MYC INHIBITION PLUS p53 STABILIZATION TARGETS LEUKEMIC STEM CELLS

Chronic myeloid leukemia (CML) is driven by the fusion tyrosine kinase BCR-ABL, which transforms hematopoietic stem cells (HSC). Tyrosine kinase inhibitors (TKI) have been effective in treating CML, but do not kill the leukemic stem cells (LSC), which persist in a BCR-ABL-independent manner. Abraham, Hopcroft, and colleagues therefore sought to identify critical kinase-independent protein networks in CML that could potentially be exploited for curative therapies. Isobaric-tag mass spectrometry identified deregulated proteins in treatment-naive CML compared with normal CD34\(^+\) HSCs, and revealed p53 and MYC as central nodes in a 30-protein CML network, with p53 targets primarily downregulated in CML, and MYC targets both upregulated and downregulated. To test the hypothesis that p53 activation and MYC inhibition would kill LSCs, MYC and p53 were targeted using RITA, which binds to p53 and blocks its degradation by HDM2, and CPI-203, a bromodomain and extra terminal protein (BET) inhibitor that downregulates MYC. Treatment of CML CD34\(^+\)LSCs with either RITA or CPI-203 reduced cell viability, and the combination was synergistic. CPI-203 resulted in a rapid loss of CD34 expression, suggesting that MYC inhibition promoted differentiation of CD34\(^+\) CML cells, whereas RITA enhanced apoptosis, suggesting that p53 stabilization enhanced cell death. Normal CD34\(^+\) cells were not susceptible to treatment with RITA and CPI-203, whereas the long-term engrafting potential of treated leukemic cells was significantly decreased, indicating that RITA and CPI-203 selectively target CML LSCs. In preclinical mouse models of CML, combination therapy with BET inhibitors and HDM2 inhibitors currently in clinical trials was well tolerated, and synergistically reduced leukemic cells in the bone marrow. Together, these findings reveal a critical importance of the p53 and MYC signaling network in CML LSCs. In preclinical mouse models of CML, combination therapy with BET inhibitors and HDM2 inhibitors currently in clinical trials was well tolerated, and synergistically reduced leukemic cells in the bone marrow. Together, these findings reveal a critical importance of the p53 and MYC signaling network in CML LSCs, which may be exploited to eradicate CML LSCs and develop curative CML therapies.


Clinical Trials

Major finding: Pembrolizumab is well tolerated and active in patients with melanoma or NSCLC with brain metastases.

Approach: Safety and activity of the PD-1 inhibitor pembrolizumab was tested in an open-label phase II trial.

Impact: Systemic immunotherapy with pembrolizumab may be effective in patients with brain metastases.

PEMBROLIZUMAB HAS ACTIVITY IN PATIENTS WITH BRAIN METASTASES

Immunotherapy with immune checkpoint inhibitors has been successful in multiple tumor types, and the PD-1 inhibitor pembrolizumab has been approved for the treatment of metastatic melanoma and non–small cell lung cancer (NSCLC). Brain metastases occur in a substantial number of patients with melanoma and NSCLC; however, it is unclear if these drugs are active in the central nervous system (CNS), as patients with untreated brain metastases are excluded from most clinical trials. To test the safety and activity of pembrolizumab in patients with untreated or progressive brain metastases, Goldberg and colleagues performed a non-randomized, open-label, phase II trial. A total of 36 patients with brain metastases were enrolled: 18 with melanoma and 18 with NSCLC. Patients with NSCLC were required to have PD-L1 positive tumors; patients with melanoma were not. The primary endpoint was brain metastasis response, and the secondary endpoints included toxicity and overall response. Partial brain metastasis responses were achieved in 4 patients with melanoma (22%). A brain metastasis response rate of 33% was achieved in patients with NSCLC, with 4 complete responses and 2 partial responses. The responses were durable, with all but one patient experiencing an ongoing response. The CNS response (including only brain metastases) corresponded to the systemic response (including all lesions), with a single discordant patient with NSCLC who achieved a systemic response ongoing 10 months after treatment, but experienced disease progression in several brain lesions. Pembrolizumab was generally safe and well tolerated. The treatment-related grade 3–4 events were elevated amidotransferases in patients with melanoma, and colitis, pneumonitis, fatigue, and hyperkalemia in patients with NSCLC. Neurologic adverse events included grade 3 cognitive dysfunction and grade 1–2 seizures in patients with melanoma. Taken together, these findings suggest that pembrolizumab is safe, well tolerated, and active in patients with melanoma or NSCLC with brain metastasis, and support further clinical investigation of pembrolizumab in patients with brain metastasis.

Pembrolizumab Has Activity in Patients with Brain Metastases

Cancer Discov 2016;6:813. Published OnlineFirst June 20, 2016.

Updated version  Access the most recent version of this article at: doi:10.1158/2159-8290.CD-RW2016-115

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/6/8/813.2. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.