Long-term follow-up of chemonaive patients with asymptomatic metastatic colorectal cancer treated with enzastaurin in a window of opportunity phase II study

Glimelius et al. [1] reported on the evaluation of the kinase inhibitor enzastaurin [2] in a window of opportunity design in patients with asymptomatic metastatic colorectal cancer (mCRC). This design was on the basis of the hypothesis that mCRC patients who are asymptomatic may safely delay first-line chemotherapy. Such a delay was further supported by the characteristics of the agent, which has antiangiogenic activity in animals and a favorable toxicity profile in patients.

We here report on the long-term follow-up survival information. The original protocol limited the collection of the overall survival information to only 2 years after study closure. Thus, the censor rate at 12-month was 82%. As highlighted by a recent publication, high censor rates before reaching study-defined end points may bias the clinical data [3]. In the study, overall survival was a secondary end point which is critical information to determine whether patients had been at risk for not receiving timely first-line treatment. Because the company-sponsored trial ended and the survival information was incomplete, the investigators obtained regulatory approval from the respective ethics review boards and central health authorities to report on the long-term survival time. This was particularly justified because the company had retired the

![Kaplan–Meier curve for overall survival (OS) for 28 assessable patients. Solid/bold line indicates the OS curve and the thinner lines represent the corresponding 95% confidence intervals. Tick marks indicate censored patients who were alive at the time of the analysis (mid-August 2009).](image-url)
original database in which the study information was collected and was not willing to write a new protocol to collect this information. Using standard Kaplan–Meier method to estimate overall survival, interval estimates were calculated using 95% confidence intervals. At the time of this analysis, 7 (25%) of the 28 assessable patients treated with enzastaurin [1] were alive (Figure 1). If one considers the 2-year cut-off as specified by the protocol, 13 patients were alive (46%). The median survival was 23.5 months, which compares well with the reported 20–22 months survival rates for the most recent first-line treatments [4]. However, given the small size of the study and the patient selection, the comparison of the overall survival with large phase III studies is not meaningful to interpret activity of enzastaurin. As with many such studies, there were some anecdotal reports on patients responding to enzastaurin. Because the compound has such a remarkable toxicity profile, it is worth mentioning one of these in order to illustrate the advantages of the window design. One patient responded to enzastaurin with stable disease for the 6-month treatment period and once progression was suspected, the patient was placed on ultimately several lines of chemotherapy. The patient did not respond to any of these therapies and in retrospect, the best treatment for him was enzastaurin. In summary, patients in this study were not placed at a disadvantage by having their first-line therapy delayed. Finally, it appears that carefully planned and closely monitored window trials are feasible in asymptomatic mCRC patients. On the basis of this experience, window trial designs may have considerable advantages to determine potential efficacy of a novel agent, including the evaluation of cancer vaccines, without placing the patients at risk.

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