Emerging data with immunotherapy in esophageal squamous cell carcinoma and potential impact for clinical practice: Insights from 2021

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CheckMate 648: Study design

- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0 or 1
- No prior systemic treatment for advanced disease
- Measurable disease


- n=324
  - Chemo Q4W

- n=321
  - Nivo 240 mg Q2W + chemo Q4W

- n=325
  - Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W

Nivolumab + ipilimumab or nivolumab + chemotherapy vs chemotherapy as first-line treatment for advanced ESCC

Chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; ipi, ipilimumab; nivo, nivolumab; PS, performance status; Q2/4/6W, once every 2/4/6 weeks.

CheckMate 648: Median overall survival (months)

CI, confidence interval; HR, hazard ratio; PD-L1, programmed death–ligand 1.
CheckMate 648: Median progression-free survival (months)

CheckMate 648: Treatment-related adverse events (grade 3 or 4)*

For all randomized patients and those with PD-L1 ≥1%:
- Superior median OS with both IO combinations vs chemotherapy alone
- Clinically meaningful PFS benefit with nivolumab + chemotherapy
- No new safety signals with either combined IO regimen

*Select treatment-related adverse events with potential immunologic aetiology that require frequent monitoring/intervention.

IO, immunotherapy.
**ORIENT-15: Study design**

- Unresectable locally advanced or metastatic ESCC
- ECOG PS 0 or 1
- ≥18 years old
- At least one measurable lesion

**Sintilimab + chemotherapy vs chemotherapy as first-line therapy in patients with advanced or metastatic ESCC**

**Placebo Q3W, for a maximum of 24 months + chemo Q3W for a maximum of 6 cycles**

- **n=332**

**Sintilimab Q3W, for a maximum of 24 months + chemo Q3W for a maximum of 6 cycles**

- **n=327**

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Q3W, once every 3 weeks.
ORIENT-15: Key study endpoints

CPS, combined positive score; OS, overall survival; PFS, progression-free survival; sinti, sintilimab.
ORIENT-15: Treatment-related adverse events


TRAEs with ≥15% incidence

- Anaemia
- Alopecia
- Decreased WBCs
- Decreased appetite
- Decreased neutrophils
- Hypoaesthesia
- Nausea
- Decreased platelets
- Vomiting
- Decreased weight
- Asthenia
- Rash

- Superior median overall survival and durable responses with sintilimab + chemotherapy than chemotherapy alone regardless of PD-L1 expression
- No new safety signals with the IO combination

TRAE, treatment-related adverse event; WBC, white blood cell.
JUPITER-06: Study design

- Histologically or cytologically confirmed advanced or metastatic ESCC
- Treatment-naive for metastatic disease
- ECOG PS 0 or 1
- Measurable disease

Randomized, double-blind, phase III study of toripalimab vs placebo in combination with first-line chemotherapy for treatment naïve advanced or metastatic ESCC

- Placebo + chemo Q3W for up to 6 cycles followed by maintenance placebo Q3W
- Toripalimab 240 mg + chemo Q3W for up to 6 cycles followed by maintenance 240 mg toripalimab Q3W

n=257
n=257

JUPITER-06: Median overall survival (months) – interim analysis

- **HR 0.58** (95% CI, 0.425–0.783; p=0.00036)
  - All patients PFS median 5.7 vs 5.5 months (HR, 0.58; 95% CI, 0.461–0.738; p<0.00001)

- **HR 0.61** (95% CI, 0.435–0.870)
  - PD-L1 CPS ≥1
  - PD-L1 CPS <1

NE, not estimable; tori, toripalimab.
JUPITER-06: Treatment-related adverse events – interim analysis

- Superior OS and PFS with IO than chemo alone
- OS and PFS benefits were observed regardless of PD-L1 expression
- No new safety signals

TRAEs with ≥30% incidence

- Anaemia
- Fatigue
- Leukopenia
- Decreased appetite
- Neutropenia
- Alopecia
- Nausea
- Vomiting
- Peripheral neuropathy

Grade ≥3

<table>
<thead>
<tr>
<th>Category</th>
<th>Tori</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Immune-related</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>6%</td>
<td>2%</td>
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<tr>
<td>Infusion reactions</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Death</td>
<td>2%</td>
<td>0%</td>
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</table>
ESCORT-1st: Study design

- Histologically or cytologically confirmed ESCC
- Treatment-naive
- Advanced or metastatic disease
- ECOG PS 0 or 1
- Measurable disease

Randomized, double-blind, placebo-controlled, phase III trial of camrelizumab + chemotherapy vs chemotherapy in patients with untreated advanced or metastatic ESCC
ESCORT-1st: Key endpoints – interim analysis

Cam, camrelizumab.
ESCORT-1st: Treatment-related adverse events – interim analysis

- Superior OS and PFS with IO than placebo + chemotherapy
- Manageable safety profile

**TRAEs with ≥20% incidence**

- RCCEP
- Anaemia
- Decreased WBCs
- Decreased neutrophils
- Nausea
- Asthenia
- Alopecia
- Decreased appetite
- Vomiting
- Decreased platelets
- Decreased weight
- Increased creatine

RCCEP, reactive cutaneous capillary endothelial proliferation.
RATIONALE 302: Study design

• Advanced or metastatic ESCC
• Progression during or after first-line systemic treatment
• ECOG PS 0 or 1

Investigator-chosen chemo

n=256

Tislelizumab 200 mg Q3W

n=256

Randomized, phase III study of second-line tislelizumab vs chemotherapy in advanced or metastatic ESCC
RATIONALE 302: Key endpoints

- ORR, overall response rate; vCPS, visually estimated combined positivity score.
RATIONAL 302: Treatment-emergent and -related adverse events

- Superior OS and more durable response with IO than chemotherapy alone
- OS benefit was observed regardless of PD-L1 expression
- No new safety signals

TEAE, treatment-emergent adverse event.
CheckMate 577: Study design

- Stage II/III EC or GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant chemoradiotherapy and surgical resection
- Residual pathologic disease
- ECOG PS 0 or 1


- Placebo Q2W for 16 weeks then Q4W (n=262)
- Nivolumab 240 mg Q2W for 16 weeks then 480 mg Q4W (n=532)

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy
CheckMate 577: Median disease-free survival (months)


- **All randomized**: HR 0.69 (96.4% CI, 0.56–0.86; p=0.0003)
- **Esophageal cancer**: HR 0.61
- **PD-L1 ≥1%**: HR 0.75
- **PD-L1 <1%**: HR 0.73

Nivo vs Placebo

- **Nivo**: 22.4, 24.0, 19.7, 21.3
- **Placebo**: 11.0, 8.3, 14.1, 11.1
CheckMate 577: Adverse and treatment-related adverse events

- Adjuvant IO was superior to placebo in patients following neoadjuvant chemoradiotherapy
- Acceptable safety profile

AE, adverse event.
### Summary and conclusions

<table>
<thead>
<tr>
<th>Anti-PD-1 mAb</th>
<th>Outcome vs comparator*</th>
<th>Adjuvant</th>
<th>1L combo with chemo</th>
<th>2L mono</th>
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*Comparator arms were placebo, chemo or placebo + chemo. Combo, combination; mAb, monoclonal antibody; mono, monotherapy.