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Mismatch repair-deficient tumors and immune checkpoint inhibitors

Immune checkpoint inhibitors have yielded highly effective therapeutic responses in a subset of tumors by eliciting an endogenous adaptive immune response. The determinants that define this subset of tumors are still unclear, but several markers, including PD-L1 expression and mutational burden, have been evaluated in various tumor types. Several recent reports have shown that the number of mutations in mismatch repair (MMR)-deficient cancers are associated with response to PD-1 blockade therapies. The authors undertook a study to expand these findings by prospectively evaluating the efficacy of the PD-1 blockade therapy pembrolizumab in a range of histologically distinct MMR-deficient cancers. Among the types of cancer were colorectal (47 percent), endometrial (17 percent), pancreatic (nine percent), small intestine (six percent), gastroesophageal (six percent), and other solid tumors. During a three-year period, 86 patients with MMR-deficient tumors were enrolled in the study, which also assessed inherited mutations in the MMR genes MSH2, MSH6, PMS2, and MLH1, diagnostic of Lynch syndrome, with 32 (48 percent) of the cases carrying inherited MMR mutations. A subset of 78 patients had disease that could be evaluated radiographically using the Response Evaluation Criteria in Solid Tumors (RECIST) system. Slightly more than half (53 percent) the patients achieved objective radiographic response, with 21 percent achieving complete radiographic response. The average time to any response was 21 weeks, and the average time to complete response was 42 weeks. Eleven patients achieved complete response and were taken off therapy after two years of treatment. Neither median progression-free survival nor median overall survival had been reached since the study was still ongoing. Primary clinical resistance to initial therapy with pembrolizumab was observed in 14 percent of patients. The authors compared the mutational burden for these resistant patients to that for patients with objective responses and did not observe any statistically significant differences between the two groups. Finally, the authors sought to extrapolate the number of MMR-deficient cancers that may benefit from PD-1 blockade therapies by evaluating more than 12,000 cancers representing 32 distinct tumor types for MMR deficiency. They found that more than five percent of a variety of adenocarcinomas, as well as neuroendocrine tumors, nonepithelial ovarian cancers, and uterine sarcomas were MMR deficient. The authors estimated that roughly 40,000 annual stage I to stage III cancers and 20,000 annual stage IV cancers would be MMR deficient and potentially benefit from this class of immune therapy, regardless of tumor type. While the study was limited due to the relatively small number of tumors evaluated, the prospective study design will offer insights into progression-free survival and overall survival, as well as continue to provide insights into the efficacy of PD-1 blockade therapies in a variety of tumor types harboring defects in mismatch repair.

Le DT, Durham JN, Smith KN, et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade [published online ahead of print June 8, 2017]. *Science.* doi:10.1126/science.aan6733.

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Assessing breast and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers

Understanding the risk of women who carry mutations in BRCA1 or BRCA2 genes developing breast and ovarian cancers is critical for guiding clinical management. Age-specific cancer risk estimates can be used to estimate absolute risk reduction from preventive strategies and inform decisions regarding the age at which to start cancer

screening. Cumulative risk estimates have been derived from retrospective studies. The cumulative breast cancer risk estimates to age 70 years range from 40 to 87 percent for BRCA1 mutation carriers and from 27 to 84 percent for BRCA2 carriers, and the corresponding ovarian cancer risks vary from 16 to 68 percent for BRCA1 and from 11 to 30 percent for BRCA2 carriers. The authors published the results of a large prospective study that refines the risk estimates of breast and ovarian cancers for BRCA1 and BRCA2 mutation carriers. More than 9,800 BRCA1 and BRCA2 mutation carriers from three consortia were included in the study. The combined sample, which had a five-year median follow-up, resulted in 3,886 women in the breast cancer risk analysis arm (2,276 and 1,610 BRCA1 and BRCA2 mutation carriers, respectively) and 5,066 women in the ovarian cancer risk analysis arm (2,905 and 2,161 BRCA1 and BRCA2 mutation carriers, respectively). The median age at study entry was 38 years for both the breast and ovarian cancer arms of the study. The cumulative breast cancer risk to age 80 years was 72 percent for BRCA1 carriers and 69 percent for BRCA2 carriers, and the cumulative ovarian cancer risk to age 80 years was 44 percent for BRCA1 carriers and 17 percent for BRCA2 carriers. Breast cancer risk estimates for BRCA1 and BRCA2 carriers increased with the number of first- and second-degree relatives diagnosed as having breast cancer. Interestingly, there was no significant difference in ovarian cancer risk for BRCA1 carriers with a family history of ovarian cancer compared with those without a family history. A similar pattern was observed for BRCA2 carriers, but the number of events for women with a family history of ovarian cancer was low. When the investigators looked at risk by mutation position, they found that breast cancer risk was higher if mutations were located outside versus within the respective ovarian cancer cluster regions (c.2282 to c.4071 in BRCA1 and c.2831 to c.6401 in BRCA2, respectively). However, there was no significant difference in ovarian cancer risk in either ovarian cancer cluster region. In addition, there was no increased risk for either breast or ovarian cancer with the Ashkenazi Jewish mutations BRCA1 c.68_69delAG or c.5266dupC or BRCA2 c.5946delT, when compared to other mutations within or outside the respective ovarian cancer cluster regions. The results of this study, with regard to the estimated breast and ovarian cancer risks for BRCA1 and BRCA2 carriers, are consistent with previously published retrospective studies. However, this study highlights the importance of taking into account family history and mutation location within the BRCA1 and BRCA2 genes to more accurately determine cancer risk.

Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA.* 2017;317(23):2402–2416.

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