# Supplementary materials

## **Table A1. Full search strategy for Embase.**

|  |  |
| --- | --- |
| **#** | **Searches** |
| 1 | exp Carcinoma, Non-Small-Cell Lung/ |
| 2 | (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab. |
| 3 | nsclc.ti,ab. |
| 4 | exp "Adenocarcinoma of Lung"/ or (lung$ and (adenocarcino$ or adeno-carcinoma$)).ti,ab. |
| 5 | exp Carcinoma, Squamous Cell/ and (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$ or adenocarcino\*)).ti,ab. |
| 6 | exp Carcinoma, Large Cell/ and (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$ or adenocarcino$)).ti,ab. |
| 7 | or/1-6 |
| 8 | (Advanced or metasta\* or unresectable or progress\* or refractory or recurren\* or inoperable or late-stage or stage 3 or stage 3B or stage 3C or stage III or stage IIIB or stage IIIC or stage three or stage 4 or stage 4A or stage 4B or stage IV or stage IVA or stage IVB or stage four or stage B or stage C or stage D).mp. |
| 9 | exp metastasis/ |
| 10 | 8 or 9 |
| 11 | 7 and 10 |
| 12 | exp epidermal growth factor receptor/ |
| 13 | (ErbB1 or ErbB 1 or ErbB).af. |
| 14 | (TGF$2 TGF-alpha or transforming growth factor$ or urogastrone).af. |
| 15 | (epidermal growth factor receptor$ or epidermis growth factor receptor$).af. |
| 16 | Epidermal Growth Factor$.af. |
| 17 | EGF$2.af. |
| 18 | (EGFR or EGFRTK or EGF receptor$).af. |
| 19 | or/12-18 |
| 20 | 11 and 19 |
| 21 | Clinical Trial/ |
| 22 | randomized controlled trial/ |
| 23 | controlled clinical trial/ |
| 24 | multicenter study/ |
| 25 | Phase 2 clinical trial/ |
| 26 | Phase 3 clinical trial/ |
| 27 | Phase 4 clinical trial/ |
| 28 | exp RANDOMIZATION/ |
| 29 | Single Blind Procedure/ |
| 30 | Double Blind Procedure/ |
| 31 | Crossover Procedure/ |
| 32 | PLACEBO/ |
| 33 | randomi?ed controlled trial$.tw. |
| 34 | rct.tw. |
| 35 | (random$ adj2 allocat$).tw. |
| 36 | single blind$.tw. |
| 37 | double blind$.tw. |
| 38 | ((treble or triple) adj blind$).tw. |
| 39 | placebo$.tw. |
| 40 | Prospective Study/ |
| 41 | or/21-40 |
| 42 | Case Study/ |
| 43 | case report.tw. |
| 44 | abstract report/ or letter/ |
| 45 | Editorial.pt. |
| 46 | Letter.pt. |
| 47 | Note.pt. |
| 48 | or/42-47 |
| 49 | 41 not 48 |
| 50 | 20 and 49 |

## **Table A2. Full search strategy for MEDLINE.**

|  |  |
| --- | --- |
| # | Searches |
| 1 | exp Carcinoma, Non-Small-Cell Lung/ |
| 2 | (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab. |
| 3 | nsclc.ti,ab. |
| 4 | exp "Adenocarcinoma of Lung"/ or (lung$ and adenocarcino$).ti,ab. |
| 5 | exp Carcinoma, Squamous Cell/ and (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$ or adenocarcino\*)).ti,ab. |
| 6 | exp Carcinoma, Large Cell/ and (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$ or adenocarcino$)).ti,ab. |
| 7 | or/1-6 |
| 8 | (Advanced or metasta\* or unresectable or progress\* or refractory or recurren\* or inoperable or late-stage or stage 3 or stage 3B or stage 3C or stage III or stage IIIB or stage IIIC or stage three or stage 4 or stage 4A or stage 4B or stage IV or stage IVA or stage IVB or stage four or stage B or stage C or stage D).mp. |
| 9 | exp Neoplasm Metastasis/ |
| 10 | 8 or 9 |
| 11 | 7 and 10 |
| 12 | exp epidermal growth factor receptor/ |
| 13 | (ErbB1 or ErbB 1 or ErbB).af. |
| 14 | (TGF$2 TGF-alpha or transforming growth factor$ or urogastrone).af. |
| 15 | (epidermal growth factor receptor$ or epidermis growth factor receptor$).af. |
| 16 | Epidermal Growth Factor$.af. |
| 17 | EGF$2.af. |
| 18 | (EGFR or EGFRTK or EGF receptor$).af. |
| 19 | or/12-18 |
| 20 | 11 and 19 |
| 21 | Randomized Controlled Trials as Topic/ |
| 22 | randomized controlled trial/ |
| 23 | Random Allocation/ |
| 24 | Double Blind Method/ |
| 25 | Single Blind Method/ |
| 26 | clinical trial/ |
| 27 | clinical trial, phase ii.pt. |
| 28 | clinical trial, phase iii.pt. |
| 29 | clinical trial, phase iv.pt. |
| 30 | controlled clinical trial.pt. |
| 31 | randomized controlled trial.pt. |
| 32 | multicenter study.pt. |
| 33 | clinical trial.pt. |
| 34 | exp Clinical Trials as topic/ |
| 35 | or/21-34 |
| 36 | (clinical adj trial$).tw. |
| 37 | ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. |
| 38 | PLACEBOS/ |
| 39 | placebo$.tw. |
| 40 | randomly allocated.tw. |
| 41 | (allocated adj2 random$).tw. |
| 42 | or/36-41 |
| 43 | 35 or 42 |
| 44 | case report.tw. |
| 45 | letter/ |
| 46 | historical article/ |
| 47 | or/44-46 |
| 48 | 43 not 47 |
| 49 | 20 and 48 |

## **Table A3. Full search strategy for Cochrane.**

|  |  |
| --- | --- |
| # | Searches |
| 1 | exp Carcinoma, Non-Small-Cell Lung/ |
| 2 | (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab. |
| 3 | nsclc.ti,ab. |
| 4 | exp Carcinoma, Squamous Cell/ and (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$ or adenocarcino\*)).ti,ab. |
| 5 | (lung$ and (adenocarcino$ or adeno-carcinoma$)).ti,ab. |
| 6 | exp Carcinoma, Large Cell/ and (lung$ and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$ or adenocarcino$)).ti,ab. |
| 7 | or/1-6 |
| 8 | (Advanced or metasta\* or unresectable or progress\* or refractory or recurren\* or inoperable or late-stage or stage 3 or stage 3B or stage 3C or stage III or stage IIIB or stage IIIC or stage three or stage 4 or stage 4A or stage 4B or stage IV or stage IVA or stage IVB or stage four or stage B or stage C or stage D).mp. |
| 9 | exp Neoplasm Metastasis/ |
| 10 | 8 or 9 |
| 11 | 7 and 10 |
| 12 | exp Receptor, Epidermal Growth Factor/ |
| 13 | (ErbB1 or ErbB 1 or ErbB).af. |
| 14 | (TGF$2 TGF-alpha or transforming growth factor$ or urogastrone).af. |
| 15 | (epidermal growth factor receptor$ or epidermis growth factor receptor$).af. |
| 16 | Epidermal Growth Factor$.af. |
| 17 | EGF$2.af. |
| 18 | (EGFR or EGFRTK or EGF receptor$).af. |
| 19 | or/12-18 |
| 20 | 11 and 19 |

## **Table A4. Trials identified from the SLR (n=57).**

|  |  |  |  |
| --- | --- | --- | --- |
| Study Acronym or  NCT number | Publications | Study design | Investigational interventions |
| RELAY (NCT02411448) | Nakagawa 2019 [1] (Full text and CSR)\* | RCT, DB, Phase III, MC | Ramucirumab + Erlotinib  Erlotinib + Placebo |
| An 2016 | An 2016 [2] (Full text)\* | RCT, DB | Gefitinib + Placebo  Gefitinib + Pemetrexed |
| ARCHER 1050 (NCT01774721) | Mok 2018 [3] (Full text)\*  Nakagawa 2017 [4] (Abstract)  Wu 2017b [5] (Full text)  Mok 2019a [6] (Abstract)  Nishio 2020 [7] (Full text)  Mok 2019b [8] (Abstract) | MC, RCT, OL, phase III | Dacomitinib  Gefitinib |
| BEYOND (NCT01364012) | Zhou 2015 [9] (Full text)\* | RCT, DB, MC, placebo controlled, Phase III | Bevacizumab + Carboplatin + Paclitaxel  Placebo + Carboplatin + Paclitaxel |
| CALGB 30406 Trial (NCT00126581) | Janne 2012 [10] (Full text)\* | RCT, OL, Phase II | Erlotinib  Erlotinib + Carboplatin + Paclitaxel |
| CONVINCE (NCT01719536) | Shi 2017 [11] (Full text)\* | RCT, OL, Phase III, MC | Icotinib  Cisplatin + Pemetrexed |
| Crawford 2013 | Crawford 2013 [12] (Full text)\* | RCT, OL, Phase II, MC | Carboplatin + Paclitaxel + Panitumumab  Carboplatin + Paclitaxel |
| CTONG0901 (NCT01024413) | Yang 2017 [13] (Full text)\* | RCT, Phase III, Chinese | Gefitinib  Erlotinib |
| CTONG1509 (NCT02759614) | Zhou 2019 [14] (Abstract) | RCT, OL, Phase III, MC | Bevacizumab  Bevacizumab + Erlotinib |
| CTRI/2015/08/006113 | Patil 2017 [15] (Full text)\* | RCT, OL, Phase III, SC, | Gefitinib  Pemetrexed + Carboplatin |
| CTRI/2016/08/007149 | Noronha 2019a [16] (Abstract)\*  Noronha 2019b [17] (Full text)\* | RCT, Phase III | Gefitinib  Gefitinib + Carboplatin + Pemetrexed |
| ENSURE (NCT01342965) | Wu 2015a [18] (Full text)\*  Wu 2019 [19] (Full text)  Wu 2014b [20] (Abstract) | RCT, OL, Phase III, MC | Erlotinib  Gemcitabine + Cisplatin |
| EURTAC (NCT00446225) | Rosell 2012 [21] (Full Text)\*  De Marinis 2015 [22] (Full Text) | MC, OL, RCT, Phase III | Erlotinib  Standard Chemotherapy (Cisplatin + Docetaxel or Cisplatin + Gemcitabine) or (Carboplatin + Docetaxel or Carboplatin + Gemcitabine) [For cisplatin ineligible patients, carboplatin is given] |
| FASTACT-2 (NCT00883779) | Wu 2013b [23] (Full text)\*  Mok 2016b [24] (Full text) | RCT, DB, Phase III, MC | Chemotherapy (Gemcitabine + Carboplatin/Cisplatin) + Erlotinib  Chemotherapy (Gemcitabine + Carboplatin/Cisplatin) + Placebo |
| FLAURA (NCT02296125) | Soria 2018 [25] (Full text)\*  Cho 2019 [26] (Full text)  Gray 2017 [27] (Abstract)  Leighl 2018 [28] (Abstract)  Planchard 2018 [29] (Abstract)  Reungwetwattana 2018 [30] (Full text)  Zhou 2018 [31] (Abstract)  Ramalingam 2019b [32] (Poster slides)  Ramalingam 2019a [33] (Full text)  Ohe 2019 [34] (Full text)  Leighl 2020 [35] (Full text)  Planchard 2019 [36] (Full text) | RCT, DB, Phase III, MC | Osimertinib  Gefitinib or Erlotinib |
| GENOA (NCT02319577) | Genova 2019 [37] (Abstract) | RCT, OL, Phase II, MC | Vinorelbine + gefitinib  Gefitinib |
| GOAL (NCT01513174) | Campelo 2018 [38] (Abstract)\* | RCT, OL, Phase II, MC | Gefitinib + Olaparib  Gefitinib |
| IFCT-1503 ACE-Lung (NCT02716311) | Cortot 2019 [39] (Abstract)\* | RCT, OL, Phase II, MC | Afatinib  Afatinib + Cetuximab |
| INCREASE (NCT02404675) | Li 2018 [40] (Abstract)\* | RCT, OL, Phase II | Routine-dose icotinib (L858R)  High-dose icotinib (L858R)  Routine-dose icotinib (Exon 19 deletion) |
| INNOVATIONS (NCT00536640) | Thomas 2015 [41] (Full text)\* | RCT, OL, Phase II, MC | Erlotinib + Bevacizumab  Bevacizumab + Cisplatin + Gemcitabine |
| IPASS (NCT00322452) | Mok 2009 [42] (Full text)\*  Fukuoka 2011 [43] (Full text)  Goto 2012 [44] (Full text)  Thongprasert 2011 [45] (Full text)  Wu 2017a [46] (Full text)  Wu 2013 [47] (Full text) | RCT, OL, Phase III, MC | Gefitinib  Carboplatin + Paclitaxel |
| JCOG0803/WJOG4307L | Abe 2015 [48] (Full text)\*  Takeda 2017 [49] (Abstract) | RCT, Phase III, MC (blinding NR) | Docetaxel  Docetaxel + Cisplatin |
| JO25567 (JapicCTI-111390) | Seto 2014 [50] (Full text)\*  Kato 2018 [51] (Full text)  Kato 2014 [52] (Abstract)  Seto 2018 [53] (Abstract) | RCT, OL, Phase II, MC | Erlotinib  Erlotinib + Bevacizumab |
| JPRN-JapicCTI-121887 | Kubota 2017 [54] (Full text)\* | Placebo controlled, DB, Phase III, MC | Motesanib + Paclitaxel + Carboplatin  Placebo + Paclitaxel + Carboplatin |
| KEYNOTE-021 (NCT02039674) | Yang 2019 [55] (Full text) | RCT, OL, Phase I/II, MC | Pembrolizumab + Erlotinib  Pembrolizumab + Gefitinib |
| LUX-Lung 3 (NCT00949650) | Sequist 2013 [56] (Full text)\*  Kato 2015 [57] (Full text)  Yang 2013 [58] (Full text)  Schuler 2016 [59] (Full text)  Schuler 2015 [60] (Abstract)  Yang 2015b [61] (Full text)  Schuler 2017b[62] (Abstract)  Schuler 2017a [63] (Abstract)  Wu 2018a [64] (Full text)  Wu 2018b [65] (Full text)  Schuler 2019b [66] (Full text) | RCT, OL, Phase III, MC | Afatinib  Cisplatin + Pemetrexed |
| LUX-Lung 6 (NCT01121393) | Wu 2014a [67] (Full text)\*  Schuler 2016 [59] (Full text)  Schuler 2015 [60] (Abstract)  Yang 2015b [61] (Full text)  Schuler 2017b [62] (Abstract)  Schuler 2017a [63] (Abstract)  Wu 2018a [64] (Full text)  Geater 2015 [68] (Full text)  Wu 2018c [69] (Full text)  Wu 2018b [65] (Full text)  Schuler 2019b [66] (Full text) | RCT, OL, Phase III, MC | Afatinib  Gemcitabine + Cisplatin |
| LUX-Lung 7 (NCT01466660) | Park 2016 [70] (Full text)\*  Schuler 2017b [62] (Abstract)  Schuler 2017a [63] (Abstract)  Wu 2018a [64] (Full text)  Corral 2017 [71] (Abstract)  O'Byrne 2018 [72] (Abstract)  PazAres 2017 [73] (Full text)  Schuler 2019a [74] (Full text)  Schuler 2019b [66] (Full text) | RCT, OL, Phase III, MC | Afatinib  Geﬁtinib |
| NCT00294762 | Hirsch 2011 [75] (Full Text)\* | MC, RCT, Phase II (blinding NR) | Erlotinib  Chemotherapy (Carboplatin + Paclitaxel) + Erlotinib |
| NCT01017874 | Yang 2014 [76] (Full text)\*  Yang 2016 [77] (Full text) | MC, OL, RCT, phase III | Pemetrexed + Cisplatin (Maintenance by gefitinib)  Gefitinib |
| NCT01039948 | Mok 2016 [78] (Full text)\* | MC, OL, RCT, Phase II | Gefitinib  Gefitinib + Ficlatuzumab |
| NCT01131429 | Zhao 2017 [79] (Full Text)\* | SC, RCT, Phase II (blinding NR) | Erlotinib (1st line) + Docetaxel/Cisplatin (2nd line)  Docetaxel/Cisplatin (1st line) + Erlotinib (2nd line) |
| NCT01196078 | Chen 2012 [80] (Full Text)\* | OL, RCT, Phase II | Erlotinib  Vinorelbine |
| NCT01221077 | Leighl 2017 [81] (Full text)\* | RCT, double-blinded, Phase II, MC  --> unblinded early, on February 15, 2013. | Linsitinib + erlotinib  Placebo + erlotinib |
| NCT01469000 | Cheng 2016 [82] (Full text)\*  Yang 2016 [83] (Abstract)  Yang 2020 [84] (Full text) | MC, Parallel arm, OL, RCT, Phase II | Pemetrexed + Gefitinib  Gefitinib |
| NCT01502202 | Lee 2016 [85] (Abstract)\* | RCT, Phase II, Cross-over, Placebo controlled | Gefitinib + Pemetrexed/Cisplatin  Placebo + Pemetrexed/Cisplatin |
| NCT01532089 | Stinchcombe 2018 [86] (Abstract)\*  Stinchcombe 2020 [87] (Full text) | RCT, Phase II, MC | Erlotinib + Bevacizumab  Erlotinib |
| NCT01665417 | Sun 2017 [88] (Abstract)\* | RCT | Icotinib  2 cycle docetaxel + platinum with icotinib maintenance  2 cycle of pemetrexed + platinum with icotinib maintenance  4 cycle docetaxel + platinum with icotinib maintenance  4 cycle of pemetrexed + platinum with icotinib maintenance |
| NCT01769066 | Yu 2014 [89] (Full Text)\* | RCT, OL, Phase II, SC | Gefitinib + Pemetrexed + Cisplatin/Carboplatin  Pemetrexed + Cisplatin/Carboplatin |
| NCT01810367 | Qin 2019 [90] (Full text) | RCT, OL, Phase II | nab-paclitaxel + cisplatin  Gemcitabine + cisplatin |
| NCT01864681 | Li 2019 [91] (Full text)  He 2019 [92] (Abstract) | RCT, DB, Phase II, MC | Gefitinib + Metformin  Gefitinib + Placebo |
| NCT01897480 | Scagliotti 2017 [93] (Abstract)\*  Scagliotti 2020 [94] (Full text) | RCT, OL, Phase II | Erlotinib  Erlotinib + Emibetuzumab |
| NCT02148380 | Han 2017 [95] (Full text)\*  Zhang 2019 [96] (Abstract) | RCT, OL, Phase II, SC | Pemetrexed + Carboplatin + Gefitinib  Pemetrexed + Carboplatin  Gefitinib |
| NCT02588261 | Kelly 2019 [97] (Full text) | RCT, OL, Phase III, MC | ASP8273  Erlotinib/Gefitnib |
| NEJ002 (UMIN-CTR C000000376) | Inoue 2013 [98] (Full text)\*  Maemondo 2010 [99] (Full text)\* | RCT, Phase III | Gefitinib  Carboplatin + Paclitaxel |
| NEJ005/TCOG0902 | Sugawara 2015 [100] (Full text)\*  Oizumi 2017 [101] (Full text) | RCT, Phase II | Concurrent Gefitinib + Carboplatin + Pemetrexed  Sequential alternating Gefitinib + Carboplatin + Pemetrexed |
| NEJ009 (UMIN000006340) | Nakamura 2018 [102] (Poster slides)\*  Hosomi 2019 [103] (Full text) | RCT, OL, Phase III | Gefitinib  Gefitinib + Carboplatin + Pemetrexed |
| NEJ026 (UMIN000017069) | Kawashima 2018 [104] (Abstract)\*  Saito 2019 [105] (Full text)  Maemondo 2020 [106] (Poster slides) | RCT, Phase III | Erlotinib + Bevacizumab  Erlotinib |
| OPTIMAL, CTONG-0802 (NCT00874419) | Zhou 2011 [107] (Full text)\*  Chen 2013 [108] (Full text)  Zhou 2015a [109] (Full text) | RCT, Phase III, OL, MC, first-line | Erlotinib  Gemcitabine + Carboplatin |
| Prabhash study | Prabhash 2017 [110] (Abstract)\*  Prabhash 2019a [111] (Abstract)  Prabhash 2019b [112] (Abstract) | RCT, OL, parallel study, phase III | Gefitinib + Platinum (Cisplatin or Carboplatin)  Pemetrexed + Platinum (Cisplatin or Carboplatin) |
| Singh 2014 | Singh 2014 [113] (Abstract)\* | RCT | Gefitinib  Carboplatin + Paclitaxel |
| SWOG S1403 (NCT02438722) | Goldberg 2018 [114] (Abstract)\* | RCT, OL, Phase II/3, Parallel Assignment, MC | Afatinib + Cetuximab  Afatinib |
| TOPICAL | Lee 2012 [115] (Full text)\* | RCT, DB, Phase III, MC | Erlotinib  Placebo |
| TORCH (NCT00349219) | Gridelli 2012 [116] (Full text)\*  Di Maio 2012 [117] (Full text) | QoL results from TORCH (phase III) trial, also exploratory analysis of QoL differences between the two first-line strategies in the subgroup of patients with known EGFR mutation status. | Erlotinib  Cisplatin + Gemcitabine |
| UMIN000013586 | Kitagawa 2019 [118] (Full text)\* | RCT, OL, Phase II, MC | Gefitinib  Gefitinib + Bevacizumab |
| WJTOG3405 | Mitsudomi 2010 [119] (Full text)\*  Yoshioka 2014 [120] (Poster)  Yoshioka 2019 [121] (Full text) | RCT, OL, Phase III, MC | Gefitinib  Cisplatin + Docetaxel |
| Xie 2015 | Xie 2015 [122] (Full text)\* | RCT, SC | Gefitinib  Erlotinib |

Abbreviations: DB: double blind; MC: multi-centre; NR: not reported; OL: open label; QoL: Quality of Life; RCT: randomized controlled trial; SLR: systematic literature review; SC: single-center

\*Primary publication

## **Table A5. PFS evidence for overall EGFRm+ NSCLC patient population, by mutation type, and by geographical region.**

| **Trial (Author, Year)** | **Intervention** | **Overall** | |  | **Exon 19del** | |  | **Exon 21 L858R** | |  | **East Asian** | |  | **Non-East Asian** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Median (months)** | **HR (95% CI) \*p < 0.05** |  | **Median (months)** | **HR (95% CI) \*p < 0.05** |  | **Median (months)** | **HR (95% CI) \*p < 0.05** |  | **Median (months)** | **HR (95% CI) \*p < 0.05** |  | **Median (months)** | **HR (95% CI) \*p < 0.05** |
| **Versus EGFR-TKI** | | | | | | | | | | | | | | | |
| RELAY (Nakagawa, 2019) [123] | RAM+ERL | 19.40‡ | 0.591 (0.461,0.76)\* |  | 19.60 | 0.651 (0.469,0.903) |  | 19.40 | 0.618 (0.437,0.874) |  | 19.40 | 0.636 (0.485,0.833)\* |  | 20.60 | 0.605 (0.362,1.01) |
| ERL | 12.40‡ |  | 12.50 |  | 11.20 |  | 12.50 |  | 10.90 |
| An 2016 [2] | GEF+PEM | 18.00 | NR |  | NR | NR |  | NR | NR |  | 18.00 | NR |  | NR | NR |
| GEF | 14.00 |  | NR |  | NR |  | 14.00 |  | NR |
| ARCHER 1050 (Wu, 2017) [124] | DAC | 16.60‡ | 0.62 (0.5,0.78)\* |  | 16.50 | 0.55 (0.41,0.75) |  | 12.30 | 0.63 (0.44,0.88) |  | NR | 0.51 (0.39,0.66) |  | NR | 0.89 (0.57,1.39) |
| GEF | 11.00‡ |  | 9.20 |  | 9.80 |  | NR |  | NR |
| CALGB 30406 (NCT00126581) (Janne 2012) [10] | ERL+PAC+CARBO | 17.2 | NR |  | 27.5 | NR |  | 11.2 | NR (NR,NR) |  | NR | NR |  | 17.2 | NR (NR,NR) |
| ERL | 14.1 |  | 15.7 |  | 12.6 |  | NR |  | 14.1 |
| CTONG0901 (Yang 2017) [13] | ERL | 13.20 | 0.96 (0.69,1.35) |  | NR | NR |  | NR | NR |  | NR | NR |  | NR | NR |
| GEF | 11.10 |  | NR |  | NR |  | NR |  | NR |
| CTRI/2016/08/007149 (Noronha 2019b) [17] | GEF+CARBO+PEM | 16‡ | 0.51 (0.39,0.66)\* |  | NR | NR |  | NR | NR |  | NR | NR |  | 16 | 0.51 (0.39,0.66)\* |
| GEF | 8‡ |  | NR |  | NR |  | NR |  | 8 |
| FLAURA (Soria 2018) [25] | OSI | 18.9‡ | 0.46 (0.37,0.57)\* |  | 21.40 | 0.43 (0.32,0.56)\* |  | 14.40 | 0.51 (0.36,0.71)\* |  | NR | 0.55 (0.42,0.72) |  | NR | 0.34 (0.23,0.48) |
| ERL/GEF | 10.2‡ |  | 11.00 |  | 9.50 |  | NR |  | NR |
| GENOA / NCT02319577 (Genova, 2019) [37] | VIN+GEF | 6.2 | NR |  | NR | NR |  | NR | NR |  | NR | NR |  | 6.2 | NR (NR,NR) |
| GEF | 9.5 |  | NR |  | NR |  | NR |  | 9.5 |
| GOAL (Campelo 2018) [38] | GEF+OLA | 12.8 | 0.75 (0.52,1.08) |  | NR | NR |  | NR | NR |  | NR | NR |  | 12.8 | 0.75 (0.52,1.08) |
| GEF | 10.90 |  | NR |  | NR |  | NR |  | 10.90 |
| IFCT-1503 ACE-Lung (Cortot 2019) [125] | AFA+CET | 12.80 | NR |  | NR | NR |  | NR | NR |  | NR | NR |  | 12.80 | NR (NR,NR) |
| AFA | 11.10 |  | NR |  | NR |  | NR |  | 11.10 |
| INCREASE (Li 2018) [40] | HD-ICO | 12.62¥ | NR |  | NR | NR |  | 12.62 | NR (NR,NR) |  | 12.62 | NR |  | NR | NR |
| ICO | 8.84¥ |  | NR |  | 8.84 |  | 8.84 |  | NR |
| JO25567 (JapicCTI-111390) (Seto 2014) [50] | ERL+BEV | 16.00¥ | 0.54 (0.36,0.79)\* |  | 18.00 | 0.41 (0.24,0.72)\* |  | 13.9 | 0.67 (0.38,1.18)\* |  | 16.00 | 0.54 (0.36,0.79)\* |  | NR | NR |
| ERL | 9.7¥ |  | 10.3 |  | 7.1 |  | 9.7 |  | NR |
| LUX-Lung 7 (Park 2016) [70] | AFA | 12.80‡ | 0.78 (0.61,0.99)\* |  | 12.70 | 0.76 (0.55,1.06) |  | 10.90 | 0.71 (0.47,1.06) |  | 11.00 | 0.76 (0.54,1.06) |  | 12.70 | 0.72 (0.49,1.06) |
| GEF | 11.20‡ |  | 11.00 |  | 10.80 |  | 11.00 |  | 10.60 |
| NCT01017874 (Yang, 2014) [76] | CIS+PEM+GEF\_m | 12.91 | 0.83 (0.42,1.62) |  | NR | NR |  | NR | NR |  | 12.91 | 0.83 (0.42,1.62) |  | NR | NR |
| GEF | 16.62 |  | NR |  | NR |  | 16.62 |  | NR |
| NCT01039948 (Mok, 2016) [78] | GEF+FIC | 9.20 | 0.95 (NR) |  | NR | NR |  | NR | NR |  | 9.20 | 0.95 (NR,NR) |  | NR | NR |
| GEF | 7.40 |  | NR |  | NR |  | 7.40 |  | NR |
| NCT01221077 (Leighl 2017) [78, 81] | LIN+ERL | 8.40 | 1.366 (0.763,2.445) |  | 8.40 | 2.09 (0.941,4.641) |  | 9.40 | 0.831 (0.344,2.011) |  | 8.20 | 1.48 (0.59,3.69) |  | 8.50 | 1.42 (0.66,3.09) |
| ERL | 12.36 |  | 12.90 |  | 11.70 |  | 11.00 |  | 12.90 |
| NCT01469000 (Yang 2020) [82] | GEF+PEM | 16.2 | 0.67 (0.5,0.9)\* |  | 17.1 | 0.67 (0.43,1.05) |  | 12.6 | 0.58 (0.33,1.01) |  | NR | NR |  | NR | NR |
| GEF | 11.1 |  | 11.1 |  | 10.9 |  | NR |  | NR |
| NCT01502202 (Lee 2016) [85] | CIS+PEM+GEF\_m | 13.30 | NR |  | NR | NR |  | NR | NR |  | 13.30 | NR |  | NR | NR |
| CIS+PEM | 7.80 |  | NR |  | NR |  | 7.80 |  | NR |
| NCT01532089 (Stinchcomb, 2019) [87] | ERL+BEV | 17.9‡ | 0.81 (0.5,1.31) |  | NR | NR |  | NR | NR |  | NR | NR |  | 17.9 | 0.81 (0.5,1.31) |
| ERL | 13.5‡ |  | NR |  | NR |  | NR |  | 13.5 |
| NCT01864681 (Li 2019) [91] | GEF+MET | 10.3¥ | 1.04 (0.75,1.45) |  | 13 | 0.92 (0.57,1.47) |  | 9.3 | 1.23 (0.74,1.63) |  | NR | NR |  | NR | NR |
| GEF | 11.4¥ |  | 11.7 |  | 10.3 |  | NR |  | NR |
| NCT01897480 (Scagliotti, 2020) [126] | EMI+ERL | 9.3 | 0.89 (0.64,1.226) |  | NR | NR |  | NR | NR |  | NR | NR |  | NR | NR |
| ERL | 9.5 |  | NR |  | NR |  | NR |  | NR |
| NCT02148380 (Han, 2017) [95] | GEF+CARBO+PEM | 17.50 | 0.48 (0.29,0.78)\* |  | NR | 0.6 (0.3,1.21) |  | NR | 0.31 (0.15,0.66) |  | 17.50 | 0.48 (0.29,0.78)\* |  | NR | NR |
| GEF | 11.90 |  | NR |  | NR |  | 11.90 |  | NR |
| NEJ005/TCOG0902 (Sugawara, 2015) [100, 101] | GEF+CARBO+PEM | 18.30 | 0.71 (0.42,1.2) |  | 17.90 | NR |  | 18.60 | NR (NR,NR) |  | 18.30 | 0.71 (0.42,1.2) |  | NR | NR |
| GEF+CARBO+PEM (Alter) | 15.30 |  | 15.40 |  | 11.90 |  | 15.30 |  | NR |
| NEJ009 (UMIN000006340) (Hosomi 2019) [103] | GEF+CARBO+PEM | 20.93 | 0.49 (0.39,0.62)\* |  | NR | 0.47 (0.34,0.64) |  | NR | 0.55 (0.38,0.8) |  | 20.93 | 0.49 (0.39,0.62)\* |  | NR | NR |
| GEF | 11.17 |  | NR |  | NR |  | 11.17 |  | NR |
| NEJ026 (Saito 2019) [105] | ERL+BEV | 16.9¥ | 0.605 (0.417,0.877)\* |  | 16.6 | 0.69 (0.41,1.16) |  | 17.4 | 0.57 (0.33,0.97) |  | 16.9 | 0.605 (0.417,0.877)\* |  | NR | NR |
| ERL | 13.3¥ |  | 12.4 |  | 13.7 |  | 13.3 |  | NR |
| SWOG S1403 (Goldberg 2018) [114] | AFA+CET | 10.6 | 1.17 (0.8,1.73) |  | NR | NR |  | NR | NR |  | NR | NR |  | 10.6 | 1.17 (0.8,1.73) |
| AFA | 13.1 |  | NR |  | NR |  | NR |  | 13.1 |
| UMIN000013586 (Kitagawa, 2019) [118] | GEF+BEV | 5.40 | NR |  | NR | NR |  | NR | NR |  | 5.40 | NR |  | NR | NR |
| GEF | 15.10 |  | NR |  | NR |  | 15.10 |  | NR |
| Xie 2015 [122] | GEF | 8.00 | NR |  | NR | NR |  | NR | NR |  | 8.00 | NR |  | NR | NR |
| ERL | 8.50 |  | NR |  | NR |  | 8.50 |  | NR |
| **versus Chemotherapy** | | | | | | | | | | | | | | | |
| CONVINCE (Shi 2017) [11] | ICO | 9.9‡ | 0.65 (0.48,0.88)\* |  | NR | 0.51 (0.34,0.76)\* |  | NR | 0.9 (0.6,1.35) |  | 9.9 | 0.65 (0.48,0.88)\* |  | NR | NR |
| CIS+PEM | 7.3‡ |  | NR |  | NR |  | 7.3 |  | NR |
| CTRI/2015/08/006113 (Patil 2017) [15] | GEF | 8.40 | 0.66 (0.513,0.851)\* |  | NR | 0.53 (0.28,1.04)\* |  | NR | 0.56 (0.29,1.09)\* |  | NR | NR |  | 8.40 | 0.66 (0.513,0.851)\* |
| CARBO+PEM | 5.60 |  | NR |  | NR |  | NR |  | 5.60 |
| ENSURE (Wu 2015) [18] | ERL | 11.00‡ | 0.34 (0.22,0.51)\* |  | 11.1 | 0.20 (0.11,0.37) |  | 8.3 | 0.57 (0.31,1.05) |  | 11.00 | 0.34 (0.22,0.51)\* |  | NR | NR |
| GEM+CIS | 5.5‡ |  | 4.2 |  | 7.1 |  | 5.5 |  | NR |
| LUX-Lung 3 (Sequist 2013) [56] | AFA | 11.07‡ | 0.49 (0.37,0.65)\* |  | NR | 0.27 (0.18,0.41) |  | NR | 0.6 (0.39,0.93) |  | NR | 0.45 (0.33,0.62) |  | NR | 0.62 (0.36,1.06) |
| CIS+PEM | 6.70‡ |  | NR |  | NR |  | NR |  | NR |
| LUX-Lung 6 (Wu 2014a) [67] | AFA | 13.70‡ | 0.26 (0.19,0.36)\* |  | NR | 0.2 (0.13,0.33) |  | NR | 0.32 (0.19,0.52) |  | 13.70 | 0.26 (0.19,0.36)\* |  | NR | NR |
| GEM+CIS | 5.60‡ |  | NR |  | NR |  | 5.60 |  | NR |
| NCT01769066 (Yu 2014) [89] | CIS+PEM+GEF\_m | Not reached | 0.2 (0.05,0.75)\* |  | NR | NR |  | NR | NR |  | Not reached | 0.2 (0.05,0.75)\* |  | NR | NR |
| CIS+PEM | 14.00 |  | NR |  | NR |  | 14.00 |  | NR |
| NCT02148380 (Han, 2017) [95] | GEF+CARBO+PEM | 17.50 | 0.16 (0.09,0.29)\* |  | NR | 0.15 (0.06,0.36) |  | NR | 0.11 (0.04,0.28) |  | 17.50 | 0.16 (0.09,0.29)\* |  | NR | NR |
| CARBO+PEM | 5.70 |  | NR |  | NR |  | 5.70 |  | NR |
| NCT02148380 (Han, 2017) [95] | GEF | 11.90 | 0.35 (0.21,0.6)\* |  | NR | NR |  | NR | NR |  | 11.90 | 0.35 (0.21,0.6)\* |  | NR | NR |
| CARBO+PEM | 5.70 |  | NR |  | NR |  | 5.70 |  | NR |

AFA: afatinib; BEV: bevacizumab; CARBO: carboplatin; CIS: cisplatin; DAC: dacomitinib; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFRm+: epidermal growth factor receptor mutation positive; ERL: erlotinib; FIC: ficlatuzumab; GEF: gefitinib; GEF\_m: gefitinib maintenance; GEM: gemcitabine; ICO; icotinib; ITT: intention to treat; LIN: linsitinib; MET: metformin; NSCLC, non-small-cell lung cancer; NR: not reported; OSI: osimertinib; PAC: paclitaxel; PEM: pemetrexed; PFS: progression-free survival; RAM: ramucirumab. Notes: ‡Investigator assessed; ¥ Independent review assessment.

## **Table A6. OS evidence for overall EGFRm+ NSCLC patient population.**

| **Trial (Author, Year)** | **Intervention** | **Overall survival** | |
| --- | --- | --- | --- |
| **Median (months)** | **HR (95% CI) \*p < 0.05** |
| **Versus EGFR-TKI** | | | |
| RELAY (Nakagawa, 2019) [123] | RAM+ERL | Not reached | 0.832 (0.532,1.303) |
| ERL | Not reached |
| An 2016 [2] | GEF+PEM | 34.00 | NR |
| GEF | 32.00 |
| Archer 1050 (Mok, 2019) [8] | DAC | 34.1 | 0.748 (0.591,0.947)\* |
| GEF | 27 |
| CALGB 30406 (NCT00126581) (Janne 2012) [10] | ERL+PAC+CARBO | 38.1 | NR |
| ERL | 31.3 |
| CTRI/2016/08/007149 (Noronha 2019b) [17] | GEF+CARBO+PEM | Not reached | 0.45 (0.31,0.65)\* |
| GEF | 17 |
| FLAURA (Ramalingam 2019a) [33] | OSI | 38.6 | 0.8 (0.64,1)\* |
| ERL/GEF | 31.8 |
| GENOA / NCT02319577 (Genova, 2019) [37] | VIN+GEF | 18.2 | NR |
| GEF | Not reached |
| GOAL (Campelo 2018) [38] | GEF+OLA | 23.30 | 1.22 (0.87,1.84) |
| GEF | 23.10 |
| JO25567 (JapicCTI-111390) (Seto 2018) [53] | ERL+BEV | 47.00 | 0.81 (0.53,1.23) |
| ERL | 47.40 |
| LUX-Lung 7 (Corral 2017) [71] | AFA | 27.90 | 0.85 (0.66,1.09) |
| GEF | 24.50 |
| NCT01017874 (Yang, 2016) [77] | CIS+PEM+GEF\_m | 32.40 | 1.57 (0.72,3.39) |
| GEF | 45.70 |
| NCT01039948 (Mok, 2016) [78] | GEF+FIC | NR | 0.93 (NR) |
| GEF | NR |
| NCT01221077 (Leighl 2017) [81] | LIN+ERL | NE | 0.77 (0.24,2.42) |
| ERL | 19.50 |
| NCT01469000 (Yang 2020) [84] | GEF+PEM | 43.4 | 0.77 (0.5,1.2) |
| GEF | 36.8 |
| NCT01532089 (Stinchcomb, 2019) [87] | ERL+BEV | 32.4 | 1.41 (0.71,2.81) |
| ERL | 50.6 |
| NCT01864681 (Li 2019) [91] | GEF+MET | 22 | 1.15 (0.79,1.68) |
| GEF | 27.5 |
| NCT01897480 (Scagliotti, 2020) [94] | EMI+ERL | 34.3 | 0.76 (0.52,1.12) |
| ERL | 25.4 |
| NCT02148380 (Zhang, 2019) [95] | GEF+CARBO+PEM | 37.9 | 0.56 (0.34,0.91)\* |
| GEF | 25.8 |
| NEJ005/TCOG0902 (Oizumi, 2017) [101] | GEF+CARBO+PEM | 41.90 | 0.58 (0.34,0.97)\* |
| GEF+CARBO+PEM (Alter) | 30.70 |
| NEJ009 (UMIN000006340) (Hosomi 2019) [103] | GEF+CARBO+PEM | 50.9 | 0.72 (0.55,0.95)\* |
| GEF | 38.8 |
| NEJ026 (Maemondo 2020) [106] | ERL+BEV | 50.7 | 1.007 (0.681,1.49) |
| ERL | 46.2 |
| SWOG S1403 (Goldberg 2018) [114] | AFA+CET | 26.9 | 1.23 (0.62,2.44) |
| AFA | Not reached |
| **versus Chemotherapy** | | | |
| CONVINCE (Shi 2017) [11] | ICO | 30.50 | NR |
| CIS+PEM | 32.10 |
| CTRI/2015/08/006113 (Patil 2017) [15] | GEF | 18.00 | 0.78 (0.56,1.09) |
| CARBO+PEM | 22.60 |
| ENSURE (Wu 2015) [18] | ERL | 26.3 | 0.91 (0.63,1.31)\* |
| GEM+CIS | 25.5 |
| LUX-Lung 3 (Yang 2015) [61] | AFA | 28.20 | 0.88 (0.66,1.17) |
| CIS+PEM | 28.20 |
| LUX-Lung 6 (Yang 2015) [61] | AFA | 23.10 | 0.93 (0.72,1.22) |
| GEM+CIS | 23.50 |
| NCT02148380 (Han, 2017) [95] | GEF+CARBO+PEM | 32.60 | 0.46 (0.24,0.87)\* |
| CARBO+PEM | 24.30 |
| NCT02148380 (Han, 2017) [95] | GEF | 25.80 | 1.03 (0.58,1.81) |
| CARBO+PEM | 24.30 |
| TORCH (Gridelli 2012) [116] | ERL | 18.10 | 1.58 (0.7,3.57) |
| GEM+CIS | 32.50 |

AFA: afatinib; BEV: bevacizumab; CARBO: carboplatin; CIS: cisplatin; DAC: dacomitinib; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFRm+: epidermal growth factor receptor mutation positive; ERL: erlotinib; FIC: ficlatuzumab; GEF: gefitinib; GEF\_m: gefitinib maintenance; GEM: gemcitabine; ICO; icotinib; ITT: intention to treat; LIN: linsitinib; MET: metformin; NSCLC, non-small-cell lung cancer; NR: not reported; OS: overall survival; OSI: osimertinib; PAC: paclitaxel; PEM: pemetrexed; RAM: ramucirumab.

## **Table A7. Base case PFS - pairwise comparisons of all interventions and comparators.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Treatment** | **ERL/GEF** | **AFA** | **AFA+CET** | **CARBO+PEM** | **CIS+PEM** | **CIS+PEM+GEF\_m** | **DAC** | **EMI+ERL** | **ERL+BEV** | **ERL+PAC+CARBO** | **GEF+BEV** | **GEF+CARBO+PEM** | **GEF+CARBO+PEM (Alter)** | **GEF+FIC** | **GEF+MET** | **GEF+OLA** | **GEF+PEM** | **GEM+CIS** | **ICO** | **ICO high-dose** | **LIN+ERL** | **OSI** | **RAM+ERL** | **VIN+GEF** |
| ERL/GEF | 1 (1,1) | 1.33 (1.02,1.77) | 1.27 (0.82,2.02) | 0.62 (0.44,0.85) | 0.64 (0.42,  0.97) | 1.28 (0.76,  2.17) | 1.61 (1.16,  2.25) | 1.12 (0.75,  1.68) | 1.6 (1.21,  2.1) | 1.23 (0.58,  2.6) | 0.38 (0.08,  2.06) | 2.02 (1.6,  2.56) | 1.43 (0.77,  2.69) | 1.33 (0.71,  2.55) | 0.96 (0.64,  1.44) | 1.33 (0.86,  2.06) | 1.44 (1.04,  1.98) | 0.37 (0.27,  0.52) | 0.99 (0.56,  1.74) | 1.33 (0.66,  2.71) | 0.73 (0.39,  1.38) | 2.18 (1.57,  3.02) | 1.69 (1.19,  2.38) | 0.65 (0.26,  1.57) |
| AFA | 0.75 (0.56,0.98) | 1 (1,1) | 0.95 (0.67,1.37) | 0.47 (0.29,0.7) | 0.48 (0.34,  0.68) | 0.96 (0.57,  1.63) | 1.21 (0.78,  1.85) | 0.85 (0.51,  1.36) | 1.2 (0.8,  1.75) | 0.92 (0.41,  2.03) | 0.28 (0.06,  1.59) | 1.52 (1.05,  2.16) | 1.08 (0.54,  2.12) | 1 (0.5,  2.02) | 0.72 (0.44,  1.17) | 1 (0.59,  1.67) | 1.09 (0.69,  1.64) | 0.28 (0.2,  0.38) | 0.74 (0.44,  1.24) | 1 (0.51,  1.94) | 0.55 (0.28,  1.09) | 1.64 (1.06,  2.49) | 1.27 (0.8,  1.95) | 0.49 (0.19,  1.24) |
| AFA+CET | 0.79 (0.49,1.22) | 1.05 (0.73,1.49) | 1 (1,1) | 0.49 (0.27,0.83) | 0.51 (0.3,  0.82) | 1.01 (0.53,  1.89) | 1.27 (0.71,  2.2) | 0.89 (0.47,  1.6) | 1.26 (0.73,  2.11) | 0.97 (0.4,2.3) | 0.3 (0.06,  1.71) | 1.59 (0.94,  2.61) | 1.13 (0.52,  2.41) | 1.05 (0.48,  2.3) | 0.76 (0.4,  1.37) | 1.05 (0.55,  1.94) | 1.14 (0.64,  1.96) | 0.29 (0.18,  0.47) | 0.78 (0.41,  1.44) | 1.05 (0.49,  2.21) | 0.58 (0.26,  1.24) | 1.72 (0.97,  2.95) | 1.34 (0.74,  2.32) | 0.51 (0.18,  1.39) |
| CARBO+PEM | 1.6 (1.18,2.3) | 2.13 (1.43,3.42) | 2.03 (1.2,3.71) | 1 (1,1) | 1.03 (0.62,  1.79) | 2.06 (1.13,  3.91) | 2.58 (1.66,  4.29) | 1.8 (1.09,  3.1) | 2.56 (1.7,  4.01) | 1.97 (0.87,  4.54) | 0.6 (0.13,  3.45) | 3.23 (2.22,5) | 2.3 (1.15,  4.74) | 2.14 (1.06,  4.47) | 1.54 (0.93,  2.66) | 2.14 (1.26,  3.79) | 2.31 (1.49,  3.72) | 0.59 (0.39,  0.98) | 1.58 (0.84,  3.13) | 2.14 (1.01,  4.78) | 1.18 (0.59,  2.43) | 3.48 (2.26,  5.74) | 2.71 (1.72,  4.47) | 1.04 (0.4,  2.76) |
| CIS+PEM | 1.56 (1.03,2.36) | 2.07 (1.48,2.95) | 1.97 (1.22,3.29) | 0.97 (0.56,1.61) | 1 (1,1) | 2 (1.21,  3.3) | 2.51 (1.47,  4.27) | 1.75 (0.98,  3.12) | 2.49 (1.51,  4.08) | 1.91 (0.81,  4.47) | 0.59 (0.12,  3.39) | 3.14 (1.95,  5.05) | 2.23 (1.05,  4.7) | 2.08 (0.97,  4.49) | 1.5 (0.83,  2.68) | 2.08 (1.13,  3.79) | 2.25 (1.31,  3.79) | 0.58 (0.37,  0.92) | 1.54 (1.05,  2.27) | 2.08 (1.18,  3.68) | 1.14 (0.54,  2.42) | 3.39 (2,5.74) | 2.63 (1.53,  4.49) | 1.01 (0.37,  2.7) |
| CIS+PEM+GEF\_m | 0.78 (0.46,1.32) | 1.04 (0.61,1.76) | 0.99 (0.53,1.88) | 0.49 (0.26,0.89) | 0.5 (0.3,  0.83) | 1 (1,1) | 1.26 (0.67,  2.33) | 0.88 (0.45,  1.69) | 1.25 (0.68,  2.25) | 0.96 (0.38,  2.37) | 0.29 (0.06,  1.73) | 1.57 (0.88,  2.79) | 1.12 (0.49,  2.51) | 1.04 (0.45,  2.36) | 0.75 (0.38,  1.45) | 1.04 (0.52,  2.05) | 1.12 (0.6,  2.07) | 0.29 (0.16,  0.52) | 0.77 (0.41,  1.46) | 1.04 (0.49,  2.23) | 0.57 (0.25,  1.29) | 1.7 (0.91,  3.14) | 1.32 (0.7,  2.45) | 0.5 (0.18,  1.44) |
| DAC | 0.62 (0.44,0.86) | 0.82 (0.54,1.29) | 0.79 (0.45,1.4) | 0.39 (0.23,0.6) | 0.4 (0.23,  0.68) | 0.8 (0.43,  1.48) | 1 (1,1) | 0.7 (0.41,  1.16) | 0.99 (0.64,  1.51) | 0.76 (0.34,  1.72) | 0.23 (0.05,  1.32) | 1.25 (0.84,  1.88) | 0.89 (0.44,  1.8) | 0.83 (0.4,  1.71) | 0.6 (0.35,1) | 0.83 (0.48,  1.43) | 0.9 (0.56,  1.41) | 0.23 (0.15,  0.37) | 0.61 (0.32,  1.19) | 0.83 (0.38,  1.81) | 0.45 (0.22,  0.93) | 1.35 (0.85,  2.14) | 1.05 (0.65,  1.69) | 0.4 (0.15,  1.05) |
| EMI+ERL | 0.89 (0.6,1.34) | 1.18 (0.73,1.96) | 1.13 (0.62,2.11) | 0.56 (0.32,0.92) | 0.57 (0.32,  1.02) | 1.14 (0.59,  2.23) | 1.44 (0.86,  2.42) | 1 (1,1) | 1.42 (0.87,  2.32) | 1.09 (0.47,  2.55) | 0.33 (0.07,  1.93) | 1.8 (1.13,  2.89) | 1.27 (0.61,  2.7) | 1.19 (0.56,  2.55) | 0.85 (0.48,  1.52) | 1.19 (0.66,  2.16) | 1.28 (0.77,  2.15) | 0.33 (0.2,  0.56) | 0.88 (0.44,  1.77) | 1.19 (0.53,  2.7) | 0.65 (0.31,  1.38) | 1.94 (1.16,  3.27) | 1.5 (0.89,  2.56) | 0.58 (0.21,  1.56) |
| ERL+BEV | 0.63 (0.48,0.82) | 0.83 (0.57,1.24) | 0.79 (0.47,1.37) | 0.39 (0.25,0.59) | 0.4 (0.24,  0.66) | 0.8 (0.44,  1.46) | 1.01 (0.66,  1.55) | 0.7 (0.43,  1.15) | 1 (1,1) | 0.77 (0.35,  1.71) | 0.23 (0.05,  1.32) | 1.26 (0.88,  1.82) | 0.89 (0.45,  1.78) | 0.83 (0.42,  1.68) | 0.6 (0.37,  0.98) | 0.83 (0.5,1.4) | 0.9 (0.59,  1.38) | 0.23 (0.15,  0.36) | 0.62 (0.33,  1.17) | 0.83 (0.39,  1.79) | 0.46 (0.23,  0.91) | 1.36 (0.9,  2.09) | 1.06 (0.68,  1.65) | 0.4 (0.16,  1.04) |
| ERL+PAC+CARBO | 0.81 (0.38,1.72) | 1.08 (0.49,2.43) | 1.03 (0.44,2.52) | 0.51 (0.22,1.15) | 0.52 (0.22,  1.23) | 1.05 (0.42,  2.6) | 1.31 (0.58,  2.97) | 0.92 (0.39,  2.15) | 1.3 (0.58,  2.89) | 1 (1,1) | 0.31 (0.06,  1.97) | 1.64 (0.75,  3.62) | 1.17 (0.44,  3.1) | 1.09 (0.41,  2.93) | 0.78 (0.33,  1.83) | 1.09 (0.46,  2.6) | 1.18 (0.52,  2.65) | 0.3 (0.14,  0.69) | 0.8 (0.32,  2.06) | 1.09 (0.39,  3.04) | 0.6 (0.22,  1.59) | 1.77 (0.79,  4.01) | 1.38 (0.6,  3.15) | 0.53 (0.16,  1.73) |
| GEF+BEV | 2.66 (0.49,12.03) | 3.54  (0.63,  16.32) | 3.37 (0.58,  16.55) | 1.66 (0.29,7.74) | 1.7 (0.29,  8.13) | 3.41 (0.58,  16.98) | 4.3 (0.76,  20.19) | 2.99 (0.52,  14.21) | 4.26 (0.76,  19.71) | 3.25 (0.51,  17.81) | 1 (1,1) | 5.37 (0.96,  24.79) | 3.8 (0.62,  19.63) | 3.55 (0.58,  18.12) | 2.55 (0.44,  12.21) | 3.54 (0.62,  17.13) | 3.83 (0.68,  17.75) | 0.99 (0.18,  4.62) | 2.62 (0.44,  13.37) | 3.54 (0.56,  19.09) | 1.95 (0.32,  10.08) | 5.78 (1.02,  27.28) | 4.49 (0.78,  21.17) | 1.71 (0.25,  9.93) |
| GEF+CARBO+PEM | 0.5 (0.39,0.63) | 0.66 (0.46,0.96) | 0.63 (0.38,1.06) | 0.31 (0.2,0.45) | 0.32 (0.2,  0.51) | 0.64 (0.36,  1.13) | 0.8 (0.53,  1.2) | 0.56 (0.35,  0.88) | 0.79 (0.55,  1.13) | 0.61 (0.28,  1.33) | 0.19 (0.04,  1.04) | 1 (1,1) | 0.71 (0.4,  1.26) | 0.66 (0.33,  1.32) | 0.48 (0.3,  0.76) | 0.66 (0.4,  1.08) | 0.72 (0.48,  1.06) | 0.18 (0.13,  0.28) | 0.49 (0.27,  0.91) | 0.66 (0.31,  1.39) | 0.36 (0.19,  0.71) | 1.08 (0.72,  1.61) | 0.84 (0.55,  1.27) | 0.32 (0.12,  0.81) |
| GEF+CARBO+PEM (Alter) | 0.7 (0.37,1.31) | 0.93 (0.47,1.85) | 0.88 (0.41,1.93) | 0.44 (0.21,0.87) | 0.45 (0.21,  0.95) | 0.9 (0.4,  2.03) | 1.13 (0.56,  2.29) | 0.78 (0.37,  1.65) | 1.12 (0.56,  2.21) | 0.86 (0.32,  2.28) | 0.26 (0.05,  1.6) | 1.41 (0.79,  2.52) | 1 (1,1) | 0.93 (0.38,  2.29) | 0.67 (0.32,  1.41) | 0.93 (0.43,  1.99) | 1.01 (0.5,  2.03) | 0.26 (0.13,  0.53) | 0.69 (0.3,  1.61) | 0.93 (0.36,  2.39) | 0.51 (0.21,  1.24) | 1.52 (0.75,  3.08) | 1.18 (0.58,  2.41) | 0.45 (0.15,  1.35) |
| GEF+FIC | 0.75 (0.39,1.42) | 1 (0.49,2.01) | 0.95 (0.43,2.1) | 0.47 (0.22,0.94) | 0.48 (0.22,  1.03) | 0.96 (0.42,  2.2) | 1.21 (0.59,  2.49) | 0.84 (0.39,  1.8) | 1.2 (0.59,  2.4) | 0.92 (0.34,  2.43) | 0.28 (0.06,  1.72) | 1.51 (0.76,  2.99) | 1.07 (0.44,  2.62) | 1 (1,1) | 0.72 (0.33,  1.53) | 1 (0.46,  2.16) | 1.08 (0.53,  2.19) | 0.28 (0.14,  0.57) | 0.74 (0.31,  1.74) | 1 (0.38,  2.59) | 0.55 (0.22,  1.34) | 1.63 (0.79,  3.34) | 1.27 (0.61,  2.61) | 0.48 (0.16,  1.46) |
| GEF+MET | 1.04 (0.69,1.57) | 1.38 (0.86,2.29) | 1.32 (0.73,2.47) | 0.65 (0.38,1.08) | 0.67 (0.37,  1.2) | 1.34 (0.69,  2.61) | 1.68 (1,2.85) | 1.17 (0.66,  2.07) | 1.67 (1.02,  2.72) | 1.28 (0.55,3) | 0.39 (0.08,  2.26) | 2.1 (1.32,  3.38) | 1.49 (0.71,  3.16) | 1.39 (0.65,  2.99) | 1 (1,1) | 1.39 (0.77,  2.53) | 1.5 (0.89,  2.51) | 0.39 (0.23,  0.66) | 1.03 (0.51,  2.07) | 1.39 (0.62,  3.16) | 0.76 (0.36,  1.62) | 2.27 (1.35,  3.82) | 1.76 (1.03,  3.01) | 0.67 (0.25,  1.82) |
| GEF+OLA | 0.75 (0.48,1.16) | 1 (0.6,1.69) | 0.95 (0.52,1.8) | 0.47 (0.26,0.79) | 0.48 (0.26,  0.88) | 0.96 (0.49,  1.92) | 1.21 (0.7,2.1) | 0.84 (0.46,  1.52) | 1.2 (0.71,2) | 0.92 (0.39,  2.18) | 0.28 (0.06,  1.62) | 1.51 (0.92,  2.49) | 1.07 (0.5,  2.3) | 1 (0.46,  2.18) | 0.72 (0.4,  1.3) | 1 (1,1) | 1.08 (0.62,  1.86) | 0.28 (0.16,  0.48) | 0.74 (0.36,  1.52) | 1 (0.44,  2.3) | 0.55 (0.25,  1.19) | 1.63 (0.94,  2.82) | 1.27 (0.72,  2.21) | 0.49 (0.17,  1.32) |
| GEF+PEM | 0.69 (0.51,0.96) | 0.92 (0.61,1.44) | 0.88 (0.51,1.57) | 0.43 (0.27,0.67) | 0.44 (0.26,  0.76) | 0.89 (0.48,  1.65) | 1.12 (0.71,  1.79) | 0.78 (0.46,  1.31) | 1.11 (0.73,  1.69) | 0.85 (0.38,  1.92) | 0.26 (0.06,  1.47) | 1.4 (0.95,  2.1) | 0.99 (0.49,  2.01) | 0.92 (0.46,  1.9) | 0.67 (0.4,  1.12) | 0.92 (0.54,  1.6) | 1 (1,1) | 0.26 (0.17,  0.41) | 0.68 (0.36,  1.33) | 0.92 (0.43,  2.04) | 0.51 (0.25,  1.03) | 1.51 (0.96,  2.39) | 1.17 (0.73,  1.87) | 0.45 (0.17,  1.17) |
| GEM+CIS | 2.7 (1.94,3.66) | 3.58 (2.6,4.89) | 3.42 (2.12,5.49) | 1.68 (1.02,2.58) | 1.73 (1.08,  2.69) | 3.46 (1.93,  6.13) | 4.35 (2.7,  6.77) | 3.03 (1.78,  4.99) | 4.31 (2.79,  6.46) | 3.31 (1.45,  7.36) | 1.01 (0.22,  5.7) | 5.44 (3.62,  7.97) | 3.85 (1.9,  7.69) | 3.59 (1.75,  7.28) | 2.59 (1.52,  4.28) | 3.6 (2.07,  6.08) | 3.89 (2.43,  6.03) | 1 (1,1) | 2.66 (1.45,  4.78) | 3.6 (1.71,  7.38) | 1.97 (0.97,  3.96) | 5.87 (3.67,  9.11) | 4.56 (2.79,  7.17) | 1.74 (0.66,  4.49) |
| ICO | 1.01 (0.57,1.79) | 1.35 (0.81,2.27) | 1.28 (0.7,2.44) | 0.63 (0.32,1.19) | 0.65 (0.44,  0.95) | 1.3  (0.69,  2.44) | 1.63 (0.84,  3.15) | 1.14 (0.56,  2.28) | 1.62 (0.86,  3.03) | 1.24 (0.49,  3.14) | 0.38 (0.07,  2.29) | 2.04 (1.1,  3.77) | 1.45 (0.62,  3.36) | 1.35 (0.58,  3.19) | 0.97 (0.48,  1.95) | 1.35 (0.66,  2.75) | 1.46 (0.75,  2.79) | 0.38 (0.21,  0.69) | 1 (1,1) | 1.35 (0.89,  2.06) | 0.74 (0.32,  1.72) | 2.2 (1.14,  4.25) | 1.71 (0.88,  3.29) | 0.66 (0.23,  1.88) |
| ICO high-dose | 0.75 (0.37,1.52) | 1 (0.51,1.96) | 0.95 (0.45,2.05) | 0.47 (0.21,0.99) | 0.48 (0.27,  0.85) | 0.96 (0.45,  2.06) | 1.21 (0.55,  2.63) | 0.84 (0.37,  1.89) | 1.2 (0.56,  2.55) | 0.92 (0.33,  2.54) | 0.28 (0.05,  1.8) | 1.51 (0.72,  3.18) | 1.07 (0.42,  2.75) | 1 (0.39,  2.61) | 0.72 (0.32,  1.62) | 1 (0.43,  2.28) | 1.08 (0.49,  2.33) | 0.28 (0.14,  0.59) | 0.74 (0.49,  1.13) | 1 (1,1) | 0.55 (0.21,  1.41) | 1.63 (0.75,  3.55) | 1.27 (0.57,  2.76) | 0.49 (0.15,  1.52) |
| LIN+ERL | 1.37 (0.72,2.56) | 1.82 (0.92,3.63) | 1.73 (0.8,3.81) | 0.85 (0.41,1.71) | 0.88 (0.41,  1.86) | 1.75 (0.77,  3.98) | 2.2 (1.08,  4.49) | 1.53 (0.72,  3.23) | 2.19 (1.09,  4.33) | 1.67 (0.63,  4.46) | 0.51 (0.1,  3.15) | 2.76 (1.4,5.4) | 1.95 (0.8,  4.75) | 1.83 (0.74,  4.47) | 1.31 (0.62,  2.77) | 1.82 (0.84,  3.92) | 1.97 (0.97,  3.98) | 0.51 (0.25,  1.03) | 1.35 (0.58,  3.15) | 1.82 (0.71,  4.7) | 1 (1,1) | 2.97 (1.46,  6.05) | 2.31 (1.12,  4.73) | 0.88 (0.29,  2.67) |
| OSI | 0.46 (0.33,0.64) | 0.61 (0.4,0.95) | 0.58 (0.34,1.03) | 0.29 (0.17,0.44) | 0.29 (0.17,  0.5) | 0.59 (0.32,  1.1) | 0.74 (0.47,  1.18) | 0.52 (0.31,  0.86) | 0.74 (0.48,  1.11) | 0.56 (0.25,  1.27) | 0.17 (0.04,  0.98) | 0.93 (0.62,  1.39) | 0.66 (0.32,  1.33) | 0.61 (0.3,  1.26) | 0.44 (0.26,  0.74) | 0.61 (0.36,  1.06) | 0.66 (0.42,  1.04) | 0.17 (0.11,  0.27) | 0.45 (0.24,  0.88) | 0.61 (0.28,  1.34) | 0.34 (0.17,  0.69) | 1 (1,1) | 0.78 (0.48,  1.25) | 0.3 (0.11,  0.78) |
| RAM+ERL | 0.59 (0.42,0.84) | 0.79 (0.51,1.24) | 0.75 (0.43,1.35) | 0.37 (0.22,0.58) | 0.38 (0.22,  0.65) | 0.76 (0.41,  1.43) | 0.95 (0.59,  1.55) | 0.66 (0.39,  1.13) | 0.95 (0.61,  1.47) | 0.73 (0.32,  1.67) | 0.22 (0.05,  1.27) | 1.19 (0.79,  1.83) | 0.85 (0.42,  1.74) | 0.79 (0.38,  1.64) | 0.57 (0.33,  0.97) | 0.79 (0.45,  1.39) | 0.85 (0.53,  1.36) | 0.22 (0.14,  0.36) | 0.58 (0.3,  1.14) | 0.79 (0.36,  1.74) | 0.43 (0.21,  0.89) | 1.29 (0.8,  2.09) | 1 (1,1) | 0.38 (0.14,  1.01) |
| VIN+GEF | 1.55 (0.63,3.88) | 2.06 (0.81,5.35) | 1.96 (0.72,5.47) | 0.96 (0.36,2.51) | 0.99 (0.37,  2.7) | 1.98 (0.7,  5.67) | 2.49 (0.95,  6.6) | 1.74 (0.64,  4.68) | 2.47 (0.96,  6.42) | 1.89 (0.58,  6.18) | 0.58 (0.1,4) | 3.12 (1.23,  8.04) | 2.21 (0.74,  6.66) | 2.07 (0.68,  6.36) | 1.48 (0.55,  4.02) | 2.06 (0.76,  5.72) | 2.23 (0.85,  5.89) | 0.57 (0.22,  1.51) | 1.53 (0.53,  4.44) | 2.06 (0.66,  6.46) | 1.13 (0.37,  3.44) | 3.36 (1.29,  8.86) | 2.61 (0.99,  6.94) | 1 (1,1) |

AFA: afatinib; BEV: bevacizumab; CARBO: carboplatin; CIS: cisplatin; DAC: dacomitinib; ERL: erlotinib; FIC: ficlatuzumab; GEF: gefitinib; GEF\_m: gefitinib maintenance; GEM: gemcitabine; ICO; icotinib; LIN: linsitinib; MET: metformin; OSI: osimertinib; PAC: paclitaxel; PEM: pemetrexed; PFS: progression-free survival; RAM: ramucirumab.

## **Table A8. Base case OS - pairwise comparisons of all interventions and comparators.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **ERL/GEF** | **AFA** | **AFA+CET** | **CARBO+PEM** | **CIS+PEM** | **CIS+PEM**  **+GEF\_m** | **DAC** | **EMI+ERL** | **ERL+BEV** | **ERL+PAC**  **+CARBO** | **GEF+BEV** | **GEF+**  **CARBO**  **+PEM** | **GEF+CARBO**  **+PEM(Alter)** | **GEF+FIC** | **GEF+MET** | **GEF+OLA** | **GEF+PEM** | **GEM+CIS** | **ICO** | **LIN+ERL** | **OSI** | **RAM+ERL** |
| **ERL/GEF** | 1 (1,1) | 1.16 (0.79,1.79) | 0.94 (0.39,2.34) | 0.8 (0.51,1.3) | 1.02 (0.54,2.04) | 0.64 (0.26,1.54) | 1.33 (0.8,2.19) | 1.31 (0.74,2.33) | 1.02 (0.69,1.45) | 1.21 (0.54,2.74) | 2.13 (0.22,20.94) | 1.73 (1.26,2.58) | 1.01 (0.49,2.22) | 1 (0.44,2.36) | 0.87 (0.5,1.54) | 0.82 (0.46,1.44) | 1.2 (0.75,1.91) | 1.05 (0.73,1.61) | 0.92 (0.39,2.2) | 1.3 (0.38,4.46) | 1.25 (0.76,2.06) | 1.2 (0.65,2.22) |
| **AFA** | 0.86 (0.56,1.27) | 1 (1,1) | 0.81 (0.36,1.82) | 0.69 (0.37,1.28) | 0.88 (0.52,1.49) | 0.55 (0.21,1.42) | 1.15 (0.58,2.14) | 1.14 (0.55,2.26) | 0.88 (0.49,1.47) | 1.04 (0.42,2.55) | 1.83 (0.18,18.65) | 1.49 (0.89,2.63) | 0.87 (0.37,2.09) | 0.86 (0.34,2.2) | 0.75 (0.37,1.48) | 0.71 (0.34,1.4) | 1.04 (0.54,1.9) | 0.91 (0.61,1.39) | 0.79 (0.37,1.7) | 1.12 (0.31,4.05) | 1.08 (0.56,2.01) | 1.04 (0.49,2.13) |
| **AFA+CET** | 1.06 (0.43,2.56) | 1.23 (0.55,2.74) | 1 (1,1) | 0.85 (0.31,2.33) | 1.08 (0.42,2.82) | 0.67 (0.19,2.33) | 1.42 (0.5,3.85) | 1.4 (0.47,4.01) | 1.08 (0.4,2.78) | 1.28 (0.38,4.26) | 2.25 (0.19,26.14) | 1.84 (0.71,4.86) | 1.07 (0.34,3.51) | 1.06 (0.31,3.63) | 0.92 (0.32,2.63) | 0.87 (0.3,2.47) | 1.28 (0.46,3.47) | 1.12 (0.46,2.76) | 0.97 (0.32,2.9) | 1.38 (0.3,6.24) | 1.33 (0.48,3.63) | 1.27 (0.42,3.72) |
| **CARBO+PEM** | 1.25 (0.77,1.97) | 1.45 (0.78,2.71) | 1.18 (0.43,3.25) | 1 (1,1) | 1.28 (0.57,2.91) | 0.8 (0.29,2.14) | 1.67 (0.82,3.26) | 1.65 (0.78,3.41) | 1.27 (0.68,2.25) | 1.51 (0.59,3.85) | 2.66 (0.26,27.29) | 2.17 (1.25,3.94) | 1.26 (0.53,3.1) | 1.25 (0.48,3.28) | 1.09 (0.52,2.24) | 1.02 (0.49,2.11) | 1.51 (0.76,2.87) | 1.32 (0.72,2.46) | 1.15 (0.43,3.08) | 1.63 (0.44,6.01) | 1.57 (0.78,3.05) | 1.51 (0.69,3.21) |
| **CIS+PEM** | 0.98 (0.49,1.87) | 1.13 (0.67,1.91) | 0.92 (0.35,2.39) | 0.78 (0.34,1.76) | 1 (1,1) | 0.62 (0.2,1.84) | 1.31 (0.55,2.94) | 1.29 (0.52,3.05) | 1 (0.45,2.04) | 1.18 (0.41,3.31) | 2.07 (0.19,22.28) | 1.69 (0.82,3.67) | 0.98 (0.37,2.74) | 0.98 (0.33,2.83) | 0.85 (0.35,2) | 0.8 (0.32,1.9) | 1.18 (0.51,2.59) | 1.03 (0.53,2.03) | 0.9 (0.53,1.51) | 1.27 (0.31,5.05) | 1.22 (0.52,2.74) | 1.18 (0.47,2.85) |
| **CIS+PEM+GEF\_m** | 1.57 (0.65,3.81) | 1.82 (0.7,4.87) | 1.48 (0.43,5.26) | 1.26 (0.47,3.44) | 1.6 (0.54,4.89) | 1 (1,1) | 2.09 (0.76,5.74) | 2.06 (0.72,5.92) | 1.59 (0.61,4.12) | 1.89 (0.58,6.33) | 3.33 (0.29,38.86) | 2.73 (1.07,7.26) | 1.58 (0.5,5.2) | 1.57 (0.47,5.35) | 1.37 (0.48,3.9) | 1.28 (0.45,3.68) | 1.89 (0.7,5.13) | 1.66 (0.65,4.43) | 1.44 (0.43,4.96) | 2.05 (0.45,9.24) | 1.96 (0.72,5.38) | 1.89 (0.64,5.54) |
| **DAC** | 0.75 (0.46,1.25) | 0.87 (0.47,1.71) | 0.71 (0.26,2) | 0.6 (0.31,1.22) | 0.76 (0.34,1.83) | 0.48 (0.17,1.31) | 1 (1,1) | 0.98 (0.46,2.13) | 0.76 (0.4,1.4) | 0.9 (0.35,2.37) | 1.59 (0.16,16.54) | 1.29 (0.74,2.54) | 0.75 (0.32,1.95) | 0.75 (0.29,2.02) | 0.65 (0.31,1.4) | 0.61 (0.29,1.31) | 0.9 (0.46,1.78) | 0.79 (0.44,1.55) | 0.69 (0.26,1.92) | 0.98 (0.26,3.67) | 0.94 (0.47,1.91) | 0.9 (0.41,2) |
| **EMI+ERL** | 0.76 (0.43,1.35) | 0.88 (0.44,1.82) | 0.72 (0.25,2.11) | 0.61 (0.29,1.29) | 0.78 (0.33,1.91) | 0.48 (0.17,1.38) | 1.02 (0.47,2.15) | 1 (1,1) | 0.77 (0.38,1.5) | 0.92 (0.34,2.5) | 1.62 (0.15,16.92) | 1.32 (0.69,2.69) | 0.77 (0.3,2.05) | 0.76 (0.28,2.11) | 0.66 (0.3,1.49) | 0.62 (0.28,1.4) | 0.92 (0.43,1.92) | 0.8 (0.41,1.65) | 0.7 (0.25,2) | 0.99 (0.25,3.84) | 0.95 (0.45,2.03) | 0.91 (0.4,2.11) |
| **ERL+BEV** | 0.98 (0.69,1.44) | 1.14 (0.68,2.06) | 0.93 (0.36,2.51) | 0.79 (0.44,1.47) | 1 (0.49,2.25) | 0.63 (0.24,1.64) | 1.31 (0.72,2.47) | 1.29 (0.67,2.6) | 1 (1,1) | 1.19 (0.49,2.95) | 2.1 (0.21,21.35) | 1.7 (1.07,3.03) | 0.99 (0.44,2.42) | 0.99 (0.4,2.52) | 0.85 (0.45,1.71) | 0.8 (0.42,1.61) | 1.19 (0.66,2.16) | 1.04 (0.63,1.86) | 0.9 (0.37,2.4) | 1.28 (0.36,4.65) | 1.23 (0.68,2.32) | 1.18 (0.59,2.46) |
| **ERL+PAC+CARBO** | 0.83 (0.36,1.85) | 0.96 (0.39,2.4) | 0.78 (0.23,2.64) | 0.66 (0.26,1.7) | 0.85 (0.3,2.46) | 0.53 (0.16,1.74) | 1.11 (0.42,2.82) | 1.09 (0.4,2.93) | 0.84 (0.34,2.03) | 1 (1,1) | 1.76 (0.16,19.99) | 1.45 (0.6,3.53) | 0.84 (0.28,2.58) | 0.83 (0.26,2.65) | 0.72 (0.27,1.93) | 0.68 (0.25,1.82) | 1 (0.38,2.54) | 0.88 (0.36,2.18) | 0.76 (0.24,2.49) | 1.08 (0.25,4.72) | 1.04 (0.4,2.65) | 1 (0.36,2.73) |
| **GEF+BEV** | 0.47 (0.05,4.58) | 0.55 (0.05,5.54) | 0.44 (0.04,5.19) | 0.38 (0.04,3.86) | 0.48 (0.04,5.22) | 0.3 (0.03,3.44) | 0.63 (0.06,6.43) | 0.62 (0.06,6.51) | 0.48 (0.05,4.76) | 0.57 (0.05,6.41) | 1 (1,1) | 0.82 (0.08,8.23) | 0.48 (0.04,5.3) | 0.47 (0.04,5.32) | 0.41 (0.04,4.27) | 0.38 (0.04,4.01) | 0.57 (0.06,5.8) | 0.5 (0.05,5.05) | 0.43 (0.04,4.94) | 0.61 (0.05,8.18) | 0.59 (0.06,6.04) | 0.56 (0.05,5.97) |
| **GEF+CARBO+PEM** | 0.58 (0.39,0.79) | 0.67 (0.38,1.12) | 0.54 (0.21,1.41) | 0.46 (0.25,0.8) | 0.59 (0.27,1.22) | 0.37 (0.14,0.93) | 0.77 (0.39,1.36) | 0.76 (0.37,1.44) | 0.59 (0.33,0.93) | 0.69 (0.28,1.66) | 1.22 (0.12,12.27) | 1 (1,1) | 0.58 (0.3,1.14) | 0.57 (0.23,1.42) | 0.5 (0.25,0.95) | 0.47 (0.23,0.89) | 0.7 (0.37,1.21) | 0.61 (0.35,1.02) | 0.53 (0.2,1.31) | 0.75 (0.21,2.65) | 0.72 (0.38,1.27) | 0.69 (0.33,1.36) |
| **GEF+CARBO+**  **PEM(Alter)** | 0.99 (0.45,2.06) | 1.15 (0.48,2.67) | 0.94 (0.28,2.98) | 0.79 (0.32,1.87) | 1.02 (0.37,2.72) | 0.63 (0.19,1.98) | 1.33 (0.51,3.15) | 1.31 (0.49,3.29) | 1.01 (0.41,2.25) | 1.19 (0.39,3.58) | 2.1 (0.19,23.1) | 1.72 (0.88,3.37) | 1 (1,1) | 0.99 (0.31,3.05) | 0.86 (0.33,2.15) | 0.81 (0.3,2.03) | 1.2 (0.47,2.82) | 1.05 (0.44,2.43) | 0.91 (0.28,2.8) | 1.29 (0.3,5.38) | 1.24 (0.49,2.95) | 1.19 (0.44,3.06) |
| **GEF+FIC** | 1 (0.42,2.3) | 1.16 (0.45,2.97) | 0.94 (0.28,3.23) | 0.8 (0.31,2.09) | 1.02 (0.35,3) | 0.64 (0.19,2.14) | 1.34 (0.5,3.48) | 1.31 (0.47,3.62) | 1.01 (0.4,2.5) | 1.2 (0.38,3.89) | 2.12 (0.19,24.19) | 1.74 (0.7,4.38) | 1.01 (0.33,3.18) | 1 (1,1) | 0.87 (0.31,2.37) | 0.82 (0.29,2.25) | 1.21 (0.45,3.13) | 1.06 (0.42,2.7) | 0.92 (0.28,3.06) | 1.3 (0.29,5.73) | 1.25 (0.47,3.26) | 1.2 (0.42,3.39) |
| **GEF+MET** | 1.15 (0.65,2.02) | 1.33 (0.67,2.73) | 1.08 (0.38,3.17) | 0.92 (0.45,1.94) | 1.17 (0.5,2.88) | 0.73 (0.26,2.08) | 1.53 (0.72,3.24) | 1.51 (0.67,3.39) | 1.17 (0.59,2.25) | 1.38 (0.52,3.76) | 2.44 (0.23,25.82) | 1.99 (1.06,4.03) | 1.16 (0.47,3.07) | 1.15 (0.42,3.19) | 1 (1,1) | 0.94 (0.42,2.09) | 1.39 (0.66,2.86) | 1.21 (0.62,2.47) | 1.05 (0.38,3.02) | 1.5 (0.38,5.76) | 1.44 (0.68,3.05) | 1.38 (0.6,3.18) |
| **GEF+OLA** | 1.22 (0.69,2.16) | 1.42 (0.71,2.91) | 1.15 (0.4,3.37) | 0.98 (0.47,2.06) | 1.25 (0.53,3.09) | 0.78 (0.27,2.22) | 1.63 (0.76,3.43) | 1.61 (0.72,3.62) | 1.24 (0.62,2.41) | 1.47 (0.55,4.01) | 2.6 (0.25,27.39) | 2.12 (1.13,4.29) | 1.23 (0.49,3.29) | 1.22 (0.44,3.42) | 1.06 (0.48,2.38) | 1 (1,1) | 1.47 (0.7,3.04) | 1.29 (0.66,2.64) | 1.12 (0.4,3.23) | 1.59 (0.41,6.14) | 1.53 (0.72,3.23) | 1.47 (0.64,3.36) |
| **GEF+PEM** | 0.83 (0.52,1.34) | 0.96 (0.53,1.84) | 0.78 (0.29,2.19) | 0.66 (0.35,1.31) | 0.85 (0.39,1.98) | 0.53 (0.19,1.44) | 1.11 (0.56,2.19) | 1.09 (0.52,2.31) | 0.84 (0.46,1.51) | 1 (0.39,2.61) | 1.77 (0.17,18.05) | 1.44 (0.83,2.71) | 0.84 (0.35,2.13) | 0.83 (0.32,2.22) | 0.72 (0.35,1.51) | 0.68 (0.33,1.42) | 1 (1,1) | 0.88 (0.49,1.66) | 0.76 (0.29,2.08) | 1.08 (0.29,4.04) | 1.04 (0.54,2.05) | 1 (0.46,2.18) |
| **GEM+CIS** | 0.95 (0.62,1.37) | 1.1 (0.72,1.64) | 0.89 (0.36,2.17) | 0.76 (0.41,1.38) | 0.97 (0.49,1.88) | 0.6 (0.23,1.55) | 1.27 (0.64,2.3) | 1.25 (0.6,2.44) | 0.96 (0.54,1.59) | 1.14 (0.46,2.77) | 2 (0.2,20.27) | 1.64 (0.98,2.82) | 0.95 (0.41,2.26) | 0.95 (0.37,2.39) | 0.82 (0.4,1.6) | 0.78 (0.38,1.5) | 1.14 (0.6,2.05) | 1 (1,1) | 0.87 (0.36,2.04) | 1.23 (0.33,4.41) | 1.19 (0.61,2.16) | 1.14 (0.54,2.3) |
| **ICO** | 1.09 (0.45,2.54) | 1.27 (0.59,2.69) | 1.03 (0.34,3.08) | 0.87 (0.32,2.32) | 1.12 (0.66,1.88) | 0.7 (0.2,2.33) | 1.46 (0.52,3.84) | 1.44 (0.5,4.01) | 1.11 (0.42,2.73) | 1.32 (0.4,4.19) | 2.31 (0.2,26.39) | 1.89 (0.76,4.92) | 1.1 (0.36,3.51) | 1.09 (0.33,3.59) | 0.95 (0.33,2.62) | 0.89 (0.31,2.47) | 1.32 (0.48,3.41) | 1.15 (0.49,2.77) | 1 (1,1) | 1.42 (0.31,6.24) | 1.37 (0.49,3.59) | 1.31 (0.45,3.71) |
| **LIN+ERL** | 0.77 (0.22,2.63) | 0.89 (0.25,3.27) | 0.73 (0.16,3.34) | 0.61 (0.17,2.3) | 0.79 (0.2,3.21) | 0.49 (0.11,2.22) | 1.02 (0.27,3.84) | 1.01 (0.26,3.93) | 0.78 (0.21,2.8) | 0.93 (0.21,4.07) | 1.63 (0.12,22.11) | 1.34 (0.38,4.87) | 0.78 (0.19,3.36) | 0.77 (0.17,3.41) | 0.67 (0.17,2.61) | 0.63 (0.16,2.44) | 0.92 (0.25,3.43) | 0.81 (0.23,2.99) | 0.7 (0.16,3.18) | 1 (1,1) | 0.96 (0.26,3.59) | 0.92 (0.23,3.64) |
| **OSI** | 0.8 (0.49,1.31) | 0.92 (0.5,1.78) | 0.75 (0.28,2.1) | 0.64 (0.33,1.28) | 0.82 (0.37,1.92) | 0.51 (0.19,1.39) | 1.07 (0.52,2.13) | 1.05 (0.49,2.23) | 0.81 (0.43,1.46) | 0.96 (0.38,2.5) | 1.7 (0.17,17.48) | 1.38 (0.79,2.66) | 0.8 (0.34,2.06) | 0.8 (0.31,2.11) | 0.7 (0.33,1.47) | 0.65 (0.31,1.39) | 0.96 (0.49,1.87) | 0.84 (0.46,1.63) | 0.73 (0.28,2.03) | 1.04 (0.28,3.88) | 1 (1,1) | 0.96 (0.44,2.09) |
| **RAM+ERL** | 0.83 (0.45,1.53) | 0.96 (0.47,2.04) | 0.79 (0.27,2.36) | 0.66 (0.31,1.45) | 0.85 (0.35,2.13) | 0.53 (0.18,1.56) | 1.11 (0.5,2.43) | 1.09 (0.47,2.53) | 0.84 (0.41,1.7) | 1 (0.37,2.8) | 1.77 (0.17,18.73) | 1.44 (0.73,3.03) | 0.84 (0.33,2.29) | 0.83 (0.3,2.37) | 0.72 (0.31,1.67) | 0.68 (0.3,1.57) | 1 (0.46,2.17) | 0.88 (0.43,1.86) | 0.76 (0.27,2.23) | 1.08 (0.27,4.28) | 1.04 (0.48,2.28) | 1 (1,1) |

AFA: afatinib; BEV: bevacizumab; CARBO: carboplatin; CIS: cisplatin; DAC: dacomitinib; ERL: erlotinib; FIC: ficlatuzumab; GEF: gefitinib; GEF\_m: gefitinib maintenance; GEM: gemcitabine; ICO; icotinib; LIN: linsitinib; MET: metformin; OS: overall survival; OSI: osimertinib; PAC: paclitaxel; PEM: pemetrexed; RAM: ramucirumab.

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