Summary

Background: Thymomas and thymic carcinomas (TC) are rare epithelial tumours of the thymus. Although most thymomas have organo- typic features (i.e., resemble the normal thymus), TC are morphologically undistinguishable from carcinomas in other organs. Apart from their different morphology, TC and thymomas differ also in functional terms (TC, in contrast to thymomas, have lost the capacity to promote the maturation of intratumourous lymphocytes), have different genetic features, a different immunoprofile Thus, although all the data suggest that the biology of thymomas and TC is different, in clinical practice, their therapeutic management up to now is similar. However, thymic carcinoma are more often diagnosed at a later stage, are less often radically resectable and respond less well to standard chemotherapy.

No standard treatments are available for advanced thymic epithelial tumours after failure of platinum-based chemotherapy. Therefore, new treatment options are urgently needed.

Selinexor is a new in class inhibitor of Exportin 1 (XPO1). The aim of this trial was to assess the efficacy and safety for patients with at least one prior chemotherapy in thymic carcinoma and thymoma

Methods: Between Oct 31, 2017 and Feb 04, 2019, an open-label phase 2 trial in 23 patients with histologically confirmed chemotherapy-refractory thymic epithelial tumours was performed in Denmark and France. Patients were eligible if they had disease progression after at least one previous regimen chemotherapy.

Key inclusion criteria:

- Histologically confirmed advanced TET (thymoma) and thymic carcinoma
- Progression after primary chemotherapy.
- Not more than two previous lines (Neoadjuvant or chemoradio-therapy will count as one line if disease progression has occurred within 6 months)
- Inoperable per local Investigator (Masaoka Stage III or IV)
- Progression after treatment with least one platinum containing chemotherapy regimen
- Measurable disease (RECIST 1.1)
- Age ≥18 years
- ECOG PS <2

Key exclusion criteria:

- No significant medical illness that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy, including
  - Unstable cardiovascular function
  - Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen)
  - Markedly decreased visual acuity
  - Active infection requiring intravenous antibiotics
- Pregnancy or breast-feeding
- Symptomatic brain metastasis requiring corticosteroids

- Uncontrolled autoimmune disorders. Patients with autoimmune disorders under control on medication may be included. Patients with pure red cell aplasia may be included if haemoglobin levels are relatively stable on transfusions or medication
- Any other cancer (excluding radically operated localised squamous skin cancer) with clinical activity with

Dosage: One cycle was defined as 28 days. Selinexor 60 mg oral tablets were administered twice weekly, either on Monday/Wednesday or on Tuesday/Thursday or on Wednesday/Friday in a 3-weeks-on and 1-week-off schedule. Patients received a supply of selinexor tablets for at-home dosing. However, most of the patients underwent dose reduction already before Protocol v3, due to safety reasons.

Patients received 40 mg Selinexor since protocol v3.0. The dose has been adjusted from 60 mg to 40 mg due to occurrence of unacceptable adverse events. The primary endpoint was objective response rate evaluated at by ITMIC and RECIST in the intention-to-treat population. This trial is registered on Clinical trial gov with no NCT03466827and EudraCT number is 2016-002612-40.

Findings:

For efficacy 30 patients have been evaluated. There were 7 patients from a similar trial running in US called SELECT 2 included. Safety was not evaluated in the interim analysis. From the 23 European TET-SEL patients 22 patients have at least received on cycle of treatment. One patient with thymoma was deemed ineligible after enrolment and did not receive protocol treatment.

For the distribution of patients, please see the table below:

Patient inclusion	**RH**	**Curie**	**IGR**	**Georgetown**	**Total**
Thymoma	5	3	3	4	**15**
Responses	Total of 3 by ITMIC (1002, 1012, 1015) 2 ITMIC and RECIST* (1012, 1015)	None#	None	None±	**3 by ITMIC and 2 by RECIST**
Thymic Carcinoma	7	3	2	3	**15**
Responses	None	None	None	None	**0**
Total	**12**	**6**	**5**	**7**	**30**

30 patients were enrolled in both trials, 15 with thymic carcinoma and 15 with thymoma. Of 15 patients with thymoma, three showed a response when evaluated according to ITMIC and 2 showed response when evaluated according to Recist 1.1 These figures represent 20% and 13% of the thymoma patients. All the responses occurred at the site in Copenhagen. The Thymic carcinoma patients didn't show any response at all. Therefore, the response rate was 0 %.

The median follow-up of the European patients was 14,5 months.

The pre-dominant clinical AEs were fatigue (100 % of patients), nausea (87.0 %), vomiting (69.6 %), anorexia (56.6 %), constipation (52.2 %) and dyspnea (52.2 %). The most frequently observed AEs related to laboratory values were anemia (47.8 % of patients) and platelet count decreased (34.8 %).

The most frequent grade 3 and 4 adverse events were anaemia, fatigue and platelet count decreased.

One patient died from an adverse event due to respiratory distress.

Interpretation: The efficacy and safety of Selinexor in patients with thymic carcinoma was not shown. For thymoma the data were not sufficient but the trial could not be continued due to financial constraints. Tolerability and safety were not acceptable. Although there are only data from very few patients, these results suggest that selinexor could not become a standard treatment option for patients with previously treated advanced or metastatic thymic carcinoma and thymoma.

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