# Neoadjuvant endocrine therapy

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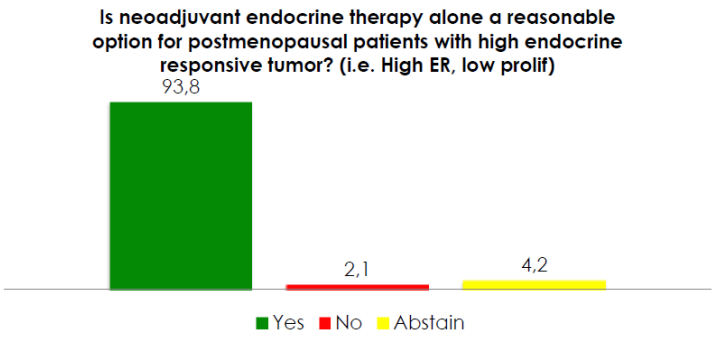
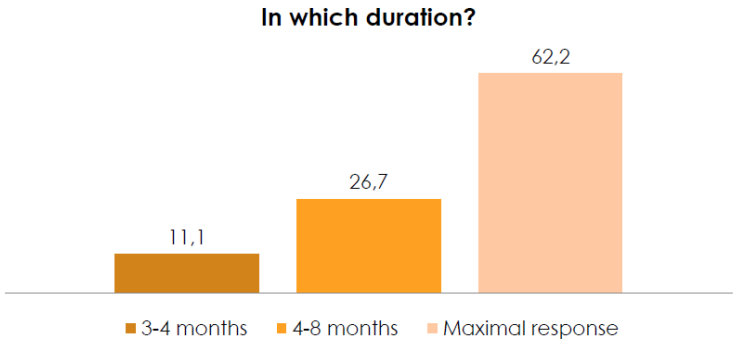
# St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013

- **Neoadjuvant endocrine therapy:**

The Panel strongly (94%) endorsed endocrine therapy alone as neoadjuvant treatment for postmenopausal patients with strongly positive hormone receptors and low proliferating disease, and most thought that such treatment should be continued until maximal response.



# NCCN Guidelines 2015

- Use of either anastrozole or letrozole alone provides superior rates of BCS and usually objective response compared with tamoxifen
- AI is preferred in NET of posmenopausal women with hormone receptor+ disease

However, the overall use of NET remains low, with 2.4% of cT2-4c ER+ breast cancer age ≥50 being treated with NET in USA:

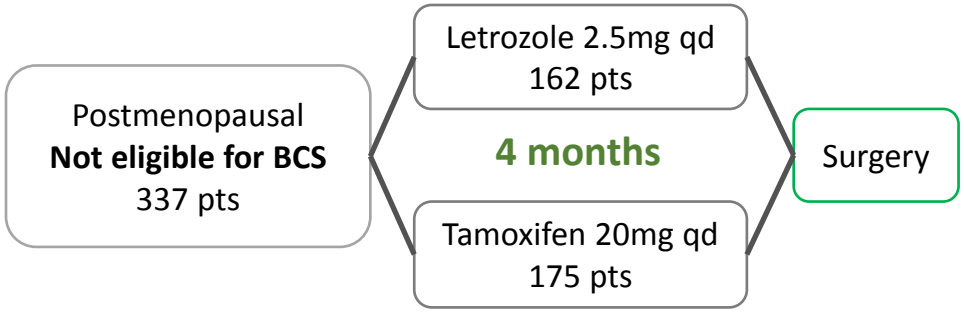
Bulletin of ACS by Leitch, Boughey, and Hunt

# Overall response of NET (trials with N>=100)

| Author | Drug | Duration | CR |
|---|---|---|---|
| Fontein (2014) | Exemestane (*n* = 102) | 6 months | 68.3% |
| Masuda (2012) | Anastrozole + Goserel in in premeno (*n* = 98) | 6 months | 70.4% |
| Olson (2011) | Letrozole (*n* = 115) | 4–6 months | 62% |
| Ellis (2011): **Z1031** | EXE (*n* = 124) vs LET (127) vs ANA (123) | 4 months | 62.9% vs 74.8% vs 69.1% |
| Dixon (2009) | Letrozole (*n* = 182) | 3 months | 69.8% |
| Baselga (2009) | Letrozole + Placebo (*n* = 132) | 4 months | 59.1% |
| Cataliotti (2005): **PROACT** | Anastrozole (*n* = 228) | 4 months | 50% |
| Smith (2005) **IMPACT** | Anastrozole (*n* = 113) | 3 months | 37% |
| Eiermann (2001): **P024** | Letrozole (*n* = 154) | 4 months | 55% |

# Tamoxifen vs. AI

# Tamoxifen vs. Letrozole
## *P024 Trial*

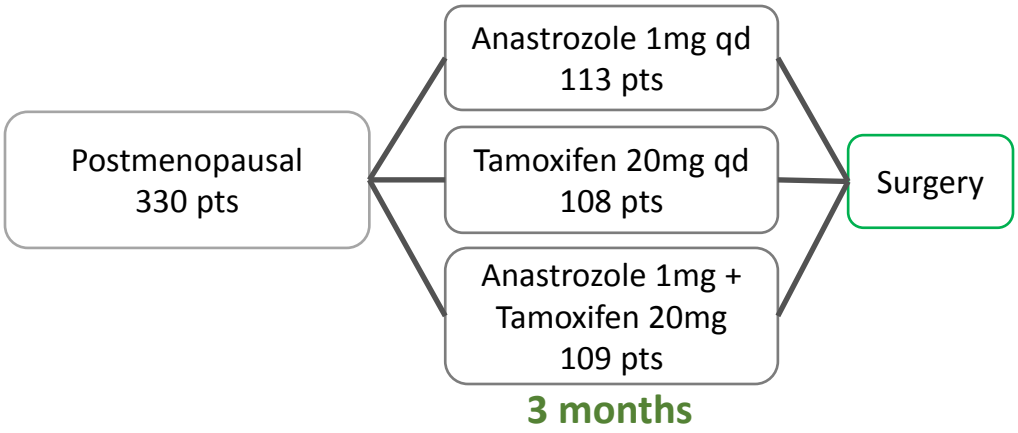



| | Letrozole (n=154) | Tamoxifen (n=170) | p value |
|---|---|---|---|
| Clinical response (palpation) | 55% | 36% | <0.001 |
| CR | 10% | 4% | |
| PR | 45% | 32% | |
| SD | 24% | 35% | |
| PD | 12% | 17% | |
| BCS rate | 45% | 35% | 0.022 |

*Eiermann et al, Ann Oncol, 2001*

*Ellis et al, J Clin Oncol, 2001*

# Tamoxifen vs. Anastrozole
## *IMPACT Trial*




Smith I E et al. JCO 2005

| | Anastrozole | Tamoxifen | Combination | p value |
|---|---|---|---|---|
| Clinical response (caliper) | 37% | 36% | 39% | Not significant |
| CR | 3% | 4% | 3% | |
| PR | 35% | 32% | 37% | |
| SD | 47% | 55% | 47% | |
| PD | 9% | 5% | 5% | |
| Conversion to BCS | 46% | 22% | 26% | A vs. T 0.03<br>T vs. C 0.68 |

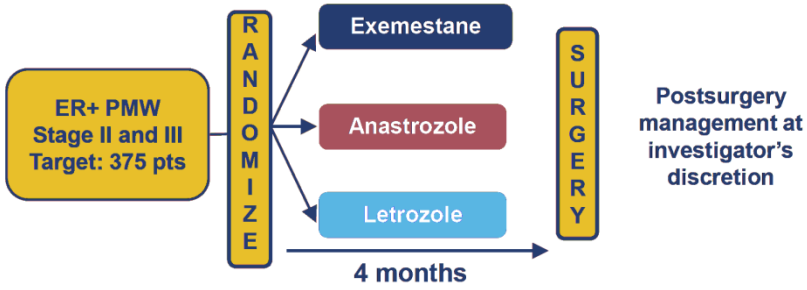
# Which AI is the best?

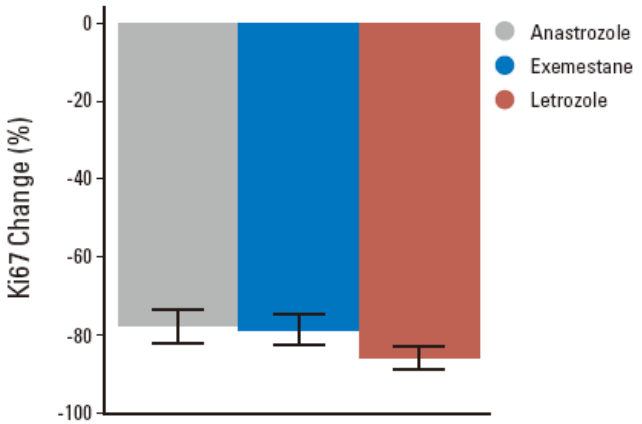
# Neoadjuvant Comparison Between Letrozole, Anastrozole, and Exemestane for Postmenopausal Women With Estrogen Receptor–Rich Stage 2 to 3 Breast Cancer – ***ACOSOG Z1031***

Ellis MJ, et al. JCO 2011

**Table 1.** Clinical Response Using WHO Criteria Based on ITT Population

| Response | Exemestane (n = 124) No. | % | Letrozole (n = 127) No. | % | Anastrozole (n = 123) No. | % |
|---|---|---|---|---|---|---|
| Clinical response at week 16 (WHO criteria with caliper measurements) | | | | | | |
| Complete response | 27 | 21.8 | 27 | 21.3 | 22 | 17.9 |
| Partial response | 51 | 41.1 | 68 | 53.5 | 63 | 51.2 |
| No change | 28 | 22.6 | 20 | 15.7 | 20 | 16.3 |
| Disease progression | 8 | 6.5 | 6 | 4.7 | 9 | 7.3 |
| Off treatment because of toxicity/refusal | 5 | 4.0 | 3 | 2.4 | 2 | 1.6 |
| Measurements not done | 5 | 4.0 | 3 | 2.4 | 7 | 5.7 |
| ITT clinical response rate, % | 62.9 | | 74.8 | | 69.1 | |
| Range | 53.8-71.4 | | 66.3-82.1 | | 60.1-77.1 | |
| 95% CI, % (difference in clinical response rates) | | | | | | |
| Letrozole and exemestane | | | 0.5 to 23.3 | | | |
| Anastrozole and exemestane | | | −5.6 to 18.0 | | | |
| Letrozole and anastrozole | | | −5.4 to 16.8 | | | |

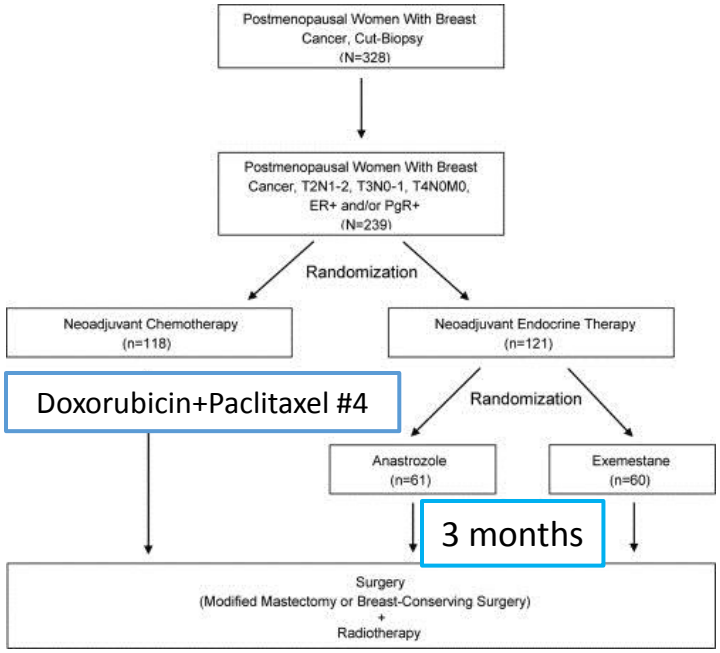



No differences in surgical outcome, PEPI score, or Ki67 suppression were detected.

# Neoadjuvant endocrine vs. chemotherapy

# Phase 2 randomized trial of primary Endocrine vs Chemotherapy in postmenopausal ER+ breast cancer

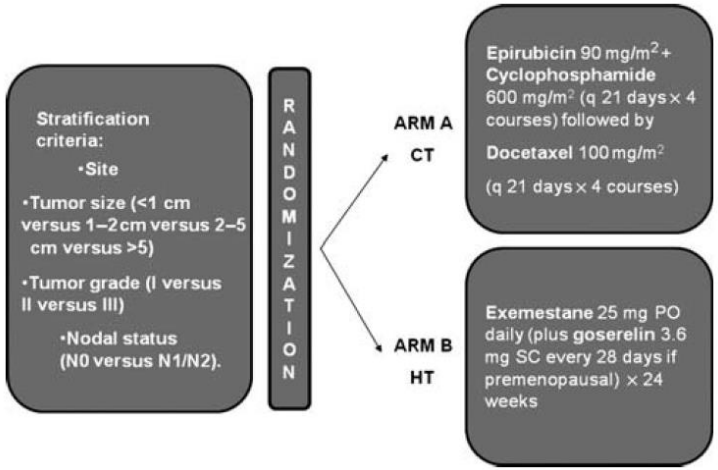



| | Endo | Chemo | P |
|---|---|---|---|
| Clinical response (palpation) | 64.5% | 63.6% | >0.5 |
| Complete response | 10% | 10% | >0.5 |
| Partial response | 55% | 53% | >0.5 |
| Mammo | 60% | 63% | >0.5 |
| USG | 40% | 46% | >0.5 |
| **BCS** | **33%** | **24%** | **0.058** |

More adverse events in NCT-treated patients (neutropenia, neuropathy, alopecia) than in NET-treated patients

Semiglazov, et al. Cancer 2007

# Chemo- vs hormone therapy as neoadjuvant tx in luminal breast ca.
## *GEICAM/2006-03*




| | ET, n=47 | CTx, n=48 | p value |
|---|---|---|---|
| **Clinical response** | 48% | 66% | 0.075 |
| **pCR** | 13% | 6% | |
| **Clinical response** | | | |
| Premenopausal | 12 (44) | 18 (75) | 0.0268 |
| Postmenopausal | 11 (52) | 13 (57) | 0.7829 |
| ER score 3-6 | 9 (69) | 6 (60) | 0.6449 |
| ER score 7-8 | 14 (41) | 25 (68) | 0.0256 |
| Ki67 ≤ 10 | 11 (58) | 12 (63) | 0.7399 |
| Ki67 > 10 | 11 (42) | 18 (67) | 0.0749 |

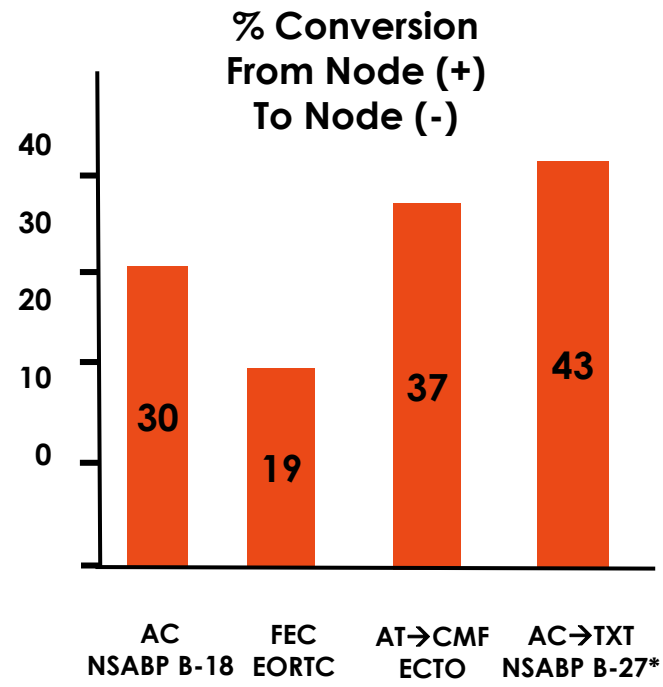
- Mastectomy rate, pCR rate similar
- Grade III-IV toxicity:
  CT (47%) vs HT (9%) P=0.00001

Alba, et al. Ann Oncol 2012

# Disadvantage of NET: LN negative conversion rate?

- LN conversion rate in Luminal A and bx confirmed LN+ patients: NEST study of Korea (Asan hospital)
  - **1/65 (1.5%) in NET (tmx+gos) group**
  - **5/66 (7.6%) in NCT (AC-T) group**
- 3/25 patients (12%) who were clinically LN+ before NET (exemestane) became pN0 after NET:

Fentein et al. Eur J Cancer 2014



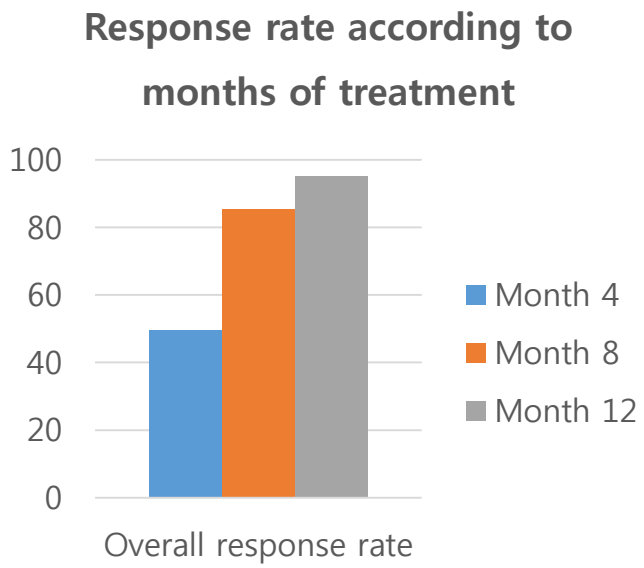

**Nodal pCR rate 41.0% in Z1071 trial**

# Duration of therapy

# Duration of therapy

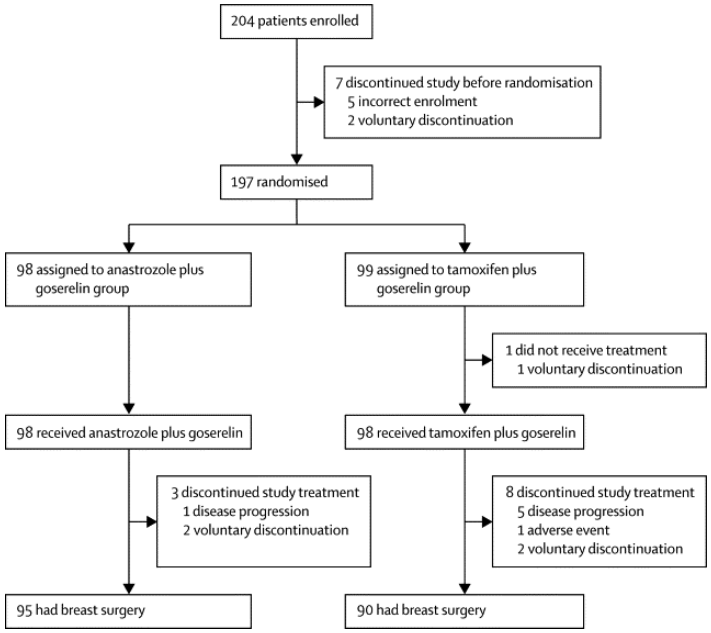
- Letrozole: Llombart-Cussac et al. (Clin Transl Oncol 2012)
  - **37.1% achieved the maximal response within 6–12 months.**
- Letrozole: Krainick-Strobel, et al. (BMC Cancer 2008)
  - **Prolonged tx for up to 8 months can result in further tumor volume reduction in some patients**
- Exemestane: Fontein, et al. (Eur J Cancer. 2014)
  - **Mean tumor size: 3.9cm (at 0) -> 2.3cm (3mo) -> 1.7cm (6mo)**

Letrozole: Allevi et al. Br J Cancer 2013



# NET in premenopausal women

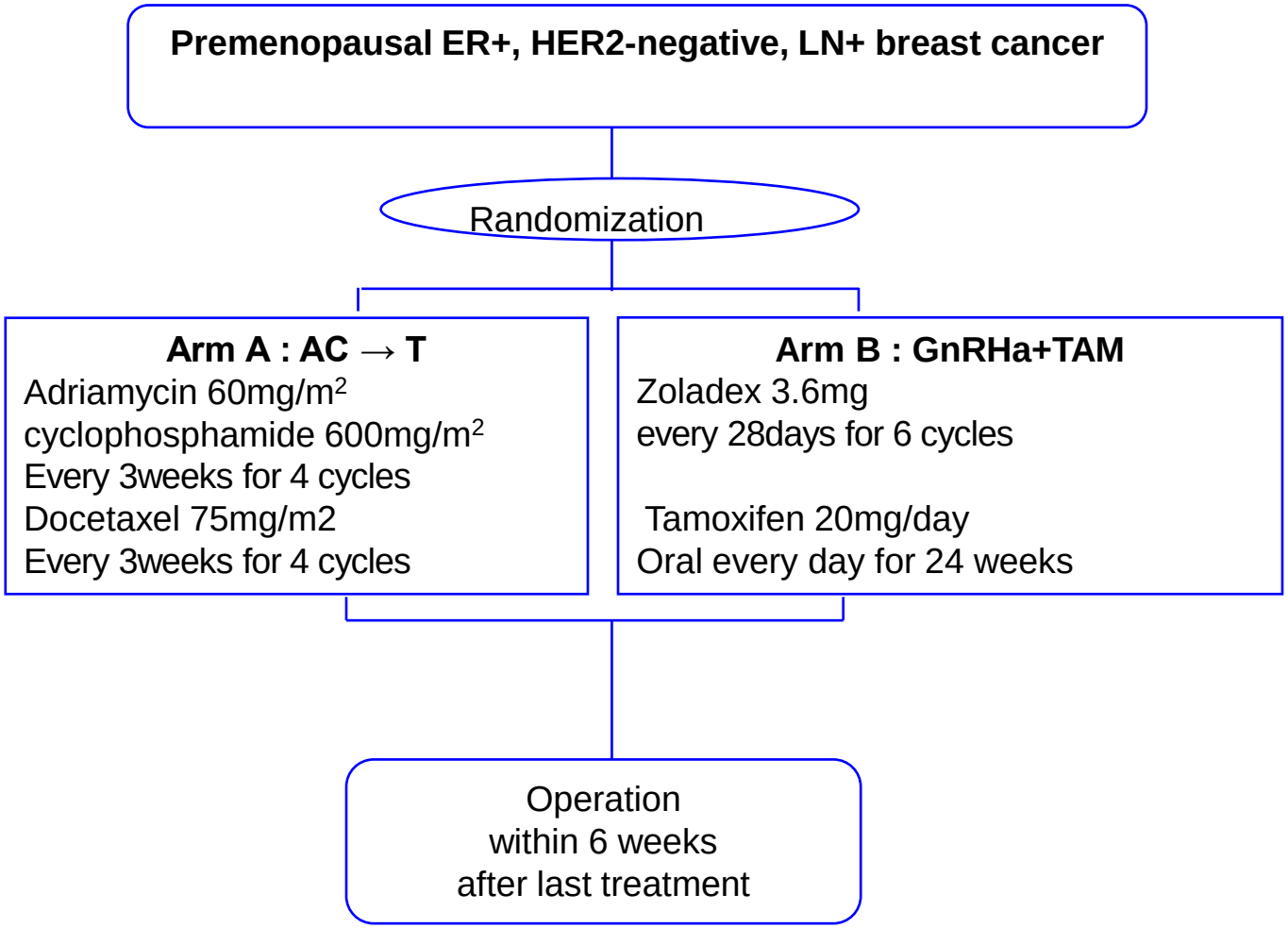
# Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (**STAGE**): a double-blind, randomised phase 3 trial




| | | ANA+goserelin (n=98) | TAM+goserelin (n=99) |
|---|---|---|---|
| Best overall tumour response | | | |
| Calliper (p=0.004) | | | |
| | CR | 12 (12·2%) | 7 (7·1%) |
| | PR | 57 (58·2%) | 43 (43·4%) |
| | CR+PR | 69 (70·4%) | 50 (50·5%) |
| Ultrasound (p=0.027) | | | |
| | CR | 1 (1·0%) | 0 |
| | PR | 56 (57·1%) | 42 (42·4%) |
| | CR+PR | 57 (58·2%) | 42 (42·4%) |
| MRI or CT (p=0.0002) | | | |
| | CR | 2 (2·0%) | 0 |
| | PR | 61 (62·2%) | 37 (37·4%) |
| | CR+PR | 63 (64·3%) | 37 (37·4%) |

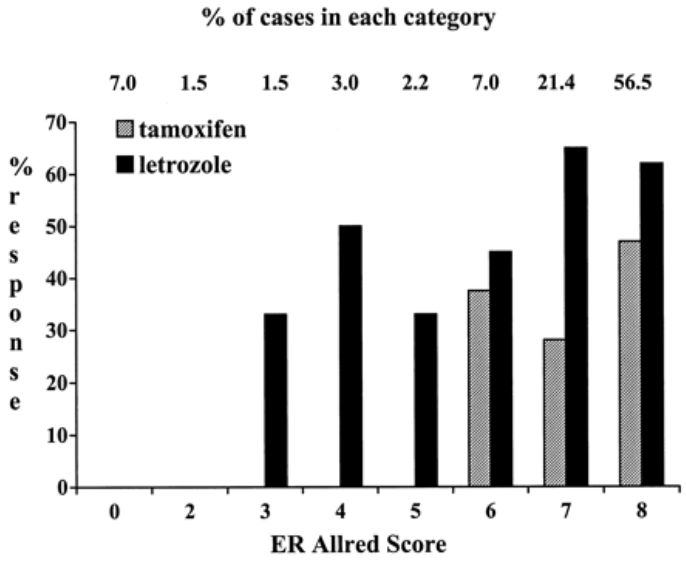
Masuda et. al., Lancet Oncol 2012

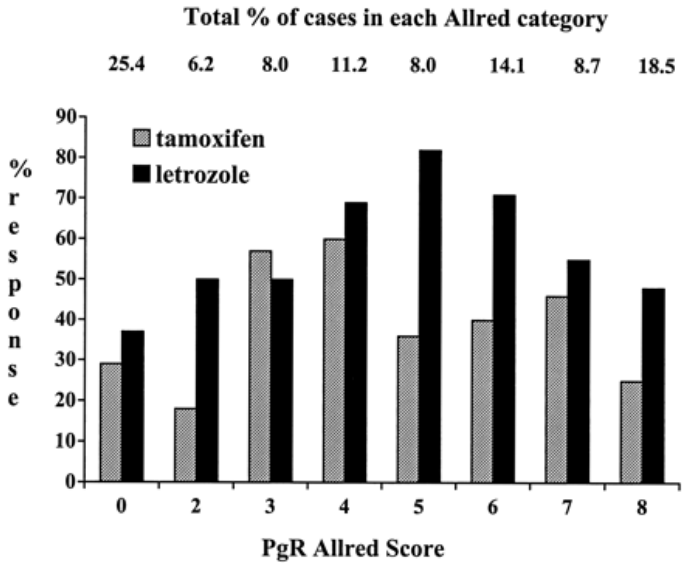
A phase III, open label, prospective, randomized, multicenter, Neo-adjuvant study of chemotherapy versus endocrine therapy in premenopausal patient with hormone responsive, HER2 negative, breast cancer (**NEST study** KBCSG 012)



# Biomarkers

# ER, PgR and response




- p value for linear logistic model:

  0.0013 (letrozole), 0.0061(tamoxifen)
- Letrozole response rate is superior to tamoxifen in every ER Allred category from 3 to 8

- Peak response rate at 5 (letrozole) & 4 (tamoxifen)
- No linear model

Ellis MJ, et al. JCO 2001

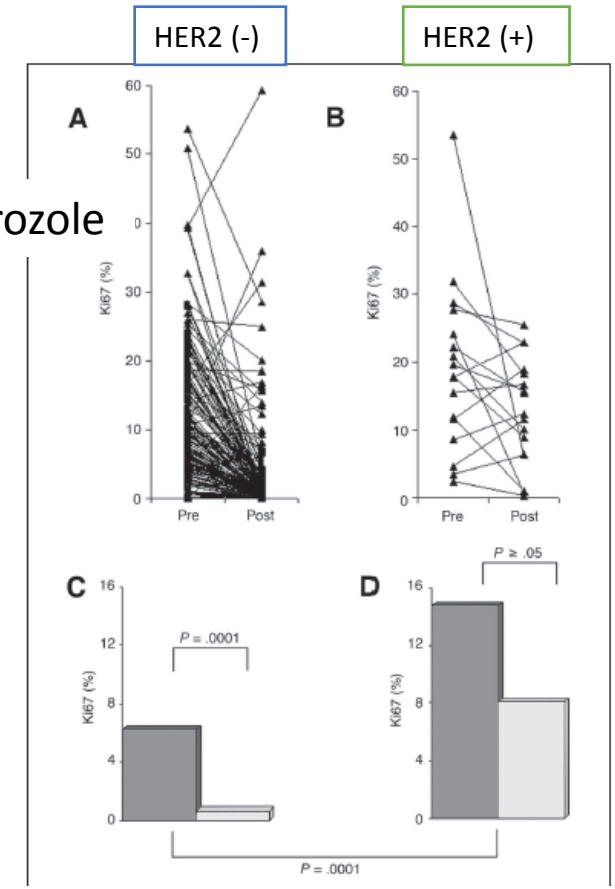
# Invasive lobular carcinoma

- Single arm study by Dixon, et al. (BCRT 2011) (N=61)
- Response rates: almost 92% after more than 3 months of treatment.
- The mean reduction in tumor volume at 3 months was 66%
- Lobular cancer is the best candidate for NHT?

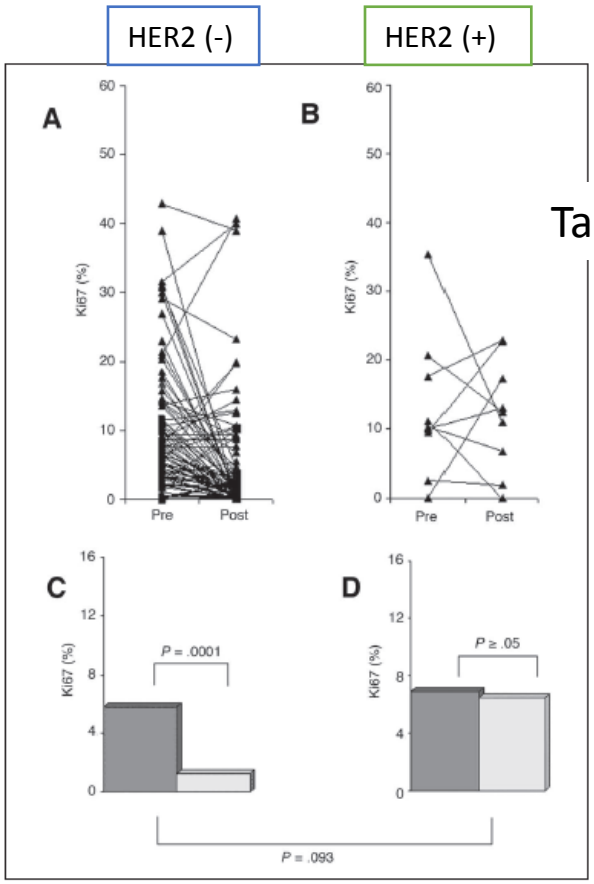
# Who will benefit?: HER2 status

*Ellis et al, J Clin Oncol, 2006*

Letrozole

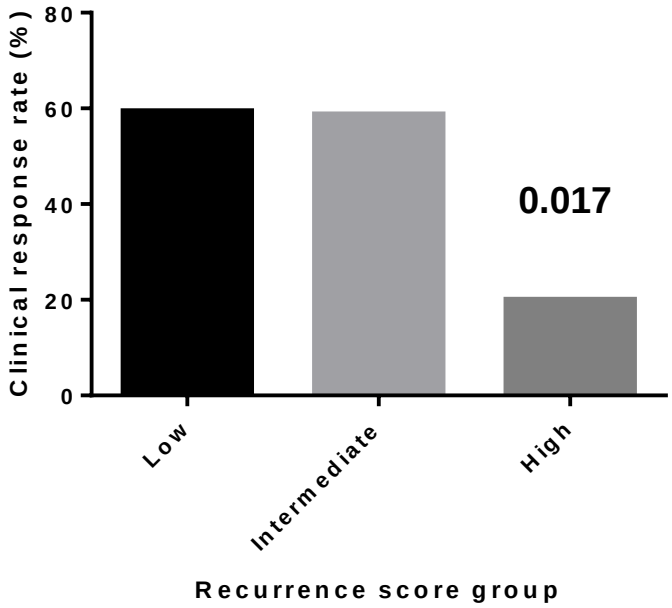


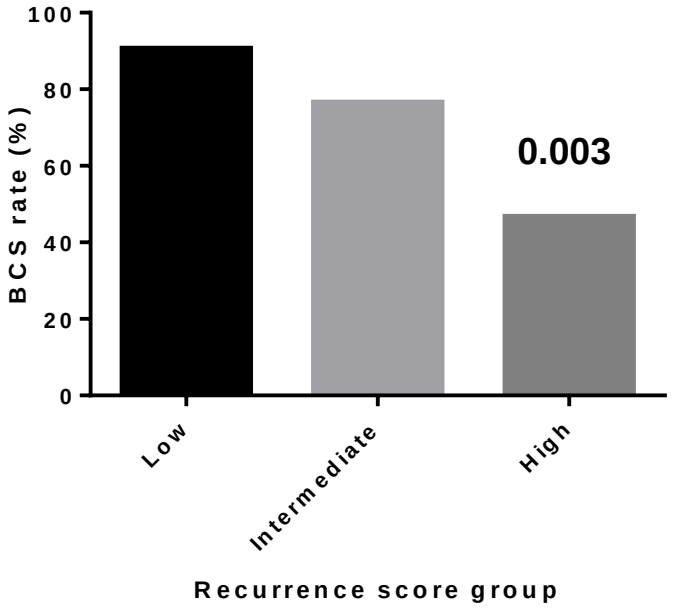

Tamoxifen




HER2 positivity is related to lower suppression of Ki67
→ Treatment resistance to endocrine therapy alone?

# 21-gene assay Recurrence Score® as a predictor of clinical response to 24 weeks of neoadjuvant exemestane

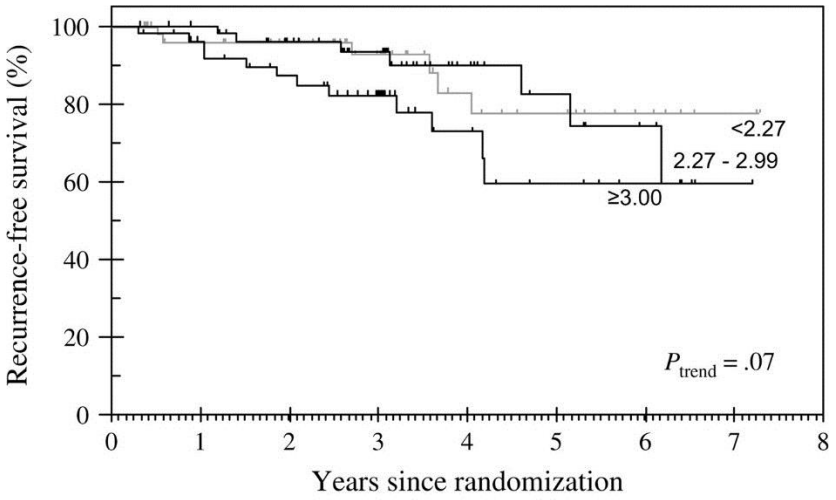


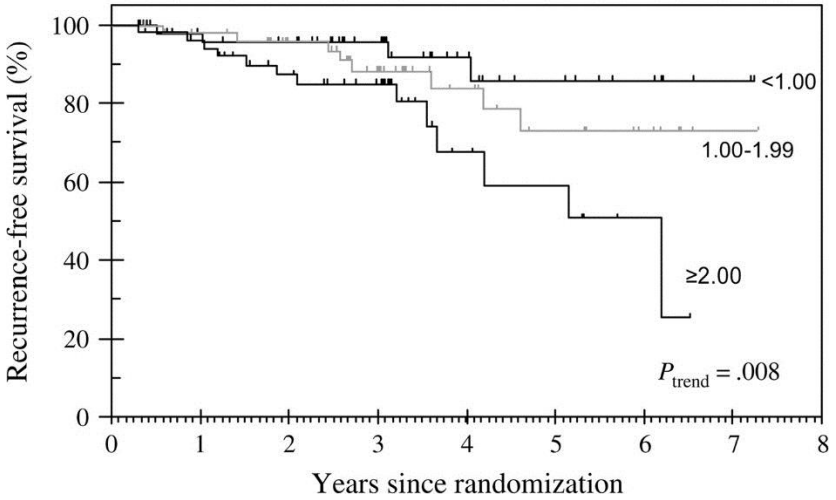

Ueno T, et al. Int J Clin Oncol 2014

# RFS according to **Ki67** tertiles in IMPACT trial

**Ki67 at baseline**




**Ki67 after 2 wks of treatment**




change in Ki-67 level after 2 weeks of tx was of prognostic value for RFS, rather than baseline Ki-67 level.

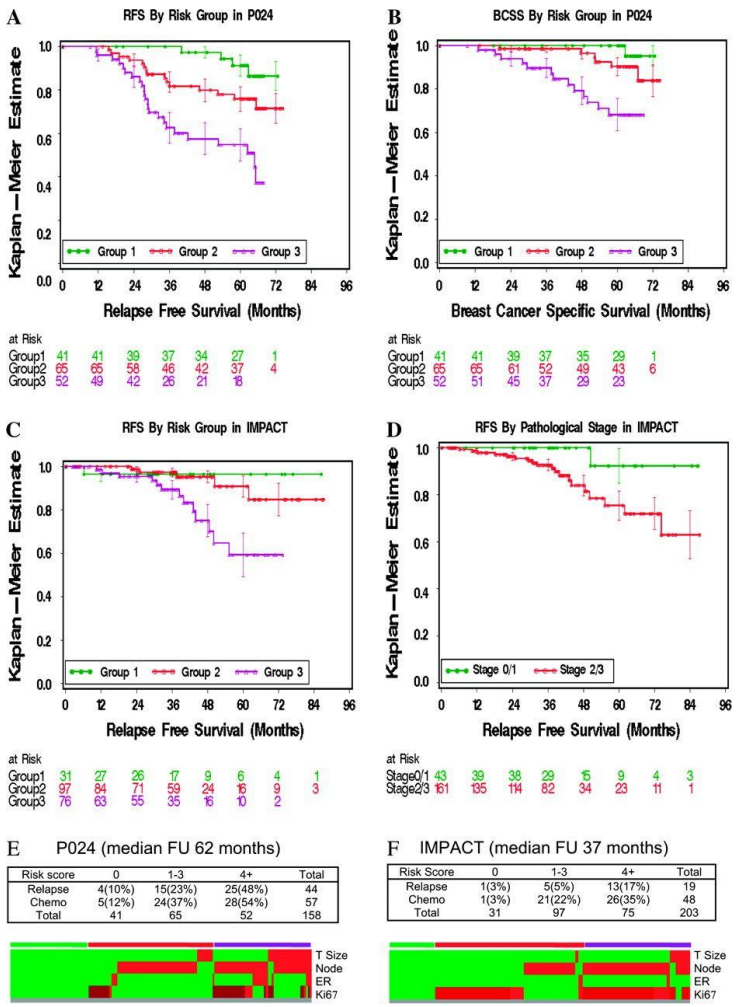
**Dowsett M et al. JNCI J Natl Cancer Inst 2007;99:167-170**

# **PEPI score** (The preoperative endocrine prognostic index)

**Table 4.** The preoperative endocrine prognostic index*

| Pathology, biomarker status | RFS | | BCSS | |
|---|---|---|---|---|
| | HR | Points | HR | Points |
| Pathological tumor size | | | | |
| T1/2 | — | 0 | — | 0 |
| T3/4 | 2.8 | 3 | 4.4 | 3 |
| Node status | | | | |
| Negative | — | 0 | — | 0 |
| Positive | 3.2 | 3 | 3.9 | 3 |
| Ki67 level | | | | |
| 0%–2.7% (0–1†) | — | 0 | — | 0 |
| >2.7%–7.3% (1–2†) | 1.3 | 1 | 1.4 | 1 |
| >7.3%–19.7% (2–3†) | 1.7 | 1 | 2.0 | 2 |
| >19.7%–53.1% (3–4†) | 2.2 | 2 | 2.7 | 3 |
| >53.1% (>4†) | 2.9 | 3 | 3.8 | 3 |
| ER status, Allred score | | | | |
| 0–2 | 2.8 | 3 | 7.0 | 3 |
| 3–8 | — | 0 | — | 0 |

**Women with PEPI score 0** have extremely low risk of relapse and are unlikely to benefit from adjuvant chemotherapy.




Ellis M J et al. JNCI 2008

# Clinical trials comparing endocrine agents conducted in the neoadjuvant and adjuvant settings

**Table 1** | Clinical trials comparing endocrine agents conducted in the neoadjuvant and adjuvant settings

| Adjuvant trials | | Neoadjuvant trials (Ki-67 analysis) | |
|---|---|---|---|
| Study (*n*) | Results (based on events) | Study (*n* with available Ki-67 data) | Results (based on levels of Ki-67) |
| BIG 1-98 (8,010)[16] | Letrozole > tamoxifen | P024 (185)[13] | Letrozole > tamoxifen |
| ATAC (9,366)[24] | Anastrozole > tamoxifen and anastrozole+tamoxifen | IMPACT (259)[14] | Anastrozole > tamoxifen and anastrozole+tamoxifen |
| MA27 (7,576)[28] | Anastrozole similar to exemestane | ACOSOG Z1031 (266*)[29] | Anastrozole similar to exemestane |
| FACE trial (estimated 4,000)[30] | Pending | ACOSOG Z1031 (266*)[29] | Letrozole similar to anastrozole |

*The number of patients with baseline and on-treatment Ki-67 values in the three-way comparison in the Z1031 trial were anastrozole, *n* = 86; exemestane, *n* = 91; and letrozole, *n* = 89. Abbreviation: > superior.

Goncalves, R. *et al*. (2012) Use of neoadjuvant data to design adjuvant endocrine therapy trials for breast cancer
*Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2012.21

nature REVIEWS CLINICAL ONCOLOGY

# Ongoing and Future trials

# ALTERNATE Schema

**Eligibility**

Post-menopausal Clinic al Stage II or III ER+ (Al lred 6-8) HER2-

**BEFORE SURGERY**

**AFTER SURGERY**

REGISTRATION

BIOPSY

RANDOMIZE

**6 cycles (each cycle is 4 weeks)**

- Arm I
- Arm II
- Arm III

4w 1 2 w BIOPSY

Ki67 <10% –

- Arm I
- Arm II
- Arm III

Ki67>10%

**Neoadjuvant Chemotherapy Group**
Chemotherapy (4-6 cycles)

Cycle 1 day 2 optional biopsy (if receiving paclitaxel)

**SURGERY**

**AFTER SURGERY**
Therapy of Physician Choice

FOLLOW

SURGERY

**Modified PEPI 0**
Chemo NOT re commended

- **Arm I** A x 4.5 yrs
- **Arm II** F x 1.5 yrs then A x 3 yrs
- **Arm III** (A+F) x 1.5 yrs then Ax3 yrs

FOLLOW

**Modified PEPI > 0**
Chemo recom mended

Endocrine therapy of Physician's Choice

FOLLOW

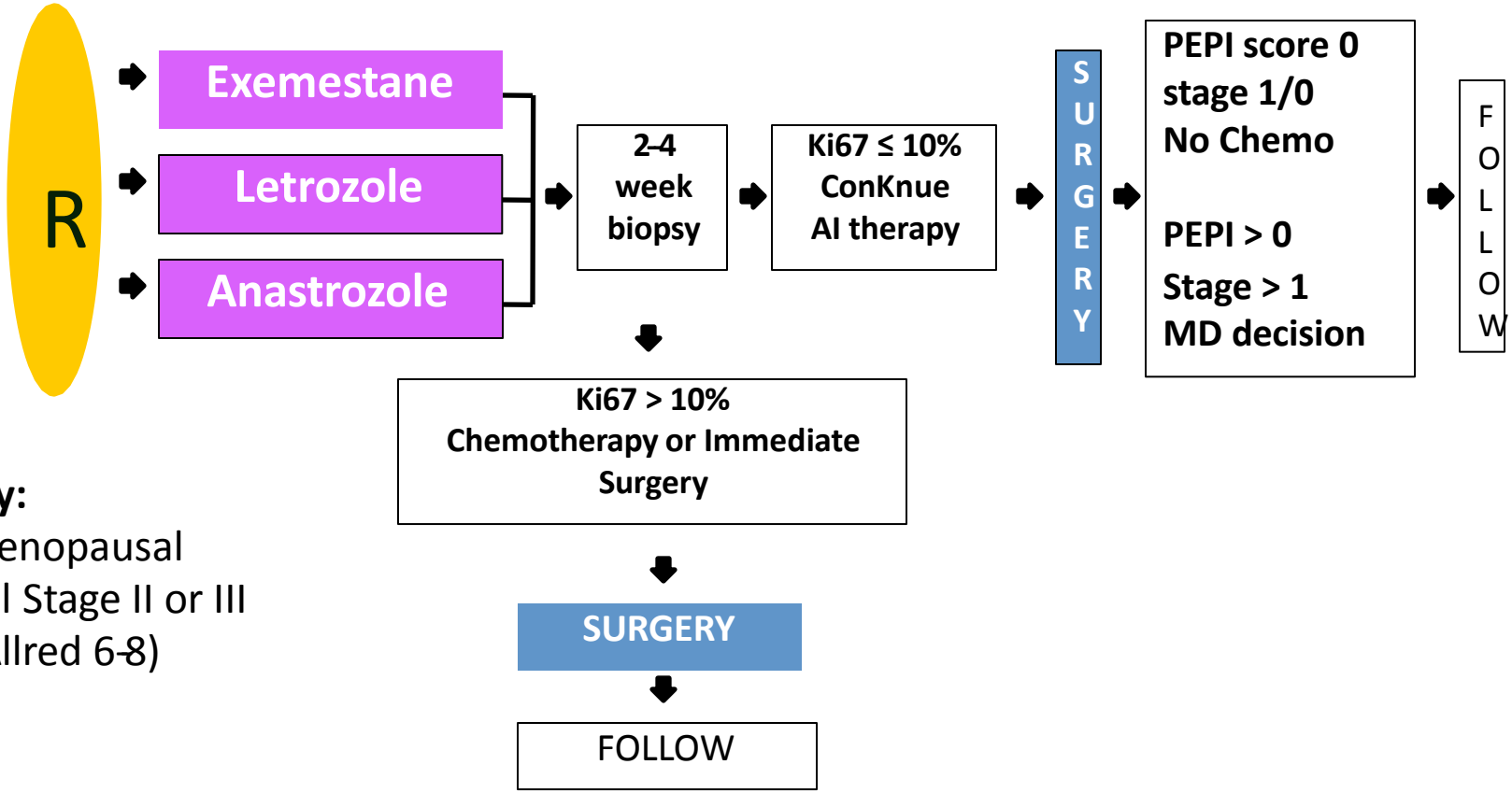
**Arm I: Anastrozole (A)**
**Arm II: Fulvestrant (F)**
**Arm III: Anastrozole + Fulvestrant**

**Red: required tissue collection**
**Blue: optional tissue collection**

**Primary Endpoints:**
**1st Phase: Modified PEPI 0 rate**
**2nd Phase: RFS in Modified PEPI 0**

**Sample size: n=2820**
**1st phase: n=400 each arm**
**2nd phase: n=540 each arm**

# ACOSOG Z1031 Cohort B

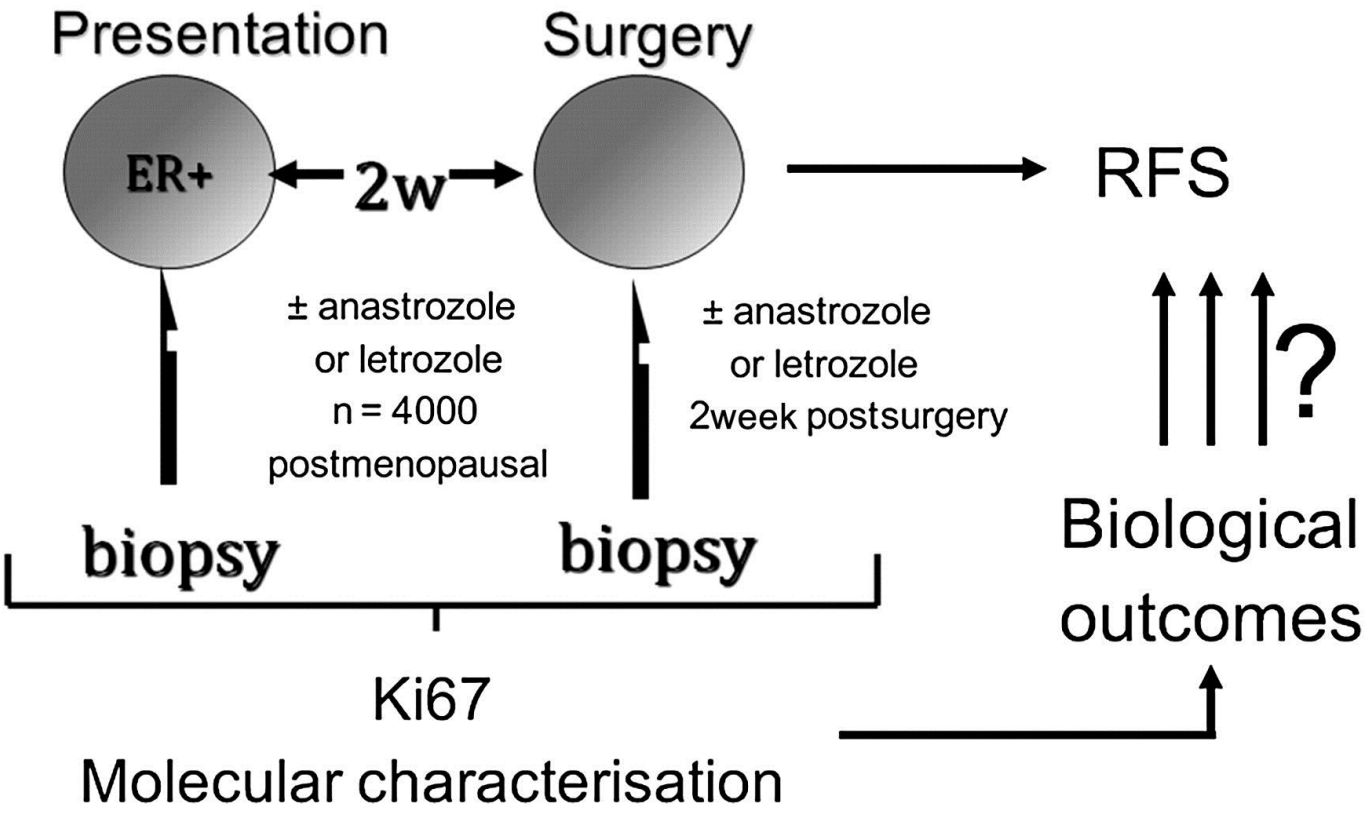



**Eligibility:**

- Postmenopausal
- Clinical Stage II or III
- ER+ (Allred 6-8)
- HER2–

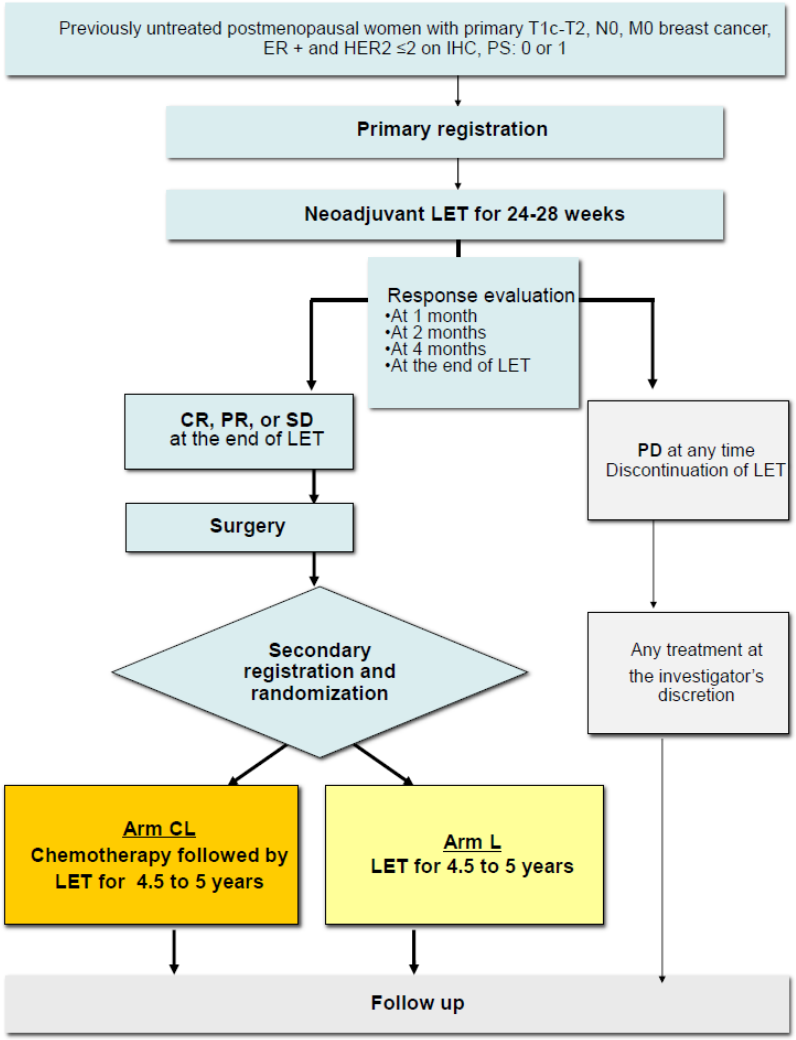
This trial demonstrated the feasibility of using 2-4 week Ki67 and PEPI sore at surgery to tailor subsequent treatment.

# POETIC: PeriOperative Endocrine Treatment for Individualized Care




Mitch Dowsett et al. J Natl Cancer Inst Monogr 2011;2011:120-123

# Adjuvant therapy after NET: NEOS trial




Iwata et al. 2013
ASCO meeting

# NEOADJUVANT TRIALS TO GENERATE PROOF-OF-PRINCIPLE DATA FOR NOVEL ENDOCRINE THERAPY COMBINATIONS

# Neoadjuvant Study to Investigate Novel Targeted Agents


**Endpoints:**

PEPI 0 rate

Ki67 suppression

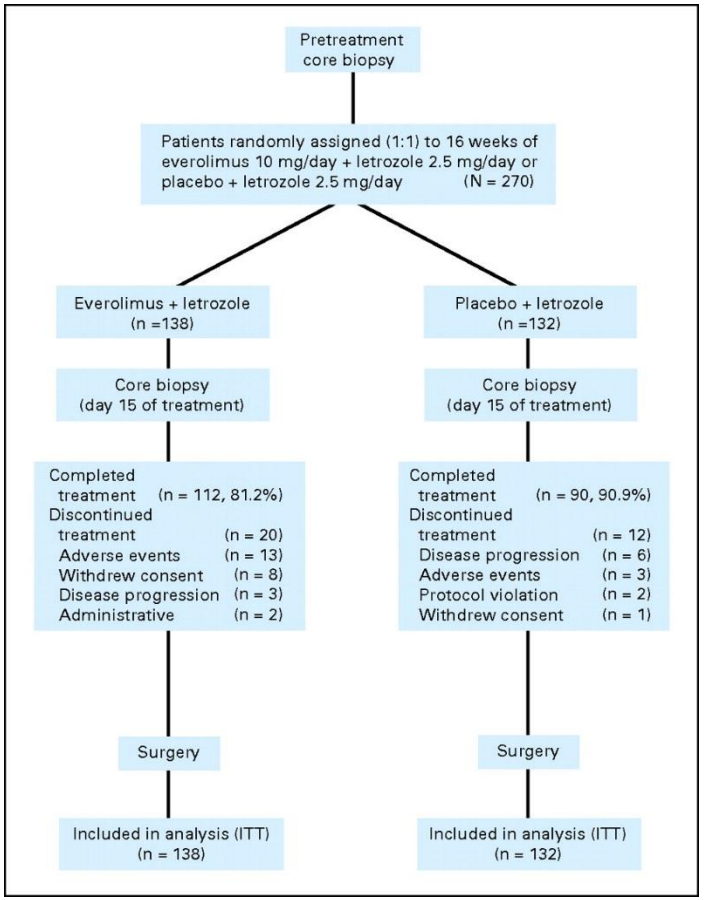

Cynthia Ma, SABCS 2015

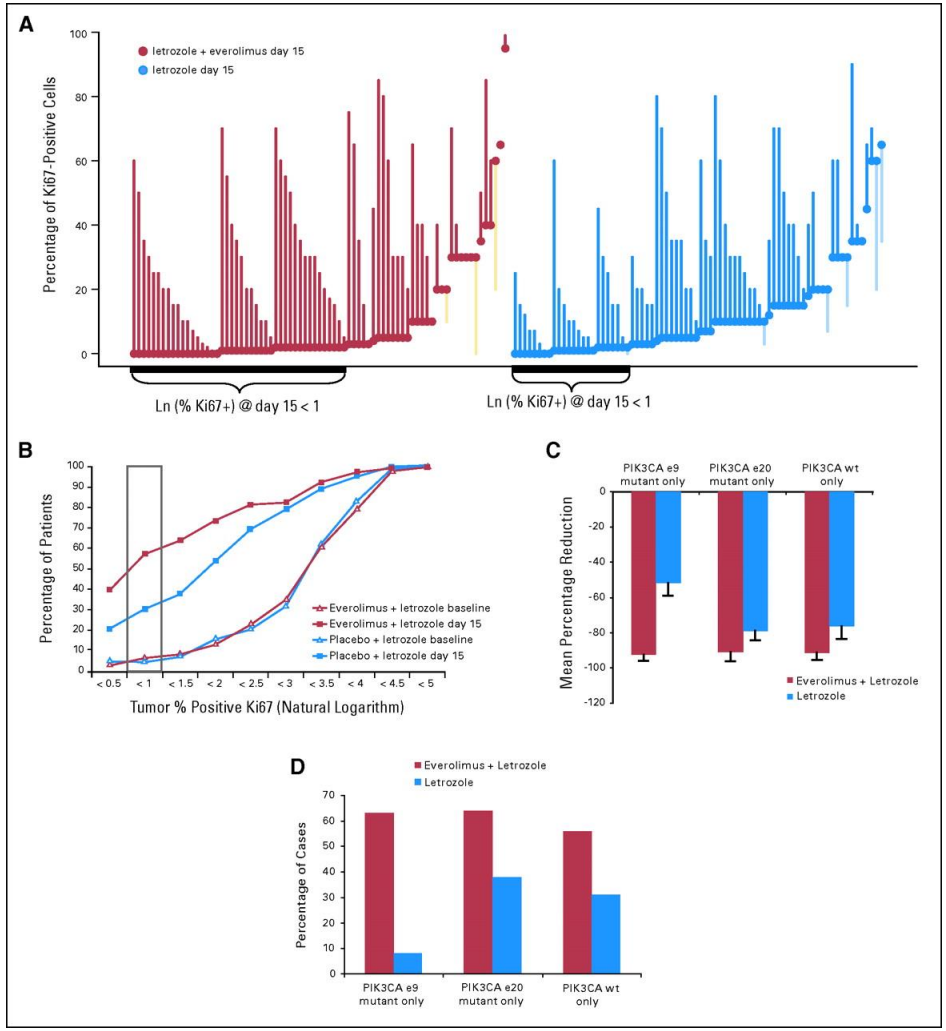
# Phase II neoadjuvant studies of endocrine therapy combined with the targeted agents

| | Targeted agent<br>(endocrine agent) |
|---|---|
| PI3K inhibitor | BYL719 or buparlisib (letrozole)<br>GDC-0032 (letrozole) |
| Akt inhibitor | MK-2206 (anastrozole) |
| Cdk 4/6 inhibitor | PD0332991 (anastrozole)<br>Palbociclib (letrozole) |
| HER2 therapy | Lapatinib (letrozole)<br>Trastuzumab (letrozole) |

Agrawal and Mayer, Curr Oncol Rep 2015

# Phase II neoadjuvant Letrozole +/- Everolimus




Baselga et. al., JCO 27:2630-2637 (2009).

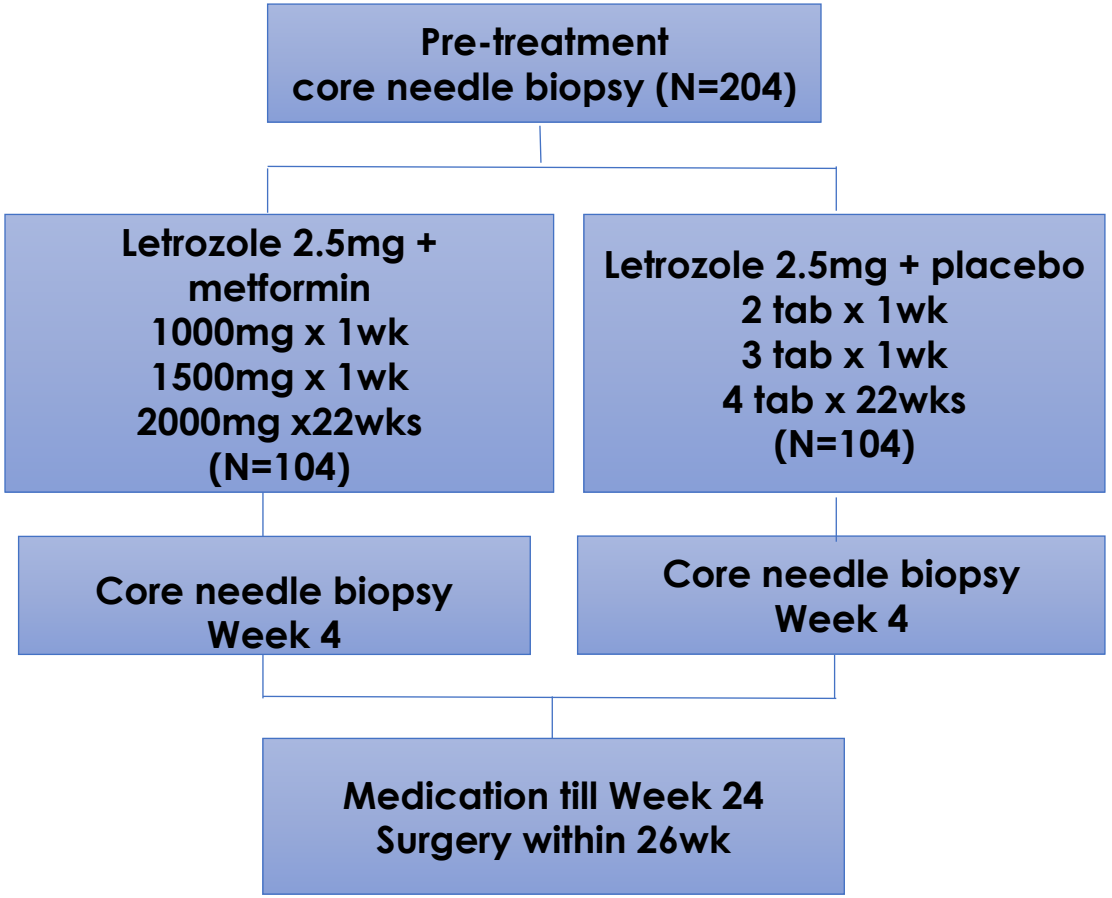
# Phase II randomized study of neoadjuvant METformin plus letrozole vs placebo plus letrozole for ER-positive pOstmenopausal bReast cancer (METEOR)

❖Inclusion Criteria

1. ER positive invasive BC
2. Clinically measurable, Stage II or III tumor
3. Postmenopausal
4. Non-diabetic

1' end point: clinical response rate

2' end point: pCR, BCS rate, toxicity, breast density change, Biomarker study




71.6% were enrolled now

P.I: Wonshik Han

# Conclusion

- NHT/NET is increasingly becoming an integral part of breast cancer management especially in postmenopausal women with ER+, HER2- BC
- NET could downsize large tumors feasible for BCS
- NET has comparable response rates vs NCT and could be a safe alternative to NCT for certain patients (LN response is a concern)
- AIs have demonstrated superior results than tamoxifen
- Continuing NET beyond 3–4 months demonstrated additional clinical responses and further reductions in tumor size
- Ki-67 change (PEPI score) is a useful biomarker for long term outcome
- NET is a very useful back bone for testing a new drug synergizing with hormone therapy


# Thank you very much for attention