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REVIEW ARTICLE

Interventional pharmacoeconomics for immune checkpoint inhibitors through alternative dosing strategies

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Immune checkpoint inhibitors (ICIs) are approved for the treatment of a variety of cancer types. The doses of these drugs, though approved by the Food and Drug Administration (FDA), have never been optimised, likely leading to significantly higher doses than required for optimal efficacy. Dose optimisation would hypothetically decrease the risk, severity, and duration of immune-related adverse events, as well as provide an opportunity to reduce costs through interventional pharmacoeconomic strategies such as off-label dose reductions or less frequent dosing. We summarise existing evidence for ICI dose optimisation to advocate for the role of interventional pharmacoeconomics.

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BACKGROUND

Immune checkpoint inhibitors (ICIs) have changed the treatment. paradigm of a variety of cancer types over the past decade [1]. Through interactions with inhibitor proteins such as programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), ICIs help overcome cancer cells' evasion of immunosurveillance and hyperactivate the immune system.

Considering the mechanism of action of ICIs, the historical method of dose escalation until achieving the maximum tolerated dose (MTD)—as has been done for decades with cytotoxic chemotherapy—is not appropriate [2–4]. Anti-PD-1/PD-L1 ICIs saturate their targets and reach the plateau of the dose-response curve at much lower doses than their approved doses [2, 3]. Alternative dosing strategies can be developed based on pharmacokinetic and pharmacodynamic data, and in silico simulations can be a helpful method for hypothesis generation, and even potentially the approval of alternative dosage regimens [5–8].

Interventional pharmacoeconomics capitalises on new dosing strategies, whether lower doses, less frequent doses, reduced duration, or therapeutic substitution, to decrease cost and side effects while maintaining efficacy [9]. A variety of these dosing strategies are relevant to reducing ICI costs given that the Food and Drug Administration (FDA) dose approval process to date for ICIs has mostly been based on the traditional clinical trial methodology where the Phase I MTD becomes the recommended Phase II dose.

Prior reviews by Araujo et al., Jiang et al., and Peer et al. have outlined published and ongoing trials on ICI dosing regimen optimisation [2, 3, 10]. In this review, we outline more recent studies of ICI dosing (Table 1) and the interplay of dose optimisation and interventional pharmacoeconomics. We explore the notion that "less is more" with ICIs and that investigation of alternative dosing strategies may impact prescribers, patients, and payers.

RECENT STUDIES OF NOVEL ICI DOSING REGIMENS

Nivolumab

Nivolumab is currently approved by the FDA for 11 indications and by the European Medicines Agency (EMA) for 13 indications at doses of 240 mg every 2 weeks or 480 mg every 4 weeks when given as monotherapy or 1 mg/kg every 3 weeks when given in combination with ipilimumab (Table 2) [11, 12]. Despite the approval of these dosing regimens, the availability and effectiveness of nivolumab, as is the case with other ICIs, can be severely hampered by the high costs of treatment in resource-limited settings. However, a recent randomised study in India compared triple metronomic chemotherapy (oral methotrexate 9 mg/m^2 weekly, celecoxib 200 mg twice daily, and erlotinib 150 mg daily) with and without low-dose nivolumab 20 mg every 3 weeks for the treatment of recurrent or newly diagnosed advanced head and neck squamous cell carcinoma [13]. The arm with low-dose nivolumab had a 1-year overall survival (OS) of 43.4% compared to 16.3% in the control arm (hazard ratio [HR] 0.545, $p = 0.0036$) with no difference in grade 3 or above adverse events (46.1% vs 50%, $p = 0.7$). This important study provides proof of concept for the effectiveness of less than 10% of the standard nivolumab dose.

Retrospective, non-randomised data from Taiwan that compared the efficacy of nivolumab 20 and 100 mg every 2 weeks among patients with hepatocellular carcinoma (HCC), with the dose largely driven by patient financial resources, might suggest that a lower dose is acceptable [14]. Patients who received 20 mg every 2 weeks had a longer progression-free survival (PFS) than those who received 100 mg every 2 weeks (4.5 months vs 2.3 months, $p = 0.007$) [14].

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Table 1. Phase II and III low-dose ICI clinical trials, retrospective reviews, and pharmacokinetic simulations.

Study sponsor	Country	Phase	Year	Study type	Dose	Cancer type(s)	Outcomes	Clinical trial ID
Nivolumab								
Homi Bhabha National Institute [13]	India	III	2022	In vivo	20 mg q3wk	H&N SCC	Superior to chemotherapy without nivolumab	CTRI/2020/11/028953
Chang Gung Memorial Hospital [14]	Taiwan	-	2022	In vivo	20 mg q2wk vs 100 mg q2wk	HCC	Superior PFS for low-dose	N/A (retrospective)
Universitair Ziekenhuis Brussel [76]	Belgium	-	2022	In vivo	10 mg q2wk	Advanced cancer	50% SD/PR/CR	N/A (retrospective)
National Cancer Institute [6]	U.S.	-	2022	In silico	480 mg q4wk vs 240 mg q4wk vs 480 mg q8wk	Solid tumours	Maintained minimum effective concentration	N/A (in silico)
Universitair Ziekenhuis Brussel [77]	Belgium	II	2022	In vivo	Nivolumab 10 mg (plus ipilimumab 50 mg), then nivolumab 10 mg 2x/wk vs Nivolumab 10 mg 2x/wk then q1wk	Metastatic melanoma after resection	One year of adjuvant low-dose nivolumab recommended for further study	NCT02941744
Queen Mary Hospital [56]	China	-	2020	In vivo	Nivolumab 40 mg q2wk vs Pembrolizumab 100 mg q3wk	cHL	Both efficacious at low doses	N/A (retrospective)
Seoul National University Hospital [78]	Republic of Korea	-	2018	In vivo	20 mg q3wk or 100 mg q3wk vs 3 mg/kg q2wk	NSCLC	Equivalent	N/A (retrospective)
Bristol-Myers Squibb [16]	U.S. Canada Finland Italy	II	2015	In vivo	0.3 mg q3wk vs 2 mg/kg q3wk vs 10 mg/kg q3wk	Metastatic RCC	Equivalent	NCT01354431
Pembrolizumab								
The University of Jordan [20]	Jordan	-	2022	In vivo	100 mg q3wk vs 200 mg q3wk	NSCLC	Equivalent	N/A (retrospective)
National Cancer Institute [6]	U.S.	-	2022	In silico	200 mg q3wk vs 400 mg q6wk vs 200 mg q6wk	N/A	Maintained minimum effective concentration	N/A (in silico)
National University of Singapore [19]	Singapore	-	2021	In vivo	100 mg q3wk vs 200 mg q3wk	NSCLC	Equivalent	N/A (retrospective)
Atezolizumab								
National Cancer Institute [24]	U.S.	-	2023	In silico	1200 mg q3wk vs 1200 mg q6–9wk vs 1200 mg q12wk vs 840 mg q6wk vs 840 mg q8wk vs 840 mg q10wk vs 840 mg q12wk	N/A	840 mg q6wk maintained minimum serum concentration	N/A (in silico)

Table 1. continued

Study sponsor	Country	Phase	Year	Study type	Dose	Cancer type(s)	Outcomes	Clinical trial ID
Ipilimumab								
Bristol-Myers Squibb [79]	Italy	II	2022	In vivo	Temozolomide 15 mg/m^2 x5d q4wk followed by ipilimumab 1 mg/kg q8wk (plus nivolumab 480 mg q4wk)	MSS and MGMT-silenced CRC	Proof-of-concept	NCT03832621
Merck & Co [80]	U.S. Australia Canada France New Zealand	II	2021	In vivo	50 mg q6wk vs 100 mg q12wk (both with pembrolizumab 200 mg q3wk)	Stg III & IV melanoma	Equivalent response with lower G3+ TRAEs with 50 mg q6wk	NCT02089685
Bristol-Myers Squibb [81]	U.S. Australia Belgium Brazil Canada Czech Republic France Germany Hungary South Africa	II	2010	In vivo	10 mg/kg q3wk vs 3 mg/kg q3wk vs 0.3 mg/kg q3wk	Previously treated Stg III & IV melanoma	Dose-dependent efficacy	NCT00289640

U.S. United States, *q#wk* every # weeks, *H&N* head and neck, *SCC* squamous cell carcinoma, *HCC* hepatocellular carcinoma, *cHL* classical Hodgkin lymphoma, *NSCLC* non-small cell lung cancer, *RCC* renal cell carcinoma, *N/A* not applicable, *MSS* microsatellite stable, *MGMT* O^6-methylguanine-DNA methyltransferase, *Stg* stage, *PFS* progression-free survival, *SD* stable disease, *PR* partial response, *CR* complete response, *G3* grade 3, *TRAEs* treatment-related adverse events.

Recent manuscripts by Peer et al. in the United States (U.S.) and Malmberg et al. in the Netherlands explored alternative dosing regimens of nivolumab [6, 15]. Using population pharmacokinetic models, Peer et al. demonstrated that nivolumab 240 mg every 4 weeks and 480 mg every 8 weeks should maintain a putative minimum effective concentration (MEC, 1.5 µg/mL) in >95% of virtual patients [6]. The MEC was reverse-engineered on the basis of a randomised dose-ranging trial in metastatic renal cell carcinoma, which demonstrated equivalent efficacy of nivolumab 0.3 mg/kg, 2 mg/kg, and 10 mg/kg [6, 16]. This is the strongest evidence for the efficacy of lower doses of nivolumab. Using pharmacokinetic and pharmacodynamic data as well as the linear kinetics range of nivolumab, Malmberg et al. recommended weight-based dosing (3 mg/kg every 2 weeks, 4.5 mg/kg every 3 weeks, or 6 mg/kg every 4 weeks) that maxed out at the FDA-approved fixed doses (240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks).

Pembrolizumab

Pembrolizumab is currently FDA-approved for 19 indications at doses of 200 mg every 3 weeks, 400 mg every 6 weeks, or 2 mg/kg every 3 weeks and EMA-approved for 11 indications at the same doses (Table 2) [17, 18]. Several retrospective studies assess alternative pembrolizumab dosing in real-world settings. As previously reviewed [2], a single-centre retrospective study in Singapore demonstrated that pembrolizumab 100 mg every 3 weeks for advanced non-small cell lung cancer (NSCLC) had a similar median PFS (6.8 vs 4.2 months; HR 0.72, 95% CI 0.36–1.46, $p = 0.36$) and 9-month OS (85% vs 58%; HR 0.27, 95% CI 0.062–1.20, $p = 0.09$) as pembrolizumab 200 mg every 3 weeks [19]. A more recent retrospective study in Jordan similarly identified that pembrolizumab 100 mg versus 200 mg fixed doses every 3 weeks for NSCLC had equivalent median PFS (8 vs 8 months, $p = 0.73$) and median OS (17.02 vs 17.60 months, $p = 0.66$) between arms [20].

Atezolizumab

Atezolizumab is currently FDA-approved for 5 indications at doses of 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks and EMA-approved for 6 indications at the same doses (Table 2) [21, 22]. Goldstein and Ratain have previously described that the current dosing of atezolizumab achieves steady-state concentrations that far exceed the target effective concentration of 6 µg/mL and that atezolizumab should be dosed at 840 mg less frequently than every two weeks [23].

Alternative dosing strategies have also been proposed for atezolizumab based on in silico models by Chou and Hsu in Taiwan and by Peer et al. in the U.S. [5, 24]. A pharmacokinetic simulation study in Taiwan showed that doubling the dosing interval for each of the FDA-approved doses of atezolizumab would still maintain minimum steady-state concentrations presumed to be sufficient [5]. These findings were refuted by Genentech scientists in a letter to the editor supporting the current dosing strategy [25]. Peer et al.'s in silico study evaluated 1200 mg every 6, 7, 8, 9, and 12 weeks and 840 mg every 6, 8, 10, and 12 weeks and determined that the dosing interval could be tripled (840 mg every 6 weeks) and maintain a steady-state trough concentration of 6 µg/mL in at least 99% of virtual patients [24]. This will be studied in patients at the National Cancer Institute (NCI) by assessing two loading doses and then proceeding to the recommended extended-interval dosing [24].

Avelumab

Avelumab is currently FDA-approved and EMA-approved for 3 indications at a dose of 800 mg every 2 weeks (Table 2) [26, 27]. Peer et al. concluded in their review that further dosing optimisation might not be needed for avelumab given that the plateau of the exposure-response curve has likely not reached the currently approved dosage [10].

Table 2. United States and European weight-based and fixed doses of ICIs.

Weight-based dose	Fixed dose	Presumed patient weight for fixed dose
Pembrolizumab		
2 mg/kg every 3 weeks	200 mg every 3 weeks 400 mg every 6 weeks	100 kg
Atezolizumab		
15 mg/kg every 3 weeks	840 mg every 2 weeks 1200 mg every 3 weeks 1680 mg every 4 weeks	80 kg
Nivolumab		
3 mg/kg every 2 weeks	240 mg every 2 weeks 360 mg every 3 weeks 480 mg every 4 weeks	80 kg
Avelumab		
10 mg/kg every 2 weeks	800 mg every 2 weeks	80 kg
Cemiplimab		
3 mg/kg every 2 weeks	350 mg every 3 weeks	78 kg
Durvalumab		
10 mg/kg every 2 weeks	1500 mg every 3–4 weeks	75–100 kg
Tremelimumab		
4 mg/kg once	300 mg once	75 kg

Cemiplimab

Cemiplimab is currently FDA-approved for 3 indications at a dose of 350 mg every 3 weeks and EMA-approved for 4 indications at the same dose (Table 2) [28, 29]. This dosage is based on a population pharmacokinetic model evaluating patients with advanced malignancies and cutaneous squamous cell carcinoma who received weight-based doses (1, 3, or 10 mg/kg every 2 weeks or 3 mg/kg every 3 weeks) or fixed doses (200 mg every 2 weeks) [30]. This model ultimately compared 350 mg every 3 weeks to 3 mg/kg every 2 weeks and determined that 350 mg every 3 weeks should be further investigated. There are no Phase II or III low-dose studies of cemiplimab to date.

Durvalumab

Durvalumab is currently FDA-approved for 4 indications at dosing of 10 mg/kg every 2 weeks or 1500 mg every 3–4 weeks and EMA-approved for 2 indications at the same doses (Table 2) [31, 32]. Given that both durvalumab and atezolizumab are anti-PD-L1 agents and that atezolizumab binds differently to PD-L1 than durvalumab and likely has a wider range of effective doses than durvalumab with more approved indications, Peer et al. suggested that dose optimisation efforts should focus on atezolizumab rather than durvalumab [10].

Dostarlimab

Dostarlimab is currently FDA-approved for 2 indications at a dose of 500 mg every 3 weeks for four cycles then 1000 mg every 6 weeks and EMA-approved for 1 indication with the same dosing strategy [33, 34]. While there are no weight-based doses approved by the FDA, a pharmacokinetic dose-escalation Phase I trial indicated dose-proportional pharmacokinetics over the range of 1–10 mg/kg and pharmacokinetic values for 500 mg every 3 weeks that corresponded to those between 3 mg/kg and 10 mg/kg [35]. Clinical pharmacology review by the FDA identified no dose-response relationship for dostarlimab, and dostarlimab had almost 3 times the half maximal inhibitory concentration as pembrolizumab for human PD-L1 and PD-L2 [36, 37]. Given that pembrolizumab is showing promising clinical efficacy at a dosage of 100 mg every 3 weeks, it is possible that dostarlimab may be effective at a dosage of 300 mg every 3 weeks.

Ipilimumab

Ipilimumab is currently FDA-approved for 7 indications at doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg every 3 weeks or 1 mg/kg every 6 weeks and EMA-approved for 6 indications at dosing of 1 mg/kg or 3 mg/kg every 3 weeks or 1 mg/kg every 6 weeks [38, 39]. Ipilimumab, a CTLA-4 inhibitor, is the only ICI with clear dose-response and dose-toxicity relationships, and it is typically administered in combination with nivolumab [2, 3, 10]. Although the dose-response and dose-toxicity relationships are consistent when ipilimumab is given as monotherapy, when given in combination with a PD-1/PD-L1 inhibitor such as when treating melanoma, higher doses of ipilimumab are associated with higher toxicity without improvement in efficacy [40]. In the context of treating patients with microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer, CheckMate 142 suggests that extending ipilimumab to every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks may be an effective dosing strategy for high response with a relatively low rate of treatment-related adverse events [41–44]. Additionally, doses of ipilimumab 1 mg/kg every 6 weeks or every 12 weeks were explored in a Phase I trial of patients with lung cancer and demonstrated similar responses at these extended intervals in combination with nivolumab [45]. Finally, CheckMate 511 demonstrated lower treatment-related adverse events of ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg than ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg when treating patients with melanoma [46]. When ipilimumab is given in combination with nivolumab, further study could be done to explore dose extension or lower doses to reduce toxicity while maintaining efficacy.

Tremelimumab

Tremelimumab, also a CTLA-4 inhibitor, is currently FDA-approved for 2 indications in combination with durvalumab at a single dose of 300 mg or 75 mg every 3 weeks if 30 kg or higher or a single dose of 4 mg/kg or 1 mg/kg every 3 weeks if under 30 kg, and it is EMA-approved for 1 indication at a single dose of 300 mg in combination with durvalumab (Table 2) [47, 48]. The clinical pharmacology review by the FDA identified no dose-response relationship for tremelimumab [49]. While a Phase Ib study of

patients with locally advanced or metastatic NSCLC recommended durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg every 4 weeks for 6 doses followed by every 12 weeks for 3 doses [50], a Phase I/II study of patients with unresectable HCC recommended the approved dose of durvalumab 1500 mg every 4 weeks plus a single 300 mg dose of tremelimumab [51]. Phase III trials of patients with NSCLC are ongoing (NCT02453282, NCT02352948). Future trials could assess 1 mg/kg as a single dose rather than for four cycles.

PHARMACOECONOMICS OF ICIS

Financial toxicities associated with ICI use

It is projected that the overall global expenditure on ICIs will almost double from 2021 to 2026 (from over $24 billion to $46 billion) [15]. If cost-effectiveness is defined as a willingness to pay threshold of $100,000 per quality-adjusted life year (QALY), then only a few ICI indications were deemed cost-effective in a systematic review, largely driven by the high cost of ICIs [52]. While this commonly used willingness to pay threshold should likely be higher given inflation [53], many included studies demonstrated costs over $200,000 per QALY [52]. Another systematic review of ICIs for NSCLC indicated mixed results on the cost-effectiveness of pembrolizumab, atezolizumab, nivolumab, and durvalumab [54]. While cost-effectiveness analyses are not part of the drug approval process in the U.S., the high costs are considerations in countries with national health insurance plans, such as Australia and the United Kingdom, where risk-sharing agreements, financial caps, and price negotiations help keep the typically high costs of ICIs within budget [55]. Price can be an even larger barrier in low- and middle-income countries (LMICs), leading to practical real-world study designs based on affordability or randomised trials evaluating extremely low doses of ICIs [13, 56].

Weight-based dosing is an opportunity to somewhat reduce ICI costs [15, 57]. A single-centre retrospective review of 1110 ICI doses showed that in 94% of cases, these drugs were given as fixed doses of pembrolizumab 200 mg or nivolumab 240 mg [58]. If alternative dosing strategies and vial sharing are used, then costs could be lowered by 9–13% for nivolumab and 19–29% for pembrolizumab [15, 58]. It is noteworthy that weight-based dosing is often lower than fixed dosing, as in most fixed doses, patients with cancer are presumed to weigh between 75 and 100 kg (Table 2) [2]. Vial sizes of ICIs are conveniently manufactured to accommodate fixed doses, so a switch from fixed to weight-based dosing would increase cost savings if there is variability in vial sizes for a given ICI or if a cancer centre has higher patient volumes and allows vial sharing [2, 15, 58].

Properly designed cost-effectiveness analyses should incorporate adverse event frequency, costs, and effects on quality of life. For ICIs, this would include the diagnosis and treatment of immune-related adverse events (irAEs), sometimes also requiring expensive immunosuppressant monoclonal antibodies. One retrospective insurance claims analysis of patients on anti-PD-1/PD-L1 monotherapy versus anti-PD-1/PD-L1 plus anti-CTLA-4 combination therapy demonstrated high rates of irAEs (46% vs 67%) and irAE-related emergency department visit rates (16% vs 23%), as well as high irAE-related medical costs ($31,000 vs $163,000) [59].

Evidence for lower or less frequent doses of ICIs

ICI dosing can be optimised through lower doses, extended dosing intervals, and shorter overall treatment duration [60]. Many randomised trials are underway to evaluate ICI dose optimisation [60], but extended-interval dosing strategies for ICIs can also be simulated in silico to generate hypotheses regarding the minimum necessary dose to achieve therapeutic target concentrations [6, 10, 15]. These in silico studies can even lead to label changes, such as when the FDA approved pembrolizumab 400 mg every 6 weeks in April 2020 [61], and these approvals will likely continue in the post-marketing setting given recent industry guidance from the FDA on pharmacokinetic-based PD-1/PD-L1 ICI alternative dosing regimen approvals [8]. A retrospective review of pembrolizumab doses for NSCLC at Veterans Affairs (VA) centers nationally identified that by January 2021 (9 months after the April 2020 approval), only one-third of patients prescribed pembrolizumab were receiving extended-interval dosing (400 mg every 6 weeks) and that this adoption rate of extended-interval dosing plateaued through the end of the study (August 2021) [62]. Implementation science will be an important aspect of optimising ICI dosing in clinical practice.

Trials evaluating significantly lower doses of ICIs can also increase access globally to these effective but expensive therapies. The aforementioned study of nivolumab 20 mg for head and neck cancer in India demonstrated significantly improved OS using a nivolumab dose that is 91–95% cheaper than standard nivolumab dosing [13]. This novel trial used nivolumab at 6–7% of the usual dose (20 mg every 3 weeks instead of 3 mg/kg every 2 weeks or 360 mg every 3 weeks), which was estimated to reduce the cost of nivolumab (based on prices in India) from $3858 per month to $429 per month [63]. Given that nivolumab and pembrolizumab are roughly interchangeable [64], significantly lower doses of pembrolizumab than those currently studied are also likely to be clinically effective. Additionally, regimens with pembrolizumab at standard dosing could potentially be replaced by the extremely low dose of nivolumab studied in India of 20 mg every 3 weeks [13].

CURRENT CHALLENGES AND OPPORTUNITIES

Selection of drug doses

Population pharmacokinetic simulation studies permit the exploration of lower doses or longer dosing intervals without the need to conduct expensive clinical trials [10]. These simulation studies can generate hypotheses for randomised, near-equivalence clinical trials to potentially guide future FDA approvals. Additionally, real-world data can be helpful in evaluating these lower doses compared to the initially approved higher doses, such as with pembrolizumab 400 mg every 6 weeks [62]. The FDA's Oncology Center of Excellence (OCE) is helping incorporate dosage considerations into pre-approval trial design through the creation of Project Optimus in 2021 [65, 66]. The impact of dose optimisation on cost savings may depend on if optimisation occurs through pre-approval or post-marketing trials. The combination of accelerated approvals and the Inflation Reduction Act of 2022 could start to fix initial drug prices, so subsequent dose optimisation could lead to price reductions if doses are subsequently reduced [2]. The Senate Appropriations Committee specifically referenced Project Optimus in S. 4661 [67], and the modified omnibus version that passed (H.R. 2617) encourages the FDA to facilitate clinical trials that evaluate dosing and frequency to decrease cost and toxicity without affecting clinical efficacy [68]. Thus, post-marketing dose optimisation studies organised with the input of the OCE would be responsive to this U.S. congressional request. Strohbehn et al. propose a self-sustaining model for the U.S. government to fund post-marketing dose optimisation trials through partnerships between payers, the National Clinical Trials Network, and the OCE [69].

Funding for interventional pharmacoeconomics of ICIs

There is rife opportunity to employ interventional pharmacoeconomic principles to ICIs as previously suggested for abiraterone, ibrutinib, and trastuzumab [70]. Payers could be incentivized to fund interventional pharmacoeconomic trials through shared cost savings, such as self-funding cost-effectiveness trials of pembrolizumab in NSCLC (NCT04909684) or of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors in breast cancer (NCT03425838) [60, 71].

Additionally, the omnibus appropriations bill for 2023 encourages FDA prioritisation of dose optimisation trials [68], and partnerships between the Centers for Medicare & Medicaid Services and the FDA could generate self-funding interventional pharmacoeconomic trials [69].

Physician and patient education

To counter the conventional wisdom that more is better, an educational campaign is needed for physicians and patients alike that "less is more" [65, 72]. This could be through published literature like the *Archives of Internal Medicine*'s "Less is More" series or the *Journal of Hospital Medicine*'s "Things We Do For No Reason" (TWDFNR) series, campaigns like the American Board of Internal Medicine's Choosing Wisely initiative, or advertisements by health-related governmental agencies for the general public [72–75].

CONCLUSIONS

There are abundant opportunities to reduce the monthly dose of most ICIs, which would markedly reduce the cost of modern oncology care and potentially also reduce toxicity. Interventional pharmacoeconomics is an opportunity to truly advocate for patients and reduce both financial toxicity and irAEs. It is paramount that global regulatory agencies and public payers require dose optimisation clinical trials and that the results of these trials are implemented in clinical practice and reimbursement policies. This will subsequently improve ICI treatment outcomes and global access to these effective drugs.

DATA AVAILABILITY

Not applicable.

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AUTHOR CONTRIBUTIONS

AW performed the literature review and drafted the manuscript. DAG, KP, CJP, and WDF contributed to the review design and revised the manuscript. MJR conceived the review design and revised the manuscript. All authors approved of the final manuscript and are accountable for all aspects of the work.

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COMPETING INTERESTS

AW, KP, CJP and WDF declare no competing interests. DAG declares the following interests: institutional research funding (Merck, Bristol-Myers Squibb, and Jennsen); consulting fees (VIVIO Health); and stock ownership (VIVIO Health and TailorMed). MJR is co-founder, director and treasurer of the Optimal Cancer Care Alliance, is an inventor on pending patent applications for low-dose tocilizumab, and has testified as an expert witness on behalf of multiple generic companies regarding the optimal dosing of anticancer agents.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

ADDITIONAL INFORMATION

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