The UCIG 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-intent chemotherapy (CT)

- Nevertheless, it is described that in patients who achieve complete response (CR) with CT infusion, median survival overall is significantly longer than patients without CR

- In combination with cytotoxic doublet, anti-EGFR therapies achieve impressive activity (>70% of objective response) and allow R0 secondary resection in patients with good performance status

- In patients with good performance status, cytotoxic triplet combined to anti-EGFR therapies is intended chemotherapy (CT) regimen (FOLFIRINOX) in RAS and BRAF wild type metastatic colorectal cancer patients (mCRC) selected from circulating DNA analysis.

Objectives

- Primary objective: To evaluate in all arms: Complete response rate

- Secondary objectives: To assess in both arms: Overall Survival (OS) , Progression Free Survival (PFS) , Depth of response (DoR) , Safety profile

- To evaluate in both arms: Diagnostic performance of ctDNA analysis compared to the tumor-tissue analysis current gold standard

Study design

- Randomization 2:1

- Expected number of patients: >60 evaluable patients

- The UCGI 28 PANIRINOX trial – one of the first interventional study using ctDNA analysis, in the whole oncology field, for selecting patients. It could definitely validate its use in daily practice.

- In a real-time blinded prospective multicentric clinical study, including 140 metastatic colorectal cancer patients, we have concluded that ctDNA analysis advantageously reduces turnaround-time before result communication compared to tissue-analysis (median time 2 vs 12 days). When no threshold is explicit, ctDNA analysis revealed much fewer mutations thereby more accurately reflecting the real-time tumour biology.

Main Inclusion Criteria

- Age between 18 and 75 years
- ECOG PS between 0 and 1
- Non liver limited disease
- Histologically confirmed colorectal 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 digital high-throughput sequencing
- Patient with at least one measurable lesion
- No history of severe or life-threatening hypersensitivity to a component of the drug
- No pregnancy
- Written informed consent

Main Exclusion Criteria

- Active or untreated infection
- Significant co-morbidity
- Treatment with another active investigational agent
- Treatment with another investigational agent for the indication
- Any form of immunotherapy and/or biologic therapy administered in the previous 2 weeks
- Continuous prophylaxis with corticosteroids
- Live donor or recipient of an organ within the previous 2 years
- Prior participation in a clinical trial

Assessments

- Before inclusion, RAS and BRAF status are determined, by Dr Alan Thiery’s team, according to plasma analysis of ctDNA by Inplex® technology. Applying the threshold used in our first study, patient with the "wild type", is considered as mutilated if ctDNA harbors a mutational load (mutation allelic frequency) >0.5%.

- Response to therapy is evaluated by measuring changes in tumor size by CT Scan and/or MRI, according to the RECIST 1.1 criteria, every 4 cycles.

- Each complete response has to be confirmed 4 to 6 weeks after the last treatment and by a new lesion if any.

- A central review of CT-Scans and/or MRIs, PET Scan will be performed in patients who reach a complete response.

- Adverse events are graded according to the National CTCAE version 4.03.

- For anatomic study, blood samples will be collected every 4 cycles and analyzed with implementation of in order to detect the occurrence of RAS and BRAF hotspot mutations in ctDNA.

Current status

- Number of opened sites: 10
- Number of expected enrollment sites: 20–30
- Number of screened patients: 5
- 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 ctDNA 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 therapy, in highly molecularly selected unresectable mCRC patients.

References


Acknowledgment

Patients and families
All the participating centers and investigational teams in France Oncology management team at Institut de Cancérologie de Montpellier AMGEN

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