

Therapeutic landscape and future direction of metastatic colorectal cancer

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Supplementary Table 1. Ongoing clinical trials of immuno-oncology therapy for patients with mismatch repair–deficient metastatic colorectal cancer

Trial name	Phase	Treatment line	Number of patients	Regimen	Primary endpoint	Recruitment status
CheckMate 8HW ¹ (NCT4008030)	III	1st, 2nd, 3rd	210 210 74	Ipilimumab (1 mg per kg Q3W) combined with nivolumab (240 mg Q3W) ×4 followed by nivolumab (480 mg Q4W) nivolumab (240 mg Q2W) ×6 followed by nivolumab (480 mg Q4W) modified FOLFOX6 or FOLFIRI with or without bevacizumab or cetuximab	PFS	Recruiting
NRG GI004/SWOG 1610 ² (NCT02997228)	III	1st	211	Modified FOLFOX6 plus bevacizumab–atezolizumab modified FOLFOX6 plus bevacizumab (closed) atezolizumab	PFS	Recruiting
NOUS-209-01 (NCT04041310)	I and II	1st	84	Nous-209 vaccine combined with pembrolizumab	DLT, safety, ORR	Recruiting
NCT04729322	I	2nd or later	15	Pembrolizumab or nivolumab combined with faecal microbiota transplant (anti-PD-1 re-introduction for anti-PD-1 non-responders)	ORR	Recruiting
NCT02982694	II	2nd or later	46	Atezolizumab plus bevacizumab	ORR	Terminated
NCT03638297	II	2nd or later	27	Pembrolizumab plus COX inhibitor (aspirin)	ORR	Recruiting
NCT04730544	II	1st, 2nd	96	Nivolumab plus ipilimumab	No. of adverse events G3 or G4 ^a , PFS	Recruiting
NCT03186326	II	2nd	132	Avelumab FOLFOX or FOLFIRI with or without targeted therapy	PFS	Active, not recruiting

^aGrade 3 or 4 adverse events in CTCAE criteria

DLT, dose limiting toxicity; ORR, overall response rate; PFS, progression-free survival

Supplementary Table 2. Ongoing clinical trials of targeted therapy for patients with *BRAF*-mutated metastatic colorectal cancer

Trial name	Phase	Treatment line	Number of patients	Regimen	Primary endpoint	Recruitment status
BREAKWATER ³ (NCT04607421)	Randomized III	1st	290 290 290	Encorafenib plus cetuximab Encorafenib plus cetuximab plus FOLFOX FOLFOX or FOLFIRI or FOLFOXIRI or CAPOX with or without anti-VEGF antibody	PFS	Recruiting
SEAMARK ⁴ (NCT05217446)	Randomized II	1st	104	Encorafenib plus cetuximab plus pembrolizumab pembrolizumab (<i>BRAF</i> V600E and dMMR–MSI-H mCRC)	PFS	Not yet recruiting
SWOG 2107 ⁵ (NCT05308446)	Randomized II	2nd or later	84	Encorafenib plus cetuximab plusnivolumab Encorafenib plus cetuximab	PFS	Not yet recruiting
NAUTICALCRC (NCT05004350)	Randomized II	2nd	103	Encorafenib plus cetuximab Irinotecan plus cetuximab FOLFIRI plus cetuximab	Safety, PFS	Recruiting
TRIDENTE (jRCTs031210511)	II	Salvage	21	Encorafenib plus binimetinib plus cetuximab rechallenge	RR	Recruiting
BAYONET (jRCTs031210510)	II	3rd or later	30	Encorafenib plus cetuximab followed by encorafenib plus binimetinib plus cetuximab	DCR	Recruiting
NCT05127759	II	2nd	25	HLX208 (<i>BRAF</i> V600E inhibitor)	ORR	Not yet recruiting
NCT05019534	I	2nd or later	12	Vemurafenib plus cetuximab plus camrelizumab (anti-PD-1 antibody)	RP2D, MTD	Recruiting
NCT04984369	II	2nd	50	HLX208 (<i>BRAF</i> V600E inhibitor) plus cetuximab	ORR	Recruiting
NCT04790448	I and II	2nd or later	37	Vemurafenib plus irinotecan plus cetuximab	ORR	Recruiting
NCT03668431	II	Any lines	25	Dabrafenib plus trametinib plus PDR001	ORR	Recruiting
NCT05233332	II	2nd or later	186	HL-085(MEK inhibitor)	ORR	Not yet recruiting

				plusvemurafenib		
BIGBANG ⁶⁸⁰ (UMIN000031857)	II	2nd or later	41	Encorafenib plus binimetinib plus cetuximab (<i>BRAF</i> non-V600E-mutated mCRC)	ORR	Recruiting

DCR, disease control rate; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose ; RR, relative risk

Supplementary Table 3. Reported clinical trials of anti-EGFR rechallenge therapy for patients with metastatic colorectal cancer

Trial name	Phase	Treatment line	ctDNA status	Number of patients	Regimen	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)
CRICKET ⁷ (NCT02296203)	II	3rd	RAS wild type RAS mutant	13 12	Irinotecan plus cetuximab irinotecan plus cetuximab	30.5 0	76.9 41.7	4.0 1.9	12.5 5.2
E-Rechallenge ⁸ (UMIN000016439)	II	3rd or later	RAS–BRAF wild type RAS–BRAF mutant	7 17	Irinotecan plus cetuximab Irinotecan plus cetuximab	42.9 0	85.8 37.5	NR NR	5.5 3.0
JACCRO-CC08&09 ⁹ (UMIN000015914) (UMIN000011440)	II	3rd or later	RAS wild type RAS mutant	10 6	Chemotherapy plus cetuximab or panitumumab Chemotherapy plus cetuximab or panitumumab	NR NR	80 33.3	4.7 2.3	16.0 3.8
CAVE ¹⁰ (NCT04561336)	II	3rd or later	All population RAS and BRAF wild type RAS and/or BRAF mutant	77 48 19	Cetuximab plus avelumab	7.8 8.3 5.3	65 72.9 47.4	3.6 4.1 3.0	11.6 17.3 10.2
CHRONOS ¹¹ (NCT03227926)	II	3rd or later	RAS and BRAF wild type	27	Panitumumab	30	70	16.4 weeks	NR
PURSUIT ¹² (jRCTs031190096)	II	Salvage	RAS wild type	50	Irinotecan plus panitumumab	14	80	3.6	NR

NCT03087071 ¹³	II	Salvage	EGFR ECD mutant (Arm A)	3	panitumumab 6 mg per kg Q2W	0	67	NR	NR
			RAS–BRAF–MAP2K1 mutant (Arm B)	20		0	63	2.1	5.9
			All wild type (Arm C)	31	Panitumumab 4.8 mg per kg Q2W combined with trametinib panitumumab 6 mg per kg Q2W	20	67	4.1	11.2

ctDNA, circulating tumour DNA; DCR, disease control rate; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks

Supplementary Table 4. Ongoing clinical trials of anti-EGFR rechallenge therapy for patients with metastatic colorectal cancer

Trial name	Phase	Treatment line	Number	Regimen	Primary endpoint	Recruitment status
VELO (EudraCT: 2018-001600-12)	Randomized II	3rd or later	112	Panitumumab plus trifluridine–tipiracil trifluoridine–tipiracil	PFS	Recruiting
PARERE ¹⁴ (NCT04787341)	Randomized II	3rd or later	214	panitumumab followed by regorafenib regorafenib followed by panitumumab	OS	Recruiting
PULSE (NCT03992456)	Randomized II	3rd or later	120	panitumumab regorafenib or trifluridine–tipiracil	OS	Recruiting
FIRE-4 (part 2) ¹⁵ (NCT02934529)	Randomized III	3rd or later	230	FOLFIRI or irinotecan combined with cetuximab regorafenib	OS	Recruiting
REGAIN (NCT02316496)	II	3rd or later	No data	Cetuximab plus irinotecan	ORR	Terminated
A-REPEAT (NCT03311750)	II	3rd	23	Panitumumab combined with FOLFOX or FOLFIRI	ORR	Terminated
REPAN (NCT03940131)	II	3rd or later	30	Panitumumab combined with FOLFOX6 or FOLFIRI	ORR	Recruiting

NCT03524820	II	3rd	60	cetuximab	ORR	Recruiting
NCT04224415	II	3rd	35	Cetuximab plus irinotecan	ORR	Unknown

ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Supplementary Table 5. Ongoing clinical trials of targeted therapy for patients with ERBB2-positive metastatic colorectal cancer

Trial name	Phase	Treatment line	Number of patients	Regimen	Primary endpoint	Recruitment status
HERACLES-RESCUE (NCT03418558)	II	After trastuzumab plus lapatinib	13	T-DM1	ORR	Unknown
NSABP FC-11 ¹⁶ (NCT03457896)	Randomized II	3rd or later	35	Neratinib plus cetuximab Neratinib plus trastuzumab	PFS	Recruiting
SWOG S1613 ^{17,112} (NCT03365882)	Randomized II	2nd or later	130	Trastuzumab plus pertuzumab Cetuximab plus irinotecan	PFS	Recruiting
MODUL (Cohort 3 for HER2+) (NCT02291289)	Randomized II	Maintenance after 1st line	No data	Capecitabine plus trastuzumab plus pertuzumab Fluoropyrimidine plus bevacizumab	No data	Completed
DESTINY-CRC02 ^{18,115} (NCT04744831)	Randomized II	3rd or later	120	trastuzumab-deruxtecan (5.4 mg per kg Q3W) trastuzumab-deruxtecan (6.4 mg per kg Q3W)	ORR	Recruiting
MOUNTAINEER-03 ¹⁹ (NCT05253651)	Randomized III	1st	400	Modified FOLFOX6 plus tucatinib plus trastuzumab modified FOLFOX6 with or without cetuximab or bevacizumab	PFS	Recruiting
NCT04430738	I and II	Depends on the cohort	120 in gastrointestinal cancers	Tucatinib plus trastuzumab plus FOLFOX Tucatinib plus trastuzumab plus CAPOX Tucatinib plus trastuzumab plus pembrolizumab plus FOLFOX Tucatinib plus trastuzumab plus pembrolizumab plus CAPOX Tucatinib plus trastuzumab plus pembrolizumab	DLT, safety	Recruiting

DASH (NCT04704661) (Solid tumour)	I	2nd or later	15	ceralasertib (AZD6738) plus trastuzumab-deruxtecan	Safety, RP2D	Recruiting
DPT01 (NCT04639219) (Solid tumour)	II	2nd or later	100	trastuzumab–deruxtecan	ORR	Recruiting
MasterKey-01 (NCT04209465) (Solid tumour)	I and II	salvage	200	BDTX-189 (EGFR and HER2 inhibitor)	RP2D, ORR	Recruiting
NCT04172597	II	salvage	30 (cohort 2)	Pozotinib (pan HER-tyrosine kinase inhibitor)	ORR	Recruiting
NCT04278144 (Solid tumour)	I and II	salvage	390	BDC-1001(HER2-targeting Boltbody) BDC-1001 plus nivolumab	Safety, DLT, MTD, ORR	Recruiting
NCT05041972 (Solid tumour)	II	salvage	250	ARX788 (anti-HER2 ADC)	ORR	Recruiting
NCT03602079 (Solid tumour)	I and II	salvage	49	A166 (anti-HER2 ADC)	MTD	Active, not recruiting
NCT05274191 (Solid tumour)	II	2nd or later	60	Pyrotinib maleate (EGFR/HER2 dual tyrosine kinase inhibitor) with or without standard treatment	ORR	Not yet recruiting

DLT, dose limiting toxicity; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose

Supplementary Table 6. Reported clinical trials of immuno-oncology therapy for patients with mismatch repair-proficient or non-selected metastatic colorectal cancer

Trial name	Phase	Treatment line	Number of patients	Regimen	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)
Combination with conventional chemotherapy								
AtezoTRIBE ²⁰ (NCT03721653)	Randomized II	1st	145 (MSS: 132) 73 (MSS: 67)	FOLFOXIRI plus bevacizumab plus atezolizumab FOLFOXIRI plus bevacizumab	59 64	NR NR	13.1 11.5 HR=0.69, P=0.012	NR NR
CheckMate 9X8 ²¹ (NCT03414983)	Randomized II	1st	127 (MSS: 95%) 68 (MSS: 90%)	Modified FOLFOX6 combined with bevacizumab plus nivolumab modified FOLFOX6 combined with	60 46	91 84	11.9 11.9 HR=0.81, P=0.3	29.4 NR HR=1.03

				bevacizumab				
NIVACOR ^{22,23} (GOIRC-03-2018) (NCT04072198)	II	1st	73 (MSS: 52/62, 11 patients were not assessed)	FOLFOXIRI plus bevacizumab plus nivolumab (8 cycles) followed by bevacizumab plus nivolumab	76.7	97.3	10.1 (12-month PFS rate: 53.4%)	NR
AVETUX ²⁴ (NCT03174405)	II	1st	43 (MSS: 40)	modified FOLFOX6 combined with cetuximab–avelumab	79.5	92.3	Not reported	Not reported
MEDITREME ²⁵ (NCT03202758) (Preliminary data)	I and II	1st	16	FOLFOX plus durvalumab plus tremelimumab	62.5	87.5	Not reported (1-year rate: 50%)	Not reported
MODUL ²⁶ (NCT02291289) (Cohort 2 for BRAF wild type)	Randomized II	Maintenance after 1st line	297 148	Fluoropyrimidine plus bevacizumab plus atezolizumab Fluoropyrimidine plus bevacizumab	NR NR	NR NR	7.13 7.39 HR=0.96, P=0.727	22.05 21.91 HR=0.86, P=0.283
BACCI ²⁷ (NCT02873195)	Randomized II	3rd or later	87 46	Capecitabine plus bevacizumab plus atezolizumab Capecitabine plus bevacizumab plus placebo	8.54 4.35	NR NR	4.4 3.3 HR=0.73, P=0.051	10.5 10.6 HR=0.94, P=0.398
Patel MR, et al. (NCT02860546)	II	3rd or later	18	Trifluridine-tipiracil plus nivolumab	0	44	2.2	NR
Kuang C, et al. (NCT02260440)	II	3rd or later	30	Pembrolizumab plus azacitidine	3	7	1.9	6.2
NCT03435107 ²⁸ (MSI-H/dMMR or <i>POLE</i> mutation)	II	2nd or later	33	durvalumab	42.4	66.7	22.6	NR
Combination with targeted therapy								
COTEZO IMblaze370 ²⁹ (NCT02788279)	Randomized III	3rd or later	183 90 90	Atezolizumab plus cobimetinib atezolizumab regorafenib	2.7 2.2 2.2	26.2 21.1 34.4	1.9 1.9 2.0 (HR=1.25)	8.9 7.1 8.5 (HR=1.00, P=0.99)
CCTG CO.26 ³⁰	Randomized II	Salvage line	119	Durvalumab plus	NR	22.7	1.8	6.6

(NCT02870920)			61	tremelimumab best supportive care	NR	6.6	1.9 HR=1.01, P=0.97	4.1 HR=0.72, P=0.07
C-800 ³¹ (NCT03860272)	I	Salvage line	41	Botensilimab with or without balstilimab	24	73	NR	NR
REGONIVO (EPOC1603) ³² (NCT03406871)	Ib	3rd or later	25 (MSS: 24)	Regorafenib plus nivolumab	33.3	87.5	7.9	NR (1-year rate: 68.0%)
Kim R., et al. (NCT03712943)	Ib	3rd or later	28 (MSS: 28)	Regorafenib plus nivolumab	4.8	71.4	4.3	11.0
REGOMUNE ³³ (NCT03475953)	II	2nd or later	48 (MSS: 48)	Regorafenib plus avelumab	0	53.5	3.6	10.8
Parikh, A., et al. (NCT03104439)	I and II	3rd or later	70 (MSS: 70)	Regorafenib plus pembrolizumab	0	49	2.0	9.6
SCOOP (EPOC1503) ³⁴ (NCT02851004)	I and II	2nd or later	40	Pembrolizumab plus napabucasin (STAT3 inhibitor)	10	45	1.6	7.3
MAYA ³⁵ (NCT03832621)	II	2nd or later	33 (TMZ sensitive cases)	Temozolomide plus ipilimumab plus nivolumab	42	100	7.0	18.4
EPOC1704 ³⁶ (UMIN000032801)	I and II	Salvage	29	Nivolumab plus pimitepib (HSP90 inhibitor)	16	Not reported	3.2	13.5
Lee MS, et al. (NCT03442569)	II	3rd or later	49 (evaluable)	Ipilimumab plus nivolumab plus cetuximab	41	80	5.7	27
CAVE ¹⁰ (NCT04561336)	II	3rd or later (rechallenge)	71 (ITT MSS) 44 (MSS <i>RAS/BRAF</i> wild type) 19 (<i>RAS/BRAF</i> mutant)	Cetuximab plus avelumab	8.5 9.1 5.3	64.8 72.7 47.4	3.6 3.9 3.0	11.6 17.3 10.4
PICASSO (NCT03274804)	I	Salvage line	20	Pembrolizumab plus maraviroc (CCR5 Inhibitor)	5	10	2.5	9.0
Bendell J, et al.	I	2nd or later	49	Cobimetinib plus	8	34.7	5.5	11.8

(NCT02876224)				bevacizumab plus atezolizumab				
Garraalda E, et al. (NCT02720068)	I	2nd or later	80	Pembrolizumab plus favezelimab	7	25.3	2.1	8.3
LEAP-005 ³⁷ (NCT03797326)	II	Salvage line	32 (expanded to 100)	Pembrolizumab plus lenvatinib	22	47	2.3	7.5
Combination with radiation								
AR Parikh, et al. ³⁸ (NCT03104439)	II	3rd or later	40	Ipilimumab plus nivolumab plus radiation (8 Gy ×3)	10	25	Not reported	Not reported
Arta M Monjazebl, et al. ³⁹ (NCT02888743)	II	2nd or later	18	Durvalumab plus tremelimumab plus radiation (high dose or low dose)	0	Not reported	1.7	3.8
Neil H. Segal, et al. ⁴⁰ (NCT03122509)	II	3rd or later	24	Durvalumab plus tremelimumab plus radiation	8.3	20.8	1.8	11.4
Floudas CS, et al. ⁴¹ (NCT02298946)	I	3rd or later	15	AMP-224 (anti-PD-1 therapy) plus cyclophosphamide plus SBRT	0	20	2.8	6.0
Combination with others								
Yarchoan M, et al. ⁴² (NCT02981524)	II	3rd or later	17	Pembrolizumab plus cyclophosphamide plus colon cancer vaccine	0	18	2.9	7.6
Wang C et al. ⁴³ (NCT03005002)	I	2nd or later	9	Durvalumab plus tremelimumab following radioembolization with SIR-spheres	0	0	Not reported	Not reported

DCR, disease control rate; HR, hazard ratio; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Supplementary Table 7. Ongoing clinical trials of immuno-oncology therapy for patients with mismatch repair-proficient or non-selected metastatic colorectal cancer

Trial name	Phase	Treatment line	Number	Regimen	Primary endpoint	Recruitment status
MEDITREME ⁴⁴ (NCT03202758)	I and II	1st	48	FOLFOX–durvalumab– tremelimumab	Safety, PFS	Recruiting
COLUMBIA-1 ⁴⁵ (NCT04068610)	I and II	1st	60	FOLFOX–bevacizumab– durvalumab–oleclumab FOLFOX–bevacizumab	Safety, ORR	Active, not recruiting
AVETRIC (NCT04513951) ⁴⁶	II	1st	58	FOLFOXIRI– cetuximab–avelumab	PFS	Active, not recruiting
ARETHUSA (NCT03519412) ⁴⁷	II	3rd or later	102	Temozolomide followed by pembrolizumab	ORR	Recruiting
LEAP-0017 ⁴⁸ (NCT04776148)	Randomized III	3rd or later	434	Pembrolizumab– lenvatinib regorafenib or trifluridine–tipiracil	OS	Active, not recruiting

ORR, overall response rate; PFS, progression-free survival

Supplementary Table 8. Reported clinical trials of targeted therapy for patients with *KRAS* or *NRAS*-mutated metastatic colorectal cancer

Trial name	Phase	Treatment line	Number	Regimen	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)
Targeted therapy for <i>KRAS</i> G12C mutation								
CodeBreaK100 ⁴⁹ (NCT03600883)	I and II	Salvage	62	Sotorasib	9.7	82.3	4.0	10.6
CodeBreaK101 ⁵⁰ (NCT04185883) (Preliminary data)	Ib	Salvage	31	Sotorasib plus panitumumab	26.9	Not reported	Not reported	Not reported
KRYSTAL-1 (NCT03785249)	I and II	Salvage	46 32	Adagrasib adagrasib plus cetuximab	22 43	87 100	5.6 Not reported	Not reported Not reported
Targeted therapy for other <i>RAS</i> mutations								
NCT03829410 ⁵¹	Ib and II	2nd	50	FOLFIRI plus bevacizumab and onvansertib	33	92	9.37	NR

NCT03597581	Ib and II	2nd	9	FOLFIRI plus bevacizumab plus RGX-202-01	56	100	NR	NR
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DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Supplementary Table 9. Ongoing clinical trials of targeted therapy for patients with *KRAS* or *NRAS*-mutated metastatic colorectal cancer

Trial name	Phase	Treatment line	Number	Regimen	Primary endpoint	Recruitment status
Targeted therapy for <i>KRAS</i> G12C mutation						
NCT04006301 ⁵² (Solid tumour)	I	Salvage	10	JNJ-74699157	DLT	Completed
NCT04165031 (Solid tumour)	I and II	Salvage	5	LY3499446	Phase I: DLT Phase II: ORR, PFS	Terminated
CodeBreaK101 (NCT04185883) ⁵⁰ (Solid tumour)	Ib	Any lines	1280 in all solid tumours	Sotorasib plus panitumumab with or without FOLFIRI Sotorasib plus MVASI® (bevacizumab-awwb) plus FOLFIRI or FOLFOX	No data	Recruiting
KRYSTAL-2 (NCT04330664) (Solid tumour)	I and II	Salvage	86	Adagrasib plus NO155 (SHP2 inhibitor)	Safety, pharmacokinetics	Active, not recruiting
KRYSTAL-10 ⁵³ (NCT04793958)	III	2nd	210 210	Adagrasib plus cetuximab FOLFIRI or modified FOLFOX6 with or without anti-VEGF therapy	PFS, OS	Recruiting
KRYSTAL-14 (NCT04975256)	I	Salvage	100	Adagrasib plus BI 170963 (SOS1 inhibitor)	Safety, pharmacokinetics, DLT	Recruiting
CodeBreaK 300 (NCT05198934)	III	Salvage	153	Sotorasib (240 mg QD) plus panitumumab sotorasib (960 mg QD) plus panitumumab trifluridine-tipiracil, or regorafenib	PFS	Not yet recruiting
NCT04585035	I and II	Salvage	200	D-1553	DLT, safety,	Recruiting

(Solid tumour)				D-1553 plus other therapies	plasma concentration of D-1553	
NCT04449874 (Solid tumour)	I	Any lines	342	GDC-6036 GDC-6036 plus atezolizumab GDC-6036 plus cetuximab GDC-6036 plus bevacizumab GDC-6036 plus erlotinib GDC-6036 plus GDC-1971 (SHP2 inhibitor)	Safety, DLT	Recruiting
NCT04956640 (Solid tumour)	I	Salvage	300	LY3537982 LY3537982 plus abemaciclib LY3537982 plus erlotinib LY3537982 plus pembrolizumab LY3537982 plus temuterkib LY3537982 plus LY3295668 (aurora kinase inhibitor) LY3537982 plus cetuximab LY3537982 plus TNO155 (SHP2 inhibitor)	RP2D, DLT	Recruiting
NCT04973163 (Solid tumour)	I	Salvage	60	BI 1823911 BI 1823911 plus midazolam BI 1823911 plus BI 1701963 (SOS1 inhibitor)	DLT, BOR	Recruiting
NCT05002270 (Solid tumour)	I and II	2nd or later	100	JAB-21822 JAB-21822 plus cetuximab	Safety, ORR, DOR	Recruiting
NCT05288205 (Solid tumour)	I and II	Salvage	72	JAB-21822 plus JAB-3312 (SHP2 inhibitor)	RP2D, DLT	Not yet recruiting
NCT05194995 (Solid tumour)	I and II	2nd or later	62	JAB-21822 plus cetuximab	DLT, ORR	Not yet recruiting
NCT05009329 (Solid tumour)	I and II	Salvage	144	JAB-21822	DLT, safety	Recruiting
NCT05010694 (Solid tumour)	I	2nd or later	38	GH35	DLT	Recruiting
Targeted therapy for other <i>RAS</i> mutations						
NCT04678648 (Solid tumour)	I	Salvage	134	RSC-1255 (Pan-RAS inhibitor)	MTD, RP2D	Recruiting

BOR, best overall response ; DLT, dose limiting toxicity; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once per day; RP2D, recommended phase 2 dose

Supplementary Table 10. Reported clinical trials of other targeted therapy for patients with metastatic colorectal cancer

Trial name	Phase	Treatment line	Number	Regimen	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)
NAVIGATE ^{54,55} (NCT02576431)	II	Salvage	153	larotrectinib	79 (CRC: 50%)	Not reported	28.3	44.4
ALKA-372-001, STARTRK-1, STARTRK-2 ⁵⁶ (NCT02097810) (NCT02568267)	I and II	Salvage	54	entrectinib	57	Not reported	11	21
FOCUS4-C ⁵⁷	Randomized II	Maintenance for TP53 and RAS mCRC	44 25	adavosertib (Wee-1 inhibitor) active monitoring	Not reported	Not reported	3.61 1.87 (HR=0.35, P=0.0022)	13.1 11.3 (HR=0.86, P=0.65)
NCT02008383 ⁵⁸	Ib	3rd or later	25	cabozantinib plus panitumumab	16	Not reported	3.7	12.1

HR, hazard ration; ORR, overall response rate; OS, overall survival; PFS, progression-free survival;

Supplementary Table 11. Ongoing clinical trials of other targeted therapy for patients with metastatic colorectal cancer

Trial name	Phase	Treatment line	Number	Regimen	Primary endpoint	Recruitment status
METBEGE (JapicCTI-194709)	I and randomized II	2nd or later	54	Cabozantinib plus panitumumab cabozantinib	DLT, ORR	Recruiting
NCT03215511	I and II	Salvage	170 in all solid tumors	Selitrectinib (TRK kinase inhibitor)	MTD, recommended dose, ORR	Active, not recruiting
TRIDENT-2 (NCT05071183)	I and II	2nd, 3rd	74 in all solid tumours	Repotrectinib (ALK–ROS1–TRK inhibitor) plus trametinib	Safety, RP2D, ORR	Recruiting
TRIDENT-1 (NCT03093116)	I and II	Depends on the	500 in all solid	Repotrectinib	DLT, RP2D, ORR	Recruiting

		cohort	tumors			
NCT05004116	I and II	Salvage	50 in all solid tumors	Repotrectinib plus irinotecan plus temozolomide	DLT, MTD	Recruiting
NCT04094610	I and II	Depends on the cohort	75 in all solid tumors	Repotrectinib	DLT, RP2D, ORR	Recruiting

DLT, dose limiting toxicity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RP2D, recommended phase 2 dose

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