Open access • Journal Article • DOI:10.1007/S11060-009-9976-3

Imatinib in combination with hydroxyurea versus hydroxyurea alone as oral therapy in patients with progressive pretreated glioblastoma resistant to standard dose temozolomide — Source link

Gregor Dresemann, Michael Weller, Mark Rosenthal, Ulrich Wedding ...+17 more authors

Institutions: University of Tübingen, Royal Melbourne Hospital, Praxis, Herlev Hospital ...+5 more institutions

Published on: 01 Feb 2010 - Journal of Neuro-oncology (Springer US)

Topics: Imatinib mesylate, Temozolomide, Combination therapy, Regimen and Dacarbazine

Imatinib in combination with hydroxyurea versus hydroxyurea alone as oral therapy in patients with progressive pretreated glioblastoma resistant to standard dose temozolomide

Dresemann, G; Weller, M; Rosenthal, M A; Wedding, U; Wagner, W; Engel, E; Heinrich, B; Mayer-Steinacker, R; Karup-Hansen, A; Fluge, O; Nowak, A; Mehdorn, M; Schleyer, E; Krex, D; Olver, I N; Steinbach, J P; Hosius, C; Sieder, C; Sorenson, G; Parker, R; Nikolova, Z

IMATINIB IN COMBINATION WITH HYDROXYUREA OR HYDROXYUREA ALONE AS ORAL THERAPY IN PATIENTS WITH PROGRESSIVE GLIOBLASTOMA PREVIOUSLY TREATED WITH TEMOZOLOMIDE

Gregor Dresemann,[1] Michael Weller,[2] Mark A. Rosenthal,[3] Ulrich Wedding,[4] Wolfgang Wagner,[5] Erik Engel,[6] Bernhard Heinrich,[7] Hartmut Döhner,[8] Anders Karup-Hansen,[9] Øystein Fluge,[10] Anna Nowak,[11] Maximilian Mehdorn,[12] Eberhard Schleyer,[13] Dietmar Krex,[14] Ian N. Olver,[15] J. Steinbach,[2] Christian Hosius,[16] Christian Sieder,[16] Richard Parker,[17] Zariana Nikolova[17]

[1]Franz-Hospital, Onkologische Abteilung, Dülmen, Germany, [2]Department of Neurology, University of Tübingen, Tübingen, Germany, [3]The Royal Melbourne Hospital, Melbourne, Australia, [4]University Hospital, Jena, Germany, [5]Paracelsus, Strahlenklinik, Osnabrück, Germany, [6]Hämatologisch-Onkologische Praxis, Altona, Hamburg, Germany, [7] Hämatologisch-onkilogische Praxis, Augsburg, Germany, [8]University Clinic, Ulm, Germany, [9]Herlev Hospital, Herlev, Denmark, [10]University of Bergen, Bergen, Norway, [11]Sir Charles Gairdner Hospital, Nedlands, Australia, [12]University Clinic, Schleswig-Holstein, Germany, [13]Karl-von-Basedow-Klinikum, Merseburg, Germany, [14]University Clinic, Dresden, Germany, [15]The Cancer Council Australia, Sydney, Australia, [16]Novartis Pharma AG, Nuernberg, Germany, [17]Novartis Pharma AG, Basel, Switzerland

Running title: Imatinib and Hydroxyurea or Hydroxyurea in Glioblastoma Patients

Key words: imatinib, glioblastoma, hydroxyurea, recurrent, GBM

Target journal: JCO

Please address correspondence to:
Dr G. Dresemann, Department of Hematology/Oncology, Franz-Hospital Du¨lmen, Innere Abteilung, Vollenstrasse 10, D-48249 Dülmen, Germany. Tel: +49-2594-92-3480; Fax: +49-2594-92-1489; E-mail: gdresemann@aol.com

Statement: Study approved by Independent Review Boards/Independent Ethics Committees and Health Authorities in the participating countries prior to patient recruitment.

Acknowledgment: This paper has been submitted on behalf of all investigators and colleagues involved in the **Ambrosia** study. We are grateful to the following colleagues who agreed to act as investigators on the trial: Dr Erika Kettner MD, Staedtisches Klinikum, Magdeburg, Germany; Dr Kea Franz, MD, University Clinic, Frankfurt, Germany; Dr Marion Ritterodt, MD, Kliniken der Med. Hochschule, Hannover, Germany; Dr Sudarshan Selva-Nayagam, Royal Adelaide Hospital, Adelaide, Australia;

Prof Klaus Koeffken, Friedrich-Schiller Universitaet, Jena, Germany; Prof A Sepehrnia, Clemenshospital, Muenster, Germany; Prof Bernhard Woermann, Staedisches Klinikum, Braunschweig, Germany; Prof Friedrich Weber, and Dr Ulrich Langenbach, Klinikum Saarbruecken, Saarbruecken, Germany. In addition to the above investigators, we wish to thank Steven Green, Novartis Pharma Basel, for excellent statistical support, to Thierry Gorlia, EORTC, Brussels, for acting as Independent DMC statistician, and to Dr. Martin van den Bent, Daniel den Hoed Oncology Center, Rotterdam, The Netherlands; Dr Alfred Yun, MD Anderson Cancer Center, Texas, USA; and Dr Riccardo Soffietti, Department of Neuroscience and Oncology, University of Turin, Italy, for being Independent clinicians on DMC; and Dr Greg Sorensen, Masschussetts General Hospital, Boston, USA. We thank as well Dr David Reardon, Duke University Medical Center, North Carolina, USA, for his numerous valuable suggestions.

ABSTRACT

Purpose: The researchers conducted a randomized, multicenter, open-label, phase 3 study of patients with recurrent GBM who had failed front-line therapy to evaluate the anti-tumor effect of imatinib in combination with HU. This study was designed to determine whether imatinib has sufficient synergistic anti-tumor activity in combination with HU in comparison to single-agent treatment with HU for recurrent GBM.

Patients and Methods: The target population consisted of patients with previously treated, confirmed progressive GBM, an Eastern Cooperative Oncology Group performance status of 0-2 with completed surgical treatment and irradiation therapy or first-line chemotherapy; if first-line chemotherapy did not contain TMZ, a second completed chemotherapy was required.

Results: The primary efficacy parameter was progression-free survival (PFS) during the study. The primary comparison of combination therapy versus monotherapy for PFS is not significant at the 5% level (adjusted $P = 0.564$). The hazard ratio (HR) is in favor of the combination therapy, but the size of the effect is very small (adjusted HR = 0.925) and not clinically relevant. The median PFS for the combination arm was low at 6.3 weeks and similar to the median PFS in the monotherapy arm (6.1 weeks). The 6-month PFS between the two treatment groups was very similar (5.3% in the combination arm versus 6.6% in the monotherapy arm).

Conclusion: Overall, no clinically meaningful differences were found between the 2 treatment arms, and the primary study end point was not met. Among patients receiving imatinib, no safety issues arose that were either previously unknown or not expected as a consequence of the disease.

INTRODUCTION

Glioblastoma (GBM) (WHO grade IV) is a high-grade malignancy of the CNS with a poor prognosis. The rate of progression-free survival (PFS) at 1 year is approximately 40%.[1] Surgical resection followed by radiotherapy and concomitant temozolomide (TMZ), followed by regular TMZ for 6 months is the standard of care. Although PFS can be prolonged by approximately 3 to 6 months, median overall survival (OS) remains unsatisfactory at 15.6 months and recurrence rates are high.[1]

Treatment at disease progression includes resection, if possible, and/or further chemotherapy; however, outcomes remain poor. A variety of new approaches have been tested in the recurrent setting, including novel chemotherapy agents, chemotherapy combinations, and, more recently, agents targeting epidermal growth factor receptor (EGFR), platelet-derived growth factor receptors (PDGFR), and vascular endothelial growth factor receptor (VEGFR).[2] In GBM, EGFR and PDGFR are amplified in approximately 50%[2] and 21% of patients, respectively.[3] All attempts to prolong the length of PFS and OS using biological agents such as thalidomide, melatonin, cis/trans retinoic acids, or gene therapy did not significantly improve prognosis.

Imatinib has limited single-agent activity in recurrent GBM.[4,5] Among other activities, imatinib is known to inhibit the activity of PDGFR and c-KIT receptors. Hydroxyurea (HU) is thought to promote the penetration of drugs across the blood-brain-barrier (BBB), as well as induce the loss of amplified genes, including the EGFR gene.[6] Because PDGFR, c-KIT, and EGFR overexpression is seen in GBM[6-11] and HU can increase permeability of the BBB, combining the drugs was considered a treatment option worth investigating. Results of a pilot study of 30 patients suggested that a combination of HU

and imatinib is active in recurrent GBM,[12-14] and the study was soon repeated in study BUS218.[15]

PATIENTS AND METHODS

The present study was a multicenter, 2-arm, open-label, phase 3 study for patients with recurrent GBM. The primary objective was to evaluate whether a combination of imatinib and HU was superior to HU alone in prolonging PFS. Secondary objectives included PFS at 12 months, overall response, duration of response, safety, and OS. Adult patients with a histologically confirmed GBM, measurable disease, and an Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2 who had previously undergone surgery and received radiotherapy and prior chemotherapy were eligible for randomization. Patients on steroids were required to have been on a stable dose for ≥ 5 days. Patients at excessive risk of intracranial hemorrhagic events or with evidence of intra-tumoral hemorrhage at baseline scan were not eligible. Patients were required to have adequate renal, hepatic, and hematologic function.

Following previous research, [16,17] patients were stratified according to their receipt of EIAEDs or not, however the dose of imatinib was not altered per stratification. The choice of 1000 mg/d HU was based on reported efficacy of the single agent in patients with recurrent or unresectable meningioma.[18]

The study included 240 patients randomized to receive 1500 mg/d of HU (500 mg 3 times daily) or imatinib 600 mg/d in combination with 1000 mg/d of HU (500 mg twice daily) (**Figure 1**). Following randomization, patients received treatment until progression or trial withdrawal. The protocol scheduled an evaluation using the Macdonald criteria[19]

to be performed every 6 weeks from treatment start. On progression, patients with good performance status who were receiving HU alone were permitted to switch to the combination arm. For patients progressing on the combination arm, the dose of imatinib was escalated to 800 mg/d while the dose of HU remained unchanged.

In the event of further progression, patients receiving 800 mg/d of imatinib were withdrawn from the trial. Only the first progression on treatment was evaluated for the primary end point.

All MRI scans and neurologic and steroid information were evaluated at the local study sites in addition to a review by a blinded central independent reviewer (CIR) (Dr Greg Sorensen, Massachusetts General Hospital, USA), applying the Macdonald criteria for tumor response.[19] Blinded CIR data were used for the primary analyses on an intent to treat (ITT) basis, and sensitivity analyses were performed to compare the CIR results to the results documented at the sites.

Statistical Analyses

The primary objective of the study was to demonstrate PFS superiority of imatinib in combination with HU over HU monotherapy. The null hypothesis stated that the PFS of the 2 treatment groups were equivalent. The alternative hypothesis stated that the PFS of either group was prolonged. A median PFS was expected to be 16 and 10 weeks for the combination and monotherapy groups, respectively. Based on a 90% power to exceed stopping boundaries defined for the interim analysis, an estimated 204 events (progression, death) were needed. Therefore, 240 patients were recruited to allow for premature withdrawals.

In the current trial, progressive disease (PD) was defined as any of the following: ≥ 25% increase in size of the sum of the products of the largest perpendicular diameters; appearance of new lesions; or neurologic progression alone. Complete response, partial response, stable disease (SD), or not assessable were alternative response evaluations at each visit. All evaluations considered the steroid and neurologic status of patients, in addition to existing or new lesions. The primary analysis was conducted on all randomized patients.

PFS was defined as the time from randomization to the first documented progression or death. Patients alive and without progression were considered to be censored at the time of the last available visit assessment. PFS rates were calculated using the Kaplan-Meier method, ignoring strata. Hazard ratios (HR) and the associated *P* values were derived from a Cox proportional hazards model stratified for EIAED use (yes, no) and ECOG status (<2, ≥ 2). The HR indicates the effect of combination therapy or monotherapy, and an HR <1 favors combination therapy.

Safety assessments consisted of recording adverse events (AEs) and serious adverse events (SAEs), with severity and drug relationship according to NCI Common Toxicity Criteria Version 3.[20] Regular monitoring of hematology and blood chemistry, vital signs, and physical condition also was performed.

RESULTS

Between October 2004 and July 2006, 240 patients from 19 institutions in 4 countries were randomized equally to receive HU alone (n = 120) or HU plus imatinib (n = 120). The characteristics of the patients were balanced between the two arms at baseline (**Table**

1). Overall, the median age was 51 years, there was a slight female predominance in the combination arm, and 23% of patients were ECOG performance status 2. The median time from initial diagnosis was 12 months in both arms. No significant differences existed between the 2 arms regarding age, performance status, time from initial diagnosis, use of EIAEDs, and prior anti-cancer therapy. Approximately 40% of patients had received multiple chemotherapy regimens prior to study entry, and some had undergone multiple resections. This extensive prior treatment could indicate difficulty to establish control over the tumor growth, or alternatively, could be a result of patients developing GBM through advancement of previously better differentiated gliomas. As GBM can quickly result in lethal outcomes, many patients are prevented from receiving multiple treatment regimens.

Patients (N = 240) were randomized in a 1:1 ratio, with 118 patients on each arm starting treatment (**Table 2**). At the time of data cutoff for the analysis (October 27, 2006), 7 patients on combination therapy (5.8%) and 14 (11.7%) on HU monotherapy were still on treatment. The majority of discontinuations were a result of disease progression, diagnosed by objective identification using follow-up MRI scan or were suspected on clinical grounds (eg, deteriorating neurologic state or performance status). AEs were responsible for discontinuation of study medication in 18 (15%) patients on combination therapy and 20 (16.7%) on monotherapy, respectively.

Primary Efficacy Results

No significant differences in PFS rates were found between combination therapy and monotherapy following CIR at the 5% level (adjusted $P = 0.564$) (**Table 3, Figure 2**). The HR of 0.925 (95% CI, 0.709-1.206) favored combination therapy but was not

clinically meaningful. The median PFS for the two treatment arms was 6.3 and 6.1 weeks for the combination versus monotherapy arms, respectively. The 6-month PFS rates were 5.3% and 6.6%, respectively.

Of note is the high number of patients who were given an assessment of PD based on neurologic assessment or steroid use alone. Given time, these patients probably would have been assessed with PD by MRI, but their early censoring in this manner would have adversely affected the PFS calculations. This is discussed further in the section on sensitivity analyses.

Secondary Efficacy Results

Figure 3 shows the OS of the ITT population but does not include patients who progressed while on monotherapy before switching to the combination arm or patients randomized to combination therapy who were then treated with a higher dose of imatinib. The HR for OS (0.920) was similar to that observed for the primary PFS analysis (0.925). The estimate is slightly in favor of the combination therapy arm. The median time to death for the combination arm was 20.6 weeks and is similar to the median time to death in the monotherapy arm (19.3 weeks). The 6-month OS rates in the two treatment groups also were similar: 39.9% in the combination arm and 36.7% in the monotherapy arm.

CIR data showed 2 confirmed responders in the combination therapy arm and 1 in the monotherapy arm. The percentage of patients with a best overall response of SD or better (complete response plus partial response plus SD) was similar for each treatment group at approximately 25%. PD or death was estimated for 67.5% of patients, and 7% were not assessable. There were no significant differences between treatment groups.

Figure 4 shows the Kaplan-Meier estimates of PFS by the local investigators. The HR, based on local assessments for PFS (0.672), varies from the main analysis (0.894). Interestingly, the estimate is in favor of the combination therapy arm (P = 0.004; 95% CI, 0.514-0.878).

Safety Evaluation

Disease progression was the most frequent cause of death during the study and accounted for 90% and 85% of deaths in the combination and monotherapy arms, respectively (**Table 4**). Other causes of death included pneumonia, pulmonary embolism, and sepsis, all of which were not unexpected for patients with recurrent GBM.

The rates of AEs leading to discontinuation were similar in both treatment groups (16% versus 18% in the monotherapy and combination therapy groups, respectively). The only AEs leading to discontinuation to occur in more than 2% of patients in any treatment group were general physical health deterioration (3.4% on combination therapy, 5.1% on monotherapy) and pneumonia (2.5% on combination therapy). The majority of AEs that led to discontinuation were considered a consequence of disease progression.

Table 5 reports grade 3-4 AEs that occurred in more than 5% of patients in any group. Both treatment arms reported similar AEs, and no difference was seen in the combination arm when reviewing patients before and after crossover. Headache, fatigue, nausea, peripheral edema, and thrombocytopenia were the most frequently observed AEs. Most were associated with the disease, and their incidence was as expected. The SAEs observed were expected for this indication and class of study drug. When the trial data

were compared to previous experience with imatinib, no new safety concerns were identified. The use of imatinib and HU appears to be well tolerated.

Sensitivity Analyses

Originally, the CIR was not included in the study design and setup. It was suspected that a difference between local and centrally reviewed results may exist. Several preplanned sensitivity analyses were included, such as the impact of including and excluding steroid and neurologic data on the response determination; the timing of recruitment to the study (later amendments had increasingly strict criteria on inclusion); censoring according to the previous assessment (as opposed to time of data cutoff); the impact of results from recruiting sites that recruited significantly more patients (approximately 60 patients, compared to 15-20 patients at other sites) on the overall results; and whether PD was reported at the time of crossover or imatinib increase.

Seven of the 8 preplanned sensitivity analyses on PFS showed no difference between the 2 treatment groups. The exception was an analysis heavily influenced by subjective judgments during the local review for all sites that showed a significant improvement for patients in the combination therapy arm (median PFS, 9.4 weeks; 6-month PFS, 11.5%, $P = 0.004$). When comparing the best overall response results of patients on combination therapy versus monotherapy, the local site results were similar to the results of the CIR of only the MRI results; the 6-month and median PFS rates were not matched.

DISCUSSION

This study shows no PFS benefit by adding imatinib to HU in patients with recurrent GBM. The median PFS was 6.3 and 6.1 weeks for imatinib plus HU versus HU alone, respectively. The 6-month PFS rates were 5.3% and 6.6% for the 2 groups, respectively. Sensitivity analyses highlighted a difference in interpretation between local and CIR assessments, but this could not be attributed to a single influencing factor. The 6-month OS was calculated as 39.9% and 36.7% in the combination and monotherapy arms, respectively. No new safety concerns were identified for either treatment group.

Direct comparison of the study results to historical data is difficult. Of note is that the exact criteria of GBM assessment across trials vary considerably between publications, mostly in the way neurologic and steroid information are used in determining progression. For example, both Brada[21] and Yung[22] scheduled assessments by MRI every 8 weeks (compared to 6 weeks in the current trial). In addition, it is not clear from their publications how neurologic assessments or steroid use affected progression events.

The primary analysis of PFS ignores missing assessments or long gaps prior to PD or death. This was the most conservative approach; including such assessments would have biased the results by censoring an event (progression, death) later than it actually occurred, simply because information was unavailable any earlier. However, various sensitivity analyses address the impact of this and other analytic assumptions. These sensitivity analyses were important to review the robustness of the primary analysis conclusions; however, they should still be interpreted with caution because of the following:

- The analysis may include an element of "informative censoring," meaning that at a particular time point the censored patients may in general be closer to progression than the patients who continue to be followed up. The usual impact is an increase in the median and 6-month PFS rate estimate, which affects comparisons with historical results.
- When patients were assessed as having PD at the local site, investigators adjusted treatment by increasing the dose of imatinib or crossing the patient over. If the PD at the local site was not a PD according to the MRI data alone (as assessed by the CIR), then any comparison between the monotherapy and combination therapy arms could be affected by the additional crossover combination treatment in the monotherapy arm. If this additional therapy has an impact, the treatment groups' results may be more similar with respect to PFS based on MRI alone.
- GBM is a rapidly progressing disease, and increasing the dexamethasone dose as a result of worsening neurologic symptoms is frequent until disease stabilization is achieved. In pilot studies,[14,16] imatinib plus HU did not achieve a significant objective response rate but a substantial rate of SD was seen within the first 2 months of treatment. Therefore, neurologic status and steroid dose might not be appropriate to define PD within the first 2 months after randomization, especially if stabilization of clinical symptoms can be achieved later while the tumor burden on MRI scan remains unchanged.
- As both treatment groups have the potential to benefit from imatinib exposure, any survival effect seen by comparing the treatments is diluted.

In the current study, a number of potential confounding factors may have resulted in an underestimation of efficacy.

Progressing GBM usually is accompanied by substantial brain edema. Imatinib may increase the likelihood of edema while simultaneously inhibiting tumor growth. Adjusting the steroid dose is used to reduce brain edema, regardless of the etiology of the edema. In the current trial, any increase in steroid dose automatically led to the classification of PD, regardless of when it happened. The tumor evaluation criteria did not optimally reflect the above described practice among neuro-oncologists, resulting in a discrepancy between local and CIR results: namely, patients classified as PD by CIR when they were assessed as SD locally. Many patients with PD were defined by either neurologic worsening or steroid increase, and many of these were defined early during patients' treatment (ie, within the first 6 weeks). Patients' continuation on the study was determined locally, not according to CIR, which was obtained primarily retrospectively. Subsequently, many patients classified as PD by CIR continued to receive medication after the first 6 weeks of treatment because they were classified locally as SD.

The differences between CIR and local responses were consistent across all sites, so although investigator bias cannot be fully excluded, it could hardly be the sole reason for the difference. The nature of the GBM progression would mean that any drug, whether cytostatic or cytotoxic, would take time to slow the advancement of the disease and even more so to start reversing its course. The local responses suggest an apparent time delay between the start of treatment and stabilization of tumor proliferation.

Evaluating the disease differently during the first 2 to 3 months would not account for all disease progressions but rather would allow time for a stabilization to be achieved, both

symptomatically and a neurologically. By adjusting the steroid dose as required within the first few months, without any dose increase to result in a tumor assessment of PD, brain edema could be adequately controlled. This in turn would permit assessment of the study drug's performance in stabilizing or reducing tumor burden, not only on its impact in controlling edema.

CONCLUSION

Overall, according to the strict Macdonald criteria,[19] no clinically meaningful differences were found in median PFS between the 2 treatment arms. OS and PFS at 6 and 12 months were generally similar to benchmarks for the treatment outcomes of patients treated for recurrent progressing GBM. No safety issues arose for patients receiving imatinib that were either previously unknown or not expected as a consequence of the disease.

A distinct difference between CIR and local evaluations were observed. A correlation between central MRI evaluation and investigator responses during the course of the trial was apparent, suggesting differences in the application of the Macdonald criteria. The nature of progressive GBM might render the Macdonald criteria not specific enough for determining a difference between medications within the first 6 to 8 weeks of treatment.

Word limit: 3000

Word count: 3087

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-96, 2005

2. Sathornsumetee S, Reardon DA, Desjardins A, et al: Molecularly targeted therapy for malignant glioma. Cancer 110:13-24, 2007

3. Joensuu H, Puputti M, Sihto H, et al: Amplification of genes encoding KIT, PDGFRalpha and VEGFR2 receptor tyrosine kinases is frequent in glioblastoma multiforme. J Pathol 207:224-31, 2005

4. Raymond E, Brandes A, Van Oosterom A, et al: Multicentre phase II study of imatinib mesylate in patients with recurrent glioblastoma: an EORTC:NDDG/BTG Intergroup Study [abstract]. Proc Am Soc Clin Oncol 23:107, 2004

5. Wen PY, Yung WK, Lamborn K: Phase I/II Study of Imatinib Mesylate (STI571) For Patients With Recurrent Malignant gliomas (NABTC 99-08) [Abstract TA63]. Society of Neuro-Oncology 9th Annual Meeting, 2004, pp p385

6. Canute GW, Longo SL, Longo JA, et al: The hydroxyurea-induced loss of double-minute chromosomes containing amplified epidermal growth factor receptor genes reduces the tumorigenicity and growth of human glioblastoma multiforme. Neurosurgery 42:609-16, 1998

7. Guha A, Dashner K, Black PM, et al: Expression of PDGF and PDGF receptors in human astrocytoma operation specimens supports the existence of an autocrine loop. Int J Cancer 60:168-73, 1995

8. Hermanson M, Funa K, Hartman M, et al: Platelet-derived growth factor and its receptors in human glioma tissue: expression of messenger RNA and protein suggests the presence of autocrine and paracrine loops. Cancer Res 52:3213-9, 1992

9. Lokker NA, Sullivan CM, Hollenbach SJ, et al: Platelet-derived growth factor (PDGF) autocrine signaling regulates survival and mitogenic pathways in glioblastoma cells: evidence that the novel PDGF-C and PDGF-D ligands may play a role in the development of brain tumors. Cancer Res 62:3729-35, 2002

10. Nister M, Claesson-Welsh L, Eriksson A, et al: Differential expression of platelet-derived growth factor receptors in human malignant glioma cell lines. J Biol Chem 266:16755-63, 1991

11. Went PT, Dirnhofer S, Bundi M, et al: Prevalence of KIT expression in human tumors. J Clin Oncol 22:4514-22, 2004

12. Dresemann G: STI 571/hydroxyurea in progressive, pretreated glioblastoma (GB) patients (pts.) [ASCO abstract 465]. Proc Am Soc Clin Oncol 22:116, 2003

13. Dresemann G: Imatinib (STI571) plus hydroxyurea: safety and efficacy in pre-treated, progressive glioblastoma multiforme (GBM) patients (pts) [abstract]. Proc Am Soc Clin Oncol 23:119, 2004

14. Dresemann G: Imatinib and hydroxyurea in pretreated progressive glioblastoma multiforme: a patient series. Ann Oncol 16:1702-8, 2005

15. Reardon DA, Friedman AH, Herndon JE, et al: Phase II trial of imatinib mesylate plus hydroxyurea in the treatment of patients with malignant glioma [Abstract T-47]. Soc Neuro Oncol meeting. Toronto, 2004

16. Reardon DA, Egorin MJ, Quinn JA, et al: Phase II study of imatinib mesylate plus hydroxyurea in adults with recurrent glioblastoma multiforme. J Clin Oncol 23:9359-68, 2005

17. Wen PY: Phase I/II Study of imatinib mesylate for recrurrent malignant gliomas: North American Brain Tumour Consortium Study 99-08. . Clin Cancer Res 12:4889-907, 2006

18. Schrell UM, Rittig MG, Anders M, et al: Hydroxyurea for treatment of unresectable and recurrent meningiomas. II. Decrease in the size of meningiomas in patients treated with hydroxyurea. J Neurosurg 86:840-4, 1997

19. Macdonald DR, Cascino TL, Schold SC, Jr., et al: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277-80, 1990

20. (CTEP) CTEP: Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. , 2005

21. Brada M, Hoang-Xuan K, Rampling R, et al: Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol 12:259-66, 2001

22. Yung WK, Albright RE, Olson J, et al: A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 83:588-93, 2000

23. S0033 study protocol: Phase III randomized, intergroup, international trial assessing the clinical activity of STI-571 at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) expressing the KIT receptor tyrosine kinase (CCD117), Protocol version dated July 11, 2005

ONLINE ONLY

Table 1. Patient Demographics and Disease Characteristics

Characteristic	Imatinib + Hydroxyurea (n = 120)	Hydroxyurea (n = 120)	Total (N = 240)
Age, years			
Mean	52.1	50.2	51.2
SD	11.3	11.4	11.4
Median	52.0	51.0	51.0
Range	26-73	19-73	19-73
Age group, n (%)			
18-34 years	9 (7.5)	14 (11.7)	23 (9.6)
35-49 years	45 (37.5)	40 (33.3)	85 (35.4)
50-64 years	47 (39.2)	55 (45.8)	102 (42.5)
≥65 years	19 (15.8)	11 (9.2)	30 (12.5)
Sex, n (%)			
Male	70 (58.3)	82 (68.3)	152 (63.3)
Female	50 (41.7)	38 (31.7)	88 (36.7)
Race, n (%)			
White	119 (99.2)	117 (97.5)	236 (98.3)
Black	0 [23]	1 (0.8)	1 (0.4)
Asian	1 (0.8)	1 (0.8)	2 (0.8)
Other	0 [23]	1 (0.8)	1 (0.4)
ECOG grade, n (%)			
0	36 (30.0)	32 (26.7)	68 (28.3)
1	54 (45.0)	62 (51.7)	116 (48.3)
2	30 (25.0)	25 (20.8)	55 (22.9)
3	0 (0.0)	1 (0.8)	1 (0.4)
EIAED use, n (%)			
No	63 (52.5)	65 (54.2)	128 (53.3)
Yes	57 (47.5)	55 (45.8)	112 (46.7)
Time since diagnosis, months			
Mean	16.7	19.9	18.3
SD	15.9	28.6	23.2
Median	12.0	12.0	12.0
Range	0-99	3-230	0-230
Tumor histology at diagnosis,[a] n (%)			
Anaplastic astrocytoma	13 (10.8)	14 (11.7)	27 (11.3)
Glioblastoma	103 (85.8)	98 (81.7)	201 (83.8)
Gliosarcoma	4 (3.3)	8 (6.7)	12 (5.0)
Total prior chemotherapy treatment regimens, n (%)			
1	75 (62.5)	63 (52.5)	138 (57.5)

Characteristic	Imatinib + Hydroxyurea (n = 120)	Hydroxyurea (n = 120)	Total (N = 240)
2	37 (30.8)	40 (33.3)	77 (32.1)
3-4	8 (6.7)	16 (13.3)	24 (10.0)
>4	0 [23]	1 (0.8)	1 (0.4)
Radiotherapy	120 (100.0)	119 (99.2)	239 (99.6)
Surgery[b]	119 (99.2)	120 (100.0)	239 (99.6)
Reason for surgery			
Curative	76 (63.3)	70 (58.3)	146 (60.8)
Palliative	51 (42.5)	58 (48.3)	109 (45.4)
Biopsy	12 (10.0)	23 (19.2)	35 (14.6)
Unknown	1 (0.8)	0 [23]	1 (0.8)
Other	4 (3.3)	4 (3.3)	8 (3.3)

[a]Tumor histology was not confirmed at time of entry to study.
[b]The outcome of the surgery was not recorded as part of the study data.

PRINT

Table 2. Patient Disposition at Time of Event

	Imatinib + Hydroxyurea (n = 120) n (%)	**Hydroxyurea** (n = 120) n (%)	**Total** (N = 240) n (%)
Treatment status			
Randomized to study treatment	120 (100.0)	120 (100.0)	240 (100.0)
Not exposed to study treatment	2 (1.7)	2 (1.7)	4 (1.7)
Discontinued study treatment[a]	111 (92.5)	104 (86.7)	215 (89.6)
On treatment at analysis cutoff date	7 (5.8)[b]	14 (11.7)[b]	21 (8.8)
Reason for discontinuation of treatment			
Unsatisfactory therapeutic effect [c]	25 (20.8)	26 (21.7)	51 (21.3)
Adverse event(s)[c]	18 (15.0)	20 (16.7)	38 (15.8)
Subject withdrew consent[c]	14 (11.7)	10 (8.3)	24 (10.0)
Death[c]	5 (4.2)	13 (10.8)	18 (7.5)
Subject's condition no longer requires study drug[c]	5 (4.2)	3 (2.5)	8 (3.3)
Lost to follow-up[c]	2 (1.7)	1 (0.8)	3 (1.3)
Abnormal laboratory value(s)	0 [23]	2 (1.7)	2 (0.8)
Protocol violation	0 [23]	1 (0.8)	1 (0.4)
Suspected progression and/or ECOG grade 3-4 [c]	44 (36.7)	30 (25.0)	74 (30.8)

[a]Discontinued treatment means that all study therapy (including crossover combination therapy following a switch from monotherapy) was discontinued at the cutoff date for analysis and includes reports of treatment completion due to suspected progression and/or ECOG grade 3-4.

[b]Patients had not had an event at analysis cutoff. Following progression, 10 of the 14 patients from monotherapy switched to combination therapy, resulting in 17 patients on combination treatment and 4 on monotherapy.

[c]Discontinuation due to progressive disease could have been captured by any of these.

PRINT

Table 3. PFS Statistics and Tests Based on CIR

	Imatinib + Hydroxyurea (n = 120)	**Hydroxyurea (n = 120**	**Total (N = 240)**
Patients with events/censorings, n	111/9	115/5	226/14
PD confirmed by MRI assessment	48	55	103
PD confirmed by neurologic examination but not MRI	21	16	37
PD confirmed only by increased steroid use	24	28	52
Death without previous PD determination	18	16	34
PFS time, weeks			
25th percentile	5.9	5.1	–
50th percentile, median (95% CI)	6.3 (6.1-6.7)	6.1 (6.0-6.7)	–
75th percentile	12.4	11.7	–
PFS rates, % (95% CI)			
6 months	5.3 (1.0-9.7)	6.6 (2.1-11.1)	–
12 months	2.1 (0.0-5.0)	2.1 (0.0-5.5)	–
Treatment comparison			
Combination versus monotherapy, HR (95% CI)	–	–	0.925 (0.709-1.206)
P for HR = 1, unadjusted for the sequential nature of the trial	–	–	0.566
P for HR = 1, adjusted for the sequential nature of the trial	–	–	0.564

Patients alive and without progression were considered to be censored at the time of last available visit assessment.
PFS time percentiles and rates were calculated using the Kaplan-Meier method, ignoring strata.
HR and the associated *P* value were derived from a Cox proportional hazards model stratified for EIAED use (yes, no) and ECOG status (<2, ≥ 2). The hazard ratio indicates the effect of combination therapy and monotherapy. An HR <1 favors combination therapy.

PRINT

Table 4. Deaths, Other Serious or Clinically Significant AEs, or Related Discontinuations

Event	Imatinib + Hydroxyurea (n = 118) n (%)	Randomized to Hydroxyurea: Total Period (n = 118) n (%)	Randomized to Hydroxyurea: Period With HU Alone (n = 118) n (%)	Randomized to Hydroxyurea: Period After Switch (n = 85) n (%)
Deaths	84 (71.1)	91 (77.1)	27 (22.9)	64 (75.3)
Death due to disease progression	76 (64.4)	77 (65.3)	23 (19.5)	54 (63.5)
SAEs	64 (54.2)	79 (66.9)	46 (39.0)	49 (57.6)
NCI/NIH grade 3 or 4	54 (45.8)	64 (54.2)	34 (28.8)	40 (47.1)
Suspected to be drug-related	12 (10.2)	12 (10.2)	4 (3.4)	8 (9.4)
Leading to dose adjustment or interruption	6 (5.1)	16 (13.6)	9 (7.6)	7 (8.2)
Leading to permanent discontinuation	9 (7.6)	13 (11.0)	6 (5.1)	7 (8.2)
AEs	113 (95.8)	113 (95.8)	98 (83.1)	79 (92.9)
NCI/NIH grade 3 or 4	79 (66.9)	88 (74.6)	58 (49.2)	51 (60.0)
Suspected to be drug-related	75 (63.6)	73 (61.9)	42 (35.6)	51 (60.0)
Leading to dose adjustment or interruption	35 (29.7)	41 (34.7)	27 (22.9)	22 (25.9)
Leading to permanent discontinuation	19 (16.1)	21 (17.8)	11 (9.3)	10 (11.8)

All AEs starting after first dose but not later than 28 days after last dose were analyzed. AEs were assigned to the treatment group of the patient at the time of onset of the AE.

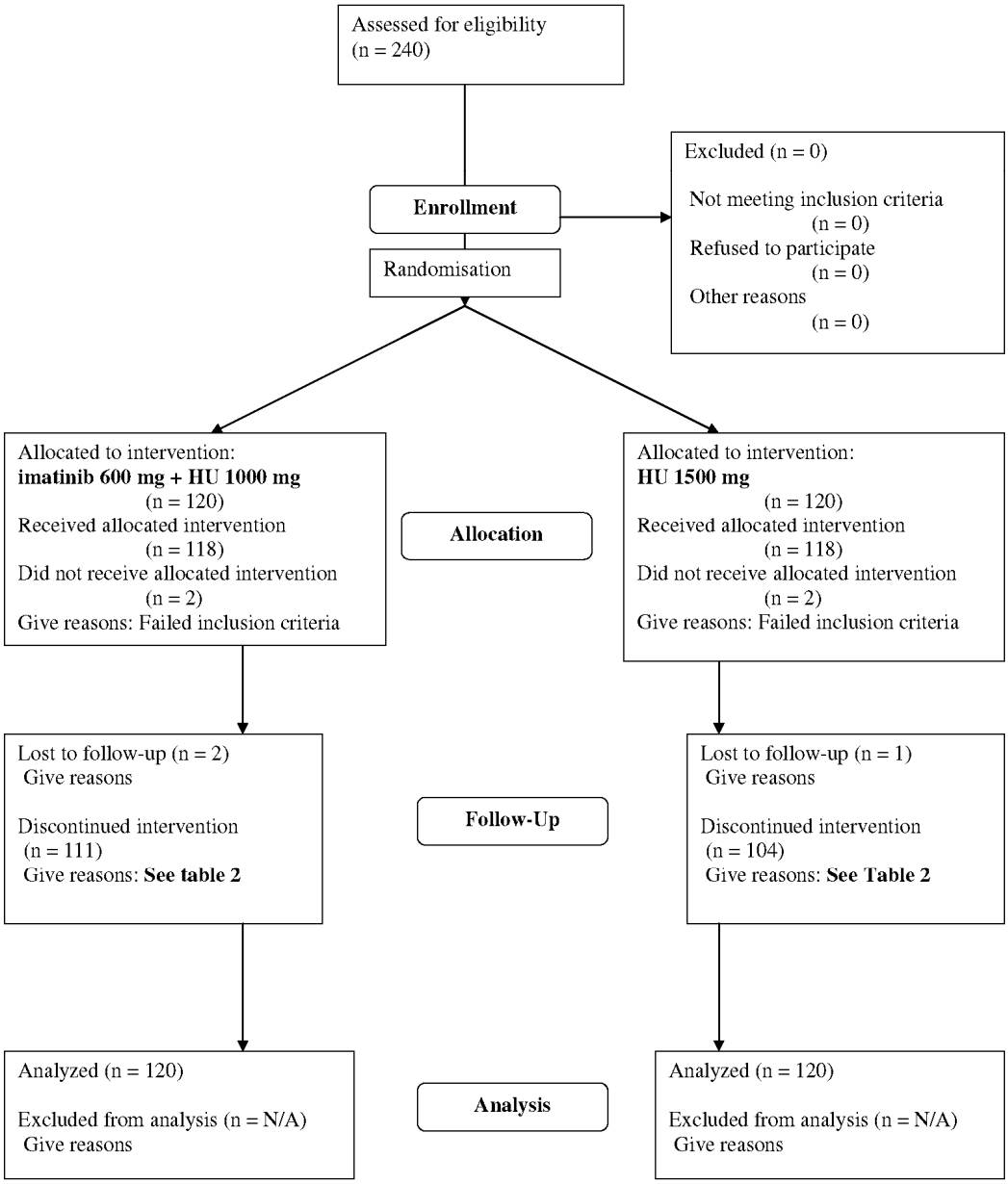
PRINT

Table 5. Frequent NCI/NIH Grade 3 or 4 AEs by Preferred Term (at Least 5% in Any Group)

		Randomized to Hydroxyurea		
Preferred Term	**Imatinib + Hydroxyurea (n = 118) n (%)**	**Total Period (n = 118) n (%)**	**Period With HU Alone (n = 118) n (%)**	**Period After Switch (n = 85) n (%)**
Patients with at least one grade 3 or 4 AE	79 (66.9)	88 (74.6)	58 (49.2)	51 (60.0)
General physical health deterioration	15 (12.7)	15 (12.7)	11 (9.3)	4 (4.7)
Epilepsy	7 (5.9)	15 (12.7)	8 (6.8)	9 (10.6)
Leukopenia	8 (6.8)	12 (10.2)	7 (5.9)	8 (9.4)
Thrombocytopenia	8 (6.8)	11 (9.3)	7 (5.9)	4 (4.7)
Hemiparesis	7 (5.9)	9 (7.6)	7 (5.9)	2 (2.4)
Pneumonia	8 (6.8)	8 (6.8)	4 (3.4)	4 (4.7)
Headache	4 (3.4)	7 (5.9)	5 (4.2)	4 (4.7)
Intracranial pressure increased	4 (3.4)	6 (5.1)	2 (1.7)	4 (4.7)
Muscular weakness	7 (5.9)	2 (1.7)	0	2 (2.4)
Aphasia	8 (6.8)	0	0	0
Convulsion	2 (1.7)	6 (5.1)	2 (1.7)	4 (4.7)

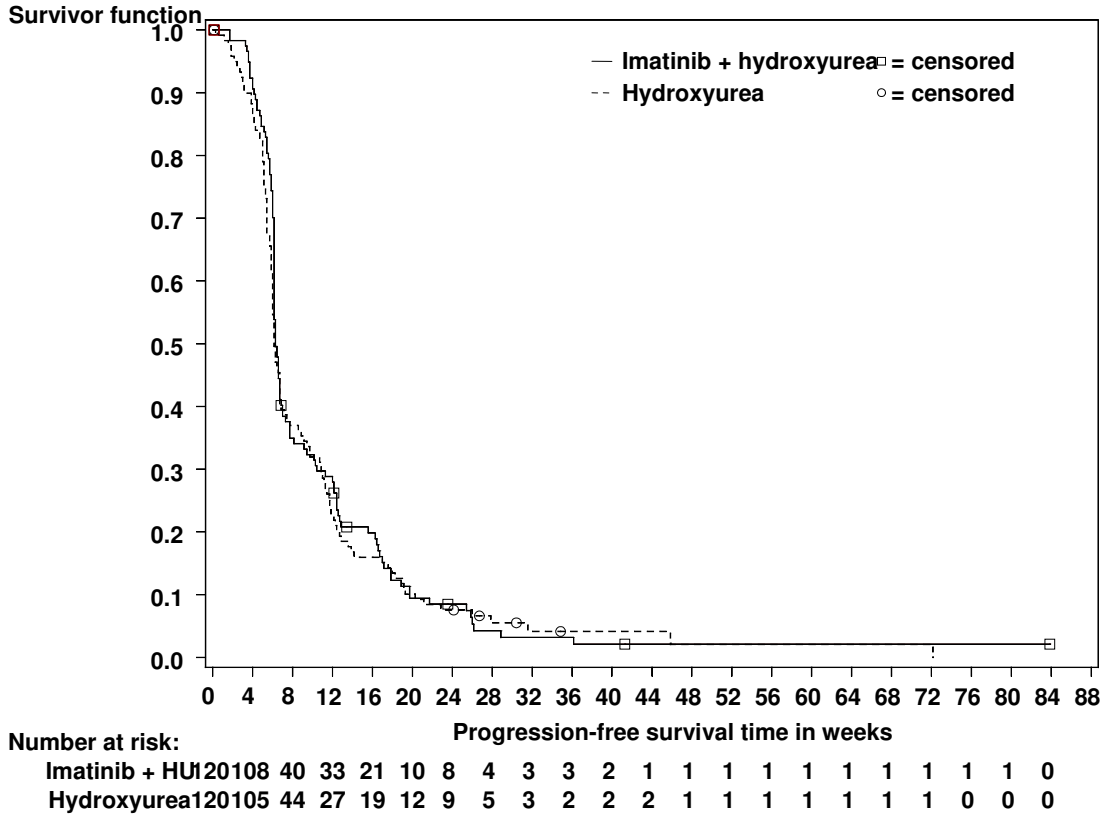
All AEs starting after first dose but not later than 28 days after last dose were analyzed. AEs were assigned to the treatment given at the time of onset of the AE. A subject with multiple occurrences of the same AE was counted only once, at the worst severity of the AE.

Figure 1. Study Design



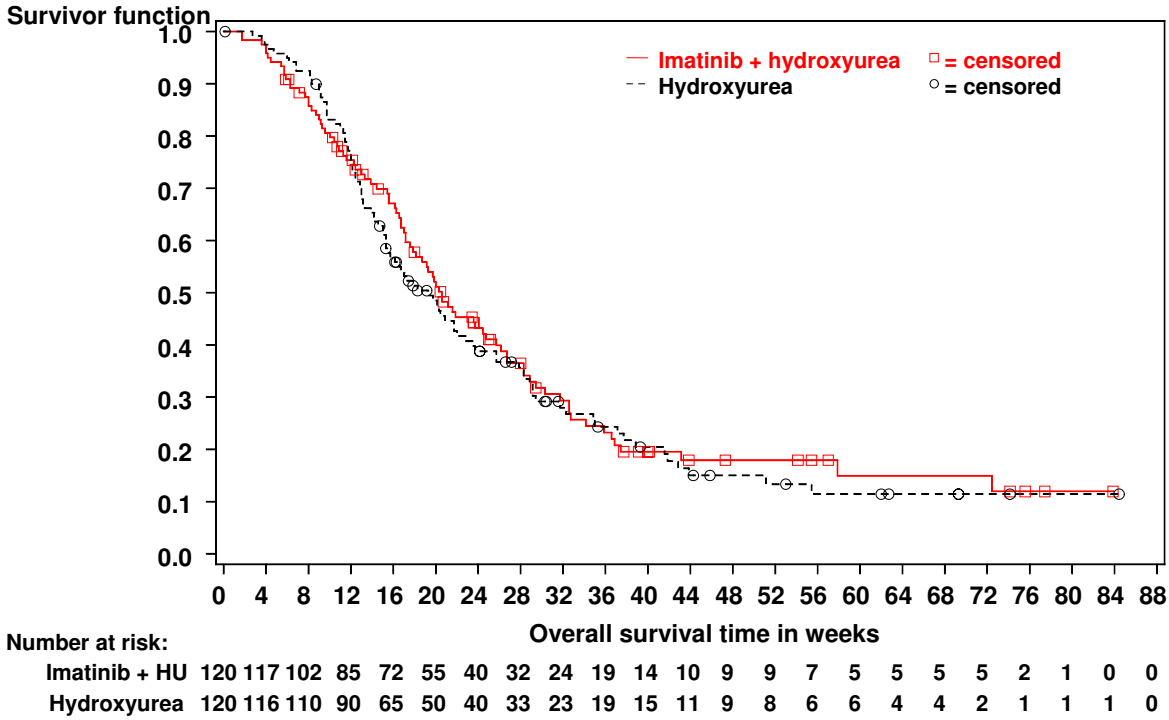
ONLINE

Figure 2. Kaplan-Meier Estimates of PFS Using CIR Data



PRINT

Figure 3. Kaplan-Meier Estimates of OS (ITT population)



PRINT

Figure 4. Kaplan-Meier Estimates of PFS Using Local Investigator Assessments