

CINATRA: Chromosomal Instability and Anti-Tubulin Response Assessment: A phase 2 study of Epo906/patupilone in metastatic colon carcinoma in patients with microsatellite instability or chromosomal instability

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1 CINATRA synopsis

Study Title	Chromosomal Instability and Anti-Tubulin Response Assessment: A phase 2 study of Epo906/patupilone in metastatic colon carcinoma in patients with microsatellite instability or chromosomal instability
Short Title	CINATRA
Start and End Dates of Study	June 2007 –
Drug Description and dose	Epo906/patupilone: starting dose 8mg/m ²
Primary Objectives	To determine the anti-tumour activity of Epo906 administered to patients with metastatic colorectal cancer.
Primary Endpoint	i. 3-months progression-free survival
Secondary Endpoints	ii. Overall survival, response rate, tumour control rate iii. 3-months PFS stratified by MSI and CIN status iv. Incidence of serious toxicity with Epo906 therapy v. Quality of life parameters
Clinical Phase	Phase 2
Study Design	Single-arm multi-centre study investigating Epo906 in metastatic or locally recurrent CRC in genetically unselected patients, followed by recruitment of patients selected for MSI positive (MSI+) tumours
Number of patients	Cohort A: 75 patients Cohort B: 35 patients
Inclusion Criteria	vi. Histologically confirmed metastatic (Stage IV) or locally recurrent carcinoma of the colon or rectum vii. Prior therapy with oxaliplatin, 5-fluoropyrimidine and irinotecan viii. Availability of paraffin embedded tumour tissue for analysis of MSI and CIN status ix. Male or female, 18 years of age or older x. Life expectancy of 12 weeks or greater xi. ECOG performance status 0 or 1 xii. Clinically and/or radiographically documented measurable disease xiii. Adequate liver function xiv. Adequate haematological function xv. Serum creatinine ≤ 130 $\mu\text{mol/L}$ xvi. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures xvii. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrolment, according to GCP, and national/local regulations xviii. For Cohort B, all patients must have tumours which are MSI positive by IHC
Cohort A	Genetically unselected patients with metastatic CRC refractory to 5-FU/capecitabine, oxaliplatin and irinotecan

Cohort B

Patients, refractory to 5-FU/capecitabine, oxaliplatin and irinotecan, with MSI+ disease determined by IHC on primary tumour sections using 3 antibodies.

2 Study rationale

2.1 Introduction

Colorectal cancer (CRC) remains a major health burden with more than one million cases worldwide in 2002, the majority of which occurred in the developed world. While strides have been made in the treatment of CRC, the disease-specific mortality remains at about 40% {Cancer Research UK, 2006 #59}.

Despite intensive research, there are currently only four cytotoxic agents with confirmed activity in metastatic colorectal cancer (CRC): 5-fluorouracil/capecitabine, irinotecan, oxaliplatin and mitomycin-C. Most other commonly used cytotoxic agents, including taxanes, have produced poor results in CRC. Targeted therapies, while demonstrating some effectiveness, have not been endorsed by NICE {NICE, 2006 #58}.

Chemotherapy has extended median survival in the metastatic setting from 6 months in the mid-1990s to 2 years {Meyerhardt, 2005 #13}, but remains predominantly palliative. Following 2-3 lines of treatment for metastatic CRC, currently the options are either Phase 1 studies for patients of good performance status or palliative care. The addition of further active chemotherapy schedules is central to improving survival and quality of life.

2.2 Rationale for Cohort A: results of Epo906/patupilone in phase 1

Recently, a novel taxane, Epo906/patupilone (an epothilone B), with a similar mode of action to paclitaxel has demonstrated promising activity in the second/third line setting. A phase 1 multi-centre trial in patients with metastatic colorectal cancer who relapsed after or were refractory to up to 4 prior chemotherapy regimens were treated with Epo906 at 3 different dose schedules {Casado, 2006 #50}. Four partial responses and 13 patients with stable disease were documented of 44 patients enrolled in the study. This is equivalent to a tumour control rate of 39%. These rates are similar to the registration studies of 5-FU and oxaliplatin in the second line setting {Rothenberg, 2003 #67} and panitumumab in the third line setting {Peeters, 2006 #56} which led to FDA licensing, and superior to other taxanes in stage IV CRC (see below).

The optimal dose schedule determined from this study was 10mg/m² administered as a bolus treatment every 3 weeks, although higher rates of diarrhoea were seen at this dose in heavily pre-treated patients, 15-20% of patients experienced grade 3 diarrhoea. 6% experienced grade 3 nausea and vomiting, other grade 3 toxicities were uncommon. No patient experienced more than Grade 2 peripheral neuropathy (Grade 1 peripheral neuropathy occurred in 20-25% of patients, Grade 2 in 10-12%).

Therefore, Epo906 appears to be a promising novel agent in the management of colorectal cancer in the third line setting requiring further investigation.

2.3 Rationale for Cohort B: a possible link between genomic instability and taxane sensitivity

Despite good activity of taxanes in breast and other cancers, the previous experience with taxanes in CRC has been very disappointing. In the case of docetaxel, combined analysis of all published Phase I/II studies in unselected patients with CRC showed minimal activity: 3 of 39 patients benefited (defined as either stable disease during treatment, minor or partial responses) {Extra, 1993 #45} {Seibel, 1999 #47} {Blaney, 1997 #46} {Taguchi, 1994 #48} {Pazdur, 1994 #49}, and studies with paclitaxel have produced equally poor responses. It is conceivable that the underlying reason for taxanes sensitivity in the few cases of CRC described above lies in genetic differences between these and taxane resistant CRCs.

In CRC, two major types of genomic instability are recognised as alternative mechanisms of carcinogenesis. The more common of these, chromosomal instability (CIN is poorly defined as the presence of multiple structural or numerical chromosome changes in tumour cells, and, in practice, is often inferred from the finding of aneuploidy and/or polyploidy on flow cytometry {Miyazaki, 1999 #63}. Microsatellite instability (MSI) is defined as instability at two or more standard microsatellite markers {Boland, 1998 #2}, and these CRC are usually characterised by a near-diploid chromosome set {Aaltonen, 1993 #60; Ionov, 1993 #61}. MSI and CIN are frequently held to be mutually exclusive, with microsatellite stable (MSI-) tumours deemed CIN+ {Lengauer, 1998 #62}.

The “Spindle Checkpoint” is a complex, evolutionary conserved mechanism to ensure the fidelity of chromosome separation during cell division. Recent work in our laboratory and others has demonstrated that genes involved in the spindle checkpoint, when disrupted by RNA interference promote chromosomal instability {Swanton, 2006 #1}. Disruption of these genes also promotes taxane resistance *in vitro* {Anand, 2003 #7; Cahill, 1998 #8; Sudo, 2004 #9; Wang, 2004 #52}. Further, MSI+ colorectal cancer cell lines are significantly more sensitive to paclitaxel than colorectal cancer cells with high levels of CIN, and MSI+ tumour xenografts are sensitive to paclitaxel or epothilone B.

Overexpression of Aurora Kinase A (involved in the spindle checkpoint) is observed in approximately 60% of breast cancers and over 50% of colon cancers, and promotes spindle checkpoint inactivation, paclitaxel resistance and aneuploidy {Anand, 2003 #7; Bischoff, 1998 #22; Sakakura, 2001 #24; Zhou, 1998 #23}. Similar findings linking the spindle checkpoint and taxane sensitivity have also been made in lung cancer cell lines, where an impaired mitotic spindle checkpoint leads to higher resistance to taxane induced apoptosis {Masuda, 2003 #21}. Lastly, it has been established that colorectal cancer cell lines with CIN but not MSI fail to undergo mitotic arrest in response to spindle damage {Cahill, 1998 #8} while CIN was consistently associated with loss of function of a mitotic checkpoint that was in some cases correlated with mutations in the spindle checkpoint regulator Bub1. It is therefore conceivable that colorectal cancers with microsatellite instability, a functional spindle checkpoint and consequent minimal chromosomal aberrations may be sensitive to microtubule inhibitors.

We propose that the same processes promoting the generation of CIN also result in relative resistance to microtubule inhibitors, and near diploid MSI+ CRC in which these pathways are intact are more sensitive taxane therapy.

2.4 Summary

CINATRA is a phase 2 study which aims to assess the activity of Epo906 at a starting dose level of 8mg/m² every three weeks in two cohorts of patients: the first (Cohort A), will recruit all patients (unselected for MSI or CIN) who have progressed on previous 5-FU, Oxaliplatin and Irinotecan containing regimens fulfilling the inclusion criteria. Cohort B will recruit patients with MSI+CRC (determined by immunohistochemistry and meeting the same inclusion criteria as Cohort A) to address if there is a differential activity of Epo906 in CIN+ and MSI+ CRC. Patients in cohort B will have their APC status assessed to determine if APC mutations influence response to EPO906 in comparison to MSI+/APCwt patients.

3 Objectives of the trial

3.1 Primary objective

To determine the anti-tumour activity of Epo906 administered to patients with metastatic colorectal cancer.

3.2 Secondary objectives

To determine the effect of CIN and MSI on the efficacy of Epo906 as an anticancer agent, assuming that CIN+ CRC will not benefit while MSI+ patients will benefit. Further assessment of response in MSI+ patients according to APC status.

To describe the safety of Epo906 and quality of life benefits associated with treatment

To correlate other genetic variation with outcome from metastatic or locally recurrent CRC or therapy with Epo906, e.g. β -catenin, Kras, Braf mutations, copy number polymorphisms, LOH.

To retrospectively assess the response to prior treatment in relation to MSI and CIN status, particularly with reference to response to Irinotecan and Oxaliplatin containing regimens.

4 Trial design

This is a single-arm multi-centre study investigating Epo906 in metastatic or locally recurrent CRC in genetically unselected patients, followed by recruitment of patients selected for MSI positive (MSI+) tumours. Outcomes in MSI+ tumours will be compared to those in CIN+ tumours. The primary endpoint is 3-months progression-free survival.

Cohort A will consist of 75 genetically unselected patients who meet the patient selection criteria. This cohort is expected to include 65 – 70 patients with MSI- tumours, and 5 – 10 patients with MSI+ tumours. Cohort B will be recruited once recruitment to Cohort A has stopped, and consist of 35 patients who meet the patient selection criteria and whose tumours are MSI+ on IHC. All patients will receive 8 cycles of Epo906 unless the indications for stopping are met. Archival tumour material and fresh frozen tumour biopsy (following informed consent) from each patient will be assessed for CIN or MSI: for Cohort A, assessment will be retrospective prior to the interim and final analyses; for Cohort B, MSI status will be assessed prospectively as an entry requirement. In the final analysis, the endpoints

will be assessed in unselected patients (Cohort A), and comparing CIN+ to MSI+ patients (Cohorts A and B).

Interim safety analysis will be performed by an independent data monitoring committee (IDMC) following recruitment of the first 30 patients. There is scope to reduce the treatment dose to $6\text{mg}/\text{m}^2$ (with escalation to $8\text{mg}/\text{m}^2$ after 4 cycles in those who tolerate $6\text{mg}/\text{m}^2$) if excessive toxicity is encountered at this point.

Patients with MSI may be pre-selected, i.e. screened for MSI status prior to commencement of recruitment into Cohort B, using immunohistochemistry as described in section. Patients offered such pre-screening when they are enjoying a period of remission from previously documented metastatic CRC will be consented using a separate consent form.

Any patients lost to follow-up or ineligible after enrolment will be replaced; attempts will be made to replace patients in whom it is not possible to evaluate the primary endpoint.

4.1 Patient selection criteria

4.1.1 Inclusion criteria

- Histologically confirmed metastatic or locally recurrent carcinoma of the colon or rectum
- Prior therapy with oxaliplatin, 5-fluoropyrimidine and irinotecan
- Availability of paraffin embedded tumour tissue for analysis of MSI status and CIN
- Male or female
- 18 years of age or older
- Life expectancy of 12 weeks or greater
- ECOG performance status 0 or 1
- Clinically and/or radiographically documented measurable disease
- Adequate liver function:
 - i. Serum aspartate transaminase (AST) ≤ 5 x upper limit of normal (ULN)
 - ii. Serum alanine transaminase (ALT) ≤ 5 x ULN
 - iii. Serum alkaline phosphatase (ALP) < 5 x ULN
 - iv. Total serum bilirubin < 1.5 x ULN
 - v. Prothrombin time (PT) ≤ 1.5 x ULN
- Adequate haematological function:
 - i. Absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$
 - ii. Platelets $\geq 100,000/\mu\text{L}$
 - iii. Haemoglobin ≥ 9.0 g/dL
- Serum creatinine ≤ 130 $\mu\text{mol}/\text{L}$
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures
- Prior radiotherapy or colostomy are allowed

- Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects prior to enrolment
- For Cohort B, all patients must have tumours which are MSI positive by IHC

4.1.2 Exclusion criteria

- Persistent toxicity from previous treatment. Neurotoxicity from prior oxaliplatin must have resolved to at least grade 1.
- Diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell or squamous cell carcinoma of the skin, or adequately treated in-situ cervical cancer
- Any of the following within the 12 months prior to study drug administration
 - Myocardial infarction or severe/unstable angina,
 - Coronary/peripheral artery bypass graft
 - Symptomatic congestive heart failure
 - Cerebrovascular accident or transient ischemic attack
 - Pulmonary embolism
- Pregnancy or breastfeeding
- Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study