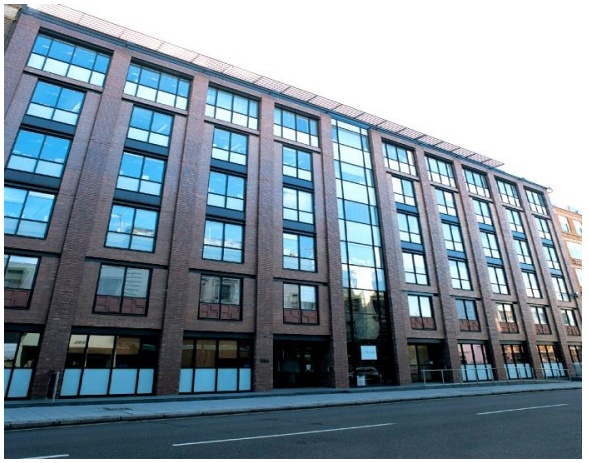
My Journey in Endocrine Therapy for Breast Cancer



Ian E Smith

Royal Marsden Hospital and Institute of Cancer Research, London

April 2019, Korea

On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions of a New Method of Treatment, with Illustrative Cases.

George Thomas Beatson Lancet, 2 (1896) 104

ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.[1]

BY GEORGE THOMAS BEATSON, M.D. EDIN.,

SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.

I HAVE no doubt it has fallen to the lot of nearly every medical man to have been consulted from time to time by patients suffering from carcinoma so widely spread or so situated that it has been quite apparent that nothing in the way of operative measures could be recommended. Such

Early Types of Endocrine Therapy for Breast Cancer

Oophorectomy

Adrenalectomy

Hypophysectomy

Oestrogens

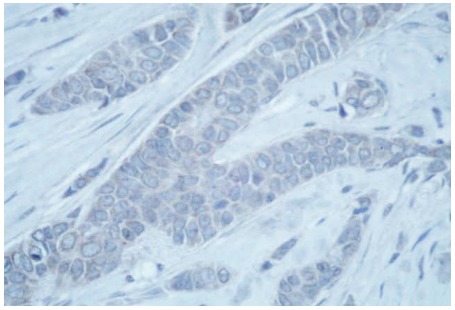
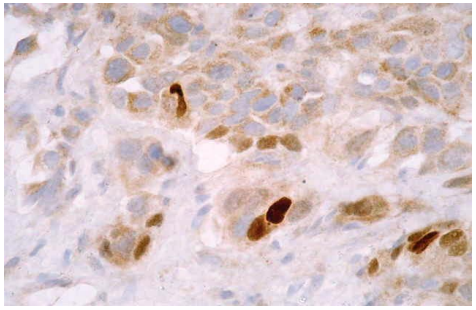
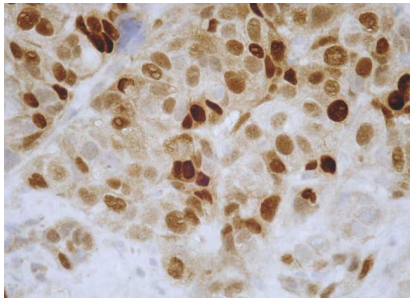
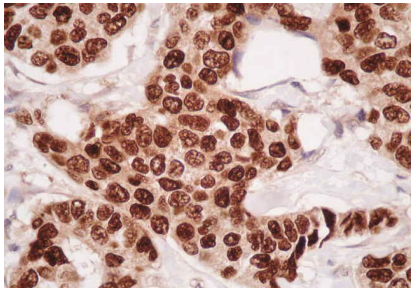
Androgens

Oestrogen Receptor (ER)
Jensen and Jacobsen (1962)

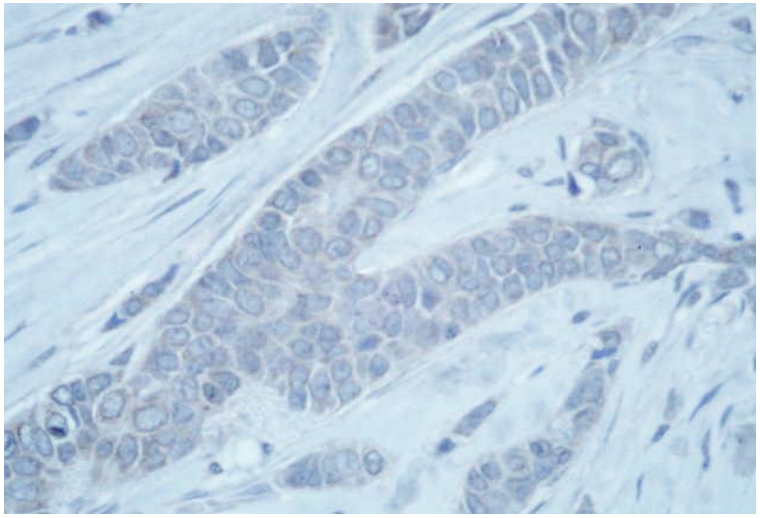
^{3}H-estrogen bound by target tissues in rats
- uterus, vagina, pituitary

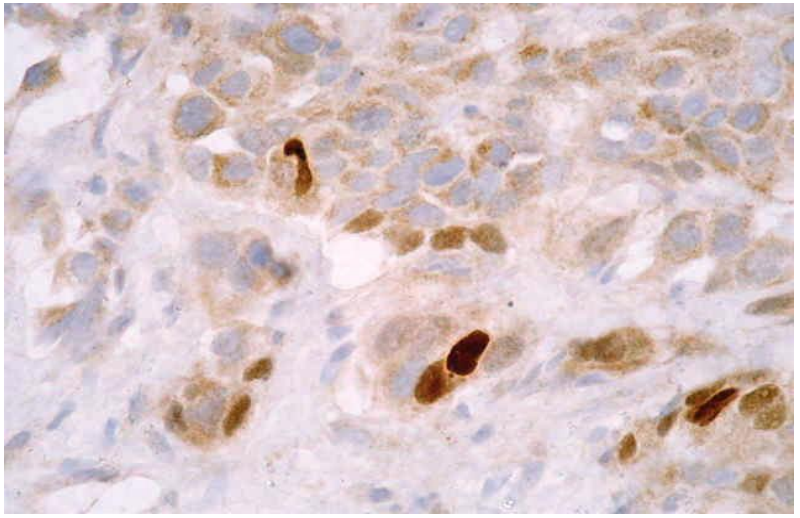
Could the binding of estrogen by breast cancer determine endocrine response?

Would the absence of estrogen binding (ER-negative) indicate poor likelihood of response?

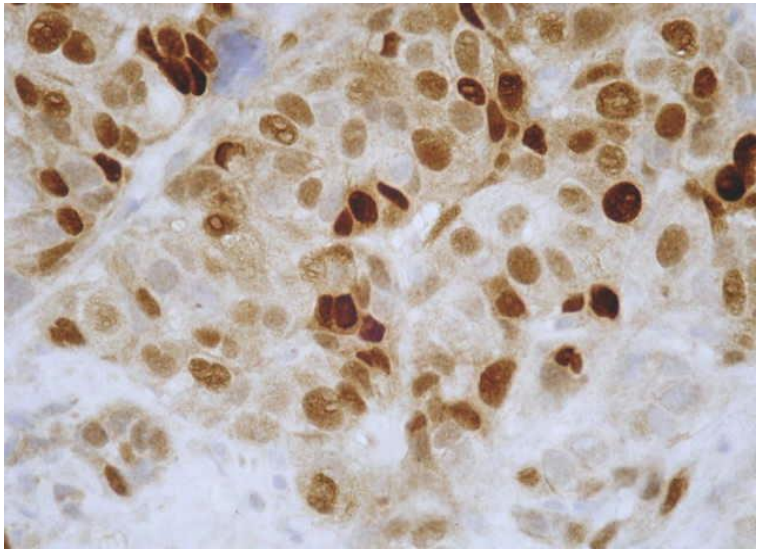





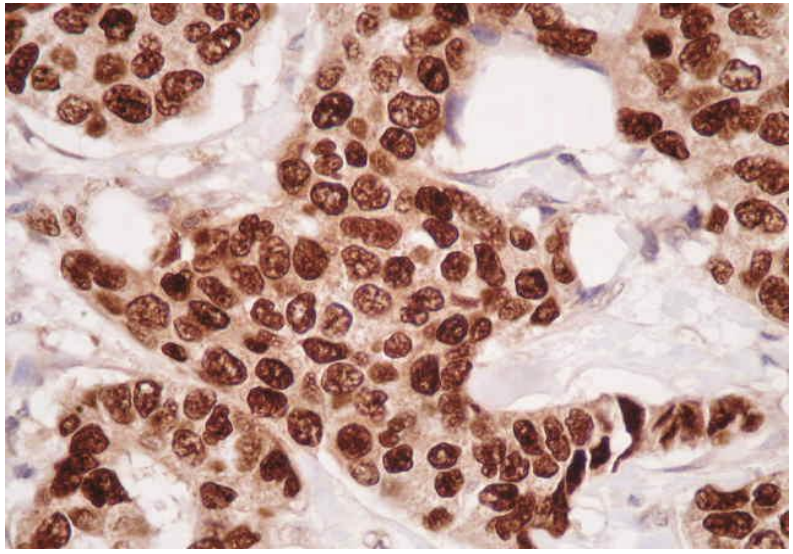
Estrogen Receptor



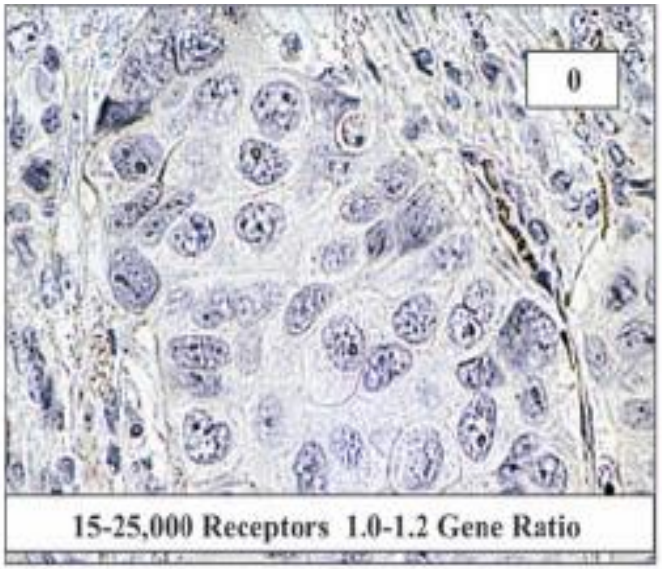


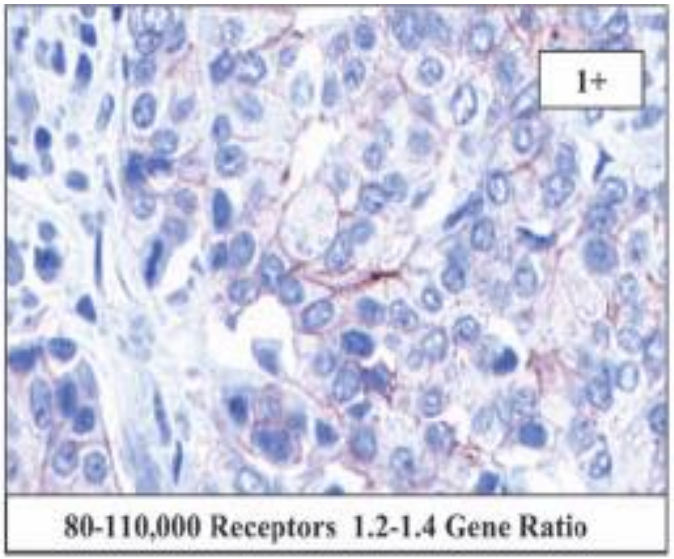
80% of Breast Cancers ER+ve

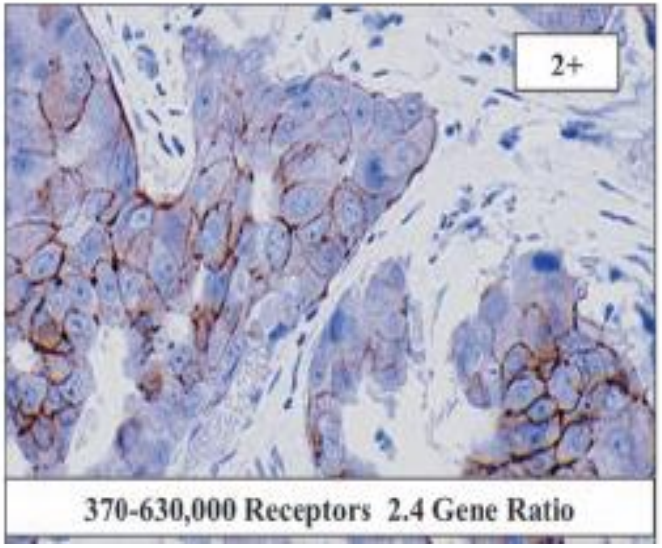


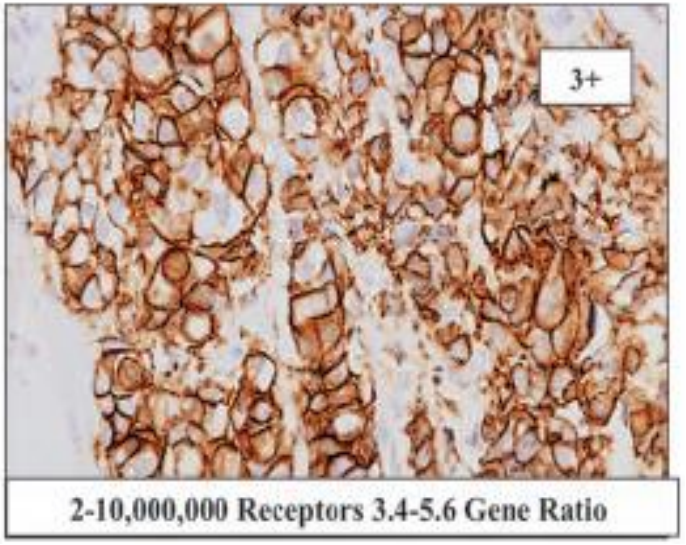


HER2 Immunohistochemical Staining

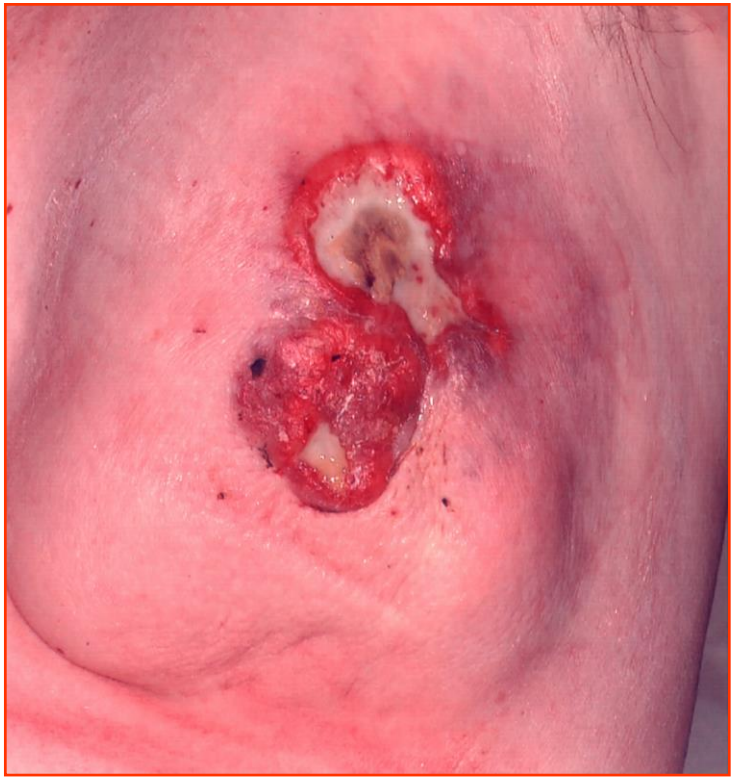






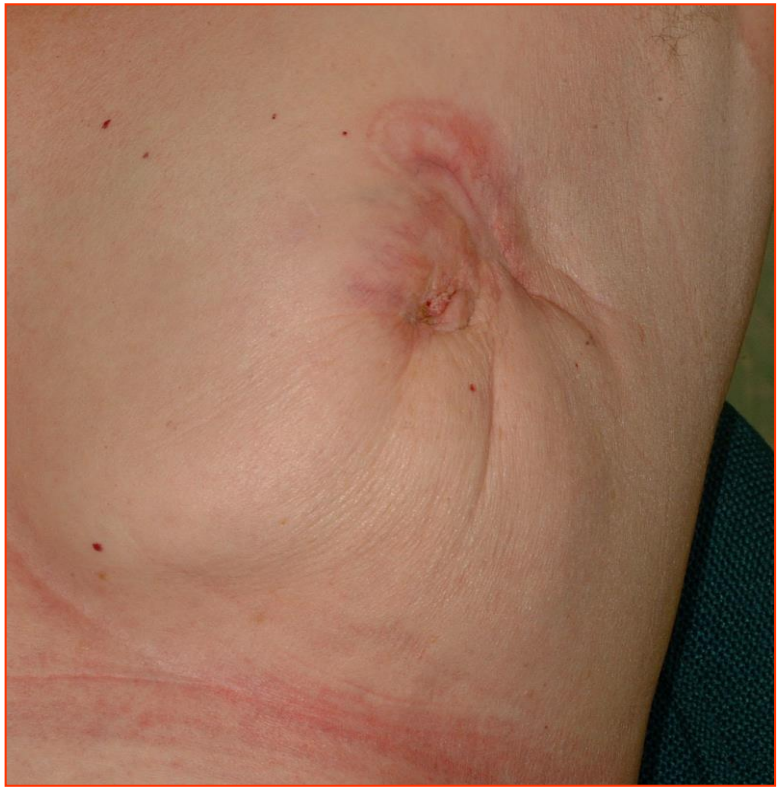


Some Breast Cancers Are Very Sensitive to Estrogen Withdrawal

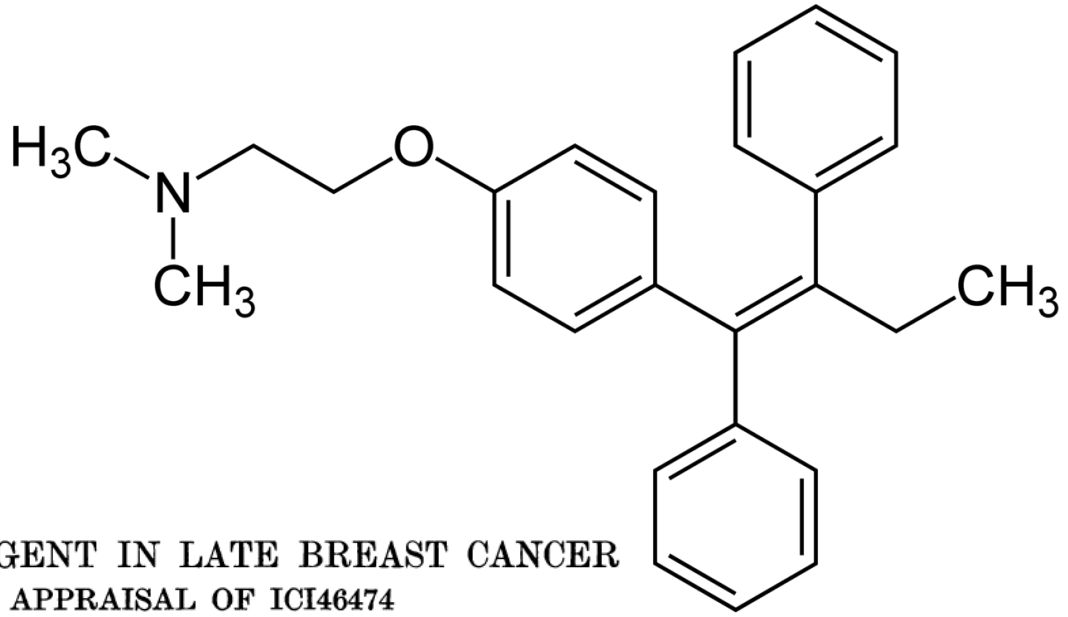


Letrozole

6 mo



Tamoxifen



A NEW ANTI-OESTROGENIC AGENT IN LATE BREAST CANCER
AN EARLY CLINICAL APPRAISAL OF ICI46474

M. P. COLE, C. T. A. JONES AND I. D. H. TODD

From the Christie Hospital and Holt Radium Institute, Manchester M20 9BX

Received for publication April 7, 1971

SUMMARY.—An introductory clinical trial of the anti-oestrogenic agent ICI46474 in late or recurrent carcinoma of the breast is described.

Forty-six patients have been treated, of whom 10 have shown a good response. This is of the same order as that seen with oestrogens and androgens.

The particular advantage of this drug is the low incidence of troublesome side effects.

Br J Cancer. 1971 June; 25(2): 270–275

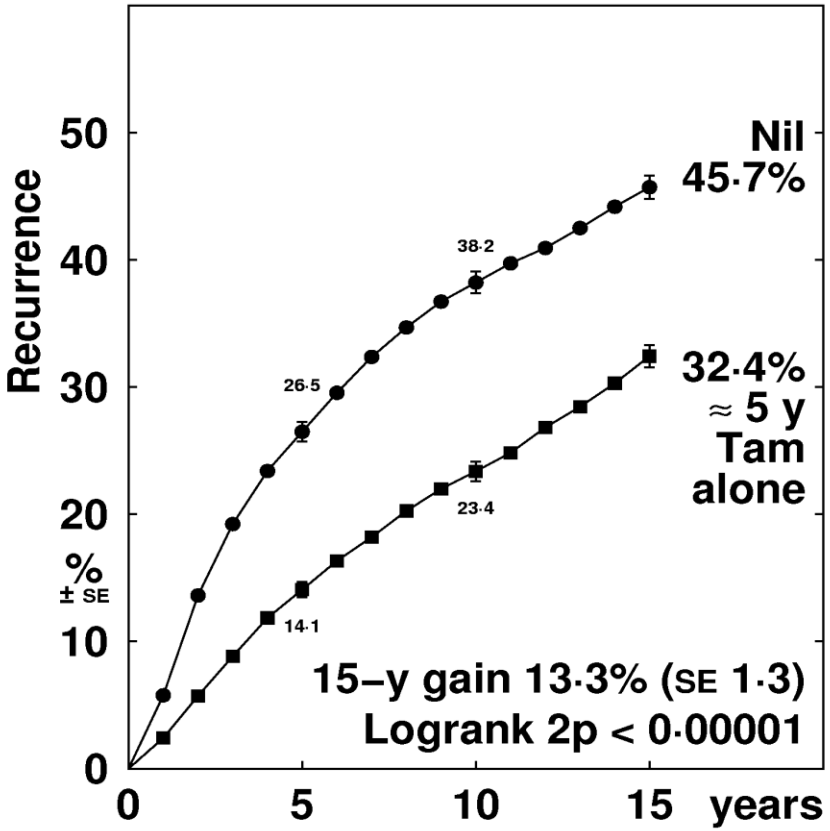
Tamoxifen Efficacy

- In ER+ve metastatic breast cancer:
- 86 clinical studies involving 5353 patients
- 30% response rate; 20% stable disease
- Median Response Durations up to 24 months
- But resistance occurs sooner or later

Litherland S and Jackson IM Cancer Treat Rev 1988;15:183–94.

Adjuvant Tamoxifen Oxford Analysis 2006

≈ 5 years tamoxifen vs. No adjuvant
RECURRENCE
ER+ / ER unknown



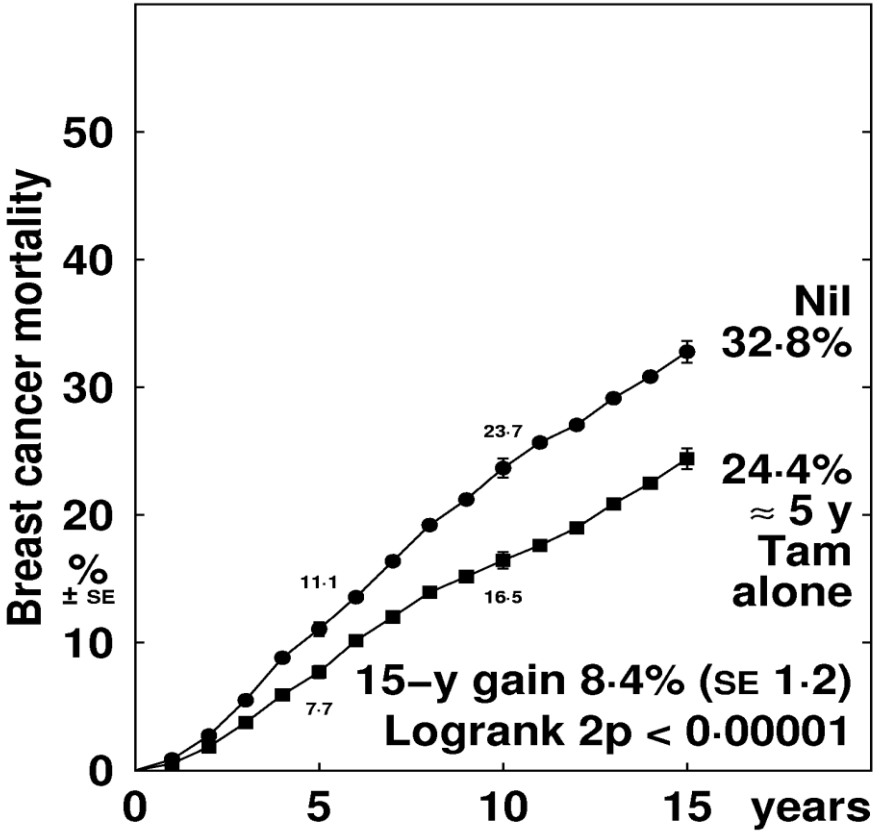
Recurrence rates (% / year) and logrank analyses

	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	3·18 (508 / 15967)	2·46 (313 / 12735)	2·51 (231 / 9187)	3·56 (167 / 4693)
Control	6·18 (907 / 14678)	3·46 (371 / 10712)	2·52 (193 / 7657)	3·28 (126 / 3846)
Rate ratio, from	0·49 SE 0·04	0·65 SE 0·07	0·96 SE 0·10	1·07 SE 0·13
(O–E) / V	–230·8 / 324·1	–66·6 / 157·0	–3·7 / 98·3	4·4 / 65·9

0.49

18:24:24 11 September 2006
Not for publication or citation

≈ 5 years tamoxifen vs. No adjuvant
BREAST CANCER MORTALITY
ER+ / ER unknown



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	1·60 (268 / 16719)	2·08 (290 / 13937)	1·95 (206 / 10562)	2·25 (161 / 7143)
Control	2·31 (379 / 16428)	3·02 (401 / 13286)	2·57 (249 / 9703)	2·39 (152 / 6363)
Rate ratio, from	0·68 SE 0·07	0·66 SE 0·06	0·77 SE 0·09	1·00 SE 0·12
(O–E) / V	–57·0 / 149·2	–65·6 / 159·6	–26·5 / 103·9	–0·3 / 70·6

0.68

0.77

18:34:11 11 September 2006
Not for publication or citation

Reprinted from THE LANCET *September 23, 1978, pp. 646-649*

AMINOGLUTETHIMIDE IN TREATMENT OF METASTATIC BREAST CARCINOMA

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Royal Marsden Hospital, Sutton

Summary 42 patients with metastatic breast carcinoma were treated with aminoglutethimide, which inhibits adrenal steroid hormone synthesis. Treatment was stopped in 2 patients before response could be assessed; of the other 40, 15 (37·5%) had an objective response, 1 (2·5%) showed a response in bone but not in soft tissue, and 4 (10%) had complete or very great relief of metastatic bone pain but no radiological evidence of improvement. 19 (53%) of 36 patients with bone metastases responded to treatment (15 had X-ray evidence and 4 had pain relief), as did 5 (45%) of 11 patients with soft tissue metastases, 2 (25%) of 8 with malignant marrow infiltration, 1 (14%) of 7 with lung metastases, and none of 13 with liver metastases. Response was commonest in patients who had previously responded to other forms of endocrine therapy. Side-effects, usually mild and transient, occurred in a few patients; the most important were an initial period of somnolence in 9 patients and a rash in 5.

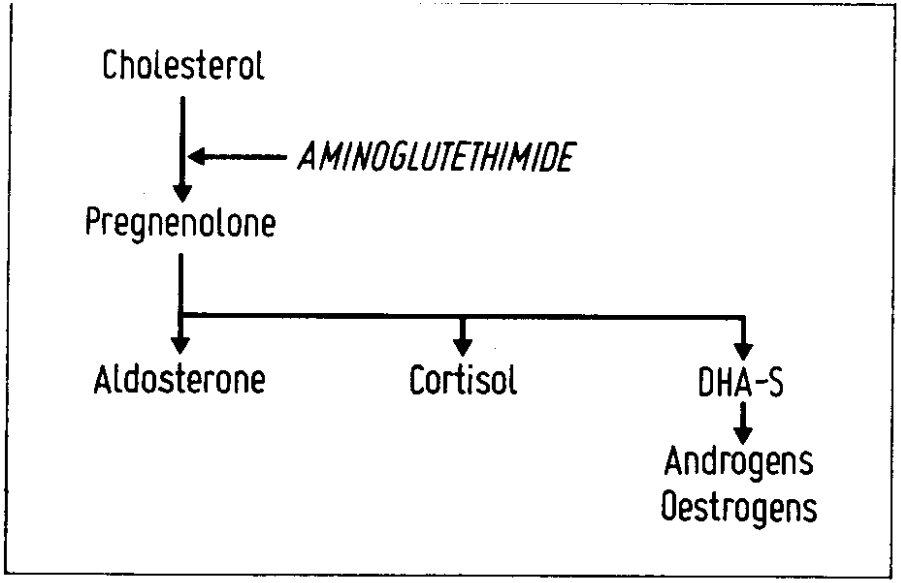
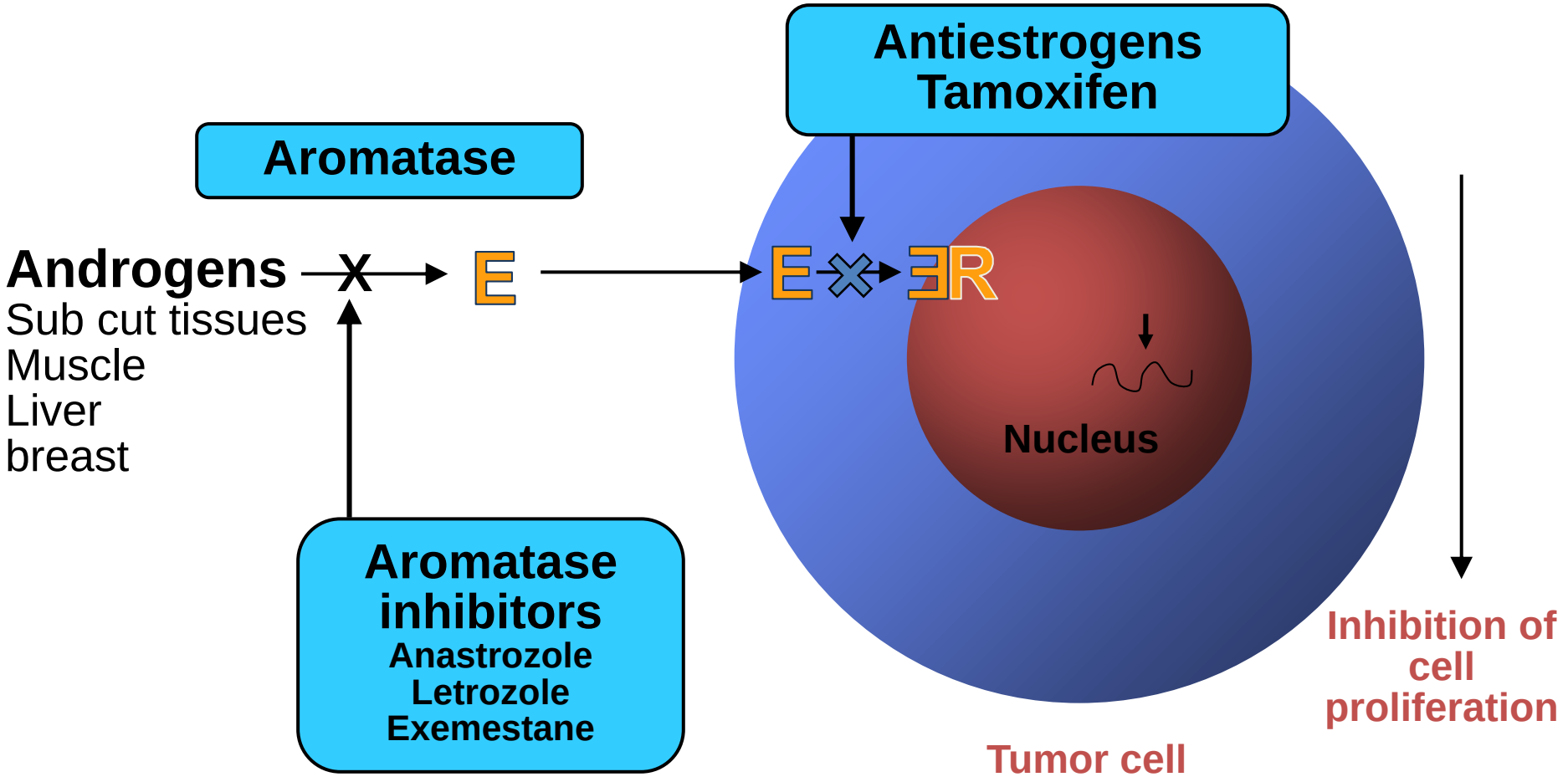


Fig. 1—Site of inhibition of andrenal-steroid synthesis by aminoglutethimide.

Led to:

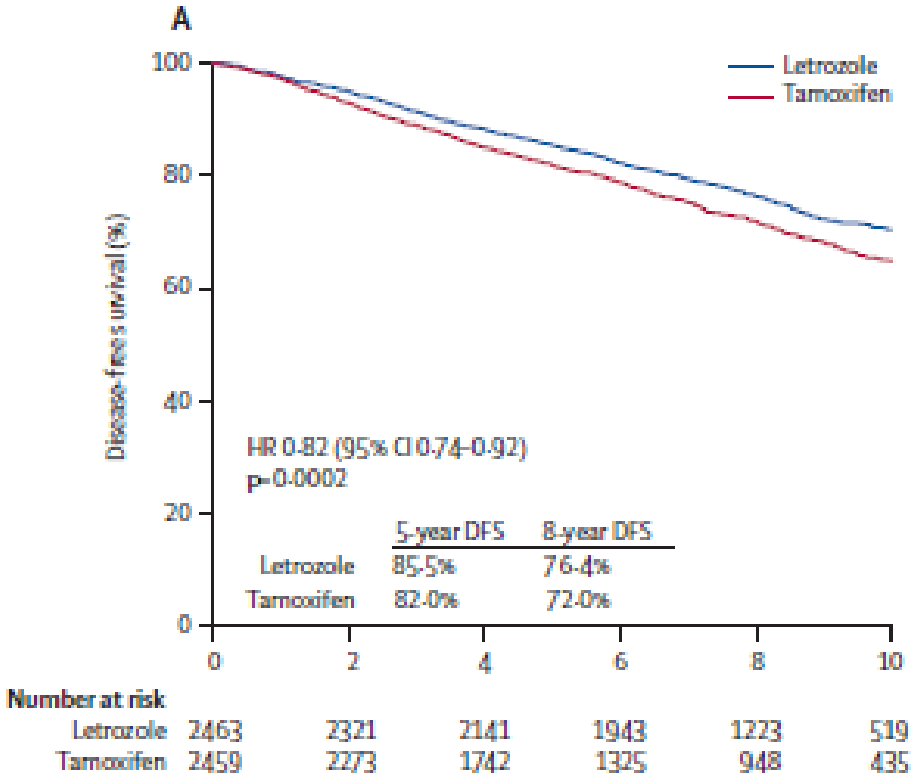
- Low dose AG as an AI
- Letrozole - first in man
- Letrozole –phase 1
- BIG 1-98

Inhibiting the Effects of Estrogen

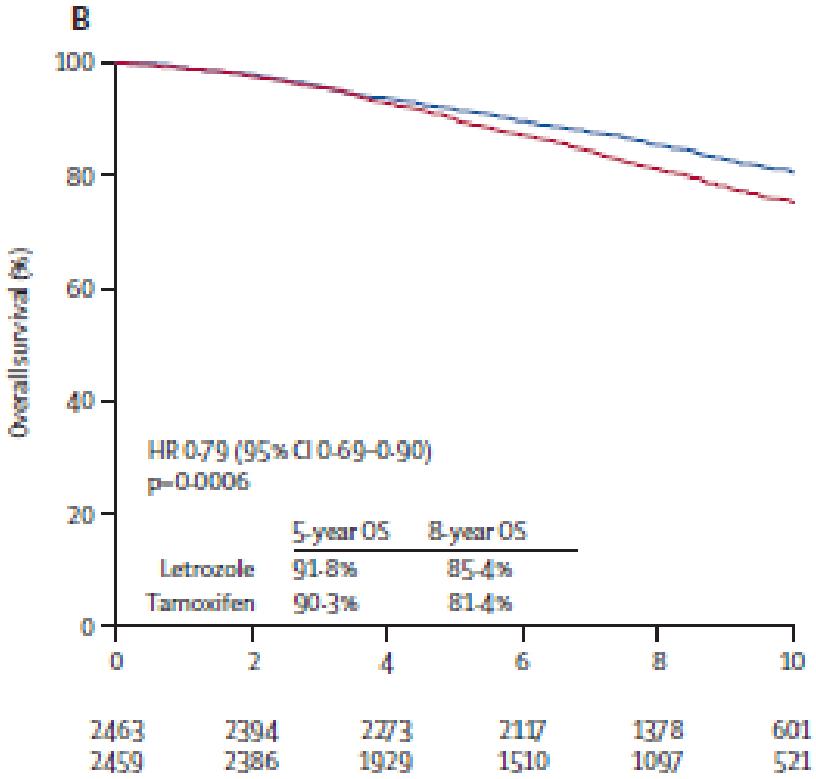


Adjuvant Letrozole v Tamoxifen: BIG 1-98 Median 8 Years FU

DFS



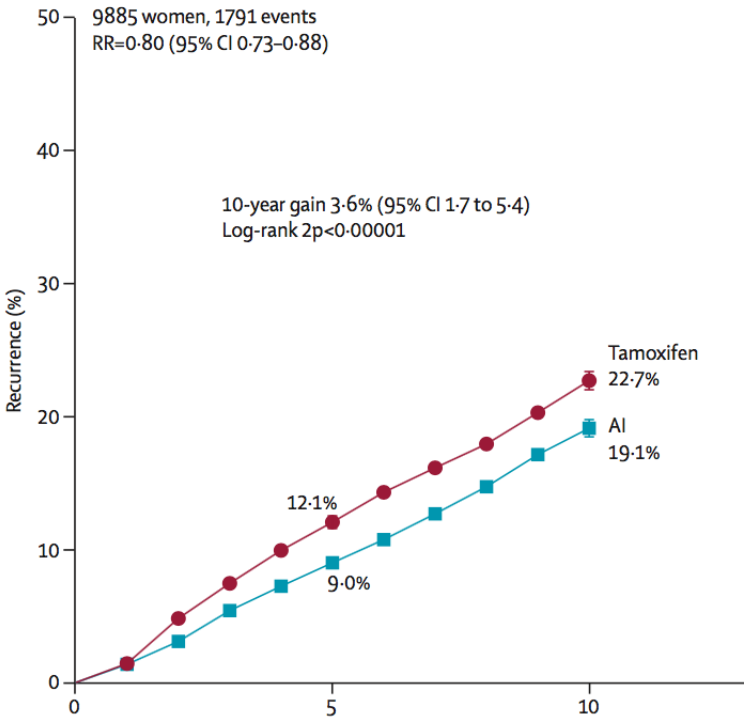
OS



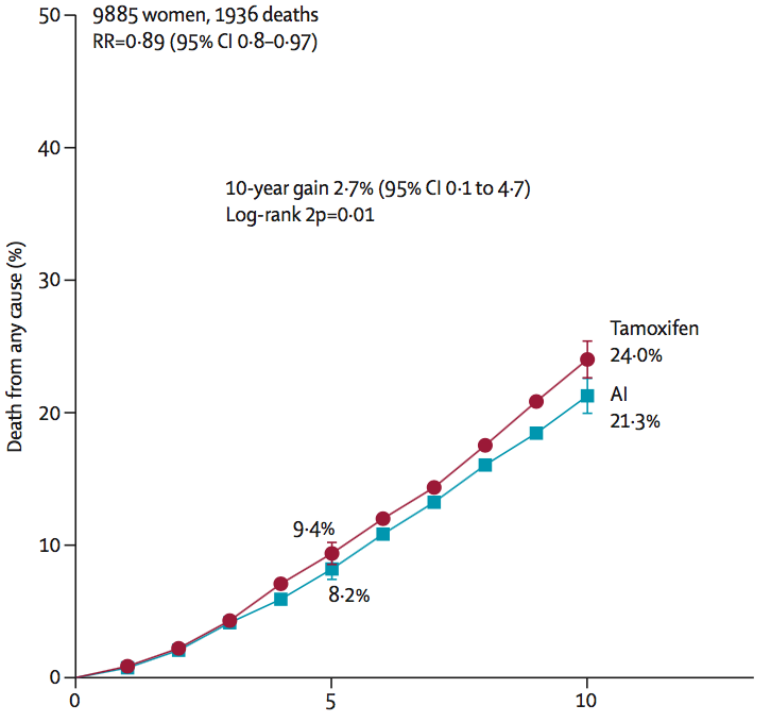
Regan et al Lancet Oncology 12:1101 2011

Aromatase Inhibitors v Tamoxifen in Early Breast Cancer: Meta-analysis

Recurrence



Deaths



EBCTCG Lancet 2015

Endocrine Therapy in Breast Cancer

- Only effective in women with ER+ve cancer (75-80%)

- Tamoxifen Oestrogen antagonist. Doesn't affect circulating E2 levels. Effective in pre-and postmenopausal women

- Aromatase Inhibitors*. Inhibit ostrogen synthesis. Dramatically reduce circulating E2 levels. Only effective in postmenopausal women. Slightly more effective than tamoxifen

*Letrozole; anastrozole; exemestane

Tamoxifen and Aromatase Inhibitors Side Effects/Morbidity

- Both usually well tolerated compared with chemotherapy

- Tamoxifen
  - Venous thrombo-embolism
  - Uterine cancer

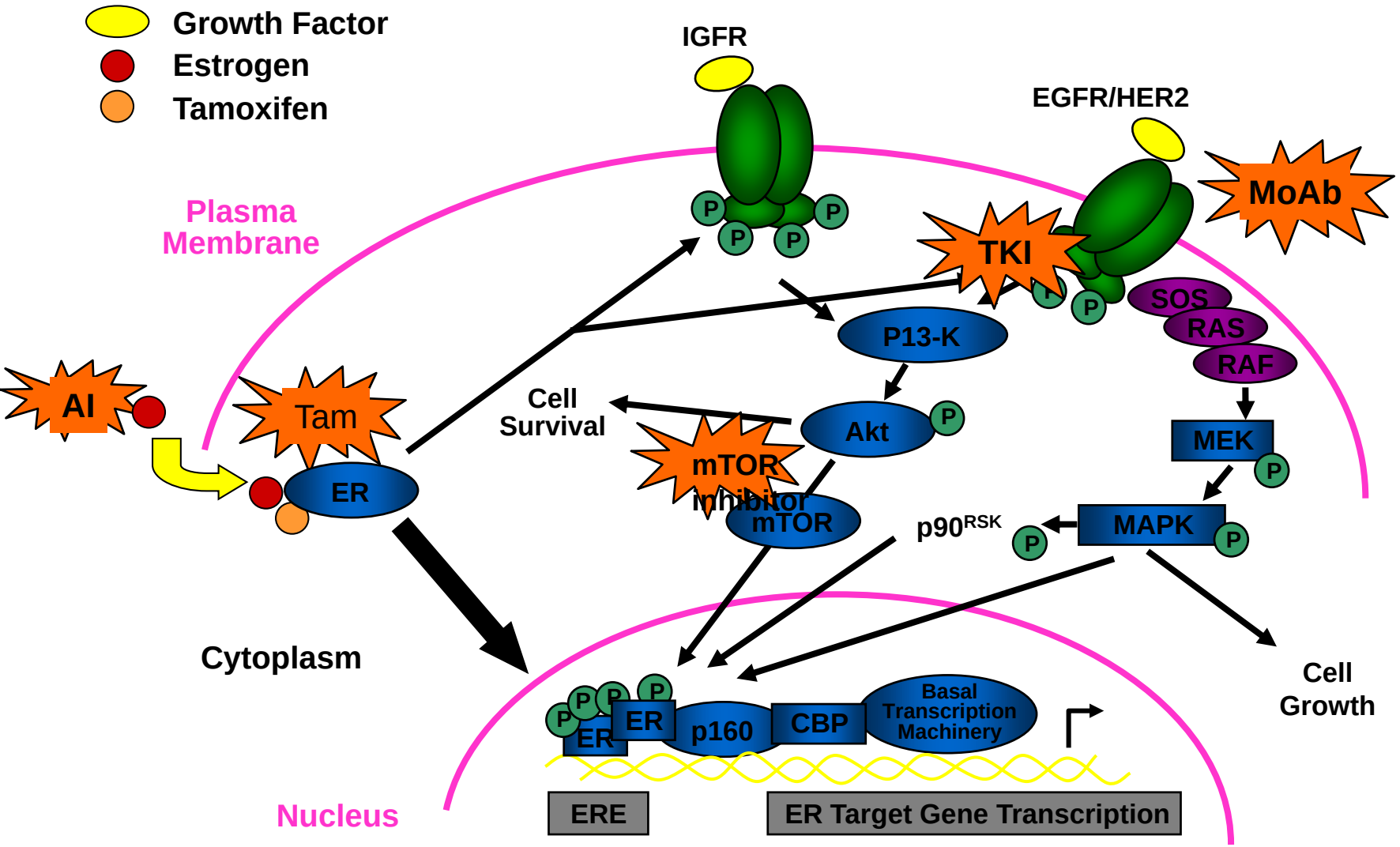
- Aromatase Inhibitors
  - Joint stiffness
  - Bone loss
  - Vaginal dryness

Only 30% of patients with ER+ve metastatic breast respond to endocrine therapy and a further 20% achieve stable disease

Likewise not all patients benefit from adjuvant endocrine therapy

Why?

Cross-talk Between Signal Transduction and Endocrine Pathways



Johnston SRD. *Clin Cancer Res.* 2005;11:889s-899s.

CDK4/6 in Breast Cancer

- Resistance to endocrine therapy presents a major clinical challenge
- The growth of HR+ breast cancer is dependent on Cyclin D1, a direct transcriptional target of ER
- Cyclin D1 activates CDK 4/6 resulting in G1–S phase transition and entry into the cell cycle[1]

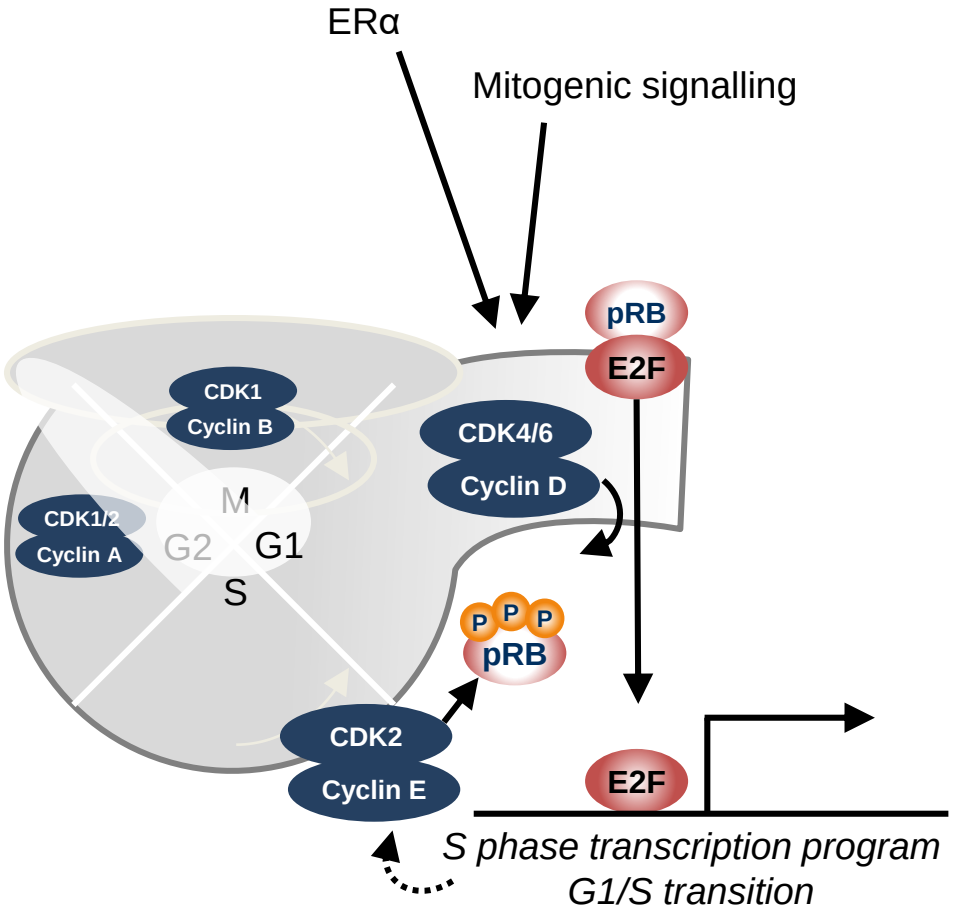
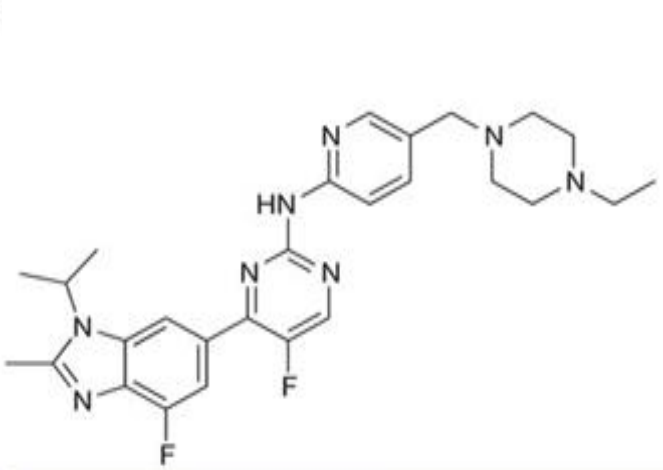
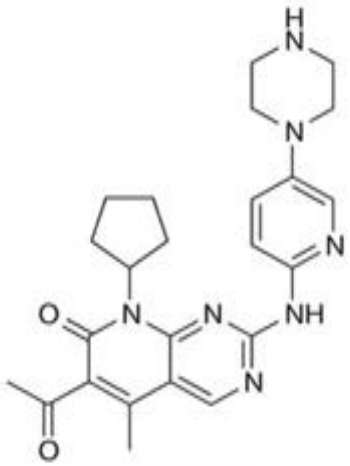


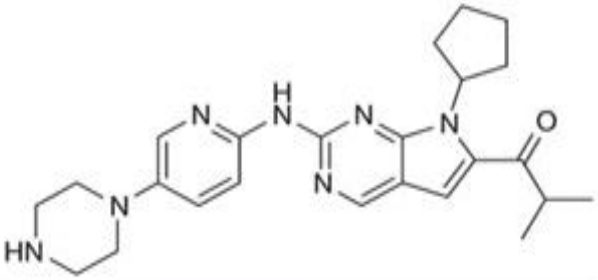
Figure adapted from Asghar, et al. Nat Rev Drug Dis. 2015;14:130-146

Selective CDK 4/6 inhibitors

Abemaciclib **Palbociclib** **Ribociclib**







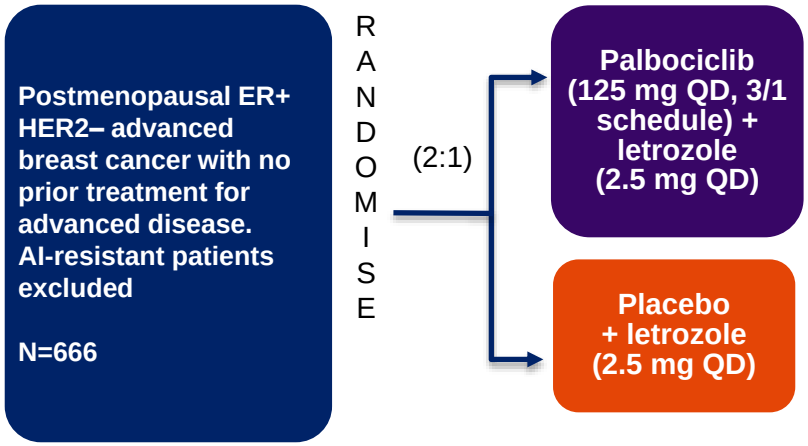
	Abemaciclib (LY-2835219)	Palbociclib (PD-0332991)	Ribociclib (LEE011)
IC_{50}	CDK1: >1 μM	CDK1: >10 μM	CDK1: >100 μM
	CDK2: >500 nM	CDK2: >10 μM	CDK2: >50 μM
	CDK4: 2 nM	CDK4: 9–11 nM	CDK4: 10 nM
	CDK5: ND	CDK5: >10 μM	CDK5: ND
	CDK6: 5 nM	CDK6: 15 nM	CDK6: 39 nM
	CDK7: 300 nM	CDK7: ND	CDK7: ND
	CDK9: 57 nM	CDK9: ND	CDK9: ND

O'Leary B, et al. Nat Rev Clin Oncol. 2016;13(7):417–430.

Nature Reviews | Clinical Oncology

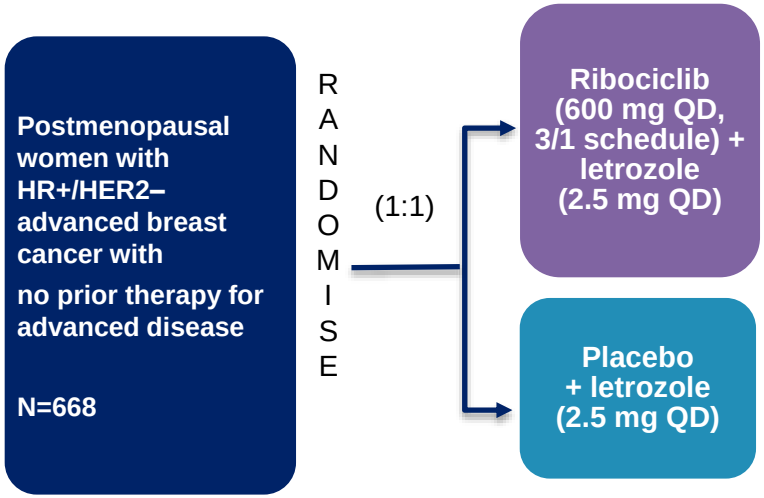
PALOMA-2 & MOLALEESA-2: Design of Phase III Studies

PALOMA-2



- **Primary endpoint:** PFS
- **Secondary endpoints**:
  - Response, OS, safety, biomarkers, PROs

MOLALEESA-2



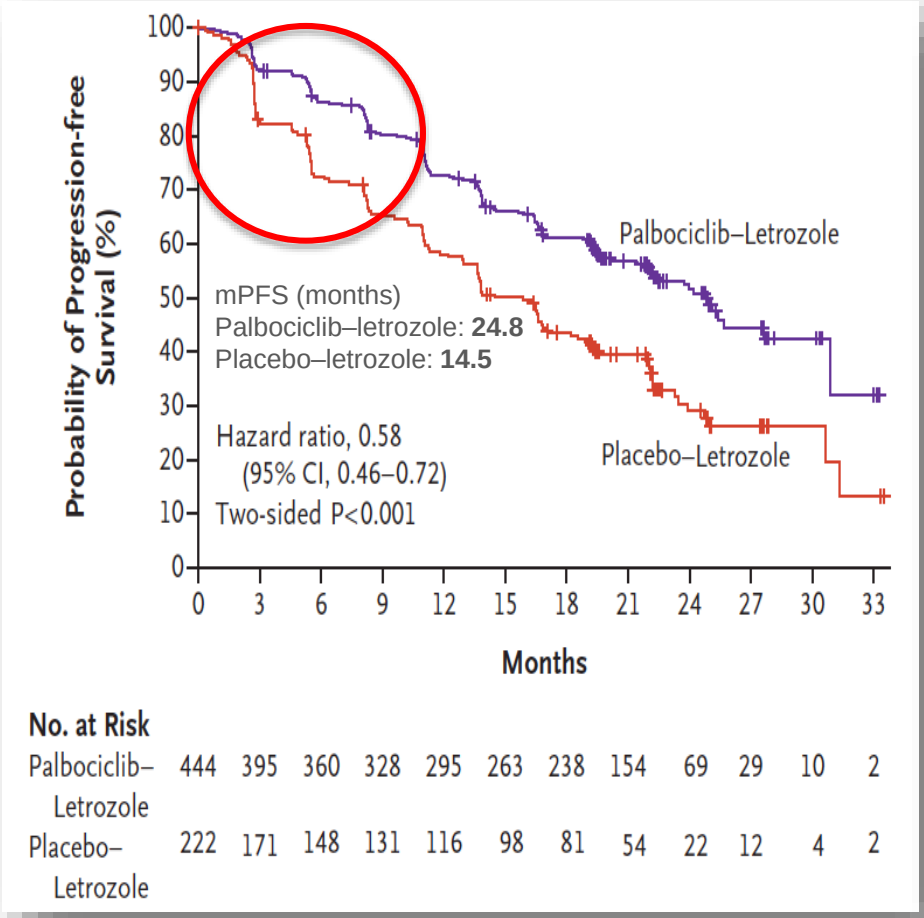
Stratified by the presence/absence of liver and/or lung metastases

- **Primary endpoint:** PFS
- **Secondary endpoints**:
  - OS (key), ORR, CBR, safety

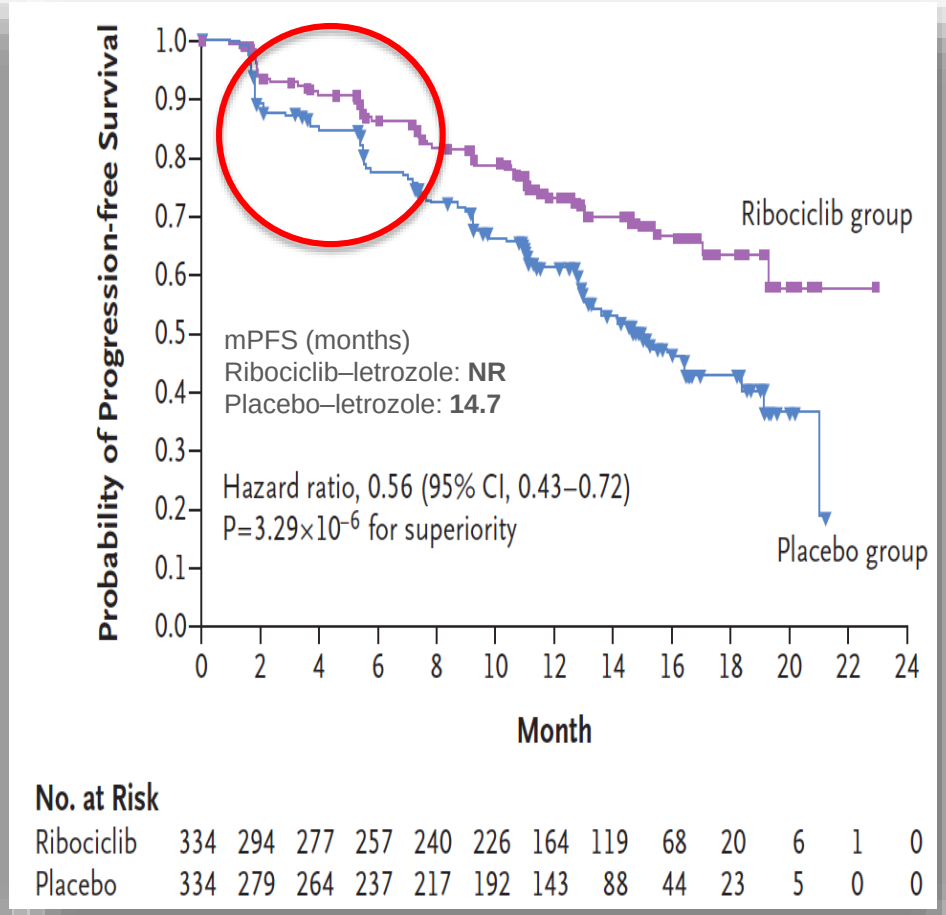
PALOMA-2 & MONALEESA-2: PFS

The NEW ENGLAND JOURNAL of MEDICINE

PALOMA-2
palbociclib



MONALEESA-2
ribociclib

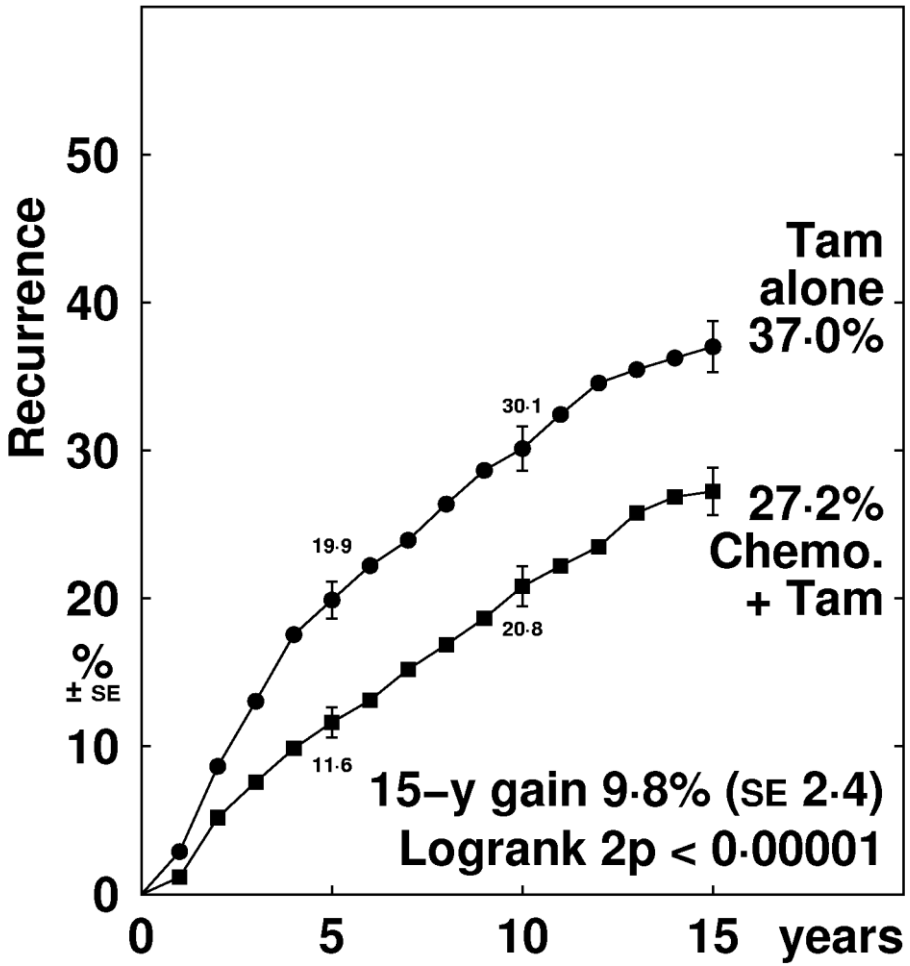


Finn R, et al. NEJM. 2016;375(20):1925–1936

Hortobagyi G, et al. NEJM. 2016;375(18):1738–1748

The Role of Adjuvant Chemotherapy in ER+ve Early Breast Cancer

Polychemo. + tamoxifen vs. Tam. alone
RECURRENCE
ER+, entry age < 50



Recurrence rates (% / year) and logrank analyses

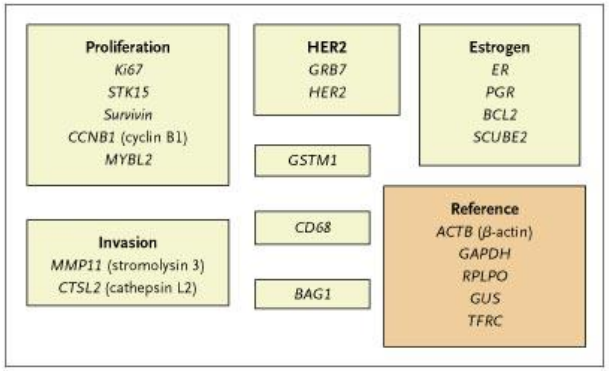
	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Polychemo.	2·62 (129 / 4931)	2·20 (84 / 3814)	1·81 (39 / 2149)	1·86 (3 / 161)
Control	4·35 (203 / 4671)	2·74 (94 / 3427)	2·49 (46 / 1850)	5·51 (7 / 127)
Rate ratio, from	0·56 SE 0·09	0·78 SE 0·14	0·76 SE 0·19	0·33 SE 0·43
(O–E) / V	–43·3 / 74·5	–10·1 / 41·5	–5·5 / 20·3	–2·2 / 2·0

The Big Current Question in the Adjuvant Treatment of Early Breast Cancer

Adjuvant chemotherapy is also an effective treatment for some patients with ER+ve breast cancer

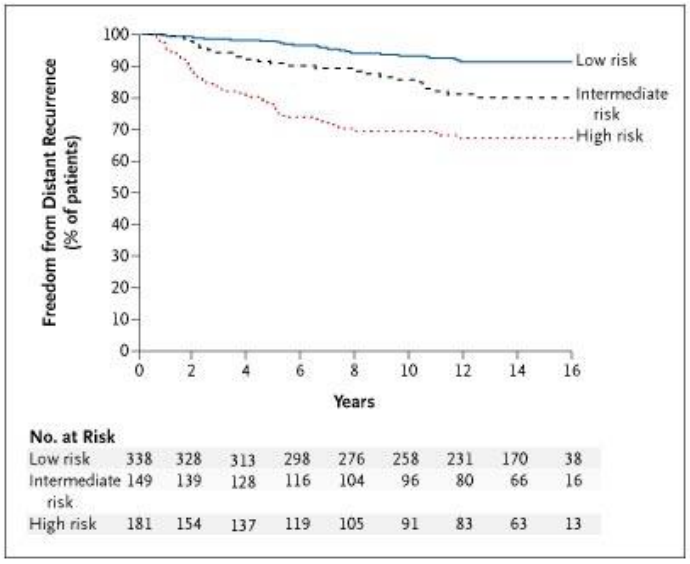
So how can we select which patients only need endocrine therapy alone, and which need additional treatment (eg chemotherapy or a CD4/6 inhibitor)?

Genomic Health Multi-Gene Assay: Oncotype DX

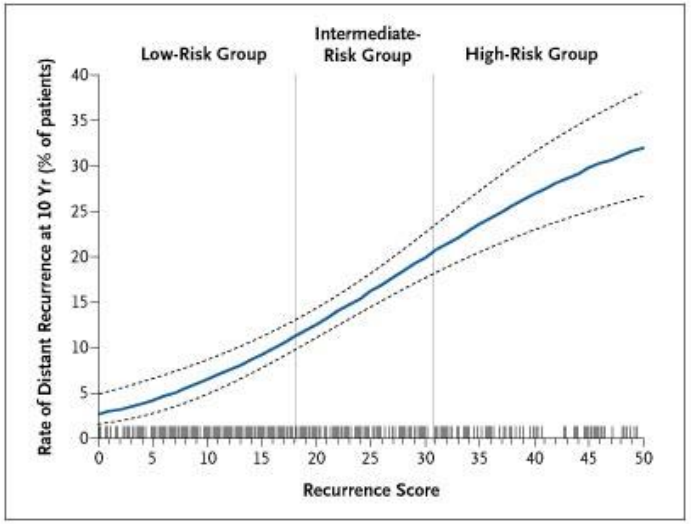


- 21 gene assay
- Includes PgR
- Formalin-fixed PE
- Based on B14 and B20 Trials
- N-ve ER+ve

Likelihood of distant recurrence according to recurrence score



Rate distant recurrence as continuous function of recurrence score



Paik et al NEJM 2004; 351;2817

Genomic Platforms to Identify Prognosis in ER+ Early Breast Cancer

Oncotype DX

Prosigna

Endopredict

Mammoprint

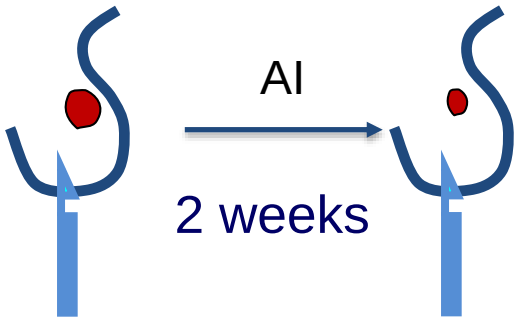
An Important Thing About Breast Cancer

- Anatomically, the primary offers a unique opportunity to assess systemic therapies

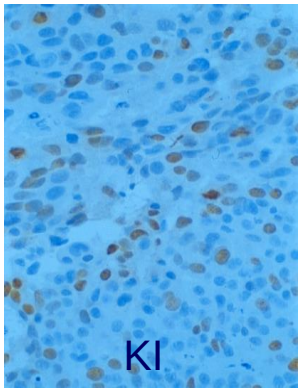
- We should take advantage of this as much as possible

Neoadjuvant Therapy for Breast Cancer:

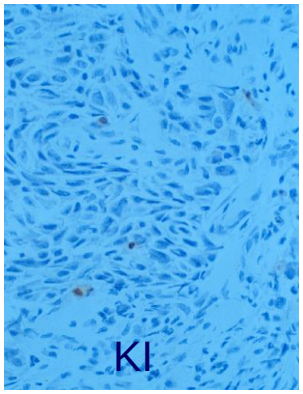
Opportunity for Serial Molecular Markers (eg Proliferation) in the Individual Patient

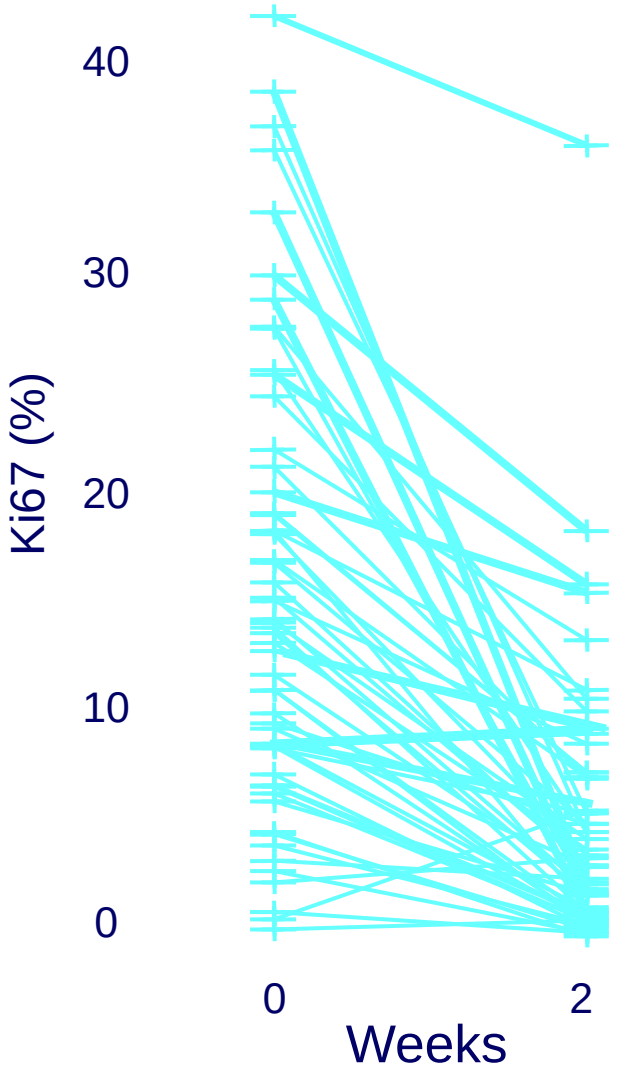


Pre-biopsy

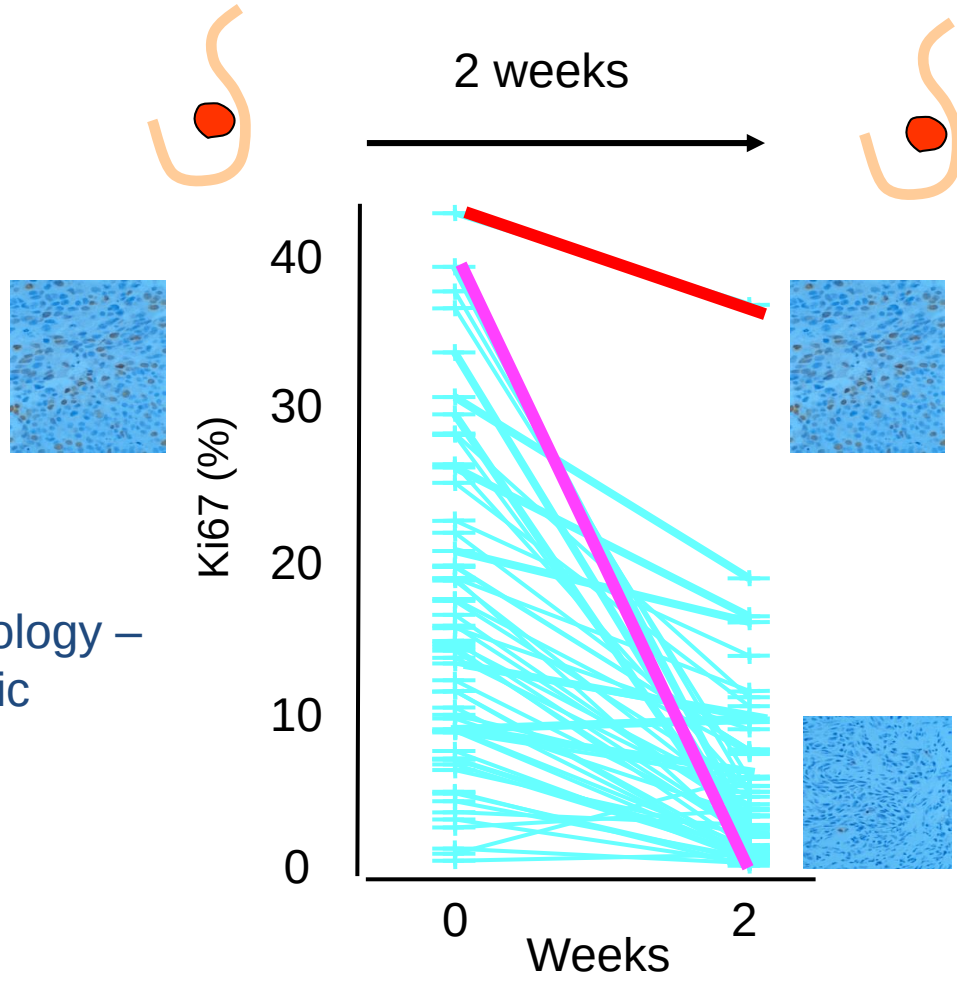


2 week biopsy





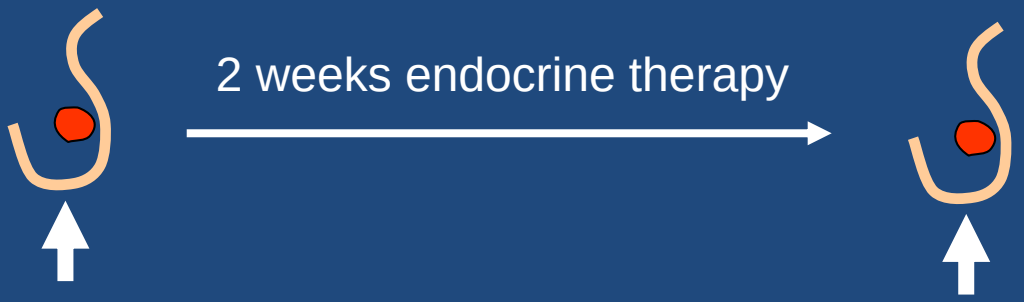
IMPACT: 2 Week Effect of Anastrozole on Ki67 in Individual Patients



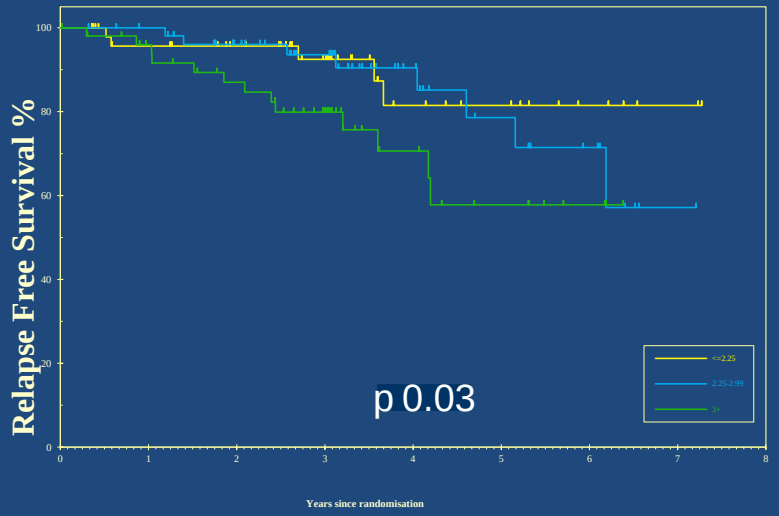
Innate biology – Prognostic

Reflects treatment sensitivity in the individual patient- Predict outcome better?

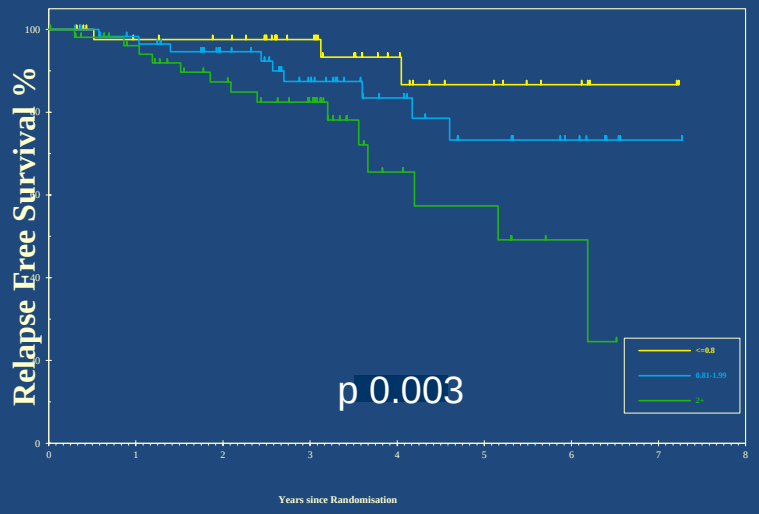
RFS by Ki67 in IMPACT: Pre vs 2 Week



Relapse Free Survival by baseline LnKi67



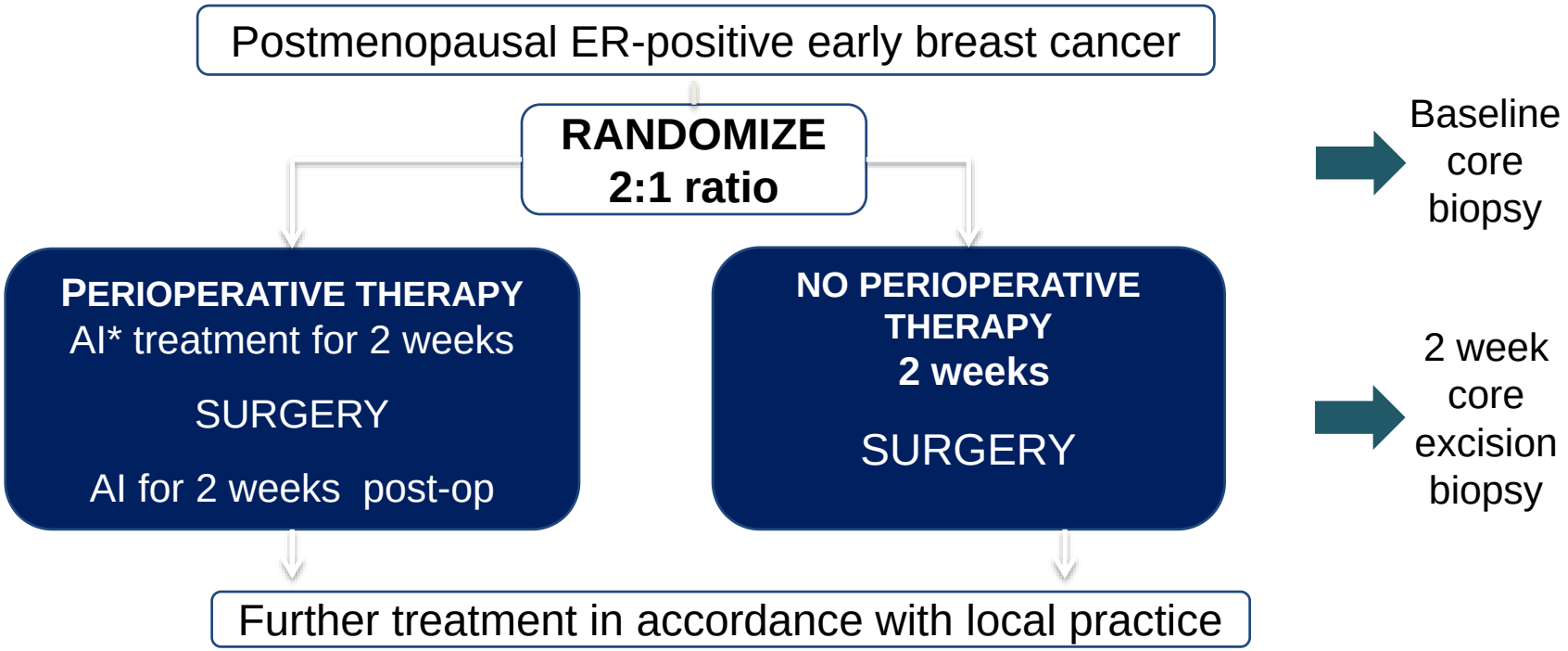
Relapse Free Survival by 2 week LnKi67



Not significant ← Multivariate analysis → HR 2.01 p 0.002

Dowsett, Smith et al JNCI 2007

POETIC: Pre-Operative Endocrine Therapy: Individualising Care (UK)

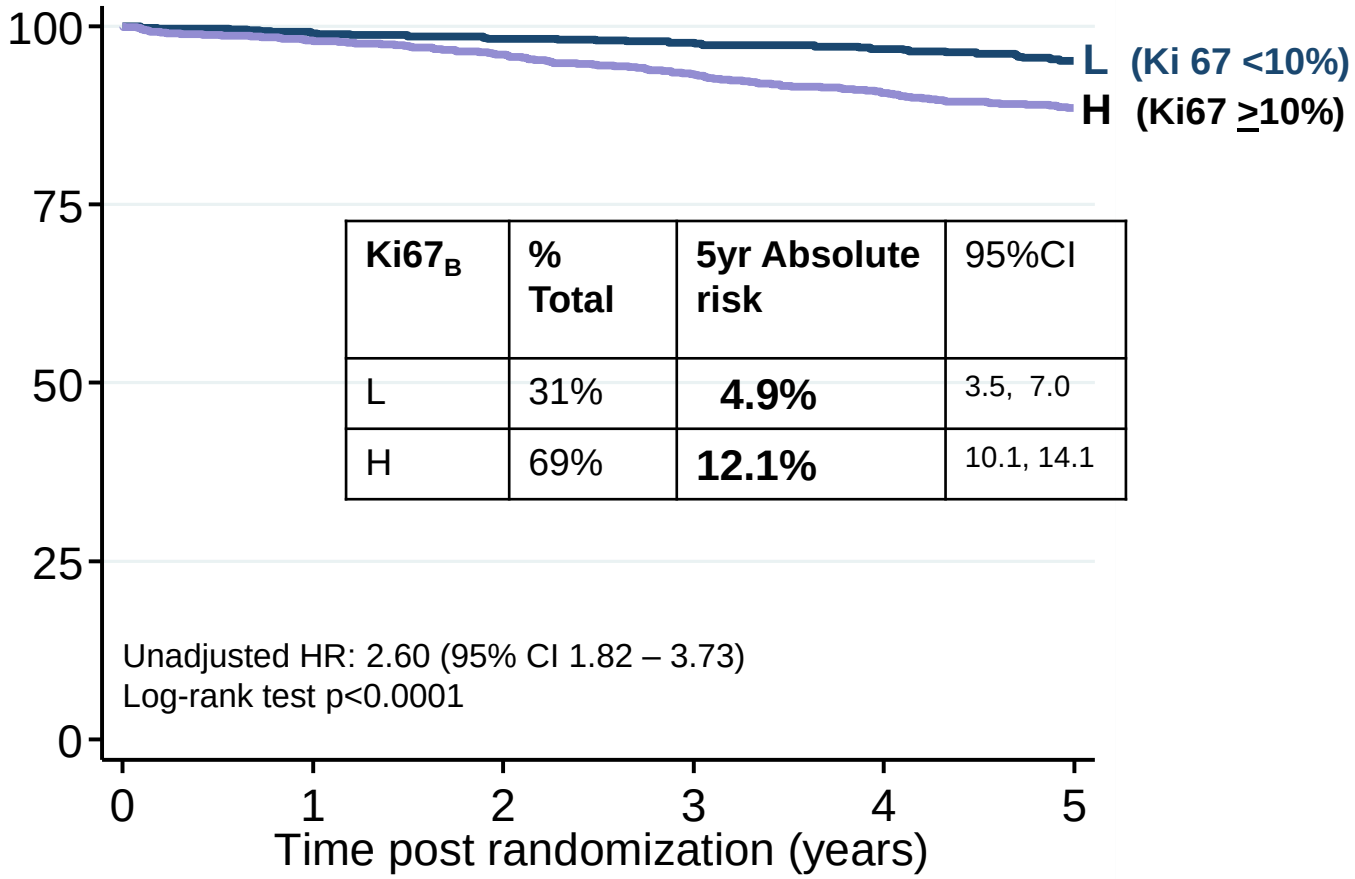


4486pts. 130 UK centres. >16,000 bloods. >10,000 tumour samples

Smith I, Robertson J, Bliss J, Dowsett M and many others

*Aromatase Inhibitor

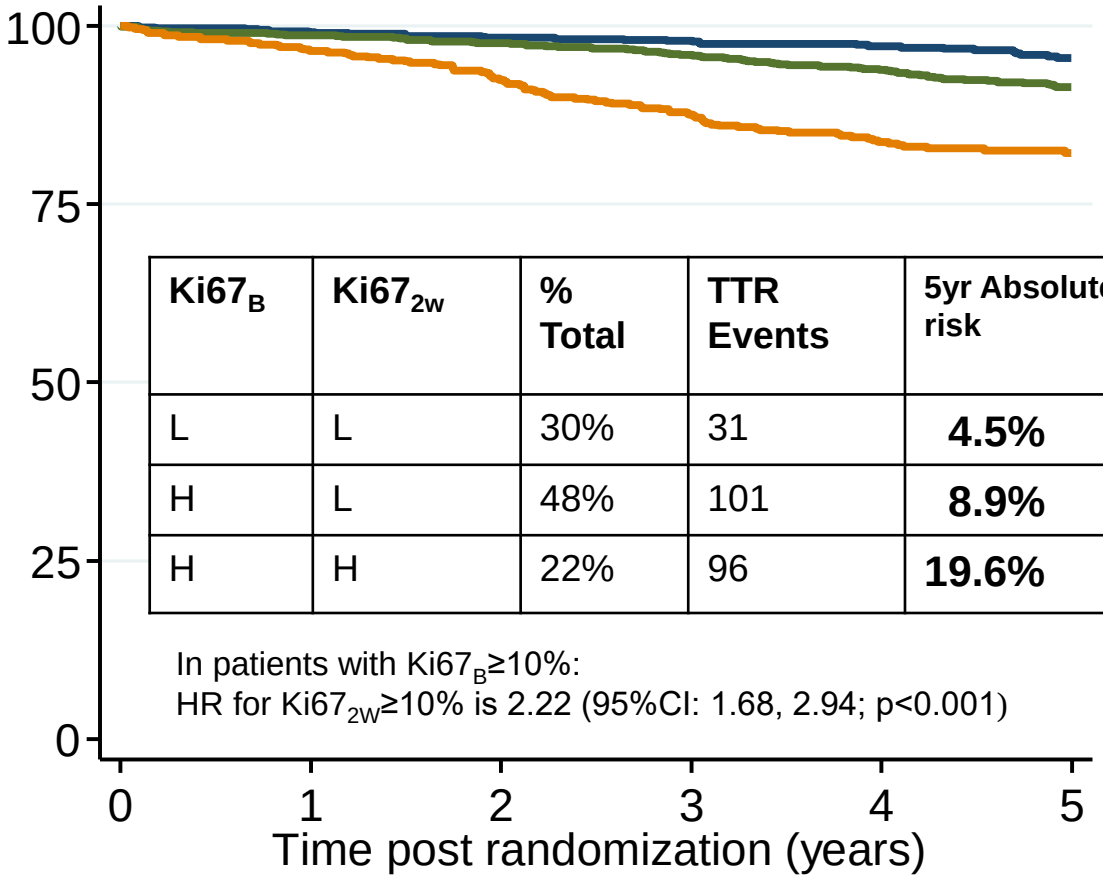
TTR* by baseline Ki67 – peri-op AI patients



$Ki67_B$	% Total	5yr Absolute risk	95%CI
L	31%	**4.9%**	3.5, 7.0
H	69%	**12.1%**	10.1, 14.1

*Time to recurrence

TTR* by baseline and 2-week Ki67 – Peri-op AI



$Ki67_B$	$Ki67_{2w}$	% Total	TTR Events	5yr Absolute risk	95%CI
L	L	30%	31	**4.5%**	3.1, 6.6
H	L	48%	101	**8.9%**	7.1, 11.0
H	H	22%	96	**19.6%**	15.9, 24.1

In patients with $Ki67_B \geq 10\%$:
HR for $Ki67_{2W} \geq 10\%$ is 2.22 (95%CI: 1.68, 2.94; p<0.001)

*Time to recurrence

Conclusions (1)

- Endocrine therapy is an enormously important treatment for women with ER+ve breast cancer (75-80% of total)

- It acts either by blocking E2 stimulation of the cancer (tamoxifen) or by switching off synthesis (aromatase inhibitors, ovarian suppression)

- It is not always effective – primary or secondary resistance

Conclusions (2)

- Targeted therapies are emerging to block endocrine resistance pathways eg CD4/6 inhibitors

- A major current challenge is to identify which patients with ER+ early breast cancer require additional adjuvant therapies (chemotherapy, CD4/6 inhibitors) to standard endocrine therapy

- Short term preoperative endocrine therapy to measure the effect of endocrine therapy on Ki67 offers a simple potential new approach to this.

Circulating Tumour DNA (ctDNA)

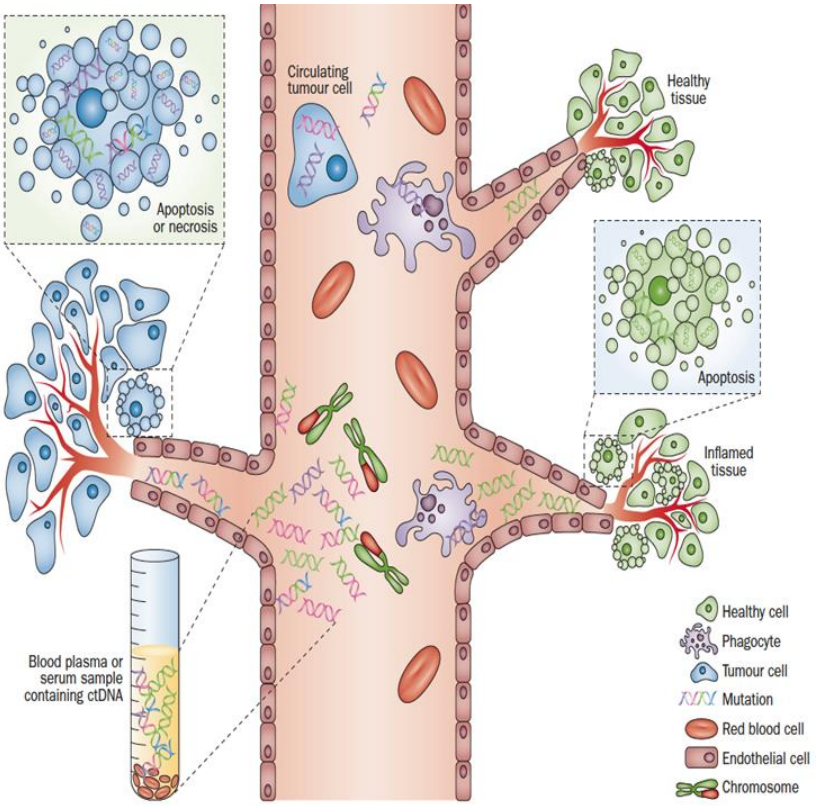
Cell free DNA (cfDNA) is released into the blood of patients with a wide range of malignancies

Only a low fraction of cfDNA constists of tumour-derived DNA or circulating tumour DNA (ctDNA) the remainder being derived from non-cancerous somatic cells

ctDNA is detected in >90% patients with metastatic breast cancer

The frequency of tumor specific alterations in the blood is as low as 0.01%

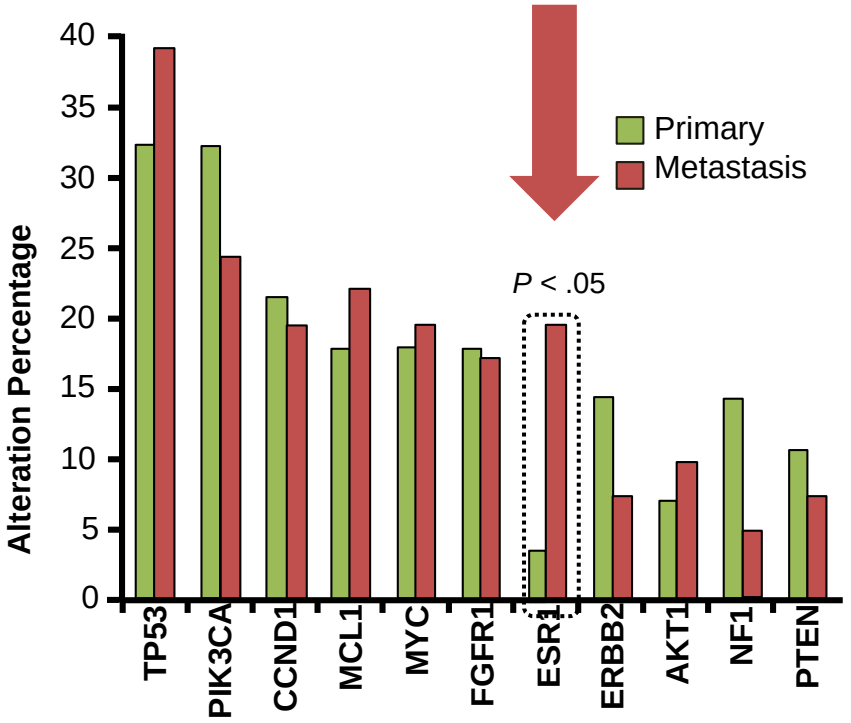
Half life short 1.5hrs



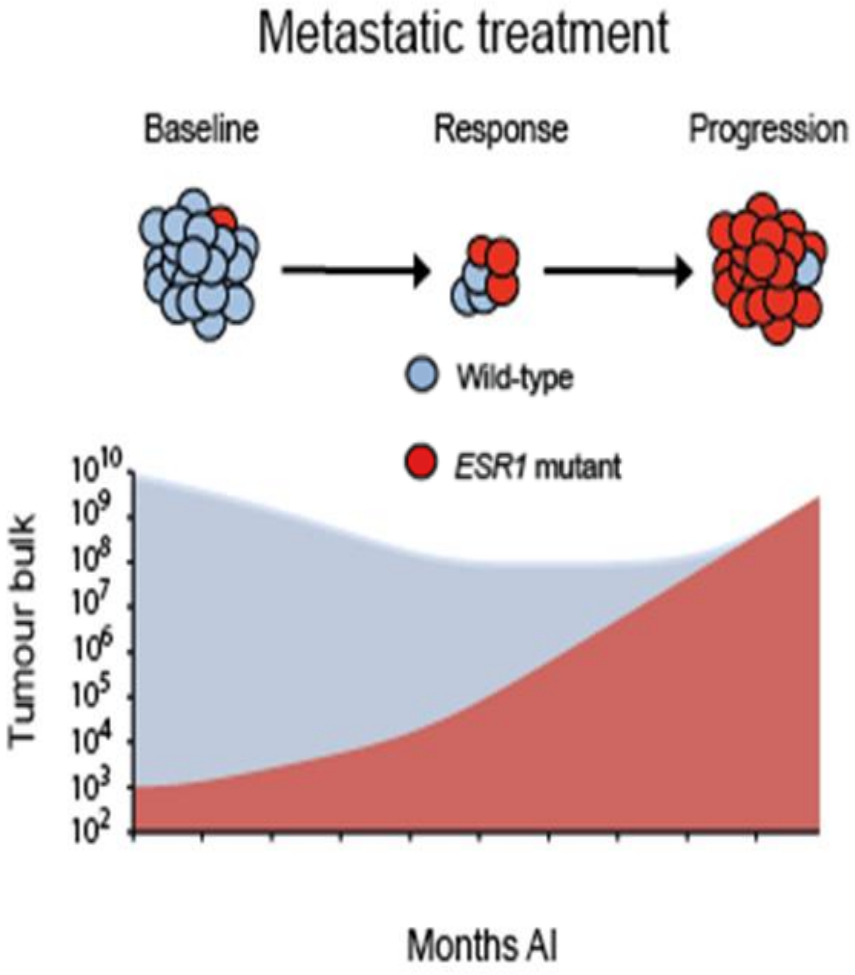
Diehl et al *Nat Med* 2008
Perkins G et al *PLoS ONE* 2011
Forshew et al *STM* 2012
Dawson et al *NEJM* 2013
Crowley et al *Nat Rev Clin Oncol* 2013
Bettegowda et al *STM* 2014

Genomic Mutations in ER+ Advanced Breast Cancer. ESR 1

Genomic alterations in ER+ tumors

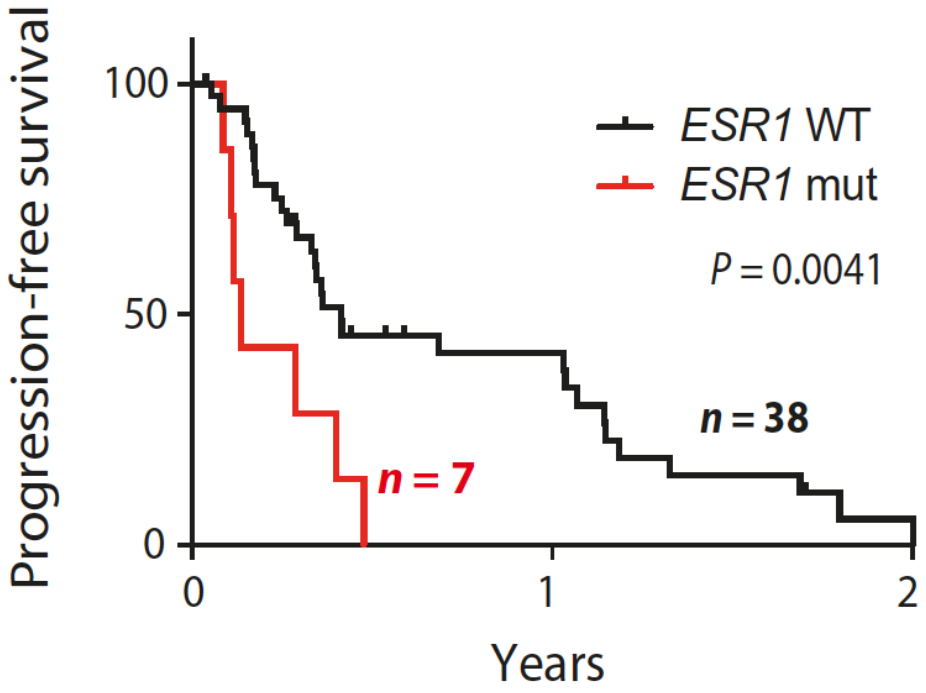


***ESR1* mutations occur in ~20% of endocrine resistant ER positive breast cancer**



Zhang Q.X et al. Cancer Res 1997 Li S et al. Cell Reports 2013 Toy W et al. Nat Gen 2013
Robinson DR et al. Nat Gen 2013 Merenbakh-Lamin K et al. Cancer Res 2013 Jeselsohn R et al. Clin Cancer Res 2014

ESR1 mutations in ctDNA Confer Resistance to Subsequent Aromatase Inhibitor



Retrospective single centre series
PFS on subsequent AI therapy

Schiavon *et al* AACR 2015, STM 2015

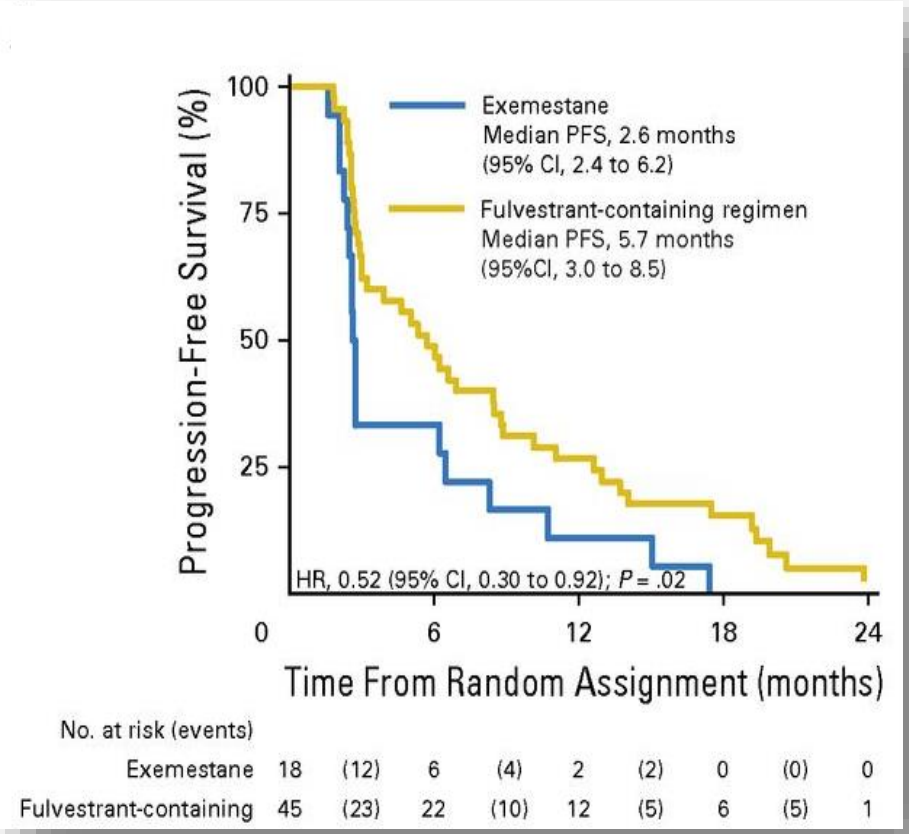
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Plasma *ESR1* Mutations and the Treatment of Estrogen Receptor–Positive Advanced Breast Cancer

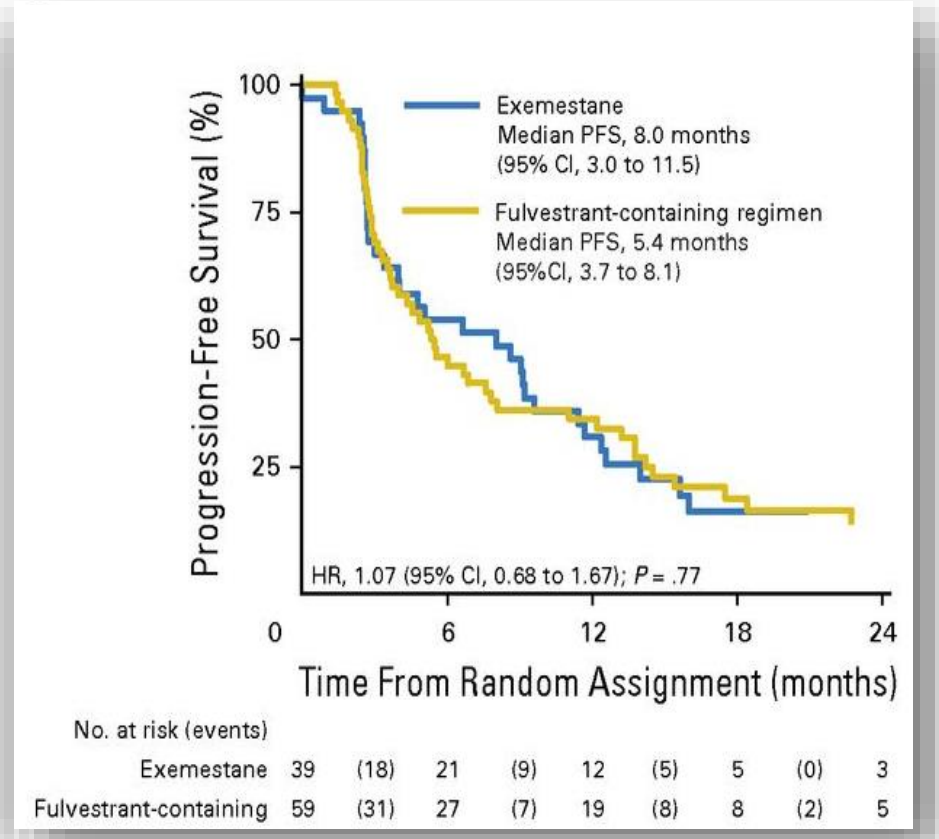
Charlotte Fribbens, Ben O'Leary, Sarah Hrebien, Isaac Garcia-Murillas, Matthew Beaney, Mitch Dowsett, and Nicholas C. Turner, Institute of Cancer Research; Charlotte Fribbens, Ben O'Leary, Stephen R.D. Johnston, and Nicholas C. Turner,

Charlotte Fribbens, Ben O'Leary, Lucy Kilburn, Sarah Hrebien, Isaac Garcia-Murillas, Matthew Beaney, Massimo Cristofanilli, Fabrice Andre, Sherene Loi, Sibylle Loibl, John Jiang, Cynthia Huang Bartlett, Maria Koehler, Mitch Dowsett, Judith M. Bliss, Stephen R.D. Johnston, and Nicholas C. Turner

***ESR1* mutated**



***ESR1* wild type**

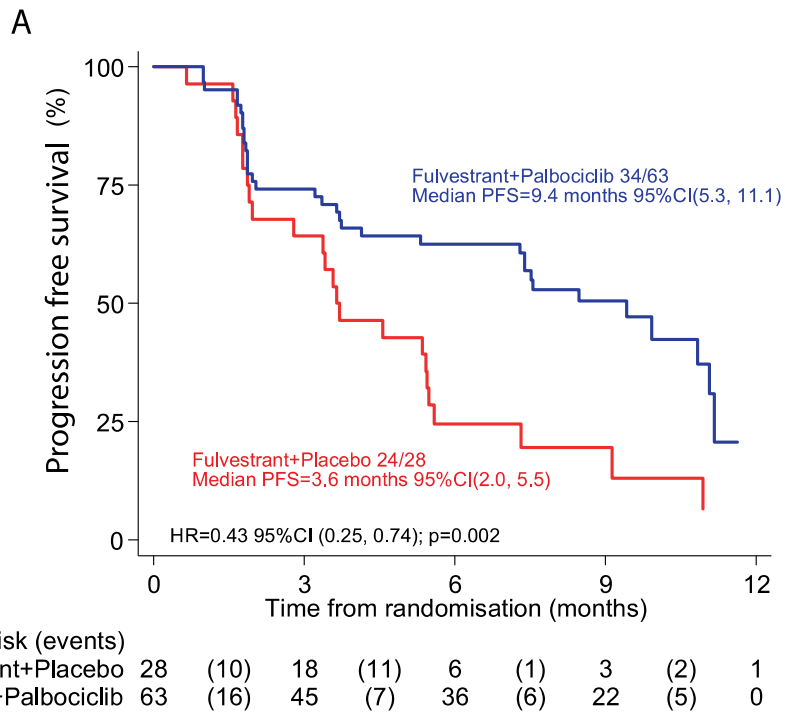


Fribbens C, et al. J Clin Onc. 2016;34(25):2961-8

PALOMA3 (Fulvestrant + Palbociclib) by *ESR1* mutation status

ESR1 Mutant (25%)

Fulvestrant-Palbociclib
Fulvestrant-Placebo



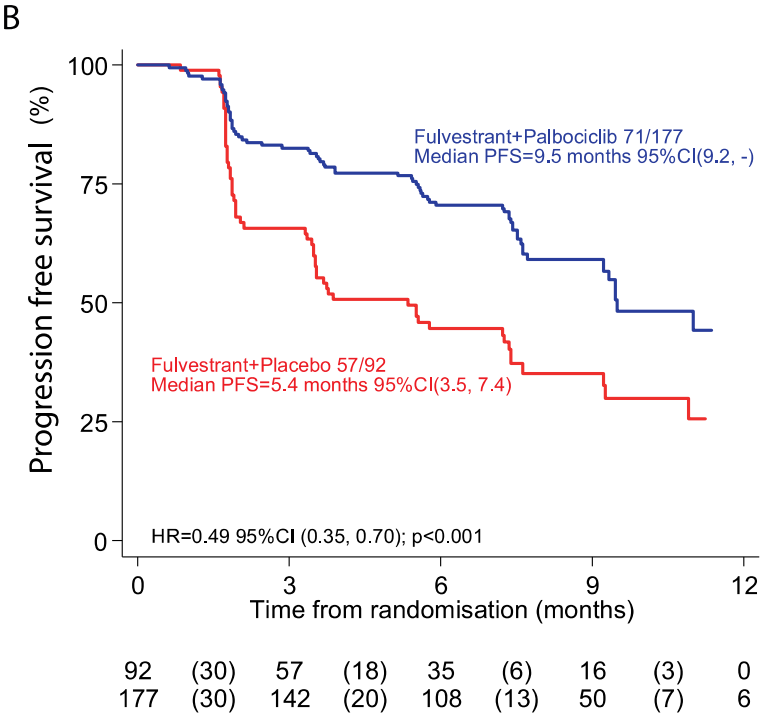
Number at risk (events)

Fulvestrant+Placebo	28	(10)	18	(11)	6	(1)	3	(2)	1
Fulvestrant+Palbociclib	63	(16)	45	(7)	36	(6)	22	(5)	0

HR = 0.43 95% CI 0.25 – 0.74, p = 0.002

ESR1 Wild type

Fulvestrant-Palbociclib
Fulvestrant-Placebo



	92	(30)	57	(18)	35	(6)	16	(3)	0
	177	(30)	142	(20)	108	(13)	50	(7)	6

HR = 0.49 95% CI 0.35 – 0.70, p < 0.001

O'Leary et al. AACR, 2016. Fribbens et al. *J Clin Oncol*, 2016

Hypothesis

- ESR-1 mutations are induced by AI exposure
- Fulvestrant overrides the mutation by degrading the receptor
- Palbociclib overrides the mutation by blocking a constitutively active ‘escape’ pathway
- Late relapses are likely to have a high incidence of ESR1 mutations
- They are therefore more likely to be controlled by fulvestrant or a CD4/6 combination therapy than by an AI alone