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ORIGINAL ARTICLE

Innovative therapeutic cancer vaccine PDC*lung01 with or without anti-PD-1: an open-label, dose-escalation phase I/II study in non-small-cell lung cancer

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Background: While immune checkpoint inhibitors have revolutionized the treatment of non-small-cell lung cancer (NSCLC), many patients still suffer from either primary or acquired treatment resistance. Stimulation of antitumor cellular immunity with a therapeutic cancer vaccine in combination with anti-programmed cell death (ligand) protein 1 [PD-(L)1] may improve outcome. PDC*lung01 is a cancer vaccine made of irradiated plasmacytoid dendritic cells loaded with six NSCLC tumor antigens (NY-ESO-1, MAGE-A3, MAGE-A4, Multi-MAGE-A, MUC1, and Survivin), and available as a ready-to-use product.

Patients and methods: This open-label, dose-escalation, multicenter, phase I/II study assessed the safety profile, clinical activity, and immunogenicity of PDC*lung01 at low or high doses, either as a single agent in resected NSCLC (cohorts A) or with anti-PD-1 in metastatic NSCLC with PD-L1 $\geq$ 50% (cohorts B). The primary objective was vaccine-related dose-limiting toxicities (DLTs). Secondary objectives included safety profile, T-cell response against vaccine antigens in all cohorts, and clinical activity in cohort B2 (high-dose PDC*lung01 with anti-PD-1): objective response rate (ORR) and 9-month progression-free survival (9mPFS).

Results: Median follow-up was 20 months [95% confidence interval (CI) 14-26 months] in all enrolled patients ($N = 73$). Most adverse events were mild to moderate; only one patient (2%) in cohort B2 reported a related DLT. In the combination of PDC*lung01 (high-dose) with anti-PD-1 ($N = 45$), the confirmed ORR was 51% (80% CI 41% to 62%), the 9mPFS estimate was 47% (80% CI 37% to 57%), and the median PFS was 9 months (95% CI 5.0-24 months). PDC*lung01 elicited tumor antigen-specific T-cell expansions in 50%-67% of patients and PFS duration correlated positively with immune response intensity ($P = 0.04$).

Conclusions: PDC*lung01 was immunogenic and had a manageable safety profile in all cohorts and met the predefined clinical objectives when combined with anti-PD-1 in metastatic NSCLC. Median PFS was positively correlated with antigen-specific T-cell expansions.

Key words: therapeutic cancer vaccine, plasmacytoid dendritic cells, immune checkpoint inhibitor, non-small-cell lung cancer, clinical trials phase I/II

INTRODUCTION

Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) expressed on the surface of activated T cells or programmed cell death ligand 1 (PD-L1) expressed by cancer cells have revolutionized the

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treatment landscape of non-small-cell lung cancer (NSCLC).[1-3] ICIs contribute to restoring the antitumoral activity of effector T cells by preventing the PD-1/PD-L1 interaction, and therefore the inhibitory signal provided by cancer cells.[1,4]

Several studies in advanced or metastatic NSCLC have demonstrated the durable clinical benefit of anti-PD-1 and anti-PD-L1 immunotherapies used as monotherapy or in combination with chemotherapy, compared with chemotherapy alone.[1-3,5-7] However, a majority of patients suffer from either primary or acquired treatment resistance, limiting the benefit of ICIs.[1,8,9] In particular, in the population of advanced and metastatic patients with high expression of PD-L1 (tumor progression score $\geq$50%), almost 60% do not respond to ICI.[7,10] Low or inappropriate level of pre-existing antitumor immunity explains part of ICI therapy failure.[11,12] Therefore, stimulation of antitumor cellular immunity with a therapeutic cancer vaccine in combination with anti-PD-1/anti-PD-L1 represents a promising approach to improve patient outcomes.

Therapeutic cancer vaccines induce antitumoral immunity by activating tumor antigen-specific CD8+ T cells (ASTCs) and eliciting immunological memory.[8,11,13-15] Vaccine-induced immunity has the potential to improve effectiveness of ICIs by increasing the response rate, while ICIs could in turn strengthen the immunostimulatory potential of the vaccine, suggesting a potential synergy.[8,11-13,15] Dendritic cells (DCs)-based therapeutic cancer vaccines activate naïve T cells through presentation of tumor antigen-derived peptides.[8,11-13,15] Allogeneic DC-based antigen-presenting platforms are important alternatives to their autologous counterparts, as more reproducible and less cumbersome in production.[11-13]

PDC*line is an allogeneic antigen-presenting platform consisting of a plasmacytoid dendritic cell (PDC) line isolated from the blood of an HLA-A*02:01-positive patient with PDC leukemia.[11-13,16] This technology leverages the high capacities of PDCs to stimulate strong antitumoral immune responses following antigen presentation.[17] Preclinical functional *in vitro* assays and studies in humanized mice have demonstrated the potency of irradiated PDC*line cells loaded with selected tumor antigen-derived peptides to prime and expand naïve T cells into fully functional ASTCs with a specific anticancer activity.[11,13,16,18-20] These promising preclinical results supported the development of the first therapeutic cancer vaccine candidate based on the PDC*line platform, PDC*mel, loaded with four melanoma antigen-derived peptides.[16] In a first-in-human phase I trial in metastatic melanoma (NCT01863108), PDC*mel monotherapy was well tolerated and was able to induce antitumoral immune responses (switch from naïve to memory ASTCs).[16]

A new PDC*line-based therapeutic product (PDC*lung01) composed of irradiated PDC*line cells loaded with six NSCLC antigen-derived peptides and one control peptide has been developed.[11] *In vitro* experiments showed that PDC*lung01-like products can activate and expand antitumor circulating ASTCs in 85% of NSCLC patients, of whom 69% presented a response for at least two tumor antigens.[12] Additionally, a synergistic effect of anti-PD-1 therapy on the vaccine-induced antitumoral immune cell expansion was observed.[12,16]

The current clinical study evaluated the safety profile, tolerability, preliminary clinical activity, and immunogenicity of PDC*lung01 at two dose levels used as a single agent in the adjuvant setting or in combination with anti-PD-1 in patients with metastatic NSCLC.

PATIENTS AND METHODS

Study design and patients

This open-label, dose-escalation, multicenter, phase I/II study (NCT03970746) recruited patients between September 2019 and December 2023 (date of treatment completion for the last patient) in Belgium, France, Germany, The Netherlands, and Poland. The study was conducted in accordance with the protocol, its amendments, the Declaration of Helsinki, and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol and all amendments were approved by the relevant ethics committees and regulatory authorities. All patients gave written informed consent.

The study included four distinct cohorts (Figure 1; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105844). A data safety monitoring board monitored the safety data of the four cohorts and provided recommendations about study progress (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105844). In cohorts A1 (low-dose, 14 million cells) and A2 (high-dose, 140 million cells), patients received single-agent PDC*lung01 in the adjuvant setting after complete resection. In cohorts B1 (low-dose) and B2 (high-dose), PDC*lung01 was administered as part of first-line combination therapy with pembrolizumab 200 mg intravenous every 3 weeks.

Since PDC*line cells express the HLA-A*02:01 molecule, only patients with documented HLA-A*02:01 expression and absence of antibodies against human leukocyte antigen (HLA) molecules expressed by PDC*line cells were eligible. The patients eligible for cohorts A1 and A2 had completely resected stage IIa/IIb/IIIa NSCLC (tumor—node—metastasis classification eighth edition)[21] and adjuvant-based chemotherapy if indicated. The patients eligible for cohorts B1 and B2 had an untreated stage IV measurable NSCLC (PD-L1 $\geq$ 50%) and received anti-PD-1 first-line monotherapy as per standard-of-care treatment. Patients who underwent radiotherapy/chemoradiotherapy for prior stage III disease were eligible if the treatment-free interval was >1 year. Inclusion and exclusion criteria are further detailed in the Supplementary material, available at https://doi.org/10.1016/j.esmoop.2025.105844.

During the treatment period [visit (V)1-V7], the patients received PDC*lung01 weekly via both subcutaneous and intravenous routes at each administration over 6 weeks (V1-V6). In cohorts A1 and A2, the first study dose was

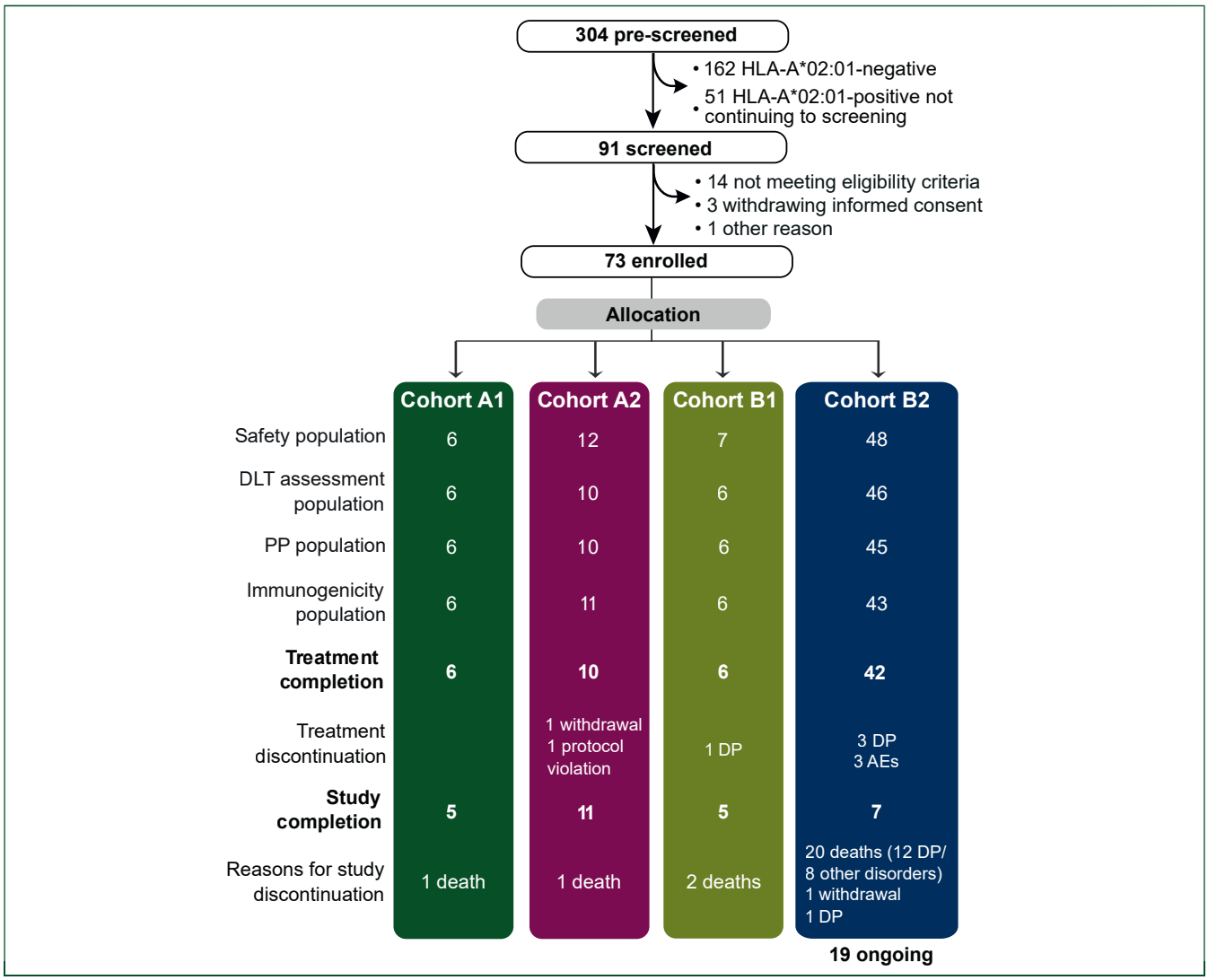

Figure 1. Flow chart presenting the disposition of patients.
AE, adverse event; DLT, dose-limiting toxicity; DP, disease progression; HLA, human leukocyte antigen; PP, per-protocol.

administered at least 4 weeks after the last standard-of-care treatment. Occurrence of dose-limiting toxicities (DLTs) was assessed from V1 to V6 with a final measurement at V7, 1 week after the last study dose. The end-of-treatment visit (V8) took place 4 weeks after the last vaccine administration.

Patients were followed up for up to 2 years after V8 to record serious adverse events (SAEs) related to study intervention, clinical response assessment according to RECIST, v1.1,[22] next anticancer treatments, and survival (every 3 months during the first year and every 6 months during the second year).

As detailed in Supplementary material, available at https://doi.org/10.1016/j.esmoop.2025.105844, immunogenicity was assessed before vaccination, at V7, V8, and during the follow-up phase at V9, 10 weeks after the last vaccine administration.

Study product

PDC*lung01 is a therapeutic vaccine comprising irradiated PDC*line cells,[16] each loaded individually with one of seven HLA-A*02:01-restricted peptides derived from six NSCLC antigens i.e. NY-ESO-1, MAGE-A3, MAGE-A4, Multi-MAGE, MUC1, and Survivin, with Melan-A melanoma antigen as control. The vaccine is provided in ready-to-use aliquots containing a frozen suspension of a mixture, in equal proportions, of PDC*line cells loaded separately with one distinct peptide.

Study endpoints and assessments

The primary safety objective was the assessment of safety of PDC*lung01 vaccination at two dose levels in all cohorts, in terms of vaccine-related DLTs from V1 to V7. DLTs were defined as all grade 4 toxicities, grade 3 non-laboratory toxicities, grade 3 laboratory toxicities (excluding hematological toxicity), grade 3 or higher cytokine release syndrome, grade 3 or higher allergic reaction and/or anaphylaxis and/or infusion-related reaction occurring within 24 h after injection, and grade 5 toxicities (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105844). DLTs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[23]

The secondary safety objectives included the assessment of safety profile of PDC*lung01 in combination with pembrolizumab in terms of treatment-emergent adverse events (TEAEs) and SAEs, and assessment of the allogeneic humoral response against PDC*line cells (anti-HLA class I and II serum antibodies and allelic specificity).

The secondary efficacy objective was the clinical activity of PDC*lung01 in combination with pembrolizumab in cohort B2 in terms of objective response rate (ORR) and progression-free survival (PFS) at 9 months (9mPFS), based on RECIST v1.1 radiological assessments by investigators at screening, week 7, and confirmed 4-6 weeks later.

PDC*lung01 immunogenicity, as also a secondary objective, was evaluated by assessing the specific cellular immune response against vaccine antigens through *ex vivo* detection and characterization of antitumor ASTCs by flow cytometry. A description of methods used for immunomonitoring is provided in the Supplementary methods and in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105844.

Further details of the study objectives and endpoints, including exploratory objectives, are presented in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105844.

Demographic characteristics, and medical and disease history were collected at screening. The performance status (PS), vital signs, and concomitant medications were recorded at screening and at V1-V8. A physical examination was carried out at screening and V8.

Statistical analysis

A total of 64 assessable patients (6 in cohort A1, 10 in cohort A2, 6 in cohort B1, 42 in cohort B2) were planned to be enrolled in this study. The primary safety endpoint was evaluated in the DLT assessment population. The other safety endpoints were assessed in the safety population. Efficacy endpoints were assessed in the per-protocol (PP) population. Analyses of immunogenicity endpoints were conducted in the immunogenicity population. Definitions of population sets are provided in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105844.

The occurrences of DLTs, TEAEs, and SAEs were expressed as numbers and percentages of patients reporting each event. AEs were classified using the Medical Dictionary for Regulatory Activities terminology and graded according to the CTCAE v5.0 system.[23]

For the secondary objective of PDC*lung01 preliminary clinical activity in cohort B2, the results from the population with PD-L1 $\geq$ 50% in the Keynote-042 study[7] were considered as expected baseline activity with pembrolizumab (ORR of 39% and 9mPFS of 43%). The target benefit was an absolute increase of 15%, i.e. an ORR of 54% and a 9mPFS of 58% or more. The objective was considered as reached when the lower limit of the confidence interval (CI) of the ORR excluded the null hypothesis, i.e. 39% ORR in historical control. A Sargent two-stage design was considered, with type I error at one-sided 0.1 level and type II error level at 0.3 (corresponding to a power of 70%) with a sample size of 42 assessable patients.

The number and percentage of patients with an ORR and disease control rate (DCR) were calculated with 80% CIs. Details on statistical analysis are available in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105844. Individual objective responses and best overall response (BOR) were represented using waterfall, swimmer, and spider plots. PFS, time to progression (TTP), and overall survival (OS) were assessed using Kaplan—Meier methodology; median PFS/TTP/OS (95% CIs) and their estimates at 9 months (80% CIs) were computed. The number of events determining the duration of response (DOR) and median DOR (95% CIs) were documented.

The frequencies of antitumor ASTCs were compared before and after vaccination using non-parametric paired Wilcoxon tests. The correlation between PFS and immunological response (frequencies of antitumor ASTCs) was investigated with a non-parametric Spearman test.

Data were analyzed using SAS software (v.9.4 or higher, Cary, NC) or PRISM 10.0 (GraphPad software, LLC, Boston, MA).

RESULTS

Study patients

Of the 304 pre-screened patients, 142 (47%) were HLA-A*02:01-positive, 91 (30%) entered the screening phase, and 73 (24%) were allocated to the study cohorts. Study completion rates ranged from 15% in cohort B2 to 92% in cohort A2 (Figure 1).

In all cohorts, most patients were male, Caucasian, past smokers, and had a median age of 64-69 years (Table 1). At least half of the patients in cohorts A had a PS of 0, while most patients in cohorts B had a PS of 1 (Table 1). Three patients (50%) in cohort A1 and 11 (92%) in cohort A2 received adjuvant chemotherapy. Five (10%) patients in cohort B2 received previous palliative radiotherapy. Brain metastases were present at baseline in 29% (cohort B1) and 25% (cohort B2) of patients. Those patients were required to have asymptomatic or stable brain metastases.

Safety

In the DLT assessment population ($N = 68$), only one patient in cohort B2 experienced a DLT considered possibly related to the study intervention. This event was reported as a grade 4 anaphylactic reaction occurring within 24 h following PDC*lung01 administration, associated with complement component C3d elevation and increase in C-reactive protein; the patient recovered on the same day following anti-allergic treatment.

Most patients in the safety population ($N = 73$) received six doses of PDC*lung01 [6 (100%), 10 (83%), 6 (86%), and 42 (88%) in cohorts A1, A2, B1, and B2, respectively], with a median treatment duration of 36 days in all cohorts. Overall, 71 (97%) patients experienced at least one TEAE, including 62 (85%) reporting at least one vaccine-related

Table 1. Demographic characteristics of enrolled patients

	Cohort A1 (*N* = 6)	Cohort A2 (*N* = 12)	Cohort B1 (*N* = 7)	Cohort B2 (*N* = 48)
Gender (male), *n* (%)	5 (83)	10 (83)	4 (57)	27 (56)
Age (years), median (range)	64.0 (40-71)	65.5 (50-71)	64.0 (39-78)	68.5 (50-83)
Ethnicity, *n* (%)				
Caucasian	4 (67)	8 (67)	6 (86)	47 (98)
Asian	0 (0)	0 (0)	1 (14)	0 (0)
Missing	2 (33)	4 (33)	0 (0)	1 (2)
Smoking status, *n* (%)				
Current	0 (0)	1 (8)	1 (14)	12 (25)
Past	6 (100)	11 (92)	5 (71)	34 (71)
Never	0 (0)	0 (0)	1 (14)	2 (4)
Performance status, *n* (%)				
0	3 (50)	7 (58)	3 (43)	13 (27)
1	3 (50)	5 (42)	4 (57)	35 (73)
PD-L1 expression (%), median (range)	NA	NA	80 (50-100)	70 (50-100)
Presence of CNS metastases, *n* (%)	0	0	2 (29)	12 (25)
Stage, *n* (%)				
IIA	—	2 (17%)	NA	NA
IIB	3 (50)	6 (50.0)	NA	NA
IIIA	3 (50)	4 (33)	NA	NA
IVA	NA	NA	3 (43)	19 (40)
IVB	NA	NA	4 (57)	29 (60)
Histopathology subtype, *n* (%)				
Squamous-cell carcinoma	1 (17)	5 (42)	2 (29)	10 (21)
Adenocarcinoma	5 (83)	7 (58)	3 (43)	36 (75)
Other[a]	0	0	2 (29)	2 (29)

CNS, central nervous system; *N*, number of patients in each cohort; *n* (%), number (percentage) of patients in a given category; NA, not available; PD-L1, programmed death-ligand 1.
[a]B1: pleomorphic and large cells not otherwise specified, B2: not otherwise specified for both.

TEAE, mostly of mild-to-moderate severity. Four patients reported at least one TEAE leading to treatment discontinuation: one (14%) in cohort B1 and three (6%) in cohort B2 (Table 2). The most common vaccine-related TEAEs were general disorders and administration-site conditions (mostly fatigue, fever, injection-site pain, and reaction), reported in 5 (83%) patients in cohort A1, 7 (58%) in cohort A2, 4 (57%) in cohort B1, and 26 (54%) in cohort B2.

Nineteen (26%) patients reported at least one SAE (Table 2). SAEs considered related/possibly related to study intervention were reported in four patients: one (14%) in cohort B1 [immune-mediated encephalopathy (possibly related)] and three (6%) in cohort B2 [fever (possibly related), anaphylactic reaction, and infusion-related reaction (both related)]. None of the 24 (33%) deaths reported in the safety population were considered related to study intervention. Three (6%) patients in cohort B2 experienced one non-Investigational Medicinal Product related fatal AE, including dyspnea, immune-mediated lung disease, and arrhythmia.

No anti-nuclear antibody was detected after vaccination, indicating that PDC*lung01 injections did not trigger autoimmune disorders. No trends or abnormalities were observed in the vital sign parameters during treatment (up to 4 h after administration) compared with the pre-vaccination period. In the safety population, 19 patients

Table 2. Summary of safety results in all evaluated cohorts (safety population)

	Cohort A1 (*N* = 6)	Cohort A2 (*N* = 12)	Cohort B1 (*N* = 7)	Cohort B2 (*N* = 48)
DLT, *n* (%)	**0**	**0**	**0**	**1 (2)**
≥1 TEAE, *n* (%)	5 (83)	12 (100)	7 (100)	47 (98)
≥1 related TEAE	5 (83)	11 (92)	6 (86)	40 (83)
≥1 TEAE leading to treatment discontinuation	0 (0)	0 (0)	1 (14)	3 (6)
≥1 TEAE leading to dose delay	0 (0)	1 (8)	0 (0)	9 (19)
≥1 SAE, *n* (%)	1 (17)	1 (8)	3 (43)	14 (29)
≥1 related SAE	0 (0)	0 (0)	1 (14)	3 (6)
≥1 grade 3 or higher AE, *n* (%)	0 (0)	1 (8)	3 (43)	15 (31)
≥1 related grade 3 or higher AE	0 (0)	0 (0)	1 (14)	3 (6)
≥1 fatal AE (all not related), *n* (%)	0 (0)	0 (0)	0 (0)	3 (6)
Related TEAE >15% of patients, *n* (%)				
Fatigue	1 (17)	1 (8)	3 (43)	9 (19)
Pyrexia	1 (17)	1 (8)	1 (14)	10 (21)
Positive anti-HLA antibodies at V8	1 (17)	10 (83)	0	19 (37)

AE, adverse event; DLT, dose-limiting toxicity; HLA, human leukocyte antigen; *N*, number of patients in each cohort; *n* (%), number (percentage) of patients in a given category; SAE, serious AE; TEAE, treatment-emergent AE; V, visit.

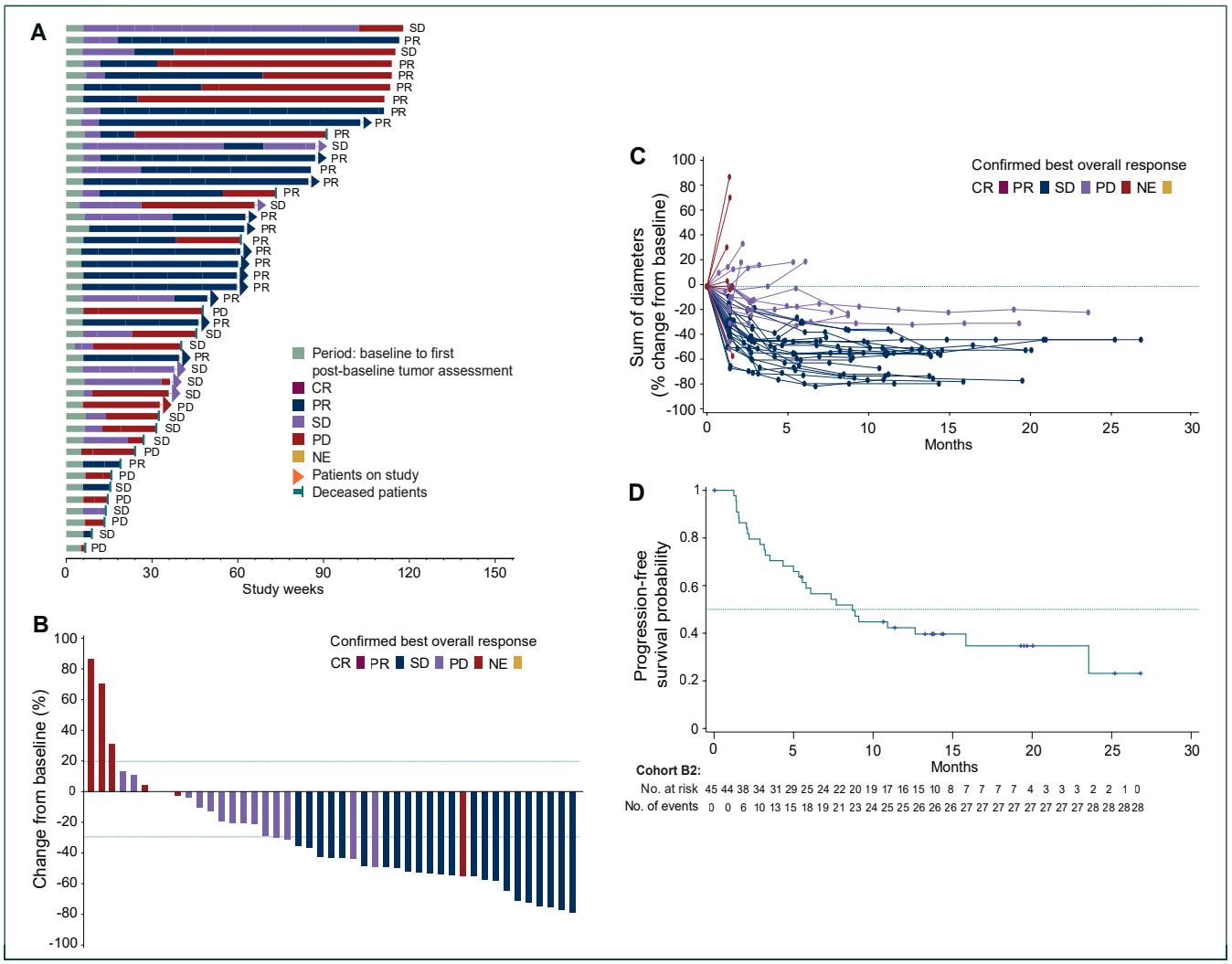

Figure 2. Clinical activity in the per-protocol population of cohort B2. (A) Swimmer plot presenting individual objective responses. (B) Waterfall plot presenting the best changes in target lesions. (C) Spider plot illustrates changes in target lesions over time. (D) Kaplan–Meier estimating the progression-free survival in cohort B2. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

were tested positive for anti-HLA antibodies at V8: 1 (17%), 10 (83%), and 19 (40%) in cohorts A1, A2, and B2, respectively (Table 2). These allogeneic humoral immune responses were not accompanied by any specific AEs.

Efficacy/clinical activity

In the B2 PP population ($N = 45$), the median follow-up time was 20 months (95% CI 14-26 months). In cohort B2, the confirmed ORR was 51% (80% CI 41% to 62%), excluding the null hypothesis defined in the statistical analysis plan (detailed in the 'Patients and methods' section). All 23 responders achieved a partial response (PR), 15 patients (33%) had stable disease (SD), and 7 (16%) had progressive disease (PD) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105844). Individual objective responses and BORs are shown in Figure 2A-C. The estimated 9mPFS in cohort B2 was 47% (80% CI 37% to 57%), and the median PFS was 9 months (95% CI 5.0-23.6 months) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105844, Figure 2D). Of the 45 patients of the PP population of cohort B2, 22 (49%; 80% CI 38% to 59%) were disease progression free at 9 months.

In cohort B1, four (67%) patients had PR, one (17%) had SD, and one (17%) presented with PD, leading to a confirmed ORR of 67% (80% CI 33% to 91%) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105844). Individual objective responses and BORs in cohort B1 are represented in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105844. The estimated 9mPFS was 67% (80% CI 36% to 85%); the median PFS was not reached throughout the study period (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105844).

Median DOR (months) was not reached in both cohorts (ranges, B1: 12-not reached; B2: 8-not reached). Among confirmed responders, one (25%) DOR event was recorded in cohort B1 and nine (39%) in cohort B2 (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2025.105844). In cohort B2, median time to response was 2 months (range 1.2-8.7 months) (Supplementary

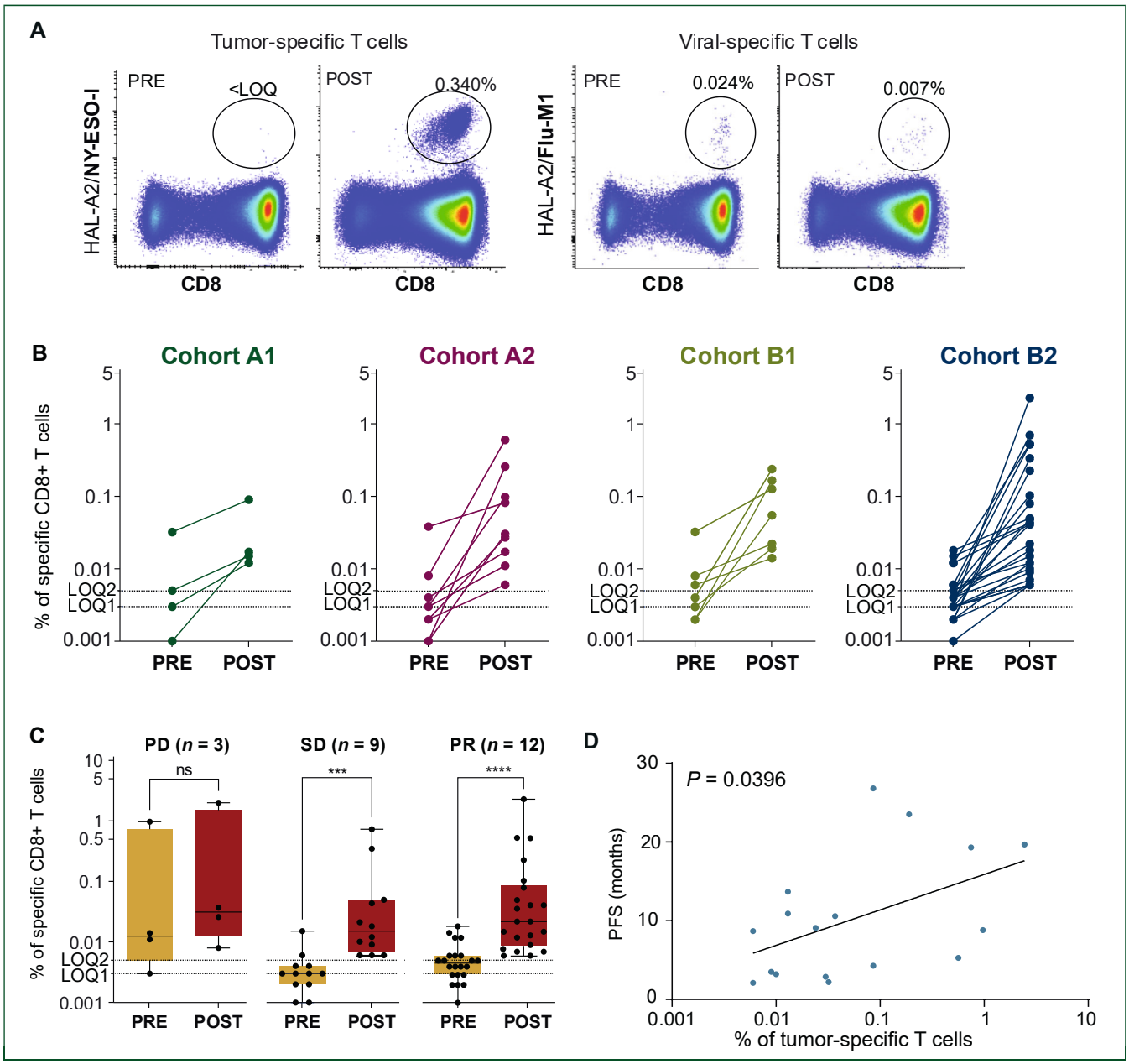

Figure 3. PDC*lung01-induced immune response. (A) Representative expansion of antigen-specific T cells (ASTCs) against NY-ESO-1 and Flu-M1 peptides in a patient from cohort B2 before (PRE) or after (POST) six administrations of PDC*lung01. (B) Frequencies of antitumor ASTCs PRE and POST injections of the PDC*lung01 vaccine in each cohort. Each line represents one patient. (C) Frequencies of antitumor ASTCs in patients of cohort B2 with progressive disease (PD), stable disease (SD), or partial response (PR). (D) Correlation between progression-free survival (PFS) duration and the cumulative frequencies of antitumor ASTCs in patients of cohort B2 having an SD or PR in the immunogenicity population ($P = 0.0396$, non-parametric Spearman test). LOQ1 (0.003%) is the LOQ for MAGE-A4-, NY-ESO-I-, Multi-MAGE-, MUC1-, EBV-, and Flu-specific T cells and LOQ2 (0.005%) is the LOQ of MAGE-A3-, Survivin-, and Melan-A-specific T cells.
ns: $P > 0.05$; ***$P < 0.001$; ****$P < 0.0001$, Wilcoxon non-parametric test. LOQ: limit of quantification; *n*, number of patients in each category.

Table S3 and Figure S5, available at https://doi.org/10.1016/j.esmoop.2025.105844), TTP estimate at 9 months was 53% (80% CI 42% to 62%), and the median TTP was 11 months (Supplementary Table S3 and Figure S6, available at https://doi.org/10.1016/j.esmoop.2025.105844). DCR was 67% (80% CI 33% to 91%) in cohort B1 and 76% (80% CI 65% to 84%) in cohort B2 (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105844). OS analysis is still immature; median was not reached as 60% patients were alive at the study cut-off date, but OS estimate at 9 months in cohort B2 was 73% (80% CI 64% to 81%) (Supplementary Table S3 and Figure S7, available at https://doi.org/10.1016/j.esmoop.2025.105844).

Immunogenicity

In the immunogenicity population ($N = 66$), the frequency of antitumor ASTCs at baseline was not detectable for most patients [equal or lower than the limit of quantification (LOQ) in 67% and 57% of samples from cohorts A and B, respectively]. In a large proportion of patients, ASTC expansions were observed after vaccination in contrast to

control viral-specific T cells (Figure 3A and B). Across all cohorts, targeted ASTC expansions were observed in 3 (50%), 7 (64%), 4 (67%), and 24 patients (56%) in cohorts A1, A2, B1, and B2, respectively. ASTC responses were detected against all lung cancer antigens except for MAGE-A4, for which the frequency remained below the LOQ at all time points. Most expanded T cells displayed an effector memory phenotype suggesting their cytotoxic potential (data not shown).

Following expansion, the frequencies of antitumor ASTCs in individual patients ranged from 0.001% to 0.09% in cohort A1, 0.001% to 0.598% in cohort A2, 0.001% to 0.233% in cohort B1, and 0.001% to 2.321% in cohort B2 (Figure 3B). The mean fold changes of cell expansion versus baseline were 3, 15, 20, and 27, for cohorts A1, A2, B1, and B2, respectively. Statistically significant increases in the frequency of antitumor ASTCs were observed following PDC*lung01 vaccination versus baseline in patients with PR ($P < 0.0001$) or SD ($P < 0.001$), but not in those with PD (Figure 3C). In patients with PR or SD, a statistically significant positive correlation ($P = 0.04$) was found between PFS duration and the immune response intensity assessed by the antitumor ASTC cumulative frequencies (Figure 3D).

DISCUSSION

In this study, the new allogeneic PDC*line-based vaccine, PDC*lung01, was used as a single agent in the adjuvant setting or in combination with anti-PD-1 in patients with metastatic NSCLC. To our knowledge, this is the first time that clinical results are presented on the efficacy of a therapeutic cell vaccine in combination with first-line pembrolizumab in untreated metastatic NSCLC. The vaccine was well tolerated by the patients either as a single agent or in combination with anti-PD-1 with most AEs of mild-to-moderate severity and provided meaningful clinical benefit in patients with metastatic NSCLC. Antitumor ASTC responses were observed in a large proportion of vaccinees, with a dose effect and a combined effect with anti-PD-1 on the expansion of ASTCs.

PD-1 and PD-L1 inhibitors have become a standard of care for the first-line treatment of advanced NSCLC without oncogene addiction and PD-L1 $\geq$50%.[24] However, a significant proportion of those patients still do not benefit from ICIs.[7,25,26]

Here, we aimed to determine first the occurrence of DLTs when PDC*lung01 was used at low and high dose in monotherapy or in combination with anti-PD-1. Only one patient in cohort B2 had a high-grade anaphylactic reaction within 24 h after vaccination. The C3d elevation and the rapid recovery after anti-allergic medications were strongly indicative of a severe allergic reaction. An allergic reaction to an ingredient used to cryopreserve the cells could not be excluded, as reported previously for pharmaceutical-grade human serum albumin.[27]

Overall, our results show an acceptable safety profile of the PDC*lung01 vaccine when used in monotherapy, consistent with the phase I trial with the PDC*mel vaccine in patients with melanoma.[16] No major safety concerns were observed when the vaccine was used in combination with anti-PD-1 therapy either. This is in line with expectations for DC-based cancer vaccines, which rarely cause high-grade systemic adverse events.[15,28,29] This is in contrast to other anticancer immunotherapy combination therapies, such as the combination of nivolumab plus ipilimumab, for which the occurrence of grade 3 or higher AEs was 33%.[30] In our study, only three (6%) patients who received the high-dose formulation of PDC*lung01 combined with pembrolizumab discontinued the treatment due to AEs. Higher treatment discontinuation rates due to treatment-related AEs were observed with ICI combination treatment or even pembrolizumab monotherapy (18%[30] and 9%,[7] respectively). SAEs related/potentially related to the study vaccine were only reported in patients who received combination therapy, of which only two, an infusion-related reaction and the aforementioned anaphylactic reaction, were considered vaccine related (the latter leading to treatment withdrawal). No safety issues were associated with the generation of anti-HLA antibodies.

Clinical activity of PDC*lung01 vaccine was assessed in patients with stage IV NSCLC who received high-dose PDC*lung01 in combination with pembrolizumab. Compared with the patients with PD-L1 $\geq$50% treated with pembrolizumab alone in the KEYNOTE-042 trial,[7] our results, even on only 45 patients, showed an improved ORR (51% versus 39%). Median PFS was longer than that in the KEYNOTE-042 publication in 2019[7] (8.5 versus 7.1 months) with a median follow-up of 20 versus 13 months, respectively, and even longer than the one published in 2022 (8.5 versus 6.5 months).[6] Efficacy analyses in cohort B1 (low-dose) also showed encouraging activity for PFS, ORR, and other clinical parameters, despite the very limited number of patients ($N = 6$).

Overall, our results suggest that PDC*lung01/pembrolizumab combination may provide a clinically meaningful antitumoral response in a population with untreated stage IV NSCLC.

In addition, the clinical results of patients treated with the high-dose monotherapy vaccine (cohort A2) show encouraging signs in terms of disease-free survival events in line with the immune response (Supplementary Figure S8, available at https://doi.org/10.1016/j.esmoop.2025.105844).

Given their potential to generate/amplify antitumor responses through activation or priming of naïve ASTCs by antigen-presenting cells, therapeutic cancer vaccines can increase the effectiveness of ICIs.[11] Recently, neoantigen-based cancer vaccines have been developed for NSCLC patients, demonstrating the induction of neoantigen-specific T cells in combination with an ICI[31] or in monotherapy.[28] In a phase I trial, the neoantigen-based cancer vaccine NEO-PV-01 in combination with nivolumab in maintenance led to an ORR of 39% and median PFS of 9 months in 18 patients with NSCLC.[31] In another study of a therapeutic vaccine composed of two peptides highly selected to induce CD4+ T-helper-1 response against

telomerase, disease control and improved OS were observed in immune responders with refractory metastatic NSCLC.[14] In the study assessing the neoantigen-targeted autologous DC-based vaccine (Neo-mDCs), a durable neoantigen-specific T-cell response was observed in patients with surgically resected NSCLC.[28] This approach is similar to the PDC*lung01 vaccine, bypassing the recruitment or targeting of *in vivo* antigen-presenting DCs needed to properly prime and activate naïve antitumor ASTCs in lymph nodes.[8] Finally, in a phase III study with a therapeutic vaccine containing synthetic peptides from five tumor-associated antigens, a significant OS improvement was observed in HLA-A*02:01-positive patients with advanced NSCLC and secondary ICI resistance.[32,33]

By contrast to all other studies, the PDC*lung01 vaccine candidate's efficacy was assessed directly in untreated metastatic NSCLC in combination with pembrolizumab. PDC*lung01 was able to efficiently prime and expand antitumor ASTCs, with frequencies up to 2% among the circulating CD8+ T-cell population (cohort B2). Furthermore, PDC*lung01 was biologically active in a substantial proportion of patients, as shown by targeted ASTC expansions observed in 50%-67% of patients across cohorts. The extent of the immune response was dose dependent and synergistic with pembrolizumab, confirming previous *in vitro* results.[12,16] These findings support the use of high doses of PDC*lung01 in combination with ICIs to enhance the induction of functional antitumor response in patients with NSCLC.

In immune responders, we observed a statistically significant positive correlation between the PFS duration and the cumulative frequencies of antitumor ASTCs. These results suggest a relationship between the induction of an immune response and the clinical activity of PDC*lung01. However, some patients did not achieve any detectable immune response, presumably linked to the limits of immunological assays or indicative of real lack of immune response. The latter may have several causes including absence of targeted tumor antigen expression or remaining treatment resistance. Immunotherapy resistance can also be linked to the immunosuppressive tumor microenvironment that includes infiltration of regulatory T cells, myeloid-derived suppressor cells, and macrophages, as well as alternative expression of immune checkpoints.[9] Altogether, this could explain the lack of response even in patients with PD-L1 $\geq$50%, for whom stimulation of antitumor ASTCs would not bring any benefit even in combination with anti-PD-1. Other combinations should be considered for these patients.

In addition, the PDC*lung01 vaccine candidate has the significant advantage to be ready to use compared with the time-consuming preparation of vaccines based on autologous DCs, and it can be rapidly available for many patients, contrary to neoantigen-based vaccines. Furthermore, the vaccine homogeneity ensures consistent clinical results.

The limitations of this study include the lack of randomized design, the small number of patients, and a limited follow-up for OS assessment in cohort B2. Furthermore, the limited sensitivity of the immunological assay and the immune response kinetics did not allow appraising the full immunostimulatory potential of the vaccine. Finally, the study population was restricted to HLA-A*02:01-positive patients, but the PDC*line could be engineered to add other HLA molecules to enlarge the target population, as demonstrated in a previous study.[20]

Conclusion

Overall, this study indicates that PDC*lung01 has a manageable safety profile and could provide promising clinical benefit for patients with metastatic NSCLC in combination with anti-PD-1. This study also demonstrates the immunological activity of the PDC*lung01 vaccine despite the limitations of the assay and the sample size. This immunological response was associated with clinical benefit in patients without primary or acquired treatment resistance, and the intensity of the immune response was associated with PFS duration. This suggests that additional (consolidation/maintenance) injections might increase immune response and, thus, clinical activity. In this context, a randomized clinical trial with additional injections of the PDC*lung product in patients with untreated metastatic NSCLC is planned.

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