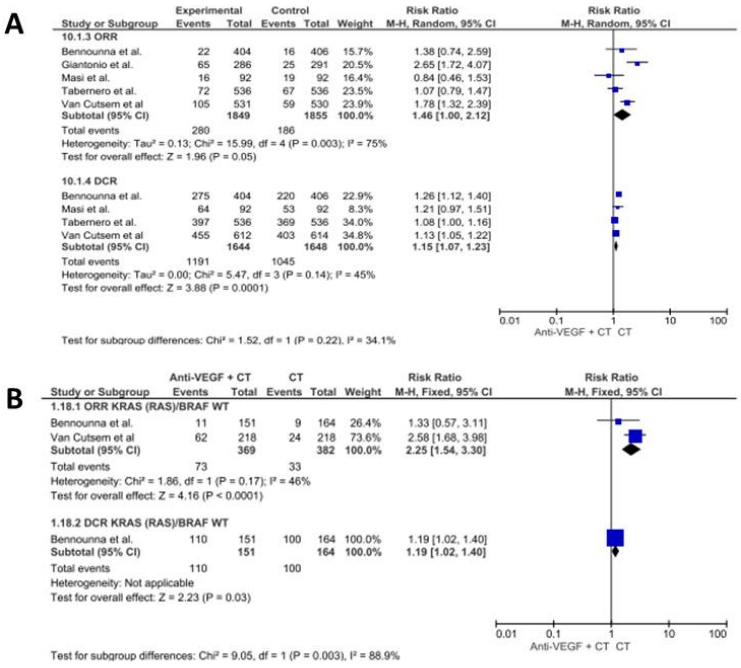
TableS1. Characteristics of trials included in our indirect comparisons.

Study (reference)	n1/n2	Drug	ORR n.(%)	DCR n(%)	PFS HR (95% CI)	OS HR (95% CI)
Giantonio et al 2007	286/291	Folfox + Bevacizumab Folfox	65/286(22.7%) 25/291(8.6%)	N/A	0.61 (0.48-0.78)	0.75 (0.63-0.89)
Bennouna et al 2013	409/411	Doublet + Bevacizumab Doublet	22/404 (6%) 16/406 (4%)	275/404 (69%) 220/406 (54%)	0.68 (0.59-0.58)	0.81 (0.69-0.94)
Masi et al 2015	92/92	Doublet + Bevacizumab Doublet	19/92 (21%) 16/92 (17%)	64/92 (70%) 53/92 (58%)	0.70 (0.52-0.95)	0.77 (0.56-1.06)
Van Cutsem et al 2012	612/614	Folfiri + Aflibercept Folfiri	105/531 (19.8%) 59/530(11.2%)	455/531(85.7%) 403/530(76%)	0.76 (0.67-0.87)	0.82 (0.71-0.94)
Tabernero et al 2015	536/536	Folfiri + Ramucirumab Folfiri	72/536 (13.4%) 67/536 (12.5%)	397/536(74.1%) 369/536(68.8%)	0.79 (0.70-0.90)	0.84 (0.73-0.98)
Sobrero et al 2008	648/650	Irinotecan+Cetuximab Irinotecan	106/648(16.4%) 27/650 (4.2%)	398/648 (61.5%) 298/650 (45.9%)	0.69 (0.62-0.78)	0.97 (0.85-1.11)
Peeters et al 2010	591/595	Folfiri+Panitumumab Folfiri	134/529(25.3%) 61/522(11.7%)	378/529(71.5%) 334/522(64%)	N/A	N/A
Seymour et al 2013	230/230	Irinotecan+Panitumumab Paniumumab	79/230(34.3%) 27/230(11.7%)	135/230(58.7%) 118/230(51.3%)	0.78(0.64-0.95)	1.01(0.83-1.23)

Study (reference)	KRAS WT/mut	PFS (RAS WT) HR(95% CI)	PFS (RAS Mut) HR(95% CI)	OS (RAS WT) HR(95% CI)	OS (RAS Mut) HR(95% CI)	ORR (RAS WT) n.(%)	ORR (RAS Mut) n.(%)
Giantonio et al 2007	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bennouna et al 2013	151/164 165/136	0.61 (0.49-0.77)	0.70 (0.56-0.89)	0.69 (0.53-0.90)	0.92 (0.71-1.18)	11/151 (7.3%) 9/164(5.5%)	6/164(3.7%) 4/134 (3%)
Masi et al 2015	32/40 36/32	N/A	N/A	N/A	N/A	N/A	N/A
Van Cutsem et al 2012	218/264	0.67(0.49-0.93)	0.80(0.60-1.07)	0.70(0.50-0.97)	0.93(0.7-1.23)	N/A	34/264(12.9%) 36/264(13.6%)
Tabernero et al 2015	267/269 275/261	0.77(0.65-0.92)	084(0.70-1.00)	0.82(0.67-1.00)	0.89(0.73-1.09)	N/A	N/A
Sobrero et al 2008	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Peeters et al 2010	303/238 294/248	0.70 (0.54-0.91)	0.86 (0.71-1.05)	0.81 (0.63-1.03)	0.91 (0.76-1.10)	105/297 (35%) 28/285 (10%)	30/232 (13%) 33/237 (14%)
Seymour et al 2013	N/A	0.68(0.53-0.87)	1.20(0.83-1.74)	0.92(0.73-1.16)	1.64(1.15-2.35)	70/160(43.8%) 20/163(12.3%)	9/70(12.9%) 7/67(10.4%)

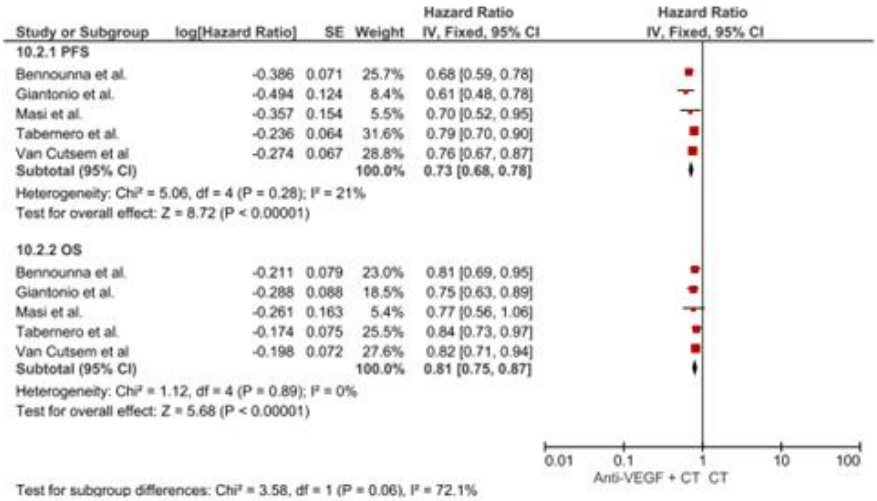
Study (reference)	DCR (RAS WT) n.(%)	DCR (RAS Mut) n.(%)	BRAF WT/mut	OS BRAF WT HR(95% CI)	OS BRAF Mut HR(95% CI)	PFS BRAF WT HR(95% CI)	PFS BRAF Mut HR(95% CI)
Giantonio et al 2007	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bennounna et al 2013	110/151 (72,85%) 100/164 (61%)	114/164 (69,5%) 75/134 (56%)	N/A	N/A	N/A	N/A	N/A
Masi et al 2015	N/A	N/A	65/7 64/3	N/A	N/A	N/A	N/A
Van Cutsem et al 2012	N/A	N/A	446/36	0.84(0.67-1.05)	0.42(0.16-1.09)	0.76(0.61-0.94)	0.59(0.22-1.58)
Tabernero et al 2015	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sobrero et al 2008	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Peeters et al 2010	220/297 (74%) 185/285 (65%)	162/232 (68%) 149/237 (63%)	186/22 190/23	0.83(0.70-0.98)	0.64(0.32-1.28)	0.68(0.51-0.90)	0.69(0.32-1.49)
Seymour et al 2013	N/A	N/A	N/A	N/A	1.84(1.16-2.92)	N/A	1.40(0.82-2.39)

FigureS2

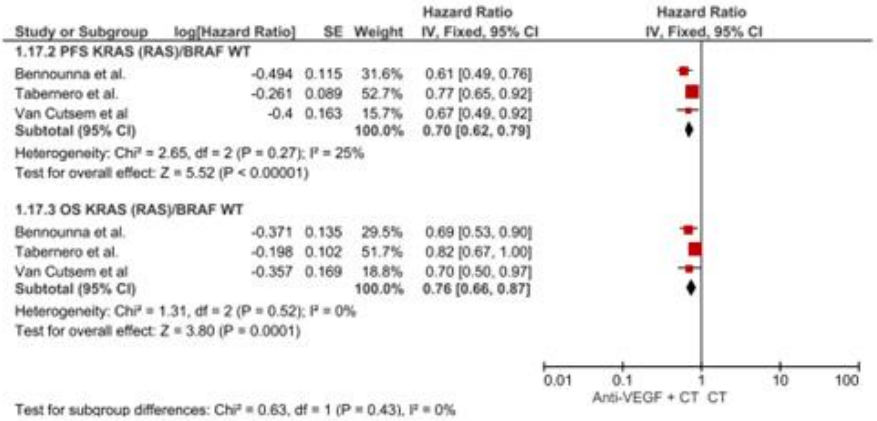

A
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
10.1.3 ORR
Bennounna et al. 22 404 16 406 15.7% 1.38 [0.74, 2.59]
Giantonio et al. 65 286 25 291 20.5% 2.65 [1.72, 4.07]
Masi et al. 16 92 19 92 16.4% 0.84 [0.46, 1.53]
Tabernero et al. 72 536 67 536 23.5% 1.07 [0.79, 1.47]
Van Cutsem et al 105 531 59 530 23.9% 1.78 [1.32, 2.39]
Subtotal (95% CI) 1849 1855 100.0% 1.46 [1.00, 2.12]
Total events 280 186
Heterogeneity: Tau² = 0.13; Chi² = 15.99, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 1.96 (P = 0.05)
10.1.4 DCR
Bennounna et al. 275 404 220 406 22.9% 1.26 [1.12, 1.40]
Masi et al. 64 92 53 92 8.3% 1.21 [0.97, 1.51]
Tabernero et al. 397 536 369 536 34.0% 1.08 [1.00, 1.16]
Van Cutsem et al 455 612 403 614 34.8% 1.13 [1.05, 1.22]
Subtotal (95% CI) 1644 1648 100.0% 1.15 [1.07, 1.23]
Total events 1191 1045
Heterogeneity: Tau² = 0.00; Chi² = 5.47, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 3.88 (P = 0.0001)
0.01 0.1 1 10 100
Anti-VEGF + CT CT
Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.1%
B
Anti-VEGF + CT
CT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.18.1 ORR KRAS (RAS)/BRAF WT
Bennounna et al. 11 151 9 164 26.4% 1.33 [0.57, 3.11]
Van Cutsem et al 62 218 24 218 73.6% 2.58 [1.68, 3.98]
Subtotal (95% CI) 369 382 100.0% 2.25 [1.54, 3.30]
Total events 73 33
Heterogeneity: Chi² = 1.86, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 4.16 (P < 0.0001)
1.18.2 DCR KRAS (RAS)/BRAF WT
Bennounna et al. 110 151 100 164 100.0% 1.19 [1.02, 1.40]
Subtotal (95% CI) 151 164 100.0% 1.19 [1.02, 1.40]
Total events 110 100
Heterogeneity: Not applicable
Test for overall effect: Z = 2.23 (P = 0.03)
0.01 0.1 1 10 100
Anti-VEGF + CT CT
Test for subgroup differences: Chi² = 9.05, df = 1 (P = 0.003), I² = 88.9%

FigureS3

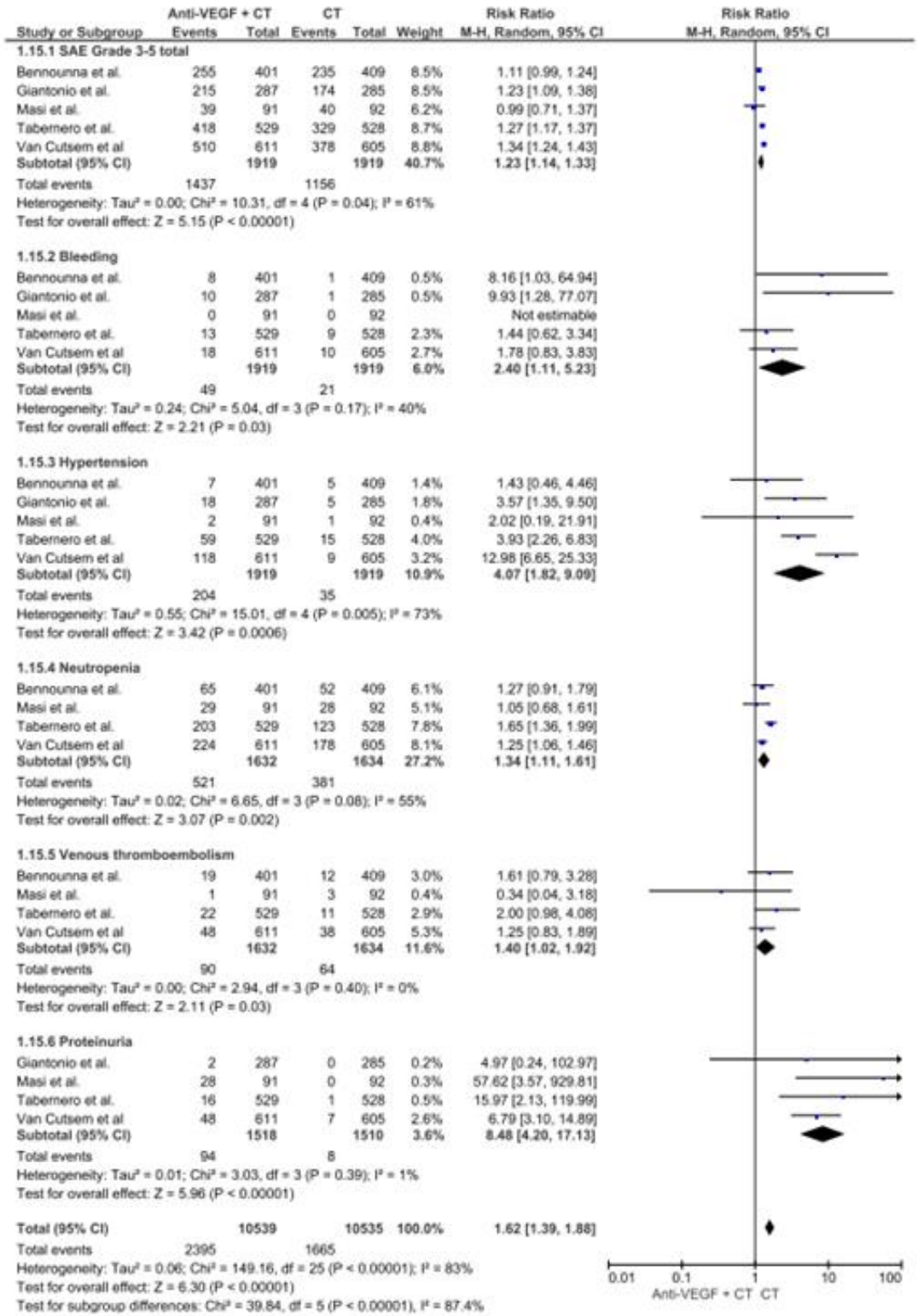
A


Study or Subgroup
log[Hazard Ratio]
SE
Weight
Hazard Ratio IV, Fixed, 95% CI
Hazard Ratio IV, Fixed, 95% CI
10.2.1 PFS
Bennounna et al. -0.386 0.071 25.7% 0.68 [0.59, 0.78]
Giantonio et al. -0.494 0.124 8.4% 0.61 [0.48, 0.78]
Masi et al. -0.357 0.154 5.5% 0.70 [0.52, 0.95]
Tabernero et al. -0.236 0.064 31.6% 0.79 [0.70, 0.90]
Van Cutsem et al -0.274 0.067 28.8% 0.76 [0.67, 0.87]
Subtotal (95% CI) 100.0% 0.73 [0.68, 0.78]
Heterogeneity: Chi² = 5.06, df = 4 (P = 0.28); I² = 21%
Test for overall effect: Z = 8.72 (P < 0.00001)
10.2.2 OS
Bennounna et al. -0.211 0.079 23.0% 0.81 [0.69, 0.95]
Giantonio et al. -0.288 0.088 18.5% 0.75 [0.63, 0.89]
Masi et al. -0.261 0.163 5.4% 0.77 [0.56, 1.06]
Tabernero et al. -0.174 0.075 25.5% 0.84 [0.73, 0.97]
Van Cutsem et al -0.198 0.072 27.6% 0.82 [0.71, 0.94]
Subtotal (95% CI) 100.0% 0.81 [0.75, 0.87]
Heterogeneity: Chi² = 1.12, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 5.68 (P < 0.00001)
0.01
0.1
1
10
100
Anti-VEGF + CT
CT
Test for subgroup differences: Chi² = 3.58, df = 1 (P = 0.06), I² = 72.1%

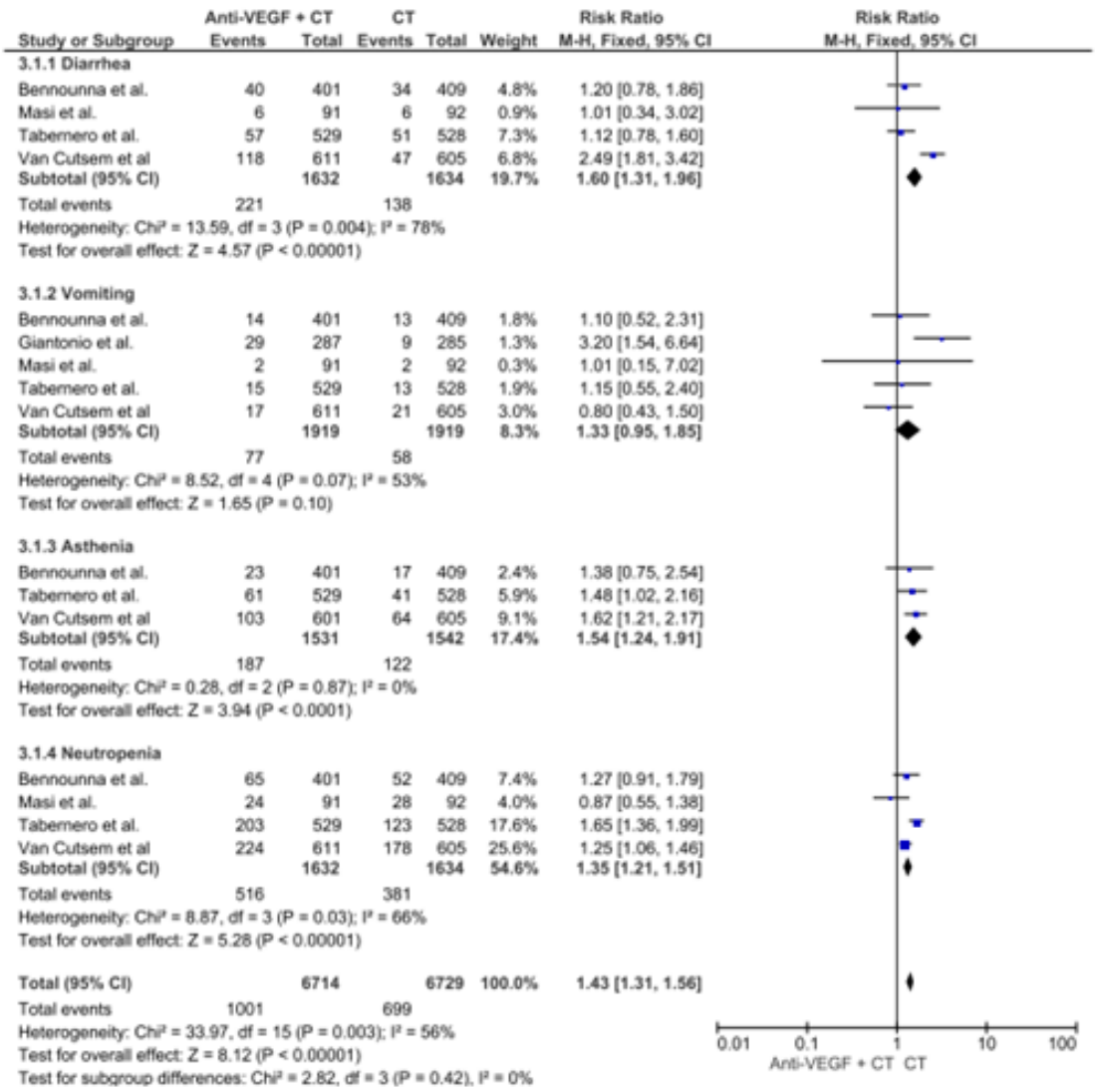
B


Study or Subgroup
log[Hazard Ratio]
SE
Weight
Hazard Ratio IV, Fixed, 95% CI
Hazard Ratio IV, Fixed, 95% CI
1.17.2 PFS KRAS (RAS)/BRAF WT
Bennounna et al. -0.494 0.115 31.6% 0.61 [0.49, 0.76]
Tabernero et al. -0.261 0.089 52.7% 0.77 [0.65, 0.92]
Van Cutsem et al -0.4 0.163 15.7% 0.67 [0.49, 0.92]
Subtotal (95% CI) 100.0% 0.70 [0.62, 0.79]
Heterogeneity: Chi² = 2.65, df = 2 (P = 0.27); I² = 25%
Test for overall effect: Z = 5.52 (P < 0.00001)
1.17.3 OS KRAS (RAS)/BRAF WT
Bennounna et al. -0.371 0.135 29.5% 0.69 [0.53, 0.90]
Tabernero et al. -0.198 0.102 51.7% 0.82 [0.67, 1.00]
Van Cutsem et al -0.357 0.169 18.8% 0.70 [0.50, 0.97]
Subtotal (95% CI) 100.0% 0.76 [0.66, 0.87]
Heterogeneity: Chi² = 1.31, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.80 (P = 0.0001)
0.01
0.1
1
10
100
Anti-VEGF + CT
CT
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%

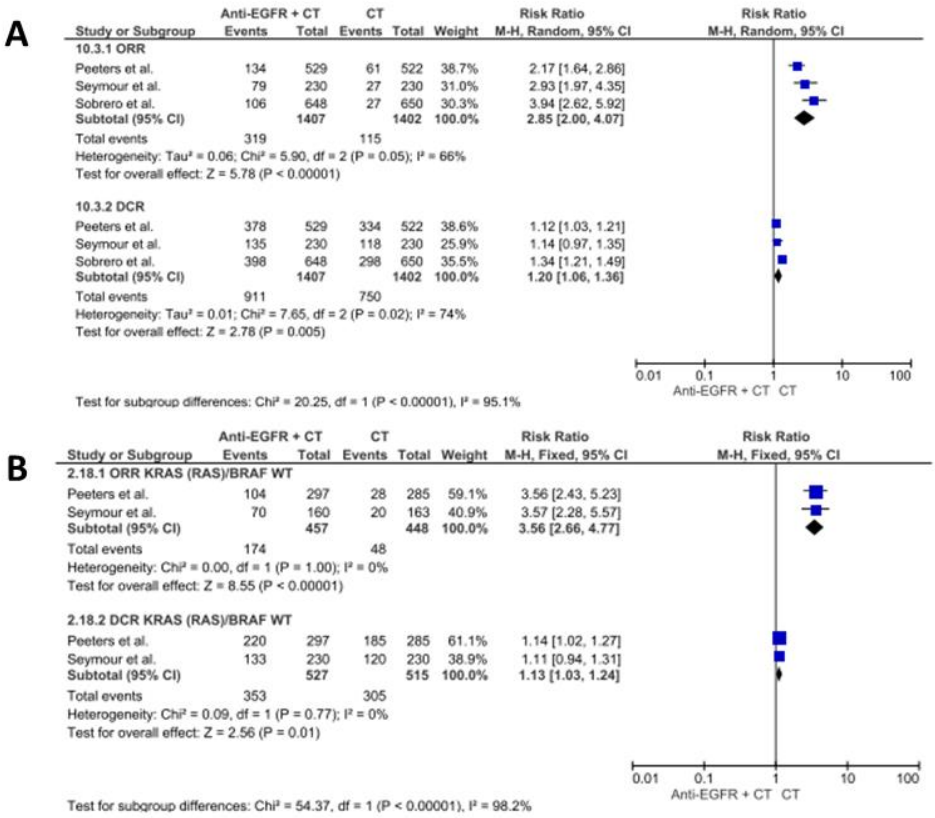
FigureS4


Anti-VEGF + CT
CT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.15.1 SAE Grade 3-5 total
Bennounna et al. 255 401 235 409 8.5% 1.11 [0.99, 1.24]
Giantonio et al. 215 287 174 285 8.5% 1.23 [1.09, 1.38]
Masi et al. 39 91 40 92 6.2% 0.99 [0.71, 1.37]
Tabernero et al. 418 529 329 528 8.7% 1.27 [1.17, 1.37]
Van Cutsem et al 510 611 378 605 8.8% 1.34 [1.24, 1.43]
Subtotal (95% CI) 1919 1919 40.7% 1.23 [1.14, 1.33]
Total events 1437 1156
Heterogeneity: Tau² = 0.00; Chi² = 10.31, df = 4 (P = 0.04); I² = 61%
Test for overall effect: Z = 5.15 (P < 0.00001)
1.15.2 Bleeding
Bennounna et al. 8 401 1 409 0.5% 8.16 [1.03, 64.94]
Giantonio et al. 10 287 1 285 0.5% 9.93 [1.28, 77.07]
Masi et al. 0 91 0 92 Not estimable
Tabernero et al. 13 529 9 528 2.3% 1.44 [0.62, 3.34]
Van Cutsem et al 18 611 10 605 2.7% 1.78 [0.83, 3.83]
Subtotal (95% CI) 1919 1919 6.0% 2.40 [1.11, 5.23]
Total events 49 21
Heterogeneity: Tau² = 0.24; Chi² = 5.04, df = 3 (P = 0.17); I² = 40%
Test for overall effect: Z = 2.21 (P = 0.03)
1.15.3 Hypertension
Bennounna et al. 7 401 5 409 1.4% 1.43 [0.46, 4.46]
Giantonio et al. 18 287 5 285 1.8% 3.57 [1.35, 9.50]
Masi et al. 2 91 1 92 0.4% 2.02 [0.19, 21.91]
Tabernero et al. 59 529 15 528 4.0% 3.93 [2.26, 6.83]
Van Cutsem et al 118 611 9 605 3.2% 12.98 [6.65, 25.33]
Subtotal (95% CI) 1919 1919 10.9% 4.07 [1.82, 9.09]
Total events 204 35
Heterogeneity: Tau² = 0.55; Chi² = 15.01, df = 4 (P = 0.005); I² = 73%
Test for overall effect: Z = 3.42 (P = 0.0006)
1.15.4 Neutropenia
Bennounna et al. 65 401 52 409 6.1% 1.27 [0.91, 1.79]
Masi et al. 29 91 28 92 5.1% 1.05 [0.68, 1.61]
Tabernero et al. 203 529 123 528 7.8% 1.65 [1.36, 1.99]
Van Cutsem et al 224 611 178 605 8.1% 1.25 [1.06, 1.46]
Subtotal (95% CI) 1632 1634 27.2% 1.34 [1.11, 1.61]
Total events 521 381
Heterogeneity: Tau² = 0.02; Chi² = 6.65, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 3.07 (P = 0.002)
1.15.5 Venous thromboembolism
Bennounna et al. 19 401 12 409 3.0% 1.61 [0.79, 3.28]
Masi et al. 1 91 3 92 0.4% 0.34 [0.04, 3.18]
Tabernero et al. 22 529 11 528 2.9% 2.00 [0.98, 4.08]
Van Cutsem et al 48 611 38 605 5.3% 1.25 [0.83, 1.89]
Subtotal (95% CI) 1632 1634 11.6% 1.40 [1.02, 1.92]
Total events 90 64
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.11 (P = 0.03)
1.15.6 Proteinuria
Giantonio et al. 2 287 0 285 0.2% 4.97 [0.24, 102.97]
Masi et al. 28 91 0 92 0.3% 57.62 [3.57, 929.81]
Tabernero et al. 16 529 1 528 0.5% 15.97 [2.13, 119.99]
Van Cutsem et al 48 611 7 605 2.6% 6.79 [3.10, 14.89]
Subtotal (95% CI) 1518 1510 3.6% 8.48 [4.20, 17.13]
Total events 94 8
Heterogeneity: Tau² = 0.01; Chi² = 3.03, df = 3 (P = 0.39); I² = 1%
Test for overall effect: Z = 5.96 (P < 0.00001)
Total (95% CI) 10539 10535 100.0% 1.62 [1.39, 1.88]
Total events 2395 1665
Heterogeneity: Tau² = 0.06; Chi² = 149.16, df = 25 (P < 0.00001); I² = 83%
Test for overall effect: Z = 6.30 (P < 0.00001)
Test for subgroup differences: Chi² = 39.84, df = 5 (P < 0.00001), I² = 87.4%
0.01 0.1 1 10 100
Anti-VEGF + CT CT

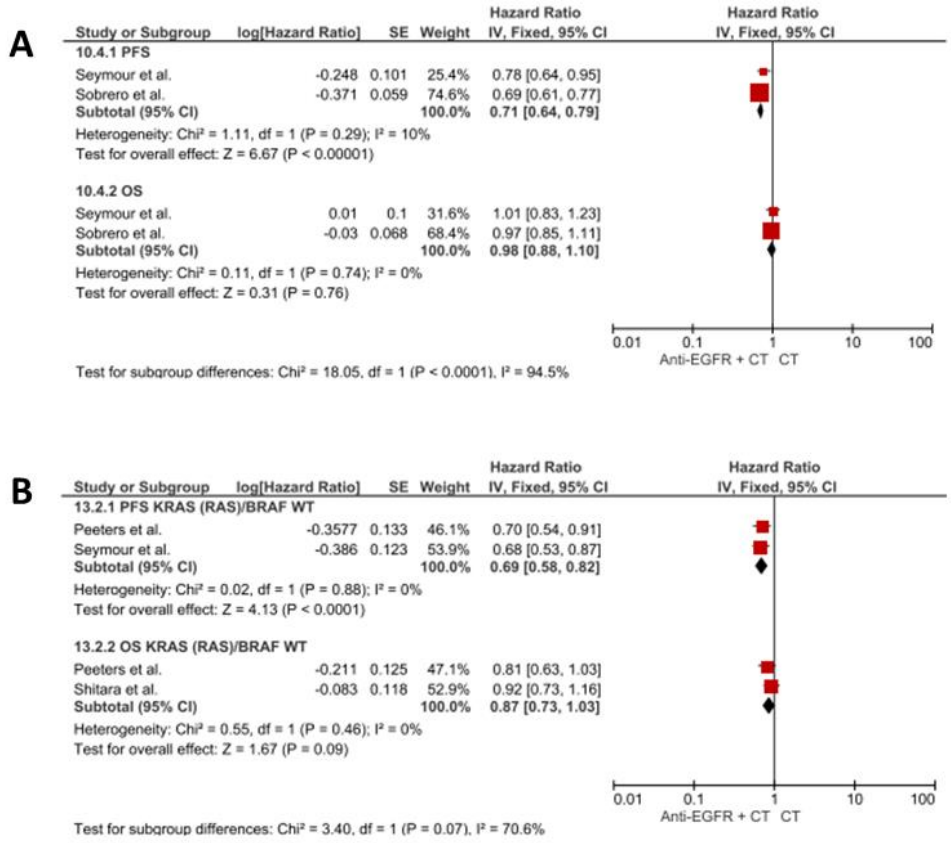
FigureS5


Anti-VEGF + CT
CT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
3.1.1 Diarrhea
Bennounna et al. 40 401 34 409 4.8% 1.20 [0.78, 1.86]
Masi et al. 6 91 6 92 0.9% 1.01 [0.34, 3.02]
Tabernero et al. 57 529 51 528 7.3% 1.12 [0.78, 1.60]
Van Cutsem et al 118 611 47 605 6.8% 2.49 [1.81, 3.42]
Subtotal (95% CI) 1632 1634 19.7% 1.60 [1.31, 1.96]
Total events 221 138
Heterogeneity: Chi² = 13.59, df = 3 (P = 0.004); I² = 78%
Test for overall effect: Z = 4.57 (P < 0.00001)
3.1.2 Vomiting
Bennounna et al. 14 401 13 409 1.8% 1.10 [0.52, 2.31]
Giantonio et al. 29 287 9 285 1.3% 3.20 [1.54, 6.64]
Masi et al. 2 91 2 92 0.3% 1.01 [0.15, 7.02]
Tabernero et al. 15 529 13 528 1.9% 1.15 [0.55, 2.40]
Van Cutsem et al 17 611 21 605 3.0% 0.80 [0.43, 1.50]
Subtotal (95% CI) 1919 1919 8.3% 1.33 [0.95, 1.85]
Total events 77 58
Heterogeneity: Chi² = 8.52, df = 4 (P = 0.07); I² = 53%
Test for overall effect: Z = 1.65 (P = 0.10)
3.1.3 Asthenia
Bennounna et al. 23 401 17 409 2.4% 1.38 [0.75, 2.54]
Tabernero et al. 61 529 41 528 5.9% 1.48 [1.02, 2.16]
Van Cutsem et al 103 601 64 605 9.1% 1.62 [1.21, 2.17]
Subtotal (95% CI) 1531 1542 17.4% 1.54 [1.24, 1.91]
Total events 187 122
Heterogeneity: Chi² = 0.28, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 3.94 (P < 0.0001)
3.1.4 Neutropenia
Bennounna et al. 65 401 52 409 7.4% 1.27 [0.91, 1.79]
Masi et al. 24 91 28 92 4.0% 0.87 [0.55, 1.38]
Tabernero et al. 203 529 123 528 17.6% 1.65 [1.36, 1.99]
Van Cutsem et al 224 611 178 605 25.6% 1.25 [1.06, 1.46]
Subtotal (95% CI) 1632 1634 54.6% 1.35 [1.21, 1.51]
Total events 516 381
Heterogeneity: Chi² = 8.87, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 5.28 (P < 0.00001)
Total (95% CI) 6714 6729 100.0% 1.43 [1.31, 1.56]
Total events 1001 699
Heterogeneity: Chi² = 33.97, df = 15 (P = 0.003); I² = 56%
Test for overall effect: Z = 8.12 (P < 0.00001)
Test for subgroup differences: Chi² = 2.82, df = 3 (P = 0.42), I² = 0%
0.01 0.1 1 10 100
Anti-VEGF + CT CT

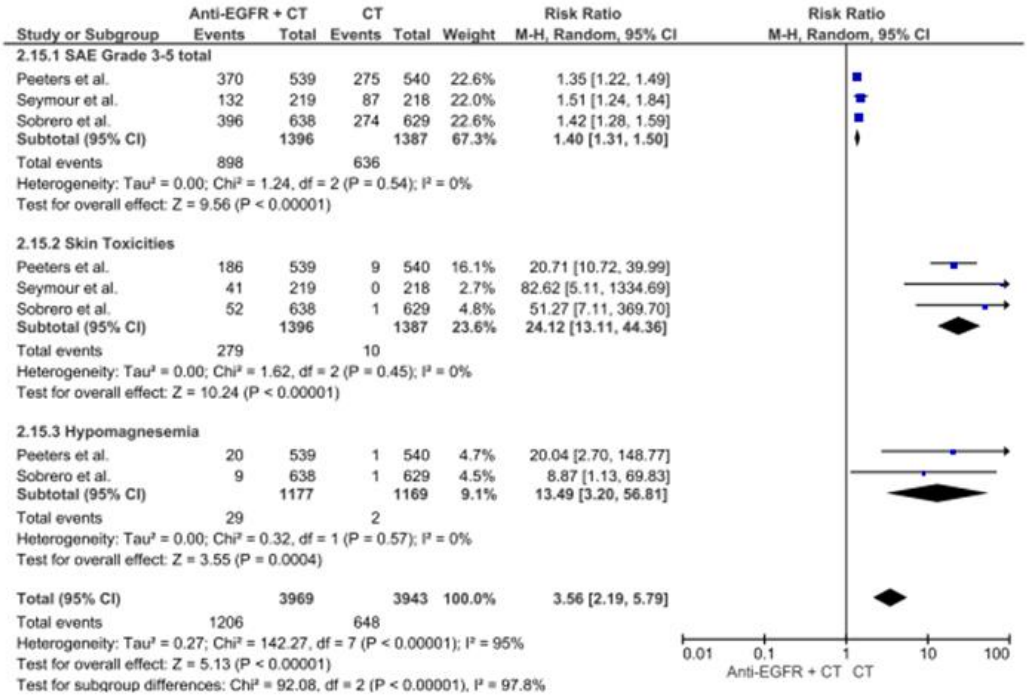
FigureS6


A
Anti-EGFR + CT
CT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
10.3.1 ORR
Peeters et al. 134 529 61 522 38.7% 2.17 [1.64, 2.86]
Seymour et al. 79 230 27 230 31.0% 2.93 [1.97, 4.35]
Sobrero et al. 106 648 27 650 30.3% 3.94 [2.62, 5.92]
Subtotal (95% CI) 1407 1402 100.0% 2.85 [2.00, 4.07]
Total events 319 115
Heterogeneity: Tau² = 0.06; Chi² = 5.90, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 5.78 (P < 0.00001)
10.3.2 DCR
Peeters et al. 378 529 334 522 38.6% 1.12 [1.03, 1.21]
Seymour et al. 135 230 118 230 25.9% 1.14 [0.97, 1.35]
Sobrero et al. 398 648 298 650 35.5% 1.34 [1.21, 1.49]
Subtotal (95% CI) 1407 1402 100.0% 1.20 [1.06, 1.36]
Total events 911 750
Heterogeneity: Tau² = 0.01; Chi² = 7.65, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 2.78 (P = 0.005)
0.01 0.1 1 10 100
Anti-EGFR + CT CT
Test for subgroup differences: Chi² = 20.25, df = 1 (P < 0.00001), I² = 95.1%
B
Anti-EGFR + CT
CT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.18.1 ORR KRAS (RAS)/BRAF WT
Peeters et al. 104 297 28 285 59.1% 3.56 [2.43, 5.23]
Seymour et al. 70 160 20 163 40.9% 3.57 [2.28, 5.57]
Subtotal (95% CI) 457 448 100.0% 3.56 [2.66, 4.77]
Total events 174 48
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 8.55 (P < 0.00001)
2.18.2 DCR KRAS (RAS)/BRAF WT
Peeters et al. 220 297 185 285 61.1% 1.14 [1.02, 1.27]
Seymour et al. 133 230 120 230 38.9% 1.11 [0.94, 1.31]
Subtotal (95% CI) 527 515 100.0% 1.13 [1.03, 1.24]
Total events 353 305
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.56 (P = 0.01)
0.01 0.1 1 10 100
Anti-EGFR + CT CT
Test for subgroup differences: Chi² = 54.37, df = 1 (P < 0.00001), I² = 98.2%

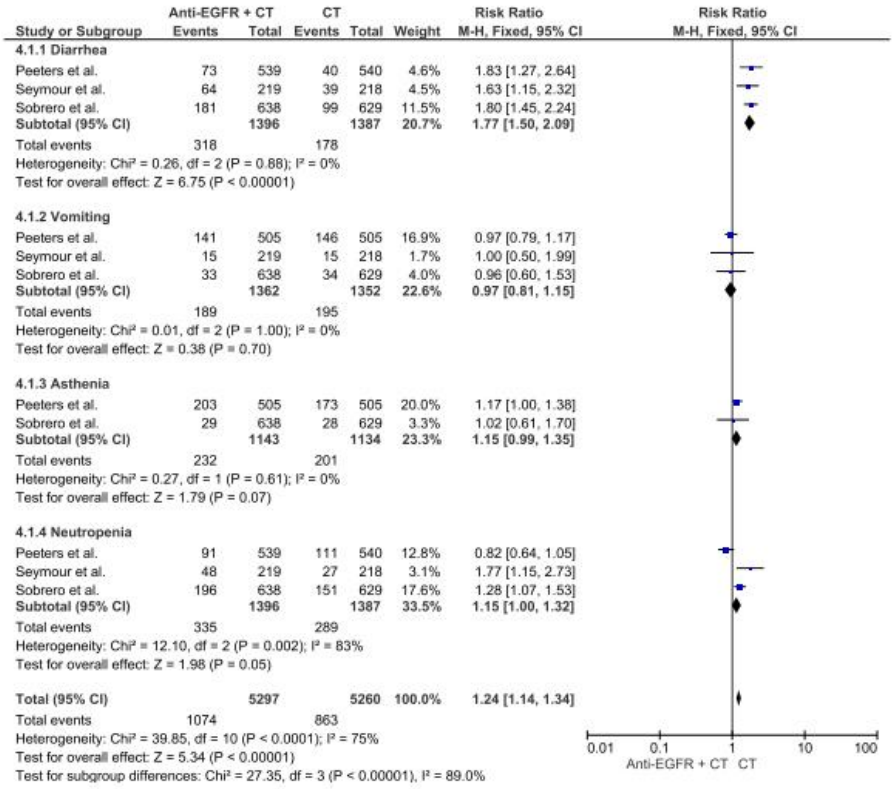
FigureS7


A
Study or Subgroup log[Hazard Ratio] SE Weight Hazard Ratio IV, Fixed, 95% CI
Hazard Ratio IV, Fixed, 95% CI
10.4.1 PFS
Seymour et al. -0.248 0.101 25.4% 0.78 [0.64, 0.95]
Sobrero et al. -0.371 0.059 74.6% 0.69 [0.61, 0.77]
Subtotal (95% CI) 100.0% 0.71 [0.64, 0.79]
Heterogeneity: Chi² = 1.11, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 6.67 (P < 0.00001)
10.4.2 OS
Seymour et al. 0.01 0.1 31.6% 1.01 [0.83, 1.23]
Sobrero et al. -0.03 0.068 68.4% 0.97 [0.85, 1.11]
Subtotal (95% CI) 100.0% 0.98 [0.88, 1.10]
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)
0.01 0.1 1 10 100
Anti-EGFR + CT CT
Test for subgroup differences: Chi² = 18.05, df = 1 (P < 0.0001), I² = 94.5%
B
Study or Subgroup log[Hazard Ratio] SE Weight Hazard Ratio IV, Fixed, 95% CI
Hazard Ratio IV, Fixed, 95% CI
13.2.1 PFS KRAS (RAS)/BRAF WT
Peeters et al. -0.3577 0.133 46.1% 0.70 [0.54, 0.91]
Seymour et al. -0.386 0.123 53.9% 0.68 [0.53, 0.87]
Subtotal (95% CI) 100.0% 0.69 [0.58, 0.82]
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)
13.2.2 OS KRAS (RAS)/BRAF WT
Peeters et al. -0.211 0.125 47.1% 0.81 [0.63, 1.03]
Shitara et al. -0.083 0.118 52.9% 0.92 [0.73, 1.16]
Subtotal (95% CI) 100.0% 0.87 [0.73, 1.03]
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
0.01 0.1 1 10 100
Anti-EGFR + CT CT
Test for subgroup differences: Chi² = 3.40, df = 1 (P = 0.07), I² = 70.6%

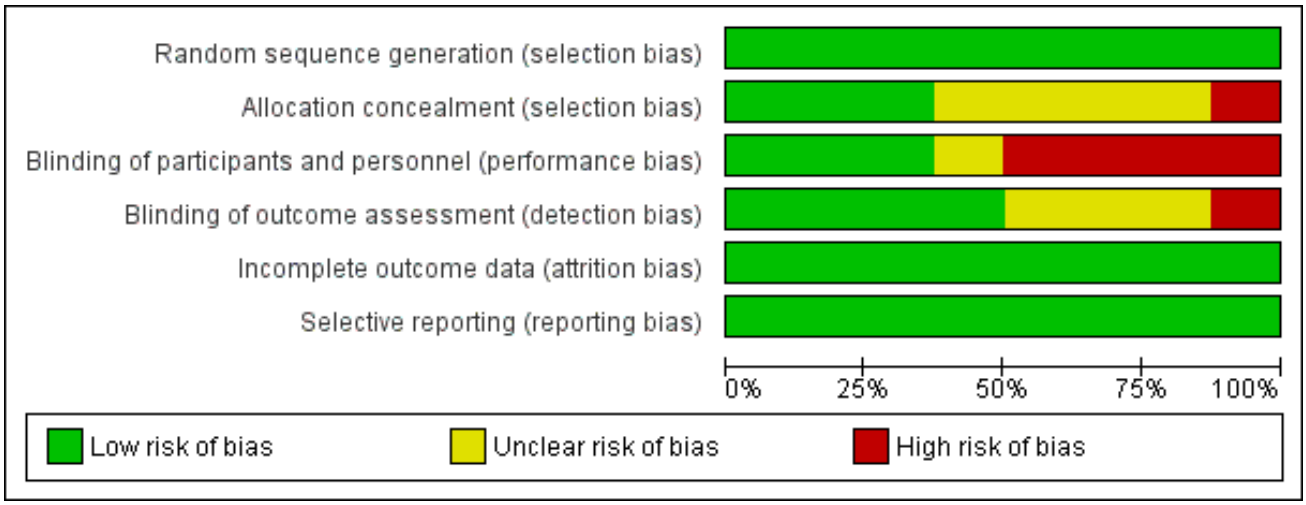
FigureS8


Anti-EGFR + CT
CT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.15.1 SAE Grade 3-5 total
Peeters et al. 370 539 275 540 22.6% 1.35 [1.22, 1.49]
Seymour et al. 132 219 87 218 22.0% 1.51 [1.24, 1.84]
Sobrero et al. 396 638 274 629 22.6% 1.42 [1.28, 1.59]
Subtotal (95% CI) 1396 1387 67.3% 1.40 [1.31, 1.50]
Total events 898 636
Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 9.56 (P < 0.00001)
2.15.2 Skin Toxicities
Peeters et al. 186 539 9 540 16.1% 20.71 [10.72, 39.99]
Seymour et al. 41 219 0 218 2.7% 82.62 [5.11, 1334.69]
Sobrero et al. 52 638 1 629 4.8% 51.27 [7.11, 369.70]
Subtotal (95% CI) 1396 1387 23.6% 24.12 [13.11, 44.36]
Total events 279 10
Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 10.24 (P < 0.00001)
2.15.3 Hypomagnesemia
Peeters et al. 20 539 1 540 4.7% 20.04 [2.70, 148.77]
Sobrero et al. 9 638 1 629 4.5% 8.87 [1.13, 69.83]
Subtotal (95% CI) 1177 1169 9.1% 13.49 [3.20, 56.81]
Total events 29 2
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.55 (P = 0.0004)
Total (95% CI) 3969 3943 100.0% 3.56 [2.19, 5.79]
Total events 1206 648
Heterogeneity: Tau² = 0.27; Chi² = 142.27, df = 7 (P < 0.00001); I² = 95%
Test for overall effect: Z = 5.13 (P < 0.00001)
Test for subgroup differences: Chi² = 92.08, df = 2 (P < 0.00001), I² = 97.8%
0.01 0.1 1 10 100
Anti-EGFR + CT CT

FigureS9


Anti-EGFR + CT
CT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
4.1.1 Diarrhea
Peeters et al. 73 539 40 540 4.6% 1.83 [1.27, 2.64]
Seymour et al. 64 219 39 218 4.5% 1.63 [1.15, 2.32]
Sobrero et al. 181 638 99 629 11.5% 1.80 [1.45, 2.24]
Subtotal (95% CI) 1396 1387 20.7% 1.77 [1.50, 2.09]
Total events 318 178
Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 6.75 (P < 0.00001)
4.1.2 Vomiting
Peeters et al. 141 505 146 505 16.9% 0.97 [0.79, 1.17]
Seymour et al. 15 219 15 218 1.7% 1.00 [0.50, 1.99]
Sobrero et al. 33 638 34 629 4.0% 0.96 [0.60, 1.53]
Subtotal (95% CI) 1362 1352 22.6% 0.97 [0.81, 1.15]
Total events 189 195
Heterogeneity: Chi² = 0.01, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)
4.1.3 Asthenia
Peeters et al. 203 505 173 505 20.0% 1.17 [1.00, 1.38]
Sobrero et al. 29 638 28 629 3.3% 1.02 [0.61, 1.70]
Subtotal (95% CI) 1143 1134 23.3% 1.15 [0.99, 1.35]
Total events 232 201
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)
4.1.4 Neutropenia
Peeters et al. 91 539 111 540 12.8% 0.82 [0.64, 1.05]
Seymour et al. 48 219 27 218 3.1% 1.77 [1.15, 2.73]
Sobrero et al. 196 638 151 629 17.6% 1.28 [1.07, 1.53]
Subtotal (95% CI) 1396 1387 33.5% 1.15 [1.00, 1.32]
Total events 335 289
Heterogeneity: Chi² = 12.10, df = 2 (P = 0.002); I² = 83%
Test for overall effect: Z = 1.98 (P = 0.05)
Total (95% CI) 5297 5260 100.0% 1.24 [1.14, 1.34]
Total events 1074 863
Heterogeneity: Chi² = 39.85, df = 10 (P < 0.0001); I² = 75%
Test for overall effect: Z = 5.34 (P < 0.00001)
Test for subgroup differences: Chi² = 27.35, df = 3 (P < 0.00001), I² = 89.0%
0.01 0.1 1 10 100
Anti-EGFR + CT CT

FigureS10


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

FigureS11

Search Strategy

ELECTRONIC SEARCH

1. We used a search strategy Medline through Pubmed. The same search was then modified for searches in other databases (EMBASE, Controlled Cochrane Trial Register - CCTR).

The query was adapted from **Robinson &coll: [Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. International journal of epidemiology 2002;31:150-153].**

2. (("Colorectal Neoplasms"[Mesh] OR "colorectal cancer"[tiab] OR "CRC"[tiab]) AND ("second line"[tiab] OR "beyond first"[tiab] OR "progressing"[tiab]) AND ("bevacizumab"[tiab] OR "cetuximab"[tiab] OR "panitumumab"[tiab] OR "ramucirumab"[tiab] OR "aflibercept"[tiab]))

3. We used the free text strategy

Second line– advancedcolorectal cancer – Bevacizumab – Cetuximab – Panitumumab – Aflibercept - Ramucirumab

for trials on-line searches in Clinical Trials registers (www.clinicaltrials.gov)

3. We searched meta-analyses for any other published data concerningsecond line or advanced colorectal cancer OR The strategy in Pubmed for meta-analysis searching was:

"second line"[tiab] AND meta-analysis[pt]

"advanced colorectal cancer"[tiab] AND meta-analysis[pt]

("Colorectal Neoplasms"[Mesh] OR "CRC"[tiab] OR "colorectal"[tiab]) AND meta-analysis[pt]

FigureS12

Search Strategy

ELECTRONIC SEARCH

1. We used a search strategy Medline through Pubmed. The same search was then modified for searches in other databases (EMBASE, Controlled Cochrane Trial Register - CCTR).

The query was adapted from **Robinson &coll: [Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. International journal of epidemiology 2002;31:150-153].**

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"advanced colorectal cancer"[tiab] AND meta-analysis[pt]

("Colorectal Neoplasms"[Mesh] OR "CRC"[tiab] OR "colorectal"[tiab]) AND meta-analysis[pt]