SUPPLEMENT

Figure S1. Trial selection and flow diagram.

Figure S2. Trends in trials accounting for post-progression therapy (PPT) confounding over time.

Table S1. Details of trials with a primary endpoint of overall survival that permitted crossover from the control arm to the experimental arm at the time of progression.

Table S2. Characteristics for trials included in a sensitivity analysis, where trials testing second-line or later therapy were excluded.

Table S3. Characteristics for trials included in a sensitivity analysis, where trials not powered for overall survival as the primary or co-primary endpoint were excluded.

Sherry AD, *et al. BMJ Oncology* 2024; 3:e000322. doi: 10.1136/bmjonc-2024-000322

Figure S1. Trial selection and flow diagram.

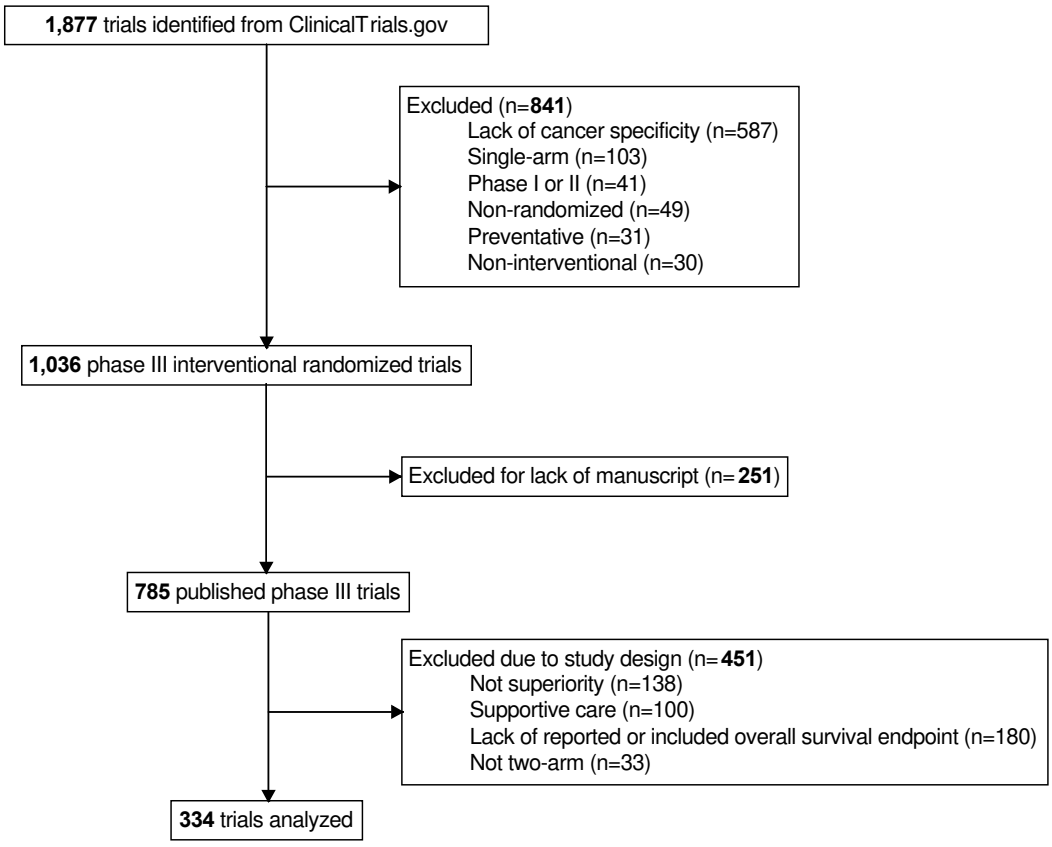

Figure S2. Trends in trials accounting for post-progression therapy (PPT) confounding over time. The linear regression over time is shown with the shaded regions representing the 95% confidence interval of the slope (m). Because of the small number of trials analyzed in this dataset published in the years prior to 2007 (N=6) or after 2019 (N=1), data prior to 2007 or after 2019 were excluded from the graph.

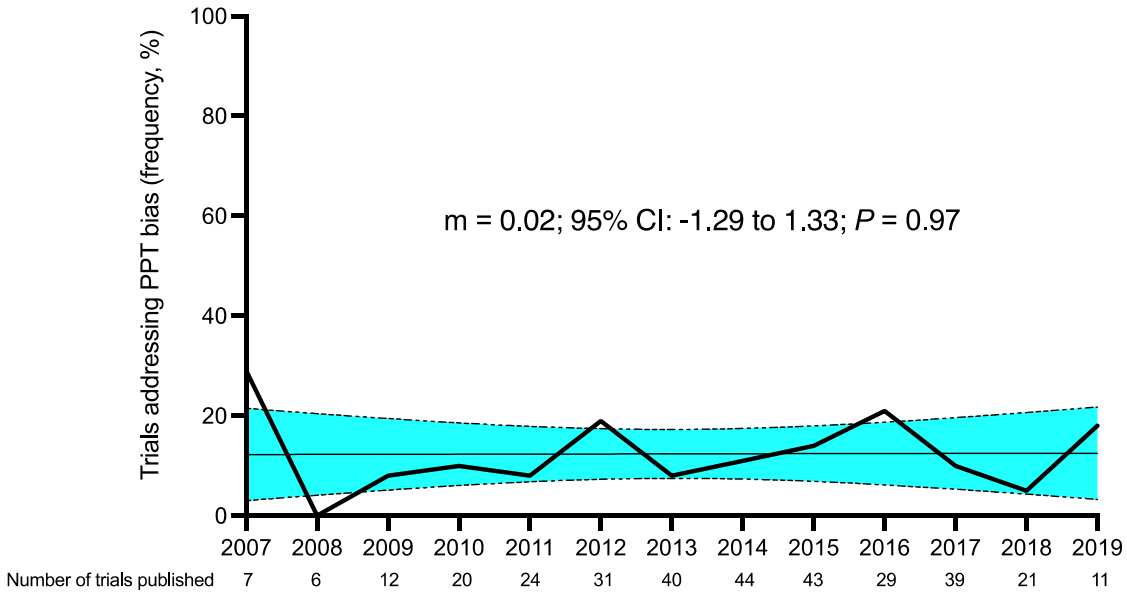

Table S1. Details of phase III trials with a primary endpoint of overall survival that allowed crossover from the control arm to the experimental arm at the time of progression.

Abbreviation: NCT, ClinicalTrials.gov identifier.

NCT	Control arm
NCT00309985	Active therapy
NCT00673049	Active therapy
NCT00281658	Active therapy plus placebo
NCT00073307	Placebo
NCT00088907	Placebo
NCT01328951	Placebo
NCT01774344	Placebo

Table S2. Characteristics for 187 trials included in a sensitivity analysis, where trials evaluating localized or first-line settings were included.

Characteristic	N, (%)
Disease Stage	
Solid M0	59 (32%)
Solid M1	103 (55%)
Hematologic	25 (13%)
Disease Site	
Breast	32 (17%)
Gastrointestinal	35 (19%)
Genitourinary	17 (9%)
Hematologic	25 (13%)
Thoracic	46 (25%)
Other[a]	32 (17%)
Treatment Type	
Systemic Therapy	175 (94%)
Local Therapy	12 (6%)
Cooperative Group Study	
Yes	75 (40%)
No	112 (60%)
Industry-Sponsored	
Yes	142 (76%)
No	45 (24%)
Enrollment, median (IQR)	630 (362 to 983)
Crossover (allowed or required)	
Yes	24 (13%)
No	163 (87%)
Blinding	
Double-Blind	57 (30%)
Open-Label	130 (70%)
Overall Survival Primary or Co-Primary Endpoint	
Yes	90 (48%)
No	97 (52%)
Surrogate Survival and Overall Survival Discordance	
Yes	48 (26%)
No	139 (74%)

Abbreviations: M0 (non-metastatic); M1 (metastatic); IQR (interquartile range).

[a]Other disease sites: central nervous system, gynecologic, head and neck, pediatric, and skin.

Table S3. Characteristics for 168 trials included in a sensitivity analysis, where trials not powered for overall survival as the primary or co-primary endpoint were excluded.

Characteristic	N, (%)
Disease Stage	
Solid M0	27 (16%)
Solid M1	124 (74%)
Hematologic	17 (10%)
Disease Site	
Breast	8 (5%)
Gastrointestinal	41 (24%)
Genitourinary	32 (19%)
Hematologic	17 (10%)
Thoracic	43 (26%)
Other[a]	27 (16%)
Treatment Type	
Systemic Therapy	159 (95%)
Local Therapy	9 (5%)
Cooperative Group Study	
Yes	46 (27%)
No	122 (73%)
Industry-Sponsored	
Yes	139 (83%)
No	29 (17%)
Enrollment, median (IQR)	638 (420 to 908)
Crossover (allowed or required)	
Yes	14 (8%)
No	154 (92%)
Blinding	
Double-Blind	75 (45%)
Open-Label	93 (55%)
Overall Survival Primary or Co-Primary Endpoint	
Yes	168 (100%)
No	0 (0%)
Surrogate Survival and Overall Survival Discordance	
Yes	52 (31%)
No	116 (69%)

Abbreviations: M0 (non-metastatic); M1 (metastatic); IQR (interquartile range).

[a]Other disease sites: central nervous system, endocrine, gynecologic, head and neck, sarcoma, and skin.