**Systematic literature review and network meta-analysis of pembrolizumab versus other interventions for previously untreated, unresectable or metastatic, microsatellite instability-high or mismatch repair deficient colorectal cancer**

**Supplementary Tables**

Table S1: Search strategy for Embase

Database: Embase 1974 to July 12, 2019

Search executed on July 15, 2019

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Criteria | Strings | Hits |
| 1 | SIGN filter for clinical trials | Clinical Trial/ | 960,800 |
| 2 | Randomized Controlled Trial/ | 558,380 |
| 3 | controlled clinical trial/ | 464,023 |
| 4 | multicenter study/ | 221,201 |
| 5 | Phase 3 clinical trial/ | 40,735 |
| 6 | Phase 4 clinical trial/ | 3,473 |
| 7 | exp RANDOMIZATION/ | 83,369 |
| 8 | Single Blind Procedure/ | 35,752 |
| 9 | Double Blind Procedure/ | 162,673 |
| 10 | Crossover Procedure/ | 59,859 |
| 11 | PLACEBO/ | 337,644 |
| 12 | randomi?ed controlled trial$.tw. | 206,375 |
| 13 | rct.tw. | 33,023 |
| 14 | (random$ adj2 allocat$).tw. | 40,273 |
| 15 | single blind$.tw. | 23,241 |
| 16 | double blind$.tw. | 199,780 |
| 17 | ((treble or triple) adj blind$).tw. | 987 |
| 18 | placebo$.tw. | 292,535 |
| 19 | Prospective Study/ | 532,956 |
| 20 | or/1-19 | 2,163,784 |
| 21 | Case Study/ | 62,350 |
| 22 | case report.tw. | 387,117 |
| 23 | abstract report/ or letter/ | 1,111,876 |
| 24 | Conference proceeding.pt. | 0 |
| 25 | Conference abstract.pt. | 3,465,656 |
| 26 | Editorial.pt. | 624,297 |
| 27 | Letter.pt. | 1,075,753 |
| 28 | Note.pt. | 762,274 |
| 29 | or/21-28 | 6,354,079 |
| 30 | 20 not 29 | 1,629,662 |
| 31 | Population terms | exp colorectal cancer/ | 164,843 |
| 32 | (colorectal cancer or colorectal neoplasm or colorectal carcinoma).mp. | 200,650 |
| 33 | 31 or 32 | 201,001 |
| 34 | Intervention terms | exp pembrolizumab/ | 9,946 |
| 35 | (pembrolizumab or MK-3475 or MK3475 or lambrolizumab or keytruda).mp. | 10,545 |
| 36 | (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. | 1,306 |
| 37 | (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. | 3,235 |
| 38 | exp nivolumab/ | 12,029 |
| 39 | (nivolumab or ONO-4538 or BMS-936558 or MDX1106 or opdivo).mp. | 12,605 |
| 40 | exp atezolizumab/ | 3,152 |
| 41 | (atezolizumab or MPDL-3280A or MPDL3280A or RO5541267 or tecentriq).mp. | 3,589 |
| 42 | exp panitumumab/ | 7,590 |
| 43 | (panitumumab or vectibix or ABX-EGF).mp. | 7,912 |
| 44 | exp raltitrexed/ | 2,314 |
| 45 | (raltitrexed disodium or ZD-1694).mp. | 250 |
| 46 | (Folinic Acid or leucovorin or folate).mp. | 69,071 |
| 47 | (Fluorouracil or 5-fluorouracil or 5FU or 5-FU or edufex or fluoroplex or carac or adrucil or tolak).mp. | 139,149 |
| 48 | exp capecitabine/ | 26,957 |
| 49 | (capecitabine or xeloda).mp. | 28,444 |
| 50 | (Irinotecan or camptosar or onivyde).mp. | 36,756 |
| 51 | (Oxaliplatin or eloxatin).mp. | 37,583 |
| 52 | exp cetuximab/ | 26,270 |
| 53 | (cetuximab or erbitux).mp. | 27,100 |
| 54 | (FOLFOX or FOLFOX6 or FOLFOX-6).mp. | 4,740 |
| 55 | exp tegafur/ | 6,468 |
| 56 | (tegafur or ftorafur or Tetrahydrofuranyl-5-Fluorouracil or UFT or UFUR or fluorouracil or "tegafur/uracil" or tegafur-uracil).mp | 144,791 |
| 57 | or/34-56 | 259,285 |
| 58 | Combined | 30 and 33 and 57 | 8,937 |
| 59 | Language | limit 58 to english | 8,259 |

Table S2: Search strategy for MEDLINE

Databases: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to July 12, 2019

Search executed on July 15, 2019

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Criteria | Strings | Hits |
| 1 | SIGN filter for clinical trials | Randomized Controlled Trials as Topic/ | 125,042 |
| 2 | randomized controlled trial/ | 485,397 |
| 3 | Random Allocation/ | 99,596 |
| 4 | Double Blind Method/ | 152,159 |
| 5 | Single Blind Method/ | 27,029 |
| 6 | clinical trial/ | 516,915 |
| 7 | clinical trial, phase i.pt | 19,114 |
| 8 | clinical trial, phase ii.pt | 30,820 |
| 9 | clinical trial, phase iii.pt | 15,229 |
| 10 | clinical trial, phase iv.pt | 1,727 |
| 11 | controlled clinical trial.pt | 93,156 |
| 12 | randomized controlled trial.pt | 485,397 |
| 13 | multicenter study.pt | 253,038 |
| 14 | clinical trial.pt | 516,915 |
| 15 | exp Clinical Trials as topic/ | 327,892 |
| 16 | or/1-15 | 1,302,384 |
| 17 | (clinical adj trial$).tw | 337,005 |
| 18 | ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw | 164,872 |
| 19 | PLACEBOS/ | 34,402 |
| 20 | placebo$.tw | 205,672 |
| 21 | randomly allocated.tw | 26,546 |
| 22 | (allocated adj2 random$).tw | 29,718 |
| 23 | or/17-22 | 594,981 |
| 24 | 16 or 23 | 1,547,712 |
| 25 | case report.tw | 290,868 |
| 26 | letter/ | 1,034,075 |
| 27 | historical article/ | 352,747 |
| 28 | or/25-27 | 1,662,674 |
| 29 | 24 not 28 | 1,512,663 |
| 30 | Population terms | exp colorectal cancer/ | 190,766 |
| 31 | (colorectal cancer or colorectal neoplasm or colorectal carcinoma).mp. | 100,768 |
| 32 | 30 or 31 | 217,120 |
| 33 | Intervention terms | (pembrolizumab or MK-3475 or MK3475 or lambrolizumab or keytruda).mp. | 2,706 |
| 34 | (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. | 701 |
| 35 | (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. | 1,330 |
| 36 | (nivolumab or ONO-4538 or BMS-936558 or MDX1106 or opdivo).mp. | 3,659 |
| 37 | (atezolizumab or MPDL-3280A or MPDL3280A or RO5541267 or tecentriq).mp. | 723 |
| 38 | (panitumumab or vectibix or ABX-EGF).mp. | 1,682 |
| 39 | (raltitrexed disodium or ZD-1694).mp. | 8 |
| 40 | (Folinic Acid or leucovorin or folate).mp. | 37,342 |
| 41 | (Fluorouracil or 5-fluorouracil or 5FU or 5-FU or edufex or fluoroplex or carac or adrucil or tolak).mp. | 54,911 |
| 42 | (capecitabine or xeloda).mp. | 6,519 |
| 43 | (Irinotecan or camptosar or onivyde).mp. | 10,375 |
| 44 | (Oxaliplatin or eloxatin).mp. | 10,676 |
| 45 | exp cetuximab/ | 4,127 |
| 46 | (cetuximab or erbitux).mp. | 6,848 |
| 47 | (FOLFOX or FOLFOX6 or FOLFOX-6).mp. | 2,759 |
| 48 | exp tegafur/ | 5,540 |
| 49 | (tegafur or ftorafur or Tetrahydrofuranyl-5-Fluorouracil or UFT or UFUR or fluorouracil or "tegafur/uracil" or tegafur-uracil).mp | 56,471 |
| 50 | or/33-48 | 108,558 |
| 51 | Combined | 29 and 32 and 50 | 6,814 |
| 52 | Language | limit 51 to english | 6,162 |

Table S3: Search strategy for CENTRAL

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials October 2019

Search executed on July 15, 2019

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Criteria | Strings | Hits |
| 1 | Population terms | exp colorectal cancer/ | 7,110 |
| 2 | colorectal cancer.mp. | 11,888 |
| 3 | 1 or 2 | 15,167 |
| 4 | Intervention terms | (pembrolizumab or MK-3475 or MK3475 or lambrolizumab or keytruda).mp. | 1,042 |
| 5 | (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. | 490 |
| 6 | (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. | 943 |
| 7 | (nivolumab or ONO-4538 or BMS-936558 or MDX1106 or opdivo).mp. | 1,322 |
| 8 | (atezolizumab or MPDL-3280A or MPDL3280A or RO5541267 or tecentriq).mp. | 490 |
| 9 | (panitumumab or vectibix or ABX-EGF).mp. | 642 |
| 10 | (raltitrexed disodium or ZD-1694).mp. | 1 |
| 11 | (Folinic Acid or leucovorin or folate).mp. | 5,854 |
| 12 | (Fluorouracil or 5-fluorouracil or 5FU or 5-FU or edufex or fluoroplex or carac or adrucil or tolak).mp. | 11,702 |
| 13 | (capecitabine or xeloda).mp. | 3,510 |
| 14 | (Irinotecan or camptosar or onivyde).mp. | 2,995 |
| 15 | (Oxaliplatin or eloxatin).mp. | 4,015 |
| 16 | (FOLFOX or FOLFOX6 or FOLFOX-6).mp. | 1,106 |
| 17 | (cetuximab or erbitux).mp. | 2,107 |
| 18 | exp tegafur/ | 549 |
| 19 | (tegafur or ftorafur or Tetrahydrofuranyl-5-Fluorouracil or UFT or UFUR or fluorouracil or "tegafur/uracil" or tegafur-uracil).mp | 10,939 |
| 20 | or/4-19 | 23,701 |
| 21 | Combined | 3 and 20 | 5,482 |
| 22 | Language | limit 21 to english | 3,275 |

Table S4: Search strategy for Embase - Update

Database: Embase 1974 to April 27, 2020

Search executed: April 28, 2020

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Criteria | Strings | Hits |
| 1 | Population terms | exp colorectal cancer/ |  177,266  |
| 2 | (colorectal cancer or colorectal neoplasm or colorectal carcinoma).mp. |  215,560  |
| 3 | or/1-2 |  215,930  |
| 4 | Intervention terms | exp pembrolizumab/ |  14,209  |
| 5 | (pembrolizumab or MK-3475 or MK3475 or lambrolizumab or keytruda).mp. |  15,010  |
| 6 | exp Nivolumab/ |  16,512  |
| 7 | (nivolumab or ONO-4538 or ONO 4538 or BMS-936558 or BMS 936558 or MDX-1106 or MDX 1106 or MDX1106 or opdivo).mp. |  17,366  |
| 8 | exp atezolizumab/ |  4,681  |
| 9 | (atezolizumab or MPDL-3280A or MPDL3280A or RO5541267 or tecentriq).mp. |  5,202  |
| 10 | exp panitumumab/ |  8,005  |
| 11 | (panitumumab or vectibix or ABX-EGF).mp. |  8,358  |
| 12 | (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. |  1,458  |
| 13 | (FOLFOX\* or FOLFOX6 or FOLFOX-6 or "folfox regimen").mp. |  6,242  |
| 14 | (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. |  3,604  |
| 15 | exp ipilimumab/ |  13,436  |
| 16 | ("Anti-CTLA-4 MAb" or "Anti CTLA 4 MAb Ipilimumab" or "Ipilimumab, Anti-CTLA-4 Mab" or Yervoy or "MDX 010" or "MDX010" or "MDX-010" or "MDX-CTLA-4" or "MDX CTLA 4").mp. |  1,284  |
| 17 | exp bevacizumab/ |  57,246  |
| 18 | (Bevacizumab or Mvasi or "Bevacizumab-awwb" or "Bevacizumab awwb" or Avastin).mp. |  58,930  |
| 19 | exp raltitrexed/ |  2,352  |
| 20 | (raltitrexed disodium or ICI D1694 or ICI-D1694 or ZD-1694 or ZD 1694 or D 1694 or D-1694 or Tomudex).mp. |  808  |
| 21 | exp Leucovorin/ |  36,321  |
| 22 | (Folinic Acid\* or leucovorin\* or folate).mp. |  72,022  |
| 23 | exp fluorouracil/ |  136,981  |
| 24 | (Fluorouracil or 5-fluorouracil or 5FU or 5-FU or edufex or fluoroplex or carac or adrucil or tolak).mp. |  144,121  |
| 25 | exp capecitabine/ |  28,688  |
| 26 | (capecitabine or Xeloda).mp. |  30,404  |
| 27 | exp irinotecan/ |  37,389  |
| 28 | (Irinotecan or CPT-11 or camptosar or onivyde).mp. |  39,134  |
| 29 | exp oxaliplatin/ |  38,806  |
| 30 | (Oxaliplatin or eloxatin).mp. |  40,765  |
| 31 | exp cetuximab/ |  27,750  |
| 32 | (cetuximab or erbitux).mp. |  28,663  |
| 33 | exp tegafur/ |  6,596  |
| 34 | (tegafur or ftorafur or Tetrahydrofuranyl-5-Fluorouracil or UFT or UFUR or fluorouracil or "tegafur/uracil" or tegafur-uracil).mp |  149,945  |
| 35 | or/4-34 |  316,648  |
| 36 | SIGN filter for clinical trials | Clinical Trial/ |  974,317  |
| 37 | Randomized Controlled Trial/ |  601,675  |
| 38 | controlled clinical trial/ |  464,105  |
| 39 | multicenter study/ |  249,739  |
| 40 | Phase 3 clinical trial/ |  46,875  |
| 41 | Phase 4 clinical trial/ |  3,857  |
| 42 | exp RANDOMIZATION/ |  87,020  |
| 43 | Single Blind Procedure/ |  38,786  |
| 44 | Double Blind Procedure/ |  171,947  |
| 45 | Crossover Procedure/ |  62,964  |
| 46 | PLACEBO/ |  349,595  |
| 47 | randomi?ed controlled trial$.tw. |  226,621  |
| 48 | rct.tw. |  36,742  |
| 49 | (random$ adj2 allocat$).tw. |  42,720  |
| 50 | single blind$.tw. |  24,788  |
| 51 | double blind$.tw. |  208,529  |
| 52 | ((treble or triple) adj blind$).tw. |  1,160  |
| 53 | placebo$.tw. |  306,739  |
| 54 | Prospective Study/ |  596,686  |
| 55 | or/36-54 |  2,305,684  |
| 56 | Case Study/ |  68,503  |
| 57 | case report.tw. |  410,313  |
| 58 | abstract report/ or letter/ |  1,141,887  |
| 59 | Conference proceeding.pt. |  -  |
| 60 | Conference abstract.pt. |  3,764,535  |
| 61 | Editorial.pt. |  650,996  |
| 62 | Letter.pt. |  1,112,321  |
| 63 | Note.pt. |  794,343  |
| 64 | or/56-63 |  6,766,492  |
| 65 | 55 not 64 |  1,713,849  |
| 66 | Combined | 3 AND 35 AND 65 |  9,773  |
| 67 | Language | Limit 66 to English Language |  9,067  |
| 67 | Time | limit 67 to dc=20190715-20200428 |  423  |

Table S5: Search strategy for MEDLINE

Databases: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 27, 2020

Search executed: April 28, 2020

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Criteria | Strings | Hits |
| 1 | Population terms | exp colorectal cancer/ |  198,609  |
| 2 | (colorectal cancer or colorectal neoplasm or colorectal carcinoma).mp. |  108,136  |
| 3 | or/1-2 |  227,879  |
| 4 | Intervention terms | (pembrolizumab or MK-3475 or MK3475 or lambrolizumab or keytruda).mp. |  3,748  |
| 5 | exp Nivolumab/ |  2,218  |
| 6 | (nivolumab or ONO-4538 or ONO 4538 or BMS-936558 or BMS 936558 or MDX-1106 or MDX 1106 or MDX1106 or opdivo).mp. |  4,755  |
| 7 | (atezolizumab or MPDL-3280A or MPDL3280A or RO5541267 or tecentriq).mp. |  996  |
| 8 | exp panitumumab/ |  956  |
| 9 | (panitumumab or vectibix or ABX-EGF).mp. |  1,793  |
| 10 | (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. |  742  |
| 11 | (FOLFOX\* or FOLFOX6 or FOLFOX-6 or "folfox regimen").mp. |  3,289  |
| 12 | (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. |  1,429  |
| 13 | exp ipilimumab/ |  1,786  |
| 14 | ("Anti-CTLA-4 MAb" or "Anti CTLA 4 MAb Ipilimumab" or "Ipilimumab, Anti-CTLA-4 Mab" or Yervoy or "MDX 010" or "MDX010" or "MDX-010" or "MDX-CTLA-4" or "MDX CTLA 4").mp. |  191  |
| 15 | exp bevacizumab/ |  11,369  |
| 16 | (Bevacizumab or Mvasi or "Bevacizumab-awwb" or "Bevacizumab awwb" or Avastin).mp. |  17,984  |
| 17 | (raltitrexed disodium or ICI D1694 or ICI-D1694 or ZD-1694 or ZD 1694 or D 1694 or D-1694 or Tomudex).mp. |  246  |
| 18 | exp Leucovorin/ |  9,939  |
| 19 | (Folinic Acid\* or leucovorin\* or folate).mp. |  38,779  |
| 20 | exp fluorouracil/ |  46,264  |
| 21 | (Fluorouracil or 5-fluorouracil or 5FU or 5-FU or edufex or fluoroplex or carac or adrucil or tolak).mp. |  56,561  |
| 22 | exp capecitabine/ |  4,222  |
| 23 | (capecitabine or Xeloda).mp. |  6,934  |
| 24 | exp irinotecan/ |  6,906  |
| 25 | (Irinotecan or CPT-11 or camptosar or onivyde).mp. |  11,245  |
| 26 | exp oxaliplatin/ |  6,290  |
| 27 | (Oxaliplatin or eloxatin).mp. |  11,595  |
| 28 | exp cetuximab/ |  4,392  |
| 29 | (cetuximab or erbitux).mp. |  7,275  |
| 30 | exp tegafur/ |  5,686  |
| 31 | (tegafur or ftorafur or Tetrahydrofuranyl-5-Fluorouracil or UFT or UFUR or fluorouracil or "tegafur/uracil" or tegafur-uracil).mp |  58,139  |
| 32 | or/4-31 |  131,720  |
| 33 | SIGN filter for clinical trials | Randomized Controlled Trials as Topic/ |  132,273  |
| 34 | randomized controlled trial/ |  504,474  |
| 35 | Random Allocation/ |  102,598  |
| 36 | Double Blind Method/ |  157,262  |
| 37 | Single Blind Method/ |  28,409  |
| 38 | clinical trial/ |  522,356  |
| 39 | clinical trial, phase i.pt |  20,201  |
| 40 | clinical trial, phase ii.pt |  32,449  |
| 41 | clinical trial, phase iii.pt |  16,500  |
| 42 | clinical trial, phase iv.pt |  1,866  |
| 43 | controlled clinical trial.pt |  93,636  |
| 44 | randomized controlled trial.pt |  504,474  |
| 45 | multicenter study.pt |  270,384  |
| 46 | clinical trial.pt |  522,356  |
| 47 | exp Clinical Trials as topic/ |  339,355  |
| 48 | or/33-47 |  1,355,450  |
| 49 | (clinical adj trial$).tw |  360,848  |
| 50 | ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw |  171,151  |
| 51 | PLACEBOS/ |  34,831  |
| 52 | placebo$.tw |  213,827  |
| 53 | randomly allocated.tw |  28,236  |
| 54 | (allocated adj2 random$).tw |  31,518  |
| 55 | or/49-54 |  627,776  |
| 56 | 48 or 55 |  1,618,340  |
| 57 | case report.tw |  306,811  |
| 58 | letter/ |  1,072,443  |
| 59 | historical article/ |  357,756  |
| 60 | or/57-59 |  1,721,316  |
| 61 | 56 NOT 60 |  1,581,754  |
| 62 | Combined | 3 AND 32 AND 61 |  7,406  |
| 63 | Language | Limit 62 to English Language |  6,737  |
| 64 | Time | limit 63 to dt=20190715-20200428 |  120  |

Table S6: Search strategy for CENTRAL

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials March 2020

Search executed on April 28, 2020

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Criteria | Strings | Hits |
| 1 | Population terms | exp colorectal cancer/ |  7,955  |
| 2 | (colorectal cancer or colorectal neoplasm or colorectal carcinoma).mp. |  13,827  |
| 3 | or/1-2 |  17,254  |
| 4 | Intervention terms | (pembrolizumab or MK-3475 or MK3475 or lambrolizumab or keytruda).mp. |  1,425  |
| 5 | (nivolumab or ONO-4538 or ONO 4538 or BMS-936558 or BMS 936558 or MDX-1106 or MDX 1106 or MDX1106 or opdivo).mp. |  1,690  |
| 6 | (atezolizumab or MPDL-3280A or MPDL3280A or RO5541267 or tecentriq).mp. |  684  |
| 7 | (panitumumab or vectibix or ABX-EGF).mp. |  711  |
| 8 | (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6 ).mp. |  582  |
| 9 | (FOLFOX\* or FOLFOX6 or FOLFOX-6 or "folfox regimen").mp. |  1,679  |
| 10 | (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. |  1,068  |
| 11 | ("Anti-CTLA-4 MAb" or "Anti CTLA 4 MAb Ipilimumab" or "Ipilimumab, Anti-CTLA-4 Mab" or Yervoy or "MDX 010" or "MDX010" or "MDX-010" or "MDX-CTLA-4" or "MDX CTLA 4").mp. |  121  |
| 12 | (Bevacizumab or Mvasi or "Bevacizumab-awwb" or "Bevacizumab awwb" or Avastin).mp. |  6,386  |
| 13 | (raltitrexed disodium or ICI D1694 or ICI-D1694 or ZD-1694 or ZD 1694 or D 1694 or D-1694 or Tomudex).mp. |  56  |
| 14 | (Folinic Acid\* or leucovorin\* or folate).mp. |  6,342  |
| 15 | (Fluorouracil or 5-fluorouracil or 5FU or 5-FU or edufex or fluoroplex or carac or adrucil or tolak).mp. |  12,415  |
| 16 | (capecitabine or Xeloda).mp. |  3,936  |
| 17 | (Irinotecan or CPT-11 or camptosar or onivyde).mp. |  3,447  |
| 18 | (Oxaliplatin or eloxatin).mp. |  4,539  |
| 19 | (cetuximab or erbitux).mp. |  2,342  |
| 20 | exp tegafur/ |  580  |
| 21 | (tegafur or ftorafur or Tetrahydrofuranyl-5-Fluorouracil or UFT or UFUR or fluorouracil or "tegafur/uracil" or tegafur-uracil).mp |  11,548  |
| 22 | or/4-21 |  30,562  |
| 23 | Combined | 3 AND 22 |  6,462  |
| 24 | Language | limit 23 to english  |  3,726  |
| 25 | Time | limit 24 to up=201907-202004 |  1,011  |

Table S7: Eligibility criteria from trials included in systematic review

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial ID** | **NCT code** | **Age** | **Study population** | **Performance score** | **Life expectancy** | **Prior chemotherapy** |
| **Included in network meta-analysis** |
| **Falcone et al., 2007** | NCT01219920 | 18 - 75 years | mCRC | ECOG 0-2 | -- | No previous palliative chemotherapy for metastatic disease; No previous chemotherapy including irinotecan or oxaliplatin |
| **GOIM 2802** | 2010-022091-31 | ≥ 18 years | mCRC | ECOG 0-1 | -- | No previous first line chemotherapy treatment; No more than one line of treatment |
| **KEYNOTE 177** | NCT02563002 | ≥ 18 years | dMMR or MSI-H stage IV CRC (100% MSI-h mCRC patients) | ECOG 0-1 | ≥ 3 months | No prior chemotherapy |
| **METHEP** | NCT00208260 | 18 - 75 years | mCRC | WHO 0-1 | ≥ 3 months | No previous adjuvant chemotherapy with irinotecan or oxaliplatin or any treatment for liver metastasis |
| **OLIVIA** | NCT00778102 | ≥ 18 years | mCRC | ECOG 0-1 | -- | No prior systemic or local treatment of metastatic disease; No prior (neo)adjuvant chemotherapy/radiotherapy completed within 6 months prior to study entry |
| **PEAK** | NCT00819780 | ≥ 18 years | mCRC KRAS WT | ECOG 0-1 | -- | No prior chemotherapy or other systemic anticancer therapy for treatment of metastatic colorectal carcinoma |
| **Porschen et al., 2007** | -- | ≥ 18 years | mCRC with MSI-H subgroup  | ECOG 0-2 | > 3 months | No prior treatment for mCRC |
| **PRIME** | NCT00364013 | ≥ 18 years | mCRC/mCRC KRAS WT | ECOG 0-2 | -- | No prior chemotherapy or systemic therapy for the treatment of metastatic colorectal carcinoma except: adjuvant fluoropyrimidine-based chemotherapy or prior fluoropyrimidine therapy administered solely for the purpose of radiosensitization |
| **Souglakos et al., 2006** | -- | ≥ 18 years | mCRC | ECOG 0-2 | ≥ 3 months | No previous chemotherapy for metastatic disease |
| **TREE-1** | NCT00399750 | ≥ 18 years | mCRC | ECOG 0-1 | -- | No prior treatment with oxaliplatin or bevacizumab |
| **TREE-2** | NCT00399750 | ≥ 18 years | mCRC | ECOG 0-1 | -- | No prior treatment with oxaliplatin or bevacizumab |
| **TRIBE** | NCT00719797 | 18 - 75 years | mCRC | ECOG 0-2 (≤ 70 years) or ECOG 0 (71-75 years) | ≥ 12 weeks | No prior concurrent therapy: More than 4 weeks since prior radiotherapy; More than 10 days since prior and no concurrent ongoing treatment with anticoagulants for therapeutic purposes; More than 28 days since prior and no concurrent major surgical procedure; More than 28 days since prior open biopsy; More than 30 days since prior investigational agents; No concurrent chronic daily high-dose acetylsalicylic acid (> 325 mg/day) |
| **VISNU-1** | 2012-000846-37 | 18 - 70 years | mCRC | ECOG 0-1 | ≥ 3 months | No previous chemotherapy for metastatic disease; No prior treatment with Bevacizumab, or epidermal growth factor receptor inhibitor |
| **Excluded from network meta-analysis** |
| **2012-03** | NCT01564810 | 18 - 75 years | mCRC KRAS WT | ECOG 0-1 | ≥ 3 months | No previous exposure to target therapy, chemotherapy, radiotherapy or intervention therapy for colorectal liver metastases allowed prior to study entry |
| **ARTIST** | NCT00642577 | ≥ 18 years | mCRC | ECOG 0-1 | > 3 months | No prior systemic therapy for advanced or metastatic disease; No adjuvant or neo-adjuvant treatment for non-metastatic disease in past 6 months. |
| **ATOM** | NCT01836653 | 20 - 80 years | mCRC KRAS WT | ECOG 0-1 | ≥ 3 months | -- |
| **AVF2107** | NCT00109070 | ≥ 18 years | mCRC | ECOG 0-1 | > 3 months | No prior chemotherapy other than adjuvant fluoropyrimidines in combination with leucovorin and/or levamisole.; No administration of adjuvant fluoropyrimidines in combination with leucovorin and/or levamisole completed ≤ 12 months prior to Day 0; No administration of fluoropyrimidines as a radiosensitizer during pelvic radiotherapy for rectal cancer completed ≤ 12 months prior to Day 0; No prior radiotherapy to a measurable, metastatic lesion(s) to be used to measure response; No radiation therapy within 14 days prior to Day 0; No prior biotherapy for colorectal cancer   |
| **CALGB 80405** | NCT00265850 | ≥ 18 years | mCRC with MSI-H subgroup | ECOG 0-1 | -- | No prior chemotherapy |
| **CHARTA** | NCT01321957 | ≥ 18 years | mCRC | ECOG 0-2 | > 3 months | -- |
| **CRYSTAL** | NCT00154102 | ≥ 18 years | mCRC KRAS WT | ECOG 0-1 | -- | No prior chemotherapy |
| **FIRE-3** | NCT00433927 | 18 - 75 years | mCRC KRAS WT | ECOG 0-2 | > 3 months | No prior treatment directed against the epidermal growth factor receptor; No prior treatment with bevacizumab; No prior chemotherapy for colorectal cancer, except for adjuvant chemotherapy dating back > 6 months prior to study entry. |
| **GERCOR DREAM** | NCT00265824 | 18 - 80 years | mCRC | ECOG 0-2 | -- | No previous therapy for metastatic disease |
| **ITACa** | NCT01878422 | 18 - 70 years | mCRC | ECOG 0-2 | ≥ 12 weeks | No prior treatment with cetuximab, bevacizumab or other anti-epidermal growth factor receptor or anti-angiogenesis agents; No prior chemotherapy or immunotherapy for metastatic or advanced disease. |
| **Kato et al., 2018** | -- | ≥ 20 years | mCRC | ECOG 0-1 | -- | No prior use of any chemotherapy, immunotherapy or radiation therapy |
| **Madajewicz et al., 2012** | -- | -- | mCRC | ECOG 0-2 | -- | No prior adjuvant chemotherapy or chemoradiation unless completed >6 months before entering this study. |
| **NO16966** | NCT00069095 | ≥ 18 years | mCRC | ECOG 0-1 | -- | No previous treatment with oxaliplatin or bevacizumab; No previous systemic chemotherapy or immunotherapy for advanced or metastatic disease; No progressive disease during or within 6 months of completion of previous adjuvant therapy. |
| **NORDIC VII** | NCT00145314 | 18 - 75 years | mCRC | ECOG 0-2 | > 3 months | No prior chemotherapy for advanced/metastatic disease; No FU-based adjuvant chemotherapy the last 6 months before inclusion; No previous oxaliplatin; |
| **OPUS** | NCT00125034 | ≥ 18 years | mCRC | ECOG 0-2 | ≥ 12 weeks | No previous chemotherapy for colorectal cancer except adjuvant treatment with progression of disease documented > 6 months after end of adjuvant treatment; No previous exposure to epidermal growth factor receptor-targeted or chemotherapy (except adjuvant treatment) for mCRC |
| **Personeni et al., 2013** | NCT01068132 | 18 - 80 years | mCRC KRAS WT | ECOG 0-1 | -- | No previous chemotherapy for metastatic CRC (any). Adjuvant therapy is allowed if the chemotherapy treatment free interval is > 6 months; No surgery (excluding diagnostic biopsy) or irradiation within 4 weeks prior to study entry; No concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol; No investigational agent(s) within 4 weeks prior to entry; No previous exposure to HER-axis -pathway targeting therapy |
| **Stathopoulos et al., 2010** | -- | ≥ 18 years | mCRC | WHO 0 - 2 | ≥ 12 weeks | -- |
| **TAILOR** | NCT01228734 | ≥ 18 years | mCRC KRAS WT | ECOG 0-1 | ≥ 12 weeks | No previous chemotherapy for CRC except adjuvant treatment if terminated > 9 months (oxaliplatin-based chemotherapy) or > 6 months (non-oxaliplatin-based chemotherapy) before the start of treatment in this trial; No radiotherapy or surgery (excluding prior diagnostic biopsy) in the 30 days before trial treatment; No previous treatment with monoclonal antibody therapy, vascular endothelial growth factor pathway-targeting therapy, epidermal growth factor receptor pathway-targeting therapy, or other signal transduction inhibitors |

Abbreviations: dMMR, DNA mismatch repair; MSI-H, microstatellite instability high; mCRC, metastatic colorectal cancer; WT, Wild-type.

Table S8: Patient characteristics from trials included in systematic review

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial ID** | **Population** | **Treatment** | **Sample****size** | **Age,** **median (range)** | **Male,** **N (%)** | **ECOG 0,** **N (%)** | **ECOG 1,** **N (%)** | **ECOG 2,****N (%)** | **Rectum site,** **N (%)** | **Colon site, N (%)** |
| **Included in network meta-analysis** |
| **Falcone et al., 2007** | mCRC | FOLFIRI | 122 | 64 (21-75) | 69 (56.6) | 74 (60.7) | 41 (33.6) | 7 (5.7) | 27 (22) | 95 (78) |
| FOLFOXIRI | 122 | 62 (27-75) | 75 (61.5) | 74 (60.7) | 45 (36.9) | 3 (2.5) | 41 (34) | 81 (66) |
| **GOIM 2802** | mCRC | FOLFOX4 + bevacizumab | 45 | 62 (42-73) | 22 (48.9) | 14 (31.1) | 31 (68.9) | -- | 7 (15.6) | 35 (77.8) |
| XELOX2 + bevacizumab | 87 | 66 (32-77) | 46 (52.9) | 34 (39.1) | 53 (60.9) | -- | 18 (20.9) | 64 (74.4) |
| **KEYNOTE 177** | MSI-H mCRC | Pembrolizumab | 153 | 63 (24-93) | 71 (46.4) | 75 (49) | -- | -- | -- | 148 (96.7) |
| SOC | 154 | 62.5 (26-90) | 82 (53.2) | 84 (54.5) | -- | -- | -- | 149 (96.8) |
| **METHEP** | mCRC | FOLFIRI/FOLFOX4 | 30 | 62.5 (47-73) | 15 (50) | 21 (70) | 8 (26.7) | -- | 3 (10) | 27 (90) |
| FOLFIRI-HD | 32 | 62.5 (46-73) | 12 (37.5) | 24 (75) | 7 (21.9) | -- | 6 (19) | 26 (81.2) |
| FOLFOX7 | 30 | 59 (39-80) | 24 (80) | 21 (70) | 9 (30) | -- | 5 (17) | 25 (83.3) |
| FOLFOXIRI | 30 | 64 (43-74) | 18 (60) | 23 (76.7) | 7 (23.3) | -- | 4 (13) | 18 (60) |
| **OLIVIA** | mCRC | FOLFOXIRI + bevacizumab | 41 | 63 (32-77) | 29 (70.7) | 23 (56.1) | 16 (39) | 2 (4.9) | 8 (20) | 29 (71) |
| mFOLFOX6 + bevacizumab | 39 | 57 (28-80) | 18 (46.2) | 31 (79.5) | 8 (20.5) | 0 (0) | 9 (23) | 27 (69) |
| **PEAK** | mCRC KRAS WT | mFOLFOX6 + panitumumab | 142 | 63 (23-82) | 86 (60.6) | 89 (62.7) | 53 (37.3) | -- | 46 (32) | 96 (68) |
| mFOLFOX6 + bevacizumab | 143 | 61 (28-82) | 96 (67.1) | 91 (63.6) | 51 (35.7) | -- | 51 (36) | 92 (64) |
| **Porschen et al., 2007** | mCRC | FOLFOX | 233 | 64 (34-86) | 146 (62.7) | -- | -- | 17 (7.3) | -- | -- |
| XELOX | 241 | 66 (32-81) | 150 (62.2) | -- | -- | 22 (9.1) | -- | -- |
| **PRIME** | mCRC KRAS WT | FOLFOX4 + panitumumab | 325 | 62 (27-85) | 217 (66.8) | -- | -- | -- | 111 (34) | 214 (66) |
| FOLFOX4 | 331 | 61 (24-82) | 204 (61.6) | -- | -- | -- | 115 (35) | 216 (65) |
| **Souglakos et al., 2006** | mCRC | FOLFIRI | 146 | 66 (39-84) | 82 (56.2) | 55 (37.7) | 74 (50.7) | 17 (11.6) | 36 (25) | 110 (75) |
| FOLFOXIRI | 137 | 66 (25-82) | 76 (55.5) | 49 (35.8) | 73 (53.3) | 15 (10.9) | 37 (27) | 100 (73) |
| **TREE-1** | mCRC | mFOLFOX6 | 49 | 62 (35-79) | 28 (57) | 30 (61) | 19 (31) | -- | -- | -- |
| bFOLFOX | 50 | 62 (31-84) | 31 (62) | 29 (58) | 21 (42) | -- | -- | -- |
| XELOX | 48 | 62.5 (32-84) | 31 (65) | 25 (52) | 23 (39) | -- | -- | -- |
| **TREE-2** | mCRC | mFOLFOX6 + bevacizumab | 71 | 64 (31-83) | 43 (61) | 43 (61) | 28 (39) | -- | -- | -- |
| bFOLFOX + bevacizumab | 70 | 57 (30-85) | 34 (49) | 38 (54) | 32 (46) | -- | -- | -- |
| XELOX + bevacizumab | 72 | 62 (32-82) | 42 (58) | 47 (65) | 25 (35) | -- | -- | -- |
| **TRIBE** | mCRC | FOLFIRI + bevacizumab | 256 | 60 (29-75) | 156 (60.9) | 229 (89.5) | -- | -- | -- | 240 (93.8) |
| FOLFOXIRI + bevacizumab | 252 | 60.5 (29-75) | 150 (59.5) | 227 (90.1) | -- | -- | -- | 240 (95.2) |
| **VISNU-1** | mCRC | mFOLFOX6 + bevacizumab | 177 | 59 (27-70) | 119 (67.2) | 85 (48) | 92 (52) | -- | -- | 177 (100) |
| FOLFOXIRI + bevacizumab | 172 | 61 (37-70) | 118 (68.6) | 81 (47.1) | 91 (52.9) | -- | -- | 172 (100) |
| **Excluded from network meta-analysis** |
| **2012-03** | mCRC KRAS WT | mFOLFOX6 or FOLFIRI + cetuximab | 70 | 57 (26-75) | 46 (65.7) | 58 (82.9) | 12 (17.1) | -- | 26 (37.1) | 44 (62.9) |
| mFOLFOX6 or FOLFIRI | 68 | 59 (35-75) | 42 (61.8) | 54 (79.4) | 14 (20.6) | -- | 30 (44.1) | 38 (55.9) |
| **ARTIST** | mCRC | mFOLFIRI + bevacizumab | 139 | 53 (23-77) | 70 (50.4) | 66 (47.5) | 73 (52.5) | -- | 66 (47.5) | 66 (47.5) |
| mFOLFIRI | 64 | 50 (22-72) | 36 (56.2) | 23 (35.9) | 41 (64.1) | -- | 32 (50) | 31 (48.4) |
| **ATOM** | mCRC KRAS WT | mFOLFOX + bevacizumab | 57 | 64 (32-80) | 34 (59.6) | 51 (89.5) | 6 (10.5) | -- | -- | 57 (100) |
| mFOLFOX + cetuximab | 59 | 65 (42-79) | 34 (57.6) | 51 (86.4) | 8 (13.6) | -- | -- | 59 (100) |
| **AVF2107** | mCRC | FOLFIRI + placebo | 411 | 60 (21-83) | 248 (60.3) | 227 (55.2) | 182 (44.3) | 2 (0.5) | 77 (18.7) | 334 (81.3) |
| FOLFIRI + bevacizumab | 402 | 60 (23-86) | 237 (59) | 234 (58.2) | 166 (41.3) | 1 (0.2) | 92 (22.9) | 310 (77.1) |
| **CALGB 80405** | mCRC KRAS WT | FOLFOX or FOLFIRI + bevacizumab | 559 | 59 (21.8-85) | 348 (62.6) | 324 (58) | 233 (41.7) | 2 (0.4) | -- | 476 (85.2) |
| FOLFOX or FOLFIRI + cetuximab | 578 | 59.2 (20.8-89.5) | 349 (60.4) | 333 (57.6) | 245 (42.4) | 0 (0) | -- | 493 (85.3) |
| **CHARTA** | mCRC | FOLFOX + bevacizumab | -- | -- | -- | -- | -- | -- | -- | -- |
| FOLFOXIRI + bevacizumab | -- | -- | -- | -- | -- | -- | -- | -- |
| **CRYSTAL** | mCRC KRAS WT | FOLFIRI + cetuximab | 316 | 61 (24-79) | -- | -- | -- | -- | -- | -- |
| FOLFIRI  | 350 | 59 (19-84) | -- | -- | -- | -- | -- | -- |
| **FIRE-3** | mCRC | FOLFIRI + cetuximab | 297 | 64 (38-79) | 214 (72.1) | 154 (51.9) | 136 (45.8) | 7 (2.4) | 115 (39) | 168 (57) |
| FOLFIRI + bevacizumab | 295 | 65 (27-76) | 196 (66.4) | 158 (53.6) | 133 (45.1) | 4 (1.4) | 106 (36) | 177 (60) |
| **GERCOR DREAM** |  mCRC | mFOLFOX7 + bevacizumab | 156 | -- | -- | -- | -- | -- | -- | -- |
| XELOX2 + bevacizumab | 154 | -- | -- | -- | -- | -- | -- | -- |
| **ITACa** |  mCRC | FOLFOX4 or FOLFIRI + bevacizumab | 176 | 66 (34-83) | 108 (61.4) | 144 (81.8) | -- | -- | 41 (23.3) | 135 (76.7) |
| FOLFOX4 or FOLFIRI | 194 | 66 (33-82) | 115 (59.3) | 154 (79.4) | -- | -- | 51 (26.3) | 143 (73.7) |
| **Kato et al., 2018** |  mCRC | mFOLFOX6 + bevacizumab | 49 | 63 (35-81) | 33 (67.3) | 40 (81.6) | 5 (10.2) | -- | 20 (40.8) | 29 (59.2) |
| XELOX + bevacizumab  | 19 | 68 (47-77) | 17 (89.5) | 16 (84.2) | 1 (5.3) | -- | 5 (26.3) | 14 (73.7) |
| **Madajewicz et al., 2012** |  mCRC  | FOLFOX4 | 24 | 64 (32-81) | 9 (37.5) | 13 (54.2) | 11 (45.8) | -- | 4 (16.7) | 18 (75) |
| FOLFOX4 + bevacizumab | 18 | 64 (42-81) | 11 (61.1) | 7 (38.9) | 11 (61.1) | -- | 0 (0) | 17 (94.4) |
| **NO16966** |  mCRC  | XELOX | 317 | 61 (24-84) | 194 (61.2) | 160 (50.5) | 157 (49.5) | 0 (0) | 83 (26) | 204 (64) |
| FOLFOX4 | 317 | 62 (24-83) | 204 (64.4) | 163 (51.4) | 154 (48.6) | 0 (0) | 100 (32) | 200 (63) |
| XELOX + placebo | 350 | 61 (18-83) | 205 (58.6) | 207 (59.1) | 143 (40.9) | 0 (0) | 87 (25) | 233 (67) |
| FOLFOX4 + placebo | 351 | 60 (26-83) | 189 (53.8) | 211 (60.1) | 138 (39.3) | 0 (0) | 94 (27) | 232 (66) |
| XELOX + bevacizumab | 350 | 61 (18-86) | 213 (60.9) | 207 (59.1) | 142 (40.6) | 1 (0.3) | 82 (23) | 236 (67) |
| FOLFOX4 + bevacizumab | 349 | 60 (19-82) | 205 (58.7) | 198 (56.7) | 147 (42.1) | 0 (0) | 98 (28) | 223 (64) |
| **NORDIC VII** | mCRC KRAS WT | FOLFOX | 97 | 60 (35.2-74.6) | -- | -- | -- | -- | 35 (36) | 62 (64) |
| FOLFOX + cetuximab | 97 | 60 (24.1-74.4) | -- | -- | -- | -- | 42 (43) | 55 (57) |
| **OPUS** |  mCRC | FOLFOX4 | 168 | 60 (30-82) | 92 (54.8) | 75 (44.6) | 76 (45.2) | 17 (10.1) | 79 (47) | 89 (53) |
| FOLFOX4 + cetuximab | 169 | 62 (24-82) | 89 (52.7) | 65 (38.5) | 89 (52.7) | 15 (8.9) | 75 (44) | 92 (54) |
| **Personeni et al., 2013** | mCRC KRAS WT | FOLFIRI + cetuximab | 54 | -- | -- | -- | -- | -- | -- | -- |
| FOLFIRI | 35 | -- | -- | -- | -- | -- | -- | -- |
| **Stathopo-ulos et al., 2010** | mCRC | FOLFIRI + bevacizumab | 114 | 67 (45-82) | 73 (64) | -- | -- | 29 (25.4) | -- | -- |
| FOLFIRI | 108 | 62 (30-87) | 68 (63) | -- | -- | 30 (27.8) | -- | -- |
| **TAILOR** | mCRC RAS WT | FOLFOX4 + cetuximab | 193 | 56 (21-83) | 127 (65.8) | 63 (32.6) | 130 (67.4) | -- | 90 (46.6) | 93 (48.2) |
| FOLFOX4 | 200 | 56 (21-78) | 139 (69.5) | 66 (33) | 134 (67) | -- | 93 (46.5) | 105 (52.5) |

Abbreviations: bFOLFOX, bolus fluorouracil + low-dose leucovorin + oxaliplatin; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, 5-fluorouracil + leucovorin + irinotecan; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; HD, High dose; mCRC, metastatic colorectal cancer; MSI-H, microstatellite instability high; SOC, standard of care; WT, wild-type; XELOX, oxaliplatin + Capecitabine.

Table S9: Outcomes from trials included in systematic review

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial ID** | **Population** | **Treatment** | **Sample size** | **Median follow-****up time** | **ORR, %** | **Median OS,****month (95% CI)** | **OS HR** **(95% CI)** | **Median PFS,****month (95% CI)** | **PFS HR** **(95% CI)** |
| **Included in network meta-analysis** |
| **Falcone et al., 2007** | mCRC | FOLFIRI | 122 | 60.6 months | -- | 16.7 (13.8-19.4) | -- | 6.8 (5.5-7.8) | -- |
| FOLFOXIRI | 122 | 60.6 months | -- | 23.4 (19.8-25.6) | 0.74 (0.56-0.96) | 9.8 (9.4-10.6) | 0.59 (0.45-0.76) |
| **GOIM 2802** | mCRC | FOLFOX4 + bevacizumab | 45 | 47.2 months | 55.6% | 29.8 | -- | 10 | -- |
| XELOX2 + bevacizumab | 87 | 47.2 months | 48.3% | 25 | 1.21 (0.77-1.92) | 9.9 | 0.96 (0.65-1.41) |
| **KEYNOTE 177** | MSI-H mCRC | Pembrolizumab | 153 | -- | 43.8% | NR  | 0.77 (0.54-1.09) | 16.5 (5.4-32.4) | 0.6 (0.45-0.8) |
| SOC | 154 | -- | 33.1% | 34.8 (26.3-NR) | -- | 8.2 (6.1-10.2) | -- |
| **METHEP** | mCRC | FOLFIRI/FOLFOX4 | 30 | 50.4 months | 33% | 17.7 (13.7-43) | -- | 9.2 (6.8-13.4) | -- |
| FOLFIRI-HD | 32 | 50.4 months | 47% | 29.4 (26.1-42.4) | -- | 12.1 (10.3-16.6) | -- |
| FOLFOX7 | 30 | 50.4 months | 43% | 26.9 (18.7-45) | -- | 8.5 (6.4-10.9) | -- |
| FOLFOXIRI | 30 | 50.4 months | 57% | 48.8 (21.9-NR) | -- | 14.1 (11.2-21.7) | -- |
| **OLIVIA** | mCRC | FOLFOXIRI + bevacizumab | 39 | -- | 62% | 32.2 | -- | 11.5 (9.6-13.6) | -- |
| mFOLFOX6 + bevacizumab | 41 | -- | 81% | NR | 0.35 (0.15-0.8) | 18.6 (12.9-22.3) | 0.43 (0.26-0.72) |
| **PEAK** | mCRC KRAS WT | mFOLFOX6 + panitumumab | 142 | -- | 57.8% | 34.2 (26.6-NR) | 0.62 (0.44-0.89) | 10.9 (9.4-13) | 0.87 (0.65-1.17) |
| mFOLFOX6 + bevacizumab | 143 | -- | 53.5% | 24.3 (21-29.2) | -- | 10.1 (9-12.6) | -- |
| **Porschen et al., 2007** | mCRC | FOLFOX | 233 | 17.3 months | 54% | 18.8 | -- | 8 | -- |
| XELOX | 241 | 17.3 months | 48% | 16.8 | 1.12 (0.92-1.38) | 7.1 | 1.17 (0.96-1.43) |
| **PRIME** | mCRC KRAS WT | FOLFOX4 + panitumumab | 325 | 89 weeks | 57% | 23.8 (20-27.7) | 0.83 (0.7-0.98) | 10 (9.3-11.4) | 0.8 (0.67-0.95) |
| FOLFOX4 | 331 | 74 weeks | 48% | 19.4 (17.4-22.6) | -- | 8.6 (7.5-9.5) | -- |
| **Souglakos et al., 2006** | mCRC | FOLFIRI | 146 | 26 months | 33.6% | 19.5 | -- | -- | -- |
| FOLFOXIRI | 137 | 26 months | 43% | 21.5 | 0.93 (0.69-1.25) | -- | -- |
| **TREE-1** | mCRC | mFOLFOX6 | 49 | 16.9 months | 41% | 19.2 (14.2-24.9) | -- | -- | -- |
| bFOLFOX | 50 | 15.1 months | 20% | 17.9 (11.5-24.6) | -- | -- | -- |
| XELOX | 48 | 15 months | 27% | 17.2 (12.5-22.3) | -- | -- | -- |
| **TREE-2** | mCRC | mFOLFOX6 + bevacizumab | 71 | 17.9 months | 52% | 26.1 (18-NR) | -- | -- | -- |
| bFOLFOX + bevacizumab | 70 | 17.6 months | 39% | 20.4 (18.4-25.3) | -- | -- | -- |
| XELOX + bevacizumab | 72 | 18.5 months | 46% | 24.6 (21.4-31.6) | -- | -- | -- |
| **TRIBE** | mCRC | FOLFIRI + bevacizumab | 256 | 48.1 months | 54% | 25.8 (22.5-29.1) | -- | 9.7 (9.2-10.9) | -- |
| FOLFOXIRI + bevacizumab | 252 | 48.1 months | 65% | 29.8 (26-34.3) | 0.8 (0.65-0.98) | 12.3 (11-13.3) | 0.77 (0.65-0.93) |
| **VISNU-1** | mCRC | mFOLFOX6 + bevacizumab | 177 | 50.7 months | 52% | 17.6 | -- | 9.3 | -- |
| FOLFOXIRI + bevacizumab | 172 | 50.7 months | 59% | 22.3 | 0.84 (0.66-1.06) | 12.4 | 0.64 (0.49-0.82) |
| **Excluded from network meta-analysis** |
| **2012-03** | mCRC KRAS WT | mFOLFOX6 or FOLFIRI + cetuximab | 70 | 25 months | 57.1% | 30.9 (16.5-41.5) | 0.54 (0.33-0.89) | 10.2 (8.6-11.4) | 0.6 (0.41-0.87) |
| mFOLFOX6 or FOLFIRI | 68 | 25 months | 29.4% | 21 (16.7-23.4) | -- | 5.8 (3.9-6.1) | -- |
| **ARTIST** | mCRC | mFOLFIRI + bevacizumab | 139 | -- | 35.3% | 18.7 (15.8-19.6) | 0.62 (0.41-0.95) | 8.3 (7.4-8.9) | 0.44 (0.31-0.63) |
| mFOLFIRI | 64 | -- | 17.2% | 13.4 (9.7-17.2) | -- | 4.2 (3.7-4.9) | -- |
| **ATOM** | mCRC KRAS WT | mFOLFOX + bevacizumab | 57 | 24.3 months | 68.4% | 30.4 | -- | 11.5 (9.2-13.3) | -- |
| mFOLFOX + cetuximab | 59 | 24.3 months | 84.7% | -- | 0.83 (0.44-1.56) | 14.8 (9.7-13.3) | 0.80 (0.51-1.26) |
| **AVF2107** |  mCRC | FOLFIRI + placebo | 411 | -- | 34.8% | 15.6 | 0.66 (0.55-0.82)\* | 6.2 | 0.54 (0.48-0.68) \* |
| FOLFIRI + bevacizumab | 402 | -- | 44.8% | 20.3 | -- | 10.6 | -- |
| **CALGB 80405** | mCRC KRAS WT | FOLFOX or FOLFIRI + bevacizumab | 559 | 47.4 months | 55.2% | 29 | 0.88 (0.77-1.01) | 10.6 (6.4-16.6) | 0.95 (0.84-1.08) |
| FOLFOX or FOLFIRI + cetuximab | 578 | 47.4 months | 59.6% | 30 | -- | 10.5 (5.8-17.7) | -- |
| **CHARTA** | mCRC | FOLFOX + bevacizumab | -- | -- | 60% | 24.9 | -- | 9.76 | -- |
| FOLFOXIRI + bevacizumab | -- | -- | 70% | 27.9 | -- | 12 | 0.77 |
| **CRYSTAL** | mCRC KRAS WT | FOLFIRI | 350 | 46.2 months | 39.7% | 20 (17.4-21.7) | -- | 8.4 (7.4-9.2) | -- |
| FOLFIRI + cetuximab | 316 | 46.8 months | 57.3% | 23.5 (21.2-26.3) | 0.80 (0.67-0.95) | 9.9 (9-11.3) | 0.80 (0.56-0.87) |
| **FIRE-3** | mCRC | FOLFIRI + cetuximab | 297 | 33 months | 62% | 28.7 (24-30.6) | 0.77 (0.62-0.96) | 10 (8.8-10.8) | 1.06 (0.88-1.26) |
| FOLFIRI + bevacizumab | 295 | 39 months | 58% | 25 (22.7-27.6) | -- | 10.3 (9.8-11.3) | -- |
| **GERCOR DREAM** | mCRC | mFOLFOX7 + bevacizumab | 156 | -- | 50% | 26.6 | 1.24 (0.98-1.59) | 7.9 | 0.98 (0.74-1.31) |
| XELOX2 + bevacizumab | 154 | -- | 49.3% | 23.4 | -- | 8.7 | -- |
| **ITACa** | mCRC | FOLFOX4 or FOLFIRI + bevacizumab | 176 | 36 months | 50.6% | 20.8 (15.9-23.2) | 1.13 (0.89-1.43) | 9.6 (8.2-10.3) | 0.86 (0.7-1.07) |
| FOLFOX4 or FOLFIRI | 194 | 36 months | 50% | 21.3 (19.9-24.1) | -- | 8.4 (7.2-9) | -- |
| **Kato et al., 2018** | mCRC | mFOLFOX6 + bevacizumab | 49 | -- | 55.1% | 29 (24.4-40.9) | -- | 11.3 (9.1-15.5) | -- |
| XELOX + bevacizumab  | 19 | -- | 42.1% | 22.5 (15.5-34.9) | -- | 8 (4.2-16.8) | -- |
| **Madajewicz et al., 2012** | mCRC  | FOLFOX4 | 24 | -- | 33.3% | 10.9 (9.1-21.3) | -- | -- | -- |
| FOLFOX4 + bevacizumab | 18 | -- | 50% | 32 (19.7-NR) | -- | -- | -- |
| **NO16966** | mCRC  | XELOX + Placebo/XELOX | 667 | -- | -- | 19 | -- | -- | -- |
| FOLFOX-4 + Placebo/FOLFOX-4 | 668 | -- | -- | 18.9 | -- | -- | -- |
| XELOX + Bevacizumab | 350 | -- | -- | 21.6 | -- | -- | -- |
| FOLFOX4 + Bevacizumab | 349 | -- | -- | 21 | -- | -- | -- |
| **NORDIC VII** | mCRC KRAS WT | FOLFOX | 97 | -- | 47% | 22 (17.9-26.1) | -- | 8.7 (7.4-9.9) | -- |
| FOLFOX + cetuximab | 97 | -- | 46% | 20.1 (14.5-25.7) | 1.14 (0.8-1.61) | 7.9 (6.3-9.5) | 1.07 (0.79-1.45) |
| **OPUS** | mCRC | FOLFOX4 | 168 | -- | 36% | 18 (16.7-21.8) | -- | 7.2 (6-7.8) | -- |
| FOLFOX4 + cetuximab | 169 | -- | 46% | 18.3 (14.8-20.4) | 1.02 (0.79-1.30) | 7.2 (5.6-7.7) | 0.93 (0.71-1.2) |
| **Personeni et al., 2013** | mCRC KRAS WT | FOLFIRI + cetuximab | 54 | -- | 52.3% | 23.3 | -- | 6.8 | -- |
| FOLFIRI | 35 | -- | 52% | 17.7 | -- | 8.2 | -- |
| **Stathopoulos et al., 2010** | mCRC | FOLFIRI + bevacizumab | 114 | 36 months | 36.8% | 22 (18.1-25.9) | 1.26 (0.95-1.66)\* | -- | -- |
| FOLFIRI | 108 | 36 months | 35.2% | 25 (18.1-31.9) | -- | -- | -- |
| **TAILOR** | mCRC RAS WT | FOLFOX4 + cetuximab | 193 | 44.4 months | 61.1% | 20.7 (15.9-22.1) | 0.76 (0.61-0.95) | 9.2 (7.7-9.4) | 0.69 (0.54-0.89) |
| FOLFOX4 | 200 | 48.7 months | 39.5% | 17.8 (14.9-19.6) | -- | 7.4 (5.6-7.9) | -- |

Abbreviations: bFOLFOX, bolus fluorouracil + low-dose leucovorin + oxaliplatin; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, 5-fluorouracil + leucovorin + irinotecan; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; HD, High dose; HR, hazard ratio; mCRC, metastatic colorectal cancer; MSI-H, microstatellite instability High; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care; WT, wild-type; XELOX, oxaliplatin + capecitabine.

\* Hazard ratios or confidence intervals derived from Kaplan-Meier curves

Table S10: Proportional hazard assumption test (Grambsch and Therneau test) of trials included in the analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Intervention | Comparator | Test for proportional hazard (Overall Survival)\* | Test for proportional hazard (Progression-free Survival)\* |
| **Falcone et al., 2007** | FOLFIXIRI | FOLFIRI | p = 0.221 | p = 0.029 |
| **GOIM 2802** | XELOX2 + Bevacizumab | FOLFOX4 + Bevacizumab | p = 0.262 | p = 0.225 |
| **KEYNOTE-177** | Pembrolizumab | SOC | p = 0.062 (unadjusted for crossover)p = 0.008 (adjustment for crossover using 2-stage model)p = 0.018 (adjustment for crossover using RPSFT method) | p < 0.001 |
| **METHEP** | FOLFIXIRI | Pooled FOLFOX or FOLFIRI | p = 0.353 | p = 0.08 |
| **OLIVIA** | FOLFIXIRI + Bevacizumab | mFOLFOX6 + Bevacizumab | -- | p = 0.693 |
| **PEAK** | mFOLFOX6 + Panitumumab | mFOLFOX6 + Bevacizumab | p = 0.397 | p = 0.796 |
| **Porschen et al., 2007** | XELOX | FOLFOX | p = 0.643 | p = 0.213 |
| **PRIME** | FOLFOX4 + Panitumumab | FOLFOX4  | p = 0.712 | p = 0.567 |
| **Souglakos et al., 2006** | FOLFIXIRI | FOLFIRI | p = 0.98 | -- |
| **TREE-1** | XELOX | Pooled FOLFOX | p = 0.003 | -- |
| **TREE-2** | XELOX + Bevacizumab | Pooled FOLFOX + Bevacizumab | p = 0.173 | -- |
| **TRIBE** | FOLFIXIRI + Bevacizumab | FOLFIRI + Bevacizumab | p = 0.455 | p = 0.022 |
| **VISNU-1** | FOLFIXIRI + Bevacizumab | mFOLFOX6 + Bevacizumab | p = 0.519 | p = 0.266 |

Abbreviations: FOLFIRI, 5-fluorouracil + leucovorin + irinotecan; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; HD, High dose; HR, hazard ratio; mCRC, metastatic colorectal cancer; SOC, standard of care; XELOX, oxaliplatin + capecitabine.

\* p < 0.05 considered violation of proportional hazards assumption

Table S11: Estimated constant hazard ratios of overall survival with pembrolizumab versus competing interventions from fixed-effect and random-effects network meta-analysis; no adjustment for crossover in KEYNOTE-177

|  |
| --- |
| **Hazard Ratio (95% credible intervals), fixed-effect** |
| **SOC** |  |  |  |  |  |  |
| 1.05 (0.87, 1.25) | **XELOX** |  |  |  |  |  |
| 1.06 (0.81, 1.38) | 1.01 (0.73, 1.39) | **XELOX + Bevacizumab** |  |  |  |  |
| **0.81 (0.67, 0.97)** | 0.77 (0.59, 1.00) | 0.76 (0.55, 1.06) | **FOLFOXIRI** |  |  |  |
| **0.80 (0.68, 0.93)** | **0.76 (0.60, 0.96)** | 0.75 (0.56, 1.02) | 0.98 (0.77, 1.25) | **FOLFOXIRI + Bevacizumab** |  |  |
| **0.79 (0.67, 0.92)** | **0.75 (0.60, 0.95)** | 0.74 (0.55, 1.01) | 0.97 (0.77, 1.24) | 0.99 (0.80, 1.23) | **FOLFOX + Panitumumab** |  |
| 0.77 (0.54, 1.09) | 0.73 (0.49, 1.09) | 0.73 (0.47, 1.13) | 0.95 (0.64, 1.41) | 0.96 (0.66, 1.41) | 0.98 (0.66, 1.43) | **Pembrolizumab** |
| **Hazard Ratio (95% credible intervals),** **random-effects** |
| **SOC** |  |  |  |  |  |  |
| 1.02 (0.72, 1.37) | **XELOX** |  |  |  |  |  |
| 1.07 (0.75, 1.54) | 1.05 (0.67, 1.74) | **XELOX + Bevacizumab** |  |  |  |  |
| 0.81 (0.61, 1.05) | 0.79 (0.53, 1.24) | 0.76 (0.48, 1.17) | **FOLFOXIRI** |  |  |  |
| **0.77 (0.55, 0.98)** | 0.76 (0.49, 1.13) | 0.72 (0.43, 1.10) | 0.96 (0.62, 1.37) | **FOLFOXIRI + Bevacizumab** |  |  |
| 0.76 (0.54, 1.00) | 0.75 (0.48, 1.16) | 0.72 (0.43, 1.11) | 0.95 (0.61, 1.37) | 0.99 (0.66, 1.53) | **FOLFOX + Panitumumab** |  |
| 0.77 (0.47, 1.26) | 0.76 (0.43, 1.40) | 0.72 (0.39, 1.32) | 0.96 (0.54, 1.69) | 1.00 (0.58, 1.83) | 1.01 (0.58, 1.86) | **Pembrolizumab** |

**Abbreviations**: FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; SOC, standard of care; XELOX, oxaliplatin + capecitabine.

**Notes**: Each cell represents the comparison (hazard ratio and 95% credible intervals) of the row treatment versus the column treatment; All bolded values are statistically meaningful at the 0.05 significance level.

Table S12: Estimated constant hazard ratios of overall survival with pembrolizumab versus competing interventions from fixed-effect and random-effects network meta-analysis; adjustment for crossover in KEYNOTE-177 using 2-stage model

|  |
| --- |
| **Hazard Ratio (95% credible intervals), fixed-effect** |
| **SOC** |  |  |  |  |  |  |
| 1.05 (0.88, 1.25) | **XELOX** |  |  |  |  |  |
| 1.06 (0.81, 1.38) | 1.01 (0.73, 1.39) | **XELOX + Bevacizumab** |  |  |  |  |
| **0.81 (0.67, 0.97)** | **0.78 (0.60, 0.99)** | 0.76 (0.56, 1.05) | **FOLFOXIRI** |  |  |  |
| **0.79 (0.68, 0.92)** | **0.76 (0.60, 0.96)** | 0.75 (0.55, 1.01) | 0.98 (0.77, 1.24) | **FOLFOXIRI + Bevacizumab** |  |  |
| **0.79 (0.68, 0.91)** | **0.75 (0.59, 0.95)** | 0.74 (0.55, 1.01) | 0.97 (0.77, 1.23) | 0.99 (0.80, 1.23) | **FOLFOX + Panitumumab** |  |
| 0.59 (0.29, 1.16) | 0.56 (0.27, 1.13) | 0.56 (0.27, 1.15) | 0.73 (0.36, 1.47) | 0.75 (0.36, 1.47) | 0.75 (0.37, 1.49) | **Pembrolizumab** |
| **Hazard Ratio (95% credible intervals),** **random-effects** |
| **SOC** |  |  |  |  |  |  |
| 1.02 (0.72, 1.38) | **XELOX** |  |  |  |  |  |
| 1.07 (0.74, 1.56) | 1.05 (0.65, 1.80) | **XELOX + Bevacizumab** |  |  |  |  |
| 0.81 (0.61, 1.07) | 0.79 (0.53, 1.27) | 0.76 (0.47, 1.20) | **FOLFOXIRI** |  |  |  |
| **0.77 (0.55, 0.98)** | 0.76 (0.48, 1.14) | 0.72 (0.42, 1.11) | 0.96 (0.60, 1.37) | **FOLFOXIRI + Bevacizumab** |  |  |
| 0.77 (0.54, 1.01) | 0.75 (0.47, 1.18) | 0.72 (0.42, 1.13) | 0.94 (0.60, 1.40) | 0.99 (0.66, 1.56) | **FOLFOX + Panitumumab** |  |
| 0.59 (0.27, 1.32) | 0.58 (0.25, 1.41) | 0.55 (0.23, 1.32) | 0.73 (0.32, 1.71) | 0.76 (0.34, 1.85) | 0.77 (0.34, 1.86) | **Pembrolizumab** |

**Abbreviations**: FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; SOC, standard of care; XELOX, oxaliplatin + capecitabine.

**Notes**: Each cell represents the comparison (hazard ratio and 95% credible intervals) of the row treatment versus the column treatment; All bolded values are statistically meaningful at the 0.05 significance level.

Table S13: Estimated constant hazard ratios of overall survival with pembrolizumab versus competing interventions from fixed-effect and random-effects network meta-analysis; adjustment for crossover in KEYNOTE-177 using RPSFT model

|  |
| --- |
| **Hazard Ratio (95% credible intervals), fixed-effect** |
| **SOC** |  |  |  |  |  |  |
| 1.05 (0.87, 1.25) | **XELOX** |  |  |  |  |  |
| 1.06 (0.81, 1.37) | 1.01 (0.73, 1.39) | **XELOX + Bevacizumab** |  |  |  |  |
| **0.81 (0.67, 0.97)** | 0.77 (0.60, 1.00) | 0.77 (0.55, 1.06) | **FOLFOXIRI** |  |  |  |
| **0.79 (0.68, 0.93)** | **0.76 (0.60, 0.96)** | 0.75 (0.56, 1.02) | 0.98 (0.77, 1.24) | **FOLFOXIRI + Bevacizumab** |  |  |
| **0.79 (0.68, 0.92)** | **0.75 (0.59, 0.95)** | 0.74 (0.55, 1.01) | 0.97 (0.76, 1.24) | 0.99 (0.80, 1.23) | **FOLFOX + Panitumumab** |  |
| 0.68 (0.41, 1.15) | 0.65 (0.38, 1.13) | 0.64 (0.36, 1.16) | 0.84 (0.48, 1.47) | 0.85 (0.50, 1.47) | 0.86 (0.50, 1.49) | **Pembrolizumab** |
| **Hazard Ratio (95% credible intervals),** **random-effects** |
| **SOC** |  |  |  |  |  |  |
| 1.02 (0.72, 1.36) | **XELOX** |  |  |  |  |  |
| 1.07 (0.74, 1.54) | 1.05 (0.67, 1.77) | **XELOX + Bevacizumab** |  |  |  |  |
| 0.81 (0.61, 1.07) | 0.79 (0.53, 1.26) | 0.76 (0.48, 1.20) | **FOLFOXIRI** |  |  |  |
| **0.77 (0.55, 0.98)** | 0.76 (0.49, 1.13) | 0.73 (0.44, 1.09) | 0.95 (0.61, 1.35) | **FOLFOXIRI + Bevacizumab** |  |  |
| 0.77 (0.54, 1.01) | 0.75 (0.48, 1.17) | 0.72 (0.43, 1.13) | 0.95 (0.60, 1.38) | 0.99 (0.67, 1.53) | **FOLFOX + Panitumumab** |  |
| 0.68 (0.36, 1.29) | 0.67 (0.34, 1.37) | 0.64 (0.31, 1.32) | 0.84 (0.42, 1.68) | 0.89 (0.46, 1.82) | 0.89 (0.45, 1.85) | **Pembrolizumab** |

**Abbreviations**: FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; SOC, standard of care; XELOX, oxaliplatin + capecitabine.

**Notes**: Each cell represents the comparison (hazard ratio and 95% credible intervals) of the row treatment versus the column treatment; All bolded values are statistically meaningful at the 0.05 significance level.

Table S14: Estimated constant hazard ratios of progression-free survival with pembrolizumab versus competing interventions from fixed-effect and random-effects network meta-analysis

|  |
| --- |
| **Hazard Ratio (95% credible intervals), fixed-effect** |
| **SOC** |  |  |  |  |  |  |
| 1.17 (0.96, 1.43) | **XELOX** |  |  |  |  |  |
| 0.96 (0.65, 1.42) | 0.82 (0.53, 1.26) | **XELOX + Bevacizumab** |  |  |  |  |
| **0.60 (0.47, 0.75)** | **0.51 (0.38, 0.69)** | **0.62 (0.40, 0.97)** | **FOLFOXIRI** |  |  |  |
| **0.70 (0.61, 0.80)** | **0.59 (0.47, 0.76)** | 0.73 (0.48, 1.10) | 1.17 (0.89, 1.53) | **FOLFOXIRI + Bevacizumab** |  |  |
| **0.82 (0.70, 0.95)** | **0.70 (0.55, 0.89)** | 0.85 (0.56, 1.28) | **1.37 (1.05, 1.79)** | 1.17 (0.96, 1.43) | **FOLFOX + Panitumumab** |  |
| **0.60 (0.45, 0.80)** | **0.51 (0.36, 0.72)** | 0.62 (0.38, 1.01) | 1.00 (0.69, 1.45) | 0.86 (0.63, 1.19) | 0.73 (0.53, 1.01) | **Pembrolizumab** |
| **Hazard Ratio (95% credible intervals),** **random-effects** |
| **SOC** |  |  |  |  |  |  |
| 1.17 (0.65, 2.04) | **XELOX** |  |  |  |  |  |
| 0.96 (0.50, 1.85) | 0.82 (0.35, 1.93) | **XELOX + Bevacizumab** |  |  |  |  |
| **0.60 (0.39, 0.92)** | 0.51 (0.25, 1.04) | 0.63 (0.28, 1.33) | **FOLFOXIRI** |  |  |  |
| **0.67 (0.44, 0.88)** | 0.57 (0.28, 1.05) | 0.69 (0.31, 1.37) | 1.11 (0.61, 1.84) | **FOLFOXIRI + Bevacizumab** |  |  |
| 0.82 (0.56, 1.23) | 0.71 (0.36, 1.42) | 0.86 (0.41, 1.84) | 1.38 (0.78, 2.49) | 1.24 (0.79, 2.21) | **FOLFOX + Panitumumab** |  |
| 0.60 (0.33, 1.08) | 0.51 (0.23, 1.19) | 0.62 (0.26, 1.50) | 1.00 (0.48, 2.05) | 0.90 (0.49, 1.89) | 0.73 (0.35, 1.45) | **Pembrolizumab** |

**Abbreviations**: FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; SOC, standard of care; XELOX, oxaliplatin + capecitabine.

**Notes**: Each cell represents the comparison (hazard ratio and 95% credible intervals) of the row treatment versus the column treatment; All bolded values are statistically meaningful at the 0.05 significance level.

Table S15: Estimated time-varying hazard ratios of overall survival with pembrolizumab versus competing interventions from random-effect network meta-analysis; adjustment for crossover in KEYNOTE-177 using RPSFT model

| **Mos.** | **Pembrolizumab vs. comparator hazard ratio (95% credible intervals)** |
| --- | --- |
| **SOC** | **XELOX** | **XELOX + Bevacizumab** | **FOLFOXIRI** | **FOLFOXIRI****+ Bevacizumab** | **FOLFOX + Panitumumab** |
| 4 | 0.92 (0.53, 1.60) | 0.69 (0.36, 1.39) | 0.87 (0.39, 1.86) | 1.38 (0.74, 2.67) | 0.94 (0.49, 1.80) | 1.25 (0.66, 2.48) |
| 8 | 0.78 (0.48, 1.29) | 0.64 (0.36, 1.20) | 0.74 (0.36, 1.45) | 1.13 (0.65, 2.07) | 0.83 (0.46, 1.50) | 1.04 (0.59, 1.95) |
| 12 | 0.67 (0.42, 1.08) | 0.59 (0.34, 1.09) | 0.63 (0.33, 1.17) | 0.93 (0.54, 1.66) | 0.74 (0.42, 1.29) | 0.87 (0.51, 1.59) |
| 16 | **0.57 (0.34, 0.95)** | 0.55 (0.31, 1.02) | 0.53 (0.28, 1.00) | 0.76 (0.44, 1.39) | 0.65 (0.36, 1.17) | 0.72 (0.41, 1.35) |
| 20 | **0.49 (0.27, 0.88)** | 0.51 (0.27, 1.01) | **0.45 (0.23, 0.89)** | 0.63 (0.34, 1.22) | 0.58 (0.30, 1.10) | 0.61 (0.32, 1.20) |
| 24 | **0.41 (0.21, 0.83)** | 0.48 (0.22, 1.04) | **0.38 (0.18, 0.83)** | 0.52 (0.25, 1.10) | 0.51 (0.24, 1.08) | 0.51 (0.24, 1.10) |
| 28 | **0.35 (0.16, 0.79)** | 0.44 (0.18, 1.09) | **0.33 (0.13, 0.80)** | 0.42 (0.18, 1.01) | 0.45 (0.19, 1.07) | 0.42 (0.17, 1.03) |
| 32 | **0.30 (0.12, 0.77)** | 0.41 (0.15, 1.16) | **0.28 (0.10, 0.79)** | **0.35 (0.13, 0.94)** | 0.40 (0.15, 1.07) | **0.35 (0.13, 0.98)** |
| 36 | **0.26 (0.09, 0.75)** | 0.38 (0.12, 1.25) | **0.24 (0.07, 0.78)** | **0.29 (0.09, 0.88)** | 0.35 (0.11, 1.10) | **0.29 (0.09, 0.93)** |
| 40 | **0.22 (0.06, 0.74)** | 0.36 (0.09, 1.35) | **0.20 (0.05, 0.77)** | **0.24 (0.07, 0.83)** | 0.31 (0.09, 1.11) | **0.24 (0.07, 0.90)** |
| 44 | **0.19 (0.05, 0.72)** | 0.33 (0.07, 1.46) | **0.17 (0.04, 0.77)** | **0.19 (0.05, 0.79)** | 0.28 (0.07, 1.15) | **0.20 (0.05, 0.87)** |
| 48 | **0.16 (0.04, 0.71)** | 0.31 (0.06, 1.59) | **0.14 (0.03, 0.78)** | **0.16 (0.03, 0.75)** | 0.25 (0.05, 1.18) | **0.17 (0.03, 0.84)** |

**Abbreviations**: FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; SOC, standard of care; XELOX, oxaliplatin + capecitabine.

**Notes**: Model presented is P1=1, P2=0 (scale and 1st shape); All bolded values are statistically significant at the 0.05 significance level.

Table S16: Odds ratios estimated from fixed-effect network meta-analysis for treatment-related Grade 3+ adverse events

|  |
| --- |
| **Odds ratios (95% credible intervals)** |
| **SOC** |  |
| **2.23 (1.11, 4.68)** | **XELOX** |  |
| 1.32 (0.92, 1.91) | 0.59 (0.26, 1.30) | **XELOX + Bevacizumab** |  |
| **1.75 (1.10, 2.86)** | 0.79 (0.32, 1.86) | 1.33 (0.72, 2.44) | **FOLFOXIRI + Bevacizumab** |  |
| **2.69 (1.89, 3.85)** | 1.21 (0.53, 2.68) | **2.03 (1.22, 3.41)** | 1.53 (0.84, 2.75) | **FOLFOX + Panitumumab** |  |
| **0.14 (0.08, 0.24)** | **0.06 (0.03, 0.15)** | **0.11 (0.06, 0.20)** | **0.08 (0.04, 0.16)** | **0.05 (0.03, 0.10)** | **Pembrolizumab** |

**Abbreviations**: FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; SOC, standard of care; XELOX, oxaliplatin + capecitabine.

**Notes**: Each cell represents the comparison (odds ratio and 95% credible intervals) of the row treatment versus the column treatment; All bolded values are statistically meaningful at the 0.05 significance level.

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