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A trial to assess whether the addition of atezolizumab to current standard treatment for patients with relapsed or refractory Diffuse Large B-Cell Lymphoma, who are not able to have high dose therapy, improves survival outcomes

Submission date 06/11/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 30/11/2017	**Overall study status** Completed	
Last Edited 29/03/2021	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-atezolizumab-with-standard-treatment-for-diffuse-b-cell-lymphoma-argo

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2016-002654-21

IRAS number
205320

ClinicalTrials.gov number

Secondary identifying numbers
36300, IRAS 205320

Study information

Scientific Title
A phase II study of atezolizumab with rituximab, gemcitabine and oxaliplatin in patients with relapsed or refractory diffuse large b-cell lymphoma who are not candidates for high-dose therapy

Acronym
ARGO

Study objectives
This study of atezolizumab in combination with rituximab, gemcitabine and oxaliplatin aims to address the unmet need of patients with relapsed and refractory DLBCL. It is based upon a sound mechanistic approach, investigating the activity of novel agents and will aim to compressively explore biomarkers of response. The primary objective will be to document the durability of anti-tumour activity in patients with relapsed or refractory DLBCL and to determine the safety and toxicity profile of the combination. A maintenance phase of atezolizumab has been added as this may induce an on-going T-cell response to neo-antigens released as a result of chemotherapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
REC – South Central Hampshire A, 17/SC/0533

Study design
Randomised; Interventional; Design type: Treatment, Drug, Immunotherapy

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Lymphoma

Interventions
Participants are randomly allocated to one of two treatment arms: Arm A or Arm B. Treatment involves 1 cycle of rituximab-gemcitabine-oxaliplatin for all patients.

For those in the Arm B, the treatment is followed by 5 cycles of atezolizumab-rituximab-gemcitabine-oxaliplatin. Arm A continue with another 5 cycles of rituximab-gemcitabine-oxaliplatin. Each cycle lasts 14 days.

Subsequently prticipants in Arm B with stable disease or better (determined by PET/CT) move onto a maintenance phase atezolizumab receiving 8 cycles of atezolizumab over 6 months, requiring 1 day of atezolizumab every 21 days. Participants in Arm A go into an observational phase during this same period. Follow up for continues for 36 months post initiation of trial treatment.

Intervention Type
Other

Phase
Phase II

Primary outcome measure
Progression free-survival rate is measured using patient notes at 1 year from study entry.

Secondary outcome measures
1. The toxicity and causality of each adverse event (AE) with R-GemOx-Atezo is measured and severity graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) at Cycles 2-6, End of Treatment, Maintenance cycles 1-8, week 42, and during follow up visits at month 12, 16, 20, 24, 30 and 36 for patients in Arm B
2. Objective response (partial or complete metabolic response (PR or CR)) is assessed by PET in any of the patients as determined by the Lugano response criteria at Baseline, End of Treatment and at the End of Maintenance in week 42
3. Progression free survival from study entry will be measured from the day of registration to the date of progression or death from any cause using patient notes. Patients who do not die will be censored at their date of last follow up.
4. Overall survival from study entry ismeasured from the day of registration to the date of death from any cause from patient notes. Patients who do not die are censored at their date of last follow up.

Overall study start date
12/12/2015

Completion date
31/01/2021

Eligibility

Key inclusion criteria

Current participant inclusion criteria as of 05/07/2019:
1 Histologically proven CD20 +ve diffuse large B-cell lymphoma (including transformation of previous low-grade lymphoma and primary mediastinal B-cell lymphoma), preferably with sufficient diagnostic material, available to forward to the Haematological Malignancies Diagnostic Service (HMDS). (See screening procedure for details on biopsy requirements)
2. Refractory to, or relapsed following, first-line or second-line treatments with rituximab concurrently with anthracycline or anthracenedione-based chemotherapy (etoposide or gemcitabine allowed if comorbid). Patients who have received further lines of treatment may be included.
Refractory disease must fulfil one of the following:
2.1 Continuing partial response (PR) from termination of first-line treatment. It is strongly recommended the lymphoma be reconfirmed by biopsy however, if these procedures are deemed to be inappropriate, the CI may determine eligibility following review of the imaging results and disease history.
2.2 Continuing stable disease (SD) from termination of first-line treatment. Reconfirmation of the lymphoma by biopsy (preferred) is recommended but not mandatory.
2.3 Progressive disease (PD). Biopsy or reconfirmation of the lymphoma is recommended but not mandatory.
3. Not eligible for high-dose therapy with peripheral blood progenitor cell rescue at Investigator discretion as a result of: (a) Age; (b) Co-morbidity; (c) Previous HDT.Rationale to be clearly documented on eCRF and medical notes.
4. Baseline FDG-PET scans must demonstrate positive lesions compatible with CT defined anatomical tumour sites.
5. CT/PET scan showing at least: 2 or more clearly demarcated lesions/nodes with a long axis >1.5cm and short axis ≥1.0cm
OR 1 clearly demarcated lesion/node with a long axis >2.0cm and short axis ≥1.0cm.
6. Resolution of toxicities from previous therapy to a grade that in the opinion of the investigator does not contraindicate study participation.
7. Patients aged 16 years or over.
8. Willingness to participate in appropriate pregnancy prevention measures.
8.1Female patients who are fertile and of childbearing potential must have a negative serum or urine pregnancy test during screening (within 14 days prior to the start of trial treatment) and agree to use two highly effective forms of contraception (oral, injected or implanted hormonal contraception and condom; an intra-uterine device and condom) effective from the first administration of all study drugs, throughout the trial and for 12 months after last dose of study therapy are considered eligible. Unless they are surgically sterile or ≥ 2 years after the onset of menopause.
8.2 Male patients with partners of child-bearing potential who agree to take measures not to father children by using two forms of highly effective contraception (oral, injected or implanted hormonal contraception and condom; an intra-uterine device and condom) effective from the first administration of all study drugs, throughout the trial and for 12 months after last dose of study therapy are considered eligible. Male subjects must also refrain from donating sperm during this period. Unless they are surgically sterile.
8.3 Men with pregnant or lactating partners must be advised to use barrier method contraception (for example: condom plus spermicidal gel) to prevent exposure to the foetus or neonate
9. Written informed consent using current version of Protocol, Patient Information Sheet and

Informed Consent Form.
10. ECOG performance status ≤ 3

Previous participant inclusion criteria:
1. Histologically proven CD20 +ve diffuse large B-cell lymphoma with sufficient diagnostic material, obtained either at diagnosis or relapse (the latter is preferable) that is available to forward to the Haematological Malignancies Diagnostic Service (HMDS) for gene expression profiling and central pathology review. (See screening procedure for details on biopsy requirements)
2. Refractory to, or relapsed following, first-line or second-line treatments with rituximab concurrently with anthracycline or anthracenedione-based chemotherapy (etoposide or gemcitabine allowed if comorbid).
Refractory disease must fulfil one of the following:
2.1. Continuing partial response (PR) from termination of first-line treatment. It is strongly recommended the lymphoma be reconfirmed by biopsy however, if these procedures are deemed to be inappropriate, the CI may determine eligibility following review of the imaging results and disease history.
2.2. Continuing stable disease (SD) from termination of first-line treatment. Reconfirmation of the lymphoma by biopsy (preferred) is recommended but not mandatory.
2.3. Progressive disease (PD). Biopsy or reconfirmation of the lymphoma is recommended but not mandatory.
3. Not eligible for high-dose therapy with peripheral blood progenitor cell rescue at Investigator discretion as a result of:
3.1. Age
3.2. Co-morbidity
3.3. Previous HDT.
Rationale to be clearly documented on eCRF and medical notes.
4. Baseline FDG-PET scans must demonstrate positive lesions compatible with CT defined anatomical tumour sites.
5. CT/PET scan showing at least: 2 or more clearly demarcated lesions/nodes with a long axis >1.5cm and short axis ≥1.0cm
or 1 clearly demarcated lesion/node with a long axis >2.0cm and short axis ≥1.0cm.
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8.2. Male patients with partners of child-bearing potential who agree to take measures not to father children by using one form of highly effective contraception (oral, injected or implanted hormonal contraception and condom; an intra-uterine device and condom) effective from the first administration of all study drugs, throughout the trial and for 12 months after last dose of study therapy are considered eligible. Male subjects must also refrain from donating sperm during this period. Unless they are surgically sterile.
8.3. Men with pregnant or lactating partners must be advised to use barrier method contraception (for example: condom plus spermicidal gel) to prevent exposure to the foetus or neonate

9. Written informed consent using current version of Protocol, Patient Information Sheet and Informed Consent Form
10. ECOG performance status ≤3

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 112; UK Sample Size: 112

Total final enrolment
53

Key exclusion criteria
Current participant exclusion criteria as of 05/07/2019:
1 Received any of the following treatments within two weeks prior to start of study therapy (unless otherwise stated):
1.1 Anti-cancer cytotoxics (excluding corticosteroids)
1.2 Radiotherapy unless it is to a limited field to control life/organ-threatening symptoms.
2. DLBCL that is refractory to or relapsed within 3 months of a gemcitabine regimen for DLBCL
3. Major surgery within 4 weeks of registration.
4. Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half-lives or 4 weeks prior to registration.
5. History of stroke or intracranial haemorrhage within 6 months prior to registration.
6. Pre-existing peripheral neuropathy grade >2.
7. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to registration, congestive heart failure (NYHA III-IV), a current LVEF of <40%
8. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator contraindicates participation in this study
9. Known lymphoma involvement of the CNS.
10. Known or suspected hypersensitivity to study treatments that in the opinion of the investigator contraindicates their participation. Patients with known history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug induced pneumonitis or idiopathic pneumonitis, or evidence of active pneumonitis will be excluded from study participation.
11. Known HIV positivity; positive serology for Hep B (defined as positivity for Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc)) or C; chronic or current infectious disease (except evidence of prior vaccination).
12. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection or any major episode of infection requiring treatment with IV antibiotics or hospitalization within 2 weeks of the start of Cycle 1. Suspected active or latent tuberculosis needs to be confirmed by positive interferon gamma (IFN-) release assay.
13. Other past or current malignancy within 2 years prior to registration unless in the opinion of the investigator it does not contraindicate participation in the study. Subjects who have a history

of completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma, are eligible.
14. Screening laboratory values:
14.1 Platelets <75x109/L (unless due to lymphoma involvement of the bone marrow)
14.2 Neutrophils <1.0x109/L (unless due to lymphoma involvement of the bone marrow)
14.3 Creatinine clearance <60mL/min (should be calculated using Cockcroft and Gault equation)
14.4 Creatinine >2.0 times upper normal limit (unless due to lymphoma or unless creatinine clearance >60mL/min)
14.5 Total bilirubin >1.5 times upper normal limit (unless due to lymphoma or a known history of Gilbert's disease, no higher than >3 times upper normal limit)
14.6 ALT/AST >2.5 times upper normal limit (unless due to lymphoma, no higher than >5 times upper normal limit)
14.7 Alkaline phosphatase >2.5 times upper normal limit (unless due to lymphoma, no higher than >5 times upper normal limit)
15. Subjects known or suspected of being unable to comply with the study protocol.
16. Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test at screening.
17. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone will be eligible as will be patients with controlled Type I diabetes mellitus on a stable dose of insulin). Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
17.1 Rash must cover < 10% of body surface area
17.2 Disease is well controlled at baseline and requires only low-potency topical corticosteroids
17.3 No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months
18. Patients who have previously undergone allogeneic transplantation.
19. Vaccination with a live vaccine within 28 days of study treatment or anticipation of need for such a vaccine during the course of the study and up to 5 months after the last dose of atezolizumab.
20. History of severe allergic anaphylactic reactions to chimeric, human or humanised antibodies, or fusion proteins.
21. Known hypersensitivity to CHO cell products or any component of the atezolizumab formulation.

Previous participant exclusion criteria:
1. Received any of the following treatments within two weeks prior to start of study therapy (unless otherwise stated):
1.1. Anti-cancer cytotoxics (excluding corticosteroids)
1.2. Radiotherapy unless it is to a limited field at to control life/organ-threatening symptoms.
2. DLBCL that is refractory to or relapsed within 3 months of a gemcitabine regimen for DLBCL
3. Major surgery within 4 weeks of registration.
4. Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half-lives or 4 weeks prior to registration.
5. History of stroke or intracranial haemorrhage within 6 months prior to registration.
6. Pre-existing peripheral neuropathy grade > 2.
7. Clinically significant cardiac disease including unstable angina, acute myocardial infarction

within six months prior to registration, congestive heart failure (NYHA III-IV), a current LVEF of < 40%
8. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator contraindicates participation in this study
9. Known lymphoma involvement of the CNS.
10. Known or suspected hypersensitivity to study treatments that in the opinion of the investigator contraindicates their participation. Patients with known history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug induced pneumonitis or idiopathic pneumonitis, or evidence of active pneumonitis will be excluded from study participation.
11. Known HIV positivity; positive serology for Hep B (defined as positivity for Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc)) or C; chronic or current infectious disease (except evidence of prior vaccination).
12. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection or any major episode of infection requiring treatment with IV antibiotics or hospitalization within 2 weeks of the start of Cycle 1. Suspected active or latent tuberculosis needs to be confirmed by positive interferon gamma (IFN-y) release assay.
13. Other past or current malignancy within 2 years prior to registration unless in the opinion of the investigator it does not contraindicate participation in the study. Subjects who have a history of completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma, are eligible.
14. Screening laboratory values:
14.1. Platelets < 75x109/L (unless due to lymphoma involvement of the bone marrow)
14.2. Neutrophils < 1.0x109/L (unless due to lymphoma involvement of the bone marrow)
14.3. Creatinine > 2.0 times upper normal limit (unless due to lymphoma or unless creatinine clearance > 60mL/min (calculated using Cockcroft and Gault equation))
14.4. Total bilirubin > 1.5 times upper normal limit (unless due to lymphoma or a known history of Gilbert's disease, no higher than > 3 times upper normal limit)
14.5. ALT/AST > 2.5 times upper normal limit (unless due to lymphoma, no higher than > 5 times upper normal limit)
14.6. Alkaline phosphatase > 2.5 times upper normal limit (unless due to lymphoma, no higher than > 5 times upper normal limit)
15. Subjects known or suspected of being unable to comply with the study protocol.
16. Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test at screening.
17. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone will be eligible as will patients with controlled Type I diabetes mellitus on a stable dose of insulin). Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g. patients with psoriatic arthritis are excluded) are eligible for the study provided all of the following conditions are met:
- Rash must cover < 10% of body surface area
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids
- No occurance of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
18. Patients who have previously undergone allogeneic transplantation.
19. Vaccination with a live vaccine within 28 days of study treatment or anticipation of need for such a vaccine during the course of the study and up to 5 months after the last dose of

atezolizumab.
20. History of severe allergic anaphylactic reactions to chimeric, human or humanised antibodies, or fusion proteins.
21. Known hypersensitivity to CHO cell products or any component of the IMP

Date of first enrolment
12/06/2018

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
England

Scotland

United Kingdom

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

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

Study participating centre
Harrogate District Hospital
Lancaster Park Road
Harrogate
United Kingdom
HG2 7SX

Study participating centre

Royal Cornwall Hospital
Treliske
Truro
United Kingdom
TR1 3LQ

Study participating centre
Beatson West of Scotland Cancer Centre
Gartnavel General Hospital
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

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

Study participating centre
University Hospital Aintree
Longmoor Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
Royal Oldham Hospital
Rochdale Road
Oldham
United Kingdom
OL1 2JH

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Salisbury District Hospital
Odstock Road
Salisbury
United Kingdom
SP2 8BJ

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre
Northwick Park Hospital
Watford Road
Harrow
United Kingdom
HA1 3UJ

Study participating centre
Colchester General Hospital
Turner Road
Colchester
United Kingdom
CO4 5JL

Study participating centre
Maidstone Hospital
Hermitage Lane

Maidstone
United Kingdom
ME16 9QQ

Study participating centre
Royal Devon and Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Torbay District General Hospital
Lowes Bridge
Torquay
United Kingdom
TQ2 7AA

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

Sponsor details
R&D Department
SGH - Level E, Laboratory & Pathology Block, SCBR - MP 138
Southampton
England
United Kingdom
SO16 6YD

Sponsor type
Hospital/treatment centre

Website
www.uhs.nhs.uk

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.The Southampton Clinical Trials Unit will publish the results of the trial on their website when these are available.

Intention to publish date
31/12/2022

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?
Participant information sheet	version V2		30/11/2017	No	Yes

Participant information sheet	version v6	25/07/2018	24/08/2018	No	Yes
Participant information sheet	version v7	29/11/2018	02/03/2020	No	Yes
HRA research summary			28/06/2023	No	No