Antibody Drug Conjugates in Urological Cancers: A Review of the Current Landscape

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Abstract

Purpose of Review Our review delves into the progress across urological malignancies and discusses ongoing challenges and future directions in antibody-drug conjugate (ADC) development, emphasizing their transformative potential in cancer care.

Recent Findings ADCs have advanced from hematologic to solid tumors, notably in breast cancer, and are now pivotal in metastatic urological cancers as both monotherapies and in combination regimens, underscored by the FDA's approval of enfortumab vedotin and sacituzumab govitecan for metastatic urothelial cancer. Progress in metastatic prostate cancer, particularly with ADCs targeting PSMA and STEAP1, is noteworthy, although renal cell cancer presents ongoing challenges. There is a continual search for agents in the metastatic, relapsed testicular cancer landscape.

Summary ADCs have emerged as a pivotal innovation in oncology, blending targeted antibody therapy with potent cytotoxic drugs, significantly advancing treatment options for urological malignancies.

Introduction

With the age of monoclonal antibodies (mabs) ushered in by Köhler and Milstein's 1975 breakthrough in hybridoma technology, there came potential for developing specific, targeted cancer therapeutics. One of the most significant has been antibody-drug conjugates (ADCs) composed of monoclonal antibodies and cytotoxic agents conjugated by chemical linkers. ADCs target select antigens on the cancer cell surface, allowing precise delivery of cytotoxic drugs minimising systemic toxicity **(1, 2)**. From the 1970s to 1990s, ADCs have been involving various agents from traditional chemotherapy regimens like vinca alkaloids (vinblastine) and anthracyclines (Daunorubicin and Doxorubicin) **(3, 4, 5)**.

It was not until 2000 that an ADC would pass clinical trials and be approved by the United States Food and Drug Administration (US FDA). Gemtuzumab ozogamicin (Mylotarg®) for the treatment of acute myeloid leukaemia (AML) marked a milestone during its accelerated approval on May 17th, 2000, making use of humanised anti-CD33 mabs linked to the cytotoxic antibiotic, calicheamicin **(6, 7, 8)**. Although safety concerns regarding hepatic veno-occlusive disease would lead to the drug's withdrawal in 2010, safety evaluation studies led to regular approval by the FDA on September 2nd, 2017, albeit at lower dosing within a modified treatment schedule **(8, 9, 10)**.

The first approved ADC for use within the solid oncology landscape was trastuzumab emtansine (Kadcyla® or T-DM1) consisting of humanised trastuzumab covalently linked to the cytotoxic small molecule, emtansine. On February 22nd, 2013, it was licensed for human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer after two lines of treatment including trastuzumab and a taxane-based chemotherapy **(11)**.

On December 18th, 2019, Enfortumab vedotin (EV) gained accelerated FDA approval for metastatic urothelial cancer (mUC) in the third line setting post progression on immune

checkpoint inhibitors (ICIs) and platinum-containing chemotherapy **(12)**. Another ADC, sacituzumab govitecan (Trodelvy®) (SG) was granted accelerated approval by the FDA on April 13th, 2021, for the same indication **(13)**. The EV-pembrolizumab combination in cisplatin ineligible mUC was the first combination in urological cancers with accelerated FDA approval on April 3rd, 2023, and regular on December 15th, 2023 **(14, 15)**.

In addition to the above, several other ADCs are in clinical drug development in the mUC landscape. Our comprehensive review article provides an update on these emerging ADCs in early phase clinical trials with interim/final results in the context of renal, urothelial, prostate and testicular cancers.

Renal Cell Cancer

Renal Cell Carcinomas (RCCs) contribute to 3% of cancers globally with an approximate incidence of 430,000 in 2020 and mortality of 180,000 in 2022. More than a third of these statistics are from Europe **(16)**. Five-year survival rates for stage I-II and III RCC are 80% and 60% respectively. Stage IV or metastatic RCC (mRCC) has a 10% 5-year survival prognosis with a median overall survival (mOS) of 10-15 months **(17)**.

The last few decades have witnessed a transition from vascular endothelial growth factor - tyrosine kinase inhibitors (VEGF-TKIs) to ICIs to combination therapies (ICI/ICI or ICI/TKI) as standard of care in the mRCC setting. Such advances have prolonged the mOS to about 2 years or more **(18)**. There is also evidence indicating that a TKI drug-free interval strategy is non-inferior to a conventional continuation strategy for the first-line treatment of mRCC **(19)**. However, despite the improvement of survival outcomes, the problem of treatment resistance remains. Additionally, the lack of a predictive biomarker also means that treatment selection can be challenging **(20)**. Interestingly, in numerous studies, exosomes

derived from dendritic cells have been employed as carriers for anti-tumour agents such as peptides or as effectors subsequent to the stimulation of dendritic cells with specific cancer biomarkers **(21)**.

Therapeutic options post ICI and TKI failure are limited, emphasising the need for innovation. ADCs in the mRCC treatment landscape have made comparatively slower progress when compared with the other genitourinary counterparts. This can be alluded to by the high degree of intratumour heterogeneity, poor tumour uptake, limited tumour-specific proteins, increased drug efflux via overexpression of ATP-driven pumps and alternative forms of the target protein in circulation. Currently there are zero Phase II or III clinical trials studying ADCs within the mRCC setting. Those ADCs that have been evaluated in Phase I are described below **(22) (Table 1)**.

AGS-16M8F(Hyb)/AGS-16C3F(CHO)

Ectonucleotide phosphodiesterases-pyrophosphatase 3 (ENPP3) is expressed in RCC, with negligible expression in healthy tissue, making it an effective target. Two ADCs targeting ENPP3, conjugated to monomethyl auristatin F (MMAF) but derived differently i.e., hybridoma derived AGS-16M8F and Chinese Hamster Ovary (CHO) derived AGS-16C3F. These were trialled sequentially in Phase I by Thompson et al on mRCC patients with progression on at least one treatment line. The AGS-16M8F(Hyb) study looked at various dosing levels of AGS-16M8F within 26 participants –. AGS-16M8F was administered at five dosing levels ranging from 0.6 to 4.8mg/kg every three weeks until unacceptable toxicity or progression **(23)**. One participant had a partial response (PR) of 83 weeks, and one had prolonged stable disease (SD) for 48 weeks. The maximum tolerated dose (MTD) was not reached due to the closure of the study. The AGS-16C3F(CHO) study recruited 34 participants. Fourteen were part of the dose-determining phase (two at 4.8 mg/kg, and six at

3.6 and 2.7 mg/kg) and the remaining participants were part of the dose-escalating phase (2.7 and 1.8 mg/kg dose levels). The disease control rate (DCR) for the whole trial was 59%. Around 12% more patients experienced grade 3 or 4 adverse effects (AEs) in the AGS-16C3F(CHO) study compared to the AGS-16M8F(Hyb) study (61.5% vs 73.5% respectively). Overall, a wider range of AEs were experienced in the AGS-16C3F(CHO) study in comparison to the AGS-16M8F(Hyb) study. AGS-16C3F(CHO), due to its more specific targeting to ENPP3, was recommended for use in metastatic RCC at a lower, more tolerable dose of 1.8mg/kg **(23)**.

CDX-014

T cell Immunoglobulin Mucin-1 (TIM-1) has an expression of more than 70% in RCC especially clear cell or papillary variants and less than 10% expression in normal tissue; hence its potential as a putative target and biomarker. CDX-014 is an ADC consisting of a humanised immunoglobulin G1 directed against TIM-1, covalently linked with monomethyl auristatin E (MMAE) through maleimide conjugation. The safety and preliminary activity of CDX-014 was evaluated in a phase 1 in human trial (**24)**. CDX-014 was administered to 16 mRCC patients who had progressed on at least 2 lines of treatment including VEGF-TKIs (single agent or in combination with ICIs), ICIs and mTOR inhibitors. CDX-014 was administered at dose ranges between 0.15 to 2.0 mg/kg every 2 or 3 weeks until progression or unacceptable toxicity **(24)**.

A median of 4 cycles of CDX-014 were administered using doses of 2mg/kg every 3 weeks and 1.2mg/kg every 2 weeks. Grade 3-4 adverse events were experienced in 31% of patients. These included rash, urosepsis, liver dysfunction, hyperglycemia and neutropenia. One treatment-related death was recorded because of multi-organ failure. CDX-014 did however exhibit anti-tumour activity. Three participants did not show signs of disease progression

with an overall 31% maintaining stable disease > 6 months. Progression-free survival (PFS) was 2.7 months (95%CI 1.2–8.0) and OS was 12.6 months (95%CI 5.7–12.6) **(24)**. In this study, CDX-014 displayed a tolerable toxicity profile in addition to early signs of anti-tumoural activity, thus supporting the further evaluation of ADCs in patients with mRCC as well as other TIM-1 expressing cancers **(24)**.

Urothelial Cancer

Bladder cancer is the tenth most common cancer worldwide with an incidence of 573,000 and mortality of 213,000 in 2020 **(25)**. Urothelial cancers (UC) constitute 90% of bladder cancers. There has been a significant disease uptrend in East Asia, Middle East, North Africa and Central Europe **(25)**. Metastatic urothelial carcinoma (mUC) hosts a 5-year survival of 8%, in comparison to 97% in carcinoma in situ of the bladder and 71% in localised bladder cancer **(26)**.

Traditionally, platinum-based chemotherapy has formed the cornerstone in the management of mUC, achieving an overall survival (OS) of 14-15 months **(27)**. Following progression to platinum, response to second-line chemotherapy agents have been poor. The approval of ICIs across the last decade has revolutionised the management of mUC. As of now, there is no data from randomised trials supporting the hypothesis that DNA damage repair genes predict the response to ICIs among patients with mUC **(28)**. Results from phase III clinical trials demonstrated superiority of pembrolizumab and atezolizumab in improving overall survival in mUC after first-line chemotherapy. Hence, ICIs were established as a new standard of care **(29, 30)**. Despite this, there remains an area of unmet clinical need for non-responders to ICIs, and third-line treatment options for patients who progress after chemotherapy and ICI **(31, 32)**.

ADCs have broadened the mUC treatment horizon over the last decade. Till date, 2 ADCs i.e., EV and SG have been FDA approved as touched upon previously **(Table 2)**.

Enfortumab Vedotin (EV)

EV utilises an antibody directed against nectin-4, a cell adhesion molecule overexpressed in 80% of bladder cancers **(33)** and 60% of upper urinary tract cancers **(34)**. The cytotoxic payload of EV contains the microtubule inhibitor MMAE. Its accelerated approval in 2019, as mentioned aforesaid, was based on interim results of the EV-201 phase II trial by Rosenberg et al **(35)**. Cohort 1 consisted of 301 participants with mUC previously treated with 2 lines assigned to receive EV, with another 307 participants assigned to control with standard chemotherapy. mOS with EV was significantly greater than that of the chemotherapy arm (12.88 vs 8.97 months; HR=0.75; 95% CI, 0.56 to 0.89; p=0.001), as was PFS (5.55 vs 3.71 months; HR=0.62; 95% CI, 0.51 to 0.75; p<0.001) **(35)**. EV-201 also demonstrated similar results in Cohort 2 of mUC patients ineligible for standard chemotherapy, showing a benefit of EV second line in cisplatin ineligible mUC patients **(36, 12) (Figure 1)**. Full FDA approval for the use of EV monotherapy in mUC following failure of platinum chemotherapy and ICI was achieved in 2021 following the preliminary results of the phase III EV-301 trial **(37, 38)**. Two years of follow up from the EV-301 cohort confirmed a significantly meaningful and maintained benefit of EV in this setting, with a tolerable side effect profile similar to control (grade 3 adverse events 52.4% vs 50.5%) **(39)**.

Long-term outcomes of mUC remain poor despite ADC advancements in the second- and third-line setting. Accelerated FDA approval for the use of combination EV and pembrolizumab was granted in 2023 for mUC patients ineligible for platinum-based chemotherapy. This approval followed results from Cohort K of the phase Ib/II EV-103 trial, which showed EV plus pembrolizumab in comparison to EV monotherapy had a higher ORR

(64.5%, 95% CI 52.7-75.1 vs 45.2%, 95% CI, 33.5-57.3) with no new safety concerns **(40)**. This approval was confirmed by the phase III EV-302/KEYNOTE-A39 trial, leading to regular FDA approval for EV plus pembrolizumab first-line in treatment-naive mUC. The EV-302 trial, a Phase 3 study, assessed the efficacy of EV combined with pembrolizumab versus platinum-gemcitabine chemotherapy in previously untreated mUC. It demonstrated statistically significant improvements in progression-free survival (PFS) and overall survival (OS), nearly doubling median PFS and OS for patients in the EV + pembrolizumab arm compared to chemotherapy. The treatment was well-tolerated, with a manageable safety profile **(41)**. Additionally, an update presented at the 2024 ASCO GU demonstrated the efficacy of the treatment is independent of cisplatin eligibility, PD-L1 expression, and the presence of liver metastasis. Current data suggests that this combination significantly surpasses platinum-based treatments as a first-line therapy after a long period, indicating it should become the standard first-line treatment. However, challenges such as EV-related toxicities, the necessity of continuing EV until progression, and issues of cost and accessibility remain significant barriers to its widespread adoption **(42) (Figure 1)**.

Sacituzumab Govitecan (SG)

Trop-2 is a calcium signalling receptor overexpressed in 95% of urothelial cancers, thought to mediate tumour growth and metastasis **(43)**. SG is an anti-trop-2 mab conjugated with SN-38, a topoisomerase IB inhibitor. Accelerated FDA approval of SG use in mUC was granted in 2021 based on the phase II TROPHY trial which assessed the safety and efficacy profile of SG in mUC patients previously treated with platinum chemotherapy and ICI. For 113 participants with mUC (cohort 1), TROPHY demonstrated an ORR of 27.4% (95% CI 19.9-36.9), including 6 patients achieving a complete response (CR) (5.3%) **(44)**. FDA approval of SV monotherapy in this setting is expected to be confirmed by the ongoing phase III TROPiCS-04 study (NCT04527991) evaluating SG versus physician's choice of

chemotherapy in mUC with progression on platinum therapy and ICI. Additionally, further cohorts of the TROPHY trial are set to investigate SG in combination settings, such as Cohort 3 which is set to evaluate SG with pembrolizumab in mUC progressed on first-line platinum therapy. Preliminary reports from TROPHY-U-01 Cohort 3 identified a tolerable safety profile with an optimistic ORR of 41% (95% CI; 26.3-57.9) for a group of 41 patients **(45)**. Results from long-term follow up are anticipated.

Disitimab Vedotin (DV)

Another target of interest in UC is the human epidermal growth factor receptor 2 (HER2). Multiple ADCs targeting HER2 in mUC have been assessed in early phase clinical trials but await approval for widespread use. Disitamab vedotin (DV) is being tested in various small phase II trial cohorts as monotherapy in mUC, and in combination with ICI and radiotherapy. The NCT04264936 clinical phase Ib/II trial of DV with toripalimab in mUC showed an overall ORR of 76.6% in 2022, but median PFS and OS were not reached **(46)**. Analyzing data from two recently published phase II trials, DV showed a 50.5% objective response rate with manageable side effects. The median duration of response was 7.3 months, with progression-free survival at 5.9 months and overall survival at 14.2 months. Notably, DV was effective even in patients with liver metastases and those previously treated with anti-PD-1/L1 therapies **(47)**. Other trials have yet to reach an endpoint.

Double ADC

The revolutionary phase I Double Antibody Drug Conjugate (DAD) trial was the first to investigate the use of multiple ADCs in combination treatment after 2 lines of therapy. 24 participants received combination EV/SG at a dose of 1.25mg/kg/10mg/kg respectively, achieving an ORR of 70% (95% CI, 47-87%) with 3 patients achieving CR. Grade >=3 AEs were noted in 78% patients, commonest being neutropenia, anaemia, and fatigue. With an

encouraging safety profile and drug activity, the DAD trial paves the way for a new avenue of treatment in mUC **(48)**. Further phase II studies will further evaluate the dose-efficacy relationship of combination EV/SG.

Prostate Cancer

Prostate cancer (PC) has an annual global incidence of greater than 1.2 million men and a mortality burden of greater than 350,000 deaths **(49)**. Five-year survival rates for metastatic hormone sensitive PC (mHSPC) can vary from 30% in de novo synchronous high-volume disease to 70% in metachronous LV disease **(50)**. Metastatic castrate resistant PC (mCRPC) has a median survival of 3.5 years **(51)**.

The treatment landscape has shifted from androgen deprivation therapy (ADT) to treatment intensification strategies i.e., doublet therapy [ADT + chemotherapy/docetaxel or ADT + androgen receptor pathway inhibitor (ARPI)] or triplet therapy (ADT + chemo/docetaxel + ARPI) in the mHSPC setting **(50,52)**. Other than ARPIs and chemotherapy, the spectrum for mCRPC treatment options is multifaceted, including PARP inhibitors, radioligands and immunotherapy along with their combination strategies **(53)**.

Multiple mechanisms of ADT resistance have been established, thus warranting treatment intensification and ARPIs such as enzalutamide or abiraterone. New resistance mechanisms to ARPIs are a pressing issue and strategies to overcome them are an unmet need **(54)**.

In this context, ADCs are being explored in the mCRPC setting as follows **(Table 3)**.

MLN2704

The Prostate Specific Membrane Antigen (PSMA) is a transmembrane protein which is significantly upregulated after androgen deprivation in greater than 70% of the mCRPC

population and is therefore a putative target **(55)**. MLN2704 is an ADC composed of the PSMA targeting mab MLN591 which is linked with the cytotoxic maytansinoid (DM1). A phase I/II ascending dose trial of MLN2704 in 62 treatment naïve mCRPC patients revealed significant neurotoxicity i.e., peripheral neuropathy as the commonest AE (71%) with grade 3 being 10%. PSA_{50} or rather PSA decline of at least 50% was achieved in 8% patients. This ADC also had a narrow therapeutic window. All the above could have been secondary to the rapid deconjugation of the cytotoxic molecule from the mab **(56)**.

PSMA ADC

The PSMA ADC used an IgG1 mab targeting PSMA conjugated to cytotoxic MMAE. Three weekly PSMA ADC at a dosing level of 2.3mg or 2.5 mg/kg was used for 8 cycles in 119 patients, 35 of which were chemotherapy naive. Overall PSA_{50} in 14% patients and 21% of the chemotherapy-naive patients were noted. Response in circulating tumour cells (CTCs) was evidenced as $\geqslant$50% decline in 78% and 89% of all and chemotherapy-naive patients respectively. 5.7% of chemo-naive patients had partial response whereas 60.7% of the overall population had stable disease as best response. Grade 3 or 4 adverse events were experienced during the trial, these included neutropenia and neuropathy **(57)**.

MEDI3726

MEDI3726 contains an IgG1 anti PSMA mab conjugated to a pyrrolobenzodiazepine dimer payload (PBD). A phase I/Ib dose escalation trial (0.015 -> 0.03 -> 0.06 -> 0.15 -> 0.3 -> 0.6 mg/kg) on 33 mCRPC patients with prior ARPI or chemotherapy showed grade 3/4 AEs in 15 patients with treatment discontinuation in 11 of them. Most common AEs were thrombocytopenia and hepatotoxicity. Although only 4 patients showed disease response according to composite PSA_{50} and CTC criteria, considering AEs, the trial was discontinued **(58)**.

ARX517

ARX517 also has a PSMA targeting mab conjugated to amberstatin-269 payload. A phase I/II dose escalation (three weekly) trial on 24 mCRPC patients with >=1 ARPI treatment lines showed PSA_{50} in 8 patients and good CTC decline in 12 patients. Responses increased on higher doses. However, no serious AEs were reported except four grade 3 AEs including thrombocytopenia and lymphopenia. This was a good positive trial with durable response and plans for dose expansion **(59)**.

DSTP3086S

Six-transmembrane epithelial antigen of the prostate 1 (STEAP1) is another transmembrane protein with minimal expression in non-prostatic tissue but greater than 70% expression in mCRPC and therefore, another promising target. Targeting it is an IgG1 mab MSTP2109A linked to MMAE, together comprising the DSTP3086S. A phase I dose escalation (0.3mg to 2.8mg/kg every three weeks) trial on 77 high STEAP1 expressing treatment naive mCRPC patients showed grade ≥ 3 AEs in 26 patients with 4 having neutropenia. 62 out of 77 patients tolerated a dosing level of greater than2mg/kg, out of which 11 showed PSA_{50} response and 16 had good CTC response. Two out of46 RECIST evaluable patients showed partial response. Owing to acceptable tolerability and antitumour activity data, phase II is being planned with a dose of 2.4mg/kg every three weeks **(60)**.

SG

SG, as discussed above, is an approved ADC for urothelial cancer. TROP-2 having expression levels of greater than 80% in mCRPC, SG was trialled in the phase II setting on 20 mCRPC patients having progressed on ARPIs. PSA stabilisation occurred in all patients although there were PSA_{50} nil responses. Six-month rPFS was a modest 45%. Four had grade

3 AEs of which neutropenia was the most commonly occuring. This was another promising trial with an acceptable safety profile **(61)**.

FOR46

CD46 is a tumour selective isotope specific to mCRPC with high expression after treatment with ARPIs. FOR46 is an anti CD46 mab conjugated to MMAE. A phase Ia/Ib dose escalation (0.1mg - 3mg/kg every three weeks) trial on 33 mCRPC patients progressing on ARPI showed neutropenia as the only significant grade 3 AE. Four out of 18 RECIST evaluable patients had a partial response. Fourteen out of 31 PSA evaluable patients yielded PSA_{50} responses. In terms of good safety profile and antitumour activity, FOR46 warrants further steps into clinical trial investigation **(62)**.

MGC018

B7-H3 is a member of the B7 protein family, a type of peripheral membrane protein situated on activated antigen presenting cells. B7-H3 has been shown to have high levels of expression in various types of solid tumours but minimal expression in normal tissue. MGC018 contains anti-B7-H3 mab connected to a duocarmycin payload. This was trialled in a phase I clinical trial using a 3mg/kg dosing schedule every three weeks. Out of the 80 participants recruited to the trial, 50% had a background of mCRPC whilst the remaining 50% of participants had malignancies originating from head and neck squamous cell cancer, non-small cell lung cancer and triple negative breast cancer. Thirteen out of 40 mCRPC patients had measurable disease, out of which 7 were evaluable and 4 out of 7 experienced partial response. Eleven patients demonstrated a good PSA_{50} response. These promising results have encouraged further trial enrollment **(63)**.

Testicular Cancer

Testicular Germ Cell Tumours (TGCTs) are rare, with a global incidence of 1.5 per 100, 000 **(64)**. They comprise 1% of male malignancies and are the most common type of cancer found in young men aged between 15 and 35 **(64)**. Metastatic TGCTs (mTGCTs) of the International Germ Cell Cancer Collaborative Group (IGCCCG) "good risk" category have high cure rates i.e., 5-year survival rates of greater than 90% after frontline platinum-based chemotherapy regimens **(65)**. However, these rates drop to 80% in the "intermediate" and 50-60% in the "poor risk" categories, with a significant degree of platinum resistance **(66)**. Relapse after cure may usually occur within 2 years in the minority but late relapse carrying a poor prognosis occurs in 1%-4% cases. These usually present with unresectable multisite disease where high-dose or dose-intense chemotherapy regimens are used to enhance surgical resection rates and hence optimal survival outcomes **(67)**.

The immunotherapy and targeted therapy landscape for mTGCTs are very limited till date. However, CD30, found on activated T cells, is expressed in around 95% of testicular embryonal carcinoma. Persistence after multiple chemotherapy options, making it a putative target. The ADC brentuximab vedotin (BV), containing a chimeric CD30 antibody linked to MMAE has been recently trialled in phase II as follows **(68, 69)**.

Necchi et al's single centre experience implemented a constant dosing schedule of 3 weekly 1.8mg/kg BV on 24 biopsy proven CD30+ mTGCT patients having progressed on ≥ 2 lines of platinum-based chemotherapy (+/- high dose). Efficacy wise, an appreciable tumour marker decline was noted in 7 patients after first dose and 4 patients after second dose. Overall metabolic PR in 3 patients was noted on PET/CT imaging whereas RECIST criteria yielded 1 PR (>80%) and 1 CR. The 3-month PFS was 22.2% (95% CI 3.4-51.3%) and 6-month OS was 77.8% (95% CI 36.5 - 93.9%). Safety wise, there was 1 case of grade 3 AE (hyperglycaemia) with consequent dose reduction but nil cases of treatment discontinuation.

BV was henceforth tolerable with acceptable antitumor activity potentiating a more upfront usage, possibly before high dose in anticipation of developing rapid resistance **(68)**.

Akshar et al's multicentre experience trialled the same dose of BV as previous in 18 non seminomatous mTGCTs refractory to first line platinum-based chemotherapy and at least 1 salvage regimen. Depending on biopsy proven CD30 status, 7 patients were in the CD30+ cohort while the rest in the CD30- counterpart. Although there were 2 grade 3 AEs from a safety perspective, disease response was not noted efficacy wise. Rather, there was disease progression in 10 patients and stable disease in 6 (with 5 of them demonstrating a transient tumour marker decline of >50%). This trial showed nil clinical benefit of BV **(69)**.

The above conflicting results of the only 2 clinical trials completed till date on BV only warrant the continual search for ADCs in the testicular cancer landscape **(Table 4)**.

Conclusion

The development of ADCs in the field of oncology highlights the potential of personalised therapies; the seminal "magic bullet" that Paul Ehrlich spoke of more than a century ago. The approval and successful use of ADCs has given direction for these developments to be aimed at urological cancers, where late stage/advanced/metastatic cancers respond poorly to traditional systemic therapies or surgery. Enfortumab vedotin has emerged as a pivotal treatment with its high efficacy and manageable toxicity profile, underscoring the ability of such therapeutics to fulfil unmet needs in second-line therapy for advanced urothelial cancer patients. Ongoing trials are exploring the use of EV in early-line treatments as well as alternative ADC treatments, such as disitamab vedotin and multiple ADC combination treatments. While treatments as effective as EV are yet to be approved in other urological cancers, early-stage studies show promising results. In prostate cancer, the trials of

MLN2704, MGC018, and sacituzumab govitecan among others, have shown varying degrees of efficacy and safety profiles, emphasising the complexity of treating mCRPC and the need of the hour being to understand pharmacokinetics, dosing, and toxicity to optimise these treatment options. For renal cell carcinoma, agents such as AGS-16M8F and CDX-014 have undergone Phase I trials and show clear potential as treatment options, despite the challenging barrier of high treatment resistance. In testicular cancer, when conventional treatments fail, ADCs such as brentuximab vedotin have been identified as possible salvage therapies for patients with relapsed or refractory germ cell tumours. In conclusion, the development and implementation of ADCs represent a significant advance in oncology, embodying the concept of targeted therapy envisioned over a century ago. Ongoing and future research is pivotal in expanding the utility of ADCs across various stages of urological cancers, including early treatment settings and as potential standard care options. Challenges remain in overcoming resistance, optimizing ADC components, cost and accessibility and integrating ADCs with existing treatments to enhance therapeutic outcomes. Continued exploration for novel targets and combination strategies, alongside managing adverse events, will be crucial in harnessing the full potential of ADCs in urological oncology.

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Conflicts of Interest

None declared

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Conceptualisation and design – AG1

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