Supplementary Table.

Supplementary Table I. Summary of the most representative clinical trials for immune checkpoint blockade therapy in gastric cancer.

Study* / Regimen	**Study population**	**Biomarker**	**Main results****	**Reference**
KEYNOTE-012 Phase Ib Cohort D Pembrolizumab	36 patients with advanced PD-L1+ GC	PD-L1 (staining in ≥1% tumor and immune cells)	ORR= 22% (CI 10-39), all PR Patients with tumor size reduction = 53% PFS = 1.9 months (CI 1.8-3.5) OS = 11.4 months (CI 5.7-not reached)	[1]
	33 GC patients: 61% with high Youden index-based cutoff value for the IFN-γ-driven GEP	IFN-γ-driven GEP	IFN-γ-driven GEP associated with a better OR ($p<0.10$) and PFS ($p<0.05$). Youden index-based cutoff value for the IFN-γ-driven GEP was necessary, but not always sufficient, for clinical benefit (PPV = 45%, NPV = 92%).	[2]
KEYNOTE-059 Phase II Cohort 1 Pembrolizumab	259 patients with previously treated advanced GC: 57% PD-L1+	Total cases	ORR in general = 12% (CI 8-16), CR = 2% (CI 1-5) PFS in general = 2.0 months (CI 2.0-2.1) OS in general = 5.6 months (CI 4.3 – 4.3-6.9)	[3]
		PD-L1 (CPS ≥1)	ORR in PD-L1+ patients = 16% (CI 10-22) ORR in PD-L1- patients = 6% (CI 3-13) PFS in PD-L1+ patients = 2.1 months (CI 2.0-2.1) PFS in PD-L1- patients = 2.0 (CI 1.9-2.0)	
	174 patients with previously treated advanced GC: 4% MSI-high	MSI	ORR in MSI-high patients = 57% (CI 18-90) ORR in non-MSI-high patients = 9% (CI 5-14)	
	144 patients with previously treated advanced GC	T-cell-inflamed-GEP	A higher GEP score was associated with improved propensity for response and PFS ($p=0.010$ and $p=0.002$, respectively).	

Study* / Regimen	Study population	Biomarker	Main results**	Reference
			All PD-L1 CPS ≥20 had T-cell-inflamed GEP scores in the upper half of the range, but PD-L1 CPS <20 cases were associated with a broad range of T-cell-inflamed GEP scores.	
KEYNOTE-059 **Phase II** **Cohort 2** Pembrolizumab + Chemotherapy	25 patients with untreated advanced GC: 64% PD-L1+	Total cases	ORR in general = 60% (CI 39-79), CR = 4% (one patient) PFS in general = 6.6 months (CI 5.9-10.6) OS in general = 13.8 months (CI 8.6-not estimable)	[4]
		PD-L1 (CPS ≥1)	ORR in PD-L1+ patients = 69% (CI 41-89) ORR in PD-L1- patients = 38% (CI 8-76) OS in PD-L1+ patients = 11.1 months (CI 5.4-22.3) OS in PD-L1- patients = 19.8 (CI 1.8-not estimable)	
KEYNOTE-059 **Phase II** **Cohort 3** Pembrolizumab	31 patients with untreated advanced PD-L1+ GC	PD-L1 (CPS ≥1)	ORR = 26% (CI 12-45), CR = 6% (two patients) PFS = 3.3 months (CI 2.0-6.0) OS = 20.7 months (CI 9.2-20.7)	
KEYNOTE-061 **Phase III** Pembrolizumab vs. Chemotherapy	395 patients with previously treated PD-L1 CPS ≥1 advanced GC	PD-L1 (CPS ≥1)	ORR (Pembrolizumab) = 16% (CI 11-22), CR = 4% ORR (Chemotherapy) = 14% (CI 9-12) , CR = 3% PFS (Pembrolizumab) = 1.5 months (CI 1.4-2.0) PFS (Chemotherapy) = 4.1 months (CI 3.1-4.2) OS (Pembrolizumab) = 9.1 months (CI 6.2-10.7) OS (Chemotherapy) = 8.3 months (CI 17.6-9.0)	[5]
	592 patients with previously treated advanced GC	PD-L1 (CPS ≥10)	Pembrolizumab OS was longer than chemotherapy OS for patients with a PD-L1 CPS ≥10 (HR 0.64, CI 0.41-1.02).	
		MSI	Pembrolizumab OS was greater	

Study* / Regimen	Study population	Biomarker	Main results**	Reference
			than chemotherapy OS for patients with a MSI-high (HR 0.42, CI 0.13-1.31).	
CheckMate 032 Phases I & II Nivolumab	59 advanced or metastatic esophageal and GC patients: 27% PD-L1+ 12% MSI-high	Total cases	ORR in general = 12% (CI 5-23), CR = 2% (one patient)	[6]
		PD-L1 (CPS ≥1)	ORR in PD-L1+ patients = 19% (CI 4-46) ORR in PD-L1- patients = 12% (CI 2-30)	
		MSI	ORR in MSI-high patients = 29% (CI 4-71) ORR in non-MSI-high patients = 11% (CI 1-35)	
NCT02589496 Phase II Pembrolizumab	61 previously treated metastatic GC patients: 12% MSI-high 10% EBV+ 10% EMT GEP+	Total cases	ORR in general = 25% (CI = 21-46), CR = 5% (CI 1-14)	[7]
		MSI	ORR in patients with MSI-high = 86%, CR = 43% Clinical response was associated with MSI-associated GEP ($p<0.0001$).	
		EBV	ORR in patients EBV + = 100%, all PR	
		Immune GEP	Clinical response was associated with immune GEP ($p=0.007$).	
		Proliferation-related GEP	Clinical response was associated with proliferation-related GEP ($p=0.030$).	
		EMT GEP	ORR in patients EMT GEP + = 0% ORR in patients EMT GEP - = 31%	
	23 previously treated metastatic GC patients	ctDNA sequencing	ctDNA mutational load scores correlated with tumor tissue mutational load scores. ORR in upper tertile of ctDNA mutational load = 83% ORR in two lower tertile of ctDNA mutational load = 8% Change in ctDNA post-treatment predicts response: all patients (n=4) with increasing ctDNA	

Study* / Regimen	Study population	Biomarker	Main results**	Reference
			experienced disease progression within 100 days, all patients with decreasing ctDNA demonstrated significant improvement.	
	55 previously treated metastatic GC patients: 51% PD-L1+	PD-L1 (CPS ≥1)	ORR in PD-L1+ patients = 50% (CI) ORR in PD-L1- patients = 0% (CI)	
JAVELIN Gastric 300 Phase III Avelumab vs. Chemotherapy	85 previously treated PD-L1+ advanced GC patients	PD-L1	PFS (Avelumab) = 1.4 months PFS (Chemotherapy) = 2.8 months OS (Avelumab) = 4.0 months OS (Chemotherapy) = 4.5 months	[8]
JAVELIN Solid tumor JPN trial Phase I Avelumab	40 previously treated advanced GC patients: 28% PD-L1+	PD-L1 (staining in ≥1% tumor cells)	ORR in PD-L1+ patients = 27% (CI 6-61) ORR in PD-L1- patients = 4% (CI 0.1-19) PFS in PD-L1+ patients = 1.4 months (CI 0.7-4.0) PFS in PD-L1- patients = 2.6 (CI 1.4-2.8) OS in PD-L1+ patients = 10.9 months (CI 1.0-not estimable) OS in PD-L1- patients = 9.1 (CI 4.9-11.0)	[9]
ATTRACTION-2 (ONO-4538-12) Phase III Nivolumab	192 previously treated advanced GC patients: 14% PD-L1+	PD-L1 (staining in ≥1% tumor cells)	OS in PD-L1+ patients (Nivolumab) = 5.2 months (CI 2.8-9.4) OS in PD-L1+ patients (Placebo) = 3.8 months (CI 0.8-5.0) OS in PD-L1- patients (Nivolumab) = 6.0 months (CI 4.8-8.5) OS in PD-L1- patients (Placebo) = 4.2 months (CI 3.0-6.9) Exploratory analyses according to PD-L1 positivity in these patients suggest an OS benefit regardless of PD-L1 expression status, with HRs for OS favoring Nivolumab	[10]

Study* / Regimen	Study population	Biomarker	Main results**	Reference
			over Placebo across PD-L1+ and PD-L1+ patient groups.	

CI: 95% confidence interval; CPS: combined positive score; CR: complete response; EBV: Epstein-Barr virus; ; EMT: epithelial-to-mesenchymal transition; GC: gastric cancer (some references include gastro-esophageal junction cancer in this category); GEP: gene expression profile; HR: hazard ratio; IFN-γ: interferon gamma; MSI: microsatellite instability; MSS: microsatellite stable; NPV: negative predictive value; OR: objective response; ORR: objective response rate; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PPV: positive predictive value; PR: partial response.

*Only clinical trials that had a companion test were included.

**Central reviewer's criteria reported when available.

Supplementary References

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