Efficacy and safety of first line Cemiplimab in advanced BCC: A phase 2 trial (IMPACT)

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This protocol describes Efficacy and safety of first line Cemiplimab in advanced BCC: A phase 2 trial (IMPACT).

This trial will be conducted in compliance with the approved protocol. It will be performed according to the UK Policy Framework for Health and Social Care and the Medicines for Human Use (Clinical Trials) Regulations 2004 SI 2004/1031 (as amended) the World Medical Association Declaration of Helsinki Principles of Good Clinical Practice (GCP), Data Protection Legislation (European General Data Protection Regulation 2016 ((EU) 2016/679) and the Data Protection Act 2018) and other regulatory requirements as appropriate.

Protocol Authorised By:

Chief Investigator

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Dr Amarnath Challapalli

Date.....

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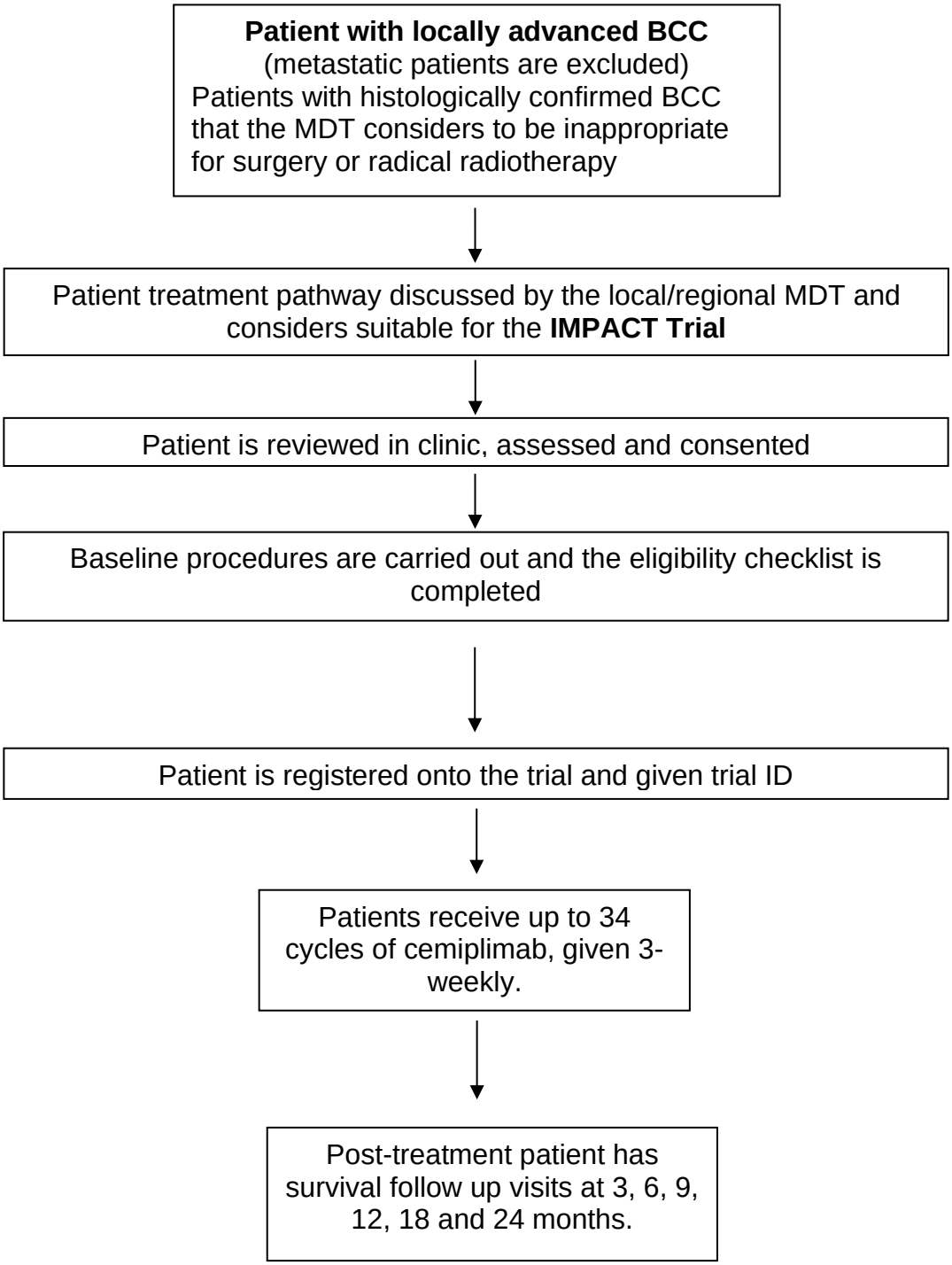
TRIAL SCHEMA



TRIAL SUMMARY

Title	Efficacy and safety of first line Cemiplimab in advanced BCC: A phase 2 trial (IMPACT)
Objective	To evaluate the benefit and safety of cemiplimab, a fully human anti-PD-1 monoclonal antibody in patients with locally advanced BCC
Endpoints	Primary: To assess the objective response rate (ORR) of cemiplimab in patients with locally advanced BCC at 6 months, by independent central review. Secondary: • To evaluate safety and tolerability including the frequency, severity and relatedness of adverse events (AEs) to the study treatment. AEs will be assessed according to CTCAE v5.0. • To assess ORR: Proportion of patients having achieved partial (PR) or complete (CR) remission at 12 and 24 months. • To assess disease control rate (DCR) at 6, 12 and 24 months. DCR is ORR plus stable disease (SD) • To assess progression-free survival (PFS) defined as the time from registration to the first of one of the following: development of clinical/radiological disease progression (composite criteria/RECIST 1.1) or death from any cause. • To assess overall survival (OS) defined as time from registration to the date of death from any cause. • To assess patient health status and quality of life (QoL) using the patient reported outcome measures EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire.
Trial Design	Open label, single arm, two stage, phase II non-randomised multi-centre trial
Type and number of patients	41 patients with locally advanced BCC will be recruited

Treatment	Up to 34 cycles of treatment with cemiplimab alone (maximum of 24 months of treatment)
Main inclusion criteria	• Aged 18 years or over • Histologically proven locally advanced BCC • ECOG performance status 0 or 1 • Adequate renal, liver and bone marrow function • At least 1 measurable target lesion
Main exclusion criteria	• Eligible for curative surgical treatment • Eligible for curative radiation treatment • Contraindication to immunotherapy

Please refer to pages 11-14 for the full inclusion and exclusion criteria.

1 BACKGROUND

Basal cell carcinoma (BCC) is the most common type of skin cancer worldwide. Risk factors for the development of BCC include fair skin type, exposure to ultraviolet radiation, age, history of BCC, genetic disorders (e.g., Gorlin syndrome, xeroderma pigmentosum), and immunosuppression (1). BCC tumours are generally slow growing and rarely metastasize, and the prognosis for patients who receive appropriate therapy is typically very good (2, 3). The most common treatment strategies are surgery, radiotherapy, topical treatments and photodynamic therapy (PDT).

In a small proportion of patients, BCCs can progress to an advanced stage (aBCC), including locally advanced BCC (laBCC) and metastatic BCC (mBCC) which become more difficult to treat. LaBCCs are large, aggressive, or recurrent tumours or those that penetrate deeper into the underlying skin and surrounding tissues (4, 5). LaBCCs may not be amenable to radiotherapy and can be challenging to treat effectively with surgery without causing significant morbidity, loss of function, or disfigurement when they are located in a difficult-to-treat area (e.g. periorbital) (4). LaBCCs are also associated with a high risk of recurrence (4, 5). Metastatic disease is rare, occurring in only 0.0028–0.55% of BCCs, and arises more frequently with primary tumours that are large, untreated, or aggressive or with recurrent tumours (6). The most frequent sites of metastasis are the bone, lung, liver and regional lymph nodes.

The proposed criteria to help define when surgery and irradiation are inappropriate are:

- >5 BCCs, if patient suffers from genetic syndromes
- BCC >10 mm, relapsing after 2 surgeries in critical locations (e.g. periocular and perioral areas)
- BCC infiltrating in bone/cartilage/other structures and curative resection unlikely
- Relapsing BCC after multiple surgeries and/or radiotherapy
- Advanced BCC in patients who do not qualify for general anaesthesia

In an attempt to facilitate appropriate management of patients with laBCC, several experts have proposed guidelines for defining laBCC (4, 7). Lear et al, suggested that BCCs should be defined as locally advanced if they are stage II or above according to the American Joint Committee on Cancer guidelines and if current treatment options are contraindicated by disease- or patient-driven factors (4). The disease-driven factors contributing to a diagnosis of laBCC include tumour size, location in mask area, higher number of BCCs, aggressive histological and recurrent disease with reduced chance of cure. Patient-driven factors contributing to a diagnosis of laBCC include young age where radiotherapy is discouraged, poor performance status, loss of cosmesis affecting quality of life, patient not inclined for treatment, and patients with genodermatoses (e.g. Garlin syndrome, xeroderma pigmentosum) or the presence of immunosuppression (4).

Aberrations in the hedgehog pathway are significant in the pathophysiology of BCC (8), and two licensed hedgehog pathway inhibitors (HHIs), vismodegib (based on ERIVANCE study: (9) and sonidegib (based on BOLT study: (10) have been approved for the treatment

of laBCC in cases where surgery and radiotherapy are inappropriate and in symptomatic metastatic BCC.

In clinical trials of hedgehog pathway inhibitors for laBCCs, objective response rates are estimated at 45%, with a median duration of response of 9.5 months (9, 11). Development of resistance is common, cures are rare, and adverse effects can be bothersome, leading to dosing interruptions or drug discontinuation (12).

BCC has one of the highest rates of somatic mutations among all cancer types because of effects of ultraviolet radiation (13), suggesting sensitivity to anti-programmed cell death 1 (PD-1) T-cell inhibition like other highly ultraviolet-mutated tumours. Small series have reported clinical activity of PD-1 inhibitors as second line treatment in both laBCC and mBCC (14-16). Small nonrandomized trials also showed efficacy of second-line pembrolizumab (17) and trials of second-line cemiplimab have been successful (18). Indeed, cemiplimab has been licensed as a second line treatment in patients who progress with or are intolerant to hedgehog pathway inhibitors.

In the UK, NICE has appraised that vismodegib is not recommended within its marketing authorisation for treating symptomatic mBCC, or laBCC that is inappropriate for surgery or radiotherapy, in adults because of the uncertainty in the evidence and because it is not cost effective (https://www.nice.org.uk/guidance/ta489/chapter/1-Recommendations). To date sonidegib has not been appraised by NICE. Hence, there is no valid, effective first-line treatment option for patients with laBCC or mBCC in the UK. Recently there has been a case series of 2 cases treated with nivolumab and pembrolizumab as first-line therapy in laBCC showing impressive responses (19). The potential advantages to using anti-PD-1 over hedgehog pathway inhibitors include improved medication compliance (intravenous route of administration) and the potential for long-term durable responses including complete responses. This suggests that anti-PD-1 therapy may be a feasible frontline therapeutic option in patients with advanced BCC.

Hence, we propose to evaluate the safety and efficacy of first line cemiplimab in patients with advanced BCC in this phase II trial.

2 AIMS OF THE STUDY

2.1 Hypothesis

Administration of the immunotherapy cemiplimab is well tolerated in patients with locally advanced basal cell carcinoma (laBCC) who will benefit from administration of cemiplimab with a response to treatment.

2.2 Primary endpoint

To assess objective response rate (ORR) of cemiplimab in laBCC at 6 months, by independent central review.

ORR is defined as proportion of patients achieving a complete response (CR) or partial response (PR).

Clinical response criteria (see Appendix 2 table 1) will be used to determine ORR, for externally visible tumour(s) that require bidimensional measurements according to World Health Organization (WHO) criteria. Composite response criteria (see Appendix 2 table 2) will be used for patients who have both target lesions measurable by clinical response criteria and radiologically by RECIST 1.1 to determine ORR.

In patients achieving CR, histological assessment of tumour biopsies will be required to confirm CR, otherwise this will be reported as PR.

2.3 Secondary endpoints

- To evaluate safety and tolerability including the frequency, severity and relatedness of AEs to the study treatment. AEs will be assessed according to CTCAE v5.0.
- To assess ORR at 12 months and 24 months.
- To assess disease control rate (DCR) at 6, 12 and 24 months. DCR is ORR plus stable disease (SD).
- To assess progression-free survival (PFS) defined as the time from registration to the first of one of the following: development of clinical/radiological disease progression (composite criteria/ RECIST 1.1) or death from any cause.
- To assess overall survival (OS) defined as time from registration to the date of death from any cause.
- To assess patient health status and quality of life (QoL) using the patient reported outcome measures EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire.
- To estimate the time to response (TTR: defined as the time from the start of treatment to the first objective tumour response (tumour shrinkage of ≥30%)) and duration of response (DOR: the time from response to progression/death) to cemiplimab.

2.4 Translational Objective

Patient tissue samples, previously collected as part of the patient's standard of care, will be collected for evaluation of PD-L1 immunohistochemistry, TMB assessments, or MHC-I immunohistochemistry and correlation with efficacy analyses.

3 TRIAL DESIGN

This is a non-randomised, open, single arm, two-stage, multi-centre phase II trial evaluating efficacy of cemiplimab (continue until progression) in patients with laBCC.

The trial aims to recruit 41 patients with laBCC, who will receive the following regimen:

cemiplimab 350mg on day 1 only of each 21 day cycle, over a maximum period of 2 years.

Assessment of response will be done after cycle 4 and then every 12 weeks whilst on trial and progression free.

The planned recruitment duration for this study is 2 years. Patients will have up to 24 months of treatment and will be followed for a further 24 months after treatment ends at 3, 6, 9, 12, 18 and 24 months.

4 PATIENT SELECTION AND ELIGIBILITY

4.1 Source of patients

Locally advanced basal cell carcinoma is a rare disease and there is a requirement that all patients are managed under the auspices of a super-specialist (SS-MDT) multidisciplinary team.

Patients with laBCC will be eligible if they have measurable disease (either a bi-dimensional visible lesion that is ≥10 mm in both the longest diameter and the perpendicular diameter to be followed by digital medical photography or a target lesion according to RECIST 1.1 that can be followed radiologically) and are fit to receive immunotherapy. Discussion within the SS-MDT of all eligible patients is encouraged.

Patients participating in the IMPACT Trial will not be denied access to any standard of care therapy,

4.2 Number of patients

41 patients will be recruited across multiple sites, aiming to recruit 37 evaluable patients.

4.3 Inclusion Criteria

1. Signed informed consent
2. Men and women age ≥ 18 years
3. ECOG performance status 0 or 1
4. Histologically confirmed disease (from diagnostic biopsy) that is considered to be inappropriate for surgery (see below), in the opinion of a Super Specialist-MDT (SS-MDT) reason must be fully documented:

Acceptable inoperable / medical contraindications to surgery include:

a. BCC that has recurred in the same location after two or more surgical procedures and curative resection is deemed unlikely
b. BCC ≥10 mm, and relapsing after 2 surgeries in critical locations (e.g. periocular and perioral areas)
c. BCC infiltrating in bone/cartilage/other structures or with significant local invasion and curative resection is unlikely

d. Relapsing BCC after multiple surgeries and/or radiotherapy
e. BCC in patients whose co-morbidities preclude them from general anaesthesia/surgery.
f. BCC in anatomically challenging locations/size for which surgery may result in substantial morbidity and/or deformity (e.g. removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation); or patient's reluctance to accept the consequences of surgery.

5. Patients must be deemed as inappropriate for radiotherapy in the opinion of a SS-MDT. Specifically, patients must meet at least 1 of the following criteria (reason must be fully documented):
    a. A patient previously received radiotherapy for BCC, such that further radiotherapy would exceed the threshold of acceptable cumulative dose, as per the clinical oncologist.
    b. Judgment of clinical oncologist that such tumour is unlikely to be curative or radiotherapy was deemed to be contraindicated.

    Acceptable contraindications to radiotherapy for patients who have not received any prior radiation include:
    a. laBCCs in anatomically challenging locations for which radiotherapy would be associated with unacceptable toxicity risk in the context of the patient's overall medical condition in the opinion of the multidisciplinary team.
    b. Radiotherapy is contraindicated or inappropriate (limitations because of location of tumour, or cumulative prior radiotherapy dose).
6. There must be at least 1 measureable baseline lesion. For visible lesions the longest diameter (LD) and the perpendicular diameter must both be ≥10 mm if followed by digital medical photography. Non-measurable disease for laBCC is defined as either uni-dimensionally measurable lesions, tumours with margins that are not clearly defined, or lesions with maximum perpendicular diameters less than 10 mm. Patients without measureable disease at baseline are not eligible for the study
    In patients with a deeply invasive lesion that the investigator deems is best measured by magnetic resonance imaging (MRI) or computed tomography (CT), measurement for that target lesion will be done according to RECIST 1.1 criteria. The requirement for a lesion to be measurable by RECIST 1.1 is that it must be ≥10 mm in longest dimension.
    If a previously radiated lesion is to be followed as a target lesion, progression must be confirmed by biopsy after radiotherapy. Previously irradiated lesions may be followed as non-target lesions if there is at least 1 other measurable target lesion
7. Hepatic function:
    a. Total bilirubin ≤1.5x upper limit of normal (ULN).
    b. Patients with Gilbert's Disease and total bilirubin up to 3x ULN are eligible
    c. Transaminases ≤3x ULN
    d. Alkaline phosphatase (ALP) ≤2.5x ULN
8. Renal function: estimated creatinine clearance
    >30 mL/min (calculated using the CKD-EPI formula – see Appendix 3)
9. Bone marrow function:
    a. Haemoglobin ≥9.0 g/dL
    b. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    c. Platelet count ≥75 x 109/L

10. Anticipated life expectancy >12 weeks

4.4 Exclusion Criteria

1. ECOG Performance Status ≥ 2
2. Patients with metastatic BCC or Gorlins syndrome are excluded.
3. History of severe hypersensitivity reaction (≥grade 3) to polysorbate 80 containing drugs
4. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab
    - Note in clarification: Patients who require brief courses of steroids (e.g. as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded
5. Active infection requiring therapy, including positive tests for human immunodeficiency virus (HIV)-1 or HIV-2 serum antibody, hepatitis B virus (HBV), or hepatitis C virus (HCV). Patients with controlled HIV (undetectable viral load and CD4 count above 350) can be included in the study
6. History of pneumonitis within the last 5 years
7. Treatment with systemic immunostimulatory agents (including, but not limited to, IFNs, IL-2) within 28 days or 5 half-lives of the drug, whichever is shorter, prior to treatment start (Cycle 1 Day 1)
8. Treatment with PI3K inhibitors e.g. idelalisib
9. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism requiring only hormone replacement, or psoriasis that does not require systemic treatment.
10. Any anticancer treatment within 30 days of the initial administration of cemiplimab or planned to occur during the study period other than palliative radiotherapy (chemotherapy, targeted systemic therapy, imiquimod, photodynamic therapy), either investigational or standard of care.
11. Breastfeeding
12. Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary)
13. Women of childbearing potential (WOCBP - fertile following menarche and until becoming post-menopausal unless permanently sterile) or sexually active men, who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Contraception is not required for men with documented vasectomy. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy.
14. Receipt of live vaccines (including attenuated) within 30 days of first study treatment

15. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation.
16. History of an additional malignancy within 5 years of registration with the exception of those malignancies with a negligible risk of metastasis or death and treated with curative intent. Patients with CLL who have not required systemic treatment within 6 months of enrolment are not excluded.
17. Other concurrent serious illness or medical condition that in the investigator's opinion precludes entry into the trial.
18. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
19. Prior treatment with other systemic immune-modulating agents within fewer than 28 days prior to the first dose of cemiplimab. Examples of immune-modulating agents include therapeutic vaccines, cytokine treatments, or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), or OX-40.
    - Note in clarification: Prior treatment with imiquimod or other topical or intralesional immune modulators will not be exclusionary

5 REGISTRATION

It is the responsibility of the Principal Investigator (PI), or a person delegated by the PI (as documented on the delegation log) to obtain written informed consent from each subject **prior** to participation in this study, following adequate explanation of the aims, methods, study procedures and any risks. Please refer to Appendix 6 for contingency measures during extenuating circumstances.

After each patient has given written informed consent and completed the necessary study specific procedures as set out under baseline procedures (section 6.1) and in the visit schedule (section 6.6), an eligibility checklist must be completed prior to registration. The following information will be required:

- Confirmation that the patient is eligible for the trial by completion of the checklist;
- Confirmation that the measurable disease being followed in the trial has been assessed by photography and/or MRI/ CT scan within 6 weeks of scheduled start date of treatment;
- Confirmation that the patient has given written informed consent;

Central registration will be performed by the investigator-led study (ILS) team part of the Clinical Trials Unit (Bristol Haematology and Oncology Centre), on behalf of the sponsor (UHBW). The checklist will be sent to the ILS team who will confirm eligibility and register the patient onto the trial. The patient will be assigned a unique trial identification number (Trial ID). This Trial ID is recorded on all documentation and will be used for identification purposes in the IMPACT study only.

To register a patient, please send the eligibility checklist by email to:

IMPACT@uhbw.nhs.uk (08.30 – 17.00 Monday to Friday)

Patients should commence trial treatment within 3 weeks of registration.

6 STUDY PROCEDURES AND EVALUATIONS

6.1 **Baseline** (within 7 days of registration)

Patients will undergo general assessment and assessment of their disease to include:

- Physical examination to assess fitness (including height and weight); ECOG performance status; vital signs (blood pressure, heart rate, oxygen saturation, temperature).
- Recording of concomitant medication use, with relevant dates.
- Medial and cancer history.
- ECG.
- Photography of skin lesion(s), including those to be followed as target lesions **within 6 weeks of scheduled start date of immunotherapy**. Target lesions need to be ≥10mm in both the longest diameter and the perpendicular diameter.
- MRI/ CT scan (with IV contrast) of the area encompassing the primary tumour (e.g. head and neck, chest, abdomen etc) to be performed within **6 weeks of scheduled start date of immunotherapy.** If the lesions are in the head and neck region an MRI scan would be preferred. This scan will document any deeper extent of disease and whether this modality will be used to follow any target lesion(s). The same modality used to document target lesion extent at baseline must be used throughout the study.
- Full blood count, U+Es (including urea, sodium, potassium, total calcium and creatinine), liver function tests (to include ALP, ALT, Albumin and Bilirubin), LDH, thyroid function tests (including TSH, T4 and if required T3), cortisol and glucose (random). NB cortisol levels need to be measured ideally before 9am.
- Viral screen to include HIV, Hepatitis B and Hepatitis C. Patients with well controlled HIV will need to show undetectable viral load and CD4 counts over 350 to confirm inclusion into the study.
- Serum pregnancy test if required
- Estimated GFR to be assessed according to local practice (recommended technique of eGFR using the CKD-EPI formula (see Appendix 3)).
- Baseline assessment of symptoms using common toxicity scoring (CTCAE v5.0).
- Completion of Quality of life questionnaires EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire.

6.2 **On-treatment** assessments (within 7 days prior to cycle 1 and then within 5 days prior to each subsequent cycle of treatment)

Patients will be seen and assessed prior to each cycle of treatment. Please refer to Appendix 6 for contingency measures during extenuating circumstances. Assessment should include:

- Limited symptom-directed physical examination including vital signs (weight, blood pressure, heart rate, oxygen saturation and temperature).
- ECOG performance status.
- Full blood count, U+Es (including urea, sodium, potassium, total calcium and creatinine), liver function tests (to include ALP, ALT, Albumin and Bilirubin) and LDH. Thyroid function tests (including TSH, T4 and if required T3), cortisol and glucose (random) to be performed at each pre-assessment up to and including cycle 5 then every other cycle.
- Serum pregnancy test if required

- Estimated GFR to be assessed according to local practice (preferred technique of eGFR using the CKD-EPI formula (see Appendix 3)).
- Toxicity assessment (CTCAE v5.0) from day 1 of treatment up to and including 95 days after the last trial treatment.
- Updated recording of concomitant medication use, with relevant dates.
- Photography of skin lesion(s), including those being followed as target lesions. To be performed 12 weeks (+/- 7 days) after cycle 1 day 1 and before cycle 5. Subsequent photography will be taken every 12 weeks (+/- 7 days) from the previous photography whilst patient is on treatment. NB Target lesions need to be measured in both the longest diameter and the perpendicular diameter.
- MRI/CT scan (with contrast) only if being used to follow target lesions. Use the same modality and scan the same areas as in the baseline scan. Scan 1 to be performed 12 weeks (+/- 7 days) after cycle 1 day 1 and before cycle 5. Subsequent scans will then be performed every 12 weeks (+/- 7 days) from the previous scan whilst patient is on treatment.
- Completion of Quality of life questionnaires EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire at pre cycle 5, 9, 13, 17, 21, 25, 29, 33, and end of treatment visits.

6.3 **End of treatment visit**

Patients should be seen 3-6 weeks from the first day of their final cycle of treatment. Assessments should include:

- Limited symptom-directed physical examination including vital signs (weight, blood pressure, heart rate, oxygen saturation and temperature).
- ECOG performance status.
- Full blood count, U+Es (including urea, sodium, potassium, total calcium and creatinine), liver function tests (to include ALP, ALT, Albumin and Bilirubin) and LDH, thyroid function tests (including TSH, T4 and if required T3), cortisol and glucose (random).
- Serum pregnancy test if required
- Estimated GFR to be assessed according to local practice (preferred technique of eGFR using the CKD-EPI formula (see Appendix 3)).
- Toxicity assessment (CTCAE v5.0) from day 1 of treatment up to and including 95 days after the last trial treatment. Any AEs ongoing after this time will be followed to resolution.
- Updated recording of concomitant medication use, with relevant dates.
- Completion of Quality of life questionnaire EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire.

If the patient remains progression-free then the photography and MRI/CT scans will continue 12 weeks (+/- 7 days) from the previous scan

- Photography of skin lesion(s), including those being followed as target lesions. NB Target lesions need to be measured in both the longest diameter and the perpendicular diameter
- MRI/CT scan ONLY if being used to follow target lesions. Use the same modality and scan the same areas as in the baseline scan.

6.4 **Follow-up** (3, 6, 9 and 12 months plus survival data at 18 and 24 months)

Patients will be seen and clinically assessed every 3 months from the first day of their final cycle of treatment for a total of 12 months. Please refer to Appendix 6 for

contingency measures during extenuating circumstances

3 month safety visit

Patients should be seen 95 days (+/- 7 days) after the first day of their final cycle of treatment. Assessments should include:

- Limited symptom-directed physical examination including vital signs (weight, blood pressure, heart rate, oxygen saturation and temperature).
- ECOG performance status.
- Full blood count, U+Es (including urea, sodium, potassium, total calcium and creatinine), liver function tests (to include ALP, ALT, Albumin and Bilirubin) and LDH, thyroid function tests (including TSH, T4 and if required T3), cortisol and glucose (random).
- Serum pregnancy test if required
- Estimated GFR to be assessed according to local practice (preferred technique of eGFR using the CKD-EPI formula (see Appendix 2)).
- Toxicity assessment (CTCAE v5.0) from day 1 of treatment up to and including 95 days after the last trial treatment. Any AEs ongoing after this time will be followed to resolution.
- Updated recording of concomitant medication use, with relevant dates.

6, 9 and 12 month follow up visits

Patients will be seen and clinically assessed every 3 months. Assessments should include:

- Limited physical examination including vital signs (weight, blood pressure, heart rate, oxygen saturation and temperature).
- ECOG performance status.

If the patient remains progression-free then the photography and MRI/CT scans will continue during the follow up period 12 weeks (+/- 7 days) from the previous scan until the 12 month follow up visit.

- Photography of skin lesion(s), including those being followed as target lesions. NB Target lesions need to be measured in both the longest diameter and the perpendicular diameter
- MRI/CT scan ONLY if being used to follow target lesions. Use the same modality and scan the same areas as in the baseline scan.

18 and 24 month survival follow up

Survival data will be collected for all patients at 18 and 24 months post treatment.

6.5 Procedures for assessing efficacy

6.5.1 Photography of skin lesions and MRI/CT scan of the area encompassing the primary tumour

The primary endpoint ORR will be assessed for externally visible tumour(s) which are

being used as target lesions using **clinical response criteria** (Appendix 2 table 1) according to World Health Organisation (WHO) criteria. This requires photography that shows bi-dimensional measurements (≥10mm in longitudinal dimension and ≥10mm in the perpendicular dimension). If patients only have target lesions being assessed radiologically using MRI/CT scan (target lesion ≥10mm in the longest diameter) ORR will be assessed using **RECIST 1.1 criteria**. Patients who have target lesions measurable by both clinical response criteria and radiologically by RECIST 1.1 will have their outcome assessed using **composite response criteria** (Appendix 2 table 2).

Please see Appendix 1 and Appendix 2 for more information.

The MRI/CT scan and photography must be completed at baseline (within 6 weeks of the first dose of trial treatment) in order to identify the target lesions. Photographs and scans must be sent to the study team for central review within 5 days of assessment. Please refer to the imaging manual for more information.

Objective tumour response to treatment will be assessed after cycle 4 (12 weeks +/- 7 days from cycle 1 day 1) and before cycle 5, and then every 12 weeks (+/- 7 days from the previous photography/scan) whilst the patient is on treatment. If the patient stops treatment for any reason other than disease progression target lesions will continue to be assessed every 12 weeks (+/- 7 days) until disease progression for a maximum of 12 months. Photographs and scans must be sent to the study team for central review within 5 days of assessment. Please refer to the imaging manual for more information.

Please refer to Appendix 6 for contingency measures during extenuating circumstances.

Complete response can only be confirmed with clinical biopsy otherwise response remains as partial response.

Baseline	**Scan 1**	**Subsequent scans on treatment**	**End pf treatment and in follow up**
Within 6 weeks of Cycle1 Day1	12 weeks (+/- 7 days) from Cycle1 Day1 but before Cycle 5	Every 12 weeks (+/- 7 days) from previous photography/scan	If no progression, photography and MRI/CT scans should continue every 12 weeks (+/- 7 days) from previous photography/scan

6.5.2 Quality of Life

The EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire questionnaires will be used in this trial to assess quality of life whilst the patient is on treatment. These should be completed at baseline and then at the pre-cycle assessment visits for cycle 5, 9, 13, 17, 21, 25, 29, 33 and end of treatment visit.

Please refer to Appendix 6 for contingency measures during extenuating circumstances.

6.6 **Visit schedule**

Trial Evaluation	Baseline	cycle 1	cycle 2	cycle 3	cycle 4	cycles 5-34	End of treatment	Months following completion of treatment visit[7]					
								3	6	9	12	18	24
	Within 7 days of registration	Within 7 days pre treatment	Within 5 days pre treatment	Within 5 days pre treatment	Within 5 days pre treatment	Within 5 days pre treatment	Within 6 weeks of day 1 of last treatment cycle						
Physical exam[1]	X	X	X	X	X	X	X	X	X	X	X		
ECOG	X	X	X	X	X	X	X	X	X	X	X		
Vital signs and observations	X	X	X	X	X	X	X	X	X	X	X		
12 lead ECG	X												
Medical & cancer history	X												
Haematology & biochemistry[2] including serum pregnancy test if required and eGFR assessment.	X	X	X	X	X	X	X	X					
Thyroid function tests[3]	X	X	X	X	X	X[4]	X	X					
Serology - Viral screen (HIV, Hep B and Hep C)	X												
Concomitant medications	X	X	X	X	X	X	X	X					
Adverse Events[5]	X	X	X	X	X	X	X	X					
Photography and MRI/CT scan of area encompassing the primary lesion)	X[6]				X[7]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]		
Administration of cemiplimab[9]		X	X	X	X	X							
Quality of life questionnaire - EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire	X					X[10]	X						
Survival and anti-cancer therapy								X	X	X	X	X	X

1. Full physical examination to be carried out at baseline. All subsequent visits a limited physical examination to be performed.
2. Full blood count; urea, sodium, potassium, total calcium, creatinine (U&Es), ALP, ALT, Albumin, Bilirubin (LTFs) and LDH.
3. Thyroid function tests (TSH, T4 and T3), cortisol and glucose (random).
4. Thyroid function tests to be performed at cycle 5 and then every other cycle whilst on treatment.
5. To be collected from day 1 of treatment until 95 days from day 1 of the final treatment cycle. Any AEs that are ongoing at this time point will be followed to resolution.
6. Within 6 weeks prior to commencing first cycle of cemiplimab
7. Photography and MRI/CT scan (if required) to be performed within 12 weeks of C1D1 treatment +/- 7 days but prior to cycle 5.
8. Photography and MRI/CT scan (if required) to be performed within 12 weeks of previous scan +/- 7 days.
9. Cemiplimab 350mg to be administered on day 1 (- 2 days + 4 days) of a 21-day cycle
10. EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire to be performed at baseline, pre cycle 5, 9, 13, 17, 21, 25, 29, 33 and end of treatment visits.

7 TRIAL TREATMENT

7.1 Investigational Medicinal Products

The regimen consists of cemiplimab, total fixed dose of 350mg, given on day 1 (- 2 days + 4 days) of each 21 day cycle as an intravenous infusion over 30 minutes. Cemiplimab (REGN2810) is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD-L1 mediated T cell inhibition. Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours.

Treatment will continue until disease progression or unacceptable toxicity for a maximum of 2 years.

Cemiplimab will be supplied free of charge.

Study medication will be stored and dispensed by the investigator site's pharmacy department in accordance with Good Clinical Practice, Good Manufacturing Practice and pharmacy department SOPs.

Please see pharmacy manual and Investigator's Brochure (IB) for product information, handling and preparation instructions. Vials should be stored according to their labelling and kept in their kit until use.

7.3 Concomitant Medications

Any treatment administered, other than anti-cancer therapy, from the time of informed consent until 90 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the follow-up period to treat a study drug related AE. All concomitant treatments must be recorded in the study eCRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

Patients should receive full supportive care during the study including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin or bisphosphonates where appropriate.

7.3.1 Permitted concomitant treatments

- Antiemetics
- Antiallergic measures
- Standard anti-diarrhoeal treatments
- Supportive treatment as medically indicated for the patient's well-being (including hyperalimentation and blood transfusion) may be prescribed at the investigator's discretion.
- Palliative radiotherapy (8Gy/single fraction, 20Gy/5#, 30Gy/10#), except to target lesions.
- Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune

conditions (e.g. delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
- Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the assigned treatment may be given at the discretion of the investigator.

7.3.2 Prohibited Medications

Patients must **not** receive:

- Any other non-licensed, investigational drug or approved anticancer treatment including immunotherapy, targeted-therapy or biological therapies until end of study treatment other than the treatment assigned at registration.
- Immunosuppressive doses of systemic corticosteroids (>10mg/day prednisolone or equivalent) such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®) or dexamethasone (Decadron®) within 4 weeks prior to starting cemiplimab and whilst on trial except in the case of a life-threatening emergency or to treat a drug-related adverse event.
  NOTE: Bisphosphonates and denosumab are not prohibited.
- Live vaccines for the duration of the study treatment and for up to 5 half-lives after the last dose of study drug.

7.4 Post-Study treatment

On completion of the study treatment or on stopping study treatment, subsequent treatment is at the discretion of the individual investigator. The investigator will record further treatment for the disease on the appropriate eCRF, including name/type of treatment and start and end dates.

7.5 Guidelines for the Management of Toxicity

Subjects will be monitored continuously for adverse events (AEs) whilst on the study from day 1 of treatment until 95 days after the last treatment date.

If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to improve signs and symptoms including antiemetics for nausea and vomiting, antidiarrhoeals for diarrhoea, and antipyretics, and/or antihistamines for drug fever.

See below for management of cemiplimab related toxicities.

AEs associated with cemiplimab may represent an immunologic aetiology. These immune-related AEs (irAEs) can differ from and be more severe than AEs caused by agents belonging to other therapeutic classes. Early recognition and management may mitigate severe toxicity. Most irAEs are reversible and can be managed by interrupting cemiplimab, administration of corticosteroids and /or other supportive care. The following are the most common identified immune-related AEs associated with cemiplimab. Evaluation criteria for the complete list of identified risks can be found in the Investigator Brochure:

- Pneumonitis
- Colitis

- Hepatitis
- Endocrinopathies
- Skin adverse reactions
- Nephritis
- Infusion related reactions including systemic hypersensitivity

7.5.1 **Cemiplimab dose reduction**

No dose reduction will be permitted for cemiplimab.

7.5.2 **Cemiplimab dose delay**

Cemiplimab should be delayed for the following:

- Any grade 3 or grade 2 lasting longer than a week, skin drug related AE, or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis
- Any grade 3 drug related laboratory abnormality including Hypothyroidism/Hyperthyroidism and Type 1 diabetes related hyperglycaemia; exception for leukopenia and lymphopenia, ALT and bilirubin.
  - ALT/bilirubin delay dosing for drug-related grade ≥2 toxicity
- Any grade ≥2 non-skin, drug related AE except fatigue.
- Any AE, laboratory abnormality or intercurrent illness which in the judgment of the investigator warrants delaying the dose of study medication.

Please also refer to Appendix 5.

Management and safety of individual patients is under the clinical judgement of the investigator who may choose to withhold study treatment even if hold criteria are not formally met as per protocol.

All treatment delays will be reported in the eCRF. A treatment delay >4 days for cemiplimab should be justified. Treatment may be delayed no more than 12 weeks to allow recovery from acute toxicity. After cycle 5 patients may have up to 3 weeks break in their treatment for reasons other than toxicity at the discretion of the PI (maximum of two breaks in the course of a patient's treatment). The reason for the break needs to be provided. Please also see Appendix 6 for contingency measures during extenuating circumstances. In case of treatment delay of greater than 12 weeks, the patient should discontinue the study treatment, unless there is strong evidence for tumour response justifying continuation. The investigator must discuss the rationale with the Chief Investigator before a decision is taken.

Subjects may resume treatment with cemiplimab when drug-related AEs resolve to grade 1 or baseline value and steroid use is reduced to ≤ 10mg/day prednisolone or equivalent.

Exceptions:

- Subjects may resume treatment in the presence of grade 2 fatigue.
- Drug-related pulmonary toxicity, diarrhoea or colitis must have resolved to baseline levels before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

Please also refer to Appendix 5.

7.5.3 **Infusion-related reactions**

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs and graded. In the event of an infusion reaction of grade 3 or greater severity during or directly following cemiplimab infusion, dosing should be stopped and the patient must be permanently discontinued from cemiplimab treatment.

To assist investigators in identifying cemiplimab-related infusion reactions, the following case definition is provided.

- Typical symptoms may include fever, chills, rigors, skin flushing, dyspnea, back pain, abdominal pain, and nausea
- Infusion reactions usually occur either during the infusion or within 2 hours after the infusion is completed
- Vital signs may be notable for hypotension and/or tachycardia

Case report forms will capture start and stop time of the event, signs and symptoms, and management interventions (medications, interruption of infusion, rate reduction).

The infusion should be interrupted if any of the following are observed:

- Cough
- Rigors/chill
- Rash
- Pruritis
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnoea (shortness of breath)
- Vomiting
- Flushing

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice

After symptomatic treatment the infusion may be restarted at 50% of the original rate. For patients who experience infusion-related hypersensitivity reactions that are less than grade 3 and who plan to continue treatment, premedication will be required for re-treatment

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent cemiplimab infusions.

For grade 2 symptoms (moderate reaction that requires therapy or infusion interruption, but for which symptoms resolve promptly with appropriate treatment such as antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and/or IV fluids; prophylactic medications indicated 24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg

to 1000 mg at least 30 minutes prior to subsequent cemiplimab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

Termination of infusion

In the event of an infusion reaction grade ≥3 during or directly after cemiplimab infusion, treatment should be discontinued permanently

If any of the following AEs occur the infusion should be terminated and NOT restarted

- Anaphylaxis
- Laryngeal/pharyngeal oedema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesis, paralysis etc.)
- Any other symptom or sign that, in the opinion of the investigator, warrants discontinuation of the infusion

7.5.4 Treatment Discontinuation

- Any grade 4 drug-related AE or laboratory abnormality.
    - Exceptions for immune related (irAEs); grade 3 or recurrent grade 2 pneumonitis, grade 3 hepatitis, nephritis, neurological toxicity, myocarditis or pericarditis, any recurrent grade 3 irAE.
- Any infusion reaction grade ≥3 during or directly after cemiplimab infusion.
- Any dosing interruption to cemiplimab lasting longer than 12 weeks
- Any AE, laboratory abnormality or intercurrent illness which in the judgment of the investigator presents a substantial risk to the subject with continuing drug dosing.
- Patients diagnosed with progressive disease, unless continuation of cemiplimab is deemed to be of clinical benefit e.g. it is within the first 12 weeks of treatment and thought to be pseudo-progression, in which case it should be discussed with the Chief Investigator or nominated representative (if treatment continues trial activity also needs to be performed as per the visit schedule).

7.6 Contraception

Patients with reproductive potential need to adhere to accepted and effective methods of birth control during treatment with immunotherapy and for at least 6 months after last administration. These include the oral contraceptive pill, hormonal injections or implants, an intrauterine device (IUD), bilateral tubal occlusion, vasectomy or sexual abstinence if this is your usual lifestyle choice. Male participants with WOCBP partners are required to use a condom.

8 SAFETY AND PHARMACOVIGILANCE

8.1 Definitions

8.1.1 Adverse Events (AEs)

An adverse event is any untoward medical occurrence in a patient administered a drug; the event does not necessarily have a causal relationship with the treatment or usage.

The following should not be recorded as AEs if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Pre-existing conditions found as a result of screening procedures unless the condition worsens from the first trial related activity after the subject has signed the informed consent.

Procedure for collecting Adverse Events

- For the purpose of this trial, any detrimental change in the patient's condition that occurs after the subject has started trial treatment, up to and including 95 days after last trial treatment should be considered an AE.
- All AEs regardless of their seriousness or relationship to the product should be recorded on the relevant Case Report Form (eCRF) from day 1 of treatment until 95 days after last treatment date. Investigator's assessment of the seriousness and causal relationship between the AE and the study medication should also be provided on the eCRF. AEs will continue to be followed until resolution or patient comes off trial.
- Whenever one or more signs and/or symptoms correspond to a disease or a well-defined syndrome only the main disease/syndrome should be reported. The severity of adverse events will be graded according to the NCI-CTC criteria (CTCAE v5.0).

8.1.2 Serious Adverse Events (SAEs)

An SAE is any untoward medical occurrence or reaction that occurs after the commencement of treatment and within 95 days of the last administration of the trial regimen, that:

- Results in death
- Is life threatening
  Note: the term "life-threatening refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Is a congenital anomaly/birth defect; or
- Is a medically important event or reaction.

Note: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

The following list of medically important events is intended to serve as a guideline for determining which conditions should be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
- Allergic bronchospasm
- Blood dyscrasias (i.e., agranulocytosis, aplastic anaemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.),
- Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
- Development of drug dependence or drug abuse
- Alanine aminotransferase (ALT) >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicide
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).
- Suspected transmission of an infectious agent: if any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination)
- Required intervention to prevent permanent impairment or damage related to device use.

The following events should be immediately reported to the Marketing Authorisation holder by the chief investigator.

- Pregnancy
- Overdose both serious and non-serious with the IMP

In this patient population disease progression itself is not considered to be an AE, unless the investigator believes the progression is atypical or possibly related to the IMP. However, if progression is accompanied by an untoward medical occurrence that is experienced within 95 days of the last treatment dose this should be recorded as an AE as specified in section 8.1.1 or as an SAE if it meets the criteria as per section 8.1.2.

8.1.3 Adverse Reaction (AR)

There is a reasonable possibility according to the investigator and/or the sponsor that the Product may have caused the adverse event.

8.1.4 Unexpected AR

An adverse reaction (AR) is considered unexpected if the nature, severity, specificity, or outcome is not consistent with the term or description used in the reference safety information (RSI). This can be found in the cemiplimab investigator brochure edition 09 (21/04/2022) (section 6.4). An expected AR with a fatal outcome should be considered unexpected.

8.1.5 Serious Adverse Reactions (SAR)

A serious related adverse event i.e. adverse reaction (SAR) is an SAE that has a definite, probable or possible causal relationship to the trial drug.

8.1.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any adverse reactions that have a suspected relationship to the trial drug that are both serious and unexpected, as judged by the Investigator.

An unexpected serious adverse reaction is one that is not listed as a known toxicity of the investigational drug in the RSI.

8.2 **Pregnancy**

Pregnancy occurring in a female patient or female partner of a male patient during the study or within 180 days of the last dose of study drug must be reported to the ILS team within 1 working day of identification using the pregnancy eCRF. Pregnancy per se is not considered as an AE however any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE. Outcomes for all pregnancies should be reported to the sponsor.

8.3 **Causality (relatedness)**

Investigators must assess whether there is a reasonable causal relationship with the IMP administered, or with the study procedure(s), for each reported AE. “Reasonable causal relationship” means that there are facts/evidences or arguments to suggest a causal relationship [based on ICH E2A Guideline].

- Associated to investigational product
- Not associated to investigational product

The assignment of causality for serious adverse events should be made by the investigator responsible for the care of the patient and delegated by the PI the task of undertaking causality assessment, using the definitions in Table 2 (below). If there is any doubt about the causality the investigator should assume that it is related until further information becomes available.

Table 2 Definitions for causality

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship

Outcome Categories and Definitions for SAEs:

- Resolved: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
- Resolved with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
- Ongoing
- Died
- Unknown

8.4 Reporting of Serious Adverse Events/Reactions to the Sponsor

These will be recorded and reported in accordance with the sponsor's Safety Reporting SOP.

Serious adverse events should be reported using the initial SAE form. They require immediate reporting by email to the sponsor within 24 hours of a member of the research team becoming aware of the event. Additionally any SAE which the

investigator considers related to the IMP i.e. a SAR must be reported as above even if more than 95 days have elapsed from the date of last treatment.

Please scan and email the SAE form indicating it is an SAE to

UHBW (the sponsor) **research@uhbw.nhs.uk**

AND

The ILS team **BHOC-CTU-safety@uhbw.nhs.uk**

Forms must be completed, signed and dated by the site Principal Investigator or delegated clinician. Any missing information from the initial SAE form must be provided within 72 hours of the first report.

8.5 Review of Serious Adverse Events/Reactions

Events reported using the SAE form will be forwarded to the Chief Investigator (CI) immediately (or designated representative) for assessment of causality and expectedness. The CI can upgrade an investigator assessment of expectedness from unrelated to related for purposes of regulatory reporting but can never downgrade the expectedness from related to unrelated.

Centres should respond as soon as possible to requests from the CI or designated representative (via the sponsor) for further information that may be required for final assessment.

8.6 Expedited Reporting of SUSARs

If an SAE/SAR is defined as a SUSAR (both related and unexpected and is fatal or life threatening, the sponsor will report this to the MHRA within 7 days from the date of being notified of the event.

If an SAE/SAR is defined as a SUSAR and is not fatal or life threatening, the sponsor will report this to the MHRA within 15 days.

The main REC must be informed of all SUSARs within the same timeframes detailed above and this responsibility is delegated by the sponsor to the BHOC-CTU ILS team.

The Principal Investigator at all actively recruiting centres will be informed by the ILS team of any SUSARs occurring within the trial.

8.7 Follow-up of Serious Adverse Events/Reactions

The patient must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Follow-up SAE reports should be submitted to the sponsor, as specified in section 8.4. The first follow-up report is expected 10 days from the onset of the event unless it is a SUSAR then the follow up should be sent within 5 days with subsequent submissions as and when there is a significant change or update to the SAE,

8.8 Annual Reporting of Serious Adverse Events/Reactions

An annual Development Safety Update Report (DSUR) will be submitted to the MHRA and the main REC by the sponsor on the anniversary of the date when the Clinical Trials Authorisation (CTA) was obtained. This will include all SARs and SUSARs.

9 END OF TREATMENT (EOT)

End of treatment for a patient is defined as no later than 6 weeks after the first day of the last treatment cycle. The reason for treatment discontinuation will be documented on the appropriate CRF.

9.1 Permanent treatment discontinuation from the IMP

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the investigator or the patient not to re-expose the patient to the IMP at any time.

If a patient shows one of the following reasons, the study treatment must be discontinued:

- Progression of basal cell carcinoma as per clinical response criteria/RECIST 1.1/composite response criteria (unless continuation of cemiplimab is deemed to be of clinical benefit e.g. it is within the first 12 weeks of treatment (scan 1) and thought to be pseudo-progression, in which case it should be discussed with the CI or nominated representative).
- Unacceptable toxicity or adverse event requiring discontinuation of treatment
- Patient requests to stop treatment including if they change their mind about wanting curative surgery e.g. if the surgery is curative but potentially disfiguring
- Patient shows non-compliance (including persistent patient attendance failure).

The patients may withdraw from treatment with IMP at any time and irrespective of the reason, or this may be the investigator's decision. The reason for treatment discontinuation will be documented as far as possible on the appropriate eCRF.

Further medical or surgical treatment following trial immunotherapy is at the discretion of the treating clinician in consultation with the patient.

9.1.1 Handling of patients after permanent treatment discontinuation

In the case of permanent treatment discontinuation patients should be followed up according to the study procedures as specified in this protocol. The patient will be assessed according to the procedures set out for the end of treatment visit and then enter the follow up period.

9.2 Procedure for withdrawal of patients from study

The patients may withdraw from the study, before study completion if they choose to do so, at any time and irrespective of the reason, or at the investigator's decision.
All study withdrawals should be documented by the investigator in the source data but it should be very clear what the patient is withdrawing from – trial treatment, follow up visits, survival status data collection. A patient can withdraw from trial treatment but continue to be followed up with data collected according to the protocol, likewise

if a patient does not want any further follow up procedures but is happy to have progression and survival status collected then this should be recorded.

9.2.1 Consequence

Patients who have been withdrawn from the study cannot be re-included in the study. Their inclusion and treatment number must not be reused. In specific situations to be discussed between the investigator and the sponsor, patients who have not yet been registered can be re-included in the study.

10 END OF STUDY (EOS)

Recruitment is planned for 24 months. Patients will be treated for up to 24 months and then followed up every 3 months for a further 12 months. Survival follow up will then be conducted at 18 and 24 months post end of treatment. The end of study is defined as last patient last visit (LPLV) which will be the last survival follow up visit (at 24 months after end of treatment) completed by a patient on the trial.

10.1 Premature Termination of Study

The study may be terminated prematurely for safety reasons, slow accrual, or upcoming new data impairing the relevance of the study objective, by the University Hospitals Bristol and Weston NHS Trust (UHBW) as the sponsor, or the data monitoring committee. The Independent Data Monitoring Committee will provide advice. The sponsor is allowed to close the trial for any reason at any time. A decision to prematurely terminate the study is binding to all investigators of all study sites. Responsible ethics committees and regulatory authorities will be informed about the reason(s) and time of termination according to the applicable laws and regulations.

10.2 Premature Termination of Study at a Particular Study Site

The sponsor (UHBW) reserves the right to discontinue the study at a particular study site at any time. The reasons will be discussed with the investigator.
The sponsor (UHBW) may terminate this study in one particular study site for one of the following reasons:

- Non-compliance with GCP and/or regulatory requirements.
- Insufficient number of recruited patients.
- Failure to comply with trial protocol and guidelines
- Inadequate co-operation with UHBW or its representatives.
- The Investigator requests to close his/her study site.

If the study is prematurely terminated in a study site, the responsible investigators have to inform their patients and take care of appropriate follow-up and further treatment of the patients.

11 STATISTICAL CONSIDERATIONS

The statistical analysis of the present study is performed in accordance with the principles stated in the Consensus guideline E9 (Statistical Principles for Clinical Trials) of the International Conference on Harmonisation (ICH).

11.1 Sample size calculations

The hedgehog pathway inhibitors (HHIs) have shown an ORR of about 45% in the first line setting. In the ERIVANCE study, the ORR with vismodegib was 42.9% at 9 months follow-up which increased to 47.6% at 21 months follow-up (9). In the BOLT study of sonidegib, the ORR was 47.0% at primary 6 month follow-up, increasing to 56.1% (95% CI: 43.3–68.3) at 18 month follow-up (10). In the second line setting, cemiplimab showed an ORR of 31%, in a recently reported phase 2 study in the 2nd line setting (18), after a median follow-up of 15 months.

Assuming an ORR of cemiplimab to be around 45% at 6-months in the first line setting, this study is powered as a single arm Simon II Stage design. This will be used to differentiate between a poor treatment (success rate of 25%) and a good treatment (success rate 45%) using a nominal significance level alpha = 5% and a power of 80%.

Once 18 patients are recruited, an interim analysis will be performed with the decision rule of progression to Stage II if 6 or more of the 18 patients achieve a response. If ≤5 patients have responded (poor response) or if 15 out of the 18 patients have responded (exceptional response) the trial will be stopped.

Stage II will be the recruitment of a further 19 patients. To account for a potential loss of non-evaluable patients (assuming a 10% drop out rate) the sample size will be inflated to N = 41.

11.2 Analysis methods

All analyses will proceed using standard analytical techniques including Kaplan-Meier survival curves. Analysis will include tabulation of baseline characteristics of recruited patients. Intention to treat analysis will be used. Baseline characteristics for those patients not completing trial treatment will be tabulated for comparison with treated patients, to ensure the ability to generalise results. Baseline characteristics will include (but are not limited to) demographic data, tumour stage and grade. Categorical data will be reported as a percentage. Numeric data will be reported as median, mean, range and SD.

11.3 Primary endpoint

- Objective Response rate

  To assess objective response rate (ORR) of cemiplimab in laBCC patients by independent central review at 6 months. ORR is defined as the proportion of patients having achieved partial or complete remission. This will be assessed for patients with visible tumour(s) only, using the clinical response criteria (see Appendix 2 table 1) according to World Health Organization (WHO) criteria and for patients who have target lesions measurable by both clinical response and radiologically by RECIST1.1, using the composite response criteria (see

Appendix 2 table 2). ORR will be reported with 80% and 95% CI (Confidence Intervals) using the Wilson score interval.

11.4 **Secondary endpoints**

- ORR and DCR at 12m and 24m reported with 80% and 95% CI

- Progression-free survival
  - Progression free survival will be calculated from the date of registration until clinically or radiologically documented disease progression or death from any cause, whichever comes earlier.
  - Patients free from a progression event will be censored on the date of last follow up.
  - A progression-free survival curve will be generated using the methods of Kaplan and Meier. All patients registered in the study will be included. Median PFS rate will be reported with 80% and 95% CI.
  - Duration of response as measured by Kaplan-Meier at each follow-up, or until progression, will be reported.

- Overall survival
  - An overall survival curve will be generated using the methods of Kaplan and Meier. The median overall survival will be reported with 80% and 95% CI.

- Toxicity
  - The proportion of patients experiencing grade 3 or 4 toxicity as measured by NCI-CTCAE v5.0 whilst on treatment. The number of SAEs will be reported.

- Quality of Life data
  - EQ-5D-5L, EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire Data collection within 14 days prior to cycles 5, 9, 13,17, 21, 25, 29, 33 and within 6 weeks of final cycle of treatment in the study. Analysis will use EQ-5D-5L Index Scores, EQ-5D-5L VAS and EORTC QLQ-C30, Skindex-16, FNAE and the Hornheide questionnaire domain scores. Absolute means at each assessment point will be compared against baseline. Percentage of respondents experiencing change +/- 0.3 SD and +/- 0.5 SD will be used to assess those experiencing a degree of meaningful substantive change.

11.5 **Missing Data**

In the event that data for an individual patient has not been collected, after the response assessment has taken place but in the absence of an event, a Last-Observation-Carried-Forward analysis will be performed. However, for PRO outcomes any missing data will not be imputed using a last-observation-carried-forward analysis. These data will be compared to baseline using the partially overlapping samples framework and subject to an NMAR (not-missing-at-random) sensitivity analysis if more than 10% of data is missing.

11.6 **Non-evaluable patients**

In the principal analysis, where a patient is not evaluable, additional patients will be recruited to replace them. Every attempt should be made to obtain disease

assessments for all patients. The TMG will centrally review all patients to determine if any are non-evaluable and need to be replaced.

A patient is considered not evaluable if:

1) The patient has not completed any cycles of cemiplimab for one of the following reasons:

- Death from any cause
- Withdrawal from trial due to progressive disease
- Withdrawal from trial for a reason unrelated to drug or disease (e.g. patient preference, administrative reasons)

2) Disease cannot be measured after treatment for one of the following reasons:

- Death from causes other than basal cell carcinoma
- Withdrawal from trial for a reason unrelated to drug or disease (e.g. patient preference, administrative reasons)

11.7 **Frequency of analyses**

The Trial Management Group and Trial Steering Committee will meet at least annually to examine patient recruitment, safety and efficacy. The Independent Data Monitoring Committee will meet 6 months after the FPFV, to assess safety data in particular and then at least annually thereafter. An interim report will be prepared after 18 patients have been recruited into the study (see section 11.1).

12 RESEARCH GOVERNANCE

12.1 **Trial Administration**

The sponsor for this trial is University Hospitals Bristol and Weston NHS Foundation Trust (UHBW)

Sponsorship activities and delegated responsibilities are in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the UK Policy Framework for Health and Social Care and the principles of Good Clinical Practice.

All parties agree to allow inspection of their premises by the competent authorities.

12.1.1 **Responsibilities**

The study will be performed subject to favourable opinion/ authorisation/permission or equivalent from all necessary regulatory and other bodies. This includes but is not limited to REC, MHRA, HRA, NHS trusts.

UHBW has sponsorship responsibility for obtaining authorisation and appropriate research ethics committee (REC) opinion (Part 3 of the Regulations) and for pharmacovigilance (Part 5 of the Regulations).

The sponsor warrants that the Study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

The sponsor shall be responsible for the respect of all obligations required by applicable local and international laws and regulations.

The sponsor shall be responsible for all required periodic updates to the health authorities and expedited reporting of all Serious Adverse Events occurring during the performance of the study, in accordance with local and regional regulations.

The sponsor shall also be responsible to provide to the investigators and the Ethics Committee all relevant study related information (including information submitted to the Health Authorities and any “Dear Investigator Letter” received from Sanofi.

The sponsor must report the following information in English to the Sanofi Pharmacovigilance contact:

- Copy of all individual Suspected (drug related) and Unexpected Serious Adverse Reactions (SUSARs) at time of submission to MHRA and REC (format sent to MHRA and REC) or, if submission of SUSAR is not required in the participating country, such individual reports shall be sent to Sanofi on an ongoing basis.
- In addition to SUSARs, any other events that have been submitted to the MHRA and REC according to local regulatory requirements in the participating country shall be sent to Sanofi at time of submission to these bodies.
- Any significant safety issues, events or results, e.g., Data Safety Monitoring Board recommendations, occurring or found during the course of the Study which might affect performance thereof shall be sent to Sanofi on an ongoing basis.

The reference safety information (RSI) text to be used for evaluation of expectedness of adverse events relating to the IMP will be the current approved Investigator Brochure (v9.0 dated 21/04/2022 section 6.4). Any updates made to the document described above will be reviewed by the Chief Investigator and in consultation with the sponsor, a decision whether the updated document will be submitted to the MHRA for use as the RSI will be made.

Responsibilities may be delegated to the Chief Investigator (or named Deputy in his absence) and to the ILS team within the Clinical Trials Unit, Bristol Haematology and Oncology Centre, as deemed appropriate by the sponsor.

The delegation of responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between the ILS team, Bristol Haematology and Oncology Centre, UHBW and the Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

This is an NHS-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial.

NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

Ex-gratia payments may be considered in the case of a claim.

12.2 **Protocol Compliance & Initiation**

This trial will be conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Directive.

12.3 **Monitoring**

The study will be monitored in accordance with UHBW's Monitoring and Oversight of Research Activity SOP, the ILS team monitoring SOP and the sponsor's IMPACT monitoring plan, based on its risk assessment. This monitoring plan will be risk based, determined by the number of patients recruited, quality of data returned, % data returned and occurrence of protocol deviations etc.

All study related documents will be made available on request for monitoring and audit by UHBW and the relevant Research Ethics Committee and for inspection by the MHRA or other licensing bodies

All sites will have a site initiation visit (SIV) where a Study Manager will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and sponsor's requirements. All pertinent staff members will be trained on the IMPACT study protocol. New site staff members can be trained by already trained staff members and this must be documented on the training log.

Following the SIV, the Study Manager will ensure that an SIV checklist is completed and all items required for site activation have been actioned. A site will only be deemed open and permitted to recruit patients once a green light activation letter has been received

12.4 **Archiving**

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the trial data collected. Essential documents will be maintained by the ILS team, Bristol Haematology and Oncology Centre and at participating centres in a way that will facilitate the management of the trial and inspection. Documents will be securely stored and access restricted to authorised personnel. Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents including patient notes will be retained for a period of 15 years following the end of the study.

Where trial related information is documented in the hard copy medical records, those records will be identified by a 'Do not destroy before dd/mm/yyyy' label, where the date is 15 years after the projected last patient last visit. Where electronic records are in use, local investigator site policy will be followed.

12.5 **Data Management**

UHBW will comply with all aspects of the Data Protection Legislation. Data will be collected and retained in accordance with the UK Data Protection Act 2018 and General Data Protection Regulation (GDPR) 2016. Any requests from patients for access to data held about them should be directed to the Trial Coordinator in the first instance, who will refer the request to the Data Protection Officer.

A Data Management Plan will be put in place prior to the study opening to recruitment.

13 TRIAL MANAGEMENT

13.1 Trial Management Group

A Trial Management Group (TMG) will be set up and will include the Chief Investigator and identified collaborators, the trial statistician and trial managers. Principal Investigator(s) and key study personnel will be invited to join the TMG as appropriate to ensure representation from relevant professionals.

Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will have operational responsibility for the conduct of the trial.

13.2 Trial Steering Committee

A Trial Steering Committee (TSC) will be set up and will include independent clinicians, independent statistician and patient representatives. The TSC will convene, at least annually during the recruitment and treatment period and at the end of the study. A representative from Sanofi may be invited to attend TSC meetings as appropriate.

13.3 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to oversee the safety and efficacy of the trial. This committee will be constituted according to Good Clinical Practice. The IDMC will meet 6 months after the FPFV and then on a regular basis as they see fit, but no less than annually. Following each meeting, the IDMC will report their findings and recommendations to the TSC and to the TMG.

A TSC, TMG and IDMC charter will be produced to outline the representation, roles, responsibilities and decision making procedures of each group

14 PUBLISHING POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the Trial Management Group. All participating centres and clinicians will be acknowledged in this publication. All presentations and publications relating to the trial must be reviewed and approved by the Trial Management Group on whose behalf publications should usually be made. Authorship of any secondary publications, will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the trial without prior permission from the Trial Management Group.

The Sponsor, Sanofi and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Sanofi and the investigators, and as such, the parties agree that the

recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Sanofi for review and approval 30 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable subject matter which, at Sanofi's discretion, warrants intellectual property protection, Sanofi may delay any publication or presentation for up to 90 days for review and approval.

15 CONFIDENTIALITY AND LIABILITY

15.1 Risk assessment

The Sponsor will perform a risk assessment for the trial which takes into account risks to patients, the study and the organisation.

15.2 Liability/Indemnity/Insurance

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

15.3 Patient Confidentiality

The database will be designed so as to protect patient information in line with the Data Protection legislation. Patient study ID will be the only personal data recorded on the study database.

Study staff will ensure that the participant's anonymity is maintained through protective and secure handling and storage of patient information at the investigator sites and in accordance with ethics approval. Documentation will only be accessible to study staff and authorised personnel. Data will be collected and retained in accordance with Data Protection Legislation. No identifiable data should be transferred to the study management team.

The Principal Investigator must ensure that the patients' confidentiality is maintained. Representatives of the sponsor and the regulatory authorities are required to have access to patient notes for quality assurance purposes. Patient confidentiality will be respected at all times.

16 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. A Research Ethics Committee (REC) will review all

appropriate study documentation in order to safeguard the rights, safety and wellbeing of patients. The study will only be conducted at sites where appropriate approval has been obtained.

Potential participants will be identified by standard methods of identifying this patient population within each organisation, e.g. via patient referrals or MDT meetings. The patient information sheet should be provided in addition to any standard patient information sheets that are provided by the centre and which are used in routine practice. Patients should only be asked to sign consent after having received both verbal and written information. Patients should be given sufficient time to consider the study (at least 24 hours is recommended). The consent form must be countersigned by the Principal Investigator or a designated individual. A record of who the designated individuals are and the circumstances under which they may countersign consent forms must be clearly documented at the research site as part of the Delegation Responsibilities Log. This log, together with original copies of all signed patient consent forms, must be available for inspection.

Patients should be reminded that they can withdraw their consent at any time and continued consent should be sought at each patient visit.

17 FINANCIAL MATTERS

This trial is investigator designed and led.

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APPENDIX 1: RECIST CRITERIA v1.1

Response Evaluation Criteria in Solid Tumours (RECIST) Quick Reference Eligibility
Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

Measurable disease: the presence of at least one measurable lesion/lymph node. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions: lesions that can be accurately measured in at least one dimension with longest diameter a minimum of size of 10mm by CT scan (CT scan slice no greater than 5mm).

Bone lesions:

- Bone scan, PET scan or plain films are not adequate imaging techniques to measure lesions but can be used to confirm presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic/blastic lesions, with identifiable soft tissue components, which can be evaluated using e.g. CT or MRI scan are considered measurable if the *soft tissue component* meets the criteria for measurable lesions described previously.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts are not considered as malignant lesions.
- 'Cystic lesions' that are thought to represent cystic metastases are considered measurable if they meet the criteria for measurable lesions described previously.
- If non-cystic lesions are present in the same patient then these are preferred for selection as target lesions.

Malignant Lymph nodes:

- To be considered pathologically measurable a lymph node must be ≥15mm in *short* axis when assessed by CT scan (CT scan slice thickness no greater than 5mm).
- At baseline and in follow-up, only short axis will be measured and followed.

Skin lesions:

- See appendix 2 for measurement of skin lesions.

Non-measurable lesions: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis), i.e. bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions and also abdominal masses that are not confirmed and followed by imaging techniques.

Lesions with prior local treatment: Tumour lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are not considered measurable unless progression in the lesion is demonstrated.

All measurements should be taken and recorded in metric notation, using a ruler. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 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. For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is required.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Measurability by CT scan is based on the assumption that CT slice thickness is 5mm or less. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumour lesions. If new lesions are identified by US then confirmation by CT or MRI is desired.
- The utilization of endoscopy and laparoscopy for objective tumour evaluation is not advised. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centres. Therefore, the utilization of such techniques for objective tumour response should be restricted to validation purposes in specialized centres. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- The short axis of Lymph nodes should be noted since they are normal anatomical structures which may be visible by imaging.
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumour.
- All other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up

Documentation of New Lesions

- The presence of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions).

- A lesion identified at a follow-up visit in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

Response Criteria	**Evaluation of target lesions**
* Complete Response (CR):	Disappearance of all target lesions. Pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition, the smallest sum LD must also demonstrate an absolute increase of at least 5mm.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
	Evaluation of non-target lesions
* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level
*Non-CR/non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions (1). The appearance of one or more new lesions is also considered progression.

(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 be confirmed later on by the review panel (or study chair).

Lesions that become ‘too small to measure’

- All lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation – even if very small (e.g. 2mm).
- If lesion is reported as ‘too small to measure’ and the radiologist feels the lesion has disappeared, then the measurement should be recorded as 0mm on the CRF.
- If the lesion is reported as ‘too small to measure’ and is believed to be present but only faintly seen then a default value of 5mm should be assigned.
- However, if the radiologist is able to provide an exact measurement, even if below 5mm, then this value should be recorded.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The table below provides a summary of the overall response calculation:

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
PR	Non-CR/non-PD or not all evaluated	No	PR
SD	Non-CR/non-PD or not all evaluated	No	SD
Not all evaluated	Non-CR/non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

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 four 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 six-eight weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumour types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) Non-evaluable for response: specify reasons (early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify))
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided

APPENDIX 2: CLINICAL AND COMPOSITE RESPONSE CRITERIA FOR PATIENTS WITH aBCC

These criteria are designed for externally visible lesions that can be measured bi-dimensionally using digital medical photography. This appendix also provides clinical and composite response criteria for disease that is measureable by both clinical response criteria and RECIST 1.1.
Patients will be followed by digital medical photography and also undergo radiologic imaging (MRI/CT scan) at baseline, and this will also be performed serially at each response assessment unless the investigator deems that baseline radiologic imaging was uninformative. Radiologic imaging will be essential in the evaluation of tumours that have subdermal components that cannot be adequately assessed by digital medical photography. Standardised digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each subsequent tumour assessment.
Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumour assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

For target lesions that are measured by digital medical photography, measurements will be bi-dimensional.

SPECIAL ISSUES FOR EXTERNALLY VISIBLE TUMOURS:

1) Anatomic Defects
Regarding tumour around a surgical cavity/anatomic defect (e.g. rhinectomey), such lesions should be considered non-measureable unless there is a nodular lesion measuring ≥10 mm in maximal bidimensional perpendicular diameters. The surgical cavity or anatomic defect should not be considered in measuring the lesion.

2) Indeterminate-Appearing Tissue
If there is uncertainty about whether a given lesion or area of a lesion represents malignancy versus benign process (e.g. scarring, fibrosis), biopsies should be obtained. Indeterminate-appearing areas (e.g. scarring, fibrosis) are included in the tumour measurements unless biopsies are obtained to establish benign status.

Note on timeline for finalisation of measurement/response assessment: Generally, baseline disease measurements and response assessments should be completed on the day of the visit at which digital medical photography was performed.
When biopsies are performed to confirm pCR, the annotated photograph for that visit should clearly indicate the region of the tumour that was biopsied. It is not necessary to hold study treatment while the local pathology report is pending.

3) Central Review
An independent central review, with access to de-identified digital medical photography results and biopsy results, will provide response assessments to address study objectives. Central reviews will not be continuous or “real-time.” Clinical management decisions generally will be as per investigator response assessments and local pathology review. In the unlikely event that central review yields major differences with the local response assessment that could have implications for the ongoing management of an active patient

on study; the situation will be discussed between the sponsor and the investigator in order to determine patient management.

4) Confirmation of Responses
For any complete responses observed in digital medical photography of externally visible target lesions, confirmatory biopsies are required to establish status of complete response.

5) Patients with Deeply Invasive Tumours
Tumour measurements for these patients will generally be performed with digital medical photography (bi-dimensional measurements). However, some patients may have deeply invasive target lesions in which tumour measurements can better be obtained with cross-sectional imaging (MRI/CT scans). For any target lesions that are measured by cross-sectional imaging, measurements will be unidimensional according to RECIST 1.1.

Clinical Response Criteria for Externally Visible Tumours

A. Externally Visible Tumour Dimension
The externally visible component of target lesion(s) will be measured using bi-dimensional WHO criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension – at each tumour assessment and will be documented using standardised digital photography. In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and the investigator should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments.

Clinical response criteria for externally visible tumour(s) require bi-dimensional measurements according to WHO criteria, and are as follows:

- Complete response of externally visible disease (vCR): all target lesion(s) and non-target lesions no longer visible, maintained for at least 4 weeks. Documentation of vCR requires confirmation by biopsies of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy. In the absence of such histologic confirmation, a patient cannot be deemed to have experienced vCR and the best response would be partial response.
- Partial response of externally visible disease (vPR): decrease of 50% (WHO criteria) or greater in the sum the products of perpendicular longest dimensions of target lesion(s), maintained for at least 4 weeks
- Stable externally visible disease (vSD): not meeting criteria for vCR, vPR, or progressive disease
- Progression of visible disease (vPD): increase of ≥25% (WHO criteria) in the sum of the products of perpendicular longest dimensions of target lesion(s). In rare cases, unequivocal progression of a non-target lesion may be accepted as vPD.

B. New Lesions
A new cutaneous lesion consistent with BCC will be considered as cPD if the lesion is ≥10 mm in both maximal perpendicular diameters and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with BCC. If a new cutaneous lesion is not biopsied or if the histology is inconclusive, it should be considered BCC and deemed cPD.

TABLE 1: Overall Clinical Responses For Advanced BCC Lesions that are Measured by Digital Medical Photography

Externally Visible Tumour Dimension[a]	**New Lesions[a]**	**Clinical Response**
vCR	No	cCR[b,c]
vPR	No	cPR[d]
vSD	No	cSD[e]
vPD	Yes or No	cPD[f]
Any	Yes	cPD+

a See above for definitions
b Clinical Complete Response
c Negative biopsy showing no residual malignant cells is required for any lesion be deemed cCR
d Clinical Partial Response
e Clinical Stable Disease
f Clinical Progression of Disease

Composite Response Criteria

For patients with advanced BCC that is measurable by BOTH clinical response criteria by digital medical photography and RECIST 1.1 using radiologic imaging. The "Clinical Response" column in this table will be based on the results of the "Clinical Response" (far right) column of the table above**.** A Central Review of the results from independently evaluated radiological scans, photographs and clinical tumour biopsies (if performed) to derive overall composite responses.

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable due to response to cemiplimab, the CI should be consulted prior to any surgical procedure being performed.

TABLE 2: Composite response criteria

Clinical response (digital medical photography)	**RECIST 1.1 response (radiolgy)**	**Composite (overall): clinical + RECIST 1.1 response**
Clinical complete response	Complete response or not applicable	Complete response
Not applicable	Complete response	Complete response
Clinical complete response	Partial response or stable disease	Partial response
Clinical partial response	Complete response, partial response, stable disease, or not applicable	Partial response
Not applicable	Partial response	Partial response
Clinical stable disease	Complete response or partial response	Partial response
Clinical stable disease	Stable disease or not applicable	Stable disease
Not applicable	Stable disease	Stable disease
Clinical Progressive disease	Any	Progressive disease
Any	Progressive disease	Progressive disease

C. Ulcerated Lesions

This section only pertains to target lesions that have extensive ulceration at baseline that prevents measurement by the above methods in this appendix. Response criteria are as follows:

- Complete response: re-epithelialization of the entire baseline area of ulceration of target lesion(s), maintained over at least 4 weeks.
- Partial response: there are no criteria for partial response
- Stable disease: not meeting criteria for complete response or progressive disease
- Progressive disease: new ulceration of target lesion(s) not related to (i.e. in a location separate from) tissue biopsy or other known trauma, persistent without evidence of healing for at least 2 weeks

D. Non-Target Lesions

Measurements of non-target lesions are not required. The presence, absence, or in rare cases unequivocal progression of these lesions should be noted throughout follow up.

APPENDIX 3: MEASUREMENT OF eGFR

Estimated GFR is required. One of the following 3 methods is allowed.

1. The recommended technique is eGFR calculated using the CKD-EPI formula according to the table below
2. By accessing the online calculator for the CKD-EPI GFR calculation at http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr
3. Modified Cockcroft and Gault

Race and Sex	Serum Creatinine Level, µmol/L (mg/dl)	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.7)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$

- For patients with borderline renal function (CKD-EPI formula produces a result that is lower than 60ml/min) a direct measurement of GFR as per standard of care at the patient's institution is recommended. A result of >60ml/min from this method should be regarded as the more accurate estimate.

Reference

Levey AS, Stevens LA, Schmid CH et al. for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) A New Equation to Estimate Glomerular Filtration Rate *Ann Intern Med.* 2009;150:604-612.

APPENDIX 4: PHOTOGRAPHING SKIN LESIONS

Photographic records of cutaneous target lesions used in assessing disease response need to be kept. Photographs will be taken by medical photography departments.

The minimum standards for study photography are:

- Colour photographs with a millimetre ruler (or other measuring scale) adjacent to the lesion / site; or if digital photography is used measurement on the photo of the lesion in the longest dimension. Reference should be made to the previous visit's annotated photographs as a starting point to ensure measurements are comparable between visits.

- Global view of the target BCC area

- complementary images in different planes to be considered where thick lesions are elevated above the skin surface

- patient anonymity must be assured

- Anonymised photographs to be sent to the sponsor for central review within 5 days of assessment.

APPENDIX 5: GUIDELINES FOR MANAGEMENT OF SELECTED IMMUNE-RELATED ADVERSE EVENTS

Recommended Adverse Event Management for Pneumonitis			
Pneumonitis Grade	**Study treatment Management**	**Action & Supportive Care Guidelines**	**Diagnostic Considerations**
Grade 1	Consider withholding study treatment.	• Monitor symptoms every 2-3 days • Consider consultation with pulmonologist • Consider chest imaging (CT or X-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • May resume study treatment upon improvement or resolution. If no improvement treat as G2	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
Grade 2	Withhold study treatment. Permanently discontinue study treatment if patient develops a 2nd episode of ≥G2 pneumonitis upon re-challenge	• Monitor symptoms daily; consider hospitalisation • Consider consultation with pulmonologist • Consider chest imaging (CT or X-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • Consider bronchoscopy with bronchoalveolarlavage (BAL) to rule out infection and malignant lung infiltration • Consider pulmonary function tests and laboratory work up for infections • Treatment with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least a month • If symptoms do not improve within 48-72 hours of corticosteroid treatment treat as G3 • Consider empiric antibiotics if infection has not yet been fully excluded	
Grade 3-4	Permanently discontinue study treatment.	• Inpatient care • Consultation with pulmonologist and infectious disease specialist • Consider bronchoscopy with bronchoalveolarlavage (BAL) to rule out infection and malignant lung infiltration • Empiric antibiotics if infection has not yet been fully excluded • Add prophylactic antibiotics for opportunistic infections • Treatment with systemic corticosteroids (2-4 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least a month • If symptoms do not improve within 48-72 hours of corticosteroid treatment consider additional immunosuppressive treatment i.e. mycophenolate mofetil 1-1.5 g BID, infliximab 5mg/kg IV • If symptoms worsen during steroid reduction , initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper	

Recommended Adverse Event Management for Collitis/Diarrhoea			
Colitis/ Diarrhoea Grade	**Study treatment Management**	**Action & Supportive Care Guidelines**	**Diagnostic Considerations**
Grade 1	No change	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet) • Consider consultation with gastroenterologist for prolonged symptoms • If symptoms are persistent, consider endoscopic evaluation. • If persists for >2 weeks treat as G2	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, or viral gastroenteritis
Grade 2	Withhold study treatment	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). • Consultation with gastroenterologist. • Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy • Consider stool evaluation to rule out infectious aetiology • Consider stool inflammatory marker evaluation (i.e. lactoferrin and calprotectin) to differentiate functional vs inflammatory diarrhoea. • Consider abdominal and pelvic CT with contrast • Treatment with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least a month • If no improvement within 2-3 days treat as G3	
Grade 3	Withhold study treatment Permanently discontinue study treatment if recurrent G3 colitis is experienced	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). • Consultation with gastroenterologist. • Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy • Consider stool evaluation to rule out infectious aetiology • Consider stool inflammatory marker evaluation (i.e. lactoferrin and calprotectin) to differentiate functional vs inflammatory diarrhoea. • Consider abdominal and pelvic CT with contrast • Inpatient care for close monitoring and supportive care • Treatment with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least a month • If no improvement within 2-3 days treat as G3 • If no improvement with corticosteroid within 2-3 days, consider additional immunosuppressive treatment i.e. mycophenolate 0.5-1 g BID, infliximab 5mg/kg IV	
Grade 4	Permanently discontinue study treatment	• Same as above • Consider lower GI endoscopy if symptoms are refractory despite the treatment or there is a concern of new infections	

Recommended Adverse Event Management for Immune-Mediated Hepatitis			
Immune-Mediated Hepatitis Grade*	**Study treatment Management**	**Action & Supportive Care Guidelines**	**Diagnostic Considerations**
Elevated ALT & AST> ULN – 3 x ULN without elevated bilirubin	No change	• Monitor liver function tests (LFT) more frequently until resolution to baseline values	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis *Please note that the gradings of immune-mediated hepatitis are not according to CTCAE v5.0
Elevated ALT & AST> 3 and≤ 5 x ULN or if total bilirubin >1.5 and ≤ 3 x ULN	Withhold study treatment	• Monitor liver function tests (LFT) more frequently until resolution to baseline values • Consider appropriate consultation with hepatologist and liver biopsy to establish aetiology of hepatic injury, if necessary • Consider inpatient monitoring for patients with ALT/AST>8x ULN and/or elevated bilirubin >3x ULN • Treatment with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least 1 month • If no improvement within 3 days after initiation of systemic steroids, consider additional immunosuppressive treatment i.e. mycophenolate mofetil 0.5-1 g BID • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased	
Elevated ALT & AST> 5 x ULN or if total bilirubin > 3 x ULN	Permanently discontinue study treatment	• Same as above	

Recommended Adverse Event Management for Endocrine Events			
Grade 1	No Change	• Hypo/hyperthyroid: monitor thyroid function or other hormonal level more frequently (every 3-6 weeks) until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	Immune related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance. All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection.

Grade 2-4	Withhold Study treatment if clinically necessary	• Consult with endocrinologist and provide supportive care per institutional guidelines
		• Rule out infection and sepsis with appropriate cultures and imaging
		• Hypo/hyperthyroid:
		  • Replacement of thyroid hormone or thyroid suppression therapy as indicated.
		  • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency	

Recommended Adverse Event Management for Immune-related Skin Toxicities			
Immune-related skin toxicities include maculopapular rash, dermatitis rash generalised, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic and skin reaction. Guidance here is provided for maculopapular rash. For other immune-related skin toxicities, see the cemiplimab IB.			
Mild (grade 1) Rash covering <10% BSA with or without symptoms	No change	Treatment with mild to moderate potency topical steroids Treatment with oral antihistamine	All attempts should be made to rule out other causes such as metastatic disease, infection, contact dermatitis, effect of another drug or skin condition linked to another systemic disease.
Moderate (grade 2) Rash covering 10-30% BSA with or without symptoms, limiting instrumental ADL	Consider withholding study treatment. Withhold study treatment if grade 2 lasts longer than 1 week	Consider consultation with dermatologist and skin biopsy for diagnosis of bullous dermatitis. Treatment with medium to high potency topical steroids AND/OR with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least 1 month Treatment with oral antihistamine	
Severe (grade 3 and above) Rash covering >30% BSA with moderate or severe symptoms, limiting self-care ADL OR suspected Stevens-Jonson syndrome (SJS) or toxic epidermal necrolysis (TEN).	Withhold study treatment	Consider consultation with dermatologist and skin biopsy Treatment with high potency topical steroids AND with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least 1 month Treatment with oral antihistamine	

Recommended Adverse Event Management for Renal Events			
Mild Elevated creatinine > 1.5-2 x above baseline; increase of ≥0.3 mg/dL	Consider withholding study treatment	• Provide symptomatic treatment • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease or injury from other chemotherapy agents. *Please note that the gradings of renal events are not according to CTCAE v5.0
Moderate Elevated creatinine > 2-3 x above baseline	Withhold study treatment	• Consultation with nephrologist • Treatment with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least 1 month • Consider prophylactic antibiotics for opportunistic infections • Consider renal biopsy • If elevations persist >7days or worsen, treat as severe AE.	
Severe or life-threatening **Severe** >3 x baseline; increase of ≥ 4 mg/dL **Life-threatening**	Permanently discontinue study treatment	• Consultation with nephrologist in consideration of ultrasound and/or biopsy as appropriate • Consider inpatient care and monitor creatinine daily • Treatment with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least 1 month	

Elevated creatinine > 6 x baseline increase; dialysis indicated		• If no improvements within 7 days after initiation of systemic steroids, consider additional immunosuppressive therapy i.e. mycophenolate mofetil 0.5-1 g BID	

APPENDIX 6 – CONTINGENCY MEASURES DURING EXTENUATING CIRCUMSTANCES

The following contingency measures can be applied during periods of extenuating circumstances due to the SARS-Cov-2 virus and the consequent global pandemic.

However, sites <u>MUST</u> contact the trials team prior to implementing any measures outlined below to discuss what changes they want to make and the reasons why.

Extenuating circumstances are those events that are out of the control of sites running the trial but will impact on delivery at their site. They can include national and/or local measures put in place to control the COVID-19 pandemic (or subsequent surges of the SARS-Cov2 virus). These may also include changes to working practices mandated by individual Trusts in place for the duration (or a large part) of the trial even after the COVID-19 pandemic has ended.

CONSENT

Every effort should be made to avoid a subject coming into hospital only for the purpose of signing the informed consent form (ICF). It is recommended that the subject has at least 24 hours to consider the trial before being asked to sign the ICF (section 16). In most cases a subject will need to return to the hospital to perform baseline assessments and the ICF can be signed then. However, if a patient is not going to return to hospital before treatment starts it is permissible for a subject to sign the ICF on the same day that the trial is initially discussed with them. This needs to be fully documented in the patient's notes. A follow up phone call to the subject at least 2 working days later to confirm they are still happy to take part in the trial also needs to take place, again with full documentation in the patient's notes. As with all subjects, continued consent should be verified at every trial visit.

TREATMENT

Baseline Assessments
All baseline assessments are mandatory.

Pre-assessment visits
Up to and including cycle 5 all pre-assessment visits must be conducted in person. After this the subject can be assessed via a telephone consultation although if feasible every third visit should be performed face-to-face. The protocol specified symptom-directed physical examination can be omitted but please ensure that side effects including known issues are fully discussed with the patient. It should be possible to assess ECOG remotely and bloods must be completed prior to treatment and results reviewed by the PI/Co-I.

End of treatment Visit
This visit should be conducted in person.

Follow up visits
As long as the subject is well, these can be carried out as telephone consultations. The limited physical examination can be omitted but please ensure that any long term side effects including known issues are fully discussed with the patient and ECOG is assessed.

CT SCANS/PHOTOGRAPHY

All photography and MRI/CT scans required need to be carried out as per the protocol schedule.

QUALITY OF LIFE (QoL) QUESTIONNAIRES

If the patient is having a telephone pre-assessment for a cycle when a QoL is due these can be administered in one of the following ways:

1. Posted to the patient for completion 5 working days prior to cycle treatment with a stamped-addressed-envelope for return.
2. Provided to the patient when they come in for treatment at that cycle. The QoLs should be completed prior to treatment commencing.

TREATMENT BREAK

After cycle 5 patients can have a break in cemiplimab treatment for up to 12 weeks due to extenuating circumstances as defined above at the discretion of the PI/Co-I. CT scans/photography should continue during this period as per the protocol schedule.

Sites <u>MUST</u> contact the trials team prior to implementing any measures outlined above to discuss what changes they want to make and the reasons why.