

Response Form for the Final Performance Review Report*

1. Name of Grantee: NSABP
2. Year of Grant: 2008 Formula Grant

A. For the overall grant, briefly describe your grant oversight process. How will you ensure that future health research grants and projects are completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) are submitted to the Department in accordance with Grant Agreements? If any of the research projects contained in the grant received an “unfavorable” rating, please describe how you will ensure the Principal Investigator is more closely monitored (or not funded) when conducting future formula funded health research.

The projects conducted at the NSABP Foundation using grants received from the Pennsylvania Department of Health are tightly monitored and supervised by the Director of the Division of Pathology. The director provides day-to-day data discussions with Principal Investigators and their staffs and, therefore, provides real-time supervision of all projects. Financial officers alert the director and Principal Investigators about upcoming deadlines for filing reports in a timely manner. Regulatory department staff provide oversight for IRB compliance. Since this project received a favorable score (2.00), no actions will be taken to change the monitoring of projects in the future.

* Please note that for grants ending on or after July 1, 2007, grantees' Final Performance Review Reports, Response Forms, and Final Progress Reports ***will be made publicly available on the CURE Program's Web site.***

Project Number: 0864301
Project Title: Development of Prognostic Index for
Colon Cancer Patients Using Gene Expression Profiling
Investigator: Paik, Soonmyung

B. Briefly describe your plans to address each specific weakness and recommendation in Section B of the Final Performance Summary Report using the following format. As you prepare your response please be aware that the Final Performance Review Summary Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

Reviewer Comment on Specific Weakness and Recommendation (*Copy and paste from the report the reviewers' comments listed under Section B - Specific Weaknesses and Recommendations*):

Response (*Describe your plan to address each specific weakness and recommendation to ensure the feedback provided is utilized to improve ongoing or future research efforts*):

Reviewer 1

The investigators are focused on developing a predictive marker for use of oxaliplatin in colon cancer patients. The investigators have access to samples from NSABP C-07 study which randomized stages two and three colon cancer patients to either 5-FU and leucovorin or 5FU/LV and addition of oxaliplatin. The biggest issue is that C-07 improved DFS and not OS for stage three colon cancer patients but not for stage two patients. The investigators did not take this into account in their sample size and planning of the studies, which should have been done.

Response:

The reviewer states that C-07 demonstrated that the addition of oxaliplatin did not improve OS in stage II patients and that we should have taken that into account in our studies. When we started these studies in 2008 the published results demonstrated that the entire C-07 cohort (stage II and III) was shown to benefit from oxaliplatin based on DFS using a median follow up time of 3.5 years and a trend for benefit was also seen in stage II but the size of the sample was underpowered to evaluate the efficacy of oxaliplatin in stage II patients¹. Based on these results we did gene expression profiling of a discovery cohort which consisted of 1/2 of C-07 patients and included both stage II and III patients. We included stage II patients also because we were aware that a subset of stage II patients had a worse prognosis than a subset of stage III patients and these high risk patients are most often treated with FOLFOX or FLOX. We also included both stage II and III patients in our study so that we would be able to determine whether gene expression profiling was able to improve the identification of patients who would receive benefit from oxaliplatin. Later analysis with an 8 year median follow-up demonstrated that there was no significant benefit from oxaliplatin in stage II for both OS and DFS but the study was underpowered to detect the relative differences observed in stage III². These studies together suggested that stage II patients received little benefit but it could not be ruled out that there was

some positive effect for oxaliplatin in some subset of stage II patients and being able to identify such a subset would be of great clinical benefit. We are currently analyzing our data now and we are examining various subsets within the discovery cohort for model building. Some models are being built which include only stage III patients as one avenue for study but we will continue to evaluate stage II patients as well.

Reviewer 2

1. The researchers should perform mutation analysis for key colon cancer pathway genes, such as APC, K-Ras, PIK3CA, P53 mutation analysis. This mutation analysis should be incorporated into the prognostic analysis.
2. The researchers are encouraged to identify whether responsiveness to the treatment data (for example, imaging studies or serum carcinoembryonic antigen data) are available in addition to the patient survival data.

Response:

1. Mutation profiling was not a part of this grant but we have performed mutation analysis of *KRAS*, *PIK3CA* for C-07 patients as a part of NSABP 2007 Formula Grant and are currently incorporating it into our analyses for predictive and prognostic models. We have not yet profiled the C-07 samples for mutations in *p53* and *APC* because until very recently we did not have the proper platform to do mutation profiling for mutations in tumor suppressor genes because these mutations do not occur in hot spots. We have detailed more reasons for why we did not do mutation profiling for tumor suppressor genes like *APC* and *p53* in our final performance review for NSABP Formula Grant 2007.
2. I think the reviewers are suggesting that we associate gene expression data to CEA or imaging data. To specifically answer the reviewer's question, CEA chemistry was done post operatively, before randomization and at 6 and 12 months after randomization. The tumors in these patients were completely resected and imaging was done only in the presence of hepatomegaly before randomization and at 12 months after randomization if the patient had an abnormal liver function test or a hepatomegaly. CEA and imaging information is not included in our data set. In order to carry out such a study it would be necessary to write a protocol for approval from both NSABP and NCI, this process alone would take 6 months and then the analysis could begin. We do not currently have the resources to undertake such a study and we are not sure that CEA could be used as a surrogate for response to treatment for the development of a clinical test. With regards to using imaging results may be a problem since the tumors were all completely resected at the time of surgery.

Reviewer 3

1. mRNA profiles have been under development for some time, and several panels are now in clinical use. In this case, the investigator addresses a very specific question, comparing two complex treatment schedules, one of which includes the additional highly-toxic oxaliplatin. Early results suggest that small increments in predictability of outcomes may be possible, but

the scope of intended application is rather narrow. Whether the results can be transferred to other therapies (even those with similar strategies) is questionable.

2. The investigator needs to address the value of his methodology versus newly emerging techniques, in a field that is very rapidly evolving. Also, therapies against colon cancer are in flux, so that biomarker tests for efficacy of drug combinations may be short-lived.

Response:

1. We disagree that our application is narrow. The combination of 5-fluorouracil + leucovorin (5Fu+LV) and oxaliplatin (FLOX or FOLOX) are the worldwide standard of care for stage III colon and rectal cancers. Whether you use it as FLOX or FOLFOX is not relevant since they have nearly identical clinical benefit. All stage II patients receive 5-FU +LV and some stage II, mostly high risk, patients will also be treated with oxaliplatin. Together this represents about 60-80,000 patients annually in the US and probably at least a half-million people worldwide. Additionally, in the U.S. approximately 45,000 metastatic patients will be treated with the 5-FU-oxaliplatin combination. Furthermore, the 5-FU-oxaliplatin is now a preferred combination for patients with esophageal and gastric cancer and is commonly used for pancreatic cancers. Given the toxicity of oxaliplatin, we feel that any improvement in the identification of patients who do not benefit from oxaliplatin provides an important step in improving clinical outcomes. We do not believe that our application is narrow given the large number of patients that are treated with oxaliplatin. It seems plausible that a validated model that predicts benefit from oxaliplatin within C-07 is likely to be useful to any 5-FU +LV+oxaliplatin regimen. It is true that the degree of benefit from oxaliplatin is not large within the entire cohort of C-07 but if we identify a smaller subset which incurs most of the benefit then consequently this benefit will be larger.
2. We appreciate that the field is rapidly evolving but we believe that we have used the most up to date gene expression profiling techniques available to us at the time. Initially we did whole genome expression profiling of our discovery cohort using DASL arrays, which we believe represented the best technology for whole genome expression profiling for degraded RNAs isolated from FFPE material. We selected genes prognostic and predictive genes from this data and then rebuilt a nCounter code set which is probably the best method now available for gene expression profiling of degraded RNAs because it requires no enzymology, no amplification, only 100ng of total RNA for the profiling of 800 genes and is an extremely easy procedure. These characteristics make it potentially superior to qRT-PCR as a clinical test. Nanostring now is releasing a PAM50 as a clinical test for breast cancer thus demonstrating that it is able to launch oncological clinical tests. It is true that therapies for colon cancer are in flux, due to the rapid development of targeted therapies. However, most of these therapies are still under evaluation with metastatic patients. It is not clear that these expensive targeted therapies will show benefit in stage II and III colon cancer patients because cetuximab has not shown benefit in stage II and III colon cancer even in KRAS wt patients. In breast cancer where the ideal targeted therapy, Herceptin, has been so successful in treating patients in both the metastatic and adjuvant setting, chemotherapy still shows significant benefit in both HER2+ and negative patients and a chemotherapy base is almost always included in the treatment of breast cancer patients. Thus we believe that 5 FU and oxaliplatin will continue to be used in stage II and III colon cancer for many years to come.

C. If the research project received an “unfavorable” rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive “unfavorable” ratings.

Response: None required.

D. Additional comments in response to the Final Performance Review Report (OPTIONAL):

Response:

1. Kuebler JP, Wieand HS, O'Connell MJ, et al: Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol* 25:2198-204, 2007
2. Yothers G, O'Connell MJ, Allegra CJ, et al: Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 29:3768-74, 2011