Multicentre phase II studies evaluating imatinib plus hydroxyurea in patients with progressive glioblastoma

DA Reardon*,1, G Dresemann2, S Taillibert3, M Campone4, M van den Bent5, P Clement6, E Blomquist7, L Gordower8, H Schultz9, J Raizer10, P Hau11, J Easaw12, M Gil13, J Tonn14, A Gijtenbeek15, U Schlegel16, P Bergstrom17, S Green18, A Weir18 and Z Nikolova18

1The Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC, USA; 2Zentrum für Neuro-Onkologie am Ärztehaus Velen, Velen, Germany; 3Hôpital Pitié Salpêtrière, Paris, France; 4Centre René Gauducheau, Saint-Herblain, France; 5Daniel den Hoed Cancer Center, Erasmus University Hospital, Rotterdam, The Netherlands; 6UZ Gasthuisberg, Leuven, Belgium; 7Onkologiföreningen Sjukhuset, Uppsala, Sweden; 8CHU Ensamte, Brussels, Belgium; 9Aarhus University Hospital, Aarhus, Denmark; 10Northwestern University, Feinberg School of Medicine, Northwestern Memorial Hospital, Chicago, IL, USA; 11Klinik und Poliklinik für Neurologie der Universität Regensburg, Universitätsklinikum Regensburg, Regensburg, Germany; 12Tom Baker Cancer Center, Calgary, Alberta, Canada; 13Institut Català d'Oncologia: Hospital Duran i Reynals, L'Hospitalet de Llobregat, Barcelona, Spain; 14LMU München, Münich, Germany; 15Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; 16Knappschaftskrankenhaus, Ruhr-University Bochum, Germany; 17Onkologikliniken, Norlands Universitetssjukhus, Umeå, Sweden; 18Novartis Pharma AG, Basel, Switzerland

BACKGROUND: We evaluated the efficacy of imatinib mesylate in addition to hydroxyurea in patients with recurrent glioblastoma (GBM) who were either on or not on enzyme-inducing anti-epileptic drugs (EIAEDs).

METHODS: A total of 231 patients with GBM at first recurrence from 21 institutions in 10 countries were enrolled. All patients received 500 mg of hydroxyurea twice a day. Imatinib was administered at 600 mg per day for patients not on EIAEDs and at 500 mg twice a day if on EIAEDs. The primary end point was radiographic response rate and secondary end points were safety, progression-free survival at 6 months (PFS-6), and overall survival (OS).

RESULTS: The radiographic response rate after centralised review was 3.4%. Progression-free survival at 6 months and median OS were 10.6% and 26.0 weeks, respectively. Outcome did not appear to differ based on EIAED status. The most common grade 3 or greater adverse events were fatigue (7%), neutropaenia (7%), and thrombocytopenia (7%).

CONCLUSION: Imatinib in addition to hydroxyurea was well tolerated among patients with recurrent GBM but did not show clinically meaningful anti-tumour activity.

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There are currently few effective treatment options available for adults with glioblastoma (GBM), the most common malignant primary brain tumour. Median survival for newly diagnosed GBM patients survives 2 years (Stupp et al, 2005). Although recent studies with therapeutics targeting vascular endothelial growth factor (VEGF) have shown encouraging results (Vredenburgh et al, 2007; Friedman et al, 2009), most salvage therapies after progression have proven ineffective, with a median time to progression of only 9 weeks, low response rates and life expectancy of only a few months (Wong et al, 1999; Ballman et al, 2007; Lamborn et al, 2008).

Imatinib mesylate (Glivec or Gleevec), a tyrosine kinase inhibitor of platelet-derived growth factor receptor (PDGFRs) α and β; c-KIT, the receptor for stem cell factor; c-Fms, the receptor for macrophage-colony stimulating factor; Abl, and Arg TK, is currently approved for several indications including Philadelphia chromosome-positive (Ph+) chronic myelogenous leukaemia, Ph+ acute lymphoblastic leukaemia, KIT (CD 117)-positive, unrectasable or metastatic malignant gastrointestinal stromal tumours, and four rare diseases (hypereosinophilic syndrome, dermatofibrosarcoma protuberans, myelodysplastic/myeloproliferative diseases, and systemic mastocytosis).

Several factors suggest that imatinib may be an active therapeutic for malignant glioma. First, gliomas frequently over-express PDGF and PDGFRs in an autocrine/paracrine manner (Nister et al, 1988; Hermanson et al, 1992; Guha et al, 1995; Lokker et al, 2002). Second, c-KIT is expressed by many GBM tumours (Went et al, 2004; Joensuu et al, 2005). Third, imatinib inhibits the growth of human GBM cell lines and prolongs survival of nude mice with intracranial GBM cell implants (Kilic et al, 2000), whereas expression of PDGFR and the chemokine CXCL12/SDF-1 (stromal cell-derived factor-1) predict imatinib sensitivity in vitro
Clinical Studies

Imatinib and hydroxyurea for recurrent GBM
DA Reardon et al

(Patients and Methods)

Study design and treatment

We conducted two, parallel open-label, multicentre, single-arm, phase II trials. In study H2201, patients were not allowed to be on EIAEDs whereas patients were enrolled on study H2202 if they were on EIAEDs. The dose of imatinib differed between the trials to account for the effect of EIAEDs on imatinib metabolism (Reardon et al, 2005; Wen et al, 2006). Patients enrolled on study H2201 received 600 mg once a day, whereas those on study H2202 received 500 mg twice a day. For both trials, patients received 500 mg of HU twice a day. The studies were identical in all other respects. Medically appropriate efforts were used to maintain study-specific EIAED exposure for patients on each study; however, H2201 patients were deemed off study if they initiated EIAEDs and H2202 patients were similarly censored if they discontinued EIAEDs. Patients remained on study unless they withdrew consent, developed tumour progression or unacceptable toxicity. During the first year of treatment, patients were assessed every 4 weeks, changing to every 8 weeks thereafter. The study was designed according to respective national regulations and was approved by local ethical review boards before patient accrual started. All patients provided written informed consent according to local and national regulations.

Patient eligibility

All patients were required to have institutional histological confirmation of GBM that was at first recurrence after conventional therapy and measurable disease on gadolinium-enhanced MRI. After study entry, centralised review was conducted to confirm histopathology. Satisfactory haematologic (haemoglobin >10 g per 100 ml, absolute neutrophil count >1500 cells per litre, platelets >100 000 cells per litre), biochemical (serum creatinine <1.5 mg per 100 ml, BUN <25 mg per 100 ml; AST and bilirubin <1.5 × upper limit of normal) and performance status (ECOG score ≤2 or Karnofsky ≥60%) parameters were also required.

Key exclusion criteria included peripheral oedema ≥grade 2; pulmonary, pericardial or peritoneal effusions of any grade; an excessive risk of an intracranial haemorrhage; major surgery within 2 weeks before study entry; and concurrent warfarin administration.

Patient assessments

Disease status was assessed using a modified version of the Macdonald criteria (Macdonald et al, 1990), including an increase in corticosteroid dosage, regardless of radiographic or clinical assessment, as a criteria to define progressive disease (PD). Sites performed each assessment, before submitting the data to a central independent review (CIR) team. The CIR team included three radiologists (two reviewers and an adjudicator) as well as a neuro-oncologist who conducted a two-stage evaluation of each patient assessment. First, steroid and MRI assessments were independently determined and included in the database. Second, the site neurologic assessment was incorporated to provide an overall outcome assessment. Visits were assessed in sequence; older visits could be reviewed, but newer visits could only be seen after completion of the preceding visit. Adjudication occurred if the overall visit conclusion differed between the two radiologists. To minimise bias, all CIR team members were blinded to the patient study identifier, the results of the other reader, and the final outcome of the patient. Final outcome was hidden by presenting data of each time point only after the previous time point had been assessed.

Safety assessments included weekly complete blood counts and monthly chemistry profiles. Treatment was held until any non-haematologic grade 3 or 4 event resolved to grade ≤1, after which the study regimen was resumed with a reduction in daily imatinib dosage by 200 mg. If the event recurred, HU was reduced to 500 mg a day. If the event recurred despite these dose modifications, patients were taken off study. The above guidelines were also followed for grade 3 or 4 events for thrombocytopenia and grade 4 neutropenia. Myeloid and erythroid growth factors were permitted according to established guidelines.

Tumour biomarker analysis

Archival tumour samples from either initial diagnosis or after prior therapy failure were analysed at the Duke University Hospital Cell Imaging Laboratory (Durham, NC, USA). Methylguanine methyltransferase (MGMT), PDGFRA and PDGFB, phospho-p44/42 MAPK, phospho-S6 ribosomal protein, phospho-AKT, PTEN, EGFR, and EGFRVIII were assessed using immunohistochemistry (IHC) reagents and methods (Supplementary Methods). Similarly, dual-colour fluorescent in situ hybridisation (FISH) was...

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(Patients and Methods)

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performed on formalin-fixed, paraffin-embedded tissue specimens using commercially available probes, including EGFR/CEP 7, PTEN/CEP 10 (Vysis, Downers Grove, IL, USA), and c-KIT/CEP 4 for EGFR, PTEN, and c-KIT DNA locus copy number (Supplementary Methods). Genes were classified as polysomic or amplified if their copy number relative to respective centromere probe exceeded 1 or 2, respectively.

Pharmacokinetic analysis

Blood samples were collected from a subset of patients on each study on days 6 and 29 before treatment and 0.5, 1, 2, 3, 4, 8, 12, 13, 14, and 24 h after their morning dose. For these patients, HU was initiated after the 24-h sample for day 6 was obtained. Plasma supernatants were separated by centrifugation and immediately frozen (−20°C). The day 29 plasma supernatants were split for both imatinib and HU analyses. Plasma concentrations of imatinib and its metabolite, CGP74588, were determined by high-pressure liquid chromatography/mass spectrometry (Parise et al, 2003) whereas HU plasma concentrations were measured by gas chromatography and mass spectrometry. The individual plasma concentration of data for each subject was used to calculate pharmacokinetic parameters according to the model-independent approach using WinNonlin software (Version 5.2; Pharsight Corporation, Mountain View, CA, USA). Nominal sampling times were used for calculating summary statistics of the plasma concentration data.

Statistical considerations

A total of 220 adult patients (110 in each study) were planned to enroll. Wong et al (1999) previously reported a 5% radiographic response rate among patients with GBM treated with TMZ at first recurrence. In the current studies, 110 patients were estimated as required per study to provide a 95%, two-sided confidence interval for radiographic response to have a lower limit of 5%, including a 10% expected dropout rate.

An interim analysis was performed after 101 patients were enrolled in both studies combined. Accrual continued until a data cut-off occurred 4 months after the 101st patient had been enrolled to allow for at least 16 weeks of treatment. At the interim analysis, if there were ≤4 responses (CR or PR) observed from 101 patients, both studies were to be terminated due to lack of efficacy. If the studies continued, combination therapy was to be declared as having insufficient activity if there were ≤15 responses observed from the 220 patients to be recruited.

A log-rank test was used to compare the OS and PFS experience of patient subgroups defined by various biomarkers. Patients with inadequate samples to analyse for a particular marker were excluded from that specific statistical analysis. Within subgroups, the Kaplan–Meier estimator was used to generate estimates of median OS and PFS, as well as 6-, 12-, and 24-month OS and PFS rates.

RESULTS

Patient characteristics

The intent-to-treat (ITT) population consisted of 231 enrolled patients including 131 on study H2201 and 100 on study H2202. Study H2201 accrued more rapidly, hence a higher percentage of eligible patients were not on EIAACDs. Otherwise, characteristics of patients accrued to both studies were comparable (Table 1).

Adequate tumour material for central histopathology review was available from 177 patients (77.7%) and confirmed GBM in 158 cases (89.3%). This rate is comparable to that previously reported in other multi-institutional studies (Stupp et al, 2005; Raymond et al, 2008). The remaining patients had either grade 3 malignant glioma (n = 11, 7.0%), grade 2 glioma (n = 2, 1.3%), or were non-diagnostic (n = 6, 3.8%). Most patients (88.7%) had just one measurable lesion at baseline. Only 11.7% of patients had additional lesions documented for evaluation, which were too small to measure (‘evaluable lesions’). According to the CIR, 9 patients (3.9%) had only evaluable lesions at their baseline MRI scan. Thirty-three patients (14%) enrolled within 3 months of XRT/daily TMZ completion; however, outcome among this subset did not differ compared to the remaining patients (data not shown).

Table 1

| Variable                                | Statistic/category | Study H2201 N = 131 | Study H2202 N = 100 | All patients N = 231 |
|-----------------------------------------|--------------------|----------------------|---------------------|----------------------|
| Age (years)                             | Median             | 55.0                 | 56.5                | 56.0                 |
|                                         | Range              | 18–80                | 21–75               | 18–80                |
| Age group, n (%)                        |                    | 18–34 years          | 35–49 years         | 35–49 years          |
|                                         |                    | 35–49 years          | 50–64 years         | 50–64 years          |
|                                         |                    | 50–64 years          | ≥65 years           | ≥65 years            |
| Sex, n (%)                              | Male               | 79 (60.3)            | 65 (65.0)           | 144 (62.3)           |
|                                         | Female             | 52 (39.7)            | 35 (35.0)           | 87 (37.7)            |
| Performance status                      |                    | ECOG 0–1            | 107 (81.6)          | 86 (86.0)            |
|                                         |                    | ECOG 2              | 24 (18.3)           | 14 (14.0)            |
| Time since initial diagnosis (months)   | Median             | 9.0                  | 10.0                | 9.0                  |
|                                         | Range              | 3–45                 | 2–63                | 3–63                 |
| Initial tumour histology, n (%)         | AA                 | 6 (4.6)              | 6 (6.0)             | 12 (5.2)             |
|                                         | GBM                | 124 (94.7)           | 94 (94.0)           | 218 (94.4)           |
|                                         | Gliosarcoma        | 1 (0.8)              | 0                   | 1 (0.4)              |
| Time since last recurrence (days)       | Median             | 27.0                 | 26.0                | 26.0                 |
|                                         | Range              | 1–165                | 0–222               | 0–222                |
| Measurable lesions, n (%)               | 0                  | 5 (6.8)              | 2 (7.1)             | 7 (6.9)              |
|                                         | 1                  | 65 (89.0)            | 25 (89.3)           | 90 (89.1)            |
|                                         | 2                  | 2 (2.7)              | 1 (3.6)             | 3 (3.0)              |
|                                         | ≥2                 | 1 (1.4)              | 0 (0.0)             | 1 (1.0)              |

*All patients must have independent histological confirmation of their diagnosis as part of their inclusion. This review is still ongoing at the time of the interim analysis. †Tumour burden measurements are based on central independent review (CIR) data. ‡Tumour assessment information was assigned at baseline assessment (first MRI scan). All other data were collected at screening (in some cases this equalled baseline).
indicating that enrolment of patients with possible pseudo-progression (Brandes et al, 2008; Brandsma et al, 2008) did not influence the outcome of this study. No patients had to discontinue study participation due to changing enzyme-inducing anti-epileptic drug (EIAED) status.

Toxicity

The median times on study were 6 weeks (range, 1.3–91 weeks) and 4 weeks (range, 0.1–102 weeks) for study H2201 and H2202, respectively. A total of 195 patients (84.8%) received less than 180 days of therapy whereas 20 patients (8.7%) and 15 patients (6.5%) remained on study for 180–365 days and > 365 days, respectively.

The adverse events seen in the study were as expected for this population and these agents. In general, they were mild and transient (Table 2). There were no major differences in adverse events between the two studies. Dose adjustment or interruption due to adverse events affected 34% of H2201 patients and 39% of H2202 patients. Patients on each study (8%) discontinued therapy due to toxicity. Among grade 3 or higher events, the most common included fatigue (7.0%), neutropaenia (6.9%), and thrombocytopaenia (6.9%). There were no grade 5 attributable to adverse events.

Table 2 Adverse events in at least 10% of patients (Safety population)

| Adverse event          | Study H2201 | Study H2202 | All patients |
|------------------------|-------------|-------------|--------------|
|                        | N = 131     | N = 99      | N = 230      |
| Nausea                 |             |             |              |
| Grade 3                | 0           | 2 (2.0)     | 2 (0.9)      |
| Grade 4                | 0           | 0           | 0            |
| All grades             | 50 (38.2)   | 39 (39.4)   | 89 (38.7)    |
| Fatigue                |             |             |              |
| Grade 3                | 7 (5.3)     | 6 (6.1)     | 13 (5.7)     |
| Grade 4                | 3 (2.3)     | 0           | 3 (1.3)      |
| All grades             | 41 (31.3)   | 37 (37.4)   | 78 (33.9)    |
| Peripheral oedema      |             |             |              |
| Grade 3                | 1 (0.8)     | 2 (2.0)     | 3 (1.3)      |
| Grade 4                | 0           | 0           | 0            |
| All grades             | 31 (23.7)   | 24 (24.2)   | 55 (23.9)    |
| Diarrhoea              |             |             |              |
| Grade 3                | 0           | 1 (1.0)     | 1 (0.4)      |
| Grade 4                | 0           | 0           | 0            |
| All grades             | 27 (20.6)   | 16 (16.2)   | 43 (18.7)    |
| Thrombocytopaenia      |             |             |              |
| Grade 3                | 8 (6.1)     | 2 (2.0)     | 10 (4.3)     |
| Grade 4                | 4 (3.1)     | 2 (2.0)     | 6 (2.6)      |
| All grades             | 23 (17.6)   | 11 (11.1)   | 34 (14.8)    |
| Anaemia                |             |             |              |
| Grade 3                | 5 (3.8)     | 0           | 5 (2.2)      |
| Grade 4                | 0           | 0           | 0            |
| All grades             | 21 (16.0)   | 11 (11.1)   | 32 (13.9)    |
| Constipation           |             |             |              |
| Grade 3                | 0           | 1 (1.0)     | 1 (0.4)      |
| Grade 4                | 0           | 0           | 0            |
| All grades             | 22 (16.8)   | 10 (10.1)   | 32 (13.9)    |
| Rash                   |             |             |              |
| Grade 3                | 0           | 0           | 0            |
| Grade 4                | 0           | 0           | 0            |
| All grades             | 14 (10.7)   | 13 (13.1)   | 27 (11.7)    |

Pharmacokinetic analyses

Population PK samples were obtained from 15 patients on study H2201 and 6 patients on study H2202. Overall, imatinib, CGP74588, and HU pharmacokinetic results were consistent with those previously reported and confirm the marked impact of EIAEDs on imatinib metabolism (Table 3; Reardon et al, 2005).

Specifically, dose-normalised Cmax and AUCs of imatinib were lowered for patients on EIAEDs compared with those who were not on EIAEDs. Slight elevations of CGP74588 compared with parent drug ratio were noted for patients on EIAEDs (0.23 vs 0.19) or not receiving EIAEDs (0.41 vs 0.35) in the presence of HU. Imatinib exposure on day 29 (with HU) was slightly increased compared with day 6 (imatinib alone) for patients on study H2201, but was slightly decreased for patients on study H2202, although these differences did not achieve statistical significance. The exposure and elimination of HU were not different between patients receiving or not receiving EIAEDs.

Tumour biomarker analysis

Table 4 summarises the number of patients who had sufficient archival tumour material available for biomarker analysis by IHC and FISH, as well as the association of marker expression with outcome. Of note, 80 of 91 (88%) assessable tumours were positive for PDGFRα, whereas 47 of 67 (70%) assessable tumours expressed PDGFRβ. Among 25 tumours that were assessable for c-KIT copy number analysis by FISH, 1 (4%) had evidence of gene amplification (Figure 1) and 1 (4%) was polysomic.

Outcome

Table 5 shows the study analysis populations. The safety population was one less than the ITT population because one patient was lost to follow-up immediately after baseline assessments. At the time of data analysis, most patients were off study with disease progression or death (82%), whereas adverse events, withdrawal of consent, completion of planned therapy, and miscellaneous factors accounted for 8, 5, 3, and 3% of study discontinuations, respectively.

Overall, five patients on study H2201 (3.8%) and three on study H2202 (3%) achieved either a PR or CR confirmed by the CIR giving an ORR of 3.4% (Table 5). In addition, 19% of patients on each study achieved stable disease (SD), whereas adverse events, withdrawal of consent, completion of planned therapy, and miscellaneous factors accounted for 8, 5, 3, and 3% of study discontinuations, respectively.

With one confirmed responder and three unconfirmed responders between enrolment of the 101st patient and completion of the accrual. However, accrual was sufficiently robust in the interval between enrolment of the 101st patient and completion of the interim analysis that study H2201 actually over-accrued, and study H2202 accrued 100 of the planned 110 patients.

Progression-free survival rates at 6 months were 11.2% (95% CI, 5.7–16.6) for study H2201 and 9.9% (95% CI, 3.8–15.9) for study H2202 (Table 5; Figure 2A). Progressive disease was defined by MRI assessment in 114 patients (51.6%), whereas 41 patients (19%) had either c-KIT amplification (Figure 1) and 1 (4%) was polysomic. Nineteen patients (8.2%) had either a confirmed CR or PR, or achieved SD lasting 6 months or more. With one confirmed responder and three unconfirmed responders at the interim analysis, a lack of efficacy for the drug combination was concluded as per the statistical design, and the trial was closed for accrual. However, accrual was sufficiently robust in the interval between enrolment of the 101st patient and completion of the interim analysis that study H2201 actually over-accrued, and study H2202 accrued 100 of the planned 110 patients.

Progression-free survival rates at 6 months were 11.2% (95% CI, 5.7–16.6) for study H2201 and 9.9% (95% CI, 3.8–15.9) for study H2202 (Table 5; Figure 2A). Progressive disease was defined by MRI assessment in 114 patients (51.6%), whereas 41 patients (18.6%) were defined as progressive by increased corticosteroid use only and 26 patients (11.8%) solely by neurologic decline. Forty patients (18.1%) died, without previous PD determination, presumably due to PD. Median OS was 25.3 weeks (95% CI, 19.9–33.0) for study H2201 and 27.1 weeks (95% CI, 19.9–39.1) for study H2202 (Table 4; Figure 2B).

None of the tumour markers assessed by IHC among archival tumour material obtained from patients correlated with PFS (Table 4). However, single patients with either c-KIT amplification or polysomy remained progression-free for 290 and 232 days,
respectively. Compared with patients with normal c-KIT copy 
number (n = 23), PFS was increased among those with either 
c-KIT polysomy or amplification (P = 0.021).

| Variable | Result | Number of patients | Median | 95% CI | P-value |
|----------|--------|--------------------|--------|--------|---------|
| Immunohistochemistry | | | | | |
| MGMT Positive | 25 | 37.0 | 28.0, 75.0 | 0.68 |
| MGMT Negative | 62 | 49.0 | 30.0, 55.0 |
| EGFR Positive | 52 | 50.0 | 29.0, 55.0 | 0.083 |
| EGFR Negative | 2 | 26.0 | 99.0, 43.0 |
| EGFRvIII Positive | 17 | 49.0 | 29.0, 57.0 | 0.863 |
| EGFRvIII Negative | 73 | 50.0 | 30.0, 55.0 |
| PTEN Positive | 27 | 54.0 | 28.0, 62.0 | 0.88 |
| PTEN Negative | 54 | 39.0 | 30.0, 54.0 |
| S6 Positive | 13 | 54.0 | 28.0, 56.0 | 0.579 |
| S6 Negative | 5 | 49.0 | 9.0, 57.0 |
| MAPK Positive | 27 | 31.0 | 29.0, 54.0 | 0.467 |
| MAPK Negative | 10 | 41.0 | 28.0, 56.0 |
| AKT Positive | 24 | 43.0 | 29.0, 55.0 | 0.983 |
| AKT Negative | 16 | 31.0 | 29.0, 57.0 |
| VEGF Positive | 39 | 39.0 | 29.0, 55.0 | 0.409 |
| VEGF Negative | 25 | 55.0 | 50.0, 83.0 |
| PDGFRα Positive | 80 | 49.0 | 31.0, 55.0 | 0.26 |
| PDGFRα Negative | 11 | 55.0 | 28.0, 232.0 |
| PDGFRβ Positive | 47 | 55.0 | 37.0, 57.0 | 0.192 |
| PDGFRβ Negative | 20 | 43.0 | 29.0, 55.0 |
| Fluorescence in situ hybridisation | | | | | |
| EGFR Increased | 13 | 57.0 | 49.0, 112.0 | 0.802 |
| EGFR Normal | 19 | 54.0 | 29.0, 83.0 |
| PTEN Deleted | 7 | 54.0 | 29.0, 135.0 | 0.804 |
| PTEN Normal | 18 | 55.0 | 43.0, 83.0 |
| c-KIT Increased | 2 | 261.0 | 232.0, 290.0 | 0.021 |
| c-KIT Normal | 23 | 54.0 | 43.0, 75.0 |

Abbreviations: EIApDs = enzyme-inducing anticonvulsant drugs; HU = hydroxyurea.

Figure 1: Representative example of c-KIT gene amplification detected by fluorescence in situ hybridisation (FISH). High-level amplification of c-KIT (red signals) detected along with two copies of chromosome 4 centromeres (green signals).

Table 3: Pharmacokinetic results

| Drug | AUC (0–24 h) (h ng/ml) | AUC (0–12 h) (h ng/ml) | AUC (0–tlast) (h ng/ml) | Cmax (ng/ml) | Tmax (h) | t1/2 (h) | CL/F (L/h) | Lambda_z (1/h) | Vz/F (L) | Cmax/ dose (1) | Cmax ratio (2) | AUC/ dose (1) |
|------|------------------------|------------------------|------------------------|--------------|----------|---------|----------|-------------|----------|---------------|----------------|---------------|
| Imatinib | Study H2201 | Imatinib alone (N = 15) 49764.9 (49.93) | 31984.7 (48.71) | 3819.6 (39.81) | 3.0 (1–8) | 15.017 (43.96) | 12.052 (37.68) | 0.04618 (44.00) | 289.31 (65.97) | 3.0 (1–8) | 15.017 (43.96) | 12.052 (37.68) | 0.04618 (44.00) |

Table 4: Tumour marker analysis and progression-free survival

| Variable | Result | Number of patients | Median | 95% CI | P-value |
|----------|--------|--------------------|--------|--------|---------|
| MGMT | Positive | 25 | 37.0 | 28.0, 75.0 | 0.68 |
| MGMT | Negative | 62 | 49.0 | 30.0, 55.0 |
| EGFR | Positive | 52 | 50.0 | 29.0, 55.0 | 0.083 |
| EGFR | Negative | 2 | 26.0 | 99.0, 43.0 |
| EGFRvIII | Positive | 17 | 49.0 | 29.0, 57.0 | 0.863 |
| EGFRvIII | Negative | 73 | 50.0 | 30.0, 55.0 |
| PTEN | Positive | 27 | 54.0 | 28.0, 62.0 | 0.88 |
| PTEN | Negative | 54 | 39.0 | 30.0, 54.0 |
| S6 | Positive | 13 | 54.0 | 28.0, 56.0 | 0.579 |
| S6 | Negative | 5 | 49.0 | 9.0, 57.0 |
| MAPK | Positive | 27 | 31.0 | 29.0, 54.0 | 0.467 |
| MAPK | Negative | 10 | 41.0 | 28.0, 56.0 |
| AKT | Positive | 24 | 43.0 | 29.0, 55.0 | 0.983 |
| AKT | Negative | 16 | 31.0 | 29.0, 57.0 |
| VEGF | Positive | 39 | 39.0 | 29.0, 55.0 | 0.409 |
| VEGF | Negative | 25 | 55.0 | 50.0, 83.0 |
| PDGFRα | Positive | 80 | 49.0 | 31.0, 55.0 | 0.26 |
| PDGFRα | Negative | 11 | 55.0 | 28.0, 232.0 |
| PDGFRβ | Positive | 47 | 55.0 | 37.0, 57.0 | 0.192 |
| PDGFRβ | Negative | 20 | 43.0 | 29.0, 55.0 |
| Fluorescence in situ hybridisation | | | | | |
| EGFR | Increased | 13 | 57.0 | 49.0, 112.0 | 0.802 |
| EGFR | Normal | 19 | 54.0 | 29.0, 83.0 |
| PTEN | Deleted | 7 | 54.0 | 29.0, 135.0 | 0.804 |
| PTEN | Normal | 18 | 55.0 | 43.0, 83.0 |
| c-KIT | Increased | 2 | 261.0 | 232.0, 290.0 | 0.021 |
| c-KIT | Normal | 23 | 54.0 | 43.0, 75.0 |

Abbreviations: MGMT = methylguanine methyltransferase; PDGFR = platelet-derived growth factor receptor; VEGF = vascular endothelial growth factor.
DISCUSSION

Two prior, single-institutional studies independently suggested that the combination of imatinib and HU had anti-tumour activity among patients with recurrent GBM. Dresemann (2005) first reported that 6 of 30 patients (20%) achieved a radiographic response whereas 11 additional patients (37%) achieved SD for a median of 6 months (range 3–32 months). In a follow-up phase II study among 33 patients, Reardon et al (2005) noted a radiographic response rate of 9% and PFS-6 of 27%. The current phase II studies...
were conducted to further evaluate imatinib in addition to HU in a multi-institutional setting. If the current multi-institutional studies achieved evidence of anti-tumour benefit comparable to that observed in the two prior single-institutional studies, a randomised, multicentre phase III study comparing imatinib in addition to HU to alternative salvage therapy was anticipated.

Figure 2  Kaplan–Meier plots of progression-free survival (A) and overall survival (B) for patients enrolled on H2201 and H2202 studies.
Toxicity in the current studies was similar to that reported previously confirming that imatinib in addition to HU is well tolerated among patients with recurrent GBM. The most common toxicities were haematologic and included neutropenia (grade 3, n = 12, 5%; grade 4, n = 5, 1.7%) and thrombocytopenia (grade 3, n = 10, 4%; grade 4, n = 6, 3%). The most common non-haematologic toxicities included nausea (39%), fatigue (34%), peripheral oedema (24%), and diarrhoea (19%), although the majority of these events were grade 2.

Outcome on the current studies was poorer than noted on the prior single-institutional studies, and the trials were closed after the interim analysis. Specifically, only 3.4% of patients achieved a confirmed radiographic response, and the PFS-6 was only 10.6%. Of note, we did not observe a significantly different outcome among patients treated on the study H2201 and H2202 trials. Several factors may have contributed to the discrepancy in outcome between the current multicentre studies and the previously reported single-institutional studies. First, single-centre studies may bias towards enrolment of more favourable patients. Approximately 28% of patients in the current studies received less than 25 days of treatment, typically progressing or dying within this 25-day period. Such patients probably had a poor prognosis and rapid disease advancement on entry to the trial, such that receipt of treatment may have been too late to control disease. In contrast, none of the patients reported by Reardon et al. (2005) discontinued therapy prematurely due to rapidly progressive tumour. Imatinib achieves plasma steady-state concentrations after approximately 6 days, but additional time to achieve stable concentrations within the brain is likely required among patients with GBM due to the impact of the blood–brain barrier.

Second, incorporation of rigorous independent, blinded, centralised outcome review with strict assessment guidelines in the current studies may have impacted the rates of determined response (Dodd et al., 2008). In contrast, responses were assessed solely by study investigators in the prior single-centre studies.

Third, this study included an increase in corticosteroid dosing, independent of clinical status and radiologic findings, to define PD. The Macdonald criteria define PD based on ‘≥25% increase in size of enhancing tumour or any new tumour on CT or MRI scans, or neurologically worse, and steroids stable or increased.’ In fact, the original publication stated, ‘Patients requiring escalating or neurologically worse, and steroids stable or increased.’ In fact, the original publication stated, ‘Patients requiring escalating or neurologically worse, and steroids stable or increased.’ In fact, the original publication stated, ‘ Patients requiring escalating or neurologically worse, and steroids stable or increased.'”

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