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Temozolomide and nivolumab as a treatment for cancer of the gullet

Submission date 09/07/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 14/07/2021	**Overall study status** Completed	
Last Edited 29/04/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Patients with advanced or metastatic cancer of the stomach or gullet (oesophagogastric cancer) cannot be cured with current treatments and do not have good survival outcomes compared to other cancers. This study is investigating whether chemotherapy treatment with temozolomide (TMZ) plus nivolumab (NIVO), an immunotherapy drug that is not currently licensed in Europe for oesophagogastric cancer (but is licensed and used in other cancers), will allow patients with MGMT-methylated tumours to improve their survival rates. There is evidence from laboratory models and other tumours to show that when TMZ is used in MGMT-methylated tumours that the number of mutations (mistakes in DNA) in the tumour increases. Tumours with high numbers of mutations tend to respond better to immunotherapy like nivolumab (NIVO). It is hoped that MGMT-methylated tumours will become sensitive to nivolumab by treating them with TMZ, which could lead to tumour shrinkage.

Who can participate?
Patients aged 18 years and over who have been diagnosed with advanced, previously treated and currently unresectable (inoperable) oesophagogastric cancer that is methylated in MGMT (an enzymatic protein) and have been treated with 3-6 months of first-line chemotherapy.

What does the study involve?
Patients will undergo screening to ensure that this trial is right for them. Once screened eligible patients will start the TMZ. TMZ is a capsule that participants will take every day for up to 3 months. During treatment with TMZ, they will have weekly blood tests and every 4 weeks a clinic visit to monitor their health and have a physical examination. If their disease progresses whilst on TMZ participants will stop that treatment and receive nivolumab treatment. If their disease doesn’t progress (grow) on TMZ, they will start NIVO at 3 months and continue with TMZ as well. Participants will visit the clinic every 2 weeks during nivolumab treatment to be monitored for health and progression. The nivolumab treatment will be given by an infusion (injected into a vein). At regular intervals participants will have CT scans to monitor the effect of the treatment. These are the same as what they would have normally to monitor their well-being although one would be additional to the standard of care. To ensure that the heart is well enough to receive the treatment participants will also have either an echocardiogram or a MUGA scan (multi-gated acquisition scan). At 3 months or when the TMZ treatment is stopped participants will undergo

an endoscopy where a biopsy (sample) will be taken. Participants will also be asked to have one at the end of nivolumab treatment – but this one would be optional. Following disease progression (tumour growth) on nivolumab, participants will move into the follow-up phase of the trial to monitor for overall survival. Participants will give up to five additional blood samples; one at the start of the trial and the others during the treatment.

What are the possible benefits and risks of participating?
Participants may benefit from a longer period of disease remission by having the combination treatment of TMZ followed by nivolumab. However, this cannot be guaranteed and there may be no additional benefit in relation to how long the cancer is controlled.
The information from this study may help to treat future patients with the same condition in a more effective way. The inconvenience, side effects and impact on quality of life are similar to that of any course of chemotherapy and immunotherapy. Participants will be helping to further knowledge of how to treat cancer and this will also benefit society as a whole. During the trial, participants will have contrast-enhanced CT scans to assess their cancer. These tests use radiation, which has a limited increase to the risk of cancer in the future. These tests are part of standard care but participants will receive one additional scan by taking part in the trial. Participants will also be required to have an echocardiogram or MUGA, depending on their hospital's practice, to ensure they are well enough to receive the full dose of chemotherapy. A contrast-enhanced CT scan involves radiation, using x-rays to get a detailed image of the body area. Participants will have up to 12 CT scans of their chest, abdomen and pelvis. Participants may also have a nuclear medicine MUGA scan to assess their heart function. Some of these will be extra to those that they would have if they did not take part. These procedures use ionising radiation to form images of the body or provide the doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. For the patients in this study the chance of this happening is extremely small.

Where is the study run from?
Southampton Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
November 2020 to October 2024

Who is funding the study?
Bristol Myers Squibb (USA)

Who is the main contact?
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Contact information

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Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04984733

Clinical Trials Information System (CTIS)
2020-004771-41

Integrated Research Application System (IRAS)
282284

Central Portfolio Management System (CPMS)
48157

Study information

Scientific Title
ELEVATE: Temozolomide + nivolumab in MGMT-deficient oesophagogastric cancer

Acronym
ELEVATE

Study objectives
In O-6-methylguanine-DNA methyltransferase (MGMT)-methylated oesophagogastric adenocarcinoma, temozolomide will induce a hypermutated state and increase sensitivity to

nivolumab. The aim of the trial is to determine the activity and safety of maintenance temozolomide (TMZ) dosing followed by nivolumab treatment to evaluate the potential for a future randomised trial against a standard of care control arm. The rationale to continue TMZ for 3 months or until disease progression (PD) is to evaluate the emergence of mismatch repair deficiency both with and without radiological PD, as clinically relevant mismatch repair deficiency (MMRd) may emerge before radiological progression. This will also reduce the number of patients who drop out due to symptomatic progressive disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/03/2021, Cambridge South Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8104; cambridgesouth.rec@hra.nhs.uk), REC ref: 21/EE/0017

Primary study design
Interventional

Study design
Non-randomized; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Oesophagogastric cancer

Interventions
Patients previously treated with at least 3 months of platinum and fluoropyrimidine-based chemotherapy, with a known MGMT deficiency, will be recruited from secondary care settings.

Once all screening procedures have been done and the patient is confirmed eligible, they will receive 50 mg/m² TMZ continuously for 3 months. TMZ is taken by mouth, daily. If their disease progresses during the 3 months they will stop TMZ and start nivolumab at a dose of 240 mg every 2 weeks. If there is no progression after 3 months the patient will continue taking TMZ alongside nivolumab. All treatment will stop once the patient progresses on nivolumab.

During TMZ treatment patients will have weekly blood tests and 4 weekly physical exams to monitor their health and monitor any progression of disease. On the weeks when they are not in clinic for a physical exam, the site staff will contact them by phone to check on adverse events and TMZ compliance and confirm they are to continue taking them following blood results. During nivolumab treatment patients will be seen in clinic every 2 weeks, for physical exams and blood tests to monitor health and disease progression.

Patients will have a CT scan at week 6, week 12 and then every 12 weeks until they cease nivolumab treatment.

Patients will have a mandatory endoscopy for research purposes and they will be asked to have an optional one (for research) at progression.

Following disease progression on nivolumab, patient notes will be used to monitor overall survival.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Temozolomide, nivolumab

Primary outcome(s)
Objective response rate to nivolumab measured using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and iRECIST at 24 months

Key secondary outcome(s)
1. Disease control rate, according to RECIST v1.1 and iRECIST, 6 months after starting nivolumab, and 3 months after starting TMZ, respectively
2. Progression-free survival (PFS), calculated from the time of registration to evidence of progression (RECIST v1.1 and iRECIST) or any death
3. Progression-free survival (PFS2), calculated from the time of starting nivolumab to evidence of progression (RECIST v1.1 and iRECIST) or any death
(N.B. disease control rate at 3 months and progression-free survival will be assessed on TMZ before nivolumab therapy)
4. Overall survival (OS), calculated using [medical records] from the time of registration to any cause death
5. Overall survival (OS2), calculated using [medical records] from the time of starting nivolumab to any death
6. Toxicity assessed according to CTCAE version 5.0 at progression on NIVO/end of treatment
7. Tolerability assessed by the percentage of intended treatment dose delivered, and numbers of patients needing dose reductions and/or treatment breaks for each drug administration period at progression on NIVO/end of treatment
8. Quality of life measured using QLQ-C30, QLQ-OG25 and EQ-5D-5L questionnaires at progression on NIVO/end of treatment

Exploratory:
1. Mismatch repair deficiency in tumours, according to standard immunohistochemistry testing for MLH1, MSH2, MSH6 or PSM2 at 24 months
2. MGMT protein expression and MGMT methylation in tumours measured using PCR method at progression on NIVO/end of treatment
3. Tumour mutation burden using 10/mB as a cut off for high vs low measured using next-generation sequencing of tumour tissue at progression on NIVO/end of treatment
4. Tumour immune cell infiltration quantifying CD8, CD4, Treg using cross validation testing at progression on NIVO/end of treatment
5. Relative abundance of peripheral blood T cell populations measured using mass cytometry at progression on NIVO/end of treatment

Completion date
23/10/2024

Eligibility

Key inclusion criteria
1. Patients ≥18 years of age
2. Pathologically confirmed advanced unresectable or metastatic OGA
3. Loss of MGMT protein on IHC
4. Mismatch repair proficient (MSI-normal or MMR intact)
5. Previously treated with at least 3 months of platinum and fluoropyrimidine-based chemotherapy for advanced disease and suitable for maintenance therapy
6. Measurable disease per RECIST 1.1 and iRECIST guidelines
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
8. Can swallow TMZ capsules
9. Adequate organ function assessed within 7 days before randomization
10. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to randomization

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
13

Key exclusion criteria
1. Previous treatment with TMZ
2. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways
3. Active central nervous system metastases
4. Candidate for curative surgery
5. Previous malignancies are excluded unless a complete remission was achieved at least 5 years prior to study entry. Adequately treated cervical carcinoma in situ, and localized non-melanoma skin cancer are not exclusion criteria, regardless of time point of diagnosis.
6. Active, known, or suspected infectious or autoimmune disease (except for patients with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enrol)
7. Conditions requiring systemic treatment with either corticosteroids (≥10 mg daily

prednisolone or equivalent) or other immunosuppressive medications within 14 days of study drug administration
8. Interstitial lung disease
9. > Grade 1 peripheral neuropathy
10. Positive test result for HBV or HCV indicating acute or chronic infection
11. Known history of testing positive for HIV or known AIDS
12. Known hypersensitivity to the components or excipients of co-trimoxazole, temozolomide or nivolumab. (Please refer to nivolumab IB and SmPC for TMZ and co-trimoxazole)
13. Known hypersensitivity to dacarbazine (DTIC)
14. Clinically significant abnormal 12-lead ECG. If clinically indicated, cardiac function assessment using either echocardiography or MUGA Scan, if clinically significant the patient is ineligible
15. In the past 6 months serious cardiac illness or medical condition including but not confined to:
15.1. History of documented congestive heart failure (CHF)
15.2. High-risk uncontrolled arrhythmias
15.3. Angina pectoris requiring antianginal medication
15.4. Clinically significant valvular heart disease
15.5. Evidence of transmural infarction
15.6. Poorly controlled hypertension (e.g. systolic >180 mmHg or diastolic greater than 100 mmHg)
16. Patients with severe liver parenchymal damage
17. Patients with severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed
18. Patients with a history of drug-induced immune thrombocytopenia with the use of trimethoprim and/or sulfonamides
19. Patients with acute porphyria
20. Patients with severe myelosuppression

Date of first enrolment
01/09/2021

Date of final enrolment
31/12/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge

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CB2 0QQ

Study participating centre
Kings Cross Hospital
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Southampton General Hospital
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Study participating centre
Nottingham City Hospital
Nottingham Cancer Clinical Trials Team
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Sponsor information

Organisation
University of Southampton

ROR
https://ror.org/01ryk1543

Funder(s)

Funder type
Industry

Funder Name
Bristol-Myers Squibb

Alternative Name(s)
Bristol-Myers Squibb Company, Bristol Myers Squibb, Bristol-Myers Company, BMS

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing statement as of 08/03/2023:
The datasets generated during and/or analysed during the current study will be available upon request from Southampton Clinical Trials Unit (ctu@soton.ac.uk). As a minimum, anonymous data will be available for request from three months after the publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data-sharing documentation. Researchers interested in the trial data are asked to complete the Request for Data Sharing form [template located on the SCTU website, www.southampton.ac.uk /ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

Previous IPD sharing statement:
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	01/09/2022	08/03/2023	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version V3	13/05/2021	14/07/2021	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes