

Table SI. Search strategy.

Database	Search strategy
Pubmed	<p>((("KRAS"[Mesh] OR "NRAS"[Mesh] OR "ras Proteins"[Mesh]) AND ("wild type"[tw] OR "wild-type"[tw] OR "wildtype"[tw])) OR ("RAS wild type"[tw] OR "RAS wild-type"[tw] OR "RAS wildtype"[tw] OR "KRAS wild type"[tw] OR "KRAS wild-type"[tw] OR "KRAS wildtype"[tw] OR "NRAS wild type"[tw] OR "NRAS wild-type"[tw] OR "NRAS wildtype"[tw]))</p> <p>AND</p> <p>(("Colorectal Neoplasms"[Mesh] OR "Colonic Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh]) OR ("colorectal cancer"[tw] OR "colorectal carcinoma"[tw] OR "colorectal neoplasm"[tw] OR "colon cancer"[tw] OR "colon carcinoma"[tw] OR "rectal cancer"[tw] OR "rectal carcinoma"[tw] OR "CRC"[tw] OR "mCRC"[tw]))</p> <p>AND</p> <p>(("Neoplasm Metastasis"[Mesh] OR "Neoplasm Staging"[Mesh]) OR ("metastatic"[tw] OR "metastases"[tw] OR "advanced"[tw] OR "stage IV"[tw] OR "stage 4"[tw] OR "unresectable"[tw]))</p> <p>AND</p> <p>(("Drug Therapy, Combination"[Mesh] OR "Antineoplastic Agents"[Mesh] OR "Targeted Molecular Therapy"[Mesh] OR "Immunotherapy"[Mesh]) OR ("bevacizumab"[tw] OR "cetuximab"[tw] OR "panitumumab"[tw] OR "FOLFOX"[tw] OR "FOLFIRI"[tw] OR "CAPOX"[tw] OR "XELOX"[tw] OR "oxaliplatin"[tw] OR "irinotecan"[tw] OR "fluorouracil"[tw] OR "5-FU"[tw] OR "capecitabine"[tw] OR "leucovorin"[tw] OR "pembrolizumab"[tw] OR "nivolumab"[tw] OR "chemotherapy"[tw] OR "targeted therapy"[tw] OR "immunotherapy"[tw] OR "first line"[tw] OR "first-line"[tw] OR "firstline"[tw]))</p> <p>AND</p> <p>("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR "randomized"[tw] OR "randomised"[tw] OR "randomly"[tw] OR "trial"[tw] OR "clinical trial"[tw])</p> <p>NOT</p> <p>("adjuvant"[tw] OR "neoadjuvant"[tw] OR "preoperative"[tw] OR "postoperative"[tw] OR "surgical"[tw])</p> <p>Filters: Humans</p>
Ovid	<ol style="list-style-type: none"> 1. exp ras protein/ OR (("KRAS" OR "NRAS" OR "RAS") adj3 ("wild type" OR "wild-type" OR "wildtype")).tw. 2. exp colorectal cancer/ OR exp colon cancer/ OR exp rectum cancer/ 3. (colorectal adj (cancer OR carcinoma OR neoplasm OR tumor OR tumour)).tw. 4. (colon adj (cancer OR carcinoma OR neoplasm OR tumor OR tumour)).tw. 5. (rectal adj (cancer OR carcinoma OR neoplasm OR tumor OR tumour)).tw. 6. (CRC OR mCRC).tw. 7. 2 OR 3 OR 4 OR 5 OR 6 8. exp metastasis/ OR exp cancer staging/ 9. (metastatic OR metastases OR advanced OR "stage IV" OR "stage 4" OR unresectable).tw. 10. 8 OR 9 11. exp combination chemotherapy/ OR exp targeted therapy/ OR exp immunotherapy/ 12. (bevacizumab OR cetuximab OR panitumumab).tw. 13. (FOLFOX OR FOLFIRI OR CAPOX OR XELOX).tw.

	<p>14. (oxaliplatin OR irinotecan OR fluorouracil OR "5-FU" OR capecitabine OR leucovorin).tw. 15. (pembrolizumab OR nivolumab OR ipilimumab).tw. 16. (chemotherapy OR "targeted therapy" OR immunotherapy).tw. 17. ("first line" OR "first-line" OR firstline).tw. 18. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 19. exp randomized controlled trial/ OR exp controlled clinical trial/ 20. (randomized OR randomised OR randomly OR trial OR "clinical trial").tw. 21. 19 OR 20 22. 1 AND 7 AND 10 AND 18 AND 21 23. limit 22 to (human)</p>
Web of science	<p>TS=((("KRAS wild type" OR "KRAS wild-type" OR "KRAS wildtype" OR "NRAS wild type" OR "NRAS wild-type" OR "NRAS wildtype" OR "RAS wild type" OR "RAS wild-type" OR "RAS wildtype") AND ("colorectal cancer" OR "colorectal carcinoma" OR "colorectal neoplasm" OR "colon cancer" OR "colon carcinoma" OR "rectal cancer" OR "rectal carcinoma" OR "CRC" OR "mCRC") AND ("metastatic" OR "metastases" OR "advanced" OR "stage IV" OR "stage 4" OR "unresectable") AND ("bevacizumab" OR "cetuximab" OR "panitumumab" OR "FOLFOX" OR "FOLFIRI" OR "CAPOX" OR "XELOX" OR "oxaliplatin" OR "irinotecan" OR "fluorouracil" OR "5-FU" OR "capecitabine" OR "leucovorin" OR "pembrolizumab" OR "nivolumab" OR "chemotherapy" OR "targeted therapy" OR "immunotherapy" OR "first line" OR "first-line" OR "firstline") AND ("randomized" OR "randomised" OR "trial" OR "clinical trial" OR "RCT")) NOT TS=("adjuvant" OR "neoadjuvant" OR "preoperative" OR "postoperative" OR "surgical") Filters: Document Types: Article;</p>

Table III. Sensitivity analysis league table.

A, Overall survival (nine nodes and all 15 trials)										
Treatment	A140 + Chemo	Bev + Chemo	Bev + FOLFIRI (UGT1A1)	Bev + FOLFOX + VitC	Cet + Chemo	Cet(maint.)	FOLFIRI	FOLFOX	5-FU/LV	Pan + Chemo
A140 + Chemo	A140 + Chemo	0.94 (0.71-1.24)	1.35 (0.88-2.07)	0.90 (0.62-1.31)	1.10 (0.85-1.43)	0.89 (0.56-1.40)	0.85 (0.61-1.19)	0.82 (0.58-1.14)	1.10 (0.70-1.71)	1.10 (0.80-1.50)
Bev + Chemo	1.07 (0.81-1.41)	Bev + Chemo	1.44 (1.05-1.99)*	0.96 (0.75-1.23)	1.17 (1.07-1.29)*	0.95 (0.64-1.39)	0.91 (0.73-1.12)	0.87 (0.70-1.09)	1.17 (0.82-1.66)	1.17 (1.01-1.35)*
Bev + FOLFIRI (UGT1A1)	0.74 (0.48-1.13)	0.69 (0.50-0.95)*	Bev + FOLFIRI (UGT1A1)	0.67 (0.44-1.00)*	0.81 (0.58-1.14)	0.66 (0.40-1.08)	0.63 (0.43-0.93)*	0.60 (0.41-0.89)*	0.81 (0.50-1.30)	0.81 (0.57-1.15)
Bev + FOLFOX + VitC	1.11 (0.76-1.61)	1.04 (0.81-1.33)	1.50 (1.00-2.25)*	Bev + FOLFOX + VitC	1.22 (0.93-1.59)	0.98 (0.62-1.55)	0.94 (0.68-1.31)	0.91 (0.65-1.27)	1.22 (0.79-1.87)	1.22 (0.91-1.62)
Cet + Chemo	0.91 (0.70-1.18)	0.85 (0.77-0.94)*	1.23 (0.88-1.72)	0.82 (0.63-1.07)	Cet + Chemo	0.81 (0.56-1.17)	0.77 (0.63-0.95)*	0.74 (0.60-0.92)*	1.00 (0.70-1.43)	1.00 (0.84-1.18)
Cet(maint.)	1.13 (0.71-1.78)	1.06 (0.72-1.55)	1.53 (0.92-2.52)	1.02 (0.64-1.61)	1.24 (0.85-1.80)	Cet(maint.)	0.96 (0.63-1.47)	0.92 (0.60-1.41)	1.24 (0.74-2.07)	1.24 (0.82-1.86)
FOLFIRI	1.17 (0.84-1.64)	1.10 (0.89-1.36)	1.59 (1.08-2.33)*	1.06 (0.76-1.47)	1.29 (1.05-1.58)*	1.04 (0.68-1.59)	FOLFIRI	0.96 (0.72-1.28)	1.29 (0.87-1.90)	1.29 (1.03-1.61)*
FOLFOX	1.22 (0.87-1.71)	1.15 (0.92-1.43)	1.66 (1.12-2.45)*	1.10 (0.79-1.54)	1.35 (1.09-1.66)*	1.08 (0.71-1.66)	1.04 (0.78-1.39)	FOLFOX	1.34 (0.90-2.01)	1.34 (1.05-1.72)*
5-FU/LV	0.91 (0.58-1.42)	0.86 (0.60-1.22)	1.23 (0.77-1.99)	0.82 (0.54-1.26)	1.00 (0.70-1.44)	0.81 (0.48-1.36)	0.78 (0.53-1.15)	0.75 (0.50-1.12)	5-FU/LV	1.00 (0.73-1.37)
Pan + Chemo	0.91 (0.67-1.24)	0.86 (0.74-0.99)*	1.23 (0.87-1.76)	0.82 (0.62-1.10)	1.00 (0.85-1.18)	0.81 (0.54-1.22)	0.78 (0.62-0.97)*	0.75 (0.58-0.96)*	1.00 (0.73-1.37)	Pan + Chemo
B, Progression-free survival (nine nodes)										
Treatment	A140 + Chemo	Bev + Chemo	Bev + FOLFIRI (UGT1A1)	Bev + FOLFOX + VitC	Cet + Chemo	Cet(maint.)	FOLFIRI	FOLFOX	5-FU/LV	Pan + Chemo
A140 + Chemo	A140 + Chemo	0.91 (0.66-1.25)	1.68 (1.04-2.73)*	1.05 (0.69-1.62)	1.03 (0.77-1.38)	0.87 (0.51-1.48)	0.56 (0.39-0.80)*	0.76 (0.51-1.13)	0.88 (0.53-1.46)	0.82 (0.57-1.16)
Bev + Chemo	1.10 (0.80-1.53)	Bev + Chemo	1.86 (1.29-2.66)*	1.16 (0.88-1.54)	1.14 (0.99-1.31)	0.96 (0.60-1.53)	0.61 (0.49-0.77)*	0.83 (0.62-1.12)	0.97 (0.65-1.46)	0.90 (0.75-1.08)

Bev + FOLFIRI (UGT1A1)	0.59 (0.37-0.97)*	0.54 (0.38-0.77)*	Bev + FOLFIRI (UGT1A1)	0.63 (0.40-0.99)*	0.61 (0.42-0.90)*	0.51 (0.28-0.93)*	0.33 (0.22-0.51)*	0.45 (0.28-0.72)*	0.52 (0.31-0.90)*	0.49 (0.32-0.73)*
Bev + FOLFOX + VitC	0.95 (0.62-1.46)	0.86 (0.65-1.14)	1.60 (1.01-2.52)*	Bev + FOLFOX + VitC	0.98 (0.71-1.34)	0.82 (0.48-1.42)	0.53 (0.37-0.76)*	0.72 (0.48-1.08)	0.84 (0.51-1.37)	0.77 (0.55-1.08)
Cet + Chemo	0.97 (0.72-1.30)	0.88 (0.77-1.01)	1.63 (1.11-2.40)*	1.02 (0.75-1.40)	Cet + Chemo	0.84 (0.54-1.32)	0.54 (0.43-0.67)*	0.73 (0.56-0.96)*	0.86 (0.57-1.29)	0.79 (0.65-0.97)*
Cet(maint.)	1.16 (0.68-1.97)	1.05 (0.65-1.67)	1.94 (1.07-3.51)*	1.22 (0.70-2.11)	1.19 (0.76-1.86)	Cet(maint.)	0.64 (0.39-1.06)	0.87 (0.52-1.48)	1.02 (0.55-1.87)	0.94 (0.58-1.54)
FOLFIRI	1.80 (1.25-2.60)*	1.63 (1.29-2.06)*	3.03 (1.97-4.65)*	1.90 (1.32-2.73)*	1.85 (1.49-2.31)*	1.56 (0.95-2.57)	FOLFIRI	1.36 (0.98-1.90)	1.59 (1.04-2.41)*	1.47 (1.19-1.82)*
FOLFOX	1.32 (0.89-1.97)	1.20 (0.89-1.61)	2.22 (1.40-3.54)*	1.39 (0.93-2.09)	1.36 (1.04-1.79)*	1.14 (0.68-1.93)	0.73 (0.53-1.02)	FOLFOX	1.17 (0.73-1.86)	1.08 (0.80-1.46)
5-FU/LV	1.13 (0.68-1.88)	1.03 (0.69-1.54)	1.91 (1.11-3.28)*	1.19 (0.73-1.95)	1.17 (0.77-1.76)	0.98 (0.53-1.80)	0.63 (0.41-0.96)*	0.86 (0.54-1.37)	5-FU/LV	0.93 (0.65-1.33)
Pan + Chemo	1.22 (0.86-1.75)	1.11 (0.93-1.33)	2.06 (1.37-3.09)*	1.29 (0.92-1.81)	1.26 (1.03-1.54)*	1.06 (0.65-1.73)	0.68 (0.55-0.84)*	0.93 (0.69-1.25)	1.08 (0.75-1.55)	Pan + Chemo

Analysis included UGT1A1-guided Bev + FOLFIRI, VitC + Bev + FOLFOX and A140 + FOLFOX nodes. *P<0.05. Bev, bevacizumab; Chemo, chemotherapy; UGT1A1, UDP glucuronosyltransferase family 1 member A1; VitC, vitamin C; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; 5-FU/LV, 5-fluorouracil/leucovorin; Cet, cetuximab; Cet(maint.), Cet maintenance.

Table SIII. League table.

A, Overall survival (primary analysis, six nodes)							
Treatment	Bev + Chemo	Cet + Chemo	Cet(maint.)	FOLFIRI	FOLFOX	5-FU/LV	Pan + Chemo
Bev + Chemo	Bev + Chemo	1.17 (1.07-1.29)*	0.95 (0.64-1.39)	0.91 (0.73-1.12)	0.87 (0.70-1.09)	1.17 (0.82-1.66)	1.17 (1.01-1.35)*
Cet + Chemo	0.85 (0.77-0.94)*	Cet + Chemo	0.81 (0.56-1.17)	0.77 (0.63-0.95)*	0.74 (0.60-0.92)*	1.00 (0.70-1.43)	1.00 (0.84-1.18)
Cet(maint.)	1.06 (0.72-1.55)	1.24 (0.85-1.80)	Cet(maint.)	0.96 (0.63-1.47)	0.92 (0.60-1.41)	1.24 (0.74-2.07)	1.24 (0.82-1.86)
FOLFIRI	1.10 (0.89-1.36)	1.29 (1.05-1.58)*	1.04 (0.68-1.59)	FOLFIRI	0.96 (0.72-1.28)	1.29 (0.87-1.90)	1.29 (1.03-1.61)*
FOLFOX	1.15 (0.92-1.43)	1.35 (1.09-1.66)*	1.08 (0.71-1.66)	1.04 (0.78-1.39)	FOLFOX	1.34 (0.90-2.01)	1.34 (1.05-1.72)*
5-FU/LV	0.86 (0.60-1.22)	1.00 (0.70-1.44)	0.81 (0.48-1.36)	0.78 (0.53-1.15)	0.75 (0.50-1.12)	5-FU/LV	1.00 (0.73-1.37)
Pan + Chemo	0.86 (0.74-0.99)*	1.00 (0.85-1.18)	0.81 (0.54-1.22)	0.78 (0.62-0.97)*	0.75 (0.58-0.96)*	1.00 (0.73-1.37)	Pan + Chemo
B, Progression-free survival (primary analysis, six nodes)							
Treatment	Bev + Chemo	Cet + Chemo	Cet(maint.)	FOLFIRI	FOLFOX	5-FU/LV	Pan + Chemo
Bev + Chemo	Bev + Chemo	1.14 (0.99-1.31)	0.96 (0.60-1.53)	0.61 (0.49-0.77)*	0.83 (0.62-1.12)	0.97 (0.65-1.46)	0.90 (0.75-1.08)
Cet + Chemo	0.88 (0.77-1.01)	Cet + Chemo	0.84 (0.54-1.32)	0.54 (0.43-0.67)*	0.73 (0.56-0.96)*	0.86 (0.57-1.29)	0.79 (0.65-0.97)*
Cet(maint.)	1.05 (0.65-1.67)	1.19 (0.76-1.86)	Cet(maint.)	0.64 (0.39-1.06)	0.87 (0.52-1.48)	1.02 (0.55-1.87)	0.94 (0.58-1.54)
FOLFIRI	1.63 (1.29-2.06)*	1.85 (1.49-2.31)*	1.56 (0.95-2.57)	FOLFIRI	1.36 (0.98-1.90)	1.59 (1.04-2.41)*	1.47 (1.19-1.82)*
FOLFOX	1.20 (0.89-1.61)	1.36 (1.04-1.79)*	1.14 (0.68-1.93)	0.73 (0.53-1.02)	FOLFOX	1.17 (0.73-1.86)	1.08 (0.80-1.46)
5-FU/LV	1.03 (0.69-1.54)	1.17 (0.77-1.76)	0.98 (0.53-1.80)	0.63 (0.41-0.96)*	0.86 (0.54-1.37)	5-FU/LV	0.93 (0.65-1.33)
Pan + Chemo	1.11 (0.93-1.33)	1.26 (1.03-1.54)*	1.06 (0.65-1.73)	0.68 (0.55-0.84)*	0.93 (0.69-1.25)	1.08 (0.75-1.55)	Pan + Chemo
C, Objective response rate (primary analysis, six nodes)							
Treatment	Bev + Chemo	Cet + Chemo	Cet(maint.)	FOLFIRI	FOLFOX	5-FU/LV	Pan + Chemo
Bev + Chemo	Bev + Chemo	0.62 (0.42-0.92)*	0.43 (0.19-0.99)*	1.70 (0.92-3.14)	1.75 (0.91-3.36)	0.33 (0.11-0.99)*	0.70 (0.31-1.55)
Cet + Chemo	1.61 (1.09-2.39)*	Cet + Chemo	0.69 (0.33-1.44)	2.74 (1.71-4.39)*	2.81 (1.67-4.76)*	0.54 (0.20-1.48)	1.12 (0.56-2.25)
Cet(maint.)	2.32 (1.01-5.33)*	1.44 (0.69-2.99)	Cet(maint.)	3.94 (1.65-9.41)*	4.05 (1.65-9.97)*	0.78 (0.22-2.70)	1.62 (0.59-4.43)
FOLFIRI	0.59 (0.32-1.09)	0.37 (0.23-0.59)*	0.25 (0.11-0.61)*	FOLFIRI	1.03 (0.54-1.97)	0.20 (0.08-0.51)*	0.41 (0.23-0.75)*
FOLFOX	0.57 (0.30-1.10)	0.36 (0.21-0.60)*	0.25 (0.10-0.61)*	0.97 (0.51-1.87)	FOLFOX	0.19 (0.07-0.54)*	0.40 (0.19-0.84)*
5-FU/LV	2.99 (1.01-8.83)*	1.85 (0.68-5.09)	1.29 (0.37-4.48)	5.08 (1.97-13.09)*	5.22 (1.84-14.83)*	5-FU/LV	2.08 (1.00-4.34)*
Pan + Chemo	1.43 (0.65-3.18)	0.89 (0.45-1.78)	0.62 (0.23-1.69)	2.44 (1.34-4.44)*	2.51 (1.19-5.27)*	0.48 (0.23-1.00)*	Pan + Chemo

*P<0.05. Bev, bevacizumab; Chemo, chemotherapy; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; 5-FU/LV, 5-fluorouracil/leucovorin; Cet, cetuximab; Cet(maint.), Cet maintenance.

Table SIV. Node-splitting: Direct vs. indirect evidence consistency.

Outcome	Comparison	k (direct)	NMA (RE)	Direct	Indirect	P-value (inconsistency)
OS	Cet + Chemo vs. Bev + Chemo	3	0.853 (0.775-0.938)	0.855 (0.774-0.944)	0.824 (0.570-1.192)	0.853
OS	Pan + Chemo vs. Bev + Chemo	2	0.855 (0.738-0.992)	0.850 (0.722-1.001)	0.881 (0.624-1.244)	0.853
OS	Cet + Chemo vs. Cet_mono	1	0.806 (0.556-1.170)	0.806 (0.556-1.170)		
OS	Cet + Chemo vs. FOLFIRI	2	0.775 (0.632-0.949)	0.745 (0.587-0.946)	0.856 (0.583-1.256)	0.547
OS	Cet + Chemo vs. FOLFOX	1	0.743 (0.604-0.915)	0.760 (0.606-0.953)	0.659 (0.389-1.117)	0.627
OS	FOLFIRI vs. Pan + Chemo	1	1.287 (1.028-1.610)	1.190 (0.849-1.669)	1.368 (1.014-1.845)	0.547
OS	FOLFOX vs. Pan + Chemo	1	1.341 (1.047-1.718)	1.493 (0.907-2.456)	1.295 (0.973-1.722)	0.627
OS	5-FU/LV vs. Pan + Chemo	1	1.000 (0.727-1.375)	1.000 (0.727-1.375)		
PFS	Cet + Chemo vs. Bev + Chemo	3	0.880 (0.766-1.011)	0.909 (0.782-1.055)	0.711 (0.484-1.045)	0.245
PFS	Pan + Chemo vs. Bev + Chemo	2	1.110 (0.925-1.331)	1.040 (0.841-1.286)	1.329 (0.933-1.893)	0.245
PFS	Cet + Chemo vs. Cet + Chemo	1	0.840 (0.537-1.315)	0.840 (0.537-1.315)		
PFS	Cet + Chemo vs. FOLFIRI	2	0.539 (0.433-0.673)	0.505 (0.381-0.670)	0.598 (0.420-0.851)	0.467
PFS	Cet + Chemo vs. FOLFOX	1	0.734 (0.559-0.964)	0.690 (0.502-0.948)	0.873 (0.514-1.482)	0.455
PFS	FOLFIRI vs. Pan + Chemo	1	1.470 (1.187-1.820)	1.389 (1.068-1.806)	1.643 (1.136-2.376)	0.467
PFS	FOLFOX vs. Pan + Chemo	1	1.080 (0.799-1.458)	0.935 (0.576-1.516)	1.182 (0.805-1.736)	0.455
PFS	5-FU/LV vs. Pan + Chemo	1	0.926 (0.646-1.326)	0.926 (0.646-1.326)		

OS, overall survival; PFS, progression-free survival; Bev, bevacizumab; Chemo, chemotherapy; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; 5-FU/LV, 5-fluorouracil/leucovorin; Cet, cetuximab; Cet_mono, cetuximab monotherapy as maintenance treatment; NMA, network meta-analysis; RE, random effects.

Table SV. Sensitivity analysis league table: Objective response rate (nine nodes).

Treatment	A140 + Chemo	Bev + Chemo	Bev + FOLFIRI (UGT1A1)	Cet + Chemo	Cet(maint.)	FOLFIRI	FOLFOX	5-FU/LV	Pan + Chemo
A140 + Chemo	A140 + Chemo	1.50 (0.85-2.63)	0.37 (0.15-0.92)*	0.93 (0.62-1.39)	0.65 (0.28-1.49)	2.55 (1.37-4.74)*	2.62 (1.35-5.08)*	0.50 (0.17-1.49)	1.04 (0.47-2.33)
Bev + Chemo	0.67 (0.38-1.17)	Bev + Chemo	0.25 (0.12-0.50)*	0.62 (0.42-0.92)*	0.43 (0.19-0.99)*	1.70 (0.92-3.14)	1.75 (0.91-3.36)	0.33 (0.11-0.99)*	0.70 (0.31-1.55)
Bev + FOLFIRI (UGT1A1)	2.71 (1.09-6.76)*	4.07 (1.98-8.33)*	Bev + FOLFIRI (UGT1A1)	2.52 (1.11-5.72)*	1.75 (0.58-5.25)	6.91 (2.69-17.76)*	7.10 (2.69-18.77)*	1.36 (0.37-4.99)	2.83 (0.97-8.28)
Cet + Chemo	1.08 (0.72-1.61)	1.61 (1.09-2.39)*	0.40 (0.17-0.90)*	Cet + Chemo	0.69 (0.33-1.44)	2.74 (1.71-4.39)*	2.81 (1.67-4.76)*	0.54 (0.20-1.48)	1.12 (0.56-2.25)
Cet(maint.)	1.55 (0.67-3.57)	2.32 (1.01-5.33)*	0.57 (0.19-1.71)	1.44 (0.69-2.99)	Cet(maint.)	3.94 (1.65-9.41)*	4.05 (1.65-9.97)*	0.78 (0.22-2.70)	1.62 (0.59-4.43)
FOLFIRI	0.39 (0.21-0.73)*	0.59 (0.32-1.09)	0.14 (0.06-0.37)*	0.37 (0.23-0.59)*	0.25 (0.11-0.61)*	FOLFIRI	1.03 (0.54-1.97)	0.20 (0.08-0.51)*	0.41 (0.23-0.75)*
FOLFOX	0.38 (0.20-0.74)*	0.57 (0.30-1.10)	0.14 (0.05-0.37)*	0.36 (0.21-0.60)*	0.25 (0.10-0.61)*	0.97 (0.51-1.87)	FOLFOX	0.19 (0.07-0.54)*	0.40 (0.19-0.84)*
5-FU/LV	1.99 (0.67-5.91)	2.99 (1.01-8.83)*	0.74 (0.20-2.69)	1.85 (0.68-5.09)	1.29 (0.37-4.48)	5.08 (1.97-13.09)*	5.22 (1.84-14.83)*	5-FU/LV	2.08 (1.00-4.34)*
Pan + Chemo	0.96 (0.43-2.13)	1.43 (0.65-3.18)	0.35 (0.12-1.03)	0.89 (0.45-1.78)	0.62 (0.23-1.69)	2.44 (1.34-4.44)*	2.51 (1.19-5.27)*	0.48 (0.23-1.00)*	Pan + Chemo

*P<0.05. Bev, bevacizumab; Chemo, chemotherapy; UGT1A1, UDP glucuronosyltransferase family 1 member A1; VitC, vitamin C; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; 5-FU/LV, 5-fluorouracil/leucovorin; Cet, cetuximab; Cet(maint.), Cet maintenance.

Table SIV. Safety profiles: Grade ≥ 3 TEAEs.

Trial ID	Year	Treatment arm 1	Grade ≥ 3 TEAEs (arm 1)	Treatment arm 2	Grade ≥ 3 TEAEs (arm 2)
NCT01161316	2018	Cet(maint.)	70.0%	Cet + FOLFOX	68.0%
NCT02256800	2020	Bev + FOLFIRI (UGT1A1)	23.4%	Bev + FOLFIRI (std)	23.6%
NCT00265850	2017	Cet + Chemo	53.0%	Bev + Chemo	53.0%
NCT02394795	2023	Pan + Chemo	NR	Bev + Chemo	NR
NCT01228734	2018	Cet + FOLFOX	43.2%	FOLFOX	26.0%
NCT01991873	2021	Pan + FU/FA	43.2%	FU/FA	26.0%
NCT04835142	2025	A140 + FOLFOX	66.6%	Cet + FOLFOX	68.3%
NCT03206151	2025	Cet- β + FOLFIRI	83.3%	FOLFIRI	66.9%
NCT02162563	2023	Pan + Chemo	54.0%	Bev + Chemo	69.0%
Douillard2014	2014	Pan + FOLFOX	NR	FOLFOX	NR
NCT00433927	2021	Cet + FOLFIRI	64.0%	Bev + FOLFIRI	51.0%
Wang2022	2022	VitC + Bev + FOLFOX	33.5%	Bev + FOLFOX	30.3%
NCT01328171	2019	Pan + FOLFOX	81.3%	FOLFOX	66.7%
NCT02404935	2023	Cet + FOLFIRI	NR	FOLFIRI	NR
NCT02904031	2019	Pan + mFOLFOX	60.0%	5-FU/LV + Pan	37.0%

Bev, bevacizumab; Chemo, chemotherapy; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; 5-FU/LV, 5-fluorouracil/leucovorin; FU/FA, fluorouracil/folinic acid; Cet, cetuximab; NMA, network meta-analysis; RE, random effects; Cet(maint.), Cet maintenance; VitC, vitamin C; UGT1A1, UDP glucuronosyltransferase family 1 member A1; mFOLFOX, modified FOLFOX; NR, not reported; std, standard dose; TEAEs, treatment-emergent adverse events.