MOLOGEN AG

CLINICAL STUDY REPORT

A Phase 2, Randomized, Double-blind, Placebo-controlled, Multi-Center Clinical Study to Evaluate Efficacy and Safety of a Maintenance Therapy with Immunomodulator MGN1703 in Patients with Advanced Colorectal Carcinoma with Disease Control after Initial First-line Therapy (IMPACT Study)

Trial product:	MGN1703	
Indication:	Advanced colorectal carcinoma	
Phase of development:	II	
Sponsor	MOLOGEN AG Fabeckstraße 30 14195 Berlin Germany	
Study period:	First patient enrolled (informed consent): 15 June 2010 Last patient's last study treatment: 27 February 2013 Study discontinuation by protocol amendment: 16 April 2012	
Study protocol number:	MGN1703-C02	
EudraCT number:	2009-017432-40	
Sponsor's contact person: Manuel Schmidt Scientific Officer Telephone: +49 (30) 8417 8855 Facsimile: +49 (30) 8417 8850 E-mail: maschmidt@mologen.com		Sponsor's signatory: Dr. Alfredo Zurlo Chief Medical Officer Telephone: +49 (30) 8417 880 Facsimile: +49 (30) 8417 8850 E-mail: zurlo@mologen.com
Date of report: 17 January 2014		

This study, including the archiving of essential documents, was performed in compliance with
Good Clinical Practice (GCP) and with all relevant laws and regulations

SYNOPSIS

Name of Sponsor/Company: MOLOGEN AG Fabeckstraße 30 14195 Berlin, Germany	Individual Study Table Referring to Part of the Dossier Volume Page	*(For National Authority Use only)*
Name of Finished Product: *not yet allotted*		
Name of Active Ingredient: MGN1703		

Study title

A Phase 2, randomized, double-blind, placebo-controlled, multi-center clinical study to evaluate efficacy and safety of a maintenance therapy with immunomodulator MGN1703 in patients with advanced colorectal carcinoma with disease control after initial first-line therapy (IMPACT Study)

Indication

Advanced colorectal carcinoma (American Joint Committee on Cancer (AJCC) Stage IV) with disease control after initial first-line therapy.

Principal Investigator

Prof. Dr. med. Hans-Joachim Schmoll
Specialist for Internal Medicine, Haematology, Internal Oncology
Director of the University Hospital for Internal Medicine IV, Oncology/Haematology,
Martin Luther University Halle–Wittenberg, Germany
Telephone +49 (345) 557 2924. E-mail joachim.schmoll@medizin.uni-halle.de

Study centres

A total of 59 patients were recruited at 22 centres (6 sites in Austria, 18 patients; 1 site in France, 1 patient; 12 sites in Germany, 36 patients; 3 sites in Russia, 4 patients).

Test substance

MGN1703 (dSLIM-30L1 = double-Stem-Loop Immunomodulator 30L1), solution in Dulbecco's phosphate-buffered saline, administered subcutaneously at a dose level of 60 mg twice a week.

Reference substance

Matching placebo administered in an identical manner.

Duration of the study for each patient

The patient received study treatment until disease progression (or withdrawal for whatever other reason). The planned total study duration was 144 weeks including surveillance. If the patient dropped out before reaching a treatment duration of 144 weeks, then surveillance for up to a maximum total of 144 weeks followed. If the treatment of the patient lasted longer than 144 weeks, there was no further surveillance, but treatment continued until progression. At the time of reporting, four patients are receiving continued off-study treatment on a compassionate basis.

Objectives

Primary objective: To demonstrate that the efficacy of MGN1703 in the maintenance treatment of patients with advanced colorectal carcinoma with disease control after initial first-line therapy is superior to that of placebo, according to the criterion of median progression-free survival.

Secondary objective: To demonstrate that further efficacy variables support the finding from the primary objective and to assess the safety of the trial drug.

Methods

This was a randomised, double-blind, multi-centre study. Patients with advanced colorectal carcinoma who showed with disease control after initial first-line therapy (oral or intravenous fluoropyrimidines/leucovorin, irinotecan or oxaliplatin with or without a standard dose of bevacizumab, lasting 4.5–6 months) received maintenance treatment with MGN1703 or placebo (randomised, 2:1). Patients were to have histological confirmation of colorectal carcinoma, radiological confirmation of unresectable advanced colorectal carcinoma before initial first-line therapy, performance status 0 or 1 and adequate organ function.

Number of subjects planned and analysed

Originally planned: 129 patients (86 in the MGN1703 group, 43 in the placebo group)

Actually treated: 59 patients (43 in the MGN1703 group, 16 in the placebo group)

The smaller number treated than planned was due to the early termination of recruitment.

Criteria for evaluation

Efficacy: Evaluation of treatment efficacy in terms of median progression-free survival (PFS) in both treatment groups (primary efficacy variable), PFS from the start of induction therapy, PFS rates at various time points (12, 18 and 24 weeks after treatment start, and then every 12 weeks until treatment stop), median overall survival (OS) and OS from the start of induction therapy, OS rates at the same time points, objective response rate (ORR), and duration of response as time from initial determination of response to progressive disease, dynamic of clinical and laboratory signs, quality of life.

Safety: Incidence of adverse events (AEs) graded according to Common Terminology Criteria for AEs version 4.0; changes in clinical and safety laboratory test results, and autoimmunity of MGN1703 in terms of rheumatoid factor, antinuclear antibodies, and anti-double-stranded-DNA antibodies were monitored throughout the study.

Statistical methods

Efficacy: The primary endpoint was median PFS. The level of significance was α = 5%. PFS was compared between the treatment groups by the Kaplan–Meier method. Other variables – OS, OS from the start of induction therapy, ORR, and duration of response as time from initial determination of response to progressive disease – were compared in a similar manner. Standard immunological standard markers were analysed, and quality of life was assessed by the QLQ-CR29 and QLQ-C30 questionnaires.

Safety: All subjects who received at least one dose of the randomised study treatment were included in the safety and autoimmunity analyses. Safety was assessed by the incidence and type of adverse events, including those related to laboratory values; vital signs, electrocardiography and autoimmunity variables and results of physical examination were likewise monitored.

Results: Study population and treatment compliance

The patients' demographic and baseline data revealed no unexpected features, and the two treatment groups were well matched in respect of these and of their medical history and pre-treatment. There were no issues of inadequate compliance with study treatment.

Results: Efficacy and immunology

In the primary (intention-to-treat) analysis, MGN1703 improved PFS, with a hazard ratio of 0.55 (CI 0.3–1.0; $p = 0.04$) as assessed by the local investigator and 0.56 (95% confidence interval (CI) 0.29–1.08; $p = 0.07$) as assessed by independent radiological review. MGN1703 significantly improved PFS as measured from the start of induction therapy, compared with placebo (local assessment, HR 0.50 with CI 0.31–1.02 and $p = 0.02$; independent review, HR 0.49 with CI 0.26–0.94 and $p = 0.03$). At the time of the final analysis, OS data were still incomplete after a median follow-up of 17.7 months. Three patients in the MGN1703 group had a confirmed objective tumour response during maintenance treatment, observed respectively 3, 9 and 9 months after randomisation. These three patients, plus a fourth patient in complete response after induction chemotherapy, remain stable without relapse (treatment duration more than 16–30 months) at the time of this report. Results in the per-protocol population, and in subsets of patients who showed at least partial response in induction therapy, supported those of the intention-to-treat analysis, giving clearer indications of an advantage of MGN1703 over placebo.

A more pronounced effect of MGN1703 on PFS (compared with placebo; statistically significant at the descriptive level) was observed (i) in patients with greater than median tumour-size reduction, (ii) in those with carcinoembryonic antigen within the normal range following induction therapy, and (iii) in those with activated natural killer T cells ≥3.08%. The quality-of-life analysis was inconclusive owing to the small number of patients.

Results: Safety

The administrations were generally well tolerated. Some adverse event types (back pain, diarrhoea, headache, ileus and oral herpes) and event-associated SOCs ('gastrointestinal disorders' and 'general disorders and administration site conditions') were encountered more frequently in the MGN1703 group than in the placebo group, though this must be interpreted in the light of the (nearly threefold) greater size of the MGN1703 group and their longer treatment duration. Almost all severe (Grade 3 or 4) adverse events were considered unrelated, or unlikely to be related, to the study treatment. One patient was withdrawn from the study because of an adverse event, Grade 3 sensory polyneuropathy, after treatment with MGN1703 for 2.7 months; the event was considered to be possibly related to the study treatment. Another patient developed mild to moderate atypical pneumonia for a total of 42 days leading to treatment stop and to hospitalisation for 4 days, and which resulted in a report of an SAE/SUSAR. The patient did not restart MGN1703 treatment, since the patient showed disease progression as well; the patient was withdrawn from the study because of the disease progression, the SAE and intolerable toxicity, having received MGN1703 for 1.81 months. No other patients were withdrawn because of a drug-related adverse event of any kind. Apart from the above-mentioned SAE atypical pneumonia no further MGN1703-related SAE was reported in the study.

Vital signs, body weight, physical examination, ECG, performance status and assessment of local tolerability and laboratory values raised no concern about the tolerability of the treatment with MGN1703.

Conclusions

The treatment with MGN1703 showed a hazard ratio for the primary endpoint (progression-free survival) of 0.55 (investigator assessment) and 0.56 (independent radiological review). At the time of reporting, four patients remain stable without relapse (treatment duration up to 30 months). A more pronounced effect of MGN1703 on progression-free survival (compared with placebo) was observed in subgroups of patients with greater than median tumour-size reduction and carcinoembryonic antigen concentrations within normal ranges following induction therapy, and in patients with activated natural killer T cells ≥3.08%. Overall survival results were still incomplete at the time of this analysis. The treatment with MGN1703 was found to be safe and well tolerated. No unexpected adverse events related to the study treatment were reported.

DATE OF REPORT: 17th January 2014