Site of recurrence after neoadjuvant therapy: Clues to biology and impact on endpoints

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Achieving a pathologic complete response (pCR) has been shown on the patient level to predict excellent long-term event-free survival outcomes. Residual cancer burden (RCB) quantifies the extent of residual disease for patients who did not achieve pCR. A propensity for the central nervous system (CNS), a known chemotherapy sanctuary site, as the site of first relapse was previously observed among the small number of relapses in patients achieving a pCR (Symmans et al 2017), raising the possibility that these CNS events may be independent of response in the breast. In this study, we evaluated the types and sites of recurrences by RCB classes in the I-SPY 2 TRIAL.

Methods

I-SPY 2 patients enrolled prior to 11/2016 across 9 experimental and control arms, with available RCB and event-free survival (EFS) data were included in this analysis. The median follow-up is 3.8 years. We summarized the EFS event type, further sub-dividing the distant recurrence events by their site of relapse (CNS-only, CNS and other sites, Non-CNS). We estimated the overall and site-specific distant recurrence incidence in each RCB class at 3 years using a competing risk (Fine-Gray) model. In addition, we assessed the association between RCB and distant recurrence free survival including all distant recurrences (DRFS), as well as excluding the CNS-only recurrences (non-CNS-DRFS) using a Cox model. Our statistics do not adjust for multiplicities beyond variables evaluated in this study.

Results

Incidence of CNS-only recurrences are low and are similar across RCB classes.

Conclusions

1. CNS-only recurrences are uncommon and similar across RCB groups
2. CNS is likely a sanctuary site and its involvement at first relapse appears independent of response
3. All RCB groups show increasing distant recurrence rates as RCB increases
4. Exclusion of CNS-only recurrences as an outcome event may improve association between neoadjuvant therapy response and DRFS
5. These findings support the use of RCB to identify patients with excellent outcome beyond those achieving pCR

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I-SPY TRIAL

Background

Inclusion criteria: Patients who are HER2+ may also receive trastuzumab (Herceptin)

Abbreviations: RCB, Response Criteria Based; pCR, pathologic complete response; RCB-0, RCB with pCR; RCB-I, RCB with pCR and ≤ 25% residual cancer burden; RCB-II, RCB with pCR and > 25% residual cancer burden; RCB-III, RCB with ≤ 25% residual cancer burden and no pCR.

Methods

I-SPY 2 TRIAL

I-SPY 2: A multicenter, phase 2 platform trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents and combinations in the neoadjuvant setting for women with high-risk primary breast cancer.

Inclusion criteria: Tumor Size ≥ 2.5cm, HR+ HER2- MammalPrint (MP) high risk or HR-HER2+ or HER2+.

Primary Endpoint: Pathologic complete response (pCR).

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of achieving a pCR.

Regimens may leave the trial for one of four reasons: Futility (< 10% probability of success); Maximum sample size (with probability of success ≥ 10% and < 85%); Graduation (≥ 85% predictive probability of success); or as recommended by the independent DSMB.

To date: 11 experimental regimens have been evaluated for efficacy

Results

Among 938 subjects, there were 180 EFS events, including 28 (16%) local recurrences (without distant recurrence and/or death) and 152 DRFS events.

Conclusions

1. CNS-only recurrences are uncommon and similar across RCB groups
2. CNS is likely a sanctuary site and its involvement at first relapse appears independent of response
3. All RCB groups show increasing distant recurrence rates as RCB increases
4. Exclusion of CNS-only recurrences as an outcome event may improve association between neoadjuvant therapy response and DRFS
5. These findings support the use of RCB to identify patients with excellent outcome beyond those achieving pCR

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