Urothelial cancer:
Bladder-preserving strategies followed by systemic relapse
Clinical Case Discussion

Shahrokh F. Shariat, MD
Professor and Chair of Urology
Medical University of Vienna, Vienna, AUT

Adjunct Professor of Urology at
✓ Weill Cornell Medical University, New York, USA
✓ University of Texas Southwestern, Dallas, USA
✓ Charles University, Prague, CZ
✓ Sechenov University, Moscow, RU
Disclosure

Personal financial interests
- Advisory board and speaker:
  Astellas; AstraZeneca; Bayer; Bristol-Myers Squibb; Cepheid; Ferring; Ipsen; Janssen; Lilly; MSD; Olympus; Pfizer; Roche; Richard Wolf; Sanochemia; Sanofi
- Advisory board: Urogen
- Patent:
  Method to determine prognosis after therapy for prostate cancer;
  Methods to determine prognosis after therapy for bladder cancer;
  Prognostic methods for patients with prostatic disease;
  Soluble Fas urinary marker for the detection of bladder transitional cell carcinoma

Non-financial interests
- Professor and Chairman, Department of Urology; Comprehensive Cancer Center; Medical University Vienna, Vienna, Austria
- Adjunct Professor; Weill Medical College of Cornell University, New York, NY, USA
- Adjunct Professor; UT Southwestern, Dallas, TX, USA
- Adjunct Professor; Charles University, Prague, CZ Republic
- Adjunct Professor; I.M. Sechenov First Moscow State Medical University, Moscow, Russia
- Bladder Cancer Research Consortium
- The Bladder Cancer Detection Group
- The Upper Tract Urothelial Carcinoma Collaboration
- Movember Foundation
Discussion points

✓ Treatment of non-metastatic muscle invasive Bca
✓ Neo-adjuvant chemotherapy
✓ 1\textsuperscript{st} line therapy for metastatic BCa
✓ 2\textsuperscript{nd} line therapy for metastatic BCa
✓ Novel therapies for metastatic BCa

BCa, bladder cancer
Discussion points

✓ Treatment of non-metastatic muscle invasive Bca
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✓ 2nd line therapy for metastatic BCa
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BCa, bladder cancer
Treatment of MIBC

- **Radical cystectomy & extended lymphadenectomy** *(standard)*
  - extended LAE has potentially shown to be beneficial (III, A)
  - may be curative in few node & micro-metastasis

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer RC in T2-T4a, N0M0, and high-risk non-MIBC.</td>
<td>Strong</td>
</tr>
<tr>
<td>Perform a lymph node dissection as an integral part of cystectomy.</td>
<td>Strong</td>
</tr>
</tbody>
</table>


LAE, lymphadenectomy; MIBC, muscle-invasive bladder cancer
Rational for bladder preservation

Radical cystectomy is morbid
→ 4\% perioperative mortality
→ 66\% morbidity
→ 25\% readmission / ~6\% go to an ICU!

pT0 rate with over 85\% alive @ 5 years
→ 15\% pT0 at RC
→ 38\% after NAC

Bochner et al. Eur Urol 2015
Shabsigh et al. Eur Urol 2009
Hu et al. Cancer 2014

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer


Snapshot of data: July 2016

- Randomized phase 3 trial
- Median follow-up of 117.1 months

Chemotherapy + radiotherapy
- 39% reduction loco-regional recurrence
- 45% reduction invasive recurrence
- 12% reduction all-cause mortality
- 46% reduction need for salvage RC
# TMT bladder preservation trials

<table>
<thead>
<tr>
<th>Trial, Phase</th>
<th>Stage</th>
<th>No</th>
<th>Radiation (Gy)</th>
<th>Concomitant chemotx</th>
<th>Adjuvant chemotx</th>
<th>Complete Response</th>
<th>Bladder intact survival</th>
<th>5-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC2001, III</td>
<td>T2–T4a</td>
<td>360</td>
<td>55 to 64</td>
<td>5FU and Mitomycin</td>
<td></td>
<td></td>
<td></td>
<td>48%</td>
</tr>
<tr>
<td>RTOG 02–33, Randomized II</td>
<td>T2–4a</td>
<td>93</td>
<td>40.3 + 24</td>
<td>Paclitaxel/Cis 5FU/Cisplatin</td>
<td>Gemcitabine/Cis/Pac x 4</td>
<td>72% Pac 62% 5FU</td>
<td>67% Pac 71% 5FU</td>
<td>71% Pac 75% 5FU</td>
</tr>
<tr>
<td>RTOG 99-06, I/II</td>
<td>T2–T4a</td>
<td>80</td>
<td>40.3 + 24</td>
<td>Cis + Paclitaxel</td>
<td>GC x 4</td>
<td>81%</td>
<td>47%</td>
<td>56%</td>
</tr>
<tr>
<td>RTOG 97-06, I/II</td>
<td>T2–T4a</td>
<td>46</td>
<td>40.8 + 24</td>
<td>Cis + Paclitaxel</td>
<td>GC x 4</td>
<td>81%</td>
<td>47% (3 yr)</td>
<td>61% (3 yr)</td>
</tr>
<tr>
<td>RTOG 95-06, I/II</td>
<td>T2–T4a</td>
<td>34</td>
<td>24 + 40</td>
<td>Cis + 5-FU</td>
<td>MCV x 3</td>
<td>67%</td>
<td>66% (3 yr)</td>
<td>83% (3 yr)</td>
</tr>
<tr>
<td>RTOG 89-03, III</td>
<td>T2–T4a</td>
<td>123</td>
<td>39.6 + 25.2</td>
<td>Cis</td>
<td>MCV x 3</td>
<td>74%</td>
<td>66%</td>
<td>83%</td>
</tr>
<tr>
<td>RTOG 85-12, II</td>
<td>T2–T4</td>
<td>42</td>
<td>40 + 24</td>
<td>Cis</td>
<td>MCV x 3</td>
<td>66%</td>
<td>66%</td>
<td>83%</td>
</tr>
<tr>
<td>Range</td>
<td>T2-T4</td>
<td>34-360</td>
<td>~60-65</td>
<td>-</td>
<td>-</td>
<td>62-81%</td>
<td>44-71%</td>
<td>52-83%</td>
</tr>
</tbody>
</table>


TMT, trimodal therapy
External beam radiotherapy may be considered as curative option as part of a **multimodality bladder-preservation approach** (III)
- in patients unfit for surgery also or palliation (bleeding, pain)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not offer radiotherapy alone as primary therapy for localised bladder cancer.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer MMT as an alternative to selected, well-informed and compliant patients, especially for whom cystectomy is not an option.</td>
<td>Strong</td>
</tr>
</tbody>
</table>
Comparative Effectiveness

Death from Any Cause

![Graph showing survival rates for RC (n=1426) vs BPT (n=417).]

Death from Bladder Cancer

![Graph showing survival rates for RC (n=1426) vs TMT (n=11586).]

HR = 1.37, 95% CI = 1.2-1.6; P < 0.001

Adverse treatment effect of TMT vs. RC decreased with age (P = 0.004).

The optimal candidate for TMT!

<table>
<thead>
<tr>
<th>Preferred or Ideal</th>
<th>Less than Ideal</th>
<th>Relative Contraindications</th>
<th>Absolute Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T2</td>
<td>• T3a</td>
<td>• T3b–T4a</td>
<td>• T4b</td>
</tr>
<tr>
<td>• No hydronephrosis</td>
<td>• Incomplete TURBT</td>
<td>• Diffuse CIS</td>
<td>• Tumor-Related Hydronephrosis</td>
</tr>
<tr>
<td>• No CIS</td>
<td>• Multifocal tumor</td>
<td>• Lymph node positive disease</td>
<td>• Prior pelvic radiation therapy</td>
</tr>
<tr>
<td>• Visibly complete TURBT</td>
<td>• Poor bladder function or capacity</td>
<td></td>
<td>• Not a candidate for chemotherapy</td>
</tr>
<tr>
<td>• Unifocal tumor</td>
<td></td>
<td></td>
<td>• Prostatic stromal invasion</td>
</tr>
<tr>
<td>• Good bladder function and capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TMT, trimodal therapy; TURBT, transurethral resection of bladder tumour; CIS, carcinoma in-situ

Discussion points

✓ Treatment of non-metastatic muscle invasive Bca
✓ Neo-adjuvant chemotherapy
✓ 1\textsuperscript{st} line therapy for metastatic BCa
✓ 2\textsuperscript{nd} line therapy for metastatic BCa
✓ Novel therapies for metastatic BCa
Neoadjuvant CTx

➢ Platinum-based NAC before RC or definitive RT (I, A)

Rationale

• Deaths generally not local events → as a result of metastatic disease
• Local interventions will not deal with micrometastases
• Best when pelvic blood supply is intact
• In vivo chemo-sensitivity trial
• Chemotherapy can cure some patients with metastatic BCa
<table>
<thead>
<tr>
<th>Series</th>
<th>ChemoRx</th>
<th>No Pts</th>
<th>Primary Rx</th>
<th>Survival Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shearer</td>
<td>MTX</td>
<td>376</td>
<td>RT/RC</td>
<td>No</td>
</tr>
<tr>
<td>Wallace</td>
<td>Cisplatin</td>
<td>225</td>
<td>RT</td>
<td>No</td>
</tr>
<tr>
<td>Martinez-Pin</td>
<td>Cisplatin</td>
<td>121</td>
<td>RC</td>
<td>No</td>
</tr>
<tr>
<td>Nordic-2</td>
<td>MTX-cisplatin</td>
<td>317</td>
<td>RC</td>
<td>No</td>
</tr>
<tr>
<td>Vitale</td>
<td>Cis/FU/RT</td>
<td>104</td>
<td>RC</td>
<td>No</td>
</tr>
<tr>
<td>Shipley</td>
<td>CMV</td>
<td>121</td>
<td>Cisplatin-RT</td>
<td>No</td>
</tr>
<tr>
<td>Pellegrini</td>
<td>MVEC</td>
<td>171</td>
<td>RC</td>
<td>No</td>
</tr>
<tr>
<td>Malmstrom</td>
<td>Doxorubicin/Cis</td>
<td>325</td>
<td>RT/RC</td>
<td>T3,T4</td>
</tr>
<tr>
<td>Hall</td>
<td>CMV</td>
<td>975</td>
<td>RT/RC/both</td>
<td>Yes</td>
</tr>
<tr>
<td>Grossman</td>
<td>MVAC</td>
<td>317</td>
<td>RC</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Improved median OS by ~3 years; 5% @ 5 yrs
Decreased risk of cancer-specific death by 25%

No. at Risk
M-VAC and cystectomy 153 112 92 75 46 23 6
Cystectomy alone 154 88 67 50 37 18 7

p = 0.05 unstratified
p = 0.06 stratified for age and stage

Grossman et al. NEJM 2003
CMV for MIBC - BA06 30894 Trial

- Long-term results, median F-U is 8.0 years
- N = 976
- Randomized to 3 cycles of CMV
- Cystectomy and/or RT

→ pT0: 33% for CMV vs 12% in surgery alone
→ 6% absolute survival improvement @ 10 years
→ 16% reduction in the risk of death

HR 0.84
P = 0.037

HR 0.87
P = 0.067
Discussion points

- Treatment of non-metastatic muscle invasive Bca
- Neo-adjuvant chemotherapy
- 1\textsuperscript{st} line therapy for metastatic BCa
- 2\textsuperscript{nd} line therapy for metastatic BCa
- Novel therapies for metastatic BCa
Clinical considerations are currently the drivers of our treatment decisions in metastatic urothelial cancer

**Patient/clinical characteristics**
- Age
- Treatment history
- **Performance status**
- Comorbidities
  - Renal function
  - Cardiac dysfunction/failure
  - Peripheral vascular disease
- General health status (e.g. haemoglobin)

**Tumour/disease characteristics**
- Disease or treatment-related comorbidities
  - Renal function
  - Peripheral neuropathies
- Symptomatic disease or disease burden
- Presence of **visceral metastases**

**Treatment/logistical factors**
- Eligibility for a clinical trial
- Tolerability of proposed therapy and symptom management
- Site of administration and proposed schedule
- Need for supportive agents to minimise dose delays and dose reductions
- Patient preference

NCCN, National Cancer Care Network.

Options in the management of metastatic UC before 2016?

Management of metastatic disease

- **PS ≤ 2 + poor renal function**
  - Clinical trial
  - BSC

- **Cisplatin-based combination chemotherapy** (e.g. MVAC, GC, HDMVAC, PCG)

  - **Patients with poor comorbid status or impaired renal function “unfit”**
    - Carboplatin-based regimens or single agents: taxane, gemcitabine

  - **Progression < 12 months**
    - Second-line chemotherapy
      1. Vinflunine
      2. Taxane-based chemotherapy
      3. Clinical trial

  - **Progression > 12 months**
    - Second-line chemotherapy
      1. Platinum-based re-challenge

BSC, best supportive care; GC, gemcitabine–cisplatin; PCG, paclitaxel–cisplatin–gemcitabine; PS, performance status.

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BSC, best supportive care; GC, gemcitabine–cisplatin; PCG, paclitaxel–cisplatin–gemcitabine; PS, performance status.

1st line platinum-based CTx

• Cisplatin-based chemotherapy
  • ORR 50-60%
  • 1yr OS 60%
  von der Maase et al. J Clin Oncol 2005

• Carboplatin-based chemotherapy
  • ORR 36%
  • 1yr OS 37%
  de Santis et al. J Clin Oncol 2011
Evolution of systemic therapy for urothelial cancer

Cisplatin-based chemotherapy

- Standard MVAC\(^1\) 1989
- HDMVAC\(^4\) 2000
- DOC taxel\(^2\)
- Gemcitabine + cisplatin\(^3\)
- Paclitaxel\(^5\)
- Vinflunine\(^6\)


Atezolizumab FDA approval prior platinum 02 February 2017
Atezolizumab FDA approval first-line cisplatin-eligible 17 April 2017
Atezolizumab FDA approval first-line cisplatin-eligible AND prior platinum 18 May 2017
Nivolumab FDA approval prior platinum 02 June 2017
Nivolumab EU prior platinum 02 June 2017
Pembrolizumab FDA approval first-line cisplatin-eligible AND prior platinum 05 September 2017
Pembrolizumab FDA approval first-line cisplatin-eligible AND prior platinum 05 September 2017
Durvalumab FDA accelerated approval prior platinum, May 2017
Durvalumab FDA accelerated approval prior platinum, May 2017
Avelumab FDA accelerated approval prior platinum, May 2017
Avelumab FDA accelerated approval prior platinum, May 2017

Immune-checkpoint inhibitors in the front-line in the cisplatin-ineligible setting

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab(^1)</th>
<th>Pembrolizumab(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Phase II (IMvigor210 Cohort 1)</td>
<td>Phase II (KEYNOTE-052)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>119</td>
<td>370</td>
</tr>
<tr>
<td>Dosing</td>
<td>1,200 mg every 3 weeks</td>
<td>200 mg every 3 weeks</td>
</tr>
<tr>
<td>ORR</td>
<td>23% (9% CR)</td>
<td>24% (5% CR)</td>
</tr>
<tr>
<td>Duration of response</td>
<td>70% ongoing at 17.2 months</td>
<td>78% ongoing at ≥ 6 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>15.9 months</td>
<td>11.5 months</td>
</tr>
<tr>
<td>Median PFS</td>
<td>2.7 months</td>
<td>2 months</td>
</tr>
<tr>
<td>Gr 3/4 treatment-related AEs</td>
<td>16%</td>
<td>16%</td>
</tr>
</tbody>
</table>

AE, adverse event; CR, complete response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

\(^1\)Balar et al. Lancet 2017
\(^2\)Balar et al. Lancet Oncol. 2017
\(^3\)Balar et al. Lancet Oncol. 2017
PD-L1 expression

• Preliminary data from KEYNOTE-361 and IMvigor130 show reduced survival with pembrolizumab and atezolizumab compared with chemotherapy in patients with locally advanced or metastatic urothelial cancer who have not received prior therapy and whose tumours have low expressions of PD-L1.

→ 1 June 2018: the CHMP issued an update to the pembrolizumab and atezolizumab labels for first-line treatment of urothelial cancer in cisplatin-ineligible patients

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score ≥ 10

Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are considered cisplatin-ineligible and whose tumours have a PD-L1 expression ≥ 5%

CHMP, Committee for Medicinal Products for Human Use.
Immune-checkpoint inhibitors in the front-line in the cisplatin-ineligible setting

Pembrolizumab or atezolizumab is a reasonable therapeutic choice for front-line patients with PD-L1-positive advanced UC who are not eligible for cisplatin-based chemotherapy [III, B]
What are the current options in the management of mUC in clinical practice? Updated ESMO Guidelines

HDMVAC, high dose MVAC; PCG, paclitaxel cisplatin gemcitabine.
What are the current options in the management of mUC in clinical practice? Updated ESMO Guidelines

- **Management of metastatic disease**
  - **PS ≤ 2 + poor renal function**
    - Clinical trial
    - BSC
  - **Cisplatin-eligible**
    - First-line:
      - Gemcitabine and cisplatin
      - MVAC
      - HDMVAC
      - PCG

- **Cisplatin-ineligible**
  - First-line:
    - Cisplatin ineligible
    - First-line: Gemcitabine and carboplatin
  - PD-L1 negative
  - PD-L1 positive
    - First-line:
      - Atezolizumab
      - Pembrolizumab

HDMVAC, high dose MVAC; PCG, paclitaxel cisplatin gemcitabine.

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✓ Novel therapies for metastatic BCa
## 2nd line post-platinum single agent studies

<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>Witte$^1$</td>
<td>Ifosfamide</td>
<td>56</td>
<td>20</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>McCaffrey$^2$</td>
<td>Docetaxel</td>
<td>30</td>
<td>13</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Lorusso$^3$</td>
<td>Gemcitabine</td>
<td>31</td>
<td>23</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vaughn$^4$</td>
<td>Paclitaxel</td>
<td>31</td>
<td>10</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Sweeney$^5$</td>
<td>Pemetrexed</td>
<td>47</td>
<td>28</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Wunmg$^6$</td>
<td>Lapatinib</td>
<td>39</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Gallagher$^{12}$</td>
<td>Sunitinib</td>
<td>77</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Ko$^{13}$</td>
<td>Nab-paclitaxel</td>
<td>48</td>
<td>28</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Quinn$^{14}$</td>
<td>Eribulin</td>
<td>150</td>
<td>34</td>
<td>4</td>
<td>9.5</td>
</tr>
</tbody>
</table>

**Response Rate = 12%**

**Progression-free survival = 3 months**

**Overall survival = 7 months**

---

2nd line Vinflunine

Vinflunine + BSC: 6.9 mo
BSC: 4.6 mo

2nd line immune-checkpoint inhibition

These are different studies and there is no comparative intent

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Avelumab</th>
<th>Durvalumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Phase III randomized vs chemotherapy</td>
<td>Phase II single-arm</td>
<td>Phase III randomized vs chemotherapy</td>
<td>Phase Ib</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Number of patients</td>
<td>931</td>
<td>265</td>
<td>542</td>
<td>249</td>
<td>191</td>
</tr>
<tr>
<td>(161 patients, ≥6 months f/u)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>1,200 mg every 3 weeks</td>
<td>3 mg/kg every 2 weeks</td>
<td>200 mg every 3 weeks</td>
<td>10 mg/kg every 2 weeks</td>
<td>10 mg/kg every 2 weeks</td>
</tr>
<tr>
<td>ORR</td>
<td>13.4%</td>
<td>19.6%</td>
<td>21.1%</td>
<td>17%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Duration of response</td>
<td>63% of responses ongoing at median f/u of 21.7 months</td>
<td>77% of responses ongoing at median f/u of 7 months</td>
<td>72% of responses ongoing at median f/u of 14.1 months</td>
<td>96% of responses ongoing at f/u of 7 months</td>
<td>50% of responses lasting ≥6 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>8.6 months</td>
<td>8.7 months</td>
<td>10.3 months</td>
<td>6.5 months</td>
<td>18.2 months</td>
</tr>
<tr>
<td>Median PFS</td>
<td>2.1 months</td>
<td>2.0 months</td>
<td>2.1 months</td>
<td>1.5 months</td>
<td>1.5 months</td>
</tr>
<tr>
<td>Rate of Grade 3/4 treatment-related AEs</td>
<td>20%</td>
<td>18%</td>
<td>15%</td>
<td>8%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

f/u, follow-up.

Post-platinum pembrolizumab KN 045 – updated data

OS in all patients

Adapted from: Fradet Y et al. ASCO 2018.

OS in patients with PD-L1 CPS ≥10
KEYNOTE-045: ORR & DOR in the total population

CI, confidence interval; CR, complete response; NR, not reached; ORR, objective response rate; PR, partial response.

Adapted from: Fradet Y et al. ASCO 2018.
Immune-checkpoint inhibitors in the second-line treatment of metastatic urothelial cancer

**Pembrolizumab** should be considered in patients with platinum-refractory urothelial cancer, as it improves OS [I, A]

The therapeutic use of other immune-checkpoint inhibitors that are EMA-approved can be considered, supported with lower level evidence:

atezolizumab [II, B]; nivolumab [III, B]
What are the current options in the management of mUC in clinical practice? Updated ESMO Guidelines

Management of metastatic disease

PS ≤ 2 + poor renal function

Clinical trial

BSC

Cisplatin-eligible

Cisplatin-eligible

First-line:
- Gemcitabine and cisplatin
- MVAC
- HDMVAC
- PCG

PD-L1 negative

First-line:
- Gemcitabine and carboplatin

PD-L1 positive

First-line:
- Atezolizumab
- Pembrolizumab

Second-line Immune-checkpoint inhibitors
- Pembrolizumab
- Atezolizumab
- Nivolumab

Second-line Chemotherapy
1. Platinum-based chemotherapy
2. Vinflunine
3. Taxane-based chemotherapy

Clinical trial

Discussion points

✓ Treatment of non-metastatic muscle invasive Bca
✓ Neo-adjuvant chemotherapy
✓ 1st line therapy for metastatic BCa
✓ 2nd line therapy for metastatic BCa
✓ Novel therapies for metastatic BCa
How should we select patients?
Biomarkers to identify patients more likely to respond

- **Criteria for therapy based on molecular characteristics**
  - Patients most likely to respond
  - Faster and more conclusive answers

**OLD MODEL:** large populations
- Low efficacy with unnecessary side effects

**NEW MODEL:** small populations with relevant molecular defects
- All patients have the potential to respond
Erdafitinib FDA-approved for platinum-treated urothelial cancer with selected FGFR2/3 alterations

Siefker-Radtke et al. ASCO 2018; abstract 4503.

75/99 (76%) patients treated with 8 mg continuous erdafitinib had a reduction in the sum of target-lesion diameters.

CI, confidence interval; Mo, months; No., number; NR, not reached.
Erdafitinib FDA-approved for platinum-treated urothelial cancer with selected FGFR2/3 alterations

Median DOR 5.6 months (95% CI: 4.2–7.2)

DOR, duration of response

~ 30% of these responses maintained for > 12 months

Enfortumab vedotin targets nectin 4-expressing urothelial carcinoma

Results from EV-201

<table>
<thead>
<tr>
<th></th>
<th>KEYNOTE-045 phase 3 trial</th>
<th>EV-101</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Paclitaxel/docetaxel/vinflunine</td>
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<tr>
<td>ORR, %</td>
<td>21.1&lt;sup&gt;2&lt;/sup&gt;</td>
<td>11.0&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>mPFS, months</td>
<td>2.1</td>
<td>3.3</td>
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<tr>
<td>mOS, months</td>
<td>10.1</td>
<td>7.2</td>
</tr>
<tr>
<td>DOR, months</td>
<td>29.7</td>
<td>4.4</td>
</tr>
</tbody>
</table>

mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate.

These are different studies and there is no comparative intent.

1. Necchi et al. Abstract ESMO 2019; abstract 919P

1. Necchi et al. Abstract ESMO 2019; abstract 919P
What are the current options in the management of mUC in clinical practice? Updated ESMO Guidelines

Management of metastatic disease

PS ≤ 2 + poor renal function

Clinical trial  BSC

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- Gemcitabine and cisplatin
- MVAC
- HDMVAC
- PCG

Cisplatin-ineligible

Cisplatin-eligible

BSC

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Pending regulatory approval

Erdaftinib
Enfortumab vedotin

Clinical trial

Thank you