

ANICCA-CLASS II

A phase II trial assessing nivolumab in class II expressing microsatellite stable colorectal cancer

CHIEF INVESTIGATOR: PROF. GARY MIDDLETON | TRIAL SPONSOR: UNIVERSITY OF BIRMINGHAM

TRIAL DESIGN

An open-label, single arm, phase II, multicentre clinical trial to determine the durable clinical benefit (DCB) of nivolumab in patients with class II expressing microsatellite stable colorectal cancer (MSS CRC).

TRIAL OBJECTIVES

Primary objective:

To allow detection of durable clinical benefit in patients with MSI-like MSS CRC treated with single agent nivolumab, to justify further investigation in subsequent studies.

Secondary objectives:

To evaluate the benefit of single agent nivolumab to patients with class II expressing MSS CRC in terms of other clinical outcomes relating to tumour response and progression-free and overall survival time.

Exploratory objectives:

To discover possible biomarkers for the prediction of a response to treatment with nivolumab.

To investigate whether CD8+ and PD-1 T cells are supplementary biomarkers of response to treatment with nivolumab.

OUTCOME MEASURES

Primary outcome measure:

Durable clinical benefit (DCB defined as the occurrence of complete response (CR), partial response (PR) or stable disease (SD) for 24 weeks or greater.

Secondary outcome measures:

- Objective response
- Best percentage change in sum of target lesion diameters (PCSD)
- Time to maximal response
- Progression-free survival time
- Overall survival time

PATIENT POPULATION AND SAMPLE SIZE

36 patients with class-II expressing MSS CRC

CORE INCLUSION CRITERIA (not exhaustive – refer to protocol section 4)

- Histologically confirmed locally advanced or metastatic CRC with greater than 50% cancer cell positivity for class II expression on immunohistochemistry indicating MSI-like MSS disease confirmed by central laboratory testing using the CR3/43 antibody (ab17101)) (Abcam, Cambridge, UK).
- Patients must have completed all standard of care therapy that the treating oncologist deems appropriate. All lines of therapy will be allowed, except if treated previously with PD1/PDL1 inhibitors. Entry in to the trial as first line therapy is allowed if the patient declines standard chemotherapy.
- Age \geq 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2

- CT scan of chest and abdomen within 28 days of starting nivolumab demonstrating uni-dimensionally measurable disease as per RECIST version 1.1
- Demonstrate adequate haematological function:
 - Platelet count $\geq 100 \times 10^9 /L$
 - Neutrophils $\geq 1.5 \times 10^9/L$
 - Haemoglobin $\geq 90 \text{ g/L}$
- Demonstrate adequate renal function
 - Creatinine clearance < 1.5 times ULN concurrent with creatinine clearance $> 50 \text{ ml/min}$ (calculated by Cockcroft and Gault equation (Appendix 3). If this is $\leq 50 \text{ ml/min}$ then an isotopic Glomerular Filtration Rate (GFR) may be carried out and must be $> 50 \text{ ml/min}$
- Demonstrate adequate hepatic function:
 - Serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN)
 - Serum transaminases $\leq 2.5 \times$ ULN
- Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses.

CORE EXCLUSION CRITERIA (not exhaustive – refer to protocol section 4)

- Untreated symptomatic brain or leptomeningeal metastatic disease.
- Medical or psychiatric conditions comprising informed consent.
- Any medical condition which in the opinion of the investigator would compromise the ability of the patient to participate in the trial or which would jeopardise compliance with the protocol.
- Patient who has had chemotherapy, radioactive or biological cancer therapy within 4 weeks prior to the first dose of trial therapy, or who has not recovered to CTCAE grade 1 or better from the Adverse Event (AE) due to cancer therapeutics administered more than 4 weeks earlier.
- Active autoimmune disease that has required systemic treatment in past 2 years.
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Risk factors for bowel obstruction or bowel perforation.
- History of tuberculosis, non-infectious pneumonitis, has active pneumonitis or significantly reduced transfer coefficient (KCO).
- Patient had prior treatment targeting PD-1: PD-L1 axis.
- Patient has a known history of other malignancy, unless the patient has undergone potentially curative therapy with no evidence of that disease for 3 years.
- Positive for HIV, Hepatitis B or C

TREATMENT SCHEDULE

Patients will be administered nivolumab for up to two years or until disease progression; each cycle being 28 days. Trial treatment should be administered on day 1 of each cycle (+/- 3 days) after all procedures/assessments have been completed as details on the schedule of events.. Trial treatment will be administered on an outpatient basis.

Dosing instructions for nivolumab:

Drug	Dose	Frequency	Route	Regimen	Use
Nivolumab	480mg/kg	Q4W	60 minute IV infusion	Until progressive disease, unacceptable toxicity, withdrawal of consent or completion of two years treatment	Experimental

Schedule of Events	Microsatellite Status and Class II Expression Screening	Screening		TRIAL ENTRY	Treatment					Follow up		
		Within 28 days of registration	Within 7 days of registration		Day 1, cycle 1	Day 1, Every cycle (every 4 weeks) +/- 3 days	Every alternate cycle from cycle 3 onwards (approx. every 8 weeks) +/- 3 days	Every 9 weeks	Every 12 weeks	Treatment discontinuation visit (end of treatment)	Safety follow up visit (28 days post treatment discontinuation) 21	Every 4 weeks for 6 months then every 12 weeks
Informed consent ¹	x	x										
Archival diagnostic tumour biopsy sample for Class II and MS testing ²	x											
Demographics/Medical History/Prior Medications ³		x										
Vital Signs ⁴			x	x	x				x	x		
Physical Examination (including weight)			x	x	x				x	x		
ECOG performance status ⁵			x	x	x				x	x		
Review Concomitant Medications ⁶			x	x	x				x	x		
Review Adverse Events ⁷			x	x	x				x	x	x	
Full blood count (FBC) ⁸			x	x	x				x	x		
Comprehensive serum chemistry panel ⁸			x	x	x				x	x		
Urinalysis			x						x			
Coagulation parameters ⁹		x							x			
HIV, Hepatitis B and C ¹⁰		x										
Pregnancy Test –Serum β-HCG ¹¹			x									
Pregnancy Test – Urine ¹²				x	x							
Renal function – GFR ¹³			x							x		
Thyroid function and cortisol ¹⁴			x		x				x	x		
Cytokine/Chemokine Panel and proteomics ¹⁵				x	x				x			
Germline DNA ¹⁶				x								
ctDNA ¹⁷				x	x				x			
CT scan with contrast (chest, abdomen, pelvis) ¹⁸		x					x (up to 45 weeks)	x (after 45 weeks)			x (see notes)	
Nivolumab administration ¹⁹				x	x							
Survival assessment ²⁰									x	x	x	

Notes

1. Written informed consent must be obtained prior to testing patient's biopsy for MSS/Class II status and then further informed consent prior to any protocol specific procedure and within 28 days to starting treatment.
2. The minimum requirement for a biopsy sample must be five slides of stained sections from formaldehyde fixed paraffin embedded (FFPE) tissue, or preferably representative blocks of tumour tissue. Cytology samples will also be accepted if a formalin fixed clot is available. For patients who have already had their MS status determined as MSS ensure pathology report confirming this is sent with their tumour biopsy sample. RAS testing results need to be provided on the pathology report sent with the biopsy sample.
3. Includes smoking and alcohol history, any relevant significant medical conditions (other than colorectal cancer) and autoimmune conditions, history of treatment for the primary diagnosis, prior systemic treatment, radiation treatment and surgical treatment, including best response to prior treatments where applicable. Date of last prior cancer treatment must be documented and must not be within 4 weeks of registration.
4. Vital signs to include: temperature, pulse, respiratory rate and blood pressure (average of 3 BP readings). Do not need repeating on day 1 of cycle 1 if performed within 7 days of intended IMP administration date.
5. For ECOG performance status criteria see Appendix 1. Do not need repeating on day 1 of cycle 1 if performed within 7 days of intended IMP administration date.
6. Concomitant medications taken within four weeks prior to registration should be recorded at baseline. Do not need repeating on day 1 of cycle 1 if performed within 7 days of intended IMP administration date.
7. Adverse Events (AEs) and laboratory safety measurements will be graded per NCI Common Terminology Criteria for Adverse Events (CTCAE) version v4.03 (see Appendix 2). All adverse events, whether gradable by CTCAE or not, will also be evaluated for seriousness. In addition to AE review at each cycle, extra safety monitoring will be performed at monthly intervals up to 6 months after treatment discontinuation. During follow-up, AE review can be performed via telephone call. If at the 6 month follow up review there are any toxicities at grade 2 or higher that the investigator considers to be related to the trial treatment then these should be followed up until they have reduced to grade 1 or less. Do not need repeating on day 1 of cycle 1 if performed within 7 days of intended IMP administration date.
8. Routine laboratory tests (e.g., Full blood count (FBC); comprehensive serum chemistry panel; urinalysis) will be performed by the local trial site laboratory or their contract laboratory. FBC to include: white blood cells, haematocrit, haemoglobin, platelets, neutrophils, lymphocytes, red blood cells, monocytes, basophils, eosinophils, absolute neutrophil count and serum chemistry to include: sodium, potassium, urea nitrogen, creatinine, magnesium, calcium (total), bilirubin (total), direct bilirubin, albumin, alkaline phosphatase (ALP), aspartate transferase (AST), alanine transferase (ALT), glucose, lactate dehydrogenase (LDH), phosphate, total protein, C reactive protein (CRP), Carcinoembryonic antigen (CEA). Routine laboratory tests may be performed up to 3 days prior to treatment administration visit. Do not need repeating on day 1 of cycle 1 if performed within 7 days of intended IMP administration date.
9. Prothrombin (PT) / International Normalised Ratio (INR) and partial thromboplastin (aPTT) should be collected at screening and at Treatment Discontinuation Visit. Coagulation parameters should be determined throughout the trial when clinically indicated.
10. Testing will be performed by the local laboratory at screening. Include Hepatitis C Virus (HCV) RNA (qualitative), Hepatitis B surface Antigen (HBsAg), and Human Immunodeficiency Virus (HIV) 1/2 antibodies.
11. Women of a child bearing potential must have a negative serum pregnancy test prior to registration, this must be performed within 7 days of patient registration.
12. Women of a child bearing potential must have a negative serum or urine pregnancy test (Minimum sensitivity 25 IU/L or equivalent units of HCG) this should be performed before the first IMP administration and then at every cycle before IMP administration (approx.. 4 weeks) i.e before cycle 1, cycle 2, cycle 3 etc.

13. To be eligible for trial entry patients must have adequate renal function as defined by Creatinine clearance $<1.5 \times \text{ULN}$ and creatinine clearance $>30 \text{ ml/min}$ (calculated as per institutional standard).
14. Analysis of cortisol, T3, T4 and Thyroid Stimulating Hormone (TSH) will be performed by the local site laboratory. During treatment, testing will be performed at every cycle (approx. every 4 weeks), at Treatment Discontinuation Visit and at Safety Follow up Visit (28 days post treatment discontinuation).
15. Collected before start of infusion at cycle 1 followed by every alternate cycle from cycle 3 onwards e.g. cycle 3, 5, 7 etc. and at Treatment Discontinuation Visit. Processing and storage of blood samples are to be carried out as described in ANICCA-Class II Laboratory Manual.
16. Collected before start of infusion at cycle 1.
17. Collected before start of infusion at cycle 1, followed by every alternate cycle from cycle 3 onwards e.g. cycle 3, 5, 7 etc. and at Treatment Discontinuation Visit. Processing and storage of blood samples are to be carried out as described in ANICCA- Class II Laboratory Manual.
18. Tumour imaging by CT with contrast (chest, abdomen, pelvis) will be performed within 28 days prior to registration. The same imaging technique has to be used in a patient throughout the trial. Scans will be reported by RECIST 1.1 (Appendix 3). Tumour imaging will be performed every 9 weeks from treatment commencement up to 45 weeks and following this every 12 weeks until disease progression. Patients may initially show evidence of disease progression as a response to immunotherapy therefore patients may be allowed to continue treatment beyond RECIST defined disease progression if they are clinically stable and tolerating therapy. Trial treatment must then be discontinued upon further progression defined as the presence of any new lesion or an additional 10% increase in existing tumour burden from time of the initial progression. Following treatment discontinuation if patient has stopped trial treatment without progressive disease they should continue to be scanned according to this schedule until progressive disease is identified. NOTE. In this situation, it is important if treatment is discontinued earlier than 45 weeks from commencement of treatment, scans should continue to be performed every 9 weeks until this time point or disease progression. If disease progression has not been identified at 45 week scan then scans should continue to be performed every 12 weeks until disease progression or end of follow up. If patient discontinues without progressive disease after 45 weeks from commencement of treatment they should have scans every 12 weeks until disease progression. Response status will be assessed by the trial site.
19. First administration of nivolumab should be given within 7 days of registration.
20. Follow up will be completed every 4 weekly for 6 months then 12 weekly thereafter to obtain further treatment details and overall survival status.
21. For patients who begin another cancer therapy within 28 days after discontinuation of study therapy, the Safety Follow-Up Visit should occur prior to the patient receiving another cancer therapy.