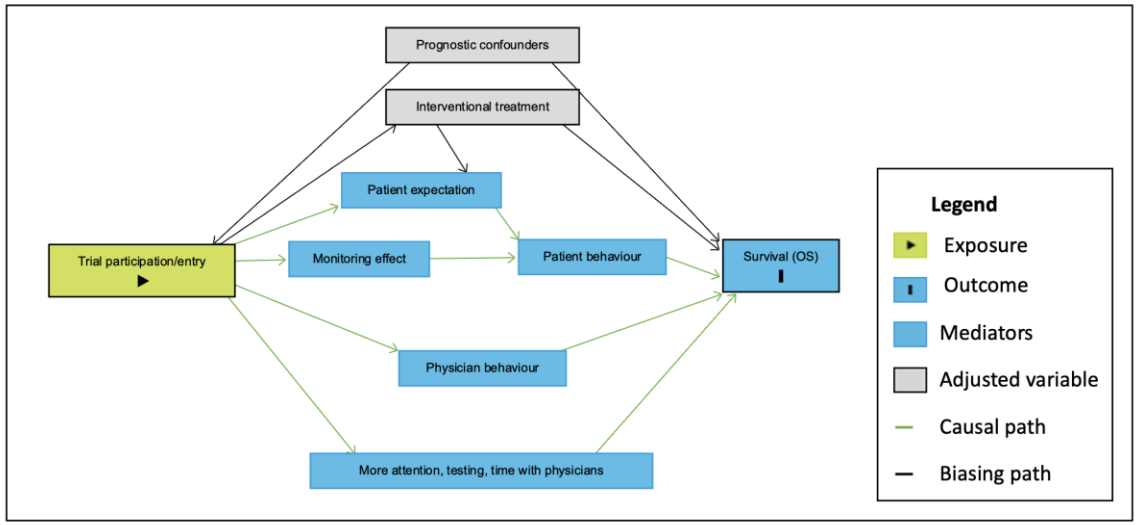
SUPPLEMENTARY MATERIALS
TABLE OF CONTENTS

30 imputed missing studies (white circles) using the trim-and-fill method. The original pooled hazard ratio for overall survival is 0.76 (95% CI, 0.69-0.82). The pooled hazard ratio for overall survival with imputed missing studies is 0.94 (95% CI, 0.86-1.03).	

4
5

(1) DEFINING THE "TRIAL EFFECT"

While the magnitude of the treatment effect depends on the efficacy of the experimental drug (and determining this is the focus of all drug trials), it is not clear what factors might contribute to the "participation effect." Based on a review of the literature and our own discussions, we assumed several mechanisms might cause participation effects (eFigure 1). First, there are protocol effects, which can be represented by the "monitoring effect" node (i.e. extra monitoring of adverse effects in trials for patients leads to better outcomes) and the "physician behaviour" node (i.e. physicians are more attentive to patients on trials), which are the differences in delivery of interventions because of trial protocol adherence (e.g. improved physician adherence to guidelines and standards of care). Second, there are placebo/nocebo effects, represented by the "patient expectation" and "patient behaviour" nodes. These include psychological benefits/harms to patients from awareness of trial participation, possible changes in mental outlook, better adherence to medication on trial, better self-care on trial, and other health behaviours. Third, there are care effects ("more attention, testing, time with physicians"), which are incidental differences in care of groups that may be related to increased access to healthcare services, including clinicians and nursing staff, better screening, and access to diagnostic services. eTable 1 defines the trial effect and the participation effect and separates it into different components.



eFigure 1. Directed Acyclic Graph (DAG) showing our definition of the participation effect (based on blue mediators) that excludes the experimental treatment or prognostic confounders.[1]

eTable 1. Term definitions to describe the different reasons why trial participant and routine care patient outcomes may differ. These could be attributed to a participation effect, trial effect, or observed differences in general.

Term	Definition	Components
Participation effect	Benefit (indirect/collateral) from trial participation due to differences in outcomes that are unrelated to receiving an investigational drug, unrelated to confounding differences between groups, and unrelated to differences in measurement. The effect can include the protocol effect, the placebo effect, the care effect, and the Hawthorne effect.	**Protocol effect:** differences in delivery of interventions because of trial protocol adherence (related to mediator—*physician compliance*)
		Placebo effect: psychological benefits for patients from awareness of trial participation (related to mediators—*patient expectation* and *patient compliance*)
		Care effect: incidental differences in care of trial and routine care groups (related to mediator—*more attention, testing, time with physicians*)
		Hawthorne effect: changes in patient or clinical behaviour because patients know they are being observed in a trial (related to mediators—*monitoring effect, patient expectation,* and *patient compliance*). Patient compliance includes better self-care, protocol compliance, and overall improved behaviours.
Trial effect	Benefit from participating in drug trials because of a) more time with physicians or medical testing and attention (i.e. participation effect) and b) access to experimental treatments (i.e. treatment effect).	**Participation effect:** defined above
		Treatment effect: benefit resulting from access to experimental treatments, which could influence patient expectation (mediator) as well as overall survival time (outcome).
Observed differences	Overall differences in outcomes between trial participants and routine care patients. Differences can be attributed to: a) access to experimental treatments (i.e. treatment effect), b) more time with physicians or medical testing and attention	**Trial effect (i.e. participation effect and treatment effect):** defined above

	(i.e. participant effect), c) confounding of baseline characteristics (e.g. sampling bias where recruited trial participants are healthier compared to routine care patient populations), and d) differences in outcome measurement (e.g. differences in tumour assessment frequencies or patient reporting practices).[2]	**Confounding:** confounding or sampling biases (e.g. recruited trial participants are healthier compared to routine care patients) result from differences in the distribution of important prognostic factors between the trial participants and the control groups, often because of strict trial eligibility criteria or access to clinical trial sites
		• Differences in outcome measurement (d)

Beyond the trial effects, differences between trial participants and routine care patients could be artifactual, the result of confounding or sampling biases (e.g. recruited trial participants are healthier compared to routine care patients) and measurement errors that inevitably bedevil observational research. Confounding results from differences in the distribution of important prognostic factors between the trial participants and the control groups, often because of strict trial eligibility criteria or access to clinical trial sites.

eTable 2. Prognostic confounders relevant to observing trial effects with definitions and examples.

Prognostic confounder category	Definition	Examples
Demographic factors	Characteristics relevant to patients.	• Age, sex, race/ethnicity • For example, an older patient may be less likely to be eligible for a trial and their age would also impact their overall survival time.
Pre-existing illnesses	Measures or characteristics that indicate multiple diseases.	• Comorbidities • For example, a patient with severe cardiovascular disease may not be eligible to participate in trials and the presence of more diseases would also impact their overall survival time.
Cancer-specific variables	Characteristics related to a patient's cancer that can affect both their trial eligibility and survival.	• Performance status, histology, stage • For example, a patient's cancer stage impacts both their trial eligibility and their overall survival.
Pre-trial treatment factors	Variables that relate to previously used treatment regimens.	• Adjuvant therapies, surgical status • For example, whether a patient previously had surgery to remove a tumour may impact both trial eligibility and overall survival time.

Measurement errors include the Hawthorne effect (represented by “monitoring effect”, “patient expectation”, and “patient behaviour” nodes in eFigure 1), which are changes in patient or clinician behaviours in response to being observed (e.g. trial participants might be motivated to please those who monitor them). However, since we are focused on overall survival, measurement errors are less applicable as they would be for progression-free survival or quality of life outcomes. We set out to understand how trial participation may influence outcomes like quality of life, but studies did not measure these outcomes, so we decided to focus on differences in overall survival time because it is the outcome most found in the reviewed literature and because it is less susceptible to measurement errors.

References

1. Textor J, Hardt J, Knüppel S. DAGitty: A Graphical Tool for Analyzing Causal Diagrams. *Epidemiology*. 2011;22(5):745. doi:10.1097/EDE.0b013e318225c2be

2. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *The Lancet*. 2004;363(9405):263-270. doi:10.1016/S0140-6736(03)15383-4

52 **(2) SEARCH STRATEGY AND SCREENING INFORMATION**

eTable 3. Search strategy for Embase and PubMed databases.

Database	Search Strategy
Embase	"trial effect*".tw **OR** (((neoplasm.sh OR neoplastic.tw OR carcinoma.tw OR tumo?r*.tw OR cancer*.tw OR oncolog*.tw) **AND** ("clinical trials".sh OR randomized.tw OR randomised.tw OR nonrandomized.tw OR nonrandomised.tw OR controlled.tw)) **AND** (cohort.tw OR case-control.tw OR "patient registry".tw OR quasiexperiment*.tw OR quasi-experiment*.tw OR "natural experiment*".tw OR matching.tw OR "historical control*".tw OR "wait list control".tw OR "waitlist control".tw OR "retrospective cohort*".tw OR "three arm".tw) **AND** ("trial participa*".tw OR nonparticipa*.tw OR non-participa*.tw OR non-trial.tw OR nontrial.tw OR "not enrolled".tw OR "non enrol*".tw OR "enrol*".tw OR "non-treatment*".tw OR "standard care".tw OR "usual care".tw OR off-protocol.tw OR "participation bias".tw OR hawthorne.tw OR "care effect*".tw OR "enrollment effect".tw OR "trial benefit*".tw OR "inclusion benefit*".tw))
PubMed	“trial effect*”[tw] **OR** (((“neoplasms”[mesh] OR neoplastic[tw] OR carcinoma[tw] OR tumour*[tw] OR tumor*[tw] OR cancer*[tw] OR oncolog*[tw]) **AND** (“clinical trials as topic”[mesh] OR randomized[tw] OR randomised[tw] OR nonrandomized[tw] OR nonrandomised[tw] OR controlled[tw])) **AND** (cohort[tw] OR case-control[tw] OR “patient registry”[tw] OR quasiexperiment*[tw] OR quasi-experiment*[tw] OR “natural experiment*”[tw] OR matched[tw] OR matching[tw] OR “historical control*”[tw]

	OR “wait list control”[tw] OR “waitlist control”[tw] OR “retrospective cohort*”[tw] OR “three arm”[tw] OR “medical record*”[tw] OR “intervention study”[tw]) **AND** (“trial participa*”[tw] OR nonparticipa*[tw] OR non-participa*[tw] OR non-trial[tw] OR nontrial[tw] OR refuse*[tw] OR “not enrolled”[tw] OR “non enrol*”[tw] OR “enrol*”[tw] OR eligibility[tw] OR “non-treatment*”[tw] OR “standard care”[tw] OR “usual care”[tw] OR off-protocol[tw] OR “participation bias”[tw] OR hawthorne[tw] OR “care effect*”[tw] OR “enrollment effect”[tw] OR “trial benefit*”[tw] OR “inclusion benefit*”[tw]))

(3) FULL-TEXT ARTICLES EXCLUDED

eTable 4. Full-text articles excluded with reasons (n = 135).

Reason	References
Wrong outcome (n = 37)	1–37
Published before 2000 (n = 31)	38–68
Wrong study design (n = 26)	69–94
Conference abstract (n = 21)	95–115
Wrong intervention (n = 9)	116–124
Wrong patient population (n = 7)	125–131
Systematic/literature review (n = 4)	132–135

References

1. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *The Lancet Oncology*. 2012;13(5):518-527. doi:10.1016/S1470-2045(12)70112-2

2. Andersson Y, Bergkvist L, Frisell J, de Boniface J. Do clinical trials truly mirror their target population? An external validity analysis of national register versus trial data from the Swedish prospective SENOMIC trial on sentinel node micrometastases in breast cancer. *Breast Cancer Res Treat*. 2019;177(2):469-475. doi:10.1007/s10549-019-05328-3

3. Augustin A, Le Gouill S, Gressin R, et al. Survival benefit of mantle cell lymphoma patients enrolled in clinical trials; a joint study from the LYSA group and French cancer registries. *J Cancer Res Clin Oncol*. 2018;144(4):629-635. doi:10.1007/s00432-017-2529-9

4. Bertelli G, Drews F, Lutchman-Singh K. Bevacizumab for Ovarian Cancer at High Risk of Progression: Reproducibility of Trial Results in 'Real-world' Patients. *Anticancer Research*. 2016;36(9):4947-4950. doi:10.21873/anticanres.11061

5. Brennan M, Gass P, Häberle L, et al. The effect of participation in neoadjuvant clinical trials on outcomes in patients with early breast cancer. *Breast Cancer Research and Treatment*. 2018;171(3):747-758. doi:10.1007/s10549-018-4829-4

6. Burgers JA, Arance A, Ashcroft L, Hodgetts J, Lomax L, Thatcher N. Identical chemotherapy schedules given on and off trial protocol in small cell lung cancer: response and survival results. *British Journal of Cancer*. 2002;87(5):562-566. doi:10.1038/sj.bjc.6600433

7. Chen CI, Skingley P, Meyer RM. A comparison of elderly patients with aggressive histology lymphoma who were entered or not entered on to a randomized phase II trial. *Leukemia & Lymphoma*. 2000;38(3-4):327-334. doi:10.3109/10428190009087023

8. de Boniface J, Ahlgren J, Andersson Y, et al. The generalisability of randomised clinical trials: an interim external validity analysis of the ongoing SENOMAC trial in sentinel lymph node-positive breast cancer. *Breast Cancer Res Treat*. 2020;180(1):167-176. doi:10.1007/s10549-020-05537-1

9. De Placido S, Giuliano M, Schettini F, et al. Human epidermal growth factor receptor 2 dual blockade with trastuzumab and pertuzumab in real life: Italian clinical practice versus the CLEOPATRA trial results. *Breast*. 2018;38:86-91. doi:10.1016/j.breast.2017.12.012

10. Dix D, Aplenc R, Bowes L, et al. Impact of registration on clinical trials on infection risk in pediatric acute myeloid leukemia. *Int J Cancer*. 2016;138(7):1785-1791. doi:10.1002/ijc.29905

11. Dowling AJ, Czaykowski PM, Krahn MD, Moore MJ, Tannock IF. Prostate specific antigen response to mitoxantrone and prednisone in patients with refractory prostate cancer: prognostic factors and generalizability of a multicenter trial to clinical practice. *Journal of Urology*. 2000;163(5):1481-1485.

12. Enzinger AC, Zhang B, Weeks JC, Prigerson HG. Clinical trial participation as part of end-of-life cancer care: associations with medical care and quality of life near death. *J Pain Symptom Manage*. 2014;47(6):1078-1090. doi:10.1016/j.jpainsymman.2013.07.004

13. Estey EH, Thall PF, Giles FJ, et al. Gemtuzumab ozogamicin with or without interleukin 11 in patients 65 years of age or older with untreated acute myeloid leukemia and high-risk myelodysplastic syndrome: Comparison with idarubicin plus continuous-infusion, high-dose cytosine arabinoside. *Blood*. 2002;99(12):4343-4349. doi:10.1182/blood.V99.12.4343

14. Fraser J, Steele N, Al Zaman A, Yule A. Are patients in clinical trials representative of the general population? Dose intensity and toxicities associated with FE100C-D chemotherapy in a non-trial population of node positive breast cancer patients compared with PACS-01 trial group. *Eur J Cancer*. 2011;47(2):215-220. doi:10.1016/j.ejca.2010.10.001

15. Fujiya K, Tokunaga M, Nishiwaki N, et al. Feasibility of Laparoscopic Distal Gastrectomy for Stage I Gastric Cancer in Patients Outside of Clinical Trials. *J Gastrointest Surg*. 2018;22(10):1665-1671. doi:10.1007/s11605-018-3842-6

16. Gross CP, Filardo G, Mayne ST, Krumholz HM. The impact of socioeconomic status and race on trial participation for older women with breast cancer. *Cancer*. 2005;103(3):483-491. doi:10.1002/cncr.20792

17. Harter P, du Bois A, Schade-Brittinger C, et al. Non-enrollment of ovarian cancer patients in clinical trials: reasons and background. *Ann Oncol*. 2005;16(11):1801-1805. doi:10.1093/annonc/mdi367

18. Hehr T, Classen J, Schreck U, Glocker S, Bamberg M, Budach W. Hyperfractionated accelerated radiotherapy alone and with concomitant chemotherapy to the head and neck: treated within and outside of randomized clinical trials. *International Journal of Radiation Oncology*Biology*Physics*. 2004;58(5):1424-1430. doi:10.1016/j.ijrobp.2003.08.036

19. Janson M, Edlund G, Kressner U, et al. Analysis of patient selection and external validity in the Swedish contribution to the COLOR trial. *Surg Endosc*. 2009;23(8):1764-1769. doi:10.1007/s00464-008-0203-7

20. Julian-Reynier C, Genève J, Dalenc F, et al. Assessment of Care by Breast Cancer Patients Participating or Not Participating in a Randomized Controlled Trial: A Report With the Patients' Committee for Clinical Trials of the Ligue Nationale Contre le Cancer. *Journal of Clinical Oncology*. 2007;25(21):3038-3044. doi:10.1200/JCO.2006.08.9367

21. Koo KC, Lee JS, Kim JW, et al. Impact of clinical trial participation on survival in patients with castration-resistant prostate cancer: a multi-center analysis. *BMC Cancer*. 2018;18(1):468. doi:10.1186/s12885-018-4390-x

22. Koschmann C, Thomson B, Hawkins DS. No evidence of a trial effect in newly diagnosed pediatric acute lymphoblastic leukemia. *Archives of Pediatrics and Adolescent Medicine*. 2010;164(3):214-217. doi:10.1001/archpediatrics.2009.282

23. Kuo SH, Yang CH, Yu CJ, Hsu C, Cheng AL, Yang PC. Survival of stage IIIB/IV non-small cell lung cancer patients who received chemotherapy but did not participate in clinical trials. *Lung Cancer*. 2005;48(2):275-280. doi:10.1016/j.lungcan.2004.10.004

24. Mandelblatt JS, Makgoeng SB, Luta G, et al. A planned, prospective comparison of short-term quality of life outcomes among older patients with breast cancer treated with standard chemotherapy in a randomized clinical trial vs. an observational study: CALGB #49907 and #369901. *Journal of Geriatric Oncology*. 2013;4(4):353-361. doi:10.1016/j.jgo.2013.05.004

25. McGrath-Lone L, Ward H, Schoenborn C, Day S. The effects of cancer research participation on patient experience: a mixed-methods analysis. *European Journal of Cancer Care*. 2016;25(6):1056-1064. doi:10.1111/ecc.12336

26. Mengis C, Aebi S, Tobler A, Dähler W, Fey MF. Assessment of differences in patient populations selected for excluded from participation in clinical phase III acute myelogenous leukemia trials. *J Clin Oncol*. 2003;21(21):3933-3939. doi:10.1200/jco.2003.03.186

27. Mitchell AP, Harrison MR, Walker MS, George DJ, Abernethy AP, Hirsch BR. Clinical Trial Participants With Metastatic Renal Cell Carcinoma Differ From Patients Treated in Real-World Practice. *J Oncol Pract*. 2015;11(6):491-497. doi:10.1200/jop.2015.004929

28. Moke DJ, Oberley MJ, Bhojwani D, Parekh C, Orgel E. Association of clinical trial enrollment and survival using contemporary therapy for pediatric acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2018;65(2). doi:10.1002/pbc.26788

29. Østgård LS, Nørgaard M, Sengeløv H, et al. Improved outcome in acute myeloid leukemia patients enrolled in clinical trials: A national population-based cohort study of Danish intensive chemotherapy patients. *Oncotarget*. 2016;7(44):72044-72056. doi:10.18632/oncotarget.12495

30. Rajappa S, Gundeti S, Uppalapati S, et al. Is there a positive effect of participation on a clinical trial for patients with advanced non-small cell lung cancer. *Indian journal of cancer*. 2008;45(4):158-163. doi:10.4103/0019-509X.44664

31. Robinson WR, Ritter J, Rogers AS, Tedjarati S, Lieberenz C. Clinical Trial Participation Is Associated With Improved Outcome in Women With Ovarian Cancer. *International Journal of Gynecologic Cancer*. 2009;19(1):124-128. doi:10.1111/IGJ.0b013e31819a1ce8

32. Roy P, Vaughan Hudson G, Vaughan Hudson B, Esteve J, Swerdlow AJ. Long-term survival in Hodgkin's disease patients. *European Journal of Cancer*. 2000;36(3):384-389. doi:10.1016/S0959-8049(99)00267-1

33. Sorbye H, Pfeiffer P, Cavalli-Björkman N, et al. Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients. *Cancer*. 2009;115(20):4679-4687. doi:10.1002/cncr.24527

34. Svensson J, Andersson E, Persson U, Edekling T, Ovanfors A, Ahlgren G. Value of treatment in clinical trials versus the real world: the case of abiraterone acetate (Zytiga) for postchemotherapy metastatic castration-resistant prostate cancer patients in Sweden. *Scandinavian Journal of Urology*. 2016;50(4):286-291. doi:10.3109/21681805.2016.1172254

35. Thompson CA, Hugo SE, Swetz KM, et al. End-of-life care in a population-based cohort of cancer patients: clinical trial participation versus standard of care. *BMJ Support Palliat Care*. 2013;3(2):181-187. doi:10.1136/bmjspcare-2012-000295

36. van der Biessen DA, Oldenmenger WH, van der Helm PG, et al. Self-reported quality of life and hope in phase-I trial participants: An observational prospective cohort study. *Eur J Cancer Care (Engl)*. 2018;27(6):e12908. doi:10.1111/ecc.12908

37. Yennurajalingam S, Kang JH, Cheng HY, et al. Characteristics of Advanced Cancer Patients With Cancer-Related Fatigue Enrolled in Clinical Trials and Patients Referred to Outpatient Palliative Care Clinics. *Journal of Pain and Symptom Management*. 2013;45(3):534-541. doi:10.1016/j.jpainsymman.2012.02.013

38. Akaza H, Hinotsu S, Aso Y, Kakizoe T, Koiso K. Bacillus Calmette-Guérin treatment of existing papillary bladder cancer and carcinoma in situ of the bladder. Four-year results. The Bladder Cancer BCG Study Group. *Cancer*. 1995;75(2):552-559. doi:10.1002/1097-0142(19950115)75:2<552::aid-cncr2820750219>3.0.co;2-h

39. Antman K, Amato D, Wood W, et al. Selection bias in clinical trials. *J Clin Oncol*. 1985;3(8):1142-1147. doi:10.1200/JCO.1985.3.8.1142

40. Balmukhanov SB, Beisebaev AA, Aitkoolova ZI, et al. Intratumoral and parametrial infusion of metronidazole in the radiotherapy of uterine cervix cancer: Preliminary report. *International Journal of Radiation Oncology*Biology*Physics*. 1989;16(4):1061-1063. doi:10.1016/0360-3016(89)90916-4

41. Berglund G, Bolund C, Gustafsson UL, Sjödén PO. Is the wish to participate in a cancer rehabilitation program an indicator of the need? Comparisons of participants and non-participants in a randomized study. *Psycho-Oncology*. 1997;6(1):35-46. doi:10.1002/(SICI)1099-1611(199703)6:1<35::AID-PON241>3.0.CO;2-J

42. Bergmann JF, Chassany O, Gandiol J, et al. A randomised clinical trial of the effect of informed consent on the analgesic activity of placebo and naproxen in cancer pain. *Clinical Trials and Meta-Analysis*. 1994;29(1):41-47.

43. Bertelsen K. Protocol allocation and exclusion in two Danish randomised trials in ovarian cancer. *British Journal of Cancer*. 1991;64(6):1172-1176. doi:10.1038/bjc.1991.485

44. Blichert-Toft M, Brincker H, Andersen JA, et al. A Danish Randomized Trial Comparing Breast-Preserving Therapy with Mastectomy in Mammary Carcinoma: Preliminary results. *Acta Oncologica*. 1988;27(6):671-677. doi:10.3109/02841868809091767

45. Cottin V, Arpin D, Lasset C, et al. Small-cell lung cancer: Patients included in clinical trials are not representative of the patient population as a whole. *Annals of Oncology*. 1999;10(7):809-816. doi:10.1023/A:1008399831512

46. Creutzig U, Ritter J, Zimmermann M, Schellong G. Does cranial irradiation reduce the risk for bone marrow relapse in acute myelogenous leukemia? Unexpected results of the Childhood Acute Myelogenous Leukemia Study BFM-87. *Journal of Clinical Oncology*. 1993;11(2):279-286. doi:10.1200/JCO.1993.11.2.279

47. Dahlberg M, Glimelius B, Påhlman L. Improved survival and reduction in local failure rates after preoperative radiotherapy: evidence for the generalizability of the results of Swedish Rectal Cancer Trial. *Annals of Surgery*. 1999;229(4):493-497. doi:10.1097/00000658-199904000-00007

48. Davis S, Wright PW, Schulman SF. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. *Cancer*. 1985;56(7):1710-1718. doi:10.1002/1097-0142%2819851001%2956:7%3C1710::AID-CNCR2820560741%3E3.0.CO;2-T

49. Diehl LF, Perry DJ. A comparison of randomized concurrent control groups with matched historical control groups: are historical controls valid? *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 1986;4(7):1114-1120. doi:10.1200/JCO.1986.4.7.1114

50. Edsmyr F, Esposti PL, Johansson B, Strindberg B. Clinical experimental randomized study of 2.6-cis-diphenylhexamethylcyclotetrasiloxane and estramustine-17-phosphate in the treatment of prostatic carcinoma. *The Journal of Urology*. 1978;120(6):705-707. doi:10.1016/s0022-5347(17)57336-x

51. Feuer EJ, Frey CM, Brawley OW, et al. After a treatment breakthrough: a comparison of trial and population-based data for advanced testicular cancer. *Journal of Clinical Oncology*. 1994;12(2):368-377. doi:10.1200/JCO.1994.12.2.368

52. Greil R, Holzner B, Kemmler G, et al. Retrospective assessment of quality of life and treatment outcome in patients with Hodgkin's disease from 1969 to 1994. *European Journal of Cancer*. 1999;35(5):698-706. doi:10.1016/S0959-8049%2899%2900025-8

53. Helsing M, Bergman B, Thaning L, Hero U. Quality of life and survival in patients with advanced non-small cell lung cancer receiving supportive care plus chemotherapy with carboplatin and etoposide or supportive care only. A multicentre randomised phase III trial. *European Journal of Cancer*. 1998;34(7):1036-1044. doi:10.1016/S0959-8049(97)10122-8

54. Hjorth M, Holmberg E, RÃ¶der S, Westin J, for the Myeloma Group of Western Sweden. Impact of active and passive exclusions on the results of a clinical trial in multiple myeloma. *British Journal of Haematology*. 1992;80(1):55-61. doi:10.1111/j.1365-2141.1992.tb06400.x

55. Karjalainen S, Palva I. Do treatment protocols improve end results? A study of survival of patients with multiple myeloma in Finland. *BMJ (Clinical research ed)*. 1989;299(6707):1069-1072. doi:10.1136/bmj.299.6707.1069

56. Lennox EL, Stiller CA, Jones PH, Wilson LM. Nephroblastoma: treatment during 1970-3 and the effect on survival of inclusion in the first MRC trial. *BMJ*. 1979;2(6190):567-569. doi:10.1136/bmj.2.6190.567

57. Lidbrink E, Frisell J, Brandberg Y, Rosendahl I, Rutqvist LE. Nonattendance in the Stockholm mammography screening trial: Relative Mortality and reasons for nonattendance. *Breast Cancer Research and Treatment*. 1995;35(3):267-275. doi:10.1007/BF00665978

58. Link MP, Goorin AM, Horowitz M, et al. Adjuvant Chemotherapy of High-Grade Osteosarcoma of the Extremity: Updated Results of the Multi-Institutional Osteosarcoma Study. *Clinical Orthopaedics and Related Research*. 1991;NA;(270):8???14. doi:10.1097/00003086-199109000-00003

59. Marubini E, Mariani L, Salvadori B, et al. Results of a breast-cancer-surgery trial compared with observational data from routine practice. *The Lancet*. 1996;347(9007):1000-1003. doi:10.1016/S0140-6736(96)90145-2

60. Moertel CG, Childs DS, O'Fallon JR, Holbrook MA, Schutt AJ, Reitemeier RJ. Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. *Journal of Clinical Oncology*. 1984;2(11):1249-1254. doi:10.1200/JCO.1984.2.11.1249

61. Quoix E, Finkelstein H, Wolkove N, Kreisman H. Treatment of small-cell lung cancer on protocol: potential bias of results. *Journal of Clinical Oncology*. 1986;4(9):1314-1320. doi:10.1200/JCO.1986.4.9.1314

62. Schea RA, Perkins P, Allen PK, Komaki R, Cox JD. Limited-stage small-cell lung cancer: patient survival after combined chemotherapy and radiation therapy with and without treatment protocols. *Radiology*. 1995;197(3):859-862. doi:10.1148/radiology.197.3.7480770

63. Schmoor C, Olschewski M, Schumacher M. Randomised and non-randomised patients in clinical trials: experiences with comprehensive cohort studies. *Statistics in medicine*. 1996;15(3):263-271.

64. Stiller CA, Draper GJ. Treatment centre size, entry to trials, and survival in acute lymphoblastic leukaemia. *Archives of Disease in Childhood*. 1989;64(5):657-661. doi:10.1136/adc.64.5.657

65. Sullivan MP, Fuller LM, Chen T, et al. Intergroup Hodgkin's disease in children study of stages I and II: a preliminary report. *Cancer Treatment Reports*. 1982;66(4):937-947.

66. Verdonck LF, van Putten WLJ, Hagenbeek A, et al. Comparison of CHOP Chemotherapy with Autologous Bone Marrow Transplantation for Slowly Responding Patients with Aggressive Non-Hodgkin's Lymphoma. *New England Journal of Medicine*. 1995;332(16):1045-1051. doi:10.1056/NEJM199504203321601

67. Wagner HP, Dingeldein-Bettler I, Berchthold W, et al. Childhood NHL in Switzerland: Incidence and Survival of 120 Study and 42 Non-Study Patients. *Medical and Pediatric Oncology*. 1995;24(5):281-286. doi:10.1002/mpo.2950240503

68. Ward LC, Fielding JW, Dunn JA, Kelly KA. The selection of cases for randomised trials: a registry survey of concurrent trial and non-trial patients. The British Stomach Cancer Group. *Br J Cancer*. 1992;66(5):943-950. doi:10.1038/bjc.1992.390

69. Aboda A, Taha W, Elkady A, Kanwar JR. A pilot study for randomized controlled trial of the benefits of a physical exercise program for cancer cachexia patients. *Journal of cachexia, sarcopenia and muscle*. 2018;9(1):211-. doi:10.1002/jcsm.12284

70. Abou-Alfa GK, Blanc JF, Miles S, et al. Phase II study of first-line trebananib plus sorafenib in patients with advanced hepatocellular carcinoma. *Oncologist*. 2017;22(7):780-e65. doi:10.1634/theoncologist.2017-0058

71. Apolone G, Bertetto O, Caraceni A, et al. Pain in cancer. An outcome research project to evaluate the epidemiology, the quality and the effects of pain treatment in cancer patients. *Health and Quality of Life Outcomes*. 2006;4. doi:10.1186/1477-7525-4-7

72. Banck-Petersen A, Olsen CK, Djurhuus SS, et al. The “Interval Walking in Colorectal Cancer” (I-WALK-CRC) study: design, methods and recruitment results of a randomized controlled feasibility trial. *Contemporary clinical trials communications*. 2018;9:143-150. doi:10.1016/j.conctc.2018.01.008

73. Biasoli I, Franchi-Rezgui P, Sibon D, et al. Analysis of factors influencing inclusion of 102 patients with stage III/IV Hodgkin’s lymphoma in a randomized trial for first-line chemotherapy. *Annals of Oncology*. 2008;19(11):1915-1920. doi:10.1093/annonc/mdn391

74. Decensi A, Robertson C, Viale G, et al. A Randomized Trial of Low-Dose Tamoxifen on Breast Cancer Proliferation and Blood Estrogenic Biomarkers. *JNCI Journal of the National Cancer Institute*. 2003;95(11):779-790. doi:10.1093/jnci/95.11.779

75. Du Bois A, Rochon J, Lamparter C, Pfisterer J. Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer. *International Journal of Gynecologic Cancer*. 2005;15(2):183-191. doi:10.1136/ijgc-00009577-200503000-00001

76. Goebell PJ, Staehler M, Muller L, et al. Changes in Treatment Reality and Survival of Patients With Advanced Clear Cell Renal Cell Carcinoma - Analyses From the German Clinical RCC-Registry. *Clin Genitourin Cancer*. 2018;(no pagination). doi:10.1016/j.clgc.2018.06.006

77. Guerra CE, Kelly S, Redlinger C, Hernández P, Glanz K. Pancreatic Cancer Clinical Treatment Trials Accrual: A Closer Look at Participation Rates. *Am J Clin Oncol*. 2021;44(6):227-231. doi:10.1097/COC.0000000000000807

78. Harrison MR, Hirsch BR, George DJ, et al. Real-World Outcomes in Metastatic Renal Cell Carcinoma: Insights From a Joint Community-Academic Registry. *Journal of Oncology Practice*. 2014;10(2):e63-e72. doi:10.1200/JOP.2013.001180

79. Heng DYC, Choueiri TK, Rini BI, et al. Outcomes of patients with metastatic renal cell carcinoma that do not meet eligibility criteria for clinical trials. *Annals of Oncology*. 2014;25(1):149-154. doi:10.1093/annonc/mdt492

80. Janni W, Kiechle M, Sommer H, et al. Study participation improves treatment strategies and individual patient care in participating centers. *Anticancer Research*. 2006;26(5B):3661-3667.

81. Kwekkeboom KL, Abbott-Anderson K, Cherwin C, Roiland R, Serlin RC, Ward SE. Pilot randomized controlled trial of a patient-controlled cognitive-behavioral intervention for the pain, fatigue, and sleep disturbance symptom cluster in cancer. *Journal of pain and symptom management*. 2012;44(6):810-822. doi:10.1016/j.jpainsymman.2011.12.281

82. Marschner N, Staehler M, Müller L, et al. Survival of Patients With Advanced or Metastatic Renal Cell Carcinoma in Routine Practice Differs From That in Clinical Trials-Analyses From the German Clinical RCC Registry. *Clin Genitourin Cancer*. 2017;15(2):e209-e215. doi:10.1016/j.clgc.2016.08.022

83. Mascarenhas J, Hoffman R. A comprehensive review and analysis of the effect of ruxolitinib therapy on the survival of patients with myelofibrosis. *Blood*. 2013;121(24):4832-4837. doi:10.1182/blood-2013-02-482232

84. Meadows AT, Kramer S, Hopson R, Lustbader E, Jarrett P, Evans AE. Survival in Childhood Acute Lymphocytic Leukemia: Effect of Protocol and Place of Treatment. *Cancer Investigation*. 1983;1(1):49-55. doi:10.3109/07357908309040932

85. Nct. Understanding the Post-Surgical Non-Small Cell Lung Cancer Patient's Symptom Experience. *https://clinicaltrials.gov/show/NCT03724331*. Published online 2018. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01918268/full

86. Noronha V, Patil VM, Joshi A, et al. Epidermal growth factor receptor positive lung cancer: The nontrial scenario. *Indian J Cancer*. 2017;54(1):132-135. doi:10.4103/0019-509x.219583

87. Rock K, McArdle O, Forde P, et al. A clinical review of treatment outcomes in glioblastoma multiforme--the validation in a non-trial population of the results of a randomised Phase III clinical trial: has a more radical approach improved survival? *British Journal of Radiology*. 2012;85(1017):e729-33. doi:10.1259/bjr/83796755

88. Shmuel S, Yang JY, Thai S, Webster-Clark M, Lund JL. Assessing clinical trial effects on outcomes among pediatric and adolescent and young adult (AYA) patients with cancer. *Cancer*. 2021;127(4):648-649. doi:10.1002/cncr.33252

89. Shukuya T, Takamochi K, Sakurai H, et al. Efficacy of Adjuvant Chemotherapy With Tegafur-Uracil in Patients With Completely Resected, Node-Negative NSCLC-Real-World Data in the Era of Molecularly Targeted Agents and Immunotherapy. *JTO Clin Res Rep*. 2022;3(5):100320. doi:10.1016/j.jtocrr.2022.100320

90. Socinski MA, Manikhas GM, Stroyakovsky DL, et al. A dose finding study of weekly and every-3-week nab-paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer. *J Thorac Oncol*. 2010;5(6):852-861. doi:10.1097/JTO.0b013e3181d5e39e

91. Stein A, Petersen V, Schulze M, et al. Bevacizumab plus chemotherapy as first-line treatment for patients with metastatic colorectal cancer: Results from a large German community-based observational cohort study. *Acta Oncologica*. 2015;54(2):171-178. doi:10.3109/0284186X.2014.961649

92. Treweek S, Dryden R, McCowan C, Harrow A, Thompson AM. Do participants in adjuvant breast cancer trials reflect the breast cancer patient population? *Eur J Cancer*. 2015;51(8):907-914. doi:10.1016/j.ejca.2015.01.064

93. Unger JM, Blanke CD, Leblanc M, et al. Association of Patient Demographic Characteristics and Insurance Status with Survival in Cancer Randomized Clinical Trials with Positive Findings. *JAMA Netw Open*. 2020;3(4):e203842. doi:10.1001/jamanetworkopen.2020.3842

94. Wright AA, Cronin A, Milne DE, et al. Use and effectiveness of intraperitoneal chemotherapy for treatment of ovarian cancer. *J Clin Oncol*. 2015;33(26):2841-2847. doi:10.1200/JCO.2015.61.4776

95. Ascierto PA, Chiarion Sileni V, Del Vecchio M, et al. The european ipilimumab expanded access programme (EAP): Efficacy and safety data from the Italian cohort of patients with pretreated, advanced melanoma. *Ann Oncol*. 2012;23(SUPPL. 9). doi:10.1093/annonc/mds404

96. Baba S, Sawaki M, Uemura Y, et al. A cohort study to evaluate the efficacy and safety of postoperative adjuvant therapy in HER2-positive elderly breast cancer patients (RESPECT-cohort study). *Cancer Res*. 2020;80(4). doi:10.1158/1538-7445.SABCS19-P3-14-02

97. Berger R, Ish-Shalom M, Maimon N, et al. Comparison between the outcome of metastatic RCC patients treated with sunitinib as part of clinical trials and matched nonparticipants receiving sutent as standard therapy. *J Clin Oncol*. 2013;31(15 SUPPL. 1). http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/e15597?sid=66f76291-44a4-4eb7-9975-45d04a25a720

98. Cassidy RJ, Liu Y, Zhong J, Gillespie TW, Landry JC. Survival impact of neoadjuvant chemotherapy alone versus neoadjuvant chemoradiation therapy for patients with T2N1, T3N0, and T3N1 rectal adenocarcinomas. *International journal of radiation oncology biology physics Conference: 58th annual meeting of the american society for radiation oncology, ASTRO 2016 United states*. 2016;96(2 Supplement 1):E148.

99. Cathcart P, Van Der Meulen J, Emberton M. Can the findings of randomised clinical trials concerning the efficacy of prostate cancer therapy in men with early disease be replicated in national cancer registries? *European urology, supplements*. 2013;12(1):e181-.

100. Eduafo A., Metheny L., Driscoll J., et al. Patient selection bias limits the real world efficacy of randomized clinical trials in multiple myeloma. *Blood*. 2020;136(SUPPL 1):1-2. doi:10.1182/blood-2020-139856

101. Grande Pulido E, Castelo B, Fonseca PJ, et al. Efficacy and tolerability of sunitinib in patients with advanced thyroid cancer out of a trial: A Spanish multicenter cohort. *J Clin Oncol*. 2011;29(15 SUPPL. 1). http://meeting.ascopubs.org/cgi/content/abstract/29/15-suppl/e16024?sid=404fb8ff-8950-43f5-bcfd-2c47c08062d8

102. Harrison MR, George DJ, Walker MS, et al. Outcomes of “real world” treatment for metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2012;30(5 SUPPL. 1). http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71008688

103. Introini C, Naselli A, Puppo P, Germinale F. Feasibility, safety and 1 year follow up of en bloc transurethral resection of bladder tumor compared to a matched cohort of patients submitted to standard tur. *Anticancer Research*. 2012;32(5):1906.

104. Joseph RW, Liu FX, Macahilig C, et al. Real-world utilization and patient outcomes associated with pembrolizumab in advanced melanoma in US academic centers and affiliated satellite clinics. *J Clin Oncol*. 2018;36(15 Supplement 1). doi:10.1200/JCO.2018.36.15-suppl.e21500

105. Marschner N, Potthoff K, Schnell R, et al. Overall survival of 4865 patients with metastatic solid tumours treated in German routine practice - Combined results from four prospective, multicentre cohort studies. *Oncology research and treatment*. 2016;39:43-. doi:10.1159/000449050

106. Merkhofer C, Eaton KD, Martins RG, Ramsey SD, Goulart BHL. Potential impact of clinical trial (CT) participation on survival of patients with metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2019;37. doi:10.1200/JCO.2019.37.27-suppl.137

107. Narui K, Ohno S, Mukai H, et al. Overall survival of participants compared to non-participants in a randomized-controlled trial (SELECT BC): a prospective cohort study. *J Clin Oncol*. 2016;34. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01780537/full

108. Rousey S, Lassi KK, Wieczorek J, et al. Early use of home health care on health care utilization for patients with advanced lung cancer. *J Clin Oncol*. 2013;31(15 SUPPL. 1). http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/e19015?sid=ddb5fb2e-7dfe-43c6-8e9f-d189bd78548f

109. Ryan S, Jamieson C, Shabaik A, et al. B cell concentration in high risk prostate cancer specimens after neoadjuvant rituximab. *Journal of Urology*. 2018;199(4 Supplement 1):e942.

110. Saito T, Sawaki M, Hozumi Y, et al. A randomized controlled trial of postoperative adjuvant therapy for elderly breast cancer patients: Comparison of health-related quality of life between clinical trial participants and decliners. *Cancer Res*. 2016;76(4 SUPPL. 1). doi:10.1158/1538-7445.SABCS15-P4-11-09

111. Sakurai H, Goto Y, Yoh K, et al. P1.17-04 Multicenter Observational Study of Node-Negative Non-Small Cell Lung Cancer Patients Who Are Excluded from a Clinical Trial. *J Thorac Oncol*. 2019;14(10 Supplement):S608-S609. doi:10.1016/j.jtho.2019.08.1278

112. Shacham Abulafia A, Shemesh S, Pasvolsky O, Vaxman J, Raanani P, Rozovski U. The impact of enrollment in clinical trials of patients with multiple myeloma. *Hemasphere*. 2019;3:982-.

113. Tini G, Sarocchi M, Sirello D, et al. Cardiovascular profile of oncologic patients scheduled to receive anti VEGF therapy and implications for the risk of cardiotoxicity. *Giornale Italiano di Cardiologia*. 2019;20(12 Supplement 1):101S.

114. Wagner LI, Toomey K, Ailawadhi S, et al. Clinical outcomes and health-related quality of life (HRQoL) among randomized clinical trial (RCT)-eligible and RCT-ineligible patients: results from the Connect® MM registry. *Hemasphere*. 2020;4:460-461. doi:10.1097/HS9.0000000000000404

115. Yin X., Davi R., Lamont E.B., et al. Phase Ib trial single-arm efficacy estimates via comparison to a historical clinical trial synthetic control arm. *Cancer Research*. 2022;82(12 Supplement). doi:10.1158/1538-7445.AM2022-1025

116. Bijker N, Peterse JL, Fentiman IS, et al. Effects of patient selection on the applicability of results from a randomised clinical trial (EORTC 10853) investigating breast-conserving therapy for DCIS. *British Journal of Cancer*. 2002;87(6):615-620. doi:10.1038/sj.bjc.6600514

117. Boesen, Boesen SH, Frederiksen K, et al. Survival after a psychoeducational intervention for patients with cutaneous malignant melanoma: a replication study. *J Clin Oncol*. 2007;25(36):5698-5703. doi:10.1200/JCO.2007.10.8894

118. Boesen E, Boesen S, Christensen S, Johansen C. Comparison of participants and non-participants in a randomized psychosocial intervention study among patients with malignant melanoma. *Psychosomatics*. 2007;48(6):510-516. doi:10.1176/appi.psy.48.6.510

119. Dussel V, Orellana L, Soto N, et al. Feasibility of Conducting a Palliative Care Randomized Controlled Trial in Children With Advanced Cancer: assessment of the PediQUEST Study. *Journal of pain and symptom management*. 2015;49(6):1059-1069. doi:10.1016/j.jpainsymman.2014.12.010

120. Gilson MM, Diener-West M, Hawkins BS. Comparison of survival among eligible patients not enrolled versus enrolled in the Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma. *Ophthalmic Epidemiol*. 2007;14(4):251-257. doi:10.1080/01658100701473275

121. Khera N, Majhail NS, Brazauskas R, et al. Comparison of Characteristics and Outcomes of Trial Participants and Nonparticipants: Example of Blood and Marrow Transplant Clinical Trials Network 0201 Trial. *Biology of Blood and Marrow Transplantation*. 2015;21(10):1815-1822. doi:10.1016/j.bbmt.2015.06.004

122. Martelli G, Boracchi P, Orenti A, et al. Axillary dissection versus no axillary dissection in older T1N0 breast cancer patients: 15-year results of trial and out-trial patients. *European Journal of Surgical Oncology*. 2014;40(7):805-812. doi:10.1016/j.ejso.2014.03.029

123. Morris EJA, Jordan C, Thomas JD, et al. Comparison of treatment and outcome information between a clinical trial and the National Cancer Data Repository. *British Journal of Surgery*. 2011;98(2):299-307. doi:10.1002/bjs.7295

124. Vis AN, Roemeling S, Reedijk AMJ, Otto SJ, Schröder FH. Overall Survival in the Intervention Arm of a Randomized Controlled Screening Trial for Prostate Cancer Compared with a Clinically Diagnosed Cohort. *European Urology*. 2008;53(1):91-98. doi:10.1016/j.eururo.2007.06.001

125. Aaltonen KJ, Ylikylä S, Tuulikki Joensuu J, et al. Efficacy and effectiveness of tumour necrosis factor inhibitors in the treatment of rheumatoid arthritis in randomized controlled trials and routine clinical practice. *Rheumatology (Oxford)*. 2017;56(5):725-735. doi:10.1093/rheumatology/kew467

126. Anveden A, Taube M, Peltonen M, et al. Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish Obese Subjects Study. *Gynecol Oncol*. 2017;145(2):224-229. doi:10.1016/j.ygyno.2017.02.036

127. Dallal CM, Brinton LA, Bauer DC, et al. Obesity-related hormones and endometrial cancer among postmenopausal women: a nested case-control study within the B~FIT cohort. *Endocr Relat Cancer*. 2013;20(1):151-160. doi:10.1530/erc-12-0229

128. Flasinski M, Scheibke K, Zimmermann M, et al. Low-dose cytarabine to prevent myeloid leukemia in children with Down syndrome: TMD Prevention 2007 study. *Blood Adv*. 2018;2(13):1532-1540. doi:10.1182/bloodadvances.2018018945

129. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *The Lancet*. 2007;369(9573):1603-1613. doi:10.1016/S0140-6736(07)60747-8

130. Taube M, Peltonen M, Sjöholm K, et al. Association of Bariatric Surgery With Skin Cancer Incidence in Adults With Obesity: A Nonrandomized Controlled Trial. *JAMA Dermatol*. 2020;156(1):38-43. doi:10.1001/jamadermatol.2019.3240

131. Wang A, Aragaki AK, Tang JY, et al. Statin use and all-cancer survival: prospective results from the Women's Health Initiative. *Br J Cancer*. 2016;115(1):129-135. doi:10.1038/bjc.2016.149

132. Braunholtz DA, Edwards SJL, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." *Journal of Clinical Epidemiology*. 2001;54(3):217-224. doi:10.1016/S0895-4356(00)00305-X

133. Mantarro S, Rossi M, Bonifazi M, et al. Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer. *Internal and Emergency Medicine*. 2016;11(1):123-140. doi:10.1007/s11739-015-1362-x

134. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: Conceptual framework and structured review. *Lancet*. 2004;363(9405):263-270. doi:10.1016/S0140-6736%2803%2915383-4

135. Vist GE, Bryant D, Somerville L, Birminghem T, Oxman AD. Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database of Systematic Reviews*. 2008;(3):MR000009. doi:10.1002/14651858.MR000009.pub4

(4) ADJUSTMENT FACTORS, QUALITY SCORING SYSTEM, AND LEAVE-ONE-OUT ANALYSIS

Our quality scoring system was built inductively after extraction was initiated, using the aforementioned directed acyclic graph (DAG) as a framework. In particular, during extraction, we identified items that various primary reports used to adjust in comparisons of trial participant and routine care patient outcomes. From this, we created a list of recurring adjustment factors. We added other factors to this list, based on biases or confounders captured in our DAG above.

eTable 5. Quality score system and adjustment factor descriptions. For categories where the data are missing, 1 point was subtracted (score = -1). The quality scores were categorized as low (≤6 points), medium (7 points), and high (≥8 points).

Adjustment Factor Description	Score
Studies that account for age	1
Studies that do not account for age	0
Studies that account for sex	1
Studies that do not account for sex	0
Studies that account for race/ethnicity	1
Studies that do not account for race/ethnicity	0
Studies that account for comorbidities	1
Studies that do not account for comorbidities	0
Studies that account for stage	1
Studies that do not account for stage	0
Studies that account for histology	1
Studies that do not account for histology	0
Studies that account for performance status	1
Studies that do not account for performance status	0
Studies that account for line of treatment	1
Studies that do not account for line of treatment	0
Studies that accounted for trial eligibility	1
Studies that did not account for trial eligibility	0
Studies in which the routine care group do not include trial refusers	1
Studies in which the routine care group includes trial refusers[a]	0
Studies that accounted for treatment effect (same treatments)	1

Studies that did not account for treatment effect (different treatments)	0
Studies that are conducted in a similar time period for comparison groups	1
Studies that are not conducted in a similar time period for comparison groups	0
Studies that compare the routine care group to the same trial	1
Studies that compare the routine care group to multiple trials	0
Studies that use registries for the source of routine care group data	1
Studies that use medical records for the source of routine care group data	0
Studies that account for the same trial and routine care group sources	1
Studies that do not account for the same trial and routine care group sources	0
Studies with a large trial sample size (≥200)[b]	1
Studies with a small trial sample size (<200)	0

Cancer site was not included as an adjustment factor because all studies in our sample adjusted for same cancer type. However, this is an important adjustment factor to consider for a sample that does not all adjust for the same cancer site. [a] We examined whether studies included trial refusers in their routine care patient groups. The justification for this point allocation is that we might expect that including trial refusers in the routine care group would lead to increased differences between the groups because trial refusers might be less motivated to adhere to treatment schedules or medications. [b] Only the trial participant group sample size was considered, not the routine care group sample size. This could have led to more points for studies with small sample sizes in the routine care group and large sample sizes in the trial participant group and less points for studies with small sample sizes in the trial participant group but large sample sizes in the routine care group.

379

380

381

eTable 6. Pooled hazard ratio by quality grouping (low-quality, medium-quality, and high-quality). The first row shows the pooled hazard ratios when including all causal effects that make up the quality score. Subsequent rows show the pooled hazard ratios when one of the adjustment factors are omitted from the quality score calculation. For example, the "Age" row shows the quality subgroups without consideration of adjustment for age. For each row, the quality score cut-offs were the same (low = ≤6 points; medium = 7 points; high = ≥8 points) and not changed to have similarly sized subgroups.

	Low			Medium			High		
Leave out	**N**	**HR**	**95% CI**	**N**	**HR**	**95% CI**	**N**	**HR**	**95% CI**
None	35	0.64	0.58-0.72	24	0.85	0.73-0.98	26	0.91	0.80-1.05
Age	57	0.68	0.62-0.75	17	0.97	0.80-1.17	11	0.98	0.89-1.09
Sex	58	0.69	0.63-0.77	17	0.92	0.76-1.12	10	0.98	0.87-1.09
Race/ethnicity	57	0.69	0.63-0.76	15	0.97	0.79-1.20	13	0.92	0.81-1.03
Comorbidities	38	0.64	0.58-0.72	27	0.90	0.77-1.06	20	0.92	0.83-1.03
Stage	55	0.69	0.63-0.77	17	0.88	0.73-1.06	13	0.97	0.88-1.07
Histology	53	0.69	0.62-0.77	17	0.88	0.73-1.06	15	0.91	0.81-1.04
Performance status	37	0.64	0.58-0.72	27	0.91	0.77-1.06	21	0.89	0.79-1.01
Line of treatment	38	0.65	0.59-0.72	28	0.91	0.79-1.07	19	0.89	0.78-1.00
Eligibility	37	0.65	0.59-0.73	21	0.96	0.84-1.09	27	0.86	0.75-0.98
Trial refusers	36	0.65	0.59-0.73	3	0.82	0.60-1.12	46	0.88	0.79-0.99
Treatment	40	0.65	0.58-0.72	19	1.00	0.92-1.08	26	0.89	0.77-1.02
Same timeframe	57	0.69	0.63-0.76	17	0.93	0.77-1.12	11	0.98	0.89-1.09
Same trial	51	0.68	0.61-0.76	15	0.84	0.74-0.97	19	0.90	0.77-1.05
Data source	55	0.70	0.63-0.77	17	0.83	0.68-1.01	13	0.99	0.92-1.08
Group sources	42	0.66	0.60-0.73	24	0.90	0.78-1.03	19	0.94	0.79-1.12
Sample size	45	0.68	0.61-0.75	28	0.90	0.76-1.07	12	1.00	0.92-1.09

(5) eTable 7. PRISMA 2020 CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4-5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	eTable 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5-6 (and Supplement on Open Science Framework)
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-7 (and Supplement on Open Science Framework)

	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7 (and Supplement on Open Science Framework)
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	eTable 4
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 eTable 8

Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2 Table 2 eTable 9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2 Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	9-10 Table 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figure 2 Table 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-10 Table 2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-10 Table 2 eTable 6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-10 Table 2 eFigure 4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10-11
	23b	Discuss any limitations of the evidence included in the review.	11-12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	11-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	8
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Supplement on Open Science Framework

	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplement on Open Science Framework
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: **www.prisma-statement.org**.

(6) COMPARISON CHARACTERISTICS

eTable 8. Comparison characteristics (39 studies, 85 comparisons).

Study	Country	Cancer site[a]	Sample size (Trial | Routine care)[b]	Median age (Trial | Routine care)[c]	Males (%) (Trial | Routine care)[c]	Females (%) (Trial | Routine care)[c]	Median OS follow-up (years) (Trial | Routine care)	Advanced/Metastatic	Routine care group source	Timeframe information[f]
Abdel-Rahman 2019[1]	Canada	Prostate	397 | 1718	65.3[d] | 68.4[d]	100 | 100	0 | 0	13.3[e] | 10.8[e]	No	Multi-centre | Academic and community centres	January 2000 - April 2010 | 2004-2010 (diagnosis)
Abu-Hejleh 2016[2]	US	NSCLC	38 | 759	NR |NR	55 | 56	45 | 44	4.8[e] | 6.3[e]	Yes	Multi-centre | Did not enroll in a trial	September 2003 - June 2005 (diagnosis)
Arrieta 2016[3]	Mexico	NSCLC	295 | 747	60.9[d] | 60.3[d]	47.5 | 54.8	52.5 | 45.2	2.8 | 2.8	Yes	Single-centre | Instituto Nacional de Cancerología	January 2007 - December 2014 (when patients presented themselves to the institution)
Aung 2021[4]	US	Multiple myeloma	205 | 205	59.7[d] | 63.1[d]	44.5 | 41.4	55.5 | 58.6	2.4 | 2.4	No	Single-centre | Mount Sinai Health System	2012-2018 (diagnosis)
Balyasny 2021a[5]	US	CNS (intermediate-risk)	1231 | 710	NR | NR	NR | NR	NR | NR	8.5 | 8.4	No	Multi-centre | Cooperative biology study (POG 9047 or COG ANBL00B1)	1991-2011, excluding 2006 | Prior to January 1, 2017 (diagnosis)
Balyasny 2021b[5]	US	CNS (high-risk)	922 | 807	NR | NR	NR | NR	NR | NR	11 | 10.2	No	Multi-centre | Cooperative biology study (POG 9047 or COG ANBL00B1)	1991-2011, excluding 2006 | Prior to January 1, 2017 (diagnosis)
Chow 2013[6]	US	Solid tumours	1846 | 551842	NR | NR	26.8 | 35.8	73.2 | 64.2	NR | NR	No	Multi-centre (inferred) | Retrospective cohort study	2002-2008 (cancer registry and diagnosis)
Ejlertsen 2008[7]	Europe	Breast	493 | 970	NR | NR	0 | 0	100 | 100	12.1 | 12.1	No	Multi-centre (inferred) | Not enrolled but trial-eligible and treated with the same protocol	January 1990 - May 1998 (registration)
Elting 2006a[8]	US	Solid tumours (localized)	2788 | 9053	NR | NR	53.6 | 50	46.3 | 49.7	7[e] | 7[e]	No	Single-centre | MD Anderson Cancer Center	January 1990 - December 1997 (diagnosis)
Elting 2006b[8]	US	Solid tumours (metastatic)	1502 | 3297	NR | NR	NR | NR	NR | NR	7[e] | 7[e]	No	Single-centre | MD Anderson Cancer Center	January 1990 - December 1997 (diagnosis)
Elumalai 2022[9]	UK	Prostate	2070 | 178	NR | NR	100 | 100	0 | 0	4[e] | 4[e]	Yes	Single-centre | Tertiary cancer centre	August 2007 - April 2012; January 2006 - November 2007; November 2009 -

Study	Country	Cancer site[a]	Sample size (Trial | Routine care)[b]	Median age (Trial | Routine care)[c]	Males (%) (Trial | Routine care)[c]	Females (%) (Trial | Routine care)[c]	Median OS follow-up (years) (Trial | Routine care)	Advanced/Metastatic	Routine care group source	Timeframe information[f]
										November 2016; January 2008 - May 2011 | February 2005 - April 2015
Esteban 2015[10]	Europe	Leukemia	68 | 184	63 | 63	59 | 63	41 | 37	15[e] | 15[e]	No	Single-centre | Not recruited	2000-2014 (treatment)
Field 2013[11]	Australia	CNS	61 | 481	62 | 62	NR | NR	NR | NR	6.3[e] | 10.4[e]	No	Multi-centre | Two co-located hospitals (one public, one private)	1998-2010 (diagnosis)
Filion 2014[12]	Canada	Breast	1137 | 5657	NR | NR	NR | NR	NR | NR	6.1 | 6.1	No	Single-centre | Largest tertiary breast cancer centre in Canada	January 1982 - April 2008 (diagnosis)
Goldman 2017[13]	US	Melanoma	115 | 203	60.2 | 64.1	64.3 | 69	35.7 | 31	7.5[e] | 5[e]	Yes	Single-centre | Perlmutter Cancer Center	July 2006 - December 2013 (diagnosis)
Goyal 2012[14]	US	Prostate	142 | 105	67[d] | 68[d]	100 | 100	0 | 0	6.8[e] | 6.8[e]	Yes	Single-centre | Not offered clinical trials, declined to participate, or trial-ineligible	January 1998 - December 2010 (treatment)
Han 2019[15]	Asia	Gastric	78 | 78	NR | NR	73.1 | 66.7	26.9 | 33.3	1.1 | 1.1	Yes	Single-centre | Seoul National University Bundang Hospital	January 2010 - December 2012 (treatment)
Hébert-Croteau 2005[16]	Canada	Breast	207 | 569	NR | NR	NR | NR	NR | NR	6.8 | 6.8	No	Multi-centre | Five health regions	1988-1994 (diagnosis)
Kalata 2009a[17]	Europe	Colorectal (neoadjuvant CRT before resection)	379 | 106	61.6 | 62.3	71.5 | 67	28.5 | 33	3.4 | 3.4	Yes	Multi-centre | Large urban and rural areas	February 1995 - September 2002 | 1997-2003
Kalata 2009b[17]	Europe	Colorectal (resection with or without postoperative CRT)	278 | 265	61.4 | 65.1	66.9 | 56.2	33.1 | 43.8	3.4 | 3.4	Yes	Multi-centre | Large urban and rural areas	February 1995 - September 2002 | 1997-2003
Keizman 2016[18]	Asia	Kidney	49 | 49	64 | 64	67 | 67	33 | 33	7.5[e] | 5.8[e]	Yes	Multi-centre | Six centres across the US and Israel	February 2004 - December 2013 (treatment)
Khoja 2016[19]	UK	Ovarian	30 | 30	NR | NR	0 | 0	100 | 100	12.5[e] | 12.5[e]	No	Single-centre | The Christie NHS Foundation Trust	2002-2008 | NR

Study	Country	Cancer site[a]	Sample size (Trial | Routine care)[b]	Median age (Trial | Routine care)[c]	Males (%) (Trial | Routine care)[c]	Females (%) (Trial | Routine care)[c]	Median OS follow-up (years) (Trial | Routine care)	Advanced/Metastatic	Routine care group source	Timeframe information[f]
Kostos 2021a[20]	Australia	Pancreatic	431 | 139	62 | 68	57 | 49.3	43 | 50.6	0.8 | 2	Yes	Multi-centre | 13 sites	May 2009 - April 2012 | January 2014 - June 2019
Kostos 2021b[20]	Australia	Breast	402 | 167	54 | 58	0 | 0.5	100 | 99.5	8.3 | 1.9	Yes	Multi-centre | 22 sites	February 2008 - July 2010 | January 2014 - June 2019
Le Du 2016[21]	US	Breast	285 | 367	NR | NR	NR | NR	NR | NR	7.2 | 7.2	Yes	Single-centre | MD Anderson Cancer Center	January 2000 - December 2010 (treatment)
Mayers 2001[22]	Canada	Breast	160 | 519	45 | 45	0 | 0	100 | 100	9.6 | 9.6	No	Single-centre | Princess Margaret Hospital	1980-1990 (treatment)
Melnick 2022[23]	US	CNS	89 | 276	56.5[d] | 58.7[d]	NR | NR	NR | NR	6[e] | 6[e]	No	Single-centre | University of Florida Health	2011-2020 (treatment)
Merkhofer 2021[24]	US	NSCLC	40 | 175	62[d] | 62[d]	35 | 49	65 | 51	4[e] | 10[e]	Yes	Single-centre | Seattle Cancer Care Alliance	January 2007 - December 2015 (diagnosis)
Mol 2013[25]	Europe	Colorectal	394 | 224	61 | 61	65 | 59	35 | 41	8[e] | 5.5[e]	Yes	Multi-centre | 29 hospitals	January 2003 - December 2004
Ohno 2019[26]	Asia	Breast	227 | 34	58 | 58	0 | 0	100 | 100	4[e] | 4[e]	Yes	Multi-centre | Declined to participate	August 2009 - July 2010
Phillips 2020a[27]	Canada	Myelodysplastic syndromes (azacitidine)	179 | 1183	69 | 75	73.7 | NR	26.3 | NR	3[e] | 7[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	February 2004 - August 2006 | 2008-2016
Phillips 2020b[27]	Canada	Leukemia (azacitidine)	55 | 376	70 | 72	67.3 | NR	32.7 | NR	3[e] | 5.5[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	November 2003 - July 2007 | 2008-2016
Phillips 2020c[27]	Canada	Non-Hodgkin lymphoma (bendamustine)	114 | 530	69 | 69	NR | NR	NR | NR	10[e] | 4[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	October 2003 - August 2010 | 2008-2016
Phillips 2020d[27]	Canada	Multiple myeloma (bortezomib)	584 | 4193	NR | NR	NR | NR	NR | NR	6[e] | 8[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	December 2004 - September 2006; August 2005 - January 2008 | 2008-2016
Phillips 2020e[27]	Canada	Hodgkin lymphoma (brentuximab)	102 | 58	31 | 37	47 | NR	53 | NR	2[e] | 3.3[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	February 2009 - August 2009 | 2008-2016
Phillips 2020f[27]	Canada	T-cell lymphoma (brentuximab)	58 | 24	52 | 65	56.9 | NR	43.1 | NR	1.5[e] | 2.8[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	June 2009 - May 2010 | 2008-2016

Study	Country	Cancer site[a]	Sample size (Trial | Routine care)[b]	Median age (Trial | Routine care)[c]	Males (%) (Trial | Routine care)[c]	Females (%) (Trial | Routine care)[c]	Median OS follow-up (years) (Trial | Routine care)	Advanced/Metastatic	Routine care group source	Timeframe information[f]
Phillips 2020g[27]	Canada	Leukemia (obinutuzumab)	333 | 249	74 | 76	61 | NR	39 | NR	3.8[e] | 1.8[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	February 2014 - September 2018 | 2008-2016
Phillips 2020h[27]	Canada	Leukemia (rituximab)	408 | 1523	61 | 64	74 | NR	26 | NR	5.5[e] | 7[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	July 2003 - July 2007 | 2008-2016
Phillips 2020i[27]	Canada	Pancreatic (gemcitabine/nab-paclitaxel)	431 | 602	62 | 69	56.8 | NR	43.2 | NR	3[e] | 2[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	May 2009 - April 2012 | 2008-2016
Phillips 2020j[27]	Canada	Pancreatic (folforinox)	171 | 1056	61 | 70	62 | NR	38 | NR	4[e] | 5.5[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	December 2005 - October 2009 | 2008-2016
Phillips 2020k[27]	Canada	Gastric (trastuzumab)	298 | 409	59 | 64	77 | NR	23 | NR	3[e] | 5.5[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	September 2005 - December 2008 | 2008-2016
Phillips 2020l[27]	Canada	Breast (eribulin)	508 | 733	55 | 57	0 | NR	100 | NR	2.3[e] | 3.8[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	November 2006 - November 2008 | 2008-2016
Phillips 2020m[27]	Canada	Breast (pertuzumab)	402 | 827	54 | 56	0 | NR	100 | NR	6[e] | 3.5[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	February 2008 - July 2010 | 2008-2016
Phillips 2020n[27]	Canada	Breast (second-line trastuzumab emtansine)	495 | 320	53 | 56	0.2 | NR	99.8 | NR	5.5[e] | 3[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	February 2009 - October 2011 | 2008-2016
Phillips 2020o[27]	Canada	Breast (third- or subsequent-line trastuzumab emtansine)	404 | 52	53 | 58	0.7 | NR	99.3 | NR	3.3[e] | 2.8[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	September 2011 - November 2012 | 2008-2016
Phillips 2020p[27]	Canada	Cervical (bevacizumab)	227 | 54	48 | 46	0 | 0	100 | 100	3[e] | 1.3[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	April 2009 - January 2012 | 2008-2016
Phillips 2020q[27]	Canada	Ovarian (bevacizumab)	764 | 53	57 | 62	0 | 0	100 | 100	5[e] | 1.5[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	December 2006 - February 2009 | 2008-2016
Phillips 2020r[27]	Canada	Malignant pleural mesothelioma (pemetrexed)	226 | 204	61 | 71	81.4 | NR	18.6 | NR	2.5[e] | 3[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	April 1999 - March 2001 | 2008-2016
Phillips 2020s[27]	Canada	NSCLC (second-line pemetrexed)	265 | 459	59 | 65	NR | NR	NR | NR	2[e] | 8[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	March 2001 - February 2002 | 2008-2016

Study	Country	Cancer site[a]	Sample size (Trial | Routine care)[b]	Median age (Trial | Routine care)[c]	Males (%) (Trial | Routine care)[c]	Females (%) (Trial | Routine care)[c]	Median OS follow-up (years) (Trial | Routine care)	Advanced/Metastatic	Routine care group source	Timeframe information[f]
Phillips 2020t[27]	Canada	NSCLC (first-line/maintenance pemetrexed)	359 | 1424	61 | 66	56 | NR	44 | NR	3[e] | 4.5[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	February 2009 - July 2010 | 2008-2016
Phillips 2020u[27]	Canada	Melanoma (ipilimumab)	137 | 103	57 | 63	59.1 | NR	40.9 | NR	4.5[e] | 4.5[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	September 2004 - August 2008 | 2008-2016
Phillips 2020v[27]	Canada	Melanoma (pembrolizumab)	279 | 274	63 | 69	57.7 | NR	42.3 | NR	1.5[e] | 1[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	September 2013 - March 2014 | 2008-2016
Phillips 2020w[27]	Canada	Prostate (cabazitaxel)	378 | 188	68 | 70	100 | 100	0 | 0	2.5[e] | 2.8[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	January 2007 - October 2008 | 2008-2016
Phillips 2020x[27]	Canada	Prostate (docetaxel)	397 | 495	64 | 67	100 | 100	0 | 0	6[e] | 2[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	July 2006 - December 2012 | 2008-2016
Phillips 2020y[27]	Canada	Kidney (temsirolimus)	209 | 64	58 | 63	66.5 | NR	33.5 | NR	2[e] | 5[e]	No	Multi-centre | Cancer Care Ontario's New Drug Funding Program	July 2003 - April 2005 | 2008-2016
Schapira 2020[28]	US	Leukemia	214 | 214	6.5[d] | 6.9[d]	43.9 | 43	56.1 | 57	9.4 | 9.4	No	Single-centre | Children's Hospital of Philadelphia	2000-2010 (diagnosis)
Schwentner 2013[29]	Europe	Breast	1255 | 4888	55.8[d] | 62.1[d]	0 | 0	100 | 100	15[e] | 15[e]	No	Multi-centre | Department of Gynaecology and Obstetrics at the University of Ulm and 16 partner clinics	1992-2008 (diagnosis or treatment)
Shahar 2012[30]	Asia	CNS	60 | 36	55.5[d] | 54.6[d]	NR | NR	NR | NR	2.5[e] | 3.3[e]	No	Single-centre | Tel Aviv Medical Center	March 1995 - May 2008 (treatment)
Strahlendorf 2018[31]	Canada	Leukemia	1408 | 1161	NR | NR	57.5 | 55.2	42.5 | 44.8	13[e] | 13[e]	No	Multi-centre | 17 tertiary pediatric oncology centres in Canada	January 2001 - December 2012 (diagnosis)
Tanai 2009[32]	Asia	NSCLC	196 | 76	NR | NR	60.7 | 60.5	39.3 | 39.5	1.1 | 1.1	Yes	Single-centre | Declined participation in trials	October 2000 - June 2002; June 2003 - October 2005 | October 2000 - October 2005 (invitation to participate in trials)
Tanai 2011[33]	Asia	Gastric	190 | 96	NR | NR	77 | 67	23 | 33	0.9 | 0.8	Yes	Single-centre | Declined participation in trials	November 2000 - January 2006 (treatment)

Study	Country	Cancer site[a]	Sample size (Trial | Routine care)[b]	Median age (Trial | Routine care)[c]	Males (%) (Trial | Routine care)[c]	Females (%) (Trial | Routine care)[c]	Median OS follow-up (years) (Trial | Routine care)	Advanced/Metastatic	Routine care group source	Timeframe information[f]
Templeton 2013[34]	Canada	Prostate	43 | 314	68 | 71	100 | 100	0 | 0	6[e] | 6[e]	Yes	Single-centre | Princess Margaret Cancer Centre	February 2001 - December 2011 (treatment)
Toxopeus 2018[35]	Europe	Esophageal	208 | 173	60[d] | 62[d]	78 | 79	22 | 21	5[e] | 5[e]	No	Single-centre | Post-CROSS cohort	February 2001 - January 2004; March 2004 - December 2008 | July 2008 - December 2013 (treatment)
Truong 2018[36]	Canada	Leukemia	94 | 303	NR | NR	52.1 | 47.9	47.9 | 52.1	11[e] | 13[e]	No	Multi-centre | 17 tertiary pediatric oncology centres in Canada	January 2001 - December 2012 (diagnosis)
Unger 2014a[37]	US	CNS (SWOG-0001)	89 | 2264	56 | NR	62 | NR	38 | NR	5[e] | 5[e]	No	Multi-centre | SEER	2001-2005
Unger 2014b[37]	US	Breast (SWOG-9313)	1423 | 9941	NR | NR	0 | 0	100 | 100	5[e] | 5[e]	No	Multi-centre | SEER	1994-1997
Unger 2014c[37]	US	Breast (SWOG-0012)	391 | 2855	NR | NR	0 | 0	100 | 100	5[e] | 5[e]	No	Multi-centre | SEER	2001-2005
Unger 2014d[37]	US	Pancreatic (SWOG-0205)	82 | 1943	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	Yes	Multi-centre | SEER	2004-2006
Unger 2014e[37]	US	Bladder (SWOG-8795)	191 | 5059	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	No	Multi-centre | SEER	1988-1992
Unger 2014f[37]	US	Kidney (SWOG-8949)	95 | 1569	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	Yes	Multi-centre | SEER	1991-1998
Unger 2014g[37]	US	Leukemia (SWOG-9031)	85 | 1672	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	No	Multi-centre | SEER	1991-1994
Unger 2014h[37]	US	Leukemia (SWOG-9333)	129 | 2320	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	No	Multi-centre | SEER	1995-1998
Unger 2014i[37]	US	NSCLC (SWOG-8738)	94 | 4084	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	Yes	Multi-centre | SEER	1988-1990
Unger 2014j[37]	US	NSCLC (SWOG-9308)	178 | 4755	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	Yes	Multi-centre | SEER	1993-1995
Unger 2014k[37]	US	NSCLC (SWOG-9509)	205 | 4817	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	Yes	Multi-centre | SEER	1996-1997
Unger 2014l[37]	US	NSCLC (SWOG-0003)	165 | 7727	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	Yes	Multi-centre | SEER	2000-2002
Unger 2014m[37]	US	SCLC (SWOG-0124)	266 | 2790	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	Yes	Multi-centre | SEER	2002-2007
Unger 2014n[37]	US	Melanoma (SWOG-8642)	96 | 738	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	No	Multi-centre | SEER	1987-1990
Unger 2014o[37]	US	Melanoma (SWOG-9035)	299 | 1347	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	No	Multi-centre | SEER	1992-1996

Study	Country	Cancer site[a]	Sample size (Trial | Routine care)[b]	Median age (Trial | Routine care)[c]	Males (%) (Trial | Routine care)[c]	Females (%) (Trial | Routine care)[c]	Median OS follow-up (years) (Trial | Routine care)	Advanced/Metastatic	Routine care group source	Timeframe information[f]
Unger 2014p[37]	US	Multiple myeloma (SWOG-8624)	139 | 3515	NR | NR	NR | NR	NR | NR	5[e] | 5[e]	No	Multi-centre | SEER	1987-1990
Verstovsek 2012a[38]	US	Leukemia (intermediate-2-risk)	34 | 140	NR | NR	NR | NR	NR | NR	2.7 | 4.6	No	Multi-centre | MDACC, University of Pavia, and Hospital Niguarda cà Granda	June 2007 - December 2007 | 1978-2010
Verstovsek 2012b[38]	US	Leukemia (high-risk)	63 | 160	NR | NR	NR | NR	NR | NR	2.7 | 4.6	No	Multi-centre | MDACC, University of Pavia, and Hospital Niguarda cà Granda	June 2007 - December 2007 | 1978-2010
Xu 2020a[39]	Asia	Head and neck (NCT00677118)	96 | 167	44[d] | 45[d]	74 | 74.9	26 | 25.1	3.2 | 5[e]	Yes	Multi-centre | NCT04108338	June 2006 - March 2010 | April 2009 - December 2016 (treatment)
Xu 2020b[39]	Asia	Head and neck (NCT01245959)	209 | 367	44[d] | 44[d]	71.8 | 73.6	28.2 | 26.4	3.8 | 5[e]	Yes	Multi-centre | NCT04108338	March 2011 - August 2013 | April 2009 - December 2016 (treatment)
Xu 2020c[39]	Asia	Head and neck (NCT01872962)	215 | 351	45[d] | 45[d]	70.2 | 69.2	29.8 | 30.8	3.6 | 3[e]	Yes	Multi-centre | NCT04108338	December 2013 - September 2016 | April 2009 - December 2016 (treatment)

CNS: central nervous system; CRT: chemoradiotherapy; NR: not reported; NSCLC: non-small cell lung cancer; OS: overall survival; SCLC: small cell lung cancer.
[a]Additional information was provided to distinguish comparisons in multi-comparison studies.
[b]Sample sizes used to calculate the overall survival hazard ratios.
[c]Age or sex was only reported if the same sample size was used to calculate the overall survival hazard ratios, otherwise we wrote "NR".
[d]Mean.
[e]If the median was not reported, follow-up time was taken from other reported follow-up times or derived from the endpoint of survival curves.
[f]If timeframes were different, they were presented as "Trial | Routine care".

References

1. Abdel-Rahman, O. Comparison of outcomes of radiotherapy-treated localized prostate cancer patients within a clinical trial setting versus real-life setting. *Future Oncol* **15**, 1269–1277 (2019).

2. Abu-Hejleh, T. *et al.* The Effect of Receiving Treatment Within a Clinical Trial Setting on Survival and Quality of Care Perception in Advanced Stage Non–Small Cell Lung Cancer: *American Journal of Clinical Oncology* **39**, 126–131 (2016).

3. Arrieta, O. *et al.* Survival of Patients with Advanced Non-Small Cell Lung Cancer Enrolled in Clinical Trials. *Oncology* **91**, 185–193 (2016).

4. Aung, T. N. *et al.* Do Patients With Multiple Myeloma Enrolled in Clinical Trials Live Longer? *American Journal of Clinical Oncology* **44**, 603–612 (2021).

5. Balyasny, S. *et al.* Association Between Participation in Clinical Trials and Overall Survival Among Children With Intermediate- or High-risk Neuroblastoma. *JAMA Network Open* **4**, e2116248 (2021).

6. Chow, C. J. *et al.* Does enrollment in cancer trials improve survival? *Journal of the American College of Surgeons* **216**, 774–781 (2013).

7. Ejlertsen, B. *et al.* DBCG trial 89B comparing adjuvant CMF and ovarian ablation: Similar outcome for eligible but non-enrolled and randomized breast cancer patients. *Acta Oncologica* **47**, 709–717 (2008).

8. Elting, L. S. *et al.* Generalizability of cancer clinical trial results: prognostic differences between participants and nonparticipants. *Cancer* **106**, 2452–8 (2006).

9. Elumalai T. *et al.* Translation of Prognostic and Pharmacodynamic Biomarkers from Trial to Non-trial Patients with Metastatic Castration-resistant Prostate Cancer Treated with Docetaxel. *Clinical Oncology* **34**, e291–e297 (2022).

10. Esteban, D. *et al.* Patients with relapsed/refractory chronic lymphocytic leukaemia may benefit from inclusion in clinical trials irrespective of the therapy received: a case-control retrospective analsysis. *Blood Cancer Journal* **5**, e356–e356 (2015).

11. Field, K. M. *et al.* Clinical trial participation and outcome for patients with glioblastoma: Multivariate analysis from a comprehensive dataset. *Journal of Clinical Neuroscience* **20**, 783–789 (2013).

12. Provencher L, F. M. Survival Rate of Breast Cancer Patients who Participated in Clinicals Trials Versus those who did not. *Journal of Clinical Trials* **04**, (2014).

13. Goldman, C. *et al.* Outcomes in Melanoma Patients Treated with BRAF/MEK-Directed Therapy or Immune Checkpoint Inhibition Stratified by Clinical Trial versus Standard of Care. *Oncology* **93**, 164–176 (2017).

14. Goyal, J. *et al.* The effect of clinical trial participation versus non-participation on overall survival in men receiving first-line docetaxel-containing chemotherapy for metastatic castration-resistant prostate cancer: CLINICAL TRIAL PARTICIPATION AND SURVIVAL IN MEN WITH CRPC. *BJU International* **110**, E575–E582 (2012).

15. Han, J. J. *et al.* Clinical characteristics and outcomes of patients enrolled in clinical trials compared with those of patients outside clinical trials in advanced gastric cancer. *Asia-Pacific journal of clinical oncology* **15**, 158–165 (2019).

16. Hébert-Croteau, N., Brisson, J., Lemaire, J. & Latreille, J. The benefit of participating to clinical research. *Breast Cancer Research and Treatment* **91**, 279–281 (2005).

17. Kalata, P. *et al.* Differences Between Clinical Trial Participants and Patients in a Population-Based Registry: the German Rectal Cancer Study vs. the Rostock Cancer Registry. *Diseases of the Colon & Rectum* **52**, 425–437 (2009).

18. Keizman, D. *et al.* Is there a 'trial effect' on outcome of patients with metastatic renal cell carcinoma treated with sunitinib? *Cancer research and treatment* **48**, 281–287 (2016).

19. Khoja, L. *et al.* Does clinical trial participation improve outcomes in patients with ovarian cancer? *ESMO Open* **1**, e000057 (2016).

20. Kostos L *et al.* Cancer clinical trial vs real-world outcomes for standard of care first-line treatment in the advanced disease setting. *Int J Cancer* **149**, 409–419 (2021).

21. Le Du, F. *et al.* Impact of clinical trial on survival outcomes. *Breast Cancer Res Treat* **159**, 273–81 (2016).

22. Mayers, C., Panzarella, T. & Tannock, I. F. Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. *Cancer* **91**, 2246–2257 (2001).

23. Melnick KF *et al.* The trial effect in patients with glioblastoma: effect of clinical trial enrollment on overall survival. *J Neurooncol* **159**, 479–484 (2022).

24. Merkhofer, C. M., Eaton, K. D., Martins, R. G., Ramsey, S. D. & Goulart, B. H. L. Impact of Clinical Trial Participation on Survival of Patients with Metastatic Non-Small Cell Lung Cancer. *Clinical Lung Cancer* **22**, 523–530 (2021).

25. Mol, L., Koopman, M., van Gils, C. W. M., Ottevanger, P. B. & Punt, C. J. A. Comparison of treatment outcome in metastatic colorectal cancer patients included in a clinical trial versus daily practice in The Netherlands. *Acta Oncologica* **52**, 950–955 (2013).

26. Ohno, S. *et al.* Participants in a randomized controlled trial had longer overall survival than non-participants: a prospective cohort study. *Breast Cancer Res Treat* (2019) doi:10.1007/s10549-019-05276-y.

27. Phillips, C. M. *et al.* Assessing the efficacy-effectiveness gap for cancer therapies: A comparison of overall survival and toxicity between clinical trial and population-based, real-world data for contemporary parenteral cancer therapeutics. *Cancer* **126**, 1717–1726 (2020).

28. Schapira, M. M. *et al.* Outcomes among pediatric patients with cancer who are treated on trial versus off trial: A matched cohort study. *Cancer* **126**, 3471–3482 (2020).

29. Schwentner, L. *et al.* Participation in adjuvant clinical breast cancer trials: does study participation improve survival compared to guideline adherent adjuvant treatment? A retrospective multi-centre cohort study of 9,433 patients. *Eur J Cancer* **49**, 553–63 (2013).

30. Shahar, T. *et al.* The impact of enrollment in clinical trials on survival of patients with glioblastoma. *Journal of Clinical Neuroscience* **19**, 1530-1534 (2012).

31. Strahlendorf, C. *et al.* Enrolling children with acute lymphoblastic leukaemia on a clinical trial improves event-free survival: a population-based study. *Br J Cancer* **118**, 744–749 (2018).

32. Tanai, C. *et al.* Characteristics and outcomes of patients with advanced non-small-cell lung cancer who declined to participate in randomised clinical chemotherapy trials. *British Journal of Cancer* **100**, 1037–1042 (2009).

33. Tanai, C. *et al.* Characteristics and outcomes of patients with advanced gastric cancer who declined to participate in a randomized clinical chemotherapy trial. *Journal of Oncology Practice* **7**, 148–153 (2011).

34. Templeton, A. J. *et al.* Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials. *Annals of Oncology* **24**, 2972–2977 (2013).

35. Toxopeus, E. *et al.* Outcome of Patients Treated Within and Outside a Randomized Clinical Trial on Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: Extrapolation of a Randomized Clinical Trial (CROSS). *Annals of Surgical Oncology* **25**, 2441–2448 (2018).

36. Truong, T. H. *et al.* Enrollment on clinical trials does not improve survival for children with acute myeloid leukemia: A population-based study. *Cancer* **124**, 4098–4106 (2018).

37. Unger, J. M. *et al.* Comparison of Survival Outcomes Among Cancer Patients Treated In and Out of Clinical Trials. *JNCI: Journal of the National Cancer Institute* **106**, (2014).

38. Verstovsek, S. *et al.* Long-term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: survival advantage in comparison to matched historical controls. *Blood* **120**, 1202–1209 (2012).

39. Xu, C. *et al.* Association between outcome disparities and pragmatic features related to clinical trial and real-world settings in nasopharyngeal carcinoma: A population-based retrospective cohort study, 2006-2016. *Radiotherapy and oncology* **151**, 306–313 (2020).

eTable 9. Quality scoring for adjustment in individual studies. Adjusted = 1 point; not adjusted = 0 points; not reported or unclear = -1 point. The quality scores were categorized as low (≤6 points), medium (7 points), and high (≥8 points).

Study \ Adjustment	Age	Sex	Race/ethnicity	Comorbidities	Stage	Histology	Performance status	Line of treatment	Eligibility	Routine care group includes trial refusers	Treatment	Timeframe	Single trial comparison	Routine care group from registries	Similar trial and routine care group source	Sample size	Adjustment score
Abdel-Rahman 2019	1	1	1	1	1	0	1	1	1	-1	1	1	1	1	0	1	**12**
Abu-Hejleh 2016	1	1	1	1	1	1	1	0	-1	-1	1	1	0	1	1	0	**9**
Arrieta 2016	1	1	1	1	1	1	1	0	-1	-1	-1	1	0	0	1	1	**7**
Aung 2021	1	1	1	1	1	0	0	1	0	-1	0	1	0	0	1	1	**8**
Balyasny 2021a	1	1	1	0	1	1	0	0	-1	-1	0	1	0	1	1	1	**7**
Balyasny 2021b	1	1	1	0	1	1	0	0	-1	-1	0	1	0	1	1	1	**7**
Chow 2013	1	1	1	0	1	1	0	0	0	-1	0	1	0	1	1	1	**8**
Ejlertsen 2008	1	1	1	0	0	1	0	0	1	0	1	1	1	1	1	1	**11**
Elting 2006a	1	1	1	1	1	1	1	1	-1	-1	-1	1	0	1	0	1	**8**
Elting 2006b	1	1	1	1	1	1	1	1	-1	-1	-1	1	0	1	0	1	**8**
Elumalai 2022	0	1	0	0	0	0	1	0	-1	-1	1	1	0	0	0	1	**3**
Esteban 2015	1	1	1	1	1	0	1	0	1	0	1	1	0	0	1	0	**10**
Field 2013	1	1	0	0	1	0	1	0	-1	-1	0	1	0	1	1	0	**5**
Filion 2014	1	1	0	1	1	1	0	0	-1	0	1	1	0	0	1	1	**8**
Goldman 2017	1	1	0	0	0	0	0	1	-1	-1	1	1	0	1	1	0	**5**
Goyal 2012	1	1	0	0	1	0	1	0	0	0	0	0	0	0	1	0	**5**
Han 2019	1	1	1	1	0	1	0	1	-1	-1	1	1	0	0	1	0	**7**
Hébert-Croteau 2005	1	1	0	1	1	0	0	0	1	-1	0	1	0	1	1	1	**8**
Kalata 2009a	1	1	1	0	1	0	0	0	-1	-1	1	1	1	1	0	1	**7**
Kalata 2009b	1	1	1	0	1	0	0	0	-1	-1	1	1	1	1	0	1	**7**

Adjustment / Study	Age	Sex	Race/ethnicity	Comorbidities	Stage	Histology	Performance status	Line of treatment	Eligibility	Routine care group includes trial refusers	Treatment	Timeframe	Single trial comparison	Routine care group from registries	Similar trial and routine care group source	Sample size	Adjustment score
Keizman 2016	1	1	0	0	1	1	1	1	1	-1	1	1	0	0	1	0	**9**
Khoja 2016	1	1	0	0	1	1	1	1	0	1	1	0	0	0	1	0	**9**
Kostos 2021a	0	0	0	0	0	0	1	1	1	0	1	0	1	1	0	1	**7**
Kostos 2021b	0	1	0	0	0	0	1	1	1	0	1	0	1	1	0	1	**8**
Le Du 2016	1	1	1	1	0	0	0	1	1	-1	-1	1	0	0	1	1	**7**
Mayers 2001	0	1	0	0	1	0	0	0	-1	-1	1	1	0	0	1	0	**3**
Melnick 2022	1	0	0	0	0	0	1	0	-1	0	1	1	0	0	1	0	**4**
Merkhofer 2021	1	1	1	0	0	1	1	1	1	-1	-1	1	0	1	1	0	**8**
Mol 2013	1	1	0	0	1	0	1	1	1	0	1	1	1	1	0	1	**11**
Ohno 2019	1	1	1	0	0	0	1	1	1	0	-1	1	1	1	1	1	**10**
Phillips 2020a	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	0	**3**
Phillips 2020b	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	0	**3**
Phillips 2020c	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	0	**3**
Phillips 2020d	0	0	0	0	0	0	0	1	0	-1	1	0	0	1	0	1	**3**
Phillips 2020e	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	0	**3**
Phillips 2020f	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	0	**3**
Phillips 2020g	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020h	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020i	0	0	0	0	0	0	0	1	0	-1	1	1	1	1	0	1	**5**
Phillips 2020j	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	0	**3**
Phillips 2020k	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020l	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020m	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020n	0	0	0	0	0	0	0	1	0	-1	1	1	1	1	0	1	**5**

Study \ Adjustment	Age	Sex	Race/ethnicity	Comorbidities	Stage	Histology	Performance status	Line of treatment	Eligibility	Routine care group includes trial refusers	Treatment	Timeframe	Single trial comparison	Routine care group from registries	Similar trial and routine care group source	Sample size	**Adjustment score**
Phillips 2020o	0	0	0	0	0	0	0	1	0	-1	1	1	1	1	0	1	**5**
Phillips 2020p	0	0	0	0	0	0	0	1	0	-1	1	1	1	1	0	1	**5**
Phillips 2020q	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020r	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020s	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020t	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020u	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	0	**3**
Phillips 2020v	0	0	0	0	0	0	0	1	0	-1	1	1	1	1	0	1	**5**
Phillips 2020w	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Phillips 2020x	0	0	0	0	0	0	0	1	0	-1	1	1	1	1	0	1	**5**
Phillips 2020y	0	0	0	0	0	0	0	1	0	-1	1	0	1	1	0	1	**4**
Schapira 2020	1	1	1	1	0	0	0	1	1	-1	-1	1	0	1	1	1	**8**
Schwentner 2013	1	1	1	1	1	0	0	0	-1	-1	-1	1	0	0	1	1	**5**
Shahar 2012	1	0	0	0	0	0	1	0	1	-1	-1	1	0	0	1	0	**3**
Strahlendorf 2018	1	1	1	0	0	0	0	0	0	0	0	1	0	1	1	1	**7**
Tanai 2009	1	1	1	0	1	0	1	1	1	0	-1	1	0	0	1	0	**8**
Tanai 2011	1	1	1	0	1	1	1	1	1	0	1	1	1	0	1	0	**12**
Templeton 2013	1	1	0	1	1	0	1	1	0	0	1	1	0	0	1	0	**9**
Toxopeus 2018	1	1	0	0	1	1	0	0	0	1	1	0	0	0	0	1	**7**
Truong 2018	1	1	1	0	1	0	0	0	0	0	0	1	0	1	1	0	**7**
Unger 2014a	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014b	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	1	**8**
Unger 2014c	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	1	**8**

Adjustment / Study	Age	Sex	Race/ethnicity	Comorbidities	Stage	Histology	Performance status	Line of treatment	Eligibility	Routine care group includes trial refusers	Treatment	Timeframe	Single trial comparison	Routine care group from registries	Similar trial and routine care group source	Sample size	**Adjustment score**
Unger 2014d	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014e	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014f	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014g	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014h	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014i	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014j	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014k	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	1	**8**
Unger 2014l	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014m	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	1	**8**
Unger 2014n	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Unger 2014o	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	1	**8**
Unger 2014p	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Verstovsek 2012a	0	1	0	0	1	0	1	0	1	-1	0	0	1	1	0	0	**5**
Verstovsek 2012b	0	1	0	0	1	0	1	0	1	-1	0	0	1	1	0	0	**5**
Xu 2020a	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	0	**7**
Xu 2020b	0	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	1	**7**
Xu 2020c	1	1	1	0	1	1	0	0	0	-1	0	1	1	1	0	1	**8**

479

(7) SUBGROUP ANALYSES BY COMPARISON CHARACTERISTICS

eTable 10. Results of subgroup analyses of comparisons by various characteristics.

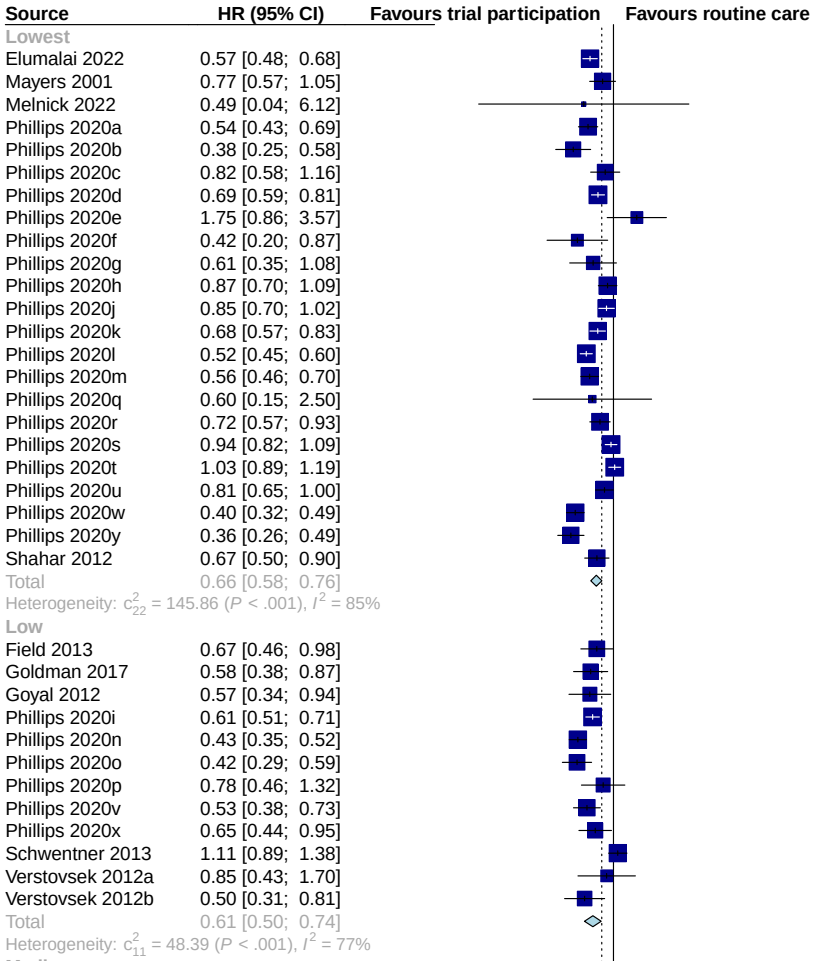
		Pooled HR-random model		Heterogeneity		Significance
Characteristics	**No. of comparisons**	**HR (95% CI)**	**P-value**	**Q**	**Q P-value**	**P-value[a]**
All comparisons	85	0.76 (0.69-0.82)	<0.001	688.56	<0.001	N/A
Patient Characteristics						
Focuses on advanced/metastatic cancer patients	28	0.82 (0.70-0.95)	0.0076	84.92	<0.001	0.25
Does not focus on advanced/metastatic cancer patients	57	0.73 (0.66-0.81)	<0.001	603.61	<0.001	
Treatment Characteristics						
Comparisons with crossover	11	0.73 (0.59-0.92)	0.0065	90.03	<0.001	0.30
Comparisons without crossover	27	0.70 (0.60-0.80)	<0.001	163.58	<0.001	
Presence of crossover is unclear	47	0.81 (0.72-0.91)	<0.001	398.02	<0.001	
Intervention type includes drugs	79	0.75 (0.69-0.81)	<0.001	380.66	<0.001	0.43
Intervention type is unknown	6	0.86 (0.61-1.20)	0.37	185.55	<0.001	
Setting Characteristics						
Comparison from the United States	31	0.87 (0.75-1.02)	0.079	238.85	<0.001	0.03
Comparison from other countries	54	0.72 (0.65-0.79)	<0.001	336.40	<0.001	
Routine care group is from a single institution	21	0.79 (0.67-0.93)	0.0052	263.64	<0.001	0.55
Routine care group is from multiple institutions	64	0.74 (0.68-0.82)	<0.001	342.99	<0.001	
Other Characteristics						
Earlier publications (2000-2009)	8	0.81 (0.62-1.06)	0.12	202.88	<0.001	0.60
Later publications (2010-2022)	77	0.75 (0.69-0.81)	<0.001	362.40	<0.001	
Includes data on trial phase	72	0.74 (0.68-0.81)	<0.001	358.82	<0.001	0.47
Missing data on trial phase	13	0.81 (0.66-0.99)	0.042	244.25	<0.001	
Trials are sponsored by industry	37	0.67 (0.59-0.75)	<0.001	234.39	<0.001	0.005
Trials are not sponsored by industry	28	0.90 (0.78-1.03)	0.13	60.93	<0.001	
Trial sponsorship is unknown	20	0.81 (0.70-0.95)	0.01	262.27	<0.001	
Studies with overall survival follow-up time of ≥4 years[b]	51	0.84 (0.76-0.94)	0.0013	325.52	<0.001	0.0039
Studies with overall survival follow-up time of <4 years[b]	33	0.66 (0.58-0.75)	<0.001	195.08	<0.001	

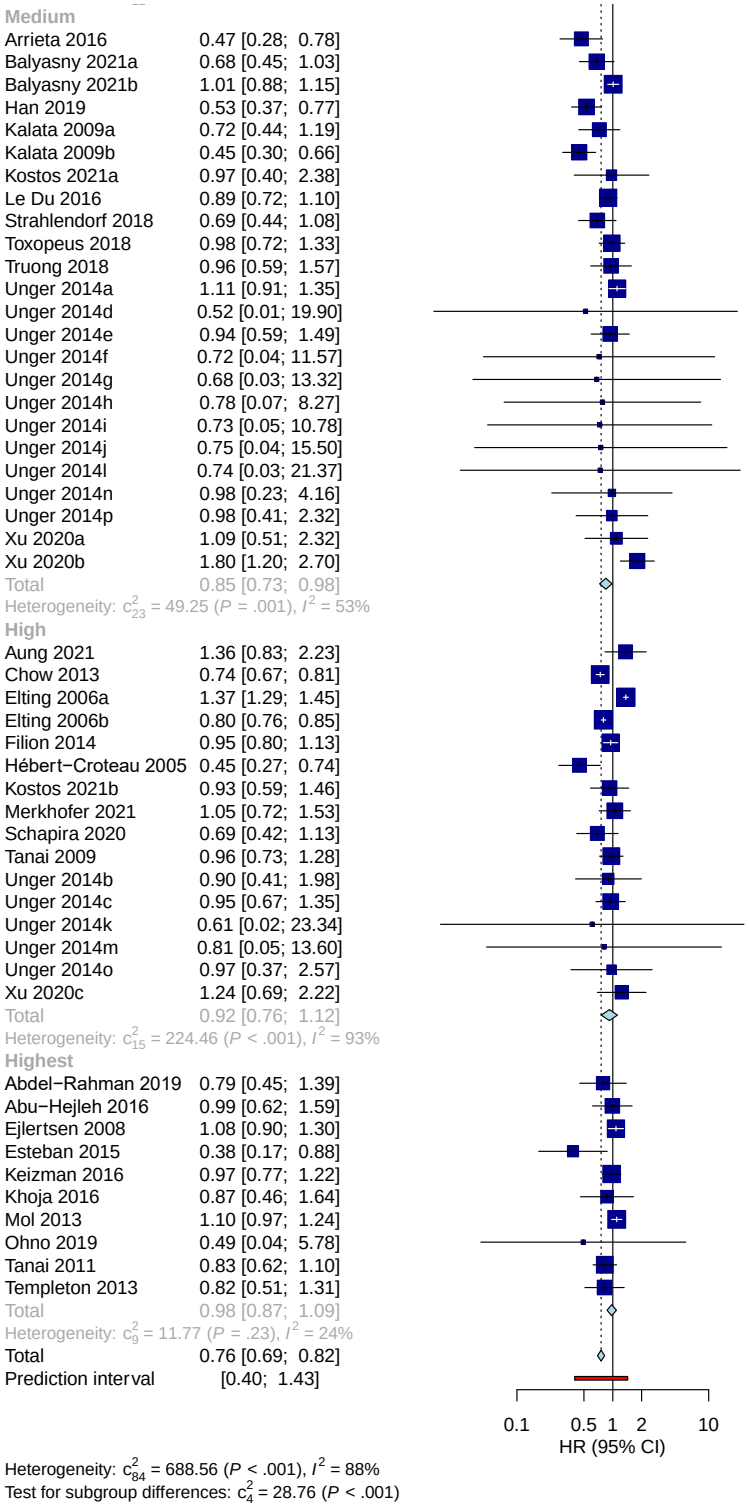
[a]The significance p-value shows whether there is a significant difference between items in each subgroup. For example, in the first category, the p-value is 0.25. This shows that there is no statistically significant difference in survival estimates for comparisons of studies focusing on advanced/metastatic patients vs. studies that did not focus on advanced/metastatic patients.

[b]If the median was not reported, follow-up time was taken from other reported follow-up times or derived from the endpoint of survival curves. This subgroup analysis combines follow-up times from medians and curves.

482

(8) POST-HOC AND EXPLORATORY ANALYSES





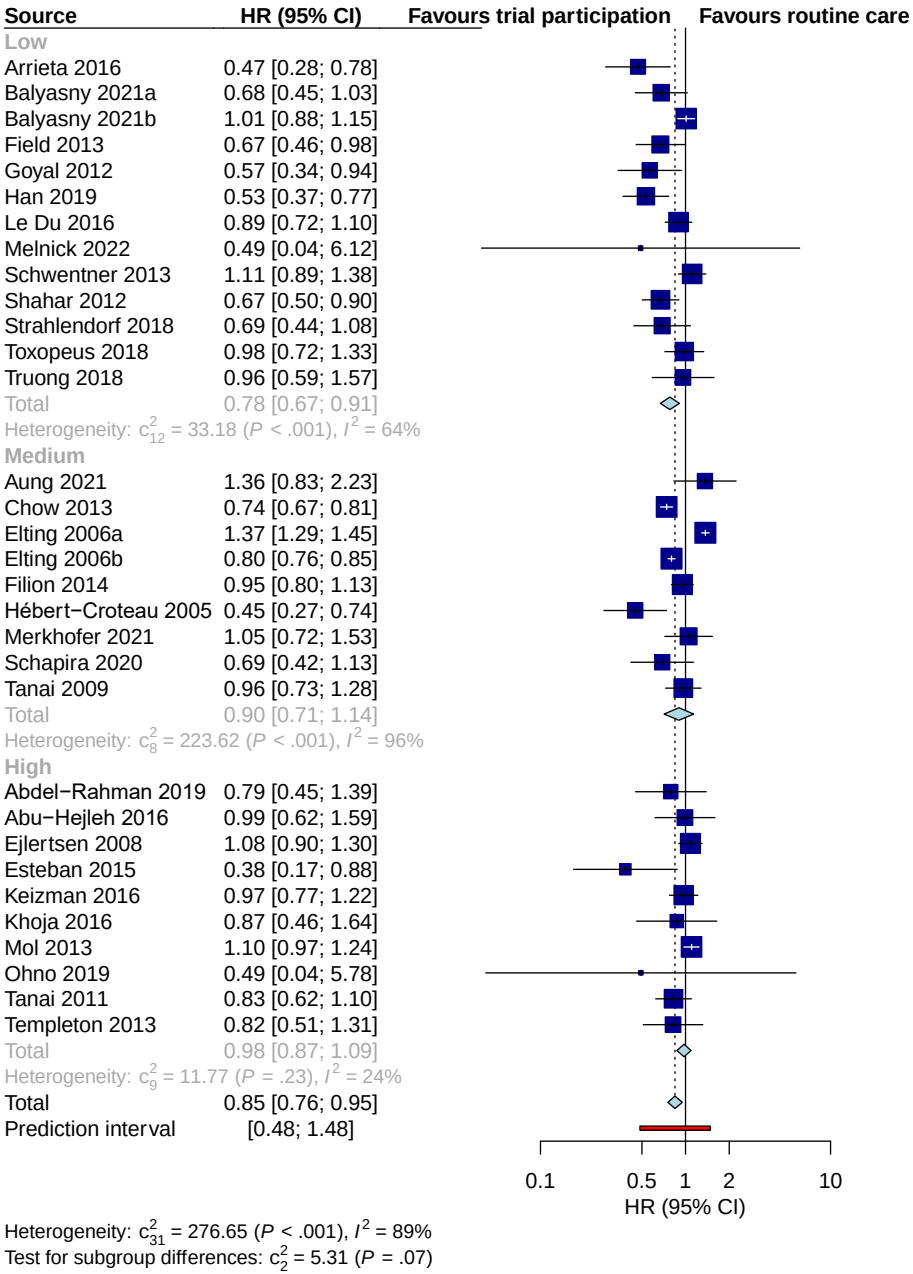
eFigure 2. Forest plot of pooled overall survival hazard ratios in five adjustment score groups: lowest-quality (≤4 points), low-quality (5-6 points), medium-quality (7 points), high-quality (8 points), and highest-quality (≥9 points).

When comparisons were divided into high-quality (≥8 points) and not high-quality (<8 points), the high-quality subgroup (n=26) had an HR of 0.91 (95% CI, 0.80-1.05) and the not high-quality subgroup (n=59) had an HR of 0.70 (95% CI, 0.63-0.77). There was a significant difference between the groups (p=0.0016).

When comparisons were divided into low-quality (≤6 points) and not low-quality (>6 points), the low-quality subgroup (n=35) had an HR of 0.64 (95% CI, 0.58-0.72) and the not low-quality subgroup (n=50) had an HR of 0.89 (95% CI, 0.80-0.98). There was a significant difference between the groups (p<0.0001).

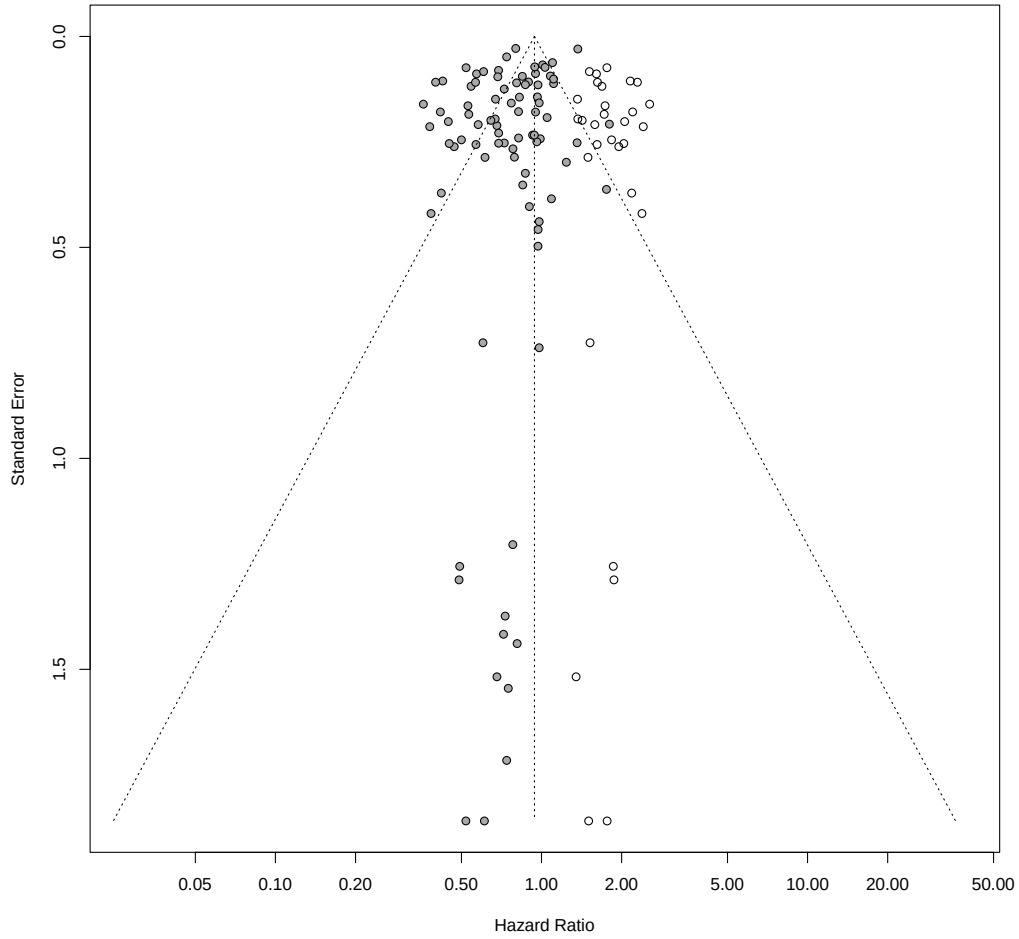
We also performed a linear regression comparing effect size and quality adjustment score, which showed a significant correlation (p = 0.0005). Therefore, quality adjustment score(predictor) influences the studies' effect size. For every increase in quality adjustment score, the effect size is expected to increase by 0.06.

Some studies were not expressly aimed at measuring the trial effect. For example, some studies were focused on comparing characteristics of trial participants and routine care patients to understand their differences (i.e. the efficacy-effectiveness gap). These studies did not try to control for different factors to make the groups more similar. They were interested in understanding the crude and unadjusted differences. When we filter our sample for comparisons that had a stated objective of estimating the trial effect (n=32), the HR was 0.85 (95% CI, 0.76-0.95). The mean quality score for this subset was 7.9. For the other comparisons that did not expressly set out to measure the trial effect or had unclear objectives (n=53), the HR was 0.70 (95% CI, 0.63-0.78). The mean quality score for this subset was 5.4. There was a significant difference between HRs for these two groups (p=0.015).



eFigure 3. Forest plot of pooled overall survival hazard ratios focusing on comparisons that stated their aim as estimating the trial effect (n=32) and grouped by low-quality (≤7 points), medium-quality (8 points), and high-quality (≥9 points) adjustment scores.

(9) FUNNEL PLOT



eFigure 4. Funnel plot showing asymmetry and suggesting possible publication bias with original studies (dark circles) and 30 imputed missing studies (white circles) using the trim-and-fill method. The original pooled hazard ratio for overall survival is 0.76 (95% CI, 0.69-0.82). The pooled hazard ratio for overall survival with imputed missing studies is 0.94 (95% CI, 0.86-1.03).