Clinical trial results:
A randomised phase 2 trial investigating the additional benefit of hydroxychloroquine (HCQ) to short course radiotherapy (SCRT) in patients aged 70 years and older with high grade gliomas (HGG)

Summary

EudraCT number	2012-000091-41
Trial protocol	GB
Global end of trial date	25 July 2019

Results information

Result version number	v1 (current)
This version publication date	13 August 2020
First version publication date	13 August 2020
Summary attachment (see zip file)	Hydroxychloroquine and short-course radiotherapy (HCQ Neuro Onc Advances 2020.pdf)

Trial information

Trial identification

Sponsor protocol code	UCL/11/0404

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01602588
WHO universal trial number (UTN)	-
Other trial identifiers	Cancer Research UK reference number: CR UK11/057, CTA number: 20363/0310/001-0001

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom,
Public contact	Public Contact, Cancer Research UK and UCL Cancer Trials Centre,, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific Contact, Cancer Research UK and UCL Cancer Trials Centre,, ctc.sponsor@ucl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 December 2017
Global end of trial reached?	Yes
Global end of trial date	25 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To examine the effect on one-year survival of giving hydroxychloroquine with SCRT to HGG patients aged 70 yrs or older and to assess the toxicity of giving HCQ with SCRT.

Primary endpoint
•One-year survival

Protection of trial subjects:

Hydroxychloroquine was being used outside of its marketing authorisation. However, it has been used successfully in a phase 2 CML trial and in small studies of brain tumours. Hydroxychloroquine will be given at the same dose and via the same route as per the marketing authorisation. Subjects were provided with a diary card which include instructions for how many tablets should have been taken in order to take the correct dose. Full drug accountability was recorded by site and provided to UCL CTC upon request.

Regular monitoring of safety data was conducted by IDMC and the trial conduct was overseen by the TMG and TSC. Patients were regularly assessed while on treatment and on follow up. Appropropriate entry criteria were in place to ensure only eligible and suitable patients entered the trial.

Assessments were carried out at different points of treatment and the trial to ensure safety of participants. Pre-treatment assessments included post-operative MRI scan and visual assessment by an opthalmologist for patients on Arm B. Assessments during treatment included review of adverse events and steroid dose. After completion of the trial, patients were assessed with a complete physical examination including full neurological examination, review of concomitant medication, review of steroid dose, review of any adverse events, ECOG performance status, mini-mental status examination, blood tests and an electrocardiogram (for Arm B patients).

The protocol also provided information on how to manage adverse events (including haematology, eye, metabolic and nutritional disorders) and possible supportive medication. As it was not known if there was a direct risk to pregnancy due to exposure to HCQ, male patients with female partners of child bearing potential were asked to use adequate contraception. As the inclusion criteria required patients to be over 70, it was anticipated that any female patients would not be of child bearing potential.

Background therapy:

Radiotherapy
Patients receive short course radiotherapy: Patients were planned using conformal radiotherapy. Radiotherapy started within 4 weeks of surgery (Day 28 post surgery). A window of +/- 3 days was permitted.

Dose fractionation
Short course radiotherapy was given as a total dose of 30Gy in 6 fractions given on alternate days (Monday, Wed and Friday) over 2 weeks prescribed to the intersection point (IP).

Evidence for comparator:

Many centres recommend short course 'high dose palliation' radiotherapy (SCRT) using hypofractionated regimes, which have been shown to be as effective as prolonged treatment courses.

Sources:
Roa, W., et al., Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. Journal of Clinical Oncology, 2004. 22(9): p. 1583-1588.

Malmstrom, A., et al., Glioblastoma in Elderly Patients: Health-Related Quality of Life (Hrqol) in a

Actual start date of recruitment	20 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

54 patients were recruited onto the trial from May 2013 to September 2016 of which 1 patient was inelgibile and therefore excluded. There were 17 sites activated in the trial. 16 recruited patients and 2 did not.

Pre-assignment

Screening details:

No screening information to provide for this trial. Patients were screened for eligibility for inclusion into the trial as per trial protocol.

Period 1

Period 1 title	Main trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - SCRT alone

Arm description:

4 weeks post surgery (day 28 post surgery +/- 3 days) patients will commence short course radiotherapy (30 Gy, 5Gy/day, 6 fractions Mon, Weds, Fri) over a 2 week period. 2 of the 18 patients did not receive radiotherapy but still included in the ITT analysis

Arm type	control

No investigational medicinal product assigned in this arm

Arm title	Arm B - SCRT + HCQ

Arm description:

Patients randomised to Arm B will commence Hydroxychloroquine 200mg per oral twice daily starting from day 14-20 post surgery until radiological or clinical progression. At 4 weeks post surgery (day 28 with a window of +/- 3days), patients will commence short course radiotherapy of 30 Gy in total over 2 weeks. (5 Gy/day, 6 fractions on Monday, Wednesday and Friday). Patients should have been taking HCQ for at least 7 days before receiving radiotherapy treatment.

36 patients were randomised to this arm. 1 was ineligible. Of the 35 eligible patients all received SCRT and HCQ but 2 did not receive the protocol radiotherapy dose (one received 30Gy over 7 fractions and one received 2 fractions). They are included in the IIT analysis.

Arm type	Experimental
Investigational medicinal product name	Plaquenil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

200mg HCQ should be taken twice daily starting from between day 14 to day 20 post surgery until radiological or clinical progression.

Number of subjects in period 1	Arm A - SCRT alone	Arm B - SCRT + HCQ
Started	18	35
Completed	18	35

Baseline characteristics

Reporting groups	
Reporting group title	Arm A - SCRT alone
Reporting group description:	
4 weeks post surgery (day 28 post surgery +/- 3 days) patients will commence short course radiotherapy (30 Gy, 5Gy/day, 6 fractions Mon, Weds, Fri) over a 2 week period. 2 of the 18 patients did not receive radiotherapy but still included in the ITT analysis	
Reporting group title	Arm B - SCRT + HCQ
Reporting group description:	
Patients randomised to Arm B will commence Hydroxychloroquine 200mg per oral twice daily starting from day 14-20 post surgery until radiological or clinical progression. At 4 weeks post surgery (day 28 with a window of +/- 3days), patients will commence short course radiotherapy of 30 Gy in total over 2 weeks. (5 Gy/day, 6 fractions on Monday, Wednesday and Friday). Patients should have been taking HCQ for at least 7 days before receiving radiotherapy treatment. 36 patients were randomised to this arm. 1 was ineligible. Of the 35 eligible patients all received SCRT and HCQ but 2 did not receive the protocol radiotherapy dose (one received 30Gy over 7 fractions and one received 2 fractions). They are included in the IIT analysis.	

Reporting group values	Arm A - SCRT alone	Arm B - SCRT + HCQ	Total
Number of subjects	18	35	53
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	18	35	53
85 years and over	0	0	0
Age continuous			
Age at entry (years)			
Units: years			
median	75.5	74	
full range (min-max)	70 to 82	70 to 83	-
Gender categorical Units: Subjects			
Female	6	14	20
Male	12	21	33
Histology Units: Subjects			
Anaplastic astrocytoma	1	2	3
Glioblastoma	15	32	47
Gliosarcoma	1	0	1
High-grade glioma	1	1	2
Surgery Units: Subjects			

Biopsy	10	21	31
Resection	8	14	22
ECOG Units: Subjects			
Fully active	7	4	11
Ambulatory but can work	11	31	42
MMSE score Units: MMSE Score			
median	28.5	27	
full range (min-max)	17 to 30	18 to 30	-

End points

End points reporting groups

Reporting group title	Arm A - SCRT alone

Reporting group description:

4 weeks post surgery (day 28 post surgery +/- 3 days) patients will commence short course radiotherapy (30 Gy, 5Gy/day, 6 fractions Mon, Weds, Fri) over a 2 week period. 2 of the 18 patients did not receive radiotherapy but still included in the ITT analysis

Reporting group title	Arm B - SCRT + HCQ

Reporting group description:

Patients randomised to Arm B will commence Hydroxychloroquine 200mg per oral twice daily starting from day 14-20 post surgery until radiological or clinical progression. At 4 weeks post surgery (day 28 with a window of +/- 3days), patients will commence short course radiotherapy of 30 Gy in total over 2 weeks. (5 Gy/day, 6 fractions on Monday, Wednesday and Friday). Patients should have been taking HCQ for at least 7 days before receiving radiotherapy treatment.

36 patients were randomised to this arm. 1 was ineligible. Of the 35 eligible patients all received SCRT and HCQ but 2 did not receive the protocol radiotherapy dose (one received 30Gy over 7 fractions and one received 2 fractions). They are included in the IIT analysis.

Primary: Overall survival

End point title	Overall survival

End point description:

From Kaplan-Meier estimates

End point type	Primary

End point timeframe:

One year

End point values	Arm A - SCRT alone	Arm B - SCRT + HCQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	35		
Units: Percentage				
number (confidence interval 95%)	41.2 (18.6 to 62.6)	20.3 (8.2 to 36.0)		

Statistical analyses

Statistical analysis title	Primary outcome

Statistical analysis description:

The OS rates at 1 year came from Kaplan-Meier estimates (life tables).

Comparison groups	Arm B - SCRT + HCQ v Arm A - SCRT alone

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Regression, Cox

Notes:

[1] - We used a single-arm phase II A'Hern design, with a target 1-year OS rate of 40% using hydroxychloroquine, assuming 25% for radiotherapy alone. With one-sided 15% statistical significance and 80% power, we required 13 patients to be alive at 1 year out of 38 patients given hydroxychloroquine to justify further investigation. We also compared OS between the two trial arms using Cox regression to produce hazard ratio, though the trial was not powered for this direct comparison.

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Radiological progression free survival at 6 months as defined from the day of randomisation to the day of local tumour progression or recurrence based on the modified RANO response criteria for MRI, or the day of death of any cause.

Clinical progression free survival at 6 months as defined from the day of randomization to the day of local tumour progression or recurrence based on clinical evaluation, or the day of death of any cause.

End point type	Secondary

End point timeframe:

From the day of randomisation to 6 months post randomisation.

End point values	Arm A - SCRT alone	Arm B - SCRT + HCQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	35		
Units: Percentage				
number (confidence interval 95%)	35.3 (19.3 to 51.7)	29.4 (10.7 to 51.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occur between informed consent and 30 days post last trial treatment administration. Non-serious AEs: not presented in line with manuscript

Adverse event reporting additional description:

Adverse events were recorded in the patient notes and reported to the coordinating centre via the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) were reported using the trial specific SAE Report. Causality assessment to study IMPs was performed by site investigator and study CI.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Arm A - SCRT alone

Reporting group description:

4 weeks post surgery (day 28 post surgery +/- 3 days) patients will commence short course radio therapy (30 Gy, 5Gy/day, 6 fractions Mon, Weds, Fri) over a 2 week period.
Serious adverse events below is defined as all grade 3-5 events.

Reporting group title	Arm B - SCRT + HCQ

Reporting group description:

Patients randomisedto Arm B will commence Hydroxychloroquine 200mg per oral twice daily from day 14-20 post surgery until radiological or clinical progression. At 4 weeks post surgery (day 28 with a window of +/- 3days), patients will commence short course radio therapy of 30 Gy in total over 2 weeks. (5 Gy/day, 6 fractions on Monday, Wednesday and Friday). Patients should have been taking HCQ for at least 7 days before receiving radiotherapy treatment. Serious adverse events is defined as all grade 3-5 events.

Serious adverse events	Arm A - SCRT alone	Arm B - SCRT + HCQ	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 18 (38.89%)	21 / 35 (60.00%)	
number of deaths (all causes)	17	30	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
Thromboembolic event			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 23			

subjects affected / exposed	1 / 18 (5.56%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Cognitive disorder			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	1 / 18 (5.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	1 / 18 (5.56%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Seizure			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	1 / 18 (5.56%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	1 / 18 (5.56%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	1 / 18 (5.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative dictionary used: MedDRA 23			

subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hip fracture			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	1 / 18 (5.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lung infection			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	5 / 35 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Steroid diabetes			
alternative dictionary used: MedDRA 23			
subjects affected / exposed	0 / 18 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A - SCRT alone	Arm B - SCRT + HCQ	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 18 (44.44%)	13 / 35 (37.14%)	
General disorders and administration site conditions			
Grade 1-2 events			
subjects affected / exposed	8 / 18 (44.44%)	13 / 35 (37.14%)	
occurrences (all)	8	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2014	The protocol amendment was primarily to make changes in 1) the randomisation period to give greater flexibility for sites to assess/screen potential subjects and 2) addition of management of a potential adverse event 'hypoglycaemia' to the protocol due to the updated version of the SPC for trial IMP 'hydroxychloroquine'. The amendment will changed the version number of the Protocol from v1.1 to v2.0. Main cahnges include: • To clarify the radiotherapy treatment should start within 4 weeks of surgery (Day 28 post surgery). A window of +/- 3 days is permitted • Arm B patients should have been taking HCQ for at least 7 days prior to receiving SCRT (A window of +/- 3 days is permitted) • Randomisation can be taken place between day 1 to day 19 post surgery. • Review of concomitant medications to identify those patients taking anti-diabetic medications is added to pre-randomisation evaluations. Diabetic patients should be made aware of the risk of hypoglycaemia and the associated clinical signs and symptoms and that their requirements for diabetic medication may decrease and that they should actively monitor their glucose measurements. • Management of adverse events due to treatment – hydroxychloroquine has been added. Actions to be taken in the event of haematological toxicities, eye disorders and hypoglycaemia • Visual assessment should be repeated every 12 months whilst patient is still taking hydroxychloroquine after their visual assessments at 6 and 12 months post completion of radiotherapy. • Sites which are participating the translational research will consent to patients to translational research in order to carry out follicle and blood sample collections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 October 2016	IDMC recommended early closure	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Serious AEs: occurrences all number can't be provided as only highest grade experienced by patients are collected on CRFs; subjects affected is entered instead (only grade 3-5 reported)
Treatment related death/relatedness to SAEs not presented

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32642699