Safety analysis and preliminary clinical results of REPROGRAM-01 phase II study evaluating regorafenib in combination with a multimodal metronomic chemotherapy in patients with metastatic colorectal cancer

Christophe Borg[1-3], Elodie Klajer[1], Jean-David Fumet[4], Antoine El Kaddissi[1-2], François Ghiringhelli[4], Morgane Stouvenot[5], Zohair Selmani[2], Marine Jary[1], Stefano Kim[3], Dewi Vernerey[6], Julie Henriques[6], Thierry N'Guyen[1], Fabien Calcagno[1], Hamadi Almotlak[1], Joelle Babre[1], Aurélia Meurisse[6], Serge Fratte[7], Francine Fein[5], Laurie Chanut[5], Laurie Spehner[2], Magali Rebucci-Peixoto[3], Angélique Vienot[1-3]

[1]Department of Medical Oncology, University Hospital of Besancon, Besançon, France, [2]INSERM, EFS BFC, UMR1098, RIGHT, University of Franche-Comté, Besançon, France, [3]Centre d'Investigation Clinique, CIC-1431, University Hospital of Besançon, Besançon, France, [4]Centre Georges-François Leclerc, Dijon, France, [5]Department of Gastroenterology, University Hospital of Besançon, Besançon, France, [6]Methodology and Quality of Life in Oncology Unit, Besançon, France, [7]Department of Medical Oncology, Nord Franche-Comté Hospital, Montbéliard, France

BACKGROUND

Angiogenesis is associated with tumor progression, and antiangiogenic molecules have become a cornerstone in the treatment of metastatic colorectal cancer (mCRC). The CORRECT study (*Grothey et al., 2013*) evaluating Regorafenib showed low objective response rate (ORR) (1%) with a median progression-free survival (PFS) of 1.9 months in heavily pre-treated patients.

Other therapies target the tumor micro-environment, as metronomic chemotherapy (CT), with continuous low dose administration of a cytotoxic agent. This allows an anti-tumor effect, an anti-angiogenic activity, a stimulation of the immune system, and a well tolerance. A recent study performed in 66 mCRC patients showed that aspirin and metronomic capecitabine administration was safe and induced promising clinical outcomes in a heavily pre-treated cohort (*Giampieri et al, 2017*).

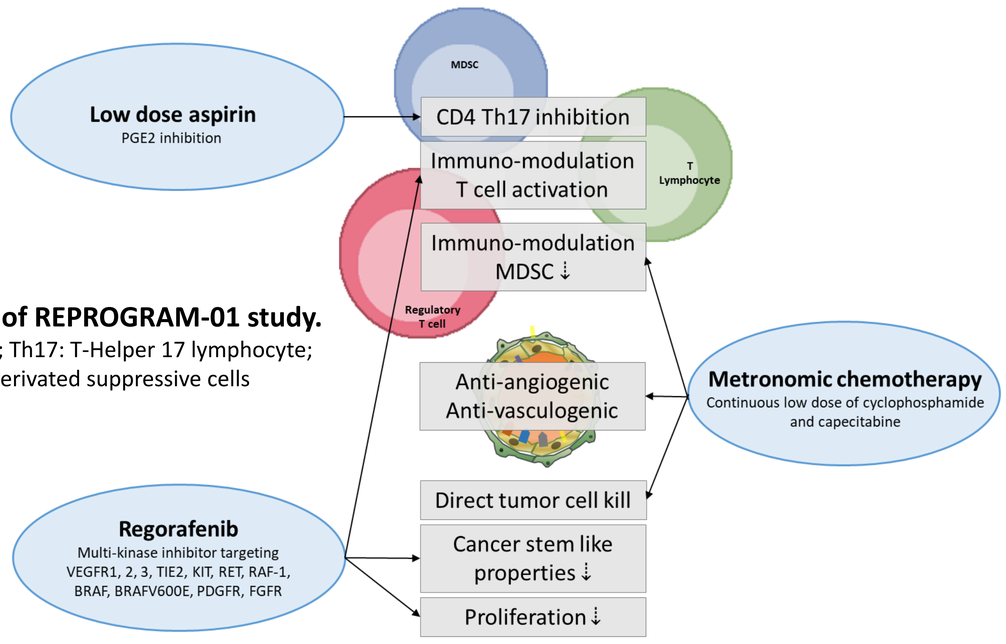

Figure 1: Rationale of REPROGRAM-01 study.
PGE2: prostaglandin E2; Th17: T-Helper 17 lymphocyte; MDSC: myeloid derivated suppressive cells

METHODS

French multi-center single-arm phase II study

mCRC patients previously exposed to conventional chemotherapies, bevacizumab, anti-EGFR if RAS wild-type, and pembrolizumab if dMMR disease

Primary end-point :
objective response rate (ORR)

Secondary end-points :
- overall survival (OS)
- progression free-survival (PFS)
- toxicity
- evaluation of exploratory biomarkers

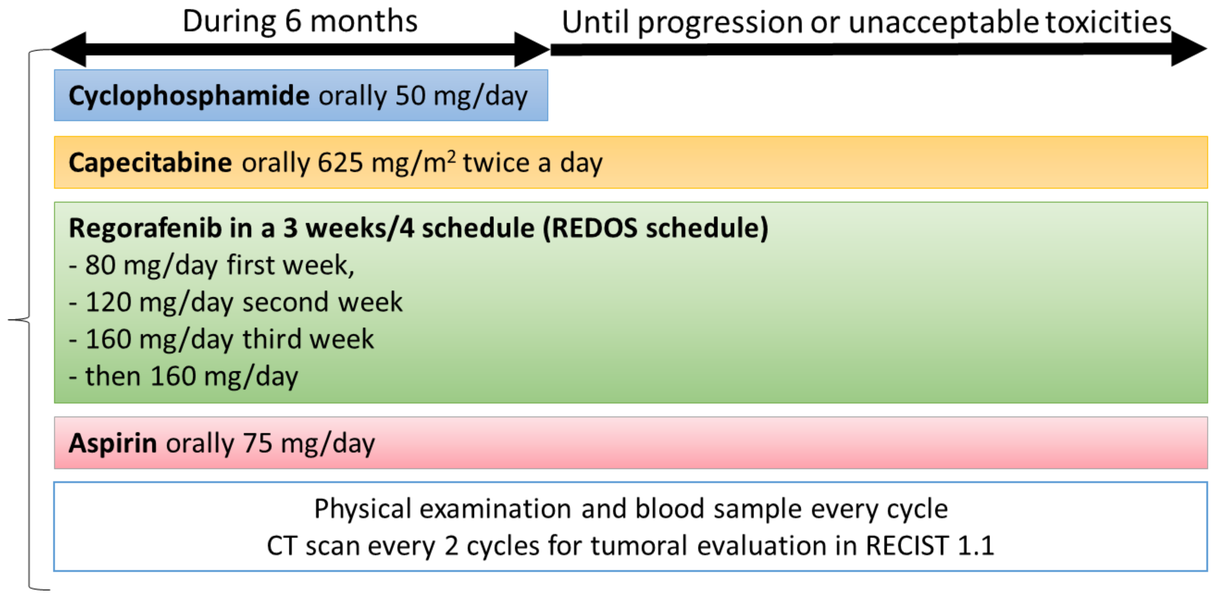

Figure 2: Study design. mCRC: metastatic colorectal cancer; mAb: monoclonal antibodies; RASwt: RAS wild type

This study is promoted by University Hospital of Besançon and supported by research grant from Bayer. The enrollment was completed December 2022.

RESULTS

Overall, 49 patients were enrolled. Patients had a good performance status (58.3% PS 0 and 41.7% PS 1) with a median age of 64.2 years (95%CI: 56.9-71.8). The median number of previous chemotherapy regimen was three (interquartile range: 2-4).

Preliminary results show that this combination was well tolerated with no serious unexpected adverse events reported. Indeed, no serious unexpected adverse event was reported. Six serious and expected adverse events were reported in these patients, notably four grade 3 (erythema, vomiting, diarrhea, and anemia), one grade 4 (neutropenia), and one grade 5 (bacterial pneumonia).

Eight patients out of 49 stopped Regorafenib treatment due to toxicities within two months without disrupting metronomic chemotherapy.

Median duration of Regorafenib was 3.4 monts (95%CI: 1.6-5.9).

After a median follow-up of 10.9 months, preliminary data show an ORR of 6.4% and a disease control rate of 76.6% according to investigators.

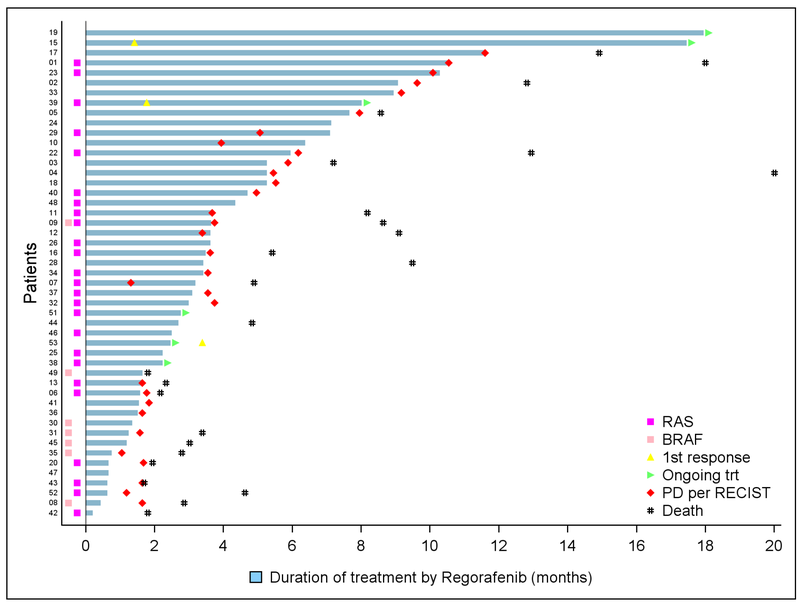

Figure 3: Swimmer plot.
PD: progression disease

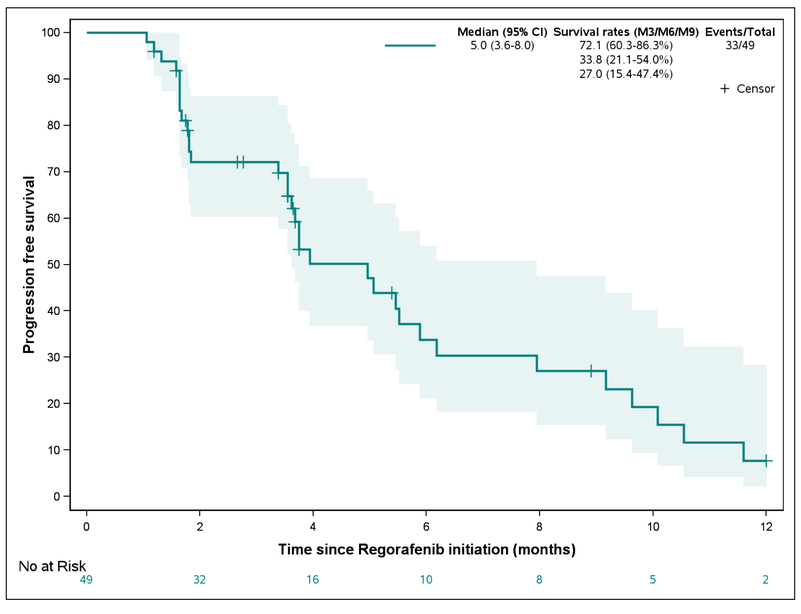

Figure 4: Kaplan-Meier curve of progression free-survival.

A median PFS of 5.0 months (95%CI: 3.6-8.0) was observed with 33.8% of patients with a PFS >6 months.

The median OS was 9.5 months (95%CI: 8.2-20) with 46.8% of patients alive at 12 months.

Of note, the median time to performance status (PS) deterioration ≥ 2 was not reached with 70% of patients who remained PS 0-1 at 6 months.

Tumor necrosis was observed in most patients with liver and lymph nodes metastases.

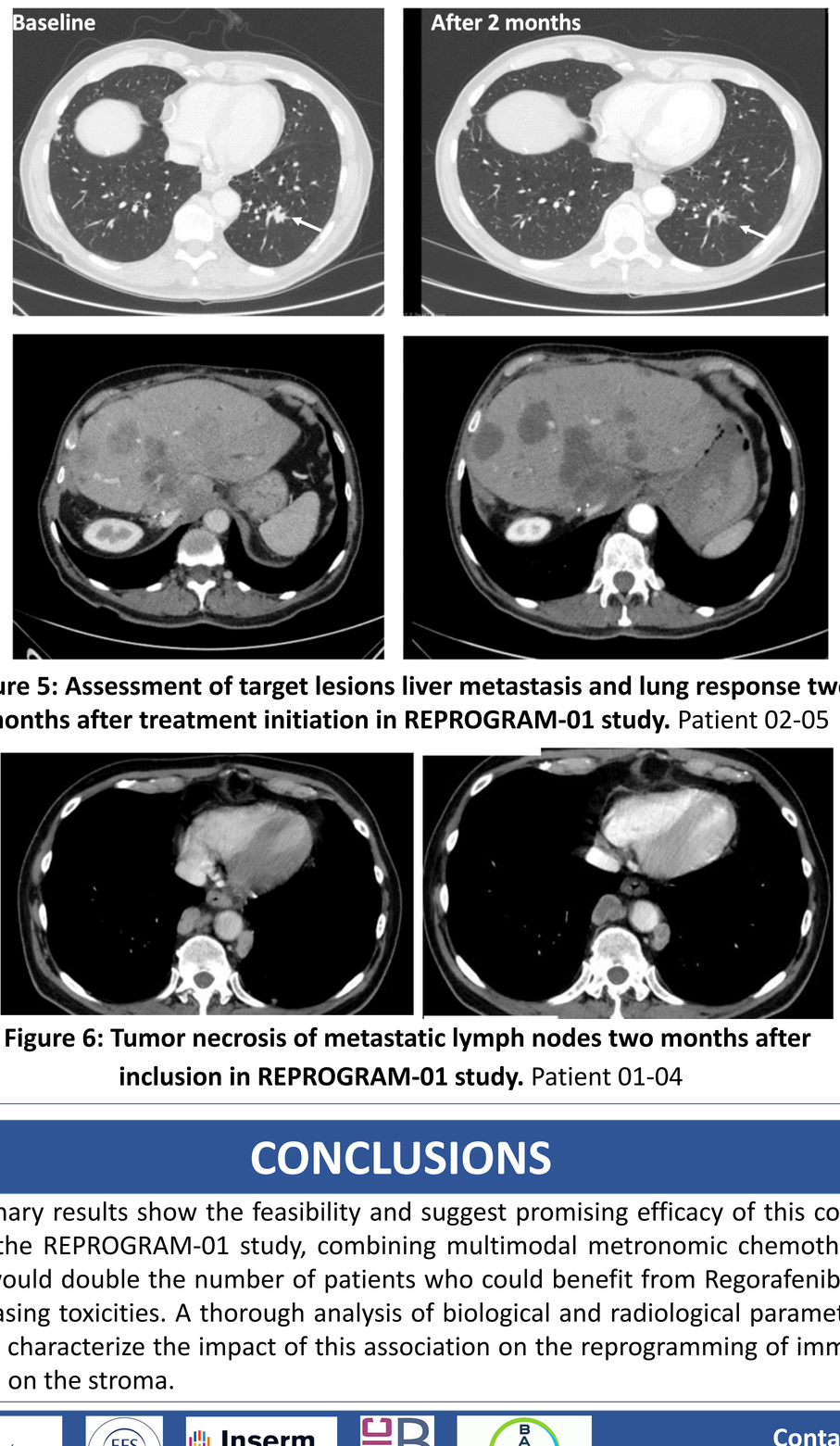

Figure 5: Assessment of target lesions liver metastasis and lung response two months after treatment initiation in REPROGRAM-01 study. Patient 02-05

Figure 6: Tumor necrosis of metastatic lymph nodes two months after inclusion in REPROGRAM-01 study. Patient 01-04

CONCLUSIONS

These preliminary results show the feasibility and suggest promising efficacy of this combination. According to the REPROGRAM-01 study, combining multimodal metronomic chemotherapy with Regorafenib would double the number of patients who could benefit from Regorafenib treatment without increasing toxicities. A thorough analysis of biological and radiological parameters will be undertaken to characterize the impact of this association on the reprogramming of immunological responses and on the stroma.

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NCT04534218

Contact
xtoph.borg@gmail.com