

P2.388: PALACE, cemiplimab trial according to ctDNA levels; a phase II clinical trial in progress

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BACKGROUND

Although first-line (1L) immunotherapy is the standard treatment for advanced non-small cell lung cancer (NSCLC) with high PD-L1 expression, many patients experience early disease progression. Therefore, there is an unmet need for additional biomarkers to identify patients who may benefit from a different treatment early.

In this context, circulating tumor DNA (ctDNA) could be a promising biomarker that may enable earlier assessment of treatment response than conventional imaging and support adaptive therapeutic strategies.

The PALACE trial aims to assess a ctDNA-guided treatment strategy in patients with advanced NSCLC and PD-L1 $\geq$ 50% receiving 1L cemiplimab.

OBJECTIVES

Primary endpoint: To determine whether treatment decision-making based on ctDNA analysis improves 24-month overall survival (OS) in the intention-to-treat (ITT) population.

Secondary endpoints: Evaluate duration of response (DoR) and overall response rate (ORR), assess progression-free survival (PFS) at 12, 24, 36, and 48 months, characterize sites of first failure, and assess the toxicity profile of the treatment strategy.

Exploratory endpoints: Association of baseline ctDNA, early ctDNA dynamics (6 weeks), and ctDNA clearance with clinical outcomes, as well as characterization of resistance alterations at progression.

KEY ELIGIBILITY CRITERIA

Inclusion criteria:

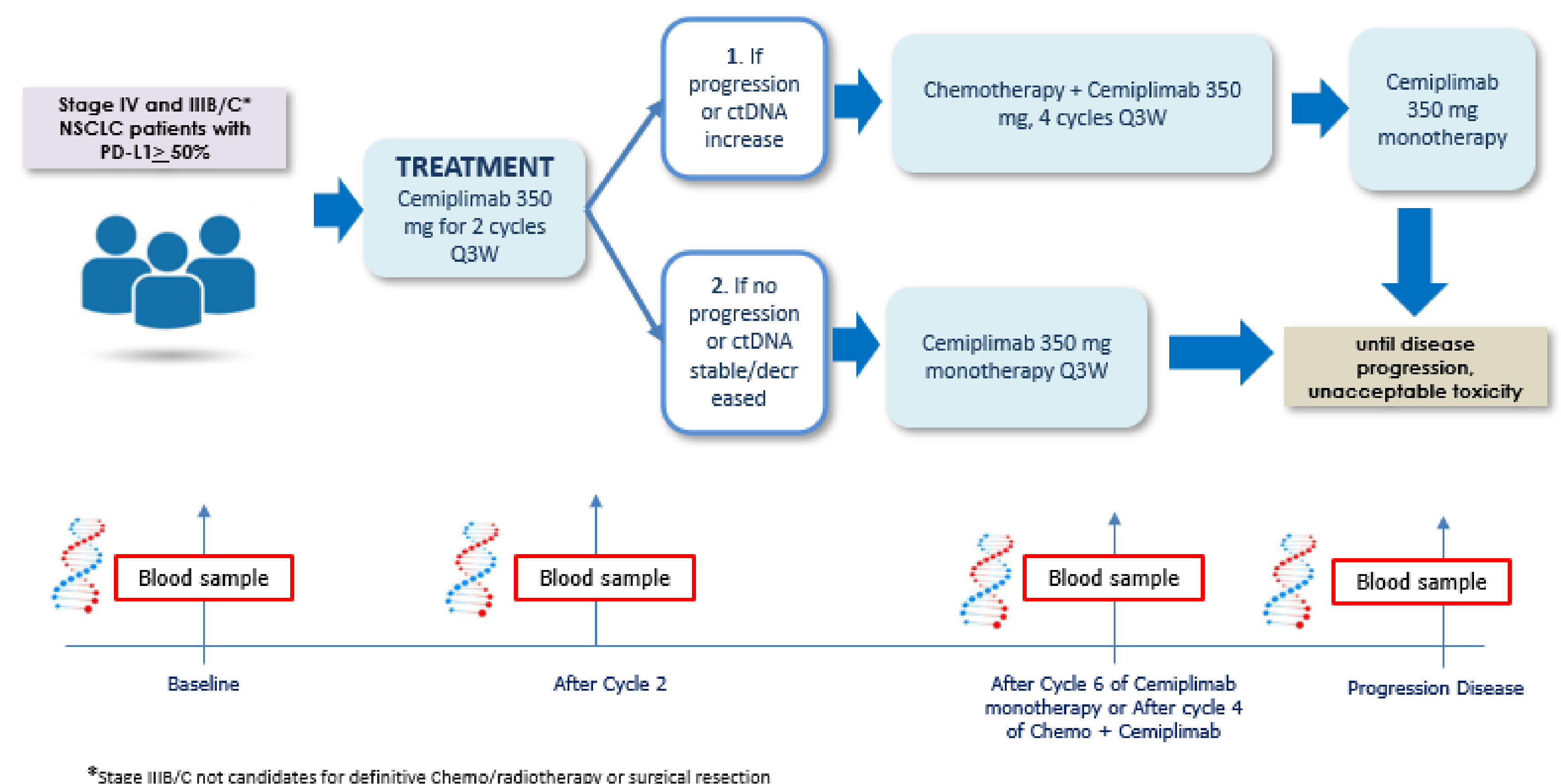
- Adults with histologically confirmed NSCLC.
- Stage IV or IIIB/C disease not eligible for definitive chemoradiotherapy or surgical resection.
- PD-L1 tumor proportion score (TPS) $\geq$ 50%.
- ECOG performance status 0-1 and at least one measurable lesion according to RECIST v1.1.
- No prior systemic treatment for advanced disease.

Exclusion criteria:

- Presence of actionable oncogenic driver alterations (EGFR, ALK or ROS1).
- Active or symptomatic untreated brain metastases.
- Active autoimmune disease or uncontrolled infections.
- Interstitial lung disease or active non-infectious pneumonitis.
- Significant comorbidities precluding study treatment.

TRIAL DESIGN AND PROCEDURES

PALACE is an ongoing, open-label, non-randomised, multicentre, phase II clinical trial (EuCT Number: 2024-518812-38-00).



A total of **63 patients** with advanced NSCLC, PD-L1 $\geq$ 50%, and no actionable oncogenic driver alterations **will be enrolled**.

At baseline, all patients will undergo thoracic CT scan, brain MRI or CT scan, and blood collection for ctDNA analysis. Subsequent radiological and ctDNA assessments will be performed according to protocol-defined schedules.

All patients will receive two induction cycles of **cemiplimab** 350 mg intravenously every 3 weeks (Q3W).

After cycle 2, **treatment adaptation** will be guided by both radiological assessment (RECIST v1.1) and ctDNA dynamics.

Patients with disease progression and/or increased ctDNA levels will receive cemiplimab plus platinum-based chemotherapy* for up to four combination cycles. Patients deriving clinical benefit from combination treatment will continue cemiplimab maintenance.

Patients without progression and with stable or decreased ctDNA levels will continue cemiplimab monotherapy.

Treatment in both groups will continue until disease progression, unacceptable toxicity, loss of clinical benefit, or a maximum of 2 years. After treatment discontinuation, patients will enter a 2-year follow-up period.

**Chemotherapy will be selected according to the investigator's choice: carboplatin-pemetrexed is recommended for non-squamous NSCLC and carboplatin-taxane for squamous NSCLC.*

STATISTICAL CONSIDERATIONS

Sample size was calculated using a one-arm survival design based on the Kaplan-Meier estimation, assuming an exponential survival distribution and uniform patient accrual.

The study is powered to detect an improvement in 24-month overall survival from 40% under the null hypothesis to 55% under the alternative hypothesis, with a one-sided α of 0.05 and 80% power. Based on these assumptions, 63 patients will be enrolled.

Efficacy analyses will be performed in the ITT population. Time-to-event endpoints will be estimated using the Kaplan-Meier method, with subgroup comparisons performed using the log-rank test and multivariable analyses using Cox proportional hazards models. Logistic regression analyses will be used to evaluate factors associated with response and toxicity.

RECRUITMENT

- Approval by health authorities received on 26 March 2025.
- Participating sites: 19
- Total patients requested: 63
- Total patients included: 53

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