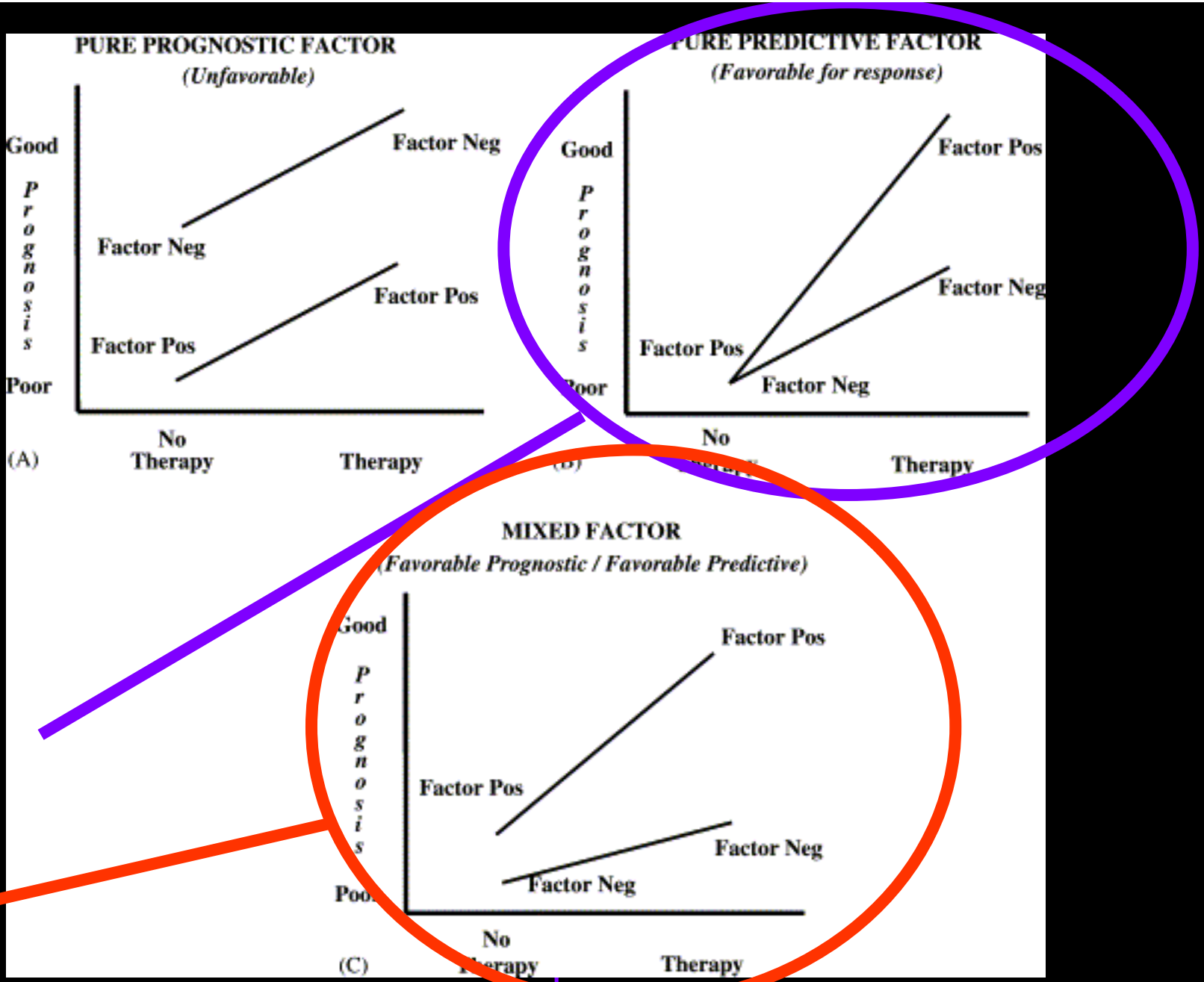
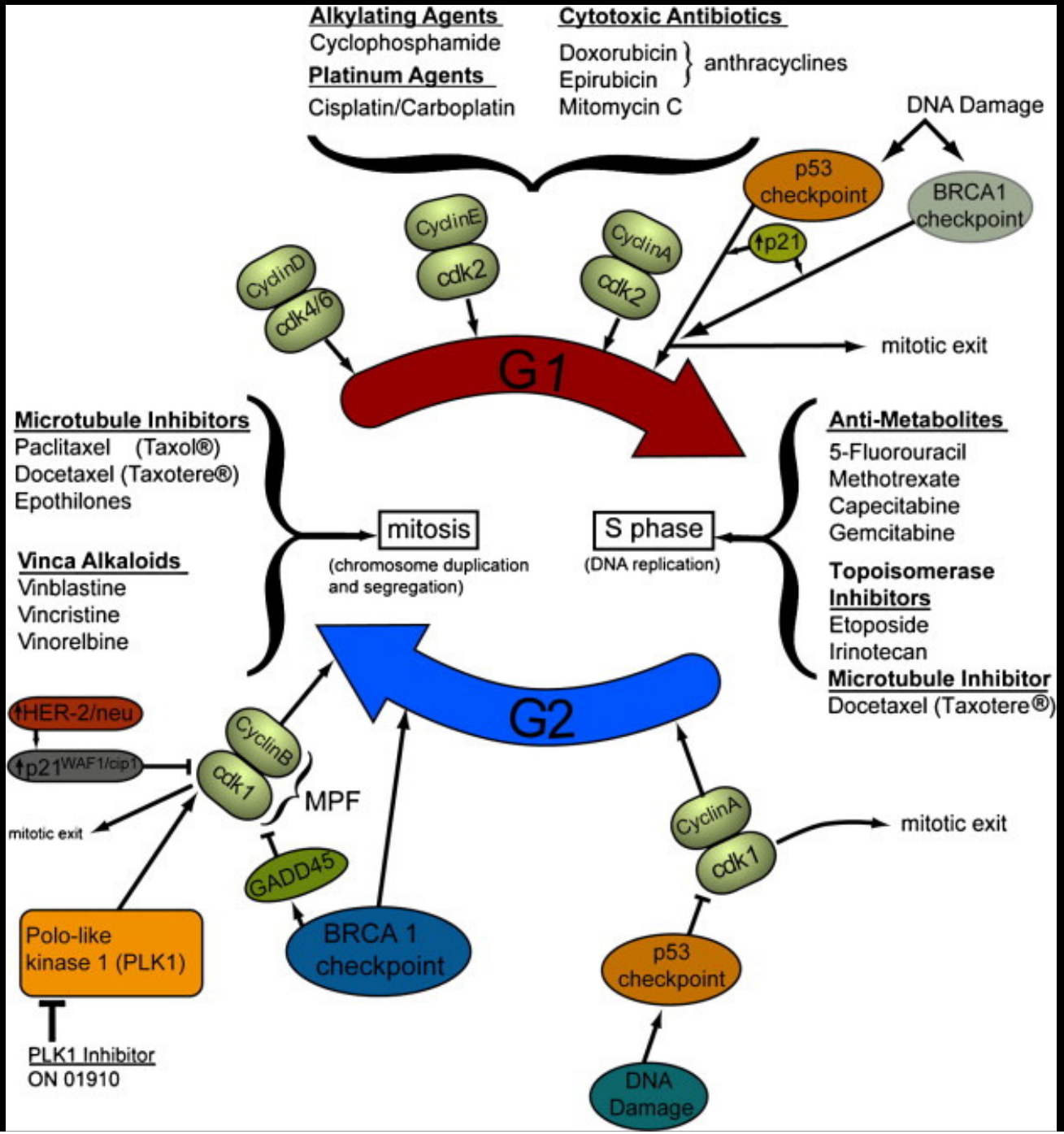
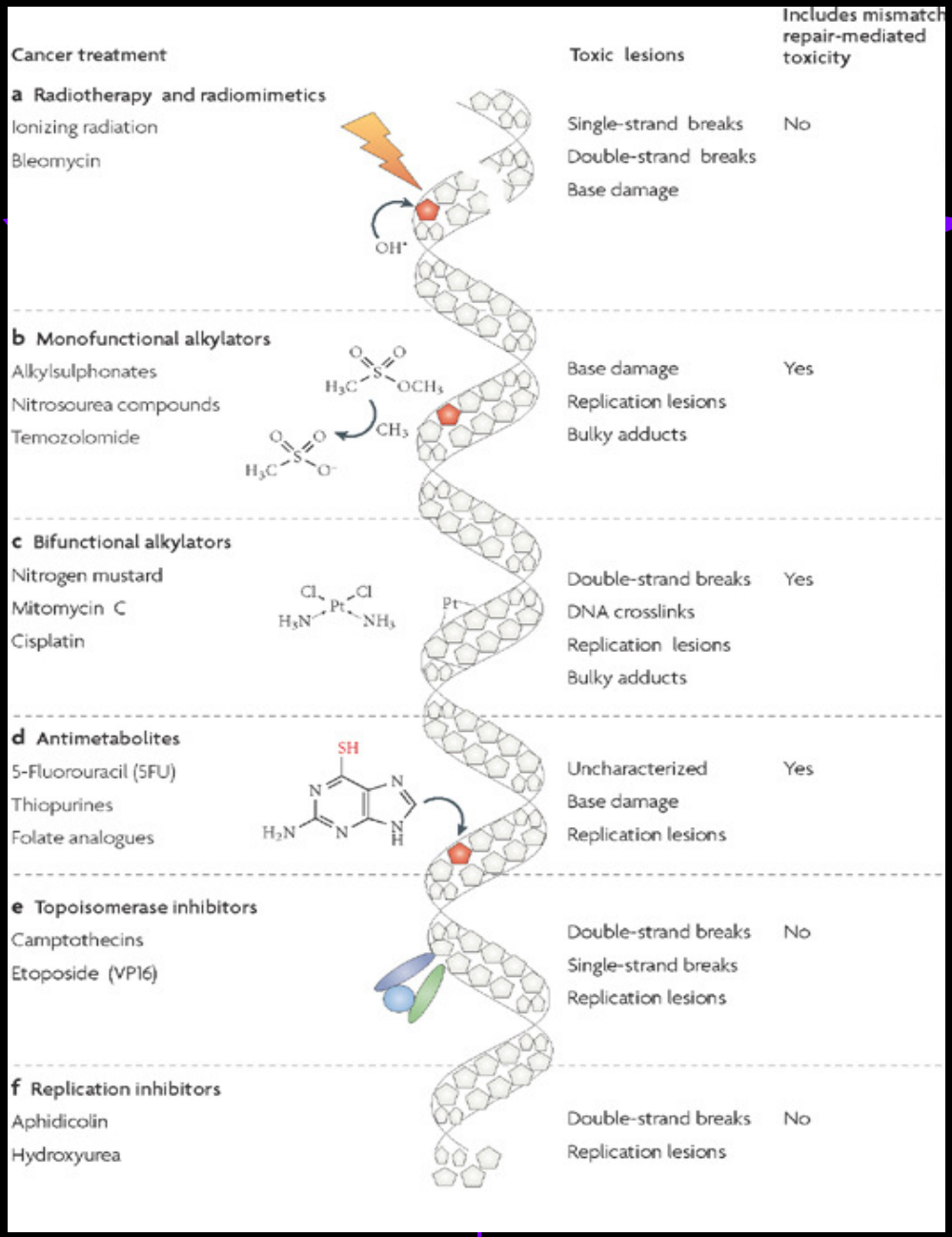
# Prædiktive faktorer for kemoterapi

DBCG's 30 års jubilæumsmøde




Hayes D F, et al. Breast Cancer Res Treat 1998; 52: 305–319.


Alkylating Agents
Cyclophosphamide
Platinum Agents
Cisplatin/Carboplatin
Cytotoxic Antibiotics
Doxorubicin
Epirubicin
anthracyclines
Mitomycin C
DNA Damage
p53 checkpoint
BRCA1 checkpoint
↑p21
CyclinE
cdk2
CyclinA
cdk2
CyclinD
cdk4/6
mitotic exit
G1
Microtubule Inhibitors
Paclitaxel (Taxol®)
Docetaxel (Taxotere®)
Epothilones
Vinca Alkaloids
Vinblastine
Vincristine
Vinorelbine
mitosis
(chromosome duplication and segregation)
S phase
(DNA replication)
Anti-Metabolites
5-Fluorouracil
Methotrexate
Capecitabine
Gemcitabine
Topoisomerase Inhibitors
Etoposide
Irinotecan
Microtubule Inhibitor
Docetaxel (Taxotere®)
G2
↑HER-2/neu
↑p21WAF1/cip1
CyclinB
cdk1
MPF
mitotic exit
GADD45
BRCA 1 checkpoint
Polo-like kinase 1 (PLK1)
PLK1 Inhibitor
ON 01910
CyclinA
cdk1
mitotic exit
p53 checkpoint
DNA Damage




Nature Reviews Cancer 8, 193-204 (March 2008) | doi:10.1038/nrc2342

# Kemoterapi

- Resistens
  - Primær – ufølsom for primær behandling
  - Sekundær – erhvervet
- Følsomhed
  - Behandling rettet mod target
- Inter-individuel forskel i pharmakokinetik og dynamik
- Ændring i efflux mekanismer (P-gp, MRP1)

# Docetaxel – mulige prædiktive faktorer

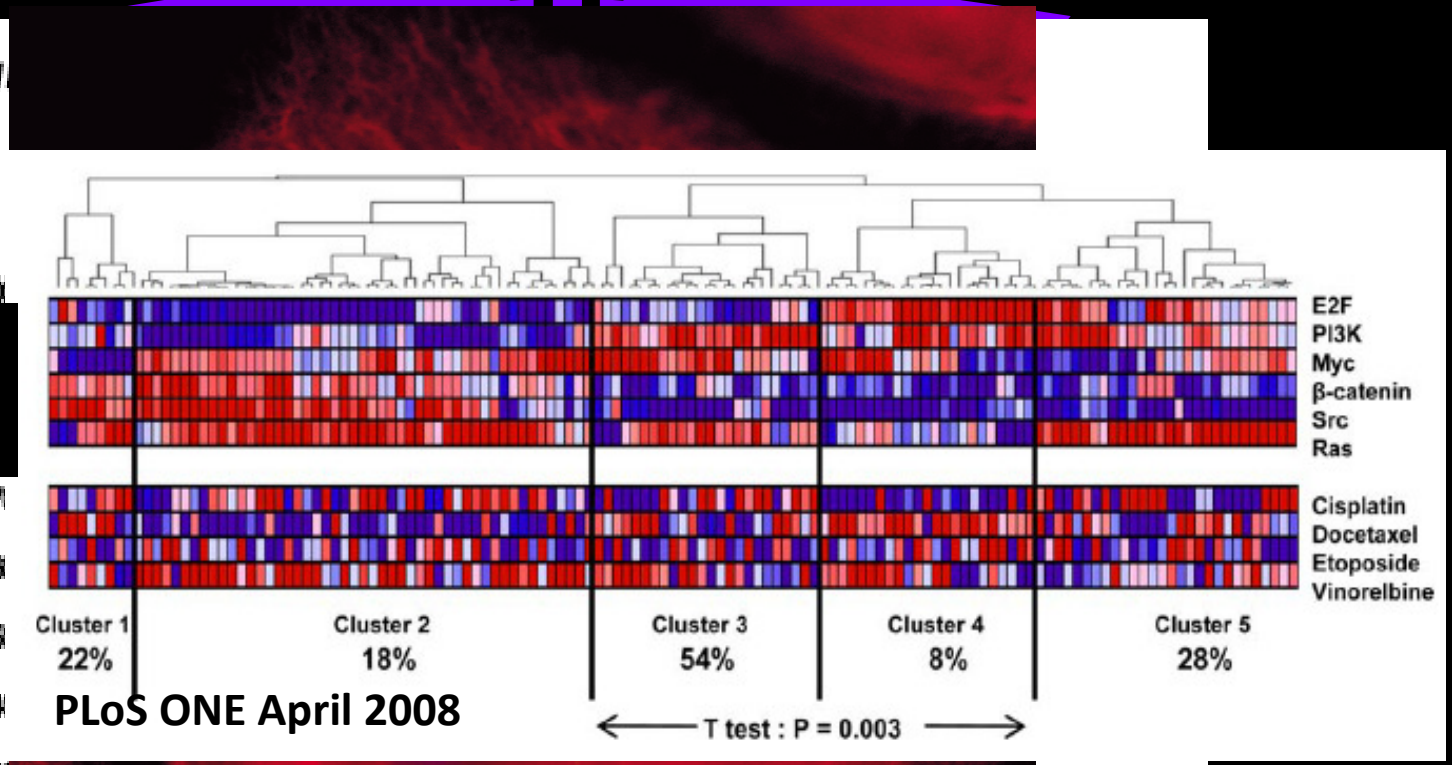
- Indgår i adjuverende og metastaserende regimer
- Årgang 2007 – inden brug af vækstfaktor – medførte
  - > 30%'s febril neutropeni
  - > 15%'s neuropati
- Så - faktorer der udpeger den gruppe der får gevinsten af behandlingen eftersøges!

# Mulige prædiktive faktorer

Neoadjuvant Therapy

Biopsi
Affymetric
Sens. pred

Response to Treatment




PLoS ONE April 2008

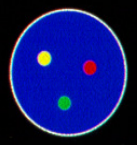
Mol Cancer Ther 2008;7 (1) Jan

Biochimica et Biophysica Acta 1785 (2008) 96-132

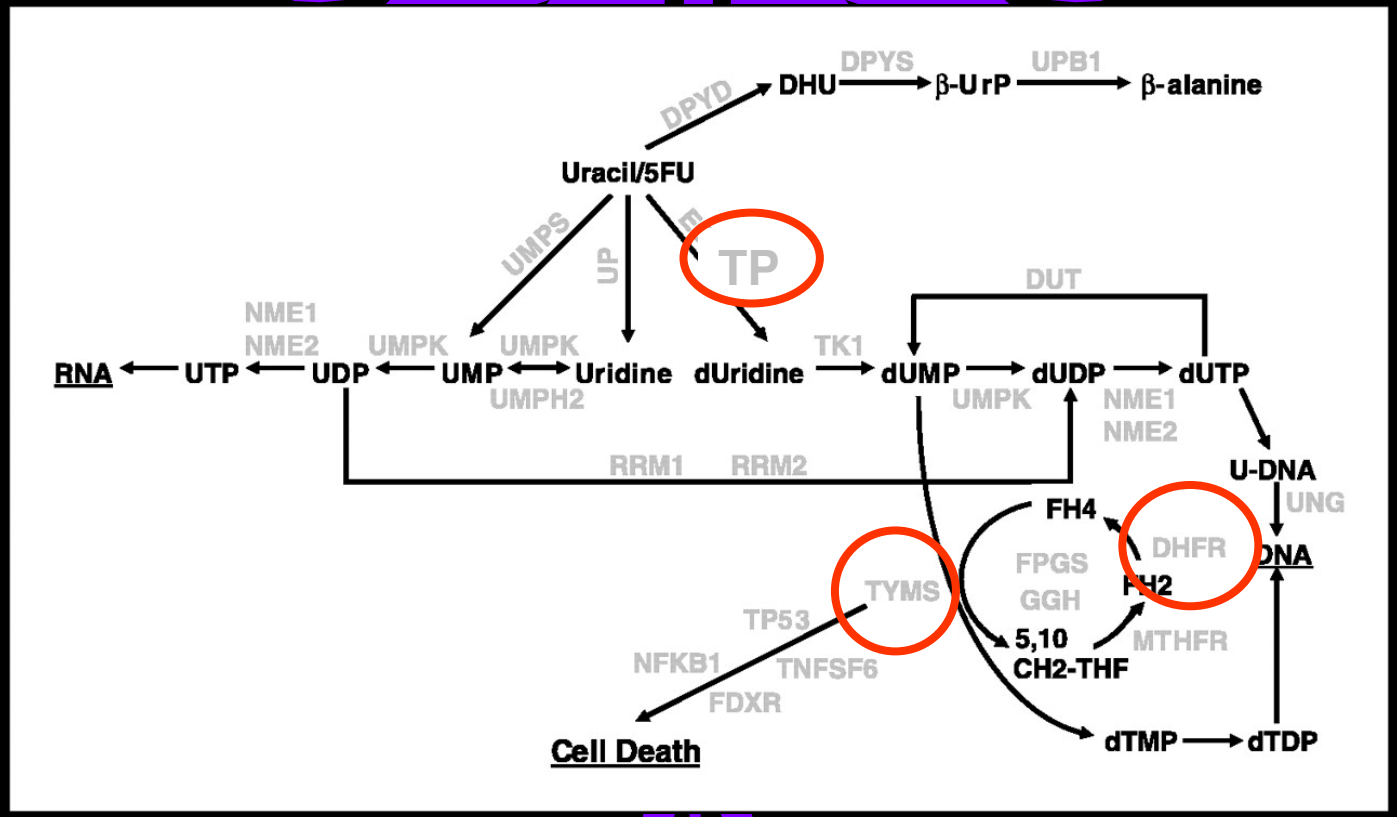
# Prædiktive Markører for 5-FU

# TYMS Projekt

DakoCytomation/DBCG



# 5-FU pathway/ carpecitabine




TYMS (Thymidylate synthase) on 18p11.32
TP (ECGF1)(Thymidine phophorylase) on 22q13.32
DHFR (Dehydrofolate reductase) on 5q11.2-q13.2

# Potentielle Prædiktive Markører for 5-FU

- FISH prober:

- **TYMS** (Thymidylate synthase) på 18p11.32
- **TP** (ECGF1)(Thymidine phophorylase) på 22q13.32
- **DHFR** (Dehydrofolate reductase) på 5q11.2-q13.2

Christensen AJ et al. 2006

# Pilot Studie Design

- 180 patienter med dissemineret mammacancer behandlet med Xeloda
  - En gruppe af non-responders TTP < 3 mdr.
  - En gruppe af "optimale" responders TTP > 6 mdr.
- Pilot study: 35 → 24 patienter
  - Non-responderes = 9
  - Optimale responderes = 15

Christensen AJ et al. 2006

# Predictive markers for 5-FU resistance in metastatic breast cancer

Christensen AJ, Jensen LB, Balslev E, Nielsen KV, Poulsen TS, Nielsen DL, Moller S, Mouridsen H, and Ejlertsen B

Danish Breast Cancer Cooperative Group, Rigshospitalet, Copenhagen, Denmark and Dako, Glostrup, Denmark

## Results

| | Patient | TYMS | | |
|---|---|---|---|---|
| TTP > 6 months | 1 | 0,92 | | |
| | 2 | 0,99 | | |
| | 3 | 0,98 | | |
| | 4 | 0,96 | | |
| | 5 | 1,02 | | |
| | 6 | 0,86 | | |
| | 7 | 1,08 | | |
| | 8 | 0,94 | | |
| | 9 | 0,96 | | |
| | 10 | 0,99 | | |
| | 11 | 0,91 | | |
| | 12 | 0,95 | | |
| | 13 | 0,86 | | |
| | 14 | 0,94 | | |
| | 15 | 1,01 | | |
| TTP < 3 months | 16 | 0,59 | | |
| | 17 | 0,90 | | |
| | 18 | 1,00 | | |
| | 19 | 0,76 | | |
| | 20 | 0,99 | | |
| | 21 | 0,99 | | |
| | 22 | 0,57 | | |
| | 23 | 0,81 | 0,77 | 0,95 |
| | 24 | 1,02 | 0,74 | 0,34 |

Deletion:
Ratio < 0.8

**TABLE 3. Distribution of normal and abnormal GCNs in relation to clinical benefit.**

| | Normal copy number of all 3 genes (TYMS, DHFR, TP) | Abnormal copy number of at least 1 of the 3 genes | Total |
|---|---|---|---|
| Clinical Benefit | 15 (100%) | 0 (0%) | 15 (62.5%) |
| No Clinical Benefit | 2 (22%) | 7 (78%) | 9 (37.5%) |
| Total | 17 (71%) | 7 (29%) | 24 (100%) |

DANISH BREAST CANCER CO-OPERATIVE GROUP

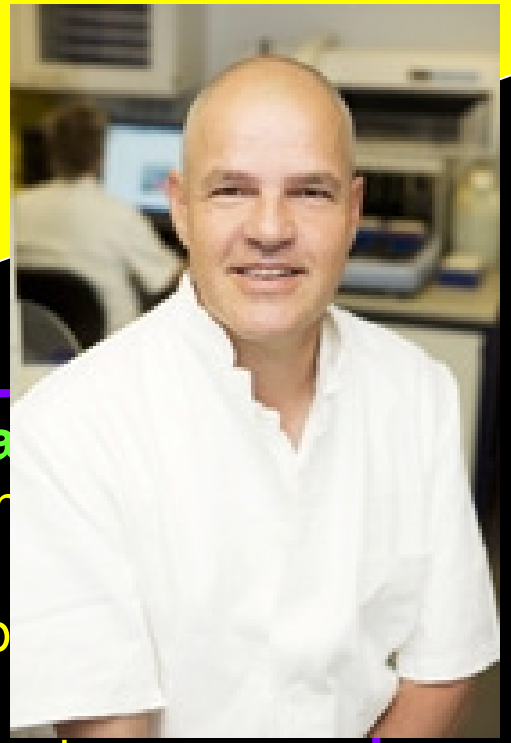
Christensen AJ et al. 2006

AVISEN.DK BETA
DANMARKS STØRSTE AVIS

# Tissue inhibitor of Metalloproteinase-1 (TIMP-1)

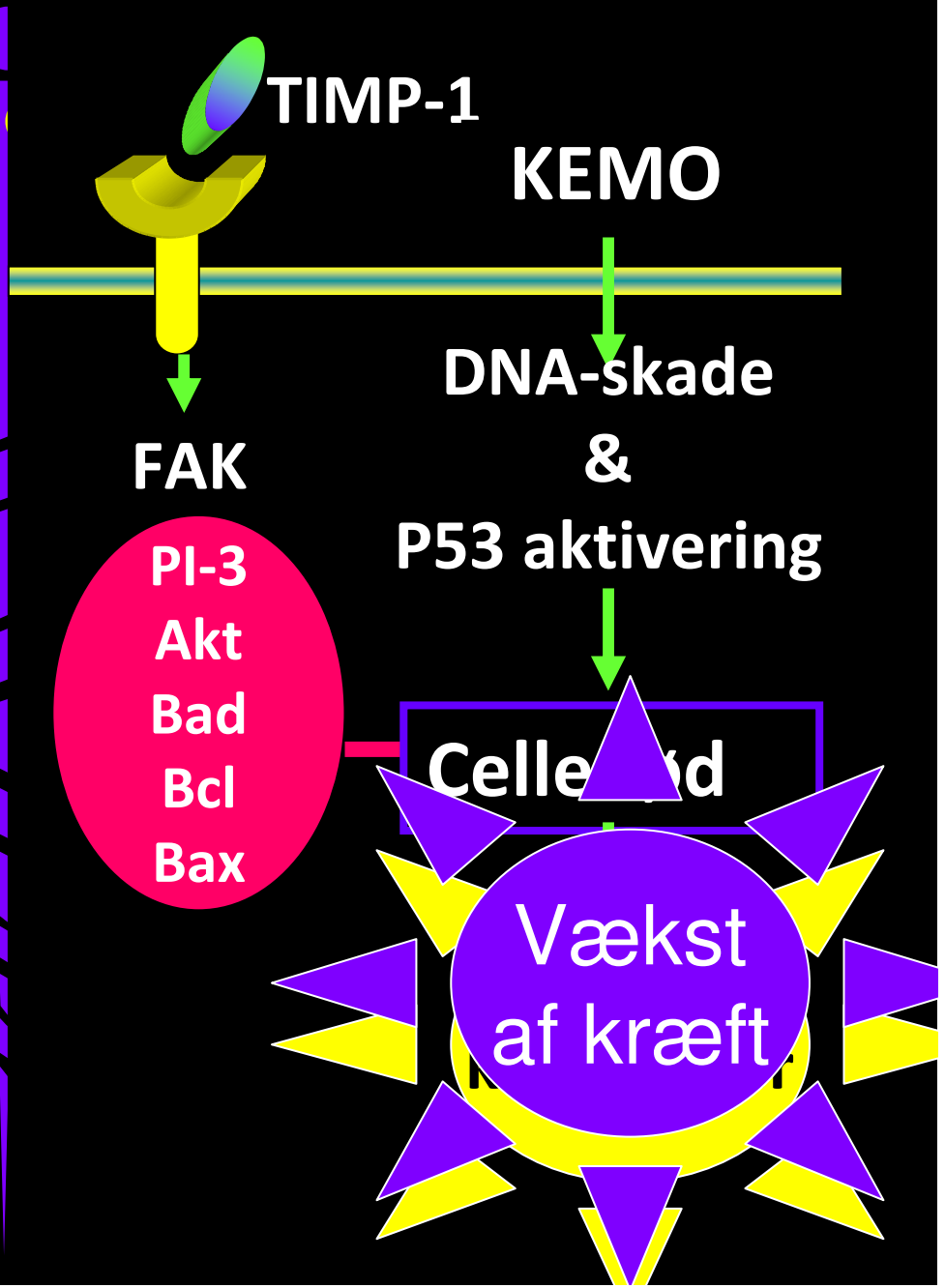
**…ner vej for bedre kra…**

…nel kemoterapi virker kun på h…
af kvinder med brystkræft.
Nu har danske forskere fundet et p…
der blokerer for kemoen,
og det kan betyde, at man fremover kan
skræddersy behandlingen, så den virker bedre



# Funktion

- TIMP-1 inhiberer matrix metalloproteinase–medieret proteolytisk nedbrydning af den extracellulære matrix



Det Biovidenskabelige Fakultet, Kbh's Universitet

- TIMP-1 hæmmer apoptose (celledød)
- Det meste kemoterapi virker ved at inducere apoptose
- Hypotese:
  - Højt niveau af TIMP-1 i tumor eller plasma forudsiger resistens til kemoterapi.

# TIMP-1 og prædiktion

Primary Tumor Levels of Tissue Inhibitor of Metalloproteinases-1 Are Predictive of Resistance to Chemotherapy in Patients with M

A
M

| TIMP-1 | Hig | |
|---|---|---|
| | | 41% |
| change/ progressive disease | 100% | 59% |

**..using TIMP-1, we identified a group of patients…., which hardly respond to the most frequently used chemothrapy regimes…**


levels were significantly associated with a poor response to chemotherapy. By using TIMP-1, we identified a group of patients with metastatic breast cancer, which hardly respond to the most frequently used chemotherapy regimes (i.e., cyclophosphamide/methotrexate/5-fluorouracil and anthracyclines).

# Kan TIMP-1 forudsige virkningen af adjuverende kemoterapi?

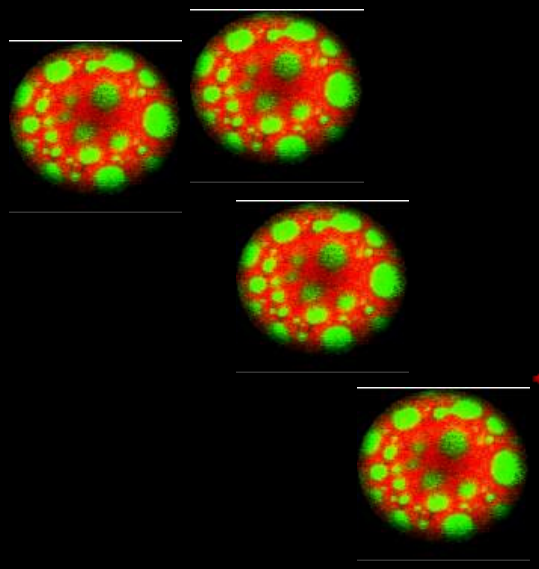
**Bliv til 15.35 og hør!!**

# Antracykliner

- Antracyklinbaserede kemoterapi giver en absolut overlevelsesgevinst på **3%** i efter 10 år sammenlignet med CMF
- Den gennemsnitlige gevinst observeret i randomiserede studier eller metaanalyser kan forklares ved, at det er en **lille gruppe** patienter der **har en meget stor effekt**
- Antracykliner er **topoisomerase II** (*TOP2A*) inhibitorer (1984)

# TOP2A

**Enzymet**
**Topoisomerase**



**Genet**
**TOP2A**

Antracykliner → Celledød

# Antracykliner og *TOP2A*

Highlights

1984

1984

1998

2000

2002

2005

NEXT

- The coding sequence of *TOP2A* was determinded by Tsai-Pflugfelder et al.
- Topoisomerase IIα is the primary target for anthrayclines (Tewey et al.)
- Is Topo IIα expression predictive? (Järvinen et al.)
- In a small pilot study Järvinen et al. demonstrated *TOP2A* amplification (41%) and deletion (43%) in 70 *HER2* amplified breast tumors.
- **Amplifikation af *TOP2A* fører til overexpression af topoisomerase og øger kræftcellens følsomhed overfor *TOP2A* inhibitorer = antracyklin.**
- **Deletion af *TOP2A* fører til nedsat expression af topoisomerase og primær kemo-resistens overfor *TOP2A* inhibitorer.**
- Results from a small Belgium study by Di Leo et al.
- **A retrospective analysis of DBCG trial 89D by Knoop et al. confirms the predictive value of *TOP2A*.**
- Full publication of other trials?
- Meta-analysis with centralized evaluation of *TOP2A?*
- **Prospective trials?**

# DBCG 89D; Design

**Patient selection**

- Premenopausal, high risk, node negative
- Premenopausal, node positive, ER-/PgR negative or unknown
- Postmenopausal, node positive, ER-/PgR negative

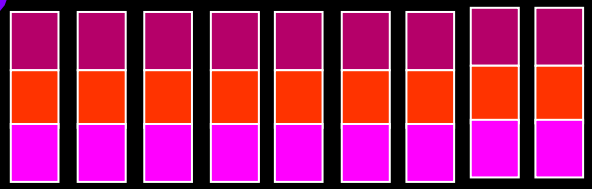
**Stratification**

- Center and
- Treatment Group

N=1224

RANDOMIZE

7 – 9 x CEF



7 – 9 x CMF

C: cyclophosphamide 600 mg/m$^2$

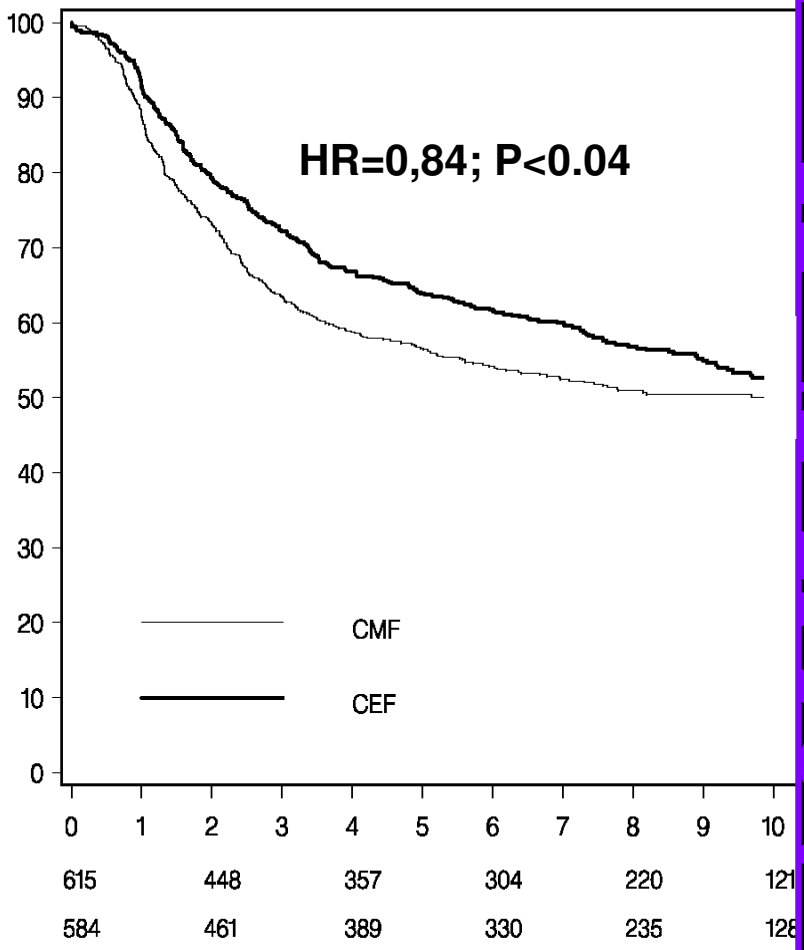
F: 5-fluorouracil 600 mg/m$^2$

M: methotrexate 40 mg/m$^2$

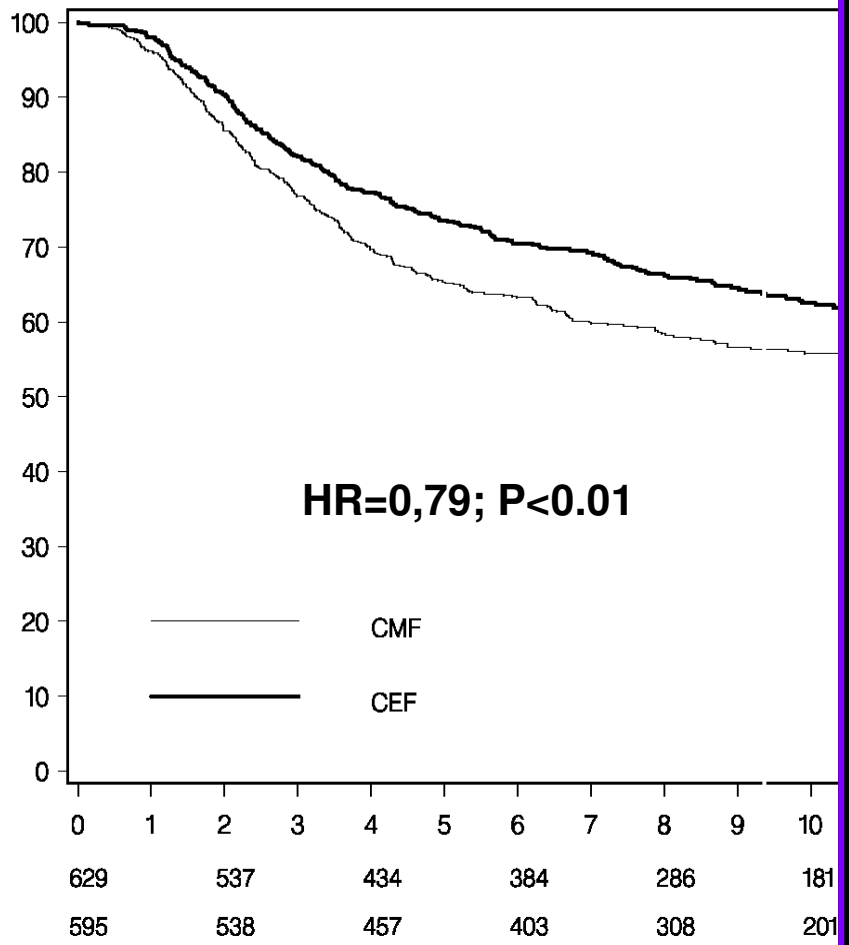
E: epirubicin 60 mg/m$^2$

# DBCG-89D

## Recurrence-free survival (%)




## Overall survival (%)




Ejlertsen B, Eur J Cancer 2007

# *TOP2A* gene aberrations as predictive and prognostic marker in high-risk breast cancer patients

## A randomized DBCG Trial (DBCG89D)

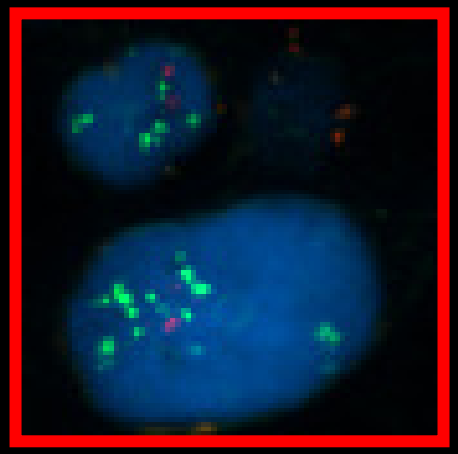
**Update of publication in JCO : 23;7483-90, 2005**

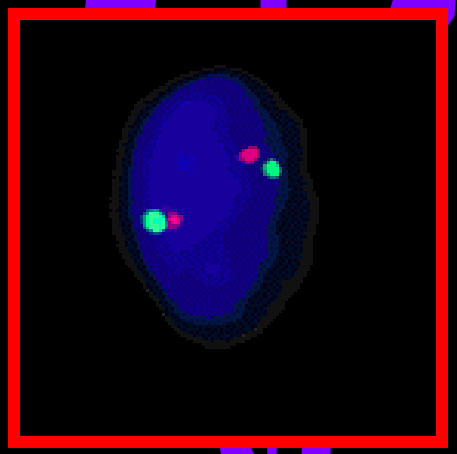

| | | |
|---|---|---|
| *DBCG:* | Medical therapy | • A Knoop, H Mouridsen, B Ejlertsen |
| | Statistics | • M Düring K Gunnarsdóttir |
| | Pathology | • H Knudsen, E Balslev, BB Rasmussen |
| | Tumour biology | • J Overgaard |
| *Dako:* | R&D Pathology | • KV Nielsen, JT Jørgensen, A Schonau |

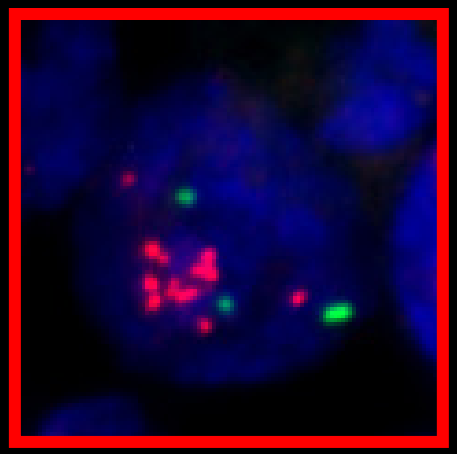
# Metode FISH

**Deletion: ratio < 0.8  Normal: ratio 0.8-2.0  Amplification: ratio ≥ 2.0**

**11%  77%  12%**

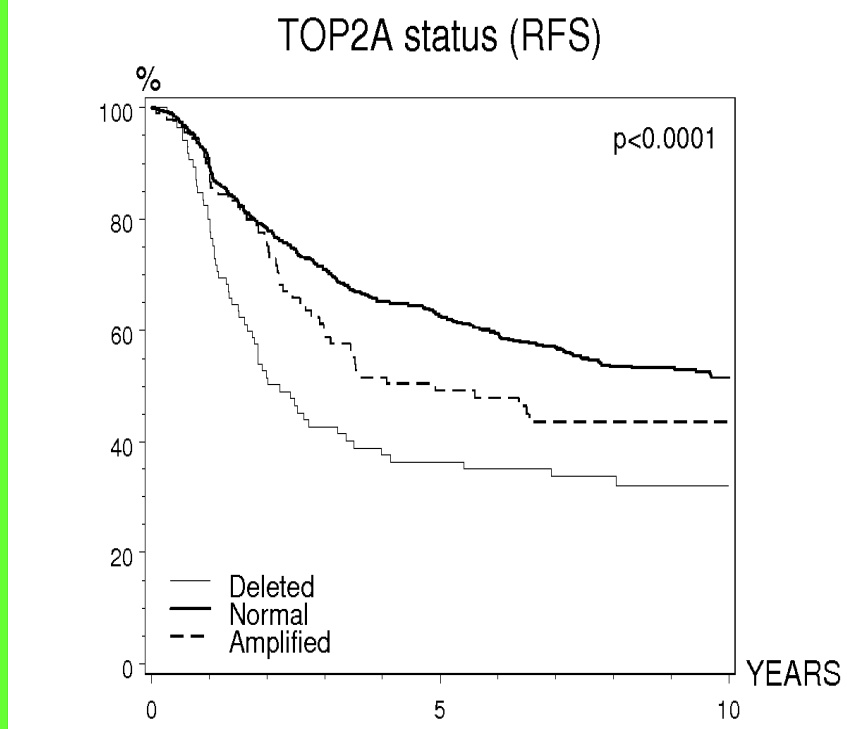






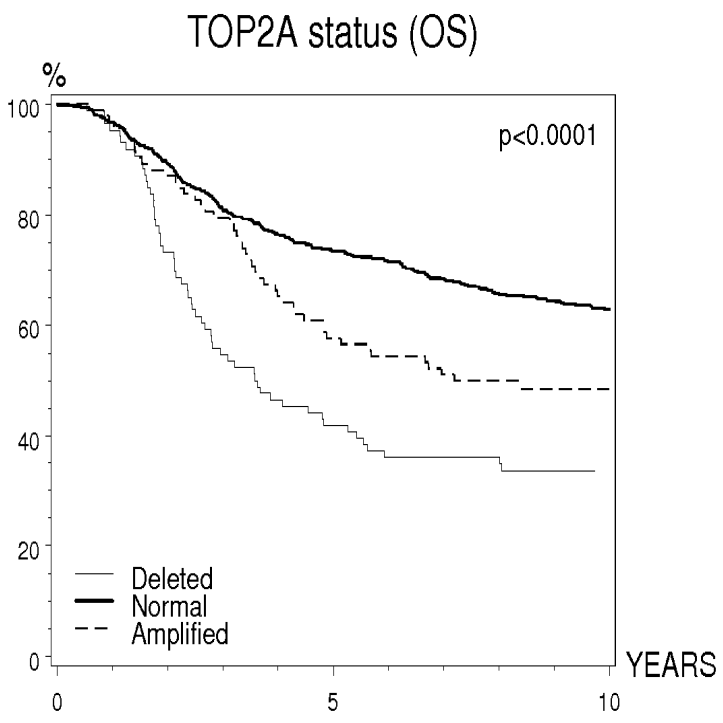
*TOP2A* FISH pharmDx™ Kit (Dako, Glostrup, Denmark)

# Prognostic value of *TOP2A*-status




Patients at risk

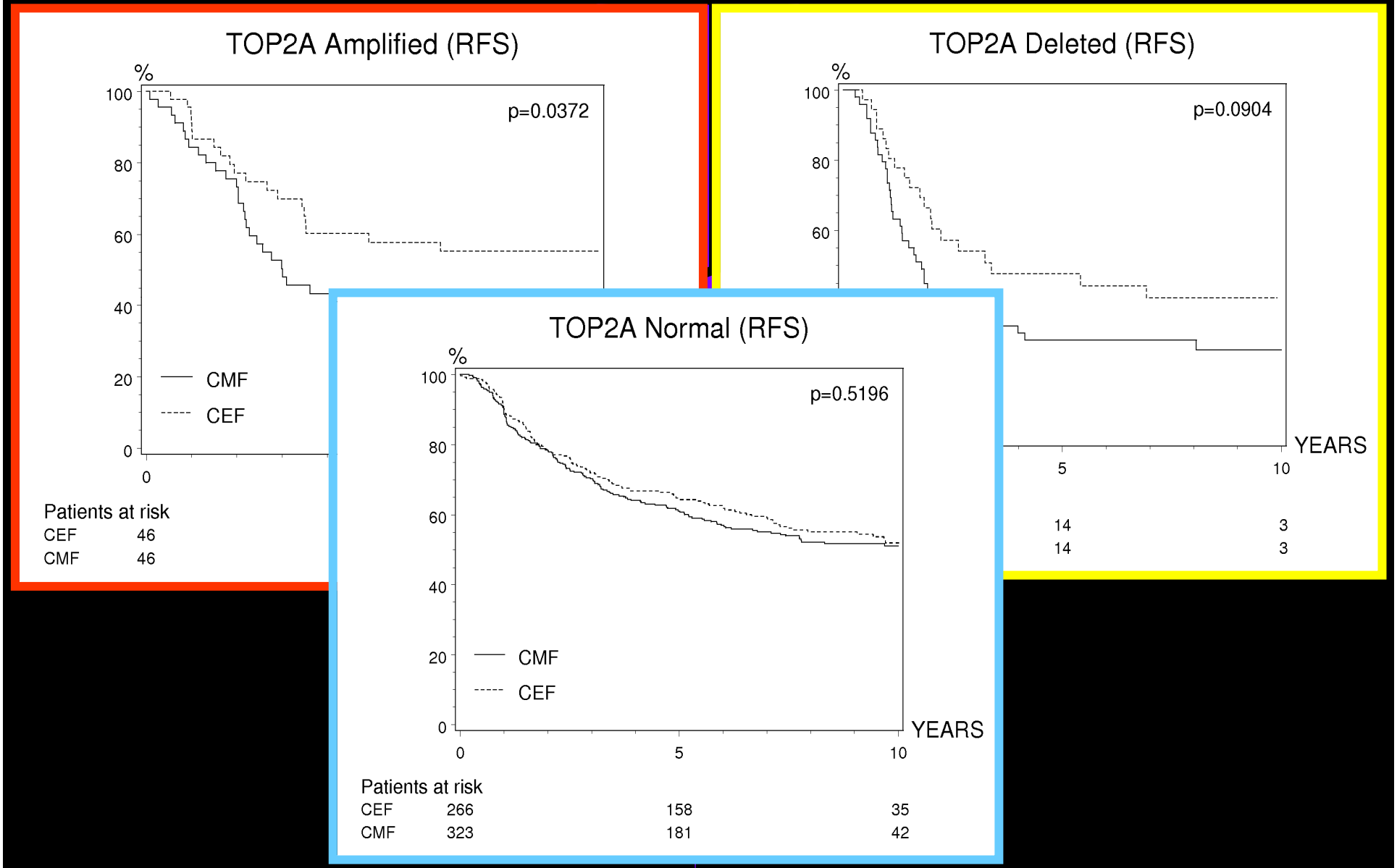
| | | | |
|---|---|---|---|
| Amplified | 92 | 40 | 8 |
| Normal | 589 | 339 | 77 |
| Deleted | 86 | 28 | 6 |




Patients at risk

| | | | |
|---|---|---|---|
| Amplified | 92 | 53 | 26 |
| Normal | 589 | 433 | 239 |
| Deleted | 86 | 36 | 18 |

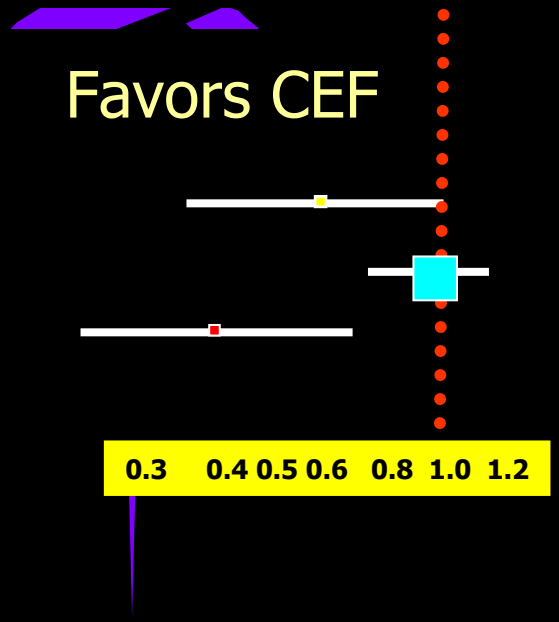
# Predictive value of *TOP2A-status*



# Relative Effekt af CEF (RFS)

- I DBCG 89D er der en samlet risikoreduktion på 16%
- 39% risikoreduktion i den *TOP2A* deleterede gruppe (N=86)
- 6% risikoreduktion i den *TOP2A* normal group (N=589)
- 61% risikoreduktion i den *TOP2A* amplifcerede group (N=92)

| *TOP2A* | HR | |
|---|---|---|
| Deleted | 0.61 | p = 0.08 |
| Normal | 0.94 | p = 0.6 |
| Amplified | 0.39 | p = 0.002 |



# DBCG 07-READ

*TOP2A* som prædiktiv markør

# Prospektivt studie i *TOP2A* normale patienter

Undgå antracyklinholdig kemoterapi!

Sammenligne med 3 x EC + 3 X D!

# DBCG 07-READ Formål

- **Det primære formål**
  - invasiv sygdomsfri overlevelse (IDFS) efter sekventiel epirubicin og cyklofosfamid (EC) efterfulgt af docetaxel (D) overfor docetaxel og cyklofosfamid (DC).

- **Sekundære mål**
  - total overlevelse (OS), overlevelse uden fjernrecidiv (DDFS) og forekomsten af alvorlige uønskede hændelser efter sekventiel EC -> D overfor DC

# DBCG 07- READ

## Randomized trial of epirubicin and cyclophosphamide followed by docetaxel against docetaxel and cyclophosphamide in patients with *TOP2A* normal early breast cancer

**PATIENTS**

- Operable breast cancer
- Any tumor size
- TOP2A normal
- Age ≤ 60 or age < 70 and receptor neg.

**ENDPOINTS**

1st. IDFS

2nd. OS, DDFS

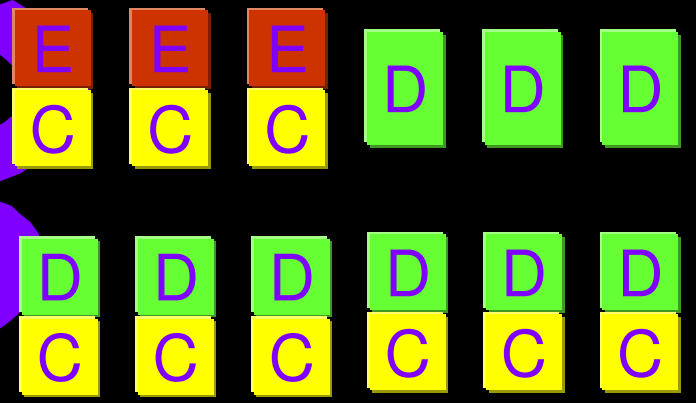
**OTHER THERAPIES**

- XRT if T3 or N+
- Tam/AI if ER or PgR+
- Herceptin if HER2 +

SURGERY

RANDOMIZE

N = 1,952




Epirubicin 90 mg/m²
CTX 600 mg/m²

Docetaxel 100 mg/m²

Docetaxel 75 mg/m²
CTX 600 mg/m²

# DBCG 07-READ

Efter mikroradikal op. af en *TOP2A* normal brystkræft, kan følgende 3 grupper af patienter inkluderes:

- **Yngre end 35 år.**
- **Hormonreceptor negativ tumor (ER og PgR negativ) og alder mellem 35 år og 75 år.**
- **Hormon receptor positiv tumor, alder mellem 35 og 59 år, og mindst en af følgende karakteristika: spredning til lymfeknuder, tumor > 2 cm, malignitetsgrad II-III eller HER2 positiv.**

**CO-MORBIDITETSSCORE PÅ < 3**

**(1 og 2 STARTER PÅ DOSISNIVEAU -1)**

# Bivirkninger

- Selv-rapporterede efter hver behandling og efter 3 mdr.
- Omhandler:
  - Slimhindeirritation i mund og svælg
  - Diarre
  - Muskel og ledsmerter
  - Nervepåvirkning
  - Hududslæt
  - Negle-ændringer
  - Opkastning/ Kvalme
  - Væske-ophobning
  - Træthed
  - Andre bivirkninger

# Status

- DBCG aktiverer randomiseringen den 26. maj 2008
- Deltagerinformation, samtykke og CRF vil fra samme dato kunne nedtages fra DBCG's hjemmeside.
- Randomisering foregår online via menupunktet 'WEB – indtastning' på DBCG's hjemmeside, eller ved at faxe inklusionsskemaet til DBCG.

# Prædiktive faktorer og kemoterapi

- Med den stigende anvendelse af kemoterapi og deraf følgende toksicitet, er der hårdt brug for kemoterapi markører
- Men - der er lang vej endnu! ;-)


Tillykke med de 30 år