In what situation is neoadjuvant therapy indicated?

Alastair M Thompson

Professor of Surgical Oncology, University of Dundee

a.m.thompson @ dundee.ac.uk

UNIVERSITY OF DUNDEE

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Disclosures:

Roche

Roche Diagnostics

Sanofi Aventis:

Research funding, travel funds, speaker fees

In what situation is neoadjuvant therapy indicated?

Alastair M Thompson

Professor of Surgical Oncology, University of Dundee

a.m.thompson @ dundee.ac.uk

In what situation is preoperative therapy indicated?

Alastair M Thompson

Professor of Surgical Oncology, University of Dundee

a.m.thompson @ dundee.ac.uk

Pre-operative therapy

- Why give pre-operative therapy?
- Pre-operative situations:
  - Neoadjuvant trials
  - Window of opportunity trials
  - (Perioperative trials)
  - (Observational trials)
- Pathology
- Imaging
- Surgery

Thompson AM & Moulder SL Ann Oncology 2012; 23:x231-6

Pre-operative therapy

- **Why give pre-operative therapy?**
- Pre-operative situations:
  - Neoadjuvant trials
  - Window of opportunity trials
  - (Perioperative trials)
  - (Observational trials)
- Pathology
- Imaging
- Surgery

Thompson AM & Moulder SL Ann Oncology 2012; 23:x231-6

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Why give pre-operative therapy?

Opportunities:

- Improve operative options (extent of surgery)
- Downsize: T2, T3 or T4 to Tx?

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Why give pre-operative therapy?

Opportunities:

- Improve operative options (extent of surgery)
- Downsize: any cancer >?1cm

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Why give pre-operative therapy?

Opportunities:

- Improve operative options (extent of surgery)
- Downsize: any cancer >?1cm
- Surrogate marker for DFS and OS (B18)

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Why give pre-operative therapy?

Opportunities:

- Improve operative options (extent of surgery)
- Downsize: any cancer >?1cm (T3 to Tx?)
- Surrogate marker for DFS and OS

- In vivo drug (?radiation) sensitivity
- Individualise therapy
- Early drug efficacy/target validation

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Why give pre-operative therapy?

Opportunities:

- Improve operative options (extent of surgery)
- Downsize: any cancer >?1cm (T3 to Tx?)
- Surrogate marker for DFS and OS
- In vivo drug (?radiation) sensitivity
- Individualise therapy
- Early drug efficacy/target validation
- Adjust anti-tumour strategy
- Minimal residual disease studies

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Pre-operative therapy

- Why give pre-operative therapy?
- **Pre-operative situations:**
  - **Neoadjuvant trials**
  - Window of opportunity trials
  - (Perioperative trials)
  - (Observational trials)
- Pathology
- Imaging
- Surgery

Thompson AM & Moulder SL Ann Oncology 2012; 23:x231-6

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant Trials

Efficacy trials:

- Endocrine approaches
- Chemotherapy
- Targeted agents (± chemotherapy)

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant Trials

Efficacy trials:

- Endocrine approaches
- Chemotherapy
- Targeted agents (± chemotherapy)

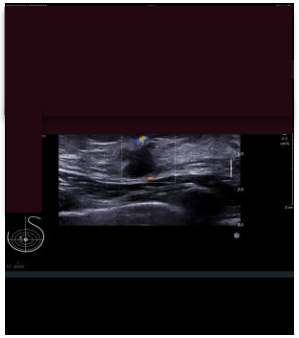
Patient's perspective:

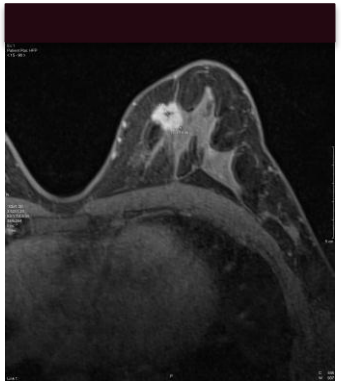
- Test individual in vivo efficacy of drugs,
- Improve surgical options,
- Identify patients with a good long term survival

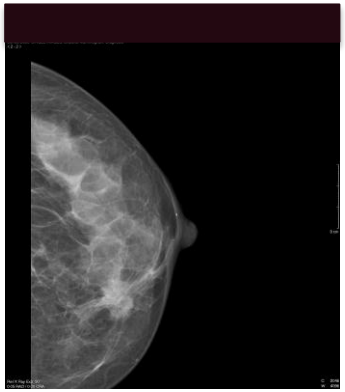
Efficacy trials

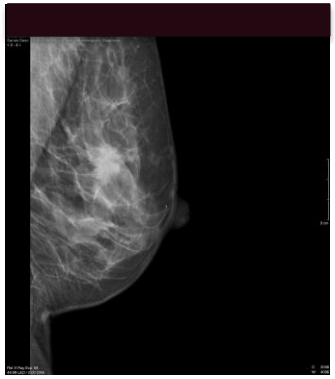
pre neoadjuvant therapy

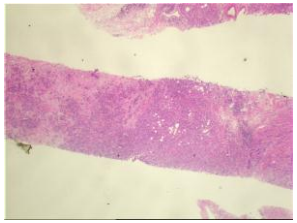
Diagnosis

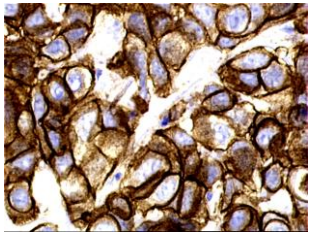










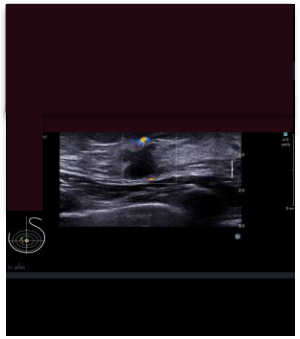
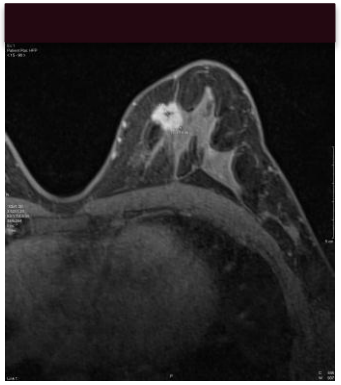
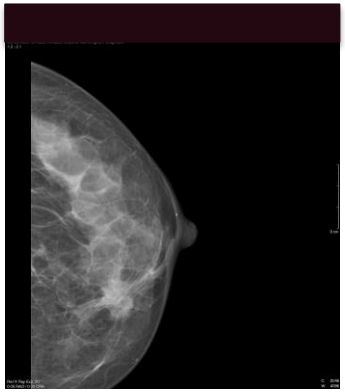
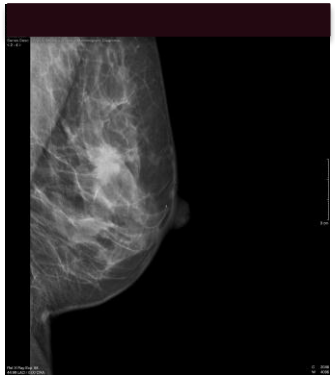


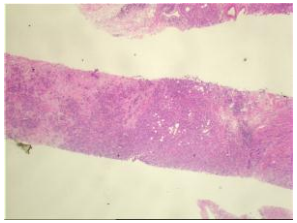
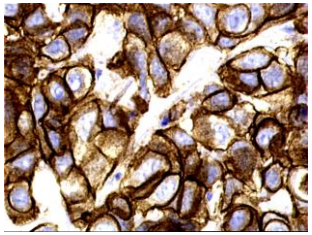
Courtesy of D McLean and C Purdie

VIENNA 2012 ESMO congress

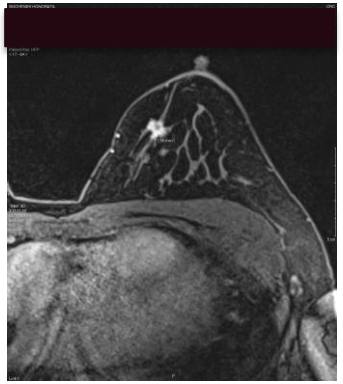
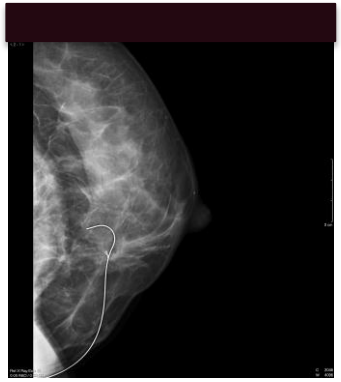
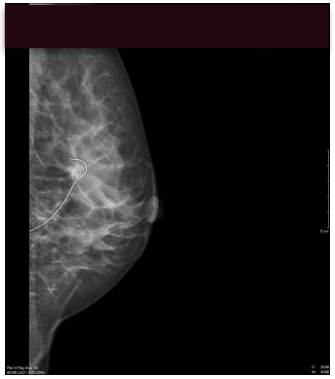
DUNDEE CANCER CENTRE

Efficacy trials

neoadjuvant therapy

Courtesy of D McLean and C Purdie

VIENNA 2012 ESMO congress

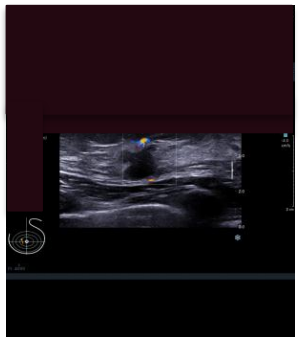
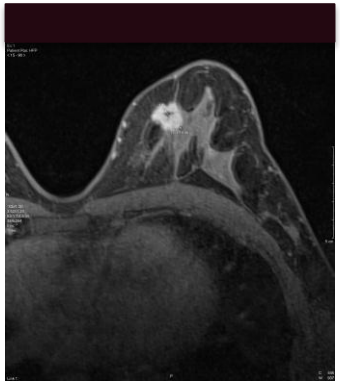
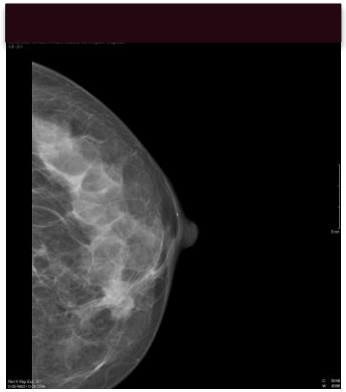
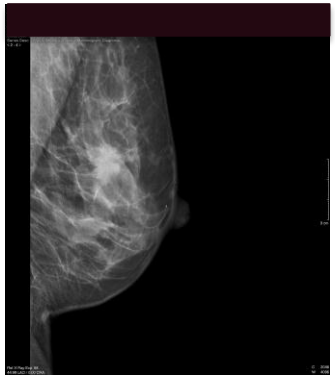
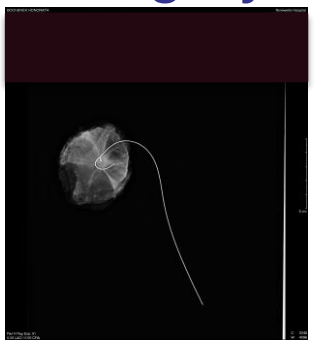
DUNDEE CANCER CENTRE

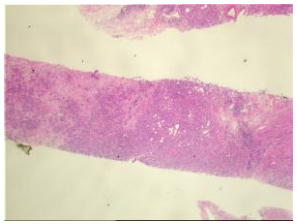
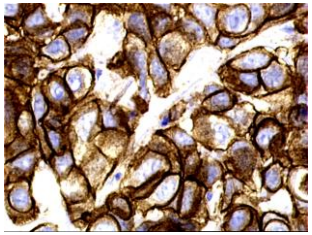
Efficacy trials

pre neoadjuvant therapy

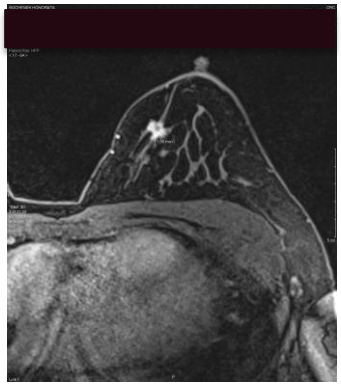
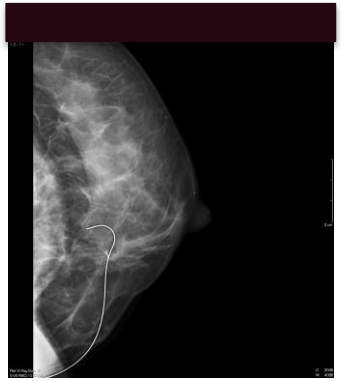
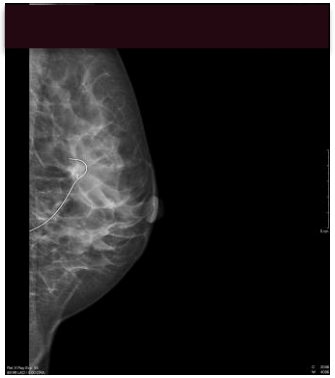
Diagnosis

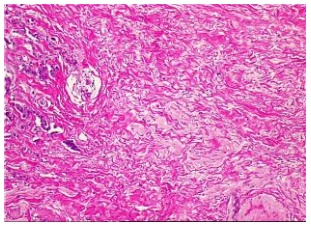
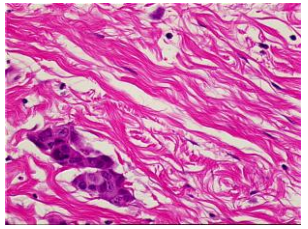
Surgery

neoadjuvant therapy

Courtesy of D McLean and C Purdie

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant trials

Efficacy trials:

- Endocrine approaches:
- AIs, duration effect
- Letrozole + chemotherapy
- Letrozole v chemotherapy
- Chemotherapy: efficacy and pCR regimen dependent
- Targeted agents (± chemotherapy)

Neoadjuvant trials

Efficacy trials:

- Endocrine approaches:
- AIs, duration effect
- Letrozole + chemotherapy
- Letrozole v chemotherapy
- Chemotherapy: efficacy and pCR regimen dependent
- Targeted agents (± chemotherapy)

Model for novel experimental designs (I-SPY trials)

Model for adjuvant therapy?

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant trials

Model for adjuvant trials?

- Endocrine (AI or Tamoxifen)

  ATAC ~6,000 v IMPACT n= 330

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant trials

Model for adjuvant trials?

- Endocrine (AI or Tamoxifen)

  ATAC ~6,000 v IMPACT n= 330

- Chemotherapy (Paclitaxel)

  MDAnderson n=258 v ECOG 1199 n~5,000

Neoadjuvant trials

Model for adjuvant trials?

- Endocrine (AI or Tamoxifen)
  - ATAC ~6,000 v IMPACT n= 330
- Chemotherapy (Paclitaxel)
  - MDAnderson n=258 v ECOG 1199 n~5,000
- Targeted therapy
  - Neo ALTTO n=455 v ALTTO n~8,000
  - NeoSphere n=417 v AFFINITY n~3,800

Neoadjuvant trials

Model for adjuvant trials?

- Endocrine (AI or Tamoxifen)
  - ATAC ~6,000 v IMPACT n= 330
- Chemotherapy (Paclitaxel)
  - MDAnderson n=258 v ECOG 1199 n~5,000
- Targeted therapy
  - Neo ALTTO n=455 v ALTTO n~8,000
  - NeoSphere n=417 v AFFINITY n~4,000
- Go/no go decisions?

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant trials

Complete pathological response (2% - 80%)

Dependence on subtype (TNBC; HER2+)*

Dependence on gene expression**

Anatomy (size, nodes)

von Minckwitz G (2012) J Clin Oncol 30:1796-1804

***Ignatiadis M (2012) J Clin Oncol 30:1994-2004*

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant trials

Complete pathological response (2% - 80%)

Dependence on subtype (TNBC; HER2+)*

Dependence on gene expression**

~~Anatomy (size, nodes)~~

**von Minckwitz G (2012) J Clin Oncol 30:1796-1804*

***Ignatiadis M (2012) J Clin Oncol 30:1994-2004*

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant trials

Complete pathological response (2% - 80%)

Dependence on subtype (TNBC; HER2+)*

Dependence on gene expression**

~~Anatomy (size, nodes)~~ v **biology (subtypes)**

**von Minckwitz G (2012) J Clin Oncol 30:1796-1804*

***Ignatiadis M (2012) J Clin Oncol 30:1994-2004*

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Neoadjuvant trials

Complete pathological response (2% - 80%)

Dependence on subtype (TNBC; HER2+)*

Dependence on gene expression**

Anatomy (size, nodes) v biology (subtypes)

Minimal residual disease/ stem cells

Ecology of cancer – *should* we be aiming to eradicate the majority of cells?

**von Minckwitz G (2012) J Clin Oncol 30:1796-1804*

***Ignatiadis M (2012) J Clin Oncol 30:1994-2004*

VIENNA 2012 ESMO congress

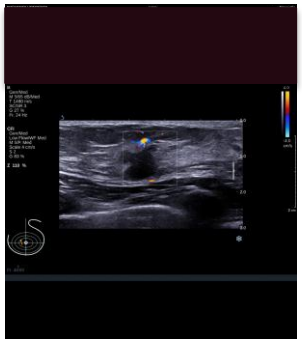
DUNDEE CANCER CENTRE

Multi disciplinary ***team*** working

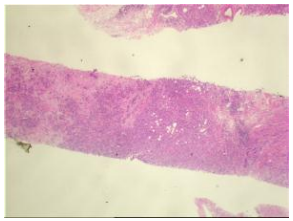
Surgery

Oncology

Imaging



Pathology



VIENNA 2012 ESMO congress

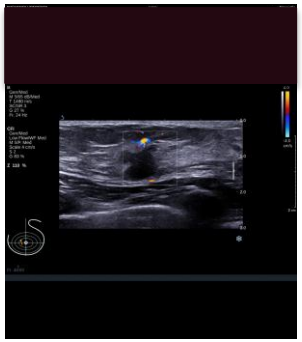
DUNDEE CANCER CENTRE

Multi disciplinary ***team*** working*

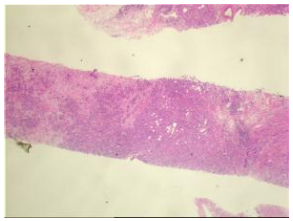
Surgery

Oncology

Imaging



Pathology



*No “I” in the word “TEAM”

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Pre-operative therapy

- Why give pre-operative therapy?
- **Pre-operative situations:**
  - Neoadjuvant trials
  - **Window of opportunity trials**
  - (Perioperative trials)
  - (Observational trials)
- Pathology
- Imaging
- Surgery

Thompson AM & Moulder SL Ann Oncology 2012; 23:x231-6

VIENNA 2012 ESMO congress

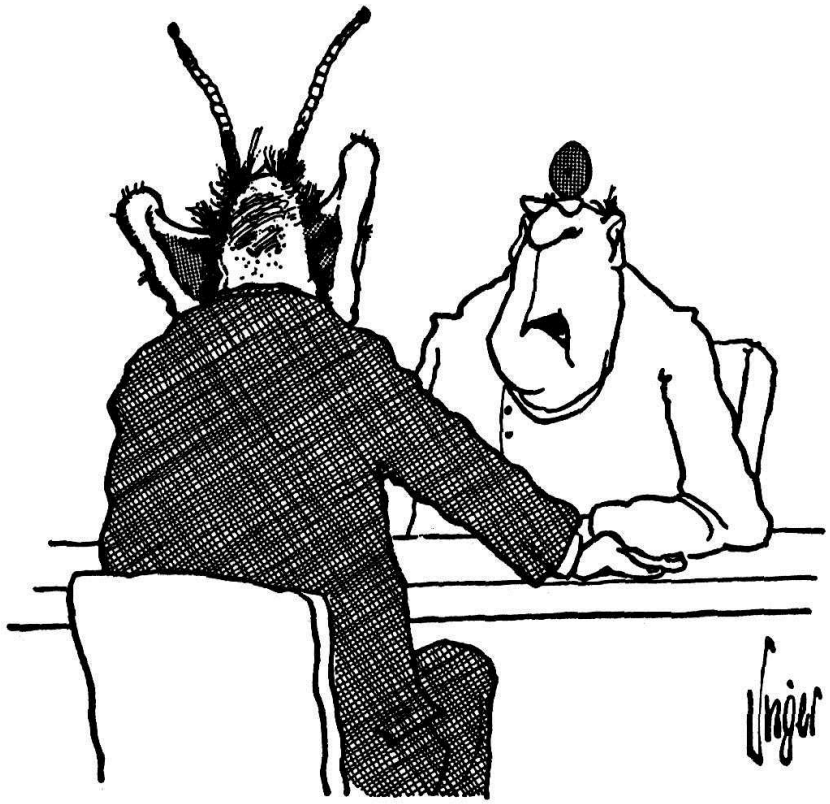
Window trials

DUNDEE CANCER CENTRE

- Effects in vivo
- On-target effects
- Exploring mechanisms of action:

  Tumour

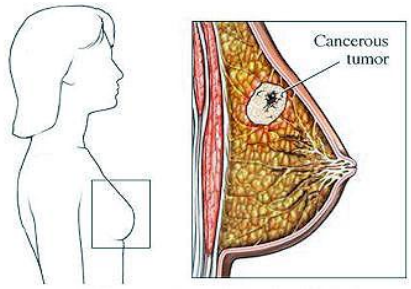
  Systemic

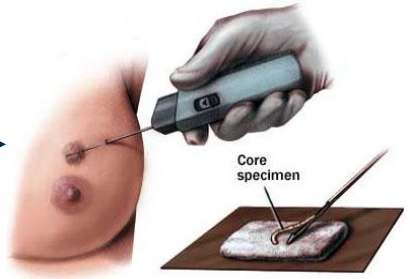


"If you remember, I did mention possible side-effects."

- Toxicities…….and safety

Window trials

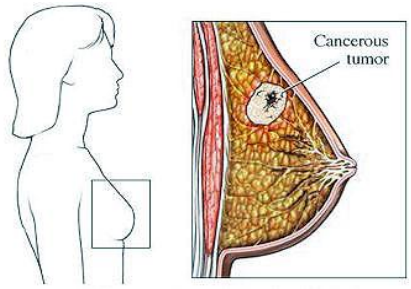


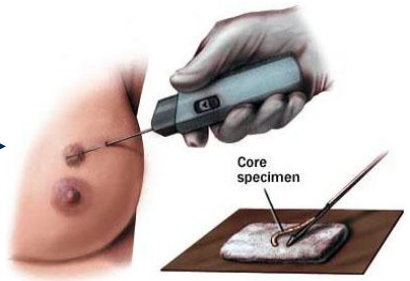


2 weeks

Hadad et al (2011) Breast Can Res Treat 8: 783-794

Window trials





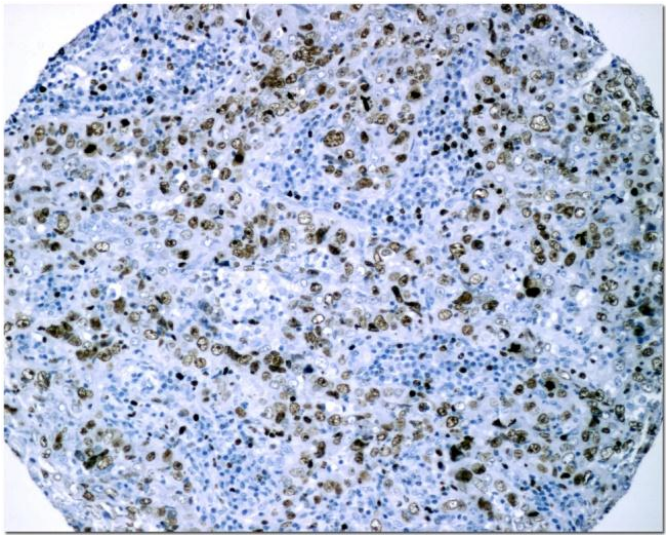
2 weeks

Hadad et al (2011) Breast Can Res Treat 8: 783-794

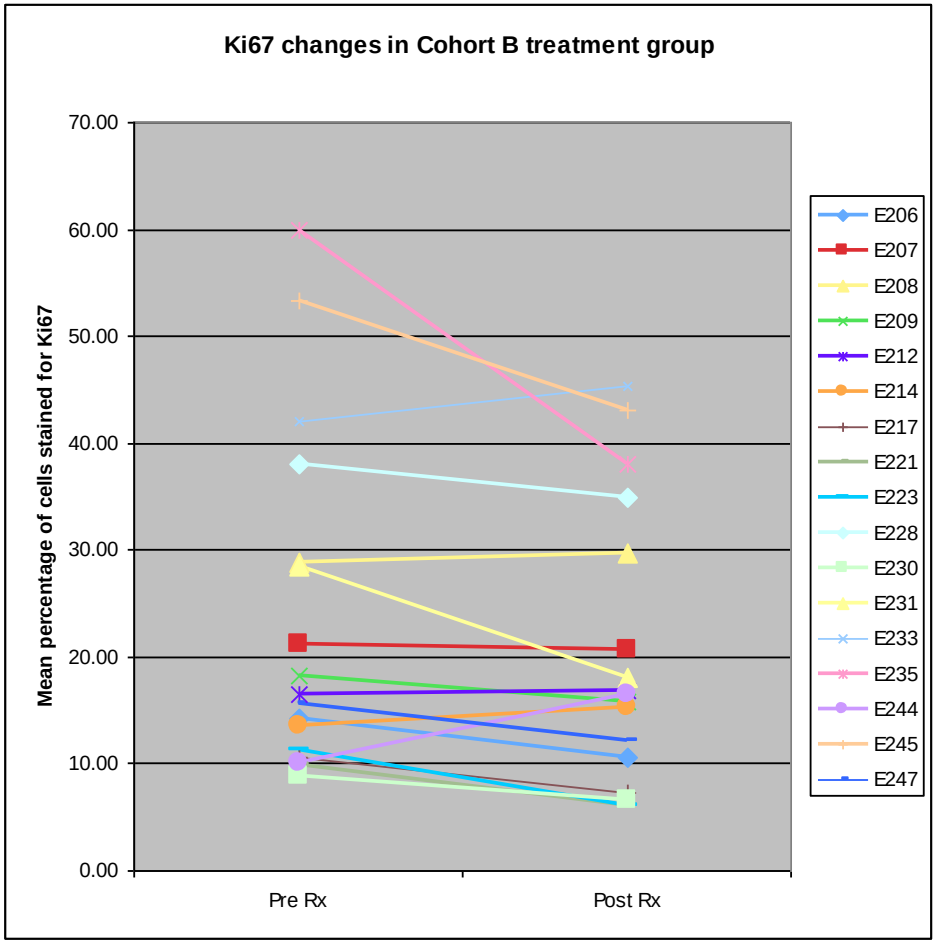
VIENNA 2012 ESMO congress

Tumour effects

DUNDEE CANCER CENTRE

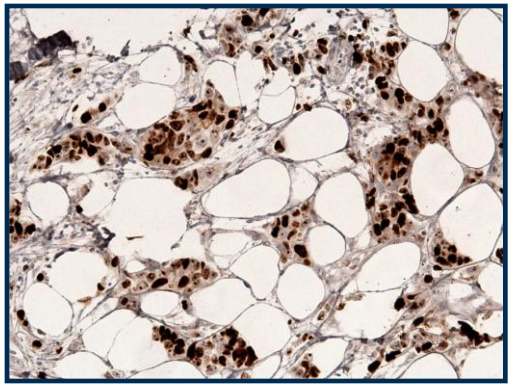


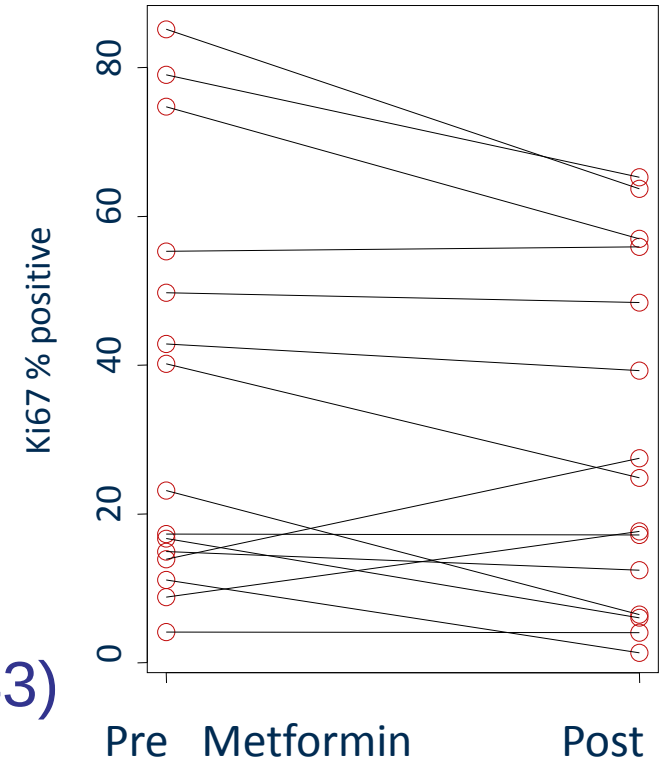
Ki67

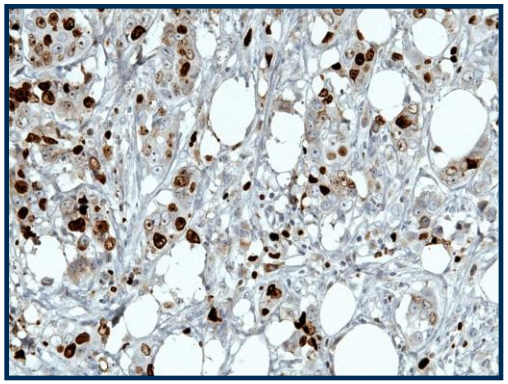


Hadad et al (2011) Breast Can Res Treat 128: 783-794

Tumour effects (reproduced)







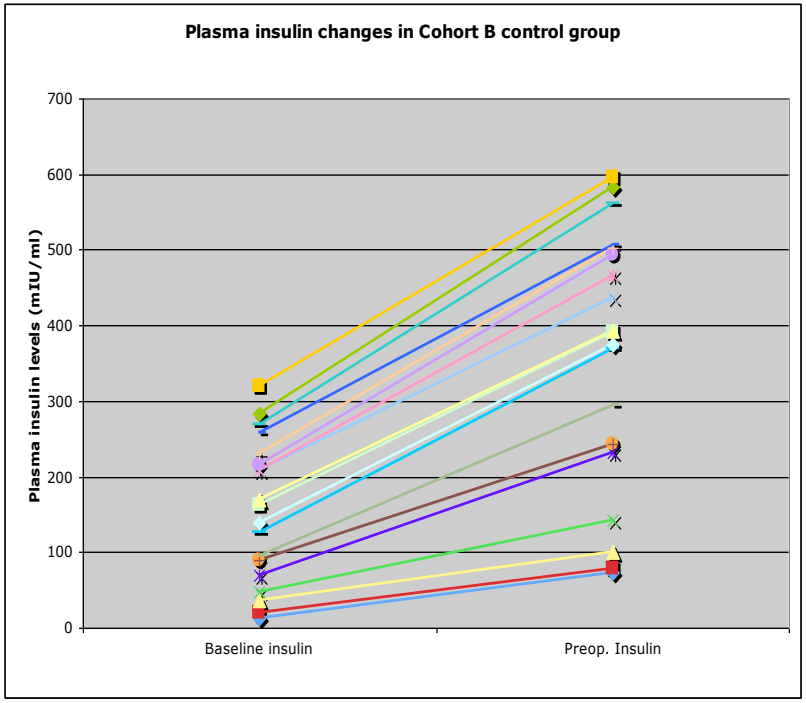
Change in Ki67:
per patient (p=0.043)

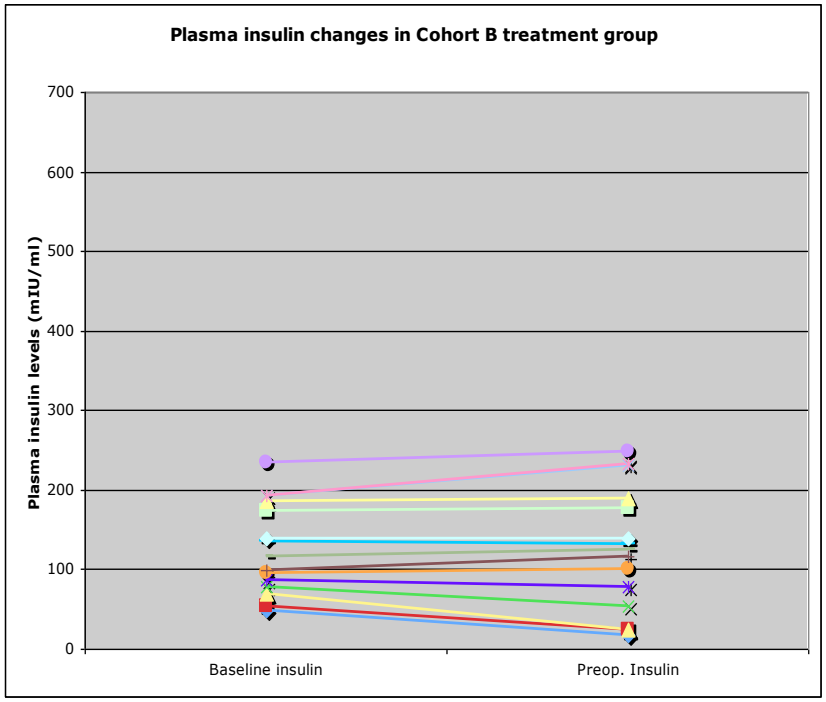
Courtesy of PJ Goodwin and V Stambolic

VIENNA 2012 ESMO congress

Systemic effects eg insulin

DUNDEE CANCER CENTRE



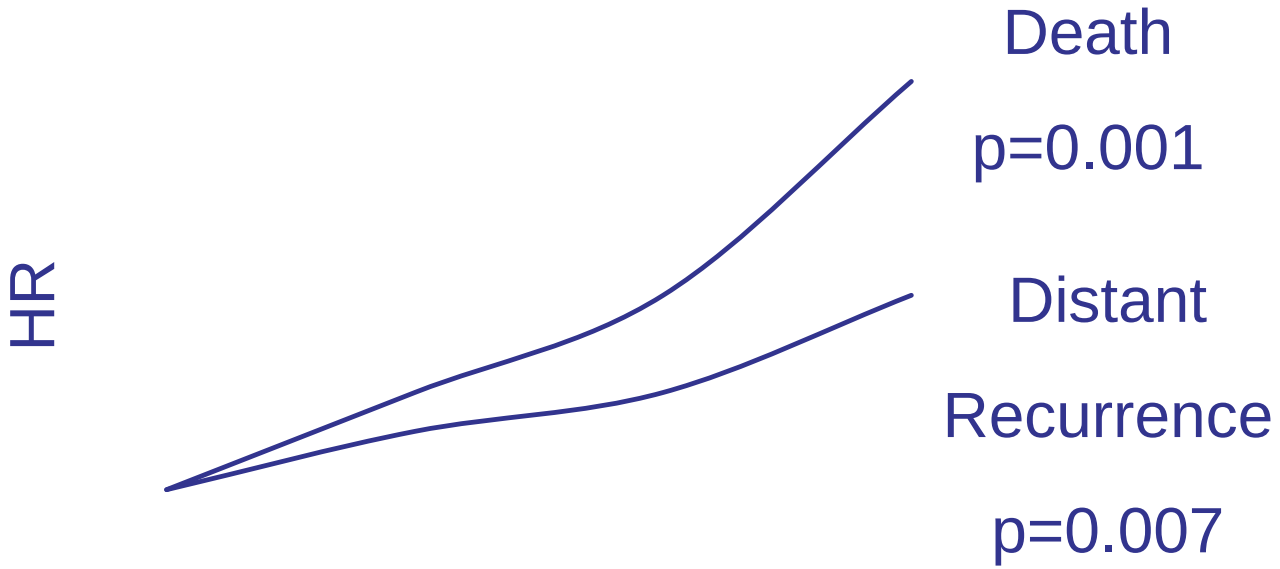


Control

Metformin

Hadad et al (2011) Breast Can Res Treat 128: 783-794

Insulin & Prognosis

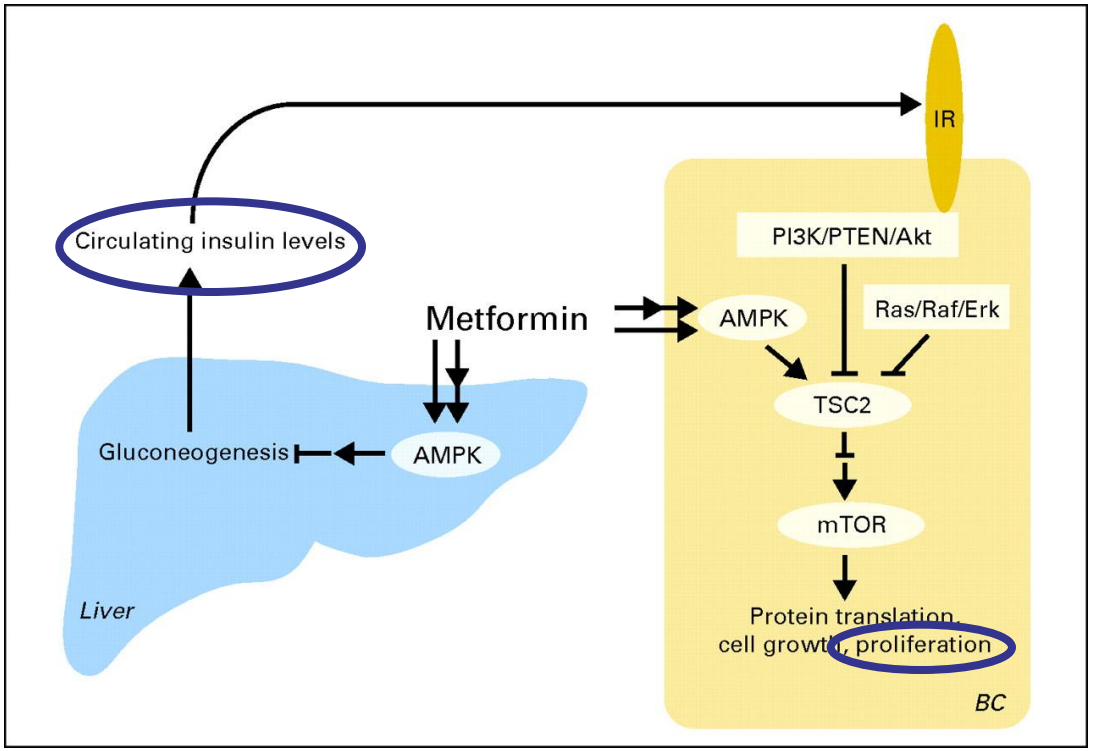


Goodwin PJ et al. (2002) J Clin Oncol 20:42-51

Hypothesis generation (and testing?)

Drug effects:

- Tumour effects in vivo
- Systemic effects in vivo



Courtesy of PJ Goodwin

Pre-operative therapy

- Why give pre-operative therapy?
- Pre-operative situations:
  - Neoadjuvant trials
  - Window of opportunity trials
  - (Perioperative trials)
  - (Observational trials)
- **Pathology**
- Imaging
- Surgery

Thompson AM & Moulder SL Ann Oncology 2012; 23:x231-6

VIENNA 2012 ESMO congress

Pathology

DUNDEE CANCER CENTRE

Immunohistochemistry

- Importance of high quality (central) pathology review for ER, HER2, Ki67

Pathology

Immunohistochemistry

- Importance of high quality pathology review, QA for ER, HER2

Residual cancer burden

- Assessment of post therapy cancer burden*

**Symmans et al (2007) J Clin Oncol 25 4414-4422*

VIENNA 2012 ESMO congress

Pathology

DUNDEE CANCER CENTRE

Residual cancer burden

- Assessment of post therapy cancer burden* www. mdanderson.org/breastcancer_RCB
- Tumour bed (mm2)/cellularity (%)/in situ (%)
- Lymph node # pos/largest met (%)
- RCB classes 0, I……..II,III

**Symmans et al (2007) J Clin Oncol 25 4414-4422*

Pathology

Residual cancer burden

- Assessment of post therapy cancer burden* www. mdanderson.org/breastcancer_RCB
- Tumour bed (mm2)/cellularity (%)/in situ (%)
- Lymph node # pos/largest met (%)
- RCB classes 0, I……..II,III

Genomic predictors eg AT chemotherapy**

**Symmans et al (2007) J Clin Oncol 25 4414-4422*

***Hatzis et al (2011) JAMA 305 1873-1881*

VIENNA 2012 ESMO congress

Pathology

DUNDEE CANCER CENTRE

Immunohistochemistry

- Importance of high quality pathology review, QA for ER, HER2

Residual cancer burden

- Assessment of post therapy cancer burden*

Specimen/sampling effects

- Which specimens to examine**

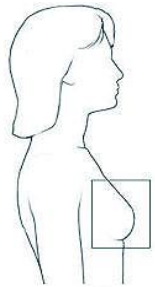
**Symmans et al (2007) J Clin Oncol 25 4414-4422*

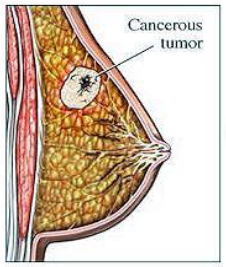
***Mann et al (2005) J Clin Oncol 23:5148-5154*

VIENNA 2012 ESMO congress

Window studies

DUNDEE CANCER CENTRE



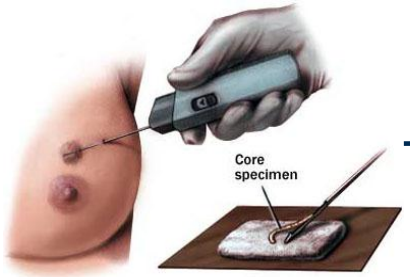


Second arm

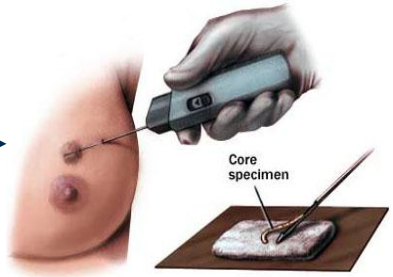
2 weeks

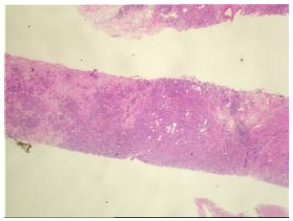
Hadad et al (2011)
Breast Can Res
Treat 8: 783-794

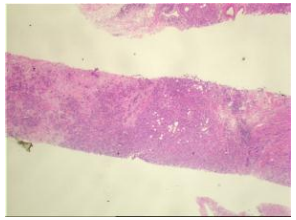
Wounding effects



No therapy







Affymetrix based microarray

Comparison of mRNA expression

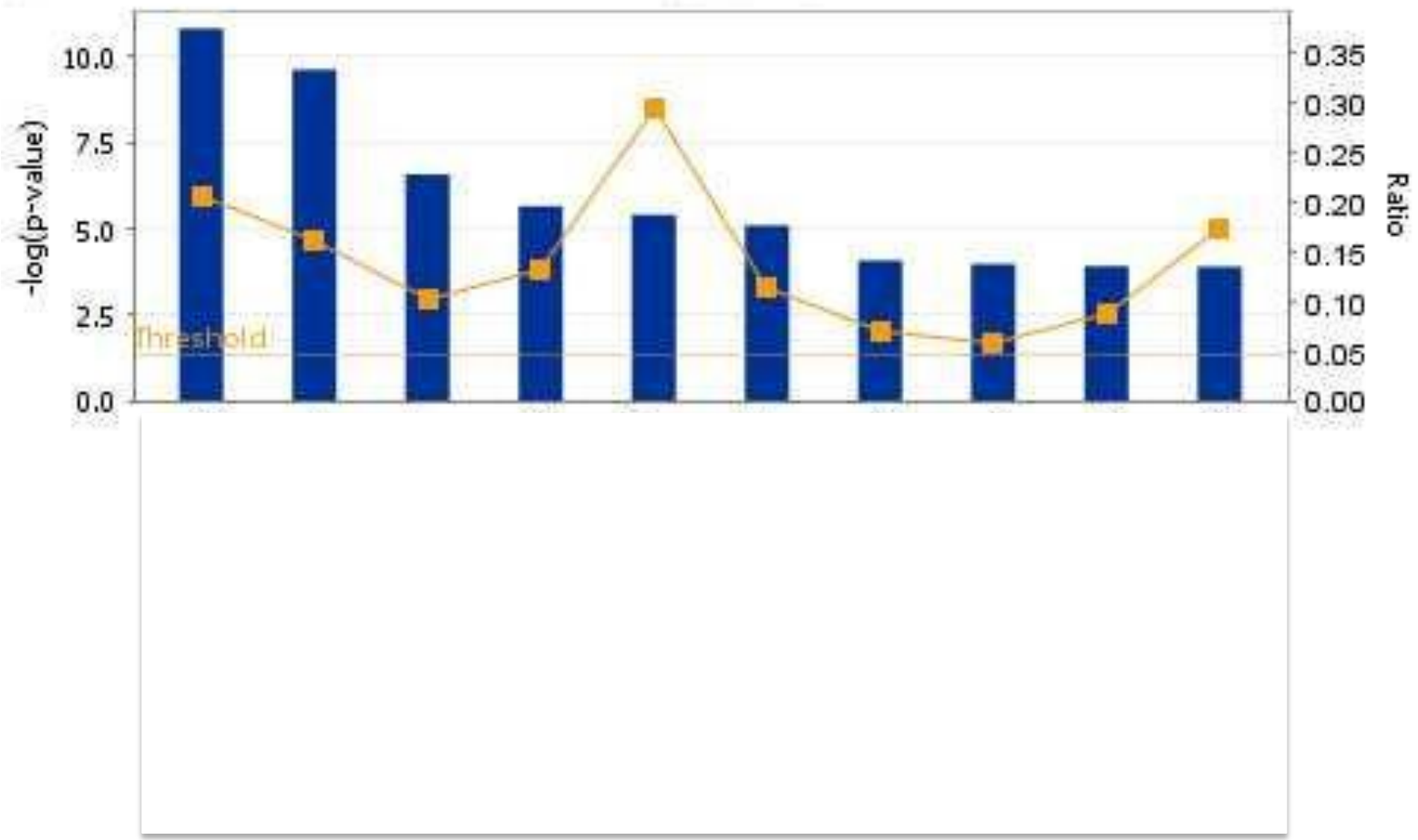
Analyses

Lajos Pustai, Taka Iwamoto

VIENNA 2012 ESMO congress

Gene overexpression

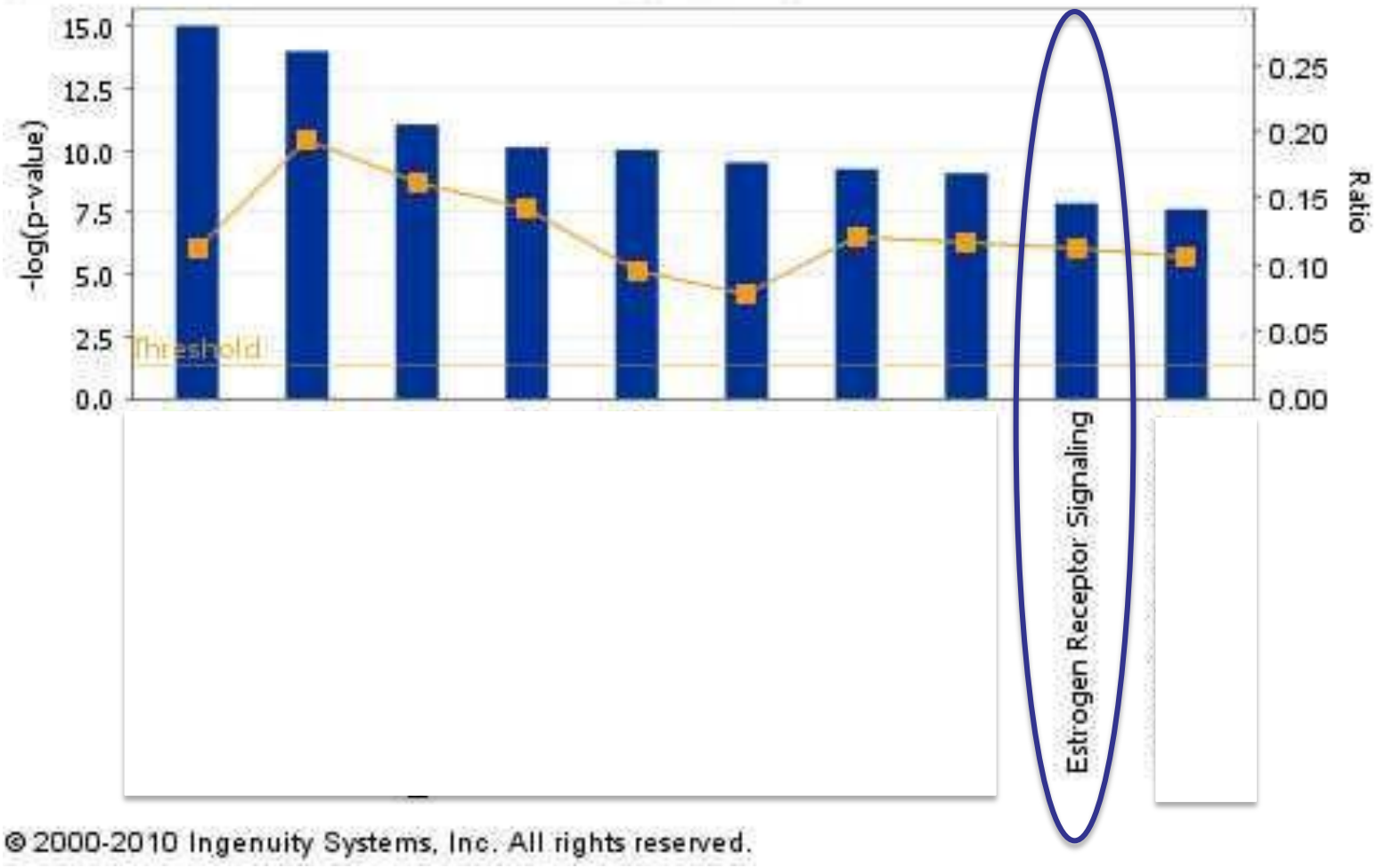
DUNDEE CANCER CENTRE



VIENNA 2012 ESMO congress

Gene underexpression

DUNDEE CANCER CENTRE



VIENNA 2012 ESMO congress

Pathology

DUNDEE CANCER CENTRE

"Wounding" effects

- One ***cannot*** assume core = resection specimen for ER* (so beware studies *still* using these comparators)
- One ***cannot*** assume no effect of core biopsy (possible need to have no-treatment arms for gene expression and IHC studies)

Critical influence of specimen and pathology quality assurance in preoperative studies

** Mann et al (2005) J Clin Oncol 23:5148-5154*

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Pre-operative therapy

- Why give pre-operative therapy?
- Pre-operative situations:
  - Neoadjuvant trials
  - Window of opportunity trials
  - (Perioperative trials)
  - (Observational trials)
- Pathology
- **Imaging**
- Surgery

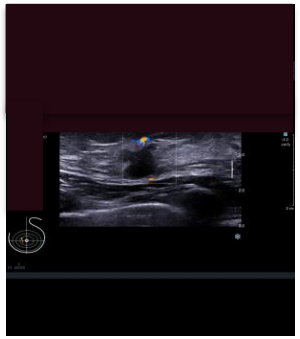
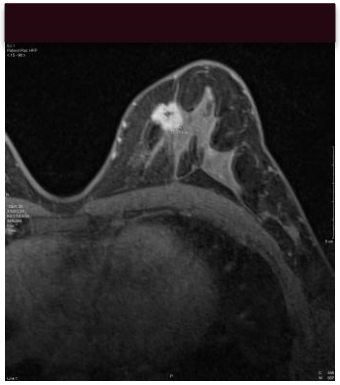
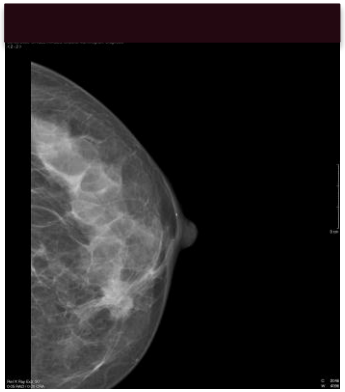
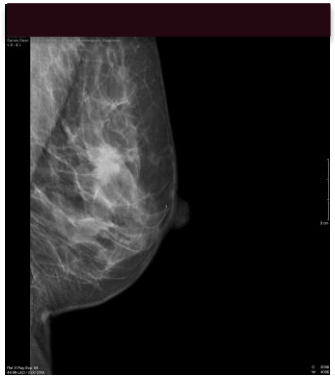
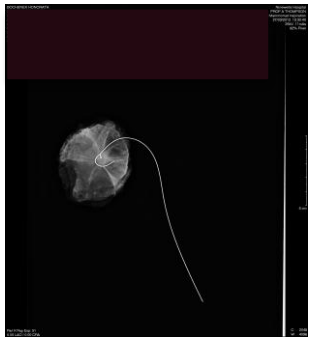
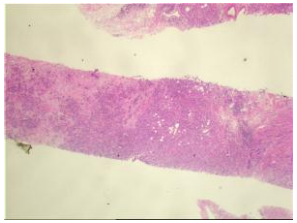
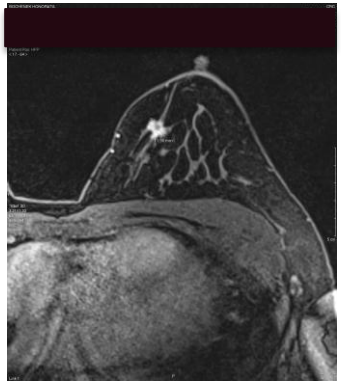
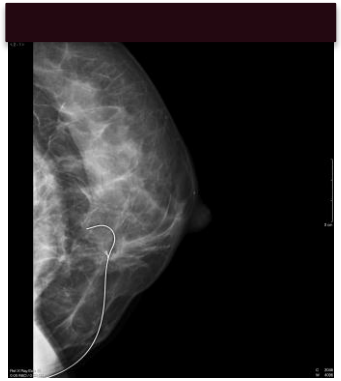
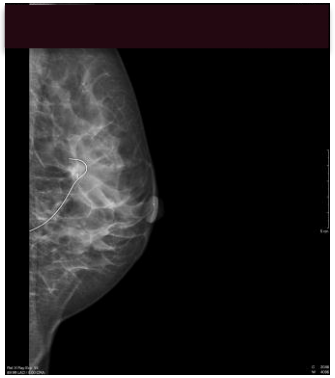
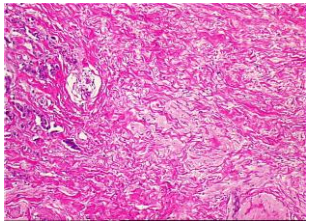
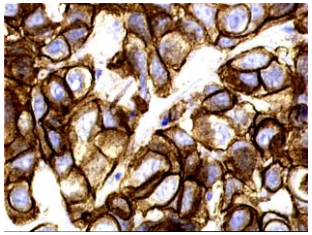
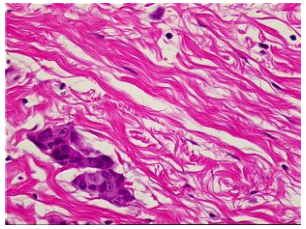
Thompson AM & Moulder SL Ann Oncology 2012; 23:x231-6

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Efficacy trials

Ultrasound…MRI…….mammography……

Courtesy of D McLean and C Purdie

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

PET(functional) Imaging

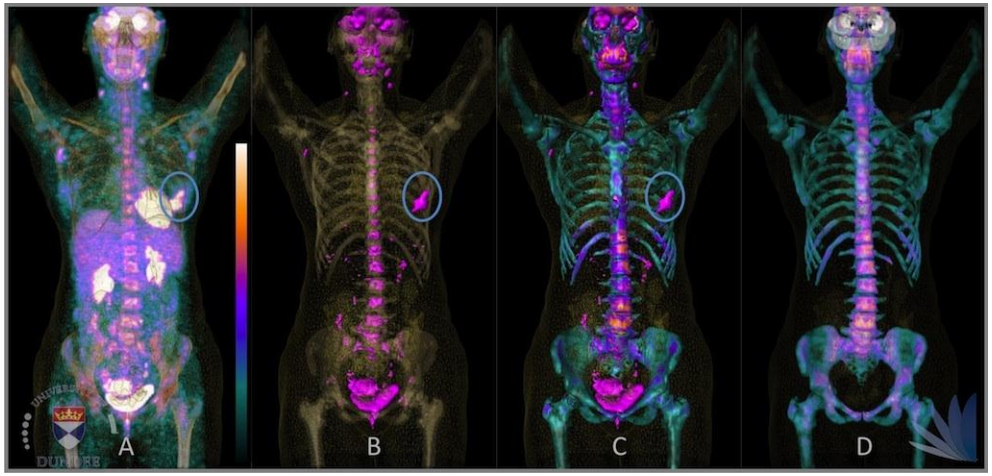
Metformin XR 500mg for 3 days

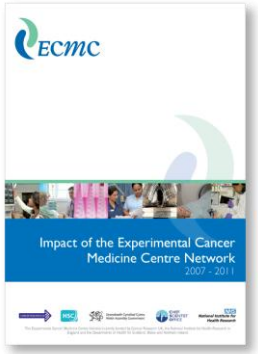
Metformin 1000mg 3 days

Metformin 1500mg 2 weeks pre chemotherapy ± continue

Surgery

Neoadjuvant chemotherapy





Simon Lord, Luc Bidaut

NeoALTTO: metabolic responders have a pCR

Pre-operative therapy

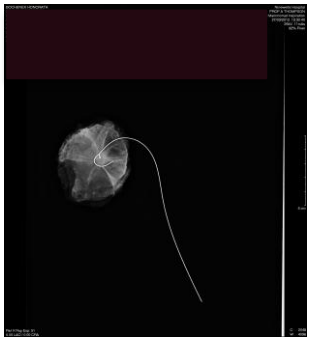
- Why give pre-operative therapy?
- Pre-operative situations:
  - Neoadjuvant trials
  - Window of opportunity trials
  - (Perioperative trials)
  - (Observational trials)
- Pathology
- Imaging
- **Surgery**

Thompson AM & Moulder SL Ann Oncology 2012; 23:x231-6

Surgery

Conservation rather than mastectomy

- Need for tumour localisation clip*
- Needle localisation for impalpable residue/clip*

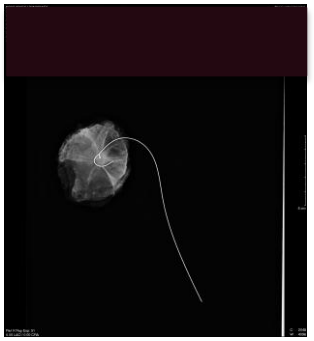


Thomassin-Naggara Breast Can Res Treat (2012) 132: 881-893

Surgery

Conservation rather than mastectomy

- Need for tumour localisation clip*
- Needle localisation for impalpable residue/clip*
- Central excision, oncoplastic approaches

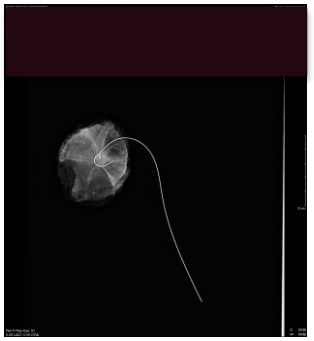


*Thomassin-Naggara Breast Can Res Treat (2012) 132: 881-893

Surgery

Conservation rather than mastectomy

- Need for tumour localisation clip*
- Needle localisation for impalpable residue/clip*
- Central excision, oncoplastic approaches
- No surgery?**



Thomassin-Naggara Breast Can Res Treat (2012) 132: 881-893

***Ring J Clin Oncol (2003) 21: 4540-4545*

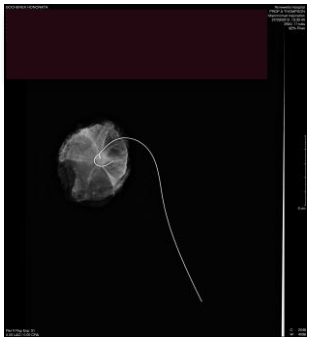
VIENNA 2012 ESMO congress

Surgery

DUNDEE CANCER CENTRE

Conservation rather than mastectomy

- Need for tumour localisation clip*
- Needle localisation for impalpable residue/clip*
- Central excision, oncoplastic approaches
- No surgery?**



If mastectomy, immediate autologous breast reconstruction: safe to irradiate ***

Thomassin-Naggara Breast Can Res Treat (2012) 132: 881-893

**Ring J Clin Oncol (2003) 21: 4540-4545*

***Chatterjee et al Brit J Surg (2009) 96: 1135-1140*

Pre-operative therapy

- Why give pre-operative therapy?
- Pre-operative situations:
  - Neoadjuvant trials
  - Window of opportunity trials
  - (Perioperative trials)
  - (Observational trials)
- Pathology
- Imaging
- Surgery

Thompson AM & Moulder SL Ann Oncology 2012; 23:x231-6

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

Challenges *and* opportunities

- Great potential of pre-operative setting for clinical studies and trials – depending on the goals
- Window of opportunity trials
- Biopsy timing and wounding effects
- Potential of imaging
- Make sure the surgery is not compromised
- May inform development of novel therapies and guide treatments in the adjuvant setting……and for advanced disease

Discovery

DUNDEE CANCER CENTRE

Implication

Preoperative trials

Application

Patient Care

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

In what situation is neoadjuvant therapy indicated?

VIENNA 2012 ESMO congress

DUNDEE CANCER CENTRE

In what situation is neoadjuvant therapy indicated?

In what situation is neoadjuvant therapy indicated?

- All patients with possible benefits
- Patients suitable for clinical trials

NHS Tayside

UNIVERSITY OF DUNDEE

DUNDEE CANCER CENTRE

SORIPTIMIST INTERNATIONAL

TENOVUS SCOTLAND

MRC Medical Research Council

BREAST CANCER CAMPAIGN TISSUE BANK

CANCER RESEARCH UK

DUNDEE CANCER CENTRE

VIENNA 2012

ESMO congress