Is fluoropyrimidindes without oxaliplatin optimal for the adjuvant treatment of mainstream stage III colon cancer?

We have read the large ACTS-CC trial by Yoshida published in September 9 issue of Annals of Oncology [1]. They have randomized 1518 stage III colon cancer patients either S-1 or UFT after curative surgery and demonstrated that S-1 was noninferior to UFT (1). We have several comments:

They stated that oxaliplatin plus 5-fluorouracil or capecitabine are recommended for the adjuvant treatment of colon cancer in the western guidelines, but fluoropyrimidine alone remains one of the options. NCCN recommends oxaliplatin plus fluoropyrimidines in the order of category 1 [2] and ESMO recommends it as standard and fluoropyrimidines alone are recommended only if oxaplatin is contraindicated [3]. However, the patients in both arms received oral fluoropyrimidine without oxaliplatin in the current trial where two thirds of the participants are below 70 years of age and about 85% had stage IIIB or IIIC disease.

We have the feeling that the patients in this trial may not have received the best standard of the time. Given the fact that superiority of oxaliplatin plus fluoropyrimidines were known when the trial was designed, we think that the authors should answer the question of why they designed the arms without oxaliplatin.

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disclosure
The authors have declared no conflicts of interest.

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Reply to the Letter to the Editor ‘Is fluoropyrimidindes without oxaliplatin optimal for the adjuvant treatment of mainstream stage III colon cancer?’ by Abali et al.

We thank Professor Huseyin et al. [1] for their consideration of our paper. Our study, ACTS-CC trial, aimed to demonstrate the efficacy of S-1 as adjuvant chemotherapy for colon cancer through evaluating the noninferiority to tegafur-uracil plus leucovorin, and the primary end point was met [2].

Oxaliplatin plus fluoropyrimidines (FUs) have been reported their superiority in disease-free survival (DFS) with a constant hazard ratio of 0.8 compared with 5-fluorouracil/LV in several ‘Western’ clinical trials [3–5]. However, we do not consider that oxaliplatin plus FUs is the best/optimal standard for all stage III colon cancer patients.

de Gramont et al. [6, 7] indicated that stage III consists of subgroups of patients with various risk of recurrence, and the expected benefits of oxaliplatin vary with the risk subgroups. So, they proposed to selecting treatment regimen according to given survival data by the risk subgroup.

When considering the risk of recurrence, impact of the surgical treatment must be taken in consideration. There are several differences between the Japanese and Western surgical approach to colon cancer. In Japan, D3 lymph node dissection which is recommended to stage II–III colorectal cancer by the Japanese Guidelines [8, 9] has been carried out nationwide as the standard surgery [10–12]. D3 lymph node dissection as well as ‘complete mesocolic excision with central vascular ligation’ proposed by Honenberger et al. [13] are anatomically and oncologically justified, and West et al. [11, 12] have reported that these surgical procedures may eradicate tumors more effectively and result in better treatment outcomes than the conventional Western approach.

JCOG0205 study which is the randomized clinical trial of adjuvant chemotherapy for stage III colon cancer [14] reported favorable outcome with D3 lymph node dissection and FUs without oxaliplatin; the 5-year overall survival rate was 88% and
the 5-year DFS rate was 74%. Both JCOG0205 [14] and ACTS-CC [2] in which oxaliplatin was not used and D3 lymph node dissection was a standard surgery showed similar or better DFS than that with oxaliplatin in the Western pivotal studies [3–5].

Prolonged peripheral neuropathy and high medical cost are clinically and socially significant problems in oxaliplatin-based adjuvant chemotherapy. We have believed that if radical surgery with sufficient lymph node dissection and anatomically optimal mesocolic excision is carried out, less-toxic and less-expensive oral FU without oxaliplatin could obtain comparable treatment outcome to oxaliplatin-containing regimens.

However, there is the poor prognostic subgroup in stage III. ACTS-CC02 trial which is a phase III study investigating benefit of adding oxaliplatin to FU under D3 dissection surgery for N2 colon cancer patients is in progress [15].

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disclosure


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A novel germline mutation of PDGFR-β might be associated with clinical response of colorectal cancer to regorafenib

We report an extraordinary response to regorafenib in a patient with metastatic adenocarcinoma of the rectum. In order to identify the molecular target of this response, we analyzed 409 cancer genes by next-generation sequencing (NGS) of the genomic DNA (patient tumor and blood) and discovered a germline mutation of the platelet-derived growth factor receptor