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Original Article

Clinical Benefit, Price and Approval Characteristics of FDA-approved New Drugs for Treating Advanced Solid Cancer, 2000-2015

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ABSTRACT

Background: Prices of anti-cancer drugs are skyrocking. We aimed to assess the clinical benefit of new drugs for treating advanced solid tumors at the time of their approval by the US Food and Drug Administration (FDA) and to search for a relation between price and clinical benefit of drugs.

Materials and methods: We included all new molecular entities and new biologics for treating advanced solid cancer that were approved by the FDA between 2000 and 2015. The clinical benefit of drugs was graded based on FDA medical review of pivotal clinical trials using the 2016-updated of the American Society of Clinical Oncology Value Framework (ASCO-VF) and the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Characteristics of drugs and approvals were obtained from publicly available FDA documents and price was evaluated according to US Medicare, US Veterans Health Administration and United Kingdom market systems.

Results: The FDA approved 51 new drugs for advanced solid cancer from 2000 to 2015; we could evaluate the value of 37 drugs (73%). By the ESMO-MCBS, five drugs (14%) were grade one (the lowest), 9 (24%) grade two, ten (27%) grade three, 11 (30%) grade four and two (5%) grade five (the highest). Thus, 13 drugs (35%) showed a meaningful clinical benefit (scale levels 4 and 5). By the ASCO-VF which had a range of 3.4 to 67, the median drug value was 37 (interquartile range 20 to 52). We found no relationship between clinical benefit and drug price ($p = 0.9$). No characteristic of drugs and of approval was significantly associated with clinical benefit.

Conclusion: Many recently FDA-approved new cancer drugs did not have high clinical benefit as measured by current scales. We found no relation between the price of drugs and benefit to society and patients.

Key Words: Value-Based Purchasing; Relative Value Scales; Prescription Drugs; Costs and Cost Analysis; Neoplasms/drug therapy.

Key Message:

A high number of new drugs approved by the FDA between 2000 and 2015 for treating advanced solid cancer did not have high clinical benefit as measured by the scales recently developed by the ASCO and the ESMO. A meaningful clinical benefit was observed for only 35% of evaluable drugs. Clinical benefit score was not associated with the drug price neither with characteristics of drugs or of approval.

introduction

The concept of the value of drugs has recently dominated oncology. Massive investments in research yielded major advances in the comprehension of tumor biology, which has translated to an increase in number of new anti-cancer drugs approved by the US Food and Drug Association (FDA). Hence, new anticancer drugs have yielded high expectations from all stakeholders. Especially, drugs for personalized medicine — patients to be treated are selected on the basis of a predictive (genomic) biomarker — represent great hope for the oncology community. [1] Similarly, first-in-class drugs (relying on a new pharmacological mechanism of action) represent a measure of innovation success and could therefore have high value. [2] An increasing number of drugs has been approved by using pathways and designations to expedite drug approval; [3] these are drugs that are intended for life-threatening conditions and unmet medical need.

The skyrocketing price of oncology drugs has led various stakeholders (patients, physicians, third-party payers) to criticize the pricing policies of manufacturers [4] and, combined with the high burden of cancer, has highlighted the question of the value of cancer drugs. [5] The high price of drugs is often justified by the need to support research and development, but an analysis of the most transformative drugs showed that, actually, government-funded academic research was the primary source of drug innovation. [6]

A critical question for the oncology community is how to assess the value of drugs. Two important oncology societies have recently taken a step forward in this endeavor: The American Society of Clinical Oncology (ASCO) published its Conceptual Framework to Assess the Value of Cancer Treatment Options (ASCO-VF), [7] which was updated in 2016, [8] and the European Society for Medical Oncology developed its Magnitude of Clinical Benefit Scale (ESMO-MCBS) for drugs indicated in the treatment of solid cancer. [9] Both

scales have been designed with the aim of evaluating the value of anti-cancer drugs by "[balancing] the magnitude of its clinical benefit […] against its cost". [9]

This study aimed to describe the clinical benefit of new drugs for treating advanced solid cancer that were recently approved by the FDA and to search for a relationship between clinical benefit and price of drugs and for characteristics associated with clinical benefit. We restricted this study to drugs for treating advanced solid cancer because the (1) ESMO-MCBS is applicable only for drugs treating solid cancers and (2) the vast majority of new anticancer drugs are indicated in the advanced setting.

methods

list of drugs

We included all new drugs (new molecular entities and novel biologics) indicated for treating advanced solid cancer that were approved by the FDA between 2000 and 2015.

description of the ASCO-VF Net Health Benefit (NHB)

The ASCO-VF NHB has 3 main components: 1) magnitude of treatment effect 2) toxicity, and 3) bonus points. [8] The magnitude of treatment effect is assessed by overall survival (OS) if reported; if OS is not reported, progression-free survival (PFS) is used; and if neither OS nor PFS are reported, overall response rate (ORR) is used. Treatment effect size for OS and PFS is quantified by hazard ratios (HR) and difference in median survival time and weighted by type of endpoint. For instance, an HR of 0.7 for OS yields 30 points, but the same HR for PFS would yield only 21 points.

The toxicity score ranges from -20 to +20. The value depends on the frequency and severity of toxic effects. A null value corresponds to a new drug with similar toxicity as for the

control. Negative points are for a new drug associated with high toxicity and positive points are awarded if the new drug reduces toxicity as compared to the control.

If a treatment is associated with long-term benefit, it can be awarded "tail of the curve" bonus points (16 points for PFS or 20 for OS). Three other possible bonuses include a ten-point bonus for treatments improving cancer-related symptoms, another ten-point bonus for improving quality-of-life (QoL), and another ten-point bonus for improving treatment-free interval. These bonuses can be cumulative. The sum of the magnitude of treatment effect, toxicity, and bonus points gives the net health benefit (ASCO-VF NHB).[8]

description of the ESMO-MCBS

The *ESMO-MCBS* has two main components: 1) a preliminary score based on the clinical benefit and 2) modification (upgrade and downgrade) of the primary score based on the toxicity and QoL, which yields the final score based on five-point scale ranging from one, lowest grade, to five, highest grade. [9] Levels four and five correspond to a meaningful clinical benefit.[9, 10] In the first part, a preliminary score is calculated on the basis of the clinical benefit of the drug according to the primary endpoint of the study. The treatment effect size is quantified by either (i) the lower limit of the 95% confidence interval (CI) for the HR and by differences in median survival or (ii) by the increase in survival at a fixed time (two or three years depending on the median survival time with the standard treatment). When HRs and the increase in survival at a fixed time yield different results, the best score is used. With OS, the preliminary value ranges from one to four and could be upgraded if the treatment improves QoL or reduced grade three to four toxicity affecting daily well-being. Hence, the final value for drugs evaluated with OS ranges from one to five. For drugs evaluated with PFS, the preliminary value ranges from one to three and could be upgraded with the same conditions as for OS. However, the score could be downgraded with increased toxicity or if a drug leads to only a benefit for PFS (ie, without a benefit for OS) and fails to

show an improvement in QoL. The maximal value for drugs evaluated with PFS is thus four. The ESMO-MCBS indicates that levels four and five correspond to ASCO guidelines for meaningful clinical benefit. [9, 10]

grading of the clinical benefit drug by using the ASCO-VF and ESMO-MCBS

We graded the drugs with the ASCO-VF and ESMO-MCBS based on data from the pivotal clinical trials submitted to the FDA for approval and described in the FDA medical review (retrieved from Drugs@fda website). Scores were assessed by one investigator and checked by a second one, with discrepancies resolved by a senior investigator.

approval characteristics

We assessed whether the drug was granted with one of the five FDA pathways and designations to expedite drug approval (orphan drug status, fast-track, priority review, breakthrough designation, and accelerated approval).

drug prices

We re-used data from the DrugAbacus database to obtain the price of drugs in 3 markets: US Medicare, US Veterans Health Administration and the United Kingdom. [11] For drugs not listed in the DrugAbacus database, we computed the cost in US Medicare terms by using publicly available data and the same methods as used in the DrugAbacus database. The primary analysis was pre-specified as using prices by the US Medicare system because it had the fewest missing values.

statistical Analyses

The association between the clinical benefit of drugs and their characteristics was tested by Mann-Whitney-Wilcoxon and Fisher exact tests. We investigated the relation with drug prices by simple linear regression. $P < 0.05$ was considered statistically significant.

results

number and characteristics of new drugs

From 2000 to 2015, the FDA approved 51 new drugs for treating advanced solid tumors (Figure S1). Three approvals were discontinued as of October 6, 2016 and thus were removed from our sample. Furthermore, we could not assess the value of 11 drugs (23%) because the pivotal trial was not a head-to-head RCT, had a non-inferiority design or did not report one of the 3 endpoints used in the value scales (OS, PFS, ORR). Thus, we analyzed data for 37 drugs. The most frequent indications were colorectal (*N*=6, 16%) and breast (*N*=6, 16%) cancers (Table S1).

clinical benefit of new drugs

By the ASCO-VF, the median net health benefit (NHB) of drugs was 37 [interquartile range 20 to 52; range 3.4 to 66.5] (Table S2 and Figure 1). The median treatment effect score was 34 [interquartile range 23 to 42] and the median toxicity score was -5 [-13 to -2]. Bonus points for a tail on PFS curves were granted for 14 drugs (38%) and for OS curves for four drugs (11%); for palliation symptoms for two drugs (5%); and for improvement in QoL for four drugs (11%). No drugs received bonus points for treatment-free interval. By the ESMO-MCBS, five drugs (14%) were grade one (the lowest), 9 (24%) grade two, ten (27%) grade three, 11 (30%) grade four and two (5%) grade five (the highest). Thus, 13 drugs (35%) had a meaningful clinical benefit (levels four and five). Toxicity assessment downgraded the value for two drugs (5%) and upgraded it for one drug (3%). Quality of life assessment downgraded the value for four drugs (11%) and upgraded it for six drugs (16%). Results of assessment of value for each drug are provided in Table 1.

characteristics associated with drug clinical benefit

We found no differences in ASCO-VF scores by innovation degree (first-in-class vs advance or addition to class: 37 vs 38, *P* = 0.29); orphan status (38 vs 36, *P* = 0.56); priority review (37 vs 39, *P* = 0.66); breakthrough designation (29 vs 52, *P* = 0.23); accelerated approval (22 vs 40, *P* = 0.13); or fast-track (46 vs 34, *P*=0.15). The presence of a pharmacogenomic biomarker in the drug label where also not statistically associated with drug value albeit drugs with a biomarker had a median of 44 vs 31 for those without, *P* = 0.06, Figure S2. Results were similar with ESMO-MCBS scores (Figure S3).

relation between price and value of drugs

We found no relation between ASCO-VF score and price as determined by US Medicare [R^2 = 0, *P* = 0.93] (Figure 2), nor any relation between price and value whatever the scale used (ASCO-VF or ESMO-MCBS) or system used to determine the price (US Medicare, US Veterans Health Administration or United Kingdom).

discussion

In our review of all anticancer agents approved by the FDA between 2000 and 2015, 1) only one third of new drugs had a meaningful clinical benefit according to the ESMO-MCBS; (2) drug price and clinical benefit were not related by the two scales and the three pricing systems; and 3) drug clinical benefit was not associated with any drug characteristics. Especially, we found no significant difference for personalized medicine drugs and first-in-class drugs.

Our results are consistent with a recent review finding that only 31% of drugs examined in published randomized controlled trials of four cancers (breast, colorectal, non-small cell lung and pancreas) had meaningful clinical benefit according to the ESMO-MCBS. [10] Another recent overview of clinical trials supporting FDA-approval cancer drugs (new drugs or new

indications) from April 2014 to February 2016 found that half met the ASCO-VF meaningful goals for future clinical trials for PFS and one fifth for OS. [12]

The absence of a price–clinical benefit relation could be theoretically surprising. However, our results agree with previous studies. [13]. Clinical benefit was not assessable for 20% of drugs mainly because the drugs were approved on the basis of a single-arm trial. This situation is not rare in oncology, especially for orphan drugs, [14] so assessing clinical benefit in this situation is highly problematic— at least at the time of marketing authorization.

The ASCO-VF and the ESMO-MCBS yielded some discrepancies which are not surprising given the differences in their construction and their somewhat different goals. The ASCO-VF is more patient-oriented and was developed to "assist in facilitating shared decision-making with patients about clinical benefits and costs," [7, 8] whereas the ESMO-MCBS is more societal-oriented and was developed to "frame the appropriate use of limited public and personal resources to deliver cost-effective and affordable cancer care". [9] Especially, the ESMO-MCBS uses the primary endpoint (often PFS), whereas the ASCO-VF uses OS if reported. However, in many cases OS was not usable to score drugs because of cross-over from experimental to control arm or because the OS were not enough mature at the time of approval. This echoes the difficulties to choose OS as a primary endpoint in many advanced cancer settings.

Our study encompasses a large period of time and used two validated scales, including the 2016 update of the ASCO-VF. However, it has some limitations. First, defining the exact clinical benefit of a drug is complex.[15] In this study, we used two scales that were previously tested and validated by various stakeholders and international experts and our results were similar whatever the scale used. The assessment of value depends on accurate reporting and analysis of clinical trial data. Notably, treatment effects have been found greater in published trials than in FDA documents. [16] In this study, we used FDA documents as the

primary source of data to limit reporting biases. The benefit of a drug refers to an benefit averaged over all patients being treated but it is well known that treatment effects are heterogeneous and some patients could derived a great benefit from a drug with a low value score.

Determining the price of a drug is complex because different prices are available depending on the country and even within the US depending on the entity that purchases the drug. Furthermore, there is only limited transparency in drug pricing because the prices available usually do not account for managed-entry agreements or other discounts granted to buyers by drug manufacturers (which are not known to the public). In our study, we used two countries and three different pricing systems, including one with negotiated prices (US Veterans Health Administration). Because the results of our analyses did not depend on the choice of pricing system, we are confident that this limitation did not impact our study.

The clinical benefit score of drugs is dynamic by nature as acknowledged by the ASCO [8] because of different reasons:

a) Within a trial, efficacy results (especially OS results) could and will evolve with time as more events occur;

b) As new clinical trials are conducted, the pooled estimate of efficacy results will also evolve;

c) A drug could have subsequent supplemental approvals for new indications, each one being associated with a different magnitude of clinical benefit compared to its original indication. This point is precisely the central argument for having an indication-specific price of drugs.[5]

Here, we focused on the first indication of new drugs and evaluated the clinical benefit based on data submitted for approval because this reflects the entry into the market. How this

benefit evolves over time and with possible new indications is of interest but is out of the scope of our study. Recently, a live cumulative network meta-analysis was proposed to reflect an up-to-date summary of trial evidence for a given indication. [17] Similarly, the clinical benefit of a drug is relative to the control and evolves with time as more evidence and more alternatives are available. ESMO has planned to score all new drugs approved after January 1, 2016 [18] and this could be incorporated in a live cumulative assessment of drugs clinical benefit.

conclusion

Patients, clinicians and policy-makers are involved in a salient debate on the clinical benefit, price and value of drugs. Regarding the evidence for new cancer drugs, the bar has been dropping, [19] which has been justified by the high benefit of new drugs. We showed, however, that the price of drugs was not related to their benefit to society and patients.

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disclosure

Dr. Zeitoun reports that he serves as an advisor for several consulting firms and communication companies linked with the pharmaceutical industry (Cepton, Oliver Wyman, Roland Berger, McCann Healthcare, Omnicom, Grey Healthcare, Saatchi and Saatchi Healthcare, Sudler& Hennessey, TBWA, inVentiv Health France, Havas). He also reports collaboration with Mayoly-Spindler, Merck, Teva, Pierre Fabre and Menarini; unpaid consultancy for EY and Allurion Technologies; conducting workshops funded by Amgen; and invitation to a French medical congress by AbbVie. He is a co-founder of Inato, a startup specialized in clinical research. Other authors do not have any possible conflict of interest to disclose.

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figure legends

Figure 1. Clinical benefit of the 37 anticancer drugs approved by the US Food and Drug Administration (FDA) from 2000 to 2015 as evaluated by the 2016 update of the American Society of Clinical Oncology Value Framework Net Health Benefit (ASCO-VF NHB) and the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). The upper scatterplot represents the distribution of the ASCO-VF NHB for each grade of the ESMO-MCBS and the upper-right boxplot represents the overall distribution of ASCO-VF NHB. The bottom-left barplot represents the overall distribution of ESMO-MCBS scores.

Figure 2. Relationship between the clinical benefit of the 37 anticancer drugs approved by the FDA from 2000 to 2015 as evaluated by the 2016 update of the ASCO-VF NHB and the ESMO-MCBS and the price according to US Medicare (data on prices retrieved from DrugAbascus).

Table 1. Clinical Benefit of FDA-approved new drugs for treating advanced solid cancer from 2000 to 2015 as evaluated by the ASCO-VF (2016 update) and the ESMO-MCBS scales.

			ASCO-VF		**ESMO-MCBS**	
Name	**Year**	**First indication**	**Endpoint**	**Score**	**Endpoint**	**Score**
Pertuzumab	2012	First-line treatment of HER-2 positive breast cancer	PFS	46.8	OS	4
Palbociclib	2015	First-line treatment of ER-positive, HER2-negative breast cancer	PFS	36.8	PFS	3
Ixabepilone	2007	Second-line treatment of breast cancer	PFS	18.3	PFS	2
Lapatinib	2007	Second-line treatment of breast cancer	PFS	54.6	PFS	2
Ado-trastuzumab	2013	Second-line treatment of HER2-positive breast cancer	OS	62.4	OS	5
Eribulin Mesylate	2010	Third-line treatment of breast cancer	OS	18.3	OS	2
Bevacizumab	2004	First-line treatment of colorectal cancer	OS	31	OS	3
Cetuximab	2004	Second-line treatment of EGFR-expressing colorectal cancer	OS	7.2	ORR	1
Panitumumab	2006	Second-line treatment of EGFR-expressing colorectal cancer	PFS	19.8	PFS	1
Regorafenib	2012	Third treatment of colorectal cancer	OS	3.4	OS	1
Ziv-aflibercept	2012	Second-line treatment of colorectal cancer	OS	16.6	OS	1
Trifluridine and tipiracil	2015	Third-line treatment of colorectal cancer	OS	49.8	OS	2
Sunitinib	2006	Second-line treatment of gastrointestinal stromal tumor	PFS	36.1	PFS	3
Vemurafenib	2011	First-line treatment of BRAF-mutated melanoma	OS	66.5	OS	4

Afatinib	2013	First-line treatment of non-small cell lung cancer with EGFR mutations	PFS	31.7	PFS	4
Necitumumab	2015	First-line treatment of squamous non-small cell lung cancer	OS	11.3	OS	2
Erlotinib	2004	Second-line treatment of non-small cell lung cancer	OS	42.1	OS	4
Trametinib	2013	First-line treatment of BRAF-mutated melanoma	PFS	52.7	PFS	4
Dabrafenib	2013	First-line treatment of BRAF-mutated melanoma	PFS	59.6	PFS	4
Cobimetinib	2015	First-line treatment of BRAF-mutated melanoma	PFS	52.2	PFS	4
Ipilimumab	2011	Second-line treatment of melanoma	OS	28.9	OS	4
Nivolumab	2014	Second-line treatment of melanoma	OS	22	OS	3
Pemetrexed	2004	First-line treatment of mesothelioma	OS	17.6	OS	3
Ramucirumab	2014	Second-line treatment of oeso-gastric cancer	OS	39.4	OS	1
Cabazitaxel	2010	Second-line treatment of prostate cancer	OS	40.5	OS	2
Abiraterone Acetate	2011	Second-line treatment of prostate cancer	OS	34.6	OS	4
Enzalutamide	2012	Second-line treatment of prostate cancer	OS	52.6	OS	4
Radium-223	2013	Second-line treatment of prostate cancer	OS	60.9	OS	5
Sorafenib	2005	First-line treatment of renal cell carcinoma	PFS	53.6	PFS	2
Temsirolimus	2007	First-line treatment of renal cell carcinoma	OS	21.6	OS	4
Pazopanib	2009	First-line treatment of renal cell carcinoma	PFS	46.3	PFS	3
Everolimus	2009	First-line treatment of renal cell carcinoma	PFS	32.8	PFS	3
Axitinib	2012	Second-line treatment of renal cell carcinoma	OS	17	PFS	3

Trabectedin	2015	Second-line treatment of liposarcoma or leiomyosarcoma	OS	14.6	PFS	3
Vandetanib	2011	First-line treatment of thyroid cancer	PFS	45.7	PFS	3
Cabozantinib	2012	Second-line treatment of medullary thyroid cancer	PFS	37.6	PFS	2
Lenvatinib	2015	Second-line treatment of thyroid cancer	PFS	59.2	PFS	2

BRAF, B-Raf proto-oncogene; EGFR, endothelium growth factor receptor; ER, estrogen-receptor, HER-2; human epidermal growth factor receptor-2.

Figure 1

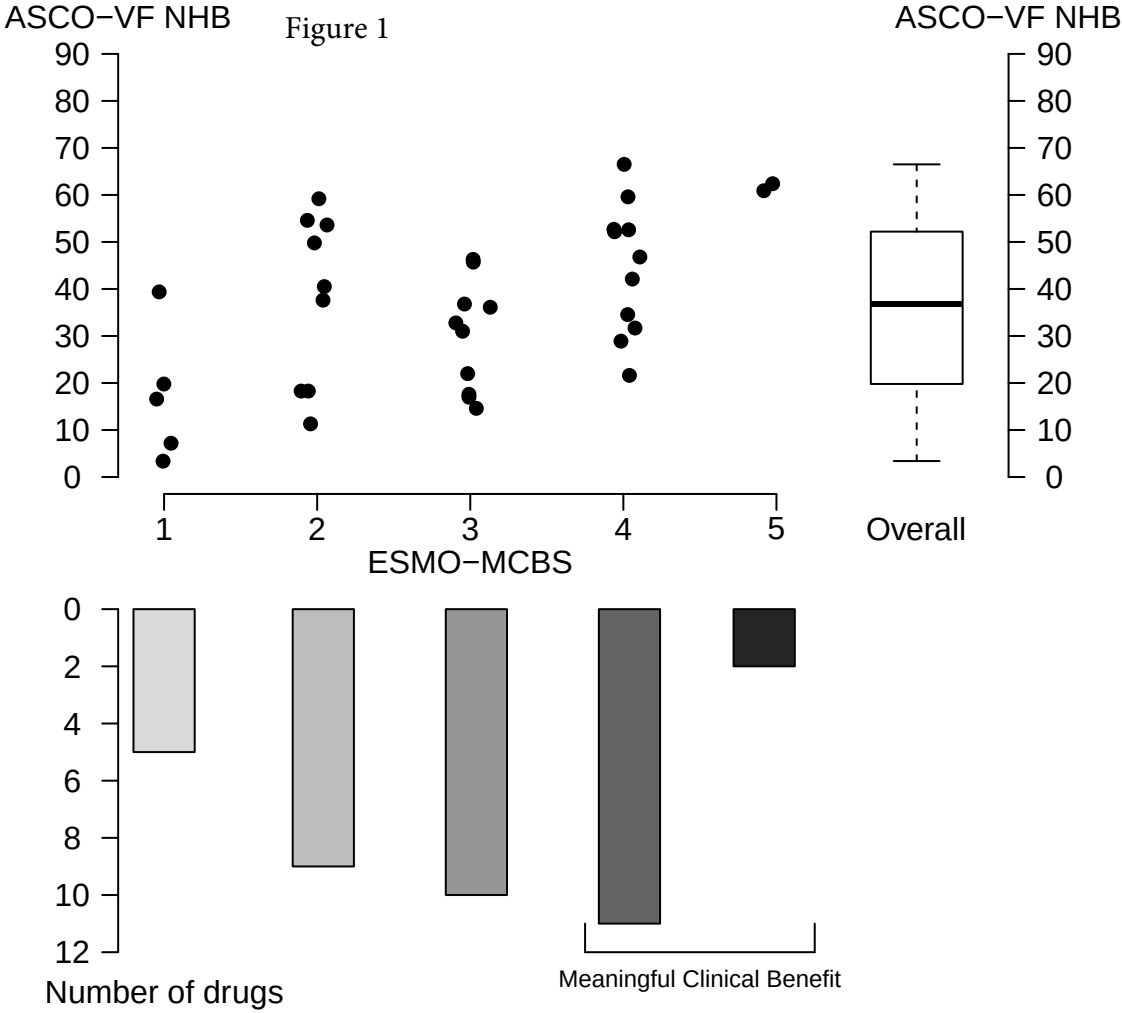
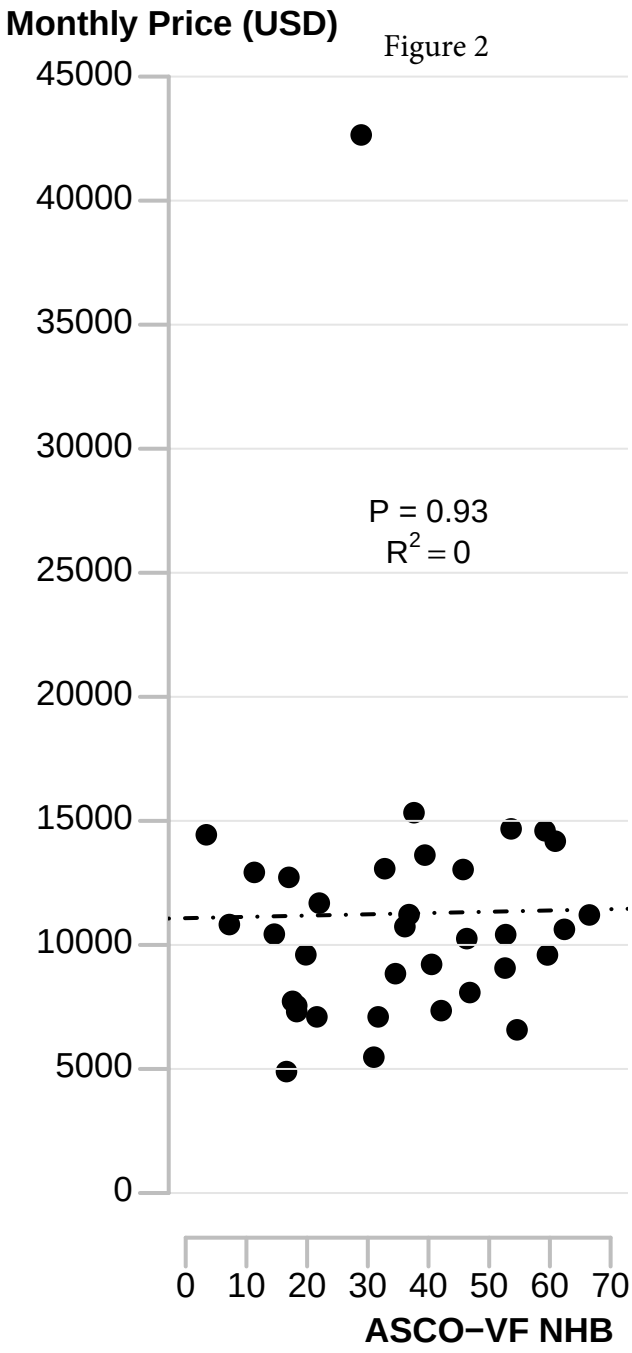
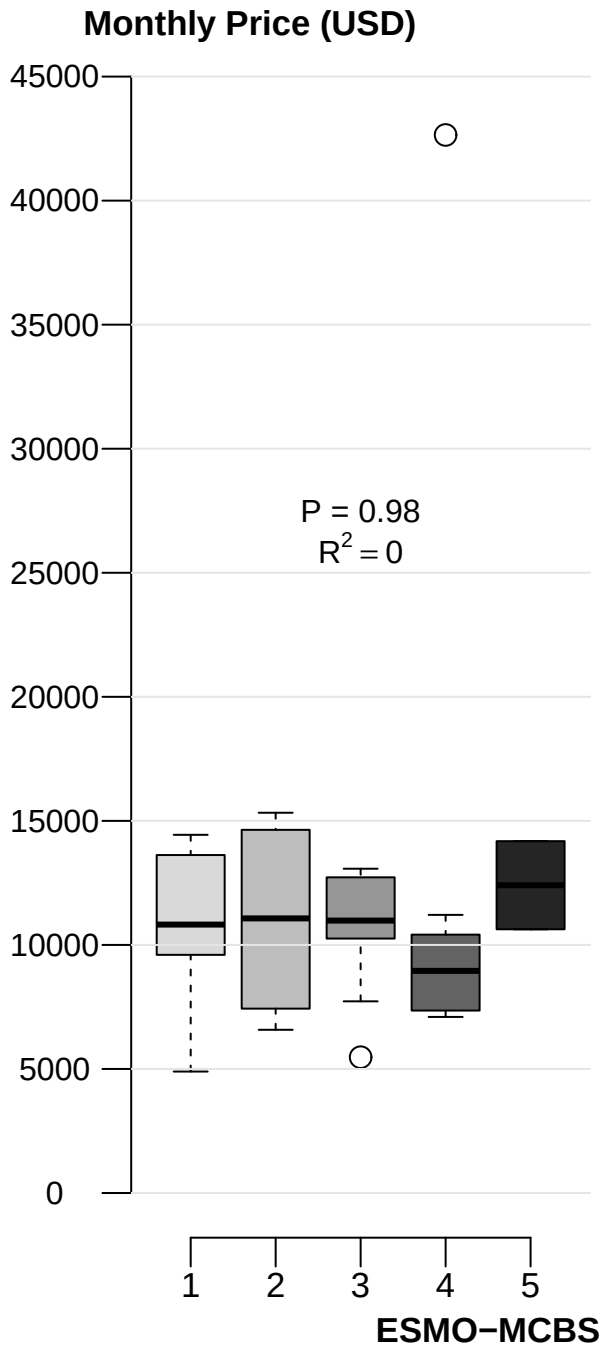

ASCO−VF NHB
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
ESMO−MCBS
ASCO−VF NHB
Overall
0
2
4
6
8
10
12
Number of drugs
Meaningful Clinical Benefit

Figure 2


Monthly Price (USD)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
P = 0.93
R2 = 0
0 10 20 30 40 50 60 70
ASCO−VF NHB


Monthly Price (USD)
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40000
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15000
10000
5000
0
P = 0.98
R2 = 0
1 2 3 4 5
ESMO−MCBS

Table S1. Characteristics of new cancer drugs for treating solid tumors that were approved by the US Food and Drug Administration (FDA) from 2000 to 2015. Drug value was assessed by the American Society of Clinical Oncology Value Framework (ASCO-VF) and European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS).

	Drug value not assessable (*N*= 11)	Drug value assessable[a] (*N* = 37)
Indication		
Breast cancer	1 (9)	6 (16)
Colorectal cancer	0 (0)	6 (16)
Melanoma	1 (9)	5 (14)
Renal cancer	0 (0)	5 (14)
Others	9 (82)	15 (40)
Approval year range		
2000–2004	2 (18)	4 (11)
2005–2009	1 (9)	10 (27)
2010–2015	8 (73)	23 (62)
Trial phase[b]		
2	7 (70)	3 (8)

3	3 (30)	34 (92)
Orphan designation	6 (55)	16 (43)
Priority review	7 (64)	29 (78)
Fast-track designation	9 (82)	18 (49)
Breakthrough designation	2 (18)	19 (51)
Accelerated approval	6 (55)	5 (14)
First-in-class	5 (45)	13 (35)
Pharmacogenomics biomarker[c]	7 (64)	16 (43)
Setting		
First-line	4 (36)	14 (38)
Second-line	7 (64)	21 (57)
Third-line	0 (0)	2 (5)

Data are *N* (%).

a. Drug value assessable refers to drugs with both an ASCO-VF and ESMO-MCBS score.

b. Data was missing for one approval.

c. Drugs included in the FDA Table of Pharmacogenomics as of May 9, 2016

Table S2. Assessment of the value of anticancer drugs that were approved by the FDA from 2000 to 2015, by ASCO-VF (2016 update) and ESMO-MCBS scores and endpoints used (*N* = 37).

ASCO-VF	
Endpoint used, *N* (%)	
OS	21 (57)
PFS	16 (43)
Net Health Benefit, median [Q1–Q3]	37 [20–52]
Clinical benefit score, median [Q1–Q3]	34 [23–42]
Points for tail of the curve, *N* (%)	
No point	19 (51)
PFS (16 points)	14 (38)
OS (20 points)	4 (11)
Toxicity score, median [Q1–Q3]	-5 [-13– -2]
Bonus scores, *N* (%)	
Palliation (10 points)	2 (5)
QoL (10 points)	4 (11)

Treatment-free interval (10 points)	0 (0)
ESMO-MCBS	
Endpoint used, *N* (%)	
ORR	1 (3)
OS	19 (51)
PFS	17 (46)
Final grade, *N* (%)	
1	5 (14)
2	9 (24)
3	10 (27)
4	11 (30)
5	2 (5)
Toxicity assessment, *N* (%)	
Downgrade score from 1 point	2 (5)
No change	34 (92)
Upgrade score from 1 point	1 (3)

QoL assessment, *N* (%)	
Downgrade score from 1 point	4 (11)
No change	27 (73)
Upgrade score from 1 point	6 (16)

OS, overall survival; PFS, progression-free survival; ORR, overall response rate; QoL, quality of life

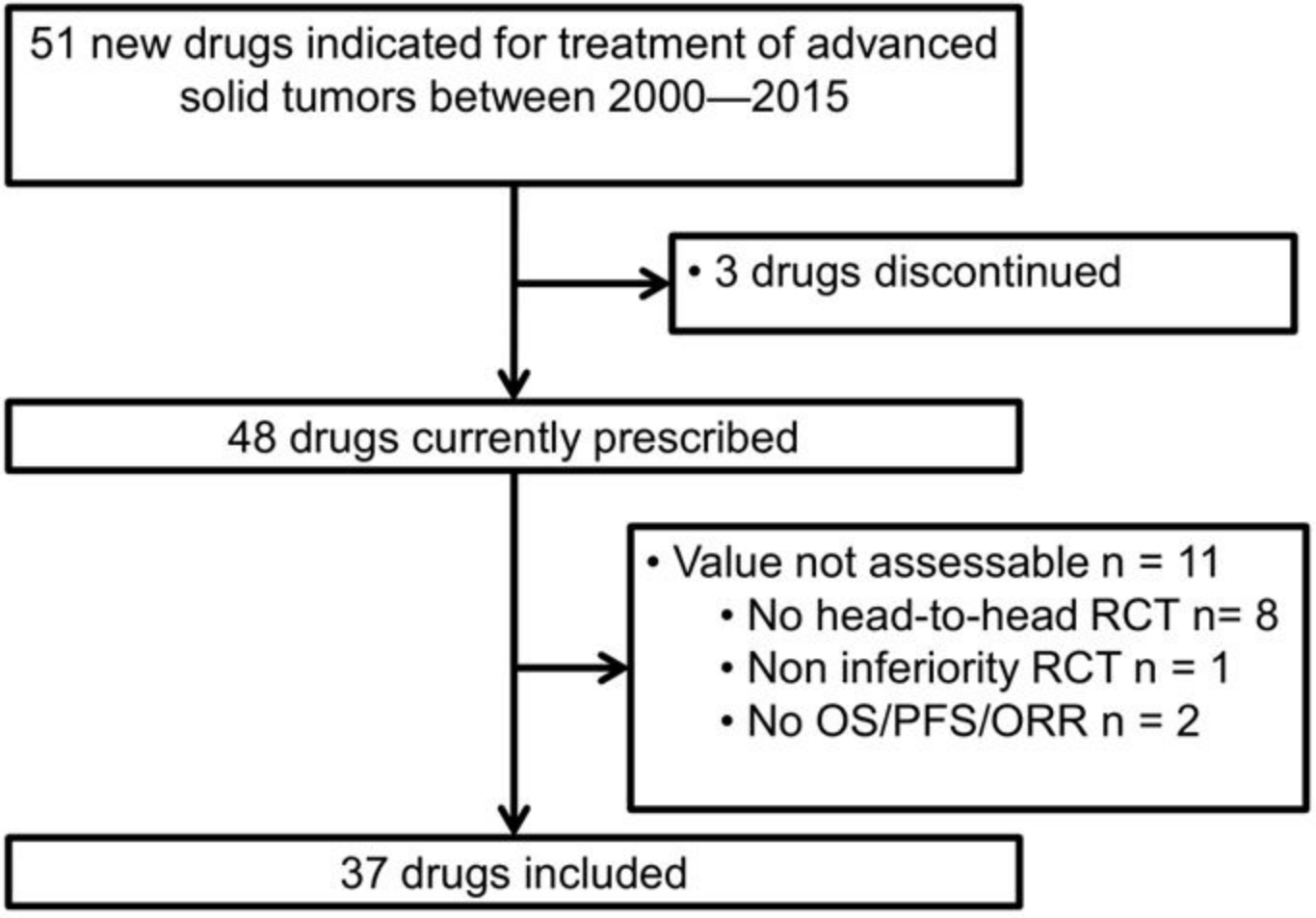


Figure S1. Flowchart of included drugs.

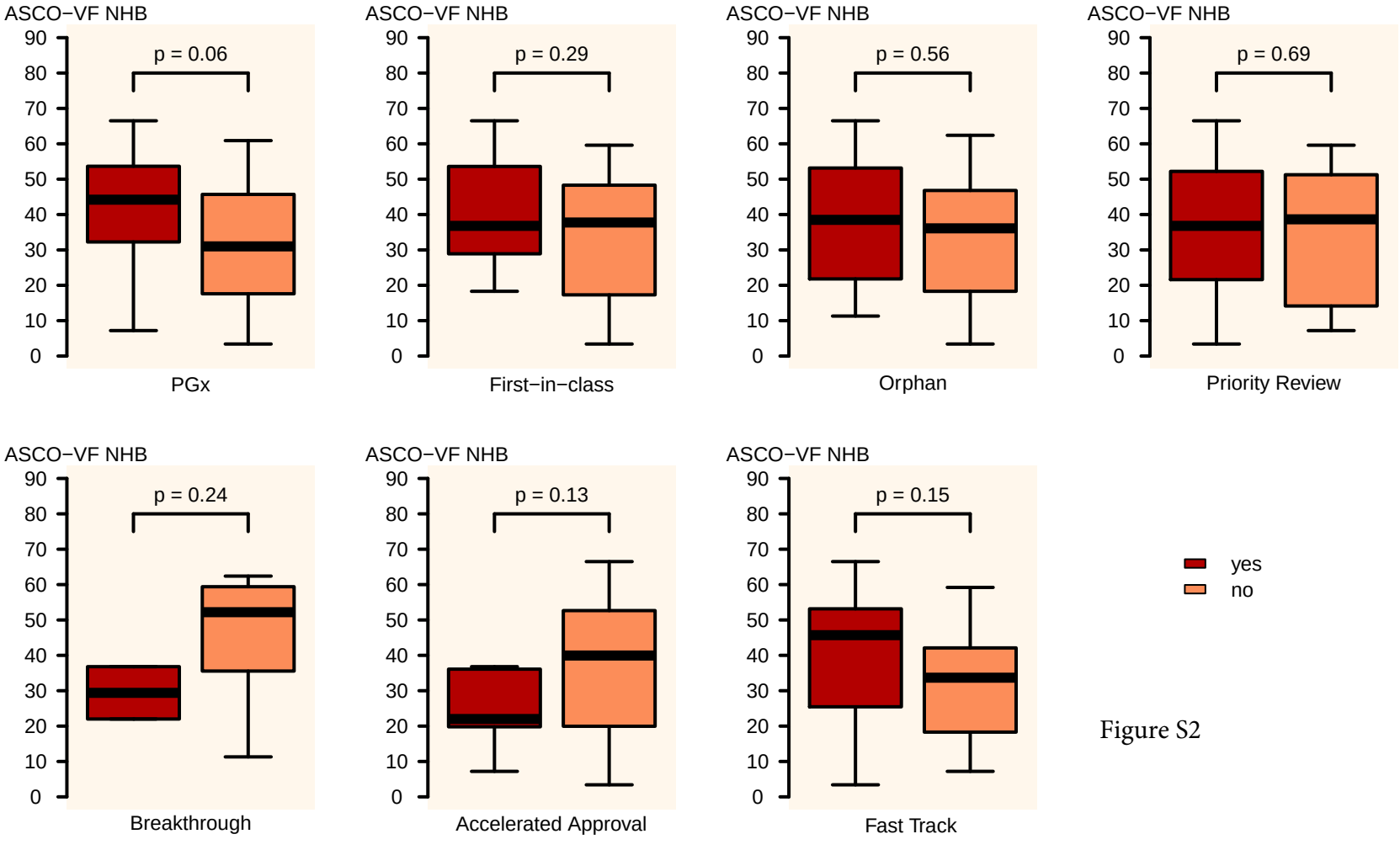
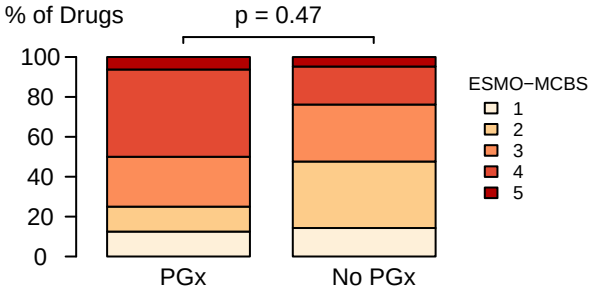
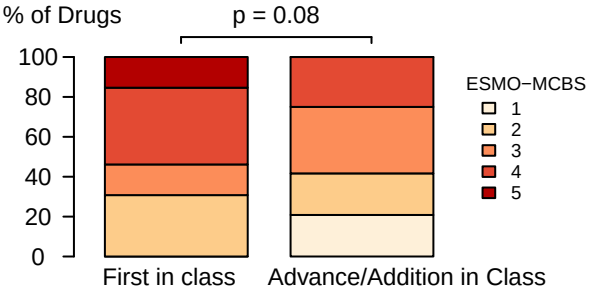
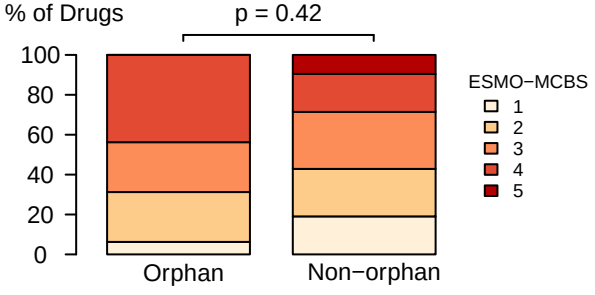
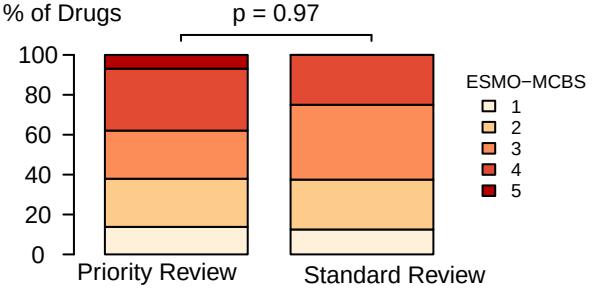

ASCO−VF NHB
p = 0.06
PGx
ASCO−VF NHB
p = 0.29
First−in−class
ASCO−VF NHB
p = 0.56
Orphan
ASCO−VF NHB
p = 0.69
Priority Review
ASCO−VF NHB
p = 0.24
Breakthrough
ASCO−VF NHB
p = 0.13
Accelerated Approval
ASCO−VF NHB
p = 0.15
Fast Track
yes
no

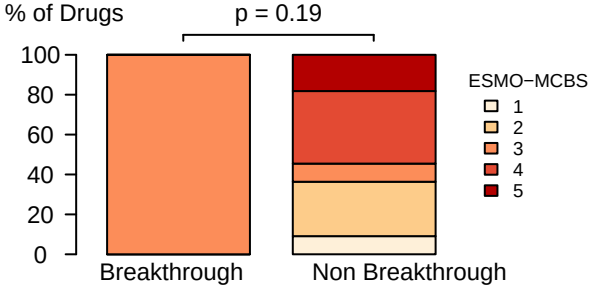
Figure S2

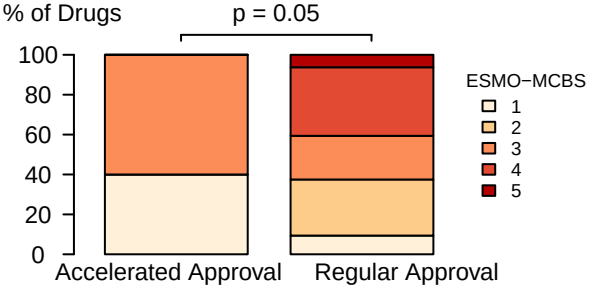

% of Drugs
p = 0.47
100
80
60
40
20
0
PGx
No PGx
ESMO−MCBS
1
2
3
4
5


% of Drugs
p = 0.08
100
80
60
40
20
0
First in class
Advance/Addition in Class
ESMO−MCBS
1
2
3
4
5


% of Drugs
p = 0.42
100
80
60
40
20
0
Orphan
Non−orphan
ESMO−MCBS
1
2
3
4
5


% of Drugs
p = 0.97
100
80
60
40
20
0
Priority Review
Standard Review
ESMO−MCBS
1
2
3
4
5


% of Drugs
p = 0.19
100
80
60
40
20
0
Breakthrough
Non Breakthrough
ESMO−MCBS
1
2
3
4
5


% of Drugs
p = 0.05
100
80
60
40
20
0
Accelerated Approval
Regular Approval
ESMO−MCBS
1
2
3
4
5

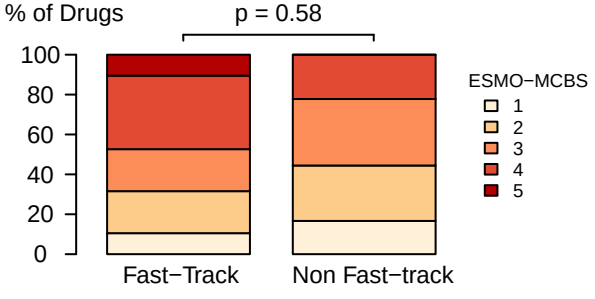

% of Drugs
p = 0.58
100
80
60
40
20
0
Fast−Track
Non Fast−track
ESMO−MCBS
1
2
3
4
5

Figure S3