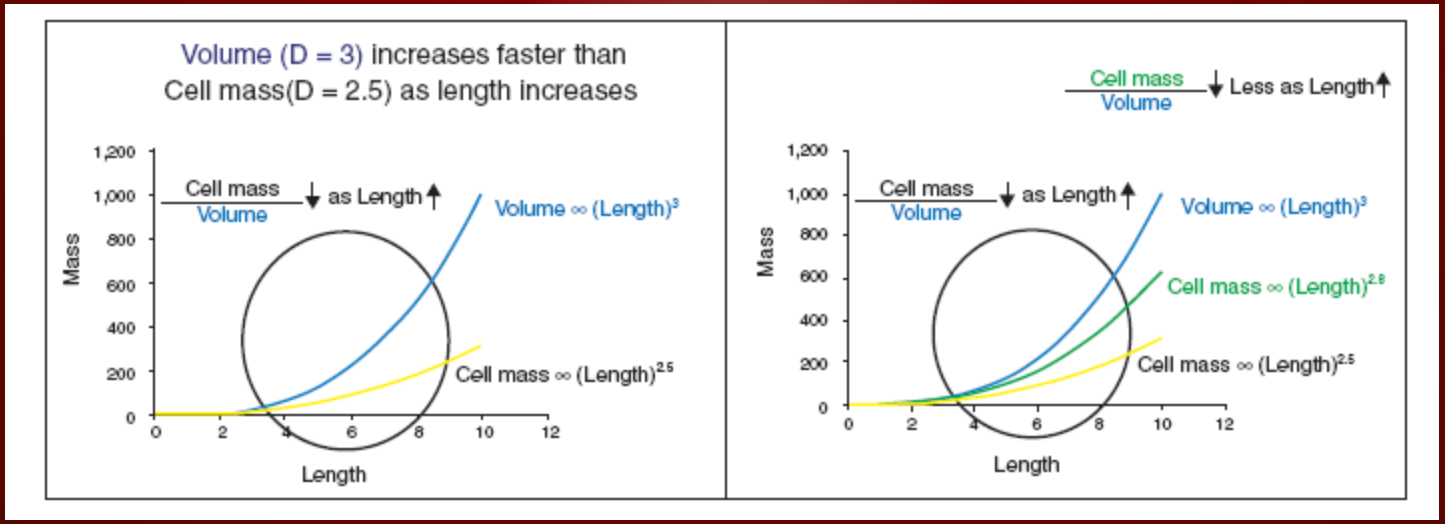
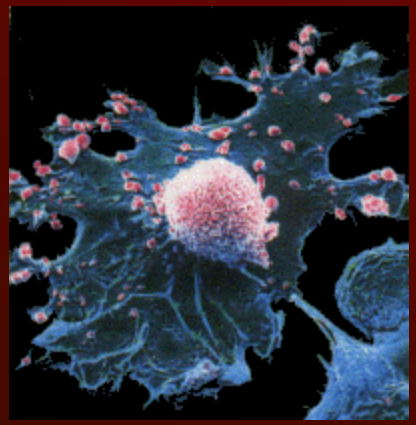
ANTRACICLINE: evoluzione di un farmaco
ROMA, 6 Febbraio 2009 – CAMPUS BIO-MEDICO

SCHEDULE SETTIMANALI CON ANTRACICLINE

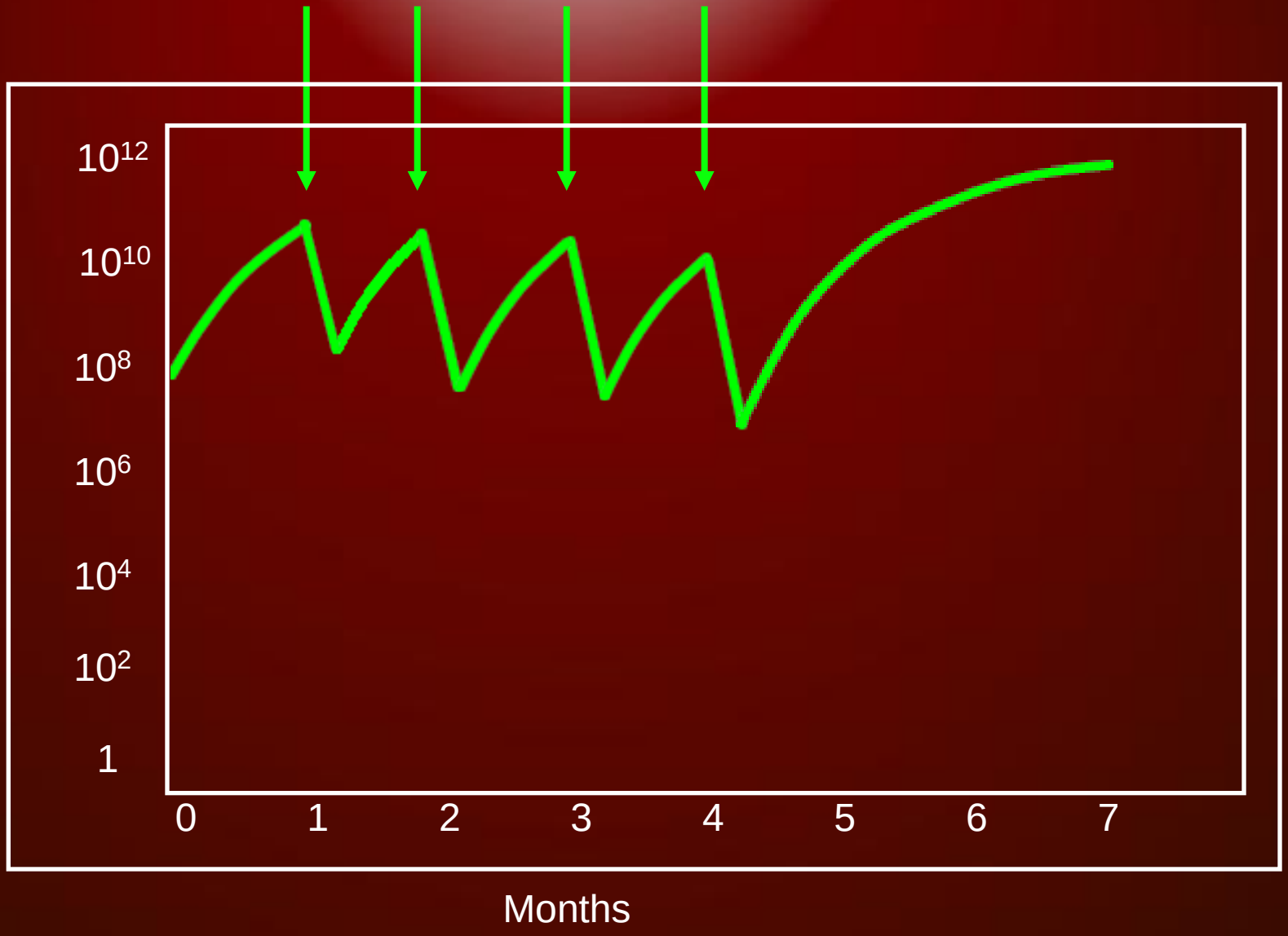
Maria Sofia Rosati

CELL DENSITY AND CANCER VOLUME

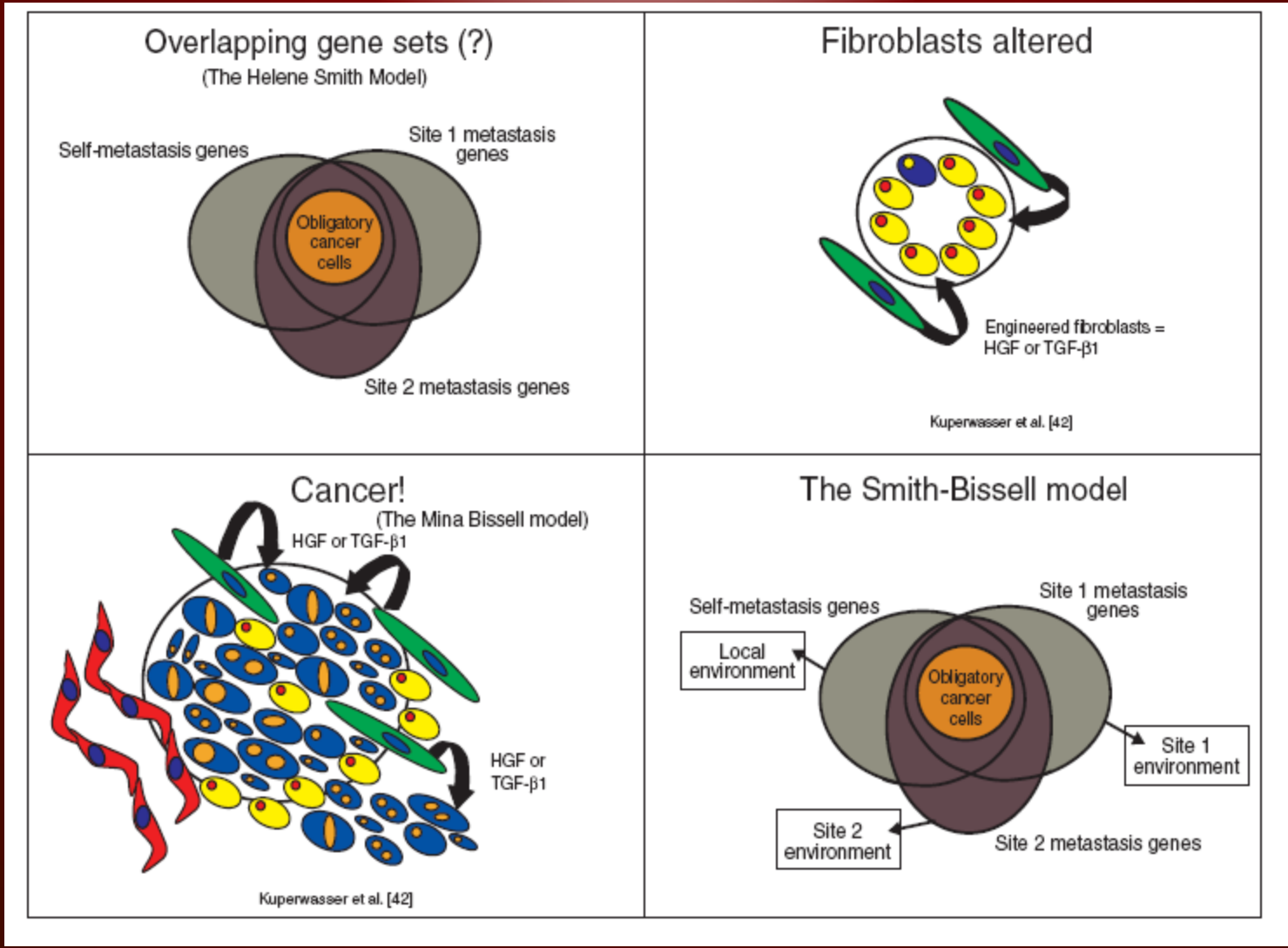




“NORMAL” DOSE INTENSITY



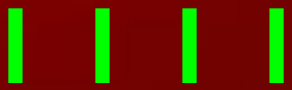
UNDERSTANDING TUMOR DEVELOPMENT: SMITH-BISSELL MODEL



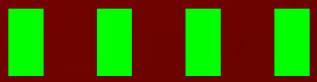
From Norton L.; **Conceptual and Practical Implications of Breast Tissue Geometry: Toward a More Effective, Less Toxic Therapy** Oncologist 2005 10: 370-381;

STRATEGIES TO INCREASE DOSE INTENSITY ABOVE STANDARD LEVELS

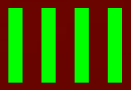
Standard dose intensity



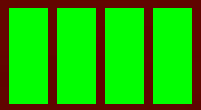
Dose escalation



Dose density

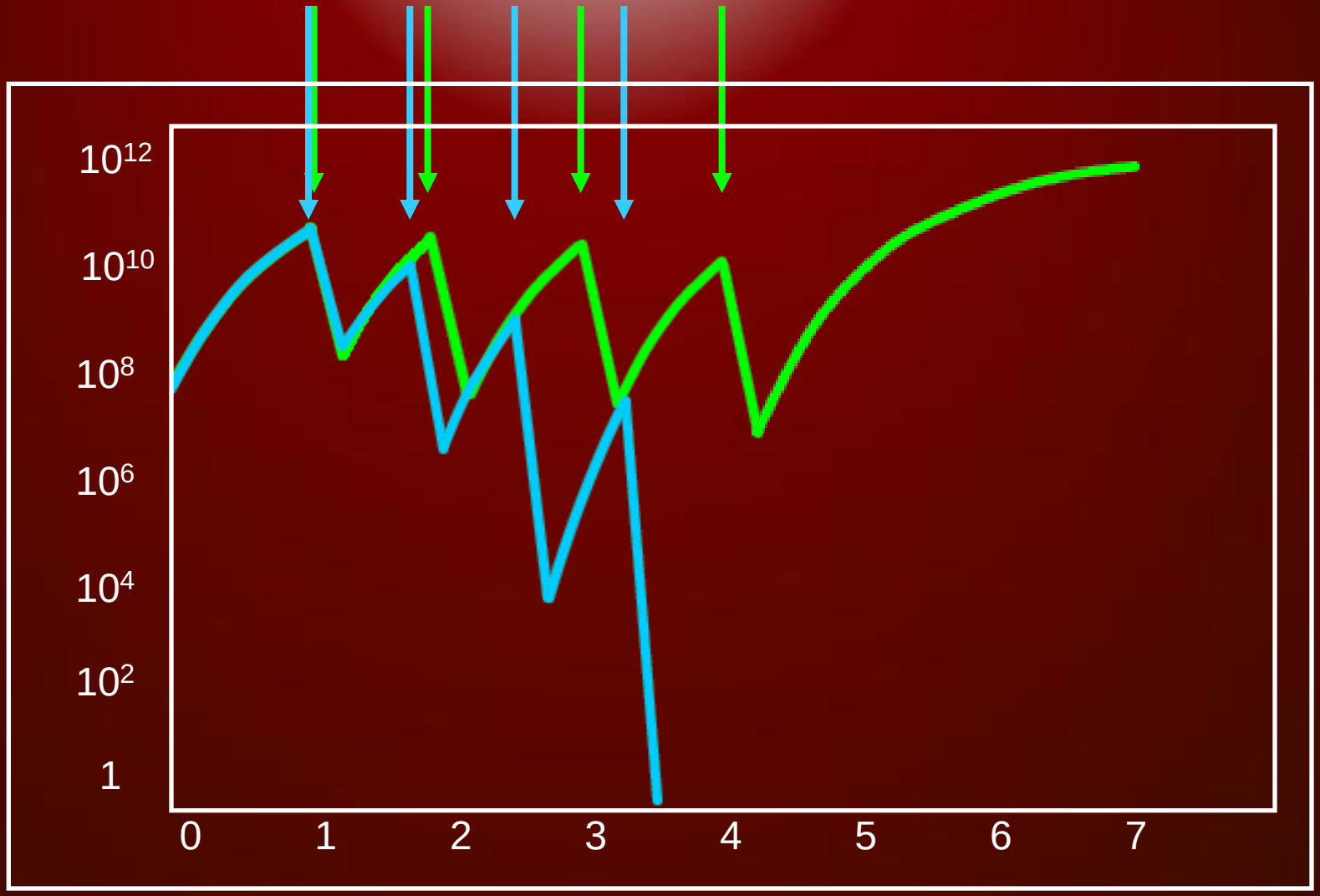


Dose escalated and dose-dense

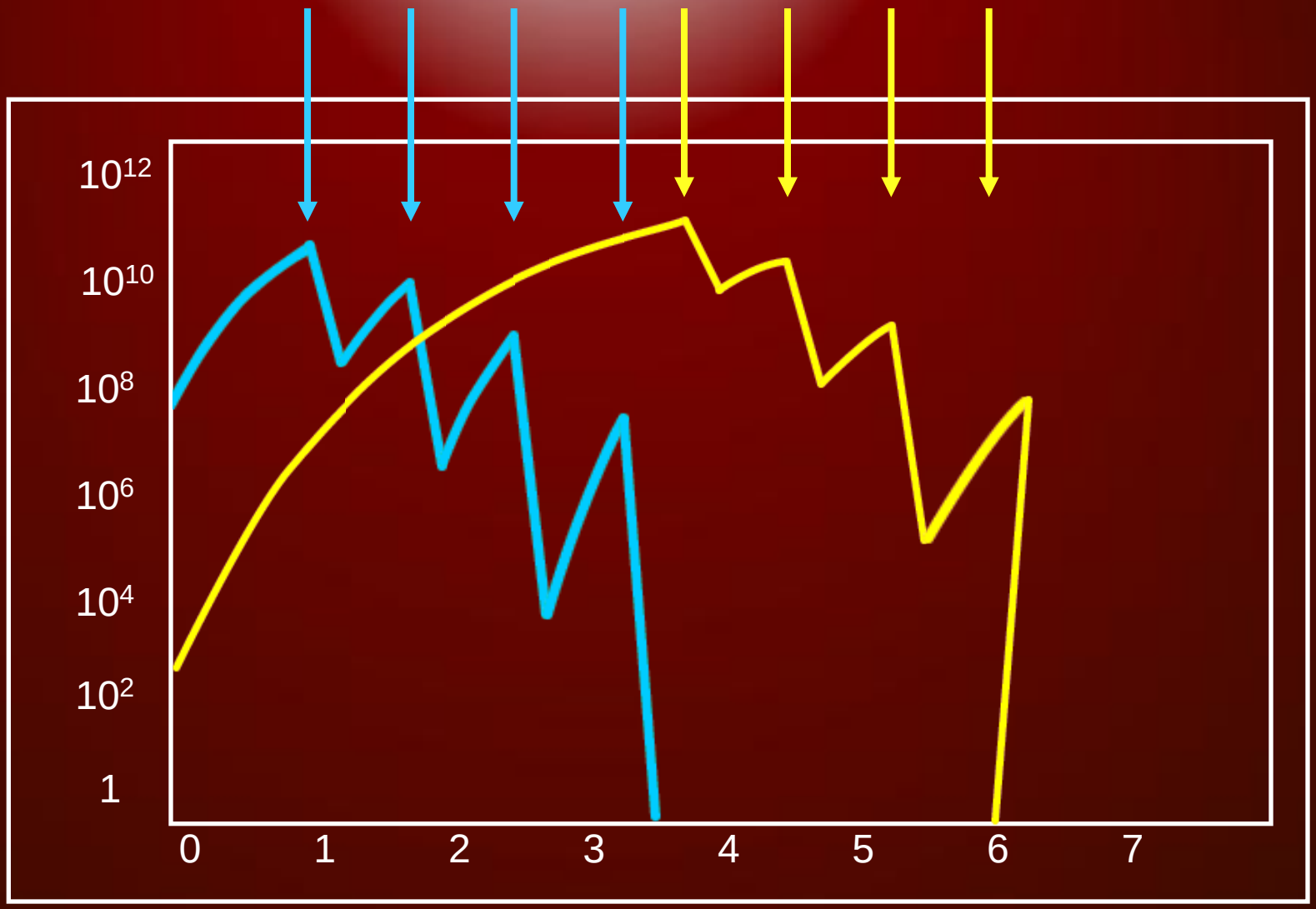


First- and all-cycle use of colony stimulating factors makes it possible to increase dose intensity to levels at which myelosuppression is normally dose-limiting

DOSE DENSE REGIMEN



SEQUENTIAL THERAPY IS DOSE DENSE



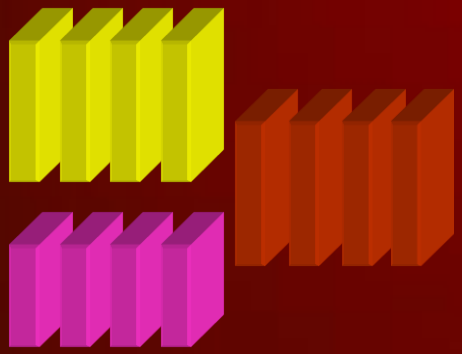
Accelerated SCHEDULES (dose dense)

- Weekly (w)
- Once every 2 weeks (q2w)

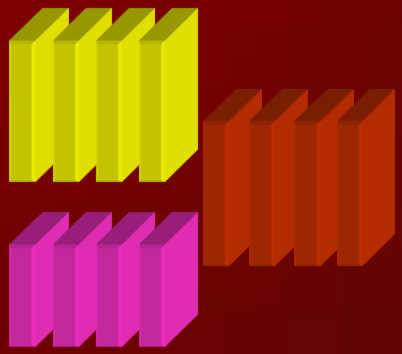
DOSE DENSE REGIMEN: ADJUVANT

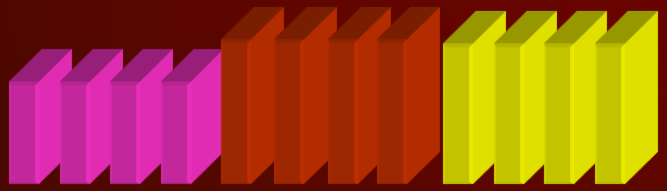
Intergroup/CALGB 9741
Stage II-IIIA N(+) Breast cancer

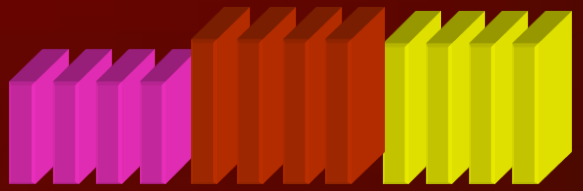
3-Week Cycles



2-Week Cycles (w/ G-CSF)







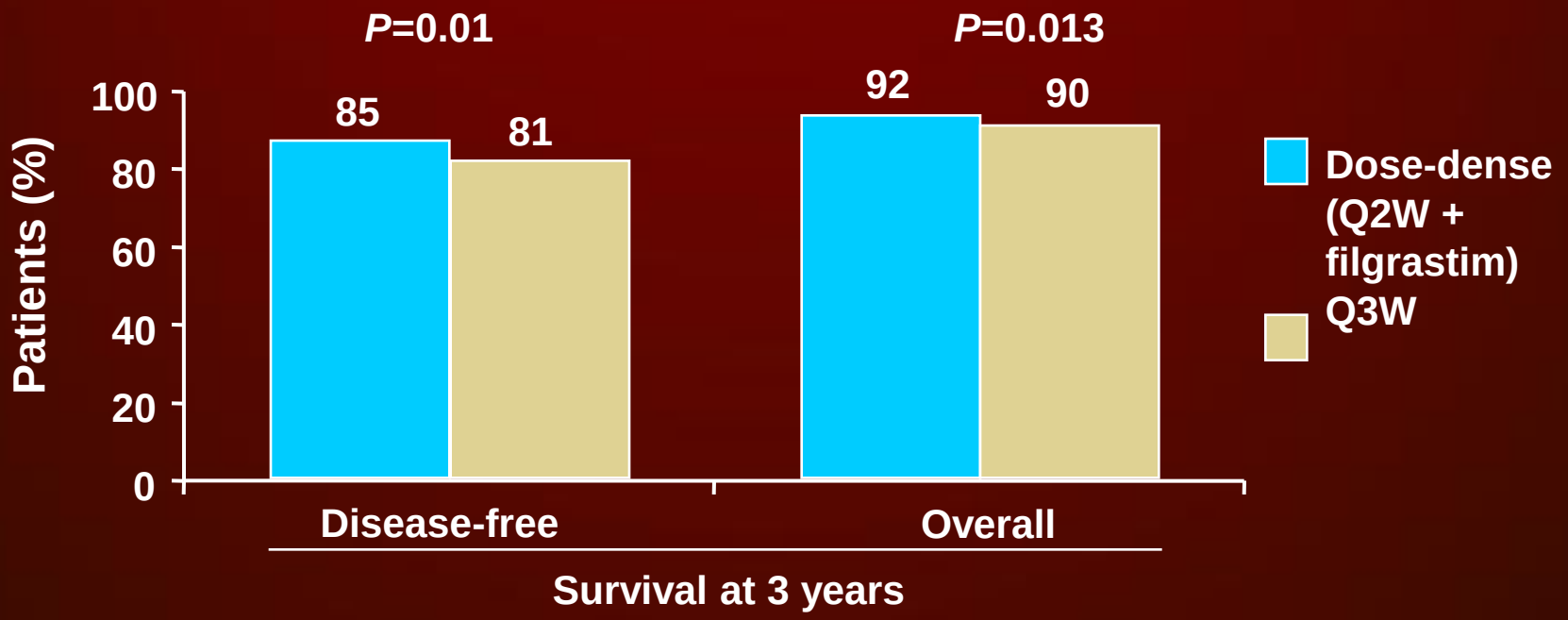
- Doxorubicin (A) 60 mg/m^2
- Paclitaxel (T) 175 mg/m^2
- Cyclophosphamide (C) 600 mg/m^2

Citron ML, J Clin Oncol 2003

DOSE-DENSE Chemotherapy Improves Outcomes in EBC (CALGB 9741)

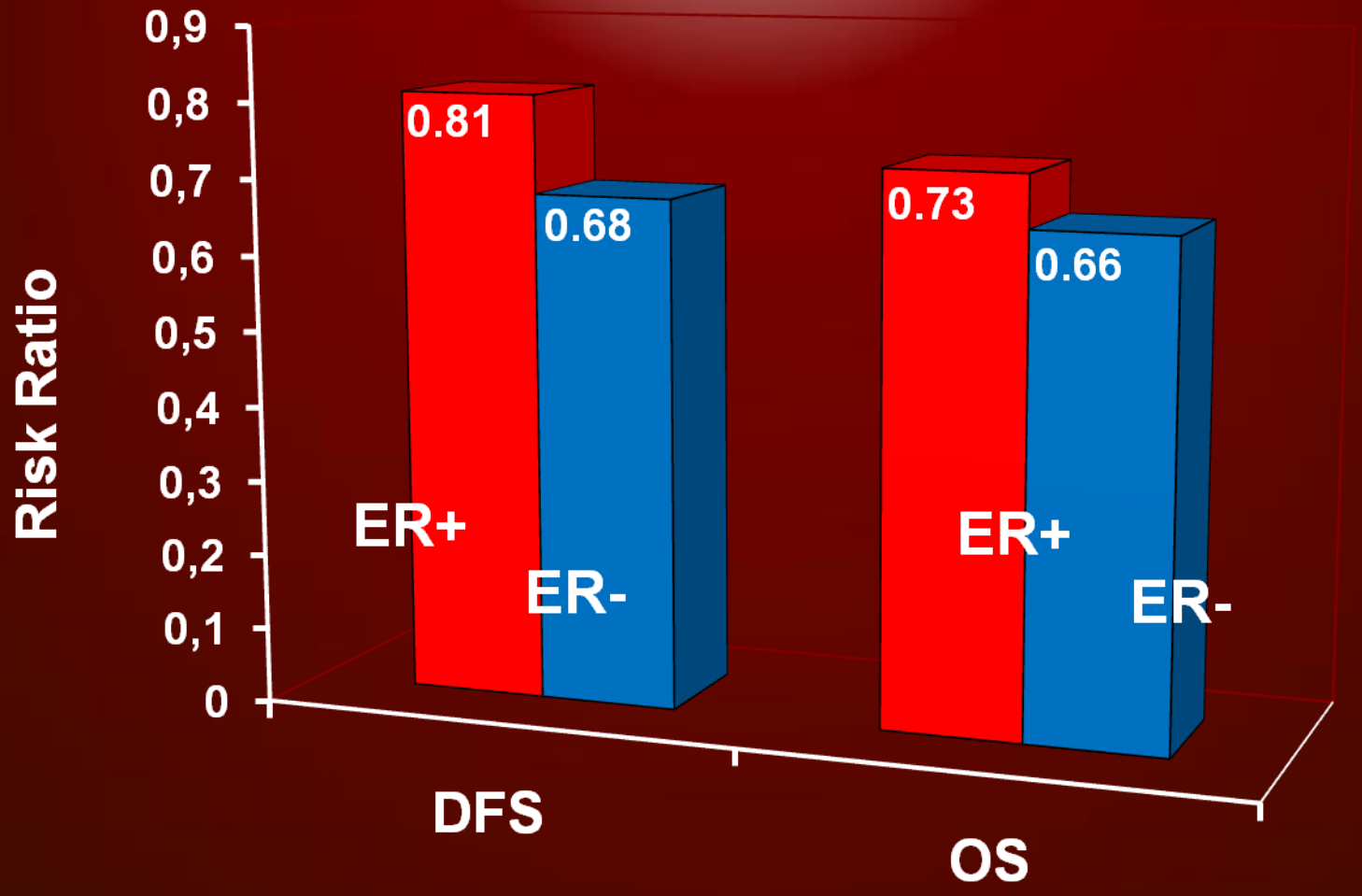
DOSE DENSE TREATMENT:

- DFS (risk ratio [RR]=0.74; *P*=0.010)
- OS (RR=0.69; *P*=0.013)



Citron ML, et al. J Clin Oncol. 2003;21:1431-1439.

CALGB 9741: COX MODEL—RETROSPECTIVE ANALYSIS OF DOSE DENSITY ARM BY ER STATUS



ER = estrogen receptor; DFS = disease-free survival; OS = overall survival

ACCELERATED vs STANDARD FEC REGIMEN (*GONO-MIG1 PROTOCOL)*

FEC_{14} = q2wk (w/G-CSF) for 10 wk

FEC_{21} = q3wk for 15 wk

F = fluorouracil 600 mg/m^2

E = epirubicin 60 mg/m^2

C = cyclophosphamide 600 mg/m^2

Accrued N = 1214

10.4 yr median follow-up

359 events

Venturini M, et al. *J Natl Cancer Inst.* 2005;97:1724-1733.

ACCELERATED vs STANDARD FEC REGIMEN (*GONO-MIG1 PROTOCOL)*

No significant differences in:

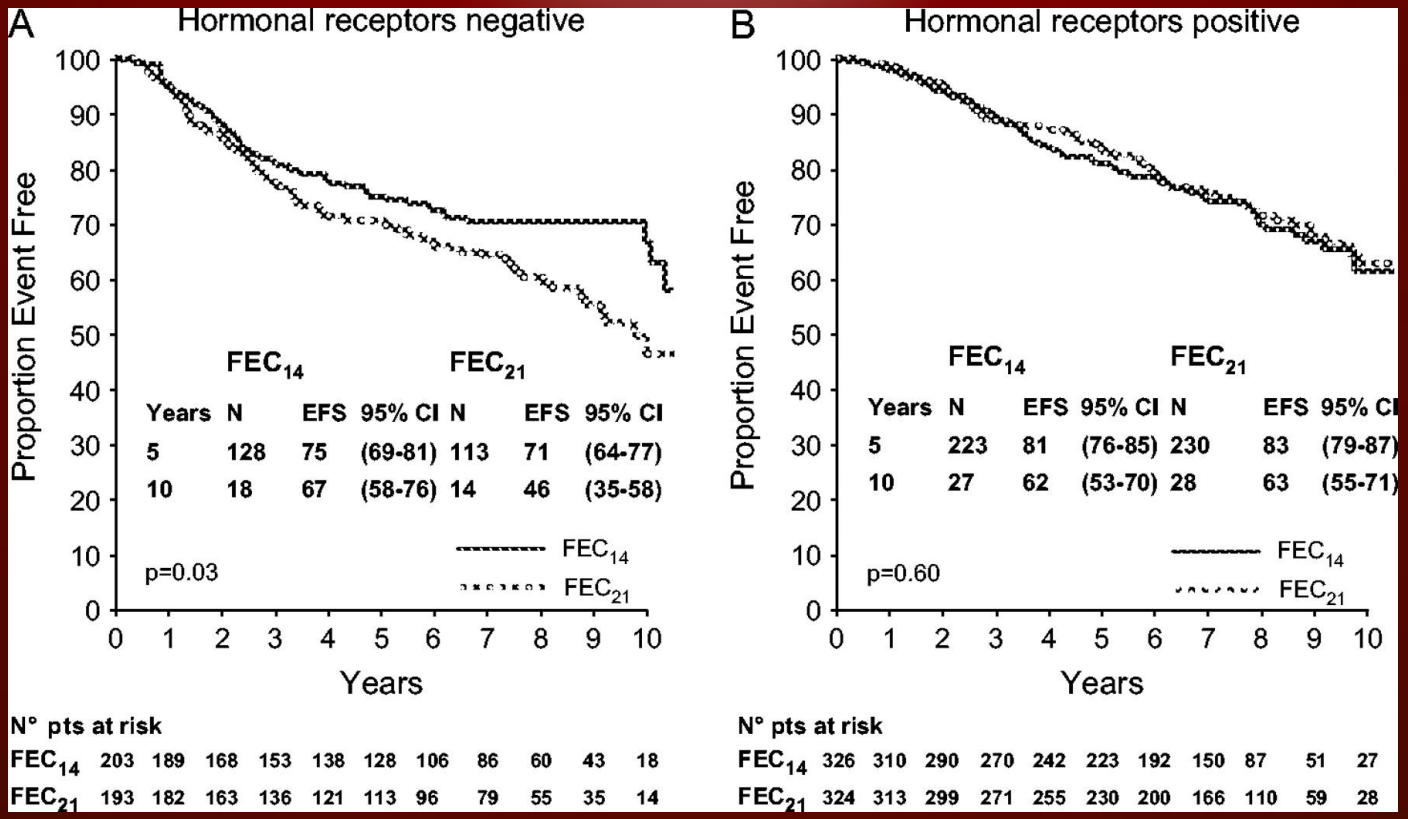
- Event-free survival
  - HR for FEC_{14}/FEC_{21} = 0.88, 95% CI (0.71–1.08) *P* =.219
- Risk of death
  - HR for FEC_{14}/FEC_{21} = 0.87, 95% CI (0.67–1.13) *P* = .293

Toxicity	*FEC_{14}*	*FEC_{21}*
Asthenia	36%	29%
Anemia	38%	19%
Bone pain	33%	4%
Leukopenia	12%	45%

FEC = fluorouracil, epirubicin, cyclophosphamide; HR = hazard ratio.

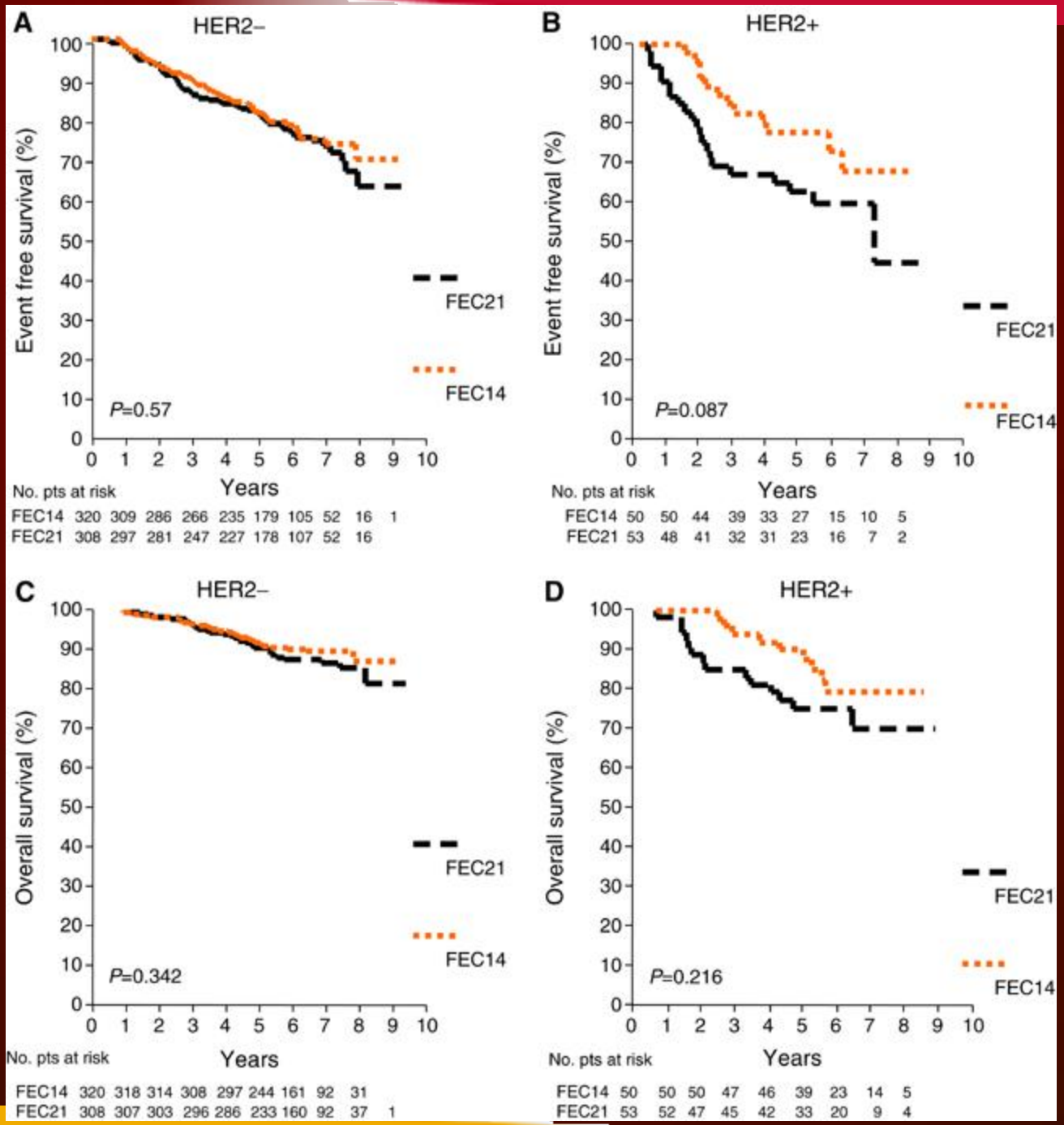
Venturini M, et al. *J Natl Cancer Inst.* 2005;97:1724-1733.

MIG-1: KAPLAN-MEIER CURVES OF EVENT-FREE SURVIVAL BY HORMONE RECEPTOR STATUS



Venturini, M. et al. J. Natl. Cancer Inst. 2005 97:1724-1733

JNCI



Del Mastro et al. Br J Cancer 2005

Weekly anthracycline regimen

Dose-Dense Anthracycline-Based Chemotherapy for Node-Positive Breast Cancer

By Georgiana K. Ellis, Robert B. Livingston, Julie R. Gralow, Stephanie J. Green, and Tove Thompson

Purpose: Theoretical considerations and clinical experience suggest that dose-dense chemotherapy may be superior to other approaches using the same drugs. We studied a dose-dense combination of doxorubicin and cyclophosphamide, with or without fluorouracil, as adjuvant therapy.

Patients and Methods: Patients with resected breast cancer were treated if they were node-positive and estrogen receptor–negative, positive for overexpression of Her-2-*neu*, or had four or more involved nodes. Doxorubicin was given weekly to a total dose of 480 mg/m^2. Cyclophosphamide 60 mg/m^2 was given daily by mouth during the period of doxorubicin treatment. The first 30 patients received fluorouracil at 300 mg/m^2/wk intravenously concurrently with doxorubicin administration. In the last 22, it was omitted because of symptomatic hand-foot syndrome in the majority of patients. Filgrastim (granulocyte colony-stimulating factor [G-CSF]) was administered during chemotherapy every day except the day of intravenous administration and continued until 1 week after the completion of the chemotherapy.

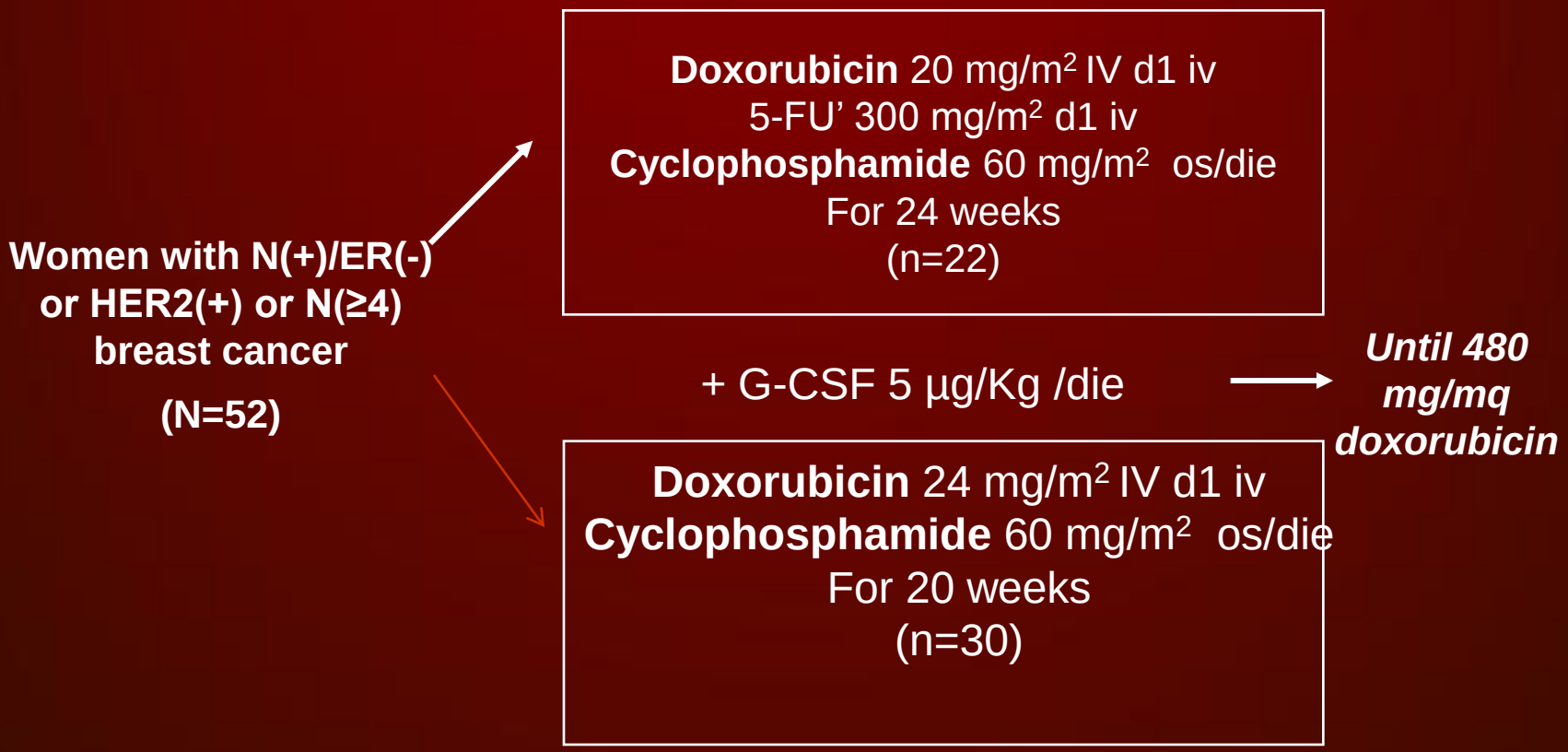
Results: Between October 20, 1992, and June 10, 1997, we enrolled 52 patients. The mean delivered dose-intensity for doxorubicin was 18.6 mg/m^2/wk. Hospitalization was required in 6% of patients for reversible febrile neutropenia. There were no acute treatment-related deaths, but one patient subsequently died of acute leukemia with a characteristic translocation for anthracycline-related exposure. At 5 years, the event-free survival was 86% for all patients (95% confidence interval, 75% to 95%).

Conclusion: Continuous dose-dense chemotherapy with G-CSF support produced encouraging results, which seem to be superior to those expected with "standard" doxorubicin and cyclophosphamide chemotherapy. It deserves a test in the form of a randomized trial where this approach to anthracycline-based treatment is compared with intermittent administration.

J Clin Oncol 20:3637-3643.

Ellis GK, et al. *Journal of Clinical Oncology, Vol 20, No 17 (September 1), 2002: pp 3637-3643*

DOSE-DENSE ANTHRACYCLINE-BASED CHEMOTHERAPY FOR NODE-POSITIVE BC



Ellis GK, et al. *Journal of Clinical Oncology, Vol 20, No 17 (September 1), 2002: pp 3637-3643*

DOSE DENSE REGIMEN: neo-ADJUVANT

SWOG 0012: Standard vs Weekly Doxorubicin + Cyclophosphamide → Paclitaxel

Women with inflammatory or locally advanced breast cancer

(N=372 randomized; 265 evaluable)

Doxorubicin 60 mg/m^2 IV
Cyclophosphamide 600 mg/m^2 IV every 3 weeks for 5 cycles
(n=132)

Stratification by disease type: inflammatory vs locally advanced breast cancer

Doxorubicin 24 mg/m^2 IV weekly
Cyclophosphamide 60 mg/m^2 PO daily
G-CSF 5 μg/kg/day for 6 days/week for 15 weeks
(n=133)

Paclitaxel 80 mg/m^2 weekly for 12 weeks followed by surgery

Ellis GK, et al. ASCO 2006. Abstract 537.

SWOG 0012:
Standard vs Weekly Doxorubicin + Cyclophosphamide → Paclitaxel

Results, %	AC → Paclitaxel	wAC + G-CSF → Paclitaxel
Response rate		
pCR	19	31
pCR + N_0	15	26
Grade 3/4 toxicity		
Hand and foot	0	13
Stomatitis	2	11
Neutropenia	47	16
Febrile neutropenia	1.8	0.6
Nausea/vomiting	11	5

Ellis GK, et al. ASCO 2006. Abstract 537.

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JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Dose-Dense and/or Metronomic Schedules of Specific Chemotherapies Consolidate the Chemosensitivity of Triple-Negative Breast Cancer: A Step Toward Reversing Triple-Negative Paradox

TO THE EDITOR: Liedtke et al[1] report a progression-free survival of 63% in patients with triple-negative breast cancer predominantly

administration doxorubicin and cyclophosphamide, in addition to the denser administration of paclitaxel.[5] Taken together, studies show benefit of accelerated schedules (weekly or once every 2 weeks) of doxorubicin, cyclophosphamide, and paclitaxel. Importantly, comparing across trials, weekly paclitaxel achieves a higher hazard rate reduction than once-every-2-weeks paclitaxel when both accelerated schedules are compared to once-every-3-weeks paclitaxel.[2,4]

Of note, Liedtke et al[1] show that 22% of patients who achieved pathologic complete response had an overall survival of 94%, and 78% of patients who did not achieve a pathologic complete response had a 68% overall survival—a 26% difference. An absolute 50% increment in pathologic complete response over a baseline of 22% would move an additional 50% of patients from 68% to 94% survival (an absolute

Rita S.Mehta, JCO Vol.26, No 19, July1, 2008

DOSE DENSE REGIMEN: METASTATIC BREAST CANCER

Ten years of experience with weekly chemotherapy in metastatic breast cancer patients: multivariate analysis of prognostic factors

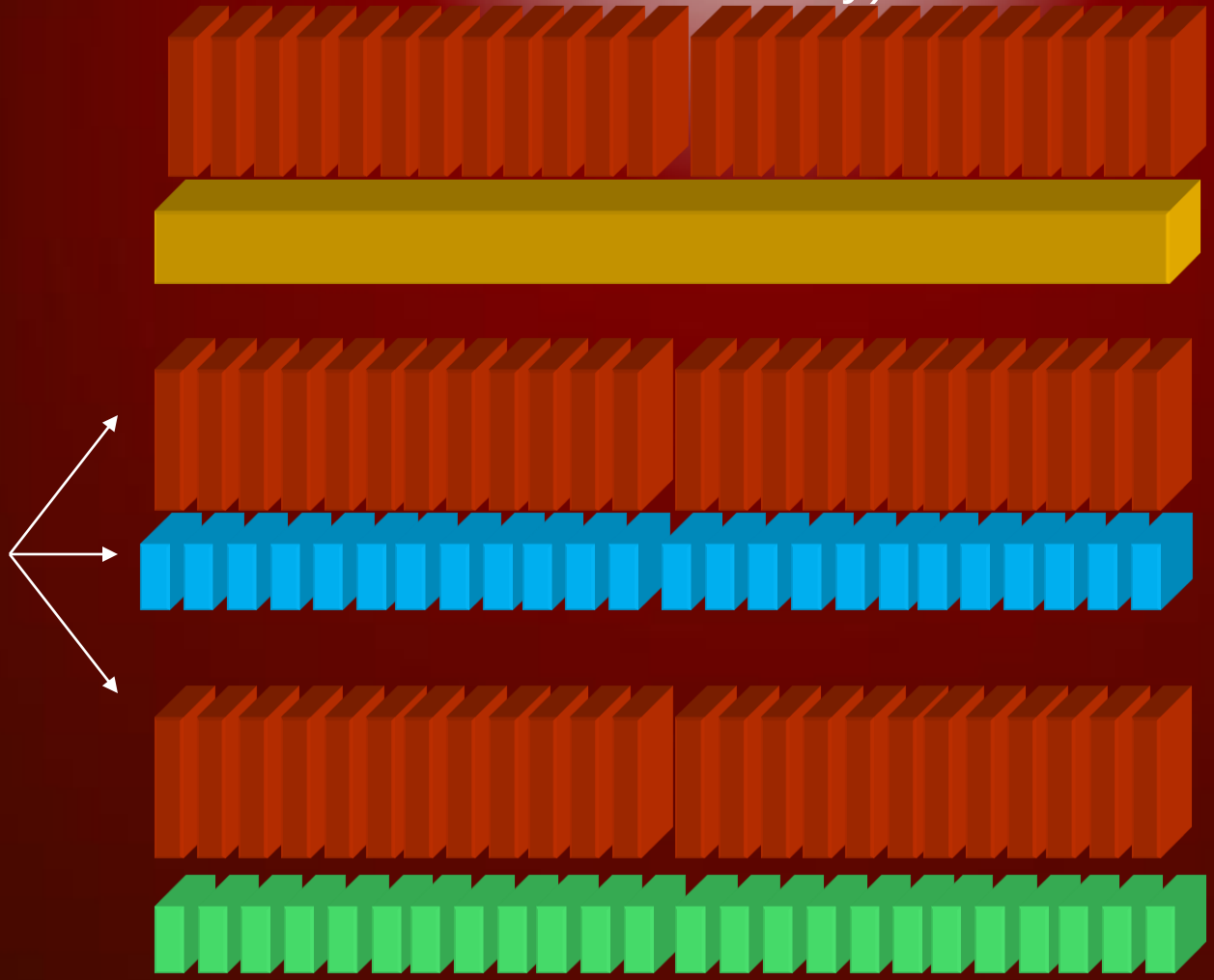
Cecilia Nisticò[a], Federica Cuppone[a], Emilio Bria[a], Monica Fornier[d], Diana Giannarelli[b], Marcella Mottolese[c], Flavia Novelli[c], Guido Natoli[a], Francesco Cognetti[a] and Edmondo Terzoli[a]

Weekly chemotherapy administration represents an emerging option for the treatment of metastatic breast cancer. In order to identify clinical and biological prognostic factors for outcome, we performed a multivariate analysis in a 10-year experience of weekly chemotherapy for metastatic breast cancer patients. The original databases of phase II trials of metastatic breast cancer patients who had undergone first-line weekly chemotherapy were collected. Clinical and biological covariables were screened for a possible relationship with time to progression and overall survival in a Cox model. From 1990 to 2003, 184 patients were enrolled in three consecutive phase II studies, to evaluate activity and tolerability of weekly survival. Although no biological factors were entered into the Cox model owing to the small sample size, some subpopulations showed a negative trend in survival. In our series of patients who had undergone weekly chemotherapy for metastatic breast cancer, independent prognostic factors for survival improvement were responders, performance status 0–1, nonvisceral dominant metastatic site and enrollment period. A greater sample population is needed to extensively screen for biological prognostic factors. *Anti-Cancer Drugs* 17:1193–1200 © 2006 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2006, 17:1193–1200

Weekly CHT in MBC: multivariate analysis (1990-2001, phase II Study)

MULTIVARIATE ANALYSIS



Epirubicin 25 mg/m^2/w
Lonidamine 400 mg os/die

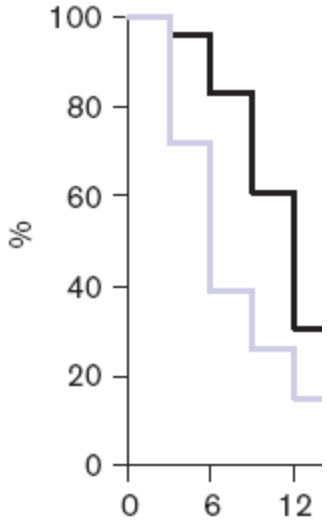
Epirubicin 25 mg/m^2/w
Vinorelbine 25 mg/m^2/w

Epirubicin 25 mg/m^2/w
Paclitaxel 80 mg/m^2/w

C. Nisticò, Anti-Cancer Drugs 2006, 17:1193–1200,

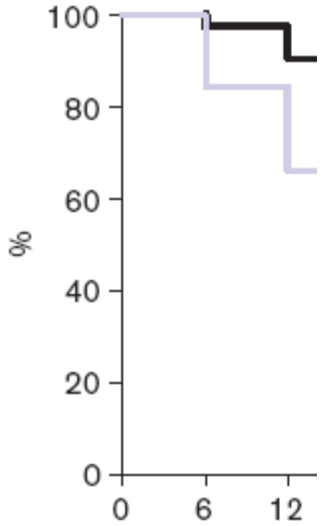
Weekly CHT in MBC: multivariate analysis (1990-2001, phase II Study)

Fig. 1



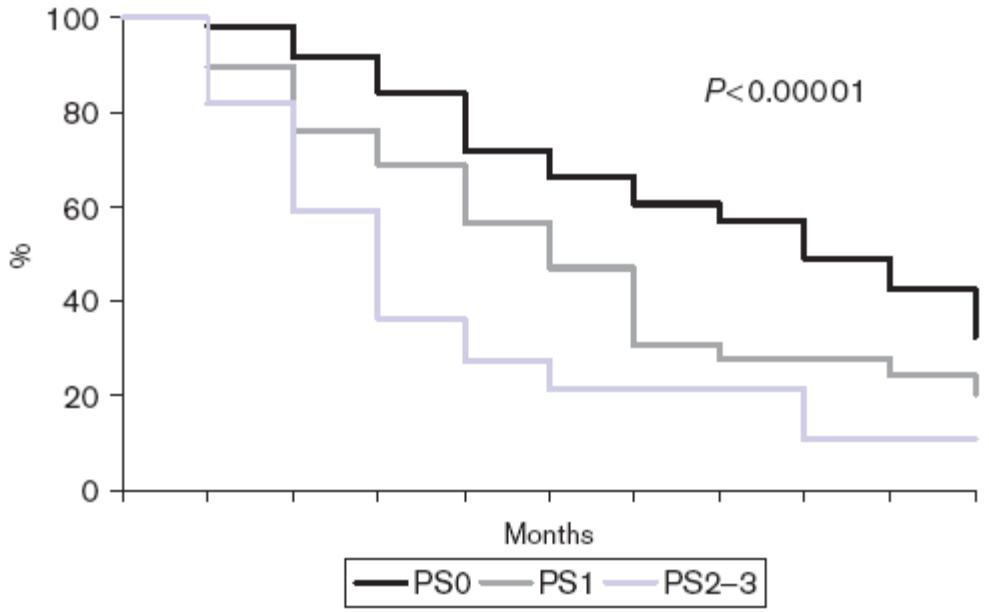
Unadjusted time to prog
responders; NR, nonres

Fig. 2



Unadjusted overall surv
responders; NR, nonres

Fig. 3



Unadjusted overall survival curve Eastern Cooperative Oncology Group performance status (PS).

Weekly CHT in MBC: multivariate analysis (1990-2001, 3 phase II Study)

INDEPENDENT VARIABILES FOR TTP:

- Response
- Hormonal receptor status
- PS

INDEPENDENT VARIABILES FOR OS:

- Response
- PS
- Dominant metastatic site
- Enrollment period

STRATEGIES TO INCREASE DOSE INTENSITY ABOVE STANDARD LEVELS

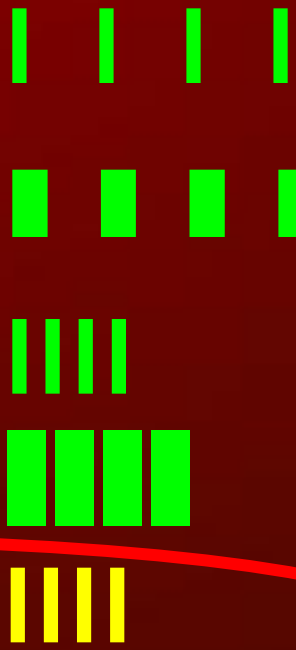
Standard dose intensity

Dose escalation

Dose density

Dose escalated and dose-dense

Use of different formulations



First- and all-cycle use of colony stimulating factors makes it possible to increase dose intensity to levels at which myelosuppression is normally dose-limiting

#Abst1097#

wALT trial (Phase II): Weekly non-pegylated liposomal anthracycline and taxane combination in first-line breast cancer chemotherapy

M. S. Rosati [1], C. Raimondi [1], S. Quadrini [1], R. De Sanctis [1],L. Stumbo [1], B. Gori [1], E. Del Signore [1], **M. Di Seri [1]**

[1]University of Rome "Sapienza", Dpt of ONCOLOGY A, Policlinico "Umberto I"; Rome, ITALY

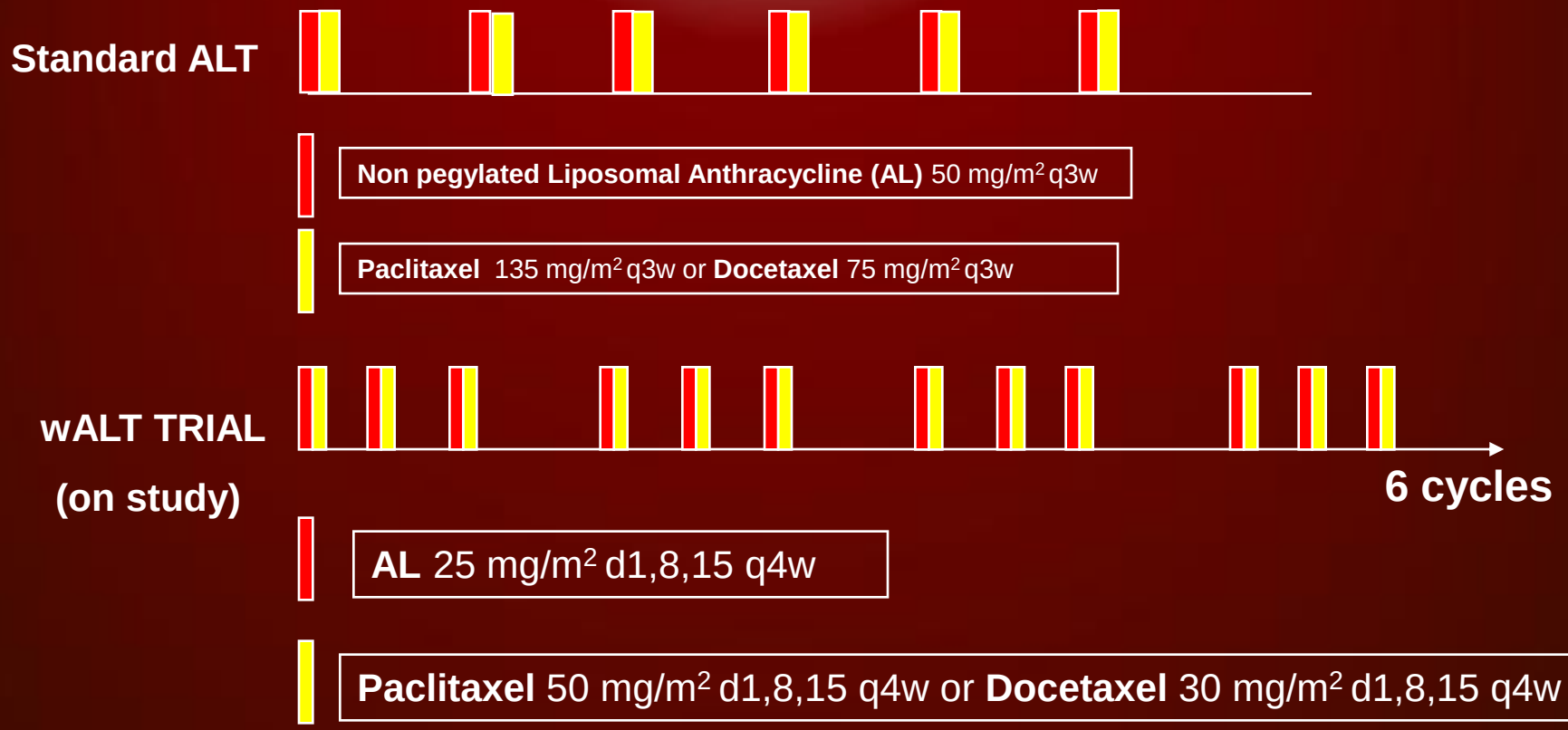
PATIENTS PROFILE (2002-2007)

Patients profile	N (%)
Tot	48
Age	
Median	55.8 years
Range	45-65
(ECOG) PS	
0	31
1	12
2	5
Type of cancer	
Ductal	32
Lobular	7
Mixed	9
Receptor status	
ER(+)	40
PgR(+)	39
HER2(FISH +)	29

Previous CHT	
Anthracycline	48
Taxane	12
Hormonotherapy	40
Adjuvant Trastuzumab	6
Metastases (n°)	
1	16
≥ 2	32
Sites of metastases	
Soft tissue	5
Nodes	10
Liver	29
Lung	4
Brain	2
Bone	34

Rosati MS, ***J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1097)**

STUDY DESIGN (from 2002 to 2007)



Rosati MS, ***J Clin Oncol*** **26: 2008 (May 20 suppl; abstr 1097)**

END-POINTS

- Phase II:
  - Primary end-points:
    - Overall response rate (ORR)
    - Toxicity
  - Secondary end-points:
    - Time to progression (TTP)
    - 2-years overall survival (2y-OS)
    - Paclitaxel arm vs Docetaxel arm RR

Rosati MS, ***J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1097)**

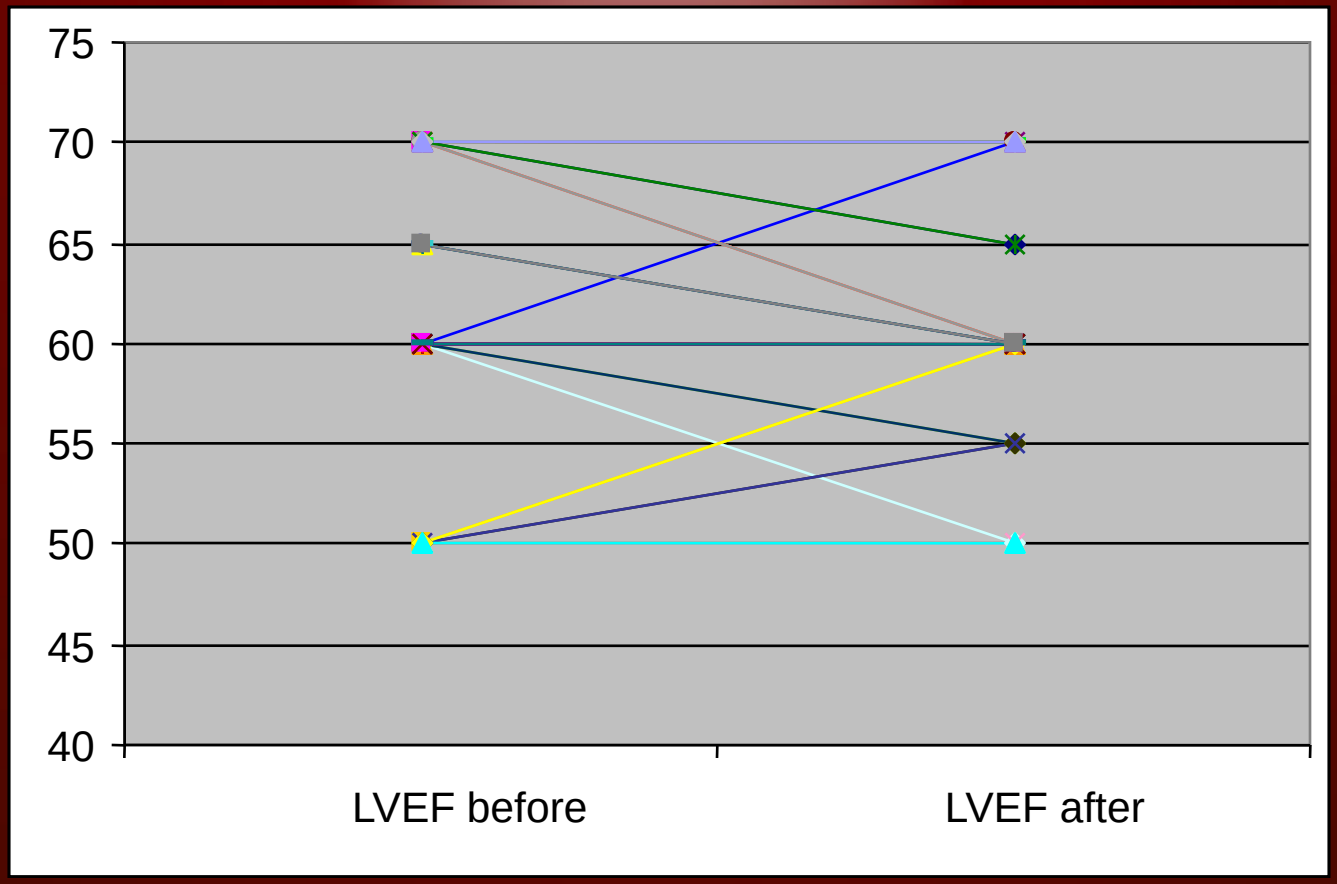
TOXICITY (PHASE II)

	Pts (n=48)		Administration (n=762)	
Grade (WHO)	**1-2 (%)**	**3-4 (%)**	**1-2 (%)**	**3-4 (%)**
Leucopenia	**39 (81.25)**	**36 (75)**	251 (32.93)	169 (22.17)
Neutropenia	**34 (70.80)**	**33 (68.75)**	202 (26.50)	158 (20.73)
Trombocitopenia	7 (14.51)	-	102 (13.38)	60 (7.87)
Anemia	28 (58.33)	24 (50)	154 (20.20)	94 (12.33)

	Pz (n=48)		Administration (n=762)	
Grade (WHO)	**1-2 (%)**	**3-4 (%)**	**1-2 (%)**	**3-4 (%)**
Mucositis	17 (35.41)	10 (20.83)	153 (20.07)	67 (8.7)
Non-neutropenic fever	3 (6.25)	-		
Sensory neuropathy	19 (39.58)	2 (4.16)	114 (14.96)	154 (20.20)
Complete Hair loss	29 (60.41)		-	
Fatigue	27 (56.25)	4 (8.3)	154 (20.20)	42 (5.5)
Nausea/Vomititing	17 (35.41)	-	40 (5.2)	-
Onicholysis	16 (33.33)		-	
Edema	15 (31.25)		-	
Allergic reaction	6 (12.5)		-	

Rosati MS. ***J Clin Oncol*** **26: 2008 (May 20 suppl; abstr 1097)**

CARDIOTOXICITY



Median % of pts who presented LVEF decline: 29.16% (n=13 pz)

LVEF reduction never > 10%, no HFS

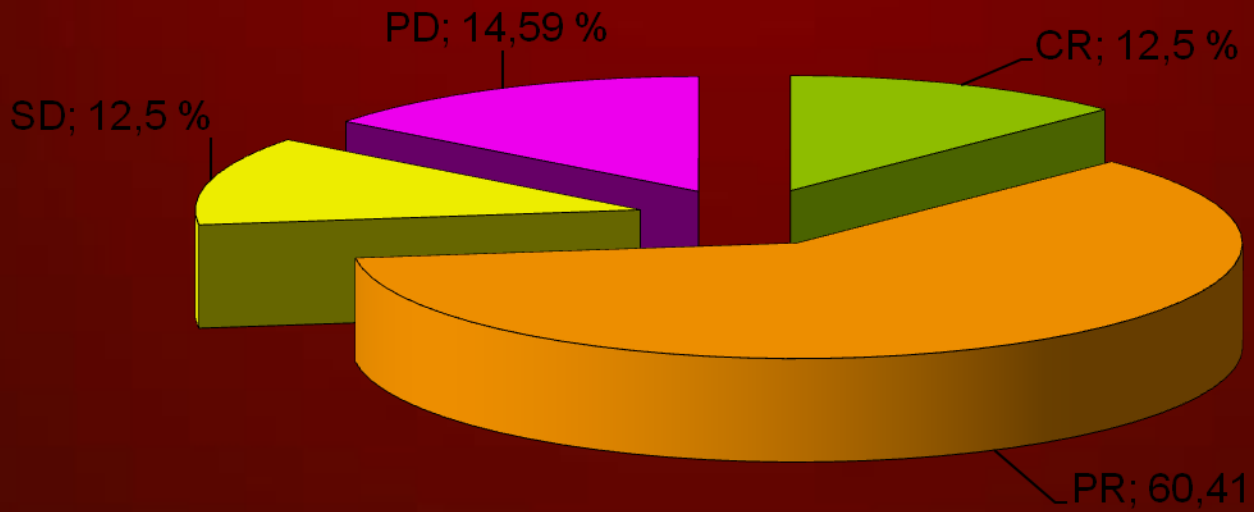
Rosati MS, ***J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1097)**

PHASE II: RESULTS

	Pz (n=48)	Paclitaxel arm (n=28)	Docetaxel arm (n=20)
CR	12.5%	14.2%	10%
PR	60.41%	67.85%	50%
SD	12.5%	3.5%	25%
PD	14.59%	14.2%	15%
Clinical benefit	85.41%	85.71% p=0,04	85% p=0,06
TTP	10.68 months	10.60 months	10.80
OS (2y)	21.60 months	21.71 months	21.45 months

Rosati MS. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1097)

PHASE II: RESULTS



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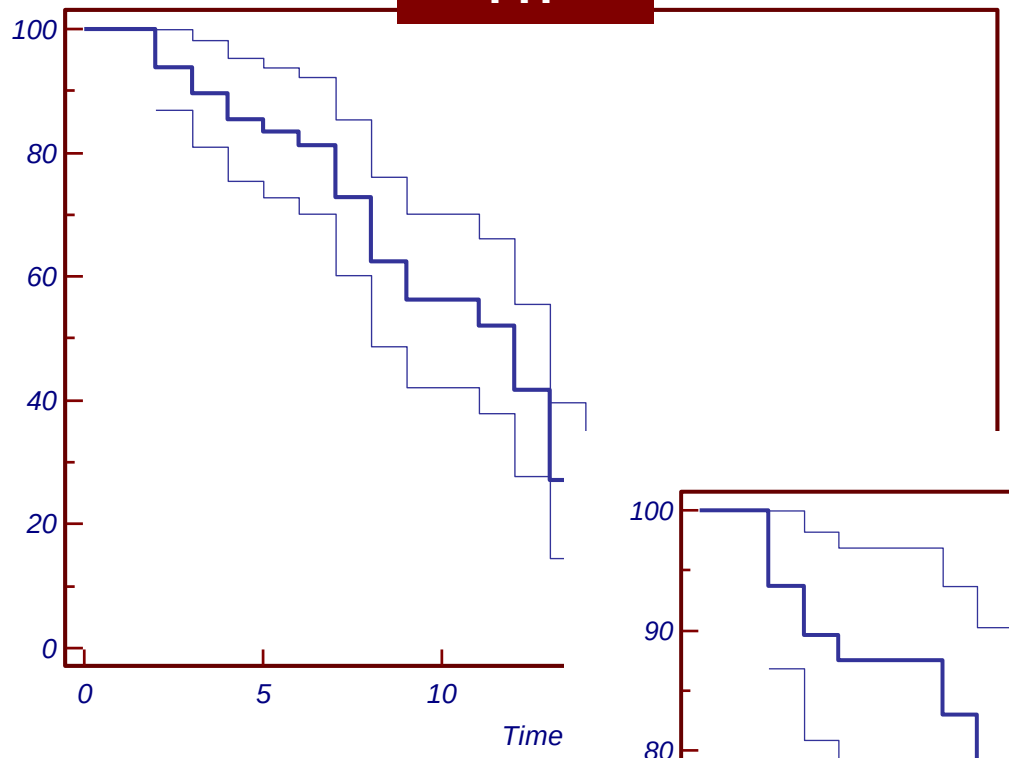
TTP

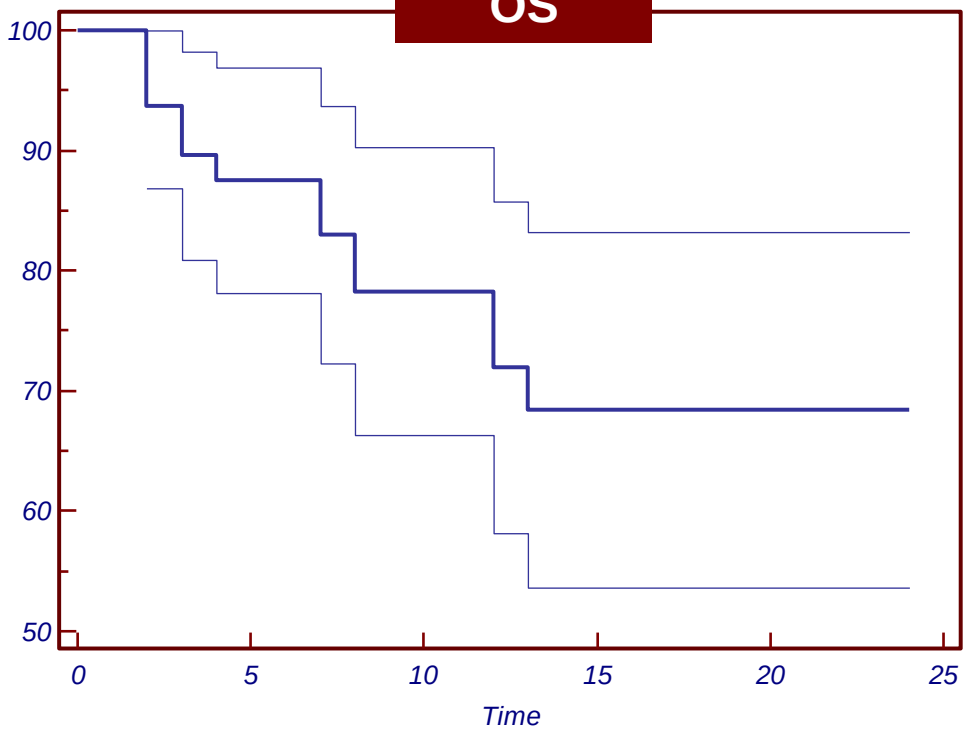


mTTP: 10.68 mesi

mOS (2y): 21.60

OS: 65.6%

OS



Rosati MS, ***J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1097)**

wALT TRIAL: PRO & CONTRA

PRO

- Significative clinical benefit (85,41%)
- TTP: 10.68 months
- Very well tolerated combination treatment

CONTRA

- Not powered to investigate the role of combined Trastuzumab
- Small number of series (48 pts)
- Overexpression of Topoisomerase-2α need to be investigated
- Not powered to investigate the role of continuig treatment after 6 cycles.
- Not powered to investigate differences between HER2(+) and HER2(-)

Rosati MS. ***J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1097)**

CONCLUSIONS

- Accelerated regimen with anthracyclines (weekly, every two weeks – dose dense) is more effective than standard-intervals regimens at least in:
  - ER (-)
  - HER2(+)
  - TRIPLE NEGATIVE
- Use of different formulations like liposome-encapsulated doxorubicin in dose-dense regimen is feasible and needs to be investigated in phase III trial

GRAZIE