**SUPPLEMENTARY MATERIAL (online only)**

**Discussion of the Study Design and Amendments to the Protocol**

**Patient groups and efficacy endpoints**

The protocol for the study described in Wen et al and Cloughesy et al specified three separate groups of patients (A, B, and C), which were added sequentially under different versions of the protocol. Group A (46 planned; 46 enrolled) had a starting dose of 140 mg/day (all cabozantinib doses are expressed as the freebase equivalent). The planned sample size of 46 was to evaluate PFS based on the following hypotheses (1-sided nominal alpha of 0.05 and power of 85%) H0: Proportion with PFS at 6 months = 25% and HA: proportion of with PFS at 6 months = 45 %. Due to a high rate of dose reductions due to adverse events, the protocol was subsequently amended to enroll subjects at a lower starting dose of 100 mg/day (Group B). Treatment Group B consisted of two subgroups: those naive to antiangiogenic therapy (B1; 80 planned) and those that had received prior antiangiogenic therapy (B2; 20 planned). In addition, the study primary endpoint was changed from progression-free survival (PFS) at 6 months assessed in Group A to objective response rate (ORR) assessed in Group B1. The protocol was later amended to add Group C, which also consisted of a subgroup naive to antiangiogenic therapy (C1; 80 patients planned; 81 enrolled) and a subgroup that had received prior antiangiogenic therapy (C2; 45 patients planned; 36 enrolled), and the planned enrollment for Group B was reduced to 15 patients in each subgroup to evaluate the initial safety and tolerability of the 100-mg/day dose (37 were enrolled in B1 and 22 were enrolled in B2). The primary endpoint of ORR was now to be assessed in Group C1.

The protocol also specified a modified intent-to-treat population for efficacy analyses that would consist of the group of patients confirmed to have glioblastoma multiforme (GBM) per retrospective pathology review. However, the modified intent-to-treat population was redefined to remove this specification. All analyses of safety and efficacy include all treated subjects unless otherwise specified.

These groups also had differences, discussed below, in entry criteria and tumor assessment schedule and criteria.

**Combination of groups for analyses**

For regulatory purposes, the protocol specified that these groups would not be combined for efficacy analyses due to differences described herein. However, for the purpose of simplifying the data for publication, groups were analyzed as follows. Group A (starting dose of 140 mg/day) was retrospectively divided into subgroups of antiangiogenic-naive and ‑pretreated patients for consistency with Groups B and C. For patients with a starting dose of 100 mg/day, Groups B1 and C1 were combined into 1 group naive to antiangiogenic therapy and Groups B2 and C2 were combined into 1 group pretreated with antiangiogenic therapy. Efficacy and safety were analyzed for each of these groups and are discussed in two separate papers, one on patients naive to antiangiogenic therapy (Wen et al) and the other on patients who had received antiangiogenic therapy (Cloughesy et al).

Therefore, the total sample size of 152 antiangiogenic-naive patients summarized in Wen et al arose from the following 3 groups: (1) 34 antiangiogenic-naive patients (retrospectively defined Group A1) from among 46 total patients planned, enrolled, and treated in Group A at 140 mg to initially evaluate PFS; (2) all 37 from a planned cohort of 15 antiangiogenic-naive (Group B1) patients that allowed preliminary qualitative evaluation of safety and tolerability at the 100-mg/day dose; and (3) all 81 patients from a planned cohort of 80 antiangiogenic-naive patients (Group C1) at the 100-mg/day dose to evaluate ORR.

The total sample size of 70 patients who had received previous antiangiogenic therapy summarized in Cloughesy et al arose from the following 3 groups: (1) 12 patients who had received previous antiangiogenic therapy (retrospectively defined Group A2) from among 46 total patients planned, enrolled, and treated in Group A at 140 mg to initially evaluate PFS; (2) all 22 from a planned cohort of 15 patients (Group B2) defined in a protocol amendment that allowed preliminary qualitative evaluation of safety and tolerability at the 100-mg/day dose; and (3) all 36 patients from a planned cohort of 45 patients (Group C2) at the 100-mg/day dose to evaluate ORR.

**Entry criteria**

Some entry criteria differed between the three treatment groups. Highlights of entry criteria that differed are shown in Supplementary Table 1 below. Group C had updated entry criteria based on those proposed by the Response Assessment in Neuro-Oncology (RANO) guidelines (Supplementary Table 2).

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| **Supplementary Table 1. Entry Criteria Differences Among Treatment Groups** | | |
| **Group A** | **Group B** | **Group C** |
| * Patient must have progressive or recurrent glioblastoma multiforme (GBM) in the first or second relapse * Karnofsky performance status of ≥60% * Must not have received >2 prior systemic antitumor therapies * Must not have received nitrosoureas within 42 days of the first dose of cabozantinib | * Patient must have progressive or recurrent GBM in the first or second relapse * Measurable disease was required * Prior radiation therapy and temozolomide required * Karnofsky performance status of ≥60% * Must not have received >2 prior systemic antitumor therapies * Must not have received nitrosoureas within 42 days of the first dose of cabozantinib | * Patients must have a Grade 4 astrocytic tumor and be in the first or second relapse * Measurable disease was required * Prior radiation therapy and temozolomide required. * Karnofsky performance status of ≥70% * Prior treatment with nitrosoureas at any time were prohibited |

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| **Supplementary Table 2. Modified RANO tumor response criteria per IRF** | |
| **Tumor Response** | **Criteria** |
| Progressive disease (PD) | MRI:   1. ≥25% increase in SPD of the target lesions compared with the prior MRI nadir SPD for the target lesions (since and including baseline); or 2. Unequivocal progression of one or more non-target lesions compared with the prior MRI nadir SPD for the non-target lesions (since and including baseline); or 3. One or more new lesions compared with baseline   And  Glucocorticoids\*:   1. Glucocorticoids stable or increased; or 2. Off glucocorticoids at both current and baseline MRI dates |
| Unable to evaluate  (UE) | MRI:   1. One or more lesions were not assessed   Or  Glucocorticoids\*:   1. Change in glucocorticoid dose could not be assessed   Or  MRI:   1. CR, PR, or SD   Glucocorticoids\*:   1. Glucocorticoids increased   Or  MRI:   1. PD   Glucocorticoids\*:   1. Glucocorticoids decreased |
| Complete response (CR) | MRI:   1. Disappearance of all target and non-target lesions and no new lesions   And  Glucocorticoids\*:   1. Off glucocorticoids |
| Partial response  (PR) | MRI:   1. ≥50% decrease in the SPD of all target lesions compared with the baseline SPD and no new lesion; or 2. Disappearance of all target lesion(s) and the non-target lesion(s) (if any) are stable at current MRI and no new lesion   And  Glucocorticoids\*:   1. Off glucocorticoids; or 2. Glucocorticoids stable or decreased |
| Stable disease  (SD) | MRI:   1. Tumor response is not assessed as CR, PR, PD or UE   And  Glucocorticoids\*:   1. Off glucocorticoids; or 2. Glucocorticoids stable or decreased |
| \*Glucocorticoids are defined to be “increased” at a timepoint if the average daily dose given during the 5 days before the current scan increases more than 20% and more than 2 mg/day (dexamethasone equivalent) than average daily dose given during the 5 days before the comparator scan (baseline scan).  Glucocorticoids are defined to be “decreased” at a timepoint if the average daily dose given during the 5 days before the current scan decreases more than 20% and more than 2 mg/day (dexamethasone equivalent) than average daily dose given during the 5 days before the comparator scan (baseline scan), but with more than 2 mg/day dexamethasone equivalent dose of glucocorticoid use.  Glucocorticoids are defined to be “stable” at a timepoint if the average daily dose given during the 5 days before the current scan is no more than 20% and no more than 2 mg/day (dexamethasone equivalent) than average daily dose given during the 5 days before the comparator scan (baseline scan), but with more than 2 mg/day dexamethasone equivalent dose of glucocorticoid use.  “Off glucocorticoids” is defined as no glucocorticoids taken in the 5 days before the current scan, other than a physiologic replacement dose (average daily dose of no more than 2 mg/day dexamethasone equivalent).  IRF, independent radiology facility; MRI, magnetic resonance imaging; RANO, Response Assessment in Neuro-Oncology; SPD, sum of the products of perpendicular diameters. | |

**Tumor Assessment Schedule and Criteria**

The protocol initially specified that the tumor assessment per independent radiology facility (IRF) for Groups A and B would be analyzed by Macdonald criteria.[1](#_ENREF_1) For Group C, the protocol specified that tumor assessments would be analyzed using modified Response Assessment in Neuro-Oncology (RANO) criteria, which had been recently developed before the protocol amendment that added treatment Group C. For consistency, all tumor assessments were analyzed using the same modified RANO criteria as was prespecified for Group C.

For Group A, tumor assessments occurred at screening, at 8 weeks (± 4 days), 16 weeks (± 4 days), 26 weeks (± 4 days), 32 weeks (± 4 days), and at 8-week (± 4 days) intervals thereafter. For Group B, tumor assessments occurred at screening, at 4 weeks (± 4 days), at 8 weeks (± 4 days), 16 weeks (± 4 days), 26 weeks (± 4 days), 32 weeks (± 4 days), and at 8-week (± 4 days) intervals thereafter. For Group C, tumor assessments occurred at screening, 4 weeks (+ 4 days), and every 6 weeks (± 7 days) thereafter.

**Reference**

1. Macdonald DR, Cascino TL, Schold SC, Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol.* 1990;8:1277‒1280.