Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Appendix

Prevention of Early Menopause with Goserelin during Adjuvant Chemotherapy

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Section A1: Inclusion of Deaths and Hysterectomy/Oophorectomy as Failures

Because both death prior to 2 years and hysterectomy/oophorectomy preclude measurement of ovarian function status (and are therefore competing events for the primary endpoint of ovarian failure), both could reasonably be considered failures. These were not specified as events in the study protocol. Nonetheless, we conducted the following secondary analyses.

In the first analysis, we considered both ovarian failure (based on amenorrhea and FSH in the postmenopausal range) and death prior to two years as failures. Since all evaluable patients are at risk of death prior to 2 years, this analysis was conducted among all 218 evaluable patients. With deaths also counted as failures, the failure rate in the standard arm was 23% (26 of 113) and in the Goserelin arm was 8% (8 of 105; OR=0.25, 95% CI: 0.11-0.60, p=.002).

We also considered ovarian failure, death prior to two years, and hysterectomy or oophorectomy as failures. With deaths and hysterectomy/oophorectomy counted as failures, the denominator was 224 (an additional 6 cases added), and the failure rate on the standard arm was 24% (28 of 115) and in the goserelin arm was 11% (12 of 109; OR=0.34, 95% CI: 0.16-0.75, p=.007). Therefore the results under both approaches are consistent with the pre-specified primary endpoint result in the paper.

Section A2: Exploratory Sensitivity Analyses

Given that the components of the primary endpoint (amenorrhea and FSH level) are positively correlated, an exploratory sensitivity analysis was conducted to assess the risk of either absent menses for the 6 months prior to the year 2 assessment *or* elevated FSH at the year 2 assessment. Conceptually, this approach maximizes available information in the numerator, while maintaining a consistent set of patients. In the same 135 patients used for the primary analysis, we found that 31 patients (45%) on the standard arm and 13 patients (20%) on the goserelin arm had either amenorrhea or postmenopausal FSH at year 2. In multivariable analysis adjusting for stratification factors, this difference was highly statistically significant (OR=0.29, 95% CI: 0.12-0.70, p=.006).

In addition, amenorrhea and FSH data were available at year 1 after registration. Therefore we also examined the risk of either absent menses for the preceding 6 months or elevated FSH at either the year 1 or year 2 assessments. This analysis was designed to prioritize the year 2 data, but to also include the year 1 data if year 2 data were missing. Specifically, a failure was defined as amenorrhea in the six months prior to year 2, or FSH at year 2 in the postmenopausal range; or, if those data were missing, amenorrhea in the six months prior to year 1, or FSH at year 1 in the postmenopausal range. This approach can be conceived of as maximizing available information in both the numerator and denominator. In total, 177 patients had available data under this approach (81% of total evaluable patients). The results were consistent with the primary analysis, showing a benefit of goserelin over placebo (OR=0.43, 95% CI: 0.22-0.85, p=.01).

Section A3: Cumulative Incidence of Pregnancy

The pregnancy rates that are provided in the manuscript are proportions and do not take censoring into account. To account for the censoring patterns, we analyzed the cumulative incidence of pregnancy, representing a time-to-event endpoint that treats death as a competing risk. The figure below illustrates the results. The 5-year cumulative incidence of pregnancy was 13.4% for standard chemotherapy patients and 24.5% for patients receiving goserelin + chemotherapy. Using Gray's test, the p-value=.05 for the comparison.

Figure S1. Cumulative incidence of pregnancy