Author's response to reviews

Title: Eukaryotic Initiation Factor 4E (eIF4E) and Angiogenesis: Prognostic Markers for Breast Cancer

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Author's response to reviews: see over
Dear Iratxe Puebla:

Please find enclosed our revised manuscript “Eukaryotic Initiation Factor 4E (eIF4E) and Angiogenesis: Prognostic Markers for Breast Cancer”. We have made changes suggested by the reviewers and addressed all concerns of the reviewers. Importantly, the English has been edited by a native English-speaking editor. We hope that this revised manuscript is now acceptable for publication.

Thank you for your consideration of this manuscript.

Sincerely,

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Response to Reviewer Tapio Visakorpi:

Major:
1. In response to Dr. Visakorpi’s comment regarding the expression of Her-2/neu in breast cancer, we think that higher percentage (45.9%) Her-2/neu expression in our group is likely due to the IHC method used. By IHC, Sidoni et al even detected 72% of breast cancer expressing Her-2/neu (Sidoni et al, Anticancer Res. 2006,5:2333), and 85.8% of breast cancer expressed this protein reported by Perez et al (Perez et al, J Clin Onc. 2006;24:3032-8).
2. Our results indeed indicate that eIF4E is associated with prognosis but not with the nodal status and expression of ER, PR and Her-2/neu as shown in Table 2. The explanation for this is that the expression of eIF4E is likely more important than nodal status and expression of ER, PR and Her-2/neu to predict breast cancer outcome. For example, in patients with node-negative breast cancer, 20% will develop systemic disease (Weidner et al, Surg Oncl Clin North Am 1997,6:415; Jatoi et al, J Clin Oncol 1999,17:2334). Conversely, in node-positive patients up to 35% cases do not develop systemic disease (Weidner et al, Surg Oncl Clin North Am 1997,6:415), suggesting that nodal status only relatively correlates with the disease outcome. Furthermore, results from a study of patients with node-positive breast cancer demonstrated that eIF4E overexpression is an independent predictor of a worse outcome independent of node status (McClusky et al, Annals of Surgery 2005, 242:584).
3. We have included ER, PR and Her-2/neu in the multivariate analysis (Table 5 and 6).
4. The English has been edited by a native English-speaking editor.

Minor:
1. The “multivariate analyses” has been added to the titles of Tables 5 and 6.
2. The English errors have been corrected.

Response to Reviewer Quyen Chu:

Major:

1. We thank Dr. Chu for pointing out our mistakes regarding data (p values) presented in the text and in the Tables. We have made corresponding corrections.
2. We have cited article by Byrnes et al.
3. We have added the statement for whether patients receive adjuvant therapy (page 4, line 14).
4. The information of 5-year survival rate, mean survival time and median survival time has been added to text (page 4, line 4 from bottom).
5. In the discussion, we have included papers from Benjamin Li’s group and compared our results with Dr. Li’s studies. We still include stage IV patients in order to evaluate the status of eIF4E expression in all breast cancer patients including stage IV. As discussed in Dr. Li’s paper (Annals of Surgery 2006,243:684), a question is asked how about the eIF4E expression in patients with stage IV disease. We presented eIF4E expression in 22 stage IV patients, although large amount of specimens from breast cancer patients needs to be tested to make conclusion for the status of eIF4E expression in stage IV patients and to estimate whether inclusion of stage IV patients affects data analysis as compared to those from Dr. Li’s group.
6. We included various histological types of breast cancer in order to evaluate the overall expression of eIF4E in all breast cancer patients, although data analysis may make a conclusion different from those excluded DCIS, LCIS and uncommon invasive subtypes. We thank Dr. Chu for pointing out this weakness.
7. We agree with Dr. Chu’s comment that high level percentage of patients with nodal disease is likely due to the inclusion of stage IV. We have analyzed this situation in Cox proportional hazard model.
8. As suggested by Dr. Visakorpi, we have included ER, PR and Her-2/neu in the multivariate analysis. Re-analysis showed that the nodal status for disease-free survival becomes borderline significance (p=0.062), whereas the nodal status for overall survival still remains borderline significance (p=0.046). Although nodal status is the most important prognosticator for breast cancer outcome, unfortunately, 20% patients with node-negative breast cancer will develop systemic disease, and conversely, up to 35% node-positive patients do not develop systemic disease, as stated in item 2 of response to Dr. Visakorpi. Based on these observations, the borderline statistical significance of nodal status for both disease-free survival and overall survival in our group may represent actual correlation between nodal status and breast cancer outcome.

Minor:

1. We have reviewed and corrected the errors of p-value numbers in the text and tables.
2. Language in page 6 has been edited.
3. The p-values in text (page 9) and in table have been corrected.
4. The p-value for eIF4E in table 5 has been changed.
5. The “months” has been added to the x-axis of Fig. 4.