# EFFICACY AND SAFETY OF BEVACIZUMAB/TEMSIROLIMUS COMBINATION AFTER FIRST-LINE anti-VEGF THERAPY IN ADVANCED RENAL CELL CARCINOMA

## HE 21/10

**EudraCT: 2010-020664-38**

**Investigational products: Bevacizumab (avastin), Temsirolimus (Torisel)**

***Report date***

***15 July 2016***

**Sponsor's name and location:**

Hellenic Cooperative Oncology Group

Chatzikonstanti 18, Athens

Tel.: 0030 210 69 12 520

**Study Coordinator**

Associate Prof. Aristotelis Bamias

"ALEXANDRA" Hospital

Tel.: 0030 210 33 81 546

# SYNOPSIS

**BACKGROUND:** Anti vascular endothelial growth factor (aVEGF) agents represent the standard 1st-line therapy for mRCC. Monotherapy with agents blocking VEGF, mTOR or PD1/PD-L1 interaction are approved therapies. Since continuing blockade of VEGF may be of value, we studied the combination of bevacizumab with temsirolimus in mRCC patients relapsing after 1st-line treatment. **METHODS:** A prospective, phase II, multicenter, trial evaluating the combination of bevacizumab (10mg/kg, every 2 weeks) with temsirolimus (25 mg weekly), until progression of the disease or unacceptable toxicity, was conducted in patients with mRCC who failed first-line aVEGF treatment. No previous therapy for relapsed disease was allowed. Percentage (%) of 6-month progression-free survival was the primary end point. **RESULTS:** 39 patients were enrolled and 37 of them were evaluable for response. 1st-line therapy included: sunitinib(16), bevacizumab/interferon (12), pazopanib (10), sorafenib (1). The median age was 67 (40-80) years. Clear cell histology was present in 97.4% of patients. The median time to progression was 6.8 months (95%CI 5.5-9.2), whereas the overall survival was 18.2 months (95%CI 12.9-27.2). Best responses were: complete-1 (2.7%), partial-9 (24.3%), stable disease-20 (54.1%), progression-7 (18.9%). Worst toxicities were of grade: 1 in 1 case (3%), 2 in 20 (51%), 3 in 15 (38%), 4 in 2 (5%), 5 in 1 (3%). The most common adverse events (AEs) were metabolic (44%), gastrointestinal (11%) and myelotoxicity (9%). The most common grade 3 and 4 AEs were infection (10%), hypertension (5%), hypertriglyceridemia (5%) and mucositis (5%). Toxicity was the most frequent cause of treatment discontinuation (33%). **CONCLUSIONS:** The combination of bevacizumab and temsirolimus is active in mRCC patients relapsing after aVEGF 1st-line treatment. Our study confirms recent encouraging data of another anti-VEGF/anti-mTOR combination in this population.

**This Report contains confidential information**

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# 1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| AST | Aspartate aminotransferase |
| CRF | Case Report Form |
| CT scan | Computed axial Tomography |
| CTPA | Computed Tomography Pulmonary Angiography |
| ECOG | Eastern Cooperative Oncology Group |
| FGF | Fibroblast Growth Factor |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyltransferase |
| HIF-a | Hypoxia-Inducible Factor a |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ICU | Intensive Care Unit |
| IFN | Interferon |
| i.v. | Intravenous |
| mTOR | mammalian Target of Rapamycin |
| NCI CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| OS | Overall Survival |
| PDGF | Platelet-Derived Growth Factor |
| PET scan | Positron Emission Tomography |
| PFS | Progression-Free Survival |
| p.o. | Oral |
| QoL | Quality of Life |
| RCC | Renal Cell Carcinoma |

| | |
|---|---|
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RR | Response Rate |
| SAE | Serious Adverse Event |
| SPC ή ΠΧΠ | Summary of Product Characteristics |
| ULN | Upper Limit of Normal |
| VEGF | Vascular Endothelial Growth Factor |
| VHL (gene) | von Hippel Lindau (gene) |

# 2 ETHICS

## 2.1 NATIONAL ETHICS COMMITTEE

The study protocol and the amendments were reviewed by the National Ethics Committee (NEC) of Greece. NEC protocol no: 54064/29-07-2010

## 2.2 ETHICAL CONDUCT OF THE STUDY

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

## 2.3 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.

# 3 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Coordinating investigator of the study is Associate Prof. Aristotelis Bamias

**Table 1.** Institutions and Principal investigators

| **Institution** | **Principal investigator** |
|---|---|
| Department of Clinical Therapeutics, "Alexandra" Hospital, National and Kapodistrian University of Athens School of Medicine, Athens | A. Bamias |
| Department of Medical Oncology, "Papageorgiou" Hospital, Aristotle University of Thessaloniki, School of Health Sciences, Faculty of Medicine, Thessaloniki | G. Fountzilas |
| Division of Oncology, Second Department of Internal Medicine, Attikon University Hospital, Athens | D. Pectasides* |

| | |
|---|---|
| Third Department of Medical Oncology, "Agii Anargiri" Cancer Hospital, Athens | A. Visvikis |
| Second Department of Medical Oncology, "Agii Anargiri" Cancer Hospital, Athens | G. Aravantinos |
| Division of Oncology, Department of Medicine, University Hospital, University of Patras Medical School, Patra | A. Koutras |
| First Department of Medical Oncology, "Metropolitan" Hospital, Piraeus | D. Bafaloukos |
| Second Department of Medical Oncology, "Metropolitan" Hospital, Piraeus | E. Galani |
| Oncology Section, Second Department of Internal Medicine, "Hippokration" Hospital, Athens | D. Pectasides |

* D. Pectasides moved to another institution

# 4 INTRODUCTION

**Renal cancer and VEGF**

Vascular endothelial growth factor (Vascular endothelial growth factor, VEGF) is a potent angiogenic factor. It plays a central role in the process of neovascularization (1), which is critical for the development of human tumors. Targeted therapies against VEGF (anti-VEGF therapies) already used for the treatment of various human malignancies, including kidney cancer (renal cell carcinoma, RCC). The clear cell renal cancer is an obvious target for anti-angiogenic treatment strategies, as the mutation of the VHL gene is often present in individual tumors(2). Inactivation of VHL gene leads to unrestricted activity induced by hypoxia-inducible factor alpha (HIF-a) and over production of angiogenic factors, in particular of VEGF and PDGF (2). The multi-kinase inhibitor sunitinib and the combination of bevacizumab with interferon alfa-2a (IFNa) have been established as a standard first-line treatment for advanced RCC, following the results of two randomized trials, which showed significantly increased progression-free survival disease (PFS) compared with monotherapy IFNa (3, 4). The effectiveness of these treatments is mainly attributed to the inhibition of VEGF action on the tumor vasculature,

as sunitinib inhibits the tyrosine kinase receptor for VEGF, and the bevacizumab is a monoclonal antibody against the VEGF receptor. But despite the initial clinical benefit, most patients will relapse and eventually will end because of the disease. Therefore, there is a need for the development of effective treatments after the failure of a first line anti-angiogenic agent.

The optimal therapy after failure of an anti-angiogenic agent remains a topic of continuing clinical research. The selection is made more difficult because the resistance mechanisms to antiangiogenic therapy are still unclear. To complicate things even more, failure of a specific agent does not necessarily lead to loss of effectiveness of another agent with similar mode of action (5, 6).

**Simultaneous horizontal inhibition of VEGF and mTOR**

HIF-a has a central role in the angiogenic process. In addition to mutations in the VHL gene, the mTOR pathway may indirectly increase the production of HIF-a (7). The importance of this interaction has been demonstrated in a recent randomized clinical trial, which showed that temsirolimus, an inhibitor of mTOR, prolonged survival of low-risk patients with advanced RCC, compared to IFNa (8). Unlike angiogenic factors, mTOR inhibitors targeting the tumor cell, rather than the tumor vasculature. It can be assumed that the combination of temsirolimus with anti-angiogenic agents may represent a more effective anti-angiogenic therapy strategy. In favor of this hypothesis are preclinical data that indicate the synergistic effect of sunitinib with mTOR inhibitors(9). Furthermore, another randomized clinical trial showed that treatment with RAD001, mTOR inhibitor, was effective in patients who had received anti-angiogenic therapy, including bevacizumab (6). This establishes the inhibition of mTOR as the current standard treatment after failure of anti-angiogenic therapy. It can be assumed that blocking 'horizontal' two related but different targets may increase efficacy in comparison to inhibition of mTOR alone. Preclinical data support the continuous inhibition of VEGF, as well as unblocking of VEGF may accelerate disease progression by rapid regrowth of tumor vasculature(10, 11). In a preliminary report, the combination bevacizumab / RAD001 was effective in patients with colorectal cancer who have experienced disease

progression on therapy with bevacizumab(12). These proposed results affect the design of clinical trials, since they support the maintenance of VEGF inhibition(13-16). The scientific interest in 'horizontal' inhibition in RCC is reflected by the fact that the combination of bevacizumab with temsirolimus or RAD001 now are investigated as the first or second line therapy in two international randomized clinical trials. Finally, the results of a recent study can be considered as proof of this principle, as the study showed that continued inhibition of VEGF further than the original disease progression in patients with colorectal cancer can improve treatment success(17).

**Predictive value of the levels of angiogenic factors**

The prediction of outcome is an important issue in the era of targeted therapies, as RECIST criteria seem inadequate to uncover the biological effect of these therapies to tumors. For this reason, it has been suggested the change of the response criteria which are based on CT or PET scans(18). Furthermore, the identification of angiogenic markers in circulation, which can provide a positive response, is an intensive research. Serum levels of VEGF and VEGFR change during therapy with anti-angiogenic factors, but their predictive value has not yet been clarified (19, 20). Finally, the PDGF levels at the start of treatment have been associated with positive treatment outcome(21), while increasing levels of FGF has also been proposed as a mechanism of resistance to anti-angiogenic therapy(22).

**Rationale**

Optimal therapy after failure of an antiangiogenic agent remains a burning issue. The selection is more difficult because the resistance mechanisms in an antiangiogenic therapy are still unclear. Failure of an agent does not necessarily lead to loss of effectiveness of a different agent with similar or different mode of action(5, 6).

Considering all the above, we believed that the combination of bevacizumab and temsirolimus may prove effective in patients with disease progression after treatment with bevacizumab and interferon alpha. Furthermore, we proposed the study of novel response criteria, as well as the change of serum levels of angiogenic factors in therapy as predictive factors of treatment outcome in these patients.

# 5 STUDY OBJECTIVES

The primary objective of the study was:

- Evaluation of efficacy (6 month PFS). To estimate 6- month Progression-free survival (PFS) after 2nd-line treatment with the combination of Bevacizumab/Temsirolimus in patients with advanced RCC progressing after 1st line treatment with anti-VEGF therapy.

The secondary endpoints of the study were:

- Median Progression Free Survival (PFS)
- Overall Survival (OS)
- Response Rate (RR)
- Tumour shrinkage
- Evaluation of safety

  Adverse events with any causal relationship with the study IMPs

  Serious adverse events with any causal relationship with the study IMPs

- Quality of Life (QoL) evaluation using the QLQ C-30 questionnaire (see Appendix 1 for the Greek QLQ C-30 questionnaire).
- Exploration of antiangiogenic parameters for response. (Pending - In process)

# 6 INVESTIGATIONAL PLAN

## 6.1 OVERALL STUDY DESIGN AND PLAN-DESCRIPTION

This was an open label, multicenter, prospective, interventional, single-arm, second line, phase II study examining the efficacy and safety of combination bevacizumab / temsirolimus (Avastin® / Torisel®), administered as second line therapy in patients with advanced renal cancer, after failure of first-line anti-VEGF therapy. Patients received

treatment with Avastin® (bevacizumab) 10 mg / kg body weight, i.v., once every two weeks and Torisel® (temsirolimus) 25 mg, i.v.ly, once per week and the efficiency and safety of the treatment were assessed. The treatment protocol continued until one of the following conditions occured first:

- Documented disease progress,
- Appearance of intolerable toxicity or medical conditions that require the permanent discontinuation one of the therapy regimen drugs,
- Patient withdrawal of consent.

For the assessment of overall survival, patients were monitored after the end of treatment (follow-up) until death or until study end (whichever came first).

The protocol of the study would accrue up to 47 patients. This number included a 5% more than the necessary number of patients for possible withdrawals in order not to risk the statistical power of the study.

The total duration of the study comprised the completion of the following stages:

- Patient inclusion stage.
- Therapy stage.
- Stage of monitoring after treatment and until death.

## 6.2 SELECTION OF STUDY POPULATION

### 6.2.1 Inclusion Criteria

- Adult patients (18th year of age completed)
- Signed and dated written informed consent form prior to any procedures related to this protocol.
- Histologically confirmed advanced clear cell renal cancer.
- Measurable disease.

- Failure of first line anti-VEGF treatment.
- Physical status 0-2, according to ECOG.
- Satisfactory hematological parameters:
    - White blood cell count > 4000 $mm^3$.
    - Platelet count 100000/$mm^3$.
    - Neutrophil blood cell count > 1200/ $mm^3$.
    - Hemoglobin > 9,0 g/dL (can be achieved with red blood cell transfusion).
- Satisfactory biochemical parameters:
    - Serum creatinine < 2 x ULN (Upper Limit of Normal).
    - AST<2,5 x ULN.
    - ALT< 2,5 x ULN.
    - Bilirubin <2 x ULN.
- (For female patients) Absence of pregnancy (negative pregnancy test for women of reproductive age before enrollment).
- (For female patients) Non-lactating women.
- Use of efficient contraceptive measures (women and men) to prevent possible pregnancy of female patients or female partner of male patients during treatment and until 6 months after the end of treatment.

### 6.2.2 Exclusion Criteria

- Prior treatment with mTOR inhibitor.
- Major surgery (including open biopsy) or insufficient recovery or existence of major trauma within 4 weeks before enrollment.

- Uncontrollable hypertension.
- Active infection requiring systemic treatment within 4 weeks prior to enrollment.
- Minor surgery (for instance, catheter placement) within 2 days before enrollment.
- Scheduled major surgery within the treatment period.
- Medical history in the last 6 months prior to enrollment of significant cardiovascular disease, diabetes, cardiac infarction, unstable angina, uncontrolled arrhythmia or significant heart failure.
- Indications of uncontrolled metastases or disease progression in CNS lesions (the suspicion of uncontrolled metastases or disease progression should be eliminated by imaging techniques within 14 days prior to enrollment).
- Medical history in the last 5 years prior to enrollment of any other malignancies (excluding the basal or squamous skin cell carcinoma or in situ carcinoma of the cervix).
- History of non-healing wound including active gastric ulcer.
- History in the last 6 months prior to enrollment of fistula.
- History of gastrointestinal perforations.
- Patient incapacity (for psychiatric or social reasons) to conform to the protocol.
- History of hemorrhagic predisposition.
- History of hypersensitivity to the medications under investigation.
- Significant proteinurea.
- Prior immunotherapy within 4 weeks prior to enrollment.
- Prior radiation treatment within 2 weeks prior to enrollment.

- Concomitant medication with inducers or strong inhibitors of the coenzyme CYP3A4 (see Appendix 2 for an indicative list of active compounds).
- Concurrent participation in other interventional clinical trials with investigational medicinal products.
- History of chronic interstitial lung disease.

### 6.2.3 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.

## 6.3 TREATMENT

### 6.3.1 Treatments Administered

Torisel® dose is 25 mg administered i.v. by infusion over a 30- to 60 minutes once a week. Patients should receive diphenhydramine 25-50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose.

The dose of Avastin is 10 mg / kg body weight administered once every two weeks as an i.v. infusion.

### 6.3.2 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.

**Avastin® (bevacizumab)**

Each vial of Avastin® (25 mg / mL) contains 100 mg bevacizumab in 4 mL or 400 mg bevacizumab in 16 mL. The bevacizumab is a recombinant humanized monoclonal antibody produced by DNA technology in ovary cells from Chinese Hamster. For a full list of excipients, refer to the SPC of the product.

### 6.3.3 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 that patients were provided the doses specified in the protocol and reconcile the investigational product received from the sponsor.

## 6.4 EFFICACY AND SAFETY VARIABLES

### 6.4.1 Efficacy and Safety Measurements Assessed

Efficacy was evaluated by PFS, OS, and RR.

PFS and OS were estimated from the date of first treatment until progression, death, treatment discontinuation (for PFS) or last follow-up, whichever occurs first.

Responses were evaluated with RECIST criteria. Baseline tumour assessment included CT scan of the thorax, abdomen and pelvis. Bone scan and Brain CT was performed only in the case of known disease at these sites or clinical indication. Tumor assessment was performed every 8 weeks of treatment and at the discontinuation of study drug, unless it was performed within the last 4 weeks. Objective responses were confirmed with a second examination, which was performed not earlier than 4 weeks.

All SAEs occurring after the signed informed consent were being reported. All patients who had at least one administration of study drug were evaluated for safety.

Haematology and biochemical measurements were performed at baseline and every 2 weeks while on treatment. Physical examination (including BP) and urine analysis for proteinuria were performed at each drug administration. A chest X-ray performed at baseline and every 4 weeks, while on treatment.

Treatment was discontinued in case of toxicity grade 3 or 4 and resumed after resolution to grade 0 or 1, except for the occurrence of special medical conditions requiring the permanent discontinuation of any of the study drugs. No dose modifications were allowed for Avastin in case of temporary discontinuation. Temsirolimus re-initiation dose was reduced by 20% in case of temporary discontinuation. In case of active infection treatment was also discontinued until resolution. In case of respiratory symptoms, a chest X-ray was performed to assess the possibility of pneumonitis. If pneumonitis was diagnosed, it was managed appropriately and temsirolimus was reintroduced at 50% of the initial dose.

According to the protocol only two temporary discontinuations of the responsible drug were allowed, without permanently discontinuing the responsible drug. Any temporary

discontinuation could last up to 6 weeks, until the toxicity degraded to a grade 0 or 1; otherwise, the treatment was permanently discontinued.

Special medical conditions requiring immediate permanent discontinuation of bevacizumab included:

Grade 3 or 4 bleeding.

Arterial thromboembolism of any grade.

Venous thromboembolism of grade 4.

Reversible posterior leukoencephalopathy syndrome.

Gastrointestinal perforation.

Grade 4 fistula.

Grade 4 hypertension (hypertensive crisis) or hypertension that could not be controlled with the co-administration of four anti-hypertensive drugs.

Grade 4 proteinuria (nephrotic syndrome).

Grade 3 or 4 of left ventricular heart dysfunction.

Special medical conditions requiring immediate discontinuation of temsirolimus included:

Grade 4 pneumonitis or second incidence of grade 3 pneumonitis.

## 6.5 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

PFS and OS were calculated using the Kaplan-Meier curves. The prognostic significance of reference characteristics was studied by log rank. The change in the score of the questionnaires on quality of life at the beginning and during treatment will be checked by Wilcoxon rank-sumtest.

**Analysis of efficacy**

The assessment of disease progression was based on RECIST criteria. Assessments were operating at every eight (8) weeks during treatment. In case of objective response, this

was confirmed by revaluation after a period of at least four (4) weeks. Median PFS and OS were calculated by survival analysis with Kaplan-Meier curves.

**Analysis of safety**

Adverse events and laboratory parameters were assessed by the investigator according to the rating system of NCI CTCAE version 3.0. Adverse events (serious or not) were coded under MedDRA system. The incidence of all adverse events was described separately for serious and non-serious in the form of frequency tables.

**Analysis of quality of life**

The change in the questionnaire score EORTC QLQ C30 during treatment will be assessed by testing Wilcoxon rank-sum test.

**Determination of Sample Size**

The primary endpoint of the study was to assess the proportion of patients with a six-month PFS. The most reliable data on the effectiveness of second-line treatment with mTOR inhibitor after previous treatment with anti-angiogenic factors (including bevacizumab) was extracted from the published study RECORD-1, which showed a six-month PFS rate of 26% for patients receiving monotherapy with RAD001(6). Assuming that the minimum acceptable value is 30% and that a substantial improvement of clinical importance is the absolute increase of 20% when patients are treated with combination bevacizumab / temsirolimus, to test the hypothesis that the proportion of patients with a six-month PFS under the conditions of the experimental treatment is 50% or higher, a sample of 44 patients was required according to the Fleming's single-stage design. Under these assumptions, this study would have 80% statistical power for a contra lateral control type I error a = 0.05. Given a number of 5% patients withdrawn, finally, a total of 47 patients should be included in the study.

# 7 STUDY PATIENTS

## 7.1 DISPOSITION OF PATIENTS

Since the completion of the study was particularly difficult due to developments in the field of the treatment of recurrent metastatic renal cancer, the sponsor (HeCOG) decided to terminate the trial earlier. Between 23 Feb 2011 and 07 Apr 2015 thirty-nine (39) patients were enrolled and 37 of them were evaluable for response. First-line therapy included: sunitinib (16), bevacizumab/interferon (12), pazopanib (10), sorafenib (1). The median age was 67 (40-80) years. Clear cell histology was present in 97.4% of patients.

**Table 2 Patients per center**

| Institution | Frequency | Percent |
|---|---|---|
| Department of Clinical Therapeutics, "Alexandra" Hospital, National and Kapodistrian University of Athens School of Medicine | 15 | 38.5 |
| Department of Medical Oncology, "Papageorgiou" Hospital, Aristotle University of Thessaloniki, School of Health Sciences, Faculty of Medicine | 11 | 28.2 |
| Third Department of Medical Oncology, "Agii Anargiri" | 6 | 15.4 |
| Second Department of Medical Oncology, "Agii Anargiri" | 3 | 7.7 |
| Division of Oncology, Department of Medicine, University Hospital, University of Patras Medical School | 2 | 5.1 |
| First Department of Medical Oncology, "Metropolitan" Hospital | 1 | 2.6 |
| Second Department of Medical Oncology, "Metropolitan" Hospital | 1 | 2.6 |

**Table 3. Discontinuation**

| Reason | Frequency | Percent |
|---|---|---|
| **Death** | 2 | 8.7 |
| **Progression** | 6 | 26 |
| **Toxicity (Not fatal / else mark death)** | 8 | 34.8 |
| **Other** | 7 | 30.4 |
| **Total** | 23 | 100 |

# 8 PROTOCOL DEVIATIONS

- In one patient the reevaluation performed in 19 weeks instead of eight weeks as requested by the protocol.
- Three patients temporary stopped the treatment for more than two times, which is the maximum according to the protocol. According to the protocol only two temporary discontinuations of the responsible drug were allowed, without permanently discontinuing the responsible drug.
- In one case the SAE form was sent two months later the investigators' awareness date of the serious event.
- One patient had undergone a surgery in 2011, for the removal of a non-invasive urothelial carcinoma of the bladder of low grade. One of the exclusion criteria refers that: "Medical history in the last 5 years prior to enrolment of any other malignancies (excluding the basal or squamous skin cell carcinoma or in situ carcinoma of the cervix)." Patient's enrolment in 2013 was PI's decision.
- According to the protocol Avastin was administered every 15 days. In one patient was administered the day 1 and the day 8 of the 1$^{st}$ cycle, by mistake.
- In one patient was administered Torisel reduced by one dose level due to Thrombopenia grade 1. According to the protocol two re-initiations were allowed for Torisel, with the dose reduced by 20% every time, if toxicities were grade 3 or 4 and no permanent discontinuation was requested.

# 9 EFFICACY EVALUATION

## 9.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Refer to **Table 4 Basic clinical characteristics_Descriptives**

## 9.2 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

### 9.2.1 Statistical/Analytical Issues

39 patients were enrolled and 37 of them were evaluable for response. The median age was 67 (40-80) years. The median time to progression was 6.8 months (95%CI 5.5-9.2), whereas the overall survival was 18.2 months (95%CI 12.9-27.2) and 6 month PFS rate was 50.9% (95% CI 33.8%-65.7%). Kaplan –Meier curves for OS and PFS are shown in Figures 1 & 2. Best responses were: complete-1 (2.7%), partial-9 (24.3%), stable disease-20 (54.1%), progression-7 (18.9%).

Regarding the questionnaires of QoL:

- 2 patients out of 39 did not complete any questionnaire
- Only 13 patients have given 4 or more answers
- 24 patients have given 3 or less answers
- Only 2 patients have completed 8 questionnaires

The respective scores are shown in Figures 3-12

# 10 SAFETY EVALUATION

## 10.1 EXTENT OF EXPOSURE

**Duration**

First subject was enrolled in 23 Feb 2011 and last patient on 07 Apr 2015. Study duration is estimated approximately at 4 years. During this period 39 patients were enrolled in the study. The cumulative exposure is estimated using the enrolment.

**Table 5. Cycles per patient**

| Cycles | 1 | 3 | 4 | 5 | 6 | 7 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 18 | 20 | 21 | 22 | 27 | 29 | 33 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients | 1 | 3 | 2 | 4 | 4 | 3 | 3 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |

## 10.2 ADVERSE EVENTS (AEs)

### 10.2.1 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 21/10, were consistent with the previously observed safety profile of bevacizumab and temsirolimus and they were mostly grade 1-3 events. Hematological toxicities were common (9%) but only of grade 1-2. Regarding non-hematological toxicities the most commonly reported AEs belonged to metabolic and gastrointestinal disorders. Nausea, 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 7**. 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.

### 10.2.2 Display of Adverse Events

Refer to **Table 6**

## 10.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

### 10.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

**Deaths**

Until the day of this report there were 26 events of death. During the reporting period (until 30 days after the last dose of study drug) four fatal events were recorded and two of them were not attributed unequivocally to study disease and reported as Serious Adverse Events. Two of these events were assessed as being related to the study treatment by the investigator or/and HeCOG.

**Other Serious Adverse Events**

List of reported Serious Adverse Events, including deaths are presented in **Table 7** and Line-listing of Serious Adverse Events in **Table 8.**

**Narrative of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events**

***Deaths***

*Patient number: HE 2110-26-0001*

*GR-HECOG-20110024*: Lung Infection Grade 5

This case concerned a 65 - year-old male patient with a history of Renal cancer diagnosed on 20 Aug 2010 and Hypertension arterial from Aug 2006 to Apr 2011. The patient also had GGT increased grade 1 since 23 Feb 2011 and Hyperglycemia grade 1.

The patient on 23 Feb 2011 started to receive Torisel 25 mg i.v. (weekly) and Bevacizumab (Avastin) 650 mg i.v. (every 2 weeks). The last dose of Temsirolimus and Bevacizumab before the SAE onset was on 13 Apr 2011. The patient presented Rash (not serious) from 13 Apr 2011 to 28 Apr 2011. The study therapy discontinued and the

patient treated with Methylprednisolone and Dimetindene and Rash abated according to the patient's daughter.

Two days before 28 Apr 2011 the patient developed Fever, which was not reported to the investigator. Twelve hours prior to death the patient visited the Accidents and Emergencies of the local Hospital according to the investigators' advice. From the description of the patient's daughter it was assumed that the patient was in Respiratory distress and a Paracentesis was performed to drain the pleural fluid. No treatment other than Paracentesis was given for the SAE. Haematuria and Haemoptysis were also noted. The patient died on 28 Apr 2011 at 06.30 a.m. No Intubation was attempted. On 03 May 2011 the investigator contacted the Hospital where the patient died. Respiratory distress, Haemoptysis grade 1 and Fever were due to Lung infection grade 5. Respiratory distress and Haemoptysis started on 27 Apr 2011. Haematuria grade 1 (not serious) started on 06 Apr 2011 due to study disease. Autopsy was not performed. The patient's daughter brought the investigator the patient's examinations performed at the hospital the day before the patient's death. There was no evidence of any acute cardiac event. The White blood cell count was increased. The investigator considered that these facts strengthen the investigator's diagnosis.

27 Apr 2011, time: 14:16

Hematocrit 51.8 % (Normal range: 40.5%-47%), Hemoglobin 17.7 g/dL (Normal range: 11.7 g/dL-15.7 g/dL), White blood cell count 24700/μL (Normal range: 4000-10000/μL) {Neutrophil count 85.2% (Normal range: 37-80%), Lymphocyte count 7.57% (Normal range: 10-50%), Monocyte count 6.92% (Normal range: 0.5-12%)}, Platelet count 330000/μL (Normal range: 142000-440000/μL), Erythrocyte sedimentation rate 5 mm 1st hour (Normal range: 0-15 mm), Prothrombin time ratio 11.5 sec (Normal range: 11-16 sec), International normalized ratio 0.95, Activated partial thromboplastin time 31.2 (Normal range: 26-45), Potassium 4.32 mmol/L (Normal range: 3.5-5.1 mmol/L), Sodium 130 mmol/L (Normal range: 136-145 mmol/L), Urea 47 mg/dL (Normal range: 10-45 mg/dL), Creatinine 0.5 mg/dL (Normal range: 0.6-1.3 mg/dL), Glucose 145 mg/dL

(Normal range: 74-106 mg/dL), Protein total 9.4 g/dL (Normal range: 6.4-8.2), Albumin 2.7 g/dL (Normal range: 3.4-5.0 g/dL), Creatine kinase 426 IU/L (Normal range: 39-308 IU/L), Creatine kinase MB 310 IU/L (Normal range: 7-25 IU/L), Alkaline phosphatase 115 IU/L (Normal range: 50-136), gamma-glutamyl transferase 98 IU/L (Normal range: 5-85 IU/L).

27 Apr 2011, time: 17: 22, same laboratory, and same normal range.

Hematocrit 47.9 %, Hemoglobin, 16.1 g/dL, White blood cell count 28800/μL {Neutrophils 80%, Lymphocytes 9.68%, Monocytes 9.66%}, Platelets 224000 /μL, Prothrombin time ratio 11.7 sec, International normalized ratio 0.97, Activated partial thromboplastin time 33.7, Fibrinogen 638 mg/dL (Normal range: 200-400 mg/dL), D-dimer [MedDRA LLT term: Fibrin D-dimer, MedDRA LLT code: 10016577] 1.52 mg/L (Normal range <0.5), Potassium 4.3 mmol/L, Sodium 130 mmol/L, Calcium [MedDRA LLT code: 10006948] 8.9 mmol/L, Urea 55 mg/dL, Creatinine 1.7 mg/dL, Glucose 209 mg/dL, Protein total 7.2 g/dL, Albumin 2.7 g/dL, Bilirubin total 1.0 mg/dL (<1), AST 22 IU/L (Normal range: 15-37 IU/L), ALT 38 IU/L (Normal range: 30-65 IU/L), Creatine kinase 56 IU/L, Alkaline phosphatase 100 IU/L, gamma-glutamyl transferase 346 IU/L, Serum amylase 30 IU/L (25-115 IU/L).

27 Apr 2011, time: 21:05, same laboratory, and same normal range.

Potassium 4.0 mmol/L, Sodium 134 mmol/L, Urea 65 mg/dL, Creatinine 2.2 mg/dL, Glucose 206 mg/dL, AST 21 IU/L, ALT 33 IU/L, Creatine kinase 65 IU/L, CPK 13 IU/L, Troponin 0.05.

27 Apr 2011, time: 21:30

Blood gases: pH=7.427 (Normal range: 6.5–8.0), pCO2=29 mmHg, pO2=50.8 mmHg, Oxygen saturation=86.9%, HCO3=19.6mmol/L (FiO2=21%).

Concomitant medications at the time of the Event included Medrol (Methylprednisolone) 16 mg tid p.o. from 20 Apr 2011 to 24 Apr 2011 and Fenistil (Dimetindene Maleate) from 20 Apr 2011 to 26 Apr 2011 both for Rash grade 3 and Co-Aprovel (Irbesartan +

Hydrochlorothiazide) p.o. for Hypertension arterial. Past medications included Interferon A 3 mIU three times per week intramuscular from 14 Sep 2010 to 11 Oct 2010 and Bevacizumab 650 mg every two weeks i.v. from 14 Sep 2010 to 08 Feb 2011 both for Renal cancer, and Coversyl (Perindopril) p.o. for Hypertension arterial.

The investigator has assessed the causal relationship of study treatment to the Serious Event as not related to Temsirolimus and Bevacizumab. The investigator considered the Chest infection as the most probable cause of the Event. The investigator considered the Event as Serious (Death).

Outcome: Death

Sponsor's comment: Suspected Unexpected Serious Adverse drug Reaction (SUSAR)

*Patient number: HE2110-32-0026*

*GR-HECOG-20130046*: Pneumonia grade 5

This case concerned a 56-year-old female patient with a history of Renal cancer diagnosed after right Nephrectomy on 31 Aug 2004, Lung metastases since 23 Nov 2012, 1st line Chemotherapy with Votrient from 13 Dec 2012 to 10 Jul 2013, Allergy to i.v. contrast media, Hypothyroidism, Anaemia grade 1, LDH increased grade 1, Dyspnoea grade 1 and Fatigue grade 1. The patient also had Phlebitis lower limb.

At the time of the Event the patient had received Temsirolimus 25 mg i.v. (weekly) from 25 Jul 2013 to 06 Sep 2013 and Bevacizumab 670 mg i.v. (every 2 weeks) from 25 Jul 2013 to 30 Aug 2013. The patient was hospitalized in another hospital since 10 Sep 2013 due to Fever 41$^{o}$C (grade 3). The diagnosis was Pneumonia NOS. On 18 Sep 2013 CT thorax showed pleural effusion needed paracentesis, mediastinal lymph nodes and round glass picture in the right lung and two small lung nodules in the left lower lobe. On 18 Sep 2013 CT abdominal showed possible osteolysis of right ilium. On 25 Sep 2013 the patient was still in hospital 'Agia Olga' due to high fever. On 30 Sep 2013 it was confirmed that the patient had Pneumonia grade 3. On 12 Oct 2013 the patient was discharged from the hospital at her will and remained at home. Fever and cough were

grade 1 from 20 Oct 2013. On 29 Oct the patient's relatives brought to the study site the reports from CT thorax and CT abdomen (22 Oct 2013) and MRI brain and MRI spine. The reports showed progression at lung, lymphnodes, peritoneum, and bones and probably at the brain. More analytical on 21 Oct MRI brain showed probable metastases at right frontal lobe, MRI spinal showed bone metastases at lagonium, sacrum, thoracic and lumbar spine. On 22 Oct 2013 CT thorax showed progression at right lobe, pleural effusion and mediastinal lymphnode and CT abdomen showed paraortic lymphnodes and peritoneal implantation. On 01 Nov 2013 the patient was hospitalised at 2nd Dept of Metropolitan Hospital with fever grade 1 (39$^{o}$C), dyspnea grade 1, vomiting grade 3 and dehydration due to relapse of the previously known Pneumonia. Dehydration was due to vomiting and it was not a serious event. The patient was treated with i.v. antibiotics, analgesics and fluids and the patient's condition was improved. The patient was also treated with i.v. mannitol for possible CNS edema due to brain metastases.

Lab tests on 01 Nov 2013 showed: Hemoglobin 9.8 gr/dL (normal range: 12-15.7), Hematocrit 30.2% (normal range: 36-47), White blood cell count 11.6 K/μL (normal range: 4.5-10.5), Neutrophil count 72.8 % (normal range: 40-75), Platelet count 539 K/μL (normal range: 150-440), Creatinine 0.65 mg/dL (normal range: 0.7-1.5), Potassium 4.9 mmol/L (normal range: 3.5-5.1), Sodium 136 mmol/L (136-147), Calcium 9.5 mg/dL (normal range: 8.6-10.2), C-reactive protein 25.7 mg/dL (normal range: <0.5). On 30 Oct 2013 Bronchial cytology showed 89% probability of *Staphylococcus aureus*, 95% probability of *Enterobacter cloacae* complex.

X-Ray thorax on 01 Nov 2013: Normal. CT thorax on 03 Nov 2013: pleural effusion, atelectasis right middle and lower lobe, expanded lymph nodes. On 01 Nov 2013 A/A Abdomen was normal. On 12 Nov 2013 Sputum cytology showed *Acinetobacter baumannii.*

During patient's hospitalisation for Pneumonia the patient became septic despite the i.v. antibiotics. The patient was transferred to the ICU on 14 Nov 2013 and the patient died on 16 Nov 2013 due to sepsis. On 15 Nov 2013 blood and sputum cytology were

negative. Treatment given for the SAE started on 01 Nov 2013 and it was stopped on 16 Nov 2013.

Tests performed on 16 Nov 2013 showed: Hemoglobin 8.5 gr/dL, Hematocrit 26.3%, White blood cell count 11.1 K/μL, Neutrophil count 73.7 %, Platelet count 97 K/μL, C-reactive protein 15.31 mg/dL, Procalcitonin 3.530 ng/mL (normal range: 0-0.05, ≥ 2: sepsis is possible, >10: high likelihood of severe sepsis).

Actions taken as a result of the Event included hospitalization and the administration of Meronem (meropenem) i.v., Zyvoxid (linezolid) i.v., Fungustatin (fluconazole) i.v., Tygasil (tigecycline), Ecalta (adidulafungin), Colistin (polymyxin), Tazocin (tazobactam) p.o., Briklin (amikacin) p.o., Begalin (ampicillin+sulbactam). The study drugs were permanently discontinued and the SAE did not abate. During second hospitalisation the patient received Durogesic/Matrifen tts (fentanyl), Lactated ringers and sodium chloride, Paracetamole Kabi, Zyrolen (ipratropium), Flixotide nebules (flucaticasone), Voncon (Vancomycin) i.v., Briklin (amikacin) i.v., Targocid (teicoplanin) i.v. and Meronem (meropenem), Avelox (Moxiflocasin) i.v., Ronepem (Meropenem) i.v., Primaxin (Imipenem & enzyme inhibitor) i.v., Flagyl (metronidazole), Tygasil (tigelycline), Collistin (Colistimethade sodium) i.v. and Tadim (Colistimethade sodium), Atrovent (ipatropium bromide) i.v., Pulmicort (Budesonibe), Sinecod syr (Butamirate), Apotel (paracetamol) i.v., Biosonide budesonide neb), Dexaton (dexamethasone) i.v..

Concomitant medications at the time of the event included Xozal (levocetirizine dihydrocloride) p.o. for Rash and Glucophage (metformin hydrocloride) p.o. for Diabetes mellitus, Thyrormone (L-thyroxin sodium) p.o. for Hypothyroidism and Cyclo 3 fort (ascorbic acid) p.o. The concomitant medications also included Voltaren (diclofenac) p.o. for pain chest/thorax. Past medications included Votrient (pazopanib) from 15 Dec 2012 to 15 Jul 2013 for Metastatic renal cancer, which caused headache grade 1 and dyspnoea grade 1.

The investigator has assessed the causal relationship of study treatment to the Event as not related considering as the most probable cause of the event the obstruction of the

right middle pulmonary lobe and atelectasis, noting: "Obstruction of the right middle pulmonary lobe and atelectasis can cause obstructive pneumonia. Obstruction of the right middle pulmonary lobe and atelectasis were due to pathological lymph nodes known at screening". The Event caused the patient's hospitalization and finally her death (Serious).

Sponsor's comment: Suspected Unexpected Serious Adverse drug Reaction (SUSAR)

Initially the event was Pneumonia grade 3 and was assessed as SAR, but Pneumonia grade 5 is unexpected with Torisel and thus the event was considered SUSAR. Although we noted that the investigator believed the event was pneumonia secondary to obstruction from disease (lymph nodes), we reported the event as reasonably related to study drugs, since infection could be a secondary attribute to study treatment.

*Patient number: HE2110-2-0030*

*GR-HECOG-20140002*: Pulmonary-pneumothorax grade 5

The case concerned a 66- year-old male patient with a history of Renal cancer diagnosed after Nephrectomy on 01 Nov 2012, Lung metastases since 11 Sep 2012, 1st line Chemotherapy with Votrient from 20 Dec 2012 to 11 Nov 2013, Chronic obstructive pulmonary disease, mass Pleural metastases since 11 Oct 2013, Anaemia grade 1, Alkaline phosphatase increased grade 1, Hyponatraemia grade 1, Fatigue grade 1 and Anorexia grade 1.

At the time of the Event the patient had received Temsirolimus 25 mg i.v. (weekly) from 19 Dec 2013 to 27 Dec 2013 and Bevacizumab 700 mg i.v. (every 2 weeks) on 19 Dec 2013. On 21 Jan 2014 patient's family informed the investigation center that the patient had passed away. Further information on this case was that the patient developed spontaneous pneumothorax after a bout of paroxysmal cough (not related to the clinical procedure). It was mentioned that the patient developed respiratory distress and subcutaneous emphysema, which lead to the patient's hospitalization in a regional medical center. The patient's condition was stabilized and was transiently alleviated by chest decompression with needle thoracostomy. However, the following day, after a new

bout of paroxysmal cough patient's condition rapidly deteriorated and tension pneumothorax probably developed which resulted on respiratory failure and the patient's fatal outcome.

Relevant laboratory data showed:

On 28 Dec 2013 CT of Thorax showed extensive subcutaneous emphysema of cervic-thorax, extensive pneumomediastinum and a peural-based mass on the thoracic vertebrae with erosions of the adjacent bone cortex. No other relevant laboratory findings were mentioned.

Concomitant medications at the time of the event included Zofron (ondansetron) 8 mg, Zantac (ranitidine) 50 mg, Fenistil (dimetindene) 8 mg and dexamethazone 4 mg all i.v. every therapy as premedication. Past medications included Votrient (pazopanib) from 20 Dec 2012 to 11 Nov 2013 for Renal cancer.

The investigator has assessed the causal relationship of study treatment to the Event as not related with study drugs Bevacizumab and Temsirolimus, considering as most possible cause of the Serious Adverse Event the study disease.

Outcome: Death

Sponsor's comment: Serious Adverse Event (SAE). The event is most likely related to the underlying disease and chronic obstructive lung disease.

*Patient number: HE2110-4-0025 (same patient as GR-HECOG-20130042)*

This 48- year-old male patient had a history of Renal cancer since 05 Nov 2012, right Nephrectomy on 02 Nov 2012, 1st line Chemotherapy with Sunitinib from 10 Dec 2012 to 29 Apr 2013, Lung metastases and Bone metastases and Liver metastases since 19 Oct 2012, Radiotherapy to bone on 18 Jan 2013 (mediastinal) and on 02 May 2013, Pain grade 1 (bones) since 04 Jan 2013, Surgery of Aneurysm cerebral, Hypoalbuminemia grade 1 since 08 Jan 2013, Serum calcium decreased grade 1 since 05 Apr 2013,

Hemoglobin low grade 1 since 10 Dec 2012, and Testicular inflammation chronic relapsing.

The patient had received Temsirolimus 25 mg i.v. and Bevacizumab 630 mg i.v. from 07 Jun 2013. The last dose of Avastin and Temsirolimus was on 02 Aug 2013. The patient died on 14 Aug 2013 due to tumour.

#### *10.3.1.1 Other Serious Adverse Events*

*Patient number: HE2110-26-0004*

*GR-HECOG-20120003*: Ileus grade 3

This case concerned a 81 - year-old male patient with a history of Renal cancer since 01 Apr 2010, Coronary disease, Diabetes mellitus and Thyroidectomy, COPD, Prostatectomy, Hyponatremia grade 1, Hyperlipidemia grade 2 and Anemia. The patient received Temsirolimus 25 mg i.v. and Bevacizumab 800 mg i.v. from 29 Jun 2011 to 18 Jan 2012.

The patient developed Abdominal pain and Vomiting grade 1 on 23 Jan 2012 and visited another hospital. On 24 Jan 2012 the investigator was informed by the patient's son, that the patient was hospitalized due to Ileus. The diagnosis of Ileus was based on clinical examination and CT scan findings (performed on 23 Jan 2012). Abdominal pain and Vomiting were symptoms of Ileus. The patient was discharged from the hospital on 28 Jan 2012 in a good condition.

Actions taken as a result of the Event included the patient's hospitalization and the administration of 0.9 % Normal saline i.v., 5 % Dextrose water i.v., Paracetamol (Apotel) i.v., Cefoxitin (Mefoxil) i.v., Omeprazole (Vevalox) i.v. The study drugs were permanently discontinued due to Ileus.

Concomitant medications at the time of the Event included Irbesartan (Aprovel) p.o., Amlodipine (Norvasc) p.o., Sotalol hydrochloride p.o., Atorvastatin (Lipitor) p.o.,

Acetylsalicylic acid (Salospir) p.o. all for Coronary disease, Metformin (Glucophage) p.o. for Diabetes mellitus and Levothyroxine (Thyrormone) p.o. for Thyroidectomy.

Past medications included Interferon A 3 mIU three times per week intramuscular and Bevacizumab 860 mg every two weeks i.v. both from 07 Oct 2010 to 26 May 2011 for Renal cancer.

Outcome: Complete recovery

The investigator has assessed the causal relationship of study treatment to the Serious Event as unknown to Temsirolimus and Bevacizumab. The investigator considered the Event as Serious (Involved or prolonged hospitalisation).

Pfizer as MAH of Torisel assessed the case:

The event, ILEUS is unlisted in the Investigator's Brochure of the Pfizer suspect product Temsirolimus and related per company assessment. The event is also related to the non-Pfizer suspect product Bevacizumab per company assessment.

There is a reasonable association between the event, Ileus, and administration of temsirolimus and bevacizumab based on a positive drug - event tempp.o. relationship and for lack of known risk or contributory factors from the patient. The patient's advanced age of 80 years (presumably with decreased mobility) and being on multiple concomitant medications may be contributory and provide an alternative cause for the event. Worth mentioning is atorvastatin, which the patient has been taking for approximately 4 years and which is known to cause constipation. Hypothyroidism from inadequate doses of levothyroxine, which the patient used after thyroidectomy, may also offer another alternative cause towards the event.

Sponsor’s comment: Suspected Unexpected Serious Adverse drug Reaction (SUSAR)

The event Ileus is unlisted in the investigator brochure for temsirolimus. The event is considered as unexpected and there is reasonable possibility to be related to study drugs as no other known reason from the patient’s medical history has been identified.

*Patient number: HE2110-2-0008*

*GR-HECOG-20120004*: Renal failure grade 3 (creatinine increased grade 3)

This case concerned a 76-year-old female patient with a history of Renal cancer diagnosed on 22 Sep 2011, Biopsy Renal on 27 Jul 2011 (non-diagnostic) and on 22 Sep 2011 (diagnostic), Lung metastases, Bone metastases, Liver metastases and Lymph nodes metastases since 18 Jul 2011, Pain bone, Hypertension, Diabetes mellitus, Anaemia, Nasal catarrh grade 1, 1st line Chemotherapy with Avastin and Roferon from 16 Oct 2011 to 30 Nov 2011, and therapy with Zometa from 30 Nov 2011 to 22 Dec 2011. The patient received palliative Radiotherapy to bones from 22 Jul 2011 to 29 Jul 2011.

The patient on 22 Dec 2011 started to receive Temsirolimus 25 mg i.v. and Bevacizumab 750 mg i.v.. The last dose of Temsirolimus and Bevacizumab before the SAE onset was on 19 Jan 2012. The study drugs were temporarily discontinued.

On 26 Jan 2012 Biochemical blood test was performed before patient's scheduled chemotherapy administration. The test results revealed creatinine grade 3 (3.04 mg/dL, normal values: 0.6-0.9). Also, on 26 Jan 2012 Urea was 74 mg/dL (normal values: 10-50 mg/dL) and Sodium was 134 mmol/L (normal values: 135-145). The patient was transferred to Hospital's clinical department for hydration and surveillance. Biochemical tests the following days showed:

27 Jan, Creatinine: 2.99 mg/dL, Urea: 67 mg/dL, Sodium: 153 mmol/L (grade 1)

28 Jan, Creatinine: 2.68 mg/dL, Urea: 60 mg/dL, Sodium: 141 mmol/L (grade 0)

29 Jan, Creatinine: 2.52 mg/dL, Urea: 53 mg/dL, Sodium: 139 mmol/L (grade 0)

30 Jan, Creatinine: 2.47 mg/dL, Urea: 38 mg/dL, Sodium: 138 mmol/L (grade 0)

31 Jan, Creatinine: 2.21 mg/dL, Urea: 35 mg/dL, Sodium: 134 mmol/L (grade 1).

Normal values for uric acid and Potassium. No renal ultra sound was performed.

On 31 Jan 2012 the patient was discharged from the hospital with Creatinine increased grade 2. On 29 Feb 2012 Creatine became 0.98 mg/dL and the severity of the event was

grade 0 (complete recovery). On 19 Feb 2012 the patient was diagnosed with progression to lung, nodes and renal and discontinued from the study. The last dose of the study drugs was on 19 Jan 2012. On 19 Mar 2012 the patient started new therapy.

Actions taken as a result of the Event included the patient's hospitalization and the administration of 9 Normal saline 0.9 % + 6 Kadalex, 18 NaCO3 and Furosemide (Lasix) for Creatinine increased.

On 26 Jan 2012 the patient presented also Urinary tract infection grade 2 (Klebsiella pneumoniae) and received Ciprofloxacin (Ciproxin) (not a SAE).

Concomitant medications at the time of the Event included Dimetindene (Fenistil) i.v., Ranitidine (Zantac) i.v. and Dexamethasone i.v. all for Premedication, Gliclazide (Diamicron), Metformin (Glucophage) both of them for Diabetes mellitus, Perindopril (Coversyl), and Furosemide (Lasix) both of them for Hypertension, and Amlodipine (Norvasc) when vital signs were elevated.

Past medications included Roferon and Bevacizumab i.v. both from 16 Oct 2011 to 30 Nov 2011 for Chemotherapy and Zometa i.v. from 30 Nov 2011 to 22 Dec 2011.

The investigator has assessed the causal relationship of study treatment to the Serious Event as related to Temsirolimus and Bevacizumab. The investigator considered the Event as Serious (Involved or prolonged hospitalisation).

Outcome: Complete recovery

Sponsor's comment: Expected Serious Adverse Reaction

*Patient number: HE2110-40-0006*

*GR-HECOG-20120005: Osteonecrosis grade 2 (stage 0)*

This case concerned a 70 - year-old female patient with a history of Renal cancer since 30 May 2011, left Nephrectomy on 30 May 2011, Bone metastases since 17 Jun 2011, Hypertension, Hyperlipidemia and Total abdominal hysterectomy with Bilateral

salpingo-oophorectomy twelve years ago. Creatinine serum increased grade 1, AST increased grade 1, ALT increased grade 1, GGT increased grade 2, Alkaline phosphatase increased grade 1, all from prescreening period. The patient on 24 Nov 2011 started to receive Temsirolimus 25 mg i.v. and Bevacizumab 700 mg i.v. The last dose of Temsirolimus and Bevacizumab before the SAE onset was on 10 Feb 2012.

On 17 Feb 2012 the patient went for scheduled treatment complaining for pain on the right jaw. It was thought that the patient presented an infection at the oral mucosa of the right under jaw. The patient did not receive the planned treatment and was admitted to the hospital for i.v. antibiotics. The patient was released from the hospital on 17 Feb 2012 and then was examined by a specialist dentist. No obvious dental cause was found and the event was considered as Osteonecrosis stage 0 (AAOMS classification). The patient was prescribed with p.o. antibiotics for 10 days. On 24 Feb 2012 the patient was re-examined for Osteonecrosis. The event severity became grade 1 from grade 2. The patient on 24 Feb 2012 according to the protocol had a dose rechallenge with both study drugs due to grade change from 2 to 1. The patient was re-examined on 02 Mar 2012 for Osteonecrosis. Grading was in a transitional phase from 1 to 0 but it was not grade 0. Nevertheless, the patient's condition had improved. On 09 Mar 2012 the patient was re-examined by the specialized dentist who had diagnosed the Osteonecrosis. The specialized dentist agreed that the patient was completely recovered with grade 0 Osteonecrosis on 09 Mar 2012. The event abated after study drugs withdrawal and did not reappear after the reintroduction.

Actions taken as a result of the Event included the patient's hospitalization and the administration of Amoxicillin trihydrated (Amoxyl) i.v. and Metronidazole (Flagyl) i.v. The patient was also prescribed with Fluconazole (Fungustatin) p.o., Amoxicillin trihydrated (Amoxyl) p.o., Metronidazole (Flagyl) p.o., Doxxicycline (Vibramycin) p.o., Miconazole nitrate (Daktarin) transmucosal, Dexamethasone (Soldesanil) and Chlorexidine digluconate (Plak out 0.12%) p.o.

Concomitant medications at the time of the Event included Valsartan p.o., Moxonidine

p.o., Amlodipine p.o. all three for Hypertension, Atorvastatin p.o. for Hyperlipidemia and Zoledronic acid i.v. for Bone metastases. Past medications included Interferon (IFN) 3 x $10^6$ IU, 3 days a week i.v. and Bevacizumab 600 mg i.v. both from 12 Jul 2011 to 07 Oct 2011 for Renal cancer.

The investigator has assessed the causal relationship of study treatment to the Serious Event as related with suspect drugs being Temsirolimus and Bevacizumab but also Zoledronic acid noting "There is reasonable possibility for relation to both study drugs (Bevacizumab-Temsirolimus) as well as the Zoledronic acid (Zometa). The investigator considered the Event as Serious (Involved or prolonged hospitalisation).

Outcome: Complete recovery

Pfizer as MAH of Torisel assessed the case:

The event, osteonecrosis of jaw, is unlisted in the Investigator's Brochure of the Pfizer suspect product temsirolimus and related per company assessment.

There is a positive drug event temporal relationship, the patient having received therapy for 12 weeks, hence, causality secondary to temsirolimus and bevacizumab cannot be ruled out. The underlying disease with metastases to the bones and concomitant administration of zoledronic acid, a bisphosphonate known to cause osteonecrosis of the jaw, may provide an alternative cause towards the event onset.

Sponsor's comment: Suspected Unexpected Serious Adverse drug Reaction (SUSAR).

The event Osteonecrosis is unexpected for Temsirolimus and expected for Bevacizumab. There is reasonable possibility to be related to study drugs as well as concomitant drug Zometa (Zoledronic acid).

*Patient number: HE2110-40-0006*
*GR-HECOG-20120009: Creatinine grade 1*

This case concerned a 70 - year-old female patient (same patient as GR-HECOG-20120005). The patient had previously experienced the SAE Osteonecrosis grade 2 and the outcome was complete recovery. The patient received Temsirolimus from 24 Nov 2011 to 12 Apr 2012 and Bevacizumab from 24 Nov 2012 to 06 Apr 2012. On 19 Apr 2012 the patient went for scheduled treatment bringing the results of her blood tests. Creatinine value was high (2.10 mg/dL). The patient did not receive the planned treatment and was admitted for i.v. hydration. Blood test was performed again the same day after hydration and the creatinine value was better. The patient stayed at the Hospital for 5 hours and then left since there was no reason for hospitalisation. The patients did repeatedly follow-up tests for the creatinine value and grading remained the same (grade 1). Nevertheless, the study treatment permanently discontinued on 30 Apr 2012 due to uncontrolled creatinine value and hypertension (not SAE). The last dose of Temsirolimus and Bevacizumab was on 23 Apr 2012 and on 06 Apr 2012, respectively. Actions taken as a result of the Event included the patient's hydration i.v.

Concomitant medications at the time of the Event included Valsartan, Moxonidine, Amlodipine p.o. all the three of them for Hypertension, Atorvastatin p.o. for Hyperlipidemia and Zoledronic acid i.v. for Bone metastases. Past medications included Interferon (IFN) i.v. and Bevacizumab i.v. both from 12 Jul 2011 to 07 Oct 2011 for Metastatic renal cancer.

The investigator has assessed the causal relationship of study treatment to the Serious Event as related with suspect drug being Temsirolimus noting, "There is reasonable possibility for relation to study drug Temsirolimus". The investigator considered the Event as Serious (Important medical event).

Outcome: Not recovered

Sponsor's comment: Serious Adverse drug Reaction (SAR) to temsirolimus.

*Patient number: HE2110-2-0013*

*GR-HECOG-20120015: Diarrhea grade 3*

This case concerned a 49- year-old female patient with a history of TAH (Total abdominal hysterectomy, and BSO (Bilateral salpingo-oophorectomy) on 07 Nov 2011 due to Endometrial cancer, 1st line Chemotherapy from 28 Jun 2005 to 25 Oct 2005 due to Endometrial cancer, Lung metastases from Endometrial cancer from Jun 2005, Radiotherapy and short therapy for Endometrial cancer, left Nephrectomy on 21 Sep 2011 and diagnosis of Renal cancer, 1st line chemo from 19 Oct 2011 to 21 Feb 2012 due to Renal cancer, Lung metastases from Renal cancer from Feb 2012, Biopsy lung after Lympadenectomy (low pulmonary vein, tumor left lower lobe and nodules upper lobe), new lung progression on 27 Apr 2012, Anorexia grade 2, Fatigue grade 2, Anaemia grade 2, LDH increased, Alkaline phosphatase increased grade 1, AST increased grade 1, ALT increased grade 1, Hyperglycemia grade 2, Hypoalbuminemia grade 1 from 10 May 2012, Hyperkalemia grade 2 and Depression. The patient referred that he had Colitis.

At the time of the Event the patient had received Temsirolimus 25 mg i.v. (weekly) and Bevacizumab 830 mg i.v. (every 2 weeks) from 10 May 2012. The last dose of study drugs before the Event was on 14 Jun 2012.

On 21 Jun 2012 the patient did not go to the hospital for her scheduled visit due to Diarrhea grade 2. On 30 Jun 2012 the patient was hospitalized due to Diarrhea grade 3.

The laboratory tests performed during hospitalization showed:

Potassium (K): 2.80 mmol/l (grade 3) on 01 Jul 2012, 3.00 mmol/l (grade 1) on 03 Jul 2012 and 3.90 mmol/l (grade 0) on 12 Jul 2012. Normal values: 3.5-5.3 mmol/l.

Urea: normal, Creatinine: normal, C-reactive protein: 7.61 (Normal value: <0.8). Stool culture: negative.

Actions taken as a result of the Event included hospitalization and the administration of Normal saline 0.9 % + KCl, Saccharomyces bulardii (Ultra levure) and Loperamide

(Immodium) tablet both of them for Diarrhea, Ciprofloxacin (Ciproxin) tablet for probable Gastrointestinal infection (not documented). The study treatment was temporarily discontinued. On 03 Jul 2012 the patient was discharged from the hospital with Diarrhea grade 1. On 12 Jul 2012 the patient had completely recovered.

Concomitant medications at the time of the Event included Zofron, Zantac, Fenistil and Dexamethasone all of them i.v. for Premedication and Zolotrin tablet for Depression.

The investigator has assessed the causal relationship of study treatment to the Event Diarrhea as related with suspect drug Temsirolimus and not related with suspect drug Bevacizumab. The Event caused the patient's hospitalization (Serious).

Sponsor's comment: Expected Serious Adverse drug Reaction to temsirolimus

*Patient number: HE2110-2-0013*

*GR-HECOG-20120019: Bowel perforation grade 3*

This case concerned a 49- year-old female patient (same as GR-HECOG-20120015). On 30 Jun 2012 the patient was hospitalized due to Diarrhea grade 3 (related with Temsirolimus) which recovered completely on 12 Jul 2012.

At the time of the Event the patient had received Temsirolimus 25 mg i.v. and Bevacizumab 830 mg i.v. from 10 May 2012 to 09 Aug 2012. On 16 Aug 2012 the patient presented with Abdominal pain (symptom). The patient was diagnosed with Bowel perforation and underwent a Hartmann's Sigmoidectomy. On 17 Aug 2012 the patient was transferred to another's hospital ICU.

Actions taken as a result of the Event included hospitalization and the administration of ringer/12h and Kadalex/12h for hydration, Ciprofloxacin (Ciproxin) and Flagyl (Metronidazole) for perforation and Morphine for Abdominal pain. The study treatment was temporarily discontinued. Concomitant medications at the time of the Event included Zofron, Zantac, Fenistil and Dexamethasone for Premedication and Zolotrin tablet.

The investigator has assessed the causal relationship of study treatment to the Event Bowel perforation as related with suspect drug Bevacizumab and not related with suspect drug Temsirolimus, noting: "Bevacizumab treatment has been associated with bowel perforation". The Event caused the patient's hospitalization (Serious).

Outcome: Not recovered

Sponsor's comment: Expected Serious Adverse drug Reaction to Bevacizumab

*Patient number: HE2110-2-0009*

*GR-HECOG-20120028: Pain abdominal grade 1, Fever grade 1*

This a case concerned a 68-year-old male patient with a history of Gastrectomy on 14 Apr 1999 due to Gastric cancer, Prostatectomy on 20 May 2008 due to Prostate cancer, Renal cancer diagnosed after Nephrectomy and Cholecystectomy on 29 Oct 2008, Lymph node excision on 20 Oct 2012 due to local relapse, Hypertension, Bone metastases since Jul 2011 ongoing, Radiotherapy to bone from 29 Jul 2011 to 04 Aug 2011, 1st line Chemotherapy from 30 Aug 2011 to 20 Jan 2012 (Roferon+Avastin), Liver metastases and Pleural metastases from 20 Jan 2012, Esophagitis grade 1, LDH increased, GGT increased grade 1, Hyponatremia grade 3 (NCS), Depression grade 1, Anxiety grade 1 and Pain abdominal grade 1. At the time of the Event the patient had received Temsirolimus 25 mg i.v. (weekly) from 15 Feb 2012 to 14 Aug 2012 and Bevacizumab 600 mg i.v. (every 2 weeks) from 15 Feb 2012 to 08 Aug 2012.

On 16 Aug 2012 the patient was hospitalized to Poligiros District Hospital for Fever and Abdominal pain. CT scan to the abdomen on 16 Aug 2012 had no findings. On 17 Aug 2012 the patient was discharged from the hospital with no symptoms (Complete recovery from both events). According to the medical judgment of the treating physician the event Abdominal pain was attributed to Anxiety while there was no diagnosis for Fever. Possibly Fever was due to Dental infection-tooth (No SAE).

Actions taken as a result of the Event included hospitalization and the administration of Depon (paracetamol) tablet for Fever, Losec (omeprazole) tablet and Primperan (metoclopramide) tablet both for Abdominal pain. No action was taken with the study treatment.

Concomitant medications at the time of the Event included Zofron, Zantac, Fenistil and Dexamethasone all of them i.v. for Premedication Norvasc (amlodipine) tablet and Triatec plus (ramiprile + hydrochlorothiazine) tablet both for Hypertension.

The investigator has assessed the causal relationship of study treatment to the Event Abdominal pain as not related with suspect drugs Bevacizumab and Temsirolimus, noting: "It's very common for patients suffer from anxiety to report abdominal pain, which no other medical condition can explain". The investigator has assessed the causal relationship of study treatment to the Event Fever as not related with suspect drugs Bevacizumab and Temsirolimus, noting: Possibly no reasonable causality between the SAE and the suspect drugs, but there was no diagnosis for Fever. (It was) possibly, due to Dental infection (tooth)". Both Events caused the patient's hospitalization (Serious).

Outcome: Complete recovery

Sponsor's comment: Serious Adverse Event

*Patient number: HE2110-26-0017*

*GR-HECOG-20120030: Pneumonitis grade 3*

This 67- year-old male patient had a history of Renal cancer diagnosed after right Nephrectomy on 22 Aug 2011, Renal cancer Metastatic since 04 Oct 2011, Diabetes, Hypertension, Benign prostatic hyperplasia, Anaemia.

At the time of the Event the patient had received Torisel 25 mg i.v. from 04 Sep 2012 to 16 Oct 2012 and Avastin 700 mg i.v. from 04 Sep 2012 to 02 Oct 2012. The patient stopped treatment due to grade 3 Stomatitis from 16 Oct 2012 to 25 Oct 2012 (not

serious). The patient received p.o. metronidazole. Stomatitis was probably not related to current event. Since 02 Nov 2012 the patient developed Fever (39$^{o}$C) and was hospitalised at another hospital since 04 Nov 2012 receiving IV antibiotics. Although the patient was febrile since 02 Nov 2012 he clinically deteriorated on 04 Nov 2012 and hospitalization was needed. The patient was treated with i.v. Tazocin and Tavanic for Respiratory tract infection. The patient was discharged on 12 Nov 2012. The patient was prescribed with p.o. Tavanic.

Chest X-ray performed on 05 Nov 2012 showed no infiltrates. Laboratory data showed:

On 05 Nov 2012: White blood cell count 12850/u, Neutrophil count 78.7%, C-reactive protein 182 mg/L

On 12 Nov 2012: White blood cell count 9970/u, C-reactive protein 62 mg/L

Normal values: White blood cell count 5200-12400/u, Neutrophil count 40-70%, C-reactive protein 0-5 mg/L

On 19 Nov 2012 the patient was still recovering. On 21 Nov 2012 the patient was still febrile and had not recovered from respiratory infection. Chest CT scan on 16 Nov 2012 revealed Pleural effusion deterioration and Hilar lymph node enlargement (disease progression). Since the patient had skipped treatment for 6 weeks the patient stopped investigational drug treatment. The patient underwent Bronchoscopy on 21 Nov 2012 in order to exclude Lower respiratory tract infection since Fever had not been resolved after p.o. levofloxacin (Tavanic) initiation. All cultures were negative for infection (negative sputum and bronchoalveolar lavage – BAL cultures). The patient started treatment with prednisolone (Prezolon) daily from 23 Nov, since the patient's symptoms were attributed to Pneumonitis grade 3 by the Principal investigator, related to previous Temsirolimus treatment. All symptoms were related to Pneumonitis and event onset was considered the 2$^{nd}$ of Nov 2012. The patient was precautionaly hospitalized after bronchoscopy for investigational purposes on 21 Nov 2012 and was discharged on 26 Nov 2012, afebrile

with p.o. steroids (prednislolone every day). The patient was continuing treatment for Pneumonitis in an outpatient basis.

Chest CT on 11 Mar 2013 showed radiographic findings of worsening pneumonitis and further disease progression. The patient was receiving treatment for pneumonitis with prednisolone 3. The event did not abate after stopping study drugs. The patient would receive 3rd line treatment with sorafenib.

Concomitant medications at the time of the Event included Norvasc (amlodipine) p.o. and Exforge (Valsartan + Amlodipine) p.o. both for Hypertension, Glucophage (Metformin) p.o. and Levemir (Insulin) subcutaneous both for Diabetes, Omnic tocas (tamsulosin) p.o. for Benign prostatic hyperplasia, Binocrit (Epoetin) subcutaneous for Anaemia.

The investigator has assessed the causal relationship of study treatment to the Event Pneumonitis as related with suspect drug Temsirolimus and not related with Bevacizumab, noting: "Pneumonitis is related to temsirolimus treatment (m-TOR). Investigator's comment: Pneumonitis was not related either to clinical trial procedure or concomitant medications.

Outcome: Not recovered

Sponsor's comment: Expected Serious Adverse drug Reaction to Torisel

*Patient number: HE2110-26-0016*

*GR-HECOG-20120031: Pulmonary embolism grade 4*

This 70- year-old male patient had a history of Renal cancer metastatic diagnosed after left Nephrectomy on 13 Jul 2011, Deep vein thrombosis at vena cava since May 2011, neoplasmatic Thrombosis of vena cava inferior which was diagnosed on 12 Jul 2011 on CT scan prior to nephrectomy, Hypertension, 1st line therapy for Metastatic renal cancer, maintenance with Avastin from 29 Mar 2012 to 31 May 2012, Anaemia grade 1, Urea

increased grade 1 and GGT increased grade 1. Urea refers to renal impairment grade 1 starting in 2011 ongoing.

At the time of the Event the patient had received Torisel 25 mg i.v. from 30 Aug 2012 to 01 Nov 2012 and Avastin 940 mg i.v. from 30 Aug 2012 to 25 Oct 2012.

The patient was diagnosed with Pulmonary embolism on 31 Oct 2012, detected on CTPA while being asymptomatic. He was on warfarin due to Thrombosis vena cava inferior (Deep vein thrombosis) since 07 Oct 2012 and received concomitant low molecular weight heparin (Innohep) from 31 Oct 2012 to 03 Nov 2012 in order to achieve therapeutic rates of INR. From 02 Nov 2012 to 08 Nov 2012 the patient received the antibiotic Avelox (moxifloxacin) for Respiratory tract infection (not serious). Pneumonitis grade 1 was also detected on CTPA (not serious – not clinical significant – not related to SAE). On 08 Nov 2012 the patient was without Fever - Respiratory infection resolved. Due to upper Lip oedema – Lip infection, Amoxicillin twice a day was prescribed by stomatology professor commencing on 08 Nov 2012 (NCS). Warfarin (Sintrom) oral was administered both as concomitant medication for Deep vein thrombosis since 07 Oct 2011and as SAE treatment for Pulmonary embolism. The patient continued treatment with Sintrom for Pulmonary embolism. Due to disease progression the patient began 3$^{rd}$ line treatment for mRCC with pazopanib since 05 Feb 2013. Since Pulmonary embolism was considered as a result of neoplasmatic superior vena cava thrombus, it would probably never resolve and the patient would receive anticoagulant therapy for life.

INR on 30 Nov 2012 was 1.26, and on 02 Nov 2012 INR was 2.29 (Normal range: 0.85-1.15 & Therapeutic range: 2-3).

Actions taken as a result of the Event included hospitalization and the administration of Innohep daily subcutaneous for Pulmonary embolism. Vectibix was permanently discontinued and Torisel was temporarily discontinued. The patient also received Avelox daily p.o. for Respiratory tract infection, Bactroban nasal ointment daily for Nasal disorder and Amoxicillin twice a day p.o. from for upper Lip oedema-infection.

Concomitant medications at the time of the Event included Sintrom.

The investigator has assessed the causal relationship of study treatment to the Event Pulmonary embolism as not related with suspect drugs Bevacizumab and Temsirolimus, noting: "Pulmonary embolism probably caused by neoplasmatic inferior vena cava thrombus extension". The investigator has assessed that the SAE is probably not related to trial procedures. The Event caused the patient's hospitalization (Serious).

Outcome: Not recovered

Sponsor's comment: Expected Serious Adverse drug Reaction to both study drugs Pulmonary embolism is expected with both study drugs. There is a reasonable possibbiltiy of relation of the event to study drugs, primarily Bevacizumab, although the patient's history of inferior vena cava thrombosis is an important causative underlying factor. However, study drugs could be reasonable attributable to the event Pulmonary embolism.

*Patient number: HE2110-2-0011*

*GR-HECOG-20130031: Colitis grade 3*

This 72- year-old male patient had a history of Renal cancer diagnosed after left Nephrectomy on 12 Oct 2011, 1st line Chemotherapy with Sunitinib from 24 Nov 2011 to 22 Mar 2012, Lung metastases and Bone metastases since 27 Sep 2011, Radiotherapy to bone from 30 Mar 2012 to 05 Apr 2012, Osteoporosis, Anaemia grade 1, Hypertension, Diarrhea and Infection viral.

At the time of the Event the patient had received Torisel 25 mg i.v. and Avastin 570 mg i.v. from 30 Apr 2012. The last dose of Avastin and Temsirolimus before the Event was on 03 Jun 2013 and 17 Jun 2013, respectively.

On 26 Jun 2013 the patient went for her scheduled chemotherapy. The patient was presented with Fever grade 2 (40$^{o}$C) and Pain abdominal grade 2. There was suspicion

for Diverticulitis but the final diagnosis was Colitis grade 3. A CT scan was performed on 26 Jun 2013 and Ro abdomen on 27 Jun 2013. CT scan on 26 Jun 2013 showed no evidence of obstruction and X-Ray to abdomen on 27 Jun 2013 was with evidence of Ileus. Fever and Abdominal pain, change in bowel habits with ileus, peritoneal signs were symptoms of Colitis. On 29 Jun 2013 the patient was discharged from the hospital without symptoms. On 26 Jun 2013 blood culture was negative, CRP: 37.40 mg/dL (Normal range: <0.8), White blood cell count: 10.57x10e3/u (Normal range: 4.2-10.5), Neutrophil count: 7.21x1000/μL (Normal range: 1.5-6.6). On 08 Jul 2013 White blood cell count: 9.35x10e3/u, Neutrophil count: 7.21 x1000/μL.

Actions taken as a result of the Event included hospitalization and the administration of N/S + KCl + D/W + Mg for Hydration, Enema (sodium phosphate) rectal, Flagyl (metronidazole) i.v., Primperan (metoclopramide) i.v., Tramal (tramadol) i.v., Nexium (esomeprazole) i.v., Begalin (ampicillin+sulbactam) i.v. and Ultra levure (saccharomyces boulardii) tablet. No action was taken with the study drugs as a result of the SAE. The patient was off study because a CT scan performed on 19 Jun 2013 showed clinical progression to lung.

Concomitant medications at the time of the Event included Zofron, Zantac, Fenistil 8 mg and dexamethazone all four of them every therapy day i.v. for Premedication, Controloc (pantoprazole) tablet occasionally for gastric Prophylaxis and Dilatrend (carvedilol) tablet for Hypertension. Past medications included Lonarid (paracetamol) for Bone metastases, Capoten (captopril) and Carvepen (carvedilol) for Hypertension, Zinadol for Viral infection and Ultra levure (saccharomyces boulardii) for Diarrhea.

The investigator has assessed the causal relationship of study treatment to the Event as related with suspect drug Bevacizumab and not related with the study drug Temsirolimus, noting: “Avastin can cause those symptoms”. The Event caused the patient’s hospitalization (Serious).

Outcome: Complete recovery

Sponsor's comment: Unexpected Serious Adverse drug Reaction to both study drugs.

Colitis is unexpected according to study drugs' Investigator brochures. Since the initial symptoms reported were Abdominal pain and Fever, there is a reasonable possibility that the event is related to the study drugs and an interaction between the two drugs cannot be ruled out. The diagnosis of colitis is further supported by abdominal x-ray showing ileus, infectious markers such as CRP and leukocytosis.

*Patient number: HE2110-4-0025*

*GR-HECOG-20130042: Pain grade 3*

This 48- year-old male patient had a history of Renal cancer since 05 Nov 2012, right Nephrectomy on 02 Nov 2012, 1st line Chemotherapy with Sunitinib from 10 Dec 2012 to 29 Apr 2013, Lung metastases and Bone metastases and Liver metastases since 19 Oct 2012, Radiotherapy to bone on 18 Jan 2013 (mediastinal) and on 02 May 2013, Pain grade 1 (bones) since 04 Jan 2013, Surgery of Aneurysm cerebral in 2006 and Testicular inflammation chronic relapsing. The patient suffered from pain - which was located mainly at the pelvic bones - since 04 Jan 2013 with changes in the intensity (pain grade 0 - grade 2). So far, he had been taking analgesic medication at home, depending on the intensity of the pain.

At the time of the Event the patient had received Temsirolimus 25 mg i.v. and Bevacizumab 630 mg i.v. from 07 Jun 2013. The last dose of Avastin and Temsirolimus before the Event was on 02 Aug 2013.

On 05 Aug 2013, the patient visited the clinic for the scheduled appointment for the assessment of his tumor (CTs). Because of his bone metastases the patient suffered from severe pain (grade 3) and the patient remained hospitalised in order to control the pain. The patient felt nausea and had had no bowel movement since 05 Aug 2013. An abdominal radiogram was performed, which showed bowel distention and the left colic flexure full of air. Then the patient was assessed by surgeon, who recommended that the

patient should not receive anything orally, a new abdominal radiogram the other day and administration of enemas, which had no result. An anaesthesiologist assessed the patient during hospitalisation, and administered medications for the pain. On 09 August 2013, Temsirolimus 25 mg (day 8 of Cycle 5) was administered normally without interruption and the patient remained hospitalised for analgesics' dose titration.

On 10 Aug 2013 patient's belly became flatulent with reduced intestinal tone. On 11 Aug 2013, a new abdominal radiogram was performed, which showed formation of water gas levels and the intestinal tone remained reduced. This clinical picture was probably the result of the use of analgesic medication. The doctor administered enemas again, Duphalac (lactulose syrup), Dulcolax (bisacodyl p.o.), which resulted to a great amount of stool and gas and reduction to the flatulence of patient's belly. The patient's diet continued to be nothing p.o.ly after surgeon's instruction until 12 Aug 2013, when the patient started hydric diet.

On 13 Aug 2013 the patient presented loss of consciousness (Vital Signs: SpO2=72%, BP=60/40mmHg, Heart Rate=150/min) and he developed bilateral miosis, probably because of the pain medications. The doctor administered ½ amp Narcan (Naloxone) and the patient recovered.

On 14 Aug 2013 the patient's clinical condition deteriorated, presenting breathlessness, discomfort, tachypnea, tachycardia, low blood pressure (Systolic Blood Pressure 80 mmHg) ABGs: pH=7.346, pO2=78.7, pCO2=29.6, SO2=94.4%, HCO3=15.8 (oxygen administration with venturi mask 50% at 10 L), ECG: sinus tachycardia (125-130 bpm)

The patient reported severe abdominal pain and an urgent abdomen CT was performed which excluded abdominal perforation. The patient lost consciousness again and the doctor administered Narcan and increased the oxygen saturation given to 100% with windbag. Because of the breathlessness and the findings of the last CT (pleural effusion and air bronchogram), patient was given Avelox (moxifloxacin hydrochloride) and Meronem (Meropenem). Finally, the patient passed away in the evening of the 14 Aug 2013 due to his disease, according to the death certificate.

Actions taken as a result of the Event included hospitalization and the administration of Hydration, Vefron (ondansetron hydrochloride) p.o. and i.v., Losec (omeprazole) i.v. and p.o., Tramal (tramadol hydrochloride) p.o. and i.v., Lonalgal (codein+paracetamol), Abstral (fentanyl citrate), Morphine subcutaneous, Dynastat (parecoxib sodium) i.v., Durogesic (fentanyl) transdermal, Lyrica (pregabalin) p.o., Dexaton (dexamethasone) i.v., Apotel (paracetamol) i.v., Depon maximum (paracetamol), and Xefo (lornoxicam) i.v. all for pain, Seropram (citalopram hydrochloride) and Largactil (chloropromazine) p.o. No action was taken with the study drugs as a result of the SAE. Concomitant medications at the time of the event included Medrol (methylprednisolone) and Lonalgal (codein+paracetamol) from 04 Jan 2013 to 05 Aug 2013 for pain

The investigator has assessed the causal relationship of study treatment to the Event as not related with study drugs Bevacizumab and Temsirolimus, noting: "The patient had bone metastases". The Event caused the patient's hospitalization (Serious).

Outcome: Not recovered

Sponsor's comment: Serious Adverse Event (SAE). In agreement with the investigator the events were due to bone pain, analgesics and the study disease. There is no reasonable possibbiltiy of relation of the event to study drugs.

*Patient number: HE2110-4-0027*

*GR-HECOG-20130067: Diarrhea grade 3*

This 65- year-old male patient had a history of Renal cancer since 10 Apr 2013, right Nephrectomy on 28 Mar 2013, Bone metastases since 13 May 2013, Diabetes mellitus type 2, Haematuria (initial symptom of renal cancer), Orthopnea, intermittent Pain in (r) hip grade 2 and Sensory neuropathy, intermittent Pruritus grade 1 and Hypertriglyceridaemia grade 1, Hyperuricaemia grade 1, Hypercholesterolaemia grade 1, Hyperkalemia grade 2, Fatigue grade 3, Urea increased grade 1, Creatinine increased grade 1, Edema legs, Hypertension, Thyroiditis, Anaemia and Thrombocytopenia and

Amylase increased grade 1. At the time of the Event the patient had received Torisel 25 mg i.v. from 04 Nov 2013 to 11 Nov 2013 and 20 mg from 25 Nov 2013 to 09 Dec 2013 and Avastin 680 mg i.v. from 04 Nov 2013 to 02 Dec 2013.

On 19 Dec 2013 the patient was admitted to hospital due to diarrhea grade 3. Doctors administered hydration and antidiarrheal drugs. On 19 Dec 2013 CT scans were performed (chest, upper and lower abdominal) which were negative for secondary malignancies or anything acute from the digestive track. Due to diarrhea, the patient felt rectal pain grade 1 (not serious), and was administered Rectogesic cream (Glyceryl trinitrate) and Nujol syr (Paraffin liquide). On 22 Dec 2013 the patient experienced headaches grade 1 because of the Rectogesic cream (a non serious but known side effect of the glyceryl trinitrate cream), and has completely recovered on the same day without medication. On the same date, during patient's hospitalization pruritus grade 1 (non serious) was presented, probably due to patient's past medical record, for which 1tb Atarax (Hydroxyzine) was administered and the patient had complete recovery. Since 23 Dec 2013 diarrhea was significantly decreased and on 23 Dec 2013 the patient was discharge from the hospital with complete recovery.

On 19 Dec 2013 relevant laboratory data showed: WBC: 6700/μl, PTL: 108000/μl, Urea: 106 mg/dl, K: 4.8mmol/l, Na: 135mmol/l, Cr: 2,3 mg/dl, Sterile urine culture, stools negative for WBC.

On 22 Dec 2013 the same examinations showed: WBC: 7100/μl, PTL: 168000/μl, Ht: 38,5%, Urea: 64 mg/dl, K: 4 mmol/l, Na: 137 mmol/l, Cr: 1,9 mg/dl

Normal values: WBC: 3800-8600/μl, PTL: 140000-360000/μl, Ht: 33-57%, Urea: 15-45 mg/dl, K: 3.5-5.1 mmol/l, Na: 136-145 mmol/l, Cr: 0.8-1,3 mg/dl

Actions taken as a result of the Event included hospitalization and the administration of Ultra Levure (Saccharomyces Boulardii) p.o. and i.v. fluids for hydration. Avastin and Temsirolimus were temporarily discontinued. Concomitant medications at the time of the event included Fisiotens (moxonidine) p.o., Lobivon (nebivolol hydrochloride) and

Norvasc (amlodipine besylate) p.o. all for hypertension, Lantus (insuline glargine) subcutaneous, Glucophage (metformin) p.o. and Humalog (insulin lispro) subcutaneous all for diabetes.

The investigator has assessed the causal relationship of study treatment to the Event as related with study drugs Bevacizumab and Temsirolimus. The Event caused the patient's hospitalization (Serious).

Outcome: Recovered

Sponsor's comment: Serious Adverse drug Reaction (SAR). In agreement with the investigator there is reasonable possibbiltiy of relation of the event to study drugs.

*Patient number: HE2110-117-0035*

*GR-HECOG-20150006: Hypertension grade 3*

This case concerned a 66- year-old male patient with a history of Renal cancer metastatic diagnosed on 02 May 2011, left Nephrectomy on 08 Nov 2010, Hypertension since 2008.

The patient had received Torisel 25 mg i.v. and Avastin 1000 mg i.v. from 11 Jul 2014 to 30 Jan 2015. The last dose of Avastin and Temsirolimus before the Event was on 02 Jan 2015. The patient with known medical history of hypertension during the visit on 09 Jan 2015 reported hypertension grade 3 between 03 Jan 2015 and 08 Jan 2015 with highest 170/95 mmHg. On 09 Jan 2015 the AE was resolved and the patient received the scheduled therapy. Another hypertensive drug - Norvasc 5 mg – was added to the patient treatment. No further investigations were performed regarding the AE. Previous blood pressure higher value was 140/90 mmHg.

Lab tests on 02 Jan 2015: Creatinine: 1.2 mg/dL (Normal values: 0.6-1.4 mg/dL), Proteinuria: 124 mg/24 hours (Normal values: 0)

The patient was on treatment with Triatec 5 mg from 2008 (concomitant medication) for hypertension and with Norvasc 5 mg from 09 Jan 2015. Concomitant medications at the

time of the event included Zocor (simvastatin) p.o. for Hypertriglyceridaemia, Zyloric (allopurinol) p.o. for Gout, Importal (lactitol) p.o. and xylocaine local application both for rectal ulcer.

The investigator has assessed the causal relationship of study treatment to the Event as possible related with the study drug Bevacizumab and not related to the study drug Temsirolimus.

Outcome: Recovered

Sponsor's comment: Serious Adverse Reaction (SAR). Hypertension is expected with both study drugs.

## 10.4 SAFETY CONCLUSIONS

According to the above data, the combination of Bevacizumab plus Temsirolimus seems to be safe for patients with advanced renal cell carcinoma. The observed AEs in the study were consistent with the previously observed safety profile of both drugs. Hematological toxicities were grade 1 to 2. Most common non-hematological toxicities were metabolic disorders (44%), followed by gastrointestinal (11%). The vast majority of metabolic disorders were grade 1 (%). Expected events with Avastin like Proteinuria and Hypertension were observed in 20 (51%) and 12 (31%) patients, respectively while hypertension, which is associated with Torisel, was observed in 4 patients (10.25%). The incidence of these events is higher in our study compared with INTORACT trial but the number of patients enrolled in the current study is small. Adverse events were the most common cause for treatment discontinuation. 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 mostly consistent with the ones previously observed with the study drugs and the underlying malignancy. Five serious gastrointestinal events were reported. One event of pneumonitis (grade 3) and one

event of hypertension (grade 3) were reported as serious. The sponsor assessed two of the fatal events as toxic deaths.

## 11 DISCUSSION AND OVERALL CONCLUSIONS

The study HE 21/10 was terminated prior the completion of the accrual since the completion was considered difficult due to advances in the treatment of recurrent metastatic renal cancer. The approval of Axitinib for the treatment of adult patients with advanced renal-cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine, offered a new, effective option for researchers while studies with PD-1 factor inhibitors also attracted great interest. Also, the study results of INTORACT (J Clin Oncol 32: 752-759, 2014) (23) showed that treatment with the combination of temsirolimus / bevacizumab was no better than treatment with interferon / bevacizumab as first-line treatment in patients with metastatic clear cell kidney cancer.

In total 39 patients received treatment with Avastin and Torisel. Among them, 16 patients completed treatment and 37 were evaluable for response. The median time to progression was 6.8 months (95%CI 5.5-9.2) and 6-month PFS rate was 50.9% (95% CI 33.8%-65.7%). Kaplan –Meier curves for OS and PFS are shown in Figures 1 and 2. The QLQ C30 scores did not show significant changes during treatment and in comparison with baseline.

Combination treatment with bevacizumab and temsirolimus did not cause significant toxicities and most of the reactions were consistent with the safety profile of the study drugs or the medical history of the patients.

In conclusion, due to the above, the information from our study are likely to become obsolete and in combination with the slow recruitment rate in the study, the sponsor decided the discontinuation of the study.

# 12 TABLES, FIGURES AND GRAPHS

**Table 4. Basic patient characteristics_Descriptives**

| | N | % |
|---|---|---|
| Sex | | |
| Female | 12 | 31 |
| Male | 27 | 69 |
| Nephrectomy | | |
| Yes | 32 | 82 |
| No | 7 | 18 |
| Clear cell | | |
| Yes | 38 | 97 |
| No | 1 | 3 |
| Fuhrmangrade | | |
| 1 | 1 | 3 |
| 2 | 6 | 15 |
| 3 | 15 | 39 |
| 4 | 9 | 23 |
| Unknown | 8 | 20 |
| sarcomatfeatures_ | | |
| Yes | 2 | 5 |
| No | 32 | 82 |
| Unknown | 5 | 13 |
| Performance Status | | |
| 0 | 27 | 69 |
| 1 | 10 | 26 |
| 2 | 2 | 5 |
| Peviouscytokines | | |
| Yes | 12 | 31 |
| No | 27 | 69 |
| Firstline | | |
| Bevaciz/avast/roferon | 12 | 31 |
| Sunitinib/sutent | 16 | 41 |
| Votrient | 10 | 26 |
| Sorafenib | 1 | 2 |
| | Median | Range |
| Age | 67 | 40-80 |
| Duration from initial diagnosis to metastatic disease diagnosis in months | 2.1 | 0-98.8 |
| Duration from metastases to start of chemotherapy | 9.4 | 0.3-107.4 |

**Table 5. Adverse events with maximum grade**

| | Grades (n) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **Missing/Unknown** | **Total** |
| **Infection** | **12** | **6** | **4** | **0** | **0** | **2** | **24** |
| **Pain** | **18** | **9** | **0** | **0** | **0** | **0** | **27** |
| **Ocular/nails** | **4** | **2** | **0** | **0** | **0** | **0** | **6** |
| **Hemoglobin** | **11** | **3** | **0** | **0** | **0** | **0** | **14** |
| **Dental** | **1** | **1** | **0** | **0** | **0** | **1** | **3** |
| **Ldh** | **15** | **0** | **0** | **0** | **0** | **0** | **15** |
| **Fall/dizzy** | **4** | **1** | **1** | **0** | **0** | **0** | **6** |
| **Nose** | **2** | **1** | **0** | **0** | **0** | **0** | **3** |
| ALT | 11 | 1 | 0 | 0 | 0 | 0 | 12 |
| AST | 7 | 1 | 0 | 0 | 0 | 0 | 8 |
| Acne | 4 | 1 | 0 | 0 | 0 | 0 | 5 |
| Alkaline phosphatase | 9 | 0 | 0 | 0 | 0 | 0 | 0 |
| Allergic Reaction | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Alopecia | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Amylace | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Anorexia | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Arthritis | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Biliburin | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Cardiac general | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Cheilitis | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Cholesterol | 14 | 4 | 0 | 0 | 0 | 0 | 18 |
| Colitis | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Constipation | 4 | 2 | 0 | 0 | 0 | 0 | 6 |
| Cough | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Creatinine | 16 | 2 | 0 | 0 | 0 | 0 | 18 |
| Cystitis | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Dermatology & other | 7 | 0 | 0 | 0 | 0 | 0 | 7 |
| Diarrhea | 4 | 2 | 0 | 0 | 0 | 0 | 6 |
| Dry skin | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| Dyspnea | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Edema: head and neck | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Edema: limb | 4 | 1 | 0 | 0 | 0 | 0 | 5 |
| Enteritis | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Erythema multiforme | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Fatigue | 8 | 0 | 0 | 0 | 0 | 0 | 8 |
| Fever | 4 | 1 | 0 | 0 | 0 | 0 | 5 |
| Fistula, GI | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| GGT | 9 | 3 | 1 | 0 | 0 | 0 | 13 |
| GI Other (Specify) | 2 | 3 | 0 | 0 | 0 | 0 | 5 |
| Hand-foot | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Hemorrhage pulmonary | 7 | 1 | 0 | 0 | 0 | 0 | 8 |
| Hemorrhage Other .. | 2 | 2 | 0 | 0 | 0 | 0 | 4 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hemorrhage, GI | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Hemorrhage, GU | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| Hemorrhoids | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| Hypercalcemia | 3 | 0 | 0 | 0 | 0 | 0 | 3 |
| Hyperglycemia | 15 | 6 | 0 | 0 | 0 | 0 | 21 |
| Hyperkalemia | 2 | 1 | 1 | 0 | 0 | 0 | 4 |
| Hypermagnesemia | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Hypernatremia | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Hypertension | 3 | 7 | 2 | 0 | 0 | 0 | 12 |
| Hypertriglyceridemia | 14 | 1 | 2 | 0 | 0 | 0 | 17 |
| Hyperuricemia | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| Hypoalbuminemia | 3 | 1 | 0 | 0 | 0 | 0 | 4 |
| Hypocalcemia | 6 | 1 | 1 | 0 | 0 | 0 | 8 |
| Hypoglycemia | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Hypokalemia | 5 | 0 | 0 | 0 | 0 | 0 | 5 |
| Hyponatremia | 12 | 0 | 0 | 1 | 0 | 0 | 13 |
| Hypophosphatemia | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| Ileus | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Insomnia | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Left ventricular systolic dysfunction | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Leukocytes | 6 | 0 | 1 | 0 | 0 | 0 | 7 |
| Lymphatics Other | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Lymphopenia | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Metabolic/Lab Other | 16 | 1 | 0 | 0 | 0 | 0 | 17 |
| Mucositis (clinical exam) | 8 | 3 | 2 | 0 | 0 | 0 | 13 |
| Nausea | 3 | 1 | 0 | 0 | 0 | 0 | 4 |
| Neurology & Other | 1 | 0 | 1 | 0 | 0 | 0 | 2 |
| Neutrophils | 5 | 2 | 1 | 0 | 0 | 0 | 8 |
| Osteonecrosis | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| Perforation, GI | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Periodontal | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| Platelets | 10 | 2 | 0 | 0 | 0 | 0 | 12 |
| Pneumonitis | 2 | 1 | 1 | 0 | 0 | 0 | 4 |
| Pneumothorax | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Proteinuria | 16 | 4 | 0 | 0 | 0 | 0 | 20 |
| Pruritus | 3 | 1 | 0 | 0 | 0 | 0 | 4 |
| Pulmonary & Other | 2 | 1 | 0 | 0 | 0 | 0 | 3 |
| Rash | 10 | 2 | 0 | 0 | 0 | 0 | 12 |
| Renal & Other | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Rigors/chills | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Teeth | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Thrombosis/thrombus/embolism | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Ulceration | 0 | 3 | 0 | 0 | 0 | 0 | 3 |
| Vomiting | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Watery eye | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Weight loss | 1 | 0 | 0 | 0 | 0 | 0 | 1 |

**Table 7.** List of reported Serious Adverse Events, including deaths

| | Local Report Number | Patient Number | SAE Term | Related? | | Expected? | SUSAR? | Outcome | Age |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Inv | MA | | | | |
| 1 | GR-HECOG-20110024 | HE 2110-26-0001 | Lung Infection Grade 5 | No | Yes | No | Yes | Death | |
| 2 | GR-HECOG-20120003 | HE2110-26-0004 | Ileus grade 3 | Unknown | Yes | No (Torisel) | Yes | Recovered | |
| 3 | GR-HECOG-20120004 | HE2110-2-0008 | Renal failure grade 3 | Yes | Yes | Yes | No | Recovered | |
| 4 | GR-HECOG-20120005 | HE2110-40-0006 | Osteonecrosis grade 2 (stage 0) | Yes | Yes | No (Torisel) | Yes | Recovered | |
| 5 | GR-HECOG-20120009 | HE2110-40-0006 | Creatinine grade 1 | Yes (Torisel) | Yes (Torisel) | Yes | No | Not recovered | |
| 6 | GR-HECOG-20120015 | HE2110-2-0013 | Diarrhea grade 3 | Yes (Torisel) | Yes (Torisel) | Yes | No | Recovered | |
| 7 | GR-HECOG-20120019 | HE2110-2-0013 | Bowel perforation grade 3 | Yes (Avastin) | Yes (Avastin) | Yes | No | Not recovered | |
| 8 | GR-HECOG-20120028 | HE2110-2-0009 | Pain abdominal grade 1, Fever grade 1 | No | No | NA | NA | Recovered | |
| 9 | GR-HECOG-20120030 | HE2110-26-0017 | Pneumonitis grade 3 | Yes (Torisel) | Yes (Torisel) | Yes | No | Not recovered | |
| 10 | GR-HECOG-20120031 | HE2110-26-0016 | Pulmonary embolism grade 4 | No | Yes | Yes | No | Not recovered | |
| 11 | GR-HECOG-20130031 | HE2110-2-0011 | Colitis grade 3 | Yes (Avastin) | Yes | No | Yes | Recovered | |
| 12 | GR-HECOG-20130042 | HE2110-4-0025 | Pain grade 3 | No | No | NA | NA | Not recovered | |
| 13 | GR-HECOG-20130046 | HE2110-32-0026 | Pneumonia grade 5 | No | Yes | No | Yes | Death | |
| 14 | GR-HECOG-20130067 | HE2110-4-0027 | Diarrhea grade 3 | Yes | Yes | Yes | No | Recovered | |
| 15 | GR-HECOG-20140002 | HE2110-2-0030 | Pulmonary-pneumothorax grade 5 | No | No | NA | NA | Death | |
| 16 | GR-HECOG-20150006 | HE2110-117-0035 | Hypertension grade 3 | Yes (Avastin) | Yes (Avastin) | Yes | No | Recovered | |

## Table 8. 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 21/10** | GR-HECOG-20120003 | Bevacizumab | 800 mg i.v. | 29/06/2011–18/01/2012 | Ileus grade 3 | 23/01/2012 | Recovered | **SUSAR Investigator's**: Unknown **Sponsor's**: Related |
| **2010-020664-38** | HE2110-26-0004 | Temsirolimus | 25 mg i.v. | 29/06/2011–18/01/2012 | | | | |
| **Greece** | | | | | | | | |
| **81** | | | | | | | | |
| **Male** | | | | | | | | |
| **HE 21/10** | GR-HECOG-20120015 | Bevacizumab | 830 mg i.v. | 10/05/2012-14/06/2012 | Diarrhea grade 3 | 30/06/2012 | Recovered | **Investigator's**: Related Torisel **Sponsor's**: Related Torisel |
| **2010-020664-38** | HE2110-2-0013 | Temsirolimus | 25 mg i.v. | 10/05/2012-14/06/2012 | | | | |
| **Greece** | | | | | | | | |
| **49** | | | | | | | | |
| **Female** | | | | | | | | |
| **HE 21/10** | GR-HECOG-20120019 | Bevacizumab | 830 mg i.v. | 10/05/2012–09/08/2012 | Bowel perforation grade 3 | 16/08/2012 | Not recovered | **Investigator's**: Related Avastin **Sponsor's**: Related Avastin |
| **2010-020664-38** | HE2110-2-0013 | Temsirolimus | 25 mg i.v. | 10/05/2012–09/08/2012 | | | | |
| **Greece** | | | | | | | | |
| **49** | | | | | | | | |
| **Female** | | | | | | | | |

| | **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 21/10** | GR-HECOG-20120028 | Bevacizumab | 600 mg i.v. | 15/02/2012-08/08/2012 | Pain abdominal grade 1 | 16/08/2012 | Recovered | **Investigator's**: Not Related<br>**Sponsor's**: Not Related |
| **2010-020664-38** | HE2110-2-0009 | Temsirolimus | 25 mg i.v. | 15/02/2012-14/08/2012 | Fever grade 1 | | | |
| **Greece** | | | | | | | | |
| **68** | | | | | | | | |
| **Male** | | | | | | | | |
| **HE 21/10** | GR-HECOG-20130031 | Bevacizumab | 570 mg i.v. | 30/04/2013–03/06/2013 | Colitis grade 3 | 26/06/2013 | Recovered | **SUSAR Investigator's**: Related Avastin<br>**Sponsor's**: Related |
| **2010-020664-38** | HE2110-2-0011 | Temsirolimus | 25 mg i.v. | 30/04/2013–17/06/2013 | | | | |
| **Greece** | | | | | | | | |
| **72** | | | | | | | | |
| **Male** | | | | | | | | |
| **HE 21/10** | GR-HECOG-20130067 | Bevacizumab | 680 mg i.v. | 04/11/2013 – 02/12/2013 | Diarrhea grade 3 | 19/12/2013 | Recovered | **Investigator's**: Related<br>**Sponsor's**: Related |
| **2010-020664-38** | HE2110-4-0027 | Temsirolimus | 25 mg i.v. | 04/11/2013 – 11/11/2013 | | | | |
| **Greece** | | Temsirolimus | 20 mg i.v. | 25/11/2013 – 09/12/2013 | | | | |
| **65-year old** | | | | | | | | |
| **Male** | | | | | | | | |

| | **Body System: General disorders** | | | | **No of cases for this body system: 1** | | | |
|---|---|---|---|---|---|---|---|---|
| **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 21/10** | GR-HECOG-20130042 | Bevacizumab | 630 mg i.v. | 07/06/2013-02/08/2013 | Pain grade 3 | 05/08/2013 | Not recovered | **Investigator's**: Not Related<br>**Sponsor's**: Not Related |
| **2010-020664-38** | HE2110-4-0025 | Temsirolimus | 25 mg i.v. | 07/06/2013-02/08/2013 | | | | |
| **Greece** | | | | | | | | |
| **48** | | | | | | | | |
| **Male** | | | | | | | | |

| | **Body System: Infections and Infestations** | | | | **No of cases for this body system: 2** | | | |
|---|---|---|---|---|---|---|---|---|
| **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 21/10** | GR-HECOG-20110024 | Bevacizumab | 650 mg i.v. | 23/02/2011-13/04/2011 | Lung Infection grade 5 | 28/04/2011 | Death | **SUSAR**<br>**Investigator's**: Not Related<br>**Sponsor's**: Related |
| **2010-020664-38** | | Temsirolimus | 25 mg i.v. | 23/02/2011-13/04/2011 | | | | |
| **Greece** | | | | | | | | |
| **65** | | | | | | | | |
| **Male** | | | | | | | | |

| | **Body System: Infections and Infestations** | | | | **No of cases for this body system: 2** | | | |
|---|---|---|---|---|---|---|---|---|
| **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 21/10** | GR-HECOG-20130046 | Bevacizumab | 670 mg i.v. | 25/07/2013- 30/08/2013 | Pneumonia | 10/09/2013 | Death | **Investigator's**: Not Related<br>**Sponsor's**: Related |
| **2010-020664-38** | HE2110-32-0026 | Temsirolimus | 25 mg i.v. | 25/07/2013- 06/09/2013 | | | | |
| **Greece** | | | | | | | | |
| **56** | | | | | | | | |
| **Female** | | | | | | | | |

| | **Body System: Investigations** | | | | **No of cases for this body system: 1** | | | |
|---|---|---|---|---|---|---|---|---|
| **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 21/10** | GR-HECOG-20120009 | Bevacizumab | 650 mg i.v. | 24/11/2011-06/04/2011 | Creatinine grade 1 | 19/04/2011 | Not recovered | **Investigator's**: Related Torisel<br>**Sponsor's**: Related Torisel |
| **2010-020664-38** | HE2110-40-0006 | Temsirolimus | 25 mg i.v. | 24/11/2011-12/04/2011 | | | | |
| **Greece** | | | | | | | | |
| **70** | | | | | | | | |
| **Female** | | | | | | | | |

| | **Body System: Musculosceletal & connective tissue disorders** | | | | **No of cases for this body system: 1** | | | |
|---|---|---|---|---|---|---|---|---|
| **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 21/10** | GR-HECOG-20120005 | Bevacizumab | 700 mg i.v. | 24/11/2011-10/02/2012 | Osteonecrosis grade 2 | 17/02/2012 | Recovered | **Investigator's**: Related **Sponsor's**: Related Plus Zometa |
| **2010-020664-38** | HE2110-40-0006 | Temsirolimus | 25 mg i.v. | 24/11/2011-10/02/2012 | | | | |
| **Greece** | | | | | | | | |
| **70** | | | | | | | | |
| **Female** | | | | | | | | |

| | **Body System: Renal & urinary disorders** | | | | **No of cases for this body system: 1** | | | |
|---|---|---|---|---|---|---|---|---|
| **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 21/10** | GR-HECOG-20120004 | Bevacizumab | 750 mg i.v. | 22/12/2011-19/01/2012 | Renal failure grade 3 | 26/01/2012 | Recovered | **Investigator's**: Related **Sponsor's**: Related |
| **2010-020664-38** | HE2110-2-0008 | Temsirolimus | 25 mg i.v. | 22/12/2011-19/01/2012 | | | | |
| **Greece** | | | | | | | | |
| **76** | | | | | | | | |
| **Female** | | | | | | | | |

| | **Body System: Respiratory, thoracic & mediastinal 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 21/10** | GR-HECOG-20120030 | Bevacizumab | 700 mg i.v. | 04/09/2012-02/10/2012 | Pneumonitis grade 3 | 04/11/2012 | Not recovered | **Investigator's**: Related Torisel<br>**Sponsor's**: Related Torisel |
| **2010-020664-38** | HE2110-26-0017 | Temsirolimus | 25 mg i.v. | 04/09/2012-16/10/2012 | | | | |
| **Greece** | | | | | | | | |
| **67** | | | | | | | | |
| **Male** | | | | | | | | |
| **HE 21/10** | GR-HECOG-20120031 | Bevacizumab | 700 mg i.v. | 30/08/2012-01/11/2012 | Pulmonary embolism grade 4 | 31/10/2012 | Not recovered | **Investigator's**: Not Related<br>**Sponsor's**: Related |
| **2010-020664-38** | HE2110-26-0016 | Temsirolimus | 25 mg i.v. | 30/08/2012-25/10/2012 | | | | |
| **Greece** | | | | | | | | |
| **70** | | | | | | | | |
| **Male** | | | | | | | | |
| **HE 21/10** | GR-HECOG-20140002 | Bevacizumab | 700 mg i.v. | 19/12/2013 - 27/12/2013 | Pneumothorax grade 5 | 29 Dec 2013 | Death | **Investigator's**: Not Related<br>**Sponsor's**: Not Related |
| **2010-020664-38** | HE2110-2-0030 | Temsirolimus | 25 mg i.v. | 19/12/2013 - 27/12/2013 | | | | |
| **Greece** | | | | | | | | |
| **66** | | | | | | | | |
| **Male** | | | | | | | | |

**Table 11. Best objective response to treatment**

| | | |
|---|---|---|
| Patients | N | 39 |
| BestResponse_ | Complete Response | 1 (2.7%) |
| | Partial Response | 9 (24.3%) |
| | Stable Disease | 20 (54.1%) |
| | Progressive Disease | 7 (18.9%) |
| | Non evaluable | 2 |

## FIGURES

**Figure1.** Kaplan-Meier estimates of overall survival

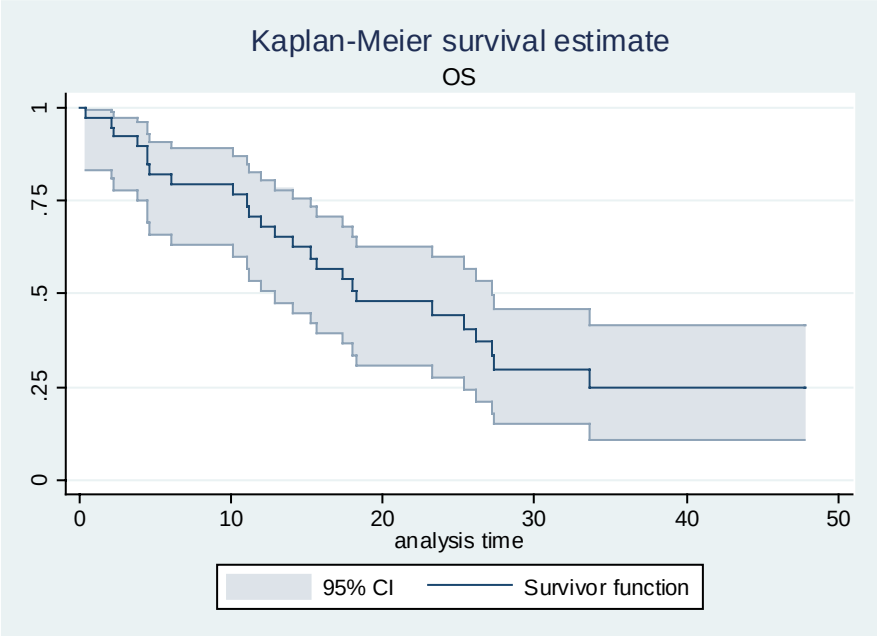



**Figure2.** Kaplan-Meier estimates of progression free survival

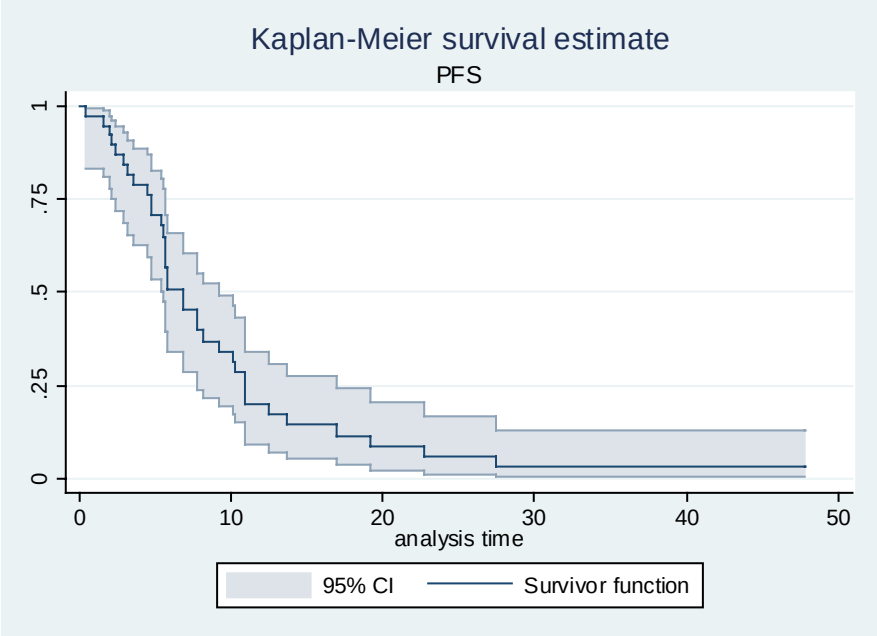


**Figure 3.**

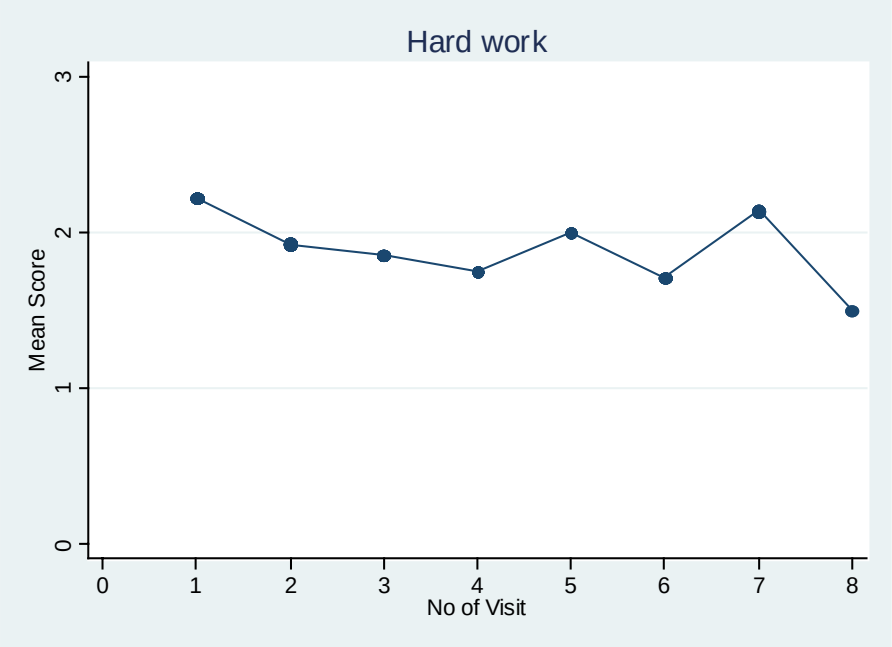



**Figure 4.**

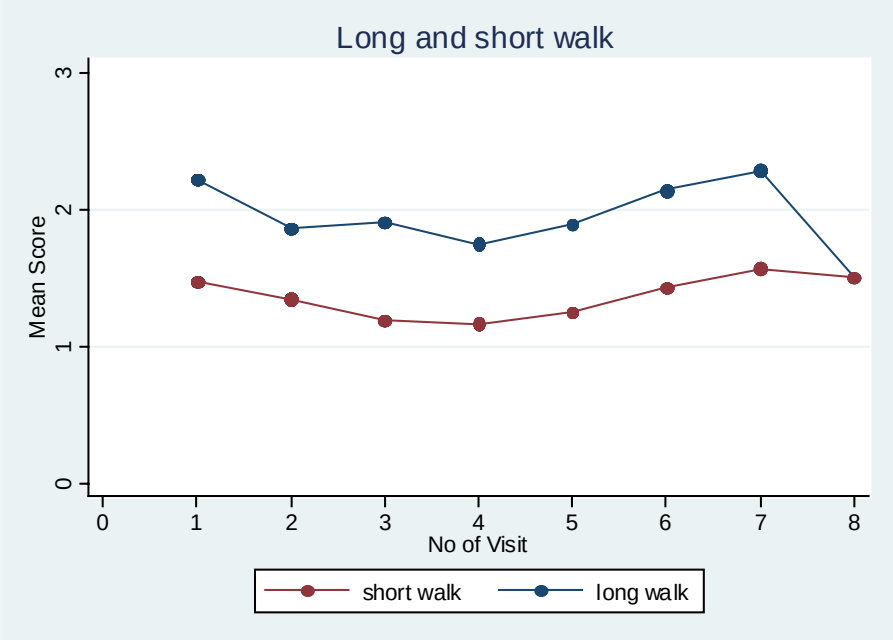


**Figure 5.**

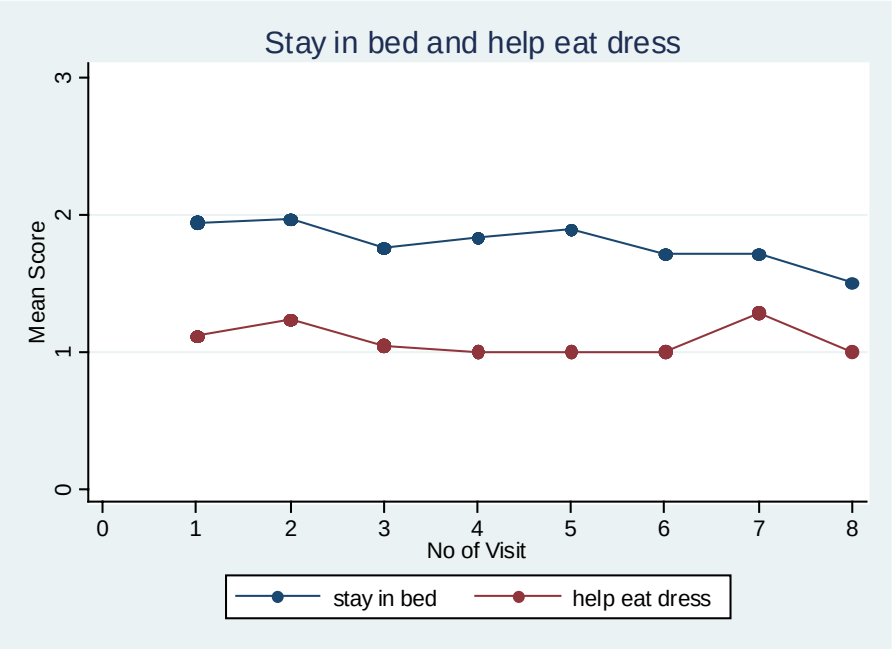



**Figure 6.**

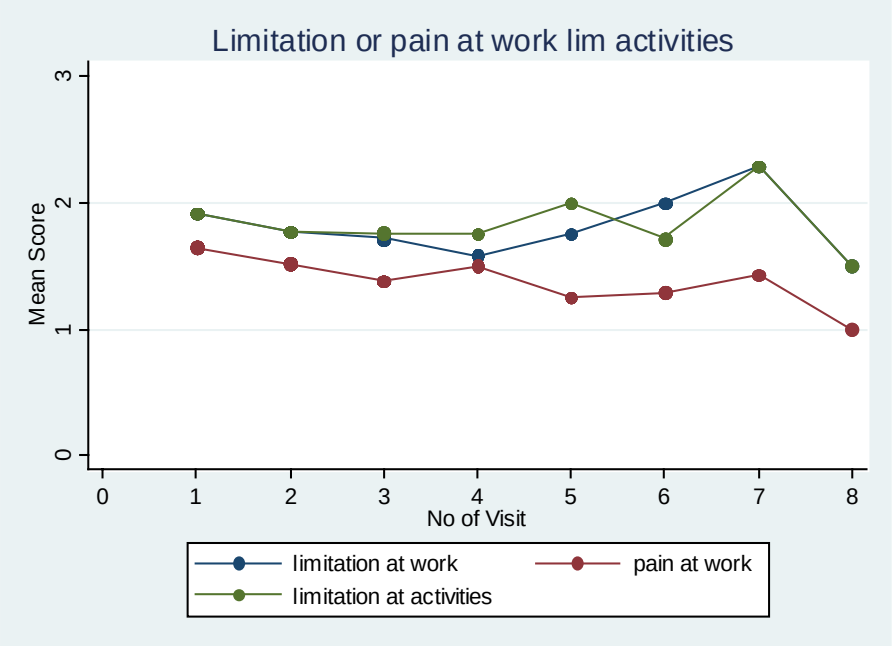


**Figure 7.**

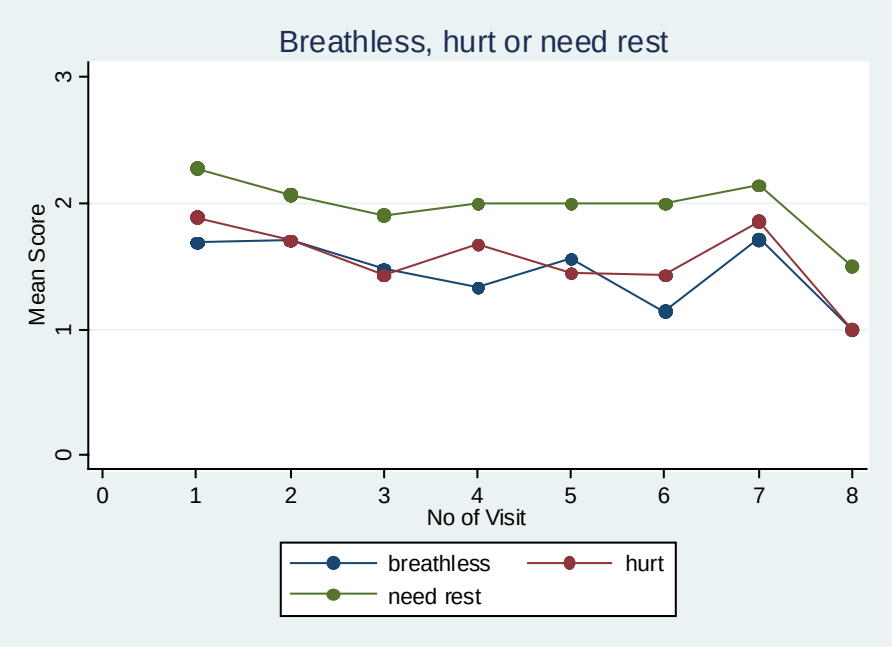



**Figure 8.**

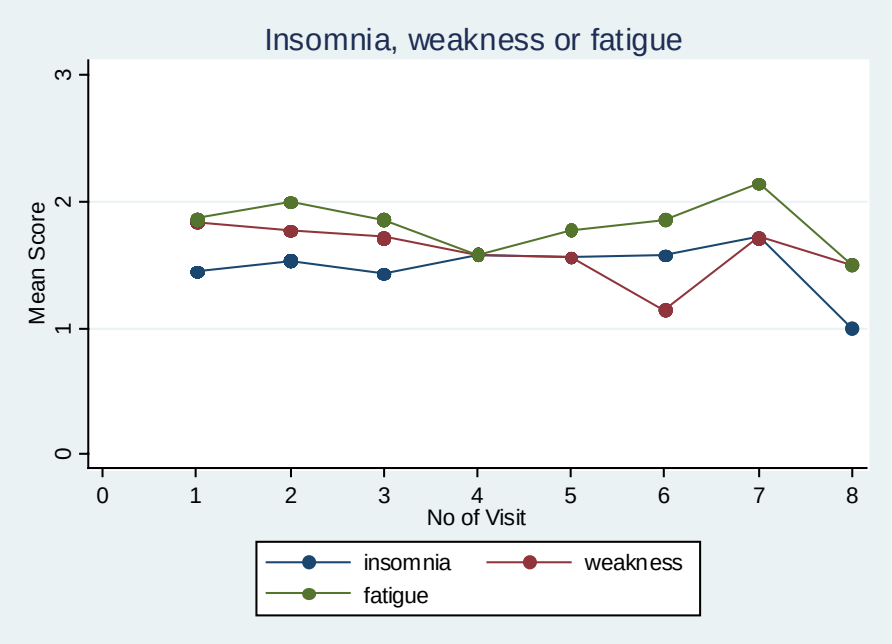


**Figure 9.**

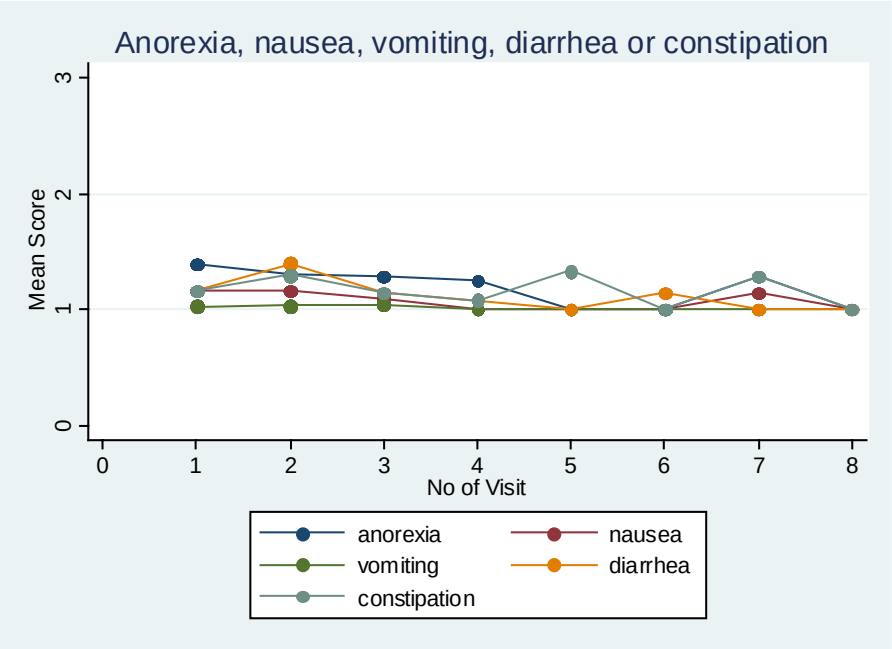



**Figure 10.**

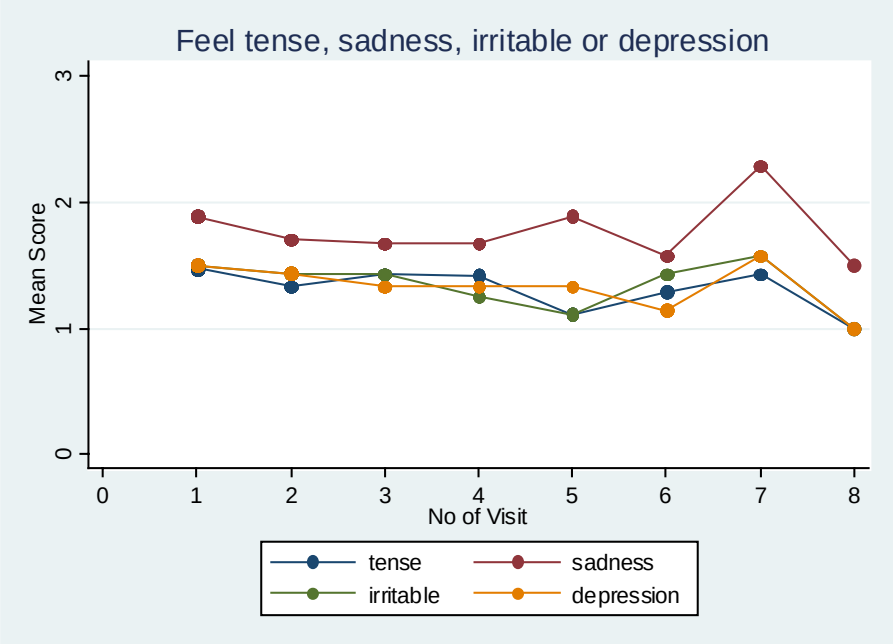


**Figure 11.**

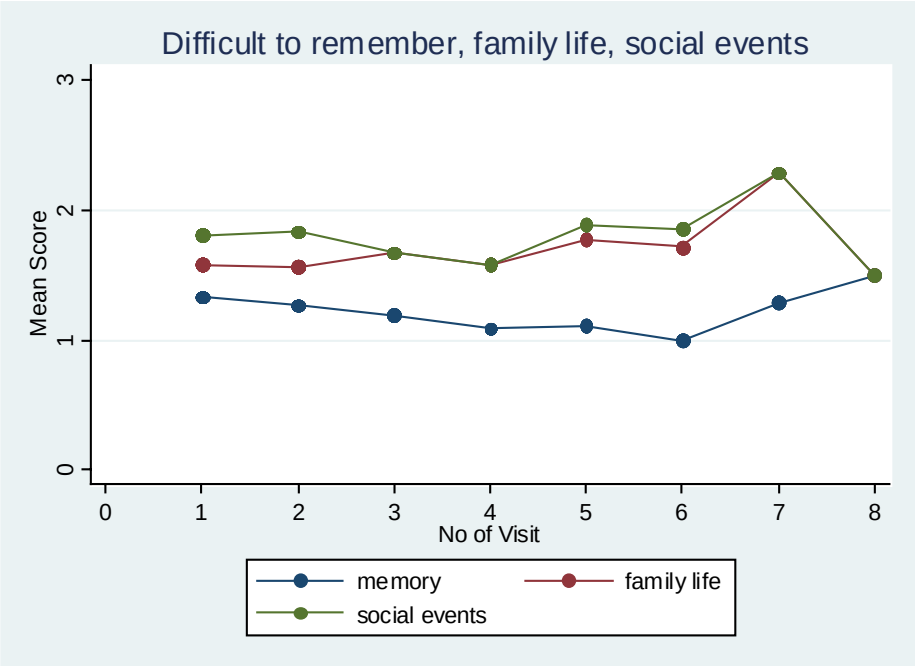
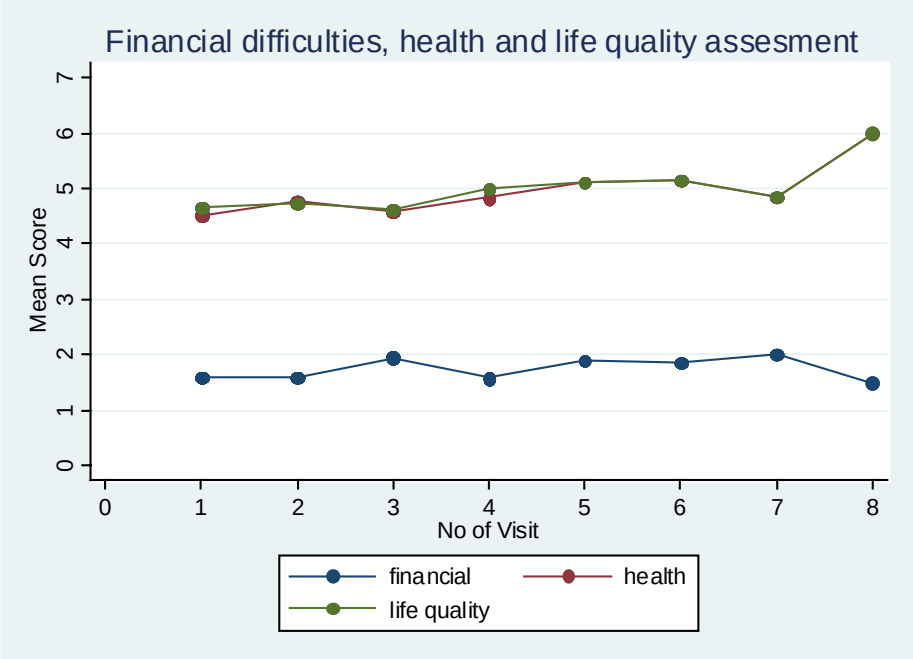



**Figure 12.**



# 13 APPENDICIES

## 13.1 APPENDIX 1. Greek QLQ C-30 questionnaire

# EORTC QLQ-C30

***THIS SECTION FOR USE BY STUDY PERSONNEL ONLY.***

Were data collected? 2 ☐ **No** *(provide reason in comments)*

If **Yes**, data collected on visit date 1 ☐ Yes **or** specify date: ☐☐ ☐☐☐ 2 0 ☐☐ (DD MMM YYYY)

*Comments:*

***Only the patient (subject) should enter information onto this questionnaire.***

Ενδιαφερόμαστε για ορισμένες πληροφορίες που αφορούν εσάς και την υγεία σας. Παρακαλούμε απαντήστε εσείς προσωπικά σε όλες τις ερωτήσεις, σημειώνοντας μέσα σε ένα κύκλο τον αριθμό που σας ταιριάζει καλύτερα. Δεν υπάρχουν σωστές και λάθος απαντήσεις. Οι πληροφορίες που θα δώσετε θα παραμείνουν αυστηρώς εμπιστευτικές.

| | | **Καθό-λου** | **Λίγο** | **Αρκετά** | **Πολύ** |
|---|---|---|---|---|---|
| 1. | Αισθάνεστε ενοχλήσεις όταν κάνετε κοπιαστικές εργασίες, όπως κουβαλώντας μια βαριά τσάντα με ψώνια ή μια βαλίτσα; | 1 | 2 | 3 | 4 |
| 2. | Αισθάνεστε ενοχλήσεις όταν κάνετε ένα <u>μεγάλο</u> περίπατο; | 1 | 2 | 3 | 4 |
| 3. | Αισθάνεστε ενοχλήσεις όταν κάνετε ένα <u>μικρό</u> περίπατο έξω από το σπίτι; | 1 | 2 | 3 | 4 |
| 4. | Χρειάζεται να μένετε στο κρεβάτι ή σε μια καρέκλα κατά τη διάρκεια της ημέρας; | 1 | 2 | 3 | 4 |
| 5. | Χρειάζεστε βοήθεια όταν τρώτε, ντύνεστε, πλένεστε ή όταν πηγαίνετε στην τουαλέτα; | 1 | 2 | 3 | 4 |

| **Κατά τη διάρκεια της τελευταίας εβδομάδας:** | | **Καθό-λου** | **Λίγο** | **Αρκετά** | **Πολύ** |
|---|---|---|---|---|---|
| 6. | Περιοριστήκατε στην εργασία σας ή σε άλλες καθημερινές ασχολίες σας; | 1 | 2 | 3 | 4 |
| 7. | Περιοριστήκατε στις ερασιτεχνικές σας ασχολίες ή σε άλλες δραστηριότητες του ελεύθερού σας χρόνου; | 1 | 2 | 3 | 4 |
| 8. | Λαχανιάσατε; | 1 | 2 | 3 | 4 |
| 9. | Πονούσατε; | 1 | 2 | 3 | 4 |
| 10. | Είχατε ανάγκη από ξεκούραση; | 1 | 2 | 3 | 4 |
| 11. | Είχατε αϋπνίες; | 1 | 2 | 3 | 4 |
| 12. | Αισθανθήκατε αδυναμία; | 1 | 2 | 3 | 4 |
| 13. | Είχατε ανορεξία; | 1 | 2 | 3 | 4 |
| 14. | Είχατε τάση για εμετό; | 1 | 2 | 3 | 4 |
| 15. | Κάνατε εμετό; | 1 | 2 | 3 | 4 |
| 16. | Είχατε δυσκοιλιότητα; | 1 | 2 | 3 | 4 |

Παρακαλείστε να συνεχίσετε στην επόμενη σελίδα

| ***I have reviewed this information.*** | Staff's initials: | Date: |
|---|---|---|

# EORTC QLQ-C30

| Κατά τη διάρκεια της τελευταίας εβδομάδας: | Καθόλου | Λίγο | Αρκετά | Πολύ |
|---|---|---|---|---|
| 17. Είχατε διάρροια; | 1 | 2 | 3 | 4 |
| 18. Αισθανόσασταν κουρασμένος/η; | 1 | 2 | 3 | 4 |
| 19. Αισθανόσασταν πόνο κατά τη διάρκεια της καθημερινής σας εργασίας; | 1 | 2 | 3 | 4 |
| 20. Είχατε δυσκολία να συγκεντρωθείτε σε διάφορα πράγματα, όπως να διαβάσετε εφημερίδα ή να παρακολουθήσετε τηλεόραση; | 1 | 2 | 3 | 4 |
| 21. Αισθανόσασταν υπερένταση; | 1 | 2 | 3 | 4 |
| 22. Αισθανόσασταν στεναχώρια; | 1 | 2 | 3 | 4 |
| 23. Αισθανόσασταν ευέξαπτος/η; | 1 | 2 | 3 | 4 |
| 24. Αισθανόσασταν κατάθλιψη; | 1 | 2 | 3 | 4 |
| 25. Είχατε δυσκολία να θυμηθείτε διάφορα πράγματα; | 1 | 2 | 3 | 4 |
| 26. Η φυσική σας κατάσταση ή τα φάρμακα που παίρνατε για τη θεραπεία σας, εμπόδισαν την οικογενειακή σας ζωή; | 1 | 2 | 3 | 4 |
| 27. Η φυσική σας κατάσταση ή τα φάρμακα που παίρνατε για τη θεραπεία σας, εμπόδισαν τις κοινωνικές σας εκδηλώσεις (κοινωνική ζωή); | 1 | 2 | 3 | 4 |
| 28. Η φυσική σας κατάσταση ή τα φάρμακα που παίρνατε για τη θεραπεία σας, προξένησαν οικονομικές δυσκολίες; | 1 | 2 | 3 | 4 |

**Για τις επόμενες ερωτήσεις παρακαλούμε βάλτε σε κύκλο τον αριθμό που σας ταιριάζει καλύτερα από το 1 έως το 7**

29. Πώς θα εκτιμούσατε συνολικά την υγεία σας κατά τη διάρκεια της περασμένης εβδομάδας;

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Πολύ κακή | | | | | | Εξαιρετική |

30. Πώς θα εκτιμούσατε την ποιότητα ζωής σας κατά τη διάρκεια της περασμένης εβδομάδας;

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Πολύ κακή | | | | | | Εξαιρετική |



| **Επιβεβαιώνω ότι αυτή η πληροφορία είναι ορθή** | Αρχικά ασθενούς/υποκειμένου | Ημερομηνία: |
|---|---|---|

| ***I have reviewed this information.*** | Staff's initials: | Date: |
|---|---|---|

## 13.2 Appendix 2. Concomitant medication with inducers or strong inhibitors of the coenzyme CYP3A4

Inducers:

- carbamazepine
- phenobarbital
- phenytoin
- pioglitazone
- rifabutin
- rifampin
- St.John'swort
- troglitazone

Strong inhibitors:

- HIV antivirals (indinavir, nelfinavir, ritonavir)
- clarithromycin
- itraconazole
- ketoconazole
- nefazodone

Moderate inhibitors:

- erythromycin
- grapefruit juice
- verapamil
- diltiazem

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