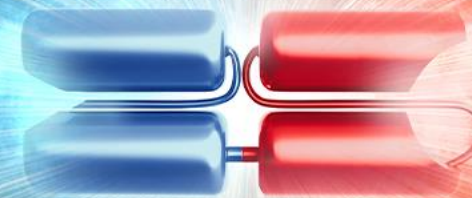


INVESTIGATING DLL3-TARGETED IMMUNOTHERAPY: THE POTENTIAL OF T CELLS TO FIGHT SMALL CELL LUNG CANCER (SCLC)



AMGEN[®]

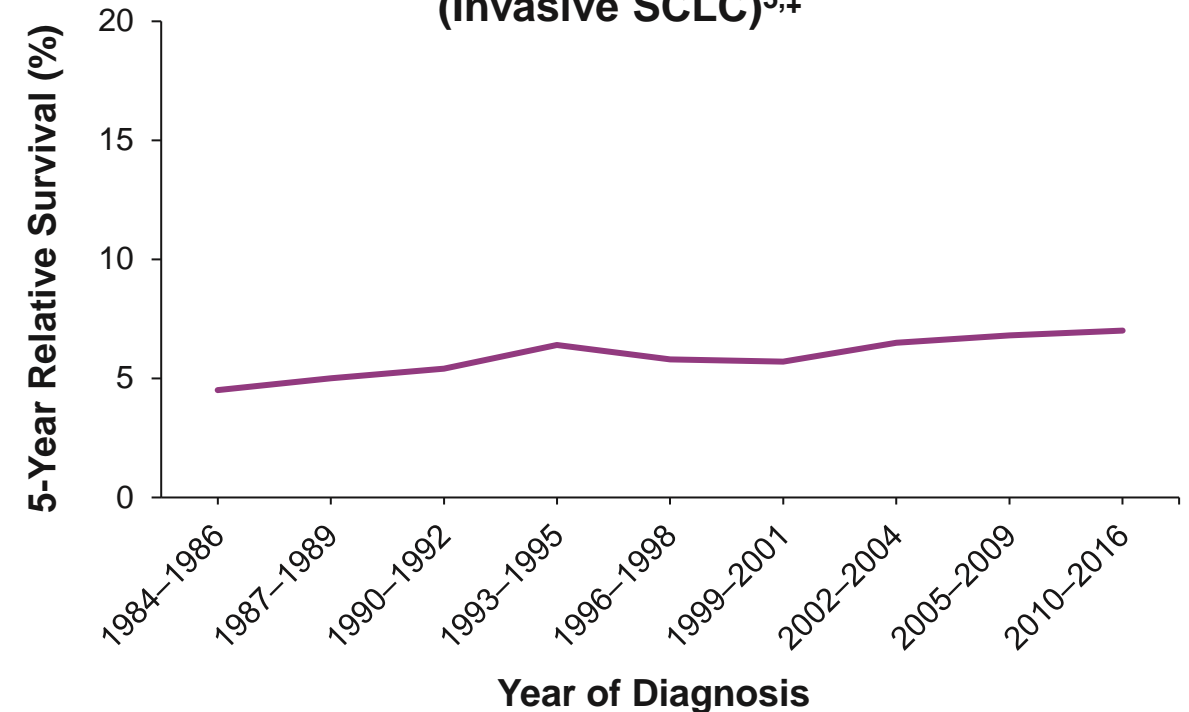
OBJECTIVES

- Discuss the disease burden and unmet need in patients with SCLC
- Provide an overview of investigational T-cell engagers
- Describe the potential of delta-like ligand 3 (DLL3) as a target for BiTE[®] immunotherapy in SCLC

SCLC IS AN AGGRESSIVE CANCER ASSOCIATED WITH POOR OUTCOMES

- SCLC is an aggressive disease with **rapid growth** and early **metastases**¹
- It is estimated that there will be ~ 30,000 new cases of SCLC in the US in 2023²
- Approximately two-thirds of patients with SCLC are diagnosed with **extensive-stage disease**¹
- While SCLC is usually sensitive to initial treatment, many patients can progress within months^{3,4}
- ES-SCLC is associated with a median survival of **10–13 months**^{3,4,*;†}
- SCLC has a **high rate of molecular alterations**, yet there are currently no actionable biomarkers¹

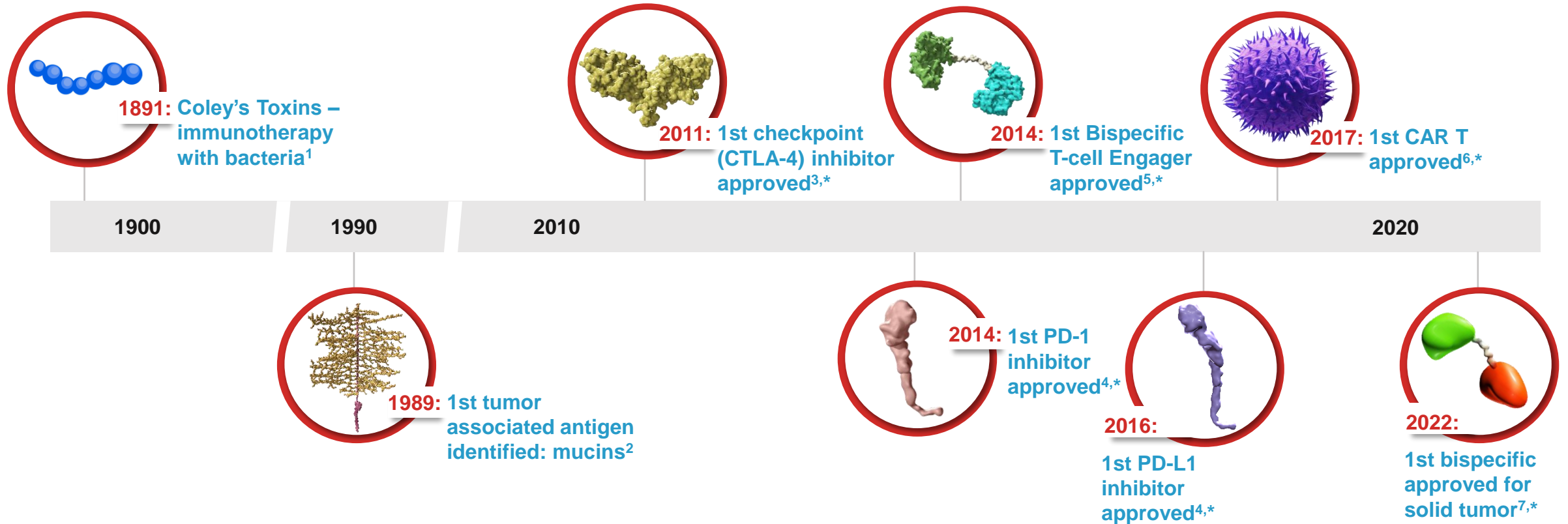
5-Year Relative Survival by Year of Diagnosis (Invasive SCLC)^{5;‡}



THERE REMAINS A HIGH UNMET NEED FOR PATIENTS WITH SCLC¹

*Based on a phase 3, randomized, open-label trial demonstrating median OS of 13.0 months for anti-PD-L1 therapy plus platinum-based chemotherapy (n=268) versus 10.3 months for platinum-based chemotherapy alone (n=269) as first-line therapy in patients with ES-SCLC enrolled between March 27, 2017 and May 29, 2018.³ †Based on a phase 3, randomized, double-blind trial demonstrating median OS of 12.3 months for anti-PD-L1 therapy plus platinum-based chemotherapy (n=201) versus 10.3 months for platinum-based chemotherapy alone (n=202) as first-line therapy in patients with ES-SCLC enrolled between June 6, 2016 and May 31, 2017.⁴ ‡Based on SEER 9 in patients with invasive small cell cancer of the lung and bronchus.⁵ ES-SCLC, extensive-stage small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; SCLC, small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results. 1. Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561. 2. American Cancer Society. www.cancer.org. Accessed February 14, 2023. 3. Paz-Ares L, et al. *Lancet*. 2019;394:1929-1939. 4. Horn L, et al. *N Engl J Med*. 2018;379:2220-2229. 5. National Cancer Institute. www.cancer.gov. Accessed February 14, 2023.

OVER THE LAST FEW DECADES, THERE HAS BEEN SIGNIFICANT INNOVATION IN CANCER IMMUNOTHERAPY



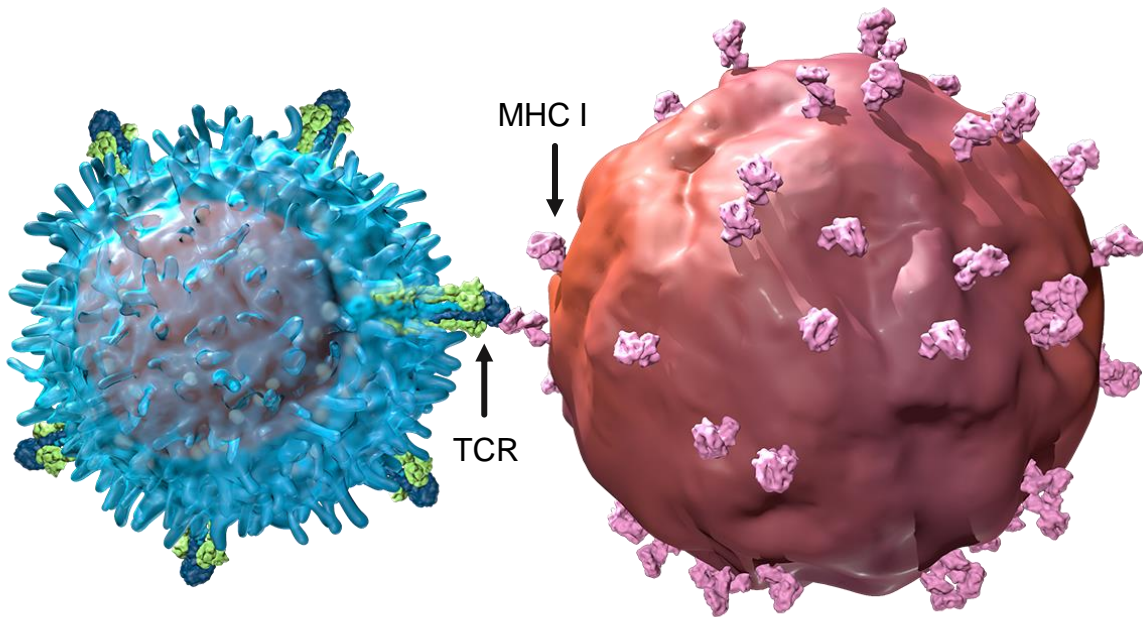
IMMUNOTHERAPIES, THROUGH DIFFERENT MECHANISMS, ARE DESIGNED TO HARNESS THE PATIENT'S IMMUNE SYSTEM TO TARGET AND ELIMINATE TUMOR CELLS⁸

*Represents accelerated or full FDA approval dates.³⁻⁷

CAR T, chimeric antigen receptor T cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

1. American Association for Cancer Research. www.aacr.org. Accessed February 15, 2023. 2. Barnd DL, et al. *Proc Natl Acad Sci U S A*. 1989;86:7159-7163. 3. Cancer Research Institute. www.cancerresearch.org. Accessed February 15, 2023. 4. Cancer Research Institute. www.cancerresearch.org. Accessed February 14, 2023. 5. Einsele H, et al. *Cancer*. 2020;126:3192-3201. 6. Food and Drug Administration. www.fda.gov. Accessed February 17, 2023. 7. Food and Drug Administration. www.fda.gov. Accessed February 17, 2023. 8. Waldman AD, et al. *Nat Rev Immunol*. 2020;20:651-668.

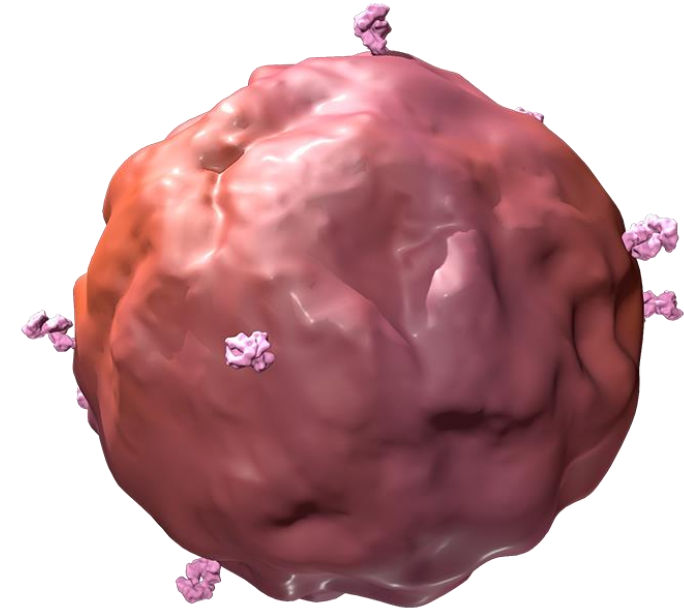
CYTOTOXIC T CELLS PLAY AN IMPORTANT ROLE IN RECOGNIZING AND ELIMINATING TUMOR CELLS



T cell

Tumor cell

Cytotoxic T cells can recognize cancer cells via TCR-MHC I binding, which results in T-cell-mediated tumor cell lysis¹



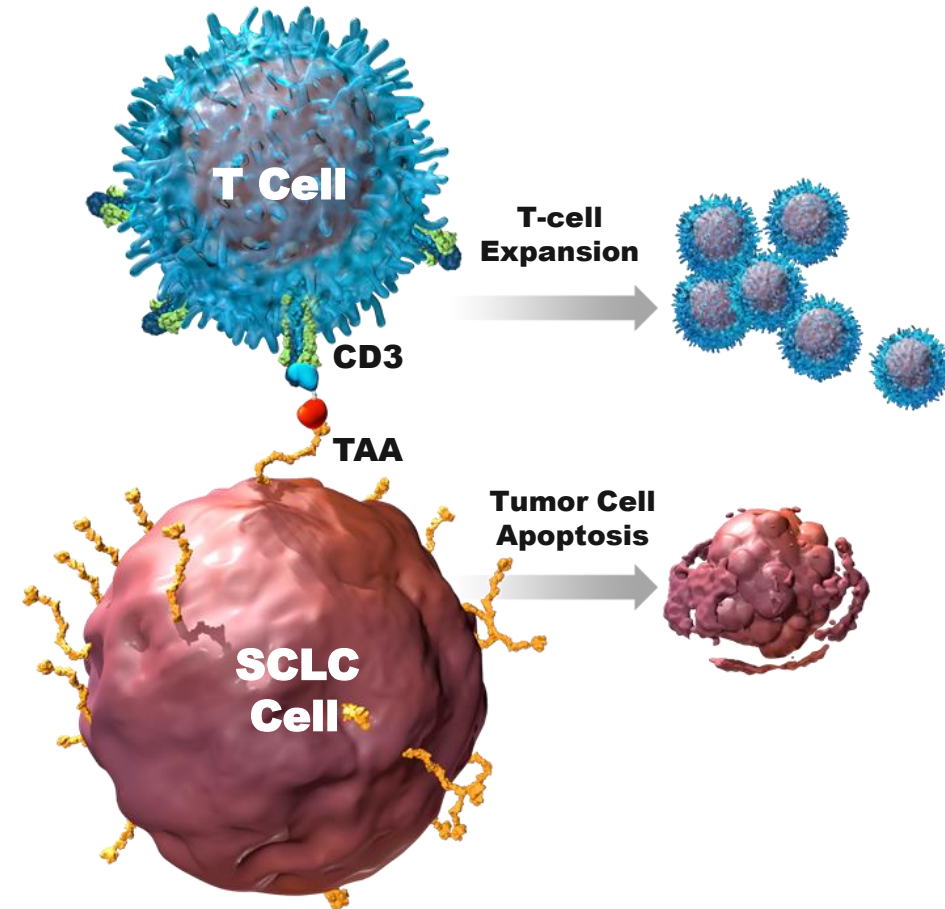
Tumors can evade immune detection by downregulating MHC I and through an immunosuppressive tumor microenvironment²

MHC I, major histocompatibility class I; TCR, T-cell receptor.

1. Baeuerle PA, et al. *Curr Opin Mol Ther.* 2009;11:22-30. 2. Yuraszek T, et al. *Clin Pharmacol Ther.* 2017;101:634-645.

INVESTIGATIONAL T-CELL ENGAGERS ARE DESIGNED TO REDIRECT CYTOTOXIC T CELLS TO TARGET AND KILL TUMOR CELLS

- Investigational T-cell engager molecules are designed to bind both a tumor-associated antigen (TAA) on tumor cells and CD3 on T cells¹
- They are designed to create an immunological synapse between T cells and tumor cells, and can activate T cells without relying on normal TCR/MHC I recognition^{2,3}
- Activated T cells:
 - Create perforin pores in the tumor cell membrane, allowing for the transfer of granzymes, which may induce apoptosis³
 - Proliferate, resulting in expansion of T cells to facilitate additional T-cell–dependent killing³

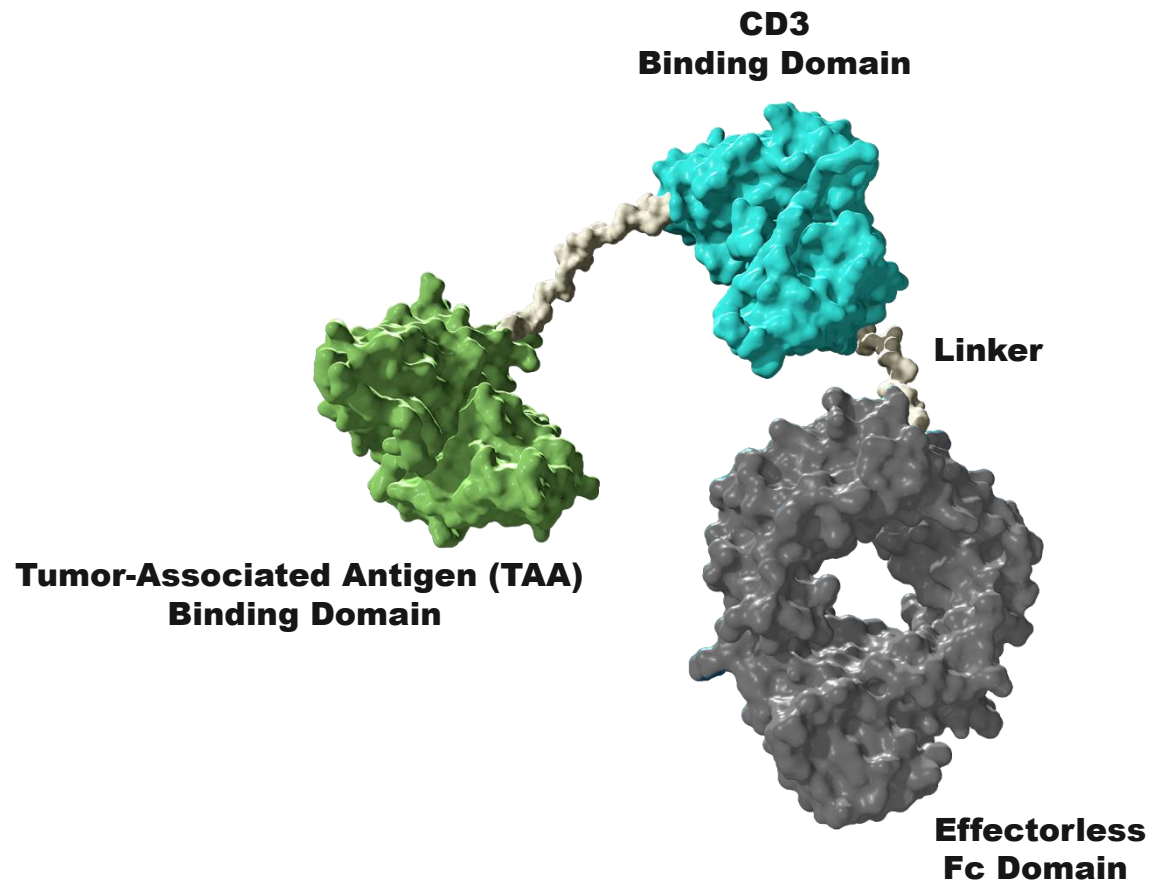


CD, cluster of differentiation; MHC I, major histocompatibility class I; SCLC, small cell lung cancer; TCR, T-cell receptor.

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. Nagorsen D, et al. *Exp Cell Res*. 2011;317:1255-1260.

BiTE[®] (BISPECIFIC T-CELL ENGAGER) TECHNOLOGY

- BiTE[®] molecules targeting different tumor-associated antigens are being investigated in hematologic and solid tumor malignancies¹
- The BiTE[®] molecule consists of two scFv domains that are designed to bind a cell surface antigen on tumor cells and CD3 on T cells, with a silenced Fc domain for extended half-life^{2,3}

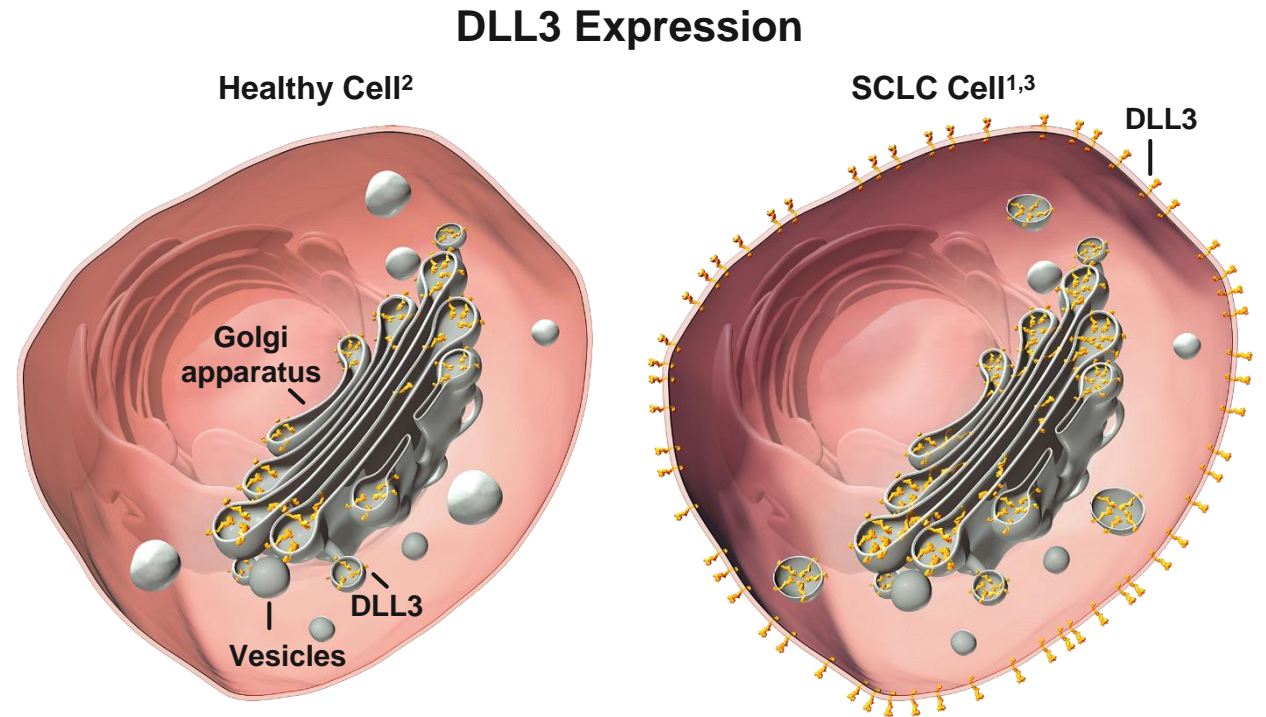


CD, cluster of differentiation; Fc, fragment crystallizable; scFv, single chain variable fragment.

1. Einsele H, et al. *Cancer*. 2020;126:3192-3201. 2. Yuraszek T, et al. *Clin Pharmacol Ther*. 2017;101:634-645. 3. Weidle UH, et al. *Cancer Genomics Proteomics*. 2013;10:1-18.

DELTA-LIKE LIGAND 3 (DLL3) IS EXPRESSED ON THE CELL SURFACE OF SCLC AND RARELY ON NORMAL CELLS

- DLL3 is an inhibitory protein of Notch signaling, a pathway that is involved in embryonic development and neuroendocrine cell differentiation¹
- In healthy cells, DLL3 is typically located in the Golgi apparatus and cytoplasmic vesicles, and is rarely found on the cellular surface²
- In high-grade neuroendocrine tumors, including SCLC, DLL3 is expressed on the cell surface¹
 - ~ 85% of patients with SCLC have cell surface expression of DLL3^{3,*}



DLL3 IS A TUMOR-ASSOCIATED ANTIGEN AND A POTENTIAL TARGET FOR BiTE[®] IMMUNOTHERAPY

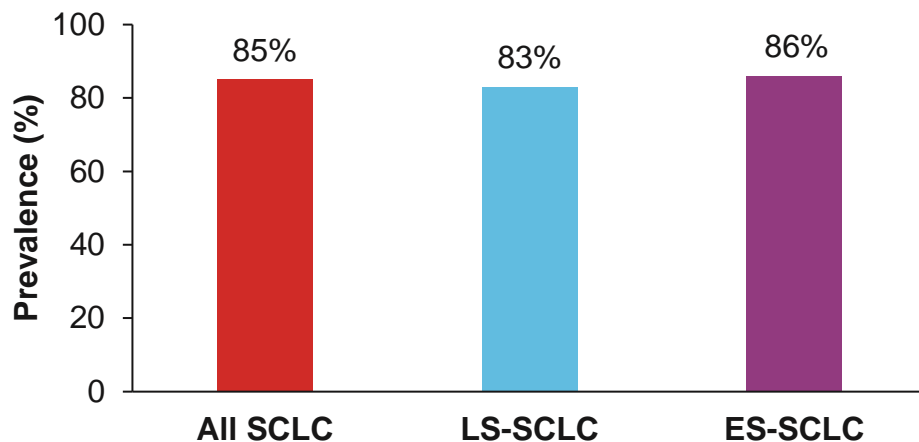
*Based on a multicenter, international, noninterventional study of 1,050 patients with 1 specimen and evaluable DLL3 expression. DLL3 positivity was based on immunohistochemistry staining with $\geq 25\%$ of tumor cells that expressed DLL3. DLL3 staining defined as present if tumor cells showed punctate and/or diffuse cytoplasmic and/or partial or circumferential membranous staining.³

BiTE, Bispecific T-cell Engager; SCLC, small cell lung cancer.

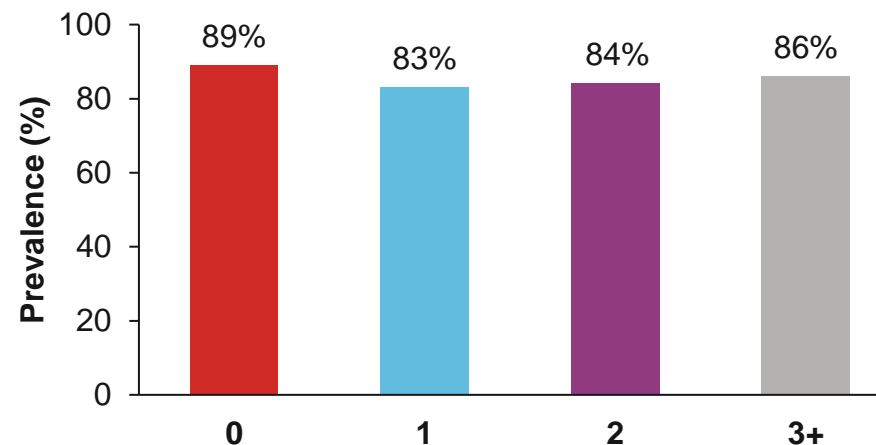
1. Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561. 2. Leonetti A, et al. *Cell Oncol (Dordr)*. 2019;42:261-273. 3. Rojo F, et al. *Lung Cancer*. 2020;147:237-243.

DLL3 IS EXPRESSED ON THE SURFACE OF MOST SCLC TUMORS

Prevalence of DLL3 Expression in Patients With SCLC*



Prevalence of DLL3 Expression Across SCLC Lines of Therapy*



- A large, multicenter study found that **85% of patients with SCLC** (n=895/1,050) had $\geq 25\%$ tumor cells that expressed DLL3 by immunohistochemistry
- The proportion of patients that expressed DLL3 remained consistently high ($\geq 83\%$) **across disease stage and lines of therapy** in patients with SCLC

*Based on a multicenter, international, noninterventional study of 1,050 patients with 1 specimen and evaluable DLL3 expression. DLL3 positivity was based on immunohistochemistry staining with $\geq 25\%$ of tumor cells that expressed DLL3. DLL3 staining defined as present if tumor cells showed punctate and/or diffuse cytoplasmic and/or partial or circumferential membranous staining.

DLL3, delta-like ligand 3; ES-SCLC, extensive-stage small cell lung cancer; LS-SCLC, limited-stage small cell lung cancer; SCLC, small cell lung cancer.

Rojo F, et al. *Lung Cancer*. 2020;147:237-243.

SUMMARY



There remains a high unmet need for patients with SCLC¹



Investigational T-cell engagers are designed to direct the patient's own T cells to target tumor cells²



Due to its high expression on the surface of SCLC cells and minimal expression on normal cells, DLL3 is a potential therapeutic target for BiTE[®] immunotherapy^{2,3}

BiTE, Bispecific T-cell Engager; DLL3, delta-like ligand 3; SCLC, small cell lung cancer.

1. Rudin CM, et al. *Nat Rev Dis Primers*. 2021;7:3. 2. Yuraszeck T, et al. *Clin Pharmacol Ther*. 2017;101:634-645. 3. Leonetti A, et al. *Cell Oncol (Dordr)*. 2019;42:261-273.

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