

Cancer Vaccines

Subjects: **Oncology**

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Therapeutic cancer vaccines target TAAs alongside adjuvant molecules that can elicit specific antibodies or cytotoxic immune responses against cancer cells. There are different ways to present TAAs to the immune system. DNA and RNA encoding TAAs or whole peptides can be recognized and processed by the APCs; tumor cell lines express TAAs and can chemotactically attract APCs; viral vectors transfect APCs after being loaded with prespecified antigens; finally, DCs act as APCs and can be loaded with TAAs.

prostate cancer

renal cancer

urothelial cancer

vaccines

immunotherapy

1. Introduction

Immunotherapy has represented a breakthrough therapy for many cancer subtypes in the last years. Among genitourinary (GU) neoplasms, the urothelial carcinoma (UC) and the renal cell carcinoma (RCC) have benefitted mainly from immune checkpoint inhibitors (ICIs) both as single agents and in combination with other ICIs or tyrosine kinase inhibitors (TKIs) [\[1\]\[2\]\[3\]\[4\]\[5\]\[6\]\[7\]\[8\]\[9\]\[10\]\[11\]\[12\]\[13\]](#). However, in prostate cancer (PCa), ICIs have shown limited efficacy primarily due to an immunologically 'cold' and immunosuppressive tumor microenvironment (TME) [\[14\]\[15\]\[16\]\[17\]\[18\]](#).

Improving immunotherapy efficacy requires combination therapies or different pharmacological approaches [\[19\]](#). In fact, the two principal ways to enhance the immune system's antitumor activity are blocking the immune-suppressive signals responsible for the decreased antitumor response (that is, how ICIs work) or stimulating the immune activation against specific tumor-associated antigens (TAAs). The latter is the mechanism used by anticancer vaccines, capable of triggering the immune response actively by administering antigens conjugated with co-stimulatory molecules or loaded on patients' immune cells [\[20\]\[21\]\[22\]\[23\]](#). In this way, antigen-presenting cells (APCs) can recognize, uptake, process, and present TAAs to naïve T-cells. Generally, intracellular antigens are presented with the class I major histocompatibility complex (MHC) molecules to CD8⁺ cells, turning them into effector cytotoxic lymphocytes (CTLs) [\[24\]](#). It is more difficult to elicit a cytotoxic response in the case of extracellular antigens. The class II MHC molecules usually present them to CD4⁺ cells [\[24\]\[25\]](#). However, APCs—especially dendritic cells (DCs)—can process and present some extracellular antigens through the class I MHC to CD8⁺ cells, a process known as antigen cross-presentation whose discovery has been of great importance for therapeutic vaccines development [\[25\]](#).

2. Vaccine Therapy in Prostate Cancer (PCa)

PCa represents the most frequent tumor and the second leading cause of death among the Western male population [26]. PCa is an ideal candidate for vaccine therapies, given its high targetable number of TAAs, prostatic acid phosphatase (PAP), prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA) among the most important [27][28]. The majority of studies focused on mCRPC. Only three phase III trials have been conducted. Even if specific immune activation was detectable, vaccines usually did not determine significant survival improvement (Table 1).

3. Vaccine Therapy in Urothelial Cancer (UC)

UC has a long and successful history of vaccines use, starting from the *Bacillus Calmette–Guerin* (BCG), which represents a cornerstone for the treatment of non-muscle invasive bladder cancer (NMIBC) since the 1990s [29]. However, BCG failure occurs in 20–50% of patients [30]. Intending to potentiate BCG efficacy, in a randomized phase I study (NCT01498172), 24 NMIBC patients received a vaccine containing the recombinant MAGE-A3 protein + the adjuvant AS15 before BCG instillations. In half of the patients, specific T-cells were subsequently detectable in blood. No survival data are available [31].

Some UC TAAs have been tested mainly on DCs or as peptide vaccines, inducing immune responses with controversial survival effects in phase I/II trials (Table 1). Survivin-2B80-88 improved OS in phase I ($p = 0.0009$) [32]. CDX-1307, targeting the mannose receptor, induced immune responses in bladder cancer (BCa), but it did not get over phase I because the N-ABLE NCT01094496 phase II study was stopped early due to slow enrollment [33]. DCs loaded with Wilms tumor (WT)-1 in seven patients with mUC or mRCC determined specific immune responses and decreased T-regs [34]. S-288310, derived from DEP domain-containing 1 (DEPDC1) and M-phase phosphoprotein 1 (MPHOSPH1), was administered to pretreated mUC patients in a phase I/II trial: 89% of patients developed specific T-cells, reaching mOS of 14.4 mos, with better results if a double induction against both peptides was obtained [35]. NEO-PV-01 peptide derives by the genomic profiling of patients' BCa: in a phase Ib trial, 10/14 patients achieved PR or stable disease (SD) [36].

The PPV strategy has been evaluated in the platinum-progressing mUC. A phase I trial did not meet its primary endpoint of prolonging PFS among 80 BCa patients; however, a significantly longer OS was reached than best supportive care (7.9 vs. 4.1 mos; $p = 0.049$) [37]. In a phase II trial enrolling 48 patients with metastatic upper tract urothelial cancer (mUTUC), the development of specific T-cells was associated with longer OS ($p = 0.019$). A median OS of 7.7 mos was achieved, reaching 13.0 mos if salvage chemotherapy was associated [38]. Finally, among 12 mUC patients, a phase I trial reported one complete response (CR), one PR, two SDs, mPFS of 3 mos, and mOS of 8.9 mos [39].

Current trials are ongoing: the peptide vaccine ARG1 (targeting arginase-1) is under evaluation as a single agent in a phase I trial (NCT03689192); the NCT03715985 study is evaluating the multi-peptides neo-antigen vaccine NeoPepVac in combination with anti-PD1/PD-L1 in many solid tumors, including mUC (Table 2).

4. Vaccine Therapy in Renal Cell Cancer (RCC)

In the mRCC, different DCs and peptide vaccines have been tested, mostly in phase I/II trials, with only two published phase III studies (Table 1). With a similar Sipuleucel-T mechanism, Rocapuldencel-T is composed of DCs plus amplified tumor RNA plus CD40L RNA. In the ADAPT phase III trial, 462 patients were randomized 2:1 to receive Rocapuldencel-T plus sunitinib versus standard of care. Even if immune responses were recorded, the trial failed its primary endpoint of improving OS compared to the control group (mOS 27.7 vs. 32.4 mos; HR = 1.10, 95% CI, 0.83–1.40). Still, a trend toward better OS was evidenced in the case of more robust immune responses [40]. In the adjuvant setting, autologous-antigens loaded DCs plus cytokine-induced killer cells (CIK) were compared to α -interferon (IFN) in 410 patients, improving PFS and OS (3-year OS rate 96% vs. 83%; 5-year OS rate 96% vs. 74%; $p < 0.01$) [41].

Among the peptide vaccines, EC90, a folate-targeted vaccine, plus α -IFN and IL-2, induced seven SDs and one PR in 24 patients in a phase I/II study [42]. Nine patients with progressive mRCC, treated with hypoxia-inducible protein-2 (HIG-2) peptide vaccine obtained a DCR of 77.8% and an mPFS of 10.3 mos [43]. GX301 vaccine is composed by four telomerase peptides plus Imiquimod and Montanide ISA-51 as adjuvant [44]. Telomerase contributes to tumor immortalization, but it is not expressed by somatic cells [45]. GX301 induced specific immunological responses in over 2/3 of vaccinated mRCC or mCRPC patients, with a trend for better OS (around 11 mos) [44].

Among the different subtypes of renal cancer, clear-cell renal cell carcinoma (ccRCC) is exceptionally responsive to immunotherapy and has been historically considered the ideal subtype to treat with vaccines [46]. However, in the IMPRINT phase III trial, IMA901 (composed of 10 tumors-associated peptides) plus GM-CSF, cyclophosphamide and sunitinib did not improve OS for the 339 randomized patients in the first-line setting (mOS 33.2 vs. 33.7 mos; HR = 1.34, 95% CI, 0.96–1.86; $p = 0.087$), even if immune activation had previously been evidenced in phase II [47] [48]. PPV with vascular endothelial growth factor receptor (VEGFR)-1 was administered in 18 ccRCC patients. Among them, two PRs and five SDs with a median duration of response of 16.5 mos were observed [49]. TG-4010 is an MVA vector-based vaccine of IL-2 and MUC-1 that induced an mOS of 19.3 mos among the 27 ccRCC patients in a phase II trial [50].

Aiming to identify predictive biomarkers for therapeutic vaccines, blood parameters at baseline (platelets, neutrophils, monocytes, hemoglobin, and LDH), the presence of bone metastases, the MSKCC score, the Fuhrman grade, and the ECOG-performance status have been investigated in RCC [51][52][41].

Novel vaccine targets have been proposed for future clinical studies: hypoxia-inducible factor (HIF)-1 α , being the RCC often associated with the mutation of Von Hippel-Lindau (VHL) gene and dependent on the upregulation of HIF; PD-L1 derived peptides, as RCC is sensitive to immunotherapy control [53][54]. Among the ongoing trials, NCT02950766 evaluates the neo-antigen NeoVax plus Ipilimumab (phase I); the NCT03289962 phase I study is testing the vaccine RO7198457 plus atezolizumab; the NCT03294083 phase Ib trial is assessing the Pexa-Vec vaccine (Thymidine Kinase-Deactivated Vaccinia Virus) plus the anti-PD1 Cemiplimab. Finally, the NCT02643303

phase I/II study evaluates the combination of tremelimumab as in situ vaccination, durvalumab and the TME modulator polyICLC, in subjects with advanced solid tumors, including RCC, UC, PCa and testicular cancer (Table 2).

Table 1. Vaccine therapies in genitourinary malignancies. Principal TAAs and key findings of the studies with therapeutic cancer vaccines are reported.

TAA	Vaccine Name	Type of Vaccine	Combination	Population	Phase	Key Findings	Reference
PAP	Sipuleucel-T (Provenge®)	DC	/	mCRPC	III	mOS: 25.8 vs. 21.7 mos (HR = 0.78; 95% CI, 0.61–0.98; p = 0.03); no PFS improvement; lower baseline PSA levels predictive of OS	[55][56]
			ADT	nmCRPC	II	Humoral response with Sipuleucel-T → ADT than vice versa, related to longer TTP for PSA (p = 0.007)	[57]
			Abiraterone	mCRPC	II	Immune responses, not reduced by prednisone	[58]
			Ipilimumab	mCRPC	I	>4 years OS in 6/9 pts	[59][60]
			/	Neoadjuvant PCa	II	T-cells activation in tumor biopsies	[61]
	pTVG-HP	DNA	/	mCRPC		PSA decline in ~60% patients	[62]
			Pembrolizumab	Recurrent PCa	II	No MFS improvement	[63]

TAA	Vaccine Name	Type of Vaccine	Combination	Population	Phase	Key Findings	Reference
PSA	PROSTVAC (PSA-TRICOM)	Viral vector	/	mCRPC	III	No survival improvement; early terminated	[64]
			/(intraprostatic)	Recurrent PCa	I	Increased CD4 ⁺ /CD8 ⁺ in tumor biopsies, PSA SD in 10/19 pts	[65][66]
			Ipilimumab	mCRPC	I	PSA decline in ~50% pts, low PD1 ⁺ /high CTLA4 ⁺ Tregs associated with longer OS	[67][68]
PSMA		DNA	/	nmCRPC	I/II	PSA-DT 16.8 vs. 12.0 mos (p = 0.0417)	[69]
		VRP	/	mCRPC	I	Antibodies production; no clinical benefit	[70]
PSA + PSMA	INP-5150	DNA	/	nmCRPC	I/II	18 mos PFS rate: 85%	[71]
PSMA + Survivin		DC	(vs. Docetaxel + prednisone)	mCRPC	I	ORR: 72.7% vs. 45.4%	[72]
PSMA + PS + PSCA + STEAP1	CV-9103	RNA	/	mCRPC	I/II	Immune responses	[73]
AR	pTGV-AR	DNA	/	mHSPC	I	Longer PSA-PFS in case of T-cells activation (p = 0.003)	[74]
MUC1		DC	/	nmCRPC	I/II	Improved PSA-DT (p = 0.037)	[75]
MUC1 + PSA +		Viral	/	mCRPC	I	PSA decline in 2/12 pts	[76]

TAA	Vaccine Name	Type of Vaccine	Combination	Population	Phase	Key Findings	Reference
Brachyury							
MUC1 + IL2	TG-4010	Viral vector	/	ccRCC	II	mOS: 19.3 mos	[50]
NY-ESO-1		Peptide	/	Stage IV PCa	I	T-cell responses in 9/12 pts, no survival data	[77]
NY-ESO-1 + MAGE-C2 + MUC1		DC	/	mCRPC	Ila	T-cell responses in ~30% pts, related to radiological responses	[78]
HER-2	AE37	Peptide	/	HER-2 ⁺ PCa	I	Long memory (4 years) with multiple boosters; pre-existing immunity related to PFS, TGF- β inversely related to OS, HLA-A*24/DRB1*11 related to OS	[79][80][81][82]
CDCA1		Peptide	/	mCRPC	I	mOS: 11 mos	[83]
UV1		Peptide	/	mHSPC	I	Immune responses in 85.7%, PSA declining in 64% pts	[84]
TARP		Peptide + DC	/	D0 PCa	I	Specific immune responses, reduced PSA velocity	[85]
RhoC		Peptide	/	PCa after RP	I/II	CD4 ⁺ responses in 18/21 pts	[86]

TAA	Vaccine Name	Type of Vaccine	Combination	Population	Phase	Key Findings	Reference
5T4		Double viral vector	/	Neoadjuvant, active surveillance —PCa	I	T-cell responses before RP and during active surveillance	[87]
	TroVax	Viral	Docetaxel	mCRPC	II	mPFS: 9.67 mos (vs. 5.1 docetaxel alone; p = 0.097), related to baseline PSA	[52] [88]
Modified PCa cells	GVAX	Cell line	Docetaxel	Neoadjuvant PCa	II	Gleason score downstaging in 4/6 pts	[89] [90]
			Degarelix + cyclo-phosphamide	Neoadjuvant PCa	I/II	Immune responses	[91]
PPV							
		Peptide	/	mCRPC	III	No survival advantage (HR = 1.04; p = 0.77); OS benefit with very low/high baseline lymphocytes	[92] [93] [94] [95]
	DCvac	DC	Docetaxel	mCRPC	II	Immune responses, no survival advantage	[96]
		Peptide	/	BCa	I	mOS: 7.9 mos (vs. 4.1 BSC; p = 0.049), no PFS advantage	[37]
			Alone or plus chemotherapy	mUTUC	II	Longer OS in case of immune response (p = 0.019); mOS: 7.7 mos (13.0 mos plus CT);	[38]

TAA	Vaccine Name	Type of Vaccine	Combination	Population	Phase	Key Findings	Reference
		Peptide	/	mUC	I	1/12 CR, 1/12 PR, 2/12 SD, mPFS 3 mos, mOS 8.9 mos	[39]
			/	mCRPC	I	2/17 PR, 1/17 PSA stability	[97]
20-peptides	KRM-20	Peptide	Docetaxel + dexamethasone	mCRPC	II	Increased specific antibodies and T-cells, no PSA/OS differences vs. PBO	[98]
MAGE-A3		Peptide	Before BCG	NMIBC	I	Specific T-cells in ~50% pts, no survival data	[31]
Survivin		Peptide	/	mUC	I, II	Improved OS (p = 0.0009)	[32]
Mannose receptor	CDX-1307	Peptide	/	mUC	I	Immune responses, early stopping of phase II due to slow enrollment	[33]
WT1		DC	/	mUC, mRCC	I/II	Specific immune responses, decreased Tregs	[34]
DEPDC1 + MPHOSPH1	S-288310	Double peptide	/	mUC	I/II	mOS: 14.4 mos, better results with immune response against two peptides	[35]
NEO-PV-01		Peptide	/	BCa	Ib	PR/SD in 10/14 pts	[36]
CD40L + RCC RNA	Rocapuldencel-T	DC + RNA	Sunitinib	mRCC	III	No OS improvement	[40]

TAA	Vaccine Name	Type of Vaccine	Combination	Population	Phase	Key Findings	Reference	division
						over Sunitinib (mOS 27.7 vs. 32.4 mos; HR = 1.1, 95% ci, 0.83–1.40); trend for better OS in case of robust immune response		therapy;
Autologous antigens		DC	CIK	Resected RCC	III	Compared to α-IFN, PFS improvement; 3-year OS rate 96% vs. 83%; 5-year OS rate 96% vs. 74%; p < 0.01	[41]	ulocyte– nducible mCRPC, asis-free median er; mUC, PC, non- , overall peptide prostate disease; P, T-cell
Folate	EC-90	Peptide	α-IFN, IL-2	mRCC	I/II	7/24 SD, 1/24 PR	[42]	gression;
HIG-2		Peptide	/	mRCC	I	DCR 77.8%, mPFS 10.3 mos	[43]	
Clinicaltrials.gov								
Registration Number	Phase	Setting	Vaccine	Antigen	Combination			
NCT01804465	II	mCRPC	Sipuleucel-T	PAP	Ipilimumab (immediate vs. delayed)			
NCT02463799	II	mCRPC	Sipuleucel-T	PAP	Radium-223			
NCT01881867	II	mCRPC	Sipuleucel-T	PAP	Glycosylated recombinant human IL-7			
NCT03600350	II	nmCRPC	pTGV-HP	PAP	Nivolumab			
NCT04090528	II	mCRPC	pTGV-HP + pTGV-AR	PAP, AR	Pembrolizumab			
NCT02933255	I/II	NAD PCa	PROSTVAC	PSA	Nivolumab			
NCT03532217	I	mHSPC	PROSTVAC	PSA	Neoantigen DNA vaccine, Nivolumab, Ipilimumab			
NCT02649855	II	mHSPC	PROSTVAC	PSA	Docetaxel			

NCT03315871	II	nmCPRC	PROSTVAC	PSA	M7824 (anti-PD-L1/TGF- β R2), CV301
NCT02325557 (KEYNOTE-146)	I/II	mCRPC	ADX31-142	PSA	Pembrolizumab
NCT02362451	II	nmCRPC	TARP DC	TARP	/
NCT02111577	III	mCRPC	DCvac	PPV	Docetaxel vs. PBO
NCT03412786	I	mHSPC	Bcl-xl_42-CAF09b peptide vaccine	BCI-xl	/
NCT04701021	I	Relapsing PCa after RP	TENDU peptide conjugate	TET	/
NCT04114825	II	Biochemical recurrent PCa after RT/RP	RV001V peptide vaccine	RhoC	/
NCT03493945	I/II	mCRPC	BN-Brachyury	Brachyury	M7824, ALT-803, Epacadostat
NCT03689192	I	mUC	ARG1	Arginase-1	/
NCT03715985	I/II	mUC	NeoPepVac	Personalized neoantigen	Anti-PD1/PD-L1
NCT02950766	I	mRCC	NeoVax	Personalized neoantigen	Ipilimumab
NCT03289962	I	mRCC	RO7198457	20 TAAs	Atezolizumab
NCT03294083	Ib	mRCC	Pexa-Vec	Thymidine-kinase	Cemiplimab
NCT02643303	I/II	Advanced RCC, UC, PCa, testicular cancer	In situ vaccination with tremelimumab		Durvalumab, polyICLC

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