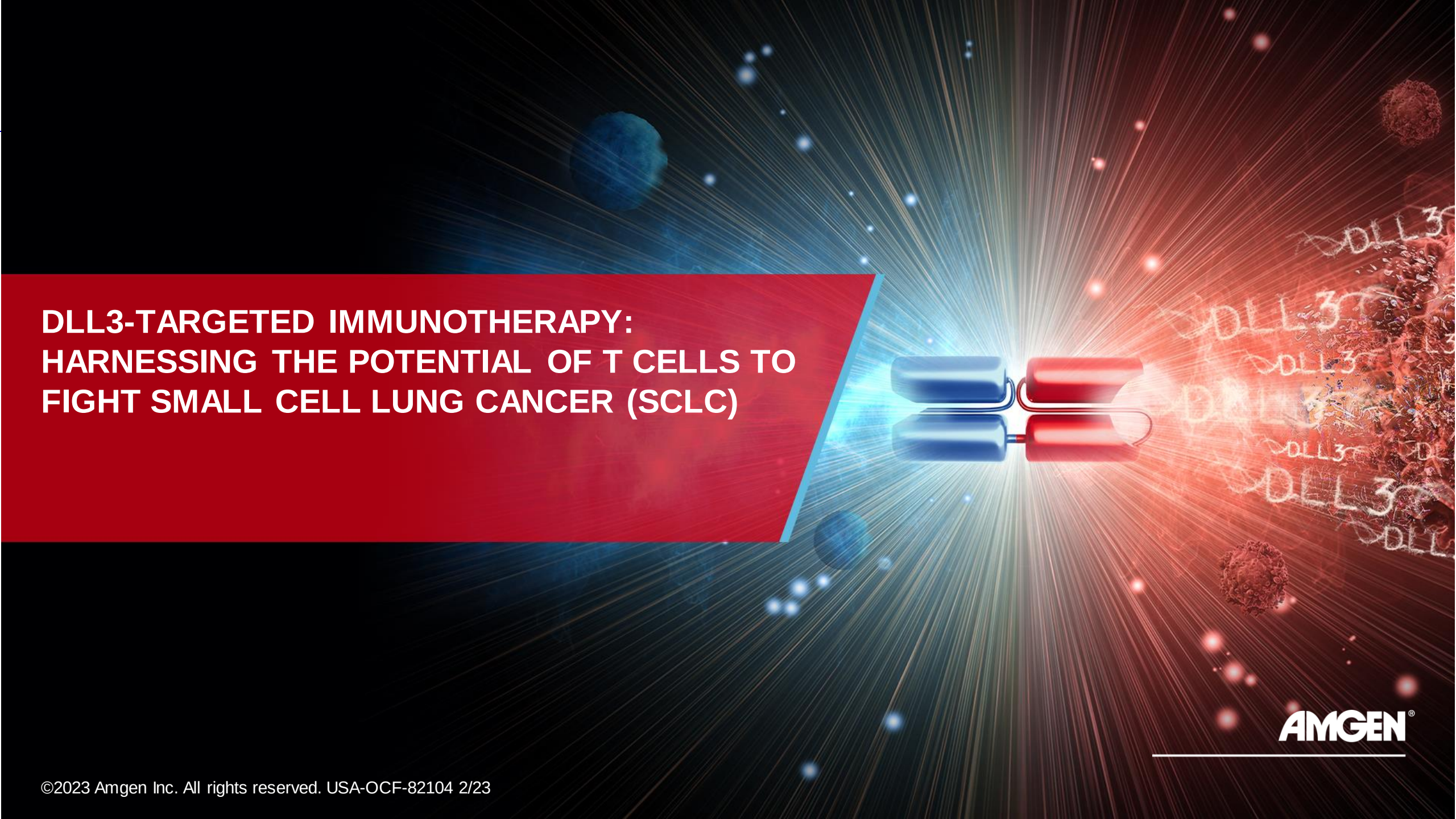
DLL3-TARGETED IMMUNOTHERAPY: HARNESSING THE POTENTIAL OF T CELLS TO FIGHT SMALL CELL LUNG CANCER (SCLC)



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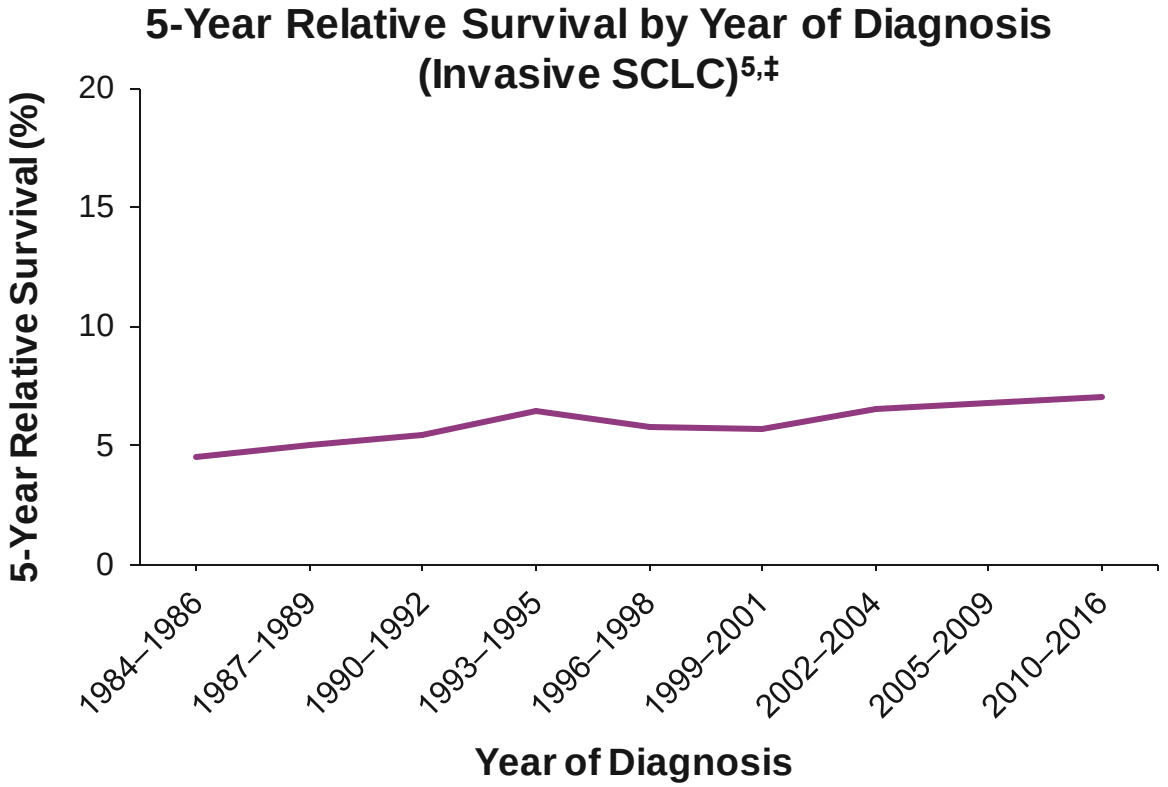
OBJECTIVES

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

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

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 2023[2]
- 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 biomarkers[1]

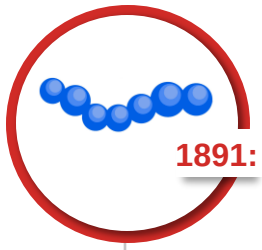


THERE REMAINS A HIGH UNMET NEED FOR PATIENTS WITH SCLC[1]

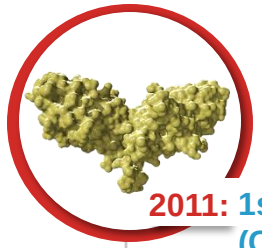
*Based on a phase 3, randomized, open-label trial demonstrating median OS of 13.0 months for anti–PD-L1 therapy plus platinum-based chemotherapy (n=268) versus 10.3 months for platinum-based chemotherapy alone (n=269) as first-line therapy in patients with ES-SCLC enrolled between March 27, 2017 and 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



1891: Coley's Toxins – immunotherapy with bacteria[1]



2011: 1st checkpoint (CTLA-4) inhibitor approved[3,*]

2014: 1st BiTE® molecule approved[5,*]

2017: 1st CAR T approved[6,*]

1900 | 1990 | 2010 | 2020

1989: 1st tumor associated antigen identified: mucins[2]

2014: 1st PD-1 inhibitor approved[4,*]

2016: 1st PD-L1 inhibitor approved[4,*]

2022: 1st bispecific approved for solid tumor[7,*]

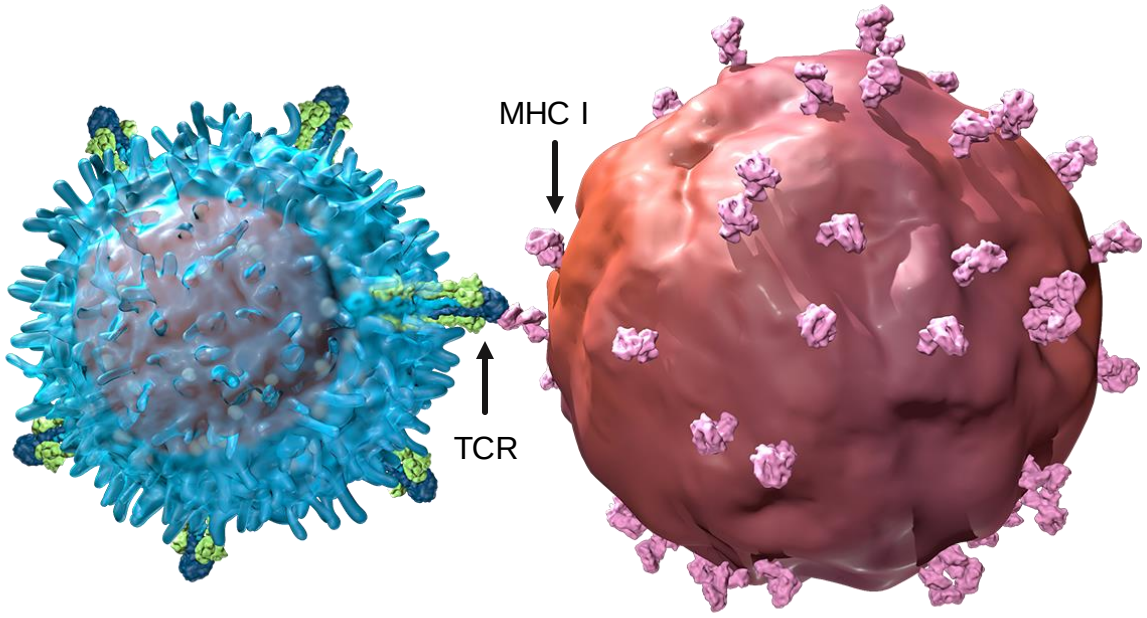
IMMUNOTHERAPIES, THROUGH DIFFERENT MECHANISMS, ARE DESIGNED TO HARNESS THE PATIENT'S IMMUNE SYSTEM TO TARGET AND ELIMINATE TUMOR CELLS[8]

*Represents accelerated or full FDA approval dates.[3-7]

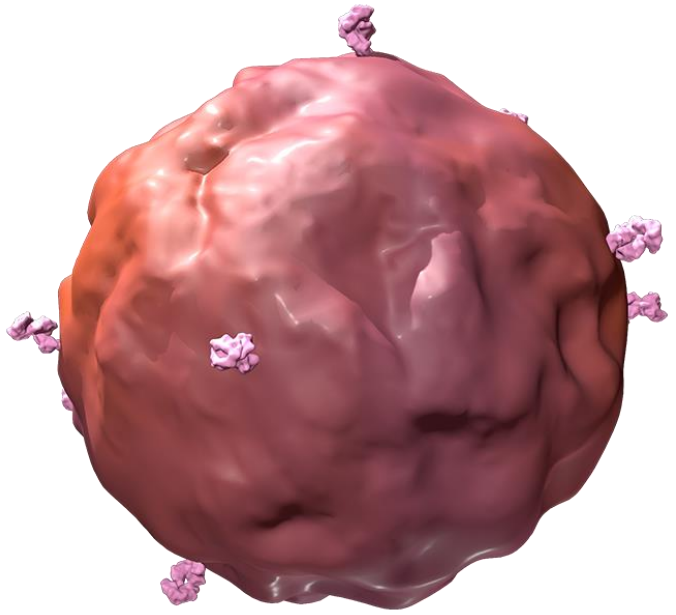
BiTE, Bispecific T-cell Engager; CAR T, chimeric antigen receptor T cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

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



Cytotoxic T cells can recognize cancer cells via TCR-MHC I binding, which results in T-cell–mediated tumor cell lysis[1]



Tumors can evade immune detection by downregulating MHC I and through an immunosuppressive tumor microenvironment[2]

MHC I, major histocompatibility class I; 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.

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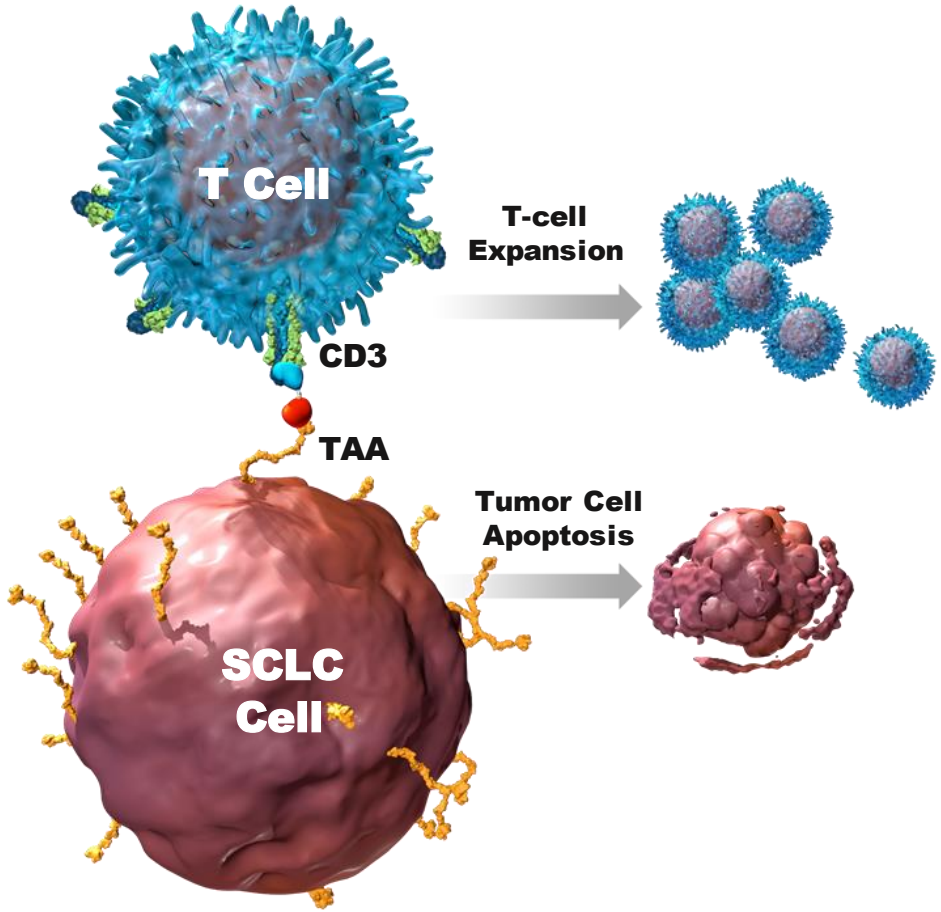
T-CELL ENGAGERS ARE DESIGNED TO REDIRECT CYTOTOXIC T CELLS TO TARGET AND KILL TUMOR CELLS

- T-cell engager molecules are designed to bind both a tumor-associated antigen (TAA) on tumor cells and CD3 on T cells[1]
- 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 apoptosis[3]
  - Proliferate, resulting in expansion of T cells to facilitate additional T-cell–dependent killing[3]

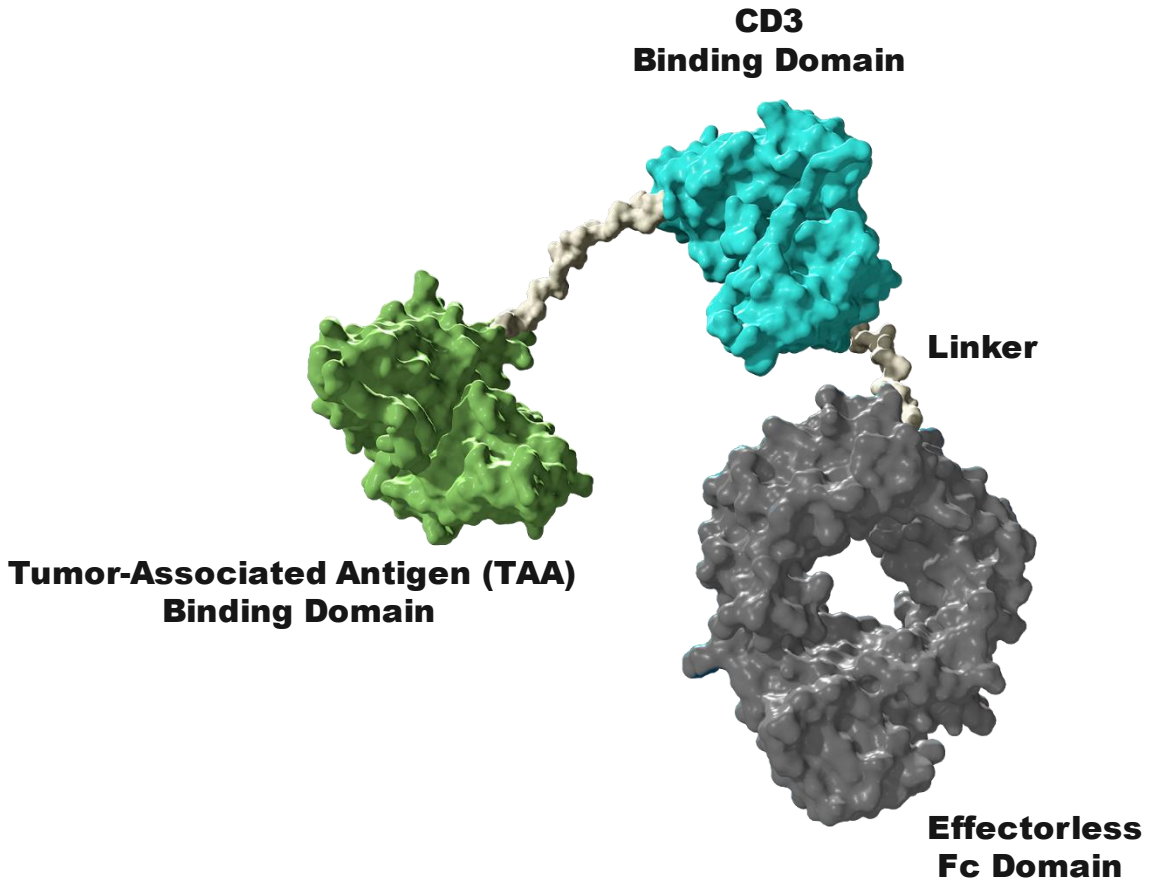


CD, cluster of differentiation; MHC I, major histocompatibility class I; SCLC, small cell lung cancer; TCR, T-cell receptor.

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® technology is a clinically validated T-cell engager platform[1]
  - The first BiTE® molecule was approved in 2014[1]
  - BiTE® molecules targeting different tumor-associated antigens are being investigated in hematologic and solid tumor malignancies[1]
- The BiTE® molecule consists of two scFv domains that bind a cell surface antigen on tumor cells and CD3 on T cells, with a silenced Fc domain for extended half-life[2,3]

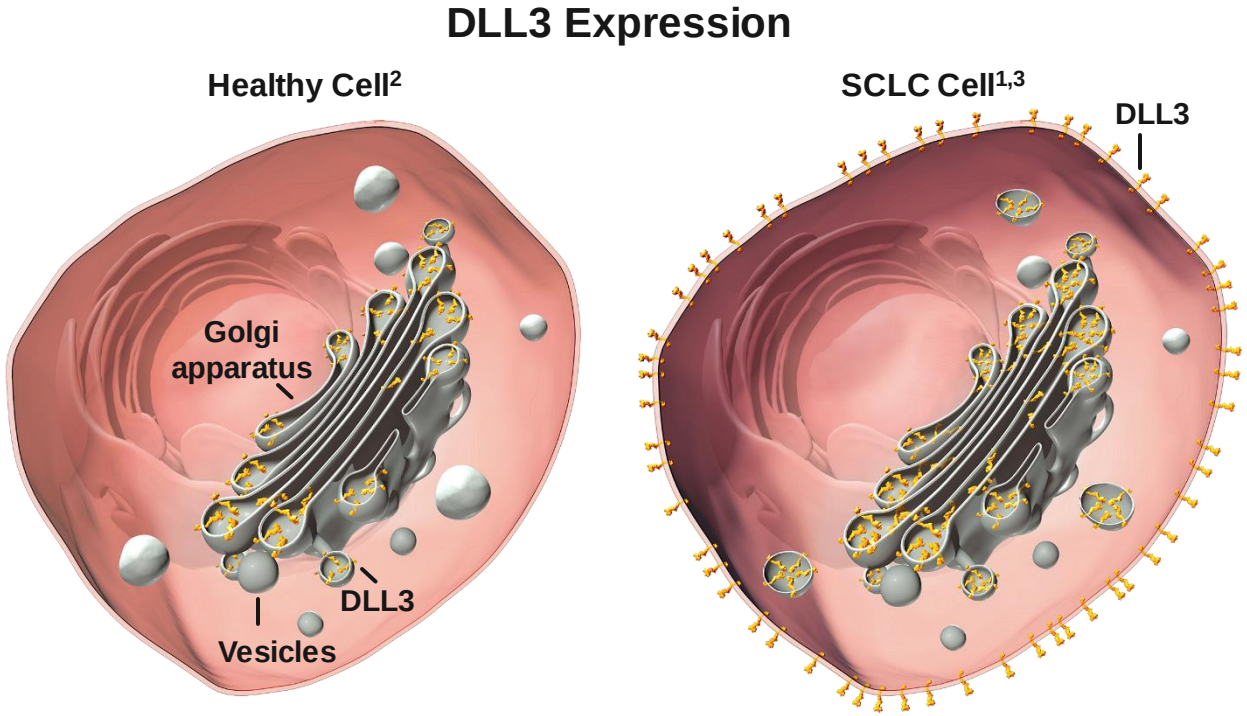


CD, cluster of differentiation; Fc, fragment crystallizable; scFv, single chain variable fragment.

1. Einsele H, et al. *Cancer*. 2020;126:3192-3201. **2.** Yuraszeck 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 differentiation[1]
- In healthy cells, DLL3 is typically located in the Golgi apparatus and cytoplasmic vesicles, and is rarely found on the cellular surface[2]
- In high-grade neuroendocrine tumors, including SCLC, DLL3 is expressed on the cell surface[1]
  - ~ 85% of patients with SCLC have cell surface expression of DLL3[3,*]



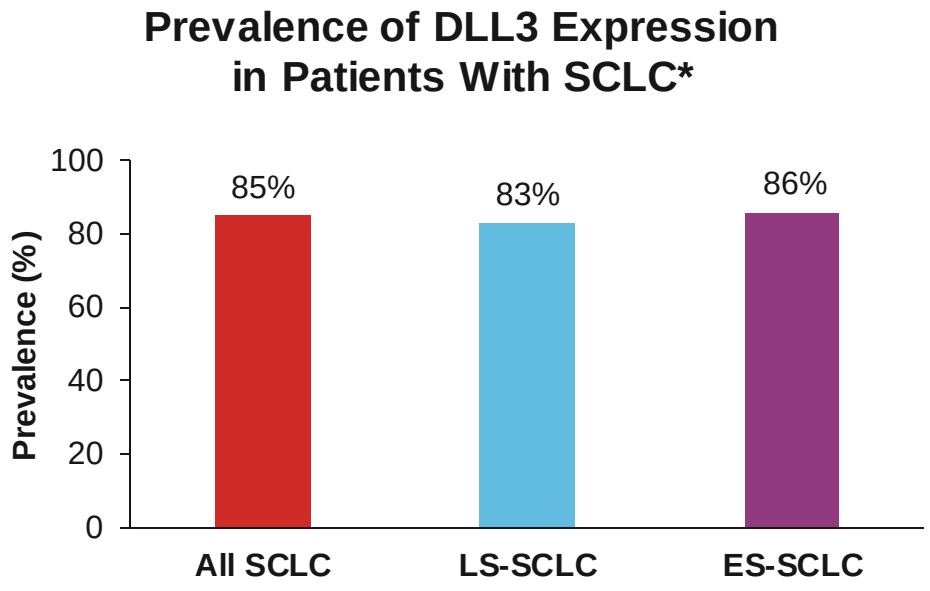
DLL3 IS A TUMOR-ASSOCIATED ANTIGEN AND A POTENTIAL TARGET FOR BiTE® IMMUNOTHERAPY

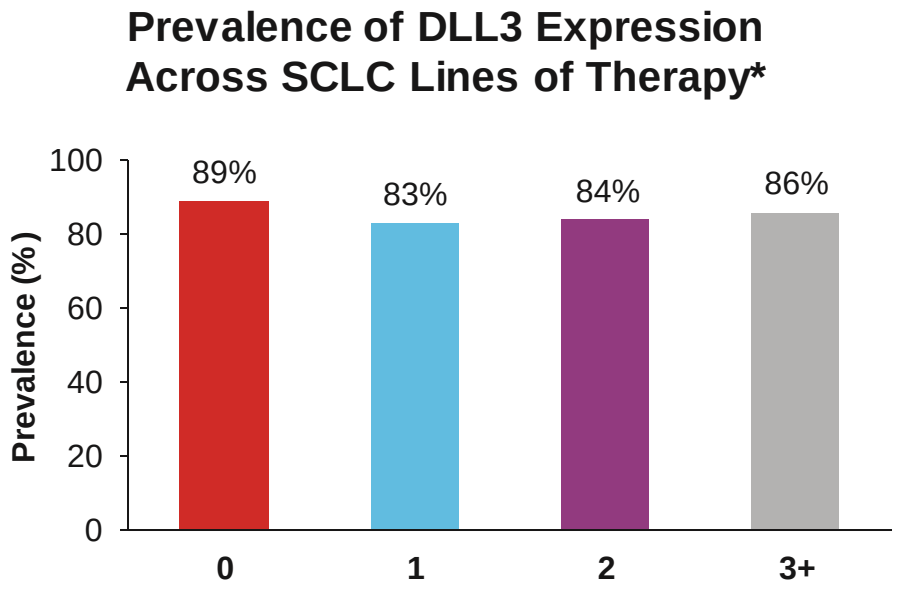
*Based on a multicenter, international, noninterventional study of 1,050 patients with 1 specimen and evaluable DLL3 expression. DLL3 positivity was based on immunohistochemistry staining with ≥ 25% of tumor cells that expressed DLL3. DLL3 staining defined as present if tumor cells showed punctate and/or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





- A large, multicenter study found that **85% of patients with SCLC** (n=895/1,050) had ≥ 25% tumor cells that expressed DLL3 by immunohistochemistry
- The proportion of patients that expressed DLL3 remained consistently high (≥ 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 ≥ 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.

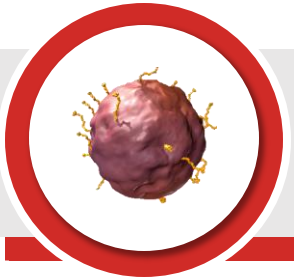
DLL3, delta-like ligand 3; ES-SCLC, extensive-stage small cell lung cancer; LS-SCLC, limited-stage small cell lung cancer; SCLC, small cell lung cancer.

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

SUMMARY

There remains a high unmet need for patients with SCLC[1]

T-cell engagers, including BiTE® molecules, are designed to direct the patient's own T cells to target tumor cells[2]



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.