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A clinical trial assessing the addition of continuous ketogenic diet therapy to standard chemotherapy and immunotherapy treatment for patients with advanced squamous cell lung cancer

Submission date 03/07/2024	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 15/07/2024	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 20/06/2025	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

Squamous cell lung cancer (LUSC), a type of non-small cell lung cancer (NSCLC), accounts for 9000 deaths each year in the UK alone. Some lung cancers respond well to treatments that target the genetic changes that drive cancer growth. However, that approach does not work in LUSC so different approaches are urgently needed.

There has long been interest in whether changing diet can affect cancer and its treatment, but studies have been too small to prove if they have any effect. It is likely that only certain cancers will respond to changes in diet. LUSC is a prime candidate as it takes up high levels of glucose from the bloodstream to fuel its growth and to protect itself from damaging substances known as reactive oxygen species (ROS).

Standard treatment for LUSC involves a combination of chemotherapy and immunotherapy: the immunotherapy enables the patients' immune cells to fight their own cancer, and the chemotherapy produces a lot of ROS.

Experiments have shown that reducing the glucose uptake of cancer cells increases chemotherapy effects in LUSC by reducing the ability of cancer cells to protect themselves from ROS. One way of reducing glucose availability is to follow a ketogenic diet, a very low carbohydrate, high fat, moderate protein diet. The low carbohydrate intake causes the body to convert fats into ketones to use as an additional source of energy. Experiments have shown that combining chemotherapy with a ketogenic diet is more effective at controlling LUSC growth than chemotherapy alone. Importantly, the ketogenic diet and ketone bodies have been shown to improve the effects of immunotherapy. LUSC could respond to dietary change using a ketogenic diet, enabling both chemotherapy and immunotherapy to work more effectively, hopefully improving patient outcomes.

Who can participate?
Patients aged 16 years or older who would be having chemotherapy and immunotherapy in combination in the first-line treatment of squamous cell cancer of the lung (LUSC)

What does the study involve?
The study involves continuously following an experimental ketogenic diet therapy for 12 weeks (plus 1-week run-in) alongside the standard-of-care chemotherapy and immunotherapy used in the treatment of squamous cell cancer of the lung (LUSC).

What are the possible benefits and risks of participating?
The researchers cannot promise that participants will benefit directly from this trial. It is possible that the KDT will be more effective and participants may experience different or worse side effects. However, the researchers will not know this until the results of the trial are available. All the information that they get from this trial will help improve the treatment of patients with squamous cell lung cancer in the future.

Where is the study run from?
Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
January 2022 to July 2027

Who is funding the study?
Cancer Research UK

Who is the main contact?
Dr Joshua Savage, keto-lung@trials.bham.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-personalised-ketogenic-diet-therapy-standard-treatment-lung-cancer-keto-lung#undefined

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
333096

Protocol serial number
CPMS 62260, CRCEMA-Nov22/100002, IRAS 333096

Study information

Scientific Title
KETO-Lung: Assessing the impact of the adoption of a continuous ketogenic diet therapy on the efficacy of combination chemo-immunotherapy using paclitaxel/carboplatin/pembrolizumab in advanced squamous cell cancer of the lung

Acronym
KETO-Lung v1.0

Study objectives
To assess if the addition of a continuous ketogenic diet therapy (KDT) to standard first-line chemoimmunotherapy in squamous cell lung cancer (LUSC) is acceptable to, feasible and well tolerated by patients and in particular, what is the proportion of patients that can tolerate at least 6 weeks of the diet on treatment and does it lead to the induction of maintained ketosis.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 25/06/2024, West Midlands Solihull Research Ethics Committee (Equinox House, City Link, East Midlands REC Centre, NG2 4LA, UK; +44 (0)207 104 8191; solihull.rec@hra.nhs.uk), ref: 24/WM/0096

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

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Treatment will consist of standard-of-care chemo/immunotherapy paclitaxel/carboplatin /pembrolizumab for four (21 days) together with continuous ketogenic diet therapy (KDT) with an introductory week prior to chemo/immunotherapy to allow patients to familiarise themselves with the diet. This is followed by standard-of-care maintenance pembrolizumab.

Intervention Type
Mixed

Primary outcome(s)
Compliance to maintain experimental Ketogenic diet therapy (KDT) for a minimum of 6 weeks and maintaining therapeutic ketosis for a minimum of 6 weeks (after a 1-week introductory period). This will be measured by returning at least 85% of Glucose-Ketone Index (GKI) measurements ≤3.0 from glucose monitoring and twice-daily ketone finger-prick blood tests.

Key secondary outcome(s))
1. Compliance to maintain experimental ketogenic diet therapy (KDT) associated therapeutic ketosis for a minimum of 12 weeks. This will be measured by returning at least 85% of GKI measurements ≤3.0 (from glucose monitoring and twice-daily ketone finger-prick blood tests)
2. Overall patient-reported adherence to KDT over 6 and 12 weeks determined from responses on a visual analogue scale in the patients' daily food diaries
3. Overall patient-reported adherence to KDT over 6 and 12 weeks determined by dietitian review of patients' daily food diaries and recorded as a response on a visual analogue scale on the case report form
4. Overall patient-reported tolerability to KDT over 6 and 12 weeks, determined from responses on a visual analogue scale in the patients' daily food diaries
5. Acceptability, feasibility and tolerability of KDT for both participants and professionals will also be assessed through an optional embedded qualitative process evaluation at the end of the trial
6. Health-related quality of life will be generated from patient completion of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (15 measures) and EQ-5D-5L questionnaire (2 measures) at multiple points over time. This will be assessed at the beginning of every cycle of treatment and at the beginning and end of the maintenance period.
7. Qualitative process evaluation interviews will be used to identify meaningful lifestyle changes

in participants at the end of the trial
8. Occurrence of an objective response (as measured by RECIST 1.1) from the patient's scans after each standard of care scan during trial treatment and follow-up (every 9-12 weeks)
9. Occurrence of durable clinical benefit (DCB), defined as being free of disease progression for at least 6 months from the start of trial treatment.
10. Progression-free survival time, defined as the time in whole days from the date of registration to the date of the first documented evidence of disease progression or death (from any cause).
11. Overall survival time, measured from the start of trial treatment to the date the patient dies.
12. Occurrence and grade of all adverse events experienced according to the National Cancer Institute Common Terminology Criteria of Adverse Events (NCI-CTCAE) version 5.0 from screening up to progression or withdrawal.
13. Occurrence of at least one immune-related AE caused by the standard of care chemo-immunotherapy after each patient visit during trial treatment and throughout follow-up.

Exploratory outcome measures:
1. Differential metabolic profile (tumour and plasma) between participants successfully maintaining a GKI Index ≤3.0 and those not achieving this threshold at the end of the trial
2. Differential glucose metabolism in the tumour of participants successfully maintaining a GKI Index ≤3.0 and those not achieving this threshold at the end of the trial
3. Measures of peripheral immune proficiency including:
3.1. Cytokine/chemokine analysis at the end of the trial
3.2. Changes in T cell biomarkers predictive of benefit on checkpoint blockade at the end of the trial
3.3. Beneficial changes in T cell immunometabolism at the end of the trial

Completion date
31/07/2027

Eligibility

Key inclusion criteria
1. Histologically proven locally advanced or metastatic squamous cell lung cancer not amenable to definitive local therapy and suitable for first-line systemic therapy of chemo-immunotherapy (paclitaxel, carboplatin, pembrolizumab)
2. Aged 16 years or older
3. Willing to undertake dietary modification for up to 12 weeks (+ 1 week introductory period)
4. Willing to self-monitor blood glucose and ketones daily and feedback/discuss weekly
5. Life expectancy greater than trial treatment period >12 weeks
6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 with no deterioration over the previous 2 weeks
7. Disease measurable according to RECIST v1.1
8. Disease amenable to biopsy for metabolic studies
9. Adequate haematological function within 7 days of treatment
9.1. Haemoglobin > = 100 g/L
9.2. Absolute neutrophil count (ANC) > = 1.5 x 10^9/L
9.3. Platelet count > = 100 x 10^9/L
10. Adequate hepatic function within 7 days of treatment:
10.1. Total serum bilirubin < = 1.5 x upper limit of normal (ULN)
10.2. Alanine transferase (ALT) < = 2.5 x ULN.
10.3. Aspartate transferase (AST) < = 2.5 x ULN

11. Adequate renal function within 7 days of treatment:
11.1. Creatinine clearance <1.5 times ULN concurrent with creatine clearance >50 ml/min (calculated by Cockcroft and Gault equation). If this is <=50 ml/min then an isotopic Glomerular Filtration Rate (GFR) may be carried out and must be >50 ml/min
12. Willing to accept paired biopsies at week 5 and blood samples at pre- and post- 12 weeks KDT treatment for translational metabolic analyses
13. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal participants
14. Male and female participants of childbearing potential willing to use highly effective contraception
15. Willing and able to comply with scheduled visits, treatment plan and other trial procedures
16. Willing and able to give written informed consent for the trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Sex
All

Key exclusion criteria
1. Patients who do not meet the criteria of performance status <=1 on the ECOG Performance scale i.e. patients that are not be ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work
2. Untreated symptomatic brain or leptomeningeal metastatic disease
3. Medical or psychiatric conditions compromising informed consent
4. Any pre-existing autoimmune disease besides well-controlled thyroid disease
5. Patients with active concurrent cancer or cancer within the past 3 years excepting non-melanomatous skin cancer and in situ cancers
6. Anyone diagnosed with fatty acid oxidation defects, organic acidurias (organic acid disorders), pyruvate carboxylase deficiency, porphyria or other disorders requiring a high carbohydrate treatment
7. Anyone who knows they respond to fasting by becoming significantly unwell or unconscious
8. Any disorder affecting the ability to eat or digest food; swallowing problems, digestive or reflux issues or difficulties with the bowel such as chronic constipation or diarrhoea
9. Patients requiring regular steroid therapy with steroids at a dose higher than prednisolone 10 mg/day or equivalent
10. History of anorexia
11. Diabetes on medication (Type 2 on oral medication - adjustment needed. Type 1 – not appropriate for trial)
12. Familial hyperlipidaemia
13. Acute pancreatitis or history of pancreatitis
14. Patients with a current or recent history of clinically significant renal, cardiac, hepatic,

haematological, pulmonary, gastroenterological, cerebrovascular or neurological disease as determined by the investigator
15. Patients with a history of organ transplant including Allogeneic Stem Cell Transplantation (allo-SCT)
16. Patients with superior vena cava syndrome
17. No contraindications to anti-PD1 therapy or KDT, such as metabolic disorders
18. Carnitine deficiency (primary) and carnitine palmitoyltransferase I or II deficiency (myopathic form may present in adolescence) or carnitine translocase deficiency
19. Previous cholecystectomy
20. Osteopenia or osteoporosis
21. Corrected calcium > ULN within 7 days of treatment
21.1. Corr. Calcium = Total Calcium (mmol/L) + ([40 – Albumin (G/L)] x 0.02)
22. Phosphate > ULN within 7 days of treatment
23. Hepatic function (in patients with liver metastasis)
23.1. Alanine transferase (ALT) and Aspartate transferase (AST) >5 x ULN
24. Patient is positive for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA (qualitative) is detected); patients with negative Hepatitis C antibody testing may not need RNA testing
25. Known history of tuberculosis
26. Female patients of childbearing potential should be using adequate contraceptive measures, should not be breastfeeding and must have a negative pregnancy test prior to the start of treatment. Pregnant patients will be ineligible
27. Patient has an active infection requiring therapy
28. Patient is, at the time of signing informed consent, a regular user (including “recreational use”) of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol)
29. Participation in another therapeutic clinical trial whilst taking part in this trial
30. Any psychological, familial, sociological or geographical condition hampering protocol compliance
31. Any medical condition which in the opinion of the Investigator would compromise the ability of the patient to participate in the trial or which would jeopardise compliance with the protocol

Date of first enrolment
27/11/2024

Date of final enrolment
01/02/2026

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre

Queen Elizabeth Hospital
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Christie Hospital
Wilmslow Road
Manchester
United Kingdom
M20 4BX

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
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G12 0YN

Study participating centre
Weston General Hospital
Grange Road
Uphill
Weston-super-mare
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BS23 4TQ

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Southampton General Hospital
Tremona Road
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United Kingdom
SO16 6YD

Study participating centre
Velindre Cancer Centre
Velindre Road
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United Kingdom
CF14 2TL

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

Scientifically sound proposals from appropriately qualified researchers will be considered for data sharing. Requests should be made by returning a Data Sharing Request Form to newbusiness@trials.bham.ac.uk; this captures the research requirements, statistical analysis plan, and intended publication schedule. Requests will be reviewed by the Cancer Research UK Clinical Trials Unit (CRCTU) Directors in discussion with the Chief Investigator (CI), Trial Management Group (TMG) and independent Governance Committees. They will consider the scientific validity of the request, qualifications of the researchers, CI, TMG & TSC views, consent arrangements, practicality of anonymizing the requested data & contractual obligations. If supportive of the request, and where not already obtained, Sponsor consent for data transfer will be sought before notifying applicants of the outcome. It is anticipated that applicants will be notified within 3 months of receipt of the original request.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes