Editorial Commentary

Neoantigen personalized vaccine plus anti-PD-1 antibody in cancer patients

María González-Cao[1], Rafael Rosell[2]

[1]Translational Cancer Research Unit, Instituto Oncológico Dr Rosell, Quirón Dexeus University Hospital, Barcelona, Spain; [2]Germans Trias i Pujol Research Institute and Hospital (IGTP), Badalona, Spain

Correspondence to: Rafael Rosell. Germans Trias i Pujol Research Institute and Hospital (IGTP), Badalona, Spain. Email: rrosell@icononcologia.net; María González-Cao. Translational Cancer Research Unit, Instituto Oncológico Dr Rosell, Quirón Dexeus University Hospital, Barcelona, Spain. Email: mgocao@gmail.com.

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In recent years, the novel immunotherapy treatments based on the use of checkpoint inhibitors that block anti anti-programmed cell death protein 1 (PD-1) or its ligand PD-L1 have produced unprecedented results in different advanced solid tumors, and now they are the standard of care for more than 15 distinct types of malignancies (1). Treatment with anti PD-1/PD-L1 antibodies, alone or in combination with other drugs, obtains long term responses that are maintained for years in some patients who previously did not have any effective treatment options. Long-term survival is now achieved in 15% to 50% of patients, depending on different tumor histologies (1). However, most patients still do not benefit from these treatments, and their survival rarely exceeds 12 months from diagnosis. Therefore, new strategies are necessary to improve the prognosis for these cases. One of the main ways is based on the development of treatments that can stimulate the specific immune response against tumor antigens. Tumors present new antigens "neoantigens", since they have somatic mutations that can encode proteins recognizable by the immune system (2). Vaccination with peptides or messenger RNA (mRNA) encoding these neoantigens is a promising strategy.

The study from Ott *et al.* published last year in *Cell* (3) demonstrated the safety of treating advanced cancer patients with the long-peptide neoantigen vaccine NEO-PV-01 in combination with the anti PD-1 antibody nivolumab. The primary end point of this phase 1b study was achieved, demonstrating the safety of the combination with no treatment related serious adverse events. The striking finding of the study and, probably, the most relevant, was the demonstration of the induction of *de novo* neoantigen specific cytotoxic T cell responses in the vaccinated patients (3). Why this immune response is achieved with the subcutaneous administration of peptides identified as neoantigens and is not produced spontaneously by the immune system against the tumor cells present in the body, is unknown, although several general mechanisms defined by more basic immunology, such as Toll-like receptor (TLR) co-stimulation, role of adjuvants, and the involvement of dendritic cell presentation can provide reasonable explanations that could and should be tested.

The NEO-PV-01 vaccine consists of up to 20 peptides, about 20 amino acids in length, with the coadministration of adjuvant poly-L-lysine and carboxymethylcellulose (poly-ICLC). The peptides were designed after whole exome sequencing and RNA sequencing of tumor samples from each individual patient. The most immunogenic neoepitopes encoded by tumor mutations were selected according to bioinformatics algorithms that predict their binding to HLA-A and HLA-B (3).

Nevertheless, some technical issues for personalized cancer vaccination remain challenging. The techniques used for neoantigen identification and for evaluating their immunogenicity are critical for a precise selection of candidate peptides. Analysis through whole exome

sequencing of tumor DNA for identification of non-synonymous mutations and in silico prediction of their capacity for binding to HLA-I is currently employed for novel cancer vaccine development, such as in this long-peptide vaccine, and more recently, also for mRNA vaccines. The techniques for prediction of HLA binding are imperfect and probably the "best" neoantigens are still not selected for every case. Nevertheless, in the current study the proportion of $CD8^+$ T cell specific response (24%), and especially the $CD4^+$ T cell response (42%), was very high. It is remarkable that, even though neoantigen identification used HLA-I binding algorithms rather than HLA-II, a high rate of specific $CD4^+$ T cells was also observed (3). Identification of neoantigen epitopes presented by major histocompatibility complex II (MHC II) molecules requires additional software-based estimations of peptide-MHC II binding affinity, and it is expected that including such technologic in vaccine development, will improve their anti-cancer activity in the near future. Other techniques for neoantigen identification, such as mass spectrometry based immunopeptidomics (4), which relies on the study of tumor HLA immunopeptidome, and especially techniques using tandem mini genes, identified not only HLA-I candidate peptides, but also HLA-II binding peptides, generating also the essential B cell activation for cancer immune response (5).

Although specific T-cell response was durable in this study, later to be confirmed by the same group in melanoma patients treated after surgical removal of the disease (6), the clinical responses observed in this Phase 1b trial are lower and not clearly due to the vaccination. The authors previously demonstrated specific immune responses and good safety profile of this vaccine as a single agent in melanoma (7) and glioblastoma (8) patients, but with very limited clinical activity. Data about clinical activity in the current study must be interpreted with caution, since it is a phase 1b trial and it is not the primary objective of the study. It is not possible to rule out that clinical responses were due exclusively to the activity of the anti PD-1 antibody, as vaccination was combined with nivolumab that has antitumoral activity as single agent in different tumor types, including those treated in the present study (melanoma, non-small cell lung cancer from smokers, and bladder cancer) (9-11). Moreover, the design of the study could contribute to a selection bias, since vaccination was received after three months on treatment with nivolumab as a single agent, so only those patients surviving and maintaining a good performance status, and without severe toxicity, go ahead with the vaccination. Only 60 out of 82 patients included received the vaccine. If we consider the intention to treat population (ITT), including also those patients that progressed or died before vaccine administration, those with a low number of neoantigen, those with a low tumor cellularity that precluded vaccine elaboration, and those not vaccinated for other reasons, the tumor response rate observed is in the range of the response rate observed with nivolumab as a single agent in these cancers (response rate according to ITT in this study was 47%, 26% and 19%, in melanoma, non-small cell lung cancer, and blabber carcinoma, respectively) (3).

The clinical development of the NEO-PV-01 vaccine was on hold by the original company, Neon Therapeutics, to focus on neoantigen-based adoptive T-cell therapies. Finally, the company was bought by BioNTech, a pharmaceutical company dedicated to mRNA vaccine development for cancer and other diseases. mRNA personalized vaccines have simpler and faster synthesis and GMP quality control than those using long peptide vaccines. Moreover, with the success of the COVID-19 vaccine using mRNA technology, technical development and practical production issues have been partly solved. Nevertheless, preliminary data of antitumoral activity of these mRNA vaccines in the context of advanced cancer is somewhat below expectations, and further results of the ongoing larger studies are awaited with interest. Currently, results from phase I studies testing the personalized mRNA vaccine RO 198457 (also known as BNT122) have demonstrated objective response in 4% of patients treated in monotherapy (12), and in 8% of patients when it is used in combination with the anti PD-L1 antibody atezolizumab (13). However, both trials observed neoantigen specific T cell responses in the blood of treated patients, in 87% and 73%, respectively, so it is possible that a better clinical activity is obtained in the ongoing studies that are testing BNT 122 in combination with pembrolizumab in previously untreated melanoma patients (NCT03815058).

Other strategies include the development of mRNA vaccines and long peptide vaccines encoding commonly shared non-mutated tumor antigens present in most cancer patients. Surprisingly, although these are not personalized vaccines, preliminary clinical data have showed promising results. The BO111 vaccine (FixVac) targets four well known melanoma antigens (MAGE-A3, NY-ESO-1, tyrosinase and TPTE). After intravenous administration in melanoma patients as single agent or in combination with anti PD-1 antibody, FixVac produces a clinical response rate in 12% and 35% of patients, respectively, with a good safety

profile (14). Similarly, a long peptide vaccine targeting indoleamine-2,3-dioxygenase 1 (IDO)/PD-L1 (IO102/103) in combination with the anti PD-1 antibody nivolumab in a phase 1b/2 study in 30 naïve treatment advanced melanoma patients demonstrated 80% of clinical objective responses, including 43% of complete responses (15). Recently, data from a preclinical study compared in animal breast cancer models, the antitumoral effect of a personalized vaccine versus a vaccine based on the use of shared antigens showed similar antitumoral activity. These vaccines employed frameshift peptides created from errors in the production of RNA. These results suggest that a non-personalized vaccination using shared tumor antigens could be more convenient, faster and cheaper, allowing for a broader applicability (16).

Several novel cancer vaccines with different formulations have achieved robust specific T cell responses. Unfortunately, clinical objective responses are still limited, but with the improvement of technical issues, such as cancer neoantigen determination, delivery methods, and clinical design, high clinical efficacy may be achieved sooner rather than later, both for the treatment of established tumors, and as preventive vaccines for pre-malignant stages of disease, and even in high-risk healthy persons (17).

In summary, the study from Ott *et al.* confirms the feasibility of triggering a specific immune response using a personalized vaccine. A new era of cancer vaccines has just begun.

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