**BACKGROUND**

In women with breast cancer receiving neoadjuvant chemotherapy, residual cancer burden (RCB) predicts distant recurrence and survival. In those with high risk and locally advanced tumors, locoregional recurrence (LRR) remains a concern, often associated with type of local therapy received. We evaluated the impact of local therapy on LRR in the I-SPY2 TRL.

**TRIAL ELIGIBILITY & STUDY METHODS**

- **Clinical Eligibility Criteria**: Stage II or III, or T4, any N, MO, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supraclavicular lymph nodes are the only sites of metastases.
- **Molecular Eligibility Criteria**: Triple Negative, or HER2+, or MammaPrint
- **Data were analyzed in Stata 14.2, using Chi2 test, log rank test, and a Cox proportional hazards model**. Primary endpoint was LRR.
- **RCB** was considered a categorical variable (0/1 versus 2/3).
- Breast surgery categories were lumpectomy or mastectomy.

**ADVOCATE’S PERSPECTIVE**

This advocate highlights the importance of investigating new trials to discover emerging findings, including, in this case, safely undergoing less extensive surgery.

- Despite many trials showing no difference in distant recurrence and long-term survival, with breast conservation vs mastectomy, this study now allows even women with high risk tumors who have a good response to therapy, to feel confident in choosing lumpectomy in terms of LRR. RCB as one of two key determinants of LRR underscores that RCB is a reliable biomarker for long-term outcomes. We need to continue to work to get all women to an RCB of 0/1.

**I-SPY2’S ADAPTIVE TRIAL DESIGN**

I-SPY2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate a series of novel agents when added to standard neoadjuvant therapy for women with high-stage IB/II breast cancer (Figure 1). Within each patient subtype, participants are assigned to one of several investigational therapies or the control regimen (4:1). Randomization probabilities are weighted with high probability of achieving a pCR within each subtype for each agent and adapts over the course of the trial. The primary endpoint is pathologic complete response (pCR, no residual disease in breast or locoregional nodes) at surgery.

The goal is to identify/generate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial, defined by HR+ HER2 status & MammaPrint (MP). Regimens may leave the trial for one of four reasons: Graduate, Drop for futility (<5% probability of success), Drop for safety issues, or accruing maximum sample size (10%< probability of success <85%).

**LOCAL THERAPY**

- **TRIAL ELIGIBILITY & STUDY METHODS**
  - **Eligibility Criteria**: Stage II or III, or T4, any N, MO, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supraclavicular lymph nodes are the only sites of metastases.
  - **Molecular Eligibility Criteria**: Triple Negative, or HER2+, or MammaPrint
  - **Data were analyzed in Stata 14.2, using Chi2 test, log rank test, and a Cox proportional hazards model**. Primary endpoint was LRR.
  - **RCB** was considered a categorical variable (0/1 versus 2/3).
  - Breast surgery categories were lumpectomy or mastectomy.

**ADVOCATE’S PERSPECTIVE**

This advocate highlights the importance of investigating new trials to discover emerging findings, including, in this case, safely undergoing less extensive surgery.

- Despite many trials showing no difference in distant recurrence and long-term survival, with breast conservation vs mastectomy, this study now allows even women with high risk tumors who have a good response to therapy, to feel confident in choosing lumpectomy in terms of LRR. RCB as one of two key determinants of LRR underscores that RCB is a reliable biomarker for long-term outcomes. We need to continue to work to get all women to an RCB of 0/1.

**I-SPY2’S ADAPTIVE TRIAL DESIGN**

I-SPY2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate a series of novel agents when added to standard neoadjuvant therapy for women with high-stage IB/II breast cancer (Figure 1). Within each patient subtype, participants are assigned to one of several investigational therapies or the control regimen (4:1). Randomization probabilities are weighted with high probability of achieving a pCR within each subtype for each agent and adapts over the course of the trial. The primary endpoint is pathologic complete response (pCR, no residual disease in breast or locoregional nodes) at surgery.

The goal is to identify/generate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial, defined by HR+ HER2 status & MammaPrint (MP). Regimens may leave the trial for one of four reasons: Graduate, Drop for futility (<5% probability of success), Drop for safety issues, or accruing maximum sample size (10%< probability of success <85%).

**LOCAL THERAPY**

- **TRIAL ELIGIBILITY & STUDY METHODS**
  - **Eligibility Criteria**: Stage II or III, or T4, any N, MO, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supraclavicular lymph nodes are the only sites of metastases.
  - **Molecular Eligibility Criteria**: Triple Negative, or HER2+, or MammaPrint
  - **Data were analyzed in Stata 14.2, using Chi2 test, log rank test, and a Cox proportional hazards model**. Primary endpoint was LRR.
  - **RCB** was considered a categorical variable (0/1 versus 2/3).
  - Breast surgery categories were lumpectomy or mastectomy.

**ADVOCATE’S PERSPECTIVE**

This advocate highlights the importance of investigating new trials to discover emerging findings, including, in this case, safely undergoing less extensive surgery.

- Despite many trials showing no difference in distant recurrence and long-term survival, with breast conservation vs mastectomy, this study now allows even women with high risk tumors who have a good response to therapy, to feel confident in choosing lumpectomy in terms of LRR. RCB as one of two key determinants of LRR underscores that RCB is a reliable biomarker for long-term outcomes. We need to continue to work to get all women to an RCB of 0/1.

**I-SPY2’S ADAPTIVE TRIAL DESIGN**

I-SPY2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate a series of novel agents when added to standard neoadjuvant therapy for women with high-stage IB/II breast cancer (Figure 1). Within each patient subtype, participants are assigned to one of several investigational therapies or the control regimen (4:1). Randomization probabilities are weighted with high probability of achieving a pCR within each subtype for each agent and adapts over the course of the trial. The primary endpoint is pathologic complete response (pCR, no residual disease in breast or locoregional nodes) at surgery.

The goal is to identify/generate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial, defined by HR+ HER2 status & MammaPrint (MP). Regimens may leave the trial for one of four reasons: Graduate, Drop for futility (<5% probability of success), Drop for safety issues, or accruing maximum sample size (10%< probability of success <85%).

**LOCAL THERAPY**

- **TRIAL ELIGIBILITY & STUDY METHODS**
  - **Eligibility Criteria**: Stage II or III, or T4, any N, MO, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supraclavicular lymph nodes are the only sites of metastases.
  - **Molecular Eligibility Criteria**: Triple Negative, or HER2+, or MammaPrint
  - **Data were analyzed in Stata 14.2, using Chi2 test, log rank test, and a Cox proportional hazards model**. Primary endpoint was LRR.
  - **RCB** was considered a categorical variable (0/1 versus 2/3).
  - Breast surgery categories were lumpectomy or mastectomy.

**ADVOCATE’S PERSPECTIVE**

This advocate highlights the importance of investigating new trials to discover emerging findings, including, in this case, safely undergoing less extensive surgery.

- Despite many trials showing no difference in distant recurrence and long-term survival, with breast conservation vs mastectomy, this study now allows even women with high risk tumors who have a good response to therapy, to feel confident in choosing lumpectomy in terms of LRR. RCB as one of two key determinants of LRR underscores that RCB is a reliable biomarker for long-term outcomes. We need to continue to work to get all women to an RCB of 0/1.