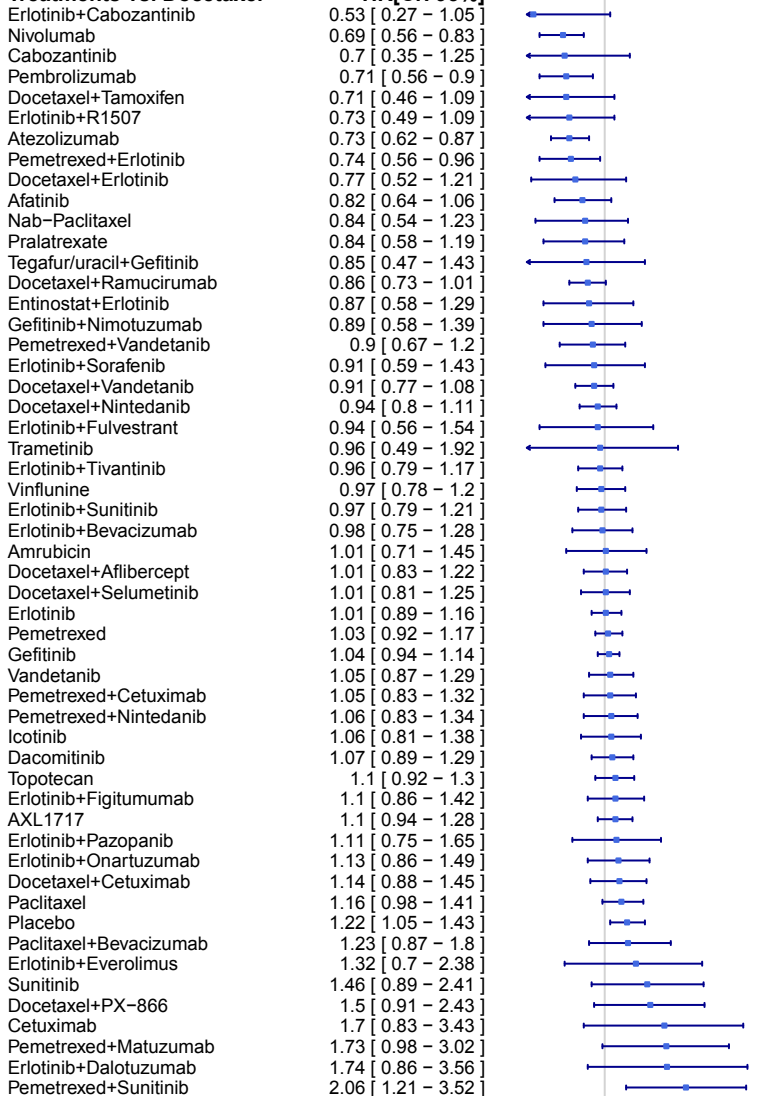


Supplementary appendix figures for

“Comparative efficacy and safety of second-line treatments for advanced non–small-cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analyses”

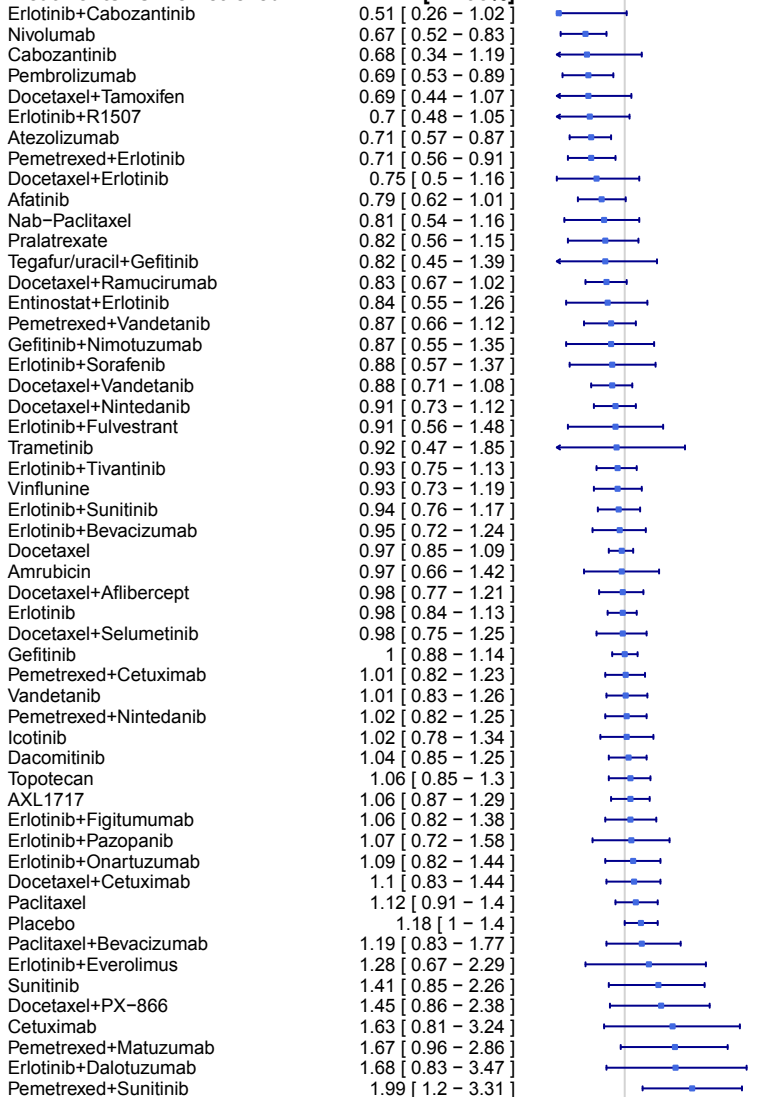
Appendix Figure 1: Forest plots for 4 outcomes.....	p2
Appendix Figure 2: Cumulative ranking curves and SUCRA values for 4 outcomes.....	p55
Appendix Figure 3: Rankograms for 4 outcomes.....	p60
Appendix Figure 4: Evaluation of inconsistency.....	p65
Appendix Figures 5: Subgroup analyses by histology and ethnicity: network graphs of trials for OS, forest plots and SUCRA values for OS and PFS.....	p70
Appendix Figure 6: Funnel plots of small-study effects.....	p120
Appendix Figure 7: Overall assessment of bias.....	p122

Appendix Figure 1: Forest plots for 4 outcomes

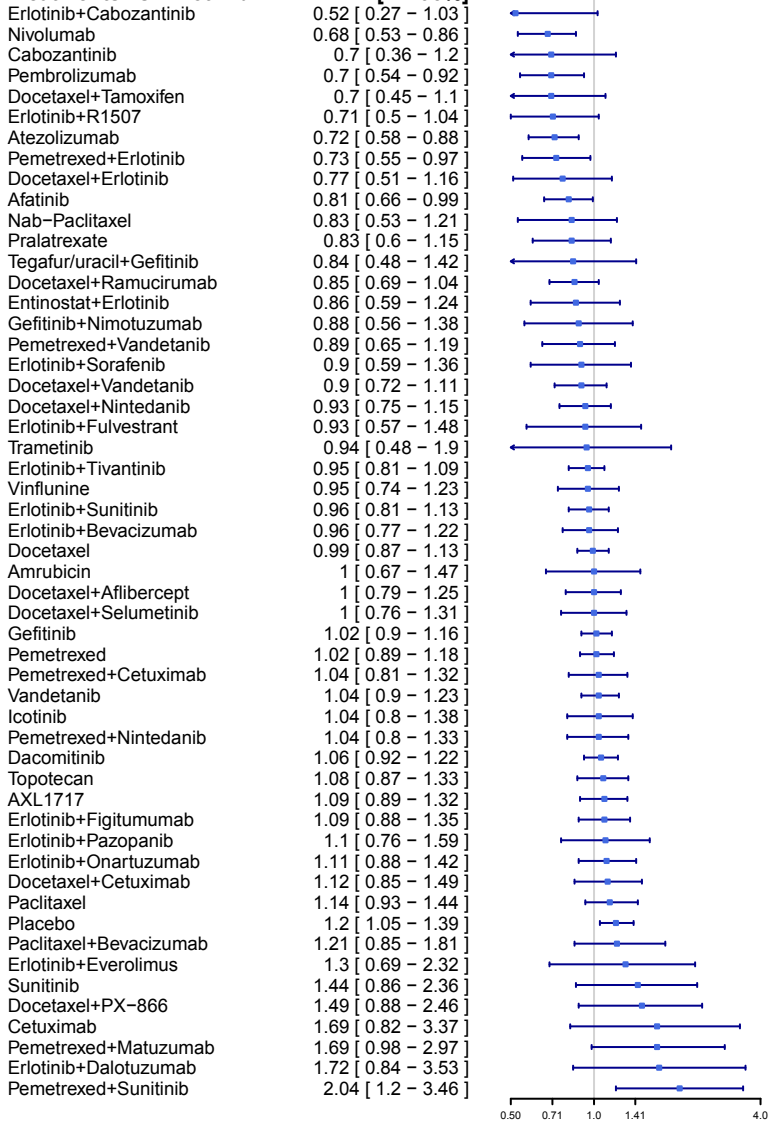
(a) Overall survival**Treatments vs. Docetaxel**

0.50 0.71 1.0 1.41 4.0

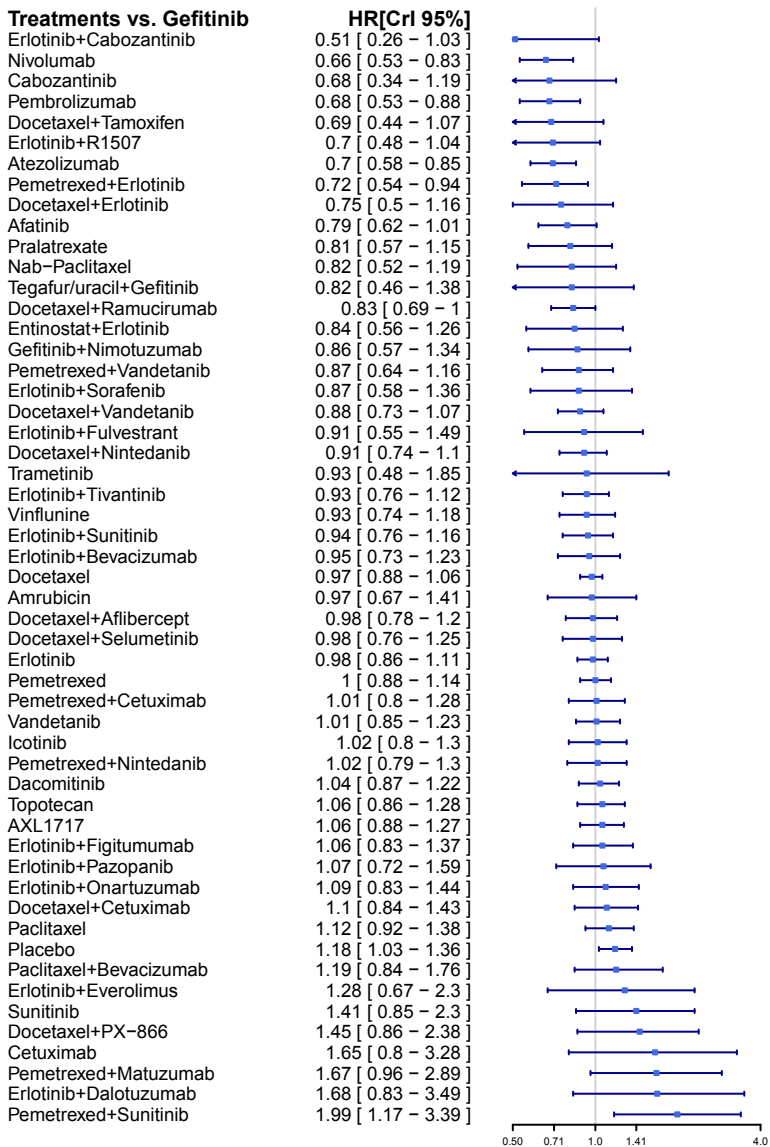
Treatments vs. Pemetrexed

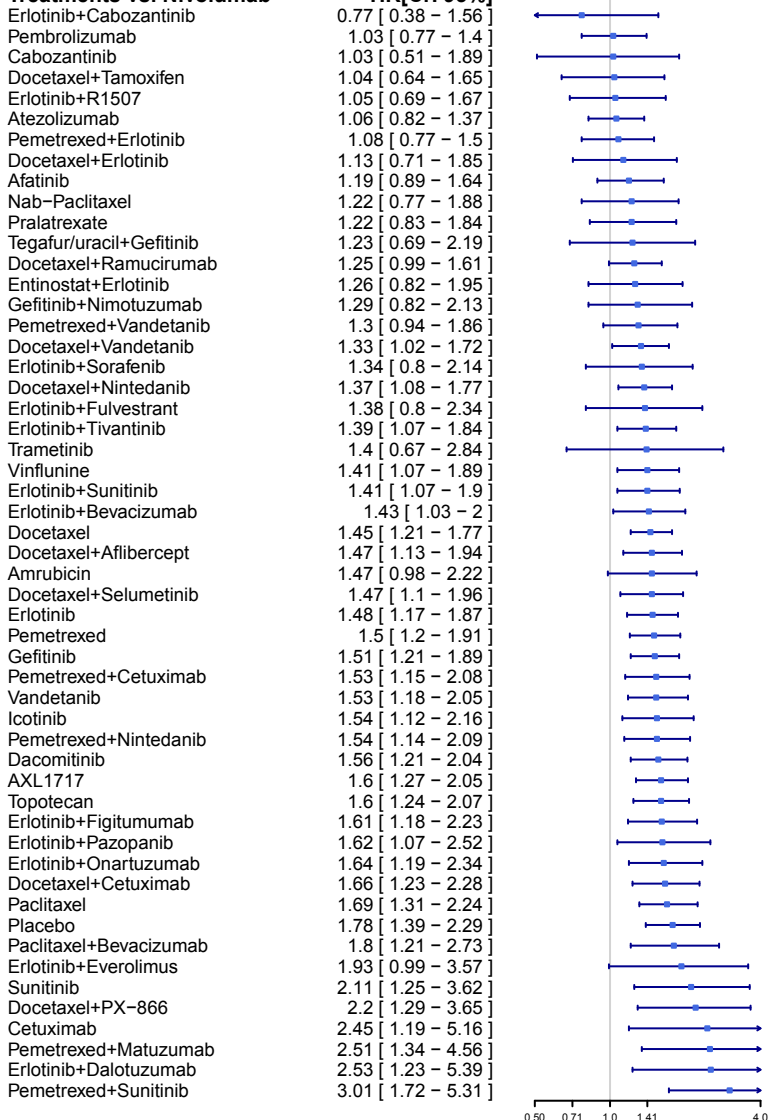


Treatments vs. Erlotinib

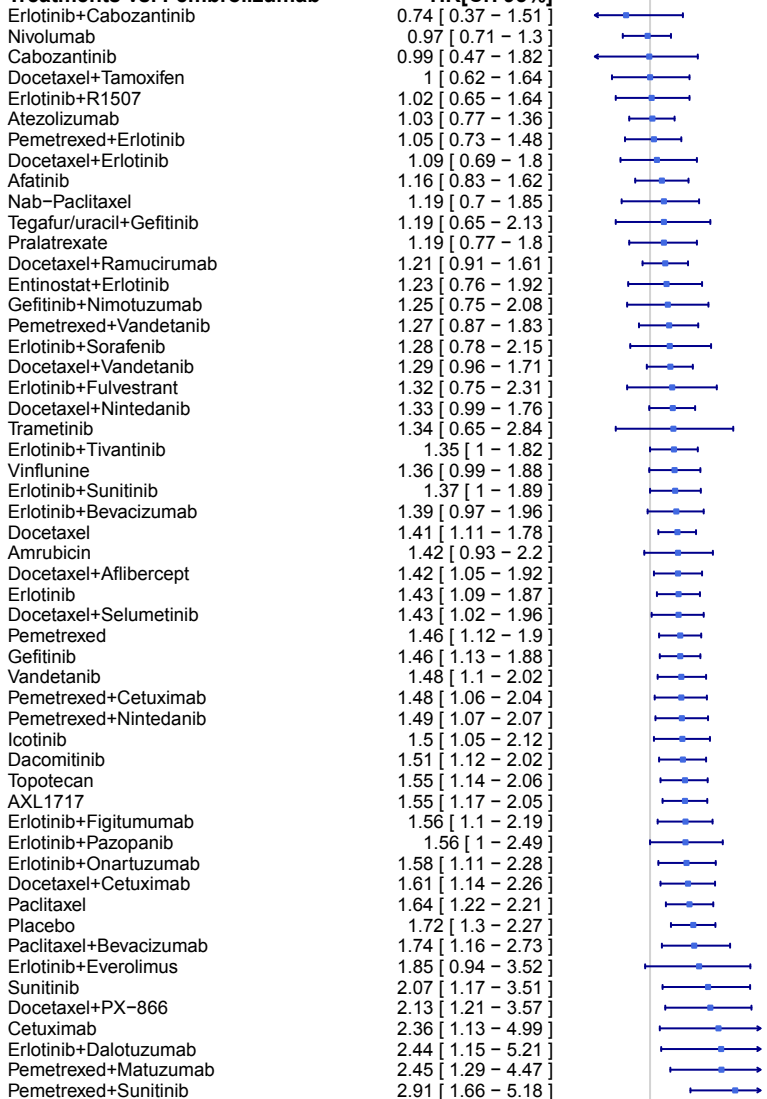


Treatments vs. Gefitinib



Treatments vs. Nivolumab

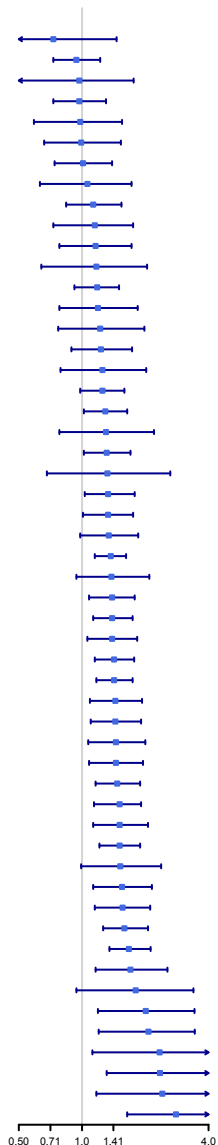
Treatments vs. Pembrolizumab

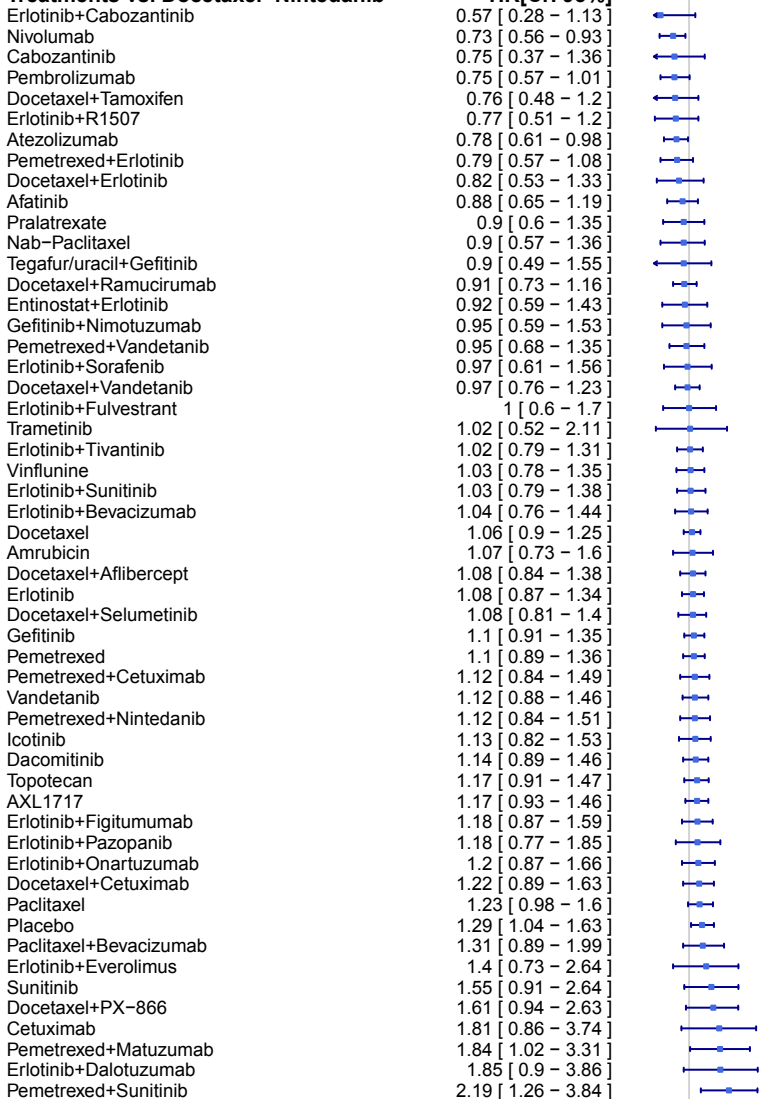


0.50 0.71 1.0 1.41 4.0

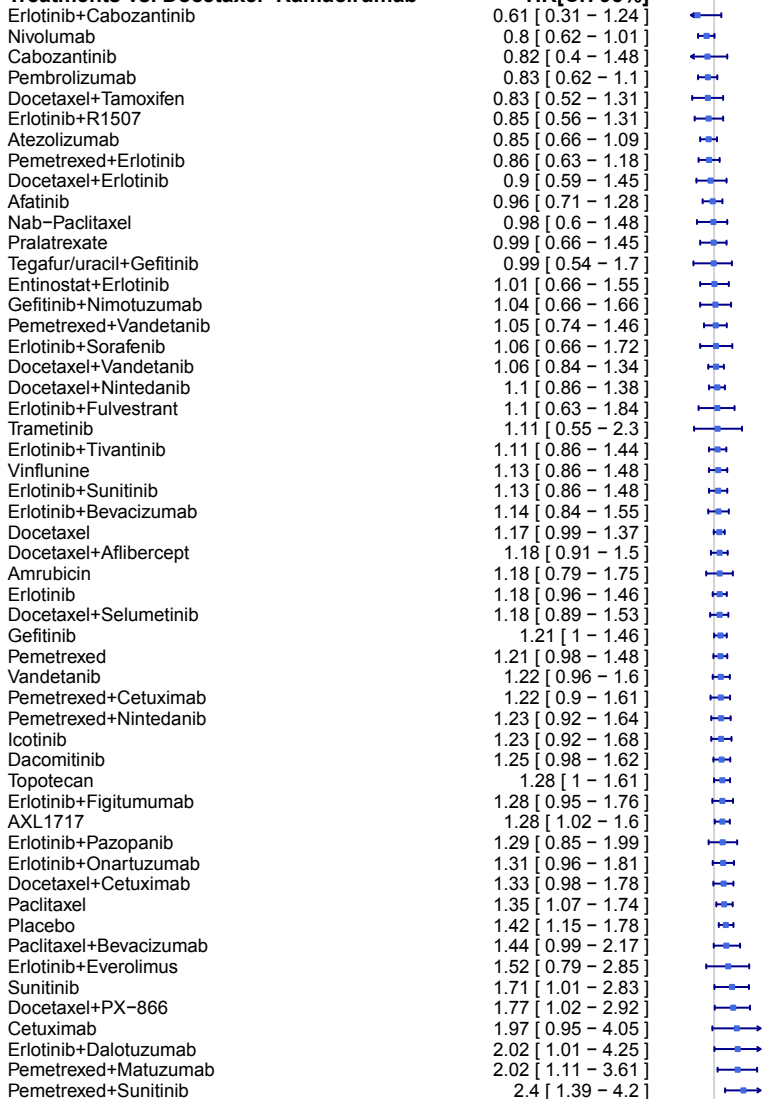
Treatments vs. Atezolizumab

Treatment	HR [CrI 95%]
Erlotinib+Cabozantinib	0.73 [0.36 - 1.46]
Nivolumab	0.94 [0.73 - 1.22]
Cabozantinib	0.97 [0.48 - 1.76]
Pembrolizumab	0.97 [0.73 - 1.3]
Docetaxel+Tamoxifen	0.98 [0.59 - 1.55]
Erlotinib+R1507	0.99 [0.66 - 1.53]
Pemetrexed+Erlotinib	1.01 [0.74 - 1.39]
Docetaxel+Erlotinib	1.06 [0.63 - 1.72]
Afatinib	1.13 [0.84 - 1.54]
Nab-Paclitaxel	1.15 [0.73 - 1.75]
Pralatrexate	1.16 [0.78 - 1.72]
Tegafur/uracil+Gefitinib	1.17 [0.64 - 2.04]
Docetaxel+Ramucirumab	1.18 [0.92 - 1.5]
Entinostat+Erlotinib	1.19 [0.78 - 1.84]
Gefitinib+Nimotuzumab	1.22 [0.77 - 1.98]
Pemetrexed+Vandetanib	1.23 [0.89 - 1.73]
Erlotinib+Sorafenib	1.25 [0.79 - 2.02]
Docetaxel+Vandetanib	1.25 [0.98 - 1.59]
Docetaxel+Nintedanib	1.29 [1.02 - 1.64]
Erlotinib+Fulvestrant	1.3 [0.78 - 2.2]
Erlotinib+Tivantinib	1.31 [1.02 - 1.7]
Trametinib	1.32 [0.68 - 2.63]
Erlotinib+Sunitinib	1.33 [1.03 - 1.78]
Vinflunine	1.33 [1.01 - 1.75]
Erlotinib+Bevacizumab	1.34 [0.98 - 1.85]
Docetaxel	1.37 [1.15 - 1.62]
Amrubicin	1.38 [0.94 - 2.09]
Docetaxel+Aflibercept	1.39 [1.08 - 1.78]
Erlotinib	1.39 [1.13 - 1.74]
Docetaxel+Selumetinib	1.39 [1.06 - 1.83]
Pemetrexed	1.42 [1.15 - 1.77]
Gefitinib	1.42 [1.17 - 1.74]
Pemetrexed+Cetuximab	1.44 [1.09 - 1.93]
Vandetanib	1.44 [1.1 - 1.91]
Icotinib	1.45 [1.07 - 2]
Pemetrexed+Nintedanib	1.45 [1.08 - 1.95]
Dacomitinib	1.47 [1.16 - 1.89]
Topotecan	1.51 [1.14 - 1.91]
Erlotinib+Figitumumab	1.51 [1.13 - 2.06]
AXL1717	1.51 [1.21 - 1.89]
Erlotinib+Pazopanib	1.52 [0.99 - 2.38]
Erlotinib+Onartuzumab	1.55 [1.13 - 2.15]
Docetaxel+Cetuximab	1.56 [1.15 - 2.11]
Paclitaxel	1.59 [1.26 - 2.06]
Placebo	1.67 [1.35 - 2.12]
Paclitaxel+Bevacizumab	1.7 [1.16 - 2.55]
Erlotinib+Everolimus	1.8 [0.94 - 3.39]
Sunitinib	2.01 [1.19 - 3.43]
Docetaxel+PX-866	2.07 [1.2 - 3.44]
Cetuximab	2.34 [1.12 - 4.83]
Pemetrexed+Matuzumab	2.35 [1.31 - 4.28]
Erlotinib+Dalotuzumab	2.41 [1.17 - 5]
Pemetrexed+Sunitinib	2.8 [1.64 - 4.93]

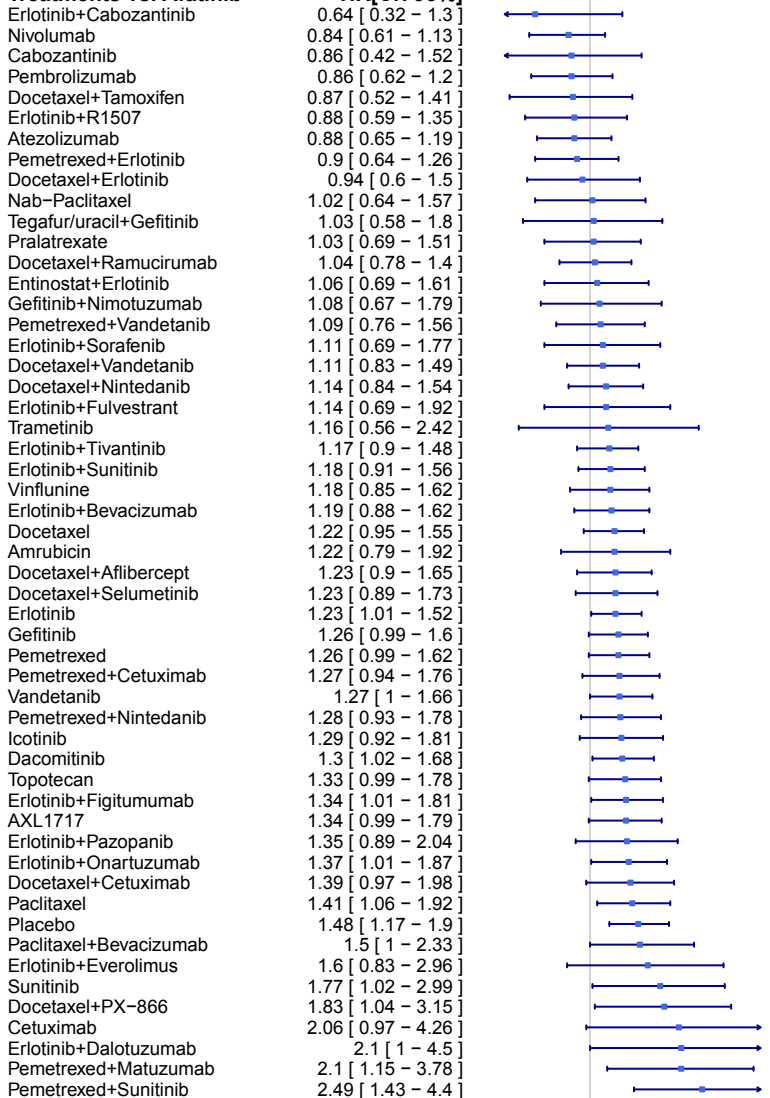


Treatments vs. Docetaxel+Nintedanib

0.50 1.0 4.0

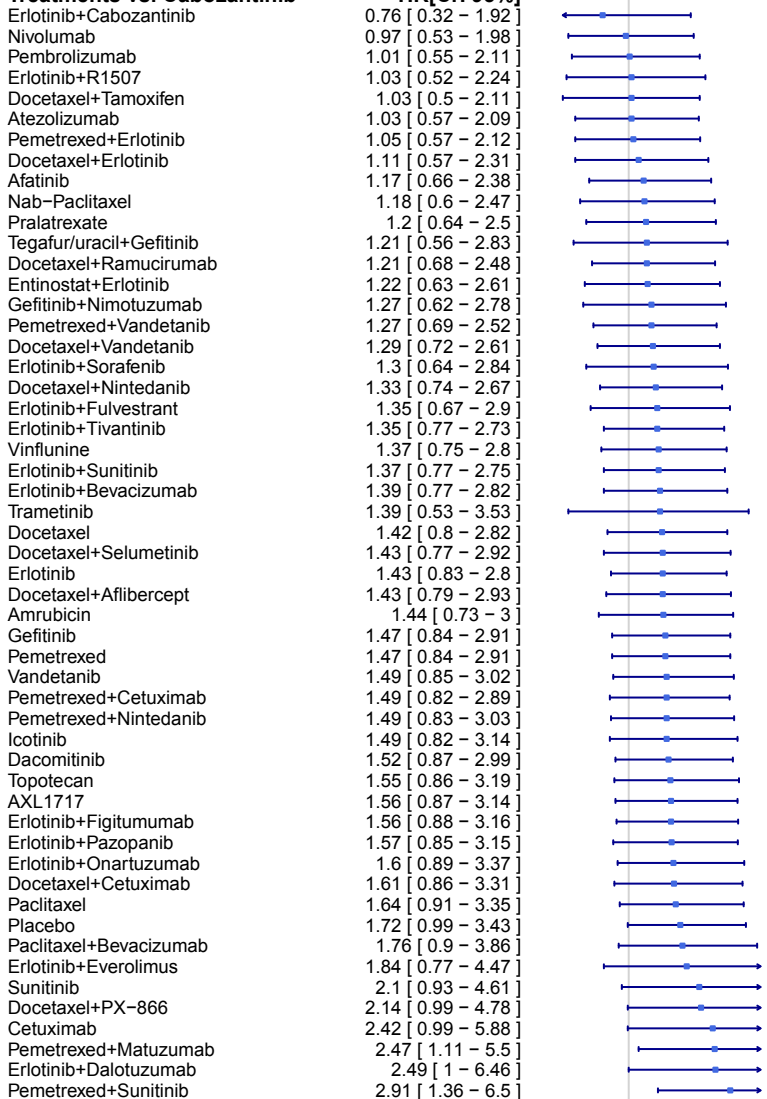
Treatments vs. Docetaxel+Ramucirumab

Treatments vs. Afatinib



0.50 0.71 1.0 1.41 4.0

Treatments vs. Cabozantinib

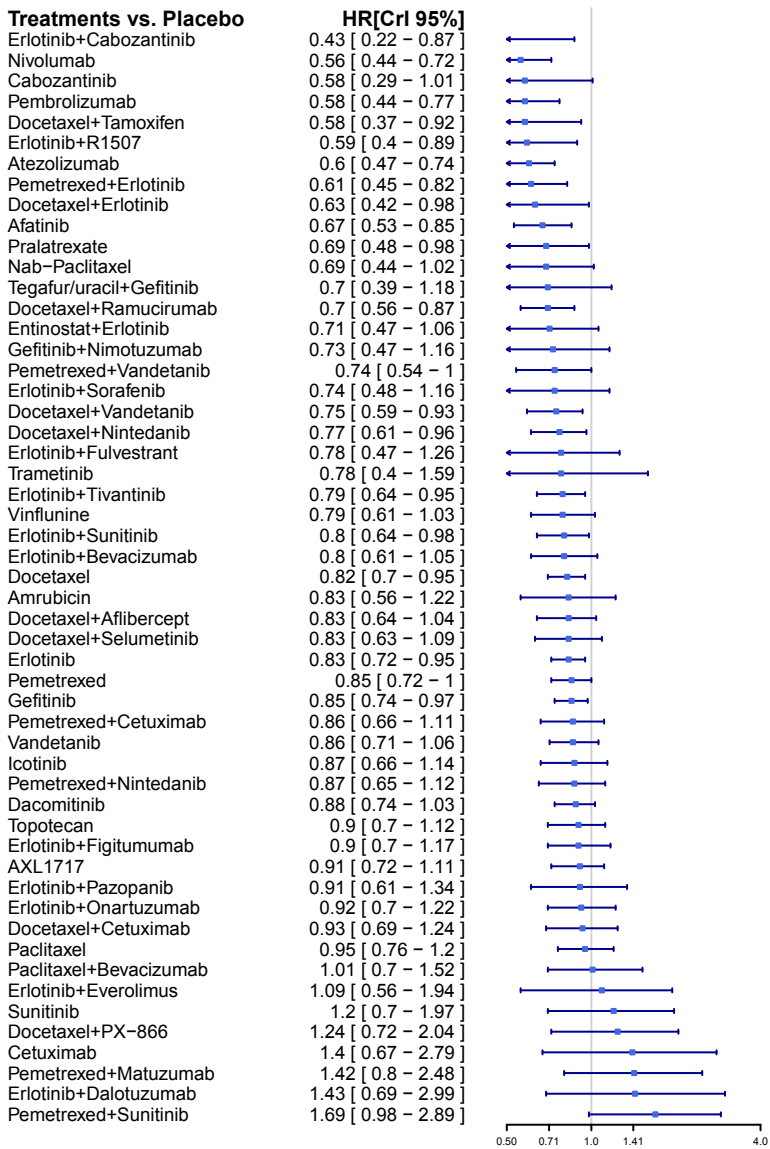


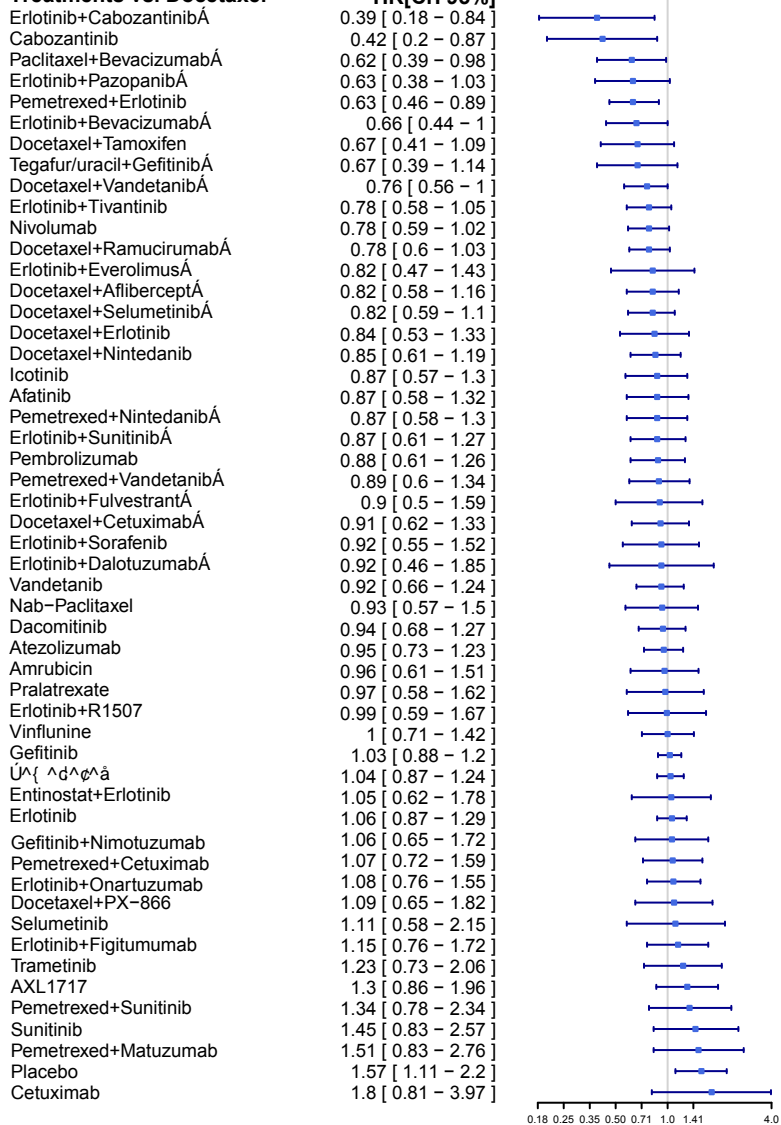
0.50 0.71 1.0 1.41 4.0

Treatments vs. Erlotinib+Cabozantinib

Treatment	HR [CrI 95%]
Nivolumab	1.29 [0.64 – 2.62]
Cabozantinib	1.31 [0.52 – 3.08]
Pembrolizumab	1.35 [0.66 – 2.73]
Docetaxel+Tamoxifen	1.35 [0.55 – 3.04]
Atezolizumab	1.37 [0.69 – 2.75]
Pemetrexed+Erlotinib	1.38 [0.67 – 2.9]
Erlotinib+R1507	1.38 [0.65 – 2.89]
Docetaxel+Erlotinib	1.47 [0.59 – 3.25]
Afatinib	1.55 [0.77 – 3.1]
Nab-Paclitaxel	1.57 [0.71 – 3.51]
Tegafur/uracil+Gefitinib	1.58 [0.69 – 3.78]
Pralatrexate	1.58 [0.77 – 3.29]
Docetaxel+Ramucirumab	1.63 [0.81 – 3.24]
Entinostat+Erlotinib	1.63 [0.78 – 3.44]
Pemetrexed+Vandetanib	1.68 [0.82 – 3.54]
Gefitinib+Nimotuzumab	1.7 [0.71 – 3.83]
Erlotinib+Sorafenib	1.72 [0.75 – 3.78]
Docetaxel+Vandetanib	1.73 [0.83 – 3.47]
Docetaxel+Nintedanib	1.77 [0.88 – 3.56]
Erlotinib+Fulvestrant	1.8 [0.75 – 4.1]
Erlotinib+Tivantinib	1.81 [0.92 – 3.53]
Trametinib	1.82 [0.7 – 4.93]
Vinflunine	1.82 [0.89 – 3.73]
Erlotinib+Sunitinib	1.83 [0.93 – 3.63]
Erlotinib+Bevacizumab	1.85 [0.91 – 3.72]
Docetaxel	1.9 [0.95 – 3.74]
Amrubicin	1.91 [0.88 – 4.1]
Docetaxel+Selumetinib	1.91 [0.93 – 3.99]
Docetaxel+Afiibercept	1.92 [0.93 – 3.87]
Erlotinib	1.93 [0.97 – 3.69]
Pemetrexed	1.96 [0.98 – 3.9]
Gefitinib	1.96 [0.97 – 3.84]
Pemetrexed+Cetuximab	1.97 [0.98 – 4.02]
Vandetanib	1.99 [1 – 3.9]
Pemetrexed+Nintedanib	1.99 [0.97 – 4.07]
Icotinib	2.01 [0.93 – 4.04]
Dacomitinib	2.02 [1.02 – 3.97]
Erlotinib+Pazopanib	2.08 [0.97 – 4.48]
AXL1717	2.08 [1.03 – 4.17]
Erlotinib+Figitumumab	2.08 [1.02 – 4.17]
Topotecan	2.09 [1.02 – 4.2]
Erlotinib+Onartuzumab	2.14 [1.03 – 4.29]
Docetaxel+Cetuximab	2.17 [1.04 – 4.43]
Paclitaxel	2.22 [1.09 – 4.43]
Placebo	2.32 [1.15 – 4.51]
Paclitaxel+Bevacizumab	2.35 [1.06 – 5.14]
Erlotinib+Everolimus	2.43 [1.04 – 5.76]
Sunitinib	2.74 [1.24 – 6.19]
Docetaxel+PX-866	2.79 [1.24 – 6.85]
Cetuximab	3.17 [1.21 – 8]
Pemetrexed+Matuzumab	3.26 [1.32 – 8.4]
Erlotinib+Dalotuzumab	3.31 [1.17 – 8.78]
Pemetrexed+Sunitinib	3.82 [1.7 – 9.67]

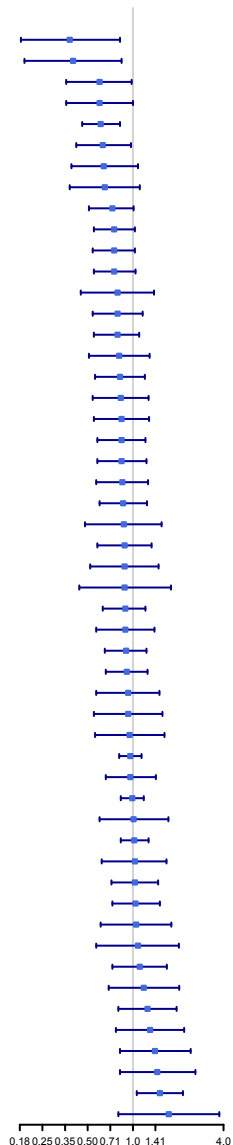
Treatments vs. Placebo



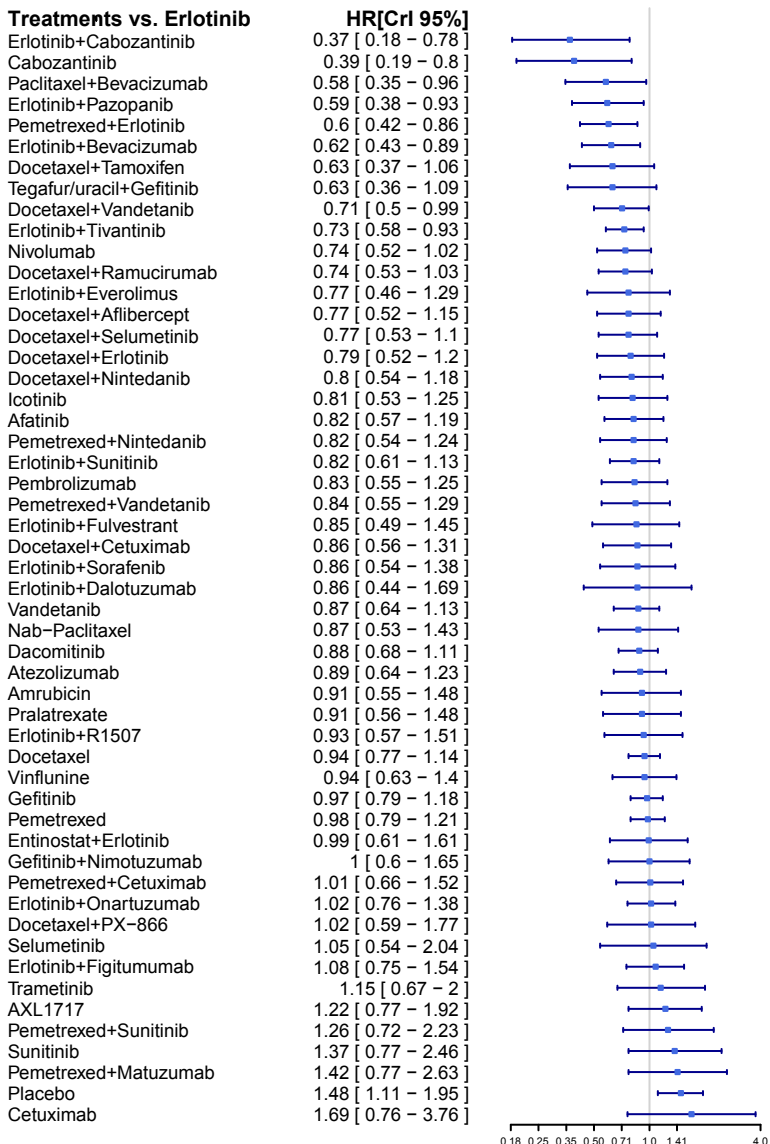
(b) Progression free survival**Treatments vs. Docetaxel**

Treatments vs. Pemetrexed

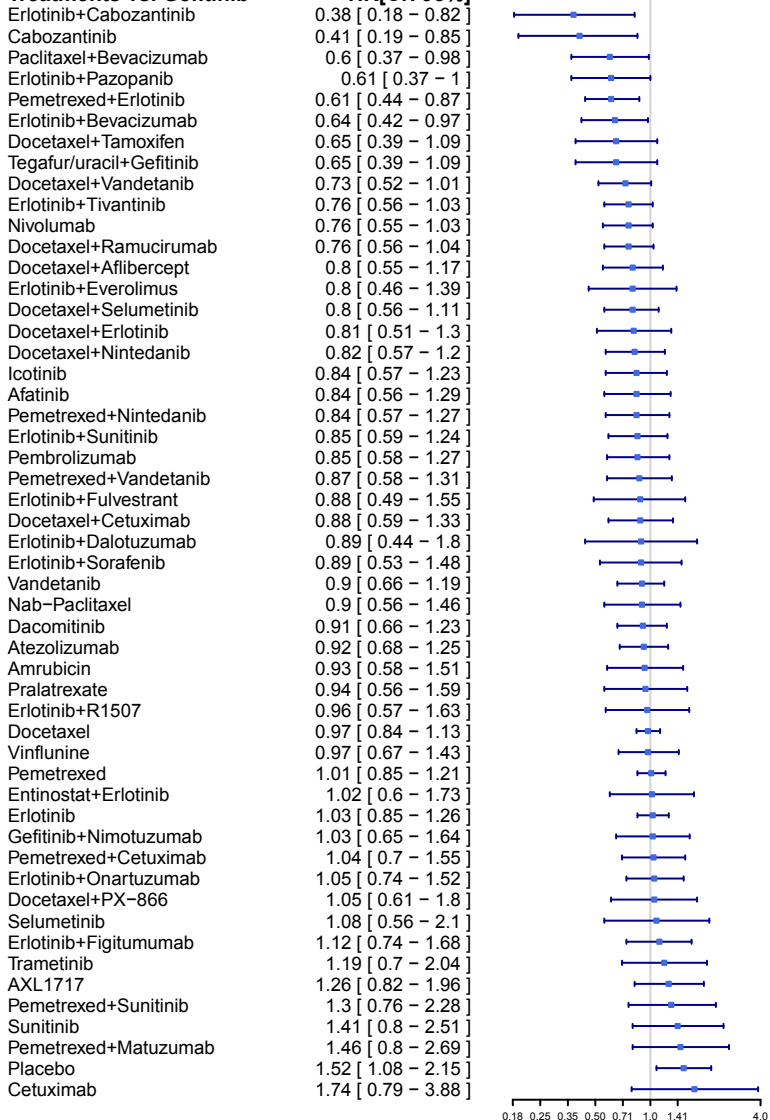
Treatment	HR [CrI 95%]
Erlotinib+Cabozantinib	0.38 [0.18 - 0.82]
Cabozantinib	0.4 [0.19 - 0.84]
Paclitaxel+Bevacizumab	0.6 [0.36 - 0.98]
Erlotinib+Pazopanib	0.6 [0.36 - 1]
Pemetrexed+Erlotinib	0.61 [0.46 - 0.82]
Erlotinib+Bevacizumab	0.63 [0.42 - 0.97]
Docetaxel+Tamoxifen	0.64 [0.39 - 1.08]
Tegafur/uracil+Gefitinib	0.65 [0.38 - 1.11]
Docetaxel+Vandetanib	0.73 [0.51 - 1.01]
Erlotinib+Tivantinib	0.75 [0.55 - 1.03]
Nivolumab	0.75 [0.54 - 1.03]
Docetaxel+Ramucirumab	0.75 [0.55 - 1.04]
Erlotinib+Everolimus	0.79 [0.45 - 1.38]
Docetaxel+Aflibercept	0.79 [0.54 - 1.16]
Docetaxel+Selumetinib	0.79 [0.55 - 1.1]
Docetaxel+Erlotinib	0.81 [0.51 - 1.29]
Docetaxel+Nintedanib	0.82 [0.56 - 1.2]
Icotinib	0.83 [0.54 - 1.27]
Afatinib	0.84 [0.55 - 1.28]
Pemetrexed+Nintedanib	0.84 [0.58 - 1.21]
Erlotinib+Sunitinib	0.84 [0.58 - 1.23]
Pembrolizumab	0.85 [0.57 - 1.26]
Pemetrexed+Vandetanib	0.86 [0.6 - 1.24]
Erlotinib+Fulvestrant	0.87 [0.48 - 1.55]
Docetaxel+Cetuximab	0.88 [0.58 - 1.33]
Erlotinib+Sorafenib	0.88 [0.52 - 1.48]
Erlotinib+Dalotuzumab	0.88 [0.44 - 1.79]
Vandetanib	0.89 [0.63 - 1.21]
Nab-Paclitaxel	0.89 [0.57 - 1.39]
Dacomitinib	0.9 [0.65 - 1.23]
Atezolizumab	0.91 [0.66 - 1.25]
Amrubicin	0.93 [0.57 - 1.5]
Pralatrexate	0.93 [0.55 - 1.57]
Erlotinib+R1507	0.95 [0.56 - 1.62]
Docetaxel	0.96 [0.81 - 1.14]
Vinflunine	0.96 [0.66 - 1.42]
Gefitinib	0.99 [0.83 - 1.18]
Entinostat+Erlotinib	1.01 [0.6 - 1.72]
Erlotinib	1.02 [0.83 - 1.27]
Gefitinib+Nimotuzumab	1.03 [0.62 - 1.67]
Pemetrexed+Cetuximab	1.03 [0.72 - 1.47]
Erlotinib+Onartuzumab	1.04 [0.73 - 1.51]
Docetaxel+PX-866	1.05 [0.61 - 1.8]
Selumetinib	1.08 [0.57 - 2.02]
Erlotinib+Figitumumab	1.11 [0.73 - 1.68]
Trametinib	1.18 [0.69 - 2.03]
AXL1717	1.25 [0.8 - 1.95]
Pemetrexed+Sunitinib	1.3 [0.77 - 2.19]
Sunitinib	1.4 [0.82 - 2.42]
Pemetrexed+Matuzumab	1.45 [0.82 - 2.6]
Placebo	1.51 [1.06 - 2.15]
Cetuximab	1.73 [0.8 - 3.75]



Treatments vs. Erlotinib

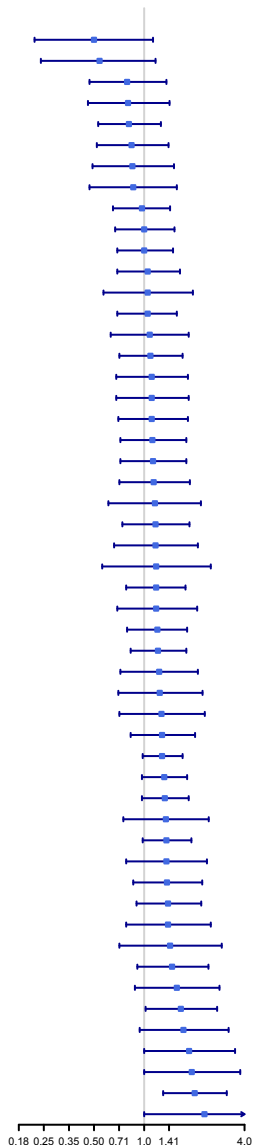


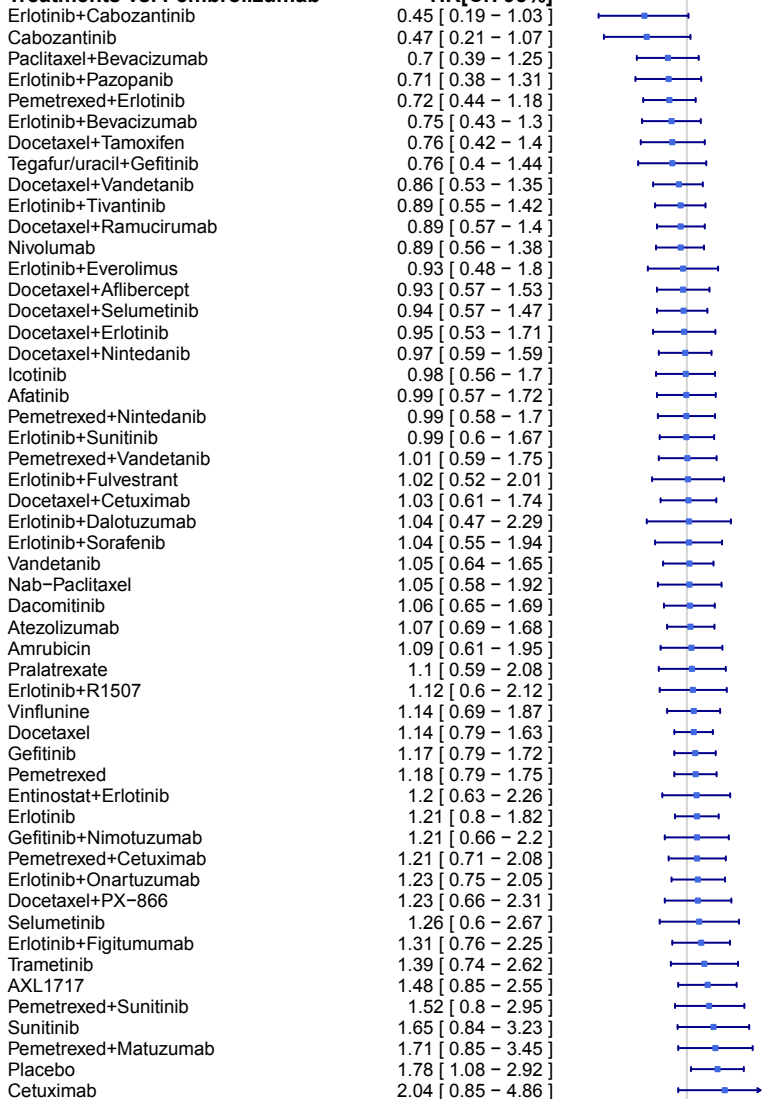
Treatments vs. Gefitinib



Treatments vs. Nivolumab

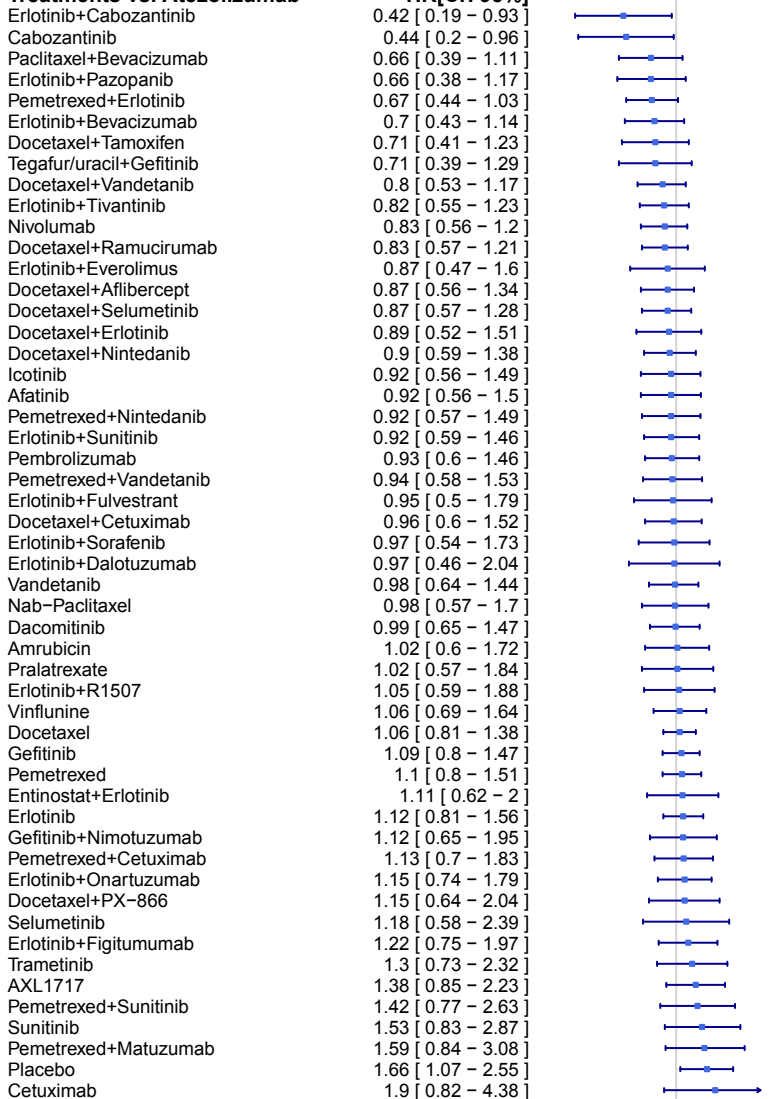
Treatment	HR [CrI 95%]
Erlotinib+Cabozantinib	0.5 [0.22 - 1.13]
Cabozantinib	0.54 [0.24 - 1.17]
Paclitaxel+Bevacizumab	0.79 [0.47 - 1.36]
Erlotinib+Pazopanib	0.8 [0.46 - 1.42]
Pemetrexed+Erlotinib	0.81 [0.53 - 1.26]
Erlotinib+Bevacizumab	0.84 [0.52 - 1.4]
Docetaxel+Tamoxifen	0.85 [0.49 - 1.51]
Tegafur/uracil+Gefitinib	0.86 [0.47 - 1.57]
Docetaxel+Vandetanib	0.97 [0.65 - 1.43]
Erlotinib+Tivantinib	1 [0.67 - 1.52]
Docetaxel+Ramucirumab	1 [0.69 - 1.49]
Docetaxel+Aflibercept	1.05 [0.69 - 1.64]
Erlotinib+Everolimus	1.05 [0.57 - 1.96]
Docetaxel+Selumetinib	1.05 [0.69 - 1.57]
Docetaxel+Erlotinib	1.08 [0.63 - 1.85]
Docetaxel+Nintedanib	1.09 [0.71 - 1.7]
Icotinib	1.11 [0.68 - 1.83]
Afatinib	1.11 [0.68 - 1.85]
Pemetrexed+Nintedanib	1.11 [0.7 - 1.83]
Erlotinib+Sunitinib	1.12 [0.72 - 1.79]
Pembrolizumab	1.13 [0.72 - 1.79]
Pemetrexed+Vandetanib	1.14 [0.71 - 1.88]
Erlotinib+Fulvestrant	1.16 [0.61 - 2.19]
Docetaxel+Cetuximab	1.17 [0.74 - 1.87]
Erlotinib+Sorafenib	1.17 [0.66 - 2.1]
Erlotinib+Dalotuzumab	1.18 [0.56 - 2.51]
Vandetanib	1.18 [0.78 - 1.77]
Nab-Paclitaxel	1.18 [0.69 - 2.08]
Dacomitinib	1.2 [0.79 - 1.81]
Atezolizumab	1.21 [0.83 - 1.79]
Amrubicin	1.23 [0.72 - 2.1]
Pralatrexate	1.24 [0.7 - 2.24]
Erlotinib+R1507	1.27 [0.71 - 2.31]
Vinflunine	1.28 [0.83 - 2.02]
Docetaxel	1.28 [0.98 - 1.7]
Gefitinib	1.32 [0.97 - 1.81]
Pemetrexed	1.33 [0.97 - 1.85]
Entinostat+Erlotinib	1.35 [0.75 - 2.44]
Erlotinib	1.36 [0.98 - 1.92]
Gefitinib+Nimotuzumab	1.36 [0.78 - 2.38]
Pemetrexed+Cetuximab	1.37 [0.86 - 2.23]
Erlotinib+Onartuzumab	1.39 [0.9 - 2.2]
Docetaxel+PX-866	1.39 [0.78 - 2.51]
Selumetinib	1.43 [0.71 - 2.92]
Erlotinib+Figitumumab	1.47 [0.91 - 2.43]
Trametinib	1.57 [0.88 - 2.83]
AXL1717	1.66 [1.02 - 2.74]
Pemetrexed+Sunitinib	1.72 [0.94 - 3.21]
Sunitinib	1.86 [1 - 3.51]
Pemetrexed+Matuzumab	1.93 [1 - 3.77]
Placebo	2.01 [1.3 - 3.13]
Cetuximab	2.3 [1 - 5.34]

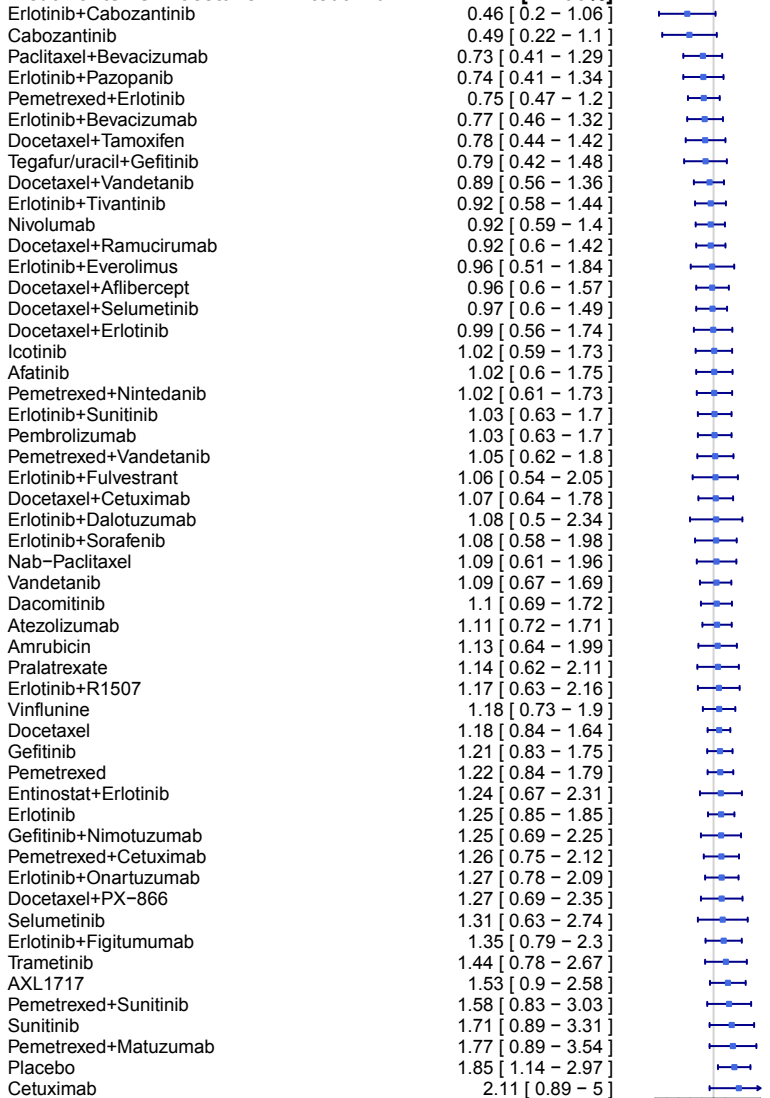


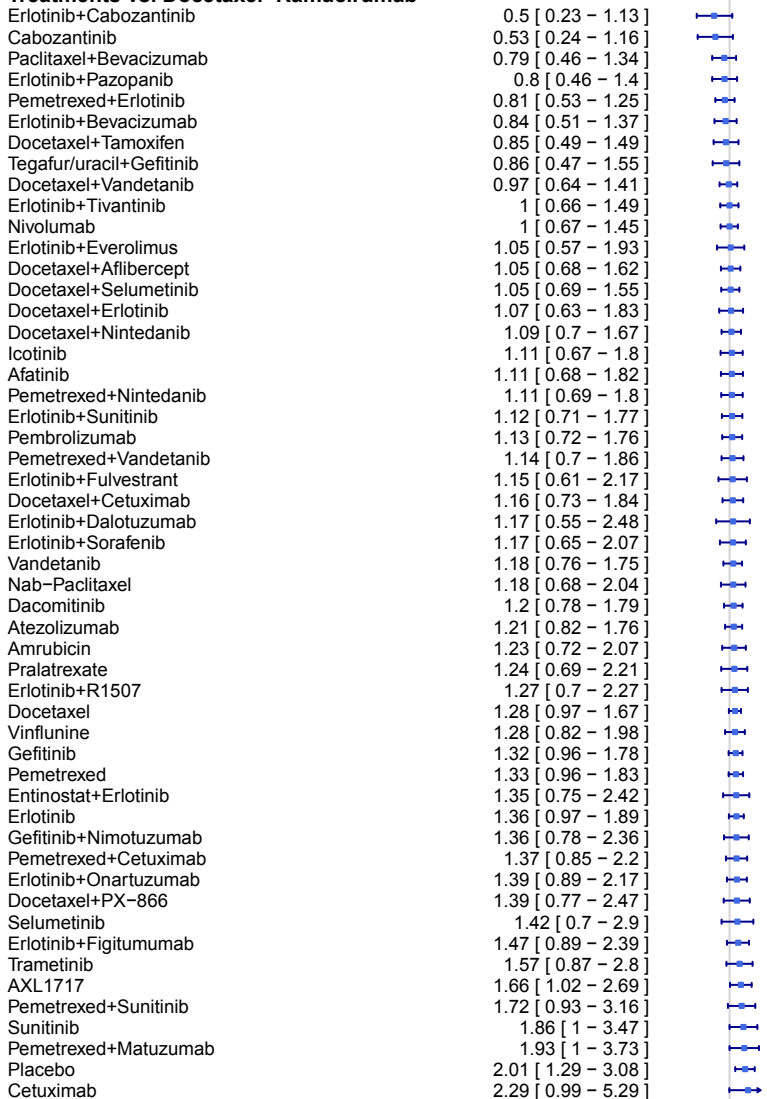
Treatments vs. Pembrolizumab

0.18 0.35 0.71 1.01 1.41 4.0

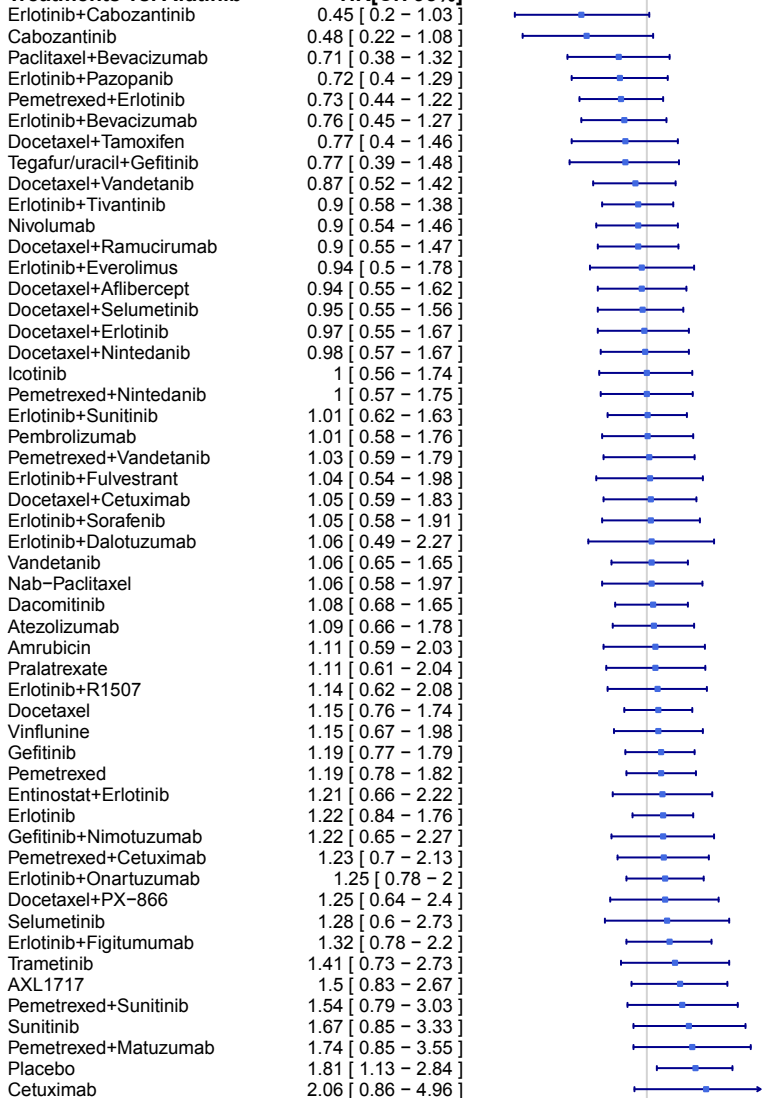
Treatments vs. Atezolizumab



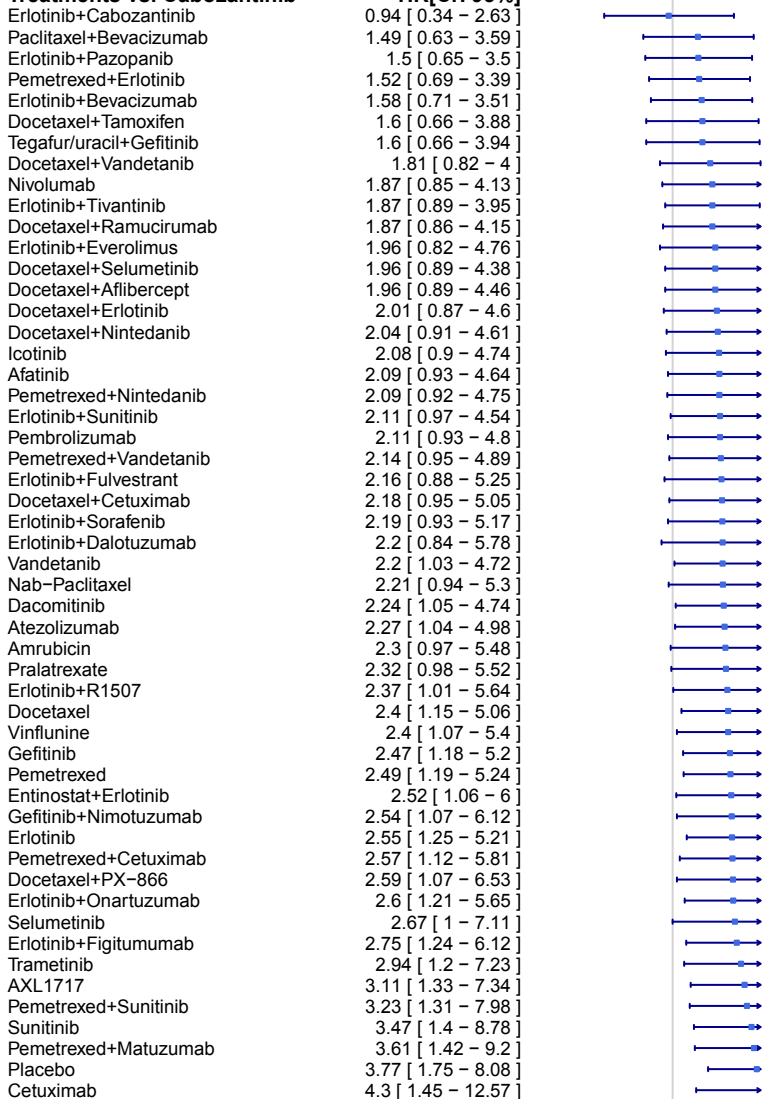
Treatments vs. Docetaxel+Nintedanib

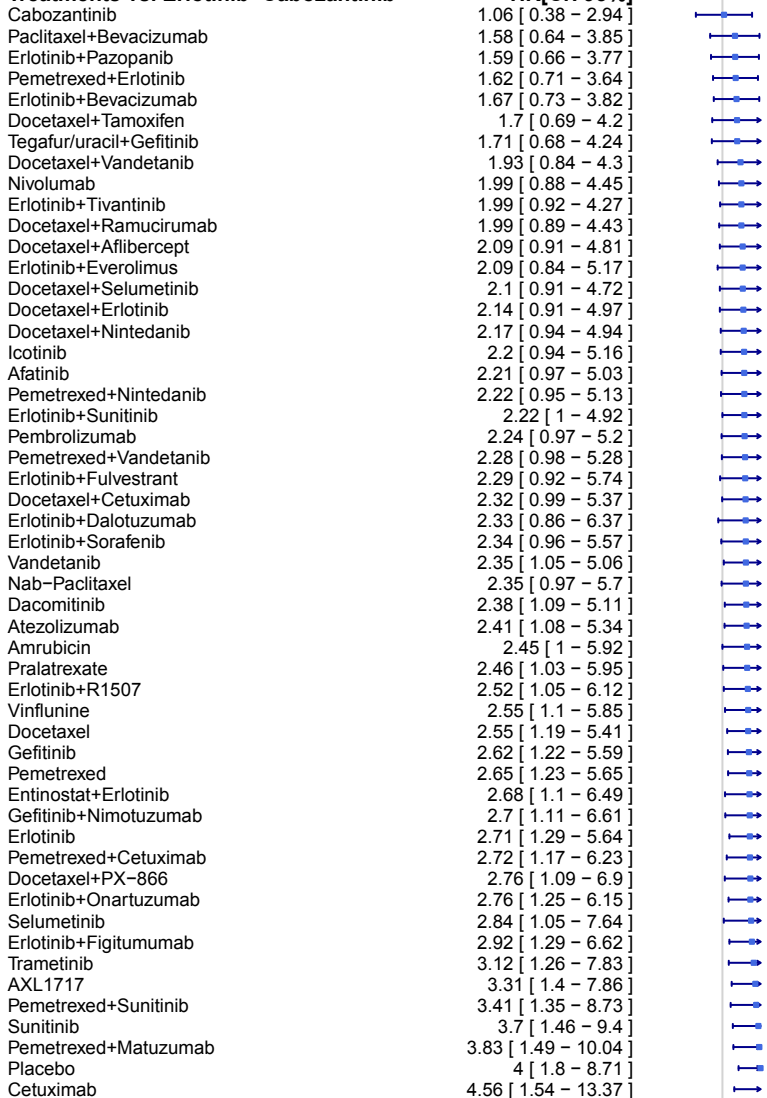
Treatments vs. Docetaxel+Ramucirumab

Treatments vs. Afatinib



Treatments vs. Cabozantinib

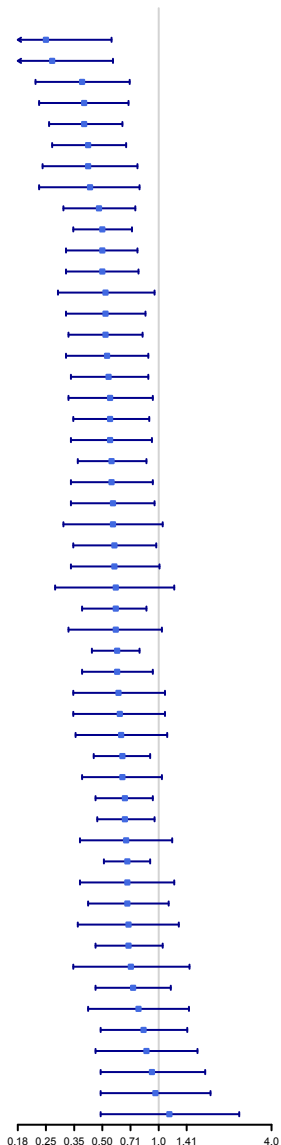


Treatments vs. Erlotinib+Cabozantinib

0.18 0.501.0 4.0

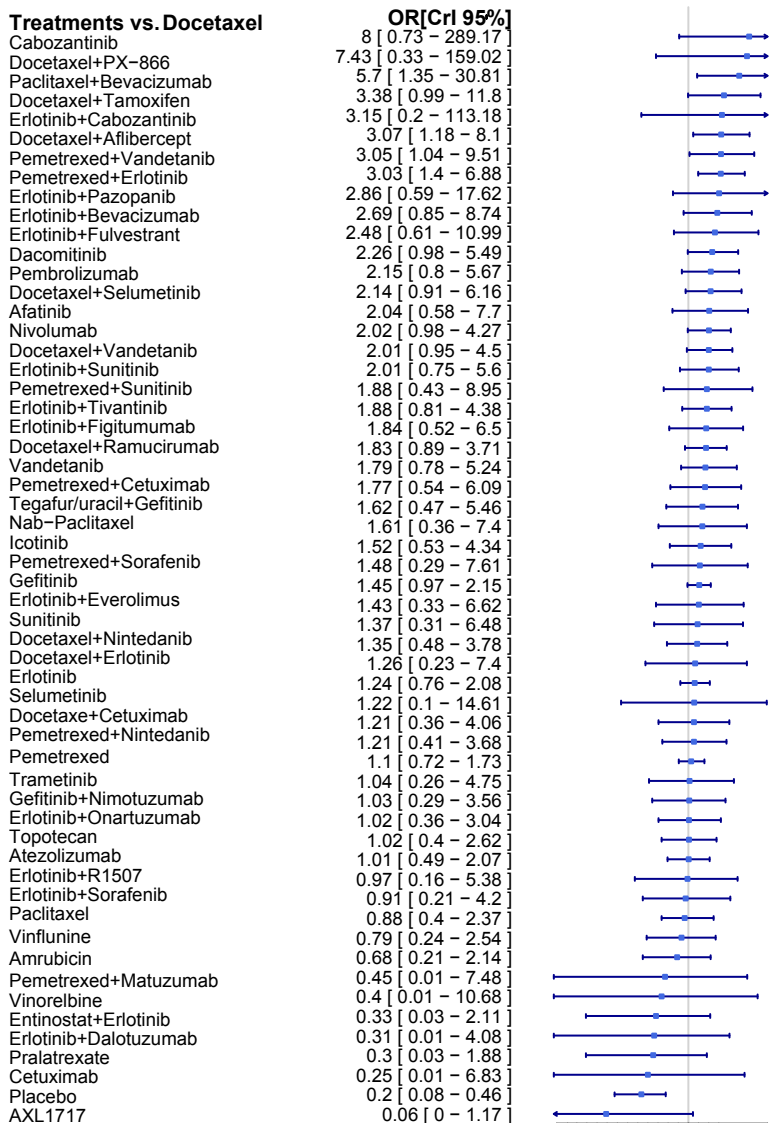
Treatments vs. Placebo

	HR[CrI 95%]
Erlotinib+Cabozantinib	0.25 [0.11 - 0.56]
Cabozantinib	0.27 [0.12 - 0.57]
Paclitaxel+Bevacizumab	0.39 [0.22 - 0.7]
Erlotinib+Pazopanib	0.4 [0.23 - 0.69]
Pemetrexed+Erlotinib	0.4 [0.26 - 0.64]
Erlotinib+Bevacizumab	0.42 [0.27 - 0.67]
Docetaxel+Tamoxifen	0.42 [0.24 - 0.77]
Tegafur/uracil+Gefitinib	0.43 [0.23 - 0.79]
Docetaxel+Vandetanib	0.48 [0.31 - 0.75]
Erlotinib+Tivantinib	0.5 [0.35 - 0.72]
Nivolumab	0.5 [0.32 - 0.77]
Docetaxel+Ramucirumab	0.5 [0.32 - 0.78]
Erlotinib+Everolimus	0.52 [0.29 - 0.95]
Docetaxel+Aflibercept	0.52 [0.32 - 0.85]
Docetaxel+Selumetinib	0.52 [0.33 - 0.82]
Docetaxel+Erlotinib	0.53 [0.32 - 0.88]
Docetaxel+Nintedanib	0.54 [0.34 - 0.88]
Icotinib	0.55 [0.33 - 0.93]
Afatinib	0.55 [0.35 - 0.89]
Pemetrexed+Nintedanib	0.55 [0.34 - 0.92]
Erlotinib+Sunitinib	0.56 [0.37 - 0.86]
Pembrolizumab	0.56 [0.34 - 0.93]
Pemetrexed+Vandetanib	0.57 [0.34 - 0.95]
Erlotinib+Fulvestrant	0.57 [0.31 - 1.05]
Docetaxel+Cetuximab	0.58 [0.35 - 0.97]
Erlotinib+Sorafenib	0.58 [0.34 - 1.01]
Erlotinib+Dalotuzumab	0.59 [0.28 - 1.21]
Vandetanib	0.59 [0.39 - 0.86]
Nab-Paclitaxel	0.59 [0.33 - 1.04]
Dacomitinib	0.6 [0.44 - 0.79]
Atezolizumab	0.6 [0.39 - 0.93]
Amrubicin	0.61 [0.35 - 1.08]
Pralatrexate	0.62 [0.35 - 1.08]
Erlotinib+R1507	0.63 [0.36 - 1.11]
Docetaxel	0.64 [0.45 - 0.9]
Vinflunine	0.64 [0.39 - 1.04]
Gefitinib	0.66 [0.46 - 0.93]
Pemetrexed	0.66 [0.47 - 0.95]
Entinostat+Erlotinib	0.67 [0.38 - 1.18]
Erlotinib	0.68 [0.51 - 0.9]
Gefitinib+Nimotuzumab	0.68 [0.38 - 1.21]
Pemetrexed+Cetuximab	0.68 [0.42 - 1.13]
Docetaxel+PX-866	0.69 [0.37 - 1.28]
Erlotinib+Onartuzumab	0.69 [0.46 - 1.05]
Selumetinib	0.71 [0.35 - 1.46]
Erlotinib+Figitumumab	0.73 [0.46 - 1.16]
Trametinib	0.78 [0.42 - 1.45]
AXL1717	0.83 [0.49 - 1.42]
Pemetrexed+Sunitinib	0.86 [0.46 - 1.61]
Sunitinib	0.92 [0.49 - 1.77]
Pemetrexed+Matuzumab	0.96 [0.49 - 1.89]
Cetuximab	1.14 [0.49 - 2.69]

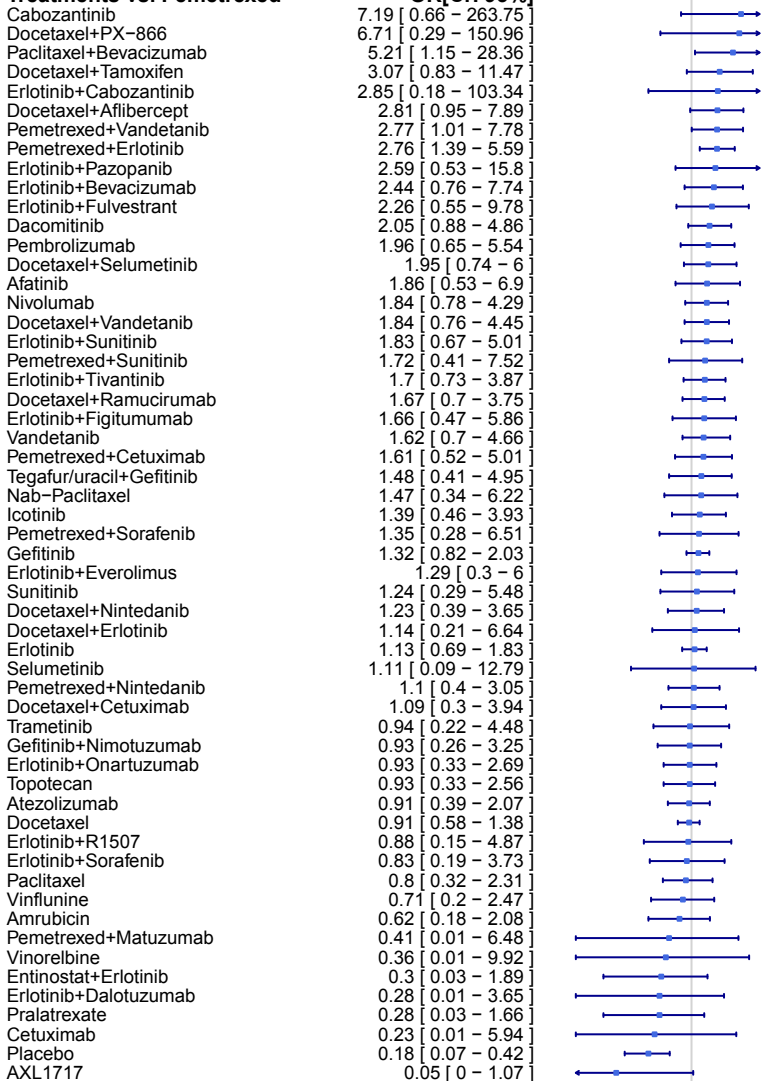


(c) Objective response

Treatments vs. Docetaxel

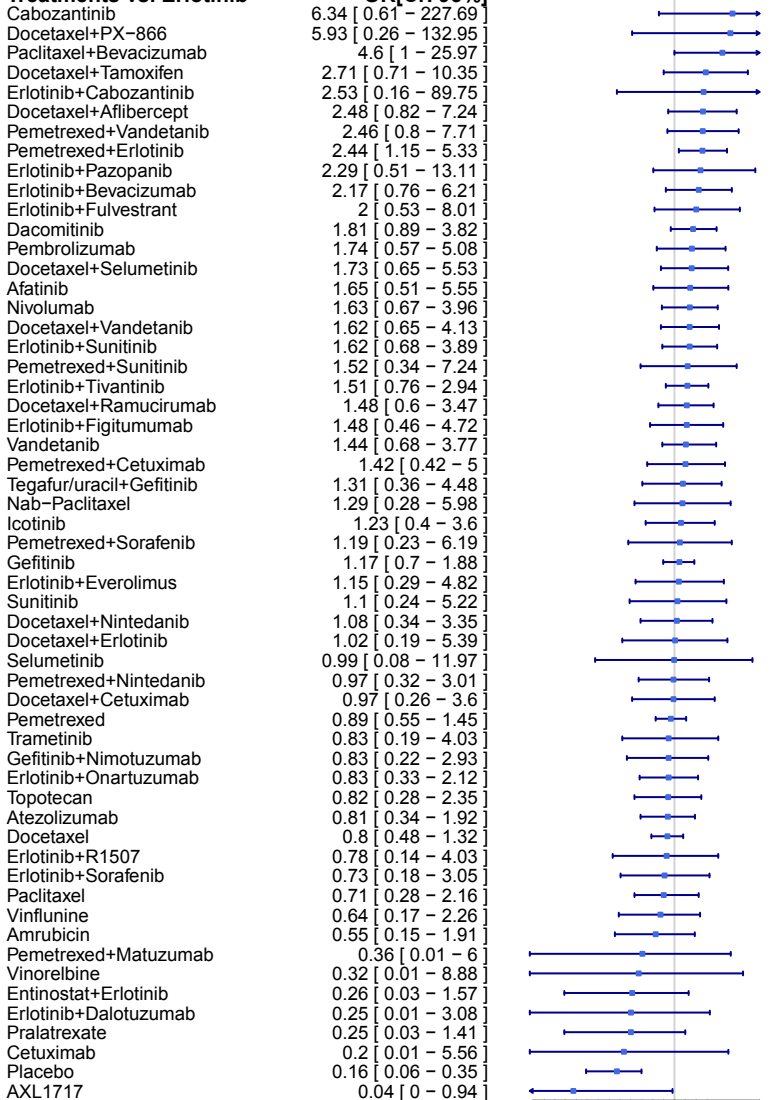


Treatments vs. Pemetrexed



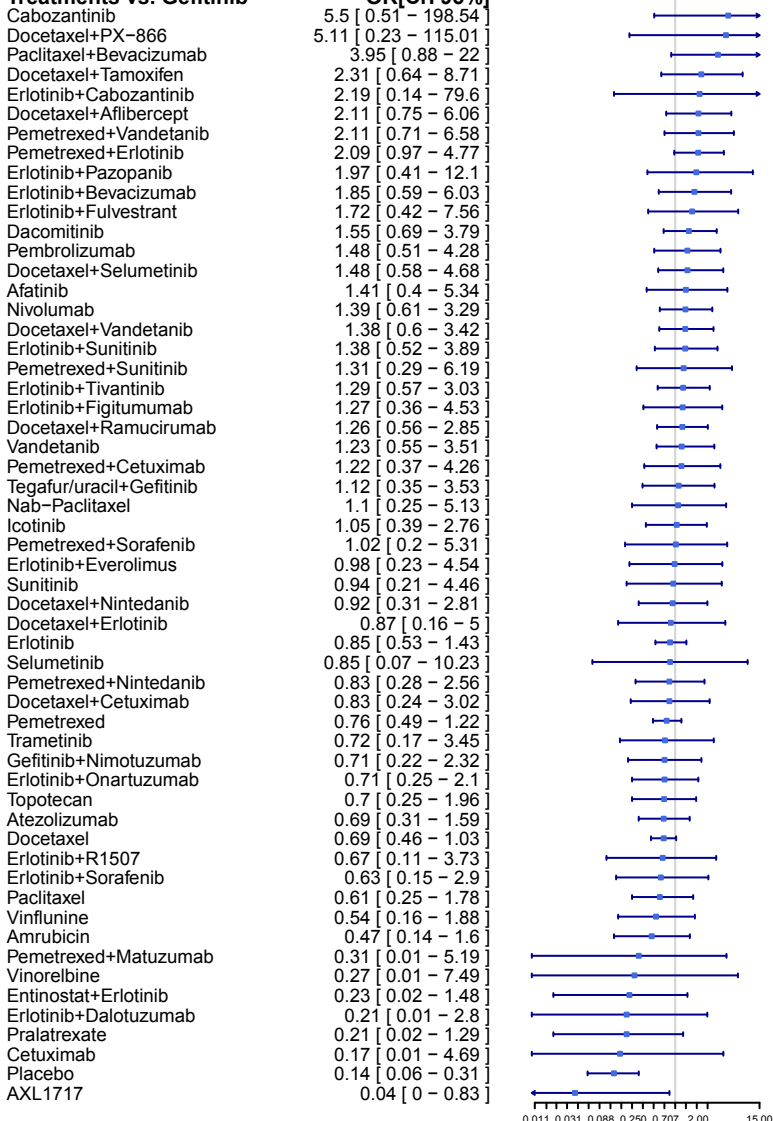
0.011 0.044 0.177 0.707 2.830 15.00

Treatments vs. Erlotinib



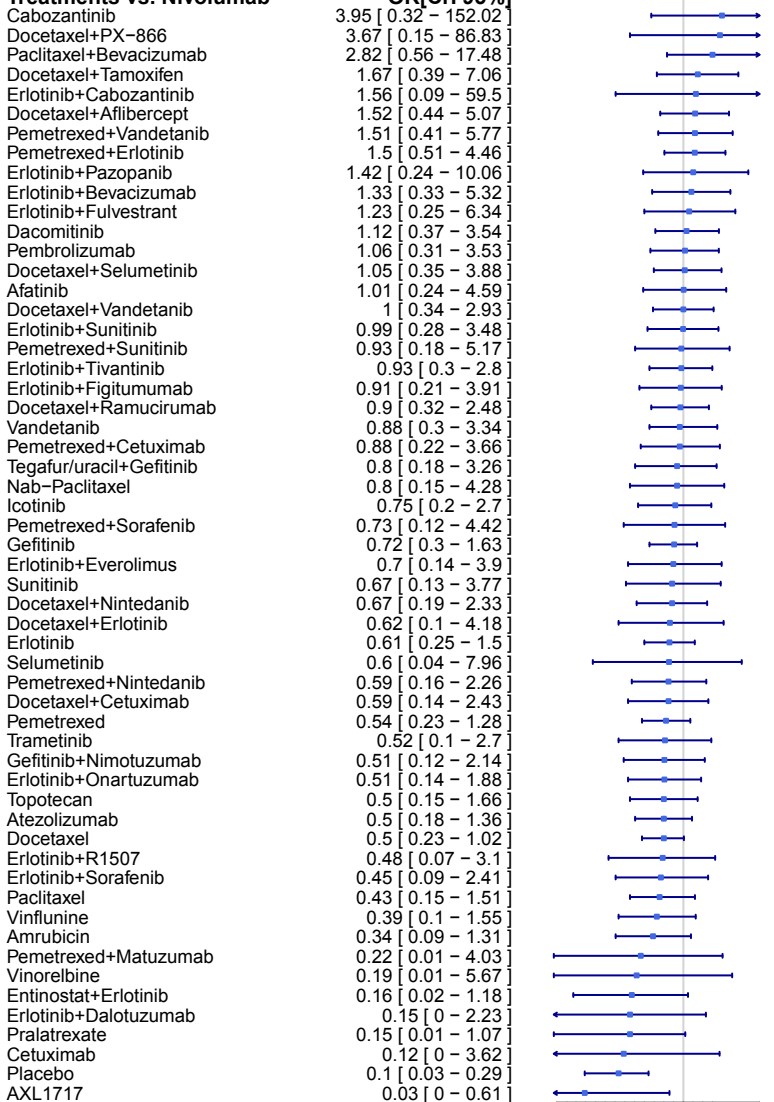
0.011 0.031 0.088 0.250 0.707 2.00 15.00

Treatments vs. Gefitinib



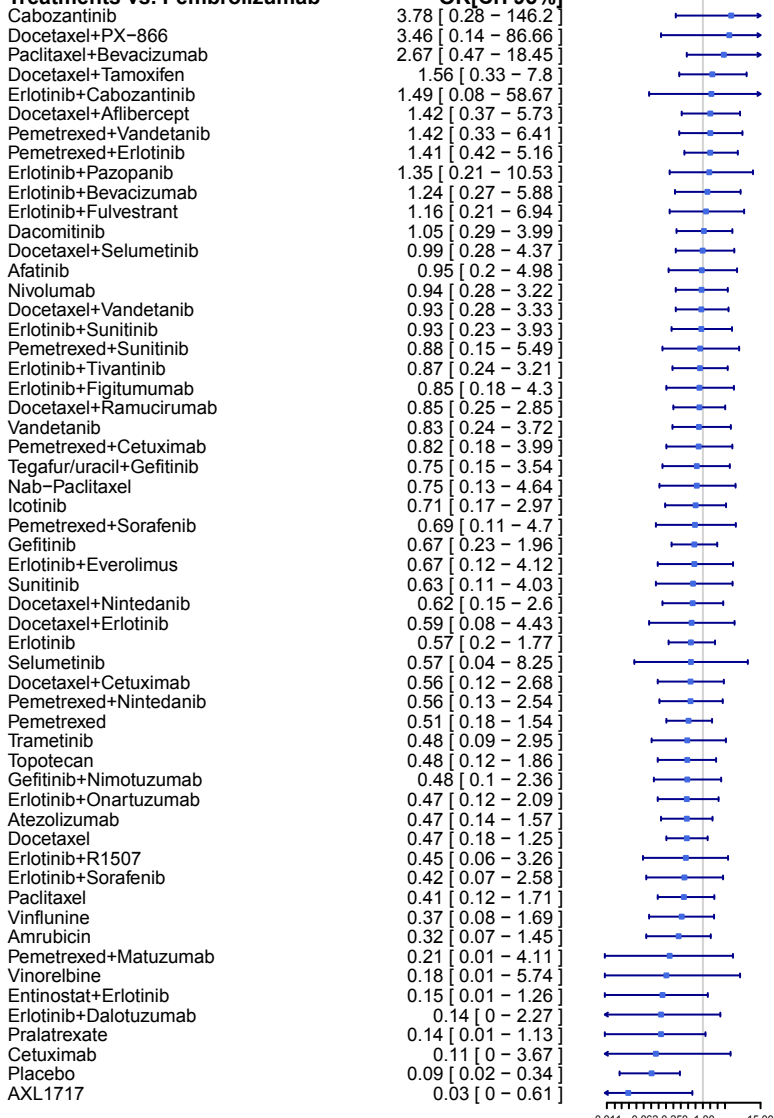
0.011 0.031 0.088 0.250 0.707 2.00 15.00

Treatments vs. Nivolumab

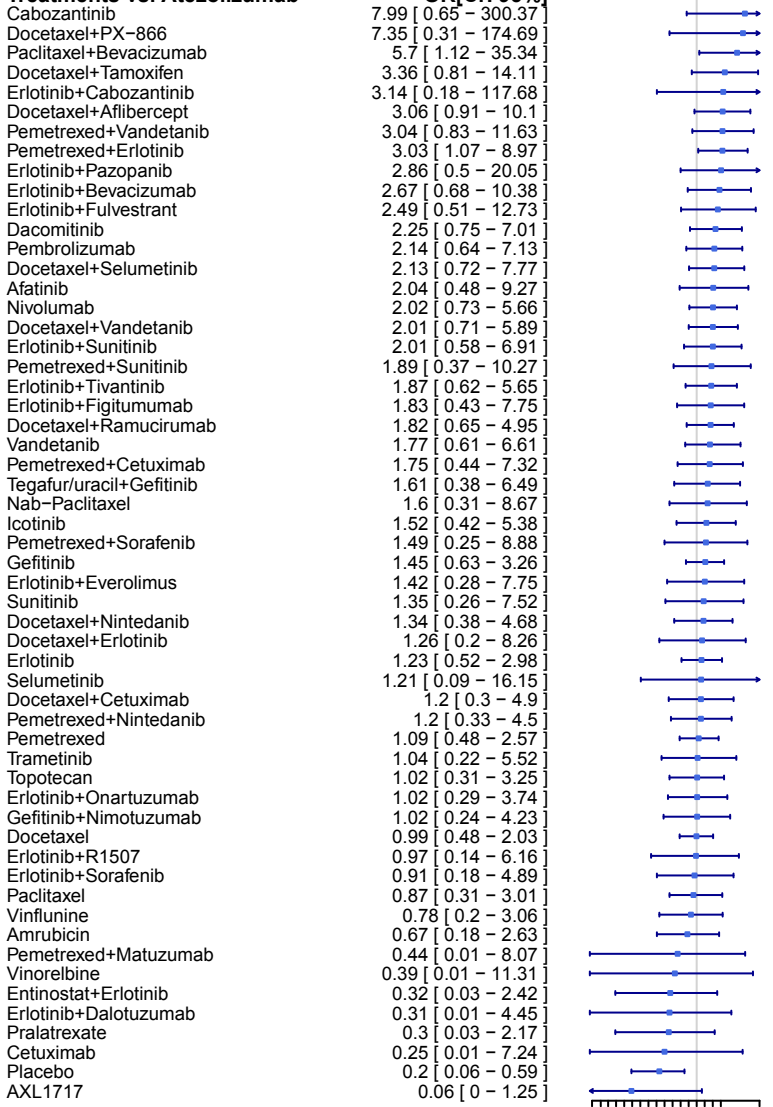


0.011 0.044 0.177 0.707 2.00 15.00

Treatments vs. Pembrolizumab

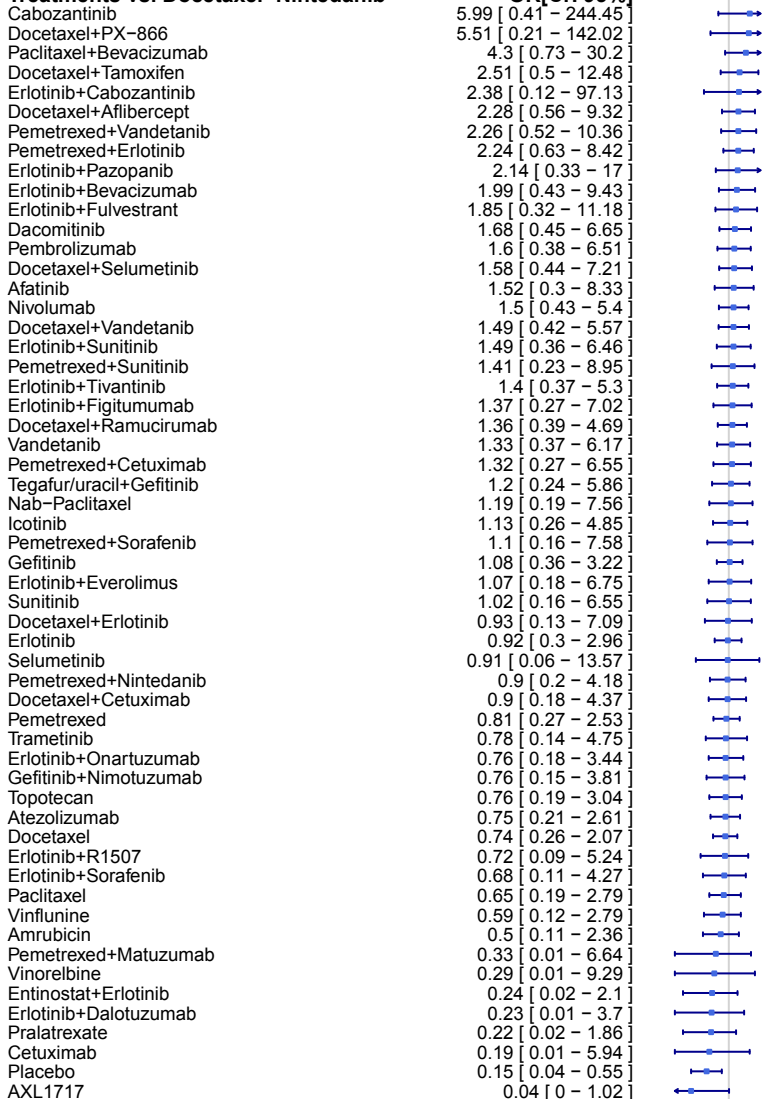


Treatments vs. Atezolizumab

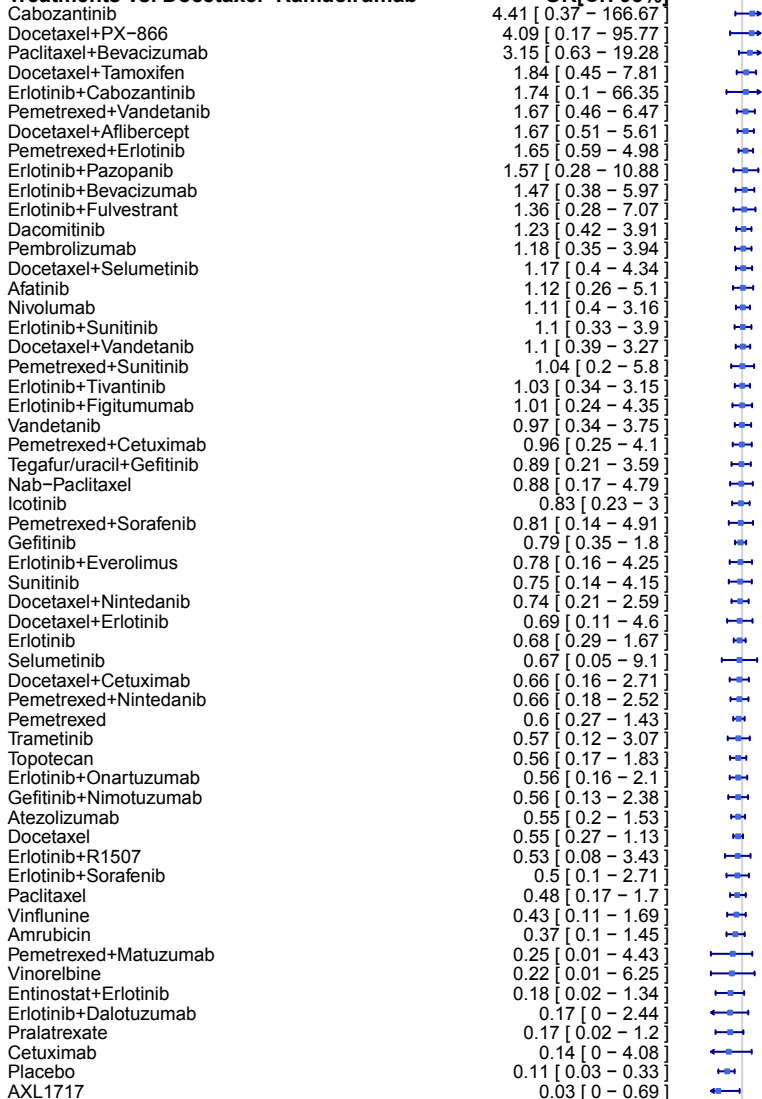


0.011 0.044 0.177 0.707 2.830 15.00

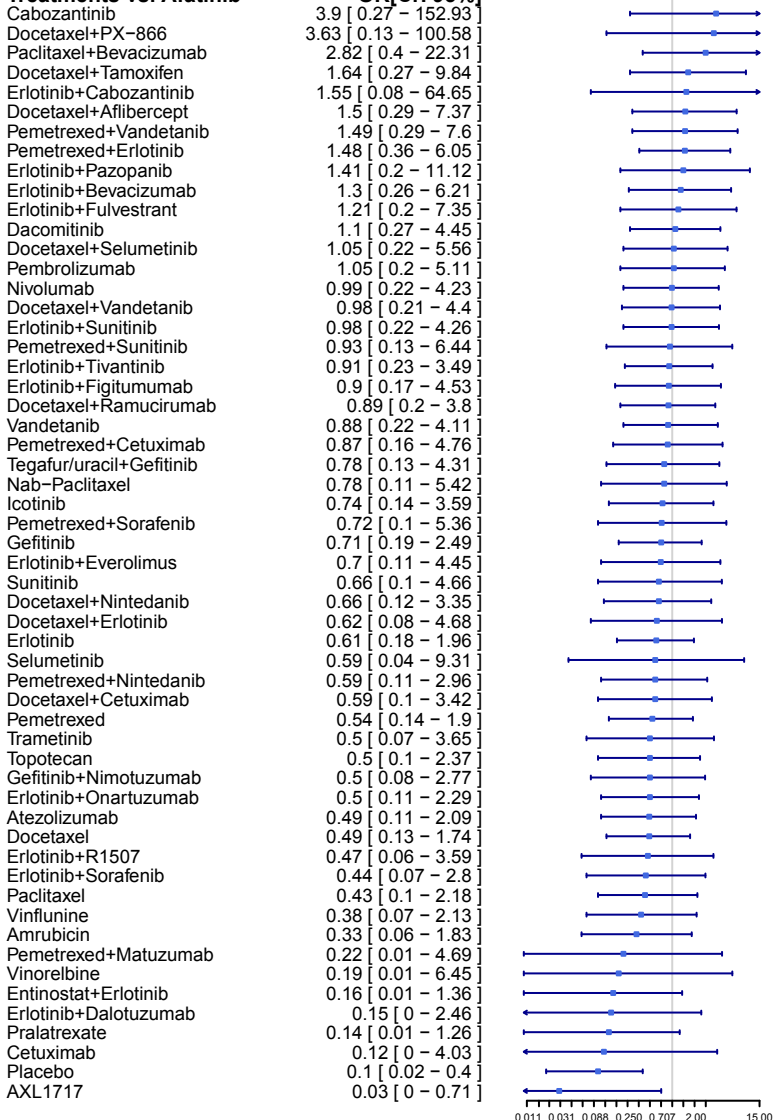
Treatments vs. Docetaxel+Nintedanib



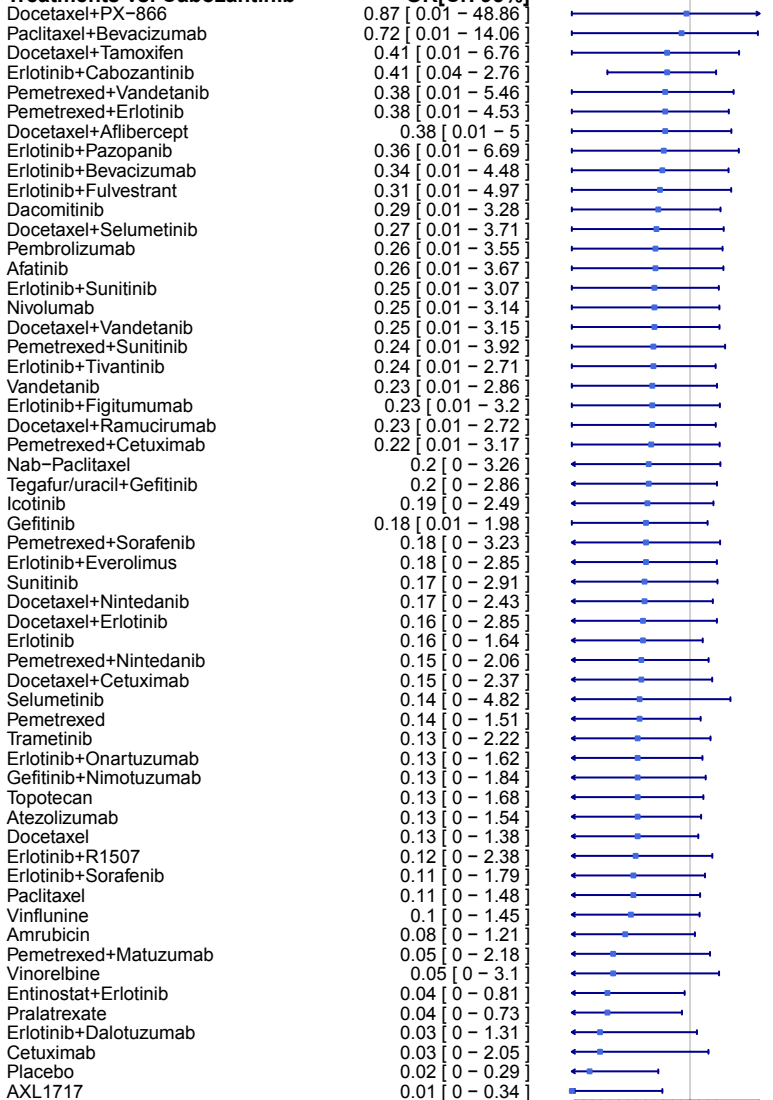
Treatments vs. Docetaxel+Ramucirumab



Treatments vs. Afatinib

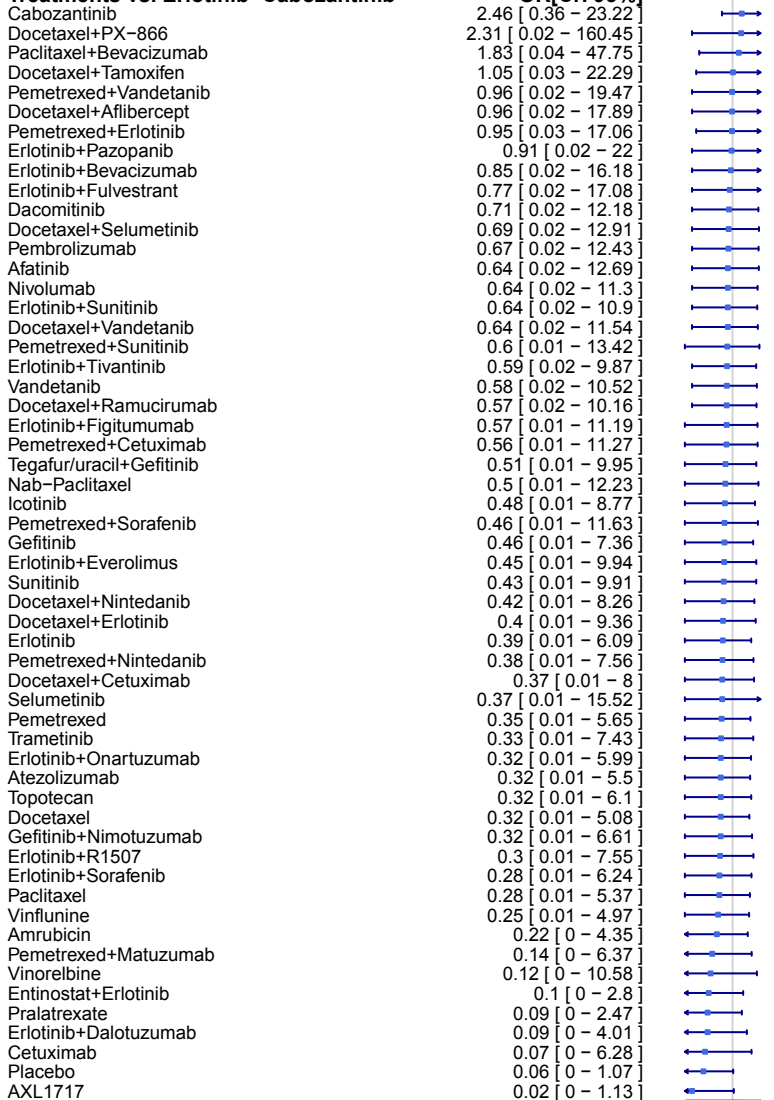


Treatments vs. Cabozantinib

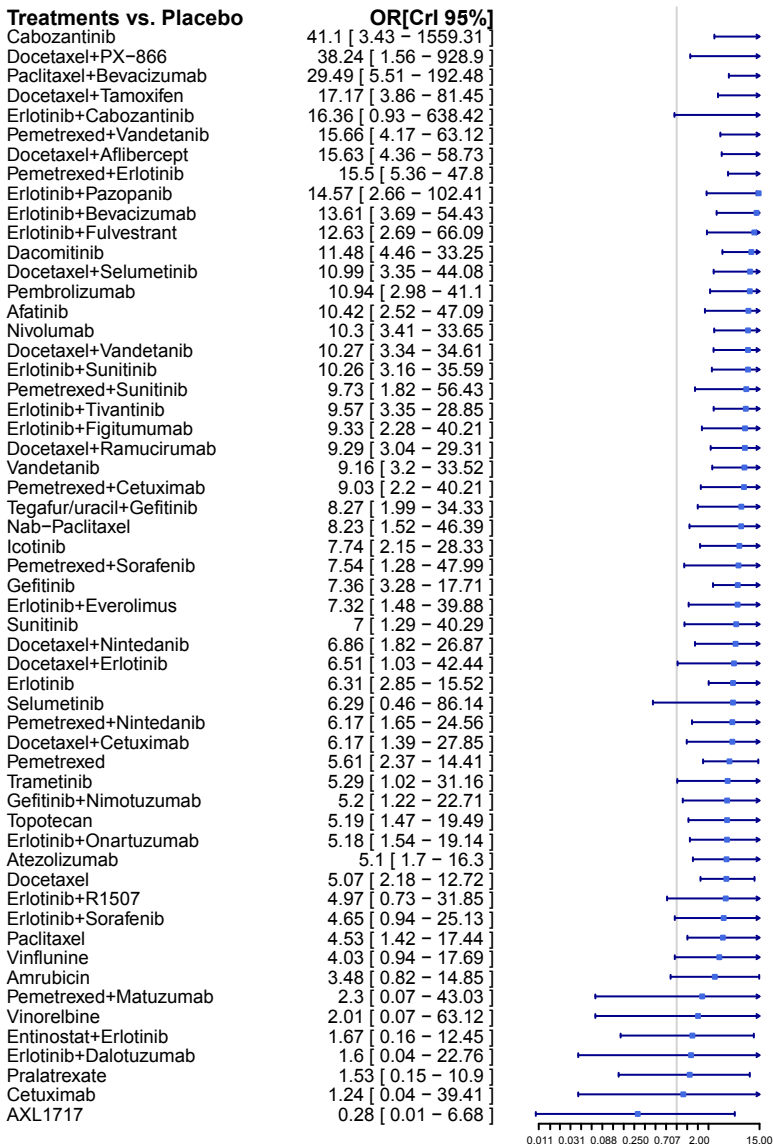


0.011 0.044 0.177 0.707 2.830 15.00

Treatments vs. Erlotinib+Cabozantinib



Treatments vs. Placebo

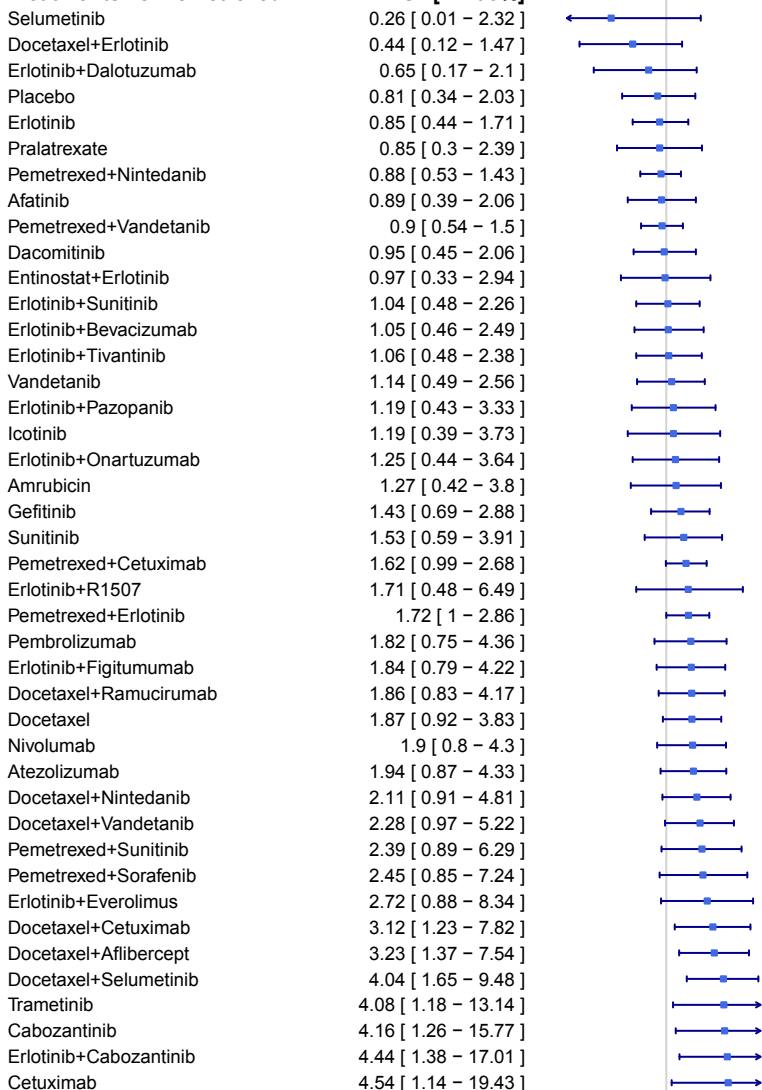


(d) Serious adverse events**Treatments vs. Docetaxel****OR[CrI 95%]**

Selumetinib	0.13 [0 - 1.42]	
Docetaxel+Erlotinib	0.24 [0.06 - 0.93]	
Erlotinib+Dalotuzumab	0.35 [0.08 - 1.32]	
Placebo	0.44 [0.15 - 1.33]	
Pralatrexate	0.45 [0.15 - 1.57]	
Erlotinib	0.45 [0.19 - 1.16]	
Pemetrexed+Nintedanib	0.47 [0.2 - 1.13]	
Afatinib	0.48 [0.18 - 1.38]	
Pemetrexed+Vandetanib	0.48 [0.2 - 1.2]	
Dacomitinib	0.51 [0.2 - 1.39]	
Entinostat+Erlotinib	0.52 [0.15 - 1.88]	
Pemetrexed	0.53 [0.26 - 1.09]	
Erlotinib+Sunitinib	0.55 [0.21 - 1.53]	
Erlotinib+Bevacizumab	0.56 [0.21 - 1.63]	
Erlotinib+Tivantinib	0.57 [0.21 - 1.59]	
Vandetanib	0.61 [0.23 - 1.73]	
Erlotinib+Pazopanib	0.64 [0.19 - 2.16]	
Icotinib	0.64 [0.25 - 1.64]	
Erlotinib+Onartuzumab	0.66 [0.19 - 2.37]	
Amrubicin	0.68 [0.29 - 1.52]	
Gefitinib	0.76 [0.56 - 1.06]	
Sunitinib	0.8 [0.27 - 2.77]	
Pemetrexed+Cetuximab	0.87 [0.37 - 2.06]	
Pemetrexed+Erlotinib	0.91 [0.38 - 2.17]	
Erlotinib+R1507	0.93 [0.21 - 3.86]	
Pembrolizumab	0.97 [0.59 - 1.59]	
Erlotinib+Figitumumab	0.97 [0.35 - 2.82]	
Docetaxel+Ramucirumab	0.99 [0.69 - 1.43]	
Nivolumab	1.02 [0.68 - 1.47]	
Atezolizumab	1.03 [0.72 - 1.48]	
Docetaxel+Nintedanib	1.13 [0.73 - 1.74]	
Docetaxel+Vandetanib	1.22 [0.78 - 1.89]	
Pemetrexed+Sunitinib	1.27 [0.4 - 4.42]	
Pemetrexed+Sorafenib	1.33 [0.37 - 4.91]	
Erlotinib+Everolimus	1.47 [0.42 - 5.37]	
Docetaxel+Cetuximab	1.65 [0.94 - 2.96]	
Docetaxel+Aflibercept	1.74 [1.08 - 2.72]	
Docetaxel+Selumetinib	2.15 [1.38 - 3.43]	
Trametinib	2.17 [0.88 - 5.66]	
Cabozantinib	2.2 [0.61 - 9.4]	
Cetuximab	2.41 [0.51 - 13.68]	
Erlotinib+Cabozantinib	2.42 [0.64 - 10]	

0.088 0.177 0.354 0.707 1.410

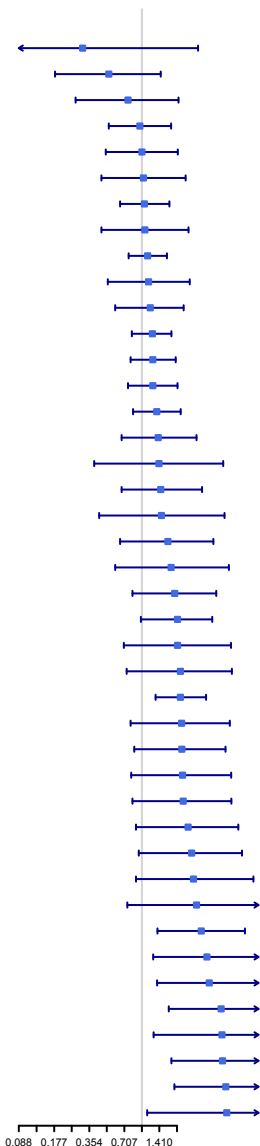
Treatments vs. Pemetrexed

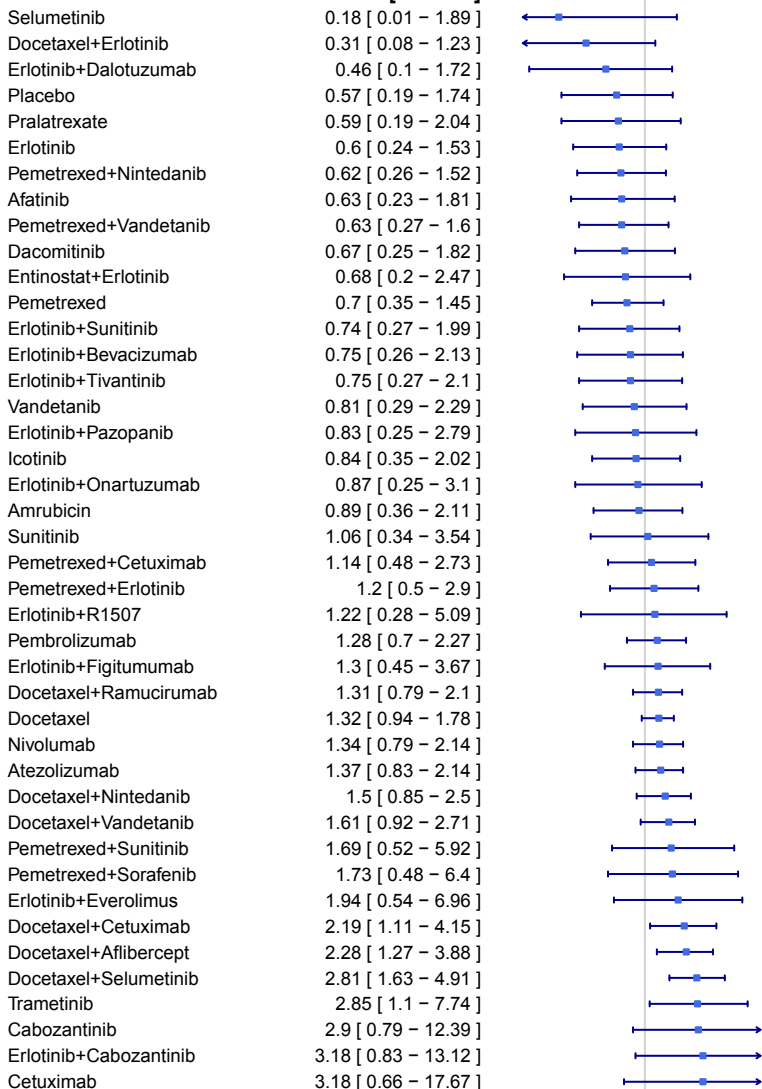


0.088 0.177 0.354 0.707 1.410

Treatments vs. Erlotinib

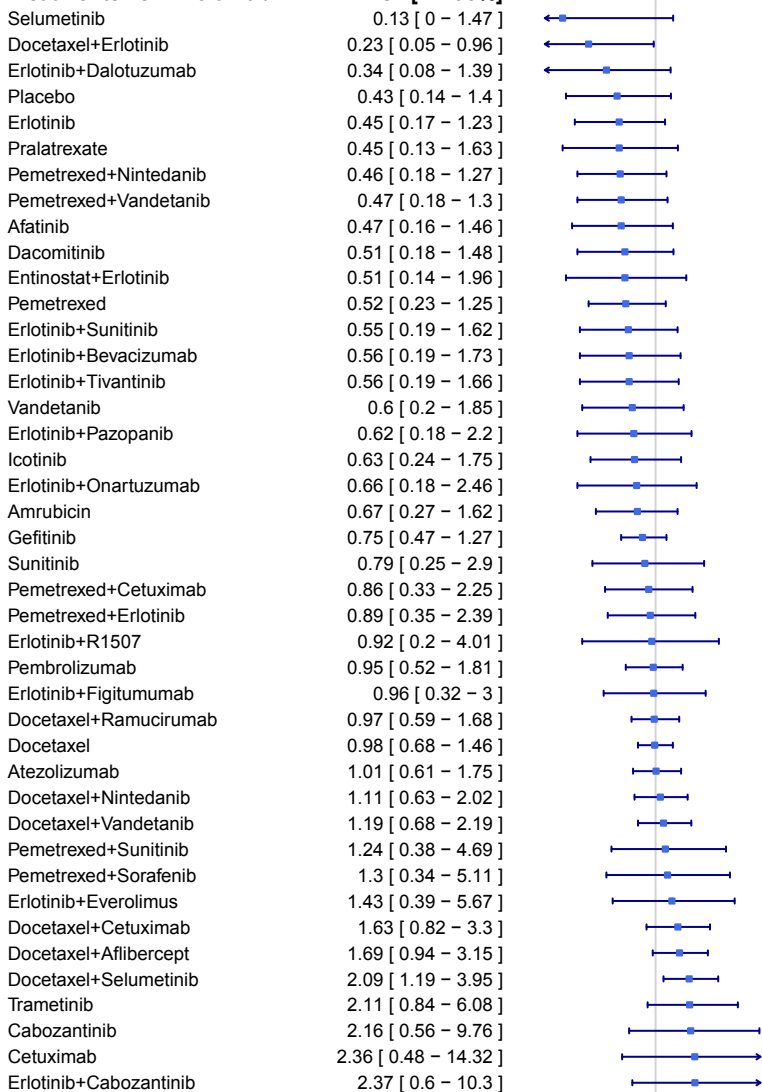
Treatment	OR [CrI 95%]
Selumetinib	0.31 [0.01 – 3.03]
Docetaxel+Erlotinib	0.52 [0.18 – 1.45]
Erlotinib+Dalotuzumab	0.76 [0.27 – 2.06]
Placebo	0.96 [0.52 – 1.78]
Pralatrexate	1 [0.49 – 2.03]
Pemetrexed+Nintedanib	1.03 [0.45 – 2.37]
Afatinib	1.05 [0.65 – 1.72]
Pemetrexed+Vandetanib	1.06 [0.45 – 2.51]
Dacomitinib	1.12 [0.77 – 1.64]
Entinostat+Erlotinib	1.14 [0.51 – 2.57]
Pemetrexed	1.18 [0.59 – 2.28]
Erlotinib+Sunitinib	1.23 [0.82 – 1.79]
Erlotinib+Tivantinib	1.24 [0.8 – 1.95]
Erlotinib+Bevacizumab	1.24 [0.76 – 2.02]
Vandetanib	1.34 [0.84 – 2.15]
Erlotinib+Pazopanib	1.38 [0.67 – 2.94]
Icotinib	1.4 [0.39 – 4.98]
Erlotinib+Onartuzumab	1.45 [0.67 – 3.28]
Amrubicin	1.47 [0.43 – 5.11]
Gefitinib	1.67 [0.65 – 4.1]
Sunitinib	1.78 [0.59 – 5.57]
Pemetrexed+Cetuximab	1.91 [0.83 – 4.34]
Pemetrexed+Erlotinib	2.02 [0.98 – 4.01]
Erlotinib+R1507	2.02 [0.7 – 5.81]
Pembrolizumab	2.14 [0.74 – 5.91]
Erlotinib+Figitumumab	2.14 [1.31 – 3.55]
Docetaxel+Ramucirumab	2.19 [0.8 – 5.67]
Docetaxel	2.2 [0.86 – 5.21]
Nivolumab	2.23 [0.81 – 5.83]
Atezolizumab	2.26 [0.83 – 5.85]
Docetaxel+Nintedanib	2.49 [0.89 – 6.71]
Docetaxel+Vandetanib	2.67 [0.94 – 7.22]
Pemetrexed+Sunitinib	2.77 [0.89 – 9.04]
Pemetrexed+Sorafenib	2.94 [0.75 – 10.17]
Erlotinib+Everolimus	3.23 [1.36 – 7.65]
Docetaxel+Cetuximab	3.61 [1.25 – 10.78]
Docetaxel+Aflibercept	3.78 [1.35 – 10.26]
Docetaxel+Selumetinib	4.78 [1.7 – 13]
Trametinib	4.86 [1.26 – 17.5]
Cabozantinib	4.91 [1.79 – 14.82]
Erlotinib+Cabozantinib	5.24 [1.9 – 16.33]
Cetuximab	5.34 [1.11 – 25.15]



Treatments vs. Gefitinib

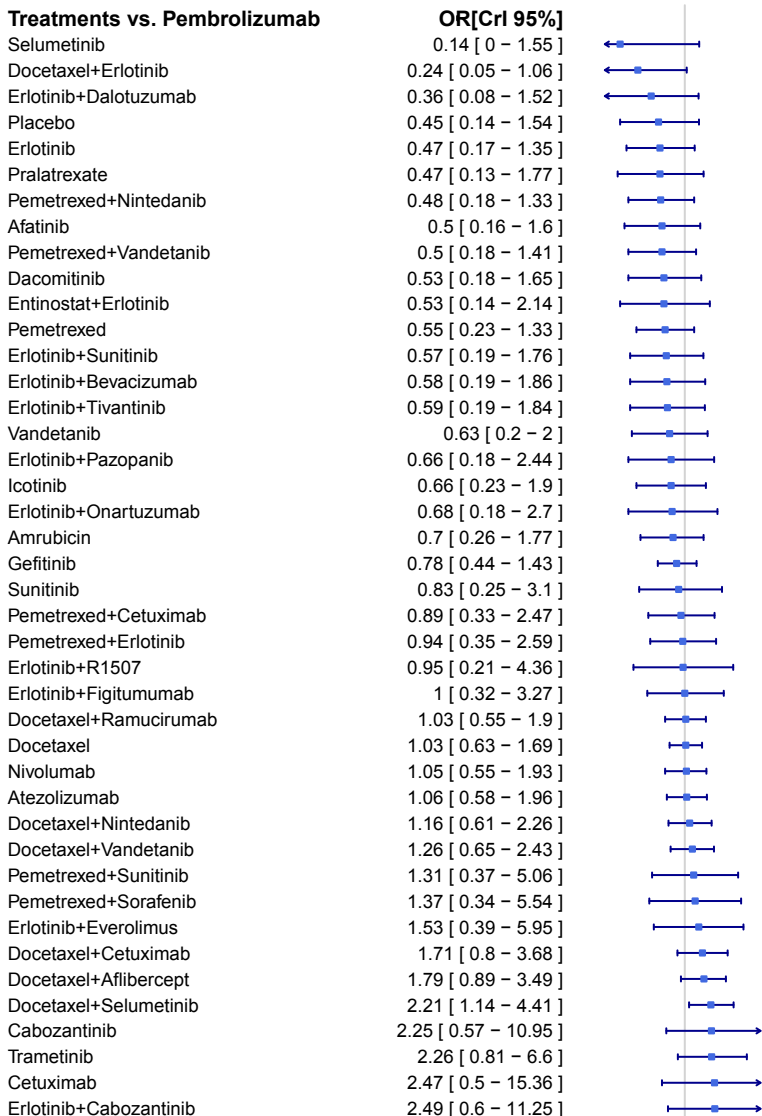
0.088 0.177 0.354 0.707 1.410

Treatments vs. Nivolumab



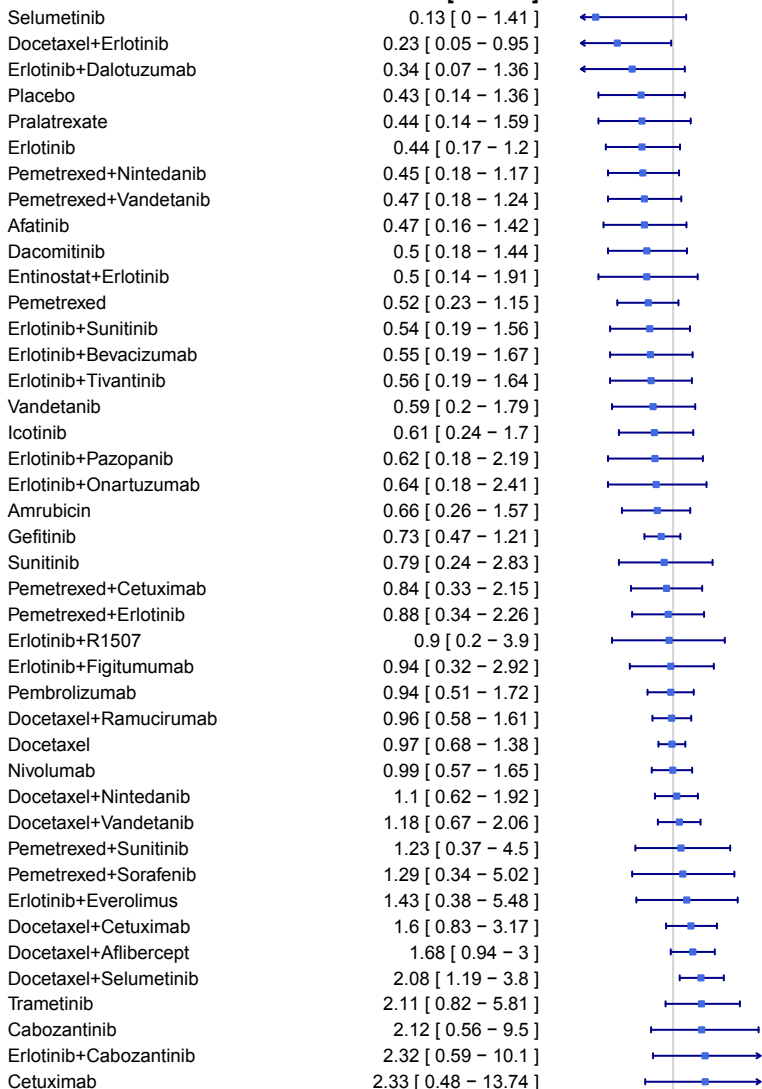
0.088 0.177 0.354 0.707 1.410

Treatments vs. Pembrolizumab



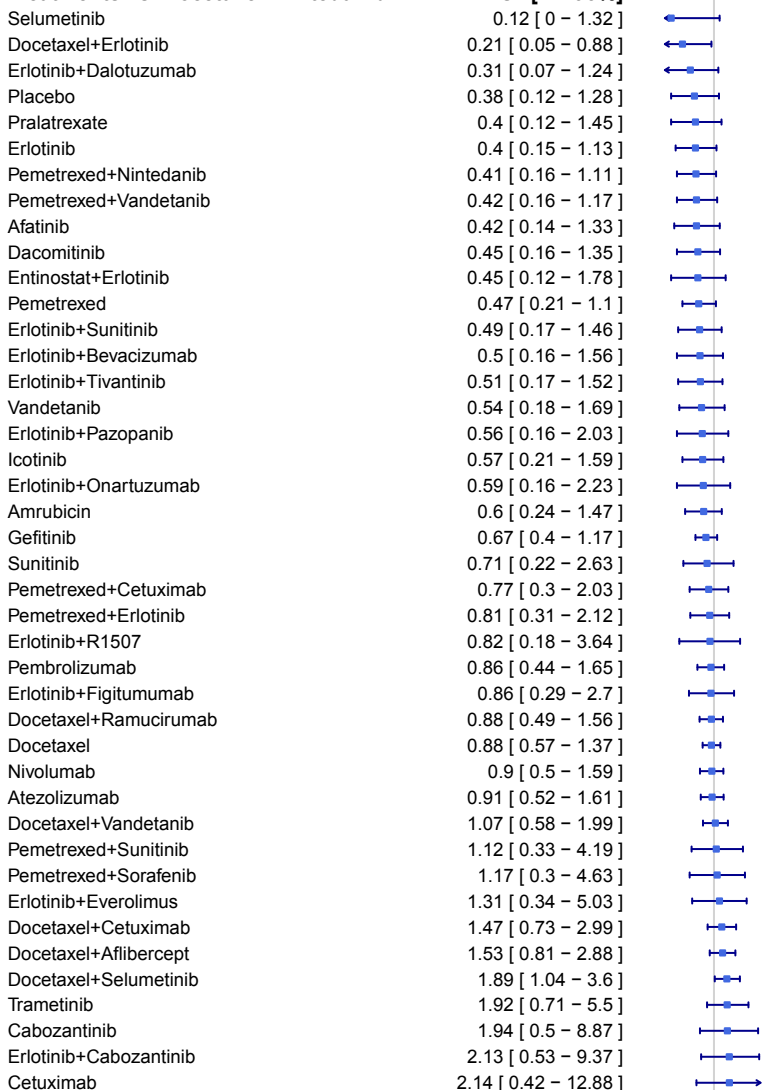
0.088 0.250 0.707 2.00

Treatments vs. Atezolizumab



0.088 0.250 0.707 2.00

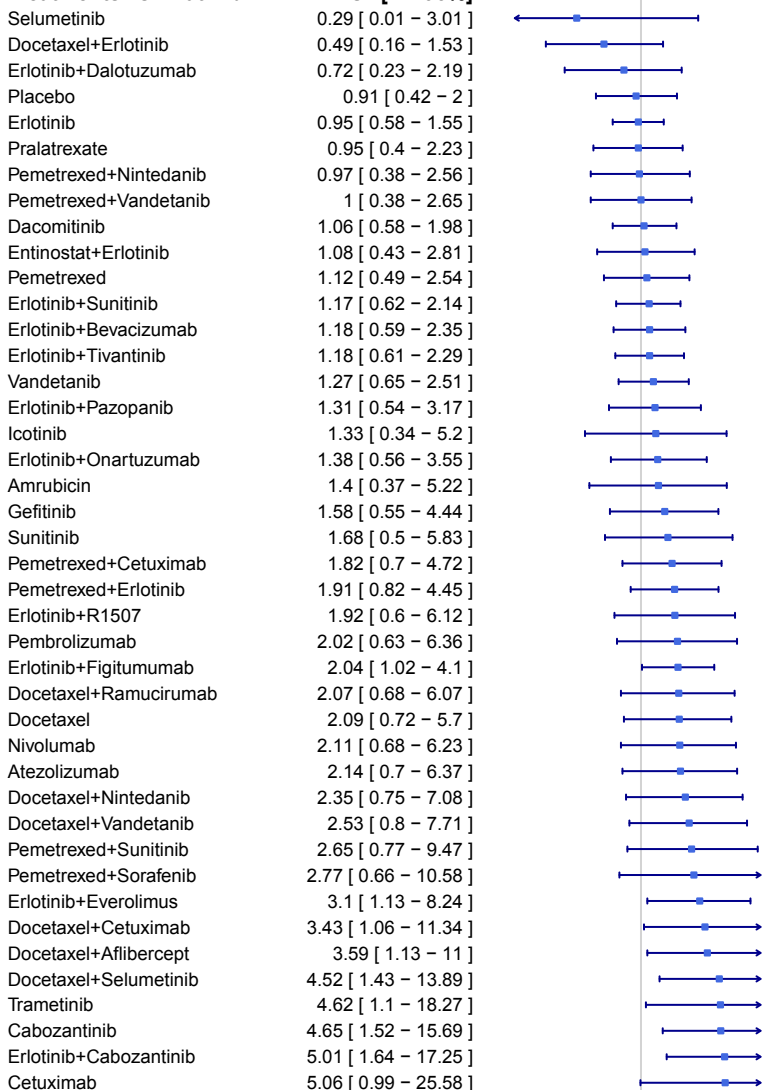
Treatments vs. Docetaxel+Nintedanib



Treatments vs. Docetaxel+Ramucirumab

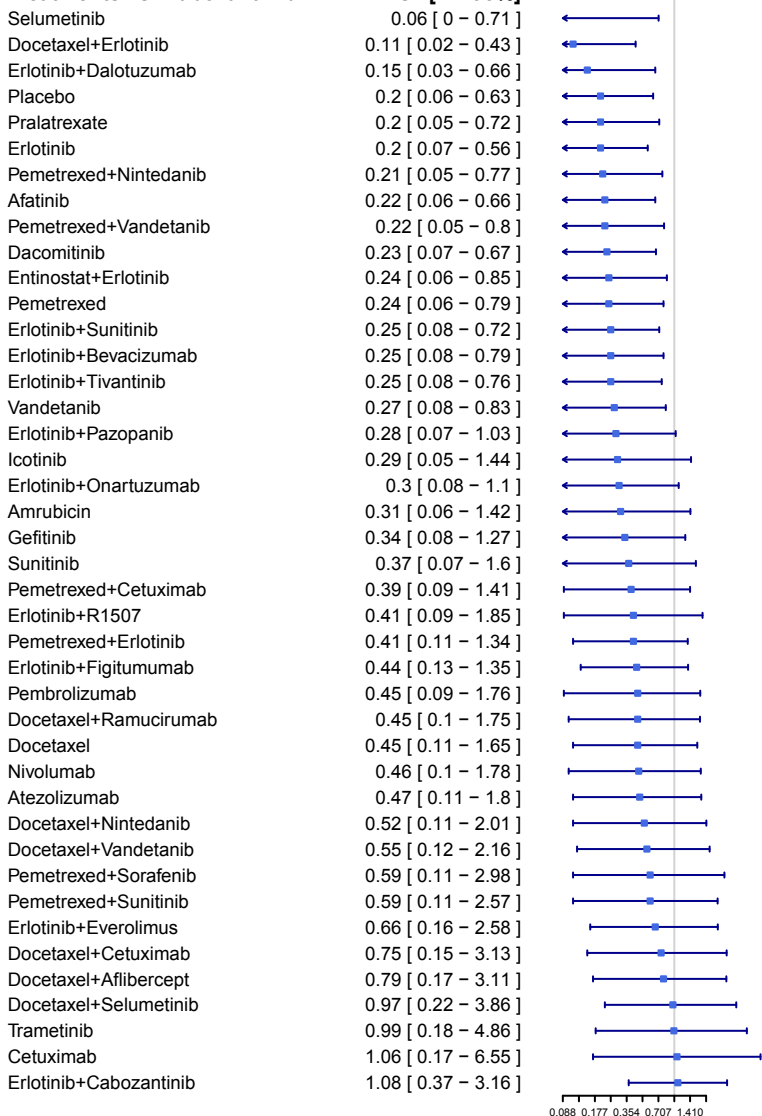
Treatment	OR [CrI 95%]
Selumetinib	0.14 [0 - 1.49]
Docetaxel+Erlotinib	0.24 [0.05 - 0.99]
Erlotinib+Dalotuzumab	0.35 [0.08 - 1.41]
Placebo	0.44 [0.14 - 1.43]
Erlotinib	0.46 [0.18 - 1.25]
Pralatrexate	0.46 [0.14 - 1.64]
Pemetrexed+Nintedanib	0.47 [0.19 - 1.21]
Afatinib	0.48 [0.16 - 1.47]
Pemetrexed+Vandetanib	0.48 [0.19 - 1.3]
Dacomitinib	0.52 [0.19 - 1.51]
Entinostat+Erlotinib	0.52 [0.14 - 1.98]
Pemetrexed	0.54 [0.24 - 1.2]
Erlotinib+Sunitinib	0.56 [0.2 - 1.63]
Erlotinib+Bevacizumab	0.57 [0.19 - 1.73]
Erlotinib+Tivantinib	0.58 [0.2 - 1.71]
Vandetanib	0.62 [0.21 - 1.87]
Erlotinib+Pazopanib	0.64 [0.19 - 2.28]
Icotinib	0.64 [0.24 - 1.79]
Erlotinib+Onartuzumab	0.68 [0.19 - 2.51]
Amrubicin	0.69 [0.27 - 1.64]
Gefitinib	0.76 [0.48 - 1.27]
Sunitinib	0.81 [0.25 - 2.84]
Pemetrexed+Cetuximab	0.88 [0.34 - 2.25]
Pemetrexed+Erlotinib	0.92 [0.36 - 2.35]
Erlotinib+R1507	0.93 [0.21 - 4.06]
Pembrolizumab	0.97 [0.53 - 1.81]
Erlotinib+Figitumumab	0.98 [0.33 - 3.05]
Docetaxel	1.01 [0.7 - 1.46]
Nivolumab	1.03 [0.6 - 1.71]
Atezolizumab	1.04 [0.62 - 1.74]
Docetaxel+Nintedanib	1.14 [0.64 - 2.02]
Docetaxel+Vandetanib	1.23 [0.69 - 2.18]
Pemetrexed+Sunitinib	1.28 [0.38 - 4.7]
Pemetrexed+Sorafenib	1.33 [0.34 - 5.21]
Erlotinib+Everolimus	1.49 [0.4 - 5.5]
Docetaxel+Cetuximab	1.67 [0.85 - 3.3]
Docetaxel+Aflibercept	1.74 [0.96 - 3.13]
Docetaxel+Selumetinib	2.16 [1.21 - 3.95]
Trametinib	2.19 [0.84 - 6.18]
Cabozantinib	2.22 [0.57 - 10.02]
Erlotinib+Cabozantinib	2.43 [0.61 - 10.56]
Cetuximab	2.44 [0.5 - 14.59]

Treatments vs. Afatinib

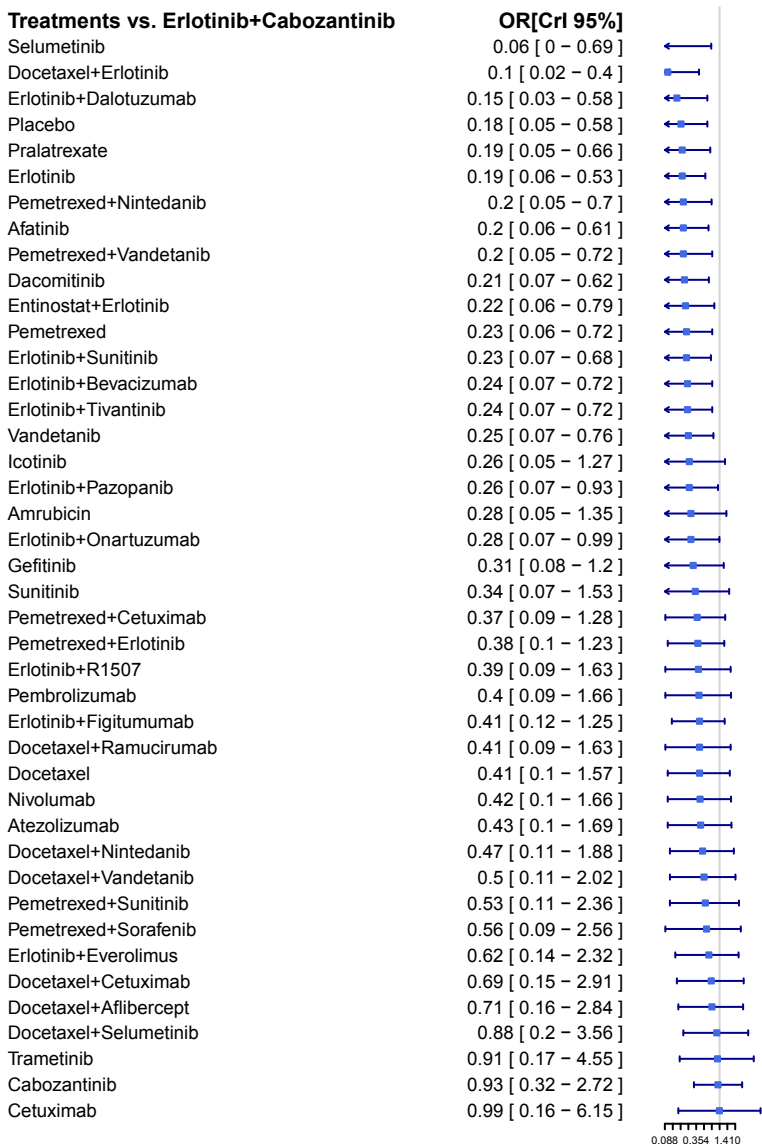


0.088 0.177 0.354 0.707 1.410

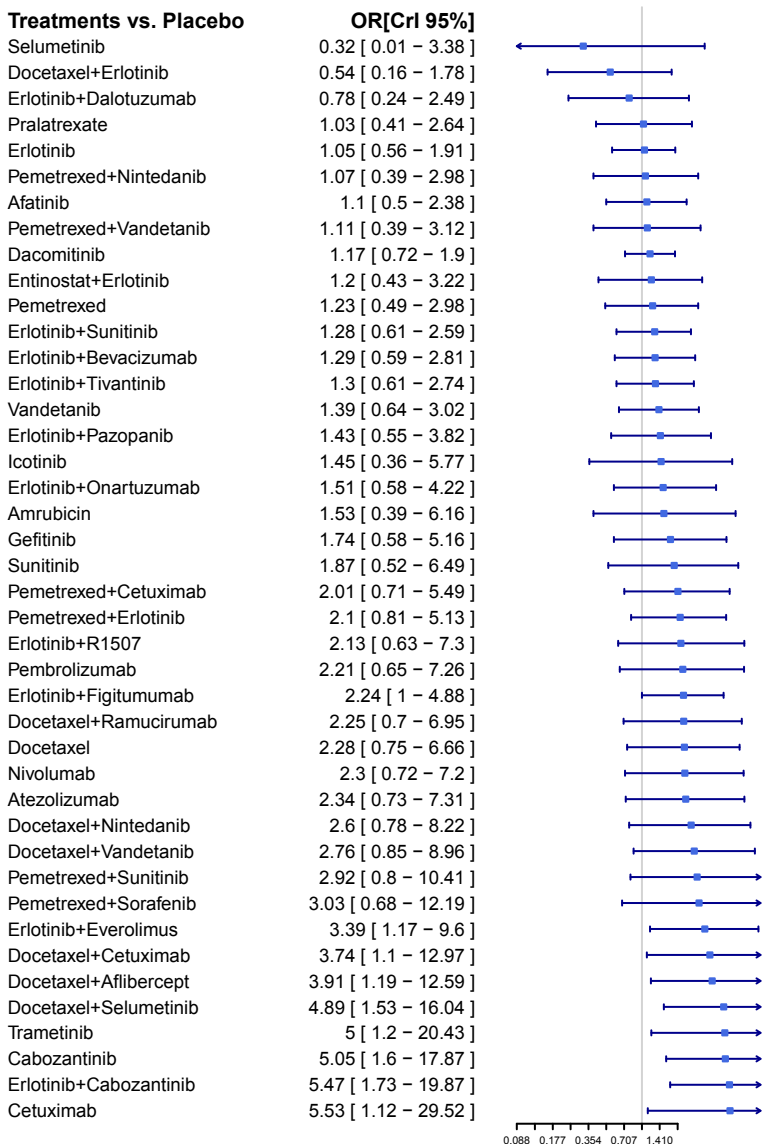
Treatments vs. Cabozantinib



Treatments vs. Erlotinib+Cabozantinib

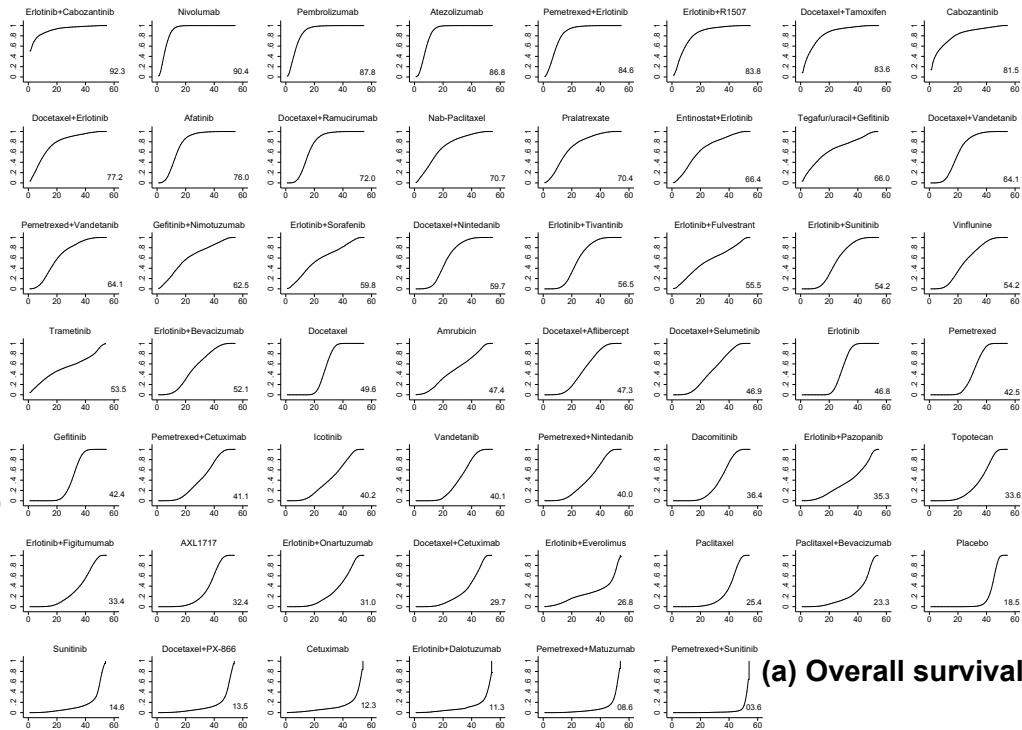


Treatments vs. Placebo



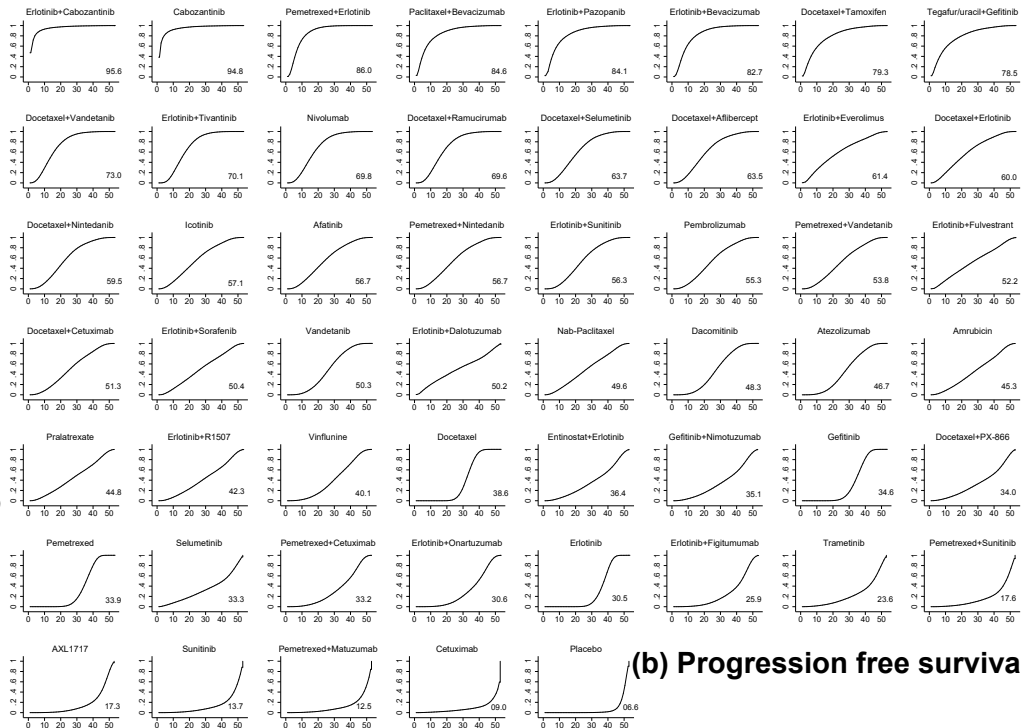
Appendix Figure 2: Cumulative ranking curves and SUCRA values for 4 outcomes

Cumulative Probabilities



(a) Overall survival

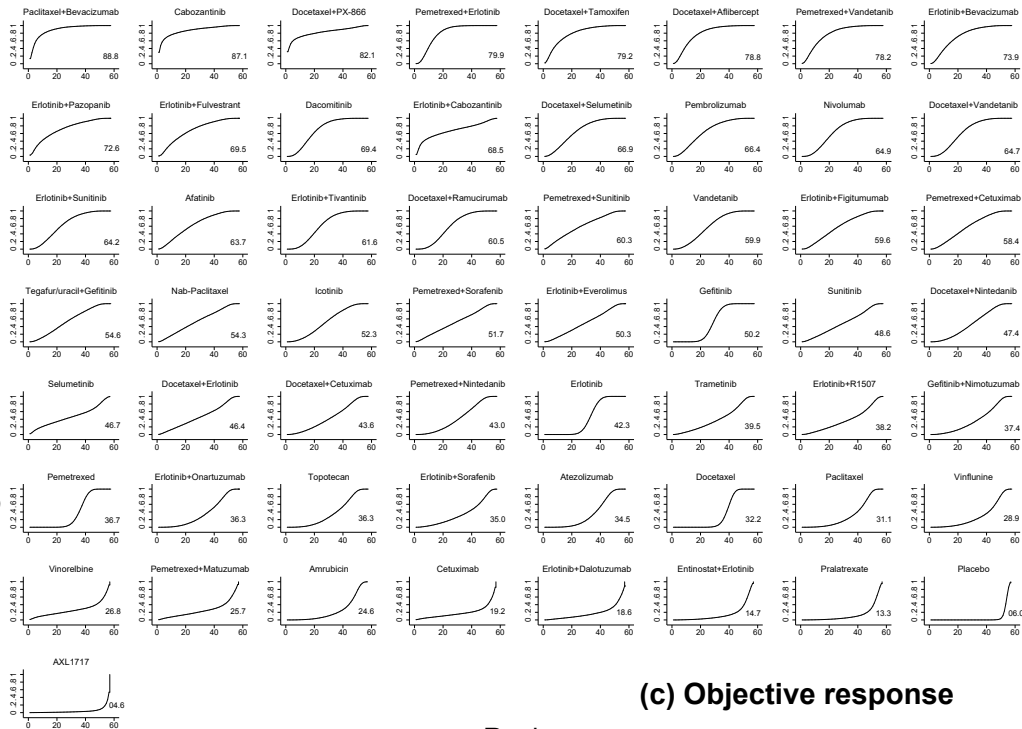
Rank



(b) Progression free survival

Rank

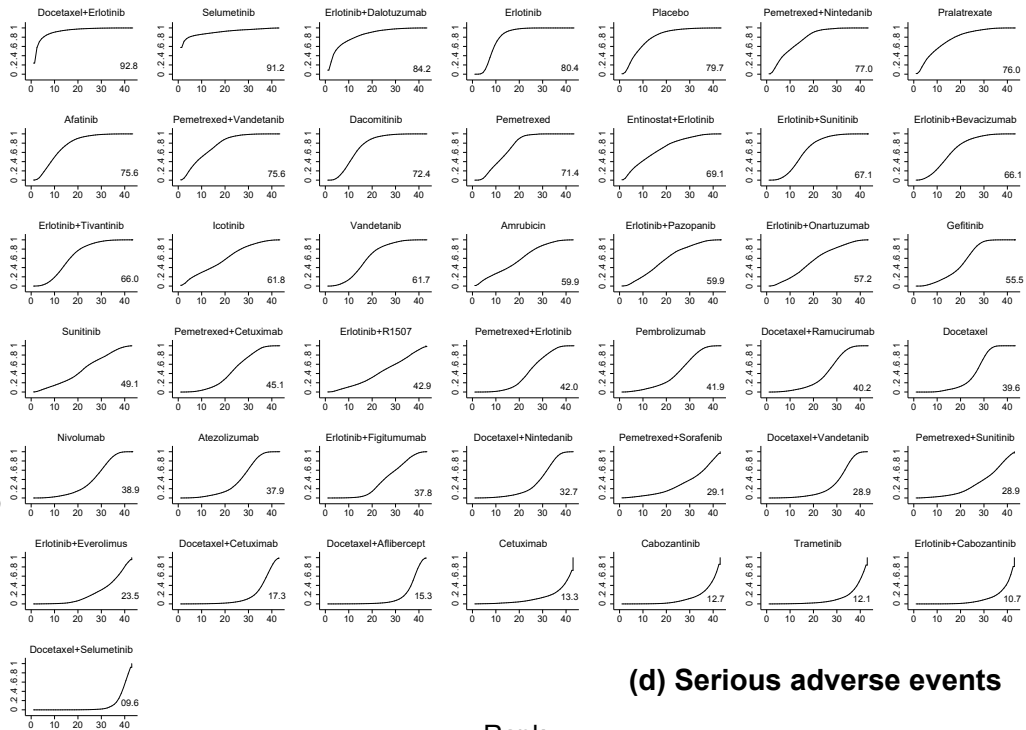
Cumulative Probabilities



(c) Objective response

Rank

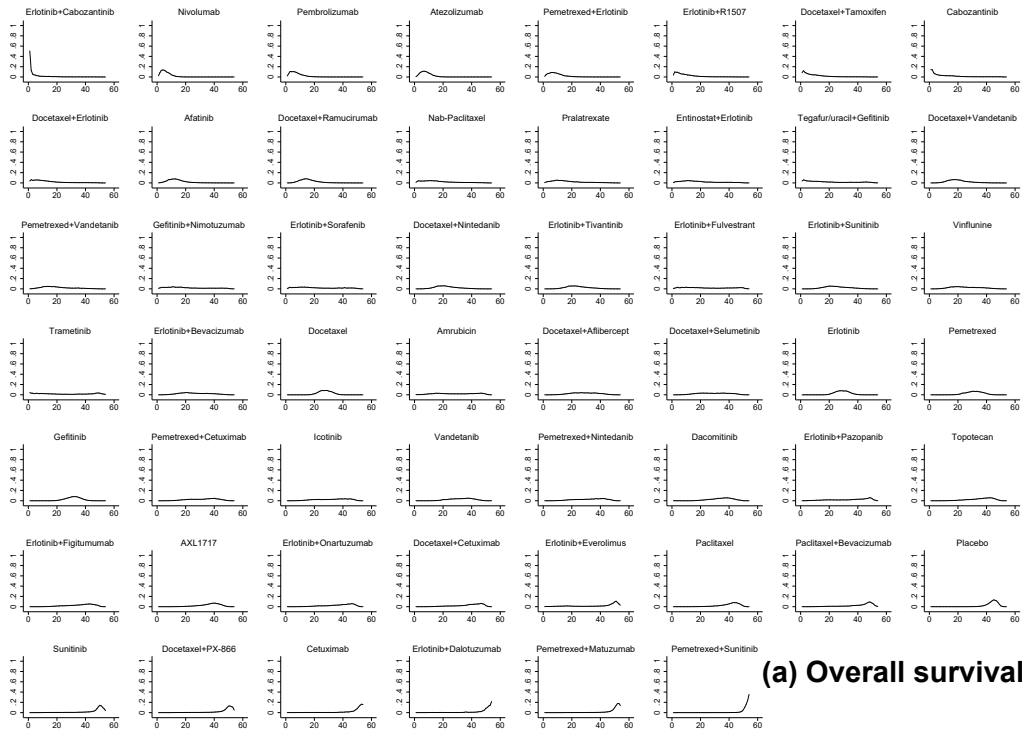
Cumulative Probabilities



(d) Serious adverse events

Appendix Figure 3: Rankograms for 4 outcomes

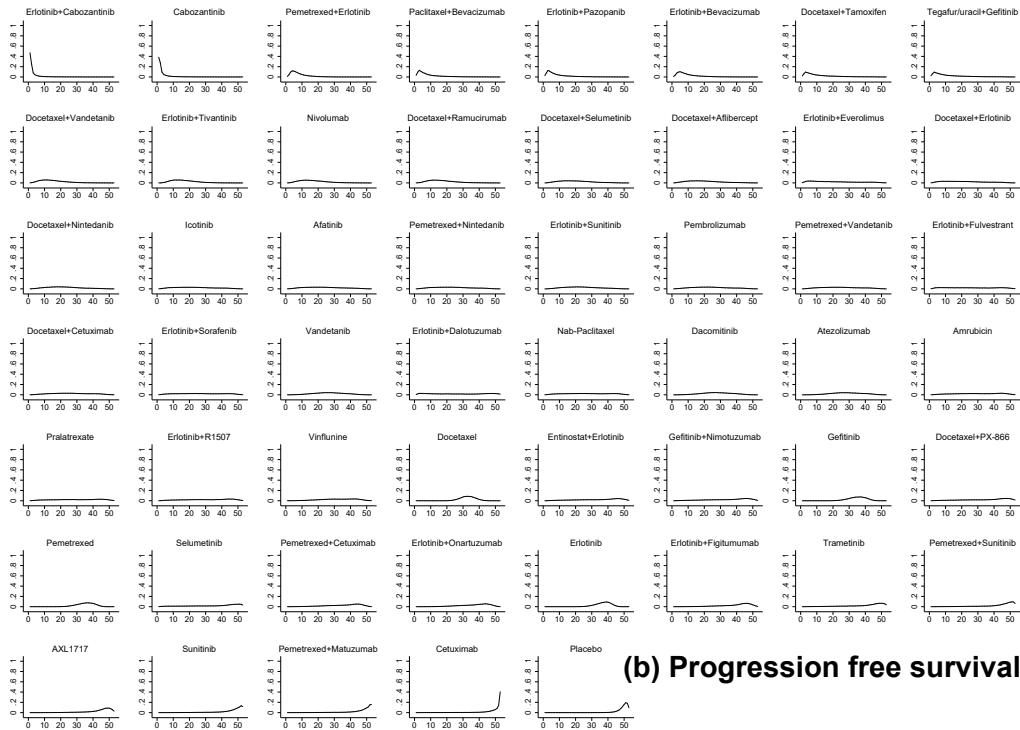
Probabilities



(a) Overall survival

Rank

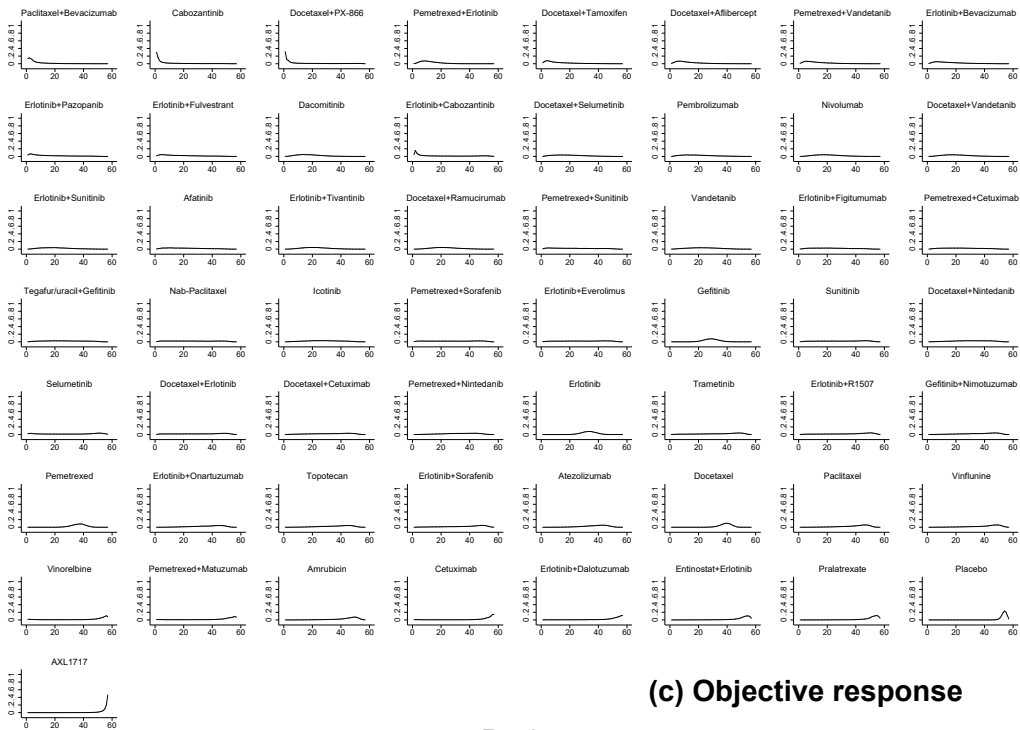
Probabilities



(b) Progression free survival

Rank

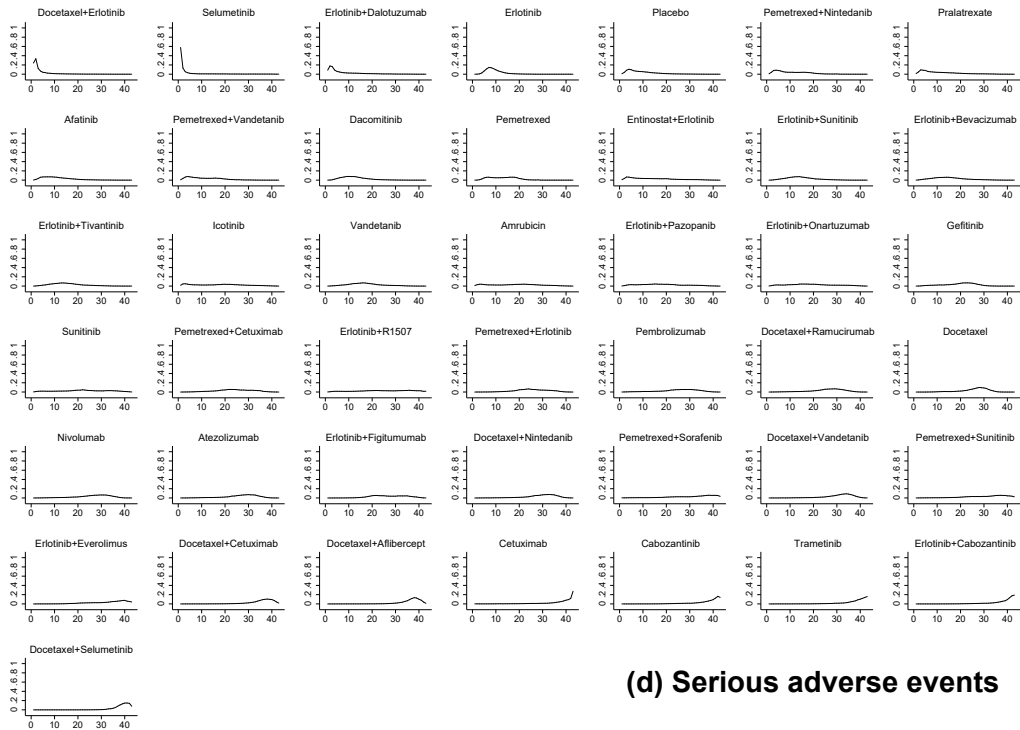
Probabilities



(c) Objective response

Rank

Probabilities

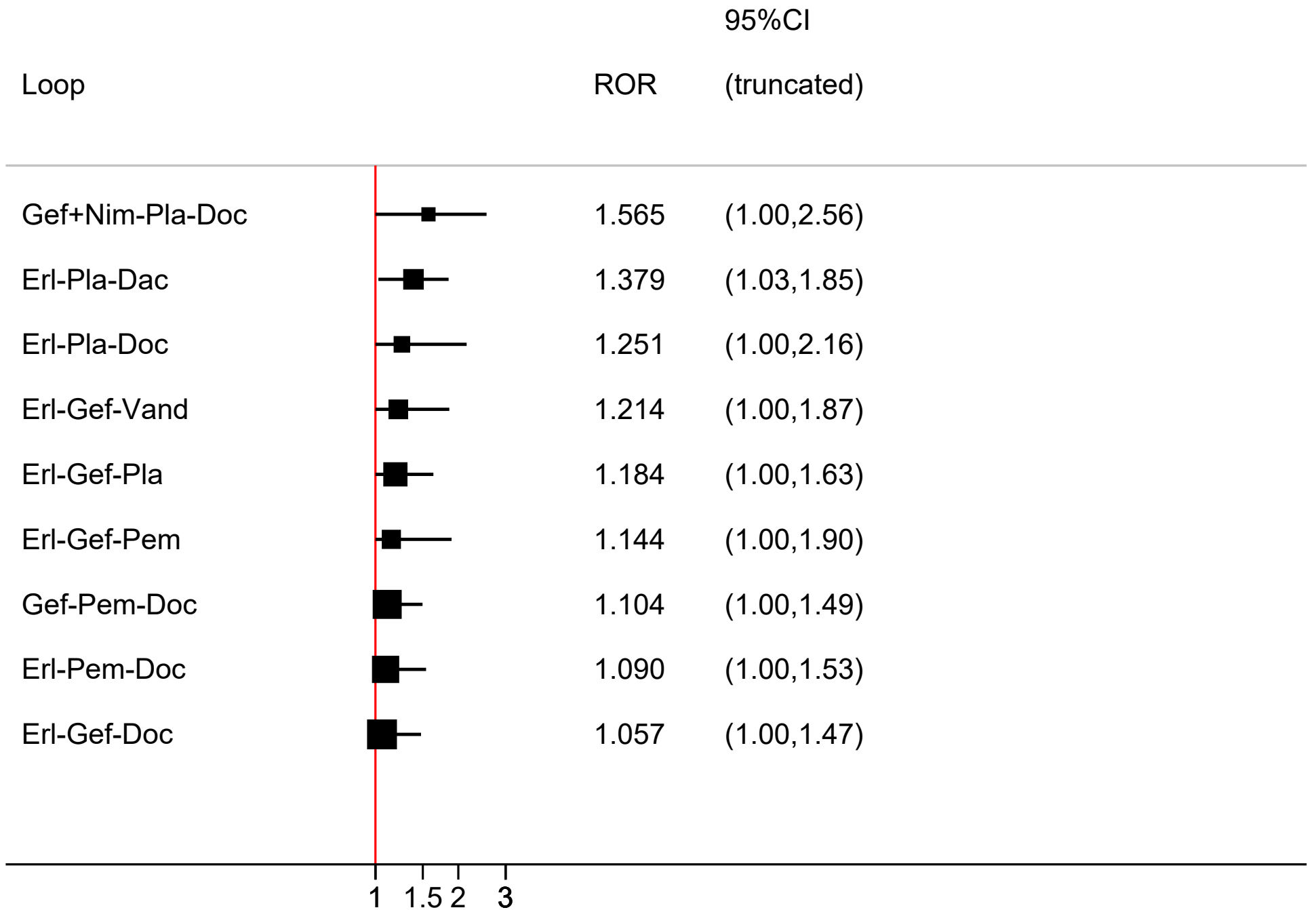


(d) Serious adverse events

Rank

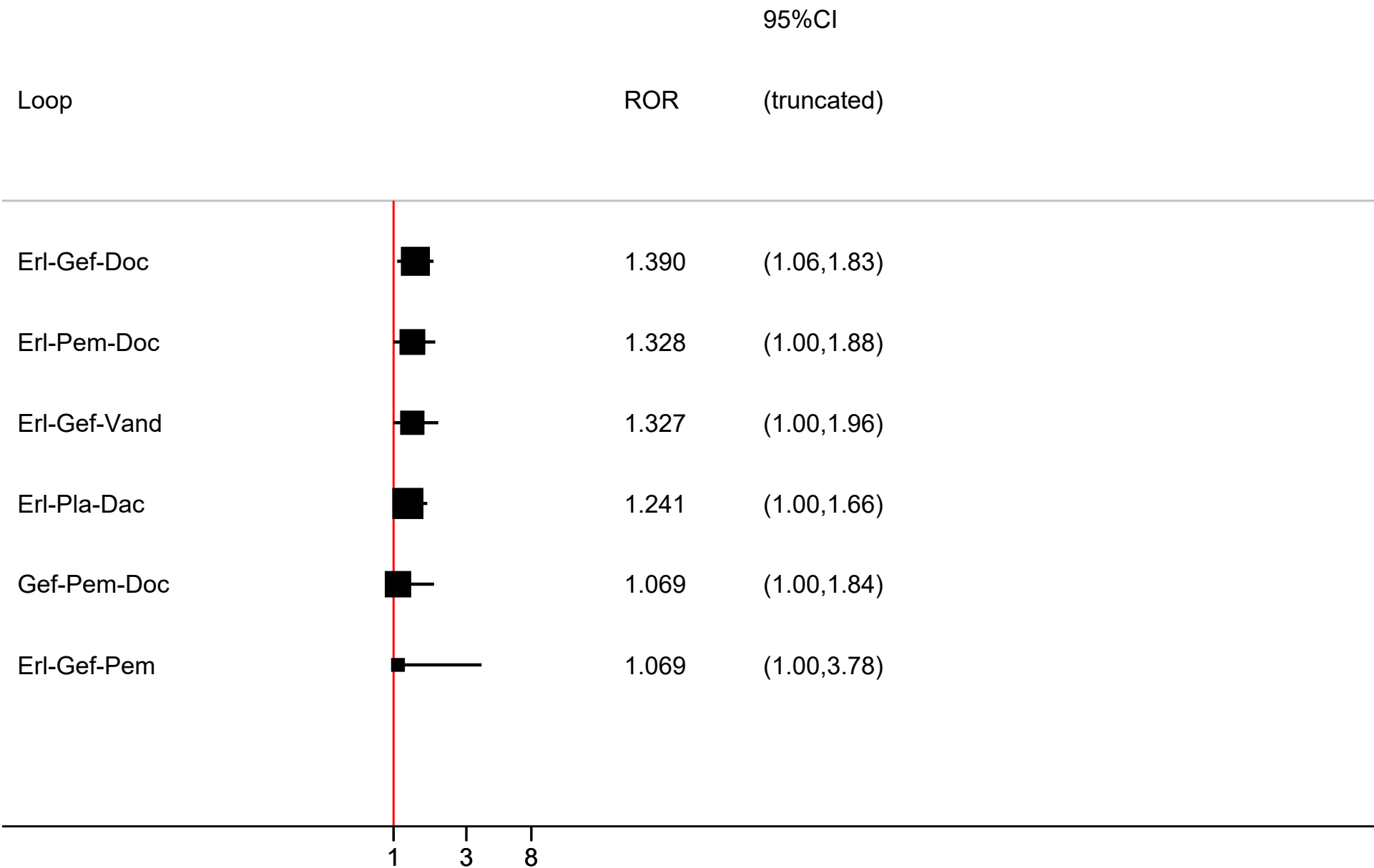
Appendix Figure 4: Evaluation of inconsistency

Overall Survival



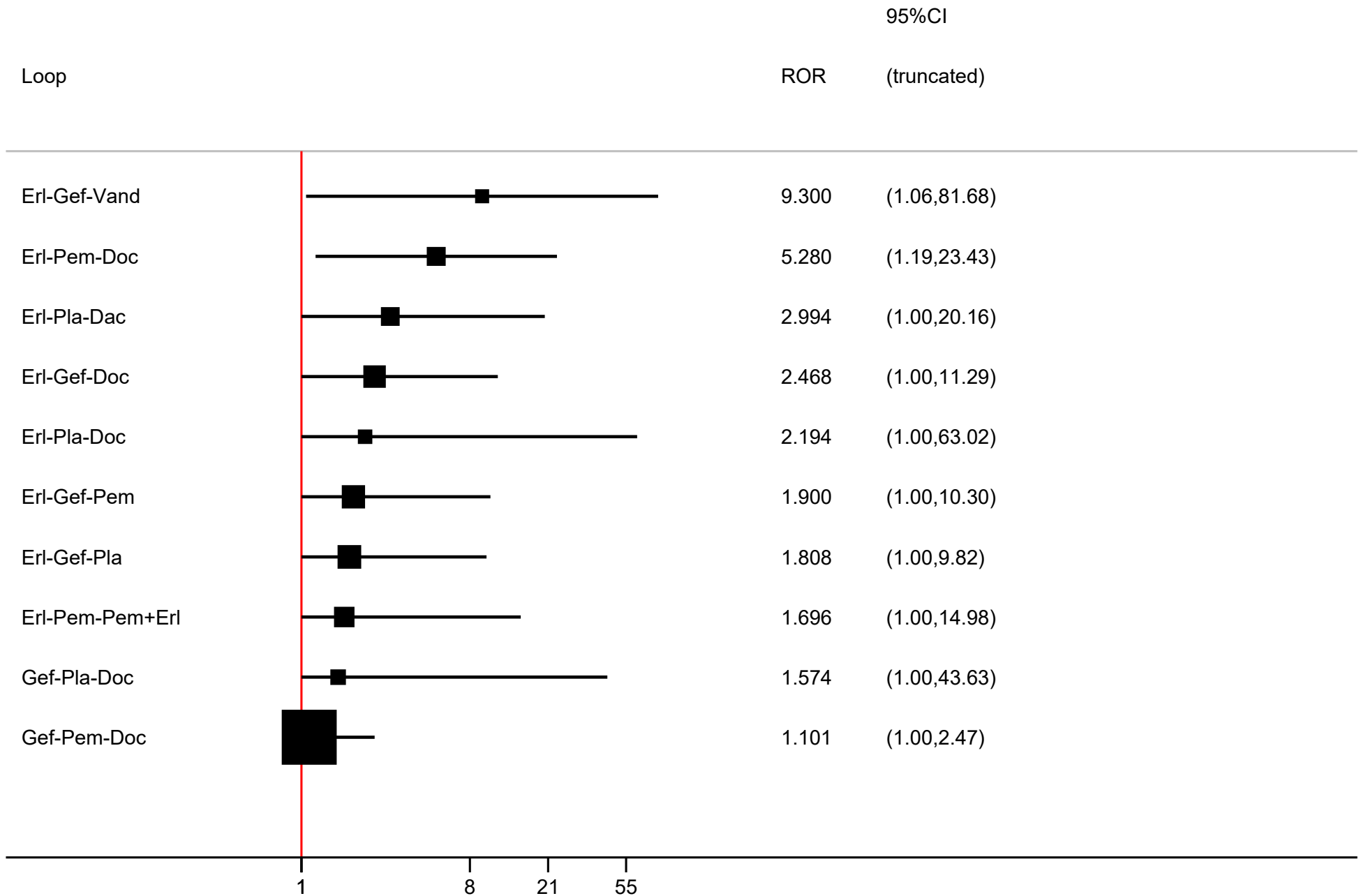
Design-by-treatment interaction model p-value=0.22

Progression free survival



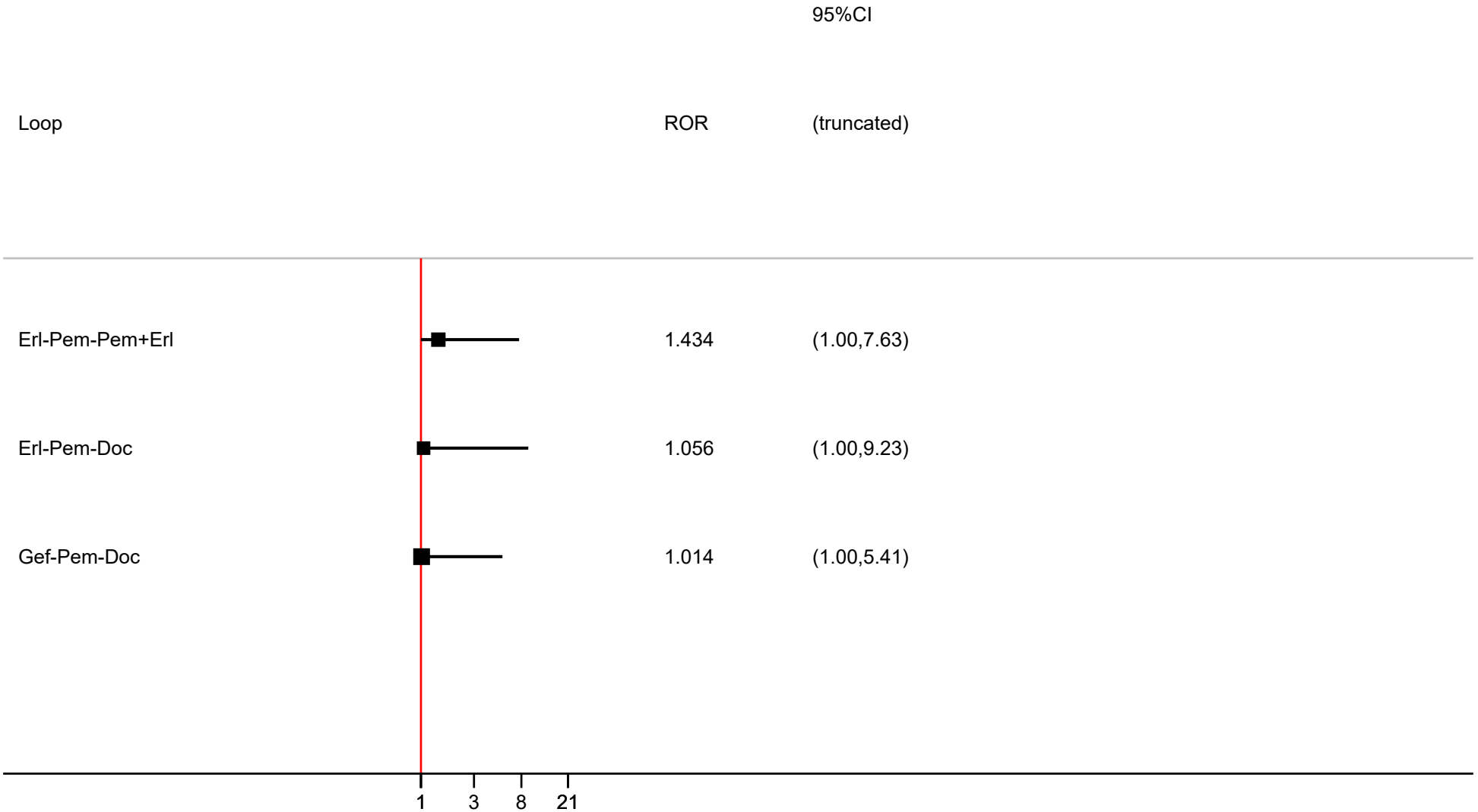
Design-by-treatment interaction model p-value=0.26

Objective response



Design-by-treatment interaction model p-value=0.07

Serious adverse events



Design-by-treatment interaction model p-value=0.81

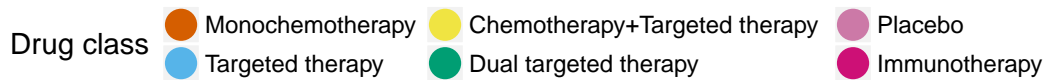
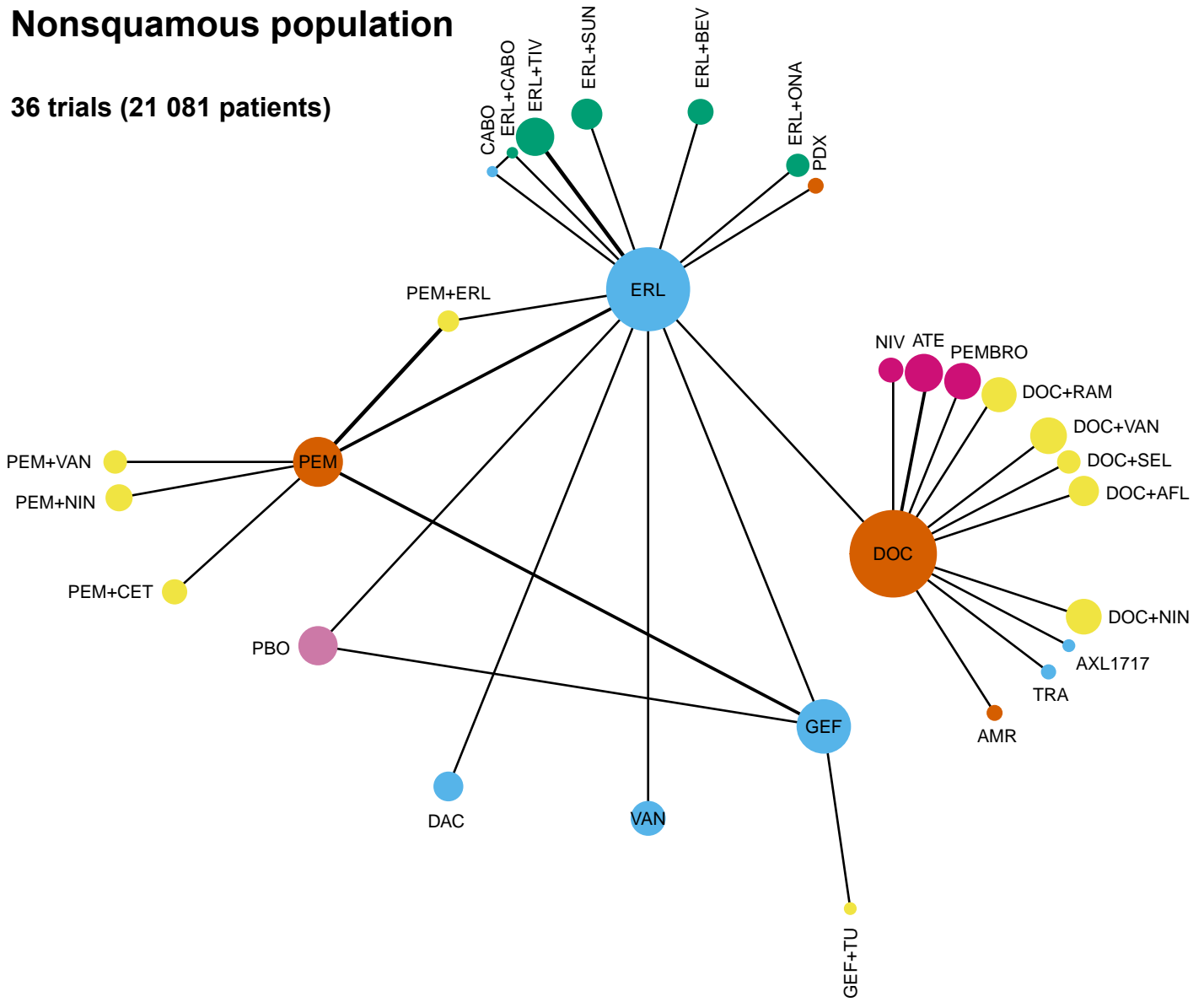
Appendix Figures 5: Subgroup analyses by histology and ethnicity: network graphs of trials for OS, forest plots and SUCRA values for OS and PFS

For each network, we have included both:

- trials performed in a specific subtype of population (i.e., including only asian population, only squamous cell carcinoma, or only nonsquamous)
- trials providing results from subgroup analyses either for asian, squamous or nonsquamous population.

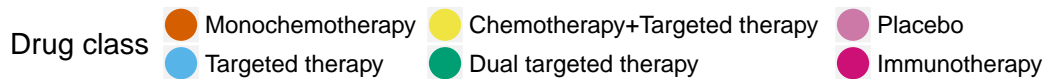
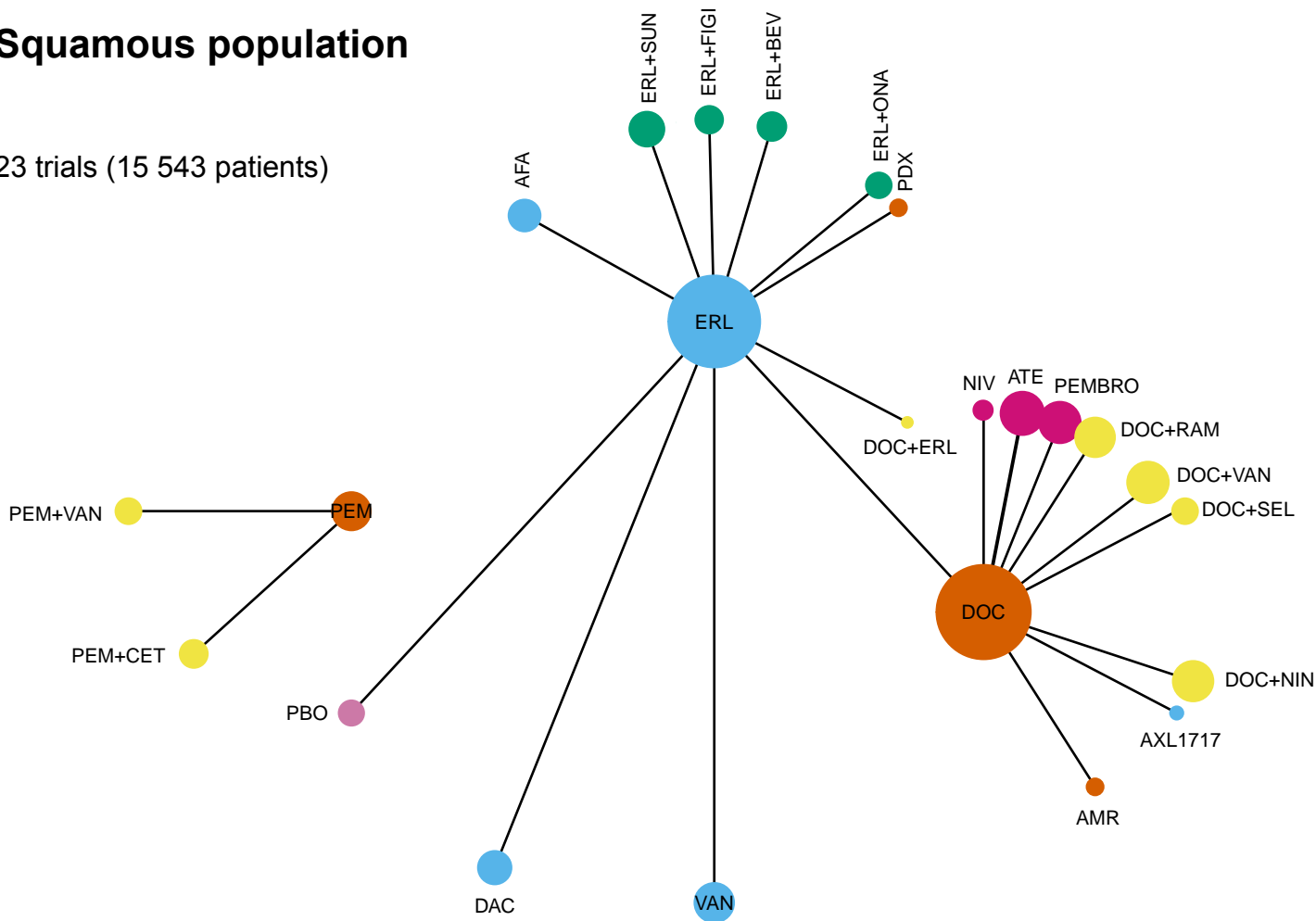
Nonsquamous population

36 trials (21 081 patients)



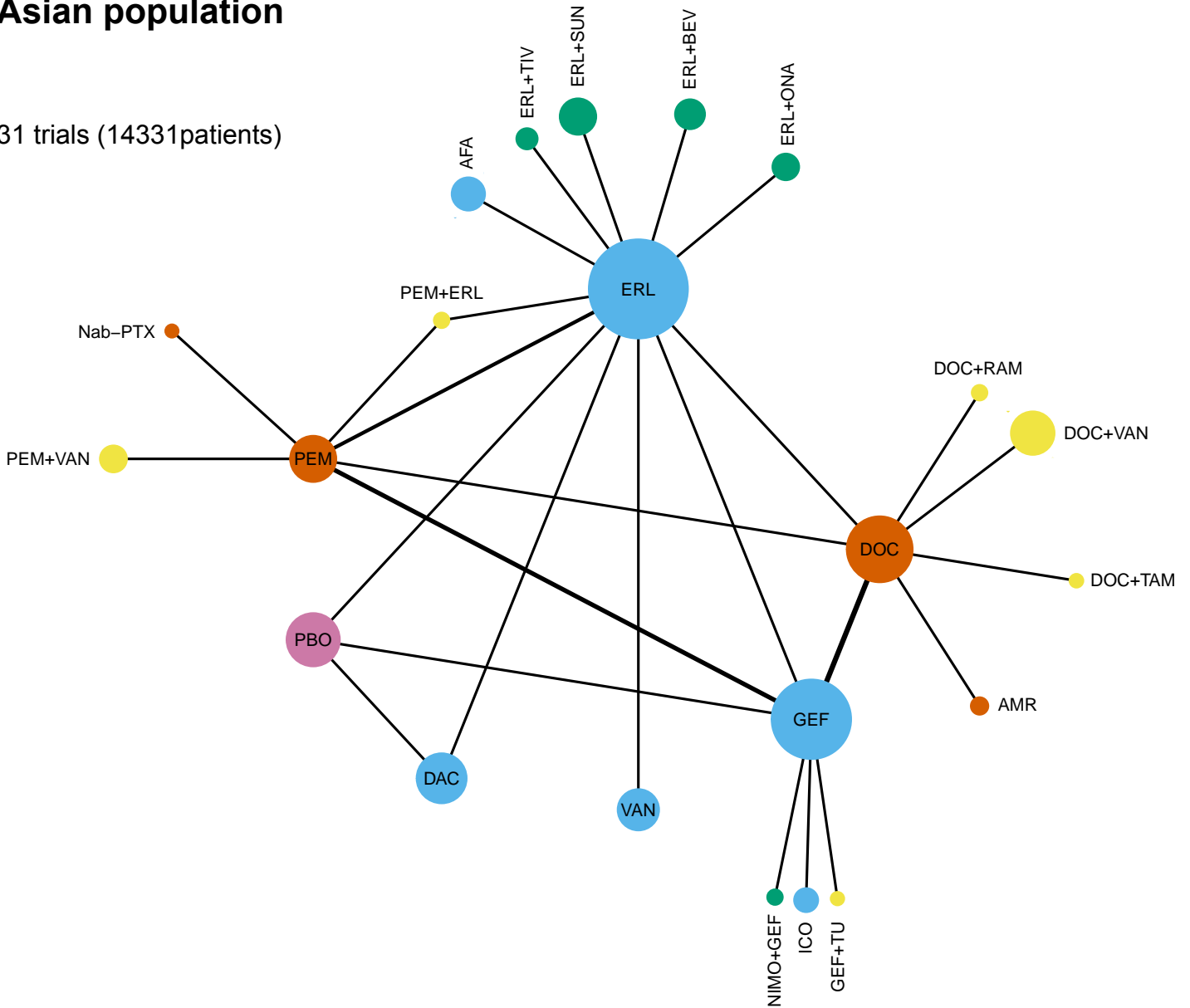
Squamous population

23 trials (15 543 patients)



Asian population

31 trials (14331patients)



Drug class

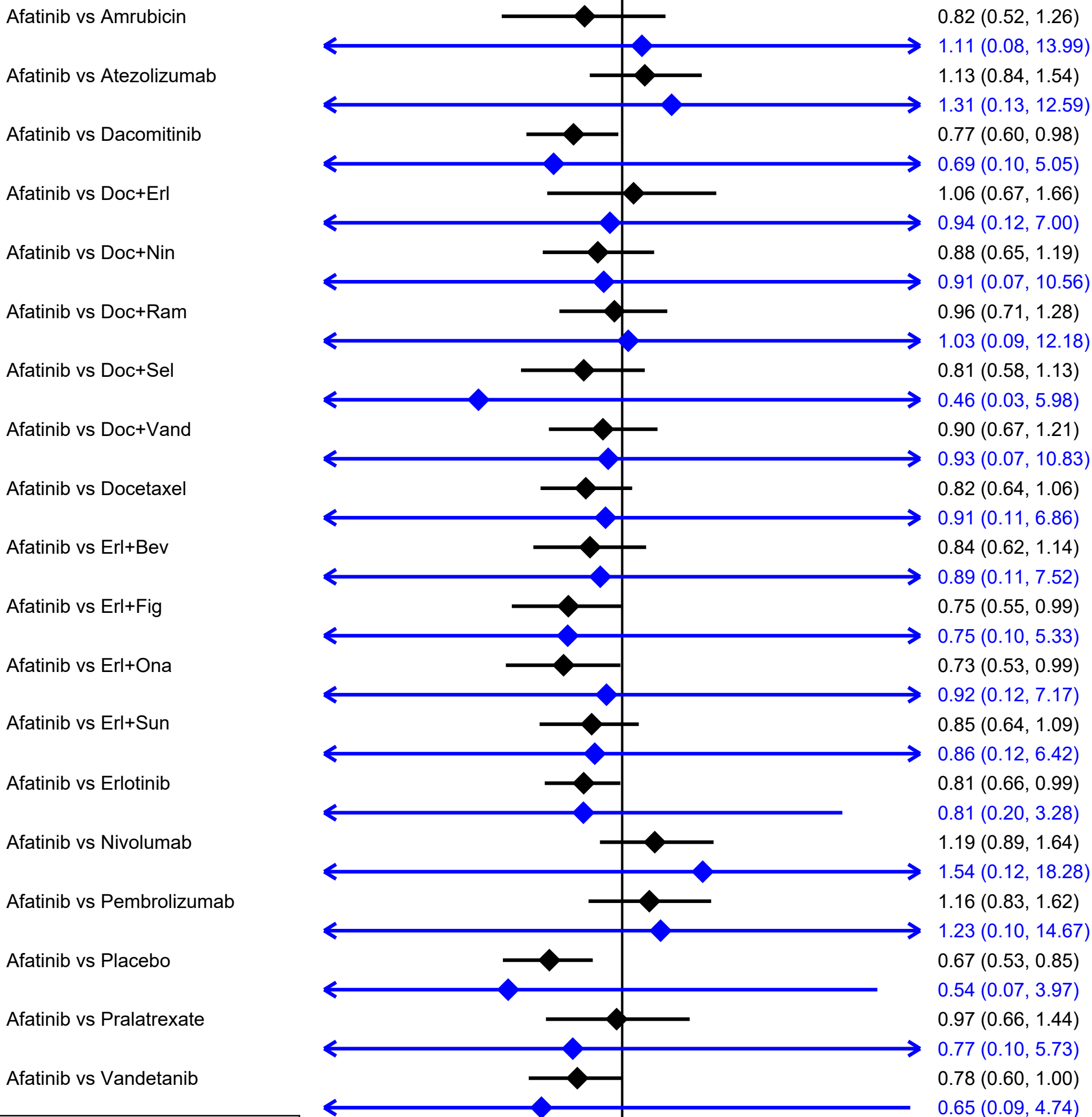
- Orange circle: Monochemotherapy
- Yellow circle: Chemotherapy+Targeted therapy
- Pink circle: Placebo
- Blue circle: Targeted therapy
- Green circle: Dual targeted therapy
- Magenta circle: Immunotherapy

Comparison

Overall Survival

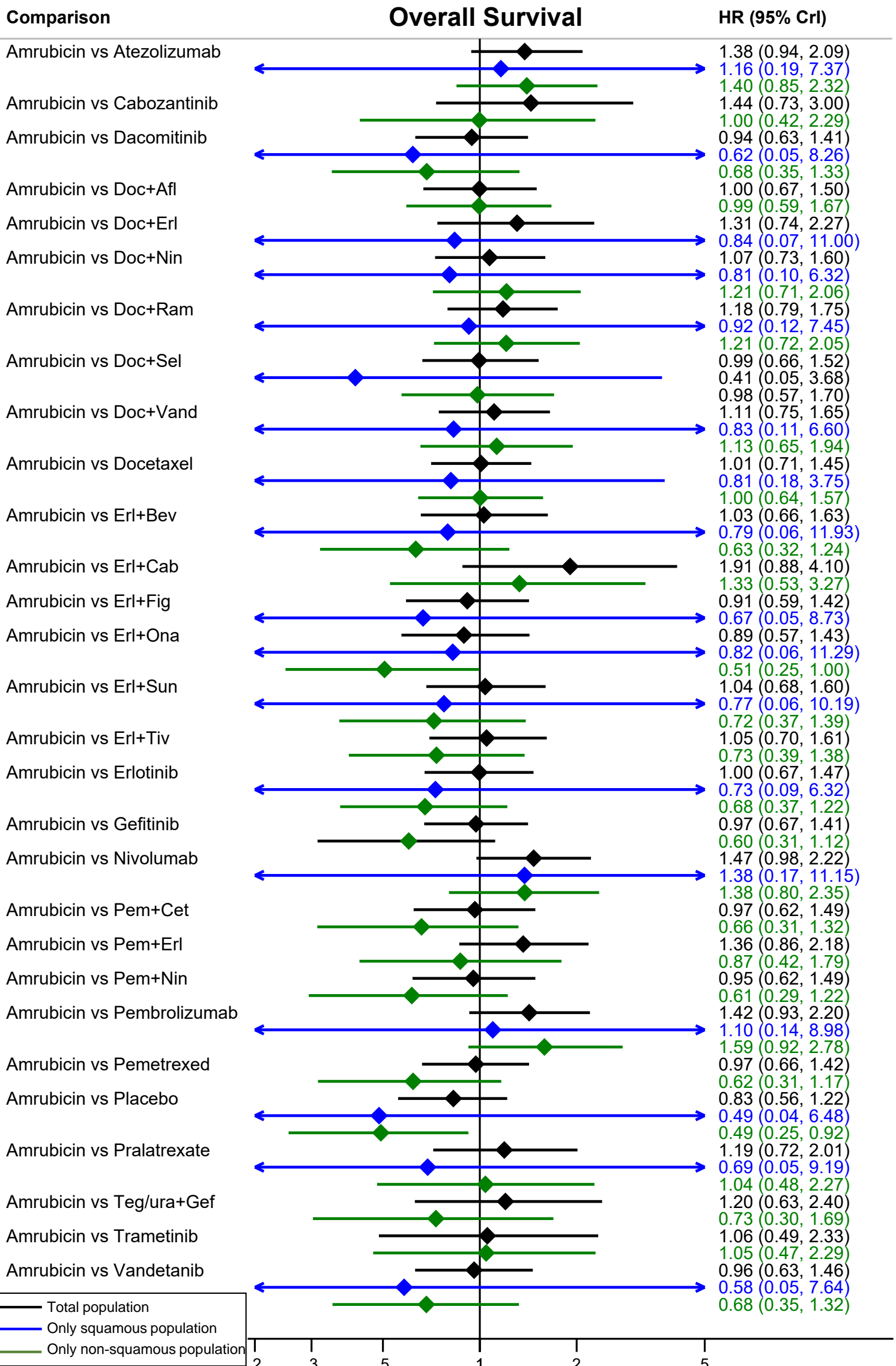
HR (95% CrI)

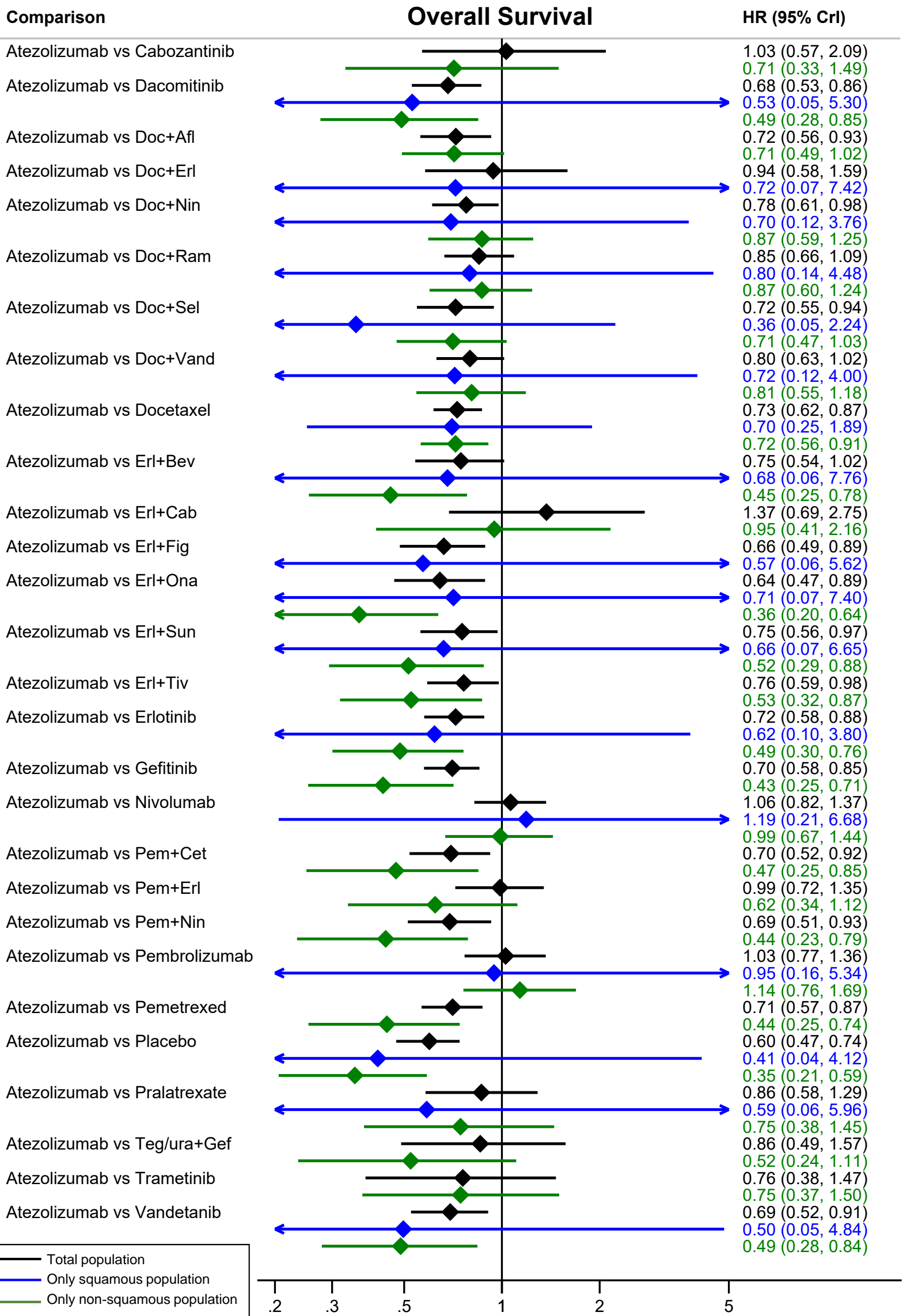
Favors first treatment ← → *Favors second treatment*



— Total population
— Only squamous population
— Only non-squamous population

.2 .3 .5 1 2 5

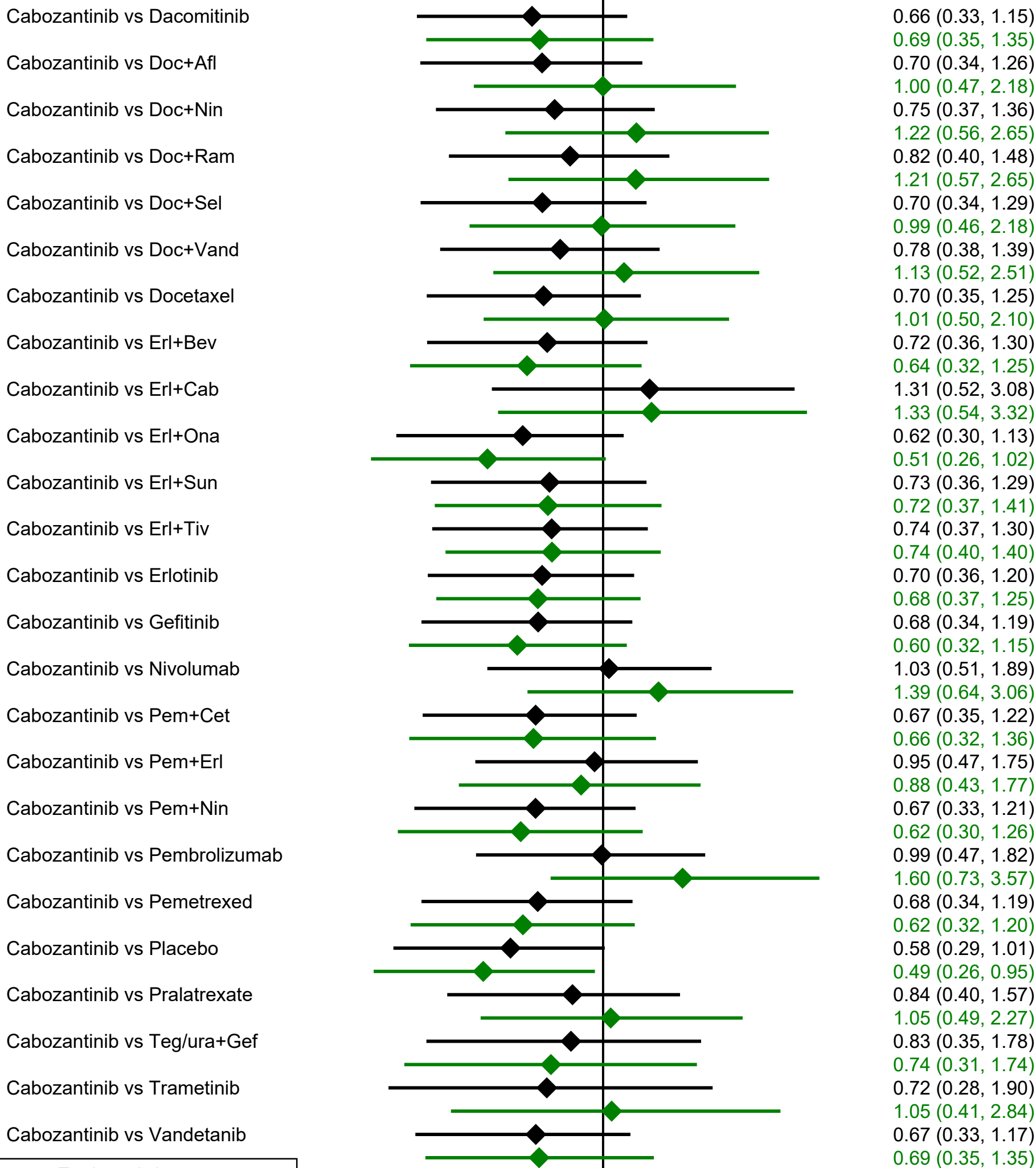




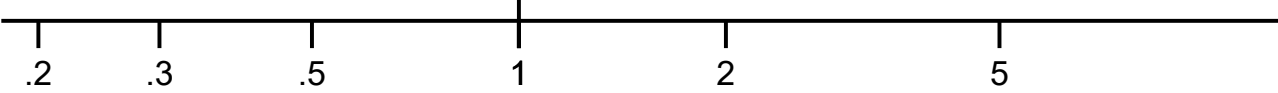
Comparison

Overall Survival

HR (95% CrI)



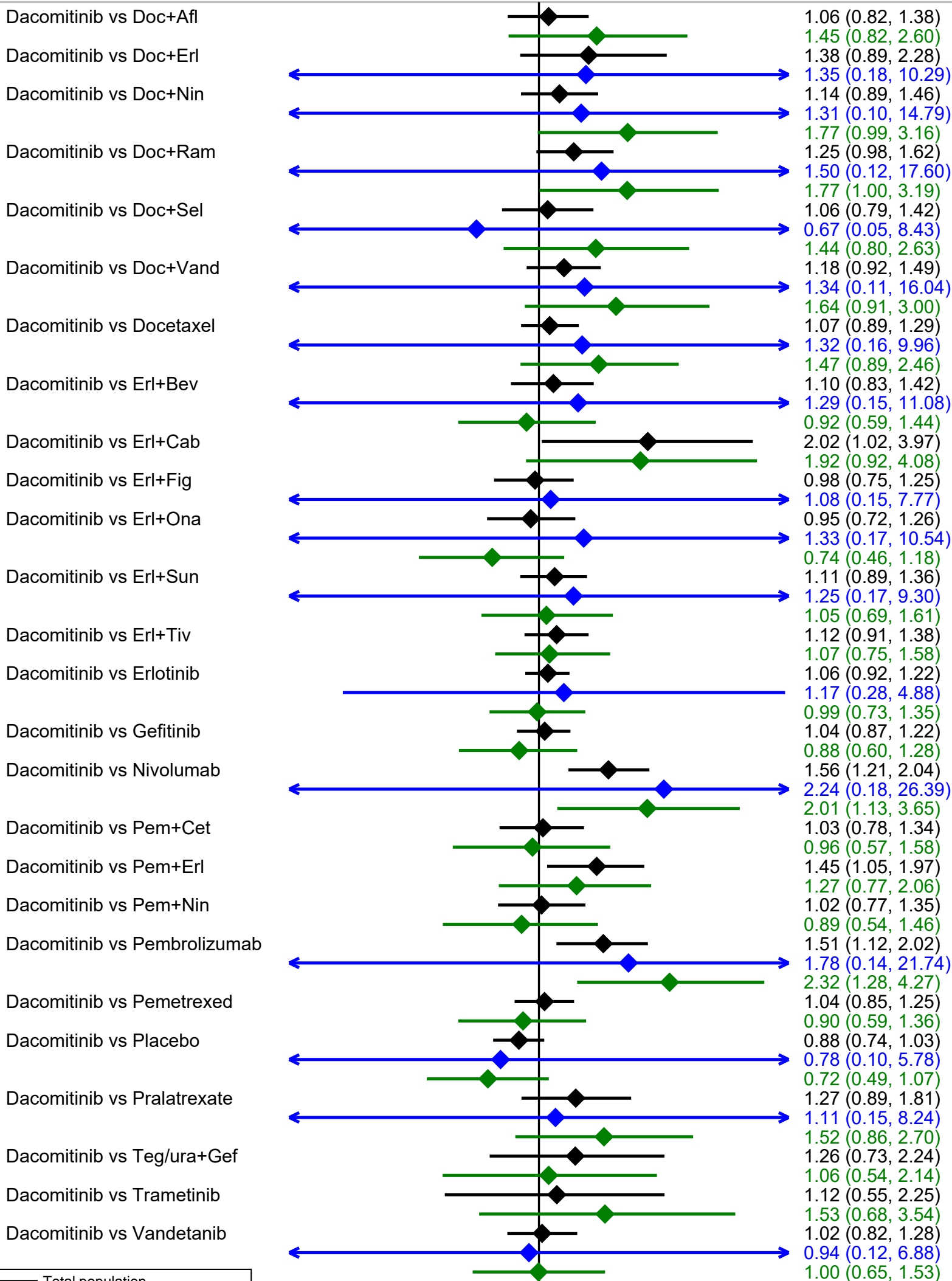
— Total population
— Only squamous population
— Only non-squamous population



Comparison

Overall Survival

HR (95% CrI)



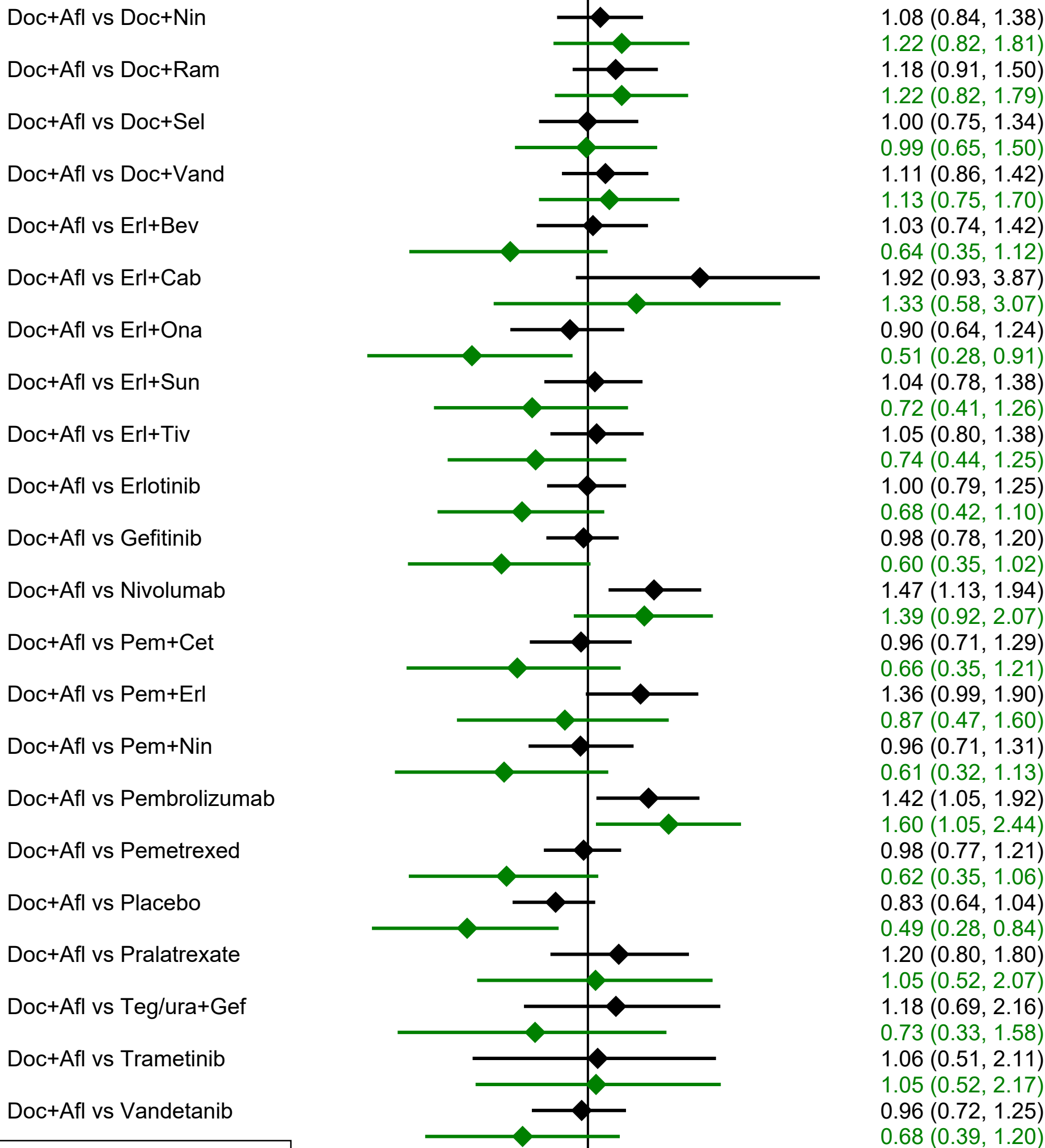
— Total population
— Only squamous population
— Only non-squamous population

— 0.2 0.3 0.5 1 2 5

Comparison

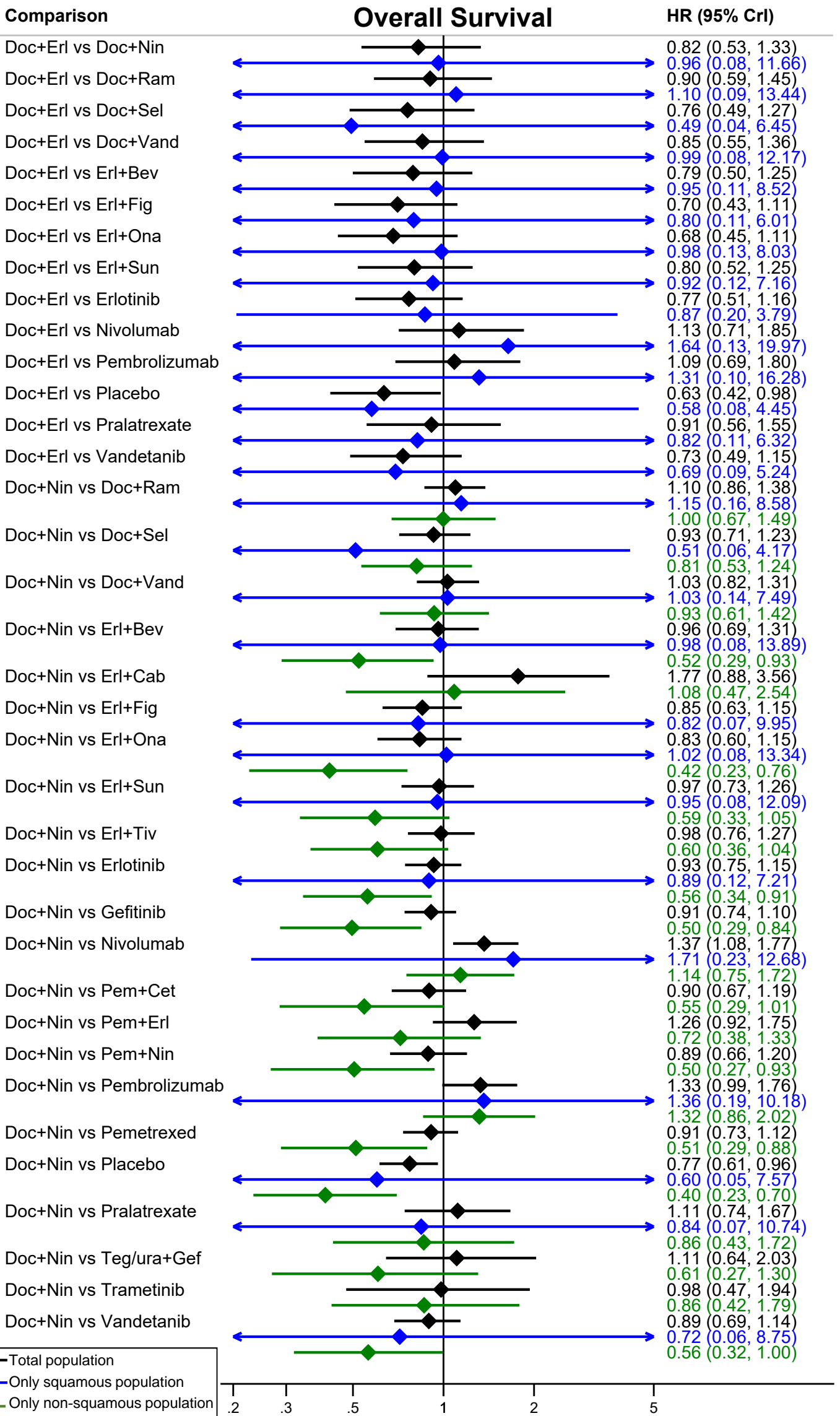
Overall Survival

HR (95% CrI)



— Total population
— Only squamous population
— Only non-squamous population

.2 .3 .5 1 2 5

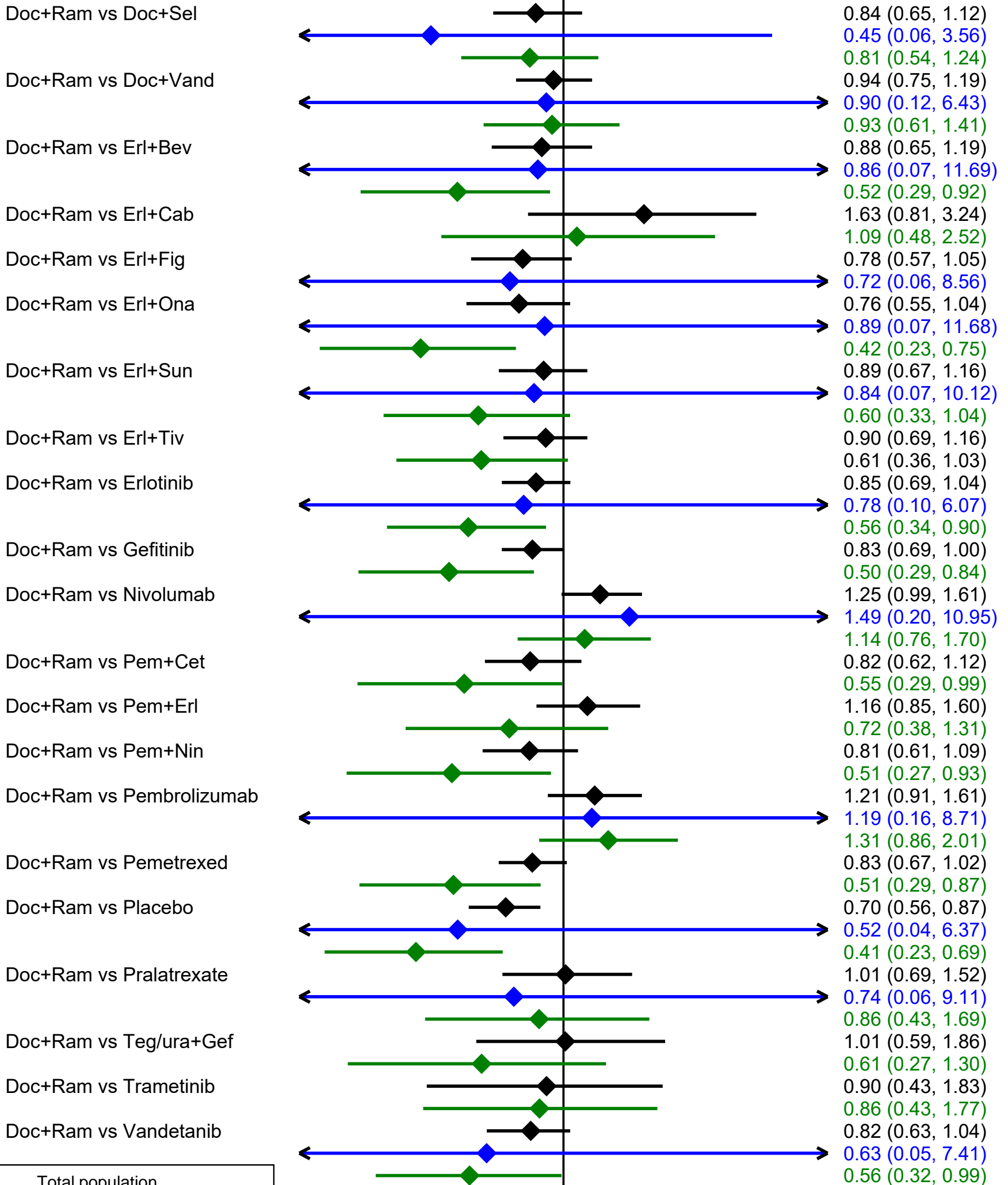


— Total population
— Only squamous population
— Only non-squamous population

Comparison

Overall Survival

HR (95% CrI)



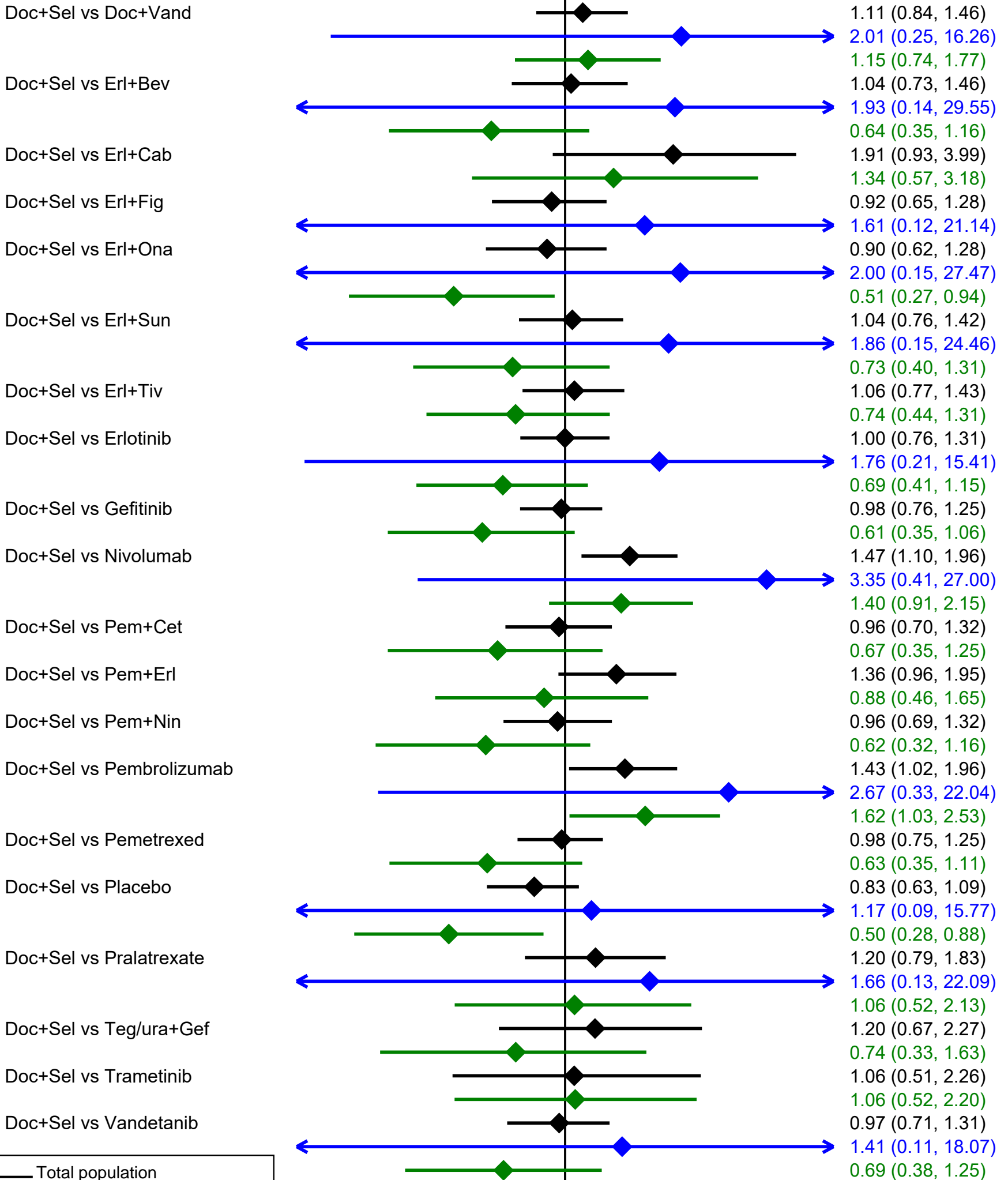
— Total population
— Only squamous population
— Only non-squamous population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)



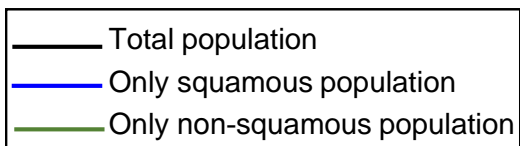
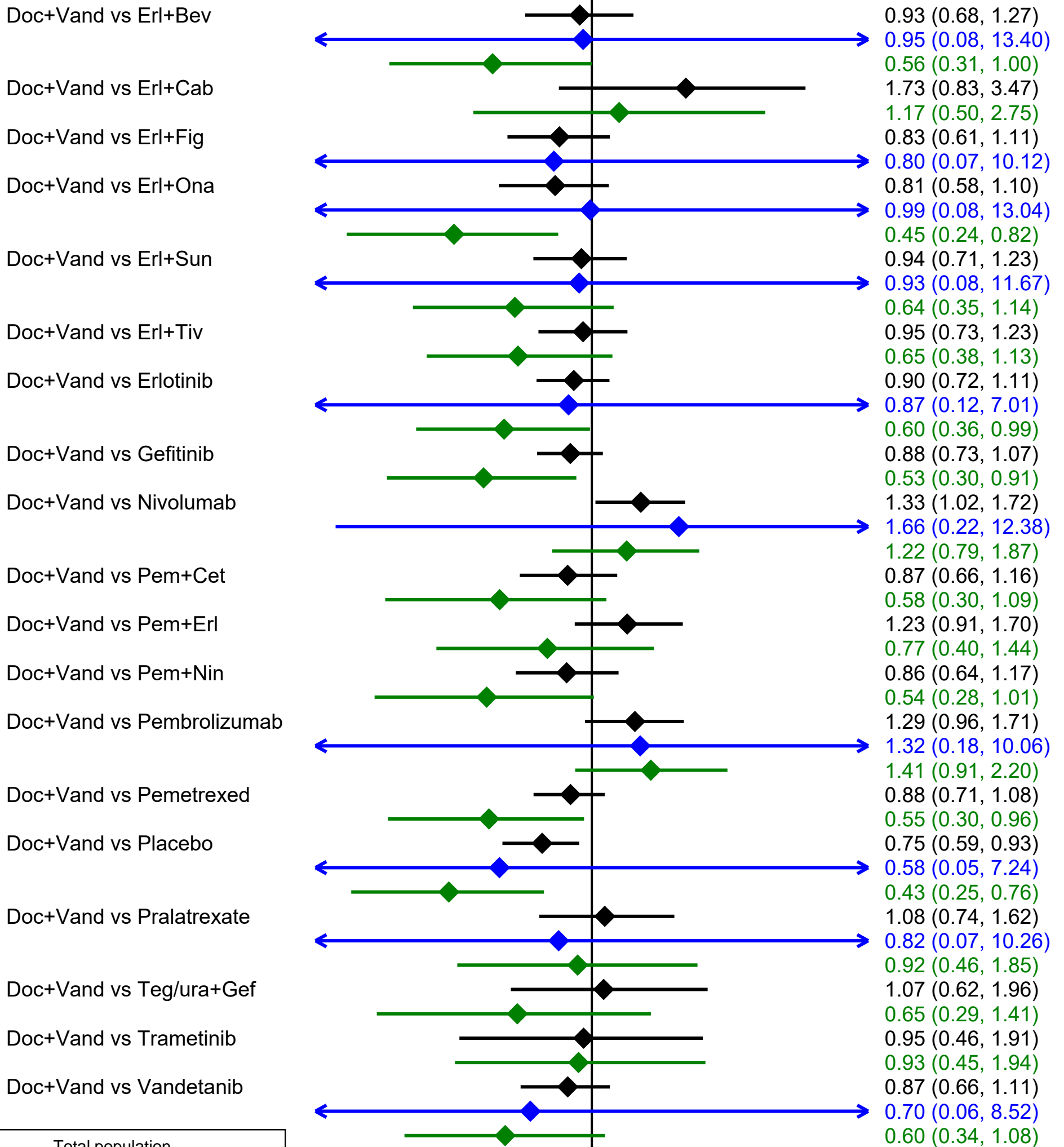
— Total population
— Only squamous population
— Only non-squamous population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)

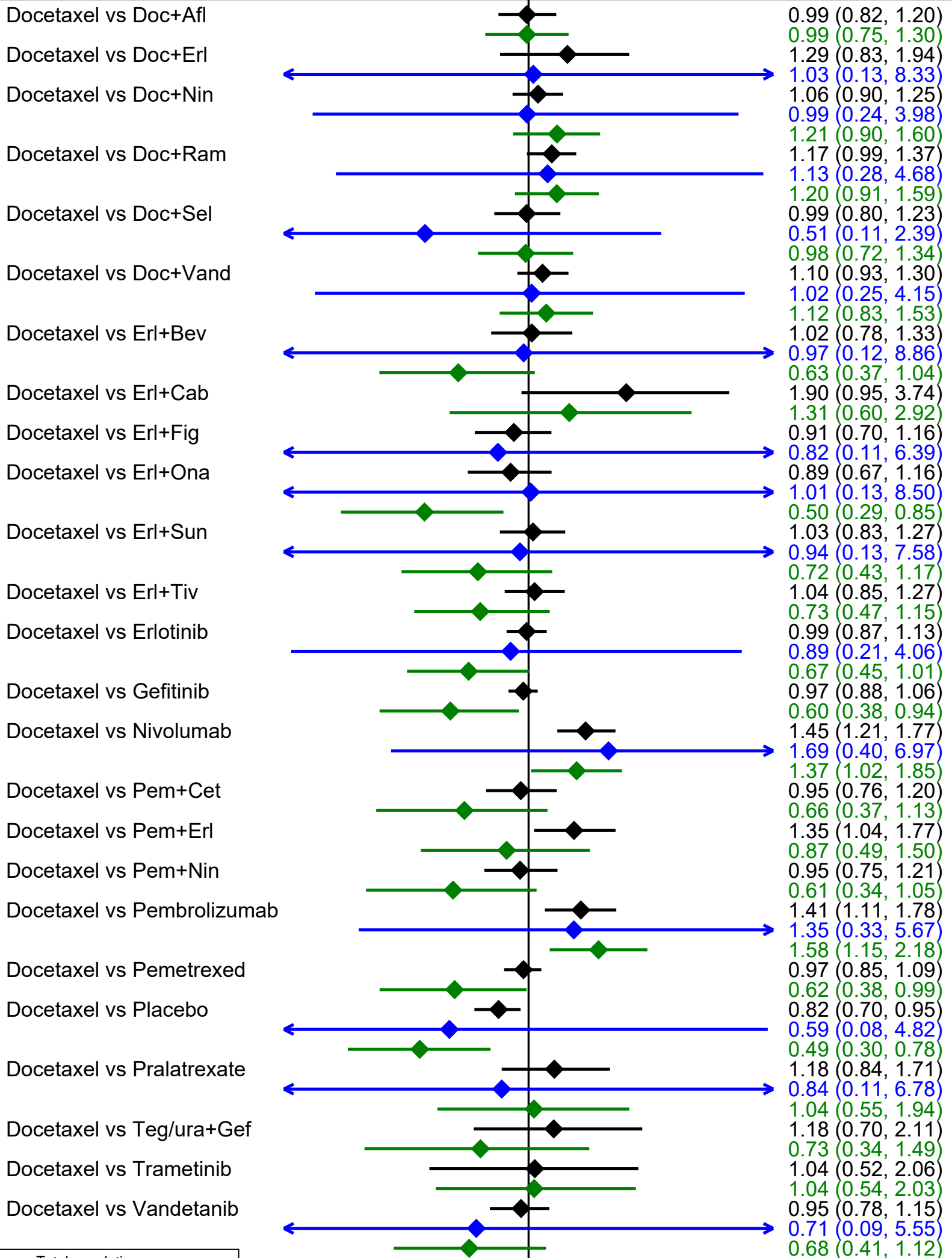


.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)



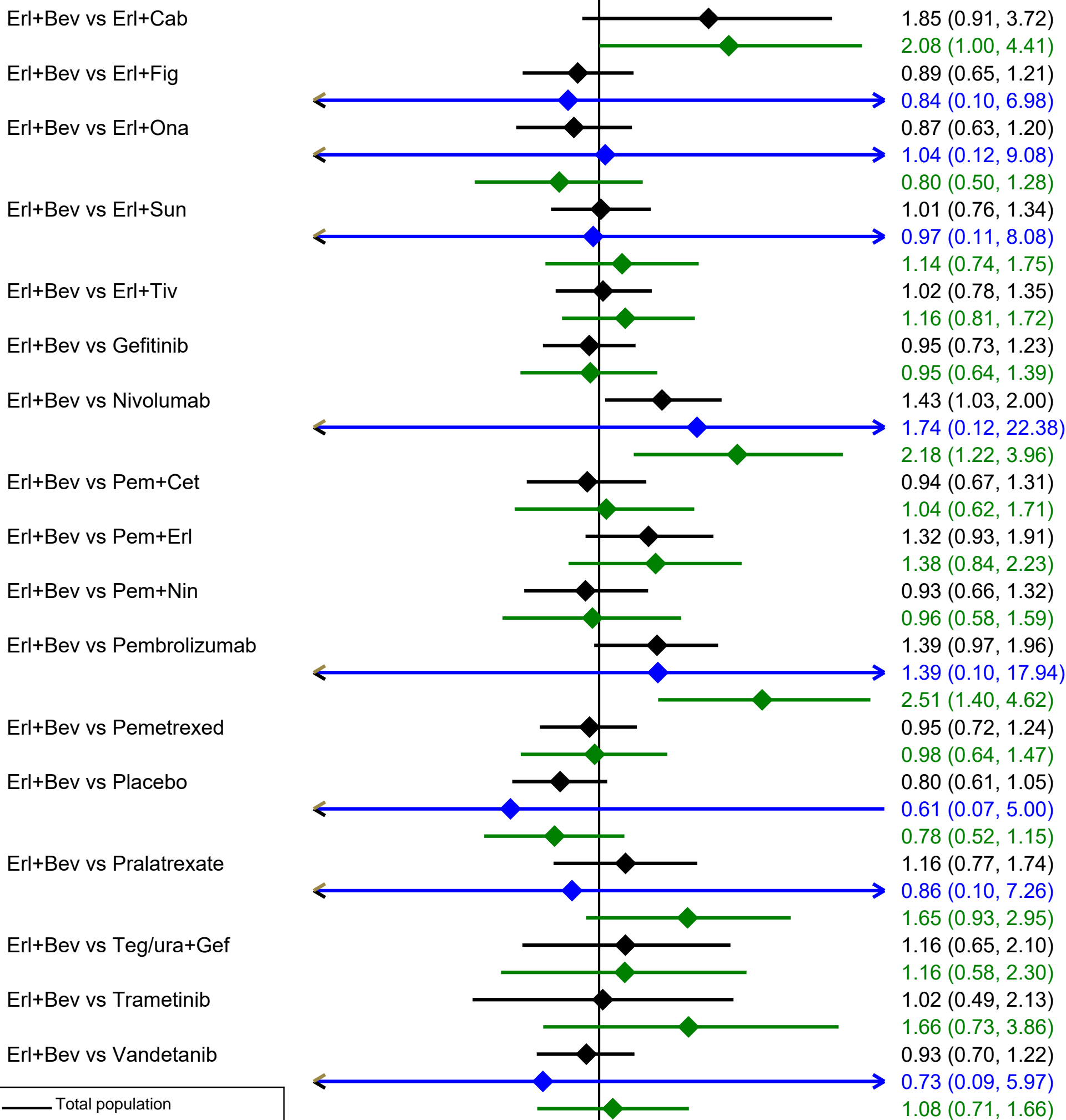
— Total population
— Only squamous population
— Only non-squamous population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)



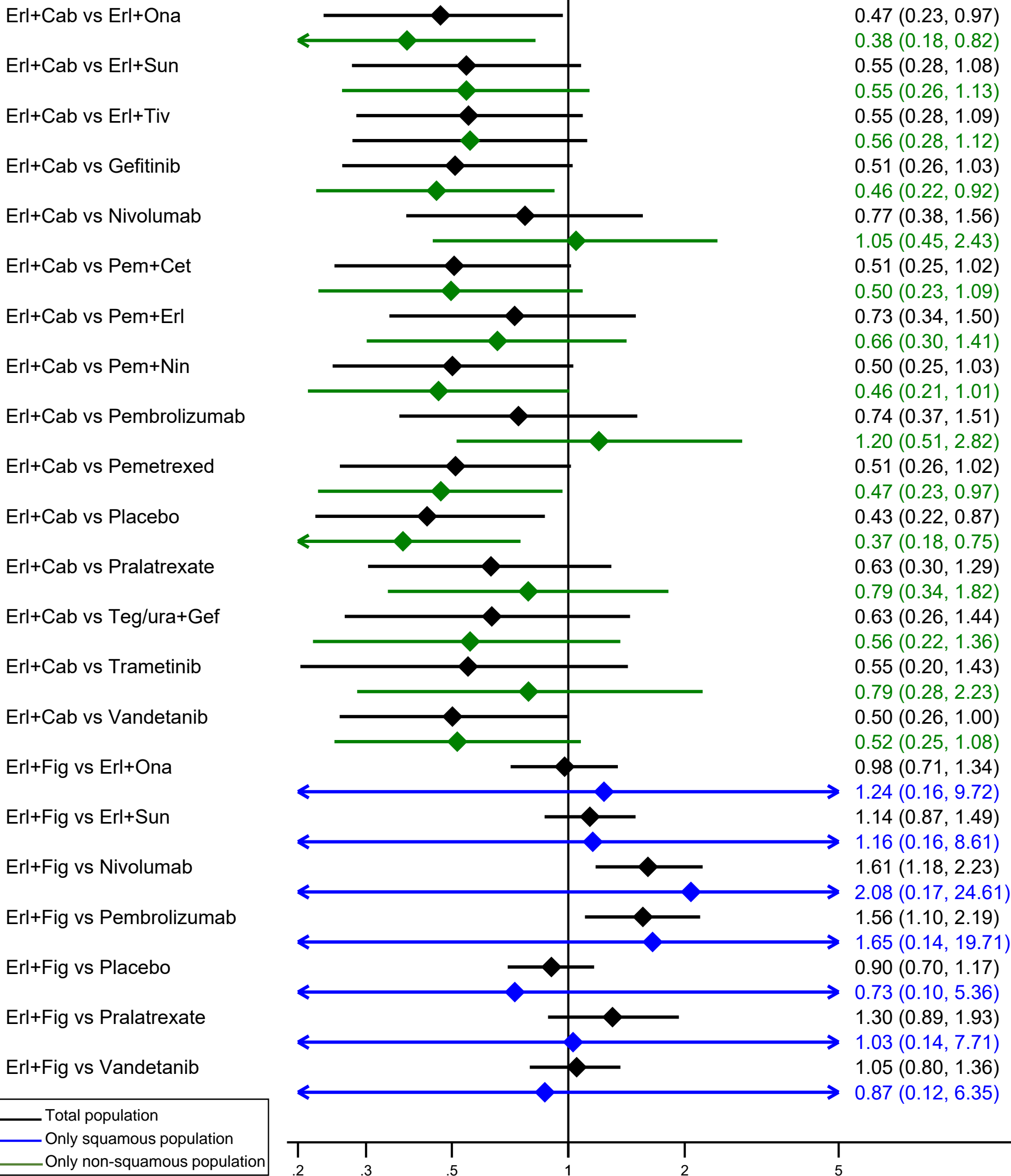
— Total population
— Only squamous population
— Only non-squamous population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)

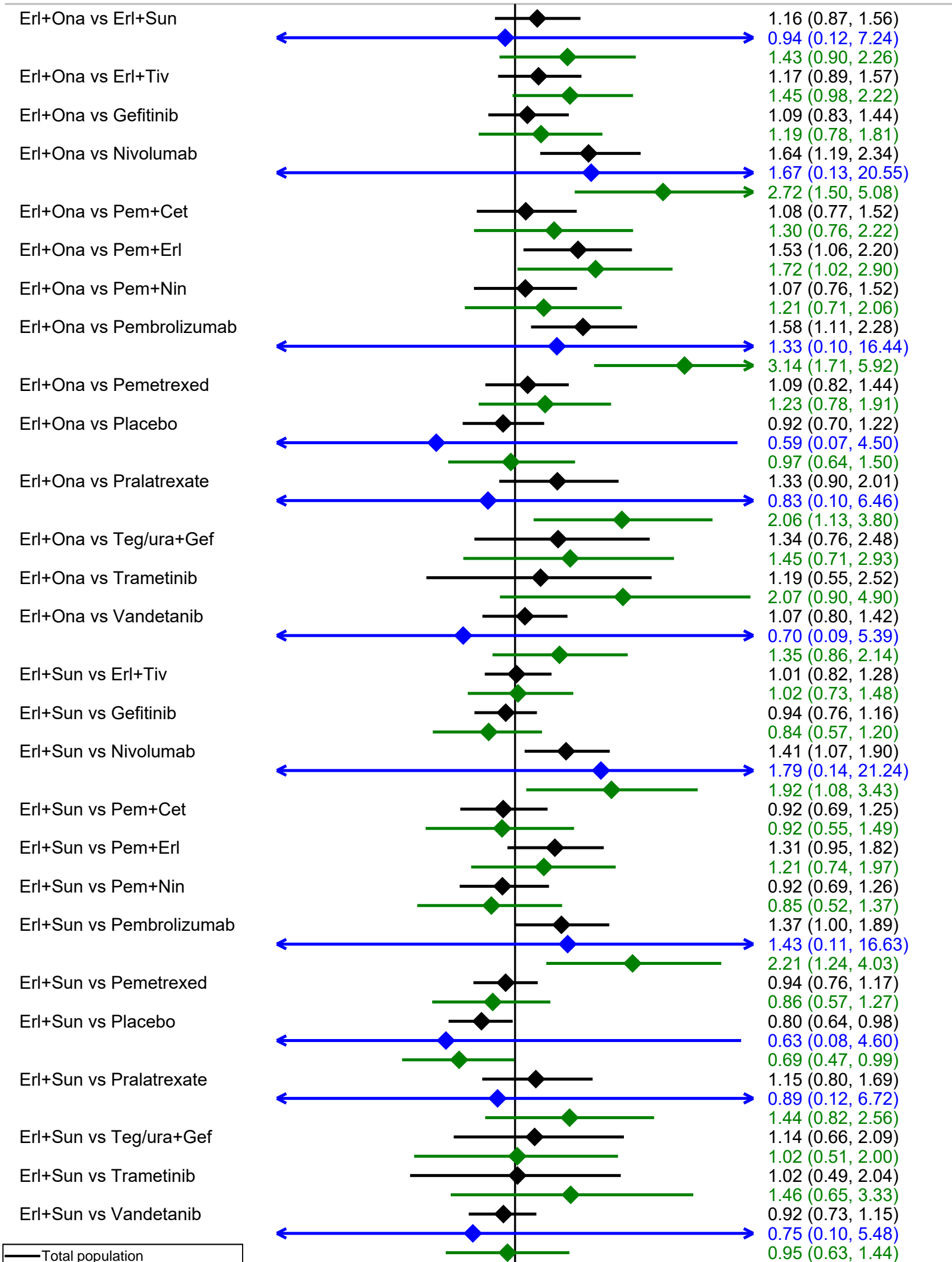


— Total population
— Only squamous population
— Only non-squamous population

Comparison

Overall Survival

HR (95% CrI)



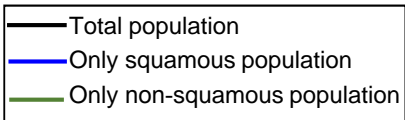
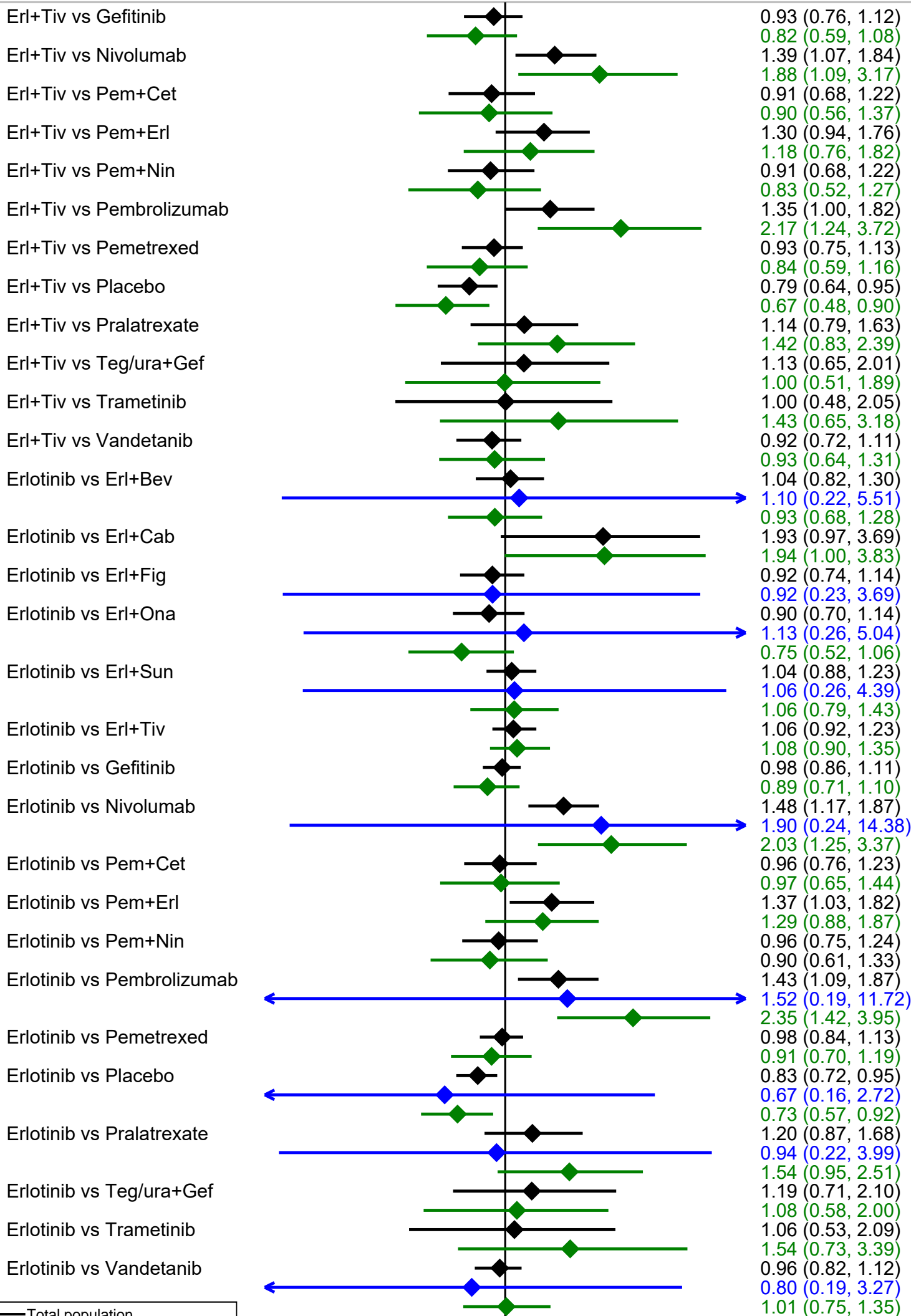
— Total population
— Only squamous population
— Only non-squamous population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)

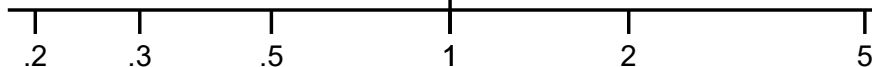
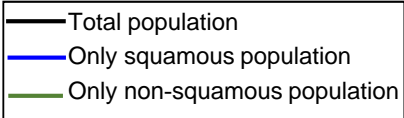
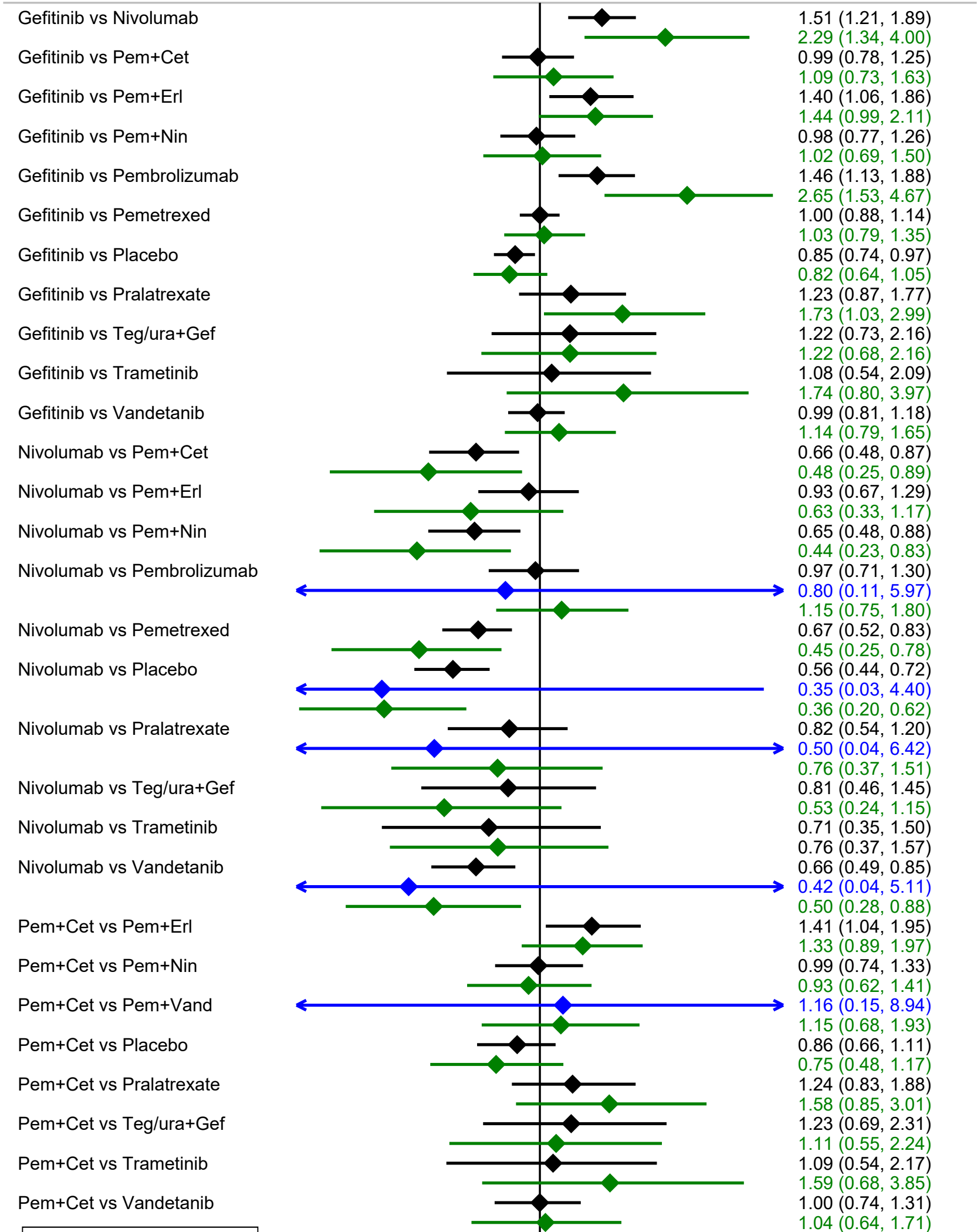


.2 .3 .5 1 2 5

Comparison

Overall Survival

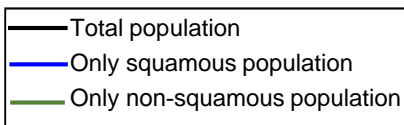
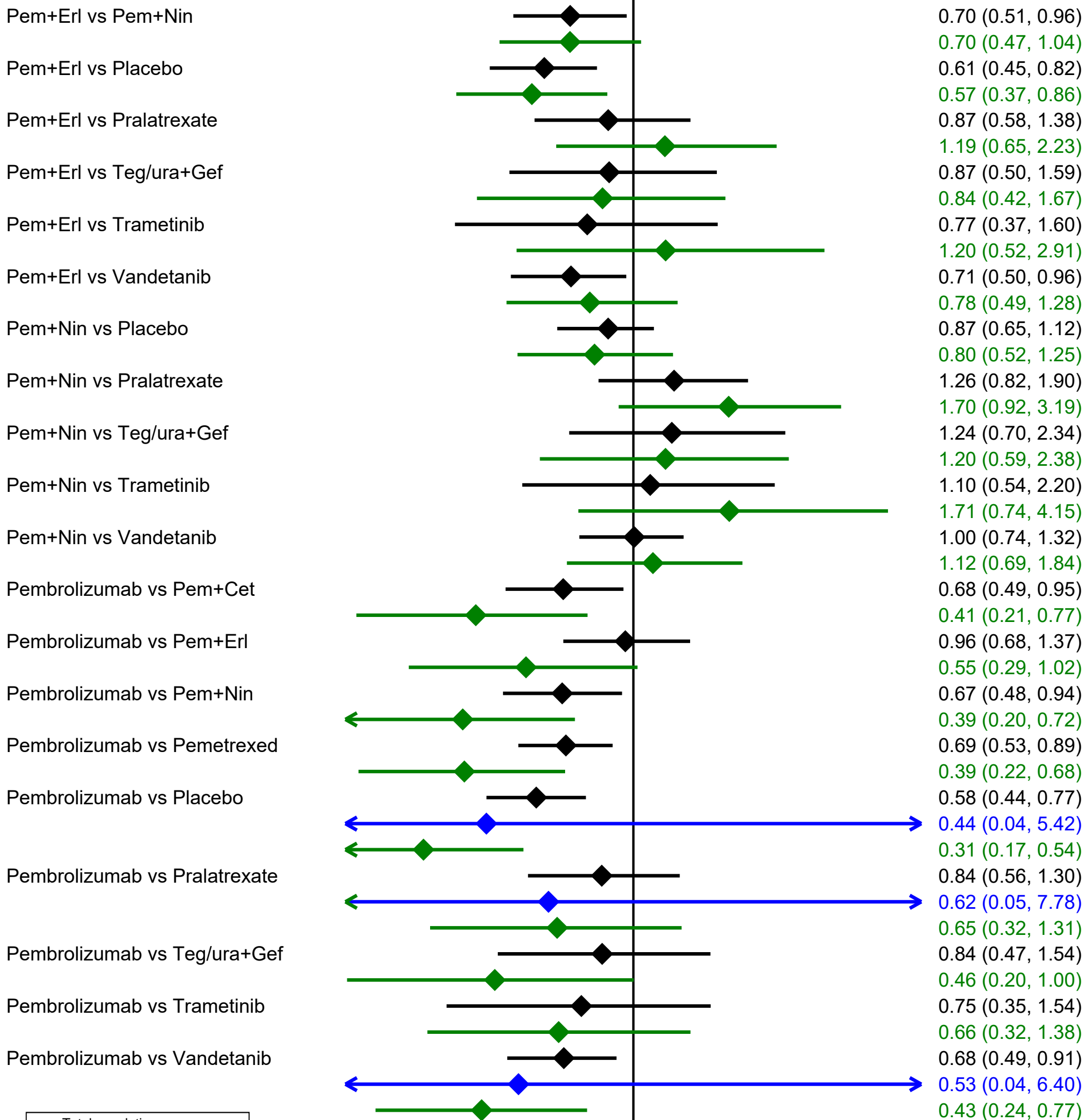
HR (95% CrI)



Comparison

Overall Survival

HR (95% CrI)

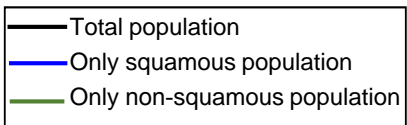
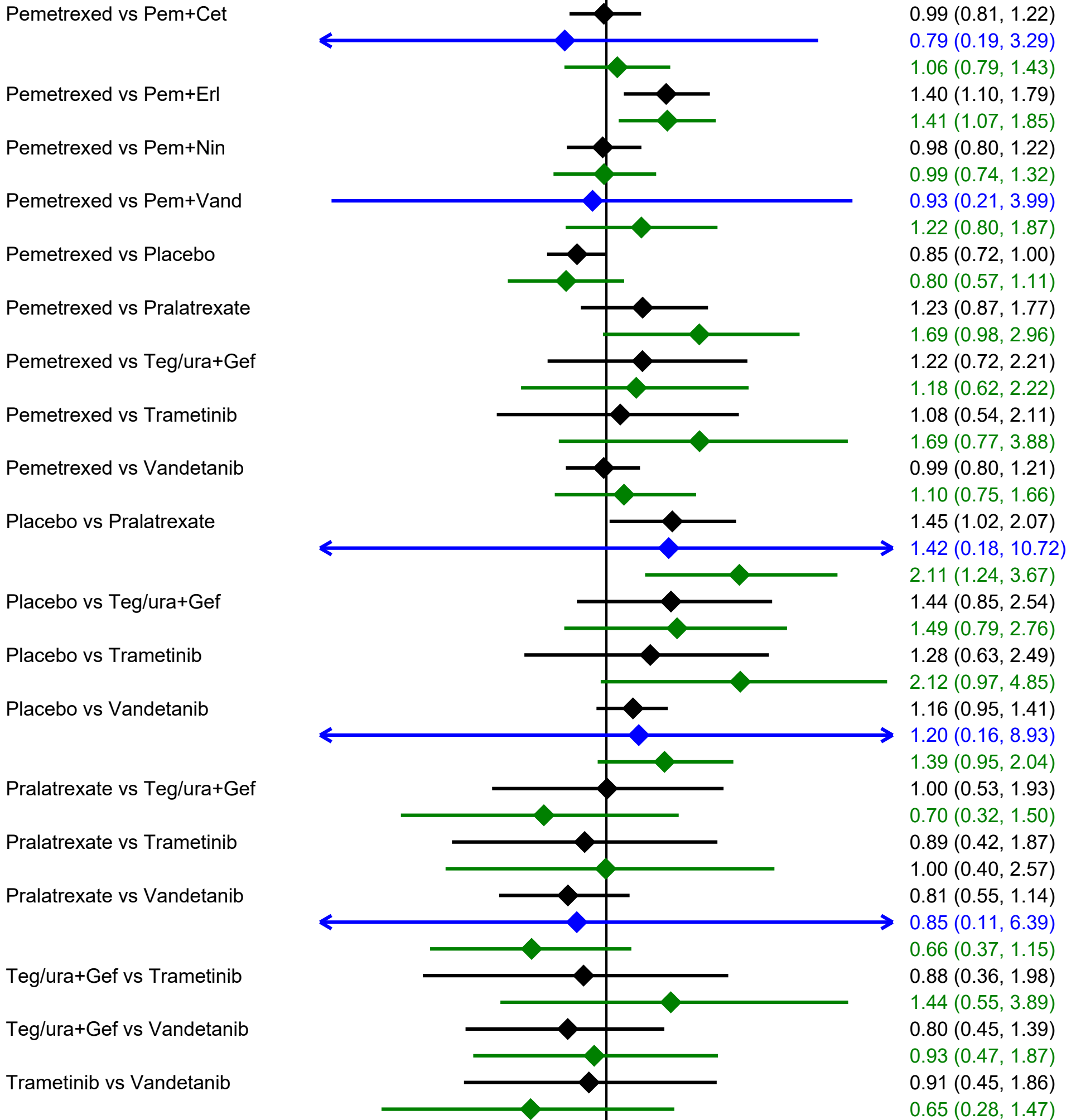


.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)



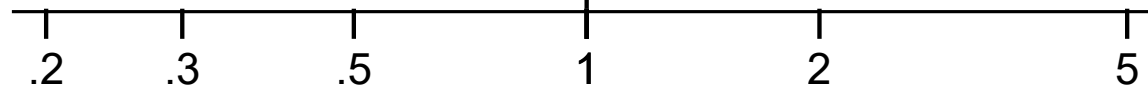
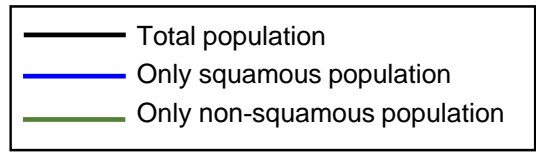
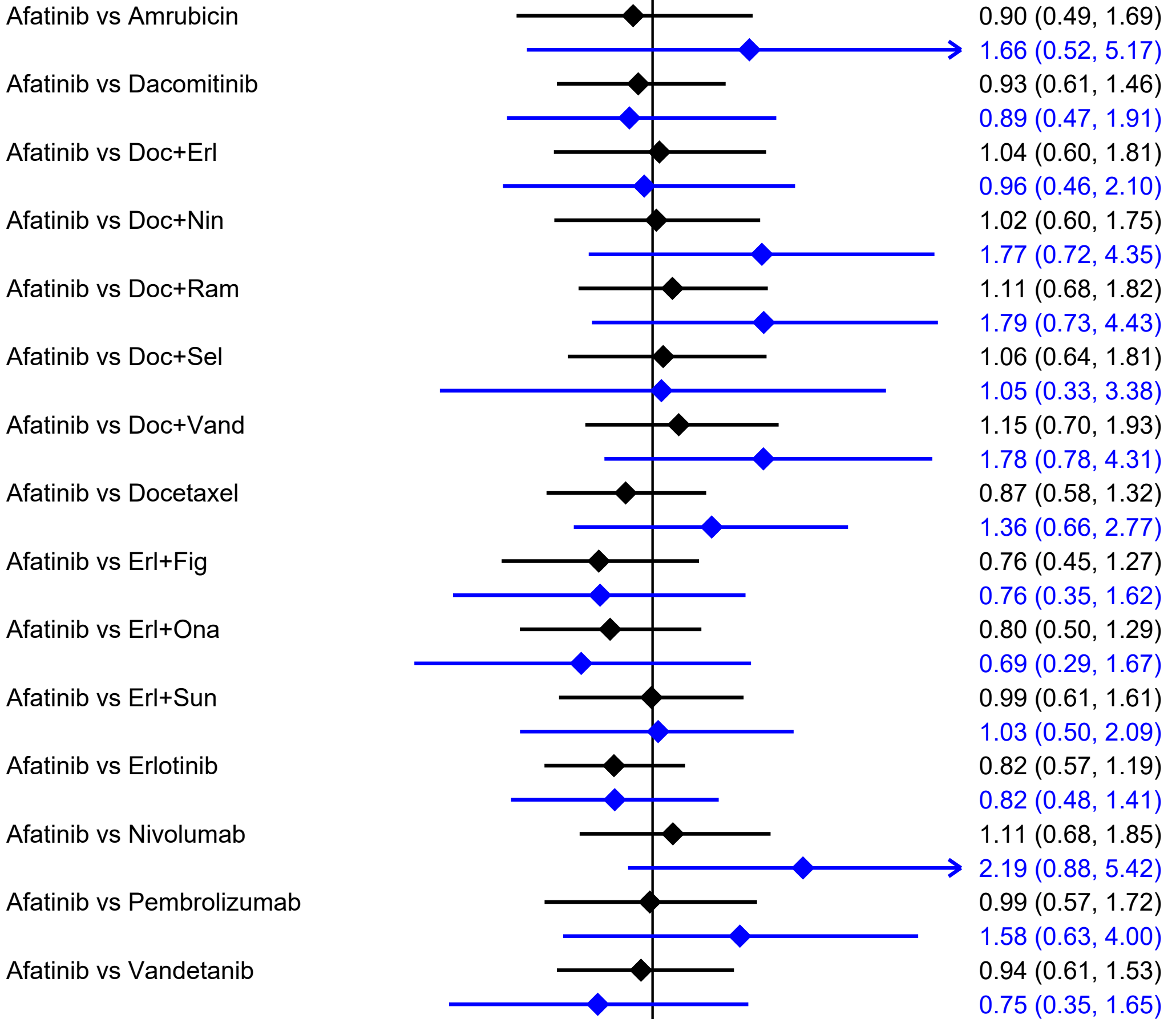
.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)

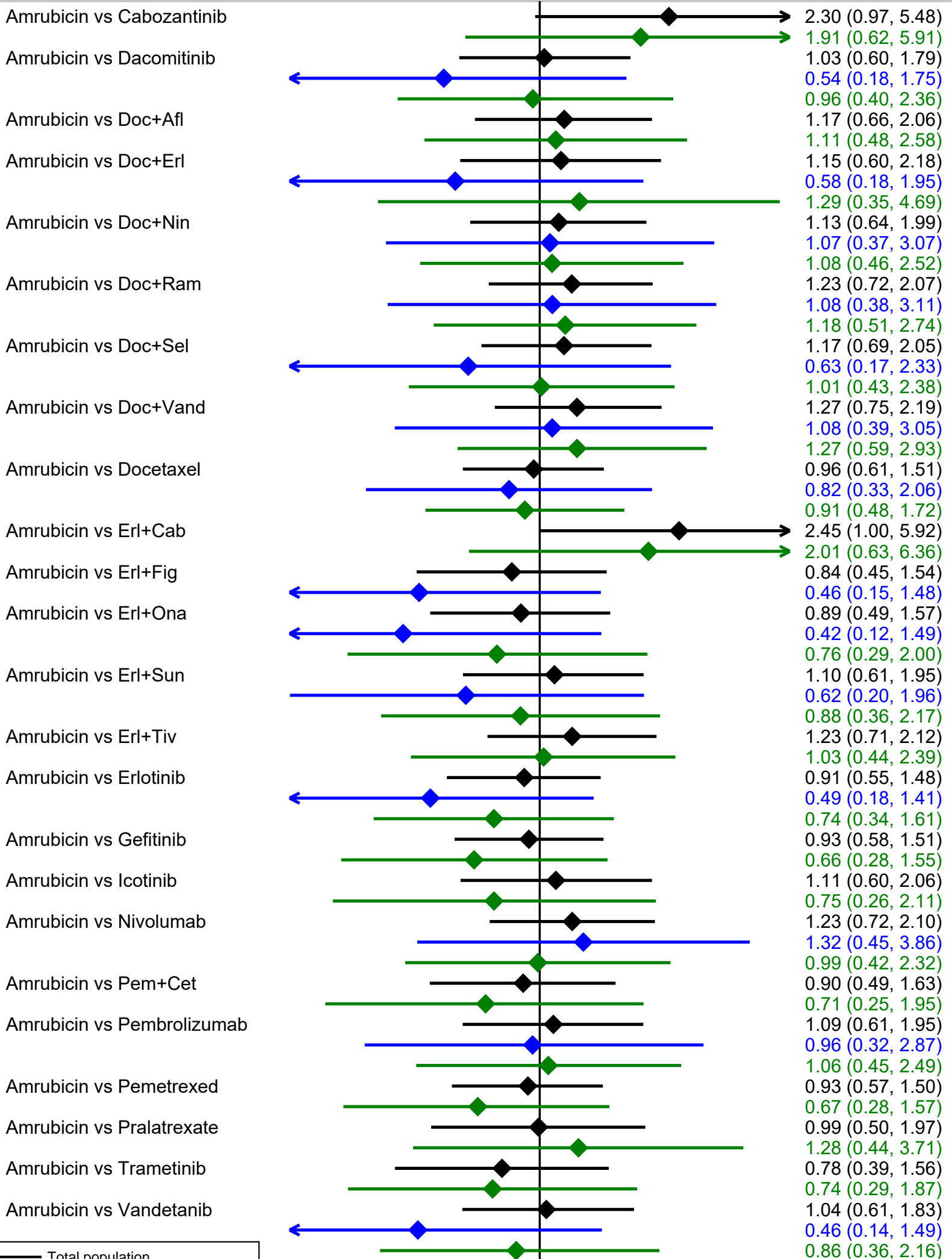
Favors first treatment ← → *Favors second treatment*



Comparison

Progression Free Survival

HR (95% CrI)



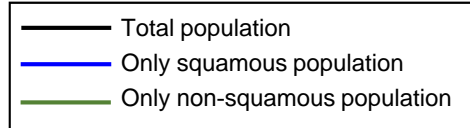
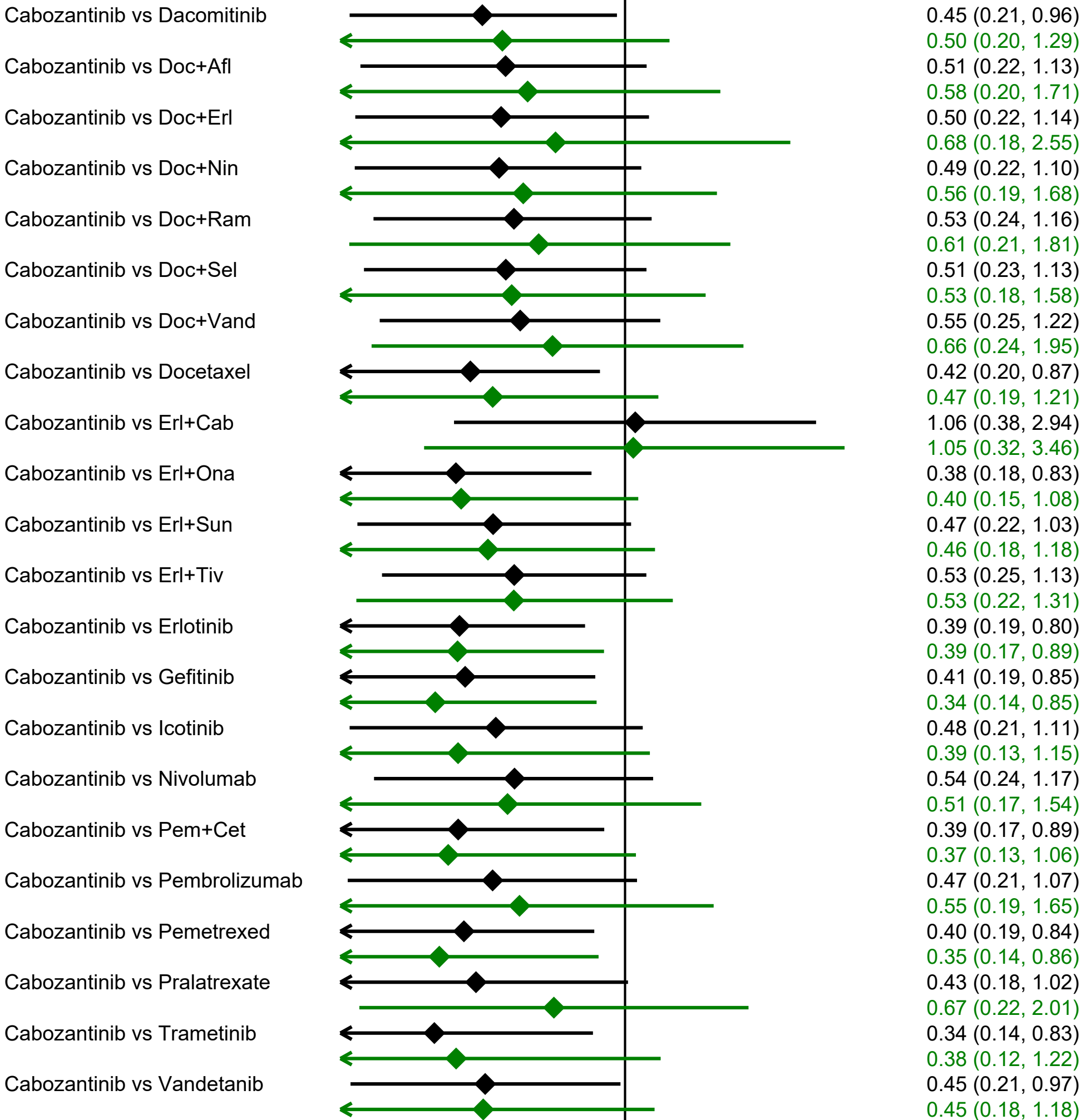
— Total population
— Only squamous population
— Only non-squamous population

.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)

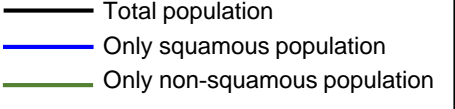
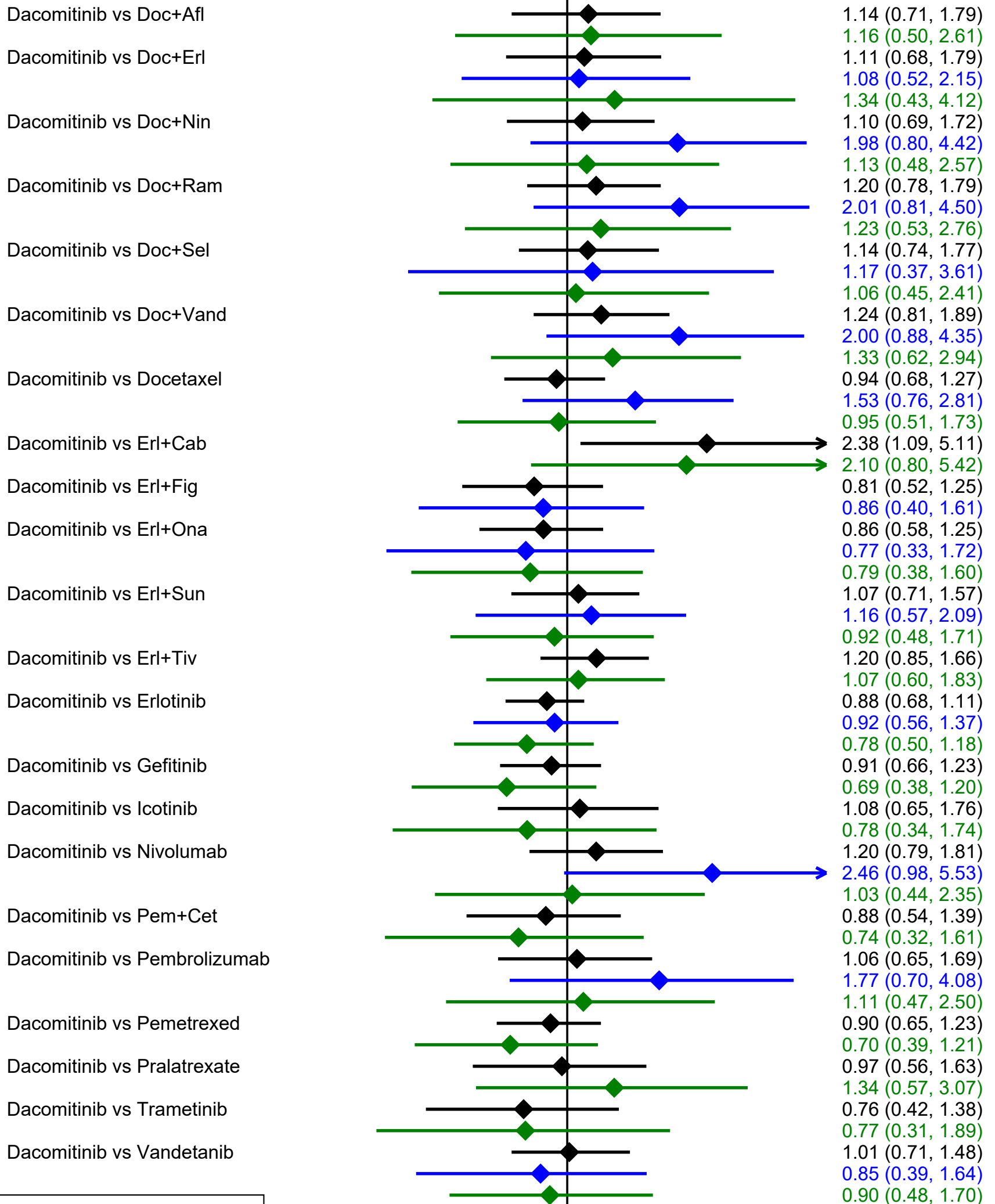


.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)

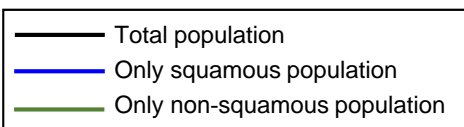
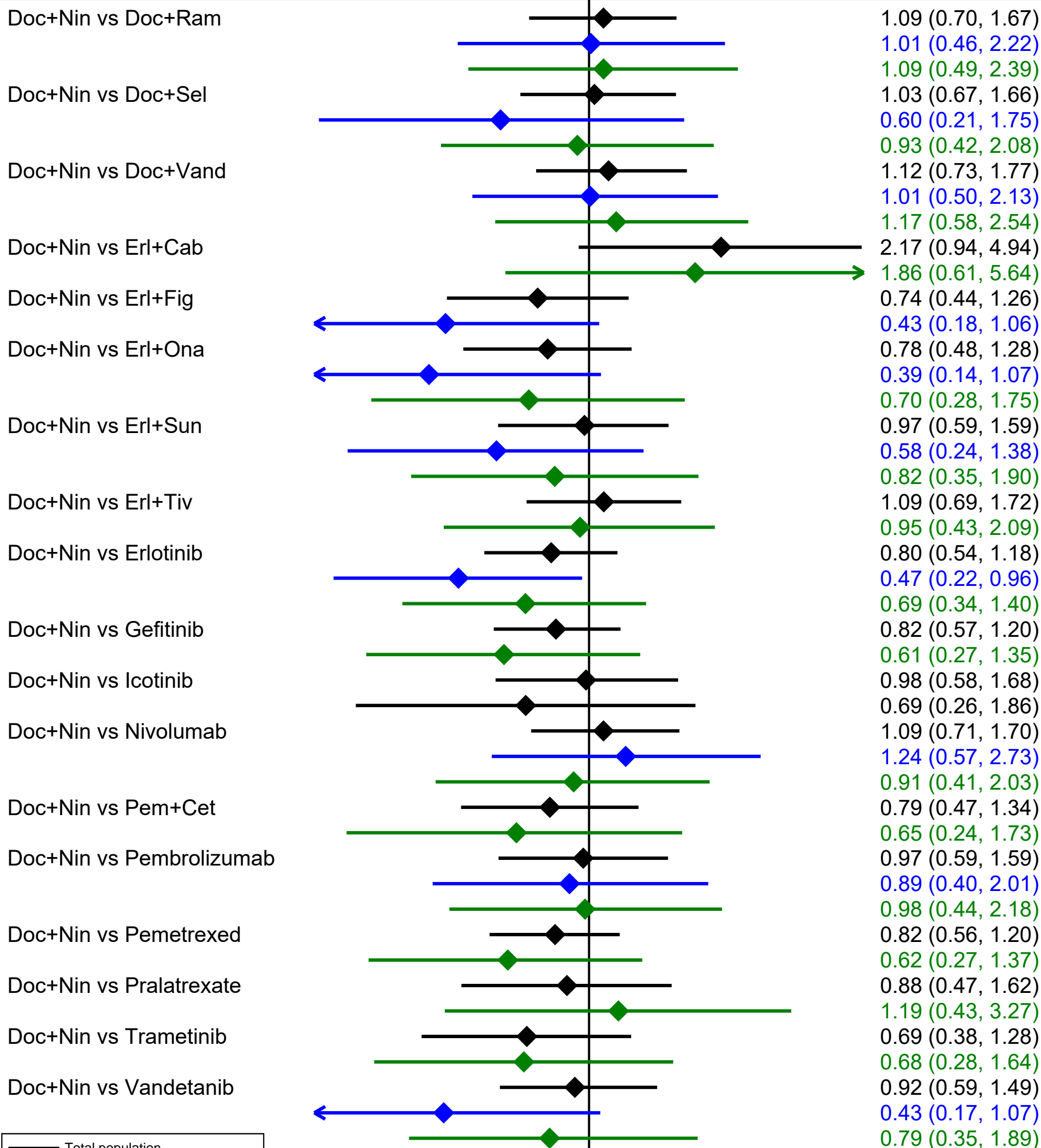


.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)

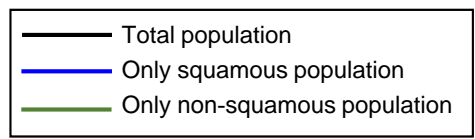
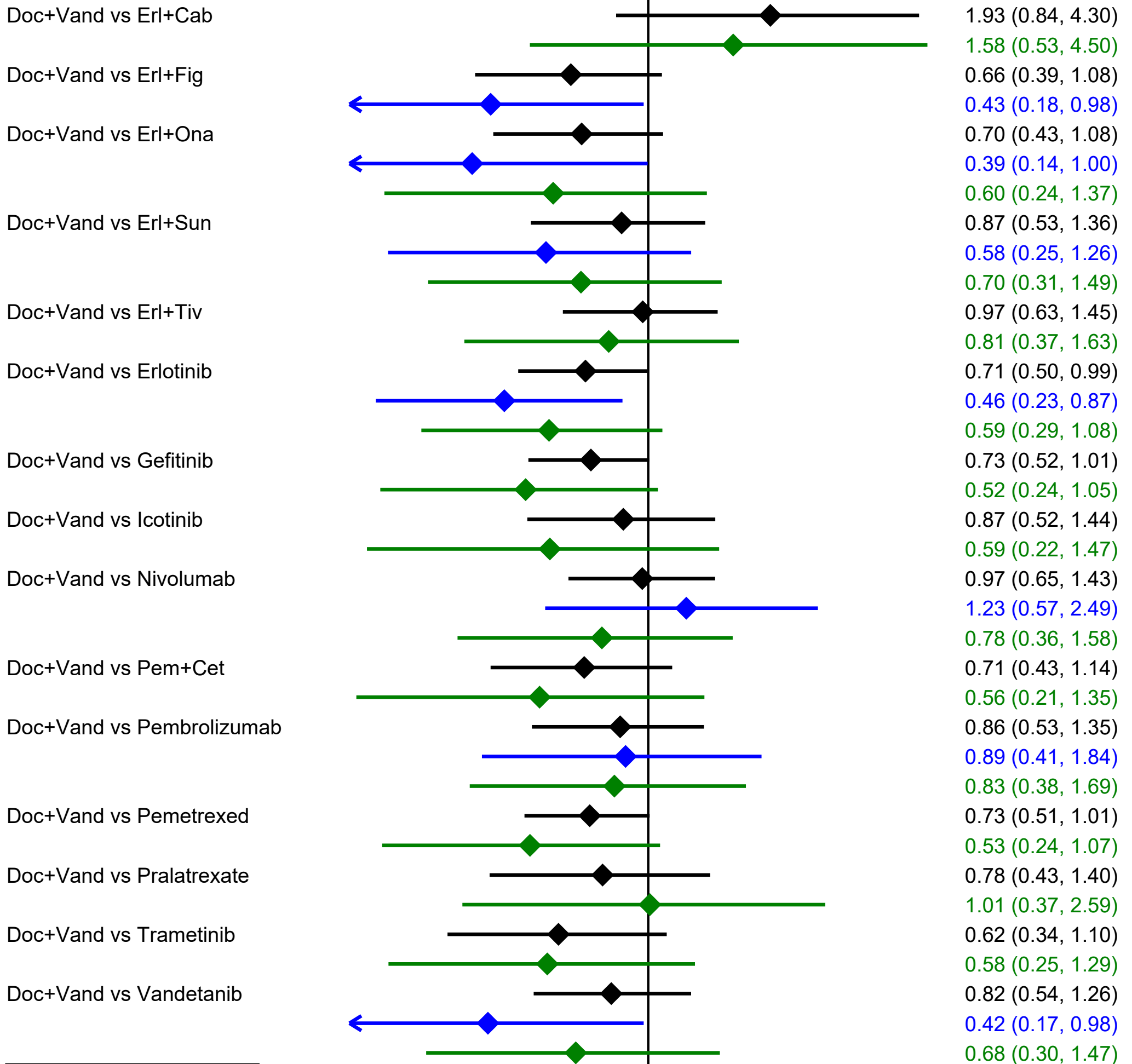


.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)

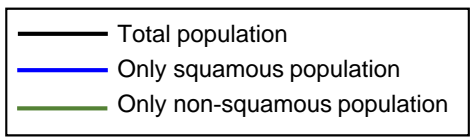
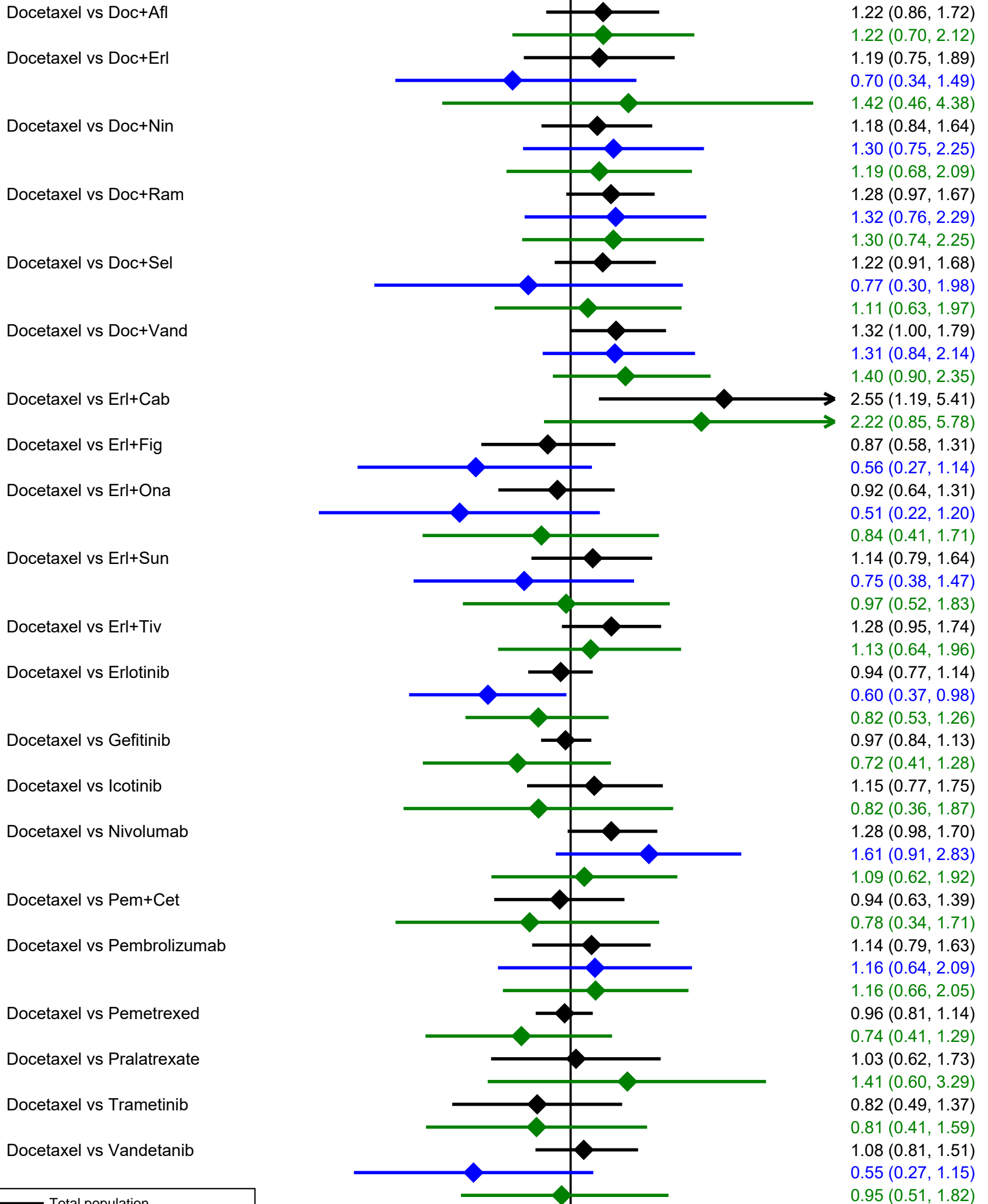


.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)

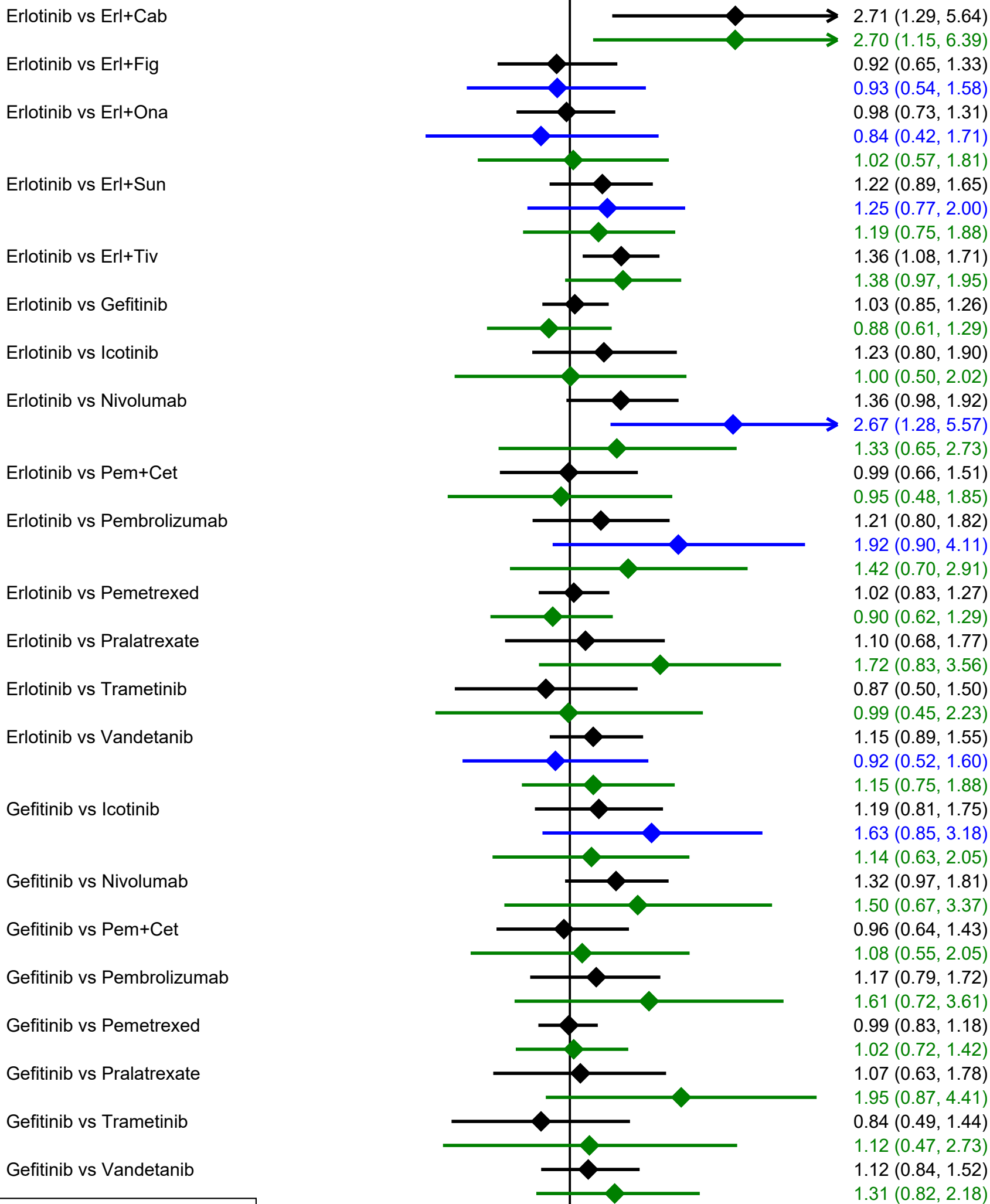


.2 .3 .5 1 2 5

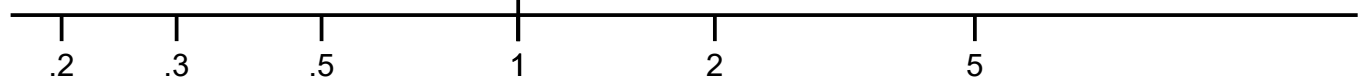
Comparison

Progression Free Survival

HR (95% CrI)



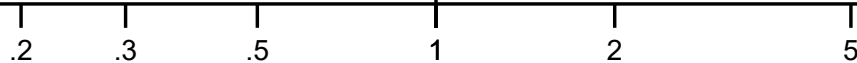
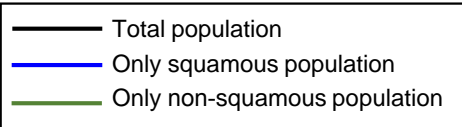
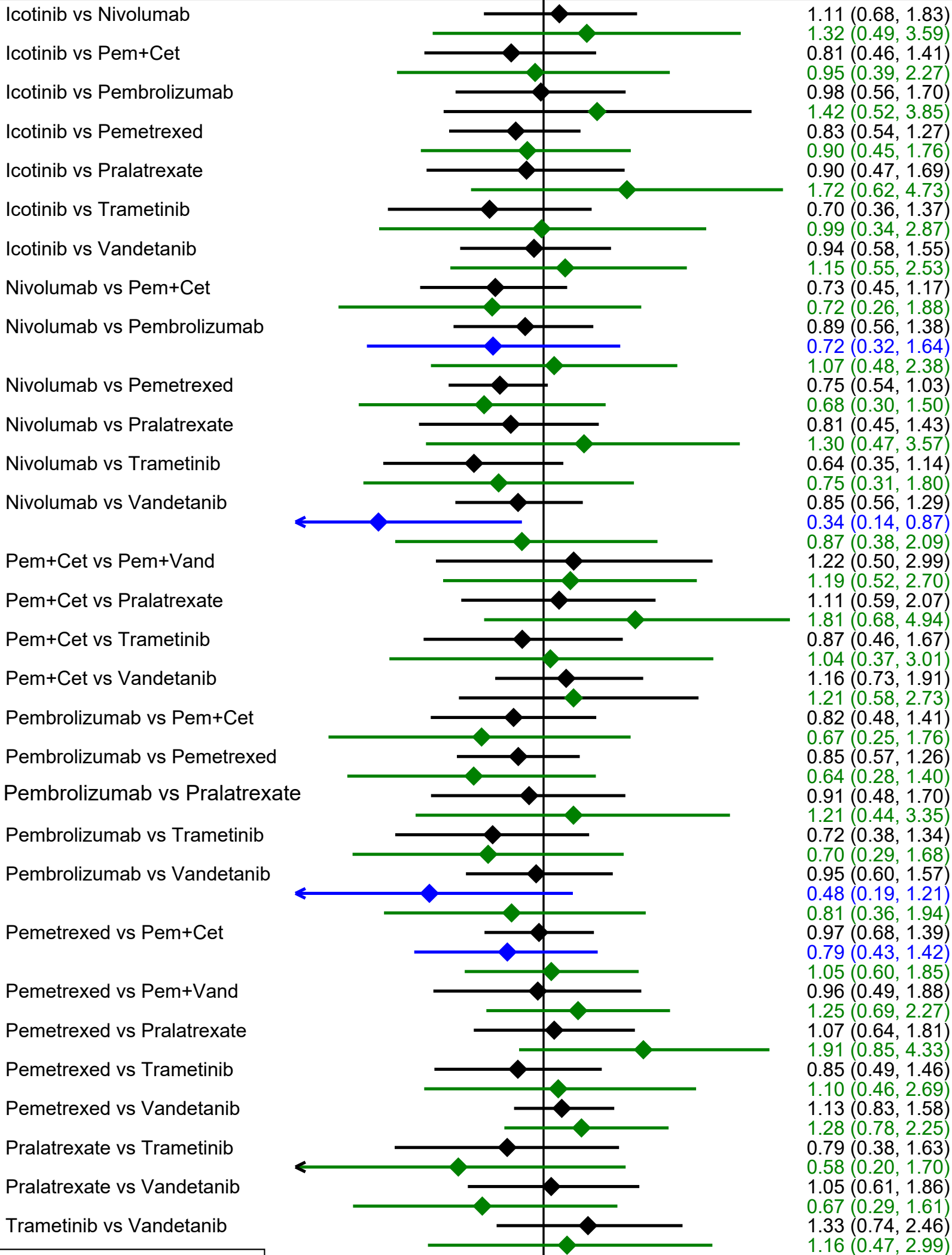
— Total population
— Only squamous population
— Only non-squamous population



Comparison

Progression Free Survival

HR (95% CrI)

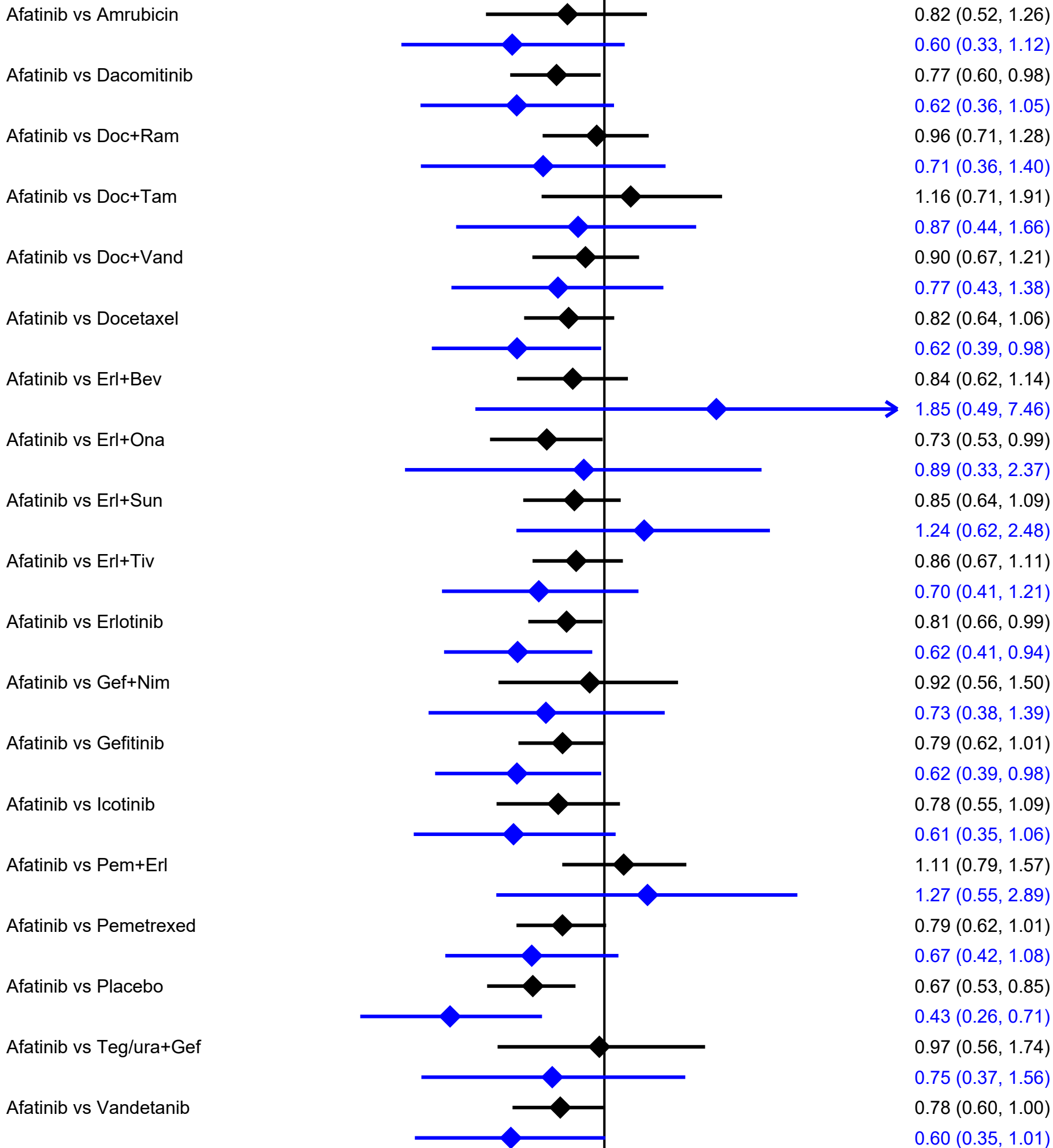


Overall Survival

Comparison

HR (95% CrI)

Favors first treatment ← *Favors second treatment*



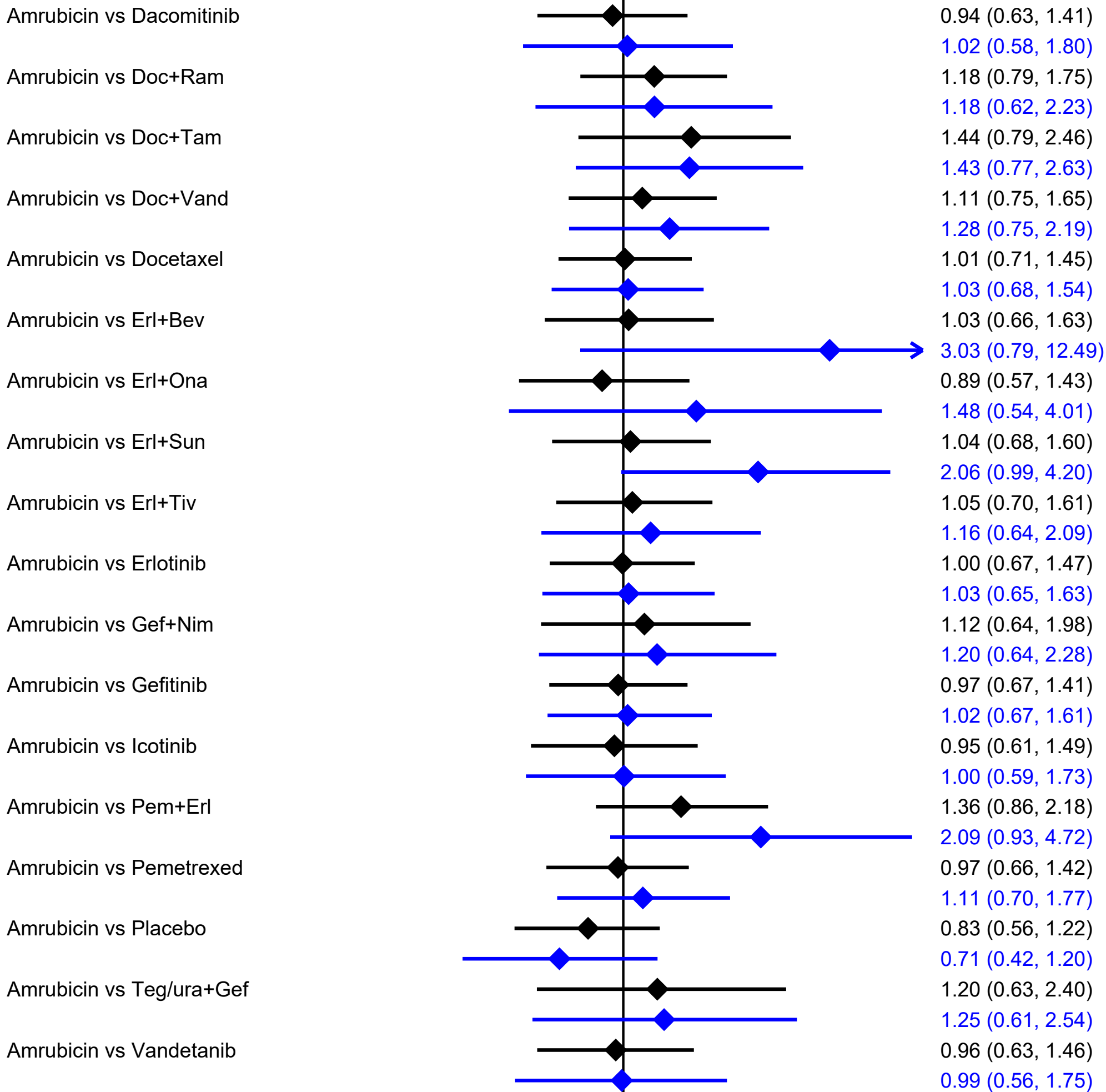
— Total population
— Only Asian population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)



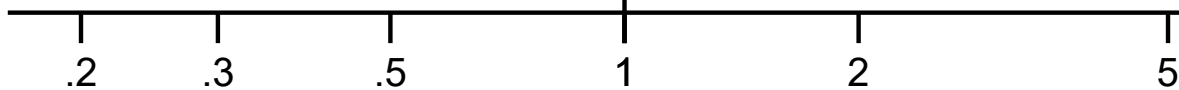
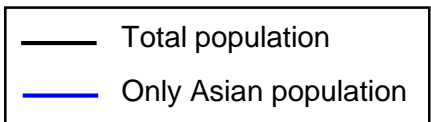
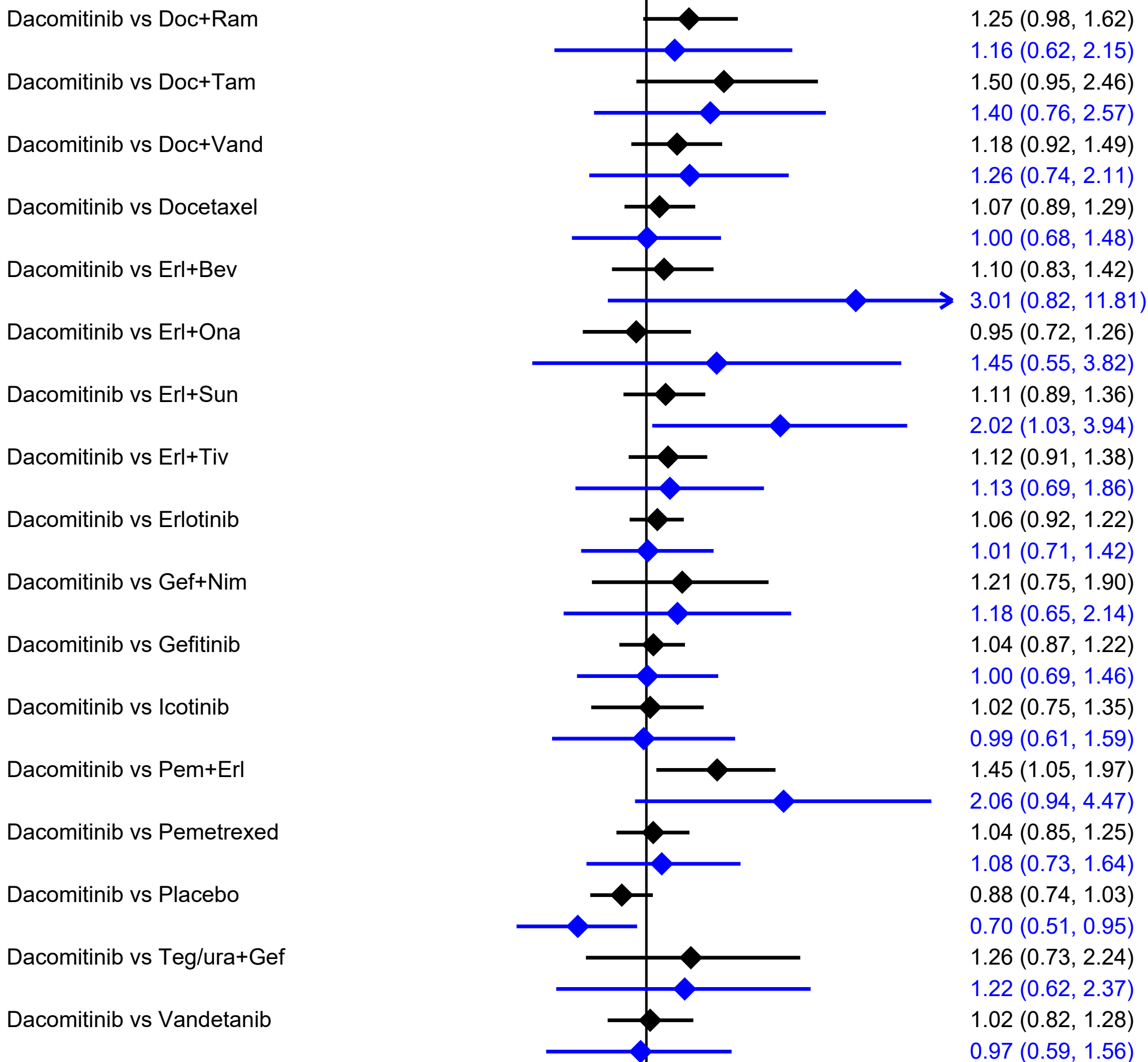
Total population
 Only Asian population

.2 .3 .5 1 2 5

Comparison

Overall Survival

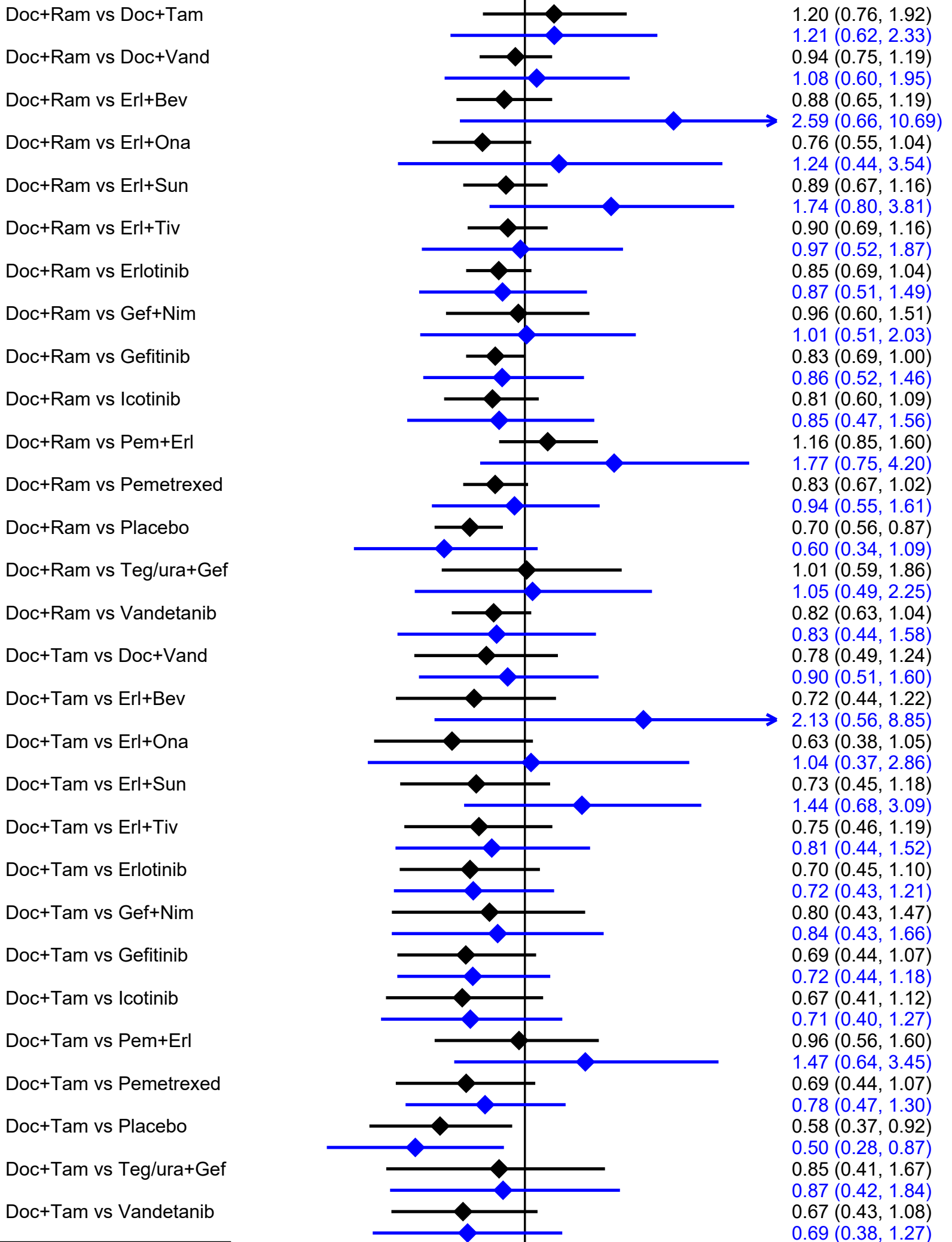
HR (95% CrI)



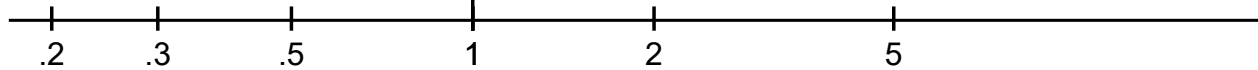
Comparison

Overall Survival

HR (95% CrI)



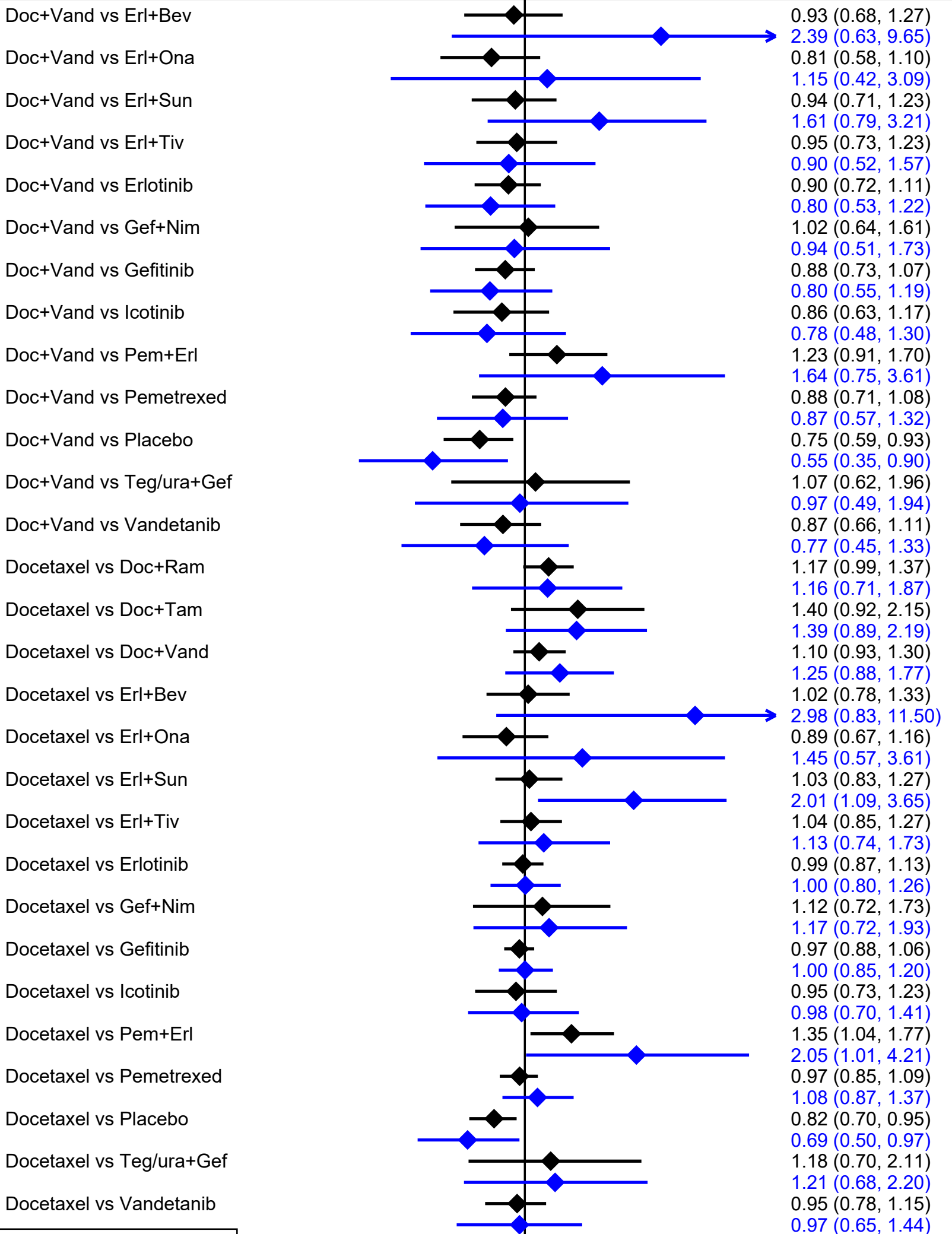
— Total population
— Only Asian population



Comparison

Overall Survival

HR (95% CrI)



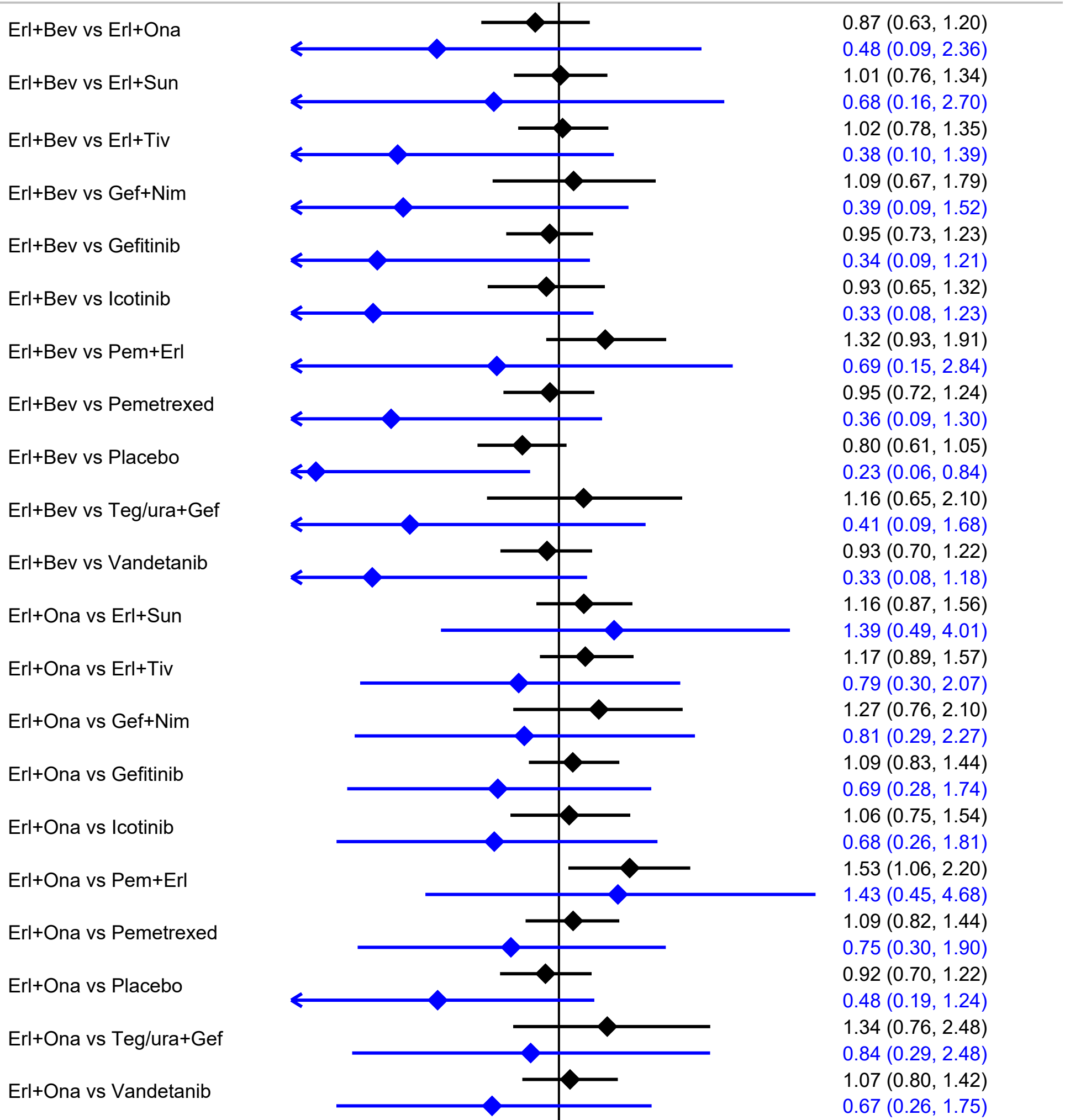
— Total population
— Only Asian population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)



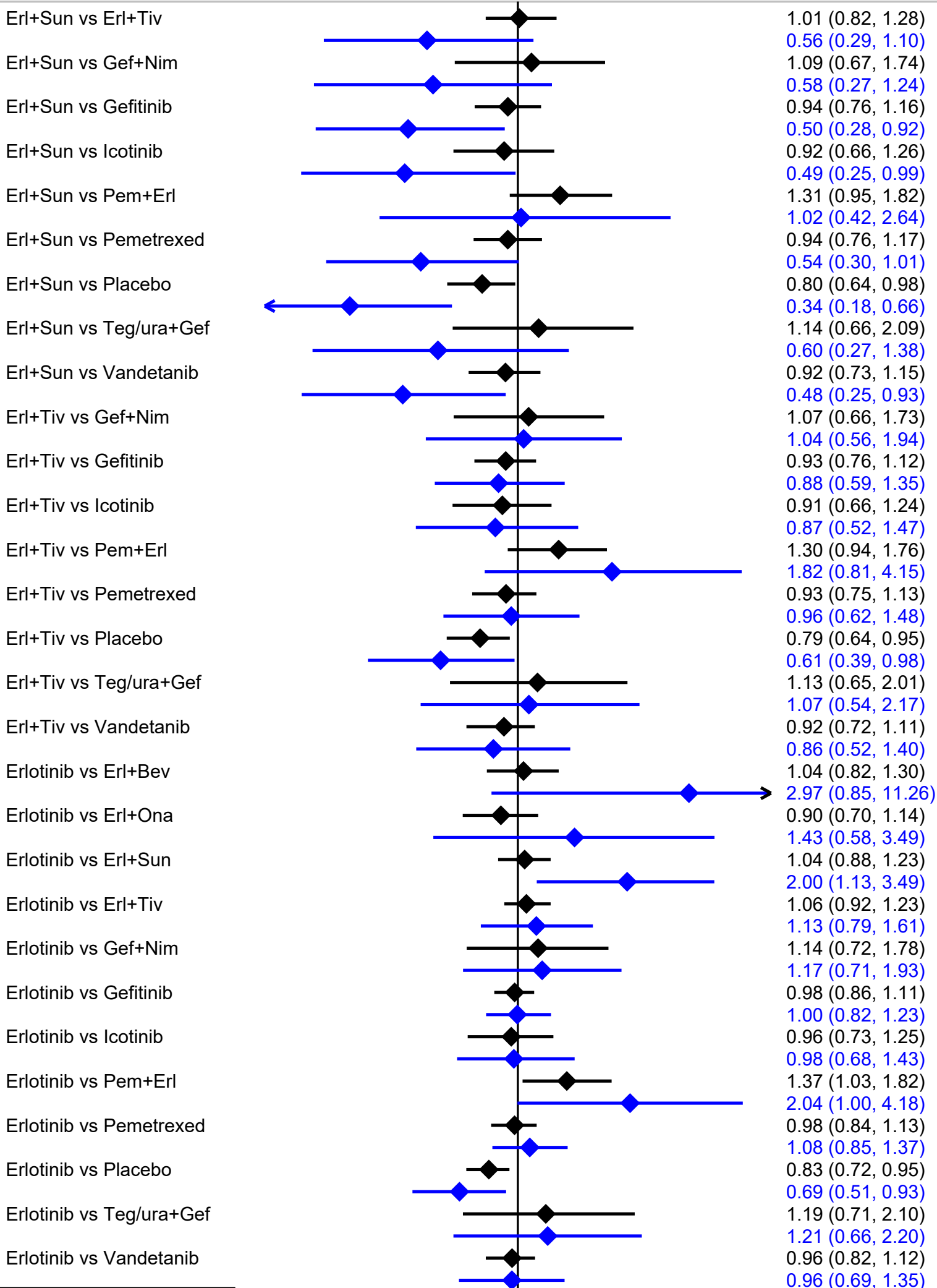
— Total population
— Only Asian population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)



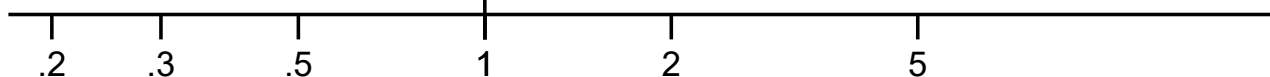
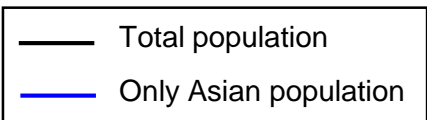
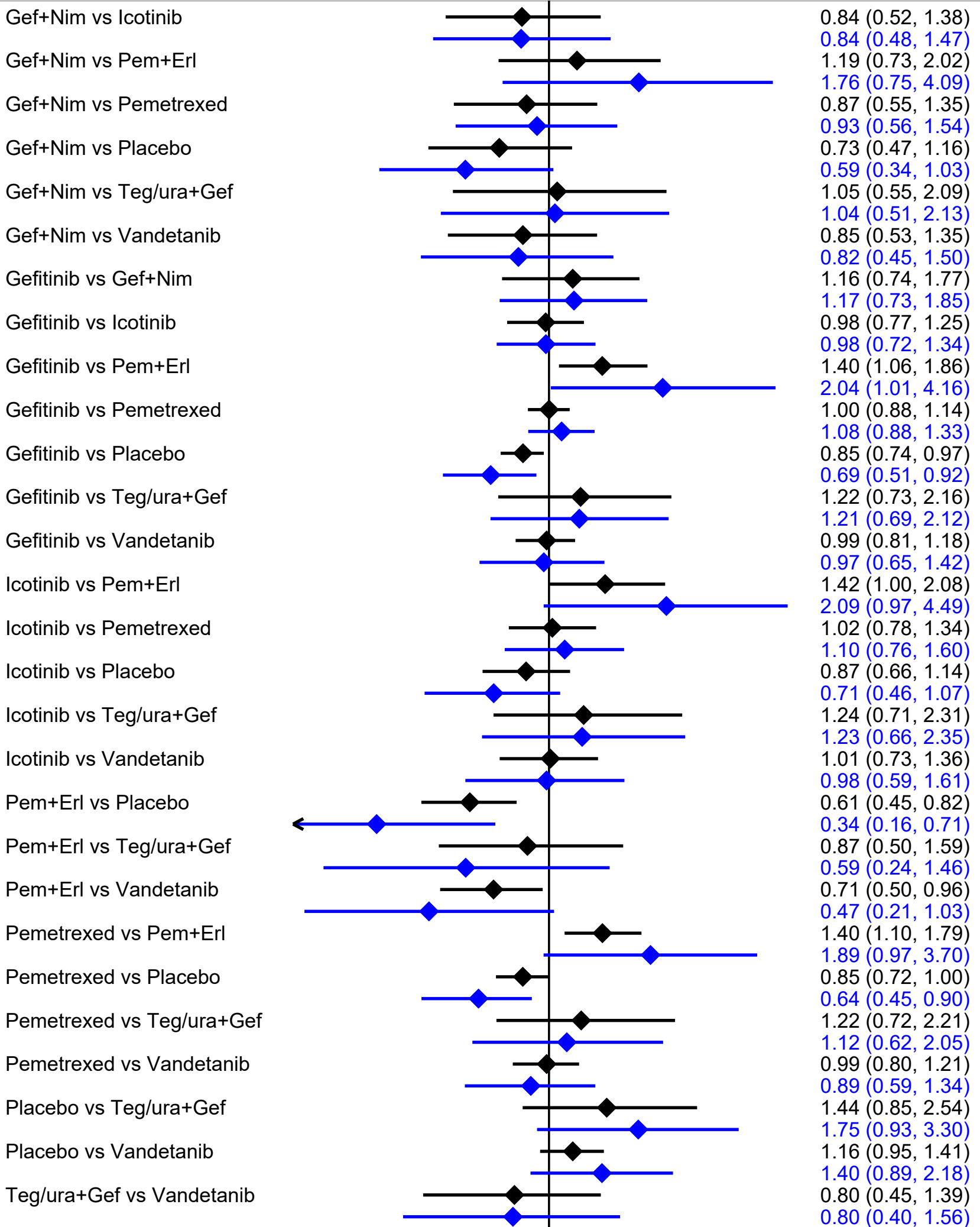
— Total population
— Only Asian population

.2 .3 .5 1 2 5

Comparison

Overall Survival

HR (95% CrI)

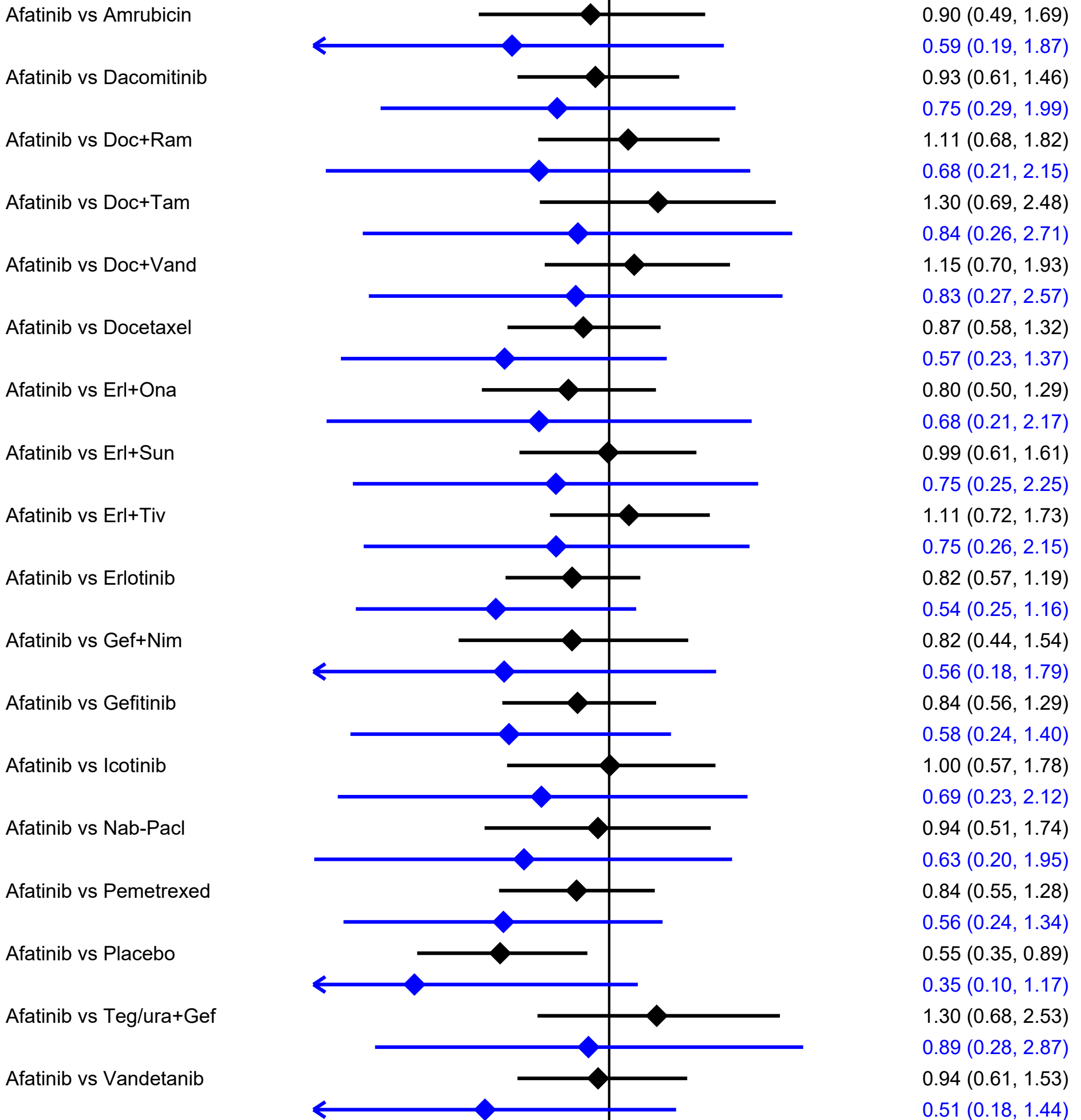


Comparison

Progression Free Survival

HR (95% CrI)

Favors first treatment ← *Favors second treatment* →



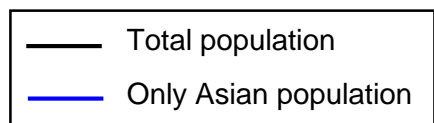
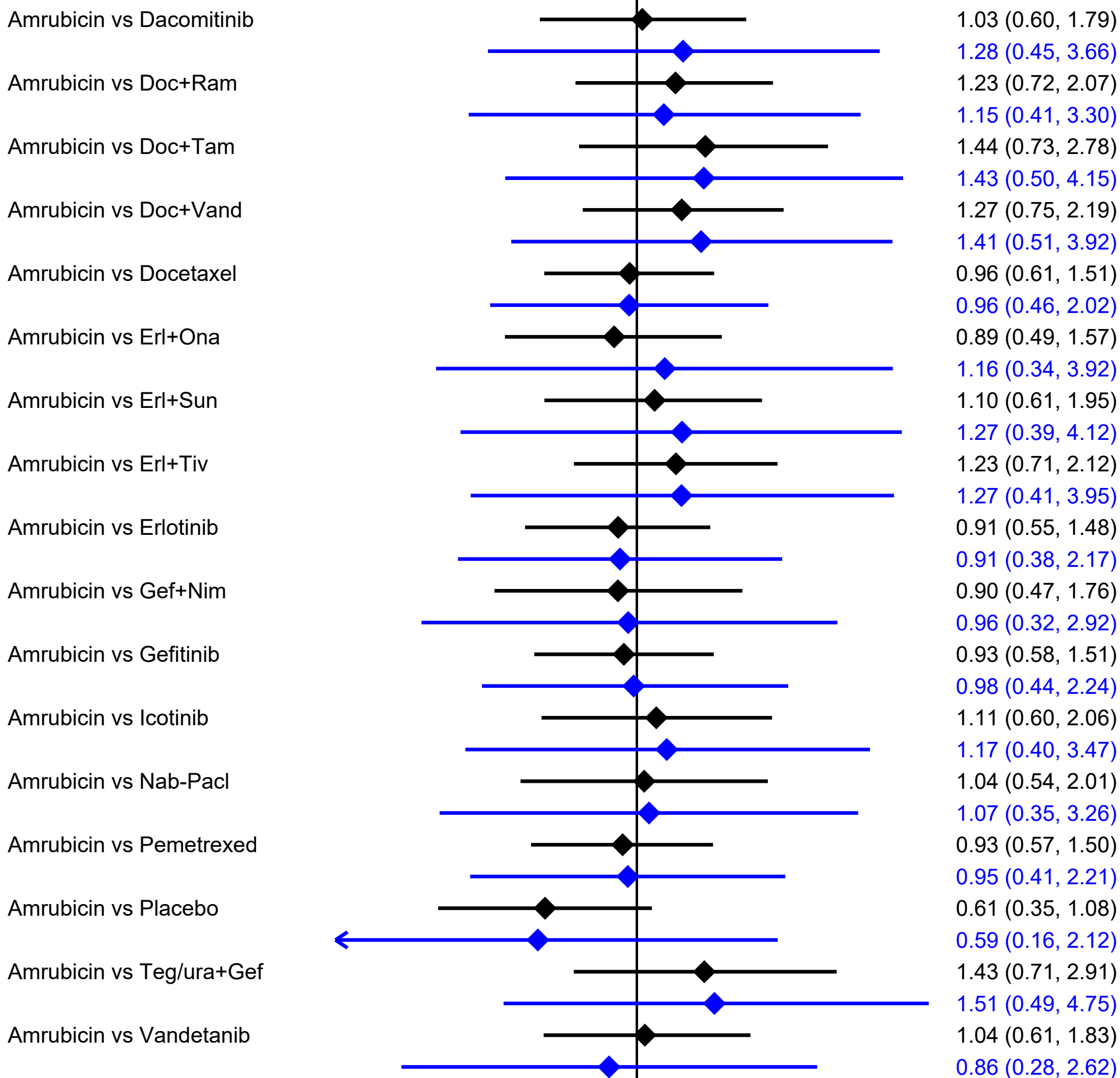
— Total population
— Only Asian population

.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)

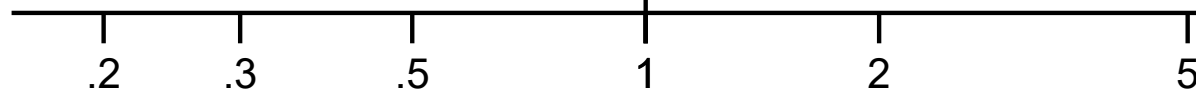
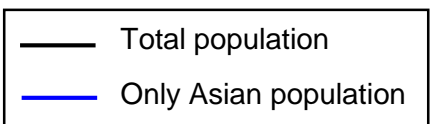
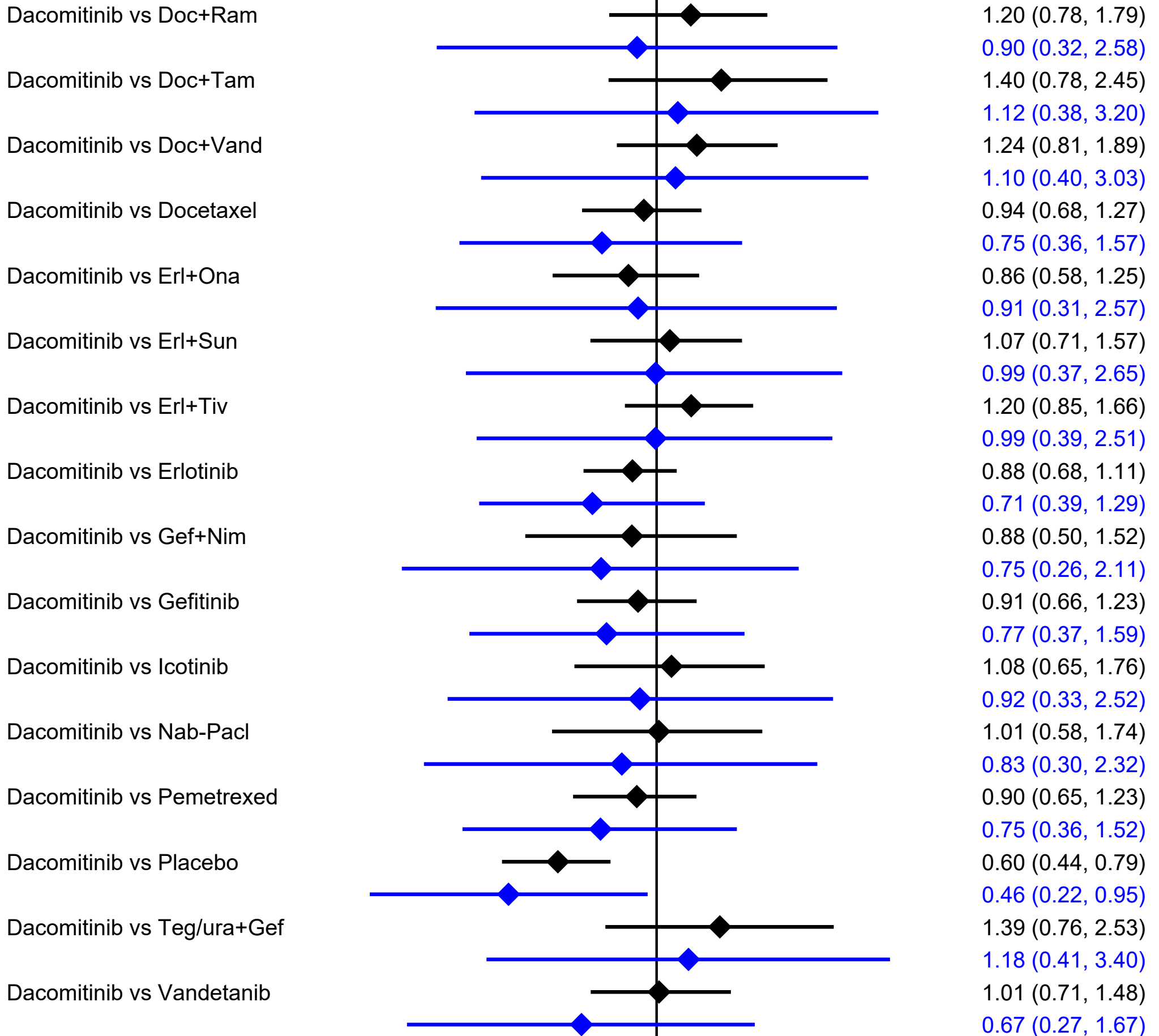


.2 .3 .5 1 2 5

Comparison

Progression Free Survival

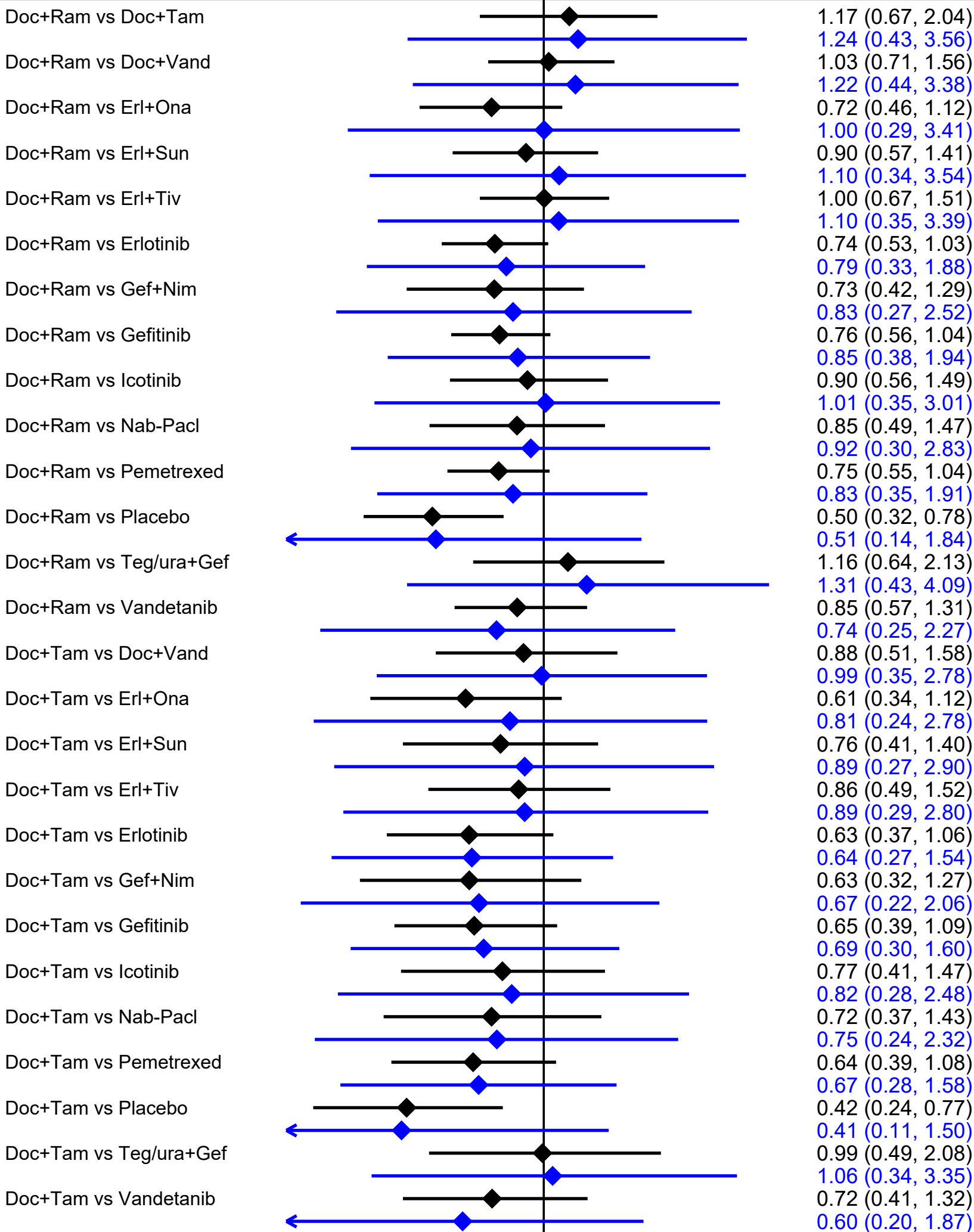
HR (95% CrI)



Comparison

Progression Free Survival

HR (95% CrI)



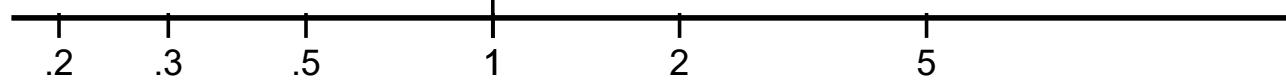
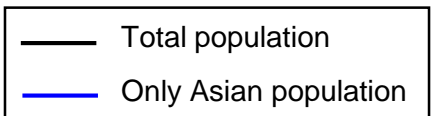
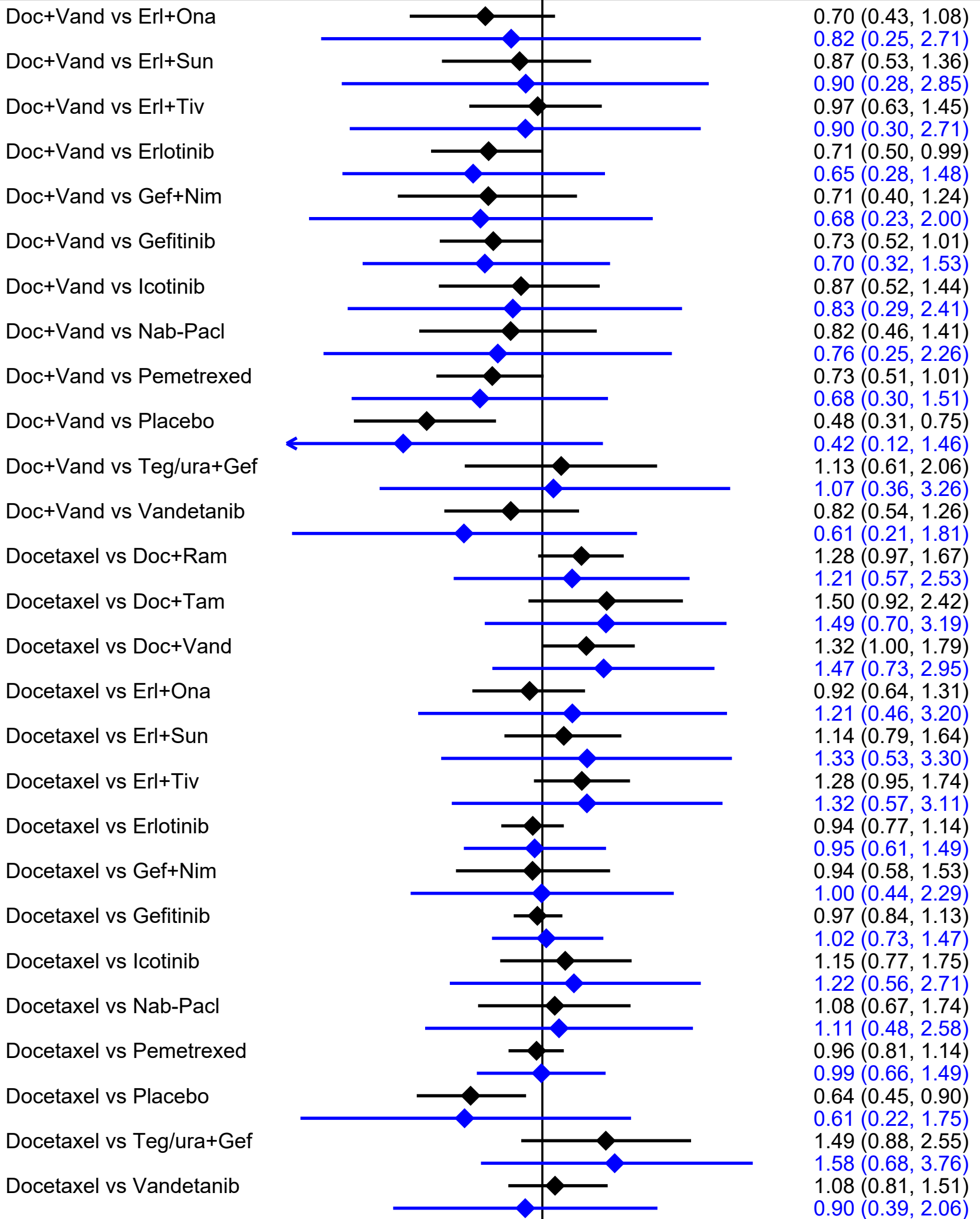
— Total population
 — Only Asian population

.2 .3 .5 1 2 5

Comparison

Progression Free Survival

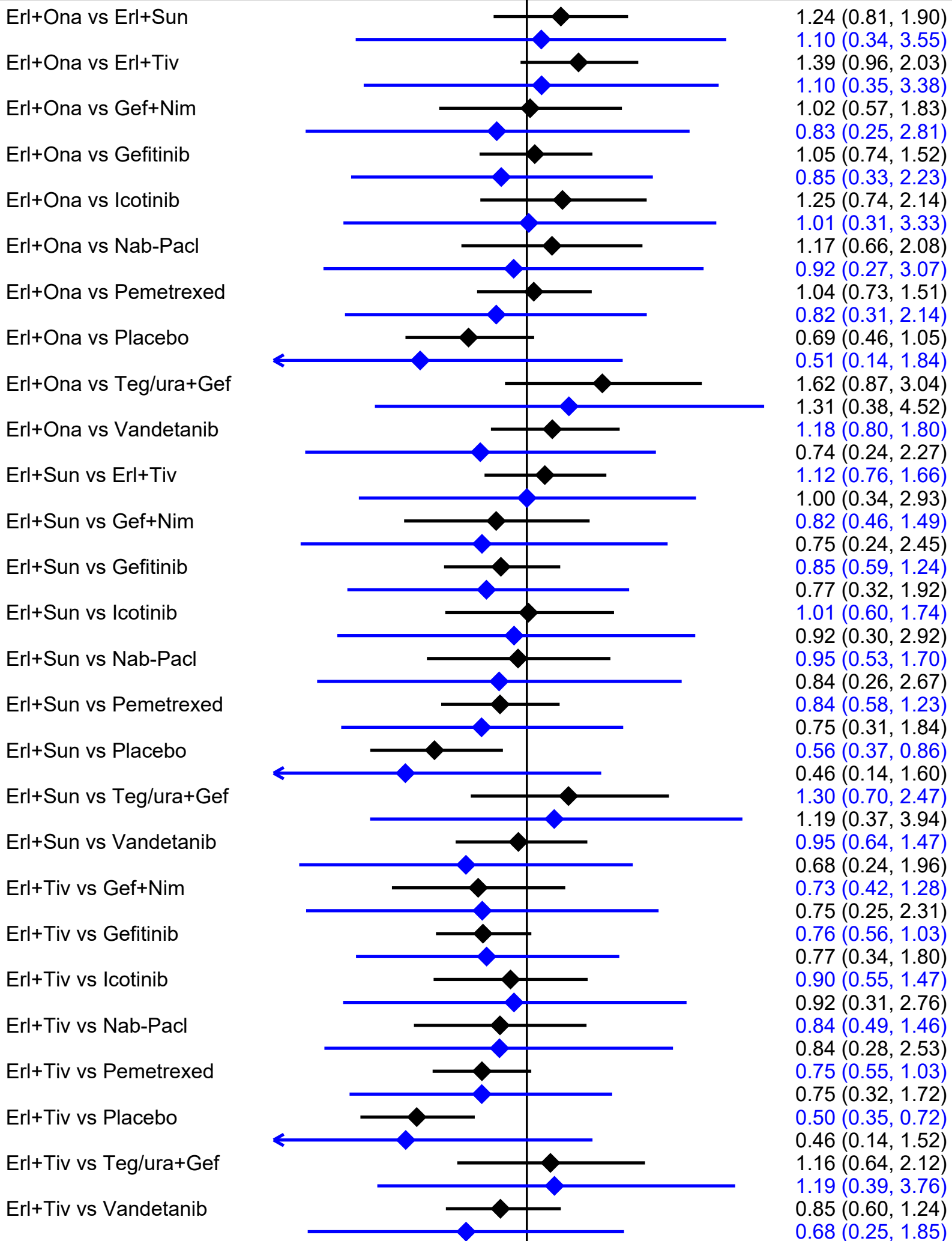
HR (95% CrI)





Comparison

Progression Free Survival

HR (95% CI)



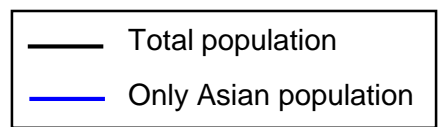
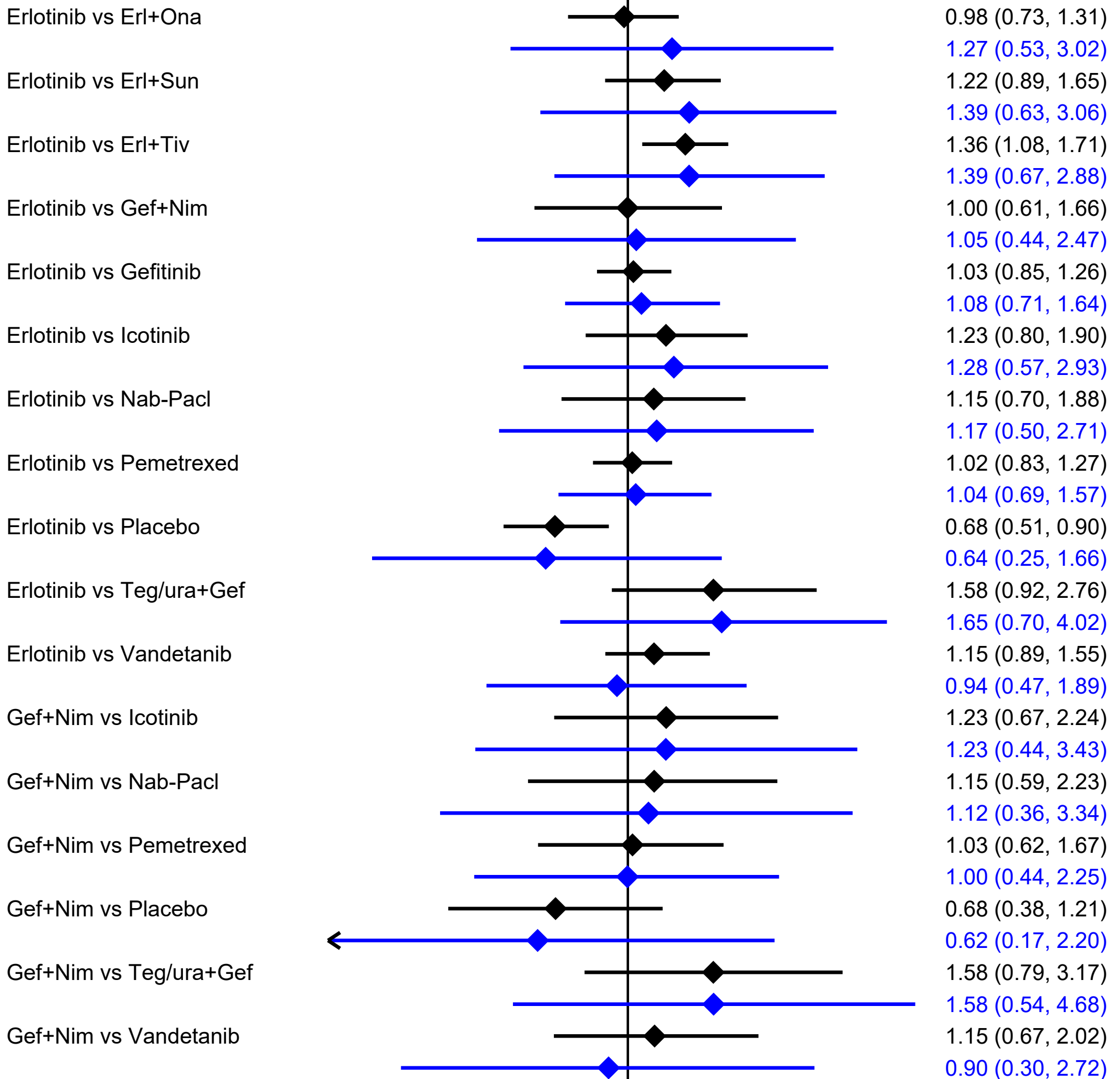
 Total population
 Only Asian population

.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)

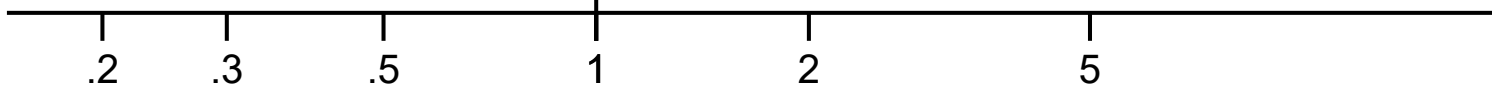
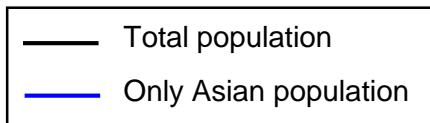
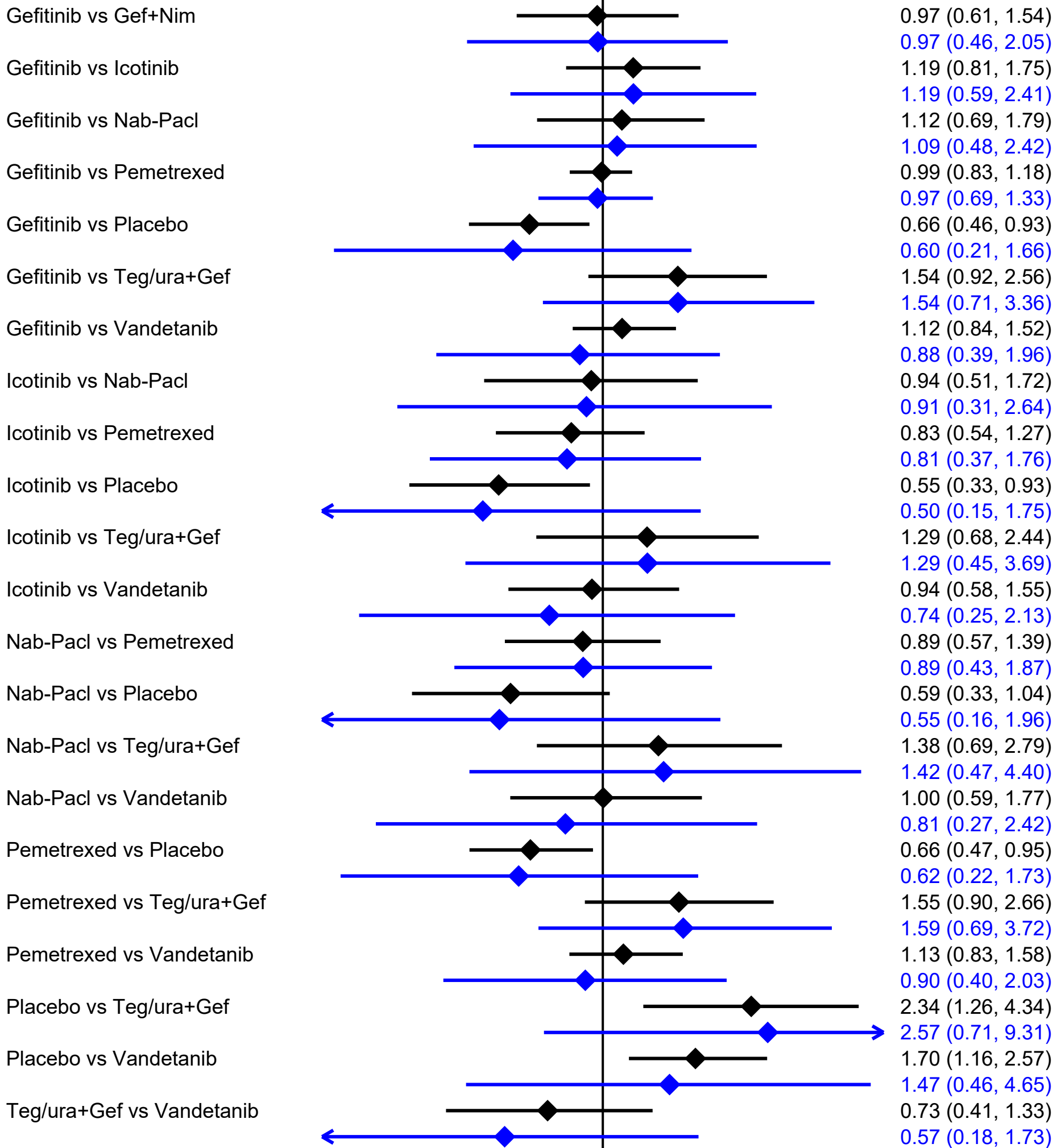


.2 .3 .5 1 2 5

Comparison

Progression Free Survival

HR (95% CrI)



SUCRA values for OS for second-line treatments assessed in squamous and nonsquamous NSCLC EGFR wild-type or unknown

Nonsquamous cell carcinoma

Treatment	SUCRA
Pembrolizumab	94.2
Atezolizumab	88.9
Nivolumab	87.6
Erlotinib+Cabozantinib	80.2
Docetaxel+Nintedanib	78.7
Docetaxel+Ramucirumab	78.7
Docetaxel+Vandetanib	72.8
Pralatrexate	67.5
Trametinib	64.5
Cabozantinib	62.9
Docetaxel	62.5
Amrubicin	61.9
Docetaxel+Aflibercept	61.5
Docetaxel+Selumetinib	60.7
Pemetrexed+Erlotinib	54.9
Pemetrexed+Vandetanib	41.1
Erlotinib+Tivantinib	39.6
Gefitinib+Tegafur-uracil	38.6
Erlotinib+Sunitinib	36.9
Dacomitinib	31.6
Vandetanib	31.3
Erlotinib	29.9
Pemetrexed+Cetuximab	28.2
Erlotinib+Bevacizumab	23.8
Pemetrexed+Nintedanib	20.8
Pemetrexed	20.6
Gefitinib	17.6
Erlotinib+Onartuzumab	07.8
Placebo	04.6

Squamous cell carcinoma

Treatment	SUCRA
Nivolumab	75.5
Atezolizumab	69.8
Pembrolizumab	65.8
Amrubicin	59.7
Afatinib	58.2
Docetaxel+Ramucirumab	57.5
Docetaxel+Erlotinib	53.5
Erlotinib+Onartuzumab	52.5
Docetaxel+Vandetanib	51.4
Erlotinib+Bevacizumab	50.5
Docetaxel	49.8
Docetaxel+Nintedanib	49.6
Erlotinib+Sunitinib	49.5
Erlotinib	45.5
Pralatrexate	43.0
Erlotinib+Figitumumab	40.6
Dacomitinib	36.7
Vandetanib	33.5
Placebo	25.7
Docetaxel+Selumetinib	24.9

SUCRA values for PFS for second-line treatments assessed in squamous and nonsquamous NSCLC EGFR wild-type or unknown

Nonsquamous cell carcinoma

Treatment	SUCRA
Erlotinib+Cabozantinib	89.8
Cabozantinib	88.7
Docetaxel+Vandetanib	74.2
Pralatrexate	71.3
Docetaxel+Ramucirumab	67.6
Docetaxel+Erlotinib	67.5
Pemetrexed+Erlotinib	63.4
Docetaxel+Aflibercept	62.6
Docetaxel+Nintedanib	60.4
Pembrolizumab	58.4
Erlotinib+Tivantinib	57.8
Gefitinib+Tegafur-uracil	54.7
Docetaxel+Selumetinib	54.3
Amrubicin	53.1
Nivolumab	52.3
Dacomitinib	51.0
Docetaxel	43.8
Erlotinib+Sunitinib	43.2
Vandetanib	40.9
Pemetrexed+Vandetanib	39.4
Pemetrexed+Nintedanib	35.2
Erlotinib+Onartuzumab	30.0
Icotinib	29.9
Trametinib	29.0
Pemetrexed+Cetuximab	25.1
Erlotinib	24.6
Pemetrexed	16.9
Gefitinib	15.3

Squamous cell carcinoma

Treatment	SUCRA
Nivolumab	79.5
Docetaxel+Vandetanib	71.4
Docetaxel+Ramucirumab	71.1
Docetaxel+Nintedanib	70.5
Amrubicin	64.6
Pembrolizumab	64.4
Docetaxel	56.3
Erlotinib+Sunitinib	44.2
Docetaxel+Selumetinib	43.6
Afatinib	42.7
Docetaxel+Erlotinib	39.9
Dacomitinib	35.5
Erlotinib	28.9
Erlotinib+Figitumumab	25.5
Vandetanib	25.4
Erlotinib+Onartuzumab	23.6

SUCRA values for OS and PFS for second-line treatments assessed in Asian population of NSCLC EGFR wild-type or unknown

OS

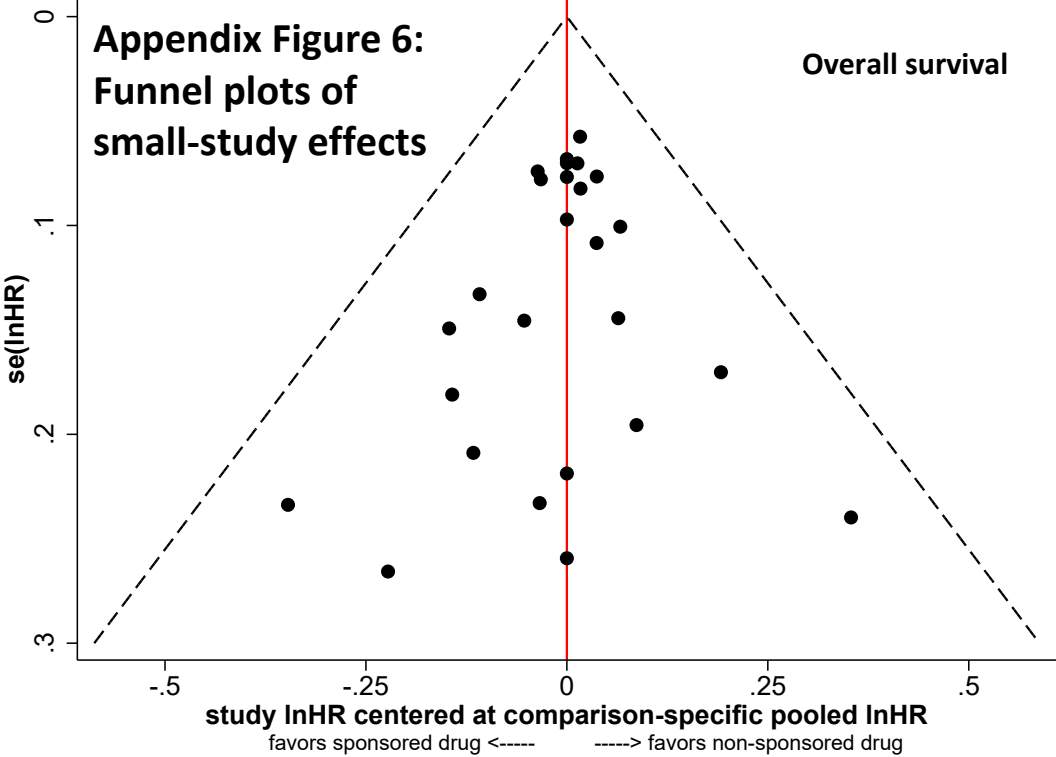
Treatment	SUCRA
Erlotinib+Onartuzumab	89.2
Erlotinib+Tivantinib	86.7
Pemetrexed+Nintedanib	86.2
Afatinib	78.4
Docetaxel+Tamoxifen	67.1
Pemetrexed	63.6
Erlotinib+Sunitinib	62.9
Docetaxel+Vandetanib	58.8
Tegafur/uracil+Gefitinib	53.3
Icotinib	50.6
Docetaxel+Ramucirumab	49.3
Gefitinib	47.4
Pemetrexed+Erlotinib	43.5
Pemetrexed+Vandetanib	43.2
Dacomitinib	32.7
Erlotinib	31.8
Gefitinib+Nimotuzumab	31.1
Docetaxel	30.9
Amrubicin	30.8
Nab-Paclitaxel	30.3
Vandetanib	28.9
Placebo	03.5

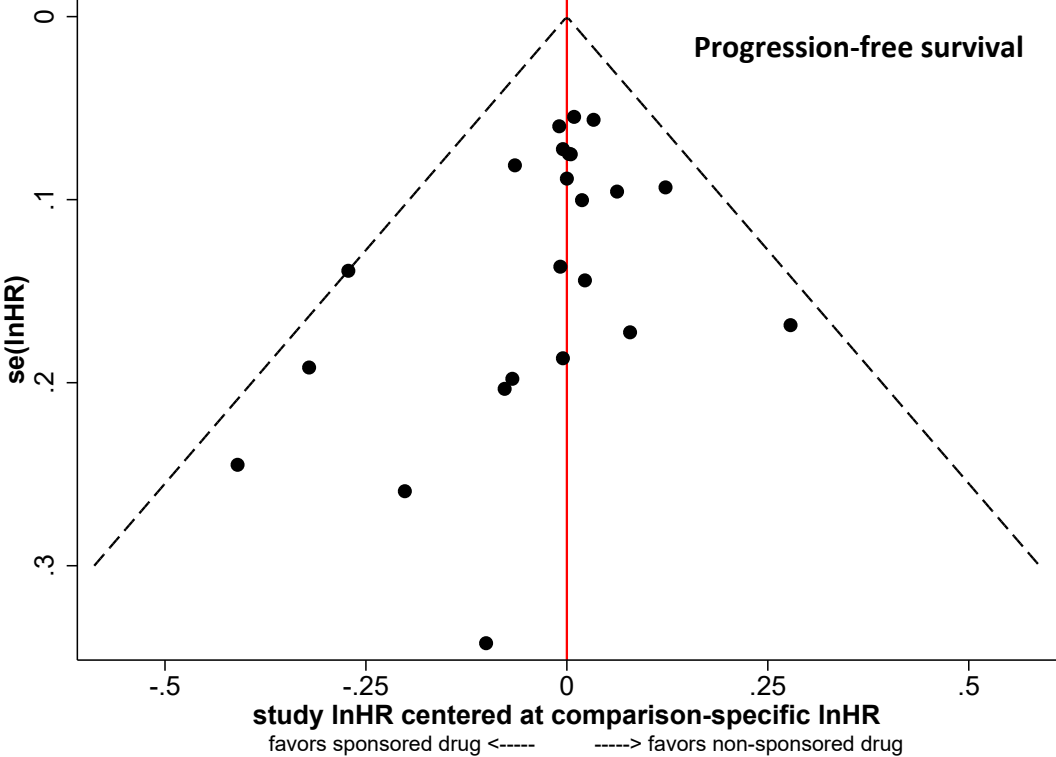
PFS

Treatment	SUCRA
Pemetrexed+Erlotinib	89.8
Afatinib	77.4
Tegafur/uracil+Gefitinib	70.7
Docetaxel+Tamoxifen	67.3
Docetaxel+Vandetanib	67.2
Dacomitinib	60.8
Erlotinib+Tivantinib	59.4
Erlotinib+Sunitinib	58.7
Icotinib	53.4
Docetaxel+Ramucirumab	52.0
Erlotinib+Onartuzumab	51.8
Pemetrexed+Vandetanib	47.0
Nab-Paclitaxel	45.9
Pemetrexed+Nintedanib	41.9
Amrubicin	40.8
Gefitinib	37.6
Gefitinib+Nimotuzumab	37.4
Docetaxel	34.8
Pemetrexed	34.2
Erlotinib	29.9
Vandetanib	29.3
Placebo	12.6

**Appendix Figure 6:
Funnel plots of
small-study effects**

Overall survival





Appendix Figure 7: Overall assessment of bias

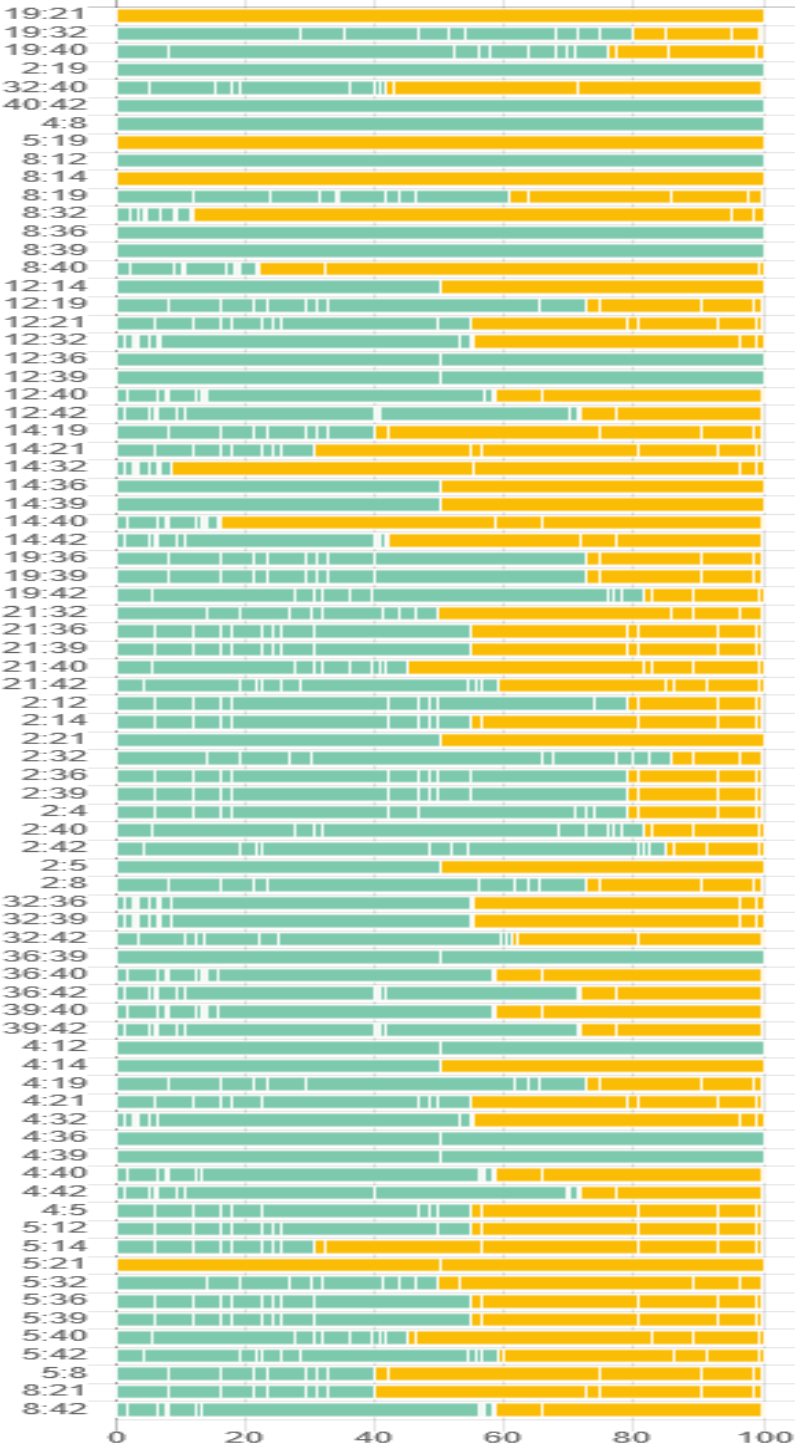
We evaluated the credibility of the evidence from network meta-analysis based on the approach suggested by *Salanti G et al. Evaluating the quality of evidence from a network meta-analysis. PloS One. 2014;9(7): e99682* that extends the GRADE system into network meta-analysis.

To evaluate study limitations we used the online tool CiNeMA available from <http://ec2-52-28-232-32.eu-central-1.compute.amazonaws.com:8004/ocpu/library/contribution/www/> that combines the contribution of each direct comparison to the estimation in the network (see Chaimani et al. Graphical tools for network meta-analysis in Stata. Plos One 2013 and Krahn et al. A graphical tool for locating inconsistency in network meta-analyses. BMC Med Res Methodol 2013) with the risk of bias assessments for each direct comparison and produces a bar-graph. The bar-graph shows for the network estimate of every pairwise comparison how much information comes from low (green), moderate (yellow) or high (red) risk of bias trials.

Below we present our GRADE evaluation for the two primary outcomes and all comparisons presented in our league tables.

GRADE evaluation for Overall survival

Study limitations



Treatment codes:

8=Docetaxel, 40=Pemetrexed, 19=Erlotinib, 32=Gefitinib, 36=Nivolumab, 39=Pembrolizumab, 4=Atezolizumab, 12=Docetaxel+Nintedanib, 14=Docetaxel+Ramucirumab, 2=Afatinib, 5=Cabozantinib, 21=Erlotinib+Cabozantinib, 42=Pemetrexed+Erlotinib

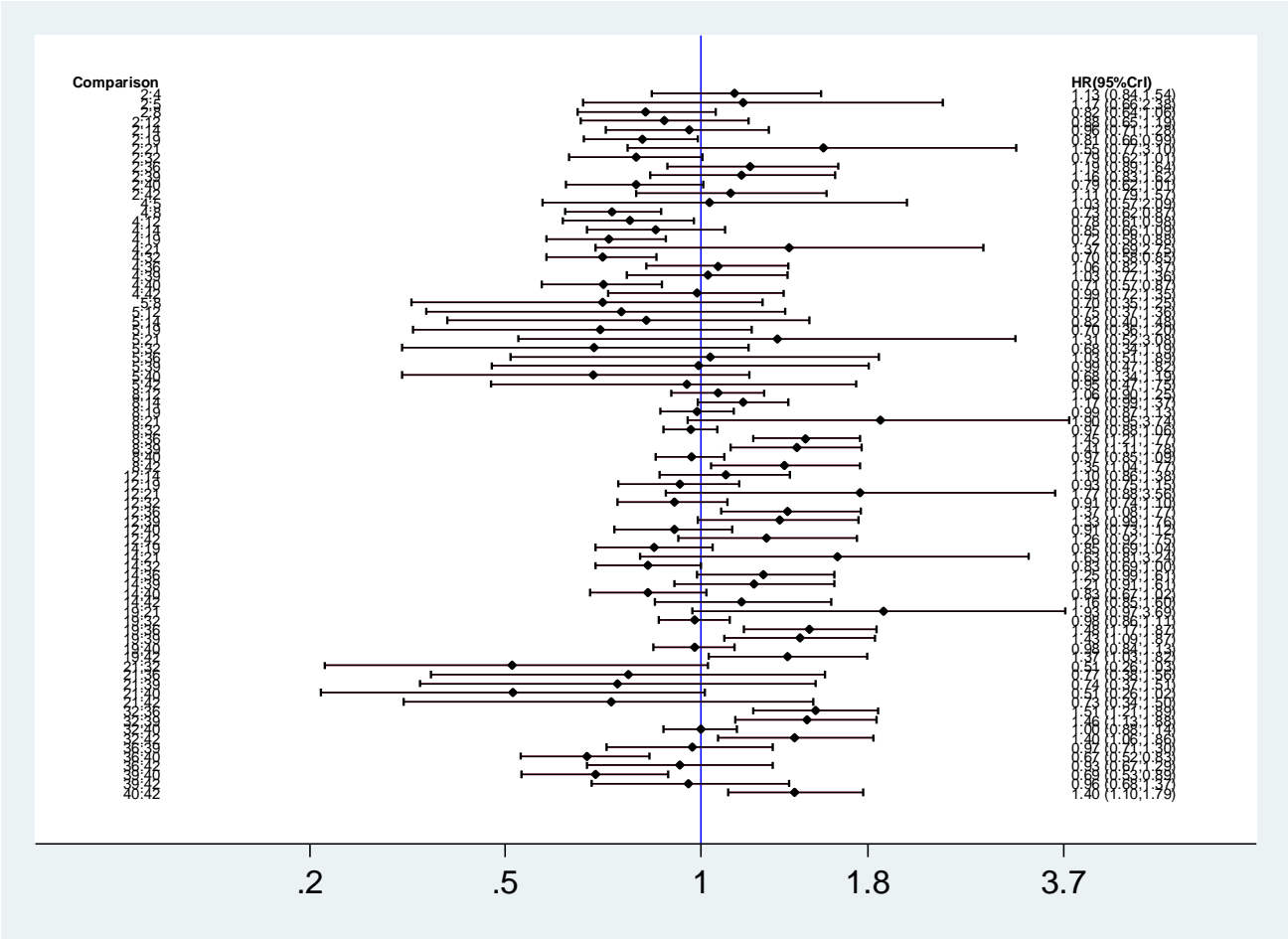
We have serious concerns for all comparisons that at least 50% of the evidence is at moderate risk of bias

Indirectness

Given the small number of trials for most comparisons the transitivity assumption could not be evaluated properly. Therefore, we have serious concerns about intransitivity for all pairwise comparisons.

Imprecision

We downgraded all non-significant HRs for imprecision.



Heterogeneity

No empirical distributions for heterogeneity have been suggested for survival outcomes and therefore we rely on the prediction intervals. Given the very small value of the estimated heterogeneity ($\tau=0.04$) the prediction intervals were almost identical with the credible intervals and therefore are not presented in the above graph.

Inconsistency

Appendix Figure 4

We have serious concerns for comparisons included in inconsistent loops.

Publication bias

Based on the comprehensive search that identified also unpublished trials we do not have serious concerns about the presence of publication bias. Appendix Figure 6 also does not imply the presence of small-study effects.

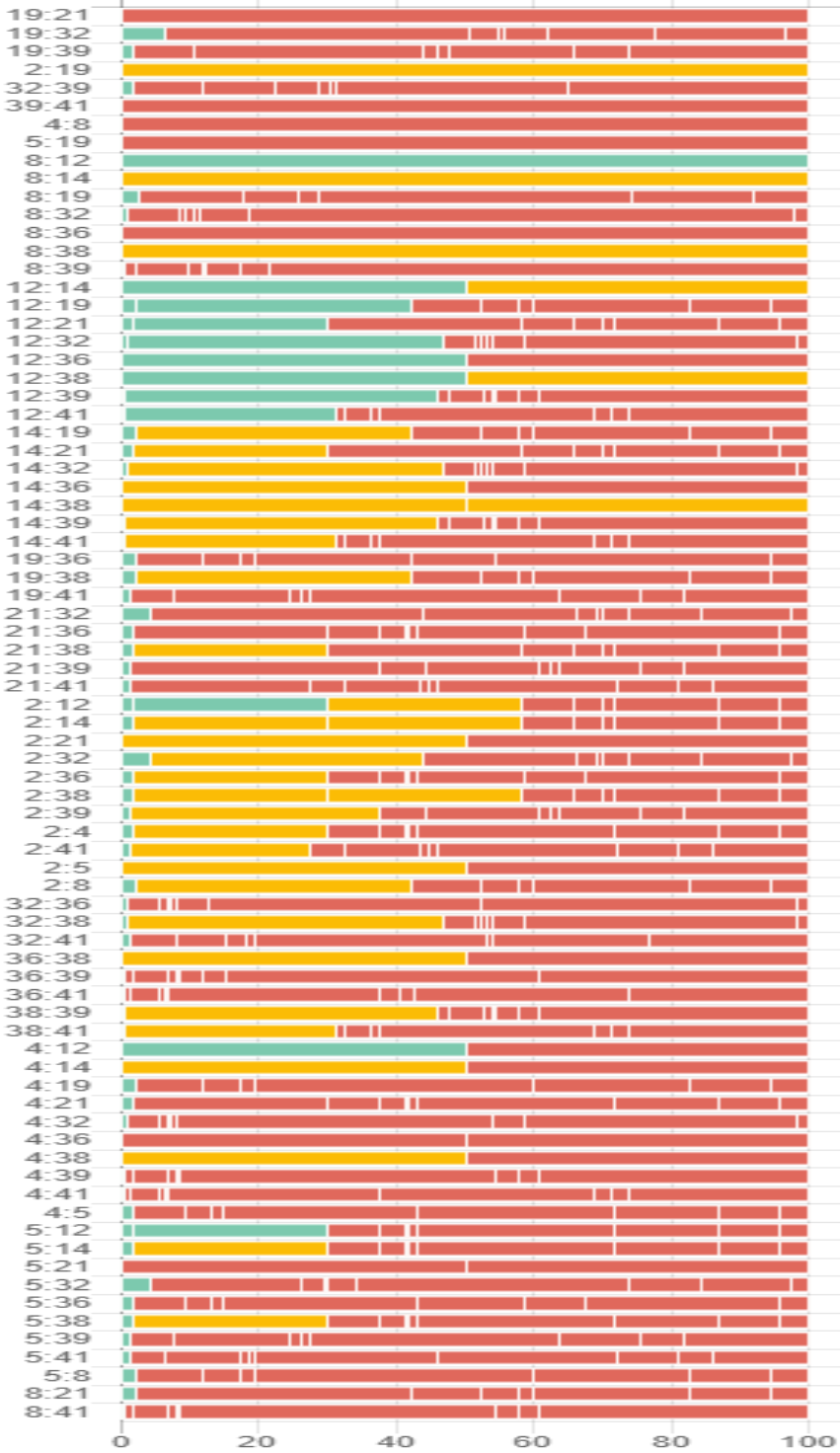
Final assessments

Comparison	Study Limitations	Indirectness	Inconsistency	Imprecision	Publications bias	GRADE	Downgraded for
2:4	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:5	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:8	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:12	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:14	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:19	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness
2:21	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:32	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:36	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:39	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:40	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
2:42	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
4:5	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
4:8	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness
4:12	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
4:14	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
4:19	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness
4:21	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
4:32	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness
4:36	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
4:39	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
4:40	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness
4:42	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
5:8	Serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Low	Study limitations, Indirectness, Imprecision
5:12	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision

32:42	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness
36:39	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
36:40	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness
36:42	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
39:40	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness
39:42	No serious concerns	Serious concerns	No serious concerns	Serious concerns	No serious concerns	Moderate	Indirectness, Imprecision
40:42	No serious concerns	Serious concerns	No serious concerns	No serious concerns	No serious concerns	Moderate	Indirectness

GRADE evaluation for Progression-free survival

Study limitations



Treatment codes:

8=Docetaxel, 39=Pemetrexed, 19=Erlotinib, 32=Gefitinib, 36=Nivolumab, 38=Pembrolizumab,
 4=Atezolizumab, 12=Docetaxel+Nintedanib, 14=Docetaxel+Ramucirumab, 2=Afatinib,
 5=Cabozantinib, 21=Erlotinib+Cabozantinib, 41=Pemetrexed+Erlotinib

We have serious concerns for all comparisons that at least 50% of the evidence is at moderate risk of bias and very serious concerns when at least 50% of the evidence is at high risk of bias.

Indirectness

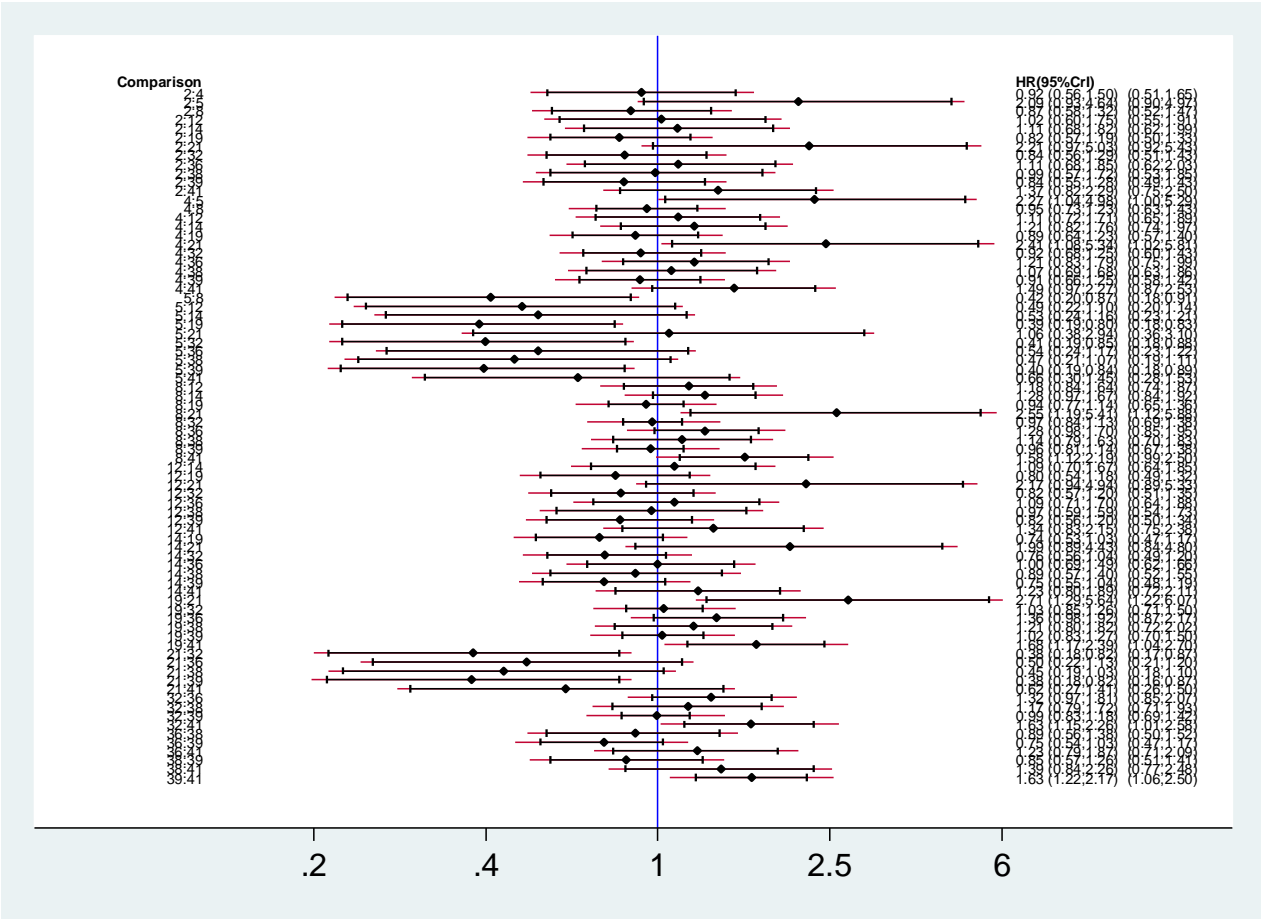
Given the small number of trials for most comparisons the transitivity assumption could not be evaluated properly. Therefore, we have serious concerns about intransitivity for all pairwise comparisons.

Imprecision

We downgraded all non-significant HRs for imprecision.

Heterogeneity

No empirical distributions for heterogeneity have been suggested for survival outcomes and therefore we rely on the prediction intervals. We downgraded comparisons that were statistically significant but the prediction interval crossed the line of no effect.



Inconsistency

Appendix Figure 4

We have serious concerns for comparisons included in inconsistent loops.

Publication bias

Appendix Figure 6 implies the presence of small-study effects which might be due to selective reporting bias and therefore we have serious concerns for all comparisons.

Final assessments

Comparison	Study Limitations	Indirectness	Inconsistency	Imprecision	Publication bias	GRADE	Downgraded for
2:4	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
2:5	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
2:8	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
2:12	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
2:14	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
2:19	Serious concerns	Serious concerns	No serious concerns	No serious concerns	Serious concerns	Low	Study limitations, Indirectness, Publication bias
2:21	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
2:32	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
2:36	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
2:38	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
2:39	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
2:41	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
4:5	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
4:8	Very serious concerns	Serious concerns	No serious concerns	No serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Publication bias

5:38	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
5:39	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
5:41	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
8:12	No serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Indirectness, Imprecision, Publication bias
8:14	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
8:19	Very serious concerns	Serious concerns	Serious concerns (incoherence)	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Inconsistency, Publication bias
8:21	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
8:32	Very serious concerns	Serious concerns	Serious concerns (heterogeneity)	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Inconsistency, Publication bias
8:36	Very serious concerns	Serious concerns	No serious concerns	No serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Publication bias
8:38	Serious concerns	Serious concerns	No serious concerns	No serious concerns	Serious concerns	Low	Study limitations, Indirectness, Publication bias
8:39	Very serious concerns	Serious concerns	Serious concerns (incoherence)	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Inconsistency, Publication bias
8:41	Very serious concerns	Serious concerns	No serious concerns	No serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Publication bias
12:14	No serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Indirectness, Imprecision, Publication bias
12:19	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
12:21	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
12:32	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
12:36	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness,

							Imprecision, Publication bias
12:38	No serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Indirectness, Imprecision, Publication bias
12:39	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
12:41	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
14:19	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
14:21	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
14:32	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
14:36	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
14:38	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
14:39	Serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Low	Study limitations, Indirectness, Imprecision, Publication bias
14:41	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
19:21	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias
19:32	Very serious concerns	Serious concerns	Serious concerns (incoherence)	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Inconsistency, Imprecision, Publication bias
19:36	Very serious concerns	Serious concerns	No serious concerns	No serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Publication bias
19:38	Serious concerns	Serious concerns	No serious concerns	No serious concerns	Serious concerns	Low	Study limitations, Indirectness, Publication bias
19:39	Very serious concerns	Serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low	Study limitations (2 levels), Indirectness, Imprecision, Publication bias

