IMPAKT
BREAST CANCER CONFERENCE

IMPROVING CARE AND KNOWLEDGE THROUGH TRANSLATIONAL RESEARCH IN BREAST CANCER

WELCOME TO IMPAKT

Brussels, Belgium **7-9 MAY 2015**

IMPAKT Chairs: Nicholas Turner London, UK and Carsten Denkert, Berlin, Germany

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IMPAKT 2015
Oral Abstracts Discussion 1

Lisa A. Carey, MD

University of North Carolina, USA

3 Abstracts

- #860 (Herrera-Abreu MT et al): Early adaption and acquired resistance to CDK4/6 inhibition in ER positive breast cancer
- #400 (Migliaccio I et al): Identification of gene expression signatures of palbociclib response in breast cancer
- #390 (Sonnenblick A et al): Constitutively activated STAT3 signature is predictive for trastuzumab resistance in primary HER2 positive breast cancer.

Biomarker Assessment

"I think you should be more explicit here in step 2"

Elements of assay development:

1. **Analytical validity (reproducible and accurate?)**
2. **Clinical validity (differentiate cancers?)**
3. **Clinically useful (testing = better decisions)**

Level	Characteristics
I	Prospective marker trial or prospective trials with planned marker analyses
II	1 prospective trial or ≥ 2 prospective cohorts with preplanned analyses
III	1 prospective cohort with preplanned analyses
IV-V	Unplanned tumor analyses or retrospective cohorts

Adapted from Simon R, JNCI 2009

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Use in clinical decisions

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Adapted from Simon R, JNCI 2009

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

Lancet Oncol 2015; 16: 25–35

Open-label phase II, first-line endocrine therapy in MBC
Cohort 1 (n=66): unselected other than ER+ HER2-
Cohort 2 (n=99):

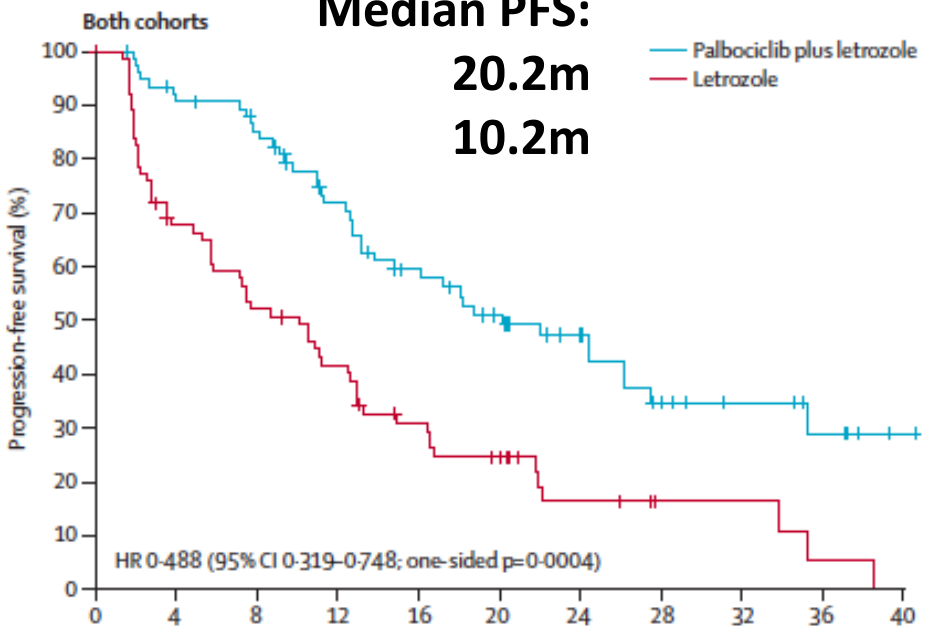
- **CCND1 amp (CCND1:CEP11 > 1.5) or**
- **p16 LOH (CCND1:CEP9 < 0.8)**

Primary endpoint: Investigator-assessed PFS

- **Original design: primary analysis cohort 2**
- **Amended mid-trial: combined cohort analysis**
  (Due to activity in cohort 1 noted in interim analysis)

Finn R, Lancet Oncol 2015

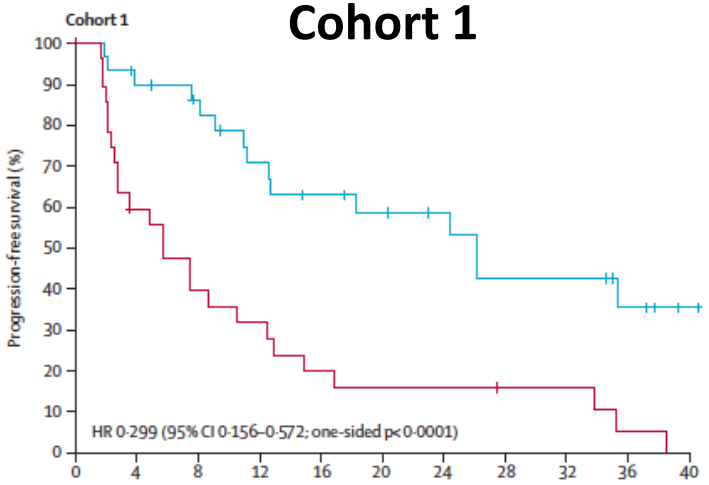
PALOMA-1: Investigator-Assessed PFS



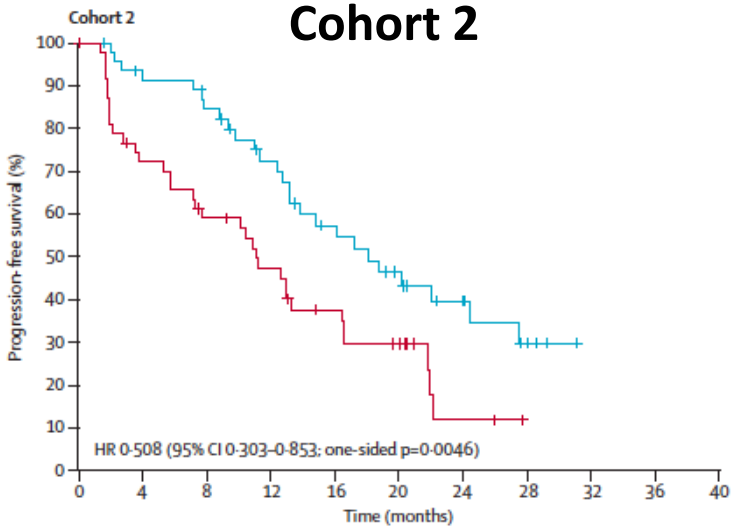
Median PFS:
20.2m
10.2m

Drug worked
Predictive biomarkers didn't

Cohort 1

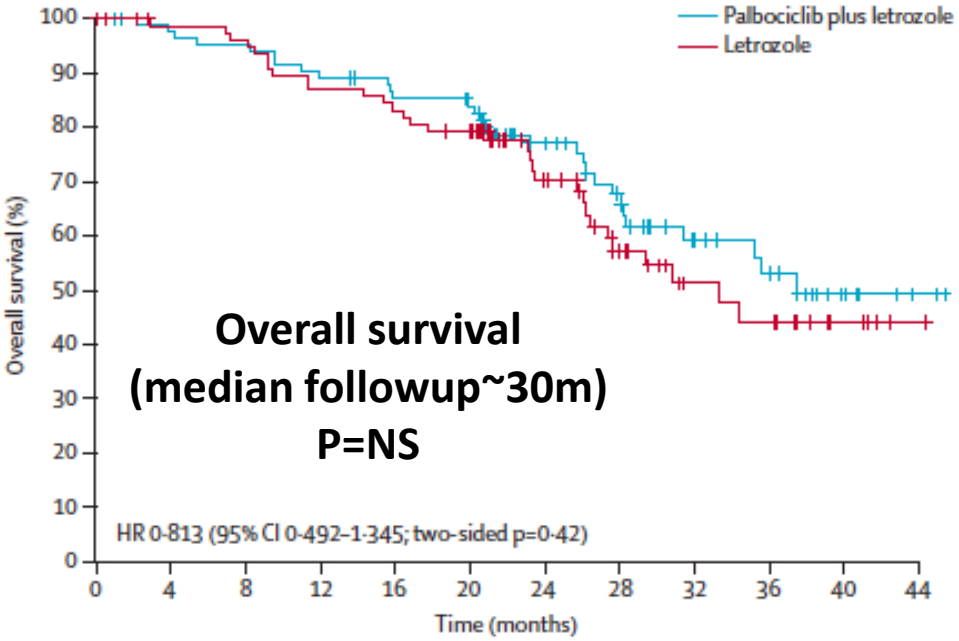


Cohort 2



Finn R, Lancet Oncol 2015

PALOMA-1: Key Secondary Endpoints



Overall survival (median followup~30m) P=NS

80% clinical benefit in P+L

Toxicity	Palbo+letrozole	letrozole
Any AE (grade 3+)	100% (66%)	85% (1%)
ANC ↓ (grade 3+)	54%	0
Fatigue (grade 3+)	40% (4%)	23% (1%)
Nausea (grade 3+)	23% (2%)	12% (1%)
Alopecia	22%	3%

33% dose interruptions, 40% dose reductions P+L (4% / NA with L alone)

Finn RS, Lancet Oncol 2015

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Pfizer Announces PALOMA-3 Trial For IBRANCE® (Palbociclib) Stopped Early Due To Efficacy Seen In Patients With HR+, HER2- Metastatic Breast Cancer Whose Disease Has Progressed Following Endocrine Therapy

Phase 3 Top-Line Results Show IBRANCE in Combination with Fulvestrant Meets Progression-Free Survival (PFS) Primary Endpoint

Wednesday, April 15, 2015 - 8:00am EDT

- **PALOMA-2 phase III pending**
- **PALOMA-3 phase III 2nd line fulvestrant + palbo positive (for PFS)! (data at ASCO)**

Very very promising drug!
At $5,000- 10,000 USD per month,
predictive biomarkers needed

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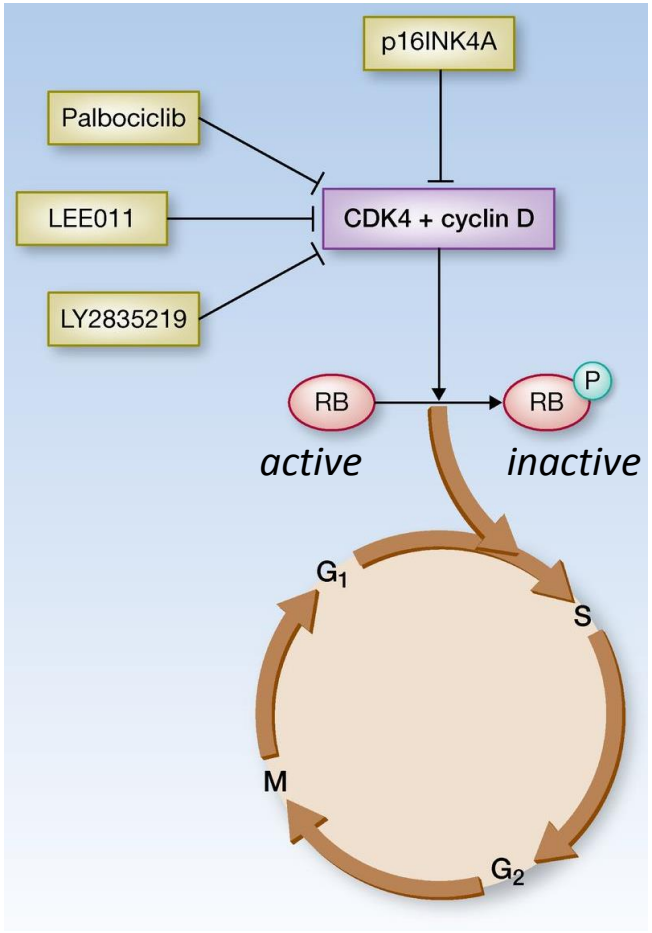
CDK4/6 Inhibition

CDK4/6 inhibitors in development



Adapted from Dickson MA. CCR 2014

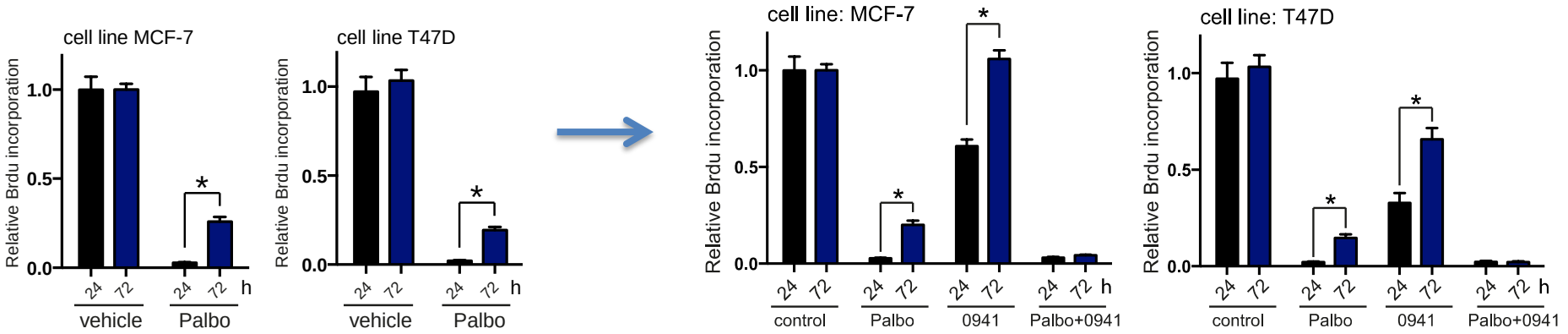
Resistance to CDK4/6 inhibitors:

- **No Rb (loss or inactivation)**
- **Deregulated CDK2 (alternate pathway)**
- **E2F overexpression (regardless of Rb)**

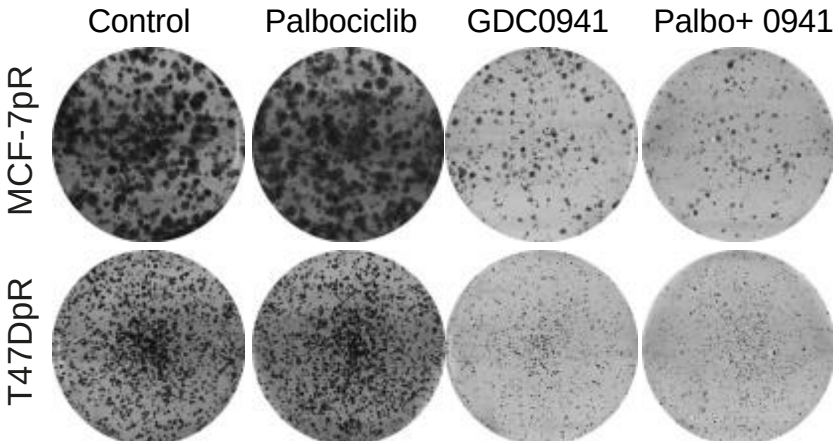
Etc.

Abstract #860 (Herrera-Abreu et al): Highlights

Early loss of cell cycle inhibition with palbociclib, improved with dual targeting PI3K+CDK4/6. Cytotoxic. Even better if add ER-targeting with fulvestrant.



Late resistance not salvaged by dual targeting



Abstract #860
Take Home Messages

- Cell cycle inhibition erodes - ***resistance to these drugs is real, too***
- CDK2 implicated in both early and late (acquired) resistance – ***consistent, has been implicated by others***
- Co-targeting PI3K + CDK4/6 at least additive but works only against early adaptive resistance – ***consistent with work using CDK4/6i to circumvent PI3Ki resistance. Early vs late distinction less certain.***
- Triple targeting (ER/PI3K/CDK4/6) best of all. Phase I trial underway. ***May be true with other ET combinations***

Rational combinations may need to be used early and comprehensively

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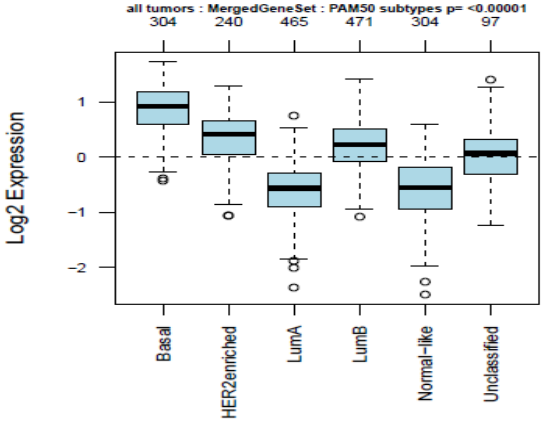
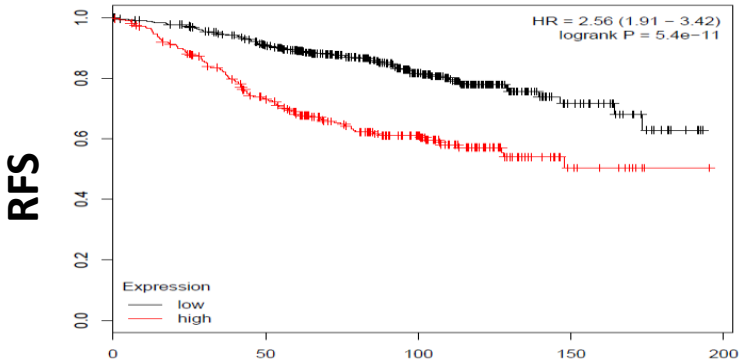
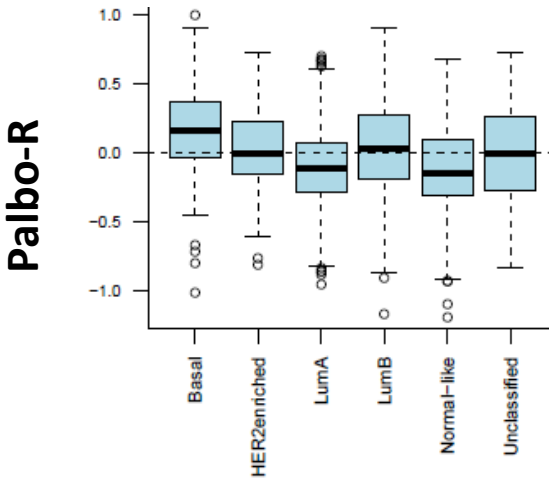
Abstract #400 (Migliaccio et al): Highlights

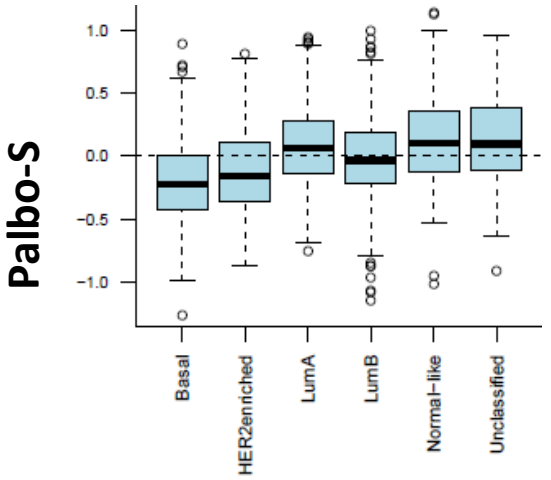
Functional Rb loss signature correlates with Lum B > A, poor px





Palbo-sensitivity and –resistance signatures correlate with expected subtype and prognosis with ET alone





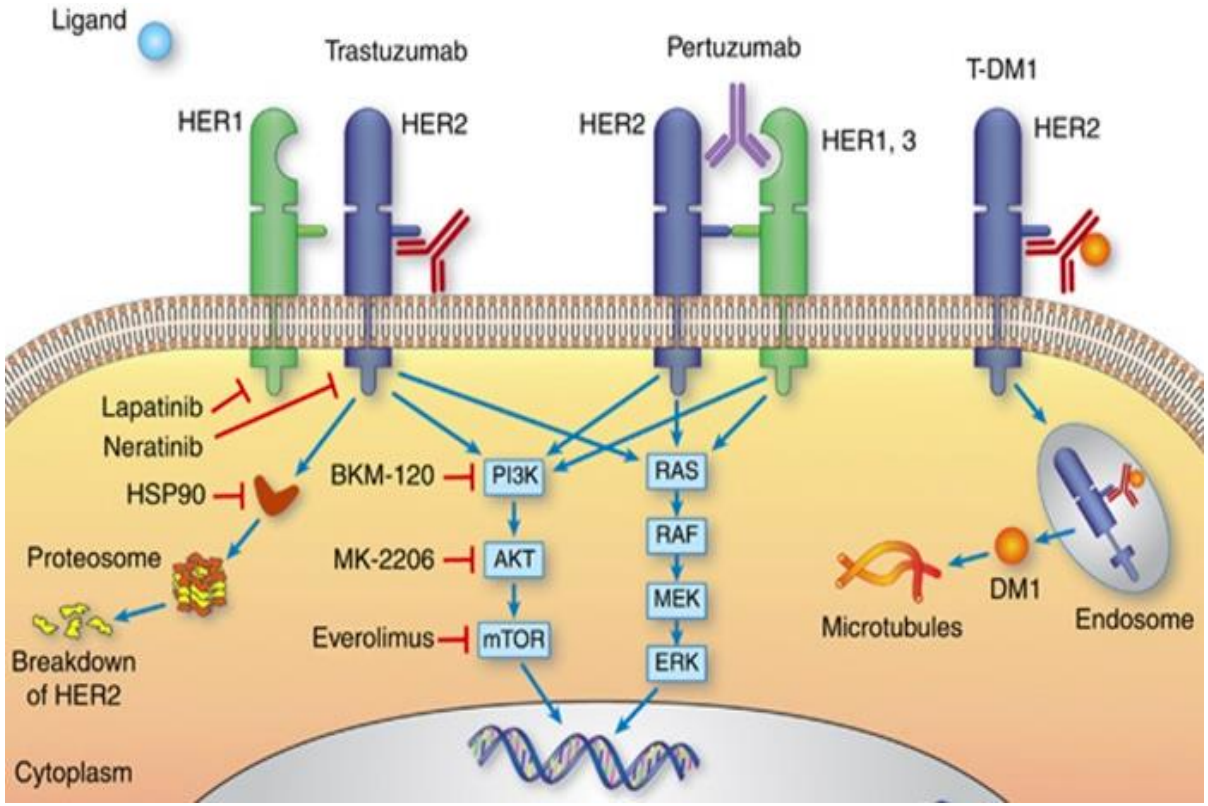
Abstract #400
Take Home Messages

- Functional Rb loss signature associated with Lum B, prognostic – ***plausible and consistent. CDK4/6 inhibitor resistance may relate to subtype. Signature based on E2F, may reflect proliferation more than Rb.***

- Palbociclib sensitivity and resistance signatures can be created and modestly track with expected phenotype and behavior. ***Not validated but important. Will it be better than just Rb-based assay?***

With this emerging class of drugs, predictive biomarker efforts are important but not yet successful, and may need to take known variables into account (e.g. subtype)

Response/Resistance to HER2 Targeting



Singh J, Br J Ca 2014

Predictive variables:

- **Aberrant receptor / dimerization / kinase domain**
- **PIK3CA and other signaling pathway ↑**
- **Reprogramming**
- **Immune activation**

Etc.

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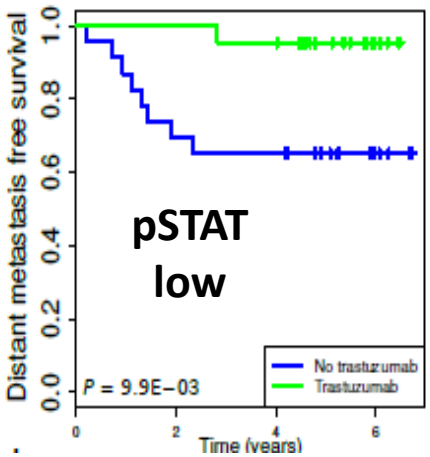
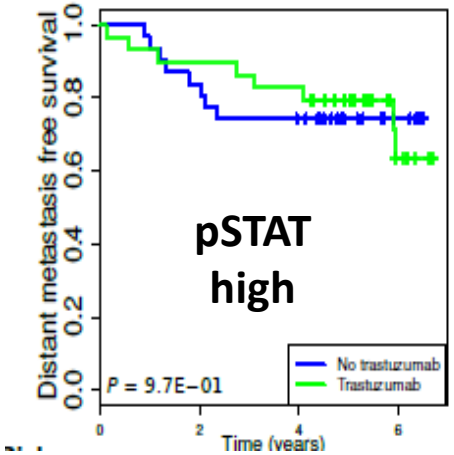
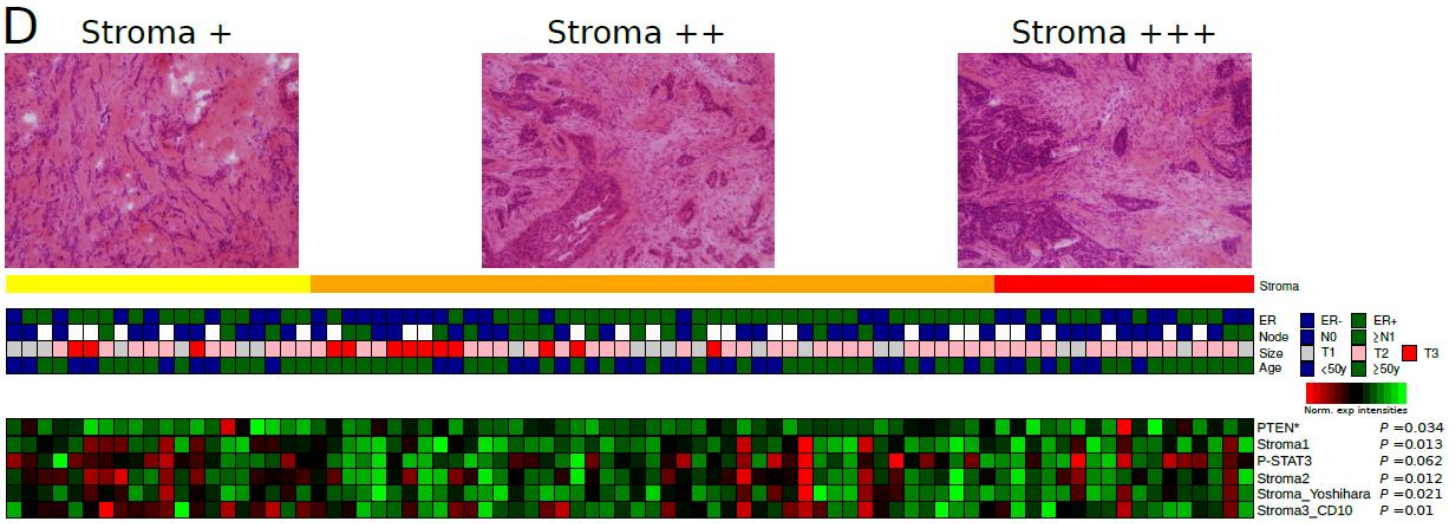
Abstract #390 (Sonnenblick et al): Highlights

Low pSTAT3 signature predicts trastuzumab benefit in ER-/HER2+





pSTAT3 signature associated with stromal reactivation and PTEN↓



Abstract #390
Take Home Messages

- pSTAT3 expression segregates HER2+ into two molecularly distinct groups – ***consistent. HER2 segregates into luminal and HER2-Enriched. HER2E has relatively low STAT3 expression.***
- Low pSTAT3 relevant for HER2-targeting only in ER-negative - ***also plausible, known association ER status with molecular subtype (ER- is >50% HER2E)***
- pSTAT3 associated with stromal reactivation – ***intriguing given stromal reactivation and EMT both associated with drug resistance***

Given explosion of good (but expensive) options for HER2-targeting, need to know who needs more and who needs less

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Central Themes

- The importance of cross-talk in drug resistance
- Need for predictive biomarkers for targeted therapy.
  - Rigor in development – what sounds good often doesn't work!
- Across multiple platforms similar biology is emerging – this is reassuring.


Thank you