

# The Challenge of Doing Less

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## Disclosures

- Roche - advisory board
- Lilly - advisor board
- Jounce - advisor board
- GSK - advisor board
  
- LEAP - scientific advisory board
- VERASTEM - former member scientific advisory

Nancy Brinker  
Founder of Susan G. Komen for the  
Cure



Doing less was not a consideration when Susan Komen died of breast cancer in 1980

- Breast cancer was a very different disease in 1980
- Early detection was not common
- Treatment approaches were limited
- Mortality rates were high



## Why do we care about doing less if breast cancer mortality is on the decline?

*Because treatment can lead to short term toxicity and long term morbidity, albeit in a minority*

### Reducing Therapy is Not Right for Everyone!

- The goal is to optimize survival and minimize toxicity
- Three distinct challenges exist:
  - Need to improve treatment for patients who are still at risk of breast cancer relapse and death
  - Need to provide access to high quality care to the many patients who are receiving suboptimal care
  - Need to minimize therapy in those patients who are likely to do well with less

## Some Women Are “Over-diagnosed” With Breast Cancer, And By Definition Are All Over-treated

- Over 42,000 women randomized to screening x 5 years vs not
- Women 55-69 not offered screening at end of 5 years

WOMEN 55-69	Period 1 (years 0-5)	Period 2 (years 6-10)	Period 3 (years 11-15)
Excess Mammo to Control	1.32 (1.14-1.53)	0.92 (0.79-1.06)	1.10 (0.99-1.22)

Over entire 15 year period, over-diagnosis rate 10%  
How do we identify these individuals?

Zackrisson et al, BMJ 2006

## Many Women Are Not “Over-diagnosed”, but Have Disease That is Unlikely to be Lethal

- For example:
  - Palpable 2.2 cm well differentiated ER+ cancer, Oncotype 6
  - Mammographically detected 1.1 cm, high grade, HER2+ cancer
- For these patients, the question is how little we can do and avoid mortality
- In recent years, there have been efforts to reduce therapy
  - Surgery
  - Radiotherapy
  - Systemic therapy
- But it has been challenging to conduct these trials and change clinical practice

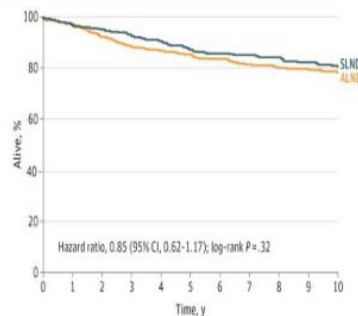
## Selected Trials That Have Reduced Extent of Local Therapy

- Elimination of node dissection for women receiving radiotherapy who have 1-2+ sentinel nodes (ACOSOG Z0011)
- Elimination of node dissection for selected women who present with positive nodes that become node negative after neoadjuvant therapy (ACOSOG Z1071)
- Accelerated whole breast hypofractionated radiotherapy (NCIC trial and others)

### ACOSOG Z0011: 2017 Update Local-Regional Recurrence

- Clinical T1-2 N0 breast cancer with 1-2 positive SLN, randomized to ALND or obs
- In ALND group, 97 (27.3%) pts had additional positive nodes

	ALND N=420	SLN only N=436
<b>Regional recurrence</b>	<b>2 (0.5%)</b>	<b>5 (1.1%)</b>
<b>Local-regional RFS</b>	<b>93.2%</b>	<b>94.1</b>



No. at risk	0	1	2	3	4	5	6	7	8	9	10
SLND alone	435	399	374	303	237	137					
ALND	418	376	352	295	233	126					

**Median follow-up 9.25yrs**

Giuliano et al. JAMA 2017

## Z0011 Was Not Easy To Conduct

- Slow accrual, presumably due to reluctance to back off
- Trial ended early because of accrual
- The results were impressive and changed practice
- What if the findings had been somewhat less dramatic?
- If there had been a 1% non-significant difference in DFS, would we still be doing node dissections in all patients with a single positive node?

## Why was uptake slow?

- Many physicians were concerned about patient population studied
- Others felt follow-up was initially too short when first presented in 2010
- Some of us live by the motto: “All change is to be resisted”
- Similar problems with uptake seen with standard radiotherapy vs. hypofractionated approach

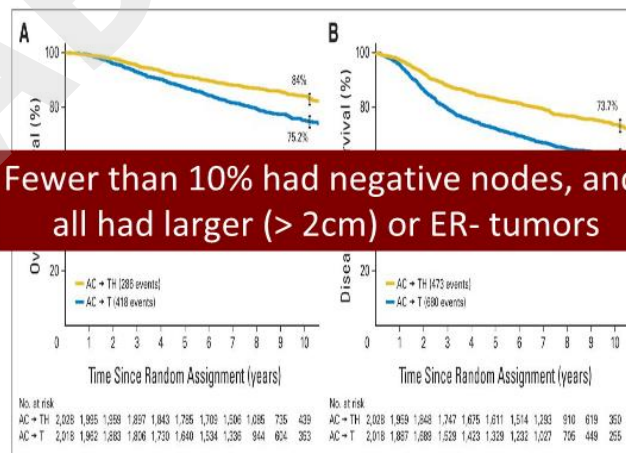
# Backing Off On Systemic Therapy

- Easiest to start in low risk patients or those with significant co-morbidity
- De-escalation can involve:

❖ Decreasing chemotherapy ➔ Two Examples

- ❖ Decreasing biologic therapy
- ❖ Shortening duration of therapy

## Overall Survival Joint Analysis of AC-T +/- Trastuzumab

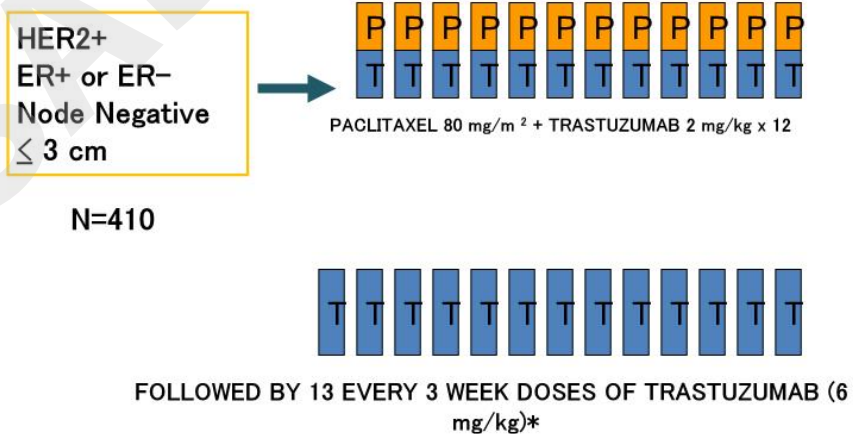


Perez et al, JCO 2014

## In 2006, we were uncertain what to do with patients who had stage I HER2+ cancers

- Best Estimates From Historical Cohorts
  - T1a: 3-10%
  - T1b: 5-15%
  - T1c: 10-25%
- Would have been impossible to randomize chemo vs chemo + trastuzumab
- No data to support trastuzumab vs chemo + trastuzumab
- Randomized trial would have been huge
- Given lower risk and presumed benefits of trastuzumab + chemo, we opted for single arm trial with less intensive chemotherapy

### APT: Study Design



Tolaney et al, NEJM 2015



## Statistical Considerations

- DFS primary endpoint
- Differentiate between 3 yr DFS < 90.8% vs.  $\geq$  95%
- One sided type 1 error of .05; type 2 also .05
- Analysis planned after 1600 pt years with rejection of null hypothesis if fewer than 39 events
- Recurrence-free interval, OS, toxicity considered secondary endpoints

### Disease-Free Survival Events at 7 Years

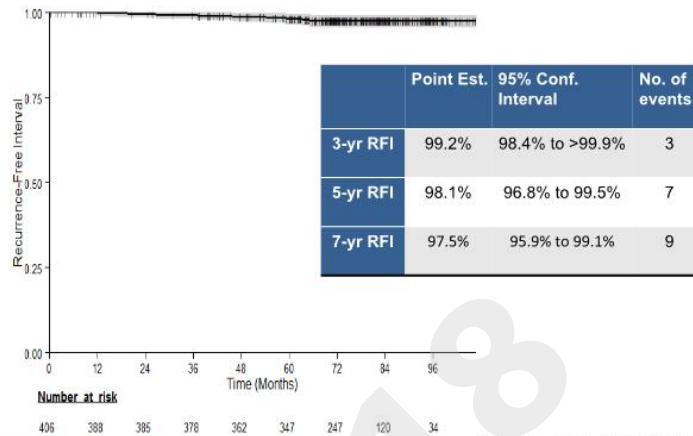
DFS Event	N (%)	Time to event [months; mean(range)]
Any recurrence or death	23 (5.7)	
Local/Regional Recurrence*	5 (1.2)	
Ipsilateral axilla (HER2+)	3	29 (12-54)
Ipsilateral breast (HER2+)	2	51 (37-65)
New Contralateral Primary Breast Cancer	6 (1.5)	
HER2+	1	56
HER2-	3	36 (12-59)
Unknown	2	87 (84-90)
Distant Recurrence	4 (1.0)	49 (27-63)
Death		
Non-breast cancer related	8 (2.0)	58 (13-71)

Tolaney et al, ASCO 2017

# APT: Updated Recurrence Free Interval

## RFI Events

- Invasive Local/Regional
- Distant recurrence
- Death from breast cancer

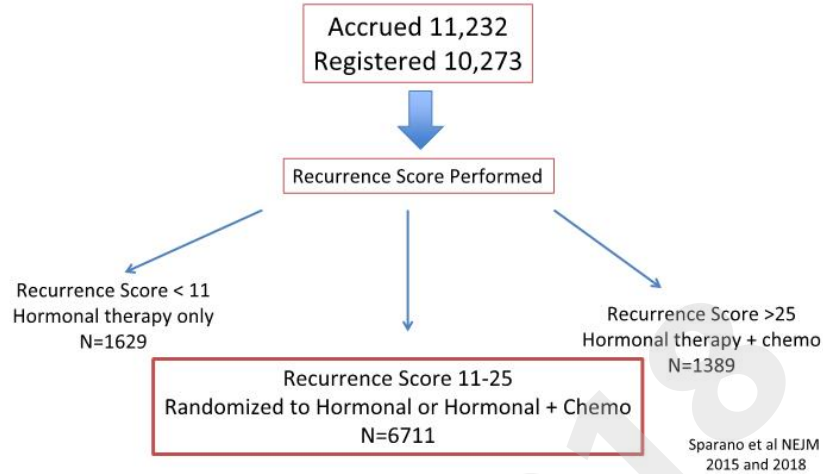


## APT Conclusions

- Study does NOT prove that treatment is better than no treatment
- But, given very small number of recurrences, it is hard to imagine that any regimen could be better if one is planning to give chemo + trastuzumab
- Has led to widespread adoption of paclitaxel-trastuzumab for stage 1 disease
- Had the results merely met our definition of success would it have been incorporated into practice?

# TailorX Design

2006-2010



## TailorX: Recurrence Score < 11

Assigned to  
Hormonal Therapy  
Only



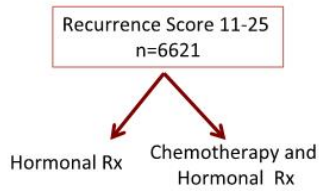
5 Year Results

Distant Relapse Free Survival	99.3%
Invasive Disease Free Survival	93.8%
Overall Survival	98.0%

No Randomization Needed to Change Practice

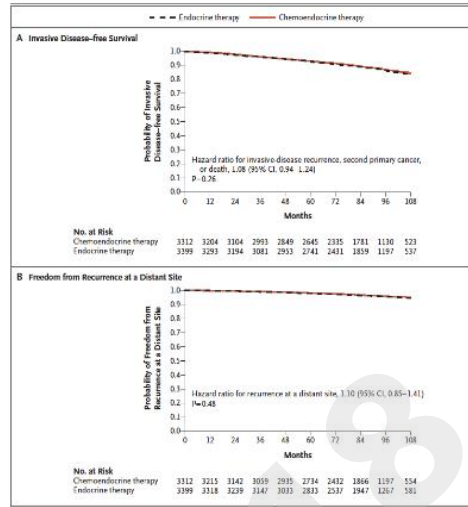
Sparano JA et al. NEJM 2015

# TailorX Results



Null hypothesis = no difference

5 year IDFS of 87% vs 90% unacceptable and would disprove null hypothesis



## Practice Changes From TailorX

- For women over 50, there is NO benefit for chemotherapy with RS up to 25 in setting of node negative disease
  - Role of chemo in 26-30 range is unclear
- For women under 50, an exploratory analysis suggested benefit for chemotherapy in women with scores of 16-25, particularly 21-25
- Benefit may be due to ovarian suppression, but cannot rule out role for chemotherapy

# What About Patients With Node Positive Disease?

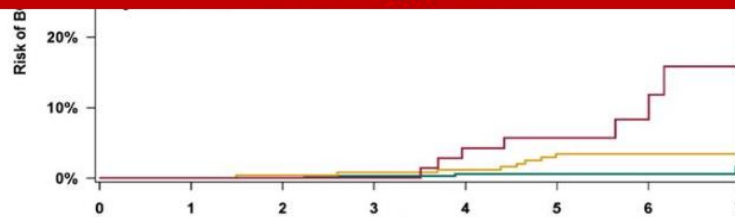
## Can We Extrapolate Now?

### QUESTION:

*Do any prognostic or predictive factors behave very differently in node negative and positive patients, particularly those with limited nodal involvement?*

## Breast Cancer Death in Israeli Node Positive Population Registry

See P3 11-02 on Thursday morning for SEER-Oncotype Analysis in Node Positive Disease  
Hortobagyi et al

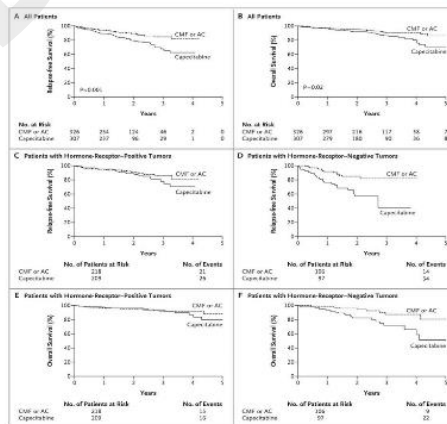


Stemmer et al, NPJ Breast Cancer, 2017

## Additional Thoughts About Node Positive Disease

- Data will not be available from RxPonder for several years
  - Are we going to treat all patients with 1-3+ nodes with chemotherapy?
  - MINDACT supports use of genomic assay in node positive disease
  - Hopefully we can extrapolate to patients with multiple positive nodes when we have RxPonder results
- I think we have no choice but to extrapolate because we cannot answer all questions in all subgroups

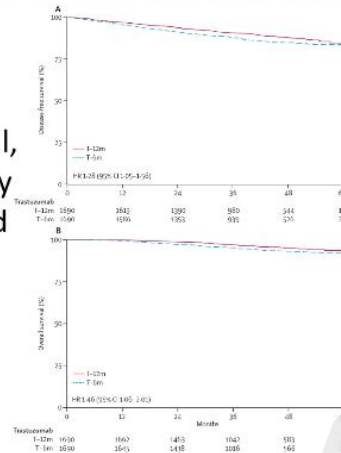
## Not All Efforts to Minimize Therapy Succeed AC/CMF vs Capecitabine in Elderly Women



Muss et al, NEJM 2010

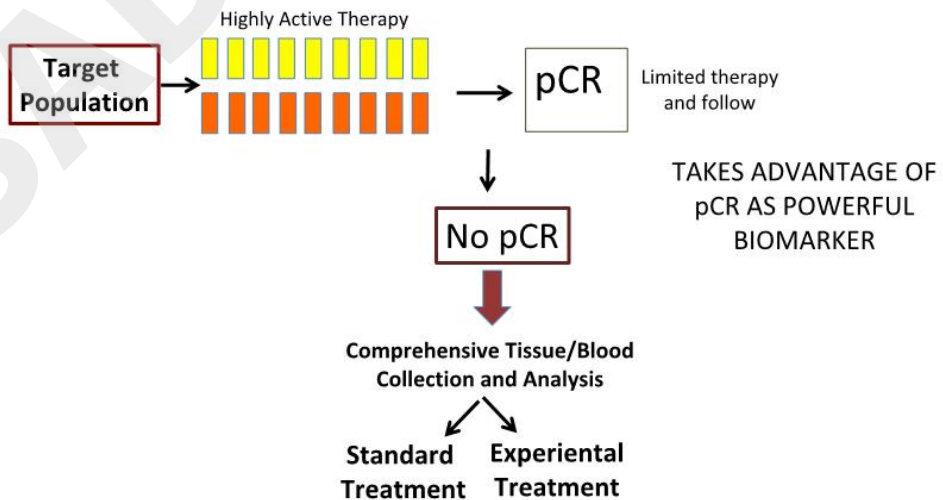
## Multiple Efforts to Decrease Duration of Trastuzumab Have Failed or Left Doubts

Difference is small, but non-inferiority not demonstrated



Pivot et al, Lancet Oncology 2013

## A Design to Use Preoperative Therapy to Decrease Treatment and Increase Treatment



## So why is it so hard to back off?

- Statistical issues
- Poor alignment of incentives and objective in our health care systems
- Doctors tend to underestimate short and long-term toxicity
- Psychological issues and risk perceptions
  - Patients are scared
  - Doctors are worried for their patients and for themselves

## Statistical Considerations (1) Non-Inferiority Designs Can Be Daunting

- Imagine standard of care has 5-year DFS of 80%
- You are willing to accept DFS of 77% in exchange for less toxicity (HR 1.17)
  - Alternative hypothesis:  $\Delta < 3\%$  (HR  $< 1.17$ )
- Null hypothesis:  $\Delta \geq 3\%$  (HR  $\geq 1.17$ )
- Type 1 error 0.05, power 90% (1371 events needed)
- If trial accrues over 3 years with 3 years additional f/u then sample size = **7600**
- Only small number of such studies can be conducted

Courtesy of Meredith Regan, PhD



## Statistical Considerations (2)

- Can a Phase II approach be used?
  - Yes, but best in situations where the outcome is expected to be excellent
  - Sample size has to be large enough so that confidence intervals are tight
  - Does not prove that treatment better than nothing
- However, if expected outcome is less than excellent, it is difficult to consider a non-randomized approach if the trial is meant to change practice

## Incentives Not Always Aligned With Doing Less

- As doctors, we are trained to intervene
- Easier for many to proceed with treatment rather than talk about not doing it
- \$\$\$\$

## Psychological Issues and Risk Perceptions



For Both Patients and Their Health Care Team

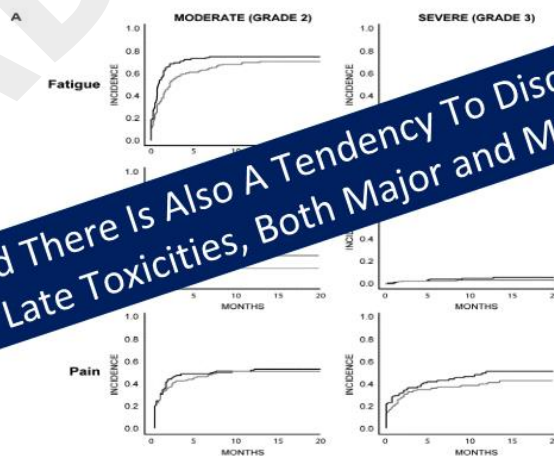
### Prospect Theory: People Are Risk Averse When They Are Considering Losses

- Demonstrated in multiple psychology and economics experiments (Tversky and Kahneman)
- We are risk averse when it comes to loss and risk seeking in the face of gains – we don't want to give up what we already have!
- For example, 93% of PhD students registered early when a penalty fee for late registration was emphasized, with only 67% doing so when presented as a discount for earlier registration
- Patients and doctors preferentially opt for interventions, sometimes inconsistent with their own value systems, because they want to avoid any risk of loss

## Framing Also Matters

- How a choice is portrayed affects decision
- Positive messages are more persuasive than negative ones
- In general, doctors frame benefit messages positively and minimize toxicity
- These messages are particularly powerful when there is fear, anxiety, and compromised decision-making

## Physicians Tend to Underestimate Side Effects and Symptoms



Bausch et al, JCO 2009

## Final Thoughts

- Trials that decrease therapeutic intensity are critical if we are to deliver the right treatment to the right patient
- Multiple de-escalation trials have been conducted and have changed the standard of care, but with great effort
- Statistical issues, fear, anxiety, and a natural tendency to avoid loss of any magnitude make de-escalation studies difficult for patients and doctors
- In the future, we will extrapolate more than in the past because not all studies can be conducted in all patient populations – these decisions will include those focused on de-escalation as well as escalation

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