Supplemental Information

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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Supplementary Figure 1: Assessment of Risk of Bias Across RCTs Included

Trial	Q1	Q2	Q3	Q4	Q5	Q6	Q7
ASTRUM-007	+	+	+	+	+	+	-
CheckMate 648	+	+	+	-	+	+	!
ESCORT-1st	+	+	+	+	+	+	!
JUPITER-06	+	+	+	+	+	+	-
KEYNOTE-590	+	+	+	+	+	!	!
ORIENT-15	+	+	+	+	+	+	-
RATIONALE-306	+	+	+	+	+	+	!

Q1	Was randomization carried out appropriately? (Yes/No/Not clear)
Q2	Was the concealment of treatment allocation adequate? (Yes/No/Not clear)
Q3	Were the groups similar at the outset of the study in terms of prognostic factors? (Yes/No/Not clear)
Q4	Were the care providers, participants, and the outcome assessors blind to treatment allocation? (Yes/No/Not clear)
Q5	Were there any unexpected imbalances in drop-outs between groups? (Yes/No/Not clear)
Q6	Is there any evidence to suggest that the authors measured more outcomes than they reported? (Yes/No/Not clear)
Q7	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data? (Yes/No/Not clear)

+	Low risk of bias
!	Unclear risk of bias
-	High risk of bias

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Supplementary Table 1: Subgroups Analysis: Efficacy Results for Racial, Geographic, and Disease Status at Study Entry

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) SER + CT vs. PBO + CT CT regimen: FLU + CIS	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)
	Locally advanced (75)[1]	SER + CT (NR)	NR	**0.52 (0.26–1.04)**	NR	**0.71 (0.35–1.44)**	NR	NR	NR
		PBO + CT (NR)	NR		NR		NR	NR	NR
	Distantly metastatic (476)[1]	SER + CT (NR)	NR	0.70 (0.54–0.92)	NR	0.58 (0.46–0.74)	NR	NR	NR
		PBO + CT (NR)	NR		NR		NR	NR	NR
CheckMate 648 (NCT03783442) NIV + CT vs. CT NIV + IPI vs. CT CT regimen: FLU + CIS	All patients (970)[2]	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[3]	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[3]	11.1 (7.1–14.3)
		CT (324)	10.7 (9.4–12.1)	Ref	5.6 (4.3–5.9)	Ref	27 (NR–NR)	6/21[3]	7.1 (5.7–8.2)
	Race Japanese (394)[4]	NIV + CT (126)	15.5 (12.1–20.3)	0.73 (0.54–0.99)	4.2 (2.6–5.6)	0.76 (0.56–1.03)	56.3 (47.2–65.2)	19.8/36.5	8.2 (6.8–12.5)
		NIV + IPI (131)	17.6 (12.7–22.8)	0.68 (0.51–0.92)	4.0 (2.3–4.4)	1.16 (0.85–1.57)	35.9 (27.7–44.7)	15.3/20.6	9.9 (5.9–NA)
		CT (137)	11.0 (9.1–14.0)	Ref	4.3 (3.2–5.8)	Ref	24.1 (17.2–32.1)	4.4/19.7	6.9 (4.3–8.5)
	Geographic Non-Asia (290)[3]	NIV + CT (96)	10.5 (NR–NR)	0.74 (0.54–1.02)	NR	NR	NR	NR	NR
		NIV + IPI (96)	11.4 (NR–NR)	0.83 (0.66–1.04)	NR	NR	NR	NR	NR
		CT (98)	8.5 (NR–NR)	Ref	NR	NR	NR	NR	NR
	Metastatic (567)[3]	NIV + CT (NR)	13.4 (NR–NR)	0.63 (0.49–0.81)	NR	NR	NR	NR	NR
		NIV + IPI (NR)	12.1 (NR–NR)	0.75 (0.59–0.96)	NR	NR	NR	NR	NR
		CT (NR)	9.4 (NR–NR)	Ref	NR	NR	NR	NR	NR
	Recurrent locoregional (71)[3]	NIV + CT (NR)	14.8 (NR–NR)	**0.91 (0.44–1.89)**	NR	NR	NR	NR	NR
		NIV + IPI (NR)	13.9 (NR–NR)	**1.13 (0.57–2.23)**	NR	NR	NR	NR	NR
		CT (NR)	13.5 (NR–NR)	Ref	NR	NR	NR	NR	NR
	Recurrent distance (205)[3]	NIV + CT (NR)	12.3 (NR-NR)	**1.00 (0.65–1.53)**	NR	NR	NR	NR	NR
		NIV + IPI (NR)	15.5 (NR–NR)	0.88 (0.57–1.35)	NR	NR	NR	NR	NR
		CT (NR)	12.8 (NR–NR)	Ref	NR	NR	NR	NR	NR
	Unresectable advanced (127)[3]	NIV + CT (NR)	12.8 (NR–NR)	**0.73 (0.45–1.16)**	NR	NR	NR	NR	NR
		NIV + IPI (NR)	17.4 (NR–NR)	**0.63 (0.37–1.05)**	NR	NR	NR	NR	NR
		CT (NR)	12.1 (NR–NR)	Ref	NR	NR	NR	NR	NR
ESCORT-1st (NCT03691090) CAM + CT vs. PBO + CT CT regimen: PAC + CIS	All patients[b] (596)[5]	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)
		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)
	Regional recurrence (118)[5]	CAM + CT (NR)	NR	**0.84 (0.51–1.37)**	NR	0.65 (0.43–1.00)	NR	NR	NR
		PBO + CT (NR)	NR		NR		NR	NR	NR
	Distant metastasis (478)[5]	CAM + CT (NR)	NR	0.66 (0.51–0.86)	NR	0.53 (0.40–0.66)	NR	NR	NR
		PBO + CT (NR)	NR		NR		NR	NR	NR

Note: GEMSTONE -304 did not report any subgroup data.
[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
Results of subgroup analysis favor the opposite treatment arm compared to main trial analysis.
CAM, camrelizumab; CAP, capecitabine; CI, confidence interval; CIS, cisplatin; CR, complete response; CT, chemotherapy; CR, complete response; DoR, duration of response; FLU, fluorouracil; HR, hazard ratio; IPI, ipilimumab; NIV = nivolumab; NE, not estimable; NR, not reported; ORR, objective response rate; OS, overall survival; OXA, oxaliplatin; PAC, paclitaxel; PBO, placebo; PEM, pembrolizumab; PFS, progression-free survival; PR, partial response; SER, serplulimab; SIN, sintilimab; TIS, tislelizumab; TOR, toripalimab.

Supplemental Information

Supplementary Table 1: Subgroups Analysis: Efficacy Results for Racial, Geographic, and Disease Status at Study Entry cont.

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)
JUPITER-06 (NCT03829969) TOR + CT vs. PBO + CT CT regimen: PAC + CIS	All patients[b] (514)[6]	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)
		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)
	Metastatic (404)[6]	TOR + CT (NR)	15.2 (13.1–NE)	0.59 (0.43–0.83)	5.7 (5.6–6.9)	0.54 (0.42–0.70)	NR	NR	NR
		PBO + CT (NR)	11.0 (9.6–13.0)		5.4 (4.3–5.5)		NR	NR	NR
	Locally advanced (109)[6]	TOR + CT (NR)	17.0 (10.3–NE)	**0.50 (0.22–1.14)**	6.1 (5.6–NE)	**0.63 (0.36–1.10)**	NR	NR	NR
		PBO + CT (NR)	11.6 (10.5–15.2)		6.4 (5.6–7.0)		NR	NR	NR
KEYNOTE-590 (NCT03189719) PEM + CT vs. PBO + CT CT regimen: FLU + CIS	All patients (548)[7]	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)
		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)
	Geographic Japan (126)[8]	PEM + CT (67)	17.7 (13.7–NE)	**0.69 (0.44–1.08)**	6.4 (6.0–8.4)	0.57 (0.38–0.85)	56.7 (NR–NR)	NR	10.4 (NR–NR)
		PBO + CT (59)	11.7 (9.6–18.3)		6.1 (4.2–6.3)		40.7 (NR–NR)	NR	6.1 (NR–NR)
ORIENT-15 (NCT03748134) SIN + CT vs. PBO + CT CT regimen: FLU + CIS or PAC + CIS	All patients (659)[9]	SIN + CT (327)	17.4 (16.0–19.8)	0.661 (0.554–0.788)[10]	7.2 (7.0–9.6)	0.56 (0.46–0.68)	66 (61–71)	2/64	9.7 (7.1–13.7)
		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)
	Geographic China (640)[9]	SIN + CT (319)	NR	0.63 (0.51–0.78)	NR	0.56 (0.46–0.68)	NR	NR	NR
		PBO + CT (321)	NR		NR		NR	NR	NR
	Metastatic (572)[9]	SIN + CT (NR)	NR	0.62 (0.49–0.77)	NR	0.57 (0.46–0.69)	NR	NR	NR
		PBO + CT (NR)	NR		NR		NR	NR	NR
	Locally advanced (87)[9]	SIN + CT (NR)	NR	**0.77 (0.41–1.44)**	NR	**0.54 (0.29–1.00)**	NR	NR	NR
		PBO + CT (NR)	NR		NR		NR	NR	NR
RATIONALE-306 (NCT03783442) TIS + CT vs. PBO + CT CT regimen: FLU or CAP or PAC + CIS or OXA	All patients (649)[11]	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)	14/52	7.1 (6.1–8.1)
		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)
	Geographic Asia (486)[12]	TIS + CT (243)	18.3 (15.8–22.6)	0.67 (0.54–0.84)	NR	0.62 (0.50–0.76)	64.2 (57.8–70.2)	3.3/60.9	7.1 (5.6–8.4)
		PBO + CT (243)	11.5 (9.4–13.6)		NR		42.8 (36.5–49.3)	1.6/41.2	5.6 (4.4–7.1)
	Geographic Non-Asia (163)[13]	TIS + CT (83)	16.3 (11.1–20.8)	0.66 (0.45–0.96)	NR	0.59 (0.41–0.83)	61.4 (50.1–71.9)	8.4/53.0	7.1 (5.6–9.6)
		PBO + CT (80)	9.0 (6.9–11.1)		NR		41.3 (30.4–52.8)	5.0/36.3	5.7 (3.8–8.3)
	Metastatic (561)[11]	TIS + CT (NR)	16.3 (14.3–18.4)	0.72 (0.59–0.88)	NR	NR	NR	NR	NR
		PBO + CT (NR)	10.4 (9.1–12.0)		NR	NR	NR	NR	NR
	Locally advanced (88)[11]	TIS + CT (NR)	25.6 (19.4–NE)	0.44 (0.25–0.78)	NR	NR	NR	NR	NR
		PBO + CT (NR)	11.5 (8.6–21.7)		NR	NR	NR	NR	NR

Note: GEMSTONE -304 did not report any subgroup data.
[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
Results of subgroup analysis favor the opposite treatment arm compared to main trial analysis.
CAM, camrelizumab; CAP, capecitabine; CI, confidence interval; CIS, cisplatin; CR, complete response; CT, chemotherapy; CR, complete response; DoR, duration of response; FLU, fluorouracil; HR, hazard ratio; IPI, ipilimumab; NIV = nivolumab; NE, not estimable; NR, not reported; ORR, objective response rate; OS, overall survival; OXA, oxaliplatin; PAC, paclitaxel; PBO, placebo; PEM, pembrolizumab; PFS, progression-free survival; PR, partial response; SER, serplulimab; SIN, sintilimab; TIS, tislelizumab; TOR, toripalimab.

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