LIV-1 Expression in Primary Breast Cancers in the I-SPY 2 TRIAL

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Background

LIV-1 is an estrogen-inducible gene that has been implicated in epidermal-to-mesenchymal transition (EMT) in preclinical models of progression and metastasis. Its expression is associated with node-positivity in breast cancer; and has been detected in a variety of cancer types, including estrogen receptor positive breast cancers. SGN-LIV1A is a novel antibody drug conjugate targeting LIV-1 that is currently being evaluated in the I-SPY 2 TRIAL. In this pilot study, we evaluated LIV-1 levels by IHC within HR/HER2/MammaPrint (MP) defined subtypes among patients screening for the I-SPY 2 TRIAL and its correlation to microarray assessed LIV-1 expression levels.

I-SPY 2 TRIAL

I-SPY 2: Phase 2 platform trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents when added to standard neoadjuvant therapy for women with high-risk stage II/III breast cancer

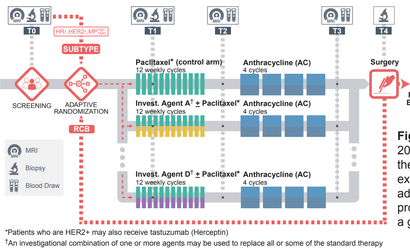
Inclusion criteria: Tumor Size ≥ 2.5cm; HR+HER2- MammaPrint (MP) high risk or HR-HER2- or HER2+.

Primary Endpoint: Pathologic complete response (pCR).

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of increased pCR rate if tested in a neoadjuvant 300-patient phase 3 trial within a (graduating) signature defined by HR, HER2 and MP.

Regimens may leave the trial for one of four reasons: Graduate, Drop for futility (< 10% probability of success), Drop for safety issues, or accruing maximum sample size (10%< probability of success <85%).

To date: 10 experimental regimens have been evaluated for efficacy



*Patients who are HER2+ may also receive tastuzumab (Herceptin)
†An investigational combination of one or more agents may be used to replace all or some of the standard therapy

Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

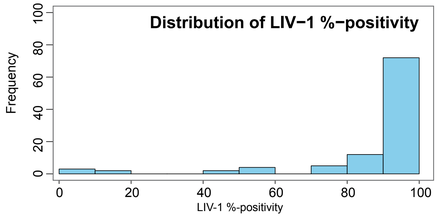
Methods

Pilot Study: LIV-1 IHC staining was performed by Quest Diagnostics on the pre-treatment samples of 100 patients screening for the I-SPY 2 TRIAL. Pre-treatment expression data generated on a custom Agilent 44K platform was also available. We summarized the LIV-1 H-Scores and percent (%)-positivity across the population and within HR/HER2/MP subtypes; and we assessed the Pearson correlation between LIV-1 H-Score and LIV-1 gene expression levels.

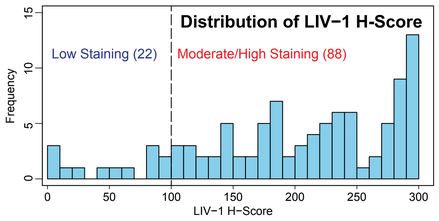
Leveraging the entire existing I-SPY 2 population: We also compared the pre-treatment LIV-1 mRNA expression levels within HR/HER2/MP subtypes across I-SPY 2 TRIAL patients from completed arms and their relevant controls (n=989) using ANOVA and post-hoc Tukey tests. Our statistics are descriptive rather than inferential; and does not take into account multiplicities of other biomarkers outside of this study.

LIV-1 IHC Staining

Of the 100 patients evaluated, 98 have LIV-1 %-positivity > 0; and 47 have 100% LIV1 positivity.



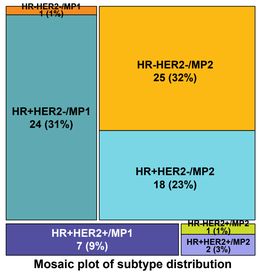
The median LIV-1 H-Score is 220; and 88% of patients have moderate/ high LIV-1 staining (with H-Score≥100).

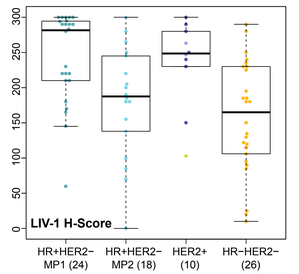


LIV-1 IHC Staining by Subtype

Of the 78 patients who proceeded onto the trial (and have known HR/HER2/MP status), 26 are triple negative, 42 are HR+HER2-, and 10 are HER2+.

- Due to our small sample size, we did not further subset the triple negative and HER2+ cases for analysis of H-Score; but within the HR+HER2- patients, 24 are MP1 compared to 18 who are MP2 class.

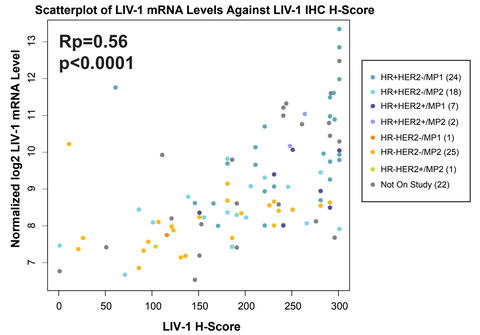




LIV-1 H-Score appears highest within the HR+HER2-MP1 cases (median: 282), followed by the HER2+ (median: 249), then the HR+HER2-/MP2 (median: 188), and HR-HER2- (median: 165) subtype.

Correlation between LIV-1 IHC and mRNA

LIV-1 H-score is significantly correlated with LIV-1 mRNA expression levels.



LIV-1 mRNA expression by Subtype

Consistent with these observations, LIV-1 pre-treatment mRNA expression levels are significantly higher in the HR+HER2-MP1 group relative to all other HR/HER2/MP defined subtypes (Tukey HSD p < 0.0001) across the entire I-SPY 2 TRIAL population.

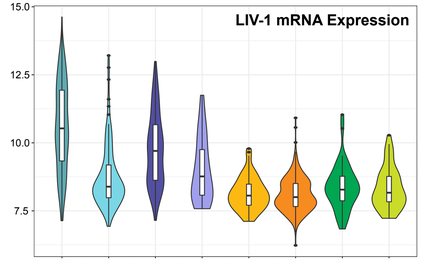


Figure: Distribution of pre-treatment LIV-1 mRNA expression levels across the I-SPY 2 TRIAL population (n=989) within HR/HER2/MP defined subtypes

The HR+HER2+MP1 group also have high LIV-1 expression levels.

Conclusions

Our result suggest that although LIV-1 expression differs by subtype, it is expressed at a moderate/high level in the majority of patients. The good correlation between IHC and array-based LIV-1 expression levels enables us to leverage the entire existing I-SPY 2 dataset and confirm the high rates of LIV-1 expression across the I-SPY 2 population. Further studies to evaluate LIV-1 expression as a biomarker of response to LIV-1 targeting therapies for the neoadjuvant treatment of breast cancer are warranted and ongoing in I-SPY 2.

Advocate's Perspective - Susie Brain

The positive results from the LIV-1 expression analysis shown here from breast cancer patients being screened for the I-SPY 2 TRIAL are encouraging. Furthermore, research has shown that a new antibody drug conjugate, known as SGN-LIV1A, can target LIV-1. This precision medicine approach is intended to kill cancer cells yet spare healthy ones. Currently, this agent is being evaluated in the I-SPY 2 TRIAL. Hopefully, this LIV-1 targeted drug will improve patient outcomes, produce fewer side effects, and provide scientists and clinicians with a reliable agent-biomarker pair for women diagnosed with aggressive estrogen-positive/Her2 negative breast cancer.

ACKNOWLEDGEMENTS:
With support from Quantum Leap Healthcare Collaborative, FNIH, NCI (Grant 28XS197 P-0518835, Safeway Foundation, William K. Bowes, Jr. Foundation, Breast Cancer Research Foundation, UCSF), the Biomarkers Consortium, Salesforce, Novella Clinical, CCS Associates, Berry Consultants, OHSU, and Give Breast Cancer the Boot. Initial support from IQVIA, Johnson & Johnson, Genentech, Amgen, San Francisco Foundation, Eli Lilly, Pfizer, Eisai Company, Side Out Foundation, Harlan Family, Avon Foundation for Women, Alexandria Real Estate Equities and Agendia. Sincere thanks to Anna Barker, our DSMB (Harold Burstein, Elizabeth Frank, Steven Goodman, Clifford Hudis, Robert Mass, Musa Meyer, Janet Wittes, Tiffany Traina and Deborah Laxague), Ken Buetow and CaBIG, our patients, advocates and investigators