State of the Art in Urothelial Cancers

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Outline

- Overview of urothelial carcinomas and their current management
- Discuss current approaches in the development of novel targeted agents in the treatment of urothelial cancer
Overview of Urothelial Carcinoma
Urothelial Carcinomas Are Malignant Tumours Arising From the Urothelial Epithelium

- Urothelial carcinomas are malignant tumours arising from the urothelial epithelium of the lower urinary tract (bladder and urethra) or upper urinary tract (renal pelvis and ureter)\(^1\)
- Bladder cancer accounts for 90-95% of urothelial carcinomas with \(\approx 430,000\) new cases and \(\approx 165,000\) deaths per year worldwide\(^1,2\)
- US\(^3\):  
  - \(74,000\) new cases of bladder cancer and 16,000 deaths in 2015
- Mexico, Central, and South America\(^2\):  
  - \(\approx 25,705\) new cases and 10,256 deaths per year

90-95% are bladder carcinoma

Common Presenting Symptoms

- Painless haematuria (≈80% of patients)
- Irritative symptoms (dysuria, frequency, urgency; invasive or high-grade tumours)
- Bone pain (advanced metastatic cases) or flank pain (from retroperitoneal metastases or ureteral obstruction)
Bladder Cancer: Grading and Staging

ISUP - International Society of Urological Pathology.
PUNLMP - papillary urothelial malignancy of low malignant potential.
Management of Non–Muscle-Invasive Bladder Cancers (NMIBCs)
Prognosis of Non–Muscle-Invasive Bladder Cancers (NMIBCs)

- Bladder cancer is more common in men than women (3:1)
- At diagnosis, majority of bladder cancers (60%) are NMIBCs papillary tumours of low grade
- Recurrence: 50-70%, but infrequently progress to invasive disease (10-15%)
- 5-year survival of NMIBCs: 90%

Management of NMIBCs (ESMO Guideline)

- **Initial bladder tumour:**
  - Complete TURBT is the treatment of choice, followed by instillations of chemotherapy per risk stratification

- **High-risk NMIBC:**
  - A second TURBT is a reasonable option either before intravesical therapy or after

- **Very high-risk NMIBC** (eg. multiple grade 3 T1 tumours with TIS or increased depth of invasions):
  - Cystectomy may be considered
  - Cystectomy should be considered in patients with TIS or high-grade T1 failing Bacillus Calmette-Guérin (BCG) due to high risk of progression

Management of Muscle-Invasive Bladder Cancers (MIBCs)
Prognosis of Muscle-Invasive Bladder Cancers (MIBCs)

- 5-year survival: only \(\approx 50\%\)
- 50% develop metastatic disease
- Median survival for these patients: 12-15 months
Management of MIBCs (ESMO Guideline)


Randomised Phase III Neoadjuvant Chemotherapy Plus Cystectomy Compared to Cystectomy Alone

Stage T2-T4aN0M0
- Candidates for radical cystectomy
- No prior pelvic irradiation
- Adequate renal, hepatic, & hematologic function
- SWOG performance status of 0 or 1

N=317*

*10 patients were not eligible

Primary endpoint: OS

Radical Cystectomy
N=154

M-VAC
3 x 28 day cycles
- Methotrexate days 1, 15, & 22
- Vinblastine days 2, 15, & 22
- Doxorubicin & cisplatin on day 2
Followed by radical cystectomy
N=153

M-VAC→Radical Cystectomy vs Radical Cystectomy: OS (Primary Endpoint)

The Absence of Residual Disease Following M-VAC at the Time of Cystectomy Was Associated With Improved Survival

Meta-Analysis of the Role of Neoadjuvant Chemotherapy in MIBCs: OS, DFS, and Types of Chemotherapy

Results based on 11 randomised controlled trials with 3005 patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Chemotherapy type</th>
<th>Number of patients/events</th>
<th>HR (95% CI)</th>
<th>Effect p-value</th>
<th>Absolute benefit at 5 yrs (95% CI)</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>Single agent platinum</td>
<td>261/376</td>
<td>1.15 (0.90–1.47)</td>
<td>0.26</td>
<td>−5% (−14% to 4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platinum based combinations</td>
<td>1430/2433</td>
<td>0.86 (0.77–0.95)</td>
<td>0.003</td>
<td>5% (2% to 9%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>All trials</td>
<td>1691/2890</td>
<td>0.89 (0.81–0.98)</td>
<td>0.022</td>
<td>4% (0% to 7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single agent platinum</td>
<td>166/217</td>
<td>1.14 (0.83–1.55)</td>
<td>0.42</td>
<td>−5% (−16% to 7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platinum based combinations</td>
<td>1681/2629</td>
<td>0.78 (0.71–0.86)</td>
<td>&lt;0.0001</td>
<td>9% (5% to 12%)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>All trials</td>
<td>1847/2846</td>
<td>0.81 (0.74–0.89)</td>
<td>&lt;0.0001</td>
<td>8% (4% to 11%)</td>
<td></td>
</tr>
</tbody>
</table>

- Platinum-based neoadjuvant chemotherapy is associated with:
  - 5% absolute benefit in OS at 5 years
  - 9% absolute benefit in DFS at 5 years
Management of MIBCs (ESMO Guideline)

**Management of Local Disease**

Depending on the findings at TUR

**Muscle Invasive**

- Neoadjuvant Chemotherapy
  - Radical Cystectomy with Lymphadenectomy

Further Adjuvant Chemotherapy (limited data)

Adjuvant Chemotherapy (if no neoadjuvant)

Every three months follow up (see text)

Surgical Approaches in the Management of MIBCs (NCCN and ESMO Guidelines)

• Initial treatment (part of the workup)\(^1,2\):
  – TURBT to correctly identify the stages of MIBC

• Cystectomy\(^1,2\):
  – Radical cystectomy with extended lymphadenectomy is considered to be the standard treatment
  – Partial cystectomy (<5% of the cases) in select patients

Organ-Preserving Therapy for Patients Ineligible for or Preferred Not to Undergo Cystectomy

Organ Preservation Therapy (cystectomy ineligible, patient preference)

TURBT (should aim for complete)

Combined chemoradiotherapy 40 Gy

Combined chemoradiotherapy Total dose 55-64 Gy

Radiotherapy alone

Imaging + TURBT evaluation

Salvage cystectomy if persisting tumour

Complete Radiotherapy if complete response (CR)

Surveillance Cystoscopic evaluation (3 months) with TUR bladder biopsy (every 6 months)

The Role of Adjuvant Therapies in the Management of MIBCs
Management of MIBCs (ESMO Guideline)

Management of Local Disease

Depending on the findings at TUR

Muscle Invasive

Neoadjuvant Chemotherapy

Radical Cystectomy with Lymphadenectomy

Further Adjuvant Chemotherapy (limited data)

Adjuvant Chemotherapy (if no neoadjuvant)

Every three months follow up (see text)
The Role of Adjuvant Chemotherapy in MIBCs (Meta-analysis)

Results based on 9 randomised controlled trials with 945 patients

### OS

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OS (ES 95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin-based combinations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bono</td>
<td>0.65 (0.34-1.25)</td>
<td>9.83</td>
</tr>
<tr>
<td>Froith</td>
<td>0.74 (0.38-1.53)</td>
<td>8.61</td>
</tr>
<tr>
<td>Otto</td>
<td>0.82 (0.49-1.39)</td>
<td>12.37</td>
</tr>
<tr>
<td>Lehmann</td>
<td>0.75 (0.45-1.18)</td>
<td>14.22</td>
</tr>
<tr>
<td>Studer</td>
<td>0.57 (0.31-1.05)</td>
<td>10.57</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.880)</td>
<td>0.74 (0.56-0.94)</td>
<td>61.95</td>
</tr>
<tr>
<td>Single agent cisplatin:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studer</td>
<td>1.11 (0.45-2.73)</td>
<td>6.35</td>
</tr>
<tr>
<td>Subtotal (I² = %, p = .)</td>
<td>1.11 (0.45-2.73)</td>
<td>6.35</td>
</tr>
<tr>
<td>Gemcitabine-cisplatin combinations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian</td>
<td>1.29 (0.84-1.99)</td>
<td>14.83</td>
</tr>
<tr>
<td>Spanish</td>
<td>0.38 (0.22-0.65)</td>
<td>12.13</td>
</tr>
<tr>
<td>Subtotal (I² = 91.8%, p = 0.000)</td>
<td>0.71 (0.21-2.35)</td>
<td>26.90</td>
</tr>
<tr>
<td>Overall (I² = 46.5%, p = 0.080)</td>
<td>0.77 (0.59-1.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random-effects analysis.

### DFS

<table>
<thead>
<tr>
<th>Study ID</th>
<th>DFS (ES 95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin-based combinations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bono</td>
<td>0.73 (0.46-1.15)</td>
<td>14.06</td>
</tr>
<tr>
<td>Froith</td>
<td>0.46 (0.22-0.81)</td>
<td>10.78</td>
</tr>
<tr>
<td>Otto</td>
<td>0.75 (0.40-1.40)</td>
<td>11.73</td>
</tr>
<tr>
<td>Lehmann</td>
<td>0.35 (0.18-0.71)</td>
<td>10.96</td>
</tr>
<tr>
<td>Studer</td>
<td>0.96 (0.45-2.12)</td>
<td>9.55</td>
</tr>
<tr>
<td>Subtotal (I² = 26.7%, p = 0.244)</td>
<td>0.92 (0.45-1.87)</td>
<td>57.28</td>
</tr>
<tr>
<td>Single agent cisplatin:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studer</td>
<td>1.02 (0.59-1.81)</td>
<td>12.54</td>
</tr>
<tr>
<td>Subtotal (I² = %, p = .)</td>
<td>1.02 (0.59-1.81)</td>
<td>12.54</td>
</tr>
<tr>
<td>Gemcitabine-cisplatin combinations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>0.38 (0.25-0.58)</td>
<td>15.14</td>
</tr>
<tr>
<td>Italian</td>
<td>1.08 (0.70-1.66)</td>
<td>15.04</td>
</tr>
<tr>
<td>Subtotal (I² = 91.3%, p = 0.001)</td>
<td>0.64 (0.23-1.78)</td>
<td>30.18</td>
</tr>
<tr>
<td>Overall (I² = 63.7%, p = 0.007)</td>
<td>0.66 (0.46-0.92)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random-effects analysis.

Current ESMO and NCCN Treatment Guidelines on Adjuvant Therapies in MIBCs

**ESMO:**
- Adjuvant chemotherapy\(^1\)
  - Insufficient evidence to support routine use of adjuvant chemotherapy in clinical practice
  - High-risk patients, those with extravesical and/or node-positive disease that may not have received neoadjuvant chemotherapy will benefit most from adjuvant chemotherapy

**NCCN:**
- Adjuvant chemotherapy\(^2\)
  - Adjuvant chemotherapy may delay recurrences in those at high risk for relapse
  - A minimum of 3 cycles of a cisplatin-based combination may be used

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Treatment of Advanced and/or Metastatic Disease
Prognostic Factors in First-line Advanced Disease

Risk factors:
0 = KPS > 80, no visceral mets
1 = KPS < 80, or visceral mets
2 = KPS < 80, and visceral mets

Proportion surviving

Time in months

n=199

ESMO¹:

- Cisplatin-containing combination chemotherapy with GC or MVAC is standard
- GC is less toxic than MVAC
- MVAC is better tolerated with G-CSF support
- ddMVAC with G-CSF support may be suitable for fit patients with limited advanced disease
- Carboplatin-containing regimen or single-agent taxane or gemcitabine may be used in patients unfit for cisplatin-containing regimens

NCCN²:

- GC and ddMVAC are commonly used regimens in the first-line
- MVAC is inferior to ddMVAC in toxicity and efficacy and inferior to GC in terms of toxicity and should no longer be used
- Triplet regimen (PGC) currently not recommended
- Non–cisplatin-containing regimens may be considered for patients who cannot tolerate cisplatin (renal impairment or other comorbidities)

GC = Gemcitabine and cisplatin; ddMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; PGC = Paclitaxel, gemcitabine, and cisplatin

Second-line Treatment of Bladder Carcinoma

ESMO¹:
- Second-line phase 2 data are highly variable, with results depending on patient selection
- Vinflunine + BSC vs BSC:
  - The only randomised phase 3 showing a modest activity (8.6% ORR)
  - Favourable safety profile with a survival benefit in favor of vinflunine
  - The only option approved in Europe

NCCN²:
- Second-line chemotherapy data are highly variable and unclear in this setting
- No standard therapy exists
- NCCN panel highly recommends enrollment in a clinical trial

The Need for Better Therapeutic Options for the Treatment of Metastatic Bladder Cancer

- The ORRs to standard cisplatin-containing combination therapy: 50-70% (CR: 15-25%)¹
- However, almost all responding patients will ultimately relapse within the first year¹
- The median survival of these patients is only about 12 months¹
- Plateaued in the improvements in cytotoxic chemotherapy²
  - Adding paclitaxel to cisplatin or increasing the dose intensity of cisplatin have not translated to increased survival benefit
- No drug has been approved by the FDA for urothelial carcinoma in over two decades³,⁴
- Better treatment options are urgently needed¹,²

Targeted Approaches for the Treatment of Advanced and/or Metastatic Bladder Cancer
High Rates Of Somatic Mutations in High-Grade Muscle-Invasive Bladder Carcinoma

Pathways Mutated in High-Grade Muscle-Invasive Bladder Carcinoma

Genomic analysis of 131 high-grade and muscle-invasive bladder carcinomas by TCGA

Potential Targets in High-Grade Muscle-Invasive Bladder Carcinoma

Whole genome sequencing revealed TSC1 and NF2 inactivating mutations. In vitro evaluation shows TSC1 sensitizes urothelial cancer cells to mTOR inhibition.

G Iyer et al. Science 2012;338:221
BGJ398 has clinical activity in patients with FGFR3-mutated urothelial carcinoma

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Tumor</th>
<th>Schedule (125 mg/day)</th>
<th>Best Overall Response (% tumor change)</th>
<th>Duration on Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>88 ♀</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>PR (-48%)</td>
<td>5 cycles</td>
</tr>
<tr>
<td>62 ♀</td>
<td>FGFR3-mutated</td>
<td>3 weeks on/1 week off</td>
<td>PR (-45%)</td>
<td>9+ cycles</td>
</tr>
<tr>
<td>53 ♂</td>
<td>FGFR3-mutated</td>
<td>3 weeks on/1 week off</td>
<td>SD (-28%)</td>
<td>4 cycles</td>
</tr>
<tr>
<td>77 ♂</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>SD (-27%)</td>
<td>4 cycles</td>
</tr>
<tr>
<td>52 ♂</td>
<td>FGFR3-mutated</td>
<td>Continuous</td>
<td>SD (+11.4%)</td>
<td>3 cycles</td>
</tr>
<tr>
<td>80 ♀</td>
<td>FGFR1-amplified</td>
<td>3 weeks on/1 week off</td>
<td>PD</td>
<td>&lt; 2 weeks</td>
</tr>
</tbody>
</table>

In FGFR3-mutated urothelial carcinoma
- Overall response rate 40% (2/5)
- Disease control rate 100% (5/5)

Clinical Activities of JNJ-42756493 in Patients with FGFR Aberration in Tumor Treated at ≥ 6mg Dose

UC with FGFR3 Translocation

Sequist. AACR 2014.
Bahleda. ASCO 2014.
Somatic ERCC2 Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma


B

- Responders vs. Nonresponders
- Mutations by Type: Missense, Splice site, In-frame indel, Nonsense
- Cases with mutations by type
- Genes: TP53, RB1, KDM6A, AFRDA, ERCC2
- Allelic fraction
- J. Bellmunt 2015
Mutations of tyrosine kinase receptors such as EGFR, HER2, HER3, and FGFR3 activate the MAP kinase pathway and PI3K pathways. Altered cell-cycle regulatory pathways. Abnormalities in histone modification factors.

ErbB Family Inhibition in Treatment of Advanced and/or Metastatic Bladder Cancer
ErbB Family in Bladder Carcinoma

- **EGFR:**
  - EGFR is overexpressed in MIBC (35-53%) relative to NMIBC and normal tissues\(^1\)
  - Amplification: 9% (TCGA study)\(^2\)

- **ErbB2/HER2:**
  - Mutation or amplification: 9% (TCGA study)\(^1\)
  - mRNA levels were highly up-regulated in NMIBC and MIBC samples vs normal tissues\(^3\)
  - Expression correlates with metastatic MIBC and tumour recurrence\(^4\)

- **ErbB3:**
  - Mutation: 6%\(^1\)
  - Reported to be associated with tumour size, number of tumours, and histological grade\(^5\)

- **ErbB4**
  - Reported to be underexpressed in NMIBC and MIBC; clinical relevance not clear\(^6\)

Prognostic Value of HER2/ErbB2 in Bladder Carcinoma

- Protein overexpression or gene amplifications reported to be associated with negative prognostic values\(^1\)

<table>
<thead>
<tr>
<th>Author/reference</th>
<th>Correlative outcome/HER2 marker</th>
<th>Patients/Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chakravarti et al [61]</td>
<td>lower complete response rate to chemoradiation / protein expression</td>
<td>73</td>
</tr>
<tr>
<td>Lönn et al [63]</td>
<td>aneuploidy, higher grade, shorter overall survival / protein expression</td>
<td>91</td>
</tr>
<tr>
<td>Lipponen et al [62]</td>
<td>higher stage and grade, shorter overall survival / gene amplification</td>
<td>178</td>
</tr>
<tr>
<td>Masliukova et al [68]</td>
<td>shorter relapse-free survival/ protein expression / protein expression</td>
<td>63</td>
</tr>
<tr>
<td>Kolla et al [69]</td>
<td>higher stage and grade, positive lymph node status, shorter disease-free and disease-related survival / protein expression</td>
<td>90</td>
</tr>
<tr>
<td>Krüger et al [70]</td>
<td>higher grade, shorter disease-free and disease-related survival / protein expression</td>
<td>138</td>
</tr>
<tr>
<td>Tsai et al [71]</td>
<td>site (bladder vs upper urinary tract), shorter progression-free and disease-related survival / protein expression</td>
<td>114</td>
</tr>
<tr>
<td>Skagias et al [72]</td>
<td>higher stage, grade, shorter disease-specific and overall survival / protein expression</td>
<td>80</td>
</tr>
<tr>
<td>Bolenz et al [73]</td>
<td>lymph nodes (vs primary site), lymphovascular invasion, higher recurrence risk, shorter disease-specific survival / protein expression</td>
<td>198</td>
</tr>
<tr>
<td>Alexa et al [74]</td>
<td>higher grade/ protein expression</td>
<td>59</td>
</tr>
</tbody>
</table>

### Preliminary Studies/Data With ErbB Family Receptor Inhibition in Bladder Carcinoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Setting</th>
<th>ORR (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib¹</td>
<td>31</td>
<td>2nd-line</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gefitinib²*</td>
<td>58</td>
<td>1st-line + GC</td>
<td>42.6</td>
<td>7.4</td>
<td>15.1</td>
</tr>
<tr>
<td>Cetuximab³</td>
<td>28</td>
<td>2nd-line ± paclitaxel</td>
<td>25</td>
<td>16.4 weeks</td>
<td>42 weeks</td>
</tr>
<tr>
<td>Cetuximab⁴</td>
<td>88</td>
<td>1st-line + GC</td>
<td>61.4 vs 57.1</td>
<td>7.6 vs 8.5</td>
<td>14.3 vs 17.4</td>
</tr>
<tr>
<td>Lapatinib⁵</td>
<td>59</td>
<td>2nd-line ± GC</td>
<td>1.7</td>
<td>8.6 weeks</td>
<td>17.9 weeks</td>
</tr>
<tr>
<td>Lapatinib⁶</td>
<td>232</td>
<td>1st-line maint. vs placebo</td>
<td>13.8 vs 7.8</td>
<td>4.6 vs 5.3</td>
<td>12.6 vs 11.9</td>
</tr>
<tr>
<td>Trastuzumab⁷</td>
<td>44</td>
<td>1st-line + PCaG</td>
<td>70</td>
<td>9.3</td>
<td>14.1</td>
</tr>
<tr>
<td>Afatinib⁸**</td>
<td>15</td>
<td>2nd-line platinum-refractory</td>
<td>21</td>
<td>8.1</td>
<td>--</td>
</tr>
</tbody>
</table>

GC = Gemcitabine + cisplatin; PCaG = Paclitaxel + carboplatin + gemcitabine; *No significant improvement vs GC alone.

#### Notes:
- All the responses were seen in patients with ErbB2 or ErbB3 molecular alterations**
- Time-to-progression: with molecular alteration vs without**
  - 8.1 months vs 1.8 months \((P=0.02)\)

Afatinib is approved in a number of markets, including the EU, Japan, Taiwan and Canada under the brand name GIOTRIF® and in the U.S. under the brand name GILOTRIF® for use in patients with distinct types of EGFR mutation-positive NSCLC. Registration conditions differ internationally, please refer to locally approved prescribing information. Afatinib is under regulatory review by health authorities in other countries worldwide. Afatinib is not approved in other indications.

Antiangiogenesis in Treatment of Advanced and/or Metastatic Bladder Cancer
Angiogenesis in Bladder Carcinoma

- Angiogenesis is an essential process for enabling tumour growth beyond a minimal size and for metastasis to other organs\(^1\)

- Expression of VEGF and its receptors VEGFR1 and VEGFR2 is associated with invasiveness of bladder cancer\(^2\)

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Increased VEGF Expression and High Microvessel Density Are Associated With Poor DFS in Bladder Cancer

*Biopsy specimens

## Preliminary Studies/Data With Antiangiogenic Agents in Bladder Carcinoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Setting</th>
<th>ORR (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib(^1)</td>
<td>77</td>
<td>2nd-line 50 mg/d; 4/2 schedule 37.5 mg daily</td>
<td>7</td>
<td>2.4</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>2.3</td>
<td>6</td>
</tr>
<tr>
<td>Sunitinib(^2)</td>
<td>38</td>
<td>1st-line cisplatin-ineligible</td>
<td>8</td>
<td>4.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Sorafenib(^3)</td>
<td>17</td>
<td>1st-line</td>
<td>0</td>
<td>1.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Sorafenib(^4)</td>
<td>22</td>
<td>2nd-line</td>
<td>0</td>
<td>2.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Sorafenib(^5)*</td>
<td>40</td>
<td>1st-line ± GC</td>
<td>52.5</td>
<td>6.3</td>
<td>11.3</td>
</tr>
<tr>
<td>Pazopanib(^6)</td>
<td>41</td>
<td>2nd-line</td>
<td>17.1</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Bevacizumab(^7)</td>
<td>43</td>
<td>1st-line ± GC</td>
<td>72</td>
<td>8.2</td>
<td>19.1</td>
</tr>
<tr>
<td>Bevacizumab(^8)</td>
<td>51</td>
<td>1st-line + GCa</td>
<td>49</td>
<td>6.5</td>
<td>13.9</td>
</tr>
<tr>
<td>Ramucirumab(^9)**</td>
<td>90</td>
<td>2nd-line + Doc</td>
<td>19.6 vs 4.5</td>
<td>5.1 vs 2.4</td>
<td>Pending</td>
</tr>
</tbody>
</table>

GC = gemcitabine and cisplatin; Gca = gemcitabine and carboplatin

*No significant differences in ORR, median PFS or OS between the 2 arms

**There’s a significant improvement in median PFS in favor of ramucirumab + docetaxel vs docetaxel arm

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## Ongoing Trials With Antiangiogenic Agents in Bladder Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patients</th>
<th>Regimen</th>
<th>1° Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (NCT00942331)</td>
<td>1st-line</td>
<td>GC ± Bev</td>
<td>OS</td>
<td>This study is ongoing but not recruiting participants; completed accrual</td>
</tr>
<tr>
<td>Ramucirumab (NCT02426125)</td>
<td>Patients with locally advanced or unresectable or metastatic urothelial carcinoma who progressed on or after platinum-based therapy</td>
<td>Ram + docetaxel vs placebo + docetaxel</td>
<td>PFS</td>
<td>Currently recruiting</td>
</tr>
</tbody>
</table>

Immunotherapy in the Treatment of Advanced and/or Metastatic Bladder Cancer
• Multiple costimulatory and inhibitory interactions regulate cytotoxic T-cell responses

PD-L1 (B7-H1) Expression Is Associated With Increased Stage and Survival in Bladder Carcinoma

167 patients with organ-confined urothelial cell carcinoma of the bladder

Immune Checkpoint Inhibition in the Treatment of Bladder Carcinoma

- Tumour-specific T-cell recognition in the periphery
- Lymphocyte priming to tumour antigens

Anti-PD-1/PD-L1 mAbs

- Immune checkpoints play an important role in suppressing the body’s antitumour response

Anti-PD-1/PD-L1 in Heavily Pretreated Metastatic Urothelial Cancers Including Bladder Carcinoma

**Atezolizumab (MPDL3280A)**

- **ORR:**
  - IC2/3: 50%; IC0/1: 17%

- **Median PFS:**
  - IC2/3: 6 months; IC0/1: 1 month

- **Median OS:**
  - IC2/3: Not reached; IC0/1: 8 months

**Pembrolizumab**

- **ORR:** 28%
- **Median PFS:** 2 months
- **Median OS:** 12.7 months

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## Phase 3 Trials With Immunotherapeutic Agents in Urothelial/Bladder Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patients</th>
<th>Regimen</th>
<th>1° Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>Recurrent or progressive metastatic urothelial cancers</td>
<td>Pembrol vs paclitaxel or docetaxel or vinflunine</td>
<td>OS, PFS</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>Atezolizumab (MPDL3280A) (NCT02302807)</td>
<td>Locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy</td>
<td>Atezo vs paclitaxel or docetaxel or vinflunie</td>
<td>OS</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>Atezolizumab (MPDL3280A) (NCT02450331)</td>
<td>Patients with PD-L1 positive, high-risk muscle-invasive bladder cancer after cystectomy</td>
<td>Atezo vs placebo</td>
<td>DFS</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>MEDI4736 (NCT02516241)</td>
<td>Unresectable stage IV urothelial bladder cancer</td>
<td>MEDI + tremelimumab vs MEDI vs platinum-doublet</td>
<td>PFS</td>
<td>Not yet recruiting</td>
</tr>
</tbody>
</table>

Current Issues With the Development of Targeted Agents in the Treatment of Bladder Carcinoma
Current Development of Targeted Therapies in the Treatment of Bladder Carcinoma

• With a few exceptions, the results of current trials evaluating targeted agents for the treatment of bladder carcinoma have not been particularly promising.

• In general, there’s a lack of genetic pre-selection of patients enrolled into these studies.

• Novel trial design based on the presence of specific genetic alteration or driver mutations may improve study outcome and expedite the development of new treatment options.

• Improvement in sequencing technology (eg. NGS) has allowed the identification of a number of genetic alterations as potential targets; however, more efforts are needed to establish/validate these alterations as key driver mutations in order to increase clinical success.

NGS = next-generation sequencing

Summary/Conclusions

• Surgical resection (TURBT) with or without intravesical therapy is the main therapeutic approach for the treatment of NMIBCs.

• For patients with MIBCs, neoadjuvant chemotherapy and cystectomy are main key therapeutic approaches. Adjuvant chemotherapy may also be considered in select patients.

• Cisplatin-containing combination chemotherapies are the standard-of-care in the management of advanced or metastatic disease.

• However, the majority of responding patients will relapse within the first year, and the median OS is only 12 months. Therefore, there’s an urgent need for more effective treatment options.

Seront E et al. Can Treat Rev. 2015;41;341-53.
• A better understanding of the pathobiology of urothelial cancer has led to the identification of key genetic lesions and survival pathways and the development of agents targeting these genetic alterations or survival pathways for the treatment of this disease

• However, preliminary studies with these targeted agents have been disappointing

• More efforts in translation research and in innovative trial design are needed to expedite the development of new and more viable treatment options
Back-up
Management of Metastatic Bladder Carcinoma (ESMO Guideline)

Patients with poor comorbid status or impaired renal function “unfit”

- Carboplatin-based regimens or single-agents: taxane, gemcitabine

- PS≤2 + Poor renal function

  - Clinical trial

- Best Supportive Care

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

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

  - Progression > 12 months
    - 1. Platinum based rechallenge

Cisplatin-Containing Combination Chemotherapy Is the Standard-of-Care in 1st-line Bladder Carcinoma

- GC provides a similar survival advantage to MVAC with a better safety profile and tolerability