Supplementary Online Content

Chen EY, Joshi SK, Tran A, Prasad V. Estimation of study time reduction using surrogate end points rather than overall survival in oncology clinical trials. *JAMA Intern Med*. Published online April 1, 2019. doi:10.1001/jamainternmed.2018.8351

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Methods in Detail

Eligibility Criteria for Each Entry in the Data sets

Inclusion Criteria:

1. Every new drug
2. Subsequent new disease indication (ex. nivolumab approved in melanoma, then in lung cancer)
3. Expansion of prior disease indication by line of treatment (ex. pembrolizumab in second-line treatment of metastatic non-small cell lung cancer moved to first-line treatment)
4. Expansion of prior disease indication by patient population (ex. nivolumab in metastatic squamous cell lung cancer followed by nivolumab in metastatic adenocarcinoma lung cancer)
5. Expansion of prior disease indication by novel therapy combinations particularly if the FDA reports this combination as new indication (ex. gemtuzumab ozogamicin alone and in combination with chemotherapy for AML)

Exclusion Criteria:

1. Drugs previously approved prior to February 1, 2006 but had been granted regular approval only after 2006 (ex. sunitinib for renal cell carcinoma)
2. Drug previously approved prior to February 1, 2006 but withdrawn after 2006 (ex gefitinib for non-small cell lung cancer)
3. Dose changes (ex. cabazitaxel decreased to 20mg/m2 from 25mg/m2 for prostate cancer)
4. Formulation changes (ex. subcutaneous instead of intravenous rituximab for follicular lymphoma)
5. Redefinition of smaller patient population within an existing disease indication using sub-analysis from licensing trials already in the dataset (ex. ibrutinib for CLL and then also CLL with 17p deletion)
6. Drugs approved with both monotherapy indication and combination therapy indication together were counted once only (toward the combination therapy) if the monotherapy was a smaller, earlier-phase study or if the monotherapy becomes irrelevant in the context of combination therapy (ex. ixabepilone approved as monotherapy due to a prior single-arm study and as combination therapy with capecitabine due to a subsequent phase 3 trial)
7. Disease indications almost exclusively pediatric cancers (ex. native *E.coli* asparaginase for pediatric ALL)
8. Genetic syndromes (ex. everolimus for renal angiomyolipoma in tuberous sclerosis)
9. Adjunctive cancer therapies (ex. degarelix for prostate cancer and denosumab for osseous metastases)
10. Pre-cancer condition or risk factors (ex. raloxifene for patients at high risk for breast cancer)
11. Preventative vaccines (ex. HPV vaccine for prevention of cervical cancer)
12. Generally non-neoplastic hematologic disorders (ex. eculizumab for paroxysmal nocturnal hemoglobinuria)
13. Pembrolizumab for treatment-refractory microsatellite-high solid tumor (inclusive of colorectal cancer) was counted only once within colorectal cancer rather than as multiple indications for every solid tumor

Data Collection:

1. While establishing either the original trials or updated trials dataset, if there were still multiple trials within the package insert for specific indication approval, the trial that was primarily listed in section 14 of package insert, conducted in North America, and/or had the highest sample size was chosen for data extraction.

2. Patient reported outcomes (PRO) were collected from studies only if they contributed to FDA approval (ex. ruxolitinib for myeloproliferative disorders and siltuximab for Castleman's disease). They were categorized within OS endpoint because both OS and PRO are definite endpoints important to patients and FDA regulators.

3. With regards to missing data, estimated enrollment start and end dates were taken from https://clinicaltrials.gov/ records if they were not reported in published studies. If only month and year were reported, then the date was set at the first day of the month. Missing data related to RR, PFS, or OS were extracted from subsequent publications of

the same trial or from other relevant similar clinical trials that also have led to the same indication label (ex. studies not conducted in North America, from prior accelerated approval, or with smaller sample size). If subsequent trials or long-term follow-up were not yet published by March 23, 2018 as full publications, preliminary results from national meeting abstracts were recorded. Data from the FDA package insert was also used if no other published data was available. Studies not noted by the FDA website or package insert were not used.

4. With regards to RR results, the radiographic response rate by a blinded independent review (instead of investigator-assessed) was preferred for data extraction. Complete response rate (ex. acute leukemia) and biomarker-based response rate (ex. chronic myelogenous leukemia and multiple myeloma) were accepted for clinically relevant disease indications. Study duration for RR was a conservative estimate by assigning median TTR or median DOR to zero if only either one is missing. It was counted as truly missing if both are missing. A second definition of study duration for RR was defined by the sum of enrollment duration in half length, median time to response (TTR), and median duration of response (DOR). The third definition used the sum of TTR and DOR only without the enrollment duration. The second and third definitions of study duration for RR were based on 'updated trials' only as part of sensitivity analysis.

5. With regards to PFS results, the median radiographic PFS done by a blinded independent review (instead of investigator-assessed) was preferred for data extraction. Recurrence-free survival, disease-free survival, and event-free survival were accepted for adjuvant and pertinent hematologic malignancy trials. Time to progression was used only if other endpoints listed above were not available. The second definition of study duration for PFS was defined by the sum of enrollment duration in half length and median PFS of the drug. The third definition used median PFS only without enrollment duration. The second and third definitions of study duration for PFS were based on 'updated trials' only as part of sensitivity analysis.

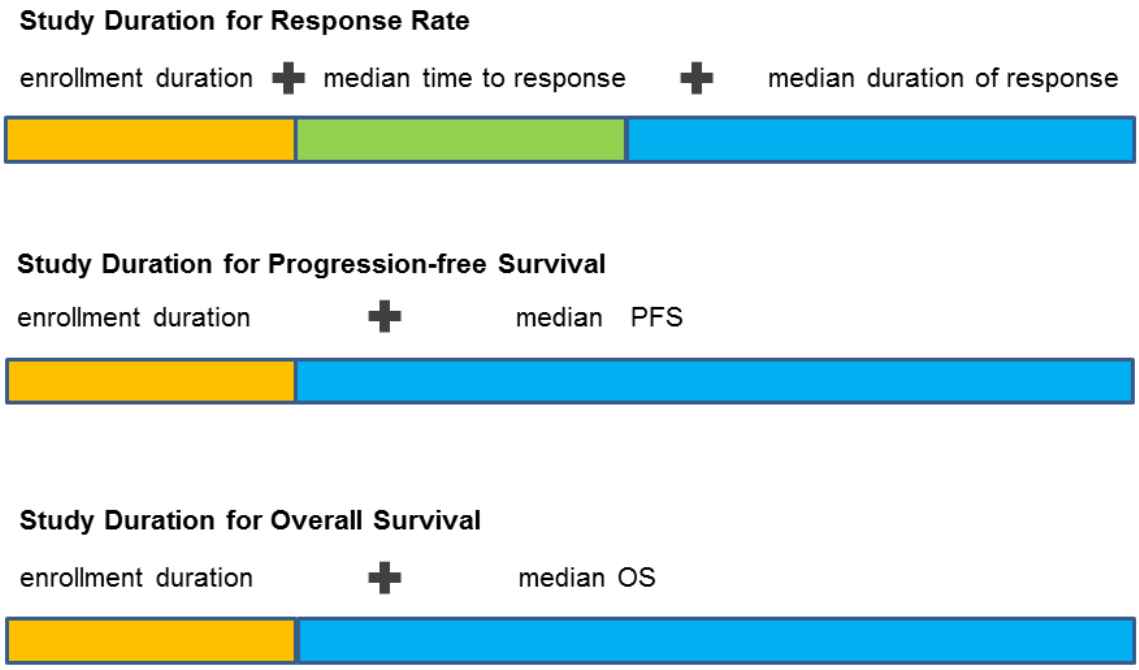
6. With regards to OS results, the median OS was collected, if available. The second definition of study duration for OS was defined by the sum of enrollment duration in half length and median OS and did not account for PRO. The third definition used median OS without enrollment duration and did not account for PRO.

Statistical Analysis:

The multivariate model was completed by selecting variables of interest hypothesized to affect the outcome variable. All of these variables were logically framed into numeric variables that could be tested with the main outcome. For analyzing the endpoint basis for FDA approval (RR, PFS, OS), each category was created as a 'dummy variable,' with the value 1 and reference given the value 0. Only RR and PFS 'dummy variables' (variable 1 and variable 2) were used because OS was the reference (value=0). Variable 3 was the accrual rate with the median (18.12725 in the initial trials dataset and 19.304808 in the updated trials dataset) set up as the reference to have the value 0. Variable 4 was the line of therapy with first-line given the value -1, second-line given the value 0 as the reference, and third-or-later-line given the value of 1. Setting the median and intermediate category as the reference allows the intercept to be as representative of the dataset as possible. Only variables (or a component of the variables) with p value less than 0.05 was kept in the final model, and statistically insignificant variables were eliminated. For this reason, drug activity (either response rate or change in response rate) was not included in the final model. The regression model using only hypothesized variables that were statistically significant with the highest R-Square value was chosen for the final model.

The specific equation used in the linear regression model is Y (study duration) = variable X_1 (PFS=1 vs. OS=0 as reference), variable X_2 (RR=1 vs. OS=0 as reference), variable X_3 (accrual rate= patients accrued per month with median shifted to the value 0 as the reference), variable X_4 (first line=-1, second line=0 as the reference, and third-or-later line=1).

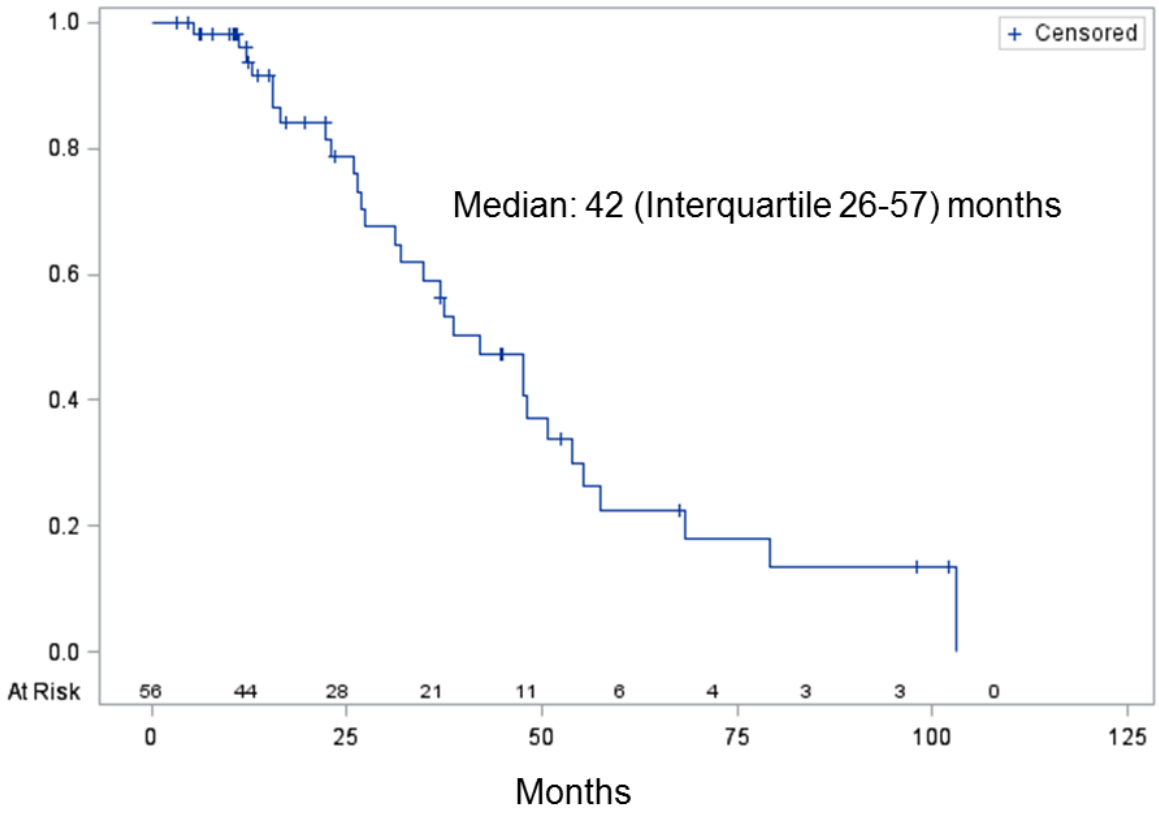
eFigure 1. Definition of Study Duration for RR, PFS, and OS & PRO When the Data Cutoff Date Is Not Available



eTable 1. Most Common Cancer Types and Cancer Drugs That Were Granted Multiple Drug Indications by the FDA From 2006 to 2017

Top 13 Most Common Disease Types	**Counts (percentage)**
Lung cancer	21 (11%)
Breast cancer	15 (8%)
B cell non-Hodgkin lymphoma	14 (7%)
Melanoma	14 (7%)
Multiple myeloma	12 (6%)
Myeloproliferative neoplasms	11 (6%)
Colorectal cancer	10 (5%)
Kidney cancer	10 (5%)
Chronic lymphocytic leukemia	9 (5%)
Acute lymphoblastic leukemia	6 (3%)
Acute myeloid leukemia	6 (3%)
Head and neck cancer	6 (3%)
Ovarian cancer	6 (3%)
Top 15 Most Common Cancer Drugs	
Nivolumab	11 (6%)
Bevacizumab	8 (4%)
Pembrolizumab	8 (4%)
Everolimus	4 (2%)
Imatinib	4 (2%)
Ramucirumab	4 (2%)
Rituximab	4 (2%)
Dabrafenib and trametinib	4 (2%)
Brentuximab	3 (2%)
Cabozantinib	3 (2%)
Cetuximab	3 (2%)
Ibrutinib	3 (2%)
Lenalidomide	3 (2%)
Obinutuzumab	3 (2%)
Ofatumumab	3 (2%)
Drug Mechanism Class	
Targeted	81 (43%)
Biologic	45 (24%)
Immunotherapy	27 (14%)
Cytotoxic	22 (12%)
Other (cellular, hormonal, radioactive particle)	13 (7%)

eFigure 2. Kaplan-Meier Analysis of Duration of Conversion From Accelerated to Regular Approval



eTable 2. Sensitivity Analysis Using All Study Durations for RR, PFS, and OS End Points Across Line of Therapy Settings per Updated Trials Data Set

N=172	**Median (range) in months**	**P value**
All studies in advanced or metastatic setting	N=172	
Study duration for RR (N=122)	28 (8-108)	<0.01
Study duration for PFS (N=159)	27 (6-105)	<0.01
Study duration for OS & PRO (N=130)	37 (12-117)	ref
First-line setting	N=71	
Study duration for RR (N=44)	29 (8-89)	<0.01
Study duration for PFS (N=66)	33 (10-104)	0.02
Study duration for OS & PRO (N=55)	46 (12-101)	ref
Second-line setting	N=77	
Study duration for RR (N=57)	27 (12-108)	0.04
Study duration for PFS (N=72)	25 (6-105)	<0.01
Study duration for OS & PRO (N=60)	33 (13-117)	ref
Third-or-later-line setting	N=24	
Study duration for RR (N=21)	28 (13-52)	0.22
Study duration for PFS (N=21)	27 (12-52)	0.08
Study duration for OS & PRO (N=15)	37 (18-76)	ref

RR=response rate, PFS=progression-free survival, OS=overall survival, PRO=patient reported outcome, ref=reference

eTable 3. Sensitivity Analysis Using Second Definition of Study Duration for RR, PFS, and OS End Points per Updated Trials

N=172	**Median (range) in months**	**P value**
All studies in advanced or metastatic setting	N=172	
Study duration for RR (N=120)	20 (5-64)	<0.01
Study duration for PFS (N=151)	19 (4-74)	<0.01
Study duration for OS & PRO (N=112)	28 (9-98)	ref
First-line setting	N=71	
Study duration for RR (N=42)	21 (6-64)	<0.01
Study duration for PFS (N=63)	23 (7-74)	<0.01
Study duration for OS & PRO (N=44)	35 (16-98)	ref
Second-line setting	N=77	
Study duration for RR (N=57)	20 (5-57)	0.01
Study duration for PFS (N=68)	16 (4-55)	<0.01
Study duration for OS & PRO (N=54)	25 (9-56)	ref
Third-or-later-line setting	N=24	
Study duration for RR (N=21)	18 (7-41)	0.08
Study duration for PFS (N=20)	19 (7-31)	0.01
Study duration for OS & PRO (N=14)	29 (12-60)	ref

RR=response rate, PFS=progression-free survival, OS=overall survival, PRO=patient reported outcome, ref=reference

eTable 4. Sensitivity Analysis Using Third Definition of Study Duration for RR, PFS, and OS End Points per Updated Trials Data Set

N=172	**Median (range) in months**	**P value**
All studies in advanced or metastatic setting	N=172	
Time to RR (N=120)	9 (1-40)	<0.01
Time to PFS (N=151)	7 (2-36)	<0.01
Time to OS or PRO (N=112)	15 (5-75)	ref
First-line setting	N=71	
Time to RR (N=42)	10 (1-40)	<0.01
Time to PFS (N=63)	10 (3-36)	<0.01
Time to OS or PRO (N=44)	23 (9-75)	ref
Second-line setting	N=77	
Time to RR (N=57)	9 (1-34)	<0.01
Time to PFS (N=68)	5 (2-29)	<0.01
Time to OS or PRO (N=54)	13 (5-31)	ref
Third-or-later-line setting	N=24	
Time to RR (N=21)	9 (1-24)	0.09
Time to PFS (N=20)	6 (2-19)	<0.01
Time to OS or PRO (N=14)	16 (5-48)	ref

RR=response rate, PFS=progression-free survival, OS=overall survival, PRO=patient reported outcome, ref=reference

eTable 5. Median (Range) of Sample Size, Enrollment Duration, and Accrual Rate per Original Trials and Updated Trials Data Sets

N=172	**Basis for initial FDA approval**			
	RR	**PFS**	**OS**	**P value**
Original trials	(N=70)	(N=53)	(N=49)	
Sample size in persons (N=172)	136 (12-1052)	399 (133-1202)	676 (79-1725)	<0.01
Enrollment duration in months (N=169)	15 (3-44)[a]	22 (5-82)	23 (5-102)	<0.01
Accrual rate in persons per month (N=169)	9 (1-66)[a]	24 (2-49)	32 (2-153)	<0.01
	RR	**PFS**	**OS**	
Updated trials	(N=70)	(N=53)	(N=49)	
Sample size in persons (N=172)	192 (20-1052)	416 (133-1221)	676 (79-1725)	<0.01
Enrollment duration in months (N=172)	17 (2-55)	21 (7-82)	23 (5-102)	0.02
Accrual rate in person per month (N=172)	11 (1-84)	26 (2-118)	32 (2-153)	<0.01

[a]N=67 instead of 70

eTable 6. Multivariate Linear Regression Examining the Association Between Study Duration (Y, Main Outcome) and Hypothesized Variables (X, Exposures) per Updated Trials Data Set

Reference	**Intercept (95% CI)**	**P value**
Estimated study duration per reference	44 (39-49)	<0.01
Variables	***B* coefficient (95% CI)**	
Basis for approval		
Months saved if OS used for approval	0 (reference)	
Months saved if PFS used for approval[a]	-10 (-15 – -4)	<0.01
Months saved if RR used for approval[b]	-15 (-21 – -9)	<0.01
Accrual rate		
Months decreased with each patient accrued per month[c]	-0.3 (-0.4 – -0.2)	<0.01
Line of therapy		
Months decreased if first-line treatment[d]	4 (0.8-8)	
Months decreased if second-line treatment[d]	0 (reference)	
Months decreased if third-or-later-line treatment[d]	--4 (-8 – -0.8)	0.02
Variable 1[a]; variable 2[b]; variable 3[c]; variable 4[d];		