A phase II trial assessing nivolumab in strong 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 strong 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:
- Objective response
- Progression free survival time
- Overall survival time

Exploratory objectives:
To discover possible biomarkers for the prediction of a 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
- Progression free survival time
- Overall survival time

PATIENT POPULATION AND SAMPLE SIZE
36 patients with strong 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 ≥ 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

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

ANICCA Class II Trial Summary
- Demonstrate adequate haematological function:
  - Platelet count $\geq 100 \times 10^9$ /L
  - Neutrophils $\geq 1.5 \times 10^9$ /L
  - Haemoglobin $\geq 90$ g/L
- Demonstrate adequate renal function
  - Creatinine clearance $< 1.5$ times ULN concurrent with creatinine clearance $>50$ ml/min (calculated by Cockcroft and Gault equation (Appendix 3). If this is $\leq 50$ ml/min then an isotopic Glomerular Filtration Rate (GFR) may be carried out and must be $>50$ 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 14 days. Trial treatment should be administered on day 1 of each cycle after all procedures/assessments have been completed as details on the schedule of events. Trial treatment may be administered up to three days before or after the scheduled day 1 of each cycle due to administrative reasons. Trial treatment will be administered on an outpatient basis.

Dosing instructions for nivolumab:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Route</th>
<th>Regimen</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>3mg/kg</td>
<td>Q2W</td>
<td>60 minute IV infusion</td>
<td>Until progressive disease, unacceptable toxicity, withdrawal of consent or completion of two years treatment</td>
<td>Experimental ANICCA Class II Trial Summary</td>
</tr>
</tbody>
</table>
## SCHEDULE OF EVENTS

<table>
<thead>
<tr>
<th></th>
<th>Pre-Screening</th>
<th>Screening</th>
<th>Treatment</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 28 days of registration</td>
<td>Within 7 days of registration</td>
<td>Week 0, treatment Day 1</td>
<td>Every 2 weeks (±3 days)</td>
</tr>
<tr>
<td>Check with trial office that registration slot is available</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archived/fresh Tumour Sample for Class II and MS testing</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics/Medical History/Prior Medications</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-Lead ECG</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review Concomitant Medications</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review Adverse Events</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full blood count (FBC)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehensive serum chemistry panel</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation parameters</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV, Hepatitis B and C</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test – Urine or Serum β-HCG</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal function – GFR</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid function and cortisol</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine/Chemokine Panel and proteomics</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germline DNA</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ctDNA</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT scan with contrast (chest, abdomen, pelvis)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab administration</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Survival assessment</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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. Patient will need to be re-consented to ANICCA- Class II if over 28 days to treatment start.

2 Fresh biopsy will be required if archival sample not available or MSS/Class II testing is unsuccessful.

3 Includes smoking and alcohol history, history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented.

4 Vital signs to include: temperature, pulse, respiratory rate and blood pressure (average of 3 BP readings).

5 For ECOG performance status criteria see Protocol Appendix 1.

6 A standard 12-lead ECG will be performed, in triplicate if clinically abnormal rhythm detected, using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as it should be reported as a concurrent condition. Additional time points may be performed as clinically necessary.

7 Adverse Events (AEs) and laboratory safety measurements will be graded per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, Appendix 2. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. At follow-up visits AE and concomitant medication review can be performed via telephone call.

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) may be collected up to 3 days prior to treatment administration. Routine laboratory tests (serum chemistry; haematology) for screening should be performed within 7 days of first treatment.

9 Prothrombin (PT) / International Normalised Ratio (INR) and partial thromboplastin (aPTT) should be collected at screening and at the end of treatment. 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.

ANICCA Class II Trial Summary
For women of reproductive potential, a urine pregnancy test will be performed within 24 hours prior to administration of first IMP dosing. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. See Protocol Section 4.3 (Contraception).

Patients must have adequate renal function as defined by Creatinine clearance <1.5 x ULN concurrent with creatinine clearance >50 ml/min (calculated by Cockcroft and Gault equation – see Appendix 3. If this is ≤50 ml/min then an isotopic GFR may be performed and must be ≥50 ml/min.

Analysis of cortisol, T3, T4 and TSH (Thyroid Stimulating Hormone) will be performed by the local site laboratory. Whilst on treatment testing will be performed every 8 weeks.

Collected before start of infusion at cycle 1, followed by day 1 of every forth cycle (every 8 weeks) and at end of treatment. Processing and storage of blood samples are to be carried out as described in ANICCA- Class II Laboratory Manual. Analysis will be performed by a central laboratory.

Collected before start of infusion at cycle 1. Analysis will be performed by a central laboratory.

Collected before start of at cycle 1, followed by day 1 of every forth cycle (every 8 weeks) and at end of treatment. Analysis will be performed by a central laboratory. Processing and storage of blood samples are to be carried out as described in ANICCA- Class II Laboratory Manual.

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 (Protocol Appendix 4). Tumour imaging will be performed every 8 weeks for first 10 months i.e. prior to cycles 4, 8, 12, 16, 20 and following this every 12 weeks until disease progression. CT scan results must be ready prior to treatment visits to allow the treating clinician to make decision about treatment continuation. Response status will be assessed by the trial site.

Follow up will be completed every 4 weeks for 6 months then every 12 weeks to obtain further treatment details and survival status.

ANICCA Class II Trial Summary