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REVIEW

Ovarian suppression in combination endocrine adjuvant therapy in premenopausal women with early breast cancer

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Abstract
Purpose The benefits of adding ovarian suppression to either tamoxifen or aromatase inhibitors as adjuvant breast cancer therapy in premenopausal women are controversial. Therefore, we performed a systematic literature review and meta-analysis of relevant randomized trials.
Methods We identified and combined four qualifying trials reporting disease-free survival (DFS) and overall survival (OS) using meta-analysis.
Results Combining ABCSG-12, SOFT, and TEXT studies, there were 65 fewer DFS events (HR 0.89, 95% CI 0.57–1.39) but 30 more deaths for ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen (HR 1.31, 95% CI 0.93–1.84, $P = 0.12$, $\tau = 0.03$, heterogeneity, $P = 0.18$). DFS and OS were more concordant for combined SOFT and E-3193 findings; for ovarian suppression plus tamoxifen compared to tamoxifen alone, there were 24 fewer DFS events (HR 0.83, 95% CI 0.67–1.07, $P = 0.09$, $\tau^2 = 0$) and 14 fewer deaths (HR 0.76, 95% CI 0.53–1.07). The SOFT Estrogen Substudy demonstrated inconsistent estrogen suppression with combined ovarian suppression and aromatase inhibitor.
Conclusion Given the discordance between DFS and OS and inconsistent estrogen suppression with ovarian suppression plus aromatase inhibitor, adding aromatase inhibitor to ovarian suppression as adjuvant therapy in premenopausal women is premature.

Keywords Breast cancer · Ovarian suppression · Aromatase inhibitor · Tamoxifen · Premenopausal · Gonadotropin-releasing hormone agonists

Introduction

Several randomized trials provide evidence on the benefits and harms of adding ovarian suppression using gonadotropin-releasing hormone (GnRH) agonists to tamoxifen or aromatase inhibitors in premenopausal women with early-stage breast cancer: the Suppression of Ovarian Function Trial (SOFT) [1], Tamoxifen and EXemestane Trial (TEXT) [2], the Austrian Breast Cancer Study Group (ABCSG-12) [3], and the Eastern Cooperative Oncology Group 3193 (E-3193) [4]. However, differences have emerged regarding how findings from these trials should inform clinical practice. Guidelines from the American Society of Clinical Oncology (ASCO) [5], the National Comprehensive Cancer Network (NCCN) [6], and the St Gallen International Expert Consensus [7] tend to follow the recommendations of the SOFT and TEXT investigators [2], namely that premenopausal women at higher recurrence risk may be offered ovarian suppression combined with either tamoxifen or aromatase inhibitor. Nonetheless, some have raised concerns regarding the addition of ovarian suppression to aromatase inhibitors [8–10], while others recommend combining ovarian suppression with aromatase inhibitor only with serial monitoring of endocrine changes [11].

In combined analyses of the SOFT and TEXT trials, disease-free survival was significantly greater with ovarian

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suppression plus aromatase inhibitor than with ovarian suppression plus tamoxifen (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.60–0.85, $P < 0.001$) [2]. In contrast, in the ABCSG-12 trial, no disease-free survival difference was seen between ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen (HR 1.13, 95% CI 0.88–1.45, $P = 0.34$). The combined SOFT and TEXT trials demonstrated no difference in overall survival between the two treatments (HR 1.14, 95% CI 0.86–1.51, $P = 0.37$), while the ABCSG-12 trial demonstrated significantly greater overall survival with ovarian suppression plus tamoxifen compared to ovarian suppression plus aromatase inhibitor (HR 1.63, 95% CI 1.05–2.52) [8].

There are study design differences among these trials, including differences in the aromatase inhibitor studied, chemotherapy used, timing of endocrine therapy initiation, and duration of intervention and follow-up. However, given the discordant clinical findings, we sought to re-examine the evidence pertaining to adding ovarian suppression to endocrine therapy in premenopausal women with hormone receptor-positive, early-stage breast cancer.

Methods

We conducted a meta-analysis of randomized clinical trials addressing adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer. Only randomized controlled studies were included (phase II or III); articles were excluded if they were non-comparative studies, abstract reports only, or published in a non-English language. The recent ASCO guideline addressing adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer conducted a literature search on PubMed through June 24, 2015 using the keywords "breast cancer," "ovarian function suppression," "tamoxifen," and "aromatase inhibitor" [5]. We updated the PubMed search, using the same keywords, from June 25, 2015 through July 1, 2016. The ASCO guideline search yielded four studies. Our updated search identified 683 reports (675 after removing duplicates); 54 of these were reviewed as being of potential relevance. Only two full-text manuscripts were assessed for eligibility, which were excluded as secondary analyses. Therefore, our analysis incorporated the same four trials included in the ASCO guideline [5].

Information on type of adjuvant therapy and disease-free survival and overall survival findings were extracted from the trials for the examined comparisons using the HR and 95% CI. Because significant heterogeneity was found in one of the meta-analyses we performed, the more conservative random effects method was used to estimate the combined relative risk for studies [12]. A random effects model weighs studies according to the inverse of their within-study variance and also incorporates between-study variance [13, 14]. Analyses were performed using Open MetaAnalyst.

Study designs differed among the ABCSG-12, SOFT, TEXT, and E-3193 trials [1–4] (Fig. 1). In the ABCSG-12 trial, goserelin was used for ovarian suppression. Anastrozole was the aromatase inhibitor, the comparison group was ovarian suppression plus tamoxifen, and only neoadjuvant chemotherapy was allowed. The endocrine therapy duration was 3 years, and a definition of premenopausal status was not provided. In the TEXT trial, ovarian suppression approaches included the GnRH agonist triptorelin, bilateral oophorectomy, or ovarian radiation. Exemestane was the aromatase inhibitor, the comparison group was ovarian suppression plus tamoxifen, and chemotherapy was allowed and was started concurrently with triptorelin. The endocrine therapy duration was 5 years, with premenopausal status defined as regular menses during the prior 6 months and/or estradiol level in the premenopausal range.

In the SOFT trial, patients who received chemotherapy before randomization were eligible if post-chemotherapy estradiol level was in the premenopausal range. Otherwise, premenopausal status was defined as in the TEXT trial. Endocrine therapy duration was 5 years and exemestane was the aromatase inhibitor. In addition to the ovarian suppression plus exemestane and the ovarian suppression plus tamoxifen groups, the SOFT trial included a tamoxifen-only group. The E-3193 trial involved a comparison of tamoxifen plus ovarian suppression to tamoxifen alone for 5 years' duration. Chemotherapy was not permitted. Premenopausal status was defined as a menstrual period within the past 6 months or age less than 55 years with estradiol in the premenopausal range.

Results

Combining findings from the ABCSG-12, SOFT, and TEXT trials [2, 3], use of ovarian suppression plus aromatase inhibitor resulted in 65 fewer disease-free survival events compared to ovarian suppression plus tamoxifen (350 events in 3246 women vs. 415 events in 3247 women, respectively, HR 0.89, 95% CI 0.57–1.39, $P = 0.62$, $\tau^2 = 0.09$, heterogeneity $P < 0.01$). In contrast, 30 more deaths were seen with ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen (155 deaths in 3249 women vs. 125 deaths in 3244 women, respectively, HR 1.31, 95% CI 0.93–1.84, $P = 0.12$, $\tau^2 = 0.03$, heterogeneity $P = 0.18$) (Fig. 2).

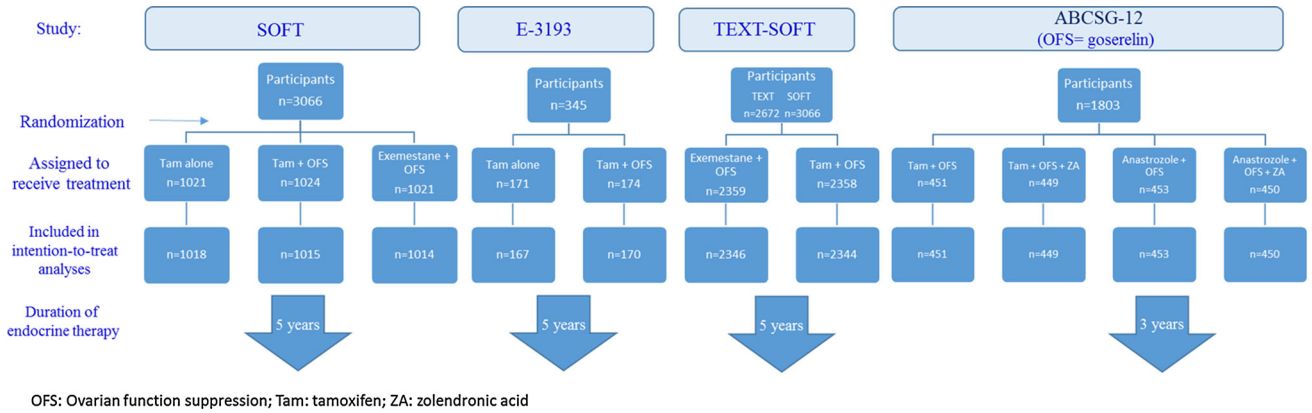


Fig. 1 Overall design of studies included in meta-analyses

Combining findings from the SOFT and E-3193 trials for ovarian suppression plus tamoxifen versus tamoxifen alone reveals better concordance between disease-free survival and overall survival [1, 4]. While the findings were not statistically significant, there were 24 fewer disease-free survival events with ovarian suppression plus tamoxifen compared to tamoxifen alone (160 disease-free survival events in 1185 women vs. 184 disease-free survival events in 1185 women, respectively, HR 0.83, 95% CI 0.67–1.03, $P = 0.09$, $\tau^2 = 0$, heterogeneity $P = 0.94$). Similarly, there were 14 fewer deaths with ovarian suppression plus tamoxifen compared to tamoxifen alone (58 deaths in 1185 women vs. 72 deaths in 1185 women, respectively, HR 0.76, 95% CI 0.53–1.07, $P = 0.12$, $\tau^2 = 0$, heterogeneity $P = 0.78$) (Fig. 2).

Discussion

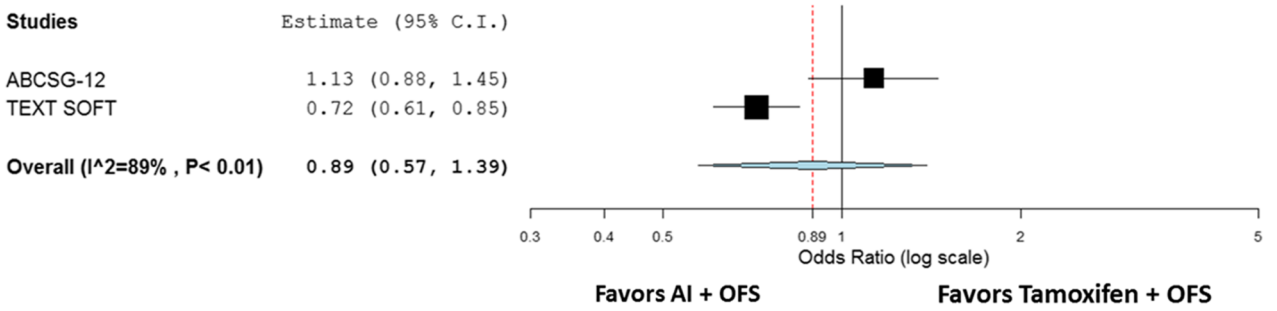
It has been established that absent or minimal ovarian estrogen production is required in order for aromatase inhibitors to be effective. However, the question remains whether long-term estrogen suppression with GnRH agonists is sufficient to support aromatase inhibitor efficacy in premenopausal women. Review of the discordant clinical results among the three randomized trials evaluating ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen, combined with the suboptimal ovarian suppression in these trials, suggests that it is premature to recommend an ovarian suppression plus aromatase inhibitor combination as adjuvant breast cancer therapy in premenopausal women.

When the disease-free survival and overall survival results are examined in the SOFT, TEXT, and ABCSG-12 trials comparing ovarian suppression plus aromatase inhibitor to ovarian suppression plus tamoxifen, there were 65 fewer disease-free survival events but 30 more deaths with ovarian suppression plus aromatase inhibitor. Even though numbers are small, fewer deaths in the group with fewer disease-free survival events would be expected, especially in a young premenopausal population at low risk for other causes of death. A re-analysis of the SOFT and TEXT results found the greatest absolute benefit for ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen on 5-year breast cancer-free interval in those at the highest composite recurrence risk [15]. This finding makes the disease-free survival and overall survival discordance even more difficult to explain as almost all the deaths, at least in those two trials, occurred in the high recurrence risk chemotherapy subgroup [2, 16].

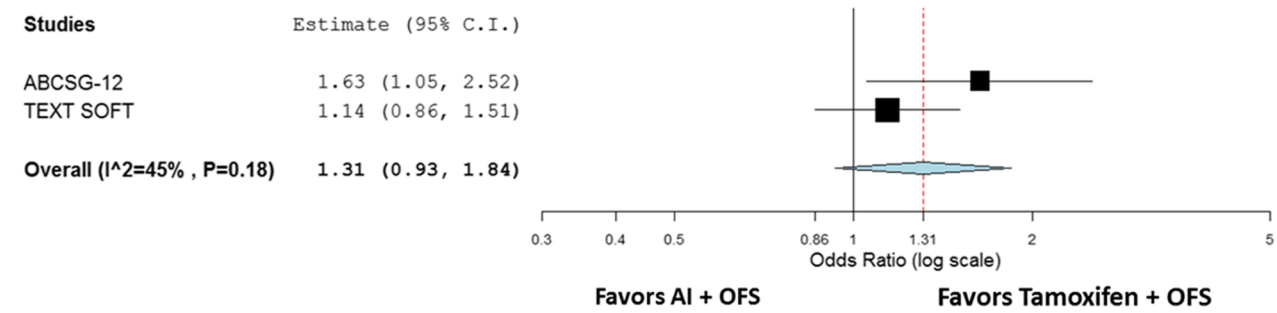
The discordant clinical findings for disease-free survival and overall survival when comparing ovarian suppression plus aromatase inhibitor to ovarian suppression plus tamoxifen could represent the play of chance in a small sample, but emerging information from the ABCSG-12 and SOFT Estrogen Substudy (SOFT-EST) [17] supports an alternative interpretation. In the ABCSG-12 trial, in secondary analyses, overweight and obese women in the ovarian suppression plus aromatase inhibitor group had a threefold increase in their risk of death compared to women in the ovarian suppression plus tamoxifen group (HR 3.03, 95% CI 1.35–6.82, $P = 0.004$) [18], suggesting greater difficulty achieving estrogen suppression in that population. Supporting this hypothesis are findings from studies examining estrogen suppression with aromatase inhibitors. In one such study, 68 postmenopausal breast cancer patients, 28 of whom were obese, were treated with adjuvant anastrozole or letrozole. After 3 months of aromatase inhibitor use, BMI was positively associated with estradiol level ($r = 0.35$, $P = 0.05$), with higher BMI associated with less estradiol suppression [19]. Of direct relevance to the interpretation of trials of adjuvant endocrine therapy in premenopausal women are findings from the SOFT-EST. When estrogen levels were determined in a subset of 86 SOFT participants, where 45% of women were overweight

a

Disease-free Survival:

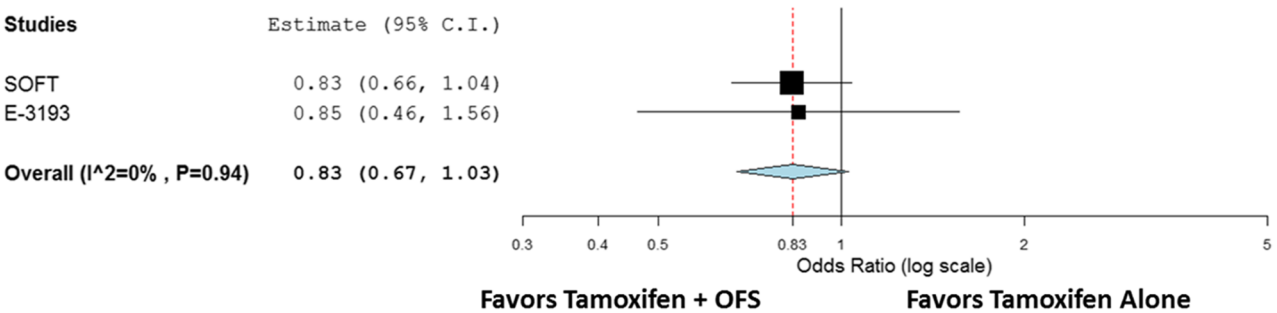


Overall Survival:

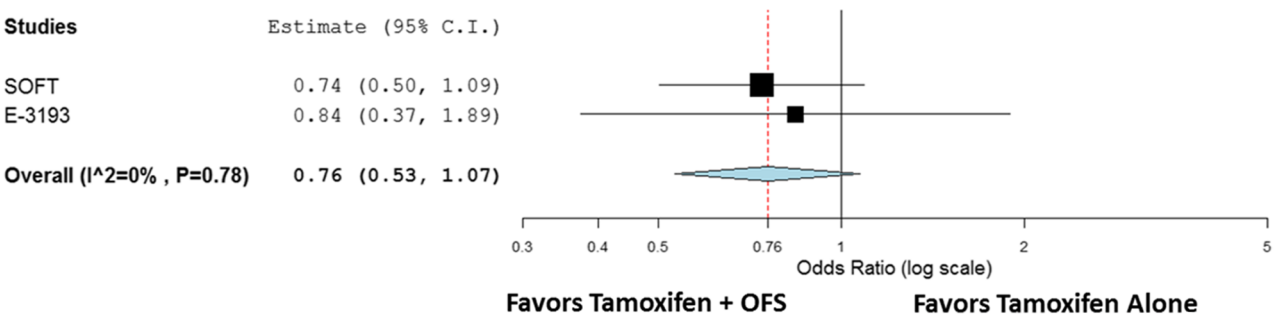


b

Disease-free Survival:



Overall Survival:



◀**Fig. 2** **a** Influence of ovarian suppression plus aromatase inhibitor (AI) compared to ovarian suppression plus tamoxifen on disease-free survival and overall survival. **b** Influence of ovarian suppression plus tamoxifen compared to tamoxifen alone on disease-free survival and overall survival

or obese, estradiol levels above the optimal target (2.72 pg/ml) were found in 25, 24 and 17% of ovarian suppression plus aromatase inhibitor users at 3, 6, and 12 months, respectively [17]. Thus, even in the short-term, a substantial proportion of women in the SOFT trial had estradiol levels higher than in postmenopausal women receiving aromatase inhibitors. Taken together, these findings bear special relevance for breast cancer patients in the US where 65% of adult women with breast cancer are overweight or obese [20].

Differences in study design do not appear to explain the observed differences in DFS when comparing the TEXT and SOFT results to the ABCSG-12 results. However, compared to the tamoxifen groups, the HR for overall survival in the aromatase inhibitor groups was greater than one in the combined SOFT and TEXT analysis and was significantly greater than one in the ABCSG-12 analysis.

The discordance between DFS and overall survival seen in the combined SOFT and TEXT results is puzzling. In ABCSG-12, the only trial where information on cause of death is available, nearly all deaths were breast cancer-related (only 4 of 88 total deaths occurred without prior recurrence) [8]. This is an expected result as younger premenopausal women have few competing causes of death. These findings indicate shorter survival after initial progression in the aromatase inhibitor plus ovarian suppression groups, perhaps reflecting subsequent therapy choices usually reserved for postmenopausal women. This hypothesis cannot be explored at this time as information on cancer therapy following disease progression is not available in these trials.

In the SOFT trial, there was a trend toward greater improvement in disease-free survival in the ovarian suppression plus aromatase inhibitor group for younger women ($\leq$35 years) at higher recurrence risk [2] and, in a combined SOFT and TEXT analysis, for women at higher recurrence risk [21]. However, information on overall survival in this subgroup has not been presented. In women with chemotherapy-induced amenorrhea, menopausal status cannot be reliably determined [10, 22] and these women are well documented to more commonly resume menstruation, especially when treated with aromatase inhibitors, which can stimulate ovarian function [22–24]. In this regard, Dowsett and colleagues [10] recently summarized mechanisms whereby GnRH analog use for ovarian suppression in premenopausal women could stimulate estradiol secretion via recovery of FSH levels, with stimulation of ovulation.

In ABCSG-12, a decrease in overall survival with ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen was not initially observed after 48 months follow-up but did emerge after longer follow-up, with the final report after 94 months follow-up [8]. In contrast, the median follow-up was 67 months in SOFT and 72 months in TEXT [22]. Thus, longer follow-up is needed before overall survival results from the SOFT and TEXT trials can be reliably interpreted.

The difficulty of achieving and maintaining optimal ovarian suppression with GnRH analogs has also been recognized by investigators from the Karolinska Institute [11]. Nonetheless, they endorsed adjuvant ovarian suppression plus aromatase inhibitor in younger, high recurrence risk premenopausal women only with serial monitoring of endocrine function [11]. However, the optimal method of estradiol monitoring is under debate and sensitive assays are not readily available [10]. Importantly, a single estradiol determination reflects present ovarian function but does not predict future ovarian function [19]. Because established monitoring protocols are not available, monitoring of endocrine function does not guarantee safety when using ovarian suppression plus aromatase inhibition in premenopausal women in the adjuvant setting.

There are alternative endocrine therapy strategies available other than ovarian suppression plus aromatase inhibitor in premenopausal, hormone receptor-positive breast cancer. Tamoxifen is proven to be effective in both high and low estrogen environments and serves as an effective adjuvant therapy in both premenopausal and postmenopausal women [25]. In the SOFT trial, when analyzed after adjustment for covariates, ovarian suppression plus tamoxifen significantly reduced breast cancer recurrence compared with tamoxifen alone (HR 0.75, 95% CI 0.59–0.96, $P = 0.02$) [1] and, while not statistically significant, there were fewer deaths in the ovarian suppression plus tamoxifen group. Current evidence from the SOFT [1] and E-3193 [4] trials suggests that ovarian suppression plus tamoxifen may be superior to tamoxifen alone, making this a reasonable combination to consider. Oophorectomy plus aromatase inhibitor avoids issues related to potential suboptimal estrogen suppression by GnRH analogs and provides a safe approach. In addition, oophorectomy among older premenopausal women and among those in the menopausal transition raises fewer concerns regarding the long-term health effects of estrogen deprivation.

In conclusion, the available evidence suggests that it is premature to recommend the routine use of ovarian suppression plus aromatase inhibitor as adjuvant therapy in premenopausal women with early-stage, hormone receptor-

positive breast cancer. The apparent discordance between disease-free survival and overall survival findings with ovarian suppression plus aromatase inhibitor may represent incomplete and/or intermittent estrogen suppression with GnRH analogs as seen in the SOFT-EST study. Given the relatively short follow-up of the SOFT and TEXT trials, longer follow-up is needed before reliable risks and benefits of ovarian suppression plus aromatase inhibitor as adjuvant therapy in premenopausal women can be determined.

Author contributions Drs. Chlebowski and Col had full access to the data and take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chlebowski, Col. Acquisition, analysis, or interpretation of data: Chlebowski, Col, Pan. Drafting of the manuscript: Chlebowski. Critical revision of the manuscript for important intellectual content: Col, Pan. Statistical analysis: Col. Administrative, technical, or material support: Chlebowski.

Compliance with ethical standards

Conflict of interest RTC has received speaker's fees and honorarium from Novartis and Genentech; honorarium for advisory boards and consulting for Novartis, Novo Nordisk, Pfizer, Genentech, Genomic Health and Amgen. NFC has received speaker's fees and honorarium from Janssen Scientific Affairs, Biogen, and research grants from Pfizer and Biogen (none related to breast cancer or the treatments discussed). KP reported no conflicts.

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