Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

The Changing Landscape of Therapeutic Cancer Vaccines—Novel Platforms and Neoantigen Identification

Jessica Jou[1], Kevin J. Harrington[2], Mai-Britt Zocca[3], Eva Ehrnrooth[3], and Ezra E.W. Cohen[1]

ABSTRACT

Therapeutic cancer vaccines, an exciting development in cancer immunotherapy, share the goal of creating and amplifying tumor-specific T-cell responses, but significant obstacles still remain to their success. Here, we briefly outline the principles underlying cancer vaccine therapy with a focus on novel vaccine platforms and antigens, underscoring the renewed optimism. Numerous strategies have been investigated to overcome immunosuppressive mechanisms of the tumor microenvironment (TME) and counteract tumor escape, including improving antigen selection, refining delivery platforms, and use of combination therapies. Several new cancer vaccine platforms and antigen targets are under development. In an effort to amplify tumor-specific T-cell responses, a heterologous prime-boost antigen delivery strategy is increasingly used for virus-based vaccines. Viruses have also been engineered to express targeted antigens and immunomodulatory molecules simultaneously, to favorably modify the TME. Nanoparticle systems have shown promise as delivery vectors for cancer vaccines in preclinical research. T-win is another platform targeting both tumor cells and the TME, using peptide-based vaccines that engage and activate T cells to target immunoregulatory molecules expressed on immunosuppressive and malignant cells. With the availability of next-generation sequencing, algorithms for neoantigen selection are emerging, and several bioinformatic platforms are available to select therapeutically relevant neoantigen targets for developing personalized therapies. However, more research is needed before the use of neoepitope prediction and personalized immunotherapy becomes commonplace. Taken together, the field of therapeutic cancer vaccines is fast evolving, with the promise of potential synergy with existing immunotherapies for long-term cancer treatment.

Introduction

Cancer immunotherapy is defined as the manipulation of the immune system to recognize and destroy cancer cells. Among approved immunotherapeutic agents, therapeutic cancer vaccines have the advantage of eliciting specific immune responses to tumor antigens. Accordingly, choice of target antigen is of utmost importance when considering vaccine design (1). Tumor-associated antigens (TAA) are self-antigens abnormally expressed by tumor cells. As a result of central and peripheral tolerance mechanisms, the bank of high-affinity T cells for TAAs may be insufficient to elicit an immune response. Cancer vaccines using TAAs must, therefore, be potent enough to "break" these tolerance mechanisms (2). In contrast, tumor-specific antigens (TSA), some of which are neoantigens, are tumor and often patient specific, arising from nonsynonymous mutations, genetic alterations, or virally introduced genetic information in cancer cells. TSAs recognized by high-affinity T cells are, therefore, less likely to be subject to central tolerance and induce autoimmunity (1, 3). **Figure 1** provides a summary of TAAs and TSAs in terms of specificity, central tolerance, and prevalence.

Platforms for cancer vaccines are categorized as cellular, viral vector, or molecular (peptide, DNA, or RNA; ref. 1). Cellular vaccines are developed using autologous patient-derived tumor cells or allogeneic tumor cell line–derived cells (4). Dendritic cells (DC) are used to develop cellular cancer vaccines due to their role as consumers, processors, and presenters of tumor antigens. Genetically modified oncolytic viral vaccines are designed to replicate within and eradicate tumor cells (5). Beyond their oncolytic mechanisms, viral vector vaccines also promote tumor-directed immune responses by delivering tumor antigens via more conventional T-cell priming mechanisms (3). MHC proteins present peptides on the cell surface for recognition by T cells (6). Peptide-based cancer vaccines are designed through understanding of peptide–MHC and T-cell receptor/peptide–MHC interactions. Short peptides (typically nine amino acid residues in length) bind directly to MHC molecules, potentially inducing tolerance, and are subject to degradation (7). Longer (typically 30-mer) peptides may be more immunogenic as they are internalized by antigen-presenting cells (APC) and processed for MHC presentation, inducing memory $CD4^+$ and $CD8^+$ T-cell immune responses (7). DNA vaccines are closed circular DNA plasmids (naked DNA) encoding TAAs and immunomodulatory molecules, aimed at inducing tumor-specific responses (8). Advantages include simplicity, ease of manufacture, and safety; however, naked DNA vaccines have limited efficacy as a result of low transfection rates into target tumor cells. Similarly, mRNA vaccines are synthesized *in vitro* to encode antigen(s) and express proteins following internalization that stimulate an immune response. mRNA vaccines can deliver a high number of antigens and costimulatory signals, with no risk of infection or insertional mutagenesis, and manufacturing is rapid and inexpensive; however, they are limited by instability and inefficient delivery (8).

Two major advances in the field of therapeutic vaccines, therefore, have been novel platforms and characterization of TSAs. This review focuses on these two essential elements for successful immunotherapy.

[1]Moores Cancer Center, University of California, San Diego Health, La Jolla, California. [2]The Institute of Cancer Research/Royal Marsden National Institute for Health Research Biomedical Research Centre, London, United Kingdom. [3]IO Biotech ApS, Copenhagen, Denmark.

Corresponding Author: Ezra E.W. Cohen, University of California, San Diego Health, 3855 Health Sciences Drive, MC0385, La Jolla, CA 92093. Phone: 858-822-5800; Fax: 858-534-2157; E-mail: ecohen@ucsd.edu

Clin Cancer Res 2021;27:689–703

doi: 10.1158/1078-0432.CCR-20-0245

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

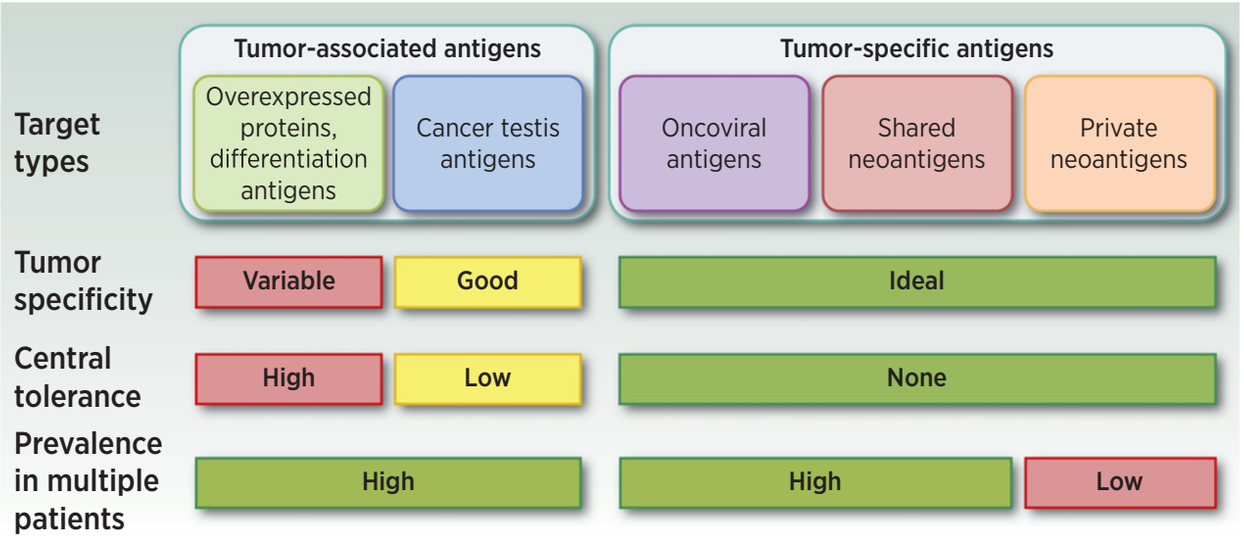

Figure 1.
Therapeutic cancer vaccine target types. Shared antigens are neoantigens encoded by oncogenic driver mutations prevalent across both patients and tumor types; private neoantigens are unique to individual patients' tumors. Adapted from ref. 1: Figure 1 in Hollingsworth, R.E., Jansen, K. Turning the corner on therapeutic cancer vaccines. NPJ Vaccines 2019; 4:7 doi: 10.1038/s41541-019-0103-y; © Springer Nature Limited (http://creativecommons.org/licenses/by/4.0/).

Ongoing Challenges for Cancer Immunotherapy and Therapeutic Cancer Vaccines

Challenges facing T-cell–based cancer immunotherapy include low immunogenicity, as a result of aging or immune cell exhaustion (9, 10) after multiple previous treatment lines; high disease burden; and the immunosuppressive tumor microenvironment (TME), whereby potent immunosuppressive mechanisms evolve throughout cancer progression, enabling cancer cells to escape immune attack (11). Objective responses can be limited to specific subsets of patients with particular genetic mutations, molecular profiles, or recruitment of tumor-infiltrative T cells (12).

Tumor immunogenicity depends on antigenicity and the TME (13). Antigenicity is determined by immune cell infiltration (inflammation) and high mutational burden (genomic instability). High mutational burden in the absence of inflammation can lead to increased antigens with mechanisms for preventing immune cells from infiltrating the TME, as seen in small-cell lung cancers (14). Inflammation without high mutational burden is present in cancers such as renal cell carcinoma, hepatocellular carcinoma, triple-negative breast cancer, gastric cancer, and, to an extent, head and neck cancers (14).

Mechanisms of primary escape (nonresponse to cancer immunotherapy) are thought to depend on underlying drivers of the associated tumor (14). Tumors in sites such as the lymph nodes, lungs, and skin, with a relatively high presence of immune cells, exogenous DNA-damaging insults, or oncolytic viral infections, may be promising sites for anticancer immunity. Conversely, sites such as the bone, intraperitoneal cavity, or blood–brain barrier may be more challenging targets as a result of the high concentration of cytokines, myeloid-derived suppressor cells, and unique stromal interactions indicative of immune-excluded tumors (where $CD8^+$ T cells accumulate, but cannot infiltrate; ref. 14). Mechanisms of secondary escape (cancer progression despite previous clinical response), or acquired resistance, can develop from genetic changes in antigen presentation machinery or target antigen loss. Acquired resistance to anti-programmed death (PD)-1 agents in patients with melanoma is associated with loss-of-function mutations in genes encoding IFN receptor–associated JAK1 or JAK2 (15). Immune pressure shapes intratumor genetic heterogeneity, favoring clonal restriction and dominance, and can have important implications for designing therapeutic strategies (16). Loss of antigenicity leads to weak immune response, allowing tumor cells to develop immune evasion mechanisms (13, 17). Thus, different approaches to cancer immunotherapy may be required in these varying TMEs.

Several strategies have been investigated to overcome immunosuppressive mechanisms of the TME and counteract tumor escape, including improving antigen selection, refining immunotherapy delivery platforms, and combination therapies (1). Chemotherapeutic agents, immunomodulatory molecules, checkpoint inhibitors (CPI), and radiation, together with cancer vaccines, may induce neoantigens and work synergistically to target the TME (18–20).

The Current Landscape of Cancer Vaccines

Cell-based vaccines

Table 1 presents an overview of current cell-based vaccine strategies under investigation. Examples of cancer vaccines using whole-tumor cells include GVAX (4), which has shown promising activity in several pancreatic cancer trials (21–24) and in hormone-refractory prostate cancer (25, 26). Vigil, an autologous tumor cell vaccine, is also currently being evaluated in phase I and II studies of patients with advanced-stage ovarian cancer, with prolonged relapse-free survival

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

Table 1. Cell-based vaccines.

Vaccine	Design	Clinical trial and intervention (key results, where available)	Publication/status
GVAX	Whole-tumor cell vaccine in which cancer cells are genetically modified to express GM-CSF to attract and activate DCs.	Pilot study of GVAX + cyclophosphamide vs. GVAX alone in patients with PDAC ($n = 50$) Median OS: GVAX alone, SD 16.7%; median OS, 2.3 months GVAX + cyclophosphamide, SD 40.0%; median OS, 4.3 months	n/a (completed; ref. 21)
		Phase Ib study of GVAX + ipilimumab vs. ipilimumab alone in patients with PDAC ($n = 30$) Median OS: GVAX + ipilimumab, 5.7 months; ipilimumab, 3.6 months (HR, 0.51; 95% CI, 0.23–1.08; $P = 0.072$)	NCT00836407 (completed; refs. 22, 23)
		Phase I/II study of GVAX ± nivolumab and urelumab in patients with PDAC ($n = 62$)	NCT02451982 (recruiting)
		Phase II study of GVAX + adjuvant chemoradiotherapy in patients with PDAC ($n = 60$) 1-year survival, 86% 2-year survival, 61% Median DFS, 17.3 months Median OS, 24.8 months	NCT00084383 (completed; ref. 24)
		Phase II study of GVAX (+ cyclophosphamide) and CRS-207 ± nivolumab in patients with PDAC ($n = 32$)	NCT02243371 (completed; ref. 23)
		Phase II study of GVAX + pembrolizumab + SBRT + cyclophosphamide in patients with PDAC ($n = 54$)	NCT02648282 (recruiting)
		Phase I/II study of GVAX in patients with HRPC ($n = 80$) Median OS: high dose, 35.0 months; mid dose, 20.0 months; low dose, 23.1 months	NCT00140348 (completed; ref. 25)
		Phase II study of GVAX, prime dose followed by low or high dose boost, in patients with HRPC ($n = 55$) Median OS: overall, 26.2 months; high dose, 34.9 months; low dose, 24.0 months	NCT00140400 (completed; ref. 26)
		Phase III study of GVAX + docetaxel vs. docetaxel + prednisone in patients with CRPC ($n = 600$ planned; $n = 408$ accrued) Median OS: GVAX + docetaxel, 12.2 months; docetaxel + prednisone, 14.1 months (HR, 1.70; 95% CI, 1.15–2.53; $P = 0.0076$)	NCT00133224 (terminated early because of lack of effect; ref. 29)
Vigil	Autologous tumor cells transfected with a DNA plasmid encoding GM-CSF and bi-shRNA-furin, creating transforming growth factor β expression control and enhancing immune activation.	Phase II study of Vigil ($n = 46$) vs. placebo ($n = 45$) in advanced-stage ovarian cancer (interim results) Median RFS: HR, 0.69; $P = 0.088$ in favor of Vigil Median RFS in *BRCA1/2* wt patients: Vigil, 19.4 months; placebo, 8 months (HR 0.51; $P = 0.050$ since randomization and HR, 0.49; $P = 0.038$ since surgery)	NCT02346747 (active, not recruiting; ref. 27)
		Phase I 3-part cross-over study of Vigil + atezolizumab in recurrent advanced-stage ovarian cancer Preliminary part 2 results (Vigil first, $n = 11$; atezolizumab first, $n = 10$) Median OS: Vigil first, not reached; atezolizumab first, 10.8 months (HR, 0.33; $P = 0.097$) Median OS in *BRCA1/2* wt patients: Vigil first ($n = 7$), not reached; atezolizumab first ($n = 7$), 5.2 months (HR, 0.12; $P = 0.015$)	NCT03073525 (active, not recruiting; ref. 28)
Canvaxin	Allogeneic whole-cell cancer vaccine.	Phase III study of Bacillus Calmette–Guerin (BCG) + canvaxin vs. BCG + placebo in patients with: Stage III MM; $n = 1{,}118$, NCT00052130 (discontinued because of futility) Stage IV MM; $n = 496$, NCT00052156 (stage IV MM, discontinued as a result of futility) Stage IV MM results: Median OS on termination of trial: BCG + placebo, 38.6 months; BCG + canvaxin, 31.4 months (HR, 1.18; $P = 0.250$)	NCT00052156 (stage IV MM) (discontinued due to futility; ref. 31) NCT00052130 (stage III MM) (discontinued because of futility; ref. 30)

(Continued on the following page)

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

Table 1. Cell-based vaccines. (Cont'd)

Vaccine	Design	Clinical trial and intervention (key results, where available)	Publication/status
Sipuleucel-T	*Ex vivo*–generated DC, whereby peripheral blood mononuclear cells and APCs are harvested and exposed to a unique recombinant antigen, combining PAP, expressed in 95% of prostate cancers, and GM-CSF. Administered by infusion.	Phase III (D9901 and D9902A) studies of Sipuleucel-T vs. placebo in patients with CRPC ($n = 127$)	D9901 study: NCT00005947 (completed)
		Integrated analysis	D9902A study: NCT01133704 (completed; ref. 98)
		Median OS: sipuleucel-T, 23.2 months; placebo, 18.9 months (HR, 1.50; 95% CI 1.10–2.05; $P = 0.011$)	NCT00065442 (completed; ref. 99)
		Median TTP: sipuleucel-T, 11.1 weeks; placebo, 9.7 weeks (HR, 1.26; 95% CI, 0.95–1.68; $P = 0.111$)	
		Phase III IMPACT study of sipuleucel-T vs. placebo in patients with CRPC ($n = 512$)	
		Median OS: sipuleucel-T, 25.8 months; placebo, 21.7 months (HR, 0.78; 95% CI 0.61–0.99; $P = 0.032$)	
MART-1 vaccine	Multiepitope vaccine composed of tyrosinase, gp100, and MART-1 peptides.	Phase III study of GM-CSF vs. peptide vaccination vs. GM-CSF + peptide vaccination vs. placebo in patients with MM ($n = 815$)	NCT01989572 (completed; ref. 33)
		Median OS: GM-CSF, 69.6 months; placebo, 59.3 months (HR, 0.94; 95% CI, 0.77–1.15; $P = 0.53$)	
		Median RFS: GM-CSF, 11.4 months; placebo, 8.8 months (HR, 0.88; 95% CI, 0.74–1.04; $P = 0.13$)	
OC-DC	Autologous DC vaccine loaded *in vitro* with lysate from autologous oxidized whole-tumor cells.	Phase I study of OC-DC alone or + intravenous bevacizumab and cyclophosphamide or + intravenous bevacizumab and cyclophosphamide and aspirin in patients with ovarian cancer ($n = 25$)	NCT01132014 (completed; ref. 34)
		PFS was significantly longer in patients whose on-treatment peripheral blood mononuclear cells recognized autologous tumor cells (tumor responders; $P = 0.0005$) or *ex vivo* autologous tumor lysate–pulsed DCs (vaccine responders; $P = 0.05$) relative to patients showing no such responses.	
		2-year OS: 100% in responders; 25% in nonresponders	
TLPLDC vaccine	Uses YCWP to load autologous TL into autologous DCs.	Phase I/IIa study of autologous TL + YCWP + DCs vaccine + SoC CPIs in MM ($n = 50$, to date)	NCT02678741 (active, not recruiting; ref. 35)
		Evaluable patients, $n = 28$ PD: $n = 13$ (median 3-month follow-up) SD: $n = 12$ (median 7.5-month follow-up) PR: $n = 2$ (7- and 13-month follow-up) CR: $n = 1$ (18-month follow-up) ORR: 11%	
		Phase IIb study of TLPLDC vaccine ($n = 103$) vs. unloaded YCWP ($n = 41$, control) in resected stage III/IV high-risk melanoma patients	NCT02301611 (active, not recruiting; refs. 36, 37)
		24-month DFS Recurrent (disease-free interval of >3 months) group ($n = 48$): vaccine 52.6%; control 23.5% ($P = 0.214$) Primary group ($n = 96$): vaccine, 32.9%; control, 31.8% ($P = 0.451$) OS Recurrent group: vaccine, 94.4%; control, 50.5% ($P = 0.011$) Primary group: vaccine, 83.4%; control, 90.2% ($P = 0.779$) 24-month DFS in stage IV patients, subgroup analysis Intention-to-treat population ($n = 144$): vaccine, 44%; control, 0% ($P = 0.41$) Per-treatment population ($n = 98$): vaccine, 73.3%; control, 0% (HR, 0.14; $P = 0.002$)	
		Phase I/IIa study of autologous TLPLDC vaccine + SoC in solid tumors ($n = 44$)	n/a
		Of 31 late-stage patients with residual/measurable disease, 12 demonstrated clinical benefit: CR: $n = 2$ PR: $n = 4$ SD: $n = 6$ 46% remain disease free at a median of 22.5 months	ISRCTN81339386 (completed; ref. 38)

(Continued on the following page)

Table 1. Cell-based vaccines. (Cont'd)

Vaccine	Design	Clinical trial and intervention (key results, where available)	Publication/status
Ilixadencel	Allogeneic off-the-shelf product aimed to prime anticancer immune response when injected intratumorally.	Phase II study of ilixadencel + pre- and post-nephrectomy sunitinib (COMBO, $n = 58$) vs. sunitinib monotherapy post-nephrectomy (SUN, $n = 30$) as first-line systemic therapy in mRCC. For COMBO treatment vs. SUN: CR: COMBO, 11%; SUN, 4% ORR: COMBO, 42.2%; SUN, 24.0% Median duration of response: COMBO, 7.1 months; SUN, 2.9 months Median PFS: COMBO, 11.8 months; SUN, 11.0 months OS was not reached in either treatment arm.	NCT02432846 (active, not recruiting; ref. 39)

Abbreviations: APC, antigen-presenting cell; CI, confidence interval; CR, complete response; CRPC, castration-resistant prostate cancer; DC, dendritic cell; DFS, disease-free survival; GVAX, GM-CSF secreting tumor immunotherapy; HR, hazard ratio; HRPC, hormone-refractory prostate cancer; MM, malignant melanoma; mRCC, metastatic renal cell carcinoma; n/a, not applicable (study does not have an NCT number); mRCC, metastatic renal cell carcinoma; OC-DC, oxidized autologous whole-tumor cell lysate; ORR, objective response rate; OS, overall survival; PAP, prostatic acid phosphatase; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PR, partial response; RFS, relapse-free survival; SBRT, stereotactic body radiotherapy; SD, stable disease; SoC, standard of care; TL, tumor lysate; TTP, time to progression; wt, wild-type; YCWP, yeast cell wall particles.

compared with placebo observed in a recent interim analysis of the phase II study (27, 28). Other cell-based vaccine studies have been discontinued as a result of futility (29–31).

Sipuleucel-T (PROVENGE), targeting prostatic acid phosphatase, is approved for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. However, despite positive efficacy and safety data, since its approval, barriers to administration of sipuleucel-T and approval of competing cancer therapies have hampered its widespread adoption (32). Several other vaccines derived from *ex vivo* DCs are being investigated, for example, against melanoma antigen, MART-1 (33). In a phase I trial, a vaccine using autologous monocyte-derived DCs pulsed with oxidized autologous whole-tumor lysate significantly prolonged survival in patients with recurrent ovarian cancer (34). In addition, a vaccine using yeast cell wall particles (YCWP) to load autologous tumor lysate into autologous DCs is being studied for melanoma and for solid tumors (35–38); in a phase II trial, the YCWP vaccine resulted in prolonged disease-free survival in patients with resected melanoma, with a disease-free interval of >3 months, compared with those who received unloaded YCWP (36, 37). A further phase II study of ilixadencel, an off-the-shelf, cell-based immune primer, in combination with sunitinib, pre- and post-nephrectomy, showed greater rates of complete and objective response, but similar progression-free survival, compared with sunitinib monotherapy in patients with newly diagnosed metastatic renal cell carcinoma (39).

Virus-based vaccines

Table 2 provides an overview of current virus-based vaccine strategies. The first FDA-approved oncolytic virus for cancer treatment was talimogene laherparepvec (T-VEC; ref. 40). T-VEC relies on direct intratumoral injection, which overcomes dilution and neutralization in blood, to induce cell lysis and promote antitumor immune responses in distant lesions (40–43). A phase II trial of T-VEC in combination with ipilimumab, first or second line, demonstrated a significantly higher objective response rate (ORR) compared with ipilimumab alone in patients with pancreatic ductal adenocarcinoma, with no additional safety concerns (42). The phase III OPTiM study also demonstrated improved progression-free survival, ORR, and overall survival (OS) with T-VEC compared with GM-CSF, particularly in previously untreated patients (41, 43).

A heterologous prime-boost strategy has more recently been used to educate T cells and achieve a robust immune response, where a tumor antigen is delivered with one virus vector first, followed by a boost with the same tumor antigen delivered by a different viral vector or vector type. PROSTVAC-VF/Tricom, using a vaccinia virus encoding prostate-specific antigen (PSA) for priming, followed by subsequent booster doses of a fowlpox virus encoding PSA, demonstrated OS benefit in prostate cancer (44). However, a more recent phase III trial of PROSTVAC in castration-resistant prostate cancer was discontinued as a result of futility (45).

Viruses have also been engineered to simultaneously express targeted antigens and immunomodulatory molecules to disrupt the TME. TG4010 contains the modified vaccinia virus (MVA)-expressing tumor antigen, MUC-1, and immunostimulatory cytokine, IL2 (46, 47). TroVax is an MVA-expressing oncofetal antigen 5T4 (MVA-5T4; ref. 48). MG1 is a version of the oncolytic Maraba virus engineered with added transgene capacity for targeted expression of TAAs and immunomodulatory agents (49) being evaluated in non–small cell lung cancer (NSCLC; ref. 50) and human papilloma virus (HPV)-positive tumors (51).

Table 2. Virus-based vaccines.

Vaccine	Design	Administration	Clinical trial and intervention (key results, where available)	Publication/status
Talimogene laherparepvec (T-VEC)	First FDA-approved oncolytic virus for cancer treatment. Genetically engineered vector utilizes an attenuated HSV coding for GM-CSF production and relies on direct intratumoral injection to induce cell lysis as a form of *in situ* vaccination that promotes antitumor immune responses in uninjected adjacent and distant lesions.	Cutaneous, s.c., and/or intranodal	Phase III OPTiM study of T-VEC vs. GM-CSF in patients with MM ($n = 436$) DRR: T-VEC, 16.3%; GM-CSF, 2.1% (OR, 8.9; 95% CI, 2.7–29.2; $P < 0.001$) ORR: T-VEC, 26.4%; GM-CSF, 5.7% Median OS: T-VEC, 23.3 months; GM-CSF, 18.9 months (HR, 0.79; 95% CI, 0.62–1.00; $P = 0.051$) PFS: significantly improved with T-VEC vs. GM-CSF (HR, 0.68; 95% CI, 0.54–0.85; $P < 0.001$) 12-month PFS: T-VEC, 14.4%; GM-CSF, 4.6%	NCT00769704 (completed; refs. 41, 43)
			Phase II study of T-VEC + ipilimumab vs. ipilimumab in patients with MM ($n = 198$) ORR: T-VEC + ipilimumab, 39%; ipilimumab, 18% (OR, 2.9; 95% CI, 1.5–5.5; $P = 0.002$)	NCT01740297 (active, not recruiting; ref. 42)
Heterologous prime-boost strategy				
PROSTVAC-VF/TRICOM	PROSTVAC-VF/TRICOM uses a vaccinia virus encoding PSA for priming, followed by subsequent booster doses of a fowlpox virus encoding PSA, demonstrated OS benefit in prostate cancer (44).	s.c.	Phase II study of PROSTVAC + GM-CSF vs. control (empty vector) in patients with mCRPC ($n = 125$) Median OS: PROSTVAC + GM-CSF, 26.2 months; control, 16.3 months (HR, 0.50; 95% CI, 0.32–0.78; $P = 0.0019$)	n/a (completed; ref. 44)
			Phase I/II study of PROSTVAC + nivolumab in patients with prostate cancer ($n = 29$)	NCT02933255 (recruiting)
			Phase II study of PROSTVAC + ipilimumab in patients with localized prostate cancer undergoing radical prostatectomy ($n = 15$)	NCT02506114 (active, not recruiting)
			Phase III study of PROSTVAC vs. PROSTVAC + GM-CSF vs. placebo in patients with mCRPC (planned $n = 1,297$) Median OS: PROSTVAC, 34.4 months (HR vs. placebo, 1.01; 95% CI, 0.84–1.20; $P = 0.47$) PROSTVAC + GM-CSF, 33.2 months (HR vs. placebo, 1.02; 95% CI, 0.86–1.22; $P = 0.59$) Placebo, 34.3 months	NCT01322490 (terminated early because of futility; ref. 45)
Viruses expressing both targeted antigens and immunomodulatory molecules				
TG4010	TG4010 contains the MVA-expressing tumor antigen MUC-1 and immunostimulatory cytokine IL2.	s.c.	Phase II study of TG4010 (weekly for 6 weeks, then every 3 weeks until progression), then TG4010 + IFNα2a + IL2 in patients with MUC1-positive RCC ($n = 37$) Induction of an immunologic response against MUC-1 observed and safety established, but no objective clinical responses occurred SD for >6 months: TG4010 alone, 18%; TG4010 + cytokines, 30% Median TTF: TG4010 alone, 4.1 months; TG4010 + cytokines, 3.6 months Median OS: TG4010 + cytokines, 22.4 months	n/a (completed; ref. 46)
			Phase IIb/III TIME study of TG4010 + chemotherapy in patients with NSCLC ($n = 222$) Median OS: MUC-1 responders, 32.1 months; MUC-1 nonresponders, 12.7 months (HR, 0.43; 95% CI, 0.20–0.93; $P = 0.03$)	NCT01383148 (terminated; ref. 47)

(Continued on the following page)

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

Table 2. Virus-based vaccines. (Cont'd)

Vaccine	Design	Administration	Clinical trial and intervention (key results, where available)	Publication/status
TroVax	TroVax is an MVA-expressing oncofetal antigen 5T4 (MVA-5T4).	i.m.	Phase III study of TroVax + 1L SoC in patients with RCC ($n = 700$) Median OS: MVA-5T4, 20.1 months; SoC, 19.2 months ($P = 0.55$)	NCT00397345 (completed; ref. 48)
MG1 Maraba/ MAGE-A3 (MG1MA3)	MG1 is a version of the oncolytic Maraba virus engineered with added transgene capacity for targeted expression of the MAGE-A3 antigen.	i.m.	Phase I/II study of MG1MA3 ± AdMA3 in patients with MAGE-A3–expressing solid tumors ($n = 56$)	NCT02285816 (active, not recruiting; ref. 50)
			Phase I/II study of MG1MA3+ AdMA3 + pembrolizumab in patients with NSCLC ($n = 75$)	NCT02879760 (active, not recruiting; ref. 50)
MG1-E6E7	MG1 Maraba virus engineered to express *E6* and *E7*, found in HPV$^+$ cells.	i.v., i.m., i.t.	Phase Ib study in patients with HPV-associated cancers ($n = 75$) • Arm 1: i.v. MG1-E6E7 following i.m. Ad-E6E7 priming and subsequent i.v. atezolizumab • Arm 2: i.t. and i.v. MG1-E6E7 following i.m. Ad-E6E7 priming and subsequent i.v. atezolizumab	NCT03618953 (active, not recruiting; ref. 51)
Oncolytic virus directly targeting tumor				
RP1	HSV-1–based virus expressing GALV-GP-R and GM-CSF. Fusion-enhanced oncolytic immunotherapy based on HSV-1 engineered to express GALV envelope proteins.	i.t.	Phase I/II study of RP1 ± nivolumab in patients with solid tumors ($n = 168$)	NCT03767348 (recruiting; ref. 52)
MEDI5395	NDV-based virus expressing GM-CSF. MEDI5395 has the intrinsic ability to infect and kill tumor cells and has been inserted with a GM-CSF transgene to potentiate a stronger adaptive immune response.	i.v.	Phase I study of MEDI5395 + durvalumab in patients with selected advanced solid tumors ($n = 164$)	NCT03889275 (active, not recruiting)
BVAC-C	B cell/monocyte-based vaccine (BVAC-C) transfected with recombinant *HPV 16/18 E6/E7* and loaded with alpha-galactosyl ceramide, a natural killer T-cell ligand.	i.v.	Phase I study of BVAC-C in patients with cervical cancer ($n = 11$) Overall response rate, 11% Duration of response, 10 months Median PFS, 6.8 months OS, 89% at 6 months; 65% at 12 months Phase II study of BVAC-C in patients with cervical cancer ($n = 30$)	NCT02866006 (phase I and II, recruiting; ref. 54)
BVAC-B	Autologous B cell- and monocyte-based vaccine transfected with recombinant HER2/neu antigen, and loaded with alpha-galactosyl ceramide, a natural killer T-cell ligand.	i.v.	Phase I study of BVAC-B in patients with HER2/Neu-positive gastric cancer ($n = 8$)	NCT03425773 (completed; ref. 55)

Abbreviations: AdMA3, adenovirus/MAGE-A3; CI, confidence interval; DRR, durable response rate; GALV, gibbon ape leukemia virus; HR, hazard ratio; i.m., intramuscular; i.t., intratumoral; i.v., intravenous; mCRPC, metastatic castration-resistant prostate cancer; MM, malignant melanoma; n/a, not applicable (study does not have an NCT number); PFS, progression-free survival; RCC, renal cell carcinoma; s.c., subcutaneous; SD, stable disease; SoC, standard of care; TTF, time to treatment failure.

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

More recently, several fusion-enhanced oncolytic immunotherapies based on herpes simplex virus (HSV-1; RP1, RP2, and RP3) were engineered to express gibbon-ape leukemia virus envelope proteins (52). In addition, MEDI5395, an attenuated Newcastle disease virus (NDV) genetically modified to express GM-CSF, entered phase I clinical trials for intravenous administration late in 2019. In murine models, intravenous delivery of NDV leads to long-lasting tumor-selective replication, transgene expression, and TME transformation (53). Finally, a B cell/monocyte-based vaccine, BVAC-C, transfected with recombinant *HPV 16/18 E6/E7* showed efficacy in activating virus-specific T cells in a phase I study of patients with recurrent cervical cancer. A phase II study of BVAC-C in patients with cervical cancer is underway (54), as is a phase I study of BVAC-B, transfected with recombinant *HER2*/neu, in patients with gastric cancer (55).

Recent Developments in Cancer Vaccine Platforms

Nanoparticles as vaccine delivery systems

Nanoparticle-based cancer vaccines and adjuvants have been used to target cancers through modification of surface properties and/or composition to prolong bioavailability, protect antigens from degradation, and control antigen release (56). Nanoparticles tested include polymeric nanoparticles, liposomes, micelles, carbon nanotubes, mesoporous silica nanoparticles, gold nanoparticles, and virus nanoparticles, which have been assessed in cancer types such as melanoma, NSCLC, breast, prostate, and cervical (56). However, further studies are needed to address concerns of poor reproducibility with uniform size and shape, aggregation, instability, and rapid clearance before widespread clinical use (56). To date, only one nanoparticle vaccine, tecemotide (L-BLP25), an MUC1 antigen-specific vaccine, has reached clinical trial. In a phase III trial of tecemotide compared with placebo for stage III NSCLC no difference in OS was found (57). Similarly, a phase II trial in early breast cancer demonstrated a good safety profile, but showed no significant difference in residual cancer burden or pathologic complete response with tecemotide compared with standard of care (58).

Peptide-based vaccines

Synthetic long peptide (SLP) immunotherapeutics have been developed, consisting of highly immunogenic long peptides designed to avoid central tolerance mechanisms by efficiently delivering antigens to DCs, inducing $CD4^+$ and $CD8^+$ T-cell responses (59). In a phase II trial, an SLP vaccine, ISA101, combined with the anti-PD-1 immune checkpoint antibody, nivolumab, was found to be well-tolerated in patients with HPV-16–positive cancer ($n = 24$), with additive effects observed relative to nivolumab monotherapy (60). In addition, a phase I/II study of ISA101 in combination with standard-of-care chemotherapy in patients with HPV-16–positive cervical cancer ($n = 77$) demonstrated a longer OS in patients who expressed a stronger-than-median vaccine-induced HPV-16–specific T-cell response (61). A phase II study of ISA101 with cemiplimab for oropharyngeal cancer is underway (NCT03669718).

SVN53-67/M57-KLH (SurVaxM) is a vaccine containing an SLP mimic designed to stimulate an immune response targeting survivin, a TSA which is highly expressed in glioblastomas, among other cancers types (62, 63). In a phase II trial (NCT024455557), patients with newly diagnosed glioblastoma who received SurVaxM in the adjuvant setting demonstrated a significantly longer 12-month OS of 93.4% from diagnosis, compared with 65% survival from historic studies (64, 65). Interestingly, SurVaxM is now being investigated in a phase I study of patients with survivin-positive neuroendocrine tumors (NCT03879694; ref. 66).

A novel technology platform, T-win, was developed to allow identification, design, and validation of immune modulatory peptide-based vaccine candidates targeting the TME (67). T-win vaccines engage and activate a subset of naturally occurring proinflammatory T cells specific for immune inhibitory molecules, for example, indoleamine 2,3 dehydrogenase (IDO), PD-ligand 1 (L1), PD-L2, arginase, or CCL22 (68, 69). These T cells were initially termed "antiregulatory T cells" ("anti-Tregs") for their specificity against cells with immunoregulatory functions. These autoreactive T cells, found in high frequencies in patients with cancer, recognize and kill both tumor cells and normal immune cells that express their cognate targets (70, 71), as well as assist in expansion of effector T cells against viral and tumor antigens *in vitro* (70, 72). Importantly, both $CD4^+$ and $CD8^+$ T cells also contribute to the immunoregulatory function of anti-Tregs through the secretion of proinflammatory cytokines (73, 74). Thus, these T cells assist the adaptive immune response either through their involvement in the direct elimination of the immunosuppressive cells or through the secretion of proinflammatory cytokines (75, 76). In preclinical models, T-win vaccination has led to an antitumor response and synergizes with anti-PD-1 antibody treatment (77). In mice treated with a T-win vaccine against IDO, a substantial reduction of IDO^+ immune suppressor cells in the TME was observed, accompanied by an increased expansion of infiltrating tumor-specific T cells (77). Taken together, evidence suggests that T-win vaccination can lead to the expansion of T cells that counteract and modulate the immune suppressive environment within TME, allowing for efficient antitumor responses to take place. Because T-win vaccines aim to expand intrinsic/preexisting T cells in patients with cancer, T-win vaccines do not need to "break tolerance" in the same way as cancer vaccines targeting TAAs (67).

The major challenge of the T-win technology is to activate the most potent anti-Treg immune response without inducing autoimmunity and toxicity. However, circulation of a measurable number of such specific T cells in patients with cancer has been described without autoimmunity; thus, the risk of potential long-term toxicity because of vaccine-induced autoimmune mechanisms appears to be minimal, illustrated in murine *in vivo* studies and clinical trials to date (67). **Table 3** summarizes the T-win technology compounds currently in clinical trials.

Personalized vaccine strategies

With the availability of next-generation sequencing, personalized neoantigen-based immunotherapies are emerging. Sequence data from a patient's tumor biopsy are analyzed to predict which mutations will generate tumor-specific neoantigens likely to be presented by MHC molecules on the tumor cell surface in that patient. Most efforts focus on identifying antigen sequences that generate epitopes fitting the groove of a patient's MHC-I molecules. Although personalized cancer vaccines have shown encouraging results (78, 79), neoepitope prediction algorithms return a large number of "candidates," of which very few trigger genuine antitumor responses (80). To eliminate the tumor, it is likely to be necessary to target clonal or truncal neoantigens present in every cancer cell. Targeting only subclonal or branch mutations, present in a subset of cells, will not eliminate the tumor and can cause resistance to therapy (81). Interestingly, some have proposed that neoantigens may have inhibitory properties that enable

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

Table 3. T-win technology compounds in clinical development.

T-win technology Compound	Target tumor antigen	Clinical trials	Publication/status
IO101	IDO	Phase I IO102 + aldara + montanide Stage III–IV NSCLC $n = 15$ • 3 of 15 patients are still alive corresponding to a 6-year OS of 20% • 2 patients continued monthly vaccinations for 5 years; 1 of these developed a PR of liver lesions 15 months after the first vaccine and has remained in PR ever since	NCT01219348 (completed; refs. 76, 100)
IO102	IDO	Phase I IO102 + ipilimumab MM	n/a (101)
		Phase I/II IO102 + pembrolizumab alone or with chemotherapy Stage III–IV NSCLC	IO102–012/KN-764; NCT03562871 (recruiting; ref. 102)
IO103	PD-L1	Phase IIa IO103 monotherapy + montanide BCC	NCT03714529 (recruiting)
		Phase II IO103 + IO120 (targeting PD-L2) Untreated CLL	NCT03939234 (recruiting)
		Phase IIa IO103 monotherapy High-risk smoldering multiple myeloma	NCT03850522 (recruiting)
		Phase I/II IO102 + IO103 + nivolumab Treatment-naïve and PD-1/PD-L1 mAb refractory MM	NCT03047928 (recruiting; ref. 103)
IO112	Arginase 1	Phase I IO112 Arginase-positive solid tumors	NCT03689192 (recruiting; ref. 104)
IO160	CalR exon 9–mutant peptide	Phase I IO160 CalR-mutant myeloproliferative neoplasms	NCT03566446 (active, not recruiting; ref. 105)

Abbreviations: BCC, basal cell carcinoma; CalR, calreticulin R; CLL, chronic lymphatic leukemia; MM, metastatic melanoma; n/a, not applicable (study does not have an NCT number).

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

Table 4. Neoantigen-targeted cancer vaccines.

Vaccine	Off the shelf?	Mechanism of action	Clinical trial and intervention	Publication
GRANITE-001	No	Personalized Targeting a cassette of 20 patient- and tumor-specific neoantigens identified by EDGE	Phase I/II GRT-C901 and GRT-R902 (heterologous prime/boost) + nivolumab and ipilimumab NSCLC, microsatellite stable CRC, gastroesophageal adenocarcinoma, urothelial cancer	NCT03639714 (recruiting; ref. 83)
SLATE	Yes	Shared Targeting the top 20 tumor-specific shared neoantigens, identified by EDGE	Phase I GRT-C903 and GRT-R904 (heterologous prime/boost) + CPIs (anti-PD-L1 and anti-CTLA-4) NSCLC, microsatellite stable CRC, pancreatic cancer, shared neoantigen-positive tumors	NCT03953235 (recruiting; ref. 84)
GEN-009	No	Personalized Targeting neoantigens to which patients have preconfirmed responses *in vitro*	Phase I/II GEN-009-101 trial Part A: GEN-009 adjuvanted vaccine monotherapy; solid tumors Part B: GEN-009 + nivolumab or pembrolizumab; cutaneous melanoma, NSCLC, SCCHN, urothelial carcinoma, RCC $N = 8$ • No recurrent disease, to date. • OR for immune response against individual peptide with peptide concentration: 1.26, $P \leq 0.0001$	NCT03633110 (active, not recruiting; refs. 86, 87)
NEO-PV-01	No	Personalized	Phase I NEO-PV-01 + pembrolizumab + carboplatin + pemetrexed vs pembrolizumab + carboplatin + pemetrexed NSCLC	NCT03380871 (active, not recruiting)
			Phase I NEO-PV-01 + nivolumab MM, NSCLC or transitional cell carcinoma of the bladder	NCT02897765 (active, not recruiting)
			Phase I NEO-PV-01 + (APX005M or ipilimumab) + nivolumab MM	NCT03597282 (active, not recruiting)
BNT111, BNT113, and BNT114 mRNA-based	Yes	Shared Targeting shared tumor-specific neoantigens (FixVac platform)	Phase I BNT111; Lipo-MERIT (tetravalent RNA-lipoplex cancer vaccine targeting 4 TAAs (RBL001.1, RBL002.2, RBL003.1, and RBL004.1) MM $N = 89$ (interim analysis) Monotherapy group ($n = 25$) • PR: $n = 3$; SD: $n = 7$; complete metabolic remission: $n = 1$ FixVac + anti-PD-1 ($n = 17$) • PR: $n = 6$, all 6 had polyepitopic and strong $CD4^+$ and $CD8^+$ T-cell immunity against vaccine antigens	NCT02410733 (recruiting; ref. 90)
			Phase I/II BNT113 HPV-positive cancers including but not exclusively HNSCC	(ongoing)
			Phase I BNT114 TNBC	(ongoing)

(Continued on the following page)

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

Table 4. Neoantigen-targeted cancer vaccines. (Cont'd)

Vaccine	Off the shelf?	Mechanism of action	Clinical trial and intervention	Publication
RO7198457 (BNT122)	No	Personalized (iNeST platform)	Phase II RO7198457 (BNT122) + pembrolizumab MM	NCT03815058 (ongoing)
mRNA-based			Phase Ia/Ib RO7198457 (BNT122) Solid tumors Phase Ia $N = 29$ • CR ongoing for ≥10 months: 4% • SD: 42% • Discontinued due to PD (prior to completing 6 weeks of therapy): 28% Phase Ib $N = 132$ • ORR: 8% (including CR, $n = 1$) • SD: 49% • Discontinued due to PD (prior to completing 6 weeks of therapy): 16%	NCT03289962 (ongoing; refs. 91, 92)
			Phase II RO7198457 (BNT122) + atezolizumab Stage II-III NSCLC	NCT04267237 (recruiting)
mRNA-4157 mRNA-based	No	Personalized	Phase I (KEYNOTE-603) mRNA-4157; resected solid tumors mRNA-4157 + pembrolizumab; unresectable solid tumors $N = 33$ (monotherapy, $n = 13$; +pembrolizumab, $n = 20$) • CR: $n = 1$ of 20 • PR: $n = 2$ of 20 • SD: $n = 5$ of 20	NCT03313778 (recruiting; ref. 56)
NCI-4650	No	Personalized	Phase I/II NCI-4650 MM, CC, GI cancer, GU cancer, HCC	NCT03480152 (terminated)
mRNA-5671/V941	Yes	Shared	Phase I mRNA-5671/V941 ± pembrolizumab *KRAS*-mutant NSCLC, CRC, or pancreatic adenocarcinoma	NCT03948763
GAPVAC-101	APVAC1: yes APVAC2: no	APVAC1: shared APVAC2: personalized	Phase I APVAC1 vaccine plus poly-ICLC and GM-CSF followed by APVAC2 vaccine plus poly-ICLC and GM-CSF Newly diagnosed glioblastoma	NCT02149225 (completed; ref. 96)

Abbreviations: CC, colon cancer; CR, complete response; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; GI, gastrointestinal; GU, genitourinary; HCC, hepatocellular cancer; HNC, head and neck cancer; MM, metastatic melanoma; PR, partial response; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease; TNBC, triple-negative breast cancer.

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

tumors to evade immune detection. A few recently emerging personalized neoantigen vaccines and technologies are summarized here and in **Table 4**.

EDGE is an artificial intelligence platform used to investigate sequence data from tumor biopsies and identify tumor-specific neoantigens (82). GRANITE-001 is a personalized cancer vaccine based on individual patients' predicted neoantigens, targeting a cassette of 20 patient- and tumor-specific neoantigens identified by EDGE. An ongoing phase I/II clinical study is evaluating GRANITE-001 in combination with CPIs for solid tumor treatment (83). Similarly, SLATE is an immunotherapy directed at the top 20 tumor-specific neoantigens shared by a subset of patients, identified by EDGE. For these patients, an "off-the-shelf" therapy that works across multiple tumor types may be appropriate. An ongoing phase I study is evaluating SLATE in combination with CPIs for solid tumor treatment (84). Both GRANITE-001 and SLATE use a priming adenoviral vector and a self-amplifying RNA vector to deliver the neoantigen cassette in a repeated boost sequence.

ATLAS is another technology platform that uses patient's T-cell immune response machinery to identify optimal patient- and tumor-specific neoantigens (85). By including neoantigens to which patients have had preconfirmed responses *in vitro*, personalized cancer vaccines are created that the patients' immune systems are already primed for. GEN-009 is being investigated in a phase I/IIa trial for multiple tumor types (GEN-009-101), with positive initial results (86, 87), and GEN-011 is in preclinical development.

A RECON Bioinformatics Engine for prediction and identification of therapeutically relevant neoantigen targets (88) was used to investigate cancer vaccines targeting both patient- and tumor-specific and shared neoantigens (present on the same tumor type in multiple patients). NEO-PV-01, a personalized neoantigen vaccine, custom designed on the basis of unique mutational fingerprints of individual patients, is under investigation in multiple phase Ib clinical trials. NEO-SV-01, an "off-the-shelf" multivalent neoantigen vaccine for treatment of a genetically defined subset of hormone receptor–positive breast cancer, is in preclinical development (88).

Several candidate mRNA-based cancer vaccines are being evaluated in phase I trials, based on a "FixVac" platform (fixed combination of shared cancer antigens; ref. 89). These include BNT111 in metastatic melanoma (90), BNT113 in HPV-positive head and neck cancers, and BNT114 in triple-negative breast cancer. Another mRNA-based cancer vaccine candidate, RO7198457 (BNT122), based on an individualized Neoantigen Specific Immunotherapy (iNeST) platform, is being investigated in combination with pembrolizumab for melanoma (phase II), alone and with atezolizumab for solid tumors (phase I; refs. 91, 92), and with atezolizumab for NSCLC (phase II).

Additional personalized mRNA-based cancer vaccines in phase I testing include (93): mRNA-4157 alone or combined with pembrolizumab in solid tumors (KEYNOTE-603; ref, 56) and NCI-4650 (study now terminated). A vaccine encoding the four most common *KRAS* mutations, mRNA-5671, is also in phase I testing for patients with *KRAS*-mutant NSCLC, colorectal cancer, or pancreatic adenocarcinoma (93).

Response to immunotherapy often correlates with high tumor mutation load (94) and consequent higher numbers of predicted neoantigens. Researchers at La Jolla Institute for Immunology (La Jolla, CA) and University of California San Diego (San Diego, CA) are working to identify clinically relevant neoantigens in malignancies of moderate or low mutational burden, for example, head and neck squamous cell carcinoma (HNSCC). Validated neoantigens will be further analyzed in HNSCC tumor models (95). They also plan to explore the role of T-cell exhaustion in mouse and human HNSCC, with a view to being able to counteract this and reinvigorate T cells.

Hilf and colleagues are investigating more effective immunotherapies for low mutational load tumors, by integrating highly individualized vaccinations with unmutated antigens and tumor neoepitopes (96). A phase I trial is investigating novel patient-tailored vaccines, APVAC1 ("off the shelf" glioblastoma-associated peptides) and APVAC2 (*de novo* synthesized patient-specific glioblastoma-associated tumor-mutated peptides), in glioblastoma (96).

Conclusions/Future Perspectives

It is an exciting time in the field of therapeutic cancer vaccines, with promising developments in both existing strategies for cancer vaccines and in several new cancer vaccine platforms, antigen targets, and methods to identify them. More research is required before the ultimate goal of personalized cancer therapies can be achieved, but there are currently a wealth of ongoing and upcoming trials in therapeutic cancer vaccine that are expected to lend credence to the value of these strategies. In the move toward personalized cancer immunotherapy, panels of genomic and proteomic biomarkers predictive for response following molecular profiling of tumor and host cells using next-generation sequencing, are expected to further aid decision making and improve outcomes (97).

Overall, cancer vaccines could be the next preferred combination partner for long-term cancer treatment, providing a platform that is easily combined with existing therapies, with minimal toxicity and a good safety profile established in vaccines studied to date.

Authors' Disclosures

K.J. Harrington reports personal fees from Amgen, Arch Oncology, ISA Therapeutics, Merck-Serono, Oncolys, and Pfizer, and grants and personal fees from AstraZeneca, Boehringer-Ingelheim, MSD, and Replimune during the conduct of the study (all of the aforementioned were paid to institution). M.-B. Zocca reports personal fees from IO Biotech (CEO and shareholder) and Valo Therapeutics (member, board of directors) outside the submitted work. E. Ehrnrooth reports other from IO Biotech (employment) outside the submitted work. E.E.W. Cohen reports personal fees from BioNTech and Pact Pharma outside the submitted work. No disclosures were reported by the other author.

Acknowledgments

The authors thank Jane Blackburn and Jacqueline Harte, of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc (funded by IO Biotech ApS), for medical writing and editing assistance. The authors would also like to thank Ayako Wakatsuki Pedersen, employee of IO Biotech ApS, for assisting the authors in addressing peer reviewer comments in relation to antiregulatory T cells. This work was supported by IO Biotech ApS.

Received January 23, 2020; revised June 12, 2020; accepted October 26, 2020; published first October 29, 2020.

References

1. Hollingsworth RE, Jansen K. Turning the corner on therapeutic cancer vaccines. NPJ Vaccines 2019;4:7.
2. Pedersen SR, Sorensen MR, Buus S, Christensen JP, Thomsen AR. Comparison of vaccine-induced effector CD8 T cell responses directed against self- and

non-self-tumor antigens: implications for cancer immunotherapy. J Immunol 2013;191:3955–67.
3. Osipov A, Murphy A, Zheng L. From immune checkpoints to vaccines: the past, present and future of cancer immunotherapy. Adv Cancer Res 2019; 143:63–144.
4. Le DT, Pardoll DM, Jaffee EM. Cellular vaccine approaches. Cancer J 2010;16: 304–10.
5. Harrington K, Freeman DJ, Kelly B, Harper J, Soria JC. Optimizing oncolytic virotherapy in cancer treatment. Nat Rev Drug Discov 2019;18:689–706.
6. Wieczorek M, Abualrous ET, Sticht J, Álvaro-Benito M, Stolzenberg S, Noé F, et al. Major histocompatibility complex (MHC) class I and MHC class II proteins: conformational plasticity in antigen presentation. Front Immunol 2017;8:292.
7. Slingluff CL Jr. The present and future of peptide vaccines for cancer: single or multiple, long or short, alone or in combination? Cancer J 2011;17:343–50.
8. Liu J, Miao L, Sui J, Hao Y, Huang G. Nanoparticle cancer vaccines: design considerations and recent advances. Asian J Pharm Sci 2020;15:576–90.
9. Hurez V, Padron A, Svatek RS, Curiel TJ. Considerations for successful cancer immunotherapy in aged hosts. Exp Gerontol 2018;107:27–36.
10. Thommen DS, Schumacher TN. T cell dysfunction in cancer. Cancer Cell 2018; 33:547–62.
11. Wang M, Zhao J, Zhang L, Wei F, Lian Y, Wu Y, et al. Role of tumor microenvironment in tumorigenesis. J Cancer 2017;8:761–73.
12. Xu X, Li J, Zou J, Feng X, Zhang C, Zheng R, et al. Association of germline variants in natural killer cells with tumor immune microenvironment subtypes, tumor-infiltrating lymphocytes, immunotherapy response, clinical outcomes and cancer risk. JAMA Netw Open 2019;2:e199292.
13. Blankenstein T, Coulie PG, Gilboa E, Jaffee EM. The determinants of tumour immunogenicity. Nat Rev Cancer 2012;12:307–13.
14. Hegde PS, Chen DS. Top 10 challenges in cancer immunotherapy. Immunity 2020;52:17–35.
15. Zaretsky JM, Garcia-Diaz A, Shin DS, Escuin-Ordinas H, Hugo W, Hu-Lieskovan S, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med 2016;375:819–29.
16. Milo I, Bedora-Faure M, Garcia Z, Thibaut R, Perie L, Shakhar G, et al. The immune system profoundly restricts intratumor genetic heterogeneity. Science immunology 2018;3:eaat1435.
17. Beatty GL, Gladney WL. Immune escape mechanisms as a guide for cancer immunotherapy. Clin Cancer Res 2015;21:687–92.
18. Kaneno R, Shurin GV, Kaneno FM, Naiditch H, Luo J, Shurin MR. Chemotherapeutic agents in low noncytotoxic concentrations increase immunogenicity of human colon cancer cells. Cell Oncol 2011;34:97–106.
19. Chiriva-Internati M, Grizzi F, Pinkston J, Morrow KJ, D'Cunha N, Frezza EE, et al. Gamma-radiation upregulates MHC class I/II and ICAM-I molecules in multiple myeloma cell lines and primary tumors. In Vitro Cell Dev Biol Anim 2006;42:89–95.
20. Prendergast GC, Smith C, Thomas S, Mandik-Nayak L, Laury-Kleintop L, Metz R, et al. Indoleamine 2,3-dioxygenase pathways of pathogenic inflammation and immune escape in cancer. Cancer Immunol Immunother 2014;63:721–35.
21. Laheru D, Lutz E, Burke J, Biedrzycki B, Solt S, Onners B, et al. Allogeneic granulocyte macrophage colony-stimulating factor-secreting tumor immunotherapy alone or in sequence with cyclophosphamide for metastatic pancreatic cancer: a pilot study of safety, feasibility, and immune activation. Clin Cancer Res 2008;14:1455–63.
22. Le DT, Lutz E, Uram JN, Sugar EA, Onners B, Solt S, et al. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. J Immunother 2013;36:382–9.
23. Hopkins AC, Yarchoan M, Durham JN, Yusko EC, Rytlewski JA, Robins HS, et al. T cell receptor repertoire features associated with survival in immunotherapy-treated pancreatic ductal adenocarcinoma. JCI insight 2018;3:e122092.
24. Lutz E, Yeo CJ, Lillemoe KD, Biedrzycki B, Kobrin B, Herman J, et al. A lethally irradiated allogeneic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine for pancreatic adenocarcinoma. A phase II trial of safety, efficacy, and immune activation. Ann Surg 2011;253:328–35.
25. Higano CS, Corman JM, Smith DC, Centeno AS, Steidle CP, Gittleman M, et al. Phase 1/2 dose-escalation study of a GM-CSF-secreting, allogeneic, cellular immunotherapy for metastatic hormone-refractory prostate cancer. Cancer 2008;113:975–84.
26. Small EJ, Sacks N, Nemunaitis J, Urba WJ, Dula E, Centeno AS, et al. Granulocyte macrophage colony-stimulating factor - secreting allogeneic cellular immunotherapy for hormone-refractory prostate cancer. Clin Cancer Res 2007;13:3883–91.
27. Rocconi R, Grosen E, Ghamande S, Chan J, Barve M, Oh J, et al. Randomized double-blind placebo-controlled trial of primary maintenance vigil immunotherapy (VITAL study) in stage III/IV ovarian cancer: efficacy assessment in BRCA1/2 -wt patients. J Clin Oncol 2020;38:6017.
28. Rocconi RP, Stevens EE, Bottsford-Miller JN, Ghamande SA, Aaron P, Wallraven G, et al. A phase I combination study of vigil and atezolizumab in recurrent/refractory advanced-stage ovarian cancer: efficacy assessment in BRCA1/2-wt patients. J Clin Oncol 2020;38:3002.
29. Small EJDT, Gerritsen WR, et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC) [abstract]. In: ASCO Annual Meeting Abstracts 2009;2009 May 29–Jun 2; Orlando, FL. LBA150;a07.
30. Hsueh EC, Morton DL. Antigen-based immunotherapy of melanoma: canvaxin therapeutic polyvalent cancer vaccine. Semin Cancer Biol 2003;13:401–7.
31. Faries MB, Mozzillo N, Kashani-Sabet M, Thompson JF, Kelley MC, DeConti RC, et al. Long-term survival after complete surgical resection and adjuvant immunotherapy for distant melanoma metastases. Ann Surg Oncol 2017;24: 3991–4000.
32. Rinde M. Sipuleucel-T shows potential with new trial data, but questions regarding clinical relevance remain. Targeted Therapies Oncol 2019;8.
33. Lawson DH, Lee S, Zhao F, Tarhini AA, Margolin KA, Ernstoff MS, et al. Randomized, placebo-controlled, phase III trial of yeast-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) versus peptide vaccination versus GM-CSF plus peptide vaccination versus placebo in patients with no evidence of disease after complete surgical resection of locally advanced and/or stage IV melanoma: a trial of the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group (E4697). J Clin Oncol 2015;33:4066–76.
34. Tanyi JL, Bobisse S, Ophir E, Tuyaerts S, Roberti A, Genolet R, et al. Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. Sci Transl Med 2018;10:eaao5931.
35. Hickerson A, Clifton GT, Brown TA, Campf J, Myers JW, Vreeland TJ, et al. Clinical efficacy of vaccination with the autologous tumor lysate particle loaded dendritic cell (TLPLDC) vaccine in metastatic melanoma. J Clin Oncol 2019;37: e21025.
36. Chick R, Kemp Bohan P, Vreeland T, Hickerson A, Cindass J, Hale D, et al. Impact of disease-free interval on recurrence in high-risk melanoma patients in a phase IIb trial of the tumor lysate particle loaded dendritic cell (TLPLDC) vaccine. [abstract]. In: Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27–28 and Jun 22–24. Philadelphia (PA): AACR; 2020. Abstract nr 6537.
37. Chick R, Faries M, Hale D, Bohan P, Hickerson A, Vreeland T, et al. Multi-institutional, prospective, randomized, double-blind, placebo-controlled phase IIb trial of the tumor lysate, particle-loaded, dendritic cell (TLPLDC) vaccine to prevent recurrence in high-risk melanoma patients: a subgroup analysis. J Clin Oncol 2020;38:63.
38. Herbert GS, Vreeland TJ, Clifton GT, Greene JM, Jackson DO, Hardin MO, et al. Initial phase I/IIa trial results of an autologous tumor lysate, particle-loaded, dendritic cell (TLPLDC) vaccine in patients with solid tumors. Vaccine 2018;36:3247–53.
39. Lindskog M, Laurell A, Kjellman A, Melichar B, Niezabitowski J, Maroto P, et al. A randomized phase II study with ilixadencel, a cell-based immune primer, plus sunitinib versus sunitinib alone in synchronous metastatic renal cell carcinoma. J Clin Oncol 2020;38:11.
40. Conry RM, Westbrook B, McKee S, Norwood TG. Talimogene laherparepvec: first in class oncolytic virotherapy. Hum Vaccin Immunother 2018;14:839–46.
41. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015;33:2780–8.
42. Chesney J, Puzanov I, Collichio F, Singh P, Milhem MM, Glaspy J, et al. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. J Clin Oncol 2018;36: 1658–67.
43. Milhem MM, Harrington KJ, Collichio FA, Amatruda T, Chesney JA, Agarwala SS, et al. Progression-free survival (PFS) in unresectable melanoma patients (pts) treated with talimogene laherparepvec (T-VEC) versus granulocyte

macrophage colony-stimulating factor (GM-CSF) in OPTiM. J Clin Oncol 2019;37:9524.
44. Kantoff PW, Gulley JL, Pico-Navarro C. Revised overall survival analysis of a phase II, randomized, double-blind, controlled study of PROSTVAC in men with metastatic castration-resistant prostate cancer. J Clin Oncol 2017;35: 124–5.
45. Gulley JL, Borre M, Vogelzang NJ, Ng S, Agarwal N, Parker CC, et al. Phase III trial of PROSTVAC in asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. J Clin Oncol 2019;37:1051–61.
46. Oudard S, Rixe O, Beuselinck B, Linassier C, Banu E, Machiels JP, et al. A phase II study of the cancer vaccine TG4010 alone and in combination with cytokines in patients with metastatic renal clear-cell carcinoma: clinical and immunological findings. Cancer Immunol Immunother 2011;60:261–71.
47. Tosch C, Bastien B, Barraud L, Grellier B, Nourtier V, Gantzer M, et al. Viral based vaccine TG4010 induces broadening of specific immune response and improves outcome in advanced NSCLC. J Immunother Cancer 2017;5:70.
48. Amato RJ, Hawkins RE, Kaufman HL, Thompson JA, Tomczak P, Szczylik C, et al. Vaccination of metastatic renal cancer patients with MVA-5T4: a randomized, double-blind, placebo-controlled phase III study. Clin Cancer Res 2010;16:5539–47.
49. Pol JG, Zhang L, Bridle BW, Stephenson KB, Resseguier J, Hanson S, et al. Maraba virus as a potent oncolytic vaccine vector. Mol Ther 2014;22:420–9.
50. Pol JG, Acuna SA, Yadollahi B, Tang N, Stephenson KB, Atherton MJ, et al. Preclinical evaluation of a MAGE-A3 vaccination utilizing the oncolytic Maraba virus currently in first-in-human trials. Oncoimmunology 2019;8: e1512329.
51. Atherton MJ, Stephenson KB, Pol J, Wang F, Lefebvre C, Stojdl DF, et al. Customized viral immunotherapy for HPV-associated cancer. Cancer Immunol Res 2017;5:847–59.
52. Thomas S, Kuncheria L, Roulstone V, Kyula JN, Mansfield D, Bommareddy PK, et al. Development of a new fusion-enhanced oncolytic immunotherapy platform based on herpes simplex virus type 1. J Immunother Cancer 2019; 7:214.
53. Harper JA, Burke S, Leinster A, Rath N, Cheng X, Jin H, et al. MEDI5395: a recombinant oncolytic virus with oncolytic and immune modulatory properties. [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019; 2019 Mar 29–Apr 3; Atlanta, GA. Philadelphia (PA): AACR; 2019. Abstract nr 1456.
54. Choi CH, Choi HJ, Lee JW, Kang ES, Cho D, Park BK, et al. Phase I study of a B cell-based and monocyte-based immunotherapeutic vaccine, BVAC-C in human papillomavirus type 16- or 18-positive recurrent cervical cancer. J Clin Med 2020;9:147.
55. Lee JB, Kwon WS, Kim HS, Jung M, Kim S, Park M, et al. First-in-human phase I study of BVAC-B cell therapy in HER2-positive advanced gastric cancer. J Clin Oncol 2020;38:4534.
56. Burris HA, Patel MR, Cho DC, Clarke JM, Gutierrez M, Zaks TZ, et al. A phase I multicenter study to assess the safety, tolerability, and immunogenicity of mRNA-4157 alone in patients with resected solid tumors and in combination with pembrolizumab in patients with unresectable solid tumors. J Clin Oncol 2019;37:2523.
57. Butts C, Socinski MA, Mitchell PL, Thatcher N, Havel L, Krzakowski M, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15:59–68.
58. Singer CF, Pfeiler G, Hubalek M, Bartsch R, Stöger H, Pichler A, et al. Efficacy and safety of the therapeutic cancer vaccine tecemotide (L-BLP25) in early breast cancer: Results from a prospective, randomised, neoadjuvant phase II study (ABCSG 34). Eur J Cancer 2020;132:43–52.
59. Melief CJM, van Hall T, Arens R, Ossendorp F, van der Burg SH. Therapeutic cancer vaccines. J Clin Invest 2015;125:3401–12.
60. Massarelli E, William W, Johnson F, Kies M, Ferrarotto R, Guo M, et al. Combining immune checkpoint blockade and tumor-specific vaccine for patients with incurable human papillomavirus 16-related cancer: a phase 2 clinical trial. JAMA Oncol 2019;5:67–73.
61. Melief CJM, Welters MJP, Vergote I, Kroep JR, Kenter GG, Ottevanger PB, et al. Strong vaccine responses during chemotherapy are associated with prolonged cancer survival. Sci Transl Med 2020;12:eaaz8235.
62. Fenstermaker RA, Figel SA, Qiu J-X, Barone TA, Dharma SS, Winograd EK, et al. Survivin monoclonal antibodies detect survivin cell surface expression and inhibit tumor growth *in vivo*. Clin Cancer Res 2018;24: 2642–52.
63. Fenstermaker RA, Ciesielski MJ, Qiu J, Yang N, Frank CL, Lee KP, et al. Clinical study of a survivin long peptide vaccine (SurVaxM) in patients with recurrent malignant glioma. Cancer Immunol Immunother 2016;65:1339–52.
64. Ahluwalia MS, Reardon DA, Abad AP, Curry WT, Wong ET, Belal A, et al. SurVaxM with standard therapy in newly diagnosed glioblastoma: phase II trial update. J Clin Oncol 2019;37:2016.
65. Ostrom QT, Cote DJ, Ascha M, Kruchko C, Barnholtz-Sloan JS. Adult glioma incidence and survival by race or ethnicity in the United States from 2000 to 2014. JAMA Oncol 2018;4:1254–62.
66. Hanif A, Lee S, Gupta M, Chander A, Kannisto ED, Punnanitinont A, et al. Exploring the role of survivin in neuroendocrine neoplasms. Oncotarget 2020; 11:2246–58.
67. Andersen MH. The T-win(R) technology: immune-modulating vaccines. Semin Immunopathol 2019;41:87–95.
68. Andersen MH. Anti-regulatory T cells. Semin Immunopathol 2017;39:317–26.
69. Pedersen AW, Kopp KL, Andersen MH, Zocca MB. Immunoregulatory antigens-novel targets for cancer immunotherapy. Chin Clin Oncol 2018;7:19.
70. Sørensen RB, Hadrup SR, Svane IM, Hjortsø MC, Thor Straten P, Andersen MH. Indoleamine 2,3-dioxygenase specific, cytotoxic T cells as immune regulators. Blood 2011;117:2200–10.
71. Munir S, Andersen GH, Met Ö, Donia M, Frøsig TM, Larsen SK, et al. HLA-restricted CTL that are specific for the immune checkpoint ligand PD-L1 occur with high frequency in cancer patients. Cancer Res 2013;73:1764–76.
72. Ahmad SM, Svane IM, Andersen MH. The stimulation of PD-L1-specific cytotoxic T lymphocytes can both directly and indirectly enhance antileukemic immunity. Blood Cancer J 2014;4:e230.
73. Munir S, Larsen SK, Iversen TZ, Donia M, Klausen TW, Svane IM, et al. Natural CD4+ T-cell responses against indoleamine 2,3-dioxygenase. PLoS One 2012; 7:e34568.
74. Munir S, Andersen GH, Svane IM, Andersen MH. The immune checkpoint regulator PD-L1 is a specific target for naturally occurring CD4+ T cells. Oncoimmunology 2013;2:e23991.
75. Andersen MH. Immune regulation by self-recognition: novel possibilities for anticancer immunotherapy. J Natl Cancer Inst 2015;107:djv154.
76. Kjeldsen JW, Iversen TZ, Engell-Noerregaard L, Mellemgaard A, Andersen MH, Svane IM. Durable clinical responses and long-term follow-up of stage III-IV non-small-cell lung cancer (NSCLC) patients treated with IDO peptide vaccine in a phase I study -a brief research report. Front Immunol 2018;9:2145.
77. Dey S, Sutanto-Ward E, Kopp KL, DuHadaway J, Mondal A, Ghaban D, et al. Peptide vaccination directed against IDO1-expressing immune cells elicits $CD8^+$and $CD4^+$T-cell-mediated antitumor immunity and enhanced anti-PD1 responses. J Immunother Cancer 2020;8:e000605.
78. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Lower M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017;547:222–6.
79. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature 2017;547: 217–21.
80. The problem with neoantigen prediction. Nat Biotechnol 2017;35:97. Available from: https://www.nature.com/articles/nbt.3800#citeas
81. Joshi K, Chain BM, Peggs KS, Quezada SA. The "Achilles' Heel" of cancer and its implications for the development of novel immunotherapeutic strategies. Cold Spring Harb Perspect Med 2018;8:a027086.
82. Gritstone Oncology Inc. Available from: https://gritstoneoncology.com.
83. Gritstone Oncology Inc. Gritstone oncology announces first patient dosed in a clinical study evaluating its personalized immunotherapy, GRANITE-001. Available from: https://www.globenewswire.com/news-release/2019/03/21/1758939/0/en/Gritstone-Oncology-Announces-First-Patient-Dosed-in-a-Clinical-Study-Evaluating-its-Personalized-Immunotherapy-GRANITE-001.html.
84. Gritstone Oncology Inc. Gritstone oncology announces first patient dosed with SLATE, its 'off-the-shelf' neoantigen immunotherapy. Available from: https://www.globenewswire.com/news-release/2019/08/14/1901707/0/en/Gritstone-Oncology-Announces-First-Patient-Dosed-with-SLATE-its-Off-The-Shelf-Neoantigen-Immunotherapy.html.
85. Flechtner JB. Antigen-screening system - perfecting the promise of T cell therapies for infectious disease & cancer. Available from: https://drug-dev.com/antigen-screening-system-perfecting-the-promise-of-t-cell-therapies-for-infectious-disease-cancer/.
86. Cohen RB, Johnson ML, Twardowski P, Stein MN, Vaishampayan UN, Dobson JR, et al. A phase 1/2a study of GEN-009, a neoantigen vaccine based on

autologous peptide immune responses. J Clin Oncol 37:15s, 2019(suppl; abstr 2611).
87. Cohen RB, Twardowski P, Johnson ML, Gillison ML, Stein MN, Vaishampayan UN, et al. GEN-009, a neoantigen vaccine containing ATLAS selected neoantigens, to generate broad sustained immunity against immunogenic tumor mutations and avoid inhibitory peptides. J Clin Oncol 2020;38:3107.
88. Neon Therapeutics. Available from: https://neontherapeutics.com/.
89. BioNTech. Available from: https://biontech.de/science/individualized-cancer-medicine.
90. Loquai C, Hassel JC, Oehm P, Derhovanessian E, Jabulowsky RA, Gold M, et al. A shared tumor-antigen RNA-lipoplex vaccine with/without anti-PD1 in patients with checkpoint-inhibition experienced melanoma. J Clin Oncol 2020;38:3136.
91. Braiteh F, LoRusso P, Balmanoukian A, Klempner S, Camidge DR, Hellmann M, et al. A phase Ia study to evaluate RO7198457, an individualized Neoantigen Specific immunoTherapy (iNeST), in patients with locally advanced or metastatic solid tumors. [abstract]. In: Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27–28 and Jun 22–24. Philadelphia (PA): AACR; 2020. Abstract nr CT169.
92. Lopez JS, Camidge R, Iafolla M, Rottey S, Schuler M, Hellmann M, et al. A phase Ib study to evaluate RO7198457, an individualized Neoantigen Specific immunoTherapy (iNeST), in combination with atezolizumab in patients with locally advanced or metastatic solid tumors. [abstract]. In: Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27–28 and Jun 22–24. Philadelphia (PA): AACR; 2020. Abstract nr CT301.
93. Moderna. Available from: https://www.modernatx.com/pipeline/therapeutic-areas/immuno-oncology.
94. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124–8.
95. La Jolla Institute for Immunology. La Jolla Institute receives $4.5 mill cancer moonshot award. Available from: https://www.lji.org/news-events/news/post/la-jolla-institute-receives-4-5-mill-cancer-moonshot-award/.
96. Hilf N, Kuttruff-Coqui S, Frenzel K, Bukur V, Stevanovic S, Gouttefangeas C, et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. Nature 2019;565:240–5.
97. Lee EY, Kulkarni RP. Circulating biomarkers predictive of tumor response to cancer immunotherapy. Expert Rev Mol Diagn 2019;19:895–904.
98. Higano CS, Schellhammer PF, Small EJ, Burch PA, Nemunaitis J, Yuh L, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer 2009;115:3670–9.
99. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.
100. Iversen TZ, Engell-Noerregaard L, Ellebaek E, Andersen R, Larsen SK, Bjoern J, et al. Long-lasting disease stabilization in the absence of toxicity in metastatic lung cancer patients vaccinated with an epitope derived from indoleamine 2,3 dioxygenase. Clin Cancer Res 2014;20:221–32.
101. Bjoern J, Iversen TZ, Nitschke NJ, Andersen MH, Svane IM. Safety, immune and clinical responses in metastatic melanoma patients vaccinated with a long peptide derived from indoleamine 2,3-dioxygenase in combination with ipilimumab. Cytotherapy 2016;18:1043–55.
102. Spicer J, Provencio M, Garrido Lopez P, Bosch-Barrera J, de Castro Carpeño FJ, Felip E, et al. An open-label, randomized, phase I/II trial of IO102 and pembrolizumab, or IO102, pembrolizumab and chemotherapy, as first-line treatment for patients with metastatic non-small cell lung cancer. Ann Oncol 2019;30:ii38–ii68.
103. Kjeldsen JW, Andersen MH, Svane I-M. 94TiP: combination therapy with nivolumab and PD-L1/IDO peptide vaccine to patients with metastatic melanoma. A clinical trial in progress. Ann Oncol 2017;28:mdx711.075.
104. Martinenaite E, Mortensen REJ, Hansen M, Orebo Holmstrom M, Munir Ahmad S, Gronne Dahlager Jorgensen N, et al. Frequent adaptive immune responses against arginase-1. Oncoimmunology 2018;7:e1404215.
105. Holmstrom MO, Martinenaite E, Ahmad SM, Met O, Friese C, Kjaer L, et al. The calreticulin (CALR) exon 9 mutations are promising targets for cancer immune therapy. Leukemia 2018;32:429–37.

Published OnlineFirst October 29, 2020; DOI: 10.1158/1078-0432.CCR-20-0245

Clinical Cancer Research

The Changing Landscape of Therapeutic Cancer Vaccines—Novel Platforms and Neoantigen Identification

Jessica Jou, Kevin J. Harrington, Mai-Britt Zocca, et al.

Clin Cancer Res 2021;27:689-703. Published OnlineFirst October 29, 2020.