Clinical Trial

Major Finding: The primary endpoint of disease control rate at 12 weeks was met with a partial response in two patients.

Concept: Manageable toxicities were observed, with no treatment-related deaths being observed.

Impact: Safety and antitumor activity of an EZH2 inhibitor was shown in malignant pleural mesothelioma.

TAZEMETOSTAT SHOWS ANTITUMOR ACTIVITY IN MALIGNANT PLEURAL MESOTHELIOMA

Patients with malignant pleural mesothelioma have not benefited from the therapeutic targeting of oncogenic drivers, in part, due to the large number of mutations in tumor suppressors in this disease. Systemic chemotherapy has therefore remained the standard of care for over a decade, with progression and relapse typically occurring within 6 months after treatment, supporting the urgent need for second-line therapies. *BAP1* has been found to be inactivated in a majority of cases, which leads to increases in EZH2 expression, and, in preclinical models of pleural mesothelioma, *BAP1* inactivation increased sensitivity to EZH2 inhibition. Building upon this, Zauderer and colleagues conducted a single-arm phase II clinical trial using the oral histone methyltransferase inhibitor tazemetostat in 74 patients with malignant pleural mesothelioma. The primary endpoint of this study was disease control rate, with secondary endpoints of objective response rate at 12 weeks, progression-free survival (PFS) at 12 and 24 weeks, and overall survival (OS) at 12 and 24 weeks. Disease control rate among those with *BAP1* inactivation was 54% at 12 weeks and 33% at 24 weeks, but no confirmed complete responses were observed, with a partial response seen in 3% of patients. Similar trends were observed in the overall patient population, with the overall population also having a median PFS of 18 weeks and a median OS of 36 weeks. Treatment-emergent adverse events (AE) were observed in 99% of patients, with fatigue, decreased appetite, dyspnea, cancer pain, and nausea being the most common. Grade 3–4 treatment-emergent AEs occurred in 49% of patients, with the most common including hyperglycemia, hyponatremia, and anemia, with no treatment-related deaths observed. Overall, the results of this trial showed that the primary endpoint of disease control at 12 weeks was met in approximately half the patients studied and was able to predict positive patient survival outcomes. This study also supports further investigation into biomarkers that predict the efficacy of tazemtostat to provide better patient stratification. ■

Zauderer MG, Szlosarek PW, Le Moulec S, Popat S, Taylor P, Planchard D, et al. EZH2 inhibitor tazemetostat in patients with relapsed or refractory, BAP1*-inactivated malignant pleural mesothelioma: a multicentre, open-label, phase 2 study. Lancet Oncol 2022; 23:758–67.*

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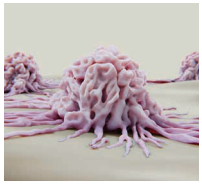
Metastasis

Major Finding: Colonization of the lymph node promotes distant organ metastasis through induction of immune tolerance.

Concept: IFN signaling induces epigenetic changes increasing MHC-1 and PD-L1 expression and altering tumor immunity.

Impact: This work reveals a conserved mechanism of distant metastasis that can be targeted in patients with advanced disease.

LYMPH NODE METASTASIS INDUCES IMMUNE TOLERANCE AND DISTANT METASTASIS



Metastatic disease is typically preceded by lymph node (LN) involvement, which serves as a prognostic factor in many solid tumors. LNs serve as immune cell education sites that can contribute to potent antitumor immunity; however, the possible role for LNs in tumor dissemination and the mechanisms that underlie tumor immune escape in this location remain unknow. Reticker-Flynn and colleagues sought to address this through development and use of a syngeneic melanoma LN metastasis model to investigate the effects LN metastases may have on distant tissue colonization. LN metastasis was found to enhance the ability of tumors to colonize distant organs, and analysis of differential gene expression revealed an enrichment of genes related to immune response, specifically type I and II IFN responses, while those related to cell cycle were the most reduced. Additionally, parental and LN metastatic lines were epigenetically distinct, with LN metastases showing activity of IFN-stimulated response elements and other IFN-regulatory factor binding motifs suggesting that epigenetic reprogramming aids in driving the LN metastatic phenotype. Both *Cd274* (which encodes PD-L1) and *B2m* gene expression, which are known IFN-inducible genes, were also upregulated in LN metastatic cell line generations leading to increased PD-L1 and major histocompatibility complex (MHC) class I molecules on the cell surface, with the more immediate upregulation of MHC class I molecules contributing to natural killer cell evasion and PD-L1 upregulation facilitating T-cell suppression. Furthermore, along with suppression of T-cell response, induction of regulatory T cells (T_{reg}) was observed with LN metastases, with these T_{regs} being antigen specific and demonstrating the ability to promote distant metastasis. In summary, this study developed a model that revealed LN metastases play a large role in promotion of subsequent metastasis to distant tissues through induction of immune tolerance making distant tissues amenable to metastatic colonization. This suggests immune response repolarization in the LNs as a potential approach to enhance therapy response in patients with advanced disease. ■

Reticker-Flynn NE, Zhang W, Belk JA, Basto PA, Escalante NK, Pilarowki GOW, et al. Lymph node colonization induces tumor-immune tolerance to promote distant metastasis. Cell 2022;185: 1924–42.e23.

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