Systematic Literature Review (SLR) of Randomized Controlled Trials (RCTs) of Treatments for First-Line (1L) Gastric Cancer/Gastroesophageal Junction Adenocarcinoma (GC/GEJ) in Adult Patients

SA31

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Conclusions

- **Overall, this SLR demonstrates that the addition of immuno-oncology agents to chemotherapy provides survival and response benefits for patients with 1L unresectable, locally advanced, or metastatic GC/GEJ adenocarcinoma**
- **Benefits were observed following the addition of PD-1/PD-L1 inhibitors to chemotherapy, and these benefits extended to PD-1/PD-L1–positive subgroups**
- **These results highlight the need for increasing availability of PD-1/PD-L1 inhibitors in this setting**

Background

- Gastric cancer is the fifth most common cancer worldwide and the third leading cause of cancer-related deaths, with an estimated 1.1 million new cases and 770,000 deaths in 2020,[1,2] approximately 90%-95% of which were adenocarcinomas[3]
- For both GC and GEJ adenocarcinoma, programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors such as tislelizumab[4,5] have demonstrated statistically significant and clinically meaningful improvements in overall survival (OS) compared with chemotherapy (CT) alone, with a tolerable safety profile and better health-related quality of life (HRQoL)
- The objective was to conduct an SLR summarizing the efficacy and safety data from RCTs in 1L, unresectable, locally advanced, or metastatic GC and/or GEJ adenocarcinoma

Methods

- Embase, Ovid MEDLINE®, Ovid MEDLINE® Daily, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews searches were conducted on February 16, 2024, to identify English-language RCTs for immuno-oncology (IO), targeted therapies, and chemotherapies in 1L metastatic GC/GEJ
- Hand searches of health technology assessment agencies, conference proceedings, and trial registries were also conducted to supplement database searches
- Study selection of phase 2 and/or 3 trials was assessed by:
  - Population: Adult patients (≥18 years) with 1L unresectable, locally advanced, or metastatic human epidermal growth factor receptor 2 (HER2)–negative GC/GEJ adenocarcinoma
  - Interventions/comparators: IO agents ± CT/targeted therapy/any other IO, targeted therapy ± CT/IO/any other targeted therapy, CT, or placebo
  - Outcomes: OS, progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), HRQoL, and adverse events (AEs)

Results

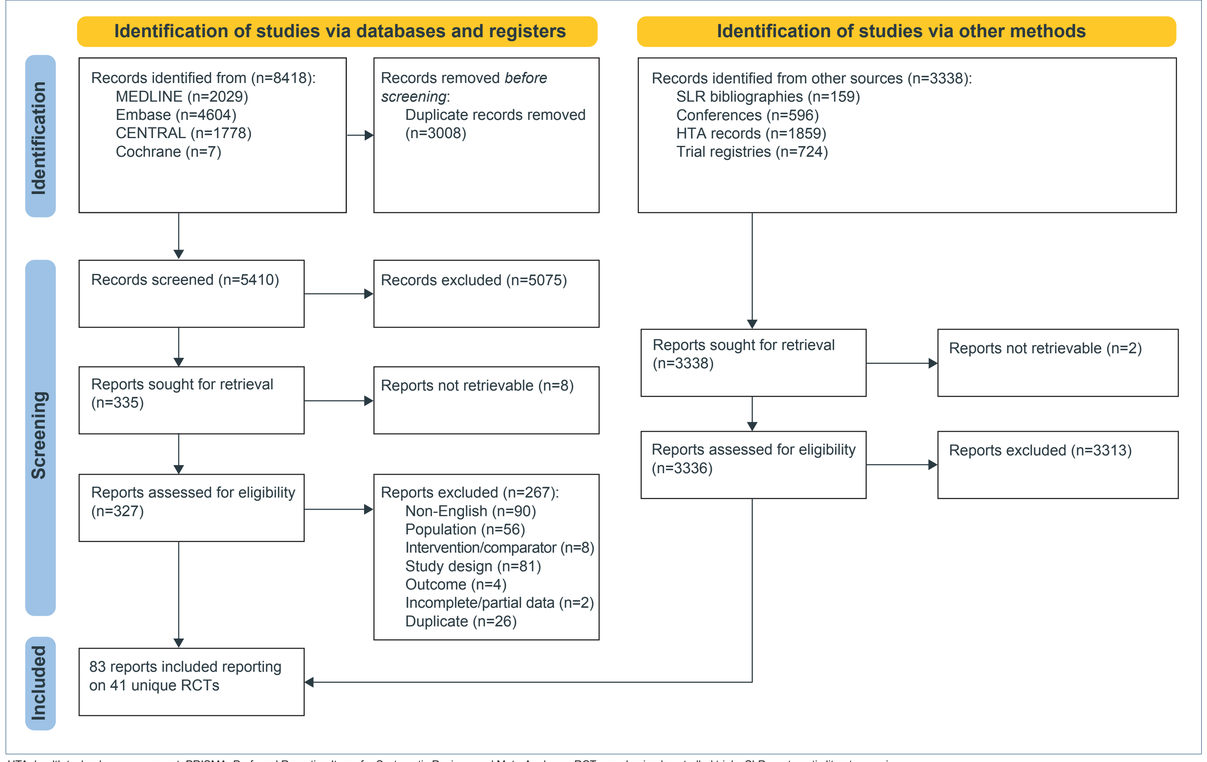
Study Characteristics

- Of 8418 records identified in the database/registry searches and 3338 records across gray literature sources, 83 records of 41 RCTs met inclusion criteria (**Figure 1**)
- Of these, 13 were IO agents + CT versus CT, 11 were targeted therapies + CT versus CT, and 17 compared various CT regimens
- Median age was 50.0-68.5 years with 15.8%-84.0% males. Of 33 trials reporting primary cancer diagnosis, 36.7%-100.0% were patients with GC, and 4.0%-61.7% were patients with GEJ adenocarcinoma (**Supplementary Table 1**† demonstrates quality assessments)

Efficacy Outcomes

- Among PD-1/PD-L1 inhibitors, tislelizumab, nivolumab (nivo), pembrolizumab (pembro), sintilimab, and sugemalimab with CT had statistically significant improvements in OS and PFS versus CT. Pembro monotherapy, nivo + ipilimumab (ipi), and nivo + ipi + CT showed no OS or PFS benefit versus CT (**Table 1**)
- Among targeted therapies, only zolbetuximab + CT had statistically significant improvement in OS and PFS (**Supplementary Table 2**†)
- Among PD-1/PD-L1 inhibitors, improvements in ORR were observed for tislelizumab, nivo, pembro, sintilimab, sugemalimab, and camrelizumab, combined with CT, versus CT. Only tislelizumab provided a statistically significant odds ratio for ORR (1.33 [95% CI, 1.03-1.72]). Pembro monotherapy, nivo + ipi, and nivo + ipi + CT had lower ORRs versus CT (**Table 1**)
- Among targeted therapies, improvements in ORR were noted for andecaliximab, bemarituzumab, and onartuzumab versus CT, with statistically significant improvement for andecaliximab (**Supplementary Table 2**†)
- Benefits for OS, PFS, and ORR were observed in PD-1/PD-L1–positive subgroups (**Table 1**)
- Race and/or region subgroup results were similar to those of the intent-to-treat (ITT) population

Figure 1. PRISMA Diagram



HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized controlled trials; SLR, systematic literature review.

Treatment-Related Adverse Events and HRQoL

- Ten PD-1/PD-L1 inhibitor trials reported overall and/or grade ≥3 treatment-related adverse events (TRAEs) (**Supplementary Table 3**†)
- Among PD-1/PD-L1 inhibitors, TRAEs ranged from 75% to 100%, while grade ≥3 TRAEs ranged from 17.3% to 73.2%
- Of the 41 included trials, 13 reported HRQoL data related to the 1L treatment of GC/GEJ adenocarcinoma, and reported HRQoL measures included the EQ-5D, EORTC-QLQ-C30, EORTC QLQ-STO22, and FACT-Ga (**Supplementary Table 4**†)

Table 1. Efficacy Results in PD-1/PD-L1 Inhibitor Trials From Included Trial Populations and PD-1/PD-L1 Subgroups

Trial; NCT	Patient Group	Arm (Patients, n)	Median OS, Months (95% CI)	OS HR (95% CI)	Median PFS, Months (95% CI)	PFS HR (95% CI)	ORR, % (95% CI)
RATIONALE-305; NCT03777657[4]	All patients	TIS + CT (n=501)	15.0 (13.6-16.5)	**0.80 (0.70-0.92)**[a] **0.80 (0.69-0.92)**[b]	6.9 (5.7-7.2)	**0.78 (0.67-0.90)**[a] **0.78 (0.68-0.90)**[b]	**47.3 (42.9-51.8)**[c]
		PBO + CT (n=496)	12.9 (12.1-14.1)		6.2 (5.6-6.9)		40.5 (36.2-45.0)[c]
	TAP ≥5%	TIS + CT (n=274)	16.4 (13.6-19.1)	**0.71 (0.58-0.86)**[a] **0.72 (0.59-0.88)**[b]	7.2 (5.8-8.4)	**0.68 (0.56-0.83)**[a] **0.69 (0.57-0.84)**[b]	51.5 (45.4-57.5)
		PBO + CT (n=272)	12.8 (12.0-14.5)		5.9 (5.6-7.0)		42.6 (36.7-48.8)
	TAP <5%	TIS + CT (n=227)	14.1 (11.9-15.6)	0.92 (0.75-1.13)[a] 0.91 (0.74-1.12)[b]	NR	0.91 (0.74-1.13)[d]	42.3 (35.8-49.0)
		PBO + CT (n=224)	12.9 (11.3-14.7)		NR		37.9 (31.6-44.7)
ATTRACTION-4 (Part 1); NCT02746796[6]	All patients	NIV + CT (SOX) (n=21)[e]	Not reached (11.9 to not reached)	NR	9.7 (5.8 to not reached)	NR	57.1 (34.0-78.2)
		NIV + CT (CAPOX) (n=17)[e]	Not reached (11.2 to not reached)		10.6 (5.6-12.5)		76.5 (50.1-93.2)
ATTRACTION-4 (Part 2); NCT02746796[7]	All patients	NIV + CT (n=362)	17.45 (15.67-20.83)	0.90 (0.75-1.08)	10.94 (8.44-14.03)	**0.70 (0.57-0.86)**	57.5 (52.2-62.6)
		PBO + CT (n=362)	17.15 (15.18-19.65)		8.41 (7.03-9.69)		47.8 (42.5-53.1)
CheckMate 649; NCT02872116[8-10]	All patients	NIV + CT (n=789)	13.7 (12.4-14.5)[9]	**0.79 (0.71-0.88)**[9]	7.7 (7.1-8.6)[9]	**0.80 (0.71-0.89)**[9]	58.0 (54.0-62.0)
		CT (n=792)	11.6 (10.9-12.5)[9]		6.9 (6.7-7.2)[9]		46.0 (42.0-50.0)
		NIV + IPI (n=409)	11.7 (9.6-13.5)	0.91 (0.77-1.07)	2.8 (2.6-3.6)	**1.66 (1.40-1.95)**	23.0 (18.0-28.0)
		CT (n=404)	11.8 (11.0-12.7)		7.1 (6.9-8.2)		47.0 (41.0-53.0)
	CPS ≥5	NIV + CT (n=473)	14.4 (13.1-16.2)	**0.70 (0.61-0.81)**	8.1 (7.0-9.2)	**0.70 (0.60-0.81)**	60.0 (55.0-65.0)[10]
		CT (n=482)	11.1 (10.0-12.1)		6.1 (5.6-6.9)		45.0 (40.0-50.0)[10]
		NIV + IPI (n=234)	11.2 (9.2-13.4)	0.89 (0.71-1.10)	2.8 (2.6-4.0)	**1.42 (1.14-1.76)**	27.0 (20.0-33.0)
		CT (n=239)	11.6 (10.1-12.7)		6.3 (5.6-7.1)		47.0 (40.0-54.0)
	CPS <5	NIV + CT (n=308)	12.4 (NR)	0.94 (0.79-1.11)[b]	NR	NR	55.0 (NR)
		CT (n=299)	12.3 (NR)		NR		46.0 (NR)
		NIV + IPI (n=168)	13.8 (NR)	0.98 (0.78-1.23)[b]	NR	NR	17.0 (NR)
		CT (n=157)	12.1 (NR)		NR		45.0 (NR)
MOONLIGHT; NCT03647969[11]	All patients	NIV + IPI + CT (n=60)	10.0 (NR)	NR	5.7 (NR)	NR	45.0 (NR)
		CT (n=60)	12.0 (NR)		6.6 (NR)		48.0 (NR)
MOONLIGHT; NCT03647969[12]	All patients	NIV + IPI + CT (parallel) (n=30)	Not reached (NR)	NR	8.4 (NR)	NR	47.0 (NR)[12]
		NIV + IPI + CT (sequential) (n=60)	9.1 (NR)		4.0 (NR)		30.0 (NR)[12]
KEYNOTE-062; NCT02494583[13,14]	All patients	PEM (n=256)	10.6 (NR)	0.90 (0.75-1.08)	2.0 (1.5-2.8)[13]	**1.66 (1.37-2.01)**[13,f]	15.0 (NR)
		PEM + CT (n=257)	12.5 (NR)	0.85 (0.71-1.02)	6.9 (NR)	0.84 (0.70-1.01)	49.0 (NR)
		PBO + CT (n=250)	11.1 (NR)	Ref	6.5 (NR)	Ref	37.0 (NR)
KEYNOTE-859; NCT03675737[15]	All patients	PEM + CT (n=790)	12.9 (11.9-14.0)	**0.78 (0.70-0.87)**	6.9 (6.3-7.2)	**0.76 (0.67-0.85)**	51.0 (NR)
		PBO + CT (n=789)	11.5 (10.6-12.1)		5.6 (5.5-5.7)		42.0 (NR)
NCT03472365[16]	All patients	CAM + CT then CAM + APA (n=48)	NR	NR	6.768 (5.552-9.495)	NR	58.3 (43.2-72.4)
		CAM + APA (n=19)	NR		2.793 (1.380-4.764)		10.5 (1.3-33.1)
ORIENT-16; NCT03745170[17,18]	All patients	SIN + CT (n=327)	15.2 (NR)[17]	**0.681 (0.571-0.812)**[17]	NR	**0.638 (0.530-0.768)**[17]	58.2 (NR)[17]
		PBO + CT (n=323)	12.3 (NR)[17]		NR		48.8 (NR)[17]
	CPS ≥5	SIN + CT (n=197)	18.4 (NR)	**0.66 (0.50-0.86)**[a] **0.64 (0.49-0.84)**[b]	7.7 (NR)	**0.63 (0.49-0.81)**	63.6 (NR)
		PBO + CT (n=200)	12.9 (NR)		5.8 (NR)		49.4 (NR)
	CPS <5	SIN + CT (n=130)	11.7 (NR)	0.88 (0.65-1.19)[a] 0.90 (0.66-1.21)[b]	7.0 (NR)	**0.66 (0.49-0.89)**	NR
		PBO + CT (n=123)	12.0 (NR)		5.6 (NR)		NR
GEMSTONE-303; NCT03802591[19]	All patients	SUG + CT (n=241)	15.64 (13.27-17.81)	**0.75 (0.61-0.92)**[g]	7.62 (6.37-7.89)	**0.66 (0.54-0.81)**[g]	68.6 (NR)
		PBO + CT (n=238)	12.65 (10.64-14.06)		6.08 (5.06-6.44)		52.7 (NR)
	PD-L1 ≥5%[h]	SUG + CT (n=241)	15.64 (13.27-17.81)	**0.75 (0.61-0.92)**[g]	7.62 (6.37-7.89)	**0.66 (0.54-0.81)**[g]	68.6 (NR)
		PBO + CT (n=238)	12.65 (10.64-14.06)		6.08 (5.06-6.44)		52.7 (NR)

Results are significantly in favor of the IO treatment.
Results are significantly in favor of the comparator.
PD-1/PD-L1 expression defined by TAP, CPS, or TPS. Cutoffs of interest included 10%, 5%, and 1% for all 3 measurement systems.
Additional IO data for non–PD-1/PD-L1 inhibitor IO therapy trials are presented in **Supplementary Table 2**.†
Stratified HRs are presented unless otherwise specified.

[a]Stratified HR. [b]Unstratified HR. [c]The odds ratio for TIS + CT versus PBO + CT is 1.33 (95% CI, 1.03-1.72). [d]Longest follow-up time was reported. [e]Full analysis set. [f]HR when compared with CT at 29.4 months of follow-up. [g]Stratification unclear. [h]Overall population.
APA, apatinib; CAM, camrelizumab; CAPOX, capecitabine + oxaliplatin; CI, confidence interval; CPS, combined positive score; CT, chemotherapy; HR, hazard ratio; IO, immuno-oncology; IPI, ipilimumab; NCT, National Clinical Trial; NIV, nivolumab; NR, not reported; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PEM, pembrolizumab; PFS, progression-free survival; Ref, reference group; SIN, sintilimab; SOX, S-1 + oxaliplatin; SUG, sugemalimab; TAP, tumor area positivity; TIS, tislelizumab; TPS, tumor proportion score.

References

Provided in Supplementary Material (view using Supplementary Material QR code)†

†**Supplementary Material Download**
Please scan the QR code to the left to view and download supplementary materials.

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