Hepatic artery infusion (HAI) of irinotecan, 5-fluorouracil and oxaliplatin plus intravenous cetuximab (Cet) (Optiliv) after failure therapy on one versus two or three chemotherapy protocols in patients (pts) with unresectable liver metastases from wt KRAS colorectal cancer (LM-CRC) (European Phase II clinical trial NCT00852288).

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**Authors:** M. Ducros, Dr. I. Novinlesca, M. Mehra, G. Smith, C. Leper, E. Hafner, S. Guevara, D. G. S. Tambor, S. A. Tavares, T. Couto, D. Costa, C. Abadía, J. de la Peña, R. Kondlinger, M. Bouchara, F. Borde, V. Rougé, S. Aidan, E. Fariñas, on behalf of ARTBC International

**Institutions:** Gustave Roussy Institute, Villejuif, France; Medical Oncology, Department of Medical Oncology, Gustave Roussy, Villejuif, France; Medical Oncology, Sect, Hauteur Hospital, Lille, France; Saint Joseph Hospital, Brest, France; Saint Germain Hôpital Européen Lille, France; Toulouse Saint Joseph Clinic, Ligue, Languedoc, France; University Hospital, Toulouse, France; Medical Oncology, Fernande Hospital, Carcassonne, France; Hospital Sangue e Drum Angel Herrera, Medellin, Colombia; Hospital Trujillo Mano de Dios, Caracas, Venezuela.

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**Submitted by:** P. Rougier

**Views**

**Background:** Despite the approval of several new targeted agents in recent years, 50% of patients (pts) with colorectal cancer (CRC) present with liver metastases (LM-CRC) at diagnosis. Surgery remains the only curative treatment for LM-CRC. Resectability depends on the presence of liver-sparing metastases (grade II) and performance status (PS). In patients with non-resectable LM-CRC, hepatic artery infusion (HAI) chemotherapy has been shown to be effective in prolonging progression-free survival (PFS) and overall survival (OS) compared to second-line chemotherapy. In patients with LM-CRC and poor PS, the optimal treatment is unknown because of the lack of randomized studies. In these patients, HAI chemotherapy using irinotecan, 5-fluorouracil and oxaliplatin plus intravenous cetuximab (Cet) (Optiliv) is a treatment option. Optiliv was validated in patients with LM-CRC and poor PS who received first-line chemotherapy containing oxaliplatin and cetuximab (NCT00852288). The primary objective of this study was to assess the tolerability and efficacy of the Optiliv regimen in patients who received first-line chemotherapy with oxaliplatin, cetuximab and irinotecan in the presence of unresectable LM-CRC (without control of LM-CRC and poor PS). The secondary objectives were to describe the impact of Optiliv on the rate of complete macroscopic resections of LM-CRC, PFS and OS.

**Methods:** Pt characteristics were similar in both groups. Overall, there were 22F and 42 M, aged 33-76 years, with good PS (0/1/2: 40/22/2 3). All pts received IV Cet (500 mg/m²) and chronomodulated or conventional HAI of Irinotecan (180 mg/m²), 5-fluorouracil (2,400 mg/m²) and Oxaliplatin (85 mg/m²) q2 wks. Liver surgery was performed according to q6wks multidisciplinary reviews. Pts were categorized into groups according to the type of previous chemotherapy. Pts were categorized into groups according to the type of previous chemotherapy: 1. Pts treated in a previous chemotherapy line (N=35 pts). 2. Pts treated in a previous chemotherapy line (N=35%, p=0.07), diarrhea (7% vs 24%, p=0.09), thrombocytopenia and febrile neutropenia (0% vs 9%, p=0.25). Four CR were achieved in 2 of the 2 groups except for abdominal pain (2 vs 9%, p=0.17). The rate of adverse events was significantly higher in the Optiliv group than in the conventional HAI group (p<0.001).

**Results:** The rate of complete macroscopic resections of LM-CRC was 45% in the Optiliv group and 13% in the conventional HAI group (p=0.027), resulting in respective median PFS of 11.9 months (6.9-27.9) and 6.9 months (3.4-23.7, p=0.007). Median overall survival (OS) was 31.2 months (27.9-36.0) in the Optiliv group and 10.1 months (8.0-25.8) in the conventional HAI group (p<0.001).

**Conclusions:** Intravenous Cetuximab and triplet hepatic artery infusion resulted in the near doubling of secondary surgical resection rate of LM-CRC, PFS and OS in 2 line vs 3 line. Optiliv allowed complete macroscopic resection (R0 resections were performed in 13/29 pts (45%) on 2 line vs 6/35 pts (17%) on 3 line. OPTILIV now deserves upfront testing.

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**Keywords:** Hepatic artery infusion; intravenous cetuximab; triplet hepatic artery infusion; unresectable liver metastases from colorectal cancer; secondary surgery; rate of complete macroscopic resection of liver metastases from CRC; progression-free survival; overall survival.

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