Systematic Literature Review (SLR) and Network Meta-Analysis (NMA) of First-Line Therapies (1L) for Locally Advanced/Metastatic Urothelial Carcinoma (la/mUC)

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Background

- Locally advanced or metastatic urothelial carcinoma (la/mUC) is an incurable disease with poor long-term survival.[1]
- The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guideline recommendation for first-line (1L) treatment of la/mUC is gemcitabine + cisplatin (GC) or gemcitabine + carboplatin (GCa). For patients whose disease has not progressed following a platinum-based therapy, avelumab maintenance therapy is recommended.[2,3]
- 1L treatment of la/mUC is an area of ongoing innovation and evaluation of novel treatment regimens with new clinical trials completed in recent years aiming to improve on standard of care (SOC).
- The objective of this study was to compare outcomes of all approved and investigational 1L regimens with SOC in the context of recently published data by updating and expanding a previously reported systematic literature review (SLR) and network meta-analysis (NMA) of phase 2/3 randomized controlled trials (RCTs).

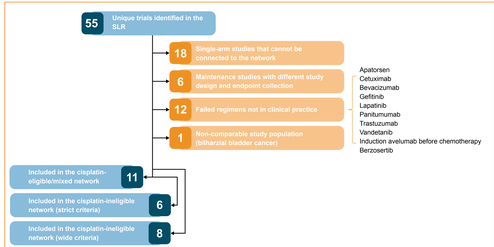
Methods

- An SLR conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and National Institute for Health and Care Excellence (NICE) guidelines, originally from January 2000 to May 2020, was updated to include publications through September 2021.
  - The SLR included phase 2/3 RCTs that assessed efficacy and safety of 1L regimens in la/mUC.
  - Studies in the non-metastatic setting or for previously treated la/mUC were excluded.
- In the NMA, 3 networks were formed:
  1. Cisplatin (cis)-eligible/mixed (studies including cis-eligible patients, and results from studies which included both cis-eligible and cis-ineligible patients, with investigator's choice of platinum chemotherapy).
  2. Cis-ineligible strict (studies including cis-ineligible patients only).
  3. Cis-ineligible wide (cis-ineligible patients expanded to include more contemporary trials and study arms, with an investigator's choice of carboplatin regardless of criteria for cis-ineligibility; KEYNOTE-361,[4,5] IMvigor130,[6,7] and DANUBE[8]).
- SOC in the cis-eligible/mixed network was GC, and in the cis-ineligible (strict and wide) network was GCa.
- In the cis-ineligible wide network trials, cis-ineligibility was guided by the Galsky criteria,[9] but final treatment choice was left to investigator's discretion.
- Analyses examined comparative efficacy of overall survival (OS) and progression-free survival (PFS) with 1L la/mUC regimens vs SOC (GC/GCa) using a Bayesian framework.[10]

Results

- Of 1,645 citations identified in the SLR that underwent title and abstract screening, 55 unique trials were selected for data extraction.
- Each of these was evaluated for potential inclusion in the NMA (**Figure 1**), which then comprised:
  - 11 studies in the cis-eligible/mixed network
  - 6 studies in the cis-ineligible (strict) network
  - 8 studies in the cis-ineligible (wide) network.

Figure 1. Study identification and attrition



SLR, systematic literature review.

- The DANUBE study[8] was the only PD-1/L1 inhibitor study to include results for the cis-ineligible subgroup and is therefore included in the cis-eligible/mixed network for the overall study population and the cis-ineligible network for the cis-ineligible subgroup.
- The KEYNOTE-361[4,5] and IMvigor130[6,7] studies provided data for the subgroup of patients with investigator's choice of carboplatin and are included in the cis-ineligible (wide) network for some outcomes.

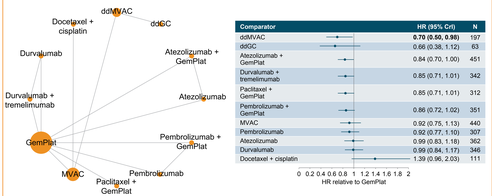
OS with SOC by treatment network

- Median (95% confidence interval [CI]) OS with SOC varied by treatment network:
  - 13.2 (12.4–14.0) months for cis-eligible/mixed
  - 9.7 (6.7–12.8) months for cis-ineligible (strict)
  - 12.0 (10.4–13.5) months for cis-ineligible (wide).

OS with treatment regimens compared with SOC by treatment network

- OS with different treatment regimens was similar to SOC within all treatment networks.
- For the cis-eligible/mixed network, hazard ratios (HRs) compared with SOC ranged from 0.7 to 1.4 with no statistically significant differences from SOC, with the exception of dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (ddMVAC; **Figure 2**).

Figure 2. Network diagram and HR for OS by treatment network for the cis-eligible/mixed network

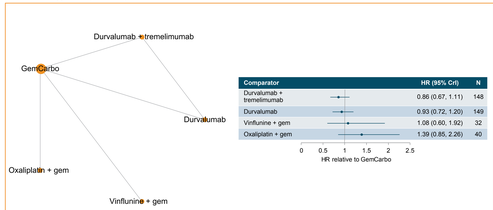


Comparator	HR (95% CrI)	N
ddMVAC	**0.70 (0.50, 0.98)**	197
ddGC	0.66 (0.38, 1.12)	63
Atezolizumab + GemPlat	0.84 (0.70, 1.00)	451
Durvalumab + tremelimumab	0.85 (0.71, 1.01)	342
Paclitaxel + GemPlat	0.85 (0.71, 1.01)	312
Pembrolizumab + GemPlat	0.86 (0.72, 1.02)	351
MVAC	0.92 (0.75, 1.13)	440
Pembrolizumab	0.92 (0.77, 1.10)	307
Atezolizumab	0.99 (0.83, 1.18)	362
Durvalumab	0.99 (0.84, 1.17)	346
Docetaxel + cisplatin	1.39 (0.96, 2.03)	111

cis, cisplatin; CrI, credible interval; ddGC, dose-dense gemcitabine + cisplatin; ddMVAC, dose-dense methotrexate + vinblastine + doxorubicin + cisplatin; GemPlat, gemcitabine + platinum; HR, hazard ratio; OS, overall survival.

- For the cis-ineligible (strict) network, HRs compared with SOC ranged from 0.9 to 1.4 with no statistically significant differences (**Figure 3**).

Figure 3. Network diagram and HR for OS by treatment network for the cis-ineligible (strict) network

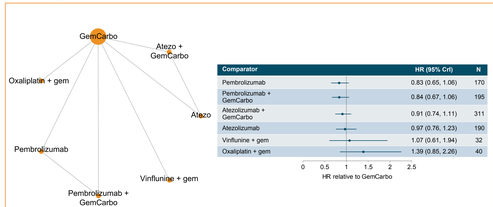


Comparator	HR (95% CrI)	N
Durvalumab + tremelimumab	0.86 (0.67, 1.11)	148
Durvalumab	0.93 (0.72, 1.20)	149
Vinflunine + gem	1.08 (0.60, 1.92)	32
Oxaliplatin + gem	1.39 (0.85, 2.26)	40

cis, cisplatin; CrI, credible interval; gem, gemcitabine; GemCarbo, gemcitabine + carboplatin; HR, hazard ratio; OS, overall survival.

- For the cis-ineligible (wide) network, HRs compared with SOC ranged from 0.8 to 1.4 with no statistically significant differences (**Figure 4**).

Figure 4. Network diagram and HR for OS by treatment network for the cis-ineligible (wide) network



Comparator	HR (95% CrI)	N
Pembrolizumab	0.83 (0.65, 1.06)	170
Pembrolizumab + GemCarbo	0.84 (0.67, 1.06)	195
Atezolizumab + GemCarbo	0.91 (0.74, 1.11)	311
Atezolizumab	0.97 (0.76, 1.23)	190
Vinflunine + gem	1.07 (0.61, 1.94)	32
Oxaliplatin + gem	1.39 (0.85, 2.26)	40

Atezo, atezolizumab; cis, cisplatin; CrI, credible interval; gem, gemcitabine; GemCarbo, gemcitabine + carboplatin; HR, hazard ratio; OS, overall survival.

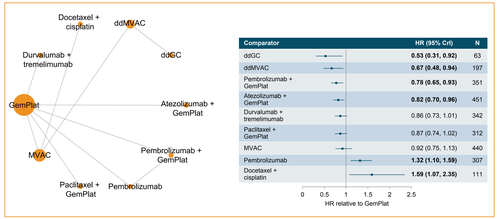
PFS with SOC by treatment network

- Median (95% CI) PFS with SOC was 6.6 (6.3–6.9) months for the cis-eligible/mixed network, 5.6 (5.0–6.3) months for cis-ineligible (strict), and 5.6 (5.0–6.3) months for cis-ineligible (wide).

PFS with treatment regimens compared with SOC by treatment network

- PFS with different treatment regimens was similar to SOC within the cis-ineligible strict and wide treatment networks as all HR credible intervals (CrIs) for PFS crossed or approached 1.
- For the cis-eligible/mixed network, HRs compared with SOC ranged from 0.5 to 1.6 with significantly longer PFS reported for dose-dense GC, ddMVAC, pembrolizumab + gemcitabine + platinum (GemPlat), atezolizumab + GemPlat, and significantly shorter PFS for pembrolizumab and docetaxel + cisplatin (**Figure 5**).

Figure 5. Network diagram and HR for PFS by treatment network for the cis-eligible/mixed network

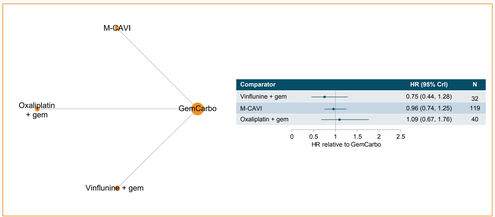


Comparator	HR (95% CrI)	N
ddGC	**0.53 (0.31, 0.92)**	63
ddMVAC	**0.67 (0.48, 0.94)**	197
Pembrolizumab + GemPlat	**0.78 (0.65, 0.93)**	351
Atezolizumab + GemPlat	**0.82 (0.70, 0.96)**	451
Durvalumab + tremelimumab	0.86 (0.73, 1.01)	342
Paclitaxel + GemPlat	0.87 (0.74, 1.02)	312
MVAC	0.92 (0.75, 1.13)	440
Pembrolizumab	**1.32 (1.10, 1.59)**	307
Docetaxel + cisplatin	**1.59 (1.07, 2.35)**	111

cis, cisplatin; CrI, credible interval; ddGC, dose-dense gemcitabine + cisplatin; ddMVAC, dose-dense methotrexate + vinblastine + doxorubicin + cisplatin; GemPlat, gemcitabine + platinum; HR, hazard ratio; PFS, progression-free survival.

- For the cis-ineligible (strict) network, HRs compared with SOC ranged from 0.8 to 1.1 with no statistically significant differences (**Figure 6**).

Figure 6. Network diagram and HR for PFS by treatment network for the cis-ineligible (strict) network

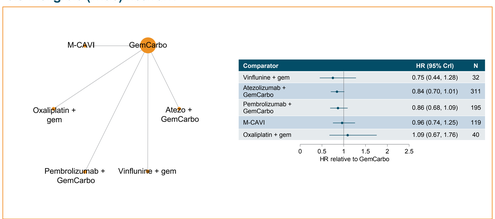


Comparator	HR (95% CrI)	N
Vinflunine + gem	0.75 (0.44, 1.28)	32
M-CAVI	0.96 (0.74, 1.25)	119
Oxaliplatin + gem	1.09 (0.67, 1.76)	40

cis, cisplatin; CrI, credible interval; gem, gemcitabine; GemCarbo, gemcitabine + carboplatin; HR, hazard ratio; M-CAVI, methotrexate + carboplatin + vinblastine; PFS, progression-free survival.

- For the cis-ineligible (wide) network, HRs compared with SOC ranged from 0.8 to 1.1 with no statistically significant differences (**Figure 7**).

Figure 7. Network diagram and HR for PFS by treatment network for the cis-ineligible (wide) network



Comparator	HR (95% CrI)	N
Vinflunine + gem	0.75 (0.44, 1.28)	32
Atezolizumab + GemCarbo	0.84 (0.70, 1.01)	311
Pembrolizumab + GemCarbo	0.86 (0.68, 1.09)	195
M-CAVI	0.96 (0.74, 1.25)	119
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cis, cisplatin; CrI, credible interval; gem, gemcitabine; GemCarbo, gemcitabine + carboplatin; HR, hazard ratio; M-CAVI, methotrexate + carboplatin + vinblastine; PFS, progression-free survival.

Limitations

- Substantial differences in study design and outcome assessment meant that it was not possible to investigate the impact of SOC followed by maintenance therapy within the same network as all other 1L therapies.
- Networks were primarily constructed of single connections and there was heterogeneity across studies.
- Data for ddMVAC come from a single study with notably long OS and may represent a patient population with improved survival as a result of underlying patient characteristics.[11]
- Adjusting for differences across studies with meta-regression was not feasible because of the small number of RCTs identified.

Conclusions

- To our knowledge, this is the most recent SLR/NMA to evaluate treatment outcomes in both a mixed population (including both cis-eligible and cis-ineligible patients with la/mUC), and a cis-ineligible population.
- OS was similar to SOC across all interventions and remained poor among established and recently evaluated therapies in 1L la/mUC, despite inclusion of recent trial data.
  - Credible intervals for OS HRs all crossed 1, with the exception of ddMVAC.
- These results are consistent with the lack of clinical trials showing superior clinical efficacy compared to SOC in 1L.
- This SLR/NMA further highlights the continued unmet need in this patient population.

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