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Comparing alternative regimens for escalating treatment of intermediate and high-risk oropharyngeal cancer

Submission date 29/04/2015	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 29/04/2015	**Overall study status** Completed	
Last Edited 16/04/2025	**Condition category** Cancer	

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-different-treatments-for-people-with-oropharyngeal-cancer-compare

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04116047

Clinical Trials Information System (CTIS)
2014-003389-26

Protocol serial number
18621

Study information

Scientific Title
Phase III randomised controlled trial Comparing Alternative REgimens for escalating treatment of intermediate and high-risk oropharyngeal cancer

Acronym
CompARE

Study objectives
Pragmatic phase III open-label randomised controlled trial using an efficient, adaptive, multi-arm multi-stage (MAMS) design, with an integrated qualitative recruitment investigation aiming to optimise recruitment and consenting, to determine the optimum treatment of intermediate and high-risk OPC with the aim of improving survival outcomes without significantly worsening toxicity, Quality of Life (QoL) or swallowing function, compared to the current standard treatment of chemoradiotherapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West Midlands - Solihull, 27/11/2014, ref: 14/WM/1170

Primary study design
Interventional

Study design
Randomized; Interventional; Design type: Treatment

Study type(s)
Treatment

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

Interventions
Current intervention as of 29/10/2021:

1. Arm 1: Control arm, concomitant chemoradiotherapy, 3-weekly cisplatin 100mg/m2 or weekly 40mg/m2 with Intensity Modulated Radiotherapy (IMRT) using 70Gy in 35F +/- neck dissection as indicated by clinical and radiological assessment 3-months post treatment. This is the international gold standard.
2. Arm 2: Induction chemotherapy (3 cycles at 3-weekly intervals: Docetaxel 75mg/m2 + Cisplatin 80mg/m2 + 5-Fluorouracil (5-FU) 800mg/m2/day, daily for 4 days), followed by Arm 1.
3. Arm 3: Dose-escalated chemoradiotherapy using intensity modulated radiotherapy (IMRT) 64Gy in 25F + Cisplatin 100mg/m2 day 1 of week 1 and of week 5 or weekly 40mg/m2 (neck dissection as indicated by clinical and radiological assessment at 3-months post-treatment).

4. Arm 4: Resection of primary + selective neck dissection followed by chemoradiotherapy. For T1 & T2 primary tumour, resection must be transoral. For T3 & T4 primary tumour, resection preferably transoral if possible otherwise by open surgery.
Arm 5: Induction durvalumab plus arm 1 and then adjuvant durvalumab: One dose of induction durvalumab 1500mg by intravenous (IV) infusion followed by arm 1 within four weeks. Within one-two weeks after the completion of arm 1, durvalumab 1500mg every four weeks will be initiated for a total of 6 months.
Follow Up Length: 24 month(s); Study Entry : Registration and One or More Randomisations

(updated 12/12/2022: Arms 2, 3, 4 are now closed to recruitment).

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Follow Up Length: 24 month(s); Study Entry : Registration and One or More Randomisations

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Not provided at time of registration

Primary outcome(s)
1. Definitive (efficacy) endpoint: Overall Survival (OS) - Interval in whole days between the date of randomisation and the date of death from any cause
2. Interim outcome measure (activity stages): Disease Free Survival (DFS) - Interval between the date of randomisation and the date of death or the 1st documented relapse

Key secondary outcome(s)
1. Total number of acute (<3 months post-treatment) and late (up to 2 years) severe (grade 3-5) toxicity events at 2 years post randomisation, measured by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
2. Overall and head and neck specific QoL at 2 years post randomisation, using the European Organisation for Research and Treatment of Cancer (EORTC) C30 and H&N35 Questionnaires
3. Swallowing outcomes using M.D. Anderson Dysphagia Inventory (MDADI) Questionnaire at 24

months and percutaneous endoscopic gastrostomy (PEG) utilisation rates at 1 year
4. Cost effectiveness using EuroQol Group (EQ-5D), patient diaries and primary and secondary resource utilisation data
5. Surgical complication rates in each arm

Completion date
30/11/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 28/02/2022:
1. Oropharyngeal squamous cell carcinoma (OPSCC) in base of tongue and tonsil (includes bilateral tumours) and uvula, with an Multidisciplinary Team (MDT) recommendation for treatment with definitive concurrent chemoradiotherapy.
2. All OPC T4 or N3 (HPV-pos and HPV-neg) OR All HPV–neg OPC T1-T4, N1-N3 or T3-4, N0 OR HPV-pos) OPC T1-T4 with N2b-N3, AND who are smokers ≥ 10 pack years current or previous smoking history
3. Minimum life expectancy of 3 months
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (APPENDIX 3)
5. Body weight >30kg
6. Adequate renal function, estimated glomerular filtration rate (eGFR) >50mL/min calculated using Cockcroft-Gault formula (APPENDIX 4)*
7. Adequate bone marrow function (absolute neutrophil count (ANC) ≥1.5 x 109/L, haemoglobin ≥9.0g/dL and platelets ≥100 x 109/L)
8. Adequate liver function i.e. serum bilirubin ≤1.5 times the upper limit of normal (ULN) ,AST (SGOT)/ ALT(SGPT) ≤2.5 x institutional upper limit of normal
9. Prothrombin time (PT) ≤1.5 x ULN or International Normalised Ratio (INR) ≤1. 5
10. No cancers in previous 5 years, except basal cell carcinoma of skin and cervical intra-epithelial neoplasia (CIN)
11. Age 18-70
12. Written informed consent given for the trial
13. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
- Women
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiationinduced menopause with last menses >12 months ago, had chemotherapy-induced menopause with last menses >12 months ago or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
14. Willingness to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations including follow up

Previous inclusion criteria:
1. Oropharyngeal squamous cell carcinoma in base of tongue and tonsil with an Multidisciplinary Team recommendation for treatment with definitive concurrent chemoradiotherapy
2. Intermediate risk [HPV +ve OPC with N2b+ disease and greater than 10 pack year history of smoking] or high -risk (HPV–ve OPC) as per Ang classification
3. Minimum life expectancy of 3 months

4. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
5. Adequate renal function, glomerular filtration rate >50mL/min calculated using Cockcroft-Gault formula
6. Adequate bone marrow function (absolute neutrophil count ≥1.5 x 109/L and platelets ≥100 x 109/L)
7. Adequate liver function i.e. plasma bilirubin ≤1.5 times the upper limit of normal, and alanine aminotransferase and Alkaline phosphatase ≤2.5 x upper limit of normal
8. Prothrombin time ≤1.5 x upper limit of normal or International Normalised Ratio ≤1. 5
9. Magnesium ≥ lower limit of normal
10. No cancers in previous 5 years, except basal cell carcinoma of skin and cervical intra-epithelial neoplasia
11. Age 16--70
12. Written informed consent given
13. Surgically resectable disease if being randomised to all 4 arms

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
70 Years

Sex
All

Total final enrolment
794

Key exclusion criteria
Current exclusion criteria as of 28/02/2022:
1. All T1-T2,N0 OPC (HPV-pos or HPV-neg)
2. HPV positive patients who are:
• T1-T3, N0-N2c non-smokers
• T1-T3, N0-N2c smokers with ≤10 pack years or
• T1-T3, N0-N2a smokers with ≥10 pack years
3. Unfit for chemoradiotherapy regimens
4. Creatinine Clearance
5. Treatment with any of the following, prior to randomisation:
a. Any Investigational Medicinal Products (IMP) within 30 days
b. Any other chemotherapy, immunotherapy or anticancer agents within 3 weeks
c. Major surgical procedure (as defined by the Investigator) within 4 weeks, unless for diagnostic urposes
d. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone

replacement therapy is acceptable)
6. History of allergic reactions or hypersensitivity to any of the IMPs and excipients used in this trial
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhoea, including any patient known to have psychiatric illness/social situations that would limit compliance with study requirements, substantially increase the risk of incurring AEs or compromise the ability of the patient to give written informed consent
8. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
9. Women who are pregnant or breast feeding. Women of child-bearing potential must have a negative pregnancy test performed within 7 days prior to randomisation
10. Men or women who are not prepared to practise methods of contraception of proven efficacy during treatment and for 6 months following the end of treatment
11. Any condition that, in the opinion of the Investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
12. Any previous treatment with a PD-L or PD-L1 inhibitor, including durvalumab
13. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
• Intranasal, inhaled, topical steroids, or local steroid injections (e.g. intra articular injection)
• Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
• Steroids as premedication for hypersensitivity reactions (e.g, CT scan, premedication).
14. Active or prior documented autoimmune or inflammatory disorders including inflammatory bowel disease e.g. colitis or Crohn's disease, diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc). The following are exceptions to this criterion:
• Patients with vitiligo or alopecia
• Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement
• Any chronic skin condition that does not require systemic therapy
• Patients without active disease in the last 5 years may be included but only after consultation with the study physician
• Patients with celiac disease controlled by diet alone
15. History of active primary immunodeficiency
16. History of allogeneic organ transplant
17. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab. Inactivated viruses, such as those in the influenza vaccine are permitted

Previous exclusion criteria:
1. Low- risk OPSCC defined as:
1.1. HPV+ OPC non-smokers or
1.2. HPV+ OPC smokers <10 pack years or
1.3. HPV+ OPC smokers >10 pack years with N0-2A nodal disease
2. Unfit for surgery or chemoradiotherapy regimens

3. Creatinine Clearance <50ml/min
4. Treatment with any of the following, prior to first dose of trial treatment:
4.1. Taxanes
4.2. Any Investigational Medicinal Products (IMP) within 30 days
4.3. Any other chemotherapy, immunotherapy or anticancer agents within 3 weeks
4.4. Major surgery within 4 weeks
4.5. Radiotherapy:
4.5.1. With a wide field of radiation or involving >30% of total bone marrow volume, within 4 weeks
4.5.2. With a limited field of radiation, for palliation, within 2 weeks
5. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 (with the exception of alopecia) at the time of registration
6. History of allergic reactions to any of the IMPs used in this trial
7. Women who are pregnant or breast-feeding. Women of child-bearing potential must have a negative pregnancy test performed within 7 days prior to the start of trial treatment
8. Men or women who are not prepared to practise methods of contraception of proven efficacy during treatment and for 6 months following the end of treatment
9. Pre-existing tinnitus or hearing impairment ischaemic heart disease, cerebro-vascular disease, peripheral vascular disease or previous arterial embolic event

Date of first enrolment
01/05/2015

Date of final enrolment
31/01/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
School of Cancer Sciences
University of Birmingham
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Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

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
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		15/01/2024	15/01/2024	Yes	No
HRA research summary			28/06/2023	No	No