The intradermal delivery route, a promising method for breast cancer disease staging and breast cancer immunotherapy strategies.

Manon Randrianantoandro | José Tijsen | Danielle Pasmans | Koen CL Beyers | Vanessa Vankerckhoven
Antwerp, Belgium | May 2026

Introduction

Representing one of the most significant advances in oncology in recent years, cancer immunotherapy has demonstrated impressive anti-tumor activity and a durable clinical benefit in diverse malignancies (1). Its primary objective is to prevent tumor growth, recurrence, or metastasis, while enhancing the immune system's capacity to identify and eliminate cancer cells (2).
Cancer vaccines can be used to prevent cancer (**prophylactic vaccines**) and as a treatment option (**therapeutic vaccines**) for individuals already diagnosed with cancer (3).

Breast cancer burden

With an estimated 2.3 million new cases (11.6% of all cancer cases) female breast cancer is the second leading cause of global cancer incidence in 2022 and the fourth leading cause of cancer mortality worldwide (6.9% of all cancer deaths) (4).

Incidence		Mortality	
Rank	Cases	Rank	Deaths
2	2.296.840	4	666.103

Among women, breast cancer is the most diagnosed cancer and together with cervix cancer, it is causing almost half of all maternal cancer orphans. Therefore, the World Health Organization (WHO) launched the **Global Breast Cancer Initiative** and the **Cervical Cancer Elimination Initiative** (5,6).

Importantly, breast cancer often spreads to distant organs, such as the brain, lungs, liver, and bones through lymph nodes or blood vessels, resulting in metastasized—and often fatal—form of cancer (7).

Read more in our White Paper on SLN and Lymphoscintigraphy (8). As a result, the patient's "personal" treatment will be tailored to the molecular characteristics of the individual tumor, as well as to the size and spread of the cancer and the patient's menopausal status. Common treatment strategies include various combinations of surgery, chemotherapy, radiotherapy, hormone therapy, targeted therapy, and immunotherapy.

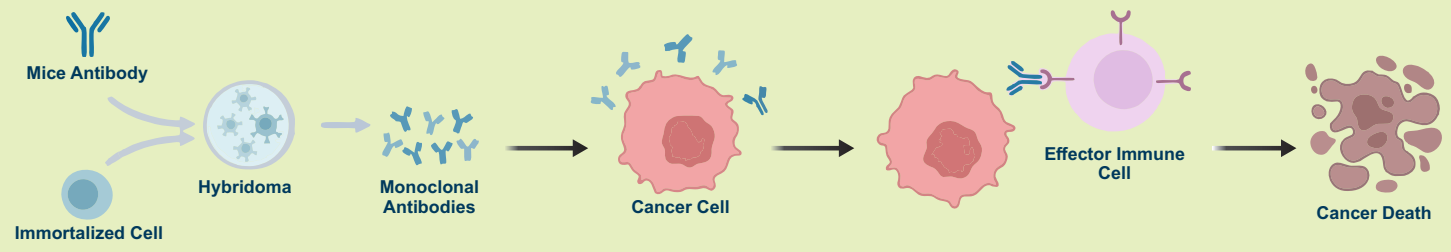
In 2024, a total of 13,733 clinical trials for breast cancer treatment were ongoing, of which 434 were utilizing immunotherapy as a treatment option (7). **Immunotherapy strategies** for cancer treatment are broadly categorized into passive and active approaches.

Passive immunotherapy involves administering pre-prepared immune components, such as monoclonal antibodies (mAbs) and immune cells, to provide immediate but temporary defense against cancer.

Active immunotherapy, in contrast, works by engaging the patient's own immune system to generate a sustained and long-lasting response. Examples of active immunotherapy include cancer vaccines adoptive cell transfer (ACT), immune-checkpoint inhibitors and cytokines (9).

There are several primary immunotherapy types for breast cancer:

Antibody-based treatment utilizes mAbs which upon recognition of specific proteins in cancer cells trigger an immune response. mAbs are used to treat Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer. Trastuzumab and Petuzumab are two first-line FDA-approved mAbs (7).

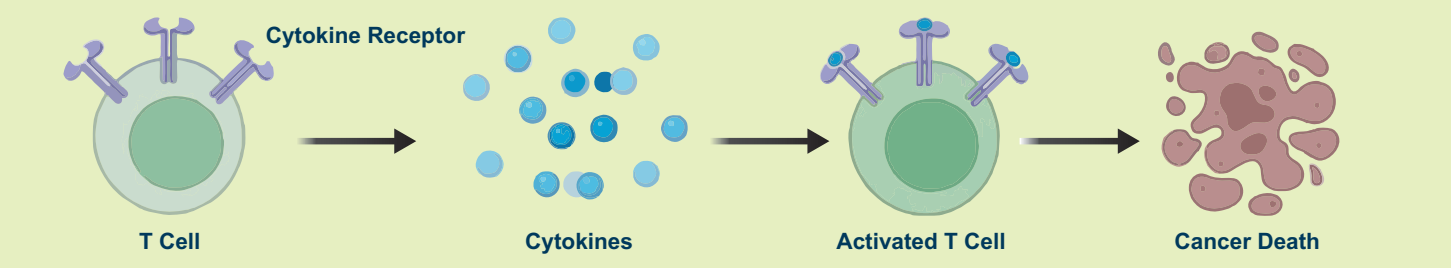


Adapted from (7)

Novel treatment strategies: cancer vaccines and immunotherapy

Precise disease staging, particularly the evaluation of lymph node involvement, plays a pivotal role in defining treatment strategies. The standard for assessing nodal metastasis is **Sentinel lymph node (SLN) mapping**, a method involving radioisotopes or fluorescent dyes.

Cytokines have an important role within the tumor microenvironment, where they coordinate immune and inflammatory responses. Most anticancer cytokines do not specifically target cancer cells but act on the broader tumor microenvironment. Due to their low direct cytotoxicity against cancer cells, most cytokines are used in combination with other treatments (10).



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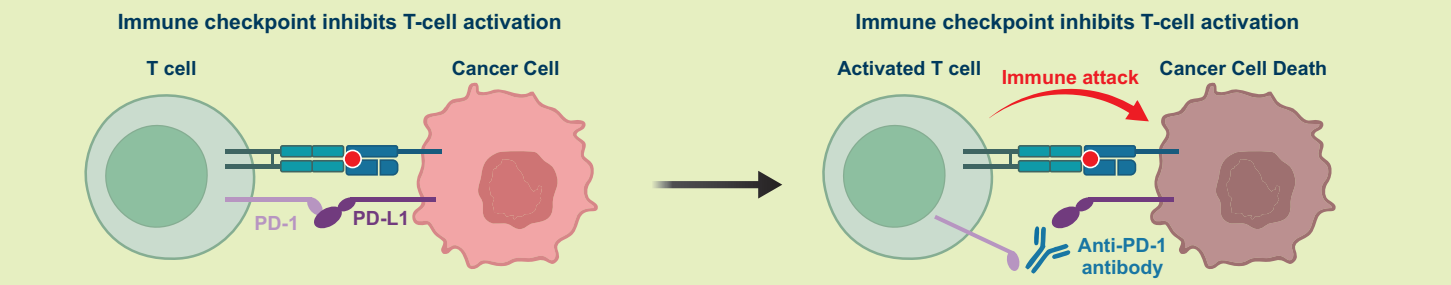
Immune checkpoint inhibitors are designed to block checkpoint proteins resulting in the activation of the T-cell response, subsequently killing the cancer cells (7). The recent approval of immune checkpoint inhibitors in triple-negative breast cancer offers new therapeutic possibilities in aggressive tumors and hard-to-treat populations (1).



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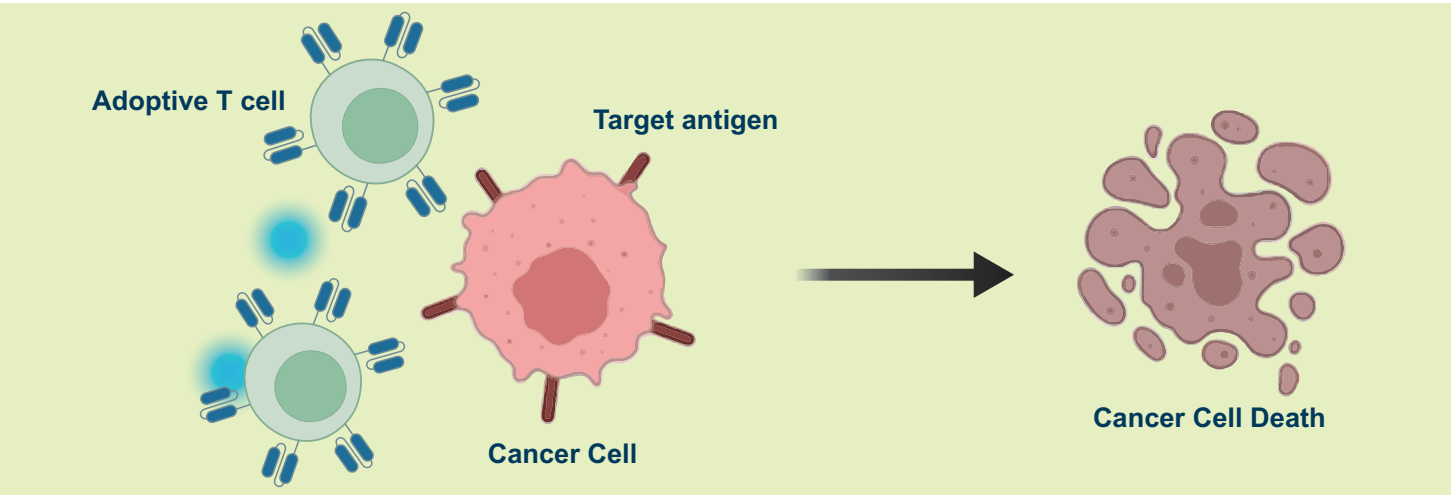
Adoptive cell therapies (ACTs) consist of identifying and isolating peripheral blood or tumor-resident T cells to modify, activate and expand these cells *ex vivo* before transferring them back into the patient (1). There are a variety of adoptive T-cell therapies, which include TIL-based therapy, chimeric antigen receptor (CAR) therapy, engineered T-cell receptor (TCR) therapy, dendritic cell-based (DC) therapy, and natural killer cell-based (NK) therapy (7).



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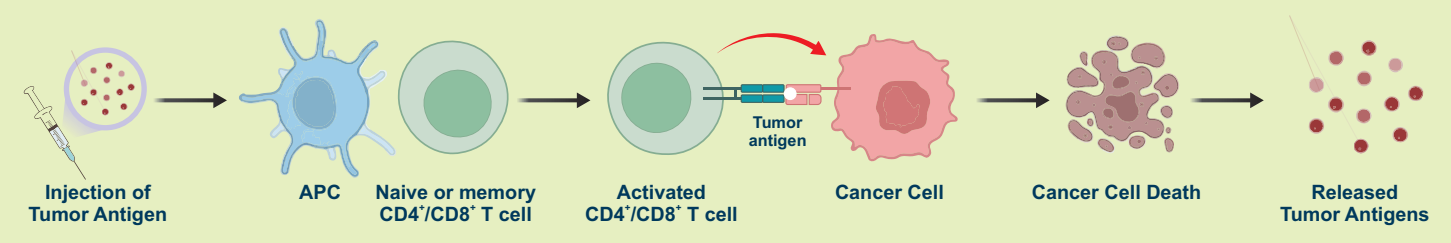
Anti-cancer vaccines intend to encourage an antigen specific T-cell-based activation of the immune system with the goal of eliminating cancer cells (7).



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There are **different types of breast cancer vaccines**, but they all need to make the targeted antigen recognizable by the autologous immune system to induce a therapeutic effect (11).

Peptide Vaccines

Peptides derived from tumor antigens are currently the most common vaccination approach for breast cancer. However, the results of different peptide vaccines indicates that vaccine formulation should be specific to the features of the tumor being targeted.

Protein-Based Vaccines

The protein-based vaccine is developed using the whole or a shortened fragment of tumor antigen protein. However, the presentation process may be less efficient, and the response to this kind of vaccine is difficult to measure due to the lack of a specific marker.

Carbohydrate Vaccines

Carbohydrate antigens abnormally expressed by tumor cells can also be recognized by immune cells. Hence, such carbohydrate antigens have become an ideal candidates for incorporation into a cancer vaccine.

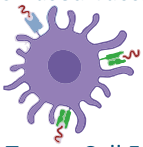
Tumor Cell Vaccines

Tumor cell vaccines are based on a pool of unknown antigens derived from autologous or allogeneic tumor cells. These vaccines contain endogenous cellular antigens that may cause an autoimmune reaction. Additionally, there is a lack of a standardized method for preparing tumor cell vaccines.

DNA-Based Vaccines

DNA genetic material is usually delivered in the forms of a plasmid or vector. The DNA sequence is then taken up by antigen presenting cells (APCs) and translated into the tumor antigen.
Unfortunately, due to the low efficiency of plasmid uptake and antigen expression, the immunogenicity is relatively weak.

DC-Based Vaccines



DC-based vaccines utilize *ex vivo*-generated DCs loaded with tumor antigens or transfected to express tumor antigens. The production of DC-based vaccines can be technically demanding due to the individualized *ex vivo* process for DC maturation.

DC-Tumor Cell Fusion Vaccines

Fusion of DCs with tumor cells aims to improve the DC-based vaccination strategy, but this kind of vaccine is even more difficult to produce than DC-based vaccines.

To enhance the immunogenicity of cancer vaccines, different types of **adjuvants** can be used: cytokines, microbes and microbial derivatives, mineral salts, oil emulsions or surfactants, articulates or viral vectors (11). Additionally, the administration routes of cancer vaccines help to effectively present the antigens to autologous APCs. Major administration routes of breast cancer vaccines include intradermal, subcutaneous, intramuscular, and intranodal injection (11).
Several peptide vaccines targeting HER2 have adopted **intradermal vaccination** strategies as there is a dense network of cutaneous DCs. Studies demonstrated that intradermal inoculation with low doses of the peptide was safe and stimulated antigen-specific T cell responses in most of the healthy population. Subcutaneous injection, used in a variety of breast cancer vaccines, also elicited immune responses, but the large volumes of antigen delivered subcutaneously with adjuvants may have contributed to severe injection site reactions (11).

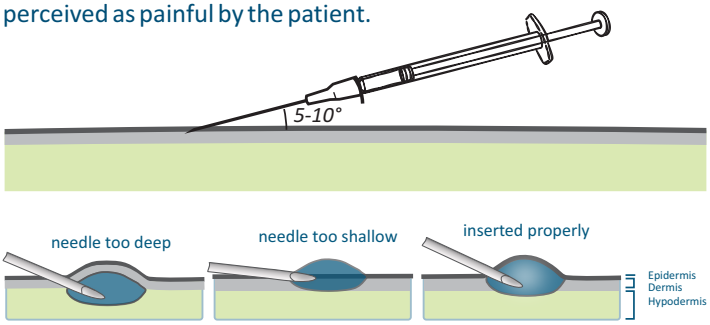
Although none of the different types of breast cancer vaccines that have been evaluated in clinical trials has led to significant benefits, the possibility of applying vaccines in combination with anti- HER2 monoclonal antibodies or immune checkpoint blockade looks promising (11).

More general, ongoing research and clinical trials continue to explore ways to enhance the efficacy and safety of both passive and active strategies, such as combining mAbs with checkpoint inhibitors or integrating cytokine therapy with other treatment modalities (9).

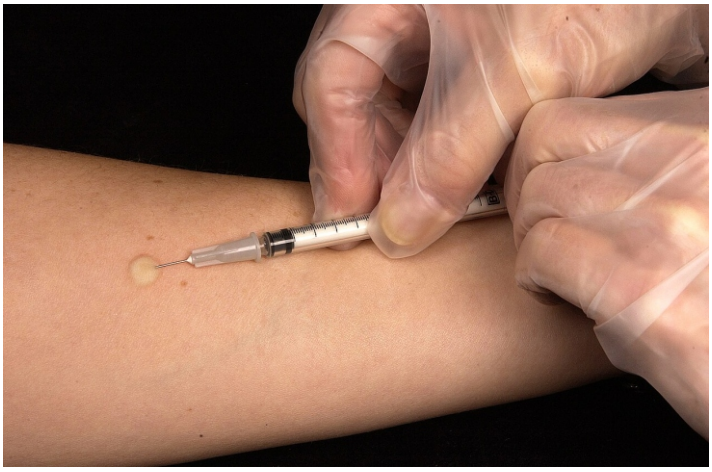
While immunotherapy has been shown to be a promising cancer treatment, there are also limitations that must be addressed. Before becoming a standardized therapy, these treatments still require further development (7).

VAX-ID® a promising approach for reliable intradermal cancer vaccine and immunotherapy delivery

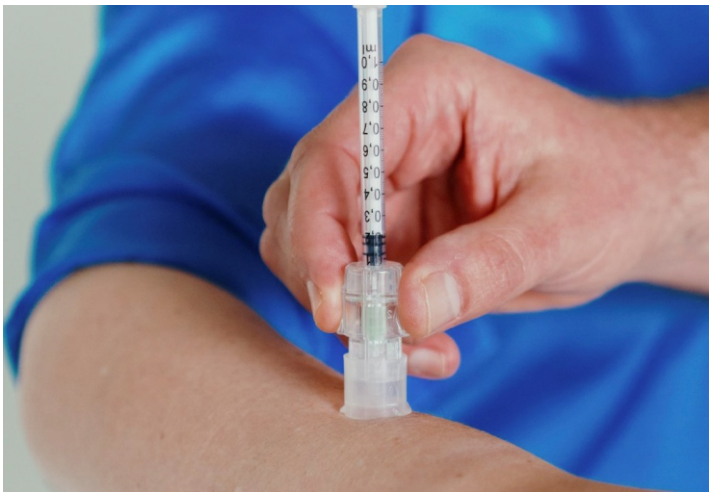
Intradermal injections are usually performed using the Mantoux technique, in which the needle is inserted at a shallow angle and requires special training to reliably target the skin (12). This technique is the current standard of care for intradermal injection, but it is difficult to perform and prone to failure. It has been shown that about 70% of intradermal injections using the Mantoux technique are incorrectly administered by injecting either too deep (into the hypodermis) or too shallow (13). Additionally, intradermal injections with a standard needle and syringe are perceived as painful by the patient.



Mantoux technique with possible incorrect administrations of the injection.

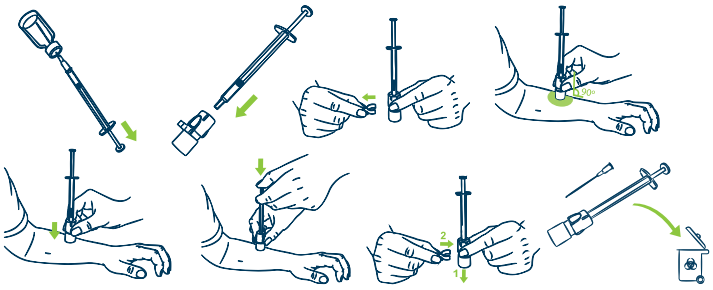


To overcome the challenges with the traditional Mantoux technique, IDEVAX developed VAX-ID® as an easy-to-use drug delivery device enabling standardized, accurate and reliable delivery in the dermal layer of the skin.



VAX-ID® can be preconfigured with a 32G, 30G, or 27G needle with an injection depth of 0.5mm, 0.6mm, and 0.8mm, respectively. As accuracy of penetration depth is very important, the penetration depth of the needle was predefined based on skin thickness evaluations by high frequency ultrasound executed in adults, adolescents as well as children (14,15).

Demonstrating minimal dead volume and high dose accuracy, VAXID® consistently achieves successful injections at the designated dermal depth, while making ID injections safe and easy for healthcare professionals (16).



By enabling standardized, accurate and reliable intradermal delivery, VAX-ID® offers a game-changing approach for **intradermal delivery of cancer vaccines including cell-based approaches**. For the latter, it was shown during a feasibility study that VAX-ID® configured with needles ranging from 27G up to 32G showed no increase in shear stress upon ejection of tolerogenic dendritic cells (tolDCs) nor of T cells.The four phenotypic markers (CD86, CD80, HLADR, CD40) as well as cell viability did not show significant differences before and after ejection (3).

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