A Systematic Review and Meta-Analysis of the Role of Immune Checkpoint Inhibitors (ICI) as Adjuvant Treatment for Localized High-Risk Muscle-Invasive Urothelial Carcinoma (MIUC)

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Abstract

Nivolumab, a PD-1 ICI has been recently approved for the adjuvant treatment of high-risk MIUC patients. However, conflicting data from another randomized controlled trial (RCT) with atezolizumab makes the benefit of this treatment uncertain. We performed a systematic review and study-level meta-analysis to evaluate the benefit in terms of disease-free survival (DFS) with ICI adjuvant treatment for patients with high-risk MIUC. Considering the Preferred Reporting Items for Systematic Review statement, a systematic search was performed in PUBMED/MEDLINE, Scopus and EMBASE up to October 30, 2021. The statistical analysis was performed by RevMan 5.4 software in intention-to-treat (ITT) population and in predetermined subgroups. Two RCTRCT, with a total of 1518 patients, met the inclusion criteria. Systemic immunotherapy was atezolizumab for 406 patients and nivolumab for 353 patients. In the ITT population there was a nonsignificant benefit with the systemic adjuvant immunotherapy (HR:0.79, 95% CI 0.62-1.00; z = 2.00) but with high heterogeneity (I^2 = 65%). Regarding the subgroups, there was no benefit in PD-L1 negative (HR:0.81, 95% CI 0.70-1.00; z = 1.96, I^2 = 0%) and in non-neoadjuvant chemotherapy (HR:0.95, 95% CI 0.78-1.15; z = 0.56, I^2 = 0%). Adjuvant treatment with ICI to patients with high-risk MIUC reveals a nonsignificant impact in DFS. The lack of clinical benefit was demonstrated in all subgroups. These data reinforce the need for a careful selection of patients before offering this approach in daily practice.

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Introduction

Muscle-invasive urothelial carcinoma (MIUC) represents 30% of newly diagnosed cases, and for these patients, systemic neoadjuvant cisplatin-based chemotherapy (NAC) prior to radical cystectomy and pelvic lymph node dissection is the standard of care by major international guidelines.[1,2] However, there is real-world evidence showing that around 10% to 40% of patients do not receive NAC due to cisplatin ineligibility or treatment refusal.[3-5] In addition, there is a population of higher risk who are those with pathologic T3 or T4 disease and/or pathologic node involvement and thus with an increased risk of recurrence.[2] For these patients, adjuvant chemotherapy (AC) may be considered, but this remains a medical challenge given the conflicting data on the survival benefit with AC treatment so far.[6-8]

Systemic immunotherapy with immune checkpoint inhibitors (ICI) has demonstrated activity and survival benefit in metastatic UC (mUC) in both first- and second-line treatment setting.[9,10] ICI has also promising results in MIUC in the neoadjuvant setting when used alone or in combination with another ICI or chemotherapy in both cisplatin eligible or ineligible patients.[11-14] Regarding the adjuvant treatment setting ICI was evaluated in two randomized controlled trials (RCT), the IMvigor010 with atezolizumab and Disease-Free Survival (DFS) in intention-to-treat (ITT) population as primary endpoint and CheckMate274 with nivolumab and DFS

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in ITT and PD-L1 ≥1% as primary endpoints.[15,16] These 2 RCT had different results, raising questions about the real benefit of ICI as an adjuvant treatment.

In this context, we aimed to perform a systematic review and a study-level meta-analysis of the latest available evidence of randomized controlled trials evaluating the role of ICI in adjuvant treatment setting of MIUC.

Patients and Methods

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD296298).

Search Strategy

This meta-analysis was carried out according to the guidelines of the Preferred Reporting Items for Systematic Reviews for Meta-Analyses (PRISMA).[17] In October 2021, a literature search on PUBMED/MEDLINE, Scopus and EMBASE databases was performed to identify clinical trials that evaluated adjuvant systemic immunotherapy in patients with localized high-risk MIUC. The keywords used were: (muscle-invasive bladder carcinoma) OR (muscle-invasive urothelial carcinoma) AND (localized) AND (PD-L1) AND (PD-1) OR (immunotherapy).

Inclusion and Exclusion Criteria

Only phase three RCT that evaluated adjuvant systemic immunotherapy with ICI (anti PD1, anti PD-L1 and/or anti CTLA-4) in resected high-risk MIUC carcinoma were included. Trials that used radiotherapy to treat the primary tumor, reviews, case reports, meeting abstracts and non-English articles were excluded.

Data Extraction

Two reviewers (F.S.M.M and V.C.S) independently screened articles to determine eligibility according to the inclusion and exclusion criteria. If there was any disagreement, a third reviewer (A.S) was consulted. The following data were extracted: first author, name of the trial, number of patients, experimental and control arms, DFS, site of primary tumor, pathological staging of primary tumor (pT), pathological lymph node status (pN), use of NAC, and PD-L1 expression.

Statistical Methods and Analysis

RevMan Software 5.4 (Cochrane Collaboration) was used to perform the statistical analysis. Hazard ratios (HRs) were used for time-to-event outcome (DFS) using the estimates reported by the studies. Meta-analyses were made using Inverse Variance method, with random effects model. Analyses were conducted initially for the ITT population of the studies, then repeated in specific subgroups as follow: PD-L1 expression (positive and negative), use of NAC (yes and no) and site of primary tumor (bladder and UTUC). Statistical heterogeneity was assessed using the Cochran's Q and I^2 statistics. Statistically significant heterogeneity was defined as a Cochran Q $P < .10$ or $I^2 > 50\%$. Statistical significance was defined as $P < .05$. Quality assessment of studies was performed by one reviewer (F.S.M.M) using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[18]

Results

The systemic search identified 78 studies potentially eligible for inclusion. After removal duplicates papers and those that did not meet the criteria inclusion, 2 studies were considered for the meta-analysis. Details of literature search and selection of the studies are shown in the PRISMA flowchart (Figure 1). There was no bias identified in the selected studies (Figure 2). In total 1518 patients with resected high-risk MIUC were included in this analysis. The systemic immunotherapy was atezolizumab for 406 patients and nivolumab for 353 patients and 759 patients did not receive any systemic treatment. The details of eligible trials and characteristics of the patients are shown in Table 1a as well as the outcomes and median follow-up are shown in Table 1b.

ITT Population Analysis

The DFS results for ITT population were based on 1518 patients of selected trials.[15,16] In an indirect comparison of the selected trials, the forest plot (Figure 3a) demonstrated a statistically non-significant benefit in DFS for the use of adjuvant systemic immunotherapy (pooled HR:0.79, 95% CI 0.62-1.00; z = 2.00). The Cochrane's Q test ($Chi^2 = 2.88$; $P = .09$) and I^2 test ($I^2 = 65\%$) revealed a significant heterogeneity.

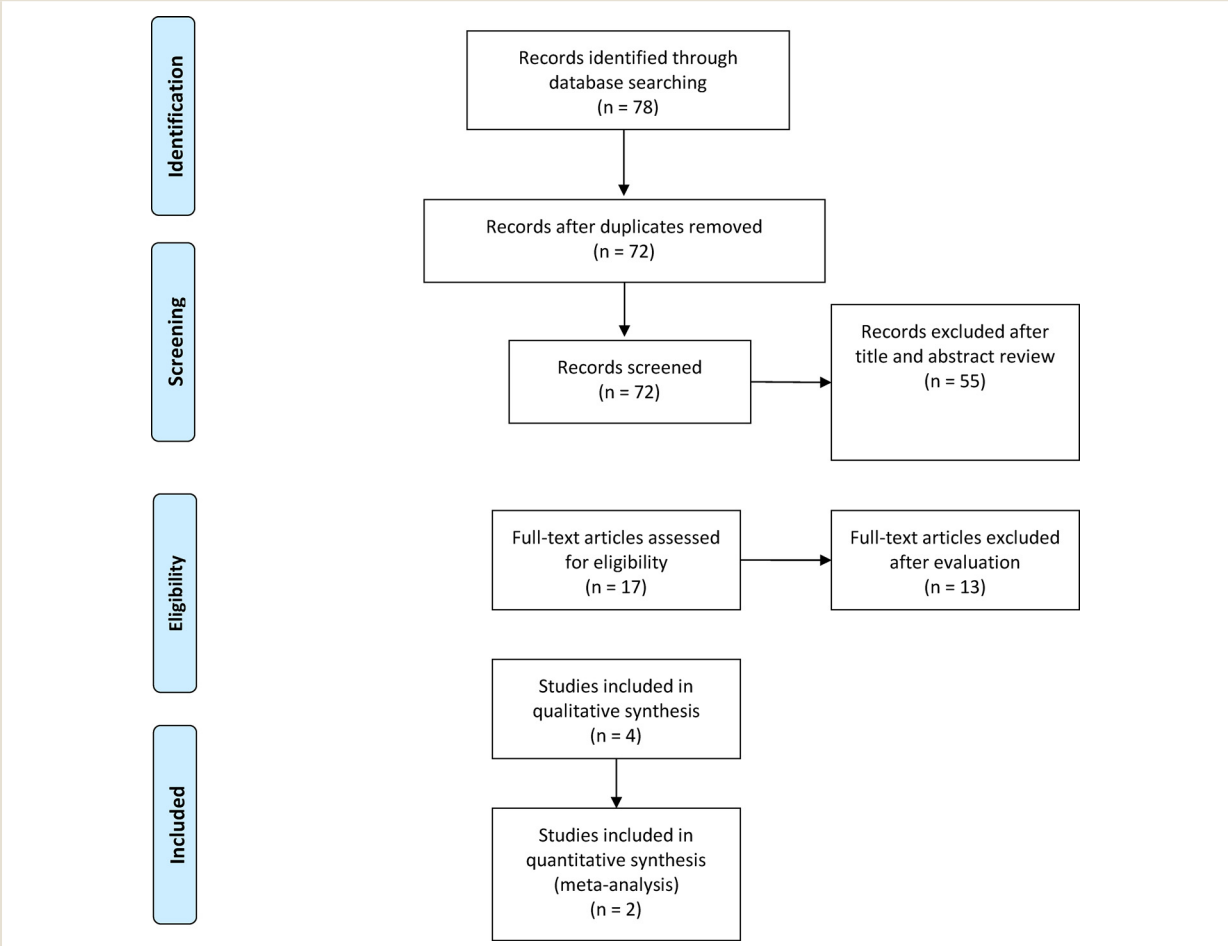
Subgroup Analysis According to PD-L1 Expression

The DFS result for PD-L1 positive patients was based on 392 and 280 PD-L1 positive patients from IMvigor010 and CheckMate274 trials, respectively.[15,16] For this subgroup the forest plot (Figure 3b) demonstrated no benefit in DFS for the use of adjuvant systemic immunotherapy (pooled HR:0.76, 95% CI 0.43-1.35; z = 0.94). The Cochrane's Q test ($Chi^2 = 6.34$; $P = .01$) and I^2 test ($I^2 = 84\%$) revealed a high and significant heterogeneity. The DFS result for PD-L1 negative patients was based on 417 and 419 PD-L1 negative patients from Imvigor010 and CheckMate274 trials, respectively.[15,16] For this subgroup the forest plot (Figure 3c) demonstrated no benefit in DFS for the use of adjuvant systemic immunotherapy (pooled HR:0.81, 95% CI 0.70-1.00; z = 1.96). The Cochrane's Q test ($Chi^2 = 0.05$; $P = .83$) and I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity.

Subgroup Analysis According to use of NAC

The DFS result for those patients who received NAC was based on 385 and 319 patients from Imvigor010 and CheckMate274 trials, respectively.[15,16] For this subgroup the forest plot (Figure 4a) demonstrated no benefit in DFS for the use of adjuvant systemic immunotherapy (pooled HR:0.68, 95% CI 0.42-1.11; z = 1.55). However, the Cochrane's Q test ($Chi^2 = 5.31$; $P = .02$) and I^2 test ($I^2 = 81\%$) revealed a significant heterogeneity. The DFS result for those patients who did not receive NAC was based on 424 and 390 patients from Imvigor010 and CheckMate274 trials, respectively.[15,16] For this subgroup the forest plot (Figure 4b) demonstrated no benefit in DFS for the use of adjuvant systemic immunotherapy (pooled HR:0.95, 95% CI 0.78-1.15; z = 0.56). The Cochrane's Q test ($Chi^2 = 0.13$; $P = .58$) and I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity.

Figure 1 Flowchart showing literature search and trial selection.



Subgroup Analysis According to Site of Primary Tumor

The DFS result for those patients with bladder primary tumor was based on 755 and 560 patients from Imvigor010 and CheckMate274 trials, respectively.[15,16] For this subgroup the forest plot (Figure 5a) demonstrated no benefit in DFS for the use of adjuvant systemic immunotherapy (pooled HR:0.76, 95% CI 0.52-1.11; z = 1.43). The Cochrane's Q test (Chi^2 = 6.23; P = .01) and I^2 test (I^2 = 84%) revealed a significant heterogeneity. The DFS result for those patients with UTUC tumor was based on 54 and 149 (renal pelvis = 96 and ureter = 53) patients from Imvigor010 and CheckMate274 trials, respectively.[15,16] For this subgroup the forest plot (Figure 5b) demonstrated no benefit in DFS for the use of adjuvant systemic immunotherapy (pooled HR:1.31, 95% CI 0.87-1.98; z = 1.30). The Cochrane's Q test (Chi^2 = 0.22; P = .89) and I^2 test (I^2 = 0%) revealed no significant heterogeneity.

Discussion

As far as we know, this is the first systematic review and meta-analysis exploring the role of only ICI in systemic adjuvant treatment setting of MIUC. This is of great clinical relevance considering that some resected MIUC patients are ineligible for platinum-based AC as well as may not have received NAC. The two studies that were identified by our search strategy evaluated different ICIs and had different results. The Imvigor010 study evaluated atezolizumab in the experimental treatment arm, and the primary endpoint, DFS in ITT, was not met.[15] On the other hand, the CheckMate274 study evaluated nivolumab in the experimental treatment arm and the two primary endpoints, DFS in ITT and PD-L1 ≥1% population, were met.[16] Another difference is related to the design and control treatment arms of the studies. While Imvigor010 is an open-label trial and the control treatment arm is observation, the CheckMate274 is a double-blind trial, and the control treatment arm is placebo-controlled. In an open-label trial design, there is a greater risk of bias, especially regarding to the measurement of the outcomes. Thus, the attrition bias, when there is a greater risk that patients who are not receiving active treatment to drop out of the trial, could affect the final evaluation of the outcomes.[19] In this context of cross-study comparisons, the medians DFS in control

Figure 2 Cochrane risk-of-bias tool for RCT.

arms in CheckMate274 and IMvigor010 were unexpectedly very different, 10.8 versus 16.6 months respectively and could have, at least partially, influenced in different hazard ratios between these studies. Additionally, the differences in the schedule of imaging assessments that were different in the trial design and the possibility of some assessment's deviations due to observation only in the Imvigor010 could also be responsible for subtle trial differences. Another point to be highlighted, which could also be related to this difference in median DFS in control arms, is the fact that the CheckMate274 study included a higher number of patients with worse prognosis, such as UTUC and pT4 and a lower number of patients who had received NAC (details of the studies are presented in Table 1).

The evaluation of PD-L1 expression in both trials was performed by different methodologies. While in the IMvigor 010 trial the VENTANA SP142 immunohistochemical assay (Ventana Medical Systems, Oro Valley, AZ, USA) was used, in the CheckMate274 trial the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (DAKO) was used. Perhaps this can also be an important issue, considering the published data that compared four PD-L1 immunohistochemical assays in 368 tumor sample of resected lung cancer which demonstrated that the VENTANA SP142 assay has the lower score than the other three assays.[20]

Regarding the meta-analysis data, despite the trend toward benefit of DFS with the systemic adjuvant immunotherapy in the ITT population, the high heterogeneity of available data for now raises

Table 1 1a. Characteristics and Details of Eligible Trials

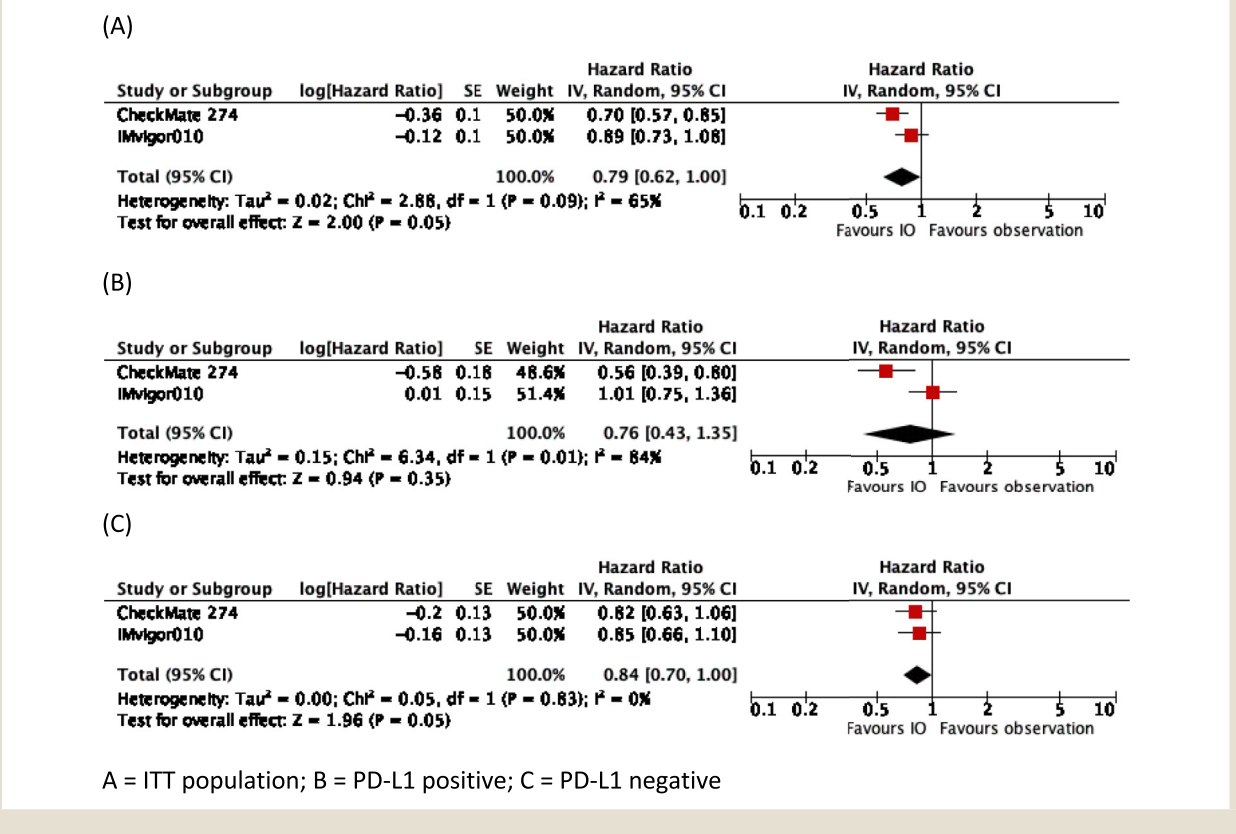
Trial	N	Experimental Arm (Dose and schedule)	Primary Endpoint	Bladder (%)	UTUC (%)	pT4 (%)	pN+ (%)	Prior NACT (%)	PD-L1+ (%)
IMvigor010(15)	809	Atezolizumab (1200mg q3w up to 1 yr)	DFS (ITT)	93	7	8	52	48	48
CheckMate274(16)	709	Nivolumab (240mg q2w up to 1 yr)	DFS (ITT and PD-L1 ≥ 1%)	79	21	16.1	47.3	43.3	39.7

1b. Results of Eligible Trials

Trial	N	Endpoint		Follow-up, mo
IMvigor010(15)		**DFS (ITT), mo**	**DFS (PD-L1 ≥ 1%), mo**	
Atezolizumab	406	19.4	24.8	21.9
Observation	403	16.6	41.4	
HR (CI); P value		0.89 (0.74-1.08); .24	1.01 (0.76-1.35); NI	
CheckMate274(16)		**DFS (ITT), mo**	**DFS (PD-L1 ≥ 1%), at 12 mo (%)**	
Nivolumab	353	20.8	67.2	20.9
Placebo	356	10.8	45.9	
HR (CI); P value		0.70 (0.54-0.89); <.001	0.55 (0.35-0.85); <.001	

ITT = Intention-to-Treat; NACT = Neoadjuvant Chemotherapy; NI = Not Informed; mo = months; UTUC = Upper Tract Urothelial Carcinoma.

Figure 3 Forest Plot for DFS for ITT population and according to PD-L1 expression. A = ITT population; B = PD-L1 positive; C = PD-L1 negative.



A = ITT population; B = PD-L1 positive; C = PD-L1 negative

Figure 4 Forest Plots for DFS according to use of neo-adjuvant chemotherapy (NACT). A = NACT; B = Non-NACT.

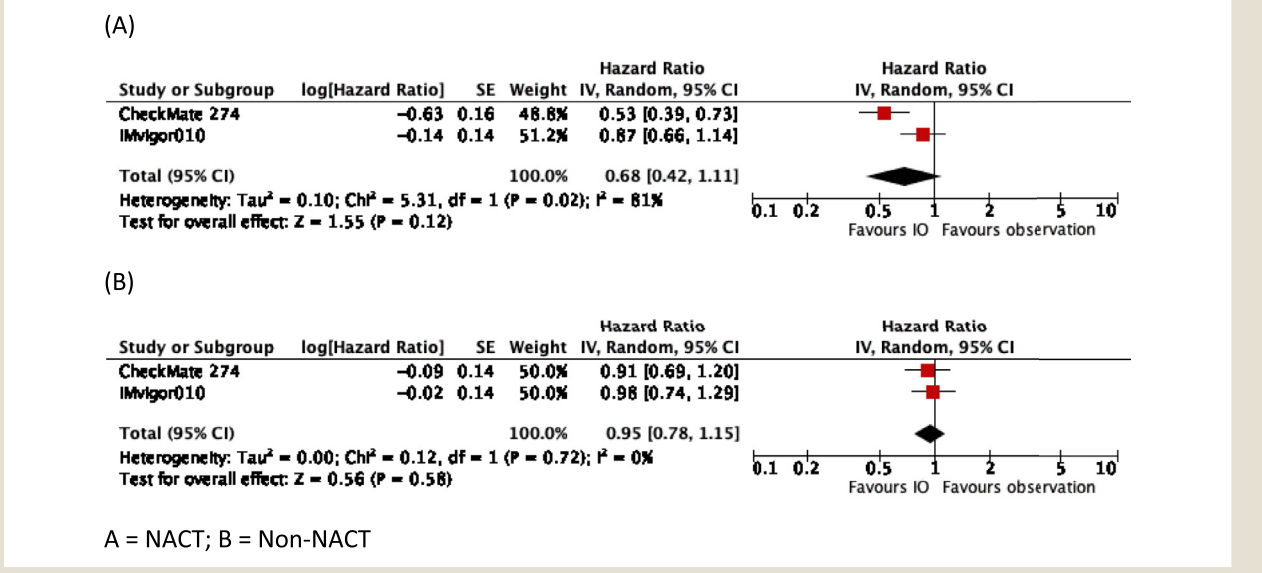
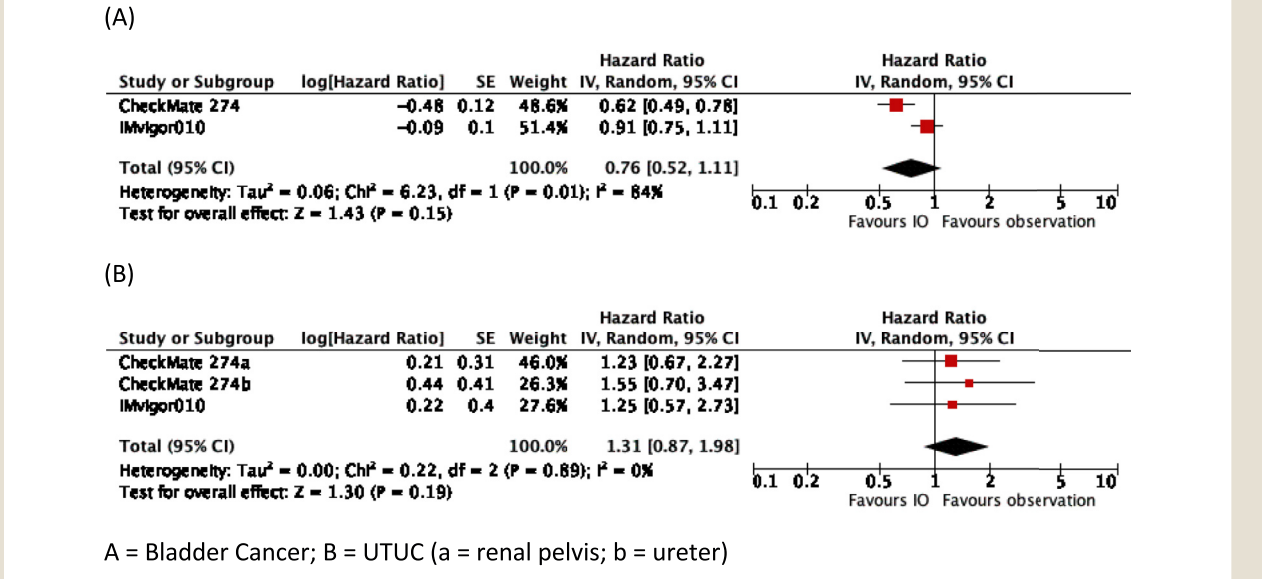


Figure 5 Forest Plots for DFS according to primary tumor site. A = Bladder Cancer; B = UTUC (a = renal pelvis; b = ureter).



questions over the results reliability. Thus, to better assess this heterogeneity subgroup analysis were performed. Looking at PD-L1 subgroup analysis, the difference between the number of PD-L1 positive patients is due to trial design. IMvigor010 was initially designed to accrual only patients with PD-L1 positive tumors, receiving an amendment to recruit all patients after the results from IMvigor210 cohort 1. The analysis of PD-L1 positive patients failed to show an improvement with ICI, but this analysis showed a high heterogeneity. The benefit with nivolumab seems to be clearly positive, while there are not benefit with atezolizumab. It confirms the challenge to use PD-L1 as a biomarker in urothelial carcinoma, and again, raise the question about the confidence in the Ventana – SP142 assay as a valid marker. Zajac M et al., evaluated 335 urothelial carcinoma samples and showed that Ventana – SP142 has lower sensitivity to classified high PD-L1 positive tumors, missing a high number of patients who could benefit more with ICI.[21] The analysis of PD-L1 negative patients showed a trend towards benefit of DFS with systemic adjuvant immunotherapy with no heterogeneity.

This is an important finding because, as in the treatment with ICI for mUC, apparently the use of PD-L1 expression as a biomarker for selecting patients who would likely benefit from the treatment with ICI does not seem to be appropriate and should not be used.

Another interesting finding in the subgroup analysis, with no heterogeneity, was the absence of DFS benefit with systemic adjuvant immunotherapy in the population who did not receive NAC. This may suggest the hypothesis that the systemic adjuvant immunotherapy would be more effective and would only show benefit after a previous NAC. This strategy of sequencing chemotherapy and ICI has already been evaluated in the Javelin Bladder 100 trial which demonstrated an important OS benefit in those patients who had any response or stable disease with platinum-based chemotherapy followed by maintenance with avelumab in the first-line treatment setting of mUC, and other trials did not showed any benefit of ICI alone or in combination with chemotherapy in patients with mUC comparing with chemotherapy.[9,22-24] These findings raise questions about the use of ICI as adjuvant therapy in patients ineligible to cisplatin or patients who refuse NAC. It seems that ICI only, do not confer or has limited benefit in these populations.

Regarding of the site of primary tumor, our analysis did not demonstrated benefit of DFS with systemic adjuvant immunotherapy in the population with UTUC, including, numerically the use of ICI in this population seems to be detrimental. This data should be interpreted with caution because both trials included small numbers of patients with UTUC and our meta-analysis may have amplified this lack of benefit making this result unreliable. In this context, a meta-analysis evaluating ICI and chemotherapy in adjuvant setting recently published by Laukhtina et al demonstrated that UTUC seems to respond better with chemotherapy instead of ICI.[25] However, the hypothesis of molecular subtypes with different response rate to certain treatments can be raised. In this context, alterations in the fibroblast growth factor receptor (FGFR) may be present in up to 35% of UTUC. Theses FGFR alterations are more common in the luminal papillary subtype, which appears to be the molecular subtype less responsive to treatment with immunotherapy.[26,27] Moreover, the UTUC can be considered cold tumors with lower PD-L1 expression, and immune-depleted microenvironment with low lymphocytes CD-8 infiltration.[28-30] There is retrospective data showing similar results in patients with mUC treated with ICI with UTUC and lower tract urothelial carcinoma, but a meta-analysis with six prospective trials failed to show a statistically benefit of ICI over chemotherapy in patients with UTUC.[31-33] All the sub-analysis based on low PD-L1 IHC, upper tract site of primary and NAC were not significant but may have been cofounded by lower power. The trends do show these groups may benefit less. Potentially, individual level analysis will provide better granularity and control for patient stage better.

Lastly, the difference between the drugs could play a role. Nivolumab is an anti PD-1 drug, while atezolizumab is an anti PD-L1 drug. ICI that blocks PD-1, block the interaction between PD-1 with PD-L1 and PD-L2, while an anti PD-L1, block only the interaction between PD-1 and PD-L1, leaving PD-L2 free to interact. Urothelial carcinoma express PD-L2, and this expression seems to be related to poor prognosis and related to regulate T-cell response.[34-36] Although, there are no head-to-head comparison between anti PD-1 and anti PD-L1 in clinical practice, some retrospective data and some pooled studies analysis showed better results with anti PD-1 over anti PD-L1 drugs.[37-39]

Future Directions

For a better selection of patients with MIUC who could benefit from adjuvant immunotherapy, the assessment of biomarkers is essential. In this context, a posthoc analysis of IMvigor010 with 581 patients who had circulating tumor DNA (ctDNA) after surgery demonstrated that the population who was positive for ctDNA and received atezolizumab had improved DFS (HR:0.58, 95%CI:0.43-0.79; $P = .0024$) and overall survival (OS) (HR:0.59, 95%CI:0.41-0.86). It is interesting to note that this benefit has not been demonstrated for patients who were negative for ctDNA.[40] Based on these data, an ongoing prospective randomized trial, IMvigor011 (NCT04660344) is randomizing patients with the same characteristics of both studies in this meta-analysis, and that has ctDNA positive within 21 months from surgery to receive atezolizumab or placebo.[41] From now on, further studies are needed to validate these findings and soon we may have this biomarker tool for use in daily clinical practice. And also to add more data and understand the real benefit of adjuvant immunotherapy, as soon as possible, the results of the AMBASSADOR trial (NCT03244384) that is evaluating the use of pembrolizumab in the adjuvant setting in the high-risk MIUC population are expected.[42] A meta-analysis preferably using individual level data after the publication of these new studies will be warranted.

Conclusion

Although, the use of ICI, seems to confer benefit in disease free survival in the adjuvant setting in patients with high risk of relapse, there are some groups that may not have benefit. Patients with PD-L1 negative tumors, UTUC, and in patients who did not receive NAC the use of ICI is questionable. These data reinforce the importance of NAC with cisplatin in all eligible patients and did not permit the omission of NAC in patients who will receive an ICI as adjuvant therapy. Based on these data, the use of ICI as adjuvant therapy in patients ineligible to cisplatin, should be recommended carefully. There is a need to keep on trying to identify those patients in whom adjuvant use of ICI may translate in a higher clinical impact.

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