Current Update Chemotherapy in Breast Cancer

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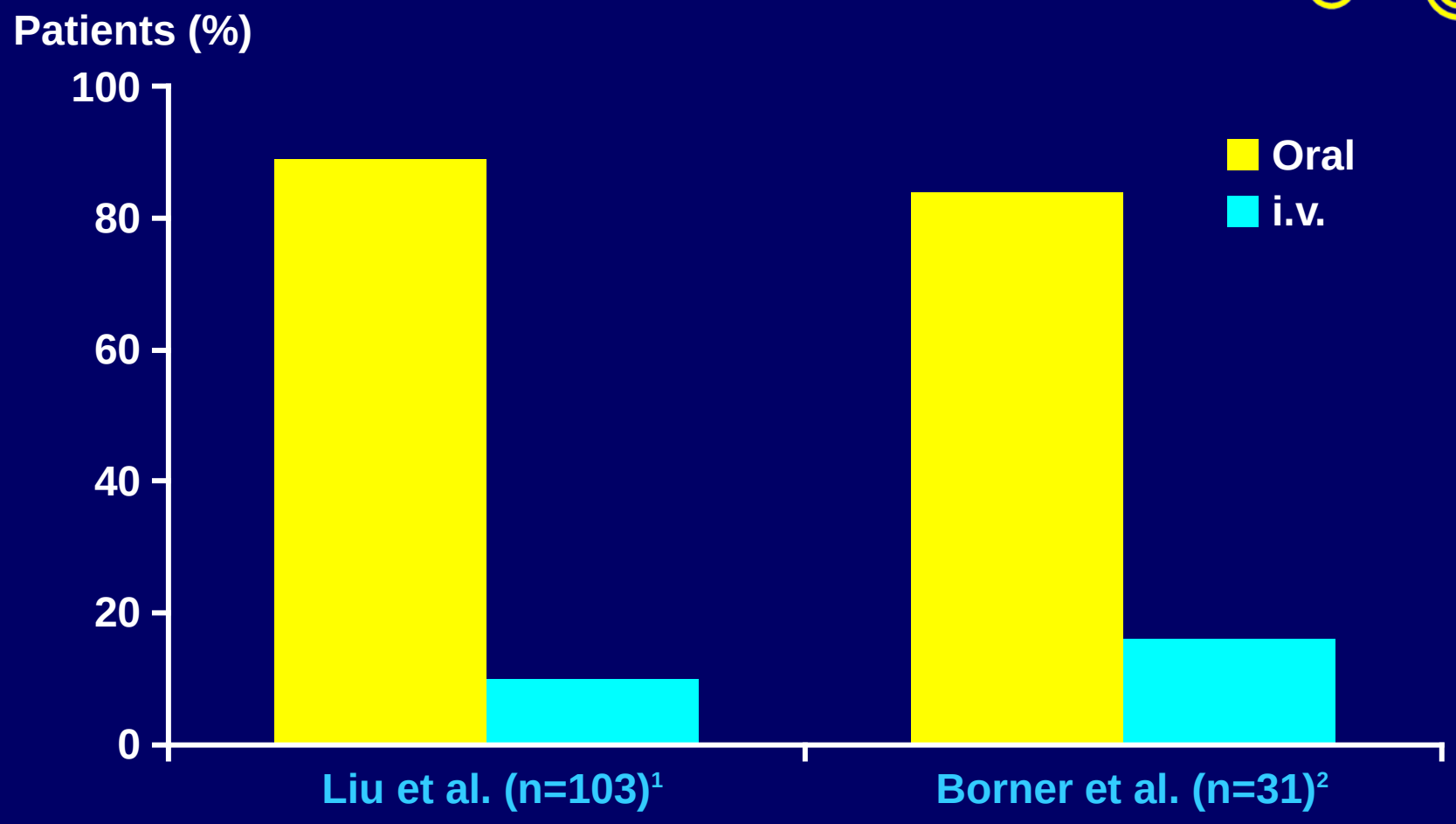
PADANG

Capecitabine

Targeting Chemotherapy

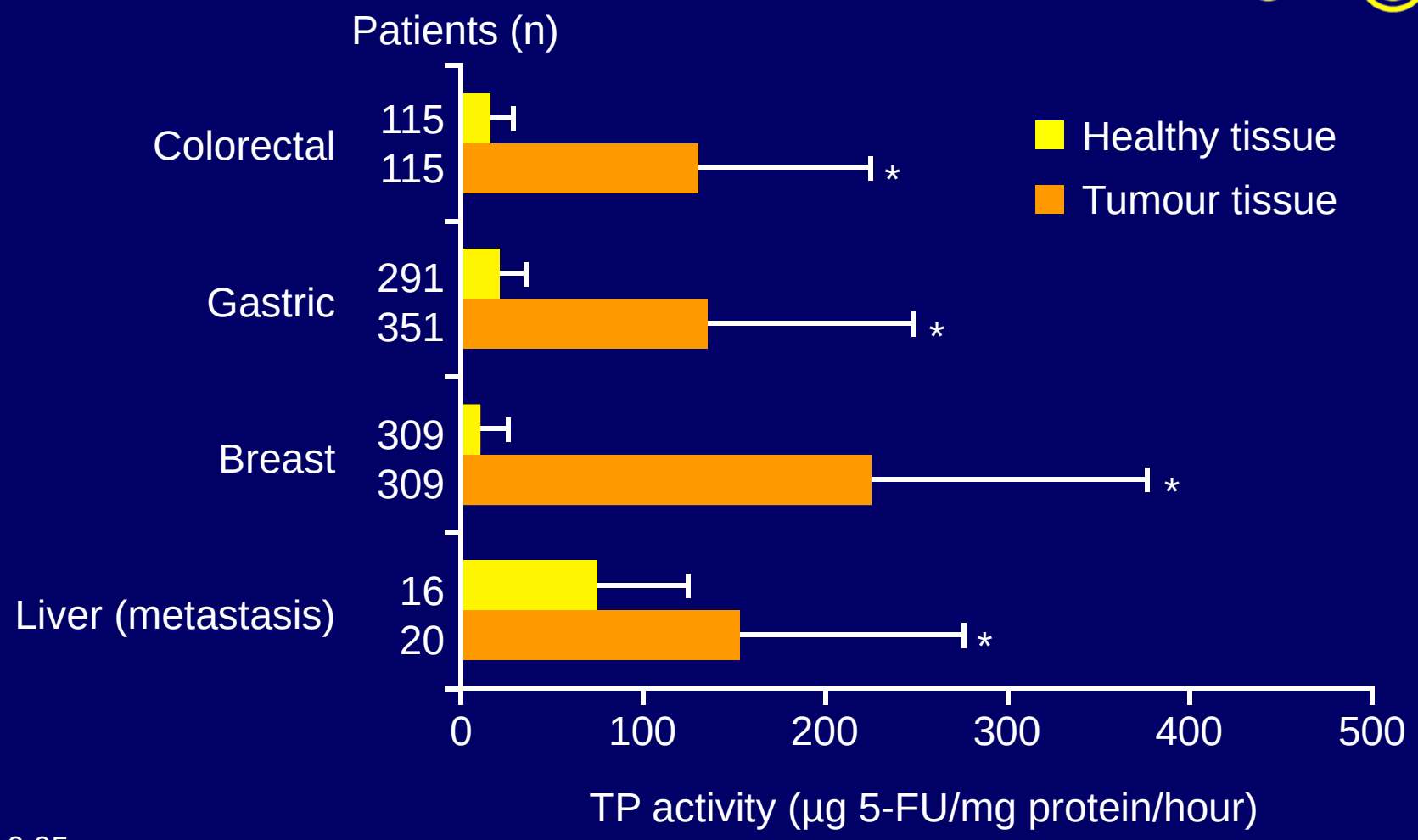
It targets Cancer Cells

Most patients prefer oral chemotherapy, providing efficacy is not compromised



[1]Liu G et al. J Clin Oncol 1997;15:110–15
[2]Borner M et al. Eur J Cancer 2002;38:349–58

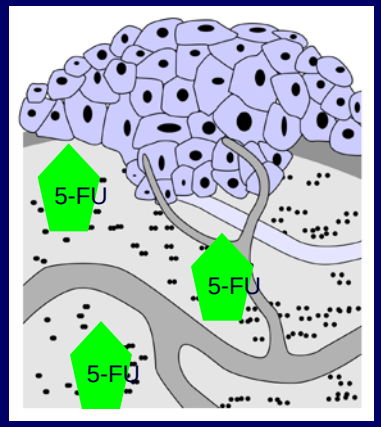
TP is significantly more active in human tumour than healthy tissue



*p<0.05
5-FU = 5-fluorouracil

Adapted from Miwa M, et al. Eur J Cancer 1998;34:1274–81

No tumour selectivity with 5-FU



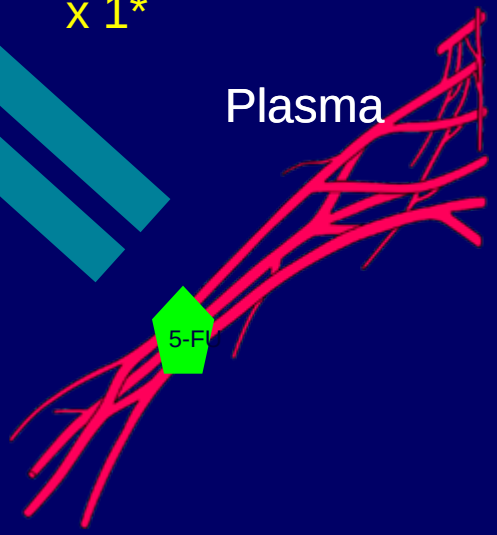
x 1*

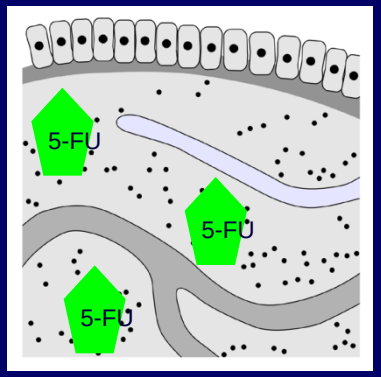
Normal tissue

Tumour tissue

x 1*

Plasma

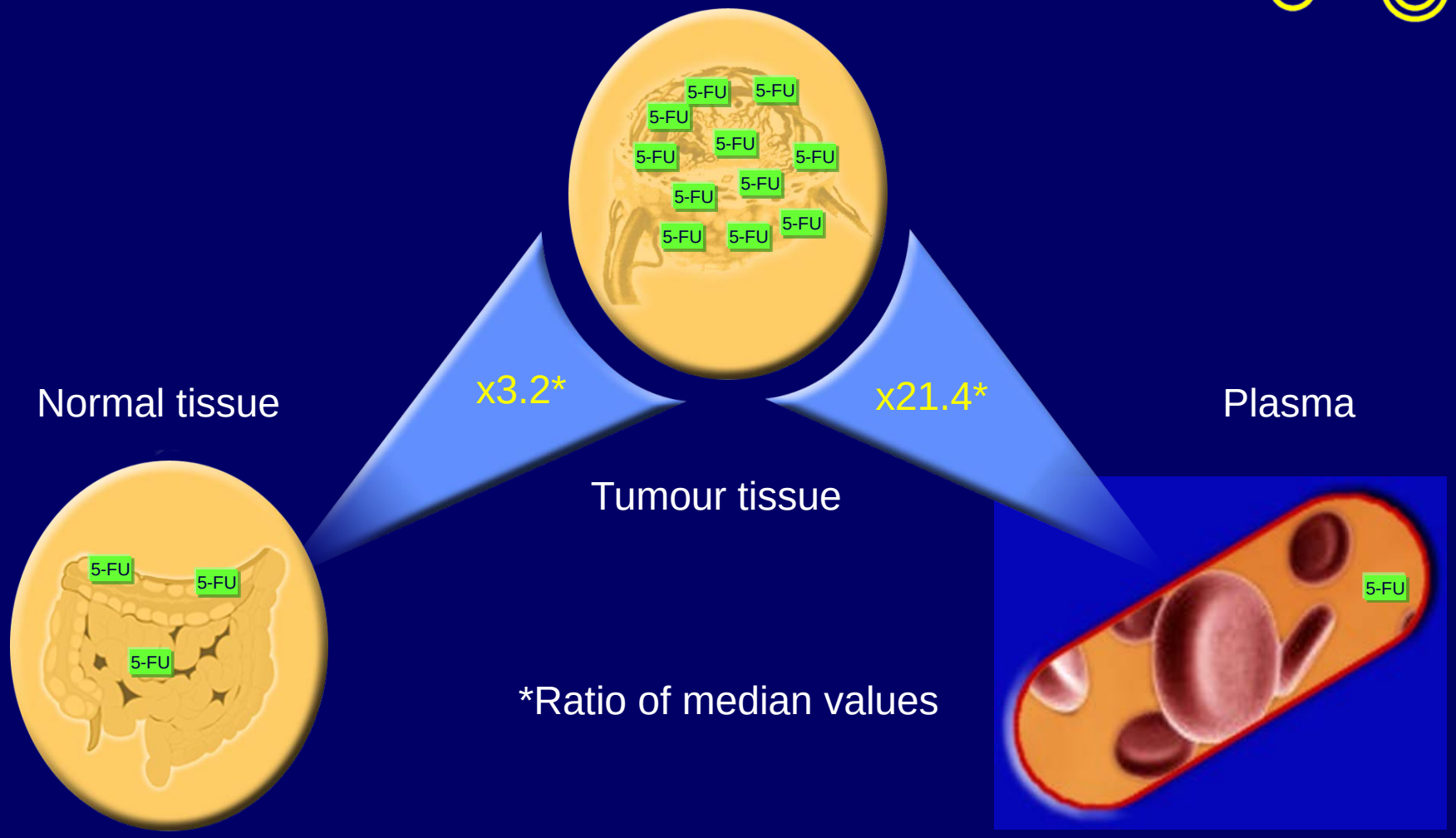




*Ratio of median values

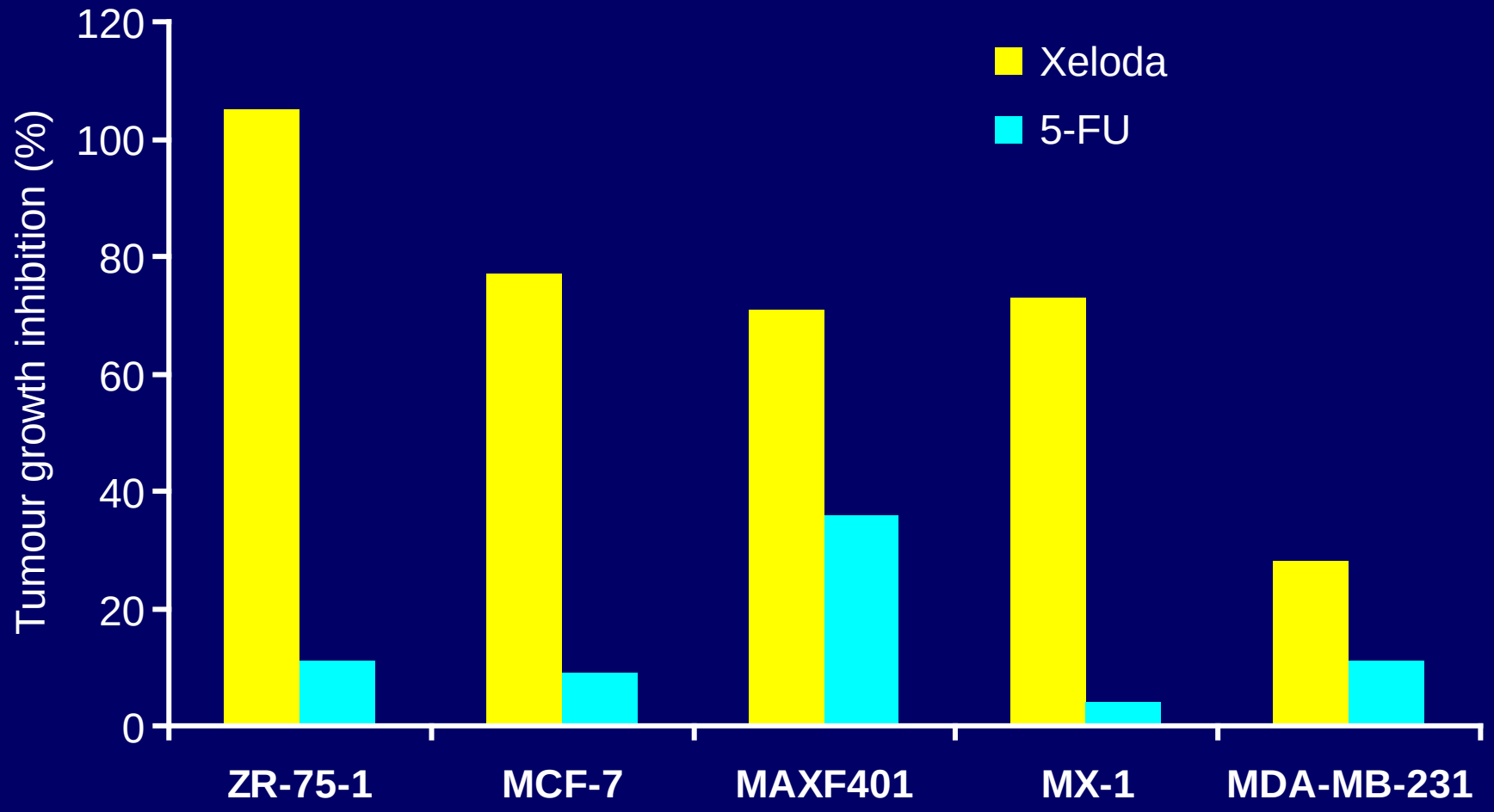
Kovach JS, Beart RW Jr. Invest New Drugs 1989;7:13–25

More 5-FU in the tumour with TP-activated Capecitabine



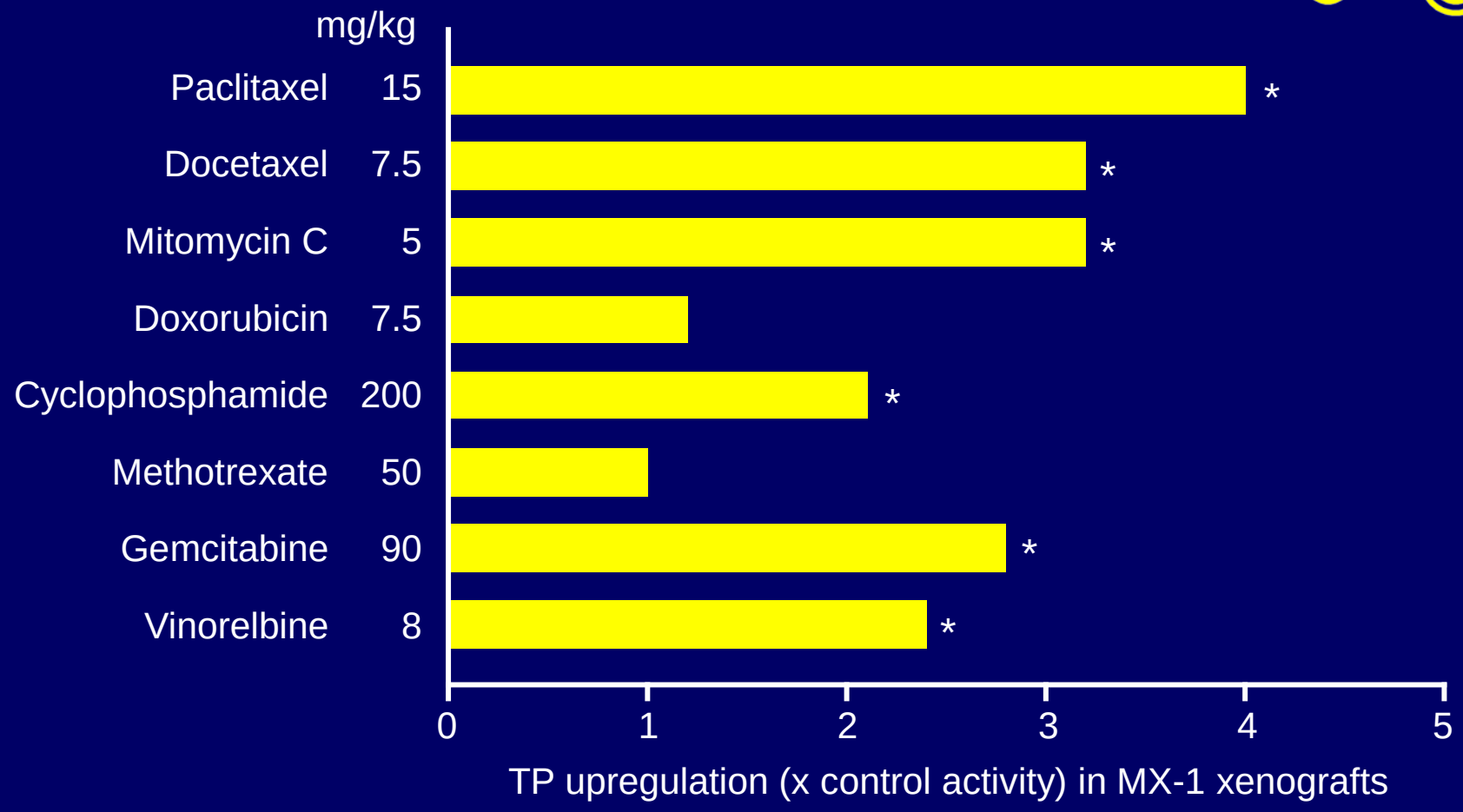
Schüller J et al. Cancer Chemother Pharmacol 2000;45:291–7

Tumour growth inhibition by Xeloda 2–10-fold greater than with 5-FU



Ishikawa T, et al. Cancer Res 1998;58:685–90

Agents that upregulate TP are rational combination partners for Capecitabine

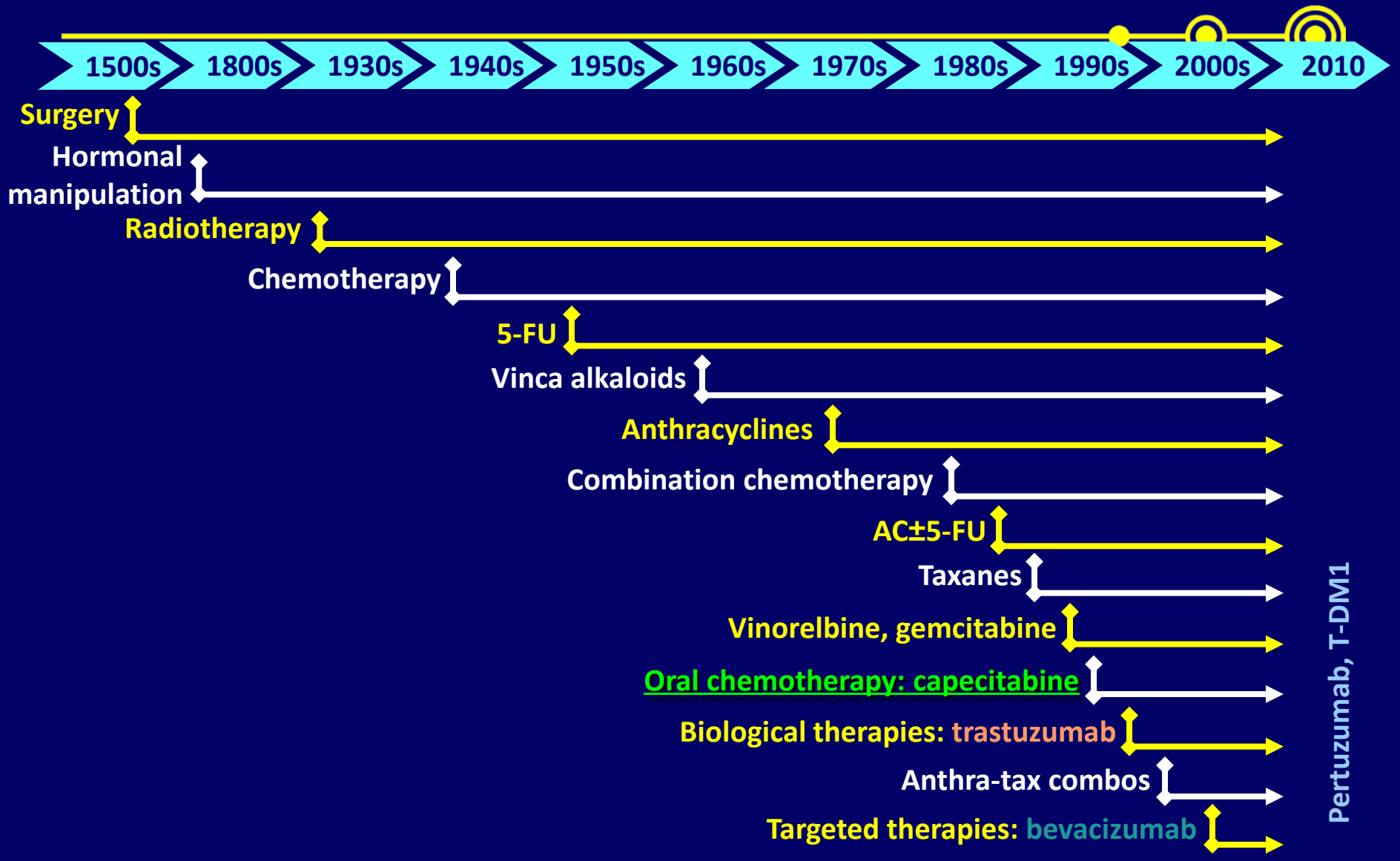


*p<0.05

Endo M, et al. Int J Cancer 1999;83:127–34
Sawada N, et al. Proc Am Assoc Cancer Res 2002 (Abst 5388)

Capecitabine evidences in Breast Cancer

Key milestones in breast cancer treatment



Meta Analysis of Capecitabine in EBC

OPEN ACCESS Freely available online

PLoS one

First Efficacy Results of Capecitabine with Anthracycline- and Taxane-Based Adjuvant Therapy in High-Risk Early Breast Cancer: A Meta-Analysis

Yiwei Jiang[1], Wenjin Yin[2], Liheng Zhou[2], Tingting Yan[1], Qiong Zhou[1], Yueyao Du[1], Zhenzhou Shen[2], Zhimin Shao[2], Jinsong Lu[2]*

1 Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, People's Republic of China, 2 Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China

Total 4,107 breast cancer patients
-2,058 received a taxane–anthracycline–capecitabine-containing regimen
-2049 received a taxane–anthracycline-based regimen

Jiang Y, Yin W, Zhou L, Yan T, Zhou Q, et al. (2012) First Efficacy Results of Capecitabine with Anthracycline- and Taxane-Based Adjuvant Therapy in High-Risk Early Breast Cancer: A Meta-Analysis. PLoS ONE 7(3): e32474. doi:10.1371/journal.pone.0032474

Meta-analysis Result : DFS & OS

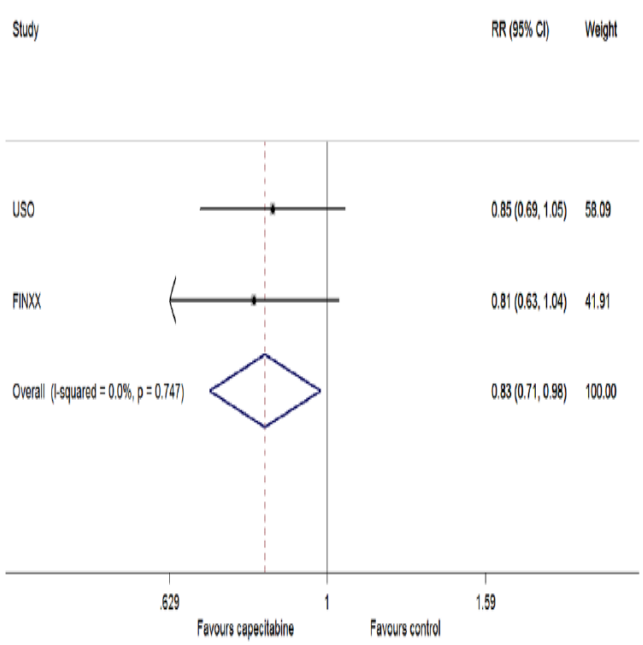


Figure 1. Forest plot of meta-analysis on the disease-free survival for the addition of capecitabine to standard treatment.
doi:10.1371/journal.pone.0032474.g001

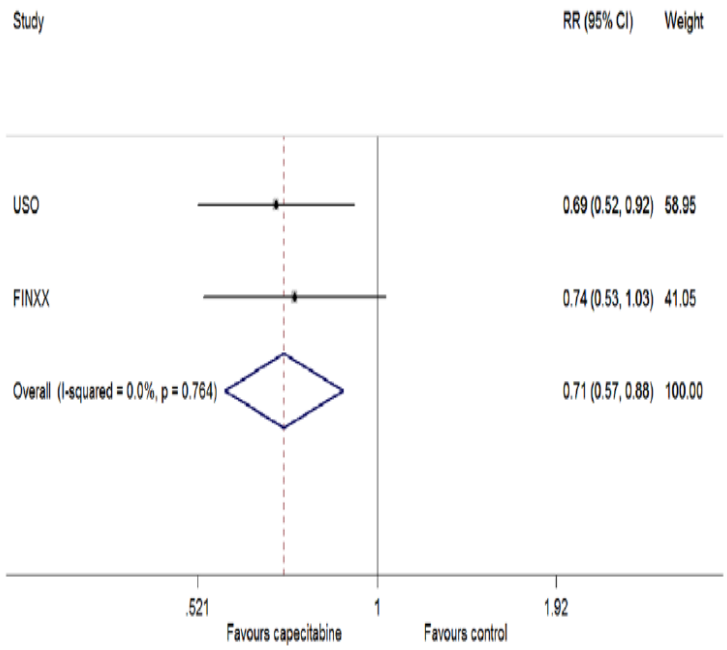


Figure 2. Forest plot of meta-analysis on the overall survival for the addition of capecitabine to standard treatment.
doi:10.1371/journal.pone.0032474.g002

Jiang Y, Yin W, Zhou L, Yan T, Zhou Q, et al. (2012) First Efficacy Results of Capecitabine with Anthracycline- and Taxane-Based Adjuvant Therapy in High-Risk Early Breast Cancer: A Meta-Analysis. PLoS ONE 7(3): e32474. doi:10.1371/journal.pone.0032474

Metastatic Breast Cancer (mBC)

- mBC remains essentially incurable and goals of therapy include:
  - Palliative of symptoms
  - Delay of disease progression
  - Prolonging overall survival
  - While minimizing impact on QOLs
- Treatment should be individuals based on multiple factors including:
  - HER2 and hormone receptor (ER/PgR) status
  - Prior therapy
  - Patients preference
  - Tumor related symptoms

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred Single Agents

Anthracyclines
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other Single Agents
- Cyclophosphamide
- Mitoxantrone
- Cisplatin
- Etoposide (po) (category 2B)
- Vinblastine
- Fluorouracil CI
- Ixabepilone

Preferred Agents With Bevacizumab[2]
- Paclitaxel

Preferred Chemotherapy Combinations
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

Other Combinations
- Ixabepilone + capecitabine (category 2B)

Preferred First-line Agents For HER2-positive Disease
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other First-line Agents For HER2-positive Disease

Trastuzumab with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

Agents For Trastuzumab-exposed HER2-positive Disease
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

Xeloda Monotheraphy for mBC

Breast Cancer Res Treat
DOI 10.1007/s10549-012-2288-x

CLINICAL TRIAL

Pooled analysis of individual patient data from capecitabine monotherapy clinical trials in locally advanced or metastatic breast cancer

Joanne L. Blum · Carlos H. Barrios · Nancy Feldman · Sunil Verma · Edward F. McKenna · Luen F. Lee · Nana Scotto · Julie Gralow

Received: 19 July 2012 / Accepted: 3 October 2012

	1st Line Capecitabine	2nd / 3rd Line Capecitabine	p Value
ORR	25%	19%	
PFS	4.9 months	3.7 months	$p < 0.0001$
OS	21.9 months	13 months	$p < 0.0001$

Blum JL, et al. Breast Cancer Res. Treat 2012 DOI 10.1007

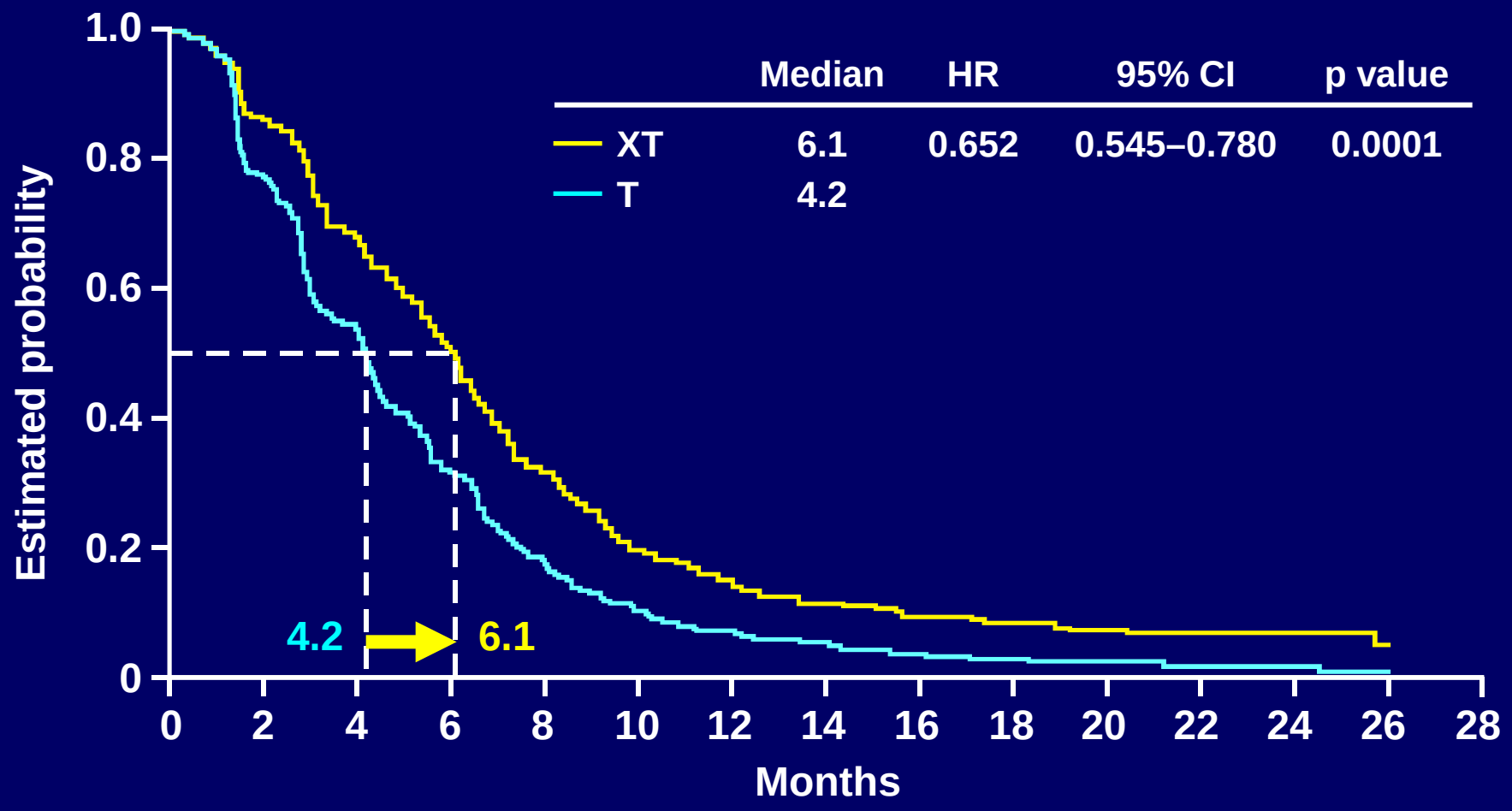
XT (Capecitabine+ Taxane) as first line: superior objective tumour response rate

	XT (n=255) % (95% CI)	T (n=256) % (95% CI)	p value
Confirmed ORR*	42 (36–48)	30 (24–36)	0.006
CR	5 (2–8)	4 (2–7)	
SD	38 (32–44)	44 (38–50)	
PD	11 (7–15)	20 (15–25)	

*WHO response criteria
ORR = overall response rate; CI = confidence interval
CR = complete response; SD = stable disease
PD = progressive disease

O'Shaughnessy J, et al.
J Clin Oncol 2002;20:2812–23

XT: superior TTP

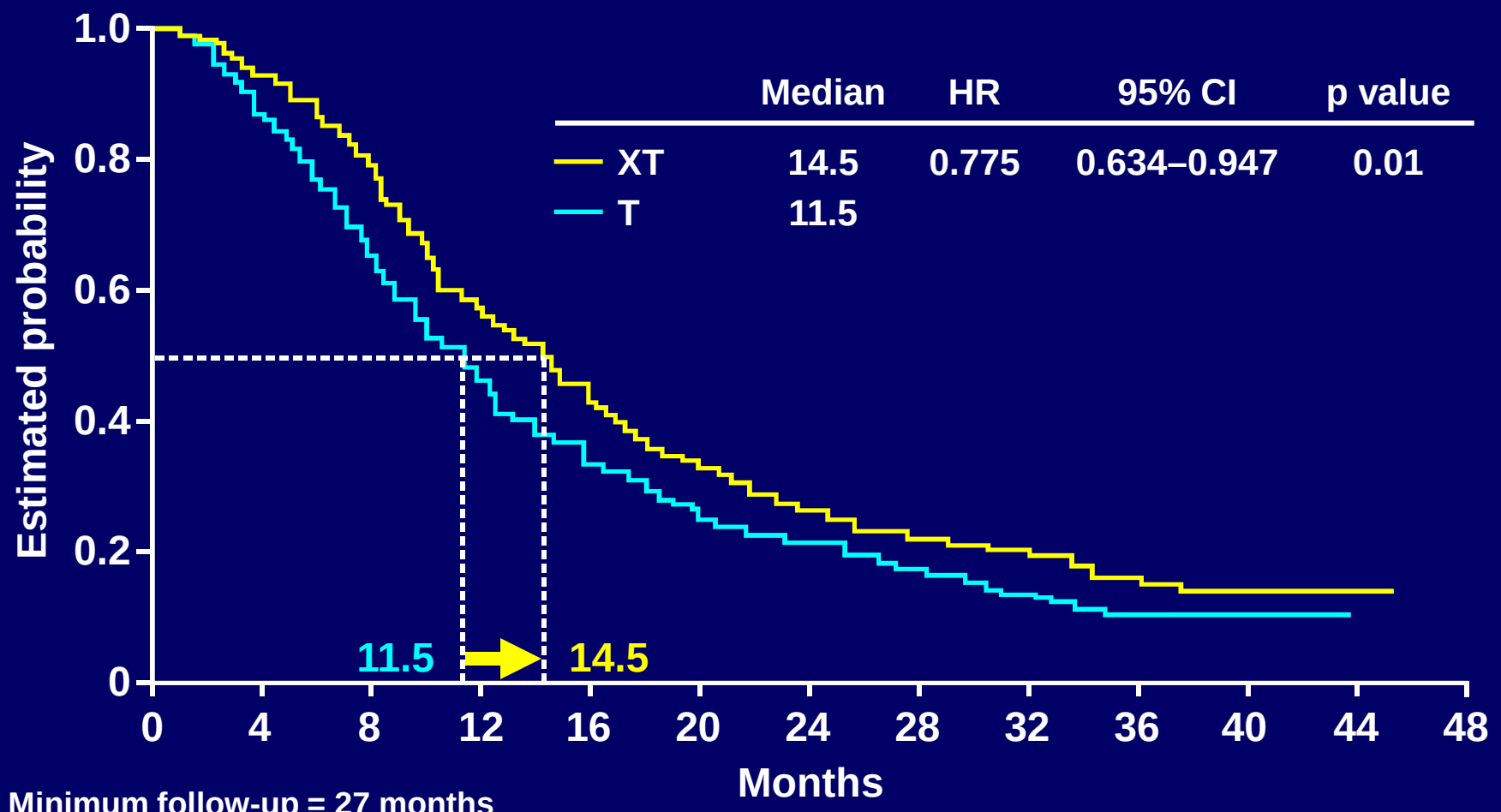


	Median	HR	95% CI	p value
XT	6.1	0.652	0.545–0.780	0.0001
T	4.2			

HR = hazard ratio

O'Shaughnessy J, et al. J Clin Oncol 2002;20:2812–23

XT significantly extends OS

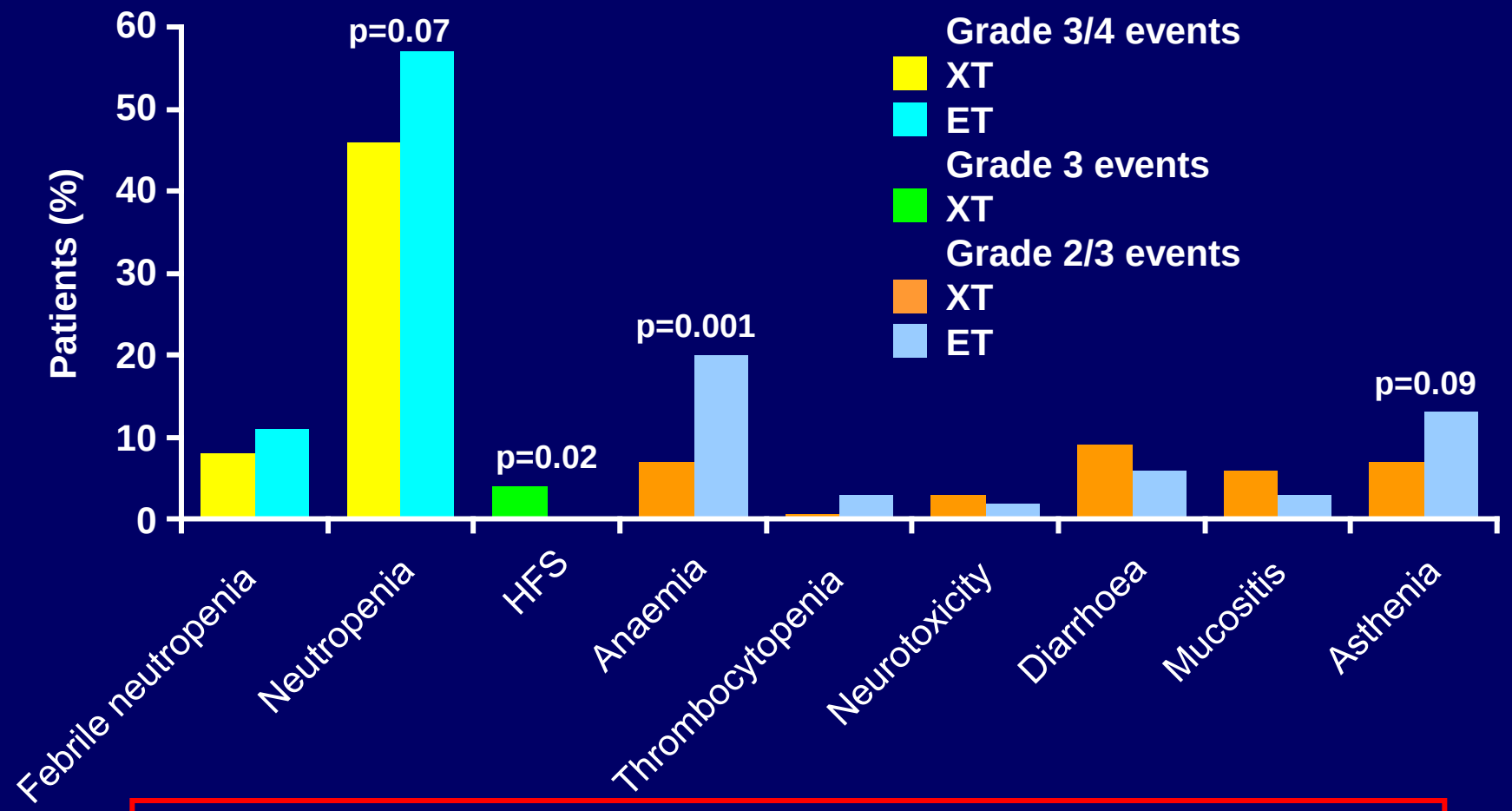


	Median	HR	95% CI	p value
XT	14.5	0.775	0.634–0.947	0.01
T	11.5			

Minimum follow-up = 27 months
Note: extended follow up was not pre-planned
OS = overall survival

Miles D, et al. Clin Breast Cancer 2004;5:273–8

XT vs ET: adverse event profile



- **Adverse event-related hospitalisations: 13% with ET vs 5% with XT (p=0.02)**

Mavroudis D, et al. Ann Oncol 2008;19(Suppl. 8):viii64 (Abst 136O)

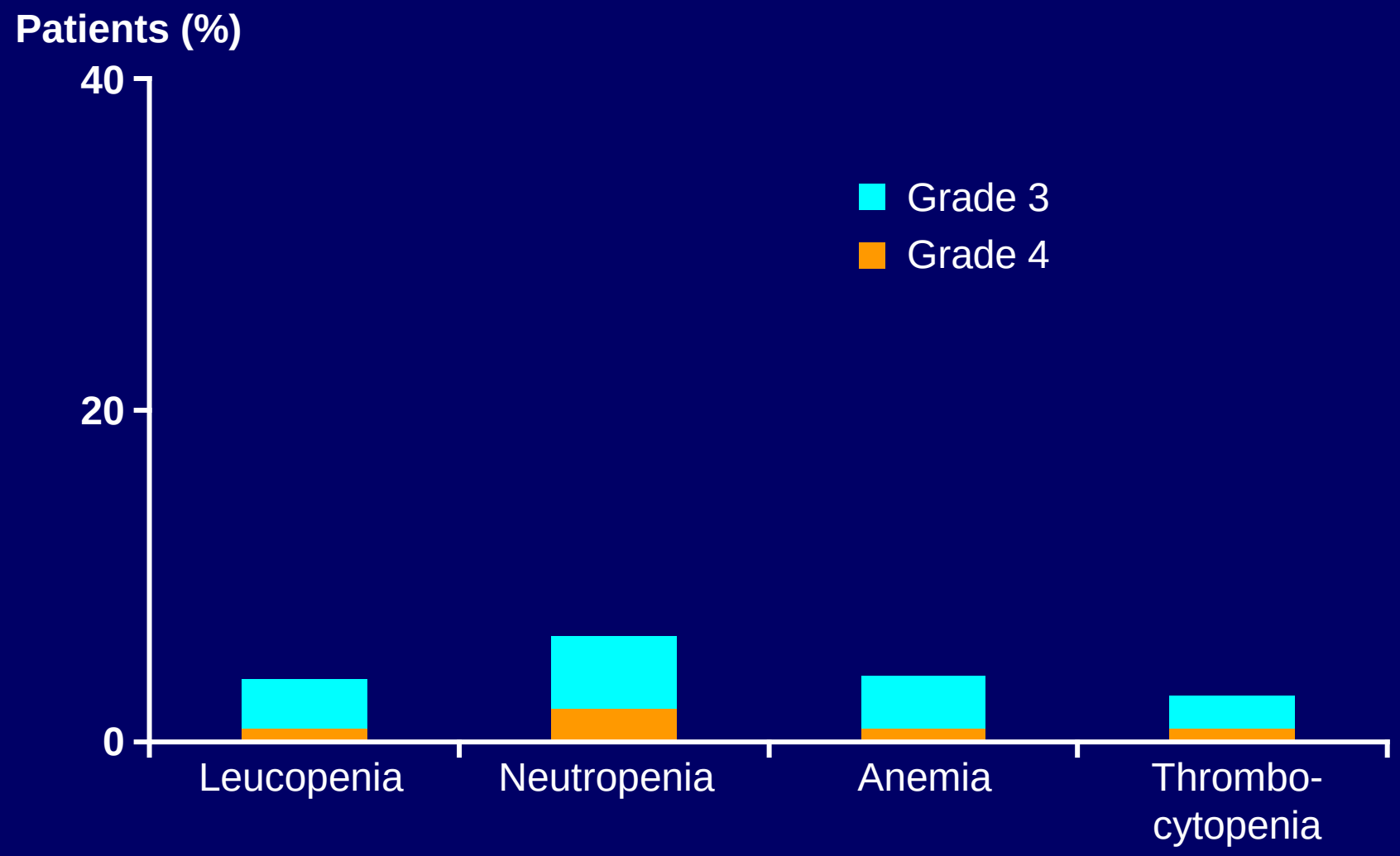
Resiko rambut rontok (alopecia) minimal dengan Xeloda

	Alopecia (%) all grades
Cape[1–4]	0–8
Docetaxel[5,6]	56–91
Paclitaxel[4,7]	26–93
Doxorubicin[6]	91
Epirubicin[8]	59

- Dengan Capecitabine rambut pasien yang awalnya rontok tumbuh kembali[1]

[1]Blum J et al. J Clin Oncol 1999;17:485–93; [2]Reichardt P et al. Ann Oncol 2003;14:1227–33
[3]O'Shaughnessy J et al. Ann Oncol 2001;12:1247–54; [4]Talbot D et al. Br J Cancer 2002;86:1367–72
[5]Mouridsen H et al. Breast Cancer Res Treat 2002;76 (Abst 327)
[6]Chan S et al. J Clin Oncol 1999;17:2341–54; [7]Nabholtz JM et al. J Clin Oncol 1996;14:1858–67
[8]Joensuu H et al. J Clin Oncol 1998;16:3720–30

Capecitabine monotherapy: memberikan efek samping myelosuppression minimal (n=498)*



*Taxane-pretreated patients

Resiko infeksi lebih kecil dengan Capecitabine

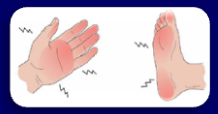
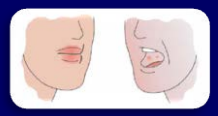
	Infection (%)
Cape[1–6]	0–7
Docetaxel[7]	33
Paclitaxel[7,8]	10–23
Epirubicin[9]	24

*Beberapa study tidak melaporkan kejadian infeksi yang berhubungan dengan terapi[2–4,6]

[1]Blum J et al. J Clin Oncol 1999;17:485–93; [2]Blum J et al. Cancer 2001;92:1759–68
[3]Reichardt P et al. Ann Oncol 2003;14:1227–33; [4]Fumoleau P et al. Eur J Cancer 2004;40:536–42
[5]O'Shaughnessy J et al. Ann Oncol 2001;12:1247–54; [6]Talbot D et al. Br J Cancer 2002;86:1367–72
[7]Jones S et al. Breast Cancer Res Treat 2003;82:S9 (Abst 10)
[8]Nabholtz JM et al. J Clin Oncol 1996;14:1858–67
[9]Joensuu H et al. J Clin Oncol 1998;16:3720–30

Penanganan respon pasien terhadap Xeloda

Interrupting Xeloda

- If moderate (grade 2) or worse non-haematological adverse events occur, Xeloda should be interrupted
  - hand-foot syndrome 
  - diarrhoea 
  - stomatitis 

INTERRUPT

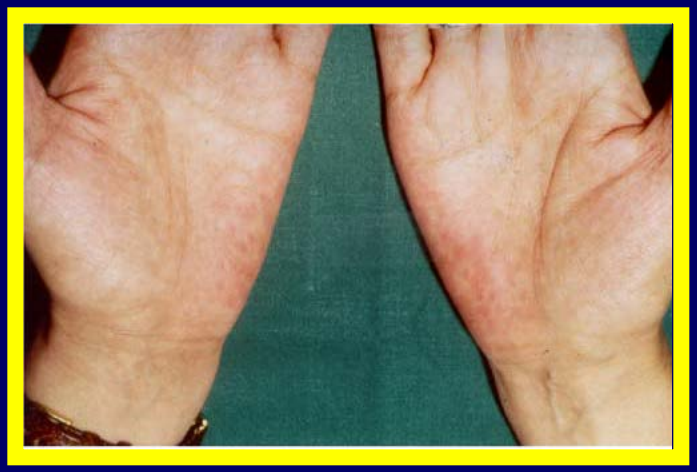
Xeloda

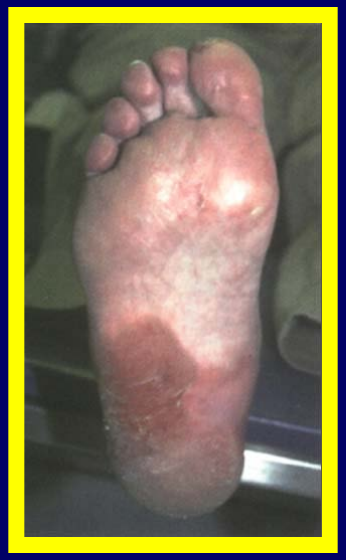
RESUME ON RESOLUTION

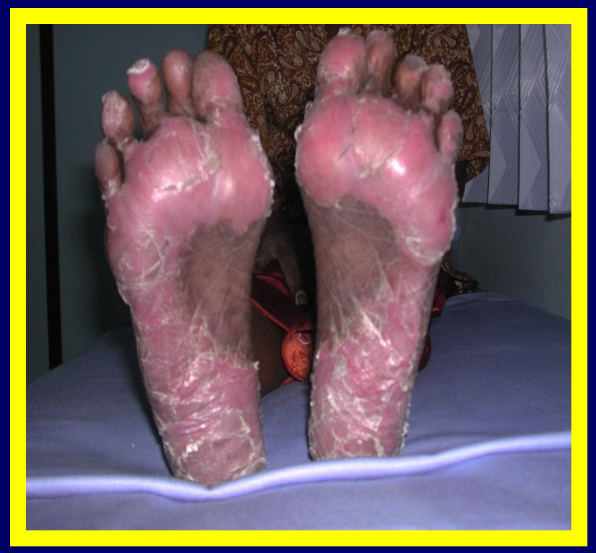
Interrupting Xeloda is not the only action that patients should take!

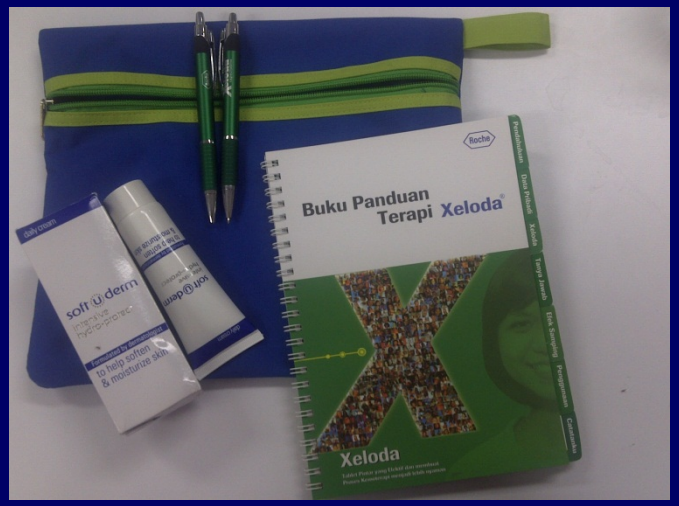
- You should advise patients that if they develop moderate or more severe adverse events, stopping Xeloda is the right action, but not the only action
  - patients <u>must</u> seek further advice from you or their physician!

Hand Foot Syndrome (HFS): reaksi side effect Capecitabine yang khas









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DOSE ADJUSTMENT

Terapi & pencegahan HFS

- Pencegahan
  - Gunakan sabun yang lembut
  - Gunakan krim & lotion pada kaki & tangan (Uredrem, Tupepe, Soft-U-derm)
  - Hindari bau yang merangsang atau produk parfum sebab dapat mengiritasi dan mengeringkan kulit.
  - Berikan pyridoxine (vitamin B6), (3 x 50 mg/hari atau 3 x 100 mg/hari)
  - Berikan Vitamin E 300 mg per hari

- Terapi yang dianjurkan:
  - Terapi dihentikan atau turunkan dosis (paling penting !)
  - Rendam kaki dan tangan dalam air dingin.
  - Hindari temperatur, tekanan yang tinggi & friksi pada kulit.
  - Salep untuk luka
  - Corticosteroid dapat mengurangi inflamasi.
  - berikan Vitamin E 300 mg per hari
  - Gunakan topikal 99% dimethyl-sulfoxide (Uredrem, Putete, Soft-U-derm)
  - NSAID (anti COX-2)

1.Ismail Oguz Kara, et al. j.breast.2005.07.007,
2.*Journal of Clinical Oncology*, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 8105
3.Sarah M Gressett, PharmD1 J Oncol Pharm Practice (2006) 12: 131141

What does dose modification mean?

Dose modification of Xeloda treatment may involve

- **dose interruption**
- **dose reduction**
- **dose interruption and reduction**

Capecitabine-based therapy for Colorectal Cancer and Breast cancer: Rethinking Possibilities

Efficacy

- ✓ Superior than 5-FU in neoadjuv. Rectal Cancer
- ✓ Equivalent to Infusional 5-FU/LV-based therapy

Safety

- ✓ Less:
  - – neutropenia
  - – febrile neutropenia
  - – venous thromboembolism

Flexibility

- ✓ Simplifies combination therapy
- ✓ Less administration time
- ✓ Flexibility to tailor dose adjustments

Cost

- ✓ Reduces resource utilisation
- ✓ More cost-effective than 5-FU/LV

For your kind attention

THANK YOU