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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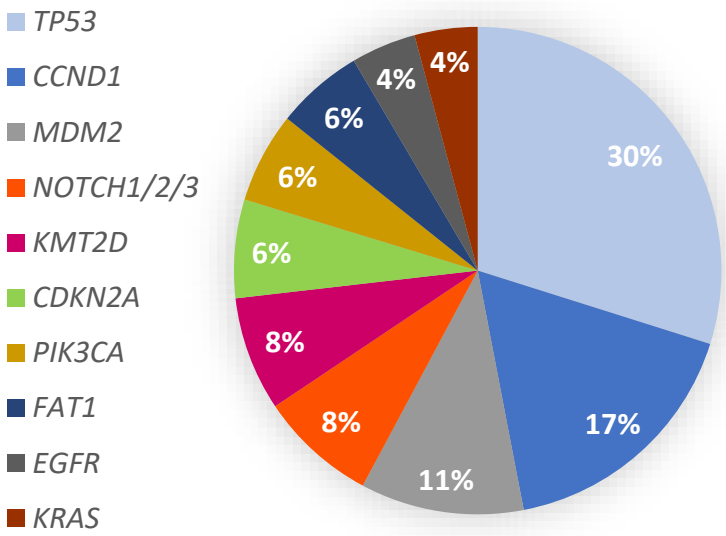
Common mutations observed in ESCC



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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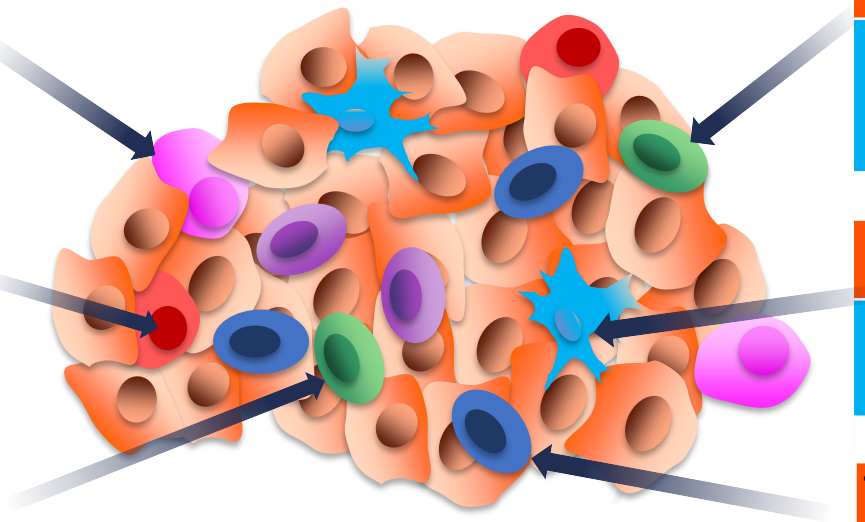
Tumour immune microenvironment in ESCC

Anti-tumourigenic function

Pro-tumourigenic function



MDSCs

–

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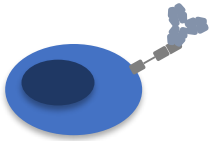
Which tumour cell-extrinsic factors can be potentially used as biomarkers to individualize therapy?

Tumour cell-extrinsic factors in ESCC

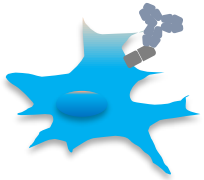


TILs

- 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

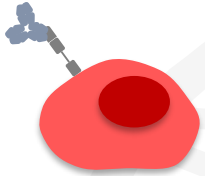
MDSCs

- 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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Review of current and emerging first-line therapies for esophageal squamous cell carcinoma

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What key mechanisms of action are being exploited for the potential first-line treatment of ESCC?

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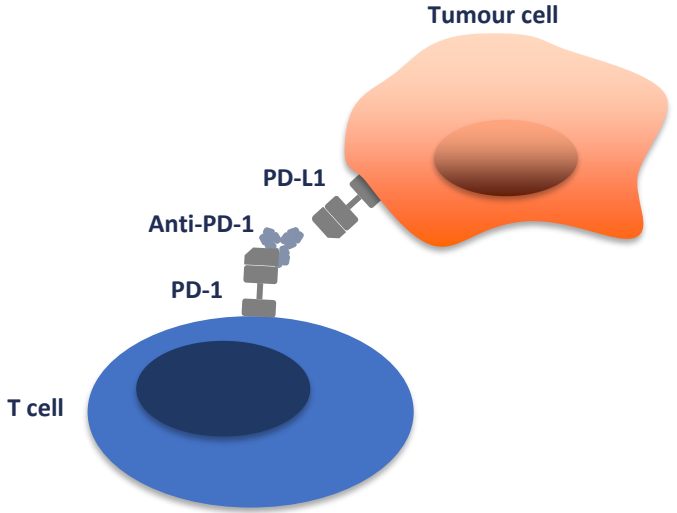
Mechanisms of action of immunotherapy

Anti-PD-1

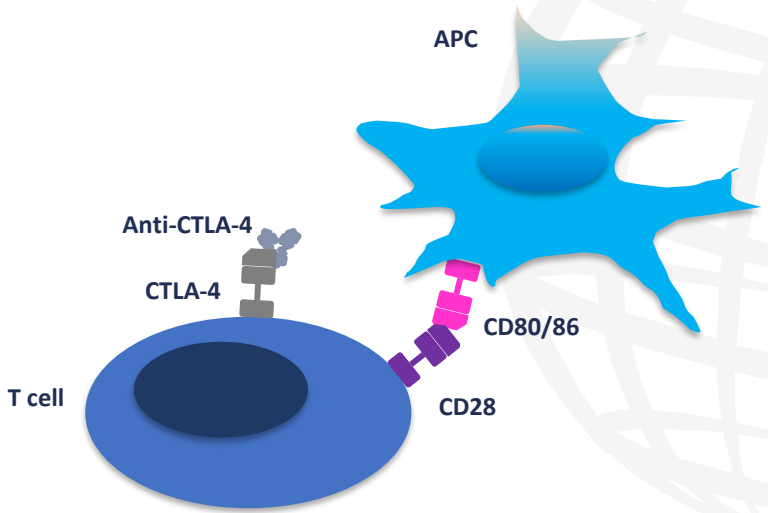
E.g. Camrelizumab, nivolumab, pembrolizumab, sintilimab, tislelizumab, toripalimab



Blocking the interaction of PD-1 and PD-L1 releases the immunosuppression of T cells

Anti-CTLA-4

E.g. Ipilimumab, tremelimumab



Anti-CTLA-4 binds CTLA-4 allowing CD28 to bind to CD80, which then activates T cells

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Yang YM, et al. *Signal Transduct Target Ther*. 2020;5:229; Enomoto N, et al. *Glob Health Med.* 2021;3:378–85.

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What phase III clinical trials have investigated or are investigating first-line therapies for ESCC?

KEYNOTE-590[1,2]

- Pembrolizumab + chemotherapy vs placebo + chemotherapy
- Phase III study in 26 countries
- N=749
- 73% ESCC
- NCT03189719

- Long-term follow-up data confirm that pembrolizumab + chemotherapy is a new first-line SoC option for patients with locally advanced or metastatic EC

13.9 vs 8.8 months

OS: ESCC + PD-L1 CPS ≥10
(HR 0.57; 95% CI 0.43–0.75; p<0.0001)

12.6 vs 9.8 months

OS: all ESCC
(HR 0.72; 95% CI 0.60–0.88; p=0.0006)

6.3 vs 5.8 months

PFS: all ESCC
(HR 0.65; 95% CI 0.54–0.78; p<0.0001)

CI, confidence interval; CPS, combined positivity score; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; OS. overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; SoC, standard of care.

1. Sun JM, et al. *Lancet.* 2021;398:759–71; 2. Metges J-P, et al. Presented at: ASCO-GI, San Francisco, CA,USA, 20–22 January 2022 and online: Abstr. 241.

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Chinese phase III trials

ESCORT-1st[1,2] (interim analysis)

- Camrelizumab + chemotherapy vs placebo + chemotherapy
- N=596
- NCT03691090

JUPITER-06[3,4] (interim analysis)

- Toripalimab + chemotherapy vs placebo + chemotherapy
- N=514
- NCT03829969

ORIENT-15[5,6] (interim analysis)

- Sintilimab + chemotherapy vs placebo + chemotherapy
- N=659
- NCT03748134
- An open-label treatment arm will continue in regions outside of China to further evaluate efficacy and safety in a western population

1. Xu R, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4000; 2. Xu R, et al. Presented at: ASCO, Chicago, IL, USA. 4–8 June 2021. Abstr 4000;
3. Xu R, et al. *Ann Oncol*. 2021;32(Suppl. 5):S1040–75; 4. Xu R, et al. Presented at: ESMO, Paris, France. 16–21 September 2021. Abstr 1373MO;
5. Shen L, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1330; 6. Shen L, et al. Presented at: ESMO, Paris, France. 16–21 September 2021. Abstr LBA52.

CheckMate 648

- Nivolumab + ipilimumab or nivolumab + chemotherapy vs chemotherapy
- Phase III study in 27 countries
- N=970
- NCT03143153

Nivolumab + ipilimumab

12.7 vs 10.7 months

OS: all patients
(HR 0.78, 98.2% CI 0.62–0.98; p=0.01)

13.7 vs 9.1 months

OS: PD-L1 ≥1%
(HR 0.64; 98.6% CI 0.46–0.90; p=0.001)

Nivolumab + chemotherapy

13.2 vs 10.7 months

OS: all patients
(HR 0.74; 99.1% CI 0.58–0.96; p=0.002)

15.4 vs 9.1 months

OS: PD-L1 ≥1%
HR 0.54; 99.5% CI 0.37–0.80; p<0.001)

CI, confidence interval; HR, hazard ratio; OS. overall survival; PD-L1, programmed cell death-ligand 1.
Doki Y, et al. *N Engl J Med*. 2022;386:449-62.

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What have we learned so far in terms of the safety of current and emerging first-line therapies for ESCC?

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Based on the latest data, what are the likely clinical implications for the first-line treatment of ESCC?

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Recent changes to first-line practice

For metastatic or locally advanced esophageal or GEJ carcinoma, pembrolizumab is approved in combination with platinum- and fluoropyrimidine-based chemotherapy

New anti-PD-1 inhibitors may join the therapeutic armamentarium in the future following more trials[3–8]

CPS, combined positivity score; GEJ, gastroesophageal junction; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

1. FDA. 2021. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma (accessed 7 February 2022);
2. EMA, 2021. Available at: www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-keytruda-ii-108_en.pdf (accessed 7 February 2022);
3. Xu R, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4000; 4. Xu R, et al. Presented at: ASCO, Chicago, IL, USA. 4–8 June 2021. Abstr 4000;
5. Xu R, et al. *Ann Oncol*. 2021;32(Suppl. 5):S1040–75; 6. Xu R, et al. Presented at: ESMO, Paris, France. 16–21 September 2021. Abstr 1373MO;
7. Shen L, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1330; 8. Shen L, et al. Presented at: ESMO, Paris, France. 16–21 September 2021. Abstr LBA52.

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Review of current and emerging second-line therapies for esophageal squamous cell carcinoma

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What phase II/III clinical trials have investigated or are investigating second-line therapies for ESCC?

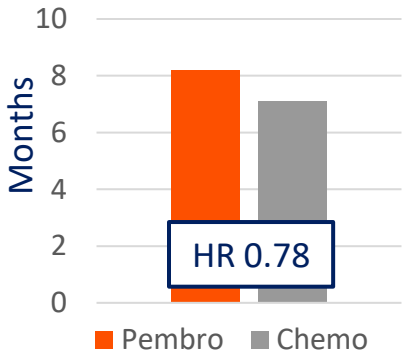
Phase III clinical trials: Efficacy

KEYNOTE-181[1]

Phase III global study of ESCC/EAC

Pembrolizumab vs chemotherapy

mOS (ESCC subgroup)

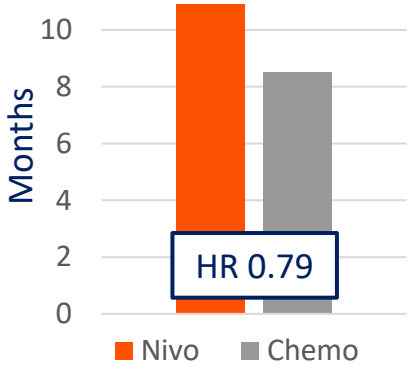


ATTRACTION-3[2,3]

Phase III primarily Asian study of ESCC

Nivolumab vs chemotherapy

mOS

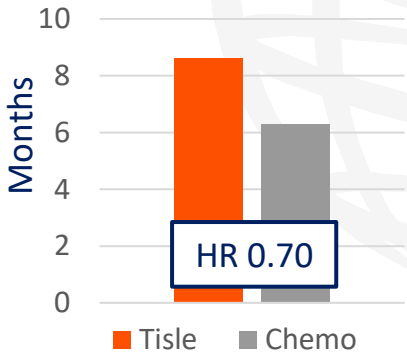


RATIONALE-302[4]

Phase III global study of ESCC

Tislelizumab vs chemotherapy

mOS



EAC, adenocarcinoma; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; mOS, median overall survival.

1. Kojima T, et al. *J Clin Oncol*. 2020;38:4138–48; 2. Kato K, et al. *Lancet Oncol.* 2019;20:1506–17; 3. Chin K, et al. *J Clin Oncol.* 2021;39(Suppl. 3):204; 4. Shen L, et al. *J Clin Oncol*. 2022:JCO2101926.

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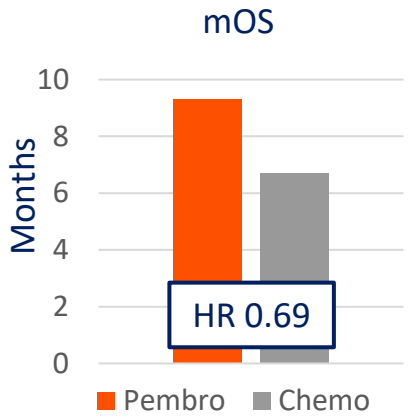
PD-L1 as a biomarker for predicting efficacy

KEYNOTE-181[1]

PD-L1 CPS ≥10



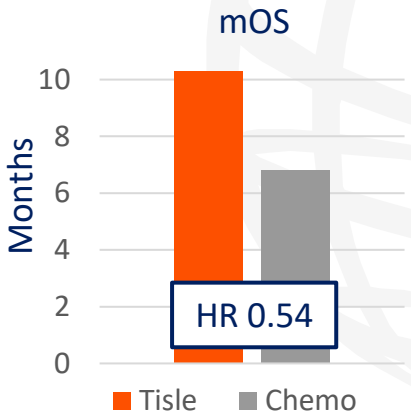
Evaluating PD-L1

- **CPS**: Expression on tumour cells and immune cells combined[2]
- **TPS**: Expression only within tumour cells[2]

Prolonged mOS benefit seen with IO vs chemo in both global phase III trials for patient groups with PD-L1 CPS ≥10 or TAP ≥10%

RATIONALE-302[3,4]

PD-L1 TAP* ≥10%



*The TAP score methodology has been previously referred to as vCPS.

CI, confidence interval; CPS, combined positivity score;HR, hazard ratio; IO, immunotherapy; mOS, median overall survival; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumour area positivity; TPS, tumour proportion score; vCPS, visually estimated CPS.

1. Kojima T, et al. *J Clin Oncol*. 2020;38:4138–48; 2. Sundar R, et al. *Front Oncol*. 2020; 10:763; 3. Shen L, et al. *J Clin Oncol*. 2022:JCO2101926; 4. Zhao K, et al. *J Clin Oncol*. 2022;40(Suppl. 4):279.

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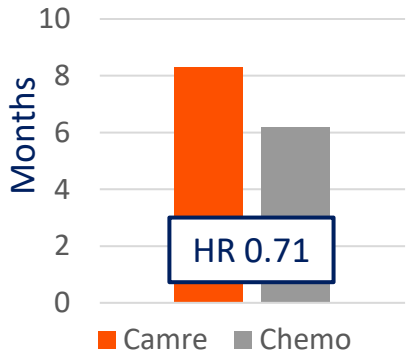
Phase II/III clinical trials: Efficacy

ESCORT[1]

Phase III Chinese study of ESCC

Camrelizumab vs chemotherapy

mOS

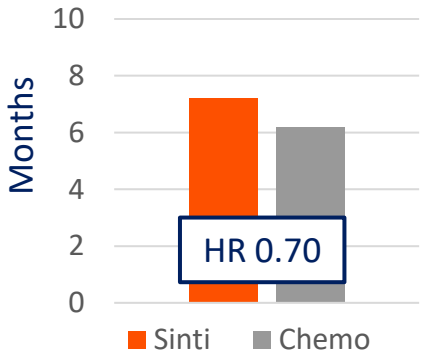


ORIENT-2[2]

Phase II Chinese study of ESCC

Sintilimab vs chemotherapy

mOS



RAMONA[3,4]

Phase II German study of ESCC in elderly (≥65 years)

Nivolumab/ipilimumab combination or nivolumab alone vs historical standard chemotherapy data

Estimated study completion date June 2022

ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; mOS, medial overall survival.

1. Huang J, et al. *Lancet Oncol.* 2020;21:832–42; 2. Xu J, et al. *Nat Commun*. 2022;13:857; 3. Hartel N, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4029; 4. NCT03416244. Available at: https://clinicaltrials.gov/ct2/show/NCT03416244 (accessed 24 May 2022).

What have we learned so far in terms of the safety of current and emerging second-line therapies for ESCC?

Phase III clinical trials: Safety

	KEYNOTE-181[1]	ATTRACTION-3[2]	RATIONALE-302[3]
Grade ≥3 TRAEs	• Pembrolizumab 18% • Chemotherapy 41%	• Nivolumab 18% • Chemotherapy 64%	• Tislelizumab 19% • Chemotherapy 56%
Most common AEs	• Anaemia 1%* • Asthenia 1%*	• Anaemia 2%*	• AST increase 11%† • Anaemia 11%†

*Grade ≥3 in the investigational agent arm. †All adverse event grades.
AE, adverse event; AST, aspartate aminotransferase; TRAE, treatment-related AE.
1. Kojima T, et al. *J Clin Oncol*. 2020;38:4138–48; 2. Kato K, et al. *Lancet Oncol.* 2019;20:1506–17; 3. Shen L, et al. *J Clin Oncol*. 2022:JCO2101926.

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Phase II/III clinical trials: Safety

	ESCORT[1]	ORIENT-2[2]	RAMONA[3]
Grade ≥3 TRAEs	• Camrelizumab 19% • Chemotherapy 40%	• Sintilimab 20% • Chemotherapy 39%	• Monotherapy 44% • Combination 21%
Grade ≥3 TRAEs*	• Anaemia 3% • Abnormal liver function 2% • Diarrhoea 1%	• Pulmonary inflammation 5% • Elevated lipase levels 4%	Interim analysis – details not yet reported

*Most common in the investigational agent arm.
AE, adverse event; TRAE, treatment-related adverse event.
1. Huang J, et al. *Lancet Oncol.* 2020;21:832–42; 2. Xu J, et al. *Nat Commun*. 2022;13:857; 3. Hartel N, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4029.

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Based on the latest data, what are the likely clinical implications for the second-line treatment of ESCC?

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Time for a new algorithm for second-line treatment of ESCC?

First-line therapy

Chemotherapy[1]

- Best-supportive care
- Palliative monotherapy

Immunotherapy ± chemotherapy

- Camrelizumab
- Nivolumab*[2]
- Nivolumab/ipilimumab
- Pembrolizumab
- Sintilimab
- Tislelizumab

?

Which factors will guide the choice of second-line therapy?

*Approved by the EMA as a monotherapy after chemotherapy.
EMA, European Medicines Agency; ESCC, esophageal squamous cell carcinoma.
1. Lordick F, et al. *Ann Oncol*. 2016;27(Suppl. 5):v50–7; 2. EMA SmPC for nivolumab. Available at: www.ema.europa.eu/ (accessed 24 May 2022).

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How will data from first-line trials influence second-line treatment of ESCC?

KEYNOTE-590[1]
- Pembrolizumab plus chemotherapy vs placebo plus chemotherapy

CheckMate 648[2]
- Nivolumab plus chemotherapy or nivolumab plus ipilimumab vs chemotherapy

ESCORT-1st[3]
- Camrelizumab plus chemotherapy vs placebo plus chemotherapy

ORIENT-15[4]
- Sintilimab plus chemotherapy vs placebo plus chemotherapy

JUPITER-06[5]
- Toripalimab plus chemotherapy vs placebo plus chemotherapy

First-line EMA approvals in combination with chemotherapy[6]
- Pembrolizumab for patients with PD-L1 CPS ≥10
- Nivolumab for patients with PD-L1 TPS ≥1%

CPS, combined positivity score; EMA, European Medicines Agency; ESCC, esophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; TPS, tumour proportion score.

1. Sun JM, et al. *Lancet.* 2021;398:759–71; 2. Doki Y, et al. *N Engl J Med*. 2022;386:449–62; 3. Luo H, et al. *JAMA*. 2021;326:916–25; 4. Lu Z, et al. *BMJ*. 2022;377:e068714; 5. Wang ZX, et al. *Cancer Cell*. 2022;40:277–88.e3; 6. EMA SmPC for pembrolizumab and nivolumab. Available at: www.ema.europa.eu/ (accessed 24 May 2022).