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RESEARCH REPORT NO. 1

Final Clinical Study Report – ML 25526 - An open label study of the effect of adjuvant treatment with capecitabine in combination with oxaliplatin on disease-free survival in patients with stage III colon cancer – Research report No. 1, April 4th, 2016

Study Sponsor(s)

Study Dates:	First Patient/Subject Entered: 28-OCT-2011
	Last Patient/Subject Entered: 2
	Data cut-off / LPLV:
	Date of early termination: not applicable
Trial Phase:	IV
Indication:	
Name of Principal Investigator:	Affiliation:
Assoc. Prof. Igor Andrašina, MD	
Sponsor's Signatory:	Not applicable

Personnel Responsible for Clinical and Statistical Analyses:

Katarina Zaleska

Assoc. Prof. Igor Andrašina, MD

GCP Compliance: **This study was conducted in accordance with the principles of GCP.**

Design of the ML 25526 trial:

	Screening	Adjuvant treatment capecitabine+oxaliplatin	Evaluation of efficacy and safety every 6 months
		←	→

3.2 DISCUSSION OF STUDY DESIGN

Not applicable.

3.3 ADMINISTRATIVE STRUCTURE

The study was sponsored by Roche Slovakia, who was responsible for the administration and conduct of the study procedures listed in Table 1. In addition, external organization were given roles and responsibilities for the administration or conduct of the study (see Table 1).

Table 1 Study Administrative Structure

Role/Responsibility	Company/Organization
Clinical study management	Roche Slovensko s.r.o., Cintorinska 3/A, 811 08 Bratislava, Slovakia
Monitoring	Calvin Company s.r.o.,Majerská 31, 821 07 Bratislava, Slovakia
Drug supply	As per standard commercial supply
Data management and statistical analysis	Calvin Company s.r.o.,Majerská 31, 821 07 Bratislava, Slovakia
Medical writing	Peter Pichňa, MD, Medical Manager, Roche Slovensko s.r.o., Cintorinska 3/A, 811 08 Bratislava

3.4 ETHICS AND STUDY CONDUCT

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP), Guidelines for Good Pharmacoepidemiology Practices (GPP) and according to the regulations and procedures described in the following sections of the protocol.

3.5.2 Exclusion Criteria

1. Contraindications according to the valid Summary of the Product Characteristics
2. Signed informed consent is not available

3.6 STUDY TREATMENTS

3.6.1 Dosage and Administration

This was a non-interventional trial, study drugs (capecitabine and oxaliplatin) were administered according to the Summary of the Product Characteristics.

3.6.2 Formulation and Packaging

This was a non-interventional trial, study drugs were available in standard commercial packaging.

3.6.3 Rationale for Dosage Selection

Not applicable, this was a non-interventional trial, study drugs (capecitabine and oxaliplatin) were administered according to the Summary of the Product Characteristics.

3.6.4 Method of Treatment Assignment

Not applicable

3.6.5 Blinding

Not applicable

3.6.6 Criteria for Dose Modification or Withdrawal from Treatment

Study drugs were administered according to the Summary of the Product Characteristics, patients were treated according to the standard of care.

3.6.7 Treatment Accountability and Compliance

Not applicable, this was a non-interventional trial.

3.7 CONCOMITANT MEDICATIONS

Concomitant medications used in clinical practice according to the Summary of the Product Characteristics were allowed. Concomitant medication was recorded in the Case Report Form.

3.8 ASSESSMENTS

3.9 DATA REPORTING AND ANALYSIS PLAN

3.9.1 Statistical Hypothesis and Planned Sample Size

This is an open label, phase 4 study, to assess effectiveness and safety profile of adjuvant XELOX chemotherapy in stage III colon cancer patients. One stage design will be used for patients accrual. The protocol will accrue up to 70 patients. Because we presume 10% of ineligibility, total 77 patients will be accrued. For this phase IV study, no hypothesis testing was planned. Sample size determination was not based on the analysis of statistical significance. With the recruitment of 77 patients and estimated analysis of 70 patients, there will be estimated probability of recurrence 0,74 (lower limit 0,62, upper limit 0,83) with 95% confidence interval.

3.9.2 Analysis Populations

Analyzed population was identical with the ITT population.

3.9.3 Efficacy Analysis

Primary efficacy endpoint was to assess the effectiveness of adjuvant XELOX in stage III colon cancer patients as measured by disease-free survival.

3.9.4 Pharmacodynamic and Pharmacokinetic Data Analysis

Not applicable.

3.9.5 Safety Reporting and Analysis

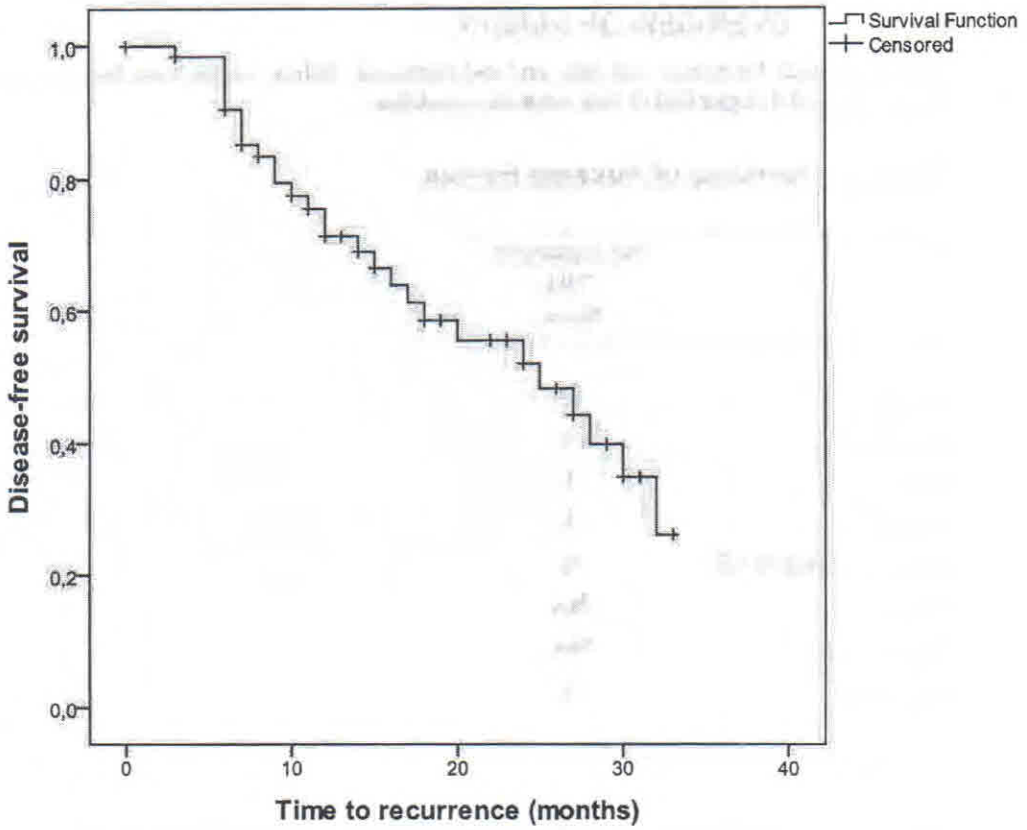
Safety assessments included adverse events (AEs) and standard laboratory assessments (see protocol Chapter 6).

3.9.6 Changes in Conduct of Study or Planned Analyses

Not applicable

4. RESULTS: STUDY POPULATION

76 patients were screened, 2 patients were screen failures, 74 patients were treated in this trial.



5.3 SECONDARY EFFICACY ENDPOINTS

There were no secondary efficacy endpoints in this non-interventional trial.

5.4 SUBGROUP AND EXPLORATORY ANALYSES

Not applicable

6. RESULTS: PHARMACODYNAMICS AND PHARMACOKINETICS

Not applicable

7.4 ADVERSE EVENTS BY INTENSITY

Number of patients with mild AEs: 18 (24,3%)

Number of patients with moderate AEs: 14 (18,92%)

Number of patients with severe AEs: 0

Number of patients with life threatening AEs: 1 (1,4%)

7.5 DEATHS

There was 1 death recorded during this trial, it was a death as a result of a reported serious adverse event (patient with cystic fibrosis and inflamed bronchiectasia died due to the respiratory failure). This serious adverse event was not related to the study treatment as assessed by the investigator.

7.6 SERIOUS ADVERSE EVENTS

There was 1 serious adverse event reported during this trial (patient with cystic fibrosis and inflamed bronchiectasia died due to the respiratory failure). This serious adverse event was not related to the study treatment as assessed by the investigator.

Progression of the underlying disease was not reported as an adverse event in the case when is evident that the symptoms are consistent with the definition of progression as defined in the RECIST criteria version 1.1.

There were 2 serious adverse events (breast cancer and bladder cancer) randomly captured during the final reconciliation. However, these SAEs developed more than 28 days after the last dose of study drugs and they were not related to study drugs as assessed by the investigators. According to the latest version of the protocol, not related SAEs must be collected and reported up to 28 days after the last dose of study drug. Therefore, these 2 SAEs were not recorded within the results of ML25526.

7.7 ADVERSE EVENTS THAT LED TO WITHDRAWAL OF STUDY TREATMENT

6 patients discontinued treatment for safety reasons (3 patients for thrombocytopenia, 1 patient for neuropathy, 1 patient for nausea and 1 patient for hypoproteinemia). There were no treatment discontinuations for non-safety reasons.

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7.12.2 Vital Signs

Heart rate and blood pressure were measured during baseline visit, they were not measured later during the trial.

8. DISCUSSION AND CONCLUSION

Colorectal cancer is one of the most frequent cancers in Slovak Republic (Healthcare Yearbook of Slovak republic, 2007). Adjuvant treatment is standard and well established treatment option in patients with stage III colon cancer. Efficacy and safety of capecitabine in combination with oxaliplatin was demonstrated in phase III clinical trial (Schmoll HJ, 2015).

ML 25526 was a non-interventional trial with the primary objective of assessing the effectiveness of adjuvant XELOX in stage III colon cancer patients measured by disease-free survival. 76 patients were screened and 74 patients were treated in this trial. Primary efficacy endpoint - disease-free survival was 25 months, with 95% confidence intervals 15,1 - 34,9 months. Due to much smaller sample size and the non-interventional design of this trial, it is difficult to compare it to the large randomized trials (Schmoll HJ et al.) with the different endpoints (e.g. 1 year, 2 years disease-free survival measured in %) in this patients population. Safety profile was also assessed as a secondary objective and it was as expected in this patients population. Purpose of this non-interventional open label trial - to obtain additional efficacy and safety data in Slovakia in general practice context – was fullfilled.

9. REFERENCES

1. De Vita VT et al., Cancer: Principles and Practice of Oncology, 1993, pp 1264-1332.
2. Healthcare Yearbook of Slovak Republic 2007, National Center for Healthcare Information, Bratislava 2008, pp. 40-41.
3. Twelves C et al, Capecitabine as adjuvant treatment for stage III colon cancer, N Engl J Med 2005, 352, 2696-2704.
4. Schmoll HJ et al., Capecitabine Plus Oxaliplatin Compared With Fluorouracil/ Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the NO16968 Randomized Controlled Phase III Trial, J Clin Oncol, 2015, 33, 3733-3740.