SYSTEMIC CHEMOTHERAPY IS THE STANDARD FOR mUC

YES vs NO

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DISCLOSURE OF INTEREST

- Advisory role:
  - MSD, Pfizer, BMS, Astellas, Janssen, Clovis, Bayer, Roche

- Speaker role:
  - Pfizer, MSD, Astellas, Sanofi Aventis, Janssen, Bayer, BMS, Roche, AstraZeneca

- Research funding:
  - Takeda, Pfizer, MSD
CHEMOTHERAPY WILL BE “THE OPTION”

- In 1\textsuperscript{st} line cisplatin eligible patients: **DEFINITELY YES**

- In 1\textsuperscript{st} line cisplatin ineligible PD-L1 negative patients: **YES**

- In 1\textsuperscript{st} line cisplatin ineligible PD-L1 positive patients: **PROBABLY NOT**

- In 2\textsuperscript{nd} line post-platinum: **DEFINITELY NOT**

- In 3\textsuperscript{rd} line post-platinum and IO: **MAYBE YES**

*Pending Phase IIIs with IO single agent or doublet IO-chemotherapy...*
Combination chemotherapy improves survival

**Overall survival**

- **12.5 months** for DDP (n=120)
- **8.2 months** for MVAC (n=126)
- **p=0.0002**

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>DDP n=120</th>
<th>MVAC n=126</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR, %</strong></td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td><strong>PR, %</strong></td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td><strong>PFS, months</strong></td>
<td>4.3</td>
<td>10</td>
</tr>
</tbody>
</table>

CR, complete response; DDP, cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; PFS, progression-free survival; PR, partial response.


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**NCCN Guidelines Version 5.2018**

**Bladder Cancer**

**PRINCIPLES OF SYSTEMIC THERAPY**

**First-line systemic therapy for locally advanced or metastatic disease (Stage IV)**

- **Cisplatin eligible**
  - Preferred regimens
    - Gemcitabine and cisplatin (category 1)
    - DDMVAC with growth factor support (category 1)**

**NCCN**
National Comprehensive Cancer Network®
FIRST LINE CISPLATIN ELIGIBLE

NCT02853305 (KEYNOTE-361) \(^3\) N=990
- First-line unresectable or metastatic
- ECOG PS ≤2
Co-primary endpoints: PFS and OS

Pembrolizumab + cisplatin/gemcitabine OR
Pembrolizumab + carboplatin/gemcitabine

NCT02516241 (DANUBE) \(^2\) N=1,005
- First-line unresectable stage IV
- Eligible/ineligible for cisplatin-based chemotherapy
Co-primary endpoints: PFS and OS

Durvalumab
Durvalumab + tremelimunumab
Cisplatin + gemcitabine OR carboplatin + gemcitabine

NCT02807636 (IMvigor130) \(^1\) N=1,200
- First-line cisplatin-ineligible, locally advanced/metastatic
- ECOG PS ≤2
Co-primary endpoints: PFS, OS and safety

Atezolizumab
Platinum-based chemotherapy + atezolizumab
Cisplatin + gemcitabine OR carboplatin + gemcitabine

NCT03036098 (CheckMate-901) \(^4\) N=897
- First-line unresectable or metastatic
- ECOG PS ≤1
Co-primary endpoints: PFS and OS

Nivolumab + ipilimumab
Nivolumab + cisplatin + gemcitabine
Cisplatin + gemcitabine OR carboplatin + gemcitabine
# First Line Cisplatin Ineligible

## PD-L1 Positive

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab INVIGOR 210 cohort 1 ASCO 2018</th>
<th>Pembrolizumab KEYNOTE 052 ASCO 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>119</td>
<td>370</td>
</tr>
<tr>
<td><strong>Cisplatin ineligibility</strong></td>
<td>Renal impairment ECOG PS2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21%</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>66%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>ORR: Overall population</strong></td>
<td>24% CR: 8.0%</td>
<td>28.9% CR: 8.1%</td>
</tr>
<tr>
<td></td>
<td>IC0: 21%</td>
<td>CPS&lt;10%: 23%</td>
</tr>
<tr>
<td></td>
<td>IC1: 23%</td>
<td>CPS≥10%: 47.3%</td>
</tr>
<tr>
<td></td>
<td>IC2/3: 28%</td>
<td></td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td>16.3 m 1-year OS rate 58%</td>
<td>11.5 m 1-year OS rate 47%</td>
</tr>
<tr>
<td></td>
<td>12m (PD-L1+)</td>
<td>18.5m (PD-L1+)</td>
</tr>
<tr>
<td><strong>Treatment related adverse event (all/grade 3-4)</strong></td>
<td>66% / 16%</td>
<td>67% / 20%</td>
</tr>
</tbody>
</table>

FIRST LINE CISPLATIN INELIGIBLE

PD-L1 NEGATIVE

PD-L1 negative patients treated with IO monotherapy had worse outcome than those treated with gem/carbo in KEYNOTE-361 and IMvigor130

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm612484.htm
### NCCN Guidelines Version 5.2018
#### Bladder Cancer

## PRINCIPLES OF SYSTEMIC THERAPY

<table>
<thead>
<tr>
<th>Cisplatin ineligible</th>
<th><strong>Preferred regimens</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Gemcitabine and carboplatin&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Atezolizumab&lt;sup&gt;12&lt;/sup&gt; (only for patients whose tumors express PD-L1&lt;sup&gt;a&lt;/sup&gt; or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)</td>
</tr>
<tr>
<td></td>
<td>• Pembrolizumab&lt;sup&gt;13&lt;/sup&gt; (only for patients whose tumors express PD-L1&lt;sup&gt;b&lt;/sup&gt; or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)</td>
</tr>
</tbody>
</table>

**Other recommended regimens**

- Gemcitabine<sup>14</sup>
- Gemcitabine and paclitaxel<sup>15</sup>

**Useful under certain circumstances**

- Ifosfamide, doxorubicin, and gemcitabine<sup>16</sup> (for patients with good kidney function and good PS)
SECOND LINE POST-PLATINUM

The beginning of the curve matters

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma


The National Comprehensive Cancer Network

NCCN Guidelines Version 5.2018
Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum) is recommended.

Preferred regimen
- Pembrolizumab (category 1)

Other recommended regimens
- Nab-paclitaxel
- Paclitaxel or docetaxel
- Gemcitabine
- Pemetrexed
THIRD LINE POST-PLATINUM AND IO

Response Rate to Chemotherapy After Immune Checkpoint Inhibition in Metastatic Urothelial Cancer


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**A**
Cohort A - chemotherapy naïve
- Immune therapy
- Chemotherapy

Cohort B - chemotherapy resistant
- Chemotherapy
- Immune therapy
- Chemotherapy

**B**
Cohort A - chemotherapy naïve
- At baseline
- After two cycles of gemcitabine and carboplatin

Cohort B - chemotherapy resistant
- Response to first-line CT
- After two cycles of gemcitabine and carboplatin

**C**
Graph showing change from baseline over time for Cohort A and Cohort B.

**D**
Graph showing progression over time for Cohort A and Cohort B.
Updated Results From the Enfortumab Vedotin Phase 1 (EV-101) Study in Patients With Metastatic Urothelial Cancer

J. Rosenberg,1 S.S. Sridhar,2 J. Zhang,3 D. Smith,4 J. Ruether,5 T.W. Flaig,6 J. Baranda,7 J. Lang,8 E.R. Pflimack,9 R. Sangha,10 E. Heath,11 J. Merchant,12 D. Quinn,13 S. Srir,14 C. Wu,16 E. Gartner,17 A. Melhem-Bertrandt,16 D. Petrylak18

Enfortumab Vedotin is an Antibody-Drug Conjugate Targeting Nectin-4

• Enfortumab vedotin (EV) consists of a fully humanized monoclonal antibody targeting Nectin-4 and the microtubule-disrupting agent monomethyl auristatin E, conjugated by a protease-cleavable linker
• Nectin-4, a transmembrane cell adhesion molecule,1 is highly expressed in cancer cells, particularly in urothelial cancers2
• Nectin-4 was found to be highly expressed in 93% of mUC patient samples3

Change in Tumor Burden From Baseline

![Graph showing change in tumor burden from baseline](image)

<table>
<thead>
<tr>
<th>Change in Tumor Burden From Baseline (%)</th>
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<tbody>
<tr>
<td>1.25 mg/kg (N=112)*</td>
</tr>
<tr>
<td>Confirmed complete response</td>
</tr>
<tr>
<td>Confirmed partial response</td>
</tr>
<tr>
<td>Confirmed ORR (95% CI)</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>DCR (95% CI)</td>
</tr>
</tbody>
</table>

| Abbreviations: DCR, disease control rate (ORR+FATD)/ORR; overall response rate (ORR+CR+PR); patients must have at least one post-baseline assessment; response assessed per RECIST 1.1; 95% CI based on the Clopper-Pearson method. |
• IO and chemotherapy have an impact on both tumor and the immune environment.

• Defining the optimal strategies (sequential/combination) will be one of the challenges of coming years.

• Treatment sequence strategy have to take into consideration the tumor underlying biology and the effect of prior exposure to systemic therapy (and radiation therapy).

• ...Especially to cisplatin chemotherapy (impact on mutational load?)
Envisioning the future of therapeutic options across the clinical stages

<table>
<thead>
<tr>
<th>Cis-eligibility</th>
<th>1L therapy</th>
<th>≥2L therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant/adjuvant setting</td>
<td>OLD PARADIGM: Cis-eligible: CT Cis-ineligible: IO, CT</td>
<td>OLD PARADIGM: Cis rechallenge Vinflunine/Taxane IO</td>
</tr>
</tbody>
</table>

IO-eligibility (PD-L1; TMB...); Anti-FGFR-eligibility; targeted therapy eligibility
Other strategies are possible…

Phase II randomized study of first-line avelumab with carboplatin-gemcitabine versus carboplatin-gemcitabine alone in patients with metastatic urothelial carcinoma ineligible for cisplatin-based therapy.


https://clinicaltrials.gov/ct2/show/NCT03390595
CONCLUSIONS:

• PD-1/PD-L1 inhibition is a revolution in the treatment of metastatic UC patients
• However a significant proportion of patients do not benefit from IO
• PD-L1 expression doesn’t allow patient selection in many settings
• Chemotherapy is therefore still here to stay
• Phase III are ongoing/pending both in first line (fit/unfit) and subsequent lines

It's not a matter on what is “the Standard”: Optimal sequence and combo IO-chemo are THE NEXT STEPS!