

Improving Accessibility and Affordability of Immune Checkpoint Inhibitors using Markedly Lower Doses at Reduced Frequency

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Abstract

Immune checkpoint inhibitors (ICIs), specifically agents blocking the programmed death-1 (PD-1) protein and its ligand (PD-L1), have revolutionized cancer therapy by offering durable responses and favorable toxicity profiles across a broad spectrum of malignancies. However, their widespread adoption at a global level remains severely limited by high costs, which particularly affect their accessibility and affordability in low-and-middle-income countries (LMICs). This review explores emerging strategies to optimize ICI dosing—specifically, low-dose (LD) and reduced-frequency dosing (RFD)—to enhance global accessibility and affordability, while maintaining clinical efficacy. We summarize pharmacokinetic and pharmacodynamic evidence supporting the biological efficacy of LD and RFD dosing strategies of ICIs. Emerging data from several clinical studies further validate these two strategies, demonstrating comparable outcomes to standard regimens. We also discuss the rationale for combining the LD and RFD approaches, which could significantly lower treatment costs, maintain clinical efficacy, enhance patient convenience, and enable the safe extension of immunotherapy over multiple years. We also introduce the AFFORD-IO (Attenuated Frequency and Reduced Dose of Immuno-Oncology treatment) trial, a first-of-its-kind study in sub-Saharan Africa, evaluating a novel combined LD plus RFD regimen of nivolumab in ICI-responsive cancers. Adoption of such a regimen could lead to marked reduction in the cost of ICI therapy and hence, transform cancer care delivery in both resource-constrained and resource-abundant settings, offering a powerful tool against the rapidly increasing global cancer burden.

Take Home Messages

1. Immune checkpoint inhibitors (ICIs) have transformed cancer care by offering effective and safer treatments for many types of cancer, but their high cost makes them inaccessible to most patients around the world.
2. Lower doses of ICIs and less frequent administration can still be effective, offering a promising way to make these treatments more affordable.
3. The AFFORD-IO clinical trial, which combines markedly lower doses with markedly less frequent administration of nivolumab, is being launched in Uganda, where ICIs are currently unavailable, and may lead to a 50-fold reduction in the costs of ICI and improve access in low-resource settings.

Introduction

The global burden of cancer continues to rise at an alarming rate. According to estimates from the International Agency for Research on Cancer (IARC), approximately 20 million new cancer cases and 9.7 million cancer-related deaths occurred worldwide in 2022; these figures are projected to escalate by 77% by the year 2050.¹ Majority of the global cancer burden is now concentrated in low- and middle-income countries (LMICs), which account for approximately 57% of all new cancer cases worldwide.² Cancer mortality rates in LMICs are higher compared to high-income countries (HICs) and continue to rise. For instance, the five-year survival rate for lung cancer in Japan is approximately 33%, whereas in India, it is only 4%.³ One of the primary drivers of this disparity is the absence of primary care and cancer screening programs in LMICs, leading to late-stage diagnoses when curative treatment options are limited. Access to essential cancer treatment modalities remains severely limited in many LMICs. For example, radiotherapy services are still unavailable in countries such as Ethiopia and Malawi.² Consequently, LMICs account for nearly 65% of global cancer-related deaths.^{2,3}

In addition to access issues, toxicities of standard therapeutic modalities, including chemotherapy, radiotherapy, and surgery, pose another formidable challenge in a resource-constrained environment.

Chemotherapy is linked to potentially life-threatening toxicities such as myelosuppression, febrile neutropenia, oral mucositis, and sepsis.⁴ Similarly, radiotherapy is known to cause complications such as radiation dermatitis, tissue fibrosis, vascular injury, infertility, and an elevated risk of secondary malignancies.^{5,6} These treatment-related toxicities often lead to a significant decline in patients' quality of life, compounding the burden imposed by the disease itself and dissuading patients from seeking treatment at all.⁷ All these issues are further compounded by affordability challenges. In India, over 75% of households affected by cancer experience catastrophic health expenditures, underscoring the financial toxicity imposed by cancer care in LMICs.⁸

Hence, there is a growing demand for innovative, targeted, and less toxic therapeutic strategies that can improve clinical outcomes while preserving quality of life in patients with cancer. One such candidate strategy is immunotherapy, specifically immune checkpoint inhibitors (ICIs) targeting inhibitory receptors such as programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) expressed on T cells.⁵ Under normal conditions, engagement of these inhibitory receptors with their ligands (e.g., PD-L1)—often expressed on healthy cells—attenuates T cell activation to maintain self-tolerance. However, many tumors upregulate these ligands to evade immune surveillance. ICIs block these interactions, restoring T cell effector function within the tumor microenvironment.⁹

ICIs represent a monumental advance in cancer treatment in the last decade and offer several therapeutic advantages over conventional systemic therapies, such as cytotoxic chemotherapy:

1. ICIs are relevant to the treatment of several cancer types, due to shared mechanisms of immune evasion across these malignancies. FDA-approved ICIs such as nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, cemiplimab, tremelimumab, retifanlimab, dostarlimab, toripalimab, ipilimumab, tislelizumab, cosibelimab and relatlimab are indicated for a broad spectrum of malignancies, including melanoma, non-melanoma skin cancers, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), renal cell carcinoma (RCC), urothelial carcinoma, Hodgkin lym-

phoma, head and neck squamous cell carcinoma (HNSCC), colorectal cancer, hepatocellular carcinoma (HCC), and gastric and esophageal cancers.¹⁰

2. Importantly, ICIs can induce durable responses, often persisting for years after treatment discontinuation.¹¹ Even a single dose of ICI has the potential to induce long-lasting benefit, explained by protective immunity from memory T-cells that surveil against cancer progression.
3. ICIs, specifically agents blocking the PD-1 pathway, are mostly well tolerated with an observed risk of serious (grade 3 or higher) treatment-related adverse events (AEs) being less than 20% in clinical trials. While immune-related adverse events (irAEs) do occur in some patients, these are generally reversible (with some exceptions, such as endocrinopathies and neuropathies) and typically manageable with readily available and inexpensive corticosteroids.¹² This risk profile compares favorably to conventional cytotoxic chemotherapy, which is commonly associated with mucositis, immunosuppression, and a risk of life-threatening neutropenic fever requiring major infrastructure for supportive care not readily available in LMICs.

Despite these favorable characteristics, the use of ICIs on a global scale is limited by their unaffordable high cost. For instance, the cost of annual treatment with standard doses of nivolumab (480 mg given every 4 weeks) is around \$210,000, posing substantial barriers to access.¹² Coverage remains under 5% in countries like Peru, with similar challenges across India and Eastern Europe.^{13–15} In a retrospective study conducted in India, only 1.5% of ICI-eligible cancer patients were actually able to receive it, due to financial constraints.¹⁶ In nations such as Uganda, Rwanda, and Kenya—regions burdened with ICI-responsive cancers—these therapies are often entirely unavailable.¹⁷ Less than 1% of immunotherapy clinical trials are conducted in the African continent due to various issues, including financial barriers, lack of standard healthcare facilities, and proper regulation to administer these medications.¹⁸ Even in HICs like the US, the national costs of cancer care are projected to increase by 34% to \$246 billion by 2030, highlighting the need for optimizing the costs of the existing and new cancer therapies.¹⁹

In this review, we discuss the data and rationale behind several ICI dose optimization strategies being investigated to reduce treatment costs and enhance global accessibility and affordability. A fundamental approach to reducing drug regimen costs is *dose minimization*. However, a key concern is ensuring that lower doses still maintain comparable clinical efficacy to standard dosing. Pharmacokinetic (PK) and pharmacodynamic (PD) assessments at reduced doses and frequency can provide valuable insights to support this strategy. We discuss below the existing and emerging correlative and clinical data behind several dose optimization strategies being pursued. We also introduce the **AFFORD-IO** (Attenuated Frequency and Reduced Dose Immunotherapy) trial, which aims to evaluate a combination of markedly low doses and a reduced-frequency administration schedule of nivolumab in eligible cancer patients in an LMIC setting.

Low-Dose (LD) Strategy

In the phase 1 study of nivolumab (previously known as MDX-1106), an anti-PD-1 monoclonal antibody, the PD-1 receptor occupancy (PD-1 RO) on peripheral blood T-cells was found to be dose-independent across a broad range of doses from 0.3 to 10 mg/kg. Peak PD-1 RO averaged 85% (range: 70–97%), while sustained PD-1 RO at ≥57 days averaged 72% (range: 59–81%). These findings indicate that even the lowest dose of 0.3 mg/kg elicited a PK/PD profile comparable to the highest dose.²⁰ These correlative data were also supported by observations of clinical responses and toxicity at lower doses. The dose choice of 3 mg/kg every 2 weeks (Q2W) for subsequent clinical development of nivolumab was somewhat arbitrary, as was the common practice in oncology trials at that time, but that dose and frequency ultimately became the "standard" dose for nivolumab across cancer types. Similarly, another phase 1 study of pembrolizumab, also an anti-PD-1 antibody, demonstrated antitumor activity across all tested doses (1, 3, and 10 mg/kg Q2W), with similar PD-1 RO across doses. Mechanism-based translational modeling suggested that effective clinical activity could be achieved at doses as low as 2 mg/kg Q3W.²¹ In a subsequent phase 2/3 trial comparing low (2 mg/kg) and high (10 mg/kg) doses of pembrolizumab Q3W, no significant difference in efficacy or toxicity outcomes was observed between the pembrolizumab arms.²²

Table 1: Studies Evaluating Lower Doses of Immune Checkpoint Inhibitors

Study identifier	Year of publication; place of conduct	Study design	Cancer studied (N)	Study Intervention	Key findings
Yoo SH et al ⁴¹	2018; South Korea	Retrospective	NSCLC(LD: 18; StD: 29)	LD (20 or 100 mg Q3 weeks) vs StD nivolumab	Similar ORR, PFS and OS in both groups
Chan et al ⁴²	2020; Hong Kong	Retrospective	Relapsed/refractory classical HL (LD: 17; no StD cohort)	LD pembrolizumab (100 mg Q3W) or nivolumab (40 mg Q2W)	ORR: 100%Median PFS: 35 months (pembrolizumab), 33 months (nivolumab)Median OS: Not reachedAll AEs (7 patients): Grade 1/2
Joris et al ⁴³	2022; Belgium	Retrospective case series	Advanced cancers (LD: 18; no StD cohort)	LD nivolumab (10 mg Q2W)	Disease control: 9 patients (CR: 2 patients; PR: 2 patients; SD: 5 patients)
Chen et al ⁴⁴	2022; Taiwan	Retrospective	Advanced HCC (LD: 78; no StD cohort)	LD nivolumab (20 mg or 100 mg Q2W)	ORR: 5.1%, DCR: 32%Median PFS: 2.4 months, median OS: 12.3 monthsAll AEs: Grade 1/2
Devabhaktuni et al ⁴⁵	2023; India	Retrospective	Recurrent/metastatic cervical cancer (LD: 20; no StD cohort)	LD nivolumab	ORR: 50% (CR: 50%, SD: 50%) Median PFS: 7.97 monthsAEs grade 1/2: 5 patients, AEs grade 3: 3 patients
Georgy et al ⁴⁶	2023; India	Retrospective	HNSCC (LD: 111; no StD cohort)	LD nivolumab (20 mg Q2W, 40 mg Q3W or 100 mg Q4W) + induction chemotherapy	ORR: 78.2% PFS at 1 year: 64.6%, OS at 1 year: 82.6%
Khadela et al ⁴⁷	2024; India	Phase IV superiority study	HNSCC (LD + TMC: 60; chemo only: 52; no StD cohort)	LD nivolumab (20 mg Q3W) + TMC (TMC-I arm) vs Paclitaxel and Carboplatin (P+C arm)	ORR: 68% in TMC-I vs 42% in P+C (P < .05)Median PFS: 13.3 months in TMC-I vs 7.4 months in P+C (P = .0054)Median OS: 17.1 months in TMC-I vs 10.4 months in P+C (P = .0054) No difference in ≥ grade 3 AEs
Meleamadathil et al ⁴⁸	2024; India	Retrospective	Metastatic solid tumors (LD: 18; no StD cohort)	LD nivolumab (40 mg)	SD: 16.7%, PD: 83.3%Early use of LD nivolumab

					associated with a statistically significant event-free survival vs when multiple chemotherapy options are exhausted
Tiwari et al ⁴⁹	2024; India	Retrospective	Advanced cancers (LD: 46 patients; no StD cohort)	LD nivolumab (40 mg Q4W)	ORR: 28.5%, DCR: 52%Median OS: 7.6 months
Bhatt et al ⁵⁰	2024; India	Retrospective	HNSCC (LD: 50; no StD cohort)	LD nivolumab (20 mg Q3W) + TMC	ORR: 64%, CBR: 80%
Dhanawat et al ⁵¹	2024; India	Retrospective	Advanced G/GE adenocarcinoma (LD: 35; StD: 41)	LD nivolumab (20 mg Q2W or 40 mg Q3W) vs StD nivolumab/ pembrolizumab	Median OS: 11 months in LD cohort vs 8.7 months in StD cohort; p = 0.44
Gandhi et al ⁵²	2024; India	Prospective	Malignant solid tumors (LD: 9; StD: 11)	LD nivolumab (40mg) vs StD nivolumab	ORR: 4/9 in LD cohort vs 5/11 in StD cohortSimilar PFS in both cohorts (P = 0.31)No significant difference in Cmax (P = 0.10) and AUC0-t (P = 0.33)No grade ≥ 3 toxicities in the LD cohort vs 28.57% in the StD cohort
Trikha et al ⁵³	2024; India	Retrospective	Microsatellite instable-high (MSI-H) advanced/metastatic CRC (LD: 30; StD: 35)	LD nivolumab (20 mg Q3W or 40 mg Q6W) vs StD nivolumab or StD pembrolizumab	ORR: 23.3% in LD cohort vs 34.2% in StD cohort12-month PFS: 90% in LD cohort vs 75.8% in StD cohortSimilar survival in LD and StD cohorts4 irAEs in LD cohort vs 1 irAE in SD cohort
Patel et al ⁵⁴	2024; India	Retrospective	All cancers (LD: 75; StD: 25)	LD nivolumab(40 mg Q2W or 80 mg Q4W) or LD pembrolizumab (1 mg/kg Q6W) or LD atezolizumab (1 mg/kg Q3W) vs StD ICIs	ORR did not differ statistically among different dosing groups
Kumar et al ⁵⁵	2024; India	Retrospective	All cancers in palliative setting (LD: 54; no StD cohort)	LD nivolumab (40 mg Q2W or Q3W)	CBR: 33.3%, PR: 18%, SD: 10%Median PFS: 2.5 months, median OS: 4.2 monthsAll grade toxicities:

					46% patients
Kate et al ⁵⁶	2024; India	Prospective	HNSCC (LD: 85; no StD cohort)	LD nivolumab (20 mg Q2W) + TMC	Median PFS: 4.3 months, median OS: 8.8 monthsNo grade ≥3 irAEs
Souza et al ⁵⁷	2024; Brazil	Retrospective	Solid tumors (LD: 49; StD: 22)	LD pembrolizumab (< 2mg/Kg Q3W) or LD nivolumab (< 3mg/Kg Q3W) or LD Atezolizumab (< 840 mg Q3W) or LD Durvalumab (< 10mg/Kg Q2W) vs StD ICIs	No significant differences in clinical ORR (38.1% in LD cohort vs 35.2% in StD cohort)Similar PFS and OS
Colunga-Pedraza et al ⁵⁸	2024; Mexico	Retrospective	Relapsed/refractory classical HL (LD: 23; no StD cohort)	LD nivolumab (40 mg, 100 mg, 140 mg Q2W) +- chemotherapy/brentuximab	ORR: 73%1-year PFS: 89.4%, 1-year OS: 94.4% AEs in 61% patients, no grade ≥3 AEs
Zhao et al ⁵⁹	2024; Taiwan	Retrospective	RCC (LD: 16; high-dose: 16)	LD nivolumab (<2.15 mg/kg) vs high-dose (≥ 2.15 mg/kg)	ORR: 50% in LD cohort vs 43.8% in high-dose cohort (P = 1.00)Similar PFS and OSSimilar irAE rates

AEs: Adverse events, AUC0-t: Area under the concentration vs. time curve from time zero to time t, CBR: Clinical benefit ratio, Cmax: Maximum (or peak) plasma concentration, CRC: Colorectal cancer, CR: Complete response, DCR: Disease control rate, G/GE: Gastric/gastroesophageal, HCC: Hepatocellular carcinoma, HL: Hodgkin's lymphoma, HNSCC: Head and neck squamous cell carcinoma, irAE: Immune-related adverse event, LD: Low-dose, NSCLC: Non-small cell lung cancer, ORR: Objective response rate, OS: Overall survival, PD: Progressive disease, PFS: Progression-free survival, PR: Partial response, RCC: Renal cell carcinoma, SD: Stable disease, StD: Standard-dose, TMC: Triple metronomic chemotherapy

In the last few years, several investigators have started using alternative doses and frequencies of commonly used anti-PD-1 agents in an attempt to reduce the economic and logistical footprint of the "standard" doses. As a representative example, a phase 3 study in India evaluated a markedly lower dose of nivolumab (20 mg/dose given Q3W) added to triple metronomic chemotherapy (TMC) in HNSCC showed a significant survival benefit (10.1 vs. 6.7 months; $p = 0.0052$), suggesting that LD PD-1 blockade is biologically effective in a clinical setting.²³ However, a major limitation of the study is that it used nivolumab in combination with chemotherapy and lacks rigorous data to support its use as a monotherapy to induce a reliable response in a patient with advanced cancer. A recent systematic review on low-dose PD-(L)1 strategies, which included data from five clinical trials and twenty-seven observational studies, concluded that low-dose anti-PD-(L)-1 monotherapy shows radio-

logical responses similar to standard-dose ICI trials, especially in lymphoma, lung, and kidney cancers.²⁴ A summary of other studies exploring LD strategies is presented in **Table 1**.

Reduced Frequency Dosing (RFD) Strategy

Another key strategy to reduce the cost of ICI therapy is to decrease dosing frequency. Similar to the dose level, the choice of frequency of administration appeared arbitrary during the early development of these agents. Initial FDA-approved regimens used pembrolizumab at 2 mg/kg (later, changed to a flat dose of 200 mg) Q3W and nivolumab at 3 mg/kg (later, changed to a flat dose of 240 mg) Q2W. Subsequently, the frequencies of administration were reduced by half, but at double doses for both pembrolizumab (400 mg Q6W) and nivolumab (480 mg Q4W), hence avoiding any reduction in the total drug costs (i.e.,

pharmaceutical profits).^{25,26} However, considerable evidence suggests that the therapeutic effects of anti-PD-1 agents may persist well beyond current dosing intervals. For example, in the phase 1 study of nivolumab, the PD-1 RO was sustained for up to 100 days.²⁰ This raises an important question of what the optimal dosing frequency is and what the additional value of frequent administration strategies at Q2-3W might be. Based on this rationale, several investigators have been exploring reduced-frequency dosing (RFD) strategies both in clinical use and in prospective trials.

Our group published a single-institution, retrospective study reporting long-term clinical outcomes of 23 patients with metastatic skin cancer who were treated with an RFD regimen of anti-PD-1 agents administered every 3 months. In this study, patients who had achieved disease control on standard schedules of ICI regimens were transitioned to every 3-month administration of anti-PD-1 agents. The 3-year progression-free survival rates of 73% in melanoma and 100% in MCC were comparable to historical outcomes and suggested no obvious detrimental effects of switching to the RFD regimen. Importantly, the RFD approach also resulted in major estimated savings of \$1.1 million in drug costs and 384 hours in patient clinic/travel time.²⁷

Several prospective trials are also currently evaluating RFD strategies. The MOIO study, a randomized phase III trial in France, compares standard ICI dosing to a 3-monthly regimen in patients with metastatic cancer who achieve PR or CR after six months of treatment.²⁸ The REFINE trial, a UK-based phase II multi-arm study, is enrolling patients with locally advanced RCC who have responded to initial nivolumab/ipilimumab. Participants are randomized to receive maintenance nivolumab at either the standard 480 mg every 4 weeks or an extended 480 mg every 8 weeks; the study will also explore additional tumor types and up to five dosing intervals.²⁹ Another multicenter phase II trial is assessing pembrolizumab administered Q12W versus Q3W in patients with advanced non-small cell lung cancer.³⁰

In addition to the obvious drug cost savings, another potential advantage of the RFD strategy is to allow an extension of the duration of therapy without exacerbating financial and time toxicity for the patients. This may be relevant as several retrospective analyses of real-world outcomes have

reported lower PFS rates following ICI discontinuation compared to historical outcomes with continued therapy, likely influenced by shorter treatment durations.^{31–35} In the retrospective study previously discussed (Tachiki et al), it was observed that most patients continued ICI treatment beyond the conventional 2 years (median 3.4 years).²⁷

A summary of other studies exploring reduced frequency dosing strategies is presented in **Table 2**.

Combining LD and RFD Strategies

The data presented above provide a tantalizing rationale for exploring a combination of the LD and RFD strategies in order to achieve a substantial reduction in ICI treatment costs to a level that can make it affordable to the LMICs. Our group is actively conducting rigorous correlative studies in patients receiving nivolumab at varying doses (40 mg, 240 mg, 480 mg) and at varying dosing intervals (ranging from every 4 to 12 weeks), collecting serial blood samples at multiple time points to assess pharmacodynamic and pharmacokinetic parameters.³⁶ The preliminary findings (presented in a poster form at the 2024 Annual SITC meeting) demonstrated that PD-1 receptor occupancy remained sustained for up to 12 weeks following a single administration of nivolumab. Nivolumab administered at a 480 mg dose is associated with 55.1% PD-1 receptor occupancy (PD-1 RO) at 4 weeks and 39.7% at 12 weeks post-infusion. Even the lower 40 mg dose maintained substantial receptor engagement, with 41.7% PD-RO at 4 weeks and 33.7% at 12 weeks. These results support two key conclusions:

1. The pharmacodynamic characteristics of 40 mg nivolumab are comparable to the much higher standard doses of 240 or 480 mg.
2. The sustenance of receptor occupancy over a 12-week period suggests that the standard 4-week dosing interval may be unnecessarily frequent. Extending the dosing interval up to 12 weeks could potentially preserve efficacy while reducing drug exposure and treatment cost.

These conclusions are further corroborated by pharmacokinetic data, which showed that serum nivolumab concentrations remained above the minimum effective concentration (MEC) of 1.5 µg/mL for up to 12 weeks following a 40 mg dose, and for over 8 months following a 240 mg dose. This obser-

Table 2: Studies Evaluating Reduced Frequency Immune Checkpoint Inhibitor Dosing Strategies

Study identifier	Year of publication; place of conduct	Study design	Cancer studied (N)	Study Intervention	Key findings
Peer et al ⁶⁰	2021; USA	In silico pharmacokinetic simulation analysis	Randomly generated virtual patients (RFD: 1000; no StD cohort)	RFD nivolumab (240 mg Q4W, 480 mg Q8W) or pembrolizumab (200 mg Q6W)	>95% of patients maintained MEC ($\geq 1.5 \mu\text{g/mL}$)
Sehgal et al ⁶¹	2021; USA	Retrospective cohort	Advanced NSCLC (RFD: 27; StD: 65)	RFD pembrolizumab (200 mg for ≥ 2 cycles at intervals > 3 weeks + 3 days) vs StD dosing	No significant difference in OS or PFS
Hijmering-Kappelle et al ⁶²	2022; Netherlands	Retrospective	Stage III/IV NSCLC (RFD: 117; StD: 88)	RFD pembrolizumab (400 mg Q6W) or RFD nivolumab (480 mg Q4W) or RFD durvalumab (1500 mg Q4W) vs StD ICI	Better PFS and OS in RFD nivolumab cohort vs StD cohort Similar PFS and OS in RFD pembrolizumab and RFD durvalumab cohorts vs StD cohort Grade ≥ 3 AEs: 8.9% in RFD cohort vs 17.0% in StD cohort, $P = 0.42$
Cantini et al ⁶³	2023; multicenter	Retrospective cohort	Solid tumors (RFD: 812; StD: 550)	RFD pembrolizumab (400 mg Q6W) or RFD nivolumab (480 mg Q4W) vs StD ICIs	RFD associated with a lower probability of any grade irAEs (adjusted odds ratio [aOR] = 0.83) vs StD No difference for grade ≥ 3 irAEs Patients with irAEs during RFD had improved overall survival (HR = 0.53) vs StD
Colard-Thomas et al ⁶⁴	2023; France	Retrospective	All eligible cancers (RFD: 256; StD: 430)	RFD nivolumab (480 mg Q4W) or RFD pembrolizumab (400 mg Q6W) or RFD durvalumab (1500 mg Q4W)	Similar risk of grade ≥ 3 irAEs (adjusted HR = 1.40) in RFD and StD cohorts Increased risk of any-grade irAEs in RFD cohort (adjusted HR 1.46) vs StD cohort
Ito et al ⁶⁵	2023; Japan	Retrospective	Unresectable/high risk melanoma (RFD: 21; StD: 50)	RFD nivolumab (480 mg Q4W) or RFD	Similar probability of irAE occurrence in RFD vs StD

				pembrolizumab (400 mg Q6W) vs StD ICIs	cohortsGrade ≥ 3 irAEs occurred in only two StD patients
Rischin et al ⁶⁶	2024: multicenter	Open label, single arm phase II trial	CSSC (RFD: 63; no StD cohort)	RFD cemiplimab (600 mg Q4W)	ORR: 62%, DCR: 78%, CR: 22%, PR: 40%PFS at 12 months: 65%, OS at 12 months: 73%irAEs in 76% patients, grade ≥ 3 irAEs in 16%

AE: Adverse event, CR: Complete response, CSSC: Cutaneous squamous cell carcinoma, DCR: Disease control rate, HR: Hazard ratio, irAE: Immune-related adverse event, MEC: Minimum effective concentration, NSCLC: Non-small cell lung cancer, ORR: Objective response rate, OS: Overall survival, PFS: Progression-free survival, PR: Partial response, RFD: Reduced-frequency dosing, StD: Standard dosing

vation suggests possible advantages of the LD-RFD approaches in mitigating the toxicity of ICIs. While preserved PD-1 receptor occupancy with the LD approach argues for a similar incidence of irAEs, the less prolonged serum concentration with the LD approach may facilitate easier control/reversal of irAEs when these occur. This potential benefit will need to be investigated in future prospective trials.

Together, these findings provide a strong pharmacological basis for reevaluating current dosing amounts and frequency. A low-dose, reduced-frequency regimen could yield substantial cost and time savings. As shown in **Figure 1**, the drug acquisition costs of the standard dosing nivolumab regimen (480 mg Q4W) is approximately \$210,000 per year, whereas the LD-RFD regimen (40 mg q12W) would reduce annual acquisition costs to around \$6500—a nearly 33-fold decrease.³⁷ Additionally, patient time commitment would be significantly reduced. These data have led us to propose a prospective clinical trial to evaluate the efficacy and safety of this combined approach.



Figure 1: Cost/year analysis of standard dose/schedule versus low-dose/reduced-frequency administration of immune checkpoint inhibitors (ICI), specifically nivolumab. (NOTE: Costs represent only the drug acquisition costs, not the cost of administration and supportive care.)

The AFFORD-IO (Attenuated Frequency and Reduced Dose of Immunotherapy) Trial

This first-in-kind trial would evaluate the combined low-dose reduced-frequency approach to nivolumab administration in cancers responsive to ICIs, including lung, cervical, renal, urothelial, triple-negative breast, skin cancers, and Kaposi’s sarcoma. Conducted in collaboration with the Uganda Cancer Institute (UCI), this study would be the first prospective ICI trial in sub-Saharan Africa, where ICIs are currently unavailable. Eligible patients would receive nivolumab at 40 mg Q12W, compared to the standard 480 mg Q4W. The trial would assess the safety and efficacy of this regimen. Positive outcomes could substantially reduce treatment costs, enabling broader adoption of ICIs in low- and middle-income countries (LMICs) and increasing affordability for self-paying patients as

well. The study could also provide evidence supporting extended ICI therapy duration and would generate safety data in populations often excluded from trials, including those with latent tuberculosis [up to 49% prevalence³⁸] and well-controlled HIV [5.8% prevalence³⁹] in Uganda. Given the high prevalence of virus-associated cancers such as Kaposi's sarcoma, which are highly responsive to ICIs,⁴⁰ the UCI setting would provide a good proof-of-concept for this dosing strategy. It would also generate practice-informing evidence on the clinical effectiveness of this dosing strategy across a diverse spectrum of tumor types and biological profiles.

Conclusion

Immune checkpoint inhibitors hold significant promise for the treatment and potential cure of advanced cancers. However, the unaffordable high costs render ICIs inaccessible to most cancer patients on a global scale. Emerging correlative and clinical trials data suggest biological and clinical efficacy of ICI at markedly lower doses and at reduced frequency of administration, offering opportunities for substantial reduction in treatment costs. It is important to acknowledge that much of the currently available evidence is derived from retrospective analyses, which inherently carry limitations such as selection bias and confounding factors. Particularly, patients who transitioned to low-dose or reduced-frequency approaches may represent a subset with favorable disease biology or prior response to standard-dose ICI therapy. However, such approaches could immediately expand global accessibility, particularly benefiting patients from LMICs, underinsured patients, and even those in the rural areas of the developed world with relatively limited or no access to ICIs. Reduced treatment frequency would also alleviate time toxicity for patients and ease the burden on healthcare delivery systems. The cost-effectiveness of this approach could facilitate easier incorporation of ICIs in clinical trials and lead to further innovations in immuno-oncology.

Conflict(s) of Interest

HK declares no conflicts of interests.

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All authors (HK, LT, SB) approved the final version of the manuscript and agree to be accountable for all aspects of the work, in accordance with the International Committee of Medical Journal Editors criteria.

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