STUDY OF THE mTOR INHIBITOR TEMSIROLIMUS (CCI-779) IN PATIENTS WITH CA125 ONLY RELAPSE OF OVARIAN CANCER. A phase II study by the Hellenic Cooperative Oncology Group.

HE 4/09

EudraCT: 2008-007925-38

Investigational product: Temsirolimus (Torisel)

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Sponsor's name and location:

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SYNOPSIS

BACKGROUND: Various studies have demonstrated that the PI3K pathway is activated in ovarian adenocarcinoma and that it is important for the survival, proliferation and drug resistance of pancreatic cancer cells. mTOR, one of the main downstream effectors in the PI3K pathway, is also activated in ovarian cancer cell lines. In addition, the mTOR inhibitor, Everolimus, showed significant antitumor activity in ovarian cancer cell lines and xenograft models. Temsirolimus has already showed promising activity associated with minimal toxicity in Phase I, II and one Phase III trial in a variety of human cancers. **METHODS:** This was a multi-center, open-label, non-comparative phase II trial. Patients who meet the selection criteria received treatment consisting of temsirolimus (25mg weekly in a 30-minute intravenous [iv] infusion, 30 minutes after premedication with 4mg of iv dimethindene). Treatment duration was set until clinical progression.
Patients on treatment were evaluated every 2 months with physical examination, CA125 and CT scan of the abdomen and pelvis or earlier if there was symptomatic or clinical indication of disease progression. CA125 response was determined using the GCIC criteria. **RESULTS:** 9 patients were enrolled and 7 of them were evaluable for response. The study ended prematurely due to the low accrual rate (24% of the expected accrual rate) in the first two years of patients' enrolment. **CONCLUSIONS:** The study HE 4/09 would accrue up to 38 patients but was prematurely terminated due to the slow rate of patient inclusion in the study (only 9 patients were recruited in two (2) years study duration. There were no clinically important emerging efficacy and safety findings obtained from this trial.

This Report contains confidential information

1 ETHICS

1.1 NATIONAL ETHICS COMMITTEE

The study was approved by the NEC with protocol no: 78015/1.12.08 and 42699/12.6.09 and 54066/29.06.2010 and EOF protocol no: 78013/11.03.09 and 42700/12.06.09 and 54067/29.07.2010.

1.2 ETHICAL CONDUCT OF THE STUDY

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

1.3 PATIENT INFORMATION AND CONSENT

Patients were screened for eligibility before entering the study and signed the informed consent, which was obtained before any study procedure.

2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Coordinating investigator of the study is Associate Prof. Aristotelis Bamias

Table 1. Institutions and Principal investigators

Institution	**Principal investigator**
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3 INTRODUCTION

Temsirolimus

Temsirolimus (CCI-779), a water-soluble ester of sirolimus, is a specific inhibitor of the mammalian target of rapamycin (mTOR) kinase, an enzyme that regulates cell growth and proliferation, one of the main downstream effectors in the PI3K/Akt pathway. Temsirolimus has shown activity against a wide variety of human tumor types in vitro and in vivo in nude mouse xenografts. The finding that mTOR regulates protein synthesis of hypoxia-inducible factors (HIFs, which regulate tumor angiogenesis and survival pathways that permit tumor growth in the harsh microenvironment induced by hypoxia)

suggests that many solid tumors could be negatively affected by temsirolimus inhibition of mTOR.

The primary oxidative metabolism is via CYP3A4, indicating that inhibitors and inducers of CYP3A4 enzyme system may alter the metabolism of temsirolimus, although temsirolimus does not induce CYP3A4. Temsirolimus may inhibit the metabolic clearance of substrates of CYP3A4/5 or CYP2D6 but not CYP2C9 or CYP2C8. However, a clinical study to assess the ability of temsirolimus to inhibit disposition of desipramine, a sensitive CYP2D6 substrate, was negative. This finding indicates that the effect of temsirolimus on other agents metabolised by either CYP2D6 or CYP3A4/5 is expected to be low. In vitro studies showed that temsirolimus is subject to P-gp-mediated efflux; in addition, temsirolimus inhibited the transport of digoxin, a P-gp substrate. The clinical relevance of these in vitro determined P-gp data is currently unknown.

In phase I studies temsirolimus has shown anti-tumor effects in subjects with various solid tumors which were refractory to standard therapies or where no appropriate treatment was available, suggesting that temsirolimus may be useful in the treatment of various cancers. In phase II studies temsirolimus has demonstrated clinically significant anti-tumor activity in previously treated patients with advanced breast cancer, metastatic renal cell cancer, extensive small cell lung cancer and relapsed mantle cell lymphoma. In a phase III study temsirolimus significantly increased the overall survival of patients with poor risk advanced renal cell cancer compared with interferon, with an acceptable safety profile.

Clinical studies suggest that temsirolimus is generally well tolerated with skin toxicities, mucositis and asthenia the commonest side effects.

Skin toxicities (rash, folliculitis, pruritus, ulceration and nail toxicities) have been reported in about 70% of patients treated in Phase I and Phase II studies. Mucositis has also been reported in up to 70% of patients. Asthenia (40%) and nausea (40%) are also commonly observed. Hematologic sequelae include grade III thrombocytopenia at doses

of 19.1 mg/m2/d for 5 days and 45 mg/m2/week and anemia and leucopenia at doses of 7.5 to 220 mg/m2/week. Asymptomatic grade III hypocalcemia and grade III elevation of transaminase were noted when the drug was delivered at a daily 30min IV infusion for 5 days every 2 weeks at doses of 2.16 mg/m2/day and 19.1 mg/m2/day respectively. Asymptomatic increases of triglyceride and cholesterol levels and hyperglycemia have also been reported. A reversible decrease in testosterone associated with increased level of luteinizing hormone and follicle-stimulating hormone were observed after repeated doses in some men. When temsirolimus was administered at a dose of 45mg/m2 in conjuction with 5FU and leucovorin in patients with advanced solid tumors, two toxicity-related deaths from gastrointestinal perforation, 15 grade III toxicities in nine patients and four grade IV toxicities in one patient occurred including fatigue, dehydration, leucopenia, and an acute abdomen.

Rationale

Epithelial ovarian cancer (EOC) is the leading cause of death among gynaecological malignancies. It is typically diagnosed in advanced stages (International Federation of Gynecology and Obstetrics [FIGO] stages III and IV) and in spite of initial response to surgical cytoreduction and platinum-paclitaxel chemotherapy in the majority of cases, still recurrence (and death from the disease) will occur in 60-70% of patients. CA125 is a useful tumor marker, which is used in the diagnosis and monitoring of treatment effect in ovarian carcinoma. Recently, clearly defined criteria of disease progression based on CA125 in the absence of measurable disease have been established by GCIC. Following first-line treatment, CA125 progression predates the occurrence of recurrence by RECIST criteria in the majority of cases. In a recent study, the use of CA125 as a criterion for progression did not affect the magnitude of the therapeutic benefit shown by standard criteria of radiological progression. The median lead time of CA125 progression without any evidence of measurable or evaluable disease was estimated at 3 months. Although a rise of CA125 almost certainly indicates a relapse of ovarian cancer, there is no consensus on the appropriate management of “CA125-only” recurrence.

Various studies have demonstrated that the PI3K pathway is activated in ovarian adenocarcinoma and that it is important for the survival, proliferation and drug resistance of pancreatic cancer cells. mTOR, one of the main downstream effectors in the PI3K pathway, is also activated in ovarian cancer cell lines. In addition the mTOR inhibitor, Everolimus, showed significant antitumor activity in ovarian cancer cell lines and xenograft models. As already mentioned in the background, temsirolimus has already showed promising activity associated with minimal toxicity in Phase I, II and one Phase III trial in a variety of human cancers. We therefore decided to investigate in a phase II non-randomised study the efficacy of temsirolimus in patients with CA125-only recurrence of ovarian carcinoma following first-line, platinum-based chemotherapy.

STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study was to determine the efficacy of Temsirolimus in patients with ovarian cancer with CA125 only relapse after first-line platinum-based chemotherapy.

2.2. Primary endpoint

The primary endpoint was the estimation of the 6-month clinical progression free survival.

2.3 Secondary endpoints

The secondary endpoints of the trial were:

- Progression Free Survival (PFS)
- Overall Survival (OS)
- CA125 response rate
- Safety

4 INVESTIGATIONAL PLAN

4.1 OVERALL STUDY DESIGN AND PLAN-DESCRIPTION

This was an open label, multicenter, prospective, interventional, single-arm, second line, phase II study examining the efficacy of temsirolimus in patients with CA125-only recurrence of ovarian carcinoma following first-line, platinum-based chemotherapy. Patients received treatment receive treatment consisting of temsirolimus (25mg weekly in a 30 minute intravenous [iv] infusion, 30 minutes after premedication with 4mg of iv dimethindene). The treatment protocol continued until one of the following conditions occured first:

- Evidence of measurable or evaluable disease,
- Appearance of intolerable toxicity or medical conditions that require the permanent discontinuation one of the therapy regimen drugs,
- Patient withdrawal of consent.
- Physician's decision

For the assessment of overall survival, Patients on treatment will be evaluated every 2 months with physical examination, CA125 and CT scan of the abdomen and pelvis or earlier if there is symptomatic or clinical indication of disease progression. CA125 response will be determined using the GCIC criteria.

The protocol of the study would accrue up to 38 patients.

4.2 SELECTION OF STUDY POPULATION

4.2.1 For inclusion in the trial patients must fulfill the following criteria:

1. Histologic proof of epithelial ovarian, fallopian or peritoneal carcinoma of the following histological types: serous, endometrioid, mucinous, clear cell, low differentiation
2. Age 18 years or older
3. Patients should have received first-line platinum-based chemotherapy
4. Documented CA125 progression according to GCIC criteria.
5. No evidence of measurable or evaluable disease.
6. Provision of written informed consent
7. ECOG PS 0-2
8. Life expectancy of greater than 12 weeks
9. WBC>4000/μl, platelets > 100,000/μl and a hemoglobin level > 9.5 g/dl. Adequate baseline hepatic function, defined as a total bilirubin level < 2 mg/dl, SGPT and SGOT < 2.5 times the upper limits of normal. Creatinine < 1.5 mg/dl or creatinine clearance > 60 ml/min.
10. All females of childbearing potential must have a negative serum or urine pregnancy test obtained within 2 days prior to initiation of treatment and use effective contraception during the period of therapy.
11. At least one month from the last chemotherapy administration.
12. Provision of adequate paraffin-embedded tumor tissue for translational studies (optional).

4.2.2 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Other histological types (germ cell, granulose tumors etc)

2. History of atrial or ventricular arrhythmias and/or history of congestive heart failure, even if medically controlled. History of clinical and electrocardiographically documented myocardial infarction within the last 6 months from study entry

3. Any evidence of clinically active interstitial lung disease (patients with chronic stable radiographic changes who are asymptomatic need not be excluded)

4. Pre-existing motor or sensory neurotoxicity grade 2 according to the WHO criteria (intolerable paresthesia and/or marked motor loss or worse)

5. History of any treatment for CA125 relapse

6. Known, severe hypersensitivity to temsirolimus or any of the excipients of this product

7. Other coexisting malignancies or malignancies diagnosed within the last 5 years with the exception of basal cell carcinoma or cervical cancer in situ

8. Any unresolved chronic toxicity greater than CTC grade 2 from previous anticancer therapy

9. As judged by the investigator, any evidence of severe or uncontrolled systemic disease (eg unstable or uncompensated respiratory, cardiac, hepatic or renal disease)

10. Alanine amino transferase (ALT) or aspartate amino transferase (AST) greater than 2.5 times the ULRR.

11. Active infection or evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the trial/ receive protocol treatment

12. Concomitant use of Cyp3 A inducers (phenytoin, carbamazepine, rifampicin, barbiturates or St John's Wort) should be avoided and as should treatment with strong CyP 3A inhibitors

13. Treatment with a non-approved or investigational drug within 30 days before Day 1 of trial treatment.

4.2.3 Removal of Patients from Therapy or Assessment

Patients had the right to withdraw from the study at any time and for any reason, without any impact on future medical care and monitoring. Except for the case of voluntary withdrawal or the patient's death, the investigator terminated the participation of a patient in the study protocol in the following cases:

- The patient did not comply with the instructions of the investigator,
- Documented communication loss with the patient (lost to follow-up),
- Termination of the study (locally in a participating center or in all participating centers) from the sponsor or relevant regulatory authorities and ethics committees (National Medicines Agency, Scientific Hospital Councils or National Ethics Committee), or
- Termination of the conduct of the study when the sponsor found that the study failed to enrol the estimated number of patients needed for adequate statistical power.

It is noted that the sponsor or the competent (regulatory) authority and ethics committees (National Agency for Medicines, Hospitals Scientific Councils or the National Ethics

Committee) had the right to temporarily or permanently discontinue the conduct of the study, if there were data (e.g. efficiency or safety) indicating this interruption. If there were significant new safety data, which might affect the willingness of already enrolled patients for participation, the sponsor was required to inform them immediately by the investigator.

4.3 TREATMENT

4.3.1 Treatments Administered

Temsirolimus (25mg weekly in a 30-minute intravenous [iv] infusion, 30 minutes after premedication with 4mg of iv dimethindene).

4.3.2 Identity of Investigational Products

Torisel® (temsirolimus)

Each vial Torisel® 25 mg / mL concentrate contains 30 mg temsirolimus dissolved in a total volume of 1,2 mL. After dilution of Torisel® 25 mg / ml concentrate with 1.8 mL of the withdrawn diluent, the concentration of temsirolimus is 10 mg / mL.

Each vial of Torisel® 25 mg / mL concentrate for solution contains 474 mg anhydrous ethanol. Each vial of the provided diluent contains 358 mg anhydrous ethanol.

4.3.3 Treatment Compliance

The Investigator/ Institution and / or a pharmacist or other appropriate individual, who was designated by the Sponsor maintained records of the inventory at the site of the use for each subject / delivery, storage and destruction. Investigators maintained records that adequately document patients were provided the doses specified in the protocol and reconcile the investigational product received from the sponsor.

4.4 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

It was assumed that the 6-month clinical progression free survival (CPFS) rate after marker elevation is 25% without treatment. According to the Fleming's single stage phase II design, a sample of 36 patients is needed to test the hypothesis that the CPFS rate after marker elevation under the experimental treatment will be at least 50%, with a power of 90% and a two-sided α=0.05. Taking into account a 5% withdrawal rate, 38 patients are required for this study.

5 STUDY PATIENTS

5.1 DISPOSITION OF PATIENTS

The study was prematurely terminated when the Sponsor found that the study failed to enrol the estimated number of patients needed for adequate statistical power.

Between 26 June 2009 and 09 June 2011 nine (09) patients were enrolled and were treated with the study treatment.

Table 1 Patients per center

Institution	Frequency	Percent
Department of Clinical Therapeutics, "Alexandra" Hospital, National and Kapodistrian University of Athens School of Medicine	6	66.66
Department of Medical Oncology, "Papageorgiou" Hospital, Aristotle University of Thessaloniki, School of Health Sciences, Faculty of Medicine	1	11.11
3rd Department of Medical Oncology, "Agii Anargiri"	1	11.11
Department of Medical Oncology, University Hospital of Larissa, Larissa	1	11.11

Table 2. Discontinuation

Reason	Frequency	Percent
Progression	5	55.56
Toxicity (Not fatal / else mark death)	1	11.11
Doctor's decision	1	11.11

Patient refused to continue	2	22.22
Total	9	100

6 EFFICACY EVALUATION

6.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Overall, nine patients were enrolled in the study and treated with Temsirolimus between June 2009 and June 2011. The median age was 58 (51-84) years.

6.2 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

6.2.1 Statistical/Analytical Issues

More than half of the patients experienced disease progression (n=7; 77.8%), while a total of 5 deaths (55.6%) were reported in the 9 enrolled patients. One death was reported six months post treatment initiation with Temsirolimus, while the rest of deaths occurred later than one year post study treatment administration. All reported disease progressions occurred within 2-7 months post initiation of treatment with Temsirolimus. Due to the low number of patients enrolled in our study, despite the initial power calculation for the estimation of the required sample size, medians of time-to-event endpoints, including PFS and OS, were not calculated in order to avoid arbitrary outcomes that could lead to ministerpetation of the results and the study overall. Regarding CA125, two of the nine enrolled patients (22.2%) had a decrease in CA125 of at least 50%. In one of them the decrease was noted at cycle 7 and was maintened until cycle 9 of treatment, while in the other patient a decrease of 89% in CA125 was observed at cycle 21 but was not retained for 28 days as per protocol.

7 SAFETY EVALUATION

7.1 EXTENT OF EXPOSURE

Duration

First subject was enrolled on 26 June 2011 and last patient on 09 June 2011. Study duration was estimated approximately at 2 years. During this period 9 patients were enrolled in the study. The cumulative exposure is estimated using the enrolment.

Table 4. Cycles per patient

Cycles	3	5	8	11	17	25	26	30
Patients	1	1	1	1	1	1	1	1

7.2 ADVERSE EVENTS (AEs)

7.2.1 Brief Summary of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) was used for the coding of adverse events and Common Terminology Criteria for Adverse Events v.3 (CTCAE v3) were used for the severity assessment.

The adverse events observed in trial HE 4/09, were consistent with the previously observed safety profile of temsirolimus and they were mostly grade 1-3 events. Hematological toxicities were common enough (11.5%) but only of grade 1-2. Regarding non-hematological toxicities the most commonly reported AEs belonged to metabolic and gastrointestinal disorders. Cholesterol high, diarrhea are common events with both drugs and mucositis is a known AE with mTOR inhibitors. Abnormal values of creatinine are expected due to study disease and proteinuria (20 patients with grade 1-3) is a common event with anti-VEGF agents. Another frequent event in this study was Hypertension (12 patients with grade 1-3) that is another common anti-VEGF side effect.

The most common grade 3 and 4 adverse events were infection (n=4, 10%), hypertension (n=2, 5%) hypertriglyceridemia (n=2, 5%) and mucositis (n=2, 5%).

The Serious Adverse Events during the reporting period were sixteen (Table 4. List of reported Serious Adverse Events) and three of them had fatal outcome. Two of these events were attributed to study regimen by the investigator or/and the sponsor but the study disease was considered co-factor. The third fatal event was assessed as related with the study disease. The most common SAEs belong to SOC Gastrointestinal disorders. Five SAEs were unexpected with at least one of the study drugs and reported in expedite manner to Regulatory Authorities and National Ethics Committee. Analysis of the data did not reveal any new safety issue.

7.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

7.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

Deaths

Until the day of this report there were 2 events of death. Two fatal events were recorded and one of them was not attributed to study disease, the other was attributed to under study treatment and was reported as Serious Adverse Events.

Other Serious Adverse Events

List of reported Serious Adverse Events, including deaths are presented in **Table 6** and Line-listing of Serious Adverse Events in **Table 7.**

Narrative of Serious Adverse Events and Certain Other Significant Adverse Events

Patient number: HE409-2-0002

HECOG-20100008: Aspartate aminotransferase increased
Alanine aminotransferase increased
Gamma-glutamyltransferase increased

Bilirubinemia

Gastrointestinal pain

A 61- year-old female patient with a history of Nervous disorder (anxiety) since 15 Jun 1985, Hypercholesterolemia since 15 Jun 2000, Hypertension since 15 Jun 2003, Total abdnominal hysterectomy, Bilateral salpingo-oophorectomy, Omentectomy and Appentectomy on 02 Aug 2008, Hypoalbuminemia grade 1, diagnosed with Ovarian cancer on 22 Aug 2008 and relapse of CA-125 (12 May 20009 CA-125: 15.8, 09 Jun 2009 CA-125: 19.43, 16 Sep 2009 CA 125 : 43.5, 15 Oct 2009 CA-125: 106.7, 19 Oct 2009 CA-125: 152.7, 17 Nov 2009 CA-125: 186) was enrolled in a HeCOG phase II study for the treatment of Ovarian cancer.

The patient started to receive Torisel (Temsirolimus) 25 mg i.v. every week, on 31 Dec 2009. The patient received the study drug on 10 Dec 2009, 17 Dec 09, 24 Dec 2009, 31 Dec 2009, 07 Jan 2010, 14 Jan 2010, 28 Jan 2010 and the last dose on 04 Feb 2010. Therapy duration: 60 days.

On 11 Dec 2010 the patient was admitted to hospital due to AST (209 U/L) grade 3, ALT (528 U/L) grade 3, GGT (747 U/L) grade 4, Bilirubin (1.89 mg/dL) grade 2 – not serious, Pain - Gastroindestinal grade 1 – not serious.

The patient underwent an abdomen ECHO and was diagnosed with Cholecystitis to Biliary sludge.

Actions taken as a result of the Events included patient's hospitalisation. The patient was recovering at the time of this report.

Concomitant medications at the time of the Events included Zofron (Ondansetron hydrochloride) 8 mg i.v., Zantac (Ranitidine) 150 mg i.v., Fenistil (Dimetindene) 8 mg i.v. and Dexamethasone 20 mg i.v. all as Premedication and all administered on 03 Jan 2008 ongoing, Centrac (Prazepam) 20 mg p.o. and Nevrorestol (Buspirone) 10 mg p.o. from 15 Jun 1985 occasionally for prescreening Anxiety and Triatec Plus (Ramipril + Hydrochlorothiazide) 25 mg p.o. from 15 Jun 2003 occasionally for Hypertension. The patient was receiving Prazepam and Buspirone before enrollment in the study protocol.

After starting chemotherapy the patient was not supposed to receive drugs for anxiety but she had received these drugs occasionally.

The investigator has assessed the causal relationship of study treatment to the Events as unrelated with suspect drug being Torisel (Temsirolimus) noting that the most probable cause of the Events was Cholecystitis. The investigator considered the Events Aspartate aminotransferase increased, Alanine aminotransferase increased and Gamma-glutamyltransferase increased as Serious (Involved or prolonged hospitalization and the events Bilirubinemia and Gastrointestinal pain as not medically significant.

Follow up 1 report received on 12 Mar 2010:

The investigator stated that Cholecystitis is not related to Temsirolimus but to cholate sludge. Gallbladder stone is still present.

Study drug dose was reduced from 25 mg to 20 mg from 04 Mar 2010.

On 25 Feb 2010 AST was grade 0. On 14 Feb 2010 Bilirubin was grade 0. On 04 Mar 2010 ALT was grade 0 and Gastrointestinal pain was grade 0. On 11 Mar 2010 GGT was grade 2.

Medical history added: Partial arthroplasty (right knee) on 15 Jun 2007.

Concomitant medication added:

Inegy (Simvastatin + Ezetimibe) 10 + 20 mg p.o. from 15 Jun 2000 occasionally, for Hypercholesterolemia and Seropram (Citalopram) 20 mg daily p.o. from 19 Feb 2010 ongoing for nervous Anxiety.

Past medication added: The patient was receiving Paroxetine, Prazepam and Buspirone before enrollment in the study protocol. After starting chemotherapy the patient was not supposed to receive drugs for anxiety but she had received these drugs occasionally. Exact dates are unknown.

Follow up 2 report received on 09 Apr 2010:

On 08 Apr 2010 GGT was grade 0.

Outcome: Complete recovery

Sponsor comment: Serious Adverse Event

Patient number: HE409-4-0005

GR-HECOG-20100023: Vomiting

A 68-year-old female patient with a history of psoriasiki arthritis from unknown date ongoing, Hyperlipidemia from unknown date ongoing, Laparotomy on 17 Apr 2008, cholesterol grade 1 and Neuropathy was enrolled in a HeCOG phase II study for the treatment of Ovarian cancer.

The patient started to receive Temsirolimus 25 mg intravenous weekly, on 27 May 2010. The patient received the study drug on 27 May 2010, 04 Jun 2010, 11 Jun 2010, 18 Jun 2010, 25 Jun 2010, 16 Jul 2010, 30 Jul 2010 and the last dose on 06 Aug 2010. Therapy duration: three months.

On 27 Aug 2010 the patient was admitted to hospital with Vomiting grade 3, Fatigue grade 2 and Diarrhea. Patient's hospitalization was due to multiple vomiting. The patient was recovered and discharged from the hospital on 02 Sep 2010.

Actions taken as a result of the Events included patient's hospitalisation, the administration of fluids: 12 Lt D/W 5% and 2Na+2K (totally) and the following medications: Primperan (Metoclopramide) 2 mg (2x2) intravenous from 27 Aug 2010 to 31 Aug 2010 for Vomiting, Imodium (Loperamide) 2 mg orally from 27 Aug 2010 to 30 Aug 2010 for Diarrhea, Duphalac (Lactulose) 10 ml orally (daily) from 02 Sep 2010 to 08 Sep 2010 for Constipation and Vomex (Dimenhydrinate) orally (daily) from 27 Aug 2010 to 08 Sep 2010 for Vomiting. Temsirolimus was permanently discontinued.

Concomitant medications at the time of the Events included Imodium tabs 2 mg from 27 May 2010 to 06 Aug 2010 for Diarrhea, Lonalgal (Codeine + Paracetamol) tabs (1x3) from 27 May 2010 ongoing for Pain, Depon (Paracetamol) tabs (weekly 1x1) and Fenistil (Dimetindene) intravenous (weekly 1x1) both from 27 May 2010 to 06 Aug 2010 as Premedication, Bepanthol cream and Vaseline cream daily from 25 Jun ongoing for Hand-&-foot syndrome.

Past medications included Taxol, Epirubicin, Carboplatin Cisplatin, Aromasin and Femara as first line Chemotherapy.

The investigator has assessed the causal relationship of study treatment to the Events as unknown with suspect drug being Torisel (Temsirolimus). The investigator considered the Event Vomiting as Serious (Involved hospitalization) and the events Fatigue and Diarrhea as not serious (not medically significant).

Outcome: Recovered.

Sponsor comment: Serious Adverse Reaction

Follow-up # 1

Follow-up information received on 29 Jan 2013 from the investigator.

After reviewing the patient's file the investigator considered that the cause of the event of Vomiting was the study disease due to progression.

7.4 SAFETY CONCLUSIONS

The observed AEs in the study were consistent with the previously observed safety profile of the Investigational Medicinal Product temsirolimus. Hematological toxicities were grade 1 to 2. Most common non-hematological toxicities were metabolic disorders (32.65%), followed by gastrointestinal (14.28%). The most common grade 3 adverse events belonged to Dermatology/Skin Disorders (n=2, 4.1%), Gastrointestinal disorders (n=2, 4.1%) Metabolic disorders (n=2, 4.1%).

The Serious Adverse Events during the reporting period were mostly consistent with the ones previously observed with the study drug and the underlying malignancy. One serious gastrointestinal event was reported (Vomiting grade 3). All other serious events belonged to Metabolic Disorders. All events were maximum grade 3. Only the gastrointestinal event was related to the study treatment (SAR).

8 DISCUSSION AND OVERALL CONCLUSIONS

The study HE 4/09 was terminated prematurely due to low accrual rate - only 9 patients were recruited in two (2) years study duration. There were no clinically important emerging efficacy and safety findings obtained from this trial.

Table 6. List of all Serious Adverse Events (including all SARs & SUSARs)

	Local Report Number	Patient Number	SAE Term	Related?		Expected?	SUSAR?	Outcome
				Inv	MA			
1	HECOG-20100008	409-2-0002	Aspartate aminotransferase increased Alanine aminotransferase increased Gamma-glutamyltransferase increased Bilirubinaemia Gastrointestinal pain	No	NO	NA	NO	Recovered
2	GR-HECOG-20100023	HE409-4-0005	Vomiting	NO	Yes	YES (Torisel)	NO	Recovered

Table 7. Line-Listing of all Serious Adverse Events (including all SARs & SUSARs)

	Body System: Gastrointestinal disorders				**No of cases for this body system: 6**			
Study ID: EudraCT no: Country: Age: Sex:	**Case ID Patient ID**	**Suspect Drugs [IMP]**	**Daily Dose Route of Administration**	**Dates of Treatment**	**SAR terms [MedDRA coding]**	**Onset Date or Time to Onset**	**Outcome**	**Causality assessment**
HE 4/09	GR-HECOG-20100023	Temsirolimus	25 mg i.v.	03.12.2009 – 04.02.2010	Gastrointestinal pain grade 1	11.02.2010	Recovered	**SAE Investigator's**: Not related **Sponsor's**: Not related
2008-007925-38	HE409-2-0002	Temsirolimus	20 mg i.v.	04.03.2010	Alanine aminotransferase increased grade 3	11.02.2010	Recovered	
Greece					Gamma-glutamyltransferase increased grade 4	11.02.2010	Recovered	
61- years old					Bilirubinaemia grade 2	11.02.2010	Recovered	
Female					Aspartate aminotransferase increased grade 3	11.02.2010	Recovered	
HE 4/09	GR-HECOG-20100023	Temsirolimus	25 mg i.v.	27/03/2010-06/08/2010	Vomiting grade 3	27.08.2010	Recovered	**Investigator's**: Unknown Torisel **Sponsor's**: Related Torisel
2008-007925-38	HE409-4-0005							
Greece								
68								
Female								

	Body System: Metabolic Disorders				**No of cases for this body system: 3**			
Study ID: EudraCT no: Country: Age: Sex:	**Case ID Patient ID**	**Suspect Drugs [IMP]**	**Daily Dose Route of Administration**	**Dates of Treatment**	**SAR terms [MedDRA coding]**	**Onset Date or Time to Onset**	**Outcome**	**Causality assessment**
HE 4/09	GR-HECOG-20130042	Temsirolimus	25 mg i.v.	03.12.2009 – 04.02.2010	Alanine aminotransferase increased grade 3	11.02.2010	Recovered	**Investigator's**: Not Related **Sponsor's**: Not Related
2008-007925-38	HE409-2-0002	Temsirolimus	20 mg i.v.	04.03.2010	Gamma-glutamyltransferase increased grade 4	11.02.2010	Recovered	
Greece					Bilirubinaemia grade 2	11.02.2010	Recovered	
61- years old					Aspartate aminotransferase increased grade 3	11.02.2010	Recovered	
Female					Gastrointestinal pain grade 1	11.02.2010	Recovered	