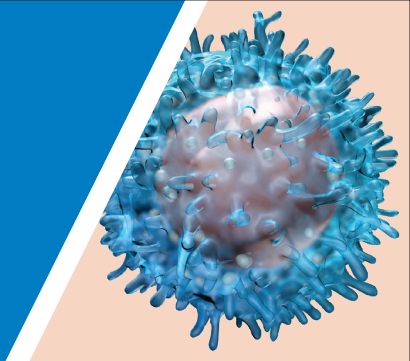
BiTE® (BISPECIFIC T-CELL ENGAGER) IMMUNOTHERAPY AND DLL3 IN SCLC

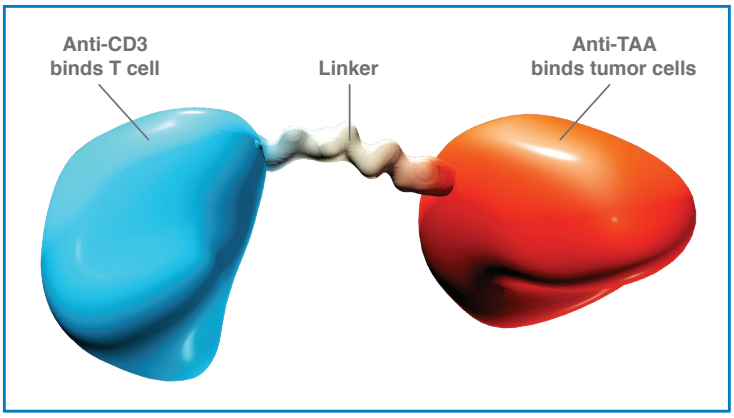


Tumor cells can be eliminated by cytotoxic T cells[1]

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]

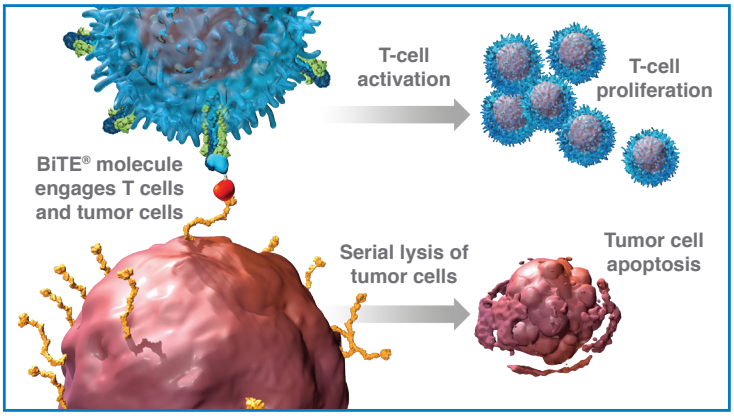
BiTE® (Bispecific T-cell Engager) molecules redirect cytotoxic T cells to targeted tumor cells and activate T cells without relying on normal TCR/MHC I recognition. They are designed to create a physical link between T cells and tumor cells, and may bypass the normal mechanism of T-cell receptor–mediated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

BiTE® molecules can engage a patient's own T cells with the goal of eliminating tumor cells[2]



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.

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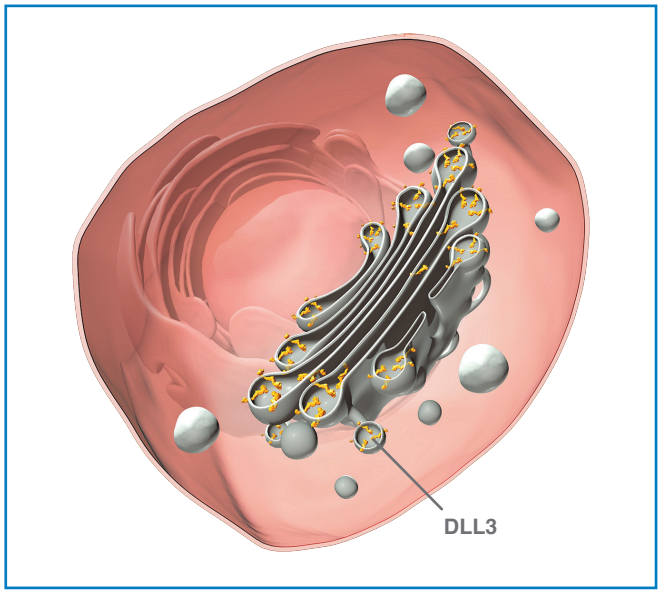
DELTA-LIKE LIGAND 3 (DLL3) IN SCLC AND OTHER NEUROENDOCRINE TUMORS

DLL3 is expressed on the surface of SCLC and other neuroendocrine tumors and rarely on normal cells[7,8]

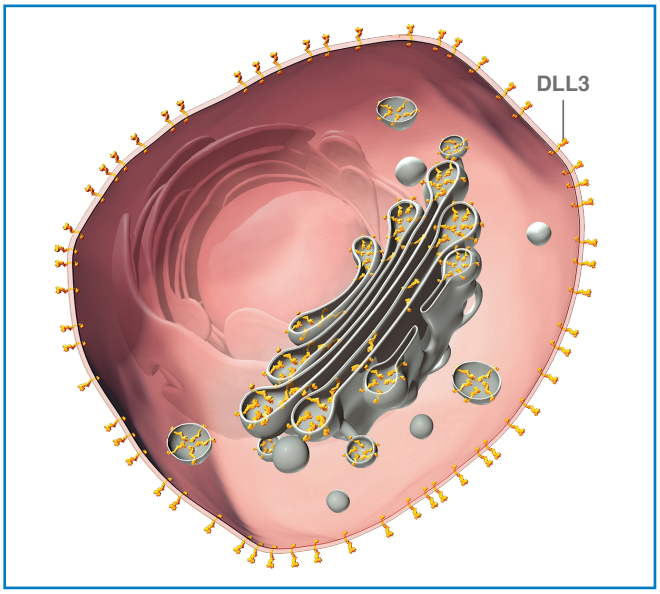
DLL3 is an inhibitory protein of Notch signaling, a pathway that is involved in embryonic development and neuroendocrine cell differentiation.[7] DLL3 is typically located in the Golgi apparatus and cytoplasmic vesicles, and is rarely found on the cellular surface.[8] However, in high-grade neuroendocrine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

DLL3 EXPRESSION IN HEALTHY AND SCLC CELLS

HEALTHY CELL[8]
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 ≥ 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.** Yuraszeck 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.

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