PDC-LUNG-101: Primary analysis of safety, efficacy and immunogenicity of the therapeutic cancer vaccine PDC*lung01 with or without pembrolizumab in NSCLC: A multicenter phase I/II study

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BACKGROUND

Cancer vaccines may synergize with immune checkpoint inhibitors. PDC*lung01 (IMP) is based on an irradiated plasmacytoid dendritic cell line loaded with 6 HLA-A*02:01-restricted NSCLC peptides (NY-ESO-1, MAGE-A3, MAGE-A4, Multi-MAGE-A, MUC1, Survivin) and control peptide Melan-A, able to prime and expand antigen-specific CD8+ T-cells in vitro and in vivo. It was shown to expand antitumor CD8+ T-cells from patient's PBMC with melanoma or NSCLC and to be synergistic with anti-PD-1 (Pembrolizumab®). (Charles 2020, Hannani 2023, Plumas 2022).

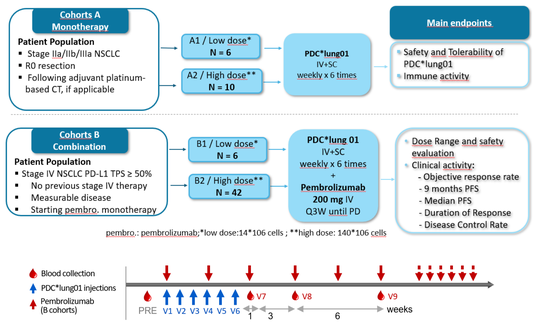
OBJECTIVES

- To evaluate the safety of PDC*lung01 (IMP) in monotherapy or in combination with pembrolizumab
- To evaluate the efficacy of PDC*lung01 in combination with pembrolizumab
- To assess immune response

METHODS

Study design

- Open-label, multicentre, dose-escalation, phase I/II study with PDC*lung01 administered weekly by subcutaneous and intravenous route for 6 consecutive doses (Q1W).
- HLA-A*02:01 positive patients were enrolled in 4 cohorts at two dose levels



Statistical analysis

- Primary endpoint: DLT in all cohorts and safety profile
- Secondary/exploratory endpoints: efficacy in cohorts B2/B1 and immunological responses
- For cohorts B, the per protocol (PP) population included evaluable patients defined by measurable disease confirmed by RECIST V.1.1, received at least 5 PDC*lung01 vaccine, undergone at least one post-baseline radiographic tumor assessment.
- Predefined Sargent 2 design setting the type I error at one sided 0.1 level and the type II error level at 0.3 (power of 70%) with a sample size of 42 evaluable participants considered as the design per protocol (DPP) population
- Target benefit considered of medical significance with detection of ORR absolute increase of 15% (achieving ORR of 54%)
- Study considered as positive when lower limit of the CI of the ORR rate excluded the null hypothesis (39% ORR for the historical control) (De Castro 2022)

RESULTS

- At the data cut off (18Jul2024), treatment was completed in all cohorts.
- 73 patients were enrolled: 6 in cohort A1, 12 in cohort A2, 7 in cohort B1 and 48 in cohort B2
- Median study follow-up was 20.1 months (mo) (95%CI 14.3-26.1).

Demographics and baseline characteristics

Characteristics participants	A1 cohort N = 6	A2 cohort N = 12	B1 cohort N = 7	B2 Cohort N = 48
Male	5 (83.3)	10 (83.3)	4 (57.1)	27 (56%)
Age, median (range), y	64.0 (40.0-71.0)	65.5 (50.0-71.0)	64.0 (39.0-78.0)	69 (50-83)
Smoking status				
Current	0	1 (8.3)	1 (14.3)	12 (25%)
Past	6 (100)	11 (91.7)	5 (71.4)	34 (71%)
Non-smoker	0	0	1 (14.3)	2 (4%)
ECOG PS				
0	3 (50.0)	7 (58.3)	3 (42.9)	13 (27%)
1	3 (50.0)	5 (41.7)	4 (57.1)	35 (73%)
PD-L1 expression ≥50%, median (range)	NA	NA	80.0 (50.0-100)	70 (50-100)
Tumor stage at current diagnosis				
IIA	0	2 (16.7)	0	0
IIB	3 (50.0)	6 (50.0)	0	0
IIIA	3 (50.0)	4 (33.3)	0	0
IVA	0	0	3 (43%)	19 (40%)
IVB	0	0	4 (57%)	29 (60%)
Histopathology subtype				
Squamous cell carcinoma	1 (16.7)	5 (41.7)	2 (29)	10 (21%)
Adenocarcinoma	5 (83.3)	7 (58.3)	3 (43)	36 (75%)
Other	0	0	2 (29)	2 (4%)
Brain metastases (baseline) Yes	0	0	2 (28.6)	12 (25%)

Safety

Within the safety population (n=73), treatment-related adverse events (AEs) were mostly grades 1-2 with only one grade 4 (anaphylactic reaction/DLT). No DLT was observed in cohorts A and B1. 19 pts (26%) experienced a serious AE, 4 (5.5%) considered related to the IMP.

Overview adverse events/SAEs and DLT	Cohort B1 (N=7)	Cohort B2 (N=48)
DLT, n (%)	**0**	**1 (2.2)**
≥1 TEAE, n (%)	7 (100)	47 (97.9)
≥1 related TEAE	6 (85.7)	40 (83.3)
≥1 TEAE leading to tt discontinuation	1 (14.3)	3 (6.3)
≥1 TEAE leading to dose delay	0 (0.0)	9 (18.8)
≥1 SAE, n (%)	3 (42.9)	14 (29.2)
≥1 related SAE	1 (14.3)	3 (6.3)
≥1 grade 3 or higher AE, n (%)	3 (42.9)	15 (31.3)
≥1 related grade 3 or higher AE	1 (14.3)	3 (6.3)*
≥1 fatal AE (all not related), n (%)	0 (0.0)	3 (6.3)
Related TEAE > 15% of participants, n (%)		
Fatigue	3 (42.9)	9 (18.8)
Pyrexia	1 (14.3)	10 (20.8)
Positive anti-HLA antibodies at V8	0	19 (36.6)

References: Charles OncoImmunology 2020; Hannini, Int J Mol Science 2023; Plumas, COO 2022; De Castro, 2022, Keynote-042 (PDL-1>50%, n=299)

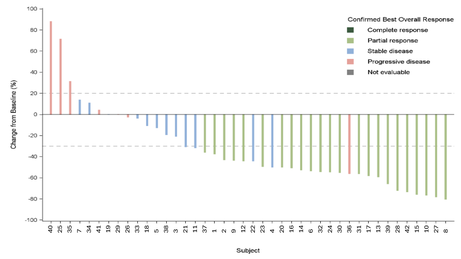
Efficacy

The confirmed objective response rate (ORR) in cohort B2 DPP population (n=42) was 55%, reaching the predefined clinical study objective and in line with the preliminary results observed in cohort B1 in 6 pts (ORR: 67%). The median progression-free survival (PFS) in cohort B2 was 8.87 months. Overall survival of cohorts B is immature but 63% of pts are still alive at the cut-off date.

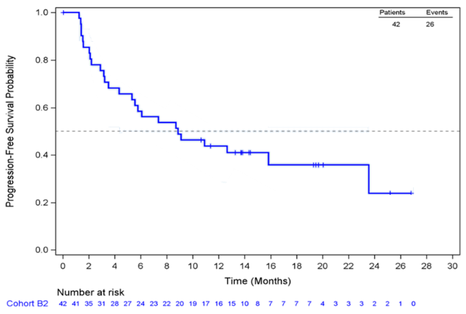
Efficacy in B1 and B2 cohorts

Clinical endpoints	B1 cohort PP population N=6	B2 cohort DPP Population N=42
Follow-up, median	26.3 95% CI [26.1-NR]	19.5 95% CI [13.8-25.6]
Confirmed ORR, n (%)	4 (67) 80% CI [33.3-90.7]	23 (55) 80% CI [43.7-65.4]
DoR median, mo	Not reached 95% CI [12.2-NR]	Not reached 95% CI [7.7-NR]
PFS, median, mo	Not reached 95% CI [2.1-NR]	8.87 95% CI [4.3-23.6]

Best change in target lesion for 42 evaluable patients in DPP population



KM PFS in 42 evaluable patients in DPP population

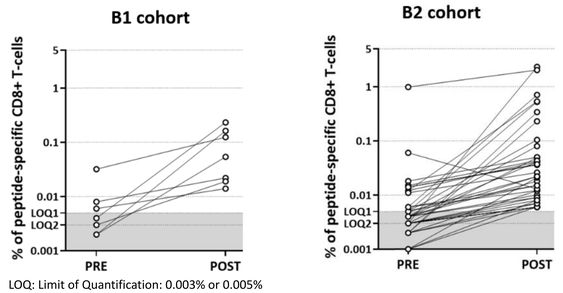


Abbreviation: DLT: dose-limiting toxicities; DPP: design per protocol; DoR duration of response; ORR: objective response rate; PFS: progression free survival.

Immunological results

Antigen-specific CD8+ T-cell responses were observed in 50% and 64% of cases with vaccine alone (cohorts A1, A2), and in 67% and 56% in combination with pembrolizumab (cohorts B1, B2) with a dose effect and synergy with anti-PD-1 in the immune response intensity. There was a significant positive correlation between the intensity of the immune response and the PFS (months) in cohort B2 (p=0.0396).

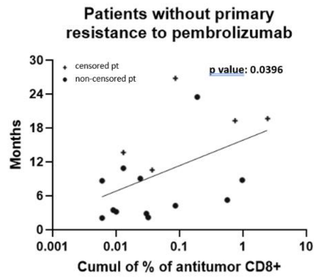
Expansion of circulating peptide-specific anti-tumor CD8+ T-cells without any prior in vitro stimulation evaluated by flow cytometry in B1 and B2 cohorts. PRE and POST % are indicated for each expansion.



LOQ: Limit of Quantification: 0.003% or 0.005%

Relationship between PFS and expansion of anti-tumor CD8+ T- cells

Spearman correlation r=0.571, nXY pairs=17



CONCLUSIONS

In cohort B2, the confirmed ORR of 55% and the mPFS of 8.87 months showed an increase of 16% and an improvement of 2.4 months, respectively, compared to the Keynote-042 PD-L1 ≥50% population.
PDC*lung01 combined with pembrolizumab provides meaningful clinical activity in untreated PD-L1 ≥50% stage IV NSCLC, with a mild safety profile, and a confirmed correlation between the immune response intensity and the PFS.

Study information/disclosures
Protocol Number: PDC-LUNG-101, Clinical Trial Identification: NCT03970746, Status: active, not recruiting;
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