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# The screening with the liquid biopsy for the rechallenge with anti-epidermal growth factor receptor antibodies in metastatic colorectal cancer. A perspective based on pharmacological costs

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Dear Editor,
the use of anti-epidermal growth factor receptor antibodies (EGFRs) can be considered the standard of care in the first-line of therapy in patients with left-sided RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC). Re-using anti-EGFRs in mCRC patients who previously achieved benefit from a first-line anti-EGFR-based treatment seem to benefit in terms of activity, as showed in retrospective analyses and phase II single-arm trials[1,2]. In daily clinical practice, rechallenge with anti-EGFR monoclonal antibodies is often empirically, used with some benefit as late-line therapy. Recently, the CHRONOS Trial[3], a multicenter phase II trial of anti-EGFR therapy rechallenge guided by monitoring of the mutational status of RAS, BRAF and EGFR in circulating tumor DNA (ctDNA), showed that the detection of RAS mutations in ct-DNA at the time of re-treatment may be useful to identify resistant patients. The liquid biopsy was used for driving anti-EGFR rechallenge therapy in mCRC. The introduction of the rechallenge with active new agent is associated with a relevant increase of costs and it is important to make a balance between the costs of treatment and the added value represented by the improvement of the clinical parameters of interest such as PFS. It is also important to find a predictor of response that can drive therapy (and reduce potentially only toxic and consequently only expensive therapy) and this factor could be represented by liquid biopsy. The aim of this paper was to assess the gain in economic terms (pharmacological costs) derived from the rechallenge with panitunumab in RAS/BRAF wt mCRC based on the screening of liquid biopsy. We referred exclusively to the data relating to direct pharmacological costs to provide a quick estimate of the costs and potential savings deriving from the introduction of the screening with the liquid biopsy rechallenge with panitunumab in RAS/BRAF wt mCRC. We have considered CHRONOS Trial[3]. We have considered a standard patient of 70 kg with BSA= 1.8. We have assumed the following costs (VAT excluded): panitunumab (ex-factory) 1 vial of 5 ml (20 mg/ml)= 425 € (= 100 mg)[4], liquid biopsy for the screening of ctDNA for RAS/BRAF/EGFR mutations= from 400 € to 500 €.

Twenty-seven patients were included. Median progression free survival (PFS) was 3.68 months[3]. The pharmacological cost of each month of treatment is 4250 € per patient, which added to the costs of the liquid biopsy (from 400 € to 500 €), with entire costs that range from 4650 € to 4750 € per patient. It means a total cost from 360,850 € to 360,900 € every 100 mCRC patients (from 40,000 € to 50,000 € for the screening with liquid biopsy in the entire population and 320,850 € for each month of treatment with panitunumab in the 69% of population[3]) (table 1). Based on the data of CHRONOS Trial[3], 31% more

**Table 1.** Direct costs for the rechallenge with panitunumab in mCRC based on the screening with the liquid biopsy for the detecting of ctDNA for RAS/BRAF/EGFR mutations applied to the CHRONOS Trial.

| Trial | Regimen | Total N patients | Primary endpoint | PFS (months) | Pharmacological cost of each month of treatment per patient (€) | Cost of liquid biopsy[a] per patient (€) | Total costs every 100 patients treated (€)[b] |
|---|---|---|---|---|---|---|---|
| CHRONOS[3] | Panitunumab | 27 | ORR | 3.68 | 2800 | 400-500 | 233,200-243,200 |

*Legend*: N= number; PFS= progression free survival; ORR= objective response rate; [a]= for the screening of ctDNA for RAS/BRAF/EGFR mutations; [b]= it means the entire cost (treatment plus liquid biopsy) for 69% of patients (from 40,000 € to 50,000 € for the screening with liquid biopsy in the entire population and 137,200 € for each month of treatment with panitunumab) plus the cost of liquid biopsy for the remaining 31% (excluded in the CHRONOS trial[3] based on liquid biopsy).

patients would have ineffective treatment (with potentially only toxicity) with panitunumab without the screening with liquid biopsy and it means that the screening with liquid biopsy for the detecting of ctDNA for RAS/BRAF/EGFR mutations of the entire population of mCRC patients potentially candidates for rechallenge with panitunumab allows us a total saving on pharmacological costs alone of 1042 € for each month of therapy for each mCRC patient treated).

The relation between efficacy of treatment (strictly related to the patient's inclusion criteria in randomized controlled trials (RTCs)) and pharmacological costs is the main bias. In turn, the price of drugs could reflect differences in pharmacy costs within different European Countries (in Italy there are no significant pharmacy cost differences between the different regional realities). Third, the consideration of only the pharmacological costs of drugs (the data would undoubtedly be greater if we also considered the treatments toxicities) could represent another bias (even knowing that it account for about 55% of total medical expenses). This new type of resistance can be called "costs resistance" and in several Countries this could results in precluding new oncological treatments[4]. Actually, in our Country, the rechallenge with anti-EGFR monoclonal antibodies in mCRC patients is empirically, due to the fact that the registered indications by the Regulatory Authorities do not include the liquid biopsy for the screening of ctDNA for RAS/BRAF/EGFR mutations.

In conclusion, the introduction of the screening with the liquid biopsy for the detecting of ctDNA for RAS/BRAF/EGFR mutations would save money in terms of unnecessary treatments with anti-EGFRs rechallenge in mCRC.

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