The Battle Against Epithelial Cancers

Epithelial Cancers Are Common and Have a Poor Prognosis Despite an Established Target, EGFR[1,2]

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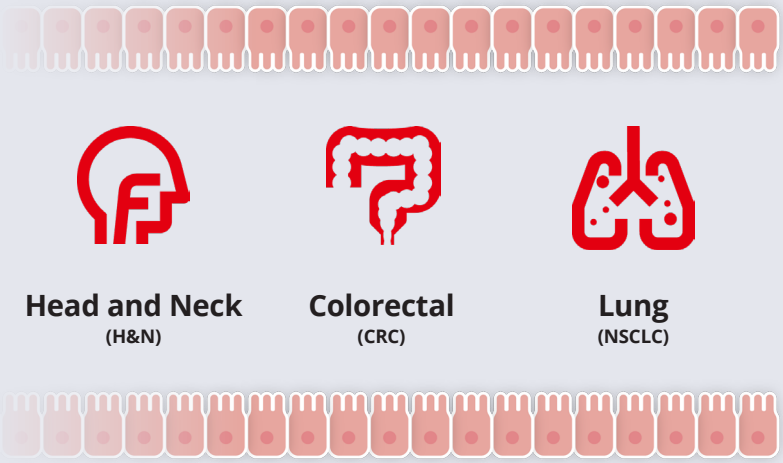
Head and Neck, Colon, and Lung Cancers Are Examples of Epithelial Cancers With Poor Outomes[1,3–6]



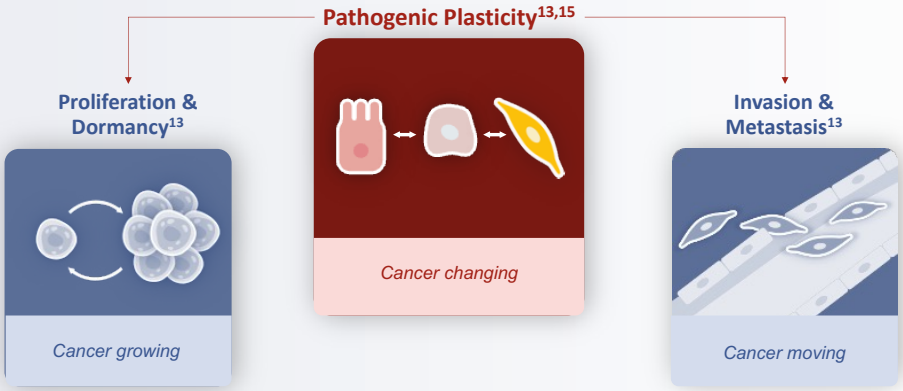
- Epithelial cancers (carcinomas) arise from cells that line the surfaces and organs of the body[3,7,8]
- Head and neck cancer (H&N), colorectal cancer (CRC), and lung cancer (NSCLC) are common examples and collectively account for approximately 450,000 new cases and 200,000 deaths annually in the US (2026 estimate)[1]
- These cancers share risk factors (eg, smoking, alcohol)[6,9,10] and have high rates of recurrence, treatment resistance, and metastasis[4–6,11,12]

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Plasticity Is a Critical Hallmark That Helps Orchestrate Cancer Pathogenesis[13]

- Plasticity has recently emerged as a critical hallmark of epithelial cancers[13]
- Plasticity is a characteristic of stem-like–cells that enables self-renewal and differentiation into other cell phenotypes.[14,15] Plasticity is found in adult stem cells that coordinate tissue homeostasis and injury repair[15-18]

Cancer cells that acquire plasticity can use regenerative capabilities to drive tumor initiation, metastasis, and treatment resistance (pathogenic plasticity)[13,15,18]



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Treatment Resistance to EGFR-targeted Therapy is an Example of Pathogenic Plasticity[19–21]

- EGFR overexpression occurs in 40%–97% of H&N, CRC, and NSCLC tumors, and is implicated in proliferation, metastasis, and survival[2,22,23]
- EGFR-targeted therapies are available and can block receptor signaling[2,22,23]
  - However, after an initial response to treatment, it is common for epithelial cancers to develop resistance[2,22,23]
- **Epithelial-Mesenchymal Transition (EMT) is an example of pathogenic plasticity and an established resistance mechanism to EGFR-targeted therapy[19–21,a]**
  - EMT is the process of epithelial cells losing their stationary characteristics (eg, cell-to-cell adhesion) and acquiring mesenchymal traits that facilitate motility and invasion[24,25]
  - Mesenchymal-epithelial-transition (MET) is the complementary process where epithelial characteristics are restored[25,b]

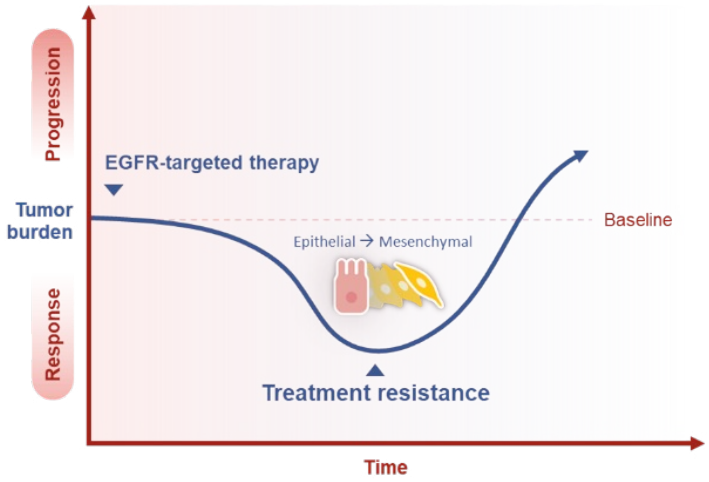

Figure is hypothetical and does not reflect data from a specific clinical study.[27–29]

[a]Other resistance mechanisms include EGFR mutations (interference with treatment binding site) and downstream mutations (activation of signaling pathways that bypass EGFR).[19–21]
[b]"Mesenchymal" refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue.[26]

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1. Siegel RL, et al. *CA Cancer J Clin*. 2026;76(1):e70043; **2.** Halder S, et al. *Expert Opin Ther Targets*. 2023;27(4-5):305-324; **3.** Cleveland Clinic. Carcinoma. Accessed March 2026. https://my.clevelandclinic.org/health/diseases/23180-carcinoma; **4.** Haring CT, et al. *Cancer*. 2023;129(18):2817-2827; **5.** Oh JM, et al. *Front Immunol*. 2025;16:1571731; **6.**Tahayneh K, et al. *J Clin Med*. 2025;14(3):1025; **7.** National Cancer Institute. What is cancer? Accessed April 2026. https://www.cancer.gov/about-cancer/understanding/what-is-cancer; **8.** Features of Epithelial Tissues. In: Price T, et al. *Integrated Human Anatomy and Physiology.* Accessed April 8, 2026. https://uen.pressbooks.pub/anatomyphysiology/; **9.** Amitay EL, et al. *Br J Cancer*. 2020;122(11):1604-1610; **10.** Hashibe M, et al. *Cancer Epidemiol Biomarkers Prev*. 2009;18(2):541-550; **11.** Barham WT, et al. *Cancers (Basel)*. 2025;17(1)144; **12.** Cervantes A, et al. *Ann Oncol*. 2023;34(1):10-32; **13.** Hanahan D. *Cancer Discov*. 2022;12(1):31-46; **14.** Du X, et al. *Front Cell Dev Biol*. 2026;14:1752590; **15**. Torborg SR, et al. *Trends Cancer*. 2022;8(9):735-746; **16.** National Institutes of Health. Stem cell basics. Accessed March 2026. https://stemcells.nih.gov/info/basics/stc-basics; **17.** Brunet A, et al. *Nat Rev Mol Cell Biol*. 2023;24(1):45-62; **18**. Ge Y, Fuchs E. *Nat Rev Genet*. 2018;19(5):311-325; **19.** Carosi F, et al. *Crit Rev Oncol Hematol*. 2026;221:105207; **20.** Chhouri H, et al. *Cancers (Basel)*. 2023;15(2):504; **21.** Zhou J, et al. *J Exp Clin Cancer Res*. 2021;40(1):328; **22.** London M, Gallo E. *Cell Biol Int*. 2020;44(6):1267-1282; **23.** Xu MJ, et al. *Cancer Metastasis Rev*. 2017;36(3):463-473; **24.** Makitie AA, et al. *Head Neck*. 2019;41(10):3712-3718; **25.** Thompson EW, et al. *Nat Rev Clin Oncol*. 2025;22(10):711-733; **26.** National Cancer Institute. Mesenchymal. Accessed March 2026. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/mesenchymal; **27.** Kobayashi S, et al. *J Respir*. 2023;3:223-236; **28.** Ciardiello D, et al. *JAMA Netw Open*. 2024;7(4):e245635; **29.** Khattri A, et al. *Cancer Gene Ther*. 2024;31(10):1477-1485.

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