PD-1 Blockade in Tumors with Mismatch Repair Deficiency

Details

First Author:

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Meeting:

2015 ASCO Annual Meeting

Session Type:

Clinical Science Symposium

Session Title:

Immunotherapy for Every Patient: Check Your Enthusiasm

Track:

Special Sessions

Sub Track:

Colorectal Cancer

Clinical Trial Registration Number:

NCT01876511

ation:

lin Oncol 33, 2015 (suppl; abstr LBA100)

l:

10.1200/jco.2015.33.18_suppl.lba100

Abstract #:

LBA100

Feedback

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JHU 2003
Merck Sharp v. Johns Hopkins
IPR2024-00650

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The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, Johns Hopkins Cancer Ctr, Baltimore, MD, Providence Cancer Center, Portland, OR, Stanford University School of Medicine, Stanford, CA, Bons Secours Cancer Insitute, Richmond, VA, University of Pittsburgh, Pittsburgh, PA, Merck & Co., Inc., Kenilworth, NJ, Johns Hopkins University School of Medicine, Baltimore, MD, The Johns Hopkins University School of Medicine, Baltimore, MD, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Abstract Disclosures

Research Funding

NIH

Background:

Somatic mutations have the potential to be recognized as “non-self” immunogenic antigens. Tumors with genetic defects in mismatch repair (MMR) harbor many more mutations than tumors of the same type without such repair defects. We hypothesized that tumors with mismatch repair defects would therefore be particularly susceptible to immune checkpoint blockade.

Methods:

We conducted a phase II study to evaluate the clinical activity of anti-PD-1, pembrolizumab, in 41 patients with previously-treated, progressive metastatic disease with and without MMR-deficiency. Pembrolizumab was administered at 10 mg/kg intravenously every 14 days to three cohorts of patients: those with MMR-deficient colorectal cancers (CRCs) (N = 11); those with MMR-proficient CRCs (N = 21), and those with MMR-deficient cancers of types other than colorectal (N = 9). The co-primary endpoints were immune-related objective response rate (irORR) and immune-related progression-free survival (irPFS) at 20 weeks.

Results:

The study met its primary endpoints for both MMR-deficient cohorts. The irORR and irPFS at 20 weeks for MMR-deficient CRC were 40% and 78%, respectively, and for MMR-deficient other cancers were 71% and 67%, respectively. In MMR-proficient CRC, irORR and irPFS at 20 weeks were 0% and 11%, respectively. Response rates and Disease Control Rates (CR+PR+SD) by RECIST criteria were 40% and 90% in MMR-deficient CRC, 0% and 11% in MMR-proficient CRC, and 71% and 71% in MMR-deficient other cancers, respectively. Median PFS and overall survival (OS) were not reached in the MMR-deficient CRC group but was 2.2 and 5.0 months in the MMR-proficient CRC cohort (HR for PFS = 0.103; 95% CI, 0.029 to 0.373; $p < 0.001$ and HR for OS = 0.216; 95% CI, 0.047 to 1.000; $p = 0.05$). Whole exome sequencing revealed an average of 1,782 somatic mutations per tumor in MMR-deficient compared to 73 in MMR-proficient tumors ($p = 0.0015$), and high total somatic mutation loads were associated with PFS ($p = 0.02$).

Conclusions:

MMR status predicts clinical benefit of immune checkpoint blockade with pembrolizumab. Clinical trial information: NCT01876511

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