Examining the Use of Checkpoint Inhibitors in Bladder Cancer

Management of the Cisplatin-Ineligible Patient

- Introduction/Case Scenario
  Robert Dreicer, MD, MS, MACP, FASCO
- POSITION 1: Chemotherapy Remains the Primary Therapy Modality
  Andrea B. Apolo, MD
- POSITION 2: Checkpoint Inhibitors are the Primary Therapy Modality
  Arjun V. Balar, MD

Presented by Creative Educational Concepts, Inc. in collaboration with the Bladder Cancer Advocacy Network (BCAN)

Supported through an independent educational grant from AstraZeneca.
A 73-year-old male with a large renal pelvis mass has biopsy-proven urothelial cancer with evidence of liver, lung, and nodal metastases. He notes progressive pain and fatigue.

His ECOG PS is 2, and his serum creatinine is 1.68 mg/dL (calculated creatinine clearance is 42 mL/min).

His past medical history is remarkable for mild hypertension. He was working as an office manager until the most recent diagnosis.

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Position 1: Chemotherapy Remains the Primary Therapy Modality

Andrea B. Apolo, MD
National Cancer Institute
Bethesda, Maryland
Bladder Cancer Management by Stage

**Primary Discipline**

**Urology**

Non–Muscle–Invasive Bladder Cancer 70% of newly diagnosed cases

- Ta: Noninvasive papillary carcinoma
- Tis: Carcinoma in situ
- T1: Tumor invades lamina propria

Muscle–Invasive Bladder Cancer 25% of newly diagnosed cases

- Stages 2 and 3
  - T2: Tumor invades muscle
  - T3: Tumor invades perivesical fat
  - T4a: Tumor invades contiguous organ (prostate, uterus, vagina)

*First-line* Cisplatin-based combination chemotherapy

Cisplatin-eligible

Cisplatin-ineligible

Neoadjuvant cisplatin-based combination chemotherapy

Radical cystectomy and lymph node dissection

Trimodality bladder-sparing therapy

TURBT +/- intravesical therapy

15%–30% Progress

50% Progress

Standard of care

Salvage for muscle-invasive recurrence

May be offered in a select group of patients

*Always consider participation in a clinical trial*

**Medical Oncology**

Stages 4

- T4b: Tumor invades the pelvic wall, abdominal wall
- N 1–3: Any lymph node involvement
- M1: Distant metastasis

*First-line* Cisplatin-based combination chemotherapy

Cisplatin-eligible

Cisplatin-ineligible

*Second-line* atezolizumab or pembrolizumab

*Second-line* nivolumab or durvalumab or avelumab

**Urology, Medical Oncology, Radiation Oncology**

Radical cystectomy and lymph node dissection

Trimodality bladder-sparing therapy

**Bladder Cancer Management by Stage**

**Urology**
- Non–Muscle-Invasive Bladder Cancer
  - 70% of newly diagnosed cases
  - Stages 0–1
  - T1a: Noninvasive papillary carcinoma
  - Tis: Carcinoma in situ
  - T1: Tumor invades lamina propria

**Urology, Medical Oncology, Radiation Oncology**
- Muscle-Invasive Bladder Cancer
  - 25% of newly diagnosed cases
  - Stages 2 and 3
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**Medical Oncology**
- Metastatic Bladder Cancer
  - 5% of newly diagnosed cases
  - Stages 4
  - T4b: Tumor invades the pelvic wall, abdominal wall
  - N 1–3: Any lymph node involvement
  - M1: Distant metastasis

- TURBT +/- intravesical therapy
- Neoadjuvant cisplatin-based combination chemotherapy
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**Definition of “Cisplatin Ineligible” for Clinical Trial Enrollment**

**Criteria for Patients Entering Clinical Trials with Metastatic Urothelial Carcinoma Deemed “Unfit” for Cisplatin-based Chemotherapy**

- WHO or ECOG PS ≥2 or Karnofsky PS 60% to 70%
- Measured or calculated creatinine clearance <60 mL/min
- CTCAE v4 grade ≥2 audiometric hearing loss
- CTCAE v4 grade ≥2 peripheral neuropathy
- NYHA Class III heart failure

* ≥1 must be present

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### Bladder Cancer Management by Stage

#### Urology

**Non–Muscle–Invasive Bladder Cancer**
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#### Urology, Medical Oncology, Radiation Oncology

**First–line Cisplatin–based combination chemotherapy**
- Cisplatin–eligible
- Cisplatin–ineligible

**Neoadjuvant**
- Cisplatin–based combination chemotherapy

**Trimodality**
- Bladder–sparing therapy

**Radical**
- Cystectomy and lymph node dissection

**Cisplatin–eligible**
- Radical cystectomy and lymph node dissection

**Cisplatin–ineligible**
- Neoadjuvant cisplatin–based combination chemotherapy

#### Medical Oncology

**First–line Cisplatin–based combination chemotherapy**
- Cisplatin–eligible
- Cisplatin–ineligible

**Second–line Atezolizumab**
- Pembrolizumab
- Nivolumab
- Durvalumab
- Avelumab

**Neoadjuvant**
- Cisplatin–based combination chemotherapy

**Trimodality**
- Bladder–sparing therapy

**Radical**
- Cystectomy and lymph node dissection

**Cisplatin–eligible**
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- **TURBT +/- intravesical therapy**
- **Neoadjuvant cisplatin-based combination chemotherapy**
- **Radical cystectomy and lymph node dissection**
- **Trimodality bladder-sparing therapy**

- **Standard of care**
- **Salvage for muscle-invasive recurrence**
- **May be offered in a select group of patients**
- **Always consider participation in a clinical trial**


---

Cisplatin-Ineligible Metastatic Bladder Cancer Patients

*Immunotherapy or Carboplatin-based Chemotherapy?*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Atezolizumab&lt;sup&gt;1&lt;/sup&gt; Pembrolizumab&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Carboplatin + Gemcitabine&lt;sup&gt;3&lt;/sup&gt; (Phase II Trial)</th>
<th>Carboplatin + Gemcitabine&lt;sup&gt;4&lt;/sup&gt; (EORTC Phase II/III Trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>~ 24 (up to 39% in selected pts)</td>
<td>38.4</td>
<td>36.1 confirmed</td>
</tr>
<tr>
<td>DCR, %</td>
<td>~ 30–45</td>
<td>63.3</td>
<td>70.6 unconfirmed</td>
</tr>
<tr>
<td>TTP, mos</td>
<td>~ 2–3</td>
<td>7.6</td>
<td>5.8 PFS</td>
</tr>
<tr>
<td>OS, mos</td>
<td>15.9&lt;sup&gt;1&lt;/sup&gt;</td>
<td>16.3</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Fatigue</td>
<td>Anemia</td>
<td>Grade 5</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>Neutropenia</td>
<td>Thrombocytopenia grade 4</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>Febrile neutropenia</td>
<td>Renal grade 3/4</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>Nausea, emesis</td>
<td>Neutropenic fever</td>
</tr>
<tr>
<td></td>
<td>irAEs</td>
<td>Grade 3: 18.3%</td>
<td>Mucositis</td>
</tr>
<tr>
<td></td>
<td>Grade 3/4: 16%</td>
<td>Grade 4: 51.7%</td>
<td>9.3% overall</td>
</tr>
</tbody>
</table>

FDA Alters Approved Use of Two Checkpoint Inhibitors for Bladder Cancer

June 20, 2018

Early data from

- KEYNOTE‐361 (pembrolizumab)
- IMvigor 130 (atezolizumab)

The agency reported that patients with low PD‐L1 levels who received the checkpoint inhibitor alone “had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy.”
Cisplatin-ineligible patients do poorly.

- PS 2 and impaired renal function are commonly accepted criteria to define this population.
- Outcomes are very poor with alternative chemotherapy.
- Gemcitabine and carboplatin considered a “standard”.
- 20%–40% or more never treated.

Median OS: 9 months

**Subgroup Analysis**

**PS 2 and Impaired Renal Function**
- Worst survival with Gemcitabine and Carboplatin.

**PS 2 and Visceral Metastatic Disease (Bajorin Risk Factors)**
- Worst survival with Gemcitabine and Carboplatin.

Our patient has all 3 risk factors!
Examining the Use of Checkpoint Inhibitors in Bladder Cancer

First-line Atezolizumab
*Cohort 1 IMvigor210 LT Follow Up*


First-line Pembrolizumab
*KN52 Long-term Follow-up*

Examining the Use of Checkpoint Inhibitors in Bladder Cancer

**Novel Combinations**

**Chemotherapy**

- KEYNOTE-189 and 407 in NSCLC: Platinum + IO better than Platinum alone
- Similar outcomes expected in mUC and platinum-IO likely to be a new standard of care
- For platinum-eligible patients (cis OR carbo), reduces anxiety of “waiting” for an immune response
- Does not address chemo-ineligible patients

**Audience Re-vote: Which one of the following would you recommend?**

A. Pembrolizumab or atezolizumab
B. Gemcitabine/carboplatin
C. Split-course cisplatin/gemcitabine
D. Obtain PD-L1 status to decide checkpoint inhibitor vs chemotherapy
E. Symptomatic supportive care/Hospice
A 66-year-old female has a TURBT biopsy that finds evidence of high-grade urothelial cancer into muscularis propria following a first episode of gross hematuria. A CT of the chest/abdomen/pelvis is without evidence of metastatic disease.

Her ECOG PS is 1, hemoglobin is 13.2 g/dL, liver function tests are within normal limits, and serum creatinine is 1.45 mg/dL (calculated creatinine clearance is 58 mL/min).

She has a past medical history of diabetes that is diet controlled, and she stopped smoking 20 years prior.
Position 1: Use of ICI in Neoadjuvant Setting Based on Existing Data?
Yes!

- This patient clearly has curative disease
- Standard of care is neoadjuvant chemotherapy—cisplatin based
  - Does she qualify?

Criteria for Patients Entering Clinical Trials with Metastatic Urothelial Carcinoma Deemed “Unfit” for Cisplatin-based Chemotherapy*

<table>
<thead>
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<tr>
<td>WHO or ECOG PS ≥2 or Karnofsky PS 60% to 70%</td>
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<td>CTCAE v4 grade ≥2 peripheral neuropathy</td>
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<td>NYHA Class III heart failure</td>
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</table>

* ≥1 must be present

Neoadjuvant Chemotherapy Underutilized

- National Cancer Database
- 1998–2003
  - 10.4% received adjuvant chemotherapy,
  - 1.2% received neoadjuvant chemotherapy
- Increased to 20.8% in 2010


Why is Chemotherapy Underutilized?
Lack of referral from urologists:
if referred to medical oncologist, majority get chemotherapy.
Why is Chemotherapy Underutilized?

1. “I’m not convinced” or “the benefit is too small”
2. “Treatment is too toxic for my patients”
3. “I give adjuvant chemotherapy after surgery; it is just as good”
4. “I am smarter than everyone else, and I can predict who needs chemotherapy”

MD Anderson Cancer Center Algorithm

Resectable Tumor  \(\rightarrow\)  Radical Cystectomy

High-risk features
- Lymphovascular invasion
- Locally advanced
- cT3 or cT4a
- Hydronephrosis
- Variant Histology

Neoadjuvant Chemotherapy

Examining the Use of Checkpoint Inhibitors in Bladder Cancer

**Upfront Cystectomy**


- 5 year DSS = 81%
- 30% ≤pT1 following TUR alone...
- ...but 40% were upstaged to >pT2

Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy


- High risk—unchanged
- Low risk—upstaged
- High risk—downstaged
- Low risk—unchanged
Examining the Use of Checkpoint Inhibitors in Bladder Cancer

**PURE-01 (NCT02736266)**
Neoadjuvant Pembrolizumab before Radical Cystectomy for MIBC

- Fit and planned for cystectomy
- Predominant (ie, 50% at least) UC histology
- cT ≤3bN0 stage
- Residual disease after TURB (surgical opinion, cystoscopy or radiological presence)
- GFR ≥20 mL/min (Cockcroft–Gault formula)
- ECOG-PS 0–1

3x3 weekly cycles of pembrolizumab 200 mg IV

- Pre-post treatment tissue/blood sample collection for biomarker analyses
- Pre-post treatment imaging: multiparametric bladder MRI (mpMRI); 18F-FDG-PET/CT scan, T/A CT scan
- Cystectomy
- Post-cystectomy management according to EAU guidelines
- Survival data collected until 2 years post cystectomy

**Baseline Characteristics (N=50)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time frame of accrual</strong></td>
<td>Feb. 2017 to Mar. 2018</td>
</tr>
<tr>
<td><strong>Median age, years (IQR)</strong></td>
<td>66 (60–72)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 (82)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (18)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (18)</td>
</tr>
<tr>
<td><strong>Clinical T stage</strong></td>
<td></td>
</tr>
<tr>
<td>T2N0</td>
<td>21 (42)</td>
</tr>
<tr>
<td>T3N0</td>
<td>27 (54)</td>
</tr>
<tr>
<td>T2-3N1</td>
<td>2 (4)</td>
</tr>
<tr>
<td><strong>History of previous non-muscle-invasive UC</strong></td>
<td>7 (14)</td>
</tr>
<tr>
<td><strong>Previous BCG intravesical instillations</strong></td>
<td>5 (10)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Pure UC</td>
<td>41 (82)</td>
</tr>
<tr>
<td>UC and squamous cell carcinoma component</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Micropapillary variant</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Lymphoepitheliomatous-like variant</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Concomitant carcinoma in situ component</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time frame of accrual</strong></td>
<td>Feb. 2017 to Mar. 2018</td>
</tr>
<tr>
<td><strong>Median bladder tumor volume, cm³ (range)</strong></td>
<td>0.7 (0.4–1.5)</td>
</tr>
<tr>
<td><strong>Cisplatin eligibility (Galsky criteria)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46 (92)</td>
</tr>
<tr>
<td>No</td>
<td>4 (8)</td>
</tr>
<tr>
<td><strong>No. of cycles of pembrolizumab administered</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (1)</td>
</tr>
<tr>
<td>2</td>
<td>2 (4)</td>
</tr>
<tr>
<td>3</td>
<td>47 (94)</td>
</tr>
<tr>
<td><strong>Type of RC</strong></td>
<td></td>
</tr>
<tr>
<td>RARC</td>
<td>32 (64)</td>
</tr>
<tr>
<td>ORC</td>
<td>18 (36)</td>
</tr>
<tr>
<td><strong>Type of urinary diversion</strong></td>
<td></td>
</tr>
<tr>
<td>Neobladder</td>
<td>23 (46)</td>
</tr>
<tr>
<td>Ileal conduit</td>
<td>26 (52)</td>
</tr>
<tr>
<td>Ureterocutaneostomy</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy post-RC</td>
<td>3 (6)</td>
</tr>
<tr>
<td><strong>Median time from end pembrolizumab-RC, days (IQR)</strong></td>
<td>22 (15–30)</td>
</tr>
<tr>
<td><strong>Total treatment period</strong></td>
<td></td>
</tr>
<tr>
<td>Median No. of days (IQR)</td>
<td>63 (57–70)</td>
</tr>
</tbody>
</table>

PURE-01 Study
Prepping for Cancer Surgery with Immunotherapy

Pathologic Response to Pembrolizumab

<table>
<thead>
<tr>
<th>Response</th>
<th>All Treated Patients (N=50)</th>
<th>PD-L1 CPS ≥10% (n=35)</th>
<th>PD-L1 CPS &lt;10% (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point Pathologic complete response, No. (%)</td>
<td>21 (42)</td>
<td>19 (54.3)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>95% CI</td>
<td>28.2–56.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary end point Pathologic downstaging to pt &lt;T2, No. (%)</td>
<td>27 (54)</td>
<td>23 (65.7)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>39.3–68.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2N0</td>
<td>2 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3-4N0</td>
<td>6 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pTanyN+</td>
<td>10 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional MVAC chemotherapy†</td>
<td>5 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECIST v1.1 PD</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


ABACUS
A Phase II Study Investigating the Safety and Efficacy of Neoadjuvant Atezolizumab in Muscle-Invasive Bladder Cancer

74 patients received study drug
59 received 2 cycles
15 received 1 cycle
67 had cystectomy
68 assessable for primary efficacy endpoint
7 did not have cystectomy


Examining the Use of Checkpoint Inhibitors in Bladder Cancer
ABACUS: Results

PD-L1 Positivity at Baseline and at Surgery

% PD-L1 positive
0% 10% 20% 30% 40% 50% 60% 70% 80%
Pre-treatment Post-treatment

35% 73%

Change in Mean CD8 Count with Treatment (n=26)

CD8 cells/mm²
5000 4000 3000 2000 1000 0
* Pre-treatment Post-treatment

*P<0.05

ABACUS: Results

• 56/68 (82%) patients had PD-L1 analysis; remainder ongoing assessment
• 45% of 56 patients were PD-L1 positive at baseline (≥5% immune component with SP142 Ab)
• pCR=pT0 (n=16) and Tis (n=4)

*Patients who had cystectomy (n=67) or those who progress prior to cystectomy (n=1)

Complete Response Rates (n=68)

% pCR rate
0% 5% 10% 15% 20% 25% 30% 35% 40% 45%

All comers*
29%
(95% CI: 19%–42%)

PD-L1 positive
40%
(95% CI: 21%–61%)

PD-L1 negative
16%
(95% CI: 5%–34%)


Examining the Use of Checkpoint Inhibitors in Bladder Cancer

ABACUS: Results

pCR Rate According to T Stage at Baseline

<table>
<thead>
<tr>
<th>T Stage</th>
<th>% pCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>35%</td>
</tr>
<tr>
<td>T3 or T4</td>
<td>15%</td>
</tr>
</tbody>
</table>

Immune Infiltration in a Complete Response Post Treatment Surgical Sample

Granulomatous reaction
Foam cell macrophages


Advantages

- Low toxicity
- Easier to accept—patient and urologists
- Potential benefit to IO while tumor in place
- NAC studies suggest p0 rates that are impressive
Disadvantages

• No randomized studies
• (but that has never stopped us)
• (...and is better than no NAC at all)

Position 2: Use of ICI in Neoadjuvant Setting
Based on Existing Data? No!

Andrea B. Apolo, MD
National Cancer Institute
Bethesda, Maryland
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**TURBT +/- intravesical therapy**

**Trimodality bladder-sparing therapy**

**Radical cystectomy and lymph node dissection**

**Cisplatin-eligible**

**Cisplatin-ineligible**

*Always consider participation in a clinical trial*

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Phase III Trial of Neoadjuvant MVAC Followed by Radical Cystectomy

- Phase III Intergroup trial of 3 cycles of MVAC followed by radical cystectomy vs immediate radical cystectomy (N=317)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVAC + cystectomy (n=153)</td>
<td>77</td>
</tr>
<tr>
<td>Cystectomy alone (n=154)</td>
<td>46</td>
</tr>
<tr>
<td>HR (OS): 1.33 (95% CI: 1.00–1.76; P=.06)</td>
<td></td>
</tr>
<tr>
<td>HR (disease-specific survival): 1.66 (P=0.002)</td>
<td></td>
</tr>
</tbody>
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*First-line Cisplatin-based combination chemotherapy*

*Second-line atezolizumab or pembrolizumab or nivolumab or durvalumab or avelumab*

Phase III Trial of Neoadjuvant MVAC Followed by Radical Cystectomy

5-Year Survival

MVAC x 3 followed by cystectomy vs immediate cystectomy (N=317)

- pT0: 38% with MVAC vs 15% with cystectomy alone
- 5-year survival (pT0): 85%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Deaths</th>
<th>Median Survival, yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVAC + cystectomy, pT0</td>
<td>14</td>
<td>NR</td>
</tr>
<tr>
<td>Cystectomy, pT0</td>
<td>6</td>
<td>11.3</td>
</tr>
<tr>
<td>MVAC + cystectomy, RD</td>
<td>76</td>
<td>3.8</td>
</tr>
<tr>
<td>Cystectomy, RD</td>
<td>94</td>
<td>2.4</td>
</tr>
</tbody>
</table>


Phase II Trial of Accelerated MVAC as Neoadjuvant Therapy for MIBC

- Phase II trial in patients with cT2-T4a and N0-N1 MIBC (N=44); 60% with stage III or IV disease
- 3 cycles accelerated MVAC + pegfilgrastim → surgery
  - Methotrexate 30 mg/m² D1
  - Vinblastine 3 mg/m² D1
  - Doxorubicin 30 mg/m² D1
  - Cisplatin 70 mg/m² D1 (split dose if CrCl <60 mL/min)

Pathologic Response

Downstaged 65%

Phase II Trial of Neoadjuvant Dose-Dense MVAC + Pegfilgrastim in Patients with MIBC

- Phase II trial in patients with cT2-T4a, N0-N1, M0 MIUC (N = 39); 64% with stage III or IV disease
- 4 cycles dose-dense MVAC + pegfilgrastim → surgery
  - Methotrexate 30 mg/m² D1
  - Vinblastine 3 mg/m² D2
  - Doxorubicin 30 mg/m² D2
  - Cisplatin 70 mg/m² D2

Pathologic Response

<table>
<thead>
<tr>
<th>Achieved</th>
<th>Achieved ≤T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts (%)</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>49%</td>
</tr>
<tr>
<td>10%</td>
<td>26%</td>
</tr>
<tr>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Downstaged ≤pT1N0M0 49%


Single-arm Neoadjuvant Monotherapy Trials

Atezolizumab (ABACUS)
- Phase II
- 2 cycles q3 weeks
- Cisplatin-ineligible (or refuse)
- T2-4aNOM0
- Primary endpoint:
  - pCR≥20% & increase CD8 count

Atezolizumab (ABACUS)
- N=68 evaluable
- 12% had prior BCG
- 76% smoker/prior
- 71% T2

Atezolizumab (ABACUS)
- pCR = 29%
- PD-L1+ pCR 40%
- T2 pCR 35% (T3 15%)
- PD-L1+ increased 35% → 73% post-treatment
- CD8 expression increased post-treatment (500 → 952 cells/mm²)

Atezolizumab (ABACUS)
- pCR pT0 = 42%
- <pT2 = 54%
- PD-L1+ pCR 54%
- PD-L1- pCR 13%

Pembrolizumab (PURE-01)
- Phase II
- 3 cycles q3 weeks
- Cisplatin-eligible 92%
- T2-3N0-1
- Primary endpoint
  - pCR

Pembrolizumab (PURE-01)
- N=55 evaluable

Pembrolizumab (PURE-01)
- pCR pT0 = 42%
- <pT2 = 54%
- PD-L1+ pCR 54%
- PD-L1- pCR 13%

Concerns

• No randomized data
• No survival data
• Toxicity

Randomized Trials of Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Chemotherapy</th>
<th>No. Pts</th>
<th>Survival benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner</td>
<td>1991</td>
<td>cisplatin, cyclophosphamide, and doxorubicin</td>
<td>102</td>
<td>Yes</td>
</tr>
<tr>
<td>Studer</td>
<td>1994</td>
<td>cisplatin</td>
<td>77</td>
<td>No</td>
</tr>
<tr>
<td>Stockle</td>
<td>1995</td>
<td>cisplatin, methotrexate, vinblastine, doxorubicin or epirubicin</td>
<td>49</td>
<td>Yes</td>
</tr>
<tr>
<td>Freiha</td>
<td>1996</td>
<td>cisplatin, methotrexate, vinblastine</td>
<td>55</td>
<td>No</td>
</tr>
<tr>
<td>Bono</td>
<td>1997</td>
<td>cisplatin, methotrexate</td>
<td>93</td>
<td>No</td>
</tr>
<tr>
<td>Otto</td>
<td>2001</td>
<td>cisplatin, methotrexate, vinblastine, epirubicin</td>
<td>108</td>
<td>No</td>
</tr>
<tr>
<td>Cognetti</td>
<td>2008</td>
<td>cisplatin, gemcitabine</td>
<td>192</td>
<td>No</td>
</tr>
<tr>
<td>Stadler</td>
<td>2009</td>
<td>cisplatin, methotrexate, vinblastine, doxorubicin</td>
<td>114</td>
<td>No</td>
</tr>
<tr>
<td>Paz-Ares</td>
<td>2010</td>
<td>cisplatin, paclitaxel, gemcitabine</td>
<td>142</td>
<td>Yes</td>
</tr>
<tr>
<td>Sternberg</td>
<td>2014</td>
<td>GC/MVAC/ddMVAC</td>
<td>284</td>
<td>No</td>
</tr>
</tbody>
</table>
Phase III Checkpoint-Inhibitor Adjuvant Trials in Muscle-Invasive Bladder Cancer

AMBASSADOR Alliance (NCT 03244384)
High-risk muscle-invasive urothelial carcinoma of the bladder, ureter, and renal pelvis
R (1:1) N=739
Pembrolizumab 200 mg IV Q3W x 1 year
Observation
Co-primary DFS & OS

CheckMate 274 (NCT 02632409)
High-risk muscle-invasive urothelial carcinoma of the bladder, ureter, and renal pelvis
R (1:1) N=640
Nivolumab 240 mg IV Q2W x 1 year
Placebo Q2W
DFS
• PD-L1+
• All

IMvigor 010 (NCT 02450331)
High-risk muscle-invasive urothelial carcinoma of the bladder, ureter, and renal pelvis
R (1:1) N=700
Atezolizumab 1200 mg IV Q3W x 1 year
Observation
DFS

Management of Advanced Urothelial Cancer:
Is There an Optimal Setting for ICI Delivery in the Community?

- Introduction/Case Scenario
  Robert Dreicer, MD, MS, MACP, FASCO

- POSITION 1: It’s Time for Expansion of Urologic Involvement in IO Therapy
  Ashish M. Kamat, MD, MBBS, FACS

- POSITION 2: Not So Fast
  Arjun V. Balar, MD

Ashish M. Kamat, MD, MBBS, FACS
University of Texas
MD Anderson Cancer Center
Houston, Texas

Arjun V. Balar, MD
NYU Langone Health
New York, New York
A 78-year-old male has biopsy-proven metastatic urothelial cancer (lung biopsy) with 50% PD-L1 expression. He has received 4 cycles of an anti–PD-1 agent, which he has tolerated well to date, and he now presents for cycle 5. He is more fatigued than previously but, otherwise, is without complaint.

Currently, his hemoglobin is 12.2 g/dL (stable), white blood cell count is 5.6 K/uL, AST is 866 IU/L, ALT is 678 IU/L, bilirubin is 1.9 mg/dL, and TSH is 15.4 mIU/L.
Examining the Use of Checkpoint Inhibitors in Bladder Cancer

Evolution of Systemic Therapy for Urothelial Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Regimen</th>
<th>Response Rate</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>MVAC(^1)</td>
<td>40%–50%</td>
<td>12–15 months</td>
</tr>
<tr>
<td>1998</td>
<td>Gemcitabine + cisplatin(^2)</td>
<td>40%–50%</td>
<td>12–15 months</td>
</tr>
<tr>
<td>2001</td>
<td>Gemcitabine + Carboplatin(^4)</td>
<td>36%–56%</td>
<td>7–9 months</td>
</tr>
<tr>
<td>2005</td>
<td>Atezolizumab, Pembrolizumab</td>
<td>~24%</td>
<td>~15.9 months (atezolizumab)</td>
</tr>
<tr>
<td>2009</td>
<td>Atezolizumab, Nivolumab, Durvalumab, Avelumab, Pembrolizumab</td>
<td>15%–19%</td>
<td>7.9–10.3 months</td>
</tr>
<tr>
<td>2013</td>
<td>Single-agent chemotherapy</td>
<td>~10%</td>
<td>5–8 months</td>
</tr>
</tbody>
</table>

Standard Therapy in Advanced Urothelial Cancer

<table>
<thead>
<tr>
<th>Setting</th>
<th>Regimen</th>
<th>Response Rate</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Line</td>
<td>Cisplatin eligible</td>
<td>MVAC(^1)</td>
<td>40%–50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine + cisplatin(^2)</td>
<td>40%–50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine + Carboplatin(^4)</td>
<td>36%–56%</td>
</tr>
<tr>
<td></td>
<td>Cisplatin ineligible</td>
<td>Atezolizumab, Pembrolizumab</td>
<td>~24%</td>
</tr>
<tr>
<td>Second Line</td>
<td>Atezolizumab,(^7) Nivolumab, Durvalumab, Avelumab, Pembrolizumab</td>
<td>15%–19%</td>
<td>7.9–10.3 months</td>
</tr>
<tr>
<td></td>
<td>Single-agent chemotherapy</td>
<td>~10%</td>
<td>5–8 months</td>
</tr>
</tbody>
</table>

---

### Current Clinical Development of Anti–PD-1/L1 in NMIBC

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Trial Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02792192</td>
<td>Phase Ib/II Safety and Pharmacology Study of Atezolizumab Alone and in Combination with BCG in High-risk NMIBC</td>
</tr>
<tr>
<td>WO29635</td>
<td>Phase II Study of Atezolizumab in Subjects with Non-Metastatic TCC of the Bladder (PI: L Fong, UCSF)</td>
</tr>
<tr>
<td>NCT02451423</td>
<td>Phase II Study of Atezolizumab in Recurrent BCG-Unresponsive NMIBC (PI: P. Black)</td>
</tr>
<tr>
<td>NCT02844816</td>
<td>Phase Ib/II Safety and Pharmacology Study of Atezolizumab Alone and in Combination with BCG in High-risk NMIBC</td>
</tr>
<tr>
<td>S1605</td>
<td>Phase II Durable Survival and Tolerability of Durvalumab in BCG-Refractory Urothelial Carcinoma in Situ of the Bladder</td>
</tr>
<tr>
<td>NCT03317158</td>
<td>CheckMate 951: Phase II Nivolumab or Nivolumab + BMS-986205 +/- BCG in BCG-Unresponsive NMIBC</td>
</tr>
<tr>
<td>NCT02625961</td>
<td>KEYNOTE-057: Phase II Study of Pembrolizumab in BCG-Refractory High-risk NMIBC (ESMO 2018)</td>
</tr>
<tr>
<td>NCT03167151</td>
<td>Phase I/II Marker Lesion Study Assessing Safety, Tolerability, and Efficacy of Pembrolizumab in Intermediate-risk Recurrent NMIBC</td>
</tr>
<tr>
<td>NCT03711032</td>
<td>KEYNOTE-676: Phase III BCG +/- Pembrolizumab for High-risk NMIBC That Is Persistent or Recurrent following BCG Induction</td>
</tr>
</tbody>
</table>

---

### KEYNOTE-057—ESMO 2018

**Single-arm, Open-label Phase 2 Study (NCT02625961)**

**Patients**
- HR NMIBC patients unresponsive to BCG who refuse or are ineligible for cystectomy
- Patients with papillary disease must have newly resected disease at study entry
- Two cohorts:
  - Cohort A (n=130)—CIS with or without papillary disease (high-grade Ta or T1)
  - Cohort B (n=130)—papillary disease (high-grade TA or any T1) without CIS

**Primary End Points**
- CR (absence of HR NMIBC) in Cohort A
- DFS in Cohort B

**Secondary End Points**
- CR (absence of any disease—high-risk or low-risk NMIBC) in Cohort A
- DOR in Cohort A
- Safety/tolerability

**Evaluation Schedule**
- Pembrolizumab 200 mg Q3W
- Evaluations with cystoscopy, cytology, ± biopsy Q12 weeks x 2 years and once yearly thereafter and CT urogram Q24 weeks x 2 years or more frequently as clinically indicated

**Treatment Continuation**
- Continue assessments and pembrolizumab until recurrence of HR NMIBC, PD, or 24 months of treatment complete
- Discontinue treatment, enter survival follow-up

---

## KEYNOTE-057

### Overall Response Rate at Month 3<sup>a</sup>

<table>
<thead>
<tr>
<th>Response</th>
<th>N=103</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>40</td>
<td>38.8, 29.4–48.9</td>
</tr>
<tr>
<td>Non-CR</td>
<td>57</td>
<td>55.3, 45.2–65.1</td>
</tr>
<tr>
<td>Persistent&lt;sup&gt;b&lt;/sup&gt;</td>
<td>47</td>
<td>45.6, 35.8–55.7</td>
</tr>
<tr>
<td>NMIBC stage progression&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9</td>
<td>8.7, 4.1–15.9</td>
</tr>
<tr>
<td>Extravesical disease&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1</td>
<td>1.0, 0.0–5.3</td>
</tr>
<tr>
<td>Progression to T2</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Nonevaluable&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6</td>
<td>5.8, 2.2–12.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Summary of overall responses of HR NMIBC per central assessment at month 3 in all patients who received ≥1 dose of trial treatment, had baseline evaluations, and also had ≥1 post-baseline disease assessment.  
<sup>b</sup>Defined as patients with CIS at baseline who at month 3 also had CIS ± papillary tumor.  
<sup>c</sup>Increase in stage from CIS and/or high-grade Ta at baseline to T1 disease.  
<sup>d</sup>Defined as presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging.  
<sup>e</sup>Patient developed new liver lesions on imaging and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer.  
<sup>f</sup>Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than PD are considered not evaluable for efficacy. Database cutoff: July 18, 2018.

---

## KEYNOTE-057

### Time to CR and Development of Recurrent HR NMIBC

- Median (95% CI) time to CR
  - 12.4 (10.4–19.3) weeks
- 29 (72.5%) patients had an ongoing response
- 10 (25.0%) patients experienced recurrent NMIBC after CR
- 1 patient in CR underwent cystectomy
- No patient developed muscle invasive or metastatic disease

<sup>*</sup>Reappearance of HR NMIBC (CIS and/or high-grade Ta and/or T1 disease) after a disease-free interval (at each month or afterward). Database cutoff: July 18, 2018.

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Examining the Use of Checkpoint Inhibitors in Bladder Cancer

KEYNOTE-057
Duration of Response for Patients Who Achieved CR at Month 3a

- 80% had a CR duration of ≥6 months
- Median (range) CR duration not reached (0+ to 14.1+ months)

![Graph showing CR duration from KEYNOTE-057](image)

a1 month = 30.4367 days.
Database cutoff: July 18, 2018.


CA209-9UT
Ph2, Randomized, Nivolumab +/- BMS-986205 +/- Intravesical BCG in BCG-Unresponsive NMIBC

**Screening**
- BCG-unresponsive NMIBC
- High-risk disease after adequate BCG (CIS, any T1, high-grade Ta)

**Stratification Factors**
- CIS pts: CIS alone vs CIS with T1
- Non-CIS pts: Ta vs T1
- All pts: PD-L1>1% or indeterminate/not evaluable vs ≤1%

**Treatment**

- **Arm A**
  - Nivo 480 mg Q4W x 52 weeks

- **Arm B**
  - Nivo 480 mg Q4 weeks x 2 weeks + BCG (induction, maintenance, 52 wks)

- **Arm C**
  - Nivo 480 mg Q4 weeks x 2 weeks + BMS-986205 100 mg QD x 52 weeks

- **Arm D**
  - Nivo 480 mg Q4 weeks x 2 weeks + BMS-986205 100 mg QD x 52 weeks + BCG (induction, maintenance, 52 weeks)

**Follow every 13 weeks with cystoscopy and cytology. Biopsy for CIS participants at 26, 52 weeks**

**Decision Point**
- CR in ≥11 of first 27 CIS pts with 6 months of F/U: expand arm to full enrollment N=177 (77 CIS, 100 non-CIS)
- CR in ≤10 of first 27 CIS pts with 6 months of F/U: hold enrollment pending DMC and sponsor review

**Follow-Up**
- Follow participants until recurrence, progression, or for 5 years. Cystoscopy, cytology, biopsy per AUA/EAU guidelines after 18 months

BCG, bacillus Calmette-Guerin; CIS, carcinoma in situ; F/U, follow-up; Pts, participants; Q4W, once every 4 weeks; QD, once daily; wks, weeks; DMC, Data Monitoring Committee.

Clinicaltrials.gov; NCT03519256
KEYNOTE-676 (NCT03711032)

KEYNOTE-676: Phase 3 Study of Bacillus Calmette-Guérin (BCG) with or without Pembrolizumab (pembro) for High-risk (HR) Non–Muscle-Invasive Bladder Cancer (NMIBC) That Is Persistent or Recurrent Following BCG Induction

Investigators: Kamat A, Shore N, Hahn N, Alanee S, Nishiyama H, Shariat S, Nam K, Kapadia E, Frenkl T, Steinberg G


KEYNOTE-676 Study Design Diagram

A Phase 3, Randomized, Comparator-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Bacillus Calmette-Guerin (BCG) in Participants with High-risk Non–muscle Invasive Bladder Cancer (HR NMIBC) That Is Persistent or Recurrent Following BCG Induction (KEYNOTE-676)

Eligibility
- Has histologically-confirmed diagnosis of non–muscle invasive (T1, high grade Ta and/or CIS) transitional cell carcinoma (TCC) of the bladder
- Has been treated with one adequate course of BCG induction therapy for the treatment of HR NMIBC

Estimated enrollment: 550

Randomization 1:1

Primary Endpoint
- CR rate by BICR

Key Secondary Endpoints
- EFS
- RFS
- OS
- DOR
- Time-to-Cystectomy
- Safety
- Time to True Deterioration
- QLQ-C30, QLQ-NMIBC24, etc.

ClinicalTrials.gov. Identifier: NCT03711032.

BICR, blinded independent central review; EFS, Event-Free Survival; RFS, Recurrence-Free Survival; DOR, duration or response.
• Urologic oncologists (surgeons) are the first to see patients with bladder cancer
• Long-term relationships with patients, especially those with NMIBC
• Have a significant influence in decisions

• Treat patients with immunotherapy—BCG
  • Manage severe immune-related side effects
• Treat patients with radical cystectomy
  • Manage patients with severe complications
    • Bowel related
    • Immune related
    • ...and more!
Optimal Management of Bladder Cancer Requires a Multidisciplinary Approach

“Providing the best management for patients with bladder neoplasia relies on close cooperation and teamwork among urologists, oncologists, radiologists, and pathologists”

—2nd International Consultation on Bladder Cancer¹

“Multidisciplinary input via tumor board discussions and/or directed consultations is critical to the optimal management of patients with bladder cancer”

—ASCO Clinical Practice Guideline Endorsement²


Examining the Use of Checkpoint Inhibitors in Bladder Cancer

Position 2: Not So Fast

Arjun V. Balar, MD
NYU Langone Health
New York, New York
Chemotherapy vs Immunotherapy

Chemotherapy

- Attacks the tumor directly by targeting rapidly dividing cells
- Side effects are a direct result of toxicity to normal tissues.
- Generally predictable in timing, nature and severity

Immunotherapy

- Engages the body’s immune system. Has no direct effect on the tumor
- Side effects are a direct result of over activation of the immune system.
- Highly unpredictable in timing, nature or severity

Kinetics of irAE Appearance Varies with the Specific Adverse Event and May Be Delayed

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

Symptoms may exacerbate at any time

Data reflect irAE incidence with anti-CTLA-4 treatment.

Immune-Related Adverse Reactions Can Affect Any Tissue

**Common**
- Rash, pruritus
- Fatigue
- Diarrhea
- Arthralgia
- Pneumonitis

**Rare**
- Adrenal insufficiency
- Colitis
- Encephalopathy
- Nephritis
- Neuropathies, Guillain-Barré myasthenia gravis
- Thrombocytopenia
- Type I diabetes
- Stevens-Johnson syndrome

---

The skin and GI tract were sites of the most common irAEs across immune checkpoint targets.

CTLA-4 targeting yielded a higher overall incidence of irAEs compared with PD-1/PD-L1.

---

Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high-grade, immune-related adverse events can occur, particularly with combination immunotherapy. We report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T-cell and macrophage infiltrates. Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T-cell–driven drug reaction. (Funded by Vanderbilt–Ingram Cancer Center Ambassadors and others.)

Phase 2 Study of Pembrolizumab Monotherapy for High-Risk, Non–Muscle Invasive Bladder Cancer Unresponsive to Bacillus Calmette-Guérin

Interim Results from KEYNOTE-057

Arjun V. Balar, Girish Kulkarni, Edward Uchio, Joost Boormans, Loïc Mourey, Laurence Krieger, Eric A. Singer, Dean Bajorin, Ashish Kamat, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit

Presented Friday 2/15/19 in Poster Session B at 2019 Genitourinary Cancers Symposium; Board B1-Abstract 350.
Exchanging the Use of Checkpoint Inhibitors in Bladder Cancer

irAE Management
*Dose Modifications and/or Medical Treatment with Steroids and Immunosuppressants*

---

**CTCAE grade**

1 2 3 4

**Ambulatory**

- Consider infliximab or other “rescue” medication for steroid-refractory irAE
- Consider steroids
- Hold study drug
- Start IV steroids
- May need to permanently stop study drug

**Hospitalized**

- Symptomatic therapy

---

**GENERAL MANAGEMENT STRATEGIES FOR irAEs**

- Relative response to irAEs

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**CTCAE, Common Terminology Criteria for Adverse Events**


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**Multi-Disciplinary Care Redefined**

- Checkpoint blockade will likely be a standard of care in NMIBC
- Ideal model will involves co-management
- Expertise of *both* urologic oncology and medical oncology requisite for safe and effective care