SINGLE-ARM PHASE II STUDY OF PANITUMUMAB RECHALLENGE IN COMBINATION WITH OXALIPLATIN OR IRINOTECAN-BASED CHEMOTHERAPY IN PATIENTS WITH RAS WILD TYPE ADVANCED COLORECTAL CANCER.

A-REPEAT: ANTI EGFR RECHALLENGE AND PLASMA GENOTYPING OF PATIENTS WITH ADVANCED COLORECTAL TUMORS.

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FINAL REPORT

Sponsor

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SYNOPSIS

Introduction

Colorectal cancer (CRC) is one of the most frequent types of malignancy worldwide and the second leading cause of cancer death in developed countries. Although mortality rates have been decreasing due to improved treatment options and early detection, once metastases are present, median overall survival with available combination therapy is approximately 24 months. Today's standard treatments for mCRC have evolved to include the addition of targeted biologic therapies to the combination of 5-FU/LV with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), and since the commencement of the current study, immunotherapy in a minority of these patients. Targets for biologic therapies include vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR).

Few clinical studies have evaluated the role of anti-EGFR therapy rechallenge in mCRC patients and there is still no prospective clinical trial assessing the activity of treatment rechallenge with panitumumab-based therapy after initial progression.

Aim of the study-Materials-Methods

This study aimed at exploring the concept of evolution and expansion of RAS WT clones in order to restore sensitivity of the tumor to prior anti-EGFR therapy after a time interval in which a different, non-anti-EGFR 2nd line therapy was administered. Based on aforementioned data, it was hypothesized that rescue through rechallenge with panitumumab-based 3rd-line therapy combined with chemotherapy could be associated with further response and clinical benefit. A significant component of the proposed prospective trial was exploratory translational: cell free plasma and platelet-based genotyping for genetic mutations in different time points have been undertaken in order to study the genetic composition of the metastatic tumour at initiation of and at progression through, anti-EGFR rechallenge therapy.

In the context of a prospective, single arm, phase II clinical trial, patients with RAS wild type advanced colorectal cancer received therapy consisting of Panitumumab in combination with FOLFOX, FOLFIRI or Irinotecan

until progression or intolerable toxicity, or investigator's decision or informed consent withdrawal. Panitumumab was administered at a dose of 6 mg/Kg every 2 weeks or 9 mg/Kg every 3 weeks and FOLFOX, FOLFIRI every 2 weeks or Irinotecan every 3 weeks. The primary endpoint of the trial was to evaluate the efficacy, in terms of overall response rate (ORR), of the addition of panitumumab rechallenge to standard 3rd-line irinotecan-based or oxaliplatin-based chemotherapy in patients with mCRC initially treated with, and benefiting from, 1st line irinotecan-based or oxaliplatin-based chemotherapy combined with an anti-EGFR moAb, followed by 2nd line chemotherapy not containing anti-EGFR agents.

Secondary endpoints were:

a. To evaluate the efficacy, in the subgroups of RAS status (mutation and wild type), in terms of ORRb. To study the survival parameters, i.e. progression free survival (PFS) and overall survival (OS) and c. To evaluate the safety of the combination of standard 3rd-line irinotecan-based or oxaliplatin-based chemotherapy with panitumumab rechallenge The Exploratory Objectives were to identify, in the context of translational research, tumor tissue and blood-based biomarkers with prognostic/predictive significance in patients with metastatic colorectal cancer (mCRC) treated with the protocol defined treatments.

Results

Initially 33 patients were planned to be recruited. However, the study has been terminated prematurely due to very slow accrual with only 23 patients included (from March 2018 until February 2021). Patients were recruited from 6 Oncology Centers affiliated to HeCOG. 18 were men and 5 women with a median age of 65 years. The most common organ involved with metastases was the liver as 78% of the patients had liver metastases. The median interval between termination of first line therapy (with the use of an anti-EGFR agent) to the commencement of treatment within this protocol was 15 months. The most common regimen used within the study was Panitumumab-FOLFIRI (in 61% of the patients). No safety issues have been raised by analyzing the data from the patients. Side-effects occurring to the study's patients are already known to the scientific community. The efficacy results of the treatment used in our study show that 3 patients (13.0%) exhibited PR as best overall

response during the study. Median overall survival (Figure 1) in the entire cohort was 8.7 months (95% C.I: 5.7-16.4) while the median progression free survival (Figure 2) was 2.8 months (95% C.I.: 2.3-5.7).

Conclusions

The study did not meet the target accrual and it is a negative study for that reason. No new safety issues have been raised.

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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-FU	5-Fluorouracil
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT (SGPT)	Alanine Aminotransferase (or Serum Glutamate-Pyruvate Transferase)
ANC	Absolute Neutrophil Count
AST (SGOT)	Aspartate Aminotransferase (or Serum Glutamate-Oxaloacetate Transferase)
BSA	Body Surface Area
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DPD	dihydropyrimidine dehydrogenase (deficiency)
DRF	Discrepancy Resolution Form
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
ECOG **EGFR**	Eastern Cooperative Oncology Group Epidermal Growth Factor Receptor
FU	Follow-up
FOLFIRI	Irinotecan/bolus-infusion-5-Fluorouracil/Leucovorin
FOLFOX	Oxaliplatin/bolus-infusion-5-Fluorouracil/Leucovorin
GCP **HeCOG**	Good Clinical Practices Hellenic Cooperative Oncology Group
HCG	Human Chorionic Gonadotrophin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQL	Health-Related Quality of Life
HSR	Hypersensitivity Reaction
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFL	Irinotecan/5-Fluorouracil (weekly 4/6)/Leucovorin
Ig	Immunoglobulin
INR	International Normalized Ratio
IMP	Investigational Medicine Product
IND	Investigational New Drug
IRB/IEC **ITT** **KRAS**	Institutional Review Board/Independent Ethics Committee Intent To Treat Kirsten Rat sarcoma viral oncogene homolog
IV	Intravenous
LDH	Lactate Dehydrogenase
LV	Leucovorin
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities

moAb	Monoclonal Antibody
MRI	Magnetic Resonance Imaging
Mut	Mutant
NCI	National Cancer Institute
Non-IMP	Non-Investigational Medicinal Product
NYHA	New York Heart Association
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PIL	Package Insert
PS	Performance Status
RBC	Red Blood Cell
ORR	Overall Response Rate
SAE	Serious Adverse Event
SD	Standard Deviation
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WOCBP	Women of childbearing potential

2 ETHICS

2.1 NATIONAL ETHICS COMMITTEE

The study protocol and the amendments were reviewed by the National Ethics Committee (NEC) of Greece and National Bioethics Committee of Cyprus NEC protocol no: 52420/2017/02.08.2017, 79806/2017/31.10.2017, 107928/2018-108954/2018-111489/2018/26.11.2018, 76811/2020/11.09.2020 and ΕΕΒΚ/ΕΠ/2018/14/15.06.2018, ΕΕΒΚ/ΕΠ/2018/14/24.09.2020.

ETHICAL CONDUCT OF THE STUDY

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

2.2 PATIENT INFORMATION AND CONSENT

Patients were screened for eligibility before entering the study and signed the Informed Consent Form (ICF), which was obtained before any study procedure.

3 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Coordinating investigators of the study is Dr. Joseph Sgouros, Dr. Panagiota Oikonomopoulou

Table 1. Principal Investigators

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4 INTRODUCTION

4.1 COLORECTAL CANCER

Colorectal cancer (CRC) is one of the most frequent types of malignancy worldwide and the second leading cause of cancer death in developed countries. It is the third most commonly diagnosed cancer in males (after lung and prostate cancer) and the second most common in females (after breast cancer). In 2012, it accounted for more than 1.3 million cases worldwide, with a mortality of over 600000 cases (1).

CRC develops slowly, over several years of progression through different molecular and cytological stages, becoming a carcinoma with the potential for invasion and metastasis. If diagnosis is made early, CRC is generally curable, with a 93% 5-year survival rate, which decreases to approximately 60-65% after spread to adjacent organ(s) or lymph nodes. However, the 5-year survival rate is less than 10% in subjects with metastatic disease (2).

Despite the fact that 75% to 80% of all the patients with colorectal carcinoma will present at a stage when all gross carcinomas can be surgically removed, almost half of these patients will develop metastatic disease. Furthermore, typically 15% to 25% of the patients present with metastatic disease at diagnosis. Although mortality rates have been decreasing

due to improved treatment options and early detection, once metastases are present, median overall survival with available combination therapy is approximately 24 months (3, 4).

4.2 METASTATIC COLORECTAL CANCER TREATMENT

For many years, chemotherapy for colorectal cancer has been based on the use of the antimetabolite 5-fluorouracil (5-FU), co-administered with leucovorin (LV). Modifications in the administration schedules of this combination have yielded improvements in its use, with the fortnightly administration of bolus 5-FU and LV followed by 5-FU infusion, demonstrating improved activity (in terms of response rate and PFS) and safety over the so-called Mayo regimen (monthly 5-day bolus regimen) (5). This combination, however, did not result in any improvement on survival (6).

Improved survival in patients with colorectal cancer was observed with the development of the cytotoxic agents oxaliplatin and irinotecan when phase 3 studies combining any of those agents with 5-FU and LV in a first-line metastatic setting showed median overall survival of 15 to 19 months (7, 8).

Currently, initial therapy for most patients with metastatic colorectal cancer (mCRC) is based on oxaliplatin-based chemotherapy (FOLFOX, capecitabine/oxaliplatin) or FOLFIRI (fortnightly leucovorin/bolus-infusional 5-FU/irinotecan) with the addition of targeted biologic therapies. Targets for biologic therapies most of the primes in patients with mCRC are vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR).

Anti-VEGF therapy

The growth and proliferation of several malignant tumors depends on angiogenesis, a complex process by which new blood vessels are formed from endothelial precursor in order to maintain a source of nutrition and oxygen to the tumor and support invasion and metastasis. VEGF has become a major target for anti-angiogenic therapy because its overexpression in several tumor types (including tumors of the gastro-intestinal tract) has

been associated with increased tumor vascularity, proliferation, progression, invasion, metastasis, and poor prognosis (9, 10).

Metastatic CRC is one of the first malignancies in which a clear benefit was demonstrated with an anti-VEGF treatment in randomized clinical trials. Bevacizumab is a humanized monoclonal antibody that targets VEGF-A, a member of the VEGF-receptor activating ligands. It has demonstrated a survival benefit in randomized trials in the first-line setting in combination with IFL, FOLFIRI and FOLFOX (3, 11) and second-line setting (in combination with FOLFOX) treatment of mCRC (12). On the other hand, Aflibercept is a recombinantly-produced fusion protein consisting of human VEGF receptor extracellular domains (from both VEGFR1 and VEGFR2) fused to the F_c portion of human IgG_1 (Immunoglobulin G1). In a randomized trial, it has been shown to improve overall survival as second line treatment, when combined with FOLFIRI in oxaliplatin pretreated patients, regardless of whether patients are pretreated with bevacizumab in first line therapy (13). Antiangiogenic agents are effective against both RAS-wild type and RAS-mutated tumors, as no formal interaction has been shown between VEGF inhibitors and RAS gene status in terms of antineoplastic effect.

Anti-EGFR antibodies: Panitumumab, Cetuximab

Cetuximab, a chimeric monoclonal antibody against EGFR and Panitumumab, a humanised monoclonal antibody, have demonstrated activity in patients with refractory mCRC (14, 15). After early indications that cetuximab could improve efficacy when combined with irinotecan in mCRC (16), the phase 3 CRYSTAL study of FOLFIRI with or without cetuximab in first-line patients was able to demonstrate a significant improvement in PFS (the primary objective) and response rate in patients treated with cetuximab and FOLFIRI, but showed no statistically significant improvement in overall survival. Post-hoc analysis, performed to evaluate the impact of KRAS status on the effect of adding cetuximab to FOLFIRI, demonstrated that patients with KRAS mutations received no benefit from cetuximab, while those with KRAS wild type exon 2 (WT) tumors demonstrated overall survival improvement (17, 18). Similar results in the same patient

setting were reported with the combination of cetuximab with the FOLFOX regimen (19). Clinical data on the activity of Panitumumab are shown in detail in section 1.3

4.3 PANITUMUMAB BACKGROUND

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds with high affinity and specificity to the human EGFR (20). EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1/c-ErbB-1), HER2, HER3, and HER4. EGFR promotes cell growth in normal epithelial tissues, including the skin and hair follicle, and is expressed on a variety of tumor cells (21).

Panitumumab binds to the ligand binding domain of EGFR and inhibits receptor autophosphorylation induced by all known EGFR ligands. Binding of panitumumab to EGFR results in internalization of the receptor, inhibition of cell growth, induction of apoptosis and decreased production of interleukin 8 (IL-8) and VEGF.

RAS is a key downstream intermediate in the EGFR signaling pathway. KRAS (Kirsten rat sarcoma 2 viral oncogene homologue) and NRAS (Neuroblastoma RAS viral oncogene homologue) are highly related members of the RAS oncogene family. KRAS and NRAS genes encode small, GTP-binding proteins involved in signal transduction. A variety of stimuli, including that from the EGFR, activate KRAS and NRAS which in turn stimulate other intracellular proteins to promote cell proliferation, cell survival and angiogenesis. Activating mutations in the RAS genes occur frequently in a variety of human tumors and have been implicated in both oncogenesis and tumor progression (22, 23). Consistent data from exploratory analyses of multiple clinical studies have supported the clinical utility of KRAS and NRAS as predictive biomarkers in subjects with mCRC (24, 25).

In preclinical studies panitumumab inhibited tumor growth and survival of tumor cells expressing EGFR. No anti-tumor effects of panitumumab were observed in human tumor xenografts lacking EGFR expression. The addition of panitumumab to radiation, chemotherapy or other targeted therapeutic agents, in animal studies resulted in an increase

in anti-tumor effects compared to radiation, chemotherapy or targeted therapeutic agents alone (26).

Panitumumab administered as a single agent or in combination with chemotherapy exhibits nonlinear pharmacokinetics. Following a single-dose administration of panitumumab as a 1-hour infusion, the area under the concentration-time curve (AUC) increases in a greater than dose-proportional manner and clearance (CL) of panitumumab decreases from 30.6 to 4.6 mLl/day/Kg as the dose increases from 0.75 to 9 mg/kg. However, at doses above 2 mg/Kg, the AUC of panitumumab increases in an approximately dose-proportional manner.

Following the recommended dose regimen (6 mg/Kg given once every 2 weeks as an 1-hour infusion), panitumumab concentrations reach steady-state levels by the third infusion with mean (± Standard Deviation [SD]) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/ml, respectively. The elimination half-life is approximately 7.5 days (range: 3.6 to 10.9 days).

In the United States (US), panitumumab is currently approved for the treatment of WT RAS mCRC as first-line therapy in combination with FOLFOX and as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. In the European Union (EU), panitumumab is currently approved for the treatment of WT RAS mCRC (no mutations in exons 2,3,4 of KRAS and NRAS oncogenes) as first-line therapy in combination with FOLFOX or FOLFIRI, as second-line therapy in combination with FOLFIRI, and as monotherapy with or without irinotecan after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

The benefit of panitumumab monotherapy was initially shown in a multicenter trial in which 463 patients refractory to FU, irinotecan and oxaliplatin were randomly assigned to best supportive care (BSC) with or without panitumumab (6 mg/Kg every two weeks) (27). The objective response rate with panitumumab was 10 percent, and 27 percent had SD; the

corresponding rates with BSC alone were 0 and 10 percent. Patients receiving panitumumab were significantly more likely to be alive and progression-free at eight weeks (49 versus 30 percent). The lack of a survival difference was likely due to panitumumab use after crossover in the BSC group (28).

In a later reanalysis, efficacy was limited to patients whose tumors were WT KRAS (PR and SD in 17 and 34 percent, respectively, versus 0 and 12 percent with mutated KRAS) (29). Adverse effects that were significantly more frequent with panitumumab were skin toxicity (90 versus 9 percent in the BSC group), diarrhea (21 versus 11 percent), abdominal pain (23 versus 17 percent), fatigue (24 versus 15 percent), and nausea (22 versus 15 percent).

Efficacy of panitumumab is similar to cetuximab monotherapy, and the two drugs might be interchangeable as single agents in this setting. In an open-label trial in patients with WT *KRAS* (exon 2) mCRC, a total of 1010 patients refractory to chemotherapy were randomized 1:1 to receive panitumumab or cetuximab; the primary endpoint was OS assessed for non-inferiority (30). There was no difference between panitumumab and cetuximab in terms of OS (10.4 vs. 10 months respectively, HR=0.97, 95% CI=0.84-1.11) and PFS (4.1 vs. 4.4 months, respectively, HR=1, 95% CI=0.88-1.14). Overall, the safety profile of panitumumab was similar to that of cetuximab, in particular regarding skin toxicity. However, infusion reactions were more frequent with cetuximab (13% vs. 3%) but electrolyte disturbances were more frequent with panitumumab, especially hypomagnesaemia (29% vs. 19%). Whether panitumumab is of benefit in patients who are refractory to cetuximab is unclear.

A PFS benefit for adding panitumumab to first-line oxaliplatin-based regimen (FOLFOX) was shown in the phase III PRIME trial (median PFS 9.6 versus 8 months) (31); the OS benefit, while potentially clinically meaningful, was not statistically significant with median follow-up of 55 weeks (23.9 versus 19.7 months, HR 0.88, 95% CI 0.73-1.06) but the difference achieved statistical significance in a later exploratory analysis of updated

survival at median follow-up 80 weeks (HR for death 0.83, 95% CI 0.70-0.98) (32). Survival was impaired in patients with exon 2 KRAS mutant mCRC who were treated with panitumumab plus FOLFOX. A later analysis of data from this trial, 108 patients (17 percent) without KRAS mutations in exon 2 had other RAS mutations in KRAS exons 3 and 4 and in NRAS exons 2, 3, and 4 (25). These additional mutations predicted a lack of response to panitumumab, and in fact, their presence was associated with inferior PFS and OS in patients receiving panitumumab plus FOLFOX compared with FOLFOX alone.

The efficacy of panitumumab as second-line treatment in combination with irinotecan-based regimen (FOLFIRI) was evaluated in a randomized, controlled trial of 1186 patients with mCRC with the primary endpoints of OS and PFS. In primary analysis, KRAS (exon 2) status was available for 91% of patients: 597 (55%) with WT KRAS tumors and 486 (45%) with mutant KRAS tumors. In the final analysis, in patients with WT KRAS tumors, panitumumab-FOLFIRI significantly improved PFS vs. FOLFIRI [median 6.7 versus 4.9 months; hazard ratio (HR) 0.82 [95% confidence interval (CI) 0.69-0.97]; P=0.023]. A trend toward longer OS was observed (median 14.5 versus 12.5 months; HR 0.92 [95% CI 0.78, 1.10]; P = 0.37). Response rates improved from 10% to 36% (P < 0.0001). In patients with mutant KRAS, there was no difference in efficacy (33, 34).

A predefined retrospective subset analysis of 586 patients of the 597 patients with WT KRAS (exon 2) mCRC was performed, where tumor samples from these patients were tested for additional RAS and BRAF mutations as previously described. The incidence of these additional RAS mutations (KRAS exons 3,4 and NRAS exons 2,3,4) in the WT KRAS (exon 2) population was approximately 18%. For PFS and OS, the hazard ratio for panitumumab plus FOLFIRI vs. FOLFIRI alone favored more strongly panitumumab in the WT RAS population than in the WT KRAS exon 2 population (PFS HR, 0.70 [95%CI=0.54–0.91]; P=0.007 vs. 0.73 [95%CI=0.59-0.90]; P=0.004; OS HR, 0.81 [95%CI=0.63–1.03]; P=0.08 vs. 0.85 [95%CI=0.70–1.04]; P=0.12). Patients with RAS mutations were unlikely to benefit from panitumumab (35).

The efficacy of panitumumab in first-line treatment in combination with FOLFIRI was evaluated in a phase II single-arm study of 154 patients with the primary endpoint of ORR. KRAS status was WT in 59 percent of patients and mutant in 41 percent of patients. In the WT KRAS group, ORR was 58% (vs. 38% in KRAS mutant group) and median PFS was 8.9 months (vs. 7.2 months in the KRAS mutant group).

4.4 NON – CLINICAL PHARMACOLOGY

EGFR is constitutively expressed in tissues of epithelial origin and in a variety of solid tumors (21, 36) . EGFR is a member of the
ErbB receptor tyrosine kinase family that consists of 4 family members: EGFR, ErbB2 (Her2), ErbB3, and ErbB4 (37, 38).
Upon ligand (EGF, TGF-α, amphiregulin, betacellulin, HB-EGF, and epiregulin) binding, ErbB family receptors homo- or hetero-dimerize with each other resulting in trans-autophosphorylation of the dimer partners and initiation of intracellular signaling pathways.
These intracellular signaling pathways influence pleiotropic changes in target cells, such as cellular morphogenesis, proliferation, angiogenesis, and survival (38-41). Functionally, these ligand-receptor combinations serve to increase the combinatorial repertoire of phosphorylated substrates and activated effector pathways in cells (37, 38, 42, 43).

4.5 SUMMARY OF NON-CLINICAL PHARMACOLOGY IN VIVO

Treatment with panitumumab as monotherapy or in combination with a chemotherapeutic agent or a targeted agent results in growth inhibition as well as eradication, in some cases, of tumor xenografts. Anti-tumor effects have been observed after treatment with both hybridoma- and Chinese hamster ovary (CHO)-derived panitumumab in a wide range of human carcinoma xenografts with variable EGFR expression levels using colorectal, renal, breast, pancreatic, lung, head and neck,

ovarian, prostate, and glioblastoma tumor cell lines, but not in human tumor xenografts not expressing EGFR. These data indicate that EGFR must be present to demonstrate an anti-tumor response.

4.6 ACTIVITY OF PANITUMUMAB WITH CHEMOTHERAPY

Panitumumab in combination with standard chemotherapy (irinotecan, cisplatin, docetaxel, or gemcitabine) has been evaluated in a wide range of tumor cell lines and xenograft model systems (HT-29, A549, NCl-H1975, NCl-H1650, Fadu squamous cell carcinoma of the head and neck or MiaPaCa). Combination therapy of panitumumab and standard chemotherapy has demonstrated additive anti-tumor effects compared with the treatment effects of either agent alone.

4.7 SAFETY AND EFFICACY OF PANITUMUMAB IN HUMANS

Panitumumab in the Treatment of mCRC

In the US, panitumumab is currently approved for the treatment of wild-type RAS mCRC as first-line therapy in combination with FOLFOX and as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. The USPI provides detailed product information for investigators in the US.

Link to USPI:

http://pi.amgen.com/united_states/vectibix/vectibix_pi.pdf

In the EU, panitumumab is currently approved for the treatment of adult patients with wild-type RAS mCRC as first-line therapy in combination with FOLFOX and FOLFIRI, as second-line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-base chemotherapy (excluding irinotecan), and as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. The EU SPC provides detailed product information for investigators in the EU.

Link to EU SPC:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000741/WC500047710.pdf

For regions outside the US and EU, detailed information on the nonclinical effects of panitumumab and its clinical effects in this patient population is provided in the current country-specific prescribing information for panitumumab.

Panitumumab Monotherapy in Colorectal Cancer

Panitumumab has been evaluated as monotherapy for the treatment of mCRC.

The primary evidence of clinical benefit comes from 3 phase 3 studies (20020408,20080763, and 20100007) in the mCRC setting that provide efficacy and safety data on panitumumab monotherapy. Results from Studies 20020408 and 20080763 in subjects that were wild-type for *KRAS* are summarized in both the USPI and the EU SPC (links included above). Additional results from Study 20100007 are summarized in the USPI and further support the clinical benefit in subjects wild-type RAS mCRC.

Study 20020408 is a randomized, multicenter, open-label study designed to compare the efficacy and safety of panitumumab plus best supportive care (BSC) versus BSC alone in subjects with mCRC. Study 20080763 is a randomized, multicenter, open-label study designed to compare the efficacy and safety of panitumumab versus cetuximab in subjects with previously treated, wild-type KRAS exon 2 mCRC. Study 20100007 is a multicenter, randomized, open-label study designed to evaluate the survival benefit of panitumumab plus BSC compared with BSC alone in subjects with chemorefractory, wild-type KRAS exon 2 mCRC.

Panitumumab in Combination with Chemotherapy in mCRC

Panitumumab has also been evaluated in combination with oxaliplatin- and irinotecan-based chemotherapy regimens for the treatment of mCRC. The primary evidence of clinical benefit comes from 2 phase 3 studies (20050203 and 20050181) in the mCRC setting that

provide efficacy and safety data on panitumumab in combination with chemotherapy. Study 20050203 is a multicenter, randomized, open-label, comparative study to evaluate the efficacy of panitumumab in combination with FOLFOX chemotherapy relative to FOLFOX alone in subjects with previously untreated mCRC. The primary objective of this study was to assess whether panitumumab in combination with FOLFOX chemotherapy improves PFS compared to FOLFOX alone as first-line therapy. Results from the primary analysis from Study 20050203 in subjects who were KRAS wild-type are summarized in both the USPI and the EU SPC; results from the primary analysis in subjects who were RAS wild-type (pre-defined, retrospective subset analysis, excluding subjects with mutant KRAS exon 2/3/4 and NRAS 2/3/4) are also summarized in both the USPI and the EU SPC. Results from Study 20050181 are summarized in the EU SPC (links included above). Study 20050181 was a multicenter, randomized, open-label, comparative study to evaluate the efficacy of panitumumab in combination with FOLFIRI chemotherapy relative to FOLFIRI alone as second-line treatment in subjects with mCRC. The primary objective of this study was to evaluate the treatment effect of panitumumab plus FOLFIRI on OS and PFS compared with FOLFIRI alone as second-line therapy for mCRC among subjects with wild-type KRAS tumors (exon 2) and mutant KRAS tumors (exon 2). Results from the primary analysis from Study 20050181 in subjects who were *RAS* wild-type (pre-defined, retrospective subset analysis, excluding subjects with mutant *KRAS* exon 2/3/4 and *NRAS* 2/3/4) are summarized in the EU SPC (links included above).

In addition, results from Study 20060314 provide evidence of clinical benefit of panitumumab in combination with FOLFIRI as first-line therapy in subjects with mCRC. Study 20060314 was a single-arm, multicenter, phase 2 study of panitumumab in combination with FOLFIRI as first-line therapy in subjects with mCRC. The primary objective of the study was to estimate the effect of *KRAS* mutation status (wild-type vs mutant *KRAS* exon 2) on objective response rate (ORR) and other measures of efficacy

for subjects treated with panitumumab in combination with FOLFIRI as first-line therapy for mCRC. Results from the primary analysis from Study 20060314 in subjects who were *RAS* wild-type and *RAS* mutant are summarized in the EU SPC (links included above).

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

The primary objective of this study was to evaluate the efficacy, in terms of overall response rate (ORR), of the addition of panitumumab rechallenge to standard 3rd-line irinotecan-based or oxaliplatin-based chemotherapy in patients with mCRC initially treated with, and benefiting from, 1st line irinotecan-based or oxaliplatin-based chemotherapy combined with an anti-EGFR moAb, followed by 2nd line chemotherapy not containing anti-EGFR agents.

5.2 SECONDARY OBJECTIVES

- To evaluate the efficacy, in the subgroups of RAS status (mutation and wild type), in terms of ORR, of the addition of panitumumab rechallenge to standard 3rd-line irinotecan-based or oxaliplatin-based chemotherapy in patients with mCRC initially treated with, and benefiting from, 1st line irinotecan-based or oxaliplatin-based chemotherapy combined with an anti-EGFR moAb, followed by 2nd line chemotherapy not containing anti-EGFR agents.
- To study the survival parameters, i.e. progression free survival (PFS) and overall survival (OS), of the combination of standard 3rd-line irinotecan-based or oxaliplatin-based chemotherapy with panitumumab rechallenge in patients with mCRC initially treated with, and benefiting from, 1st line irinotecan-based or oxaliplatin-based chemotherapy combined with an anti-EGFR monoclonal antibody (moAb), followed by 2nd line chemotherapy not containing anti-EGFR agents.
- To evaluate the safety of the combination of standard 3rd-line irinotecan-based or oxaliplatin-based chemotherapy with panitumumab rechallenge in patients with mCRC

initially treated with, and benefiting from, 1st line irinotecan-based or oxaliplatin-based chemotherapy combined with an anti-EGFR moAb.

5.3 EXPLORATORY OBJECTIVES

To identify, in the context of translational research, tumour tissue and blood-based biomarkers with prognostic/predictive significance in patients with(mCRC) treated with rechallenge panitumumab in combination with standard 3rd-line irinotecan-based or oxaliplatin-based chemotherapy, who were initially treated with, and benefiting from 1st line irinotecan-based or oxaliplatin-based chemotherapy combined with an anti-EGFR moAb, followed by 2nd line chemotherapy not containing anti-EGFR agents (Appendix E).

6. STATISTICAL DESIGN AND METHODS

6.1 DETERMINATION OF SAMPLE SIZE AND METHODS

It had been estimated that improvement of objective response rate (ORR) according to RECIST 1.1 criteria would improv from 10% (null hypothesis) to 30% (alternative hypothesis) with the addition of panitumumab rechallenge to standard 3rd-line irinotecan-based or oxaliplatin-based chemotherapy in patients with mCRC initially treated with, and benefiting from, 1st line irinotecan-based or oxaliplatin-based chemotherapy combined with an anti-EGFR moAb, followed by 2nd line chemotherapy not containing anti-EGFR agents. Using the exact one-stage Fleming's design, in order to reject the null hypothesis in a one-sided test with a type I error of 5% and power 90%, 33 patients were required to enter the study.

6.2 EXTENT OF INVESTIGATIONAL MEDICINAL PRODUCT EXPOSURE

The overall extent of exposure will be assessed for each patient as:

Cycle duration is the period in weeks between two patient's visits for the administration of the study drugs. Total number of cycles (K), determined by the highest number of cycles of each individual drug/ Cumulative dose, for each compound in case of combination: The

cumulative dose at cycle k is the sum of all doses from cycle 1 to and including cycle k, where k is based on Investigator's report.

The actual dose intensity (ADI) is defined as the cumulative dose divided by the number of weeks on study.

The relative dose intensity (RDI) is defined as the ratio of the actual dose intensity to the planned dose intensity. RDI, as an indicator of the feasibility of the chosen schedule of administration.

Dose reduction and reason for dose reduction: Dose reduction will be derived using the definition provided in the protocol compared to the previous dose. For the second and subsequent cycles, a dose is deemed to have been reduced if the dose level a patient receives is lower than the previous actual dose level.

Dose delays: A cycle is deemed to have been delayed if start date of the current cycle – start date of previous cycle > 2 days.

Dose omission: for each drug at a given cycle, if the drug is missing but the other in the combination is not missing, then the missing drug is considered as "omitted" for that cycle

Dose interruption: for each drug at a given cycle.

6.3 ANALYSIS POPULATION

-The intent to treat (ITT) population: all patients who will have given their informed consent and who will have been correctly registered to the study.

-Evaluable population for tumor response: all treated patients, without major protocol deviation, with at least one tumor evaluation while on treatment (except for early disease progression or death) and evaluable for response.

-Safety population: the subset of the ITT population that took at least one dose of study medication.

6.4 PROTOCOL DEVIATIONS

The compliance with the protocol will be examined with regard to inclusion and exclusion criteria, prohibited therapies, timing and availability of planned assessments. Protocol deviations will be identified before database lock and will be classified as minor or major deviations.

6.5 STATISTICAL ANALYSIS PLAN

Demographic and baseline characteristics

Standard demographic and baseline characteristics (including age, gender, race, height and weight), medical and surgical history, cancer diagnosis and prior anticancer therapy will be summarised at baseline. Baseline safety variables will also be assessed. These variables include vital signs and main laboratory parameters.

Baseline value is defined as the last value or measurement taken before the first dose of panitumumab.

Efficacy variables

Analysis of primary efficacy variable

The primary efficacy parameter will be ORR and it will be calculated in the ITT population. ORR will be described in a frequency table along with the corresponding percentages and 95% exact confidence intervals. Analysis for ORR will additionally be presented in the evaluable population for tumor response.

Analysis of secondary variables

ORR will also be calculated separately in the subgroups defined by RAS status (mutant and wild type) in the ITT population. It will be described in a frequency table by RAS status along with the corresponding percentages and 95% exact confidence intervals. Analysis for ORR will additionally be presented in the evaluable population for tumor response. Kaplan-Meier method will be used to estimate median PFS and OS values and

95% confidence intervals. Comparison of survival curves will be compared using the log-rank statistical test. All of these analyses will be performed in the ITT population. AEs of the safety population for the Panitumumab/FOLFOX, FOLFIRI or Irinotecan treatment will be presented in frequency tables according to grade, along with the corresponding percentages (N, %).

Exploratory analysis

Univariate and multivariate Cox regression analyses will also be performed to explore prognostic factors among basic clinicopathological characteristics and evaluated biomarkers, with respect to PFS and OS. Time-to-event distributions for the expression of examined markers will be estimated by the Kaplan-Meier method and compared using the log-rank test.

Safety variables

The safety variables include:

- AEs

AEs (including SAEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

- Discontinuation (including reason for discontinuation and discontinuation due to AEs)
- Blood pressure and ECOG performance status
- Major laboratory safety parameters
    - Haematology: WBC, neutrophil, platelets, and haemoglobin.
    - Blood chemistry: sodium, potassium, calcium, BUN/urea, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, LDH, glucose.

AEs of the safety population for the panitumumab plus FOLFIRI or FOLFOX or Irinotecan treatment part will be presented in frequency tables according to grade, along with the corresponding percentages (N, %).

7. ELECTION OF STUDY POPULATION

7.1 INCLUSION CRITERIA

1. Signed and dated informed consent, and willing and able to comply with protocol requirements,
2. Histologically proven adenocarcinoma of the colon and/or rectum,
3. Metastatic disease confirmed clinically/radiologically,
4. Patients with Formalin-Fixed, Paraffin-Embedded (FFPE) tissue RAS wild type CRC at diagnosis, who had initial clinical benefit [complete response (CR), partial response (PR) or stable disease (SD)] during 1st line irinotecan-based or oxaliplatin-based chemotherapy in combination with cetuximab or panitumumab,
5. 1st line treatment duration (FOLFIRI, FOLFOX + anti EGFR moAb, of whom at least 2/3 of cases will have involved panitumumab) of at least 3 months,
6. 2nd line therapy consisting of any chemotherapy (with or without Bevacizumab) definitely without anti-EGFR therapy of at least 2 months, followed by disease progression,
7. Eligible 3rd line regimens include FOLFIRI or Irinotecan or FOLFOX, according to standard practice and approved indications. It is required that the 3rd line regimen used will be different from the 2nd line and similar to the 1st line regimen,
8. At least one measurable or evaluable lesion as assessed by computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) according to RECIST v1.1,
9. First course of treatment planned less than 1 week (7 days) after registration,
10. Age ≥18 years,
11. ECOG Performance status (PS) 0-2,
12. Adequate hematological status: neutrophils (ANC) ≥1.5x10^9/L; platelets ≥100x10^9/L; haemoglobin ≥9g/dL,
13. Adequate renal function: serum creatinine level ≤1.5 mg/dL or Glomelular Filtration Rate >50mL/min by Cockroft/Gault formula,

14. Adequate liver function: serum bilirubin ≤1.5 x upper normal limit (ULN), alkaline phosphatase, AST, ALT <5xULN,
15. Regular follow up feasible,
16. For female patients of childbearing potential, negative serum or urine pregnancy test within 1 week (7 days) prior of starting study treatment,
17. Female patients must commit to using reliable and appropriate methods of contraception until at least three months after the end of study treatment (when applicable). Male patients with a partner of childbearing potential must agree to use contraception in addition to having their partner use another contraceptive method during the trial,
18. Archival tumor tissue is required for exploratory research at enrolment,
19. Ability to undergo plasma sampling during the therapy course.

7.2 EXCLUSION CRITERIA

1. Presence of CNS metastasis unless adequately treated (e.g. non irradiated CNS metastasis, seizures not controlled with standard medical therapy constitute non-eligibility criteria),
2. Active infection (ie, body temperature ≥38°C due to infection),
3. Intestinal obstruction, pulmonary fibrosis or interstitial pneumonitis, renal failure, liver failure, or cerebrovascular disorder,
4. Uncontrolled diabetes,
5. Myocardial infarction within the last 6 months, severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV,
6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or hepatitis B or C,
7. Autoimmune disorders or history of organ transplantation that require immunosuppressive therapy,
8. Other concomitant or previous malignancy, except i/ adequately treated in-situ carcinoma of the uterine cervix, ii/ basal or squamous cell carcinoma of the skin, iii/ cancer in complete remission for >5 years,
9. Major surgery or traumatic injury within the last 28 days,
10. Pregnant or breastfeeding women,
11. Patients with known allergy to any excipients to study drugs,
12. Other serious and uncontrolled chronic non-malignant disease,
13. Known dihydropyrimidine dehydrogenase deficiency,
14. Palliative radiation therapy within 4 weeks prior to registration,
15. Life expectancy less than 12 weeks in the opinion of the Investigator,
16. Treatment with any other investigational medicinal product within 28 days prior to study entry.

8. INVESTIGATIONAL PLAN

8.1 OVERALL STUDY DESIGN AND PLAN-DESCRIPTION

8.1.1 Study treatment schedule: Panitumumab plus FOLFIRI, or Panitumumab plus FOLFOX or Panitumumab plus Irinotecan monotherapy and then Panitumumab maintenance.

On day 1 of each cycle patients received panitumumab followed by 5-FU and leucovorin in combination with either irinotecan (FOLFIRI regimen) or oxaliplatin (FOLFOX regimen) or followed by irinotecan monotherapy. This treatment was repeated every 2 weeks for FOLFIRI and FOLFOX regimens and every 3 weeks for irinotecan monotherapy.

Investigational arm: Panitumumab in combination with FOLFOX or FOLFIRI or Irinotecan.

IMP: Panitumumab (Vectibix) 6 mg/Kg was adninistered IV over 1 hour on Day 1 every 2 weeks or 9 mg/Kg every 3 weeks.

1. FOLFIRI administration immediately followed the panitumumab one. The dosage and schedule are described hereafter:

- Irinotecan 180 mg/m^2 IV infusion in 500 mL N/S 0.9% over 30-90 minutes and dl leucovorin* 400 mg/m^2 IV infusion over 2 hours, at the same time, in bags using a Y-line, followed by:
- 5-FU 400 mg/m^2 IV bolus given over 2-4 minutes, followed by:
- 5-FU 2400 mg/m^2 continuous IV infusion in 1 L N/S 0.9% over 46-48hours.

2. FOLFOX administration immediately followed the panitumumab one. The dosage and schedule are described hereafter:

- Oxaliplatin 85 mg/m^2 IV infusion in 500 mL D/W 5% over 60-120 minutes and dl leucovorin* 400 mg/m^2 IV infusion over 2 hours, at the same time, in bags using a Y-line, followed by:
- 5-FU 400 mg/m^2 IV bolus given over 2-4 minutes, followed by:
- 5-FU 2400 mg/m^2 continuous IV infusion in 1 L N/S 0.9% over 46-48 hours.

- For elderly patients >70 years, FOLFOX might be administered with a 20% decrease in the dose of oxaliplatin and bolus 5-FU, at investigator`s discretion.

**400 mg/m² of leucovorin expressed in dl racemic. When the l-isomer form was used the dose should be divided by 2, i.e. 200 mg/m²*

Doses should be based upon actual body weight measured before each administration.

3. Irinotecan administration immediately followed the panitumumab one. The dosage was 250-300 mg/m² diluted in 500 mL N/S 0.9% and administered IV over 30-90 minutes.

In case BSA > 2.0 m², the actual doses of irinotecan, oxaliplatin and 5-FU should be adjusted to a maximum BSA of 2.0 m², for safety reasons.

i. Prior and Concomitant Therapy

Premedication

The prophylactic routine anti-emetic treatment was indicated according to the standards for good clinical practice at each site. It could consist of 5HT3 receptor blockers, dexamethasone, domperidone or metoclopramide for a period decided by the doctor responsible.

ii. Treatment Compliance

The investigator or a person authorized by the investigator, e.g. a pharmacist, ensured that all the products associated with the study were stored in a safe place at conditions recommended for such materials (controlled temperature 15-30ºC), and under the provisions of the normative framework currently in effect. All pharmaceutical supplies for the study were stored in a locked room and had restricted access. These pharmaceutical supplies were not used outside the framework of this protocol. At no event the investigator or any other member of the study personnel had the right to supply study medications to other investigators, patients or clinics, or the right to allow usage of these supplies for any other purpose but those mentioned in this protocol.

The investigator had the responsibility of keeping an appropriate documentation archive as regards the supply, usage, loss or any other event relevant to the investigational product. The dosage to be administered to each patient were recorded in the patient's medical file.

Assessment	**Baseline**	**Every cycle**	**End of Study** (30 days after last panitumumab treatment)	**Post treatment follow-up**
Informed Consent Form	×			
Inclusion/Exclusion Criteria	×			
Medical History	×			
Height, weight, BSA	×	×	×	
Physical examination/Vital Signs	×	×	×	
Blood tests & serum biochemistry	×	×		
Pregnancy test	×			
Assessment of signs and symptoms	×	×	×	
ECG (Echocardiogram)	×			
Concomitant medications	×	×	×	
Adverse Events Assessment		×	×	×
Panitumumab/chemotherapy administration		×		
Imaging (CT/MRI)	× (whithin 4 weeks from treatment start)	Every 8 +/- 2 weeks		×

Assessment	**Baseline**	**Every cycle**	**End of Study** (30 days after last panitumumab treatment)	**Post treatment follow-up**
Tissue sample for translational research	×			
Blood sample for translational research	×	X At cycles 3-4	X At Progressive Disease	

Table 2: Summary of the trial's procedures and observations

8.1.2 PRIMARY ENDPOINT: OVERALL RESPONSE RATE (ORR)

Overall Response Rate (ORR): is defined as the proportion of patients with confirmed Complete Response (CR) or confirmed Partial Response (PR) as best overall response to treatment, based on Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 guidelines [(relative to the total number of patients in the considered analysis population (ITT or evaluable for response)]. Tumor assessments will be performed up to progression or initiation of another anti-tumor therapy.

Tumor response will be evaluated at baseline and every 8 +/- 2 weeks with the use of consistent imaging techniques [computed tomography (CT) and magnetic resonance imaging (MRI)]. Same imaging must be used throughout the study for all tumor assessments. Each of these scans must be documented and recorded in the source documents and in the CRF.

The overall response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.

8.1.3 SECONDARY EFFICACY ENDPOINTS

All secondary endpoints will be analyzed at the end of the study as described.

- **ORR by RAS status**

ORR will be calculated separately for RAS mutant and wild type patients. ORR is defined as the proportion of patients with confirmed CR or PR as best overall response to treatment, based on Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 guidelines [(relative to the total number of patients in the considered analysis population (ITT or evaluable for response)]. Tumor assessments will be performed up to progression or initiation of another anti-tumor therapy.

- **Progression Free Survival (PFS)**

PFS is defined as the time interval from registration to the first date of documented tumor progression or death from any cause. Patients alive that have not progressed or patients lost to follow up or patients who received other anti tumor therapy before tumor progression

will be censored at the date of their last tumor assessment. Deaths occurring after initiation of subsequent anticancer therapy will be considered PFS events.

- **Overall Survival (OS)**

OS is defined as the time interval from registration to the date of death due to any cause. Patients who have not died or who are lost to follow-up will be censored on the last date on which they were known to be alive. Patients alive at the end of the study will be censored at this timepoint.

- **Safety**

Adverse event data, clinical examination, vital signs (blood pressure, pulse and respiratory rate), body weight, ECOG PS and laboratory data (complete blood count, biochemistry profile, urinalysis and other tests as clinically indicated) will be recorded in the source documents and in the subject's CRF. Laboratory safety will be carried out by local laboratory according to standard operating procedures. Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of permanent discontinuation of Investigational Product for the concerned patient.

8.1.4 EXPLORATORY ENDPOINTS

Formalin-fixed paraffin-embedded (FFPE) tumor blocks and baseline peripheral blood samples stored in -20^{o}C refrigeration in EDTA tubes and plasma samples/platelet aliquots stored in -80^{o} C refrigeration have been collected from patients enrolled in the study. Mutational status of KRAS and NRAS genes have been performed. Biomarkers with prognostic and predictive significance will be investigated in cell-free plasma DNA, platelet-resorbed tumour RNA and formalin-fixed paraffin-embedded tissue.

Next generation sequencing will be performed on plasma cell-free DNA (Ion-Torrent NGS, LiquidBiopsy workflow). NGS panel will contain primer pairs to analyze mutations in the following genes: ALK, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, MET, KRAS, PIK3CA, BRAF, AKT1, PTEN, NRAS, CTNNB1, SMAD4 and TP53. Codons 12 and 61

KRAS and NRAS mutations, exon 15 BRAF mutations, exon 20 PIK3CA mutations will be analyzed on platelet-resorbed tumour RNA (RTPCR). The translational research program will be dynamic and enriched constantly and biomarkers examined for prognostic and predictive utility, as well as toxicity predictive profile.

9. DATA QUALITY ASSURANCE

The Sponsor, HeCOG (Hellenic Cooperative Oncology Group) took all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs.

This clinical trial was conducted in accordance with the clinical trial protocol, HeCOG SOPs, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and all applicable laws and regulations.

The qualified personnel from the principal investigator's team recorded the data required by the Protocol in an electronic case report form (e-CRF). The principal investigator was responsible for ensuring complete, accurate and timely recording of data in the e-CRF. Compliance with the drug reconciliation form was guaranteed by the investigator.

The investigator maintained a file in the clinic for each patient in the study, which included notes about the event and visits (records of hospital medical records or clinical follow-up) containing demographic data and medical information, laboratory data, electrocardiograms and the results of any examinations or other assessments. All information relating to drug administration can be identified within the patient's file. The investigator also kept the original consent form signed by the patient (a signed copy was given to the patient). The retention of trial records was in the study center in accordance with the Legislation.

The investigator ensured the anonymity of the patients. Patients were not identified by their name in the e-CRFs and in documents submitted for publication. The signed informed consent forms and patient's file remained strictly confidential, but it was possible to recognize the patient at the study center.

The completed original CRFs were available to HeCOG, to the Study Monitors, to the National Organization for Medicines (EOF) or other Regulatory Authorities (eg. FDA, EMA) and the National Ethics Committee (NEC) for any inspection.

10. TRANSLATIONAL RESEARCH

Formalin-fixed paraffin-embedded (FFPE) tumor blocks and baseline peripheral blood samples stored in -20^{o} C refrigeration in EDTA tubes and plasma samples stored in -80^{o} C refrigeration will be collected from patients enrolled in the study. Tissue mutational status of KRAS and NRAS econ 2,3,4 genes will be performed. Biomarkers with prognostic and predictive significance will be investigated in cell-free plasma DNA, platelet-resorbed tumour RNA and formalin-fixed paraffin-embedded tissue.

Next generation sequencing will be performed on plasma cell-free DNA (Ion-Torrent NGS, LiquidBiopsy workflow). NGS panel will contain primer pairs to analyze mutations in 60 hotspot regions of the following 22 genes: ALK, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, MET, DDR2, KRAS, PIK3CA, BRAF, AKT1, PTEN, NRAS, MAP2K1,STK11, NOTCH1, CTNNB1, SMAD4, FBXW7 and TP53. Codons 12 and 61 KRAS and NRAS mutations, exon 15 BRAF mutations, exon 20 PIK3CA mutations will be analyzed on platelet-resorbed tumour RNA (RTPCR). The translational research program will be dynamic and enriched constantly and biomarkers examined for prognostic and predictive utility, as well as toxicity predictive profile. Plasma/peripheral blood sampling will be performed at the following time periods: baseline, cycles 3-4, progressive disease.

11. RESULTS

11.1 DISPOSITION OF PATIENTS

Between 26 Mar 2019 and 25 Feb 2021 twenty-three (23) patients were enrolled at 6 Departments of Medical Oncology in Greece and in Cyprus affiliated to HeCOG. More details about the disposition of the patients, can be found in Table 3 “Patients per center”.

Table 3: Patients per center

Institution	**No of Patients**
Dept of Medical Oncology, Ioannina University Hospital, Ioannina	6
3rd Dept of Medical Oncology, Agii Anargiri Cancer Hospital, Athens	8
2nd Dept of Medical Oncology, "Metropolitan" Hospital, Athens	2
Division of Oncology, Dept of Internal Medicine, University Hospital of Patras, Patras	1
2nd Dept of Medical Oncology, Euromedica General Clinic, Thessaloniki	2
Department of Medical Oncology, Bank of Cyprus Oncology Centre	4

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The median age at study entry of the 23 patients included in the study was 66 years (range 50-81). Eighteen were men (78.3%) and 5 (21.7%) were women and they were generally in good condition based on performance status when they started treatment. The most frequent locations of the primary tumor were the sigmoid colon (12 patients, 52.2%) and the rectum (6 patients, 26.1%). The most common sites of metastasis were he liver (18 patients, 78.3%) followed by the lung (10 patients, 43.5%). Patients' characteristics are presented in Table 4 below.

Table 4: Patients' characteristics

Variable	Total (N=23)
Age at study entry	65.8 (50.2,81.1)
Gender	
. Men	18 (78.3)
. Women	5 (21.7)
PS	
. 0	17 (73.9)
. 1	6 (26.1)
Number of metastatic sites at study entry	
. 1	12 (52.2)
. 2	6 (26.1)
. 3	3 (13.0)
. 4	2 (8.7)
Sites of metastatic target lesions at study entry	
Lung	10 (43.5)
Lymph nodes	5 (21.7)
Liver	18 (78.3)
Adrenal glands	2 (8.7)
Soft tissue mass	2 (8.7)
Kidney	1 (4.3)
Large bowel	3 (13.0)
Sites of metastatic non-target lesions at study entry	
Lung	6 (26.1)
Lymph nodes	3 (13.0)
Liver	7 (30.4)
Bones	3 (13.0)
Pleural effusion	1 (4.3)
Grade*	
. 1	1 (5.0)
. 2	14 (70.0)

Variable	Total (N=23)
. 3	5 (25.0)
Laterality*	
. Left	17 (94.4)
. Right	1 (5.6)
Primary site of cancer at study entry	
Cecum	1 (4.3)
Hepatic flexure	1 (4.3)
Transverse colon	2 (8.7)
Descending colon	3 (13.0)
Sigmoid colon*	12 (52.2)
Rectum	6 (26.1)
Rectosigmoid	1 (4.3)
Time elapsed from previous anti-EGFR treatment (months)	12.2 (3.3, 33.1)
Time elapsed from previous first line therapy (months)	11.7 (3.3-33.1)
Time elapsed from previous second line therapy (months)	1.1 (0.5-12.3)
Number of patients who had cetuximab at first line	13 (56.5)
Number of patients who had panitumumab at first line	10 (43.5)

*Data not available for all subjects. Missing values: Histology Grade = 3, Laterality = 5, Primary Site of cancer at study entry: Sigmoid = 1.
Values presented as Median (min, max) or N (column %).

11.3 TREATMENT CHARACTERISTICS

Sixteen (61%) of the 23 patients in the study received Panitumumab in combination with FOLFIRI while 8 (35%) received Panitumumab – FOLFOX and only 1 patient (4%) Panitumumab- Irinotecan. The mean number of treatment cycles patients received was 6.5 (range 1 to 32).

At the study entry timepoint, the median number of months elapsed since the administration of previous anti-EGFR treatment and first-line treatment for patients was

12.2 months (3.3-33.1) and 11.7 months (3.3-33.1) respectively. The median number of months elapsed since second line therapy was 1.1 months (0.5-12.3). Thirteen patients (56.52%) had received cetuximab at first line and 10 patients (43.48%) had received panitumumab.

11.4 PROTOCOL DEVIATIONS

Minor Deviations:

- INR at baseline was not performed in 4 cases
- ECG at baseline was not performed in 5 cases
- ECG was performed after cycle 1 instead of baseline in 1 case
- Cl was not performed throughout study in 2 cases
- Not all Biochemistry tests were done throughout study at all cycles for 5 cases
- For 1 case at cycle 1 drugs from the clinic and not from study were used

Major Deviations:

- HE6B16-4-0008: CT chest at baseline was not performed according to timelines (≤14 days prior to 1st cycle)
- HE6B16-3-0006: According to protocol patient should have taken same treatment at 1st & 3rd line. In 1 case FOLFOX was administered at 1st line and in 3rd line the PI decided to administer FOLFIRI

11.5 EFFICACY EVALUATION

Three patients (13.0%) exhibited partial response (PR) as best overall response during the study. The primary endpoint is summarized in table 5 below.

Table 5: Best overall response recorded during the study

Best response	**N (%)**
PR	3 (13.0)
SD/PD/Toxic death/Treatment discontinuation prior to evaluation	20 (87.0)

Median overall survival (Figure 1) in the entire cohort was 8.7 months (95% C.I: 5.7-16.4).

Median progression free survival (Figure 2) was 2.8 months (95% C.I.: 2.3-5.7).

Figure 1: OS in the entire cohort

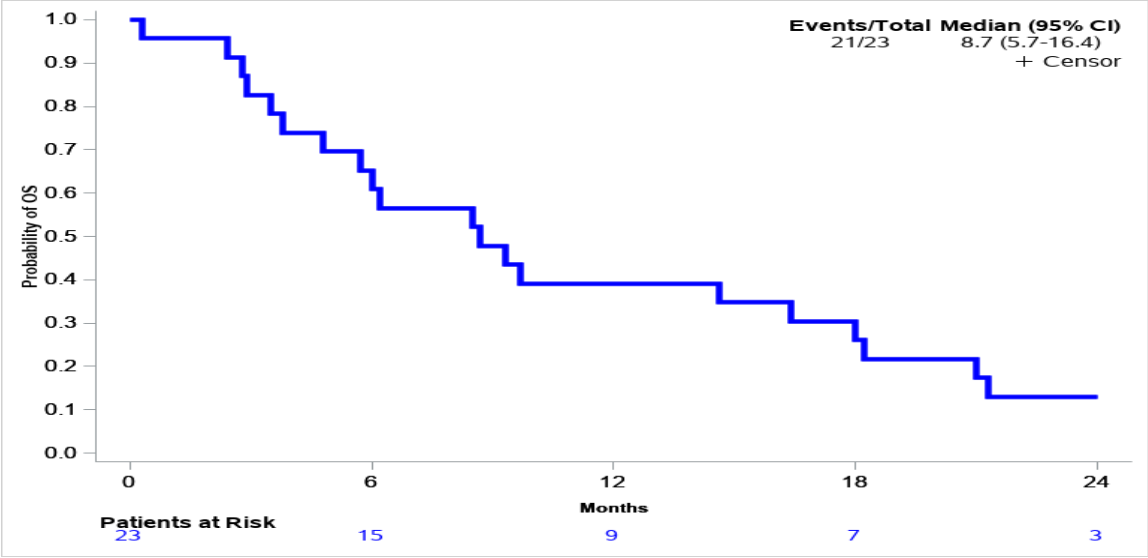
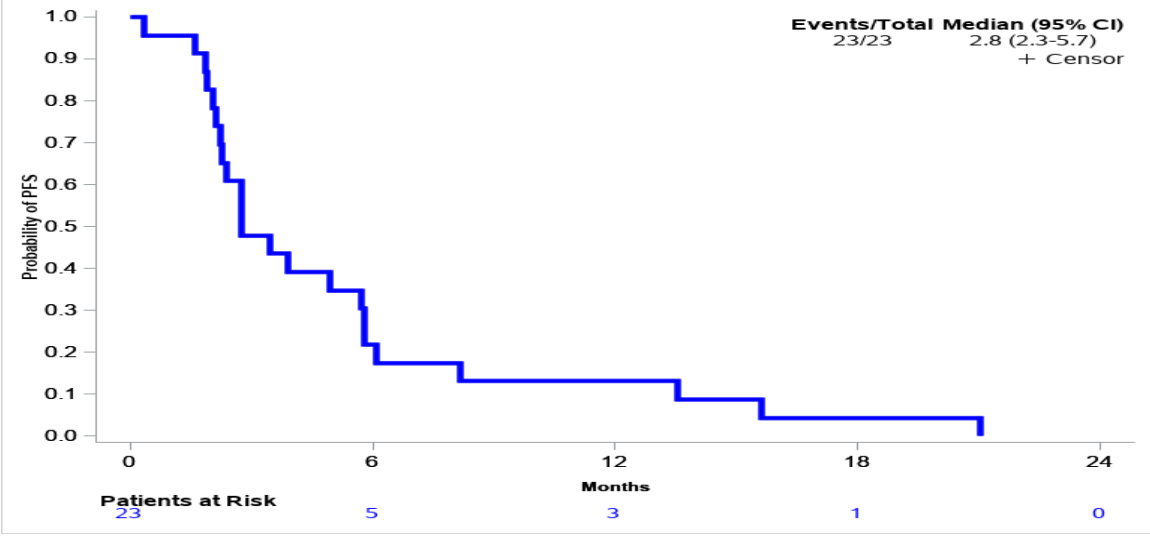


Figure 2: PFS in the entire cohort



Translational analysis

Results from the main endpoints were calculated in patient subgroups based on the presence or absence of microsatellite instability and specific mutations in the liquid biopsies.

Figure 3: PFS by MSI presence

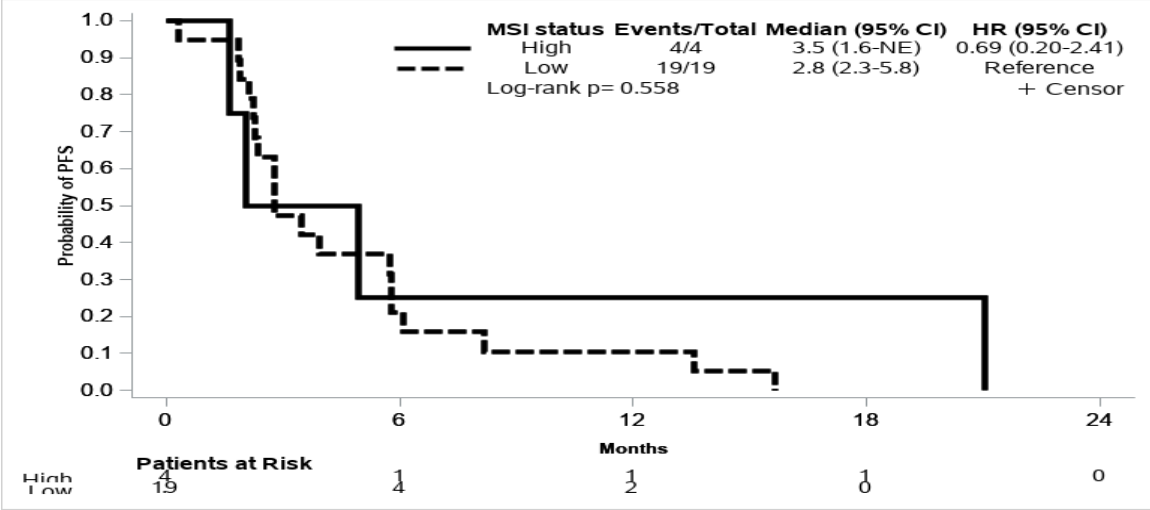


Table 6: Best response rate by MSI presence

	Frequency	Best response rate (N, %)
MSI high	4	0 (0)
MSI low	19	3 (15.6)

Figure 4: PFS by anti-EGFR mutation group

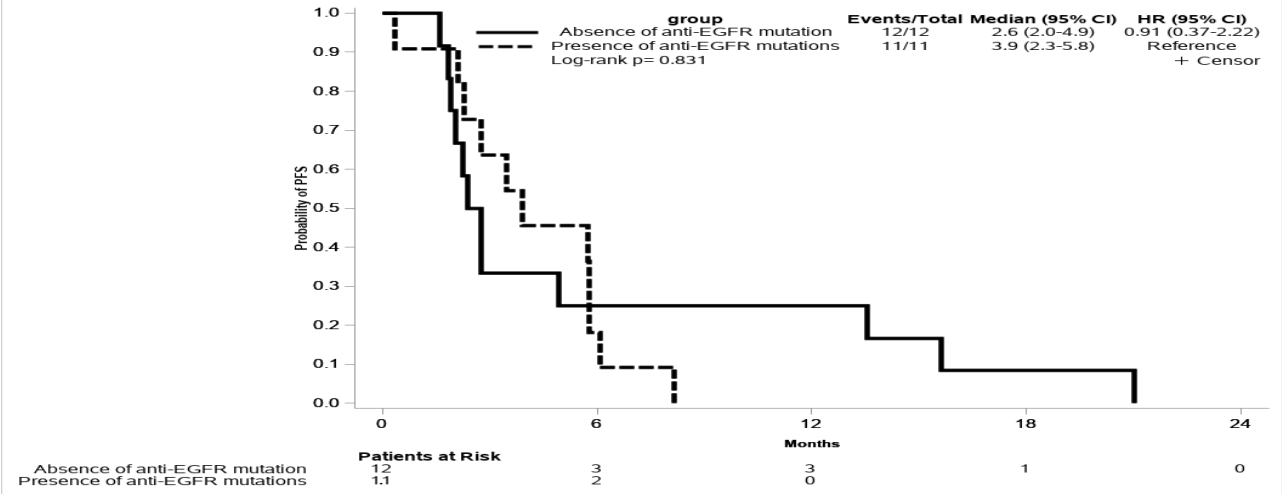


Table 7: Best response rate by mutation presence

Anti-EGFR mutation presence	PR	SD/PD/Early toxic death/Treatment discontinuation prior evaluation
No (12)	1 (8.3%)	11 (91.7%)
Yes (11)	2 (18.2 %)	9 (81.8%)

In the anti-EGFR mutations group, PR was observed in two patients (25%) and stable disease in 5 (41.6%). Median PFS was 3.9 (0.3-8.2) months.

Table 8: Outcomes of patients with mutation presence in one of KRAS, NRAS, BRAF or HER2 genes

PNUMBER	**PFS**	**Best Response**
55446	2.27	PD
56192	8.16	PR
56251	2.76	SD
56280	3.45	SD
56654	6.09	PR
57230	3.91	SD

57613	2.11	PD
57620	5.79	SD
57683	0.33	Early toxic death
58945	5.72	SD
58956	5.79	Treatment discontinuation prior evaluation

Blood and tumor samples were collected at baseline for the purposes of genetic analysis. Figures 5 and 6 depict the different types of mutations observed in both types of samples.

Figure 5: Mutations' map in blood samples

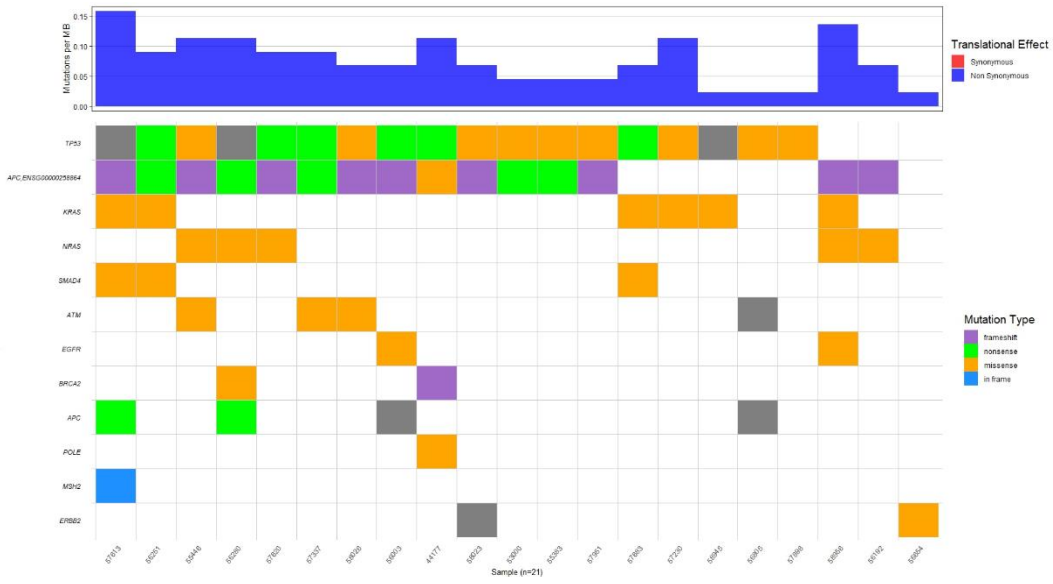
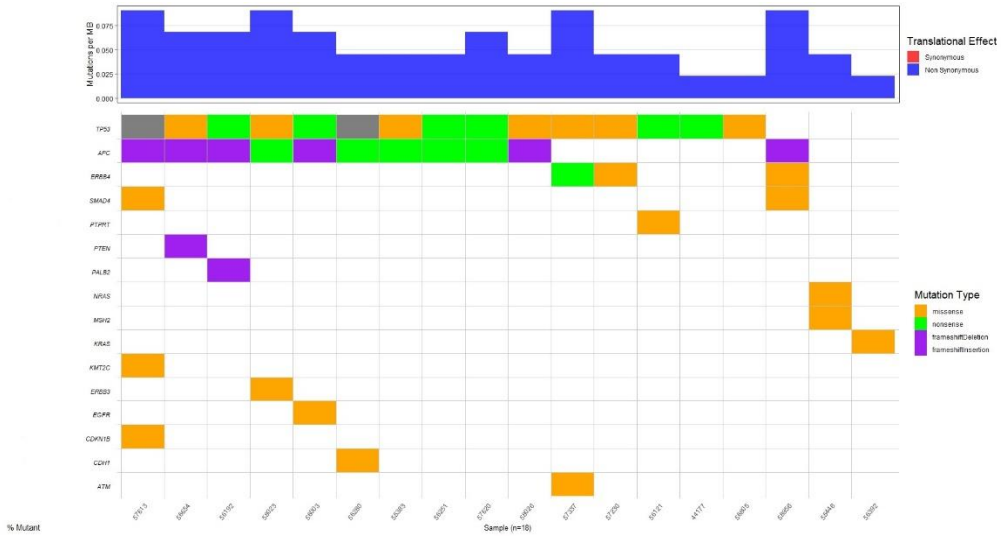


Figure 6: Mutations' map in tumor samples



12. SAFETY EVALUATION

12.1EXTENT OF EXPOSURE

First subject was enrolled on 26 Mar 2018 and the Study covered a 4-year period (EOF approval occurred on 19-05-2017). The cumulative exposure is estimated using the enrolment.

Table 9: Maximum cycles per patient per group

Cycles	1	2	3	4	5	6	8	10	14	28	32
Patients Group A	0	1	2	2	0	1	0	2	0	0	0
Patients Group B	1	1	1	4	0	1	2	1	1	1	1
Patients Group C	0	0	0	0	1	0	0	0	0	0	0

12.2DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.2.1 Serious Adverse Events

List of reported Serious Adverse Events are presented in

Table 12 and Aggregate Summary tabulation of Serious Adverse Events in Table 11.

12.2.2 Narrative of Serious Adverse Events and Certain Other Significant Adverse Events

Patient number: HE6B16-4-0002

Palmar-plantar erythrodysaesthesia syndrome grade 3

Oral mucositis grade 3

Initial information in this case was received on 09 May 2018. The case concerned a 62 - year-old male patient with a history of Rectal carcinoma since 16 Sep 2013, Lung metastases since 30 Jun 2016, Anterior resection on 24 Mar 2014, Closure of loop ileostomy on 30 Jul 2014, Anaemia since 25 Apr 2018, Rectourethral fistula since 27 Aug 2014, Radiotherapy to rectum from 23 Jan 2014 to 07 Mar 2014, 1st line therapy for metastatic colorectal cancer with panitumumab/ folfiri from 18 Aug 2016 to 20 Apr 2017, 2nd line therapy for metastatic colorectal cancer with Bevacizumab/ folfox from 05 May 2017 to 11 Apr 2018 and Adjuvant chemotherapy (MD for dates) who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of advanced colorectal cancer.

The patient had developed Palmar-plantar erythrodysaesthesia syndrome and oral mucositis during first line therapy for metastatic colorectal cancer with the combination of panitumumab and Folfiri.

The patient received Vectibix (panitumumab) 355 mg, Irinotecan 300 mg, Leucovorin 650 mg and Fluorouracil 4550 mg all every two weeks intravenous on 25 Apr 2018.

The patient proceeded to the study site on 09 May 2018 for a scheduled visit in order to receive cycle 2. The patient was in good condition (PS=1) however the patient had developed oral mucositis grade 3 from 29 Apr 2018 and palmar-plantar erythrodysaesthesia syndrome grade 3 from 29 Apr 2018 still not recovered on 09 May 2018. The patient had lost 3 Kg due to reduced food intake. The investigators decided to delay therapy for one week because the patient also had neutropenia grade 2.

Concomitant medications at the time of the Event(s) included Minocin (minocycline) 100 mg everyday oral from 25 Apr 2018 to 08 May 2018 onoing for the prvention of rash, Dexamethasone rosemnt oral sol. (dexamethasone) 4 mg and Ondansentron Generics (ondansentron) 8 mg both every 12 hours oral from 26 Apr 2018 to 27 Apr 2018 for vomiting prophylaxis.

The investigator believed that the oral mucositis was caused by the drugs irinotecan and fluorouracil and palmar-plantar erythrodysaesthesia syndrome was caused by the drug fluorouracil. The case is considered as Serious (Important medical event).

Outcome: Not Recovered

Follow-up # 1

Follow-up information received on 23 May 2018

The events had improved one week later on 17 May 2018: mucositis rade 1, palmar-plantar erythrodysaesthesia syndrome grade 1 and the event of neutropenia had resolved completely (grade 0). The patient was in good condition (ps=1) and received the second cycle of therapy with panitumumab/folfiri with the appropriate dose reductions of the drugs irinotecan and fluorouracil (because of the adverse events). The doses of the medications panitumumab and leucovorin also recalculated according to the new BSA, as the patient had lost 3 Kg from the initiation of the treatment:

Panitumumab 336 mg, irinotecan 232 mg, leucovorin 644 mg all three intravenous on 17 May 2018 and fluorouracil 3605 intravenous from 17 May 2018 to 19 May 2018.

Minocin 100 mg from 25 Apr 2018 to 17 May 2018.

Outcome: Recovering

Follow-up # *2*

Follow-up information received on 27 Jun 2018

On 01 Jun 2018 the event of mucositis had recovered completely and the Palmar-plantar erythrodysaesthesia syndrome was grade 1 as it was at the last scheduled visit on 11 Jun 2018.

Dexamethasone rosemnt oral sol. 4 mg and Ondansentron Generics 8 mg both every 12 hours oral from 18 May 2018 to 19 May 2018 for vomiting prophylaxis.

Outcome: Palmar-plantar erythrodysaesthesia syndrome – Recovering, Oral mucositis - Recovered

Follow-up # *3*

Follow-up information received on 19 Jul 2018

On 05 Jul 2018 the event Palmar- plantar erythrodysaesthesia syndrome was still grade 1 and as the patient had progression of disease as shown on 03 Jul 2018 on the recent Computer Tomography (CT) assessment performed, the physician decided patient's discontinuation from the study treatment with panitumumab/FOLFIRI. On 03 Jul 2018 patient was started on 4th line therapy with TAS-102.

Outcome: Palmar-plantar erythrodysaesthesia syndrome – Not recovered, Oral mucositis - Recovered

Sponsor's comment: Serious Adverse Reaction

Patient number: HE6B16-3-0003

Febrile neutropenia grade 3

Urinary tract obstruction grade 2

Initial information in this case was received on 22 Jun 2018. The case concerned a 77 - year-old female patient with a history of colorectal adenocarcinoma diagnosed after biopsy on 28 Sep 2011, left hemicolectomy on 22 Aug 2011, pelvic metastases diagnosed after CT scan on 12 Dec 2014, lung metastases and pelvic metastases diagnosed after CT scan on 02 Feb 2017, liver metastases and pelvic metastases and paraortic lymph node metastases after CT scan on 18 May 2018, hypertension from pre-screening and diabetes mellitus from prescreening, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of advanced colorectal cancer.

The patient received Vectibix (panitumumab) 260 mg, Irican (irinotecan) 240 mg and Leucovorin (calcium folinate) 400 mg all intravenous (day 1 every 2 weeks) on 11 Jun 2018 and Fluorouracil (5-FU) 2200+1650 mg intravenous every two weeks from 11 Jun 2018 to 13 Jun 2018.

On 21 Jun 2018 the patient was submitted in hospital due to febrile neutropenia grade 3 related with folfiri as the physician stated. The necessary lab tests were performed and the patient was being treated with the necessary medication for the event.

Lab tests on 21 Jun 2018 showed: White blood cell count (WBC) 1160x10^3/μL (Reference range: 4000-11000), Neutrophils (ANC) 780x10^3/μL (Reference range: 2000-7700), Platelets (PLT) 138000x10^3/μL (Reference range: 150000-400000).

Actions taken as a result of the Event included hospitalisation and the administration of Tazocin (piperacillin) 2.25 g three times a day intravenous from 21 Jun 2018, Targocid (teicoplanin) 400 mg every two days from 21 Jun 2018 and Zarzio (filgrastim) 48 MU once a day. The patient also, received Losec (omeprazole) 40 mg once a day from 21 Jun 2018 to 25 Jun 2018 and Lobivon (nebivolol) 2.5 mg once a day from prescreening to 25 Jun 2018.
Concomitant medications at the time of the Event included Trajenta (linagliptin) 5 mg once a day oral and Diamicron (gliclazide) 30 mg once a day oral both from prescreening for diabetes mellitus, Sevikar (amlodipine) 20+5 mg once a day oral and Lobivon (nebivolol) 2.5 mg once a day oral both from prescreening for hypertension and Losec (omeprazole) 40 mg once a day oral from prescreening to 21 Jun 2018 for gastroprophylaxis.
The investigator believe that the Febrile neutropenia was caused by FOLFIRI regimen and not Vextibix. The case is considered as Serious (Hospitalisation).

Outcome: Not Recovered

Follow-up # 1

Follow-up information received on 26 & 28 & 29 Jun 2018.

On 23 Jun 2018 Febrile neutropenia was resolved. On 25 Jun 2018 after further review of lab tests the physician reported that the patient suffers from renal failure grade 2, which is still under investigation. On 27 Jun 2018 was reported that when the patient was hospitalized the increased creatinine values were under investigation regarding the seriousness or not of the event. Study investigator reviewed the creatinine lab values since 21 Jun 2018 and decided on 25 Jun 2018 that the increased creatinine should be considered as a serious adverse event and the seriousness date is 21 Jun 2018. On 29 Jun 2018 as per study investigator stated renal failure was caused by obstruction from metastatic pelvic mass.

Lab tests on 21 Jun 2018 showed: Creatinine (CRE) 2.19 mg/dL (Reference range: 0.6-1.2).
Lab tests on 22 Jun 2018 showed: CRE 3.08 mg/dL.
Lab tests on 23 Jun 2018 showed: WBC 8980x10^3/µL, ANC 7170x10^3/µL, CRE 3.10 mg/dL.
Lab tests on 24 Jun 2018 showed: WBC 4010x10^3/µL, ANC 2960x10^3/µL, CRE 3.17 mg/dL.
Lab tests on 25 Jun 2018 showed: CRE 2.88 mg/dL.
Lab tests on 26 Jun 2018 showed: CRE 3.20 mg/dL.
Lab tests on 27 Jun 2018 showed: CRE 3.47 mg/dL.
Lab tests on 28 Jun 2018 showed: CRE 2.29 mg/dL.
Lab tests on 29 Jun 2018 showed: CRE 1.74 mg/dL.

Addition to Zarzio (filgrastim) 48 MU once a day from 21 Jun 2018 to 25 Jun 2018, Human albumine (albumine) 10 g once a day from 25 Jun 2018.

The investigator believe that renal failure was caused by obstruction due to metastatic pelvic mass and it is not related to folfiri or vectibix. The case is considered as Serious (Prolonged hospitalisation & Important medical event).

Outcome: Febrile neutropenia – recovered, Obstruction – not recovered

Follow-up # 2
Follow-up information received on 03 Jul 2018
On 22 Jun 2018 the patient had a renal urinary ultrasound that revealed the obstruction. On 27 Jun 2018 the pigtail was replaced and as a result obstruction started to recover. On 02 Jul 2018 the physician decided that patient's obstruction was recovered and that creatinine value was recovering. Patient was discharged from hospital on 02 Jul 2018 and the next scheduled visit is on 09 Jul 2018. The patient was prescribed with tavanic (levofloxacin) 500 mg once a day from 02 Jul 2018. The patient received tazocin, targocid, losec and albumin until 02 Jul 2018.

Lab tests on 30 Jun 2018 showed: CRE 1.61 mg/dL.
Lab tests on 01 Jul 2018 showed: CRE 1.68 mg/dL.

Outcome: Recovered

Sponsor's comment: Serious Adverse Reaction. Febrile neutropenia was due to FOLFIRI and obstruction is attributed to metastatic pelvic mass.

Patient number: HE6B16-3-0003

Pancytopenia grade 4
Renal failure grade 3
Hyperbilirubinaemia grade 3

Initial information in this case was received on 26 & 27 Jul 2018. The case concerned a 77 - year-old female patient with a history of colorectal adenocarcinoma diagnosed after biopsy on 28 Sep 2011, left hemicolectomy on 22 Aug 2011, pelvic metastases diagnosed after CT scan on 12 Dec 2014, lung metastases and pelvic metastases diagnosed after CT scan on 02 Feb 2017, liver metastases and pelvic metastases and paraortic lymph node metastases after CT scan on 18 May 2018, hypertension from pre-screening and diabetes mellitus from prescreening, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of advanced colorectal cancer.

The patient received Vectibix (panitumumab) 260 mg, Irinotecan 240 mg and Leucovorin 400 mg all intravenous (day 1 every 2 weeks) on 11 Jun 2018 and Fluorouracil infusion 1650 +1650 mg intravenous every two weeks from 11 Jun 2018 to 13 Jun 2018 and Fluorouracil bolus 550 mg every two weeks on 11 Jun 2018. After dose reduction the patient received Vectibix 250 mg, Irinotecan 220 mg and Leucovorin 300 mg all intravenous on 09 Jul 2018 and Fluorouracil infusion 1500 +120 mg intravenous on 10 Jul 2018 Fluorouracil bolus 300 mg on 09 Jul 2018.
A SAE form had completed previously for febrile neutropenia and urinary tract obstruction (21 Jun 2018).

On 09 Jul 2018 the patient went for the scheduled visit and there has been dose reduction 20%. On 10 Jul 2018 after Cre evaluation, it was confirmed as a serious important medical event renal failure grade 3 and decided for 5FU c.i withhold. On 10 Jul 2018 a U/S of kidney/ureter performed. Urologist evaluation is pending. On 09 Jul 2018: vectibix 250 mg administration completed, irinotecan 220 mg administration completed, leucovorin 300 mg administration completed, 5fu bolus 300 mg administration completed. On 10 Jul 2018 5FU ci administration was stopped after one-and-a-half-hour after doctor’s decision.
On 15 Jul 2018 creatinine value became grade 2 and was ongoing.
During hospitalization on 16 Jul 2018 doctor after evaluating the patient’s lab tests confirmed pancytopenia grade 4 which was related to folfiri.

On 16 Jul 2018 Cre grade 1 was still ongoing.
On 18 Jul 2018 renal failure was recovered (grade 0).

Lab tests on 09 Jul 2018 showed: CRE 5.75 mg/dL (Reference range: 0.6-1.2).
Lab tests on 11 Jul 2018 showed: CRE 4.79 mg/dL.
Lab tests on 12 Jul 2018 showed: CRE 4.30 mg/dL.
Lab tests on 13 Jul 2018 showed: CRE 3.75 mg/dL.
Lab tests on 15 Jul 2018 showed: CRE 2.38 mg/dL.
Lab tests on 16 Jul 2018 showed: CRE 1.70 mg/dL, White blood cells count (WBC) 780/µL (Reference range: 4000-11000), Neutrophils (ANC) 270/µL (Reference range: 2000-7700), Platelet count (PLT) 59000/µL (Reference range: 150000-400000), Hemoglobin (Hgb) 9.6 mg/dL (Reference range: 11.2-16).
Lab tests on 17 Jul 2018 showed: WBC 820/µL, ANC 340/µL, PLT 74000/µL, Hgb 8.6 mg/dL, CRE 1.33 mg/dL.
Lab tests on 18 Jul 2018 showed: WBC 1000/µL, ANC 400/µL, PLT 57000/µL, Hgb 8.5 mg/dL, CRE 1.19 mg/dL.

Actions taken because of the Event included the administration of Begalin (sultamicillin) 3 g x 2 from 10 Jul 2018 ongoing, Ciproxin (ciprofloxacin) 400 mg x 1 from 11 Jul 2018 ongoing, Losec (omeprazole) 40 mg x 1 from 10 Jul 2018 ongoing, Human albumin (ALBUMINE) 10 g once a day from 11 Jul 2018 ongoing, Duphalac (lactulose) 40 cc x 1 from 10 Jul 2018 ongoing, and Lasix (furosemide) from 11 Jul 2018 ongoing and Tevagrastim (filgrastim) once a day from 16 Jul 2018.

Concomitant medications at the time of the Event included Trajenta (linagliptin) 5 mg once a day oral and Diamicron (gliclazide) 30 mg once a day oral both from prescreening for diabetes mellitus, Sevikar (amlodipine) 20+5 mg once a day oral and Lobivon (nebivolol) 2.5 mg once a day oral both from prescreening for hypertension and Losec (omeprazole) 40 mg once a day oral from prescreening to 21 Jun 2018 for gastroprophylaxis.

The investigator believe that the Pancytopenia has no causal relationship with the IMP panitumumab and the most probable reason is FOLFIRI. The case is considered as Serious (prolonged hospitalisation and important medical event).
The investigator believe that the Renal failure has no causal relationship with the study regimen and the most probable reason is the study disease. The case is considered as Serious (Important medical event).

Outcome: Pancytopenia - Not Recovered, Renal failure - Recovered

Follow-up #1
Follow up information received on 20 & 24 Jul 2018.

On 20 Jul 2018 Pancytopenia turned to grade 1 and was considere recovered. Doctors reviewed lab test results and reported hyperbilirubinaemia grade 3 which cause initially was under investigation. On 21 Jul 2018 Hyperbilirubinemia was grade 1. On 24 Jul 2018 Hyperibilirubinemia was related to medication given for the other Serious Events (Renal Failure and Pancytopenia) and was recovering. Patient was withdrawn from the study because patient did not tolerate chemotherapy well and patient's clinical condition / Performance Status (PS) has been deteriorated both due to chemotherap and disease. The patient underwent acute renal failure (due to disease) and pancytopenia (due to therapy). By the time this report was sent patient's PS was 4.

Lab tests on 19 Jul 2018 showed: WBC 1280/μL, ANC 400/μL, PLT 65000/μL and Hgb 8.2 mg/dL.
Lab tests on 20 Jul 2018 showed: WBC 3250/μL, ANC 1900/μL, PLT 101000/μL, Hgb 8.4 mg/dL and Total bilirubin (Tbil) 3.9 mg/dL (Reference range: 0.1- 1).
Lab tests on 21 Jul 2018 showed: Tbil 1.2 mg/dL
Lab tests on 23 Jul 2018 showed: Tbil 1.2 mg/dL

Lab tests on 24 Jul 2018 showed: Tbil 1.1 mg/dL

Additions to the actions taken included the administration of Zyvoxid (linezolid) 600 mg twice daily from 18 Jul 2018 ongoing and Tazocin (piperacillin) 2,25 gr x 4 from 18 Jul 2018 to 24 Jul 2018. The admninistration of Begalin 3 g x2 was from 10 Jul 2018 to 18 Jul 2018 and Ciproxin (ciprofloxacin) 400 mg x1 was from 11 Jul 2018 to 18 Jul 2018.

The investigator believe that the Hyperbilirubinaemia was related to the treatment patient received for Renal Failure and Pancytopenia and not to study drugs. The case is considered as Serious (prolonged hospitalisation and important medical event).

Outcome: Pancytopenia - Recovered, Renal failure – Recovered, Hyperbilirubinaemia – Recovering

Follow-up #2
Follow up information received on 26 Jul 2018.
On 25 Jul 2018 Hyperbilirubinemia was recovered (grade 0).
Lab tests on 25 Jul 2018 showed: Tbil 1.0 mg/dL.
Addition information on action taken as a result of all three events included the administration of Human albumin 10gr x1 and Lasix (furosemide) once daily was from 11 Jul 2018 to 26 Jul 2018, the administration of Tevagrastim (filgrastim) once daily was from 16 Jul 2018 to 24 Jul 2018 and of Zyvoxid (linezolid) 600 mg x2 was from 18 Jul 2018 to 24 Jul 2018.
Outcome: Pancytopenia - Recovered, Renal failure – Recovered, Hyperbilirubinaemia – Recovered
Sponsor’s comment: Serious Adverse Reaction

Patient number: HE6B16-3-0003

Renal failure grade 3

Initial information in this case was received on 26 & 27 Jul 2018. The case concerned a 77 - year-old female patient with a history of colorectal adenocarcinoma diagnosed after biopsy on 28 Sep 2011, left hemicolectomy on 22 Aug 2011, pelvic metastases diagnosed after CT scan on 12 Dec 2014, lung metastases and pelvic metastases diagnosed after CT scan on 02 Feb 2017, liver metastases and pelvic metastases and paraortic lymph node metastases after CT scan on 18 May 2018, hypertension from pre-screening and diabetes mellitus from prescreening, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of advanced colorectal cancer.

The patient received Vectibix (panitumumab) 260 mg, Irinotecan 240 mg and Leucovorin 400 mg all intravenous (day 1 every 2 weeks) on 11 Jun 2018 and Fluorouracil infusion 1650 +1650 mg intravenous every two weeks from 11 Jun 2018 to 13 Jun 2018 and Fluorouracil bolus 550 mg every two weeks on 11 Jun 2018. After dose reduction the patient received Vectibix 250 mg, Irinotecan 220 mg and Leucovorin 300 mg all intravenous on 09 Jul 2018 and Fluorouracil infusion 1500 +120 mg intravenous (ci administration was stopped after one-and-a-half-hour after doctor's decision) on 10 Jul 2018 and Fluorouracil bolus 300 mg on 09 Jul 2018.
Two SAE forms had been completed previously for febrile neutropenia and urinary tract obstruction (21 Jun 2018) and for Renal failure, Pancytopenia and Hyperilirubinemia (09 Jul 2018).

On 26 Jul 2018 during patient's hospitalisation since 09 Jul 2018 for Renal failure grade 3 which was recovered on 18 Jul 2018, doctor reviewed lab tests on 25 Jul 2018 and confirmed renal failure relapse grade 3 which was related to study disease. Creatinine value on 24 Jul 2018 was grade 2 and was not considered serious. On patient's last hospitalisation from 09 Jul 2018 ongoing, patient also had Pancytopenia grade 4 and Hyperbilirubinemia grade 3 which were both recovered by 25 Jul 2018, but later that day after reviewing lab tests doctor confirmed Renal failure relapse grade 3.

Lab tests on 24 Jul 2018 showed: CRE 2.50 mg/dL (Reference range: 0.6-1.2).
Lab tests on 25 Jul 2018 showed: CRE 3.09 mg/dL.
Lab tests on 26 Jul 2018 showed: CRE 3.57 mg/dL.
Lab tests on 27 Jul 2018 showed: CRE 4.00 mg/dL.

Actions taken because of the Event included the prolonged administration of Losec (omeprazole) 40 mg x 1 from 10 Jul 2018 ongoing and Duphalac (lactulose) 40 cc x 1 from 10 Jul 2018 ongoing which were started since the first event of Renal failure on 09 Jul 2018.

Concomitant medications at the time of the Event included Trajenta (linagliptin) 5 mg once a day oral and Diamicron (gliclazide) 30 mg once a day oral both from prescreening for diabetes mellitus, Sevikar (amlodipine) 20+5 mg once a day oral and Lobivon (nebivolol) 2.5 mg once a day oral both from prescreening for hypertension, Losec (omeprazole) 40 mg once a day oral from prescreening to 21 Jun 2018 and from 10 Jul 2018 ongoing for gastroprophylaxis and Duphalac (lactulose) 40 cc x 1 from 10 Jul 2018 ongoing for constipation prophylaxis.

The investigator believe that the Renal failure has no causal relationship with the study regimen and the most probable reason is the study disease. The case is considered as Serious (Prolonged hospitalisation and Important medical event).

Outcome: Renal failure – Not Recovered

Follow-up #1
Follow-up information received on 07 Aug 2018.

On 06 Aug 2018 a Computer tomography scan was performed,the result was still pending by the time this event was sent. On 07 Aug 2018 Creatinine value was still grade 3, event considered ongoing.

More recent information on laboratory date included:
Lab tests on 29 Jul 2018 showed: CRE 3.78 mg/dL.
Lab tests on 30 Jul 2018 showed: CRE 3.50 mg/dL.
Lab tests on 31 Jul 2018 showed: CRE 3.73 mg/dL.
Lab tests on 01 Aug 2018 showed: CRE 4.07 mg/dL.
Lab tests on 02 Aug 2018 showed: CRE 4.08 mg/dL.
Lab tests on 03 Aug 2018 showed: CRE 4.29 mg/dL.
Lab tests on 05 Aug 2018 showed: CRE 4.69 mg/dL.
Lab tests on 07 Aug 2018 showed: CRE 4.48 mg/dL.

More recent information on action taken as a result of the event included the prophylactic administration on 29 Jul 2018 of Innohep (tinzaparin) 0.35 IU subcutaneously once daily for Thromboprophylaxis and on 01 Aug 2018 of Rocephin (ceftriaxone) 1 g once daily intraveously for Infection prophylaxis.

Outcome: Renal failure – Not Recovered
Follow-up #2
Follow-up information received on 10 Aug 2018.
On 09 Aug 2018 patient was discharged from the hospital with Renal failure grade 3 not recovered. Doctor confirmed Chronic Renal Failure. Patient was prescribed on Lonalgal and Nujol at home. Follow up visit is scheduled in two weeks. On 09 Aug 2018 patient completed the 30 day follow up as per protocol since the last administration of Vectibix and FOLFOX.
More recent information on action taken due to event included that the last administration of both Rocephin and Innohep was on 09 Aug 2018.

Investigator's assessment on the event has not changed.

Outcome: Not recovered

Sponsor's comment: Serious Adverse Event

Patient Number: HE6B16-3-0006

Diarrhoea grade 2

Neutropenia grade 2

Initial information in this case was received on 04 Mar 2019. The case concerned a 79 - year-old male patient with a history of Colorectal adenocarcinoma diagnosed after Biopsy on 23 May 2017, Liver metastases and Lung metastases diagnosed after CT scan since 16 May 2017, Diabetes mellitus and Hypertension both from pre-screening, Hyperglycaemia and Bilirubin increased both from 08 Feb 2019 ongoing, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of Metastatic colorectal cancer.

The patient received Vectibix (panitumumab) 450 mg (6 mg/kg), Irinotecan 300 mg (180 mg/m^2) and Leucovorin 600 mg (400 mg/m^2) all intravenous (day 1 every 2 weeks) from 11 Feb 2019 to 25 Feb 2019 and Fluorouracil 5100 mg (400 mg/m^2 & 2400 mg/m^2) intravenous (day 1 to day 3 every 2 weeks) from 11 Feb 2019 to 13 Feb 2019.

On 03 Mar 2019 patient was admitted to hospital due to Neutropenic colitis grade 2, patient was treated with necessary medication for the event.

Lab tests on 03 Mar 2019 showed:

White blood cells count (WBC): 2800/μL (Reference range: 4000-11000).

Neutrophils: 1060/μL (Reference range: 2000-7700)

C-reacting protein: 13 mg/L (Reference range: <6)

Actions taken as a result of the Event included, the patient's hospitalisation and the administration of Tazocin (piperacillin + tazobactam) 4,5 g x4 and Flagyl (metronidazole) 500 mg x1 both from 03 Mar 2019 ongoing, Innohep (tinzaparin) 0.35 IU x1 from 04 Mar 2019, Zarzio (filgrastim) 48 MU and Losec (omeprazole) 40 mg both once a day.

Concomitant medications at the time of the Event included Gliclazid/Diamicron (gliclazide) and Pioglitazone/Actos (pioglitazone) both oral from pre- screening for Diabetes mellitus, Amlodipine/Orizal (Olmesartan + amlodipine) oral from pre- screening for Hypertension, ondasetron, dexamethasone, dimetindene and ranitidine all four intravenous from 11 Feb 2019 to 25 Feb 2019 as Premedication [MedDRA LLT code: 10036500].

The investigator's comment on causality is that on 03 Mar 2019 the Neutropenic colitis was due to FOLFIRI scheme. The case is considered as Serious (Hospitalisation).

Outcome: Not Recovered

Follow-up #1
Follow-up information received on 08 Mar 2019.

On 03 Mar 2019 the patient went to hospital with diarrhea, lab tests were performed and there was no sign of infection. Patient did not have abdominal pain and went to hospital with almost three diarrheas and did not have fever. On 05 Mar 2019 Neutropenia was recovered (Grade 0) but the patient still had diarrhea grade 2. On 06 Mar 2019 Diarrhea was grade 1. On 07 Mar 2019 Diarrhea was grade 0, patient was completely recovered. On 08 Mar 2019 patient would be discharged from hospital.

Lab tests on 05 Mar 2019 showed:
White blood cells count (WBC): 5660/μL.

Neutrophils: 4230/μL

C-reacting protein: 16 mg/L (Reference range: <6)

Lab tests on 07 Mar 2019 showed:

White blood cells count (WBC): 6520/μL.

Neutrophils: 3630/μL

C-reacting protein: 12 mg/L (Reference range: <6)

Additions on action taken for the event included that Zarzio and Losec were started on 04 Mar 2019, Ciproxin (ciprofloxacin) 400 mg 1x2 started on 04 Mar 2019 and Rifacol (rifaximin) 200 mg 1x3 started on 07 Mar 2019. Tazocin was stopped on 04 Mar 2019.

Additional information on concomitant medication included that the dose of Gliclazide was 60 mg 1x1, Pioglitazone 30 mg 1x1, Amlodipine 40 +10 mg 1x1, Ondasetron and Dexamethasone 8 mg 1x1, Dimetindene 4 mg 1x1 and Ranitidine 50 mg 1x1.

Outcome: Recovered

Investigator's assessment has not changed.

Follow-up # 2

Follow-up information received on 29 Mar 2019 and on 02 Apr 2019.

On 29 Mar 2019 after reassessment of the event the Prinicipal investigator informed thath the event was better described as Diarrhea grade 2 and Neutropenia grade 2. On 02 Apr 2019 the new information added was that the patient was prescribed Ciproxin and Flagyl to be treated at home started from 08 Mar 2019 to 15 Mar 2019.

Additional information on treatment given for the event included the administration of Tazocin from 03 Mar 2019 to 04 Mar 2019, Flagyl , Zarzio and Losec from 03 Mar 2019 to 08 Mar 2019, Innohep and Ciproxin from 04 Mar 2019 to 08 Mar 2019, Rifacol from 07

Mar 2019 to 08 Mar 2019. Ciproxin 500 mg 1x2 and Flafyl 500 mg 1x3 were precribed to be administered at home oral for seven days from 08 Mar 2019 to 15 Mar 2019.

Investigator's assessment on the events Diarrhea and Neutropenia was that both events were due to FOLFIRI .

Outcome of the event Diarrhea: Recovered on 07 Mar 2019.
Outcome of the event Neutropenia: Recovered on 05 Mar 2019.

Sponsor's comment: Serious Adverse Reaction

Patient Number: HE6B16-3-0006

Renal failure grade 3

Initial information in this case was received on 26 & 27 Jul 2018. The case concerned a 77 - year-old female patient with a history of colorectal adenocarcinoma diagnosed after biopsy on 28 Sep 2011, left hemicolectomy on 22 Aug 2011, pelvic metastases diagnosed after CT scan on 12 Dec 2014, lung metastases and pelvic metastases diagnosed after CT scan on 02 Feb 2017, liver metastases and pelvic metastases and paraortic lymph node metastases after CT scan on 18 May 2018, hypertension from pre-screening and diabetes mellitus from pre-screening, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of advanced colorectal cancer.

The patient received Vectibix (panitumumab) 260 mg, Irinotecan 240 mg and Leucovorin 400 mg all intravenous (day 1 every 2 weeks) on 11 Jun 2018 and Fluorouracil infusion 1650 +1650 mg intravenous every two weeks from 11 Jun 2018 to 13 Jun 2018 and Fluorouracil bolus 550 mg every two weeks on 11 Jun 2018. After dose reduction the patient received Vectibix 250 mg, Irinotecan 220 mg and Leucovorin 300 mg all intravenous on 09 Jul 2018 and Fluorouracil infusion 1500 +120 mg intravenous (ci

administration was stopped after one-and-a-half-hour after doctor's decision) on 10 Jul 2018 and Fluorouracil bolus 300 mg on 09 Jul 2018.
Two SAE forms had been completed previously for febrile neutropenia and urinary tract obstruction (21 Jun 2018) and for Renal failure, Pancytopenia and Hyperilirubinemia (09 Jul 2018).

On 26 Jul 2018 during patient's hospitalisation since 09 Jul 2018 for Renal failure grade 3 which was recovered on 18 Jul 2018, doctor reviewed lab tests on 25 Jul 2018 and confirmed renal failure relapse grade 3 which was related to study disease. Creatinine value on 24 Jul 2018 was grade 2 and was not considered serious. On patient's last hospitalisation from 09 Jul 2018 ongoing, patient also had Pancytopenia grade 4 and Hyperbilirubinemia grade 3 which were both recovered by 25 Jul 2018, but later that day after reviewing lab tests doctor confirmed Renal failure relapse grade 3.

Lab tests on 24 Jul 2018 showed: CRE 2.50 mg/dL (Reference range: 0.6-1.2).
Lab tests on 25 Jul 2018 showed: CRE 3.09 mg/dL.
Lab tests on 26 Jul 2018 showed: CRE 3.57 mg/dL.
Lab tests on 27 Jul 2018 showed: CRE 4.00 mg/dL.

Actions taken because of the Event included the prolonged administration of Losec (omeprazole) 40 mg x 1 from 10 Jul 2018 ongoing and Duphalac (lactulose) 40 cc x 1 from 10 Jul 2018 ongoing which were started since the first event of Renal failure on 09 Jul 2018.

Concomitant medications at the time of the Event included Trajenta (linagliptin) 5 mg once a day oral and Diamicron (gliclazide) 30 mg once a day oral both from prescreening for diabetes mellitus, Sevikar (amlodipine) 20+5 mg once a day oral and Lobivon (nebivolol) 2.5 mg once a day oral both from prescreening for hypertension, Losec (omeprazole) 40 mg once a day oral from prescreening to 21 Jun 2018 and from 10 Jul 2018 ongoing for

gastroprophylaxis and Duphalac (lactulose) 40 cc x 1 from 10 Jul 2018 ongoing for constipation prophylaxis.

The investigator believe that the Renal failure has no causal relationship with the study regimen and the most probable reason is the study disease. The case is considered as Serious (Prolonged hospitalisation and Important medical event).
Outcome: Renal failure – Not Recovered
Sponsor's comment: Serious Adverse Event

Patient Number: HE6B16-4-0007

Ileus grade 2
Initial information in this case was received on 22 & 30 Apr 2019. The case concerned a 68 - year-old male patient with a history of Colorectal cancer diagnosed since 26 Mar 2014 with Liver metastases since 23 Nov 2015 and Lung metastases since 18 May 2017, Surgery due to Laryngeal leukoplakia in vocal cords and Radiotherapy in vocal cords due to Leukoplakia both in 2009, Non-small cell lung cancer since 20 Dec 2013 which is under Follow up and Anaemia grade 1 since 26 Feb 2019, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of Metastatic colorectal cancer.

The patient received Vectibix (panitumumab) 425 mg (6 mg/kg) from 26 Feb 2019 to 29 Mar 2019, Irinotecan 335 mg (180 mg/m^2) on 26 Feb 2019, reduced to 268 mg on 15 Mar 2019 and then reduced again to 200 mg on 29 Mar 2019, Leucovorin 745 mg (400 mg/m^2) from 26 Feb 2019 to 29 Mar 2019 all on Day 1 every 2 weeks and Fluorouracil 5230 mg (400 mg/m^2 & 2400 mg/m^2) from 26 Feb 2019 to 28 Feb 2019, reduced to 4175 mg from 15 Mar 2019 to 17 Mar 2019 and then reduced to 3140 mg since 29 Mar 2019 intravenous (day 1 to day 3 every 2 weeks).

On 21 Apr 2019 the patient was admitted to Agii Anargiri Hospital due to mild abdominal pain and absence of bowel movements. On the same day (21 Apr 2019) the patient

performed an abdominal CT scan which revealed Ileus. The patient was hospitalized for further treatment. On 25 Apr 2019, the patient had had a laparotomy for the Ileus. During the operation it was found that the Ileus was due to adhesions from a previous abdominal operation. The Ileus was not related to his primary disease nor to the study treatment. The patient was still hospitalized and recovering from the operation, however his condition was improving by the time this report was sent.

Relevant tests and laboratory data were not available by the time this report was sent.

Actions taken as a result of the Event included the patient's hospitalisation and the administration of intravenous fluids, omeprazole 40 mg 1x2, paracetamol amp 1gr 1x3 and metoclopramide 10 mg 1x3 all intravenous since 21 Apr 2019, metronidazole 500 mg 1x3 and cefoxitin 1,5 g 1x2 both intravenous since 22 Apr 2019.

Concomitant medications at the time of the Event included ondasetron 8 mg, dexamethasone 8 mg, Fenistil (dimetindene) 4 mg all 3 intravenous as Premedication [MedDRA LLT code: 10036500] from 26 Feb 2019 to 29 Mar 2019, Minocin (minocycline) 50 mg once daily for Prophylaxis [MedDRA LLT code: 10036898] since 26 Feb 2019 and Augmentin (amoxycillin) 625 mg once daily oral from 10 Apr 2019 to 17 Apr 2019 for Upper respiratory infection [MedDRA LLT code: 10046300].

The investigator's comment on causality is that the event was due to Adhesions. The case is considered as Serious (Hospitalisation).

Outcome: Recovering

Follow-up #1
Follow-up information received on 02 & 14 May 2019.

Additions on study drug information included that date of last dose of Fluorouracil before the event was on 31 Mar 2019. All study drugs had been stopped as the patient was sent off study protocol.

On 02 May 2019 the additional information included that the previous surgery that was responsible for the adhesions that had caused the Ileus, was an rectal anterior resection which was performed on 26 Mar 2014. On 13 May 2019 patient was discharged in a relative good clinical condition. After that Serious Adverse Event and since the maximum acceptable treatment delay, according to study protocol was two weeks the patient was withdrawn from the study on 14 May 2019.

Relevant tests and laboratory date included that the patient underwent a CT scan on 21 Apr 2019 and the result confirmed the event Ileus.

Date of last dose with the concomitant drug Monicin was on 21 Apr 2019.

Investigator's comment on causality has not changed.

Follow-up #2
Follow-up information received on 12 Jul 2019.

Corrected information on patient's study drug concerened the administration of Panitumumab from 26 Feb 2019 to 19 Apr 2019, the administration of Irican from 29 Mar 2019 to 19 Apr 2019 and of Leucovorin from 26 Feb 2019 to 19 Apr 2019.

Respectively the dates of administration of relevant concomitant drugs used as Premedication, Ondaseron, Dexamethasone and Fenistil from 26 Feb 2019 to 19 Apr 2019.

On 12 Jul 2019, the corrections in Study Drug Information and In Relevant concomitant information concerning the date of last dose, were corrected after monitoring visit. No other new information icluded.

Investigator's assessment has not changed.
Outcome: Recovered
Sponsor's comment: Serious Adverse Event

Patient Number: HE6B16-3-0014

Rash grade 3
Initial information in this case was received on 07 & 15 Jan 2020. The case concerned a 64 - year-old male patient with a history of Colorectal diagnosed after a Biopsy since 06 Jul 2018, Liver metastases, epigastric Metastases to lymph nodes and Lung metastases since 18 Jun 2018, Parkinson's disease, Hyperglycaemia and Urinary incosistence all three from pre-screening period ongoing, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of Metastatic colorectal cancer.

The patient received Vectibix (panitumumab) 390 mg (6 mg/kg) on 17 Dec 2019, Rectoxal (oxaliplatin) 150 mg (85 mg/m^2) on 17 Dec 2019, Leucovorin 700mg (400 mg/m^2) on 17 Dec 2019 all on Day 1 every 2 weeks and Fluorouracil 4900 mg (400 mg/m^2 & 2400 mg/m^2) from 17 Dec 2019 to 19 Dec 2019(day 1 to day 3 every 2 weeks).

On 01 Jan 2020 patinet had gone to the hospital due to Rash. Doctor had examined patient and had ascertained that the event was Rash grade 3 and was due to panitumumab. Lab tests were performed without any pathological result. Patient was hospitalised for observation and was discharged from the hospital on 02 Jan 2020. On 05 Jan 2020 patient went to hospital for evaluation and doctor confirmed that the event was recovered.

Relevant tests and laboratory data performed on 01 Jan 2020 included:

WBC: 7.56 x 10 ^3/µL (Reference range: 4.0 – 11.0)

Neut: 5.22 x 10 ^3/µL (Reference range: 2.0 – 7.7)

Hb: 14.0 g/dL (Reference range: 13.8 – 18.0)

Hct: 41.4 % (Reference range: 42.0 – 55.0)

Plt: 175 x 10 ^3/µL (Reference range: 150 - 400)

CRP: 20 mg/L (Reference range: 0 – 0.5) - non-Serious

Actions taken as a result of the Event included the patient's hospitalisation and the administration of Begalin (sultamicillin) 3g and Dalacin (clindamycin) 600 mg both 1x3 intravenous from 01 Jan 2020 to 02 Jan 2020 and Fucidin (fusidic acid) 20 mg 1x2 cream from 01 Jan 2020 to 10 Jan 2020.

Concomitant medications at the time of the Event included Neurobion (vitamin B1 + pyridoxine + hydroxocobalamin) and Clonotril (clonazepam) both oral from pre-screening ongoing for Parkinson's disease, Ditropan (oxybutynin) oral from pre-screening ongoing for Urinary incontinence, dexamethasone 16 mg, ondansetron 16 mg, Fenistil (dimetindene) 4 mg and Zantac (ranitidine) 50 mg all four intravenous every two weeks from 17 Dec 2019 ongoing for Prophylaxis.

The investigator's comment on causality is that the event Rash was due to study drug Panitumumab. The case is considered as Serious (Hospitalisation).

Outcome: Recovered

Sponsor's comment: Serious Adverse drug Reaction (SAdR)

Hepatic failure grade 5

Pleural effusion grade 4

Pericardial effusion grade 4

Initial information in this case was received on 08 & 09 Jan 2020. The case concerned a 59 - year-old male patient with a history of Metastatic colorectal cancer and more specific of Colorectal adenocarcinoma from Feb 2018 to 03 Jan 2020, Hyperlipidaemia from unknown period to 03 Jan 2020, Hypertension from 2017 to 03 Jan 2019, Ex- smoker from unknown period to 1980, Appendicitis and Peritonitis and Appendectomy in 2008 and Radiotherapy from 26 Feb 2018 to 12 Apr 2018 in the rectal area, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of Metastatic colorectal cancer.

The patient received Vectibix (panitumumab) 480 mg (6 mg/kg), Irinotecan 350 mg (180 mg/m^2) and Leucovorin 780 mg (400 mg/m^2) on 24 Dec 2019all on Day 1 every 2 weeks and Fluorouracil 3110 mg (400 mg/m^2 & 2400 mg/m^2) from on 24 Dec 2019to on 26 Dec 2019.

Patient had known malignant pleural effusions that had undergone successful drainage and known pericardial effusion that was substantially improved prior to patient's enrolment to the study and any study drug administration. Heart Ultrasound performed on 19 Dec 2019 had showed: left ventricular ejection fraction > 55% with mild pericardial effusion (max diameter 1.5 cm), Inferior vena cava: distended, Right ventricle: normal dimensions with good contractibility and left ventricle: normal dimensions with good contractibility and diastolic dysfunctions. On 24 Dec 2019 patient was hospitalised for the study drug administration and was discharged on 27 Dec 2019. Patient had normal vital signs throughout the hospitalisation and the chemotherapy administration was uneventful. On 30 Dec 2019, patient was presented to the ER complaining of worsening dyspnoea during the last 48h. Upon presentation, Liver function tests were impaired, Platelet count was low, Constrictive pericarditis was documented (Heart Ultrasound: on 31 Dec 2019) and bilateral malignant effusions were present and under continuous drainage via previously inserted drainage tubes (that had been discharged at home with). Cardiology consultation was called and advice was provided for medical treatment of constrictive pericarditis. Hepatologist

consultation was called and advice was provided for the impaired liver function. Despite all efforts, thrombocytopenia and liver function impairment progressed and constructive pericarditis was not improving. Thus patient was transferred to the ICU and was warranted on 02 Jan 2020. Patient had been immediately sedated, incubated and vasoconstrictive medication was initiated in no avail. On 03 Jan 2020 patient had passed away.

Relevant tests and laboratory data performed on 30 Dec 2019:
Hbg: 12 gr/dL (Normal ranges: 13.3 – 17.4)
WBC: 6000 /μL (Normal ranges: 4500 – 10500)
ANC: 5700 /μL
Platelets: 100000/μL (Normal ranges: 150000 – 450000)
AST: 722 U/L (Normal ranges: 8-42)
ALT: 1029 (Normal ranges: 8-45)
Na: 126 mmol/L (Normal ranges: 136-145)
Creatinine: 0.82 mg/dL (Normal ranges: 0.7- 1.4)
CRP: 6.24 mg/dL (Normal ranges: 0- <0.5)

Relevant tests and laboratory data performed on 31 Dec 2019:
Platelets: 65000/μL
Na: 123.9 mmol/L
K: 5.4 mmol/L (Normal ranges: 3.5-5.1)
AST: 937 U/L
ALT: 1780 U/L
ALP: 101 U/L (Normal ranges: 40- 130)
γGT: 143 U/L (Normal ranges: 8-61)
Total bilirubin: 2.6 mg/dL (Normal ranges: 0.3 -1.2)
Direct bilirubin: 1.2 mg/dL (Normal ranges: 0.1 – 0.5)
CRP: 7.23 mg/dL
INR: 1.51

HBsAg: negative

Anti- HBs: negative

Anti- HBc: negative

Hepatitis A IgG: negative

HCV: negative

HIV Ag/Ab combo: negative

CMV IgG: negative

CMV IgM: negative

HSV-1 IgG: negative

HSV-1 IgM: negative

HSV-2 IgG: negative

HSV-2 IgM: negative

EBV- IgG: negative

EBV- IgM: negative

Relevant tests and laboratory data performed on 01 Jan 2020:

Platelets: 35000/μL

Na:119 mmol/L

K: 5.3 mmol/L

AST: 714 U/L

ALT: 1781 U/L

ALP: 96 U/L

γGT: 156 U/L

Total bilirubin: 2.8 mg/dL

Direct bilirubin: 1.3 mg/dL

CRP: 5.78 mg/dL

Relevant tests and laboratory data performed on 02 Jan 2020:

Platelets: 29000/μL

Na:115.9 mmol/L

K: 5.6 mmol/L

AST: 1090 U/L

ALT: 2178 U/L

Total bilirubin: 4.1 mg/dL

Direct bilirubin: 2.0 mg/dL

CRP: 4.49 mg/dL

NH3: 81.90 μg/dL (Normal ranges: 19-60)

Fibrinogen: 1.6 gr/dL (Normal ranges: 2.0- 4.0)

INR: 1.8

Relevant tests and laboratory data performed on 03 Jan 2020:

Na:121.7 mmol/L

K: 4.5 mmol/L

AST: 7326 U/L

ALT: 1468 U/L

ALP: 107 U/L

γGT: 160 U/L

CRP: 3.44 mg/dL

Platelets: 13000/μL

NH3: 156.8 μg/dL

INR: 5.84

Actions taken as a result of the Event included the patient's hospitalisation and the administration of Lyo-Drol (methylprednisolone) 20 mg 1x1 for Pericarditis, Losec (omeprazole) 40 mg 1x1 for gastric protection due to multidrug and corticosteroid use, Human albumin (albumin) 50 ml 1x1 for Hypoalbuminaemia, Lasix (furosemide) 10 mg 1x1 for Prophylaxis after albumin administration and Apotel 2g (paracetamol) 1x1 all intravenous from 30 Dec 2019 to 21 Dec 2019, Medrol (methylprednisolone) 48 mg 1x3

oral for Pericarditis from 31 Dec 2019 to 02 Jan 2020, Losec (omeprazole) 40 mg 1x2 intravenous for gastric protection due to multidrug and corticosteroid use on 01 Jan 2020, Human albumin (albumin) 50 ml 1x2 and Lasix (furosemide) 20 mg 1x2 from 31 Dec 2019 to 02 Jan 2020, Apotel 1 g intravenous from 31 Dec 2019 to 01 Jan 2020, Colchicine 0.5 mg 1x2 oral from 01 Jan 2020 to 02 Jan 2020 for Pericarditis, Atarax (hydroxyzine) 100 mg as needed on 02 Jan 2020, Lyo – Drol 20 mg 1x1, Pantosec (pantoprazole) 40 mg 1x1 for gastric protection due to multidrug and corticosteroid use, Lopresor (metoprolol) as needed oral and Verapamil (isoptin) as needed both for Supraventricular tachycardia all intravenous on 02 Jan 2020, Lasix 20 mg as needed intravenous for decreased diuresis, Dormicum (midazolam) as needed intravenous from 02 Jan 2020 to 03 Jan 2020 for intubation, Dextrose 5% 1 lt 1x1 intravenous from 31 Dec 2019 to 02 Jan 2020, Dextrose 20% 1 lt 1x2 from 02 Jan 2020 to 03 Jan 2020 and Normal saline 0,9% 1 lt 1x1 on 02 Jan 2020 all for hemodynamic and electrolyte support.

Concomitant and Past Drug information at the time of the Event included the administration of Cozaar (losartan)100 mg 1x1 from 2017 to 03 Jan 2020 for Hypertension, Keytruda (pebrolizumab) 200 mg q21 days intravenous from 30 Sep 2019 to 02 Dec 2019, Zometa (zoledronic acid) 4 mg q6 weeks intravenous on 21 Oct 2019, Capecitabine 1650 mg 1x2 (d1- d5) for 5 weeks oral from 26 Feb 2018 to 12 Apr 2018, 5-fluorouracil 5600 mg d1-d3 q2 weeks, Irovorin 175 mg q2 weeks and Irinotecan 360 mg q 2 weeks all three intravenous from 25 Jun 2018 to 27 Nov 2018, Capecitabine 2 g 1x2 for 14 days q 21 days oral, Erbitux (cetuximab) 1000 mg q 2 weeks, Zometa 4 mg both intravenous and all from 17 Dec 2018 to 13 Mar 2019, Avastin (bevacizumab) 460 mg, oxaliplatin 170 mg, isovorin 175 mg and 5-fluorouracil 5600 mg all intravenous q2 weeks from 27 mar 2019 to 05 Aug 2019 and Zometa 4 mg q 6 weeks from 22 Apr 2019 to 22 Jul 2019 all for Metastatic Colorectal Cancer.

The investigator’s comment on causality is that patient’s fatal hepatic failure may be attributed to constrictive pericarditis but also the administered drugs might have been

involved to a certain degree. Bilateral pleural effusion (cytology – proven malignant) has contributed to an increased heart load, thus are also involved, to a certain degree to patient's hepatic strainl. The case is considered as Serious (Death, Life threatening and Hospitalisation).

Outcome: Fatal (Hepatic failure)

Not recovered (Pleural & Pericardial effusion)

Follow-up #1

Follow-up information received on 10 & 13 Jan 2020.

Additional information on patient's medical history concerned that Metastatic colorectal cancer was diagnosed on 08 Feb 2018 with Liver metastases from 15 Feb 2018 to 03 Jan 2020, Bone metastases and Lung metastases from 08 Feb 2018 to 03 Jan 2020, Disease recurrence locoregional from 12 Jun 2018 to 03 Jan 2020, Bilateral pleural effusion and Pericardial effusion both from 12 Dec 2019 to 03 Jan 2020.

On 10 Jan 2020 the investigator has mentioned that Hyponatremia was addition to the presenting clinical picture of the patient.

Additional tests and laboratory data performed on 31 Dec 2020:
Heart Ultrasound: Pericardial effusion, pericardial thickening and constriction of the lateral and dorsal wall of the left ventricle, of the right ventricle and the apex. Distended inferior cava. LVEF >55%
CT upper abdomen: Liver metastases. No distention of the biliary tree. No ascites.

Relevant tests and laboratory data performed on 02 Jan 2020:
Liver/biliary tree/ spleen ultrasound: Liver metastases. No distention of the biliary tree. No ascites.

Heart ultrasound: Pericardial effusion, significant pericardial thickening and constriction of the lateral and dorsal wall of the left ventricle, of the right ventricle and the apex. Distended inferior cava. LVEF >55%.

Additional information on patient's relevant concomitant drug information included the administration of Minocin (minocycline) 100 mg for Skin rash prophylaxis (due to panitumumab administration), Medrol (methylpresolone) 16 mg for Pericardial effusion, Lasix (furosemide) 40 mg for Pleural effusion, oedema lower extremities and Cozaar (losartan) 100 mg for Hypertension all 1x1 oral from 27 Dec 2019 to 30 Dec 2019.

On 10 Jan 2020 investigator's has additionally commented on causality that constrictive pericarditis (pericardial effusions and thickening of the pericardium as proven by heart ultrasound) and bilateral pleural effusions (cytology-proven to be malignant) are part of the study disease and are not related to the study drugs. Upon patient's hospital admission, thrombocytopenia (grade 1) and hyponatremia (grade 3) were documented and considered to be related to the causes that warranted the admission of the patient to the hospital (hepatic failure, heart and pleural effusions).

Outcome: Fatal (Hepatic failure)
Not recovered (Pleural & Pericardial effusion)

Follow-up #2
Follow-up information received on 21 Jan 2020.

Additional information on relevant tests and laboratory data concerned the result of Upper abdomen CT scan on 31 Dec 2019: Liver metastases (unchanged compared to the previous CT scan performed).

Corrections on concomitant medication concerned that patient had received Cozaar and Lasix from pre-screening period to 30 Dec 2019.

Investigator's comment on causality has not changed.

Outcome: Fatal (Hepatic failure)

Not recovered (Pleural & Pericardial effusion)

Infection grade 3

Initial information in this case was received on 08, 11 & 19 Jan 2021. The case concerned a 63 - year-old female patient with a history of Colorectal carcinoma diagnosed after Biopsy since 13 May 2019, with Liver metastases diagnosed after a CT scan since 02 May 2019 and Facial rash due to panitumumab from 08 Dec 2020 to 15 Dec 2020, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of Metastatic colorectal cancer.

The patient received Vectibix (panitumumab) 380 mg (6 mg/kg) from 13 Oct 2020 to 24 Nov 2020, Oxaliplatin 135 mg (85 mg/m^2) from 13 Oct 2020 to 15 Dec 2020, Leucovorin 640 mg (400 mg/m^2) on 13 Oct 2020 and then reduced to 600 mg from 27 Oct 2020 to 15 Dec 2020 all on Day 1 every 2 weeks and Fluorouracil 4440 mg (400 mg/m^2 & 2400 mg/m^2) from on 13 Oct 2020 and then reduced to 4100 mg from 27 Oct 2020 to 15 Dec 2020 on Days 1-3 every 2 weeks.

On 06 Jan 2021 the patient went to the hospital with epigastric pain, an electrocardiogram and cardiogram were performed and doctors diagnosed heart attack. Laboratory tests were also performed and the patient was hospitalised in Intensive Care Unit and the reason of the event was under investigation. On 11 Jan 2021 after reevaluating the event, the symptoms and the lab tests doctor came to the conclusion that the event was Infection grade 3 which was still under investigation and myocardial infarction (heart attack) and fever were symptoms of the infection. Myocardial infarction was considered as a symptom since

cardiac enzymes were minimally abnormal and there was no evidence of ischemic ECG changes. A COVID-19 test was also performed due to fever and was negative. CRP values were increased, urine culture was negative and blood cultures were still pending. On 18 Jan 2021, the patient was still hospitalised, fever was grade 1, blood cultures were negative, patient's condition was stable seeming to be recovering considering the fact that CRP values were decreased. The event infection was still under investigation by the time this report was sent.

Relevant tests and laboratory data performed on 06 Jan 2021:

WBC: 13.05 * 10 ^ 3 /µL (Normal ranges: 4.0 – 11.0)

Neutrophils count: 11.33 * 10 ^3 /µL (Normal ranges: 2.0 – 7.7)

Troponine: 409.5 pg/mL (Normal ranges: 0 – 11.6)

Relevant tests and laboratory data performed on 08 Jan 2021:

Urine culture: negative

Blood culture: negative

Relevant tests and laboratory data performed on 09 Jan 2021:

CRP: 284 mg/L (Normal ranges: <6)

Relevant tests and laboratory data performed on 11 Jan 2021:

CRP: 243 mg/L

Relevant tests and laboratory data performed on 18 Jan 2021:

WBC: 11.42 * 10 ^ 3 /µL

Neutrophils count: 8.69 * 10 ^3 /µL (Normal ranges: 2.0 – 7.7)

CRP: 110 mg/L

Actions taken as a result of the Event included the patient's hospitalisation and the administration of Pantium (pantoprazole) 40 mg, 1x1, Salospir (acetylsalicylic acid) 100 mf 1x1, Blocatens (bisoprolol) 10 mg 1x1 and Inspra (eplerenone) 25 mg 1x1 all four oral from 08 Jan 2021 ongoing, Ciproxin (ciprofloxacin) 400 mg 1x2 intravenous from 08 Jan 2021 to 15 Jan 2021, Tazocin (tazobactam) 4.5g 1x4 intravenous from 08 Jan 2021 ongoing and Voncon (vancomycin) 1g 1x2 from 12 Jan 2021 ongoing.

Concomitant and Past Drug information at the time of the Event included the administration of Ondasetreon 16 mg, dexamethasone 16 mg, omeprazole 40 mg and dimetindene 4 mg all four intravenous from 13 Oct 2020 to 05 Jan 2021 as Premedication, Fucidin (fusidic acid) 1x2 ointment from 08 Dec 2020 to 15 Dec 2020 for Facial rash, Medrol (methylprednisolone) 16 mg 1x2 oral from 15 Dec 2020 ongoing and Lyo-cortin (cortisol) 250 mg 1x1 intravenous on 05 Jan 2021 both for Allergic reaction.
The investigator's comment on causality is that Infection grade 3 is still under investigation but is not considered related to the study drugs. The case is considered as Serious (Hospitalisation).
Outcome: Recovering
Follow-up #1
Follow-up information received on 25 Jan 2021.

Additional informationon patient's medical history included that the patient had an Allergic reaction due to oxaliplatin on 15 Dec 2020.
On 22 Jan 2021 the patient was discharged from the hospital with instructions from the investigator. The patient was given a treatment to continue at home and the next appointment was scheduled in 10 days form the discharge. The event infection was considered recovered but the cause of the event remained of unknown etiology but still unrelated to the study drugs. The symptom of fever was grade 1 since the beginning and was not increased during the event of infection. The patient had fever grade 0 on 21 Jan 2021.
Relevant tests and laboratory data performed on 20 Jan 2021:
CRP: 83 mg/L
Additional information on the action taken due to event included that the drugs Platium, Blocates, Tazocin and Vancon were stopped on 22 Jan 2021 and Spectracef (cefditoren) 400 mg 1x2 oral was started on 22 Jan 2021 for 10 days.

Investigators assessment on causality was that the event infection was of unknown aetiology but unrelated to any of the study drugs. The case is considered as Serious (Hospitalisation).

Outcome: Recovered on 22 Jan 2021

Follow-up #2
Follow-up information received on 02 Feb 2021.
Additional information on the study drug informed that the study drug Oxaliplatin 135 mg was administered from 13 Oct 2020 to 24 Nov 2020 and then on 15 Dec 2020 patient received 72 mg of the study drug.

On 05 Jan 2021 the patient had received 20 mg of the study drug oxaliplatin due to allergic reaction to the drug. On 01 Feb 2021 doctor decided the discontinuation of the patient from the study due to allergic reaction to oxaliplatin and the adverse event (facial rash) to the IMP panitumumab. Discontinuation of the patient from the study was unrelated to the event infection.

Investigator's comment on causality has not changed.

Outcome: Recovered on 22 Jan 2021

Follow-up #3
Follow-up information received on 29 Sep 2021.

On 29 Sep 2021 after monitoring review, it was discovered that patient was also treated with Innohep from 08 Jan 2021 but no further information was available about the stop date and Zarzio once on 08 Jan 202. Both drugs were administered for prophylaxis.

Additional information on the action taken for the event included the administration of Innohep (tinzaparin) 4500 IU 1x1 since 08 Jan 2021 and Zarzio (filgrastim) inj. 48 MU once on 08 Jan 2021.

Investigator's comment on causality has not changed.
Outcome: Recovered on 22 Jan 2021

Sponsor's comment: Serious Adverse Event (SAE)
Catheter related infection grade 3

Initial information in this case was received on 12 Apr 2021. The case concerned a 77-year-old male patient with a history of Colorectal cancer since 27 Jan 2016, with Liver metastases since 13 Feb 2019, who was enrolled in a HeCOG Phase: II, Multicenter, Single arm study for the treatment of Metastatic colorectal cancer.

The patient received Vectibix (panitumumab) 396 mg (6 mg/kg) from 13 Oct 2020 to, Irinotecan 326 mg (180 mg/m^2), Leucovorin 724 mg (400 mg/m^2) all on Day 1 every 2 weeks and Fluorouracil 5044 mg (400 mg/m^2 & 2400 mg/m^2) all intravenous from 25 Feb 2021 to 10 Mar 2021 for Metastatic colorectal cancer.

On 17 Mar 2021 the patient was hospitalised with fever, fatigue and diarrhoea. Blood culture and CRP had showed *Staphylococcus epidermidis,* due to the port-a-cath placement. The patient had received cephalosporins from 26 Mar 2021 to 04 Apr 2021 which was also the date of hospital discharge. On the same date, 04 Apr 2021, the patient was stopped from the administration of cephalosporins. Patient's temperature was within normal ranges. Patient's port-a-cath was scheduled to be removed on 05 Apr 2021.

Relevant tests and laboratory data performed on 28 Mar 2021:
CRP: 72.6 mg/L (Normal ranges: 0-5)

Blood culture: positive for *Staphylococcus epidermidis*

Actions taken as a result of the Event included the patient's hospitalisation and the administration of ceftazidime from 17 Mar 2021 to 26 Mar 2021, metronidazole from 17 Mar 2021 to 02 Apr 2021, amikacin from 26 Mar 2021 to 02 Apr 2021, piperacillin and tazobactam both from 26 Mar 2021 to 04 Apr 2021 and vancomycin from 28 Mar 2021 to 04 Apr 2021.

No relevant Concomitant and Past Drug information were administered.

The investigator's comment on causality is that Catheter related infection grade 3 was not related to any of the study drugs and was considered related to the *Staphylococcus epidermidis* infection of the catheter. The case is considered as Serious (Hospitalisation).

Outcome: Recovered on 04 Apr 2021.

Sponsor's comment: Serious Adverse Event (SAE**)**

12.3 SAFETY CONCLUSIONS

Table 10. Reasons for treatment discontinuation

Reason	**N**	**%**
Death *	1	4.4
AE (Not fatal) **	2	8.7
Doctor's decision ***	2	8.7
Progression	15	65.2
Informed consent withdrawal	2	8.7
Other****	1	4.4

* Early tumor death

** 1 patient delayed treatment due to SAE "Ileus grade 2" – the event was attributed to patient's previous medical condition-.

1 patient was discontinued due to pancytopenia & febrile neutropenia caused by FOLFIRI.

*** 1 patient was discontinued with doctor's decision due to allergic reaction to Oxaliplatin.

1 patient was discontinued by the investigator since was not compliant with the study's procedures

**** Clinical PD.

Table 11. Aggregate Summary Tabulations of Serious Adverse Events

Aggregate Summary Tabulations		
SOC (System Organ Class)	MedDRA Preferred Term	Counts N
Blood & lymphatic system disorders	Febrile neutropenia	1
	Pancytopenia	1
	Neutropenia	1
Cardiac disorders	Pericardial effusion	1
Gastrointestinal disorders	Ileus	1
	Diarrhea	2
	Mucositis oral	1
Hepatobiliary disorders	Hepatic failure	1
Infections & infestations	Catheter related infection	1
	Infection	1
Metabolism & nutrition disorders	Hyperbilirubinaemia	1
Renal & urinary disorders	Urinary tract obstruction	1
	Renal failure	2
Respiratory, thoracic and mediastinal disorders	Pleural effusion	1
Skin & subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome	1
	Rash	1
Total	-	18

Table 12. List of reported Serious Adverse Events

	Local Report Number	Randomization No	SAE Term	Related?		Expected?	SUSAR?	Outcome
				Inv	MA			
1	GR-HECOG-20180001	HE6B16-4-0002	Palmar-plantar erythrodysaesthesia syndrome grade 3 - Oral mucositis grade 3	Yes (Irinotecan , Irinotecan & 5FU)	Yes	NA	NA	Not recovered Recovered
2	GR-HECOG-20180004	HE 6B16-3-0003	Febrile neutropenia grade 3 - Urinary tract obstruction grade 2	FOLFIRI – NO	FOLFIRI – NO	NA	NA	Recovered
3	GR-HECOG-20180005	HE6B16-3-0003	Renal failure grade 3, Pancytopenia grade 4, Hyperbilirubinaemia grade 3	No, YES FOLFIRI, NO	No, YES FOLFIRI, NO	NA	NA	Recovered
4	GR-HECOG-20180007	HE6B16-3-0003	Renal failure grade 3	No	No	NA	NA	Not recovered
5	GR-HECOG-20190005	HE6B16-3-0006	Diarrhea grade 2 Neutropenia grade 2	Yes (FOLFIRI)	Yes (FOLFIRI)	NA	NA	Recovered
6	GR-HECOG-20190007	HE6B16-3-0006	Diarrhea grade 1	NO	NO	NA	NA	Recovered
7	GR-HECOG-20190012	HE6B16-4-0007	Ileus grade 2	No	No	NA	NA	Recovered
8	GR-HECOG-20200001	HE6B16-3-0014	Rash grade 3	YES (panitumumab)	YES (panitumumab)	NA	NA	Recovered
9	GR-HECOG-20200002	HE6B16-32-0015	Hepatic failure grade 5 Plural effusion grade 4	Yes (FOLFIRI	Yes (FOLFIRI	No	Yes	Death

			Pericardial effusion grade 4	+panitumumab) Study disease	+panitumumab) Study disease			Not recovered
10	GR-HECOG-20210002	HE6B16-3-0021	Infection grade 3	No	No	NA	NA	Recovered
11	GR-HECOG-20210007	HE6B16-125-0023	Catheter related infection grade 3	No	No	NA	NA	Recovered

13. DISCUSSION AND OVERALL CONCLUSIONS

This was a phase II single arm study with Panitumumab and chemotherapy in 3rd line treatment in patients with RAS- wild type mCRC previously treated in 1st line setting with an anti-EGFR agent. The study was done at 5 Oncology Departments of Greek hospitals and at one Oncology Department in Cyprus under HeCOG coordination.
The hypothesis on which the current clinical trial was based, has been described in the past. In more details an anti-EGFR–based therapy in the 1st line setting would be able to substantially decrease the bulk of sensitive (wild-type RAS) cells, thus making the resistant (mutant) clones progressively predominant until the clinical evidence of disease progression. During a subsequent treatment that is not anti-EGFR based, sensitive clones would be at least partially restored, thus laying the foundation for the potential and reported activity of anti-EGFR (with Cetuximab or Panitumumab) rechallenge (44).
It is very interesting the fact that in medical literature occur articles, although only few, accessing the hypothesis we have try to examine with our study. As an example, Cremolini et al presented the results of a prospective study with a similar design of our study with the exception of the anti-EGFR agent used and showed that 54% of the 29 patients included in their study succeeded to have control of their disease (45). Or another example is the study underway in Japan where the investigators are checking ctDNA in wild type RAS mCRC patients and based on these results they retreat them with Panitumumab -Irinotecan (46).
Unfortunately, the study terminated early due to poor accrual. Even though the study did not complete its accrual, from the data analysis not safety issues seem to have been raised.
The efficacy results of the treatment used in our study show that 3 patients (13.0%) exhibited PR as best overall response during the study. Median overall survival (Figure 1) in the entire cohort was 8.7 months (95% C.I: 5.7-16.4) while the median progression free survival (Figure 2) was 2.8 months (95% C.I.: 2.3-5.7).

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