New emerging targets in cancer immunotherapy: the role of neoantigens

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ABSTRACT

The success of cancer therapies with immune checkpoint inhibitors is transforming the treatment of patients with cancer and fostering cancer research. Therapies that target immune checkpoint inhibitors have shown unprecedented rates of durable long-lasting responses in patients with various cancer types, but only in a fraction of patients. Thus, novel approaches are needed to make immunotherapy more precise and also less toxic. The advances of next-generation sequencing technologies have allowed fast detection of somatic mutations in genes present in the exome of an individual tumour. Targeting neoantigens, the mutated peptides expressed only by tumour cells, may enable antitumour T-cell responses and tumour destruction without causing harm to healthy tissues. Currently, neoantigens can be identified in tumour clinical samples by using genomic-based computational tools. The two main treatment modalities targeting neoantigens that have been investigated in clinical trials are personalised vaccines and tumour infiltrating lymphocytes-based adoptive T-cell therapy. In this mini review, we discuss the promises and challenges for using neoantigens as emergent targets to personalise and guide cancer immunotherapy in a broader set of cancers.

INTRODUCTION

Cancer immunotherapies prompting the immune system to attack tumours have mediated durable clinical responses in patients with metastatic melanoma, lung cancer, bladder cancer and other tumour types.12 The common goal of immunotherapies is to invigorate the immune system to destroy cancer cells. The activation of T-cell killing activity is a balance between positive signals provided by the specific recognition of tumour antigens, activating receptors and negative signals provided by immune checkpoint receptors.3 Therefore, the therapeutic manipulation of this balance can be achieved inhibiting negative signals using immune checkpoint inhibitors (ie, antiprogrammed cell death protein 1 (PD-1), antiprogrammed death-ligand 1 (PD-L1) or anticytotoxic T-lymphocyte antigen 4 antibodies) intended to restore T-cell function in a immunosuppressed tumour environment.45 The actions of immune checkpoint inhibitors rely on the presence of tumour infiltrating lymphocytes (TILs) on the tumour.6,7 Previous data suggest that melanoma regression after therapeutic PD-1 inhibition requires pre-existing CD8+ T cells that are negatively regulated by the interaction between PD-1 and PD-L1.6 More recently, PD-1-expressing neoantigen-specific T-cells have been identified in the peripheral blood of patients with melanoma and gastrointestinal cancers, correlating with the recently documented activity of PD-1 inhibitors in these populations.8,9 Evidence suggests that clinical responses in patients with cancer after the administration of immune checkpoint inhibitors may also be mediated by neoepitope-reactive T-cells.10–12

Tumours with high TILs (‘hot tumours’) have, in general, better responses to checkpoint inhibitors than those lacking or having sparse TILs (‘cold tumours’).3 Additionally, TILs can be isolated from tumour biopsies, expanded and activated in vitro, and reinfused to the same individual, showing antitumour activity in vivo.1 However, the inhibition of immune checkpoint is not antigen-specific and may modify the global T-cell response causing immunological side effects.13 In addition, and apart from a few exceptions (eg, microsatellite instability high cancers),14 approximately one-third of patients will derive benefit from checkpoint inhibitors, while many patients will experience disease progression. More precise and specific therapeutic approaches to direct T-cell responses against the tumour are needed. Here, we review an emerging tool for cancer immunotherapy, the so-called neoantigens and discuss their role as targets for cancer vaccines and adoptive T-cell therapies.

Neoantigens as targets for personalised immunotherapies

Neoantigens represent a class of tumour antigens generated by non-synonymous somatic mutations that can be identified by T-cells as non-self-proteins. Single-nucleotide variants (SNV), mutational frameshifts, splice variants
or gene fusions can result in new peptide sequences (neoepitopes), which are strictly tumour specific and absent in healthy tissues.15–18

T-cells recognise neoantigens after they are processed into small peptides and presented by the major histocompatibility complex molecules (MHC or human leucocytes antigens, HLA, in humans) on the surface of the cells.19 It has been shown that 1%–2% of tumour mutations result in neoantigens that bind to HLA and is recognised by T-cell repertoire.1 While CD8+ T-cells recognise peptides in the context of MHC-I molecules, which are expressed by all nucleated cells, CD4+ T-cells recognise peptides presented by MHC-II molecules, which are only produced by a reduced number of immune cell subsets (mainly dendritic cells (DCs), but also B-cells and macrophages) called professional antigen presenting cells (APCs).20

Advances and widespread use of next-generation sequencing (NGS) has facilitated the rapid identification of non-synonymous somatic mutations in clinical specimens. Computational analyses of DNA sequencing (either whole exome or whole genome sequencing) and RNA sequencing detect expressed gene mutations.21 NGS data can also be used for genotyping HLA alleles of each patient.21 A number of computational pipelines for neoantigen prediction are available22 23 and they are usually based on MHC class I and II processing and presentation. Most pipelines provide peptide-HLA binding affinity predictions, and have also incorporated features like variant allele fraction, gene expression and clonality of mutations. However, there is no standard universal workflow for neoantigen prediction yet.

The critical importance of neoantigens relies on their capability of being targets for antitumour-specific T-cell responses because they selectively target tumour relative to healthy tissues. Furthermore, the potential for expanding T-cell clones is intact for neoantigens, since they are completely new for the immune system, while this possibility is lower for unmutated tumour targets, such as tumour-associated antigens and cancer testis antigens, whose T-cell clones may be absent due to the mechanisms of central or peripheral tolerance. This raises the possibility that vaccines targeting specific individual mutated immunogenic epitopes may be more effective.

Robust work demonstrated that T-cells target neoantigens in patients that respond to immune checkpoint inhibition, adoptive T-cell therapies and therapeutic vaccines.10 11 24–30 In general, cancers with high mutational burden and high number of predicted neoantigens exhibited better objective responses to checkpoint inhibitors.10 12 14 Neoantigens can also be potentially predicted in cancers with low tumour mutation burden. In fact, non-SNV mutations (ie, frameshifts, fusions) can be sources of potent immunogenic neoantigens.16–18

To make immunotherapy more precise, two main treatment modalities targeting neoantigens have been investigated in clinical trials: (1) personalised vaccines27 28 30–32 and, (2) TILs-based adoptive T-cell therapies24–26 31–35 (figure 1). Both approaches have demonstrated early promise in patients with advanced solid tumours, opening the gateway to new personalised immunotherapies against cancer.

**Personalised cancer vaccines**

Therapeutic vaccines targeting tumour-specific neoantigens are intended not only to enhance pre-existing memory or effector T-cell responses, but also to expand new antitumour naive T-cell clones against otherwise poorly immunogenic mutations, broadening T-cell responses and contributing to tumour destruction.36 37 Because each patient shows a particular HLA type composition and a unique tumour genomic make-up, its specific neoantigen set can be identified, selected and then presented to the immune system as a personalised vaccine preparation.38

The genome-based identification of immunogenic neoantigens via NGS and further computation analyses, coupled with mass spectrometry or T-cell reactivity assays are relevant and need to be robust to maximise the immunogenicity of neoantigens loaded into the vaccine. However, for the design of cancer vaccines, several aspects beyond tumour-specific neoantigens have to be taken under consideration. Among them, formulation, immune adjuvants and the delivery system are specially relevant because they may strongly impact on the immunogenicity and vaccination outcome.38

Neoantigen vaccines can be formulated as DNA or RNA coding for neoantigens, as synthetic peptides, as virus-based systems and also as cellular preparations of DC-loaded with neoantigens or tumour cell lysates.36 However, more sophisticated presentation strategies are under development, including DC targeted recombinant immunogens,39 viral vectors or polymeric multivalent neoantigen preparations.40

Following on from encouraging neoantigen vaccine studies in mouse models,41–44 the first-in-human clinical trials testing vaccines in melanoma and glioblastoma patients have shown safety and feasibility.27–32 In a pivotal study, in vitro generated DCs loaded with neoepitopes improved pre-existing anti-tumour T-cell responses and induced responses to neoepitopes that were undetectable prior to vaccination in metastatic melanoma patients.31

In a phase 1 study, six patients with high-risk melanoma received long peptide neoantigen vaccines, two of them (stage IV) achieved complete responses after receiving subsequent PD-1 inhibitor and the other four (high-risk stage IIIIB-C) showed no recurrence at follow-up.28 In another phase 1 study, 13 patients with high-risk or advanced melanoma received RNA vaccines encoding neoantigens derived from expressed mutations.27 Two of the five patients with advanced disease experienced vaccine-related objective responses; one patient developed a complete response to vaccination in combination with PD-1 inhibitor.

In these first published studies, vaccines induced both CD8+ and CD4+ T-cell responses, probably due to the use of long peptides that may also bind to MHC-II.27 28 36 45
fact could be relevant as effective antitumour responses seem to require both CD8 and CD4 tumour-specific T-cells, even in tumours that do not express class-II MHC molecules. However, the prediction of specific neoantigen to MHC-II is not yet standardised.

These clinical trials showed the feasibility and safety of single agent personal vaccination. The adverse events were, in general, mild including injection site reactions, flu-like symptoms, rash and fatigue. The response assessment used diverse criteria. Either standard RECIST 1.1 criteria or immune-related response criteria guidelines. In the response assessment of gliomas, the Response Assessment in Neuro-oncology (RANO) criteria and the Immunotherapy Response Assessment in Neuro-Oncology criteria were applied. These studies evidenced that clinical responses with single agent vaccine were observed in a minority of cases, and highlighted the potential to combine vaccine with checkpoint inhibitors. How these results will be translated into clinical benefit of cancer patients remains to be demonstrated by future clinical trials.

Personalised neoantigen vaccines in combination with immune checkpoint inhibitors or other therapies are being tested in clinical trials for a variety of solid tumours (table 1). An alternative to personalised vaccines is based on the observation that some cancer types share tumour somatic mutations among affected individuals. Although a significant minority of patients with certain common cancers may have HLA class I shared neoantigens (eg, \textit{KRAS} mutation in up to 15% of colon and lung cancers), those common neoantigen specificities can be exploited to define ‘off-the-shelf’ vaccines across cancer types. For example, current clinical trials are investigating off-the-shelf neoantigen vaccines for patients with metastatic colorectal cancer with microsatellite instability-high status (NCT04041310), or neoantigens derived from \textit{KRAS} mutation among non-small-cell lung cancer, pancreatic ductal adenocarcinoma and microsatellite-stable
### Table 1 Selected clinical trials targeting neoantigens as targets for personalised or off-the-shelf vaccines

| Strategy | ClinicalTrials.gov identifier | Tumour type | Setting | Phase | Treatment | Target accrual |
|----------|------------------------------|-------------|---------|-------|-----------|---------------|
| Personalised neoantigen vaccine | NCT03558945 | Pancreatic tumour | Advanced | Phase 1 | Personalised neoantigen vaccine | 60 |
| | NCT04087252 | Solid tumour | Advanced | Phase 1 | Personalised neoantigen vaccine | 30 |
| | NCT03715985 | Melanoma, lung cancer, kidney cancer | Advanced | Phase 1 | EVAX-01-CAF09b | 25 |
| Personalised neoantigen vaccine with checkpoint inhibitors | NCT03609967 | Breast cancer (oestrogen receptor negative, HER2/Neu negative, triple-negative) | Advanced | Phase 2 | Carboplatin, durvalumab gemcitabine, nab-paclitaxel, personalised synthetic long peptide vaccine, poly ICLC | 70 |
| | NCT02950766 | Kidney cancer | Advanced | Phase 1 | NeoVax, Ipilimumab | 15 |
| | NCT03359239 | Urothelial, bladder cancer | Advanced | Phase 1 | Atezolizumab, PGV001, Poly ICLC | 15 |
| | NCT02287428 | Glioblastoma | Advanced | Phase 1 | Radiation Therapy, personalised neoantigen vaccine, pembrolizumab | 46 |
| | NCT03289962 | Melanoma, lung cancer, bladder cancer, colorectal cancer, triple negative breast cancer, renal cancer, head and neck cancer, other solid cancers | Advanced | Phase 1 | RO7198457/mRNA+atezolizumab | 770 |
| | NCT03532217 | Prostate cancer | Advanced | Phase 1 | PROSTVAC-V, PROSTVAC-F, Nivolumab, Ipilimumab, Neoantigen DNA vaccine | 20 |
| | NCT03639714 | Lung cancer, microsatellite stable colorectal cancer, gastro-oesophageal adenocarcinoma, urothelial carcinoma | Advanced | Phase 1/2 | GRT-C901/GRT-R902 +nivolumab/ipilimumab | 241 |
| | NCT02897765 | Melanoma, lung cancer, bladder cancer | Advanced | Phase 1b | NEO-PV-01+nivolumab | 55 |
| Off-the-shelf neoantigen vaccine | NCT03391232 | Colorectal cancer | Advanced | Phase 1/2 | PolyPEPI1018 colorectal cancer vaccine | 15 |
| Off-the-shelf neoantigen vaccine with checkpoint inhibitors | NCT03953235 | Lung cancer, colorectal cancer, pancreatic cancer, and other mutation-positive tumours | Advanced | Phase 1/2 | A fixed set of neoantigens that are shared across a subset of cancer patients+nivolumab | 144 |
| | NCT04041310 | Mismatch repair deficient or microsatellite instability high colorectal cancer, gastric, gastro-oesophageal junction and endometrial tumours | Advanced | Phase 1 | Nous-209 (FrameShift Peptides neoantigen-encoding genetic vaccines)+pembrolizumab | 34 |
| | NCT03893903 | Glioma | Advanced | Phase 1 | 3 arms: IDH1R132H peptide vaccine, IDH1R132H peptide vaccine and avelumab, avelumab alone. | 60 |

IDH, isocitrate dehydrogenase; Poly ICLC, Polynosinic-Polyribidylic acid stabilized with polylysine and carboxymethylcellulose.
colorectal cancer in combination with an anti-PD-1 therapy (NCT03953235).

**TILs-based adoptive T-cell therapies**

The enhancement of T-cell responses can be also achieved by expanding or generating tumour reactive T-cells ex vivo and using them as cellular therapeutic products that, once infused into cancer patients, can kill tumour cells.\(^{24-26,33,34}\)

TIL-based adoptive cell transfer has shown the most encouraging clinical activity to date. Most strategies use bulk, randomly isolated TILs from the tumour tissue for ex-vivo expansion and infusion.\(^{49,50}\) However, targeting unique, tumour-specific neoantigens have been pursued as an attractive cell therapy strategy. Current methodology employed to identify and expand neoantigen-reactive TILs involve NGS of tumour derived DNA and RNA, tumour culture in high-dose interleukin-2 (IL-2) to expand antitumour TILs in the presence of neoantigens and APCs.\(^1\) The T-cells are then analysed for upregulation of activation markers to identify neoantigen-reactive T-cells. The resulting cell preparation can be then infused as a cellular therapeutic product (figure 1).

Adoptive transfer of autologous TILs that specifically target proteins encoded by somatic mutations have mediated objective clinical regressions in patients with metastatic melanoma,\(^{34,35}\) bile duct,\(^{26}\) colon\(^{24}\) and breast cancers\(^{25}\) demonstrating that treatment enhances T-cell recognition of tumour-specific neoantigens.

A patient with metastatic cholangiocarcinoma was treated with ERBB2IP mutation-reactive T-cells isolated from TILs (containing 25% of mutation-specific T-cells),\(^{26}\) resulting in reduction in size of target lesions of 30% at 7 months post-treatment with prolonged stabilisation of the disease. After disease progression, patient was retreated with a >95% pure population of mutation-reactive CD4 + T cells, showing again a reduction in size of target lesions in lung and liver. These results provide evidence that a CD4 + T cell response against a mutated antigen can be

| **Table 2** Selected clinical trials for using TIL-based adoptive T-cell therapy |
|---|---|---|---|---|---|
| **Strategy** | **ClinicalTrials.gov identifier** | **Tumour type** | **Setting** | **Phase** | **Treatment** | **Target accrual** |
| TIL-based adoptive T-cell therapy | NCT04072263 | Ovarian cancer | Advanced | Phase 1, Phase 2 | TILs, interferon alfa 2A, carboplatin, paclitaxel | 12 |
| | NCT03992326 | Solid tumour | Advanced | Phase 1 | TILs, cyclophosphamide, fludarabine, IL-2, radiotherapy | 60 |
| | NCT03412526 | Ovarian cancer | Advanced | Phase 2 | Fludarabine, radiation, TIL administration, IL-2 | 15 |
| TIL-based adoptive T-cell therapy with checkpoint inhibitors | NCT03296137 | Cancer | Advanced | Phase 1/2 | Autologous TILs, ipilimumab, nivolumab, IL-2, cyclophosphamide, fludarabine | 25 |
| | NCT03158935 | Ovarian cancer, melanoma | Advanced | Phase 1 | Cyclophosphamide, fludarabine, pembrolizumab, TILs, IL-2 | 24 |
| | NCT02652455 | Melanoma | Advanced | Early Phase 1 | Nivolumab, surgery to remove tumour for growth of TIL, CD137 cyclophosphamide, fludarabine, TIL Infusion, IL-2 | 11 |
| | NCT03935347 | Urothelial | Advanced | Phase 2 | Cyclophosphamide, fludarabine, pembrolizumab, autologous TILs, LN-145, IL-2 | 12 |
| | NCT02621021 | Melanoma | Advanced | Phase 2 | Cyclophosphamide, fludarabine, IL-2, pembrolizumab, young TIL | 170 |
| | NCT03645928 | Melanoma, head and neck, lung cancer | Advanced | Phase 2 | Lifileucel, LN-145, pembrolizumab | 48 |
| Clonal neoantigen adoptive T-cell therapy | NCT04032847 | Lung cancer | Advanced | Phase I/IIa | ATL001, autologous clonal neoantigen T cells | 50 |
| | NCT03997474 | Melanoma | Advanced | Phase I/IIa | ATL001, autologous clonal neoantigen T-cells | 20 |

IL-2, interleukin-2; TILs, tumour infiltrating lymphocytes.
employed to mediate regression of a metastatic epithelial cancer.

A metastatic colorectal cancer patient that showed the KRAS mutation G12D and the HLA-C*08:02 was treated with mutant KRAS-specific CD8+ T-cells. After T-cell infusion, an objective regression of all lung metastases of the patient was observed. After a 9-month period of partial response, one lung metastasis showed clinical progression associated with the loss of the HLA-C*08:02 locus in the chromosome 6. The loss of expression of this molecule provided a direct mechanism of tumour immune evasion and T-cell-mediated selection pressure.

A third case report revealed a chemorefractory hormonal receptor-positive metastatic breast cancer patient who was treated with TILs reactive against mutant versions of four proteins—SLC3A2, KIAA0368, CADPS2 and CTSB. Following an infusion of TILs with high levels of neoantigen-specific T-cell reactivity in conjunction with interleukin-2 and PD-1 inhibitor, a complete durable regression of the metastatic breast cancer was observed. The patient’s complete tumour regression did not seem to respond to a short course of single-agent pembrolizumab.

In general, the most common toxicities during TIL therapy are due to the effects of the lymphodepleting preparative regimens and the subsequent IL-2 after TIL infusion. TIL-related toxicity is less common, but patients may develop, mostly transient, dyspnoea, chills and fever shortly after infusion of TIL. Autoimmune-like toxicity such as uveitis, hearing loss and vitiligo after TIL therapy can also occur.

Alternatively, targeting neoantigens derived from clonal mutations (ie, present in all cancer cells) are expected to effectively enhance the ability of the immune system to attack all of the tumour cells in the body. Previous data showed that clonal neoantigens elicit T-cell immunoreactivity and sensitivity to immune checkpoint inhibition. This strategy is being explored in clinical trials. Clonal neoantigens are identified, TILs are ex vivo primed to recognise them and patients receive their own expanded clonal neoantigen-reactive T-cell product.

Several clinical trials are ongoing to explore adoptive cellular therapy as monotherapy or in combination with checkpoint inhibitors (table 2).

CONCLUSIONS
Vaccines and TILs-based adoptive T-cell therapies hold promise to make individually tailored medicines to a wide range of patients while targeting individual neoepitopes. They have shown to be safe, feasible and capable of eliciting strong T-cell responses. However, it should be noted that T-cell recognition may not be necessarily translated into long-term clinical objective responses.

The use of a personal neoantigen vaccine is anticipated to help address two major challenges for effective cancer immunotherapy. First, addressing tumour heterogeneity and clonal evolution when analysing clinical specimens. A single resected metastasis might not reflect the most up to date landscape of tumour neoantigens. Targeting highly heterogeneous tumours might likely need to target a diversity of malignant clones per patient, as well as minimising the chance of tumour escape by loss of antigen. Second, these therapies are selectively targeting tumours relative to healthy tissues, potentially reducing side effects.

The selection of ideal antigens is still deficient and lacks validation. Such a validation will need the definition of the role of elicited immune responses in clinical efficacy. However, classical technologies to quantify T-cell responses (ELISPOT, tetramer) require large amount of blood, thus limiting their use in large clinical trials. Therefore, high-throughput and unbiased computational strategies for prediction and new single cell sequencing techniques for in vivo measurements will be required to definitively validate, understand and improve neoantigen-based immunotherapies.

Expansion of T-cell responses (either by vaccination or cellular therapy) and checkpoint inhibition represent synergic strategies to drive immune control of tumours, and therefore, it is plausible that their combination may enhance efficacy. It is currently unknown whether neoantigen-based immunotherapy should be given before, after or concurrently with checkpoint inhibitors.

The combination of vaccination with adoptive T-cell therapy might cause a sustained immune response that could be coupled to enhance the efficacy of transferred T-cells, and if feasible, should be tested in clinical trials.

The field is expected to advance in the next few years in terms of better detection of immunogenic neoantigens, standardisation of techniques and delivery platforms, in addition to have trained staff personal in centres with high expertise.

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