The UCGI 28 PANIRINOX trial - a randomized phase II study assessing Panitumumab + FOLFIRINOX or mFOLFOX6 in RAS and BRAF wild type metastatic colorectal cancer patients (mCRC) selected from circulating DNA analysis

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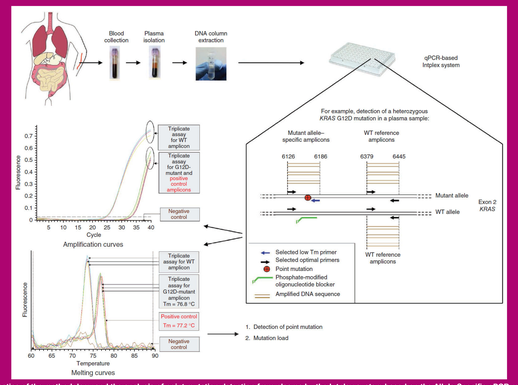
Background and rationale

- A majority of patients with mCRC are not suitable for potentially curative resection and their management consists in palliative-intended chemotherapy (CT) [1].
- Nevertheless, it is described that in patients who achieve complete response (CR) with CT alone or after multimodality treatment, median overall survival is significantly longer than in other patients [2,3].
- In combination with cytotoxic doublet, anti-EGFR antibodies appear to be the biological agents of choice in order to reach the best response rate as long as tumors are RAS wild-type [4-6]. In this setting, FOLFOX plus panitumumab has become one of standard treatment since PRIME study results [7].
- In patients with good performance status, cytotoxic triplet combined to anti-EGFR therapies achieve impressive activity (>70% of objective response) and allow R0 secondary metastasectomies (rate from 28 to 35%) in several phase II studies [8-10]. Nevertheless, comparison of the association anti-EGFR with doublet versus triplet backbone is still missing.
- To determine RAS and BRAF mutational status, we have already demonstrated the clinical validity and utility of circulating DNA (ctDNA) analysis using IntPlex® method:
  - in a prospective multicenter study, gathering 106 mCRC patients before anti-EGFR therapy initiation, ctDNA was detected in 100% of patients. For the seven tested KRAS point mutations, the method exhibited 98% specificity and 92% sensitivity with a concordance value of 96% compared to tissue routine gold-standard methods. It also showed 100% specificity and sensitivity for the BRAF V600E mutation [11].
  - in a real-time blinded prospective multicenter clinical study, including 140 metastatic colorectal patients, we then concluded that ctDNA analysis advantageously reduced turnaround-time before result communication compared to tumour-tissue analysis (median time=2 days vs 12 days). When no threshold is applied, ctDNA analysis also revealed much more mutations thereby more accurately reflecting the real-time tumor biology [12].

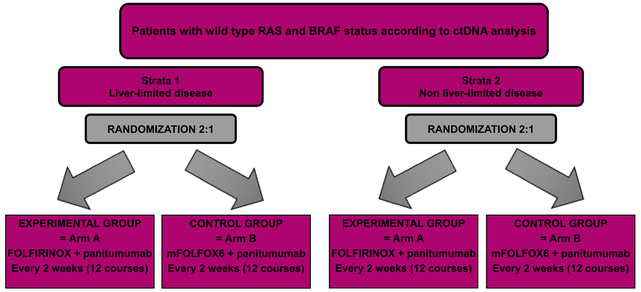


Schematics of the methodology and the analysis of point mutation detection from plasma by the Intplex system based on the Allele-Specific qPCR method Applied for KRAS G12D mutation, from Thierry et al, Nature Med 2014

- Selecting patients with this technology, we aim to investigate response rate and outcomes reached with panitumumab in combination with a standard (mFOLFOX6) or an intensified CT regimen (FOLFIRINOX) in RAS and BRAF wild-type (WT) metastatic patients.

Study design

- **PANIRINOX** (ClinicalTrials.gov ID: NCT02980510) is a national multicentric open-label randomized phase II trial assessing FOLFIRINOX + Panitumumab versus mFOLFOX6 + Panitumumab in metastatic colorectal cancer patients selected by RAS and BRAF status from ctDNA analysis.
- Patients will be randomized 2:1 to either FOLFIRINOX-panitumumab or mFOLFOX6-panitumumab with 12 planned cycles in each arm.
- For each arm, patients are stratified according to disease-extent (non/liver limited disease).
- Its design is summarized below:



In each arm, **Panitumumab** over 1 hour at 6mg/kg every 2 weeks on day 1 before:

-FOLFIRINOX : oxaliplatin 85mg/m² IV infusion over 2 hours immediately followed by folinic acid 400mg/m² given as a 2-hour IV infusion with the addition, after 30 minutes of irinotecan 150mg/m² given as a 90-minute intravenous infusion through a Y-connector immediately followed by Fluorouracil 400mg/m² IV bolus then 5-FU 2400 mg/m² over 46 hours continuous infusion.

-or, **mFOLFOX6:** oxaliplatin 85mg/m² IV infusion over 2 hours immediately followed by folinic acid 400mg/m² IV infusion over 2 hours followed by fluorouracil 400mg/m² IV bolus then 5-FU 2400mg/m² over 46 hours continuous infusion.

Main Inclusion Criteria

- Age between 18 and 75 years
- ECOG PS between 0 and 1
- Histologically confirmed colo-rectal adenocarcinoma
- Untreated synchronous or metachronous metastatic disease deemed unresectable with curative intent
- KRAS(codons 12, 13, 59, 61, 117, 146), NRAS(codons 12, 13, 59, 61) and BRAF (codon 600) WT tumor status according to plasma analysis of ctDNA by Intplex technology
- Measurable disease according to RECIST version 1.1
- Adequate hematologic, hepatic and renal functions

Main Exclusion Criteria

- Adjuvant treatment with oxaliplatin
- Previous treatment for metastatic disease
- Brain metastases
- Patients with a history of severe or life-threatening hypersensitivity to the active substances or to any of the excipients delivered in this study
- Previous organ transplantation, HIV or other immunodeficiency syndromes
- Concomitant medications/comorbidities that may prevent the patient from receiving study treatment
- History of other malignancy within the previous 5 years
- Other concomitant cancer

Objectives

Primary objective

To evaluate in both arms:

- Complete response rate

Secondary objectives

To assess in both arms:

- Overall Survival (OS)
- Progression Free Survival (PFS)
- Secondary resection
- Early tumor shrinkage (ETS)
- Depth of response (DpR)
- Safety profile
- Diagnostic performance of ctDNA analysis compared to the tumor-tissue analysis (current gold standard)

Ancillary objective:

To detect in both arms:

- Emergence of ctDNA RAS and BRAF mutations under anti-EGFR-based chemotherapy

Primary endpoint

Complete response=complete disappearance of metastatic lesions according to RECIST 1.1 and CEA level normalization (if initially increased) after a maximum of 12 cycles of chemotherapy.
It can be reached with chemotherapy only or with a multimodal approach (surgical resection, regional procedures as radiofrequency, cryoablation, radiation therapy).

Required number of patients

- **Strata 1 (liver-limited disease):**

One-stage Fleming design with α=5%, β=10%, p0 (the probability of inefficiency maximum)=20%, p1 (the probability of minimum efficiency)=35%
=>72 evaluable patients (76 patients/ 5% non-evaluable patients).
FOLFIRINOX-panitumumab sufficiently effective if at least 20 successes (complete response) out of 72 evaluable patients.

mFOLFOX6+panitumumab=internal control to validate the hypothesis of a complete response rate equal to 20% in the strata 1 (liver limited disease). Calculation of 95% Confidence Interval (95%CI) on 38 patients of the control group.

- **Strata 2 (non-liver-limited disease)**:

One-stage Fleming design with α=5%, β=10%, p0 (the probability of inefficiency maximum)=3%, p1 (the probability of minimum efficiency)=12%
=>60 evaluable patients (63 patients/ 5% non-evaluable patients).
FOLFIRINOX-panitumumab sufficiently effective if at least 4 successes (complete response) out of 60 evaluable patients.

mFOLFOX6+panitumumab=internal control to validate the hypothesis of a complete response rate equal to 3% in the strata 2 (non-liver-limited disease). Calculation of 95% Confidence Interval (95%CI) on 32 patients of the control group.

Total of 209 patients included: 139 patients in the FOLFIRINOX+panitumumab group (Strata 1 N=76 and Strata 2 N=63) and 70 patients in the mFOLFOX6+panitumumab group (Strata 1 N=38 and Strata 2 N=32).

Assessments

- Before inclusion, RAS and BRAF status are determined, by Dr Alain Thierry's team, according to plasma analysis of ctDNA by Intplex® technology. Applying the threshold used in the first study that validated the test[11], patient is considered as mutated if ctDNA harbors a mutational load (mutation allelic frequency=mA%) higher than 0.5%.
- Response to therapy is evaluated by measuring changes in tumor size by CT Scan and/or MRI, according to the RECIST v1.1 criteria, every 4 cycles.
- Every complete response has to be confirmed 4 to 6 weeks after the last treatment and by no residual disease activity on PET Scan done 3 months after the end of the last treatment.
- A central review of CT-Scans and/or MRIs, PET Scans will be performed in patients who reach a complete response.
- Adverse events are graded according to the National CTCAE version 4.03.
- For ancillary study, blood samples will be collected every 4 cycles and analyzed with Intplex® technology in order to detect the occurrence of RAS and BRAF hotspot mutations in ctDNA.

Current status

- Number of opened sites= 10
- Number of expected enrollement sites= 20-30
- Number of screened patients= 54
- Number of recruited patients= 14
- Number of expected patients= 209 randomized/464 screened
- Inclusion period= 3 years

Expected results

- This study will be the **first interventional study using cfDNA analysis,** in the whole oncology field, for selecting patients. It could definitely validate its use in daily practice.
- It will be the **first study to directly compare activity of triplet vs doublet chemotherapy backbone in combination with panitumumab**, as upfront treatment, in highly molecularly selected unresectable mCRC patients.

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