FINAL STUDY REPORT

BSG Temozolomide

(A Phase II Multi-Centre Study of Concomitant and Prolonged Adjuvant Temozolomide with Radiotherapy in Diffuse Pontine Gliomas)

Chief Investigator:	Dr Simon Bailey
Sponsor:	University of Birmingham
Sponsor's Protocol No:	RG_09-200
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First Study Approval by MHRA:	16th July 2007
Substantial Amendments to Date:	Amendment 01: 7th September 2007 Amendment 02: 4th March 2008 Amendment 03: 21st July 2008 Amendment 04: 4th February 2009 Amendment 05: 4th February 2010 Amendment 06: 2nd July 2010 Amendment 07: 28th January 2011

Objectives

To pilot the administration of a concomitant daily low dose schedule of temozolomide with standard radiotherapy in children and adolescents with newly diagnosed brainstem gliomas, followed by maintenance therapy with low dose temozolomide for one year if there is no evidence of tumour progression.

Primary Aim:

To evaluate the time to death in patients with newly diagnosed diffuse pontine gliomas, when treated with the combination of concomitant low dose oral temozolomide and radiation therapy, followed by up to 12 months maintenance therapy with extended low dose temozolomide, and, to assess the quality of life in patients with diffuse pontine gliomas during and after the above treatment.

Secondary Aims:

- To evaluate the time to tumour progression in patients with newly diagnosed diffuse pontine gliomas, when treated with the combination of concomitant low dose oral temozolomide and radiation therapy, followed by up to 12 months maintenance therapy with extended low dose temozolomide.
- To evaluate and document toxicities from the administration of temozolomide combined with radiotherapy and to further study any toxicities associated with the chronic administration of the extended low dose temozolomide schedule in this population group.
- To document radiological response to treatment with MR imaging and where available functional imaging.

Methodology
The paediatric maximum tolerated dose (MTD) - 75mg/m2 daily for 42 days, was determined by the published recommended oral dose. This was given with standard radiotherapy for newly diagnosed brainstem and high grade gliomas. There was no dose escalation. Toxicity was monitored using the NCI Common Toxicity Criteria and response was evaluated both clinically and radiologically following initial combined therapy. If there was no evidence of clinical progression 4 weeks post-radiotherapy, patients were eligible to commence maintenance therapy with courses of temozolomide at 75mg/m2 daily for 21 days, repeated after a 7 day break (or upon count recovery). After 2 courses at this dose the maintenance dose was escalated to 100mg/m2 daily for 21 days for a maximum of 1 year total therapy unless there was significant toxicity at 75mg/m2. Toxicity and response were evaluated throughout the treatment period.

Recruitment
Recruitment took place between February 2008 – July 2010.
43 patients were recruited and follow up of patients continued for at least 3 years after diagnosis.

Opened sites:

SITE	LOCATION	DATE OPENED
Royal Aberdeen Children's Hospital	Aberdeen, UK	11th Sep 2008
Birmingham Children's Hospital	Birmingham, UK	25th Jan 2008
Bristol Royal Hospital for Sick Children	Bristol, UK	11th Dec 2008
Addenbrooke's Hospital	Cambridge, UK	10th Mar 2008
Children's Hospital for Wales	Cardiff, UK	24th Oct 2008
Royal Hospital for Sick Children	Edinburgh, UK	13th Mar 2008
Royal Hospital for Sick Children	Glasgow, UK	1st Aug 2008
St James' Hospital	Leeds, UK	3rd Jun 2008
Alder Hey Children's Hospital	Liverpool, UK	31st Mar 2008
Great Ormond Street Hospital	London, UK	24th Mar 2009
University College London Hospital	London, UK	11th Sep 2008
Royal Manchester Children's Hospital	Manchester, UK	25th Jan 2008
Royal Victoria Infirmary	Newcastle, UK	31st Jan 2008
Queen's Medical Centre	Nottingham, UK	24th Jun 2008
Sheffield Children's Hospital	Sheffield, UK	2nd Sep 2008
Royal Marsden Hospital	Surrey, UK	21st Jul 2008

Results
Median age at diagnosis was 8 years (2-20). 81% of patients presented with cranial nerve abnormalities, 76% with ataxia and 57%with long tract signs.
Mean Karnofsky/Lansky score was 79 (10-100). Patients received a median of 3 courses of maintenance temozolomide, 5 received all 12 courses and 7 did not start maintenance. Three patients were withdrawn from the study due to hematological toxicity and 10 had a dose reduction on at least one course. No other significant toxicity related to temozolomide was noted.
Overall survival (95%CI) was 0.56 (0.40, 0.69) at 9 months, 0.35 (0.21, 0.49) at 1 year and 0.17 (0.07, 0.30) at 2 years. Median survival was 9.5 months (7.5, 11.4).

Toxicity
18 Serious Adverse Reactions (SARs) and 1 Suspected Unexpected Serious Adverse Reaction (SUSAR) were reported with no withdrawals for safety reasons.

Common grade 3-4 toxicities during the BSG study included neurological (16 events), fever (2 events), gastro-intestinal (6 events), infection (11 events), thrombocytopenia (6 events).

Serious Adverse Reaction Listing
(CTC Dec 1994)

Date of SAR/SUSAR	Description of SAR	CTCAE	Causality
07/05/2008	Fever in absence of neutropenia	2	General
14/02/2008	Vomiting	2	Gastrointestinal
14/02/2008	Ataxia	3	Nervous system
09/02/2009	Typhilitis (SUSAR)	4	Gastrointestinal
30/09/2009	Febrile neutropenia	3	Blood & Lymphatic
08/12/2009	Thrombocytopenia	4	Blood & Lymphatic
10/12/2009	Prolonged low platelets	3	Blood & Lymphatic
02/02/2010	Thrombocytopenia	1	Blood & Lymphatic
08/03/2010	Persistent low platelet count	3	Blood & Lymphatic
28/06/2010	Haemorrhage into glioma	5	Nervous system
22/07/2010	Shingles	3	Infection
26/07/2010	Shingles	3	Infection
01/10/2010	Opportunistic infection	3	Infection
14/10/2010	Bone marrow aspiration under GA	Not known	Surgical & Medical
21/10/2010	Thrombocytopenia delaying therapy	Not known	Blood & Lymphatic
12/11/2010	Opportunistic infection	3	Infection
10/01/2011	Opportunistic infection	3	Infection
25/03/2011	Infection	3	Infection
10/06/2011	Encephalopathy	4	Nervous system

Abstracts

Simon Bailey, Andrew Howman, Barry Pizer, Dee Harris, Deborah Jones, Pamela Kearns, Susan Picton, Frank Saran, Keith Wheatley, Michael Gibson, Adam Glaser, Daniel Connolly, and Darren Hargrave.
Cancer Research UK. Schering-Plough Ltd.
DIFFUSE INTRINSIC PONTINE GLIOMA TREATED WITH PROLONGED TEMOZOLOMIDE AND RADIOTHERAPY – RESULTS OF THE UNITED KINGDOM TRIAL (CNS 2007 04).
Neuro-Oncology, Abstracts from the 15th International; Symposium on Pediatric Neuro-Oncology (ISPNO). Toronto, Ontario, Canada June 24-27, 2012.

Publications

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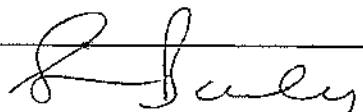
Diffuse intrinsic pontine glioma treated with prolonged temozolomide and radiotherapy – Results of a United Kingdom phase II trial (CNS 2007 04)
Eur J Cancer (2013).

Conclusion
Temozolomide, even when administered in this alternative regimen, offers no benefit to standard radiotherapy in DIPG. Recent reports using either biopsy or autopsy tumour material are starting to elucidate the underlying molecular biology of DIPG and future trials will aim to select and target novel therapies based on this emerging data.

Study End date:
The last patient was recruited into the trial in July 2010. The trial was closed with the MHRA on 29 January 2014.

Declaration

Signature of Chief Investigator:	
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