New Advances in Bladder Cancer 2021

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Associate Professor of Urology
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Disclosures

• Immunity Bio
  – Scientific Advisory Board

• UroGen Pharma
  – Consultant
  – Research Funding

• Salix/Bausch Health
  – Research Funding
Outline

• New agents in metastatic bladder cancer
  – Checkpoint inhibitors
  – Antibody drug conjugates
  – Targeted therapy

• New agents in non-muscle-invasive bladder cancer
  – Checkpoint inhibitors
  – Adenoviral therapy (IFNα−2b)
  – IL-15 superagonist

• New agents in UTUC
  – Jelmyto
  – Systemic checkpoint inhibitors and antibody drug conjugates
  – Future direction
Checkpoint Inhibitors

Ghatalia P et al., Ther Adv in Med Onc., 2018
Response Rates in Platinum Refractory

<table>
<thead>
<tr>
<th></th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>13.4%</td>
</tr>
<tr>
<td>ImVigor 211</td>
<td>18.2%</td>
</tr>
<tr>
<td>Apolo et al.</td>
<td>17.8%</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>19.6%</td>
</tr>
<tr>
<td>ENRICHED</td>
<td>21.1%</td>
</tr>
<tr>
<td>Powles et al.</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
</tr>
<tr>
<td>Sharma et al.</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Bellmunt et al.</td>
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</tbody>
</table>

Historical control with chemotherapy ~ 10%
Response Rates in First Line

- DD MVAC: Sternberg et al.²
- Gem Cis: Von der masse et al.³
- Gem Carbo: De Santis et al.⁶
- Pembrolizumab: Balar et al.²⁶
- Atezolizumab: Balar et al.²⁷

Partial response
Complete response

Cisplatin eligible
Cisplatin ineligible
Response Rates in Neoadjuvant Immunotherapy

• Systemic Pembrolizumab x 3 cycles in 50 pts
  – Complete response 42% (54% if PD-L1 >10%)
  – NMIBC in 54% (66% if PD-L1 >10%)

• Systemic Atezolizumab x 2 cycles in 69 pts
  – Complete response in 23%
  – NMIBC in 39%

Necchi A et al., J Clin Oncol., 2018
Powles T et al., ASCO., 2018
### Neoadjuvant Immunotherapy

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Phase</th>
<th>Number Enrolled</th>
<th>NCT Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative Pembrolizumab (MK-3475) Plus Cystectomy Versus Cystectomy Alone in Cisplatin-ineligible Participants With Muscle-invasive Bladder Cancer (MK-3475-905/KEYNOTE-905)</td>
<td>Phase 3</td>
<td>610</td>
<td>NCT03924865</td>
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<tr>
<td>Durvalumab and Standard Chemotherapy Before Surgery in Treating Patients With Variant Histology Bladder Cancer</td>
<td>Phase 2</td>
<td>24</td>
<td>NCT03912936</td>
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<tr>
<td>Pembrolizumab-Eopicadostat Combination To Treat Muscle-invasive Bladder Urothelial Cancer: PECuliar Study</td>
<td>Phase 2</td>
<td>38</td>
<td>NCT03832573</td>
</tr>
<tr>
<td>A Feasibility Study of Durvalumab +/- Oleclumab as Neoadjuvant Therapy for Muscle-invasive Bladder Cancer (BLASST-2)</td>
<td>Phase 1</td>
<td>1</td>
<td>NCT03773866</td>
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<tr>
<td>Durvalumab+/+ Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC</td>
<td>Phase 1</td>
<td>1</td>
<td>NCT03732577</td>
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<tr>
<td>Avelumab as Neoadjuvant Therapy in Subjects With Urothelial Muscle Invasive Bladder Cancers (AURA Trial)</td>
<td>Phase 2</td>
<td>99</td>
<td>NCT0674424</td>
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<tr>
<td>Pembrolizumab Plus Olaparib Administered Prior to Surgery of Resectable Urothelial Bladder Cancer (NEODURVARI)</td>
<td>Phase 2</td>
<td>33</td>
<td>NCT03544492</td>
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<tr>
<td>A Radio-Immunotherapy Before Cystectomy in Locally Advanced Urothelial Cancer</td>
<td>Phase 2</td>
<td>45</td>
<td>NCT03529880</td>
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<tr>
<td>A Study to Test the Safety of Immunotherapy With Pembrolizumab</td>
<td>Phase 2</td>
<td>45</td>
<td>NCT03520491</td>
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<tr>
<td>DUvalumab (MEDI4736) and TREmalimab (MEDI4690) Prior to Neoadjuvant Chemotherapy</td>
<td>Phase 2</td>
<td>99</td>
<td>NCT03472274</td>
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<tr>
<td>Neo-Adjuvant Bladder Urothelial Cancer: A Study of Pembrolizumab</td>
<td>Phase 1</td>
<td>24</td>
<td>NCT03387761</td>
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<tr>
<td>Pembrolizumab</td>
<td>Phase 2</td>
<td>20</td>
<td>NCT03316745</td>
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<tr>
<td>Bi-Rational Regimen in Treatment of Muscle Invasive Bladder Cancer (MIBC) Undergoing Cystectomy</td>
<td>Phase 2</td>
<td>20</td>
<td>NCT03258430</td>
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<tr>
<td>Pembrolizumab For Bladder Cancer Patients Ineligible for Cisplatin</td>
<td>Phase 2</td>
<td>68</td>
<td>NCT03234153</td>
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<tr>
<td>Study of Pembrolizumab Monotherapy in Patients With Muscle-Invasive Bladder Cancer To Explore In Vivo the Mechanisms of Action of Pembrolizumab</td>
<td>Phase 2</td>
<td>40</td>
<td>NCT03212851</td>
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<tr>
<td>A Phase 1 Study of Pembrolizumab in Combination With Cisplatin + Gemcitabine Before Surgery to Remove the Bladder Cancer</td>
<td>Phase 1</td>
<td>30</td>
<td>NCT02989584</td>
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<tr>
<td>Pembrolizumab With and Without Urolumab in Patients With Cisplatin-Ineligible Muscle-Invasive Urothelial Carcinoma</td>
<td>Phase 2</td>
<td>44</td>
<td>NCT02945323</td>
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<tr>
<td>Pembrolizumab for Muscle-invasive Urothelial Bladder Carcinoma</td>
<td>Phase 2</td>
<td>20</td>
<td>NCT02738266</td>
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<tr>
<td>Phase 2 Study of Pembrolizumab in Combination With Gemcitabine and Cisplatin as Neoadjuvant Therapy</td>
<td>Phase 2</td>
<td>39</td>
<td>NCT02690558</td>
</tr>
<tr>
<td>Pembrolizumab in Localized Bladder Cancer</td>
<td>Phase 2</td>
<td>42</td>
<td>NCT02451423</td>
</tr>
<tr>
<td>Pembrolizumab in Combination With Gemcitabine Therapy in Ca-eligible/Ineligible UC Subjects</td>
<td>Phase 1</td>
<td>30</td>
<td>NCT02385766</td>
</tr>
</tbody>
</table>

**Suggested Therapies:**
- **Atezolizumab:** 2/24
- **Nivolumab:** 7/24
- **Pembrolizumab:** 8/24
- **Durvalumab:** 6/24
- **Pembrolizumab:** 6/24

**UCLA Urology**

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Antibody Drug Conjugate in Metastatic Cancer (Enfortumab Vedotin)
Nectin-4 Expression

**EV-201: Cohort 1 Nectin-4 Expression**

- Detected in all patients tested
- Median H-score 290 (range: 14–300)

H-Score scale: 0–300

*Five patients did not have adequate tissue for Nectin-4 testing*
Enfortumab Vedotin

- EV-201: Phase 2 Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors.
  - Presented at ASCO 2019

- 125 pts with mUC received EV with a median follow up of 13.4 months
  - Confirmed ORR was 44% (CR=12%; PR=32%).
  - Among responders, median duration of response was 8 months
  - Estimated median PFS and OS were 5.8 and 11.7 months, respectively
  - 84% had tumor shrinkage
Enfortumab Vedotin + Pembrolizumab

- Phase 2 study of 71 pts with metastatic urothelial cancer and are cis-ineligible (first line)
  - Objective response rate 71%
    - Complete response in 13%
    - Partial response in 58%

Hoimes CJ et al., ESMO 2019
Erdafitinib

- Erdafitinib is an oral pan-FGFR (1–4) inhibitor
- Taken up by lysosomes → sustained intracellular release → long activity

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Frequency of FGFR alterations¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic UC</td>
<td>15-20%</td>
</tr>
<tr>
<td>NMIBC</td>
<td>40-70%</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>14-22%</td>
</tr>
<tr>
<td>NSCLC</td>
<td>4%</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (FGF19 amp by FISH)</td>
<td>21%</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>23%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3-5%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>7%</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>9-17%</td>
</tr>
</tbody>
</table>

*FGFR3 mutations are particularly common (37%) in upper tract UC.*²
Erdafitinib

- Phase 2 trial of 99 patients with metastatic urothelial carcinoma who have failed prior chemotherapy/immunotherapy or are cis-ineligible
  - 43% have failed 2 or more lines of therapy
  - Objective response rate in 40%
    - Complete response in 3%
    - Partial response in 37%
    - Tumor shrinkage in 76%
  - 22 pts received prior immunotherapy (5% ORR to IO)
    - Objective response rate in 59%

Siefker-Radtke AO et al., ASCO, 2018
BCG Unresponsive NMIBC
Pembrolizumab

• Phase 2 study of 102 patients with BCG-unresponsive CIS bladder cancer receiving pembrolizumab IV q 3 weeks until recurrence or 2 years
  – 78 discontinued therapy
  • 43 for persistent disease
  • 22 for recurrent disease
  • 9 for adverse effects
  • 4 for other reasons
  – Complete response in 40%
  – Median duration of complete response is 12 months
    • In other words at 1 year only 20% of all patients are disease free

FDA Approved Pembrolizumab for BCG-Unresponsive Bladder Cancer in January 2020

Balar AV et al., GU ASCO, 2019
## Checkpoint Inhibitors in NMIBC

<table>
<thead>
<tr>
<th>Row</th>
<th>Status</th>
<th>Study Title</th>
<th>Phase</th>
<th>Number Enrolled</th>
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<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td>Avelumab Plus Bacillus Calmette-Guerin (BCG) in Patients With Non-muscle Invasive Bladder Cancer</td>
<td>Phase 1</td>
<td>975</td>
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<tr>
<td>2</td>
<td>Recruiting</td>
<td>Atezolizumab Plus One-year BCG Bladder Instillation in BCG-naive High-risk Non-muscle Invasive Bladder Cancer Patients</td>
<td>Phase 2</td>
<td>436</td>
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<tr>
<td>3</td>
<td>Recruiting</td>
<td>Efficacy of Durvalumab in Non-muscle-invasive Bladder Cancer</td>
<td>Phase 3</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Recruiting</td>
<td>Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Bacillus Calmette-Guerin (BCG) in High-Risk Non-Muscle Invasive Bladder Cancer That Has Not Invaded Into the Muscle Wall of the Bladder</td>
<td>Phase 2</td>
<td>186</td>
</tr>
<tr>
<td>5</td>
<td>Recruiting</td>
<td>Assessment of Efficacy and Safety of Durvalumab Plus BCG Compared to the Standard Therapy</td>
<td>Phase 2</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>Recruiting</td>
<td>A Study of Nivolumab or Nivolumab Plus Experimental Medication BMS-857066 in Patients With Unresectable or Metastatic Bladder Cancer That Has Not Invaded Into the Muscle Wall of the Bladder</td>
<td>Phase 1</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>Recruiting</td>
<td>Pembrolizumab (MK-3475) as First-line Therapy in Patients With Locally Advanced or Metastatic Bladder Cancer</td>
<td>Phase 1</td>
<td>34</td>
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<tr>
<td>8</td>
<td>Recruiting</td>
<td>ADAPT-BLADDER: Moderately Advanced Bladder Cancer</td>
<td>Phase 2</td>
<td>162</td>
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<tr>
<td>9</td>
<td>Recruiting</td>
<td>Pembrolizumab in Patients With Recurrent BCG-Untreated Non-muscle Invasive Bladder Cancer</td>
<td>Phase 1</td>
<td>27</td>
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<tr>
<td>10</td>
<td>Recruiting</td>
<td>Durvalumab in Bladder Cancer (NMIBC)</td>
<td>Phase 2</td>
<td>260</td>
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<tr>
<td>11</td>
<td>Recruiting</td>
<td>Pembrolizumab and BCG Solution in Treating Patients With Recurrent Non-Muscle-Invasive Bladder Cancer</td>
<td>Phase 1</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>Recruiting</td>
<td>Study of Pembrolizumab (MK-3475) in Participants With High Risk Non-muscle Invasive Bladder Cancer (MK-3475-057/KEYNOTE-057)</td>
<td>Phase 2</td>
<td>15</td>
</tr>
<tr>
<td>13</td>
<td>Recruiting</td>
<td>MK-3475/BCG in High Risk Superficial Bladder Cancer</td>
<td>Phase 1</td>
<td>15</td>
</tr>
</tbody>
</table>

**Checkpoint Inhibitors:**
- Atezolizumab: **3/15**
- Nivolumab: **1/15**
- Pembrolizumab: **6/15**
- Durvalumab: **5/15**
Adenoviral IFNα-2b (Nadofaragene Firadenovec)

• Phase 2 study of 102 pts with BCG-unresponsive CIS bladder cancer
  – Complete response rate in 53%
  – At 12 months 45% of complete responders are disease free
    • In other words, at 12 months 24% of all pts are disease free
  – 5% pts progressed to MIBC

Boorjian SA et al., Lancet Oncology, 2021
IL-15 Superagonist N-803 (Anktiva)

• Phase 2 study of BCG + N-803 to 80 patients with CIS
  – Complete response rate in 71%
  – At 12 months 56% of complete responders are disease free
    • In other words, at 12 months 40% of all pts are disease free
  – 88% patients have not progressed to radical cystectomy
# Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>CR Rate at Anytime</th>
<th>Median Duration of CR in responders</th>
<th>Among all pts CR at 12 months</th>
<th>Median follow up (months)</th>
<th>Cystectomy Free Rate to date</th>
<th>% with Extra Vesical Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-803</td>
<td>80</td>
<td>71%</td>
<td>19.2 Months</td>
<td>40%</td>
<td>10.7</td>
<td>88%</td>
<td>1</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>97</td>
<td>41%</td>
<td>16.2 Months</td>
<td>20%</td>
<td>24.1</td>
<td>63%</td>
<td>3</td>
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<tr>
<td>Nadofaragene</td>
<td>103</td>
<td>53%</td>
<td>9.7 Months</td>
<td>24%</td>
<td>19.7</td>
<td>71%</td>
<td>1</td>
</tr>
</tbody>
</table>
Jelmyto delivery

1. Easy delivery to target area
2. Does not interfere with kidney function
3. Therapeutic activity: 4 to 6 hours

UCLA Urology
Chemoablation for Low-Grade Disease

- **OLYMPUS Trial of UGN-101**
  - 71 patients with known biopsy proven low-grade disease
  - Sample size for 90% power to detect a CR rate of 15%
  - 6-weekly instillations of UGN-101 followed by monthly maintenance therapy
  - UGN 4 mg of mitomycin C per 1 ml of gel

- **Interim Analysis**
  - 71 evaluable patients
  - 42 patients CR (59%)
  - Durability: 85% (17/20) disease-free at 12 mo F/U

*FDA Approved Jelmyto for low-grade UTUC in April 2020*
What about patients with high-grade UTUC?

- No approved intraluminal agents
  - BCG for UTUC may not be safe
  - Single-agent chemotherapy (e.g. MMC) is ineffective

- No effective minimally invasive options

- Paucity of clinical trials in UTUC
  - 24 trials in UTUC, only 3 include HG disease
  - No trials are organ-sparing
UroGen Pharma Announces Early Stage Feasibility Agreement with Janssen

*Focused Agreement is on Therapeutic Area of Mutual Interest*

April 23, 2019 08:00 AM Eastern Daylight Time

NEW YORK--(BUSINESS WIRE)--UroGen Pharma Ltd. (Nasdaq:URGN), a clinical-stage biopharmaceutical company developing treatments to address unmet needs in the field of uro-oncology, today announced that it has entered into an agreement with Janssen Research & Development, LLC (Janssen) to conduct an early-stage feasibility evaluation in a therapeutic area of mutual interest. UroGen and Janssen will each conduct certain activities under the terms of the agreement.
- **CTLA-4 and TLR 7/8 agonist** for high-grade non-muscle-invasive urothelial carcinoma
2.2 Trial Schema

Eligible patients:
- 18 years or older
- Histologically confirmed UC
- HG disease
- GFR at least 20mL/min
- ECOG 0-2
- Fit for RNU with LND

Exclusion criteria:
- Unresectable cN+ disease
- Distant metastatic disease
- Inability to tolerate MRU with gadolinium-based contrast
- Pure variant histology (differentiation and variant components allowed)

Primary outcomes:
- Overall response
  - Partial response (spT1 N0)
  - Complete response (pT0 N0)

Secondary outcomes:
- Treatment tolerability
- Treatment completion
- Dose reduction
- Surgical complications
  - Intraoperative complications
  - Perioperative complications within 30 days
- Biomarker analysis
  - Correlation of MRI and URS with pathologic response
  - PD-L1 status
  - Tissue-based biomarkers

Screening

Treatment

Outcomes

Pembrolizumab + Envortumab Vedotin

Pembrolizumab
(200mg IV on day 1 of a 21-day cycle x 3 cycles)

Enfortumab vedotin
(1.25mg/kg IV on days 1 and 8 of a 21-day cycle x 3 cycles)
Multitude of Targets
Conclusion

• Significant breakthroughs in the last decade
  – Checkpoint inhibitors alone and combination
  – Targeted therapy

• Many of the agents may be amenable to local delivery
  – Liquid form into the bladder
  – Gel form in the upper urinary tract

• Novel targets
  – Follow the lead of medical oncology
Thank You