Author's response to reviews

Title: A Randomized, Phase III Trial of Capecitabine plus Bevacizumab versus Capecitabine plus Irinotecan plus Bevacizumab in First-Line Treatment of Metastatic Colorectal Cancer: The AIO KRK 0110 Trial / ML22011 Trial

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Author's response to reviews: see over
Dear Doctor Chap,

thank you for the manuscript decision letter that we received on July, 25\textsuperscript{th} 2011. We very much appreciated the valuable comments by the reviewer which certainly contribute to an important improvement to our manuscript. Please find enclosed our revised manuscript #1234168437534476

\textbf{A Randomized, Phase III Trial of Capecitabine plus Bevacizumab versus Capecitabine plus Irinotecan plus Bevacizumab in First-Line Treatment of Metastatic Colorectal Cancer: The AIO KRK 0110 Trial / ML22011 Trial}

We took care in detail of all criticism. Please find enclosed our point-to-point replay.

All authors have read and approved the revised manuscript.

Dr. Clemens Giessen, MD
1. Professor Stephen Clarke asked to illustrate toxicity issues in the combination of capecitabine and irinotecan (CAPIRI):

Earlier trials evaluating chemotherapy regimen with capecitabine and irinotecan reported unacceptable incidences of severe gastrointestinal adverse effects with grade 3/4 diarrhea up to 36% of patients [1, 2]. Therefore reduced doses of capecitabine and irinotecan were applied in two AIO trials with a dose reduction by 20% in the CAPIRI arm (ie, capecitabine 800 mg/m2, irinotecan 200 mg/m2).

We recently reported from a German multicenter randomised phase II trial, the AIO KRK-0104 trial. This randomised phase II trial investigated two capecitabine-based regimens: CAPIRI plus cetuximab (CAPIRI+C) and CAPOX plus cetuximab (CAPOX+C) in the first-line treatment of mCRC [3]. With regard to grade 3/4 hematologic adverse events, patients treated with cetuximab plus CAPIRI showed higher rates of anemia (3.4% v 0%; P=.12) and leucopenia (5.6% v 3.4%; P=.72). Neutropenia occurred significantly more often in the CAPIRI arm (9% v 1.1%; P=.03) but did not result in an increased incidence of neutropenic fever which was generally rare across the entire study (1.1% v 0% in arm A v B).

In terms of gastrointestinal toxicities both combinations showed grade 3/4 diarrhea rates below 20%: 15.7% of patients receiving cetuximab plus CAPIRI experienced grade 3/4 diarrhea compared to 19.3% of patients receiving cetuximab plus CAPOX. Capecitabine associated hand-foot syndrome was reported less often than expected in both treatment arms with 22.5% of patients treated with CAPIRI+C and 30.7% of patients CAPOX+C.

Another German AIO trial investigated a combination regimen with capecitinib and irinotecan: the AIO 0604 trial. This randomized phase II trial investigated the activity of the combination of bevacizumab (Bev) with capecitabine/irinotecan (CAPIRI+Bev) or capecitabine/oxaliplatin (CAPOX+Bev) in advanced colorectal cancer (ACRC) [4]. Reported grade 3/4 diarrhea were 21% in the CAPOX+Bev arm and 16% in the CAPIRI+Bev arm. Hand-foot-syndrome were comparable with 11% (CAPOX+Bev) and 8% (CAPIRI+Bev). Grade 3/4 sensory neuropathy was substantially increased with CAPOX+Bev compared to CAPIRI+Bev (24 vs. 1%)

The data from both AIO trials therefore demonstrated that while both regimens are highly active and safe, the absence of neuropathy favors CAPIRI as the chemotherapy backbone for bevacizumab in this first-line mCRC trial.
References:


Accordingly we performed the following changes in the revised manuscript:

Introduction

Earlier trials evaluating chemotherapy regimen with capecitabine and irinotecan had reported unacceptable incidences of severe gastrointestinal adverse effects with grade 3/4 diarrhea up to 36% of patients [8-10]. We therefore decided for a 20% dose reduction (ie, capecitabine 800 mg/m2, irinotecan 200 mg/m2) previously investigated in two AIO randomized phase II trials [7, 11]. Acceptable gastrointestinal toxicity with grade 3-4 diarrhoea occurring in 15.7%-21.0% of patients were reported for the combination of capecitabine and irinotecan [7, 11]. The data from the two AIO trials also demonstrated that while both, CAPOX and CAPIRI, regimens are highly active and safe, the absence of sensory neuropathy favors CAPIRI as the chemotherapy backbone for bevacizumab in this first-line mCRC trial.

Discussion

As described in the above the CAPIRI regimen with a dose of capecitabine 800 mg/m2, irinotecan 200 mg/m2 previously investigated in two AIO randomized phase II trials is expected to have an acceptable toxicity profile [7, 11].