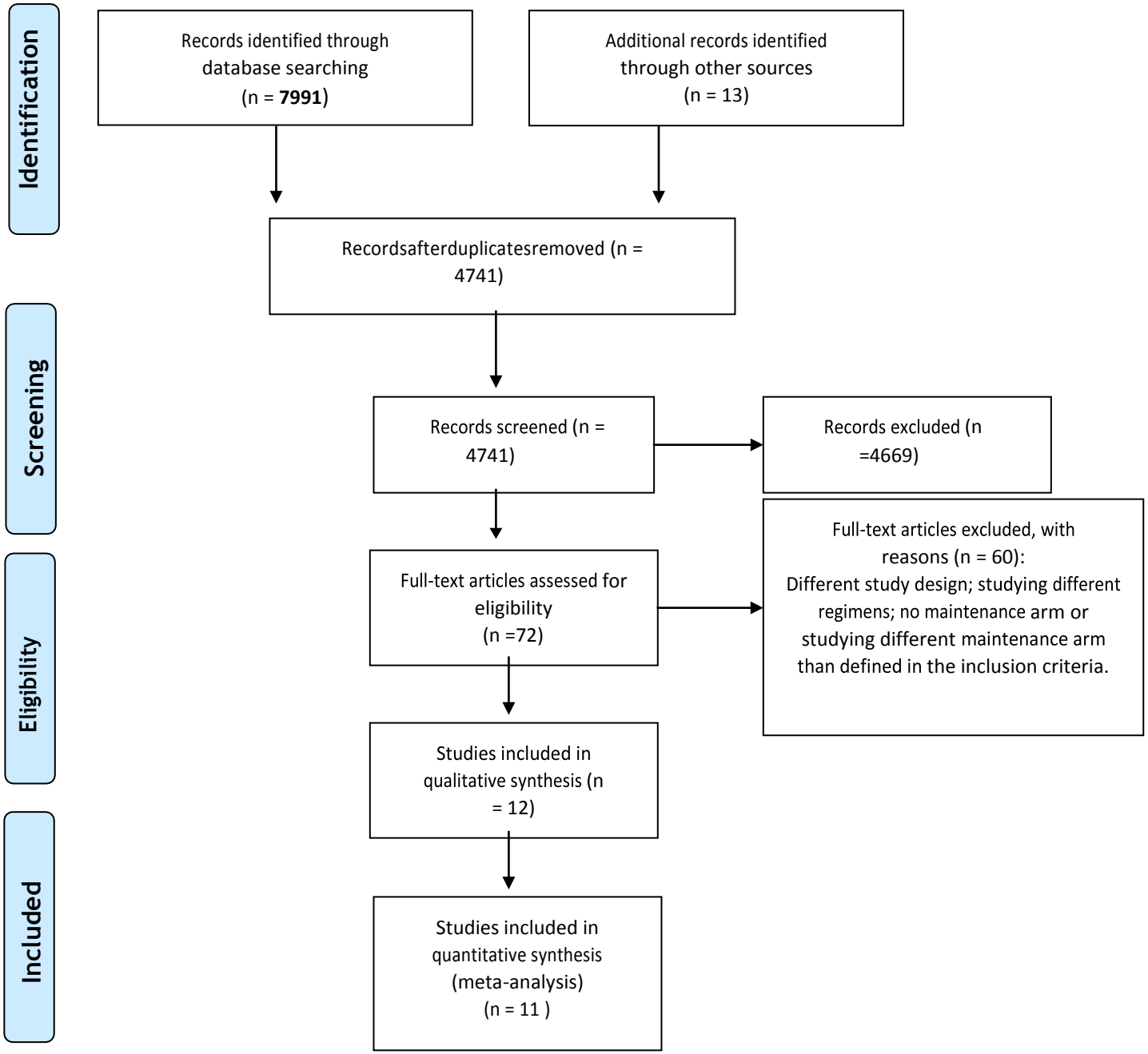
# Supplementary Online Content

Sonbol MB, Mountjoy LJ, Firwana B, et al. The role of maintenance strategies in metastatic colorectal cancer: a systematic review and network meta-analysis of randomized clinical trials. *JAMA Oncol.* Published online December 19, 2019. doi:10.1001/jamaoncol.2019.4489

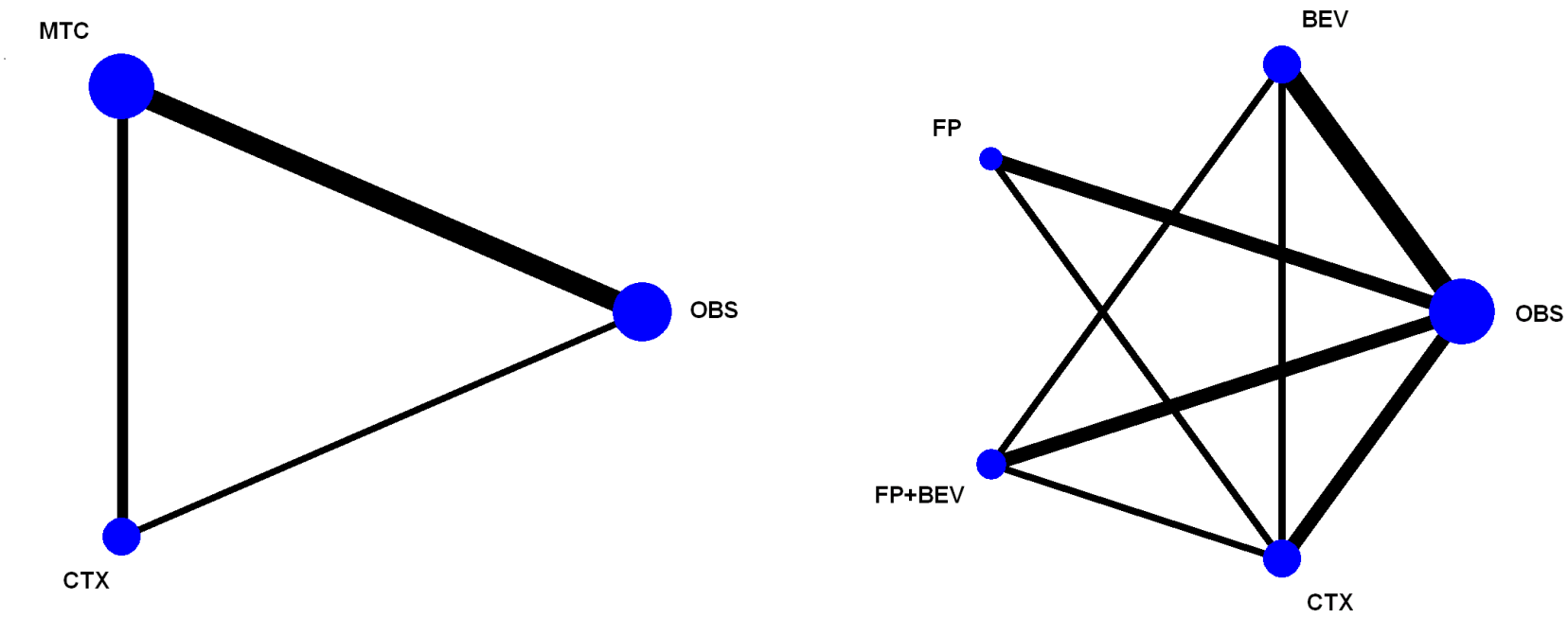


This supplementary material has been provided by the authors to give readers additional information about their work.

**eFigure 1.** Screening and Selection Process

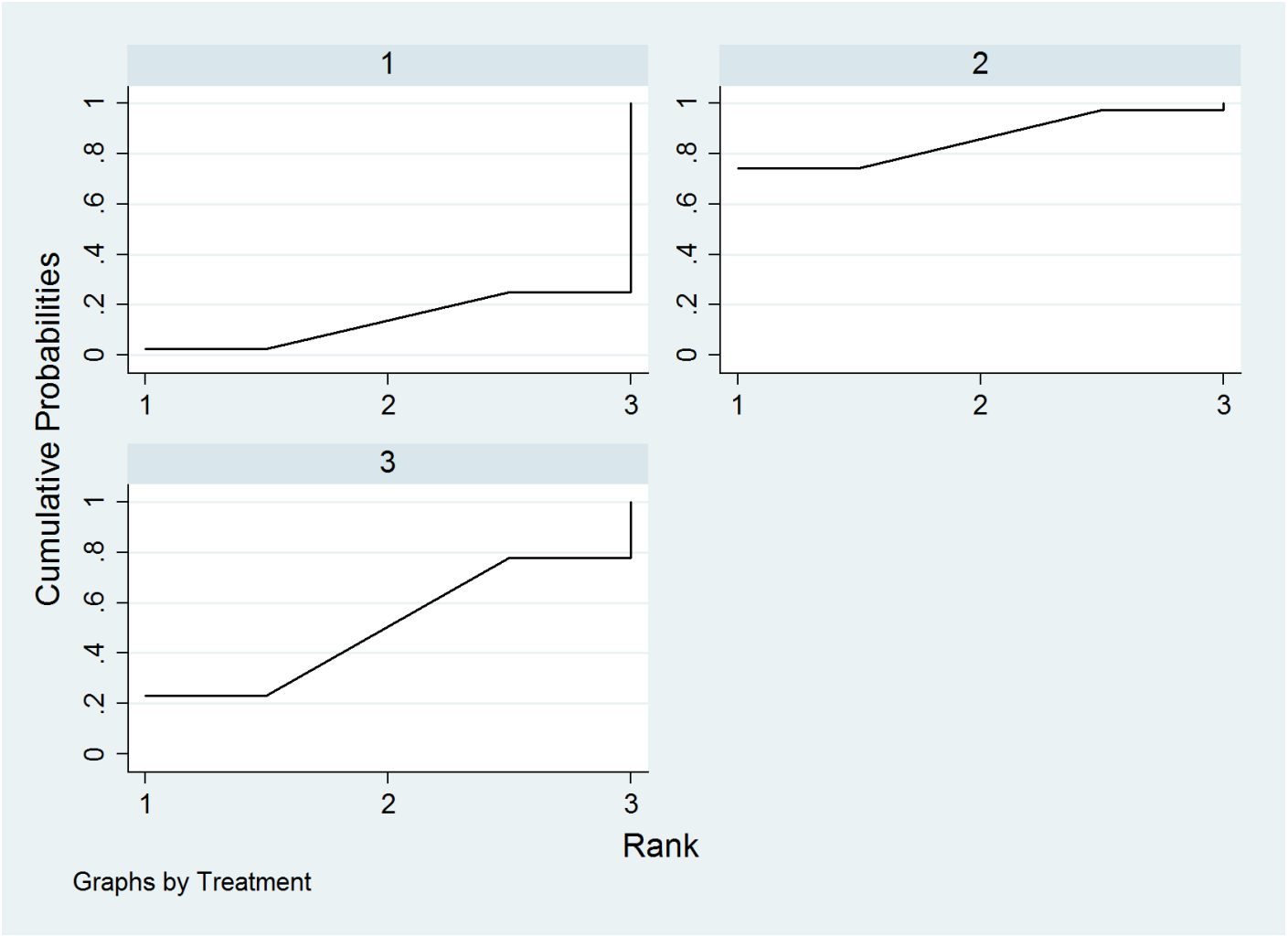


**eFigure 2.** Evidence Network



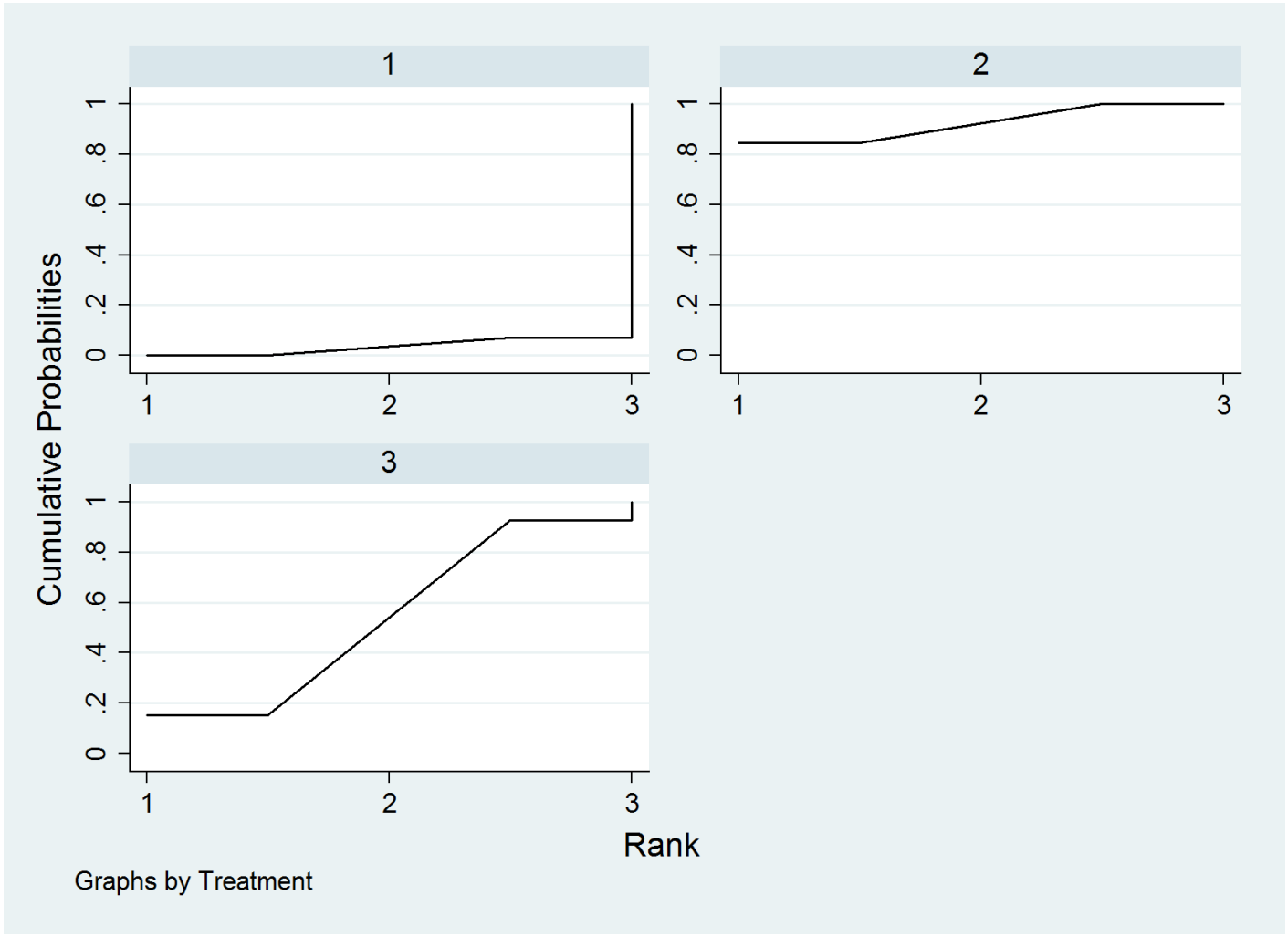

Evidence network of different maintenance strategies used after induction chemotherapy included in the network meta-analysis. Please note that one of the included RCTs was three-arm trials. The thickness of the connecting line corresponds to the number of trials between comparators. MTC: maintenance treatment; OBS: observation; CTX: continuing induction chemotherapy; FP: fluoropyrimidine; BEV: bevacizumab.

**eFigure 3**. Ranking Probabilities of the Different Comparisons for Overall Survival



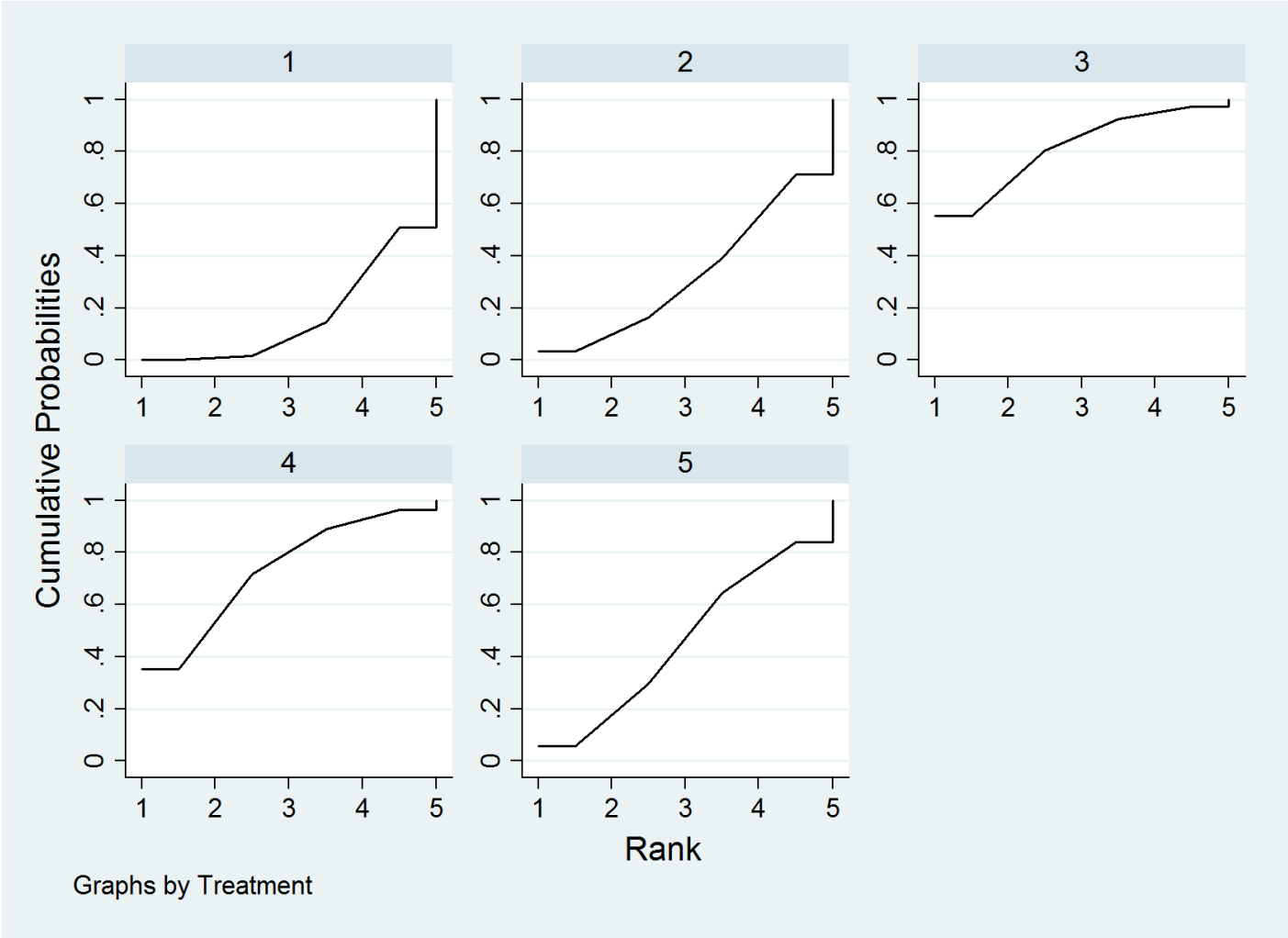

Ranking probabilities of the different comparisons for overall survival. 1: observation; 2: any maintenance treatment with fluoropyrimidine or bevacizumab or the combination of the two ; 3: continuing induction regimen.

**eFigure 4.** Ranking Probabilities of the Different Comparisons for Progression-Free Survival



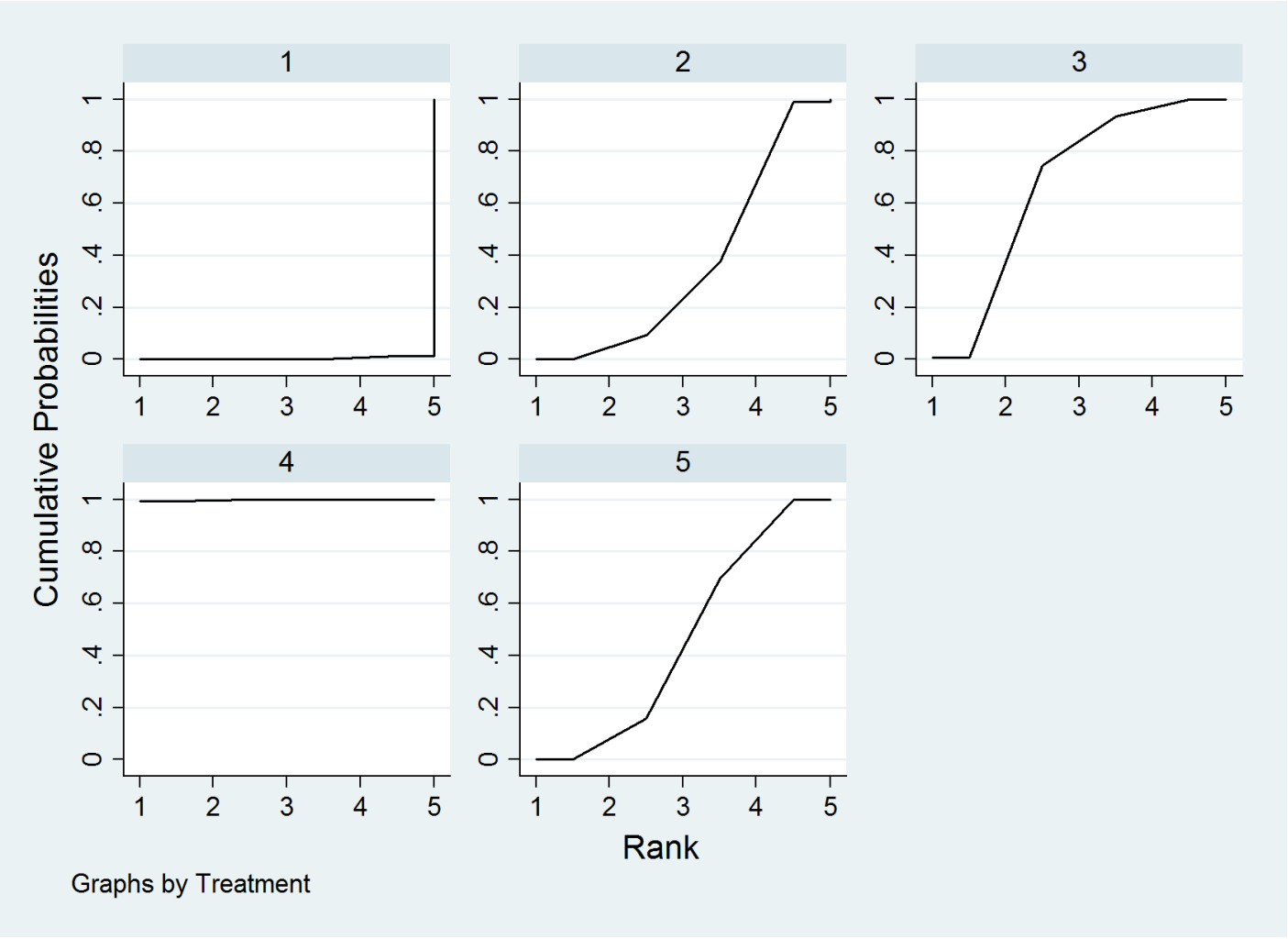

Ranking probabilities of the different comparisons for progression free survival. 1: observation; 2: any maintenance treatment with fluoropyrimidine or bevacizumab or the combination of the two ; 3: continuing induction regimen

**eFigure 5.** Ranking Probabilities of the Different Comparisons for Overall Survival



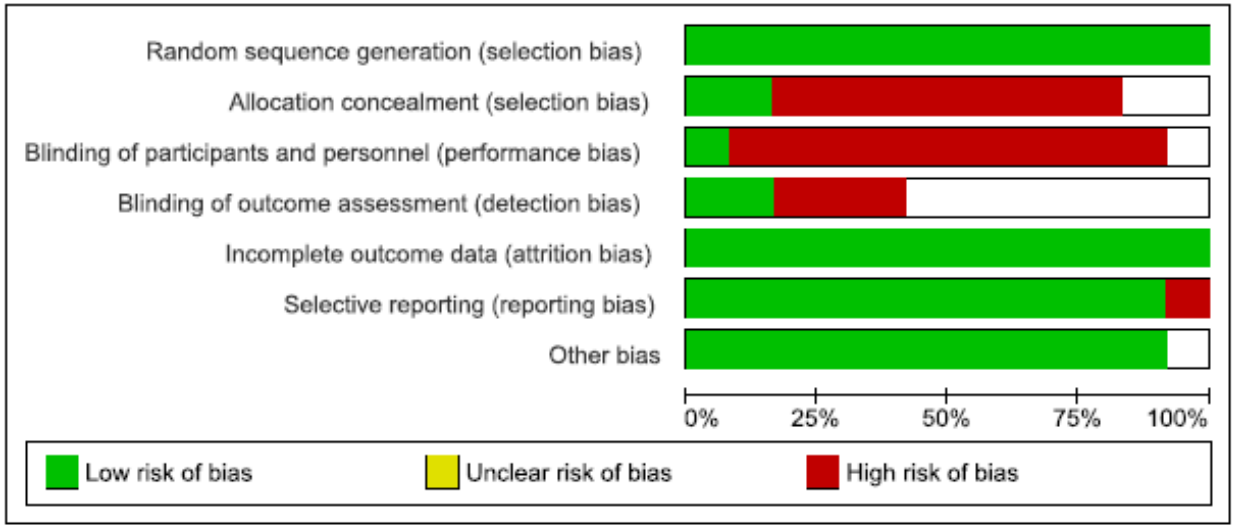

Ranking probabilities of the different comparisons for overall survival. 1: observation; 2: bevacizumab; 3: fluoropyrimidine; 4: fluoropyrimidine+bevacizumab; 5: continuing induction regimen.

**eFigure 6.** Ranking Probabilities of the Different Comparisons for Progression-Free Survival



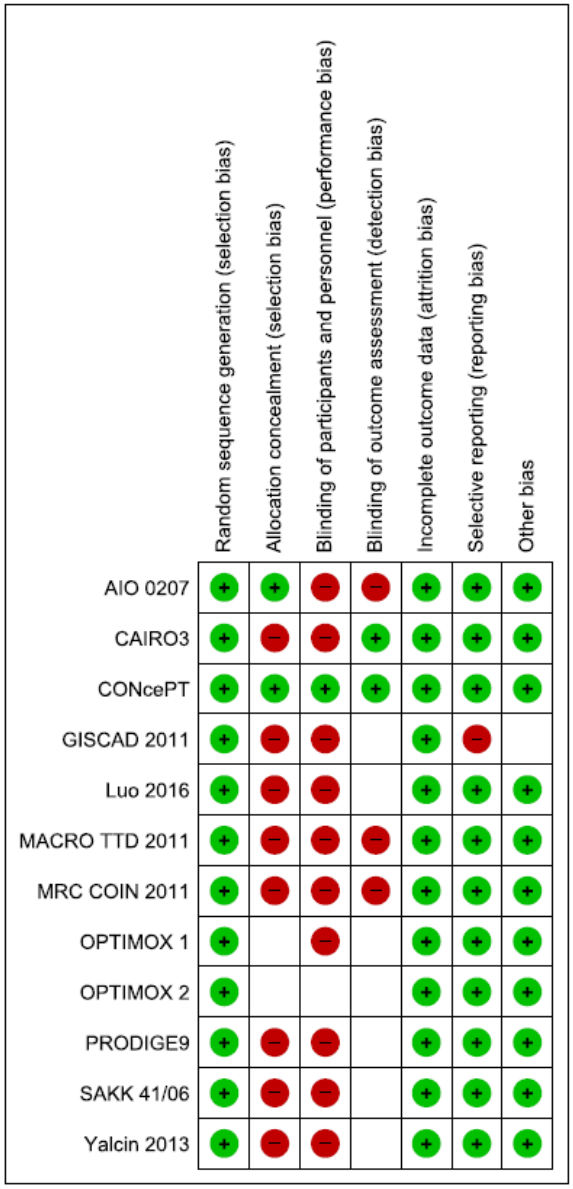

Ranking probabilities of the different comparisons for progression free survival. 1: observation; 2: bevacizumab; 3: fluoropyrimidine; 4: fluoropyrimidine+bevacizumab; 5: continuing induction regimen.

**eFigure 7.** Risk of Bias Graph




Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

**eFigure 8.** Risk of Bias Graph



**eTable 1.** Baseline Characteristics

| Study Title | Induction Chemo | Maintenance | NO of Patients | Induction Chemo length | ECOG PS | Median Age (Range) | RAS mutated | Study Sites | Randomization before or after induction? | Was re-induction allowed | Location of primary | Male % | NO of metastatic sites |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRODIGE9 (2018)** [1] | FOLFIRI+ Bev | Obs | 243 | **24 weeks** | 0,1, 2 | 65 | mKRAS 46.6 % | France; 66 centers | Before | Yes 69.5 % | right (35%); left (64.2 %); rectum (23.9 %) | 67 % | 1 site (36.6%); >1 site (63.4%) |
| | FOLFIRI+ Bev | Bev | 245 | **24 weeks** | 0,1, 2 | 64.2 | mKRAS45.7% | | | Yes 60.2% | right (41.7 %); left (57.6 %); rectum (17.8 %) | 62 % | 1 site (42 %); |
| | | | | | | | | | | | | | |
| **CAIRO3 (2015)**[2] | CapeOx+ Bev | Obs | 279 | 18 weeks | 0,1 | 64 | mRAS 61% | Netherlands; 64 hospitals | After | Yes 60% | colon (52%); rectum (27%); rectosigmoid (21%) | 64 % | 1 site (40 %); >1 site (54 %) |
| | CapeOx+ Bev | Cape+ Bev | 279 | 18 weeks | 0,1 | 63 | mRAS 54% | | | yes 47% | colon (48%); rectum (30%); rectosigmoid (22%) | 65 % | 1 site (42 %); >1 site (54 %) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Luo (2016)[3]** | CapeOx/FOLFOX | Obs | 138 | 18-24 weeks | 0,1 | 54 (23-78) | NR | China; 11 sites | After | Yes 26.8% | colon (60.9%); rectum (39.1%) | 62.3% | NR |
| | CapeOx/FOLFOX | Cape | 136 | 18-24 weeks | 0,1 | 56 (27-78) | NR | | | yes 19.1% | colon (61.8%); rectum (38.2%) | | NR |
| | | | | | | | | | | | | | |
| **Sakk 41/06 (2015)[4]** | Bev +(FPIRI; FPOX; FP) | Obs | 131 | 16-24 weeks | 0,1 | 65 (23-85) | NR | Switzerland; 26 centers | After | Not clear | NR | 73.1% | 1 site (35%); >1 site (65%) |
| | Bev +(FPIRI; FPOX; FP) | Bev | 131 | 16-24 weeks | 0,1 | 63 (40-83) | NR | | | Not clear | NR | 71% | 1 site (37%); >1 site (63%) |
| **Study Title** | **Induction Chemo** | **Maintenance** | **NO of Patients** | **Induction Chemo length** | **ECOG PS** | **Median Age (Range)** | **RAS mutated** | **Study Sites** | **Randomization before or after induction?** | **Was re-induction allowed** | **Location of primary** | **Male %** | **NO of metastatic sites** |
| **AIO 0207 (2015)[5]** | Bev+FPOX | Obs | 158 | 24 weeks | 0,1,2 | 66 (32-82) | mRAS 53% | Germany; 106 centers | After | Yes 46% | colon (63%); rectum (37%) | 63% | 1 site (38%); >1 site |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | (61 %) |
| | Bev+FPOX | Bev | 156 | 24 weeks | 0,1, 2 | 65 (32-82) | mRAS 52% | | | Yes 43% | colon (61%); rectum (39%) | 68 % | 1 site (44 %); >1 site (56 %) |
| | Bev+FPOX | FP+Bev | 157 | 24 weeks | 0,1, 2 | 64 (25-82) | mRAS 49% | | | Yes 19% | colon (65%); rectum (35%) | 67 % | 1 site (45 %); >1 site (54 %) |
| | | | | | | | | | | | | | |
| **CONcePT (2014)[6]** | FOLFOX +Bev | 5-FU/LV +Bev | 71 | 16 weeks | 0,1 | 61 | NR | Multicenter | Before | Yes | colon (83%); rectum (11%) | 50.7% | NR |
| | FOLFOX +Bev | FOLFOX+Bev | 68 | 16 weeks | 0,1 | 62 | NR | | | | colon (76.4 %); rectum (16%) | 58.8% | NR |
| | | | | | | | | | | | | | |
| **Yalcin (2013)[7]** | CapeOx+ Bev | Cape+ Bev | 61 | 18 weeks | 0,1, 2 | 56 (34-82) | NR | Turkey; multicenter | Before | NR | colon (72.4 %); rectum (27.6 %) | 62 % | 1 site (13.1%); >1 site (86.9%) |
| | CapeOx+ Bev | CapeOx+Bev | 62 | 18 weeks | 0,1, 2 | 59 (25-77) | NR | | | | colon (47.5 %); rectum | 63 % | 1 site (47.5%); >1 site |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | (52.5 %) | | (52.5%) |
| | | | | | | | | | | | | | |
| **MACROTTD (2011)[8]** | CapeOx+Bev | CapeOx+Bev | 239 | 18 weeks | 0,1,2 | 63 (30-80) | NR | Spain | Before | Not clear | colon (57%); rectum (31%) | 64 % | NR |
| | CapeOx+Bev | Bev | 241 | 18 weeks | 0,1,2 | 63 (33-82) | NR | | | | colon (66%); rectum (23%) | 64 % | NR |
| **Study Title** | **Induction Chemo** | **Maintenance** | **NO of Patients** | **Induction Chemo length** | **ECOG PS** | **Median Age (Range)** | **RAS mutated** | **Study Sites** | **Randomization before or after induction?** | **Was re-induction allowed** | **Location of primary** | **Male %** | **NO of metastatic sites** |
| | | | | | | | | | | | | | |
| **GISCAD (2011)[9]** | FOLFIRI | FOLFIRI | 146 | 8 weeks | 0,1,2 | 64.6 (30-76) | NR | Italy; 27 centers | Before | Yes (implemented even without progression) | colon (68%); rectum (32%) | 60 % | NR |
| | FOLFIRI | Obs | 147 | 8 weeks | 0,1,2 | 64.2 (29-76) | NR | | | | colon (79%); rectum (21%) | 69 % | NR |
| | | | | | | | | | | | | | |
| **MRC COIN (2011)[10]** | FOLFOX/CapeOx | FOLFOX/CapeOx | 815 | 12 weeks | 0,1,2 | 63 (56-69) | NR | UK and Ireland; 111 centers | Before | | rectum (31%) | 64 % | 1 site (35 %); >1 site (64 %) |
| | FOLFOX/CapeOx | Obs | 815 | 12 weeks | 0,1,2 | 63 (58-70) | NR | | | Yes 64% | rectum (30%) | 64 % | 1 site (35 %); >1 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | site (65 %) |
| | | | | | | | | | | | | | |
| **OPTIMOX2 (2009)[11]** | mFOLFOX7 | Obs | 104 | 12 weeks | 0,1, 2 | 67 (31-80) | NR | 12 centers | Before | yes63% | colon (70.2 %); rectum (25%) | 58.6% | 1 site (51.9%); >1 site (48.1%) |
| | mFOLFOX7 | 5-FU/LV | 98 | 12 weeks | 0,1, 2 | 67 (35-80) | NR | | | yes 55% | colon (61.2 %); rectum (37.8 %) | 60.2% | 1 site (41.8%); >1 site (58.2%) |
| | | | | | | | | | | | | | |
| **OPTIMOX 1 (2006)[12]** | FOLFOX4 | FOLFOX4 | 311 | 12 weeks | 0,1, 2 | 65 (29-80) | NR | 56 centers in 5 countries | Before | | colon (65%); rectum (32%) | 59 % | 1 site (59 %); >1 site (40 %) |
| | FOLFOX7 | 5-FU/LV | 309 | 12 weeks | 0,1, 2 | 64 (32-80) | NR | | | Yes 40% (implemented even without progression) | colon (62%); rectum (36%) | 61 % | 1 site (59 %); >1 site (41 %) |

eTable 1. Baseline characteristics of the included studies. . OBS: observation; CTX: continuing induction chemotherapy; FP: fluoropyrimidine; BEV: bevacizumab.

**eTable 2.** Ranking Probabilities of Different Maintenance Strategies

| Strategy | SUCRA % for OS | SUCRA % for PFS |
|---|---|---|
| **OBS vs. MTC vs. CTX** | | |
| **OBS** | 13.9 | 3.6 |
| **MTC** | 85.7 | 92.2 |
| **CTX** | 50.4 | 54.1 |
| **OBS vs. BEV vs. FP vs. FP+Bev vs. CTX** | | |
| **OBS** | 0.3 | 0.3 |
| **Bev** | 32.6 | 36.5 |
| **FP** | 81.3 | 67.1 |
| **FP + Bev** | 73.2 | 99.8 |
| **CTX** | 46 | 46.3 |

Table illustrating ranking probabilities of different maintenance strategies. SUCRA: surface under the cumulative ranking; OS: overall survival; PFS: progression free survival; Obs: observation; MTC: maintenance; CTX: continuing induction regimen; Bev: bevacizumab; FP: fluoropyrimidine.

**eTable 3.** Quality of Evidence Table (GRADE)

| Certainty assessment | | | | | | | Effect | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | HR* (95% CI) | | |
| **MTC vs OBS - Overall survival** | | | | | | | | | |
| Network meta-analysis (6 trials) | Randomized trials | not serious † | not serious | not serious | Serious** | none | **HR 0.91** (0.83 - 1.009) | ⊕⊕⊕◯ Moderate | Critical |
| **CTX vs OBS - Overall survival** | | | | | | | | | |
| Network meta-analysis (2 trials) | Randomized trials | not serious † | not serious | not serious | Serious** | none | **HR 0.95** (0.85 - 1.07) | ⊕⊕⊕◯ Moderate | Critical |
| **CTX vs OBS - Overall survival** | | | | | | | | | |
| Network meta-analysis (3 trials) | Randomized trials | not serious † | not serious | not serious | Serious** | none | **HR 1.04** (0.92 - 1.17) | ⊕⊕⊕◯ Moderate | Critical |

**CI:** Confidence interval; **HR:** Hazard ratio

* Insufficient data to estimate absolute effects

**Confidence intervals include appreciable benefits and harms

† Although risk of bias is moderate for the included studies due to lack of blinding of outcome assessments, but the outcome of overall survival is independent of blinded assessment.

**eTable 4.** Adverse Events

| Study ID | Arm | NO | HTN | Thrombosis | Any Hematologic AEs | HFSR | Any GI AEs | Mucositis | Increased ALT/AST | Increased Bili | Neuropathy | All grade 3 or higher | Number that discontinued due to AE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PRODIGE9 (Aparicio 2018)** [1] | Obs | 243 | 2 (0.8%) | 1 (0.4%) | 2 (0.8%) | NR | 9 (3.7%) | NR | 1 (0.4%) | 2 (0.8) | NR | 34 (14%) | NR |
| | Bev | 245 | 15 (6.1%) | 5 (2%) | 2 (0.8%) | NR | 10 (4.1%) | NR | 6 (2.4%) | 8 (3.3%) | NR | 81 (33.1%) | NR |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **CAIRO3*(Goey2017; Simkens 2015)** [2,13] | Obs | 279 | 49 (18%) | NR | NR | 0% | NR | NR | NR | 1 (<1%) | 14 (5%) | 95 (34%) | NR |
| | FP+Bev | 278 | 68 (24%) | NR | NR | 64 (23%) | NR | NR | NR | 14 (5%) | 27 (10%) | 167 (60%) | 27 (10%) |
| | | | | | | | | | | | | | |
| **Luo 2016**[3] | Obs | 138 | NR | NR | 18 (13%) | 1 (0.7%) | 7 (5%) | 4 (2.9%) | NR | NR | NR | 31 (22.4%) | NR |
| | FP | 136 | NR | NR | 28 (22.5%) | 8 (5.9%) | 10 (7.3%) | 8 (5.9%) | NR | NR | NR | 57 (41.9%) | NR |
| | | | | | | | | | | | | | |
| **Sakk 41/06**[4] | Obs | 131 | 1 (<1%) | 0 | NR | NR | NR | NR | NR | NR | NR | 1 (1%) | NR |
| | Bev | 131 | 6 (4.5%) | 2 (1.5%) | NR | NR | NR | NR | NR | NR | NR | 8 (6%) | 0 |
| | | | | | | | | | | | | | |
| **AIO 0207 (Hegewisch-Becker 2015; Noepel-Duennebacke 2018)** [5,14] | obs | 158 | 2 (1%) | 2 (1%) | 1 (<1%) | 1 (<1%) | 0 | 1 (<1%) | 0 | NR | NR | NR | NR |

| Study ID | Arm | NO | HTN | Thrombosis | Any Hematologic AEs | HFSR | Any GI AEs | Mucositis | Increased ALT/AST | Increased Bili | Neuropathy | All grade 3 or higher | Number that discontinued due to AE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | bev | 156 | 3 (2%) | 1 (<1%) | 4 (3%) | 1 (1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | NR | NR | NR | NR |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| | obs | 158 | 2 (1%) | 2 (1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 0 | NR | NR | NR | NR |
| | FP+bev | 158 | 5 (3%) | 3 (2%) | 3 (2%) | 4 (3%) | 5 (3%) (+1 perforation) | 1 (<1%) | 0 | NR | NR | NR | NR |
| | | | | | | | | | | | | | |
| | bev | 156 | 3 (2%) | 2 (1%) | 4 (3%) | 1 (<1%) | 0 | 1 (<1%) | 1 (<1%) | NR | NR | NR | NR |
| | FP+bev | 158 | 5 (3%) | 3 (2%) | 3 (2%) | 4 (3%) | 5 (3%) (+1 perforation) | 1 (<1%) | 0 | NR | NR | NR | NR |
| | | | | | | | | | | | | | |
| **CONcePT [6]** | FP+bev | 36 | 1 (2.8%) | NR | 6 (16.7%) | 0 | 9 (9.8%) | NR | NR | NR | 4 (11.1%) | 6 (16.7%) | NR |
| | Cont | 33 | 1 (3%) | NR | 9 (27.3%) | 0 | 4 (12.1%) | NR | NR | NR | 10 (30.3%) | 8 (24%) | NR |
| | | | | | | | | | | | | | |
| **Yalcin 2013[7]** | FP+bev | 61 | 3.30 % | NR | 3.30% | 1.60 % | 9.80% | NR | NR | NR | 1.60% | 34.40 % | 6 |
| | Cont | 62 | 1.60 % | NR | 11.30% | 1.60 % | 22.60% | NR | NR | NR | 8.10% | 48.40 % | 9 |
| | | | | | | | | | | | | | |
| **MACRO TTD[8]** | Cont | 238 | 9 (4%) | 2 (<1%) | NR | 30 (13%) | 26 (11%) * 2 perforations | NR | NR | NR | 61 (26%) | 132 (55%) | 132 (55%) |
| | bev | 238 | 17 (7%) | 3 (1%) | NR | 16 (7%) | 31 (13%) *1 perforation | NR | NR | NR | 18 (8%) | 114 (47%) | 114 (47%) |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **GISCAD[9]** | cont | 146 | NR | NR | 11 (7.5%) | NR | 32 (21.9%) | 0 | 21 (14.4%) | NR | NR | NR | 6 (4.1%) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | obs | 147 | NR | NR | 8 (5.4%) | NR | 29 (19.7%) | 0 | 15 (10.2%) | NR | NR | NR | NR |
| | | | | | | | | | | | | | |
| **MRC COIN** [10] | cont | 815 | NR | NR | 75 (9.2%) | 21 (5%) | 55 (6.7%) | NR | NR | NR | 126 (27%) | NR | NR |
| | Obs | 815 | NR | NR | 62 (7.6%) | 15 (3%) | 105 (12.9%) | NR | NR | NR | 25 (5%) | NR | NR |
| | | | | | | | | | | | | | |
| **OPTIMOX2**[11] | Obs | 104 | NR | NR | NR | | 0 | NR | NR | NR | NR | NR | NR |
| | FP | 98 | NR | NR | 11.40% | 4.90 % | NR | 0.30% | NR | NR | 4.90% | NR | NR |
| | | | | | | | | | | | | | |
| **OPTIMOX 1**[12] | cont | 311 | NR | NR | 38.00% | NR | 16% | 3.00% | NR | NR | 18% | 54.40 % | NR |
| | FP | 309 | NR | NR | 31% | NR | 20% | 6% | NR | NR | 13% | 48.20 % | NR |

NO: number of patients; HTN: hypertension; AEs: adverse events; HFSR: hand-foot skin reaction; GI: gastrointestinal; NR: not reported. * reported only AEs that occurred in >5% frequency.

**eMethods.** Search Strategy

**4.25.19 PubMed Search Strategy (2133)**: Search: ((((((((((("Antineoplastic Agents"[Mesh] OR "Antineoplastic Combined Chemotherapy Protocols"[Mesh])) OR bevacizumab) OR 5-fu) OR capecitabine) OR fluoropyrimidine) OR avastin) OR panitumumab) OR cetuximab) OR (oxaliplatin OR folfox))) AND ((((("colorectal cancer") OR "Colorectal Neoplasms"[Mesh])) AND (("Neoplasm Metastasis"[Mesh]) OR (advanced OR metastat* OR metastas*))))) AND ((("Drug Administration Schedule"[Mesh]) OR (continuous AND intermittent)) OR (maintenance[tiab] OR "stop and go" OR continuous[tiab] OR continuation[tiab] OR intermittent[tiab])) Filters: to 2019/04/01, English

**4.25.19 Database: Embase <1988 to 2019 Week 16> Search Strategy (2804)**

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1 exp colorectal cancer/ or exp colorectal carcinoma/ (159163)
2 exp antineoplastic agent/ (1856057)
3 bevacizumab.mp. (53811)
4 5-fu.mp. or fluorouracil/ (117969)
5 capecitabine plus oxaliplatin/ or capecitabine.mp. (27797)
6 fluoropyrimidine.mp. (6890)
7 avastin.mp. (9746)
8 panitumumab.mp. (7766)
9 cetuximab.mp. (26570)
10 oxaliplatin.mp. (36647)
11 folfox.mp. (4315)
12 exp combination chemotherapy/ (111963)
13 exp cancer combination chemotherapy/ (77024)
14 advanced.ti. or advanced.ab. (531272)
15 exp advanced cancer/ (86727)
16 metastatic.mp. (303605)
17 metastasis.mp. or metastasis/ (594668)
18 metastases.mp. (198745)
19 14 or 15 or 16 or 17 or 18 (1170703)
20 1 and 19 (61636)
21 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1879733)
22 (continuous or intermittent or maintenance or continuation).ab. or (continuous or intermittent or maintenance or continuation).ti. (810007)
23 stop-and-go.mp. (514)
24 drug administration schedule.mp. (186)
25 exp drug intermittent therapy/ (4181)
26 exp continuous infusion/ (40617)
27 exp maintenance therapy/ (50009)
28 22 or 23 or 24 or 25 or 26 or 27 (852830)
29 20 and 21 and 28 (2963)
30 limit 29 to english language (2821)
31 201904*.em. (65374)
32 30 not 31 (2804)

**5.1.19 Scopus (1821)** ( ( ( TITLE-ABS-KEY ( "colorectal cancer" ) AND TITLE-ABS-KEY ( advanced OR metastatic OR metastasis OR metastases ) ) ) AND ( ( TITLE-ABS-KEY ( "antineoplastic combined chemotherapy" ) OR TITLE-ABS-KEY ( bevacizumab OR f-fu OR capecitabine OR fluorpyrimidine OR avastin OR panitumumab OR cetuximab OR oxaliplatin OR folfox ) OR TITLE-ABS-KEY ( "combination chemotherapy" OR "cancer combinatin chemotherapy" ) ) ) AND ( TITLE-ABS-KEY ( continuous OR intermittent OR maintenance OR stop-and-go ) ) ) AND NOT ( PUBDATETXT ( april 2019 ) OR PUBDATETXT ( may 2019 ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) )

**5.1.19 Web of Science (1190)**
TOPIC: (" advanced colorectal cancer" OR "metastatic colorectal cancer") *AND*
TOPIC: ("antineoplastic combined chemotherapy") OR TOPIC: (bevacizumab OR avastin OR 5-fu OR capecitabine OR fluoropyrimidine OR panitumumab OR cetuximab OR oxaliplatin OR folfox) AND TOPIC: (continuous OR maintenance OR intermittent OR continuation) Refined by: LANGUAGES: ( ENGLISH ) Indexes=SCI-EXPANDED, ESCI Timespan=All years

**5.1.19 Cochrane Database of Systematic Reviews <2005 to April 26, 2019> Search Strategy: (43)**
**---**
1 colorectal cancer.mp. [mp=title, short title, abstract, full text, keywords, caption text] (275)
2 colorectal carcinoma.mp. [mp=title, short title, abstract, full text, keywords, caption text] (32)
3 advanced.mp. [mp=title, short title, abstract, full text, keywords, caption text] (1821)
4 metastatic.mp. [mp=title, short title, abstract, full text, keywords, caption text] (431)
5 metastasis.mp. [mp=title, short title, abstract, full text, keywords, caption text] (303)
6 metastases.mp. [mp=title, short title, abstract, full text, keywords, caption text] (362)
7 3 or 4 or 5 or 6 (2054)
8 1 or 2 (279)
9 7 and 8 (153)
10 combination chemotherapy.mp. [mp=title, short title, abstract, full text, keywords, caption text] (88)
11 combined chemotherapy.mp. [mp=title, short title, abstract, full text, keywords, caption text] (119)
12 antineoplastic combined chemotherapy.mp. [mp=title, short title, abstract, full text, keywords, caption text] (107)
13 antineoplastic agents.mp. [mp=title, short title, abstract, full text, keywords, caption text] (217)
14 (bevacizumab or 5-fu or capecitabine or fluoropyrimidine or avastin or panitumumab or cetuximab or oxaliplatin or folfox).mp. [mp=title, short title, abstract, full text, keywords, caption text] (177)
15 10 or 11 or 12 or 13 or 14 (389)
16 9 and 15 (57)
17 (continuous or continuation or maintenance or intermittent).mp. [mp=title, short title, abstract, full text, keywords, caption text] (8118)
18 16 and 17 (43)

**9.7.18 Author supplied (13)**

| DATABASE | RESULTS | DUPLICATES | REMAINING |
|---|---|---|---|
| PubMed | 2133 | 28 | 2105 |
| Embase | 2804 | 879 | 1925 |
| Scopus | 1821 | 1661 | 160 |
| Web of Science | 1190 | 693 | 497 |
| Cochrane Database of Systematic Reviews | 43 | 2 | 41 |
| **TOTAL** | 7991 | 3263 | 4728 |

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