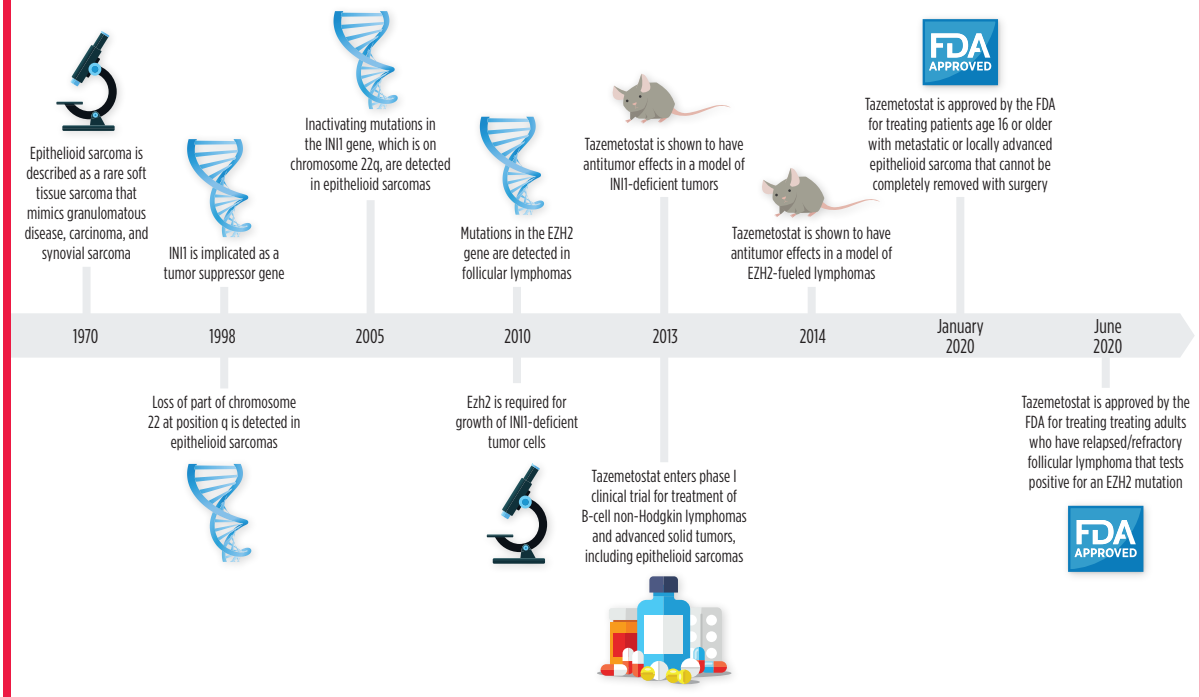
FIGURE 16 RESEARCH MILESTONES ON THE ROAD TO DEVELOPING TAZEMETOSTAT



In January 2020, tazemetostat (Tazverik) became the first epigenetic therapy to be approved by the U.S. Food and Drug Administration (FDA) for treating a solid tumor, epithelioid sarcoma. It was specifically approved for treating patients age 16 or older with metastatic or locally advanced epithelioid sarcoma that cannot be completely removed with surgery. It was subsequently approved for treating certain patients with an aggressive type of non-Hodgkin lymphoma called follicular lymphoma. The initial description of epithelioid sarcoma as a distinct type of cancer in 1970 was followed by decades of basic, translational, and clinical research, before the approval of tazemetostat as a treatment for the disease. One of the first research milestones on the way to the FDA approval was the discovery that damage to chromosome 22 at position q is characteristic of epithelioid sarcomas.

This was followed by the demonstration that INI1, which is found at chromosome 22q, is a tumor suppressor gene, the identification of inactivating mutations in the INI1 gene in epithelioid cancers, and the discovery that INI1-deficient tumors cells are dependent on EZH2 for their growth. Other research showed that mutations in EZH2 frequently occur in follicular lymphoma and other types of B-cell non-Hodgkin lymphoma and that targeting EZH2 has antitumor effects in preclinical models of lymphoma and solid tumors fueled by EZH2 mutations and INI1 mutations, respectively. Together, this body of research led to the development of tazemetostat, which targets EZH2, and its testing in clinical trials as a treatment for B-cell non-Hodgkin lymphomas and advanced solid tumors, including epithelioid sarcomas.