Out-of-Pocket Spending Not Associated with Oral Oncolytic Survival Benefit

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ABSTRACT

BACKGROUND: With total and out-of-pocket spending for oral oncolytics rising, there is increased interest in choosing oncology treatments based on their clinical value relative to cost.

OBJECTIVE: To determine if out-of-pocket spending varied for higher versus lower benefit oral oncology drugs reimbursed by commercial insurers.

METHODS: This study was a retrospective analysis of commercial insurer prescription drug claims filed between 2007 and 2014 for 13 oral oncolytics approved before 2009. We calculated mean monthly out-of-pocket payment for each fill by patient. We then categorized oral oncolytics by their overall and progression-free survival benefits for each FDA-approved indication, using evidence from published studies. We assessed the relationship of survival benefit with mean monthly out-of-pocket payment, adjusting for demographic and plan characteristics.

RESULTS: Our population included 44,113 patients aged 18-65 years (mean 52.5 [SD 9.4]) with a cancer diagnosis who filled 731,354 prescriptions. The most commonly represented oncolytics were imatinib (37.4% of fills), lenalidomide (17.7% of fills), and dasatinib (10.0% of fills). Approximately 32.3% of fills were for drug-indication pairs with an overall survival benefit of 4+ years. In adjusted analyses, there was no clear pattern to suggest that out-of-pocket payments differed with drug indication-specific survival benefits. Drugs for indications providing >0 to 1 year of overall survival benefit were significantly more likely to have a lower out-of-pocket payment versus those prescribed off-label, but there were no significant differences in out-of-pocket payments between drugs and associated indications in any other survival category versus drugs used off-label.

CONCLUSIONS: Out-of-pocket payments for oral oncolytics were not clearly related to indication-specific value in commercially insured patients. This finding suggests that despite increased attention to value- and indication-based drug pricing, cost sharing for oral oncolytics does not currently reflect these goals.

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What this study adds

- Out-of-pocket payments for oral oncolytics from 2007-2014 were not clearly related to indication-specific value.
- Despite increasing interest in value-based pricing, out-of-pocket payment design is not congruent with the goal of aligning costs with health outcomes.

Cancer drug costs continue to rise in the United States,¹ and spending on targeted oral oncolytics has increased particularly rapidly, with mean monthly expenditures in the year of product launch increasing from \$1,869 in 2000 to \$11,325 in 2014.² Rising drug prices and expanded use of cost sharing have translated to higher out-of-pocket spending for targeted oral oncolytics.^{2,3} For example, 1 study found that average out-of-pocket monthly expenditures rose from \$88 in 2001 to \$198 in 2011.⁴

Concurrently, there is increasing interest in choosing treatments based on their value—or health outcomes relative to their cost⁵—with definitions of outcomes in oncology integrating clinical benefits, toxicities, and patient preferences.^{6,7} Evidence of the relationship between drug prices and outcomes in oncology is mixed but largely suggests that overall price is not correlated with benefit.⁸⁻¹⁰ With regards to prices that patients see, there is a lack of evidence that insurers have employed cost sharing to preferentially encourage use of higher- versus lower-efficacy oncology drugs. Institution of lower cost-sharing levels for interventions with greater evidence of efficacy is known as value-based insurance design and has previously been shown to increase adherence to medications and improve clinical outcomes.¹¹ Given the known inverse relationship between out-of-pocket spending and adherence to or continuation of oncology drugs,^{12,13} use of value-based cost sharing could potentially drive patient adherence to high-efficacy oral oncolytics and thus enhance outcomes.

Within this context, we sought to describe out-of-pocket spending by patients with commercial insurance who had a diagnosis of cancer during 2007-2014 and were treated with oral cancer drugs approved before 2009. We specifically assessed if patients using drugs with higher versus lower benefit had lower out-of-pocket spending, with benefit defined in terms of overall or progression-free survival as per the American Society of Clinical Oncology's (ASCO) 2016 Value Framework.⁶

What is already known about this subject

- Spending on cancer drugs, particularly oral oncolytics, continues to rise in the United States, with 1 study showing an average monthly out-of-pocket spending increase from \$88 in 2001 to \$198 in 2011.
- There is interest in choosing treatments based on their value, and institution of lower-cost sharing levels for interventions with greater efficacy has been shown to increase adherence and improve clinical outcomes.

Methods

Data and Patients

We used the MarketScan Commercial Claims and Encounters Database for 2007-2014 to examine drug use and expenditures among cancer patients who had filled any orally administered, targeted nonhormonal anticancer medications approved before 2009.^{4,14} We restricted our analysis to the 13 drugs approved before 2009 to ensure availability of 5 years of data for analysis, thus, allowing for adjustment for changes in spending over time. The MarketScan database represents >50 million employees and their dependents enrolled in commercial health insurance plans sponsored by approximately 100 large and medium-sized U.S.-based employers. About 56% of the non-elderly U.S. population was covered by employer-sponsored coverage in 2014, making the MarketScan database largely representative of our population of interest.¹⁵ We identified 731,354 prescription drug claims filled by 44,113 patients with a cancer diagnosis in the year of the fill. We excluded 5,063 claims with patient or plan payment <\$0 or days supplied <0.

Measures

Out-of-Pocket Expenditures. We summed monthly copayments, coinsurance, and deductibles for each fill. We adjusted fills for >1-month supply to a single month supply to generate mean monthly total out-of-pocket payments. We did not consider employee contributions to commercial health insurance coverage via monthly paycheck deductions because we sought to estimate the cost to patients of an oral oncolytic at the time of prescription fill. Patient cost sharing at the point of service is a formulary tool that may influence a patient's use of a prescription drug.¹⁶

Clinical Benefit of Oral Oncolytics. We categorized drugs by overall survival benefit (defined as time from randomization in a trial to death) and progression-free survival benefit (defined as time from randomization in a trial to disease progression or death; used if overall survival data were lacking) for each indication approved by the U.S. Food and Drug Administration (FDA) for the particular oncolytic (as described in the product label for that oncolytic). We examined evidence from randomized controlled clinical trials that compared the drug against standard of care or placebo for each particular FDA-approved indication. We reported overall or progression-free survival benefit as a relative survival benefit (i.e., overall survival or progression-free survival with drug minus overall or progression-free survival with standard of care or placebo, depending on what was reported in the included trial). If multiple similar trials were available for a drug and indication, we selected the trial presenting the largest estimate of survival differences between patients receiving treatment versus control. If median overall survival or progression-free survival were not reached in published trials (most commonly due to high overall

survival), we used estimates from cost-effectiveness analyses and, where appropriate, focused on the survival measure for which a significant effect had been shown in randomized controlled trials.

Drugs and associated indications were partitioned into the following 8 categories of increasing evidence for benefit, based on the relative distribution of survival estimates for all fills: (1) off-label use (i.e., prescribed to a patient with a diagnosis that was not an FDA-approved indication for that drug); (2) no survival benefit for an on-label indication; (3) >0-5 months progression-free survival benefit; (4) >5-10 months progression-free survival benefit; (5) 10+ months progression-free survival benefit; (6) >0-12 months overall survival benefit; (7) >12-48 months overall survival benefit; and (8) 48+ months overall survival benefit. If a drug was associated with statistically significant overall survival and progression-free survival benefits, it was only put into an overall survival category, given the clinical superiority of overall survival benefits over progression-free survival benefits. The distribution of each drug and its associated assignment into these categories, as well as the study from which information about benefit was derived, is described in Table 1. Each of these categories was assigned a sequential numeric code, which was applied individually to each fill for each patient based on the drug and associated cancer diagnosis for that fill.

As an example of this process, pazopanib is approved for use in soft tissue sarcoma. In a 2012 study by van der Graaf et al.,¹⁷ use of the drug was associated with a progression-free survival benefit of 4.6 months, while use of placebo was associated with a progression-free survival benefit of 1.6 months. We thus calculated the relative progression-free survival benefit as 3 months. This placed pazopanib for an indication of soft-tissue sarcoma in category number 3 for >0-5 months of progression-free survival benefit.

In the case of imatinib, since median overall and progression-free survival was not reached even in trials with longer-term follow-up,¹⁸ we used estimates of these metrics from economic modeling studies based on randomized controlled trial data.¹⁹ Given that randomized controlled trials had demonstrated an overall survival benefit of imatinib versus interferon alpha, we defined the relative survival benefit of imatinib as the difference between the 19.1 remaining life-years associated with first-line imatinib versus the 9.1 life-years associated with first-line interferon alpha.¹⁹

Covariates. For each patient in each year, we documented age, health plan type, and census region, as reported in the MarketScan database. We also calculated previous year comorbidity based on the Klabunde modification of the Charlson comorbidity score, using diagnoses reported in MarketScan for each patient.²⁰ We also measured total monthly drug reimbursement (out-of-pocket and plan payments for each fill

TABLE 1 Indications, Survival Benefit Categories, and Survival Comparisons for Targeted Oral Oncolytics Approved, 1995-2009

Drug	Year	Indication	Survival Benefit Category	Source	Survival Comparisons
Imatinib	2001	Philadelphia chromosome positive CML	OS 4+ years	Reed et al., 2008 ¹⁹	229.2 months (treatment) vs. 109.2 months (control) OS benefit
	2002	Gastrointestinal stromal tumors	PFS 10+ months	Howell et al., 2008 ³²	45.3 months (treatment) vs. 5.6 months (control) PFS benefit
	2006	Philadelphia chromosome positive ALL	OS > 1-4 years	Botteman et al., 2006 ³³	51.72 months (treatment) vs. 13.2 months (control) OS benefit
	2006	Myelodysplastic/myeloproliferative diseases	No OS/PFS benefit in RCT. Approval based on white blood cell/genetic responses in single drug study.		N/A
	2006	Chronic eosinophilic leukemia	No OS/PFS benefit in RCT. Approval based on white blood cell response in single drug study.		N/A
	2006	Dermatofibrosarcoma protuberans	No PFS/OS benefit in RCT. Approval based on decrease in tumor size in single-drug study.		N/A
Gefitinib	2003	EGFR positive non-small cell lung cancer	PFS > 5-10 months	Maemondo et al., 2010 ³⁴	10.8 months (treatment) vs. 5.4 months (control) PFS benefit
Erlotinib	2004, 2013	Non-small cell lung cancer	PFS > 5-10 months	Zhou et al., 2015 ³⁵	13.1 months (treatment) vs. 4.6 months (control) PFS benefit
	2005	Pancreatic cancer	OS > 0-1 year	Moore et al., 2007 ³⁶	6.4 months (treatment) vs. 6 months (control) OS benefit
Sorafenib	2005	Renal cell carcinoma	PFS > 0-5 months	Escudier et al., 2007 ³⁷	5.5 months (treatment) vs. 2.8 months (control) PFS benefit
	2007	Liver carcinoma	OS > 0-1 year	Llovet et al., 2008 ³⁸	10.7 months (treatment) vs. 7.9 months (control) OS benefit
	2013	Thyroid cancer refractory to radioactive iodine	PFS > 0-5 months	Brose et al., 2014 ³⁹	10.8 months (treatment) vs. 5.8 months (control) PFS benefit
Lenalidomide	2006	Multiple myeloma	OS > 0-1 year	Dimopolous et al., 2009 ⁴⁰	38 months (treatment) vs. 31.6 months (control) OS benefit
	2013	Mantle cell lymphoma	PFS > 0-5 months	Trněný et al., 2016 ⁴¹	8.7 months (treatment) vs. 5.2 months (control) PFS benefit
Dasatinib	2006	Philadelphia chromosome positive CML	OS > 1-4 years	Hoyle et al., 2011 ⁴²	78 months (treatment) vs. 32.2 months (control) OS benefit
	2006	Philadelphia chromosome positive ALL	No PFS/OS benefit in comparator-controlled trial. Approval based on white blood cell response in single drug study.		N/A
Sunitinib	2006	Advanced renal cell carcinoma	OS > 0-1 year	Motzer et al., 2009 ⁴³	26.4 months (treatment) vs. 21.3 months (control) OS benefit
	2006	Gastrointestinal stromal tumors	PFS > 0-5 months	Demetri et al., 2006 ⁴⁴	5.5 months (treatment) vs. 1.4 months (control) PFS benefit
	2011	Pancreatic neuroendocrine tumors	PFS > 5-10 months	Favire et al., 2017 ⁴⁵	12.6 months (treatment) vs. 5.8 months (control) PFS benefit
Thalidomide	2006	Multiple myeloma	PFS 10+ months	Rajkumar et al., 2006 ⁴⁶	22.4 months (treatment) vs. 6.5 months (control) PFS benefit
Vorinostat	2007	Cutaneous T-cell lymphoma	No PFS/OS benefit in RCT. Approval based on decrease in tumor size in single-drug studies.		N/A
Lapatinib	2007	Breast cancer	PFS > 5-10 months	Johnston et al., 2009 ⁴⁷	8.2 months (treatment) vs. 3 months (control) PFS benefit
Nilotinib	2007	Philadelphia chromosome positive CML	OS 4+ years	Hoyle et al., 2011 ⁴²	81.3 months (treatment) vs. 24.4 months (control) OS benefit

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TABLE 1 Indications, Survival Benefit Categories, and Survival Comparisons for Targeted Oral Oncolytics Approved, 1995-2009 (continued)

Drug	Year	Indication	Survival Benefit Category	Source	Survival Comparisons
Pazopanib	2009	Advanced renal cell carcinoma	PFS > 0-5 months	Sternberg et al., 2013 ⁴⁸	9.2 months (treatment) vs. 4.2 months (control) PFS benefit
	2012	Soft tissue sarcoma	PFS > 0-5 months	van der Graaf et al., 2012 ¹⁷	4.6 months (treatment) vs. 1.6 months (control) PFS benefit
Everolimus	2009	Renal cell carcinoma	PFS > 0-5 months	Motzer et al., 2010 ⁴⁹	4.9 months (treatment) vs. 1.9 months (control) PFS benefit
	2011	Neuro-endocrine tumors of pancreatic origin	PFS > 5-10 months	Yao et al., 2011 ⁵⁰	11 months (treatment) vs. 4.6 months (control) PFS benefit
	2011	Neuro-endocrine tumors of GI or lung origin	PFS > 5-10 months	Yao et al., 2016 ⁵¹	11 months (treatment) vs. 3.9 months (control) PFS benefit
	2012	Breast cancer	PFS > 0-5 months	Piccart et al., 2014 ⁵²	7.8 months (treatment) vs. 3.2 months (control) PFS benefit
	2012	Renal angiomyolipoma	No PFS/OS benefit in RCT. Approval based on decrease in tumor size in RCT.		N/A
	2012	Subependymal giant cell astrocytoma	No PFS/OS benefit in RCT. Approval based on decrease in tumor size in RCT.		N/A

^aNo significant OS benefit shown in RCTs.

^bSignificant OS benefit shown versus historical controls in trials not reporting median OS.

^cP = 0.051, considered significant.

ALL = acute lymphocytic leukemia; CML = chronic myelogenous leukemia; EGFR = epidermal growth factor receptor; N/A = not available; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial.

adjusted to a per-month value) to account for differences in drug prices. Variables are categorized in Table 2.

Analysis

After describing out-of-pocket expenditures by drug benefit and patient characteristics, we estimated a 2-part model,²¹ predicting changes in out-of-pocket payments by drug survival benefit and adjusting for the previously described covariates. The first part of the model consisted of a logit function that assessed the association of drug survival benefit with having any out-of-pocket spending (vs. none). The second part used a generalized linear model with a gamma distribution and a log-link function to assess the association of drug survival benefit with level of non-zero out-of-pocket spending. Estimates from these 2 models were combined using a margins function.²¹

In sensitivity analyses, we conducted stratified analyses, first, considering overall survival as a continuous variable among patients treated with drugs with evidence for an overall survival benefit and, second, considering progression-free survival as a continuous variable among patients treated with drugs, with evidence for only progression-free survival benefit. Finally, in a sensitivity analysis, we conducted a version of the original 2-part model excluding the top 5% of monthly out-of-pocket spending claims. All dollars were inflation adjusted to 2014 U.S. dollars based on the medical component of the Consumer Price Index.

Because pricing decisions are often made at launch when only 1 indication for a drug is known, it is possible that cost sharing may be more closely related to the first indication's benefit rather than that of subsequent indications.⁹ Accordingly, in a secondary analysis, we reassigned the survival benefit for each drug and all its associated indications based on the benefits associated with the drug's first approved indication. Finally, we repeated analyses within subgroups of drugs or indications, including among tyrosine kinase inhibitors only, among drugs for treating renal cell carcinoma, and for a single drug (i.e., lenalidomide) when considering all of its indications.

Two-sided *P* values < 0.05 were considered statistically significant. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC). This study was deemed not human subjects research by the Harvard University Institutional Review Board.

Results

The 44,113 patients who filled 731,354 prescriptions for oral anticancer drugs between 2007 and 2014 had a mean age of 52.5 (standard deviation [SD] 9.4) years, and approximately half of the patients were male (Table 2). The most commonly represented oncolytics were imatinib (37.4% of fills), lenalidomide (17.7% of fills), and dasatinib (10.0% of fills). Overall, 18.3% of prescription fills were for drugs used off-label, and 1.2% were for drugs and associated indications with no survival benefit. Approximately 6.3% of fills were for drugs

TABLE 2 Demographic Characteristics of Patient-Fills in Sample

Characteristic	Percentage
Age, years	
18-35	6.7
36-45	12.8
45-55	33.5
56-65	47.0
Gender	
Male	52.3
Female	47.7
Region	
Northeast	17.0
Midwest	24.7
South	38.6
West	18.5
Unknown	1.3
Charlson comorbidity score	
0	79.7
1	12.6
2	5.0
3+	2.7
Health plan type	
Consumer-driven/high deductible	7.0
Comprehensive	4.1
Exclusive provider organization/health maintenance organization	16.0
Point of service/point of service with capitation	7.4
Preferred provider organization	61.1
Unknown health plan	4.4

and associated indications with >0-5 months of progression-free survival benefit; 9.7% for drugs and associated indications with >5-10 months of progression-free survival benefit; and 5.4% for those drugs and associated indications with 10+ months of progression-free survival benefit. Finally, 16.8% of fills were for drugs and associated indications with >0-1 year of overall survival benefit; 10.1% for those with >1-4 years of overall survival benefit; and 32.3% for those with more than 4 years of overall survival benefit. Monthly per-fill out-of-pocket payments ranged from \$0 to \$14,167.30, with a mean of \$82.82 (SD \$353.45). The mean monthly total (plan plus patient) was \$5,884 (SD \$2,901.46). Table 3 depicts numbers of patient-fills and mean out-of-pocket payment by drug and indication.

In adjusted analyses, there was no clear pattern to suggest that out-of-pocket payments differed with drug indication-specific survival benefits (Table 4). While drugs for indications providing >0-1 year of overall survival benefit were significantly more likely to have a lower copayment versus those prescribed off-label, there were no significant differences in out-of-pocket payments between drugs and associated indications in any other survival category versus drugs used off-label. Having a more recent year of fill was associated

with lower out-of-pocket spending ($P < 0.001$). In addition, fills for drugs with higher total costs (plan plus patient payment) were associated with higher out-of-pocket spending ($P < 0.001$; Table 4). Notably, the correlation coefficient for total drug cost and survival benefit was 0.06, suggesting that total drug prices were not associated with benefit).

Results of sensitivity analyses including only (a) patients filling drugs with evidence of an overall survival benefit or (b) patients filling drugs with a progression-free survival benefit and examining overall or progression-free survival as continuous variables similarly revealed no significant relationship between out-of-pocket payment and survival benefit (change in mean monthly out-of-pocket spending for each additional month of progression-free survival = 0.11, 95% confidence interval [CI] -0.42-0.63, $P = 0.69$; change for each additional month of overall survival = 0.01, 95% CI = -0.04-0.05, $P = 0.77$).

Results of sensitivity analyses excluding payments in the top 5% yielded results similar to those in our primary model (not shown). Our findings also held within subgroups of drugs or indications such as among only tyrosine kinase inhibitors, only drugs for renal cell carcinoma, and only for lenalidomide when considering all of its indications (data not shown; available from authors).

Finally, analyses examining survival benefit based on the benefit reported for the drug's first approved indication also showed no association of out-of-pocket payments with benefit (Table 5).

Discussion

Despite consistently rising out-of-pocket spending for oral oncolytics and increasing interest in value-based pricing,^{4,6,7} we found that out-of-pocket payments for oral oncolytics from 2007-2014 were not clearly related to indication-specific survival benefit in a commercial population. Although drugs with >0-1 year of overall survival benefit were associated with significantly lower out-of-pocket spending, there was no difference in out-of-pocket payments for drugs in any other survival category versus drugs used off-label. In addition, while previous analyses have examined drug pricing in relation to first indication survival benefit,⁹ our analysis did not show any relationship between the survival benefit of the first approved indication and out-of-pocket payment.

Cancer therapy is associated with significant financial toxicity, including bankruptcy,²² and there is evidence that beneficiaries with higher-out-of-pocket costs are more likely to discontinue cancer therapy.^{12,13} Notably, substantial financial toxicity of cancer therapy has been associated with worse outcomes, including early mortality.²³ Value-based insurance designs have been shown to improve adherence in nononcology clinical areas,²⁴⁻²⁶ and ideally, cost sharing could be aligned to encourage greater use of and adherence to high-value cancer treatments. However, we saw no association between

TABLE 3 Patient-Fills and Out-of-Pocket Payment Statistics by Drug and Indication for Targeted Oral Oncolytics Approved, 1995-2009

Drug	Year	Indication	Number of Patient-Fills	Mean OOP Payment in \$ (SD)
Imatinib	2001	Philadelphia chromosome positive CML	196,801	70.9 (281.92)
	2002	Gastrointestinal stromal tumors	26,030	85.24 (372.36)
	2006	Philadelphia chromosome positive ALL	15,693	52.40 (199.88)
	2006	Myelodysplastic/myeloproliferative diseases	N/A	N/A
	2006	Chronic eosinophilic leukemia	197	39.85 (40.42)
	2006	Dermatofibrosarcoma protuberans	N/A	N/A
Gefitinib	2003	EGFR positive non-small cell lung cancer	692	36.23 (72.23)
Erlotinib	2004, 2013	Non-small cell lung cancer	38,805	82.67 (316.30)
	2005	Pancreatic cancer	7,113	75.26 (304.46)
Sorafenib	2005	Renal cell carcinoma	5,427	98.70 (327.40)
	2007	Liver carcinoma	8,161	95.00 (366.92)
	2013	Thyroid cancer refractory to radioactive iodine	1,593	72.70 (237.90)
Lenalidomide	2006	Multiple myeloma	86,472	102.32 (449.10)
	2013	Mantle cell lymphoma	7,933	148.43 (748.56)
Dasatinib	2006	Philadelphia chromosome positive CML	57,907	86.53 (369.52)
	2006	Philadelphia chromosome positive ALL	7,494	71.95 (366.88)
Sunitinib	2006	Advanced renal cell carcinoma	21,086	88.15 (378.53)
	2006	Gastrointestinal stromal tumors	4,084	69.31 (311.94)
	2011	Pancreatic neuroendocrine tumors	4,010	103.83 (399.96)
Thalidomide	2006	Multiple myeloma	13,107	82.34 (347.54)
Vorinostat	2007	Cutaneous T-cell lymphoma	923	77.23 (294.50)
Lapatinib	2007	Breast cancer	21,023	68.19 (231.41)
Nilotinib	2007	Philadelphia chromosome positive CML	39,612	104.73 (432.55)
Pazopanib	2009	Advanced renal cell carcinoma	8,613	89.87 (398.24)
	2012	Soft tissue sarcoma	2,728	100.73 (382.97)
Everolimus	2009	Renal cell carcinoma	5,773	92.89 (403.11)
	2011	Neuro-endocrine tumors of pancreatic origin	2,799	76.55 (310.37)
	2011	Neuro-endocrine tumors of GI or lung origin	3,529	69.90 (271.83)
	2012	Breast cancer	9,614	96.83 (387.76)
	2012	Renal angiomyolipoma	90	39.31 (145.59)
	2012	Subependymal giant cell astrocytoma	17	12.47 (20.44)

ALL=acute lymphocytic leukemia; CML=chronic myelogenous leukemia; EGFR=epidermal growth factor receptor; N/A=not available; OOP=out of pocket; SD=standard deviation.

out-of-pocket payments and drug survival benefit. This finding suggests that despite some payers and pharmacy benefit managers announcing or considering value-based drug pricing,^{7,27} the complex U.S. drug reimbursement and distribution system still does not lend itself to cost sharing that reflects value.^{7,28}

Previous work has demonstrated that out-of-pocket spending increased substantially between 2001 and 2011 for oral oncolytics and that Medicare enrollees are more likely to discontinue more expensive cancer drugs.^{4,12} In addition, several payers have publicly cited interest in value-based pricing for oncology drugs.^{27,29} However, the fact that a relationship does not exist between value as defined by survival and out-of-pocket costs has not been previously demonstrated in the oncology realm. Possibly reflecting the increasing prevalence of oral chemotherapy parity laws,^{30,31} we observed lower out-of-pocket payments

for fills in more recent calendar years. As expected, we observed higher out-of-pocket payments for more expensive drugs.

Limitations

Our study has limitations that need to be considered. Given the composition of the MarketScan database, we studied only commercial health insurance claims for individuals with employer-sponsored insurance; out-of-pocket payments and their relation to drug benefit may differ for other payers, including individuals enrolled in Medicare Part D. Although the MarketScan database provides some information about employee health plan types, it does not provide more granular data regarding copay, coinsurance, or drug coverage arrangements for individual plans, which limited our ability to adjust for more granular differences in coverage. The database also

TABLE 4 Factors Associated with Out-of-Pocket Spending for Oral Oncolytics: Survival Categorized by Drug and Indication

	Change in Mean Monthly Out-of-Pocket Spending, \$	P Value
Survival benefit, mean (95% CI)		
Off-label	Reference	
No benefit	33.99 (-68.02, 136.00)	0.510
>0-5 months PFS	-2.17 (-11.37, 7.03)	0.640
>5-10 months PFS	29.42 (-30.43, 89.28)	0.340
10+ months PFS	19.14 (-19.99, 58.27)	0.340
>0-1 year OS	-21.04 (-34.8, -7.27)	0.003
>1-4 years OS	21.89 (-44.2, 87.96)	0.520
4+ years OS	26.16 (-43.46, 95.78)	0.460
Year	-3.89 (-5.46, -2.32)	<0.001
Total (plan + patient) payment	5.28 (4.37, 6.21)	<0.001

Note: Analysis adjusts for variables in the table, as well as for age, sex, region, comorbidity, and health plan type. Full model results are included in Appendix A (available in online article).

CI = confidence interval; OS = overall survival; PFS = progression-free survival.

TABLE 5 Factors Associated with Out-of-Pocket Spending for Oral Oncolytics: Survival Categorized by Drug's First Approved Indication

	Change in Mean Monthly Out-of-Pocket Spending, \$	P Value
Survival benefit, mean (95% CI)		
Off-label	Reference	
No benefit	300.63 (-6484.95, 7086.20)	0.930
>0-5 months PFS	159.01 (-3575.37, 3893.39)	0.930
>5-10 months PFS	1094.58 (-24981.46, 27170.62)	0.930
10+ months PFS	-56.44 (-608.30, 495.42)	0.840
>0-1 year OS	-56.47 (-608.20, 495.27)	0.840
>1-4 years OS	469.23 (-10186.67, 11125.13)	0.930
4+ years OS	429.99 (-9226.77, 10086.76)	0.930
Year	-3.85 (-5.68, 2.03)	<0.001
Total (plan + patient) payment	4.89 (2.93, 6.85)	<0.001

Note: Analysis controls for variables in the table, as well as for age, sex, region, comorbidity, and health plan type. Full model results are included in Appendix B (available in online article).

CI = confidence interval; OS = overall survival; PFS = progression-free survival.

does not provide information regarding employee contributions to health insurance coverage, such as paycheck deductions. We were also limited to evaluating filled prescriptions, which by nature of patient-pharmacy interactions and the composition of the MarketScan database means those for which claims were paid in full. It is possible that patients prescribed lower value treatments were less likely to fill them if faced with high out-of-pocket costs. Prescriptions not filled were excluded from our analysis, thus, potentially excluding a segment of our population of interest facing significant costs.

Our analysis included only oral oncolytics approved through 2009, so findings could differ for more recently approved drugs, particularly given the recent focus on the value of care delivered in the context of health care reform. In addition, we described value in terms of survival benefit. This metric has been designated as a cornerstone of defining value in ASCO's 2016 Value Framework.⁶ However, there are certainly other aspects that contribute to a therapy's clinical value, including safety, tolerability, and ease of use. Further analyses should examine the relationship between these additional measures and out-of-pocket costs.

Finally, since information about cancer stage is not available in the MarketScan database, it was assumed that any drug used for a particular FDA-approved indication was used for the correct stage of disease based on oncologist expertise. While this was largely true, there may have been exceptions not captured in our analysis.

Conclusions

Our study demonstrated that for commercially insured patients, out-of-pocket payments were not associated with indication-specific survival for oral oncolytics approved before 2009.

This finding highlights opportunities for commercial health insurers to address the complexities of implementing value-based cost sharing for oncolytics in a health care landscape that will increasingly emphasize benefit reaped for dollars spent.

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DISCLOSURES

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Out-of-Pocket Spending Not Associated with Oral Oncolytic Survival Benefit

APPENDIX A Two-Part Model Predicting Out-of-Pocket Spending for Oral Oncolytics: Survival Categorized by Drug and Indication

	Change in Mean Monthly Out-of-Pocket Spending, \$	P Value
Survival benefit		
Off-label	Reference	
No benefit	33.99 (-68.02, 136.00)	0.510
>0-5 months PFS	-2.17 (-11.37, 7.03)	0.640
>5-10 months PFS	29.42 (-30.43, 89.28)	0.340
10+ months PFS	19.14 (-19.99, 58.27)	0.340
>0-1 year OS	-21.04 (-34.8, -7.27)	0.003
>1-4 years OS	21.89 (-44.2, 87.96)	0.520
4+ years OS	26.16 (-43.46, 95.78)	0.460
Year	-3.89 (-5.46, -2.32)	<0.001
Total (plan + patient) payment	5.28 (4.37, 6.21)	<0.001
Age		
18-35	Reference	
36-45	3.42 (-17.22, 24.07)	0.750
46-55	1.76 (-8.28, 11.80)	0.730
56-65	0.33 (-14.40, 15.06)	0.970
Sex		
Male	Reference	
Female	3.18 (-4.24, 10.61)	0.400
Region		
Northeast	Reference	
Midwest	21.07 (-2.05, 44.18)	0.070
South	12.07 (-2.28, 26.43)	0.100
West	25.77 (10.34, 41.20)	0.001
Unknown	76.89 (30.15, 123.64)	0.001
Charlson comorbidity score		
0	Reference	
1	10.21 (-26.00, 46.42)	0.580
2	-47.73 (-110.59, 15.13)	0.140
3+	-47.93 (-110.53, 14.66)	0.130
Health plan type		
CDHP/HDHP	Reference	
Comprehensive	-3343.86 (-25811.27, 19123.56)	0.770
EPO/HMO	-3696.78 (-28348.36, 20954.79)	0.770
POS/POS with capitation	-3268.04 (-25447.03, 18910.95)	0.770
PPO	-3705.51 (-28370.51, 20959.48)	0.770
Unknown	-952.26 (-5612.63, 3708.11)	0.690

Note: Models adjust for all variables in the table. Values are presented as mean, (95% CI).

CDHP=consumer-driven health plan; EPO=exclusive provider organization; CI=confidence interval; HDHP=high deductible health plan. HMO=health maintenance organization; OS=overall survival; PFS=progression-free survival; POS=point of service; PPO=preferred provider organization.

APPENDIX B Two-Part Model Predicting Out-of-Pocket Spending for Oral Oncolytics: Survival Categorized by Drug's First Approved Indication

	Change in Mean Monthly Out-of-Pocket Spending, \$	P Value
Survival benefit		
Off-label	Reference	
No benefit	300.63 (-6484.95, 7086.20)	0.930
>0-5 Months PFS	159.01 (-3575.37, 3893.39)	0.930
>5-10 months PFS	1094.58 (-24981.46, 27170.62)	0.930
10+ Months PFS	-56.44 (-608.30, 495.42)	0.840
>0-1 year OS	-56.47 (-608.20, 495.27)	0.840
>1-4 years OS	469.23 (-10186.67, 11125.13)	0.930
4+ years OS	429.99 (-9226.77, 10086.76)	0.930
Year	-3.85 (-5.68, -2.03)	<0.001
Total (plan + patient) payment	4.89 (2.93, 6.85)	<0.001
Age, years		
18-35	Reference	
36-45	0.87 (-18.05, 19.78)	0.930
46-55	-0.73 (-13.93, 12.48)	0.910
56-65	-1.83 (-18.31, 14.64)	0.830
Sex		
Male	Reference	
Female	1.37 (-7.04, 9.78)	0.750
Region		
Northeast	Reference	
Midwest	19.60 (9.94, 29.26)	<0.001
South	8.97 (-6.18, 24.12)	0.250
West	16.65 (-23.37, 56.67)	0.420
Unknown	47.81 (-37.85, 133.47)	0.270
Charlson comorbidity score		
0	Reference	
1	8.10 (-95.75, 111.95)	0.880
2	-87.96 (-298.68, 122.77)	0.410
3+	-88.09 (-298.70, 122.52)	0.410
Health plan type		
CDHP/HDHP	Reference	
Comprehensive	-2422.64 (-47338.87, 42493.59)	0.920
EPO/HMO	-2626.83 (-51439.13, 46185.47)	0.920
POS/POS with capitation	-2564.24 (-51006.45, 45877.98)	0.920
PPO	-2627.59 (-51448.48, 46193.31)	0.920
Unknown	-405.97 (-6671.37, 5859.42)	0.900

Note: Models adjust for all variables in the table. Values are presented as mean, (95% CI).

CDHP=consumer-driven health plan; EPO=exclusive provider organization; CI=confidence interval; HDHP=high deductible health plan; HMO=health maintenance organization; OS=overall survival; PFS=progression-free survival; POS=point of service; PPO=preferred provider organization.