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CDX2 as a Prognostic Biomarker in Colon Cancer

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THE AUTHORS REPLY

Coebergh van den Braak et al. report that they found no association between *CDX2* mRNA expression and prognosis in two cohorts of patients with stage II colon cancer. In their own cohort of 144 patients, tumors were analyzed by means of RNA sequencing (unpublished data). In the cohort of 90 patients from the Academic Medical Center in Amsterdam, tumors were analyzed by means of gene-expression arrays and the results were deposited in the National Center for Biotechnology Information Gene Expression Omnibus under accession number GSE33113.

It is difficult for us to comment on the first cohort, since we have no access to the primary data, the methods used to collect and normalize them, and the clinical information about these patients. With regard to the second cohort, the Academic Medical Center group published their findings on the GSE33113 data set, and they reported that lack of CDX2 expression was characteristic of a tumor subgroup that is associated with a poor prognosis.[1] This finding is consistent with those of our study, and it was validated at the mRNA-expression level by means of real-time quantitative polymerase-chain-reaction assays and at the protein-expression level by means of immunohistochemical analysis. The association between a lack of CDX2 protein expression and decreased patient survival was recently observed in a study from Seoul National University that involved an independent cohort of 713 patients.[2]

We fully agree with Schirripa et al. regarding the need for our findings to be further confirmed, ideally within the framework of prospective and randomized clinical trials. We also agree on the importance of microsatellite instability and *BRAF* mutations as prognostic covariables, the role of which will need to be further elucidated.

With regard to the role of microsatellite instability, we would like to point out two findings. First, CDX2-negative tumors and tumors with microsatellite instability are two distinct

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categories that overlap but do not coincide (Fig. S4 in Supplementary Appendix 1, available with the full text of the article at NEJM.org). The majority of CDX2-negative tumors are microsatellite-stable tumors, whereas the majority of tumors with microsatellite instability are CDX2-positive.

Second, recent data indicate that among tumors with microsatellite instability, CDX2-negative tumors might be associated with a prognosis that is worse than that associated with CDX2-positive tumors.[3] Finally, our findings were independently validated in the cohort of patients with stage II disease and in the cohort of patients with stage III disease (Fig. 5 of the article), and these findings were not confounded by major prognostic variables (Fig. S19 and Fig. S21 through S24 in Supplementary Appendix 1 of the article). These variables included the depth of invasion of the primary tumor (T3 vs. T4), the number of examined lymph nodes (≥12 vs. <12), and the number of metastatic lymph nodes (N1 vs. N2).

We agree with Chiche and colleagues regarding the possibility that CDX2 could be used as a prognostic biomarker in patients with inflammatory bowel disease. Unfortunately, our database was not annotated with such information. It would be interesting to test that hypothesis.

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