Temporary treatment cessation versus continuation of first-line tyrosine kinase inhibitor in patients with advanced clear cell renal cell carcinoma (STAR): an open-label, non-inferiority, randomised, controlled, phase 2/3 trial

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Summary

Background Temporary drug treatment cessation might alleviate toxicity without substantially compromising efficacy in patients with cancer. We aimed to determine if a tyrosine kinase inhibitor drug-free interval strategy was non-inferior to a conventional continuation strategy for first-line treatment of advanced clear cell renal cell carcinoma.

Methods This open-label, non-inferiority, randomised, controlled, phase 2/3 trial was done at 60 hospital sites in the UK. Eligible patients (aged ≥18 years) had histologically confirmed clear cell renal cell carcinoma, inoperable locoregional or metastatic disease, no previous systemic therapy for advanced disease, uni-dimensionally assessed Response Evaluation Criteria in Solid Tumours-defined measurable disease, and an Eastern Cooperative Oncology Group performance status of 0–1. Patients were randomly assigned (1:1) at baseline to a conventional continuation strategy or drug-free interval strategy using a central computer-generated minimisation programme incorporating a random element. Stratification factors were Memorial Sloan Kettering Cancer Center prognostic group risk factor, sex, trial site, age, disease status, tyrosine kinase inhibitor, and previous nephrectomy. All patients received standard dosing schedules of oral sunitinib (50 mg per day) or oral pazopanib (800 mg per day) for 24 weeks before moving into their randomly allocated group. Patients allocated to the drug-free interval strategy group then had a treatment break until disease progression, when treatment was re-instated. Patients in the conventional continuation strategy group continued treatment. Patients, treating clinicians, and the study team were aware of treatment allocation. The co-primary endpoints were overall survival and quality-adjusted life-years (QALYs); non-inferiority was shown if the lower limit of the two-sided 95% CI for the overall survival hazard ratio (HR) was 0·812 or higher and if the lower limit of the two-sided 95% CI of the marginal difference in mean QALYs was –0·156 or higher. The co-primary endpoints were assessed in the intention-to-treat (ITT) population, which included all randomly assigned patients, and the per-protocol population, which excluded patients in the ITT population with major protocol violations and who did not begin their randomisation allocation as per the protocol. Non-inferiority was to be concluded if it was met for both endpoints in both analysis populations. Safety was assessed in all participants who received a tyrosine kinase inhibitor. The trial was registered with ISRCTN, 06473203, and EudraCT, 2011-001098-16.

Findings Between Jan 13, 2012, and Sept 12, 2017, 2197 patients were screened for eligibility, of whom 920 were randomly assigned to the conventional continuation strategy (n=461) or the drug-free interval strategy (n=459; 668 [73%] male and 251 [27%] female; 885 [96%] White and 23 [3%] non-White). The median follow-up time was 58 months (IQR 46–73 months) in the ITT population and 58 months (46–72) in the per-protocol population. 488 patients continued on the trial after week 24. For overall survival, non-inferiority was demonstrated in the ITT population only (adjusted HR 0·97 [95% CI 0·83 to 1·12] in the ITT population; 0·94 [0·80 to 1·09] in the per-protocol population). Non-inferiority was demonstrated for QALYs in the ITT population (n=919) and per-protocol (n=871) population (marginal effect difference 0·06 [95% CI –0·11 to 0·23] for the ITT population; 0·04 [–0·14 to 0·21] for the per-protocol population). The most common grade 3 or worse adverse events were hypertension (124 [26%] of 485 patients in the conventional continuation strategy group *vs* 127 [29%] of 431 patients in the drug-free interval strategy group); hepatotoxicity (55 [11%] *vs* 48 [11%]); and fatigue (39 [8%] *vs* 63 [15%]). 192 (21%) of 920 participants had a serious adverse reaction. 12 treatment-related deaths were reported (three patients in the conventional continuation strategy group; nine patients in the drug-free interval strategy group) due to vascular (n=3), cardiac (n=3), hepatobiliary (n=3), gastrointestinal (n=1), or nervous system (n=1) disorders, and from infections and infestations (n=1).

Interpretation Overall, non-inferiority between groups could not be concluded. However, there seemed to be no clinically meaningful reduction in life expectancy between the drug-free interval strategy and conventional

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continuation strategy groups and treatment breaks might be a feasible and cost-effective option with lifestyle benefits for patients during tyrosine kinase inhibitor therapy in patients with renal cell carcinoma.

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Introduction

In the past 15 years, there have been major advances in the targeted therapy of advanced renal cell carcinoma, through the introduction of tyrosine kinase inhibitors, mTOR inhibitors, and immunotherapy drugs administered as monotherapy or in combination with tyrosine kinase inhibitors.[1] In a randomised phase 3 registration trial of the tyrosine kinase inhibitor sunitinib, overall survival was 26·4 months compared with 21·8 months for interferon-α,[2,3] which resulted in sunitinib becoming the standard of care globally. However, the proportion of patients with grade 3 or worse adverse events in the sunitinib group was high, including hypertension (12%), fatigue (11%), diarrhoea (9%), and hand-foot syndrome (9%).[3] An alternative tyrosine kinase inhibitor (pazopanib) was subsequently approved globally, but has also been associated with substantial toxicity.[4,5]

Targeted treatments for advanced cancers are typically continued for many months or even years until disease progression. Considering their toxicity, survival benefits are achieved at the expense of serious impacts on lifestyle and potentially reduced quality of life (QOL), with many patients commenting that the toxicity burden reduces

Research in context

Evidence before this study

Tyrosine kinase inhibitors, which are normally administered continuously until disease progression, result in improved survival outcomes for patients with advanced or metastatic renal cell carcinoma; however, such treatment causes considerable toxicity and reduced quality of life. We searched PubMed from database inception until STAR recruitment (Jan 13, 2012) for published articles using the terms "treatment break", "intermittent therapy", "cancer", "renal cell carcinoma", "advanced/metastatic kidney cancer", "targeted therapy", "tyrosine kinase inhibitors", "sunitinib", and "pazopanib". The search identified no relevant phase 3 studies of treatment breaks or intermittent treatment in renal cell carcinoma, but a number of small phase 2 or case studies, which suggested that patients with renal cell carcinoma who initially responded but subsequently progressed on tyrosine kinase inhibitor treatment sometimes responded again to the same tyrosine kinase inhibitor after a treatment break. Our search data were complemented by advice from key opinion leaders in renal cell carcinoma. We updated our search after the STAR trial commenced recruitment until October, 2022. No relevant randomised phase 3 studies in renal cell carcinoma were identified by the updated search, but additional relevant phase 2 studies were identified, including that of Rini and colleagues, published in 2017, which suggested that treatment breaks in renal cell carcinoma were feasible without compromising efficacy.

Added value of this study

The STAR trial compared continuous treatment with a treatment break strategy in patients with renal cell carcinoma, with the co-primary endpoints of overall survival and quality-adjusted life-years (QALYs). To our knowledge, this is the first study of temporary treatment cessation done in patients with renal cell carcinoma or in any cancer using a tyrosine kinase inhibitor to investigate the co-primary endpoints of overall survival and QALYs. The study included participants receiving tyrosine kinase inhibitor treatment across the UK with study sites ranging from large comprehensive cancer centres to smaller cancer units, therefore being representative of the real-world environment. The primary analysis showed that while temporary treatment cessation was non-inferior to continuous treatment for the QALY endpoint in both intention-to-treat (ITT) and per-protocol populations, and for the overall survival endpoint in the ITT population, non-inferiority was not demonstrated for overall survival in the per-protocol population. Therefore, non-inferiority of temporary treatment cessation cannot be concluded from the trial. However, no clinically meaningful reduction in life expectancy was identified between the treatment groups. The study also included an economic analysis that demonstrated cost-effectiveness of the treatment break strategy.

Implications of all the available evidence

Although the primary endpoint of non-inferiority in both overall survival and QALYs could not be concluded, the STAR trial demonstrated that breaks in tyrosine kinase inhibitor treatment in patients with renal cell carcinoma had potential lifestyle and health economic benefits and preserved quality of life, and are not likely to have a materially detrimental effect on patient outcomes. The available evidence, now considerably enhanced by the STAR trial, provides reassurance that planned breaks in tyrosine kinase inhibitor treatment in patients with renal cell carcinoma represent a reasonable option when there is a patient or health-care need (eg, a pandemic or drug shortage) to disrupt treatment. These findings also provide a rationale for further exploration of treatment breaks in patients with renal cell carcinoma receiving treatment with drugs other than tyrosine kinase inhibitors and in patients with other cancers.

their ability to enjoy life and maintain their activities. This balance is one that patients and oncologists constantly try to optimise and there is a need to explore new ways of achieving this balance.

Treatment breaks might reduce the negative impacts of systemic anti-cancer therapy (including the effects of long-term toxicities, such as sarcopenia, mucositis, and fatigue), while maintaining treatment efficacy, with potential health economic benefits. Considering the high cost of cancer medicines, strategies that reduce cost might also enable greater access overall, for example in low-income and middle-income countries. However, large phase 3 studies of treatment break strategies with overall survival primary endpoints are rare. In colorectal cancer, several studies employed treatment breaks without a clinically meaningful survival deficit, but with QOL advantages.[6–8] Although the large, randomised phase 3 COIN study in colorectal cancer[7] did not demonstrate non-inferiority of intermittent chemotherapy compared with continuous chemotherapy in terms of overall survival, it was concluded that intermittent treatment was an acceptable treatment option, resulting in reduced time on chemotherapy, reduced cumulative toxicity, and improved QOL.

In renal cell carcinoma, small studies have demonstrated that patients who initially responded to but subsequently progressed on tyrosine kinase inhibitor treatment sometimes responded again when re-challenged with the same tyrosine kinase inhibitor after a treatment break.[9–11] This finding suggests that sensitivity to sunitinib therapy was restored (and therefore resistance reduced) by a treatment break, thus supporting the rationale for a tyrosine kinase inhibitor treatment break strategy. In a phase 2 study,[12] patients with metastatic renal cell carcinoma were treated with four cycles of sunitinib, which was then withheld in patients who had achieved at least a 10% reduction in tumour burden. Sunitinib was restarted in patients who had an increase of more than 10% in tumour burden and again withheld if another 10% reduction or higher was achieved. It was concluded that such treatment breaks were feasible and that efficacy was not compromised.

Although immunotherapy is the standard first-line treatment for many patients with renal cell carcinoma, tyrosine kinase inhibitors remain the first-line treatment for a substantial proportion of patients and are widely used as second-line and subsequent-line therapy. The STAR trial is a large, multicentre, phase 2/3 study to assess the potential benefits of a treatment break strategy compared with a conventional treatment continuation strategy in patients with renal cell carcinoma receiving tyrosine kinase inhibitor therapy.

Methods

Study design and participants

The STAR trial was an open-label, non-inferiority, randomised, controlled, phase 2/3 trial done at 60 hospital sites in the UK (appendix pp 52–53). Details on the STAR study design have been published previously[13] and the study protocol is available online. When initial data from the COMPARZ trial were published,[14] the STAR trial was amended on Feb 15, 2013, to include pazopanib as an alternative tyrosine kinase inhibitor. A summary of the formal interim analysis done at the end of the phase 2 part of the trial is included in the appendix (p 2).

For the **study protocol** see https://fundingawards.nihr.ac.uk/award/09/91/21

Eligible participants (aged ≥18 years) had histologically confirmed clear cell renal cell carcinoma, inoperable loco-regional or metastatic disease, no previous systemic therapy for advanced disease, an Eastern Cooperative Oncology Group performance status of 0–1, uni-dimensionally assessed Response Evaluation Criteria in Solid Tumours (RECIST)-defined measurable disease, and life expectancy of at least 6 months. Participants also had to have haemoglobin concentration of at least 9 g/L, a neutrophil count of at least 1×10^9 per L, a platelet count of at least 80×10^9 per L, an estimated glomerular filtration rate of at least 30 mL/min per 1·73 m², aspartate aminotransferase or alanine aminotransferase concentrations of 2·5 times the upper limit of normal (ULN) or lower, and bilirubin concentrations of 1·5 times the ULN or lower. Previous radiotherapy or concomitant bisphosphonates or denosumab for bone metastasis were permitted, but patients were excluded if they had received any previous tyrosine kinase inhibitors, or any concomitant medication known to affect tyrosine kinase inhibitor activity, or if they had received previous systemic therapy for inoperable loco-regional or metastatic disease or had poorly controlled hypertension, despite maximal medical therapy. Additionally, potential participants were excluded if they had pulmonary or mediastinal disease, causing obstruction or clinically significant bleeding or haemoptysis risk or untreated CNS metastasis.

Participants were recruited from outpatient clinics after providing written informed consent. Ethical approval was obtained from Liverpool Central Research Ethics Committee (11/NW/0246) and the UK Medicines and Healthcare products Regulatory Agency.

Randomisation and masking

We randomly assigned patients before administration of tyrosine kinase inhibitor. Eligible participants were randomly assigned (1:1) to a conventional continuation strategy or drug-free interval strategy using a central computer-generated minimisation programme coordinated by Leeds Clinical Trials Unit, which incorporated a random element to ensure treatment group balance and allocation concealment until the point of randomisation (ie, after consent was provided and eligibility was confirmed). The minimisation factors were: Memorial Sloan Kettering Cancer Center (MSKCC) prognostic group risk factor[15] (favourable, intermediate, or poor); trial site; sex; age (<60 years or ≥60 years); disease status (metastatic or locally advanced); previous nephrectomy; and sunitinib or pazopanib. The decision regarding use of sunitinib or pazopanib, which was made before randomisation, was at

See **Online** for appendix

the discretion of the treating clinician and could not be changed. Patients, treating clinicians, and the study team were aware of treatment allocation.

Procedures

All participants received oral sunitinib (50 mg per day; 4 weeks on treatment followed by 2 weeks off) or oral pazopanib (800 mg per day) for at least 24 weeks (four cycles), as per standard drug dosing schedules. Participants underwent clinical assessment at the end of every treatment cycle (every 6 weeks) and radiological assessment every 12 weeks (appendix p 5). If disease was not evaluable using CT scan, then an MRI scan of the abdomen and pelvis could be used. Participants who at 24 weeks had a complete response, partial response, or stable disease began their randomised treatment allocation. Participants assigned to the conventional continuation strategy continued on their tyrosine kinase inhibitor (with the aforementioned dosing strategy) until progressive disease as defined by RECIST, unacceptable cumulative toxicity, or participant decision to stop treatment or withdraw from the study. Participants assigned to the drug-free interval strategy stopped treatment until progressive disease (as per RECIST criteria), when they recommenced treatment with their tyrosine kinase inhibitor (with the aforementioned dosing strategy) for a minimum of four cycles. For the drug-free interval strategy group, to assess progressive disease or response, radiological images taken after the treatment break were compared with those done immediately before the treatment break commenced rather than the baseline scan that was done before tyrosine kinase inhibitor treatment commenced. Assuming ongoing disease control, although not mandated, participants could take further treatment breaks following the same schedule. This drug-free interval strategy was continued until progressive disease during tyrosine kinase inhibitor treatment, cumulative toxicity, or participant decision to stop treatment. Central review of CT imaging was only done during phase 2 of the trial. During phase 3 of the trial, scans were reported locally.

Up to two dose reductions of sunitinib and pazopanib were permitted (as per the drug summaries of product characteristics[16,17]). All participants were assessed clinically for symptoms and toxicity at the start of each treatment cycle and biochemically as recommended by the drug summaries of product characteristics. More frequent monitoring of liver function was required for pazopanib than for sunitinib as recommended in the summaries of product characteristics.[16] Adverse events were collected on 6-weekly on-study review clinical report forms. Serious adverse events were collected until 30 days after permanent cessation of trial treatment. Serious adverse reactions and suspected unexpected serious adverse reactions were collected for 30 days after the end of trial follow-up. Adverse events were reported per the Common Terminology Criteria for Adverse Events, version 4. Participants were seen in clinic 6 months after permanently discontinuing protocol treatment and annually thereafter until the end of follow-up on Dec 31, 2020. All randomly assigned participants were followed up for survival unless consent was withdrawn.

Three paper-based patient-reported questionnaires were completed during the trial: The Functional Assessment of Cancer Therapy-General (FACT-G),[18] Functional Assessment of Cancer Therapy–Kidney Symptom Index-15 (FKSI-15),[19] and EQ-5D-3 Level version or EuroQoL-vertical visual analogue scale.[20,21] FACT-G is a 27-item questionnaire, which when scored results in four subscales relating to physical, social or family, emotional, and functional wellbeing. A total score is also obtained by taking the sum of the subscales. FKSI-15 is a 15-item questionnaire, which when scored results in an overall score and a disease-related subscale. The EQ-5D-3L is a questionnaire with five domains, which when scored produces an overall utility index. Because of the importance of QOL data in this trial, measures were taken to ensure maximum compliance of questionnaire completion, including allowing recruiting sites to post paper questionnaires out to participants. Booklet A was due at baseline; booklet B at weeks 6, 12, and 18 after randomisation; booklet C at weeks 24, 30, 36, and 42; booklet D at 2-weekly intervals between weeks 24 and 46; booklet E at 6-weekly intervals from week 48 while participants remained on treatment; and booklet F at 6 months after the end of trial treatment and annually thereafter. Booklets A, B, and E contained all three questionnaires. Booklets D and F contained only the EQ-5D questionnaire and booklet C contained the FKSI-15 and the FACT-G questionnaires.

Outcomes

The co-primary endpoints for phase 3 of the trial were overall survival, defined as time to death from any cause, and quality-adjusted life-years (QALYs), defined as the area under the utility curve derived from the utility index of the EQ-5D-3L questionnaire.

Secondary endpoints were: time to strategy failure (defined as the time to first instance of death [appendix p 6], progression while on treatment, progression assuming no further response or stabilisation occurs in the drug-free interval strategy group, or participant requires a new systemic anti-cancer drug); time to treatment failure (defined as time to permanent protocol-based treatment discontinuation for any reason); progression-free survival (defined as time to first progression or death from any cause); summative progression-free interval (defined as the sum of intervals during which the participant was progression free; appendix pp 7–8); toxicity through the collection of safety events; cost-effectiveness (defined as the cost per QALY over a lifetime); and QOL (scored using patient-reported FACT-G and FKSI questionnaires; appendix p 3).

All time-to-event endpoints were measured from randomisation and were censored at a participant's last known date to be alive and event free.

The additional QOL measures from the EQ-5D questionnaire are not reported separately since they are incorporated into the QALY co-primary endpoint. We did four trial substudies: a patient preference and understanding study; a tissue study; a CT imaging study; and a dynamic-contrast-enhanced-MRI substudy. The substudies will be reported separately.

Statistical analysis

For the co-primary endpoints, the null hypothesis was that a drug-free interval strategy is inferior to a conventional continuation strategy for overall survival at 2 years by more than 7·5% and by more than 10% for QALYs measured during the trial and follow-up period. The original sample size calculations (n=1000) for phase 2 and 3 have been published previously.[13] With the consent of the data monitoring committee, sample sizes were adjusted in February, 2017, to account for reduced drop-out rates (ie, 2% rather than the 5% assumed) and a model-based approach suggesting the conventional continuation strategy survival rate was 48·5% at 2 years. The original non-inferiority margin of 7·5% absolute difference in survival rates at 2 years, with a conventional continuation strategy rate of 48·5%, was still considered by the data monitoring committee to be relevant, which under an assumed exponential distribution led to a hazard ratio (HR) of 0·812. From this amendment, the sample size for overall survival was reduced to 920, requiring 720 events for 80% power at a 2·5% significance level. This adjustment translated to a conventional continuation strategy QALY estimate of 1·42 and a power of 77·6% with a 10% non-inferiority margin. A later extension to trial follow-up on May 23, 2019 adjusted the conventional continuation strategy QALY estimate to 1·56, yielding a power of 69·9% (appendix pp 2–3).

The primary non-inferiority analysis was done in the intention-to-treat (ITT) population, which included all randomly assigned patients with renal cell carcinoma, and the per-protocol population, which included all participants who received the assigned treatment without any major protocol violations (as determined by the trial management group) and only participants who, if they reached 6 months after randomisation, began their randomisation allocation as per the protocol. ITT and per-protocol data were summarised by randomisation allocation. Safety was assessed in all participants who received a tyrosine kinase inhibitor and participants were summarised as per actual treatment received. If a participant in the drug-free interval strategy group declined or did not have a treatment break in error at 6 months after randomisation and it was not rectified by their next scan, their data were summarised and included in the conventional continuation strategy group for the safety analysis. A QOL population was defined for each questionnaire; a participant was included if they had a baseline questionnaire that could be scored (appendix p 3). Unless specifically excluded from the analysis population being used, all participants were assessable for all endpoints. Since both primary outcomes were to assess non-inferiority, analyses were done in both the per-protocol and ITT populations. If the drug-free interval strategy was found to be non-inferior in both overall survival and QALY in both populations then the analysis would conclude that the drug-free interval strategy was non-inferior to the conventional continuation strategy.[22] A formal interim analysis was done at the end of phase 2 (June 26, 2014; appendix p 2). All analyses were pre-specified in the protocol, unless otherwise stated.

Overall survival was estimated using the Kaplan-Meier method and presented as median survival with corresponding 95% CIs. Formal comparisons between randomisation allocations were made using a Cox proportional hazards model, adjusted for the categorical minimisation factors, excluding centre. Proportional hazards were assessed using both the supremum test and log(-log) plots. Non-inferiority between the treatment groups (conventional continuation strategy *vs* drug-free interval strategy, where drug-free interval strategy was used as the reference in the statistical model) was to be concluded if the lower bound of the two-sided 95% CI around the HR for the treatment covariate was 0·812 or higher. Analysis of pre-specified subgroups was done for overall survival in the ITT population only, by including the main effect term for the subgroup of interest and an interaction term for the subgroup and randomisation allocation to the Cox proportional hazards model and applying a likelihood ratio test to investigate heterogeneity. HRs for randomisation allocation, accounting for the modelled interaction (interaction contrasts) and with 2-year overall survival estimates were also obtained. The subgroups considered were BMI risk group (underweight or normal <25 kg/m² *vs* overweight or obese ≥25 kg/m²); number of comorbidities (0, 1, or ≥2); International Metastatic Renal Cell Carcinoma Database Consortium risk group; age older than 70 years; age older than 75 years; bone involvement; liver involvement; and the corrected stratification factors (MSKCC prognostic group, sex, age group <60 years *vs* ≥60 years, disease status, tyrosine kinase inhibitor received, and previous nephrectomy).

For QALYs, missing EQ-5D utility values from trial follow-up were imputed using multiple imputation by chained equations and QALYs were derived within each imputed dataset.[23–25] The missing at random assumption was assessed through sensitivity analysis considering missing not at random scenarios in an iterative manner (appendix p 3). Formal comparisons between randomisation allocations were made using the combined results of a marginalised two-component finite mixture model, adjusted for the categorical minimisation factors of the trial, excluding centre. Different to overall survival, the

conventional continuation strategy was used as the reference level in the model. The model was assessed within each imputed dataset by investigating whether the knowledge of a participant's component, determined by the finite mixture model, improved the fit of a multivariable linear regression model by assessing the distribution and variance of the residuals using plots.[26] Non-inferiority between the two groups was to be concluded if the lower bound of the two-sided 95% CI for the treatment covariate coefficient was –0·156 or higher. A sensitivity analysis was also performed, which applied a multivariable linear regression model rather than a finite mixture model.

The secondary endpoints time to strategy failure, summative progression-free interval, time to treatment failure, and progression-free survival were analysed in a similar way to overall survival in the ITT population only, at the 5% significance level. Safety events were summarised descriptively. We did a post-hoc analysis of depth of response at week 24, assessed by the proportion of participants who achieved a complete response, partial response, and stable disease, and these results were summarised descriptively. We did an economic evaluation using the National Institute for Health and Care Excellence reference case,[27] presenting a cost-utility analysis over a lifetime horizon from the perspective of the health and personal social services provider. The primary endpoint was incremental cost per QALY gained. A within-trial analysis (time horizon of 2 years) used decision modelling to extrapolate outcomes over a lifetime horizon. A willingness-to-pay threshold range of £20 000–30 000 per QALY was assumed. We did sensitivity analyses that included taking a societal cost perspective, a per-protocol analysis, and an analysis including subsequent lines of therapy.

A summary of the secondary QOL analysis is provided in the appendix (p 3).

Statistical analysis was done using SAS (version 9.4). For the cost-effectiveness analysis, Microsoft Excel and Stata (version 14.2) were used.

The trial was registered with ISRCTN, 06473203, and EudraCT, 2011-001098-16.

Role of the funding source

The study funder had no role in the study design (with the exception of during peer review of the funding application) or in data collection, data interpretation, data analysis, or writing of the report.

Results

Between Jan 13, 2012, and Sept 12, 2017, 2197 participants were screened for eligibility, of whom 920 were randomly assigned to the conventional continuation strategy (n=461) or the drug-free interval strategy (n=459; figure 1A). Phase 2 interim analysis results, from which it was concluded the trial should proceed to phase 3, are in the appendix (pp 2, 31). Participants were followed up until Dec 31, 2020. Median follow-up was 58 months (IQR 46–73) in the ITT population and 58 months (46–72) in the per-protocol population. 432 (47%) of 920 participants discontinued treatment before beginning their randomisation allocation at week 24 (221 [48%] of 461 patients in the conventional continuation strategy group; 211 [46%] of 459 patients in the drug-free interval strategy group). 488 patients continued on trial after week 24. Over the whole trial, the main reasons for discontinuation were radiological disease progression (261 [58%] of 453 patients in the conventional continuation strategy group *vs* 231 [54%] of 425 patients in the drug-free interval strategy group) and toxicity (140 [31%] *vs* 135 [32%]).

Of the 920 participants randomly assigned, 919 (100%) were included in the ITT population (461 patients in the conventional continuation strategy group and 458 patients in the drug-free interval strategy group) and 871 (95%) were included in the per-protocol population (453 patients in the conventional continuation strategy group and 418 patients in the drug-free interval strategy group). 916 (100%) of 920 patients were included in the safety population (485 patients in the conventional continuation strategy group and 431 patients in the drug-free interval strategy group; three in the drug-free interval strategy group and one in the conventional continuation strategy group did not have any treatment and 24 moved from the drug-free interval strategy group to the conventional continuation strategy group due to continuous treatment). The reasons for exclusion are shown in figure 1A.

Regarding the QOL study, a higher proportion of patients withdrew from the conventional continuation strategy group than the drug-free interval strategy group (figure 1B). Key demographic information is presented in table 1 (ITT population) and the appendix (pp 32–33; per-protocol population). 668 (73%) of participants were male and 251 (27%) were female; 885 (96%) were White and 23 (3%) were non-White.

Overall, patients received a median of four treatment cycles (IQR 2–10) and the number of treatment cycles was similar between the two groups (5 cycles [2–10] in the conventional continuation strategy group; 4 cycles [2–9] in the drug-free interval strategy group). Before week 24, the median number of treatment cycles was identical between the two groups (4 cycles [IQR 2–4]). After week 24, the median number of cycles remained similar between the two groups (6 cycles [IQR 2–13] in the conventional continuation strategy group; 6 cycles [3–12] in the drug-free interval strategy group). Additionally, a similar proportion of patients required a dose reduction in the two groups (207 [45%] of 461 patients in the conventional continuation strategy group; 212 [46%] of 458 patients in the drug-free interval strategy group).

248 (54%) of 458 participants in the drug-free interval strategy group continued on trial after 24 weeks. Of these patients, 210 (85%) started their first treatment break according to protocol at week 24, with a similar proportion

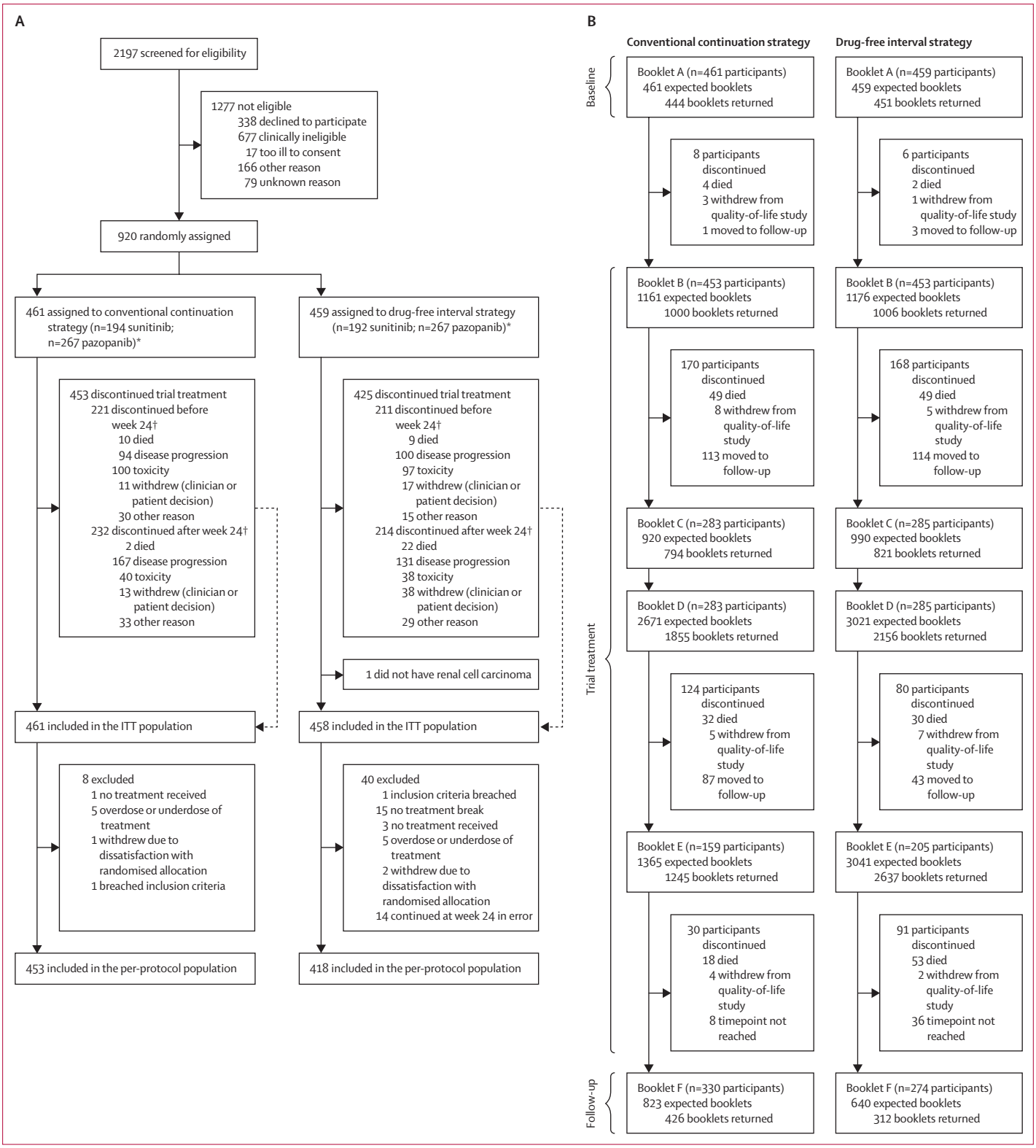

Figure 1: **Trial profile for the clinical part of the study (A) and participant flow through the QOL study (B)**
QOL=quality of life. In the QOL study, completion of booklet A was due at baseline; booklet B at weeks 6, 12, and 18 after randomisation; booklet C at weeks 24, 30, 36, and 42; booklet D at 2-weekly intervals between weeks 24 and 46; booklet E at 6-weekly intervals from week 48 while participants remained on treatment; and booklet F at 6 months after the end of trial treatment and annually thereafter. *Participants who received each tyrosine kinase inhibitor rather than the number who were randomised to each tyrosine kinase inhibitor. †Reasons are not mutually exclusive.

on each tyrosine kinase inhibitor (89 [84%] of 106 participants on sunitinib; 121 [85%] of 142 participants on pazopanib). Of the other 38 participants, 15 did not take up a treatment break but continued treatment at week 24 in error and then either withdrew from trial treatment or had radiological progression on a later scan, 12 patients took their first break at 36 weeks, six patients at 48 weeks, two patients at 60 weeks, and three patients at other timepoints. The reasons for continuing treatment past week 24 included clinical decision or, during phase 2 of the trial, that maximal radiological response had not been reached. 240 (52%) of the 461 participants randomised to the conventional continuation strategy group continued on trial after week 24. All participants were included in the ITT analysis. However, patients who did have a treatment break or continued in error were excluded from the per-protocol analysis (figure 1A).

	Conventional continuation strategy (n=461)	Drug-free interval strategy (n=458)
Ethnicity		
White	445 (97%)	440 (96%)
Non-White	14 (3%)	9 (2%)
Not stated	2 (0%)	9 (2%)
Age, years		
Median (IQR)	65 (59–72)	67 (59–72)
<60 years	122 (26%)	122 (27%)
Sex		
Male	336 (73%)	332 (72%)
Female	125 (27%)	126 (28%)
ECOG performance status		
0	246 (53%)	258 (56%)
1	215 (47%)	196 (43%)
Missing	0	4 (1%)
Bone metastasis		
Yes	108 (23%)	94 (21%)
No	352 (76%)	364 (79%)
Missing	1 (<1%)	0
Time since initial diagnosis, years		
Median (IQR)	0·74 (0·21–3·21)	0·68 (0·22–3·21)
Missing data	2 (<1%)	1 (<1%)
MSKCC prognostic group		
Favourable (0 risk factors)	202 (44%)	203 (44%)
Intermediate (1–2 risk factors)	224 (49%)	223 (49%)
Poor (≥3 risk factors)	35 (8%)	32 (7%)
Disease status		
Metastatic	451 (98%)	448 (98%)
Locally advanced	10 (2%)	10 (2%)
Previous nephrectomy	347 (75%)	345 (75%)
Tyrosine kinase inhibitor		
Sunitinib	195 (42%)	193 (42%)
Pazopanib	266 (58%)	265 (58%)
IMDC risk group		
Favourable (0 risk factors)	110 (24%)	115 (25%)
Intermediate (1–2 risk factors)	222 (48%)	223 (49%)
Poor (≥3 risk factors)	74 (16%)	65 (14%)
Missing data	55 (12%)	55 (12%)

Data are n (%), unless stated otherwise. ECOG=Eastern Cooperative Oncology Group. MSKCC=Memorial Sloan-Kettering Cancer Center. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium.

Table 1: **Baseline demographic characteristics of the intention-to-treat population (n=919)**

Although the median number of breaks in the drug-free interval strategy group was one, many participants had two or more breaks, with a maximum of nine breaks (appendix p 34). The median length of all treatment breaks was 87 days (IQR 84–119) and was similar for the two tyrosine kinase inhibitors (sunitinib, 85·5 days [84–112]; pazopanib, 87·5 days [84–137]). 12 (3%) of 458 patients in the drug-free interval strategy group withdrew from the study at the point of randomisation in order to receive continuous treatment.

Figure 2 shows overall survival Kaplan-Meier curves for each group for the per-protocol and ITT populations. Of 871 patients included in the per-protocol population, 648 (74%) died before the end of follow-up (330 [73%] of 453 patients in the conventional continuation strategy group; 318 [76%] of 418 patients in the drug-free interval strategy group). Therefore, 223 (26%) of 871 participants were censored in the per-protocol analysis. Of 919 patients included in the ITT population, 678 (74%) died before the end of follow-up (335 [73%] of 461 patients in the conventional continuation strategy group; 343 [75%] of 458 patients in the drug-free interval strategy group). Therefore, 241 (26%) of 919 participants were censored in the ITT analysis. In both populations, the sample size was lower than the sample size required for 80% power (n=720) in the overall survival comparison. The causes of death per group are included in the appendix (p 35).

For the per-protocol population, median overall survival was 28 months (95% CI 24–32) in the conventional continuation strategy group and 27 months (23–31) in the drug-free interval strategy group (adjusted HR 0·94 [95% CI 0·80–1·09]). In the ITT population, median overall survival was 28 months (95% CI 24–32) in the conventional continuation strategy group and 27 months (23–33) in the drug-free interval strategy group (adjusted HR 0·97 [95% CI 0·83–1·12]). These results are compared graphically with the non-inferiority boundary of 0·812 in the appendix (p 9). Thus, although non-inferiority of the drug-free interval compared with the conventional continuation strategy in terms of overall survival was established in the ITT population, non-inferiority was not established in the per-protocol population at the 2·5% significance level. The full model results are shown in the appendix (pp 36–37). The proportional hazards assumption was concluded to be met in both populations for randomisation allocation using both the supremum test (p=0·64 for the ITT population; p=0·57 for the per-protocol population) and

log(-log) plots (appendix p 10). Figure 3 shows the results of the pre-specified subgroup analysis for overall survival. Interaction contrast estimates are shown in the appendix (p 38).

For the analysis of QALYs, 52 imputed datasets were generated for up to 54 months. Questionnaire completion rate was high (13 147 [78·6%] of 16 726 issued questionnaires). The proportion of missing data at each timepoint and summary statistics for QALYs and baseline EQ-5D data are shown in the appendix (pp 40–41). The distribution of the QALYs was observed to be non-normal and similar across the imputed datasets (appendix p 11). The difference between the groups from the marginal model was 0·04 (95% CI –0·14 to 0·21) in the per-protocol population (n=871) and 0·06 (–0·11 to 0·23) in the ITT population (n=919). These results are compared graphically with the non-inferiority boundary of –0·156 in the appendix (p 9). At the 2·5% significance level, the drug-free interval strategy was non-inferior to the conventional continuation strategy group in terms of QALYs in both the per-protocol and ITT populations, and thus non-inferior overall for the QALY endpoint. Full model results are in the appendix (pp 42–43). The missing at random assumption was concluded to be appropriate after a sensitivity analysis did not change the conclusion of the primary analysis (difference between groups in the per-protocol population 0·04 [–0·13 to 0·21]). The two-component finite mixture model was concluded to be appropriate after a pre-specified sensitivity analysis comparing residual plots showed that the normality and homoscedasticity of residuals was improved compared with a multivariate linear regression model (appendix p 12).

Secondary outcome results for time to strategy failure, summative progression-free interval, time to treatment failure, and progression-free survival are shown in the appendix pp 13–14, 44 (time to strategy failure adjusted HR 0·75 [95% CI 0·66–0·86], p<0·0001; summative progression-free interval, 0·77 [0·67–0·89], p=0·00037; time to treatment failure, 0·75 [0·65–0·86], p<0·0001; progression-free survival 1·37 [1·19–1·57], p<0·0001). The supremum test showed that no covariates violated the proportional hazards assumption for time to strategy failure and summative progression-free interval

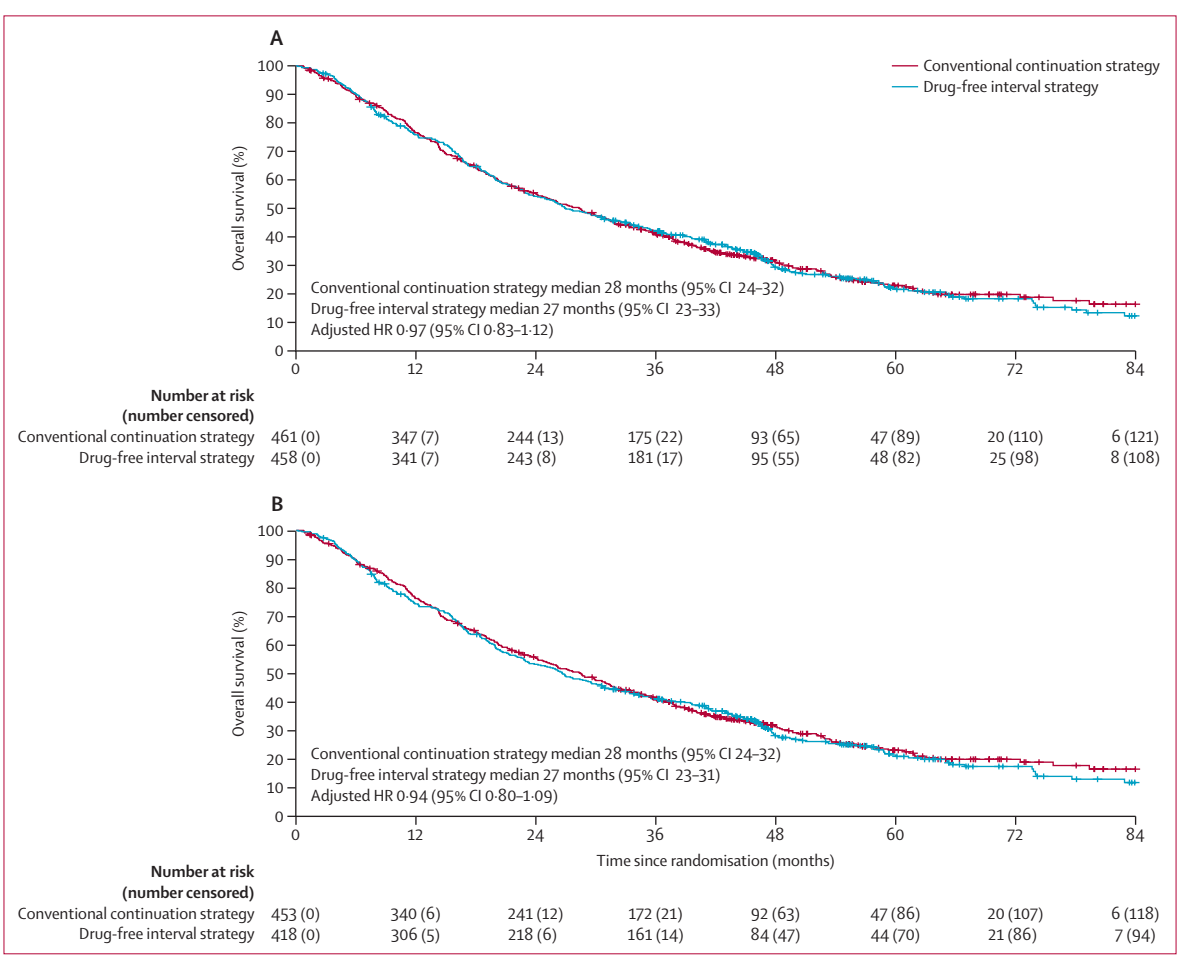

Figure 2: **Kaplan-Meier plots of overall survival**
Overall survival in the intention-to-treat population (A) and the per-protocol population (B). Cross symbols indicate censoring. HR=hazard ratio.

(1% significance level; data not shown). However, for time to treatment failure and progression-free survival, randomisation allocation did violate the proportional hazards assumption at the 1% significance level (data not shown). For the quality-of-life outcomes, no meaningful differences were identified between the groups in the FKSI or FACT-G total scores (appendix pp 15–16, 19–20, 45–48). Residual plots did not violate the model assumptions (appendix pp 29–30). Similar results were observed between groups for FACT-G and

	n/N		2-year survival estimate (95% CI)		HR (95% CI)	$p_{heterogeneity}$
	Conventional continuation strategy	Drug-free interval strategy	Conventional continuation strategy	Drug-free interval strategy		
BMI risk group at baseline						0·22
Underweight or normal (<25 kg/m²)	73/92	105/124	50·4% (39·7–60·2)	38·0% (29·4–46·5)	0·89 (0·66–1·22)	..
Overweight or obese (≥25 kg/m²)	236/333	194/273	55·5% (49·9–60·7)	60·8% (54·7–66·3)	1·08 (0·89–1·31)	..
Comorbidities recorded at baseline						0·08
0	151/202	136/178	49·1% (42·0–55·8)	51·9% (44·3–59·0)	0·95 (0·75–1·20)	..
1	124/174	100/146	60·1% (52·4–67·0)	63·2% (54·7–70·5)	1·11 (0·85–1·45)	..
≥2	55/77	82/94	60·2% (48·2–70·2)	39·9% (29·9–49·6)	0·68 (0·48–0·97)	..
IMDC risk group						0·30
Favourable (0 risk factors)	56/109	64/106	77·8% (68·7–84·5)	71·2% (61·4–78·9)	0·79 (0·55–1·15)	..
Intermediate (1–2 risk factors)	166/216	152/200	53·4% (46·4–59·8)	51·0% (43·8–57·7)	0·98 (0·78–1·23)	..
Poor (≥3 risk factors)	60/74	57/60	32·2% (21·8–43·1)	22·7% (13·1–34·1)	0·76 (0·52–1·11)	..
Age at randomisation (years)						0·56
≤70	227/323	216/290	57·3% (51·7–62·5)	54·5% (48·6–60·1)	0·92 (0·76–1·11)	..
>70	103/130	102/128	50·1% (41·1–58·4)	49·8% (40·8–58·2)	1·00 (0·76–1·33)	..
Age at randomisation (years)						0·35
≤75	275/382	267/357	55·9% (50·7–60·8)	54·5% (49·1–59·5)	0·97 (0·81–1·14)	..
>75	55/71	51/61	51·6% (39·3–62·5)	45·2% (32·4–57·2)	0·80 (0·53–1·17)	..
Bone involvement recorded at baseline						0·17
Yes	89/107	70/83	52·2% (42·3–61·2)	33·6% (23·4–44·0)	0·80 (0·58–1·11)	..
No	241/345	248/335	56·0% (50·6–61·1)	57·8% (52·3–62·9)	0·98 (0·82–1·17)	..
Liver involvement recorded at baseline						0·95
Yes	54/71	64/78	44·5% (32·5–55·8)	41·0% (30·1–51·6)	0·83 (0·56–1·23)	..
No	276/381	253/339	57·1% (51·9–61·9)	55·8% (50·3–60·9)	0·95 (0·80–1·13)	..
Motzer/MSKCC prognostic group						0·026
Favourable risk (0 factors)	126/204	128/181	68·5% (61·6–74·5)	68·9% (61·6–75·1)	0·88 (0·69–1·13)	..
Intermediate risk (1–2 factors)	175/215	156/202	47·2% (40·4–53·8)	46·1% (39·1–52·9)	1·10 (0·88–1·36)	..
Poor risk (≥3 factors)	29/34	34/35	26·5% (13·2–41·8)	11·4% (3·6–24·2)	0·78 (0·46–1·31)	..
Sex						0·66
Male	239/330	234/304	54·8% (49·2–60·0)	53·1% (47·3–58·5)	0·93 (0·77–1·11)	..
Female	91/123	84/114	56·5% (47·2–64·7)	53·2% (43·6–61·9)	0·95 (0·70–1·28)	..
Age group						0·48
<60 years	88/120	82/109	57·3% (47·9–65·6)	57·6% (47·8–66·3)	1·04 (0·77–1·41)	..
≥60 years	242/333	236/309	54·5% (48·9–59·7)	51·5% (45·7–56·9)	0·90 (0·76–1·08)	..
Disease status						0·88
Metastatic	322/443	312/409	55·1% (50·3–59·6)	53·4% (48·4–58·1)	0·94 (0·81–1·10)	..
Locally advanced only	8/10	6/9	60·0% (25·3–82·7)	38·9% (9·3–68·7)	0·62 (0·17–2·27)	..
Tyrosine kinase inhibitor						0·068
Sunitinib	146/190	132/174	50·0% (42·6–57·0)	56·0% (48·2–63·0)	1·11 (0·87–1·40)	..
Pazopanib	184/263	186/244	58·9% (52·7–64·6)	51·0% (44·5–57·1)	0·82 (0·66–1·00)	..
Previous nephrectomy						0·47
Yes	229/338	229/319	61·3% (55·8–66·3)	60·6% (54·9–65·7)	0·99 (0·82–1·19)	..
No	101/115	89/99	37·3% (28·5–46·1)	29·3% (20·7–38·4)	0·87 (0·65–1·16)	..
Overall	**330/453**	**318/418**	**55·2% (50·5–59·7)**	**53·1% (48·2–57·8)**	**0·94 (0·81–1·10)**	..

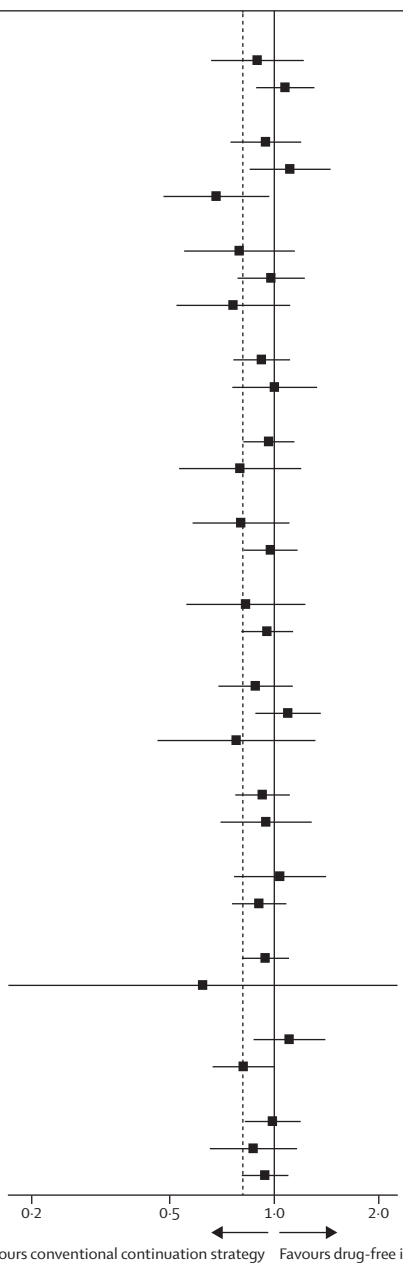

Figure 3: **Forest plot of overall survival by patient subgroups**

n=number of events. N=total number of participants in the group. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium. MSKCC=Memorial Sloan-Kettering Cancer Center. Within each subgroup, if the horizontal line crosses the dotted vertical line then there was insufficient evidence to conclude non-inferiority between the two groups at the 2·5% significance level in the level of the subgroup under consideration. The interaction contrasts are in the appendix (pp 29–30).

FKSI subscales, including the emotional wellbeing subscales (appendix pp 17–18, 21–28).

The within-trial economic evaluation found the drug-free interval strategy provided a small QALY benefit of 0·049 (95% CI –0·031 to 0·132) and annual cost savings of £3235 (95% CI 953 to 5517) when compared with the conventional continuation strategy. Over a lifetime horizon, in primary and most sensitivity analyses, the drug-free interval strategy was both cost saving (primary analysis mean £2420 [95% CI 180 to 4763) and yielded QALY gains (primary analysis mean 0·08 [95% CI –0·24 to 0·40]) compared with the conventional continuation strategy (data not shown). The probabilistic sensitivity analysis indicated that, at a willingness-to-pay threshold of £20 000 per QALY gained, the drug-free interval strategy had a 95% chance of being cost-effective. The value for money metric was principally driven by savings in medicine costs and no substantive difference in resource use costs was observed (data not shown).

In the safety population (n=916), the most common grade 3 or worse adverse events were hypertension (124 [26%] of 485 patients in the conventional continuation strategy group *vs* 127 [29%] of 431 patients in the drug-free interval strategy group); hepatotoxicity (55 [11%] *vs* 48 [11%]); and fatigue (39 [8%] *vs* 63 [15%]; appendix p 51). The overall stratification of adverse events is presented in table 2. The number of participants in the safety population who had at least one serious adverse reaction was lower in the drug-free interval strategy group than in the conventional continuation strategy group after beginning their randomisation allocation (21 [9%] of 223 *vs* 31 [12%] of 265; appendix p 50). Overall, 226 serious adverse reactions were reported and 192 (21%) of 920 participants had a serious adverse reaction (appendix p 49). Of the 226 serious adverse reactions, the most common were gastrointestinal disorders (36 [34%] of 107 patients in the conventional continuation strategy group *vs* 34 [16%] of 119 patients in the drug-free interval strategy group); infections and infestations (eight [8%] *vs* 15 [13%]); and respiratory, thoracic, and mediastinal disorders (nine [8%] *vs* 11 [9%]). 12 serious adverse reactions resulted in death (three patients in the conventional continuation strategy group; nine patients in the drug-free interval strategy group) and these were due to vascular (n=3), cardiac (n=3), hepatobiliary (n=3), gastrointestinal (n=1), or nervous system (n=1) disorders, and from infections and infestations (n=1).

Among patients who had a clinical response, had not progressed at 24 weeks, and had proceeded to their randomisation allocation, the depth of response was similar between the conventional continuation strategy and drug-free interval strategy groups (post-hoc analysis). Of 245 patients who responded to initial treatment in the conventional continuation strategy group, one (<1%) patient had a complete response, 63 (26%) had a partial response, and 181 (74%) had stable disease. Of 250 who responded to initial treatment in the drug-free interval strategy group, two (1%) patients had a complete response, 58 (23%) had a partial response, and 190 (76%) had stable disease.

Discussion

Although the primary endpoints of non-inferiority in both overall survival and QALY were not met in both the ITT and per-protocol populations, the results of this trial demonstrate that patients taking planned treatment breaks are unlikely to have a clinically meaningful reduction in overall survival (median overall survival of 27 months in the drug-free interval strategy group and 28 months in the conventional continuation strategy group). The study gives confidence that it is unlikely that patients are taking a major risk with overall survival by choosing a treatment break option. For patients for whom QOL might be their chosen priority, a strategy of planned treatment breaks might therefore provide a cost-effective alternative to continuous therapy with potential lifestyle benefits. Moreover, when there is a patient or health-care need to disrupt treatment (eg, the COVID-19 pandemic), the STAR trial provides reassurance that this is not likely to have a materially detrimental effect on patient outcomes. Although caution should be observed in translating conclusions between different health-care environments, the data are also encouraging from the global oncology perspective in which some resource settings might not be able to afford continuous treatment.

Overall, participants in the drug-free interval strategy group received a similar amount of treatment to those in the conventional continuation strategy group, although over a longer period of time. Time to strategy failure, summative progression-free interval, and time to treatment failure were significantly different between groups (favouring the drug-free interval strategy). However, these endpoints should be considered with caution, since although they are recommended for intermittent strategy trials,[16] they are lesser known than the more commonly used progression-free survival, which is less appropriate for intermittent trial design. It is important to note that in the conventional continuation strategy group, progression was assessed relative to associated with the baseline scans, whereas progression in the drug-free interval strategy group was assessed relative to the scan immediately before the treatment break was started.

The return rate of QOL questionnaires was high, as required for a QALY co-primary endpoint. The objective of the QALY analysis was to determine non-inferiority between the two groups, not a difference or superiority. Although the analysis was not a powered comparison, no meaningful difference was found between the FACT-G or FKSI overall scores. However, the patient preference study indicated that patients could readily identify examples of beneficial changes to their enjoyment of life that were the direct result of treatment breaks (Hewison J, unpublished).

	Sunitinib								Pazopanib							
	Conventional continuation strategy (n=203)				Drug-free interval strategy (n=181)				Conventional continuation strategy (n=282)				Drug-free interval strategy (n=250)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Hypertension	89 (44%)	45 (22%)	1 (<1%)	0	66 (36%)	42 (23%)	2 (1%)	0	119 (42%)	78 (28%)	0	0	109 (44%)	83 (33%)	0	0
Haemorrhage, bleeding, or coagulopathy	32 (16%)	3 (1%)	1 (<1%)	0	35 (19%)	8 (4%)	0	0	23 (8%)	7 (2%)	2 (1%)	1 (<1%)	34 (14%)	5 (2%)	1 (<1%)	1 (<1%)
Venus thrombosis	2 (1%)	0	0	0	1 (1%)	3 (2%)	0	0	8 (3%)	6 (2%)	0	0	7 (3%)	6 (2%)	0	0
Arterial thrombosis	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0	0	0	0	0	0	0	0	0	0
Neutropenia	53 (26%)	16 (8%)	2 (1%)	0	43 (24%)	5 (3%)	1 (<1%)	0	34 (12%)	1 (<1%)	0	0	21 (8%)	2 (1%)	1 (<1%)	0
Thrombocytopenia	51 (25%)	7 (3%)	1 (<1%)	0	44 (24%)	8 (4%)	2 (1%)	0	40 (14%)	0	1 (<1%)	0	45 (18%)	1 (<1%)	0	0
Fatigue	162 (80%)	17 (8%)	1 (<1%)	0	129 (71%)	34 (19%)	0	0	230 (82%)	21 (7%)	0	0	186 (74%)	28 (11%)	1 (<1%)	0
Anaemia	91 (45%)	14 (7%)	0	0	81 (45%)	13 (7%)	0	0	89 (32%)	10 (4%)	0	0	103 (41%)	8 (3%)	0	0
Hand-foot syndrome	99 (49%)	19 (9%)	0	0	71 (39%)	16 (9%)	0	0	75 (27%)	6 (2%)	0	0	64 (26%)	5 (2%)	0	0
Hepatotoxicity	35 (17%)	6 (3%)	0	0	39 (22%)	4 (2%)	1 (1%)	1 (1%)	81 (29%)	44 (16%)	4 (1%)	1 (<1%)	90 (36%)	39 (16%)	2 (1%)	1 (<1%)
Nausea or vomiting	123 (61%)	9 (4%)	0	0	96 (53%)	12 (7%)	0	1 (1%)	170 (60%)	4 (1%)	0	0	150 (60%)	13 (5%)	0	0
Pyrexia	19 (9%)	1 (<1%)	0	0	14 (8%)	2 (1%)	0	0	17 (6%)	1 (<1%)	0	0	27 (11%)	0	0	0
Dyspepsia or indigestion	97 (48%)	1 (<1%)	0	0	91 (50%)	0	0	0	68 (24%)	1 (<1%)	0	0	79 (32%)	0	0	0
Diarrhoea	121 (60%)	13 (6%)	0	0	97 (54%)	9 (5%)	0	1 (<1%)	171 (61%)	18 (6%)	0	0	148 (59%)	9 (4%)	1 (<1%)	0
Constipation	83 (41%)	0	0	0	60 (33%)	4 (2%)	0	0	77 (27%)	1 (<1%)	0	0	92 (37%)	1 (<1%)	0	0
Mucositis or stomatitis	133 (66%)	13 (6%)	0	0	101 (56%)	10 (6%)	0	0	125 (44%)	1 (<1%)	0	0	102 (41%)	7 (3%)	1 (<1%)	0
Thyroid dysfunction	62 (31%)	1 (<1%)	0	0	50 (28%)	0	0	0	66 (23%)	0	0	0	59 (24%)	0	0	0
Anorexia	121 (60%)	1 (<1%)	0	0	94 (52%)	8 (4%)	0	0	151 (54%)	4 (1%)	0	0	122 (49%)	9 (4%)	0	0
Altered taste	121 (60%)	0	0	0	112 (62%)	1 (1%)	0	0	146 (52%)	2 (1%)	0	0	135 (54%)	0	0	0
Change in hair and skin colour	70 (34%)	1 (<1%)	0	0	65 (36%)	1 (1%)	0	0	108 (38%)	0	0	0	92 (37%)	1 (<1%)	2 (1%)	0
Hypersensitivity	7 (3%)	0	0	0	5 (3%)	0	0	0	3 (1%)	0	0	0	10 (4%)	0	0	0
Dyspnoea	46 (23%)	9 (4%)	0	0	56 (31%)	5 (3%)	0	0	65 (23%)	9 (3%)	1 (<1%)	0	54 (22%)	10 (4%)	0	0
Reduced cardiac function	1 (<1%)	2 (1%)	0	0	1 (1%)	1 (1%)	0	0	4 (1%)	0	0	0	3 (1%)	1 (<1%)	1 (<1%)	0
Proteinuria or nephrotic syndrome	12 (6%)	0	0	0	6 (3%)	2 (1%)	0	0	16 (6%)	0	1 (<1%)	0	16 (6%)	3 (1%)	0	0

Table 2: **Maximum Common Terminology Criteria for Adverse Events (version 4.0) grade experienced by each participant in the safety population (n=916)**

Although 47% of patients had discontinued treatment before or at the 24-week timepoint when randomisation was initiated, this percentage was balanced between the groups. This proportion is higher than observed in the pivotal trials of these drugs, which is probably due to the pragmatic nature of our trial. Considering that taking more than one break was voluntary, the multiple number taken by many patients suggests that treatment breaks were acceptable (and desirable) to both patients and health-care professionals. The fact that only 3% of patients in the drug-free interval strategy withdrew from study in order to have continuous treatment demonstrates a high level of patient support for treatment breaks.

The safety profile for patients in the treatment break group was similar to that normally observed in continuous therapy of the respective tyrosine kinase inhibitors, but reflected the fact that patients in the drug-free interval strategy group were on study for an average median of 11 months, compared with 8 months in the conventional continuation strategy group and therefore at risk of disease-associated adverse events for longer. The number of serious adverse reactions (directly associated with treatment toxicity) was lower in the drug-free interval strategy group when participants were on trial strategy.

The STAR trial was a pragmatic study, representative of the real-world population and readily deliverable, including in smaller centres or units treating patients with a tyrosine kinase inhibitor. The trial also demonstrated the successful use of the seamless phase 2/3 design, with all patients contributing to the final phase 3 analysis.

However, the trial had several limitations. The large sample size required a long duration of recruitment, despite the relatively high number of clinical sites involved. A consequence was that, during the trial, the treatment landscape for advanced renal cell carcinoma changed substantially, to include multiple treatment options spanning three or more lines of therapy and clinically significant improvement in outcomes. This is evidenced by the 2-year survival estimate in the conventional continuation strategy group of 55·2% in the per-protocol population, a higher proportion than the 48·5% assumed. While good for patients, this meant a lower event rate (deaths) than predicted. Although follow-up was extended to include more events, funding restrictions hindered our ability to follow up participants for a longer period, resulting in lower power than originally expected. Additionally, the statistical methods applied within this analysis are those that are more commonly used instead of instrumental variable analysis[28] or G-Estimation.[29] The results therefore are subject to certain biases that more novel methods are not. These biases include selection bias in the per-protocol analysis and use of HRs and measurement bias for the analysis of the non-definite endpoints—eg, time to strategy failure and summative progression-free interval. The results are also subject to certain assumptions. The normality and homoscedasticity of residuals for the two-component finite mixture model was improved compared with that observed in the multivariate linear regression model. However, the assumption remained violated in the tails. Two of the secondary time-to-event endpoints did not meet the proportional hazards assumptions (progression-free survival and time to treatment failure). However, no conclusions were drawn from these endpoints, and the same outcome occurred for the subgroup analysis (ie, no conclusions drawn). Although MSKCC prognostic group risk factor showed statistically significant heterogeneity in the results, only a small number of trial participants were classified as having a poor prognostic group score, and therefore the results should be interpreted with caution.

Caution should be exercised in the design of a non-inferiority trial to ensure that the probability of a verdict of non-inferiority is not higher than 80%.[30] This includes the rationale for choosing non-inferiority primary endpoints and the non-inferiority margin. In our trial, the non-inferiority margins and conventional continuation strategy 2-year overall survival were set after discussions with UK and USA communities and the National Cancer Research Institute Renal Clinical Studies Group and to account for the data available on sunitinib compared with interferon-α (overall survival 54% *vs* 46% at 2 years).

For many patients with renal cell carcinoma, first-line therapy includes immunotherapy, alone or in combination with a tyrosine kinase inhibitor.[31] Nevertheless, tyrosine kinase inhibitor monotherapy remains an appropriate first-line therapy for a substantial proportion of patients who are not suitable for immunotherapy, and the STAR results apply directly to these patients. Other patients do not receive a tyrosine kinase inhibitor as first-line treatment, but might do so as monotherapy as second-line treatment. Although treatment breaks in these patients could reasonably be considered, caution should be exercised since these patients would typically have shorter progression-free survival than those receiving first-line tyrosine kinase inhibitors. In addition to the phase 3 STAR study, other approaches to reducing dosing intensity of treatments for advanced renal cell carcinoma are being explored involving not only tyrosine kinase inhibitors, but also immunotherapy and combination therapy. These include a small study of intermittent nivolumab monotherapy in metastatic renal cell carcinoma, which showed promising data (before the introduction of nivolumab–ipilimab combination therapy),[32] the ongoing phase 2 REFINE study (NCT04913025), which aims to assess whether giving the immunotherapy drug nivolumab less frequently results in fewer side-effects while continuing to be effective, a phase 2 study to reduce the starting dose of lenvatinib when used in combination with everolimus,[33] the phase 2 PRISM study, assessing

reduced frequency of ipilimumab dosing in combination with nivolumab,[34] and a meta-analysis of 1173 patients comparing the tolerability and efficacy of an alternative dosing schedule (2 weeks on and 1 week off) of sunitinib with the standard dosing schedule (4 weeks on and 2 weeks off), which showed improved tolerability and survival.[35] These developments exemplify a growing interest in further exploring the benefits of reduced dose studies in renal cell carcinoma.

Contributors

JEB, FC, PS, JBr, WG, CM, JH, TMW, PN, JL, TE, and RM contributed to conceptualisation and trial design. K-LR, JS, TMW, JEB, and WG contributed to data curation. Data analysis was led by K-LR, JBr, and WG, with contributions from JEB, AMart, VG, DM, CM, JBe, and TP. JEB, PS, WG, FC, JBr, JH, TMW, and CM led funding acquisition. JEB, FC, NV, TP, JH, TE, AH, JBe, AMara, TMW, GF, RM, JL, TW, CR, RJ, PP, OD, MW, RG, DM, PN, and CM contributed to the clinical investigation and data collection. JEB, FC, PS, VG, DM, JBr, CM, JH, TMW, WG, and K-LR contributed to methodology and JEB, FC, JBr, JS, and JH contributed to administration of the project. JEB, K-LR, FC, WG, PS, JBr, VG, TP, JH, TE, DM, AMara, TMW, GF, RM, JL, TW, AMart, NV, and PN made contributions to data interpretation, as did K-LR and TMW to software application. JH led the patient preference substudy. JEB, PS, JBr, FC, CR, RJ, JH, TMW, and WG supervised various aspects of the project. The original draft was written by JEB, K-LR, JBr, FC, PS, RG, DM, TP, JH, TE, and TMW, and all authors contributed to editing of the manuscript and approving the final draft. JEB, FC, and K-LR have directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

JEB reports having served as a consultant or adviser for Novartis, Ipsen, Amgen, Merck Sharp & Dohme, Bristol-Myers Squibb, and Bayer; honoraria from Novartis, Ipsen, Amgen, Merck Sharp & Dohme, Bristol-Myers Squibb, and Bayer; research funding paid to their institution from the National Institute for Health and Care Research; and travel expenses from Ipsen. WG reports consulting fees from Janssen and AbbVie. CR reports honoraria from Bristol-Myers Squibb and Wisai. TE reports trusteeship of Kidney Cancer UK and MacMillan Cancer Support. PN reports consulting fees from Novartis, Agensis, Ionctura, Bristol-Myers Squibb, 4SC, Pfizer, Merck Sharp & Dohme, and Merck; honoraria from Novartis and Immunocore; travel, accommodation, and expenses from Immunocore; membership of REFINE Data Safety Monitoring Board; and trusteeship of Melanoma Focus. TP reports consulting fees from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eisai, Exelixis, Incyte, Ipsen, Johnson & Johnson, Merck, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Seattle Genetics, and Mashup; honoraria from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eisai, Exelixis, Incyte, Ipsen, Johnson & Johnson, Merck, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Seattle Genetics; research funding paid to their institution from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eisai, Exelixis, Ipsen, Johnson & Johnson, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Seattle Genetics; and travel expenses from AstraZeneca, Ipsen, Merck Sharp & Dohme, Pfizer, and Roche. RJ reports consulting fees from Astellas Pharma, Bayer, Bristol-Myers Squibb, Ipsen, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche; honoraria from Astellas Pharma, Bayer, Bristol- Myers Squibb, Ipsen, Janssen, Merck Serono, Merck Sharp & Dohme, Pfizer, Roche; research funding paid to their institution from Astellas Pharma, Clovis, Exelixis, and Bayer; and participation in a data safety monitoring board for Roche. NV reports consultancy fees from Bristol-Myers Squibb, 4D Pharma, and Merck Serono; honoraria from Bristol-Myers Squibb, EUSA Pharma, Eisai, and Ipsen; and travel expenses from Ipsen. MW reports consultancy fees from Bristol-Myers Squibb and Sciensus; honoraria from Eisai and Ipsen; and travel expenses from Bristol-Myers Squibb. TW reports honoraria from Bristol-Myers Squibb, Pfizer, Eisai, and Ipsen; travel expenses from Bristol-Myers Squibb, EUSA Pharma, and Ipsen; and participation on data safety monitoring boards for Bristol-Myers Squibb, Pfizer, Eisai, Ipsen, and Merck Sharp & Dohme. RM reports travel expenses from Janssen. PP reports research funding paid to their institution from Pfizer. JL reports consultancy fees from iOnctura, Apple Tree, Merck, Bristol-Myers Squibb, Eisai, Debipharm, and Incyte; honoraria from Eisai, Novartis, Incyte, Merck, TouchIME, TouchEXPERTS, Pfizer, Royal College of Physicians, Cambridge Healthcare, Royal College of General Practioners, VJ Oncology, and Agence Unik; research funding paid to their institution from Achilles, Bristol-Myers Squibb, Merck Sharp & Dohme, Nektar, Novartis, Pfizer, Immunocore, Roche, Aveo, and Pharmacyclics; and travel expenses from Pierre Fabre, Roche, and GlaxoSmithKline. GF reports consultancy fees from Bristol-Myers Squibb and Pfizer; honoraria from Bristol-Myers Squibb, Merck, and Pfizer; and travel expenses from Novartis and Bayer. DM reports funding from Otsuka and AbbVie to their institution; being a sub-panel member for the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research; and being a member of a National Institute for Health and Care Excellence Technology Appraisal Committee. VG reports funding from Siemens Healthineers to their institution. TMW reports research funding paid to their institution from Boston Scientific and Angidynamics. JBr reports being Chair of the NIHR Health Technology Assessment General Funding Committee and NIHR Health Technology Assessment funding paid to their institution. JH reports funding to their institution from the NIHR Health Technology Assessment. PS reports funding from an NIHR Senior Fellowship, European Research Council Advanced Awards; travel expenses from the European School of Oncology Training; and several patents on the development of DNA library cancer vaccines. FC reports honoraria from Bayer. All other authors declare no competing interests.

Data sharing

Data supporting this work are available on reasonable request. All requests will be reviewed by relevant stakeholders, based on the principles of a controlled access approach. Requests to access data should be made to CTRU-DataAccess@leeds.ac.uk.

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