Site(s) of Initial Distant Recurrence after Neoadjuvant Therapy for Patients With High-Risk Early-Stage Breast Cancer (BC): Analysis of Data from the I-SPY2 Trial

LA Huppert[1], C Yau,[1] D Idossa[2], A Kahn[3], FM Howard[4], E Shagisultanova[5], A Zimmer[6], E Stringor-Reasor[7], J Perlmutter[8], D Yee[9], R Nanda[4], NM Hylton[1], F Symmans[10], R Shatsky[11], C Isaacs[12], L Van't Veer[1], HS Rugo[13], PR Pohlmann[10], AM DeMichele[14], L Pusztai[3], LJ Esserman[1]

1. University of California, San Francisco (UCSF), 2. Mayo Clinic 3. Yale School of Medicine 4. University of Chicago 5. University of Colorado 6. Oregon Health and Sciences University 7. University of Alabama 8. ISPY Advocacy Core 9. University of Minnesota 10. MD Anderson Cancer Center 11. University of California, San Diego 12. Georgetown University 13. City of Hope 14. University of Pennsylvania Cancer Center

BACKGROUND

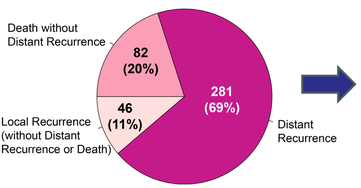
- The incidence of central nervous system (CNS) metastases varies with breast cancer (BC) subtype, but there is limited data about clinical and molecular predictors of CNS vs non-CNS recurrence risk after neoadjuvant chemotherapy (NACT).
- Here we present patterns of distant recurrence in the I-SPY2 trial.

METHODS

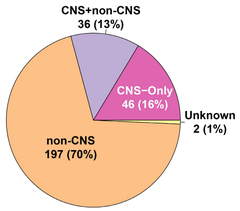
- This analysis includes 2112 patients with molecularly high-risk stage II and III BC (all subtypes) who enrolled in the I-SPY2 trial from 2010-2022 with event-free survival (EFS) data as of 7/29/25 (median f/u = 5 years).
- We analyzed type of recurrence (local vs distant) and site(s) of initial distant recurrence (CNS-only, both CNS- and non-CNS, or non-CNS only).
- We used a competing risk (Fine-Gray) model to estimate cumulative incidence of site-specific relapse at five years and assessed associations with clinical/molecular subtype, clinical staging (cT, cN), and response to NACT by Residual Cancer Burden (RCB) class.

RESULTS: Types and timing of EFS events

Types of event-free survival events (n=409, 19.4% study population)



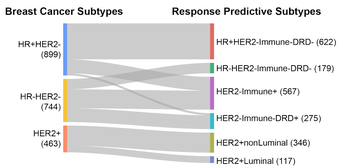
Types of initial distant recurrence events (n=281)



Timing of EFS events:

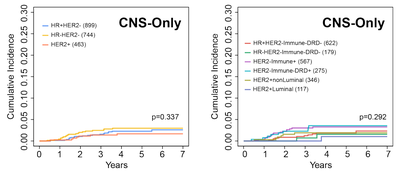
- In this molecularly-high risk population, most distant recurrence (DR) events occurred in the first three years post-surgery
- Most CNS recurrences (isolated or not) (63/82, 77%) also occurred within the first three years post-surgery

RESULTS: CNS-only recurrence by subtype



- Breast cancer subtype → Response Predictive Subtype data for patients in this cohort

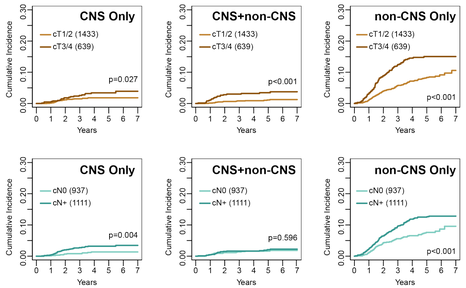
Cumulative incidence of initial CNS-only distant recurrence events by breast cancer and Response Predictive Subtypes



- Rates of CNS-only recurrence were low and similar across breast cancer subtypes (left) and Response Predictive Subtypes (right)

RESULTS: DR events by T, N status

Cumulative incidence of initial distant recurrence events by site by cT and cN status



- Incidence of distant recurrence increased in patients with larger tumors (top) and node positive disease (bottom) at both CNS- and non-CNS sites

SUMMARY TABLE AND CONCLUSIONS

	N	CNS only (n=46) Cum Inc at 5 yrs	p	CNS + non-CNS (n=36) Cum Inc at 5 yrs	p	non-CNS only (n=197) Cum Inc at 5 yrs	p
Breast Cancer Subtype			0.337		0.139		0.014
HR+HER2-	899	2%		1%		12%	
HR-HER2-	744	3%		3%		11%	
HER2+	463	2%		2%		6%	
Response Predictive Subtype			0.292		0.403		0.001
HR+HER2-Immune-DRD-	622	2%		1%		13%	
HR-HER2-Immune-DRD-	179	2%		3%		17%	
HER2-Immune+	567	3%		2%		8%	
HER2-Immune-DRD+	275	4%		2%		12%	
HER2+nonLuminal	346	2%		2%		7%	
HER2+Luminal	117	1%		1%		6%	
Clinical T			0.027		<0.001		<0.001
T1/2	1433	2%		1%		8%	
T3/4	639	3%		3%		15%	
Clinical N			0.004		0.596		0.001
cN-	937	1%		2%		8%	
cN+	1111	3%		2%		13%	
RCB Class			0.602		<0.001		<0.001
0	726	2%		1%		2%	
I	282	2%		0%		5%	
II	711	3%		3%		14%	
III	304	3%		4%		27%	

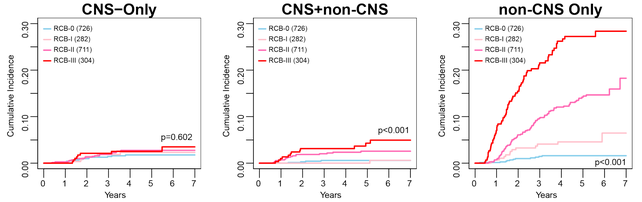
- In patients with molecularly high-risk stage II and III breast cancer who underwent NACT:
  - **The incidence of initial non-CNS events increased with increasing RCB class, whereas the incidence of initial CNS-only events was consistent across the four RCB classes**
  - The relative proportion of initial CNS-only recurrences was increased in patients with RCB 0/I vs. RCB II/III disease
  - Patients with larger tumors and node-positive disease had higher risk of both initial CNS and non-CNS recurrence; initial CNS recurrence risk increased across RCB classes for those with cTN3/4 and N+ disease
- These results support future research to identify biomarkers that predict CNS recurrence risk and incorporating CNS-penetrant therapies into early-stage therapy for high-risk patients

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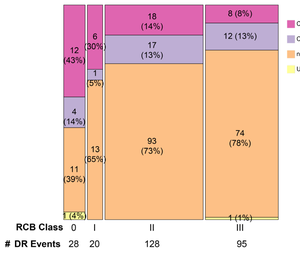
RESULTS: DR events by RCB status

Cumulative incidence of initial distant recurrence events by site by RCB status



- Rates of initial non-CNS recurrence increased with the amount of residual disease at surgery, with lowest rates in patients with RCB-0 (2%) and highest rates in patients with RCB-III (27%).
- Rates of initial CNS-only recurrence was low (2-3%) but remained similar across all RCB classes.
  - 38% (18/48) of initial DR events among RCB-0/I patients were CNS-only recurrences
  - 12% (26/233) of initial DR events among RCB-II/III patients were CNS-only recurrences
- There was a trend towards increasing initial CNS-only recurrence risk with higher T and N stage for patients with both RCB0/I and RCBII/III disease

Types of initial distant recurrence events by RCB class



Risk of initial CNS-only recurrence by RCB and cTcN status

	cT1/2cN0	cT3/4 or cN+	
RCB0/I	1%	2.8%	P=0.052
RCBII/III	1%	3.6%	P=0.055