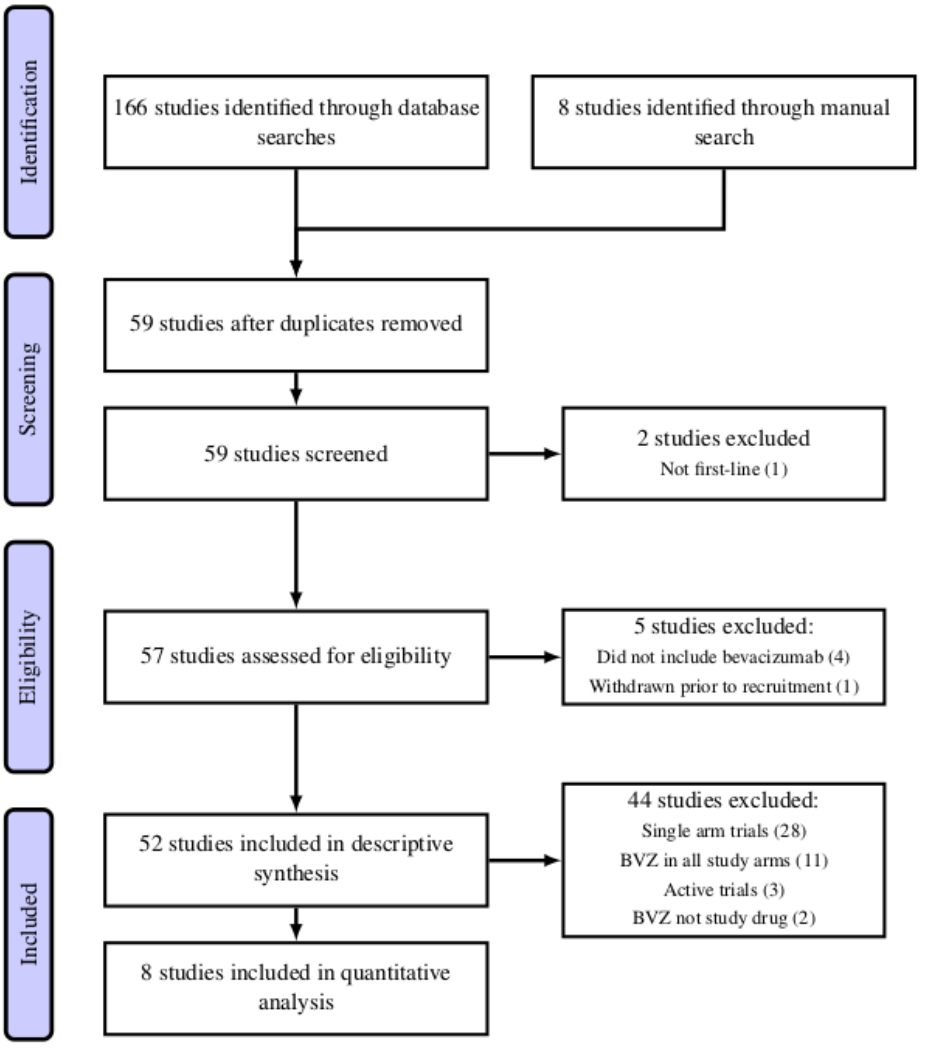
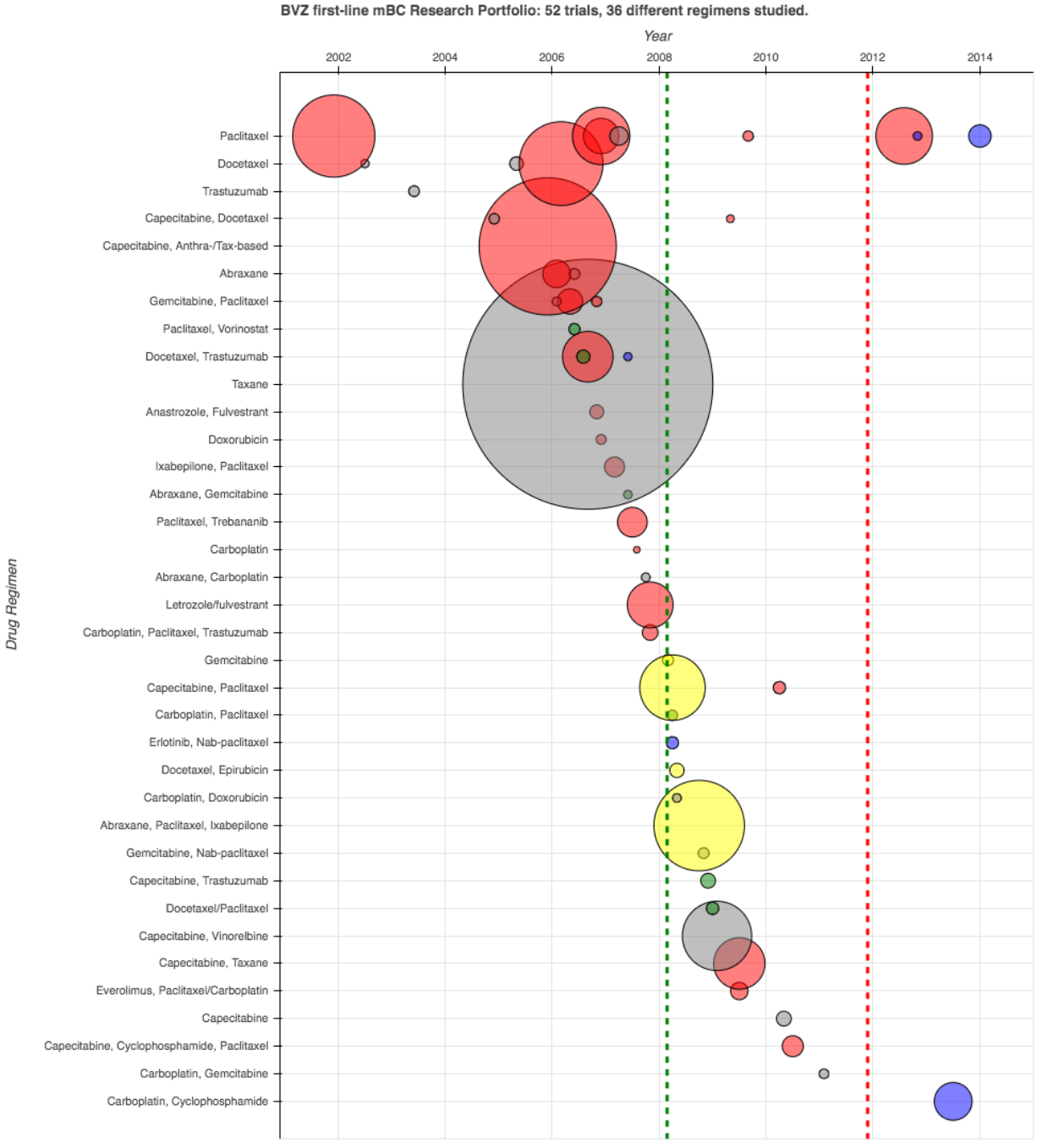
Supplementary Materials

Supplementary Figure 1. PRISMA Flow Diagram



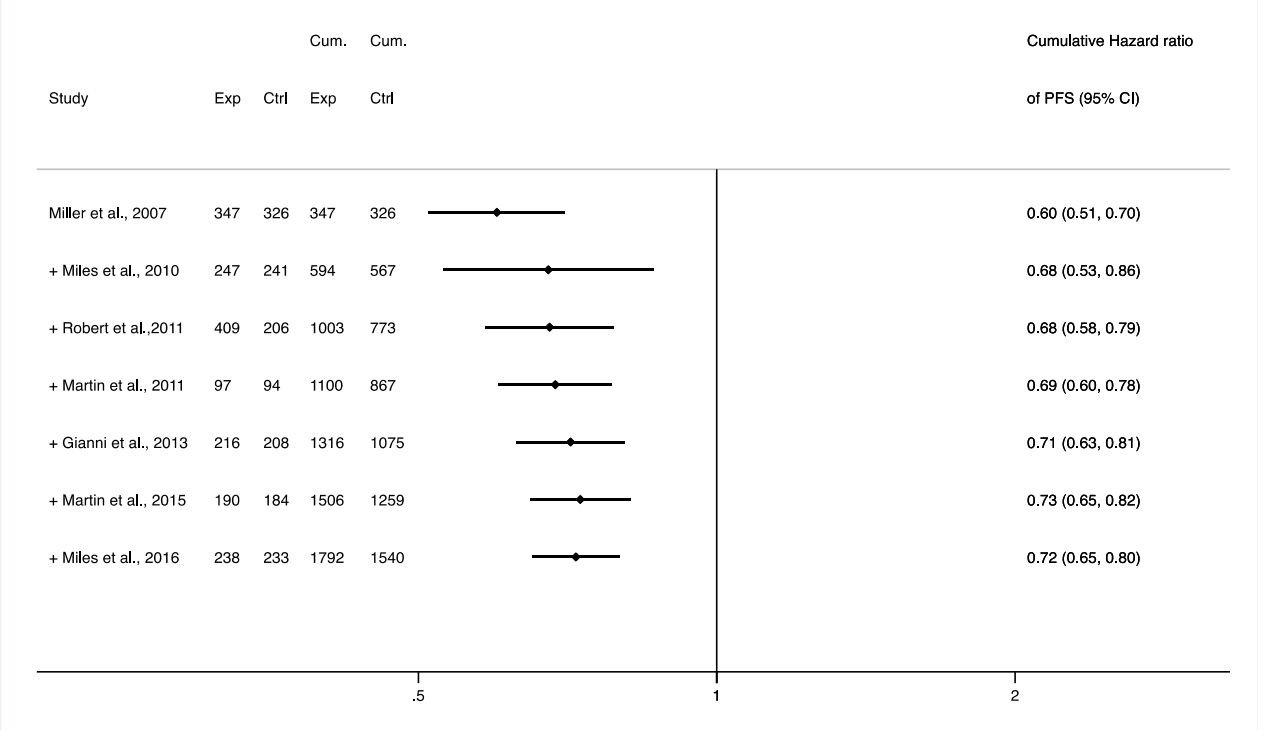
BVZ = bevacizumab

Supplementary Figure 2. Accumulating Evidence and Research Organization (AERO) Graph



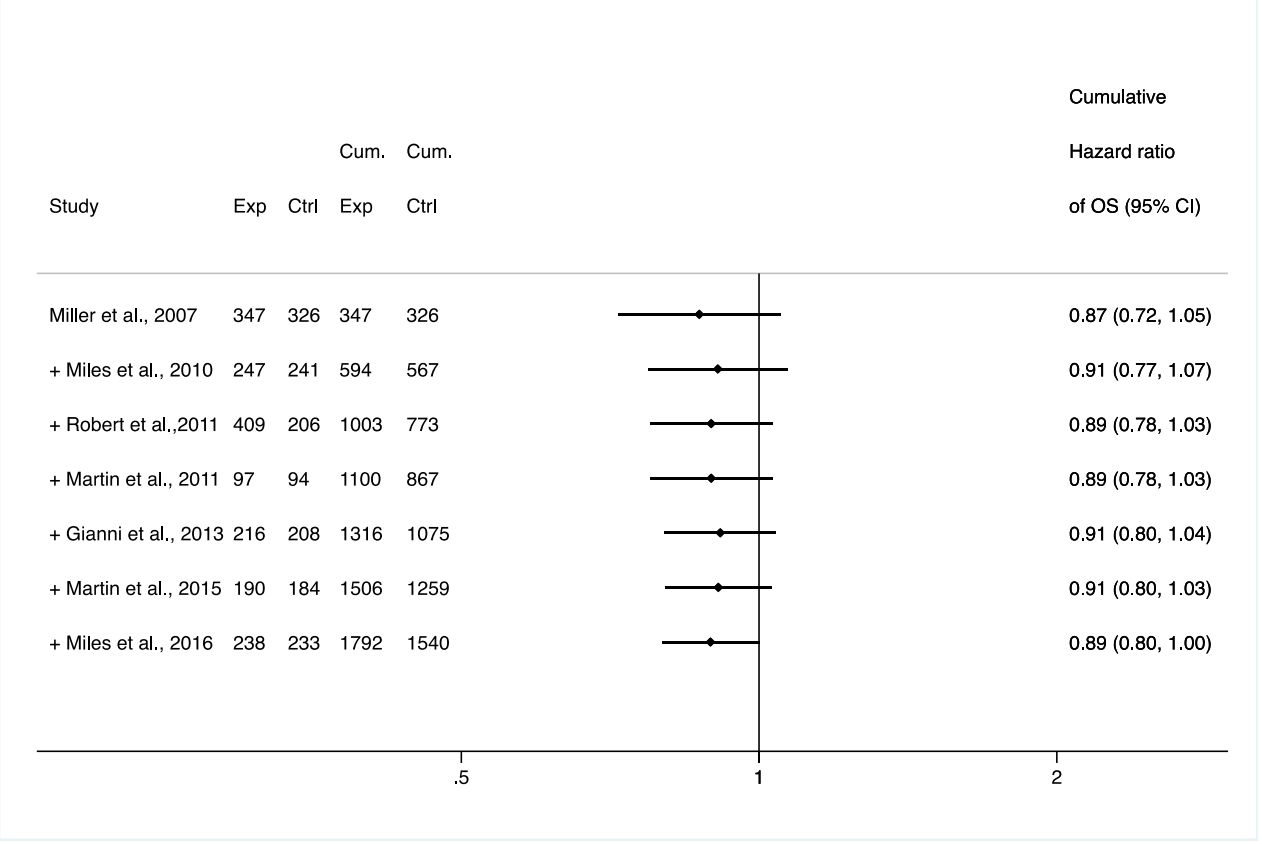
Each node corresponds to a single clinical trial. Nodes are arranged by time of study start date (as reported on ClinicalTrials.gov) along the x-axis and drug regimen tested along the y-axis. No studies evaluated bevacizumab as monotherapy, therefore all regimens listed are additions to bevacizumab. Node size corresponds to the trial sample size. Node color represents the trial outcome, either with respect to overall survival (OS) benefit or its primary endpoint (when a hazard ratio for OS is not reported). Green nodes are favorable to bevacizumab, red nodes are unfavorable or were terminated, and yellow nodes mixed. Studies that included bevacizumab in all study arms are also considered mixed and yellow. Blue nodes are active trials (at the time of this analysis). Gray nodes are completed according to ClinicalTrials.gov, but the results are unknown. The dashed lines mark the FDA's accelerated approval period for bevacizumab from February 2008 (green) to November 2011 (red). BVZ = bevacizumab; mBC = metastatic breast cancer.

Supplementary Figure 3. Forest plot of cumulative meta-analysis on the effect of bevacizumab on the hazard ratio of progression-free survival over time with unpublished trial removed



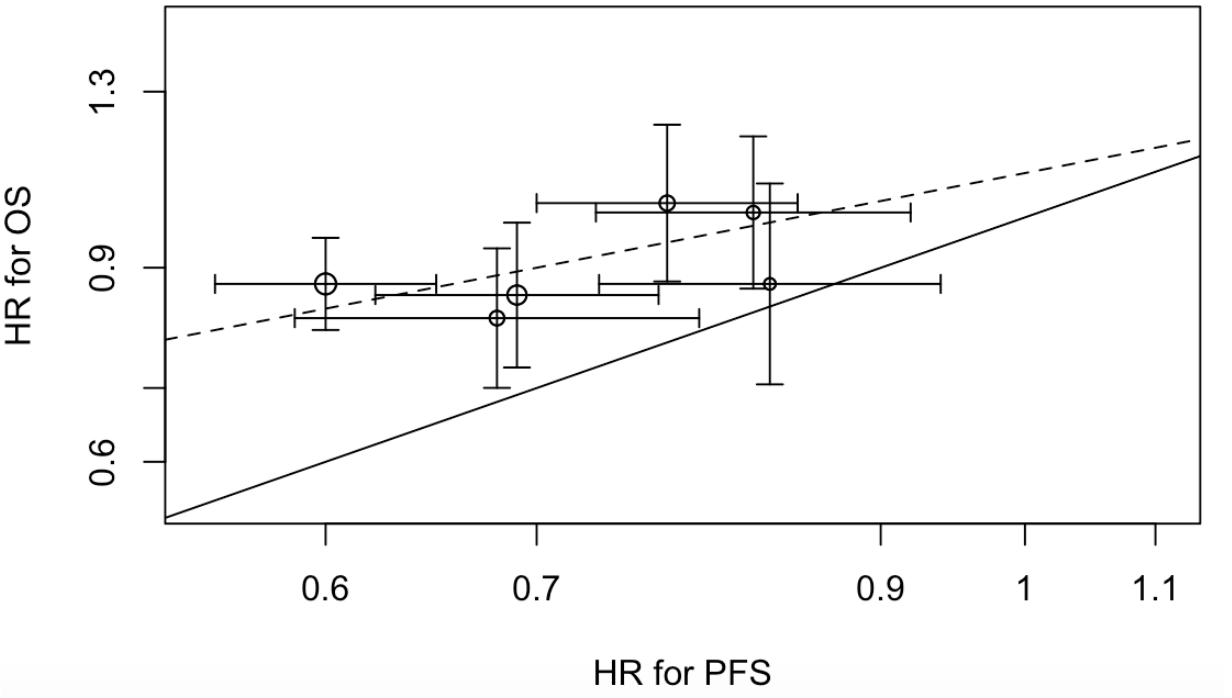
The graph shows a cumulative meta-analysis performed by adding individual trials chronologically and summarizing the point estimate as each new trial is added. The symbol plus before each trial indicates that the point estimate (ie, hazard ratio) of that trial is pooled with the previous summary estimate. The final result is a trial-level cumulative estimate over time and corresponding 95% confidence intervals. The diamonds represent the cumulative point estimates while the horizontal segments represent the 95% confidence intervals.
Exp = number of participants in the experimental group; Ctrl = number of participants in the control group; Cum. Exp = cumulative number of participants in the experimental group; Cum. Ctrl = cumulative number of participants in the control group; PFS = Progression Free Survival.

Supplementary Figure 4. Forest plot of cumulative meta-analysis on the effect of bevacizumab on the hazard ratio of overall survival over time with unpublished trial removed



The graph shows a cumulative meta-analysis performed by adding individual trials chronologically and summarizing the point estimate as each new trial is added. The symbol plus before each trial indicates that the point estimate (ie, hazard ratio) of that trial is pooled with the previous summary estimate. The final result is a trial-level cumulative estimate over time and corresponding 95% confidence intervals.The diamonds represent the cumulative point estimates while the horizontal segments represent the 95% confidence intervals.
Exp = number of participants in the experimental group; Ctrl = number of participants in the control group; Cum. Exp = cumulative number of participants in the experimental group; Cum. Ctrl = cumulative number of participants in the control group; OS = Overall Survival.

Supplementary Figure 5. Association of trial-level PFS effects and OS effects with unpublished trial removed



The graph shows the association of trial-level progression-free survival (PFS) and overall survival (OS) effects expressed as hazard ratios. The solid line represents equality between OS and PFS effects. The dashed line represents the estimated slope of the linear association from the random effects model. Areas of circles are proportional to trial sample sizes and horizontal and vertical line segments represent 95% confidence intervals for the trial-level hazard ratios.

Supplementary Table 1.Parameters for nonlinear mixed-effects model for the association of log HR for OS and log HR for PFS, excluding unpublished trials

Parameter*	Estimate	Standard error
α	0.029	0.288
β	0.398	0.792
μ	-0.332	0.055
g	0	0.001
σ^2	0.007	0.010

***** α = intercept of the linear relationship between the log HR for OS and log HR for PFS (when the HR for PFS is 1.0, the estimated HR for OS is $e^{0.045}$ = 1.05; β = coefficient of the linear relationship between the log HR for OS and log HR for PFS; μ = average log HR for PFS across trials; corresponding to a HR of $e^{-0.332}$=0.72; g = variance of log HR for OS across trials that is not explained by PFS. σ^2= variance of log HR for PFS across trials;

References

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