Health-Related Quality of Life With Adjuvant Docetaxel- and Trastuzumab-Based Regimens in Patients with Node-Positive and High-Risk Node-Negative, HER2-Positive Early Breast Cancer: Results from the BCIRG 006 Study

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Key Words. Breast cancer • BCIRG 006 • Docetaxel • Trastuzumab • Chemotherapy • Quality of life • Anthracycline-induced cardiotoxicity • Adjuvant therapy

ABSTRACT

Background. This study aims to describe and compare health-related quality of life (HRQL) in patients with node-positive and high-risk node-negative HER2-positive early breast cancer receiving adjuvant docetaxel and trastuzumab-based or docetaxel-based regimens alone.

Methods. Eligible patients ($n = 3,222$) were randomly assigned to either four cycles of adjuvant doxorubicin and cyclophosphamide followed by four cycles of docetaxel (AC→T) or one of two trastuzumab-containing regimens: adjuvant doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab administered for 1 year (AC→TH) or six cycles of docetaxel plus carboplatin combined with trastuzumab administered for 1 year (TCH). The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and BR-23 were administered at baseline, the start of cycle 4 (mid), and the end of chemotherapy (EOC), as well as at 6, 12, and 24 months after chemotherapy.

Results. Compliance rates for the EORTC questionnaires were acceptable at 72%–93% of eligible patients out to the 12-month assessment. Systemic side effect (SE) change scores were significantly improved for TCH-treated patients compared with AC→TH and AC→T at EOC, suggesting improved tolerability. Physical functioning (PF) was only slightly worse at midpoint for those receiving TCH, compared with patients who were just starting on taxane in an AC→TH regimen, but was otherwise similar between arms. All treatment arms recovered from the deterioration in SE, PF, and Global Health Scale scores by 1 year and median future perspective change scores continued to improve throughout treatment and follow-up.

Conclusion. HRQL outcomes for adjuvant docetaxel and trastuzumab-based regimens are favorable and support TCH as a more tolerable treatment option. *The Oncologist* 2013;18:812–818

Implications for Practice: While safety and efficacy data is imperative to the decision-making process, it does not fully reflect how patients experience the chemotherapy regimens. Health-related quality of life (HRQL) studies allow breast cancer patients and their oncologists to better assess the risks and benefits of each chemotherapy treatment option. Our study is the first published HRQL analysis of trastuzumab in combination with chemotherapy in the adjuvant setting, demonstrating tolerable HRQL outcomes for each arm. We suggest adjuvant docetaxel- and trastuzumab-based regimen as a more tolerable alternative to anthracycline-trastuzumab-based adjuvant therapies in patients with node-positive, and high-risk node-negative, HER2-positive early breast cancer. These additional findings of significant improvements in patient-reported side-effects change scores at the end of chemotherapy, and less clinically important deterioration in physical function and side-effects, support adjuvant docetaxel- and trastuzumab-based regimens as a more tolerable alternative to anthracycline-trastuzumab-based adjuvant therapies.

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INTRODUCTION

Breast cancer is the second leading cause of cancer-related deaths in women in the Western world [1]. The National Cancer Institute estimated that there were 230,480 new cases and 39,520 deaths from breast cancer in the U.S. in 2013 [1]. Treatment with adjuvant chemotherapy is recommended for women with resected node-positive or high-risk node-negative breast cancer, and an anthracycline-based regimen is often included [2]. Trastuzumab is a humanized monoclonal antibody targeting the extracellular domain of the HER2 receptor, and its addition to adjuvant chemotherapy has been shown to improve both disease-free survival (DFS) and overall survival (OS) in four large randomized trials, including the Breast Cancer International Research Group (BCIRG) 006 study [3–6].

The BCIRG 006 study is a multicenter, phase III trial that enrolled 3,222 patients from 41 countries. The main toxicity concern with the use of trastuzumab is increased cardiac toxicity, particularly in combination with anthracyclines [7]. The BCIRG 006 was the only adjuvant trastuzumab trial to include a non-anthracycline trastuzumab-containing chemotherapy arm [6]. The study compared adjuvant doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) (AC) for four cycles followed by docetaxel (100 mg/m²) (T) for four cycles (AC→T) with two trastuzumab-containing regimens—AC followed by T with trastuzumab (4 mg/kg loading dose and 2 mg/kg weekly) (H) for 1 year (AC→TH) or docetaxel (75 mg/m²), carboplatin (area under the curve 6 mg/mL per minute) for six cycles with trastuzumab for 1 year (TCH)—in patients with node-positive or high-risk node-negative HER2-positive breast cancer.

The addition of trastuzumab to chemotherapy improved efficacy compared with AC→T alone, and there were no differences in efficacy between the AC→TH and TCH arms of the trial. At a median follow-up of 65 months, the 5-year DFS rate was 75% for AC→T and 84% and 81% for AC→TH and TCH, respectively (hazard ratio [HR]: 0.64, $p < .001$ and HR: 0.75, $p = .04$). The 5-year OS rate was 87% for AC→T and 92% and 91% for AC→TH and TCH, respectively (HR: 0.63, $p < .001$ and HR: 0.77, $p = .04$). The safety profile was acceptable in both study arms, but more favorable for TCH than for AC→TH, including significantly reduced clinician-rated grade 3/4 neutropenia, leucopenia, arthralgia, myalgia, hand-foot syndrome, stomatitis, and vomiting, as well as significant reductions in rates of neuropathy and nail changes. Rates of congestive heart failure and sustained subclinical loss of mean left ventricular ejection fraction (>10% relative loss) were lower with TCH compared with anthracycline-based combinations.

Health-related quality of life (HRQL) is important for patients and physicians to consider when determining treatment strategy and individual patient care [8]. Collection of these patient-reported outcomes during clinical trials allows the clinical benefits of novel therapies to be weighed along with their impact on patient well-being. HRQL parameters offer information of significant prognostic value from the patient perspective [9, 10] and have the potential to influence clinical decisions regarding treatment options with otherwise comparable outcomes. The comparison of HRQL between adjuvant treatment arms was a planned secondary endpoint of the BCIRG 006 trial. Results of the HRQL analyses are reported here.

METHODS

This phase III randomized trial was conducted between April 2001 and March 2004 [6]. Participating centers received approval from their institutional ethics review boards. All patients provided written informed consent prior to participation.

Patients

Patients who were ≥ 18 years and ≤ 70 years of age with a Karnofsky performance status (PS) $\geq 80\%$ were eligible for BCIRG 006 if they had centrally confirmed HER2-positive, resected, invasive adenocarcinoma of the breast, with node-positive disease or with high-risk node-negative disease (defined by at least one of the following: tumor size > 2 cm, hormone receptor negative, histologic and/or nuclear grade 2–3, or age < 35 years). Definitive surgery with histologically clear surgical margins by either mastectomy or breast-conserving surgery needed to include assessment of axillary lymph node involvement.

Study Procedures

Eligible patients were randomized on a 1:1:1 basis to receive AC→T, AC→TH, or TCH (Fig. 1). After administration of the adjuvant therapy, patients were evaluated clinically every 3 months during the first 2 years and then every 6 months until year 5. Patients were then evaluated annually up to year 10.

HRQL Assessment

HRQL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and BR-23 instruments. The QLQ-C30 is a self-administered, 30-item, cancer-specific, multidimensional questionnaire that has been shown to be valid and reliable when used in clinical trials and cross-cultural settings [11]. This questionnaire contains a two-item global health scale (GHS), five functional scales (physical function [PF], role, cognitive, emotional, and social function), and nine symptom scales and items (fatigue, nausea/vomiting, pain, dyspnea, sleep, appetite loss, constipation, diarrhea, and financial impact). The QLQ BR-23 is a 23-item self-administered, breast cancer-specific questionnaire, selected for cross-cultural validity and reliability [12]. The QLQ BR-23 includes four functional domains (body image, sexual functioning, sexual enjoyment, and future perspective), and four symptom scales (systemic therapy side effects [SEs], breast symptoms, arm symptoms, and upset by hair loss).

All patients were eligible for participation in the HRQL assessment as long as all questionnaires were validated in the patients' first language. Patients completed questionnaires at pretreatment baseline; 9 weeks (cycle 4/mid), and 18 weeks (cycle 7/end of chemotherapy [EOC]) from the date of first study medication (± 31 days); as well as at 6, 12 (± 3 months), and 24 months (± 6 months) after planned EOC visit (Fig. 1). Patients were evaluable for HRQL analysis if they completed their baseline and at least one follow-up questionnaire. Scoring was completed according to the EORTC scoring manual. Raw scores were linearly transformed to a 0 to 100 scale. For functional and GHS scales, higher scores represent better HRQL, whereas on the symptom scales and items, lower scores represent better HRQL. A change of 10 points is considered clinically important [13].

Statistical Considerations

It was determined a priori that the HRQL domains most likely to be affected by adjuvant chemotherapy regimens would in-

Figure 1. Consolidated Standards of Reporting Trials diagram for BCIRG 006 HRQL assessment. *Based on validation of questionnaire in patients' first language. **Numerators give total number of assessments completed; denominators give total number of eligible patients at that stage of treatment.

Abbreviations: AC→T, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel for four cycles; AC→TH, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel with trastuzumab for 1 year; EOC, end of chemotherapy; HRQL, health-related quality of life; mid, 9 weeks (cycle 4); TCH, docetaxel plus carboplatin for six cycles with trastuzumab for 1 year.

clude PF, GHS, SEs, and future perspectives. Thus, the prospectively determined main HRQL endpoints compared mean changes in each of these scales from baseline to midpoint, EOC, and 12 months using a two-sample *t*-test. Positive change scores denote improved HRQL except on the SE scale, which is reversed. Change scores were also used to classify patients as having improved, being stable, or having worsened HRQL, depending whether change scores were 10 points or greater in a favorable or unfavorable direction, maintained for at least two consecutive assessments [13, 14]. Differences in the proportion improving and worsening were assessed using χ^2 tests. Because of three-arm comparisons, only $p < .017$ was considered significant, based on a Bonferroni adjustment.

Questionnaire completion rates were calculated as a percentage of all eligible subjects who completed a questionnaire at a given time point. Completion rates were computed by country and by treatment group. Missing data within assessments for which some data were present were handled according to the EORTC scoring guidelines.

To evaluate the effect of missing data, the analyses were repeated using two different data imputation approaches as sensitivity analyses. In the first approach, last-observation-carried-forward (LOCF), missing assessments were imputed with the last observed assessment, regardless of the reason for the missing assessment. The second approach used LOCF, but did not impute values for subjects who were known to be off study (e.g., for progression). The two sets of imputed data can be considered sensitivity analyses of one another.

Repeated measures analysis was used to provide a single estimate of the treatment effect for each scale score. The primary model estimated the follow-up values as a function of the baseline value, the treatment group, and the assessment period, assuming a constant treatment effect over time. A sec-

ond model estimated the follow-up values as a function of the baseline value, the time from baseline, and a time from baseline by treatment interaction, allowing for larger or smaller treatment effects at different times in the follow-up period. Analyses were performed using Base SAS and SAS/STAT software, version 9.1.3, of the SAS System (SAS Institute, Cary, NC, <http://www.sas.com>) on an intent-to-treat basis.

RESULTS

Patient Characteristics

A total of 3,222 patients were randomly assigned to one of the three adjuvant treatment arms: 1,073 to AC→T, 1,074 to AC→TH, and 1,075 to TCH. Baseline characteristics were well balanced between treatment arms [6]. In total, 3,000 patients from centers in 38 countries were potentially eligible for the HRQL study: 994 on AC→T, 1,009 on AC→TH, and 997 on TCH.

HRQL Compliance and Baseline Results

Compliance rates for HRQL questionnaires were $>90\%$ at baseline, $>80\%$ at midpoint, $>75\%$ at EOC, and remained $>72\%$ at 12 months with no major differences between arms (Table 1). No significant differences were found by geographic region (data not shown). Baseline HRQL scores were also similar across treatment arms (Fig. 2).

PF, GHS, SE, and Future Perspectives Change Scores

The change score findings for the four scales of interest are presented in Figure 3. PF was slightly worse at midpoint for TCH compared with patients just starting their taxane on AC→TH, but otherwise similar between arms, with recovery seen by 12 months. PF change scores were -5.8 for AC→T, -5.1 for AC→TH, and -7.2 for TCH at midpoint ($p = .005$ AC→TH vs. TCH); -10.0 , -8.9 , and -9.0 at EOC (not significant); and -1.8 , -1.6 , and -0.5 at 12 months (not signifi-

Table 1. Health-related quality-of-life questionnaire compliance rates by treatment and assessment

Assessment	AC→T (n = 994)	AC→TH (n = 1,009)	TCH (n = 997)
Baseline	912/994 (91.8)	919/1,009 (91.08)	928/997 (93.08)
Midpoint (9 wk, cycle 4)	783/970 (80.7)	846/1,005 (84.2)	827/981 (84.3)
End of chemotherapy	732/957 (76.5)	763/997 (76.5)	795/977 (81.4)
12-month follow-up	610/841 (72.5)	687/920 (74.7)	702/919 (76.4)

Data are received/eligible patients (%).

Abbreviations: AC→T, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel for four cycles; AC→TH, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel with trastuzumab for 1 year; TCH, docetaxel plus carboplatin for six cycles with trastuzumab for 1 year.

Figure 2. Baseline health-related quality-of-life scores. **(A):** Mean European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 scores at baseline. Data for single items of dyspnea, constipation, diarrhea, and sleep disturbance are not shown. **(B):** Mean EORTC BR-23 scores at baseline. Data for side effects of systemic therapy and upset by hair loss are not shown.

Abbreviations: AC→T, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel for four cycles; AC→TH, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel with trastuzumab for 1 year; TCH, docetaxel plus carboplatin for six cycles with trastuzumab for 1 year.

cant). These findings were supported by both imputed data analyses, which suggest that recovery at 12 months is significantly improved in the TCH arm.

Not surprisingly, GHS deteriorated mildly on chemotherapy, but patients reported improved GHS by 12 months. There were no significant differences in GHS change scores between treatment arms. GHS change scores for AC→T, AC→TH, and TCH were -7.1 , -5.2 , and -6.9 at midpoint (not significant);

-8.8 , -8.4 , and -6.6 at EOC (not significant); and 3.7 , 2.8 , and 4.2 (not significant) at 12 months, respectively. These findings were similar in both imputed data analyses.

SE change scores revealed worsening HRQL equally in all arms by midpoint, with less deterioration in the TCH arm by EOC, and again, recovery in all arms by 12 months. SE change scores were 26.6 , 25.0 , and 25.3 at midpoint (not significant); 28.8 , 25.2 , and 20.4 at EOC ($p = .001$ AC→T vs. AC→TH; $p < .001$ AC→T

Figure 3. Mean change in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BR23 scores. **(A):** Mean change from baseline in physical functioning scale. Higher score represents better physical functioning. **(B):** Mean change from baseline for global health scale. Higher score represents better global health. **(C):** Mean change from baseline in systemic side effects. Lower scores represent fewer side effects. **(D):** Mean change from baseline for future perspectives scale. Higher scores represent less worry about health in the future.

Abbreviations: AC→T, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel for four cycles; AC→TH, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel with trastuzumab for 1 year; EOC, end of chemotherapy; FU, follow-up; Mid, 9 weeks (cycle 4); TCH, docetaxel plus carboplatin for six cycles with trastuzumab for 1 year.

vs. TCH and AC→TH vs. TCH); and 4.3, 5.2, and 3.7 (not significant) at 12 months. A more rapid recovery in the TCH arm at both EOC and 12 months was supported by the imputed data analyses.

Future change scores were similar between arms and tended to improve at each time point, even while patients were still on chemotherapy. Values ranged from 3.2 to 4.6, 3.3 to 5.6, and 10.7 to 13.2 at midpoint, EOC, and 12 months, respectively, across treatment arms. The findings were similar with both imputed data analyses.

HRQL Response Analysis

Results of the HRQL response analysis are summarized in Figure 4. There were similar percentages of patients improving in PF, GHS, SEs, and future perspectives on each arm. There was a greater percentage of patients with worsening PF on the AC→T arm compared with the TCH group (39.0%, 35.3%, and 31.8% for AC→T, AC→TH, and TCH, respectively; $p < .002$ AC→T vs. TCH). Similarly, there was a trend toward a difference in the percentage of patients with worsening GHS on AC→T vs. TCH ($p < .019$), with rates of 33.8%, 32.9%, and 28.5% for AC→T, AC→TH, and TCH, respectively. The percentage of patients whose condition worsened based on SE change scores was less for the TCH group than for either anthracycline-containing arm (71.3%, 67.9%, and 56.8% for AC→T, AC→TH, and TCH, respectively; $p < .0001$ AC→T vs. TCH and AC→TH vs. TCH). No statistically significant differences were seen between arms in the response analysis of future perspectives.

Repeated Measures Analysis

On the basis of the repeated measures model, which gains power by including all follow-up assessments, the TCH group re-

ported significantly better PF, GHS, and SE follow-up means than the AC→T group and the AC→TH group. Although the model results suggest a strong overall treatment difference during the follow-up period, the random slopes model suggests that the difference may be more temporal, centered around the later cycles and the end of treatment period. For future perspectives, the means for all three groups were comparable.

DISCUSSION

The international phase III BCIRG 006 trial and other adjuvant trastuzumab trials have confirmed the safety and efficacy of trastuzumab-chemotherapy combinations for early breast cancer [3–6]. In the BCIRG 006 trial, two distinct trastuzumab-containing regimens, with and without an anthracycline base, demonstrated improved survival compared with AC→T, with a more favorable safety profile for the TCH regimen [6]. Although safety and efficacy data are imperative to the decision-making process, they do not fully reflect how patients experience the regimens. HRQL studies allow patients with breast cancer and their oncologists to better assess the risks and benefits of each adjuvant treatment option [15].

Our study is the first published HRQL analysis of trastuzumab in combination with chemotherapy in the adjuvant setting, demonstrating tolerable HRQL outcomes for each arm. A consistent pattern was seen across arms, with deterioration in PF, GHS, and (even more so) SE over the course of chemotherapy. Over time, recovery from chemotherapy-related deterioration occurred in each arm. Patients on the TCH arm had earlier deterioration in PF at the midpoint assessment and had less deterioration in SEs by EOC,

Figure 4. Health-related quality-of-life (HRQL) response analysis. (A): Proportion of patients whose HRQL improved by at least 10 units. (B): Proportion of patients whose HRQL worsened by at least 10 units.

Abbreviations: AC→T, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel for four cycles; AC→TH, doxorubicin plus cyclophosphamide for four cycles followed by docetaxel with trastuzumab for 1 year; TCH, docetaxel plus carboplatin for six cycles with trastuzumab for 1 year.

whereas the response analysis showed that fewer patients on the TCH arm had clinically important deterioration in PF or SEs.

The importance of including HRQL measures in clinical trials is clear, yet HRQL analyses present many challenges, including issues with compliance and bias that result from loss of data [16, 17]. In contrast to many other multicenter trials, there was low loss to follow-up and low loss of data overall, with no differences across treatment arms or between centers involved. The limited loss of data, combined with comparable results from sensitivity analyses involving imputed data, allowed for robust analyses of HRQL outcomes.

As with other measures of clinical benefit, HRQL is a subjective assessment and therefore susceptible to bias. Although not yet proven when these patients were receiving their treatment, it is now widely known that trastuzumab-chemotherapy combination regimens improve adjuvant treatment efficacy among patients with breast cancer [3–6]. Thus, a potential limitation of our unblinded study is that patients knew whether they were receiving trastuzumab [4]. However, mean change scores for future perspectives for patients in our study were positive and continued to improve throughout treatment and follow-up on each arm, regardless of receipt of trastuzumab therapy. This suggests that knowledge of type of treatment did not affect patient outlook in this study. We speculated that outlook improved more as a function of treatment progression, reflecting ongoing psychological processes in coming to terms with diagnosis, coping with fear of treatment, and realizing that chemotherapy is tolerable [18, 19].

A challenging aspect of the design of this HRQL study was accounting for the differences in planned regimen cycle totals between the anthracycline-containing regimens (eight) and TCH (six). A pragmatic decision was made a priori since we could not eliminate this difference. To standardize the timing of assessment, EOC was defined as the end of cycle 6 for the TCH arm and the beginning of cycle 7 for patients receiving AC→T or AC→TH. Therefore, when patients on the TCH arm completed all six cycles of chemotherapy, patients on the AC→T and AC→TH arms were midway through their docetaxel ± trastuzumab phase of therapy. This method of assessment may have introduced bias in favor of the anthracycline regimens, as these patients had completed fewer docetaxel cycles at EOC assessment. It also might have introduced bias in favor of TCH, as these patients had completed their last cycle of chemotherapy and may have begun to recover from the acute toxicities. Alternatively, we may have considered a time point when all treatment arms had completed their chemotherapy. However, TCH patients would have been even further out from their chemotherapy and well into recovery from acute toxicities, possibly introducing even more bias in favor of the TCH arm. As there was no perfect solution, a pragmatic approach was taken and this limitation is acknowledged.

HRQL was examined before, during, and after adjuvant treatment, including measures of systemic therapy side effects. HRQL compliance and baseline scores were comparable across treatment arms. Although patients experienced toxicity from each of the adjuvant regimens, all recovered well after chemotherapy. PF scores were lower at midpoint for patients receiving TCH, but were otherwise similar between arms. This initial lowering in HRQL may be explained by side effects associated with docetaxel treatment, [20–22] as patients on the TCH arm had earlier exposure to docetaxel compared with those on the AC→TH arm.

Although anthracyclines have long been standard therapy in the adjuvant breast cancer setting, the significant risk of cumulative cardiac and marrow toxicities limit its long-term use [23–28]. The nonanthracycline TCH regimen resulted in better side effect change scores at EOC and by response analysis, with less acute and cardiac toxicity, suggesting that TCH is better tolerated than the anthracycline-based regimens [6, 29]. These results may also reflect, in part, the shorter duration of the TCH therapy compared with anthracycline-based trastuzumab and taxane treatment. On all arms, patients' HRQL recovered from deterioration in PF, GHS, and SE by 1 year after completion of chemotherapy.

CONCLUSIONS

Our study is the first published HRQL analysis comparing adjuvant anthracycline and taxane-based chemotherapy, with or without trastuzumab, and has demonstrated comparable outcomes overall. Previous work has shown improved efficacy with trastuzumab for HER2-positive patients [4], with significantly better safety with a nonanthracycline-based regimen [6]. These additional findings of significant improvements in patient-reported SE change scores at EOC, and less clinically important deterioration in PF and SEs, support TCH as a more tolerable alternative to anthracycline-trastuzumab based adjuvant therapies.

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DISCLOSURES

Wolfgang Eiermann: Roche (C/A); **Nicholas J. Robert:** Genentech (RF); **John Crown:** Sanofi, Roche (H, RF); **Miguel Martin:** Roche, Amgen (C/A); **Tamas Pinter:** Amgen, Roche (C/A); **Mei-Ching Liu:** Sanofi (H); **Jean-Marc Ferrero:** Sanofi, Roche (C/A); **Dave P. Miller:** ICON Clinical Research, which receives research funding from Genentech (E); **Deepa Lalla:** Genentech (E); Roche (OI); **Dennis Slamon:** Novartis (C/A); Novartis, Sanofi-Aventis (H); Amgen (OI). The other authors reported no financial relationships.

C/A: Consulting/advisory relationship; RF: Research funding; E: Employment; H: Honoraria received; OI: Ownership interests; IP: Intellectual property rights/inventor/patent holder; SAB: scientific advisory board

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