# Treating metastatic melanoma with Stereotactic ABlative Radiotherapy and IMmune Pathway ACTivation: A phase I dose-escalation trial (SABR IMPACT I)


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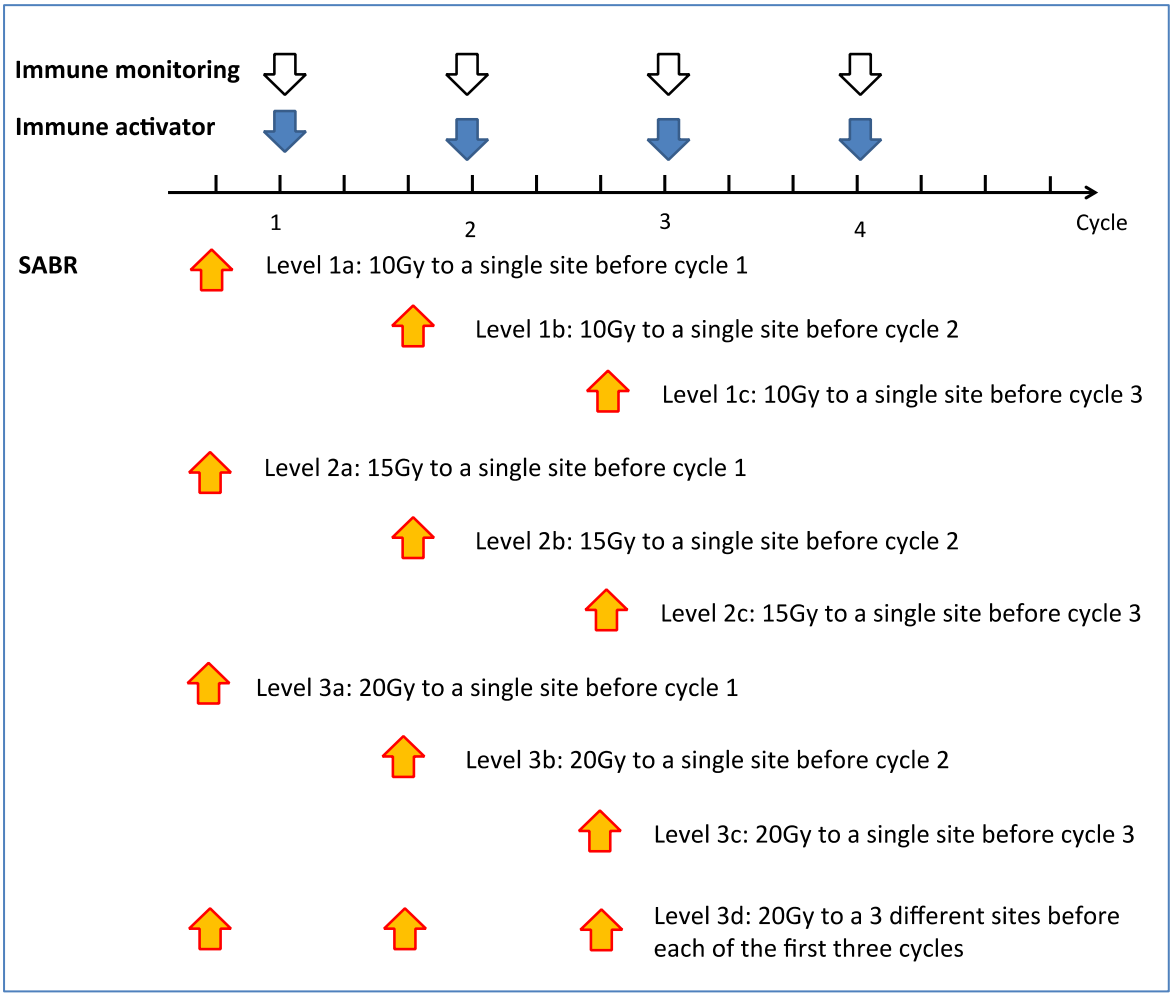
# Study overview

Patients with metastatic stage IV melanoma
Treated with Immunotherapy and dose-escalated SABR
Standard 3 + 3 phase I design




Primary objective

- To determine the maximum tolerated dose (MTD) of SABR with Immunotherapy

Secondary objectives

- To determine biologic activity of SABR with Immunotherapy
- To determine the clinical activity of SABR with Immunotherapy
- To correlate tumor genetics with biologic and clinical activity.

Required Sample Size: A minimum of 30 patients will be required if MTD is not reached

## INDEX

# 1. Background and rationale

Australia has the highest incidence of melanoma in the world [1]. Once metastatic, standard treatments are largely ineffective and the majority of patients survive less than 12 months [2]. Recently developed immunotherapy drugs which activate a person's own immune system against their melanoma have shown great promise, achieving response rates that appear significantly better than with chemotherapy [3-6]. The monoclonal antibodies Ipilimumab, Nivolumab and Pembrolizumab are examples of such drugs and are available in Australia. Ipilimumab blocks the negative regulatory receptors Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), while Nivolumab and Pembrolizumab block Programmed Cell Death 1 (PD-1).

Patients who respond to treatment with evidence of immune activation achieve the best outcomes [7-10] and can survive beyond 10 years [11]. Using Ipilimumab, Nivolumab or Pembrolizumab alone results in an objective response in just 10-30% of patients [3,4,6]. When used together, response rates increase to 40% [4]. However, concurrent treatment causes high grade immune related toxicity in more than 50% of patients as opposed to less than 20% when used alone or sequentially [3,4].

Radiotherapy is effective against melanoma, causing dose-dependent tumour cell death wherever it is targeted [12]. In addition to this, radiotherapy can cause systemic responses at non-targeted sites [13], observations that appear to be the result of immune activation [14]. Although it is unclear as to how radiotherapy activates the immune system, radiotherapy induced tumour death exposes the immune system to cellular debris that can act as antigens and trigger an immune response [15,16]. Animal models support this, with larger radiation doses and greater tumour death being more immunogenic than lower doses [17]. Using Stereotactic Ablative Radiotherapy (SABR), single fractions of 20Gy to selected brain and bone metastasis and single fractions of more than 30Gy (or multiple fractions of 20Gy) for selected lung and liver metastasis can be delivered with a 10% or lower risk of high grade toxicity [18-23].

The use of SABR with immunotherapy represents a novel therapeutic combination through which we may improve response rates. It is unclear whether enhancing the action of these drugs with SABR will increase toxicity. The aim of this study is to determine the maximum tolerated SABR dose that can be delivered with Ipilimumab, Nivolumab and Pembrolizumab with acceptable toxicity, when SABR is delivered to potentiate the action of these drugs.

## 2. OBJECTIVES

Primary objective

- To determine the maximum tolerated dose (MTD) of SABR with Immunotherapy

Secondary objectives

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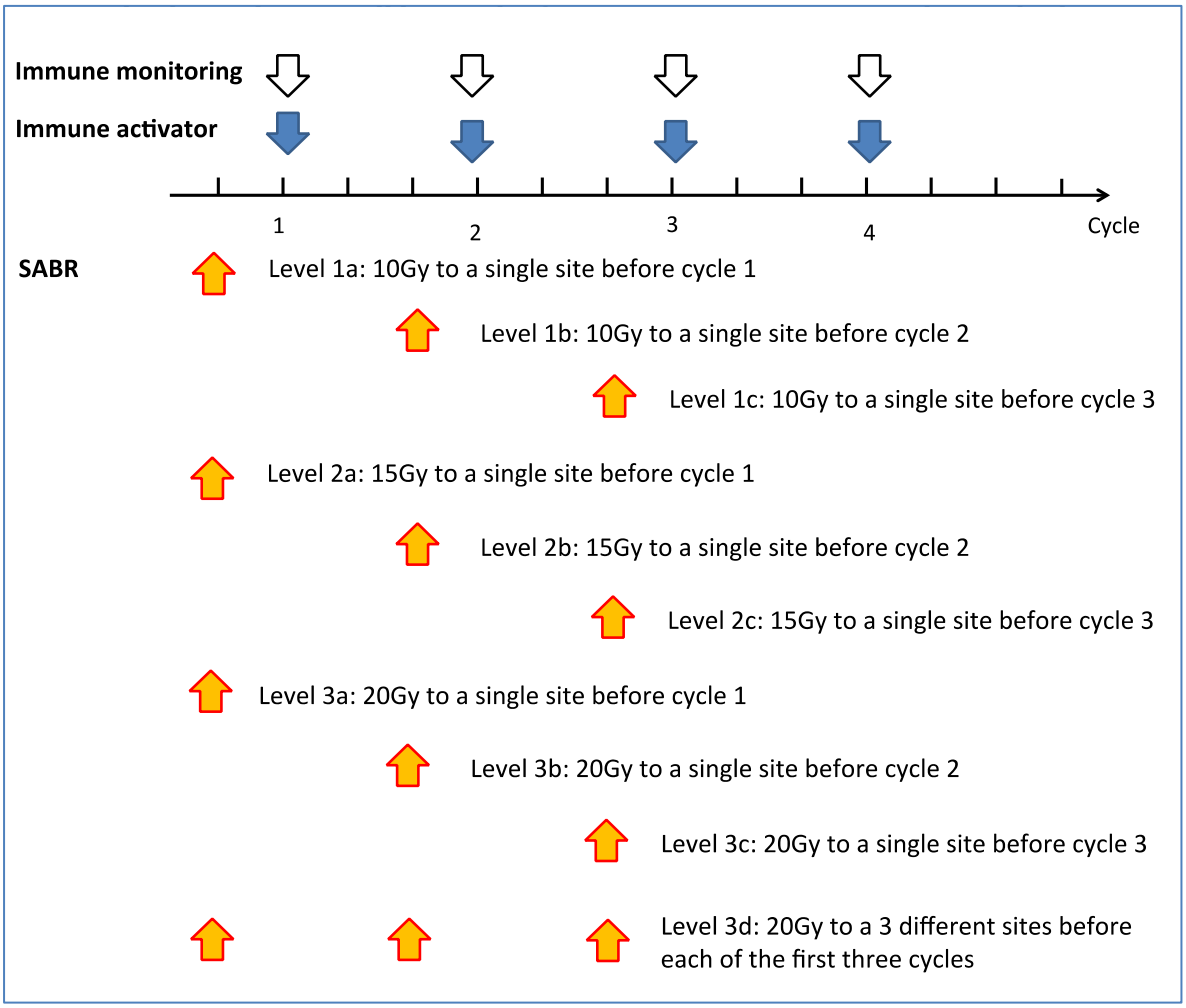
- To determine the clinical activity of SABR with Immunotherapy
- To correlate tumor genetics with biologic and clinical activity.

## 3. STUDY DESIGN

This is a prospective phase I dose-escalation study. Patients will receive SABR to a single site at different doses and times during a course of immunotherapy . If these are tolerated, patients will receive SABR to 20Gy before each of the first three cycles. The schema is detailed below.



## 4. PATIENT SELECTION

Inclusion Criteria

- Aged 18 or older.
- Willing and able to provide informed consent.
- Histologically confirmed metastatic melanoma.
- At least one metastasis that is symptomatic or imminently symptomatic or may impact quality of life or ability to tolerate ongoing treatment.
- Metastatic disease and
    - At least one metastasis that can be treated with a SABR dose of at least 20Gy (as determined by a Radiation Oncologist).
    - At least one metastasis that will not be treated with SABR to monitor response.
- Able to tolerate treatment with Immunotherapy (as determined by a Medical Oncologist).

Additional inclusion criteria apply to patients who have had prior immunotherapy

- At least one metastasis that can be safely treated with a SABR dose of at least 20Gy (as determined by a Radiation Oncologist).
    - This can include progressive peripheral lung and liver lesions that have had previous SABR if these can be safely treated
- At least one metastasis that has not and will not be treated with SABR to monitor response.

Exclusion Criteria

- Patient with a life expectancy less than 3 months, including those with malignant pleural or pericardial effusions.
- Patients requiring immediate surgical intervention
    - Clinical or radiologic evidence of spinal cord compression
    - Dominant brain metastasis requiring surgical decompression
- Pregnant or lactating females
- Significant auto-immune diseases including inflammatory bowel disease, rheumatoid arthritis and Systemic Lupus Erythematosus

## 5. PRE-TREATMENT EVALUATION

Required:

- History and Physical Examination
- Histologic confirmation of melanoma.
    - Biopsy of a metastatic site is preferred, but not required.
- Staging investigations within 4 weeks of treatment
    - CT chest, abdomen and pelvis or whole body PET scan
- Pregnancy test for women of child-bearing age
- Mucosal swab of inner cheek (can be acquired during treatment)

At discretion of treating clinicians:

- CT or MRI brain
- Whole spine MRI
- Liver function tests (AST, ALT, GGT, alkaline phosphatase) for patients with liver metastases
- FBE, U&Es, Thyroid function tests, cortisol and ACTH.

# 6. TREATMENT PLAN

## Immunotherapy

Ipilimumab will consist of four cycles of 3mg/kg, delivered every three weeks. This scheme improved survival and resulted in grade 3 or higher toxicity in 15% of patients [3].

Nivolumab will consist of ongoing treatment as long as there is clinical benefit, at 3mg/kg every two weeks.. This dose resulted in grade 3 or higher toxicity in 18% of patients who had received prior Ipilimumab [4].

Combination Ipilimumab and Nivolumab will consist of 3mg/kg Ipilimumab and 1mg/kg Nivolumab for 4 cycles, following by 3mg/kg Nivolumab alone so long as there is clinical benefit.

Pembrolizumab will consist of ongoing treatment as long as there is clinical benefit, at 2mg/kg every three weeks. This dose resulted in grade 3 or higher toxicity in 10% [6].

## Stereotactic ablative radiotherapy

SABR will be given within 1 week of each cycle of Immunotherapy for the purpose of enhancing the clinical and biologic activity of these drugs. To assess this SABR doses will be escalated using a standard phase I 3+3 design as with any study assessing drug safety [24]. The design of this study is not to assess the safety of SABR itself. The SABR doses used in this study are the same biologically or less than doses used in previous phase II studies, where the rate of grade 2 or higher toxicity was 10% or less [18-23].

The SABR doses that are being used, form the basis of routine clinical care at The Alfred and directed by approved departmental SABR treatment protocols. All treatments will fall within the scope of these guidelines.

## 7. ADVERSE EVENTS

Adverse Events (AE) or reactions are any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or outcome temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

AE severity will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading scale (http://evs.nci.nih.gov/ftp1/CTCAE).

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening or disabling
- Grade 5: Death

AEs are considered related to the research intervention if there is a reasonable possibility that the reaction or event may have been caused by the research intervention (i.e. a causal relationship between the reaction and the research intervention cannot be ruled out by the investigator). The relationship of an AE to the study treatment (causality) will be described using the following definitions:

- Unrelated: Any AE for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the study treatment and the adverse event does not follow any previously documented pattern. The AE, after careful consideration by the investigator, is clearly and incontrovertibly due to causes other than the intervention.
- Unlikely: Any AE for which the time relationship between the study treatment and the event suggests that a causal relationship is unlikely and/or the event is more likely due to the subject's clinical condition or other therapies concomitantly administered to the subject.
- Possible: Any AE occurring in a timely manner after the administration of the study treatment that follows a known pattern to the intervention and for which no other explanation is known. The AE, after careful consideration by the investigator, is considered to be unlikely related but cannot be ruled out with certainty.
- Probable: Any AE occurring in a timely manner after the administration of the study treatment that follows a known pattern to the intervention and for which no other explanation is known. The AE, after careful consideration by the investigator, is believed with a high degree of certainty to be related to the intervention.
- Definitely Related: Any AE occurring within a timely manner after administration of the study treatment that is a known sequela of the intervention and follows a previously documented pattern but for which no other explanation is known. The AE is believed by the investigator to be incontrovertibly related to the intervention.

# 8. RESPONSE EVALUATION

## 8.1 Biologic activity

Peripheral blood will be collected prior to each dose of Immunotherapy and will be assessed with the following immune monitoring profile [7-10]:

| CD8 Surface | Markers |
|---|---|
| Terminal Effector | CD45RAhi, CD95hi, CCR7lo, CD127lo |
| Naïve | CD45RAhi, CD95lo, CCR7hi |
| Stem cell memory | CD45RAhi, CD95hi, CXCR3hi, CCR7hi, CD127hi |
| Central Memory | CD45RAlo, CD95hi, CCR7hi |
| Effector Memory | CD45RAlo, CD95hi, CCR7lo |
| IL7Rhi Memory | CD45RAlo, CD95hi, CD127hi |
| Tumour antigen-specific | PD1+ |
| Exhausted | PD1+ Tim3+ |
| | |
| **CD8 Intranuclear** | **Markers** |
| Poor effector | Eomeshi, T-betlo |
| Good effector | Eomeslo, T-bethi |
| Reinvigorated effector | Eomeshi, T-betlo, Ki67hi |
| | |
| **CD8 Intracellular** | **Markers** |
| Unexhausted | IL2hi, TNFalpha hi, GzmB hi, IFNg hi |
| Early exhausted | IL2lo, TNFalpha hi, GzmB hi, IFNg hi |
| Intermediate exhausted | IL2lo, TNFalpha lo, GzmB hi, IFNg hi |
| Advanced exhausted | IL2lo, TNFalpha lo, GzmB lo, IFNg lo |

| CD4 Surface | Markers |
|---|---|
| Resting Tfh | CXCR5hi, CCR7hi, PD1lo |
| Effector Tfh | CXCR5hi, CCR7lo, PD1hi |
| GC-Tfh-like | CXCR5hi, CXCR3lo, PD1hi |
| Treg | CD25hi, CD127lo |
| Naïve | CD45RAhi, CD95lo, CCR7hi |
| Stem cell memory | CD45RAhi, CD95hi, CXCR3hi, CCR7hi, CD127hi |
| Central Memory | CD45RAlo, CD95hi, CCR7hi |
| Effector Memory | CD45RAlo, CD95hi, CCR7lo |
| Th1 CM | CXCR3hi, CCR6lo, CCR7hi, CCR4lo |
| Th1 EM | CXCR3hi, CCR6lo, CCR7lo, CCR4lo |
| Th17 CM | CXCR3lo, CCR6hi, CCR7hi, CCR4hi |
| Th17 EM | CXCR3lo, CCR6hi, CCR7lo, CCR4hi |
| Th2 CM | CXCR3lo, CCR6lo, CCR7hi, CCR4hi |
| Th2 EM | CXCR3lo, CCR6lo, CCR7lo, CCR4hi |
| | |
| **CD4 Intracellular** | **Markers** |
| IL-21-producing | IL-21hi |
| IL-10-producing | IL-10hi |

## 8.2 Clinical activity

Clinical activity will be assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) [27].

RECIST considers the sum of the longest diameter (LD) of index lesion(s) (up to 5 lesions in total, 2 per organ) on post-treatment CT scans compared to baseline. Target lesion(s) will not include those that have received SABR.

RECIST assessment outcomes are;

- Complete Response (CR) is disappearance of all target lesions
- Partial Response (PR) is at least a 30% decrease in the sum of the LD of target lesions compared to baseline
- Progressive Disease (PD) is at least a 20% increase in the sum of the LD of target lesions compared to nadir or the appearance of new lesions
- Stable Disease (SD) is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

In addition to this, the immune related response criteria (irRC) and sequential assessment of total tumour volume will be assessed to determine what radiologic criteria correlate best with survival

## 8.3 Tumor genetics

Tumor DNA will be extracted from already collected samples and compared to mucosal cheek samples. Whole exome sequencing will be performed. Genetic heterogeneity [28] (degree of variation in somatic mutations between tumor and cheek samples) will be correlated to biologic and clinical markers of activity.

# 9. PATIENT ASSESSMENTS

Patients will undergo clinical assessments on each day they receive immunotherapy or SABR. At each of these a history and examination will be performed to determine CTCAE toxicities and peripheral blood collected. In addition approximately every 3 months restaging with a CT scan of the chest, abdomen and pelvis will be performed, along with an MRI of the brain if this was an initial site of disease or if clinically indicated. For the purposes of this study, patients will be followed for a total of two years or until death.

The additional SABR planning and delivery visits are the only additional requirements of patients that will result from trial participation. Other visits are typical of routine clinical care for patients treated with Immunotherapy

## 9.1 Toxicity endpoints

Number of CTCAE grade 3 toxicities.

Any CTCAE grade 3 or higher toxicity that is possibly, probably or definitely treatment related will be considered a dose limiting toxicity (DLT). All grade 3 or higher toxicities will be assessed by an independent data monitoring committee for attribution.

Immune-related toxicities with Immunotherapy are typically rapid onset and short-lived [3,4]. The median time to grade 3-5 toxicity was 64 days with Pembrolizumab and 40 days with Ipilimumab [6]. Escalation to the next SABR dose level (from level 1a to 2a, or from level 2b to 3b) can only occur once at least 3 patients have been followed for at least 64 days. Accrual within each dose level (from level 1a to 1b, or from level 2b to 2c), where SABR timing changes, but not dose, is allowed without a follow-up period.

## 9.2 Biologic endpoints

Absolute increase peripheral blood parameters of the immune activating profile.

## 9.3 Clinical endpoints

Proportion of patients achieving CR or PR by RECIST criteria.

Overall survival will be defined as the time until death from any cause, and progression-free survival as time to either progression or death, whichever occurs first. This will be measured from the date of first treatment.

## 9.4 Genetic endpoint

Tumor heterogeneity (high vs. low, where high >100 somatic mutations per megabase) [28].

### 9.4 Statistical considerations

Using a standard 3+3 design, if 2 of 3 patients develop DLT at a particular dose, we can conclude with 90% confidence that the true probability of DLT at that dose is greater than 20%. Similarly, if 0 of 3 patients develop DLT at a particular dose, we can conclude with 90% confidence that the true probability of DLT at that dose is less than 55%. Expanding to 6 patients, when 1 of 3 patients develop DLT this ensures that there is a 91% probability escalation will be halted when the true probability of DLT is less than 10% and 92% probability escalation will not proceed when the true probability of DLT is greater than 60%.

Biologic endpoints will be correlated with clinical and survival endpoints using the Student's t-test or Fisher's Exact Test.

Survival will be calculated using the Kaplan-Meier method and differences compared using the log-rank test. A Cox multivariable regression analysis will be used to determine baseline and treatment factors predictive of survival.

## 10. ETHICAL CONSIDERATIONS

The Principal Investigator will obtain approval from the Alfred Human Research Ethics Committee (HREC). The protocol (and any amendments), the informed consent form, and any written information to be given to subjects will have been reviewed and approved by the HREC.

The written informed consent form will be provided to potential study candidates. A study investigator is responsible for obtaining written informed consent from each patient. If the subject is unable to provide informed consent, then this should be obtained from the subject's legally acceptable representative, prior to beginning any study procedures and treatment(s). As part of this, a study investigator will inform the patient, or their legally acceptable representative, of all aspects of the study, including the potential risks and benefits involved. The subject should be given ample time and opportunity to ask questions prior to deciding about participating in the study and be informed that participation in the study is voluntary and that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The informed consent must be signed and dated by the subject, or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form should be given to the subject or the subject's legally acceptable representative. The process of obtaining informed consent should be documented in the patient source documents.

The names and personal information of study participants will be held in strict confidence. All study records will only identify the subject by initials and the assigned study identification number. The research manager will maintain a confidential subject identification list during the course of the study. Access to confidential information is only permitted for direct subject management and for those involved in monitoring the conduct of the study. The subject's name will not be used in any public report of the study. Study records will be kept indefinitely.

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