# PECATI: A Multicentric, Open-Label, Single-Arm Phase II Study to Evaluate the Efficacy and Safety of Pembrolizumab and Lenvatinib in Pretreated B3-Thymoma and Thymic Carcinoma Patients

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## Abstract

Thymic epithelial tumors are rare neoplastic proliferations of thymic epithelial cells. The aggressiveness of these malignancies increases as higher is the histologic subtype, being thymic carcinoma the most aggressive subtype, with a greater tendency to metastatic spread. In metastatic setting, there is no standard treatment after progression on platinum-based chemotherapy. In this scenario, monotherapy treatment either with lenvatinib, a multi-tyrosine kinase inhibitor with antiangiogenic properties, or pembrolizumab, an immune-checkpoint inhibitor, has reported clinical activity. Potential combination of both agents may have synergistic activity as reported in other cancer types. PECATI trial is a single-arm, investigator-initiated phase II study aiming to assess the activity and safety of the combination of lenvatinib and pembrolizumab in 43 patients with advanced B3-thymoma or thymic carcinoma who progressed on or after at least one previous line of platinum-based chemotherapy. The primary endpoint of the trial is 5-month progression-free survival rate and the secondary endpoints include overall response rate, duration of response, and overall survival.

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## Introduction

Thymic epithelial tumors (TETs) are rare neoplastic proliferations of thymic epithelial cells, which are classified according to the World Health Organization as thymomas A, AB, B1, B2, B3, and thymic carcinoma (TC).[1] The aggressiveness of these malignancies increases as higher is the histologic subtype, being TC the most aggressive subtype, with a greater tendency to metastatic spread. At baseline, the diagnostic of metastatic disease is more common in B3-thymoma and TC than in other TET subtypes.[2] Finally, autoimmune disorders (AID) may occur in up to one-third of patients with TETs, mainly in thymoma and being very uncommon in TC (<5%). Myasthenia gravis is the most common AID associated with TETs, although other AIDs have been reported.[3]

Although platinum-based chemotherapy is the accepted standard-of-care treatment in first-line setting,[4] standard second-line treatment is not yet defined, and different strategies have been tested (such as everolimus, pemetrexed, or etoposide),[5-7] which may impact in patients' outcome.[8] So far, no drugs are approved by the FDA or the EMA specifically for TET. Vascular endothelial growth factor signaling plays a crucial role in TC cell physiopathology as

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well as microvessel density, both correlated with invasiveness and advanced stage.[9] In 2 single-arm phase II trials, the multi-tyrosine kinase inhibitors with antiangiogenic properties sunitinib and lenvatinib have reported meaningful activity in previously treated patients with TC, achieving a response rate ranging from 26% to 38% and a median progression-free survival (PFS) of up to 9.3 months.[10,11] Both agents are accepted as potential treatment approaches in TCs with progression after at least one previous line of platinum-based chemotherapy. Recently, immune-checkpoint inhibitors (ICI) have also been tested in pretreated patients with TETs. Globally, pembrolizumab,[12-14] nivolumab,[15] and avelumab[16] have reported clinical activity in this population. Specifically, pembrolizumab in TCs has yielded a response rate of 22.5% with a median overall survival (OS) of 25.4 months, and up to 20% of patients are alive at 5 years after treatment initiation.[12,13] Although ICI may represent a new therapeutic approach in patients with TET, it is not yet a standard strategy. Indeed, the benefit must be balanced with risk of grade 3-4 immune-related adverse events, especially in patients with thymoma due to the association with AID.[12,14] Therefore, immune-strategy should be limited to patients with TC and B3-thymoma after ruling out AID for minimizing toxicity profile.

The angiogenic factors inhibit immune cells and induce immune suppression at multiple levels, but antiangiogenic agents may enhance the efficacy of ICI.[17] Therefore, the combination of ICI and antiangiogenics is an attractive and novel approach that may provide greater antitumor activity than either single-agent alone. Indeed the combination of pembrolizumab and lenvatinib has reported activity in other malignancies.[18,19] Therefore, based on these premises and that both drugs, lenvatinib and pembrolizumab, have reported meaningful clinical activity as monotherapy in TETs, we designed the PECATI trial with the aim to investigate the activity and safety of the combination of lenvatinib and pembrolizumab in patients with advanced B3-thymoma or TC who progressed on or after at least one previous line of platinum-based chemotherapy.

## Patients and Methods

### *Study Design*

PECATI (ClinicalTrials.gov identifier, NCT04710628) is an international, multicentric, open-label, single-arm, investigator-initiated phase II trial enrolling previously treated patients with metastatic B3-Thymoma and TC, regardless of programmed death-ligand 1 (PD-L1) expression. The main selection criteria are described in Table 1. The study design is summarized in Figure 1.

Eligible patients will receive lenvatinib (20 mg orally once daily) and pembrolizumab (200 mg intravenously on day 1 of each 21-day cycle). Study treatment will continue until clinical or radiological disease progression, unacceptable toxicity according to the treating physician or patient refusal. In case of withdrawal of any of the agents due to toxicity, continuation in monotherapy will be allowed as per investigator's criteria, and the maximum duration of treatment with pembrolizumab with or without lenvatinib will be 35 cycles (2 years).

### *Study Objectives*

The primary objective is to evaluate the efficacy of the combination in terms of 5-month PFS rate (according to the Response Evaluation Criteria In Solid Tumors version 1.1), which is defined as the proportion of patients with B3-thymoma and TC without disease progression or death due to any cause within the first 5 months after treatment initiation. Radiological tumor assessment will be performed at weeks 6 and 12, then every 9 weeks during the first 12 months, and every 12 weeks thereafter.

The secondary efficacy endpoints are to evaluate overall response rate, disease control rate, duration of response, and OS. Additional secondary endpoint includes safety and toxicity profile of the combination according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v.5.0).

Although PECATI study includes exploratory objectives, these will be performed outside the scope of current protocol. In this subsequent translational research, we aim to retrospectively evaluate:

- PD-L1 expression by immunohistochemistry (22C3 anti-PD-L1 monoclonal antibody assay) with the aim to define an optimal cut-off value;
- Blood tumor mutational burden by next-generation sequencing at baseline and at the time of disease progression or end of study;
- Genomic profile by next-generation sequencing through a liquid biopsy test at baseline and at the time of disease progression or end of study.

### *Statistical Analysis*

In the PECATI trial we plan to recruit a total of 43 patients in 15 months. The sample size assumed an arcsine square root transformed confidence intervals (CIs) based on Kaplan–Meier estimator. We hypothesize that excluding a 5-month PFS rate less than or equal to 50% (null hypothesis), while targeting an improvement of 5-month PFS rate greater than or equal to 68.6% (alternative hypothesis) would be an optimal approach to evaluate the clinical activity of pembrolizumab plus lenvatinib combination. The sample size of 43 patients is necessary to attain 80% power at nominal level of one-sided alpha of 0.05. The analysis will be performed with exponential maximum likelihood estimation test. Efficacy and safety data will be assessed in the full analysis set that included all patients who received at least one dose of the combination. The PFS, duration of response, and OS will be estimated with the Kaplan–Meier method. The time-to-event endpoints will be compared between patient characteristic with Cox regression models. Clopper-Pearson 95% CIs will be used to estimate the rates of patients with overall response and disease control. These efficacy endpoints will be compared between patient characteristic with logistic regression models. For secondary and subgroup analyses, we will use 2*P*values with $\alpha$ level of significance of .05 or less.

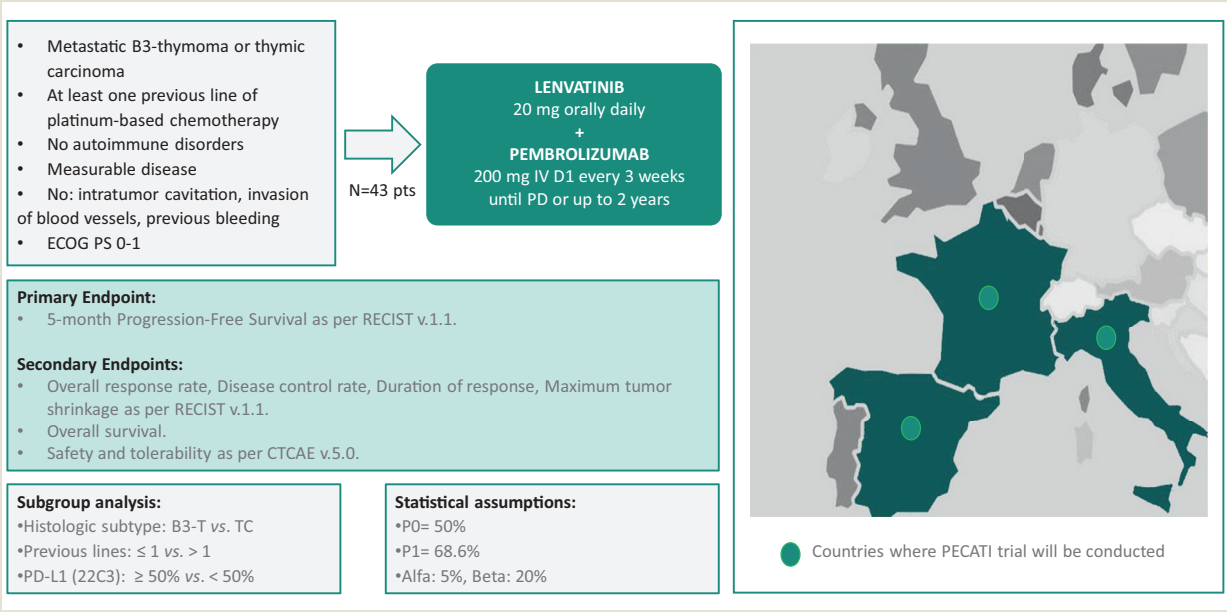
## Conclusion

The PECATI trial gives the opportunity to test the combination of lenvatinib plus pembrolizumab, two drugs showing promising efficacy as monotherapy in TETs, in previously treated advanced patients with B3-thymoma and TC. The PECATI trial will be

**Table 1** Main Selection Criteria

| Main inclusion Criteria | Main exclusion Criteria |
|---|---|
| • Histological diagnosis of metastatic/recurrent B3-thymoma or thymic carcinoma | • Previous therapy with immune-strategy or sunitinib (prior bevacizumab-based therapy is allowed) |
| • Radiological disease progression on or after at least one line of platinum-based chemotherapy | • Presence of untreated central nervous system metastases |
| • Presence of measurable disease according to the Response Evaluation Criteria In Solid Tumors (RECIST) version (v.)1.1 criteria | • Uncontrolled or poorly controlled hypertension despite standard medical therapy, significant cardiovascular impairment or fraction ejection < 50% |
| • Negative result for Myasthenia Gravis by acetylcholine receptor antibodies test | • Intratumor cavitation, direct invasion of main mediastinal blood vessels by the tumor or exist previous bleeding |
| • Age ≥18 years of age | • Active autoimmune disease |
| • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 | • Has an intestinal disease not allowing swallowing pills |
| • Availability of archived or fresh histological material | |

**Figure 1** PECATI study design.




conducted in 10 hospitals in 3 European countries (Spain, France, and Italy), giving access to innovative strategies to these patients and improving clinical research in this rare malignancy. Indeed, the results of PECATI trial may help to endorse the immune strategy in TET, which is being also tested in other ongoing clinical trials either as monotherapy (NCT03076554, NCT04321330, NCT04469725, NCT04417660, NCT03134118) or in combination (NCT03134118, NCT03463460, and CAVEATT trial).

## Disclosure

The authors have stated that they have no conflicts of interest.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2021.07.008.

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