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Review

First-line immune-checkpoint inhibitor combination therapy for chemotherapy-eligible patients with metastatic urothelial carcinoma: A systematic review and meta-analysis

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KEYWORDS
Urothelial carcinoma;
Meta-analysis;
Immune-checkpoint inhibitor;
Programmed death-ligand 1

Abstract ***Introduction:*** Platinum-based combination chemotherapy is the standard treatment for patients with chemotherapy-eligible metastatic urothelial carcinoma (mUC). Immune-checkpoint inhibitors (ICIs) are currently assessed in this setting. This review aimed to assess the role of ICIs alone or in combination as first-line treatment in chemotherapy-eligible patients with mUC.
Methods: Multiple databases were searched for articles published until November 2020. Studies were deemed eligible if they compared overall survival (OS), progression-free survival (PFS), objective response rates (ORRs), complete response rates (CRRs), durations of response (DORs) and adverse events (AEs) in chemotherapy-eligible patients with mUC.
Results: Three studies met our eligibility criteria. ICI combination therapy was associated with significantly better OS and PFS, higher CRR and longer DOR than chemotherapy alone (hazard ratio [HR]: 0.85, 95% confidence interval [CI]: 0.76–0.94, P = 0.002; HR: 0.80, 95% CI: 0.71–0.90, P = 0.0002; odds ratio [OR]: 1.48, 95% CI: 1.12–1.96, P = 0.006; and mean difference: 1.39, 95% CI: 0.31–2.46, P = 0.01, respectively). ICI-chemotherapy combination therapy was also associated with significantly better OS and PFS, higher ORR and CRR and longer DOR than chemotherapy alone. Although OS and PFS benefits of ICI combination therapy were larger in patients with high expression of programmed death-ligand 1 (PD-L1), PD-L1 low expression patients also had a benefit; HR for OS (high PD-L1: HR 0.79 versus low PD-L1: HR 0.89) and PFS (high PD-L1: HR 0.74 versus low PD-L1: HR 0.82). ICI monotherapy was not associated with better oncological outcomes but was associated with better safety outcomes than chemotherapy alone.
Conclusions: Our analysis indicates a superior oncologic benefit to first-line ICI combination therapies in patients with chemotherapy-eligible mUC over standard chemotherapy. In contrast, ICI monotherapy was associated with favorable safety outcomes compared with chemotherapy but failed to show its superiority over chemotherapy in oncological benefits. PD-L1 status alone cannot help guide treatment decision-making. However, caution should be exercised in interpreting the conclusions drawn from this study, given that there is the heterogeneity of the population of interest, risk of bias and the nature of the studies evaluated whose data remain immature or unpublished.
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1. Introduction

Patients with advanced urothelial carcinoma (UC) have poor prognoses with 5-year survival rates of <5% for those with metastatic, stage IV disease [1]. The current standard of care for the first-line treatment of advanced UC (locally advanced or metastatic, stage IV disease) is platinum-based combination chemotherapy [1,2]. Moreover, the Javelin 100 trial led to maintenance therapy with avelumab being established as the standard of care for patients with UC whose disease had not progressed on first-line chemotherapy [3]. However, the role of immunotherapy in the first-line setting as monotherapy or in combination remains unclear.

Based on the results of single-arm, phase II studies [4,5], recent treatment guidelines have included atezolizumab and pembrolizumab for the first-line treatment of cisplatin-ineligible patients with metastatic UC (mUC) and high tumour programmed death ligand 1 (PD-L1) expression [1]. The anti–PD-L1 agents atezolizumab, avelumab, and durvalumab, as well as the anti-programmed death 1 (PD-1) agents nivolumab and pembrolizumab, are approved for the second-line treatment after platinum-based chemotherapy of locally advanced UC or mUC, regardless of PD-L1 status [6–11]. Based on these developments of immune-checkpoint inhibitors (ICIs), they are now being tested as first-line treatments, alone or in combination with another ICI or standard chemotherapy, for platinum-based chemotherapy (including cisplatin)-eligible mUC patients. In the IMvigor130 trial [12], atezolizumab as add-on to platinum-based chemotherapy as a first-line treatment prolonged progression-free survival (PFS) in mUC patients. However, the IMvigor 130 trial failed to meet its coprimary efficacy endpoint, overall survival (OS). Similarly, the KEYNOTE361 [13] and DANUBE trials [14] failed to meet their primary endpoints, thus leaving the role of ICI combination as first-line treatment in chemotherapy-eligible mUC patients unsolved.

To date, no direct comparisons have been made between these agents to inform optimal treatment

decisions and guideline recommendations. Therefore, we conducted a systematic review of all clinical trials that assessed first-line ICI therapy, as monotherapy or combination therapy, for the treatment of mUC using standard chemotherapy as the control arm. We also conducted a meta-analysis and network meta-analysis of the first-line treatment options to directly and indirectly compare their efficacy and safety.

2. Material and methods

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42020218162).

2.1. Search strategy

The systematic review, meta-analysis and network meta-analysis of randomized controlled trials in chemotherapy-eligible mUC patients treated with first-line ICIs was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [15]. A completed PRISMA 2009 checklist was used to describe the methodology of our study (Supplementary Table 1). PubMed, Web of Science and Scopus were searched to identify reports published up to November 2020 that investigated first-line systemic therapy for platinum-based chemotherapy-eligible mUC. The following keywords were used in our search strategy: (urothelial carcinoma OR bladder cancer OR bladder carcinoma OR urothelial cancer) AND (metastatic OR advanced) AND (Randomized). Furthermore, we also reviewed relevant abstracts presented in major conferences including the American Society of Clinical Oncology and the European Society for Medical Oncology. The primary outcomes of interest were OS and PFS, and the secondary outcomes were objective response rate (ORR), complete response rate (CRR), duration of response (DOR) and adverse event (AE). Objective response was defined as the proportion of enrolled and randomly assigned patients who achieved the best response of complete or partial response based on investigator assessment. DOR was defined as time from date of first response to progression or death. Initial screening was performed independently by two investigators based on the titles and abstracts of the article to identify ineligible reports. Reasons for exclusions were noted. Potentially relevant reports were subjected to a full-text review, and the relevance of the reports was confirmed after the data extraction process.

2.2. Inclusion and exclusion criteria

Studies were included if they investigated platinum-based chemotherapy-eligible mUC patients (Patients) who had undergone ICI therapy as first-line treatment (Intervention) compared with those treated with chemotherapy as first-line treatment (Comparison) to assess the differential effects on OS, PFS, ORR, CRR, DOR and AE (Outcome) in phase III randomized studies only. We excluded observational studies, reviews, letters, editorials, replies from authors, case reports and articles not published in English. References of all articles included were scanned for additional studies of interest.

2.3. Data extraction

Two investigators independently extracted the following information from the included articles: study name, publication year, number of patients, treatment compound, age, sex, performance status, primary tumour site, disease status, PD-L1 status, cisplatin eligibility, subsequent therapy, oncologic outcomes, AE outcomes and follow-up. Subsequently, the hazard ratios (HRs) and 95% confidence intervals (CIs) associated with PFS and OS were retrieved.

2.4. Risk-of-bias assessment

The 'risk-of-bias' (RoB) evaluation of each study was assessed according to The Cochrane Collaboration's tool for assessing risk of bias [16]. This tool assesses selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other sources of bias (Supplementary Fig. 1). The RoB of each study was assessed independently by two authors. Disagreements were resolved by consultation with the coauthors.

2.5. Statistical analyses

2.5.1. Meta-analysis

First, forest plots were used to assess the HRs and to describe the relationships between treatment and survival outcomes (ICI therapy versus chemotherapy). Second, forest plots were used as the summary variables for dichotomous outcomes and to describe the relationships between treatment and ORR, CRR and AE (ICI therapy versus chemotherapy). Dichotomous variables are presented as proportions and compared with odds ratios (ORs) and 95% CIs. Third, forest plots were used as the summary variables for continuous outcomes and to describe the relationships between treatment and DOR (ICI therapy versus chemotherapy). Continuous variables are presented as mean ± standard deviation and compared with mean differences (MDs). Subgroup analyses of OS and PFS were performed among high−PD-L1 and low−PD-L1 status patients. Subgroup analyses of OS and PFS were performed for patients with high− and low−PD-L1 status, as well for cisplatin-eligible and cisplatin-ineligible patients. Heterogeneity among outcomes of included studies in this meta-

analysis was evaluated by using Cochrane's Q test and the I^2 statistic. Significant heterogeneity was indicated by a P ≦ 0.05 in Cochrane's Q tests and a ratio ≧ 50% in I^2 statistics. We used fixed effects models for calculation for non-heterogeneous results [17–19]. Random effect models were used in cases of heterogeneity.

2.5.2. Network meta-analysis

We conducted network meta-analysis with random and fixed effect models using a Bayesian approach for the comparison of direct and indirect treatments, with chemotherapy as the common comparator arm [20,21]. In the assessment for OS, contrast-based analyses were applied with estimated differences in the log HR and the standard error calculated from the published HR and CI [22]. The relative treatment effects were presented as HR and 95% credible interval (CrI) [20]. For the assessment of the ORR, arm-based analyses were performed to estimate ORs and 95% CrI from raw data presented in the selected manuscripts [20]. With regard to OS, analyses were conducted among high–PD-L1 and low–PD-L1 patients. We also estimated the relative ranking of different treatments for each outcome using the P-score, which can be considered a frequentist analog to the surface under the cumulative ranking curve [23,24]. Network plots were used to illustrate the connectivity of the treatment networks in terms of OS and ORR. All statistical analyses were performed using R 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria) and Review manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark); statistical significance was set at $P < 0.05$.

3. Results

3.1. Study selection and characteristics

Our initial search identified 2,014 publications, and after the elimination of duplicates, a total of 1,263 publications remained. A further 1,245 articles were excluded after screening the titles and abstracts, and full-text reviews were performed for the remaining 18 articles (Supplementary Fig. 2). In accordance with the selection criteria, we identified three articles comprising 3,255 patients for the systematic review, meta-analysis and network meta-analysis. The data extracted from these three studies are outlined in Table 1. Two studies, published between 2019 and 2020, involved an assessment of first-line therapy and compared ICI-chemotherapy combination therapy and ICI monotherapy with chemotherapy alone [12,13]. The remaining study, published in 2020, involved an assessment of first-line therapy and compared ICI–ICI combination therapy and ICI monotherapy with chemotherapy [14]. In these three RCTs, a total of 3,255 patients were treated with ICI monotherapy (n = 1,015, 31%) or ICI-based combination therapy (n = 1,144, 35%), or chemotherapy alone (n = 1,096, 34%). PD-L1 expression on

Table 1
Study demographics.

Study	IMvigor130			DANUBE			KEYNOTE361		
Year	2019			2020			2020		
Compound	Atezo Chemo	Atezo	Chemo	Durva Treme	Durva	Chemo	Pembro Chemo	Pembro	Chemo
Number	451	362	400	342	346	344	351	307	352
Age	69 (62–75)	67 (62–74)	67 (61–73)	68 (60–73)	67 (60–73)	68 (60–73)	69 (41–91)	68 (29–89)	69 (36–90)
Male	75%	77%	75%	75%	72%	80%	78%	74%	74%
ECOG PS 2	13%	9%	10%	0%	0%	0%	7%	8%	6%
Primary tumour (lower tract)	71%	75%	75%	78%	82%	75%	82%	79%	77%
Disease status (metastatic)	89%	88%	92%	96%	97%	94%	NR	NR	NR
Lymph node only	18%	19%	17%	21%	18%	22%	23%	21%	27%
Visceral meta	57%	56%	60%	78%	82%	77%	74%	78%	72%
High PD-L1	24%	24%	23%	60%	60%	60%	45%	52%	45%
Antibodies	SP142			SP263			22c3		
Platform	Ventana			Ventana			Dako		
Cell type	IC			IC/TC			TC		
Cut-off	≧5%			≧25%			CPS≧10		
Cisplatin eligible	42%	47%	44%	57%	57%	56%	NR	NR	NR
Chemotherapy (Cisplatin)	30%	37%	34%	NR	NR	NR	46%	45%	46%
Subsequent therapy	26%	40%	41%	45%	47%	54%	35%	41%	61%
Subsequent ICI therapy	5%	2%	20%	3%	5%	32%	7%	5%	48%
Follow up	11.8 months			41.2 months			NR		

Abbreviation: Atezo (Atezolizumab), Chemo (Chemotherapy), CPS (Combines positive score), Durva (Durvalumab), IC (Immune cell), ICI (Immune checkpoint inhibitor), NR (Not reported), PD-L1 (Programmed death ligand 1), Pembro (Pembrolizumab), PS (Performance status), TC (Tumour cell), Treme (Tremelimumab).

tumour cells, tumour-infiltrating immune cells or both was examined immunohistochemically. Among the patients with quantifiable PD-L1 expression, high PD-L1 expression was present in 60% of patients in the DANUBE study, 24% of patients in the IMvigor130 study and 47% of patients in the KEYNOTE361 trial.

4. Meta-analysis

4.1. ICI-combination therapy versus chemotherapy alone

4.1.1. Overall survival

The forest plot (Fig. 1A) revealed that ICI combination therapy is associated with significantly longer OS than chemotherapy alone (pooled HR: 0.85, 95% CI: 0.76–0.94, P = 0.002). The Cochrane's Q test (P = 0.96) and I^2 test (I^2 = 0%) revealed no significant heterogeneity. The forest plot (Fig. 1B) revealed ICI-chemotherapy combination therapy is associated with significantly longer OS than chemotherapy alone (pooled HR: 0.85, 95% CI: 0.75–0.96, P = 0.009). The Cochrane's Q test (P = 0.78) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

4.1.2. Progression-free survival

The forest plot (Fig. 1C) revealed that ICI combination therapy is associated with significantly longer PFS than chemotherapy alone (pooled HR: 0.80, 95% CI: 0.71–0.90, P < 0.001). The Cochrane's Q test (P = 0.68) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

4.1.3. Objective response rate

The forest plot (Fig. 1D) revealed that ICI combination therapy is not different to chemotherapy alone regarding ORR. The Cochrane's Q test (P < 0.001) and I^2 test (I^2 = 90%) revealed significant heterogeneity. The forest plot (Fig. 1E) revealed ICI-chemotherapy combination therapy is associated with significantly better ORR than chemotherapy alone (pooled OR: 0.77, 95% CI: 0.63–0.94, P = 0.01). The Cochrane's Q test (P = 0.23) and I^2 test (I^2 = 32%) revealed no significant heterogeneity.

4.1.4. Complete response rate

The forest plot (Fig. 1F) revealed that ICI combination therapy is associated with significantly better CRR than chemotherapy alone (pooled OR: 0.68, 95% CI: 0.51–0.89, P = 0.006). The Cochrane's Q test (P = 0.35) and I^2 test (I^2 = 5%) revealed no significant heterogeneity. The forest plot (Fig. 1G) revealed ICI-chemotherapy combination therapy is associated with significantly better CRR than chemotherapy alone (pooled OR: 0.64, 95% CI: 0.47–0.88, P = 0.007). The Cochrane's Q test (P = 0.19) and I^2 test (I^2 = 41%) revealed no significant heterogeneity.

4.1.5. Duration of response

The forest plot (Fig. 1H) revealed that ICI combination therapy is associated with significantly longer DOR than chemotherapy alone (pooled MD: 1.39, 95% CI: 0.31–2.46, P = 0.01). The Cochrane's Q test (P = 0.07) and I^2 test (I^2 = 61%) revealed no significant heterogeneity. The forest plot (Fig. 1I) revealed that ICI combination therapy is associated with significantly longer DOR than chemotherapy alone (pooled MD: 1.13, 95% CI: 0.03–2.23, P = 0.04). The Cochrane's Q test (P = 0.74) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

4.1.6. Adverse events

The forest plot (Supplementary Fig. 3A) revealed that ICI combination therapy is associated with significantly better any AEs than chemotherapy alone. The Cochrane's Q test (P = 0.07) and I^2 test (I^2 = 63%) revealed no significant heterogeneity. The forest plot (Supplementary Fig. 3B and Supplementary Fig. 3C) revealed that ICI combination therapy is not associated with significantly worse grade 3≧AEs or AEs leading to treatment discontinuation compared with chemotherapy alone. The Cochrane's Q test (P < 0.001 and P = 0.01) and I^2 test (I^2 = 96% and 77%) revealed significant heterogeneity.

The forest plot (Supplementary Fig. 3D, 3E, and 3F) revealed that ICI plus chemotherapy is not associated with significantly worse any AEs, grade 3≧AEs or AEs leading to treatment discontinuation compared with chemotherapy alone but chemotherapy tended to be better than ICI plus chemotherapy in all these AE outcomes.

4.2. ICI-monotherapy versus chemotherapy alone

4.2.1. Overall survival

The forest plot (Fig. 2A) revealed no difference between ICI monotherapy and chemotherapy alone with regards to OS (pooled HR: 0.97, 95% CI: 0.87–1.08, P = 0.60). The Cochrane's Q test (P = 0.73) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

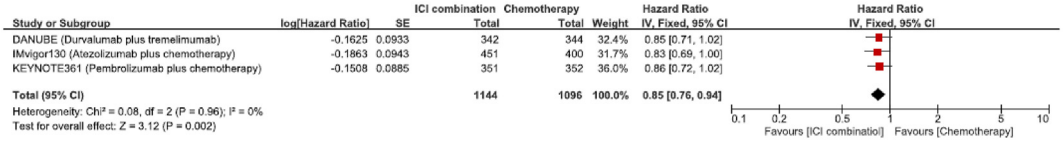
4.2.2. Objective response rate

The forest plot (Fig. 2B) revealed that ICI monotherapy is associated with significantly worse ORR compared with chemotherapy alone (pooled OR: 2.40, 95% CI: 2.00–2.89, P < 0.001). The Cochrane's Q test (P = 0.18) and I^2 test (I^2 = 42%) revealed no significant heterogeneity.

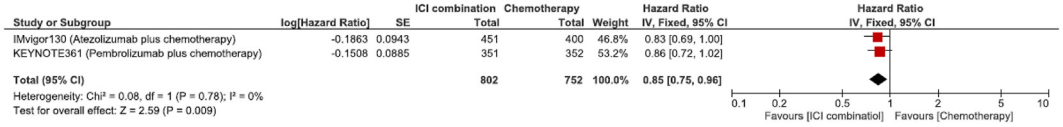
4.2.3. Complete response rate

The forest plot (Fig. 2C) revealed no difference between ICI monotherapy and chemotherapy alone with regards to CRR (pooled OR: 1.02, 95% CI: 0.75–1.39, P = 0.91). The Cochrane's Q test (P = 0.65) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

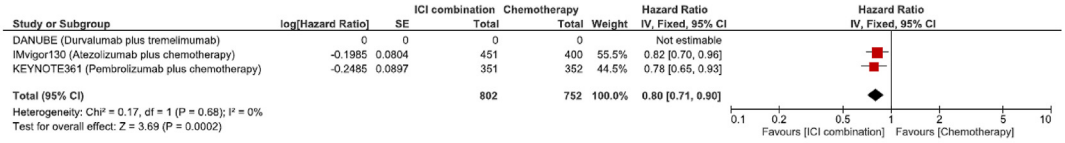
(A) OS



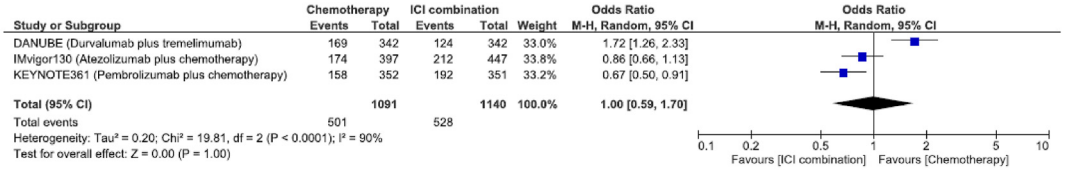
(B) OS (ICI-chemotherapy combination only)



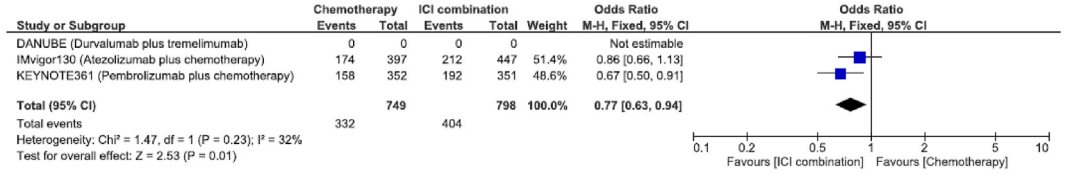
(C) PFS



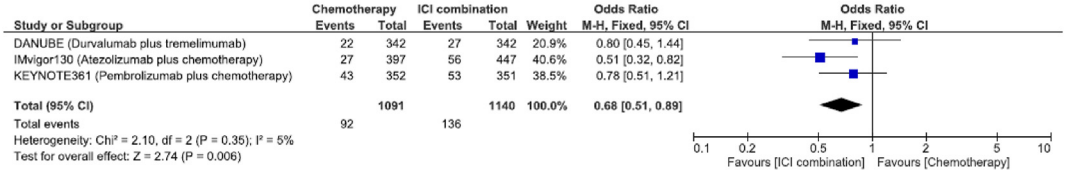
(D) ORR



(E) ORR (ICI-chemotherapy combination only)



(F) CRR



(G) CRR (ICI-chemotherapy combination only)

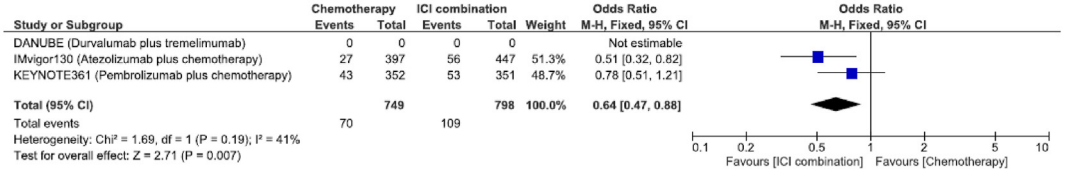
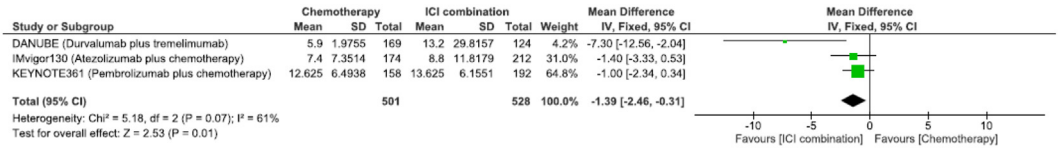


Fig. 1. Forest plots showing the association between treatment and oncological outcomes in metastatic urothelial carcinoma (immune-checkpoint inhibitors (ICI) combination therapy versus chemotherapy). (A) Overall survival, (B) overall survival (ICI-chemotherapy combination only), (C) progression free survival, (D) objective response rate, (E) objective response rate (ICI-chemotherapy combination only), (F) complete response rate, (G) complete response rate (ICI-chemotherapy combination only), (H) duration of response, (I) duration of response (ICI-chemotherapy combination only).

(H) DOR



(I) DOR (ICI-chemotherapy combination only)

Fig 1. (*continued*)

4.2.4. Adverse event

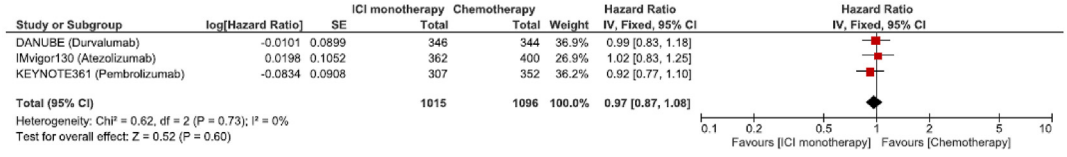
The forest plot (Supplementary Fig. 4A) revealed that ICI monotherapy is associated with significantly better any AEs than chemotherapy alone. The Cochrane's Q test ($P = 0.78$) and I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity. The forest plot (Supplementary Fig. 4B) revealed that ICI monotherapy is associated with significantly better grade 3≧AEs than chemotherapy alone. The Cochrane's Q test ($P < 0.001$) and I^2 test ($I^2 = 94\%$) revealed significant heterogeneity. The forest plot (Supplementary Fig. 4C) revealed that ICI monotherapy is not associated with significantly worse AEs leading to treatment discontinuation compared with chemotherapy alone. The Cochrane's Q test ($P < 0.001$) and I^2 test ($I^2 = 95\%$) revealed significant heterogeneity.

4.3. Association of PD-L1 status with oncological outcomes

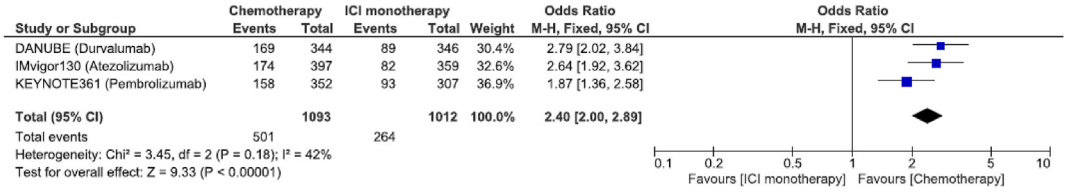
4.3.1. OS (ICI combination therapy versus chemotherapy alone)

The forest plot (Fig. 3A) revealed that ICI combination therapy is associated with significantly longer OS than chemotherapy alone in patients with high PDL1 status (pooled HR: 0.79, 95% CI: 0.68–0.93, $P = 0.004$). The

(A) OS



(B) ORR



(C) CRR

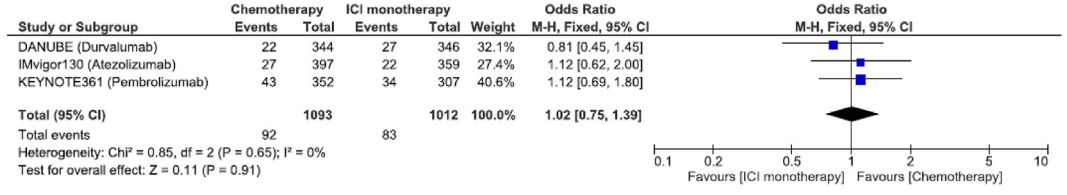
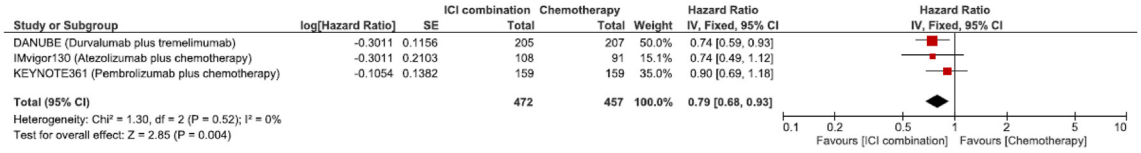
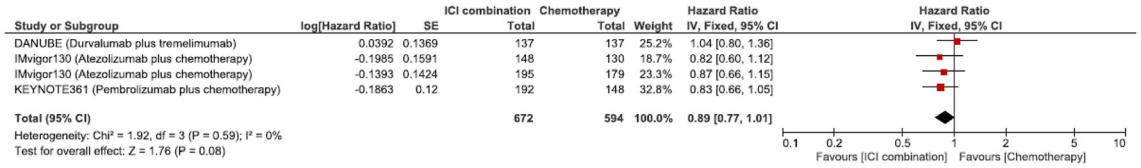


Fig. 2. Forest plots showing the association between treatment and oncological outcomes in metastatic urothelial carcinoma (immune-checkpoint inhibitors (ICI) monotherapy versus chemotherapy). (A) Overall survival, (B) objective response rate, (C) complete response rate.

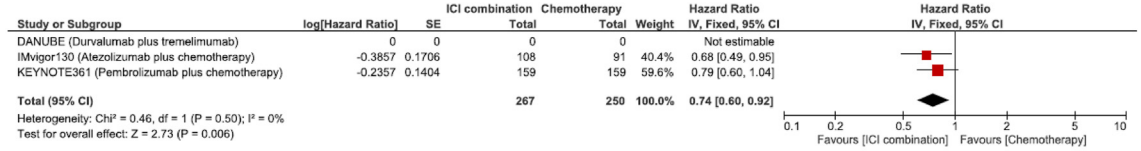
(A) OS in high PD-L1 (ICI combination therapy versus chemotherapy)



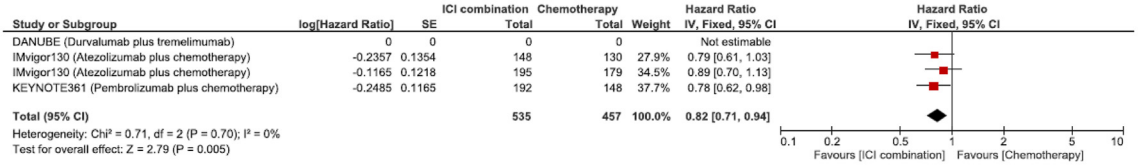
(B) OS in low PD-L1 (ICI combination therapy versus chemotherapy)



(C) PFS in high PD-L1 (ICI combination therapy versus chemotherapy)



(D) PFS in low PD-L1 (ICI combination therapy versus chemotherapy)



(E) OS in high PD-L1 (ICI monotherapy versus chemotherapy)

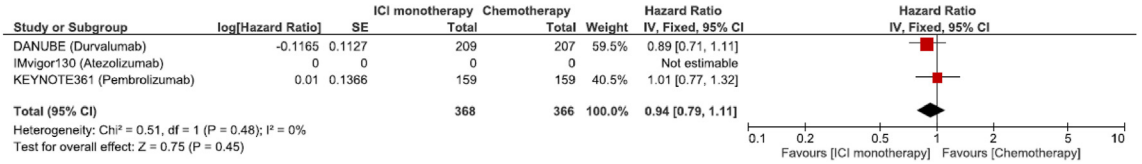


Fig. 3. Forest plots showing the association between treatment and survival outcomes in metastatic urothelial carcinoma. (A) Overall survival (OS) in patients with high programmed death ligand 1 (PD-L1) status (immune-checkpoint inhibitors (ICI) combination therapy versus chemotherapy), (B) OS in patients with low PD-L1 status (ICI combination therapy versus chemotherapy), (C) progression free survival (PFS) in patients with high PD-L1 status (ICI combination therapy versus chemotherapy), (D) PFS in patients with low PD-L1 status (ICI combination therapy versus chemotherapy), (E) OS in patients with high PD-L1 status (ICI monotherapy versus chemotherapy).

Cochrane's Q test (P = 0.52) and I^2 test (I^2 = 0%) revealed no significant heterogeneity. In contrast, in low PD-L1 status, the forest plot (Fig. 3B) revealed that ICI combination therapy is not associated with significantly longer OS (pooled HR: 0.89, 95% CI: 0.77–1.01, P = 0.08). The Cochrane's Q test (P = 0.59) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

4.3.2. PFS (ICI combination therapy versus chemotherapy alone)

The forest plot (Fig. 3C) revealed that ICI combination therapy is associated with significantly longer PFS than chemotherapy alone in patients with high PDL1 status (pooled HR: 0.74, 95% CI: 0.60–0.92, P < 0.001). The Cochrane's Q test (P = 0.50) and I^2 test (I^2 = 0%) revealed no significant heterogeneity. Similarly, in low–PD-L1 status, the forest plot (Fig. 3D) revealed that ICI combination therapy was associated with significantly longer PFS (pooled HR: 0.82, 95% CI: 0.71–0.94, P = 0.005). The Cochrane's Q test (P = 0.71) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

4.3.3. OS (ICI monotherapy versus chemotherapy alone)

The forest plot (Fig. 3E) revealed no difference between ICI monotherapy and chemotherapy alone with regards

to OS in high−PD-L1 patients (pooled HR: 0.94, 95% CI: 0.79−1.11, P = 0.45). The Cochrane's Q test (P = 0.51) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

4.4. Association of chemotherapy with oncological outcomes

4.4.1. OS (ICI combination therapy versus chemotherapy alone)

The forest plot (Supplementary Fig. 5A) revealed that ICI combination therapy is associated with significantly longer OS than chemotherapy alone in patients with cis-eligible (pooled HR: 0.82, 95% CI: 0.70−0.97, P = 0.02). The Cochrane's Q test (P = 0.37) and I^2 test (I^2 = 0%) revealed no significant heterogeneity. In cis-ineligible patients, the forest plot (Supplementary Fig. 5B) revealed that ICI combination therapy is not associated with significantly longer OS (pooled HR: 0.87, 95% CI: 0.76−1.00, P = 0.05). The Cochrane's Q test (P = 0.86) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

4.4.2. PFS (ICI combination therapy versus chemotherapy alone)

The forest plot (Supplementary Fig. 5C) revealed that ICI combination therapy is associated with significantly longer PFS than chemotherapy alone in patients with cis-eligible (pooled HR: 0.70, 95% CI: 0.57−0.85, P < 0.001). The Cochrane's Q test (P = 0.67) and I^2 test (I^2 = 0%) revealed no significant heterogeneity. Similarly, in cis-ineligible patients, the forest plot (Supplementary Fig. 5D) revealed that ICI combination therapy was associated with significantly longer PFS (pooled HR: 0.84, 95% CI: 0.73−0.98, P = 0.03). The Cochrane's Q test (P = 0.85) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

4.5. Network meta-analysis

Networks of eligible comparisons were graphically represented in network plot with respect to OS and ORR (Supplementary Fig. 6).

4.5.1. Overall survival

A network meta-analysis of seven treatments was performed with regards to OS. Of the three ICI combination therapies, none was associated with improved OS among patients with mUC in the overall, high−PD-L1 or low−PD-L1 cohorts (Supplementary Table 2). According to the analysis of treatment ranking, atezolizumab plus chemotherapy had the highest likelihood of providing the maximal OS (P score: 0.68), closely followed by the other two ICI combination therapies (P score: 0.64 and 0.62) (Supplementary Table 3).

4.5.2. Objective response rate

A network meta-analysis of seven treatments was performed with regards to ORR. Compared with chemotherapy alone, pembrolizumab plus chemotherapy resulted in significantly higher ORRs (OR: 1.48, 95% CrI: 1.10−2.00; Supplementary Table 4). In contrast, durvalumab plus tremelimumab resulted in significantly lower ORRs than chemotherapy alone among patients with mUC (OR: 0.59, 95% CrI: 0.43−0.80, Supplementary Table 4). According to the analysis of treatment ranking, pembrolizumab plus chemotherapy had the highest likelihood of providing the maximal ORR (P score: 0.98), followed by atezolizumab plus chemotherapy (P score: 0.83) (Supplementary Table 5).

5. Discussion

We conducted a systematic review and meta-analysis to assess the impact of first-line ICI therapy in platinum-based chemotherapy (including cisplatin)-eligible mUC patients. We also performed a network meta-analysis to indirectly compare ICI treatment options thought to have clinical relevance. This approach led to several findings of interest. First, ICI combination therapy was associated with significantly improved OS, PFS, CRR and DOR compared with chemotherapy alone in chemotherapy-eligible mUC patients. ICI-chemotherapy combination therapy was also associated with significantly improved OS, PFS, ORR, CRR and DOR compared with chemotherapy alone. While there was no difference in grade 3≧AEs and AEs leading to treatment discontinuation between ICI combination therapy and chemotherapy alone, any AEs were significantly more frequent in patients treated with chemotherapy. However, chemotherapy tended to be associated with better safety outcomes than ICI plus chemotherapy, while this difference was not statistically significant. Second, ICI monotherapy did not significantly improve OS or CRR; it resulted even in worse ORR than chemotherapy alone. In mUC patients with high−PD-L1 status, OS outcomes remained similar between ICI monotherapy and chemotherapy alone. However, ICI monotherapy was associated with better safety outcomes than chemotherapy. Third, although the OS and PFS benefits of ICI combination therapy were even larger in patients with high−PD-L1 status than in those with a low−PD-L1 status, the HR for OS (high PD-L1: HR 0.79 versus low PD-L1: HR 0.89) and PFS (high PD-L1: HR 0.74 versus low PD-L1: HR 0.82) indicated that the treatment effect was not much different between those with high−PD-L1 status and those with low−PD-L1 status. Thus, PD-L1 status appears to have limited value for the prediction of survival benefits in chemotherapy-eligible mUC patients treated with ICI combination therapy. Fourth, sub-analyses of OS and PFS performed for cis-eligible and cis-ineligible

patients showed that while ICI combination therapy was associated with a slightly more favorable HR for cis-eligible patients than for cis-ineligible patients, this was not much difference, suggesting the superiority of ICI combination therapy over chemotherapy, regardless of chemotherapeutic agents.

In our analysis, ICI combination therapy was associated with significantly superior OS and PFS compared with chemotherapy alone, despite being similar to chemotherapy in ORR. The underlying cause of this discrepancy between survival outcomes and ORR in patients who received ICI combination therapy remains unclear; however, ICI combination therapy was associated with a significant increase in both CR and DOR, which likely contributed to improved survival outcomes. Moreover, if we excluded ICI–ICI combination therapy, ICI-chemotherapy combination was associated with significantly better ORR than chemotherapy alone. Hence, the reason for the lack of efficacy in terms of ORR might be the absence of chemotherapy in ICI–ICI combination therapy. Again, the precise mechanism through which ICI combination therapy leads to better oncological outcomes remains unclear. In addition to having a direct cytotoxic effect on cancer cells, chemotherapy also reportedly promotes antitumour immune responses by inducing the release and presentation of cancer antigens and by decreasing regulatory immune cells [25]. In addition, an in vitro analysis of bladder cancer cells demonstrated that cisplatin led to a reduction in the proportion of granulocytic myeloid-derived suppressor cells (MDSCs) as well as an increase in the proportion of $CD8^+$ T cells [26]. Gemcitabine and cisplatin also reportedly decrease the proportion of regulatory immune cells in other cancer types [27,28]. These findings suggest that gemcitabine- and/or cisplatin-containing regimens may reduce the proportion of MDSC suggestive of poor prognosis, thereby contributing to antitumour immune responses in UC [29]. Thus, one hypothesis for the superior survival benefits observed in patients under ICI combination therapy may be from an ICI-induced enhancement of these chemotherapeutic effects. Moreover, the combination of these treatments could confer an added benefit because of the absence of cross-resistance [30]. Furthermore, only a subset of patients with mUC are reportedly able to receive subsequent therapy after failing first-line therapy; together with the convincing efficacy data, this supports the benefits of combination therapy in the first-line approach to mUC [31,32].

While ICI combination therapy is associated with favourable outcomes, it presents a safety concern. While all ICI combination regimens, including ICI–ICI regimens, were shown to be similar in safety profile to chemotherapy, this may only reflect the good safety profile of ICI–ICI regimens. In fact, a comparison of AEs between ICI plus chemotherapy and chemotherapy showed that chemotherapy was associated with better safety outcomes than ICI plus chemotherapy, while this difference was not statistically significant. Thus, in considering ICI plus chemotherapy, attention should be given not only to its favorable efficacy profile but also to its slightly unfavorable safety profile. There are other factors than just survival or AE that could influence the choice of treatments for patients with mUC and therefore the decision should still be individually tailored to each patient. For example, the treatment cost that varies from ICIs to chemotherapy is among the factors to consider in the decision-making process. Indeed, the cost-effectiveness analysis of IMvigor130 trial indicated that atezolizumab and chemotherapy would likely not be cost-effective for the first-line treatment of mUC [33]. Thus, while too high a cost may be a barrier to the spread of these treatments, unfortunately, cost-analysis was not part of the trials included in this analysis and made it difficult to address the cost considerations in the current work.

The value of PD-L1 as a biomarker to guide therapeutic decision-making in patients with mUC remains unclear, specifically in the setting of additive ICI or not [34,35]. In the current era of personalized medicine, the identification of prognostic and predictive biomarkers is crucial for determining whether patients are more likely to benefit from ICIs than from other available and effective therapeutic options, thereby avoiding unnecessary AEs in patients who are unlikely to respond to ICIs [35,36]. Moreover, these new treatments impose a high economic burden on the health-care systems, and better treatment selection based on biomarkers may help to reduce treatment-related costs. To date, PD-L1 has been the most promising biomarker for ICI response across multiple cancer types [37]. In UC, the first-line use of atezolizumab and pembrolizumab is restricted to PD-L1–positive patients with mUC who are ineligible for cisplatin-based chemotherapy [1]. Importantly, the use of ICIs being tested in other clinical settings is not based on PD-L1 status, but rather on the patients' clinical characteristics. Thus, the value of PD-L1 expression to predict ICI treatment response in mUC patients remains controversial. In our analysis, there was no notable difference in OS and PFS among patients treated with ICI combination therapy compared with chemotherapy alone when stratified by PD-L1 status. However, it is interesting to note that unlike ICI-chemotherapy combination therapy, ICI–ICI combination therapy was associated with more favorable OS (high PD-L1: HR 0.74 versus low PD-L1: HR 1.04) and ORR (OR, 3.43; 95% CI, 2.08–5.64) outcomes in patients with high–PD-L1 status than in those with low–PD-L1 status, suggesting that PD-L1 status may have the potential room to guide treatment decision-making in patients receiving ICI–ICI combination therapy.

PD-L1 expression, in general, has significant challenges. PD-L1 expression within the same lesion is highly heterogeneous and can change over time [38,39]. Moreover, PD-L1 expression may vary between spatially separated metastases [40]. Performing multiple biopsies to overcome this, in clinical practice, is very difficult. Furthermore, the ideal cutoff to define high PD-L1 remains unclear. Another caveat is that, in clinical practice, there are multiple different anti–PD-L1 antibodies (e.g. 22C3, SP263 and SP142) and platforms (Ventana and Dako) available, which are further affected by specimen type and origin (current versus archival tissue), scoring system used (immune cells versus tumour cells) and threshold of PD-L1 positivity used [41]. Although PD-L1 status may be used as a potential predictive marker, it alone may be insufficient to guide clinical decision-making. More complex predictive biomarkers, such as immune gene signatures, tumour mutational burden and intratumoural $CD8^+$ and $CD4^+$ T-cells are currently under investigation. The future of clinical efficacy and survival prediction appears to lie in the use of different biological variables that capture the full biological and clinical behavior of tumours, rather than a single time-sensitive biomarker snapshot [37].

Despite the comprehensive nature of this systematic review, some limitations should be considered. First, the differences in patient characteristics at study enrollment among the DANUBE, IMvigor130 and KEYNOTE361 trials should be considered despite similar study design, treatment line and target disease. Indeed, while all these trials included patients with performance status (PS) of 0–2, the DANUBE trial [14] included far fewer patients with PS 2. The IMvigor130 trial [12] included not only far fewer patients with visceral metastasis but also more cisplatin-ineligible patients, which led to carboplatin being used in as many as 63%–70% of patients enrolled in the trial. Therefore, these differences in patient characteristics may have affected not only oncological outcomes but also AEs. Sub-analyses of OS and PFS performed for cis-eligible and cis-ineligible patients showed that while ICI combination therapy was associated with a slightly more favourable HR for cis-eligible patients than for cis-ineligible patients, this was not significant. While this suggests the superiority of ICI combination therapy over chemotherapy, regardless of chemotherapeutic agents, further study is required to validate this finding. Moreover, 48% of patients receiving chemotherapy alone received subsequent ICI treatment in the KEYNOTE361 trial [13], a much larger proportion than in the other trials. This likely contributed to the favorable OS outcomes in the chemotherapy-alone arm and caused pembrolizumab to be underestimated in those receiving ICI combination therapy. Second, significant heterogeneity was detected in the ORR and AE analyses, thus limiting the value of these findings. Although the random effects model was used to address heterogeneity among studies, our conclusions should still be interpreted with caution. The fact that ICI–ICI and ICI-chemotherapy combinations were analyzed as distinct categories of ICI combinations may have contributed to heterogeneity in treatment outcomes between the included studies. Indeed, when analyses were confined to ICI-chemotherapy combination studies alone, the heterogeneity in ORRs and AEs tended to decrease; ICI-chemotherapy remained superior to chemotherapy in all oncological outcomes. Third, it is a major limitation of this study that the RCTs evaluated in this analysis included risk of bias. Therefore, the results should not be overinterpreted. Fourth, we included ORR as a secondary endpoint in our network meta-analysis. While there are a few studies available to suggest a correlation between OS and ORR in both ICI therapy and chemotherapy [42,43], at present, the validity of ORR as an endpoint remains unclear, and it is not an established surrogate for OS particularly in ICI combination therapy. Fifth, the OS data from the IMvigor130 trial were immature at the time of this review, and the study outcomes may vary considerably, pending their final analyses. Moreover, the KEYNOTE361 trial results have yet to be published as a full article, and we did not have access to the detailed data. Given that KEYNOTE361 contributed to more frequent AE rates in ICI combination therapy, we could not draw any conclusions regarding AEs. Furthermore, considering the CheckMate 901 and NILE trials being underway, the role of ICI combination therapy in patients with mUC may vary depending on the forthcoming outcomes. Sixth, the Javelin 100 trial contributed to maintenance therapy with avelumab being established as the standard of care for those whose disease had not progressed on first-line chemotherapy [3]. Thus, ICI combination therapy remains yet to be evaluated for its superiority in the first-line setting with this maintenance strategy in mind. In this light, PFS2 data have been made available from a sub-analysis of the KEYNOTE-361 trial [44], showing that of the patients treated with pembrolizumab plus chemotherapy in the first line, those treated with anti-PD-(L)-1 therapy in the second line setting had a median PFS2 of 17.2 months compared with 13.8 months in those treated with non–anti-PD-(L)-1 therapy in the second line setting, suggesting a role for ICI therapy after ICI combination therapy. However, it remains to be further investigated whether maintenance therapy is preferable to first-line combination therapy.

In summary, our analyses demonstrated the superiority of ICI combination therapy over chemotherapy. However, our study has a number of limitations, in that only 3 RCTs, including those whose data remained immature or unpublished, were available for inclusion in our analyses and that results will be made available from such ongoing RCTs as Checkmate 901 and NILE in the years to come. Moreover, maintenance therapy with

avelumab, which has now become the standard of care, was not considered in our analyses. Thus, while our findings are not construed as paradigm-shifting and need to be interpreted with caution, we believe they do provide clinically relevant insight into how ICI combination therapy may fit into the current therapeutic algorithm.

6. Conclusions

Our analysis indicates that first-line ICI combination therapies confer a superior oncological benefit compared with standard chemotherapy in chemotherapy-eligible mUC patients. This superiority over chemotherapy remained intact even in our analyses focused on ICI-chemotherapy combination studies alone. In contrast, ICI monotherapy does not seem as an attractive alternative to chemotherapy alone in these patients when it comes to efficacy. However, ICI monotherapy offers a better safety profile than chemotherapy alone. Moreover, PD-L1 status alone is not a sufficiently robust, reliable and reproducible biomarker to guide treatment decision-making in chemotherapy-eligible mUC. These findings may be valuable in determining personalized treatment strategies for chemotherapy-eligible mUC patients. However, the conclusions drawn from this study should be interpreted with caution, given that there is the heterogeneity of the population of interest, risk of bias and the nature of the RCTs evaluated whose data remain immature or unpublished.

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Authors' contributions

K. Mori, B. Pradere and S. F. Shariat contributed to project development. K. Mori and B. Pradere carried out data collection. K. Mori and H. Mostafaei performed data analysis. All the authors contributed to writing and editing the article.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials, discussed in the article are listed as follows: Shahrokh Shariat owns or co-owns the following patents: methods to determine prognosis after therapy for prostate cancer. Granted 2002-09-06. Methods to determine prognosis after therapy for bladder cancer. Granted 2003-06-19. Prognostic methods for patients with prostatic disease. Granted 2004-08-05. Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma. Granted 2010-07-20. He has a consulting or advisory role for the following: Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Jansen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Sanochemia, Sanofi, Takeda, Urogen and Wolff. All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.03.049.

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