**TITLE:**

# Stereotactic Radiotherapy and Anti-PD1 antibody (Pembrolizumab) for Oligometastatic Renal Tumours

**IIS Study Number:** 53346
**Short Title:** RAPPORT
**Protocol Version**: 2.2
**Protocol Date:** 16 January 2020
**SPONSOR:** Peter MacCallum Cancer Centre
**Peter Mac HREC Project Number:** HREC/15/PMCC/94

**Coordinating Principal Investigator:**

**Name:** A/Prof Shankar Siva
**Position:** Radiation Oncologist, Peter MacCallum Cancer Centre
**Email:** shankar.siva@petermac.org
**Phone:** (03) 8559 7988
**Mobile:** 0404 323 489

**Table of Contents**

1 SIGNATURE PAGE ..... 4
2 SCHEDULE OF EVENTS ..... 5
3 TRIAL SUMMARY ..... 8
4 TRIAL DESIGN ..... 8
5 SCHEMA ..... 9
6 OBJECTIVES & HYPOTHESIS ..... 10
6.1 Hypothesis ..... 10
6.2 Primary Objective ..... 10
6.3 Secondary Objectives ..... 10
6.4 Exploratory Objectives ..... 10
7 BACKGROUND & RATIONALE ..... 10
7.1 Metastatic Renal Cell Carcinoma ..... 10
7.2 The Concept of Oligometastatic Disease ..... 11
7.3 The Role of Metastasectomy in Oligometastatic Renal Cell Carcinoma ..... 11
7.4 The Role of Conventional Radiation in Renal Cell Carcinoma ..... 11
7.5 Hypofractionated Radiotherapy in Renal Cell Carcinoma ..... 12
7.6 SABR for Oligometastatic Malignancies ..... 12
7.7 SABR for Oligometastatic Renal Cell Carcinoma ..... 13
7.8 Summary Tables for Outcomes in Extracranial Renal Cell Carcinoma ..... 14
7.9 Current Standard of Care ..... 15
7.10 Summary of Risks and Benefits ..... 16
7.11 Rationale for the Trial and Selected Participant Population ..... 20
7.12 Rationale for Selection of Immunotherapy to Combine with SABR in the Oligometastatic RCC Cohort ..... 20
7.13 Rationale for Dose Selection/Regimen/Modification of pembrolizumab ..... 21
7.14 Rationale of Endpoints Definition ..... 23
8 STUDY POPULATION ..... 25
8.1 Patient Registration ..... 25
8.2 Replacement of Non-Evaluable Patients ..... 25
8.3 Participant Inclusion Criteria ..... 25
8.4 Participant Exclusion Criteria ..... 27
9 TRIAL TREATMENTS ..... 29
9.1 Megavoltage Radiotherapy ..... 29
9.2 Concomitant Medications/Vaccinations (allowed & prohibited) ..... 41
9.3 Rescue Medications & Supportive Care ..... 42
9.4 Diet/Activity/Other Considerations ..... 45
9.5 Participant Withdrawal/Discontinuation Criteria ..... 46
9.6 Withdrawal From The Trial ..... 47
10 TRIAL PROCEDURES ..... 47
10.1 Trial Procedures ..... 48

10.2 Visit Requirements ..... 50
10.3 Safety Follow-Up Visit ..... 51
10.4 Follow-up Visits ..... 51
10.5 Survival Follow-up ..... 51
10.6 Second Course Phase (Pembrolizumab Retreatment Period) ..... 51
10.7 Assessing and Recording Adverse Events ..... 52
10.8 Attribution of cause of an Adverse Event ..... 53
11 STATISTICAL ANALYSIS PLAN ..... 58
11.1 Statistical Analysis Plan Summary ..... 58
11.2 Statistical Analysis Plan ..... 58
12 Labelling, Packaging, Storage And Return Of Clinical Supplies ..... 62
12.1 Investigational Product ..... 62
12.2 Packaging and Labelling Information ..... 62
12.3 Clinical Supplies Disclosure ..... 62
12.4 Storage and Handling Requirements ..... 63
12.5 Returns and Reconciliation ..... 63
13 ADMINISTRATIVE AND REGULATORY DETAILS ..... 63
13.1 Confidentiality ..... 63
13.2 Ethical Principles and Regulatory Compliance ..... 63
13.3 Adherence to Protocol ..... 63
13.4 Informed Consent ..... 64
13.5 Data Management ..... 64
13.6 Source Documentation ..... 64
13.7 Quality Assurance Reviews ..... 64
13.8 Trial Management Committee (TMC) ..... 64
13.9 Safety Monitoring Committee (SMC) ..... 65
14 Publication and Presentation Policy ..... 65
15 Reference List ..... 66
16 APPENDICES ..... 71
Appendix 1: ECOG Performance Status ..... 71
Appendix 2: Numerical Pain Rating Scale ..... 71
Appendix 3: Spinal Stability ..... 72
Appendix 4: Radiotherapy ..... 73

## 1 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the NHMRC's *National Statement on Ethical Conduct of Research in Humans*, the TGA's *Clinical Trial Handbook*, Good Clinical Practice, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

**For and on behalf of the Study Sponsor:**

Signature Date

Name (please print)

Position

**Principal Investigator:**

Signature Date

Name (please print)

## 2 SCHEDULE OF EVENTS

### *Table 1: Schedule of Events*

| **Trial Period:** | **Screening Phase** | **Radiotherapy** | **Treatment Cycles** | | | | |
|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | **Screening** | **SABR±CRT[3]** | **Day 1 Cycle 1** | **Day 1 Cycle 2-8** | **Safety Follow-up** | **Follow-up[17]** | |
| **Scheduling Window (Days):** | -35 to -1 | Commence within 4 weeks of registration[3] | 5 days post SABR ± 3 days | 21 days post previous cycle Day 1 ± 3 days | 30 days from date of last dose of pembrolizumab ± 3 days | 3 months from SABR ± 14 days | **Progression** (Upon first progression) |
| **Clinical/Administrative Assessments** | | | | | | | |
| Informed Consent | X | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | |
| Demographics and Medical History | X | | | | | | |
| Disease Specific Medical History | X | | | | | | |
| SINS score for Spinal Targets | X | | | | | | |
| Full Physical Examination | X | | X | X | | | |
| Directed physical Examination | | | | | | X | |
| Vital Signs[1] and Body Measurements | X | | X | X | | X | |
| ECOG Performance Status | X | | X | X | | X | |
| Review Adverse Events[2] | X | | X | X | X | X | X |
| Radiotherapy planning | X | | | | | | |
| Trial Treatment Administration – SABR [3] | | X | | | | | |
| Trial Treatment Administration – Pembrolizumab[4] | | | X | X | | | See section 10.6 |
| Review Prior/Concomitant Medications | X | | X | X | | | |
| Numerical Pain Rating Score | | X | X | X | | X | |
| New Anti-Cancer Therapy Status / Second phase pembrolizumab | | | | | X | X | X |
| Survival Status[18] | | | | | | X | |
| **Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory** | | | | | | | |

| **Trial Period:** | **Screening Phase** | **Radiotherapy** | **Treatment Cycles** | | | | |
|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | **Screening** | **SABR±CRT[3]** | **Day 1 Cycle 1** | **Day 1 Cycle 2-8** | **Safety Follow-up** | **Follow-up[17]** | **Progression** (Upon first progression) |
| **Scheduling Window (Days):** | -35 to -1 | Commence within 4 weeks of registration[3] | 5 days post SABR ± 3 days | 21 days post previous cycle Day 1 ± 3 days | 30 days from date of last dose of pembrolizumab ± 3 days | 3 months from SABR ± 14 days | |
| Pregnancy Test[5] – Urine or Serum β-HCG | X | | X | X | | | |
| Haematology[6] | X | | X | X | | As clinically indicated | |
| Chemistry[7,8] | X | | X | X | | | |
| T3, FT4 and TSH[9] | X | | X | X | | | |
| PT/INR and aPTT[10] | X | | | | | | |
| HIV, Hepatitis B and C[11] | X | | | | | | |
| Tumour Evaluation | | | | | | | |
| Tumour assessment by CT scan or MRI[12] (Chest, Abdo, Pelvis) reported as per RECIST 1.1 | X | | X (Every 3 months from SABR) | | | | |
| CT scan (Brain) (if clinically indicated)[12] | X | | | X (Cycle 4 & 8 only) | | As clinically indicated | |
| Whole body bone scan (if clinically indicated)[12] | X | | | X (Cycle 4 & 8 only) | | As clinically indicated | |
| Metastatic FFPE Biopsy[13] | X | | | | | X (month 9 only) | X |
| Primary Surgery FFPE sample[14] | X | | | | | | |
| Blood Serum Sample | | X | X | X | | X (9, 12 and 24 months) | X |
| Whole Blood Sample[15,16] | | X | X | X | | X (9, 12 and 24 months) | X |

***Clinical/Administrative Assessments***

1. Vital signs include blood pressure, heart rate, respiratory rate and temperature. Height will be measured at screening only.
2. Baseline abnormalities (using CTCAE v4.03) must be recorded from signature of informed consent to prior to start of treatment. Adverse events (using CTCAE v4.03) are then required to be assessed on day 1 of every pembrolizumab cycle and at 30 days following last pembrolizumab treatment. SABR related adverse events will be collected at every subsequent follow-up visit until 2 years after completion of SABR.

3. Conventional hypofractionated radiotherapy **of 30-36Gy** may be delivered to individual lesion(s) if SABR is determined to be not technically or safely possible to deliver. If CRT is required it must be completed prior to SABR administration. **At least one lesion must receive SABR.**
4. Pembrolizumab should be administered at 5 days (+/- 3 days) of the last SABR treatment for a total of 8 cycles.

***Laboratory Procedures/Assessments –*** All diagnostic laboratory tests should be performed within 10 days of study registration (to determine eligibility), and also within 3 days prior to every cycle of pembrolizumab (unless indicated otherwise below)

5. Urine or serum pregnancy test for patient of childbearing potential should be performed within 7 days of study registration and also 72 hours within first dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
6. Haematology: Haematocrit, haemoglobin, platelet count, white blood cell count (total and differential), red blood cell count, absolute neutrophil count and absolute lymphocyte count.
7. Chemistry: Carbon dioxide (if considered standard of care only), uric acid, calcium chloride, glucose, phosphorus, potassium, sodium, magnesium, total protein.
8. Liver Function Tests: Albumin, Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), Gamma-Glutamyl Transferase (GGT, total bilirubin and direct bilirubin if total bilirubin is elevated above the ULN), Kidney Function Tests: Urea, creatinine.
9. Thyroid Function: T3, T4 and TSH.
10. Coagulation Profile: PT (INR), aPTT. These need only be done if there is clinical concern regarding patient anticoagulation.
11. HIV, Hepatitis B and C tests only need to for those patients at risk of prior or current active infection as determined by the investigating clinician. These tests only need to be performed within 7 days of study registration only.

***Tumour evaluation -*** Screening CT and WBBS should be completed within 35 days prior to study registration.

12. Clinical and radiological tumour assessments will be performed by CT scan (or MRI as required if tumour is in extremity) at screening and every 3 monthly post-SABR treatment until the last evaluable patient completes 12 months of follow-up.
    Brain CT will be performed if clinically indicated at the same time points. Whole body bone scans will be performed at 3 and 6 months post SABR treatment only in patients with bone disease at baseline and as clinically indicated at the 3 monthly post SABR treatment follow-up visits.
    Disease progression should be confirmed with repeat imaging 4 to 6 weeks later by the same imaging modality or by biopsy. If PET-CT scan has been done clinically this can be used for confirmation of disease progression provided the CT component of the PET-CT scan is of adequate resolution.

***Biological Evaluations***

13. If an archival biopsy specimen from a metastases exists then this should be submitted (block or unstained slides). An optional biopsy of metastatic site will be performed at 9 months post completion of SABR, if feasible. This will ideally be the same site as biopsied before trial related treatments (also optional). In event of disease progression - A sample from the metastatic site, if feasible, is requested. If taken, one-two formalin-fixed, paraffin-embedded (FFPE) tumour blocks should be requested.
14. If the patient had surgery for the primary tumour, one tumour block from resection should be submitted.
15. Prior to radiotherapy, first dose of pembrolizumab (all cycles), at disease progression (if this occurs) and at 9, 12 and 24 months post SABR treatment, whole blood samples will be collected for immune endpoints (refer to the RAPPORT Laboratory Manual for details on collection and processing).
16. EDTA whole blood sample (refer to the RAPPORT Laboratory Manual for details for collection and processing).

***Follow-Up Visits***

17. Study Follow-Up Visits - follow-up assessments (e.g visits @ 1, 3, 6, 9, 12, 15, 18, 21 and 24 months post end of SABR Treatment) should be undertaken within ± 14 days of the scheduled time point. In the event of overlapping visits (i.e. between day 1 of each pembrolizumab cycle and post-SABR follow-up visits), only one visit is required but all protocol mandated investigations (for both timepoints) must be undertaken.
18. All patients will be followed for survival until the last evaluable patient completes 12 months of follow-up. Participants who start a new systemic therapy, are retreated with pembrolizumab or who have distant progression will be followed for survival only.

## 3 TRIAL SUMMARY

| | |
|---|---|
| **Title** | Stereotactic Radiotherapy and Anti-PD1 antibody (Pembrolizumab) for Oligometastatic Renal Tumours |
| **Abbreviated Title** | RAPPORT |
| **Trial Phase** | Phase 1b/II |
| **Clinical Indication** | Patients with oligometastatic renal cancer (1-5 metastases) considered safe for stereotactic ablative body radiosurgery (SABR) |
| **Trial Type** | Prospective, single arm study |
| **Route of administration** | SABR treatment (18Gy-20Gy/1#) followed by 200mg pembrolizumab (MK-3475) IV once every 3 weeks for a total of 8 cycles (~6 months). |
| **Trial Blinding** | Open label |
| **Number of trial subjects** | 30 evaluable* patients in total. |
| **Estimated enrolment period** | 24 months |
| **Estimated duration of trial** | 36 months |
| **Duration of Participation** | ~20 months |

* Evaluable patients are defined as participants who complete at least one SABR treatment and receive at least one dose of study drug (18-20Gy/1# to at least one lesion with at least one dose of pembrolizumab).

## 4 TRIAL DESIGN

This is a prospective, single arm study that will evaluate the safety profile, and the clinical and biological efficacy of combining SABR with pembrolizumab.

Pembrolizumab at a dose of 200 mg IV, 3-weekly will be delivered for a total duration of 6 months, commencing 5 days (+/- 3 days) from the last dose of SABR.

Tumour response will be evaluated by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1).

Tumour tissue and peripheral blood samples will be collected pre, during and post-treatment to assess longitudinal changes in immune subsets within tumour tissue and peripheral blood.

## 5 SCHEMA

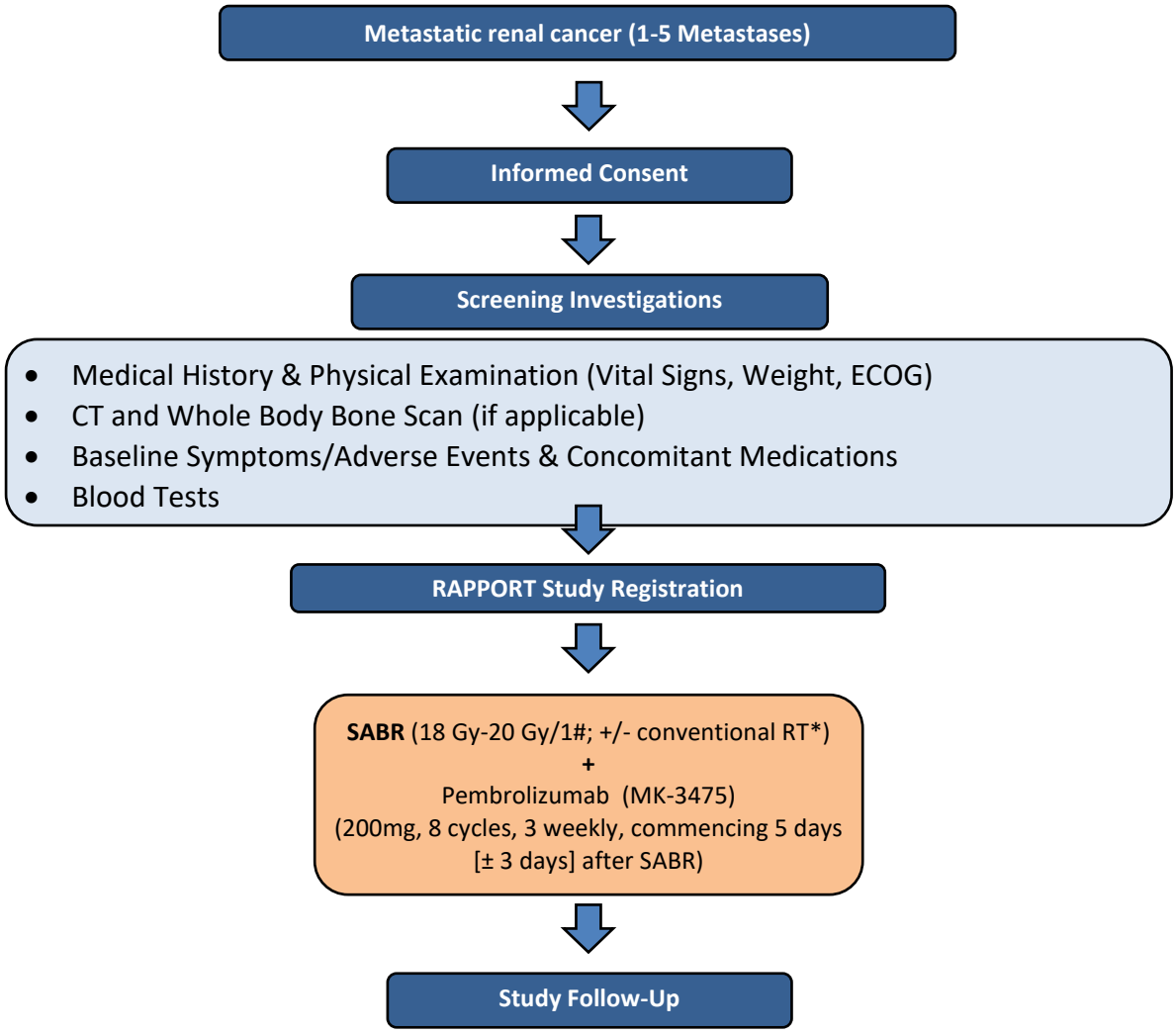



***Figure 1: Study Schema***

* Conventional hypofractionated radiotherapy may be delivered to individual lesion(s) if SABR is determined to be not technically or safely possible to deliver.

# 6 OBJECTIVES & HYPOTHESIS

## 6.1 Hypothesis

This investigator driven study will examine the safety, efficacy and biological effects of combining pembrolizumab (MK-3475) an antibody targeted against anti-programmed cell death 1 (PD-1), with stereotactic ablative body radiotherapy (SABR) for oligometastatic renal cell carcinoma (RCC). We hypothesise that the safety profile of this combination will be clinically acceptable.

## 6.2 Primary Objective

The primary objective for this study is to determine the safety profile of SABR in combination with pembrolizumab.

## 6.3 Secondary Objectives

Secondary objectives are to examine evidence of clinical efficacy of the combination:

1. To describe overall survival (OS).
2. To describe time to local progression (TTLP).
3. To describe distant progression free survival (DPFS).
4. To describe overall response rate (ORR).
5. To describe disease control rate (DCR)
6. To describe changes in pain ratings over time.

## 6.4 Exploratory Objectives

The exploratory objectives are to investigate the biological effects of the combination. These will include, but are not limited to:

1. Evaluate PD-L1 expression in primary tumour and metastatic lesions using immunohistochemistry.
2. Evaluate longitudinal cellular and molecular changes in archival tumour tissue, and/or fresh tumour biopsies. This will include tumour infiltrating lymphocytes (TILs) and other markers.
3. Evaluate longitudinal changes in immunological subsets within peripheral blood.

# 7 BACKGROUND & RATIONALE

## 7.1 Metastatic Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the ninth most common cancer in Australia and the fourteenth most common cancer worldwide [1, 2]. The incidence of RCC is rising, particularly in patients aged 70 to 90 years [3]. Overall, 17% of patients present with metastatic disease and another 50% of patients initially treated with curative intent will develop metastatic disease [4, 5]. Historically patients with metastatic renal cell carcinoma (mRCC) have a poor prognosis, with 5-year survival rates of ≤10% [6]. In patients with metastatic disease, the median survival time ranges from 6 to 12 months, and in patients with brain metastases, the mean survival time is 3 months [7, 8]. In the first line setting, the use of both sunitinib [9] and pazopanib [10] is associated with progression free survival rates of approximately 11 months, whilst sorafenib in the second line setting is associated with progression free survival rates of approximately 5 months [11].

### 7.2 The Concept of Oligometastatic Disease

The concept of oligometastases, introduced by Hellman and Weichselbaum in 1995, describes an intermediate state of metastases in which the number and site of metastatic tumours are limited [12]. This clinical entity can be broadly divided into two groups of patients: those with occult widespread and incurable but mostly subclinical metastatic disease and those with truly limited metastatic disease who might be potentially curable. The clinical implication of this hypothesis for the latter group is that locally extirpative or ablative treatments may achieve prolonged remission in these patients with small numbers of metastases. The absolute number of metastatic lesions that is considered defines the oligometastatic state remains controversial and highly dependent on the clinical scenario. Typically, this is defined as either less than 3 or less than 5 deposits [13].

Notably, prolonged survival has been observed in patients with solitary or oligometastatic renal cell carcinoma whose disease is amenable to resection [14]. With more sensitive imaging methods, the incidence of diagnosing oligometastatic is increasingly observed thereby highlighting the need to revisit optimal management strategies for this subgroup of patients. Although surgery has long been considered the main modality to offer patients with truly oligometastatic disease long term remission, this is not always feasible due to the location of the disease, the morbidity of the surgery and the patient's other medical comorbidities. The advent of stereotactic ablative body radiation therapy (SABR), allows for delivery of high biological doses of radiation using highly conformal image guided techniques. SABR is being increasingly investigated as a local ablative therapy in this setting.

### 7.3 The Role of Metastasectomy in Oligometastatic Renal Cell Carcinoma

Surgery is a long established modality in the treatment of selected patients with metastatic disease. The first case of metastasectomy for RCC was reported by Barney et al., in which the patient remained disease free for 23 years [15]. Despite this there are no randomized studies examining the role of metastasectomy in patients with stage IV disease. Nevertheless, several observational studies have examined outcomes from metastectomy in patients with limited metastatic disease. In a bi-institutional retrospective study of 109 patients, the five-year cancer specific survival (CSS) was 46.9% and median CSS was 54.7 months (range: 0.4–211) in patients undergoing resection for oligometastatic disease [14]. Of these patients, 99 (90.8%) had solitary metastasis. Similarly, in a study of 92 patients undergoing pulmonary metastasectomy at the Cleveland Clinic, the 5-year CSS was 45% [16]. These findings are similar to a series of 65 patients from Paris undergoing pulmonary metastasectomy which found a 5-year overall survival of 37% [17]. The NCCN guidelines recommend that for patients with presentation of primary disease and potentially resectable solitary metastases, that a nephrectomy and metastasectomy be performed. The European Urology Association (EUA) guidelines recommend consideration of metastasectomy for patients with oligometastatic disease based on systematic review of level 3 evidence [18].

### 7.4 The Role of Conventional Radiation in Renal Cell Carcinoma

Definitive external beam radiotherapy (EBRT) is often used to treat medically inoperable patients with cancers in many different organs. However, RCC is conventionally considered "radioresistant" to fully fractionated EBRT. Clinical trials of EBRT delivered in the neoadjuvant or adjuvant setting for primary RCC throughout the 1970's and 1980's failed to demonstrate a survival benefit [19-22]. A recently published meta-analysis of 7 randomized controlled trials involving 735 patients treated with post-operative radiotherapy (PORT) showed a significant reduction of locoregional failure in patients treated with PORT ($p = 0.0001$), but no difference

in overall survival (p= 0.29) (29). The majority of patients were treated with traditional large 2-field techniques, and the authors called for newer trials with more modern techniques. Currently the role of conventional EBRT for primary RCC is limited, possibly to patients with poor pathological features who are high risk of local tumour recurrence [23]. Consequently, conventional external beam radiotherapy is largely limited to palliative treatments. In an effort to overcome the perceived "radioresistance" of RCC, hypofractionated EBRT in the form of SABR has renewed interest in the management of primary RCC with radiotherapy.

### 7.5 Hypofractionated Radiotherapy in Renal Cell Carcinoma

In contrast, ablative stereotactic radiotherapy has been used effectively for treatment of intracranial RCC for decades. With the advent of SABR techniques, renewed interest in high-dose-per-fraction radiotherapy has led to impressive results in the context of primary RCC with local control rates in excess of 90% at 2-years [24]. The advantage of hypofractionated radiotherapy in RCC is suggested by the relatively low α/β values of RCC cell lines compared to other malignancies. Generally, cell lines with a high α/β ratio of >10 are considered radiosensitive. Ning et al. [25] at Stanford University performed a study in which two common human RCC cell lines Caki-1 and A498 were used to perform clonogenic survival assays. The cells were irradiated to doses of 0 – 15Gy and surviving fractions calculated. When cells were irradiated using conventional fractionation of 2Gy per fraction, only a small proportion of cell kill was noted, compared to an exponential rate of cell kill noted at doses above 6Gy per fraction. In this study, the α/β ratio of Caki-1 and A498 were 6.9 and 2.6 respectively. It has been hypothesized that severe hypofractionation has a different mechanism of cell kill than conventional radiation which relies largely on mitotic cell arrest. Stereotactic radiotherapy is more likely to induce ceramide-pathway cell kill and apoptosis as well as vascular endothelial cell damage [26-28].

### 7.6 SABR for Oligometastatic Malignancies

There is a large body of literature on SABR for oligometastatic malignancies. For practical reasons only the landmark SABR oligometastatic studies will be summarized to highlight tolerability and efficacy.

Salama and colleagues [29] reported on patients with 1 to 5 metastatic cancer sites based on 18F-flourodeoxyglucose positron emission tomography (FDG-PET) imaging and a life expectancy of at least 3 months who were treated with SABR. Patients received escalating doses of RT, starting at a dose 24Gy (three 8Gy fractions) 2Gy per fraction dose-escalations and a dose ceiling of 60Gy (three 20Gy fractions). The commonest metastatic sites treated were lung (36.3%), lymph nodes (19.4%), liver (19.4%), bone (13.3%) and adrenal glands (8.0%). At a median follow up of 20.9 months no dose limiting toxicity was seen. One patient with a centrally located right upper lobe metastases who received 36Gy (three 12Gy) fractions developed haemoptysis 10 months after SABR. CT and bronchoscopy revealed disease recurrence and this patient died shortly afterwards. More recent studies due to toxicity recommend excluding central lung lesions outside the contexts of clinical trials [30].

A number of phase I and II studies of SABR to spinal metastasis have demonstrated favourable local disease control rates (86-90%) for patients without spinal cord compression [31-34]. Similar to intracranial stereotactic radiosurgery, SABR has been shown to be effective in the retreatment of metastases that progress following standard EBRT [35]. Additionally, SABR has been shown to be very effective in palliating pain associated with spinal metastases [36, 37].

Several Phase I and II studies have investigated SABR for hepatic metastases using fixed RT doses [38], escalation RT doses [39, 40] and normal tissue complication probabilities [41]. These studies have consistently demonstrated high rates of disease control in the treated metastatic deposits (71-92%). However in general liver metastases control rates have been lower than observed in pulmonary or spinal metastases which may reflect challenges in defining the true extent of the metastatic target as well as organ motion with respiration.

Several studies examining SABR for oligometastases in the lung with both single dose [42] and dose-escalation [43] have demonstrated high rates of treated-metastasis control (89-96%) with promising 2-year survival rates (38-39%). Similar to SABR for early-stage non-small cell lung cancer, the use of three or less fractions for centrally located tumours, defined as within 2cm of the proximal bronchial tree, can result in high rates of treatment related toxicity and should be avoided[44].

### 7.7 SABR for Oligometastatic Renal Cell Carcinoma

Our group has recently performed a systematic review of SABR in oligometastatic RCC following the PRISMA guidelines [45]. The definition of 'oligometastatic disease' in these studies was typically 1-5 metastases. A total of 10 studies were found suitable for inclusion, of which 2 were prospective studies. There were 389 patients with 730 targets identified in the extracranial SABR literature. The patient population was heterogeneous in terms of baseline characteristics, burden of metastatic disease, and prior treatment. Median or mean age in seven studies ranged from 58 to 63 years. Five studies included patients treated with SABR to bony metastases only, predominantly to the spine, while the remaining five studies included a variety of locations, most commonly to the lung.

#### 7.7.1 Radiotherapy Characteristics

Within the extracranial studies, a wide range of total doses and dose fractionation schedules were used. The biological effective dose (BED) calculated using the α/β ratio of Caki-1 and A498 renal cell lines (discussed above) were $BED_{6.9}$ ranging 48 -143 Gy and a $BED_{2.6}$ ranging from 98 – 305 Gy. Five studies incorporated the use of single fraction regimens, with the total SRS dose ranging from 8Gy to 24Gy.

#### 7.7.2 Local Control and Survival

Nine out of 10 studies had crude local control (LC) data available. The crude LC was 89%. Median overall survival for all patients with metastatic RCC only was reported in three studies and ranged from 11.7 to 22 months. Two studies reported estimated 1 year OS of 48.9% and 72%, while another study by Ranck et al. [46] reported 2 year OS of 85%. In the latter study, 67% (12/18) of patients had oligometastatic disease (five or less metastatic lesions) and underwent SABR to all known sites of disease. Wersall et al. provided median survival outcomes for patients with limited disease (one to three lesions), and found this to be higher compared to those with greater than three lesions (37 months and 19 months respectively). Overall, the 1-year weighted LC for intracranial SRS and SABR was 88% and 86% respectively. These data are comparable to studies that have included patients with non-RCC histology [47-50], challenging the long-held view that RCC is a radio-resistant disease.

#### 7.7.3 Treatment Related Toxicity

Toxicity data was available for all ten studies. Grade 3 to 4 toxicities ranged from 0% to 4%. There were a total of two treatment related deaths. One patient who had a large metastatic

lesion (516cc) in the lung close to the pleura, died 10 weeks after receiving SABR (48Gy in 4 fractions). This patient was admitted to hospital with electromechanical dissociation (EMD). The second mortality was due to a fatal gastric haemorrhage 4 months after treatment for a metastasis in the pancreas adjacent to the stomach and duodenum. No details regarding radiotherapy dose was available in this patient.

### 7.8 Summary Tables for Outcomes in Extracranial Renal Cell Carcinoma

A summary table for outcomes in extracranial renal cell carcinoma is presented in Table 2.

***Table 2: Outcomes in Extracranial Renal Cell Carcinoma***

| Author / Date | Patients (Targets) | Locations | Median Follow Up (months) | Crude LC (%) | 1 year LC (%) | Median OS (months) | Toxicity (toxicity grading system) |
|---|---|---|---|---|---|---|---|
| Balagamwala 2012 | 57 (88) | Spine | 5 | 77 | 50 | 12 | 33% (19/57) any toxicity<br>10.5% (6/57) Grade 1<br>2% (1/57) Grade 3 nausea/ vomiting<br>No Grade 4+ toxicity |
| Gerszten 2005 | 48 (60) | Spine | 37 | 88# | 96 | NR | 0% radiation toxicity^ |
| Jhaveri 2012 | 18 (24) | 14 spine,<br>4 ribs/clavicle,<br>6 pelvis | 10 | NR | NR | NR | 6% (1/ 18) Grade I toxicity<br>(NCI CTCAE version not stated) |
| Nguyen 2010 | 48 (55) | Spine | 13 | 78 | 80 | 22 | 23% (9/48) Grade I fatigue.<br>13% Grade II fatigue<br>18% Grade II nausea and vomiting<br>2% (1/48) Grade III pain<br>2% (1/48) Grade III anaemia (NCI CTCAE v.2) |
| Staehler 2010 | 55 (105) | Spine | 33 | 98 | 94 | 17 | 2% (1/55) Grade I abdominal pain (NCI CTC v.3) |
| Zelefsky 2012 | 55* (105) | 59 spine, 22 pelvic bones, 14 other, 9 femur, 1 lymph node | 12 | 72* | 72 | NR | 4% (2/55) Grade 2 dermatitis<br>7% (4/55) fractures<br>2% (1/55) Grade 4 erythema |
| Svedman 2006 (Prospective Phase II trial) | 26 (77) | 63 lung,<br>5 kidney, 5 adrenal,<br>4 thoracic, 3 abdo lymph nodes<br>3 liver, 1 pelvis,<br>1 spleen | 52+ | 99 | 100 | 32+ | 58% (15/26) Grade I - II toxicity<br>4% (1/26) Grade V toxicity<br>(NCI CTCAE version not stated) |

| Author / Date | Patients (Targets) | Locations | Median Follow Up (months) | Crude LC (%) | 1 year LC (%) | Median OS (months) | Toxicity (toxicity grading system) |
|---|---|---|---|---|---|---|---|
| Teh 2007 | 14 (23) | head and neck, lung, mediastinum, spine, non-spine bone, abdominal wall | 9+ | 86# | 81 | NR | No grade 2 or higher toxicity<br>RTOG/ EORTC toxicity criteria |
| Wersall 2005 | 50 (154) | 117 lung,<br>7 kidney,<br>6 adrenal gland,<br>5 kidney metastases,<br>5 thoracic wall,<br>4 bone,<br>6 lymph nodes,<br>2 liver, 1 spleen,<br>1 pancreas | 37+ | 98 | 99 | NR | 40% (23/58) any toxicity<br>2% (1/58) mortality+ |
| Ranck 2012 | 18 (39) | 11 bone,<br>10 abdominal lymph node,<br>7 mediastinum,<br>4 lung, 2 kidney metastases, 2 adrenal, 2 liver, 1 soft tissue | 16 | 95 | 96 | NR | 61% (11/18) Grade I fatigue.<br>No Grade 3 or higher acute toxicity (CTCAE v3.0)<br>11% (2/18) Grade 1 rib fracture<br>6% (1/18) Grade 2 radiculitis<br>6% (1/18) Grade 2 bone pain |

*Information obtained via personal correspondence; #according to number of patients rather than targets; +includes patients with metastatic and primary RCC; ^no toxicity grading system used; NR, not reported; SABR, stereotactic ablative body radiotherapy; CRT conventional radiotherapy; EBRT, external beam radiotherapy

### 7.9 Current Standard of Care

Current standard of care for patients with metastatic renal cell carcinoma depends on the biological subtype, extent of disease and patient fitness. The mainstay is surgical resection where possible, particularly for single sites of disease. Single metastatic sites present the most feasible and best prognosis with the aim to reduce symptoms and/or prolong survival. In patients who are not suitable for surgical resection, or where surgery would be considered morbid, other local therapy (such as radiotherapy) can be considered. This is particularly true for patients with several sites of oligometastases in which multiple surgical resections can be morbid. Patients with more than one oligometastases are often considered carefully for local therapies taking into account both tumour and patient related factors. This group often undergoes a period of surveillance or receives local therapy before receiving any systemic therapies. Indeed Rini et al. presented a prospective observational study that demonstrated that patients with metastatic RCC who fit similar criteria do not require standard TKI therapy for mRCC therapy for a median of 14.1 months ((ASCO 2014, *ASCO Annual Meeting Proceedings* (Vol. 32, No. 15_suppl, p. 4520)). In total 52 patients were enrolled, with the estimated 12 month and 24 month rates of continued surveillance without systemic therapy of 58% and 33%, respectively when local therapies only were used. Neither location nor number of metastatic sites impacted the length of observation. Patient anxiety/depression were not prevalent at baseline, and scores did not worsen over time. Importantly patients could have local treatments (such as SABR) during this observation period. Similar local

experience a retrospective publication of outcomes in patients with metastatic renal cell carcinoma across four academic institutions in Melbourne and Canberra identified 125 patients with metastatic RCC who received systemic therapy with sunitinib. In all, 43% of patients who received sunitinib underwent a watchful-waiting period of >90 days before initiating treatment, with local therapies allowable; these patients had a median overall survival of 56.3 months [51]. Consensus guidelines for Canada and others also identify observation as a valid management strategy in the first instance for certain patients with metastatic RCC [52]. Conclusions from a review of data from five retrospective studies, one prospective cohort and a subgroup of a randomized phase III trial lend support to the strategy of deferral of systemic therapy and the use of local therapies where appropriate instead for carefully selected patients with metastatic RCC and does not induce patient anxiety or impair quality of life [53].

So in selected fit patients with limited oligometastatic disease, the standard of care can include aggressive local management such as extirpative metastasectomy or local high-dose radiotherapy with deferral of systemic therapy until progression. Other options could also include upfront systemic targeted therapy such as tyrosine kinase inhibitors (TKIs). While these systemic treatments may prolong survival they are not curative in the oligometastatic setting. Alternatively, patients with symptomatic bone metastases or soft tissue disease may be treated with palliative external beam radiotherapy, and bisphosphonates/denosumab. Such treatment is aimed at symptom control and not prolonging survival.

### 7.10 Summary of Risks and Benefits

SABR involves highly hypofractionated radiotherapy given as an ablative treatment. While there is extensive literature suggesting that it is safe and has low rates of major toxicities, such studies have tended to have small numbers and relatively short follow up given most patients succumb to their metastatic disease. Thus, by combining a short course of immunotherapy after SABR, we postulate that this will result in a lower likelihood of patients succumbing to further disease recurrence.

The risk of SABR treatment depends on the exact anatomical site of the oligometastatic disease irradiated. There is a low but not negligible risk of radiation pneumonitis, bone fractures, radiation enteritis, skin fibrosis, renal impairment and proctitis. There is an exceedingly low risk of transverse myelitis.

SABR is thought to provide long-term local control of known oligometastatic sites of cancer. It also provides good and durable pain relief for painful metastases. It is postulated that SABR to sites of oligometastatic or oligoprogressive renal cell carcinoma, in selected patients, may prolong survival. Clearly studies that determine whether a survival benefit occurs with such treatment remain to be conducted and reported.

It is acknowledged that patients may have received previous radiotherapy to an area where SABR is to be delivered in this protocol (equivalent dose of 30 Gy in 10 fractions). Due to the increased dose that is received in this instance, there is an increased risk of radiation toxicity in these patients. This potential increased level of risk has been highlighted in the patient information and consent form and must be discussed in each instance prior to informed consent. Patients who have received more than this RT equivalent dose schedule to an area planned for further SABR treatment are not eligible for this study.

### 7.10.1 Immunity and Control of Renal Cancer Metastases

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours.

### 7.10.2 Ablative Radiotherapy as a Means to Enhance Immune Responses

Radiotherapy has long been used a cancer therapy and is known for its direct cytotoxic effects on tumour cells through generation of DNA damage. However, interest has grown around the idea that radiotherapy can have immunological effects. This includes the generation of antigenic peptides through cell death which enhance MHC Class I and adhesion molecules, as well as the subsequent production of cytokines and peptides that can augment immune responses. Therefore, evidence suggests that radiation therapy can trigger a tumour-directed immune response.

Radiation also seems to be able to prime the immune system for an adaptive response. Direct ionizing radiation elicits innate immune recognition of tumour following tumour cell release of “danger signals” [54, 55]. Three molecular signals are required for the ‘danger’ response: dendritic cell (DC) phagocytosis of dying tumour cells, cross-presentation of tumour-derived antigens to T cells and the activation of tumour-specific T cells. Translocation of calreticulin [(CRT)/ERp57] to the surface of dying irradiated cancer cells provides an “eat-me” signal important for DC recognition and engulfment of dying tumour cells [56]. The release of inflammatory molecules from radiation-exposed tumour cells such as high-motility group protein B1 (HMGB1) and ATP, which bind to toll-like receptor 4 (TLR4) or the purinergic receptor $P2X_7$, respectively, also promote antigen processing and cross-presentation by DC and T cell priming through the release of IL-1β [57, 58]. All of these molecules provide the tools for an improved recognition and killing by tumour-specific T cells [59]. The intense localized radiotherapy provided by SABR drives release of tumour antigen, which is taken up by resident dendritic cells (DCs) the DCs mature and migrate to the draining lymph node, where they induce a tumour-specific T cell response (both CD4+ and CD8+). Effector T cells then traffic to the tumour microenvironment where they release effector molecules and induce tumour cell apoptosis.

We hypothesize that SABR is more immunogenic than conventional radiation therapy. The full immunological potential of radiotherapy may be influenced by the dose and fractionation of radiation employed, for both single fraction and fractionated approaches [60]. The ablative dose/fractionation spectrum employed by SABR heralds a potential for even greater augmentation of the tumouricidal immune response than conventional radiotherapy [28]. Immogenic responses at sites distant to the SABR therapy have already been reported by our group [61] and others [62]. Ablative doses result in a greater degree of stromal / vascular damage, ceramide-induced endothelial cell damage and increased apoptosis of tumour cells [63, 64]. This results in a tumour microenvironment enriched with tumour-derived antigens, with co-existing DC activation, antigen cross-presentation and tumour-specific T cell responses. Thus, in the B16 mouse melanoma model, tumour inhibition was more pronounced with ablative doses of radiation as compared to conventional radiation [65]. Significant cross-priming of T-cells against tumour antigens have been demonstrated to be induced by a single dose of 15Gy in the draining lymph nodes [66]. Our group at the Peter MacCallum Cancer

Centre (Peter Mac) identified that single dose (12Gy) radiotherapy did not deplete established tumours of effector cells ($CD8^+$ T, $CD4^+$ T and NK cells) critical to the antitumour activity of radiotherapy when used in combination with immunotherapy. Indeed irradiated mammary tumours were enriched for functionally active, tumour-specific T cells and Ly-$6C^+$ memory $CD8^+$ T cells [67]. It is unclear whether single fraction or hypofractionated RT is optimal in combination with immunotherapy, with reports from New York University suggesting 3 x 8Gy fraction therapy resulting in enhanced immunogenicity in comparison to single fraction ablation [68, 69]. However, more recently, single fraction 20Gy ablative RT has been shown to synergize with the T-cell checkpoint inhibitor anti-PD-1 in murine models [70], allowing for induction of an anti-tumour immune response by relief of tumour-mediated immunosuppression. Similarly a report by demonstrated that single fraction 30 Gy to tumour nodules in murine model resulted in an intense CD8+ T cell tumor infiltrate, and a loss of myeloid derived suppressor cells (MDSCs) [71]. In murine models of melanoma and renal cell carcinoma, single fraction 15Gy SABR combination with PD-1 blockade has been demonstrated to synergize for additive tumour response in both the irradiated and distant tumour sites [72]. A further study in a melanoma model also found single fraction SABR synergised with anti-PD-1, with a possible dose response as 18 Gy of radiotherapy resulted in increased activation and proliferation of antigen-specific T-cells when compared to 12Gy [73].

### 7.10.3 Combination Radiotherapy and T Cell Checkpoint Blockade can Augment Immune Responses and Reduce T Regulatory Cells

There is increasing data to suggest that radiotherapy effects may be enhanced from coincident or subsequent immunotherapy. In established triple negative mouse breast cancer models, the anti-tumour effect of radiotherapy could be enhanced by combinations of immunostimulatory antibodies including anti-PD-1 antibody. In one study from the Peter Mac (Verbrugge et al; [67]), PD-1 signaling was found to be critical and was synergistic when inhibited in order to promote rejection of triple negative mouse tumours. Of note, radiotherapy was found not to deplete tumours of functionally active tumour specific effector cells. These data support concomitant targeting of immunostimulatory and/or inhibitory checkpoints with radiotherapy. Hence, this research presents an opportunity to test this drug in the first line setting along with SABR, which is typically used in patients with treatment naïve oligometastatic disease and may help change the natural history of the disease.

The abscopal effect is a phenomenon when local radiotherapy is associated with regression of metastatic cancer distant from the irradiated site. This effect is thought to be mediated by activation of the immune system though its biological basis is not well understood. This effect was recently observed in a patient with melanoma treated with radiotherapy and ipilimumab (Postow et al. [74]. Tumour shrinkage over time was observed in the irradiated site as well as in distant sites. These correlated with changes in peripheral-blood immune cells (decrease in CD4+ ICOS high cells, increases in HLA-DR expression and decreases in myeloid derived suppressor cells (MDSCs CD14+ HLA-$DR^{low}$) as well as increases in humoral antibody response to a range of antigens after radiotherapy. We will investigate for potential immunological changes induced in the peripheral blood by the combination therapy as possible evidence of mechanisms that may support abscopal effects in future studies.

Refer to the Investigator's Brochure (IB)/approved labelling for detailed background information on pembrolizumab.

### 7.10.4 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favourable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signalling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signalling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signalling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signalling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signalling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumour-specific T-cell expansion in participants with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumour immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

### 7.10.5 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

## 7.11 Rationale for the Trial and Selected Participant Population

This study will evaluate the safety profile, efficacy and biological effects of the combination of pembrolizumab, a T cell checkpoint inhibitor and SABR for oligometastatic renal cancer (1-5 sites of disease). Our hypothesis is that this treatment combination will have a safety profile that is clinically acceptable and demonstrate anti-tumour efficacy.

The sample size of 30 is pragmatic. It is recognized that the findings of this study will serve as the basis for larger randomized studies in the future. Whilst previously, patients with oligometastatic renal cancer have been thought to be incurable, long term survival has been reported with judicious use of surgery or SABR treatment. We hypothesize that augmentation of immunity in this subgroup of patients may enhance long-term control of the disease.

Whist the overlapping toxicities of SABR and pembrolizumab are not yet fully understood, none are expected as the toxicity profiles are due to non-overlapping mechanisms. Safety will be monitored carefully throughout the trial in all patients.

## 7.12 Rationale for Selection of Immunotherapy to Combine with SABR in the Oligometastatic RCC Cohort

In the context of local therapies for patients with oligometastatic disease, the major site of disease recurrence after local therapies such as surgery or surgery is distant. In large prospective database studies, patients with a single site of metastasis have significantly longer survival and lower probability of disease recurrence than those with two or more, however, the majority of patients with a solitary metastases still recurred with distant disease. In a prospective study published in the Lancet Oncology of 1194 patients by Yamamoto et al. [75] of patients with brain metastases treated with stereotactic radiotherapy, patients with a solitary metastasis had a significantly longer survival ($p < 0.001$) than patients with 2 or more metastases. In patients with RCC the median survival for patients with a solitary metastasis was 16.3 months versus 13.7 months in those patients with 2-4 metastases. Similarly, the large multinational registry study of 5206 patients with pulmonary metastases by Pastorino et al. [76] also addressed the number of metastases as a prognostic factor for survival. Patients with a single metastasis had significantly better survival than those with two or more metastases (Figure 1). The 5-year survival was 43% for single lesions and 27% for four or more lesions ($p < 0.001$), however there was no statistically significant difference between patients with 2-3 metastases versus 4 or more.

Overall, this suggests that in patients with oligometastases, some form of systemic therapy may be useful in order to limit the risk of progression of occult micrometastatic disease. However there is no proven benefit of adjuvant systemic TKI therapy in the setting of renal cell carcinoma. Systemic targeted agents (TKI) have not been proven to prolong survival in patients in the primary setting after nephrectomy, indicating that it is incapable of totally eradicating any micrometastatic disease. This evidence could be extrapolated to those patients treated with local therapy SABR for oligometastatic disease, as there is no synergistic effect with radiation and TKIs at distant micrometastatic sites. Pembrolizumab not only can potentiate the effectiveness of radiation at the irradiated tumours, it has the potential to

evoke a sustained anti-tumour immune response at distant sites, which has resulted in a proportion of patients observed to have long-term disease control and perhaps even cure.

### 7.13 Rationale for Dose Selection/Regimen/Modification of pembrolizumab

As of the data cut-off dates for this IB (18-Apr-2014 for P001 melanoma subjects, 29-Aug-2014 for P001 NSCLC subjects, 12-May-2014 for P002, and 30-Nov-2014 for other protocols), the safety and efficacy of pembrolizumab treatment in subjects with hematologic malignancies and solid tumors have been evaluated in 18 ongoing, Merck-sponsored clinical trials: P001, P002, P006, P010, P011, P012, P013, P021, P022, P023, P024, P025, P028, P029, P030, P041, P045, and P055. An outline of selected studies and design are described below.

P001 was an open-label, Phase I, first-in-human (FIH) study of IV pembrolizumab in subjects with progressive locally advanced or metastatic carcinomas, especially melanoma or NSCLC. Part A of the study involved dose escalation that used a traditional 3+3 design. Cohorts of 3 to 6 subjects were enrolled sequentially at escalating doses of 1, 3, or 10 mg/kg administered Q2W. Once the dose escalation was completed, additional subjects were enrolled into Parts A1 and A2 to further characterize the PK and pharmacodynamics of pembrolizumab. In Parts B and D, subjects with metastatic melanoma were enrolled to assess the safety and antitumor activity of pembrolizumab. Additionally, Part B explored 3 different dose regimens in subjects with metastatic melanoma: 10 mg/kg Q2W, 10 mg/kg Q3W, and 2 mg/kg Q3W. In Part C, subjects with NSCLC (with prior systemic therapy) were enrolled at 10 mg/kg Q3W to assess the tolerability, safety, and antitumor activity of pembrolizumab in NSCLC. In Part F, subjects with NSCLC in Cohort F-1 (without prior systemic therapy) and Cohort F-2 (with prior systemic therapy), whose tumors expressed PD-L1, were enrolled at 10 mg/kg Q2W and 10 mg/kg Q3W to characterize the tolerability, safety, and antitumor activity of pembrolizumab. A small cohort of previously treated subjects with NSCLC and at least 2 lines of systemic therapy, whose tumors did not express PD-L1, were enrolled and treated at a dose of 10 mg/kg Q2W in Cohort F-2. In Cohort F-3, previously treated subjects with NSCLC whose tumors express PD-L1 were enrolled at 2 mg/kg Q3W to better characterize the efficacy, safety, and antitumor activity of pembrolizumab. Each of the 2 disease specific cohorts (melanoma and NSCLC) were enrolled to confirm tolerability and evaluate tumor response to pembrolizumab.

P006 was a multicenter, worldwide, randomized, controlled, open-label, 3-arm pivotal Phase III study of 2 dosing regimens of IV pembrolizumab versus IV IPI in subjects with unresectable or metastatic melanoma who had not received prior IPI treatment. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab at 10 mg/kg Q2W, 10 mg/kg Q3W, or IPI at 3 mg/kg Q3W for a total of 4 doses.

P010 is a multicenter, worldwide, randomized, adaptively designed Phase II/III trial of IV pembrolizumab at 2 dosing schedules versus docetaxel in subjects with NSCLC with PD-L1 positive tumors, who have experienced disease progression after platinum-containing systemic therapy. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab 10 mg/kg Q3W, 2 mg/kg Q3W, or docetaxel 75 mg/m2 Q3W.

P011 was an open-label, nonrandomized, multicenter Phase I study of pembrolizumab monotherapy in Japanese subjects with advanced solid tumors and in combination with cisplatin/pemetrexed and carboplatin/paclitaxel in subjects with advanced NSCLC in Japan. In Part A (monotherapy, 3+3 design), subjects with advanced solid tumors received escalating doses of pembrolizumab 2 mg/kg Q2W (dose level 1) or 10 mg/kg Q2W (dose level 2). In Part

B (combination, 3+6 design), subjects with advanced NSCLC receive pembrolizumab 10 mg/kg Q3W in combination with either cisplatin/pemetrexed (Cohort 1) or carboplatin/paclitaxel (Cohort 2) are to be enrolled.

P012 was a multicenter, nonrandomized, multi-cohort Phase Ib trial of pembrolizumab in subjects with PD-L1 positive advanced solid tumors. All subjects receive pembrolizumab 10 mg/kg Q2W. Cohort A enrolled subjects with triple negative breast cancer; Cohorts B and B2 enrolled subjects with squamous cell carcinoma of the head and neck; Cohort C enrolled subjects with urothelial tract cancer of the renal pelvis, ureter, bladder, or urethra; and Cohort D enrolled subjects with adenocarcinoma of the stomach or gastroesophageal junction.

P021 was a multicenter, open-label Phase I/II study of IV pembrolizumab at 2 dosing schedules in combination with chemotherapy or immunotherapy in subjects with locally advanced or metastatic NSCLC.

P022 is a multicenter, worldwide, Phase I/II 3-part trial of IV pembrolizumab in combination with oral dabrafenib and/or trametinib in subjects with advanced or metastatic melanoma. Part 1 is a non-randomized, multi-site, open-label portion of the study using a traditional 3+3 design to evaluate safety, tolerability, and dosing of pembrolizumab (MK) in combination with dabrafenib (D) and trametinib (T) in BRAF mutation-positive (V600 E or K) melanoma subjects. Additionally in Part 1, dosing of pembrolizumab in combination with trametinib only (MK+T) will be explored in BRAF mutation-negative (without V600 E or K) melanoma subjects, to evaluate safety, tolerability, and efficacy of MK+T in Part 2 in this population. Part 2 is a non-randomized, multisite, open-label portion of the study using an expansion cohort to further evaluate safety and confirm dose of MK+D+T. Also in Part 2, an expansion cohort will be used to further evaluate safety and preliminary efficacy in the MK+T combination. Part 3 is a randomized (1:1), active-controlled, multi-site, 2-arm study of the confirmed dose of the triplet combination (MK+D+T) versus placebo (PBO) in combination with D+T (PBO+D+T).

P029 is a multicenter, open-label, 3-part Phase I/II trial of IV pembrolizumab in combination with subcutaneous Pegylated Interferon Alfa-2b (PEG-IFN) or IV IPI in subjects with advanced or metastatic melanoma or renal cell carcinoma. Part 1A, the Phase I portion of the trial, will define the preliminary MTD or MAD of pembrolizumab + PEG-IFN (Group A) and pembrolizumab + IPI (Group B), and confirm the tolerability of these treatment doublets.

P030 is a multisite, worldwide, expanded access program for subjects with metastatic melanoma who have limited or no treatment options. Subjects must have progressed after prior systemic therapy, including standard-of-care agents which include IPI and a BRAF/MEK inhibitor when indicated. Subjects cannot be eligible for an available pembrolizumab clinical trial or have participated in a pembrolizumab clinical trial. Subjects are evaluated for safety at baseline and before each cycle of treatment with pembrolizumab 2 mg/kg/Q3W. Subjects are treated until progression of disease or until the subject has received up to 2 years of treatment.

P045 is a randomized, active-controlled, multisite, open-label, Phase III trial to evaluate the efficacy of treatment with pembrolizumab versus paclitaxel, docetaxel, or vinflunine in subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy. Subjects are randomized in a 1:1 ratio to receive pembrolizumab 200 mg Q3W or the Investigators' choice of paclitaxel 175

mg/m2 Q3W, docetaxel 75 mg/m2 Q3W, or vinflunine 320 mg/m2 Q3W. The study also evaluates the safety and tolerability profile of pembrolizumab in subjects with recurrent/progressive metastatic urothelial cancer.

P055 is a multicenter, unblinded, open-label, single-cohort, Phase II trial to determine the safety, tolerability, and antitumor activity of a 200 mg Q3W dose of pembrolizumab in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy. Antitumor activity is also assessed in the subset of subjects for whom a biopsy sample is determined to be PD-L1 positive.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

A favourable safety profile and preliminary evidence of clinical activity led to the design of a multi-dose trial of nivolumab (anti-PD-1) in 296 patients, confirming antitumor efficacy in melanoma, RCC and NSCLC [77]. In this study, cumulative response rates were 18% for patients with non-small-cell lung cancer (NSCLC), 28% for patients with melanoma, and 27% (9 of 33 patients) for patients with RCC. Recently, in 2015, the results of a randomized, dose-ranging phase II trial of nivolumab in 168 pretreated metastatic RCC patients were published. The median progression-free survival was 2.7 months in the 0.3 mg/kg group, 4.0 months in the 2 mg/kg group, and 4.2 months in the 10 mg/kg group. The median overall survival was 18.2 months in the 0.3 mg/kg group, 25.5 months in the 2 mg/kg group, and 24.7 months in the 10 mg/kg group. More than 50% of responders with all doses had objective responses lasting more than 12–20 month [78].

The CheckMate 025 study is a phase III randomized trial of nivolumab versus everolimus in patients with advanced RCC [ClinicalTrials.gov identifier: NCT01668784]. Patients who received one or two prior anti-angiogenic therapies for advanced RCC (but not more than three total previous therapies) were randomized to receive nivolumab at 3 mg/kg every 2 weeks versus everolimus until disease progression or unacceptable side effects. The primary endpoint of this study was overall survival. In July 2015, the independent Data Monitoring Committee concluded that the study had met its primary endpoint. While full results remain forthcoming, this study will likely establish anti-PD-1 as a new standard of care for previously treated patients with metastatic kidney cancer.

### 7.14 Rationale of Endpoints Definition

**Primary Endpoint:**

Safety (acute and long term) will be evaluated using CTCAE version 4.03 in all patients who have received at least one SABR treatment and one dose of pembrolizumab. Acute adverse events (AE) are defined as AEs occurring from the time of first SABR treatment to 30 days post

end of pembrolizumab treatment and long term AE are defined as AEs occurring after 30 days post end of pembrolizumab treatment.

**Secondary Endpoints:**

To evaluate effectiveness of the treatment combination, using the following measures:

a) Overall survival (OS), time to local progression (TTLP), distant progression free survival (DPFS) and overall response rates
   i. OS will be measured from the date of commencement of SABR treatment to the date of death from any cause.
   ii. TTLP will be measured from date of commencement of SABR treatment to the date of first local progression. Death and commencement of a further course of systemic therapy will be considered as censoring events.
   iii. DPFS will be measured from the date of commencement of SABR treatment to the date of first distant progression at site not documented at registration, or date of death from any cause for patients without distant progression. Commencement of second course of a further course of systemic therapy will be considered as censoring event.
b) Overall response is defined as complete response or partial response, measured using RECIST 1.1 criteria. The RECIST definition of complete response has been modified to include disappearance of the target tumor radiographically or complete metabolic response. The primary is excluded from the evaluation of the overall response.
c) Disease control is defined as complete response or partial response at any time after treatment commencement or stable disease for at least 6 months, measured using RECIST 1.1 criteria. The RECIST definition of complete response has been modified to include disappearance of the target tumor radiographically or complete metabolic response. The primary is excluded from the evaluation of the disease control.
d) Pain will be evaluated using the Numerical Pain Rating Scale at the following time points: pre-conventional radiotherapy treatment (if CRT performed), pre-SABR treatment, prior to each cycle of pembrolizumab, then 3 monthly until 24 months after the end of SABR treatment.

**Exploratory Endpoints**

A number of translational endpoints will be evaluated including:

1. PD-L1 expression in primary tumour and metastatic lesions using immunohistochemistry.

2. Tumour infiltrating lymphocytes (TILs) using a previously defined method at primary tumour and metastatic lesions.

3. Blood samples will be collected at multiple timepoints (prior to radiotherapy, prior to each pembrolizumab administration, at disease progression (if this occurs) and at 9, 12 and 24 months post SABR treatment). These will be analysed for the following (this is a non-exhaustive list):
   i. Absolute lymphocyte counts using a blood analyser.
   ii. The presence of CD8+ T cells by flow cytometric analysis.
   iii. Presence of tumour reactive T cells. These may include markers for HLA-DR, CD4+, CD8+ T cells, PD-1, TIM-3 signifying antigen presentation and experience.

# 8 STUDY POPULATION

Male and female patients ≥ 18 years of age with a histological or cytological diagnosis of renal cell carcinoma, with the presence of oligometastases (1-5 metastases). One or more lesions must be deemed suitable for treatment with SABR. For patients with metastases involving the spine, lesions will be highly selected so they do not pose a significant risk for spinal canal impingement or spinal cord compression.

## 8.1 Patient Registration

Recruitment will cover a 2-year period. Screening for individual participants will take place within 35 days prior to registration onto the study.

The Investigator should ensure that all requirements are met prior to registering eligible patients on the trial:

- Patient meets all inclusion and exclusion criteria requirements
- Patient has signed and dated all consent forms
- All screening assessments have been completed and recorded in the patient's medical records complete with all relevant source documents

Sites will register eligible patients electronically using the online RAPPORT electronic data capture (EDC) system. Confirmation of registration will also be provided electronically (via email) as well as, a unique 6-digit patient identification number for the patient.

Full training on the RAPPORT EDC system will be provided to sites prior to site activation.

## 8.2 Replacement of Non-Evaluable Patients

Evaluable patients are defined as participants who complete at least one SABR treatment and receive at least one dose of study drug (18-20Gy/1# to at least one lesion with at least one dose of pembrolizumab).

If a patient receives no treatment (SABR or pembrolizumab) or completes 1 x SABR treatment but does not receive any pembrolizumab treatment (i.e. withdraws or is withdrawn from the study before receiving any study drug), that patient is deemed as 'non-evaluable. Accrual will continue until 30 evaluable patients are obtained.

## 8.3 Participant Inclusion Criteria

In order to be eligible for participation in this trial, the participant must:

1. Has provided written informed consent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Have oligometastases (1-5 metastases), and measurable disease based on RECIST 1.1.

4. Participants must have a histologically or cytologically confirmed metastatic renal cell carcinoma. Oligometastatic lesions do not need to be biopsied but they must be clinically consistent to represent metastatic disease.

5. Patient can either be treatment naïve or have previously received up to 2 lines of systemic treatment (eg. Pazopanib or Sunitinib). If patient has received prior systemic therapy, the total number of metastases that have not been treated with definitive local therapies should not number more than 5.

6. Must have had surgical consideration for metastasectomy and thought appropriate for SABR due to medical inoperability, technical factors or patient declining surgery.

7. Must have at least one metastasis for which SABR is technically deliverable.

8. Be willing to provide archival tissue from a previously biopsied or excised primary or metastatic RCC lesion (if available). If safe to do so, a request for newly obtained specimen (obtained up to 5 weeks prior to trial registration) will be made, however participation for this biopsy is entirely optional.

9. Have a performance status of 0-2 on the ECOG Performance Scale (Appendix 1)

10. Demonstrate adequate organ function as defined in Table 3, all screening labs should be performed within 10 days of registration.

***Table 3: Adequate Organ Function Laboratory Values***

| System | Laboratory Value |
|---|---|
| **Haematological** | |
| Absolute neutrophil count (ANC) | ≥1.5 X 10^9/L |
| Platelets | ≥100 X 10^9/L |
| Haemoglobin | ≥90 g/L or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment) |
| **Renal** | |
| Serum creatinine **OR**<br>Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl) | ≤1.5 X upper limit of normal (ULN) **OR**<br><br>≥30 mL/min for participant with creatinine levels > 1.5 X institutional ULN |
| **Hepatic** | |
| Serum total bilirubin | ≤ 1.5 X ULN **OR** |
| | Direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 ULN |
| AST (SGOT) and ALT (SGPT) | ≤ 2.5 X ULN **OR**<br>**≤** 5 X ULN for participants with liver metastases |
| Albumin | ≥2.5 mg/dL |
| **Coagulation** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT)<br><br>Activated Partial Thromboplastin Time (aPTT) | ≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless participant is receiving anticoagulant therapy<br>as long as PT or PTT is within therapeutic range of intended use of anticoagulants |
| [a]Creatinine clearance should be calculated per institutional standard. | |

11. Life expectancy > 12 months.

12. Be willing and able to comply with all study requirements, including treatment, attending assessments and follow-up.

13. Female participant of childbearing potential should have a negative urine or serum pregnancy within 7 days prior trial registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

14. Female participants of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (see Section 9.4.2: Contraception). Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

15. Male participants should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

### 8.4 Participant Exclusion Criteria

The participant must be excluded from participating in the trial if the participant:

1. Based on clinician assessment of disease volume and rate of progression of patient's tumour deposits, the patient requires immediate TKI therapy.

2. Has had previous high dose radiotherapy (biological equivalent of >30Gy in 10#) to an area to be treated which includes vertebral bodies (see below).
   *Note: Previous high dose radiotherapy is defined as a biological equivalent dose to above that of 30 Gy in 10 fractions using an $\alpha/\beta$ ratio [82] of 3. Where a patient has received radiotherapy to an equivalent or lower dose than defined above, stereotactic radiotherapy of the area may be considered. In doing so, assessment of the volume and total dose received by any overlap region must be made, and documented by generating a cumulative plan incorporating both the previous and current treatment fields. It is the treating radiation oncologist's responsibility to review both the current plan and the cumulative plan inclusive of previous radiotherapy.*
3. Has evidence of untreated or active intracranial metastases. Patients who have had fully resected brain metastasis or those controlled by stereotactic radiotherapy are eligible as long as they are not requiring corticosteroids for symptomatic control.

4. Has evidence of Spinal Cord Compression.

5. Has a Spinal Instability Neoplastic Score ≥ 7 unless lesion reviewed by a neurosurgical service and considered stable (see Appendix 3).

6. Requires surgical fixation of bone lesion for stability. This must be performed before enrolment into the trial.

7. Has a known history of active TB (Bacillus Tuberculosis).

8. Hypersensitivity to pembrolizumab or any of its excipients.

9. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks of registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

10. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    *Note: Participants with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.*
    *Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.*

11. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

14. Has an active infection requiring systemic therapy.

15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

18. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

20. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

21. Has received a live vaccine within 30 days of registration.

# 9 TRIAL TREATMENTS

The treatment regimen involves the delivery of a single fraction of highly conformal SABR delivered with either photons, electrons or mixed modalities. No cytotoxic chemotherapy is allowed within 3 weeks either side of, or concurrently with respect to the investigational treatment. Consultation with both the treating radiation oncologist and medical oncologist is strongly recommended if chemotherapy is to be considered after the investigational treatment and before documented disease progression, to prevent unforeseen combined toxicities. The first dose of pembrolizumab will be delivered at 5 days (+/- 3 days) after the last SABR treatment for a total of 8 cycles.

## 9.1 Megavoltage Radiotherapy

The investigational treatment will be prescribed to the covering isodose, ensuring that 99% of the PTV is covered by 100% of the dose (D99=100%). However, a target coverage of D95=100% is acceptable if required to respect an organ-at-risk dose tolerance. Intensity Modulated Radiation Therapy (IMRT) is not compulsory but will be considered if very steep dose gradients have to be achieved or targets 'wrap around" a critical structure. This is the near minimum dose to the target as considered by the International Commission of Radiation Units and Measurements (ICRU) in their report 83 [83]. Multi-field photon treatment, intensity modulated radiation therapy (IMRT), dynamic conformal arcs, electrons and volumetric modulated arc therapies (VMAT) can all be considered.

A single fraction of SABR approach will be utilized, which is the most commonly used dose/fractionation schedule utilized at the Peter MacCallum Cancer Centre. The dose will be prescribed using a 'stereotactic' paradigm to an isodose line no less than 70% of the maximum dose, aiming for a prescription isodose of 80%. This allows for larger target dose inhomogeneities but results in a steeper dose fall off outside of the target volume.

If more than one lesion is to be treated in a single patient, treatment of all lesions ideally would be given in one setting for patient convenience. However for practical or logistic reasons this may not always be possible and in such cases all lesions should be treated within a time window spanning not more than 21 calendar days. Dose for each lesion will be independently verified before treatment and image guidance will be used to ensure accurate patient positioning.

### 9.1.1 Statement of Treatment Aim and Rationale

Treatment rationale is to provide long-term local and distant disease control by treating limited oligometastatic renal cancer (1-5 isolated metastases) with a single fraction of stereotactic ablative radiotherapy in conjunction with pembrolizumab.

### 9.1.2 Treatment Schedule

Radiation therapy should commence within 4 weeks of patient registration on the study. A single dose of 20 Gy should be prescribed, although a single 18Gy fraction can be used as an alternative for a centrally located lung lesion or a spinal lesion with a SINS score of $\geq$ 7 after review at SABR chart round. Typically a single fraction of 20Gy should be prescribed for spinal vertebral lesions, however, for those with a SINS score of $\geq$ 7 after review at SABR chart round, a single 18Gy fraction is preferred.

### 9.1.3 Procedures if SABR is not Technically Deliverable

If after evaluation of a tumour location and treatment plan dosimetry, SABR is not technically or safely possible to deliver, a conventional hypofractionated course of radiotherapy of 30Gy in 10 fractions or 36Gy in 12 fractions should be delivered (total dose selected at clinician discretion). In this scenario, delivery of SABR to other sites of disease should be scheduled towards the end of, or immediately after, the course of conventional radiotherapy.

### 9.1.4 Planning Simulation

Simulation procedures will vary according to treatment site. These procedures are in accordance with the Royal Australian and New Zealand College of Radiologists (RANZCR) SABR guidelines (Foote, M. et al., J Med Imaging Radiat Oncol, 2015. **59**(5): p. 646-53).

### 9.1.5 Patient Positioning

Patients will be positioned supine in a manner which isolates the region for treatment from surrounding anatomy where possible e.g. arms above the head for thoracic targets. The final treatment position used will be determined based on the clinical judgement of the treating Radiation Therapy team. The underlying principle that should always be observed is that the patient position must ensure an appropriately stable position that is both reproducible and able to be tolerated by the patient for the anticipated length of planning and treatment delivery procedures.

### 9.1.6 Reference Points/Tattoos

In room lasers will be used to setup and align the patient into the correct position.
In order to facilitate the pre-treatment setup, skin tattoos will be placed at the following locations:

1. Anteriorly at the anticipated isocentre location on an appropriately stable anatomical point.
2. Laterally at the level of the anticipated isocentre position to facilitate reproduction of patient rotation.
3. At an appropriate distance (typically 15-20cm) superior or inferior to the isocentre position to facilitate midline alignment.

Variation to the above described tattoo locations is permitted at the judgement of the planning radiation therapy team to optimise reproduction of patient position, provided there is clear documentation of the change. The position of skin tattoos will be documented in the radiation oncology management system, and photographs taken to facilitate identification of relevant tattoos by the treating radiation therapists.

### 9.1.7 Immobilisation

Effective immobilisation customised to the treatment site is essential to ensure reproducibility of patient position. A high quality customised vaclock style device capable of indexation to the treatment couch is required. The vaclock bag device must adequately encompass the treatment volume and an appropriate area beyond to permit reproducibility of the target and surrounding anatomy.

The actual design of the immobilisation will depend on the treatment site. When deciding on immobilisation consideration must be given to:

- Patient comfort as the treatment time can exceed 45 minutes in particular if more than one lesion is to be treated in a single session.
- The possible need to immobilise more than one lesion at the same time.
- Motion management (see section 9.1.9).
- Reproducibility between planning, mock-up and treatment.
- Image guidance as the field of view of CBCT is limited and patient shifts between imaging and treatment should be avoided.

### 9.1.8 Planning Imaging

A planning CT scan with patient in the treatment position will be used for treatment planning. The CT must be of 3mm slice spacing and width or less. In order to allow placement of non-coplanar beams through valid body contours, the CT scan length should extend as a minimum ten centimetres superior and inferior to the intended treatment volume. CT scan length should also include the entire volume of any organ at risk for which a volumetric dose constraint is set.

### 9.1.9 Consideration of Motion

Motion must be considered in the planning stage for lesions that may be affected by breathing motion. For target volumes in the abdomino-thoracic region, consideration of organ motion should be made as part of the radiotherapy plan when necessary. In such cases, a 4-dimensional CT scan will be acquired for planning. The internal target volume (ITV) concept developed by the International Commission on Radiation Units and measurements will be used for target delineation. An ITV is developed by combining all positions of the target across the respiratory cycle.

For target volumes outside of the abdomino-thoracic region not participant to respiratory excursion, a three-dimensional planning CT scan is adequate.

Gated delivery would only be considered in extreme cases where the lesion moves more than 1 cm.

### 9.1.10 Pre-Treatment Mock-up (only if required)

When deemed as required, a patient will be asked to attend a mock-up session on the Linear accelerator prior to the treatment delivery appointment. The purpose of the mock-up is two-fold:

- To test adequate visualisation of the target and surrounding anatomy with use of the proposed verification imaging.
- To test physical clearance of beam angles.

When a pre-treatment mock-up is required, the patient will be positioned in the treatment position and the beam isocentre set. Verification imaging will be acquired, and assessed online to ensure adequate target visualisation. All beam angles will be set to ensure deliverability on the Linear accelerator.

### 9.1.11 Target Volume Definitions/Field Borders

**Target Volumes**

Target Volumes must be defined as per ICRU 50, 62, and 83 with clear definitions, individual contouring and standardised labelling [83-85]. These include:

- Gross Tumour Volume (GTV)
- Internal Target Volume – The Internal Target Volume (ITV) is a concept developed by the International Commission on Radiation Units and Measurements (ICRU1999)[86] and will be used for lesions that move or are likely to change their shape during treatment. The ITV takes into account the total tumour excursion through respiration. It is a Boolean combination of all locations that would be occupied by the target at any phase of the breathing cycle.
- Planning Target Volume (PTV) – ITV to PTV margins must take into consideration setup uncertainties. A PTV expansion of 5mm global expansion in the axial and craniocaudal directions is required as a minimum. For locations that do not require a 4D CT for motion management – PTV = GTV + 5mm

For contouring of bone metastases all available imaging will be taken into account.

For contouring of spinal bone metastases international consensus guidelines (Appendix 4) will be followed.

**Field Borders**

Conformal field shaping must be performed using a multileaf collimator device with central leaf width of 5mm or less projected to isocentre. The margin between the target volume and the field edge is typically expected to be 0- 2mm in the axial direction, however individual beams eye views may be optimized based on the resultant dose distribution to maximise conformity of the prescription isodose to the PTV. Negative margins from field edge to target volume may also be employed to achieve greater conformity. In order to achieve coverage of the planning target volume with the prescription isodose, it may be necessary to accept a larger than 0-2mm margin from the target volume to the MLC defined field edge, particularly in the craniocaudal axis.

### 9.1.12 Dose Prescription and Fractionation

Dose is prescribed to the covering isodose of the PTV. For plan optimisation, a minimum of D99=100% of the prescription isodose will be accepted except for treatment of the spine. However, a target coverage of D95=100% is acceptable if required to respect an organ-at-risk dose tolerance. Within the spine, in the case of no previous radiotherapy a D90 of > 90% (prescription dose) is ideal, however a D90 of > 80% (prescription dose) is acceptable. In particular for small lesions treated using 3D conformal beam arrangements a large dose inhomogeneity can be expected with the maximum dose far exceeding the prescription dose. During the optimisation process, the PTV max dose should typically aim to achieve a DMax of 125%. This is common in stereotactic treatments and effectively aims for a prescription to the 80% isodose (covering isodose) when normalised to the PTV max. Prescription to lower isodose ranges (between 70 to 80%) is acceptable, particularly for smaller targets.

Maximum dose and dose to the ICRU reference point (centred on the CTV/ITV) should be reported.

The use of IMRT/VMAT in general will make target dose more homogeneous. Care must be taken to not allow any cold spots in the ITV/GTV when using IMRT/VMAT. Phantom volumes with the PTV can be used as planning objectives during plan optimisation to enable desired dose inhomogeneity.

### 9.1.13 Treatment Duration

Wherever possible, all target metastases to be treated with SABR should be treated on the same day for patient convenience. If this is not possible for practical or logistical reasons all lesions will be treated within 21 calendar days.

### 9.1.14 Normal Tissue Contouring and Dose Constraints

Targets in the head and neck region, or in the mediastinum should not be treated with SABR. Targets should generally be located > 1cm from any hollow gastrointestinal luminal structure or major nervous plexus.

***Table 4: Normal Tissue Contouring and Dose Constraints***

| Organ | Contouring | Parameter | Dose-Volume Constraints |
|---|---|---|---|
| Kidney | Entire kidney | V10 | 33% |
| Spinal planning risk volume (PRV) | Spinal Cord + 3mm expansion or Thecal Sac (1cm above and below target)* | Maximum dose | 0.03cc ≤ 12Gy |
| Brain Stem | Including midbrain, pons and medulla | Maximum Dose | 0.03cc<12.5Gy |
| Skin (5mm subcutis) | Body surface – 5mm | Maximum Dose | 0.03cc ≤ 24Gy |
| Small Bowel | All small bowel contoured 5cm above and below PTV | Maximum Dose/ Volume<br><br>Maximum Dose | 30cc ≤ 12.5Gy<br><br>0.03cc ≤ 20 Gy |
| Stomach | Entire Stomach | Maximum Dose | 0.03cc < 20Gy |
| Liver | Entire liver | Maximum Dose/ Volume | 700cc ≤ 15Gy |
| Lung | Combined Left and right Lung - GTV | Maximum Dose/Volume | 1000cc ≤ 7.4Gy |
| Oesophagus | Cricoid to gastro-oesophageal junction | Maximum Dose | 0.03cc ≤ 15.4Gy |
| Rectum | Recto-sigmoid to anal canal (solid structure) | Maximum Dose/ Volume | 20 cc ≤ 14.3Gy |
| Bladder wall | Entire structure | Maximum Dose/ Volume | 15 cc ≤ 11.4Gy |
| Heart / Pericardium | Entire Structure | Maximum Dose/ Volume | 15 cc ≤ 16Gy |
| Brachial Plexus | Including nerve roots | Maximum Dose | 0.03 cc ≤ 15.4Gy |

Dose constraints have been informed by QUANTEC recommendation guidelines (Table 4), completed RTOG protocols, and the AAPM TG101 [87] working party consensus guidelines.
* Where an MRI is not feasible or thecal sac/spinal cord cannot be clearly delineated, spinal canal may be used to define spinal PRV.

Note: Maximum dose is defined to a point. The minimum meaningful volume for a point is 0.035 cc.

When planning more than one lesion a summary plan must be created. The dose constraints apply to the summary plan.

**SPINAL CANAL:** QUANTEC summary [88] recommendations for maximum dose for a single fraction is a Dmax of 13Gy, and in 3 fractions is 20Gy. Limits for our technique are more conservative at 12Gy for a single fraction SBRT. This is also lower than the AAPM consensus recommendation of a max point dose of 14Gy [87]. In instances where the spinal cord has received previous radiotherapy, the spine should be re-imaged using an MRI or other appropriate investigations to check for radiation myelopathy/spinal necrosis if neurological symptoms are present.

**BRAINSTEM:** QUANTEC summary [89] recommends that for single fraction stereotactic radiosurgery a maximum brainstem dose of 12.5Gy is associated with a low risk of toxicity. They also note that higher doses (15-20Gy) have been used with low reported incidence of complications in patient groups with poor prognosis for long term survival (e.g brainstem metastases [90, 91]). We have used the lower recommended limit of 12.5Gy.

**SKIN:** National Comprehensive Cancer Network (NCCN) consensus guideline recommendations are that dose to skin should be limited to 26Gy for a single fraction and 30Gy in 3 fractions. Limits for our technique are more conservative than this at 24Gy for a single fraction

**SMALL BOWEL:** QUANTEC summary [92] recommendations are that dose circumferentially covering any volume of small bowel should not be > 12.5Gy in a single fraction. The maximum point dose recommendation for a 3-fraction approach is <30Gy. This 30Gy recommendation concurs with the seminal phase I/II study reported by Rusthoven et al.[39]. As an alternative, The University of Wurzberg constrains the dose to half the circumference of small bowel, which should not receive more than the prescription dose during SBRT [personal correspondence].

**STOMACH:** QUANTEC summary [92] recommendations are that a maximum point dose should be <30Gy in 3 fraction SBRT. The volume receiving >22.5Gy should be < 5cc.

**LIVER:** QUANTEC summary [93] recommendations are that ≤ 700mL of normal liver receives ≤15Gy in SBRT. University of Wurzberg do not use a dose constraint for single fraction radiosurgery of 30Gy in liver targets [M Guckenberger, personal communication]. As the proportion of irradiated liver will be considerably smaller during SABR for bone or lymph node metastases than in radiosurgery of the liver, it is reasonable not to apply a liver dose constraint to the single fraction cohort receiving 20Gy.

**LARGE VESSELS:** Conventional radiotherapy is known to cause late fibrosis and injury to small and large vessels, usually many years after the initial irradiation. In the context of SABR treatment, it is important to note that despite the pancreas' proximity to major vessels such as the superior mesenteric vessels and abdominal aorta, no toxicities secondary to large vessel injury have been reported secondary to SBRT. Similarly in the liver, no clinically relevant large vessel effects have been reported secondary to irradiation of the inferior vena cava. This may

be in part due to the patient population, who typically are medically inoperable and have life-spans limited by other medical comorbidities. To the study team's knowledge, clinically significant large vessel injuries have been reported only in the context of combined surgery and radiation, or re-irradiation using SBRT of significantly higher doses than in is allowable in the context of this study. Doses should be limited to the large vessels following ALARA principles.

**OESOPHAGUS:** Based on recommendations from AAPM Task Group 101 consensus recommendations [87], circumferential irradiation of oesophagus is not allowed.

### 9.1.15 Treatment Planning and Dosimetry

#### 9.1.15.1 Planning System Requirements

A 3D computerised planning system capable of incorporating datasets derived from 4DCT and utilising a 3D dose calculation algorithm with pixel based inhomogeneity correction (eg convolution/superposition) will be used. Systems that can account for variation in lateral scatter in the presence of 3D-CT defined heterogeneities are required. Widely available systems that have this capability currently include Philips Pinnacle, CMS XiO, and Varian Eclipse.

Other features of the planning system must include:

a) The planning system must be capable of handling the large CT datasets required for multiple lesions and non-coplanar beam arrangements.

b) Dimensions of the dose calculation grid must be equal or smaller than 2.5mm.

c) The system must be able to display summary plans.

d) Can provide hardcopy of superimposed isodose distributions on axial CT images (sagittal and coronal planes desirable).

e) Can provide digitally reconstructed radiographs (DRRs) with superimposed target volume, critical structure contours and treatment aperture.

f) Provides planning data in DICOM RT or RTOG format that can be downloaded onto a CD or via a network.

For the inclusion of IMRT, the planning system must have a suitable inverse planning module with dose optimisation including non-coplanar beams. The maximum photon energy in this case will be restricted to 6MV. The planning system must have the capability to export a patient plan to a QA phantom for physical QA. All IMRT plans for patients in the study must be verified prior to treatment using physical phantom measurements.

For the use of electron radiation, the planning system must have an adequate dose calculation algorithm that can take homogeneities from CT scans into account. This will typically be a Monte Carlo based algorithm.

If Monte Carlo calculations or Boltzman radiation transport equation solvers (ACUROS™) are used the dose calculations must be dose to water to be equivalent with other dose calculations.

Please consult with the trial physicist if in doubt.

#### 9.1.15.2 Photon Planning

Treatment plans are typically expected to be using 3D conformal radiotherapy approach. These must be delivered with at least six (6) non-opposing conformal megavoltage photon beams from linear accelerators. It is anticipated that a typical range of beam numbers would be 8 to 12, comprising of at least 6 co-planar beams and 1-2 non-coplanar beams. The treatment couch shall be included in the dosimetry of all plans. Arc therapy (including VMAT) and IMRT is allowed.

The maximum and minimum doses in the PTV shall be calculated and reported as per ICRU report 83.

A DVH must be generated for the PTV and all contoured organs at risk. DVH format and labelling of all structures must be clear.

#### 9.1.15.3 Beam Arrangements

Radiation beams are expected to be of megavoltage quality and of 6MV, 10MV or 18MV energy. Flattening-Filter-Free modes are permitted. At least six (6) non-opposing radiation beams must be used to fulfil dosimetric criteria. Conformal arcs are allowed with a variable cumulative arc length, expected to be 200 degrees or more. The minimum field size for energy of 6mv is 3cm and for 18mv is 4cm. Smaller field sizes may be permissible when using Monte Carlo planning calculations or otherwise in consultation with trial physicist.

#### 9.1.15.4 Shielding & Customised Blocks

Treatment must be delivered conformally using a multi-leaf collimator. Customised blocks are prohibited. The use of fields with a jaw setting of less than 3.0 cm x 3.0cm is discouraged to maintain accuracy of dose modelling, unless small field size geometry has been specifically commissioned. Shielding using multi-leaf collimation within field sizes smaller than this should be verified wherever possible, using phantom dosimetric measurements.

#### 9.1.15.5 IMRT and Arc Therapy

The use of IMRT is generally not required for small lesions and may unnecessarily prolong treatment delivery. However, IMRT can be used (and may be required) if steep dose gradient have to be achieved. The use of arc therapies (VMAT and Dynamic Conformal Arc) are allowed to expedite treatment delivery.

#### 9.1.15.6 Electron Planning

Electron techniques will only be used after approval from the Technical Implementation Group (TIG) of the Division of Radiation Oncology and Cancer Imaging.

Superficial lesions may be better treated using electron irradiation. In this case a single electron beam shall be used.

The electron energy and field size should be selected so that the 90% isodose line encompasses the PTV. Electrons should be prescribed and reported at the depth of maximum dose (R100). The limits for dose variation within the PTV are -10% and +10% of the dose at the reference point.

Electron energies should not exceed 12MeV. Skin dose may be a limiting factor and use of bolus will not be allowed.

The following dose values should be reported for treatment conditions:

- depth of maximum dose and nominal energy of the electron beam.
- location of and dose value at the prescription point, or ICRU Reference Point, if not located at the level of the maximum dose.

A planning CT is required to determine the tumour depth, and for mandatory outlining of the tumour bed and PTV. If planned on CT images using Monte Carlo algorithm, the maximum and minimum doses in the PTV shall be calculated and reported as per ICRU71. Junctions between electron beams and any other beam are not allowed.

The method of monitor unit calculation is at the discretion of the treating clinician, and will be determined by standard clinical practice at the Trial Site. MU calculation method will be:

- Manual calculation using data issued by the Trial Site, and including depth dose tables and factors to correct for non-standard applicator, beam shaping, and treatment distance
- Preference will be for calculation using a treatment planning system which has been commissioned for electron beams with heterogeneous tissue. MU calculations using pencil beam algorithms are generally not considered sufficiently accurate for clinical use, and an alternative (manual) method is recommended. Note that the calculated dose distribution is similarly not reliable. MU calculations using Monte Carlo algorithms may be used if that is the normal practice at the trial centre.

Therefore, if an electron field is used, the method of monitor unit calculation is at the treating clinician's discretion which is determined by the standard clinical practice at the Trial Site.

#### 9.1.15.7 Dose Distribution/Reporting

External Beam Radiation Therapy

Dose reporting requirements follow ICRU reports 50 and 62 for photons [84, 86] . Dose and volume reporting shall follow the ICRU level 2, including the dose to ICRU reference point as well as 3D dose distributions with inhomogeneity corrections, all supported by a quality assurance program covering the entire process. The following will be reported:

- The absorbed dose at the ICRU reference point.
- The mean and maximum dose in the PTV will be calculated and reported.
- The dose to the target shall be reported as the minimum dose received by the PTV, i.e. the isodose line covering the PTV.
- A dose to 99% of the PTV (D99) and 95% of the PTV (D95) should also be reported. There will be no restriction on the upper limit of maximum dose within the PTV, however this should be ideally between 125%-143% of the prescribed dose.
- The conformity index will be reported. This is defined as the ratio between the volume encompassed by the prescription isodose and the target volume (ICRU 62).

A conformity index of 1.2 should be the ideal benchmark for radiotherapy plans when IMRT or VMAT techniques are used. A conformity index of 1.2-1.3 should be the ideal with 3D conformal treatments. A $CI_{100}$ (volume encompassed by the 100% isodose and the target

volume) should usually be 1.6 or less if possible, and a $CI_{50}$ (volume encompassed by the 50% isodose and the target volume) should ideally aim to be 5 or less if possible (acknowledging that this may not possible in all cases, and will be more difficult to achieve with smaller target volumes).

#### 9.1.15.8 Treatment Verification and Delivery

All patients will be treated on a linear accelerator with megavoltage photon beams of a nominal energy between 6MV and 18MV.

The linear accelerator must be equipped with multi-leaf collimator of central leaf widths of 5mm or smaller projected to the isocentre. Due to the non-coplanar delivery required isocentre tolerance for quality assurance must be within a 3mm spherical volume in the planes of gantry, couch and collimator rotations.

The linear accelerator must be also equipped with verification imaging that allows visualisation of the target volume. This must be on board kV imaging, which is expected to be cone beam CT (CBCT) or superior technology. If 4D CBCT becomes available and is validated, this may be employed.

Verification imaging will be required pre-treatment, mid treatment and post treatment in all cases. Verification imaging must be capable of visualising the target with soft tissue matching for thoracic, abdominal and pelvic targets. For limb or peripheral targets, kV imaging for bony alignment is sufficient.

### 9.1.16 Systemic Therapy such as Chemotherapy and Systemic Targeted Agents

No systemic chemotherapy or systemic targeted agents will be allowed during the six months of treatment. Systemic chemotherapy will necessitate ceasing the study drug pembrolizumab.

### 9.1.17 Surgical Therapy

There are no specific surgical techniques included in this study. If a patient requires surgical fixation or procedure for spinal or long bone instability they will be ineligible for the study.

### 9.1.18 Dose Selection/Modification of Pembrolizumab (MK-3475)

The treatment to be used in this trial is outlined below in Table 5 below.

***Table 5: Trial Treatment***

| Drug | Dose / Potency | Dose Frequency | Route of Administration | Regimen / Treatment Period | Use |
|---|---|---|---|---|---|
| Pembrolizumab | 200 mg | Q3W | IV infusion | Day 1 of each 3 week cycle | Experimental |

Pembrolizumab treatment should begin 5 days (+/- 3 days) post the last SABR treatment. 8 cycles of pembrolizumab will be delivered.

#### 9.1.18.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 7: Background and Rationale.

### 9.1.18.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 6 below.

See Section 9.3.1 for supportive care guidelines, including use of corticosteroids.

***Table 6: Dose Modification Guidelines for Drug-Related Adverse Events***

| Toxicity | Hold Treatment For Grade | Timing for Restarting Treatment | Treatment Discontinuation |
|---|---|---|---|
| Diarrhea / Colitis | 2-3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 4 | Permanently discontinue | Permanently discontinue |
| AST, ALT, or Increased Bilirubin | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose |
| | 3-4 | Permanently discontinue (see exception below)[a] | Permanently discontinue |
| Type 1 diabetes mellitus (if new onset) or Hyperglycemia | T1DM or 3-4 | Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure | Resume pembrolizumab when patients are clinically and metabolically stable |
| Hypophysitis | 2-4 | Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| Hyperthyroidism | 3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 4 | Permanently discontinue | Permanently discontinue |
| Hypothyroidism | | Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted | Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted |
| Infusion Reaction | 2[b] | Toxicity resolves to Grade 0-1 | Permanently discontinue if toxicity develops despite adequate premedication |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Pneumonitis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Renal Failure or Nephritis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| All Other Drug-Related Toxicity[c] | 3 or Severe | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 4 | Permanently discontinue | Permanently discontinue |

| Toxicity | Hold Treatment For Grade | Timing for Restarting Treatment | Treatment Discontinuation |
|---|---|---|---|
| Stevens-Johnson Syndrome (SJS) | signs or symptoms | Refer to the PI and specialist | Withhold and refer the patient for specialized care for assessment and treatment. |
| Stevens-Johnson Syndrome (SJS) | confirmed | Permanently discontinue | Permanently discontinue |
| Toxic Epidermal Necrolysis (TEN) | signs or symptoms | Refer to the PI and specialist | Withhold and refer the patient for specialized care for assessment and treatment. |
| Toxic Epidermal Necrolysis (TEN) | confirmed | Permanently discontinue | Permanently discontinue |
| Immune-mediated myocarditis | signs or symptoms | Refer to the PI and specialist | Withhold and refer the patient for specialized care for assessment and treatment. |
| Immune-mediated myocarditis | confirmed | Permanently discontinue | Permanently discontinue |

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to
– Infusion Treatment Guidelines for further management details.
[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Participants can resume dosing for toxicity if toxicity has resolved according to Table 6 requirements, steroid dosing is 10mg or less of prednisolone, and no more than 12 weeks have passed since last dose. Patients will (or will not) receive additional pembrolizumab doses to ensure that each patient has 8 doses pembrolizumab total.

The reason for interruption should be documented in the patient's study record.

### 9.1.19 Timing of Dose Administration

Pembrolizumab treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the schedule of events (Table 1).

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks for 8 cycles. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

### 9.1.20 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and participant will know the treatment administered.

## 9.2 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the study Principal Investigator. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

### 9.2.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 10.7: Assessing and Reporting Adverse Events.

### 9.2.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. The regular use of steroid prophylaxis > 10 mg daily for flare reaction on the day of SABR delivery is permitted.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

## 9.3 Rescue Medications & Supportive Care

### 9.3.1 Supportive Care Guidelines

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 9.1.18 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

**Pneumonitis**:

- For **Grade 2** events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4** events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

**Diarrhoea/Colitis:**

Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All participants who experience diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2** diarrhoea/colitis, administer oral corticosteroids.
- For **Grade 3 or 4** diarrhoea/colitis, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to **Grade 1 or less**, steroid taper should be started and continued over no less than 4 weeks.

**Type 1 diabetes mellitus**

If new onset, including diabetic ketoacidosis [DKA] OR ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) OR metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
- Insulin replacement therapy is recommended for Type I diabetes mellitus and for **Grade 3-4** hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.

**Hypophysitis:**

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

**Hyperthyroidism or Hypothyroidism:**

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to **Grade 1 or less**, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

**Hepatic**:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
- Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

**Renal Failure or Nephritis:**

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

**Immune-mediated myocarditis:**

For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies, and administer corticosteroids as appropriate.

### 9.3.2 Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 7 below shows treatment guidelines for participants who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

***Table 7: Infusion Reaction Treatment Guidelines***

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| **Grade 1**<br>• Mild reaction; infusion interruption not indicated; intervention not indicated | • Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. | • None |
| **Grade 2**<br>• Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs | • **Stop Infusion and monitor symptoms.**<br>• Additional appropriate medical therapy may include but is not limited to:<br>• IV fluids<br>• Antihistamines<br>• NSAIDS<br>• Acetaminophen<br>• Narcotics<br>• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>• If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.<br>• **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.** | • Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:<br>• Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br>• Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). |

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| **Grades 3 or 4**<br>**Grade 3:**<br>• Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br>**Grade 4:**<br>• Life-threatening; pressor or ventilatory support indicated | • Stop Infusion.<br>• Additional appropriate medical therapy may include but is not limited to:<br>• IV fluids<br>• Antihistamines<br>• NSAIDS<br>• Acetaminophen<br>• Narcotics<br>• Oxygen<br>• Pressors<br>• Corticosteroids<br>• Epinephrine<br>• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>• Hospitalization may be indicated.<br>• Subject is permanently discontinued from further trial treatment administration. | • No subsequent dosing |
| Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. | | |

## 9.4 Diet/Activity/Other Considerations

### 9.4.1 Diet

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhoea, nausea or vomiting.

### 9.4.2 Contraception

Pembrolizumab may have adverse effects on a foetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Participants should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an oestrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Participants should be informed that taking the study medication may involve unknown risks to the foetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above)

for the duration of the study and during the follow-up period defined in Section 10.8.4: Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

#### 9.4.3 Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to the Sponsor. If a male participant impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 10.8.4 Reporting of Pregnancy and Lactation to the Sponsor and to Merck.

#### 9.4.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrolment.

### 9.5 Participant Withdrawal/Discontinuation Criteria

#### 9.5.1 Protocol Treatment Discontinuation

A participant must be discontinued from the trial treatment for any of the following reasons:

- The participant or legal representative (such as a parent or legal guardian) withdraws consent.
- Unacceptable adverse experiences as described in Section 9.1.18: Dose Modifications
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the participant
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements

When a participant discontinues/withdraws treatment prior to trial completion, all applicable activities scheduled for the End of Treatment visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements. After discontinuing treatment (for any reason), participants should attend the site for a 30 day (post end of trial treatment) safety follow-up visit (see Section 10.3) for assessment of AEs and Efficacy.

The End of Treatment and Follow-up visit procedures are listed in The Schedule of Events (Section 2) and Section 10.2: Visit Requirements. After the end of treatment, each participant will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 10.8.5 Serious Adverse

Events. Participants who discontinue treatment will have post-treatment follow-up for disease status until initiating a non-study systemic cancer treatment, withdrawing consent or becoming lost to follow-up.

### 9.5.2 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for participants who have attained a confirmed CR and had at least two cycles of pembrolizumab beyond the date when the initial CR was declared with the option of restarting treatment if they meet the criteria specified in Section 10.6: Second Course Phase.

After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 10.3) and then proceed to the Follow-Up Period of the study (described in Section 10.5).

Pembrolizumab may also be discontinued or put on hold for specified AEs, see Table 7.

Additional details about follow-up after treatment completion or discontinuation are provided in Section 10.2: Visit Requirements.

## 9.6 Withdrawal From The Trial

Participants may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur.

Total withdrawal would occur in the circumstance that the participant decides to completely withdraw from all treatment aspects of the trial, and does not agree to any further scheduled follow up assessments. The participants' total withdrawal must be documented in the medical records and transcribed onto the relevant CRF. No further information will be collected from this patient for the purpose of this trial.

### 9.6.1 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

# 10 TRIAL PROCEDURES

The Schedule of Events (Section 2) summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may

be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

## 10.1 Trial Procedures

### 10.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favourable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

The informed consent will adhere to HREC requirements, applicable laws and regulations and Sponsor requirements.

### 10.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

### 10.1.3 Demographics

Demographic will be collected including gender and date of birth.

### 10.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. The medical history will also include:

- Disease status and prior treatments
- Any new disease symptoms

### 10.1.5 Disease Specific Medical History

The investigator or qualified designee will obtain prior and current details regarding disease status, including all prior cancer treatments, e.g. systemic treatments, radiation and surgeries.

### 10.1.6 SINS Score for Spinal Targets

The investigator or qualified designee will assess the SINS score for spinal targets at Screening.

### 10.1.7 Physical Exam

The investigator or qualified designee will perform a full physical exam during the screening period and also during the treatment phase. Clinically significant findings will be recorded as adverse events.

The investigator or qualified designee will perform a directed physical exam as clinically indicated during the follow up phase.

### 10.1.8 Vital Signs and Body Measurements

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of pembrolizumab and at treatment discontinuation and during follow up as specified in the Schedule of Events (Section 2). Vital signs will include temperature, pulse, respiratory rate and blood pressure. Body measurements will include weight (all visits) and height (screening only).

### 10.1.9 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of pembrolizumab and discontinuation of trial treatment as specified in the Schedule of Events (Section 2).

### 10.1.10 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Schedule of Events and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03. AEs will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 10.7 for detailed information regarding the assessment and recording of AEs.

### 10.1.11 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 35 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

### 10.1.12 Concomitant Medications

The investigator or qualified designee will record medication, if any, related to reportable SAEs which should be recorded as defined on the SAE CRF.

### 10.1.13 Numerical Pain Rating Score

Numerical Pain Rating score (refer to Appendix 2) will be completed by the patient at the time points specified in the Schedule of Events (Section 2).

### 10.1.14 Tumour Imaging and Assessment of Disease

Imaging will be performed as per below:

- All pre-registration/screening investigations (CT Scan and WBBS) should be completed within 35 days prior to study registration.
- Clinical and radiological tumour assessments (post study registration) will be performed by CT scan or MRI (Chest, Abdo, Pelvis, and Brain if clinically indicated) reported with RECIST 1.1 (if possible) unless evidence of progression earlier or clinically inappropriate. WBBS will be performed at 3 and 6 months post SABR treatment in patients with bone disease detected at baseline, and/or if clinically indicated at any of the 3 monthly follow-up visits. Follow-up visits will continue until the last evaluable patient completes 12 months of follow-up.

Disease progression, as per RECIST 1.1, should be confirmed with repeat imaging 4 to 6 weeks later by the same imaging modality or by biopsy. If PET-CT scan has been done this can be used for confirmation of disease progression provided the CT component of the PET-CT scan is of adequate resolution. Complete response includes disappearance of the target tumor radiographically or metabolically (standardized uptake value = 0 when the pre-treatment PET, if done, was metabolically active). Efficacy will be evaluated by time to local progression as well as failures in other sites.

### 10.1.15 Laboratory Procedures/Assessments

Laboratory assessments will be performed as specified in the Schedule of Events.
Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

### 10.1.16 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

### 10.1.17 Continuing Pembrolizumab beyond Radiological Progression

There are patients who experience progression prior to response to pembrolizumab. Hence, radiological progression should be confirmed with follow-up imaging 4-6 weeks later. Pembrolizumab can be continued if there is evidence of benefit by the investigator, if there are no signs or symptoms indicating unequivocal disease progression, no decline in ECOG performance status attributed to disease progression and no growth of the tumour in critical sites. If radiological progression is still documented pembrolizumab can still be continued until there is unequivocal symptomatic deterioration attributed to disease progression that requires initiation of new systemic or local therapy.

## 10.2 Visit Requirements

Visit requirements are outlined in The Schedule of Events (Section 2). Specific procedure-related details are provided above in Section 10: Trial Procedures.

### 10.3 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted 30 days ± 3 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

### 10.4 Follow-up Visits

Participants who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 3 months by radiologic imaging to monitor disease status until the last evaluable patient completes 12 months of follow-up. Every effort should be made to collect information regarding disease status until the start of new systemic therapy, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 10.6: Second Course Phase. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. Participants who start a new systemic therapy, are retreated with pembrolizumab or have distant progression will be followed for survival only.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 10.6 Second Course Phase will move from the follow-up phase to the Second Course Phase when they experience disease progression.

### 10.5 Survival Follow-up

All patients will be followed for survival until the last evaluable patient completes 12 months of follow-up.

### 10.6 Second Course Phase (Pembrolizumab Retreatment Period)

Participants who stop pembrolizumab with SD or better response who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if:

- no cancer treatment was administered since the last dose of pembrolizumab,
- the participant meets the safety parameters listed in the Inclusion/Exclusion criteria below, and
- the trial is open.

Participants will resume therapy at the same dose and schedule at the time of initial discontinuation. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

**EITHER**

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
- Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
- Received at least two cycles of pembrolizumab beyond the date when the initial CR was declared

**OR**

- Had SD, PR or CR and stopped pembrolizumab treatment for reasons other than disease progression or intolerability

**AND**

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab

### 10.6.1 Has a performance status of 0 or 1 on the ECOG Performance Scale

- Demonstrates adequate organ function as detailed in Section 8.3.
- Female participant of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female participant of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Section 9.4.2 Contraception). Participants of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male participant should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the participant's participation for the full duration of the trial or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

Participants who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year. Management of all immunotherapy related toxicities are outlined in Section 9.3.1 Supportive Care Guideline. This guideline should be followed in the retreatment period, however, any prior events and subsequent interventions or treatment modification during the initial treatment period should be continued in the retreatment phase. Any patient having sustained immunotherapy induced severe (grade 3) pneumonitis/ colitis / haematologic events etc. corticosteroids for > 12 weeks, or life-threatening events should be excluded from retreatment.

Once any new systemic anti-cancer therapy or, second course of pembrolizumab has been initiated, the participant will have concluded their participation in the treatment phase of the study. On completion of the treatment phase of the study the participant enters the follow-up phase and will be followed up for survival from the date any new treatment starts.

## 10.7 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product (or any other protocol specified intervention including radiation therapy, surgery or use of a device) and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure (including radiation therapy, surgery or use of a device), whether or not considered related to the medicinal product or protocol-specified procedure.

Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the medicinal product, (or associated with the use of any other protocol specified intervention including radiation therapy, surgery or use of a device), is also an adverse event.

Adverse events may occur during the course of the use of protocol treatment in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened participants during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

### 10.8 Attribution of cause of an Adverse Event

The causal relationship to protocol treatment (attribution), as assessed by the Investigator is also to be recorded. Attribution of cause requires at least a reasonable possibility of a causal relationship between the event and the use of the investigational drug or any other protocol-specified intervention.

All protocol-specified interventions (including pharmaceutical products, radiation therapy, surgery or use of a device) administered prior to the date of the event must be attributed a degree of causality from one of the following codes:

- Definite: The AE is clearly related to protocol treatment
- Probable: The AE is likely related to protocol treatment
- Possible: The AE is may be related to protocol treatment
- Unlikely: The AE is doubtfully related to protocol treatment
- Unrelated: The AE is clearly NOT related to protocol treatment

An AE **does not** include:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions present or detected prior to start of study product administration, that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalisation for elective surgery, social and/or convenience admissions)
- Overdose of either study product or concomitant medication without any signs or symptoms unless the subject is hospitalised for observation.
- Progression of the disease under study

#### 10.8.1 Adverse Event Reporting

All adverse events will be recorded from the time the consent form is signed through 30 days following completion of pembrolizumab treatment. SABR related adverse events will be followed at each follow-up visit until 2 years after completion of SABR.

All adverse events, which occur whilst the participant is enrolled on the trial (including the follow-up phase), must be reported in the patients' medical records and recorded on the Adverse Events CRF. The Common Terminology Criteria for Adverse Events (CTCAE version 4.03 – see appendices) or other more specific AE tools must be used *to* grade the severity of an event. Laboratory values need reporting as AEs only if abnormal and deemed clinically significant by the investigator

All adverse events must be recorded on the Adverse Events CRF with the following information:

- The severity grade using CTCAE version 4.03
- Its relationship to the study drug(s)
- Treatment changes
- Whether it constitutes a serious adverse event (SAE)

### 10.8.2 Late Toxicities

Late toxicities (AEs) which are deemed by the investigator to be attributed to protocol specified SABR treatment are to be reported on the AE CRF. Late Toxicities are defined as AEs directly attributed by the Investigator to SABR treatment on this study, recorded from 30 days post last MK-3475 treatment until 24 months following the last SABR treatment.

### 10.8.3 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect" on the Adverse Event CRF page.

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX +1-215 993-1220).

### 10.8.4 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them), including the pregnancy of a male participant's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the participant initiates new anticancer

therapy, whichever is earlier. All participants and female partners of male participants who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX +1 215 993-1220).

### 10.8.5 Serious Adverse Events

Adverse events and adverse drug reactions are considered 'serious' if they threaten life or function.

SAEs include 'Serious Adverse Drug Reactions'. During clinical investigations, adverse events may occur, which if suspected to be medicinal product related ('adverse drug reactions') might be significant enough to lead to important changes in the way the medicinal product is developed (e.g. change in dose, population, monitoring, consent). This is particularly true for reactions, which in their most severe form threaten life or function.

Due to the significant information they provide, Serious Adverse Events (including Serious Adverse Drug Reactions) require expedited reporting. SAEs are defined as any adverse event or adverse drug reaction which:

- Results in death (i.e. fatal/grade 5 CTC AE)
- Is life-threatening (i.e. grade 4 CTC AE)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation*
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Other significant medical event

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was immediately at risk of death at the time of event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

*An event that results in hospitalisation or prolongs an existing hospitalisation will not be considered a serious adverse event if the only reason for the hospitalisation or prolongation was:

- Administration of chemotherapy
- Administration of trial procedures
- Placement of a permanent intravenous catheter
- Hospice placement for terminal care
- Pre-trial scheduled elective surgery
- Outpatient hospitalisation for procedures such as:
  - Elective day surgery
  - Convenience purposes (e.g. transportation difficulties)

- Planned admission as part of supportive care for insertion of PEG tube or naso-gastric tube for commencement of enteral feeding (i.e. did not occur following urgent admission as a result of weight loss or other patient medical events)

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any participant from the time the consent is signed through 90 days following cessation of pembrolizumab treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to protocol treatment, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to protocol treatment that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.
SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220.

#### 10.8.5.1 Serious Adverse Event Reporting

**Trial Sites/Investigators**

All SAEs that occur from the time a participant has signed consent for the Trial to within 90 days of the final protocol-specified treatment, intervention or procedure or the initiation of new anti-cancer therapy, whichever is earlier, are required to be reported to the Sponsor whether or not considered related to the treatment under investigation.

The **Principal Investigator (PI)** or delegate must:

- Determine whether an AE is 'Serious'
- For SAEs, the PI or delegate must then ascertain the suspected cause
- Ascertain severity
- Record the SAE in the patients' medical records and submit an SAE form.
- Report the SAE on the Trial SAE form to Sponsor and Merck no later than 24 hours after becoming aware of the event. The investigator may be requested by the Sponsor or Merck to provide or obtain specific additional follow-up information in an expedited fashion for the purpose of safety assessment

#### 10.8.5.2 Sponsor Responsibility

The Sponsor is responsible for:

- Implementing and maintaining a suitable recording system to record information from all SAEs received from Trial Sites.
- Ensuring that the Coordinating Principal Investigator (CPI) is notified of each SAE to enable the SAE to be assessed by the CPI and any other appropriate reviewers for nature (expected/unexpected), causality and whether the TGA needs to be notified of the SAE.
- Notifying the TGA (Australia) in accordance with the regulatory authority's detailed guidance of any SUSARs that are fatal or life threatening as soon as possible but no later than 7 days after the site gained first knowledge of the event. Incomplete reports must be completed and forwarded as soon as possible within 8 additional calendar days. All

other SUSARs should be reported to the TGA within 15 days after the site gained first knowledge of the event.

- Considering information provided by (non-serious) adverse event data.
- Informing each trial site of new information arising from serious and non-serious adverse events and adverse drug reactions that may affect the conduct of the Trial, or the rights, interests, safety or wellbeing of trial patients.
- Notifying the TGA of any significant issue that has arisen from analysis of overseas reports or action that has been taken by another country's regulatory authority within 72 hours of first knowledge.

SAEs must be reported by completing the sponsor Trial SAE form and FAXING or Emailing to the following:

| | |
|---|---|
| Sponsor | Email: Safety_BaCT@Petermac.org |
| Merck Global Safety | +1-215-993-1220 |

SAE forms are required at the following points:

| | |
|---|---|
| Initial Report | Within one working day/24 hours of discovery or notification of the event. If the reporting of an SAE is delayed by more than 24 hours, an explanation must be provided. This report may be signed by a clinician who is not the treating doctor. |
| Incomplete Reports* | If all details are not available at the time of the initial report a completed report must be sent within the next 10 days. |
| Updated Report | If the event is not resolved (or is 'on-going') at the time of the initial report, the 'UPDATE: Outcome of Event' section' of the SAE Form must be completed and the form submitted to BaCT and the SAE reviewer as soon as the event is resolved (with or without sequelae) or if death has occurred. |

*The Investigator is ultimately responsible for reporting the SAE and must sign the final SAE report(s). Should this Investigator not be available to sign the initial SAE form within the 24-hour period, a comment to this effect must be written on the form and the form signed by the clinician attending to the patient at the time and faxed to the Sponsor. The investigator must sign the SAE form as soon as possible and re-fax to the Sponsor

The Investigator at the Trial Site is responsible for determining the local SAE reporting requirements of the responsible HREC and subsequently notifying the HREC of SAEs as required.

All participants with serious adverse events must be followed up for outcome.

#### 10.8.5.3 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and

reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX +1 215 993-1220).

For the time period beginning when the consent form is signed until treatment commences, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at first treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to protocol treatment, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of pembrolizumab, as defined in Section 10.8.3 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

# 11 STATISTICAL ANALYSIS PLAN

## 11.1 Statistical Analysis Plan Summary

This is a prospective, single arm Phase 1b/II study to evaluate the safety profile, efficacy and biological effects of SABR in combination with pembrolizumab in patients with oligometastatic renal cancer.

As the sample size of 30 in this study is a pragmatic one, to demonstrate a safety and efficacy signal, results are intended to be descriptive. Evidence that the combination is well tolerated, efficacious and generates activation of immune parameters will provide confidence to move to a more definitive and larger randomized study.

## 11.2 Statistical Analysis Plan

### 11.2.1 Populations for Analyses

- Enrolled participant population includes all participants who provided informed consent.
- Treated participant population (evaluable patients) is defined as the participants who completed at least one SABR treatment and received at least one dose of pembrolizumab. This is the primary population for the safety and efficacy analyses.

- Response-evaluable participants are those treated participants who have CT/MRI scans performed at respective follow-up visit.

### 11.2.2 Statistical methods

Demographics and baseline characteristics of patients will be summarized using descriptive statistics.

The analyses of the all endpoints will occur at 12 months after the last evaluable patient is recruited.

No imputation for missing data is intended.

### 11.2.3 Safety analysis

Safety will be assessed using CTCAE v4.03 and the maximum toxicity grade of each adverse event will be derived and presented in table format. The proportion of patients who suffer from grade 3 or higher toxicities (each toxicity and overall) will be provided along with its exact 95% CI for all patients who have received at least one dose of pembrolizumab and completed at least one SABR treatment. Events of clinical interest will be also tabulated (see Section 10.8.5.3 Events of Clinical Interest).

### 11.2.4 Time-to-event analysis

A cut-off date for follow-up will be determined at the time of analysis. The cut-off date will be chosen to enable data on follow-up to that date to be collected, where possible, on all living patients. All events occurring after this date will be ignored in the analysis in order to minimise reporting bias.

The Kaplan-Meier method will be used to describe TTLP, DPFS and OS curves. Estimates at 1 and 2 years will be provided with 95% confidence interval. TTLP will be assessed at lesion level and Kaplan-Meier estimates will be adjusted for patient effect.

### 11.2.5 Pain analysis

Pain will be described as change over time using linear mixed models. The linear mixed model will include time (as a factor) as fixed effect and patients as random effect. Mean and 95% confidence intervals will be calculated for each time point and the data will be displayed graphically. If strong floor effect is observed or if the assumptions of the model do not hold, simple descriptive statistics will be provided instead for each time point.

### 11.2.6 Response analysis

All tumour response measurements (pre- and post-treatment) must be recorded using the definitions of RECIST 1.1 following SABR treatment. RECIST assessments will take into account post-treatment inflammatory processes that occur after SABR treatment in pulmonary and liver tissues.

DCR, ORR at 3, 6, 12 and 24 months and best overall response will be described as percentages with exact 95% confidence intervals for: a) DCR; b) ORR at 3, 6, 12 and 24 months and c) best overall response. If at least one patient has non-target disease only with response classified as non-CR/non-PD, then the response rate of CR will be reported instead of CR+PR.

The change in lesions size over time will be displayed graphically on the subset of lesions with measurable disease at baseline, with each lesion represented as a separate line and line colour representing the radiotherapy modality (SABR or conventional RT).

### 11.2.7 Exploratory Endpoints

All exploratory endpoints (PD-L1 expression, TILs, peripheral blood markers and other markers) will be described over time using linear mixed models. The linear mixed model will include time as fixed effect (as factor) and patients as random effect. Mean and 95% confidence intervals will be calculated for each time point and the data will be displayed graphically. Contrasts from the LMM will be used to test whether there is a change in expression levels from baseline to post-treatment sample time points, baseline to cycle 8 and baseline to 12 months post SABR. Variable transformation may be required for some of the collected variables. If the assumptions of the model do not hold, simple descriptive statistics will be provided for each variable at each time point.

A number of further exploratory translational endpoints will be evaluated including

1. Primary and metastatic lesions for PD-L1 expression using immunohistochemistry.
   Protein expression of PD-L1 will be measured using a previous defined immunohistochemistry method on H&E stained slides using Merck's diagnostic PD-L1 assay. Changes in PD-L1 in primary and metastatic lesions (if accessible) will be evaluated. Levels of PD-L1 in Primary sample will be correlated with changes in levels of T cell activation and T cell immunosuppression from baseline to cycle 8 of pembrolizumab using spearman's correlation.

2. Primary and metastatic lesions for quantity of tumour infiltrating lymphocytes (TILs) using a previously defined method.
   TILs will be measured as a continuous variable using a previous defined method on H&E stained slides using percentage (%) infiltrating stromal located lymphocytic infiltration. Changes in TILs in primary and metastatic lesions (if accessible) will be evaluated. Levels of TILs in Primary sample will be correlated with changes in levels of T cell activation and T cell immunosuppression from baseline to cycle 8 of pembrolizumab using spearman's correlation.

3. Other immune endpoints including antibody titres and peripheral blood markers of immune activation and suppression

4. Seroconversion to a range of epitopes will be measured in serum samples. An assay to detect soluble PD-L1 assay will also be used.

### 11.2.8 Immune Endpoints Evaluation

It is expected that pembrolizumab will promote the anti-tumour immune response initiated by the SABR therapy. The working hypothesis is that the induced anti-tumour immune response will be systemic, and this will promote immune surveillance of metastatic lesions. The tumour microenvironment is characterized by an inverse relationship between effector T cells (Teff) and regulatory CD4+ T cells (Treg), tumour associated macrophages (TAM2) and myeloid derived suppressor cells (MDSCs). We expect that SABR+ pembrolizumab (MK-3475) will change this inverse Teff:Suppressor cell balance so that the Teff cells predominate over Tregs and MDSCs. Peripheral blood will be collected before and at intervals during therapy. Alterations in the above immune subsets will be determined by the following (but not limited

to); multi-parameter FACS for T cells (CD3, CD4, CD8, CD45RA, CCR7, CD45Ro), B (CD19), NK (CD3-CD56+CD16+), Treg (CD3,CD4, CD127, FoxP3) and MDSC subsets (CD14+HLADR- and lin-HLADR-CD33+CD15+). We will also examine the immune suppression molecules (TIM3) as well as activation molecules (OX-40) on PB T cell subsets to determine whether these change following treatment with SABR + pembrolizumab.

In the context of renal cancer, therapy-induced tumour-specific T cell responses are difficult to assess as tumour antigens are only partially described. Therefore, we will reveal therapy-induced T cell responses indirectly by examining the TCR repertoire for clonal expansion (next generation sequencing on Illumina).

Lastly, we will examine plasma levels of PD-L1 (sPD-L1) before, during and after therapy to examine whether there is a correlation between patient baseline PD-L1, and whether clinical response correlates with changes in sPD-L1 levels during or after therapy. This will be performed using a commercial ELISA kit assay (see laboratory manual).

### 11.2.9 Sample Size Calculation

This is a Phase Ib/II study to evaluate the safety profile and efficacy that would then be evaluated in a larger and more appropriately powered future study. The sample size of 30 patients is pragmatic.

The primary objective of the study is to provide a description of the safety profile of the combined SABR and pembrolizumab therapies. Table 8 illustrates different scenarios for grade 3 or 4 AEs rate ranging from 0% to 40% with the respective 95% exact confidence intervals, assuming 30 patients.

***Table 8: Confidence Intervals for Adverse Event Rates***

| Number of patients with grade $3^+$ AE | Grade $3^+$ AE rate | 95% confidence interval |
|---|---|---|
| 1 | 3% | 0% - 17% |
| 2 | 7% | 1% - 22% |
| 3 | 10% | 2% - 27% |
| 4 | 13% | 4% - 31% |
| 5 | 17% | 6% - 35% |
| 6 | 20% | 8% - 39% |
| 7 | 23% | 10% - 42% |
| 8 | 27% | 12% - 46% |
| 9 | 30% | 15% - 49% |
| 10 | 33% | 17% - 53% |
| 11 | 37% | 20% - 56% |
| 12 | 40% | 23% - 59% |

Expected toxicities related to the pembrolizumab treatment are listed in the Investigator's Brochure. Therefore, immune related events such as hypothyroidism, pneumonitis, and colitis are expected. They should occur in <5%. Pneumonitis and colitis are considered to be the most serious but are rare events. Immune events and other events of clinical interest will be monitored for closely in this study, with early stopping rules as detailed below.

Recruitment will occur over a two-year period. An interim analysis after 15 patients completes 6 months of follow-up will be conducted for presentation purpose. The final analyses will be at the completion of 12 months after the last participant has completed SABR treatment.

#### 11.2.10 Early Termination Criteria

A Safety Monitoring Committee (SMC) will be formed prior to trial activation, to review the information from the safety analyses performed after the first 12 patients have completed SABR and 12 weeks of pembrolizumab treatment. The Trial Management Committee (TMC), will have responsibility for any final decisions about protocol stopping or modification.

Consideration of the cessation of participant accrual will occur if an unacceptable rate of toxicity is detected. The expected rates of grade 3+ pneumonitis and colitis are expected to be less than 5%. Thus, after 12 patients have completed 12 weeks of follow up following treatment, consideration by the SMC will be given to stopping the trial if any of the following is observed:

a. The number of ≥ grade 3 pneumonitis toxicity events is ≥ 2 *(expected rate of <5%)*
b. The number of ≥ grade 3 bowel toxicity events is ≥ 2 *(expected rate of <5%)*

If the true grade $3^+$ pneumonitis and bowel toxicities rates are 5%, the probability of early stopping due to unacceptable toxicity rate is 22% assuming the two types of toxicities are independent.

#### 11.2.11 Deviations

Any deviations from the statistical plan should be described and justified in the protocol (i.e. protocol amendment) or in the statistical report.

## 12 LABELLING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 12.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 9.

***Table 9: Product Descriptions***

| Product Name & Potency | Dosage Form |
|---|---|
| Pembrolizumab 100 mg/ 4mL | Solution for Injection |

### 12.2 Packaging and Labelling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

### 12.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

### 12.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

### 12.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## 13 ADMINISTRATIVE AND REGULATORY DETAILS

### 13.1 Confidentiality

The trial will be conducted in accordance with applicable Privacy Acts and Regulations. All information regarding trial participants must be treated in strict confidence. Data, which identify any trial participant, must not be revealed to anyone not directly involved in the trial or the clinical care of that participant. An exception is where the trial participant has provided written consent for his/her records to be included in source document verification. In this instance, the records may be inspected by a representative of a government regulatory authority for the purposes of official inspection. Records must be made available for inspection on the understanding that all information relating to trial participants will be treated in strict professional confidence.

### 13.2 Ethical Principles and Regulatory Compliance

The trial will be conducted according to the following regulations and guidelines:

- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Australia, July 2000)
- The Australian Code for Responsible Conduct of Research (August 2007)
- Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (last amended by the World Medical Association, 2008)
- National Statement on Ethical Conduct in Human Research, (Australia, 2007)

This Protocol, including the Participant Information Sheet and Consent Form (PICF) must be approved by the responsible HREC before enrolment of trial participants.

### 13.3 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well-being of the trial participant requires that an alternative treatment be used, the trial shall be

conducted exactly as described in the approved protocol. Any deviation from the protocol must be recorded and explained.

### 13.4 Informed Consent

The Principal Investigator or delegate is responsible for ensuring that signed written Informed Consent is obtained from trial participants before trial entry.

### 13.5 Data Management

Trial participants are to be identified by initials and trial registration number. All de-identified study data collected on electronic CRFs and source documents will be kept in a separate study specific de-identified database at BaCT. All trial data required for the monitoring and analysis of the study will be recorded electronically on the Electronic Data Capture e-system provided by BaCT. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. Site investigators will be asked to confirm the accuracy of completed eCRFs by signing key eCRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites and copies provided to BaCT when requested. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data. BaCT will conduct analysis from data stored in the patient database, kept in a secure location, with all de-identified. BaCT shall complete two reports: the first report will be after 15 patients completes 6 months of follow-up for presentation purpose only and the final report will be at 12 months from the completion of the last participant’s SABR treatment.

### 13.6 Source Documentation

Source documents relating to the study must be maintained by the study site. Source documents may include (but are not limited to) a participant’s medical history, site trial history, hospital records/charts, radiological investigations, laboratory tests, pembrolizumab drug charts and radiotherapy treatment records (including verification films and portal images). All study-related source documentation must be retained for 15 years following completion of the study and be made available for checking or clarification of queries if required, in accordance with ICH-GCP Guidelines.

### 13.7 Quality Assurance Reviews

QA processes will be employed in different departments which will conform to recommended standards for that department.

### 13.8 Trial Management Committee (TMC)

The Trial Management Committee (TMC) will oversee the study planning and progress, and assess/implement recommendations from other committees (e.g. PMCC HREC).

The TMC will also consider recommendations from the Safety Monitoring Committee (SMC) about whether to continue the study as planned, modify, or stop it, based on the planned interim analyses or other information.

The TMC will meet on a regular basis and will consist of the Study Coordinating Principal Investigator, Principal Investigators, Associate Investigators, Medical Physicist, Statistician and Trial Manager.

### 13.9 Safety Monitoring Committee (SMC)

The Safety Monitoring Committee will consist of one independent Radiation Oncologist, one independent Medical Oncologist and the study statistician. They will meet to review the information from the safety analyses in Section 11.2.3 Safety Analysis in addition to the below:

1. Assessing the conduct and progress of the trial – accrual, treatment toxicity and serious adverse events.

## 14 PUBLICATION AND PRESENTATION POLICY

The TMC will be responsible for decisions regarding presentations and publications arising from this trial according to Sponsor guidelines.

## 15 REFERENCE LIST


1. AIHW, *Cancer in Australia: An Overview.* Canberra, ACT: AIHW, 2008: Cancer, 2008. Series no. 46, Cat. no. CAN 42.
2. Ferlay, J., H.R. Shin, et al., *Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008.* International journal of cancer, 2010. **127**(12): p. 2893-2917.
3. Chow, W.-H., S.S. Devesa, et al., *Rising incidence of renal cell cancer in the United States.* JAMA: the journal of the American Medical Association, 1999. **281**(17): p. 1628-1631.
4. Kane CJ, M.K., Ritchey J, Cooperberg MR, Carroll PR, *Renal cell cancer stage migration: analysis of the National Cancer Data Base.* Cancer, 2008. **113**(1): p. 78.
5. Maldazys JD, d.J., *Prognostic factors in metastatic renal carcinoma.* J Urol, 1986. **136**: p. 376–379.
6. Motzer, R.J., N.H. Bander, et al., *Renal-cell carcinoma.* N Engl J Med, 1996. **335**(12): p. 865-75.
7. Flanigan, R.C., S.C. Campbell, et al., *Metastatic renal cell carcinoma.* Current treatment options in oncology, 2003. **4**(5): p. 385-390.
8. Decker, D.A., V. Decker, et al., *Brain metastases in patients with renal cell carcinoma: prognosis and treatment.* Journal of Clinical Oncology, 1984. **2**(3): p. 169-173.
9. Motzer, R.J., T.E. Hutson, et al., *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* New England Journal of Medicine, 2007. **356**(2): p. 115-124.
10. Sternberg, C.N., I.D. Davis, et al., Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. Journal of Clinical Oncology, 2010. **28**(6): p. 1061-1068.
11. Escudier, B., T. Eisen, et al., *Sorafenib in advanced clear-cell renal-cell carcinoma.* New England Journal of Medicine, 2007. **356**(2): p. 125-134.
12. Hellman, S. and R.R. Weichselbaum, *Oligometastases.* J Clin Oncol, 1995. **13**(1): p. 8-10.
13. Weichselbaum, R.R. and S. Hellman, *Oligometastases revisited.* Nature Reviews Clinical Oncology, 2011. **8**(6): p. 378-382.
14. Tosco, L., H. Van Poppel, et al., Survival and impact of clinical prognostic factors in surgically treated metastatic renal cell carcinoma. European urology, 2013. **63**(4): p. 646-652.
15. Barney, J.D. and E. Churchill, Adenocarcinoma of the kidney with metastasis to the lung cured by nephrectomy and lobectomy. J urol, 1939. **42**(Sept): p. 269-274.
16. Murthy, S.C., K. Kim, et al., *Can we predict long-term survival after pulmonary metastasectomy for renal cell carcinoma?* The Annals of thoracic surgery, 2005. **79**(3): p. 996-1003.
17. Assouad, J., B. Petkova, et al., *Renal cell carcinoma lung metastases surgery: pathologic findings and prognostic factors.* The Annals of thoracic surgery, 2007. **84**(4): p. 1114-1120.
18. Ljungberg, B., K. Bensalah, et al., *EAU Guidelines on Renal Cell Carcinoma: 2014 Update.* European urology, 2015.
19. Juusela, H., K. Malmio, et al., *Preoperative irradiation in the treatment of renal adenocarcinoma.* Scandinavian journal of urology and nephrology, 1977. **11**(3): p. 277-281.
20. Kjaer, M., P.L. Frederiksen, et al., Postoperative radiotherapy in stage II and III renal adenocarcinoma. A randomized trial by the Copenhagen Renal Cancer Study Group. International Journal of Radiation Oncology* Biology* Physics, 1987. **13**(5): p. 665-672.
21. Kjaer, M., P. Iversen, et al., A Randomized Trial of Postoperative Radiotherapy Versus Observation in Stage II and III Renal Adenocarcinoma. Scandinavian journal of urology and nephrology, 1987. **21**(4): p. 285-289.
22. Finney, R., The Value of Radiotherapy in the Treatment of Hypernephroma,Äêa Clinical Trial. British journal of urology, 1973. **45**(3): p. 258-269.

23. Michalski, J.M., *Kidney, renal pelvis, and ureter.* Principles and practice of radiation therapy. Perez CA, Brady LW, Halperin EC, Schmidt-Ullrich R (red.) Lippincott Williams & Wilkins, Philadelphia, USA, 2004: p. 1649-63.
24. Siva, S., D. Pham, et al., A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. BJU international, 2012. **110**(11b): p. E737-E743.
25. Ning, S., K. Trisler, et al., Radiobiologic studies of radioimmunotherapy and external beam radiotherapy in vitro and in vivo in human renal cell carcinoma xenografts. Cancer, 1997. **80**(S12): p. 2519-2528.
26. DiBiase, S.J., R.K. Valicenti, et al., Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: support for dose escalation based on a biological model. The Journal of urology, 1997. **158**(3): p. 746-749.
27. Kim, J.-G., M.-T. Park, et al., *Epigenetics Meets Radiation Biology as a New Approach in Cancer Treatment.* International Journal of Molecular Sciences, 2013. **14**(7): p. 15059-15073.
28. Finkelstein, S.E., R. Timmerman, et al., *The confluence of stereotactic ablative radiotherapy and tumor immunology.* Clinical and Developmental Immunology, 2011. **2011**.
29. Salama, J.K., M.D. Hasselle, et al., Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. Cancer, 2012. **118**(11): p. 2962-70.
30. Timmerman, R., R. McGarry, et al., Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol, 2006. **24**(30): p. 4833-9.
31. Chang, E.L., A.S. Shiu, et al., Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. J Neurosurg Spine, 2007. **7**(2): p. 151-60.
32. Nelson, J.W., D.S. Yoo, et al., *Stereotactic body radiotherapy for lesions of the spine and paraspinal regions.* Int J Radiat Oncol Biol Phys, 2009. **73**(5): p. 1369-75.
33. Ryu, S., J.Y. Jin, et al., Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. Cancer, 2007. **109**(3): p. 628-36.
34. Sahgal, A., D.A. Larson, et al., *Stereotactic body radiosurgery for spinal metastases: a critical review.* Int J Radiat Oncol Biol Phys, 2008. **71**(3): p. 652-65.
35. Masucci, G.L., E. Yu, et al., Stereotactic body radiotherapy is an effective treatment in reirradiating spinal metastases: current status and practical considerations for safe practice. Expert Rev Anticancer Ther, 2011. **11**(12): p. 1923-33.
36. Yamada, Y., D.M. Lovelock, et al., Multifractionated image-guided and stereotactic intensity-modulated radiotherapy of paraspinal tumors: a preliminary report. Int J Radiat Oncol Biol Phys, 2005. **62**(1): p. 53-61.
37. Teh, B., C. Bloch, et al., The treatment of primary and metastatic renal cell carcinoma (RCC) with image-guided stereotactic body radiation therapy (SBRT). Biomed Imaging Interv J, 2007. **3**(1): p. e6.
38. Katz, A.W., M. Carey-Sampson, et al., *Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases.* Int J Radiat Oncol Biol Phys, 2007. **67**(3): p. 793-8.
39. Rusthoven, K.E., B.D. Kavanagh, et al., Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol, 2009. **27**(10): p. 1572-8.
40. Goodman, K.A., E.A. Wiegner, et al., *Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies.* Int J Radiat Oncol Biol Phys, 2010. **78**(2): p. 486-93.
41. Lee, M.T., J.J. Kim, et al., Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol, 2009. **27**(10): p. 1585-91.

42. Okunieff, P., A.L. Petersen, et al., *Stereotactic Body Radiation Therapy (SBRT) for lung metastases.* Acta Oncol, 2006. **45**(7): p. 808-17.
43. Rusthoven, K.E., B.D. Kavanagh, et al., Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol, 2009. **27**(10): p. 1579-84.
44. Timmerman, R., R. Paulus, et al., Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA, 2010. **303**(11): p. 1070-6.
45. Kothari, G., F. Foroudi, et al., Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: A systematic review. Acta Oncol, 2014: p. 1-10.
46. Ranck, M.C., D.W. Golden, et al., Stereotactic body radiotherapy for the treatment of oligometastatic renal cell carcinoma. American journal of clinical oncology, 2012.
47. Vogelbaum, M.A., L. Angelov, et al., Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin. Journal of neurosurgery, 2006. **104**(6): p. 907-912.
48. Boyd, T.S. and M.P. Mehta, *Stereotactic radiosurgery for brain metastases.* Oncology (Williston Park, NY), 1999. **13**(10): p. 1397.
49. Lo, S.S., A.J. Fakiris, et al., *Stereotactic body radiation therapy: a novel treatment modality.* Nature Reviews Clinical Oncology, 2009. **7**(1): p. 44-54.
50. Siva, S., M. MacManus, et al., *Stereotactic radiotherapy for pulmonary oligometastases: a systematic review.* Journal of Thoracic Oncology, 2010. **5**(7): p. 1091-1099.
51. Day, D., Y. Kanjanapan, et al., *Patterns of care for metastatic renal cell carcinoma in Australia.* BJU international, 2015. **116**(S3): p. 36-41.
52. North, S.A., Management of advanced kidney cancer: Canadian Kidney Cancer Forum consensus update. Canadian Urological Association Journal, 2015. **9**(5-6): p. 164.
53. Pickering, L.M., M.O. Mahgoub, et al., *Is observation a valid strategy in metastatic renal cell carcinoma?* Current opinion in urology, 2015. **25**(5): p. 390-394.
54. Matzinger, P., *Tolerance, danger, and the extended family.* Annual review of immunology, 1994. **12**(1): p. 991-1045.
55. Matzinger, P., *The danger model: a renewed sense of self.* Science Signalling, 2002. **296**(5566): p. 301.
56. Obeid, M., A. Tesniere, et al., *Calreticulin exposure dictates the immunogenicity of cancer cell death.* Nature medicine, 2006. **13**(1): p. 54-61.
57. Apetoh, L., F. Ghiringhelli, et al., Toll-like receptor 4–dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nature medicine, 2007. **13**(9): p. 1050-1059.
58. Ghiringhelli, F., L. Apetoh, et al., Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat Med, 2009. **15**(10): p. 1170-8.
59. Chakraborty, M., S.I. Abrams, et al., External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. Cancer Research, 2004. **64**(12): p. 4328-4337.
60. Schaue, D., J.A. Ratikan, et al., *Maximizing tumor immunity with fractionated radiation.* International Journal of Radiation Oncology* Biology* Physics, 2011.
61. Siva, S., J. Callahan, et al., Asbcopal effects after conventional and stereotactic lung irradiation of non-small cell lung cancer. Journal of Thoracic Oncology, 2013.
62. Formenti, S.C. and S. Demaria, *Systemic effects of local radiotherapy.* The Lancet Oncology, 2009. **10**(7): p. 718-726.
63. Park, H.J., R.J. Griffin, et al., Radiation-induced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). Radiat Res, 2012. **177**(3): p. 311-27.

64. Fuks, Z. and R. Kolesnick, *Engaging the vascular component of the tumor response.* Cancer Cell, 2005. **8**(2): p. 89-91.
65. Lee, Y., S.L. Auh, et al., Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood, 2009. **114**(3): p. 589-595.
66. Lugade, A.A., J.P. Moran, et al., Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. The Journal of Immunology, 2005. **174**(12): p. 7516-7523.
67. Verbrugge, I., J. Hagekyriakou, et al., Radiotherapy increases the permissiveness of established mammary tumors to rejection by immunomodulatory antibodies. Cancer Res, 2012. **72**(13): p. 3163-74.
68. Dewan, M.Z., A.E. Galloway, et al., Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti–CTLA-4 antibody. Clinical Cancer Research, 2009. **15**(17): p. 5379-5388.
69. Pilones, K.A., C. Vanpouille-Box, et al., *Combination of Radiotherapy and Immune Checkpoint Inhibitors.* Semin Radiat Oncol, 2015. **25**(1): p. 28-33.
70. Deng, L., H. Liang, et al., *Irradiation and anti–PD-L1 treatment synergistically promote antitumor immunity in mice.* The Journal of clinical investigation, 2014. **124**(2): p. 0-0.
71. Filatenkov, A., J. Baker, et al., Ablative Tumor Radiation Can Change the Tumor Immune Cell Microenvironment to Induce Durable Complete Remissions. Clinical Cancer Research, 2015: p. clincanres. 2824.2014.
72. Park, S.S., H. Dong, et al., *PD-1 Restrains Radiotherapy-Induced Abscopal Effect.* Cancer immunology research, 2015: p. canimm. 0138.2014.
73. Sharabi, A., C. Nirschl, et al., Antigen-specific immune responses in melanoma using stereotactic radiotherapy combined with anti-PD1 checkpoint blockade. Cancer Research, 2014. **74**(19 Supplement): p. 635-635.
74. Postow, M.A., M.K. Callahan, et al., *Immunologic correlates of the abscopal effect in a patient with melanoma.* New England Journal of Medicine, 2012. **366**(10): p. 925-931.
75. Yamamoto, M., T. Serizawa, et al., Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. The Lancet Oncology, 2014. **15**(4): p. 387-395.
76. Pastorino, U., M. Buyse, et al., *Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases.* J Thorac Cardiovasc Surg, 1997. **113**(1): p. 37-49.
77. Brahmer, J.R., C.G. Drake, et al., Phase I study of single-agent anti–programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. Journal of Clinical Oncology, 2010. **28**(19): p. 3167-3175.
78. Motzer, R.J., B.I. Rini, et al., *Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial.* Journal of Clinical Oncology, 2015. **33**(13): p. 1430-1437.
79. Golden, E.B., A. Chhabra, et al., Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. The Lancet Oncology, 2015. **16**(7): p. 795-803.
80. Ridolfi, L., F. de Rosa, et al., Radiotherapy as an immunological booster in patients with metastatic melanoma or renal cell carcinoma treated with high-dose Interleukin-2: evaluation of biomarkers of immunologic and therapeutic response. J Transl Med, 2014. **12**: p. 262.
81. Derer, A., B. Frey, et al., Immune-modulating properties of ionizing radiation: rationale for the treatment of cancer by combination radiotherapy and immune checkpoint inhibitors. Cancer Immunol Immunother, 2015.
82. Fowler, J.F., The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol, 1989. **62**(740): p. 679-94.

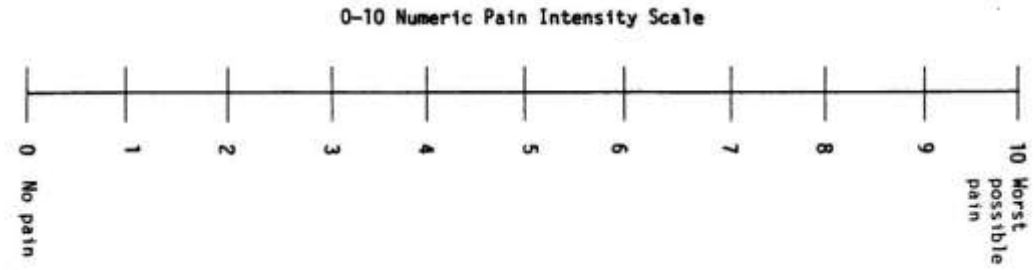
83. ICRU, Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT): Contents. Journal of the ICRU, 2010. **10**(1): p. NP.
84. ICRU, *Prescribing I. Recording and Reporting Photon Beam Therapy. ICRU Report 50*, 1993, International Comission on Radiation Units and Measurement: Bethesda MD.
85. ICRU, *Prescribing I. Recording and Reporting Photon Beam Therapy (supplement to ICRU report 50)*, 1999, International Commission on Radiation Units and Measurement: Bethesda, MD.
86. Wambersie, A. and T. Landberg, *ICRU Report 62: Prescribing, recroding, and reporting photon beam therapy (supplement to ICRU report 50)*, 1999, International Comission on Radiation Units and Measurements: Bethesda, MD.
87. Benedict, S.H., K.M. Yenice, et al., *Stereotactic body radiation therapy: the report of AAPM Task Group 101.* Med Phys, 2010. **37**(8): p. 4078-101.
88. Kirkpatrick, J.P., A.J. van der Kogel, et al., *Radiation dose-volume effects in the spinal cord.* Int J Radiat Oncol Biol Phys, 2010. **76**(3 Suppl): p. S42-9.
89. Mayo, C., E. Yorke, et al., *Radiation associated brainstem injury.* Int J Radiat Oncol Biol Phys, 2010. **76**(3 Suppl): p. S36-41.
90. Kased, N., K. Huang, et al., *Gamma knife radiosurgery for brainstem metastases: the UCSF experience.* J Neurooncol, 2008. **86**(2): p. 195-205.
91. Lorenzoni, J.G., D. Devriendt, et al., Brain stem metastases treated with radiosurgery: prognostic factors of survival and life expectancy estimation. Surg Neurol, 2009. **71**(2): p. 188-95; discussion 195, 195-6.
92. Kavanagh, B.D., C.C. Pan, et al., *Radiation dose-volume effects in the stomach and small bowel.* Int J Radiat Oncol Biol Phys, 2010. **76**(3 Suppl): p. S101-7.
93. Pan, C.C., B.D. Kavanagh, et al., *Radiation-associated liver injury.* Int J Radiat Oncol Biol Phys, 2010. **76**(3 Suppl): p. S94-100.
94. Wolchok, J.D., A. Hoos, et al., Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical Cancer Research, 2009. **15**(23): p. 7412-7420.
95. Fourney, D.R., E.M. Frangou, et al., Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. J Clin Oncol, 2011. **29**(22): p. 3072-7.
96. Fisher, C.G., C.P. DiPaola, et al., A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine (Phila Pa 1976), 2010. **35**(22): p. E1221-9.
97. Cox, B.W., D.E. Spratt, et al., International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys, 2012. **83**(5): p. e597-605.

**16 APPENDICES**

# Appendix 1: ECOG Performance Status

| Grade | Description |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |
| * As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair. | |

# Appendix 2: Numerical Pain Rating Scale




From:
Mirels, H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathological fractures. Clin Orthop Relat Res 1989;249:256-64.

# Appendix 3: Spinal Stability

Spine Instability Neoplastic Score (SINS)
*From Fourney et al[95] and Fisher et al[96]*

| SINS Component | Score |
|---|---|
| Location | |
| Junctional (occiput-C2, C7-T2, T11-L1, L5-S1) | 3 |
| Mobile spine (C3-C6, L2-L4) | 2 |
| Semirigid (T3-T10) | 1 |
| Rigid (S2-S5) | 0 |
| Pain* | |
| Yes | 3 |
| Occasional pain but not mechanical | 1 |
| Pain-free lesion | 0 |
| Bone lesion | |
| Lytic | 2 |
| Mixed (lytic/blastic) | 1 |
| Blastic | 0 |
| Radiographic spinal alignment | |
| Subluxation/translation present | 4 |
| De novo deformity (kyphosis/scoliosis) | 2 |
| Normal alignment | 0 |
| Vertebral body collapse | |
| > 50% collapse | 3 |
| < 50% collapse | 2 |
| No collapse with > 50% body involved | 1 |
| None of the above | 0 |
| Posterolateral involvement of spinal elements† | |
| Bilateral | 3 |
| Unilateral | 1 |
| None of the above | 0 |

# Appendix 4: Radiotherapy

1. Spinal Metastases Volumes

The international spine radiosurgery consortium anatomic classification (figure 1) will be used.

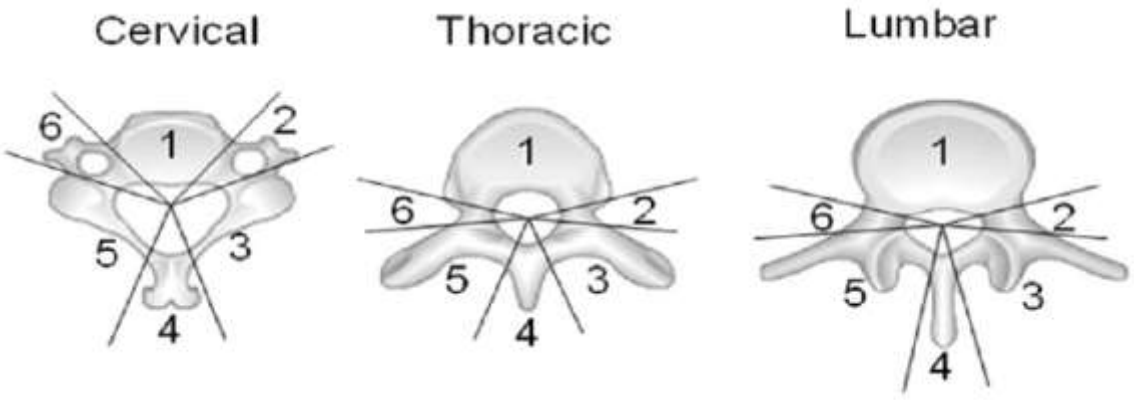



Figure 1 Anatomical Classification used by International Spine Radiosurgery Consortium (from Cox et al[97])

Underlying principles from the consensus guidelines[97] is shown in table 1

| GTV Involvement | CTV Description |
|---|---|
| Any portion of the vertebral body | Include the entire vertebral body |
| Lateralised within the vertebral body | Include the entire vertebral body and the ipsilateral pedicle/transverse process |
| Diffusely involves the vertebral body | Include the entire vertebral body and the bilateral pedicles/transverse processes |
| GTV involves vertebral body and unilateral pedicle | Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina |
| GTV involves vertebral body and bilateral pedicles/transverse processes | Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae |
| GTV involves unilateral pedicle | Include pedicle, ipsilateral transverse process, and ipsilateral lamina ± vertebral body |
| GTV involves unilateral lamina | Include lamina, ipsilateral pedicle/transverse process, and spinous process |
| GTV involves spinous process | Include entire spinous process and bilateral laminae |

In summary for spinal SABR the international guidelines[97] for contouring GTV, CTV and PTV in spinal radiosurgery are:

GTV: - Contour gross tumour using all available imaging
- Including epidural and paraspinal components of tumour

CTV: - Include abnormal marrow signal suspicious for microscopic spread
- Include bony CTV expansion to account for subclinical spread
- Should contain GTV

- Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or

when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression.

PTV: - Uniform expansion around the CTV
- CTV to PTV margin 2mm
- Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised
- Never overlaps with cord
- Should contain entire GTV and CTV

Pictorial Representations of Spinal Target Volumes
To follow consensus clinical target volume contours for spinal stereotactic radiosurgery [97].

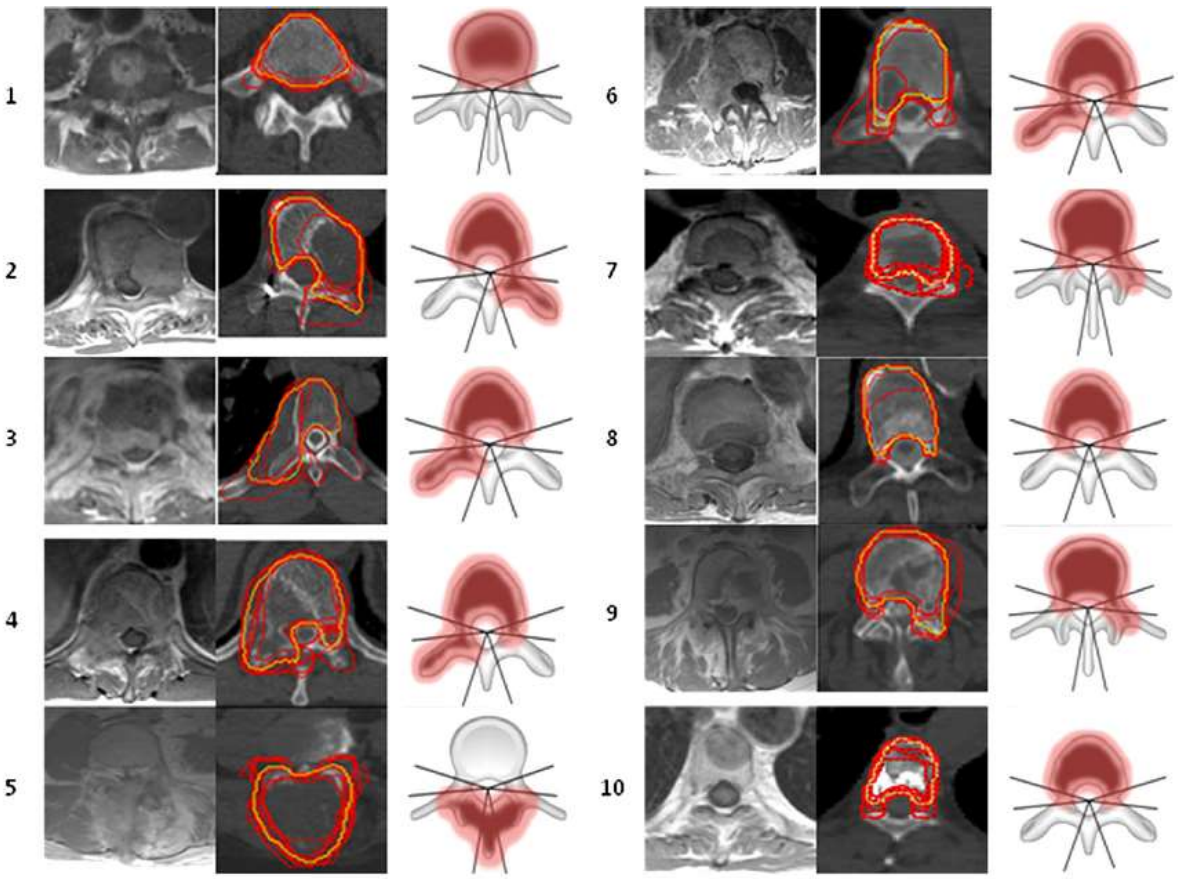



**Fig. 2.** Consensus clinical target volume contours for spinal stereotactic radiosurgery. Red indicates individual contours and orange indicates consensus contours.

Organ at Risk – Brachial Plexus Contouring
BRACHIAL PLEXUS (C5-T1)* (FROM TROG 09.02 CHISEL)
1. Identify the T1 vertebral body – T1 nerve root *(fig 2)* is inferior to the neck of first rib, at the lower half of T1 vertebral border, and C8 nerve root *(fig 1)* is cranial to the neck of first rib, at C7/T1 level
2. C7, C6 and C5 nerve roots can be found alongside the upper part of their respective vertebral bodies, but can be difficult to identify
3. Identify Scalenus Anterior and Scalenus Medius
a. The trunks of brachial plexus run between Scalenus Anterior and Scalenus