2 Synopsis

Name of Sponsor/ Company: Amgen	
Name of Finished Product: Vectibix®	
Name of Active Ingredient: Panitumumab	
Title of Study: Prospective multIcenter observational study on the Quality of life of mCRC RAS wild-type patients receiving Anti-EGFR MAbs + FOLFOX or FOLFIRI as 1st line of treatment	
Investigators: [redacted]	
Study Center(s): 40	
Publication (reference): None	
Study Period: **First Patient First Visit:** 30DEC2015 **Last Patient Last Visit:** 31DEC2020	**Phase of Development: IV**
Objectives: To assess the impact of the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients' health related quality of life (HRQoL), as measured by means of the EORTC – QLQC30 questionnaire.	
Methodology: National, multicentric, prospective, observational trial.	
Number of patients: **Planned: 300** **Enrolled: 292** **Analyzed: 271**	

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Diagnosis and main criteria for inclusion: Inclusion Criteria • Adult (>= 18 years old) RAS wild-type metastatic colorectal cancer patients candidate to receive FOLFOX or FOLFIRI plus panitumumab or FOLFOX or FOLFIRI plus cetuximab as upfront treatment as per clinical practice. • Willingness and ability to comply with the protocol. • Written informed consent to study procedures. Exclusion Criteria • Patients receiving a treatment under clinical investigation may not be included in the study. • Previous treatment with an anti-EGFR monoclonal antibody.
Test product, dose and mode of administration, batch number: commercially available Vectibix®
Duration of Treatment: As from clinical practice
Reference therapy, dose and mode of administration, batch number: None

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Criteria for evaluation

Efficacy:

The primary endpoint of the study was to assess the impact of the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients' HRQoL. HRQoL measured using the EORTC-QLQ-C30 questionnaire.

Safety:

- Evaluate the impact of dermatological adverse events during the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on subjects' skin satisfaction as measured by the Dermatology Life Quality Index (DLQI) questionnaire.
- Tolerability: the toxicity rate, defined as the percentage of subjects, relative to the total of enrolled subjects, experiencing adverse events of any grade, according to National Cancer Institute Common Toxicity Criteria (NCI CTC-AE version 4.0),
- Time to onset of dermatological toxicities.
- Treatment adherence to the treatment with anti-EGFR:
    - the percentage of delayed cycles,
    - the percentage of cycles administered with reduced doses,
    - the number of administered cycles,
    - the median treatment duration.
- Management of dermatological toxicity:
    - concomitant medications, both topical and systemic, adopted to prevent or treat dermatological adverse events.
- Effect on skin-related Quality of Life (QOL) of preventive vs reactive treatment for skin toxicities, effect on skin-related QOL of length of preventive treatment for skin toxicities, effect on skin-related QOL of events of skin toxicities and their toxicity grade.

Statistical methods:

- Analyses of Primary Endpoint

  The primary endpoint of this study was to assess the impact of the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on subjects' HRQoL.

  Each scale of the EORTC-QLQ C30 questionnaire, functional scale, symptom scale, and global health status/QOL, was presented with descriptive statistics at baseline and each timepoint, by treatment group and overall.

  Within each scale, the subscales were presented descriptively as well.

  For the functional scale, the following subscales were described: Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, and Social functioning.

  For Symptom scales the following subscales were described: Fatigue, Nausea, and vomiting, Pain, Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, and Financial difficulties.

  EORTC-QLQ-C30 scales were also presented descriptively as a percentage of the scores reported at baseline.

  The comparison of the mean total EORTC-QLQ C30 scores (functional scale, symptom scale, global health status/QOL) at baseline with the mean total EORTC-QLQ C30 scores at the last study visit was tested with a t-test (Student t-test, paired data) overall

  The same analysis above-mentioned was repeated by considering only subjects taking panitumumab i.e. FOLFOX/FOLFIRI plus panitumumab.

  In addition, the comparison of the mean change from baseline to the last study visit of the total EORTC-QLQ C30 scores (functional scale, symptom scale, global health status/QOL) between the two treatment groups (FOLFOX/FOLFIRI plus panitumumab and FOLFOX/FOLFIRI plus cetuximab) was tested with t-test (Student t-test, unpaired groups).

- Analyses of Secondary Endpoints

  To investigate the impact of dermatological adverse events during the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on subjects' skin satisfaction, the DLQI total score was calculated for each subject.

  The total DLQI score was analyzed with descriptive statistics at baseline and each timepoint, by treatment group and overall.

  The DLQI score was expressed also as a percentage of the maximum possible score of 30 and as a percentage of the DLQI scores reported at baseline and described descriptively.

  The mean change from baseline in DLQI score at the last study visit was compared between treatment groups (FOLFOX/FOLFIRI plus panitumumab and FOLFOX/FOLFIRI plus cetuximab) using a t-test (Student's t-test, unpaired groups).

  The analysis of the tolerability of administered treatments was expressed by means of toxicity grade, and time to onset of dermatological toxicities.

  The analysis of treatment adherence to the treatment with anti-EGFR was performed by analyzing the percentage of delayed cycles, the percentage of cycles administered with

reduced doses, the number of administered cycles, and the median treatment duration.

The analysis of adverse events, dermatological adverse events, the effect of preventive treatments of skin toxicities on QOL was performed.

To assess the effect on skin-related QOL of preventive vs reactive treatment of skin toxicities, descriptive statistics of QOL (as measured by the EORTC-QLQ C30 total scores and by the DLQI total score) were provided considering the following classes:

- Subjects that did not experience any skin toxicities;
- Subjects that did not take any medications for the skin toxicities;
- Subjects taking only (at least 1) preventive treatments for skin toxicities;
- Subjects taking only (at least 1) reactive treatments for skin toxicities;
- Subjects taking both preventive and reactive treatments for skin toxicities.

To assess the effect on skin-related QOL of events of skin toxicities (in particular the toxicity grade of skin toxicities), descriptive statistics of QOL (as measured by the EORTC-QLQ C30 and by the DLQI) were provided considering the following classes:

- Subjects that did not experience any skin toxicities;
- Subjects with skin toxicity with a toxicity grade ≤ 2 (mild skin toxicities);
- Subjects with skin toxicity with a toxicity grade > 2 (severe skin toxicities).

If a patient experienced more than 1 skin toxicity, the skin with the highest toxicity grade was used to classify the subject.

To assess the effect on skin-related QOL of the length of preventive treatment of skin toxicities, descriptive statistics of QOL (as measured by the EORTC-QLQ C30 total scores and by the DLQI total score) were provided considering the following classes:

- No preventive treatment if the subject did not take any preventive drug for skin toxicity.
- Use of preventive treatment for [1-14) days if the subject took a preventive treatment for more than 1 day but less than 14 days.
- Use of preventive treatment for [14-28) days if the subject took a preventive treatment for more than 14 days but less than 28 days.
- Use of preventive treatment for 28+ days if the subject took a preventive treatment for more than 28 days.

This analysis was restricted to the subset of subjects experiencing skin toxicity.

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Summary and conclusions:

Efficacy results: A total of 292 patients were eligible for the study (eligible set) and a total of 271 patients were included in the analysis (treated set) of this observational trial. Considering the treated set, the patients included in the study were mainly treated with FOLFOX plus panitumumab (226, 83.4%) performed up to 56 treatment cycles. The primary endpoint, evaluating the patient's QOL through the EORTC-QLQ C30, did not show any clinically relevant variation through the time nor between the different treatments.

The results from the analysis of the secondary outcomes, including the DLQI for the assessment of skin toxicity on the patients' QOL, confirmed the results belonging to the analysis of the primary endpoint.

The QOL of the patients observed in the study was not clinically different in patients undergoing FOLFOX plus panitumumab or plus cetuximab, or FOLFIRI plus panitumumab or plus cetuximab treatment. Most of the patients included in the study (226/271, 83.4%) received FOLFOX plus panitumumab while other treatments were used in a few of the patients, letting any inferential analysis of little relevance. Furthermore, the decreasing number of patients performing the treatment cycles did not allow any clinically relevant analysis. The subgroup analysis of the QOL questionnaires data based on the proportion of patients with skin toxicities, their frequency, and type of treatment did not allow any clinically relevant analysis. All the measures of QOL did not show clinically relevant variations, but the great difference in the sample of the patients treated with the different regimes did not allow any clinically relevant analysis comparing the effects of the different treatments on the patient's QOL.

Safety results:

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The frequency of AEs (2493 experienced by 248 [91.5%] of the patients) SAEs (103 experienced by 57 [21.0%] of the patients), and severe AEs (302 experienced by 139 [51.3%] of the patients) observed in this study were aligned with the expectations in the included population. The differences in the number of patients included in the different treatment cohorts do not allow performing any comparison. A total of 1026 of the AEs were coded as related to anti-EGFR in 214 (79.0%) of the patients while 1035 AEs in 208 (76.8%) of the patients were coded as induced by chemotherapy.

A total of 631 skin toxicities were experienced by 171 (75.7%) of the patients in the FOLFOX plus panitumumab cohort, while 77 skin toxicities were observed in 18 (75.0%) of those in the FOLFIRI plus panitumumab cohort, 82 skin toxicities were observed in 15 (93.8%) of the patients in the FOLFOX plus cetuximab cohort, and 4 skin toxicities were observed in 3 (60.0%) of the patients in the FOLFIRI plus cetuximab cohort. Rashes, eruptions, and exanthems were the most frequently observed skin toxicities.

A total of 120 (44.3%) of the patients experienced AEs leading to modification of their chemotherapy; 110 (40.6%) patients experienced AEs that lead to modification of anti-EGFR use.

The blood levels of magnesium were collected at baseline from 120 of the 271 patients included in the study; their means varied from 1.903 (0.564) mg/dl at baseline to 1.660 (0.670) mg/dl in the 57 patients having the data at the end of the study.

A total of 28 deaths were observed during the study; 9 subjects had fatal AEs (experienced after signing their Informed Consent Form - ICF) in the treated set.

Conclusion:

The results of this study show no significant differences in terms of evolution of QoL parameters (measured though EORTC-QLQ30 and DLQI questionnaires) in patients with advanced RAS wild-type metastatic colorectal cancer treated with FOLFOX plus panitumumab or plus cetuximab, or FOLFIRI plus panitumumab or plus cetuximab

Date of report: August 5th, 2022