Is less more? REFINE-Lung implements a novel trial design to address possible immunotherapy over-treatment

[previously: Determining the optimal frequency of pembrolizumab administration for non-small cell lung cancer in the REFINE-Lung study: a new paradigm in trial design]

Word count: 4238

Authors: Ehsan Ghorani[1]*, Matteo Quartagno[2]*, Fiona Blackhall[3], Duncan C. Gilbert[2], Mary O'Brien[5], Christian Ottensmeier[6], Elena Pizzo[7], James Spicer[8], [a patient representative], Alex Williams[9], Philip Badman[9], Mahesh K.B. Parmar[2]* and Michael J. Seckl[1]* on behalf of the REFINE-Lung Investigators.

Affiliations:

1. Department of Medical Oncology, Charing Cross Hospital Campus of Imperial College London, UK.
2. Institute for Clinical Trials and Methodology, University College London, 90 High Holborn, WC1V 6LJ
3. Christie National Health Service Foundation Trust, Manchester, United Kingdom
4. Royal Marsden Hospital, Fulham Rd, London, Imperial College London, UK
5. University of Liverpool, Institute of Systems, Molecular and Integrative Biology; Clatterbridge Cancer Center NHS Foundation Trust, Liverpool
6. Department of Applied Health Research, University College London, London, UK
7. King's College London, Guy's Hospital, London SE1 9RT
8. Imperial Clinical Trials Unit, School of Public Health, Imperial College London, UK

*Equal contributions

Authors for correspondence: E Ghorani, MJ Seckl, MKB Parmar

Summary

Ample evidence suggests that some immunotherapy dosing regimens for patients with advanced cancer offer overtreatment. Given the high costs of these agents, and important implications for patient quality of life and toxicity, new approaches are needed to identify and to reduce unnecessary treatment. Conventional two arm non-inferiority designs are limited in this context because they require large numbers of patients to explore a single alternative to the standard of care. Here we discuss the problem of overtreatment with anti-PD1 directed agents in general and introduce the REFINE-Lung study (NCT05085028), a UK multicentre phase III trial in advanced non-small cell lung cancer (NSCLC). REFINE-Lung utilises a novel Multi-Arm Multi-Stage Response Over Continuous Interventions (MAMS-ROCI) design to determine the optimal dose frequency of pembrolizumab. Along with a similarly designed basket study of patients with renal cancer and melanoma (NCT04913025), REFINE-Lung and the MAMS-ROCI design could contribute to practice-changing advances in patient care and form a template for future immunotherapy optimisation studies across cancer types and indications. This new trial design is applicable to many new or existing agents where optimisation of dose, frequency or duration of therapy is desirable.

Introduction

Medical overtreatment and its negative effects on the health of individuals and societies has long been recognised[1,2]. The history of cancer care is replete with examples of treatment excess evolving towards more rational, less intense use. Across diseases, a common pattern emerges of new treatments adopted with maximalist approaches to therapy, but with limited evidence to support a relationship between therapeutic intensity and outcomes. This is followed by periods of critical evaluation based on concerns around adverse consequences of overtreatment including cost, quality of life and toxicity. Justified by real world clinical data and new biological insights, definitive optimisation trials across systemic, radio- and surgical therapies[3–5] have reduced treatment intensity whilst preserving outcomes. A major bottleneck in this process is the conduct of studies aiming to optimise treatment parameters including dose, schedule and duration, given the inefficiencies of non-inferiority trial designs which are usually employed.

A similar pattern of overuse and rationalisation is emerging in the field of cancer immunotherapy. Over recent years, a new class of antibody based, T cell targeted immunotherapeutics have transformed cancer care across indications. Along with targeted small molecule inhibitors, these agents have heralded a new era of improved outcomes and rising costs of therapy[6]. As annual drug costs of over $100,000 per patient are normalised[7],

healthcare systems globally are increasingly faced with the question of how cancer treatment can be afforded now and in the future.

This debate has accelerated calls[8] to more effectively and rapidly optimise treatment regimens of new cancer drugs. Dose and schedule of multiple targeted agents have been subjected to scrutiny, resulting in post licencing rationalisation of agents including abiraterone[9], ceritinib[10] and dasatinib[11]. Regulatory bodies are increasingly focussed on the issue of dose optimisation, with support from the US Food and Drug Administration (FDA) through Project Optimus that aims to promote "a dose-finding and dose optimization paradigm across oncology"[12,13]. An immediate consequence is the FDA post-authorisation requirement that the novel KRAS-targeted drug sotorasib be tested at the approved 960 mg vs. a 240 mg dose, based on early phase evidence of a lack of relationship between dose and response in the range tested[14].

Despite this growing consensus, a key limitation is that conventional non-inferiority trial designs are ill suited to efficiently evaluate treatment parameters across a range of values. Here we discuss the mounting evidence of cancer immunotherapy overtreatment and its adverse effects. We present a novel trial design implemented in a large phase III lung cancer immunotherapy study that we propose could rapidly accelerate our advance towards rationally identifying optimal treatment regimens.

What is the optimal dose and frequency of immunotherapy? Conventional concepts based on development of cytotoxic regimens may not be relevant.

Modern concepts of early phase cancer trial design were established in the era of cytotoxic chemotherapeutics, with data to support an expected positive relationship between dose and biological effect of these drugs. Consequently, early phase trials have logically been designed to determine the maximum tolerated dose (MTD) of new agents, defined as the highest dose that does not lead to severe short-term toxicity. Pharmacokinetic analysis has focussed on measurements of blood distribution as a biomarker. Dose and administration schedules have subsequently been optimised to maximise drug delivery and availability.

But how should dose and regimen be selected for agents whose fundamental mechanism of action is poorly understood, without effective biomarkers to guide development? Monoclonal antibodies targeted to T cell inhibitory receptors (checkpoint immunotherapies; CPI) are a case in point. These drugs were developed following the observation that naturally occurring immune responses can exert anti-cancer control but effectors are functionally limited through the action of inhibitory receptors such as programmed death 1 (PD1).

CPIs such as pembrolizumab/nivolumab and atezolizumab/avelumab target PD1 and the PD1 ligand PDL1 respectively to enhance T cell anti-cancer function, but their mechanism of action and optimal distribution characteristics are poorly understood. Thus there is an ongoing debate about whether the target cell population are dysfunctional T cells[15], non-dysfunctional progenitor populations[16], or both. Similarly, CPIs may act on T cells at the cancer site or enhance the activation and migration of cells at distant sites such as draining lymph nodes. Clinical observations of responses and new toxicities observed long after treatment discontinuation highlight the potential of these drugs to exert effects even when presumably no longer active at the target receptor. Finally, even the relationship between PD1 occupancy and clinical outcomes is not established.

These biological uncertainties around the most relevant target population, site and mechanism of action indicate the inadequacy of simple heuristics (e.g. “more is better”) for determining optimal dosing of immunotherapeutics. Specifically, what is the biological parameter to maximise? Since effective pharmaco-kinetic and -dynamic biomarkers are unknown, trials with relevant clinical end points are required to determine optimal parameters of dose, administration frequency and duration.

Clinical evidence of overtreatment with anti-PD1 directed agents

It is increasingly clear from multiple lines of evidence that current immunotherapy regimens result in overtreatment[17–19].

Using conventional dose escalation approaches developed for evaluation of cytotoxic drugs, early phase studies of pembrolizumab and nivolumab sought but failed to identify a MTD for these agents, indicating no clear dose-response relationship. This was observed in the phase I KEYNOTE-001 study of pembrolizumab with doses ranging from 1 to 10 mg/kg every 2 weeks[20] and for nivolumab doses between 0.1 to 10 mg/kg every 2 weeks[21]. This lack of a clinical dose-response relationship is reflected by measurements of PD1 receptor occupancy. For nivolumab, receptor occupancy at 8 weeks was not significantly different across the dose range (0.1 to 10 mg/kg)[21]. Crucially, whilst the drug was cleared from the circulation within days, occupancy reached a dose-independent plateau of 59-81% at over 8 weeks from a single infusion[22]. Additional data are scarce, but in a recent report of five patients who discontinued nivolumab after long term use, receptor occupancy varied between 40 to over 90% between 20 to 30 weeks after discontinuation[23]. Whilst there are no published data directly measuring PD1 receptor occupancy following pembrolizumab therapy, the manufacturer has evaluated anti-PD1 effect using an IL2 release assay as a measure of T cell function. This showed little evidence of a dose-response relationship particularly in the range of 1 – 10 mg/kg[20].

Such findings are consistent with the high affinity of CPIs for PD1, yielding target saturation at low drug concentrations. For nivolumab, 0.04 μg/ml of drug is sufficient to occupy >70% of PD1 molecules in vitro. This concentration is one third of the minimum serum-detectable level by enzyme linked immunosorbent assay, suggesting conventional measurements of peak and trough serum drug levels may not be relevant markers to guide optimal dose and frequency of administration.

Although pembrolizumab phase I data demonstrated that target saturation is achieved after 1 cycle with a dose of 0.1 mg/kg, drug distribution and receptor occupancy modelling was carried out to determine the recommended phase II dose. These studies indicated that 2 mg/kg is required to achieve 90% occupancy at drug trough levels within poorly vascularised tumour regions. This model makes a number of crucial assumptions: firstly, that pre-existing tumour infiltrating T cells are the primary target of pembrolizumab, rather than circulating or lymph node resident cells; secondly, that the dynamics of drug clearance are constant and finally that drug effects are transitory, i.e. anti-cancer T cells exposed to pembrolizumab return to a baseline state of reduced functionality once PD1 is no longer bound.

The notion that there is no relationship between dose and response in the range tested has been confirmed across multiple clinical trials. In the phase I KEYNOTE-001 study there was no evidence of a difference in response rate amongst patients with non-small cell lung cancer (NSCLC) randomised to pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks in an exploratory analysis[24]. Combined analysis of KEYNOTE-001, -002 and -003 similarly found no significant reduction in response rate at doses down to 1 mg/kg every 3 weeks[25]. In larger studies, the phase 2/3 KEYNOTE-010 study found no significant difference in overall survival between patients with NSCLC randomised to pembrolizumab 2 mg/kg vs. 10 mg/kg[26]. A similar lack of association between pembrolizumab dose and survival has been reported in melanoma[27] and renal cell carcinoma trials with nivolumab doses between 0.3 to 10 mg/kg[28]. Small scale observation data demonstrate that patients with NSCLC treated with flat dose pembrolizumab at 100 mg had equivalent survival outcomes to those treated with the 200 mg standard of care dose[29]. Similar results have been reported with low dose nivolumab (20 or 100mg fixed dose vs 3 mg/kg every two weeks)[30]. Finally, patients treated with reduced frequency pembrolizumab due to toxicity, non-toxicity related medical issues or preference were found not to have compromised outcomes[31].

Whilst there is no dose-response relationship in the tested range, interestingly there is evidence of a relationship between drug clearance and response[32]. Re-analysis of KEYNOTE-002 and KEYNOTE-010 data showed that slow pembrolizumab clearance after the first dose is associated with enhanced overall survival. Strikingly, this effect was independent of the

dose delivered (2 vs. 10 mg/kg)[33]. Along with evidence that clearance declines over time in association with tumour stabilisation and metabolic normalisation[34] these data suggest clearance itself is not implicated in tumour response but rather the importance of confounding factors such as cancer cachexia that may independently impact both the rate of antibody clearance and associate with patient outcomes.

In addition to dose and schedule, there is mounting evidence that prolonged durations of treatment are similarly unnecessary. Whilst pembrolizumab therapy for NSCLC is licensed for up to 2 years, studies of responding patients who stopped therapy as planned at 2 years or earlier because of toxicity reveal durable responses off treatment [35–37]. In melanoma, there is similar evidence that patients who stop before progression because of toxicity or having achieved complete response have equivalent outcomes to those who continue treatment[38,39].

These data have motivated a number of early stopping trials currently open in melanoma[40–42], but enthusiasm for such a trial in NSCLC was dampened by results of the Checkmate 153 study. In this trial, the primary endpoint was the safety of nivolumab every 2 weeks in older patients with NSCLC (aged over 70) and those with poor performance status. Additionally, an exploratory endpoint was included of efficacy amongst 163 patients randomised at 1 year to stop or continue therapy for up to 2 years with retreatment allowed at progression in the discontinuation arm[43]. Notably, those in the continuous treatment arm had a significantly better progression free survival (hazard ratio 0.42, 95% confidence interval 0.25-0.71, median not reached). With 14.9 months follow-up, there was no evidence of a difference in overall survival between arms. Whilst these results suggest caution for future early stopping trials of immunotherapy in NSCLC, the study was not powered for overall survival.

Consequently, whilst the question of whether early stopping of immunotherapy for NSCLC is safe remains open, there remain concerns around early discontinuation of immunotherapy.

Taken together, the high affinity, prolonged receptor occupancy and flat relationship between anti-PD1 drug dose and clinical outcome across a wide range, suggest significant scope for optimisation of dose and administration frequency.

Why optimise immunotherapy usage?

Arguments in favour of optimising immunotherapy administration regimens broadly centre on considerations of cost, quality of life and toxicity.

Rising medication costs are a major cause for concern globally. In the USA, cancer care was estimated to cost $183 billion in 2015 and projected to rise to $246 billion in 2030, with similar trends around the world[44]. Rising costs place significant pressures on healthcare systems,

with ongoing debate around how care should be funded[45,46]. For individuals, the financial toxicity of cancer treatment is increasingly recognised as an important factor[47]. The cost of new drugs is particularly an issue in low and middle income countries[48,49], where a lack of access to agents including immunotherapies[50] exacerbates global health inequalities. Some have argued the problem stems from how the pharmaceutical industry is incentivised[51–53] and a solution lies in the political domain with approaches such as taxation and even nationalisation[54]. Alternatively, more effective clinical trial methodologies to determine optimal regimens may represent a more practical approach that additionally solves problems of overtreatment beyond cost alone.

CPIs are amongst the most expensive medications to be routinely prescribed, with UK list prices of pembrolizumab and nivolumab approximately £90,000 and £70,000 for one year of treatment. Efforts to reduce the dose, administration frequency and duration could have global implications in terms of patient access to such agents, in addition to enabling more efficient use of scarce healthcare resources.

Aside from reducing financial toxicity associated with drug costs, optimisation of administration frequency would be expected to yield enhancements in quality of life associated with reduced hospital visits for treatment and pre-treatment evaluation[55].

In addition, optimised regimens may result in fewer immune related toxicities since CPIs drive T cell activation and thresholds to elicit anti-cancer directed responses are usually lower than for autoimmune responses against normal tissues[56]. Finally, a proportion of patients experience rapid progression upon commencing anti-PD1 directed therapies, which may be related to effects of the drug on suppressive T cells that express particularly high levels of PD1[57]. Thus, immunotherapy regimen optimisation may yield important safety benefits.

Determining the optimal frequency of immunotherapy administration

Current regulations prohibit the sharing of single dose drug vials between multiple patients[58]. In the absence of pharmaceutical industry support, reduced dose immunotherapy studies are thus practically limited and optimisation of administration frequency is an attractive alternative. This is particular the case since reduced administration frequency has additional benefits of reduced hospital visits yielding cost reductions beyond the price of the drug, along with quality of life improvements.

But what is the optimal trial design to determine the lowest frequency of pembrolizumab administration that does not compromise efficacy? One option is a conventional two-arm non-inferiority trial comparing standard of care to a reduced frequency intervention arm. Given the

interest in reduced frequency immunotherapy, multiple two arm trials with this design are currently evaluating the performance of various extended intervals ranging between x2 to x4 the standard of care interval[59–61]. But a major limitation of this design is that it calls upon investigators to guess the optimal alternative frequency to test, in the absence of preliminary data to guide rational selection of this alternative. If the test frequency is poorly chosen, the trial will inevitably give a negative result, even if another non-inferior frequency existed. A second major limitation is that a large number of patients is required to adequately power such trials, making it difficult to test a number of dose frequencies.

Several novel approaches utilising Bayesian adaptive models exist to optimise continuous aspects of treatment such as dose in early phase (I-II) trials[62,63]. However, these are unsuitable for solving this issue in phase III studies of treatments already known to be effective and where the question of non-inferiority versus standard of care is critical. Specifically, these methods aim to determine the MTD and balance this against efficacy, measured in a short time scale. Since early phase studies of anti-PD1 directed agents have already demonstrated MTD is not reached in a 100-fold dose range, this design consideration is not relevant. Furthermore, since the allocation ratio between arms is altered based on evaluation of short term outcome data, these designs are poorly suited to cope with inherent features of late phase trials, e.g. the focus on long-term survival as primary outcome. The only proposed alternative we are aware of is the DOOR/RADAR design[64], which involves categorizing patients based on benefits and harms into an overall clinical outcome and ranking them according to better outcomes and/or reduced treatment duration. This is being used in several trials[65–67] but has been criticised[68], particularly on the ground that combining clinical outcome and some aspect of treatment administration into a single variable can hide important differences in the clinical outcome.

To address the need to explore a wide range of administration frequencies in a single, reasonably sized study, we have developed a novel MAMS-ROCI trial design. This was an extension of our prior work to design a hypothetical trial that could determine the optimal duration of antibiotic therapy for a given infectious disease[69]. The MAMS-ROCI design can in principle be used to determine the optimal value of any continuous treatment variable (i.e. dosage, duration and frequency/schedule) and we focus here on administration frequency.

Here, we propose that discovery of the optimal administration frequency can be achieved by randomising patients to multiple treatment arms evenly distributed across a clinically reasonable range of frequencies. This increases the probability of including the optimal arm in the study. Rather than comparing each test arm against the control in a 1:1 fashion, a model is fitted to estimate the frequency-response curve describing the relationship between frequency and efficacy across the entire range of alternatives tested. By sharing information

across arms, the efficiency of the study is enhanced and hence the number of patients required is reduced. Using the model, the longest frequency with efficacy non-inferior to control 6-weekly therapy can then be determined. This design is thus capable of exploring a range of alternative frequencies when the optimal one is unknown, and often does so with a comparable number of patients to that of a conventional two-arm non-inferiority study.

The REFINE-Lung study

To determine the optimally reduced frequency of 1st line pembrolizumab for advanced NSCLC, REFINE-Lung will recruit 1750 patients who do not have progressive disease after 6 months of treatment and are otherwise planning to continue pembrolizumab therapy. Patients initially treated either with single agent pembrolizumab or in combination with chemotherapy are eligible. Randomisation is evenly distributed between control (6-weekly pembroluzimab) or one of 4 frequency-reduced arms spaced at 3-weekly intervals (9, 12, 15 and 18-weekly arms; Figure 1).

To limit the risk of needlessly exposing patients to reduced frequency treatment that is significantly less effective than control, we will initially randomise to an internal pilot study comparing control 6 vs. 12-weekly therapy. If an event driven interim analysis does not show the 12-weekly treatment to be significantly less effective, subsequently recruited patients will also be randomised to 9, 15 and 18-weekly treatment frequency arms. The primary outcome measure is overall survival at 2 years, with secondary outcome measures including quality of life, toxicity and cost effectiveness of the defined optimal dose frequency. Importantly, patients who develop progressive disease on a reduced frequency arm will be offered treatment beyond progression with re-escalation to standard 6-weekly therapy.

Practical design considerations for a MAMS-ROCI frequency optimisation study

How should a MAMS-ROCI frequency optimisation study be designed in general? Major practical issues to resolve include decisions around selecting the number and distribution of reduced frequency arms that patients are randomised to, how many patients are required and how to deal with the possibility that frequencies longer than standard of care may in general be detrimental. As a guide for investigators interested in establishing similar trials including those optimising treatment variables other than administration frequency, practical design considerations with reference to REFINE-Lung are discussed below.

Choice of arms

In general, there is a clear rationale for the shortest frequency arm to be equivalent to standard of care (6-weekly in the context of pembrolizumab for lung cancer). In choosing the longest

frequency arm, we opted for 18-weekly based on two principle considerations. Firstly, phase I data had shown that a single dose of pembrolizumab was still bound to its PD1 receptor target on immune cells with high occupancy after 140 days. Secondly, we established that the thoracic oncology healthcare community as well as patients and their representatives were comfortable with this reduced frequency knowing that in the event of disease progression treatment would be escalated back to the standard of care 6 weekly frequency.

The true frequency-response relationship cannot be assumed to be linear and may take a number of forms, thus complicating conventional approaches to sample size calculation. We therefore employed simulation studies.

To model the frequency-response relationship using simulated data, we applied a fractional polynomial regression approach with binary outcome data (overall survival [OS] at 2 years post commencing therapy). This strategy was found to be robust to a variety of possible frequency-response relationship curves, with type I error (the probability of finding no evidence of a difference between 18 and 6-weekly arms where one exists) controlled across scenarios[70] (Figure 2).

In additional simulation studies, we found at least 5 arms are needed to model a likely range of relationships using the preferred analysis method and showed that little is to be gained beyond 7 arms. In general, optimal models were generated in experiments where intermediate arms are spaced approximately equidistantly. Since pembrolizumab is usually given 3 or 6-weekly, we opted to retain 3 weekly intervals in the final design. Thus, a final design of 6, 9, 12, 15 and 18-weekly arms naturally fit the constraints defined above.

Selecting the optimal administration frequency

The optimal frequency is defined prospectively as the longest one which is non-inferior to control 6-weekly therapy (Figure 3). Practically, this means the lower bound of the 95% confidence interval (CI) around the risk ratio of the selected arm (risk ratio defined as the experimental arm 2 year OS / control arm 2 year OS) is above the non-inferiority margin. In line with multiple other studies[71–73], we prospectively defined the limit of non-inferiority in REFINE-Lung as that which preserves at least 50% of the effect of treatment vs. control, yielding a risk ratio margin of 0.88. Thus, an active arm can be declared non-inferior if the lower bound of the 95% CI for the 2 year survival risk ratio against 6-weekly is above 0.88. Clearly, however, once we have plotted the frequency response curve, readers can put their own constraints to select the longest frequency which they consider non-inferior to the standard 6-weekly regimen, although the trial would not be powered for that non-inferiority margin.

Number of patients required

MAMS-ROCI once more utilises simulated data to determine the overall sample size required. In designing REFINE-Lung, this was done on the assumption of a two year OS of approximately 65% based on available data from completed trials[74–76], whilst considering that patients are enrolled having already achieved 6 months treatment.

For the sample size calculation, we first generated data under the assumption that survival is the same irrespective of treatment frequency. Based on discussions with patient groups, this was felt to be an important starting point since it would be unethical to randomise patients to treatment expected to be of suboptimal efficacy.

In each simulated trial, we randomly allocated each patient to one of the five arms and randomly generated a binary outcome of OS at 2 years from a Bernoulli distribution. We next fitted a fractional polynomial regression model to estimate the frequency-response curve.

The fitted model is used to determine the risk ratio and confidence interval for each arm compared to 6 weekly control.

With these design parameters, 1550 patients equally distributed between 5 arms were enough to achieve 80% power to find that the 18 weekly arm was non-inferior to 6 weekly, using a one-sided significance level of 5% (Figure 4). Allowing for ~10% attrition (loss of patients from the study), the total sample size is 1750.

It is instructive to compare this against a conventionally designed non-inferiority design. In a standard two-arm study comparing 12 vs. 6-weekly therapy, assuming a two year OS of 65% and an 8% risk difference margin of non-inferiority (65%-0.88*65%), 1660 patients are required for 90% power and a 2.5% one sided significance level allowing 10% attrition.

Are longer frequencies safe? An adaptive design element

Whilst we assume clinical equipoise between the arms, it is unknown whether reduced frequency therapy may in general be detrimental. Thus, it may be considered unethical to open all four frequency reduced arms simultaneously. The MAMS-ROCI design tackles this by including an adaptive element. Patients are initially randomised to standard of care 6-weekly vs. 12 weekly arms in the first stage of the study. The remaining arms will be opened only if an interim analysis finds no significant difference in progression free survival (PFS). In selecting the 12-weekly arm as the comparator, we aimed to select the longest frequency, below which there would be little scope for optimisation. Thus if 12 weekly therapy was found

to be detrimental, we would assume the standard 6-weekly regimen cannot be meaningfully lengthened.

Whilst multiple stages could be considered to ensure longer frequency arms are opened only if shorter frequencies are found not to be inferior to control, this significantly complicates the trial design. Beyond the first stage, the independent data monitoring committee will review the data every 6 months to assess whether it is appropriate to continue randomising to all arms.

Addressing overtreatment in oncology using the MAMS-ROCI design: dose, duration and frequency optimisation

Broadening the scope beyond frequency optimisation of immunotherapy, the era of high cost, targeted cancer therapeutics has brought a general need for clinical trials approaches to optimise their use. The academic community is well placed to address this need. We propose the MAMS-ROCI design implemented in REFINE-Lung could be widely adopted to reduce guesswork inherent in current approaches to determining optimal dose, frequency of administration and total duration of expensive agents. Indeed, the novel MAMS-ROCI trial design serves as a new paradigm for testing dose frequency reduction of immunotherapies across multiple cancer types and a basket approach across other cancer types is being established, with a cohort of patients with advanced renal cell carcinoma and melanoma currently open to recruitment (NCT04913025). This could have significant cost benefits for healthcare systems globally, in addition to patient centred benefits of enhanced quality of life associated with fewer hospital attendances and reduced toxicity.

Figures

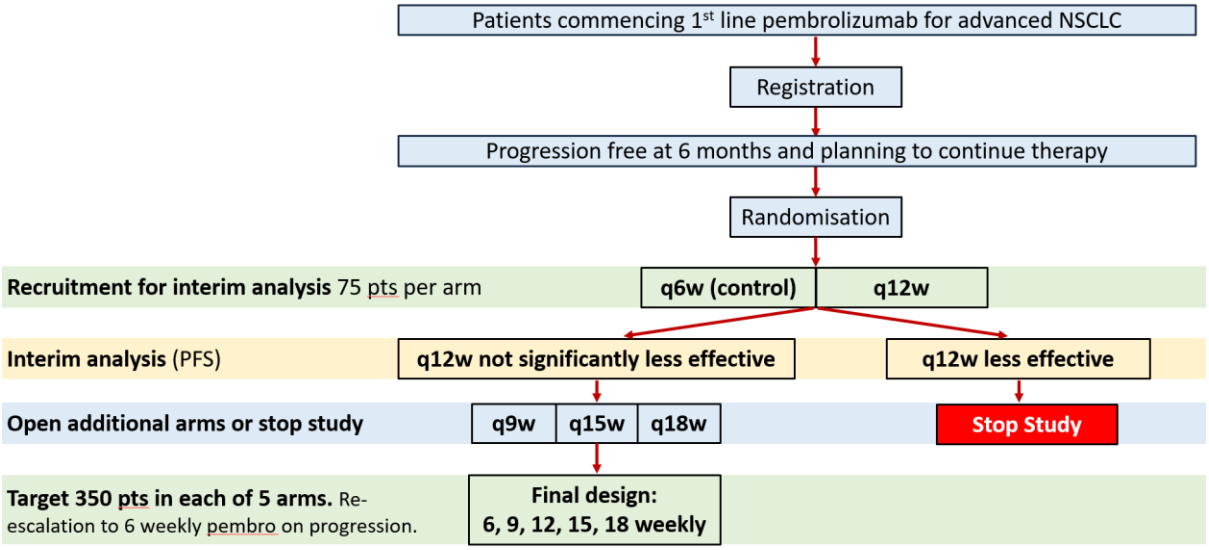

Figure 1. REFINE-Lung study flow chart. Pts, patients; Pembro, pembrolizumab; qNw, treatment given every N weeks.

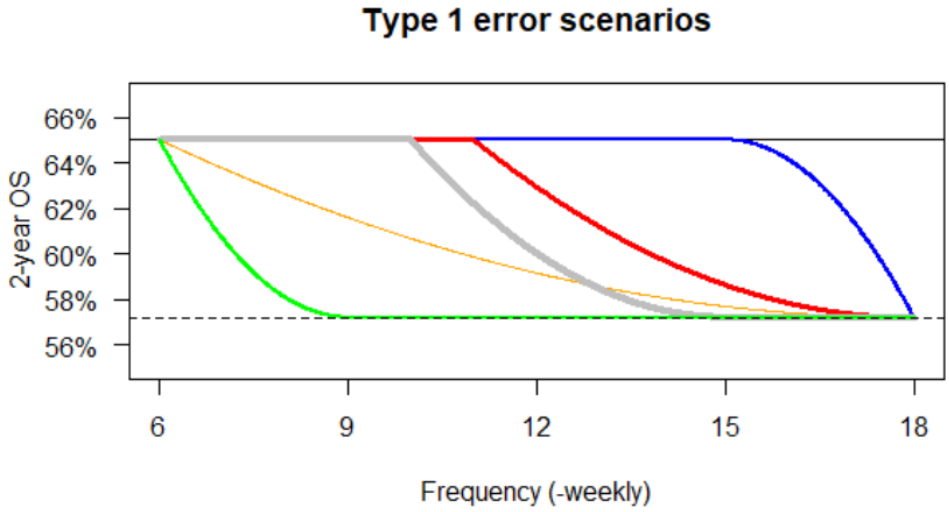

Figure 2. Type 1 error is controlled across a range of frequency-response scenarios. We modelled the frequency-response relationship for a variety of linear and non-linear scenarios, from a 2 year OS of 65% to 57.2% (the boundary of non-inferiority vs. 6-weekly control). Each scenario is represented by a different line colour. In all cases, with 1550 patients, the type 1 error rate in a comparison of 18- vs. 6-weekly arms was under 5%.

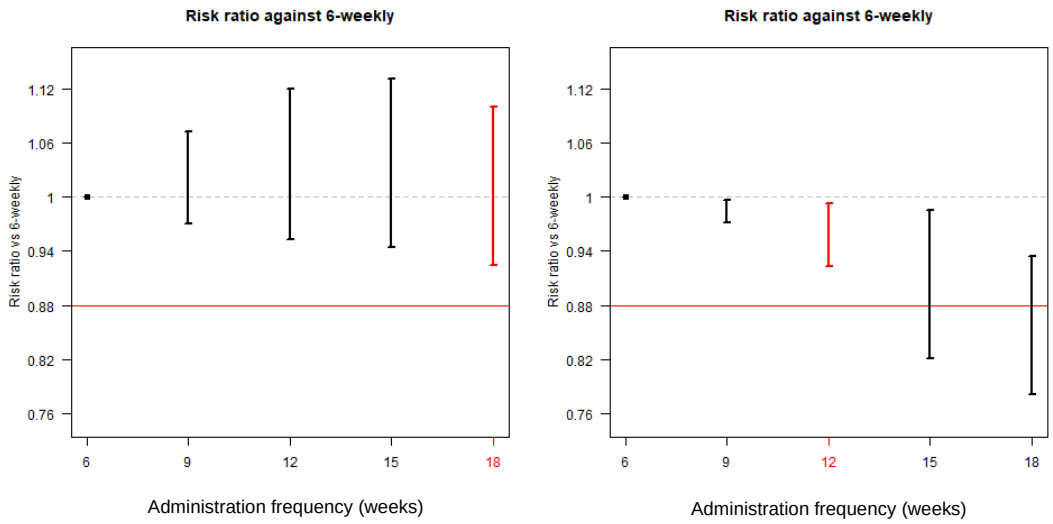

Figure 3. Illustration of how the optimal frequency to recommend will be determined. Two possible frequency-response relationships are represented using simulated data. The red horizontal lines represent the margin of non-inferiority vs. 6-weekly control. In the left panel, the 18 weekly arm is the longest frequency with a risk ratio within the non-inferiority margin. In the right panel, the 12 weekly arm meets this criterion and is optimal.

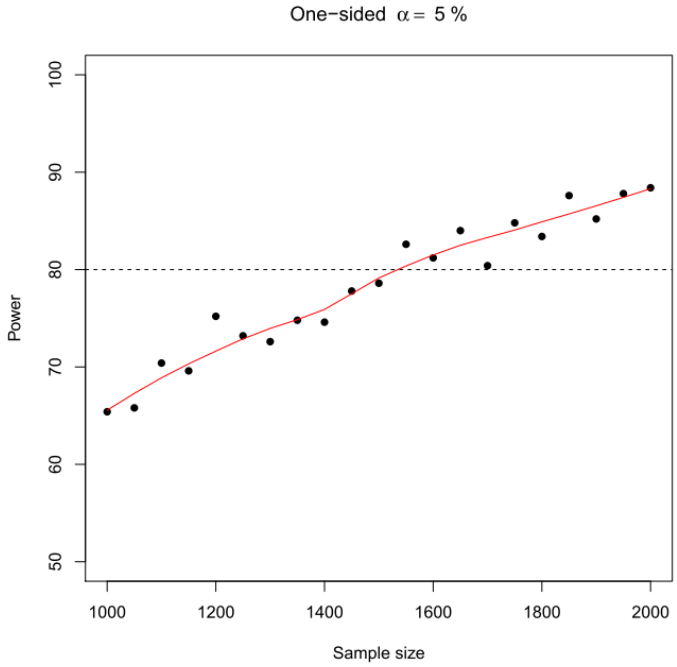

Figure 4. Sample size estimation. Power was simulated across a range of sample sizes. 80% power is achieved with 1550 patients, with a one sided alpha of 5%. Each point represents a simulated trial.

Contributors

EG, MQ, MKBP and MJS conceived this Personal View. EG and MQ searched the literature and drafted the manuscript. MQ, EG, MJS and MKBP developed the trial design along with

FB, DCG, MOB, CO, EP, JS, AW and PB [+patient representative], based on initial theoretical work carried out by MQ and MKBP. MJS and MKBP jointly supervised. All authors wrote, commented on, and revised the manuscript and are responsible for the decision to submit for publication.

Search strategy and selection criteria

Searches of PubMed, NICE and clinical trial databases were performed using various combinations of the terms immunotherapy, pembrolizumab, nivolumab, lung, cancer, trials, pharmacokinetics and pharmacodynamics. Randomised phase III trials were considered to provide best evidence. Data from ASCO and ESMO 2022 were also considered.

Declaration of interests

The authors have no relevant competing interests to declare [pending confirmation].

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