

In Reply

Overman et al. [1] addressed several critical issues in our prospective observational study of the FOLFOX4 regimen in patients with pseudomyxoma peritonei (PMP) of appendiceal origin [2].

The first point is the pathologic classification used in our study [2]. We acknowledge that classification of PMP and the associated mucinous appendiceal neoplasms has been hindered by controversy and confusion. As referenced in the text, we categorized our PMP cases into low and high grade based on the fourth edition of the World Health Organization classification [3]. Such a classification basically retains Misdraji categorization of primary appendiceal tumors into low-grade appendiceal mucinous neoplasms (typically associated with low-grade PMP), and mucinous adenocarcinoma (typically associated with high-grade PMP) [4]. Nevertheless, discordance in the degree of atypia between appendiceal and peritoneal lesions has been reported in the literature [5]. Over the past 2 years, the main PMP management centers, including our institution, have been involved in an international Delphi consensus process to establish common nomenclature and classification for this rare disease. Preliminary results were presented at the 9th International Congress on Peritoneal Surface Malignancies (October 9–11, 2014; Amsterdam, The Netherlands).

Second, Overman et al. raised the question of whether repeated cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy could have influenced outcomes such as progression-free survival and, above all, overall survival [1]. Based on our risk-benefit profile assessment of individual patients, their tumor loads, and disease biological aggressiveness, we chose to register in this study only patients for whom repeated surgical debulking was considered technically difficult or biologically useless [2]. In fact, none of the patients in our study underwent surgery twice.

The third point is the presence of 7 cases with >20% disease growth at 3 months, which may seem unusual in an usually indolent disease such as PMP. It must be noted that our series included eight patients with high-grade PMP [2]. In addition, it is well known that histologically indolent PMP may show clinically aggressive and rapidly lethal behaviors [6]. We observed median overall survival of 26.2 months in our patients. This is comparable with the median of 23.9 months obtained by modern highly effective systemic therapies in colorectal peritoneal carcinomatosis, a disease traditionally considered more aggressive than PMP [7].

The last and most relevant issue is the difficulty in quantifying disease response using current radiological tools and Response Evaluation Criteria In Solid Tumors (RECIST). We agree that this is a potential limitation of our study [2] and in any other study involving PMP because of its diffuse nature, with abundant collection of mucinous material and a scant cellular component [8]. Overman et al. hypothesize that changes in disease volume seen in four patients of our series may be explained by mechanisms other than treatment effect [1]; however, this is merely speculative. Furthermore, 4 of 20 patients in our series had partial response, and 4 of 9 with stable disease showed

a significant decrease in serum tumor markers, possibly reflecting treatment effect on the cellular component of the disease.

The trial (NCT01946854) [2] and the modified peritoneal RECIST measurement proposed by Overman et al. [1] are scientifically sound; however, the study design, which will hopefully clarify whether chemotherapy is active in PMP, cannot provide information on which drugs or combinations are active. We are currently conducting molecular and genetic research to identify new targets for therapeutic interventions and predictive biomarkers in PMP. The final aim of these studies is to rationalize the choice of treatment, which remains an unmet clinical need.

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Disclosures

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REFERENCES

- Overman MJ, Eng C, Matamoras A et al. Challenges of efficacy assessments in pseudomyxoma peritonea. *The Oncologist* 2015;20:335–336.
- Pietrantonio F, Maggi C, Fanetti G et al. FOLFOX-4 chemotherapy for patients with unresectable or relapsed peritoneal pseudomyxoma. *The Oncologist* 2014;19:845–850.
- Carr NJ, Sobin LH. Adenocarcinoma of the appendix. In: Bosman FT, Carneiro F, Hruban RH et al., eds. WHO Classification of Tumors of the Digestive System. Vol. 3. Lyon, France: International Agency for Research on Cancer, 2010:93–102.
- Misdraji J, Yantiss RK, Graeme-Cook FM et al. Appendiceal mucinous neoplasms: A clinicopathologic analysis of 107 cases. *Am J Surg Pathol* 2003;27:1089–1103.
- Carr NJ, Finch J, Ilesley IC et al. Pathology and prognosis in pseudomyxoma peritonei: A review of 274 cases. *J Clin Pathol* 2012;65:919–923.
- Mohamed F, Gething S, Haiba M et al. Clinically aggressive pseudomyxoma peritonei: A variant of a histologically indolent process. *J Surg Oncol* 2004;86:10–15.
- Elias D, Lefevre JH, Chevalier J et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009;27:681–685.
- Farquharson AL, Pranesh N, Witham G et al. A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. *Br J Cancer* 2008;99:591–596.

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