2. Synopsis

Clinical Study Report Synopsis: Study H3E-MC-S077

Title of Study: *A Feasibility study of Pemetrexed single agent and folic acid given as neoadjuvant treatment in patients with resectable rectal cancer*	
Number of Investigator(s): This single-center study included one principal investigator.	
Study Center(s): This study was conducted at one study center.	
Publication(s) Based on the Study: Journal of Clinical Oncology ASCO 2009 Abs No e15121	
Length of Study: Date of first patient enrolled: 26 Jun 2006 Date of last patient completed study: 05 Jun 2008	**Phase of Development:** II

Objectives:

Primary: To evaluate the feasibility of three neo-adjuvant cycles of single agent Pemetrexed at 500 mg/m^2 q3w prior to surgery with or without radiotherapy in patients with resectable rectal cancer. Feasibility was defined as the ability to receive the total planned dose of Pemetrexed (i.e. 3 doses of 500 mg/m^2 = 1500 mg/m^2) administered over a period of no more than 9 weeks.

As secondary objectives, the following items were evaluated:

- Pathological response rate (pCR)
- Proportion of patients with sphincter saving surgery
- Proportion of patients with complete tumor resection rate (CTRR)
- Evaluation of qualitative and quantitative toxicities including rate of postoperative complications (e.g., bleeding, anastomosis leakage, serious infection) from beginning of study treatment until the 30 day postoperative visit
- Folate tissue levels, comparisons of before vs. after folic acid dosing and tumor vs. normal mucosa
- Correlation between mTHF and serum Hcy levels.
- Correlation of folate gene polymorphisms and microarray signature profiles with clinical outcome and toxicity profiles

Study Design: This was a single center open-label feasibility study of Pemetrexed (at 500 mg/m^2) single agent with folic acid as neoadjuvant treatment, given on day 1 of 3 consecutive 3-week treatment cycles, in 40 chemo-naive patients with newly diagnosed operable rectal cancer.

Number of Patients:

Planned: 40 patients were planned in order to have 36 eligible patients
Treated (at least 1 dose): 37
Completed: 37

Diagnosis and Main Criteria for Inclusion:

1. Pathological or cytological diagnosis of adenocarcinoma of the rectum with no prior therapy for rectal cancer. Patients must have operable rectal cancer that was amenable to curative surgery.
2. Adequate organ function and performance status (PS): absolute neutrophils count (ANC) $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin ≥ 9 g/dL, bilirubin ≤ 1.5 times the upper limit of normal ($\times$ ULN), alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 3.0 \times$ ULN, calculated creatinine clearance (CrCl) ≥ 45 mL/min, and PS ≤ 1.
3. Patients were excluded if they had a second primary malignancy or if they had any medical history (e.g. significant neurological or mental disorder including seizures or dementia, active infection including HIV, cardiac disease…) that was translated into an inability or unwillingness to comply with protocol requirements.

Study Drug, Dose, and Mode of Administration:

Pemetrexed at 500 mg/m^2, given as a 10-minute IV on day 1 of 3 consecutive 3-week treatment cycles with standard co-medication (vitamin B_{12} - dose of 1000 µg, folic acid - dose of 800 µg, and dexamethasone).

Duration of Treatment:

The treatment period was defined by the first administration of study drug and ends after surgery (= study treatment). A follow-up visit was performed 30 days (± 7 days) after surgery / treatment period.

Variables:

Efficacy:

- Feasibility was defined as the ability to receive the total planned dose of Pemetrexed (i.e. 3 doses of 500 mg/m^2 = 1500 mg/m^2) administered over a period of no more than 9 weeks.
- Pathological complete response was defined as absence of any tumor cells.
- Sphincter-saving surgery: Sphincter function can be preserved after surgery.
- Complete Tumor Resection Rate: Radical tumor excision by total or partial resection of the mesorectum (TME) including safety margins (R0), preserving the anal sphincter system.

Safety: Evaluation of qualitative and quantitative toxicities including rate of postoperative complications.

Bioanalytical:

- Biopsies of normal mucosa and tumor tissue were taken: folate levels and gene expressions were measured.
- Serum total folate, homocysteine and vitamine metabolites were evaluated.

Evaluation Methods:

Statistical:

Efficacy: The primary objective of feasibility was explored by evaluating the proportion of patients who receive the planned total dose.

We assumed that at least 85% of patients would receive the planned total dose (research hypothesis). We would not accept if less to or equal than 60% of patients receive the planned total dose (null hypothesis).

Safety: All patients who received at least one dose of Pemetrexed were evaluated for safety.

Bioanalytical: Blood was collected for serum total folate samples and homocysteine and vitamine metabolite samples and tissue samples for exploratory translational research.

Summary:

- A total of 37 patients entered the study and all of them were qualified for efficacy and safety analyses. All of them underwent surgery. 28 patients received radiotherapy (RT) following chemotherapy. Patient characteristics are summarized in the following table.

	Total N=37
Age, year (SD)	60.3 (11.5)
Male, n (%)	26 (70.3)
Origin Caucasian, n (%)	36 (97.3)
Performance Status ECOG 0, n (%)	37 (100)

- All patients were able to receive 3 cycles of chemotherapy. 33 patients (89.2%, 95% CI 74.6 to 97) completed their planned dosage in time. All patients underwent R0 resection. One pathological proven complete response was evaluated. 11 out of 13 planned patients had a rectum amputation. All others, except one patient, received sphincter saving surgery.
- No dose reduction or study-drug related SAE was seen. The only grade 3 and 4 toxicities (neutropenia) occurred in 7 patients (18.9%).
- Postoperative complications occurred in 62 % of the patients.

Summary of adverse events [n (%)]

Patients with at least one SAE [1]	17 (45.9%)
Patients with at least one SAE with outcome death [1]	0 (0.0%)
Patients with at least one SAE possibly related to SD [1]	0 (0.0%)
Patients with at least one SAE possibly related to SD or PP [1]	16 (43.2%)
Patients with at least one AE leading to treatment discontinuation	0 (0.0%)
Patients who died [1]	0 (0.0%)
Patients with at least one TEAE [1]	37 (100.0%)
Patients with at least one TEAE possibly related to SD [1]	34 (91.9%)
Patients with at least one TEAE possibly related to SD or PP [1]	35 (94.6%)
Patients with at least one AE occurred between patient consented and first infusion	7 (18.9%)

Abbreviations: SAE = serious adverse event; SD = study drug; PP = protocol procedure; AE = adverse event; TEAE = treatment-emergent adverse event; n = number of patients.

[1] Summaries include those events that occurred during the study treatment period or within 30 days from the end of treatment period.

Pharmacogenomics data and folate levels are collected but results are not yet available.

Conclusions:

This explorative study suggests that the administration of 3 cycles of pemetrexed is feasible and well tolerated within a multimodality treatment strategy.