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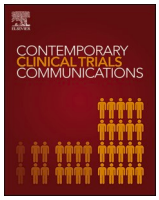

NeoAdjuvant pembrolizumab and STEreotactic radiotherapy prior to nephrectomy for renal cell carcinoma (NAPSTER): A phase II randomised clinical trial

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ABSTRACT

Background: Surgery remains the standard of care for localised renal cell carcinoma (RCC). Nevertheless, nearly 50% of patients with high-risk disease experience relapse after surgery, with distant sites being common. Considering improved outcomes in terms of disease-free survival with adjuvant immunotherapy with pembrolizumab, we hypothesise that neoadjuvant SABR with or without the addition of pembrolizumab before nephrectomy will lead to improved disease outcomes by evoking better immune response in the presence of an extensive reserve of tumor-associated antigens.

Methods and analysis: This prospective, open-label, phase II, randomised, non-comparative, clinical trial will investigate the use of neoadjuvant stereotactic ablative body radiotherapy (SABR) with or without pembrolizumab prior to nephrectomy. The trial will be conducted at two centres in Australia that are well established for delivering SABR to primary RCC patients. Twenty-six patients with biopsy-proven clear cell RCC will be recruited over two years. Patients will be randomised to either SABR or SABR/pembrolizumab. Patients in both arms will undergo surgery at 9 weeks after completion of experimental treatment. The primary objectives are to describe major pathological response and changes in tumour-responsive T-cells from baseline pre-treatment biopsy in each arm. Patients will be followed for sixty days post-surgery.

Outcomes and significance: We hypothesize that SABR alone or SABR plus pembrolizumab will induce significant tumor-specific immune response and major pathological response. In that case, either one or both arms could

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justifiably be used as a neoadjuvant treatment approach in future randomized trials in the high-risk patient population.

1. Background

Surgery is the standard for non-metastatic clear-cell renal cell carcinoma (ccRCC) [1,2]. However, relapse of a disease following surgery is common [3]. Zisman et al. categorised localised ccRCC into low, intermediate, and high risk based on T stage, ECOG performance status, and Fuhrman's grade [4]. High-risk disease was associated with loco-regional relapse of 15% at five years. Consistent with this, in the ASSURE randomised phase III trial investigating the role of adjuvant tyrosine kinase inhibitor (TKI) therapy, Lee et al. reported a significant loco-regional relapse of 15.4% [5]. Similarly, higher-risk aggressive localised ccRCC is reflected by up to 50% of systemic recurrence rates after surgery [6].

1.1. Adjuvant treatment for renal cell carcinoma

1.1.1. Adjuvant radiotherapy

There have been randomised trials in the 1970s and 80s to assess the role of adjuvant radiotherapy in reducing local relapse [7]. In a meta-analysis of 7 randomised control trials involving postoperative radiotherapy (PORT) for high-risk RCC, Tunio et al. concluded that PORT significantly reduces loco-regional failure but has no effect on overall survival (OS) and disease-free survival (DFS) [7]. However, due to small sample size and older radiotherapy techniques, there is a need for future studies with latest radiotherapy techniques (conformal and intensity-modulated radiotherapy techniques), to evaluate PORT in RCC patients. Currently, PORT is not endorsed by international guidelines [1,2].

1.1.2. Adjuvant targeted treatment

Multiple phase-III randomised trials have investigated the role of adjuvant tyrosine kinase inhibitors (TKIs) with mixed results [8–12]. The ASSURE trial was the largest study to investigate adjuvant VEGF targeted therapy in RCC [10]. A total of 1943 patients with RCC were randomised to sunitinib 50 mg daily, sorafinib 800 mg daily, or placebo for one year after nephrectomy. There was no significant difference in median DFS and OS between the three arms. In total, 44% of patients treated with sunitinib and 45% of sorafenib, discontinued treatment due to treatment related toxicity.

Contrary to the ASSURE trial, there was a statistically significant increase in DFS in patients with high risk ccRCC, treated with sunitinib than those with placebo (6.8 vs. 5.6 years, $p = 0.03$) in the S-TRAC trial [11]. However, there was no difference in OS (HR 1.01). the toxicity was like the ASSURE trial. Based on the S-TRAC trial results, the FDA approved sunitinib for patients at high risk for recurrence after nephrectomy. The European Association of Urology (EAU) do not approve sunitinib as adjuvant therapy due to lack of improved DFS in a meta-analysis of the ASSURE and S-TRAC [13].

1.1.3. Adjuvant immunotherapy

RCC is a highly immunogenic tumor due to presence of tumor-infiltrating lymphocytes [14]. Encouraging results were seen when patients with advanced/metastatic ccRCC were treated with immune checkpoint inhibitors (ICI) alone or in combination, and with TKIs [15–20]. These results have resulted in clinical trials to assess the efficacy of adjuvant ICI in ccRCC patients at high risk for relapse post-surgery (NCT03024996, NCT03138512, NCT03055013, and NCT03288532).

In a multicentre trial (KEYNOTE-564), 994 patients with intermediate-high or high risk of recurrence of RCC were randomized to pembrolizumab 200 mg intravenously every three weeks or placebo for up to 1 year [21]. In the interim analysis, adjuvant pembrolizumab was associated with longer 2-year DFS (77.3%) than placebo (68.1%). The data was not mature for OS, with 5% deaths in the study cohort. As expected, Grade 3 or higher adverse events of any cause were higher in pembrolizumab arm than placebo (32.4% vs. 17.7%). 20.7% of the patients in the pembrolizumab group discontinued treatment because of AEs.

Based on these results, FDA approved pembrolizumab for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following surgery [22]. Similarly, EMA has recommended the approval of single-agent pembrolizumab as an adjuvant treatment in RCC patients [23].

1.2. Rationale for current study

1.2.1. Safety and efficacy of neoadjuvant immunotherapy

It is hypothesised that immunomodulation in the neoadjuvant setting before nephrectomy may evoke a better immune response against tumor, due to the presentation of a new repertoire of tumor-associated antigens prior to the removal of the antigen depot. This principle is evident in other tumour streams. The phase-II (I-SPY 2) study demonstrated increased pathological complete response (pCR) rates from 20% to 60% with the addition of neoadjuvant pembrolizumab compared to standard chemotherapy alone in patients with triple-negative non-metastatic breast cancer [24]. Similarly, a recent Phase-III, randomised trial (Checkmate-816) reported an increased pCR rate with neoadjuvant nivolumab and chemotherapy compared to chemotherapy alone (24% vs 2.2%) without any impact on the ability to perform surgery [25].

Early studies have reported the safety of neoadjuvant immunotherapy in RCC patients without any significant delays or complications with surgery. In one pilot study, Carlo et al. treated 18 RCC patients with four doses of two weekly nivolumab prior to nephrectomy. There were no delays in planned surgery, with four patients experiencing surgical complications per Clavien-Dindo classification [26]. Similarly, in another single-arm, Phase-I, clinical trial, Patel et al. treated 17 non-metastatic RCC patients with three cycles of nivolumab followed by surgery within seven days of completion of 3rd cycle. Grade-3 and 4–5 AEs were 11.8% and 0%, respectively. There were no delays in surgery, and no postoperative complications of Clavien-Dindo grade 3 or higher were observed [27]. Multiple other studies are ongoing to assess the efficacy of neoadjuvant immunotherapy in RCC (NCT04118855, NCT02762006, NCT03341845, NCT03680521, and NCT04393350).

1.2.2. Safety and immunomodulatory effects of SABR prior to nephrectomy

Over the last decade, multiple prospective and retrospective studies have reported the safety and efficacy of stereotactic ablative body radiotherapy (SABR) for localised RCC [28]. In 2019, Correa et al. reported a systematic review and meta-analysis of 26 studies involving 372 patients with 383 primary tumors [28]. The local control and grade 3–4 toxicity were 97.2% and 1.5%, respectively. There is evidence that RT produces a spectrum of cellular and molecular alterations resulting in the activation and potentiation of the systemic immune response [29].

Singh et al. reported the safety of neoadjuvant SABR followed by nephrectomy in metastatic RCC [30]. Overall, the results showed that SABR followed by nephrectomy was safe. In that pilot study of 16 patients, only one patient experienced a grade 3 treatment-related adverse event, which occurred in a patient with a pre-existing history of anaemia who received a transfusion following SABR. Out of 16, three patients had partial nephrectomies and 11 had total nephrectomies. Blood loss averaged 100 cc. There was no change in the planned type of nephrectomy following SABR. No post-surgical complications were reported in

the 14 patients who underwent surgery. The qualitative clinical assessment of the surgeons did not report any difficulty in performing surgery. SABR treatment was associated with significant immunomodulation with increased expression of calreticulin and tumor-associated antigens (CA9, 5T4, NY-ESO-1, and MUC-1). Proliferating Ki67+CD8$^+$ T cells and FOXP3+ T cells were increased in SABR-treated patient specimens in tumors and at the tumor-stromal interface compared with archived patient specimens.

Furthermore, neoadjuvant SABR increased intratumoral T-cell clonality and expansion of tumour-enriched T-cell clonotypes in the blood [29]. Chow et al. analysed samples for patients treated with 15 Gy SABR to primary RCC followed four weeks later by nephrectomy [29]. The authors found broad transcriptional immune activation and increased expansion of T cell clones within the tumor microenvironment. Analysis of peripheral blood samples revealed a dynamic reshaping of the peripheral T cell repertoire within the first two weeks following radiation.

1.2.3. Synergistic effects of immunotherapy and SABR

Multiple pre-clinical studies using a combination of radiotherapy (RT) and immunotherapy have reported durable antitumour immune responses. Pre-clinical studies have reported enhanced therapeutic effects with *anti*-PD-1 or PD-L1 agents and RT [31,32]. Furthermore, combination of *anti*-PD-1 therapy and RT in melanoma and breast cancer models have resulted in increased endogenous T-cell infiltration of established tumors, this was associated with improved tumour control [33].

Good clinical evidence supports the synergistic effects and safety of RT with immunotherapy in metastatic RCC [34–37]. Combining SABR with a checkpoint inhibitor in neoadjuvant settings may produce a more robust immune response, reducing relapse rates. Another rationale for adding SABR prior to nephrectomy, beyond any putative systemic effects, is to sterilise the tumour and prevent locoregional relapse.

2. Methods/design

2.1. The trial oversight and funding

The study is designed by the authors, which is funded by the Merck-Sharp-Dohme (MSD) investigator-initiated study program. Pembrolizumab will be supplied by Merck MSD. The study is approved by the PMCC human research ethics committee. All patients are required to provide written informed consent. The safety monitoring committee will meet after the first 5, 10, 15 patients are recruited to evaluate participant safety during the trial accrual period.

2.2. Study objectives and hypothesis

The central hypothesis of this study is that neoadjuvant SABR ±pembrolizumab will induce both immunogenic cell death and expansion of tumor-specific T-cell clones, which will traffic to the tumour site and reduce tumour size. This clinical response will be associated with increased CD8$^+$ Resident memory T cells (TRM) and CD8$^+$ transcription factor T cell factor-1 (TCF-1+) stem cell-like T-cells in the tumour.

2.2.1. Primary objectives

- To assess major pathological response (MPR), defined as <10% viable cancer cells post-SABR with or without pembrolizumab
- To describe changes in tumour-responsive T-cells, TRM CD8$^+$ T-cells and/or TCF-1+ T-cells from baseline pre-treatment biopsy to post-nephrectomy in patients treated with SABR with or without pembrolizumab followed by nephrectomy

2.2.2. Secondary objectives

- To describe change in immune response from baseline to post-nephrectomy
- To investigate the percentage of tumour responsive T-cells (inclusive CD4/CD8) after neo-adjuvant treatment
- To assess safety of SABR with or without pembrolizumab in the neo-adjuvant setting
- To assess whether change in immune response is associated with MPR
- To assess change in PD-L1 and PD-L2 expression in tumour

2.2.3. Exploratory objectives

- To evaluate radiological features consistent with MPR
- To investigate baseline versus post-nephrectomy tissue for immune context changes, using a broad panel of assays which will be further developed through the lifetime of the study
- To investigate baseline versus post-nephrectomy tissue for immune network signalling, using a broad panel of assays which will be further developed through the lifetime of the study
- To investigate changes in systemic immunity of patients with primary ccRCC treated with SABR with or without pembrolizumab
- To investigate changes in tissue expression of immune checkpoints, inclusive of PD-L1, PD-L2, CTLA-4, and CD28
- To investigate changes in multi-parametric magnetic resonance imaging (mpMRI) and assess association with pathological outcomes
- To describe post-surgical outcomes, inclusive of margin status, complications, blood loss and admission duration

2.3. Trial design and participants

This is a prospective, open-label; phase II, non-comparative randomised clinical trial assessing the major pathological response and changes in tumour-responsive T-cells in patients treated with neo-adjuvant SABR with or without pembrolizumab prior to nephrectomy. The trial will recruit 26 patients over two years, with a patient follow-up of 60 days post-surgery. The trial will be conducted at two centres in Australia that are well established for delivering SABR to primary RCC patients. Study patients will be randomised to either.

Arm 1: SABR followed by nephrectomy 9–12 weeks after SABR
Arm 2: Pembrolizumab x3 cycles of 21 days with SABR performed during cycle one followed by nephrectomy 9–12 weeks after first dose of Pembrolizumab.

A nephron-sparing (partial) or total nephrectomy will be performed 9–12 weeks from commencement of treatment for both arms with choice of approach at discretion of surgeon. The trial schema is demonstrated in Fig. 1.

2.3.1. Key inclusion criteria

- Patient has provided written informed consent
- Male or female aged 18 years or older at written informed consent
- Histologically or cytologically confirmed diagnosis of RCC with clear cell, rhabdoid or sarcomatoid components
- Tumour stage T1B-T3, N0 or N1, M0 or low volume M1 planned for nephrectomy
- Patients must have adequate bone marrow, hepatic and renal function documented within two weeks prior to randomisation
- ECOG performance status of 0–1
- Patient agrees to the collection and use of their fresh tumour samples and peripheral blood for translational research

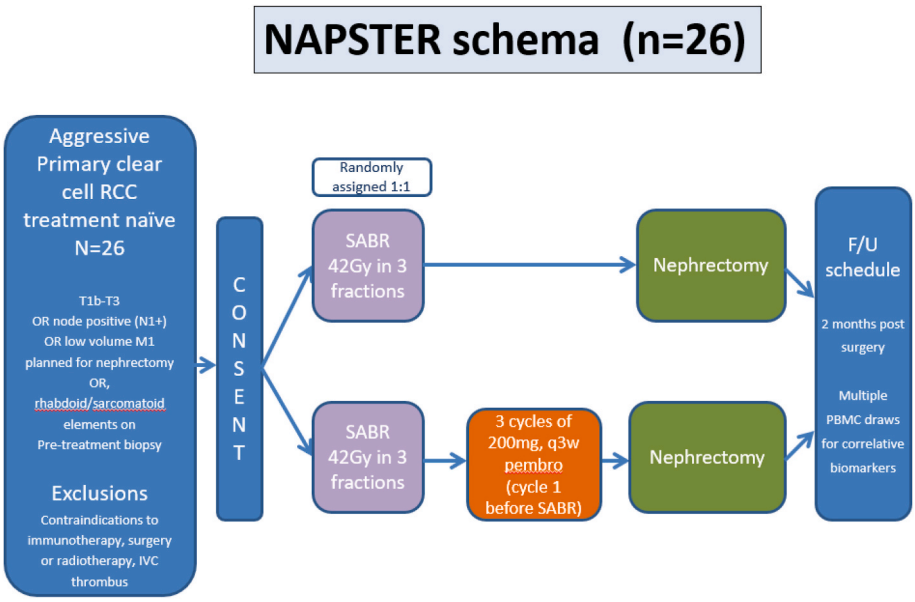

Fig. 1. Trial schema.

- Patient is willing and able to comply with the protocol for the duration of the study, including undergoing biopsies, treatment, and scheduled visits and examination
- Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test within 72 h prior to randomisation. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

2.3.2. *Key exclusion criteria*

- Prior treatment with an *anti*-PD-1, *anti*-PD-L1, or PD-L2 agent or an antibody targeting other immune-regulatory receptors or mechanisms.
- Known or active inflammatory bowel disease involving the colon and small bowels
- Previous radiotherapy to the upper abdomen with radiation dose overlap with the involved kidney
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy exceeding 10 mg daily dose of prednisone or equivalent or any other form of immunosuppressive therapy within seven days prior to randomisation
- Has an active autoimmune disease that has required systemic treatment in the last two years (using disease-modifying agents, corticosteroids, or immunosuppressive drugs).
- Has a known additional malignancy that is progressing or has required active treatment in the last 3 years
- Has known active CNS metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging and without the requirement of steroid treatment for at least 14 days prior to randomisation
- Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease
- Has a known history of HIV infection
- Has known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C (defined as HCV RNA [qualitative] is detected) infection
- Has received a live virus vaccine or live-attenuated vaccine within 30 days prior to randomisation. Administration of killed vaccines is allowed
- Has had a prior solid organ transplant

2.3.3. *Registration and randomisation*

Research Electronic Data Capture (REDCap) application will be used to develop the online NAPSTER Study electronic data capture (eDC) system. Each patient enrolled in the study will be assigned a unique identifier. Eligible patients will be randomised in a 1:1 ratio to receive either.

Arm 1: SABR plus nephrectomy
Arm 2: Pembrolizumab followed by SABR after cycle one plus nephrectomy

Any person will not know the subsequent treatment to be assigned prior to the patient's randomisation through the NAPSTER eDC. This is an open-label trial; therefore, the Sponsor, Investigator, and patient will know the treatment administered.

2.4. *Trial treatment*

2.4.1. *SABR*

All patients will receive SABR as a neo-adjuvant treatment for their primary RCC. In Arm 1 patients, SABR will begin within 28 days after randomisation. In Arm 2, Patients will receive the first fraction of SABR within seven days (±2 days) of the first cycle of pembrolizumab.

2.4.1.1. Treatment prescription. SABR will be prescribed at a dose of 42 Gy in three fractions. All patients will complete SABR within 2–3 weeks. SABR will be prescribed to the covering isodose, ensuring that 95% of the planning Target Volume (PTV) is covered by 100% of the dose (D95PTV = 100%). In the circumstance where doses to organs at risk (OAR) cannot be respected while achieving this level of coverage, an alternative prescription coverage of D90 = 100% is acceptable.

2.4.1.2. Target volumes. Target volumes will be defined as per The International Commission on Radiation Units (ICRU) report 91 [38]. These include.

- Gross Tumor Volume (GTV) - Gross demonstrable extent of tumor on available planning CT and diagnostics imaging.
- Internal Target Volume (ITV) - Generated to encompass GTV motion on the 4DCT scan if not treated with respiratory tracking or gating techniques
- Planning Target Volume (PTV) - ITV to PTV margins must consider set-up uncertainties. A 3–10 mm isotropic expansion from ITV to PTV is recommended based on centre-specific confidence in motion management.
- Planning Organ at Risk Volume (PRV) - Any movements of the Organs at Risk (OARs) during treatment and uncertainties in the set-up during the whole treatment course should be addressed by adding a right margin to the respective OAR. This margin can be 2–3 mm for hollow organ viscus.

2.4.1.3. Organs at risk and dose constraints. The organ at risk must be delineated as outlined in Table 1. Unless stated otherwise, the dose constraints listed in Table 2 apply to clinically significant volumes [39].

Table 1
Organs at risk (OAR) definitions and standardised names.

OAR	Standardised name	Contouring Guideline
Liver	Liver	Delineated on the average image set
Spinal cord	SpCord	As represented by bony spinal canal
Contralateral kidney	Kidney_C	As seen on the average image set excluding any cysts
Ipsilateral kidney	Kidney_I	As seen on the average image set excluding cysts and ITV
Small Bowel	SmallBowel	In one contour, the small bowel encompasses the duodenum, jejunum, and ileum. When considering small bowel, individual loops should be contoured. The small bowel should be contoured 5 cm above and below the PTV. A PRV margin of 2–3 mm should be used, and doses constrained to this PRV structure.
Large Bowel	LargeBowel	In one contour, the large bowel encompasses the caecum, ascending colon, transverse colon, descending colon, and sigmoid colon. Individual loops should be contoured. The large bowel should be contoured 5 cm above and below the PTV. A PRV margin of 2–3 mm should be used, and doses constrained to this PRV structure.
Stomach	Stomach	As a solid structure from gastro-oesophageal junction to Duodenum. A PRV margin of 2–3 mm should be used and doses constrained to this PRV structure.
Skin	Skin	To reduce radiation fibrosis, the subcutis, or the volume between the external contour and a contour 5 mm deep to this will be labelled 'skin'. This contour must be created on the entire circumference of the patient at the level of the PTV, and should be extended 5 cm above and below all levels of the PTV in the cranio-caudal plane to encompass entry point of non-coplanar beams
Small Bowel PRV	SmallBowel_PRV03 or SmallBowel_PRV02	Small bowel with 2–3 mm isotropic expansion. Dose constraints for the small bowel apply to this organ
Large Bowel PRV	LargeBowel_PRV03 or LargeBowel_PRV02	Large bowel with 2–3 mm isotropic expansion. Dose constraints for the large bowel apply to this organ
Stomach PRV	Stomach_PRV03 or Stomach_PRV02	Stomach with 2–3 mm isotropic expansion. Dose constraints for the large bowel apply to this organ

Table 2
Normal tissue dose constraints (Gy); based on University of Wuerzberg constraints, Cleveland University constraints, and QUANTEC recommendations [39].

Organ	Parameter	Dose
Spinal canal	D0.03 cc	18 Gy
Skin	D1.5 cc	30Gy
Small Bowel PRV	D0.03 cc	30Gy
	D30 cc	12.5Gy
	Maximum dose covering full circumference of bowel wall	22.5Gy
Large Bowel PRV	D0.03 cc	42Gy
	D3cc	30Gy
Stomach PRV	D0.03 cc	30 Gy
	D5cc	22.5Gy
Liver	Mean dose, Maximum Volume	At least 700 cc of normal liver to receive <15Gy
Ipsilateral kidney minus ITV	D1.5 cc	ALARA:
	^{V10}Gy	Minimise volume of high dose regions (>50% isodose)
Contralateral Kidney	^{V10}Gy	≤33%

In this protocol, a maximum dose is recorded as the maximum dose received to 0.03 cc of any volume (OAR/Normal Tissue), as stated in Table 2.

2.4.1.4. Treatment technique, delivery, and verification. Treatment must be delivered using 3D conformal, fixed gantry intensity-modulated radiotherapy (IMRT) or arc-based treatment such as dynamic conformal arc therapy (DCAT) or volumetric modulated arc therapy (VMAT). All patients must undergo daily online image verification. Verification imaging must be capable of visualising the target with soft tissue matching and bone alignment. It would necessitate imaging with a Cone Beam CT (CBCT) or superior pre-treatment imaging modality.

2.4.2. Pembrolizumab

In arm 2, pembrolizumab 200 mg (flat dose) will be administered as 30-min IV infusion every 21 days for three cycles. The cycle 1 will be administered before SABR.

2.4.3. Surgery

All Patients will undergo surgery within 9–12 weeks after the first treatment dose. Surgery can be either radical or partial nephrectomy based on the operating surgeon's decision. There are no procedural recommendations in the protocol. The operative surgeon will decide on open or minimally invasive procedure.

2.5. Study assessments

All enrolled patients will undergo pre-screening, screening, treatment, and follow-up assessments. An assessment schedule for arms 1 and 2 is provided in Tables 3 and 4, respectively.

As a part of translational endpoints, renal tumor tissue and peripheral blood for biomarker studies will be collected. Furthermore, Multiparametric magnetic resonance imaging (mpMRI) will be acquired during screening and following neoadjuvant therapy before nephrectomy. Translational research sample collection and imaging schema are summarised in Fig. 2.

2.6. Reporting and detection of adverse events

All AEs, regardless of seriousness, severity, or causality, must be recorded in the patients' medical records and recorded on the relevant eCRF from the start of protocol treatment until the 60-day post-nephrectomy assessment. AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a

Table 3
Arm 1 - SABR followed by nephrectomy schedule of assessments.

Trial Phase	Pre-Screening/Screening Phase		Treatment Phase		Surgery Phase		
Assessments/ Windows	**Pre-Screening**	**Screening** Within 28 days prior to randomisation	**SABR** Within 3 days prior to first fraction of SABR	**Post-SABR** 2 weeks after the end of SABR ± 3 days	**Pre-Nephrectomy** Within 2 weeks prior to nephrectomy	**Nephrectomy** (To be performed 9–12 weeks after first dose of SABR)	**60 days post-Nephrectomy Follow-up** ± 10 days
Clinical Assessments							
Informed Consent	X	X					
Diagnostic biopsy [a]	X						
Review of eligibility criteria		X					
Demographics		X					
Medical history		X					
Current cancer status		X					
Physical examination [b]		X			X		X
Vital signs, including height and weight [c]		X	X		X		X
Baseline symptoms/ abnormalities		X					
ECOG performance status		X		X	X		X
Review concomitant medications		X	X	X	X		
Review of adverse events [d]				X	X		X
Review of surgical complications [e]							X
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory							
Haematology [f]		X			X		
Biochemistry [g]		X			X		
Coagulation Studies [h]		X			X		
Thyroid function tests [i]		X			X		
Viral serology [j]		X					
Pregnancy testing [k]		X			X		
Disease Evaluation							
CT scan (or MRI) chest/abdomen/ pelvis [l]		X			X		
Whole body bone scan		X					
mpMRI scan [m]		X			X		
Intervention							
SABR			X				
Nephrectomy						X	
Translational Research Sample Collection							
Fresh tumour tissue [n]	X					X	
Peripheral blood [o]		X	X	X	X	X	X

* 1 cycle = 21 days. In exceptional circumstances, such as public holidays, the scheduled day of pembrolizumab treatment may be ±2 days.
** The first fraction of SABR to be given 7 days ±2 days after pembrolizumab cycle 1 day 1.

[a] Diagnostic biopsy: To be collected with coaxial biopsy approach, and sufficient tissue to satisfy translational specimen collection (please refer to Radiology Manual). Ideally, the diagnostic biopsy should be undertaken within 28 days prior to randomisation to the study.

[b] Physical examination: At screening a full physical examination is required. At all subsequent time points a directed physical examination should be performed as clinically indicated.

[c] Vital signs, including height and weight: Respiratory rate, heart rate, blood pressure, O_2 saturation (by pulse oximeter), and temperature. Height only required at screening.

[d] Review of adverse events: Adverse events (AE) according to CTCAE v5.0.

[e] Review of surgical complications: surgical complications according to Clavien-Dindo severity grading.

[f] Haematology: White blood cell count (WBC), neutrophils/ANC, lymphocytes, monocytes, eosinophils, basophils, red blood cell count (RBC), platelets, haemoglobin, and haematocrit. At screening to be performed within 14 days prior to randomisation.

[g] Biochemistry: Random glucose, sodium, potassium, chloride, phosphorous, magnesium, urea, corrected calcium, creatinine, bicarbonate, albumin, uric acid, alkaline phosphatase (ALP), (ALT), (AST), gamma-glutamyl transferase (GGT), total bilirubin, total protein, lactate dehydrogenase (LDH). At screening to be performed within 14 days prior to randomisation.

[h] Coagulation tests: PT, INR and aPTT to be performed within 14 days prior to randomisation.

[i] Thyroid function tests: free T3, free T4 and TSH. At screening to be performed within 14 days prior to randomisation.

[j] Viral serology: HBV, HBC and HIV serology during screening: HbSAg, HBcAb and *anti*-HCV. HBV DNA if HbcAb positive; HCV PCR if *anti*-HCV positive.

[k] Pregnancy testing: Urine or serum β-HCG testing for WOCBP.). At screening to be performed within 72 h prior to randomisation.

[l] CT scan (or MRI): To be completed at screening and within 2 weeks prior to nephrectomy. Volumetric assessment of lesions will be undertaken at both time points. *Note*: Both oral and IV contrast is required.

[m] mpMRI scan: To be completed at screening and within 2 weeks prior to nephrectomy. Please refer to Radiology Manual for further information.

[n] Fresh tumour tissue for translational research: To be collected at pre-screening and at the time of nephrectomy. Please refer to the NAPSTER Laboratory Manual for further information.

[o] Peripheral blood for translational research: To be collected for all patients in screening, on the day of the 3rd SABR fraction ±3 days, the post-SABR visit, at the time of nephrectomy and at the 60-day post-nephrectomy visit. For patients in Arm 2, addition blood collection is required within 3 days prior to day 1 pembrolizumab in cycle 2 (post-SABR) and day 21 ± 3 days of cycle 3 pembrolizumab.

patient.

3. Statistical considerations

3.1. Sample size and expected duration

The sample size of 26 patients (13 per arm) was pragmatically chosen to allow for sufficiently precise estimates of the response rate in all 26 patients (both cohorts combined), defined as half-width of the 95% confidence interval (CI) of 20% or less. We consider those confidence intervals acceptable for this early phase study and informative for designing the subsequent study.

Also, this study will have >80% power in each arm to show an absolute increase of at least 25% in TRM after neoadjuvant treatment, assuming an alpha of 0.05 using a 2-sided *t*-test, not adjusting for multiplicity and assuming a standard deviation (SD) of 28% for the change in TRM from baseline to surgery. The assumption for the standard deviation was based on data from Savas et al. at our own institution in patients with advanced breast cancer [40].

3.2. Statistical methods

A line plot will be provided for each arm, with each line representing a patient showing TRM at baseline and post-nephrectomy. It will be performed for each TRM. TRMs at baseline and post-nephrectomy will be compared using paired *t*-test. Estimates at each time point and estimates for the change in TRMs will be provided with 95% CIs. The same method will be applied for immune response, PD-L1, and PD-L2. The MPR will be the percentage with exact 95% CIs (Clopper-Pearson), overall and per treatment arm. Box-plots will be provided for immune response by MPR and compared using an independent samples *t*-test.

The maximum toxicity grade per participant of each AEs will be derived and presented in table format according to the treatment Arm. A description of surgical outcomes, including pathological margin status, surgical complications, blood loss, and admission duration, will be provided.

4. Data collection, record retention and ethics

All data will be stored in a re-identifiable form on Research Electronic Data. Data will be kept for 5 years after the publication of study results. Patient confidentiality will be always maintained. This study was approved by the Peter MacCallum Human Research Ethics Committee (HREC/73073/PMCC)

5. Discussion

Adjuvant sunitinib and pembrolizumab are FDA-approved drugs available to consider in patients at high risk of relapse [41]. However, 20–30% of patients discontinue treatment due to treatment-related toxicity in clinical trials [11,21]. This high incidence of discontinuation in trial settings can be higher in routine clinical practice. One way to improve compliance can be to incorporate neoadjuvant treatment. We hypothesise that neoadjuvant SABR alone or in combination with pembrolizumab can be safely delivered in the settings of localised RCC and will result in reduced loco-regional relapse owing to better surgical resection as well as immunomodulation. This radiation-induced immunomodulation may hypothetically improve systemic immunosurveillance and thereby reduce the risk of distant relapse.

While designing/developing the trial concept, there was discussion among the group on whether to do a single arm trial with SABR + pembrolizumab or to have an arm with SABR or Pembrolizumab alone. Neoadjuvant SABR has resulted in a complete pathological response of 60% with acceptable toxicity in patients with early-stage non-small cell lung cancer [42]. Moreover, SABR is considered the optimal definitive treatment for primary RCC in patients who are not an optimal candidate for surgery and resulted in a local control rate of above 90% with minimal toxicity [28]. Although there is data to support neoadjuvant pembrolizumab in combination with chemotherapy for patients with breast and lung cancer [24,25,43], we lack data to use single-agent pembrolizumab as a neoadjuvant or definitive treatment for any localised cancer. Thus, we opted to have one arm with SABR + pembrolizumab and one with SABR alone to explore whether any (or both) of the arms are worth assessing on a larger trial.

The decision to use 42 Gy in three fractions of SABR is based on our group's published body of evidence, which supports the use of this regimen. It is accepted as a consensus approach for kidney SABR [44–46]. In a recently published report from the International Radiosurgery Oncology Consortium for Kidney (IROCK), there was no grade 3 or 4 toxicity in patients with >4 cm Primary RCC treated with three fractions SABR [46]. In a phase-I prospective trial where patients with T1b or greater RCC received 42 Gy in three fractions SABR, our group reported 3% and 0% grade 3 or 4/5 toxicity, respectively [44].

Since the early results from the Keynote-564 trial, adjuvant pembrolizumab has been approved as a treatment option for high-risk RCC post-surgery [21]. Whether it will be safe or appropriate to consider adjuvant pembrolizumab in patients undergoing nephrectomy following NAPSTER experimental treatment can be questioned. Theoretically and radiobiological, immune modulation with neoadjuvant treatment will be advantageous prior to nephrectomy, followed by the adjuvant immune blockade to enhance ongoing immune effects. At least one ongoing PROSPER RCC (NCT03055013) evaluates this approach [47]. It is a Phase-III, randomized trial evaluating the impact of perioperative nivolumab for patients undergoing radical or partial nephrectomy for high-risk RCC.

In case of encouraging results with the NAPSTER protocol, it will be interesting to combine this regimen with adjuvant immune blockade with either pembrolizumab or nivolumab in a large, phase-III, randomised trial for patients with high-risk RCC.

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Author declaration

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Table 4
Arm 2 – Pembrolizumab Followed by SABR Post-Cycle 1 and then Nephrectomy Schedule of Assessments.

Trial Phase:	Pre-Screening/Screening Phase		Treatment Phase				Surgery Phase		
Assessments/ Windows	**Pre-Screening**	**Screening** Within 28 days prior to randomisation	**Pembrolizumab Cycle 1**[a] Within 3 days prior to dosing (day 1)	**SABR**[b] Within 3 days prior to first fraction of SABR	**Post-SABR/ Pembrolizumab Cycle 2**[a] Within 3 days prior to dosing (day 1)	**Pembrolizumab Cycle 3**[a] Within 3 days prior to dosing (day 1)	**Pre-Nephrectomy** Within 2 weeks prior to surgery	**Nephrectomy** (To be performed 9–12 weeks after first dose of pembrolizumab)	**60 Days Post-Nephrectomy Follow-up** ± 10 days
Clinical Assessments									
Informed Consent	X	X							
Diagnostic biopsy[c]	X								
Review of eligibility criteria		X							
Demographics		X							
Medical history		X							
Current cancer status		X							
Physical examination [d]		X	X		X	X	X		X
Vital signs, including height and weight [e]		X	X	X	X	X	X		X
Baseline symptoms/ abnormalities		X							
ECOG Performance Status		X	X		X	X	X		X
Review concomitant medications		X	X	X	X	X	X		
Review Adverse Events [f]			X		X	X	X		X
Review of surgical complications [g]									X
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory									
Haematology [h]		X	X		X	X	X		
Biochemistry [i]		X	X		X	X	X		
Coagulation profile[j]		X					X		
Thyroid Function tests [k]		X	X		X	X	X		
Viral serology [l]		X							
Pregnancy testing [m]		X	X				X		
Tumour Evaluation									
CT scan (or MRI) chest/abdomen/ pelvis [n]		X					X		
Whole body bone scan		X							
mpMRI scan [o]		X					X		
Intervention									
SABR				X					
Pembrolizumab			X		X	X			
Nephrectomy								X	
Translational Research Sample Collection									

(*continued on next page*)

Table 4 (*continued*)

Trial Phase:	Pre-Screening/Screening Phase		Treatment Phase				Surgery Phase		
Assessments/ Windows	**Pre-Screening**	**Screening** Within 28 days prior to randomisation	**Pembrolizumab Cycle 1**[a] Within 3 days prior to dosing (day 1)	**SABR**[b] Within 3 days prior to first fraction of SABR	**Post-SABR/ Pembrolizumab Cycle 2**[a] Within 3 days prior to dosing (day 1)	**Pembrolizumab Cycle 3**[a] Within 3 days prior to dosing (day 1)	**Pre-Nephrectomy** Within 2 weeks prior to surgery	**Nephrectomy** (To be performed 9–12 weeks after first dose of pembrolizumab)	**60 Days Post-Nephrectomy Follow-up** ± 10 days
Fresh tumour tissue [p]	X							X	
Peripheral blood [q]		X		X	X	X		X	X

[a] 1 cycle = 21 days. In exceptional circumstances, such as public holidays, the scheduled day of pembrolizumab treatment may be ±2 days.

[b] The first fraction of SABR to be given 7 days ±2 days after pembrolizumab cycle 1 day 1.

[c] Diagnostic biopsy: To be collected with coaxial biopsy approach, and sufficient tissue to satisfy translational specimen collection (please refer to Radiology Manual). Ideally, the diagnostic biopsy should be undertaken within 28 days prior to randomisation to the study.

[d] Physical examination: At screening a full physical examination is required. At all subsequent time points a directed physical examination should be performed as clinically indicated.

[e] Vital signs, including height and weight: Respiratory rate, heart rate, blood pressure, O_2 saturation (by pulse oximeter), and temperature. Height only required at screening.

[f] Review of adverse events: Adverse events (AE) according to CTCAE v5.0.

[g] Review of surgical complications: surgical complications according to Clavien-Dindo severity grading.

[h] Haematology: White blood cell count (WBC), neutrophils/ANC, lymphocytes, monocytes, eosinophils, basophils, red blood cell count (RBC), platelets, haemoglobin, and haematocrit. At screening to be performed within 14 days prior to randomisation.

[i] Biochemistry: Random glucose, sodium, potassium, chloride, phosphorous, magnesium, urea, corrected calcium, creatinine, bicarbonate, albumin, uric acid, alkaline phosphatase (ALP), (ALT), (AST), gamma-glutamyl transferase (GGT), total bilirubin, total protein, lactate dehydrogenase (LDH). At screening to be performed within 14 days prior to randomisation.

[j] Coagulation tests: PT, INR and aPTT to be performed within 14 days prior to randomisation.

[k] Thyroid function tests: free T3, free T4 and TSH. At screening to be performed within 14 days prior to randomisation.

[l] Viral serology: HBV, HBC and HIV serology during screening: HbSAg, HBcAb and *anti*-HCV. HBV DNA if HbcAb positive; HCV PCR if *anti*-HCV positive.

[m] Pregnancy testing: Urine or serum β-HCG testing for WOCBP.). At screening to be performed within 72 h prior to randomisation.

[n] CT scan (or MRI): To be completed at screening and within 2 weeks prior to nephrectomy. Volumetric assessment of lesions will be undertaken at both time points. *Note*: Both oral and IV contrast is required.

[o] mpMRI scan: To be completed at screening and within 2 weeks prior to nephrectomy. Please refer to Radiology Manual for further information.

[p] Fresh tumour tissue for translational research: To be collected at pre-screening and at the time of nephrectomy. Please refer to the NAPSTER Laboratory Manual for further information.

[q] Peripheral blood for translational research: To be collected for all patients in screening, on the day of the 3rd SABR fraction ±3 days, the post-SABR visit, at the time of nephrectomy and at the 60-day post-nephrectomy visit. For patients in Arm 2, addition blood collection is required within 3 days prior to day 1 pembrolizumab in cycle 2 (post-SABR) and day 21 ± 3 days of cycle 3 pembrolizumab.

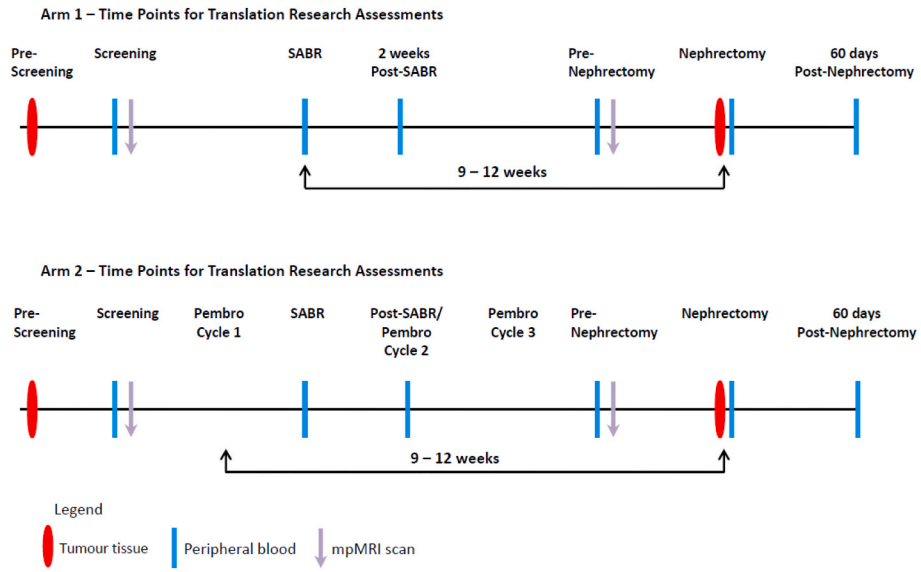

Fig. 2. Translational research schema.

Ethics and consent

The Peter MacCallum Human Research Ethics Committee approved this study (HREC/73073/PMCC). All participants will provide written informed consent.

Trials registration

clinicaltrials.gov ID: NCT05024318.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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