



# An overview: ongoing systemic therapy trials in thymic epithelial tumors around the world—will anything “hit”?

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## Introduction

Thymic epithelial tumors are rare malignancies requiring multidisciplinary management. Systemic treatments are part of this global approach in both locally advanced cases—for which combined strategy is needed—and metastatic disease, using standard chemotherapy. Current systemic treatments are insufficient, and the prognosis of advanced disease remains poor. Treatments mostly derived from general oncologic research and we lack specific thymic tumors targeting drugs to develop precision medicine strategies.

Many thymic tumors systemic therapy trials are currently ongoing around the world, facing the difficulties of rare disease research and management: lack of biomarkers, lack of patients, difficulties in establishing good landmarks and wise endpoints... To be able to hit, those trials have to fit some prerequisites. The clinical needs have to be identified clearly. Trials have to be built with adequate endpoints, good selection of patients and integration of well-defined biomarkers.

Those criteria allow the selection of trials that will possibly ultimately hit in any situation in which systemic treatments are required in the management of thymic tumors. This concerns primary treatment—systemic treatment in association with local treatment in a curative intent strategy; exclusive treatment—first line systemic treatment administered alone in thymic tumors not accessible to local treatment (surgery or radiotherapy); treatment for recurrences—systemic treatments administered in recurrent diseases not accessible to local management.

Given the rarity of thymic tumors, building up trials remains a real challenge and few trials meet the strict

conditions to be able to finally hit. The easiest way to overcome all those difficulties is probably to aim at a more collaborative approaches through international trials, tumor boards and multidisciplinary interactions.

## How can a trial “hit”?

### *Meet the clinical needs*

The preliminary main concern while conceiving a trial is to assure that it meets clinical needs. Those needs are numerous and can be difficult to precisely identify in rare diseases when any situation seems unique and few landmarks are available. The French Réseau tumeurs THYMIques et Cancer (RYTHMIC) networks records every discussion about thymic epithelial tumors since 2012 during national tumor boards. Every question raised is prospectively registered allowing a global overview of the different medical situations with a need for stronger or additional data.

Between 2012 and 2015, 1,401 questions about 1,000 patients had been discussed at the RYTHMIC national multidisciplinary tumor board. More than one third (37%) were about systemic treatments among which 11% were for primary treatment, 3% for exclusive treatment and 13% for recurrent disease. The global overview confirms the major clinical needs in those settings making room for several clinical trials.

### *Designing the trial*

The design of a trial has to be rigorous and fit various

strict criteria to become a reliable trial, allowing relevant statistical analysis and clinical applications. The aim is to avoid as many biases as possible, which are even more frequent and various in rare diseases.

### Study endpoints

The accurate definition of study endpoints leans on the deep knowledge of physiopathology and drugs molecular action. Outcomes measures for thymic malignancies are well defined in the literature. However, these tumors are characterized by a very peculiar natural history with a significantly variable evolution sometimes leading to prolonged survivals. Given the long-term follow-up and the unpredictable evolution of those thymic malignancies, overall survival may not best reflect the efficacy of systemic drugs and time to relapse. Event free survival is preferred. Moreover, new treatments may challenge our standards, needing the reassessment of our landmarks.

The choice of the adequate endpoint allows the limitation of evaluation bias. The PRIMER study is a single-arm phase II trial of nivolumab in unresectable or recurrent thymic carcinomas. The evaluation was preplanned at 24 months which is usual for the assessment of standard chemotherapy but was probably too early for immunotherapy-based treatments which can lead to prolonged survival (1). The study was discontinued after first futility analysis. More recent trials conducted with longer-term analysis showed a 30% survival rate at 4 years of follow-up (2).

### Selection of patients

The first difficulty in selecting patients with thymic epithelial tumors relies on the diagnosis by itself. A pathological review conducted by Molina *et al.* through the RYTHMIC network—showed a 30% discrepancy at pathological review (3). Most of the discordance concerned the staging of the disease. This underlines the importance of expert centers networks and pathological review for any trial.

Moreover, due to the small number of patients, it can be very difficult to follow strict selection criteria. Two strategies are usually possible. The use of loose criteria may allow a faster recruitment of a larger number of patients but leads to a very heterogeneous study population. This heterogeneity can hamper the extrapolation of trial results or even lead to negative studies. The phase II study of sunitinib in patients with refractory thymoma and thymic carcinoma by Thomas *et al.* enrolled all subtypes of thymic tumors leading to negative results whereas more recent trials have now demonstrated the efficacy of sunitinib or

other KIT inhibitors in well selected patients in thymic tumors (4,5). On the contrary, using tight selection may lead to difficulties in recruiting patients. Korst *et al.* studied neoadjuvant chemotherapy for locally advanced thymic tumors. Due to very strict inclusion criteria, the trial recruited only 22 patients through four institutions during a 5-year period (6).

### Rationale and biomarkers

Good rationale is the basis for the development of adequate research. The TCGA study results underlined the main significant mutations in thymic epithelial tumors and even identified four subsets of tumors according molecular subtypes (7). We then have access to numerous data which have to be analyzed wisely to aim for a selection of the relevant ones.

Mutations and molecular features can eventually lead to the establishment of biomarkers to improve the selection of patient and targeted therapies. The example of imatinib is striking. Giaccone *et al.* studied imatinib in B3 thymomas and thymic carcinomas regardless c-kit mutations, leading to unpredictable heterogeneous results, with two patients out of seven presenting stable disease and prolonged survival (8). Schirosi *et al.* studied the efficacy of c-kit inhibitors in a subset of thymic carcinoma. The study showed partial response and stable disease in four tumors with c-kit activating mutations (5). C-kit mutation status could be a good biomarker for c-kit inhibitors.

### Ongoing systemic trials

Even for rare tumors, many systemic trials are currently ongoing around the world. We overlook trials through [clinicaltrials.gov](https://clinicaltrials.gov) (keywords: thymic tumors, thymoma, thymic carcinoma), and we classified clinical trials and classified them according the treatment intention as previously described (9). Every trial was then analyzed according their status for each quality criteria.

### Primary treatment

Primary systemic treatments are still mostly based on standard chemotherapies. The actual challenge is to better define the strategy more than to discover new molecules. Cytotoxic agents are studied in sequential strategies combined with radiotherapy before surgery (ChiCTR-OIC-16009130) as well as in adjuvant situations (NCT02633515). Those trials are needed in a first-line

setting where the aim is for curative treatment with still insufficient results with a response rate of 80% (9,10). Enrollment is usually not the main issue—even if the good assessment of resectable cases can be tricky—since early stage diseases concern more than 80% of thymic epithelial tumors at the time of diagnosis (11). The establishment of accurate endpoint is very difficult in those combined strategies and there is a lack of biomarkers to predict chemotherapy efficacy, even with very well-known and old drugs.

### **Exclusive treatment**

Exclusive first-line systemic treatments mainly concern chemotherapies, but current trials include targeted therapies—such as ramucirumab (NCT0391671, NCT 03694002)—potentiator treatment such as S-1 (UMIN000024643)—or immunoregulators such as Thymosin  $\alpha$ 1 (NCT03663764) in combination with chemotherapy.

There is a clinical need in those palliative intent situations for which response rate varies from 30–80% depending on the chemotherapy drugs administered (9,10).

The studies may have rapid enrollment, but study endpoints are not clearly defined and vary from a study to another, leading to confusing results for response and survival. Selection of patients is facing the difficulties described above but the main limitation for those trials is again the lack of strong biomarkers to assess the efficacy of those exclusive poorly known treatments.

### **Treatments for recurrence**

Treatments for recurrence are more heterogeneous. There is a need for new molecules. Multiple immunotherapy-based protocols are ongoing with antiPDL-1 antibodies (MSB0010718) and antiPD-1 antibodies (NCT02364076, NCT03295227, NCT02721732, NCT03134118, NCT03583086, NCT03463460). The first challenge is marked by the auto-immune atmosphere surrounding thymomas that can lead to increased and more severe toxicities. For now, those immune toxicities are difficult to predict which lead to a major difficulty in selecting patients. However, auto-immune toxicities are partially prevented by preferentially including thymic carcinomas or B3 thymomas which are less associated with dysimmune conditions. The second challenge, despite the large number of patients now

benefiting from those treatments, is the lack of well-defined study endpoints to finally get to a good evaluation of those protocols and we even more lack biomarkers that could predict treatment responses.

Other trials are based on targeted therapies (KIT/VEGF inhibitors-NCT03449173, Nuclear export inhibitor-NCT03466827, CDK4/6 inhibitors-NCT03219554), possibly associated with chemotherapies (anti-VEGFR2 antibody-NCT03694002, STAT3 inhibitors). Study endpoints are usually easier to define as those molecules have a more common acting pathway and may be evaluated according to classical endpoints.

## **Perspectives**

### **Real-life data**

To better specify what actual clinical needs are, ESMO published clinical guidelines for diagnosis as well as for treatment and follow-up of thymic epithelial tumors (12). Real life data are warranted. Through the RYTHMIC prospective cohort, we aim to describe the French landscape of systemic treatments in advanced thymic epithelial tumors and we published rates and survival data according to the clinical intent of the treatment (10).

Real life data can sometimes be disappointing as for the example of imatinib. In thymic carcinoma overexpressing mutated KIT, Ströbel *et al.* showed a dramatic clinical and pathological response to imatinib (13). This was not the case in the real life cohort from RYTHMIC network trial confirming once more the difficulties to transpose results from trials to real life (14).

### **Biomarkers**

Biomarker discovery is probably the main challenge to achieve relevant trials. Several projects are currently trying to better molecularly define thymic subgroups, aiming to classify the different pathologies according genomic alterations that could lead to targeted therapies in a more accurate way. Ross *et al.*, through foundation medicine panel, analyzed thymic squamous cell carcinomas leading to the evidence of significant genomic alterations such as kit, FGFR3 and PIK3CA which are targetable pathways (15).

The European SPECTA project is currently trying to get a better understanding of rare disease genomic landscape, which could help defining strong biomarkers for thymic cancers (<https://www.eortc.org/specta/>).

### Networking

Most important is the collaboration that can lead to both easier recruitment and more ambitious trials. This is possible through national networks such as French or Italian National Cancer Institute—recognized networks, or international networks such as the European Reference Networks EURACAN (<https://euracan.ern-net.eu/>)

### Conclusions

There are many current clinical trials about systemic therapies in thymic epithelial tumors. They include chemotherapies, immunotherapies, and targeted therapies in uni/multimodal strategies. Those trials meet real clinical needs in many situations—primary and exclusive treatments as well as treatment for recurrences—but still have to fit strict prerequisite to ultimately hit. Promising ways of improving the accuracy of those trials include the development of strong biomarkers and most of all collaboration through national and international networks.

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