# Systematic Literature Review (SLR) and Network Meta-Analysis (NMA) of First-Line (1L) Therapies 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]
- For patients with la/mUC, the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend platinum-based chemotherapy as the standard first-line (1L) treatment, and for disease that has not progressed following platinum-based therapy, avelumab is recommended as maintenance therapy.[2]
- Other treatments recognised by ESMO and NCCN, based on varying degrees of evidence, include dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (ddMVAC) for cisplatin-eligible patients; programmed cell death-receptor 1/death-ligand 1 (PD-1/L1) inhibitors for cisplatin-ineligible patients whose tumours express PD-L1; and taxanes as monotherapy or in combination with gemcitabine.[2,3]
- Emerging therapies are currently under investigation for la/mUC in the 1L setting, and may define the future treatment landscape.
- Systematic literature reviews (SLRs) and network meta-analyses (NMAs) have been performed in 1L la/mUC[4–11]; however, since 2018 only one SLR/NMA has included contemporary data for PD-1/L1 inhibitors and other therapies in the 1L setting, but it is now outdated and lacks stratification by cisplatin eligibility.[11]

## Objective

- This SLR and NMA of randomised controlled trials (RCTs) compared outcomes of alternative 1L regimens for la/mUC with standard of care (SOC), stratified according to cisplatin eligibility, to better understand unmet needs in this setting.

## Methods

### Systematic literature review

- The SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the National Institute for Health and Care Excellence Decision Support Unit guidance for evidence synthesis and decision-making.[12,13]
- Phase 2/3 RCTs were included that assessed the efficacy and safety of 1L regimens in la/mUC, with single-arm studies allowed for PD-1/L1 inhibitors.
- Embase and MEDLINE® (via PubMed®) databases were searched for articles published in English from January 2000 to May 2020, with conference proceedings and Health Technology Assessment submissions and appraisals from the past 5 years (2015–2020) also reviewed.
- Following the initial search execution in June 2020, the SLR was supplemented with information presented at the ESMO Virtual Meeting in September 2020.

### Network meta-analysis

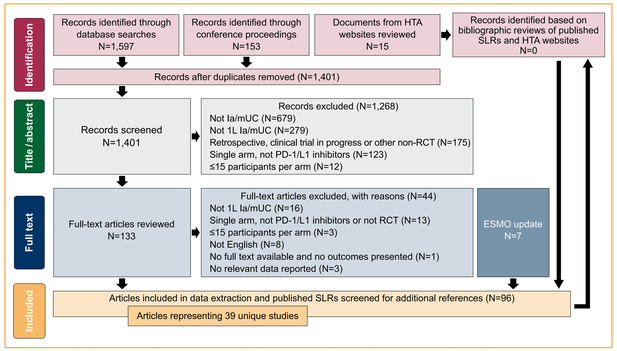
- Publications for the relevant treatments identified in the SLR were assessed for suitability for inclusion in the NMA.
  - Outcomes for maintenance therapy following 1L treatment were assessed from point of randomisation rather than initiation of 1L treatment, so it was not possible to make comparisons between maintenance vs 1L treatment studies. Therefore, maintenance studies had to be excluded as a result of these differences in study design.
  - Therapies that were not found to be effective and thus not adopted in clinical practice were excluded.
- Owing to clinically relevant differences in patient outcomes across populations, 2 networks were created:
  1) Cisplatin-eligible or mixed-eligibility network.
  2) Cisplatin-ineligible network.
- A fixed-effects NMA using a Bayesian framework was employed to compare efficacy and safety outcomes.
- The relative treatment effect of each 1L regimen was compared with SOC (listed below) and with each other:
  - Cisplatin-eligible or mixed-eligibility network SOC: gemcitabine + platinum (cisplatin or carboplatin).
  - Cisplatin-ineligible network SOC: gemcitabine + carboplatin.
- Progression-free survival (PFS) and overall survival (OS) with 1L regimens vs SOC are reported.

## Results

### Included studies

- Among 1,765 publications identified in the SLR, 96 publications (65 RCTs, 16 single-arm trial publications and 15 SLRs) representing 39 unique clinical trials were selected for data extraction (**Figure 1**).
- Of these, 11 were included in the cisplatin-eligible/mixed-eligibility network and 6 in the cisplatin-ineligible network (**Table 1**).[14–29]

### Figure 1. PRISMA diagram




1L, first-line; ESMO, European Society for Medical Oncology; HTA, health technology assessment; la/mUC, locally advanced or metastatic urothelial carcinoma; PD-1/L1, programmed cell death-receptor 1/death-ligand 1; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review.

### Table 1. Studies included in the NMA

| Study name (citation) | Treatment | Comparator |
|---|---|---|
| **Cisplatin eligible/mixed eligibility** | | |
| KEYNOTE-361 (Alva 2020)[14] | Pembrolizumab + GemPlat<br>Pembrolizumab | Gemcitabine + platinum |
| IMvigor130 (Galsky 2020)[15] | Atezolizumab + GemPlat<br>Atezolizumab | Gemcitabine + platinum |
| DANUBE (Powles 2020)[16] | Durvalumab<br>Durvalumab + tremelimumab | Gemcitabine + platinum |
| HE 16/03 (Bamias 2013)[17] | dd gemcitabine + cisplatin | ddMVAC |
| EORTC 30987 (Bellmunt 2012)[18] | Gemcitabine + cisplatin + paclitaxel | Gemcitabine + cisplatin |
| EORTC 30924 (Sternberg 2006)[19] | ddMVAC | MVAC |
| Dreicer 2004[20] | MVAC | Carboplatin + paclitaxel |
| Bamias 2004[21] | MVAC | Cisplatin + docetaxel |
| Lorusso 2005[22] | Gemcitabine + cisplatin + paclitaxel | Gemcitabine + cisplatin |
| Von der Maase 2005[23] | MVAC | Gemcitabine + cisplatin |
| Dogliotti 2007[24] | Gemcitabine + cisplatin | Gemcitabine + carboplatin |
| **Cisplatin ineligible** | | |
| DANUBE (Powles 2020)[16] | Durvalumab + tremelimumab | Gemcitabine + platinum |
| VINGEM (Holmsten 2020)[25] | Vinflunine + gemcitabine | Gemcitabine + carboplatin |
| JASINT1 (De Santis 2016)[26] | Vinflunine + carboplatin | Vinflunine + gemcitabine |
| EORTC 30986 (De Santis 2012)[27] | M-CAVI | Gemcitabine + carboplatin |
| GETUG V01 (Culine 2011)[28] | Gemcitabine + oxaliplatin | Gemcitabine |
| COACH (Park 2020)[29] | Gemcitabine + oxaliplatin | Gemcitabine + carboplatin |

dd, dose-dense; GemPlat, gemcitabine + platinum (cisplatin or carboplatin); M-CAVI, methotrexate + carboplatin + vinblastine; MVAC, methotrexate + vinblastine + doxorubicin + cisplatin; NMA, network meta-analysis.

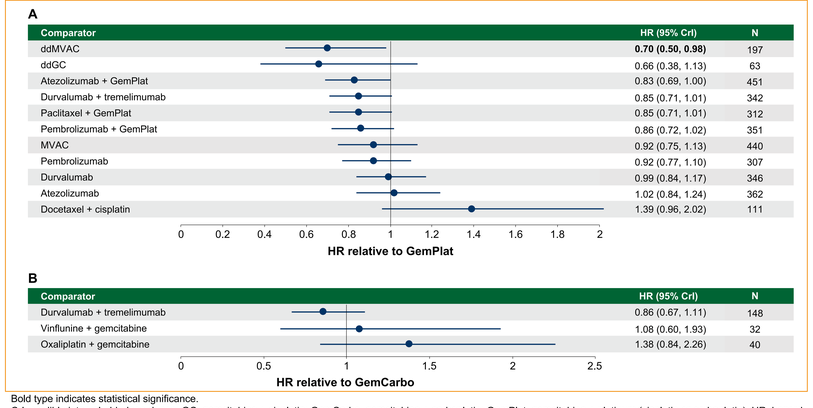
### Overall survival

- Based on a fixed-effects meta-analysis of SOC arms in each network, median OS was 13.2 months (95% confidence interval [CI]: 12.4–14.0) and 9.7 months (95% CI: 6.7–12.8) for the cisplatin-eligible/mixed-eligibility network and the cisplatin-ineligible network, respectively.
- The hazard ratio (HR) for OS for the cisplatin-eligible/mixed-eligibility network ranged from 0.70 (95% credible interval [CrI]: 0.50–0.98) for ddMVAC to 1.39 (95% CrI: 0.96–2.02) for docetaxel + cisplatin (**Figure 2A**).
- HR for OS for the cisplatin-ineligible network ranged from 0.86 (95% CrI: 0.67–1.11) for durvalumab + tremelimumab to 1.38 (95% CrI: 0.84–2.26) for oxaliplatin + gemcitabine (**Figure 2B**).

### Progression-free survival

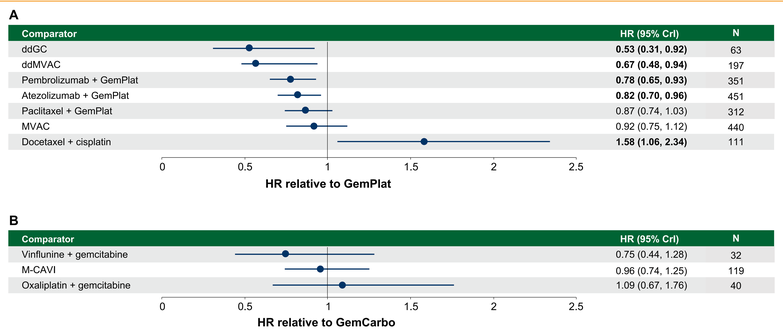
- Based on a fixed-effects meta-analysis of SOC arms in each network, median PFS was 6.6 months (95% CI: 6.3–6.9) and 5.6 months (95% CI: 4.9–6.3) for the cisplatin-eligible/mixed-eligibility network and the cisplatin-ineligible network, respectively.
- HR for PFS for the cisplatin-eligible/mixed-eligibility network ranged from 0.53 (95% CrI: 0.31–0.92) for dose-dense gemcitabine + cisplatin (ddGC) to 1.58 (95% CrI: 1.06–2.34) for docetaxel + cisplatin (**Figure 3A**).
- HR for PFS for the cisplatin-ineligible network ranged from 0.75 (95% CrI: 0.44–1.28) for vinflunine + gemcitabine to 1.09 (95% CrI: 0.67–1.76) for oxaliplatin + gemcitabine (**Figure 3B**).

### Figure 2. HR for OS forest plot: (A) cisplatin-eligible/mixed-eligibility network; (B) cisplatin-ineligible network




Bold type indicates statistical significance.
CrI, credible interval; dd, dose-dense; GC, gemcitabine + cisplatin; GemCarbo, gemcitabine + carboplatin; GemPlat, gemcitabine + platinum (cisplatin or carboplatin); HR, hazard ratio; MVAC, methotrexate + vinblastine + doxorubicin + cisplatin; OS, overall survival.

### Figure 3. HR for PFS forest plot: (A) cisplatin-eligible/mixed-eligibility network; (B) cisplatin-ineligible network




Bold type indicates statistical significance.
CrI, credible interval; dd, dose-dense; GC, gemcitabine + cisplatin; GemCarbo, gemcitabine + carboplatin; GemPlat, gemcitabine + platinum (cisplatin or carboplatin); HR, hazard ratio; M-CAVI, methotrexate + carboplatin + vinblastine; MVAC, methotrexate + vinblastine + doxorubicin + cisplatin; PFS, progression-free survival.

## Discussion

- OS and PFS were similar to SOC across all interventions included in the NMA (all CrIs crossed or were close to 1).
  - Although there were trends toward improvement (ie, higher point estimates) with interventions of interest vs SOC in the cisplatin-eligible/mixed-eligibility population, in most cases these did not reach statistical significance.
  - ddMVAC and ddGC regimens were the most effective of the included regimens for cisplatin-eligible patients.
  - OS and PFS among la/mUC patients across all recommended treatments were poor, particularly for cisplatin-ineligible patients, highlighting a need for 1L treatment options with rapid response and manageable safety profile.
- Results of this NMA were generally consistent with prior meta-analyses and NMAs that have been conducted for 1L la/mUC, despite inclusion of recent RCTs.
  - These data suggest limited survival gains have been made in 1L treatment of la/mUC, although the inability of including maintenance data in this NMA is acknowledged.[4–11]
- This NMA provides the most contemporary data in a rapidly changing treatment landscape that evaluates comparative efficacy of 1L treatment among both cisplatin-eligible/mixed-eligibility and cisplatin-ineligible patient populations.

## Limitations

- The impact of maintenance therapy could not be evaluated within the framework of this 1L NMA. Three maintenance trials were identified in the SLR; however, formal comparisons with 1L studies were not possible because of significant differences in study design and endpoint collection. Methods outside of the standard NMA process such as modelling of survival data could be considered in future analyses in order to include maintenance therapy data.
- Networks were primarily constructed of single connections and evidence for a regimen was rarely available from multiple studies, other than for SOC. Because of this, all networks appeared consistent and with acceptable heterogeneity.
- Attempts to adjust for differences across studies were unsuccessful, primarily because of the limited number of studies for each regimen.
- Heterogeneity across the studies is a limitation and this analysis is currently not adjusted for baseline risk or other covariates.

## Conclusion

- OS and PFS outcomes remain poor among existing 1L la/mUC therapies.
- Further investigation of novel therapies, including combinations, is needed to address the continued unmet need.

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