Dynamics of breast cancer relapse reveal molecularly defined late recurring ER-positive subgroups: Results from the METABRIC study

Oscar M. Rueda, Stephen-John Sammut, Suet-Feung Chin, Jennifer L Caswell-Jin, Jose A Seoane, Maurizio Callari, Rajbir Batra, Bernard Pereira, Alejandra Bruna, H Raza Ali, Elena Provenzano, Bin Liu, Michelle Parisien, Cheryl Gillett, Steven McKinney, Andrew R. Green, Leigh Murphy, Arnie Purushotham, Ian O. Ellis, Paul D. Pharoah, Cristina Rueda, Samuel AJR Aparicio, Carlos Caldas, Christina Curtis

Disclosures

Scientific Advisory Board, Consultancy, Shareholder: GRAIL

Background: breast cancer recurrence

- While prognosis for early stage breast cancer (BC) has improved dramatically, 20-30% of patients recur with incurable disease
- Spatial and temporal patterns of relapse are unknown and difficult to predict
- A subset of women with early stage ER+ BC have a persistent risk of recurrence and death up to 20 years post-diagnosis (Pan et al. NEJM 2017)
- Critical need to identify tumor characteristics that are more predictive of risk of recurrence than standard clinical covariates (nodal status, tumor size, grade)

San Antonio Breast Cancer Symposium, December 4-8, 2018

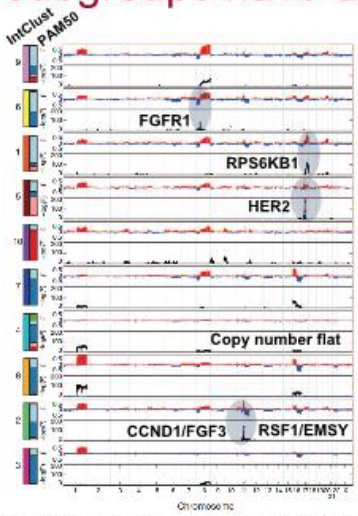
METABRIC Cohort Overview

- 3240 breast cancer patients derived from 5 tumor banks in the UK and Canada diagnosed between 1977-2005
- Genomic data on primary tumors from 1980 patients:
  - Copy Number, mRNA Expression (Curtis et al. *Nature* 2012)
  - miRNA Expression (Dvinge et al. *Nature* 2013)
  - Mutational profiles for 173 genes (Pereira et al. *Nature Comm* 2016)
- Long term clinical follow-up; median 14 years
- **Relapse: date of first relapse for all patients (n=1079/1980), dates and sites of every relapse for 57% of patients (n=618)**

This presentation is the intellectual property of the presenter. Contact **cncurtis@stanford.edu** for permission to reprint and/or distribute.

San Antonio Breast Cancer Symposium, December 4-8, 2018

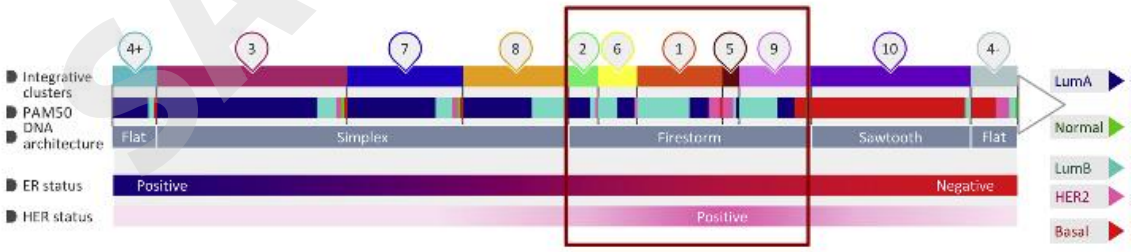
The integrative subgroups have distinct 'drivers'



Curtis et al. *Nature* 2012
Ali et al. *Genome* Bio 2014

San Antonio Breast Cancer Symposium, December 4-8, 2018

Mapping Integrative Subtypes



Russnes et al. *Am J Path* 2017

This presentation is the intellectual property of the presenter. Contact **cncurtis@stanford.edu** for permission to reprint and/or distribute.

Objectives

- To characterize the timing of distant relapse across the molecular subgroups of breast cancer
  - Immunohistochemical (IHC) subtypes - based on ER/HER2 expression
  - Intrinsic (PAM50) subtypes - based on gene expression
  - Integrative subtypes (IntClust) - based on copy number and gene expression
- To evaluate the utility of integrative subtypes relative to clinical covariates to predict late distant relapse in ER+/HER2- breast cancer

San Antonio Breast Cancer Symposium, December 4-8, 2018

Methods

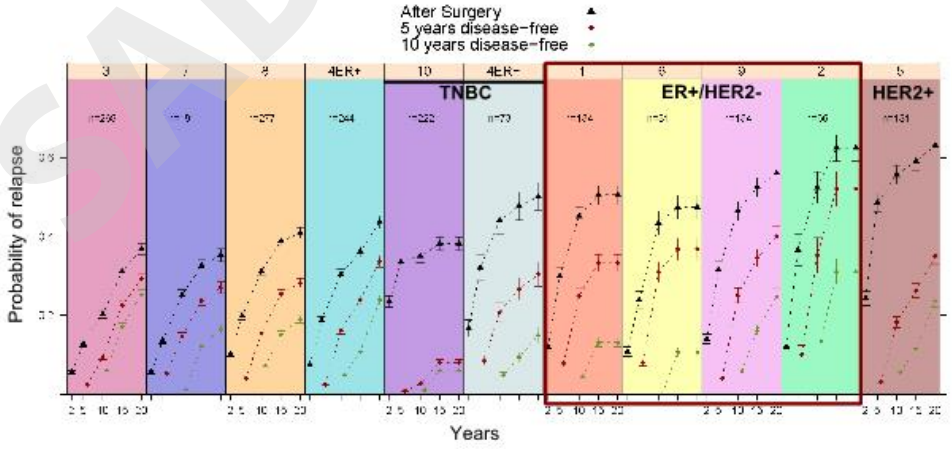
- We developed a multi-state (Cox-reset) model of breast cancer relapse allowing for competing risks, covariates and distinct baseline hazards
- We employ a 'base' clinical model accounting for:
  age, tumor size, grade, number of lymph nodes positives, time since surgery, time since loco-regional relapse
- Molecular subtype information (IHC, IntClust) can also be incorporated
- The utility of alternate models for predicting distant relapse was evaluated using the C-index in METABRIC and an external cohort (n=607 cases)

This presentation is the intellectual property of the presenter. Contact **cncurtis@stanford.edu** for permission to reprint and/or distribute.

Results

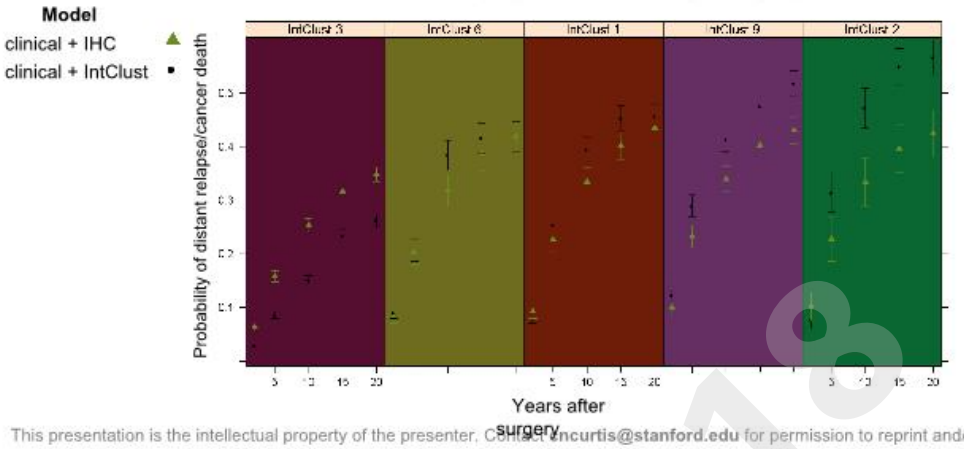
San Antonio Breast Cancer Symposium, December 4-8, 2018

The integrative subtypes have varied risk of relapse



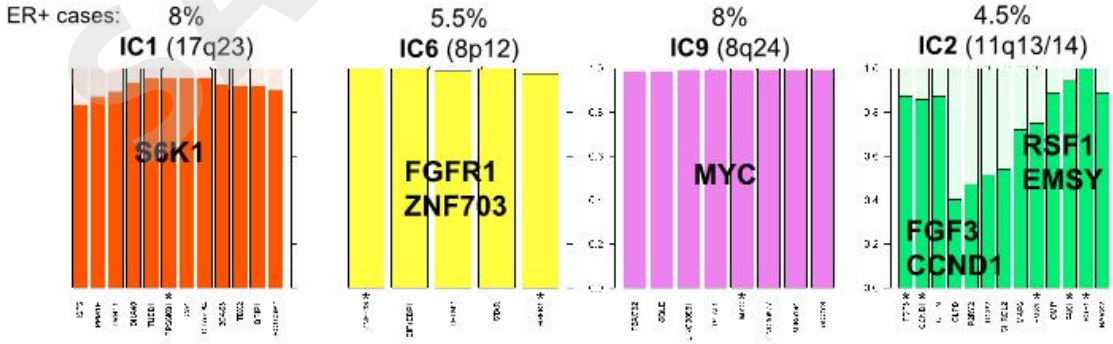
This presentation is the intellectual property of the presenter. Contact **cncurtis@stanford.edu** for permission to reprint and/or distribute.

High risk of late distant relapse in four ER+/HER2- integrative subtypes

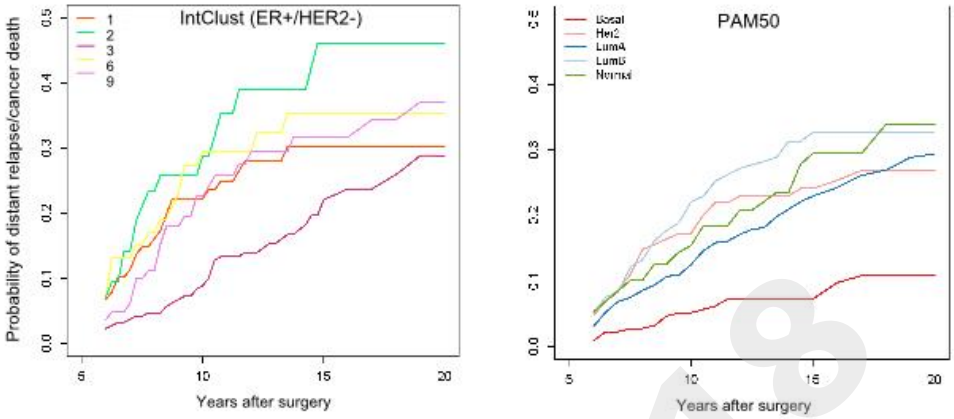


San Antonio Breast Cancer Symposium, December 4-8, 2018

Distinct genomic drivers in high-risk ER+ subtypes



Differential risk of late distant relapse: IntClust relative to PAM50 subtypes



San Antonio Breast Cancer Symposium, December 4-8, 2018

Integrative subtypes improve prediction of late distant relapse beyond clinical covariates

	10 years	15 years	20 years
METABRIC			
C-index (clinical +IHC)	0.618	0.612	0.604
C-index (clinical + IntClust)	0.672	0.647	0.643
VALIDATION COHORT			
C-index (clinical + IHC)	0.581	0.572	0.571
C-index (clinical + IntClust)	0.648	0.607	0.603

*Analysis performed on ER+/HER2- patients who were relapse free at 5 years

This presentation is the intellectual property of the presenter. Contact **cncurtis@stanford.edu** for permission to reprint and/or distribute.

Conclusions

- The risk of relapse and timing of first and subsequent relapses differ across the major breast cancer subgroups
- We identify four high-risk subgroups that account for 26% of ER+ tumors and the majority of late relapses; each with characteristic 'driver' alterations
- The integrative subtypes improve the prediction of late relapse compared with clinical covariates
- Our findings illuminate opportunities for improved patient stratification and biomarker-driven clinical trials for the quarter of ER-positive women with persistent risk of recurrence

This presentation is the intellectual property of the presenter. Contact **cncurtis@stanford.edu** for permission to reprint and/or distribute.