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Letters to the Editor

Interpretation of meta-analysis evaluating progression-free survival as a surrogate endpoint for overall survival in glioblastoma

Alexander et al[1] recently introduced a different interpretation involving our paper,[2] in which we systematically evaluated glioblastoma clinical trials published from 1991 to the present and demonstrated that progression-free survival (PFS) may be an appropriate surrogate endpoint for overall survival (OS). Although the authors did not raise any methodological and clinical questions directly to us, we wish to comment on the authors' interpretation of our results and provide our insights. Since the introduction of temozolomide 10 years ago,[3] there has been little success in developing an effective drug against glioblastoma. The prognosis remains poor, with median OS of approximately 15 months[4] and 8 months[2] for newly diagnosed and recurrent disease, respectively. To date, the increasing number of clinical trials and drug candidates has not expedited the progress but has instead created new challenges such as competing for the highly limited glioblastoma patient resource (fewer than 20 000 new cases diagnosed in the United States each year[5]). Therefore, it is critical that glioblastoma clinical trials become more efficient. One way of achieving this goal is to explore surrogate endpoints for OS. To contribute to this field, we conducted our analysis.

Our data and analysis led to 2 major findings supporting our surrogacy conclusion: (i) a strong correlation between PFS and OS hazard ratio (HR) estimates in non–bevacizumab-containing comparative studies and (ii) a significant lead time that could be gained by using PFS instead of OS as endpoint. One of the minor findings we observed was that a moderate-to-good correlation exists between point estimates of median PFS and OS within groups. Although this was not intended to contribute to the surrogacy question, it still adds value to overall understanding of the relationship between these endpoints.

We respectfully disagree with Alexander et al statement that "the strong correlation between PFS and OS reported by Han et al provides evidence that postprogression heterogeneity is limited (as in EORTC 26981/NCIC CE.3), thereby refuting one of the strongest arguments to use PFS." First, the correlation between median PFS and OS demonstrated in our paper is only moderate to good ($R2 = 0.7$) and, more importantly, to our knowledge there has been no comprehensive study supporting the assumption that "for glioblastoma, strong correlation between PFS and OS can therefore be at least partially explained by the short SPP (survival post-progression)". On the contrary, several studies (eg, Tang et al 2007 JCO[6]) have shown coexistence of long SPP and a moderate-to-good correlation between PFS and OS, the same as shown in our paper. Second, we have demonstrated a very significant lead time (a concept similar to SPP) that is close to half of the median OS (see above) of glioblastoma patients: 7.4 months and 4.2 months in newly diagnosed and recurrent cases, respectively, in Figure 5 in our paper. Finally, Figure 5 in our paper also illustrated the large postprogression heterogeneity of patients included in our analysis. The lead time ranged from 1.4 to 18 months in newly diagnosed patients and from 1.8 to 8.1 months in recurrent patients. The framework introduced by Broglio et al[7] is certainly very useful, but it also needs to be kept in mind that the framework was mainly based on simulations, while clinical data come with much more variation and complexity.

As extensively discussed in our paper, the applicability of the linear relationship between the HR of OS and PFS to anti-VEGF agents (ie, agents targeting VEGF or VEGFR) may require further validation because none of the trials in our HR correlation analysis contained an anti-VEGF agent such as bevacizumab (an anti-VEGF antibody) or cediranib (a VEGFR tyrosine kinase inhibitor). Therefore, discussion of AVAglio, RTOG-0825, and therapeutics affecting the ability to assess progression, as well as the use of them as examples (eg, in paragraphs 3, 5 and 7 in Alexander et al[1]) may be outside the scope, although we agree that it is important to standardize the definition and criteria for PFS in glioblastoma.

We also cannot fully agree with Alexander et al comment that "In non-adaptive trials, OS data is ultimately collected without the need to make decisions in the intervening few months. Small lead-time gains using PFS are outweighed by the uncertainty of the relationship with OS." As discussed at the beginning of this manuscript, the decade-long unmet medical need of this oncology indication and the challenges faced by the pharmaceutical industry put an emphasis on early decision-making. Given the significant lead time demonstrated in our paper, it is possible that making correct decisions in the intervening few months could benefit a significant portion of glioblastoma patients. Furthermore, early efficacy evaluation and early decision-making in early phases of drug development are critical for the viability and sustainability of the current drug development model of the pharmaceutical industry.

The implication of our analysis was not to replace OS with PFS. Instead, our analysis suggested that PFS may be an appropriate surrogate marker for early efficacy evaluation and decision-making, especially in early phases of drug development. As is true for any endpoint, PFS possesses both advantages and disadvantages. Use of PFS as a surrogate marker for OS may lead to opportunities for early efficacy evaluation and clinical trials that are more efficient and less confounded by subsequent therapies. At the same time, the use of PFS, especially in glioblastoma, demands continuous efforts in the advancement of

imaging technologies and the standardization of progression criteria. Reward and risk will always coexist in any field, and further evaluation weighing the reward and risk of using PFS is always warranted.

Conflict of interest statement. Kelong Han is an employee of Genentech and holds stock in F. Hoffmann–La Roche. Melanie Ren was an employee of Genentech at the time the manuscript was written. Wolfgang Wick has acted as a consultant for F. Hoffmann–La Roche, Eli Lilly (uncompensated), and MSD and has received research support from Apogenix, Boehringer Ingelheim, Eli Lilly, and MSD. Lauren Abrey is an employee of F. Hoffmann–La Roche and holds stock in F. Hoffmann–La Roche. Asha Das is an employee of Genentech and holds stock in F. Hoffmann–La Roche. Jin Jin is an employee of Genentech and holds stock in F. Hoffmann–La Roche and Eli Lilly. David A. Reardon has received remuneration (other than research funding, honoraria, and consultancy fees) from F. Hoffmann–La Roche/Genentech and Merck & Co.

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Reply to Letter

Getting it first versus getting it right: weighing the value of and evidence for progression-free survival as a surrogate endpoint for overall survival in glioblastoma

Han et al claim that progression-free survival (PFS) may be an appropriate surrogate endpoint for overall survival (OS) in glioblastoma (GBM) trials.[1] Unfortunately, the data presented do not support such a broad claim. In their current response, Han et al state that there were 2 major findings supporting the surrogacy conclusion in their original manuscript: (i) lead time using PFS over OS and (ii) the strong correlation of PFS hazard radio (HR) to OS HR in non–bevacizumab-containing comparative studies.

First, lead time for PFS over OS suggests utility rather than supporting a claim for surrogacy. It answers a question of why a surrogate for OS should be used, not whether PFS actually is a surrogate. Consequently, the only finding that supports a surrogacy claim is the strong correlation between PFS HR and OS HR in non–bevacizumab-containing studies.

Correlation between PFS HR estimates and OS HR estimates is not a sufficient argument to show or suggest a surrogacy relation in isolation. An absence of any treatment effect on PFS and OS, for example, does not imply a low correlation between PFS HR estimates and OS HR estimates. Furthermore, "non–bevacizumab-containing studies" is simply too broad a characterization given the data and implies a similar correlation for future agents. The original findings by Han et al, particularly with respect to correlation of *positive* treatment effects, are driven almost entirely by the EORTC 26981/NCIC CE.3 results. It would then be more accurate to assert a strong correlation between the positive effects of one specific agent, temozolomide (TMZ), on PFS and subsequent positive effects on OS.