Quantifying the Contribution of Doxorubicin and Cyclophosphamide (AC) to Pathologic Response Following Neoadjuvant Taxane Therapy: Analysis of the I-SPY TRIAL

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BACKGROUND

- Anthracyclines have been the backbone of breast cancer adjuvant therapy for decades
- Anthracyclines may result in long term effects for survivors including heart failure, secondary malignancy
- I-SPY 2 is a neoadjuvant trials where patients received 12 weeks of paclitaxel followed by doxorubicin and cyclophosphamide (AC)
- MRI and measurement of Functional Tumor Volume (FTV) was performed at multiple timepoints during therapy
- A subset of patients had an inter-regimen biopsy

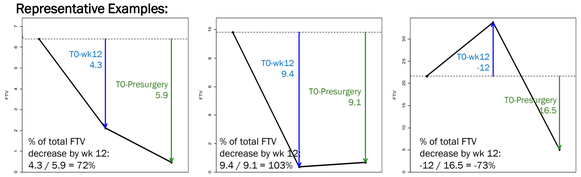
STUDY POPULATION

- Eligible patients for I-SPY2 had tumors that met one of the following criteria: Stage II or III, or T4, any N, M0, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supraclavicular lymph nodes are the only sites metastasis
- 1377 patients received paclitaxel +/- investigational agent followed by AC between 2010-2022 in I-SPY 2 had serial measurements of FTV
- Response Predictive Signatures were determined for 1374 patients (Wolf, et al. Cancer Cell 40:609 2022 PMID: 35623341)
- 150 patients received an inter-regimen biopsy
- Pathologic Complete Response (pCR) is the primary endpoint of I-SPY2 and was determined in all patients. Residual Cancer Burden (RCB) class was also determined.

METHODS

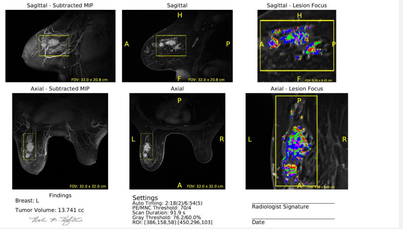
- Total FTV decrease was calculated between the pre-treatment and pre-surgical measurements
- Percent of total FTV decrease observed after 12 weeks of paclitaxel was calculated
- If <90% of occurred during 12 weeks of paclitaxel therapy, then pCR was attributed to AC

Representative Examples:



Assume FTV pre-surgery > baseline:
Fraction <1 : AC further decreases FTV. Smaller number implies AC contributes more. Negative for rare cases with FTV increase at Bw12 relative to baseline.
Fraction >=1 : FTV pre-surgery equals or greater than Bw12. AC does not further decrease FTV

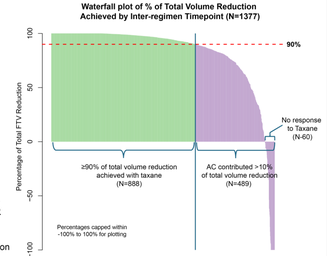
Functional Tumor Volume – FTV Measurement

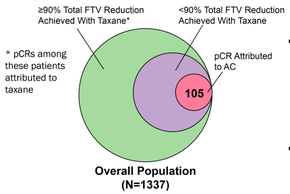


RESULTS

Measuring the Value of AC in I-SPY2: MRI FTV

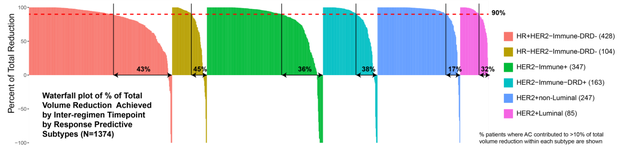
- % I-SPY2 patients where taxane regimen contributed to ≥90% of total FTV decrease = **64%**
- % I-SPY2 patients where AC contributed to >10% of total FTV decrease = **36%**
- % I-SPY2 patients with no response to taxane regimen = **4%**





- 105 (of 516 total) pCRs are observed among patients with <90% of total FTV decrease after taxane and are attributed to AC
- **Estimated % of patients with pCR from AC = 105 / 1337 = 8%**

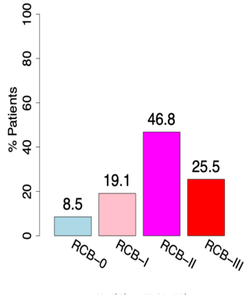
Value of AC By Response Predictive Subtype (RPS)



RESULTS

Measuring the Value of AC in I-SPY2: Biopsy

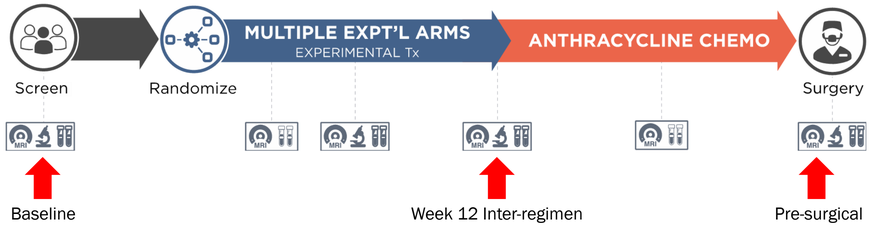
- 150 I-SPY 2 patients had a week 12 (inter-regimen) biopsy
- 63/150 (42%) had invasive cancer present in the 12-week biopsy
- Of the 63 patients with tumor present at 12 weeks, 47/63 (74%) received AC
- Of the 47 patients with tumor present at 12 weeks who received AC:
  - 4/47 = **8.5%** achieved pCR
  - (4 + 9) /47 = **28%** achieved RCB-0/I



CONCLUSIONS

- Serial measurement of FTV identifies tumors with excellent responses to paclitaxel-based therapy
- MRI FTV measurements attributed pCR rates from AC from 3-15%
  - Biggest benefit were in the Immune Positive and HER2+ (non-luminal) Response Predictive Subgroups
- Biopsy based measurements showed 8.5% (4/47) of patients achieved pCR after AC
- AC had low response rates in I-SPY2 and varied by RPS
- Discovery of more active regimens than AC is warranted

I-SPY2 DESIGN AND SERIAL MRI TIMEPOINTS



	N	≥90% Total Reduction Due to Taxane, N (%)	<90% Total Reduction Due to Taxane, N (%)	pCRs observed among <90% Reduction Group, N (of total pCRs)	Estimated % patients with pCR from AC	RCB-0/I observed among <90% Reduction Group, N (of total RCB-0/I)	Estimated % patients with RCB-0/I from AC
HR+HER2-Immune-DRD-	428	243 (57%)	185 (43%)	12 (of 43)	3%	26 (of 100)	6%
HR-HER2-Immune-DRD-	104	57 (55%)	47 (45%)	3 (of 25)	3%	9 (of 45)	9%
HER2-Immune+	347	223 (64%)	124 (36%)	53 (of 201)	15%	73 (of 256)	21%
HER2-Immune-DRD+	163	101 (62%)	62 (38%)	10 (of 76)	6%	24 (of 101)	15%
HER2+non-Luminal	247	205 (83%)	42 (17%)	24 (of 157)	10%	29 (of 183)	12%
HER2+Luminal	85	58 (68%)	27 (32%)	3 (of 14)	4%	4 (of 25)	5%

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