

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/131018/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Middleton, Gary, Brock, Kristian, Savage, Joshua, Mant, Rhys, Summers, Yvonne, Connibear, John, Shah, Riyaz, Ottensmeier, Christian, Shaw, Paul, Lee, Siow-Ming, Popat, Sanjay, Barrie, Colin, Barone, Gloria and Billingham, Lucinda 2020. Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PePS2): a single arm, phase 2 trial. *Lancet Respiratory Medicine* 8 (9), pp. 895-904.
10.1016/S2213-2600(20)30033-3

Publishers page: [http://dx.doi.org/10.1016/S2213-2600\(20\)30033-3](http://dx.doi.org/10.1016/S2213-2600(20)30033-3)

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



PePS2: A single-arm phase II trial of pembrolizumab in patients with non-small cell lung cancer and a performance status of 2

Prof Gary Middleton, MD¹, Kristian Brock, PhD², Joshua Savage, PhD², Rhys Mant MA², Yvonne Summers, PhD³, John Connibear, MD⁴, Riyaz Shah, PhD⁵, Prof Christian Ottensmeier, PhD⁶, Paul Shaw, PhD⁷, Prof Siow-Ming Lee, PhD⁸, Prof Sanjay Papat, PhD⁹, Colin Barrie MRCP¹⁰, Gloria Barone MD¹¹ & Prof Lucinda Billingham, PhD²

¹Institute of Immunology & Immunotherapy, University of Birmingham, UK, ²Cancer Research UK Clinical Trials Unit, University of Birmingham, UK, ³The Christie, Manchester, UK, ⁴St Bartholomew's Hospital, London, UK, ⁵Kent Oncology Centre, Maidstone Hospital, Maidstone, UK, ⁶Southampton CRUK Experimental Cancer Medicine Center, University of Southampton & University Hospital Southampton NHS Foundation Trust, Southampton, UK, ⁷Velindre Cancer Centre, Cardiff, UK, ⁸University College London Hospital/CRUK Lung Cancer Centre of Excellence, London, UK, ⁹ The Institute of Cancer Research, London, UK, ¹⁰Western General Hospital, Edinburgh, UK, ¹¹Lincoln County Hospital, Lincoln, UK

Corresponding author: Gary Middleton

Abstract

Background Therapeutic blockade of the PD-1/PD-L1 axis has transformed the management of non-small cell lung cancer (NSCLC). Clinical trials with pembrolizumab have enrolled patients with performance status (PS) 0-1. However, around 18% of NSCLC patients have a PS of 2 and the activity and safety of pembrolizumab in these patients is unclear. The aim of this trial was to evaluate the safety and efficacy of pembrolizumab in these patients.

Methods PePS2 is a UK multi-centre, single arm, phase II trial in which NSCLC patients with a rigorous ascertainment of PS2 were treated with pembrolizumab 200mg q3weekly. The trial is designed to stratify the treatment evaluation by TPS and line of therapy and co-primary outcomes were: i) durable clinical benefit (DCB), defined as the occurrence of complete response, partial response or stable disease that continues until at least the second CT scan scheduled at 18 weeks; and ii) toxicity (TOX), defined as the occurrence at any time of treatment-related dose delay or treatment discontinuation due to adverse event. Analysis included all patients who had any pembrolizumab. As well as reporting simple observed rates for the co-primary outcomes, DCB and TOX rates are estimated by a model-based method for correlated binary outcomes. The most common grade 3-4 adverse events were dyspnea (affecting n=9 patients), hyponatremia (n=5) and anorexia (n=4). There were 10 SAE felt to be related to treatment. PePS2 is now closed to recruitment and we present final results of the trial. The trial is registered with ClinicalTrials.gov (NCT02733159), EudraCT (2015-002241-55) and ISRCTN (10047797).

Results 60 patients were evaluable for the co-primary outcomes. The observed rate for DCB was 38% (95% CI 21-57%) in first-line patients (n=24) and 36% (95% CI 22-52%) in subsequent-line patients (n=36), and it was 22% (95% CI 11-41%) in patients with TPS<1% (n=27), 47% (95% CI 25-70%) in TPS 1-49% (n=15) and 53% (95% CI 30-75%) in TPS ≥50% (n=15). An increase in DCB rates with TPS was also demonstrated in model-based estimates. TOX was observed in 28% (95% CI 19-41%) of patients, 18% due to dose delay and 10% due to drug discontinuation. There were no G5 treatment-related adverse events and no early deaths attributed to hyperprogression.

Conclusions NSCLC patients of PS2 are a group of patients of unmet therapeutic need. The PePS2 trial shows that pembrolizumab can be safely administered to PS2 lung cancer patients, with no increase in the risk of immune-related or other toxicities. Efficacy outcomes are at least as good as those in PS0-1 patients and the data provides clinicians with the confidence to incorporate pembrolizumab into the treatment pathway of PS2 NSCLC patients.

This trial was funded by Merck, Sharp and Dohme.

Research in context

Evidence before this study Pembrolizumab, the anti-PD1 monoclonal antibody, is indicated as monotherapy in the UK in patients with NSCLC as a first line therapy in those with a tissue proportion score (TPS) of $\geq 50\%$ and in subsequent lines of therapy in those with TPS $\geq 1\%$. The studies that led to these approvals, which have revolutionised the management of NSCLC, only enrolled patients with ECOG performance status of 0-1. Indeed all randomised and registration studies of checkpoint blockade agents in NSCLC have also restricted inclusion to those of good PS. However, a significant proportion of NSCLC patients in practice are PS2. These are patients ambulatory and capable of self-care but unable to carry out any work activities and are up and about more than 50% of the time. In the 2018 UK National Lung Cancer Audit Annual Report, 6361 of 39199 (18%) patients were PS2. Data on the efficacy and safety of checkpoint blockade in this important cohort is very limited, whilst outcomes stratified by TPS are negligible. This data is crucial to evaluating the risk:benefit equation for these important therapies in this group of patients with significant unmet therapeutic need.

Added value of this study The objective of the PePS2 trial was to answer whether pembrolizumab is a beneficial treatment option in advanced PS2 NSCLC patients. A highly accurate ascription of PS2 status was crucial. Assessment of PS was performed two weeks apart to ensure stability of PS and consistency of assessment, and the ECOG definitions of

PS2 status were included in both the inclusion and exclusion criteria and incorporated into the eligibility checklist for registration. Durable clinical benefit (no evidence of progression at 18 weeks, the time of the 2nd CT evaluation), was a co-primary outcome measure and the observed rate was 38% (95% CI 21-57%) in first-line patients (n=24) and 36% (95% CI 22-52%) in subsequent-line patients (n=36). DCB rate was 22% (95% CI 11-41%) in patients with TPS<1%, 47% (95% CI 25-70%) with TPS 1-49% and 53% (95% CI 30-75%) with TPS \geq 50%. Toxicity, the second co-primary outcome measure, defined as the occurrence at any time of treatment-related dose delay or treatment discontinuation due to adverse event was observed in 28% (95% CI 19-41%) of patients, 18% due to dose delay and 10% due to drug discontinuation. There were no G5 treatment-related adverse events and no early deaths attributed to hyperprogression. Objective response rates were 11% (95% CI 4-28%), 33% (95% CI 15-58%) and 47% (95% CI 25-70%) for TPS<1%, TPS1-49% and TPS \geq 50% respectively. These data demonstrate that pembrolizumab can be safely administered to PS2 lung cancer patients, with no obvious increase in the risk of immune related or other toxicities or of the risk of hyper-progression. Efficacy outcomes are at least comparable to those obtained in PS0/1 patients treated with 2nd line pembrolizumab.

Implications of all the available evidence These data suggest that pembrolizumab can be considered as a treatment option for advanced PS2 NSCLC patients It provides clinicians with the evidence base to support the incorporation of pembrolizumab into the treatment pathway of PS2 NSCLC patients.

Introduction

The introduction of checkpoint blockade into the management of non-small cell lung cancer (NSCLC) has been transformative. Pembrolizumab monotherapy is standard of care in the UK for the management of 1st line patients with a tumour proportion score (TPS) $\geq 50\%$ based on superior overall survival (OS) when compared with platinum-containing doublet chemotherapy (1) and also for 2nd line patients with TPS $\geq 1\%$. Recent updated data from the phase I KEYNOTE-001 study of pembrolizumab monotherapy in NSCLC patients demonstrated a median OS for previously treated patients of 10.5 months and 5 year OS rate of 15.5%: the 5 year OS rate in patients with PD-L1 TPS $\geq 50\%$ was 25% and for those with TPS 1-49% it was 12.6% (2). Objective response rate in previously treated patients was 22.9%, and disease control rate 58.6%. It is also approved for use in combination with chemotherapy as a 1st line therapy in both non-squamous NSCLC and squamous cell lung cancer patients irrespective of PD-L1 TPS (3, 4). However, these studies and indeed all randomised studies have only included patients of performance status (PS) 0-1. A sizable proportion of NSCLC patients in real-world clinical practice are PS2. These are patients who are ambulatory and capable of self-care but are unable to carry out any work activities and are up and about more than 50% of the time (5). In the 2018 UK National Lung Cancer Audit Annual Report, the most comprehensive annual analysis of the management and outcome of lung cancer patients globally, 6361 of 39199 (18%) patients were PS2 (datasheet available at <https://www.rcplondon.ac.uk/projects/national-lung-cancer-audit>.) Data on the efficacy and safety of checkpoint blockade in this important cohort is very limited, whilst outcomes stratified by TPS are negligible. A recent Journal of Clinical Oncology commentary specifically drew attention to the lack of robust data on the efficacy and safety of checkpoint blockade in PS2 NSCLC patients (6). Whilst the FDA and EMA approvals are irrespective of PS, it was pointed out that it is unknown whether the available PS0/1 data can be extrapolated to those with PS2 or greater disease and clinicians are simply not in a position to adequately assess the risk-benefit equation for the use of pembrolizumab in their patients with PS2. Indeed, in the UK NHS funding for pembrolizumab is only available for patients with PS 0-1 on the basis that this is the only group for which prospective data on activity and safety are available. Prospective data are thus necessary to assess whether pembrolizumab monotherapy is a

suitable treatment for these patients. We report here the final results of the first prospective trial of the outcome of PD-1/PD-L1 blockade enrolling exclusively PS2 NSCLC patients, with a rigorous ascription of PS2 status and stratified by TPS. The aim of this study was to examine whether pembrolizumab is a beneficial treatment option in advanced PS2 NSCLC patients.

Methods

Study design

PePS2 is a multi-centre, single arm phase II clinical trial of pembrolizumab in advanced NSCLC patients with Eastern Cooperative Oncology Group (ECOG) performance status of 2 (PS2), recruiting from 10 hospitals in the United Kingdom. The trial is designed to stratify the treatment evaluation by TPS (<1%, 1-49%, ≥50%) and line of therapy (first or subsequent). Ethics approval for the trial protocol (ultimately Version 6.0, dated 10-Jul-2018, Supplementary Material) was obtained from the West Midlands-Edgbaston Research Ethics Committee in accordance with national regulatory requirements.

Participants

Participants had histologically confirmed NSCLC, aged ≥18 years, with a life expectancy of >12 weeks and had completed all lines of standard of care therapy that the oncologist deemed appropriate. The inclusion and exclusion criteria explicitly included the wording of the ECOG definitions of PS2 status and these were also incorporated into the eligibility checklist for registration. The trials unit stressed the importance of correct ascription of PS at each of the 10 site initiation visits and at monitoring visits the source data was checked to ensure participants were assessed as PS2 at time of registration. PS was assessed by the treating physician and PS2 status had to be stable for at least two weeks prior to trial entry. No molecular testing was required except PD-L1 status, and thus no specific molecular subtype of NSCLC such as EGFR mutant or STK11/KRAS double mutations were excluded. Patients were eligible regardless of TPS on the archival specimen. PD-L1 testing was only performed in laboratories approved by Merck Sharp & Dohme for PD-L1 testing using the 22C3 antibody. If the TPS could not be assessed on the sample, a repeat biopsy was mandatory. However, if TPS could not be ascertained on this repeat biopsy the patient could

be included in the trial. Patients were not allowed to have received immunosuppressive therapy within seven days prior to first dose and were excluded if there was any evidence of clinical autoimmunity or active autoimmune disease that required systemic treatment in the previous 2 years. Other key eligibility criteria include measurable disease according to RECIST1.1, adequate haematological, hepatic and renal function and being able to give written informed consent. Patients with untreated symptomatic brain or leptomeningeal metastatic disease were excluded. Patient registration into the trial by the treating clinician was by telephone to the central registration service at the Cancer Research UK Clinical Trials Unit at the University of Birmingham.

Procedures

Pembrolizumab (Merck, New Jersey, United States of America) was administered as a 30-minute intravenous infusion at a flat dose of 200mg every three weeks, defining a cycle of treatment, for up to 2 years or until disease progression. Dose adjustments and cycle delays were permitted in the event of toxicity with protocol-specific recommendations. Pre-treatment evaluation included medical history, clinical examination, laboratory analyses and tumour assessment by CT scan with measurable lesions being a requirement for the trial. Clinical evaluation and patient-reported quality of life assessment was scheduled every 3 weeks during treatment in accordance with outpatient clinic visits. CT assessments were scheduled to be performed every nine weeks and response was assessed by RECIST v1.1 (7). After discontinuation of treatment, patients were followed up every 4 weeks for 6 months and every 12 weeks thereafter.

Outcomes

The co-primary outcomes for the trial are: i) durable clinical benefit (DCB), defined as the occurrence of any one of investigator-reported confirmed complete response (CR), partial response (PR) or stable disease (SD) that continues until at least the second CT scan scheduled to occur at 18 weeks; and ii) toxicity (TOX), defined as the occurrence at any time of a treatment-related dose delay or treatment discontinuation due to an adverse event.

Lancet Respiratory Medicine Manuscript Reference: THELANCETRM-D-19-00698R1

Original Manuscript Reference: THELANCETONCOLOGY-D-19-01571

Patients with advanced NSCLC who are PS2 have a poor prognosis, especially at the point when they fail first line therapy, and therefore DCB at 18 weeks was chosen as this represents a meaningful benefit in such patients. Given the use of six month DCB rates in many studies enrolling PS0/1 participants, a post-hoc sensitivity analysis was also included using a longer-term outcome measure of the occurrence of DCB (specifically at the time of the 3rd scan scheduled at 27 weeks, DCB27). TOX was chosen to reflect the feasibility of delivering pembrolizumab to this less fit group of patients and reflects the concerns that patients express in real-world clinical practice concerning delays in treatment adversely impacting on outcome. However, given that there is no robust clinical evidence that delays have a significant negative impact on outcome with checkpoint blockade, we have also done a post-hoc sensitivity analysis using a toxicity definition that only includes discontinuations due to treatment-related toxicity (TOXDIS) and also a more traditional definition that includes the incidence of treatment-related grade3-5 adverse events at any time during the trial (TOXAE3-5)

Secondary outcomes include the occurrence of an objective response (OR), i.e. CR or PR as the best response recorded over the period of assessment. For those patients whose best response is OR, duration of objective response (DOR) from commencement of trial treatment will be reported and similarly duration of stable disease (DSD) for those whose best response is SD. Also time to progression (TTP), progression-free survival time (PFS) and overall survival time (OS) from commencement of trial treatment are included, with patients not experiencing the event censored at date last known to be free of the event. In addition, patient-reported health-related quality of life (HRQoL) was collected using the FACT-L (8) and EQ-5D-5L (9) questionnaires. Questionnaires were administered by research staff and completed by patients in clinic at the start of each cycle and generated scores for physical, functional, emotional and social well-being together with general health from the former and a score measuring the utility of their health state and visual analogue score (VAS) measuring general health from the latter.

Collection and reporting of adverse events (AEs) and serious adverse events (SAEs) was mandated throughout the trial in accordance with the Medicines for Human Use and Clinical Trials Regulation 2004 and its subsequent amendments. All medical occurrences that met

the protocol definition of an AE or SAE were reported using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Selected non-serious AEs and SAEs were specified in the protocol as Events of Clinical Interest (ECI) and included immune-mediated AEs.

Statistical analysis

For the co-primary outcomes, DCB and TOX rates are simultaneously estimated using linked logistic regression models (10, 11). The model for DCB incorporates categorical covariates for TPS (<1%, 1-49%, ≥ 50%) and line of therapy (first or subsequent) to allow efficacy estimates to vary between the 6 cohorts. No covariates are included in the model for TOX, thereby assuming uniform toxicity rate across all cohorts. A Bayesian approach with minimally informative priors was used for model estimation with median and 95% credible intervals from the posterior probability distributions providing estimates of the true DCB and TOX rates. Full details of the statistical methodology are provided in the Supplementary Material. Non-model-based estimates for DCB and TOX rates are also provided with 95% confidence intervals using Wilson's method.

There was a strong motivation to deliver findings from the trial quickly due to the patient population being a group of significant unmet therapeutic need, so the sample size was selected as 60 evaluable patients based on the feasible number to recruit within one year. In order to evaluate how well the statistical design would operate with this number of patients, the design specified Bayesian decision criteria that might inform decision-making at the final analysis. Clinically relevant critical cut-offs for positive decision-making were specified as >10% for DCB rate and <30% for TOX rate. Operating characteristics for the trial design were based on guidelines that the treatment would be considered successful if $p(\text{True DCB rate} > 10\%) > 0.7$ and $p(\text{True TOX rate} < 30\%) > 0.9$. Operating performance of the proposed model-based analysis at this sample size was investigated (10, 12) and shown to be acceptable, equivalent to approximately 90% power when true DCB rate is 30% and TOX rate is 10%, and 2.5% type I error when true DCB rate is 10% and TOX rate is 30%.

For secondary outcome measures DOR, DSD, TTP, PFS and OS, Kaplan-Meier curves are used to describe the data and estimate medians with 95% confidence intervals. OR is reported as a rate with 95% confidence intervals calculated using Wilson's method. HRQoL outcomes are

reported using means over time. The population for all analyses of efficacy and safety includes all patients that received at least one cycle of treatment i.e. one infusion of pembrolizumab. There were three patients that had missing TPS categorisation. This variable has three levels (<1%, 1-49%, ≥ 50%), meaning there were $3^3 = 27$ possible imputations. This missing data was handled in model-based analyses by using likelihood-weighted pooling of the inferences from all 27 imputations (full details are provided in the Supplementary Material). All statistical analysis was carried out in R version 3.5.2 (13) using rstan version 2.18.2 (14) and the tidyverse (15) suite of packages. Plots were produced using ggplot2 (16) and tidybayes (17).

All presented analyses were conducted in accordance with the trial protocol and the supplementary statistical analysis plan. The protocol details analyses of data from the FACT-L questionnaire that are not presented here. Analyses of all other outcomes are presented here, including health-related quality of life outcomes from the EQ-5D-5L questionnaire. Post-hoc analyses of the DCB27, TOXDIS, and TOXAE3-5 outcomes are included as described above, in response to reviewers' comments.

An independent Trial Steering Committee provided oversight of the trial on behalf of the sponsor and reviewed interim data at least once per year during recruitment to ensure patient safety. There were no formal stopping rules. The trial is registered with ClinicalTrials.gov (NCT02733159), EudraCT (2015-002241-55) and ISRCTN (10047797).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 4th January 2017 and 13th February 2018, the trial recruited 62 patients from 10 centres in the United Kingdom, 60 of whom received pembrolizumab and are evaluable for co-primary and secondary outcomes (Figure 1). We present here data collected to 8th March

2019 at which point the median follow-up was 10 months. Baseline characteristics of the study population are shown in Table 1. Median age was 72 years. 24 of the 60 patients (40%) received pembrolizumab in the trial as first-line therapy and 45% were PD-L1 negative (TPS<1%). The most common Charlson comorbidity index scores were 8 – 10, with 0 being comorbidity-free and the theoretical maximum comorbidity score being 37. In terms of baseline HRQOL, the mean EQ-5D-5L VAS score at baseline was 53%. Patients received a median of 4.5 (inter-quartile range 2 - 12.75) cycles of treatment, with one patient staying on treatment for 33 cycles (Figure 1).

The primary efficacy outcome, DCB, was observed in 22 patients (37%, 95% CI 26-49%) across all 3 levels of TPS and both lines of therapy (Table 2). The DCB rate was 38% (95% CI 21-57%) in first-line pembrolizumab therapy patients and 36% (95% CI 22-52%) in those receiving it as a subsequent line of therapy. DCB rates increased with level of TPS, both in the observed rates (Table 2), with 22% (95% CI 11-41%) in TPS<1% compared to 53% (95% CI 30-75%) in those with TPS≥50%, and in the model-based rates stratified by line of therapy (Figure 2). Bayesian estimates of DCB rates from the model gave greater than the pre-specified 70% probability that the true DCB rate is > 10% in each of the six cohorts (actually all greater than 84%). Underpinning DCB is the change from baseline in sum of longest diameters of target lesions, which shows that the benefit of pembrolizumab is more pronounced as the TPS level increases (Figure 3A and B). Post-hoc sensitivity analysis using DCB27 demonstrated that the trial remained positive for this longer term outcome, with an observed rate of 32% (see Supplementary Material for details).

The primary toxicity outcome, TOX, was observed in 17 patients (28%, 95% CI 19-41%) (Table 2). The TOX rate in first-line patients was 29% (95% CI 15-49%) and in subsequent-line patients was 28% (95% CI 16-44%). The model estimated the TOX rate as 28% (95% credible interval 17.4% - 39.5%) with 67% probability that the true TOX rate is <30% and, in relation to pre-specified benchmarks, we can be 90% certain that it is <35.2%. In those that experienced TOX, 11 were due to dose delay, 4 due to drug discontinuation and 2 experienced both, with median time to first event of 2.6 months. There were 25 events (in those 17 patients) associated with the primary toxicity outcome measure, including respiratory and thoracic disorders (n=5, one each of cough, dyspnea, hypoxia, pleural

effusion, and pneumonitis); laboratory investigations (n=5, one each of increased alanine aminotransferase, aspartate aminotransferase, blood bilirubin, and creatinine; one low cortisol); and gastrointestinal disorders (n=5, two mucositis and one each of constipation, diarrhea, and vomiting). Twenty of these events resolved, 13 with no sequelae. Of the twenty events that related to treatment delays (2 in combination with discontinuations), the median length of delay was 8 days (range, 1-90). The 7 TOX events associated with discontinuation (2 in combination with delays) occurred in six patients. One patient experienced G4 pleural effusion and G3 hypoxia. They died the following day with type II respiratory failure, advanced chronic obstructive pulmonary disease and lung cancer cited as the reasons for death, with no reports of pneumonitis. Another patient discontinued with G1 renal dysfunction. They subsequently developed G3 hepatotoxicity which was felt to be possibly related to pembrolizumab but that subsequently resolved without sequelae. Further TOX events associated with discontinuation were G3 hyponatremia, G3 arthralgia, G2 low cortisol, G2 mucositis. Post-hoc sensitivity analysis using a less stringent toxicity outcome that only included discontinuations and not delays (TOXDIS) and a more traditional toxicity outcome, treatment-related grade3-5 adverse events at any time during the trial (TOXAE3-5), demonstrated observed rates of 10% and 15% respectively and probabilities greater than 90% that the rates are less than 30% (see Supplementary Material for more detail).

The OR rate was 31% (95% CI 18-47%) in patients who had received previous therapy and 21% (95% CI 9-40%) in those receiving pembrolizumab first line (Table 2). 2nd line pembrolizumab monotherapy is licensed for patients with TPS \geq 1% and in first-line patients with TPS \geq 50%: the trial estimated OR rate was 33% (95% CI 15-58%) in those with TPS 1-49% and 47% (95% CI 25-70%) in those with TPS \geq 50% (Table 2). The relationship between TPS and response is further elucidated by Figures 3A and B. Median DOR, DSD and TTP were 14.6 months (95% CI 12.1 – NR), 4.4 months (95% CI 4.0 – 13.8) and 11.9 months (95% CI 4.0 – NR) respectively (Supplementary Figures 1 and 2). Median DOR in first-line patients was 12.6 months (95% CI 11.4 – NR) and in subsequent-line patients it was 14.6 months (95% CI 12.1 – NR). Median PFS and OS were 4.4 months (95% CI, 3.3 - 9.9) and 9.8 months (95% CI, 7.1 - 14.6) respectively (Table 2 and Figure 4) and both markedly improve with increasing TPS (Table 2 and Supplementary Figures 3 and 5). Median PFS was 4.3

months (95% CI 1.9 – 13.1) in first-line patients and 4.4 months (95% CI 3.3 – 11.9) in subsequent-line patients (Table 2 and Supplementary Figures 4 and 6).

We recorded 704 adverse events (AEs) in 58 different patients. Figure 5 shows the per-patient incidence of all immune-related AEs and non-immune-related events occurring in at least 10% of patients. Rash and hypothyroidism were the most common immune-related events. Grade 3-5 AEs occurred in 44 (73%, 95% CI 60-83%) patients. Twelve Grade 3-5 AEs classified as at least possibly related to pembrolizumab occurred in 9 (15%, 95% CI 8-26%) patients. In addition to the TOX events described above, these included urinary tract infection, dehydration, and myalgia. There were no treatment-related G5 AEs reported and no early deaths that were attributed to hyperprogression, based on a widely-used definition (18).

Patient-reported outcomes of quality of life show that for those patients remaining on treatment and alive and well enough to complete questionnaires, their scores across all timepoints on average are better than baseline (Figure 6). The mean EQ-5D-5L VAS was 0.71 (SE=0.21) for patients after one year of therapy compared to 0.53 (SE=0.09) for all patients at baseline. Similar profiles are seen in first-line and subsequent-line patients (data not shown).

Discussion

In real world practice PS2 NSCLC patients constitute a significantly-sized patient group with unmet therapeutic need. The PePS2 trial is the first ever trial to prospectively investigate the effect of checkpoint blockade in NSCLC patients with PS2 across all histologies including the most prevalent sub-type adenocarcinoma. The CHECKMATE171 trial of nivolumab therapy, which has been published in abstract form (19), prospectively enrolled PS0, 1 and 2 patients and reported PS2 outcomes separately. However, this study was only for patients with squamous cell lung cancer, did not collect PFS or DCB data and did not analyse outcome by TPS. Crucial to the conduct of the current study was a highly accurate ascription of PS2 status and minimisation of the possibility of downgrading patients with PS1 status to allow them to enter the trial. We mitigated against this by assessment of PS two weeks apart to ensure

stability of performance status and consistency of its assessment, and by including the ECOG definitions of PS2 status explicitly in both the inclusion and exclusion criteria and their incorporation into the eligibility checklist for registration. Physicians rather than patients assessed PS. There is good agreement between nurse and oncologist assessment of PS in patients with lung cancer (20) but patients tend to rate themselves of lower PS than physicians (20-21). Whilst there are clear differences in survival by PS strata determined by physicians, survival curves of patient assessed PS1 and PS2 are superimposed (6). Cox models including physician-assessed PS best fitted the observed survival. In comparing patient versus physician assessment of whether they would be eligible for a clinical trial requiring PS 0 or 1, the study showed that in 24/30 cases of disagreement, the patient would have excluded themselves and yet these 24 patients had a median OS of 8.7 months which was numerically higher than the entire patient assessed PS1 cohort (20). We were extremely keen to minimise any tendency to downgrade a true PS1 patient to PS2 and these data strongly suggest that this tendency is minimised when relying on physician assessment of PS rather than patient assessed PS, thereby justifying our choice in the PePS2 trial. Finally, we have compared the EQ5D VAS score at baseline for patients in our trial against patients in KEYNOTE-010 (22): our PS2 patients had considerably worse quality-of-life score of 53% compared to the PS0-1 patients of 69.8%.

We demonstrate that pembrolizumab can be safely administered to PS2 lung cancer patients, with no obvious increase in the risk of immune related or other toxicities or of the risk of hyper-progression. Efficacy outcomes are at least comparable to those obtained in PS0/1 patients treated with 2nd line pembrolizumab (23). In the large KEYNOTE-001 single arm study enrolling PS0/1 patients the ORR was 18%, mPFS was 3 months and median OS 9.3 months in previously treated patients. Equivalent efficacy outcomes in the previously treated PS2 patients treated in the current study were ORR 31%, mPFS 4.4 months and mOS 10.4 months. In KEYNOTE-001, the response rate was 24.8% in previously untreated patients, compared to 21% in our first-line PS2 cohort, and mPFS was 6 months, compared to 4.3 months in the current study.

Pembrolizumab is currently licensed in the UK for previously treated patients with PD-L1 TPS \geq 1% and in first line patients with TPS \geq 50%: response rates were 33% (95% CI 15-

58%) in those with PD-L1 TPS 1-49% and 47% (95% CI 25-70%) with PD-L1 TPS \geq 50%. In the KEYNOTE-001 study equivalent response rates were 16.5% and 45.2%. In the TPS \geq 50% group herein mPFS was 12.6 months, double that figure at 6.3 months in the KEYNOTE-001 study. Although, cross trial comparisons lack robust statistical validity there is evidence that PS2 patients treated with pembrolizumab are obtaining at least as useful outcomes as their PS0/1 counterparts.

Currently in the UK, for example, PS2 NSCLC patients without a targetable aberration are offered carboplatin-based chemotherapy as a first-line option. In the first study to compare single agent chemotherapy with doublet chemotherapy in PS2 advanced NSCLC patients, the mOS with pemetrexed/carboplatin was 9.3/12 months (24). The updated OS data from KEYNOTE-024 enrolling PS0/1 with TPS \geq 50% patients demonstrate a median OS of 14.2/12 months for platinum-containing doublet chemotherapy and median OS for pembrolizumab of 30 months (25). Our data provide safety and efficacy evidence that PS2 TPS \geq 50% could be considered for first line pembrolizumab monotherapy. In the 2nd line setting the only standard systemic anti-cancer therapy option for PS2 patients is docetaxel but this is usually very poorly tolerated in this patient population and very few PS2 patients would be submitted to this therapy. Our data also provides evidence to support the use of pembrolizumab monotherapy as a valuable and well tolerated second line treatment option in PS2 patients, many of whom previously were not offered 2nd line therapy.

In summary, these data suggest that pembrolizumab can now be considered as a treatment option for advanced PS2 NSCLC patients in the first-line and subsequent-line settings. This study supports the incorporation of pembrolizumab into the treatment pathway of PS2 NSCLC patients. It also supports the investigation of checkpoint blockade in patients with performance status worse than 0-1 in multiple other cancers where these treatments are active, clearly a significant number of patients.

Contributors

Lancet Respiratory Medicine Manuscript Reference: THELANCETRM-D-19-00698R1

Original Manuscript Reference: THELANCETONCOLOGY-D-19-01571

GM, KB, JS and LB designed the study, interpreted data and wrote the manuscript. KB produced the analysis and figures. JS provided sponsor oversight and collected data. RM collected data and wrote the manuscript. YS, JC, RS, CO, PS, SL, SP, CB, and GB all recruited patients to the study and contributed to critical reviews of the manuscript.

Declaration of interests

GM, KB, JS, RM and LB reports grants from Merck, Sharp and Dohme, during the conduct of the study. GM personal fees from Merck, Sharp and Dohme, Roche, Boehringer Ingelheim, BioLineRx, grants and personal fees from Bristol-Myers-Squibb, grants from Plexxikon, Kael-Gemvax, AstraZeneca, and Pfizer, outside the submitted work. KB reports other funds from Merck, during the conduct of the study; other funds from AstraZeneca, GlaxoSmithKline, and Roche, and personal fees from Eli Lilly, outside the submitted work. JS reports personal fees from Eli Lilly and Company, outside the submitted work. YS reports personal fees from Merck, Sharp and Dohme, Roche, Takeda, Astra Zeneca, and Pfizer, outside the submitted work. JC reports personal fees and non-financial support from Merck, Sharp and Dohme, Roche, Takeda, AstraZeneca, Amgen, and Pfizer, outside the submitted work. RS reports personal fees from Merck, Sharp and Dohme, outside the submitted work. CO reports grants from Pfizer and Astra Zeneca, other funds from Bristol Myers Squibb, grants and other funds from Merck Sharpe and Dohme, outside the submitted work. PS reports other from Bristol Myers Squibb, outside the submitted work. SP reports personal fees from Bristol Myers Squibb, Roche, Takeda, AstraZeneca, Pfizer, Merck Sharpe and Dohme, EMD Serono, Guardant Health, Abbvie, Boehringer Ingelheim, Tesaro, OncLive, and Medscape, outside the submitted work. GB reports personal fees from Bristol-Myers Squibb, Roche, Pfizer, Eli Lilly, and Eisai. LB reports personal fees from AstraZeneca, Novartis, and Springer Healthcare, outside the submitted work. All other authors declare no competing interests.

Data sharing

Lancet Respiratory Medicine Manuscript Reference: THELANCETRM-D-19-00698R1

Original Manuscript Reference: THELANCETONCOLOGY-D-19-01571

Scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. Requests should be made by returning a completed Data Sharing Request Form (available as part of the submission to the journal) and Curriculum Vitae of the lead applicant and statistician to newbusiness@trials.bham.ac.uk. The Data Sharing Request Form captures information on the specific requirements of the research, the statistical analysis plan, and the intended publication schedule. The request will be reviewed independently by the Cancer Research UK Clinical Trials Unit (CRCTU) Directors in discussion with the Chief Investigator and relevant Trial Management Group and independent Trial Steering Committee. In making their decision the Director's Committee will consider the scientific validity of the request, the qualifications of the Research Group, the views of the Chief Investigator, TMG and TSC, consent arrangements, the practicality of anonymising the requested data and contractual obligations. Where the CRCTU Directors and appropriate Trial Committees are supportive of the request, and where not already obtained, consent for data transfer will be sought from the Sponsor of the trial before notifying the applicant of the outcome of their request. It is anticipated that applicants will be notified of a decision within 3 months of receipt of the original request.

Acknowledgements

The Investigators and Sponsor would like to express their sincere thanks to all the patients and their families who participated in this trial. They would also like to recognise all the NHS Trusts and staff who have supported this trial, the members of trial steering committee and the patient and public involvement representative, Janette Rawlinson.. This is an Investigator-initiated and Investigator-led trial funded by Merck, Sharp and Dohme. The Cancer Research UK Clinical Trials Unit at the University of Birmingham is supported by CRUK grant C22436/A25354. PePS2 was supported by Experimental Cancer Medicine Centres (ECMC) funding and by the ECMC Network. This trial has been independently peer reviewed and has been adopted by the National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio. SP acknowledges NHS funding to the Royal Marsden Hospital-Institute of Cancer Research NIHR Biomedical Research Centre.

References

1. 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 Nov 10;375(19):1823-1833#
2. Garon EB, Hellmann MD, Rizvi NA, et al. Five-Year Overall Survival for Patients With Advanced Non-Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. *J Clin Oncol*. 2019 Jun 2;JCO1900934.
3. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 May 31;378(22):2078-2092.
4. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 Nov 22;379(21):2040-2051.
5. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982 Dec;5(6):649-55
6. Passaro A, Spitaleri G, Gyawali B, de Marinis F. Immunotherapy in Non-Small-Cell Lung Cancer Patients With Performance Status 2: Clinical Decision Making With Scant Evidence. *J Clin Oncol*. 2019 Apr 17;JCO1802118.
7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer*. 2009 Jan 1;45(2):228-47.
8. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy—Lung (FACT-L) quality of life instrument. *Lung cancer*. 1995 Jun 1;12(3):199-220.
9. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research*. 2011 Dec 1;20(10):1727-36.
10. Brock K, Billingham L, Yap C, Middleton G. (2019) A Phase II Clinical Trial Design for Associated Co-primary Efficacy and Toxicity Outcomes with Baseline Covariates. In: Argiento R., Durante D., Wade S. (eds) *Bayesian Statistics and New Generations*. BAYSM 2018. Springer Proceedings in Mathematics & Statistics, vol 296. Springer, Cham. https://doi.org/10.1007/978-3-030-30611-3_13
11. Thall PF, Nguyen HQ, Estey EH (2008). Patient-specific dose finding based on bivariate outcomes and covariates. *Biometrics* 64(4):1126-36.

Lancet Respiratory Medicine Manuscript Reference: THELANCETRM-D-19-00698R1

Original Manuscript Reference: THELANCETONCOLOGY-D-19-01571

12. Brock K (2019). Methods to Increase Efficiency in Clinical Trials with Restricted Sample Size. Ph.D. thesis, University of Birmingham. URL

<https://etheses.bham.ac.uk/id/eprint/8921/1/Brock2019PhD.pdf>

13. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2018. URL <https://www.R-project.org/>.

14. Stan Development Team. RStan: the R interface to Stan. R package version 2.18.2. 2018. URL <http://mc-stan.org/>.

15. Hadley Wickham. tidyverse: Easily Install and Load the 'Tidyverse'. R package version 1.2.1. 2017. URL <https://CRAN.R-project.org/package=tidyverse>

16. Wickham H. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016. ISBN 978-3-319-24277-4

17. Kay M. tidybayes: Tidy Data and Geoms for Bayesian Models. 2019. doi: 10.5281/zenodo.1308151

18. Champiat S, Derclé L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1; *Clinical Cancer Research* 2016; 1-9.

19. Popat S, Ardizzoni A, Ciuleanu T, et al. Nivolumab in previously treated patients with metastatic squamous NSCLC: Results of a European single-arm, phase 2 trial (CheckMate 171) including patients aged ≥ 70 years and with poor performance status, *Ann. Oncol.* 2017 Sep; 28(suppl 5).

20. Ando M, Ando Y, Hasegawa Y, et al. Prognostic value of performance status assessed by patients themselves, nurses, and oncologists in advanced non-small cell lung cancer. *Br J Cancer.* 2001 Nov 30;85(11):1634-9.

21. Dajczman E, Kasymjanova G, Kreisman H, Swinton N, Pepe C, Small D. Should patient-rated performance status affect treatment decisions in advanced lung cancer? *J Thorac Oncol.* 2008 Oct;3(10):1133-6

22. Barlesi F, Garon EB, Kim D-W, et al. Health-related quality of life in KEYNOTE-010: a phase II/III study of pembrolizumab versus docetaxel in patients with previously treated advanced, programmed death ligand 1-expressing NSCLC; *JTO* 2019, 14(5) 793-801.

23. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med.* 2015 May 21;372(21):2018-28

24. Zukin M, Barrios CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell

Lancet Respiratory Medicine Manuscript Reference: THELANCETRM-D-19-00698R1

Original Manuscript Reference: THELANCETONCOLOGY-D-19-01571

lung cancer and Eastern Cooperative Oncology Group performance status of 2. J Clin Oncol. 2013 Aug 10;31(23):2849-53

25. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019 Mar 1;37(7):537-546

Table 1: Baseline characteristics

	Study Population (n=60)
Sex	
Male	33 (55%)
Female	27 (45%)
Age (years)	
Median (Interquartile range)	72 (65-75)
Histology	
Adenocarcinoma	41 (68%)
Squamous Cell Carcinoma	12 (20%)
Other	7 (12%)
PD-L1 TPS	
< 1%	27 (45%)
1 - 49%	15 (25%)
50 - 100%	15 (25%)
Unknown	3 (5%)
Line of Therapy	
First ^a	24 (40%)
Subsequent	36 (60%)
CT delivered as part of curative-intent treatment completed <12 months previous	1
1 previous line of CT for advanced disease	
○ platinum-containing	25
○ non-platinum-containing	1
2 previous lines of CT for advanced disease	7
≥2 previous lines including targeted treatment	2
Smoking status	
Current smoker	11 (18%)
Ex-smoker	43 (72%)
Never smoked	3 (5%)
Not Reported	3 (5%)
Pack-years	
Median (IQR)	40 (26-57.5)
Charlson Comorbidity Index	
0 - 7	21 (35%)
8 - 10	33 (55%)
11 - 12	6 (10%)

^a includes 8 patients who were reported to have had previous chemotherapy as part of curative-intent treatment delivered >12 months previous

Table 2: Co-primary and key secondary outcome measures - summary statistics with 95% confidence intervals (CI), for all patients and stratified by line of therapy and TPS

	DCB rate (n) 95% CI	TOX rate (n) 95% CI	OR rate (n) 95% CI	Median PFS (months) 95% CI	Median OS (months) 95% CI
All (n=60)	37% (22) 26 - 49%	28% (17) 19 - 41%	27% (16) 17 - 39%	4.4 3.3 - 9.9	9.8 7.1 - 14.6
Line of therapy					
First-line (n=24)	38% (9) 21 - 57%	29% (7) 15 - 49%	21% (5) 9 - 40%	4.3 1.9 - 13.1	7.9 2.6 - NR
Subsequent- line (n=36)	36% (13) 22 - 52%	28% (10) 16 - 44%	31% (11) 18 - 47%	4.4 3.3 - 11.9	10.4 8.1 - 16.6
PD-L1 TPS					
<1% (n=27)	22% (6) 11 - 41%	26% (7) 13 - 45%	11% (3) 4 - 28%	3.7 2.1 - 6.0	8.1 4.5 - 13.0
1-49% (n=15)	47% (7) 25 - 70%	13% (2) 4 - 38%	33% (5) 15 - 58%	8.3 3.5 - NR	12.6 7.9 - NR
≥ 50% (n=15)	53% (8) 30 - 75%	40% (6) 20 - 64%	47% (7) 25 - 70%	12.6 1.9 - NR	14.6 4.6 - NR
Unknown (n=3)	NE (1)	NE (2)	NE (1)	NE	NE

NR – upper level of 95% confidence intervals not reached with current level of follow-up

NE – summary statistic not estimated because number of patients in category too small to be meaningful

Figure 1: Trial profile

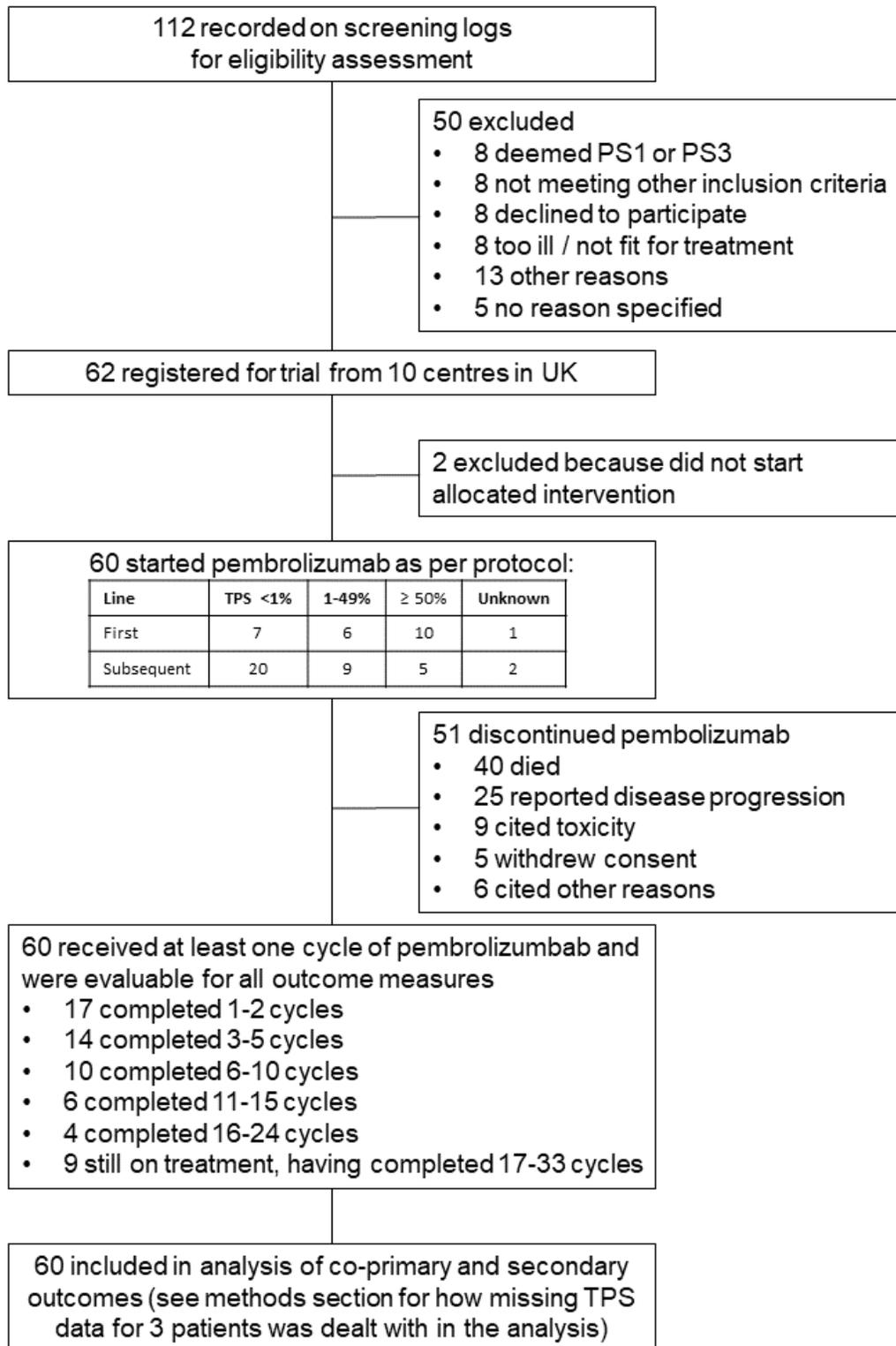


Figure 2: Primary efficacy outcome measure - DCB rates and bands for 50%, 80% and 95% credible intervals for each cohort estimated from model

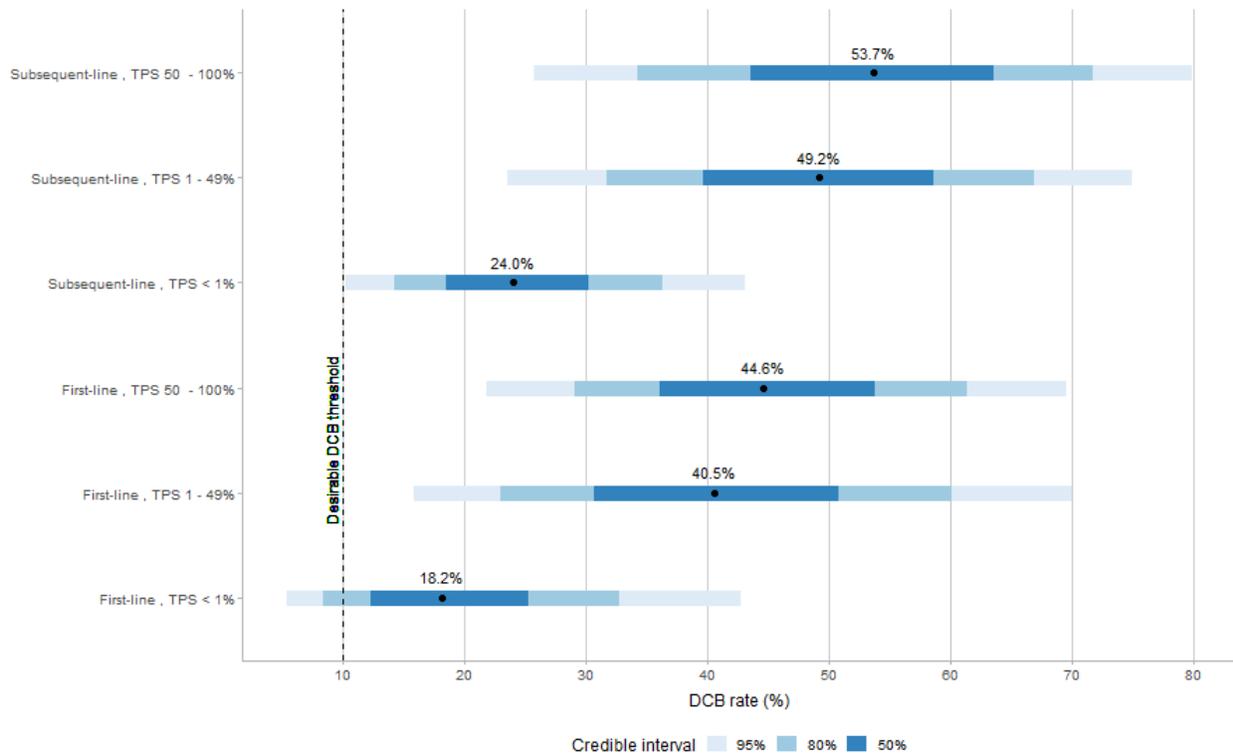


Figure 3: (A) Change from baseline in the sum of the longest diameters of the baseline-specified target lesions for patients with and without DCB. Horizontal guides show the RECIST PR and PD thresholds. 15 patients are not shown because they had no post-baseline CT scan, and 3 patients are not shown because they have unknown TPS. (B) Best change from baseline in the sum of the longest diameters of the baseline-specified target lesions. 15 patients with no post-baseline CT scan are shown with best change of +100%.

(A)

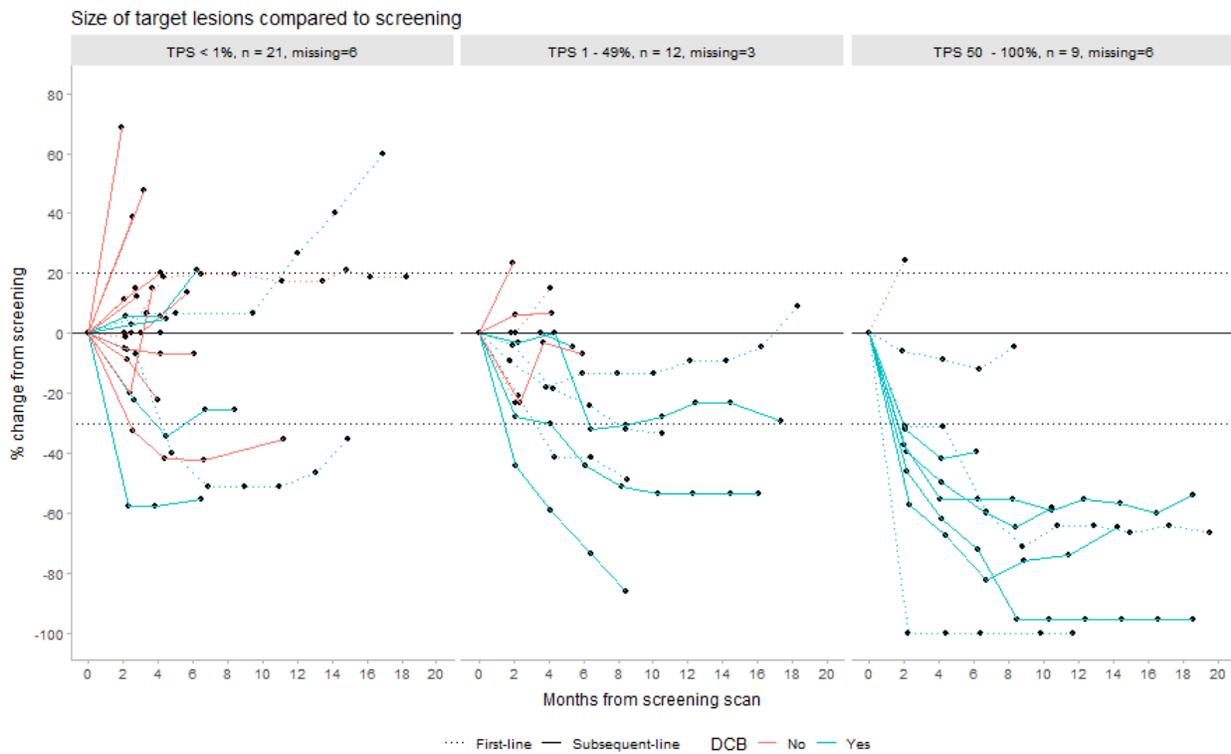
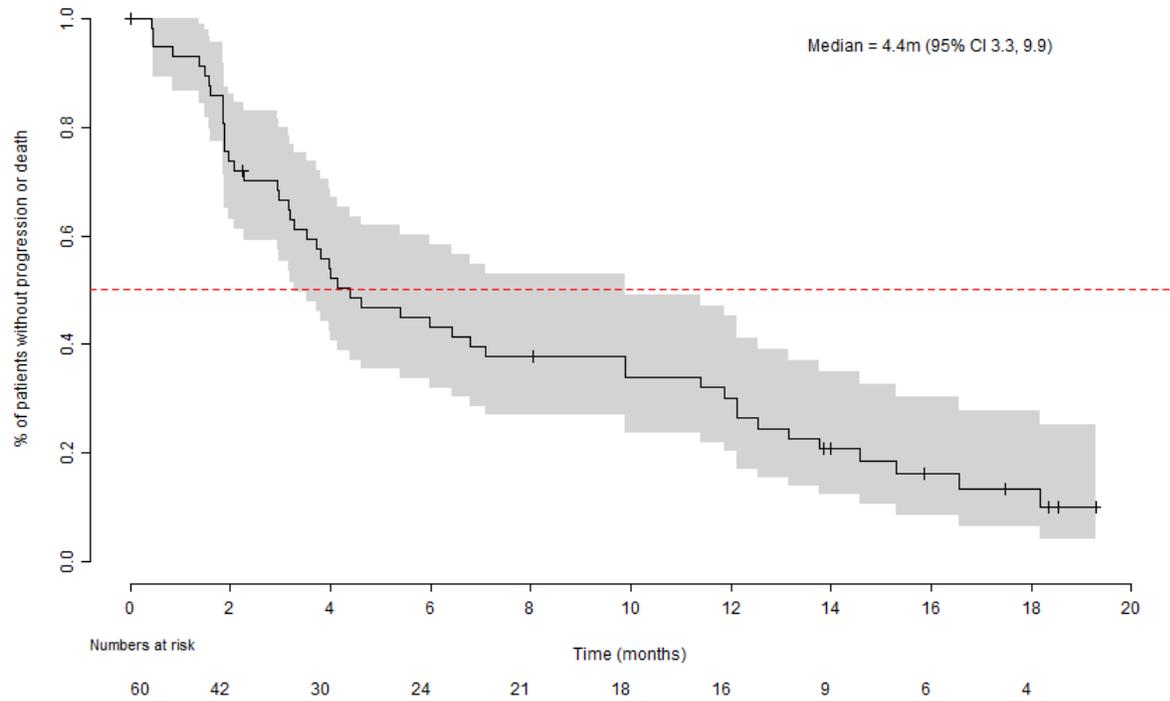


Figure 4: Progression-free survival (A) and overall survival (B) (tick marks represent censored times)

See Supplementary Material for PFS and OS curves split by TPS and line of therapy

(A)



(B)

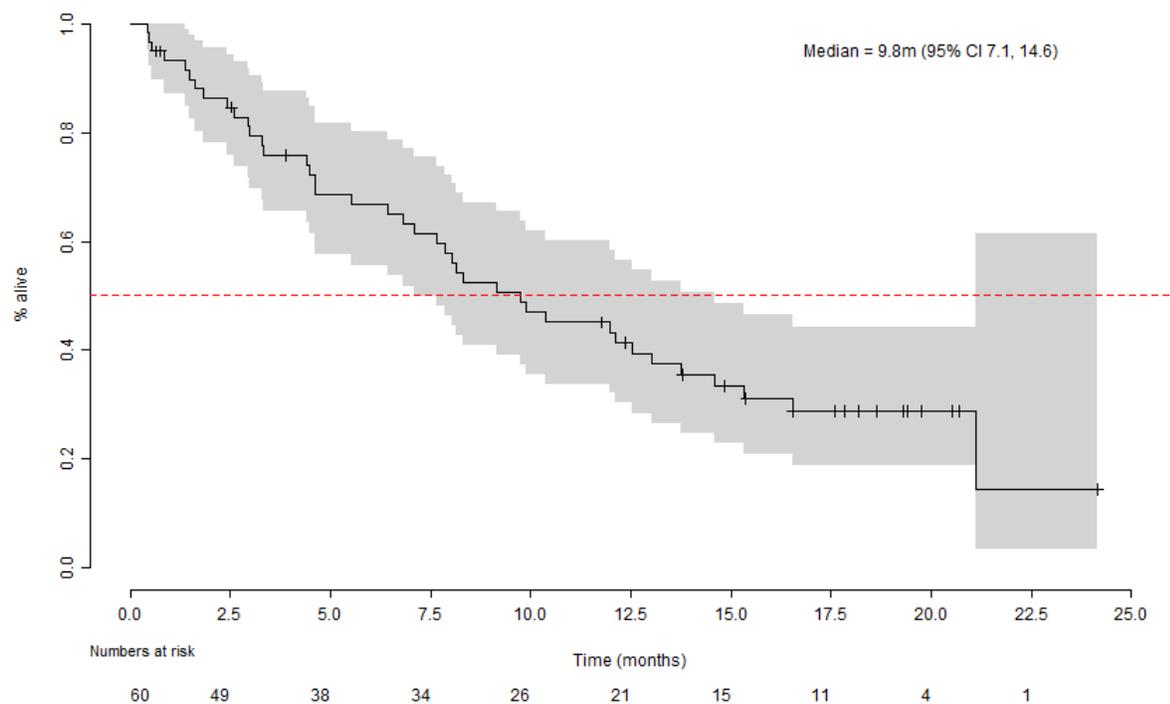


Figure 5: Incidence of adverse events grouped into potentially immune-related and non-immune-related

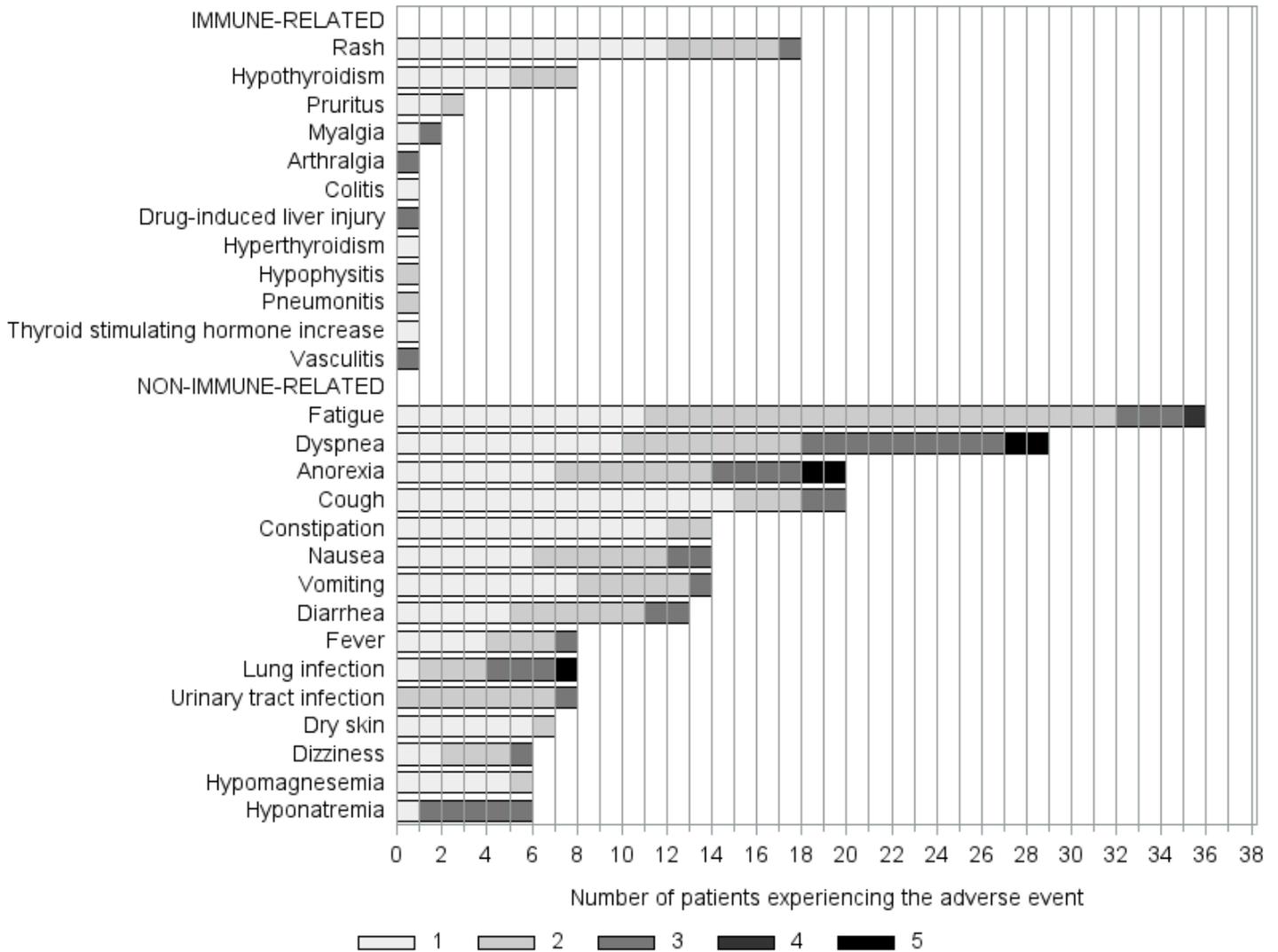


Figure 6: Mean HRQoL scores over time whilst patients were on trial treatment, for periods with at least 10 observations

