

Table SI. Key words and search results in different databases.

Database	Keyword search strategy	Filter	Date	Results, n
PubMed	((PD-1) OR (PD-L1) OR (CTLA-4) OR (immune checkpoint inhibitor) OR (checkpoint inhibitor)) AND ((colorectal tumor) OR (colorectal neoplasm) OR (colon cancer) OR (rectum cancer))	NA	April 4, 2024	4,742
Cochrane Library	('PD-1' OR 'PD-L1' OR 'CTLA-4' OR 'immune checkpoint inhibitor' OR 'checkpoint inhibitor') AND ('colorectal tumor' OR 'colorectal neoplasm' OR 'colon cancer' OR 'rectum cancer')	Trials	April 4, 2024	284
ClinicalTrials.gov	Study type: Clinical trials. Search terms: Cancer and immune checkpoint inhibitor. Study status: Completed. Results availability: With results. Phases: Phase 2, phase 3, phase 4, not applicable. Condition or disease: Colorectal cancer	NA	April 4, 2024	30
Embase	('PD-1' OR 'PD-L1' OR 'CTLA-4' OR 'immune checkpoint inhibitor'/exp OR 'checkpoint inhibitor'/exp) AND ('colorectal tumor'/exp OR 'colorectal neoplasm'/exp OR 'colon cancer'/exp OR 'rectum cancer'/exp)	Randomized controlled trial	April 4, 2024	162
Web of Science	('PD-1' OR 'PD-L1' OR 'CTLA-4' OR 'immune checkpoint inhibitor' OR 'checkpoint inhibitor') AND ('colorectal cancer' OR 'colorectal neoplasm' OR 'colon cancer' OR 'rectum cancer')	NA	April 4, 2024	5,260

CTLA-4, cytotoxic T-lymphocyte associated protein 4; NA, not applicable; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table SII. Excluded studies and reasons for exclusion.

Reference details	Reasons
<p>Diaz, L. A., Jr., Shiu, K. K., Kim, T. W., Jensen, B. V., Jensen, L. H., Punt, C., Smith, D., Garcia-Carbonero, R., Benavides, M., Gibbs, P., de la Fourchardiere, C., Rivera, F., Elez, E., Le, D. T., Yoshino, T., Zhong, W. Y., Fogelman, D., Marinello, P., & Andre, T. (2022). Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. <i>Lancet Oncol</i>, 23(5), 659-670. https://doi.org/10.1016/s1470-2045(22)00197-8</p>	<p>Duplicate entries of an included trial (KEYNOTE-177)</p>
<p>Yoshino, T., Andre, T., Kim, T. W., Yong, W. P., Shiu, K. K., Jensen, B. V., Jensen, L. H., Punt, C. J. A., Smith, D., Garcia-Carbonero, R., Alcaide-Garcia, J., Gibbs, P., de la Fouchardiere, C., Rivera, F., Elez, E., Le, D. T., Adachi, N., Fogelman, D., Marinello, P., & Diaz, L. A., Jr. (2023). Pembrolizumab in Asian patients with microsatellite-instability-high/mismatch-repair-deficient colorectal cancer. <i>Cancer Sci</i>, 114(3), 1026-1036. https://doi.org/10.1111/cas.15650</p>	<p>Duplicate entries of an included trial (KEYNOTE-177)</p>
<p>Ardeshir-Larijani, F., Althouse, S. K., Leal, T., Feldman, L. E., Hejleh, T. A., Patel, M., Gentzler, R. D., Miller, A. R., & Hanna, N. H. (2022). A Phase II Trial of Atezolizumab Plus Carboplatin Plus Pemetrexed Plus Bevacizumab in the Treatment of Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer: Big Ten Cancer Research Consortium (BTCRC)- LUN 17-139. <i>Clin Lung Cancer</i>, 23(7), 578-584. https://doi.org/10.1016/j.clcc.2022.07.001</p>	<p>Does not provide data exclusively for a colorectal cancer subgroup (e.g., ‘mixed solid tumor’ only)</p>
<p>Bellone, S., Roque, D. M., Siegel, E. R., Buza, N., Hui, P., Bonazzoli, E., Guglielmi, A., Zammataro, L., Nagarkatti, N., Zaidi, S., Lee, J., Silasi, D. A., Huang, G. S., Andikyan, V., Damast, S., Clark, M., Azodi, M., Schwartz, P. E., Tymon-Rosario, J. R., . . . Santin, A. D. (2022). A phase 2 evaluation of pembrolizumab for recurrent Lynch-like versus sporadic endometrial cancers with microsatellite instability. <i>Cancer</i>, 128(6), 1206-1218. https://doi.org/10.1002/cncr.34025</p>	<p>Does not provide data exclusively for a colorectal cancer subgroup (e.g., ‘mixed solid tumor’ only)</p>
<p>Felip, E., Moreno, V., Morgensztern, D., Curigliano, G., Rutkowski, P., Trigo, J. M., Calvo, A., Kowalski, D., Cortinovis, D., Plummer, R., Maio, M., Ascierto, P. A., Vladimirov, V. I., Cervantes, A., Zudaire, E., Hazra, A., T'Jollyn, H., Bandyopadhyay, N., Greger, J. G., . . . Calvo, E. (2022). First-in-human, open-label, phase 1/2 study of the monoclonal antibody programmed cell death protein-1 (PD-1) inhibitor cetrelimab (JNJ-63723283) in patients with advanced cancers. <i>Cancer Chemother Pharmacol</i>, 89(4), 499-514. https://doi.org/10.1007/s00280-022-04414-6</p>	<p>Does not provide data exclusively for a colorectal cancer subgroup (e.g., ‘mixed solid tumor’ only)</p>
<p>Hodi, F. S., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Rutkowski, P., Cowey, C. L., Lao, C. D., Schadendorf, D., Wagstaff, J., Dummer, R., Ferrucci, P. F., Smylie, M., Hill, A., Hogg, D., Marquez-Rodas, I., Jiang, J., Rizzo, J., Larkin, J., & Wolchok, J. D. (2018). Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. <i>Lancet Oncol</i>, 19(11), 1480-1492. https://doi.org/10.1016/s1470-2045(18)30700-9</p>	<p>Does not provide data exclusively for a colorectal cancer subgroup (e.g., ‘mixed solid tumor’ only)</p>
<p>Ludford, K., Ho, W. J., Thomas, J. V., Raghav, K. P. S., Murphy, M. B., Fleming, N. D., Lee, M. S., Smaglo, B. G., You, Y. N., Tillman, M. M., Kamiya-Matsuoka, C., Thirumurthi, S., Messick, C., Johnson, B., Vilar, E., Dasari, A., Shin, S., Hernandez, A., Yuan, X., . . . Overman, M. J. (2023). Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors. <i>J Clin Oncol</i>, 41(12), 2181-2190. https://doi.org/10.1200/jco.22.01351</p>	<p>Does not provide data exclusively for a colorectal cancer subgroup (e.g., ‘mixed solid tumor’ only)</p>

<p>Sanborn, R. E., Pishvaian, M. J., Callahan, M. K., Weise, A., Sikic, B. I., Rahma, O., Cho, D. C., Rizvi, N. A., Sznol, M., Lutzky, J., Bauman, J. E., Bitting, R. L., Starodub, A., Jimeno, A., Reardon, D. A., Kaley, T., Iwamoto, F., Baehring, J. M., Subramaniam, D. S., . . . Keler, T. (2022). Safety, tolerability and efficacy of agonist anti-CD27 antibody (varlilumab) administered in combination with anti-PD-1 (nivolumab) in advanced solid tumors. <i>JOURNAL FOR IMMUNOTHERAPY OF CANCER</i>, 10(8), Article e005147. https://doi.org/10.1136/jitc-2022-005147</p>	<p>Does not provide data exclusively for a colorectal cancer subgroup (e.g., ‘mixed solid tumor’ only)</p>
<p>Yu, Q., Zhang, H. Y., Song, Y., Chen, C., Chen, J., & Shen, J. K. (2023). Dissociated response to PD-1 inhibitors combined with radiotherapy in patients with advanced metastatic solid tumors: a single-center experience. <i>WORLD JOURNAL OF SURGICAL ONCOLOGY</i>, 21(1), Article 228. https://doi.org/10.1186/s12957-023-03122-6</p>	<p>Does not provide data exclusively for a colorectal cancer subgroup (e.g., ‘mixed solid tumor’ only)</p>
<p>Patel, S. P., Mayerson, E., Chae, Y. K., Strosberg, J., Wang, J., Konda, B., Hayward, J., McLeod, C. M., Chen, H. X., Sharon, E., Othus, M., Ryan, C. W., Plets, M., Blanke, C. D., & Kurzrock, R. (2021). A phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609: High-grade neuroendocrine neoplasm cohort. <i>Cancer</i>, 127(17), 3194-3201. https://doi.org/10.1002/cncr.33591</p>	<p>Does not provide data exclusively for a colorectal cancer subgroup (e.g., ‘mixed solid tumor’ only)</p>
<p>Andre, T., Amonkar, M., Norquist, J. M., Shiu, K. K., Kim, T. W., Jensen, B. V., Jensen, L. H., Punt, C. J. A., Smith, D., Garcia-Carbonero, R., Sevilla, I., De La Fouchardiere, C., Rivera, F., Elez, E., Diaz, L. A., Jr., Yoshino, T., Van Cutsem, E., Yang, P., Farooqui, M., & Le, D. T. (2021). Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. <i>Lancet Oncol</i>, 22(5), 665-677. https://doi.org/10.1016/s1470-2045(21)00064-4</p>	<p>No data available</p>
<p>Antonioti, C., Borelli, B., Rossini, D., Pietrantonio, F., Morano, F., Salvatore, L., Lonardi, S., Marmorino, F., Tamberi, S., Corallo, S., Tortora, G., Bergamo, F., Brunella, D., Boccaccino, A., Grassi, E., Racca, P., Tamburini, E., Aprile, G., Moretto, R., . . . Cremolini, C. (2020). AtezoTRIBE: a randomised phase II study of FOLFOXIRI plus bevacizumab alone or in combination with atezolizumab as initial therapy for patients with unresectable metastatic colorectal cancer. <i>BMC Cancer</i>, 20(1), Article 683. https://doi.org/10.1186/s12885-020-07169-6</p>	<p>No data available</p>
<p>Hou, Z. L., Jiang, W., Tang, J. H., Xiao, B. Y., Li, Y. A., Li, D. D., Zhang, X. S., Pan, Z. Z., & Ding, P. R. (2023). PACE: A phase III trial of CAPOX versus anti-PD-1 inhibitor as adjuvant therapy for patients with dMMR/MSI-H stage III colon cancer. <i>JOURNAL OF CLINICAL ONCOLOGY</i>, 41(16).</p>	<p>No data available</p>
<p>Johnson, B., Haymaker, C., Morris, V. K., Dasari, A., Higbie, V. S., Shen, J. P., Parseghian, C., Morelli, M. P., Huey, R., Lee, M. S., Willis, J., Raghav, K. P., Yuan, Y., Zebala, J., DePinho, R. A., Kopetz, S., & Overman, M. (2023). A phase I/II trial of a CXCR1/2 inhibitor in combination with anti-PD-1 for circulating tumor DNA (ctDNA) positive & refractory <i>RAS</i>-mutated microsatellite stable (MSS) colorectal cancer. <i>CANCER RESEARCH</i>, 83(8). https://doi.org/10.1158/1538-7445.AM2023-CT118</p>	<p>No data available</p>

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Table SIII. Quality assessment of included studies using the Cochrane RoB 2 tool.

First author, year	Randomization process ^a	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall RoB	(Refs.)
Eng <i>et al</i> , 2019	S	L	L	L	L	S	(17)
André <i>et al</i> , 2020	S	L	L	L	L	S	(18)
Chen <i>et al</i> , 2020	S	L	L	L	L	S	(19)
Lonardi <i>et al</i> , 2021	S	L	L	L	L	S	(20)
Antoniotti <i>et al</i> , 2022	S	L	L	L	L	S	(21)
Meltzer <i>et al</i> , 2022	S	L	L	L	L	S	(22)
Metu <i>et al</i> , 2022	L	L	L	L	L	L	(28)
Redman <i>et al</i> , 2022	S	L	L	L	L	S	(23)
Taberner <i>et al</i> , 2022	S	L	L	L	L	S	(24)
Ducreux <i>et al</i> , 2023	S	L	L	L	L	S	(25)
Monge <i>et al</i> , 2023	S	L	L	L	L	S	(26)
Taïeb <i>et al</i> , 2023	S	L	L	L	L	S	(27)

^aStudies rated as S did not provide allocation concealment details. RoB, risk of bias; L, low RoB; R, risk of bias; S, some RoB.

Table SIV. Estimates from network meta-analyses, pairwise comparison and ranking of different pharmacologic interventions for overall survival time.

PD-L1	2.30 (-1.56, 6.16)	1.95 (-0.01, -3.90)
1.00 (-1.85, 3.85)	PD-1 + CTLA-4	2.50 (-1.25, 6.25)
2.28 (0.44, 4.11)	1.28 (-1.56, 4.11)	Comparator

Treatments are ranked from best to worst along the leading diagonal. Estimates from pairwise meta-analyses are presented above the leading diagonal; estimates from network meta-analyses are presented below the leading diagonal. CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table SV. Inconsistency test results for the mean difference in overall survival time.

Comparison	No. of studies	NMA	Direct	Indirect	Mean difference	95% CI lower limit	95% CI upper limit	P-value
PD-L1 vs. comparator	4	2.28	1.95	4.80	-2.85	-8.58	2.87	0.33
PD-L1 + CTLA-4 vs. comparator	1	1.28	2.50	-0.35	2.85	-2.87	8.58	0.33
PD-L1 vs. PD-L1 + CTLA-4	1	1.00	2.30	-0.55	2.85	-2.87	8.58	0.33

CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte associated protein 4; NMA, network meta-analysis, PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table SVI. Estimates from network meta-analyses, pairwise comparison and ranking of different pharmacological interventions for progression-free survival time.

PD-1	4.79 (3.18, 6.40)	-	-
4.79 (3.18, 6.40)	Comparator	0.10 (-1.97, 2.17)	0.69 (-0.09, 1.46)
5.26 (3.04, 7.47)	0.47 (-1.05, 1.98)	PD-L1 + CTLA-4	-0.20 (-2.28, 1.88)
5.42 (3.65, 7.20)	0.63 (-0.11, 1.38)	0.17 (-1.35, 1.69)	PD-L1

Treatments are ranked from best to worst along the leading diagonal. Estimates from pairwise meta-analyses are presented above the leading diagonal; estimates from network meta-analyses are presented below the leading diagonal. CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table SVII. Inconsistency test results for the mean difference in progression-free survival time.

Comparison	No. of studies	NMA	Direct	Indirect	Mean difference	95% CI lower limit	95% CI upper limit	P-value
PD-1 vs. comparator	2	4.79	4.79	NA	NA	NA	NA	NA
PD-L1 vs. comparator	8	-0.63	-0.69	0.10	-0.79	-3.82	2.25	0.61
PD-L1 + CTLA-4 vs. comparator	1	-0.47	-0.10	-0.89	0.79	-2.25	3.82	0.61
PD-1 vs. PD-L1	0	5.42	NA	5.42	NA	NA	NA	NA
PD-1 vs. PD-L1 + CTLA-4	0	5.26	NA	5.26	NA	NA	NA	NA
PD-L1 vs. PD-L1 + CTLA-4	1	-0.17	0.20	-0.59	0.79	-2.25	3.82	0.61

CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte associated protein 4; NA, not available; NMA, network meta-analysis, PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table SVIII. Estimates from network meta-analyses, pairwise comparison and ranking of different pharmacological interventions for objective response rate.

Comparator	1.07 (0.68, 1.69)	1.12 (0.54, 2.34)	0.64 (0.02, 17.52)
1.06 (0.67, 1.66)	PD-L1	-	3.58 (0.12, 103.08)
1.12 (0.54, 2.34)	1.06 (0.45, 2.52)	PD-1	-
1.54 (0.14, 16.39)	1.45 (0.14, 15.52)	1.37 (0.11, 16.30)	PD-L1 + CTLA-4

Treatments are ranked from best to worst along the leading diagonal. Estimates from pairwise meta-analyses are presented above the leading diagonal; estimates from network meta-analyses are presented below the leading diagonal. CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table SIX. Inconsistency test results of the mean difference of objective response rate.

Comparison	No. of studies	NMA	Direct	Indirect	Mean difference	95% CI lower limit	95% CI upper limit	P-value
PD-1 vs. comparator	2	-0.12	-0.12	NA	NA	NA	NA	NA
PD-L1 vs. comparator	8	-0.05	-0.07	1.72	-1.79	-6.53	2.95	0.46
PD-L1 + CTLA-4 vs. comparator	1	-0.43	0.44	-1.35	1.79	-2.95	6.53	0.46
PD-1 vs. PD-L1	0	-0.06	NA	-0.06	NA	NA	NA	NA
PD-1 vs. PD-L1 + CTLA-4	0	0.31	NA	0.31	NA	NA	NA	NA
PD-L1 vs. PD-L1 + CTLA-4	1	0.37	1.28	-0.51	1.79	-2.95	6.53	0.46

CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte associated protein 4; NA, not applicable; NMA, network meta-analysis, PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table SX. Estimates from network meta-analyses, pairwise comparison and ranking of different pharmacological interventions for adverse events.

PD-1	0.37 (0.06, 2.15)	-	-
0.37 (0.06, 2.15)	Comparator	0.01 (0.00, 0.25)	0.86 (0.42, 1.74)
0.21 (0.02, 2.95)	0.58 (0.08, 4.06)	PD-L1 + CTLA-4	0.16 (0.02, 1.57)
0.26 (0.04, 1.73)	0.70 (0.35, 1.42)	1.22 (0.18, 8.15)	PD-L1

Treatments are ranked from best to worst along the leading diagonal. Estimates from pairwise meta-analyses are presented above the leading diagonal; estimates from network meta-analyses are presented below the leading diagonal. CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table SXI. Inconsistency test results of the mean difference of adverse events.

Comparison	No. of studies	NMA	Direct	Indirect	Mean difference	95% CI lower limit	95% CI upper limit	P-value
PD-1 vs. comparator	1	-0.99	-0.99	NA	NA	NA	NA	NA
PD-L1 vs. comparator	8	0.35	0.16	6.52	-6.37	-10.44	-2.30	0.00
PD-L1 + CTLA-4 vs. comparator	1	0.55	4.66	-1.70	6.37	2.30	10.44	0.00
PD-1 vs. PD-L1	0	-1.34	NA	-1.34	NA	NA	NA	NA
PD-1 vs. PD-L1 + CTLA-4	0	-1.54	NA	-1.54	NA	NA	NA	NA
PD-L1 vs. PD-L1 + CTLA-4	1	-0.20	1.86	-4.51	6.37	2.30	10.44	0.00

CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte associated protein 4; NA, not available; NMA, network meta-analysis, PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.