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Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PePS2): a single arm, phase 2 trial

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Abstract

Background Therapeutic blockade of the axis of programmed cell death 1 (PD-1) and its ligand (PD-L1) 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 patients with NSCLC are PS2, and the activity and safety of pembrolizumab in these patients is unclear. We aimed to evaluate the safety and efficacy of pembrolizumab in these patients.

Methods We did a multicentre, single-arm, open-label, phase 2 trial (PePS2) in ten hospitals in the UK, in which patients with NSCLC and a rigorous ascription of PS2 were given pembrolizumab 200 mg every 3 weeks. No masking was used in this trial. We stratified the treatment evaluation by tumour proportion score (TPS) and line of therapy. Co-primary outcomes were: (1) 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 (2) toxicity, defined as the occurrence at any time of treatment-

related dose delay or treatment discontinuation due to an adverse event. Analysis included all patients who received any pembrolizumab. As well as reporting simple observed incidence for the co-primary outcomes, DCB and toxicity, we also estimated incidence using a model-based method for correlated binary outcomes. This study is registered with ClinicalTrials.gov, NCT02733159; EudraCT, 2015-002241-55; and ISRCTN, 10047797.

Findings Between Jan 4, 2017, and Feb 13, 2018, of 112 patients assessed for eligibility, we recruited 62 patients. 60 patients were evaluable for the co-primary outcomes. Median age was 72 years (IQR 65–75); 33 (55%) of participants were male and 27 (45%) were female. The observed incidence for DCB was 38% (95% CI 21–57) in first-line patients (n=24) and 36% (22–52) in subsequent-line patients (n=36); DCB was 22% (11–41) in patients with a TPS less than 1% (n=27), 47% (25–70) in patients with a TPS of 1–49% (n=15), and 53% (30–75) in patients with a TPS of 50% or greater (n=15). An increase in DCB incidences with TPS was also shown in model-based estimates. Toxicity was observed in 28% (95% CI 19–41) of patients, 11 (18%) of 60 due to dose delay and 6 (10%) of 60 due to drug discontinuation. No grade 5 treatment-related adverse events were observed and no early deaths were attributed to hyperprogression. The most common grade 3–4 adverse events were dyspnoea (n=9), hyponatraemia (n=5), and anorexia (n=4). There were ten serious adverse events considered to be related to treatment, comprising diarrhoea (n=3) and acute kidney injury, adrenal insufficiency, hyperbilirubinaemia, oral mucositis, rash, urinary tract infection, and vomiting (n=1 each).

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

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Research in context

Evidence before this study Pembrolizumab, the anti-programmed cell death 1 monoclonal antibody, is indicated as monotherapy in the UK in patients with non-small-cell lung cancer (NSCLC) as a first-line therapy in those with a tumour proportion score (TPS) of 50% or greater and in subsequent lines of therapy in those with a TPS of 1% or greater. The studies that led to these approvals, which have revolutionised the management of NSCLC, only enrolled patients with an Eastern Cooperative Oncology Group performance status (PS) of 0–1. All randomised and registry studies of checkpoint blockade agents in NSCLC have also restricted inclusion to patients with good PS (ie, 0–1). However, a substantial proportion of patients with NSCLC in practice are PS2. In the 2018 UK National Lung Cancer Audit Annual Report, 6361 (18%) of 39 199 patients were PS2. These are patients who are ambulatory and capable of self-care, and are up and about more than 50% of the time, but are unable to do any work activities. Data for the efficacy and safety of checkpoint blockade in this important cohort is very limited, while outcomes stratified by TPS are negligible. A literature search on Oct 11, 2019 using the PubMed database including articles in English published since the date of database inception revealed that at the time of manuscript submission there were no published trials that prospectively evaluated the outcomes with checkpoint blockade in patients with NSCLC of PS2 specifically and where there was rigorous ascription of PS. After acceptance of the manuscript, results from the CheckMate 171 trial were published; however, that trial did not include first-line patients, included only patients with squamous cell lung cancer, and did not assess outcome by TPS. These data are crucial for evaluating the risk-benefit equation for these important therapies in this group of patients with substantial unmet therapeutic need.

Added value of this study The objective of the PePS2 trial was to assess whether pembrolizumab is a beneficial treatment option in patients with advanced NSCLC of PS2. A highly accurate ascription of PS2 status was crucial. Assessment of PS was done 2 weeks apart to ensure stability of PS and consistency of assessment, and the Eastern Cooperative Oncology Group 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 second CT evaluation), was a co-primary outcome measure. Toxicity was the second co-primary outcome measure. There were no grade 5 treatment-related adverse events and no early deaths attributed to hyperprogression. Our data showed that pembrolizumab can be safely administered to patients with NSCLC of PS2, with no obvious increase in the risk of immune related or other toxicities or hyperprogression. Efficacy outcomes are at least similar to those obtained in PS0–1 patients given second line pembrolizumab.

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

Introduction

The introduction of checkpoint blockade into the management of non-small-cell lung cancer (NSCLC) has been transformative. The percentage of tumour biopsy cells expressing programmed cell death ligand 1 (PD-L1) is referred to as the tumour proportion score (TPS). Pembrolizumab monotherapy is standard of care in the UK for the management of first-line patients with a TPS of 50% or greater on the basis of superior overall survival (OS) when compared with platinum-containing doublet chemotherapy[1] and also for second-line patients with a TPS of 1% or greater. Data from the phase 1 KEYNOTE-001 study of pembrolizumab monotherapy in patients with NSCLC showed a median OS for previously treated patients of 10·5 months and a 5 year OS rate of 15·5%; the 5 year OS rate in patients with PD-L1 TPS of 50% or greater was 25% and for those with TPS of 1–49% it was 12·6%.[2] 22·9% of patients who had been previously treated achieved an objective response, and 58·6% of patients achieved disease control. Pembrolizumab is also approved for use in combination with chemotherapy as a first-line therapy in both patients with non-squamous NSCLC and squamous cell lung cancer irrespective of PD-L1 TPS.[3,4] However, these studies, and indeed all randomised studies, have only included patients of Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1. A sizable proportion of patients with NSCLC in real-world clinical practice are PS2. In the 2018 UK National Lung Cancer Audit Annual Report, the most comprehensive annual analysis of the management and outcome of patients with lung cancer globally, 6361 (18%) of 39 199 patients were PS2 (For the 2018 UK National Lung Cancer Audit Annual Report see https://www.rcplondon.ac.uk/projects/national-lung-canceraudit). These are patients who are ambulatory and capable of self-care, and are up and about more than 50% of the time, but are unable to do any work activities.[5] Data for the efficacy and safety of checkpoint blockade in this important cohort is scarce, while outcomes stratified by TPS are negligible. A 2019 commentary specifically drew attention to the lack of robust data for the efficacy and safety of checkpoint blockade in patients with NSCLC of PS2.[6] Although the US Food and Drug Administration and European Medicines Agency approvals are irrespective of PS, it is unknown whether the available PS0–1 data can be extrapolated to those with disease of PS2 or greater 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 National Health Service, funding for pembrolizumab is only available for patients with PS0–1 on the basis that this is the only group for which prospective data for 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 programmed cell death 1 (PD-1)/PD-L1 blockade exclusively enrolling patients with NSCLC, with a rigorous ascription of PS2 status and stratified by TPS. We aimed to examine whether pembrolizumab is a beneficial treatment option in advanced patients with NSCLC of PS2.

Methods

Study design and participants

PePS2 was a multicentre, single-arm, phase 2 clinical trial of pembrolizumab in patients with advanced NSCLC with an ECOG PS of 2, which recruited from ten hospitals in the UK. The trial was designed to stratify the treatment evaluation by TPS (<1%, 1–49%, ≥50%) and line of therapy (first or subsequent).

Participants had histologically confirmed NSCLC, were aged 18 years and older, with a life expectancy of more than 12 weeks, and had completed all lines of standard of care therapy that their 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 ten site initiation visits, and the source data was checked at monitoring visits 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 2 weeks before 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 done 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 7 days before the first dose of the trial drug 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 included measurable disease according to RECIST version 1.1;7 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, Birmingham, UK.

In line with the inclusion criteria, all participants provided written informed consent. Ethics approval for the trial protocol (ultimately version 6.0, dated July 10, 2018, appendix p 20) was obtained from the West Midlands-Edgbaston Research Ethics Committee in accordance with national regulatory requirements.

Procedures

Pembrolizumab (Merck, Kenilworth, NJ, USA) was administered as a 30-min intravenous infusion at a flat dose of 200 mg every 3 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 for every 9 weeks and response was assessed by RECIST version 1.1.[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 were: (1) durable clinical benefit (DCB), defined as the occurrence of any one of investigator-reported confirmed complete response, partial response, or stable disease that continued until at least the second CT scan scheduled to

occur at 18 weeks; and (2) toxicity, defined as the occurrence at any time of a treatment-related dose delay or treatment discontinuation due to an adverse event.

Patients with advanced NSCLC of PS2 have a poor prognosis, especially at the point when they do not show benefit with first-line therapy, and therefore DCB was chosen as our primary efficacy outcome as it represents a meaningful benefit in such patients. Given the use of 6-month DCB incidences 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 third scan scheduled at 27 weeks). Toxicity was chosen to reflect the feasibility of delivering pembrolizumab to this more unwell group of patients and reflects the concerns that patients express in real-world clinical practice regarding delays in treatment adversely affecting outcomes. However, given that no robust clinical evidence exists that delays have a substantial negative effect on outcomes with checkpoint blockade, we have also done a posthoc sensitivity analysis using a toxicity definition that only includes discontinuations due to treatment-related toxicity, and also a more traditional definition that includes the incidence of treatment-related grade 3–5 adverse events at any time during the trial.

Secondary outcomes included the occurrence of an objective response—ie, complete response or partial response as the best response recorded over the period of assessment. For those patients whose best response was objective response, duration of objective response from commencement of trial treatment was reported and similarly duration of stable disease for those whose best response was stable disease. Also time to progression, progression-free survival (PFS) time, and OS time from commencement of trial treatment were included, with patients not having the event censored at date last known to be free of the event. In addition, patient-reported health-related quality of life was collected using the FACT-L[8] and EQ-5D-5L[9] questionnaires. Questionnaires were administered by research staff and completed by patients in the clinic at the start of each cycle. Scores were generated for physical, functional, emotional, and social wellbeing together with general health from the FACT-L, and a score measuring the utility of their health state and visual analogue score measuring general health from the EQ-5D-5L.

Collection and reporting of adverse events and serious adverse events 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 adverse event or serious adverse event were reported using Common Terminology Criteria for Adverse Events version 4.0. Selected non-serious adverse events and serious adverse events were specified in the protocol as events of clinical interest and included immune-mediated adverse events.

Statistical analysis

For the co-primary outcomes, DCB and toxicity incidences were simultaneously estimated using linked logistic regression models.[10,11] The model for DCB incorporated categorical covariates for TPS (<1%, 1–49%, ≥50%) and line of therapy (first or subsequent) to allow efficacy estimates to vary between the six cohorts. No covariates were included in the model for toxicity, thereby assuming uniform toxicity 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 incidences of DCB and toxicity. Full details of the statistical methods are provided in the appendix (p 11). Non-model-based estimates for DCB and toxicity incidences are also provided with 95% CIs using Wilson's method.

We were motivated to deliver findings from the trial quickly because of the patient population being a group with substantial unmet therapeutic need, so the sample size was selected as 60 evaluable patients on the basis of the feasible number that we could recruit within 1 year. 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 cutoffs for positive decision making were specified as more than 10% for DCB and less than 30% for toxicity incidence. Operating characteristics for the trial design were based on guidelines that the treatment would be considered successful if the probability is more than 0·7 for the true incidence of DCB being greater than 10% and the probability is more than 0·9 for the true incidence of toxicity being less than 30%. Operating performance of the proposed model-based analysis at this sample

size was investigated10,[12] and shown to be acceptable, equivalent to approximately 90% power when the true DCB incidence was 30% and toxicity incidence was 10%, and 2·5% type I error when the true DCB was 10% and toxicity was 30%.

For the secondary outcome measures duration of objective response, duration of stable disease, time to progression, PFS, and OS, Kapan-Meier curves were used to describe the data and estimate medians with 95% CIs. Objective response is reported as an incidence with 95% CIs calculated using Wilson's method. Health-related quality of life outcomes are reported using means over time. The population for all analyses of efficacy and safety included all patients that received at least one cycle of treatment (ie, one infusion of pembrolizumab). There were three patients that had missing TPS categorisation. This variable had three levels (<1%, 1–49%, ≥50%), meaning there were 27 possible imputations. This missing data was handled in model-based analyses by use of likelihood-weighted pooling of the inferences from all 27 imputations (appendix p 14). All statistical analysis was done 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 done in accordance with the trial protocol and the statistical analysis plan (appendix p 11). 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. This 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 Jan 4, 2017, and Feb 13, 2018, of 112 patients assessed for eligibility, we recruited 62 patients from ten centres in the UK, 60 of whom received pembrolizumab and were evaluable for co-primary and secondary outcomes (figure 1). The data presented were collected up until March 8, 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 (IQR 65–75); 33 (55%) of participants were male and 27 (45%) were female. 24 (40%) of 60 patients received pembrolizumab in the trial as first-line therapy and 27 (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 health-related quality of life, the mean EQ-5D-5L visual analogue score at baseline was 53%. Patients received a median of 4·5 (IQR 2·0–12·8) 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 three levels of TPS and both lines of therapy (table 2). The DCB incidence was 38% (21–57) in patients on first-line pembrolizumab therapy and 36% (22–52) in those receiving it as a subsequent-line of therapy. DCB incidences increased with level of TPS, both in the observed incidences (table 2), with 22% (11–41) in those with a TPS of less than 1% compared with 53% (30–75) in those with a TPS of 50% or greater, and in the modelbased incidences stratified by line of therapy (figure 2). Bayesian estimates of DCB incidences from the model gave greater than the prespecified 0·70 probability that the true DCB incidence was more than 10% in each of the six cohorts (actually all greater than 0·84). Underpinning DCB is the change from baseline in the sum of longest diameters of target lesions, which shows that the benefit of pembrolizumab is more pronounced as the TPS level increases (figures 3A, 3B). Post-hoc sensitivity analysis using DCB at 27 weeks showed that the trial remained positive for this longer term outcome, with an observed incidence of 32% (appendix p 1). The primary toxicity outcome, was observed in 17 patients (28%, 95% CI 19–41; table 2). The toxicity incidence in first-line patients was 29% (15–49) and in subsequent-line patients was 28% (16–44; table 2). The model estimated the toxicity incidence as 28% (95% credible interval 17·4–39·5) with 67% probability that the true

toxicity incidence is less than 30% and, in relation to prespecified benchmarks, there is 0·90 probability that it is less than 35·2%. In those that had toxicity (n=17), 11 cases (18%) were due to dose delay, four (7%) due to drug discontinuation, and two (3%) were due to dose delay and drug discontinuation, with a 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, dyspnoea, 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, diarrhoea, and vomiting). 20 of these events resolved, 13 with no sequelae. Of the 20 events that related to treatment delays (two in combination with discontinuations), the median length of delay was 8 days (IQR 7–21). The seven toxicity events associated with discontinuation (two in combination with delays) occurred in six patients. One patient had grade 4 pleural effusion and grade 3 hypoxia. They died the following day after the toxicity event with type 2 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 grade 1 renal dysfunction. They subsequently developed grade 3 hepatotoxicity, which was considered possibly related to pembrolizumab but that subsequently resolved without sequelae. Further toxicity events associated with discontinuation were grade 3 hyponatraemia, grade 3 arthralgia, grade 2 low cortisol, and grade 2 mucositis. Post-hoc sensitivity analysis using a less stringent toxicity outcome, which only included discontinuations and not delays, and a more traditional toxicity outcome, treatment-related grade 3–5 adverse events at any time during the trial, showed observed incidences of 10% for the outcome that measures discontinuations and 15% for the outcome that measures related grade 3–5 adverse events and probabilities greater than 0·90 that the incidences are less than 30% (appendix p 3).

31% (95% CI 18–47) of patients who had received previous therapy and 21% (9–40) of patients receiving pembrolizumab first-line achieved an objective response (table 2). Second-line pembrolizumab monotherapy is licensed for patients with TPS of 1% or greater and in firstline patients with TPS of 50% or greater. The trial estimated 33% (15–58) of

patients with TPS 1–49% and 47% (25–70) of those with TPS of 50% or greater would achieve an objective response (table 2). The relationship between TPS and response is shown in figures 3A and 3B. Median duration of objective response was 14·6 months (95% CI 12·1–not reached [NR]), median duration of stable disease was 4·4 months (4·0–13·8), and median time to progression was 11·9 months (4·0–NR; appendix pp 5–6). Median duration of objective response in first-line patients was 12·6 months (11·4–NR) and in subsequent-line patients was 14·6 months (12·1–NR; data not shown). Median PFS was 4·4 months (95% CI 3·3–9·9) and median OS was 9·8 months (7·1–14·6; table 2, figure 4) and both markedly improved with increasing TPS (table 2, appendix p 7, 9). Median PFS was 4·3 months (1·9–13·1) in first-line patients and 4·4 months (3·3–11·9) in subsequent-line patients (table 2, appendix p 8, 10).

We recorded 704 adverse events in 58 patients. Figure 5 shows the per-patient incidence of all immune-related adverse events 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 adverse events occurred in 44 (73%, 95% CI 60–83) patients. 12 grade 3–5 adverse events classified as at least possibly related to pembrolizumab occurred in nine (15%, 8–26) patients. In addition to the toxicity events described above, these included urinary tract infection, dehydration, and myalgia. There were no treatment-related grade 5 adverse events 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 mean scores across all timepoints were better than baseline (figure 6). The mean EQ-5D-5L visual analogue score was 0·71 (SD 0·17) for patients after 1 year of therapy compared with 0·53 (SD 0·21) for all patients at baseline. Similar profiles were seen in first-line and subsequent line patients (data not shown).

Discussion

In real-world practice, patients with NSCLC of PS2 constitute a patient group of substantial size with unmet therapeutic need. The PePS2 trial is the first trial, to our knowledge, to prospectively investigate the effect of checkpoint blockade in patients with NSCLC of PS2 across all histologies, including the most prevalent subtype adenocarcinoma. The CheckMate 171 trial of nivolumab therapy[19] prospectively enrolled patients of PS0, PS1, and PS2, 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 assessing PS at 2 weeks apart to ensure stability 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. Good agreement between nurse and oncologist assessment of PS in patients with lung cancer has been observed,[20] but patients tend to rate themselves of lower PS than physicians.[20,21] Although there are clear differences in survival by PS strata determined by physicians, survival curves of patients assessed as PS1 and PS2 are similar.[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 PS0 or PS1, the study showed that in 24 of 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 very keen to minimise any tendency to downgrade a true patient of PS1 to PS2 and these data strongly suggest that this tendency is minimised when relying on physician assessed PS rather than patient assessed PS, thereby justifying our choice in this trial. Finally, we compared the EQ5D visual analogue score at baseline for patients in our trial against patients in KEYNOTE-010.[22] Our patients of PS2 had considerably worse mean quality of life scores of 53% compared with the PS0–1 patients of 70%.

We showed that pembrolizumab can be safely administered to patients with NSCLC of PS2, with no obvious increase in the risk of immune related or other toxicities, or of hyperprogression. Efficacy outcomes are at least similar to those obtained in patients of PS0–1 given second-line pembrolizumab.[23] In the large KEYNOTE-001 single-arm study that enrolled patients of PS0–1, 18% of patients achieved an objective response, median PFS was 3 months, and median OS was 9·3 months in previously treated patients. Equivalent efficacy outcomes in previously treated patients of PS2 in the current study were 31% of patients achieving an objective response, median PFS of 4·4 months, and median OS of 10·4 months. In KEYNOTE-001, 24·8% of previously untreated patients achieved a response, compared with 21% in our first-line PS2 cohort, and median PFS was 6 months, compared with 4·3 months in the current study.

Pembrolizumab is currently licensed in the UK for previously treated patients with PD-L1 TPS of 1% or greater and in first-line patients with TPS of 50% or greater. 33% (95% CI 15–58) of those with PD-L1 TPS 1–49% and 47% (25–70) of those with PD-L1 TPS of 50% or greater achieved a response. In the KEYNOTE-001 study, the equivalent results were 16·5% for those with PD-L1 TPS 1–49% and 45·2% for those with PD-L1 TPS of 50% or more. In the TPS of 50% or greater group in the present study, median PFS was 12·6 months, double the equivalent figure at 6·3 months in the KEYNOTE-001 study. Although, cross-trial comparisons lack robust statistical validity, evidence suggests that patients of PS2 given pembrolizumab are obtaining at least as beneficial outcomes as their PS0–1 counterparts.

Currently in the UK, patients of PS2 with NSCLC 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 patients with NSCLC, the median OS with pemetrexed and carboplatin was 9·3 months.[24] The updated OS data from KEYNOTE-024 enrolling patients of PS0–1 with a TPS of 50% or greater showed a median OS of 14·2 months for platinum-containing doublet chemotherapy and median OS for pembrolizumab of 30 months.[25] Our data provide safety and efficacy evidence that patients of PS2 with a TPS of 50% or greater could be considered for first-line pembrolizumab monotherapy. In the second-line setting, the only standard systemic anti-cancer therapy option for patients of PS2 is docetaxel, which is usually very poorly tolerated in this patient

population and very few patients of PS2 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 patients of PS2, many of whom previously were not offered second-line therapy. Finally, these data justify prospectively comparing outcomes with pembrolizumab against chemotherapy in the first-line setting to define whether this treatment can be considered as a standard first-line option.

A limitation of this trial is the relatively small sample size. While the data suggest that pembrolizumab is both active and safe in this population, the results need to be validated in other datasets where PS2 status is carefully ascribed. This is particularly true of patients with squamous cell lung cancer, of whom only 12 were treated in this trial. During preparation of this manuscript, results of the CheckMate 171 study were published.[19] In this large series of patients with squamous lung cancer, 103 were characterised as PS2 although criteria for robust PS ascription were not stated. In this group, tolerability was similar to that in patients of PS0–1 but OS appeared inferior. No patients were treated in first-line and TPS was not assessed. Clearly, further datasets need to be analysed to confirm our findings of good tolerability and efficacy in patients with NSCLC and to fully define and assess the risk-benefit equation in patients with squamous lung cancer of PS2 given pembrolizumab.

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

Contributors

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 recruited patients to the study and contributed to critical reviews of the manuscript.

Declaration of interests

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

Data sharing

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.

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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 tumour proportion score	
< 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 (2%)
1 previous line of CT for advanced disease platinum-containing non-platinum-containing	 25 (42%) 1 (2%)
2 previous lines of CT for advanced disease	7 (12%)
≥2 previous lines including targeted treatment	2 (3%)
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%)

Data are n (%) or median (IQR). PD-L1=programmed cell death ligand 1. *Includes eight patients who were reported to have had previous chemotherapy as part of curative-intent treatment delivered more than 12 months previous.

Table 2: Co-primary and key secondary outcome measures

	Durable clinical benefit incidence	Toxicity incidence	Objective response incidence	Median progression free survival (months)	Median overall survival (months)
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 tumour proportion score					
<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 (n=1)	NE (n=2)	NE (n=1)	NE	NE

Data are % (n; 95% CI). or median (95% CI). NR=not reached. NE=summary statistic not estimated because number of patients in category too small to be meaningful.

Figure 1: Trial profile

PS=performance status. Some discontinuations were for more than one reason.
*Missing tumour proportion score data was handled in model-based analyses by use of likelihood-weighted pooling of the inferences from all 27 possible imputations.

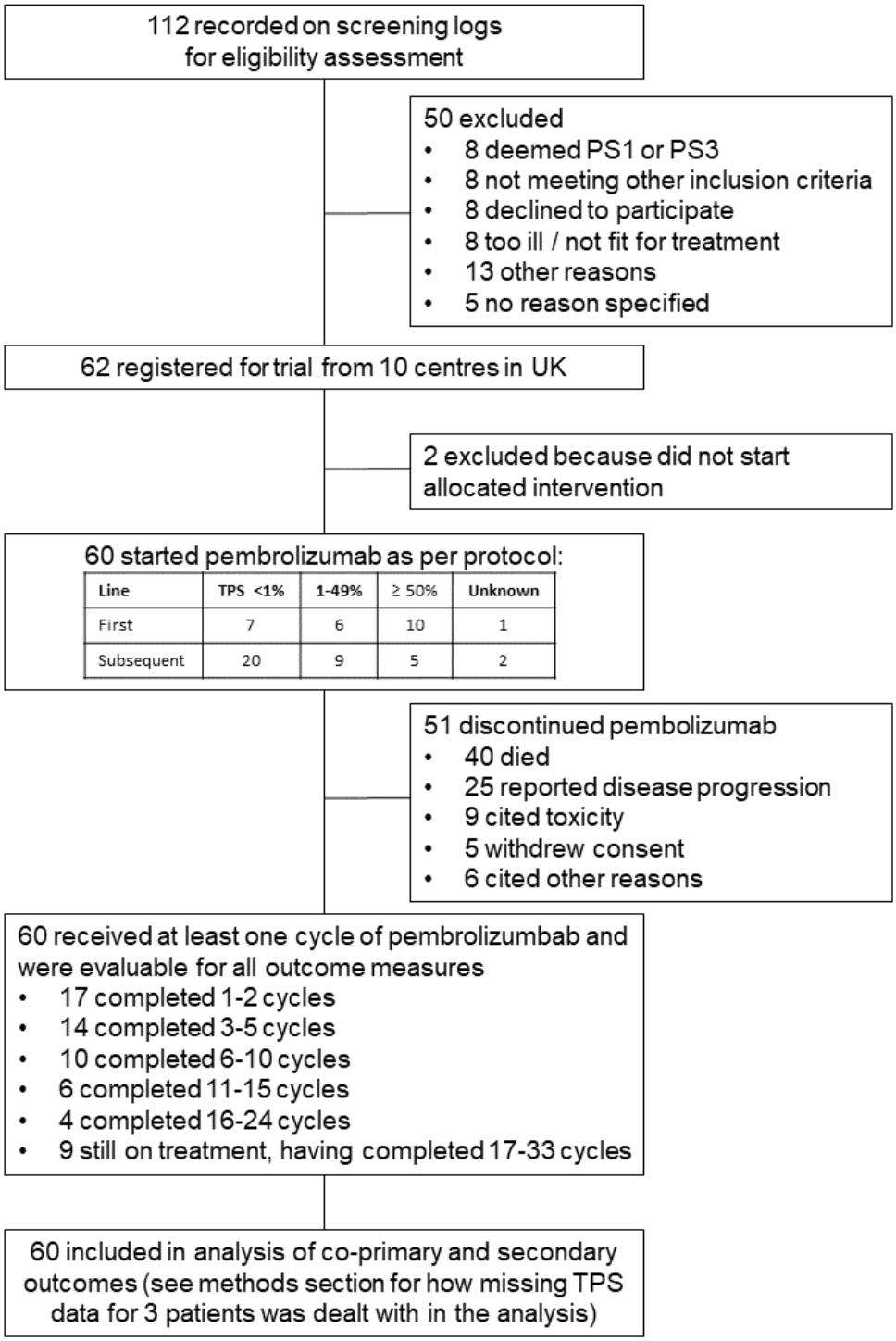


Figure 2: Durable clinical benefit for each cohort estimated from model

Data are percentage and credible interval as specified. TPS=tumour proportion score.

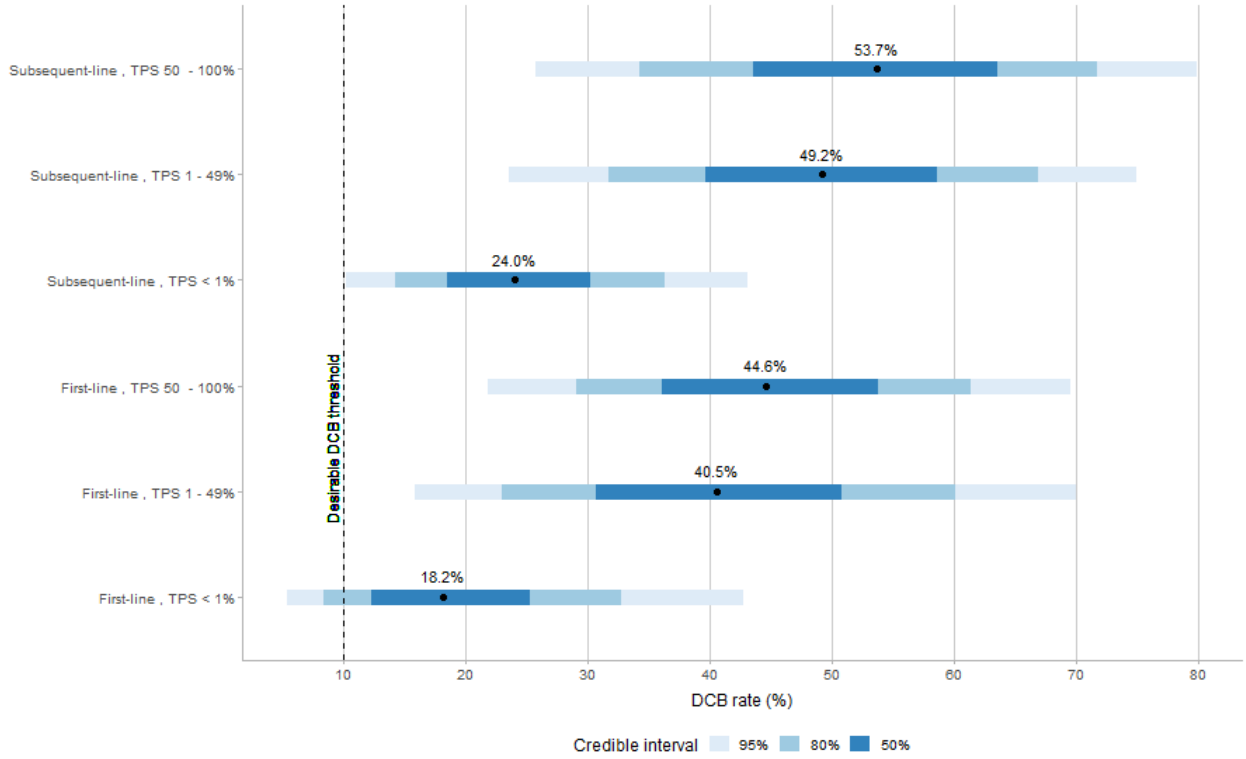
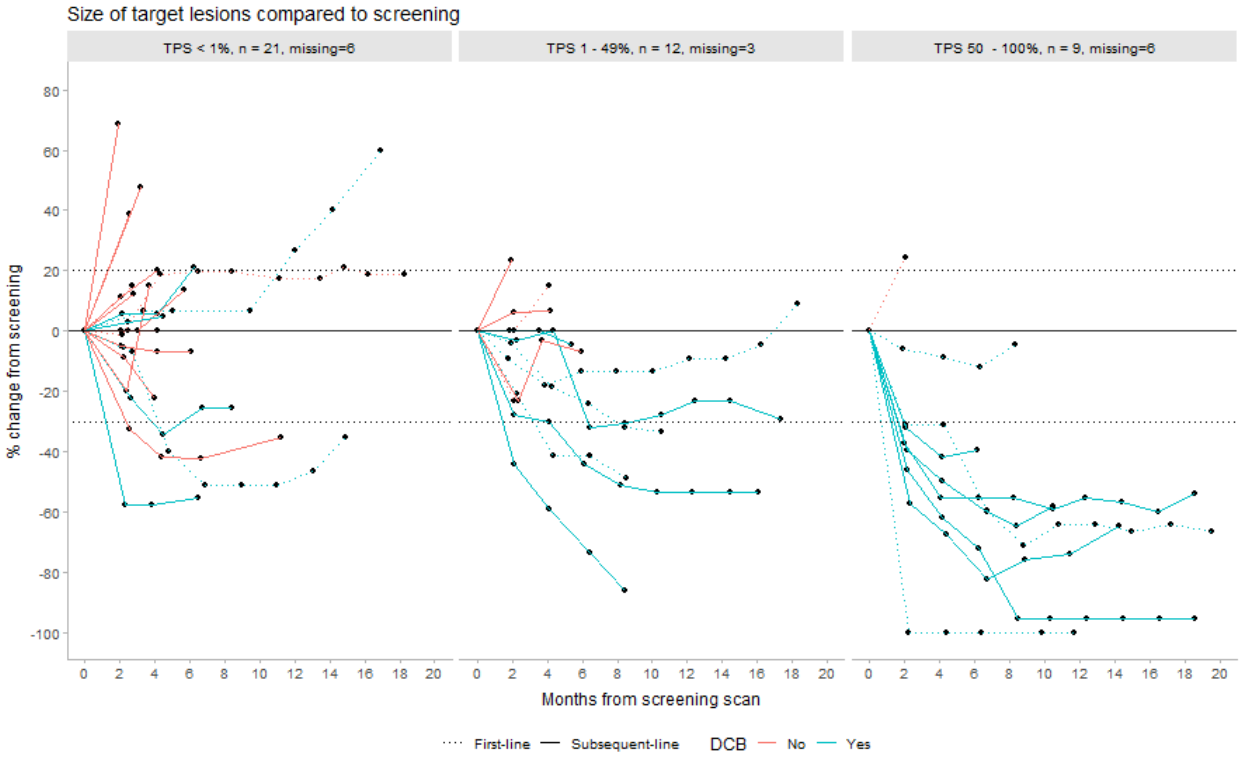


Figure 3: Change from baseline in size of target lesions

(A) Change from baseline in the sum of the longest diameters of the baseline-specified target lesions for patients with and without durable clinical benefit. Horizontal guides show the RECIST partial response and progressive disease thresholds. 15 patients are not shown because they had no post-baseline CT scan, and three 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 a best change of +100%. Each bar represents one patient. Bars ordered from largest positive change to largest negative change. TPS=tumour proportion score.

(A)



(B)

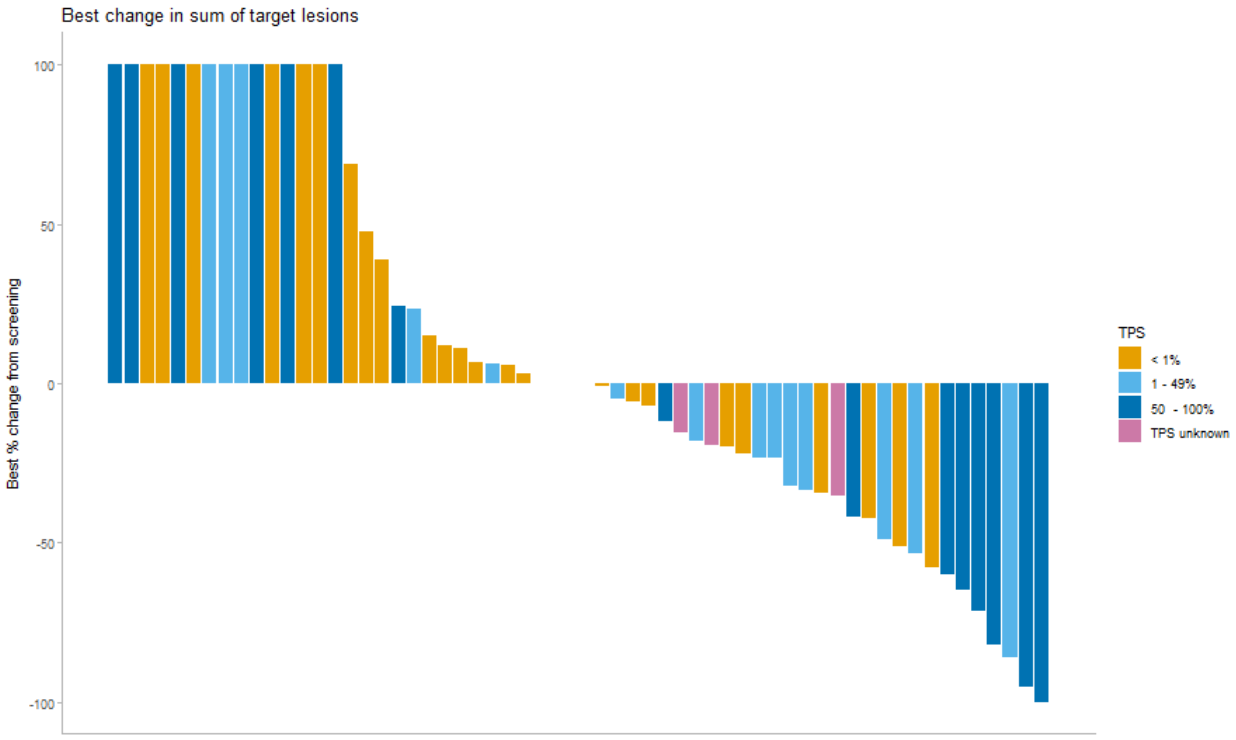
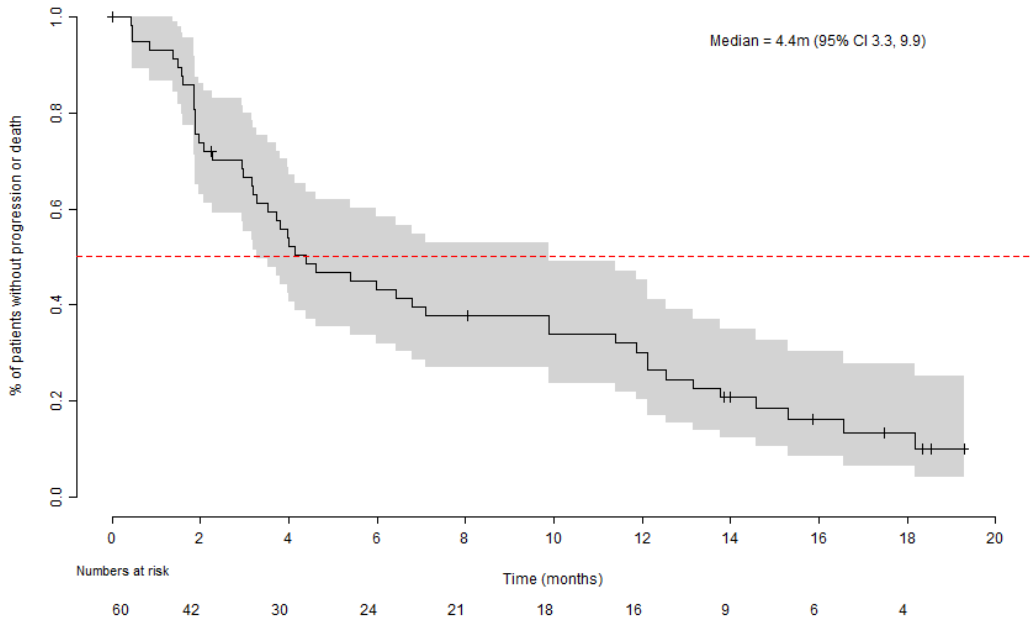

Best change in sum of target lesions
Best % change from screening
100
50
0
-50
-100
TPS
< 1%
1 - 49%
50 - 100%
TPS unknown

Figure 4: Kaplan-Meier plot

Progression-free survival (A) and overall survival (B). Tick marks represent censored times. See appendix pp 7–10 for progression-free survival and overall survival curves split by tumour proportion score and line of therapy.

(A)



(B)

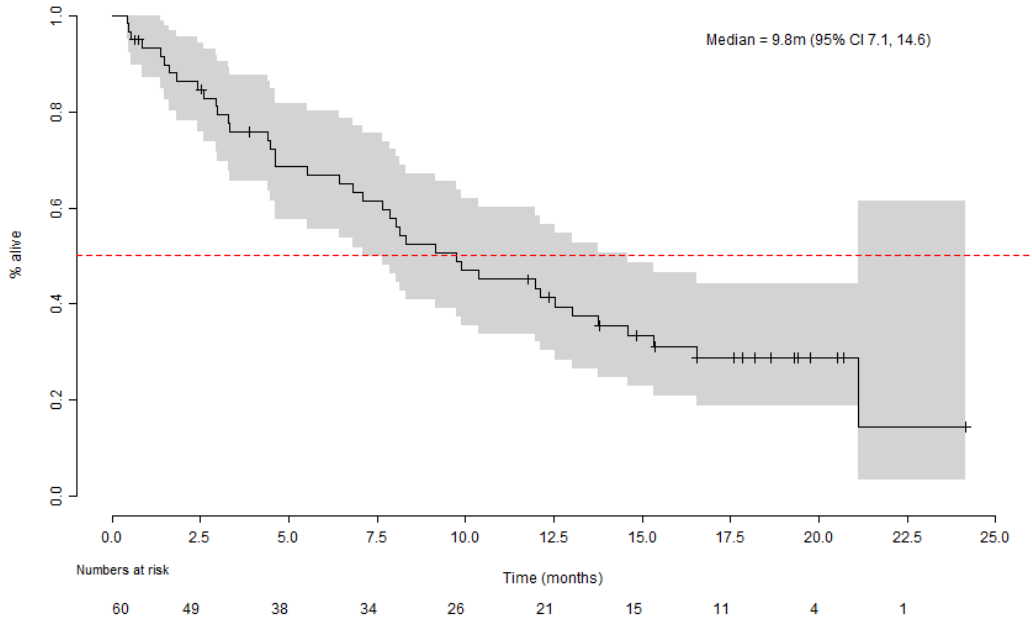


Figure 5: Incidence of adverse events grouped into potentially immune-related and non-immune-related

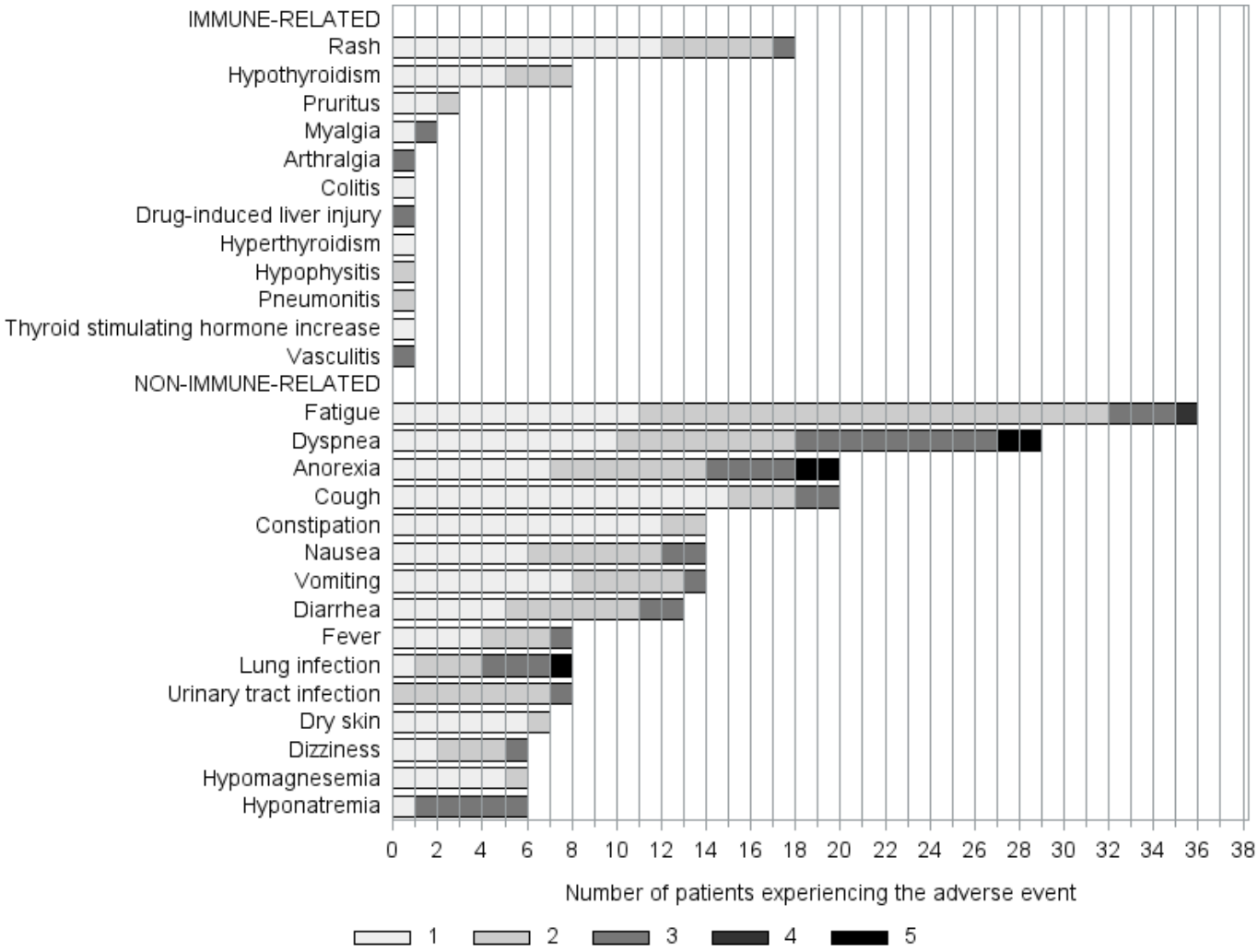


Figure 6: Mean health-related quality of life scores over time while patients were on trial treatment

For periods with at least ten observations. EQ-5D-5L= EuroQol quality of life questionnaire with five domains and five levels. EQ-VAS=EuroQol visual analogue scale.