The Breast 22 (2013) S3–S7

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Personalized adjuvant therapies: Lessons from the past
The opening address by the St. Gallen 2013 award recipient

Aron Goldhirsch [a, b, c, *]

[a] Department of Medicine, European Institute of Oncology, Via Ripamonti 435, Milan 20141, Italy
[b] International Breast Cancer Study Group (IBCSG), Bern, Switzerland
[c] Medical Oncology, Ospedale Regionale di Lugano, Lugano, Switzerland

Keywords:
Primary Breast Cancer
Breast Cancer Treatment Guidelines
St. Gallen Breast Cancer Consensus
Breast Cancer: Optimal Primary Therapy

A B S T R A C T

For several decades, personalized adjuvant therapies have been prescribed based on features that predict response to specific types of treatment. In this summary four specific issues regarding adjuvant therapies are described. Each one developed using information from past experience and is ready to be challenged by future findings from clinical trials and maturation of follow-up data. 1) Accuracy of determination of steroid hormone receptors and of HER2-status was the key feature in International Breast Cancer Study Group (IBCSG) and Breast International Group (BIG) trials. 2) Investigations on ovarian function suppression in IBCSG clinical trials led to the design of two trials (SOFT and TEXT), which are likely to lead to improved adjuvant therapy for premenopausal women with breast cancer. 3) Data from the BIG 1–98 trial of letrozole vs tamoxifen for postmenopausal patients with endocrine-responsive breast cancer provided information on which patients might obtain increased benefit from aromatase inhibitors and which might achieve similar treatment outcome with tamoxifen alone. 4) Finally, low-dose, frequently administered cytotoxics (metronomic chemotherapy) were tested in advanced disease with surprisingly favorable disease control and very low incidence of side effects. Personalized treatments are likely to improve substantially with increasingly accurate determination of their targets and by using risk- and toxicity-modulated therapies.

Targeting the estrogen receptor

The International Breast Cancer Study Group (IBCSG) began in 1978 as the Ludwig Breast Cancer Study Group (LBCSG) under the sponsorship of the Ludwig Institute for Cancer Research (LICR). At that time, Dr. Elwood Jensen was the Scientific Director of the LICR and a strong supporter of the Group. Dr. Jensen, who died in 2012 at the age of 92, is best known for his discovery of the estrogen receptor. Recognizing the technical and interpretive challenges of assaying for the estrogen receptor, Dr. Jensen insisted that all pathology laboratories from centers enrolling patients into LBCSG clinical trials had to be certified to perform estrogen receptor assessments. Drs. Craig Jordan and David Zava were recruited to establish a quality assurance program for group members [1–3]. Funds were provided for pathologists to attend every annual meeting of the Group, and to participate in workshops designed to standardize estrogen receptor assays and reporting of results. With this early groupwide initiative it is not surprising that the IBCSG clinical trials reviewed below produced substantial evidence that the presence or absence of estrogen receptor in the primary tumor was a major determining factor that can be used to select appropriate adjuvant therapy. Proficiency testing and quality control of pathology laboratories remains critically important today to optimize clinical trial results and provide proper treatment for individual patients.

IBCSG trial III

This trial was designed in the mid-seventies, when standard treatment for postmenopausal patients was surgery alone. The experimental questions were: does endocrine therapy with low-dose prednisone (p) plus tamoxifen (T) given for one year improve treatment outcome compared with observation alone? Similarly, does chemo-endocrine therapy (CMFp + T) given for one year improve outcome, compared with observation alone [4]?

463 postmenopausal breast cancer patients age 65 or younger with node-positive disease were entered from 1978 through 1981. At 26 years' median follow-up, CMFp + T provided a significantly

* Department of Medicine, European Institute of Oncology, Via Ripamonti 435, Milan 20141, Italy
E-mail address: aron.goldhirsch@ibcsg.org.

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http://dx.doi.org/10.1016/j.breast.2013.07.001

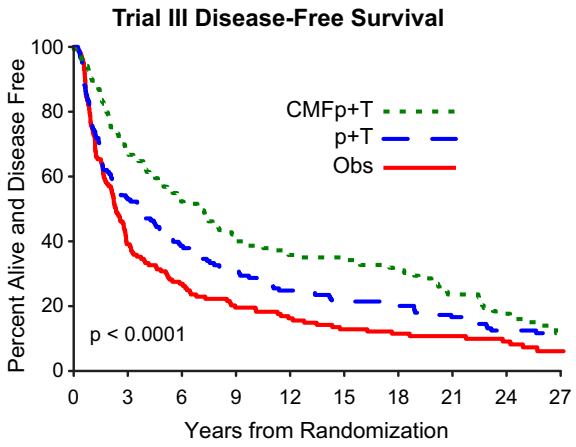

Fig. 1. Trial III in postmenopausal, node-positive breast cancer: disease-free survival at 27 years median follow-up.

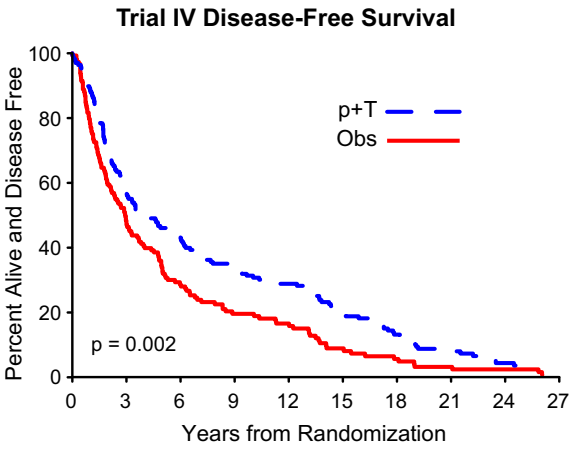

Fig. 3. Trial IV in postmenopausal, node-positive breast cancer for patients 66–80 years old at trial entry: disease-free survival at 27 years median follow-up.

better disease-free survival (DFS) compared with endocrine therapy alone (p + T) or with no adjuvant therapy (Obs) (Fig. 1). Overall survival (OS) was also better for CMFp + T compared with p + T or Obs. For the 156 patients with estrogen receptor (ER)-positive tumors, the results of CMFp + T and p + T were similar. For the 82 patients with ER-negative tumors, CMFp + T was superior to p + T and to Obs (Fig. 2 A and B).

IBCSG trial IV

This trial, also designed in the mid-seventies, was the parallel study for older patients (above the age of 65), for whom chemotherapy was not an attractive adjuvant therapy at that time. The research question was similar to the one of Trial III: does endocrine therapy with low-dose prednisone (p) plus tamoxifen (T) for one year improve outcome compared with observation only? 320 older postmenopausal patients (aged 66–80 years) with node-positive breast cancer were entered from 1978 through 1981 [4,5]. At 26 years' median follow-up, most of these older patients have died. One year of endocrine therapy (p + T) prolonged DFS and OS for this elderly population (Fig. 3). This effect was seen entirely in the subpopulation with ER + tumors.

IBCSG trial II

Amenorrhea has been studied in trials of the IBCSG since the first generation of trials accruing patients from 1978. Ovarian ablation was tested asking the following research question: does the addition of oophorectomy (Ox) to adjuvant chemotherapy plus prednisone (CMFp) improve outcome in premenopausal breast cancer patients with four or more positive axillary nodes? 327 eligible premenopausal patients with breast cancer in four or more positive axillary nodes were entered from 1978 through 1981 [6]. At 27 years' median follow-up there is no DFS or OS advantage for patients oophorectomized before receiving adjuvant CMFp compared with those given CMFp alone. CMFp was administered for the duration of 12 months. There was a trend for DFS benefit (p = 0.07) for those who received oophorectomy among the 107 patients with ER-positive disease (Fig. 4).

IBCSG trial VIII

Trial VIII compared the long-term efficacy of ovarian function suppression (OFS) with the GnRH agonist, goserelin, to chemotherapy, and the sequential combination of both for pre/perimenopausal women with lymph node-negative breast cancer. From March 1990 through October 1999, after stratification by ER status and radiotherapy plan, 1063 patients were randomly assigned to receive (a) goserelin for 24 months (n = 346), (b) six courses of "classical" CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy (n = 360), or (c) six courses of "classical" CMF followed by 18 months of goserelin (CMF→goserelin; n = 357). During the first year of accrual patients were also randomized to observation after surgery (n = 49), but this arm was discontinued.

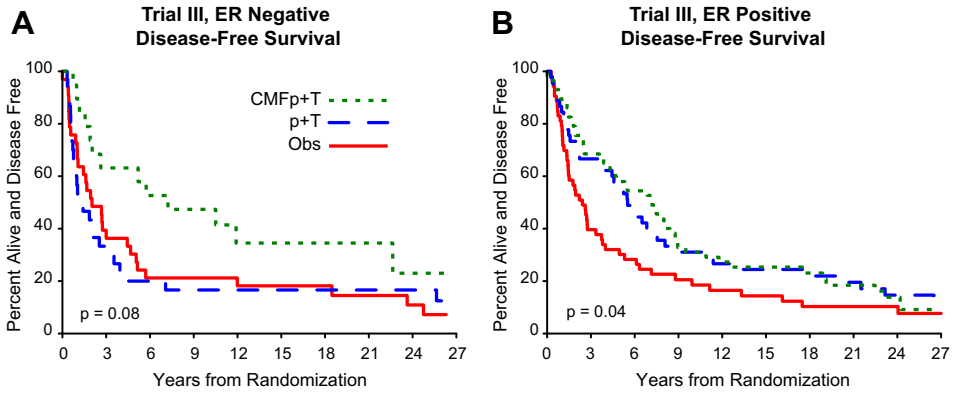

Fig. 2. Trial III in postmenopausal, node-positive breast cancer: disease-free survival at 27 years median follow-up. A. ER-negative disease. B. ER-positive disease.

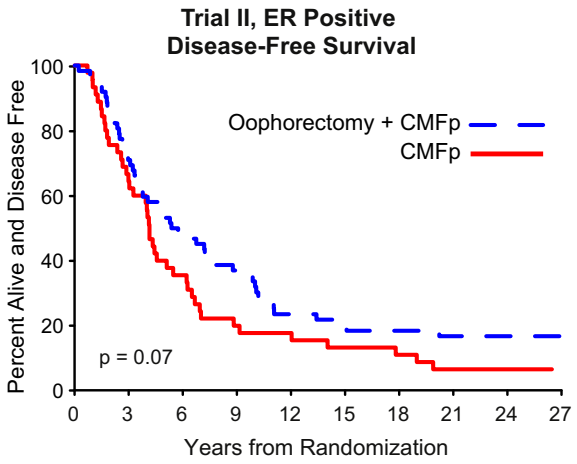

Fig. 4. Trial II in premenopausal, node-positive ≥4 breast cancer: disease-free survival at 27 years median follow-up, ER-positive disease.

Tumors were classified as ER-negative (19%), ER-positive (80%), or ER-unknown (1%), based on central review. 19% of patients were 39 years old or younger. Results have been updated to 12 years' median follow up [7]. For patients with ER-positive disease, chemotherapy alone and goserelin alone achieved similar DFS (12-year DFS = 69% and 68%, respectively), whereas sequential therapy (12-year DFS = 77%) provided a statistically significant benefit compared with either modality alone ($p = 0.04$ for both comparisons), due largely to the significant results for the younger patients. Patients with ER-negative tumors who received treatments that included CMF had better DFS (12-year DFS for CMF = 67%; and 12-year DFS for CMF → goserelin = 69%) than if they received goserelin alone (12-year DFS = 61%, p = NS). Patterns of amenorrhea were analysed by age (39 years or younger and 40 years or older) and by treatment group from time of randomization. Fig. 5 A and B illustrate the timing to menstrual cycle suppression by proportion of patients in each treatment arm of the trial.

None of the treatments included in this trial are considered to be a standard of care today, but the meticulous study of timing to ovarian function suppression from this trial led to the conclusion that each of the treatments has a lag time from treatment start to achieving OFS, that if reduced, could provide additional treatment benefit from this form of endocrine therapy. Future plans include the introduction of a GnRH antagonist (Degarelix acetate, Ferring, Switzerland), which does not cause flare and leads to a very fast downregulation of gonadotropins causing a rapid drop of sex hormones production in the gonads.

IBCSG trial 13–93

An additional piece of information on the composition of adjuvant endocrine therapy for premenopausal women with breast cancer was provided by trial 13–93. This trial had two research questions, but the one which relates to endocrine therapy was: does tamoxifen maintenance following chemotherapy improve outcome? 1246 assessable premenopausal patients with node-positive disease entered the trial between 1993 and 1999, 735 with ER+ disease and 511 with ER- disease [8]. A DFS advantage in favor of tamoxifen was seen in the ER+ cohort (Fig. 6 A and B). Interesting was the observation among the 332 patients with ER+ disease in the tamoxifen group: amenorrhea was associated with a better treatment outcome compared with no amenorrhea (Fig. 7). These retrospective results await confirmation from the prospective trial, SOFT, which, together with the TEXT trial, investigates endocrine therapies in premenopausal women with breast cancer (Fig. 8A: trials SOFT and TEXT). These include the question of OFS with tamoxifen (vs. tamoxifen alone) and the question of aromatase inhibitor vs. tamoxifen, both together with ovarian function suppression (Fig. 8 B and C).

IBCSG trial 18–98/BIG 1–98

IBCSG Trial 18–98 (BIG 1–98) was designed to compare endocrine therapy with letrozole × 5 years with tamoxifen × 5 years for postmenopausal patients with endocrine-responsive early breast cancer. Additionally, the trial compared the sequences of adjuvant endocrine therapy (letrozole followed by tamoxifen vs. tamoxifen followed by letrozole) with a continuous course of a single endocrine agent for the same duration of 5 years.

BIG 1–98 is an intergroup trial coordinated by the IBCSG. Patient accrual was from March 1998 to May 2003 with 8010 patients

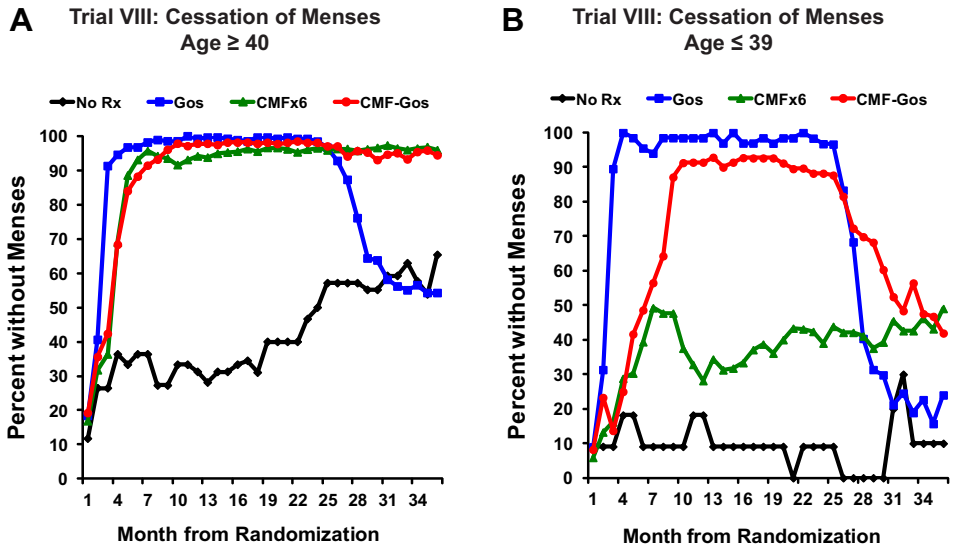

Fig. 5. Trial VIII: cessation of menses among patients undergoing either no treatment, or treatment with goserelin, or CMF chemotherapy, or CMF chemotherapy followed by goserelin. A. Patients age ≥40 years. B. Patients age ≤39 years.

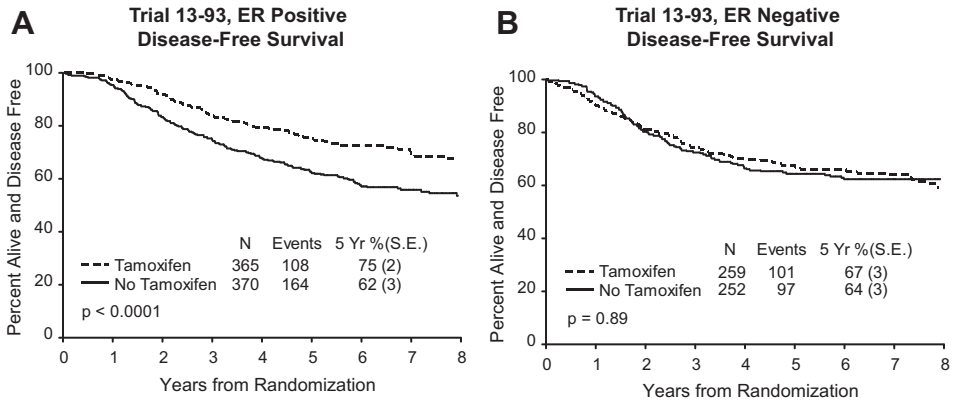

Fig. 6. Trial 13-93: premenopausal patients with node-positive disease who underwent chemotherapy before the randomized allocation to tamoxifen or no tamoxifen. Disease-free survival at 8 years median follow-up. A. ER-positive disease. B. ER-negative disease.

included [9,10]. At a median follow-up of 8.7 years, five years of letrozole after surgery significantly improved both DFS and OS. The central pathology review had determined ER, PgR, HER2 over-expression/amplification, and Ki-67 staining in samples from 6363 trial patients.

Composite risk profile in the sequential treatment population

We sought to determine whether these centrally-determined features (ER, PgR, HER2 over-expression/amplification, and Ki-67 LI), alone or in combination with other prognostic features, predicted the magnitude of letrozole effectiveness compared with either sequence or tamoxifen monotherapy, and to examine whether clinical and pathological features can identify patient groups for whom it is important for a five year program to include exclusively or some aromatase inhibitor therapy. This analysis was based on the database used for the primary outcome of the sequential treatments at 71 months median follow-up. Individually, none of the biomarkers significantly predicted differential treatment effects among the treatment groups. Subpopulation Treatment Effect Pattern Plot (STEPP) analysis of a composite measure of prognostic risk, which was based on an individual's number of involved lymph nodes, tumor grade, tumor size, presence of peritumoral vascular invasion as determined by local pathology, plus age and the four centrally-assessed tumor biomarkers, revealed three patterns of treatment effects. Patients at highest risk did best when treated with 5 years of letrozole; any of the three letrozole-containing regimens was acceptable for those patients in an intermediate risk range; whereas patients at lowest risk did similarly well with letrozole monotherapy, a sequence of letrozole and tamoxifen, or tamoxifen monotherapy. Thus, in BIG 1–98 the principle of composite assessment of risk, analogous to the clinical practice of integrating multiple risk factors, informs treatment selection better than individual biomarkers and supports the choice of five years of letrozole for patients at the highest risk for recurrence, while patients at lowest composite risk score may be treated with tamoxifen alone without compromising efficacy [11].

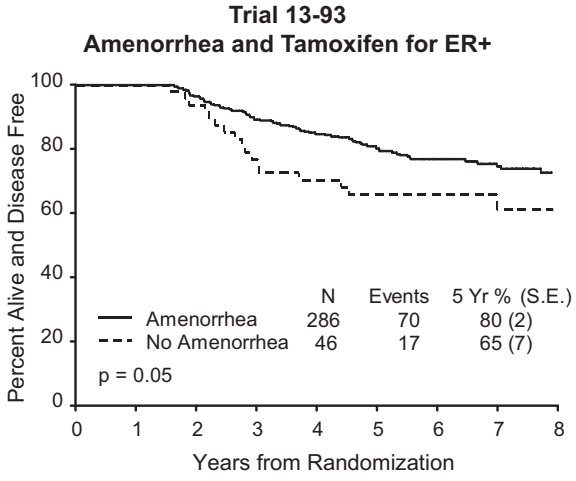

Fig. 7. Trial 13-93: disease-free survival by amenorrhea (amenorrhea versus no amenorrhea) in the cohort of patients who received tamoxifen.

Metronomic therapies

The frequent administration of cytotoxics at doses significantly less than the MTD reduces the level of toxicity and has demonstrated efficacy in cancer and metastases. It is likely that this form of treatment targets stroma, neoplastic vasculature, and the immune system in addition to tumor cells.

The experience with the first metronomic combination of cyclophosphamide and methotrexate (CM) included 153 patients with advanced breast cancer who had been heavily pretreated. Response or stable disease (for longer than 12 months) were observed in 15.7% of patients [12]. An adjuvant trial has been conducted for women with endocrine non-responsive disease who underwent surgery and standard chemotherapy. Patients were randomized to receive either CM × 12 months or no further treatment. 1086 patients entered this trial (IBCSG 22–00) from 2000 to 2012. Follow up of the enrolled patients is continuing.

Several trials in the neoadjuvant setting were conducted with one or more metronomic components to assess efficacy and tolerance. One such trial included patients with T2-T4a-d, ER and PgR negative, HER2 negative or any ER and PgR with HER2-positive breast cancer [13]. 47 patients were treated preoperatively and all underwent surgery after completion of the neoadjuvant treatment program. This consisted of 4 courses of 3-weekly epirubicin, cisplatin and continuous infusion of 5-fluorouracil (low dose), the ECF regimen, followed by weekly paclitaxel plus metronomic cyclophosphamide. Patients with HER2 positive disease also received trastuzumab. Patients with endocrine-responsive disease had OFS, if indicated, plus letrozole. 44 out of 47 patients (93.6%) had a complete remission or a partial remission (95% CI, 82.4–98.6%). The pathological complete remission (pCR) rate was 57% (27 out of 47 patients). The pCR rate in the HER2-positive and HER2-

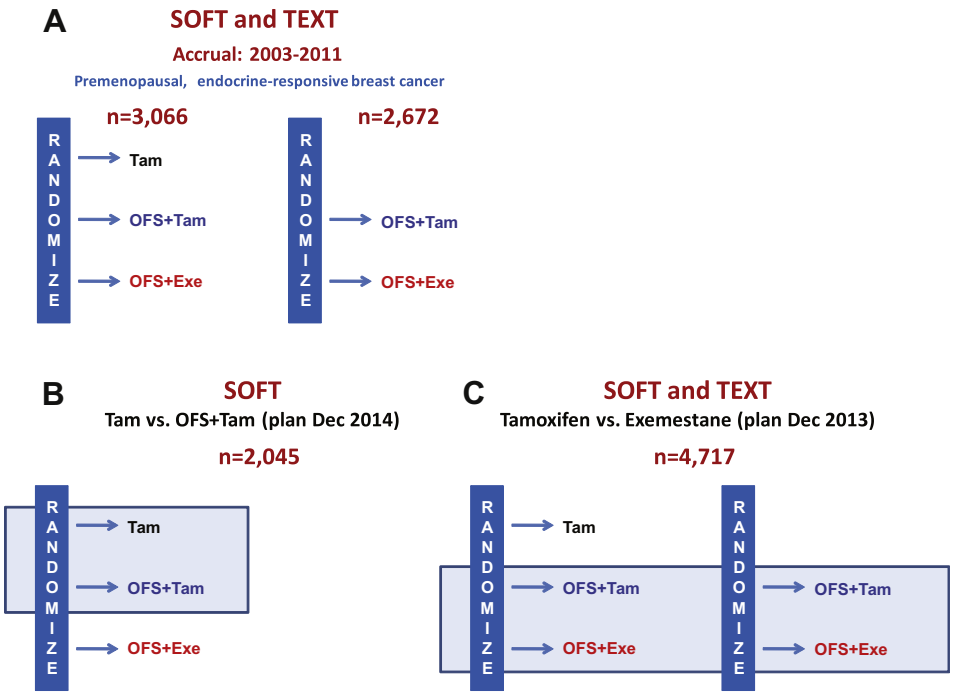

Fig. 8. Study designs of two trials, SOFT and TEXT, in premenopausal patients with endocrine-responsive breast cancer.

negative cohorts were similar. This example of a relatively small trial illustrates the very high efficacy of this combination and its low degree of toxic effects.

The low burden of personal costs to the patients and the possibility to continue the low dose treatment for a period of several months support the use of metronomic chemotherapy as an additional therapeutic tool especially in the adjuvant setting. IBCSG trial 22–00 will provide useful results for this specific type of treatment.

Conclusions

Lessons from the past illustrate the importance of accurate determination of the target, proper selection of endocrine therapies for premenopausal and postmenopausal women and especially improved selection of patients for newer endocrine treatments. New ways to administer cytotoxics may provide excellent treatment efficacy at relatively low personal costs for patients.

Conflict of interest statement

There are no conflicts of interest to declare.

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