1.1.1.1 Clinical Study Report

Version/Date: final Version 1, 01.09.2022

A PHASE II STUDY OF SELINEXOR (KPT-330) IN PATIENTS WITH ADVANCED THYMIC EPITHELIAL TUMOUR (TET) PROGRESSING AFTER PRIMARY CHEMOTHERAPY

Project code:	TET-SEL
EudraCT:	2016-002612-40
Short title:	Selinexor in patients with advanced thymoma
Investigational substance:	Selinexor (KPT-330)
Reference substance:	NA
Indication:	Advanced thymic epithelial tumour (TET)
Study phase:	Phase II
Inclusion of first patient:	31.10.2017
End of treatment of last patient:	23.08.2021
Date of final report:	01.09.2022

Sponsor
Department of Oncology, Rigshospitalet
Represented by
Morten Mau-Sørensen until Jan 2019
Peter Meidahl Petersen since Jan 2019
Blegdamsvej 9
2100 Copenhagen, Denmark

Monitoring:
GSO B.V.
Keizersgracht 62-64
1015 Amsterdam
The Netherlands

Coordinating investigator:
Gedske Daugaard
Oncologisk Klinik, Rigshospitalet
Blegdamsvej 9
2100 Copenhagen, Denmark

Study sites:
Department of Oncology 5073, Rigshospitalet, Copenhagen, Denmark
Institute Curie, Département d'Oncologie médicale - Pneumologie, Paris, France
Hospital louis Pradel, Pneumologie bat A4, Lyon (Bron) cedex, France
Institute Gustave Roussy, Department d'innovations therapeutiques precoces, Villejuif, France

GCP statement: This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

Signatures

Title of the trial: **A PHASE II STUDY OF SELINEXOR (KPT-330) IN PATIENTS WITH ADVANCED THYMIC EPITHELIAL TUMOUR (TET) PROGRESSING AFTER PRIMARY CHEMOTHERAPY**

Trial substance: Selinexor (KPT-330)

Trial code: TET-SEL

The undersigned have read this clinical study report and hereby confirm that, to the best of their knowledge, it accurately describes the conduct and the results of the study.

Sponsor Representative

02/9/22 — Date

Peter M Petersen — Peter Meidahl Petersen

GSO Representative

09.09.2022 — Date

Kranich — Dr Anne L. Kranich

1 SYNOPSIS

Name of the sponsor: Department of Oncology, Rigshospitalet, Blegdamsvej 9 2100 Copenhagen	*Individual study table* *Referring to part of the dossier:* *Volume: N/A* *Page: N/A*	*(For National Authority use only)*
Name of the finished product XPOVIO		
Name of the active substances: Selinexor (KPT-330)		

Trial title:

A PHASE II STUDY OF SELINEXOR (KPT-330) IN PATIENTS WITH ADVANCED THYMIC EPITHELIAL TUMOUR (TET) PROGRESSING AFTER PRIMARY CHEMOTHERAPY

Study centres:

For a list of study sites, please refer to Appendix 16.1.4.

Trial duration: Inclusion of first patient: 31.10.2017 End of trial (early termination): 29.07.2021	**Phase of development:** II
Methodology: International, multicenter, open label phase II, Simons two stage design	

Trial objectives:

Primary trial objective:

- To determine the efficacy of selinexor in adults with TETs determined by overall response rate (RECIST 1.1) in two parallel cohorts of patients with advanced thymomas or thymic carcinomas

Secondary objectives:

- To determine the efficacy of Selinexor in adults with TETs determined by overall response rate according to modified ITMIG response criteria
- To determine the overall response rate of selinexor in patients with advanced thymic carcinoma with squamous cell histology
- To determine six months PFS of patients with TET treated with Selinexor
- To determine overall survival of patients with TET treated with Selinexor
- To evaluate exploratory biomarkers for prediction of response to selinexor in patients with TET
- To determine progression free survival in patients with advanced, inoperable TETs treated with Selinexor
- To evaluate safety and tolerability of Selinexor

Number of patients: 23

Included in the final evaluation:

Number of patients	**Total**
Recruited	23

Name of the sponsor: Department of Oncology, Rigshospitalet, Blegdamsvej 9 2100 Copenhagen	*Individual study table* *Referring to part of the dossier:* *Volume: N/A* *Page: N/A*	*(For National Authority use only)*
Name of the finished product XPOVIO		
Name of the active substances: Selinexor (KPT-330)		

Evaluable regarding toxicity	23
Evaluable regarding efficacy	23

Diagnosis and key inclusion and exclusion criteria:

Inclusion criteria:

- Histologically confirmed advanced TET (thymoma or thymic carcinoma)
- 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
- Patients must have recovered from the toxic effects of prior therapy at the time of initiation of the study drug unless toxicity is stable.
- A 4 weeks from any investigational agents or cytotoxic chemotherapy to start of study is required
- Signed informed consent
- Adequate bone marrow function and organ function:
  - Hematopoietic function: total white blood cell count (WBC) ≥ 3000/mm³, absolute neutrophil count (ANC) ≥ 1500/mm³, platelet count ≥ 100,000/mm²
  - Hepatic function: bilirubin < 1.5 times the upper limit of normal (ULN), ALT < 2.5 times ULN or ALT < 5.0 times ULN in the presence of liver metastases

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 within the last 2 years

Name of the sponsor:	*Individual study table*	*(For National Authority use only)*
Department of Oncology, Rigshospitalet, Blegdamsvej 9 2100 Copenhagen	*Referring to part of the dossier:* *Volume: N/A*	
Name of the finished product XPOVIO	*Page: N/A*	
Name of the active substances: Selinexor (KPT-330)		

- Creatinine clearance > 30 ml/min according to Cockcroft-Gault • Patients of childbearing potential must agree to use adequate birth control during and for 3 months after participation in this study	• Significantly diseased or obstructed gastrointestinal tract, malabsorption, uncontrolled vomiting or diarrhea or inability to swallow oral medications • No dehydration of NCI-CTCAE grade ≥ 1 • Serious psychiatric or medical conditions that could interfere with treatment. • No history of organ allograft • No concurrent therapy with approved or investigational anticancer therapeutics

Treatment duration:
An interim analysis was planned according to protocol after inclusion of 15 evaluable patients in each arm across all sites and was carried out in February 2019. No response was observed at that time in the thymic carcinoma cohort, and it was decided that this cohort was closed.
In the thymoma cohort three responses in 15 patients were observed (three by ITMIC, and 2 by RECIST). It was evaluated if the thymoma cohort should be continued and 10 additional patients (stage 2) shall be included.
Due to lack of further funding by the pharmaceutical entrepreneur, it was decided by the sponsor to terminate the study after completion of stage 1 of the study, and not to open stage 2.

Trial medication, dose and method of administration:
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.

Evaluation criteria:
The primary endpoint was objective response rate evaluated at by ITMIC and RECIST in the intention-to-treat population.

Statistical methods: NA

Name of the sponsor: Department of Oncology, Rigshospitalet, Blegdamsvej 9 2100 Copenhagen	*Individual study table* *Referring to part of the dossier:* *Volume: N/A* *Page: N/A*	*(For National Authority use only)*
Name of the finished product XPOVIO		
Name of the active substances: Selinexor (KPT-330)		

Interim analysis:

An interim analysis was planned and performed after stage 1.

Summary:

Demographic data and baseline data:

Efficacy results:

Primary endpoint: Efficacy of selinexor in adults with TETs by overall response rate (RECIST 1.1) in two parallel cohorts of patients with advanced thymomas or thymic carcinomas.

(Since Prot. v4.0, dated Dec20, 2019: Efficacy of selinexor in adults with TETs by overall response rate (RECIST 1.1) in patients with advanced thymomas progressing after primary chemotherapy.)

Inclusion of 15 evaluable patients in each arm across all sites was completed on 19 February 2019.

The study was running as an investigator-initiated study in the EU There was a similar study in the US. In this interim analysis, the patients from the US site, Georgetown, were also included.

Enrolment and confirmed responses as 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**

* No other patients showed a clinical response

Patients showed stable disease, but no response

± No responses, 1 patient with SD still on treatment

Name of the sponsor:	*Individual study table*	*(For National Authority use only)*
Department of Oncology, Rigshospitalet, Blegdamsvej 9 2100 Copenhagen	*Referring to part of the dossier:* *Volume: N/A*	
Name of the finished product XPOVIO	*Page: N/A*	
Name of the active substances: Selinexor (KPT-330)		

Secondary endpoints:
Due to the low number of patients, no further endpoints have been analysed.

Toxicity:
The safety analysis was carried out on patients included in the EU countries only.

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.

Date of report: 01.09.2022

2 TABLE OF CONTENTS

3 LIST OF TABLES AND FIGURES INCLUDED IN THE TEXT

4 ABBREVIATIONS

Table 1 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
B-HCG	Beta- Human chorionic gonadotropin
BMI	Body mass index
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
Cmax	peak concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRM1	Chromosome region maintenance protein 1
CRO	Contract research organisation
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP450	Cytochrome P450
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EOS	End of study
EOT	End of treatment
GBM	Glioblastoma
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSH	Glutathione stimulating hormone
GRP	growth regulatory proteins
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDAC	Histone deacetylases
hr	Hour
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration, 50% (half maximal inhibitory concentration)
ICH	International Conference on Harmonisation
IGFR	Insulin-like growth factor 1 receptor
IMP	Investigational medicinal product
INR	International normalized ratio
ITMIG	International Thymic Malignancy Interest Group
LDH	Lactate dehydrogenase
LMW	Low molecular weight
mg	Milligram

mL	Milliliter
mM	Millimolar
MM	Multiple myeloma
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NK1	Neurokinin 1
NPC	Nuclear pore complex
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PDn	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
qRT-PCR	Quantitative reverse-transcription, polymerase chain reaction
RECIST	Response Evaluation Criteria In Solid Tumors
RBC	Red blood cell
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SD	Stable disease
SINE	Selective Inhibitor of Nuclear Export
SUSAR	Suspected unexpected serious adverse reaction
TC	Thymic carcinoma
TET	Thymoma and thymic carcinoma
TLS	Tumour lysis syndrome
T_{max}	Time to maximum serum concentration
TSH	Thyroid-stimulating hormone
TSP	Tumor suppressor protein
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WL	Weight loss
XPO1	Exportin 1

5 ETHICS AND AUTHORITIES

5.1 Independent Ethics Committee

Before recruitment of patients, the Clinical Study Protocol and other appropriate documents were submitted to the Independent Ethics Committees (IECs) responsible for the participating investigators. The IECs did not raise principal objections against the study.

Final approval of the IECs/IRBs was obtained for the following documents:

Document	**Date of approval by IEC in Denmark**
Protocol v1.4 (27.06.2016) + Danish add. V1.1	24.10.2016
ICF v1.1 (25.09.2016)	24.10.2016
ICF v2.0 (17.11.2016)	27.01.2017
Protocol v1.5 (29.01.2017)	24.08.2017
ICF v4.0 (18.08.2017)	24.08.2017
Protocol v2.0 (28.05.2018)	28.06.2018
ICF v5.0 (25.05.2018)	28.06.2018
Protocol v3.0 (04.12.2018)	04.01.2019
ICF v6.0 (05.12.2018)	04.01.2019
Protocol v4.0 (20.12.2019)	31.01.2020
ICF v7.0 (19.12.2019)	31.01.2020

Document	**Date of approval by IEC in France**
ICF v1.2 (06.06.2016)	Not approved
ICF v1.3 (20.09.2016)	Not approved
ICF v2.0 (17.11.2016)	09.01.2017
Protocol v1.4 (27.06.2016)	09.01.2017
ICF v3.0 (09.08.2017)	11.10.2017
ICF v4.0 (25.05.2018)	06.06.2018
Protocol v2.0 (28.05.2018)	06.06.2018
ICF v5.0 (16.01.2019)	12.02.2019
Protocol v3.0 (04.12.2018)	12.02.2019
ICF v6.0 (23.12.2019)	01.09.2020
Protocol v4.0 (20.12.2019)	01.09.2020

A list of the IECs/IRBs involved is presented in Appendix 16.1.3.

5.2 Ethical conduct of the study

The study was conducted in conformity with the local legal requirements , the ICH Harmonised Guideline Integrated Addendum to ICH E6 (R1): Guideline for GCP E6 (R2) (1996), and the “Ethical principles for medical research involving human subjects” of the 18th World Medical Association General Assembly in Helsinki (1964), and amended by the 29th, 35th, 41st, 48th, 52nd,

53th, and 55th World Medical Association General Assemblies (Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Seoul 2008, and Fortalezy 2013), the Note of Clarification on Paragraph 29 added by the World Medical Association General Assembly, Washington 2002, and the Note of Clarification on Paragraph 30 added by the World Medical Association General Assembly, Tokyo 2004 – as applicable in the respective countries.

In conformity with ICH guidelines and in accordance with applicable national laws, patients participating in the study were covered by an insurance policy that was taken out by the sponsor.

Country	**Insurance company**	**Address**	**Policy number**	**Max. amount insured/patient**
Denmark	**Not applicable**			
France	**Hardy (Underwriting Agencies) Limited**	**One Lime Street London EC3M 7HA United Kingdom**	**ML6BBA0538AX**	**15**

The following national regulatory authorities were informed about the conduct of the study:

Country	**National regulatory authority**	**Date of authorisation/final approval/confirmation of receipt**
Denmark	Danish Medicines Agency Clinical Trials Axel Heides Gade 1 DK-2300 København S DENMARK	Initial 20.10.2016 (Prot. v1.4 + loc. Amd., IB v5.0 + Add.1) AMD01 (IB v6.0, ICF v2.0) 09.02.2017 AMD02 (Prot. V1.5, IB v7.0) 06.09.2017 AMD03 (Prot. v2.0) 14.06.2018 AMD04 (IB v8.0, Prot. v3.0) 16.01.2019 AMD05 (IB v.9.0, Prot. v4.0, ICF v7.0) 26.02.2020 AMD06 (IB v10.0) 14.04.2021
France	ANSM 143-147, Boulevard Anatole 93285 Saint-Denis Cedex FRANCE	Initial 16.02.2017 (Prot. v1.5; IB v5.0, IB v6.0) AMD01 (IB v7.0) 13.10.2017 AMD02 (Prot. V2.0) 13.06.2018 AMD03 (IB v8.0, Prot. v3.0) 14.01.2019 AMD04 (IB v9.0, Prot. v4.0) 10.02.2020 AMD05 (IB v10.0) 20.04.2021

5.3 Patient information and informed consent

Before being enrolled in the clinical trial, each patient was informed that participation in the trial was voluntary and that he/she could withdraw from the study at any time without giving any reasons and without having to fear any detrimental effects on his/her medical care.

The patient was informed about the study medication and the possible side effects. At the same time, the purpose, significance, and scope of the study were explained to him/her. The explanation also included informing the patient about the insurance protection and the obligations of the insured.

The patient had sufficient time and opportunity to clarify any unresolved questions. Furthermore, the patient was given a copy of the Patient Information Form, containing all the important information in written form (in the local language) and a copy of the signed informed consent.

The patient's consent had to be obtained in writing before the start of the study. By signing the informed consent form, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator, and to answer the questions asked during the course of the trial. The investigator kept the signed patient informed consent form in the designated place in the investigator's file.

By giving consent, the patient also agreed to the storage of his/her medical data in the context of the trial and its forwarding to third parties in pseudonymised form for checking by the sponsor. He/she also consented to the forwarding of his/her personal data for review by the supervisory authorities or to persons authorised by the sponsor to check the proper conduct of the clinical trial.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The number of patients who were enrolled at each study site is shown in Table 2.

Table 2 Study sites and recruitment

Centre	Location	No. of patients recruited	Start of treatment
37	Rigshospitalet, Copenhagen	12	22.11.2017
63	Gustave Roussy, Villejuif	5	07.01.2019
NA	Hospital louis Pradel, Lyon	NA	NA
65	Curie Institute, Paris	6	13.08.2018

National Coordinating Investigator Denmark

Dr. med. Gedske Daugaard
Rigshospitalet, Onkologisk Klinik
Blegdamsvej 9, 2100 Copenhagen

National Coordinating Investigator France

MD Nicolas Girard
Institut Curie Department of Medicine
26 rue d'Ulm, 75005 Paris

Sponsor representative

Morten Mau-Sørensen until Jan 2019
Peter Meidahl Petersen since Jan 2019
Department of Oncology, Rigshospitalet
Blegdamsvej 9, DK-2100 Copenhagen
Denmark

Study coordination
GSO B.V.
Keizersgracht 62-64
1015 Amsterdam
The Netherlands

CRO responsible for monitoring in Denmark and France

GSO B.V.
Keizersgracht 62-64
1015 Amsterdam
The Netherlands

Statistics

Not applicable, descriptive analysis only

7 INTRODUCTION

7.1 Background

7.1.1 Thymic Epithelial Malignancies

Thymomas and thymic carcinomas (TC) are rare epithelial tumours of the thymus. Based on cancer registry data, the overall incidence of thymoma in the US is 0.13 per 100,000 person-years. Thymoma is exceedingly uncommon in children and young adults, rises in incidence in middle age, and peaks in the seventh decade of life.

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 (most TC overexpress c-KIT, whereas thymomas usually do not), and different clinical features (TC, in contrast to thymomas, are usually not associated with myasthenia gravis or other autoimmune phenomena). 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 [1]. However, thymic carcinoma is more often diagnosed at a later stage, are less often radically resectable and respond less well to standard chemotherapy. Overall survival of TC is inferior even in advanced stages.

Based on available current knowledge about the biology of these tumours, the World Health Organization (WHO) classification of thymic epithelial tumours separates thymomas from thymic carcinomas [1]. Thymomas are defined as neoplasms arising from or exhibiting differentiation

toward thymic epithelial cells, usually with a variable component of non-neoplastic lymphocytes. All types of thymomas have the potential of metastasising and are hence malignant [2].

7.1.2 Selinexor

A brief summary of key aspects of the preclinical evaluation of selinexor is presented below. Further detailed information is provided in the Investigator's Brochure.

Selinexor is an oral, first in class, potent, slowly reversible, covalent Selective Inhibitor of Nuclear Export (SINE™) that specifically blocks the karyopherin protein Exportin 1 (XPO1/Exportin 1), also called chromosome region maintenance 1 (CRM1).
XPO1 is overexpressed 2-4 fold in all cancers studied to date. XPO1 is an exclusive nuclear transporter for shuttling the major Tumour Suppressor Proteins (TSPs) and other growth regulators out of the nucleus.
Since TSPs require nuclear localization to mediate their deoxyribonucleic acid (DNA) damage assessment/tumour suppressing functions, nuclear export leads to their functional inactivation. In addition, many TSPs are degraded by the proteasome when they are transported to the cytoplasm.
Blockade of XPO1 leads to marked accumulation of TSPs in the nucleus of all cells, leading to cell cycle arrest at the G1±G2 checkpoints. Cells with damaged genomes – i.e., cancer cells – undergo apoptosis, whereas undamaged normal cells remain in cell cycle arrest until the XPO1 block is released. Consistent with its activation of multiple TSPs, selinexor has shown broad anti-cancer activity in nonclinical murine xenograft, orthotopic, primagraft, and leukemograft models, largely independent of the resistance profile of the cancer cell line being investigated.

Selinexor is orally bioavailable and exhibits dose-proportional exposure with moderate- to –high interpatient variability across a wide dose range of doses in patients with advanced hematologic malignancies or solid tumors. The elimination (terminal) half-life (t½) of selinexor is approximately 6 to 8 hours [3].

7.2 Study Rationale

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.

8 STUDY OBJECTIVES

8.1 Primary Objective

The aim of the study was to determine the efficacy of selinexor in adults with TETs determined by overall response rate (RECIST 1.1) in two parallel cohorts of patients with advanced thymomas or thymic carcinomas.

(Since Prot. v4.0, dated Dec20, 2019: Efficacy of selinexor in adults with TETs by overall response rate (RECIST 1.1) in patients with advanced thymomas progressing after primary chemotherapy.)

8.2 Secondary Objectives

Secondary objectives of the study were

- To determine the efficacy of Selinexor in adults with TETs determined by overall response rate according to modified ITMIG response criteria.
- To determine the overall response rate of selinexor in patients with advanced thymic carcinoma with squamous cell histology.
- To determine six months PFS of patients with TET treated with selinexor.
- To determine overall survival of patients with TET treated with selinexor.
- To evaluate exploratory biomarkers for prediction of response to selinexor in patients with TET
- To determine progression free survival in patients with advanced, inoperable TETs treated with Selinexor
- To evaluate safety and tolerability of Selinexor.

9 INVESTIGATIONAL PLAN

9.1 Overall study design and plan – description

9.1.1 Definition of Treatment Cycle

One cycle was defined as 28 days.
In initial protocol version, Selinexor 60 mg oral tablets were to be 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 were to receive a supply of selinexor tablets for at-home dosing.
Since protocol version 3.0, dated Dec04, 2018, the dose of Selinexor was reduced to 40 mg for better tolerability.
Study drug administration could be delayed for toxicity according to protocol section 6.3.

9.1.2 Treatment Duration

Patients discontinued treatment with selinexor if one of the following events had been occurred:

- Progression of disease demonstrated by CT scan according to RECIST 1.1
- Clinical progression in the opinion of the investigator
- Unacceptable toxicities
- Patient’s request to discontinue
- The investigator considers it in the patient’s best interest to discontinue treatment.

9.1.3 End of Treatment Visit

Patients who discontinued treatment were encouraged to undergo an end-of-treatment visit unless they had withdrawn consent to participate in the trial.

9.1.4 Follow-Up Phase

Patients who discontinued for reasons other than progression of disease (and withdrawal of consent for participation in the trial) were encouraged to attend an End-of-Study visit 30 days after discontinuation of treatment and to visit the clinic for clinical evaluation of their disease every 4 weeks and assessment by CT scan every 12 weeks until disease progression. If the patient was in follow-up and/or treated post-study, the clinical evaluation could be done by the treating physician and the patient did not need to visit the site. After disease progression all patients were evaluated for survival and further therapy by reviewing their medical charts regularly.

9.2 Discussion of study design, including the choice of control groups

This was a non-randomised, open label two-armed phase II trial. Arm A includes patients with thymoma and arm B include patients with thymic carcinoma.
The primary objective of the trial was to determine the effect of selinexor in patients with inoperable thymoma and in patients with thymic carcinomas, previously treated with at least one platinum containing chemotherapy regimen as determined by overall response rate according to RECIST 1.1.

9.3 Selection of study population

Adults with histologically confirmed, advanced, inoperable TETs who were progressing after treatment with least one platinum containing chemotherapy regimen.

9.3.1 Inclusion criteria

Patients who met all of the following criteria could be enrolled into the study:

- Histologically confirmed advanced TET (thymoma or thymic carcinoma)
- 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
- Patients must have recovered from the toxic effects of prior therapy at the time of initiation of the study drug unless toxicity is stable.
- A 4 weeks from any investigational agents or cytotoxic chemotherapy to start of study is required
- Signed informed consent
- Adequate bone marrow function and organ function:
    - Hematopoietic function: total white blood cell count (WBC) ≥ 3000/mm³, absolute neutrophil count (ANC) ≥ 1500/mm³, platelet count ≥ 100,000/mm²
    - Hepatic function: bilirubin < 1.5 times the upper limit of normal (ULN), ALT < 2.5 times ULN or ALT < 5.0 times ULN in the presence of liver metastases
    - Creatinine clearance > 30 ml/min according to Cockcroft- Gault
- Patients of childbearing potential must agree to use adequate birth control during and for 3 months after participation in this study

9.3.2 Exclusion criteria

Patients who met any of the following criteria were not allowed to be enrolled into the study:

- 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 within the last 2 years
- Significantly diseased or obstructed gastrointestinal tract, malabsorption, uncontrolled vomiting or diarrhea or inability to swallow oral medications
- No dehydration of NCI-CTCAE grade ≥ 1
- Serious psychiatric or medical conditions that could interfere with treatment.
- No history of organ allograft
- No concurrent therapy with approved or investigational anticancer therapeutics

9.3.3 Removal of patients from therapy or assessment

Trial treatment had to be terminated in the case of:

- Disease progression
- Non-compliance
- Patient no longer consents to participate in the study
- Illness that interferes with study assessments
- The patient undergoes radical surgery
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- Investigator discretion for any reason
- Pregnancy
- Termination of the study by the sponsor

9.4 Treatments

9.4.1 Treatments administered

Please refer to section 9.1 for an overview of the study treatments administered.

9.4.2 Identity of investigational product(s)

The trial medication was characterised as follows:

	Investigational product
Manufacturer:	Karyopharm Therapeutics Inc.
Mode of administration:	Oral
Batch no.:	NA
Expiry date:	NA
Storage instructions:	Selinexor tablets (20 mg) were stored at room temperature (at or below 30°C) in clear blister strips

9.4.3 Method of assigning patients to treatment groups
NA

9.4.4 Selection of doses in the study
In initial protocol version, Selinexor 60 mg oral tablets were to be administered twice weekly. Since protocol version 3.0, dated Dec04, 2018, the dose of Selinexor was reduced to 40 mg for better tolerability.

9.4.5 Selection and timing of dose for each patient
Selinexor were to be 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.

9.4.5.1 General comments
Toxicity was graded according to NCI CTCAE, version 4.03; the therapy modifications described below were applied according to this severity grading. If more than one different type of toxicity occurred concurrently, the most severe grade was determining the modification. Re-escalation of the study drug was only allowed as outlined in the sections that apply for the specific toxicity. If toxicity required a treatment delay of more than 4 weeks the patient was taken off protocol treatment. Each dose modification or treatment delay had to be documented in the eCRF, including the respective reason.

Drug Dose Level	Dose of Selinexor
Dose level 0 (starting dose)	60 mg twice weekly, 3 weeks on/1 week off
Dose level -1	40 mg twice weekly, 3 weeks on/1 week off
Dose level -2	40 mg once weekly, 3 weeks on/1 week off
Dose level -3	20 mg once weekly, 3 weeks on/1 week off
Dose level -4	Discontinue dosing, 3 weeks on/1 week off

For all selinexor related non-hematological toxicities except those mentioned in the table protocol section 6.2.1: Dosing should have been interrupted in case of grade 3 non-hematological toxicity and resume dosing when resolved to grade 1 or less.

9.4.5.2 Selinexor Dose Reduction in the Setting of Infection

Patients with active uncontrolled infections should have had Selinexor treatment withheld until the infection had resolved or the patient was clinically stable. After the infection had stabilized clinically or resolved, Selinexor treatment might have been continued at the original dose. Missed doses were not replaced. Patients might continue on antibiotics for prolonged periods while re-initiating their Selinexor regimen at the discretion of the investigator. Prophylactic antibiotics were permitted concurrently with Selinexor treatment, but were not required. In a randomised study in old patients with acute myeloid leukemia (AML), sepsis occurred more frequently in patients receiving Selinexor compared with patients receiving physician's choice of therapy.

9.4.5.3 Dose Reduction for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney, therefore, no dose alteration of selinexor was required in patients with renal dysfunction.

9.4.5.4 Dose reduction in the setting of other Selinexor related adverse events

In case of other Selinexor-related adverse events, dose modifications were as follows (AE-grade according to NCI-CTCAE 4.03):

Grade 1 or 2	Initiate standard supportive care per institutional guidelines.	Maintain dose.
Grade 3	See guidelines for Grade 1/2	Delay dose until resolved to Grade ≤ 1 or baseline, then reduce by one dose level
Grade 4	See guidelines for Grade 1/2	Delay dose until resolved to Grade ≤ 1 or baseline, then reduce by two dose levels

9.4.5.5 Missed or Vomited Doses

Missed doses
A maximum of two doses might be given per week. If the dose was missed for more than 24 hours, the dose was skipped and the next dose was taken as per schedule. If the dose was missed within 24 hours, then it was replaced. Doses should not be administered in less than 36 hours apart and all missed doses should be documented in the patient diary and the eCRF.

Vomited doses
If a dose was vomited within one hour of ingestion, it was replaced. If vomiting occurred more than 1 hour after dosing, it was still be considered a complete dose.

9.4.6 Blinding

Not applicable.

9.4.7 Prior and concomitant therapy

Use of Blood Products

During the administration of selinexor, patients might receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines.
Appropriate anti-coagulation was allowed during the study (e.g.: LMW heparin, direct factor Xa inhibitors, etc). Warfarin was allowed during the study provided that patients were monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly thereafter.
Patients might receive supportive care with erythropoietin, darbepoetin, G-CSF or GM-CSF, pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

Prohibited Medications

Concurrent therapy with an approved or investigative anticancer therapeutic, other than glucocorticoids as specified herein, was not allowed.
Other investigational agents should not be used during the study.
Although formal drug-drug interaction studies had not been undertaken, there had been no identified drug-drug interactions of any kind in the >2600 patients dosed with selinexor as of May 2018. Patients should not take glutathione stimulating hormone (GSH), S-adenosyl methionine (SAM), or N-acetylcytein (NAC) during their participation in the study, as these products might enhance the metabolism of selinexor. These agents were permitted if the patient had elevated liver function tests, but all natural products or supplements containing these should be avoided.

Prevention of Pregnancy

Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception were condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who was surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

9.4.8 Treatment compliance

The investigator should has ensured that the investigational product was used only in accordance with the protocol. All doses given were to be documented in the CRF, including exact dose, number of tablets, time and date administered. The principal investigator or the designee was to account for the number of tablets dispensed against those stored at the site. Any deviations and missed doses were to be recorded in the CRF and drug accountability logs for verification with the reasons for missed doses. The investigator/ designee had to try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. It was requested from patients to document intake of Selinexor in a patient diary.

9.5 Efficacy and safety variables

9.5.1 Efficacy and safety measurements assessed and flow chart

9.5.1.1 Study assessments

9.5.1.1.1 Tumour Assessment

The disease status was measured by CT scans and response was assessed according to RECIST 1.1 and ITMIG. Only patients with measurable disease were enrolled.
The baseline CT scan had to be recorded and measured within 28 days prior to treatment start. A CT scan performed as part of standard of care could be used as the baseline CT scan provided study treatment had been started within the 28-day window. Patients were evaluated for surgery as per institutional standards.

9.5.1.1.2 Translational and pharmacodynamics (PDn) analyses

Gene Expression Changes in RNA from Whole Blood
Patient blood samples were collected pre- and post-dosing (≥ 4 hr) on C1 D1 and processed to isolate total RNA. RNA was used to study changes in gene expression after exposure to selinexor. Changes in mRNA of genes which were up/down-regulated once XPO1 is inactivated were assessed by quantitative real time polymerase chain reaction (qRT PCR). RNA from these blood samples could be subjected to deep RNA sequencing correlative studies.

Plasma Proteins
Data from phase I studies show that serum concentration levels of the NGFR ligand BDNF pre-selinexor treatment were different in progressors vs. non-progressors patients (solid+hem). BDNF levels were measured by ELISA and were generally lower in patients with progressive disease. Blood samples were collected pre- and post-dosing and analysed for plasma BDNF and possible cytokine concentrations. The predictive potential of each marker analysed was determined by retrospective correlation with response.

Tumour Biopsies
Tumour tissue was obtained before the first dose (within 14 days of first dose/ archival tissue) and pre-dose cycle 2 day 1 provided there was technically accessible tumour and it was safe for the patient to undergo biopsy. An optionally tumour biopsy could be performed at the time of progression or if patients went off study for other reasons if consent was provided by the patient. Tissue was tested for levels of expression and cellular localization (nuclear/ cytoplasm) of biomarkers of response including XPO1; representative XPO1 cargos such as: P53, SURVIVIN, FOXO1; markers of direct-tumour response such as the proliferation marker Ki-67 and the apoptotic marker Cl. Casp3 and potential predictive biomarkers by immunohistochemistry.
Tumour tissue obtained before treatment should have been available either as paraffin embedded-formalin fixed sample or fresh biopsy. Tumour samples were stained for CRM-1 antibody and protein expression was quantified. CRM-1 expression was correlated with response to treatment. Samples (fresh or FFPE samples) collected and their normal blood pairs were sequenced using NEXTGEN technology on our recently acquired Miseq sequencer. Patients who had no available tissue were eligible for the trial. A custom-designed cancer-associated gene panel which included all the identified recurrent mutations in thymic carcinomas, published cancer driver genes and COSMIC cancer gene census (http://cancer.sanger.ac.uk/cosmic/census) were used for targeted sequencing [4-6].

Circulating Tumour DNA
Although the identification of gene mutations could be performed routinely in tumour biopsies at the time of diagnosis, the limited availability of tissue specimens in thoracic tumours such as thymoma did make it cumbersome to track mutational status longitudinally. Repeated biopsies over time were not clinically feasible due to the risk and the inconvenience for the patients. Adverse event rates of 17.1% for thoracic biopsies had been reported previously [7].
Selected mutations were tracked at multiple time points in cell free tumour DNA isolated from plasma samples by use of methods provided by QIAgen. The abundance of a specific mutation was assessed by digital PCR and presented as allele fraction of tumour mutations in plasma.
Blood samples were collected at multiple time points in order to investigate the dynamics in the allele frequency of mutations. The mutations to be tracked longitudinally were prioritized on the basis of their known roles in promoting tumour growth and drug resistance.
Contribution to the translational and pharmacodynamics analyses by each site was recommended and encouraged by the sponsor but was optional for the participating sites.

9.5.1.1.3 Safety and Tolerability Assessments
Safety was monitored by assessing physical examinations including vital signs and weight, performance status, visual acuity by Snellens chart, ophthalmic examination, concomitant medication use, and laboratory parameters. Information regarding AEs were collected, and each AE was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v 4.03) beginning at day of first administration of study drug, throughout the treatment period and to the extent possible until 30 days after last dose of study drug.

9.5.1.1.4 Laboratory assessments
The standard clinical laboratory analysis was to be performed by the study site's local laboratories according to the Schedule of Assessments. More frequent examinations could be performed at the investigator's discretion if medically indicated; results should have been recorded on the eCRFs. At any time during the study, abnormal laboratory parameters that were clinically relevant (e.g., interruption or delay of study treatment or require therapeutic intervention) had to be recorded in the CRF. When abnormal laboratory values or test results constituted an adverse event, they had to be recorded on the CRF Adverse Events page. Every effort had to be made to follow the schedule outlined in the Schedule of Assessments.

9.5.2 Study procedure

Data were collected via the completion of a Case Report Form (CRF) for each enrolled patient. The investigator should have confirmed eligibility of the patient according to the inclusion and exclusion criteria of the study. Written Informed Consent had to be obtained before any study specific assessment is performed. Screening assessments should have occurred within 28 days of the first administration of study drug. Patients should receive their first dose of study treatment as soon as possible after registration, but not later than 7 days after registration.

Table 3 FLOW CHART: SCHEDULE OF ASSESSMENTS DURING THE STUDY

	Screening		Cycle 1- 2	Cycle ≥3	EOT Visit	EOS Visit
Visit window [days]	< 28 days prior to start of therapy	< 7 days prior to start of therapy	Day 1 & 15 ± 3 days	Day 1 ± 3 days	Off treat-ment	30 days ± 7 days
Informed consent[1]	X					
Inclusion and exclusion criteria		x				
Demographics	X					
Medical History[2]	X					
Pregnancy test (if applicable)[3]		x			x	
Body height and weight[4]		x	X	x	x	X
Vital signs[5]		x	X	x	x	X
Physical examination and ECOG[6]		x	X	x	x	X
12-lead ECG	X		X	x	x	
Hematology (CBC)[7]		x	X	x	x	X
Complete Serum chemistry[8]		x	X		x	X
Limited Serum chemistry[9]				x		
Coagulation test [10]		x			x	
Assessment of disease status[11]	X			x	x	
Selinexor dosing in clinic			X	x		
Adverse events			X	x	x	X
Concomitant Medication	X	x	X	x	x	X
Prednisone doses	X	x	X	x	x	X
Tumour biopsy[12]		x[12]	x[13]			
Blood samples for biomarker[14]		x	X	x	x	X
Visual acuity by Snellens Chart[15]	X		X[16]	x	x	X
Ophthalmic examination[17]	X[18]					

Notes

[1] Prior to the first study-specific measures

[2] Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness. Evaluate the risk of TLS based on a clinical evaluation of comorbidity (such as presence of renal impairment or cardiac insufficiency).

[3] Applicable for women of childbearing potential. Serum β-HCG test within 7 days before the first dose of study drug. To be repeated by urine test, if date of first result exceeds the 7-day window

[4] Body height will be measured at screening only

[5] Vital signs: blood pressure, pulse and temperature

[6] Full physical examination for baseline and end of study visit. Physical examinations during the study should be symptom directed

[7] Hematology: hemoglobin, hematocrit, mean corpuscular volume, white blood cell (WBC) count, WBC differential, neutrophils, platelets, circulating lymphocytes. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated. Circulating lymphocytes at screening only.
[8] Complete Serum Chemistry for baseline, cycles 1&2 and end of study/treatment visit include Sodium, Potassium, Chloride, Bicarbonate, Creatinine, Glucose, Calcium ion, Magnesium, ALT, AST, Alkaline Phosphatase, Total Bilirubin, LDH, BUN or Urea, Uric Acid, Phosphorus, Albumin, TSH and blood sample for assessment of exploratory biomarkers.
[9] Limited Chemistry including: Sodium, Potassium, Creatinine, Glucose, ALT, AST, Alkaline Phosphatase, Total Bilirubin
[10] Coagulation test includes international normalization ratio (INR), and activated partial thromboplastin time (aPTT)
[11] Disease status will be measured once every two cycles with CT scan of chest and abdomen.
[12] Tumour tissue will be obtained before the first dose (within 14 days of first dose) and pre-dose cycle 2 day 1 provided there is technically accessible tumour and it is safe for the patient to undergo biopsy. Archival tissues will substitute for fresh biopsy in patients with inaccessible tumour. An optionally tumour biopsy can be performed at the time of progression or if patients go off study for other reasons if consent is provided by the patient
[13] Tumour tissue will be obtained pre-dose **only cycle 2** day 1 provided there is technically accessible tumour and it is safe for the patient to undergo biopsy.
[14]Bloodsamples for biomarkers include samples for circulating tumour DNA
[12,13,14] Contribution to the translational and pharmacodynamics analyses by each site is recommended and encouraged by the sponsor but is optional for the participating sites.
[15] Assessment of visual acuity by use of Snellens chart should be performed at baseline, every 28 days at day 1 of each cycle, at end of treatment and at end of study.
[16] Assessment of visual acuity by use of Snellens chart should only be performed on days 1 of cycle 1 and 2 and not on days 15
[17] If visual acuity deteriorates significantly compared to baseline, patients should have an ophthalmic examination by an optometrist or ophthalmologist including evaluation of best corrected visual acuity and a slit lamp examination for cataract. If no reason for visual acuity change is identified, full examination by an ophthalmologist including fundoscopý and tonometry should be performed. Patients reporting blurry vision which do not improve by lens prescription and/or wetting drops should also undergo an ophthalmic examination by an optometrist or ophthalmologist as indicated above.
[18] Patients who are at risk of cataract formation, or have known cataract at enrolment should have an ophthalmic examination by an ophthalmologist including best corrected visual acuity, slit lamp examination, tonometry and fundoscopy prior to the first dose of study treatment at baseline.

9.5.3 Appropriateness of measurements

The efficacy and safety tests used in this trial are routine tests in oncological clinical trials.

9.5.4 Primary efficacy variable(s)

The primary efficacy measure was the overall response rate according to RECIST 1.1.

9.5.5 Drug concentration measurements

NA

9.6 Data quality assurance

9.6.1 Monitoring

The trial started with an initiation visit, where a CRA representing the sponsor introduced the study to the investigational site personnel.

During the trial, a CRA representing the sponsor had regular contact with the investigational site to provide information and support the investigators. Furthermore, the CRA checked whether the facilities remained acceptable, whether the investigational team was adhering to the protocol, whether data was being accurately recorded in the CRF and whether the study drug accountability checks were correct. The CRA conducted source data verification, which required direct access to all original records for the patient.

9.6.2 Audits

NA

9.7 Statistical methods planned in the protocol and determination of sample size

9.7.1 Statistical and analytical plan

This was non-randomised, open label two-armed phase II trial. Arm A included patients with thymoma. Arm B was closed as no response was observed within fifteen patients. Nevertheless, the patients already included in arm B have of course been evaluated in the final analysis of the study.
The primary objective of the trial was to determine the effect of selinexor in patients with inoperable thymoma after progression of primary chemotherapy.

Study populations:
Thymoma
This population consists of all patients with thymoma who have received at least one dose of study drug on trial.

Thymic carcinoma
This population consists of all patients with thymic carcinoma who have received at least one dose of study drug on trial.

Safety population
This population consists of all patients who have received at least one dose of study drug on trial.

9.7.2 Determination of sample size

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.

30 patients were enrolled in both trials, 15 with thymic carcinoma and 15 with thymoma.

9.8 Changes in the conduct of the study or planned analysis

During the course of the study, four protocol amendments were submitted and approved:

Amendment 2 (protocol version 1.5, Jan29, 2017):

Visual ophthalmic examinations have been implemented into the protocol as part of the safety assessments for the patients included in the trial in order to help determine if selinexor is contributing any visual changes.

Amendment 3 (protocol version 2.0, May28, 2018):

The protocol was updated following a letter from the French competent authority ANSM on May16, 2018 about the occurrence of tumour lysis syndrome (TLS) in patients after exposure to selinexor. As of May 2018, 2600 patients have been treated with selinexor so far. Among these 2600 patients, there were 8 reports of TLS in patients with haematological malignancies. A causal relationship between selinexor and TLS cannot be completely excluded. Therefore, additional safety measures and supportive care guidelines for TLS have been added to the protocol.

Amendment 4 (protocol version 3.0, Dec04, 2018):

The dose adjustment and supportive care guidelines of this protocol version have been updated in accordance to the changes in the IB v8.0, dated Jun12, 2018. The Selinexor reference safety information (section 7 of the IB v8.0, Table 14) was updated based on all safety data as of Mar31, 2018. Frequency was changes from treatment-related adverse events (TRAEs) in v7.0 to serious adverse reactions (SARs) in v8.0 to align with regulatory agency requirements.
Further modifications in protocol v3.0 were made regarding the transition from stage 1 to stage 2 to ensure that the study would not be closed after the initial 15 patients in each cohort have been enrolled and no potential benefit of selinexor has been missed. Also, the screening period has been prolonged from 21 to 28 days, and the selinexor dose has been reduced for better tolerability. The new starting dose was now the previous dose level -1: 40 mg twice weekly for 3 weeks and 1 week off instead of 60 mg twice weekly for 3 weeks per 4-week cycle.

Amendment 5 (protocol version 4.0, Dec20, 2019):

The protocol was updated following the regular update of the Reference Safety Information (Investigator's Brochure Selinexor).
Due to the interim analysis the Arm B: Thymic carcinoma has been closed. Therefore, the primary objective changed to determination of the efficacy of Selinexor in adults with TETs in not two parallel cohorts anymore but only patients with advanced thymomas progressing after primary chemotherapy. The inclusion criteria have been updated accordingly.

10 STUDY PATIENTS

10.1 Disposition of patients

Inclusion of 15 evaluable patients in each arm across all sites was completed on 19 February 2019 (comprising both US and EU trial).

Due to the interim analysis the Arm B: Thymic carcinoma has been closed. Therefore, the primary objective changed to determination of the efficacy of Selinexor in adults with TETs in not two parallel cohorts anymore but only patients with advanced thymomas progressing after primary chemotherapy.

10.2 Protocol deviations

10.2.1.1 Inclusion and exclusion criteria
No major protocol deviations with respect to inclusion and exclusion criteria were observed.

10.2.1.2 Randomisation, treatment allocation and blinding
Not applicable.

10.2.1.3 Compliance with time windows
No major protocol deviations with respect to compliance with time windows were observed.

10.2.1.4 Treatment compliance
No major protocol deviations with respect to treatment compliance were observed.

10.2.1.5 Non-permitted concomitant medication
No major protocol deviations with respect to non-permitted concomitant medication were observed.

10.2.1.6 Demographic and baseline characteristics
No major protocol deviations with respect to demographic and baseline characteristics were observed.

11 EFFICACY EVALUATION

11.1 Data sets analysed

NA

11.2 Demographic and other baseline characteristics

NA

11.3 Measurements of treatment compliance

NA

11.4 Efficacy results and tabulation of individual patient data

11.4.1 Analysis of efficacy
Please refer to 11.4.7

11.4.2 Statistical/analytical issues
NA

11.4.2.1 Adjustment for covariates
NA

11.4.2.2 Handling of dropouts or missing data
NA

11.4.2.3 Interim analysis and data monitoring

Patient inclusion was reported to the sponsor and shared between US and EU sponsor. EU sponsor had the responsibility to monitor the inclusion rate and in collaboration with the US sponsor announced when inclusion should be halted for interim analysis. After inclusion of 15 evaluable patients in each arm (comprising both US and EU trial), an interim analysis was performed.

11.4.2.4 Multi-centre studies
NA

11.4.2.5 Multiple comparison/multiplicity
NA

11.4.2.6 Use of an "efficacy subset" of patients
NA

11.4.2.7 Active-control studies intended to show equivalence
NA

11.4.2.8 Examination of subgroups
NA

11.4.3 Tabulation of individual response data
Please refer to table under point 11.4.**7**

11.4.4 Drug dose, drug concentration, and relationship to response
NA

11.4.5 Drug-drug and drug-disease interactions
NA

11.4.6 By-patient displays
NA

11.4.7 Efficacy conclusions

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.

12 SAFETY EVALUATION

12.1 Extent of exposure

In this study 22 of 23 patients received the first induction cycle. The planned dose of Selinexor was 60 mg/m² twice weekly (Monday/Wednesday, Tuesday/ Thursday, or Wednesday/Friday). One cycle was 28 days. Patients were dosed 3 weeks on and one week off in 4 week-cycles (6 doses/cycle). With the implementation of Protocol v.3.0, dated Dec04, 2018, the dosage decreased to 40 mg twice weekly.

12.2 Adverse events (AEs)

12.2.1 Brief summary of adverse events

All of the 23 patients experienced at least one adverse event (AE).

12.2.2 Display of adverse events

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 %).

Table 4 Adverse Events observed in all patients

Adverse Event	Cohort Selinexor (N=23) n (%)	
	total	Grade 3-5
Abdominal pain	2 (8.7)	0
Acute kidney injury	1 (4.3)	1 (4.3)
Adult respiratory distress syndrome	1 (4.3)	1 (4.3)
Alanine aminotransferase increased	1 (4.3)	0
Alopecia	1 (4.3)	0
Anemia	11 (47.8)	6 (26.1)
Anorexia	13 (56.6)	1 (4.3)
Arthralgia	4 (17.4)	0
Arthritis	1 (4.3)	0
Aspartate aminotransferase increased	1 (4.3)	0
Atrial fibrillation	1 (4.3)	0
Back pain	4 (17.4)	0
Blurred vision	10 (43.5)	0
Bronchial infection	3 (13.0)	1 (4.3)
Cardiac disorders - Other, specify	2 (8.7)	1 (4.3)
Cataract	3 (13.0)	2 (8.7)
Constipation	12 (52.2)	0
Cough	11 (47.8)	0
Creatinine increased	1 (4.3)	0
Dehydration	5 (21.7)	1 (4.3)
Diarrhea	8 (34.8)	2 (8.7)
Dizziness	6 (26.1)	0
Dry eye	3 (13.0)	0
Dry skin	3 (13.0)	0
Dysgeusia	8 (34.8)	0
Dyspepsia	1 (4.3)	0
Dysphagia	1 (4.3)	0
Dyspnea	12 (52.2)	0
Edema face	2 (8.7)	0
Edema limbs	4 (17.4)	0
Eye disorders - Other, specify	1 (4.3)	0
Fatigue	23 (100)	4 (17.4)
Fever	2 (8.7)	0

Adverse Event	**Cohort Selinexor (N=23) n (%)**	
	total	**Grade 3-5**
Flu like symptoms	1 (4.3)	0
Gallbladder obstruction	1 (4.3)	1 (4.3)
Gastrointestinal disorders - Other, specify	3 (13.0)	0
Gastrointestinal pain	1 (4.3)	0
General disorders and administrative site conditions - Other, specify	1 (4.3)	0
Glaucoma	3 (13.0)	0
Headache	7 (30.4)	0
Heart failure	1 (4.3)	1 (4.3)
Hepatobiliary disorders - Other, specify	4 (17.4)	1 (4.3)
Hot flashes	1 (4.3)	0
Hypokalemia	1 (4.3)	1 (4.3)
Hypomagnesemia	2 (8.7)	0
Hyponatremia	3 (13.0)	1 (4.3)
Infections and infestations - Other, specify	2 (8.7)	0
Injury, poisoning and procedural complications - Other, specify	1 (4.3)	1 (4.3)
Investigations - Other, specify	1 (4.3)	0
Joint range of motion decreased lumbar spine	1 (4.3)	0
Localized edema	4 (17.4)	0
Lung infection	3 (13.0)	2 (8.7)
Lymphocyte count decreased	1 (4.3)	0
Mucositis oral	2 (8.7)	1 (4.3)
Muscle weakness lower limb	1 (4.3)	0
Musculoskeletal and connective tissue disorder - Other, specify	4 (17.4)	0
Myalgia	5 (21.7)	0
Nausea	20 (87.0)	1 (4.3)
Neck pain	2 (8.7)	0
Neutrophil count decreased	6 (26.1)	1 (4.3)
Pain	3 (13.0)	1 (4.3)
Pain in extremity	5 (21.7)	0
Platelet count decreased	8 (34.8)	4 (17.4)

Adverse Event	**Cohort Selinexor (N=23) n (%)**	
	total	**Grade 3-5**
Renal and urinary disorders - Other, specify	1 (4.3)	1 (4.3)
Respiratory, thoracic and mediastinal disorders - Other, specify	4 (17.4)	0
Urinary tract infection	1 (4.3)	0
Vertigo	1 (4.3)	0
Vomiting	16 (69.6)	1 (4.3)
Weight loss	8 (34.8)	1 (4.3)
White blood cell decreased	2 (8.7)	0

n: number of patients

The majority of AEs was of mild to moderate intensity (grade 1-2). The organ classes most affected in AEs were general disorders and administration site condition (100 %), gastrointestinal disorders (95.7 %) and respiratory, thoracic and mediastinal disorders (87.0 %).

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

Table 5 Number of patients with related AEs

Adverse Event	**Cohort (N=23) n (%)**
Fatigue	19 (82.6)
Nausea	19 (82.6)
Vomiting	14 (60.9)
Anorexia	10 (43.5)
Anemia	9 (39.1)
Constipation	8 (34.8)
Weight loss	8 (34.8)
Blurred vision	7 (30.4)
Diarrhea	7 (30.4)
Dysgeusia	7 (30.4)
Platelet count decreased	7 (30.4)
Neutrophil count decreased	6 (26.1)
Dehydration	4 (17.4)
Cataract	2 (8.7)
Cough	2 (8.7)

Adverse Event	**Cohort (N=23) n (%)**
Dry skin	2 (8.7)
Dyspnea	2 (8.7)
Edema face	2 (8.7)
Headache	2 (8.7)
Hepatobiliary disorders – Other, specify	2 (8.7)
Hyponatremia	2 (8.7)
Myalgia	2 (8.7)
White blood cell decreased	2 (8.7)
Abdominal pain	1 (4.3)
Acute kidney injury	1 (4.3)
Alopecia	1 (4.3)
Arthralgia	1 (4.3)
Cardiac disorders – Other, specify	1 (4.3)
Creatinine increased	1 (4.3)
Dizziness	1 (4.3)
Gastrointestinal disorders – Other, specify	1 (4.3)
Gastrointestinal pain	1 (4.3)
General disorders and administrative site conditions – Other, specify	1 (4.3)
Hypokalemia	1 (4.3)
Investigations – Other, specify	1 (4.3)
Localized edema	1 (4.3)
Lymphocyte count decreased	1 (4.3)
Mucositis oral	1 (4.3)
Musculoskeletal and connective tissue disorder – Other, specify	1 (4.3)
Paresthesia	1 (4.3)
Pleuritic pain	1 (4.3)
Rhinitis infective	1 (4.3)
Tinnitus	1 (4.3)
Tremor	1 (4.3)
Vertigo	1 (4.3)

n: number of patients

12.2.3 Analysis of adverse events

NA

12.2.4 Listing of adverse events by patient

Listings of AEs by patient are presented in Appendix 16.2.10.

12.3 Deaths, other serious adverse events, and other significant adverse events

12.3.1 Listing of deaths, other serious adverse events and other significant adverse events

12.3.1.1 Deaths

One death was reported until the end of this study (4.3 %). The cause of death was respiratory distress. This SAE was unrelated to the study medication.

12.3.1.2 Other serious adverse events

The sponsor received 27 SAE reports in total.
The majority of SAEs reported were infections that affected 21.7 % of patients. SAEs concerning respiratory, thoracic and mediastinal disorders affected 13.0 % of patients, and cardiac disorders, gastrointestinal disorders as well as blood and lymphatic system disorders were reported as SAEs in 8.7 % of patients.

Table 6 Serious adverse events (SAEs)

Serious Adverse Events	Cohort (N=23) n (%)
Blood and lymphatic system disorders	2 (8.7 %)
• Anemia	2 (8.7 %)
Cardiac disorders	2 (8.7 %)
• Cardiac disorders - Other, specify	1 (4.3 %)
• Heart failure	1 (4.3 %)
Eye disorders	1 (4.3 %)
• Cataract	1 (4.3 %)
Gastrointestinal disorders	2 (8.7 %)
• Constipation	1 (4.3 %)
• Nausea	2 (8.7 %)
• Vomiting	2 (8.7 %)

Serious Adverse Events	**Cohort (N=23) n (%)**
General disorders and administration site conditions	1 (4.3 %)
• Fatigue	1 (4.3 %)
Infections and infestations	5 (21.7 %)
• Bronchial infection	1 (4.3 %)
• Infections and infestations - Other, specify	1 (4.3 %)
• Lung infection	2 (8.7 %)
• Urinary tract infection	1 (4.3 %)
Injury, poisoning and procedural complications - Other, specify	1 (4.3 %)
• Injury, poisoning and procedural complications	1 (4.3 %)
Investigations	2 (8.7 %)
• Platelet count decreased	1 (4.3 %)
• Creatinine increased	1 (4.3 %)
Metabolism and nutrition disorders	
• Hypokalemia	1 (4.3 %)
• Hyponatremia	1 (4.3 %)
Renal and urinary disorders	1 (4.3 %)
• Renal and urinary disorders - Other, specify	1 (4.3 %)
• Acute kidney injury	1 (4.3 %)
Respiratory, thoracic and mediastinal disorders	
• Adult respiratory distress syndrome	1 (4.3 %)
• Dyspnea	2 (8.7 %)

n: number of patients

12.3.1.3 Other significant adverse events

No other significant AEs were observed during the course of the study.

12.3.2 Narratives of deaths, other serious adverse events and certain other significant adverse events

No information other than the one presented in section 12.3.1.1 is available.

SAE resulting in death:
Respiratory distress, patient 04023 (Study ID 63-5):
SAE report received on Nov14, 2019: The subject had been hospitalized on Nov10, 2019. An infectious pneumonia led to sepsis and then to organ failure. The patient died of respiratory distress on Nov17, 2019. Selinexor (60mg/dose) had been taken twice weekly between Feb20, 2019 and Nov08, 2019. The study drug had been interrupted by start of the SAE. The investigator assessed the event as not related to selinexor. The cause of the event was unknown.

12.3.3 Analysis and discussion of deaths, other serious adverse events and other significant adverse events

No information other than the one presented in section 12.3.1 and 12.3.2 is available.

12.4 Clinical laboratory evaluation

12.4.1 Listing of individual laboratory measurements by patient (16.2.8) and each abnormal laboratory value (14.3.4)

Please refer to appendices.

12.4.2 Evaluation of each laboratory parameter

NA

12.4.2.1 Laboratory values over time

NA

12.4.2.2 Individual patient changes

NA

12.4.2.3 Individual clinically significant abnormalities

NA

12.5 Vital signs, physical findings and other observations related to safety

NA

12.6 Safety conclusions

Please refer to point 13.

13 DISCUSSION AND OVERALL CONCLUSION

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.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic data

NA

14.2 Efficacy data

NA

14.3 Safety data

NA

15 REFERENCES

1. Strobel P, Hohenberger P, Marx A. Thymoma and thymic carcinoma: molecular pathology and targeted therapy. J Thorac Oncol 2010; 5: S286-290.

2. Marx A, Ströbel P, Badve SS et al. ITMIG Consensus Statement on the Use of the WHO Histological Classification of Thymoma and Thymic Carcinoma: Refined Definitions, Histological Criteria, and Reporting. Journal of Thoracic Oncology 2014; 9: 596-611.

3. Hirabayashi H, Fujii Y, Sakaguchi M et al. p16INK4, pRB, p53 and cyclin D1 expression and hypermethylation of CDKN2 gene in thymoma and thymic carcinoma. Int J Cancer 1997; 73: 639-644.

4. Petrini I, Meltzer PS, Kim IK et al. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. Nat Genet 2014; 46: 844-849.

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6. Wang Y, Thomas A, Lau C et al. Mutations of epigenetic regulatory genes are common in thymic carcinomas. Sci Rep 2014; 4: 7336.

7. Kelly RJ, Petrini I, Rajan A et al. Thymic malignancies: from clinical management to targeted therapies. J Clin Oncol 2011; 29: 4820-4827.

16 APPENDICES

16.1 TET-SEL Lab values 20220620.csv

16.2 TET-SEL Lab values with CTCAE grade 20220808.xlsx

16.3 TET-SEL patients FU period 20220810.xlsx

16.4 TET-SEL Reason for Amendments v1 20220801 final.pdf

16.5 TET-SEL AE Line Listing CTCAE Coding 20220725.xlsx

16.6 TET-SEL DrugDosage v1 20220815.xls

16.7 TET-SEL DrugDosage adapted v1 20220815.xls

16.8 TET-SEL SAE case listing 20220811 sorted by start date.xlsx

16.9 TET-SEL summary final v1 20220901.pdf