Antibody-drug conjugates in prostate cancer: Emerging strategies to enhance therapeutic index and current clinical landscape (Review)

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Abstract. The global incidence of prostate cancer (PCa) is rising. Localized PCa can be managed through surgical intervention or radiotherapy, but certain patients may experience recurrence or develop metastatic disease following localized treatment. Despite aggressive therapeutic approaches, the majority of metastatic patients with PCa will eventually progress to metastatic castration-resistant PCa, with limited treatment alternatives and a dismal prognosis. The treatment options for advanced PCa are continuously evolving, yet there remains a demand for further innovative therapeutic approaches. Antibody-drug conjugates (ADCs) represent a novel class of targeted medications comprising a humanized monoclonal antibody, a linker and a cytotoxic payload. ADCs primarily bind to antigens that are upregulated on the surface of PCa cells but are minimally expressed on normal cells. At present, a variety of targets for ADCs have been identified in the treatment of PCa, encompassing prostate-specific membrane antigen, STEAP family member 1, trophoblast cell-surface antigen 2, CD46, B7-H3, tissue factor and delta-like protein 3, each with one or more specific ADC that has shown encouraging results in the PCa field. In the present review, the developmental course, composition and mechanism of action of ADCs are explored, with a specific focus on recently published studies and ongoing trials aimed at investigating the efficacy and safety of ADCs in treating PCa. Lastly, ongoing challenges in ADC development and corresponding strategies to combat them are discussed.

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1. Introduction

The incidence of prostate cancer (PCa) is increasing yearly, and in 2022, PCa was the second most common cancer in men, with >1 million new cases and >390,000 deaths worldwide (1). Localized PCa can be treated by surgery or radiotherapy and has a good prognosis. Although the treatment of metastatic PCa is improving, the 5-year survival rate of metastatic PCa is only 32% (2). PCa is an androgen-dependent tumor and androgens can strongly promote PCa cell proliferation and metastasis. Thus, androgen deprivation therapy (ADT) is a modality that has been used to treat PCa for decades and has become one of the most effective treatment options for patients with metastatic hormone-sensitive PCa (mHSPC) (3). Recently, a number of studies have shown that ADT combined with docetaxel or androgen receptor pathway inhibitors (ARPIs) can improve the overall survival (OS) of patients with mHSPC (4-8), and this new treatment regimen has become the standard treatment for this disease (9). Unfortunately, despite the advances in therapeutic drugs, HSPC can gradually lose sensitivity to treatment and eventually develop into metastatic castration-resistant PCa (mCRPC) (10). First-line treatment of mCRPC includes ARPIs, docetaxel, sipuleucel-T, Ipatasertib and poly (ADP-ribose) polymerase inhibitors combined with an ARPI (11). All patients with mCRPC who receive first-line treatment will eventually experience disease progression (11).

Subsequent treatment options for mCRPC include several novel agents. For instance, antibody-drug conjugates (ADCs), consisting of monoclonal antibodies (mAbs) and potent cytotoxic payloads conjugated by chemical linkers, are a therapeutic option that has been rapidly developing in recent years (12). The basic principle of ADCs is the specific combination of antigens and antibodies. Antitumor drugs can specifically bind to antigens on the surface of cancer cells and eliminate these cells through antibody delivery, which reduces the toxicity of antitumor drugs (13). The enhanced antitumor efficacy of ADCs leads to an improved quality of life of the patient and reduced toxicity compared with conventional chemotherapies (14). Additionally, ADCs targeting the same molecular pathway may retain efficacy in patients who have developed resistance to specific targeted therapies, thereby expanding their potential indications for antitumor treatment (15). Human epidermal growth factor receptor 2 (HER2) serves as a crucial therapeutic target for advanced breast cancer, and in cases where patients with metastatic breast cancer develop resistance to anti-HER2 targeted agents, anti-HER2 ADCs can still effectively exert antitumor activity (16). Notably, the anti-HER2 ADC trastuzumab deruxtecan has demonstrated efficacy even in patients with advanced breast cancer and low HER2 expression (17). ADCs are also effective in targeting novel therapeutic targets. For instance, sacituzumab govitecan (SG), which specifically targets trophoblast cell-surface antigen 2 (TROP-2), offers additional treatment alternatives for advanced triple-negative breast cancer management (18).

At present, patients with advanced PCa, such as mCRPC, have few treatment options and the emergence of ADCs brings new alternatives for these patients. Although ADCs were developed decades ago for treating patients with advanced solid tumors, their use in PCa treatment is still in the clinical drug development stages. Therefore, how to further utilize ADCs in the field of PCa treatment is the current clinical challenge, including reducing adverse events (AEs) and improving effectiveness. In the treatment of PCa, several therapeutic targets of ADCs have been developed, including prostate-specific membrane antigen (PSMA), STEAP family member 1 (STEAP1), TROP-2, CD46, B7-H3, tissue factor (TF) and delta-like protein 3 (DLL3).

In the present review, first, the developmental course, structural composition and mechanism of action of ADCs is illustrated. Second, the clinical outcomes of ADCs in the field of PCa treatment as well as the ongoing clinical trials are systematically described. Finally, the ongoing challenges in ADC development and the corresponding strategies to overwhelm them are discussed.

2. Development of ADCs

ADCs originate from the idea by Paul Ehrlich in 1913 that 'antibodies are in a way magic bullets that identify their target themselves without harming the organism' (19). In 1975, Köhler and Milstein (20) developed hybridoma technology and successfully produced mAbs, which was an important step in turning this 'idea' into a treatment reality. In 1983, ADCs were first used in clinical trials; however, clinical efficacy was not successful due to the inclusion of murine mAbs (19). This prompted researchers to further develop ADCs containing humanized or chimeric antibodies that can eliminate cancer cells through multiple mechanisms, such as antibody-dependent cytotoxicity, interference with signaling, complement-dependent cytotoxicity and immune regulation (21,22). In 1990, novel ADCs containing chimeric or humanized antibodies were tested in clinical trials. Ultimately, ADCs passed clinical trials and were approved by the United States Food and Drug Administration (FDA) in 2000. The first ADC approved for use in hematological malignancies was gemtuzumab ozogamicin, which was approved by the FDA on May 17, 2000, for the treatment of $CD33^+$ acute myelogenous leukemia (23). Furthermore, the FDA granted approval to trastuzumab emtansine on February 22, 2013, marking the first authorization of an ADC for the treatment of solid tumors in patients with $HER2^+$ advanced breast cancer (24,25). On December 18, 2019, enfortumab vedotin was approved by the FDA for the treatment of metastatic urothelial carcinoma, which was the first ADC approved for the treatment of urological malignancies (Fig. 1) (26). At present, >10 ADCs have been approved by the FDA and ~200 ADCs are being evaluated in clinical trials. ADCs have changed the treatment strategy of numerous malignant tumors and have expanded the treatment options for patients with advanced tumors; however, to the best of our knowledge, there are still no approved ADCs for PCa.

3. Components and mechanism of action of ADCs

ADCs are developed based on enhanced antibody technology and comprise three essential components: A mAb that specifically targets tumor surface antigens, a potent cytotoxic payload engineered to induce damage to DNA or tubulin within the targeted cancer cells and a linker that firmly attaches the antibody to the payload (Fig. 2) (27). The general mechanism of action of ADCs is shown in Fig. 3. Briefly, once introduced into the bloodstream, ADCs specifically recognize and bind to antigens that are upregulated on the surface of cancer cells. Subsequently, these bound ADCs undergo rapid internalization into the cells, where they are then processed by intracellular lysosomes for the release of the cytotoxic payloads (28). After being released from the antibody within the cell, a portion of the hydrophobic payload has the ability to diffuse beyond the target cell and effectively eliminate surrounding antigen-negative cancer cells or non-malignant cells. This phenomenon, referred to as the bystander killing effect, has been extensively studied, and research indicates that this effect can significantly augment the antitumor activity of ADCs (29-31).

The antibody component of ADCs, which serves a crucial role in specifically binding to target cell surface antigens, has undergone significant advancements and refinements in recent decades (28). The targets of ADCs (cell surface antigens) should ideally be upregulated on cancer cells while maintaining low expression on normal cells. This specificity enables the specific binding of ADCs and the subsequent release of toxic payloads, thereby minimizing the cytotoxic effects on normal cells (32). The identification of two distinct types of tumor surface antigens, namely tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs), has been accomplished (33). TAAs are upregulated in cancer cells and downregulated in normal cells, whereas TSAs are exclusively expressed on the

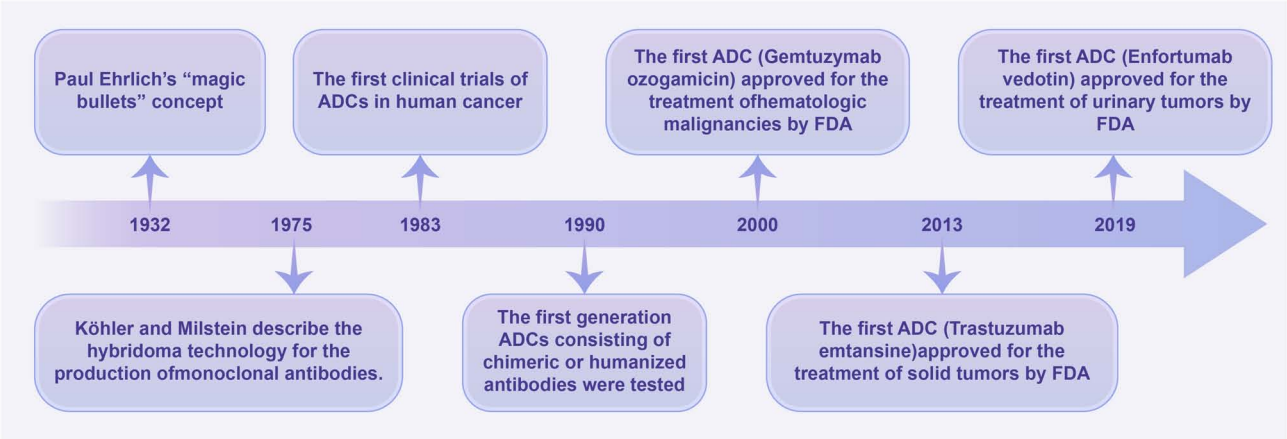

Figure 1. The development of ADCs. ADCs, antibody-drug conjugates.

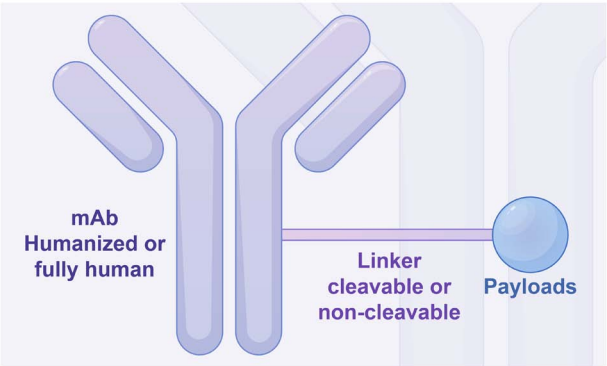

Figure 2. General structure of antibody-drug conjugates.

surface of cancer cells rather than normal cells. Consequently, TSAs can serve as markers for discriminating between tumor and normal cells (34). The use of a TSA as the target of an ADC will greatly improve the effectiveness of the ADC and reduce the toxicity to normal cells. However, most of the ADC targets in current clinical trials are TAAs (35).

The linker, a crucial component of ADCs, has a pivotal role in determining the toxicity and efficacy of ADCs. Once introduced into the bloodstream, it is imperative for the linker to maintain stability throughout circulation to prevent premature detachment of toxic payloads from the ADCs (36). The two primary types of linkers in current use are cleavable and non-cleavable linkers. At present, the majority of ADCs employ cleavable linkers that incorporate chemical triggers capable of efficient cleavage, leading to the release of cytotoxic payloads (37). These linkers are designed to be cleaved after internalization into cancer cells, ensuring optimal efficacy by releasing toxic loads at the desired site. However, premature cleavage of these cleavable linkers in circulation results in the early release of effective payloads, thereby increasing blood toxicity and diminishing the effectiveness of ADCs (38). Non-cleavable linkers consist of stable bonds and are resistant to protease degradation. These linkers are an integral part of the payload, and the release of the cytotoxic payload occurs only after complete internalization of ADCs into the cell. This mechanism enhances the efficacy while reducing the toxicity of ADCs (37). At present, research is focused on the development of novel linkers with improved stability, solubility and release characteristics.

The cytotoxic payload is the primary component responsible for the eradication of cancer cells by ADCs, which is released subsequent to ADC internalization into the cellular milieu (39). The *in vitro* toxicity levels of commonly used chemotherapies are in the micromolar range, whereas the payloads utilized for ADCs exhibit sub-nanomolar or even picomolar levels of cytotoxicity *in vitro* (40). The current repertoire of cytotoxic payloads utilized for ADCs primarily encompass potent tubulin inhibitors, DNA damage agents and recently developed immunomodulators (41). Tubulin inhibitors function by disrupting microtubule-dependent mitosis. Prominent tubulin inhibitors include monomethyl auristatin (MMA)E, MMAF and their maytansine derivatives, DM1 and DM4 (42). The half-maximal inhibitory concentration (IC_{50}) values of microtubule inhibitors typically fall within the nanomolar range, whereas DNA damaging agents can exhibit IC_{50} values as low as picomolar (43). Therefore, ADCs are occasionally more effective when conjugated to DNA damaging agents, even when targeting cells with low surface antigen expression (43). The currently utilized DNA damaging agents include calicheamicins and pyrrolobenzodiazepine dimers (PBDs), as well as topoisomerase I inhibitors such as SN-38 and the exatecan derivative (DXd). The field of ADCs is witnessing a surge in the development of novel payloads, with small molecule immunomodulators, also known as immunostimulatory antibody conjugates, emerging as a promising class of cytotoxic agents (44). This innovative payload holds great potential in enhancing the efficacy of ADCs and extending patient survival.

4. ADCs in PCa

PSMA. PSMA is a transmembrane protein consisting of 750 amino acids that is located on the surface of prostate epithelial cells (45). The expression of PSMA is typically low in normal prostate tissue, but it undergoes a notable increase of >1,000-fold in PCa. Moreover, the upregulation of PSMA expression is positively correlated with a higher tumor grade, castration resistance and tumor metastasis (46). Therefore, PSMA has

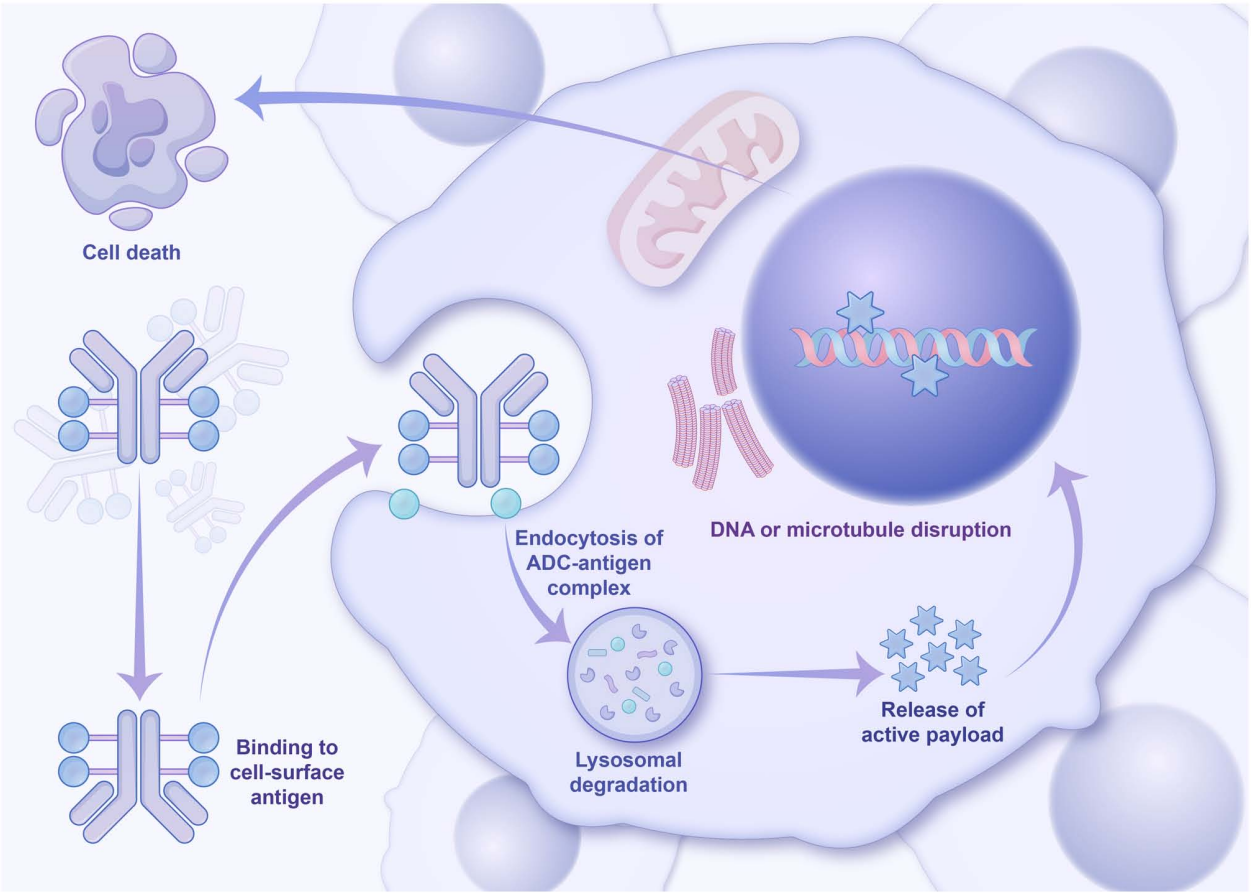

Figure 3. The general mechanism of action of ADCs. ADCs, antibody-drug conjugates.

emerged as a commonly employed target for the diagnosis and treatment of PCa. At present, four PSMA-targeting ADCs, namely MLN2704, PSMA ADC, MEDI3726 and ARX517, have been developed for clinical trials.

MLN591 is a deimmunized anti-$PSMA_{ext}$ mAb, which exhibits rapid internalization and high affinity for the external domain of PSMA, and MLN2704 is an ADC consisting of MLN591 linked to DM1, a potent chemotherapeutic drug that acts against microtubules (47). MLN2704 exhibits rapid internalization upon binding to PSMA, resulting in the intracellular release of DM1 and the subsequent eradication of PCa cells. MLN2704 has shown dose-and schedule-dependent antitumor activity in a PCa xenograft model (48). The initial human trial of MLN2704, aimed at assessing the safety profile of doses ranging 18-343 mg/m^2 administered every 4 weeks, encompassed a cohort of 23 patients with mCRPC. Among this cohort, 3 individuals experienced grade 3 drug-related AEs, and while no grade 4 toxicities were observed, 8 patients reported neuropathy. Notably, a prostate-specific antigen $(PSA)_{50}$ response was detected in ~22% of the participants. These findings unequivocally established the favorable safety profile of MLN2704 (Table I) (49). The PSA_{50} response is defined as a ≥50% decrease from the initial level of serum PSA, which is confirmed by a measurement taken at least 4 weeks after treatment. In a subsequent phase I/II trial including 62 patients with mCRPC, only 8% (5 out of 62) of patients demonstrated a PSA_{50} response, while an equal proportion of patients (8%) exhibited PSA stability lasting for ≥90 days. However, the majority of patients (71%) experienced peripheral neuropathy and a small percentage (10%) encountered grade 3/4 AEs (47). Due to the limited clinical efficacy of MLN2704 and its narrow therapeutic range, further clinical studies were not conducted.

The PSMA ADC is prepared by conjugating a fully human anti-PSMA mAb with MMAE through a valine-citrulline linker (50). The PSMA ADC undergoes rapid internalization upon binding to PSMA, leading to the release of MMAE within the cell and the subsequent induction of cell cycle arrest and apoptosis (50). The initial 2019 phase I clinical trial of PSMA ADC involved dose escalation and included patients with mCRPC who had previously undergone taxane-based chemotherapy (51). The aforementioned study aimed to determine the maximum tolerated dose of PSMA ADC and evaluate its safety, tolerability and pharmacokinetics (51). The PSMA ADC exhibited encouraging antitumor efficacy and tolerable toxicity in this phase I trial. The findings prompted a subsequent phase II trial involving 119 patients with mCRPC, wherein 14% achieved a PSA_{50} response, >75% experienced at least a 50% reduction in circulating tumor cell (CTC) counts and 65% transitioned from an unfavorable to a favorable CTC status (52). The most frequently observed treatment-related AEs (TRAEs) of grade ≥3 in this study included neutropenia, fatigue, electrolyte imbalance, anemia and neuropathy (52). Serious AEs (SAEs) encompassed dehydration, hyponatremia, febrile neutropenia and constipation. Among the subjects who received a dosage of 2.5 mg/kg, 2 succumbed to sepsis.

Table I. The clinical trial data of ADCs in PCa.

First author/s, year	Drug	Target	Conditions	Treatment	Phase	Trial number	Efficacy	Safety	(Refs.)
Ma *et al*, 2006	MLN2704	PSMA	mCRPC	Single agent	1	NCT00052000	22% PSA_{50} response.	13% Study drug-related G 3 toxicities	(50)
Milowsky *et al*, 2016	MLN2704	PSMA	mCRPC	Single agent	1/2	NCT00070837	8% PSA_{50} response; 8% PSA stabilization ≥90 days.	71% exhibited peripheral neuropathy: 10% had G 3/4.	(47)
Petrylak *et al*, 2020	PSMA ADC	PSMA	mCRPC progressing on ARSI or docetaxel	Single agent	1	NCT01414283	15% PSA_{50} response.	Most common toxicities: fatigue (40%), neutropenia (33%).	(52)
Cho *et al*, 2018	PSMA ADC	PSMA	mCRPC progressing on ARSI or docetaxel	Single agent	2	NCT01695044	14% PSA_{50} response; 78% CTC declined ≥50%.	Most common G ≥3 TRAEs: neutropenia, fatigue; most common serious AEs: dehydration, hyponatremia.	(53)
Shen *et al*, 2023	MEDI3726	PSMA	mCRPC progressing on ARSI or docetaxel	Single agent	1	NCT02991911	6.1% PSA_{50} response.	45%G3/4TRAEs.	(55)
Doronina *et al*, 2003	DSTP3086S	STEAP family member 1	mCRPC	Single agent	1	NCT01283373	17.7% PSA_{50} response.	Most common Gr ≥3 TRAEs: hyperglycaemia; hyperglycaemia and hypophosphataemia were dose limiting.	(59)
Zang and Allison, 2022	FOR46	CD46	mCRPC progressing on ARSI	Single agent	1a/1b	NCT03575819	45.5% PSA_{50} response.	Most common Gr ≥3 TRAEs: neutropenia (77%)	(68)
Shenderov *et al*, 2021	MGC018	B7-H3	mCRPC progressing on ARSI or docetaxel	Single agent	1	NCT03729596	55.5% PSA_{50} response.	At least 1 treatment emergent AEs in 87% with commonest being neutropenia.	(73)
Corti *et al*, 2023	Tisotumab vedotin	Tissue factor	Advanced solid tumours including mCRPC	Single agent	1/2	NCT02001623	None	Most common Gr ≥ 3 AEs: fatigue	(80)
Fuentes-Antras *et al*, 2023	Rovalpitu-zumab tesirine	Delta-like protein 3	Neuroendocrine including carcinomas neuroendocrine PCa	Single agent	1/2	NCT02709889	76% clinical benefit rate	Most common G3/4 AEs: anemia, . thrombocytopenia	(86)

ADC, antibody-drug conjugates; PCa, prostate cancer; G: grade; TRAEs: treatment-related adverse events; AEs: adverse events; PSA: prostate specific antigen; mCRPC: metastatic castration resistant prostate cancer; PSMA, prostate-specific membrane antigen.

Table II. The ongoing clinical trial data of antibody-drug conjugates in prostate cancer.

Drug	Target	Conditions	Treatment	Phase	Trial number	Estimated Completion Date
ARX517	Prostate-specific membrane antigen	mCRPC	Single agent	1	NCT04662580	March 2027
Datopotamab Deruxtecan (Dato-DXd)	TROP-2	Advanced/Metastatic solid tumours including mCRPC	Single agent or with Saruparib	2	NCT05489211	August 2026
Sacituzumab govitecan (SG)	TROP-2	mCRPC progressing on ARSI	Single agent	2	NCT03725761	April 2025
FOR46	CD46	mCRPC progressing on abiraterone	Combination with enzalutamide	1b/2	NCT05011188	March 2027
MGC018	B7-H3	mCRPC progressing on ARSI or docetaxel	Single agent	2	NCT05551117	May 2027
MGC018	B7-H3	Advanced/Metastatic solid tumours including mCRPC	Combination with lorigerlimab (MGD019)	1	NCT05293496	March 2026
Ifinatamab deruxtecan (I-DXd)	B7-H3	Advanced solid tumours including mCRPC	Single agent	1/2	NCT04145622	March 2027
XB002	Tissue factor	Advanced solid tumours including mCRPC	Single agent or with nivolumab	1	NCT04925284	October 2024

mCRPC, metastatic castration-resistant prostate cancer.

The ADC, MEDI3726, is composed of an anti-PSMA antibody conjugated with PBDs (53). MEDI3726 binds to the highly expressed PSMA on PCa cells and is rapidly internalized, followed by intracellular cathepsin cleavage, mediating the PBD payload release. In a phase I trial involving 33 patients with mCRPC who had experienced disease progression after prior treatment with abiraterone, enzalutamide or taxane-based chemotherapy, the rate of PSA_{50} response or a conversion in CTC count was found to be 6.1% after treatment, while the rate of composite response was 12.1% (54). TRAEs were observed in 30 patients (90.9%), predominantly presenting as skin toxicities and effusions, with grade 3/4 TRAEs occurring in 15 patients (45.5%) and SAE-related discontinuation reported in 11 patients (33.3%). Therefore, due to the lack of safety and efficacy, MEDI3726 was not tested in a phase II trial.

The recruitment of patients with mCRPC commenced in 2021 for a phase I clinical trial aimed at evaluating the safety profile of ARX517, an ADC comprising a human mAb targeting PSMA that is covalently linked to the microtubule-disrupting toxin, amberstatin-269. The study enrolled 24 patients with mCRPC who had received at least one ARPI treatment line by October 2023. The results demonstrated a PSA_{50} response in 8 patients and a significant decline in CTCs in 12 patients. No SAEs were reported, except for four grade 3 AEs, including thrombocytopenia and lymphopenia (55). An ongoing clinical trial (NCT04662580) aims to further verify the safety and efficacy of ARX517 (Table II).

STEAP1. The STEAP1 protein, also known as prostate six-transmembrane epithelial antigen 1, is recognized for its role as an ion channel or multi-transmembrane transporter (56). The expression levels of STEAP1 are 5-10-fold higher in human PCa cells compared with other cancer cell types, thus positioning STEAP1 as a promising therapeutic target for PCa (57). The DSTP3086S ADC is designed to target STEAP1, consisting of the anti-STEAP1 mAb, MSTP2109A, conjugated to MMAE via a cleavable linker (58). The DSTP3086S molecule specifically binds to the surface of PCa cells, targeting STEAP1, and undergoes rapid internalization. This leads to the intracellular release of MMAE, which effectively inhibits the mitotic process in cancer cells and ultimately induces cell death (59). In a phase I dose-escalation trial of DSTP3086S, 77 patients with mCRPC and high STEAP1 expression were enrolled. The dose range administered was escalated from 0.3-2.8 mg/kg every 3 weeks. Among these patients, doses >2 mg/kg were well tolerated by 62 individuals, and while grade ≥3 AEs occurred in 26 patients, a PSA50 response was observed in 11 patients (17.7%) (58). The safety and

efficacy of DSTP3086S need to be further evaluated through phase II trials.

TROP-2. TROP-2 is a glycoprotein expressed on the surface of prostate cells, with upregulation observed in PCa cells (60). The majority of patients with mCRPC treated with androgen receptor signaling inhibitors (ARSIs) who progressed have been reported to exhibit upregulation of TROP-2 (61). The emergence of this phenomenon has therefore prompted researchers to develop ADCs that specifically target TROP-2 for the treatment of mCRPC. SG, an ADC designed to target TROP-2, consists of a humanized RS7 mAb coupled with SN-38 via a moderately stable carbonate bond (62). An ongoing open-label phase II trial (NCT03725761) is currently enrolling patients with mCRPC who have experienced disease progression following treatment with ARSIs. At the time of the interim analysis, 20 patients had been enrolled, demonstrating a 6-month radiographic progression-free survival rate (PFS) of 45%. Among the observed AEs, neutropenia was the most frequently reported (63).

The compound, Datopotamab Dxd (Dato-DXd), is an ADC that specifically targets TROP-2 and is a humanized mAb linked to a topoisomerase 1 inhibitor (64). The safety and efficacy of Dato-DXd in patients with advanced solid tumors, including mCRPC, are currently being investigated through an ongoing phase II clinical trial (NCT05489211).

CD46. The membrane protein, CD46, is widely expressed in human cell membranes, with the exception of red blood cells. CD46 has a crucial role in regulating the deposition of C3b/C4b on various cell populations and serves as a target for numerous pathogens (65). CD46 is upregulated in mCRPC cells, and its expression is significantly elevated in patients with mCRPC undergoing abiraterone and enzalutamide treatment. Genomic analysis revealed that 45% of patients with abiraterone-resistant mCRPC had acquired the CD46 gene (66). The ADC, FOR46, consists of a mAb that specifically targets CD46 and is conjugated with MMAE. In a phase Ia/Ib dose-escalation trial involving 33 patients with mCRPC who had experienced disease progression while receiving ARPI, neutropenia emerged as the sole significant grade 3 AE, with 45.2% of the evaluable patients (14 out of 31) achieving a PSA50 response (67). The efficacy of FOR46 in patients with mCRPC necessitates further investigation, and patient recruitment is currently underway for a phase Ib/II trial evaluating the combination of FOR46 with enzalutamide in patients with mCRPC who have experienced disease progression following prior abiraterone therapy (NCT05011188).

B7-H3. B7-H3, an immunomodulatory protein, is also known as CD276 (68). Studies have demonstrated a correlation between the expression of B7-H3 on the surface of PCa cells and an unfavorable prognosis following surgical intervention, including early postoperative PSA recurrence as well as the development of CRPC (69,70). Moreover, the majority of patients with CRPC exhibit significant upregulation of B7-H3 expression (93%) (71). The humanized ADC, MGC018, specifically targets and eliminates cancer cells that upregulate B7-H3. MGC018 exhibits favorable pharmacokinetic properties and has demonstrated safety in preclinical tumor models (72). The recruitment of patients is currently ongoing in a phase I trial evaluating the efficacy and safety of MGC108 in mCRPC. As of May 3, 2021, 26 patients with mCRPC had been enrolled, of which 11/22 evaluable patients showed a PSA50 response, while the most frequently reported AEs included neutropenia, fatigue, weakness and headache (73). At present, two clinical trials of MGC018 in solid tumors, including mCRPC, are recruiting patients (NCT05551117 and NCT05293496).

Ifinatamab Dxd (I-Dxd) is an additional ADC that targets B7-H3. I-Dxd consists of a mAb that specifically binds to B7-H3, which is linked to the topoisomerase I inhibitor, Dxd, via a cleavable tetrapeptide linker (74). Enrollment is currently ongoing in a phase I/II clinical trial (NCT04145622) aimed at investigating the safety and efficacy of I-Dxd in patients diagnosed with advanced solid tumors, including mCRPC.

TF. TF is alternatively referred to as thromboplastin, factor III or CD142 (75). TF is a transmembrane glycoprotein and, under physiological conditions, TF activation marks the start of the exogenous coagulation pathway (76). TF binds to its physiological ligand, FVIIa, triggering the activation of protease-activated receptor 2 and initiating an intracellular signaling cascade that can be exploited by tumors to facilitate tumor angiogenesis, enhance cancer cell survival and growth as well as facilitate metastasis (77). The expression of TF is upregulated in numerous solid malignancies, including pancreatic, lung, breast, bladder and PCa (75). Tisolumab vedotin, an ADC composed of a fully human mAb specific to TF conjugated with MMAE, has been developed to target tumors that express TF (78). The InnovaTV 201 trial was a phase I/II open-label study that involved dose-escalation and dose-expansion in 147 patients with advanced solid tumors, including PCa. During the dose-expansion phase, fatigue emerged as the most frequently reported grade ≥3 AE (79). Among the patients with PCa included in the study, none exhibited radiographic changes or a PSA response (79). It is necessary to continue evaluating the antitumor activity of TF in the context of PCa.

XB002 is an additional ADC that specifically targets TF, consisting of a mAb directed against TF coupled with the tubulin inhibitor, MMAE, via a cleavable linker (80). The ongoing clinical trial is a phase I, open-label, multicenter study involving dose-escalation and expansion of XB002 or XB002 in combination with nivolumab for advanced solid tumors, including mCRPC (NCT04925284).

DLL3. The DLL3 ligand is involved in the Notch signaling pathway and exhibits elevated expression levels in neuroendocrine tumors, while remaining absent in normal tissues (81). The neuroendocrine carcinomas (NECs) represent a cluster of poorly differentiated neuroendocrine tumors characterized by the upregulation of DLL3. Research findings have indicated that DLL3 is upregulated in 65-74% of large-cell NECs and 77% of castration-resistant neuroendocrine PCa (NEPC) cells (82). The Rovalpituzumab tesirine (Rova-T) ADC specifically targets DLL3 and consists of a mAb that binds to DLL3 that is linked to a DNA damaging agent via a cleavable linker (83). In a phase I/II trial involving NEPC and other advanced NECs that upregulate DLL3, the primary objective of the study was to evaluate the safety profile of Rova-T. The most frequently observed grade 3/4 AEs included

anemia (17%), thrombocytopenia (15%) and elevated aspartate aminotransferase levels (8%) (84). Among the 21 patients with NEPC enrolled in the trial, the clinical benefit rate reached 76.2%, with an average PFS time of 4.5 months and an average OS time of 5.7 months. The clinical benefit rate was defined as the percentage of participants with the best overall response (confirmed or unconfirmed) of complete response, partial response or stable disease according to the Response Evaluation Criteria in Solid Tumors v1.1 (85).

5. Discussion and perspectives

The treatment options for PCa are evolving rapidly but more effective treatment options are still needed. ADCs represent a novel class of tumor targeting therapeutic drugs that have demonstrated both efficacy and safety in the treatment of solid tumors such as breast cancer. These agents possess the ability to selectively recognize antigens that are upregulated on the surface of cancer cells and subsequently deliver cytotoxic payloads within these cells to effectively target and eliminate malignant growth. In recent years, there has been notable progress in the development of ADCs for PCa. However, these therapeutic agents have also encountered numerous challenges in effectively treating PCa, including limited efficacy, safety concerns and a narrow treatment window (86).

The progression of PCa is driven by androgen signaling, resulting in a limited response to conventional chemotherapeutic agents due to slow growth kinetics and activation of the androgen receptor (87). The cytotoxic payloads in most ADCs designed for the treatment of PCa exert their action by suppressing cancer cell division, which could be one contributing factor to the relatively lower efficacy of ADCs in PCa compared with other malignancies. However, chemotherapy drugs currently used for PCa, such as docetaxel and cabazitaxel, have shown significant efficacy against, and mainly act by affecting tubulin and then inhibiting the mitotic process (88,89). The potential difference may stem from the specific expression of targeted antigens on the surface of cancer cells, as ADCs are designed to selectively target these antigens, distinguishing them from conventional chemotherapy drugs. The efficacy and toxicity of ADCs are also influenced by the inherent structure of the drug and enhancing any component of the ADC will ameliorate these issues.

The selection of appropriate targets is pivotal for the efficacy of ADCs. At present, most antigens targeted in PCa treatment with ADCs are TAAs, such as PSMA, STEAP1, TROP-2 and CD46. The development of TSA-targeted ADCs is currently in the preclinical research stage, with no clinical trials conducted thus far, to the best of our knowledge. However, it is anticipated that TSA targeting ADCs may receive approval in the future, offering potential enhancements in efficacy and a reduction in the off-target side effects associated with ADCs. In addition to the cancer cell surface antigen expression profiles, the internalization and turnover rates of ADCs have a notable impact on efficacy (90). Thus, optimizing the binding affinity between antigens and antibodies is a key step in enhancing the efficacy of ADCs. However, an excessively high binding affinity can lead to the retention of ADC molecules on the surface of cancer cells, thereby impeding their internalization capacity, a phenomenon referred to as the binding site barrier effect (91).

Optimizing the antibody structure is also a viable approach to enhance efficacy and to mitigate the toxicity of ADCs (92). Conditional antibody ADCs and bispecific ADCs are novel design ideas (13,93). The activation of conditional antibody ADCs is restricted to cancer cells, thereby significantly augmenting the efficacy of ADCs and preventing off-target toxicity (13). In addition, the advancement of bispecific antibody technology also presents enhanced prospects for ADC innovation since these antibody ADCs exhibit heightened internalization efficiency and improved tumor specificity (39). For instance, the utilization of bispecific ADCs enables the targeting of distinct epitopes on a single antigen, thereby enhancing both the antigen and antibody binding affinity while facilitating internalization of ADCs (94). Similarly, the development of dual-payload ADCs incorporating diverse cytotoxic payloads allows for the controlled delivery to cancer cells by manipulating the drug ratio, resulting in improved efficacy and reduced drug resistance (95).

Most ADC toxicities originate from off-target, non-tumor toxicities that are caused by premature detachment of ADCs in the systemic circulation and subsequent release of the payload (96). The released payload can infiltrate neighboring non-malignant cells and induce the bystander killing effect through passive diffusion or transporter-mediated uptake (97,98). Certain ADCs that use microtubule inhibitors as the payload have off-target toxicity associated with peripheral neuropathy. For instance, the majority of patients with PCa (71%) who received MLN2704, a microtubule inhibitor with M1 as the payload, experienced peripheral neuropathy and were unable to proceed to the next phase of clinical trials due to excessive toxicity (47). The exploration of novel compounds as potential payloads for ADCs is imperative to mitigate off-target toxicity and achieve comparable or superior efficacy in cancer cell eradication.

The premature release of the payload in the systemic circulation is primarily responsible for off-target toxicity, as aforementioned. Therefore, maintaining stability in the systemic circulation is crucial for linkers to minimize off-target toxicity of ADCs (99). The ideal linker should exhibit stability in the bloodstream and selectively release cytotoxic payloads upon internalization of ADCs into cancer cells. Nevertheless, existing linkers often demonstrate non-specific payload release in circulation, inevitably resulting in off-target toxicity (100). Among the ADCs designed to treat PCa, hematological toxicities, including neutropenia, thrombocytopenia, leukopenia and anemia, were observed as the most prevalent AEs. The occurrence of hematotoxicity may be attributed to the premature release of cytotoxic payloads into the systemic circulation (101). The current requirement is to further advance the development of novel linkers to ensure the stability of ADCs within the bloodstream and their targeted release of effective payloads upon internalization into cancer cells. This will effectively minimize off-target toxicity and enhance the overall efficacy of ADCs (37).

It has been suggested that combining ADCs with other therapies possessing distinct mechanisms of action and minimal overlapping toxic effects may be an effective approach for mitigating AEs and enhancing efficacy (102). The utilization of ADCs in conjunction with immune checkpoint inhibitors (ICIs) has emerged as a promising therapeutic

approach for patients with advanced PCa in recent years (103). In several studies, the combination of ADCs and ICIs has been demonstrated to significantly augment efficacy (104,105). ICIs enhance the capacity of the immune system to eliminate cancer cells (106), while ADCs selectively target and eradicate cancer cells (107). The combination of ADCs and ICIs can therefore augment the cytotoxicity of the immune system against cancer cells, facilitate targeted elimination of cancer cells and notably enhance clinical efficacy (102). Personalized studies of ADCs in combination with ICIs is currently undergoing clinical trials, indicating its potential as a promising alternative treatment for PCa in the future.

At present, ADCs are mainly used to treat patients with mCRPC. Due to excessive AEs and insufficient efficacy, the development of ADCs for PCa therapy is still at the phase I/II clinical trial stage. However, several studies are ongoing and researchers are also developing new ADCs and improving their structure. It is conceivable that additional ADCs will receive approval for the management of PCa in the foreseeable future. Although most of the ongoing clinical trials focus on patients with mCRPC, if ADCs show considerable efficacy in more clinical trials, their potential application for the treatment of patients with early-stage PCa is likely to materialize.

In conclusion, although there are numerous treatment options for advanced PCa such as mCRPC, more treatment options are currently needed. ADCs represent a new hope in the treatment of PCa. A number of clinical trials investigating ADCs for the treatment of PCa have been prematurely terminated due to inadequate efficacy or excessive toxicity. Moving forward, it is imperative to develop more stable linkers, highly specific antibodies and more potent payloads to further enhance the pharmacological properties of ADCs and expand the therapeutic options for patients with PCa.

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Authors' contributions

CY, CG and LW were the major contributors in writing and editing the manuscript. HL, ZT and MD provided direction and guidance throughout the preparation of this manuscript. DL, YH, JL, WC and SF analyzed and organized the data. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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