TITLE PAGE

ML 25523 CLINICAL STUDY REPORT NIS INFORMATION

Title	An open label study of the effect of first line treatment with bevacizumab in combination with capecitabine and oxaliplatin on progresion-free survival in patients with metastatic cancer of the colon and rectum
Version identifier of the final study report	Version 1
Date of last version of the final study report	December 30th, 2014
EU PAS register number	NA
Active substance	L01, bevacizumab L01 capecitabine L01 oxaliplatin
Medicinal product	Avastin (bevacizumab) Xeloda (capecitabine) oxaliplatin
Product reference	Avastin: Ro 4876646 Xeloda: Ro 091978
Procedure number	Not applicable
Marketing authorisation holder(s)	Roche Slovakia s.r.o., Cintorínska 3/A, 811 08 Bratislava, Slovakia, phone +421252638201, fax +421252635014
Joint PASS	No
Research question and objectives	To assess the efficacy of bevacizumab in combination with capecitabine and oxaliplatin as measured by progression-free survival. To assess the efficacy of bevacizumab in combination with capecitabine and oxaliplatin as measured by response rate. To assess the safety profile of bevacizumab in combination with capecitabine and oxaliplatin as first line treatment of metastatic cancer of the colon and rectum.
Country(-ies) of study	Slovakia
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30-DEC-2014 [redacted]

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1. ABSTRACT

Title

An open label study of the effect of first line treatment with bevacizumab in combination with capecitabine and oxaliplatin on progresion-free survival in patients with metastatic cancer of the colon and rectum

Keywords

Metastatic colorectal cancer, bevacizumab, capecitabine, oxaliplatin

Rationale and background

Bevacizumab in combination with oxaliplatin-based chemotherapy became one of the standard options in the first line treatment of metastatic colorectal cancer. Rationale for this non-interventional study was to provide for the first time data on efficacy and safety of this treatment option in the multicenter setting in Slovakia.

Research question and objectives

Primary objective: to assess the efficacy of bevacizumab in combination with capecitabine and oxaliplatin as measured by progression-free survival

Secondary objectives: a) to assess the efficacy of bevacizumab in combination with capecitabine and oxaliplatin as measured by response rate

b) to assess the safety profile of bevacizumab in combination with capecitabine and oxaliplatin as first line treatment of metastatic cancer of the colon and rectum

Study design

This is an open label, phase IV non-interventional study.

Setting

Metastatic cancer of the colon or rectum

Subjects and study size, including dropouts

This is an open label, phase 4 study in one treatment arm.
This clinical trial requires 64 patients for statistical evaluation. Because we presume 10% of ineligibility, total 70 patients were planned to be accrued.

Variables and data sources

Variables: primary: time to progression, secondary: response rate, adverse events

Data sources: patient charts, case report forms

Results

A total of 68 patients were enrolled, 60 were evaluable for the primary endpoint analysis.

Median of the progression-free survival (PFS, primary endpoint) was 7,0 months, mean of the PFS was 8,8 months.

The best obtained response included complete remission in 6,7% (n=4) patients, partial remission in 41,7% (n=25) patients, response rate was 48,4%. No change was recorded in 28,3% (n=17) and disease progression in 23,3% (n=14) patients.

Safety: A total of 102 AEs were observed throughout the study, 3 (2,9%) of which were considered as serious AEs. Overall 47 (74,6%) patients were affected by AEs.

Discussion

Median progression-free survival, response rates and toxicity profile for the combination of bevacizumab in combination with capecitabine and oxaliplatin in this trial was comparable with other non-interventional studies with this treatment regimen.

Marketing Authorisation Holder(s)

Roche Slovensko, s.r.o., Cintorínska 3/A, 811 08 Bratislava, Slovakia

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2. LIST OF ABBREVIATIONS

Not applicable

3. INVESTIGATORS

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5. MILESTONES

Table 1 Study Milestones

Milestone	Planned Date	Actual Date	Comments
Start of data collection	October 1st, 2014	February 3rd , 2014	
End of data collection	April 30th, 2015	October 31st, 2014	
Registration in the EU PAS register	NA		
<Study progress report 1>	NA		
<Study progress report 1>	NA		
<Study progress report 1>	NA		
<Interim report 1>	NA		
<Interim report 1>	NA		
<Interim report 1>	NA		
Final report of study results	February 2nd, 2015	December 30th, 2014	

6. RATIONALE AND BACKGROUND

Saltz and collaborators(1) published first randomized phase III clinical trial of the effect of bevacizumab in combination with oxaliplatin-based chemotherapy on the progression-free survival (PFS) in patients with metastatic colorectal cancer . PFS, the primary endpoint of this clinical trial was improved for the combination bevacizumab+chemotherapy in comparison with chemotherapy alone. Bevacizumab in combination with oxaliplatin-based chemotherapy became one of the standard options in the first line treatment of metastatic colorectal cancer. Rationale for this non-interventional study was to provide for the first time data on efficacy and safety of this treatment option in the multicenter setting in Slovakia. Design of this non-interventional study was comparable with other published non-interventional studies in metastatic colorectal cancer.

7. RESEARCH QUESTIONS AND OBJECTIVES

Primary objective: to assess the efficacy of bevacizumab in combination with capecitabine and oxaliplatin as measured by progression-free survival

Secondary objectives: a) to assess the efficacy of bevacizumab in combination with capecitabine and oxaliplatin as measured by response rate

b) to assess the safety profile of bevacizumab in combination with capecitabine and oxaliplatin as first line treatment of metastatic cancer of the colon and rectum

8. AMENDMENTS AND UPDATES TO PROTOCOL

There was one amendment to the study protocol, one site was added and sample size was increased accordingly.

Table 2 Summary of Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	August 21st, 2012	Sample size, sites	Amendment	Addition of new site

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an open label, phase IV non-interventional study.

9.2 SETTING

Setting: metastatic cancer of the colon or rectum, first line of treatment

Locations: 10 oncology centers in Slovakia

Period of recruitment (planned): 24 months (Q2 2011 – Q2 2013)

First patient first visit: 15-JUL-2011

Last patient first visit: 05-FEB-2013

Last patient last visit: 03-FEB-2014

Period of data collection: 9 months (February 2014-November 2014)

9.3 SUBJECTS

Patients population: patients with histologically confirmed diagnosis of metastatic colorectal cancer, untreated with chemotherapy for metastatic disease (prior adjuvant chemotherapy for colorectal cancer is allowed), who are scheduled to start first line treatment with bevacizumab in combination with capecitabine and oxaliplatin

Inclusion criteria: a) written informed consent

b) all other criteria for inclusion must be in line with approved indication according to the current Summary of the Product Characteristics and the Prescription Limitation of the Ministry of Health, that was currently valid

Exclusion criteria: a) contraindications according to the current Summary of the Product Characteristics

b) signed informed consent is not available

9.4 VARIABLES

Primary: time to progression

Secondary: response rate, adverse events

9.5 DATA SOURCE AND MEASUREMENT

General procedures for the assurance of the data quality in clinical trials are described in Roche Standard Operational Procedures. Data from patients charts were recorded in Case Report Forms (CRF). Recording of exact and reliable data will be assured by the comparison and cross control of CRFs and patient charts during the monitoring visits (source data verification). Data from CRFs will be transferred into the clinical trial database.

9.6 BIAS

Not applicable

9.7 STUDY SIZE

This is an open label, phase 4 study in one treatment arm.
This clinical trial requires 64 patients for statistical evaluation. Because we presume 10% of ineligibility, total 70 patients will be accrued.
No hypotheses testing are planned in advance for this phase IV study. If they are done they will be data-dependent. Hence, the sample size determination was not based on a power analysis. Assuming 64 study subject in the analysis population and 40% observed response rate, the half width of the 95% confidence interval (maximum error) will be 13%.

Primary endpoint is to assess the efficacy of bevacizumab in combination with oxaliplatin and capecitabine as measured by progression-free survival.
Secondary endpoints are to assess the efficacy of bevacizumab in combination with oxaliplatin and capecitabine as measured by response rate and to assess the safety profile of bevacizumab when combined with oxaliplatin and capecitabine as first line treatment of metastatic cancer of the colon and rectum.
Kaplan-Meier estimates of time to disease progression will be calculated.
Both complete and partial response rates will be calculated and the two-sided 95% confidence intervals provided.

9.8 DATA TRANSFORMATION

Data entry: study personel in trial sites enters the data into the CRF

Data collection: collection of the data starts Responsible Monitor after the written instruction from the Clinical Trial Manager

9.9 STATISTICAL METHODS

9.9.1 Main Summary Measures

Progression-free survival: median, mean

Response rate: incidence rate

Adverse events: incidence rate

9.9.2 Main Statistical Methods

This is an open label, phase 4 study in one treatment arm.
This clinical trial requires 64 patients for statistical evaluation. Because we presume 10% of ineligibility, total 70 patients will be accrued.
Primary endpoint is to assess the efficacy of bevacizumab in combination with oxaliplatin and capecitabine as measured by progression-free survival.
Secondary endpoints are to assess the efficacy of bevacizumab in combination with oxaliplatin and capecitabine as measured by response rate and to assess the safety profile of bevacizumab when combined with oxaliplatin and capecitabine as first line treatment of metastatic cancer of the colon and rectum.
Kaplan-Meier estimates of time to disease progression will be calculated.
Both complete and partial response rates will be calculated and the two-sided 95% confidence intervals provided. No hypotheses testing are planned in advance for this phase IV study. If they are done they will be data-dependent. Hence, the sample size determination was not based on a power analysis.

Assuming 64 study subject in the analysis population and 40% observed response rate, the half width of the 95% confidence interval (maximum error) will be 13%.

9.9.3 Missing Values

Since this is a non-interventional study, missing data were not addressed.

9.9.4 Sensitivity Analyses

No sensitivity analyses were performed.

9.9.5 Amendments to the Statistical Analysis Plan

There were performed no statistical analyses not foreseen in the statistical plan or deviating from the statistical plan.

9.10 QUALITY CONTROL

General procedures for the assurance of the data quality in clinical trials are described in Roche Standard Operational Procedures. Data from patients charts were recorded in Case Report Forms (CRF). Recording of exact and reliable data will be assured by the comparison and cross control of CRFs and patient charts during the monitoring visits (source data verification). Data from CRFs will be transferred into the clinical trial database.

All Clinical Research Organisation relevant study staff was trained on Roche SOPs, study protocol and study processes before the start of study. Co-monitoring visits and quality checks were performed as described in the Roche Slovakia Standard Operating Procedure "Clinical Trials".

10. RESULTS

10.1 PARTICIPANTS

68 patients were enrolled into this trial. 63 patients were included in the final analysis, 60 patients were analyzed for the primary endpoint (progression-free survival).

10.2 DESCRIPTIVE DATA

Available baseline data:

Baseline	Mean	Standard

		deviation
Age (years)	60,08	10,38
Sex (men, women)	34	29
Height (cm)	169,79	8,43
Weight (kg)	78,53	17,62
Heart rate (bpm)	78,03	7,31
Systolic blood pressure (mmHg)	130,27	14,02
Diastolic blood pressure (mmHg)	80,40	7,43
Hemoglobin (g/l)	126,13	38,00
Leukocytes (G/l)	9,05	3,42
Thrombocytes (G/l)	363,02	149,69
Bilirubin (µmol/l)	9,56	5,17
Creatinine (µmol/l)	79,13	20,99
AST (µkat/l)	0,52	0,29
ALT (µkat/l)	0,49	0,27

10.3 OUTCOME DATA

There were 63 patients included in the final analysis (43 men and 29 women), 60 of them were analyzed for the primary endpoint.

10.4 MAIN RESULTS

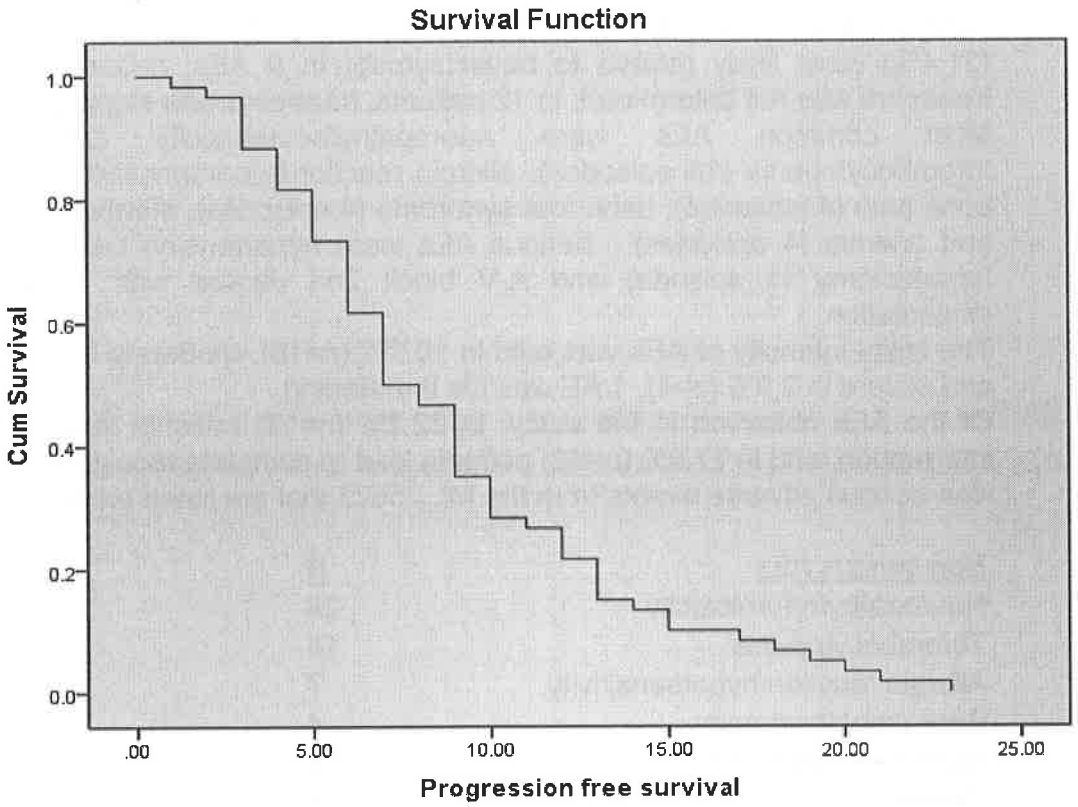
Progression free survival was defined as the time from randomization to progression or death during the study.
Median of the progression-free survival (PFS, primary endpoint) was 7,0 months (95% confidence interval 5,577-8,423 months), mean of the PFS was 8,8 months (95% confidence interval 7,572-10,095 months).

ML 25523 – Progression-free survival

Means and medians for PFS

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
8.833	.644	7.572	10.095	7.000	.726	5.577	8.423

a. Estimation is limited to the largest survival time if it is censored.



Response to treatment was evaluated by modified RECIST criteria
Complete remission – all lesions disappeared; Partial remission – decrease in sum of lesions size by more than 30%; No change – decrease in sum of lesions size less than in partial remission or by more than in disease progression; Disease progression – increase in sum of lesions size by more than 20% or new lesions.
The best obtained response included complete remission in 6,7% (n=4) patients, partial remission in 41,7% (n=25) patients, response rate was 48,4%. No change was recorded in 28,3% (n=17) and disease progression in 23,3% (n=14) patients.

10.5 OTHER ANALYSIS

Not applicable

10.6 ADVERSE EVENTS AND ADVERSE REACTIONS

Safety was evaluated according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTC-AE, version 4.0); part of screening examination was the complete patient history.

A total of 102 Adverse Events (AEs) were observed throughout the study, 3 (2,9%) of which were considered as serious AEs. Overall 47 (74,6%) patients

were affected by AEs. Fifty four (52,9%) of adverse effects were likely related to study treatment, 39 (38,2%) AEs were not related to study treatment. 32 AEs (31,4%) were likely related to bevacizumab. In 9 AEs, relationship to study treatment was not determined. In 12 patients, treatment was stopped due to AEs. Most common AEs were neuropathy/neurotoxicity (24 episodes), thrombocytopenia (14 episodes), allergic reaction/hypersensitivity (7 episodes), bone pain (4 episodes), hand-foot syndrome (4 episodes), diarrhea (4 episodes), and anemia (4 episodes). Serious AEs were hypertension crisis (1 episode), hepatectomy (1 episode) and A-V block 2nd degree with cardiostimulator implantation.
The initial intensity of AEs was mild in 15,7% (n=16), moderate in 63,7% (n=65) and severe in 3,9% (n=4). 1 AE was life threatening.
Of the AEs observed in the study, in 22,2% (n=12) patients lead to treatment interruption, and in 77,8% (n=42) patients lead to complete recovery.
Non-serious adverse events from the ML 25523 trial are listed below:

Non-serious AEs	N
Neuropathy/neurotoxicity	24
Thrombocytopenia	14
Allergic reaction/hypersensitivity	7
Back pain/chest pain	4
Hand-foot syndrome	4
Diarrhea	4
Anemia	4
Fever	3
Abdominal pain	3
Hypertension	3
Nausea/vomiting	3
Leucocytopenia	3
Thrombosis/thrombophlebitis	2
Acute respiratory infection	2
Hepatopathy	2
Constipation	2
Neutropenia	2
Fatigue	2
Urinary tract infection	1
GI toxicity	1
Toothache	1
Respiratory tract hemorrhage	1
Extravasation of contrast media leak	1
Progression of the hepatic lesions	1
Dyspnoe	1
Pancytopenia	1
Cardiotoxicity	1

Impaired vision	1

Regarding the biochemistry results, there was significant decrease in the leucocytes count (months 3,6,9) and thrombocytes count (months 3,6,9,12,15) and there was significant increase in bilirubin (months 3,6,9,12,15) and AST levels (months 9,12) in comparison to baseline.

10.7 KEY RESULTS

Median of the progression-free survival (PFS, primary endpoint) was 7,0 months (95% confidence interval 5,577-8,423 months), mean of the PFS was 8,8 months (95% confidence interval 7,572-10,095 months).
The best obtained response included complete remission in 6,7% (n=4) patients, partial remission in 41,7% (n=25) patients. No change was recorded in 28,3% (n=17) and disease progression in 23,3% (n=14) patients.

A total of 102 Adverse Events (AEs) were observed throughout the study, 3 (2,9%) of which were considered as serious AEs. Overall 47 (74,6%) patients were affected by AEs. Fifty four (52,9%) of adverse effects were likely related to study treatment, 39 (38,2%) AEs were not related to study treatment. In 9 AEs, relationship to study treatment was not determined. Most common AEs were neuropathy/neurotoxicity (24 episodes), thrombocytopenia (14 episodes), allergic reaction/hypersensitivity (7 episodes), bone pain (4 episodes), hand-foot syndrome (4 episodes), diarrhea (4 episodes), and anemia (4 episodes).

10.8 LIMITATIONS

There are some limitations of this study that need to be considered. Estimation of PFS is limited mainly by the fact that disease progression was not independently assessed and that the evaluation of response in Slovakia needs to be done at least once in 3 months. Because the study was performed mainly in major cancer centers, study population may not be truly reflective of an outpatient practice in Slovakia. Study sample was also relatively small. Finally, this was a non-interventional study and not a ramdomised trial, therefore the possibility of investigator bias must be considered.

10.9 INTERPRETATION

Oxaliplatin-based chemotherapy is one of the standard options for the patients with metastatic colorectal cancer. Combination of bevacizumab, oxaliplatin and capecitabine became a frequent option especially in the outpatient departments of Slovak cancer centers. Rationale for this non-interventional study was to

provide for the first time data on efficacy and safety of this treatment option in the multicenter setting in Slovakia. Overall, 68 patients were enrolled and 60 were analyzed for the primary endpoint. Data recorded at baseline included demographic data and medical history. At 3-monthly visits, study treatment, hematology, chemistry and response to study treatment were recorded. Adverse events during the trial were assessed using NCI-CTC-AE version 4.0.
Primary endpoint of this non-interventional trial was progression-free survival. Median of the progression-free survival (PFS, primary endpoint) was 7,0 months (95% confidence interval 5,577-8,423 months), mean of the PFS was 8,8 months (95% confidence interval 7,572-10,095 months). This was comparable with previously published data with bevacizumab in combination with oxaliplatin and capecitabine. We can just assume, what caused the fact, that numerically is median of PFS little bit lower than previously published data. There are several possible explanations: small sample size, selection bias (patients were included mainly in major cancer centers), disease progression was not independently assessed, premature stopping of bevacizumab along with chemotherapy due to AEs or at the discretion of the investigator.
Secondary endpoints were response rates and adverse events. The best obtained response included complete remission in 6,7% (n=4) patients, partial remission in 41,7% (n=25) patients, response rate was 48,4%. No change was recorded in 28,3% (n=17) and disease progression in 23,3% (n=14) patients. Response rates were comparable with published data in this setting. A total of 102 Adverse Events (AEs) were observed throughout the study, 3 (2,9%) of which were considered as serious AEs. Overall 47 (74,6%) patients were affected by AEs. Fifty four (52,9%) of adverse effects were likely related to study treatment, 39 (38,2%) AEs were not related to study treatment. Rates of the adverse events were comparable with other trials in this setting and no new safety signals were detected.

10.10 GENERALISABILITY

Not applicable

11. OTHER INFORMATION

Not applicable

12. CONCLUSION

Bevacizumab in combination with capecitabine and oxaliplatin demonstrated its efficacy and acceptable toxicity profile in the first line treatment of patients with metastatic cancer of the colon and rectum in this non-interventional trial setting. Results of this relatively small trial were comparable with the trials already published in this setting.

13. REFERENCES

1. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R et al. Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study J Clin Oncol 2008; 26 (12): 2013-2019. DOI: 10.1200/JCO.2007.14.9930
2. Van Cutsem E, Rivera F, Berry S, Kretzschmar A, Michael M, DiBartolomeo M et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol 2009; 20: 1842–1847. DOI:10.1093/annonc/mdp233
3. Bendell JC, Bekai-Saab T, Cohn AL, Hurwitz HI, Kozloff M, Tezcan H et al. Treatment Patterns and Clinical Outcomes in Patients With Metastatic Colorectal Cancer Initially Treated with FOLFOX–Bevacizumab or FOLFIRI–Bevacizumab: Results From ARIES, a Bevacizumab Observational Cohort Study. The Oncologist 2012; 17:1486-1495.DOI:10.1634/theoncologist.2012-0190
4. Kubala E, Bartos J, Petruzelka L, Prausova J, Benesova V, Gruna J et al. Safety and effectiveness of bevacizumab in combination with chemotherapy in elderly patients with metastatic colorectal cancer: Results from a large Czech observational registry. ASCO GI 2010, Abstr. No. 467.

APPENDICES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	ML 25523 v 1	4.3.2011	Protocol version 1
2	ML 25523 v 2	21.8.2012	Protocol version 2

ML 25523 Protocol version 1

ML 25523 Protocol version 2

ANNEX 2. ADDITIONAL INFORMATION

Not applicable