TITLE PAGE

An open-label, randomized phase III trial of cisplatin and 5-fluorouracil with or without panitumumab for patients with non-resectable, advanced or metastatic esophageal squamous cell cancer

Protocol Number: AIO-STO-0309

EudraCT number: 2010-020606-15

Name of Product/Test Drug/IMP:	Panitumumab
Phase of Development:	Phase III
Date of First Patient In:	18-May-2012
Date of Last Patient Out (Last Patient Last Contact):	01-Jun-2016
Indication:	Patients with nonresectable, advanced or metastatic esophageal squamous cell cancer (ESCC)
Design:	Open-label, randomized, parallel group, multicenter, multinational Phase III study Patients will receive chemotherapy or chemotherapy plus panitumumab every 3 weeks
Sponsor:	AIO-Studien-gGmbH
Coordinating Investigator:	Prof. Dr. Markus Moehler
Date of Report (FINAL 1.0):	24-May-2017

This study was performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and other applicable regulatory.

STUDY REPORT SYNOPSIS

<table>
<tr><td>Name of Company:
Amgen Ltd</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:
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<tr><td>Name of Finished Product:
Vectibix®</td></tr>
<tr><td>Name of Active Ingredient:
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An open-label, randomized phase III trial of cisplatin and 5-fluorouracil with or without panitumumab for patients with nonresectable, advanced or metastatic esophageal squamous cell cancer</td></tr>
<tr><td colspan="3">Principal Investigator:
Professor Dr. Markus Moehler</td></tr>
<tr><td colspan="3">Study Site(s):
36 study sites in Germany, centers in other European countries and in Israel</td></tr>
<tr><td colspan="3">Publication (reference):
N/A</td></tr>
<tr><td colspan="2">Study Dates:
First Patient Treated: 18-May-2012
Last Patient last contact: 01-Jun-2016</td><td rowspan="2">Phase of Development:
Phase III</td></tr>
<tr><td colspan="2">Reporting Period:
First date of data collection: May-2012
First safety interim analysis: 19-Feb-2014
Second safety interim analysis. :13-Nov-2014
Third safety interim analysis: 07-Apr-2015
Fourth efficacy interim analysis: 06-May-2015</td></tr>
</table>

Name of Company: Amgen Ltd **Name of Finished Product:** Vectibix® **Name of Active Ingredient:** Panitumumab [pINN] (rHuMAb-EGFr; ABX-EGF) is a high affinity (Kd=5x10^{-11} M) human IgG2 monoclonal antibody directed against human EGFR	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Objectives <u>Primary Objective:</u> • To demonstrate superiority of 5-fluorouracil, cisplatin and panitumumab over 5-fluorouracil and cisplatin alone in terms of overall survival in esophageal cancer <u>Secondary Objectives:</u> To compare treatment arms with respect to: • Progression-free survival • 1-year survival • Response rate • Safety and tolerability • Quality of life <u>Exploratory objectives:</u> To assess: • The potential correlation between the regimen and EGFR expression • Functional EGFR gene polymorphisms • EGFR gene amplification (FISH) • KRAS, BRAF, NRAS and PTEN mutations • EGFR downstream proteins and gene expression parameters, proteomics and epigenetics		
Methodology: Open-label, randomized (ratio 1:1), parallel group, multicenter, multinational Phase III study Patients were to receive chemotherapy or chemotherapy plus panitumumab every 3 weeks		
Number of Patients: Planned: 300 Screened: 155 Analyzed: 146		

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<tr><td colspan="3">Diagnosis and Main Criteria for Inclusion and Exclusion:
• Male or female subjects at least 18 years of age, who signed written informed consent and who had nonresectable, advanced or metastatic ESCC
• Subjects with measurable or non-measurable disease according to RECIST 1.1 and with ECOG 0–1
• Women of child-bearing potential were to have a negative pregnancy test
• Laboratory requirements:
  ○ Hematology:
    ▪ Absolute neutrophil count ≥1.5x10^9/L
    ▪ Platelet count ≥100x10^9/L
    ▪ Leukocyte count >3.0x10^9/L
    ▪ Hemoglobin ≥9 g/dL or 5.59 mmol/L
  ○ Hepatic Function:
    ▪ Total bilirubin ≤1.5 times the upper normal limit (UNL)
    ▪ AST ≤2.5xUNL in absence of liver metastases, or ≤5xUNL in presence of liver metastases
    ▪ ALT ≤2.5xUNL in absence of liver metastases, or ≤5xUNL in presence of liver metastases
  ○ Renal Function:
    ▪ Creatinine clearance ≥50 mL/min according to Cockroft-Gault formula
  ○ Metabolic Function
    ▪ Magnesium ≥0.5 mmol/L or 1.2 mg/dL
    ▪ Calcium ≥2 mmol/L or 8.0 mg/dL
• Under no circumstances were patients, who were once enrolled in this study, permitted to be re-enrolled into the same study or had previous chemotherapy of esophageal cancer in metastatic setting and previous neoadjuvant chemotherapy or definitive radiochemotherapy with maximum cumulative dose of 120 mg cisplatin and without recurrence of disease within 4 months after the end treatment were allowed</td></tr>
<tr><td colspan="3">Test Product, Dose and Mode of Administration, Batch Number:
Panitumumab, 9 mg/kg intravenously (IV) prior to administration of chemotherapy on Day 1 of each treatment cycle</td></tr>
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Duration of Treatment:

A treatment cycle in this study consisted of chemotherapy administration plus panitumumab on day 1 to day 4. Cycles were repeated every 3 weeks. Treatment was continued until progression of disease was demonstrated by computed tomography (CT) or magnetic resonance imaging (MRI), unacceptable Adverse events (AEs) occurred in individual subjects, or consent was withdrawn. If panitumumab was discontinued before progression of disease, subjects were treated with chemotherapy alone until progression of disease. If chemotherapy was discontinued before progression of disease, subjects might continue with panitumumab monotherapy.

Other therapy, Dose, and Mode of Administration, Batch Number:

Chemotherapy (5-fluorouracil and cisplatin); cisplatin was administered at a dose of 100 mg/m^2 until 28-Feb-2014, following a protocol amendment when it was changed to cisplatin 80 mg/m^2 IV infusion according to country standards on Day 1, followed by 5-FU 1000 mg/m^2 IV daily as continuous infusion according to country standards, Day 1–4; Repeated day 22.

The reason for change of cisplatin dose was to adapt to the three-weekly MRC protocol cisplatin/ 5-fluorouracil which is one of the best approved standard regimens in ESCC worldwide and has been shown to have a better toxicity profile than the classical CF regimen, often given in Central Europe or Germany.

Criteria for Evaluation:

Safety:

Throughout the treatment period until the EOT visit, patients were assessed for all adverse events. Common terminology criteria for adverse events (CTCAE V 4.03) were used for grading.

Analyses for presence of anemia were determined using the laboratory results rather than anemia as reported as adverse events.

Efficacy:

The primary efficacy parameter of this trial was overall survival (OS). Overall survival was defined as time from randomization until death. Patient without date of death were censored at the date of last contact.

The first secondary efficacy parameter of this trial was progression-free survival (PFS). PFS was defined as time from randomization until progression or death. Patients without progression and without date of death were censored at the date of last tumor assessment.

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Statistical Methods: In general, adverse events were analyzed descriptively. Statistical comparisons were performed by using Fisher's exact test for the presence of anemia of certain grades, cardiovascular events, and skin toxicity. Time-to-event efficacy variables were analyzed by means of the Kaplan-Meier method. Log rank tests were performed to compare treatment groups for the whole population and several subpopulations: • patients with prior chemotherapy of esophageal cancer • patients with prior radiotherapy of esophageal cancer • patients at high recruiting sites • patients at mediocre recruiting sites • patients at low recruiting sites Further comparisons were performed between subjects grouped by baseline BMI, patients with moderate anemia vs. patients without moderate anemia, and patients that received 5-Fu/Platin vs. other patients, respectively.		

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Summary of Results:

Between 06.2012—05.2015, 146/155 pts were randomized, 73 in each arm.
After four safety interim analyses for safety and futility, as recommended by the DSMB (see Section 16.5), the trial was stopped.

Safety interim analyses

- First safety interim analysis (n=40): Cisplatin/5-FU (CF) (active comparator arm:[n=19]) arm vs CF + Panitumumab (P) (experimental arm: [n= 21])
    - Median number of treatment cycles was 5 vs 3 months with 4 vs 3 cycles of cisplatin and 5 vs 3 cycles of 5FU
    - AEs and SAEs were numerically lower in active comparator arm than in experimental arm (181 vs 312 and 17 vs 28, respectively)
    - Number of subjects with SAEs leading to chemotherapy discontinuation were relevantly lower in active comparator arm than in experimental arm (1 vs 6) although those in experimental arm had questionable relatedness to panitumumab.
    - Comparable number of subjects with AEs leading to discontinuation of chemotherapy were observed in both arms (7 vs 7)
    - Comparable number of patients reached EOT (17 vs 18) and end of study (7 vs 8) with 6 vs 7 due to deaths in both arms
    - Grade ≥3 skin toxicity relative to prior panitumumab studies was 29% (within expected range)
    - Grade 3 or 4 on basis of (Common Terminology Criteria for Adverse Events [CTCAE] version 3) diarrhea toxicity based on within-trial differences was 10% (within expected range)
    - Toxicity as a reason for end of treatment (EOT) was higher in active comparator than in experimental arm (5 vs 3)
    - Death as reason for EOT (2 vs 2) or end of study (6 vs 7) were similar in both arms
    - No concern was raised and additional mortality and toxicity rates analyses were to be performed after the treatment of 70 patients that had received at least 2 treatment cycles.
- Second safety interim analysis (n=70)(39 vs 31)
    - patients that received at least 2 treatment cycles of cisplatin/5-FU, with or without panitumumab
    - The median number of cycles was 5 vs 5 of cisplatin and 5 vs 5 of 5FU for active comparator compared to experimental arm with panitumumab
    - Rates of AE and SAE were similar in both arms (407 vs 458 and 43 vs 42) respectively

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- SAEs leading to chemotherapy treatment discontinuation were also similar (6 vs 7)
- AEs leading to chemotherapy discontinuation were similar (16 vs 11)
- Rate of Grade ≥3 skin toxicity was 19% (within expected range)
- Grade 5 events such as death as a reason for EOT (2 vs 2) or end of study (14 vs 16) were similar in the two arms
- There was no sign of excessive toxicity or mortality due to panitumumab in combination chemotherapy

- <u>Third safety interim analysis (n=100) (52 vs 48)</u>
  - Patients treated with at least 1 cycle of cisplatin / 5-FU, with or without panitumumab.
  - Early mortality rate was significantly higher in experimental arm in expanded analysis (0 vs 47, 4 vs 48) independent of starting cisplatin dose (80 mg/m^2 versus 100 mg/m^2)
  - Panitumumab-related SAEs leading to treatment discontinuation in experimental group (16)
  - AEs leading to chemotherapy treatment discontinuation were similar (15 vs 15)
  - Chemotherapy-related SAEs leading to treatment discontinuation were more in experimental arm (7 vs 14, p=0.08)
  - Grade 3–4 such as skin toxicities were significantly more in experimental arm than in control arm (p=0.005), also dehydration due diarrhea (p=0.02)
  - Panitumumab was discontinued due to toxicity in 33% of patients
  - Grade 5 event such as EOT due to death was more in experimental arm than in standard arm (21 vs 29)
  - Most safety parameters argued against the experimental arm and a critical evaluation of study continuation was suggested
- <u>Fourth efficacy interim (expanded) analysis (n=136)</u>
  - Patients were treated with at least 1 cycle of cisplatin/5-FU, with or without panitumumab
  - Treatment was presented depending on cisplatin starting doses (80 mg/m^2 vs 100 mg/m^2)
  - Early mortality was still significantly higher than in experimental arm
  - Mortality was independent of starting cisplatin dose (2 early deaths in both groups)
  - OS was based on 136 patients with follow-up and 61 death events
  - OS favored standard arm irrespective of the starting dose of cisplatin
  - OS showed superiority of control arm over experimental arm (Hazard ratio [HR] 1.77, 95% CI, 1.06–2.98)
  - The DSMB recommended the clinical study to be stopped and the study centers to quit treating patients with panitumumab

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Safety Results

- 55/70 (79%) of control arm and 60/72 (83%) of experimental arm patients had at least one severe AE, mostly diarrhea, hypokalemia, hypomagnesaemia, rash, and hand-foot syndrome
- Experimental arm had more subjects with one severe at least one severe SAE (29/70 vs 44/72; p=0.029)
- Cisplatin starting dose of 100 mg/m^2 resulted in increased SAEs in the experimental arm (16 vs 22; p=0.05
- Cisplatin (100 mg/m^2) also resulted in more severe SAEs in the experimental arm (44.8% vs 74.1%; p=0.03)
- Subjects with at least one AEs leading to panitumumab treatment discontinuation were only observed in the experimental arm as expected (0 vs 18, p<0001)
- Subjects with at least one SAEs leading to panitumumab treatment discontinuation were only observed in the experimental arm as expected (0 vs 16, p<0001)
- Total number of AEs leading to chemotherapy discontinuation were more in the experimental arm (24 vs 30)
- Total number of SAEs leading to chemotherapy discontinuation were more in experimental arm (9 vs 19)
- Main Grade≥3 AEs were low neutrophils 21/ 24% and anemia 13/16 % for CF +/- P, respectively
- Grade 3–4 skin reactions and rash were higher in experimental arm (10%) vs control arm (0%). Overall 36/70 (51%) of control arm and 51/72 (71%) of experimental arm had SAE
- Main SAE were dysphagia (6/6%), acute kidney injury (7/4%), diarrhea (7/3%), fevers (3/6%) and febrile neutropenia (6/1%) for CF +/-P
- Subjects with at least AEs of Grade 5 CTC were significantly more in the experimental arm than in the active comparator arm (3 vs 17; p=0.0012)
- AE of Grade 4 CTC was suffered by less patients in the experimental arm (14 vs 9)
- Comparable AEs of Grade 3 CTC were observed in both arms (38 vs 34)
- Cisplatin dose reduction showed a significant difference in skin toxicity (p=0.0009)

Efficacy Results:

- Following the Post hoc analysis of the ITT (Intention-to-treat) patient population, median overall survival (OS) of CF vs CFP was 10.2 vs. 9.4 months (mo) (hazard ratio (HR) 1.17, 95% CI 0.79–1.75; p=0.43) thus favoring the active comparator group

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- Reduced doses of cisplatin (from 100 mg/m^{2}d1 to 80 mg/m^{2}d) resulted in a non-significant improvement of HR of OS which favored the experimental arm 8.3 vs 9.8 months (HR 0.84, 95% CI, 0.49–1.43, p=0.51)
- For 56 patients treated with cisplatin 100 mg/m^{2}d1, OS was in favor of the active comparator arm (12.9 vs 9.4 months (HR 1.83, 95 % CI 0.98–3.42; p=0.06).
- OS analysis of patients sub population who received cisplatin starting dose of 100 mg/m^2 dose showed a significant difference between the two treatment arms (p=0.03)
- Complete response (CR) occurred only in experimental arm (0 vs 1) while partial response was comparable (27 vs 26)
- Median progression free-survival (PFS) of control arm vs experimental arm was similar with 5.8 vs. 5.3 months (HR 1.21, 95% CI, 0.85–1.73; p=0.30) respectively
- Reduction of cisplatin dose to 80 mg/m^{2}d1 resulted in an improvement in HR (HR 0.96, 95% CI, 0.60–1.5 3)

Conclusions:

- The efficacy results did not demonstrate the superiority of experimental arm over the control arm as OS and PFS favored the active comparator though was not to a statistically significant level
- Cisplatin 100 mg/m^{2}d1 resulted in higher Grade 3–4 SAE events (particularly rash, skin toxicity and early drop-outs due to toxicities) and its reduction resulted in non-significant HR improvement in efficacy
- Safety results demonstrated the negative effect of panitumumab on chemotherapy delivery
- The EGFR-blockade-related side effects were in the range of previously published data.
- Addition of panitumumab to CF provided no additional benefit to chemotherapy alone as first-line treatment of ESCC.
- Biomarker program is going on for further correlation analyses
- Failure of panitumumab to exert the intended therapeutic objectives and the increased safety concerns, the trial was stopped.

Date of Report: 24-May-2017