Quantifying the Survival Benefits of Oncology Drugs With a Focus on Immunotherapy Using Restricted Mean Survival Time

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ABSTRACT

Background: Restricted mean survival time (RMST) overcomes limitations of current measures of survival benefits because it directly captures information of the entire area under Kaplan-Meier survival curves. Using RMST difference (absolute survival benefit) and RMST ratio (relative survival benefit), we quantified the magnitude of survival benefits of recent oncology drugs and compared immunotherapies with nonimmunotherapies. **Methods:** Kaplan-Meier curves were extracted from phase II/III randomized controlled trials used by the FDA for oncology drug approvals from January 2011 through November 2017 with overall survival (OS) or progression-free survival (PFS) as primary endpoints. RMST differences, ratios, and their 95% confidence intervals were meta-analyzed to estimate absolute and relative survival benefits of contemporary oncology drugs and to compare immunotherapies with nonimmunotherapies. Meta-regression was conducted to adjust for potential confounders. **Results:** Ninety-four trials with a total of 51,639 patients were included. Overall absolute survival benefits (RMST differences) were 1.55 months for OS (95% CI, 1.32–1.77) and 2.99 months for PFS (95% CI, 2.65–3.33). Overall relative survival benefits (RMST ratios) were 1.11 for OS (95% CI, 1.09–1.13) and 1.42 for PFS (95% CI, 1.36–1.48). Immunotherapy absolute PFS benefit was less than that of nonimmunotherapy (1.56 vs 3.23 months), whereas immunotherapy absolute OS benefit was larger than that of nonimmunotherapy by 0.59 months (2.02 vs 1.43 months). Adjusted OS RMST difference was 0.91 months greater for immunotherapy than for nonimmunotherapy after adjusting for confounders. **Conclusions:** Absolute survival benefits of recent oncology drugs are modest. Survival benefits of immunotherapies are not dramatically superior to those of nonimmunotherapies. Routine reporting and use of RMST may help patients, physicians, and payers make more informed and responsible decisions regarding the care of patients with cancer.

J Natl Compr Canc Netw 2020;18(3):278–285
doi: 10.6004/jnccn.2019.7362

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Background

In recent years, immunotherapy has emerged as an alternative to chemotherapy and has been commonly viewed as a “game changer” for its potential to improve survival in a small proportion of patients.^{1–4} Randomized controlled trials often report measures of absolute survival benefit as differences in median survival times or differences in survival rates at specific times on Kaplan-Meier (KM) curves, whereas measures of relative survival benefit are reported as hazard ratios (HRs). However, reporting survival benefits of immunotherapy using these measures is potentially challenging.

For example, differences in median survival times are not estimable when the median survival time has not been reached in at least one of the trial arms.⁵ Although median survival time is an absolute survival measure of central tendency, it ignores the rest of the shape of the survival curve and treats long-term survivors as outliers (in contrast to mean survival), especially in cases in which the survival curves diverge after the median times. For relative survival benefit measures, HRs rely on the proportional hazards assumption, which depends on the number of observed events and not directly on exposure times or sample size of the study.⁶ HRs also may vary with time and thus violate the proportional hazards assumption.^{7,8} When the proportional hazards assumption is violated, the HR estimate may not be a statistically valid measurement of the treatment effect and becomes difficult to interpret clinically.

Immunotherapy trials sometimes exhibit nonproportional hazards, often because of late postprogression benefit (ie, after median survival times) or nonuniform divergence of the survival curves with potential plateau of the immunotherapy arm, with some trials even exhibiting

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crossing of survival curves.^{9–13} Median survival time also does not account for the “tail of the curve,” where the benefit of immunotherapy is more pronounced. Conventional measures of survival benefit have clinical limitations that were previously overlooked in immunotherapy trials.⁷

An interpretable and robust measure of clinical efficacy in survival analyses is critical to capture the full context of the benefits of oncology drugs and to make more informed decisions about the cost versus benefit of treatment options. With various studies showing a steady increase in the cost and variety of novel oncology drugs, the benefits associated with these drugs are not necessarily following the same upward trend.^{14–16}

Restricted mean survival time (RMST) is increasingly being recognized as a robust and clinically interpretable summary measure alternative to HR and median survival time because it directly quantifies information of the entire observed survival curve.^{7,17} RMST is defined as the area under the KM curve up to a specific time point (t), which is the follow-up time of the study.^{18,19} Because this measure takes the average (ie, mean, not median) to summarize the entire survival profile, it does not rely on the proportional hazards assumption and captures the benefit across the entire trial.^{6,19} RMST difference is the difference between the area under the KM curve of the treatment arm and the control arm, and has been proposed as a measure of absolute survival benefit as an alternative to median survival time.⁶ RMST ratio is the ratio of the RMSTs between the treatment arm and the control arm.⁷ An RMST ratio >1 shows an improvement in survival in the treatment arm. Unlike the HR, which is a ratio of the rates of death,²⁰ RMST ratio is a ratio of survival, which is arguably clinically more meaningful. For example, if survival associated with a control arm were high, a “good” HR (such as 0.5) would still represent little relative survival gained (RMST ratio may be only 1.2 rather than 2.0 as one may incorrectly expect) (supplemental eFigure 1, available with this article at JNCCN.org). It has been shown that HR is a relative measure of the rate of death and tends to overestimate the relative survival benefit.^{4,8,21} Comparability of treatment effects of immunotherapy drugs between RMST ratios and HR estimates has also been shown to be in general agreement.²¹ It has been suggested that it may be useful to report RMST in immunotherapy trials, in which the benefit typically is at the tail of the curve.^{3,21,22}

Because RMST methods seem to be a reasonable alternative approach to measure survival benefits to overcome limitations of conventional measures, our study aimed to quantify the magnitude of survival benefit in oncology drugs recently approved by the FDA, using RMST difference (absolute survival benefit)

and RMST ratio (relative survival benefit) in a meta-analysis. We further aimed to compare whether immunotherapy drugs provide a greater survival benefit than nonimmunotherapy drugs.

Methods

Drug Identification and Trial Extraction

We conducted this meta-analysis by identifying a list of immunotherapy and nonimmunotherapy oncology drugs approved by the FDA from January 2011 through November 2017 through a search of the Hematology/Oncology (Cancer) Approvals & Safety Notifications page on the FDA website (2016–2017 notifications) and archives (2011–2015 notifications).²³ Notifications regarding marketing approvals, drug packaging changes, optical imaging agents, tests, treatments for adverse effects, biosimilars, nononcologic conditions, and announcements were excluded from our search. Clinical trials used by the FDA for drug approval were recorded and retrieved from a PubMed search. All extracted trials were published in English. Only phase II/III randomized controlled trials with a primary endpoint of overall survival (OS) and/or progression-free survival (PFS) with published KM curves were included in this study. Evidence of nonproportional hazards was examined for each curve using the Grambsch-Therneau test, with a P value $<.1$ considered as statistically significant.²⁴

RMST Calculations

DigitizeIt software (version 2.3.3) was used to digitize published KM curves (OS and PFS). An algorithm developed by Guyot et al²⁵ to solve the inverted KM equations was applied to reconstruct pseudo-individual patient data files based on the KM curves^{6,8,19,22} and to calculate the RMST of experimental and control arms, RMST difference, RSMT ratio, and their 95% confidence intervals.²⁶ RMST estimates were truncated at the time point (t) of the KM curves, which is defined as the minimum of the largest observed survival time between the treatment and control arms.^{18,19} Extraction of curve coordinates and RMST calculations were independently performed by 2 reviewers. The margin of error agreed on was RMST values ± 1 week a priori. If discrepancies greater than the margin of error were found, the 2 reviewers repeated the extraction and calculation process to determine the reason for the discrepancy. Decisions on finalized calculation results were made after discussion between reviewers.

Meta-Analysis

Meta-analyses of RMST differences and ratios were conducted using Review Manager software (version 5.3)

to estimate overall absolute and relative survival benefits of the drugs and to compare those of immunotherapy versus nonimmunotherapy. We classified drugs as either immunotherapy or nonimmunotherapy based on recently published literature focusing on checkpoint inhibitors for purposes of consistency.^{21,27} RMST differences and ratios were meta-analyzed according to type of endpoint (PFS/OS) to estimate overall aggregate survival benefits, followed by subgroup analysis for immunotherapy and nonimmunotherapy and then comparison between immunotherapy and nonimmunotherapy. Inverse variance was used as the statistical method, with random effects as the model of analysis.²⁸ Forest plots were generated for meta-analyses of RMST differences and ratios for OS and PFS separately, including analytical results of overall benefits and subgroup benefits for immunotherapy and nonimmunotherapy. Subgroup meta-analyses of immunotherapy versus nonimmunotherapy were conducted for melanoma and non-small cell lung cancer (NSCLC) because immunotherapy has been viewed as highly beneficial in these populations.^{29,30} Sensitivity analyses excluding those tumor sites were also conducted.

Meta-Regression

Meta-regression was conducted using Comprehensive Meta-Analysis software (version 31; Biostat, Inc.) to assess and adjust for the confounding effects of covariates. Four separate meta-regression analyses for the following endpoints were conducted: OS RMST differences, OS RMST ratios, PFS RMST differences, and PFS RMST ratios. The effect size measure was the difference in means for RMST difference analyses and the natural logarithm of the ratio point estimate for RMST ratio analyses. The computational model used for all analyses was random effects. Covariates used for regression analysis were immunotherapy versus nonimmunotherapy, occurrence of crossovers in the trials, time horizon of the trials, year of approval, trial phase, existence of companion diagnostics for the drug, approval type of the drug (regular/accelerated), and line of therapy (trials specific for first-line vs other). The occurrence of crossovers was included as a covariate only for OS RMST difference and ratio analyses. Results were considered statistically significant if the *P* value was <.05 (2-tailed).

Results

After the process of selection for clinical trials (Figure 1), 94 trials representing 66 drugs with a total of 51,639 patients were included. Of these trials, 13 were used for immunotherapy approval representing 4 immunotherapy drugs, and 81 were used for nonimmunotherapy approval representing 62 nonimmunotherapy drugs

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram.

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival.

(supplemental eTable 1). There were 70 trials with OS curves and 87 trials with PFS curves. Summary statistics of included trials are shown in Table 1. Of the 94 included trials, proportional hazards assumption was found to be violated in 45 trials; 9 (69%) of the immunotherapy trials and 36 (44%) of the nonimmunotherapy trials were found to have nonproportional hazards.

Meta-analyses demonstrated that overall aggregate absolute survival benefits, measured using RMST difference, showed additional benefit in the experimental arms over the control arms by 1.55 months (95% CI, 1.32–1.77) for OS and 2.99 months (95% CI, 2.65–3.33) for PFS (Figure 2). Overall aggregate relative survival benefits, measured using RMST ratio, showed a benefit in the experimental arms over the control arms

Table 1. Summary Statistics of Included Trials

	ICI Trials n (%)	Non-ICI Trials n (%)	All Included Trials n (%)
Trials, n	13	81	94
Median trial size, n	542	518	530
IQR (median)	333.0–827.5 (494.5)	338–764 (426)	345–768 (423)
Phase III	84.6 (11)	92.6 (75)	91.5 (86)
Regular approval	92.3 (12)	91.4 (7)	91.5 (86)
Companion diagnostic	38.5 (5)	24.7 (20)	26.6 (25)
First-line therapy-specific	7.7 (1)	27.2 (22)	24.5 (23)
OS as an endpoint	84.6 (11)	72.8 (59)	74.5 (70)
PFS as an endpoint	84.6 (11)	93.8 (76)	92.6 (87)
OS as primary endpoint	84.6 (11)	35.8 (29)	42.6 (40)
PFS as primary endpoint	15.4 (2)	64.2 (52)	57.5 (54)
Lung cancer	46.2 (6)	12.3 (10)	17 (16)
Breast cancer	0 (0)	9.9 (8)	8.5 (8)
Colorectal cancer	0 (0)	7.4 (6)	6.4 (6)
Prostate cancer	0 (0)	6.2 (5)	5.3 (5)
Hematologic cancer	0 (0)	24.7 (20)	21.3 (20)
Other cancer	53.8 (7)	39.5 (32)	41.5 (39)

Abbreviations: ICI, immune checkpoint inhibitor; IQR, interquartile range; OS, overall survival; PFS, progression-free survival.

by a factor of 1.11 (95% CI, 1.09–1.13) for OS and 1.42 (95% CI, 1.36–1.48) for PFS (Figure 3). RMST summary statistics and their distributions are shown in supplemental eTable 2 and eFigures 2A and 2B, respectively.

Subgroup analyses for immunotherapy versus non-immunotherapy were performed to compare survival benefits. For PFS, immunotherapy showed less absolute PFS benefit than nonimmunotherapy by 1.67 months (1.56 months [95% CI, 1.02–2.09] vs 3.23 months [95% CI, 2.85–3.61], respectively; $P < .00001$), whereas both immunotherapy and nonimmunotherapy showed similar relative benefit as measured by RMST ratios (see Figures 2 and 3). In contrast, for OS, immunotherapy showed a larger absolute survival benefit than nonimmunotherapy by 0.59 months (2.02 months [95% CI, 1.60–2.44] vs 1.43 months [95% CI, 1.18–1.68], respectively; $P = .02$) and marginally larger relative survival benefit than non-immunotherapy (1.18 [95% CI, 1.14–1.23] vs 1.09 [95% CI, 1.07–1.11], respectively; $P = .0006$) (see Figures 2 and 3).

After adjustment for potential confounding variables (occurrence of crossovers in the trials, time horizon of trials, year of FDA approval, trial phase, existence of companion diagnostics for the drug, drug approval type, and line of therapy) using meta-regression (eFigures 3–6), the adjusted absolute survival benefit for OS was 0.91 months greater for immunotherapy than for nonimmunotherapy (2.29 vs 1.38 months, respectively; $P = .01$). No other covariates were significant for this

meta-regression (supplemental eTable 3). Conversely, the adjusted absolute survival benefit for PFS was 1.28 months less for immunotherapy than for nonimmunotherapy (1.99 vs 3.27 months, respectively; $P = .02$) (supplemental eTable 4).

The adjusted relative survival benefit for OS was higher for immunotherapy than for nonimmunotherapy by a factor of 1.08 ($P = .01$) (supplemental eTable 5). The adjusted PFS relative survival benefit for immunotherapy compared with nonimmunotherapy was not significant (supplemental eTable 6). The covariate of time horizon of the trial was also significant for OS RMST ratio, PFS RMST difference, and PFS RMST ratio (see supplemental eTables 4–6).

Forest plots were generated to illustrate OS and PFS absolute and relative survival benefits (supplemental eFigures 7–10). Waterfall plots were created to visualize RMST values between immunotherapy and non-immunotherapy trials (supplemental eFigures 11–14). Sensitivity analyses for melanoma, NSCLC, and nonmelanoma and non-NSCLC subgroups (supplemental eFigures 15–20) produced results similar to those of the primary analyses, which showed that immunotherapy had greater absolute survival benefit in OS and less absolute survival benefit in PFS.

Discussion

Measures of RMST fully capture absolute and relative survival benefits presented in KM curves. Mean

Figure 2. Meta-analysis results of RMST difference (absolute survival benefit).

Abbreviations: IV, inverse variance; OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time.

overall absolute survival benefits in contemporary oncology drugs seem to be only modest for OS (1.6 months), with a slightly higher benefit in PFS (3 months). After adjusting for potential confounders, mean absolute survival benefit of immunotherapy is only approximately 1 month greater than non-immunotherapy in OS and approximately 1 month less than nonimmunotherapy in PFS. In comparing survival benefits, immunotherapy was not dramatically superior to nonimmunotherapy; outcomes were more modest than perceived.

The magnitude and clinical meaningfulness of survival benefit in contemporary oncology trials have been under scrutiny, especially with the increases in variety and price of oncology drugs. Multiple studies have measured the magnitude of clinical benefit using the ASCO Value Framework (ASCO-VF) and the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS).^{31,32} However, both frameworks have been criticized for portions of unclear grading criteria, which could lead to misinterpretations, discrepancies in measurement of clinical benefit, and low absolute concordance.¹⁴ Studies analyzing clinical benefit of FDA-approved drugs using these frameworks have concluded that most drugs did not have meaningful clinical benefit.^{33–35} Although these frameworks can be used to quantify benefits, clinicians would require an in-depth and detailed understanding of the intricacies of the framework

algorithms to understand the possibilities that lead to a specific score (ASCO-VF) or grade (ESMO-MCBS), which may make the output less accessible to clinicians or decision-makers with respect to the underlying magnitude of survival benefit of oncology drugs. RMST is an easily interpretable way to describe the magnitude of benefit because it is measured in the natural unit of time (eg, months), which makes interpretation of the magnitude directly accessible to clinicians and decision-makers. Our study quantified that contemporary oncology drugs give modest mean survival benefits of 1.6 months for OS and 3 months for PFS.

Both frameworks rely on median survival time and HR and thus do not fully quantify clinical benefit in the tail of the curve, and therefore they may not be suitable for measuring benefits of immunotherapy, because immunotherapy drugs are shown to have the most benefit at the tail.²⁷ These frameworks have recently been refined to include a tail of the curve bonus (ASCO-VF)³¹ and immunotherapy-triggered long-term plateau adjustments (ESMO-MCBS)³² and have been analyzed previously in the literature.^{27,36,37} The benefits of both immunotherapy and nonimmunotherapy oncology drugs are fully accounted for in our study because RMST was used as a mean measure of survival, thereby overcoming limitations of median survival time, HR, or specific time points in the tail of the curve, on which both ASCO-VF and ESMO-MCBS rely. Therefore,

Figure 3. Meta-analysis results of RMST ratio (relative survival benefit).

Abbreviations: IV, inverse variance; OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time.

it may be worthwhile to consider RMST as a measure to refine the frameworks and account for the full clinical survival benefit of drugs, including the tail of the curve.

The magnitude of clinical benefit of immunotherapy has been hailed as a breakthrough by the public based on results of individual immunotherapy trials showing substantial benefit compared with nonimmunotherapies. However, the percentage of patients estimated to respond to checkpoint inhibitor drugs was 0.14% in 2011 and increased to 12.46% in 2018.³⁸ Although the benefit of immunotherapies has been shown to be more significant in subgroups of patients with certain cancer types (ie, melanoma and NSCLC^{29,30}), there is a paucity of data comparing the magnitude of immunotherapy versus nonimmunotherapy options. Our meta-regression results show that immunotherapies had only 0.91 months greater absolute survival benefit than nonimmunotherapies for OS and 1.28 months less absolute survival benefit than nonimmunotherapies for PFS, suggesting that, overall, the benefits are not as outstanding as presumed.

RECIST version 1.1 is not clinically meaningful for immunotherapy because it fails to capture benefits after disease progression, even though immunotherapy benefits are more pronounced toward the tail of KM curves.³⁹ Our results showed that when quantifying absolute survival for contemporary oncology drugs overall, PFS was greater than OS; however, when comparing that of immunotherapy with nonimmunotherapy, PFS had less

magnitude of benefit than OS, which could be partly explained by the limitations of RECIST version 1.1. In addition, because of the crossing of survival curves in some immunotherapy trials,^{9–13} a subgroup of patients (eg, those with rapidly progressive disease) could seem to benefit more from cytotoxic therapy than immunotherapy, which shows its benefits later. This suggests the need for future research of immunotherapy biomarkers and clinicopathologic predictors to allow better selection of patients for immunotherapy.

Recent studies have questioned whether the magnitude of benefit of FDA-approved contemporary oncology drugs has been increasing over time, just as their costs have been. These studies have found that even though costs are consistently and rapidly increasing, the benefits do not necessarily follow the same trends.^{14–16} Although the variety of oncology drugs has increased over the years, these drugs do not necessarily provide increasing survival benefit. Our meta-regression results showed that even after adjustment for potential covariates, the magnitude of benefit of FDA-approved drugs in 2011 through 2017 did not seem to improve over the years, which is consistent with current literature. Furthermore, the benefit, on average, of all combined nonimmunotherapies using RMST was marginal.

Our study is not without limitations. First, if the KM curves extracted from published trials were of low quality, the accuracy of the RMST estimation may be affected. In our study, 1 study included pixelated KM curves,

and another had a poor time scale,^{40,41} whereas 10 studies had indistinguishable clusters of censor points.^{41–50} Another potential limitation is that our calculation of RMST is based on the inverting of KM estimates to construct the pseudo-individual patient datasets,²⁵ because individual files are not accessible.⁸ Notwithstanding this limitation, Guyot et al²⁵ showed that their method of constructing a pseudo-individual patient dataset resulted in summary statistics that approximated the use of the original individual patient dataset very closely. Also, RSMT difference and ratio may or may not increase with longer follow-up, depending on whether there are substantial separations of the survival curves at the end of the follow-up. In addition, the varying patient populations among the immunotherapy and nonimmunotherapy trials is an inherent limitation in the comparison between the 2 types of treatment. The limitations of RECIST to measure response to immunotherapy drugs is also a potential limitation. Nevertheless, our findings represent the totality of the evidence from the directly observed survival data that were available for decision-making at the time of FDA approval.

Conclusions

Overall, absolute survival benefits of recent oncology drugs are modest. Contrary to popular belief that immunotherapy provides much more benefit than

nonimmunotherapy, our findings suggest that observed survival benefits of immunotherapy were not dramatically superior to those of nonimmunotherapy. Because existent measures of survival benefits often have limitations, particularly in immunotherapy trials, we recommend that RMST values be reported alongside the conventional measures to provide a more complete and realistic picture of the survival benefits of oncology drugs. The routine reporting and use of RMST may assist patients, physicians, and payers in making more informed and responsible decisions regarding the healthcare of patients with cancer.

Submitted May 1, 2019; accepted for publication September 18, 2019.

Previous presentation: An abstract of this study was presented at the 2018 ASCO Annual Meeting, June 1–8, 2018, in Chicago, Illinois (Abstract 6617), and the Canadian Centre for Applied Research in Cancer Control 7th Annual Conference, May 27–28, 2018, in Montreal, Quebec (Abstract 131).

Author contributions: *Study design:* Everest, Chan. *Literature search and data extraction:* Parshad, Everest. *Data review and statistical analyses:* Rahmadian, Delos Santos. *Data interpretation:* Chan. *Manuscript writing:* Rahmadian, Delos Santos, Cheung, Chan.

Disclosures: The authors have disclosed that they have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

Funding: The Canadian Centre for Applied Research in Cancer Control (ARCC) received core funding from the Canadian Cancer Society Research Institute through grant 2105-703549.

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Supplemental online content for:

Quantifying the Survival Benefits of Oncology Drugs With a Focus on Immunotherapy Using Restricted Mean Survival Time

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J Natl Compr Canc Netw 2020;18(3):278–285

eFigure 1: Sample Survival Curve

eFigure 2: Histograms of OS and PFS Distributions

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eTable 1: Characteristics of Included Trials

eTable 2: RMST Summary Statistics

eTable 3: Meta-Regression Analysis Outputs of Overall Survival Restricted Mean Survival Time Differences, Adjusted Values

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eFigure 1. Sample survival curve.

Abbreviations: RMST, restricted mean survival time.

eFigure 2. Histograms of (A) OS and (B) PFS distributions.
Abbreviations: OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time.

eFigure 3. Meta-regression analysis scatterplot of OS restricted mean survival time differences.
Abbreviations: OS, overall survival; RA, regular approval.

eFigure 5. Meta-regression analysis scatterplot of PFS restricted mean survival time differences.
Abbreviations: PFS, progression-free survival; RA, regular approval.

eFigure 4. Meta-regression analysis scatterplot of OS restricted mean survival time ratios.
Abbreviations: OS, overall survival; RA, regular approval.

eFigure 6. Meta-regression analysis scatterplot of PFS restricted mean survival time ratios.
Abbreviations: PFS, progression-free survival; RA, regular approval.

eFigure 7. Forest plot of overall survival restricted mean survival time.

Abbreviation: IV, inverse variance.

eFigure 8. Forest plot of progression-free survival restricted mean survival time.

Abbreviation: IV, inverse variance.

eFigure 9. Forest plot of overall survival restricted mean survival time ratios.
Abbreviation: IV, inverse variance.

eFigure 10. Forest plot of progression-free survival restricted mean survival time ratios.

Abbreviation: IV, inverse variance.

eFigure 11. Waterfall plot of overall survival RMST differences.
Abbreviations: ICI, immune checkpoint inhibitor; RMST, restricted mean survival time.

eFigure 12. Waterfall plot of progression-free survival RMST differences.
Abbreviations: ICI, immune checkpoint inhibitor; RMST, restricted mean survival time.

eFigure 13. Waterfall plot of overall survival RMST ratios.
Abbreviations: ICI, immune checkpoint inhibitor; RMST, restricted mean survival time.

eFigure 14. Waterfall plot of progression-free survival RMST ratios.
Abbreviations: ICI, immune checkpoint inhibitor; RMST, restricted mean survival time.

eFigure 15. Subgroup analysis of melanoma trials (overall survival restricted mean survival time).
Abbreviation: IV, inverse variance.

eFigure 16. Subgroup analysis of melanoma trials (progression-free survival restricted mean survival time difference).
Abbreviation: IV, inverse variance.

eFigure 17. Subgroup analysis of non-small cell lung cancer trials (overall survival restricted mean survival time difference).
Abbreviation: IV, inverse variance.

eFigure 18. Subgroup analysis of non-small cell lung cancer trials (progression-free survival restricted mean survival time difference).
Abbreviation: IV, inverse variance.

eFigure 19. Subgroup analysis of nonmelanoma trials and trials not on non-small cell lung cancer (overall survival restricted mean survival time difference).

Abbreviation: C, chlorambucil; GC, obinutuzumab/chlorambucil; IV, inverse variance; nano+fluoro+folinic, nanoliposomal irinotecan with fluorouracil and folinic acid.

eFigure 20. Subgroup analysis of nonmelanoma trials and trials not on non-small cell lung cancer (progression-free survival restricted mean survival time difference).

Abbreviation: IV, inverse variance.

eTable 1. Characteristics of Included Trials

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Obinutuzumab	11/16/17	In combination with chemo followed by monotherapy in at least partial remission for previously untreated stage II bulky, stage III, or stage IV FL	N	RA	N	1	III	First	PFS	1,202	OS, 52.38 (51.61–53.15)	OS, 51.45 (50.57–52.38)	OS, 0.90 (0.28–2.09)	OS, 1.02 (1.00–1.04)
											PFS, 45.34 (44.01–46.67)	PFS, 42.02 (40.49–43.54)	PFS, 3.32 (1.30–5.35)	PFS, 1.08 (1.03–1.13)
Alectinib	11/6/17	ALK ⁺ metastatic NSCLC with no prior systemic therapy	N	RA	Y	1	III	First	PFS	303	OS, 22.65 (21.28–24.03)	OS, 19.04 (17.92–20.16)	OS, 0.69 (–1.29 to 2.67)	OS, 1.03 (0.94–1.13)
											PFS, 18.01 (16.40–19.61)	PFS, 13.18 (11.75–14.62)	PFS, 4.82 (2.67–6.98)	PFS, 1.42 (1.21–1.67)
Abemaciclib	9/28/17	HR ⁺ , HER2 [–] advanced or mBC progressed after endocrine therapy	N	RA	N	1	III	Other	PFS	669	PFS, 16.20 (15.20–17.19)	PFS, 11.28 (10.08–12.48)	PFS, 4.91 (3.35–6.47)	PFS, 1.44 (1.27–1.62)
Cabazitaxel	9/14/17	Lower dose with prednisone for mCRPC previously treated with docetaxel	N	RA	N	1	III	Other	OS	1,200	OS, 16.87 (15.81–17.93)	OS, 17.24 (16.22–18.26)	OS, –0.37 (–1.84 to 1.10)	OS, 0.98 (0.90–1.07)
											PFS, 4.14 (3.82–4.47)	PFS, 4.52 (4.19–4.86)	PFS, –0.38 (–0.85 to 0.09)	PFS, 0.92 (0.82–1.02)
Gemtuzumab ozogamicin	09/1/17	Newly diagnosed and relapsed CD33 ⁺ AML	N	RA	N	1	III	First	OS	237	OS, 8.01 (6.65–9.37)	OS, 5.52 (4.38–6.66)	OS, 2.49 (0.71–4.26)	OS, 1.45 (1.11–1.89)
Olaparib	8/17/17	Recurrent EOC, FTC, or PPC with CR or PR to platinum-based chemo	N	RA	Y	2	III	Other	PFS	295	PFS, 18.08 (16.70–19.46)	PFS, 9.17 (7.40–10.94)	PFS, 8.91 (6.67–11.16)	PFS, 1.97 (1.60–2.43)
							II	Other	PFS	265	PFS, 8.61 (7.77–9.44)	PFS, 5.55 (4.81–6.30)	PFS, 3.05 (1.93–4.17)	PFS, 1.55 (1.31–1.83)
Inotuzumab ozogamicin	8/17/17	Relapsed or refractory B-cell precursor ALL	N	RA	N	1	III	Other	Complete remission and OS	326	OS, 14.61 (12.35–16.87)	OS, 10.82 (8.92–12.71)	OS, 3.79 (0.84–6.74)	OS, 1.35 (1.07–1.71)
											PFS, 6.94 (6.01–7.87)	PFS, 3.84 (3.07–4.62)	PFS, 3.10 (1.89–4.31)	PFS, 1.81 (1.42–2.30)
Blinatumomab	7/11/17	Relapsed or refractory B-cell precursor ALL	N	AA	N	1	III	Other	OS	405	OS, 9.55 (8.50–10.61)	OS, 7.84 (6.37–9.31)	OS, 1.72 (–0.10 to 3.53)	OS, 1.22 (0.98–1.52)
Ceritinib	5/26/17	Metastatic NSCLC with ALK ⁺ tumors	N	RA	Y	1	III	First	PFS	376	OS, 24.58 (23.06–26.09)	OS, 22.39 (20.68–24.10)	OS, 2.19 (–0.10–4.48)	OS, 1.10 (1.00–1.21)
											PFS, 16.94 (15.23–18.64)	PFS, 11.33 (9.68–12.98)	PFS, 5.61 (3.24–7.98)	PFS, 1.50 (1.25–1.78)
Pembrolizumab	5/18/17	Locally advanced or mUC, progressed during or after platinum-containing chemo (second-line indication)	Y	RA	Y	1	III	Other	PFS and OS	542	OS, 10.91 (10.01–11.81)	OS, 9.18 (8.34–10.01)	OS, 1.73 (0.50–2.96)	OS, 1.19 (1.05–1.34)
											PFS, 5.49 (4.66–6.31)	PFS, 4.56 (4.05–5.06)	PFS, 0.93 (–0.04 to 1.90)	PFS, 1.20 (1.00–1.45)
Midostaurin	4/28/17	Newly diagnosed patients with AML who are FLT3 ⁺	N	RA	Y	1	III	First	OS	717	OS, 50.61 (46.77–54.45)	OS, 44.45 (40.47–48.44)	OS, 6.15 (0.62–11.69)	OS, 1.14 (1.01–1.28)

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eTable 1. Characteristics of Included Trials (cont.)

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Regorafenib	4/27/17	HCC previously treated with sorafenib	N	RA	N	1	III	Other	OS	573	OS, 13.57 (12.37–14.76)	OS, 10.47 (9.01–11.92)	OS, 3.10 (1.23–4.98)	OS, 1.30 (1.10–1.53)
Palbociclib	3/31/17	HR ⁺ , HER2 ⁻ advanced breast cancer or mBC in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women	N	RA	N	1	III	First	PFS	666	PFS, 21.88 (20.67–23.09)	PFS, 16.71 (15.06–18.35)	PFS, 5.18 (3.13–7.22)	PFS, 1.31 (1.17–1.47)
Osimertinib	3/30/17	Metastatic EGFR T790M mutation-positive in NSCLC, progressive during or after platinum-based chemo	N	RA	Y	1	III	Other	PFS	419	PFS, 9.64 (9.00–10.27)	PFS, 5.67 (4.99–6.35)	PFS, 3.97 (3.04–4.90)	PFS, 1.70 (1.48–1.95)
Niraparib	3/27/17	Maintenance treatment with recurrent EOC, FTC, or PPC in CR or PR to platinum-based chemo	N	RA	N	1	III	Other	PFS	553	PFS, 15.80 (14.23–17.38)	PFS, 8.24 (6.06–10.42)	PFS, 7.57 (4.88–10.25)	PFS, 1.92 (1.45–2.55)
Ribociclib	3/13/17	Postmenopausal women with HR ⁺ , HER2 ⁻ advanced breast cancer or mBC	N	RA	N	1	III	First	PFS	668	PFS, 16.51 (15.68–17.34)	PFS, 13.83 (12.40–14.72)	PFS, 2.68 (1.46–3.90)	PFS, 1.19 (1.10–1.30)
Lenalidomide	2/22/17	MM after autologous stem cell transplant	N	RA	N	1	III	Other	PFS	614	OS, 43.48 (42.09–44.87)	OS, 44.10 (42.69–45.50)	OS, -0.62 (-2.60 to 1.36)	OS, 0.99 (0.94–1.03)
Daratumumab	11/21/16	MM with at least one previous therapy	N	RA	N	2	III	Other	PFS	569	PFS, 10.03 (9.45–10.61)	PFS, 7.36 (6.75–7.97)	PFS, 2.67 (1.83–3.52)	PFS, 1.36 (1.23–1.51)
Nivolumab	11/10/16	Recurrent or metastatic SCCHN after a platinum-based therapy	Y	RA	N	1	III	Other	OS	361	OS, 8.23 (7.45–9.00)	OS, 6.36 (5.48–7.24)	OS, 1.87 (0.69–3.04)	OS, 1.29 (1.09–1.53)
											PFS, 3.67 (3.24–4.10)	PFS, 3.15 (2.73–3.58)	PFS, 0.52 (-0.09 to 1.12)	PFS, 1.16 (0.97–1.39)

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eTable 1. Characteristics of Included Trials (cont.)

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Pembrolizumab	10/24/16	First-line NSCLC high PD-L1 expression (TPS $\geq$ 50%); no EGFR or ALK mutations	Y	RA	Y	1	III	First	PFS	305	OS, 14.06 (12.91–15.21) PFS, 9.70 (8.57–10.83)	OS, 12.21 (11.01–13.42) PFS, 6.08 (5.31–6.85)	OS, 1.85 (0.19–3.51) PFS, 3.62 (2.25–4.99)	OS, 1.15 (1.01–1.31) PFS, 1.60 (1.34–1.89)
		Second-line NSCLC high PD-L1 expression (TPS $\geq$ 1%) after platinum-containing chemo; if EGFR or ALK genomic tumor aberrations present, should have disease progression after approved therapy before receiving drug	Y	RA	Y	1	III	Other	PFS and OS	1,033	OS, 12.21 (11.30–13.12) PFS, 6.08 (5.42–6.74)	OS, 10.18 (9.31–11.06) PFS, 5.16 (4.65–5.67)	OS, 2.03 (0.76–3.29) PFS, 0.92 (0.08–1.75)	OS, 1.20 (1.07–1.34) PFS, 1.18 (1.02–1.36)
Olaratumab	10/19/16	Advanced mSTS pre-anthracycline-containing regimen	N	AA	N	1	III	Other	PFS	133	OS, 27.89 (23.79–31.98) PFS, 7.44 (5.69–8.91)	OS, 18.26 (14.47–22.05) PFS, 5.80 (4.28–7.32)	OS, 9.63 (4.05–15.21) PFS, 1.64 (–0.48 to 3.75)	OS, 1.53 (1.18–1.97) PFS, 1.28 (0.92–1.78)
Atezolizumab	10/18/16	Second-line NSCLC after platinum-based therapy; if EGFR or ALK genomic tumor aberrations present, should have disease progression after approved therapy before receiving drug	Y	RA	N	2	III	Other	OS	850	OS, 14.64 (13.71–15.58)	OS, 12.15 (11.26–13.03)	OS, 2.50 (1.21–3.79)	OS, 1.21 (1.09–1.33)
			Y		N		III	Other	OS	287	OS, 11.89 (10.77–13.00)	OS, 10.50 (9.44–11.56)	OS, 1.39 (–0.15 to 2.93)	OS, 1.13 (0.99–1.30)
Erlotinib	10/18/16	NSCLC to limit use to tumors with EGFR mutations	N	RA	Y	1	III	Other	OS	643	OS, 13.16 (11.94–14.38) PFS, 5.28 (4.68–5.89)	OS, 13.40 (12.14–14.67) PFS, 5.02 (4.35–5.68)	OS, –0.24 (–2.00 to 1.52) PFS, 0.27 (–0.63 to 1.17)	OS, 0.98 (0.86–1.12) PFS, 1.05 (0.88–1.26)
Lenvatinib	5/13/16	Second-line RCC	N	RA	N	1	III	Other	PFS	153	OS, 19.57 (17.19–212.95) PFS, 11.61 (9.64–13.58)	OS, 15.95 (13.53–18.38) PFS, 6.60 (5.03–8.18)	OS, 3.62 (0.22–7.02) PFS, 5.01 (2.49–7.53)	OS, 1.23 (1.01–1.49) PFS, 1.76 (1.31–2.36)
Cabozantinib	4/25/16	Second-line RCC	N	RA	N	1	III	Other	PFS	658	OS, 15.75 (14.69–16.82) PFS, 8.32 (7.54–9.10)	OS, 14.96 (14.02–15.90) PFS, 6.06 (5.25–6.86)	OS, 0.79 (–0.63 to 2.21) PFS, 2.27 (1.15–3.38)	OS, 1.05 (0.96–1.16) PFS, 1.37 (1.17–1.62)
Everolimus	2/26/16	Progressive, well-differentiated nonfunctional, NET of gastrointestinal system or lung	N	RA	N	1	III	Other	PFS	302	OS, 23.72 (22.57–24.87) PFS, 13.13 (11.75–14.51)	OS, 21.68 (19.74–23.63) PFS, 9.23 (7.19–11.26)	OS, 2.04 (–0.22 to 4.30) PFS, 3.91 (1.45–6.36)	OS, 1.09 (0.99–1.21) PFS, 1.42 (1.12–1.82)
Obinutuzumab	2/26/16	With bendamustine after obinutuzumab monotherapy for patients with FL who relapsed from rituximab	N	RA	N	1	III	Other	PFS	396	OS, 41.80 (39.44–44.15) PFS, 30.00 (27.01–32.99)	OS, 39.44 (36.74–42.15) PFS, 20.71 (17.96–23.46)	OS, 2.35 (–1.24 to 5.94) PFS, 9.29 (5.23–13.36)	OS, 1.06 (0.97–1.16) PFS, 1.45 (1.23–1.71)

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eTable 1. Characteristics of Included Trials (cont.)

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Palbociclib	2/19/16	HR ⁺ , HER2 ⁻ advanced breast cancer or mBC	N	RA	N	1	III	Other	PFS	521	PFS, 8.83 (8.20–9.45)	PFS, 6.14 (5.39–6.90)	PFS, 2.68 (1.70–3.66)	PFS, 1.44 (1.25–1.66)
Eribulin	1/28/16	Unresectable or metastatic liposarcoma after a prior anthracycline-containing regimen	N	RA	N	1	III	Other	OS	452	OS, 16.43 (14.79–18.08)	OS, 14.58 (13.02–16.14)	OS, 1.85 (–0.42 to 4.12)	OS, 1.13 (0.97–1.31)
											PFS, 4.51 (3.82–5.20)	PFS, 3.86 (3.22–4.50)	PFS, 0.65 (–0.29 to 1.59)	PFS, 1.17 (0.93–1.46)
Ofatumumab	1/19/16	Extended treatment of CR or PR after at least 2 lines of therapy for recurrent or progressive CLL	N	RA	N	1	III	Other	PFS	474	OS, 27.43 (26.56–28.30)	OS, 27.70 (26.84–28.55)	OS, –0.27 (–1.49 to 0.96)	OS, 0.99 (0.95–1.04)
											PFS, 22.17 (20.85–23.48)	PFS, 16.35 (14.84–17.87)	PFS, 5.82 (3.81–7.82)	PFS, 1.36 (1.21–1.51)
Pembrolizumab	12/18/15	Unresectable or metastatic melanoma	Y	RA	Y	2	III	Other	PFS and OS	834	OS, 13.67 (13.03–14.31)	OS, 12.10 (11.35–12.86)	OS, 1.57 (0.58–2.56)	OS, 1.13 (1.05–1.22)
											PFS, 6.08 (5.58–6.58)	PFS, 4.34 (3.90–4.77)	PFS, 1.74 (1.08–2.41)	PFS, 1.40 (1.23–1.60)
			Y		Y		II	Other	PFS	540	PFS, 5.77 (5.01–6.53)	PFS, 3.65 (3.17–4.13)	PFS, 2.13 (1.23–3.02)	PFS, 1.58 (1.32–1.91)
Elotuzumab	11/30/15	In combination with lenalidomide and dexamethasone for MM with 1 to 3 prior therapies	N	AA	N	1	III	Other	ORR and PFS	646	PFS, 20.97 (19.49–22.46)	PFS, 17.19 (15.70–18.68)	PFS, 3.79 (1.69–5.88)	PFS, 1.22 (1.09–1.36)
Necitumumab	11/28/15	First-line squamous NSCLC combination therapy	N	RA	N	1	III	First	OS	1,093	OS, 14.74 (13.77–15.71)	OS, 13.16 (12.24–14.07)	OS, 1.58 (0.25–2.92)	OS, 1.12 (1.02–1.23)
											PFS, 7.22 (6.66–7.78)	PFS, 6.68 (6.05–7.30)	PFS, 0.54 (–0.30 to 1.38)	PFS, 1.08 (0.96–1.22)
Nivolumab	11/23/15	Second-line RCC	Y	RA	N	1	III	Other	OS	821	OS, 21.31 (20.27–22.34)	OS, 19.04 (17.91–20.16)	OS, 2.27 (0.74–3.80)	OS, 1.12 (1.04–1.21)
											PFS, 8.39 (7.52–9.27)	PFS, 7.28 (6.52–8.03)	PFS, 1.12 (–0.04 to 2.28)	PFS, 1.15 (1.00–1.34)
Trametinib and dabrafenib	11/20/15	Unresectable or metastatic melanoma BRAF V600E or V600K mutations, used in combination	N	RA	Y	2	III	First	PFS	423	OS, 21.58 (20.16–22.99)	OS, 19.18 (17.71–20.64)	OS, 2.40 (0.36–4.43)	OS, 1.13 (1.02–1.24)
											PFS, 14.75 (13.24–16.26)	PFS, 11.43 (10.08–12.78)	PFS, 3.33 (1.30–5.35)	PFS, 1.29 (1.10–1.51)
			N		Y		III	First	OS	704	OS, 16.13 (15.45–16.81)	OS, 14.65 (13.85–15.45)	OS, 1.48 (0.43–2.53)	OS, 1.10 (1.03–1.18)
											PFS, 10.71 (10.12–11.30)	PFS, 8.30 (7.70–8.89)	PFS, 2.41 (1.58–3.25)	PFS, 1.29 (1.18–1.41)
Ixazomib	11/20/15	In combination with lenalidomide and dexamethasone for relapsed MM with at least one prior therapy	N	RA	N	1	III	Other	PFS	722	PFS, 15.92 (15.01–16.83)	PFS, 14.38 (13.46–15.29)	PFS, 1.55 (0.25–2.84)	PFS, 1.11 (1.02–1.21)

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eTable 1. Characteristics of Included Trials (cont.)

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Cobimetinib	11/10/15	First-line unresectable or metastatic melanoma with BRAF V600 mutations	N	RA	N	1	III	First	PFS	495	OS, 12.52 (11.97–13.06) PFS, 9.86 (9.21–10.51)	OS, 11.63 (10.97–12.28) PFS, 7.91 (7.27–8.56)	OS, 0.89 (0.04–1.74) PFS, 1.94 (1.03–2.86)	OS, 1.08 (1.00–1.16) PFS, 1.25 (1.12–1.38)
Trabectedin	10/23/15	Second-line unresectable or metastatic liposarcoma or leiomyosarcoma after a prior anthracycline-containing regimen	N	RA	N	1	III	Other	OS	518	OS, 13.15 (12.00–14.30) PFS, 5.16 (4.67–5.66)	OS, 13.02 (11.22–14.82) PFS, 3.11 (2.60–3.62)	OS, 0.13 (–2.01 to 2.26) PFS, 2.05 (1.34–2.76)	OS, 1.01 (0.86–1.19) PFS, 1.66 (1.37–2.01)
Irinotecan liposome	10/22/15	Second-line mPC after gemcitabine-based combined therapy	N	RA	N	1	III	Other	OS	417	OS, 7.60 (6.68–8.52) PFS, 4.63 (3.83–5.43)	OS, 5.96 (5.00–6.91) PFS, 2.89 (2.27–3.50)	OS, 1.64 (0.31–2.97) PFS, 1.75 (0.74–2.76)	OS, 1.28 (1.04–1.56) PFS, 1.60 (1.22–2.11)
Nivolumab	10/9/15	Metastatic NSCLC after platinum-based chemo	Y	RA	N	1	III	Other	OS	582	OS, 13.26 (12.17–14.34) PFS, 6.61 (5.68–7.55)	OS, 11.39 (10.44–12.34) PFS, 5.33 (4.76–5.91)	OS, 1.87 (0.43–3.31) PFS, 1.28 (0.19–2.37)	OS, 1.16 (1.04–1.31) PFS, 1.24 (1.04–1.48)
Nivolumab	9/30/15	Unresectable or metastatic melanoma, and progressed after ipilimumab, or after ipilimumab and a BRAF inhibitor if BRAF V600 mutation-positive	Y	AA	N	1	III	Other	ORR and OS	405	PFS, 5.12 (4.51–5.73)	PFS, 4.36 (3.53–5.19)	PFS, 0.76 (–0.27 to 1.79)	PFS, 1.17 (0.94–1.47)
Trifluridine/tipiracil	9/22/15	Second-line mCRC	N	RA	N	1	III	Other	OS	800	OS, 8.64 (8.11–9.17) PFS, 3.58 (3.29–3.86)	OS, 6.83 (6.16–7.51) PFS, 2.06 (1.83–2.29)	OS, 1.81 (0.95–2.66) PFS, 1.51 (1.15–1.88)	OS, 1.26 (1.13–1.42) PFS, 1.74 (1.51–1.99)
Brentuximab vedotin	8/17/15	Auto-HSCT consolidation treatment of patients with cHL at high risk for relapse or progression	N	RA	N	1	III	Other	PFS	329	OS, 42.82 (40.70–44.94) PFS, 29.04 (26.36–31.73)	OS, 43.91 (41.99–45.84) PFS, 23.63 (20.64–26.63)	OS, –1.09 (–3.95 to 1.77) PFS, 5.41 (1.39–9.43)	OS, 0.98 (0.91–1.04) PFS, 1.23 (1.05–1.44)
Carfilzomib	7/24/15	In combination with lenalidomide and dexamethasone for relapsed MM with 1 to 3 previous lines of therapy	N	RA	N	1	III	Other	PFS	792	OS, 33.43 (32.04–34.83) PFS, 25.92 (24.35–27.49)	OS, 31.11 (29.57–32.66) PFS, 21.74 (20.04–23.44)	OS, 2.32 (0.23–4.40) PFS, 4.18 (1.87–6.49)	OS, 1.07 (1.01–1.15) PFS, 1.19 (1.08–1.32)
Ramucirumab	4/24/15	Second-line mCRC after bevacizumab, oxaliplatin, fluoropyrimidine	N	RA	N	1	III	Other	OS	1,072	OS, 16.83 (15.71–17.95) PFS, 7.55 (7.01–8.08)	OS, 15.12 (14.02–16.22) PFS, 6.46 (5.94–6.98)	OS, 1.71 (0.14–3.28) PFS, 1.08 (0.33–1.83)	OS, 1.11 (1.01–1.23) PFS, 1.17 (1.05–1.30)
Nivolumab	3/4/15	Second-line squamous NSCLC	Y	RA	N	2	III	Other	OS	272	OS, 11.90 (10.46–13.34) PFS, 6.74 (5.55–7.93)	OS, 8.35 (7.18–9.53) PFS, 4.09 (3.41–4.77)	OS, 3.55 (1.69–5.42) PFS, 2.66 (1.29–4.02)	OS, 1.43 (1.19–1.73) PFS, 1.65 (1.30–2.10)

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eTable 1. Characteristics of Included Trials (cont.)

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Panobinostat	2/23/15	In combination with bortezomib and dexmethasone for patients with MM who received at least 2 prior regimens	N	AA	N	1	III	Other	PFS	768	OS, 28.92 (27.28–30.57)	OS, 27.94 (26.33–29.55)	OS, 0.98 (–1.32 to 3.28)	OS, 1.04 (0.95–1.12)
Lenvatinib	2/13/15	Locally recurrent or metastatic radioactive iodine–refractory DTC	N	RA	N	1	III	Other	PFS	392	PFS, 15.69 (14.52–16.86)	PFS, 5.19 (4.25–6.13)	PFS, 10.50 (9.00–12.00)	PFS, 3.02 (2.49–3.68)
Palbociclib	2/3/15	First-line postmenopausal ER+, HER2- advanced breast cancer or mBC	N	AA	N	1	II	First	PFS	165	OS, 33.53 (30.46–36.60)	OS, 31.44 (28.09–34.78)	OS, 2.09 (–2.45 to 6.63)	OS, 1.07 (0.93–1.23)
Lanreotide	12/16/14	Unresectable, well, or moderately differentiated, locally advanced or metastatic GEP-NETs	N	RA	N	1	III	Other	PFS	204	OS, 64.94 (59.65–70.22)	OS, 65.27 (60.04–70.50)	OS, –0.34 (–7.77 to 7.10)	OS, 1.00 (0.89–1.12)
Ramucirumab	12/12/14	Second-line NSCLC	N	RA	N	1	III	Other	OS	1,253	PFS, 20.20 (18.56–21.85)	PFS, 16.88 (15.32–18.44)	PFS, 3.32 (1.06–5.59)	PFS, 1.20 (1.06–1.35)
Bevacizumab	11/14/14	Recurrent platinum-resistant EOC, FTC, PPC	N	RA	N	1	III	Other	PFS	361	OS, 18.05 (16.36–19.75)	OS, 16.43 (14.69–18.17)	OS, 1.63 (–0.80 to 4.05)	OS, 1.10 (0.95–1.27)
Ramucirumab	11/5/14	Second-line advanced gastric or GEJ adenocarcinoma	N	RA	N	1	III	Other	OS	665	PFS, 7.82 (7.02–8.63)	PFS, 4.54 (3.95–5.13)	PFS, 3.28 (2.29–4.28)	PFS, 1.72 (1.46–2.03)
Bevacizumab	8/14/14	Recurrent, persistent, or metastatic cervical cancer combined therapy	N	RA	N	1	III	Other	OS	452	OS, 17.96 (16.36–19.56)	OS, 15.68 (14.08–17.28)	OS, 2.28 (0.02–4.54)	OS, 1.15 (1.00–1.31)
Idelalisib	7/23/14	Relapsed CLL in combination with rituximab	N	RA	N	1	III	Other	PFS	220	PFS, 10.63 (9.49–11.77)	PFS, 8.66 (7.47–9.85)	PFS, 1.97 (0.33–3.62)	PFS, 1.23 (1.03–1.46)
Ramucirumab	4/21/14	Second-line gastric or GEJ adenocarcinoma after cisplatin/5-FU	N	RA	N	1	III	Other	OS	355	OS, 7.34 (6.25–8.42)	OS, 5.84 (4.57–7.10)	OS, 1.50 (–0.17 to 3.16)	OS, 1.26 (0.97–1.63)
											PFS, 3.49 (3.02–3.96)	PFS, 2.00 (1.60–2.40)	PFS, 1.49 (0.87–2.11)	PFS, 1.74 (1.37–2.22)

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Table 1. Characteristics of Included Trials (cont.)

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Ofatumumab	4/17/14	In combination with chlorambucil for previously untreated CLL	N	RA	N	1	III	First	PFS	447	OS, 44.32 (42.22–46.42) PFS, 23.32 (21.30–25.33)	OS, 43.04 (40.85–45.23) PFS, 16.11 (14.36–17.86)	OS, 1.28 (–1.76 to 4.31) PFS, 7.21 (4.54–9.88)	OS, 1.03 (0.96–1.10) PFS, 1.45 (1.26–1.66)
Trametinib and dabrafenib	1/10/14	Unresectable or metastatic melanoma with BRAF V600E or V600K mutation	N	AA	Y	1	II	Other	PFS, incidence of CSCC, response	162	PFS, 10.10 (8.94–11.26)	PFS, 6.56 (5.64–7.48)	PFS, 3.54 (2.06–5.02)	PFS, 1.54 (1.28–1.85)
Sorafenib	11/22/13	Locally recurrent or metastatic DTC	N	RA	N	1	III	Other	PFS	417	OS, 26.93 (25.20–28.45) PFS, 13.23 (11.76–14.71)	OS, 25.66 (24.03–27.29) PFS, 9.33 (7.98–10.68)	OS, 1.28 (–0.95 to 3.50) PFS, 3.91 (1.91–5.91)	OS, 1.05 (0.96–1.14) PFS, 1.42 (1.18–1.70)
Crizotinib	11/20/13	Metastatic NSCLC ALK+ after platinum-based therapy	N	RA	Y	1	III	Other	PFS	347	PFS, 9.13 (8.01–10.24)	PFS, 5.58 (4.58–6.58)	PFS, 3.55 (2.05–5.05)	PFS, 1.64 (1.32–2.03)
Obinutuzumab	11/1/13	In combination with chlorambucil for patients with previously untreated CLL	N	RA	N	1	III	First	PFS	781	OS, 32.55 (31.52–33.58) PFS, 23.36 (22.16–24.55)	OS, 29.94 (27.38–32.50) PFS, 11.81 (10.35–13.27)	OS, 2.62 (–0.14–5.37) PFS, 11.55 (9.66–13.43)	OS, 1.09 (0.99–1.19) PFS, 1.98 (1.73–2.26)
Nab-paclitaxel	9/6/13	First-line advanced pancreatic cancer or mPC combined therapy	N	RA	N	1	III	First	OS	861	OS, 10.70 (9.86–11.55) PFS, 6.73 (6.14–7.33)	OS, 8.89 (8.15–9.64) PFS, 5.49 (4.82–6.16)	OS, 1.81 (0.68–2.94) PFS, 1.25 (0.35–2.14)	OS, 1.20 (1.07–1.35) PFS, 1.23 (1.06–1.43)
Aflatinib	7/12/13	First-line stage IIb or IV NSCLC EGFR mutations (del19/L858R)	N	RA	Y	1	III	First	PFS	345	PFS, 12.31 (11.31–13.31)	PFS, 8.04 (6.83–9.25)	PFS, 4.26 (2.70–5.83)	PFS, 1.53 (1.29–1.82)
Trametinib	5/29/13	Unresectable or metastatic melanoma with BRAF V600E or V600K mutation	N	RA	Y	1	III	Other	PFS	322	OS, 7.45 (7.12–7.77)	OS, 6.74 (6.21–7.28)	OS, 0.70 (0.07–1.33)	OS, 1.10 (1.01–1.21)
Dabrafenib	5/29/13	Unresectable or metastatic melanoma with BRAF V600E or V600K mutation	N	RA	Y	1	III	First	PFS	250	PFS, 5.43 (5.09–5.77)	PFS, 3.26 (2.56–3.97)	PFS, 2.16 (1.38–2.95)	PFS, 1.66 (1.33–2.09)
Radium-223	5/15/13	mCRPC and symptomatic bone metastases	N	RA	N	1	III	Other	OS	921	OS, 16.85 (15.81–17.90)	OS, 14.15 (12.78–15.53)	OS, 2.70 (0.98–4.43)	OS, 1.19 (1.06–1.34)
Erlotinib	5/14/13	First-line NSCLC EGFR exon 19 deletions or exon 21 (L858R) mutations	N	RA	Y	1	III	First	PFS	173	PFS, 11.53 (9.68–13.38)	PFS, 6.19 (4.87–7.50)	PFS, 5.35 (3.08–7.62)	PFS, 1.86 (1.43–2.43)
Ado-trastuzumab emtansine (T-DM1)	2/22/13	Second-line HER2+ breast cancer after trastuzumab failure	N	RA	Y	1	III	Other	PFS, OS, safety	991	OS, 26.55 (25.27–27.83) PFS, 12.13 (11.13–13.12)	OS, 23.89 (22.72–25.06) PFS, 8.83 (8.01–9.64)	OS, 2.66 (0.93–4.40) PFS, 3.30 (2.01–4.59)	OS, 1.11 (1.04–1.19) PFS, 1.37 (1.21–1.56)

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e Table 1. Characteristics of Included Trials (cont.)

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Pomalidomide	2/8/13	MM with at least 2 previous therapies	N	AA	N	1	II	Other	PFS	221	OS, 11.70 (10.63–12.77) PFS, 7.49 (5.93–9.06)	OS, 10.99 (9.88–12.11) PFS, 5.29 (3.79–6.79)	OS, 0.71 (–0.83 to 2.25) PFS, 2.20 (0.03–4.38)	OS, 1.06 (0.93–1.22) PFS, 1.42 (1.00–2.02)
Bevacizumab	1/23/13	Second-line mCRC beyond progression on bevacizumab combined therapy	N	RA	N	1	III	Other	OS	820	OS, 14.05 (12.06–16.04) PFS, 6.90 (6.39–7.42)	OS, 12.24 (10.23–14.25) PFS, 5.32 (4.86–5.79)	OS, 1.81 (–1.02 to 4.64) PFS, 1.58 (0.89–2.27)	OS, 1.15 (0.92–1.43) PFS, 1.30 (1.16–1.45)
Abiraterone acetate	12/10/12	mCRPC in combination with prednisone	N	RA	N	1	III	Other	OS	1,195	OS, 15.47 (14.90–16.04)	OS, 13.55 (12.71–14.40)	OS, 1.92 (0.90–2.94)	OS, 1.14 (1.06–1.23)
Cabozantinib	11/29/12	Progressive mMTC	N	RA	N	1	III	Other	PFS	330	PFS, 10.68 (9.71–11.65)	PFS, 5.45 (4.40–6.50)	PFS, 5.23 (3.80–6.66)	PFS, 1.96 (1.58–2.42)
Pemetrexed	10/17/12	Maintenance therapy for advanced non-squamous NSCLC	N	RA	N	1	III	Other	PFS	539	PFS, 5.16 (4.69–5.64)	PFS, 3.63 (3.16–4.10)	PFS, 1.53 (0.87–2.20)	PFS, 1.42 (1.21–1.67)
Regorafenib	9/27/12	Third-line mCRC	N	RA	N	1	III	Other	OS	760	OS, 7.48 (7.02–7.93) PFS, 3.24 (3.02–3.46)	OS, 6.58 (5.94–7.21) PFS, 2.03 (1.84–2.23)	OS, 0.90 (0.12–1.68) PFS, 1.20 (0.90–1.50)	OS, 1.14 (1.01–1.27) PFS, 1.59 (1.41–1.79)
Enzalutamide	8/31/12	mCRPC after docetaxel	N	RA	N	1	III	Other	OS	1,199	OS, 16.83 (16.22–17.45) PFS, 9.92 (9.31–10.53)	OS, 14.15 (13.27–15.02) PFS, 5.37 (4.87–5.86)	OS, 2.69 (1.62–3.76) PFS, 4.55 (3.77–5.34)	OS, 1.19 (1.11–1.28) PFS, 1.85 (1.65–2.07)
Ziv-aflibercept	8/03/12	Second-line mCRC after oxaliplatin-based treatment in combination with FOLFIRI	N	RA	N	1	III	Other	OS	1,226	OS, 17.00 (16.01–17.99) PFS, 7.77 (7.24–8.30)	OS, 14.89 (14.02–15.77) PFS, 6.51 (6.00–7.01)	OS, 2.11 (0.79–3.43) PFS, 1.26 (0.53–2.00)	OS, 1.14 (1.05–1.24) PFS, 1.19 (1.08–1.32)
Everolimus	7/20/12	mBC after failure of aromatase inhibitor	N	RA	N	1	III	Other	PFS	724	PFS, 8.49 (7.86–9.13)	PFS, 5.19 (4.45–5.93)	PFS, 3.30 (2.32–4.28)	PFS, 1.64 (1.39–1.92)
Cetuximab	7/06/12	First-line KRAS wild-type mCRC in combination with FOLFIRI	N	RA	Y	3	III	First	PFS	1,198	OS, 20.30 (19.39–21.22) PFS, 9.29 (8.80–9.78)	OS, 19.86 (18.97–20.75) PFS, 8.55 (8.11–9.00)	OS, 0.45 (–0.83 to 1.72) PFS, 0.73 (0.07–1.40)	OS, 1.02 (0.96–1.09) PFS, 1.09 (1.01–1.17)
Pertuzumab	6/8/12	First-line HER2+ mBC combined therapy	N	RA	Y	1	III	First	PFS	808	OS, 31.79 (30.49–33.09) PFS, 19.59 (18.27–20.91)	OS, 29.17 (27.67–30.68) PFS, 15.41 (14.12–16.71)	OS, 2.62 (0.63–4.61) PFS, 4.17 (2.32–6.02)	OS, 1.09 (1.02–1.16) PFS, 1.27 (1.14–1.42)
Pazopanib	4/26/12	Previously treated mSTS	N	RA	N	1	III	Other	PFS	369	OS, 13.36 (12.37–14.34) PFS, 4.98 (4.52–5.44)	OS, 12.09 (10.70–13.49) PFS, 2.20 (1.81–2.60)	OS, 1.27 (–0.44 to 2.97) PFS, 2.78 (2.17–3.38)	OS, 1.11 (0.96–1.27) PFS, 2.26 (1.85–2.76)

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eTable 1. Characteristics of Included Trials (cont.)

Drug*	Approval Date	Indications	ICI?	Approval Type	Companion Diagnostic?	Number of Trials	Phase	Line of Therapy	Primary Outcome	Trial Size	Experimental RMST (95% CI)	Control RMST (95% CI)	RMST Difference	RMST Ratio
Axitinib	1/27/12	Second-line RCC	N	RA	N	1	III	Other	PFS	723	PFS, 8.72 (7.90–9.53)	PFS, 6.65 (5.86–7.44)	PFS, 2.07 (0.94–3.20)	PFS, 1.31 (1.13–1.53)
Cetuximab	11/7/11	First-line SCCHN combination therapy	N	RA	Y	1	III	First	OS	442	OS, 11.41 (10.37–12.46)	OS, 9.67 (8.65–10.69)	OS, 1.74 (0.28–3.20)	OS, 1.18 (1.03–1.36)
											PFS, 6.01 (5.45–6.56)	PFS, 4.14 (3.71–4.58)	PFS, 1.87 (1.16–2.57)	PFS, 1.45 (1.26–1.67)
Vemurafenib	8/17/11	Metastatic melanoma with BRAF V600E mutation	N	RA	Y	2	III	First	PFS and OS	672	OS, 8.42 (7.77–9.08)	OS, 6.92 (6.43–7.42)	OS, 1.50 (0.68–2.32)	OS, 1.22 (1.09–1.35)
											PFS, 5.37 (4.75–5.99)	PFS, 2.70 (2.44–2.97)	PFS, 2.66 (1.99–3.33)	PFS, 1.99 (1.71–2.31)
Sunitinib	5/20/11	Unresectable locally advanced or metastatic pancreatic NET	N	RA	N	1	III	Other	PFS	171	OS, 18.65 (17.39–19.92)	OS, 15.53 (13.75–17.31)	OS, 3.13 (0.95–5.31)	OS, 1.20 (1.05–1.37)
											PFS, 11.96 (9.94–13.99)	PFS, 6.35 (5.00–7.70)	PFS, 5.62 (3.19–8.05)	PFS, 1.89 (1.44–2.47)
Abiraterone acetate	4/28/11	mCRPC after docetaxel combined with prednisone	N	RA	N	1	III	Other	OS	1,195	OS, 13.43 (12.92–13.94)	OS, 11.47 (10.68–12.25)	OS, 1.97 (1.03–2.90)	OS, 1.17 (1.08–1.27)
											PFS, 7.52 (7.14–7.91)	PFS, 6.00 (5.52–6.47)	PFS, 1.53 (0.91–2.14)	PFS, 1.26 (1.14–1.38)
Vandetanib	4/6/11	Unresectable locally advanced or mMTC	N	RA	N	1	III	Other	PFS	331	OS, 27.25 (26.37–28.12)	OS, 26.59 (24.99–28.19)	OS, 0.65 (–1.17 to 2.48)	OS, 1.03 (0.96–1.10)
											PFS, 22.83 (21.59–24.07)	PFS, 17.83 (15.59–20.07)	PFS, 5.00 (2.44–7.56)	PFS, 1.28 (1.12–1.47)
Ipilimumab	3/25/11	Previously treated unresectable or metastatic melanoma	Y	RA	N	1	III	Other	OS	676	OS, 16.68 (13.90–19.46)	OS, 10.87 (8.87–12.87)	OS, 5.81 (2.38–9.24)	OS, 1.53 (1.20–1.97)
											PFS, 6.84 (5.20–8.48)	PFS, 3.76 (2.83–4.68)	PFS, 3.09 (1.20–4.97)	PFS, 1.82 (1.29–2.57)
Rituximab	1/28/11	Maintenance therapy previously untreated CD20 ⁺ ; B-cell FL in combination with chemo	N	RA	N	1	III	Other	PFS	1,018	OS, 50.85 (50.09–51.62)	OS, 50.65 (49.87–51.44)	OS, 0.20 (–0.89 to 1.30)	OS, 1.00 (0.98–1.03)
											PFS, 42.01 (40.49–43.53)	PFS, 35.82 (34.11–37.53)	PFS, 6.19 (3.90–8.48)	PFS, 1.17 (1.11–1.25)

Abbreviations: AA, accelerated approval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; cHL, classic Hodgkin lymphoma; chemo, chemotherapy; CLL, chronic lymphocytic leukemia; CR, complete response; CSCC, cutaneous squamous cell carcinoma; DTC, differentiated thyroid carcinoma; EOC, epithelial ovarian cancer; ER, estrogen receptor; FL, follicular lymphoma; FOLFIRI, 5-fluorouracil/leucovorin/irinotecan; FTC, fallopian tube cancer; GEJ, gastroesophageal junction; GEP, gastroenteropancreatic; HCC, hepatocellular carcinoma; HR, hormone receptor; HSCT, hematopoietic stem cell transplantation; ICI, immune checkpoint inhibitor; IV, intravenous; mBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; mCRPC, metastatic castration-resistant prostate cancer; MM, multiple myeloma; mMTC, metastatic medullary thyroid cancer; mPC, metastatic pancreatic cancer; mSTS, metastatic soft tissue sarcoma; mUC, metastatic urothelial carcinoma; NET, neuroendocrine tumor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPC, primary peritoneal cancer; PR, partial response; RA, regular approval; RCC, renal cell carcinoma; RMST, restricted mean survival time; SCCHN, squamous cell carcinoma of the head and neck; TPS, tumor proportion score.

*Drugs are listed in reverse chronological order of approval.

eTable 2. RMST Summary Statistics

	Experimental RMST (mo)	Control RMST (mo)	RMST Difference (mo)	RMST Ratio	Immune Checkpoint Inhibitor, n (Y vs N)	Crossover, n (Y vs N)	Trial Time Horizon (mo)	Year of FDA Approval	Phase III, n (Y vs N)	Companion Diagnostic (Y vs N)	Approval Type, n (RA vs Others)
OS curves											
Mean	20.44	18.61	1.83	1.14			31.74	2014.41			
SD	12.47	12.64	1.55	0.12			14.15	1.91			
Median	16.28	14.15	1.73	1.12			30.35	2015			
First quartile	12.67	10.83	1.05	1.06			21.5	2013			
Third quartile	26.06	22.28	2.31	1.19			37.98	2016			
Frequency of "Y" or "RA"					11	17			65	16	65
PFS curves											
Mean	12.07	8.71	3.36	1.47			23.65	2014.48			
SD	8.35	7.02	2.39	0.33			10.66	1.89			
Median	9.29	6.14	2.78	1.42			22.2	2015			
First Quartile	6.19	4.53	1.56	1.23			15.45	2013			
Third Quartile	15.86	10.86	4.41	1.65			28.95	2016			
Frequency of "Y" or "RA"					11				80	24	80

Abbreviations: OS, overall survival; PFS, progression-free survival; RA, regular approval; RMST, restricted mean survival time.

eTable 3. Meta-Regression Analysis Outputs of Overall Survival Restricted Mean Survival Time Differences, Adjusted Values				
Covariate	Coefficient	95% CI LL	95% CI UL	P Value (2-Sided)
Intercept	1.8756	0.3682	3.3831	.0147
Immune checkpoint inhibitor (Y vs N)	0.9140	0.2927	1.6253	.0118
Crossover (Y vs N)	−0.3685	−0.9379	0.2008	.2045
Trial time horizon (per mo)	0.0008	−0.0204	0.0221	.9376
FDA year of approval (per y)	−0.0622	−0.1934	0.0689	.3523
Phase III (Y vs N)	0.0161	−1.3660	1.3982	.9818
Companion diagnostic (Y vs N)	−0.2659	−0.8765	0.3446	.3933
Approval type (RA vs others)	−0.2508	−1.6209	1.1192	.7197
Line of therapy (specific to first-line vs other)	0.2170	−0.3942	0.8183	.4792

Abbreviations: LL, lower limit; RA, regular approval; UL, upper limit.

eTable 4. Meta-Regression Analysis Outputs of Progression-Free Survival Restricted Mean Survival Time Differences, Adjusted Values				
	Coefficient	95% CI LL	95% CI UL	P Value (2-Sided)
Intercept	1.7648	−0.1843	3.7139	.0760
Immune checkpoint inhibitor (Y vs N)	−1.2844	−2.3528	−0.2161	.0185
Trial time horizon (per mo)	0.0665	0.0298	0.1033	.0004
FDA year of approval (per y)	0.0510	−0.1410	0.2430	.6028
Phase III (Y vs N)	−0.7671	−2.4024	0.8681	.3578
Companion diagnostic (Y vs N)	0.0701	−0.8343	0.9746	.8792
Approval type (RA vs others)	0.3669	−1.2371	1.9708	.6539
Line of therapy (specific to first-line vs other)	0.4434	−0.4974	1.3842	.3557

Abbreviations: LL, lower limit; RA, regular approval; UL, upper limit.

eTable 5. Meta-Regression Analysis Outputs of Overall Survival Restricted Mean Survival Time Ratios, Adjusted Values

Covariate	Coefficient	95% CI LL	95% CI UL	P Value (2-Sided)
Intercept	0.1924	0.0886	0.2961	.0003
Immune checkpoint inhibitor (Y vs N)	0.0729	0.0160	0.1299	.0121
Crossover (Y vs N)	−0.0308	−0.0704	0.0088	.1273
Trial time horizon (per mo)	−0.0020	−0.0032	−0.0007	.0029
FDA year of approval (per y)	−0.0029	−0.0123	0.0065	.5494
Phase III (Y vs N)	−0.0212	−0.1234	0.0811	.6851
Companion diagnostic (Y vs N)	−0.0139	−0.0595	0.0316	.5490
Approval type (RA vs others)	−0.0021	−0.0960	0.0919	.9656
Line of therapy (specific to first-line vs other)	0.0073	−0.0363	0.0509	.7433

Values are on the log scale.

Abbreviations: LL, lower limit; RA, regular approval; UL, upper limit.

eTable 6. Meta-Regression Analysis Outputs of Progression-Free Survival Restricted Mean Survival Time Ratios, Adjusted Values

	Coefficient	95% CI LL	95% CI UL	P Value (2-Sided)
Intercept	0.5904	0.3764	0.8044	.0000
Immune checkpoint inhibitor (Y vs N)	−0.0954	−0.2209	0.0300	.1359
Trial time horizon (per mo)	−0.0054	−0.0091	−0.0016	.0052
FDA year of approval (per y)	−0.0141	−0.0348	0.0067	.1837
Phase III (Y vs N)	−0.1252	−0.3085	0.0581	.1805
Companion diagnostic (Y vs N)	0.0102	−0.0892	0.1096	.8406
Approval type (RA vs others)	0.0748	−0.0990	0.2486	.3989
Line of therapy (specific to first-line vs other)	−0.0292	−0.1275	0.0692	.5611

Values are on the log scale.

Abbreviations: LL, lower limit; RA, regular approval; UL, upper limit.