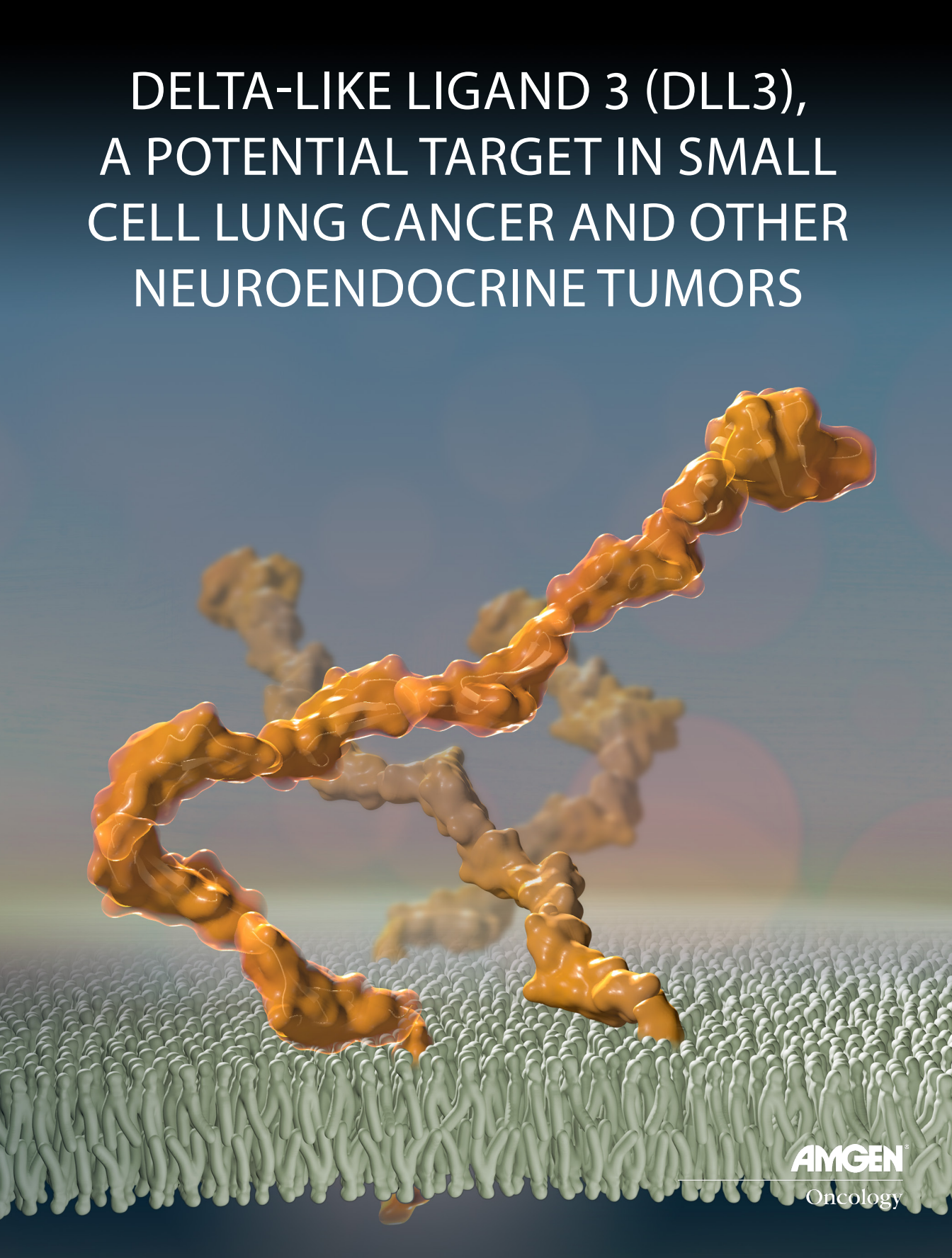
DELTA-LIKE LIGAND 3 (DLL3), A POTENTIAL TARGET IN SMALL CELL LUNG CANCER AND OTHER NEUROENDOCRINE TUMORS



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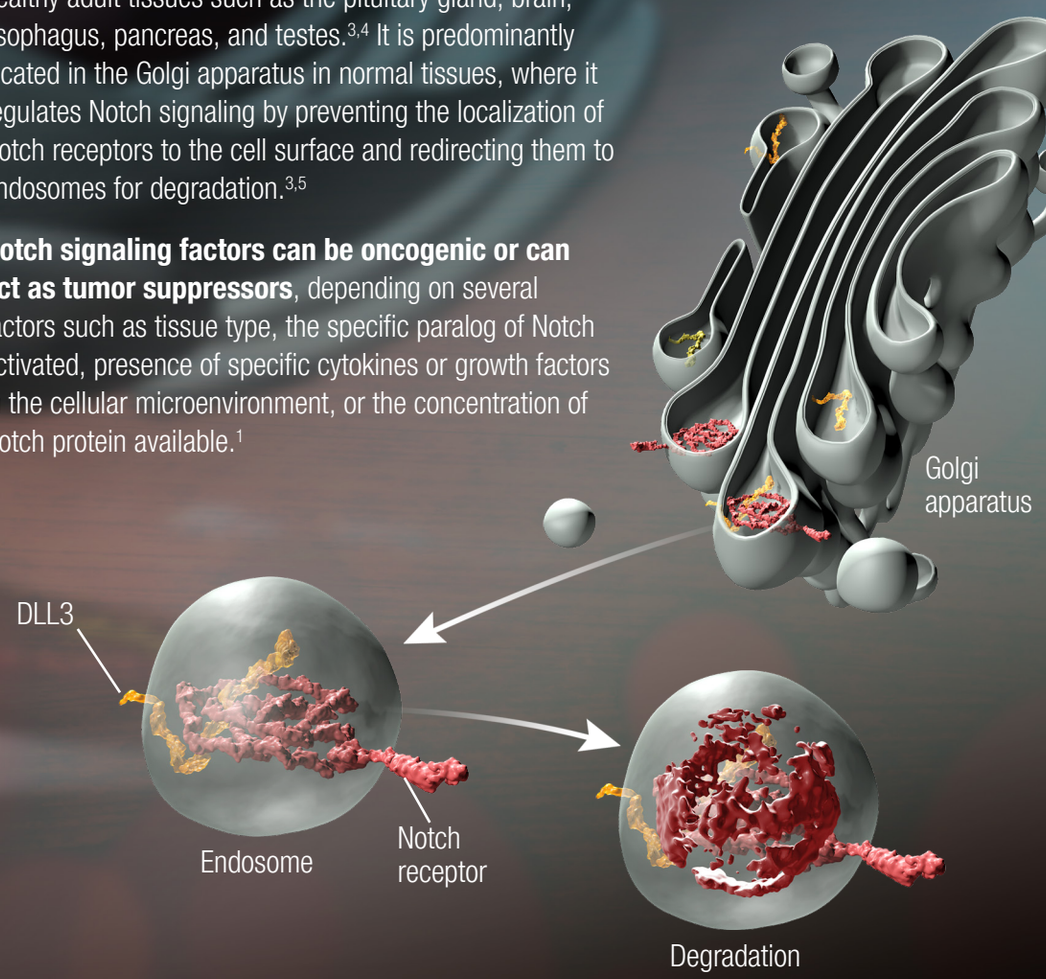
THE NOTCH SIGNALING PATHWAY, WHICH PLAYS A KEY ROLE IN CELLULAR PHYSIOLOGY, IS DEREGULATED IN CANCER

The Notch signaling pathway is central to embryonic development as well as to the development and maintenance of adult tissues.[1] This complex pathway influences a wide variety of cellular functions such as direct cell-to-cell communication, differentiation, proliferation, and apoptosis, all of which affect cell fate.[2] The Notch family of type 1 transmembrane receptors consists of four protein paralogs (Notch 1–4) and five ligands (Delta-like ligand [DLL] 1, 3, and 4; Jagged 1 and 2).[1]

DLL3 is normally expressed at relatively low levels in healthy adult tissues such as the pituitary gland, brain, esophagus, pancreas, and testes.[3,4] It is predominantly located in the Golgi apparatus in normal tissues, where it regulates Notch signaling by preventing the localization of Notch receptors to the cell surface and redirecting them to endosomes for degradation.[3,5]

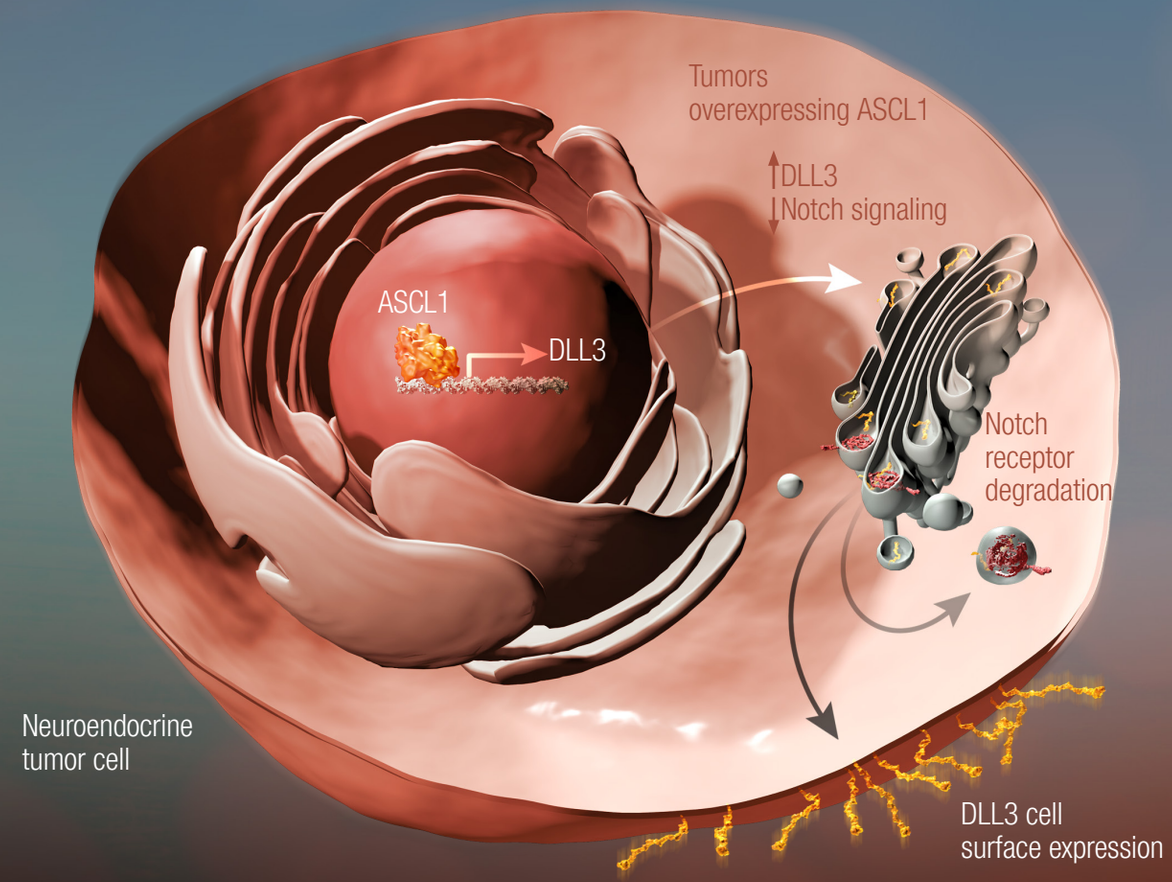
Notch signaling factors can be oncogenic or can act as tumor suppressors, depending on several factors such as tissue type, the specific paralog of Notch activated, presence of specific cytokines or growth factors in the cellular microenvironment, or the concentration of Notch protein available.[1]



DLL, delta-like ligand; JAG, jagged.

DLL3 IS AN INHIBITORY LIGAND IN THE NOTCH SIGNALING PATHWAY THAT IS EXPRESSED ON THE CELL SURFACE OF SMALL CELL LUNG CANCER AND OTHER NEUROENDOCRINE TUMOR CELLS

DLL3 is overexpressed on the cell surface of small cell lung cancer (SCLC; 80%)[3,6] and multiple other tumor types of neuroendocrine origin, including pulmonary large cell neuroendocrine carcinoma,[3] isocitrate dehydrogenase–mutant glioma,[7] small cell bladder cancer,[8] melanoma,[9] and renal cell carcinoma.[10] In addition, it is also abundantly expressed in tumor tissues of neuroendocrine prostate cancer,[11] endometrial cancer,[12] and Merkel cell carcinoma.[13]



Elevated DLL3 expression is likely induced by achaete-scute homolog 1 (ASCL1), a proneural transcription factor that plays an important role in pulmonary neuroendocrine differentiation and is highly expressed in neuroendocrine tumors.[3,14-16] Preclinical data indicate DLL3 can promote tumor growth, migration, and invasion, especially in SCLC cell lines, by modulating SNAI1/Snail expression.[17]

ASCL1, achaete-scute homolog 1; DLL, delta-like ligand; JAG, jagged; SCLC, small cell lung cancer.

INCREASED LEVELS OF DLL3 EXPRESSION HAVE BEEN ASSOCIATED WITH POOR PROGNOSIS

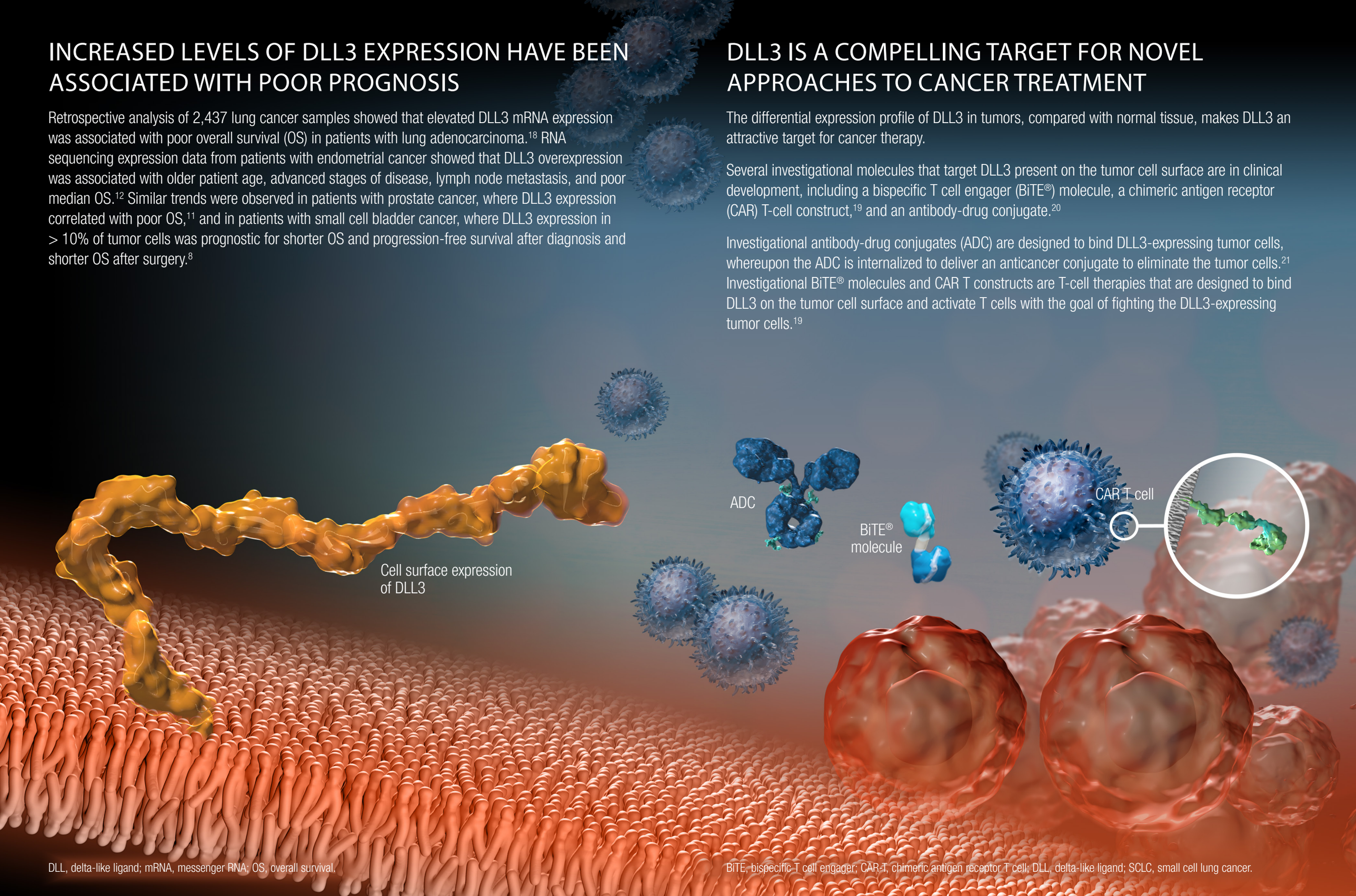
Retrospective analysis of 2,437 lung cancer samples showed that elevated DLL3 mRNA expression was associated with poor overall survival (OS) in patients with lung adenocarcinoma.[18] RNA sequencing expression data from patients with endometrial cancer showed that DLL3 overexpression was associated with older patient age, advanced stages of disease, lymph node metastasis, and poor median OS.[12] Similar trends were observed in patients with prostate cancer, where DLL3 expression correlated with poor OS,[11] and in patients with small cell bladder cancer, where DLL3 expression in > 10% of tumor cells was prognostic for shorter OS and progression-free survival after diagnosis and shorter OS after surgery.[8]

DLL3 IS A COMPELLING TARGET FOR NOVEL APPROACHES TO CANCER TREATMENT

The differential expression profile of DLL3 in tumors, compared with normal tissue, makes DLL3 an attractive target for cancer therapy.

Several investigational molecules that target DLL3 present on the tumor cell surface are in clinical development, including a bispecific T cell engager (BiTE®) molecule, a chimeric antigen receptor (CAR) T-cell construct,[19] and an antibody-drug conjugate.[20]

Investigational antibody-drug conjugates (ADC) are designed to bind DLL3-expressing tumor cells, whereupon the ADC is internalized to deliver an anticancer conjugate to eliminate the tumor cells.[21] Investigational BiTE® molecules and CAR T constructs are T-cell therapies that are designed to bind DLL3 on the tumor cell surface and activate T cells with the goal of fighting the DLL3-expressing tumor cells.[19]



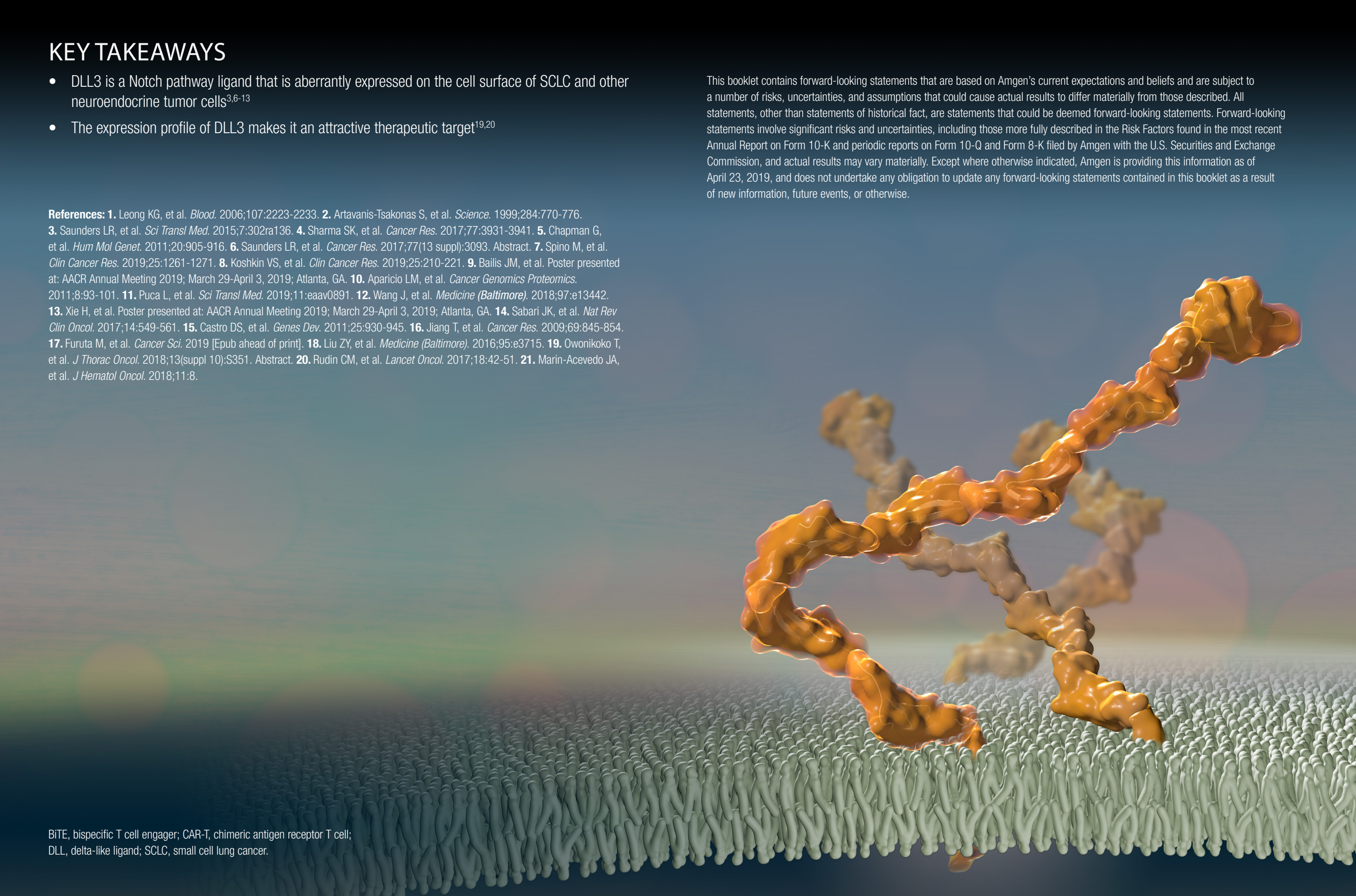
DLL, delta-like ligand; mRNA, messenger RNA; OS, overall survival.

BiTE, bispecific T cell engager; CAR-T, chimeric antigen receptor T cell; DLL, delta-like ligand; SCLC, small cell lung cancer.

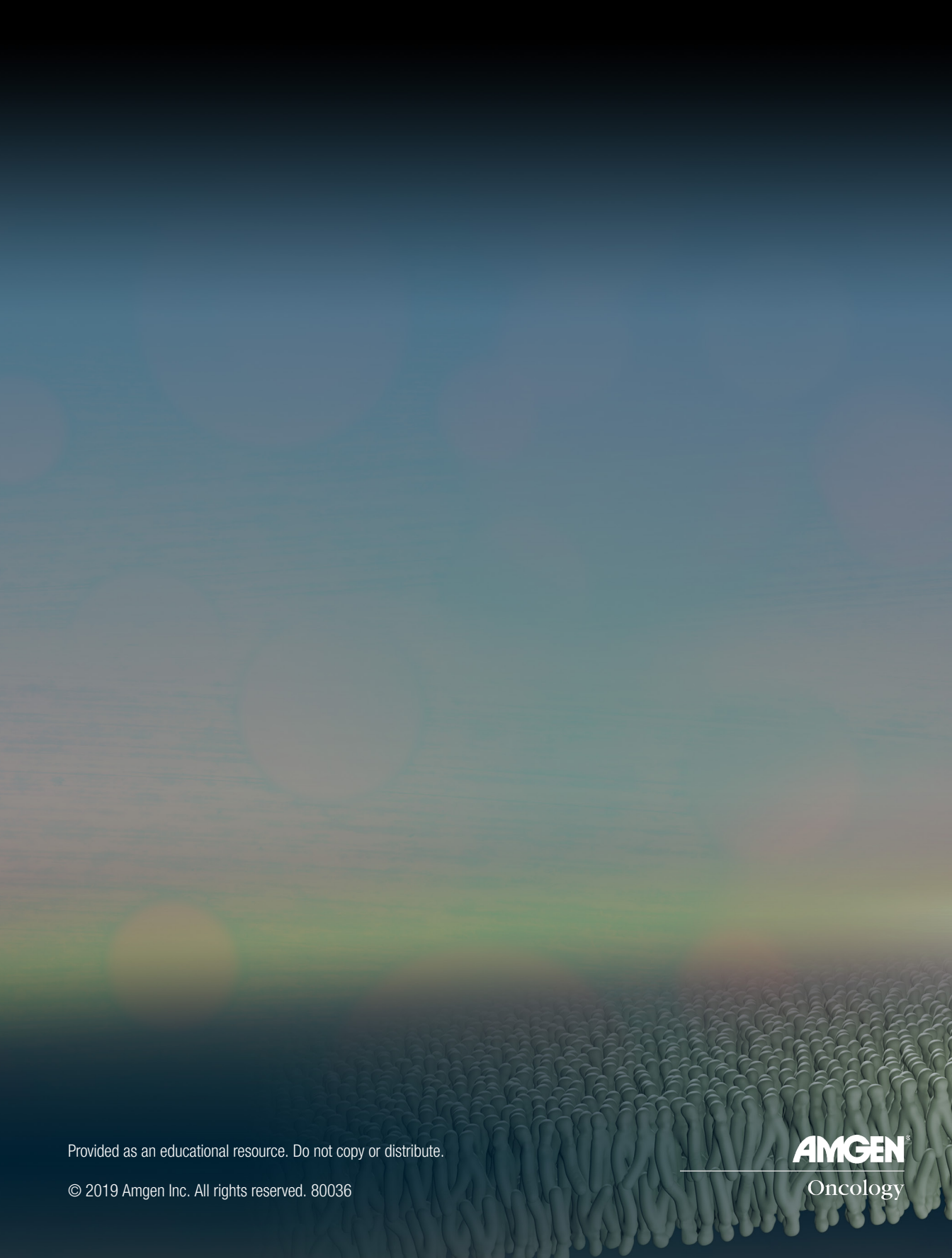
KEY TAKEAWAYS

- DLL3 is a Notch pathway ligand that is aberrantly expressed on the cell surface of SCLC and other neuroendocrine tumor cells[3,6-13]
- The expression profile of DLL3 makes it an attractive therapeutic target[19,20]

References: 1. Leong KG, et al. *Blood*. 2006;107:2223-2233. **2.** Artavanis-Tsakonas S, et al. *Science*. 1999;284:770-776. **3.** Saunders LR, et al. *Sci Transl Med*. 2015;7:302ra136. **4.** Sharma SK, et al. *Cancer Res*. 2017;77:3931-3941. **5.** Chapman G, et al. *Hum Mol Genet*. 2011;20:905-916. **6.** Saunders LR, et al. *Cancer Res*. 2017;77(13 suppl):3093. Abstract. **7.** Spino M, et al. *Clin Cancer Res*. 2019;25:1261-1271. **8.** Koshkin VS, et al. *Clin Cancer Res*. 2019;25:210-221. **9.** Bailis JM, et al. Poster presented at: AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA. **10.** Aparicio LM, et al. *Cancer Genomics Proteomics*. 2011;8:93-101. **11.** Puca L, et al. *Sci Transl Med*. 2019;11:eaav0891. **12.** Wang J, et al. *Medicine **(Baltimore)***. 2018;97:e13442. **13.** Xie H, et al. Poster presented at: AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA. **14.** Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561. **15.** Castro DS, et al. *Genes Dev*. 2011;25:930-945. **16.** Jiang T, et al. *Cancer Res*. 2009;69:845-854. **17.** Furuta M, et al. *Cancer Sci*. 2019 [Epub ahead of print]. **18.** Liu ZY, et al. *Medicine (Baltimore)*. 2016;95:e3715. **19.** Owonikoko T, et al. *J Thorac Oncol*. 2018;13(suppl 10):S351. Abstract. **20.** Rudin CM, et al. *Lancet Oncol*. 2017;18:42-51. **21.** Marin-Acevedo JA, et al. *J Hematol Oncol*. 2018;11:8.



BiTE, bispecific T cell engager; CAR-T, chimeric antigen receptor T cell; DLL, delta-like ligand; SCLC, small cell lung cancer.



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