Pre-operative cooperative group trials
Considerations for further research

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Disclaimer
Considerations for further research

- What is the problem we are trying to solve?
- What are we doing today?
- Immediate next steps
- The BIG picture
“Personalized Medicine”

Tailoring therapy
Right treatment to the Right person
Goals for Breast Cancer Therapy

- No recurrence of the cancer
- No evidence of having had breast cancer
- No evidence of having had treatment for breast cancer
- No acute toxicity of the therapy
- No late sequelae of the therapy

William Wood, NCI, March 2007
Pre-mastectomy

DURATION OF LIFE FROM ONSET OF SYMPTOMS (YEARS)

Chart 41–3. Length of survival in 250 patients with untreated breast carcinoma—Middlesex Hospital, 1805 to 1933 (Bloom).
Incremental benefit

Each incremental step assumed that no pt is cured with the previous step

- Significant overtreatment
- Necessity to conduct large trials to demonstrate small benefit

Courtesy of Soon Paik
Considerations for further research

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Molecular Profiling

- Address subtype specific questions
- Select therapies for future research
- Discovery of “targets”

Sorlie T et al, PNAS 2001
ACOSOG Z1031

Postmenopausal ER Allred 6-8 Clinical stage 2 and 3

Exemestane

Letrozole

Anastrozole

Accrual 78/375

No recurrence of the cancer

No acute toxicity of the therapy
No late sequelae of the therapy

PI M.J. Ellis.
Status Active: http://www.ctsu.org/.
ACOSOG Z1041: HER-2 Concurrent chemotherapy and targeted therapy

**Randomize**

Patients with histologically confirmed T2-T3 invasive breast carcinoma pos for HER-2/neu

**Group 1:** Paclitaxel plus Trastuzumab (Herceptin) x 12 weeks, followed by FEC x 4 cycles (+ Trastuzumab x 12 weeks)

BCT/Mastectomy and SLND/ALND Path evaluation for response

**Group 2:** FEC x 4 cycles, followed by Paclitaxel plus Trastuzumab (Herceptin) x 12 weeks

After completion of local therapy, patients will receive Trastuzumab to complete one year of therapy

**No recurrence of the cancer**

**No acute toxicity of the therapy**

**No late sequelae of the therapy**
CALGB HER-2 blockade

HER2+ Stage II-III

Paclitaxel
Trastuzumab
Paclitaxel
Lapatinib
Paclitaxel
Trastuzumab + lapatinib

S U R G E R Y

Dose-dense AC
Trastuzumab x 1y
RT prn
Endocrine Rx prn

No recurrence of the cancer
TRIPLE NEG- DNA damage

N=400
Stage II-III
"Triple Negative"

Paclitaxel
Carboplatin
No recurrence of the cancer

Paclitaxel
Carboplatin
No replacement

Dose-dense AC

S U R G E R Y

RT prn
Bevacizumab

No recurrence of the cancer
Antiangiogenesis: combination of chemotherapy and biologic

N=1200
Stage II-III
Not HER2+

Docetaxel alone + Capecitabine + Gemcitabine

Bevacizumab (through cy 2 AC)

No recurrence of the cancer
Can early response drive therapy?

No recurrence of the cancer

N=540 Her 2 neg. Non-responder

Pw = weekly Paclitaxel
R = Rad 001

Repeat Core
Sonography
Core biopsy

NC  R

Pw  Surgery
Pw + R  Surgery

continue responder part
Considerations for further research

• What is the problem we are trying to solve?
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Coordinated Global Efforts
Incorporate Specimen Collection SOPs

• To promote and ensure proper collection of high-quality research specimen such that each patient diagnosed with breast cancer can have a reliable, interpretable molecular diagnosis.

• To provide a known baseline of standardization of specimen collection and handling procedure, to the extent possible, such that more global biomarker analysis across studies is possible.

• To promote specimen collection that would allow for future technologies, particularly in the molecular arena, to be applied to specimens for research.
Incorporate Specimen Collection SOPs

• Prospective validation of predictive factors in “retrospective” clinical trials
Standardized definitions for Efficacy End Points in NEO-Adjuvant Breast Cancer Trials (STEEP)

- Malignant cells undetectable in breast and lymph nodes
- Invasive tumor undetectable in breast and lymph nodes (DCIS allowed)
- Invasive disease absent in breast
- Total or near total therapeutic effect in the primary tumor and evidence of therapeutic effect in lymph nodes, no metastasis
THE BIG Picture

• How will we get from pCR to changing practice?
Pre- or post- SLNB

• How can we answer this question?
Confirming Surrogates in prospective studies of clinical outcome

• Over-interpretation of early results
  – Will we be able to confirm high response rates in triple negative disease

• Should we “nest” the neoadjuvant studies?
  – “Less” selection bias, concurrent validation possible, more “robust” diagnostics
What if you do not get a pCR?

• Residual risk strategies
  – Problem of more of the same?
  – Systemic therapies?
  – Local therapies?
Proposed Randomized Trial for Post Preoperative Therapy

Standard Neoadjuvant Chemotherapy

Residual Invasive Breast Cancer

Targeted

Chemotherapy

Chemotherapy
  Targeted
Inflammatory Breast Cancer

• How do we study a rare disease
  – More basic science-incentives?
  – Registries?
  – International randomized trials?
Partnerships
Academia, Industry, Government, Advocacy