Published OnlineFirst June 10, 2016; DOI: 10.1158/2159-8290.CD-RW2016-107

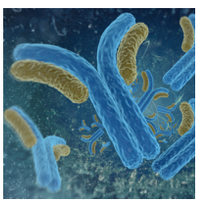
Clinical Trials

Major finding: Pembrolizumab is well tolerated and active in advanced squamous cell carcinoma of the head and neck.

Clinical relevance: Greater activity was associated with increased expression of PD-L1 and a panel of IFNγ-related genes.

Impact: Pembrolizumab warrants further investigation in patients with PD-L1–positive head and neck tumors.

PEMBROLIZUMAB HAS ANTITUMOR ACTIVITY IN ADVANCED HEAD AND NECK CANCER



Pembrolizumab is a humanized monoclonal antibody targeting programmed death 1 (PD-1) that is approved for the treatment of melanoma and has shown efficacy in multiple advanced solid tumor types. In preclinical studies, PD-1 blockade promoted antitumor activity in squamous cell carcinoma of the head and neck, prompting Seiwert and colleagues to evaluate the safety and clinical activity of pembrolizumab in a phase Ib, open-label, multicenter trial of 60 patients with PD-L1–positive recurrent or metastatic squamous cell carcinoma of the head and neck. In total, 23 patients were human papillomavirus (HPV)–positive, and 37 were HPV-negative. The primary endpoints were safety and the proportion of patients who achieved an overall response; secondary endpoints included response based on HPV status, response duration, and progression-free and overall survival. Expression of six IFNγ-related genes identified as predictive biomarkers of pembrolizumab response in melanoma was also assessed. Pembrolizumab was well tolerated and safe; treatment-related adverse events occurred in 63% of patients and most commonly included fatigue, pruritus, and rash. The most common grade 3–4 adverse events were alanine aminotransferase or aspartate aminotransferase increases and hyponatremia, each occurring in 2 patients. Central imaging review confirmed an overall response in 8 (18%) of 45 evaluable patients, including 1 complete response and 7 partial responses, as well as stable disease in 8 patients. The overall response rate was 25% in HPV-positive patients and 14% in HPV-negative patients, and 51% of patients experienced a reduction in tumor burden. The median response duration was 53 weeks and median overall survival was 13 months. Higher expression of PD-L1 and the six IFNγ-related genes was detected in responding patients compared to nonresponding patients. Altogether, this study suggests that pembrolizumab is safe, well tolerated, and exhibits antitumor activity in patients with advanced squamous cell carcinoma of the head and neck, and supports further clinical investigation of pembrolizumab in larger clinical trials. ■

Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016 May 27 [Epub ahead of print].

Oncogenes

Major finding: MDM2 regulates genes involved in serine metabolism and redox homeostasis in a p53-independent manner.

Mechanism: Serine/glycine deprivation recruits MDM2 to chromatin for ATF-dependent target gene transcription.

Impact: MDM2 may be a therapeutic target to disrupt tumor metabolism.

CHROMATIN-BOUND MDM2 PLAYS A p53-INDEPENDENT ROLE IN TUMOR METABOLISM

MDM2 is an oncogenic E3 ubiquitin ligase that is overexpressed in many tumors and negatively regulates p53. Recent evidence indicates that MDM2 also has p53-independent oncogenic functions, but these have not been well characterized. Riscal and colleagues assessed the localization of MDM2 in a panel of cancer cell lines and found that MDM2 was localized to the cyto- and nucleosoluble fractions consistent with its E3 ligase activity. However, a substantial amount of MDM2 was also detected in the chromatin-enriched fraction and was not altered by p53 knockdown, indicating p53-independent recruitment to chromatin. Chromatin immunoprecipitation sequencing and microarray analysis identified 159 genes that were upregulated by MDM2 binding. MDM2 bound loci were enriched for activating transcription factor (ATF) 3 and 4 binding motifs, and ATF3/4 was found to recruit MDM2 to target gene promoters. MDM2 target genes were enriched for those involved in serine, glycine, glutamine, and cysteine metabolism, and serine or glycine deprivation increased MDM2 chromatin binding at target genes to sustain serine/glycine biosynthesis and promote tumor growth. MDM2 targets also included genes involved in redox homeostasis, and MDM2 depletion resulted in reduced glutathione oxidation, a decreased NAD+/NADH ratio, and increased reactive oxygen species (ROS) levels. MDM2 recruitment to its target genes was regulated by pyruvate kinase isoform M2 (PKM2), an enzyme that is inhibited by ROS and allosterically activated by serine. The PKM2 complex phosphorylated MDM2, reducing its recruitment to chromatin. Together, these findings establish a p53-independent mechanism by which MDM2 promotes tumor growth via regulation of amino acid metabolism and redox homeostasis, which may have therapeutic implications for tumors in which MDM2 is overexpressed. ■

Riscal R, Schrepfer E, Arena G, Cissé MY, Bellvert F, Heuillet M, et al. Chromatin-bound MDM2 regulates serine metabolism and redox homeostasis independently of p53. Mol Cell 2016 June 2 [Epub ahead of print].

Note: *Research Watch* is written by *Cancer Discovery* editorial staff. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.

Published OnlineFirst June 10, 2016; DOI: 10.1158/2159-8290.CD-RW2016-107

AACR American Association for Cancer Research

CANCER DISCOVERY

Pembrolizumab Has Antitumor Activity in Advanced Head and Neck Cancer

Cancer Discov 2016;6:693. Published OnlineFirst June 10, 2016.