Systematic Literature Review (SLR) of Randomized Controlled Trials (RCTs) of Immuno-Oncology (IO) for First-Line (1L) Treatment of Esophageal Squamous Cell Carcinoma (ESCC) in Adult Patients

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Conclusions

- **This systematic literature review (SLR) provided a comprehensive overview of trials investigating the addition of immuno-oncology (IO) therapies to standard chemotherapy (CT) in patients with previously untreated locally advanced, unresectable, or metastatic esophageal squamous cell carcinoma (ESCC)**
- **Across the 8 randomized controlled trials (RCTs) included, there were clear advantages to adding IO agents to CT in terms of overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and duration of response (DoR)**
- **This treatment benefit was reflected in programmed death-ligand 1 (PD-L1)-positive, metastatic first-line (1L) patients with ESCC regardless of race or geographic locations**
- **Similar rates of all-grade treatment-related adverse events (TRAEs) were noted between the IO + CT and CT arms; however, favorable health-related quality of life (HRQoL) outcomes were noted among patients treated with IO + CT versus those treated with CT**

Background

- Esophageal squamous cell carcinoma (ESCC) accounts for approximately 90% of esophageal cancer (EC) cases globally[1]
- The prognosis for ESCC is poor, with a 5-year survival rate of <20%[2]
- Overexpression of PD-L1 is common in ESCC patients and is associated with poor prognosis[3]
- The addition of programmed cell death protein-1 (PD-1) inhibitors to CT improved outcomes in patients with previously untreated 1L unresectable, locally advanced, or metastatic ESCC[4,5]
- In this population, worldwide clinical practice guidelines recommend treatment with PD-1 inhibitors; however, limited PD-1-targeted therapeutic options are available, highlighting a need for global access to novel IO treatments[4-8]

Objective

- This SLR was conducted to summarize the efficacy, safety, and HRQoL data from RCTs assessing IO agents in patients with 1L unresectable, locally advanced, or metastatic ESCC

Methods

- The SLR followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Publications from inception to June 23, 2023 were searched in Embase, Ovid MEDLINE®, and Cochrane CENTRAL on June 23, 2023 to identify English-language RCTs of IO regimens for 1L ESCC
- Hand searches of health technology assessment agencies, conference proceedings, and trial registries were also conducted to supplement database searches
- Study selection was performed in duplicate and was assessed according to the following eligibility criteria:
  - Adult patients with previously unresectable, locally advanced or metastatic ESCC
  - Interventions: IO agents alone or in combination with CT, targeted therapy, or any other immunotherapy
  - Comparators: IO agents alone or in combination with CT, targeted therapy, or any other immunotherapy; CT alone; or placebo
  - Outcomes of interest: OS, PFS, ORR, DoR, TRAEs, and HRQoL
  - Only phase 2 and/or 3 RCTs were included
- Study details, patient characteristics, and outcomes of interest were extracted into a standardized form in Microsoft® Excel (Microsoft Corporation, Seattle, USA). In addition to the overall trial population, key subgroups of interest included PD-L1 subgroups, race/geographic region, and disease status at trial entry
- Study quality of included RCTs with available full-text publications was assessed using the NICE Single Technology Appraisal Evidence Submission Checklist for assessment of risk of bias in RCTs[8]

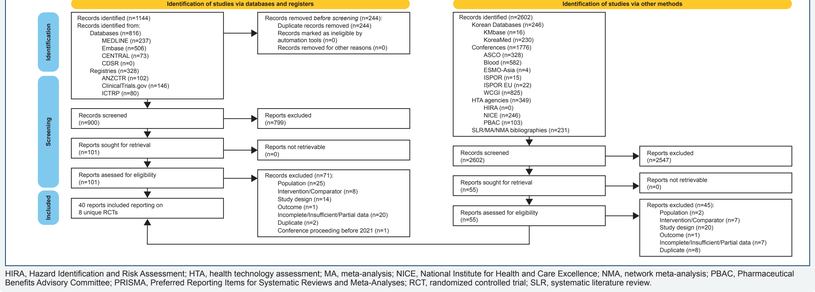
Results

Study Characteristics

- Of 1144 records identified in the database/registry searches and 2602 records across grey literature sources, 40 records pertaining to 8 unique phase 3, multicenter RCTs that investigated IO agents in combination with CT were identified (**Figure 1**)
- All trials were double-blind, except the open-label CheckMate 648 trial
- Across trials, the mean age of patients ranged from 62 to 64 years; the proportion of Asian patients ranged from 53% to 100%. ASTRUM-007, ESCORT-1st, GEMSTONE-304, JUPITER-06, were conducted exclusively in Asia[10,11,14,15]
- All trials required patients to have an Eastern Cooperative Oncology Group performance status of 0–1. 58% to 92% of patients had metastatic disease at baseline
- Proportion of PD-L1 positive patients (defined as tumor area positivity ≥10%, combined positivity score ≥10, or tumor positivity score ≥1%) ranged from 33% to 57%
- Seven out of 8 identified RCTs with available full-text publications were assessed for risk of bias (**Supplementary Figure 1**). Of the 7 trials, potential sources of bias included open-label design of CheckMate 648, and lack of clear description of intent-to-treat analyses or missing data in 6 trials. GEMSTONE-304 was not assessed, as trial data was only available in an abstract at the time of the SLR

Supplementary data

Figure 1: PRISMA Flow Diagram



HIRA, Hazard Identification and Risk Assessment; HTA, health technology assessment; MA, meta-analysis; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SLR, systematic literature review.

Survival Outcomes

- All 8 trials demonstrated statistically significant improvements in OS with IO + CT compared with CT alone
- Seven of 8 trials demonstrated statistically significant improvements in PFS with IO + CT compared with CT alone

Response Outcomes

- All 8 trials showed an ORR benefit with IO + CT compared with CT only; 2 trials (RATIONALE-306 and ASTRUM-007) demonstrated statistical significance of the ORR benefit with odds ratios
- DoR was longer in all IO + CT arms compared with CT alone

Subgroups

- Efficacy outcomes for subgroups based on PD-L1 positivity status are presented in **Table 1**. Efficacy outcomes for subgroups based on race or geographic location and disease status at trial entry (locally advanced, unresectable, metastatic) are presented in **Supplementary Table 1** (please see supplementary QR code from first column)
- Across all trials and subgroups presented, the benefits of IO + CT compared with CT alone were maintained. Outcomes with gain or loss of statistical significance in subgroup analyses compared with main analyses are highlighted in the corresponding tables
  - Survival and response benefits of IO agents were maintained in PD-L1-positive patients across trials
  - Clinical benefits of IO agents were consistent across trials in Asian and non-Asian patients
  - Survival benefits of IO + CT compared with CT alone were maintained in metastatic patients; benefits lost statistical significance in locally advanced/recurrent/unresectable patients in most trials. No trials reported response outcomes for patients based on disease status

Table 1. Efficacy Results Across Trials Included by PD-L1-Positivity

Trial (NCT)	Subgroup (Patients, N)[a]	Study arm (Patients, N)	Median OS, months (95% CI)	OS HR (95% CI)	Median PFS, months (95% CI)	PFS HR (95% CI)	ORR, % (95% CI)	CR/PR (%)	Median DoR, months (95% CI)
ASTRUM-007 (NCT03189719)	All patients[b,c] (551)[11]	SER + CT (368)	15.3 (14.0–18.6)	0.68 (0.53–0.87)	5.8 (5.7–6.9)	0.60 (0.49–0.74)	57.6 (52.4–62.7)	14/44	6.9 (5.6–8.3)
		PBO + CT (183)	11.8 (9.7–14.0)		5.3 (4.3–5.6)		42.1 (34.8–49.6)	7/36	4.6 (4.1–5.6)
SER + CT vs. PBO + CT									
CT regimen: FLU + CIS	CPS ≥10 (241)[11]	SER + CT (162)	18.6 (15.3–20.9)	0.59 (0.40–0.88)	7.1 (5.8–9.1)	0.48 (0.34–0.68)	66.0 (58.2–73.3)	NR	7.9 (5.7–12.4)
		PBO + CT (79)	13.9 (8.3–18.2)		5.3 (4.1–6.0)		41.8 (30.8–53.4)	NR	5.6 (4.2–6.9)
CheckMate 648 (NCT03783442)	All patients (970)[12]	NIV + CT (321)	12.8 (11.1–15.7)	0.78 (0.65–0.93)	5.8 (5.5–7.0)	0.83 (0.68–1.00)	47 (NR–NR)	13/34	8.2 (6.9–9.7)
		NIV + IPI (325)	12.7 (11.3–15.5)	0.77 (0.65–0.92)	2.9 (2.7–4.2)	1.26 (1.04–1.51)	27 (NR–NR)	11/17	11.1 (7.1–14.3)
NIV + CT vs. CT		CT (324)	10.7 (9.4–12.1)	Ref	4.3 (4.3–5.9)	Ref	27 (NR–NR)	6/21	5.7 (5.7–8.2)
NIV + IPI vs. CT									
CT regimen: FLU + CIS	TPS ≥1% (473)[13]	NIV + CT (158)	15.0 (11.9–18.6)	0.59 (0.46–0.76)	6.8 (5.7–8.3)	**0.67 (0.51–0.89)**	53 (NR–NR)	16/37	8.4 (6.9–12.4)
		NIV + IPI (158)	13.1 (11.2–17.4)	0.62 (0.48–0.80)	4.0 (2.3–4.4)	1.04 (0.79–1.36)	35 (NR–NR)	18/18	11.8 (6.8–18.0)
		CT (157)	9.1 (7.7–10.0)	Ref	4.4 (2.9–5.8)	Ref	20 (NR–NR)	5/15	5.7 (4.4–8.7)
ESCORT-1st (NCT03691090)	All patients[b] (596)[10]	CAM + CT (298)	15.3 (12.8–17.3)	0.70 (0.56–0.88)	6.9 (5.8–7.4)	0.56 (0.46–0.68)	72.1 (66.7–77.2)	6.7/65.4	7.0 (6.1–8.9)
CAM + CT vs. PBO + CT		PBO + CT (298)	12.0 (11.0–13.3)		5.6 (5.5–5.7)		62.1 (56.3–67.6)	3.7/58.4	4.6 (4.3–5.5)
CT regimen: PAC + CIS	TPS ≥1% (329)[10]	CAM + CT (166)	15.3 (12.4–NR)	0.59 (0.43–0.80)	6.9 (5.7–7.8)	0.51 (0.39–0.67)	74.1 (66.7–80.6)	NR	6.9 (5.7–8.9)
		PBO + CT (163)	11.45 (10.3–13.3)		5.6 (5.4–5.7)		65.6 (57.8–72.9)	NR	4.3 (4.1–5.4)
GEMSTONE-304 (NCT04187352)	All patients[b] (540)[14]	SUG + CT (358)	15.3 (NR–NR)	0.70 (0.55–0.90)	6.2 (NR–NR)	0.67 (0.54–0.82)	60.1 (NR–NR)	NR	6.0 (NR–NR)
SUG + CT vs. PBO + CT		PBO + CT (182)	11.5 (NR–NR)		5.4 (NR–NR)		45.2 (NR–NR)	NR	4.5 (NR–NR)
CT regimen: FLU + CIS									
JUPITER-06 (NCT03829969)	All patients[b] (514)[15]	TOR + CT (257)	17.0 (14.0–NE)	0.58 (0.425–0.783)	5.7 (5.6–7.0)	0.58 (0.461–0.738)	69.3 (63.2–74.8)	11.7/57.6	5.6 (4.4–8.7)
TOR + CT vs. PBO + CT		PBO + CT (257)	11.0 (10.4–12.6)		5.5 (5.2–5.6)		52.1 (45.8–58.4)	7.0/45.1	4.2 (4.2–4.4)
CT regimen: PAC + CIS	CPS ≥10 (212)[15]	TOR + CT (115)	17.0 (11.9–NE)	**0.64 (0.40–1.03)**	5.7 (5.6–7.0)	0.65 (0.45–0.92)	NR	NR	NR
		PBO + CT (97)	10.9 (9.0–13.0)		5.6 (4.5–5.7)		NR	NR	NR
KEYNOTE-590 (NCT03189719)	All patients (548)[16]	PEM + CT (274)	12.6 (10.2–14.3)	0.72 (0.60–0.88)	6.3 (6.2–6.9)	0.65 (0.54–0.78)	43.8 (37.8–49.9)	NR	9.1 (6.6–12.3)
PEM + CT vs. PBO + CT		PBO + CT (274)	9.8 (8.6–11.1)		5.8 (5.0–6.1)		31.0 (25.6–36.9)	NR	6.1 (4.4–6.4)
CT regimen: FLU + CIS	CPS ≥10 (286)[16]	PEM + CT (143)	13.9 (11.1–17.7)	0.57 (0.43–0.75)	7.3 (6.2–8.2)	0.53 (0.40–0.69)	51.0 (42.6–59.5)	NR	10.4 (8.0–16.2)
		PBO + CT (143)	8.8 (7.8–10.5)		5.4 (4.2–6.0)		28.0 (20.8–36.1)	NR	4.4 (4.1–6.2)
ORIENT-15 (NCT03748134)	All patients (659)[17]	SIN + CT (327)	17.4 (16.0–19.8)	0.661 (0.554–0.788)[18]	7.2 (7.0–9.6)	0.56 (0.46–0.68)	66 (61–71)	2/64	9.7 (7.1–13.7)
SIN + CT vs PBO + CT		PBO + CT (332)	12.8 (11.3–14.5)		5.7 (5.5–6.8)		45 (40–51)	2/44	6.9 (5.6–7.2)
CT regimen: FLU + CIS or PAC + CIS	CPS ≥10 (381)[17]	SIN + CT (188)	18.4 (16.2–24.6)	0.64 (0.50–0.80)	8.3 (6.9–12.4)	0.58 (0.45–0.75)	68 (61–74)	3/64	12.4 (7.2–15.4)
		PBO + CT (193)	14.5 (11.7–16.4)		6.4 (5.5–6.9)		49 (42–56)	2/47	5.7 (5.1–7.6)
RATIONALE-306 (NCT03783442)	All patients (649)[8]	TIS + CT (326)	17.2 (15.8–20.1)	0.66 (0.54–0.80)	8.4 (7.0–9.7)	0.60 (0.49–0.74)	68 (62–73)	15/52	7.1 (6.1–8.1)
TIS + CT vs. PBO + CT		PBO + CT (323)	10.6 (9.3–12.1)		5.7 (5.5–6.8)		49 (43–55)	7/41	5.7 (4.4–7.1)
CT regimen: FLU or CAP or PAC + CIS or OXA	TAP ≥10% (236)[8]	TIS + CT (123)	16.6 (15.3–24.4)	0.62 (0.44–0.86)	8.3 (7.0–10.2)	0.50 (0.37–0.69)	73 (64–81)	NR	NR
		PBO + CT (113)	10.0 (8.6–13.0)		5.6 (4.3–6.7)		40 (31–50)	NR	NR

[a]Disease status subgroups report n by subgroup rather than by arm.
[b]All patients in this trial were recruited from China.
[c]All randomized patients were those with PD-L1 CPS ≥1.
Hazard ratio is not statistically significant; this is different from main trial analysis.
Hazard ratio is statistically significant; this is different from main trial analysis.
CAM, camrelizumab; CAP, capecitabine; CI, confidence interval; CIS, cisplatin; CPS, combined positivity score; CR, complete response; CT, chemotherapy; DoR, duration of response; FLU, fluorouracil; HR, hazard ratio; IPI, ipilimumab; NE, not estimable; NR, not reported; ORR, objective response rate; OS, overall survival; NIV, nivolumab; OXA, oxaliplatin; PAC, paclitaxel; PBO, placebo; PEM, pembrolizumab; PFS, progression-free survival; PR, partial response; SER, serplulimab; SIN, sintilimab; SUG, sugemalimab; TAP, tumor area positivity; TIS, tislelizumab ; TOR, toripalimab; TPS, tumor positivity score.

Treatment-Related Adverse Events

- 96% to 98% of patients in IO + CT and CT arms experienced ≥1 TRAE of any grade (**Table 2**)
- All but 1 trial (ESCORT-1st)[10] reported higher incidences of Grade ≥3 TRAEs among those treated with IO + CT versus those treated with CT only

Table 2. Adverse Events Among Trials Included

Trial (NCT)	Safety reporting period from first dose	Study arm (Patients, N)	All grade TRAE, n (%)	Grade ≥3 TRAE, n (%)
ASTRUM-007 (NCT03189719)[11]	90 days after last dose or before starting a new therapy	SER + CT (382)	376 (98)	201 (53)
		PBO + CT (168)	165 (98)	81 (48)
CheckMate 648 (NCT03783442)[13]	30 days after last dose	NIV + CT (310)	297 (96)	147 (47)
		NIV + IPI (322)	256 (80)	102 (32)
		CT (304)	275 (90)	108 (38)
ESCORT-1st (NCT03691090)[10]	90 days after last dose	CAM + CT (298)	296 (99.3)	189 (63.4)
		PBO + CT (297)	288 (97.0)	201 (67.7)
GEMSTONE-304 (NCT04187352)	NR	SUG + CT (NR)	NR	NR (51.3)
		PBO + CT (NR)	NR	NR (48.4)
JUPITER-06 (NCT03829969)[15]	60 days after last dose or before starting a new therapy	TOR + CT (257)	250 (97.3)	166 (64.6)
		TOR + CT (257)	250 (97.3)	144 (56.0)
KEYNOTE-590 (NCT03189719)[16]	30 to 90 days after treatment discontinuation[a]	PEM + CT (370)	364 (98)	266 (72)
		PBO + CT (370)	360 (97)	250 (68)
ORIENT-15 (NCT03748134)[17]	90 days after last dose	SIN + CT (327)	321 (98.1)	196 (59.9)
		PBO + CT (332)	326 (98.1)	181 (54.5)
RATIONALE-306 (NCT03783442)[8]	30 days after last dose or before starting a new therapy	TIS + CT (324)	313 (97.0)	216 (66.7)
		PBO + CT (321)	309 (96.0)	207 (64.5)

[a]AEs were evaluated at 30 days; serious AEs and events of interest to pembrolizumab were assessed at 90 days.
AE, adverse event; CAM, camrelizumab; CPS, combined positivity score; CT, chemotherapy; IPI, ipilimumab; NIV, nivolumab; NR, not reported; PBO, placebo; PD-L1, programmed death-ligand 1; PEM, pembrolizumab; SER, serplulimab; SIN, sintilimab; SUG, sugemalimab; TIS, tislelizumab; TOR, toripalimab; TRAE, treatment-related AE.

Health-Related Quality of Life

- Four trials (CheckMate 648, ESCORT-1st, KEYNOTE-590, ORIENT-15) reported HRQoL outcomes (**Table 3**)

Table 3. Health-Related Quality of Life Outcomes Among Trials Included

Trial (NCT)	HRQoL scales reported	Study arm (Patients assessed for HRQoL, n)	Summary of results
CheckMate 648 (NCT03783442)[19]	FACT-E	NIV + CT (310)	Changes in score from baseline showed better HRQoL for the NIV + IPI and NIV + CT arms versus CT alone, although results were not statistically significant.
		NIV + IPI (322)	
		CT (304)	
ESCORT-1st (NCT03691090)[10]	EORTC QLQ-C30 EORTC QLQ-OES18	CAM + CT (298)	Assessment up to 36 weeks showed statistically significant results in favor of CAM + CT for improvement from baseline in some subscales of the EORTC QLQ-C30 and EORTC QLQ-OES18
		PBO + CT (298)	
KEYNOTE-590 (NCT03189719)[20]	EORTC QLQ-30	PEM + CT (356)	• No significant differences in change from baseline between treatments groups were observed for EORTC QLQ-30 • At week 18, LSM change in EORTC QLQ-OES18 pain subscale score from baseline was higher for PEM+CT compared with PBO + CT
		PBO + CT (355)	
ORIENT-15 (NCT03748134)[17]	EQ-5D-5L VAS EORTC QLQ-30	SIN + CT (NR)	Compared with PBO + CT, • SIN + CT was associated with larger improvements in EQ-5D-5L VAS at 48 weeks from baseline • SIN + CT had a decreased risk of deterioration in global health status/quality of life domain of the EORTC QLQ-C30
		PBO + CT (NR)	

CAM, camrelizumab; CT, chemotherapy; EQ-5D-5L, EuroQoL 5 dimensions 5 levels; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophageal Cancer; FACT-E, Functional Assessment of Cancer- Esophageal; HRQoL, health-related quality of life; IPI, ipilimumab; NIV, nivolumab; NR, not reported; PBO, placebo; PEM, pembrolizumab; SIN, sintilimab; VAS, visual analog scale.

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Presenter disclosures

Lin Zhan is an employee of BeiGene and may own company stock/stock options.

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