Supplementary Tables

Supplementary Table 1. Assessment of Study Quality

Trial; NCT	Was randomization carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar to the outset of the study in terms of prognostic factors?	Were the care providers, participants, and the outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
ATTRACTION-4 Part 1; NCT02746796[1]	Yes	Yes	Yes	No	No	No	Yes
ATTRACTION-4 Part 2; NCT02746796[2]	Yes	Yes	Yes	Yes	No	No	Yes
CheckMate 649; (NCT02872116) [3]	Yes	Yes	Yes	No	No	No	Yes
EXELOX[4]	Yes	Unclear	Yes	No	No	No	Yes
EXPAND; (EudraCT number 2007-004219-75[5]	Yes	Yes	Yes	No	No	No	Yes
FAST; NCT01630083[6]	Unclear	Yes	Yes	No	No	No	Yes
GAMMA-1; NCT02545504[7]	Yes	Yes	Yes	Yes	No	No	Yes
GAPSO; NCT03801668[8]	Yes	No	Yes	No	No	No	Yes

GLOW; NCT03653507[9]	Yes	Yes	Yes	Yes	No	Yes	Yes
HERBIS-2; UMIN000006105[10]	Yes	Unclear	Yes	No	No	No	Yes
Japic CTI, number 111635[11]	Yes	Unclear	Yes	No	No	No	Yes
JCOG1013; UMIN000007652[12]	Yes	Unclear	Yes	No	No	No	Yes
JCOG1108/ WJOG7312G; Nakajima 2020[13]	Yes	Yes	Yes	No	No	No	Yes
KCSG ST13-10; NCT02114359[14]	Yes	No	Yes	No	No	No	No
KEYNOTE-062; NCT02494583[15]	Yes	Yes	Yes	Yes	No	No	Yes
KEYNOTE-859; NCT03675737[16]	Yes	Yes	Yes	Yes	No	No	Yes
LEGA/GISCAD; NCT02076594/2011-005537-39[17]	Yes	Yes	Yes	No	No	No	Yes
METGastric; NCT01662869[18]	Yes	Unclear	Yes	Yes	No	No	Yes
NA[19]	No	No	Yes	No	Unclear	No	No
NCT00719550[20]	Yes	Unclear	Yes	Yes	No	No	Yes
NCT01283204[21]	Yes	Unclear	Yes	No	No	No	Unclear
NCT01896531[22]	Unclear	Unclear	Yes	Yes	No	No	Yes
NCT02445209[23]	Yes	Unclear	Yes	No	Unclear	No	Yes
NCT03472365[24]	No	No	Unclear	No	Yes	No	No
OGSG1105, HERBIS-4A; UMIN000006755[25]	Unclear	Unclear	Yes	No	No	No	Unclear
PaFLO; AIO-STO-0510[26]	No	Unclear	Yes	No	Unclear	No	Yes
RAINFALL;	Yes	Unclear	Yes	Yes	No	No	Yes

NCT02314117[27]							
RAINSTORM; NCT02539225[28]	Yes	Yes	Yes	Yes	No	No	Unclear
RATIONALE-305; NCT03777657[29]	Yes	Yes	Yes	Yes	No	No	Yes
RILOMET-1; NCT01697072[30]	Yes	Yes	Yes	Yes	No	Yes	Yes
SOLAR; NCT02322593[31]	Yes	Yes	Yes	No	No	No	Unclear
SPOTLIGHT; NCT03504397[32]	Yes	Yes	Yes	Yes	No	Yes	Yes
SYLT/FNF-004[33]	Yes	No	Yes	No	No	No	No
XParTS II; NCT01406249[34]	Yes	Yes	Yes	No	No	No	Unclear
YO28252; NCT01590719[35]	Yes	Yes	Yes	Yes	No	No	Yes

Abbreviations: ITT, intention-to-treat

Supplementary Table 2. Efficacy Results in Targeted Therapy and non-PD-1/PD-L1 Inhibitor IO Therapy Trials From Included Trial Populations Organized by Treatment Class

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)	CR/PR (%)	Median DoR, months (95% CI)
non-PD-1/PD-L1 Inhibitor IO Therapies									
EXPAND; NCT00678535[5]	All Patients	CET + CT (n=281)	9.2 (NR)	0.98 (0.82-1.19)	4.6 (NR)	0.99 (0.80-1.23)	27 (22-33)	NR	NR
		CT (n=254)	9.7 (NR)		5.5 (NR)		26 (21-32)	NR	NR
RAINFALL; NCT02314117[27]	All Patients	RAM + CT (OS=326) (PFS=255)	11.2 (9.9-11.9)	0.962 (0.801-1.156)	5.7 (5.5-6.5)	**0.753 (0.607-0.935)**	41.1 (35.8-46.4)	1.2/39.9	5.7 (5.1-6.3)
		PBO + CT (OS=319) (PFS=253)	10.7 (9.5-11.9)		5.4 (4.5-5.7)		36.4 (31.1-41.6)	1.6/34.8	4.3 (3.9-4.9)
RAINSTORM; NCT02539225[28]	All Patients	RAM + CT (n=96)	14.65 (80% CI: 12.39-15.67)	1.11 (80% CI: 0.89-1.40)	6.34 (80% CI: 5.65-6.93)	1.07 (80% CI: 0.86-1.33)	58 (NR)	1.0/NR	NR
		PBO + CT (n=93)	14.26 (80% CI: 13.83-17.31)		6.74 (80% CI: 5.75-7.13)		50 (NR)	3.2/NR	NR
Targeted Therapies									
GLOW; NCT03653507 [9, 36]	All Patients	ZOL + CT (n=254)	14.3 (NR)	**0.77 (0.62-0.95)**	8.3 (NR)	**0.68 (0.55-0.85)**	42.5 (36.36-48.85)	3.5/39.0	6.14 (NR)
		PBO + CT (n=253)	12.2 (NR)		6.8 (NR)		40.3 (34.22-46.64)	2.0/38.3	6.08 (NR)

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)	CR/PR (%)	Median DoR, months (95% CI)
SPOTLIGHT; NCT03504397 [32, 37]	All Patients	ZOL + CT (n=283)	18.2 (NR)	**0.78 (0.64-0.95)**	11.0 (NR)	**0.73 (0.59-0.91)**	48 (42-54)	7/41	9.00 (6.87-10.25)
		PBO + CT (n=282)	15.6 (NR)		8.9 (NR)		48 (42-54)	4/44	8.05 (6.47-10.81)
FAST; NCT01630083[6]	All Patients	ZOL 1000 mg/m^2 + CT (n=85)	13.0 (9.7-18.7)	**0.55 (0.39-0.77)**	7.5 (5.6-11.3)	**0.44 (0.29-0.67)**	NR	NR	NR
		ZOL 800/600 mg/m^2 + CT (n=77)	9.6 (NR)	0.75 (0.55-1.04)	7.1 (NR)	**0.58 (0.39-0.85)**	39.0 (NR)	10.4/28.6	32.6 weeks (NR)
		CT (n=84)	8.3 (6.9-10.2)	Ref	5.3 (4.1-7.1)	Ref	25.0 (NR)	3.6/21.4	21.7 weeks (NR)
GAMMA-1; NCT02545504[7]	All Patients	ANDE + CT (n=218)	12.52 (11.2-14.0)	0.93 (0.74-1.18)	7.46 (7.29-8.41)	0.84 (0.67-1.04)	50.5 (43.6-57.3)	8/42	NR
		PBO + CT (n=214)	11.76 (10.3-13.5)		7.06 (5.52-7.46)		41.1 (34.5-48.0)	5/36	NR
FIGHT; NCT03694522[38]	All Patients	BEM + CT (n=77)	19.2 (13.6-24.2)	0.77 (0.52-1.14)	9.5 (7.3-13.7)	0.72 (0.49-1.08)	48.1 (36.5-59.7)	5.2/42.9	11.9 (6.9-17.3)
		PBO + CT (n=78)	13.5 (9.3-15.9)		7.4 (5.7-8.4)		33.3 (23.1-44.9)	2.6/30.8	7.5 (4.3-13.8)

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)	CR/PR (%)	Median DoR, months (95% CI)
METGastric; NCT01662869[18]	All Patients	ONZ + CT (n=279)	11.0 (NR)	0.82 (0.59-1.15)	6.7 (NR)	0.90 (0.71-1.16)	46.1 (NR)	1.8/44.2	NR
		PBO + CT (n=283)	11.3 (NR)		6.8 (NR)		40.6 (NR)	1.9/38.6	NR
YO28252; NCT01590719[35]	All Patients	ONZ + CT (n=62)	10.61 (NR)	1.06 (0.64-1.75)	6.77 (NR)	1.08 (0.71-1.63)	60.5 (NR)	9.3/51.2[a]	NR
		PBO + CT (n=61)	11.27 (NR)		6.97 (NR)		57.1 (NR)	2.4/54.8[a]	NR
NCT00719550[20]	All Patients	RLT 15 mg/kg + CT (n=40)	9.7 (7.7-13.3)	0.68 (0.40-1.16)	5.1 (2.9-7.0)	**0.69 (0.49-0.97)**	31 (NR)	0/31	5.7 months (IQR: 3.1-7.1)
		RLT 7.5 mg/kg + CT (n=42)	11.1 (9.2-13.2)	0.79 (0.47-1.31)	6.8 (4.5-7.5)	**0.53 (0.38-0.73)**	48 (NR)	3/45	
		PBO + CT (n=39)	8.9 (5.5-11.2)	Ref	4.2 (2.9-4.9)	Ref	21 (NR)	0/21	4.1 (IQR: 2.8-7.2)
RILOMET-1; NCT01697072[30]	All Patients	RLT + CT (n=304)	8.8 (7.7-10.2)	**1.34 (1.10-1.63)**	5.6 (5.3-5.9)	**1.26 (1.04-1.51)**	29.8 (24.3-35.7)	1/29	NR
		PBO + CT (n=305)	10.7 (9.6-12.4)		6.0 (5.7-7.2)		44.6 (38.5-50.8)	3/42	NR
PaFLO trial; NCT01503372[26]	All Patients	PAZ + CT (n=51)	10.19 (5.46-14.92)	1.01 (0.62-1.65)	4.66 (2.87-6.46)	0.96 (0.60-1.55)	25 (NR)	2/23	NR
		CT (n=27)	7.33 (4.93-9.73)		4.47 (1.79-7.14)		26 (NR)	4/22	NR

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)	CR/PR (%)	Median DoR, months (95% CI)
NCT01896531[22]	All Patients	IPA + CT (n=71)	12.12 (10.28-14.55)	**1.85 (90% CI: 1.23-2.79)**	6.57 (5.72-7.52)	1.12 (90% CI: 0.81,1.55)	52 (90% CI: 42-62)	3/49	NR
		PBO + CT (n=82)	15.67 (13.54-19.81)		7.52 (6.24-8.11)		56 (90% CI: 47-65)	6/50	NR

[a] Calculated value.

Results are significantly in favor of the IO treatment or targeted therapy.

Results are significantly in favor of the comparator.

Note: PD-1/PD-L1 expression defined by tumor area positivity (TAP), combined positive score (CPS), or tumor proportion score (TPS), cutoffs of interest included 10%, 5%, and 1% for all three measurement systems

ANDE, andecaliximab; BEM, bemarituzumab; CET, cetuximab; CI, confidence interval; CR, complete response; CT, chemotherapy; DoR, duration of response; HR, hazard ratio; IO, immuno-oncology; IPA, ipatasertib; IO, immuno-oncology; IQR, interquartile range; NR, not reported; ONZ, onartuzumab; ORR, overall response rate; OS, overall survival; PAZ, pazopanib; PBO, placebo; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; RAM, ramucirumab; Ref, reference group; RLT, rilotumumab; ZOL, zolbetuximab.

Supplementary Table 3. Adverse Events Among PD-1/PD-L1 Inhibitor Trials

Trial; NCT	Arm (Patients, n)	Median Treatment Duration	TRAE, n (%)	Grade ≥3 TRAE, n (%)
RATIONALE-305; NCT03777657[29]	TIS + CT (n=498)	5.9 months	483 (97.0)	268 (53.8)
	PBO + CT (n=494)	5.7 months	476 (96.4)	246 (49.8)
ATTRACTION-4 (Part 1); NCT02746796[1]	NIV + CT (SOX) (n=21)	6.8 months	21 (100)	12 (57.1)
	NIV + CT (CAPOX) (n=18)		18 (100)	12 (66.7)
ATTRACTION-4 (Part 2); NCT02746796[2]	NIV + CT (n=359)	**NIV+SOX** NIV: 6.3 months OXP: 5.4 months S-1: 7.1 months **NIV+CAPOX** NIV: 5.2 months OXP: 4.9 months CAP: 6.0 months	351 (97.8)[a]	208 (57.9)[a]
	PBO + CT (n=358)	**PBO+SOX** PBO: 5.0 months OXP: 4.6 months S-1: 5.4 months **PBO+CAPOX** PBO: 5.7 months OXP: 4.9 months CAP: 6.1 months	349 (97.2)[a]	176 (49.2)[a]
CheckMate 649; NCT02872116[3, 39]	NIV + CT (n=782)	6.8 months	739 (95)	471 (60)
	CT (n=767)	4.9 months	682 (89)	344 (45)
	NIV + IPI (n=403)	1.9 months	323 (80)	155 (38)
	CT (n=389)	4.9 months	356 (92))	180 (46)

Trial; NCT	Arm (Patients, n)	Median Treatment Duration	TRAE, n (%)	Grade ≥3 TRAE, n (%)
MOONLIGHT; NCT03647969[40]	NIV + IPI + CT [parallel] (Arm A1, n=30)	NR	28 (93.3)	21 (70)
	NIV + IPI + CT [sequential] (Arm A2, n=60)	NR	45 (75)	26 (43.3)
KEYNOTE-062; NCT02494583[15, 41]	PEM (n=254)	NR	139 (54.7)	44 (17.3)
	PEM + CT (n=250)	NR	235 (94)	183 (73.2)
	PBO + CT (n=244)	NR	224 (91.8)	169 (69.3)
KEYNOTE-859; NCT03675737[16]	PEM + CT (n=785)	6.7 months	751 (96)	466 (59)
	PBO + CT (n=787)	5.6 months	736 (94)	402 (51)
NCT03472365[24]	CAM + CAPOX followed by CAM + APA (n=48)	NR	48 (100)	33 (68.8)
	CAM + APA (n=19)	NR	18 (95.0)	NR
ORIENT-16; NCT03745170[42]	SIN + CT (n=328)	6.1 months	319 (97.3)	196 (59.8)
	PBO + CT (n=320)	5.5 months	308 (96.3)	168 (52.5)
GEMSTONE-303; NCT03802591[43]	SUG + CT (n=241)	NR	NR	NR (31.1)

Trial; NCT	Arm (Patients, n)	Median Treatment Duration	TRAE, n (%)	Grade ≥3 TRAE, n (%)
	PBO + CT (n=238)	NR	NR	NR (28.7)

[a]Calculated value.

5-FU, 5-fluorouracil; APA, apatinib; CAM, camrelizumab; CAP, capecitabine; CIS, cisplatin; CAPOX, capecitabine + oxaliplatin; CT, chemotherapy; IO, immuno-oncology; IPI, ipilimumab; NIV, nivolumab; NR, not reported; OXP, oxaliplatin; PBO, placebo; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PEM, pembrolizumab; S-1, tegafur/gimeracil/oteracil; SIN, sintilimab; SOX, S-1 + oxaliplatin; SUG, sugemalimab; TIS, tislelizumab; TRAE, treatment-related adverse event

Supplementary Table 4: HRQoL Outcomes Among Included Trials

Trial; NCT *Reference(s)*	Follow-Up Times Assessed	Arm (Patients, n)	Scale/Category	Summary of Results
RATIONALE-305; NCT03777657[44]	Baseline Week 12 Week 18	TIS + CT (n=501) PBO + CT (n=496)	EQ-5D 5L, EORTC QLQ-C30, EORTC QLQ-STO22	Better HRQoL was generally observed in patients receiving TIS + CT compared to patients receiving PBO + CT
ATTRACTION-4 (Part 2); NCT02746796[2]	Baseline	NIV + CT (n=362) PBO + CT (n=362)	EQ-5D 3L, FACT-Ga	HRQoL was maintained following treatment with NIV + CT and was similar to treatment with PBO + CT
CheckMate 649; NCT02872116[45]	Every 6 weeks starting at baseline until week 127 (week 133 for FACT-Ga change from baseline in total patient population)	NIV + CT (n=789) CT (n=792)	EQ-5D 3L, FACT-G, FACT-Ga	HRQoL improved significantly in patients receiving NIV + CT compared to patients receiving CT alone
KEYNOTE-062; NCT02494583[46]	Baseline Week 18	PEM (n=239) PBO + CT (n=234)	EQ-5D 3L, EORTC QLQ-C30, EORTC QLQ-STO22	HRQoL was maintained following first-line treatment with PEM and was similar between PEM and PBO + CT in this population
KEYNOTE-859; NCT03675737[16]	Baseline Week 18	PEM + CT (n=771) PBO + CT (n=771)	EORTC QLQ-C30, EORTC QLQ-STO22	HRQoL change from baseline and median time to deterioration were similar between groups
RAINFALL; NCT02314117[27]		RAM + CT (n=326)	EORTC QLQ-C30	

Trial; NCT *Reference(s)*	Follow-Up Times Assessed	Arm (Patients, n)	Scale/Category	Summary of Results
	Baseline, before each cycle, and at 30-day follow-up.	PBO + CT (n=319)		Median time to HRQoL deterioration was not significantly different between the RAM + CT and PBO + CT arms
GLOW; NCT03653507[47]	Baseline Cycle 17	ZOL + CT (n=254) PBO + CT (n=253)	EORTC QLQ-C30	No clinically meaningful difference in HRQoL between the ZOL + CT and PBO + CT arms
SPOTLIGHT; NCT03504397[47]	Baseline Cycle 9	ZOL + CT (n=283) PBO + CT (n=282)	EORTC QLQ-C30	No clinically meaningful difference in HRQoL between the ZOL + CT and PBO + CT arms
FAST; NCT01630083[48]	Baseline, cycle 5, at end of EOX treatment, and every 12 weeks thereafter until disease progression	ZOL + CT (800/600 mg/m^2) (n=68) CT (n=74)	EORTC QLQ-C30, EORTC QLQ-STO22	ZOL + EOX allowed patients to maintain good HRQoL longer than EOX alone
FIGHT; NCT03694522[49]	Baseline 6 weeks	BEM + CT (n=77) PBO + CT (n=78)	EQ-5D, EORTC QLQ-C30	HRQoL did not deteriorate following treatment with BEM + CT
GASTFOX-PRODIGE 51; NCT03006432[50]	NR	FOLFOX + DTX (n=253) FOLFOX (n=254)	EORTC QLQ-C30	Median time to deterioration in HRQoL was longer in patients treated with FOLFOX + DTX compared to patients receiving FOLFOX
KCSG ST13-10; NCT02114359[14]	Baseline 6 weeks 12 weeks	Combination CT (5-FU/OXP, CAPOX,	EORTC QLQ-C30, EORTC QLQ-STO22	HRQoL was maintained and did not differ significantly between the 2 groups throughout treatment

Trial; NCT *Reference(s)*	Follow-Up Times Assessed	Arm (Patients, n)	Scale/Category	Summary of Results
	24 weeks	CAP/CIS, or S-1/CIS) (n=53)		
		Single-agent CT (5-FU, CAP, or S-1) (n=51)		
JCOG1108/WJOG7 3112G UMIN000010949[13]	Baseline 3 months	PCT + 5-FU + LV (n=51)	EQ-5D 3L	HRQoL scores did not differ significantly between treatment groups
		5-FU + LV (n=50)		

5-FU, 5-fluorouracil; BEM, bemarituzumab; CAP, capecitabine; CAPOX, capecitabine + oxaliplatin; CIS, cisplatin; CT, chemotherapy; DTX, docetaxel; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach; EOX, epirubicin + oxaliplatin + capecitabine; EQ-5D, EuroQol 5 Dimension; EQ-5D 3L, EuroQol 5 Dimension 3 Level; EQ-5D 5L, EuroQol 5 Dimension 5 Level; FACT-G, Functional Assessment of Cancer Therapy – General; FOLFOX, leucovorin/folinic acid+5-fluorouracil + oxaliplatin; HRQoL, health-related quality of life; LV, leucovorin/folinic acid; NIV, nivolumab; OXP, oxaliplatin; PBO, placebo; PCT, paclitaxel; PEM, pembrolizumab; RAM, ramucirumab; S-1, tegafur/gimeracil/oteracil; TIS, tislelizumab; ZOL, zolbetuximab

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