Receptor that downregulates MYC. Treatment of CML CD34+ 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, which may be exploited to eradicate CML LSCs and develop curative CML therapies.


Pembrolizumab is well tolerated and active in patients with melanoma or NSCLC 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 ami-notransferases 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.
