Beyond Checkpoint Inhibition: New Therapeutic Approaches to Bladder Cancer

Daniel P. Petrylak, MD
Professor of Medicine and Urology
Director, GU Translational Working Group
Co Director, Signal Transduction Program
Smilow Cancer Center, Yale University
The Problem: met Urothelial Carcinoma

1. Immunotherapy is active only in a small subset of patients.
2. Resistance to immunotherapy is often seen.
3. Significant percentage of patients are not fit enough to receive Cisplatin-combination chemotherapy.
4. In this era of precision medicine, there is no FDA approved, biomarker-selected targeted therapy for mUC.
Rational for VEGF Blockade in Bladder Cancer

- Antiangiogenic agents, particularly anti-VEGFR-2 monoclonal antibodies (MAbs), may be capable of acting as chemosensitizing agents when given in combination with docetaxel, since this effect was demonstrated in mice when an anti-VEGFR-2 MAb, DC101, was combined with paclitaxel.

- Anti-VEGFR-1 MAbs may inhibit metastasis, based on the observed impact of the anti-VEGFR-1 MAb, MF1, on VEGFR-1-positive circulating hematopoietic progenitor cells in mice.
Binding of ramucirumab to VEGFR-2 and icrucumab to VEGFR-1 inhibits subsequent signaling.
Expression of VEGFR-2 in bladder cancer but not in normal urothelium
JCDC: Study Design

**Screen Randomize**

- 1:1:1
- Docetaxel 75 mg/m² day 1 of a 21-day cycle
  - N = 44
- Docetaxel 75 mg/m² day 1 + Ramucirumab 10 mg/kg day 1 of a 21-day cycle
  - N = 46
- Docetaxel 75 mg/m² day 1 + Icrucumab 12 mg/kg days 1 and 8 of a 21-day cycle
  - N = 49

Treat until disease progression or intolerable toxicity

Survival and safety follow-up

**Primary Endpoint:**
- Progression-free survival (PFS)

**Secondary Endpoints:**
- Overall survival, objective response rate, duration of response, safety, PK/PD and immunogenicity profile

**Stratification factors:**
- Visceral metastasis (yes vs. no)
- Prior antiangiogenic therapy (yes vs. no)
Progression-free Survival - Interim Analysis

Presented by: Daniel P. Petrylak, MD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event</th>
<th>Censored</th>
<th>Median PFS, wks (95% CI)</th>
<th>Stratified HR (95% CI)</th>
<th>Stratified log-rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC</td>
<td>35 (79.5)</td>
<td>9 (20.5)</td>
<td>10.4 (6.7, 16.9)</td>
<td>0.388 (0.22, 0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAM+DOC</td>
<td>29 (63.0)</td>
<td>17 (37.0)</td>
<td>22.0 (9.3, 30.0)</td>
<td>0.988 (0.61, 1.59)</td>
<td>0.932</td>
</tr>
<tr>
<td>ICR+DOC</td>
<td>39 (79.6)</td>
<td>10 (20.4)</td>
<td>7.0 (6.0, 12.0)</td>
<td>0.988 (0.61, 1.59)</td>
<td>0.932</td>
</tr>
</tbody>
</table>

Number at Risk:
- DOC: 44
- DOC+RAM: 46
- DOC+ICR: 49

Time (Weeks):
0 10 20 30 40 50 60 70 80 90 100 110 120 130

Progression-free Survival

Presented at the Genitourinary Cancers Symposium
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**RANGE (trial I4T-MC-JVDC): Study Design**

**Presented by**: Daniel P. Petrylak, MD

**Primary Objective**
- PFS

**Key Secondary Objectives**
- OS and ORR

**Trial Design**

- **Randomization**: 1:1
- **Treatment Groups**:
  1. **Docetaxel 75 mg/m² + Placebo 10 mg/kg I.V. on day 1 of a 21-day cycle**
     - N = 262
  2. **Docetaxel 75 mg/m² + Ramucirumab 10 mg/kg I.V. day 1 of a 21-day cycle**
     - N = 262

**Treatment Duration**
- Treat until disease progression or intolerable toxicity

**Important Inclusion Criteria**:
- Locally advanced or unresectable or metastatic UC and ECOG PS 0 or 1
- Progression on or after first-line platinum-based chemotherapy (≤ 14 months; or ≤ 24 months if prior treatment with one immune checkpoint inhibitor)

**Key Exclusion Criteria**:
- Hemoglobin < 9 g/dL
- Uncontrolled bleeding or thrombotic disorder
- Known untreated brain metastasis

**Oversight**
- Oversight by an IDMC
Phase I trial Pembrolizumab + Ramicurimab in Metastatic Cancer

• PI Overall Roy Herbst
  – Bladder Petrylak
  – Fuchs Gastric
AGS15E (ASG-15ME) in a Phase I Dose Escalation Trial in Patients (Pts) with Metastatic Urothelial Cancer

ANTIBODY DRUG CONJUGATE

- ASG-15ME is an antibody drug conjugate (ADC) with the following components:
  - Fully human monoclonal antibody IgG2k directed against SLITRK6
  - Protease-cleavable linker
  - Microtubule-disrupting agent monomethylauristatin-E (MMAE)
SLITRK6 Expression by IHC

- 47/50 (94%) were positive
- 27/50 (54%) had high expression (H-Scores $\geq 150$)
## Patient Characteristics

<table>
<thead>
<tr>
<th>Age, years: Median (range)</th>
<th>64.0 (30, 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG Performance Status 1, N (%)</td>
<td>44 (81.5)</td>
</tr>
<tr>
<td>Male Sex, N (%)</td>
<td>46 (85.2)</td>
</tr>
</tbody>
</table>

## Disease Characteristics

<table>
<thead>
<tr>
<th>Site of Primary Tumor</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>34 (63.0)</td>
</tr>
<tr>
<td>Renal Pelvis</td>
<td>11 (20.4)</td>
</tr>
<tr>
<td>Ureter</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Urethra</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of Metastases</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral</td>
<td>30 (55.6)</td>
</tr>
<tr>
<td>Liver</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>Lung</td>
<td>24 (44.4)</td>
</tr>
</tbody>
</table>

## Prior Treatments

<table>
<thead>
<tr>
<th>Platinum based Chemotherapy</th>
<th>52 (96.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin-based</td>
<td>36 (66.7)</td>
</tr>
<tr>
<td>Carboplatin-based</td>
<td>23 (42.6)</td>
</tr>
</tbody>
</table>

| ≥ 2 prior systemic therapies (metastatic) | 30 (55.6%) |

| Taxanes | 23 (42.6) |
| Immune Checkpoint Inhibitors (CPI) | 17 (31.5) |

| ≤ 3 Months from Last Chemotherapy | 30 (55.6) |

| GFR < 60 mL/min | 31 (57.4%) |
| Hgb < 10 g/dL | 9 (16.7%) |

## TEAE (≥20%)

<table>
<thead>
<tr>
<th>TEAE (≥20%)</th>
<th>Related AEs (Any Grade) (N = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue / Asthenia</td>
<td>24 (44.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (22.2%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (20.4%)</td>
</tr>
</tbody>
</table>

## Grade ≥ 3 AEs (5%) N=54

<table>
<thead>
<tr>
<th>AEs</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>
AGS15E (ASG-15ME) in a Phase I Dose Escalation Trial in Patients (Pts) with Metastatic Urothelial Cancer
### ASG-15ME Best Overall Response: Evaluable Subjects*  

<table>
<thead>
<tr>
<th>Response Category, N (%)</th>
<th>0.5 mg/kg (N=8)</th>
<th>0.75 mg/kg (N=14)</th>
<th>1 mg/kg** (N=20)</th>
<th>1.25 mg/kg (N=6)</th>
<th>Total (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5.0)</td>
<td>0 (0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>1 (12.5)</td>
<td>4 (28.6)</td>
<td>9 (45.0)</td>
<td>3 (50.0)</td>
<td>17 (35.4)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>2 (25.0)</td>
<td>6 (42.9)</td>
<td>4 (20.0)</td>
<td>2 (10)</td>
<td>14 (29.2)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>5 (62.5)</td>
<td>2 (14.3)</td>
<td>5 (25.0)</td>
<td>0 (0)</td>
<td>12 (25.0)</td>
</tr>
<tr>
<td>Non-Evaluable</td>
<td>0 (0)</td>
<td>2 (14.3)</td>
<td>1 (5.0)</td>
<td>1 (16.7)</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>ORR (CR+PR) N, (%)</td>
<td>1 (12.5)</td>
<td>4 (28.6)</td>
<td>10 (50.0)</td>
<td>3 (50.0)</td>
<td>18 (37.5)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.3, 52.7</td>
<td>8.4, 58.1</td>
<td>27.2, 72.8</td>
<td>11.8, 88.2</td>
<td>24.0, 52.6</td>
</tr>
<tr>
<td>Disease Control Rate (CR+PR +SD)</td>
<td>3 (37.5)</td>
<td>10 (71.4)</td>
<td>14 (70.0)</td>
<td>5 (83.3)</td>
<td>32 (66.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.5, 75.5</td>
<td>41.9, 91.6</td>
<td>45.7, 88.1</td>
<td>35.9, 99.6</td>
<td>51.6, 79.6</td>
</tr>
</tbody>
</table>

*Evaluable Subjects are defined as subjects having at least one post-baseline assessment Response assessed per RECIST 1.1

**1mg/kg is the maximally tolerated dose and the preliminary RP2D
ASG-15ME is an antibody drug conjugate against SLITRK6, a type I transmembrane protein in the SLITRK family of neuronal receptors.

In a phase I dose escalation study in subjects with pretreated Metastatic Urothelial Cancer, ASG-15ME was well tolerated with the most common treatment related adverse events (AEs) being fatigue (44%), nausea (22%), and decreased appetite (20%).

The most common Grade ≥ 3 AEs were anemia (6%), increased lipase (6%), and urinary tract infection (6%).

The maximally tolerated dose (MTD) is 1mg/kg.

ASG-15ME shows encouraging anti-tumor activity with 1 CR and 17 PRs (ORR=38%) in patients with heavily pretreated mUC.

At the MTD the ORR was 50%.

Anti-tumor activity was observed in subjects with liver metastases (ORR=46%), in subjects previously treated with CPIs (ORR=43%), and in subjects previously treated with taxanes (41%).

The 1 mg/kg dose level has been expanded to further evaluate safety and confirm activity in patients previously treated with CPI.
ASG-22CE (ASG-22ME; enfortumab vedotin) in a Phase I Dose Escalation Trial in Patients (Pts) with Metastatic Urothelial Cancer
BISCA Y – Umbrella Study

A biomarker-directed study in patients with muscle-invasive bladder cancer

<table>
<thead>
<tr>
<th>Module</th>
<th>Treatment option</th>
<th>MOA</th>
<th>Biomarkers</th>
<th>Adjusted Prev</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Durvalumab* + AZD4547 OR AZD4547</td>
<td>FGFR inhibitor</td>
<td>FGFR3 mutations/fusions</td>
<td>~11%</td>
</tr>
<tr>
<td>B</td>
<td>Durvalumab* + Lynparza™</td>
<td>PARP inhibitor</td>
<td>ATM, BRCA1/2, HRR gene trunc or missense mut/del</td>
<td>~19%</td>
</tr>
<tr>
<td>B2</td>
<td>Durvalumab + Treme + Lynparza™</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Durvalumab* + AZD1775</td>
<td>WEE1 inhibitor</td>
<td>CCNE1 ampl MYC ampl</td>
<td>~46%</td>
</tr>
<tr>
<td>C2</td>
<td>Durvalumab + Treme + AZD1775</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Durvalumab*</td>
<td>PD-L1 only</td>
<td>None</td>
<td>~22%</td>
</tr>
</tbody>
</table>

*PD-L1

Assignment to module dependent on presence of biomarker

~11% ~22% ~46%
PI3K/AKT/mTOR pathway in Urothelial Carcinoma

PI3K
→ Akt
→ mTORC1
→ mTORC2

Cytoskeleton Organization

Cell Growth, Translation/Tumorigenesis

4E-BP
p70S6K

TSC 1
TSC 2

Ching CB et al. Lab Invest. 2010
Targeting mTORC1 in mUC

- Seront et al (Ann of Oncol 2012)
  - Phase II, N=37, 10mg a day of everolimus
    - 2 confirmed PR and 8 stable disease
    - 27% disease control rate at 8 weeks.
    - Exploratory biomarker studies showed: ? PTEN loss was seen in patients with progressive disease.

- Milowski et al: (BJU Int 2013)
  - Phase II, N=45, 10mg a day of everolimus
    - 2 patients had PR; one patient had near complete response; on therapy at 26 months
    - Additional 12 pts had tumor regression
An index patient with a major response to Everolimus

1/26/2010

3/11/2011

Milowski MI et al. BJU
An index patient with a major response to Everolimus

A.

B.
Genome Sequencing of Responders to Everolimus

C

ARID1A  KDM6A  TP53  FGFR3  NF2  TSC1
Q641*  Q331*  G279W  A83V  S249C
G1637W  E399*  R248C
S539fs  E39K  S249C
G414*  C242F
Q1262*  N239S  R248C
Q393*  S288*

Change from baseline (%)
-80  -60  -40  -20  0  20  40

TSC1-mutant  TSC1-wildtype
1.8  1.8  1.9  1.8  1.8  1.9  1.7  2.1  3.5  3.5  3.9  4.1  23

Treatment duration (mo.)

R692*
V220F
R509*
Q694*
E636fs

Iyer G et al Science
PI3K/AKT/mTOR pathway in Urothelial Carcinoma

- **PI3K**
- **Akt**
- **mTORC1**
- **mTORC2**

**Connections**:
- PI3K → Akt → mTORC1 → 4E-BP
- Akt → p70S6K
- Akt → Cell Growth, Translation/Tumorigenesis
- Akt → Cytoskeleton Organization
- TSC1, TSC2

References:
- Ching CB et al. Lab Invest. 2010
PI3K/AKT/mTOR pathway in Urothelial Carcinoma

PI3K

↓

Akt

↓

mTORC1

↓

mTORC2

↓

Cytoskeleton Organization

↓

Cell Growth, Translation/ Tumorigenesis

↓

4E-BP

p70S6K

↓

TSC1 TSC2

Ching CB et al. Lab Invest. 2010
PI3K/AKT/mTOR pathway in Urothelial Carcinoma

- PI3K
- Akt
- mTORC1
- mTORC2
- Cytoskeleton Organization
- Cell Growth, Translation/Tumorigenesis
- 4E-BP
- p70S6K
- TSC1
- TSC2

Everolimus

Ching CB et al. Lab Invest. 2010
TSC1 mutations in TCC

Frequency of TSC1 or TSC2 mutations: 8 to 15%.*

MLN-0128 (aka. TAK228): NCI Protocol 9767

- Potent, highly selective ATP-competitive inhibitor of mTOR kinase that exhibits dual specificity against both TORC1 and TORC2 complexes.
- Dual TORC1/2 inhibition mitigates the feedback activation of AKT, known to cause resistance to TORC1 selective inhibitors.
- Displays cellular inhibition of TORC1 and TORC2 pathways with IC50 less than 10 nM.
- Potential of greater clinical activity than the currently available rapalogs.
Hypothesis: MLN0128 in TSC1 mutated TCC

PI3K → Akt → mTORC1 → mTORC2

Cytoskeleton Organization

Cell Growth, Translation/Tumorigenesis

4E-BP, p70S6 K

Ching CB et al. Lab Investig. 2010
Hypothesis:
MLN0128 in TSC1 mutated TCC

- MLN0128 (TAK228)
- Cytoskeleton Organization
- Cell Growth, Translation/Tumorigenesis

PI3K → Akt → mTORC1

mTORC2

4E-BP, p70S6

TSC1

Ching CB et al. Lab Invest. 2010
TSC1 / TSC2 mutation sequencing to be done at Yale Profiling Lab by Dr. Jeff Sklar

Primary Endpoint: ORR N=25
TSC1 / TSC2 mutation sequencing to be done at Yale Profiling Lab by Dr. Jeff Sklar

OPEN as of 12/02/2016

Screening
Informed Consent
HPE, Labs, ECG, Registration
Tissue submission

Cycle 1

*Biopsy

Cycle 2

Until PD by RECIST v1.1 or

FOLLOW-UP

Significant Clinical or Laboratory abnormality will be followed until resolution or stable

Only if archival tissue no longer available
1 cycle = 28 days

2 cycles of therapy for the first 6 cycles, then after every 3 cycles thereafter

= RECIST Tumor Assessment:
Conclusions

- Checkpoint inhibition therapy demonstrates significant antitumor activity in cisplatin treated metastatic urothelial carcinoma
- Antiangiogenesis agents are being evaluated with chemotherapy and immune therapy for metastatic urothelial cancer
- ADC have activity in patients who have failed checkpoint inhibition therapy