AlfredHealth

Participant Information Sheet/Consent Form

Title	Treating metastatic melanoma with Stereotactic ABlative Radiotherapy and IMmune Pathway ACTivation: A phase I dose-escalation trial (SABR IMPACT I)
Short Title	SABR-IMPACT I
Study Sponsor	Alfred Health
Identification	Project # 545/14
Coordinating Principal Investigator/ Principal Investigator	Sasha Senthi
Associate Investigator(s)	Jeremy Ruben, Jeremy Millar, Andrew Haydon, Di Yu,
Location	Alfred Health/Monash University

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this study. This is because you have metastatic melanoma. Immune treatments are standard for patients like you. This study is testing the combination of stereotactic ablative radiotherapy with your immune treatment.

This Participant Information Sheet/Consent Form tells you about the study. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor. Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in the study, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the study
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

When cancer has spread from an original tumor to other sites of the body, it is classified as metastatic. Generally, for patients with metastatic melanoma, the goal of treatment has been to slow down the cancer growth with chemotherapy and/or radiation, as these treatments cannot get rid of the cancer altogether.

With drugs that activate the immune system, some studies have suggested melanoma may be controlled for a long period of time. This only happens for a small proportion of patients. By using stereotactic ablative radiotherapy (SABR), we hope to increase the effectiveness of the immune drugs and increase the proportion of patients who respond.

Giving immune activating drugs results in significant side effects in less than 1 in 5 patients. As SABR may increase the effectiveness of these drugs, it may also increase the side effects they cause or cause new side effects we have not seen before. The purpose of this study is to determine when these two treatments can be safely given together.

In Australia, patients with metastatic melanoma can receive the immune activating drugs Ipilimumab, Nivolumab and Pembrolizumab. Ipilimumab can be given with Nivolumab at the same time. These drugs have been approved for use Australia's drug regulatory authority, the Therapeutic Goods Administration (TGA) and their costs funded under the Pharmaceutical Benefits Scheme (PBS).

This research is being coordinated locally by Dr Sasha Senthi.

3 What does participation in this research involve?

You will be participating in a phase I study. Although SABR is generally safe on its own, it is not clear how safe it is in combination with immune activating drugs. To find out we will start by giving a very low dose of SABR, which we think will be safe for almost all patients and slowly increase the dose to a level, which we think will be effective.

Patients participating in this study will all receive drug(s) to activate their immune system and you will discuss this further with your doctor. These drugs will be delivered alone or in combination in a standard fashion, with at least 4 doses delivered 2-3 weeks apart. By participating in this study, you will also receive SABR to one of your disease sites.

The planning process for SABR, may involve construction of a plastic mask or special bean-bag to hold your head or body still for treatment. Once these have been fitted you will have a CT scan, which will be used to target the tumor and minimize the dose to normal tissues.

SABR treatments will be given as a single dose and will take approximately one hour at The Alfred, as an outpatient. During treatment we use a CT scan through the region being treated to position you accurately. Treatment will be delivered once your positioning is confirmed.

During treatment you will be assessed by a doctor and have bloods tests. This is to assess the benefits and any side effects of treatment. Routinely blood tests are done to ensure you body is coping with treatment. Following treatment, assessments will continue every 3-6 months and may include CT scans of your entire body. The CT scans will look at the effect of treatment on known sites and to look for new sites of disease. These are standard aspects of clinical care that would occur routinely.

In addition to standard care, additional blood will be taken to assess the effect of treatment on the immune system and whether your immune system is active against your melanoma. We will also look at your tumor samples and determine their genetic makeup compared to your own

body. To do this we will take scrapings from your inner cheek. This is an optional part of this study for which we require you to agree to separately.

There are no additional costs associated with participating in this study, nor will you be paid. All medication, tests and medical care required as part of the study will be provided to you free of charge. Additional costs that you incur irrespective of whether you participate in this study, such as pharmacy dispensing changes are also not covered.

If you decide to participate in this study, a doctor here will inform your local doctor and up date them regularly about your progress.

4 What do I have to do?

Participation in this study places no additional restrictions on you.

5 Other relevant information about the study

Every patient with a condition similar to yours will be asked to consider this study. We expect at least 30 patients to participate.

6 Do I have to take part in this study?

Participation in any study is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the study at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with The Alfred.

7 What are the alternatives to participation?

You do not have to take part in this study to receive treatment at the Alfred. If you do not take part in this study, you will receive the same study drugs. If any of your metastasis become hard to control with these drugs alone, you may be offered standard radiotherapy or SABR to control these.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits by participating in this study; however, possible benefits of SABR include increasing the chance you will respond to the immune treatment. If you respond, your chance of survival will increase.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get. Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Potential side effects of immune activating drugs (Ipilimumab, Nivolumab or Pembrolizumab) include the following. If Ipilimumab and Nivolumab are given together the risk of getting the side effects below is increased.

- Tiredness, fevers, chills, rashes, itch,loss of appetite and leg swelling. Rashes can rarely include areas when your skin looses its colour.

- Nausea, vomiting, constipation, diarrhea and abdominal pain.

- Pain ranging from headaches, stomach aches, joint pain and pains in the hands and legs.

- Rash, itch, tiredness, fevers, chills and changes in bowel habit.

- Inflammation of the bowel, kidney, hormone glands, pancreas, liver and lung. If the lung is involved this can cause a cough and shortness of breath. Inflammation of the pancreas, bowel and liver can cause stomach pain, diarrhea and these organs to not work properly. When this happens it is usually noticed first as changes in the blood. Inflammation of thehormone glandsmay cause high or low hormones levels. Inflammation of the kidney will cause them to loose their ability to function resulting in the inability to get rid of waste products from the body through urine.

The sides effects with these drugs are slightly different in each person and tolerating one drug does not mean you will tolerate the other. Similarly, side effects with one drug may different to side effects with the other.

Potential side effects from SABR depend on the area being treated:

- Radiation treatments to the head and neck area or brain may commonly cause headache, hair loss, mild sunburn of the skin, decreased hearing or irritation of the ears, dryness or irritation of the eyes and dry or sore mouth or throat or loss of taste during radiation treatments. Common delayed (more than 6 months after treatment) side effects from radiation treatments to the head and neck area may include persistent dry mouth (common) as well as changes in thinking or memory (rare and only if the brain is treated).

- Radiation treatments to the chest area may commonly cause a dry cough, sore throat or difficulty swallowing as well as mild sunburn of the skin. Delayed (late, >6months post treatment) side effects from radiation treatments to the chest area may rarely cause new or persistent difficulties with swallowing; shortness of breath or cough.

- Radiation treatments to the abdomen or pelvic area commonly include diarrhea or cramping of the bowels, discomfort or frequency of urination and possibly nausea. Rarely, delayed (late, >6months post treatment) side effects from radiation treatments may occur including persistent cramping, diarrhea or bleeding from the bowel; frequency or discomfort with urination or bleeding from the bladder.

- Radiation treatments to bone can be associated with increased pain, redness of the skin, and a risk of a broken bone.

- Fatigue during and following radiation treatments to any of these areas is common

- Radiation treatments are associated with a small risk of serious injury to tissues or organs that are included in the area being treated. This injury may show up months to years post treatment. In very rare instances, these side effects may result in death. Some of these side effects include (depending on whether these areas are being treated):
    - Brain injury resulting in loss of strength, sensation or thinking ability
    - Spinal cord injury resulting in paraplegia
    - Lung injury resulting in shortness of breath
    - Esophagus injury resulting in difficulty swallowing
    - Heart injury resulting in a heart attack or fluid collection on the heart
    - Bone injury resulting in a broken bone
    - Rectal or bowel injury resulting in bleeding or perforation (hole) or fistula (abnormal connection between the bowel and another organ)
    - Bladder injury resulting in bleeding or perforation (hole) or fistula (abnormal connection between the bowel and another organ)

Your doctor will monitor your therapy and make adjustments to your treatment or prescribe medicines in order to manage side effects that occur during treatment.

The potential effects of anti-cancer treatments on the unborn child can be significant. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the study. You cannot participate in this research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing this study. If you are male, you should not father a child or donate sperm for at least 12 months after the last treatment (any radiotherapy or chemotherapy). Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of 12 months after completion of the study. You should discuss methods of effective contraception with your study doctor.

If you do become pregnant whilst participating in this study, you should advise your study doctor immediately. Your study doctor will withdraw you from the study and advise on further medical attention should this be necessary. You should advise your study doctor if you father a child while participating in the study.

If you become upset or distressed as a result of participation in this study, we are able to arrange for counselling or support. This will be provided by qualified staff who are not members of the study team. This counselling will be provided free of charge.

10 What will happen to my test samples?

Some of your blood will be processed here at The Alfred. This blood is the blood that is routinely taken from people when they receive immune activating drug.

By participating in this study, additional blood, tumour tissue and cheek scrapings will be sent to Monash University. There a laboratory will do special tests to see whether your immune system is working against your melanoma and determine the genetic makeup of your tumour.

11 What if new information arises during this study?

Sometimes during the course of a study, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your study doctor will make arrangements for your regular care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor may consider it in your best interests to withdraw from the study. If this happens, your doctor will explain why and maintain your regular care.

12 Can I have other treatments during this study?

Whilst you are participating in this study, you may not be able to take some or all of the medications or treatments you have been taking. It is important to tell your study doctor about any treatments or medications you are taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the study. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the study.

13 What if I withdraw from this study?

If you decide to withdraw from the study, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the study, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the study can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the study results. If you do not want them to do this, you must tell them before you join the study.

If you withdraw, you can continue under the care of your doctor.

14 Could this study be stopped unexpectedly?

This study may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
- Unacceptable side effects
- The treatment being shown not to be effective
- The treatment being shown to work and not need further testing

15 What happens when the study ends?

You will be followed for at least 5 years after your last treatment. This would occur irrespective of your participation in this research. As soon as the results of this research are available Dr Senthi will inform you or your family in writing.

Part 2 How is the study being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you. Any information obtained in connection with this study that can identify you will remain confidential. Your information will only be used for the purpose of this study and it will only be disclosed with your permission, except as

required by law. Information about your participation in this study may be recorded in your health records.

We will maintain your confidentiality by using a unique identifier number on all documents instead of your name. A separate secure document will contain the linkage between your name and identifier number in order to minimize the possibility of a breach of your privacy. Your research records will be stored in a locked room within The Alfred. Once the data has been put into the research database, any identifying information will be removed from the database in order to protect your confidentially. If the results of the study are published, your name will not be used and no information that discloses your identity will be released or published without your explicit consent.

By signing this consent form; you hereby consent to participation in this study. By consenting to this study you agree to allow us to confidentially collect this data. If you do not consent to this data collection, then you cannot participate in this study.

Study data will be kept indefinitely. Access to your information will be limited to doctors participating in this study and the Data and Research Manager. Data will be stored on a secure, password protected database.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this study, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This study is being conducted by Dr Sasha Senthi.

No member of the research team will receive a personal financial benefit from your involvement in this study (other than their ordinary wages).

19 Who has reviewed the study?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of Alfred Health.

This study will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this study or if you have any medical problems which may be related to your involvement in the study (for example, any side effects), you can contact any of the following people:

Clinical contact person

Name	Sasha Senthi
Position	Radiation Oncologist
Telephone	9076 2000
Email	s.senthi@alfred.org.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Emily Bingle
Position	Alfred Health Human Ethics team member
Telephone	03 9076 3619
Email	research@alfred.org.au

Consent Form - *Adult providing own consent*

Title	Treating metastatic melanoma with Stereotactic ABlative Radiotherapy and IMmune Pathway ACTivation: A phase I dose-escalation trial (SABR IMPACT I)
Short Title	SABR-IMPACT I
Study Number	
Study Sponsor	Alfred Health
Principal Investigator	Sasha Senthi
Associate Investigator(s)	Jeremy Ruben, Jeremy Millar Andrew Haydon, Di Yu
Location	Alfred Health and Monash University

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the study.

☐ In addition to this, I agree to provide researchers a sample from my cheek and tumour so that the genetics of these can be determined and compared.
I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Alfred Health concerning my disease and treatment for the purposes of this study. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this study as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the study, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the study.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for this specific research project

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	Treating metastatic melanoma with Stereotactic ABlative Radiotherapy and IMmune Pathway ACTivation: A phase I dose-escalation trial (SABR IMPACT I)
Short Title	SABR-IMPACT I
Study Number	
Study Sponsor	Alfred Health
Principal Investigator	Sasha Senthi
Associate Investigator(s)	Jeremy Ruben, Jeremy Millar Andrew Haydon, Di Yu
Location	Alfred Health and Monash University

Declaration by Participant

I wish to withdraw from participation in the above study and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Alfred Health.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the study and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the study.

Note: All parties signing the consent section must date their own signature.