DOI: 10.1377/hlthaff.2023.00102
HEALTH AFFAIRS 42,
NO. 7 (2023): 946–955

By Alex K. Bryant, Zoey Chopra, Donna M. Edwards, Adam S. Whalley, Brian G. Bazzell, Julie A. Moeller, Michael J. Kelley, A. Mark Fendrick, Eve A. Kerr, Nithya Ramnath, Michael D. Green, Timothy P. Hofer, and Garth W. Strohbehn

Adopting Weight-Based Dosing With Pharmacy-Level Stewardship Strategies Could Reduce Cancer Drug Spending By Millions

Alex K. Bryant, University of Michigan, Ann Arbor, Michigan.

Zoey Chopra, University of Michigan.

Donna M. Edwards, University of Michigan.

Adam S. Whalley, Veterans Affairs (VA) Maine Health Care, Augusta, Maine.

Brian G. Bazzell, VA Ann Arbor Healthcare System, Ann Arbor, Michigan.

Julie A. Moeller, VA Ann Arbor Healthcare System.

Michael J. Kelley, Duke University and VA National Oncology Program Office, Durham, North Carolina.

A. Mark Fendrick, University of Michigan.

Eve A. Kerr, University of Michigan and VA Ann Arbor Healthcare System.

Nithya Ramnath, VA Ann Arbor Healthcare System.

Michael D. Green, University of Michigan.

Timothy P. Hofer, University of Michigan and VA Ann Arbor Healthcare System.

Garth W. Strohbehn (gstrohbe@umich.edu), VA Ann Arbor Healthcare System.

ABSTRACT **Immune checkpoint inhibitors, a class of drugs used in approximately forty unique cancer indications, are a sizable component of the economic burden of cancer care in the US. Instead of personalized weight-based dosing, immune checkpoint inhibitors are most commonly administered at "one-size-fits-all" flat doses that are higher than necessary for the vast majority of patients. We hypothesized that personalized weight-based dosing along with common stewardship efforts at the pharmacy level, such as dose rounding and vial sharing, would lead to reductions in immune checkpoint inhibitor use and lower spending. Using data from the Veterans Health Administration (VHA) and Medicare drug prices, we estimated reductions in immune checkpoint inhibitor use and spending that would be associated with pharmacy-level stewardship strategies, in a case-control simulation study of individual patient–level immune checkpoint inhibitor administration events. We identified baseline annual VHA spending for these drugs of approximately $537 million. Combining weight-based dosing, dose rounding, and pharmacy-level vial sharing would generate expected annual VHA health system savings of $74 million (13.7 percent). We conclude that adoption of pharmacologically justified immune checkpoint inhibitor stewardship measures would generate sizable reductions in spending for these drugs. Combining these operational innovations with value-based drug price negotiation enabled by recent policy changes may improve the long-term financial viability of cancer care in the US.**

Annual costs of cancer care in the US are expected to approach $250 billion by the end of this decade.[1] One commonly used cancer therapy, a class of drugs known as immune checkpoint inhibitors, is used in approximately forty unique cancer indications.[2] Together, these drugs accounted for more than $6 billion in Medicare Part B spending alone in 2020.[3]

Two of the first immune checkpoint inhibitors, pembrolizumab (brand name Keytruda) and nivolumab (brand name Opdivo), received their initial regulatory approvals at personalized weight-based dosages.[4–6] More recently, the two drugs received, at the request of sponsors, approval from the Food and Drug Administration (FDA) for "one-size-fits-all" flat doses, despite an absence of data supporting the superiority of flat

dosing over weight-based dosing.[4]

There are both patient safety and economic motivations to reconsider flat dosing of immune checkpoint inhibitors. Compared with weight-based dosing, flat dosing leads most patients to receive higher doses of a drug, potentially increasing exposure-related risks.[7] Because spending on a given drug scales with its per unit price and volume, the higher doses that result from flat dosing exacerbate the economic burden of cancer treatment relative to weight-based dosing.[8–10] Budget impact analyses suggest that adoption of weight-based immune checkpoint inhibitor dosing has the potential to reduce spending for both patients and payers.[6,11,12]

Policy attempts to curb wasteful drug spending by reducing cancer drug waste may perversely promote flat dosing, leading to the administration of drugs at excessively high dosages and, as a result, greater spending than may have occurred in the first place. Many cancer drugs are distributed in oversize, single-use vials.[13] By virtue of being personalized, a weight-based dose is unlikely to require an exact number of vials, thus generating "leftover" drug waste (for which payers have historically been financially responsible).[13]

To reduce its spending on single-use vial–related drug waste, the Centers for Medicare and Medicaid Services (CMS) announced in 2016 that it would require tracking and reporting of unused or discarded drugs payable under Medicare Part B, using the "JW modifier," a Healthcare Common Procedure Coding System modifier used to denote how much drug product within a given claim has been discarded.[14,15] Using JW modifier data, CMS identified nearly $3 billion spent in Medicare Part B on wasted drugs during the period 2017–20.[16] The Infrastructure, Investment and Jobs Act of 2021 enables CMS to seek reimbursement from drug makers for discarded amounts of a limited number of drugs ("discarded drug refund"), a policy later incorporated into 2023 Medicare reimbursement rules.[14,17] One unintended consequence of the policy is drug makers transitioning from personalized weight-based dosing to uniform flat dosing to reduce their waste-related liability. Within months of the 2016 CMS announcement, for example, pembrolizumab's manufacturer applied for and received FDA approval for a label change that replaced the weight-based dosage used in original melanoma clinical trials (2 mg/kg every three weeks) with a flat dosage (200 mg every three weeks), without providing evidence that it offered superior safety or effectiveness over weight-based dosing.[4,18]

Because weight-based dosing might not consume an entire single-use vial, distributing the drug from a vial that has been partially used in treating one patient to then treat subsequent patients is necessary to capture weight-based dosing's potential financial benefits while also avoiding waste.[19] Unlike single-use vial sharing in clinical areas by less well-trained staff, single-use vial sharing for cancer drugs is achievable using equipment standard to many hospital oncology pharmacies.[19–22] US Pharmacopeia Chapter 797 (USP 797), the compendium guiding pharmacies' procedures, requires single-use vials to be used within six hours of opening,[23] despite clinical pharmacy data suggesting that the stability, sterility, and activity of immune checkpoint inhibitors withdrawn using aseptic technique from previously opened single-use vials are good for up to twenty-eight days.[21,24–26] We define immune checkpoint inhibitor stewardship here as the coupling of administration of the lowest evidence-supported effective dose with operational strategies to minimize drug waste. Adopting and operationalizing stewardship of these drugs may allow for their more efficient use without sacrificing effectiveness.

Whether or not to pursue such stewardship efforts depends on their potential clinical and financial benefits relative to the financial and logistical costs of implementing and sustaining them. In this simulation study, we sought to inform decision making by describing the potential benefits of immune checkpoint inhibitor stewardship. We assessed the landscape of real-world usage of the drugs in the Veterans Health Administration (VHA), the largest integrated provider of cancer care in the US, using individual patient–level usage data. We estimated the impacts on immune checkpoint inhibitor usage that would be expected under these potential stewardship strategies and the financial implications. In doing so, we offer a template for health systems and payers to enumerate the costs and benefits of drug dosing policies to better inform drug price negotiations and assess expensive cancer medicines' value.

Study Data And Methods

DATA SETS AND DERIVATION OF COHORTS From the VA Corporate Data Warehouse VINCI, we extracted, using a natural language processing algorithm, all administrations of anti-programmed cell death 1 axis immune checkpoint inhibitors appearing on the Veterans Affairs (VA) national formulary (pembrolizumab, nivolumab, atezolizumab [Tecentriq], durvalumab [Imfinzi], and cemiplimab-rwlc [Libtayo; the rwlc suffix is a result of monoclonal antibody naming conventions]) that occurred between January 1, 2021, and December 31, 2021, in

the nationwide VA integrated health system. The patient cohort consisted of patients who received at least one dose of any of the listed medications at a VA medical center during calendar year 2021. The algorithm extracted information from facility-specific, semistructured chemotherapy administration notes in the electronic health record, as detailed in the online appendix.[27] We extracted patient weight (nearest to the infusion date, plus or minus one week), date of administration, original immune checkpoint inhibitor dose, and facility. For administrations without an associated weight, plus or minus one week, we imputed patient weight using the last value carried forward (for patients with a prior administration with nonmissing weight) or used the facility-level median weight (for patients without a prior administration). We excluded avelumab (brand-name Bavencio), as it was not on the VA Pharmacy Benefits Management Services' 2022 national formulary.[28] The project was declared exempt by the VA Ann Arbor Healthcare System Institutional Review Board (IRB-2020-1236).

STEWARDSHIP STRATEGY SIMULATIONS At baseline, immune checkpoint inhibitors are administered at flat dosages that use the entire contents of single-use vials. Three pharmacy-level tactics that can be used in crafting an immune checkpoint inhibitor stewardship strategy include weight-based dosing, capped at a maximum dose of the FDA-approved flat dose; dose rounding if the weight-based dose is within 10 percent of the nearest single-use vial (for example, for a 100 mg vial, 218 mg is rounded down to 200 mg); and sharing leftover drug material from single-use vials between patients (single-use vial sharing). We generated four immune checkpoint inhibitor stewardship strategies that used these tactics: strategy 1 (weight-based dosing alone), strategy 2 (weight-based dosing and dose rounding, without single-use vial sharing), strategy 3 (weight-based dosing and single-use vial sharing, without dose rounding), and strategy 4 (weight-based dosing, dose rounding, and single-use vial sharing). In our primary analysis, we evaluated the theoretically maximal potential savings by allowing an unlimited time window for single-use vial sharing (that is, leftover product is never discarded). Secondary analyses evaluated time-limited vial-sharing windows. Single-use vial–sharing algorithms are described in detail in the appendix (Supplemental Methods) and supplemental exhibits 1–5.[27]

In simulations, each immune checkpoint inhibitor flat dose extracted was recalculated as a weight-based dose, using patient weight and weight-based dosages (supplemental exhibit 6).[27] Prescribers often require clinical trial data or FDA approval before adopting alternative dosing strategies,[29] so we required alternative weight-based dosages to be supported by clinical experience in large health systems, clinical trial evidence, or FDA approval, rather than pharmacokinetic simulation alone. Using the weight-based dose, we calculated each individual dose's single-use vial use. We assumed that partially used vials could only be shared within each VA facility–based pharmacy, rather than between pharmacies. If single-use vial sharing was not employed, the individual dose's vial use was rounded up to the nearest integer. Single-use vials were summed across each VA facility over the entire year (an unlimited single-use vial–sharing window for the one-year time frame of the study) (supplemental exhibits 1 and 2).[27] Within the VHA, one single-use vial size per drug is typically procured, with the exception of atezolizumab (supplemental exhibit 7).[27] We assumed single-use vial procurement and use, at baseline, to be optimized to minimize waste with flat dosing (for example, for a 240 mg nivolumab dose, we assumed that one 240 mg single-use vial is procured and used, rather than three 100 mg single-use vials). For flat immune checkpoint inhibitor doses lacking a weight-based dose of the same frequency supported by clinical evidence (for example, durvalumab 1,500 mg every four weeks), we only modeled the flat dose.

Given potential clinical reasons for preferring one immune checkpoint inhibitor frequency over another (for example, combination with specific chemotherapies), we did not impose changes on administration frequency. Because clinic and infusion schedules may be limited by provider availability, we did not impose changes on the day of immune checkpoint inhibitor administration, despite previous evidence showing that scheduling patients by drug can reduce waste.[30] For cemiplimab-rwlc, the weight-based dose supported by clinical evidence is adminis-

We demonstrated significant potential for recurring financial benefits from the adoption of immune checkpoint inhibitor stewardship.

Widespread adoption of stewardship measures could markedly improve the cost-effectiveness of cancer care.

tered every two weeks, whereas the flat dose is every three weeks;[31] thus, we included cemiplimab-rwlc as a constant line item in our final estimates of immune checkpoint inhibitor use (totaling $8.4 million in 2021), using the flat dose.

COST CALCULATIONS In our primary financial analysis, we standardized prices using per dosing unit Medicare average sales price[3] and single-use vial size to estimate acquisition costs (supplemental exhibit 7).[27] In brief, for each stewardship strategy, we estimated the total number of single-use vials used nationally in the VHA for each drug in 2021. Drug spending was estimated as the sum of, for each immune checkpoint inhibitor, the product of total single-use vials used and acquisition cost. In the primary analysis, we assessed an unlimited duration for the sharing period, defined as follows: A partially used vial of immune checkpoint inhibitor opened on day 0 is the first source of immune checkpoint inhibitor on subsequent days, regardless of the time interval between the initial patient and any subsequent patients (supplemental exhibit 1).[27]

SENSITIVITY ANALYSES We examined two lower weight-based nivolumab doses supported by clinical evidence: 0.3 mg/kg and 1 mg/kg, both administered every three weeks.[4,32–35] Because we did not allow changes to administration frequency, patients receiving nivolumab 240 mg every two weeks at baseline could receive 0.3 mg/kg or 1 mg/kg every two weeks if the weight-based dose was less than 240 mg.[4]

To identify the minimum length of a single-use vial–sharing window that would capture appreciable cost savings, we evaluated sharing windows of one day, one week, two weeks, and one month for pembrolizumab, nivolumab, and durvalumab. Single-use vial–sharing windows required any partially used vial to be discarded at the end of the sharing window, using date cutoffs, as opposed to tracking individual vials, to simplify the analysis. Using fixed-length windows anchored to calendar dates underestimates potential cost savings, as an opened, partially used single-use vial's maximal shelf life is not necessarily achieved. These strategies are summarized in supplemental exhibits 3–5.[27]

To better understand the financial implications of immune checkpoint inhibitor stewardship within the VHA, we estimated costs using 2022 prices from the VHA Federal Supply Schedule, where the VHA is one of the designated "big four" agencies receiving preferential prices (supplemental exhibit 7),[27] in lieu of Medicare average sales price.[36]

LIMITATIONS We note several limitations unique to our data and analysis. Body weights in the VA population tend to be higher because of male predominance, thus limiting generalizability and likely underestimating the savings of immune checkpoint inhibitor stewardship, relative to prior work.[6] The unlimited time horizon of single-use vial sharing was perhaps unrealistic under USP 797 for infrequently administered immune checkpoint inhibitors, which could have marginally overestimated cost savings.[23] We held dosing frequency and duration constant, despite pharmacokinetic, pharmacodynamic, and clinical evidence supporting less frequent dosing.[9,37–39] Compared with a counterfactual policy encouraging less frequent administration, our analysis underestimated potential cost savings. For example, encouraging the administration of 4 mg/kg pembrolizumab every six weeks instead of 200 mg every three weeks would save one single-use vial every six weeks for each patient weighing less than 75 kg[40]—savings we did not capture. Our immune checkpoint inhibitor data set also was not exhaustive: Avelumab is not on the VA formulary, and by focusing exclusively on drugs inhibiting the programmed cell death protein 1 axis, we did not include drugs targeting the cytotoxic T-lymphocyte associated protein 4 axis, such as ipilimumab (which generates approximately $50 million in annual Medicare Part B drug waste[15]). We did not account for excessive dosing's potential toxicity,[7] and thus immune checkpoint inhibitor stewardship may have clinical benefits not captured by our analysis. We did not account for the potential costs of safe drug disposal, thus underestimating stewardship's potential benefits. As the VHA has an adult patient population, we cannot comment on stewardship's potential benefits in pediatric oncology, although that field's widespread use of weight-based dosing might offer cost-savings opportunities if immune checkpoint inhibitor stewardship were implemented. Finally, stewardship's costs (for example, personnel, training, and equipment) are unknown.

Study Results

PATIENT AND IMMUNE CHECKPOINT INHIBITOR ADMINISTRATION CHARACTERISTICS The natural language processing algorithm correctly identified true immune checkpoint inhibitor administration events and their dates, drugs, and dosages at rates of 95 percent or greater when compared with manual chart review, stratified by each of the five immune checkpoint inhibitor drugs to ensure adequate representation of each drug (supplemental exhibit 8).[27] Using this algorithm, we identified 49,851 administration events in 8,276 unique patients in 2021 (exhibit 1). Of these events, 25,691 (51.5 percent; 4,572 unique patients) were pembrolizumab, 11,322 (22.7 percent; 1,773 unique patients) were nivolumab, 6,023 (12.1 percent; 1,057 unique patients) were atezolizumab, and 5,934 (11.9 percent; 949 unique patients) were durvalumab. Of the pembrolizumab administrations, 17,894 (69.7 percent) employed every-three-weeks dosing and 7,716 (30.0 percent) every-six-weeks dosing (data not shown). A total of 46,081 (92.4 percent) administration events employed flat dosages. Weight-based dosing most commonly occurred with durvalumab, accounting for 2,577 (43.4 percent) administrations of that drug. Average patient weight was consistent across immune checkpoint inhibitors (mean: 84.0 kg; standard deviation: 19.7) (exhibit 2).

EXPECTED HEALTH SYSTEM SPENDING BY STEWARDSHIP STRATEGY The potential cost savings of immune checkpoint inhibitor stewardship strategies are summarized in exhibit 3. At baseline, annual immune checkpoint inhibitor expenditures in the VHA totaled $537 million in 2021, using Medicare average sales price. The greatest reduction in single-use vial use was achieved with strategies 3 and 4, with an unlimited single-use vial–sharing window, which projected estimated annual savings of $72–74 million (13.5–13.7 percent). Most cost savings identified through weight-based dosing with single-use vial sharing were due to pembrolizumab. Use of nivolumab 3 mg/kg generated up to $6 million in additional annual savings, depending on the length of the single-use vial–sharing window (supplemental exhibit 9).[27]

USE AND DRUG SPENDING BY IMMUNE CHECKPOINT INHIBITOR Pembrolizumab was the largest immune checkpoint inhibitor line item, totaling $303 million in 2021, using Medicare average sales price. Impacts of alternative dosing strategies on pembrolizumab use and costs are summarized in exhibit 4. Weight-based dosing alone (strategy 1) reduced annual pembrolizumab spending by 4.9 percent, representing potential annual savings of $14 million. The addition of dose rounding (strategy 2) reduced pembrolizumab spending by $24 million (8.1 percent) in total annual cost savings. Using an unlimited single-use vial–sharing window would reduce annual pembrolizumab dosing unit use by between 19.3 percent and 19.7 percent, representing annual cost savings of $58–$59 million.

Nivolumab was the second-largest immune checkpoint inhibitor line item, totaling $115 million in 2021 (supplemental exhibit 9).[27] Single-use vial sharing with an unlimited sharing window would generate approximately $5 million in annual nivolumab cost savings. Because most baseline nivolumab administration was every four weeks, opportunities for cost savings were limited by the absence of an every-four-weeks weight-based dosage. Spending for durvalumab, the third-largest immune checkpoint inhibitor line item, totaled $57.5 million in 2021 (supplemental exhibit 10).[27] As a result of the low rate of every-two-weeks durvalumab administration and constraints on dose frequency, weight-based dosing by itself (strategy 1) would achieve minimal reduction in durvalumab single-use vial use:

EXHIBIT 1

Veterans Health Administration immune checkpoint inhibitor (ICI) recipient cohort, January 1–December 31, 2021

			Missing data imputations		
ICI	Administration events	Missing patient weights	Last value carried forward	Site median patient weight	Unique patients
All ICIs	49,851	3,916	2,255	1,661	8,276
Pembrolizumab	25,691	2,241	1,159	1,082	4,572
Nivolumab	11,322	854	574	280	1,773
Atezolizumab	6,023	408	258	150	1,057
Durvalumab	5,934	413	264	149	949
Cemiplimab-rwlc	881	—[a]	—[a]	—[a]	112

SOURCE Authors' analysis of data from the Veterans Affairs Corporate Data Warehouse. **NOTE** "rwlc" is a result of monoclonal antibody naming conventions. [a]Not applicable (cemiplimab-rwlc is carried forward as a constant line item in simulations because of a lack of weight-based dosing strategies).

EXHIBIT 2

Characteristics of immune checkpoint inhibitor (ICI) administration events in the Veterans Health Administration immune checkpoint inhibitor recipient cohort, January 1–December 31, 2021

ICI	Unique patients	All administrations		Flat-dose administrations		Patient weight at administration (kg)	
		Number	Percent of all ICI administrations	Number	Percent[a]	Mean	SD
All ICIs	8,276	49,851	100.0	46,081	92.4	84.0	19.7
Pembrolizumab	4,572	25,691	51.5	25,610	99.7	83.4	19.8
Nivolumab	1,773	11,322	22.7	10,246	90.5	85.8	19.8
Atezolizumab	1,057	6,023	12.1	5,988	99.4	83.4	19.3
Durvalumab	949	5,934	11.9	3,357	56.6	83.8	19.6
Cemiplimab-rwlc	112	881	1.8	880	99.9	85.4	17.7

SOURCE Authors' analysis of data from the Veterans Affairs Corporate Data Warehouse. **NOTE** "rwlc" is a result of monoclonal antibody naming conventions. [a]In this column, values are percent of each row. For example, for pembrolizumab, 99.7% of all pembrolizumab administrations were flat dose.

Compared with baseline, single-use vial sharing with an unlimited window would reduce durvalumab use and spending by $5.0–$5.4 million (8.6–9.4 percent). Atezolizumab was the fourth-largest immune checkpoint inhibitor line item, totaling $53.2 million in 2021 (supplemental exhibit 11).[27] Weight-based dosing with single-use vial sharing would reduce atezolizumab use and spending, with projected annual savings of $3.3–$3.4 million annually.

SENSITIVITY ANALYSES

▶ **SINGLE-USE VIAL–SHARING WINDOW:** Longer single-use vial–sharing windows captured greater percentages of immune checkpoint inhibitor stewardship's maximum theoretical cost savings (supplemental exhibits 12 [strategy 3] and 13 [strategy 4]).[27] The one-day sharing window captured less pembrolizumab-related savings than the unlimited sharing window. A one-week window would capture approximately 80 percent of potential savings from pembrolizumab single-use vial sharing, extension of the window to two weeks would capture more than 90 percent, and extension of the window to one month would capture more than 95 percent. The one-month window would capture more than 75 percent of potential durvalumab-related savings and more than 85 percent of potential nivolumab-related savings at the 1 mg/kg dose level. The marginal nivolumab-related savings associated with the 0.3 mg/kg dose level (that is, the drug units that would be saved by using 0.3 mg/kg rather than 1 mg/kg) were not efficiently captured by any of the sharing windows.

EXHIBIT 3

Simulated immune checkpoint inhibitor (ICI) use and spending in the Veterans Health Administration under different ICI stewardship strategies, January 1–December 31, 2021

	Dosing strategies			Estimated annual ICI spending, millions of dollars[a]	% savings vs. baseline
	Weight based	Dose rounding	SUV sharing		
Baseline	–	–	–	$537	—[b]
Strategy 1	+	–	–	521	3.0
Strategy 2	+	+	–	508	5.4
Strategy 3					
1-day SUV-sharing window	+	–	+	504	6.2
Unlimited SUV-sharing window	+	–	+	465	13.5
Strategy 4					
1-day SUV-sharing window	+	+	+	496	7.6
Unlimited SUV-sharing window	+	+	+	463	13.7

SOURCE Authors' analysis of data from the Veterans Affairs Corporate Data Warehouse and Medicare Part B Drug Spending File. **NOTES** "+" is the presence of a tactic, whereas "–" is the absence of the tactic (for example, strategy 1 employs only the weight-based dosing tactic). SUV is single-use vial. [a]Medicare average sales price. [b]Not applicable (definitionally, baseline cannot generate savings relative to baseline).

EXHIBIT 4

Simulated pembrolizumab use and spending in the Veterans Health Administration under different immune checkpoint inhibitor stewardship strategies, January 1–December 31, 2021

	Dosing strategies			Pembrolizumab SUVs (100 mg)	Dosing units, millions	Estimated annual pembrolizumab spending, millions of dollars[a]	% savings vs. baseline
	Weight based	Dose rounding	SUV sharing				
Baseline	–	–	–	66,967	6.70	$303	—[b]
Strategy 1	+	–	–	63,703	6.37	289	4.9
Strategy 2	+	+	–	61,576	6.16	279	8.1
Strategy 3							
1-day SUV-sharing window	+	–	+	59,986	6.00	272	10.4
1-week SUV-sharing window	+	–	+	56,344	5.63	255	15.9
2-week SUV-sharing window	+	–	+	55,301	5.53	251	17.4
1-month SUV-sharing window	+	–	+	54,652	5.47	248	18.4
Unlimited SUV-sharing window	+	–	+	54,058	5.41	245	19.3
Strategy 4							
1-day SUV-sharing window	+	+	+	59,011	5.90	267	11.9
1-week SUV-sharing window	+	+	+	55,944	5.59	254	16.4
2-week SUV-sharing window	+	+	+	55,006	5.50	249	17.9
1-month SUV-sharing window	+	+	+	54,377	5.44	246	18.8
Unlimited SUV-sharing window	+	+	+	53,779	5.38	244	19.7

SOURCE Authors' analysis of data from VA Corporate Data Warehouse and Medicare Part B Drug Spending File. **NOTES** "+" is the presence of a tactic, whereas "–" is the absence of the tactic (for example, strategy 1 employs only the weight-based dosing tactic). SUV is single-use vial. [a]Medicare average sales price. [b]Not applicable (definitionally, baseline cannot generate savings relative to baseline).

▶ **LOWER NIVOLUMAB DOSAGES:** Savings modestly increased with nivolumab dosages of 1 mg/kg or 0.3 mg/kg (supplemental exhibits 14 and 15).[27] Both 1 mg/kg and 0.3 mg/kg generated $4 million (3.4 percent) in annual savings. Because all weight-based doses were less than 240 mg, dose rounding generated no additional savings, and 0.3 mg/kg generated no savings beyond those of 1 mg/kg in the absence of single-use vial sharing. Annual nivolumab costs were reduced from baseline by $28.3 million (24.9 percent) with 0.3 mg/kg and by $21.7 million (19.1 percent) with 1 mg/kg, using an unlimited single-use vial–sharing window.

▶ **'BIG FOUR' PRICES:** Using "Big Four" prices for immune checkpoint inhibitors and data on their use in the VHA, we estimated the VHA's immune checkpoint inhibitor expenditures for 2022 and the potential financial impact of stewardship (supplemental exhibit 16).[27] Baseline VHA immune checkpoint inhibitor expenditures are estimated to total $423 million annually, of which $246 million (58.1 percent) is pembrolizumab (data not shown). Single-use vial–sharing strategies with an unlimited sharing window were associated with the greatest annual cost savings, generating expected savings of $58–$60 million (13.8–14.2 percent) annually, 81 percent of which derive from reduced pembrolizumab use (data not shown). Applying a one-day single-use vial–sharing window to strategies 3 and 4 to all immune checkpoint inhibitors would be expected to generate $28 million (6.5 percent) and $33 million (7.8 percent) in annual cost savings, respectively.

Discussion

In this simulation analysis employing patient-level data from the VHA—the largest provider of integrated cancer care in the US—we demonstrated significant potential for recurring financial benefits from the adoption of immune checkpoint inhibitor stewardship. Incorporating weight-based dosing and single-use vial sharing within each VA hospital's pharmacy would result in an approximately 14 percent reduction in annual immune checkpoint inhibitor spending, mostly from savings associated with pembrolizumab and nivolumab, the most commonly prescribed immune checkpoint inhibitors. If flat and weight-based dosing have truly equivalent efficacy, as available evidence suggests,[4] then widespread adoption of stewardship measures could markedly improve the cost-effectiveness of cancer care. In an era of ever-rising drug prices and aging populations, combining operational innovations enabled by CMS policy changes[14] with the value-based drug price negotiation enabled by the Infrastructure, Investment, and Jobs Act of 2021 may improve the US health care system's long-term financial viability by lessening cancer care's substantial economic burden.[1]

Our work was made methodologically distinct

High-quality cancer care depends on administering the right drug at the right dose to the right patient at the right time.

by its use of patient-level usage data from a real-world, nationwide health system's population rather than a constructed hypothetical population. Unique strengths include the use of a disaggregated data set that enabled pharmacy-level analysis (necessary for evaluating vial sharing), inclusion of multiple FDA-approved immune checkpoint inhibitors, and incorporation of low-dose nivolumab. Our savings estimates are consistent with previous studies of weight-based pembrolizumab: Monte Carlo simulation on a hypothetical population suggested 24.0 percent relative savings,[6] whereas analysis of a single, high-volume center estimated cost savings of 19 percent with weight-based dosing and single-use vial sharing.[12] Our lower point estimate of savings is most likely attributable to the predominance of men (who tend to have higher body weights) in the VHA population. Most of the savings in our analysis came from pembrolizumab and nivolumab, likely because of prescribing volumes. Compared with pembrolizumab and nivolumab, the estimated savings associated with atezolizumab and durvalumab stewardship were low because of three factors: lower atezolizumab and durvalumab prescribing volumes; low frequency of every-three-weeks atezolizumab (which has a corresponding weight-based dosage based on clinical evidence) compared with every-four-weeks atezolizumab (which lacks a corresponding weight-based dosage); and high baseline use of weight-based, every-two-weeks durvalumab.

The problem of drug waste due to oversize single-use vials is well established and is being targeted by CMS through efforts to recoup these deadweight losses from manufacturers.[13] However, in addition to the questionable underlying assumption that drug makers' drug development behaviors would remain static, the current policy has shortcomings. First, it will not apply to all drugs equally,[14] nor will it be available to large, single-payer health systems such as the VHA or Kaiser Permanente that do not bill CMS. Second, reporting of the JW modifier code used to track drug waste is inconsistent. Third, in strictly disincentivizing only a specific type of waste—drug product that remains in the single-use vial after compounding is not used for another patient and is discarded—CMS policy incentivizes drug makers to develop drugs using flat dosages and to package them in single-use vials closely aligned to the flat dosage.[41,42] Administering drugs at dosages that are flat, and thus are predictable and align to single-use vial sizes, results in less drug material being discarded, producing the appearance of less waste to the payer. However, it conceals the fact that excess drug amounts may be administered to the patient, relative to what they need, and thus may increase usage and drug spending. Although immune checkpoint inhibitor stewardship may decrease medical waste by decreasing aggregate consumption, waste from partially used vials and the attendant costs of safe disposal would likely persist in some amount.

In the United States, immune checkpoint inhibitor stewardship is more likely to be implemented in health systems that use capitated payment models; ally themselves with CMS innovation models; or are government-sponsored single-payer health systems such as the VHA, Department of Defense, or Indian Health Service. These are the same parties with the incentives to pursue postapproval dose optimization clinical trials of FDA-approved cancer drugs.[43] Businesses that depend on fee-for-service revenues and Medicare 340B program markups may be perversely incentivized to use flat dosing, despite it lacking any clinical advantage over weight-based dosing. Other actions, such as incentives, coordinated payer action, government mandate, or a combination, may be necessary for the widespread adoption of immune checkpoint inhibitor stewardship. Regardless of the overarching payment model, pharmacies that routinely compound anticancer drugs are likely to employ systems already compliant with USP 797, making single-use vial sharing feasible and achievable.[19]

Conclusion

High-quality cancer care depends on administering the right drug at the right dose to the right patient at the right time. Achieving high-quality, financially sustainable cancer care will require stakeholders to acknowledge that the right dose is likely to be a personalized one and that adoption of operational, regulatory, and methodologic innovations is a necessity. For such inno-

vations to thrive, however, the value-based pharmacy ecosystem must be shaped by collaborative relationships among payers, clinicians, pharmacies, drug makers, and regulators. ■

This work was supported by the Lung Precision Oncology Program (Grant No. VA 150CU000182; Nithya Ramnath, Michael D. Green, Garth W. Strohbehn), LUNGevity (Green, Alex K. Bryant), the Department of Veterans Affairs (Grant No. I01 BX005267; Green), the Melanoma Research Alliance (Grant No. MRA689853; Green), the National Cancer Institute (Grants Nos. CA252010 and P30CA046592; Ramnath, Green, Strohbehn), and the Breast Cancer Research Foundation (Green). Adam S. Whalley, Brian G. Bazzell, Julie A. Moeller, Michael J. Kelley, Eve A. Kerr, Ramnath, Green, Timothy P. Hofer, and Strohbehn are employees of the US federal government; the views expressed do not reflect those of the US federal government. To access the authors' disclosures, click on the Details tab of the article online.

NOTES

1 Mariotto AB, Enewold L, Zhao J, Zeruto CA, Yabroff KR. Medical care costs associated with cancer survivorship in the United States. Cancer Epidemiol Biomarkers Prev. 2020; 29(7):1304–12.

2 Morad G, Helmink BA, Sharma P, Wargo JA. Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. Cell. 2021; 184(21):5309–37.

3 Centers for Medicare and Medicaid Services. Medicare Part B drug spending by drug [Internet]. Baltimore (MD): CMS; 2023 Feb 10 [last updated 2023 Mar 6; cited 2023 May 15]. Available from: https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-b-spending-by-drug

4 Walker S, de Léséleuc L, Butcher R. CADTH technology review: optimal use 360 report: dosing and timing of immuno-oncology drugs [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2019 Nov [cited 2023 May 15]. Available from: https://www.cadth.ca/sites/default/files/ou-tr/ho0008-dosing-timing-immuno-oncology-drugs.pdf

5 Ratain MJ, Goldstein DA. Time is money: optimizing the scheduling of nivolumab. J Clin Oncol. 2018 Aug 27. [Epub ahead of print].

6 Goldstein DA, Gordon N, Davidescu M, Leshno M, Steuer CE, Patel N, et al. A pharmacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in firstline PD-L1-positive non–small cell lung cancer. J Natl Cancer Inst. 2017; 109(11).

7 Eun Y, Kim IY, Sun JM, Lee J, Cha HS, Koh EM, et al. Risk factors for immune-related adverse events associated with anti-PD-1 pembrolizumab. Sci Rep. 2019;9(1):14039.

8 Serritella AV, Strohbehn GW, Goldstein DA, Lichter AS, Ratain MJ. Interventional pharmacoeconomics: a novel mechanism for unlocking value. Clin Pharmacol Ther. 2020; 108(3):487–93.

9 Peer CJ, Goldstein DA, Goodell JC, Nguyen R, Figg WD, Ratain MJ. Opportunities for using in silico–based extended dosing regimens for monoclonal antibody immune checkpoint inhibitors. Br J Clin Pharmacol. 2020;86(9):1769–77.

10 Hsieh PH, Kacew AJ, Dreyer M, Serritella AV, Knoebel RW, Strohbehn GW, et al. Alternative trastuzumab dosing strategies in HER2-positive early breast cancer are associated with patient out-of-pocket savings. NPJ Breast Cancer. 2022;8(1):32.

11 Ogungbenro K, Patel A, Duncombe R, Nuttall R, Clark J, Lorigan P. Dose rationalization of pembrolizumab and nivolumab using pharmacokinetic modeling and simulation and cost analysis. Clin Pharmacol Ther. 2018;103(4):582–90.

12 Hall E, Zhang J, Kim EJ, Hwang G, Chu G, Bhatia S, et al. Economics of alternative dosing strategies for pembrolizumab and nivolumab at a single academic cancer center. Cancer Med. 2020;9(6):2106–12.

13 Bach PB, Conti RM, Muller RJ, Schnorr GC, Saltz LB. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016;352: i788.

14 Centers for Medicare and Medicaid Services. Medicare and Medicaid programs; CY 2023 payment policies under the physician fee schedule and other changes to Part B payment and coverage policies; Medicare Shared Savings Program requirements; implementing requirements for manufacturers of certain single-dose container or single-use package drugs to provide refunds with respect to discarded amounts; and COVID-19 interim final rules. Fed Regist. 2022; 87(222):69404–70700.

15 Centers for Medicare and Medicaid Services. Medicare Part B discarded drug units [Internet]. Baltimore (MD): CMS; 2023 Feb 10 [last updated 2023 Mar 6; cited 2023 May 15]. Available from: https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-b-discarded-drug-units

16 O'Donoghue AL, White MH, Weiss AP, Stevens JP, Anderson TS. Trends in Medicare Part B spending on discarded drugs, 2017–2020. JAMA Intern Med. 2023;183(2):164–7.

17 Office of Senator Dick Durbin [Internet]. Washington (DC): US Senate. Press release, Durbin, Portman introduce bipartisan bill to save seniors, taxpayers billions in prescription drug costs from Big Pharma's wasteful pricing; 2021 Apr 21 [cited 2023 May 15]. Available from: https://www.durbin.senate.gov/newsroom/press-releases/durbin-portman-introduce-bipartisan-bill-to-save-seniors-taxpayers-billions-in-prescription-drug-costs-from-big-pharmas-wasteful-pricing-

18 Food and Drug Administration. Supplemental approval fulfillment of postmarketing commitment, BLA 125514/S-13 [Internet]. Silver Spring (MD): FDA; 2017 May 17 [cited 2023 May 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/125514Orig1s013ltr.pdf

19 Goldstein DA, Harvey RD, Chan KKW. Enabling the sharing of single-dose vials through risk mitigation to decrease financial toxicity. JAMA Oncol. 2022;8(6):821–2.

20 Matsuo K, Nomura H, Uchiyama M, Miyazaki M, Imakyure O. Estimating the effect of optimizing anticancer drug vials on medical costs in Japan based on the data from a cancer hospital. BMC Health Serv Res. 2020;20(1):1017.

21 Fukudo M, Ishikawa R, Mishima K, Ono T, Matsumoto S, Tasaki Y. Real-world nivolumab wastage and left-over drug stability assessment to facilitate drug vial optimization for cost savings. JCO Oncol Pract. 2020;16(10):e1134–42.

22 Amerine LB, Savage SW, Rowe EC, Daniels R, Valgus JM, Redding R, et al. Implementation of drug vial optimization to reduce drug waste. Oncol Issues. 2019;34(2):44–50.

23 US Pharmacopeia. USP 797 guidebook to pharmaceutical compounding: sterile preparations. First edition. Rockville (MD): United States Pharmacopeial Convention; 2008.

24 Hui A, Yin J, Liu W, Zheng K. Prolonged in-use stability of diluted atezolizumab in commercial intravenous bags. Int J Pharm Compd. 2021;25(3):246–57.

25 Sundaramurthi P, Chadwick S,

Narasimhan C. Physicochemical stability of pembrolizumab admixture solution in normal saline intravenous infusion bag. J Oncol Pharm Pract. 2020;26(3):641–6.
26 Bros A, Le Guyader G, Doillet H, Vieillard V, Paul M, Jaskowiec C, et al. Stability study of durvalumab solutions in its opened vials and after dilution and storage in 0.9% NaCl infusion polyolefin bags [Internet]. Paris: GERPAC, European Society of Hospital Pharmaceutical Technologies; 2020 Nov 24 [cited 2023 May 15]. Available from: https://www.gerpac.eu/stability-study-of-durvalumab-solutions-in-its-opened-vials-and-after-dilution-and-storage-in-0-9-nacl-infusion-polyolefin-bags
27 To access the appendix, click on the Details tab of the article online.
28 Department of Veterans Affairs, Pharmacy Benefits Management Strategic Health Group. VHA national formulary [Internet]. Washington (DC): VA; 2023 May [cited 2023 Jun 16]. Available for download from: https://www.pbm.va.gov/PBM/VA_National_Formulary_MAY_2023.xlsx
29 Strohbehn GW, Holleman R, Burns J, Klamerus ML, Kelley MJ, Kerr EA, et al. Adoption of extended-interval dosing of single-agent pembrolizumab and comparative effectiveness vs standard dosing in time-to-treatment discontinuation. JAMA Oncol. 2022;8(11):1663–7.
30 Damuzzo V, Russi A, Chiumente M, Masini C, Rebesco B, Gregis F, et al. Optimization of resources by drug management: a multicentred web-administered study on the use of ipilimumab in Italy. J Oncol Pharm Pract. 2019;25(4):787–92.
31 Rischin D, Migden MR, Lim AM, Schmults CD, Khushalani NI, Hughes BGM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. J Immunother Cancer. 2020;8(1):e000775.
32 Agrawal S, Feng Y, Roy A, Kollia G, Lestini B. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. J Immunother Cancer. 2016;4:72.
33 Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized Phase II trial. J Clin Oncol. 2015;33(13):1430–7.
34 Patil VM, Noronha V, Menon N, Rai R, Bhattacharjee A, Singh A, et al. Low-dose immunotherapy in head and neck cancer: a randomized study. J Clin Oncol. 2023;41(2):222–32.
35 Food and Drug Administration. Highlights of prescribing information—Opdivo [Internet]. Silver Spring (MD): FDA; 2022 May [cited 2023 May 15]. (FDA Package Insert for the drug nivolumab). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125554s114lbl.pdf
36 Department of Veterans Affairs, Office of Procurement, Acquisition, and Logistics. Pharmaceutical prices [Internet]. Washington (DC): VA; [last updated 2023 May 2; cited 2023 May 15]. Available from: https://www.va.gov/opal/nac/fss/pharmprices.asp
37 Hirsch I, Goldstein DA, Tannock IF, Butler MO, Gilbert DC. Optimizing the dose and schedule of immune checkpoint inhibitors in cancer to allow global access. Nat Med. 2022;28(11):2236–7.
38 Bryant AK, Sankar K, Zhao L, Strohbehn GW, Elliott D, Moghanaki D, et al. De-escalating adjuvant durvalumab treatment duration in stage III non–small cell lung cancer. Eur J Cancer. 2022;171:55–63.
39 Marron TU, Ryan AE, Reddy SM, Kaczanowska S, Younis RH, Thakkar D, et al. Considerations for treatment duration in responders to immune checkpoint inhibitors. J Immunother Cancer. 2021;9(3):e001901.
40 Goldstein DA, Ratain MJ, Saltz LB. Weight-based dosing of pembrolizumab every 6 weeks in the time of COVID-19. JAMA Oncol. 2020;6(11):1694–5.
41 Fruman B, Cortez J, Sullivan M, Hafez O, Gustafson K. 3 ways manufacturers can prepare for new 2023 discarded drug rebate [Internet]. Washington (DC): Avalere Health; 2022 Mar 17 [cited 2023 May 15]. Available from: https://avalere.com/insights/3-ways-manufacturers-can-prepare-for-new-2023-discarded-drug-rebate
42 Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size–based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012–24.
43 Strohbehn GW, Lichter AS, Ratain MJ. US government payer-funded trials to address oncology's drug-dosing conundrum: a congressional call to action? J Clin Oncol. 2023;41(14):2488–92.