De-Escalation Strategies With Immune Checkpoint Blockers in Non–Small Cell Lung Cancer: Do We Already Have Enough Evidence?

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DOI https://doi.org/10.1200/JCO-24-02347

ABSTRACT

Immune checkpoint blockers (ICBs) have revolutionized the treatment of non–small cell lung cancer (NSCLC). Currently, one-dose-fits-all maximalist regimens have been considered the standard of care, with ICBs administered at flat doses regardless of patients' weight. Treatment duration with ICBs is often arbitrary across stages, ranging from a fixed time point to until disease progression or unacceptable toxicity. However, the pharmacokinetic and pharmacodynamic properties of ICBs differ significantly from those of traditional cytotoxic drugs and the approved and selected doses on the basis of the maximum tolerated dose are often overestimated as there is limited evidence supporting a direct relationship between therapeutic intensity and outcomes. This can lead to overtreatment of patients, resulting in an increased risk of toxicity without enhanced efficacy. In addition, the use of these drugs is associated with significant costs that burden the global health care system and exacerbate disparities in access to care. De-escalating treatment by reducing the dose, duration, and frequency of administration of ICBs could optimize treatment efficacy, reduce toxicities, improve patients' quality of life, and even decrease costs. Ultimately, de-escalation strategies may help to reduce treatment inequalities and to improve drug access worldwide. The aim of this review is to summarize and discuss the main issues and challenges regarding the de-escalation of ICBs in patients with NSCLC, focusing on dose-intensity reduction and treatment duration selection. Moreover, we assess the economic impact of implementing de-escalation approaches.

Accepted November 27, 2024
Published January 21, 2025

J Clin Oncol 43:1148-1156

INTRODUCTION

In the current therapeutic landscape of non–small cell lung cancer (NSCLC), novel treatments, including immune checkpoint blockers (ICBs), have remarkably improved patients' outcomes.[1,2] In some cases, approvals have been based on maximalist approaches regarding dose or schedule, following the paradigm used for cytotoxic agents, where increasing the dose often enhances efficacy. However, considerable uncertainty exists whether this is optimal for ICBs as evidence linking therapeutic intensity to improved outcomes is limited. In addition, it is unclear whether a one-dose-fits-all strategy truly benefits all patients with NSCLC.

Personalizing dosing approaches—by tailoring doses and de-escalating treatment as needed—could help to reduce toxicity associated with unnecessary overtreatment. This approach may not only improve quality of life (QoL) but also lessen the economic burden. NSCLC management and treatment impose the highest economic cost among all cancer types worldwide, largely because of the expenses in drug costs, particularly in high-income countries.[3] Regimens involving ICBs have annual costs reaching hundreds of thousands of dollars per patient.[4] In fact, ICBs had the most significant impact on the worldwide cancer budget in 2022, accounting for nearly 50% of lung cancer treatment expenditure.[5] This consideration is becoming even more important because of the increasing number of newly diagnosed patients with NSCLC eligible for treatment. Furthermore, as new indications of ICBs are approved across all disease stages, more patients are receiving these drugs. While these treatments improve survival, there is a growing risk of prolonged overtreatment, significantly escalating annual health care expenditure and exacerbating inequalities in drug access globally. Therefore, an adaptive de-escalation treatment approach would also help to mitigate this inequality gap.

In this review, we summarize and discuss the key issues and challenges related to the de-escalation of ICBs in patients with NSCLC, focusing on dose-intensity reduction, treatment duration optimization, and dose scheduling. Moreover, we assess the economic impact of de-escalation and present currently ongoing clinical trials exploring de-escalation approaches in NSCLC.

ICBs: DRUG DEVELOPMENT AND RATIONALE FOR DE-ESCALATION

While the maximum tolerated dose (MTD) identification algorithm has traditionally been a cornerstone in the development of cytotoxic chemotherapies, this paradigm is less applicable for many antibodies, including ICBs. This is primarily because of their distinct mechanism of action, which involves unleashing the immune system to target and destroy cancer cells, rather than directly killing the cells themselves.[6]

Several studies suggest that current immunotherapy regimens, particularly those involving anti–PD-1 blockers, may lead to overtreatment. Early-phase studies with nivolumab and pembrolizumab (both anti–PD-1 blockers) failed to establish an MTD for these agents, indicating a lack of a clear dose–response relationship across various tumor types, including NSCLC.[7-12] In fact, for most ICBs (except for anti–cytotoxic T-cell lymphocyte-4 agents such as ipilimumab), the dose-response and exposure-response curves show a plateau, suggesting that increasing doses beyond a certain threshold does not improve efficacy.[8,13,14] Similarly, the efficacy of ICBs is achieved when the targeted receptor is saturated and blocked,[15] with T cells being the primary targets of these therapies. Typically, 20%-40% of peripheral blood T cells express the PD-1 receptor, and activation of these T-cells requires that 70%-75% of PD-1 receptors are occupied. Data from phase I trials with anti–PD-1 agents also indicated that ICBs can have a half-life of up to 20 days. Pharmacodynamic studies have shown that a sustained mean occupancy of 70% of PD-1 molecules on circulating T cells can be maintained for over 2 months after a single infusion of anti–PD-1, regardless of the dose administered,[7,8,16,17] and can be achieved even with low doses of anti–PD-1 therapy (0.3 mg/kg of nivolumab or 1 mg/kg of pembrolizumab administered once every 3 weeks), highlighting the high avidity of these clinical antibodies.[17,18] The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved nivolumab at 3 mg/kg once every 2 weeks as the pharmaceutical company's recommended dose for all tumor types as it resulted in higher objective response rates in patients with NSCLC when compared with 1 mg/kg and 10 mg/kg doses once every 2 weeks.[19] However, these findings might not be accurate because of the sample size of patients with NSCLC included in the phase I/II trial (n = 129 of 306). Similarly, pembrolizumab at 2 mg/kg once every 3 weeks was approved as the licensed dose by health authorities although in the phase I KEYNOTE-001 trial, saturation of ex vivo target engagement in blood began at ≥1 mg/kg once every 3 weeks.[18]

Although the initially approved doses of anti–PD-1 therapies were based on patients' weight because of the perceived impact of body size in pharmacokinetic variability of monoclonal antibodies, flat doses of ICBs were later accepted, such as nivolumab 240 mg once every 2 weeks[20] and pembrolizumab 200 mg once every 3 weeks[21] (numerically equivalent to 2 mg/kg dose of pembrolizumab once every 3 weeks for patients with a weight of 100 kg) because of an easier preparation. As the median weight of a healthy population is approximately 75-80 kg,[22,23] and even less in patients with cancer, flat dosing of ICBs may lead to overtreatment with a substantial impact on health care costs.[24] As an example, at the French national level in 2017, switching to a fixed dose regimen of anti–PD-1 correlated with an increase in the estimated annual budget of 55 million euros.[24]

The final step, after the acceptance of flat-dose ICBs, involved doubling the dose when extending the infusion interval, a practice now approved by health authorities. This adjustment was supported by models indicating, for example, that 400 mg of pembrolizumab once every 6 weeks is comparable with 200 mg once every 3 weeks[25] or nivolumab 480 mg once every 4 weeks mirrors the biweekly dose of 240 mg administered once every 2 weeks.[26] For atezolizumab (anti–PD-L1), the MTD has not been identified[13] and its half-life permits dosing at once every 4-week intervals, but flat doses of 840 mg once every 2 weeks, 1,200 mg once every 3 weeks, and 1,680 mg once every 4 weeks have been approved for NSCLC. Altogether, flat-dose regimens are now preferred because of similar efficacy and potentially reduced waste of drug vials.[28]

Currently, in NSCLC, ICBs either as monotherapy or in combination are being approved across all stages of the disease on the basis of overall survival (OS) improvement.[29-34] Most of these pivotal trials in NSCLC have used a flat-dose approach, with an arbitrary duration of treatment.[35-37] Given the long half-life of ICBs, the persistence of immune system activation even after their discontinuation, and the lack of a clear correlation between extended treatment duration and prolonged survival,[38,39] de-escalation strategies for ICBs should be explored (Fig 1).

ICBs DE-ESCALATION: AVAILABLE EVIDENCE AND ONGOING TRIALS

Treatment Dose

In patients with pretreated head and neck cancer, a flat dose of nivolumab (240 mg once every 2 weeks) significantly improved OS compared with standard therapy (hazard ratio [HR], 0.70 [97.73% CI, 0.51 to 0.96]; $P = .01$), with the 1-year OS of 36% and 17%, respectively.[40] Although these findings were clinically meaningful, a recent phase III clinical trial conducted in India with the same type of patient population (N = 151) demonstrated the feasibility of lower doses of ICBs in this setting. This trial randomly assigned patients to receive metronomic chemotherapy with or without low-dose nivolumab (20 mg once every 3 weeks), on the basis of the effective dose of 0.3 mg/kg and an assumed standard weight of 70 kg.[41] The

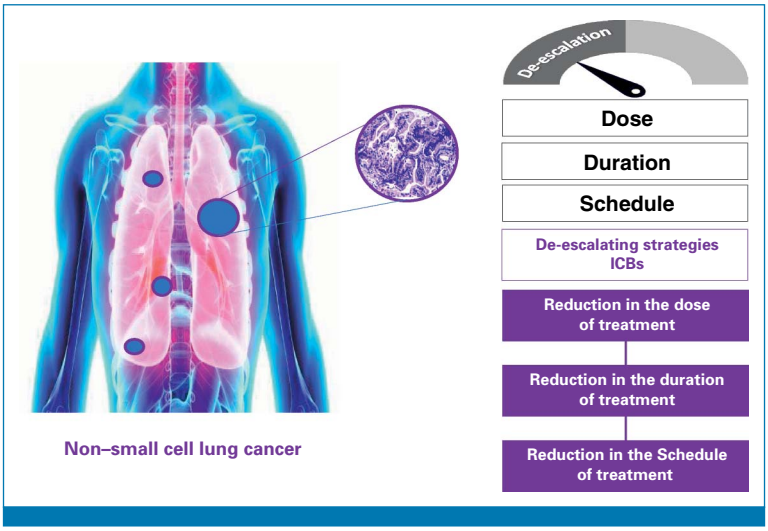

FIG 1. Therapeutic strategies for de-escalating treatment with ICBs. ICBs, immune checkpoint blockers.

experimental arm significantly improved OS compared with metronomic chemotherapy alone (HR, 0.545 [95% CI, 0.362 to 0.820]; $P = .0036$; with 1-year OS, 43.4% *v* 16.3%; HR, 0.545, $P = .0036$).[41] Despite the indirect comparisons, the twelve-fold lower dose of nivolumab suggests similar ranges of benefits to those reported in the pivotal phase III study, providing proof of concept for the efficacy of low doses of nivolumab and supporting the further exploration of this strategy in other tumor types. However, given the variation in treatment response to ICB among different solid malignancies,[42] caution is warranted, particularly for tumors in which the benefit of ICB appears to be more limited, and specific data for each histology should be addressed. In advanced NSCLC, data on the activity of low ICB doses come from retrospective cohorts (Table 1). Despite potential limitations, such as the retrospective nature and possible imbalances in the proportion of tumors with high PD-L1 expression, these data suggest that in patients with NSCLC, efficacy of lower doses of ICBs is comparable with the outcomes reported with standard doses. However, prospective, multicenter trials with a homogenous population balanced according to PD-L1 expression are mandatory. In this context, the ongoing Dutch phase III noninferiority DEDICATION-1 trial (ClinicalTrials.gov identifier: NCT04909684) compares lower dosing regimens of ICBs with the standard-of-care (SoC) dosing regimens in patients with advanced NSCLC eligible for pembrolizumab-containing therapy. The SoC dosing regimen includes pembrolizumab 400 mg once every 6 weeks or 200 mg once every 3 weeks and 150 mg once every 3 weeks (the latter dose is in accordance with the Dutch Society for Medical Oncology recommendations).[49] The lower-dose regimens are pembrolizumab 300 mg once every 6 weeks and 100 mg once every 3 weeks. Results of the

TABLE 1. Trials Exploring Lower Doses of Immune Checkpoint Blockers in Advanced Non–Small Cell Lung Cancer

Author	Type of Study	No.	Line of Treatment	Schedule	PFS, Months *P*	OS, Months *P*
Low et al[43]	Retrospective	114	Pembrolizumab first or second	100 mg once every 3 weeks *v* 200 mg once every 3 weeks	6.8 *v* 4.2 .16	14.3 *v* 19.8 .86
Abbasi et al[44]	Retrospective	88	Pembrolizumab first line	200 mg once every 3 weeks *v* 100 mg once every 3 weeks	8.0 *v* 8.0 .73	17.6 *v* 17.0 .66
Chang et al[45]	Retrospective	242	Pembrolizumab first or subsequent	≥2 mg/kg *v* <2 mg/kg	—	19.3 *v*. 14.3 .15
To et al[46]	Retrospective	64	Pembrolizumab first or subsequent	200 mg once every 3 weeks *v* 100 mg or 2 mg/kg once every 3 weeks	4.5 *v*. 6.1 .046	NR *v* 22.7 .340
Yoo et al[47]	Retrospective	47	Nivolumab first or subsequent	20 or 100 mg once every 3 weeks *v* 3 mg/kg once every 2 weeks	3.0 *v* 1.0 .242	12.5 *v* 8.2 .305
van den Heuvel[48]	Prospective	256	Pembrolizumab first line	400 mg once every 6 weeks or 150-200 mg once every 3 weeks *v* 300 mg once every 6 weeks or 100 mg once every 3 weeks	6.9 *v* 7.6	17.0 *v* 13.9

Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival.

first interim analysis were encouraging, with no negative signal for the lower dose (Table 1). Of note, the DEDICATION-1 trial has been designed to also serve as a platform for extensive biomarker research to improve personalization of pembrolizumab treatment.[50]

Another approach to reduce ICB doses is to consider a personalized weight-based strategy. As many drugs are distributed in single-use vials and weight-based dosing may not use the entire vial,[51] a weight-based dosing approach is often combined with dose rounding to minimize waste. A recent retrospective Dutch study investigated an alternative dosing of first-line pembrolizumab (100/150/200 mg once every 3 weeks or 200/300/400 mg once every 6 weeks for ≤65 kg, 65-90 kg, and ≥90 kg, respectively, for each dose once every 3 weeks or once every 6 weeks), administered to 604 patients with advanced NSCLC as a single agent or in combination therapy. Compared with SoC dosing (200 mg once every 3 weeks or 400 mg once every 6 weeks, n =1,362), alternative dosing was noninferior for OS (15.2 *v* 18.1 months; HR, 0.83 [95% CI, 0.69 to 1.003]). In addition, the median daily dose in the weight-based group was 22.0% lower than that in the standard dosing group, resulting in a more cost-effective strategy.[52]

On the basis of real-world data, hybrid-dosing regimens for both pembrolizumab (as described above) and nivolumab (3 mg/kg once every 2 weeks [maximum 240 mg], 4.5 mg/kg once every 3 weeks [maximum 360 mg], and 6 mg/kg once every 4 weeks [maximum 480 mg]) reported estimated savings of 8%-14% for nivolumab and 16%-26% for pembrolizumab.[53] More recently, a simulation analysis using patient-level data from the Veterans Health Administration demonstrated that combining weight-based dosing, dose rounding (if the weight-based dose is within 10% of the nearest single-use vial), and pharmacy-level vial sharing would generate an expected annual health system savings of $74 million in US dollars.[54] Similarly, another study demonstrated that dosing regimens on the basis of weight bands and the use of full vials to minimize drug wastage can reduce costs by up to 28%, while maintaining equivalent drug exposure.[55] This supports the implementation of these alternative regimens in clinical practice.

The dosage of ICBs is even more critical in low- and middle-income countries (LMICs) as the cost of these drugs reduces the number of patients who can access them. Recommendations for prescribing ICBs in melanoma on the basis of patient weight may reduce treatment costs by up to 50%, but it is unlikely to significantly improve access for patients in LMICs. Therefore, on the basis of data from phase I trials, off-label dosing of ICBs has been suggested for these countries (nivolumab 0.6 mg/kg once every 4 weeks, pembrolizumab 1 mg/kg once every 6 weeks; atezolizumab 2 mg/kg once every 6 weeks). This approach may reduce up to 90% the cost of treatment, increasing the number of patients who might have access to ICBs.[56]

Dose Interval

Although some mathematical models have supported doubling the dose when doubling the infusion interval, other models did not support this.[25,26,57] Therefore, another approach for de-escalating ICBs is to extend the time interval between infusions without doubling the dose. Most trials evaluating this concept only enroll patients without disease progression after three or 6 months of treatment with an ICB given at the regular infusion interval, suggesting that this strategy is mainly tested in the subgroup of patients in which benefit of ICB is more likely. The ongoing phase III PULSE trial (ClinicalTrials.gov identifier: NCT05692999) is a noninferiority trial for OS, testing maintenance treatment with pemetrexed plus two doses of pembrolizumab (200 mg once every 3 weeks *v* 200 mg once every 6 weeks) in patients with advanced nonsquamous NSCLC without progression after induction treatment with four cycles of chemoimmunotherapy.[58] The study also assesses the toxicity, the pharmacokinetic parameters of pembrolizumab, target saturation on circulating lymphocytes, the QoL, and the economic impact of increasing the interval between infusions.[58] Similarly, the ongoing REFINE-lung phase III trial (ClinicalTrials.gov identifier: NCT05085028) tests the safety and efficacy of extended interval of pembrolizumab (pembrolizumab 400 mg once every 9, 12, 15, 18 weeks) in patients with advanced NSCLC without progression after 6 months of standard first-line treatment.[59] Similarly, a phase II trial (ClinicalTrials.gov identifier: NCT04032418) is evaluating pembrolizumab 200 mg once every 3 weeks versus pembrolizumab 200 mg once every 12 weeks in patients with advanced NSCLC without disease progression after at least 6 months of pembrolizumab monotherapy. The primary end point is 1-year progression-free survival (PFS) rate. Finally, another trial from the University of Chicago (ClinicalTrials.gov identifier: NCT04295863) compares dose intervals of nivolumab or pembrolizumab in locally advanced or metastatic cancers, but in contrast to the other trials, in this trial random assignment occurs up front.

Comparison of several extended interval regimens showed that the predicted efficacy and safety of atezolizumab 1,680 mg once every 8 weeks/1,200 mg once every 6 weeks were not inferior to those of the standard regimen (1,200 mg every 3 weeks).[60] Recently, subcutaneous formulation of atezolizumab 1,875 mg once every 3 weeks also received approval from the EMA,[61] and it is currently under assessment by the FDA. However, on the basis of the half-life of 27 days and steady-state concentrations reached after 6-9 weeks,[62] alternative de-escalation schedules have been developed for subcutaneous administration. Extending the approved 3-week dosing interval of atezolizumab 1,875 mg once every 5 weeks for patients <50 kg and once every 4 weeks for patients weighing 50-65 kg resulted in equivalent exposure and maximum dose reduction, with the predicted 7% and 12% cost reduction. Similarly, a every 6-

week dosing regimen maintains efficacy, reducing costs by 50%.[63]

Altogether, these data support that de-escalating schedules with anti–PD-(L)1 is feasible and reduces costs. Increasing dose intervals could also reduce the frequency of hospital visits, leading to less disruption in patients' daily lives and minimizing their physical and logistical burdens. Indeed, for hospitals, it could help optimize resource allocation by reducing the demand for infusion chairs, nursing and support personnel, pharmacy's workload, and consumables.

Duration of Treatment

In NSCLC, the duration of ICB treatment arbitrarily varies across different disease stages: from 1 year in the adjuvant/consolidation setting to up to 2 years or until disease progression in the metastatic setting. However, there is no strong evidence supporting that prolonged treatment duration correlates with improved survival.[38,39]

In the metastatic setting, the perception that prolonged treatment may improve outcomes stems from an exploratory analysis of the phase III CheckMate 153 trial. The primary end point was to assess in advanced NSCLC the safety of nivolumab (3 mg/kg once every 2 weeks) in pretreated patients with advanced NSCLC who were elderly or had poor performance status. An amendment introduced an exploratory analysis comparing a fixed 1-year duration of nivolumab versus continuous therapy. Of the 1,458 patients initially enrolled, 252 were randomly assigned to continuous (n = 127) or 1-year fixed duration (n = 125) treatment. Of these patients randomly assigned, 78 had disease progression according to the RECIST 1.1 criteria at random assignment as these patients were perceived to derive clinical benefit from ongoing nivolumab. Continuous adminsitration of nivolumab, as opposed to fixed-duration therapy, was associated with longer PFS (24.7 months *v* 9.4 months; HR, 0.56 [95% CI, 0.37 to 0.84]) and OS (not reached *v* 28.8 months; HR, 0.62 [95% CI, 0.42 to 0.92]). This benefit was more pronounced among patients with complete or partial response at the time of random assignment.[64] However, this exploratory analysis has several limitations. It was not preplanned, patients were not stratified according to their response at the time of random assignment, the study was not blinded, and it included patients who were already receiving nivolumab beyond progression. A similar approach is being explored in the Japanese noninferiority phase III SAVE trial. Patients with metastatic NSCLC and no progressive disease after 1 year of ICBs will be randomly assigned to continue or stop treatment, with rechallenge at the time of progression. The primary end point is OS. Of note, the trial will explore the prognostic and the predictive role of circulating tumor DNA (ctDNA).[65] Other ongoing clinical trials investigating the optimal duration of ICBs in advanced NSCLCs include ClinicalTrials.gov identifiers NCT04157985, NCT04880382, and NCT05418660.

In contrast to the CheckMate153 trial, data from randomized phase III clinical trials in metastatic NSCLC do not support a correlation between treatment duration and outcomes (Fig 2). In these trials, treatment was continued for 2 years or until disease progression, with results showing similar PFS and OS. In the recent French retrospective cohort study ATHENA (N = 391,106; 43,359 of whom received up-front pembrolizumab for an advanced disease), continuation of pembrolizumab beyond 2 years (performed in 2 of 3 the patients) did not improve the OS compared with a fixed 2-year treatment (HR, 0.97 [95% CI, 0.75 to 1.26]; $P = .95$).[39] An analysis of the Flatiron Health database in the United States (N =14,406 patients treated with up-front ICBs, 1,091 of whom were still receiving ICBs at 2 years) found that only 20% of patients stopped treatment at 2 years, and prolonging treatment beyond this point did not improve OS (HR, 1.26 [95% CI, 0.77 to 2.08]; $P = .36$).[38] This suggests that prolonged treatment does not necessarily improve outcomes.[2] In addition, there is no negative survival impact for those patients with response under ICB who discontinue treatment early because of immune-related events compared with the whole population.[66,67]

However, the optimal duration of ICB therapy remains undefined. Two years appear to be a promising benchmark on the basis of data from registrational phase III trials in advanced NSCLC. These trials indicate that patients who completed 2 years of treatment (not more than 10% of those patients initially treated with combination therapies and 25% of those receiving pembrolizumab monotherapy) achieved 5-year OS rates of approximately 70%-80%.[29,30,68] Notably, nearly all patients completing 2 years of treatment achieved complete or partial responses within the 6 months after treatment initiation. This suggests that radiologic response may be a prognostic marker for prolonged ICB benefit, highlighting the possibility of exploring shorter treatment periods for certain patients.

In a postlandmark OS analysis from the CheckMate 227 phase III trial, which evaluated first-line nivolumab plus ipilimumab versus chemotherapy, patients who achieved a complete or partial response within the 6 months of the start of dual immunotherapy demonstrated a marked OS benefit regardless of the PD-L1 expression. Nearly 70% was still alive at 3 years,[69] suggesting that radiologic response could guide an ICB stop-and-go strategy. Supporting this, real-world data from the retrospective French INTEPI trial indicated that tumor response and complete metabolic response, assessed via fluorodeoxyglucose-positron emission tomography just before ICB discontinuation, may predict a prolonged disease control after treatment discontinuation.[70]

Building on this background, the noninferiority phase III DICIPLE trial randomly assigned patients with advanced NSCLC initially treated with 6 months of induction nivolumab (3 mg/kg once every 2 weeks) plus ipilimumab (1 mg/kg once every 6 weeks) without radiologic progression to either continue treatment until disease progression or enter observation.

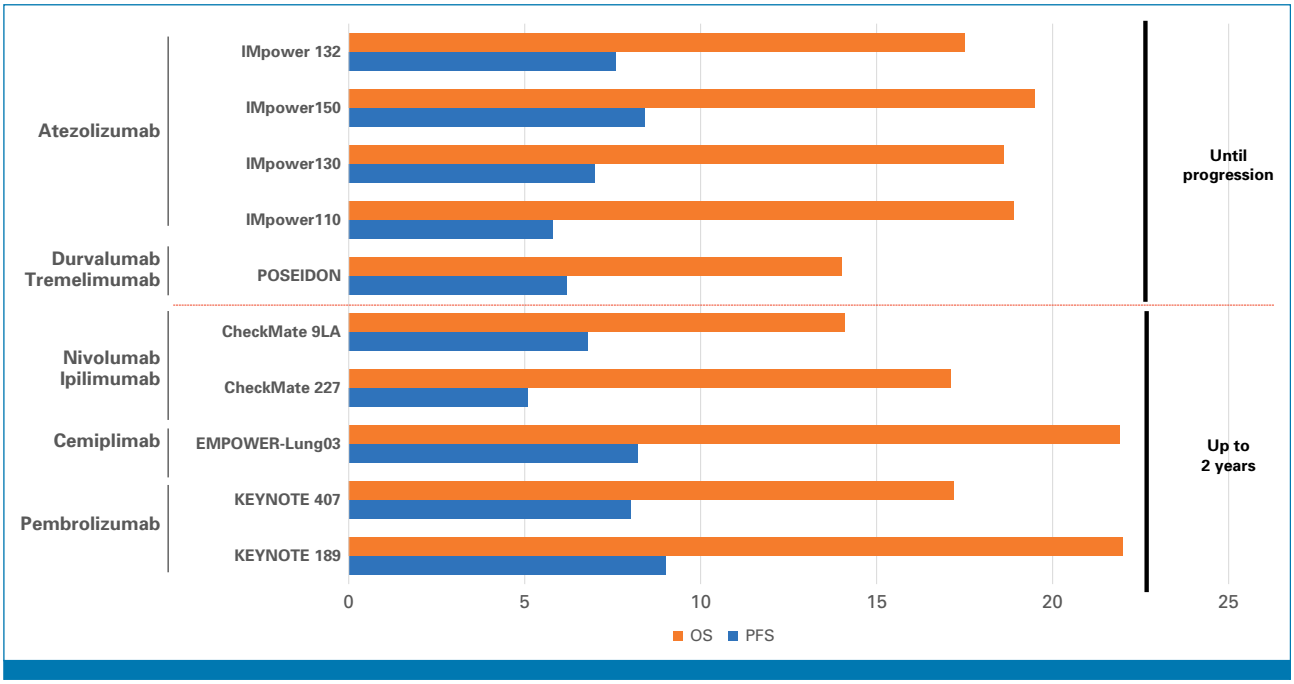

FIG 2. PFS and OS with ICBs in metastatic disease according to treatment duration (up to 2 years or up to disease progression). This figure has been created on the basis of data reported in the study by Meyer et al.[2] ICB, immune checkpoint blocker; OS, overall survival; PFS, progression-free survival.

Patients in the observation arm could restart dual ICBs on progression. The trial enrolled only 76 of the planned 265 patients as dual immunotherapy was neither registered nor reimbursed in Europe. The first analysis revealed no significant difference in PFS (HR, 0.66 [95% CI, 0.28 to 1.31], $P = .23$) or OS (HR, 0.54 [95% CI, 0.20 to 1.49]; $P = .23$) between the two arms. Notably, patients who discontinued treatment experienced a lower incidence of grade ≥3 treatment-related adverse events (TRAES: 2.9% *v* 29% among those who continued treatment).[71]

On the basis of these data, other trials have been developed, including the ongoing phase II/III DIAL trial (ClinicalTrials.gov identifier: NCT05255302). This trial enrolls patients with advanced NSCLC without disease progression after 6 months of chemo-pembrolizumab and randomly assigns to either stop treatment or continue until disease progression or for up to 2 years. The primary end point is 18-month PFS. This strategy is also being explored in other malignancies, for example, in the ongoing SAFE Stop trial, which evaluates in patients with advanced melanoma the early discontinuation of anti-PD1 ICB after complete or partial response.[72]

ICB DE-ESCALATION: FUTURE DIRECTIONS

It is important to note that de-escalating a beneficial treatment for a potentially fatal disease places both the patient and the physician in an uncharted territory as they must both balance the hope for a cure against the fear of relapse. Thus, it is paramount to involve patient advocates, physicians, and health authorities in this effort of ICB treatment optimization. Ancillary studies assessing patient QoL with different doses, schedules, and durations through patient-reported outcomes are equally important. In addition, since the long-term toxicity profile of ICB, including implications of chronic low-grade immune-related adverse events, has not yet been fully characterized,[6] correlative trials could help to fully characterize these toxicities, evaluating whether reduced doses and shorter treatment durations lead to lower (long-term) toxicity.

Moreover, to better assess the risk of relapse and to identify patients who may genuinely benefit from a de-escalation approach, reliable prognostic and predictive biomarkers are needed. ctDNA presents as a potential tool in this context. In a study involving patients with advanced NSCLC who experienced long-term benefit from ICBs (defined as no progression under ICBs at least for 12 months, N = 31), ctDNA analyses showed that among 27 patients with no detectable ctDNA (indicating a molecular response) at the time of ICB discontinuation, only two experienced disease recurrence, whereas all four patients with detectable ctDNA ultimately progressed.[73] Similar findings have been found in the nonmetastatic setting.[74] Randomized trials are still required to confirm whether ctDNA could be used to personalize the duration of ICB therapy and whether composite end points (radiologic and molecular) should be adopted to guide decisions in the stop-and-go strategy since most studies to date have been retrospective or exploratory. Imaging, including metabolic response-adapted approaches, could also be considered. Finally, these

de-escalation strategies should be evaluated across all disease stages. Duration of ICB is also a challenge in the perioperative setting of NSCLC. Currently, in resectable early-stage NSCLCs, the FDA approved both the neoadjuvant approach with nivolumab and the perioperative strategy with pembrolizumab or durvalumab, whereas the EMA has restricted the approval of neoadjuvant nivolumab to those tumors with PD-L1 ≥1% and has only approved pembrolizumab for the perioperative approach.[75] In this scenario, data from trials evaluating the perioperative strategy suggest that although the benefit of adjuvant ICB occurred regardless of the pathologic complete response (pCR) status, this benefit is more pronounced in tumors without pCR.[76-79] Again, exploring a population that could de-escalate adjuvant ICB after induction treatment is a challenge and pathologic and molecular parameters may be potential predictors for selecting the most suitable patients.

It is likely that evidence supporting de-escalation will emerge primarily from academic-led trials, which are designed to address specific clinical questions, whereas trials led by pharmaceutical companies often focus on gaining market authorization. With the same aim, the FDA has set up the OPTIMUS project and has released a guidance for industry[80] for future trials in this area.

In conclusion, current data in NSCLC support the feasibility of dose or treatment duration de-escalation approaches with ICBs across all stages of the disease. Academic efforts are needed to conduct prospective trials that provide solid evidence on a larger scale. Regulatory authorities should implement initiatives aiming to explore de-escalation strategies and reducing treatment costs. This should be a priority to ensure that more patients can access these therapies in the future, reduce treatment inequalities, and support the sustainability of our health care systems.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-02347.

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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

De-Escalation Strategies With Immune Checkpoint Blockers in Non–Small Cell Lung Cancer: Do We Already Have Enough Evidence?

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This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.
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No other potential conflicts of interest were reported.