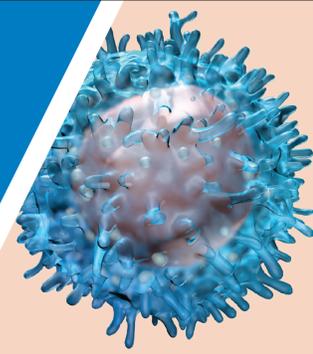


BiTE® (BISPECIFIC T-CELL ENGAGER) IMMUNOTHERAPY AND DLL3 IN SCLC

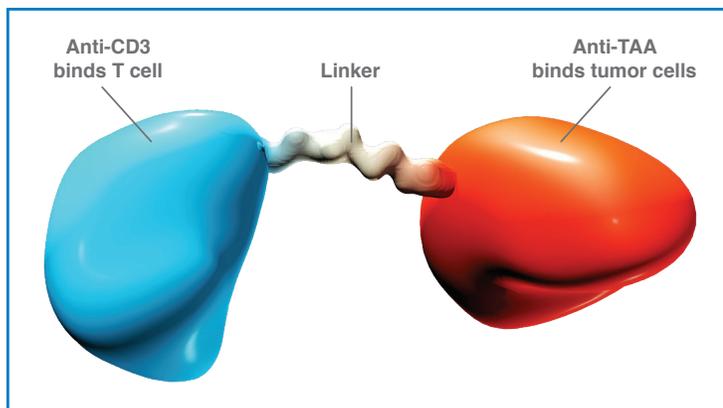


Tumor cells can be eliminated by cytotoxic T cells¹

Cytotoxic T cells play an important role in recognizing and eliminating tumor cells.¹ However, tumor cells can disrupt the ability of T cells to recognize them by downregulating MHC I and inhibiting T-cell receptor signaling, thus allowing tumor cells to evade immune surveillance.^{2,3}

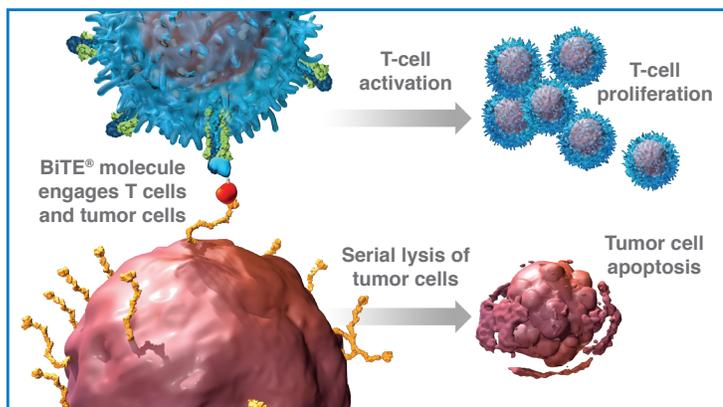
BiTE® (Bispecific T-cell Engager) molecules redirect cytotoxic T cells to targeted tumor cells and activate T cells without relying on normal TCR/MHC I recognition. They are designed to create a physical link between T cells and tumor cells, and may bypass the normal mechanism of T-cell receptor-mediated recognition.²

BiTE® molecules can engage a patient's own T cells with the goal of eliminating tumor cells²



BiTE® (BISPECIFIC T-CELL ENGAGER) IMMUNOTHERAPY

BiTE® molecules are comprised of a single chain variable fragment (scFv) that binds CD3, a short linker, and a scFv that binds a tumor-associated antigen (TAA).² BiTE® molecules can include an effectorless Fc domain to increase the serum half-life and allow for longer dosing intervals.^{4,5}



ACTIVATE AND ELIMINATE

BiTE® molecules are designed to activate T cells.^{2,6} Activated T cells can create perforin pores in the tumor cell membrane, allowing for the transfer of granzymes, which may induce tumor cell apoptosis.⁶

BiTE® molecules direct cytotoxic T cells to targeted tumor cells, resulting in T-cell-mediated apoptosis^{1,2}

CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable; MHC I, major histocompatibility class I; SCLC, small cell lung cancer; TAA, tumor-associated antigen; TCR, T-cell receptor.

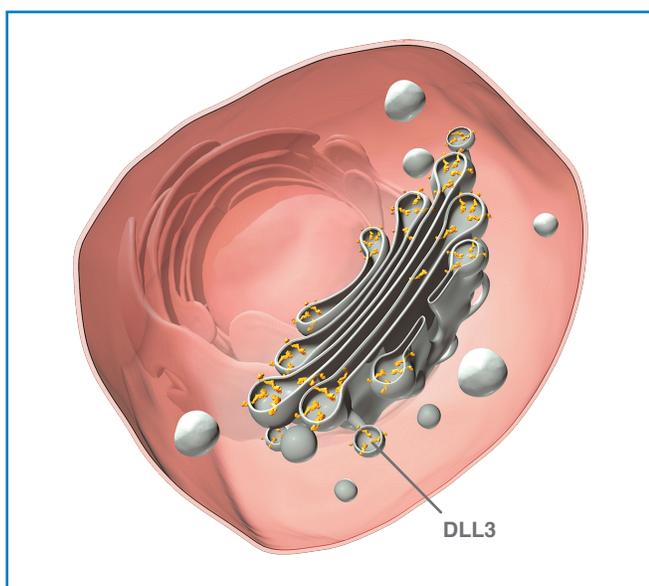
DELTA-LIKE LIGAND 3 (DLL3) IN SCLC AND OTHER NEUROENDOCRINE TUMORS

DLL3 is expressed on the surface of SCLC and other neuroendocrine tumors and rarely on normal cells^{7,8}

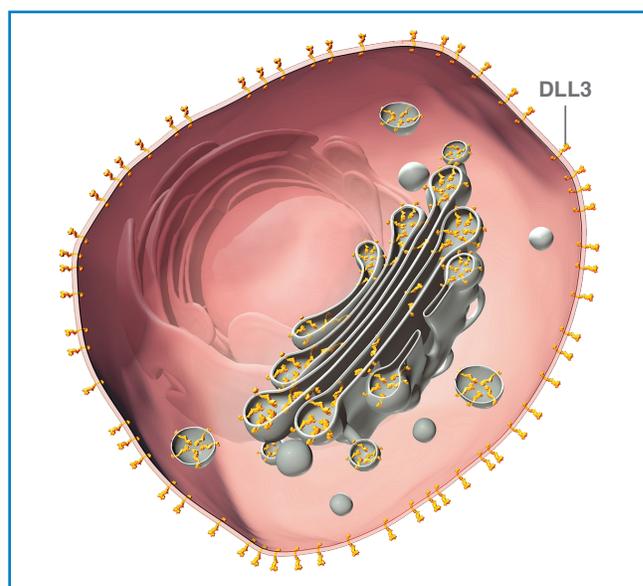
DLL3 is an inhibitory protein of Notch signaling, a pathway that is involved in embryonic development and neuroendocrine cell differentiation.⁷ DLL3 is typically located in the Golgi apparatus and cytoplasmic vesicles, and is rarely found on the cellular surface.⁸ However, in high-grade neuroendocrine tumors, including small cell lung cancer (SCLC), DLL3 is expressed on the cell surface.⁷

DLL3 EXPRESSION IN HEALTHY AND SCLC CELLS

HEALTHY CELL⁸
CYTOPLASMIC DLL3



SCLC CELL^{7,9}
CYTOPLASMIC AND CELL SURFACE DLL3



A large, multicenter study showed DLL3 expression in 85% of patients with **SCLC** (n=895/1,050), regardless of disease stage.^{9,*} In this study, DLL3 positivity was defined as staining of $\geq 25\%$ of tumor cells.^{9,†}

In an analysis of 423 patients with prostate cancer, DLL3 was expressed in 77% of **castration-resistant NEPC** samples (n=36/47).^{10,‡} In this study, DLL3 positivity was defined as any staining in total tumor cells.¹⁰

DLL3 is a tumor-associated antigen and a potential target for BiTE[®] immunotherapy^{2,7,11}

*A multicenter, international, noninterventional study of 1,050 patients with 1 specimen and evaluable DLL3 expression detected using IHC.⁹

†DLL3 staining defined as present if tumor cells showed punctate and/or diffuse cytoplasmic and/or partial or circumferential membranous staining.⁹

‡IHC DLL3 expression was only evaluated in 400 prostate cancer samples from 228 patients, with DLL3 positivity defined as any cytoplasmic or membranous staining.¹⁰

DLL3, delta-like ligand 3; IHC, immunohistochemistry; NEPC, neuroendocrine prostate cancer.

References: 1. Baeuerle PA, et al. *Curr Opin Mol Ther.* 2009;11:22-30. 2. Yuraszcek T, et al. *Clin Pharmacol Ther.* 2017;101:634-645. 3. Disis ML, et al. *Lancet.* 2009;373:673-683. 4. Weidle UH, et al. *Cancer Genomics Proteomics.* 2013;10:1-18. 5. Giffin MJ, et al. *Clin Cancer Res.* 2021;27:1526-1537. 6. Nagorsen D, et al. *Exp Cell Res.* 2011;317:1255-1260. 7. Sabari JK, et al. *Nat Rev Clin Oncol.* 2017;14:549-561. 8. Leonetti A, et al. *Cell Oncol (Dordr).* 2019;42:261-273. 9. Rojo F, et al. *Lung Cancer.* 2020;147:237-243. 10. Puca L, et al. *Sci Transl Med.* 2019;11:eaav0891. doi:10.1126/scitranslmed.aav0891. 11. Xiu MX, et al. *Onco Targets Ther.* 2020;13:3881-3901.