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CURRENT OPINION

Harnessing dendritic cells for innovative therapeutic cancer vaccines

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Purpose of review
The clinical activity of new immunotherapies in cancer, such as anti-Programmed cell death 1 (PD-1)/Programmed death-ligand 1, has revealed the importance of the patient's immune system in controlling tumor development. As in infectious diseases, dendritic cells (DCs) are critical for inducing immune responses in cancer. Unfortunately, autologous DC-based vaccines have not yet demonstrated their clinical benefit. Here, we review recent research using allogeneic DCs as alternatives to autologous DCs to develop innovative therapeutic cancer vaccines.

Recent findings
A novel approach using an allogeneic plasmacytoid dendritic cell (PDC) line as an antigen presentation platform showed great potency when used to prime and expand antitumor-specific CD8+ T cells in vitro and in vivo in a humanized mouse model. This PDC platform, named PDC*vac, was first evaluated in the treatment of melanoma with encouraging results and is currently being evaluated in the treatment of lung cancer in combination with anti-PD-1 immunotherapy.

Summary
Therapeutic cancer vaccines are of particular interest because they aim to help patients, to mount effective antitumor responses, especially those who insufficiently respond to immune checkpoint inhibitors. The use of an allogeneic plasmacytoid DC-based platform such as PDC*vac could greatly potentiate the efficacy of these new immunotherapies.

Keywords
allogeneic plasmacytoid and myeloid dendritic cells, antitumor CD8+ T cells, cancer vaccines, humanized mouse model, immune checkpoint inhibitors

INTRODUCTION

During the last ten years, we have witnessed a revolution in the treatment of cancer thanks to the effectiveness of immune checkpoint inhibitors (ICIs), i.e., monoclonal antibodies that counter the immune system inhibition induced by cancer cells [1] (see also https://www.cancerresearch.org/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape). This revolution concerns both the impressive clinical efficacy of these products in some patients and the nature of their mechanisms of action. Indeed, some ICIs have replaced chemotherapy drugs as the standard of care, and for a significant number of cancers, such as lung cancer, they are used in combination with other first-line treatments [2▪▪]. ICIs do not directly induce tumor cell lysis, but rather they act through the patient's own immune system by enhancing the activity of antitumor-specific and cytotoxic CD8+ T cells (ASTCs). As a matter of fact, ASTCs are most likely the key effectors in the mechanisms of action of ICIs due to their ability to recognize and specifically lyse cancer cells expressing tumor antigens, such as tumor-shared antigens or neoantigens. Thus, the expression of immune checkpoints in the tumor microenvironment, the expression of immunogenic tumor antigens by cancer cells, and the presence of

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Curr Opin Oncol 2022, 34:161–168

DOI:10.1097/CCO.0000000000000815

KEY POINTS

- The low number of patients responding to immune checkpoint inhibitors could be due to weak preexisting antitumor immunity
- Therapeutic cancer vaccines can overcome this limitation by priming and boosting antitumor immunity
- Due to their key role in orchestrating the immune response, dendritic cells represent the target of all strategies for developing therapeutic cancer vaccines
- Allogeneic dendritic cells are considered to be an alternative source of dendritic cells, guaranteeing the homogeneity of drug product manufacturing and clinical trial management
- The allogeneic plasmacytoid dendritic cell line PDC*line is a unique and potent tool for the development of innovative therapeutic cancer vaccines, which could be suitable for many cancers.

tumor-infiltrating CD8+ T cells are associated with the clinical efficacy of ICIs in numerous cancers [3,4,5].

Unfortunately, too many cancer patients remain refractory to ICI treatment, probably because of a low or inappropriate preexisting antitumor immunity. In this context, the efficient activation of functional antitumor T cells in association with ICI treatment is crucial to improve patient outcomes, and therapeutic cancer vaccines represent a promising option to achieve this goal [6].

Therapeutic cancer vaccines

Therapeutic cancer vaccines aim to activate patients' ASTCs or overcome tumor-induced tolerance thanks to dendritic cells (DCs). DCs are professional antigen-presenting cells (APCs), mandatory to efficiently trigger the differentiation, activity, specificity, and lytic potency of ASTCs. DCs are both sentinels and stimulators of our immune system; they patrol the body for tumor antigens and reach the lymph nodes where immune responses take place.

Two main cancer vaccine strategies have been tested so far in humans, both involving DCs – directly and indirectly [7,8▪▪,9▪▪,10▪▪,11,12▪]. The first one consists of the direct injection of a source of tumor antigens (protein, peptide, Ribonucleic acid, or Deoxyribonucleic acid) along with an adjuvant and/or a vector (virus or lipoprotein vesicle), which can recruit or target the patient's own DCs in vivo, so that they take up antigens, process them, and present them in order to activate ASTCs [10▪▪]. However, the efficacy of these approaches may be affected when the functionality of patient's DCs is compromised by their disease, their previous therapies, and by the fact that nonprofessional APCs can interfere with the stimulation or inhibition of effector CD8+ T cells. Thus far, only oncolytic viral therapy has shown significant clinical benefits, improved in combination with ICIs, for melanoma patients [13,14].

The administration of autologous DCs generated from patients' own monocytes or stem cells represents the second approach. The DCs obtained after in vitro culture generally displayed a conventional myeloid DC (MDC) phenotype, and are incubated with a source of tumor antigens before administration to patients [8▪▪,11,12▪]. The advantage of this approach is to allow the control of DC loading and activation steps. However, a dedicated manufacturing is required for each patient, which raised issues in terms of reproducibility and feasibility, specifically in regard to patient's condition. Finally, the in vitro manufacturing often leads to suboptimal DCs. At present, the objective response rate of DC-based cancer vaccines remains below 15% [7,11]. Only one DC-like cell product (Provenge) has been approved by the Food and Drug Administration for the treatment of advanced prostate cancer, although it still demonstrates little clinical benefit [15].

There is an urgent need to develop new innovative approaches using potent DC products to efficiently boost patients' antitumor responses. These products should be easy to manufacture to guarantee consistency in the immunological activity for the benefit of patients. Although autologous DCs are still being studied, allogeneic DC-based vaccines are currently the subject of intense research to achieve this goal [8▪▪,11,12▪].

Allogeneic myeloid dendritic cell-based cancer vaccines

Off-the-shelf allogeneic DC-based platforms are indeed more attractive than autologous vaccines tailored to each patient in all aforementioned aspects.

In addition, the allogeneic response due to the expression of mismatched Human leucocyte antigen (HLA) on allogeneic MDCs was expected to boost the stimulation of ASTCs activated by the classical tumor peptide presentation via shared HLA class I molecules on MDCs.

Most of the time, allogeneic MDCs were preliminarily loaded with tumor cell lysates or fused with tumor cells as a source of tumor antigens and administered to partially HLA class I-matched patients (Table 1) [16–20]. Interestingly, the MDCs

Table 1. Allogeneic DC-based therapeutic cancer vaccines evaluated in phase I/II clinical trials

Studies	Pathology	Allogeneic Product	Nb patients	Cell dose (Million)	Route	Nb injection	Frequency	AE or SAE possibly related to the product	Clinical outcome
Märten, 2003	Renal cell carcinoma	Allogeneic MDCs fused with autologous or allogeneic tumor cells	12	28	ID	3	D0, D28, D56	No detailed information	8 PD, 4 SD
Hus, 2005	B-Chronic Lymphocytic Leukemia	Allogeneic MDCs loaded with tumor lysates or/and apoptotic bodies	9	23–39	ID	4–5 + 2 boosts	W2-W3 M5-M6	Erythema, induration, pruritis at the injection site	Not reported
Höltl, 2005	Renal cell carcinoma	Allogeneic MDCs loaded with tumor lysates	22	2–10	IV, ID	3–6	Monthly	Fever	13 PD, 5 SD, 2 MR 2 not evaluable
Avigan, 2007	Renal cell carcinoma	Allogeneic MDCs fused with autologous tumor	24	40–100	SC	6	Weekly	Fatigue, coughing, rigors, erythema, ecchymosis, pruritis, tenderness, transient edema at the site of injection	12 PD, 4 SD, 2 PR 4 not evaluable
Flörcken, 2013	Renal cell carcinoma	Allogeneic MDCs loaded with tumor lysates and irradiated	8	10	SC	8	W1, W3, W5, W8, W11, W14, W17, W20	arthralgia	5 PD; 2 SD 1 not evaluable
Laurell, 2017	Renal cell carcinoma	Allogeneic MDCs	12	5, 10, 20	IT	2	D1, D14	Fever, chills, rash, hypotension	5 PD, 3 SD 4 not evaluable
van de Loosdrecht, 2018	Acute myeloid leukemia	Irradiated allogeneic myeloid-like DC-derived cell line	12	10, 25 or 50	ID	4	D0, D14, D28, D42	Diabetes insipidus	5 PD, 5 SD 2 not evaluable
Fröbom, 2020	Gastrointestinal stromal tumors	Allogeneic MDCs	6	10	IT	2	D1, D14	Fever, abdominal pain, administration site discomfort	4 PD, 2 SD

AE, adverse event; SAE, serious adverse event; W, week; D, day; M, month; MDC, myeloid dendritic cells; IV, intravenous; ID, intradermal; SC, subcutaneous; IT, intratumoral; PD, progressive disease; SD, stable disease; MR, mixed response; PR, partial response.

generated from a myeloid-like DC-derived cell line were also used to treat acute myeloid leukemia patients [21]. Other approaches were established to inject unloaded allogeneic MDCs directly into patients' tumors [22].

Despite possible humoral and cellular allogeneic responses, the current clinical experience showed that allogeneic DC-based vaccines were safe and well-tolerated. Indeed, reported adverse events were low grade, transitory, and manageable (Table 1).

Unfortunately, to date, most of these approaches have not been successful or have not yet provided a significant clinical benefit in humans (Table 1). Moreover, concerning the immunogenicity of these platforms in vitro and in vivo, few data are available making their potential optimization difficult.

PDC*vac, a plasmacytoid dendritic cells-based cancer vaccine

Among DC populations, plasmacytoid dendritic cells (PDCs) are of great interest [23], because they are potent type 1 Inteferon (IFN) producers, and can induce strong cytotoxic T lymphocyte (CTL) responses after antigen presentation [24] in both antiviral [25▪,26] and antitumoral responses [27▪▪]. Interestingly, the presence of a PDC subset (OX40+) was recently found to favor the antitumor immunity in head and neck carcinoma [28▪]. However, despite their high immunostimulatory capacity, few laboratories have studied PDCs as a potential cancer vaccine, because of the paucity of PDCs in the blood and the difficulty of producing them in large quantities in vitro, and in a reproducible manner [29].

Only two clinical trials have been carried out using autologous PDCs; one in metastatic melanoma and the other in castration-resistant prostate cancer. In the melanoma trial, favorable effects were observed: systemic IFNα signature after each vaccination, vaccine-induced in vitro expansion of high-affinity ASTC clones, and increased overall survival [30]. In the prostate cancer trial, the vaccine consisted of PDCs, MDCs, or both. Interestingly, IFNγ-producing ASTCs increased postvaccination and were correlated with nonprogressive disease. These favorable immune and clinical responses were observed with the three treatments [31].

Nevertheless, obtaining sufficient quantities of activated PDCs from patients remains difficult. Allogeneic PDC-based approaches could circumvent the drawbacks due to these autologous strategies.

Being pioneers in the identification of the leukemic counterpart of normal PDCs [32,33], we developed for research and development [34,35] first, and later for clinical applications [36▪], the first human HLA-A*02:01-positive PDC line isolated from the tumor of a patient having PDC leukemia. This cell line displayed most of the features of normal PDCs: expression of BDCA2, BDCA4, Toll-like receptor (TLR)7, and TLR9; antigen processing; TRAIL and cytokine responses following TLR9 or TLR7 activation, including type I interferon secretion [34,37–40]. However, the PDC line seemed to display a more undifferentiated state than normal PDCs, similarly to other PDC lines described since [41,42]. The PDC line developed for clinical applications was named 'PDC*line'. Unlike MDCs or normal PDCs, PDC*line cells do not express Programmed death-ligand 1 (PD-L1) or PD-L2 (Plumas J., unpublished data).

Importantly, PDC*line cells have potent antigen-presentation activity. Indeed, when PDC*line cells were loaded in vitro with HLA-A*02:01-restricted peptides, they could prime and expand HLA class I-matched antigen-specific CD8+ T cells. Encouraged by these preliminary results, a new cancer vaccine platform was developed with PDC*line cells.

Robust proof of concept with the PDC*vac platform

The PDC*vac platform consists of irradiated PDC*line cells loaded in vitro with the HLA-restricted peptides derived from the antigens of interest.

In vitro proof of concept

The PDC*line cells loaded with different types of tumor antigens (shared antigens or neoantigens) were able to prime healthy donor's naïve CD8+ T cells or to boost patient's antitumor CD8+ T cells, leading in both cases to the efficient expansion of ASTCs [43–45]. Expanded ASTCs were highly specific and functional in terms of IFNγ secretion and cytotoxic activity against cancer cells. Tumor peptide-loaded PDC*line cells were even more potent than MDCs at activating and expanding ASTCs [43]. PDC*line cells could also prime naïve $CD8^+$ T cells derived from cord blood (Plumas J., unpublished data).

Moreover, we have recently demonstrated that the PDC*line transduced with genes encoding whole viral or tumoral proteins can efficiently process the transduced antigens and stably present antigen-derived peptides to specific CD8+ T cells in the context of the different HLA molecules expressed by PDC*line cells [46▪]. The transduction of constructs encoding polyepitopes led to a multispecific CD8+ T-cell response, thereby diversifying the nature of cytotoxic effectors to potentiate the vaccine effect. In addition, retroviral engineering enabled the expression of other functional HLA molecules of interest such as HLA-A*24:02, which

is strongly represented in the Asian population, but is not expressed by PDC*line cells. The easy addition of new HLA class I molecules using retroviral engineering could thus broaden the population of patients benefiting from the PDC*vac vaccine platform [46▪].

In vivo proof of concept

To demonstrate the potency of the PDC*vac platform in terms of inducing a specific T-cell response in vivo, we developed preclinical mouse models by using immunodeficient mice engrafted either with human mononuclear cells to set up an experienced human immune system or with human stem cells to develop a more naïve human immune system, avoiding xenogeneic reactions and graft-versus-host diseases. The injection of viral or melanoma peptide-loaded PDC*line cells into mononuclear cell-humanized mice led to an efficient expansion of ASTCs [43], even greater than the expansions observed in the studies using MDCs in similar mouse models [47,48].

Using Non-Obese Diabetic/severe combined immunodeficiency disease/IL-2Rγ^{null} (NOG) mice humanized with HLA-A*02:01+ stem cells, we also recently demonstrated the priming and expansion of ASTCs in the blood and spleen of animals. Strikingly, after four weekly administrations of PDC*vac product, huge numbers of tumor peptide-specific T cells were found in the blood and spleen of animals (see Fig. 1, which is representative of unpublished results).

Finally, the vaccinations of human-tumor-bearing humanized mice with peptide-loaded PDC*line led to tumor growth inhibition, and to the recruitment of antitumor CD8+ T cells to the tumor site [43].

The PDC*vac platform in humans

The robust proof of concept data obtained in vitro and in vivo led to the development of PDC*vac as an innovative platform for cancer vaccines, as illustrated in Fig. 2. For cancer treatment, PDC*line cells are loaded in vitro with HLA-A*02:01-restricted peptides derived from the tumor antigens expressed by the cancer to be treated. Loaded PDC*line cells are

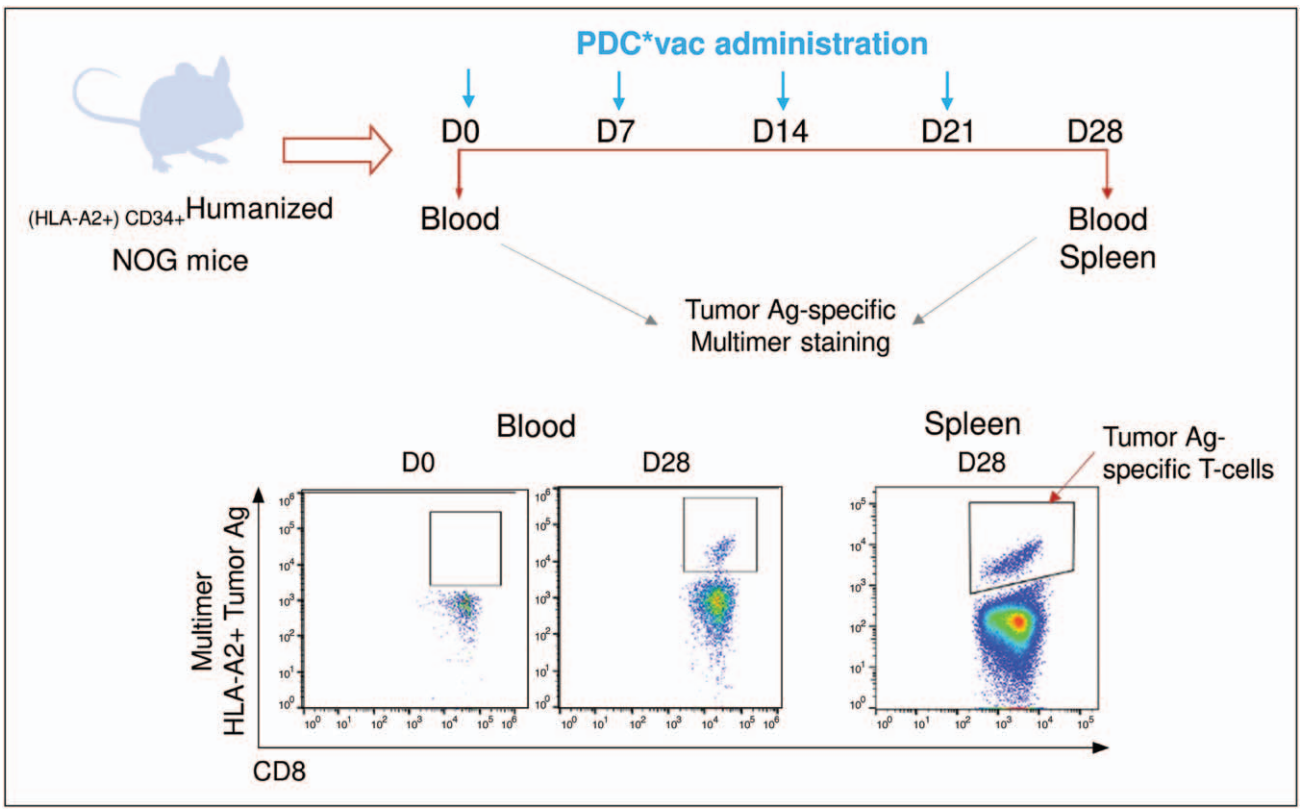

FIGURE 1. Priming and expansion of the antitumor response induced by PDC*vac in a humanized NOG mouse model. Humanized $_{CD34+}$NOG mice were immunized with tumor peptide-loaded PDC*vac. At baseline (D0) and after four immunizations at weekly intervals (D28), the blood and the spleen were collected, and the percentage of tumor-specific CD8+ T cells was measured using multimer staining and flow cytometry. Ag, antigen.

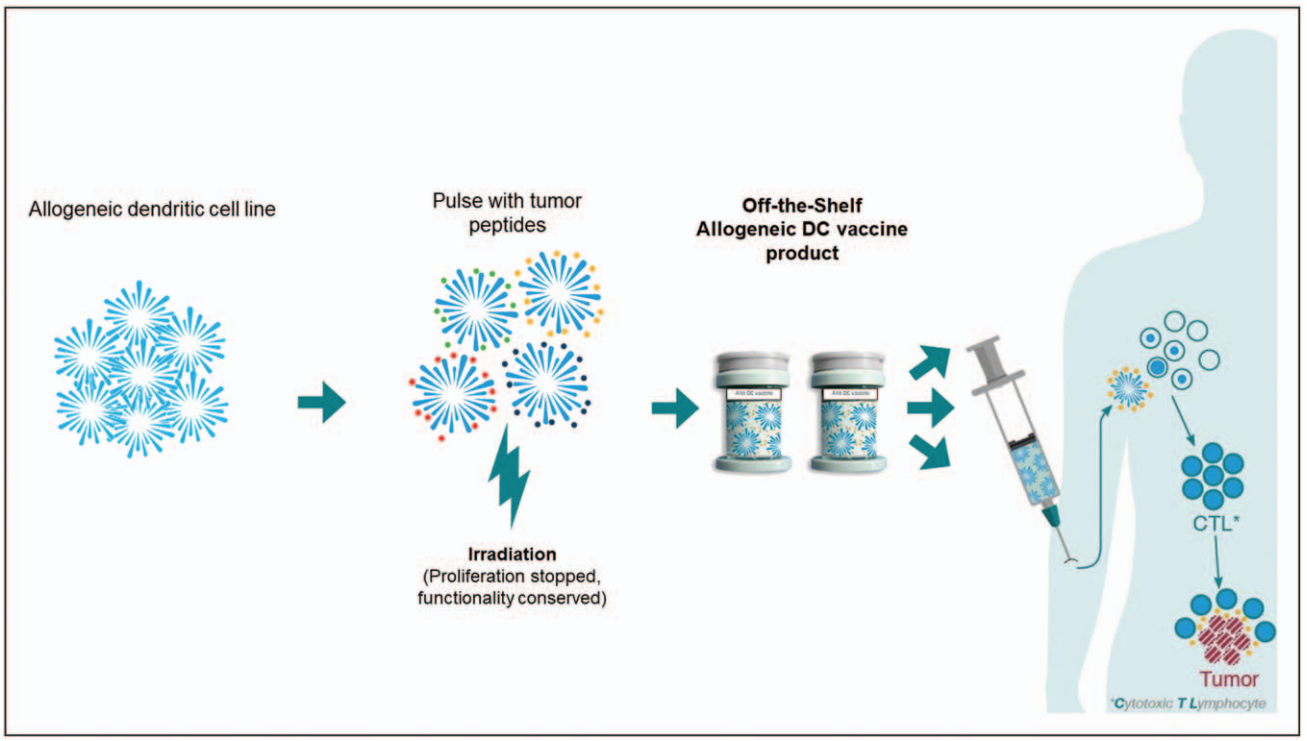

FIGURE 2. Flow chart of off-the-self allogenic dendritic cell vaccine product. CTL, cytotoxic T lymphocytes.

then irradiated to stop their proliferation whereas keeping their functionality, before long-term storage in liquid nitrogen. When needed, the product is thawed and injected into HLA-A∗02:01-compatible patients in order to prime and boost ASTC responses. PDC∗vac is thus a versatile and off-the-shelf platform ready to be used for different cancers.

Two clinical trials have been conducted thus far with PDC∗vac products: one for melanoma (PDC∗mel, NCT01863108) and one for non small-cell lung cancer (NSCLC; PDC∗lung, NCT03970746). This approach was also investigated at the preclinical level for the treatment of other cancers by targeting neoantigens (PDC∗neo). PDC∗vac was classified by the European Medicines Agency as an Advanced-Therapy Medicinal Product, precisely a Somatic-Cell Therapy Medicinal Product.

Safety and immunological responses in melanoma

A first-in-human phase I/II clinical trial was conducted in metastatic melanoma patients to evaluate the safety of the PDC∗vac platform (PDC∗mel) in monotherapy, and its ability to elicit antitumor immune responses [36▪]. Nine patients with metastatic stage IV melanoma were treated with PDC∗mel after two or more lines of therapies. Up to 60 million PDC∗line cells were loaded with four melanoma antigens (Melan-A, MAGE-A3, gp100, Tyrosinase), irradiated, and injected subcutaneously at weekly intervals.

The vaccine was well-tolerated, and no serious vaccine-induced side effects were recorded. Signs of clinical activity were observed, including four patients having a stable disease according to Immune-related Response Criteria and two patients with vitiligo lesions [36▪]. Four patients were still alive one year after starting PDC∗mel administration. Strikingly, a significant increase in the frequency of circulating antitumor-specific T lymphocytes was observed in two patients, along with a switch from naïve to memory phenotype, thereby demonstrating the priming of ASTCs in humans. Interestingly, no allogeneic reactions were observed at either humoral or cellular levels, enabling more than three injections of the cancer vaccine in order to better stimulate the immune response [36▪].

In addition, using melanoma patient mononuclear cells, we remarkably observed much better specific T-cell expansion in vitro with the combination of peptide-loaded PDC∗line and anti-Programmed cell death 1 (PD-1) antibodies, indicating synergistic effects of both products and giving preclinical evidence of the benefit of the combination in humans.

Clinical activity in lung cancer

We then adapted the PDC∗vac platform to a more prevalent cancer, i.e., NSCLC. The candidate vaccine named 'PDC∗lung' consists of the PDC∗line

cells expanded in large volume in bioreactor and loaded with peptides from six tumor antigens expressed in lung cancer: MAGE-A3, MAGE-A4, Multi-MAGE, Survivin, NY-ESO-I, and MUC1.

The final drug product (DP) is stored frozen for a long time in a ready-to-use formulation. Given its stability during storage, the DP is very attractive for bench-to-bedside transfer, because it has only to be thawed at room temperature and drawn through a syringe before being injected into patients.

In this ongoing, open-label, dose-escalation phase I/II study (NCT03970746), we are assessing the safety, tolerability, immunogenicity, and preliminary clinical activity of PDC∗lung alone, or in combination with anti-PD-1 treatment (pembrolizumab). The patients are treated six times at weekly intervals through both subcutaneous and intravenous routes with a low or high dose of PDC∗lung. Our target product profile is the treatment of patients with NSCLC displaying a PD-L1 tumor proportion score equal to or greater than 50% in combination with pembrolizumab. The first evaluation of clinical activity is expected in early 2023.

CONCLUSION

The need to improve the proportion of patients responding to ICIs has revitalized the development of cancer vaccines able to boost the insufficient antitumor immunity of nonresponders. The development of off-the-shelf allogeneic DC-based cancer vaccines such as PDC∗vac, in combination with ICIs, clearly represents a great opportunity to obtain innovative treatments avoiding the reproducibility issues inherent to the use of autologous products. The clinical activity of the PDC∗lung medicinal product in association with ICIs is currently being evaluated in lung cancer patients, and preliminary clinical an immunological activities of PDC∗vac in combination with ICIs will be available soon.

Acknowledgements

I am grateful to the team members of the R&D departments of Etablissement Francais du Sang at Grenoble and PDC∗line Pharma. I specifically thank Laurence Chaperot, Karine Laulagnier, and Marie Genin for their critical reading. I also thank Dalil Hannani and TransCure bioServices for conducting the experiments using the NOG mouse model.

Financial support and sponsorship

The research results cited in this review were partly funded by Proof-of-concept CLARA, EFS APR 2010–2011, Ligue contre le Cancer (Comité de la Savoie), Fondation SILAB, a Senior Marie Curie Research Fellowship (J.P.) of the European Union Framework 7 (FP7-PEOPLE-2009-IEF, proposal number 251033 – Acronym: PDC Therapy), by Etablissement Français du Sang (EFS APR GenAdopt), and by PDC∗line Pharma.

Conflicts of interest

J.P. is the Chief Scientific Officer and Co-founder of PDC∗line Pharma.

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An important proof of principle of the potential of a human plasmacytoid dendritic cell line to prime and expand antitumor CD8+ T-cells, following genetic modification, for the next generation of cancer vaccines.

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