC

2001: Paclitaxel

2002: Paclitaxel

2003: Paclitaxel

2006: Vinflunine

2009: Vinflunine EMA approved

2009: Gemcitabine EMA approved

2009: Atezolizumab FDA approved

Publication Agency Action

Doxorubicin FDA approved

Cisplatin FDA approved

5th ESO-ESMO Latin American Masterclass in Clinical Oncology
Identifying Patients Who Are Cisplatin-Ineligible

Chemotherapy ineligible? : Poorly controlled type 2 diabetes, vascular or coronary disease, high risk of myelosuppression.
Cisplatin-Eligible

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>mOS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>49%</td>
<td>12%</td>
<td>14</td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ddMVAC</td>
<td>72%</td>
<td>25%</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Cisplatin-Ineligible

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>mOS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>36%</td>
<td>3%</td>
<td>9.3</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Durable Responses With Cisplatin-Based CT in UC

## Cisplatin Eligible

**Gemcitabine + Cisplatin**\(^{[1,2]}\)

- **ORR:** 49%
- **CR:** 12%
- **Median OS:** 14.0 mos

**Dose Dense MVAC**\(^{[3]}\)

- **ORR:** 72%
- **CR:** 25%
- **Median OS:** 15.1 mos

## Cisplatin Ineligible

**Gemcitabine + Carboplatin**\(^{[4]}\)

- **ORR:** 36%
- **CR:** 3%
- **Median OS:** 9.3 mos

---

Cisplatin but Not Carboplatin Can Yield Durable and Complete Responses in the Frontline


Patients at Risk, n
MCAVI (n = 119) 37 13 7 3 1 1
Gem/carbo (n = 119) 44 15 5 2 2 1

Patients at Risk, n
MVAC (n = 129) 32 15 11 4 2
DD MVAC (n = 134) 45 29 23 8 0

Log-rank test $P = .64$

$\text{mOS: 9.3 mos}$

$\text{mOS: 15.1 mos}$
Evolution of Systemic Therapy for Urothelial Carcinoma

1974 - Doxorubicin FDA approved
1978 - Cisplatin FDA approved
1989 - Standard MVAC
1997 - Docetaxel
2000 - Accelerated MVAC
2002 - Paclitaxel
2003 - GC
2006 - Pembrolizumab 1st-line cis ineligible
2009 - Vinflunine EMA approved
2009 - Gemcitabine FDA approved
2012 - Pembrolizumab 2nd line
2015 - Atezolizumab FDA approved
2017 - Pembrolizumab 1st line cis ineligible
2017 - Durvalumab 2nd line
2017 - Nivolumab 2nd line
2017 - Atezolizumab 1st line cis ineligible
2017 - Avelumab 2nd line
2017 - Atezolizumab 1st line cis ineligible
2018 - Atezolizumab FDA approved
2018 - Nivolumab 2nd line
2018 - Atezolizumab 1st line cis ineligible
2018 - Avelumab 2nd line
2018 - Durvalumab 2nd line
Frontline Checkpoint Inhibition in Cisplatin Ineligible UC: Updates from Single-Arm Trials

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up, mos</td>
<td>11.5</td>
<td>29</td>
</tr>
<tr>
<td>ORR, %</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>11.5</td>
<td>16.3</td>
</tr>
<tr>
<td>12 month OS, %</td>
<td>48</td>
<td>58</td>
</tr>
</tbody>
</table>

**Pembrolizumab OS**

Patients at Risk, n

<table>
<thead>
<tr>
<th>Months</th>
<th>370</th>
<th>283</th>
<th>223</th>
<th>173</th>
<th>147</th>
<th>86</th>
<th>38</th>
<th>11</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>370</td>
<td>283</td>
<td>223</td>
<td>173</td>
<td>147</td>
<td>86</td>
<td>38</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>283</td>
<td>223</td>
<td>173</td>
<td>147</td>
<td>86</td>
<td>38</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

**Atezolizumab OS**

Patients at Risk, n

<table>
<thead>
<tr>
<th>Months</th>
<th>28</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28</td>
<td>36</td>
</tr>
</tbody>
</table>

Keytruda (pembrolizumab) or Tecentriq (atezolizumab): FDA Alerts Health Care Professionals and Investigators: FDA Statement - Decreased Survival in Some Patients in Clinical Trials Associated with Monotherapy

EMA restricts use of Keytruda and Tecentriq in bladder cancer
Data show lower survival in some patients with low levels of cancer protein PD-L1
Decreased Survival in Patients With Low Levels of PD-L1 Using ICI Monotherapy
PD-L1 Status Required in the Frontline Setting for Cisplatin Ineligible UC.

**IHC PD-L1**

**PEMBROLIZUMAB:**
Clone: 22C3
Combined positive score $\geq 10$

the ratio of PD-L1–expressing tumor-infiltrating immune cells relative to the total number of tumor cells

**ATEZOLIZUMAB:**
Clone: SP142
staining on tumor-infiltrating immune cells covering at least $\geq 5\%$
What We Know About First-line Treatment In Metastatic Bladder Cancer?

• Cisplatin Is Highly Active In This Space.

• Cisplatin-eligible Patients Should Get Cisplatin.

• Cisplatin-ineligible Patients Should Get Gemcitabine – Carboplatin Unless They Are PD-L1 Positive.

• Patients Ineligible For Any Chemotherapy Can Be Considered For Checkpoint Inhibitor Therapy Regardless Of PD-L1 Status
SECOND-LINE (POST-PLATINUM) SYSTEMIC TREATMENT FOR METASTATIC UROTHELIAL CARCINOMA OF THE BLADDER
# FDA-Approved Checkpoint Inhibitors for UC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Schedule</th>
<th>FDA Approval Type by Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post-Platinum</td>
</tr>
<tr>
<td>Atezolizumab[1]</td>
<td>PD-L1</td>
<td>Q3W</td>
<td>Accelerated</td>
</tr>
<tr>
<td>Pembrolizumab[5]</td>
<td>PD-1</td>
<td>Q3W</td>
<td>Level 1</td>
</tr>
</tbody>
</table>

KEYNOTE-045: Study Design

- International, randomized, open-label phase III study

- Primary endpoints: OS, PFS
- Secondary endpoints: ORR, DoR, safety

KEYNOTE-045: OS

HR: 0.70 (0.57-0.86; P = .0003)
Data cutoff: May 19, 2017

Median OS, Mos (95% CI)
10.3 (8.0-12.3)
7.4 (6.3-8.3)

Patients at Risk, n
Pembrolizumab 270 194 147 116 98 67 23
Chemotherapy 272 171 109 73 58 35 13

de Wit R, et al. ESMO 2017. Abstract LBA37_PR.
KEYNOTE-045: PFS

Median PFS, Mos (95% CI)

2.1 (2.0-2.2)
3.3 (2.4-3.5)

HR: 0.96 (0.79-1.16; P = .32)
Data cutoff: May 19, 2017

Patients at Risk, n

Pembrolizumab  270  86  61  44  39  24  6
Chemotherapy    272  93  39  19  12  7  2

de Wit R, et al. ESMO 2017. Abstract LBA37_PR.
Phase II Studies of Immune Checkpoint Inhibitors Leading to Accelerated Approval

Nivolumab[1]
Median OS: 8.74 mos (95% CI: 6.05 to not reached)

Durable OS
Pts at Risk, n (number censored)
All treated pts 265 (0) 198 (3) 148 (4) 63 (71) 5 (125) 0 (130)

Median OS: 13.7 mos (95% CI: 8.5 to NE)

Avelumab[2]
Overall population (n = 44)

Durvalumab[3]

Post-Platinum Urothelial Carcinoma: ORR

Data from separate studies. Not head-to-head comparisons.

Post-Platinum Urothelial Carcinoma: OS at 12 Mos

Data from separate studies. Not head-to-head comparisons.

Evolving Treatment in Advance Urothelial Carcinoma

**FIRST LINE**
(MANDATORY PD-L1 TESTING)

- SETTING
  - Cisplatin-eligible
  - Cisplatin-ineligible (PD-L1 low)
  - Cisplatin-ineligible (PD-L1 high)
  - CT-ineligible

- REGIMEN
  - Cisplatin-based CT
  - Carboplatin-based CT

**SECOND LINE**
(NO PD-L1 TESTING)

- PD-1/PD-L1 blockade
## Post-Platinum Urothelial Carcinoma: Safety

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Median F/U, Mos</th>
<th>Patients, n</th>
<th>Treatment-Related AEs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any</td>
</tr>
<tr>
<td>Atezolizumab[1]</td>
<td>III</td>
<td>17.3</td>
<td>459</td>
<td>70</td>
</tr>
<tr>
<td>Avelumab[2]</td>
<td>Ib</td>
<td>16.5</td>
<td>44</td>
<td>66</td>
</tr>
<tr>
<td>Durvalumab[3]</td>
<td>I/II</td>
<td>5.78</td>
<td>191</td>
<td>61</td>
</tr>
<tr>
<td>Nivolumab[4]</td>
<td>II</td>
<td>7.0</td>
<td>270</td>
<td>64</td>
</tr>
</tbody>
</table>

*Reported as grade 3-5.

## Immune-Related Toxicities

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Reported Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integumentary</td>
<td>Hives, eczema, vitiligo, pemphigus, lichenoid reactions</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Enterocolitis, pancreatitis, gastritis, celiac disease</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis</td>
</tr>
<tr>
<td>Renal</td>
<td>Interstitial nephritis, nephrotic syndrome, autoimmune nephropathy</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pneumonitis, interstitial lung disease, pleuritis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Myocarditis, pericarditis, cardiomyopathy</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypo/hyperthyroidism, hypophysitis, adrenal insufficiency</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Encephalitis, Guillain-Barre syndrome, myasthenia gravis, mononeuritis, autoimmune</td>
</tr>
<tr>
<td></td>
<td>inner ear disease</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Hemolytic anemia, immune thrombocytopenic purpura, thrombotic thrombocytopenic</td>
</tr>
<tr>
<td></td>
<td>purpura, hemophilia, Evans syndrome</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>Polyarthritis, systemic lupus erythematosus, antiphospholipid syndrome</td>
</tr>
</tbody>
</table>
Select Any-Grade, Treatment-Related AEs Over Time

Patients at Risk, n
Still in study 453
Still receiving treatment 298
Total with new event 239
Still in study with new event, % 53

Wks Since Initiation of Nivolumab
≤ 16 281 138 26 10 9
≤ 32 172 76 11 3 0
≤ 48 34 4 5 0 0
≤ 64 12 3 19 0 0
≤ 80 10 3 0 0 0
≤ 96 9 0 0 0 0

Most Immune-Related AEs Are Reversible With Immunosuppression/Steroids


- Rash, pruritus
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

Toxicity Grade

Wks
PERIOPERATIVE SYSTEMIC THERAPY IN BLADDER CANCER
Bladder Cancer: Spectrum of Disease

The Past

Localized: ~ 95%

Metastatic: ~ 5%

NMIBC: 70%
CIS, Ta, T1

MIBC: 30%
T2-T4

Urology

Medical Oncology
Bladder Cancer: Spectrum of Disease

The Present

- **Localized:** ~ 95%
  - NMIBC: 70%
    - CIS, Ta, T1
  - MIBC: 30%
    - T2-T4

- **Metastatic:** ~ 5%

**Urology**

**Radiation Oncology**

**Medical Oncology**
EORTC 30994: Immediate vs Deferred Adjuvant CT

- Improved PFS with immediate vs deferred adjuvant CT

HR: 0.54 (95% CI: 0.40-0.73)
P < .0001

EORTC 30994: No Impact in Overall Survival

• No difference in OS between arms

Meta-analysis of Cisplatin-Based Adjuvant CT vs Surgery

NOTE: Weights are from random-effects analysis.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin-based combinations:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bono</td>
<td>0.65 (0.34-1.25)</td>
<td>9.83</td>
</tr>
<tr>
<td>Freiha</td>
<td>0.74 (0.36-1.53)</td>
<td>8.61</td>
</tr>
<tr>
<td>Otto</td>
<td>0.82 (0.48-1.39)</td>
<td>12.37</td>
</tr>
<tr>
<td>Skinner</td>
<td>0.75 (0.48-1.18)</td>
<td>14.22</td>
</tr>
<tr>
<td>Lehmann</td>
<td>0.57 (0.31-1.05)</td>
<td>10.57</td>
</tr>
<tr>
<td>Stadler</td>
<td>1.11 (0.45-2.73)</td>
<td>6.35</td>
</tr>
<tr>
<td><strong>Subtotal (I^2 = 0%; P = .880)</strong></td>
<td>0.74 (0.58-0.94)</td>
<td>61.95</td>
</tr>
<tr>
<td><strong>Single agent cisplatin:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Struder</td>
<td>1.02 (0.57-1.83)</td>
<td>11.09</td>
</tr>
<tr>
<td><strong>Subtotal (I^2 = .%; P = .)</strong></td>
<td>1.02 (0.57-1.83)</td>
<td>11.09</td>
</tr>
<tr>
<td><strong>Gemcitabine-cisplatin combinations:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian</td>
<td>1.29 (0.84-1.99)</td>
<td>14.83</td>
</tr>
<tr>
<td>Spanish</td>
<td>0.38 (0.22-0.65)</td>
<td>12.13</td>
</tr>
<tr>
<td><strong>Subtotal (I^2 = 91.8%; P = 0)</strong></td>
<td>0.71 (0.22-2.35)</td>
<td>29.96</td>
</tr>
<tr>
<td><strong>Overall (I^2 = 46.5%; P = .060)</strong></td>
<td><strong>0.77 (0.59-1.00)</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Favors Adjuvant Chemotherapy
Favors Surgery Alone

SWOG-8710: Neoadjuvant CT Is Standard of Care for Muscle-Invasive Bladder Cancer


Median OS Benefit: 2.6 yrs

<table>
<thead>
<tr>
<th>Survival Event</th>
<th>MVAC + Cystectomy (n = 153)</th>
<th>Cystectomy Alone (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>77</td>
<td>46</td>
</tr>
</tbody>
</table>

Patients at Risk, n
- MVAC + cystectomy: 153
- Cystectomy alone: 154
NCCN Guidelines: NAC ± RT is The SOC in Stage II-IIIA UC

Stage II and IIIA

- Neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy (category 1)
- Concurrent chemoradiotherapy (category 1)
- Non-cystectomy candidates: Concurrent chemoradiotherapy or RT
- Reassess tumor status 2-3 months after treatment
- Observation
- Tumor
  - No tumor
  - Observation
  - If Tis, Ta, or T1, consider intravesical BCG
  - Surgical consolidation or Treat as metastatic disease (BL-9)
- Chemotherapy
  - Tumor
    - No tumor
    - Observation
    - Palliative TURBT and Best supportive care

- Based on pathologic risk (pT3-4 or positive nodes), consider adjuvant RT or consider adjuvant cisplatin-based chemotherapy if no neoadjuvant treatment given

See Follow-up (BL-E)
# Cisplatin-Based Neoadjuvant CT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gem/Cis(^{[1]}) (n = 42)</th>
<th>Gem/Cis(^{[2]}) (n = 154)</th>
<th>DD Gem/Cis(^{[3]}) (n = 31)</th>
<th>DD Gem/Cis(^{[4]}) (n = 46)</th>
<th>AMVAC(^{[5]}) (n = 80)</th>
<th>AMVAC(^{[6]}) (n = 40)</th>
<th>DD MVAC(^{[7]}) (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>Cycles, n</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>3-4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Wks, n</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>6-8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>pCR (pT0), %</td>
<td>26</td>
<td>21</td>
<td>32</td>
<td>15</td>
<td>43</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>PR (&lt; pT2), %</td>
<td>36</td>
<td>46</td>
<td>45</td>
<td>57</td>
<td>~ 61</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>Median days from CT start to surgery</td>
<td>138</td>
<td>120</td>
<td>~ 88</td>
<td>~ 114+</td>
<td>75</td>
<td>68</td>
<td>~ 98</td>
</tr>
<tr>
<td>Grade 3/4 AEs, %</td>
<td>NR</td>
<td>NR</td>
<td>35</td>
<td>37</td>
<td>27</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Progression free at 2 yrs, %</td>
<td>64</td>
<td>~ 68</td>
<td>~ 68</td>
<td>~ 76</td>
<td>65</td>
<td>78</td>
<td>~ 47</td>
</tr>
<tr>
<td>Alive at 2 yrs,* %</td>
<td>73</td>
<td>~ 78</td>
<td>~ 77</td>
<td>~ 87</td>
<td>77</td>
<td>83</td>
<td>≤ 80</td>
</tr>
</tbody>
</table>

*vs 58% with cystectomy alone.

## Neoadjuvant Checkpoint Inhibition in Bladder Cancer: Early Results of Phase II Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pembrolizumab (n = 43)(^{(1)})</th>
<th>Atezolizumab (n = 68)(^{(2)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility criteria</td>
<td>T2-T3b; N1 allowed</td>
<td>T2-T4a; N0 only</td>
</tr>
<tr>
<td>Cisplatin eligible, %</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Received neoadjuvant CT, %</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Duration of neoadjuvant checkpoint inhibition</td>
<td>3 cycles (9 wks)</td>
<td>2 cycles (6 wks)</td>
</tr>
<tr>
<td>Safe</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pathological CR (pT0), %</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>Available biomarker data</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**pT0 Rates**

With CT:
- Gem/Cis, 15% to 32%
- DD MVAC, 26% to 43%

---

Encouraging results; long-term outcomes needed before clinical use

**RETAIN BLADDER: Risk-Adapted Treatment After Neoadjuvant CT for Bladder Cancer**

- **Single-arm, open-label phase II trial**

  Adult patients with primary urothelial or predominantly urothelial carcinoma of the bladder, cT2-4aN0M0 disease, ECOG PS 0-2 (N = 38)

*Any alteration in ATM, RB1, FANCC, ERCC2.
†Patient and physician choice.

- **Primary endpoint:** metastasis-free survival at Yr 2

CONCLUSIONS

• Urothelial Carcinoma is a Chemosensitive Disease.

• Cisplatin-Ineligible Patients Represents a Poor-Risk Prognostic Group: Inmune Checkpoint Inhibitors (hopefully) Can Change The Natural History of The Disease.

• Neoadjuvant Chemotherapy ± RT is the Standard of Care in Stage II and IIIA bladder cancer.

• ICI are Moving from Second-Line/Post-Platinum Systemic Treatment to Neoadjuvant Setting.

• Better Biomarkers for Response to ICI and Chemotherapy are needed.
THANKS FOR YOUR ATTENTION!