Title: Sequencing of Stereotactic Ablative Body Radiotherapy in combination with PD-1 blockade using Pembrolizumab in Metastatic Non-Small Cell Lung Carcinoma (SABRseq)

Short title: Sequencing of SABR and Pembrolizumab in Lung Cancer (SABRseq)

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FOREWORD

This document contains confidential information. This information should not be disclosed, other than to those involved in the execution or ethical review of the study, without written authorisation from sponsor.

COMPLIANCE STATEMENT

This trial will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) and Good Clinical Practice (GCP). In addition, the trial will be conducted in compliance will all applicable laws and regulatory requirements relevant to the use of new therapeutic agents in Australia and any other participating country. Agreement of the investigator(s) to conduct and administer this trial in accordance with the protocol and associated regulations will be documented in the trial agreements with the Sponsor and other forms required by national authorities in the country where the trial site is located.

The Investigator(s) is responsible for ensuring the privacy, safety and welfare of the patients during and after the trial.

The Principal Investigator at each site has the overall responsibility for the conduct and administration of the trial at their site, and for conduct with the trial site management, the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), and local authorities.

VARIATIONS TO THE PROTOCOL

No changes from the final approved (signed) protocol will be initiated without the ethics committee's prior written approval of favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the patients or when the change involves only the logistics or administration.

PROTOCOL HISTORY

Version No	Date	Author	Reason
1.0	19/09/2017	Shankar Siva	
1.1	08/01/2018	Shankar Siva	Updated dose modification from MSD/Merck
1.2	18/07/2018	Shankar Siva	Updated data on PDL1 staining which will expand eligibility

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 where applicable as 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, Canadian Health Authority 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 publically 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

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ABBREVIATIONS

ANC	Absolute neutrophil count
AUC	Area under the curve
BaCT	Centre for Biostatistics & Clinical Trials
BSA	Body Surface Area
CRF	Case Report Forms
CRT	Conformal Radiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
ECOG	Eastern Co-operative Oncology Group
FBE	Full blood examination
FDG-PET	Fluorodeoxyglucose – Positron Emission Tomography
FDG-PET-CT	FDG-PET computed tomography
FFS	Failure-free survival
GCP	Good Clinical Practice
Hb	Haemoglobin
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
IHC	Immunohistochemistry
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OS	Overall survival
PET	Positron Emission Tomography
PICF	Patient Information Sheet and Consent Form
Plt	Platelets
QA	Quality Assurance
RT	Radiation Therapy
RTP	Radiotherapy Treatment Planning
SABR	Stereotactic Ablative Body Radiotherapy
SAE	Serious Adverse Event
SUSAR	Serious unexpected suspected adverse events
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee

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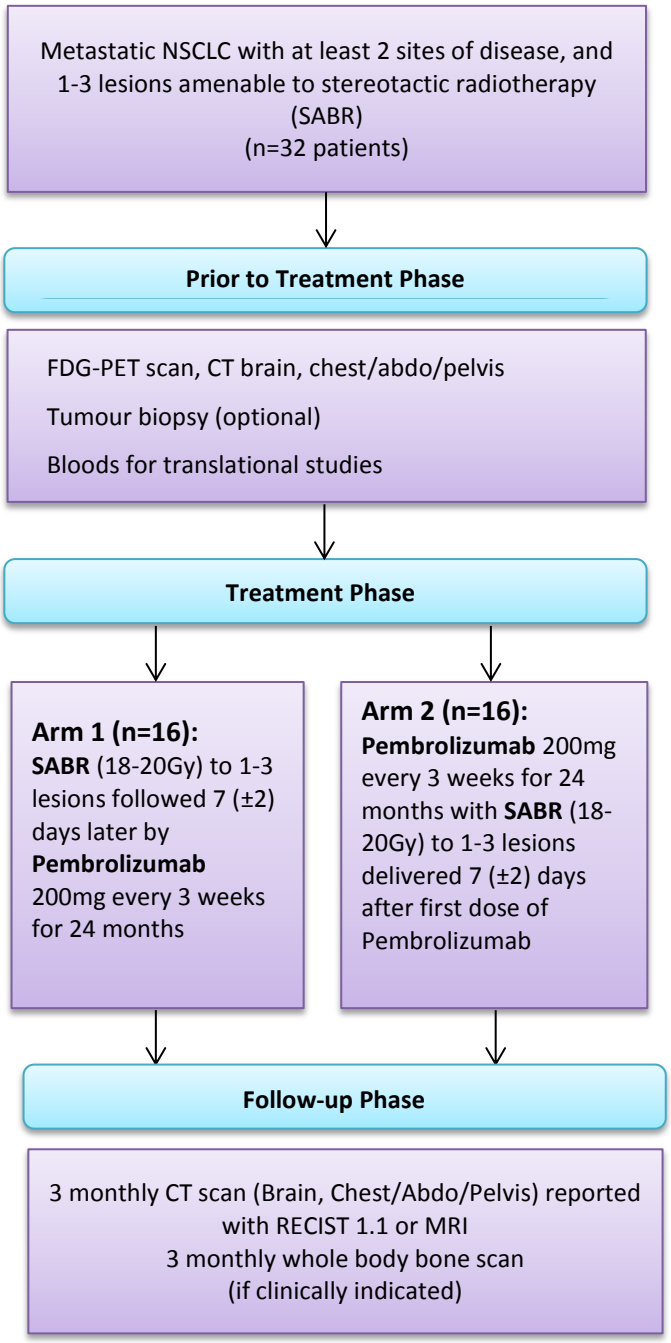
1. Synopsis

Title	Sequencing of Stereotactic Ablative Body Radiotherapy in combination with PD-1 blockade using Pembrolizumab in Metastatic Non-Small Cell Lung Carcinoma
Short title	Sequencing of SABR and Pembrolizumab in Lung Cancer (SABRSeq)
Sponsor	Peter MacCallum Cancer Centre
Study design	Phase Ib, two arm randomised study
Study objectives	**Primary Objective:** To assess common toxicities associated with pembrolizumab when given before or after SABR in patients with metastatic NSCLC. **Secondary Objectives:** • To describe response rate in: a) lesions treated with SABR, b) non-irradiated lesions and c) overall response. • To describe the event history (local progression, distant progression and death) of NSCLC patients treated with SABR in combination with pembrolizumab. • To estimate progression free survival and overall survival of NSCLC patients treated with SABR in combination with pembrolizumab. **Exploratory Objectives:** • Evaluate PD-L1 expression in baseline tissue. • Evaluate baseline and longitudinal cellular and molecular changes in archival tumour tissue, and/or fresh tumour biopsies. This will include, but not limited to tumour infiltrating lymphocytes (TILs), CD73 and other markers. • Evaluate baseline and longitudinal changes in immunological cellular subsets and cytokines within peripheral blood.
Number of sites	2 sites, one in Australia and one in Canada
Expected sample size	32 patients
Recruiting period	24 months

2. Trial Schema



3. Schedule of Events

Table 1: ARM 1 Schedule of events

Trial Phase:	**Screening Phase**	**Treatment Phase**			**Follow-up Phase**		**Progression**
Trial phase and windows	**Screening** -28 to -1	**SABR** Within 4 weeks of randomisation	**Day 1 Cycle 1** 7 days ± 2 days from SABR	**Day 1 Cycle 2-34** 3 days ± 2 days prior to each dose of pembrolizumab	**Safety Follow-up** 30 days ± 3 days from date of last dose of pembrolizumab	**Follow-up** 3 months ± 7 days from the last cycle of pembrolizumab	Upon first progression[1]
Clinical/Administrative Assessments							
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Demographics and Medical History	X						
Disease Specific Medical History including prior therapies	X						
SINS score for Spinal Targets	X						
Full Physical Examination	X		X	X			
Vital Signs and body measurements [2]	X		X	X		X	
ECOG Performance Status	X		X	X		X	
Pregnancy Test (β-HCG) [3]	X		X	X			
Review Adverse Events[4]	X	X	X	X	X	X	
SABR		X					
Pembrolizumab			X	X			
Review Prior/Concomitant Medications	X	X	X	X	X		
New Anti-Cancer Therapy Status					X	X	X
Survival status						X	

Trial Phase:	**Screening Phase**	**Treatment Phase**			**Follow-up Phase**		**Progression**
Trial phase and windows	**Screening** -28 to -1	**SABR** Within 4 weeks of randomisation	**Day 1 Cycle 1** 7 days ± 2 days from SABR	**Day 1 Cycle 2-34** 3 days ± 2 days prior to each dose of pembrolizumab	**Safety Follow-up** 30 days ± 3 days from date of last dose of pembrolizumab	**Follow-up** 3 months ± 7 days from the last cycle of pembrolizumab	Upon first progression[1]
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory							
Haematology[5]	X		X	X		As clinically indicated	
Biochemistry[6]	X		X	X			
Thyroid Function tests [7]	X		X	X			
Coagulation profile[8]	X		X	X			
Virology[9]	X						
Tumour Evaluation							
CT scan (Brain, Chest, Abdo, Pelvis) reported with RECIST 1.1 or MRI [10]	X			X		X	
Whole body bone scan [10] (if clinically indicated)	X			X		X	
Response assessment[10]				X		X	
FDG-PET[10]	X			X[11]			
Translational studies							
Metastatic tumour biopsy sample[12]	X					X	X
Primary tumour biopsy sample[13]	X						
Blood Collection[14] (serum and ctDNA)		X	X	X		X	X

Table 2: ARM 2 Schedule of events

Trial Phase:	**Screening Phase**	**Treatment Phase**			**Follow-up Phase**		**Progression**
Trial phase and windows	**Screening** -28 to -1	**Day 1 Cycle 1** 3 days ± 2 days prior to the first dose of pembrolizumab	**SABR** 7 days ± 2 days from cycle 1 day 1	**Day 1 Cycle 2-34** 3 days ± 2 days prior to each dose of pembrolizumab	**Safety Follow-up** 30 days ± 3 days from date of last dose of pembrolizumab	**Follow-up** 3 months ± 7 days from the last cycle of pembrolizumab	Upon first progression[1]
Clinical/Administrative Assessments							
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Demographics and Medical History	X						
Disease Specific Medical History including prior therapies	X						
SINS score for Spinal Targets	X						
Full Physical Examination	X	X		X			
Vital Signs and body measurements[2]	X	X		X		X	
ECOG Performance Status	X	X		X		X	
Pregnancy Test (β-HCG) [3]	X	X		X			
Review Adverse Events[4]	X	X	X	X	X	X	
SABR			X				
Pembrolizumab		X		X			
Review Prior/Concomitant Medications	X	X	X	X	X		
New Anti-Cancer Therapy Status					X	X	X
Survival status						X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory							
Haematology[5]	X	X		X		As clinically	

Trial Phase:	**Screening Phase**	**Treatment Phase**			**Follow-up Phase**		**Progression**
Trial phase and windows	**Screening** -28 to -1	**Day 1 Cycle 1** 3 days ± 2 days prior to the first dose of pembrolizumab	**SABR** 7 days ± 2 days from cycle 1 day 1	**Day 1 Cycle 2-34** 3 days ± 2 days prior to each dose of pembrolizumab	**Safety Follow-up** 30 days ± 3 days from date of last dose of pembrolizumab	**Follow-up** 3 months ± 7 days from the last cycle of pembrolizumab	Upon first progression[1]
Biochemistry[6]	X	X		X		indicated	
Thyroid Function tests [7]	X	X		X			
Coagulation profile[8]	X	X		X			
Virology[9]	X						
Tumour Evaluation							
CT scan (Brain, Chest, Abdo, Pelvis) reported with RECIST 1.1 or MRI [10]	X			X		X	
Whole body bone scan [10] (if clinically indicated)	X			X		X	
Response assessment[10]				X		X	
FDG-PET[10]	X			X[11]			
Translational studies							
Fresh tumour biopsy sample [12]	X					X	X
Archival tumour biopsy sample[13]	X						
Blood Collection [14] (serum and ctDNA)		X	X	X		X	X

Table 1 and 2 Footnotes

1. Beyond first progression, every effort should be made to record results of subsequent tumour assessments. In additional, details of any new anti-cancer treatment commenced is to be collected.
2. Vital signs include blood pressure, heart rate, respiratory rate and temperature. Body measurements including height and weight (height only required at screening).
3. Urine or serum pregnancy test for patient of childbearing potential should be performed within 7 days randomisation and also 72 hours before first dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
4. Baseline abnormalities 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 reported on completion of SABR, day 1 of every pembrolizumab cycle and at every follow-up visit. If at any time, a patient commences a new anti-cancer therapy, recording of adverse events is no longer required.

Laboratory Procedures/Assessments – All diagnostic laboratory tests should be performed within 10 days of randomisation (to determine eligibility), and also on day 1 ± 3 days of every cycle of pembrolizumab (unless otherwise specified)

5. Haematology: Haematocrit, haemoglobin, platelet count, white blood cell count (total and differential), red blood cell count, absolute neutrophil count and absolute lymphocyte count.
6. Biochemistry: calcium chloride, glucose, phosphorus, potassium, sodium, magnesium, total protein, Liver Function Tests: Albumin, Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), Gamma-Glutamyl Transferase (GGT, total bilirubin (+direct bilirubin if total bilirubin is elevated above the ULN), Kidney Function Tests: Urea, creatinine.
7. Thyroid Function tests: T3, T4 and TSH. To be performed at during screening, day 1 cycle and every 6 weeks thereafter.
8. Coagulation Profile: PT (INR), aPTT.
9. Virology: HIV, Hepatitis B and C tests only required for those patients at risk of prior or current active infection as determined by the investigator. To be performed within 21 days of randomisation.

Tumour evaluation

10. Radiological tumour assessments will be performed by CT scan (or MRI as required if tumour is in extremity) at screening (within 6 weeks of randomisation), prior to cycle 3, 5, 7 and every 3 cycles thereafter in the treatment phase. Then 3 monthly in the follow-up phase until the last patient recruited completes 24 months of follow-up, unless evidence of progression earlier. Whole body bone scan (WBBS) will be performed if clinically indicated at the same time points. Formal response assessment (using RECIST 1.1, irRECIST, Peter Mac Metabolic Response Criteria and PERCIST 1.0.) at each scheduled scan time point. Response should be confirmed with repeat imaging 4 to 8 weeks later by the same imaging modality. CT of brain only required at screening.
11. FDG PET at baseline and prior to cycle 5 of pembrolizumab. (note: a contemporaneous CT brain/chest/abdo pelvis performed at the same time will fulfill the CT requirement 3 month follow-up)

Biological Evaluations

12. A fresh biopsy of the primary or metastatic lesion will be performed at screening (within 12 weeks of randomisation). and 3 months post completion of SABR. This will ideally be the same site as biopsied before at screening. In event of disease progression, a sample from progressing metastatic site(s), if feasible, is requested. Refer to the SABRseq laboratory manual for further details on handling and shipping of tumour samples.
13. If a fresh biopsy of the primary or a metastatic lesion cannot be provided (e.g. inaccessible or patient safety concern) an archived specimen can be submitted only upon agreement from the study principal investigators. Refer to the SABRseq laboratory manual for further details on handling and shipping of tumour samples.
14. To be collected at screening, prior to SABR, prior to each pembrolizumab dose and 3 monthly during follow-up. Refer to the SABRseq laboratory manual for further details on blood sample collection, handling and shipping.

4. Background

4.1 Metastatic Non-Small Cell Carcinoma

Non-small cell carcinoma (NSCLC) is the ninth most common cancer in Australia and the fourteenth most common cancer worldwide (1, 2). The incidence of NSCLC 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 non-small cell carcinoma (mNSCLC) 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).

4.2 Stereotactic Ablative Body Radiotherapy and Evidence in 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 (1) 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 (2).

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 (3-6). Similar to intracranial stereotactic radiosurgery, SABR has been shown to be effective in the retreatment of metastases that progress following standard EBRT (7). Additionally, SABR has been shown to be very effective in palliating pain associated with spinal metastases (8, 9).

Several Phase I and II studies have investigated SABR for hepatic metastases using fixed RT doses (10), escalation RT doses (11, 12) and normal tissue complication probabilities (13). 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 (14) and dose-escalation (15) have demonstrated high rates of treated-metastasis control (89-96%) with promising 2-year survival rates (38-39%).

4.3 Stereotactic Radiotherapy for Non-Small Cell Lung Carcinoma

SABR is a therapeutic regimen associated with a high level of tumour control in the setting of primary non-small cell lung cancer. A systematic review of 3771 patients and 45 studies demonstrated a 2-year local control rate of 91% (95% CI: 90-93%) with a 2-year survival of 70% (95% CI: 67-72%). This was comparable with survival for surgery in stage I NSCLC in the cohort of 2038 patients also assessed in this study (68% [95% CI: 66-70]), regardless of patient differences in comorbidities (16). Similarly, a recent pooled meta-analysis of 2 randomised clinical trials that terminated early comparing SABR and surgery for stage I NSCLC showed survival compared favourably for the SABR cohort, with. Recurrence-free survival at 3 years was 86% (95% CI: 74–100) in the SABR group and 80% (65–97) in the surgery group (HR 0·69 [95% CI: 0·21–2·29], log-rank p=0·54)(17). Due to excellent control rates and promising survival after SABR in the setting of NSCLC, further clinical trials are underway evaluating the clinical efficacy of SABR in comparison to the current standard of care, surgery (18).

4.4 Stereotactic Ablative Body Radiotherapy for Metastatic Non-Small Cell Lung Carcinoma

Several studies have evaluated the efficacy of SABR in the context of oligometastatic NSCLC. A prospective phase II clinical trial by de Ruysscher et al. (19) evaluated 41 patients with oligometastatic disease. The 2-, and 3-year OS was 23.3%, and 17.5%, respectively in this cohort. Median progression-free survival (PFS) was 12.1 months (95% confidence interval 9.6–14.3); 1-year PFS was 51.3%, and both 2- and 3-year PFS was 13.6%. A systematic review by Ashworth et al. (20) of 49 studies reporting on outcomes of 2176 patients with 1-5 oligometastases treated with surgery or stereotactic radiotherapy. In this study (82%) had a controlled primary tumor. Overall survival (OS) outcomes were heterogeneous: 1 year OS: 15–100%, 2 year OS: 18–90% and 5 year OS: 8.3–86%. The median OS range was 5.9–52 months (overall median 14.8 months; for patients with controlled primary, 19 months). The median time to any progression was 4.5–23.7 months (overall median 12 months). Highly significant prognostic factors on multivariable analyses were: definitive treatment of the primary tumor, N-stage and disease-free interval of at least 6–12 months. In a subsequent individual patient data meta-analysis of 757 oligometastatic NSCLC cases by members of the same group (21), median OS was 26 months, 1-year OS 70.2%, and 5-year OS 29.4%. In those patients with metachronous presentation of oligometastases, the 5-year OS was 47.8%. These results suggest that local aggressive therapies including SABR may be warranted in selected patients with metastatic disease. In the context of oligoprogressive disease, the Colorado group have reported that the use of SABR at the progressing sites resulted in an increased median overall time taking crizotinib from 10.1 months to 28.1 months (22), with a subsequent median progression free survival after receiving SABR of 6.2 months (23).

4.5 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. The risk of treatment depends on the exact anatomical site of the metastatic 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 irradiated 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 non-small 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. Additionally, as there is a risk of pneumonitis with both pembrolizumab (discussed below) and radiotherapy, patients who have received more than 36Gy in 12 fractions (or equivalent) of radiotherapy to the lung within 6 months of study screening will be considered ineligible.

4.6 Immunity and Control of Lung 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.

4.7 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" (24, 25). 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 (26). 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 (27, 28). All of these molecules provide the tools for an improved recognition and killing by tumour-specific T cells (29). 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 (30). The ablative dose / fractionation spectrum employed by SABR heralds a potential for even greater augmentation of the tumouricidal immune response than conventional radiotherapy (31). Immunogenic responses at sites distant to the SABR therapy has already been reported by our group (32) and others (33). Ablative doses result in a greater degree of stromal / vascular damage, ceramide-induced endothelial cell damage and increased apoptosis of tumour cells (34, 35). 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(36). 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 (37). 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 (38). 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 (39, 40). 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 (41), allowing for induction of an anti-tumour immune response by relief of tumour-mediated immunosuppression. Similarly a report by Filatenkov et al. 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) (42). 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 (43). A further study in a melanoma model also found single fraction SABR synergised with anti-PD-1, with a possible dose response of 18 Gy of radiotherapy resulted in increased activation and proliferation of antigen-specific T-cells when compared to 12Gy (44).

4.8 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 combining immunostimulatory antibodies including anti-PD-1 antibody. In one study from Peter Mac (Verbrugge et al; (38)), 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 the combination of pembrolizumab 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. The incidence of abscopal effects have been reviewed by our group previously in both the preclinical (45) and clinical (46) settings. The abscopal effect is a rare but clinically recognised phenomenon. This effect was recently observed in a patient with melanoma treated with radiotherapy and ipilumumab (Postow et al. (47)). 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. Rationale for this study is supported by evidence of favorable immunological changes induced in the peripheral blood by the combination therapy.

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

4.9 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 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.

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). 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 ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.10 Preclinical and Clinical Trial Data

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

4.11 Safety of Pembrolizumab and Dosing Regimen

The safety profile of pembrolizumab has been well established from the initial phase I study (P001) and subsequent phase II and III studies and it has received approvals for use in Melanoma, NSCLC, head and Neck cancer.

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.

4.12 Efficacy of Pembrolizumab in Lung Cancer

The safety and efficacy of PD 1 inhibition with pembrolizumab in patients with advanced non-small cell has been investigated in a phase I clinical trial (48). Four hundred and ninety five patients with advanced NSCLC were treated with pembrolizumab (at a dose of either 2mg or 10mg per kilogram every 2 weeks or 10 mg per kilogram every 2 weeks). Treatment-related adverse events occurred in 351 patients (70.9%), with no clear difference according to dose or schedule. The most common treatment-related adverse events were fatigue, pruritus, and decreased appetite. Adverse events of grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related adverse events of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy. Pneumonitis of grade 3 or greater was observed in 9 patients (1.8%), including 1 (0.2%) who died. The overall response rate was 19.4% (95% confidence interval [CI], 16.0 to 23.2), which included a response rate of 18.0% (95% CI, 14.4 to 22.2) in the 394 previously treated patients and 24.8% (95% CI, 16.7 to 34.3) in the 101 previously untreated patients. The best overall response was stable disease in 21.8% of patients. The response rate was similar regardless of dose, schedule, and histologic analysis.

At the time of this analysis, 84.4% of patients with a response had no disease progression, and the median duration of response was 12.5 months (range, 1.0 to 23.3) in all patients, 10.4 months (range, 1.0 to 10.4) in previously treated patients, and 23.3 months (range, 1.0 to 23.3) in previously untreated patients. Median progression-free survival was 3.7 months (95% CI, 2.9 to 4.1) for all the patients, 3.0 months (95% CI, 2.2 to 4.0) for previously treated patients, and 6.0 months (95% CI, 4.1 to 8.6) for previously untreated patients. Median overall survival was 12.0 months (95% CI, 9.3 to 14.7) for all the patients, 9.3 months (95% CI, 8.4 to 12.4) for previously treated patients, and 16.2 months (95% CI, 16.2 to not reached) for previously untreated patients.

Biomarker analysis was conducted using the anti–PD-L1 antibody clone 22C3 (Merck) and a prototype immunohistochemical assay to determine the PD-L1 status. Among the 1143 screened patients, 824 had samples that could be evaluated by the clinical-trial assay, with a prevalence of 23.2% of patients with a proportion score of at least 50%, 37.6% with a score of 1 to 49%, and 39.2% with a score of less than 1% by the clinical-trial assay. After the pooling of data from the training and validation groups post hoc, evaluation according to quartile suggested that a higher proportion score was associated with a greater response rate within the group with a proportion score of 1 to 49% and the group with a score of at least 50%. The response rate for patients with a proportion score of at least 50% was 42.3% when those without disease that could be measured at baseline were included. Little difference in response rate was observed according to dose, schedule, or smoking status.

In the first line setting, In an open-label, phase 3 trial (KEYNOTE 24), 305 patients were randomly assigned with untreated advanced NSCLC with PD-L1 expression on at least 50% of tumour cells to receive either pembrolizumab (at a fixed dose of 200 mg every 3 weeks) or the investigator's choice of platinum-based chemotherapy. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. The median progression-free survival was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2 to 6.2) in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001). The estimated rate of overall survival at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P=0.005). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%), the median duration of response was longer (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+]), and treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%). This pivotal trial concluded that in patients with untreated advanced NSCLC and PD-L1 expression on at least 50% of tumour cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy. A second study, KEYNOTE 042 compared pembrolizumab with chemotherapy in previously untreated advanced NSCLC with PD-L1 expression on 1% to 100% of tumor cells. The study was positive with benefit for pembrolizumab over chemotherapy at all groups in the prespecified analysis at >50%, more than 20% and more than 1% PD-L1 expression.

In the second line and beyond setting, in a randomised phase 2/3 clinical trial (KEYNOTE-10), 1034 patients with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells were randomly assigned (1:1:1) in blocks of six per stratum with an interactive voice-response system to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m(2) every 3 weeks. In the total population, median overall survival was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg, and 8.5 months with docetaxel. Overall survival was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (hazard ratio [HR] 0.71, 95% CI 0.58-0.88; p=0.0008) and for pembrolizumab 10 mg/kg versus docetaxel (0.61, 0.49-0.75; p<0.0001). Median progression-free survival was 3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel, with no significant difference for pembrolizumab 2 mg/kg versus docetaxel (0.88, 0.74-1.05; p=0.07) or for pembrolizumab 10 mg/kg versus docetaxel (HR 0.79, 95% CI 0.66-0.94; p=0.004). Grade 3-5 treatment-related adverse events were less common with pembrolizumab than with docetaxel (43 [13%] of 339 patients given 2 mg/kg, 55 [16%] of 343 given 10 mg/kg, and 109 [35%] of 309 given docetaxel). The study concluded that pembrolizumab prolongs overall survival and has a favourable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer (>1%). These data establish pembrolizumab

as a new treatment option for this population and validate the use of PD-L1 selection.

Therefore for the purposes of this study, patients with PD-L1 staining of ≥ 1% in the previously treated setting and those with PD-L1 staining of ≥ 50% in the first line setting are of interest, as it is in these groups that pembrolizumab is FDA approved for use.

4.13 Rationale for Trial, Population and Selected 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 advanced NSCLC with disease progression that have 1-3 sites of disease amenable to SABR treatment. The primary objective of the study is to assess the safety profile, whilst efficacy and biological effects are secondary objectives. The patient cohort must have ≥ 1% PD-L1 staining on tumour biopsy or primary resection specimen for patients treated in the firstline or ≥1% PDL1 staining in patients who have had prior chemotherapy consistent with the approval status of pembrolizumab in lung cancer (US FDA, Canadian Health Authority or the Australian TGA) and with recent data from the KEYNOTE-042 study. Our hypothesis is that this treatment combination will have a safety profile that is clinically acceptable and demonstrate anti-tumour efficacy. We will test this hypothesis in the setting of two different sequences of SABR and anti-PD1 combinations.

The optimal sequence of checkpoint blockade therapy with radiotherapy into mainstream clinical practice is still subject to on-going investigation. Rationale for phased sequential treatment of anti-PD-1 therapy with radiotherapy is outlined below.

(i) Prior to Radiotherapy

* *Reverse T cell exhaustion and immunosuppression to restore tumor immunity.* There is now an intriguing link between immune microenvironment and response to therapies. Indeed, work done at the PMCC has demonstrated that tumours deficient of activated effector cells are significantly less responsive to the growth-inhibitory effects of localized radiotherapy (Haynes NM, Unpublished). PD-1 has the potential to shift the immune microenvironment of tumors in favor of immunity by reinvigorating the anti-cancer activity of tissue-resident, antigen educated T cells and reversing the suppressive phenotype of myeloid cells and plasmacytoid DCs.

(ii) Concurrent and/or Post Radiotherapy

* *Support T-cell based immune responses to newly exposed neoantigens.* Activity of checkpoint inhibitors is dependent on their being a pre-existing immune response to the cancer. Radiotherapy has the potential to engage immune responses to cancer by increasing the mutational load of tumors and in turn the expression of neoantigens needed to evoke the cytotoxic activity of T cells. Indeed there is strong evidence that neoantigens play a critical role in driving the strength of intratumoral T cell responses and may also influence tumor cell sensitivity to cancer immunotherapy (49). In this setting, anti-PD-1 has the

potential to regulate immunosuppression by augmenting the frequency and suppressive phenotype of myeloid cells within tumors post radiotherapy. It may also increase the function of newly activated tumor-reactive immune cells, by inhibiting PD-1 binding of its inhibitory ligand PD-L1; the expression of which can be induced within tumors by radiation therapy.

Whist the overlapping toxicities of SABR and pembrolizumab are not yet fully understood, few are expected. Safety will be monitored carefully throughout the trial in all patients (n=16 per arm). We hypothesize that augmentation of immunity in this subgroup of patients may enhance long-term control of the disease. It is anticipated that the findings of this study will serve as the basis for larger randomised studies in the future.

4.14 Rationale for Dose Selection/Regimen/Modification

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. On this basis the chosen dose of 200 mg q3 weekly represents an appropriate standard of care in the setting of previously treated NSCLC.

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. This dose is now the standard single-agent dose used in NSCLC and Head and Neck Cancer.

5. Trial Objectives

5.1 Hypothesis

This investigator driven Phase Ib study will examine the safety, efficacy and biological effects of two schedules of pembrolizumab, an antibody targeted against anti-programmed cell death 1 (PD-1), which will be given either before or after stereotactic ablative body radiotherapy (SABR) for metastatic NSCLC. We hypothesise that both arms i.e. 1) SABR followed by anti-PD-1 and; 2)anti-PD-1 with SABR after first cycle of pembrolizumab; will have clinically acceptable safety profiles with evidence of local and systemic efficacy; and that there will be differences in the immunological responses related to schedule of treatment.

5.2 Objectives

Primary objective:

To assess common toxicities associated with pembrolizumab in combination with SABR when SABR is given before or after first cycle of pembrolizumab in patients with metastatic NSCLC.

Secondary objectives:

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

- To describe response rate in: a) lesions treated with SABR, b) non-irradiated lesions and c) overall response, and compare between treatment arms
- To describe overall survival (OS) and progression free survival (PFS) and compare between treatment arms
- To describe the event history (progression at an irradiated lesion, progression at a non-irradiated lesion, appearance of a new lesion, ceasing treatment and death) of NSCLC patients treated with SABR in combination with pembrolizumab

Exploratory Objectives

- Evaluate PD-L1 expression in baseline tissue using immunohistochemistry.
- Evaluate baseline and longitudinal cellular and molecular changes in archival tumour tissue, and/or fresh tumour biopsies. This will include tumour infiltrating lymphocytes (TILs), CD73 and other markers.
- Evaluate longitudinal changes in immunological cellular subsets and cytokines within peripheral blood.

5.3 Endpoints

Primary Endpoint

- Toxicities associated with SABR in combination to pembrolizumab are defined as adverse events (AE's) considered possibly, probably or definitely related to the treatment. Safety (acute and long term) will be assessed using CTCAE version 4.03.

Secondary Endpoints:

- Response will be assessed by 4 different methods (RECIST 1.1, irRECIST, Peter Mac Metabolic Response Criteria and PERCIST 1.0) and will be assessed a) only considering irradiated lesions; b) only considering non-irradiated lesions and; c) considering all lesions (overall response rate)
- Overall survival will be measured from the date of randomisation to the date of death from any cause.
- Progression free survival will be measured from the date of randomisation to the date of first progression at any site or date of death due to any cause.
- Event history is defined as the time from the date of randomisation to the date of each event of interest (progression at an irradiated lesion, progression at a non-irradiated lesion, appearance of a new lesion, ceasing treatment and death). Patients alive will be censored at the date of last follow-up.

Exploratory Endpoints

A number of translational endpoints will be evaluated including:

- PD-L1 expression in tumour tissue using immunohistochemistry with the 22C3 antibody using the DAKO Autolink 48 system.

- Tumour infiltrating lymphocytes (TILs).
- Changes in host anti-tumour immunity to look for evidence of immune activation and relief of immunosuppression in tumour tissue and peripheral blood from the patient over time and at time of progression (if this occurs).
    - Blood samples will be collected at multiple time points before, during and after trial related therapies. These will be analysed for biomarkers including, but not limited to, the following (this is a non-exhaustive list):
        - Absolute lymphocyte counts using a blood analyser.
        - The presence of CD8+ T cells by flow cytometric analysis.
        - Change in frequency 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.
        - Immune cytokines

6. Trial Design

This is a prospective, open label, two arm randomised clinical trial with 1:1 allocation ratio evaluating the safety, efficacy and immunological effects of two different sequences of pembrolizumab in combination with SABR treatment in NSCLC – pembrolizumab given either before or after SABR.

Eligible patients will be randomised to either:

Arm 1: SABR followed by pembrolizumab; *or*

Arm 2: Pembrolizumab followed by SABR after cycle 1

Refer to Trial Schema

Pembrolizumab at a dose of 200 mg will be delivered every 3 weeks for a total duration of 102 weeks (34 cycles), commencing either 7 days (+/- 2 days) before the first dose of SABR or 7 days (+/-2 days) after the last dose of SABR.

Tumour response will be assessed according to RECIST 1.1, and irRECIST, Peter Mac Metabolic Response Criteria and PERCIST 1.0. Responses will be characterized in lesions treated with SABR and in un-irradiated lesions.

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

Evaluable patients are those that receive at least one dose of pembrolizumab and one dose of SABR. Non-evaluable patients will be replaced until the planned sample size has been reached.

7. Study Population

Patients with metastatic NSCLC who meet the inclusion/exclusion criteria described below will be eligible for participation in this study.

7.1 Inclusion Criteria

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

1. Have provided written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have at least one lesion not planned for SABR that is measurable disease based on RECIST 1.1.
4. Patients must have a histologically or cytologically confirmed metastatic non-small cell lung cancer.
5. Patients with disease previously untreated with systemic therapy must have ≥ 1% PD-L1 staining and patients who have previously received systemic therapy must have ≥ 1% PD-L1 staining on immunohistochemistry
6. Patients must have at least 1-3 lesions suitable for treatment with stereotactic radiotherapy.
7. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumour lesion where feasible. *Newly-obtained is defined as a specimen obtained up to 12 weeks prior to randomisation. Patients for whom newly-obtained samples cannot be provided (e.g. inaccessible or patient safety concern) may submit an archived specimen only upon agreement from the study principal investigators.*
8. Have a performance status of 0-1 on the ECOG Performance Scale (see Appendix 1).

9. Demonstrate adequate organ function as defined in table 3 below, all screening labs should be performed within 10 days of randomisation.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	≥1.5x10^9/L
Platelets	≥100x10^9L
Haemoglobin	≥90 g/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** 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** ≥30 mL/min for patients with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

10. Life expectancy > 3 months.
11. Be willing and able to comply with all study requirements, including treatment, attending assessments and follow-up.
12. Female patient of childbearing potential should have a negative urine or serum pregnancy within 7 days of randomisation. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
13. Female patients 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 8.10). Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
14. Male patients 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.

7.2 Exclusion Criteria

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

1. 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 (50) 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.

2. Has had previous thoracic radiotherapy of > 36Gy within the 6 months prior to randomisation.
3. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with small asymptomatic or previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of enlarging brain metastases, and are not using steroids for intracranial neurological symptoms at least 7 days prior to trial randomisation. This exception does not include leptomeningeal disease which is excluded regardless of clinical stability.
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 2).
6. Requires surgical fixation of bone lesion for stability. All surgical fixation and instrumentation must be completed before randomisation on study.
7. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of randomisation.
8. Has a diagnosis of immunodeficiency.
9. Has a known history of active TB (Bacillus Tuberculosis)
10. Has a hypersensitivity to pembrolizumab or any of its excipients.
11. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to randomisation or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
12. Has diagnosed and/or treated additional malignancy within 5 years prior to randomisation with the exception of: curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, curatively treated early stage cervical

cancer, breast cancer or prostate cancer with no evidence of active disease. Other exceptions may be considered following consultation with the principal investigator

13. 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.
14. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
15. Has had any systemic anti-cancer therapy or radiation therapy within 4 weeks prior to randomisation
16. Has known interstitial lung disease
17. Has an active infection requiring systemic therapy.
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
19. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
20. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
21. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
22. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
23. Has received a live vaccine within 30 days of randomisation.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

7.3 Patient Registration/Randomisation

Recruitment will cover a 2-year period. Screening for individual patients will take place within 28 days prior to randomisation onto the study.

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

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

Eligible patients will be randomised electronically using the online SABRseq electronic data capture (EDC) system. Confirmation of randomisation and randomisation ARM will be provided electronically (via email) as well as, a unique 5-digit patient identification number.

Patients will not be randomised if treatment has commenced or if consent has not been given. Once a patient is randomised on a trial, randomisation will not be cancelled.

Following randomisation, patients should begin protocol treatment within 28 days

7.4 Treatment Assignment

Thirty-two patients will be randomised between the two arms in a 1:1 allocation ratio. Stratified randomisation will be used to assign the patients to the treatment arms. Stratification will occur by the number of metastases to be treated with SABR (two groups: 1 metastasis vs 2 or 3 metastases) and by line of therapy (two groups: previously untreated vs previously treated).

The next treatment to be assigned will not be known by any person prior to eligibility criteria being established and the intention to randomise the patient being declared.

7.5 Blinding and Procedures for Unblinding

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

7.6 Patient Treatment Withdrawal/Discontinuation

Patients may withdraw consent at any time for any reason or be withdrawn from the trial treatment at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator or the Sponsor if continued enrolment into the trial is inappropriate for administrative and/or other safety reasons.

A trial patient may discontinue trial treatment for any of the following reasons:

- Disease progression
- Unacceptable adverse event
- Intercurrent illness which prevents further treatment
- Withdrawal of consent for treatment or from trial by the patient
- The investigator believes it is in the best interest of the patient
- The patient becomes pregnant or begins breastfeeding
- Noncompliance with the protocol

When a patient discontinues/withdraws prior to completion of protocol treatment, patients should attend the site for a 30-day (post end of trial treatment) safety follow-up visit for assessment of AEs and efficacy. Any AEs which are present at the time of

discontinuation/withdrawal should be followed in accordance with the safety requirements. The reason for discontinuation will be recorded on a CRF.

Discontinuation of trial treatment does not necessarily indicate withdrawal from the trial. Patients are expected to have follow-up assessments after treatment discontinuation if patients' agree and reason for trial treatment discontinuation permits.

Total withdrawal would occur in the circumstance that the patient decides to completely withdraw from all treatment aspects of the trial, and does not agree to any further scheduled follow up assessments. The patients' 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.

8. Study Assessments

The following assessments will occur during the trial. A schedule of assessments is provided on page 11.

8.1 Pre-randomisation/Screening Assessments – ALL ARMS

The following assessments must be performed 28 days prior to randomisation (unless otherwise specified):

- Informed consent
- Assessment of PD-L1 expression on new (fresh) biopsy sample or archival tissue
- Review of inclusion and exclusion criteria
- Demographics
- SINS score for spinal lesions (if applicable i.e. known spinal metastases)
- Comprehensive medical history (including disease specific medical history)
- Physical examination
- Vital signs and body measurements
- Documentation of prior medications at time of screening
- Documentation of ECOG performance status
- Radiological evaluation with a CT Brain, Chest/Abdomen and Pelvis or MRI must be performed within 6 weeks of randomisation
- Whole body bone scan (if clinically indicated) within 6 weeks of randomisation
- FDG-PET scan
- Laboratory studies no more than 10 days prior to randomisation including FBE, biochemistry and coagulation, hepatic, kidney and thyroid function tests
- Virology (HIV, Hepatitis B and C) within 21 days prior to randomisation, if clinically indicated
- Pregnancy test in female patients with child bearing potential within 7 days prior to randomisation

- New (fresh) biopsy sample within 12 weeks of randomisation, if applicable
- Blood samples for correlative studies

8.2 Treatment Phase - ARM 1 (SABR followed by pembrolizumab)

8.2.1 SABR Visit Assessments

The following assessments must be performed prior to the first dose of SABR:

- Documentation of concomitant medications
- Blood samples for correlative studies

8.2.2 Cycle 1 Assessments

The following assessments must be performed 7 days ± 2 days after the last dose of SABR:

- Physical examination
- Vital signs and weight
- Documentation of concomitant medications
- Documentation of ECOG performance status
- Laboratory studies including FBE, biochemistry and coagulation, hepatic, kidney and thyroid function tests
- Pregnancy test in female patients with child bearing potential.
- Blood samples for correlative studies

8.2.3 Cycle 2 to Cycle 34 Assessments

The following assessments will be performed within 3 days prior to pembrolizumab dosing in each cycle, unless otherwise specified.

- Physical examination
- Vital signs and weight
- Documentation of concomitant medications
- Documentation of ECOG performance status
- Laboratory studies including FBE, biochemistry and coagulation, hepatic and kidney
- Thyroid function tests (every 6 weeks)
- Radiological evaluation with a CT Chest/Abdomen and Pelvis or MRI (prior to cycle 3, 5, 7 and every 3 cycles thereafter)
- FDG-PET scan prior to cycle 5
- Whole body bone scan (prior to cycle 3, 5, 7 and every 3 cycles thereafter, only if clinical indicated)
- Response assessment (prior to cycle 3, 5, 7 and every 3 cycles thereafter)
- Adverse events assessment
- Pregnancy test in female patients with child bearing potential.
- Blood samples for correlative studies

8.3 Treatment Phase - ARM 2 (pembrolizumab followed by SABR)

8.3.1 Cycle 1 Assessments

The following assessments must be performed within 3 days prior to the first dose of pembrolizumab in cycle 1:

- Physical examination
- Vital signs and weight
- Documentation of concomitant medications
- Documentation of ECOG performance status
- Laboratory studies including FBE, biochemistry and coagulation, hepatic and kidney function tests
- Pregnancy test in female patients with child bearing potential.
- Blood samples for correlative studies

8.3.2 SABR Visit Assessments

The following assessments will be performed at the SABR visit, 7 days from Cycle 1 Day 1 (± 2 days):

- Documentation of concomitant medications
- Blood samples for correlative studies

8.3.3 Cycle 2 to Cycle 34 Assessments

The following assessments will be performed within 3 days prior to pembrolizumab dosing in each cycle, unless otherwise specified:

- Physical examination
- Vital signs and weight
- Documentation of concomitant medications
- Documentation of ECOG performance status
- Laboratory studies including FBE, biochemistry and coagulation, hepatic and kidney
- Thyroid function tests (every 6 weeks)
- Radiological evaluation with a CT Chest/Abdomen and Pelvis or MRI (prior to cycle 3, 5, 7 and every 3 cycles thereafter, only if clinical indicated)
- FDG-PET scan prior to cycle 5
- Whole body bone scan (prior to cycle 3, 5, 7 and every 3 cycles thereafter, only if clinical indicated)
- Response assessment (prior to cycle 3, 5, 7 and every 3 cycles thereafter, only if clinical indicated)
- Adverse events assessment
- Pregnancy test in female patients with child bearing potential.
- Blood samples for correlative studies

8.4 Safety Follow-up – All Arms

The following assessments will be performed during the safety follow-up visit to be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

- Adverse events assessment: Patients 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 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.
- New anti-cancer therapy status.

8.5 Follow-Up – All Arms

Patients who complete the treatment phase, or discontinue trial treatment for a reason other than disease progression will move into the follow-up phase. The following assessments will be performed every 3 months up until the last patient has completed 24 months of follow-up, until the start of new anti-neoplastic therapy, disease progression, death or end of the study.

- Physical examination
- Vital signs and weight
- Documentation of ECOG performance status
- Laboratory studies including FBE, biochemistry and coagulation, hepatic and kidney function tests (only if clinically indicated)
- Radiological evaluation with a CT Chest/Abdomen and Pelvis or MRI
- Whole body bone scan (only if clinical indicated)
- Response assessment
- Adverse Event assessment
- Blood samples for correlative studies
- New anti-cancer therapy status
- Fresh biopsy sample 3 months after the last dose of SABR if considered safe

8.6 Survival Follow-up

Patients who discontinue trial treatment due to progression, progress during following-up or commence a new systemic treatment will be followed for survival only. Survival status will be assessed every 3 months until death, withdrawal of consent, or the end of the study, whichever occurs first. Where possible, every effort should be made to record results of subsequent tumour assessments and any new anti-cancer therapies.

8.7 Concomitant Medications

All treatments that the investigator considers necessary for a patient'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 relevant 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 prior to randomisation and 30 days after the last dose of trial treatment should be recorded.

8.8 Supportive Care/Rescue Medication

Patients 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 (table 4). 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.

Table 4 Supportive care measure of adverse events of immunologic etiology

Adverse event type	CTCAE version 4.03 Grade	Treatment
Pneumonitis	**Grade 2**	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. In the event of recurrent grade 2 pneumonitis, pembrolizumab should be discontinued.
	Grade 3-4	For, 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	**General**	Patients 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 patients 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.
	Grade 2 that persists > 3 days	Administer oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks
	Grade 3 or 4 that persists > 1 week	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, insulin replacement therapy is recommended
Hyperglycemia	**Grade 3-4**	If associated with ketosis (ketonuria) or metabolic acidosis, evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide. Insulin replacement therapy is recommended
Hypophysitis	**Grade 2**	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
	Grade 3-4	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	**General**	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 **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	**Grade 2**	Monitor liver function tests more frequently until returned to baseline values (consider weekly). Treat with IV or oral corticosteroids
	Grade 3-4	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	**Grade 2**	Treat with corticosteroids When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks
	Grade 3-4	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.

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

Table 5 below shows treatment guidelines for patients who experience an infusion related reaction associated with administration of pembrolizumab.

Table 5: Infusion Related Reaction Treatment Guidelines

CTCAE version 4.03 **Grade**	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. 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 patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration**	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids	No subsequent dosing

interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	
Grade 4: Life-threatening consequences; urgent intervention indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient 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		

8.9 Diet

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

8.10 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 used; two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study pembrolizumab.

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).

Patients 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. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

8.11 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient'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 Merck and the Sponsor. If a male patient 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 8.11.

8.12 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, patients who are breast-feeding are not eligible for enrolment.

8.13 Non-Permitted Medications

Patients are prohibited from receiving the following therapies during the screening and treatment phase 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
- Radiation therapy

  Note: Radiation therapy to a symptomatic lesion(s) or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to randomisation 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 a chronic inflammatory disorder. The use of physiologic doses of corticosteroids on a regular repetitive basis for a medical condition may be approved after consultation with the Principal Investigator.

Patients 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. Patients may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria describe other medications that are prohibited in this trial.

There are no prohibited therapies during the follow-up phase.

9. Trial Radiotherapy Treatment

The treatment regimen involves the delivery of a single fraction of highly conformal SABR to 1 to 3 metastases; delivered with either photons, electrons or mixed modalities. The maximal number of metastases within this range should be irradiated, however, at least one metastases defined as measurable disease must not be irradiated. The first dose of pembrolizumab will be delivered either 7 days (+/- 2 days after (ARM 1) or 7 days (+/- 2 days) before (ARM 2) the SABR treatment and will be continued for up to 24 months (34 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%). When this coverage cannot be achieved whilst respecting surrounding organs at risk, a lower coverage of D95=100% is acceptable. 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(51). 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 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 should result in a maximum dose to the PTV of between 125% and 143%. This allows for larger target dose in homogeneities 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 7 calendar days. In the case where targets are treated on different days, then treatments should ideally be delivered on consecutive days. Dose for each lesion will be independently verified before treatment and image guidance will be used to ensure accurate patient positioning.

For further details, refer to the SABRseq Radiotherapy Manual**.**

9.2 Statement of Treatment Aim and Rationale

Treatment rationale is to provide long-term local and distant disease control in patients with NSCLC using a single fraction of stereotactic ablative radiotherapy (to 1-3 sites) in conjunction with pembrolizumab.

9.3 Treatment Schedule

Study therapy should commence within 28 days of patient randomisation 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. Ideally all treatments should be performed on the same day. One or more lesions must be deemed suitable for treatment with SABR; up to 3 lesions may be treated. The choice of treatment sites for SABR is at clinician discretion, but should encompass different types of metastatic sites where possible (e.g. bone and/or lymph node and/or visceral organ). The maximal number of metastases within this range should be irradiated, however, at least one metastases defined as measurable disease must not be irradiated. The use of single 4mg dose of prophylactic dexamethasone prior to SABR treatment is permitted.

10. Trial Pembrolizumab Treatment

Pembrolizumab treatment should begin either 7 days (+/- 2 days) before the first SABR treatment or 7 days (+/- 2 days) after the last SABR treatment

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks for 34 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).

Pembrolizumab treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in Sections 8.2 and 8.3. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

10.1 Pembrolizumab Dose Modifications and Delays

Adverse events 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 7 below. See Section 8.8 for supportive care guidelines, including use of corticosteroids. Dose reductions are not permitted.

Table 7: Dose Modification Guidelines for Drug-Related Adverse Events

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/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.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

If treatment is delayed by more than 20 days from the planned date of dose administration, patient will be considered to have missed the dose for that cycle and will proceed to the next cycle. Missed cycle doses will not be made up.

10.2 Continuing Pembrolizumab

In the event of radiological progression, pembrolizumab may be continued if there is evidence of clinical benefit in the opinion of 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 may still be continued until there is unequivocal symptomatic deterioration attributed to disease progression that requires initiation of new systemic therapy. Radiotherapy to progressing or symptomatic sites as per standard clinical practice is allowed.

11. Labeling, Packaging, Storage and Return of Clinical Supplies

11.1 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 8.

Table 8: Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

11.2 Packaging and Labelling Information

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

11.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the patient, 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.

11.4 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.

11.5 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 patients 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.

12. Adverse Events

12.1 Adverse Event Definition

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation patient 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 AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product (or associated with the use of any other protocol specified intervention including radiation therapy, surgery or use of a device).

AEs include: 'Adverse Drug Reactions', i.e. a reaction, in contrast to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected.

For unapproved medicines: any noxious and unintended response to a medicinal product, related to any dose. The phrase "response to an unapproved medicinal product" means that a causal relationship between the product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. ('Unapproved medicinal product' here includes approved products used at levels or in ways that are unapproved).

Regarding marketed medical products: a noxious and unintended response to a drug that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.

12.2 Unexpected Adverse Event Definition

An unexpected adverse event (UAE) is an AE for which the nature or severity of the event is not consistent with the information in the relevant source documents e.g. the IB, published information, product information (or with the applicable side effect risk profile for radiation therapy, surgery or use of a device).

UAEs also include unexpected adverse drug reactions (UADR) - The nature and severity of the ADR is not consistent with the information in the Investigators Brochure for an unapproved investigational product, or the product information/package insert/summary of product characteristics for an approved product.

12.3 Serious Adverse Event Definition

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

Due to the significant information they provide, serious adverse events (SAE) (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 CTCAE)
- Is life-threatening (i.e. grade 4 CTCAE)
- 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*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

The following are NOT considered SAEs:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study. Note: Hospitalizations that were planned before the signing of the PICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- Disease progression should NOT be reported as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of drug efficacy will be reported if they fulfill the serious adverse event definition.
- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a

complication of therapy administration will be reported as a serious adverse event.

- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an adverse event.

12.4 Attribution

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:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated	Unrelated	The AE *is clearly **NOT** related* to the intervention
	Unlikely	The AE *is **doubtfully related*** to the intervention
Related	*Possible*	The AE ***may be related*** to the intervention
	Probable	The AE *is **likely related*** to the intervention
	Definite	The AE *is **clearly related*** to the intervention

12.5 Severity Criteria

An assessment of severity grade will be made using the NCI-CTCAE (version 4.03). Where parameters are not addressed within the criteria, severity of AEs should be graded as:

Mild	Aware of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activities
Severe	Incapacitating with inability to work or perform usual activities
Life-threatening	Patient is ***at immediate risk of death***
Fatal	Death

12.6 Adverse Events Reporting

All adverse events, which occur whilst the patient is enrolled on the trial, must be reported in the patients' medical records and recorded on the relevant CRF.

12.7 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. All adverse events regardless of CTCAE grade must also be evaluated for seriousness. Laboratory values need reporting as AEs only if abnormal and deemed clinically significant by the investigator.

12.8 Serious Adverse Event Reporting

12.8.1 Trial sites/investigators

All SAEs that occur from the time a patient has signed consent for the Trial to within 30 days of the final protocol-specified treatment are required to be reported to the Sponsor whether or not considered related to the treatment under investigation.

The Principal Investigator (PI) must:

- Determine whether an AE is 'Serious'
- For SAEs, the PI must then ascertain the suspected cause
- The attribution to the SAE must be recorded in the patients' medical records and reported on the SAE form.

SAEs must be reported by completing the SABRseq SAE form and emailing/faxing to the following:

Sponsor (or delegate)	Safety_BaCT@petermac.org
Merck Global Safety	+1-215-993-1220
Merck Canada INC	1-800-369-3090 or +1-514-428-4934

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 on the SAE form.
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 'on-going') at the time of the initial report, the SAE Form must be submitted every 30 days until the event is resolved, death has occurred or the condition has stabilised. If a change occurs in a stable condition (i.e. either worsens or improves), then a new SAE Form should be faxed

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 SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patients participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

12.8.2 Sponsor

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 appropriate regulatory authority need to be notified of the SAE.
- Notifying the appropriate regulatory authority 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 serious, unexpected ADRs 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 appropriate regulatory authority 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.

12.9 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 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 at first treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the patient 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 12.10 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.

12.10 Overdose Definition and Reporting

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 patient 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 relevant Adverse Event eCRF.

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).

12.11 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 patient (spontaneously reported to them), including the pregnancy of a male patient'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 patient initiates new anticancer therapy, whichever is earlier. All patients and female partners of male patients 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)

13. Response Assessment

Response and progression will be evaluated in this study using RECIST 1.1, irRECIST, Peter Mac Metabolic Response Criteria and PERCIST 1.0.

13.1 Evaluation of response by RECIST1.1 and irRECIST

The same imaging modality as used at screening (i.e. CT or MRI scans) should be used at every visit. Changes only in the largest diameter (unidirectional measurement) of the tumour lesions are used in the RECIST v1.1 criteria. For tumour lymph nodes, the short axis must be measured. Lesions are measurable or non-measurable using the definitions described below. Refer to Appendix 3 and 4.

13.2 Peter Mac Metabolic Response Criteria

Metabolic response in a lesion will be assessed according to the method given in MacManus et al. Scans are read visually displayed side by side with liver uptake normalised between images. Response categories are defined as follows (comparison is with baseline PET scans in each case):

- **Complete metabolic response (CMR_V):** Activity within the tumour site has decreased to be equal to or less than adjacent soft tissue in the radiation treatment volume.
- **Partial metabolic response (PMR_V):** Any appreciable reduction in intensity of tumour FDG uptake or in tumour volume.
- **Stable metabolic disease (SMD_V):** No appreciable change in intensity of tumour FDG uptake or in tumour volume.
- **Progressive metabolic disease (PMD_V):** Appreciable increase in tumour FDG uptake or in tumour volume.

13.3 PERCIST 1.0 Criteria

A region of interest (ROI) is used to assess the maximum SUL peak. This ROI is typically the region of the baseline tumour with the highest uptake, but it can also be another lesion that was previously present and is the most active lesion after treatment.

- **Complete metabolic response (CMR)**: complete resolution of ^{18}F-FDG uptake within the measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels. Disappearance of all other lesions to background blood-pool level.
- **Partial metabolic response (PMR)**: reduction greater or equal to 30% in the target measurable tumour ^{18}F-FDG SUL peak.
- **Stable metabolic disease (SMD)**: disease other than CMR, PMR or PMD.
- **Progressive metabolic disease (PMD)**: Greater than 30% increase in ^{18}F-FDG SUL peak OR visible increase in extent of ^{18}F-FDG tumour uptake (75% of total lesion glycolysis volume with no decline in SUL OR the advent of new ^{18}F-FDG-avid lesions that are typical of cancer and not related to treatment effect or infection.

14. Statistical Considerations

14.1 Statistical Analysis Plan Summary

This is a prospective, two-arm randomised, open label, Phase Ib study assessing safety, efficacy and biological effects of two different treatment sequences of the combination of SABR with pembrolizumab in patients with metastatic NSCLC.

14.2 Treatment Assignment

Patients will be randomised in the ratio of 1:1 between the two arms. Once randomisation is assigned, cancellation will not be permitted. Patients will be stratified by number of metastases to be treated with SABR (two groups: 1 metastasis vs 2 or 3 metastases), and by line of therapy (two groups: previously treated vs previously untreated).

14.3 Populations for Analyses

- Treated patient population is defined as the patients 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 patients are those treated patients who have CT or PET scans performed at respective follow-up visit. This is the analysis population for the response endpoint.

Patients that are not part of the treated population will be replaced and no follow-up information will be collected.

14.4 Statistical Methods

Demographics and baseline characteristics of patients will be summarized using descriptive statistics. No imputation for missing values is intended. All statistical tests comparing the two arms will be 2-sided, 5% alpha will be used and no adjustment for multiplicity is intented.

14.5 Safety Analysis

Safety will be assessed using CTCAE v4.03 and the maximum toxicity grade per patient of each adverse event will be derived and presented in table format according to arm and overall. The number of patients who suffer from grade 3 or higher toxicities (for each toxicity type and overall) will be provided considering all patients who have received at least one dose of pembrolizumab and completed at least one SABR treatment. The safety analysis will be conducted twice: once for all AE's, regardless of relatedness to treatment and once considering only AE's related to the treatment (i.e. classified as possibly, probably or definitely related).

14.6 Time-to-Event Endpoint 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. Progression free survival and overall survival will be described for each arm using Kaplan-Meier methods. Estimates at key time points will be provided with 95% confidence interval. Stratified log-rank test will be used to compare the curves between arms.

An event history chart will be used to describe the individual patient's events of interest. Each patient in each arm will be represented as a line with different symbols identifying when the patient had a progression on irradiated lesions, progression on a non-irradiated lesions, appearance of new lesions, when treatment ceased, when they died and when censoring occurred.

14.7 Response Analysis

All tumour response measurements (pre- and post-treatment) must be recorded using the definitions of RECIST 1.1. RECIST assessments will take into account post-treatment inflammatory processes that occur after SABR treatment in pulmonary and liver tissues. PET response criteria will also be assessed and reported. If a criterion is met in more than one response type then the response type will be classified at the lowest possible level. The initial assessment of response will be determined after all protocol treatment has been completed, whether or not all of the planned treatment was received. In addition, irRECIST, PERCIST and Peter Mac Metabolic Response criteria will be considered in conjunction to RECIST 1.1. Metabolic response criteria and PERCIST 1.0 results or assessments will not be entered by site clinical staff and will be reported centrally. Overall patient's response rates

(CR+PR at all lesions) at 6 and 12 months after commencement of SABR treatment will be described as percentages with exact 95% confidence interval. Overall response for all irradiated lesions and un-irradiated lesions will also be assessed separately. Lesion size of measurable lesions may be plotted over time to describe patient response trajectories. Overall response rates will be compared between treatment arms using Fisher's exact test.

14.8 Exploratory Endpoints

Exploratory endpoints will be described graphically and simple descriptive statistics will be provided for each variable at each time point.

14.9 Sample Size Calculation

This is a Phase Ib study with a sample size of 32 patients (16 in each arm). This study will assess the common toxicities associated with the combination of SABR and pembrolizumab. The sample size was determined such that, within each arm, the probability of observing toxicity in at least one patient was 80% for toxicities with true incidence rates of at least 10%. Table 9 illustrates different scenarios for true toxicity rates ranging from 5% to 30% with the respective probability of at least one patient presenting with the toxicity within the arm and overall.

Table 9: Probability of at least one patient presenting with a toxicity for different true toxicity rates

True toxicity rate	Within each arm (n=16)	Overall (n=32)
5%	0.560	0.806
10%	0.815	0.966
15%	0.926	0.994
20%	0.972	0.999

The table below shows the expected confidence interval for different response rate scenarios within each arm.

Table 10: Response rate and confidence intervals for different number of responses with n=16

Number of responses	Response rate (95% confidence interval)
6	37.5 (15 – 65)
8	50 (25 – 75)
10	62.5 (35 – 85)
12	75 (48 – 93)

Recruitment will occur over a two-year period. The principal analyses will be 24 months after the last patient has commenced treatment. An interim analysis assessing patterns of failure

and response to therapy based on post-therapy PET response will be performed once all recruited patients have completed 5 cycles of pembrolizumab therapy.

14.10 Early Termination Criteria

Consideration of suspension of patient 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%. If at any given time during the trial 3 or more patients present with treatment related pneumonitis or colitis of grade 3-4 toxicity, data will be reviewed by the TMC and consideration will be given to permanently suspend recruitment and close the trial

14.11 Deviations

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

15. Trial Management & Administrative Requirements

15.1 Trial Personnel

The Investigator(s) is responsible for ensuring that all trial personnel are qualified for their designated roles and provides information about the trial to all staff members involved in the trial or any element of patient management, both before starting the practical performance of the trial and during the course of the trial (e.g. when new staff become involved).

Additional information available during the trial should be given, as agreed upon, either by the investigator or delegate and always when a new staff member becomes involved in the trial.

15.2 Audit and Inspection

According to ICH/GCP Guidelines, the Sponsor may audit the investigational site to compare raw data, source data and associated records with the interim (if applicable) or final report of the trial to assure that data have been accurately reported. The Sponsor's Clinical Quality Assurance department is responsible for the auditing of the trial. Auditing may be contracted to an external body.

The Investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the trial with GCP.

15.3 Protocol Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety and wellbeing of the patient requires immediate intervention based on the judgement of the Investigator or a responsible, appropriately trained and credentialed professional(s) designated by the

Investigator as a sub-investigator.

In the event of a significant deviation due to an emergency, accident or error, the Investigator or designee must contact the Principal Investigator and notify the Sponsor (OCR) at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the patient should continue in the trial.

16. Data Handling and Record Keeping

16.1 Case Record Form (CRF)

In this trial the CRF will be electronic (eCRF). The investigator or the designated site person must complete the CRF and supporting documentation for each patient within a timely manner of the visit occurring.

The Clinical Trial Manager(s) will review the completed data for accuracy, completeness and consistency. The Clinical Trial Manager will submit requests for correction / clarification of data (e.g. queries) to the Investigator or designee when inconsistencies are identified during review, monitoring (if applicable) or during the edit check process.

All corrections and alterations to CRF data must be made by the investigator or by the designated site personnel in a timely manner and in according to the instructions provided. Completed CRFs should be reviewed and signed by the Principal Investigator or designated site personnel. All persons appointed by the Investigator to participate in the trial must be indicated on the delegation of authority log.

16.2 Source Documents

The investigator is required to prepare and maintain adequate and accurate case histories (i.e. medicals) designed to record all observations and other data pertinent to the trial for each trial patient. The medical records must contain adequate information to allow for verification of patient identity throughout the trial.

Any date recorded directly on the CRF, as agreed by the Sponsor for which no other written or electronic record will be maintained in the patient's medical record, will be considered source data (e.g. results from physical examinations, vital signs testing or the drug administration procedure).

The eCRF and the patient's medical records pertinent to the trial may be reviewed by a designated monitor, auditors and possibly by representatives from the IRB/IEC and regulatory bodies such as the TGA, US Food and Drug Administration (FDA) or the Canadian Health Authority to the extent permitted by regulation.

The investigator is required to retain a patient identification code list to allow unambiguous identification of each patient included in the trial. This list should contain the patient's full name, data of birth, and dates of participation and trial identification number. This list is

held in confidentiality at the Investigator site.

Source documents pertaining to the trial must be maintained by investigational sites and de-identified copies provided to BaCT in accordance with the source data verification checklist (provided by BaCT). Source documents should include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of any diagnostic tests such as x-rays, CT/MRI scans, laboratory tests, ECGs etc.

16.3 Archiving of Trial Documents

Trial data and other essential documentation must be retained for a period of at least 15 years (MHRA Guidelines).

It is the responsibility of the Sponsor to inform the Investigator(s) / site(s) when these documents need no longer be retained. The original record of CRFs will be archived by the Sponsor for at least 15 years. No trial document or image will be destroyed without prior written agreement between the Sponsor and the Investigator(s). Should the Investigator(s) wish to assign the trial records to another party or move to another location, advance written notice will be given to the Sponsor.

17. Ethical Aspects

17.1 Informed Consent

This trial will be conducted in compliance with 21 CFR Part 50 for informed consent. Written informed consent will be obtained from each patient before any procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. Explanation will also be provided to the patients that they are free to refuse entry into the trial and free to withdraw from the trial at any time without prejudice to future treatment.

The patient's willingness to participate in the trial will be documented in writing on a consent form, which will be signed by the patient with the date and time of that signature indicated. The Investigator(s) will keep the original consent forms and copies will be given to the patient. In addition, the process of obtaining consent will be documented in the patient's medical record by the person conducting the informed consent discussion.

Written and/or oral information about the trial in a language understandable by the patient will be given to all patients. The information provided must include an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force.

17.2 Confidentiality Regarding Trial Patients

The Investigator must ensure the privacy of the patients, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents submitted, patients will not be identified by their names, but by an identification code (e.g. patient ID number).

A monitor, properly authorised persons on behalf of the Sponsor's quality assurance unit or competent authorities may scrutinise personal medical information for the purpose of verifying data recorded on the CRF. Personal medical information will always be treated as confidential, according to local privacy regulations.

17.3 Trial Management Committee (TMC)

The TMC will initially meet to assess safety after 3 patients in each arm has completed 8 cycles of pembrolizumab. Thereafter, the TMC will meet at 6 monthly intervals.
The TMC will comprise the following members:

- Radiation Oncology Principal Investigator
- Medical Oncology Principal Investigator
- An Independent Research Physician
- Clinical Trial Manager
- Trial Statistician

The C/PI will receive and review SAEs in real time.

The TMC will receive periodic safety reports therefore facilitating a response to potential safety issues. The TMC will also oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The primary mandate of the TMC would be to protect patient safety. If adverse events of a particularly serious type are more common than anticipated, the study can be considered for termination. Please see SABRseq TMC terms of reference for further information.

The TMC will consider whether to continue the study as planned, modify, or stop it, based on reports provided by BaCT or other information.

18. Publication and Presentation Policy

18.1 Reporting of Results

The Trial Management Committee will be responsible for decisions regarding presentations and publications arising from this trial according to the Sponsor Authorship, Publication and Spokesmanship Guidelines.

The statistician will perform the primary analysis of trial results, for publication. The principal investigator will publish the primary trial results.

Publications and abstracts must be presented to the TMC Sponsor (OCR) for review and approved prior to submission.

18.2 Trial Registry

TheC/PI is responsible for registering all trials with an appropriate clinical trials registry prior to the accrual of the first patient.

19. References

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Appendix 1

ECOG Performance Status Criteria

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	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	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	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.

Appendix 2

Spine Instability Neoplastic Score (SINS)

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 3

RECIST 1.1 criteria- Response Evaluation Criteria in Solid Tumours

These instructions are based on the guidelines recommended in Eisenhower et al., 2009 .

3. Disease and lesion definitions

3.1 Measurable Disease

Measurable tumour lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as

- ≥10 mm with CT scan or clinical examination.
- Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan).
- Malignant lymph nodes must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed.

All tumour measurements must be recorded in millimetres. Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

3.2 Non-measurable Disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be taken and recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

3.3 Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

3.4 Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion may not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.
- Only the short axis of lymph nodes identified as target lesions contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterise the objective tumour.
- All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases 'unequivocal progression' of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. multiple enlarged pelvic lymph nodes or multiple liver metastases'.

3.5 RECIST 1.1 Response Criteria

	Target lesions	**Non-target lesions**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as *reference the baseline sum diameters*	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as *reference the smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as *reference the smallest sum diameters while on study.*	
(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should ideally be confirmed later on by the review panel (or Study Chair).		

3.6 Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

3.7 Evaluation of overall response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer *et al*, 2009 (see References)

Appendix 4

irResponse Evaluation Criteria in Solid Tumors (irRECIST)

Adapted from irRECIST - ESMO 2014 abstract 4958

1.0. Baseline: Measurable Lesion Definitions and Target Lesion Selection

- Follow the definitions from RECIST 1.1.
- Measurable lesions must be accurately measured in at least one dimension with a minimum size of:
    - 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis for nodal lesions
    - 10 mm caliper measurement by clinical exam
    - 20 mm by chest X-ray

1.1. Baseline: Non-measurable Lesion Definitions

- Follow the definitions from RECIST 1.1
- Non-target lesions will include:
    - Measurable lesions not selected as target lesions
    - All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest perpendicular diameter is ≥10 and < 15 mm.
    - Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.

1.2. Baseline: Target and Non-Target Lymph Node Lesion Definitions

- Follow the definitions from RECIST 1.1

1.3. Baseline: Non-Target Lesion Selection

- All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.

1.4. Baseline: Bone Lesions

- Follow the definitions from RECIST 1.1.
- Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.

1.5. Baseline: Brain Lesions

- Lesions detected on brain scans can be considered as both target or non-target lesions.

1.6. Baseline: Cystic and Necrotic Lesions as Target Lesions

- Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumour Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

1.7. Baseline: Lesions With Prior Local Treatment

- During target lesion selection, the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.).
- Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

1.8. Baseline: No Disease at Baseline

- If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up timepoints unless new measurable lesions are identified and contribute to the TMTB.

2.0. Follow-up: Recording of Target and New Measurable Lesion Measurements

- The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.

2.1. Follow-up: Definition of Measurable New Lesions

- In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

2.2. Follow-up: Non-Target Lesion Assessment

- The RECIST 1.1 definitions for the assessment of non-target lesions apply.
- The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

2.3. Follow-up: New Non-Measurable Lesions Definition and Assessment

- All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR.

2.4. irRC Overall Tumor Assessments

- **irCR**, complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
- **irPR**, decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
- **irSD**, failure to meet criteria for irCR or irPR in the absence of irPD.
- **irNN**, no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
- **irPD**, minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.
- **irNE**, used in exceptional cases where insufficient data exists.
- **irND**, in adjuvant setting when no disease is detected.