# Update of current understanding of the pathobiology of esophageal squamous cell carcinoma

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# What are the most common mutations observed in ESCC?

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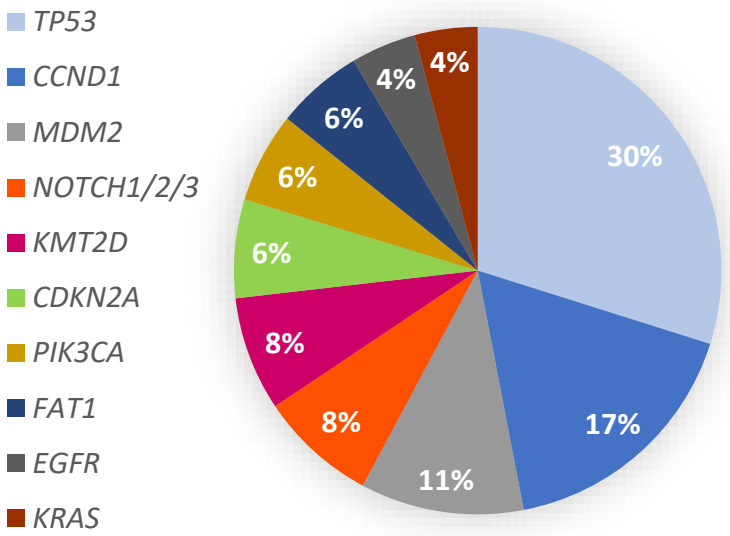
# Common mutations observed in ESCC




Relative frequency of most common mutations based on point estimates (cut-off >0.09)

- Therapies that target cancer-associated gene mutations are the current focus of research[1]
- However, research into targeted therapies for ESCC has so far yielded few promising results[2]
- A significant proportion of patients do not respond to EGFR inhibition, and in advanced ESCC, no OS benefit has been reported with an EGFR inhibitor plus chemotherapy[3,4]

EGFR, epidermal growth factor receptor; ESCC, esophageal squamous cell carcinoma; OS, overall survival.

1. Naseri A, et al. *J Gastrointest Cancer*. 2021; Online ahead of print; 2. Hassanabad AF, et al. *Cell Oncol*. 2020;43:195–209;
3. Meemanage M, et al. *Cancer Chemother Pharmacol*. 2021;87:361–77; 4. Moehler M, et al. *Ann Oncol*. 2020;31:228–35.

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# What are the primary features of the tumour microenvironment for ESCC?

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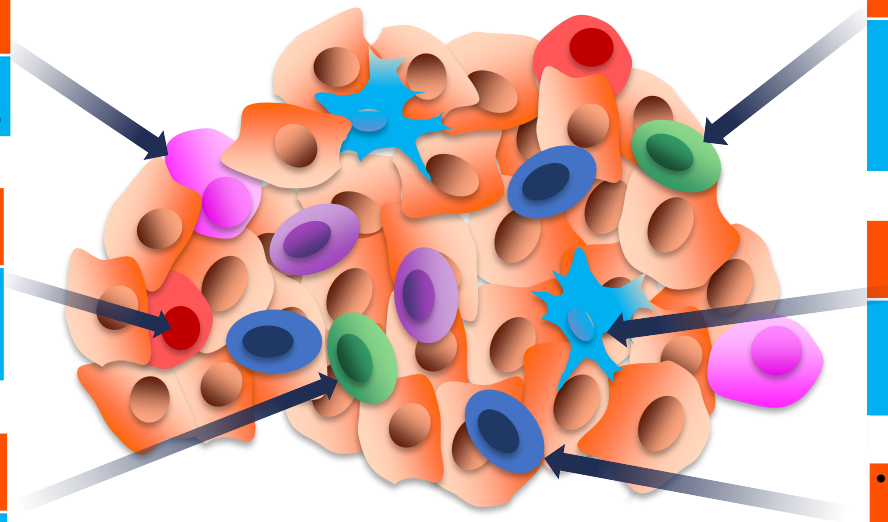
# Tumour immune microenvironment in ESCC

Anti-tumourigenic function

Pro-tumourigenic function



**MDSCs**

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- Supress T-cell function
- Recruit immunosuppressive cells

**TAMs**

- Release cytotoxic cytokines
- Present antigen to T cells

Promote angiogenesis, tumour proliferation, invasiveness and metastasis

**NK cells**

- Release cytotoxic cytokines
- Directly cytotoxic to tumour cell

–

**Treg cells**

Restore immune-system homeostasis to reduce chronic inflammation

- Supress antitumour immune responses
- Stimulate inflammatory cytokine production

**DCs**

- Release cytotoxic cytokines
- Present antigens to T cells

- Supress T-cell function
- Promote tumour growth and progression

**T cells**

- Directly break down tumour cells
- Release cytotoxic cytokines

Release tumour-promoting cytokines

DC, dendritic cell; ESCC, esophageal squamous cell carcinoma; MDSC, myeloid-derived suppressor cell; NK, natural killer; TAM, tumour-associated macrophages; Treg, regulatory T cell.

Baba Y, et al. *Cancer Sci*. 2020;111:3132–41.

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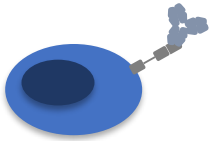
# Which tumour cell-extrinsic factors can be potentially used as biomarkers to individualize therapy?

# Tumour cell-extrinsic factors in ESCC

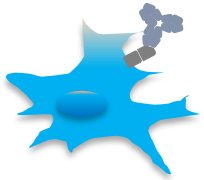


**TILs**

- A favourable prognosis in patients with ESCC is associated with peritumoral TILs
- Stratification of patients on the basis of PD-L1 expression and TIL status is associated with OS

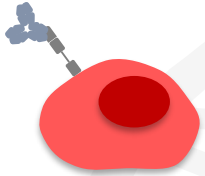
**MDSCs**

- Poor prognosis of patients with ESCC is associated with high infiltration of MDSCs



**DCs**

- Mature LAMP3-positive DCs are associated with increasing levels of CD8+ TILs in patients with ESCC



**TAMs**

- Shorter survival of patients is associated with a high density of TAMs
- TAMs increase the expression of PD-L1 in ESCC cells

PD-L1 bound to monoclonal antibody

PD-1 bound to monoclonal antibody

CD8, cluster of differentiation 8; DC, dendritic cell; ESCC, esophageal squamous cell carcinoma; LAMP3, lysosomal-associated membrane protein 3; MDSC, myeloid-derived suppressor cell; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TAM, tumour-associated macrophage; TIL, tumour-infiltrating lymphocyte.

Baba Y, et al. *Cancer Sci.* 2020;111:3132–41.

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# Which tumour cell-intrinsic factors can be potentially used as biomarkers to individualize therapy?

# Tumour cell-intrinsic factors in ESCC

**PD-L1**

- KEYNOTE-180 (phase II): Participants with high PD-L1 expression had a higher 1-year OS rate (35%) than those with low PD-L1 expression (22%)[1]
- KEYNOTE-181 (phase III): Participants with high PD-L1 expression had a mOS of 9.3 months with pembrolizumab vs 6.7 months with chemotherapy (HR=0.69)[2]

**PD-L2**

- PD-L2 is associated with unfavourable clinical outcomes in ESCC[3]
- PD-L2 exhibits distinct expression patterns during tumour development, and variations in responses to chemotherapeutic agents[4]

**MSI-high**

- Promising predictive marker for treatment with immune checkpoint inhibitors[3]
- Observed efficacy of pembrolizumab confirmed in patients with MMR-deficient tumours across 12 types of cancer, including EC[5]

**TMB**

- In 89 patients with EC treated with immunotherapy, TMB was associated with a significant improvement in OS in univariate analyses; however, the observed association did not persist after adjusting for other factors[6]
- Patients with EC and TMB ≥8.8 Mb showed a significantly improved clinical benefit following treatment with an immune checkpoint inhibitor[7]

**EGFR**

- EGFR inhibitors in EC, including ESCC, have shown mixed results[3]
- Monotherapy trials in unselected patients with EGFR inhibitors indicate that there is an EGFR-driven minority ESCC subgroup who gain survival, symptomatic control and health-related quality of life benefits[8]

EC, esophageal cancer; EGFR, epidermal growth factor receptor; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; MMR, mismatched repair; mOS, median overall survival; MSI, microsatellite instability; OS, overall survival; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; TMB, tumour mutation burden.

1. Shah MA, et al. *JAMA Oncol*. 2019;5:546–50; 2. Kojima T, et al. *J Clin Oncol.* 2019;37(Suppl. 4):2-2; 3. Baba Y, et al. *Cancer Sci*. 2020;111:3132–41;
4. Okadome K, et al. *Br J Cancer*. 2020;122:1535–43; 5. Le DT, et al. *Science*. 2017;357:409–13; 6. Greally M, et al. *Clin Cancer Res*. 2019;25:6160–9;
7. Samstein RM, et al. *Nat Genet*. 2019;51:202–6; 8. Meemanage M, et al. *Cancer Chemother Pharmacol.* 2021;87:361–77.

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