THERAPEUTIC ADVANCES in
Medical Oncology

Review

What is the optimal duration, dose and frequency for anti-PD1 therapy of non-small cell lung cancer?

Ther Adv Med Oncol

2023, Vol. 15: 1–13

DOI: 10.1177/17588359231210271

Chii Yang Kuah*, Robert Monfries*, Matteo Quartagno, Michael J. Seckl and Ehsan Ghorani

***Abstract*:** Over the past decade, immune checkpoint inhibitors (ICIs) have transformed the management of multiple malignancies including lung cancer. However, the optimal use of these agents in terms of duration, dose and administration frequency remains unknown. Focusing on anti-PD1 agents nivolumab and pembrolizumab in the context of non-small cell lung cancer, we argue that several lines of evidence suggest current administration regimens of these drugs may result in overtreatment with potentially important implications for cost, quality of life and toxicity. This review summarizes evidence for the scope to optimize anti-PD1 regimens, the limitations of existing data and potential approaches to solve these problems including with a novel multi-arm clinical trial design implemented in the recently opened REFINE-Lung study.

Keywords: non-small cell lung cancer, immunotherapy, overtreatment, checkpoint inhibitor, duration, dose

Received: 2 March 2023; revised manuscript accepted: 9 October 2023.

Introduction

Over the past decade, drugs that target immune cell inhibitory receptors (immune checkpoint inhibitors, ICIs) have transformed the management of multiple malignancies including non-small cell lung cancer (NSCLC). Agents targeting the programmed death (PD)-1/PD-ligand-1 (PD-L1) and cytotoxic T lymphocyte-4 (CTLA-4) pathways have the potential for durable effects resulting in long term survival and tolerable toxicities in advanced NSCLC. This has been shown for the anti-PD1-targeted agents pembrolizumab and nivolumab, given alone[1–4] or with chemotherapy,[5] the anti-PDL1-directed agent atezolizumab[4] and the combination of nivolumab with the anti-CTLA-4-directed agent ipilimumab.[6,7] However, the optimal use of ICIs in terms of duration, dose and administration frequency remains unknown. Since anti-PD1-directed drugs are the most frequently prescribed ICIs in advanced NSCLC with the greatest evidence base, we focus discussion on these agents.

Several lines of evidence suggest current anti-PD1 administration schedules may result in overtreatment. This includes data on the kinetics of PD1 receptor occupancy showing a high degree of receptor binding that is sustained over time after a single dose.[8] Furthermore, results from early[2] and late phase[3] clinical trials demonstrate a flat relationship between dose and response for both toxicity and patient outcomes. Supported by a series of small, non-definitive retrospective cohort studies, there is now emerging consensus that anti-PD1 treatment regimens may have considerable scope for optimization.

Overtreatment has potentially important implications for cost, quality of life and toxicity. Anti-PD1 agents are high-cost drugs with an estimated average annual cost of over $100,000 per patient.[9] Thus, overtreatment may result in a significant cost burden to healthcare services globally, with important practical implications for cancer care funding. This has driven significant interest in

Correspondence to:
Michael J. Seckl
Department of Medical Oncology, Charing Cross Hospital Campus of Imperial College London W6 8RF, UK
m.seckl@imperial.ac.uk

Ehsan Ghorani
Department of Medical Oncology, Charing Cross Hospital Campus of Imperial College London W6 8RF, UK
e.ghorani@imperial.ac.uk

Chii Yang Kuah
Robert Monfries
Department of Medical Oncology, Charing Cross Hospital Campus of Imperial College London, UK

Matteo Quartagno
Institute for Clinical Trials and Methodology, University College London, London, UK

*Joint first authors

optimizing the use of ICIs in general and anti-PD1 agents in particular across healthcare systems with different levels of resource availability.

Overtreatment may additionally impact patient quality of life through the inconvenience of additional clinic and treatment visits. The COVID pandemic has highlighted the importance of simplifying treatment regimens to minimize risks of frequent or long-term hospital attendances. Finally, overtreatment may potentially result in an unnecessarily elevated risk of immune-mediated toxicities. Clinical trial data indicate that failure to complete current recommended durations of treatment due to toxicity is a significant issue. Across studies of single agent anti-PD1 therapy, discontinuation rates due to adverse events (AEs) ranged from 8 to –20.2%.[1–5,7] There were higher rates of discontinuing anti-PD1 therapy in combination with chemotherapy at 20.2%.[5] Treatment optimization may make therapy more tolerable.

Identifying optimal immunotherapy regimens poses a unique challenge. Conventional dose-finding early phase trial designs for cytotoxic chemotherapies have aimed to determine a maximal dose with tolerable side effects. However, such an approach is arguably inappropriate for anti-PD1-directed immunotherapies, since these agents do not have direct cytotoxic effects on cancer cells. In keeping with this, anti-PD1 escalation trials have not found an optimal or maximum tolerated dose and instead revealed a flat dose–response relationship with regard to both effect and toxicity. For example, an early phase I escalation study investigating pembrolizumab found no limiting toxicities irrespective of dose ranging from 1 to 10 mg/kg and observed maximum target engagement amongst circulating T cells with all doses above or equal to 1 mg/kg.[10] The lack of correlation between dose (or even blood concentration) and likelihood, timing and severity of toxicity further suggests the paradigm of maximum tolerable dose-finding is not applicable and optimized regimens are achievable.[11] Notably however, not all ICI agents behave the same way, since agents targeting CTLA-4 have clearer evidence for a positive relationship between dose and toxicity.[12]

Additionally, unlike cytotoxic chemotherapies and targeted agents, immunotherapies can have long-lasting effects and early discontinuation has been associated with durable responses. Thus, therapy until progression may not be required, but the optimal duration of anti-PD1 therapy is unknown. A lack of biological understanding of the key immune effector population that responds to anti-PD1 therapy and the key site of drug activity complicates efforts to rationally improve treatment regimens.

Here, we discuss the current evidence for optimized anti-PD1 therapy, the limitations of existing data and potential approaches to solve these problems.

Biology of PD1 signalling and uncertainties around optimal treatment parameters

Numerous lines of evidence highlight not only the potential importance of T-cell-mediated recognition and anti-cancer effector function in tumour control, but also that the T-cell response to cancer is limited by negative regulatory mechanisms including hypofunction or 'exhaustion' of chronically stimulated T cells. These observations have led to the development of ICIs. Mechanistically, work in the late 1980s and early 1990s shed first light on negative regulation of T-cell function with cDNA library screens of activated murine T cells that discovered the genes encoding CTLA-4[13] and PD-1.[14] Focusing on PD-1, further work revealed this receptor is expressed following T-cell activation and acts to dampen T-cell activity through recruitment of src-homology two domain containing phosphatases[15] that act to limit signalling through the T-cell receptor[16] and the key co-stimulatory receptor CD28.[17] Physiologically, PD-1 signalling plays an important role in maintaining peripheral tolerance to self in addition to dampening anti-tumour immune responses.[18] In human cancers including NSCLC,[19] a large fraction of tumour infiltrating T cells express PD-1 and PD-1 positivity enriches for cells that are reactive against cancer-specific antigens, such as those that arise from mutations (neoantigens).[20,21] Finally, PD-L1 has broad expression across cell types including cancer cells, inhibitory myeloid populations and antigen-presenting cells such as dendritic cells that are crucial for initiating anti-cancer immune responses.[22] In addition to a prominent role in the control of T-cell activity, inhibitory receptors including PD1 are expressed by myeloid cells and emerging data suggests anti-PD1 may enhance immune function through acting on these populations.[23] Finally, CD4 regulatory T cells expressing the transcription factor FOXP3 (Tregs) play an important physiological role in negatively regulating T-cell responses, tumours are often enriched with activated Treg populations and depleting them can result in anti-cancer

effects.[24,25] Tumour infiltrating Tregs also express PD1 and blocking signalling may enhance their suppressive function.[26] This phenomenon has been observed in NSCLC, although the best method of modulating this suppressive response is yet to be confirmed.[27]

Whilst it is evident that anti-PD-1/PD-L1-directed agents generally act to enhance T-cell activity, there are several important unknowns in their mechanism of action, related to an incomplete understanding of PD-1 biology. One important knowledge gap is the target cell population for anti-PD1 activity. Initial reports supported by later data suggest that PD-1 signalling is most important in the negative regulation of T cells in the effector or exhausted phase that resides within the tumour.[28,29] Additionally, multiple lines of evidence now support the notion that PD-1 is also expressed early upon T-cell activation by progenitor populations including within tumour-draining lymph nodes,[30] and blockade of signalling at this point is critical for the activity of anti-PD1/PD-L1-directed agents,[31,32] although anti-PD1 can also affect early differentiated T cells within the tumour microenvironment.[33] Practically, the key T-cell population that acts to effect anti-cancer function in response to anti-PD1/PD-L1 therapy, the kinetics or PD1 expression and the critical site of action of anti-PD1-directed agents are consequently not well characterized. Despite this, the current dosing of anti-PD1 agents is based on the assumption that drug penetration into the tumour is required. For instance, the 2 mg/kg phase II recommended dose of pembrolizumab was based on modelling that suggested this dose is required to achieve 90% PD1 occupancy at drug trough levels within poorly vascularized tumours.[34] However, it is not clearly the case that drug penetration into the tumour is the critical factor in determining anti-cancer effects.

A second important but unknown area relevant to the design of treatment regimens is whether interfering with anti-PD1 signalling has short- or long-term effects on T-cell function. Whilst recent data suggest that exhausted T cells have a fixed epigenetic state,[35,36] it remains unknown whether PD-1 signalling blockade of progenitor-like T cells early in their activation has lasting functional effects. Since new toxicities and clinical responses can develop after anti-PD1 treatment discontinuation, it is possible that drug exposure has persistent effects.

This lack of biological understanding of how and where anti-PD1-directed agents act creates uncertainty around fundamental aspects of optimal administration in terms of duration, dose and frequency. In the absence of a detailed understanding to guide the design of optimal regimens, empirical investigation is required.

The following sections summarize data on completed studies related to the optimization of duration, dose and administration frequency (further summarized in Tables 1 and 2), along with ongoing prospective trials that are collectively summarized in Table 3.

Table 1. Summary of studies investigating reduced duration of anti-PD1 therapy in advanced NSCLC.

Study	Drug treatment	Design	Duration of treatment	Patient numbers	Outcome
KCSG LU20-11[37]	Pembrolizumab± chemotherapy, nivolumab, atezolizumab	Retrospective, observational, multi centre	2 years *versus* <2 years	96 *versus* 43	1 year OS – 96.4% *versus* 90.0% ($p = 0.504$) 1 year PFS 81.1 *versus* 71.0% ($p = 0.499$)
INTEPI[38]	Pembrolizumab or nivolumab.	Retrospective, observational, multi centre	>18 months	54	1 year PFS post discontinuation –71% (95% CI 56.8–81.5%) 1 year OS post discontinuation – 90% (95% CI 77.7–95.7%) 2 year PFS post discontinuation – 63% (95% CI 46.1–76.2) 2 year OS post discontinuation – 84% (95% CI 68.7–92.2)

(Continued)

Table 1. (Continued)

Study	Drug treatment	Design	Duration of treatment	Patient numbers	Outcome
CheckMate -153[39]	Nivolumab	Phase IIIb/IV RCT	Continuous *versus* cessation at 1 year	127 *versus* 125	Median PFS – 24.7 months *versus* 9.4 months (HR 0.56, 95% CI 0.37–0.84) Median OS – Not reached *versus* 28.8 months (HR 0.62, 95%CI 0.42-0.92)
IFCT-1701 DICIPLE[40]	Nivolumab + ipilimumab	Phase III RCT	Continuation *versus* cessation at 6 months	265	12-month PFS – 57.1% *versus* 77.6% ($p = 0.09$)

HR, hazard ratio; CI, confidence interval; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Table 2. Summary of studies investigating dose regimes of anti-PD1 therapy in advanced NSCLC.

Study	Drug treatment	Design	Dose of treatment	Patient numbers	Outcome
Yoo *et al.*[41]	Nivolumab	Retrospective, observational, single centre	20 mg/100 mg Q3W *versus* SOC (3 mg/kg Q2W)	18 *versus* 29	ORR: 16.7% versus 13.8% ($p = 0.788$)
To *et al.*[42]	Pembrolizumab	Retrospective, observational, single centre	100 mg Q3W *versus* SOC (200 mg Q3W)	36 *versus* 28	Median OS: 22.7 m *versus* NR ($p = 0.34$) Median PFR: 4.5 m *versus* 6.1 m ($p = 0.046$)
Low *et al.*[43]	Pembrolizumab	Retrospective, observational, single centre	100 mg Q3W *versus* SOC (200 mg Q3W)	65 *versus* 49	Median OS: 14.3 m *versus* 19.8 m ($p = 0.86$) Median PFS: 6.8 m *versus* 4.2 m ($p = 0.16$)
Chang *et al.*[44]	Pembrolizumab	Retrospective, observational, single centre	<2 mg/kg *versus* >2 mg/kg	95 *versus* 147	Median OS: 14.3 m *versus* 19.3 m ($p = 0.15$)
KEYNOTE-010	Pembrolizumab	Phase II/III RCT	2 mg/kg *versus* 10 mg/kg	345 *versus* 346	Median OS: 10.4 m *versus* 12.7 m Median PFS: 3.9 m *versus* 4.0 m

NR, not reached; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; RCT, randomized controlled trial; SOC, Standard of care.

Optimal duration of therapy

Anti-PD1 agents are licensed for up to 2 years for treatment of advanced NSCLC, based on outcomes of long-term responders in initial studies.[45–47] For instance, in the phase II/III KEYNOTE-010 trial, of 79 patients who completed 2 years of pembrolizumab, 5 year OS was 83%.[45] This suggested patients who completed 2 years of therapy without disease progression could safely discontinue treatment. However, it is not clear whether better outcomes amongst those who completed 2 years of therapy are related to treatment duration, or because the majority of those who reached the 2-year landmark had early responses to therapy.

Table 3. Summary of current trials investigating optimization of anti-PD1 therapy in advanced NSCLC.

Trial	Drug	Parameter to optimize	Treatment group	Design	Planned patient *n*
JCOG1701, SAVE (jRCT1031190032)	Pembrolizumab	Duration	Cessation at 1 year *versus* SOC (Cessation at 2 years)	Non-inferiority RCT	216
DIAL (NCT05255302)	Pembrolizumab + Chemotherapy (platinum doublet)	Duration	Cessation at 6 months *versus* SOC (Cessation at 2 years)	RCT	1360
DEDICATION-1 (NCT04909684)	Pembrolizumab	Dose	300 mg Q6W *versus* SOC (400 mg Q6W or 200 mg Q3W)	Non-inferiority RCT	750
PULSE (NCT05692999)	Pembrolizumab	Dose	200 mg Q6W *versus* SOC (400 mg Q6W or 200 mg Q3W)	Non-inferiority RCT	1100
NCT04032418	Pembrolizumab	Frequency	200 mg Q12W *versus* SOC (200 mg Q3W	Two-arm RCT	152
MOIO (NCT05078047)	Pembrolizumab	Frequency	400 mg or 200 mg Q3M after completion of 6 months of treatment *versus* SOC (continuation of 400 mg Q6W or 200 mg Q3W)	Non-inferiority RCT	646 (across various tumour types including NSCLC)
REFINE-Lung (NCT05085028)	Pembrolizumab	Frequency	400 mg Q9/12/15/18W *versus* SOC after completion of 6 months of treatment *versus* SOC (400 mg Q6W)	MAMS-ROCI	1750

MAMS-ROCI, multi-arm multi-stage response over continuous intervention; Q3M, every 3 months; Q6W, every 6 weeks; RCT, randomized controlled trial; SOC, standard of care.

These findings are supported by the French multicentre retrospective real-world INTEPI study, in which 54 patients with advanced NSCLC who discontinued anti-PD1 therapy after at least 18 months of disease control were followed up (Table 1). Primary reasons for discontinuing therapy were physician choice (46%) due to no perceived benefit beyond 2 years, toxicity (22%) and patient decision (not further specified; 20%). Twenty patients were treated for 18 to 24 months and 34 patients were treated for more than 24 months. Patients who discontinued had 24 months post-discontinuation PFS and OS of 63% and 84%, respectively.[38]

A multicentre retrospective study (KCSG LU20-11) done in South Korea reported real-world long-term follow-up data with advanced NSCLC. For those who completed 2 years of pembrolizumab, 1 year post-discontinuation PFS and OS were 81.1% and 96.4%, respectively.[37] Of those who discontinued, the majority did so due to immune-related adverse reactions (61%), followed by patient choice (not otherwise specified; 14%) and financial burden (9%). For 43 patients who discontinued pembrolizumab after more than 6 months of treatment, the 1-year post-discontinuation PFS and OS were 71% and 90%, respectively. Amongst those who discontinued treatment after less than 12 months but more than 6 months, the median PFS was 20.7 months. Amongst those with more than 1 year of treatment, the median PFS was not reached with more than 40 months of follow-up. These data suggest that whilst 6 months of therapy can result in durable long-term benefits, a minimum duration of therapy of 1 year may yield better outcomes.

In contrast, data from the Checkmate 153 study does not support reducing the duration of treatment to 1 year.[39] This study was primarily established to investigate the safety of nivolumab for a previously treated cohort of patients including those aged over 70 and with poor performance status. Following a protocol modification, an exploratory substudy was established within which patients were randomized at 1 year to stop or continue therapy. The continuous treatment population had a significantly better PFS compared to the 1-year arm, with a hazard ratio of 0.56 (95% CI 0.37–0.84). The hazard ratio for 24-month OS post-randomization for continuous treatment *versus* 1-year arm was 0.62 (95% CI, 0.42–0.92). Patients who had a complete or partial response at the point of randomization had better outcomes with continuous *versus* 1-year of treatment. Patients who had stable disease on nivolumab had similar PFS between arms. These data suggest that responders may benefit from a treatment duration of longer than 1 year, but the study was underpowered to draw a definitive conclusion.

Finally, early discontinuation has been explored in other cancer types. In melanoma, there is likewise evidence that early treatment discontinuation due to toxicity or having achieved a complete response results in similar outcomes compared to those who continue treatment.[48,49] This was investigated in a study of 105 patients within the phase I KEYNOTE-001 trial (from 655 enrolled) who had a complete response by investigator review. Ninety-one of these (87%) discontinued pembrolizumab after 6 months due to physician or patient choice. The 24 month disease-free survival (DFS) rate for all 105 patients who had complete response was 90.9 (95% CI, 82.5–95.4%) whereas the 89 patients who discontinued after 6 months had an estimated 24 month DFS of 85.8%.[49] Strikingly, in treatment-resistant gestational trophoblastic disease, the novel use of pembrolizumab has also been shown to achieve sustained remissions after only 6 months of treatment.[50]

In several of the earlier observational studies discussed above, the majority of patients who discontinued did so due to immune-related AEs. Around 5–10% discontinued for financial reasons.[37,38] Overall, the data suggest that a course of therapy <2 years has the potential to provide similar durable responses. However, the small size and lack of power of these observational studies do not allow any definitive conclusion to be drawn. Non-randomized studies in this space are liable to bias, since the duration of treatment may be determined by socioeconomic factors and patients who achieve 2 years of therapy are enriched for those who had an early response. These limitations both in terms of power and trial design highlight the importance of developing robust and sufficiently powered prospective studies to investigate the optimal duration of ICI treatment.

The recently presented phase III IFCT-1701 DICIPLE compared treatment with nivolumab plus ipilimumab for 6 months *versus* continuation until progression for patients with treatment-naïve advanced NSCLC.[40] Patients who relapsed in the discontinuation arm were permitted to be rechallenged with the same drugs. This trial was prematurely closed after 32 months as the nivolumab and ipilimumab combination failed to be licensed in Europe, where the trial was conducted. Thus, the analysis is underpowered, with only 265 patients accrued out of an intended 900. However, the 18-month OS rate was 79% and 94%, respectively, and these data may in general support the notion that early discontinuation with the option of rechallenge could be effective.

In terms of ongoing studies (Table 3), the same trial group launched the DIAL study to further explore the possibility of early discontinuation in advanced NSCLC. DIAL is a randomized, open-label multicentre study comparing the continuation of pembrolizumab to cessation and observation in patients who have completed 6 months of first-line chemotherapy plus pembrolizumab.[51] With an estimated enrolment of 1360 patients and a primary outcome of overall survival, this trial may more definitively elucidate the effect of shortening pembrolizumab duration. A similarly designed Japanese trial, SAVE, is also ongoing, comparing cessation of ICI (pembrolizumab, atezolizumab or nivolumab) at 1 year to continuation, intending to recruit 216 patients.[52]

Optimal dose of therapy

In the era of cytotoxic chemotherapies that primarily exert anti-cancer effects through direct cytotoxic activity, early phase trials were rationally developed to maximize drug exposure. However, anti-PD1 and other ICIs do not exert direct anti-cancer cell effects, and thus conventional notions of aiming to enhance drug serum

concentration do not necessarily apply. Thus, early pharmacokinetic studies of nivolumab demonstrated doses significantly below the current standard resulting in high occupancy of the PD1 target receptor. In a phase I study of nivolumab, sustained PD1 occupancy of >60% was achieved at doses from 0.3 mg/kg to 10 mg/kg.[8] *In vitro*, a nivolumab concentration of 0.04 µg/mL (one-third of the minimum serum detectable level by enzyme-linked immunosorbent assay) resulted in >70% occupancy of PD1 molecules *in vitro*. Thus, exceedingly low serum concentrations may be sufficient to result in target inhibition.

Consistent with this, prospective studies have failed to show an effect of dose reduction on clinical outcomes. Amongst patients with NSCLC in the phase I KEYNOTE-001 trial, no difference was seen in outcomes between patients treated with 2 and 10 mg/kg pembrolizumab given every 2 or 3 weeks (Table 2).[2] This was confirmed in the phase II/III KEYNOTE-010 study, investigating pembrolizumab in patients with PD-L1 positive NSCLC.[3] In total, 345 patients and 346 patients were treated with 2 and 10 mg/kg pembrolizumab, respectively, with no significant difference in overall survival. Similar findings were noted in studies of melanoma and renal cell carcinoma.[53,54] Additionally, no relationship between dose and toxicity was demonstrated for anti-PD1-directed agents in these trials. Whilst these studies suggest a flat dose–response relationship with anti-PD1 therapy, they did not investigate doses lower than the current standards of care. Several underpowered retrospective studies have attempted to address this question.

Based on the lower average weight of their local population in contrast to patients enrolled in most registration trials, a study in a Singaporean cohort investigated pembrolizumab at a lower fixed dose of 100 mg every 3 weeks for treatment of NSCLC.[43] This observational study involved 114 patients – 49 of whom received the standard 200 mg dose and 65 who received 100 mg dose. The selection of low-dose pembrolizumab was based on financial factors and a consideration of whether the lower dose would be appropriate based on similarity to the previous standard 2 mg/kg dosing regimen utilized before the advent of flat dosing. By weight, the standard dose cohort received a mean dose of 2.87 mg/kg, whereas the low-dose cohort received a mean dose of 1.85 mg/kg. Additionally, there were significant demographic differences between the standard and low-dose groups including age and ethnicity; furthermore, there was significantly higher PDL1 expression in the low-dose group (TPS > 50 = 68% in the low-dose group, 39% in the high-dose group, $p = 0.005$). This study showed no significant difference in PFS or OS with pembrolizumab given as a single agent or combined with chemotherapy, and no significant difference in response rate or immune-related toxicity.

A similarly designed Taiwanese retrospective study of 64 patients with NSCLC compared standard dose pembrolizumab to modified dose, defined in this study as either 2 mg/kg or 100 mg fixed dose every 3 weeks.[42] OS was deemed to be equivalent; however, PFS was significantly shorter in the modified dose group (4.5 months *versus* 6.1 months, $p = 0.046$).

A further Taiwanese multicentre retrospective study investigating dose-reduced pembrolizumab in NSCLC included 147 patients receiving standard dose and 95 patients receiving low-dose therapy.[44] In this study, patients were grouped based on equivalent body weight-based dosing, defining standard pembrolizumab dose as >2 mg/kg and low-dose as <2 mg/kg. Although there was a longer median OS with standard dosing, this was not statistically significant (19.3 *versus* 14.3 months, $p = 0.15$).

Similar findings have been reported with nivolumab.[41] A retrospective study of patients with NSCLC treated in South Korea investigated low-dose therapy, with 18 patients who received a reduced dose (either 20 or 100 mg Q3W) based on economic factors, compared to 29 allocated to the standard 3 mg/kg Q2W dose. Whilst limited by a small sample size, non-randomized design and demographic differences between the treatment groups, no difference in outcomes was observed (objective response rate = 16.7% in the low-dose group *versus* 13.8% in the standard dose group, $p = 0.788$).

Collectively, although the data summarized here and in Table 2 are suggestive that reduced dose anti-PD1 therapy may be effective, many of the available clinical studies are limited by their size and retrospective design. Prospective studies are warranted to explore the hypothesis in a more definitive manner.

The phase III PULSE trial aims to compare low-dose pembrolizumab (200 mg Q6W) *versus*

standard of care (SOC; either 200 mg Q3W or 400 mg Q6W).[55] The study aims to enrol 1166 patients to test a hypothesis of non-inferiority of reduced dose of pembrolizumab compared to conventional administration, with a primary outcome of overall survival (Table 3).

Another clinical trial aiming to optimize the dosing schedule for advanced NSCLC is the DEDICATION-1 study (NCT04909684). The study aims to investigate the non-inferiority of a reduced dose of pembrolizumab (300 mg every 6 weeks) compared to the standard dose (400 mg every 6 weeks). The study aims to recruit 750 patients, with a primary outcome measure of one-year overall survival.

Optimal frequency of therapy

Based on population, pharmacokinetic modelling suggesting anti-PD1 administration frequency can be reduced whilst the dose is increased to maintain treatment intensity, extended duration nivolumab and pembrolizumab regimens have been approved. However, prospective data on the clinical performance of these regimens are limited. Modelling of data from four phase III randomized trials (CheckMate 017, 025, 057 and 066) suggested maintained safety and efficacy of nivolumab given every 4 weeks at 480 mg rather than the standard 240 mg 2 weekly regimen. Interim analysis of the phase III/IV CheckMate 384 trial similarly suggests that 4 weekly 480 mg nivolumab maintains efficacy and safety compared to 2 weekly 240 mg dosing.[47] Additionally, a retrospective single-centre Dutch study evaluated the safety and efficacy of decreased anti-PD1 frequency,[56] comparing 3 weekly 200 mg *versus* 6 weekly 400 mg pembrolizumab and 2 weekly 240 mg *versus* 4 weekly 480 mg nivolumab. The efficacy of the extended frequency regimens was comparable.[56]

These studies raise the question of whether frequency can be reduced without changing the administration dose. Since current regulations[57] impose restrictions on the sharing of single-dose drug vials among multiple patients, exploring the optimal frequency of administration whilst keeping dosage fixed presents an attractive approach to regimen optimization. In addition to reducing drug costs, this approach may result in fewer hospital visits and enhanced patient quality of life related to this.

Several clinical trials are investigating whether the frequency of anti-PD1-directed agents and other ICIs can be reduced without increasing dosage including the MOIO trial (NCT05078047), a non-inferiority, randomized French multicentre phase III basket trial comparing standard *versus* 3 monthly scheduling of anti-PD1, anti-PDL1 and anti-CTLA inhibitors (Table 3). A second phase II trial (NCT04032418) compares pembrolizumab given every 12 weeks *versus* every 3 weeks for NSCLC therapy. These efforts are exemplified by the ongoing UK NIHR portfolio phase III REFINE-Lung study[58] and the similarly designed phase II REFINE basket trial currently open for patients with renal cancer and melanoma.[59]

Recognizing that there is no prior rationale for selecting any particular reduced frequency of immunotherapy administration compared to SOC, the REFINE-Lung study was designed to explore a range of pembrolizumab frequencies amongst patients with advanced NSCLC in a multi-arm study. Adapting a methodology originally designed to determine the optimal duration of antibiotic therapy of infection,[60] REFINE-Lung explores administration frequencies of 6 (SOC), 9, 12, 15 and 18 weekly treatment. Notably, this design overcomes inefficiencies associated with a conventional two-arm non-inferiority trial design that is limited to testing a single hypothesis. Patients who complete 6 months of first-line pembrolizumab (single agent or combined with chemotherapy) without progression are eligible for randomization to continue control 40 mg 6 weekly treatment or one of the four frequency reduced arms. To address efficacy concerns, patients will be initially randomized to 6 *versus* 12 weekly arms with a planned interim analysis to evaluate PFS. If there is no significant difference, the remaining arms will be opened. By evaluating the relationship between frequency and response (defined as 2 year landmark survival), REFINE-Lung will enable the selection of the optimal frequency reduced regimen, defined as the longest frequency non-inferior to control. Patients who progress on a frequency reduced arm will have the option of re-escalation to 6 weekly therapy.

Conclusion

A basic lack of biological understanding of the mechanisms of anti-PD1 activity makes rational design of administration regimens, particularly challenging. Notably, regulatory agencies are now

playing a greater role in seeking evidence that regimens for new high cost agents are optimal. For instance, the FDA Project Optimus is engaged in promoting greater consideration of dose-finding and optimization during drug development by comparing multiple dose levels and other approaches.[61]

There is however significant scientific and societal interest in whether duration, dose and frequency of anti-PD1 agents, and other ICI drugs can be safely and effectively optimized. Such changes could provide significant benefits in terms of cost, patient quality of life and potential toxicity. Significantly, high-quality prospective data on the optimization of anti-PD1 regimens in advanced NSCLC are lacking to date. In particular, much of the available data are from retrospective, underpowered studies and at risk of bias, particularly where factors such as patient financial circumstances play a role in determining the regimen utilized. As a result of this, definitive conclusions cannot be drawn. However, taken together with phase I data on high PD-1 receptor occupancy after low-dose administration and a flat dose–response relationship across multiple studies, there is a strong rationale to investigate optimized regimens. As summarized in Table 3, there are now a number of randomized prospective studies that are testing optimized treatment regimens.[62]

One major limitation is related to the design of trials to achieve this goal. Conventional two-arm non-inferiority trials are inefficient for the purpose of regimen optimization since they test a single hypothesis where multiple alternatives may be reasonable. Thus, a negative result in a two-arm trial would be inevitable if the test arm is chosen badly. The trial design developed for REFINE-Lung and implemented in the similar REFINE-basket trial attempts to resolve this by testing across a range of values for a given parameter. Although these trials explore administration frequency, they could equally be used to study duration or dose. We propose that future trials may use this or similar designs to optimize treatment parameters.

Notably, the clinical experience with anti-PD1-directed agents may not be generalizable and different targets for antibody-based immunotherapy and different agents show differences in dose–response characteristics. Thus, a randomized phase III trial comparing ipilimumab 10–3 mg/kg has demonstrated an increase in both overall survival (15.7 months *versus* 11.5 months) and treatment-related serious AEs (37% *versus* 18%) with the higher dose.[63] Agonistic antibodies targeting co-stimulatory receptors such as 4-1BB may again yield different results.[64] Notably, unlike anti-PD1-directed agents, the 4-1BB agonist urelumab was found to have dose-limiting toxicities.[65] In contrast, the 4-1BB agonistic antibody utomilumab was found not to have dose-limiting toxicities in the range tested.[66] These results demonstrate the potential for target and agent dependency with respect to the immunotherapy dose–response relationship.

In general, however, given the indirect effects of antibody-based immunotherapies on cancer cell growth and survival, conventional approaches for dose selection based on the phase I maximal tolerated dose may not be generally suitable for ICIs. One way of addressing this would be to develop biomarkers of treatment effect such as target receptor occupancy, immune cell proliferation[67] or consideration of clinical outcomes in relation to different administration regimens earlier in drug development.

Related to this, it seems plausible that pretreatment circulating or intratumoural factors may predict response to reduced intensity or duration of treatment. This could be related to the degree of pre-existing immune infiltration into the tumour, the quality or localization of the immune cell infiltrate,[19,68] factors related to cancer cell antigenicity[68,69] or other microenvironmental factors. Ongoing studies of optimized regimens should prioritize the exploration of these questions.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Chii Yang Kuah: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Robert Monfries: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Matteo Quartagno: Formal analysis; Writing – review & editing.

Michael J. Seckl: Conceptualization; Data curation; Formal analysis; Supervision; Writing – review & editing.

Ehsan Ghorani: Conceptualization; Data curation; Formal analysis; Supervision; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

ORCID iD
Chii Yang Kuah https://orcid.org/0000-0002-2673-1499

References

1. Brahmer J, Reckamp KL, Baas P, *et al.* Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; 373: 123–135.
2. Garon EB, Rizvi NA, Hui R, *et al.* Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; 372: 2018–2028.
3. Herbst RS, Baas P, Kim DW, *et al.* Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387: 1540–1550.
4. Reck M, Rodríguez-Abreu D, Robinson AG, *et al.* Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016; 375: 1823–1833.
5. Gandhi L, Rodríguez-Abreu D, Gadgeel S, *et al.* Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med* 2018; 378: 2078–2092.
6. Paz-Ares L, Ciuleanu T-E, Cobo M, *et al.* First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; 22: 198–211.
7. Hellmann MD, Paz-Ares L, Bernabe Caro R, *et al.* Nivolumab plus Ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med* 2019; 381: 2020–2031.
8. Brahmer JR, Drake CG, Wollner I, *et al.* Phase I study of single-agent anti–programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010; 28: 3167.
9. Prasad V, De Jesús K and Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncology* 2017; 14: 381–390.
10. Patnaik A, Kang SP, Rasco D, *et al.* Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res* 2015; 21: 4286–4293.
11. Cousin S, Seneschal J and Italiano A. Toxicity profiles of immunotherapy. *Pharmacol Ther* 2018; 181: 91–100.
12. Shulgin B, Kosinsky Y, Omelchenko A, *et al.* Dose dependence of treatment-related adverse events for immune checkpoint inhibitor therapies: a model-based meta-analysis. *Oncoimmunology* 2020; 9: 1748982.
13. Brunet J-F, Denizot F, Luciani M-F, *et al.* A new member of the immunoglobulin superfamily—CTLA-4. *Nature* 1987; 328: 267–270.
14. Ishida Y, Agata Y, Shibahara K, *et al.* Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J.* 1992; 11: 3887–3895.
15. Patsoukis N, Wang Q, Strauss L, *et al.* Revisiting the PD-1 pathway. *Sci Adv* 2020; 6: eabd2712.
16. Sheppard K-A, Fitz LJ, Lee JM, *et al.* PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3ζ signalosome and downstream signaling to PKCθ. *FEBS Lett* 2004; 574: 37–41.
17. Hui E, Cheung J, Zhu J, *et al.* T cell costimulatory receptor CD28 is a primary target for PD-1–mediated inhibition. *Science* 2017; 355: 1428–1433.
18. Nishimura H, Nose M, Hiai H, *et al.* Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 1999; 11: 141–151.

19. Ghorani E, Reading JL, Henry JY, *et al*. The T cell differentiation landscape is shaped by tumour mutations in lung cancer. *Nat Cancer* 2020; 1: 546–61.
20. Simoni Y, Becht E, Fehlings M, *et al*. Bystander CD8+ T cells are abundant and phenotypically distinct in human tumour infiltrates. *Nature* 2018; 557: 575–579.
21. McGranahan N, Furness AJS, Rosenthal R, *et al*. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 2016; 351: 1463–149.
22. Iwai Y, Ishida M, Tanaka Y, *et al*. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA* 2002; 99: 12293–12297.
23. Strauss L, Mahmoud MAA, Weaver JD, *et al*. Targeted deletion of PD-1 in myeloid cells induces antitumor immunity. *Sci Immunol* 2020; 5: eaay1863.
24. Vargas FA, Furness AJS, Litchfield K, *et al*. Fc effector function contributes to the activity of human anti-CTLA-4 antibodies. *Cancer Cell* 2018; 33: 649–663.
25. Solomon I, Amann M, Goubier A, *et al*. CD25-Treg-depleting antibodies preserving IL-2 signaling on effector T cells enhance effector activation and antitumor immunity. *Nat Cancer* 2020; 1: 1153–1166.
26. Kamada T, Togashi Y, Tay C, *et al*. PD-1+ regulatory T cells amplified by PD-1 blockade promote hyperprogression of cancer. *Proc Natl Acad Sci USA* 2019; 116: 9999–10008.
27. van Gulijk M, van Krimpen A, Schetters S, *et al*. PD-L1 checkpoint blockade promotes regulatory T cell activity that underlies therapy resistance. *Sci Immunol* 2023; 8: eabn6173.
28. Blank C, Brown I, Peterson AC, *et al*. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. *Cancer Res* 2004; 64: 1140–1145.
29. Thommen DS, Koelzer VH, Herzig P, *et al*. A transcriptionally and functionally distinct PD-1+ CD8+ T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade. *Nat Med* 2018; 24: 994–1004.
30. Prokhnevska N, Cardenas MA, Valanparambil RM, *et al*. CD8+ T cell activation in cancer comprises an initial activation phase in lymph nodes followed by effector differentiation within the tumor. *Immunity* 2023; 56: 107–124.
31. Im SJ, Hashimoto M, Gerner MY, *et al*. Defining CD8+ T cells that provide the proliferative burst after PD-1 therapy. *Nature* 2016; 537: 417–421.
32. Utzschneider DT, Charmoy M, Chennupati V, *et al*. T cell factor 1-expressing memory-like CD8+ T cells sustain the immune response to chronic viral infections. *Immunity* 2016; 45: 415–427.
33. Magen A, Hamon P, Fiaschi N, *et al*. Intratumoral dendritic cell-CD4(+) T helper cell niches enable CD8(+) T cell differentiation following PD-1 blockade in hepatocellular carcinoma. *Nat Med* 2023; 29: 1389–1399.
34. Li TR, Chatterjee M, Lala M, *et al*. Pivotal dose of pembrolizumab: a dose-finding strategy for immuno-oncology. *Clin Pharmacol Ther* 2021; 110: 200-9.
35. Pauken KE, Sammons MA, Odorizzi PM, *et al*. Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade. *Science* 2016; 354: 1160–1165.
36. Sen DR, Kaminski J, Barnitz RA, *et al*. The epigenetic landscape of T cell exhaustion. *Science* 2016; 354: 1165–1169.
37. Kim H, Kim DW, Kim M, *et al*. Long-term outcomes in patients with advanced and/or metastatic non–small cell lung cancer who completed 2 years of immune checkpoint inhibitors or achieved a durable response after discontinuation without disease progression: Multicenter, real-world data. *Cancer* 2022; 128: 778–787.
38. Bilger G, Girard N, Doubre H, *et al*. Discontinuation of immune checkpoint inhibitor (ICI) above 18 months of treatment in real-life patients with advanced non-small cell lung cancer (NSCLC): INTEPI, a multicentric retrospective study. Cancer Immunol Immunother. 2022; 71: 1719–1731.
39. Waterhouse DM, Garon EB, Chandler J, *et al*. Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non–small-cell lung cancer: CheckMate 153. *J Clin Oncol* 2020; 38: 3863–3873.
40. G. Zalcman AMF, Molinier O Dayen C, *et al*. Toffart. Nivolumab (Nivo) plus ipilimumab (Ipi) 6-months treatment versus continuation in patients with advanced non-small cell lung cancer (aNSCLC): Results of the randomized IFCT-1701 phase III trial. Ann Oncol 2022; 33(Suppl. 7): s448–s554.
41. Yoo SH, Keam B, Kim M, *et al*. Low-dose nivolumab can be effective in non-small cell lung cancer: alternative option for financial toxicity. *ESMO Open* 2018; 3: e000332.

42. To SY, Kao LT, Shih JH, *et al.* Modified-dose pembrolizumab and prognostic outcomes among non-small cell lung cancer patients: a chart review study. *Int J Environ Res Public Health* 2022; 19: 5999.

43. Low JL, Huang Y, Sooi K, *et al.* Low-dose pembrolizumab in the treatment of advanced non-small cell lung cancer. *Int J Cancer* 2021; 149: 169–176.

44. Chang KC, Shao SC, Chen HY, *et al.* Comparative effectiveness and safety of standard-dose and low-dose pembrolizumab in patients with non-small-cell lung cancer: a multi-institutional cohort Study in Taiwan. *Cancers (Basel)* 2022; 14: 1157.

45. Herbst RS, Garon EB, Kim D-W, *et al.* Long-term outcomes and retreatment among patients with previously treated, programmed death-ligand 1–positive, advanced non–small-cell lung cancer in the KEYNOTE-010 study. *J Clin Oncol* 2020; 38: 1580–1590.

46. Gettinger S, Horn L, Jackman D, *et al.* Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study. *J Clin Oncol* 2018; 36: 1675–1684.

47. Garon EB, Reinmuth N, Falchero L, *et al.* CheckMate 384: Phase IIIb/IV trial of nivolumab (nivo) 480 mg Q4W versus 240 mg Q2W after ⩽12 months of nivo in previously treated advanced NSCLC. *J Clin Oncol* 2019; 37(8 Suppl): 100.

48. Marron TU, Ryan AE, Reddy SM, *et al.* Considerations for treatment duration in responders to immune checkpoint inhibitors. *J Immunother Cancer* 2021; 9: e001901.

49. Robert C, Ribas A, Hamid O, *et al.* Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. *JClin Oncol* 2018; 36: 1668–1674.

50. Ghorani E, Kaur B, Fisher RA, *et al.* Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. *Lancet* 2017; 390: 2343–2345.

51. Besse B. Intergroupe Francophone de Cancerologie Thoracique. De-escalation immunotherapy maintenance duration trial for stage IV lung cancer patients with disease control after chemo-immunotherapy induction (DIAL). ClinicalTrials.gov Identifier: National Library of Medicine (U.S.) NCT05255302. 2022.

52. Mizuno T, Katsuya Y, Sato J, *et al.* Emerging PD-1/PD-L1 targeting immunotherapy in non-small cell lung cancer: current status and future perspective in Japan, US, EU, and China. *Front Oncol* 2022; 12: 925938.

53. Robert C, Ribas A, Wolchok JD, *et al.* Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* 2014; 384: 1109–1117.

54. Motzer RJ, Rini BI, McDermott DF, *et al.* Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol* 2015; 33: 1430–1437.

55. Besse B. Maintenance pembrolizumab at usual or low dose in non-squamous lung cancer: a non-inferiority study (Pulse). National Library of Medicine (U.S.) ClinicalTrials.gov Identifier: NCT05692999

56. Hijmering-Kappelle LBM, Hiltermann TJN and Bensch F. Safety and efficacy of extended interval dosing for immune checkpoint inhibitors in non–small cell lung cancer during the COVID-19 pandemic. *Clin Lung Cancer* 2022; 23: 143–150.

57. Bach PB, Conti RM, Muller RJ, *et al.* Overspending driven by oversized single dose vials of cancer drugs. *BMJ* 2016; 352: i788.

58. Ghorani E, Quartagno M, Blackhall F, *et al.* REFINE-Lung implements a novel multi-arm randomised trial design to address possible immunotherapy overtreatment. *Lancet Oncol* 2023; 24: e219–e227.

59. Merrick S, Nankivell M, Quartagno M, *et al.* REFINE (REduced Frequency ImmuNE checkpoint inhibition in cancers): a multi-arm phase II basket trial testing reduced intensity immunotherapy across different cancers. *Contemp Clin Trials* 2023; 124: 107030.

60. Quartagno M, Walker AS, Carpenter JR, *et al.* Rethinking non-inferiority: a practical trial design for optimising treatment duration. *Clin Trials* 2018; 15: 477–488.

61. Venkatakrishnan K and van der Graaf PH. Toward project optimus for oncology precision medicine: multi-dimensional dose optimization enabled by quantitative clinical pharmacology. *Clin Pharmacol Ther* 2022; 112: 927–932.

62. Hirsch I, Goldstein DA, Tannock IF, *et al.* Optimizing the dose and schedule of immune checkpoint inhibitors in cancer to allow global access. *Nat Med* 2022; 28: 2236–2237.

63. Ascierto P, Bono P, Bhatia S, *et al.* Efficacy of BMS-986016, a monoclonal antibody that targets lymphocyte activation gene-3 (LAG-3), in combination with nivolumab in pts with melanoma who progressed during prior anti–PD-1/PD-L1 therapy (mel prior IO) in all-comer

and biomarker-enriched populations. *Ann Oncol* 2017; 28: v611-v2.

64. Kim AMJ, Nemeth MR and Lim SO. 4-1BB: A promising target for cancer immunotherapy. *Front Oncol* 2022; 12: 968360.
65. Segal NH, Logan TF, Hodi FS, *et al.* Results from an integrated safety analysis of urelumab, an agonist Anti-CD137 monoclonal antibody. *Clin Cancer Res* 2017; 23: 1929–1936.
66. Segal NH, He AR, Doi T, *et al.* Phase I study of single-agent utomilumab (PF-05082566), a 4-1BB/CD137 agonist, in patients with advanced cancer. *Clin Cancer Res* 2018; 24: 1816–1823.
67. Kamphorst AO, Pillai RN, Yang S, *et al.* Proliferation of PD-1+ CD8 T cells in peripheral blood after PD-1–targeted therapy in lung cancer patients. *Proc Natl Acad Sci USA* 2017; 114: 4993–4998.
68. Rizvi NA, Hellmann MD, Snyder A, *et al.* Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. *Science* 2015; 348: 124–128.
69. Ghorani E, Rosenthal R, McGranahan N, *et al.* Differential binding affinity of mutated peptides for MHC class I is a predictor of survival in advanced lung cancer and melanoma. *Ann Oncol* 2018; 29: 271–279.