

Title: Predicting real-world effectiveness using overall survival and progression-free survival from clinical trials: Empirical evidence for the ASCO value framework

Running head: Clinical trial endpoints predicting real-world effectiveness

Authors: Darius N. Lakdawalla, PhD¹; Jason Shafrin, PhD²; Ningqi Hou, PhD²; Desi Peneva, MS²; Seanna Vine, MPH²; Jinhee Park, PhD³; Jie Zhang, PhD³; Ron Brookmeyer, PhD⁴; Robert A. Figlin MD, FACP⁵

Author affiliations:

¹ University of Southern California

² Precision Health Economics

³ Novartis Pharmaceuticals

⁴ University of California, Los Angeles

⁵ Cedars-Sinai Medical Center

Corresponding author:

Darius N. Lakdawalla, PhD

Quintiles Chair in Pharmaceutical Development and Regulatory Innovation

University of Southern California

635 Downey Way, VPD 414-K

Leonard D. Schaeffer Center for Health Policy and Economics

Los Angeles, CA 90089-3333

Email: dlakdawa@usc.edu

Phone: (213) 821-7957

Word count: 2,965 / 3,000

Funding/Support: This study was sponsored by Novartis Pharmaceuticals.

ABSTRACT (348 / 350 words)

Importance: Physicians and patients must translate clinical evidence into assessments of likely real-world benefits. To help them tackle this difficult problem, the American Society of Clinical Oncology (ASCO) recently updated a framework for measuring the real-world value of cancer treatments. The framework assumes that real-world survival benefits will be 20% below progression-free survival gains from randomized controlled trials (RCTs), but will be exactly equal to overall survival (OS) gains from RCTs. No empirical evidence has been cited to support these crucial assumptions.

Objective: To identify empirically the relationships between efficacies of oncology treatments from RCTs using OS or PFS endpoints and their effectiveness in the broader population of patients beyond those enrolled in RCTs.

Design, Setting, and Participants: We abstracted treatment efficacies relative to control using 21 phase III RCTs that reported OS and either PFS or time to progression (TTP) endpoints in breast, colorectal, lung, ovarian, and pancreatic cancer. For these treatments, we estimated real-world OS as the mortality hazard ratio (RW MHR) among patients meeting RCT exclusion/inclusion criteria in Surveillance and Epidemiology End Results (SEER)-Medicare data (1991-2010).

Main Outcome Measures: The main outcome variable was OS observed in the SEER-Medicare data. We used a Cox proportional hazard regression model to calibrate the differences between RW MHR and the hazard ratios based on clinical trials using either OS endpoints (RCT MHR) or PFS/TTP surrogate endpoints (RCT SHR).

Results: Treatment arm therapies reduced mortality in RCTs relative to controls (average RCT MHR=0.85, range: 0.56 – 1.10) and lowered progression (average RCT SHR=0.73, range: 0.43 – 1.03). Among (real-world) SEER-Medicare patients who used either the treatment or control regimen from the RCT, RW MHRs were 0.6% (95% CI: -3.5% – 4.8%) higher than RCT MHRs, and RW MHRs were 15.7% (95% CI: 11.0% – 20.5%) higher than RCT SHRs.

Conclusions and Relevance: We found that real-world OS treatment benefits were similar to those observed in RCTs based on OS endpoints, but were approximately 16% less than RCTs based on surrogate endpoints in the five tumors studied. Our findings provide an empirical basis for refining the ASCO value framework and associated clinical decision tools.

INTRODUCTION

Two-thirds of cancer drugs are approved based on surrogate endpoints such as progression-free survival (PFS) or time to progression (TTP) measured in randomized controlled trials (RCTs).¹ In real-world practice, however, clinicians selecting treatments regularly face the challenge of translating surrogate and overall survival (OS) benefits from RCTs into expectations about real-world OS benefit for their patients.

Efforts are underway to help physicians better approach this problem. One example is the American Society of Clinical Oncology (ASCO)'s value framework, which aims to help physicians and patients select preferred therapies.² The most salient feature of its “net health benefit” metric is the clinical benefit component, which depends largely on the hazard ratio (HR) measured in RCTs. In the May 2016 revised version of the value framework, the clinical benefit component assigns an 0.8 adjustment factor (i.e., 20% reduction in points) to RCTs with surrogate endpoints—such as PFS—compared to RCTs with OS endpoints.³ In other words, the ASCO framework assumes that real-world mortality reductions are 20% smaller in magnitude relative to the reduction in PFS reported in an RCT.

The fundamental question for clinicians is how treatment efficacy measured in clinical trials translates into real-world effectiveness. Most evidence on this relationship relies on comparisons of surrogate and non-surrogate endpoints within trials themselves as opposed to comparisons with real-world OS.^{1,4-9} In this study, we examined the relationship between reported RCT efficacy and real-world effectiveness for oncology treatments and examined whether this relationship varies by RCT endpoint (OS vs. surrogate measures such as PFS or TTP). Using trial endpoints from RCTs of patients with breast, colon, lung, ovarian, and pancreatic cancer, we

estimated a real-world percentage adjustment that would translate RCT efficacy into real-world effectiveness and allowed this adjustment factor to vary by the type of trial endpoint. This study proposes an evidence-based adjustment factor that could be used by ASCO's value framework to ensure that physicians are delivering accurate guidance to patients, and it also provides ASCO with a method for refining and expanding their framework in the future by incorporating fast-evolving real-world data sources.

METHODS

Data sources

We identified 25 treatments used across five tumor sites (breast, colorectal, lung, ovarian, and pancreatic cancers) using the National Comprehensive Cancer Network Treatment Guidelines.¹⁰ We selected all tumor sites that ranked among the top ten in terms of U.S. incidence rates¹¹ and had ≥ 3 treatments FDA-approved before 2009 with phase III RCTs reporting both OS and either PFS or TTP that could be included in our study. Treatment regimens were restricted to those approved by the FDA before 2009 to ensure that ≥ 2 years of real-world survival data were available in Surveillance and Epidemiology End Results (SEER)-Medicare. Since four of 25 treatment regimens were indicated for two tumor sites, we identified 29 RCTs.

We calculated real-world OS using 1991-2010 SEER-Medicare data. The SEER-Medicare database contains 1.8 million individuals and links data from National Cancer Institute cancer registries to corresponding Medicare claims.¹¹

Inclusion and exclusion criteria

From SEER-Medicare, we selected patients with a primary diagnosis for breast, colorectal, lung, ovarian, or pancreatic cancer. To control for differences between clinical trial and real-world patients, we retained only the subset of patients that met inclusion and exclusion criteria from corresponding RCT from which they would have been able to enroll based on the treatment regimen received in the real world. Specifically, we applied the inclusion and exclusion criteria related to patient age, gender, cancer histology and stage, presence of other cancers, and other comorbidities. Finally, patients were required to have initiated cancer treatment within 90 days of diagnosis. These patients—which we defined as the “baseline” cohort—represented real-world patients that were similar to patients eligible to participate in the RCT corresponding to the real-world treatment they used. Patients appeared in the sample multiple times if they received more than one of the treatments of interest. We included only treatments that had ≥ 10 observations in the SEER-Medicare data for both the treatment and control arm regimens.

SEER-Medicare patients were assigned to a treatment or a comparator arm based on their tumor, the combinations of therapies received, and line of therapy. To be assigned to one of the real-world comparator arms, patients were required to have received the exact comparator regimen outlined in the relevant RCT. In the case of combination treatments, we required that patients use all treatments in the combination within 30 days of the first date on which any treatment in the combination was used.¹² First-line therapy was defined by any anti-cancer treatment that was initiated within 3 months of diagnosis; second-line (third-line) therapy was defined as the first claim of any anti-cancer treatment occurring after a 45-day clean period since the last claim of a treatment in the first-line (second-line) regimen.¹²

To mitigate selection bias due to non-random receipt of treatment in the real world, we excluded patients assigned to comparator arms if they received the comparator treatment after the date of the relevant new therapy launch. This approach eliminated patients whose physician non-randomly treated them with the comparator therapy, even though the novel treatment was available. We also included only patients that were diagnosed with cancer ≤ 5 years before or after the treatment arm regimen had been approved by the FDA to account for the fact that cancer survival generally improves over time.

Statistical analysis

Real-world OS for each patient was measured as the time between each patient's first treatment with the treatment combination of interest and death. Data for patients who survived beyond the data collection timeframe were censored based on the last month of available data (December 2010). Clinical trial efficacy was measured using phase III trial data reporting OS and PFS/TTP endpoints. Clinical trial HRs for both OS and PFS/TTP were obtained from the literature. When HRs were not directly available, we assumed a constant hazard rate over time and estimated the HR based on the ratio between median OS (or surrogate endpoint) in the treatment arm and the median OS (or surrogate endpoint) in the control arm.¹³ All statistical analyses were performed using Stata version 14.1 (StataCorp, College Station, TX, USA).

We performed a Cox proportional hazards regression analyses to determine whether real-world treatment effectiveness in SEER-Medicare data as measured by OS is predicted by treatment efficacies from phase III RCTs based on either OS or surrogate endpoints (PFS/TTP). Separate analyses were performed using trial OS endpoints and trial surrogate endpoints as predictors in the regression analyses. The outcome variable in the analyses was real-world OS in SEER-

Medicare data. We controlled for patient age, gender, and cancer stage. For persons in the treatment arm, we included an offset term which was either the RCT OS or RCT surrogate hazard ratios (RCT SHR) (Stata command: *stcox, offset*). The primary independent variable was an indicator variable that indicated whether the patient received the treatment or control regimen. The regression coefficient (b) for that indicator variable was used to calculate the percentage difference (f) between real-world mortality hazard ratios (RW MHR) and clinical trial hazard ratios (RCT HR), and was calculated from the equation $f = 100 \times (\text{RW MHR} - \text{RCT HR}) / \text{RCT HR} = (\exp(b) - 1) \times 100$ (see eMethods for more details).

For example, suppose the RCT MHR is 0.75 which indicates a 25% reduction in risk of mortality with the treatment. If the RW MHR is only 0.90, then the percent difference in the hazard ratios is $f = 100 \times (0.9 - 0.75) / 0.75 = 20\%$. The interpretation in this example is that the RCT MHR overestimates treatment effectiveness on mortality in the real world by 20%.

We conducted three sensitivity analyses. First, whereas our “baseline cohort” limited the patient population to those who met the RCT inclusion/exclusion criteria, we also examined the “full cohort,” which we defined as all patients receiving the relevant treatment in SEER-Medicare for a given tumor site and line of therapy. Second, we examined how the relationship between treatment efficacy and effectiveness varied by cancer site, line of therapy, number of patients enrolled in the RCT, and RCT geographic location. Finally, we removed the restriction that patients who receive the treatment in the control arm had to receive the treatment prior to the approval of the anti-cancer therapy in the trial’s treatment arm.

We also compared the ASCO framework valuations to our empirically derived valuations for RCTs with PFS/TTP endpoints.

RESULTS

After applying the inclusion/exclusion criteria to 1,887,800 patients in the SEER-Medicare database, we were left with 97,401 tumor-treatment-patient observations (71,844 unique patients) that were included in the full cohort specification across 21 RCTs of interest for 18 unique treatment combinations. After applying the inclusion/exclusion criteria from each relevant RCT for our baseline cohort, we were left with 21,811 tumor-treatment-patient observations (18,148 unique patients).

The baseline cohort included primarily elderly patients with average age at treatment over 70 years across all five tumors. Overall, about four out of every five patients were Caucasian and more than half of patients had stage IV cancer at diagnosis. Average survival time from treatment—not accounting for censoring—varied across type of cancer, with the longest survival observed for breast cancer (30.7 months) and the shortest – for pancreatic cancer (5.7 months). Patients in SEER-Medicare of the relevant tumor type who took the treatment or control arm regimen of interest were older than those in RCTs (Table 2). In five of 20 simulated trials in SEER-Medicare there were >10 percentage points more females than in the corresponding RCT (1 RCT did not report patient gender).

Treatment arm efficacy relative to control arm as measured in RCTs using surrogate hazard rates (SHR) based on PFS/TTP endpoints was generally lower (i.e., reduced mortality or progression) compared to efficacy measured using MHR (OS). Across all 21 RCTs, treatment arm therapies decreased progression (average SHR=0.73, minimum SHR=0.47, maximum SHR=1.03) and mortality (average MHR=0.83, minimum MHR=0.56, maximum MHR=1.04) (Table 3).

Real-world effectiveness was similar to treatment efficacy when trials used OS endpoints, but it was somewhat lower than trial efficacy when trials used surrogate endpoints. Real-world MHRs were not different from RCT MHRs (the percent difference was $f = 0.6\%$, 95% CI: $-3.5\% - 4.8\%$), whereas RW MHRs were significantly higher than RCT SHRs (the percent difference was $f = 15.7\%$, 95% CI: $11.0\% - 20.5\%$). In other words, if an RCT uses OS endpoints, one can expect real-world effectiveness to be similar among patients that would have qualified for the trial. However, if an RCT measures efficacy by a surrogate PFS/TTP endpoint, one can expect real-world effectiveness as measured by OS to be about 16% lower than the surrogate benefit from the trial (Figure 1).

Treatments were predicted to be generally less effective when measured among all real-world patients that received the treatment compared to only those patients who would have been eligible for the clinical trial. In the full cohort that included patients even if they did not meet the RCT's inclusion/exclusion criteria, RW MHRs were 8.2% higher (95% CI: $5.7\% - 10.8\%$) than RCT MHRs, and RW MHRs were 24.9% higher (95% CI: $22.0\% - 28.0\%$) than RCT SHRs.

The correspondence between real-world and RCT outcomes varied with trial and tumor characteristics (see eTable 1). Real-world MHRs were generally more likely to be similar to RCT hazard ratios (i.e., either MHR or SHR) when patient expected survival was lower, trial sample sizes were larger, or when the RCT of interest was conducted in the U.S. For instance, RW MHRs were just 6.8% (95% CI: $1.0\% - 12.9\%$) higher than RCT SHRs among patients receiving second-line treatment, but 28.1% (95% CI: $20.4\% - 36.4\%$) higher for first-line patients. Among the full cohort of individuals who received treatments of interest, tumors with shorter expected survival (e.g., pancreas and lung) exhibited RW MHRs more similar to both RCT MHR and RCT SHR compared to tumors with longer survival (e.g., breast, colorectal, and

ovary). These general findings were less apparent within our baseline cohort, perhaps due to the smaller sample size when we stratified the analysis by tumor type. Finally, real-world effectiveness was more likely to be similar to RCT efficacy when RCT sample sizes were larger or when the trial was conducted in the U.S.

We evaluated how our empirical findings compare with the assumptions of the ASCO value framework. For example, suppose a randomized controlled trial indicates the RCT SHR=0.70; the ASCO framework suggests assigning a value of $[(1 - 0.70) \times 0.8] \times 100 = 24$; while our empirical analysis suggests assigning a value of $[1 - 0.70 \times (1 + 0.157)] \times 100 = 19$. Figure 2 compares the relationships between the RCT SHR and the valuations using both the ASCO guideline and our empirical findings. Compared to our empirically derived scores, the ASCO framework assigns higher scores to treatments with modest PFS improvements (RCT SHR > 0.56), but lower scores for those treatments with larger PFS improvements (RCT SHR \leq 0.56). When we examine the difference between the empirically derived and ASCO framework, there is no statistically significant difference in five out of 21 cases, a small difference (<10 points) in 12 of 21 cases and a large difference (>10 points) in four cases. If we use tumor-specific factors, f , then in majority of cases (11 of 21) the results using the empirical and ASCO frameworks are not statistically different (not shown).

DISCUSSION

Across 21 clinical trials of breast, colon, lung, ovarian, and pancreatic cancer treatments between 1991 and 2010, we found that real-world OS associated with these treatments was comparable to OS benefits estimated in RCTs. However, real-world OS effectiveness was 16% lower than RCT

efficacy estimates based on surrogate endpoints, suggesting that in the five tumors we studied inferences about real-world OS based on RCT surrogate endpoints should be discounted by approximately this amount. In addition, among trials using an OS endpoint, those with larger sample sizes and later lines of therapy were more likely to reliably predict real-world OS outcomes. On the other hand, a larger discount would apply when considering how an RCT outcome would apply to a broader real-world patient population, which may include patients that would not have met the RCT's inclusion/exclusion criteria.

Several previous studies have examined the relationship between surrogate endpoints (PFS/TTP) and OS within trials themselves (i.e., analyzing whether OS is correlated with surrogate endpoints within trials that report both outcomes), with most demonstrating that surrogate measures are positively but imperfectly correlated with OS.^{1,4-9} Fewer studies have examined how trial outcomes compare to survival benefits in real-world patients, but most of these studies are limited to a single therapy or cancer type¹⁴⁻¹⁷ or examine only OS outcomes.¹⁸ To the best of our knowledge, this study is the first to examine the relationship between real-world OS, and OS and surrogate efficacy in clinical trials encompassing multiple tumor types and treatments. Our findings suggest that despite differences in patient populations between clinical trials and real-world settings, greater monitoring of patients in clinical trials, and concerns about crossover contamination and patient attrition in clinical trials, real-world and clinical trial OS correlate strongly.

The results of this paper could be used in a variety of ways. First, ASCO could alter their framework to use the parameter f calculated in this study to ensure that the ASCO results are empirically grounded. Second, this study provides a general framework for estimating how surrogate endpoints are likely to translate into real-world improvements in OS. ASCO or other

researchers could apply various discounts depending on the patient population of interest (e.g., patient tumor site) and trial endpoints selected (e.g., PFS, immune-related response rate, duration of response, and disease control rate). As new real-world data sources emerge from both private companies (e.g., CancerLinQ, Flatiron Health, IBM, IMS, Optum, and NantHealth) and nonprofit organizations (Patient-Centered Outcomes Research Institute [PCORI] via PCORnet),¹⁹ this method can be applied to an increasing number of real-world databases. Third, this study could help inform trial design with respect to endpoint selection. Admittedly, the choice of endpoint in a trial is a complex question that extends beyond the confines of this study. Nevertheless, it provides new evidence to help clinicians understand under what circumstances trial data may generalize to the real world.

This study has several limitations. First, our treatment effectiveness estimates may be confounded by differences in the characteristics of patients who received treatment. To address the confounding, we included patient demographics and cancer stage as controls in the Cox model and measured survival in control arms only during the 5 years prior to the treatment arm regimen's approval. Second, our sample is limited to Medicare patients diagnosed with one of five tumor types, which may limit the generalizability of the results. Third, our ability to match our baseline sample to RCT inclusion/exclusion criteria was imperfect because SEER-Medicare does not contain patient genotype information. Fourth, treatments may be administered differently in clinical trial and real-world settings; whereas physicians may treat patients beyond disease progression in the real world, in many RCTs a well-defined disease progression requires treatment to stop. Finally, to ensure a sufficient sample size for our analysis we did not separately measure the percentage difference f for PFS and TTP, but future research should

examine the relationship between efficacy and effectiveness separately using a variety of RCT surrogate endpoints.

CONCLUSION

Based on evidence from 21 RCTs of treatments across five tumor types, real-world OS was comparable to OS benefits estimated in RCTs. On the other hand, it was approximately 16% lower than RCT efficacy measured based on surrogate endpoints in the five tumors studied.

These findings provide an empirical basis upon which to translate surrogate endpoint evidence from RCTs into meaningful and evidence-based assessments of real-world effectiveness. Our analysis not only points towards future refinements of the ASCO framework, but also demonstrates a general methodology for predicting real-world effectiveness that can be applied to rapidly growing sources of real-world oncology data.

REFERENCES

1. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US Food and Drug Administration approvals. *JAMA Intern Med.* 2015;175(12):1992-1994.
2. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. *J Clin Oncol.* 2015;33(23):2563-2577.
3. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received. *J Clin Oncol.* 2016:1-9.
4. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. *J Natl Cancer Inst.* 2009;101(23):1642-1649.
5. Saad ED, Katz A, Hoff PM, Buyse M. Progression-free survival as surrogate and as true end point: insights from the breast and colorectal cancer literature. *Ann Oncol.* 2010;21(1):7-12.
6. Burzykowski T, Molenberghs G, Buyse M, Geys H, Renard D. Validation of surrogate end points in multiple randomized clinical trials with failure time end points. *J R Stat Soc Ser C Appl Stat.* 2001;50(4):405-422.
7. Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses. *JAMA Intern Med.* 2015;175(8):1389-1398.
8. Sherrill B, Kaye JA, Sandin R, Cappelleri JC, Chen C. Review of meta-analyses evaluating surrogate endpoints for overall survival in oncology. *Onco Targets Ther.* 2012;5:287-296.
9. Suzuki H, Hirashima T, Okamoto N, et al. Relationship between progression-free survival and overall survival in patients with advanced non-small cell lung cancer treated with anticancer agents after first-line treatment failure. *Asia Pac J Clin Oncol.* 2014;11(2):121-128.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Vol http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.2014.
11. National Cancer Institute. SEER-Medicare: Number of Cases for Selected Cancers Appearing in the Data. Vol <http://healthcaredelivery.cancer.gov/seermedicare/aboutdata/cases.html?&url=/seermedicare/aboutdata/cases.html2015>.
12. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol.* 2010;28(13):2191-2197.
13. NCSS Statistical Software. Survival Parameter Conversion Tool. Available from: <http://www.ncss.com/software/ncss/ncss-documentation/>.
14. Iwashyna TJ, Lamont EB. Effectiveness of adjuvant fluorouracil in clinical practice: a population-based cohort study of elderly patients with stage III colon cancer. *J Clin Oncol.* 2002;20(19):3992-3998.
15. Meyerhardt JA, Li L, Sanoff HK, Carpenter W, Schrag D. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. *J Clin Oncol.* 2012:1-9.

16. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant Chemotherapy and Survival in Older Women With Hormone Receptor–Negative Breast Cancer: Assessing Outcome in a Population-Based, Observational Cohort. *J Clin Oncol*. 2006;24(18):2757-2764.
17. Shafrin J, Brookmeyer R, Peneva D, et al. The value of surrogate endpoints for predicting real-world survival across five cancer types. *Curr Med Res Opin*. 2016;32(4):731-739.
18. Unger JM, Barlow WE, Martin DP, et al. Comparison of survival outcomes among cancer patients treated in and out of clinical trials. *J Natl Cancer Inst*. 2014;106(3):dju002.
19. American Society of Clinical Oncology. The state of cancer care in America, 2015: A report by the American Society of Clinical Oncology. *J Oncol Pract*. 2015:1-35.
20. Nabholz J-M, Senn H, Bezwoda W, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. *J Clin Oncol*. 1999;17(5):1413-1413.
21. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol*. 2008;26(24):3950-3957.
22. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006;355(26):2733-2743.
23. Eiermann W. Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: pivotal trial data. *Ann Oncol*. 2001;12(suppl 1):S57-S62.
24. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335-2342.
25. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol*. 2001;19(8):2282-2292.
26. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet*. 1998;352(9138):1407-1412.
27. de Gramont Ad, Figuer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938-2947.
28. Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542-2550.
29. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18(10):2095-2103.
30. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non–small-cell lung cancer. *N Engl J Med*. 2005;353(2):123-132.
31. Sandler A, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non–small-cell lung cancer. *J Clin Oncol*. 2000;18(1):122-122.

32. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. *J Natl Cancer Inst.* 2002;94(3):173-181.
33. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol.* 2004;22(9):1589-1597.
34. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol.* 1999;17(2):658-658.
35. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol.* 2001;19(14):3312-3322.
36. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol.* 2006;24(29):4699-4707.
37. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996;334(1):1-6.
38. ten Bokkel Huinink W, Lane S, Ross G. Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. *Ann Oncol.* 2004;15(1):100-103.
39. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007;25(15):1960-1966.
40. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013;369(18):1691-1703.

Table 1. CONSORT table by cancer type, SEER-Medicare (1991-2009)

Observation Type	Selection Steps	Breast	Colorectal	Lung	Ovary	Pancreas	Total	Retention %
Individuals	Patients diagnosed with breast, colorectal, lung, ovarian, or pancreatic cancer	671,682	513,871	545,325	63,201	93,721	1,887,800	100%
	Primary tumor only	636,506	461,998	471,435	56,577	81,119	1,707,635	90%
	Cancer NOT diagnosed at autopsy	633,315	458,117	460,365	55,718	78,062	1,685,577	89%
	Enrolled in Medicare FFS at diagnosis AND for ≥ 3 months after or until death	317,567	293,831	372,521	33,055	67,970	1,084,944	57%
	Has a cancer treatment	132,616	89,098	115,807	15,400	19,719	372,640	20%
	Has a cancer treatment within 90 days of cancer diagnosis	40,631	48,364	80,422	11,671	15,070	196,158	10%
	Individuals who received trial treatment or comparator of interest as specific line of therapy	24,590	33,997	50,836	3,600	10,548	123,571	7%
Individuals paired with treatments	Total observations assigned in treatment or comparator arms of clinical trials	39,813	58,797	79,927	4,450	25,365	208,352	100%
	After excluding controls who were treated after new drug launch date	5,671	35,078	45,796	3,279	20,030	109,854	53%
	Full cohort observations, after dropping trials with small arms (N<10 in either arm)	2,801	34,886	45,796	2,316	11,602	97,401	47%
	Baseline cohort observations, that met clinical trial inclusion / exclusion criteria	419	5,642	12,146	856	2,748	21,811	10%

Note: The exclusion criteria were applied sequentially. The full cohort has 71,844 unique individuals and the baseline cohort is comprised of 18,148 unique individuals. The full cohort includes patients with the relevant tumor who received the treatment of interest. Controls who received treatment after new drug launch were excluded, because their disease prognosis are likely not comparable to the treatment arm. The baseline cohort includes patients with the relevant tumor who received the treatment of interest and met the inclusion/exclusion criteria of the relevant clinical trial.

*Individuals paired with treatments may be assigned to more than one of the comparator arms, e.g., commonly prescribed therapy in the comparator arm.

Table 2. Demographic and clinical characteristics of patients by trial, comparing SEER-Medicare and RCT samples

Tumor site	Regimen	Median age (range)			% of female			Stage			Line of therapy ^a			Ref
		SEER Tx	SEER Control ^b	RCT	SEER Tx	SEER Control ^b	RCT	SEER Tx	SEER Control ^b	RCT	SEER Tx	SEER Control ^b	RCT	
Breast	docetaxel	73 (59-86)	55 (44-66)	51 (30-73)	100%	100%	100%	III (56%) IV (44%)	III (50%) IV (50%)	III/IV ^g	2	2	2	20
Breast	paclitaxel + gemcitabine	72 (43-86)	73 (44-90)	53 (26-83)	100%	100%	100%	III (31%) IV (69%)	III (34%) IV (66%)	III/IV ^g	1	1	2	21
Breast	lapatinib + capecitabine	70 (32-88)	74 (50-93)	54 (26-80)	100%	100%	100%	III (46%) IV (54%)	III (45%) IV (55%)	IIIb/c (4%) IV (96%)	2	2	2	22
Breast	paclitaxel OR anthracycline + cyclophosphamide + trastuzumab	70 (43-91)	70 (29-89)	51 (25-77) ^c	100%	100%	100%	IV	IV	IV	1	1	1	23
Colorectal	irinotecan + bolus fluorouracil + leucovorin + bevacizumab	71 (47-85)	71 (40-90)	60 ^c	47%	46%	41%	IV	IV	IV	1	1	1	24
Colorectal	capecitabine	78 (35-94)	73 (28-96)	64 (23-86)	58%	49%	40%	IV	IV	IV	1	1	1	25
Colorectal	irinotecan	70 (40-75)	71 (51-75)	58 (30-75)	45%	47%	43%	IV	IV	IV	2	2	2	26
Colorectal	oxaliplatin + 5-fluorouracil + leucovorin	69 (41-75)	70 (35-75)	63 (20-76)	45%	47%	40%	IV	IV	IV	1	1	1	27
Lung	paclitaxel + carboplatin + bevacizumab	70 (44-86)	70 (35-89)	44% ≥ 65 ^d	49%	42%	50%	IV	IV	IIIb (12%) IV (74%)	1	1	1	28
Lung	docetaxel	72 (35-91)	73 (58-86)	61 (37-73)	42%	41%	36%	III (57%) IV (43%)	III (58%) IV (42%)	IIIa/b (27%) IV (73%)	2	2	2 (80%) 3 (13%) 4 (7%)	29
Lung	erlotinib	74 (41-96)	72 (35-93)	62 (34-87)	62%	43%	36%	III (49%) IV (51%)	III (50%) IV (50%)	IIIb/IV ^g	2	2	2 (51%) 3 (49%)	30
Lung	cisplatin + gemcitabine	71 (42-88)	71 (45-88)	62 (36-88)	40%	40%	30%	III (47%) IV (53%)	III (57%) IV (43%)	IIIa (7%) IIIb (26%) IV (66%)	1	1	1 (82%) 2 (18%)	31
Lung	cisplatin + paclitaxel	70 (44-82)	70 (41-85)	15% ≥ 70 ^e	29%	30%	36%	III (53%) IV (47%)	III (55%) IV (45%)	IIIb (20%) IV (80%)	1	1	-	32
Lung	pemetrexed disodium	73 (43-90)	71 (46-91)	59 (22-81)	44%	41%	31%	III (43%) IV (57%)	III (54%) IV (46%)	III/IV ^g	2	2	2	33

Lung	topotecan	71 (44-89)	70 (48-78)	^f	51%	42%	43%	IV	IV	IV	2	2	2	34
Ovary	doxorubicin hydrochloride liposome	73 (59-93)	72 (56-81)	60 (27-87)	100%	100%	100%	IV	IV	IV ^h	2	2	2	35
Ovary	carboplatin + gemcitabine	74 (50-88)	76 (38-93)	59 (36-78)	100%	100%	100%	III (52%) IV (48%)	III (48%) IV (52%)	III/IV ^h	2	2	2	36
Ovary	cisplatin + paclitaxel	69 (50-86)	71 (59-83)	59 (20-84)	100%	100%	100%	III (50%) IV (50%)	III (38%) IV (62%)	III (67%) IV (33%)	1	1	1	37
Ovary	topotecan	72 (42-92)	73 (66-87)	- ^f	100%	100%	100%	IV	IV	IV	2	2	2	38
Pancreas	gemcitabine + erlotinib	73 (47-86)	73 (49-94)	64 (38-84)	56%	53%	52%	IV	IV	III/IV ^g	1	1	1	39
Pancreas	gemcitabine + paclitaxel	73 (72-75)	73 (37-95)	62 (27-86)	75%	51%	43%	IV	IV	IV	1	1	1	40

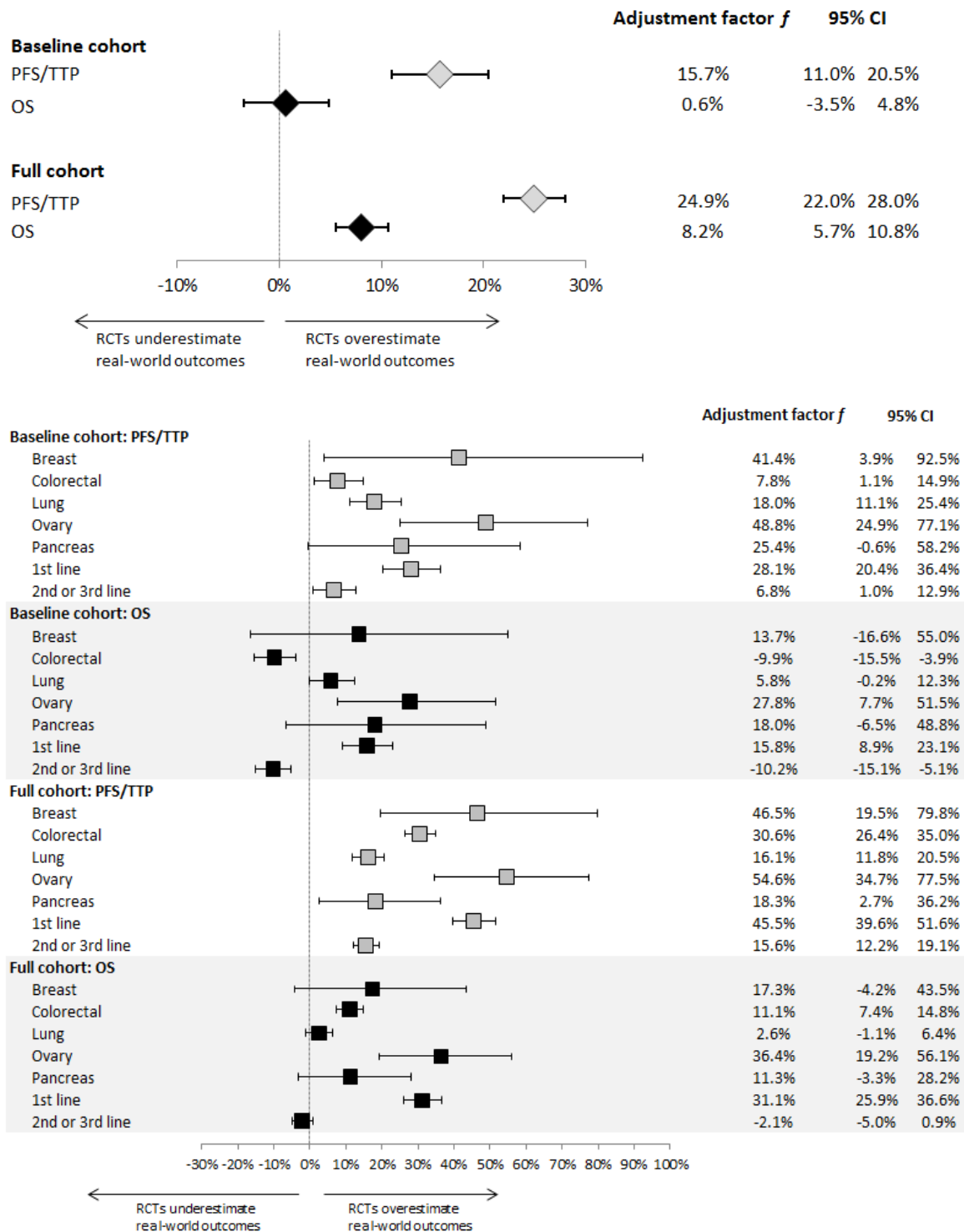
Note: "Ref" is the reference from which the RCT data were drawn. ^aLine of therapy matching occurred based on the lowest line of therapy reported in the RCT. ^bSEER-Tx means that patients in SEER-Medicare data received the treatment of interest from the RCT treatment arm; SEER Control means that patients received the treatment in the RCT control arm. ^cIndicates mean age, since the median is not available. ^dMedian or mean age not reported, but 44% of patients were over age of 65. ^e15% of patients were over age of 70. ^fReference does not report age. ^gComposition of stage at treatment of patients with locally recurrent or metastatic disease are not reported or clearly defined. ^hEligibility criterion indicates recurrent or metastatic disease; stage is only reported based on stage at diagnosis.

Table 3. Treatment median survival from phase III trials (baseline cohort)

	Treatment Arm			Comparator Arm			RCT SHR	RCT MHR	Ref
	Regimen	PFS/TTP (months)	OS (months)	Regimen	PFS/TTP (months)	OS (months)			
Breast	docetaxel	4.3 ^b	11.4	mitomycin + vinblastine	2.5 ^b	8.7	0.75	0.73	20
Breast	paclitaxel + gemcitabine	6.1 ^b	18.6	paclitaxel	4.0 ^b	15.8	0.70	0.78	21
Breast	lapatinib + capecitabine	8.4 ^a	10.4	capecitabine	4.1 ^a	8.0	0.47	0.92	22
Breast	paclitaxel OR anthracycline + cyclophosphamide + trastuzumab	7.2 ^b	25.1	paclitaxel OR anthracycline + cyclophosphamide	4.5 ^b	20.3	0.63 ^c	0.81 ^c	23
Colorectal	irinotecan + bolus fluorouracil + leucovorin + bevacizumab	10.6 ^a	20.3	irinotecan + bolus fluorouracil + leucovorin + placebo	6.2 ^a	15.6	0.54	0.66	24
Colorectal	capecitabine	4.3 ^b	12.7	5-fluorouracil + leucovorin	4.4 ^b	13.6	1.03	1.00	25
Colorectal	irinotecan	4.2 ^a	10.8	fluorouracil	2.9 ^a	8.5	0.69 ^c	0.79 ^c	26
Colorectal	oxaliplatin + 5-fluorouracil + leucovorin	9.0 ^a	16.2	5-fluorouracil + leucovorin	6.2 ^a	14.7	0.69 ^c	0.91 ^c	27
Lung	paclitaxel + carboplatin + bevacizumab	6.2 ^a	12.3	paclitaxel + carboplatin + placebo	4.5 ^a	10.3	0.66	0.79	28
Lung	docetaxel	3.1 ^b	7.5	best supportive care	1.8 ^b	4.6	0.57 ^c	0.56	29
Lung	erlotinib	2.2 ^a	6.7	placebo	1.8 ^a	4.7	0.61	0.70	30
Lung	cisplatin + gemcitabine	5.2 ^b	9.0	cisplatin	3.7 ^b	7.6	0.71 ^c	0.84 ^c	31
Lung	cisplatin + paclitaxel	4.3 ^b	9.3	cisplatin + etoposide	2.7 ^b	7.4	0.63 ^c	0.80 ^c	32
Lung	pemetrexed disodium	2.9 ^a	8.3	docetaxel	2.9 ^a	7.9	0.97	0.99	33
Lung	topotecan	3.3 ^b	6.3	cyclophosphamide + doxorubicin + vincristine	3.1 ^b	6.2	0.92	1.04	34
Ovary	doxorubicin hydrochloride liposome	4.1 ^b	14.4	topotecan	4.2 ^b	13.7	0.96	0.82	35
Ovary	carboplatin + gemcitabine	8.6 ^a	18.0	carboplatin	5.8 ^a	17.3	0.72	0.96	36
Ovary	cisplatin + paclitaxel	16.6 ^b	35.5	cisplatin + cyclophosphamide	13.0 ^b	24.2	0.78 ^c	0.68 ^c	37
Ovary	topotecan	4.7 ^b	15.8	paclitaxel	3.7 ^b	13.3	0.79 ^c	0.97	38
Pancreas	gemcitabine + erlotinib	3.8 ^a	6.4	gemcitabine + placebo	3.5 ^a	6.0	0.77	0.82	39
Pancreas	gemcitabine + paclitaxel	5.5 ^a	8.5	gemcitabine + placebo	6.7 ^a	3.7	0.69	0.72	40
Average		5.9	13.5		4.4	11.1	0.73	0.83	
Minimum		2.2	6.3		1.8	3.7	0.47	0.56	
Maximum		16.6	35.5		13.0	24.2	1.03	1.04	

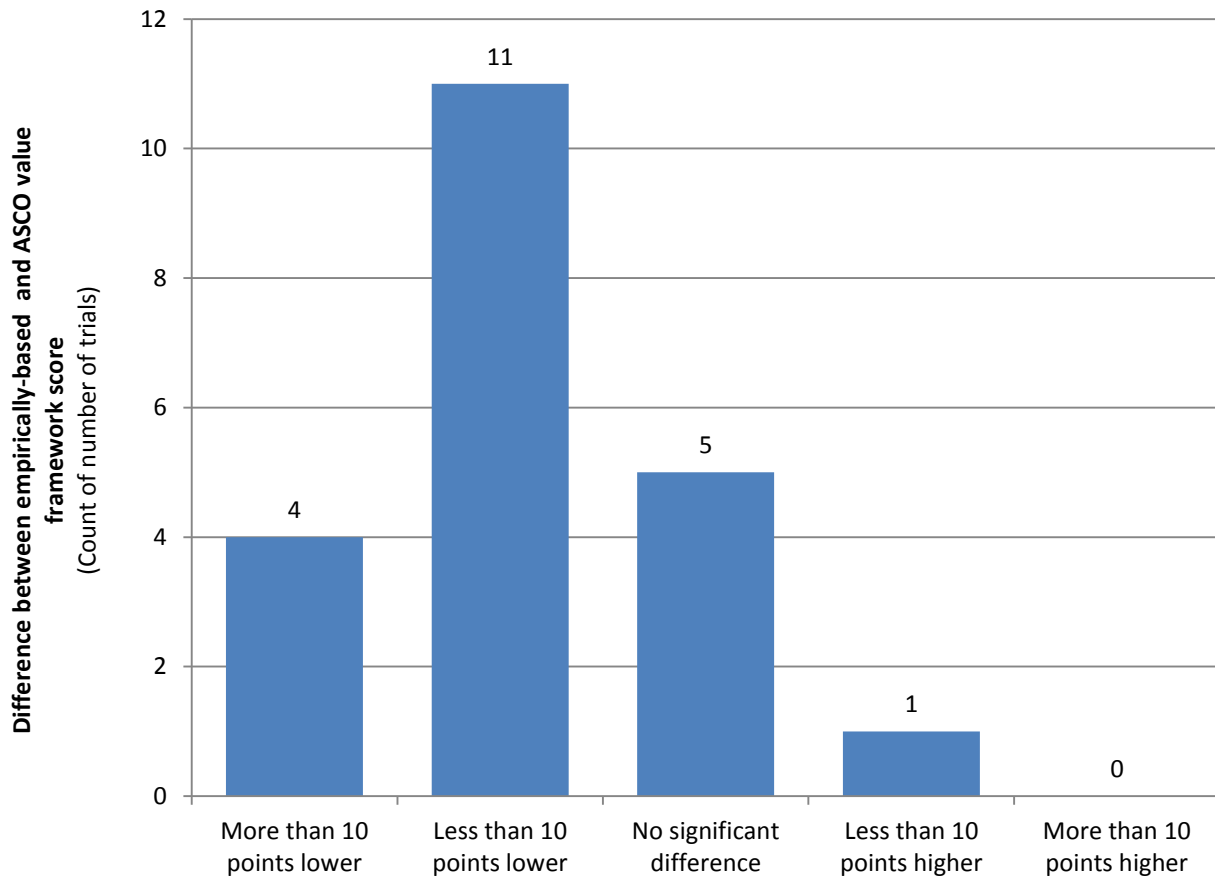
Note: Median progression-free survival (PFS) or time to progression (TTP), and overall survival (OS) come from phase III clinical trial data. “Ref” is the reference from which the RCT data were drawn. MHR = mortality hazard ratio based on OS outcomes obtained from trials. SHR = surrogate hazard ratio based on surrogate (i.e., PFS or TTP) outcomes obtained from trials. ^a Indicates PFS data obtained from trials. ^b Indicates TTP data obtained from trials. ^c For eight of 21 trials, hazard ratios were calculated based on reported PFS/TTP/OS in months as hazard ratios were not available.

Figure 1. Measuring the relationship between RCT efficacy (PFS/TTP or OS) and real-world effectiveness (OS) using a Cox proportional hazard model (Dependent variable: real-world OS)



Note: PFS = progression-free survival, TTP = time to progression, OS = overall survival. The full cohort includes patients with the relevant tumor who received the treatment of interest. The baseline cohort includes patients with the relevant tumor who received the treatment of interest and met the inclusion/exclusion criteria of the relevant clinical trial. Model controls for patient age at treatment, gender, and cancer stage. Adjustment factor $f > 1$ indicates that real-world treatment effectiveness is inferior to measured RCT efficacy due to a higher mortality rate; adjustment factor $f < 1$ indicates that real-world treatment effectiveness is superior to RCT efficacy due to a lower mortality rate.

Figure 2. Comparing value framework clinical benefit scores based on ASCO’s and empirically derived adjustment factors for clinical trials with surrogate outcomes



Note: Figure shows how the empirically-based framework score compares to the ASCO value framework score. For example, suppose a clinical trial indicates the trial SHR=0.70; then, the ASCO framework suggests assigning a value of $[(1 - 0.70) \times 0.8] \times 100 = 24$; while the empirical analysis suggests assigning a value of $[1 - 0.70 \times (1 + 0.157)] \times 100 = 19$. Lower score differences indicate that the empirically-based framework is less favorable to the treatment arm of a trial than using the ASCO framework; higher score differences represent the reverse.

APPENDIX

eMethods

The sample included each patient i that received a therapeutic regimen evaluated in RCT j . Define the binary variable $T_{ij} = 1$ if patient i in SEER-Medicare received the treatment arm therapy from trial j , or $T_{ij} = 0$ if patient i received the comparator therapy from trial j . $HR_{RCT,j}$ is the hazard ratio from trial j . We assumed that, when patient i is treated with a therapy from trial j , her real-world mortality hazard can be predicted using his/her characteristics \mathbf{X}_i (age, gender, and cancer stage), the relevant hazard ratio from trial j , and a constant percent difference estimating the discrepancy between real-world and RCT benefits. The Cox model specifying the log transformed $HR_{RCT,j}$ as an offset term (Stata command: *stcox, offset*), was stratified by the RCT based on the treatment patients in SEER-Medicare received, and can be specified formally as:

$$\lambda_{OS,i,j}^{RW}(t) = \lambda_{0,i,j}(t) \exp(\beta_1 + \ln[HR_{RCT,j}])^{T_{ij}} \exp(\mathbf{X}_i)$$

We repeated the model two times, once defining $HR_{RCT,j}$ based on trial j 's OS hazard ratio, and once defining $HR_{RCT,j}$ based on trial j 's PFS or TTP hazard ratio.

We can relate our value framework scoring system to the one from ASCO as follows. Define our empirically-based percent difference as $f = \exp(\beta_1) - 1$. A separate f is applied for each endpoint type (i.e., OS or surrogate). The ASCO scoring system for trials with PFS endpoints is $(1 - HR_{RCT}) \times 0.8 \times 100$. In other words, ASCO estimates that the real-world improvement with a PFS endpoint is $(1 - HR_{RCT}) \times 0.8$. Our estimate of the real-world change in mortality is $(1 - (1 + f) \times HR_{RCT,j})$. Thus, the estimated score using an empirically-derived approach would be $[1 - (1 + f) \times HR_{RCT,j}] \times 100$.

eTable 1. Measuring the relationship between RCT efficacy (PFS/TTP or OS) and real-world effectiveness (OS) using a Cox proportional hazard model

Key Independent Variable	Baseline Cohort						Full Cohort					
	Dependent Variable: Overall Survival						Dependent Variable: Overall Survival					
	Trial PFS/TTP			Trial OS			Trial PFS/TTP			Trial OS		
Treatment Effect	HR	95% CI Lower	95% CI Upper	HR	95% CI Lower	95% CI Upper	HR	95% CI Lower	95% CI Upper	HR	95% CI Lower	95% CI Upper
Treatment effect relative to RCT	1.157	1.110	1.205	1.006	0.965	1.048	1.249	1.220	1.280	1.082	1.057	1.108
Age at treatment	1.006	1.004	1.008	1.006	1.004	1.009	1.014	1.012	1.015	1.014	1.013	1.015
Male	1.111	1.080	1.144	1.110	1.078	1.142	1.157	1.139	1.175	1.156	1.137	1.174
Stage IV vs. III	1.458	1.398	1.521	1.462	1.402	1.524						
Stage I vs. 0							0.633	0.516	0.777	0.620	0.505	0.761
Stage II vs. 0							0.514	0.420	0.630	0.505	0.412	0.619
Stage III vs. 0							0.877	0.717	1.074	0.857	0.701	1.049
Stage IV vs. 0							1.787	1.460	2.187	1.742	1.423	2.132
Treatment effect relative to RCT ×												
Breast	1.414	1.039	1.925	1.137	0.834	1.550	1.465	1.195	1.798	1.173	0.958	1.435
Colorectal	1.078	1.011	1.149	0.901	0.845	0.961	1.306	1.264	1.350	1.111	1.074	1.148
Lung	1.180	1.111	1.254	1.058	0.998	1.123	1.161	1.118	1.205	1.026	0.989	1.064
Ovary	1.487	1.249	1.771	1.277	1.077	1.515	1.546	1.347	1.775	1.364	1.192	1.561
Pancreas	1.254	0.994	1.582	1.180	0.935	1.488	1.183	1.027	1.362	1.113	0.967	1.282
Age at treatment	1.006	1.004	1.008	1.006	1.004	1.009	1.014	1.012	1.015	1.014	1.013	1.015
Male	1.112	1.080	1.144	1.111	1.079	1.144	1.155	1.137	1.174	1.155	1.137	1.173
Stage IV vs. III	1.458	1.398	1.520	1.459	1.399	1.522						
Stage I vs. 0							0.636	0.518	0.781	0.622	0.507	0.763
Stage II vs. 0							0.519	0.423	0.636	0.508	0.415	0.623
Stage III vs. 0							0.883	0.721	1.080	0.860	0.703	1.053
Stage IV vs. 0							1.800	1.471	2.203	1.750	1.430	2.142
Treatment effect relative to RCT ×												
1st line	1.281	1.204	1.364	1.158	1.089	1.231	1.455	1.396	1.516	1.311	1.259	1.366
2nd or 3rd line	1.068	1.010	1.129	0.898	0.849	0.949	1.156	1.122	1.191	0.979	0.950	1.009

Age at treatment	1.006	1.004	1.008	1.006	1.004	1.008	1.013	1.012	1.015	1.014	1.013	1.015
Male	1.113	1.081	1.146	1.112	1.080	1.145	1.158	1.140	1.176	1.157	1.139	1.176
Stage IV vs. III	1.452	1.392	1.514	1.453	1.394	1.516						
Stage I vs. 0							0.628	0.512	0.771	0.614	0.500	0.754
Stage II vs. 0							0.508	0.414	0.622	0.498	0.406	0.610
Stage III vs. 0							0.869	0.710	1.063	0.847	0.692	1.037
Stage IV vs. 0							1.768	1.445	2.165	1.721	1.406	2.106
Treatment effect relative to RCT ×												
Small trial (N<300)	1.766	1.537	2.029	1.587	1.384	1.821	2.612	2.424	2.814	2.316	2.150	2.494
Medium trial (300≤N<600)	1.058	1.000	1.121	0.892	0.843	0.943	1.172	1.131	1.215	0.966	0.933	1.001
Large trial (N≥600)	1.176	1.100	1.258	1.062	0.994	1.136	1.113	1.071	1.155	1.011	0.974	1.050
Age at treatment	1.006	1.004	1.008	1.006	1.004	1.008	1.014	1.013	1.015	1.014	1.013	1.015
Male	1.112	1.080	1.145	1.111	1.080	1.144	1.156	1.138	1.174	1.156	1.138	1.174
Stage IV vs. III	1.460	1.400	1.523	1.464	1.404	1.527						
Stage I vs. 0							0.623	0.507	0.764	0.614	0.500	0.754
Stage II vs. 0							0.504	0.411	0.617	0.497	0.406	0.610
Stage III vs. 0							0.856	0.699	1.047	0.842	0.688	1.031
Stage IV vs. 0							1.738	1.420	2.128	1.707	1.394	2.089
Treatment effect relative to RCT ×												
US trial	1.209	1.045	1.398	1.046	0.906	1.207	1.199	1.127	1.277	1.013	0.952	1.078
US + other countries trial	1.173	1.114	1.235	1.073	1.020	1.130	1.120	1.083	1.159	1.047	1.013	1.083
Trial outside of US	1.108	1.025	1.197	0.861	0.797	0.930	1.496	1.437	1.558	1.169	1.123	1.217
Age at treatment	1.006	1.004	1.008	1.006	1.004	1.008	1.014	1.013	1.015	1.014	1.013	1.015
Male	1.112	1.080	1.145	1.112	1.080	1.145	1.154	1.136	1.173	1.154	1.136	1.173
Stage IV vs. III	1.457	1.398	1.520	1.457	1.397	1.520						
Stage I vs. 0							0.626	0.510	0.768	0.618	0.503	0.758
Stage II vs. 0							0.511	0.417	0.627	0.505	0.412	0.619
Stage III vs. 0							0.865	0.707	1.059	0.854	0.698	1.045
Stage IV vs. 0							1.759	1.437	2.153	1.734	1.417	2.123

Note: PFS = progression-free survival, TTP = time to progression, OS = overall survival, HR = hazard ratio. The full cohort includes patients with the relevant tumor who received the treatment of interest. The baseline cohort includes patients with the relevant tumor who received the treatment of interest and met the inclusion/exclusion criteria of the relevant clinical trial. The adjustment factor in the manuscript is calculated as the hazard ratio minus 1.