

Case #5
Management of
Metastatic Breast Cancer
in the Elderly Patient:
A Unique Therapeutic Challenge

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A Few Comments

- **Adjuvant treatment**
 - **Chemotherapy would have been indicated at diagnosis for this patient**
 - **Three positive nodes**
 - **High grade histology**

Under-Treatment of Breast Cancer in the Elderly

- **Older age is frequently associated with poorer treatment that can lead to shortened survival^{1,2}**
 - **Surgery, radiation and chemotherapy are used less than in younger women**
- **Comorbidities, concomitant medications³ and concerns on survival are suggested limiting factors**
- **There are limited efficacy and safety data in elderly patients**

CALGB 49907

- **Early stage breast cancer, age 65 or older**
 - Randomized to CMF or AC vs capecitabine x 6 cycles
- **Median follow up 2.4 years**
 - 60% between 70-79 years
 - ~70% node positive
- **CMF/AC superior to capecitabine**
 - For RFS: HR 2.09 (p 0.0006), 89 vs 80% alive no BC
 - For OS: HR 1.85 (p 0.019), 7 vs 12% died
- **Overall, treatment was well tolerated**

Which of the following best describes your primary goal of therapy for this 76 year old patient?

- 1. Improve QOL**
- 2. Prolong progression free survival (PFS)**
- 3. Prolong overall survival (OS)**

MBC before systemic treatments

- **Middlesex Hospital: historical data from 250 breast cancers treated between 1805 and 1933**
- **Median overall survival: 2.7 years**
- **44% alive at 3 years**
- **4% alive at 10 years**
- **At 5 years all SBRIII grade patients were dead**



Second consensus on medical treatment of metastatic breast cancer

Annals of Oncology 18: 215–225, 2007

S. Beslija, J. Bonneterre, H. Burstein, V. Cocquyt, M. Gnant, P. Goodwin, V. Heinemann, J. Jassem, W. J. Köstler, M. Krainer, S. Menard, T. Petit, L. Petruzelka, K. Possinger, P. Schmid, E. Stadtmauer, M. Stockler, S. Van Belle, C. Vogel, N. Wilcken, C. Wiltschke, C. C. Zielinski* & H. Zwierzina

- **As anthracyclines and taxanes constitute the most active cytotoxic agents in breast cancer, their use in various schedules as monotherapy and as polychemotherapy is justly widely practiced**
- **It has to be considered, however, that common practice includes anthracyclines in adjuvant chemotherapy protocols and cumulative anthracycline dosage is associated with increased rates of cardiotoxicity**
- **The increasing use of taxanes in adjuvant and neoadjuvant treatment will potentially alter treatment strategies of patients with MBC in the near future**

General Approach to the Treatment of Metastatic Disease

- **Primary goals of therapy**
 - Reduce or eliminate symptoms of disease
 - Improve quality of life
 - Allow patients to live as long as possible with the best quality of life
 - Prolong PFS
 - Prolong OS
- **For a 76 year old woman with hormone resistant metastatic breast cancer, respiratory symptoms and an ECOG PS of 2**
 - My primary goal is to improve quality of life and reduce cancer related symptoms

Which of the following systemic therapy options would you choose for this patient?

1. Third line endocrine therapy
2. Weekly taxane
3. Pegylated liposomal doxorubicin (Caelyx®)
4. Capecitabine (Xeloda®)
5. Vinorelbine (Navelbine®)
6. Gemcitabine (Gemzar®)
7. Combination Chemotherapy
8. Clinical trial of sunitinib (Sutent®) vs capecitabine (SUN 1107)

Treatment Issues

- **Disease specifics**
 - **Visceral disease in lung**
 - Symptomatic
 - **NOT clearly hormone sensitive**
 - Metastatic diagnosis after relatively short duration adjuvant hormone therapy
 - No evidence of response to tamoxifen

NCCN Preferred Chemotherapy Regimens for Metastatic Breast Cancer v.2.2008

Preferred Single Agents	Preferred Combinations ¹	Other Active Options
Doxorubicin	CAF / FAC	Cisplatin/Carboplatin
Epirubicin	FEC	Etoposide (po)
Pegylated liposomal doxorubicin	AC/EC	Vinblastine
Paclitaxel	AT	Fluorouracil (CI)
Docetaxel	CMF	Ixabepilone
Capecitabine	XT	Ixabepilone and capecitabine
Vinorelbine	GT	
Gemcitabine	Paclitaxel/bevacizumab	
Albumin-bound paclitaxel		

1. There is no compelling evidence that combination regimens are superior to sequential single agents

Choice of Therapy

- **Considerations**
 - **Rapidity of response**
 - **Tolerability/side effects**
 - **Performance status, other general factors**
 - **Patient preferences – oral or IV, hair loss, etc**
- **Sequential single agent vs combination therapy?**
 - **Combinations with chemotherapy or targeted agents?**

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TAX 311: Paclitaxel vs Docetaxel in Metastatic Breast Cancer

Docetaxel 100 mg/m² vs paclitaxel 175 mg/m² every 3 weeks as first-line therapy for MBC

Endpoint	Docetaxel	Paclitaxel	P value
ORR	32%	25%	0.10
TTP	5.7mo	3.6mo	<0.0001
OS	15.4 mo	12.7 mo	0.03
Toxicity			
Febrile Neutropenia	15%	2%	<0.05

CALGB 9840

- Weekly vs every 3 week paclitaxel as first-line therapy for MBC
- **Response rate**
 - 40 vs 28%, $p=0.017$
- **TTP**
 - 9 vs 5 mo., $p=0.0008$
- **Overall survival**
 - 24 vs 16 mo., NS
- **Toxicity**
 - More peripheral sensory neuropathy with weekly schedule
 - More marrow suppression with every 3 week schedule

Anglo-Celtic IV: Weekly vs Q 3 Week Paclitaxel for MBC

RANDOMIZATION

Paclitaxel 175 mg/m² Q3 week
x 6 cycles

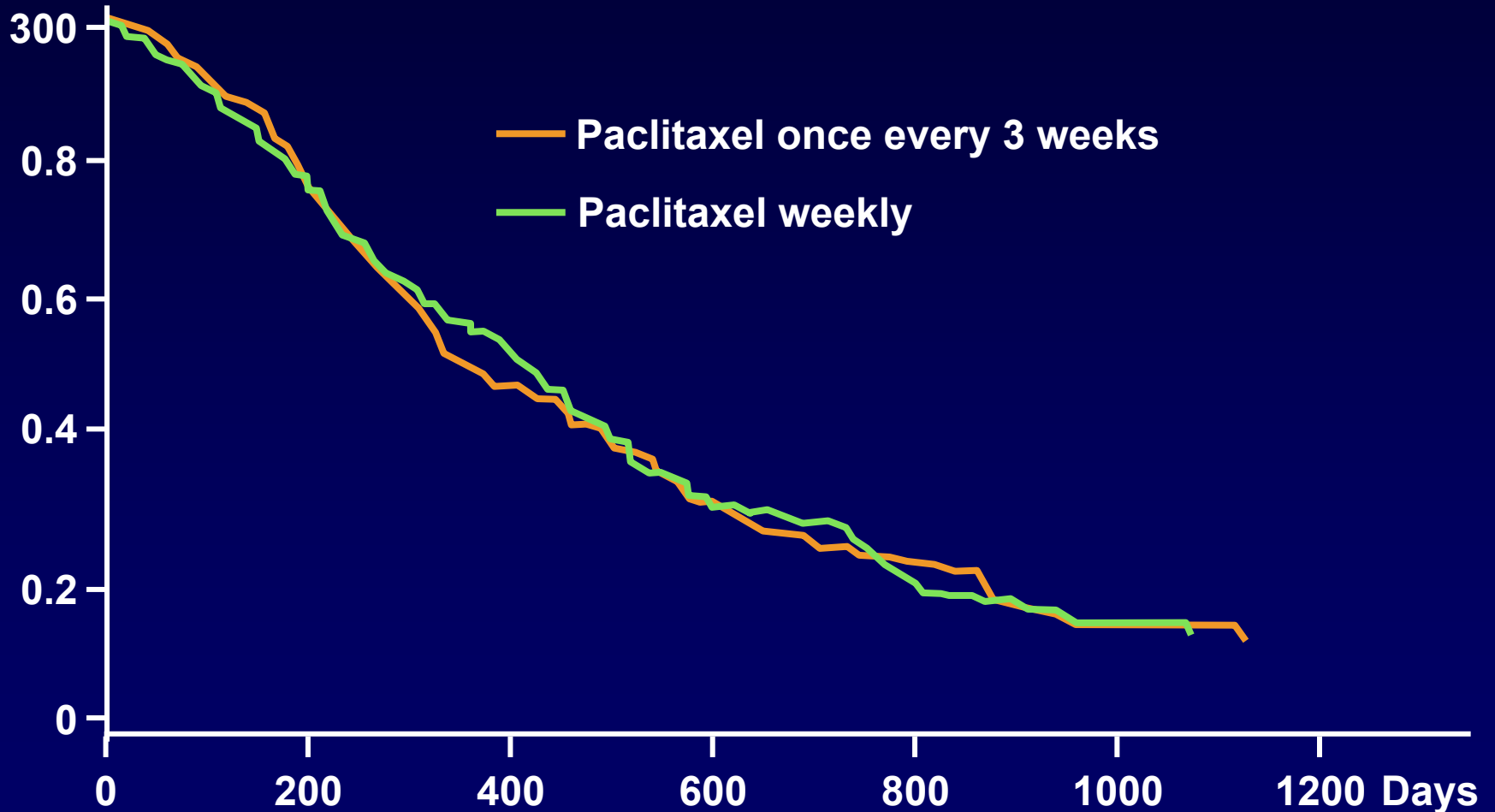
Paclitaxel 90 mg/m² weekly
x 12 cycles

	Q 3 Week Paclitaxel		Weekly Paclitaxel
Objective Response Rate	27%	P = 0.002	43%
Complete Response	5%		6%
Partial Response	22%		37%
Stable Disease	33%		25%
Time to Progression	22 weeks		24 weeks

Paclitaxel weekly vs once every 3 weeks

No difference in global survival

Proportion of surviving patients



Pegylated Liposomal Doxorubicin vs Conventional Doxorubicin in Patients with Metastatic Breast Cancer

Inclusion criteria

- 1st line MBC (IIIB/IV)
- 509 patients
- 68 International sites

Endpoints

Primary

- PFS
- Cardiotoxicity

Secondary

- Overall survival
- Event-free survival
- Response rate
- Toxicity

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Pegylated Liposomal Doxorubicin
50 mg/m² q 4 wks*

Conventional doxorubicin 60 mg/m² q 3 wks†

*Treatment until progressive disease (PD) or unacceptable toxicity

†Treatment until PD or cum. anthracycline dose of 550 mg/m²

Pegylated Liposomal Doxorubicin vs Conventional Doxorubicin: Incidence of Cardiotoxicity

	Number of Patients	
	Pegylated Liposomal Doxorubicin (n = 254)	Conventional Doxorubicin (n = 255)
Patients developed cardiotoxicity (LVEF defined)	10	48
Cardiotoxicity (+ signs and symptoms of CHF)	0	10
Cardiotoxicity (no signs and symptoms of CHF)	10	38
Signs and symptoms of CHF only	2	2

Phase III

Pegylated Liposomal Doxorubicin vs Conventional Doxorubicin: Results

	Pegylated Liposomal Doxorubicin N=254	Doxorubicin N=255	<i>P</i>
PFS (months)	6.9	7.8	0.99
OS* (months)	20.1	22	0.5

*Based on 52% of subjects.



PELICAN – Pegylated Liposomal Doxorubicin vs Capecitabine: Treatment Plan

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1st line MBC

N=344



Capecitabine 1250 mg/m²
p.os. BID q21 (14d, 7d rest)

Patients will be stratified
for age (<65, 66 and older)
and anthracycline
pretreatment



PLD 50 mg/m² i.v. q28
pegylated liposomal doxorubicin



Cycles in both arms will be repeated as scheduled for until disease progression or unacceptable toxicity.

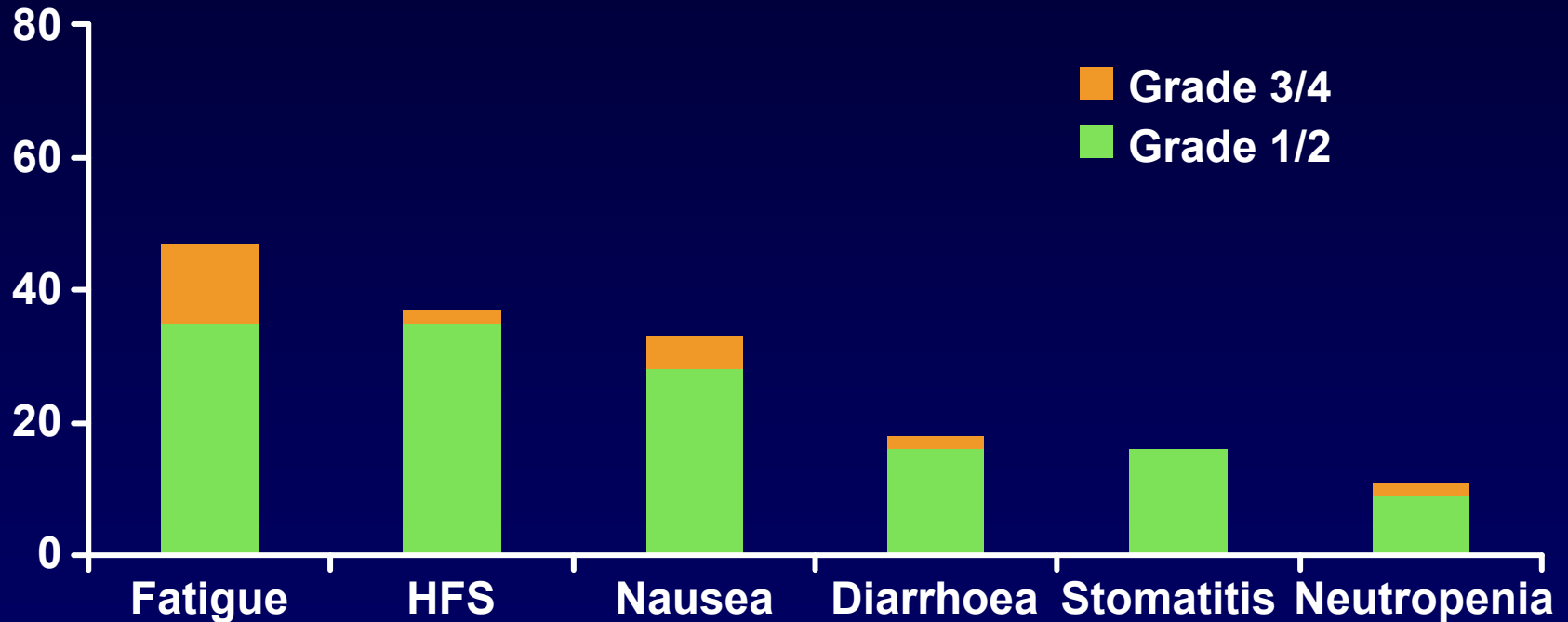
Capecitabine monotherapy in patients ≥ 65 years: Highly effective in first-line MBC

	Capecitabine 1250mg/m ² (n=30)	Capecitabine 1000mg/m ² (n=43)
Median age (years)	73 (range: 65–89)	
ORR (%)	37	35
CR	3	2
PR	33	32
Disease control (ORR + stable disease) (%)	70	81
Median TTP (months)	3.9	4.1
Median overall survival (months)	10.0	16.0

ORR = overall response rate
CR = complete response
PR = partial response

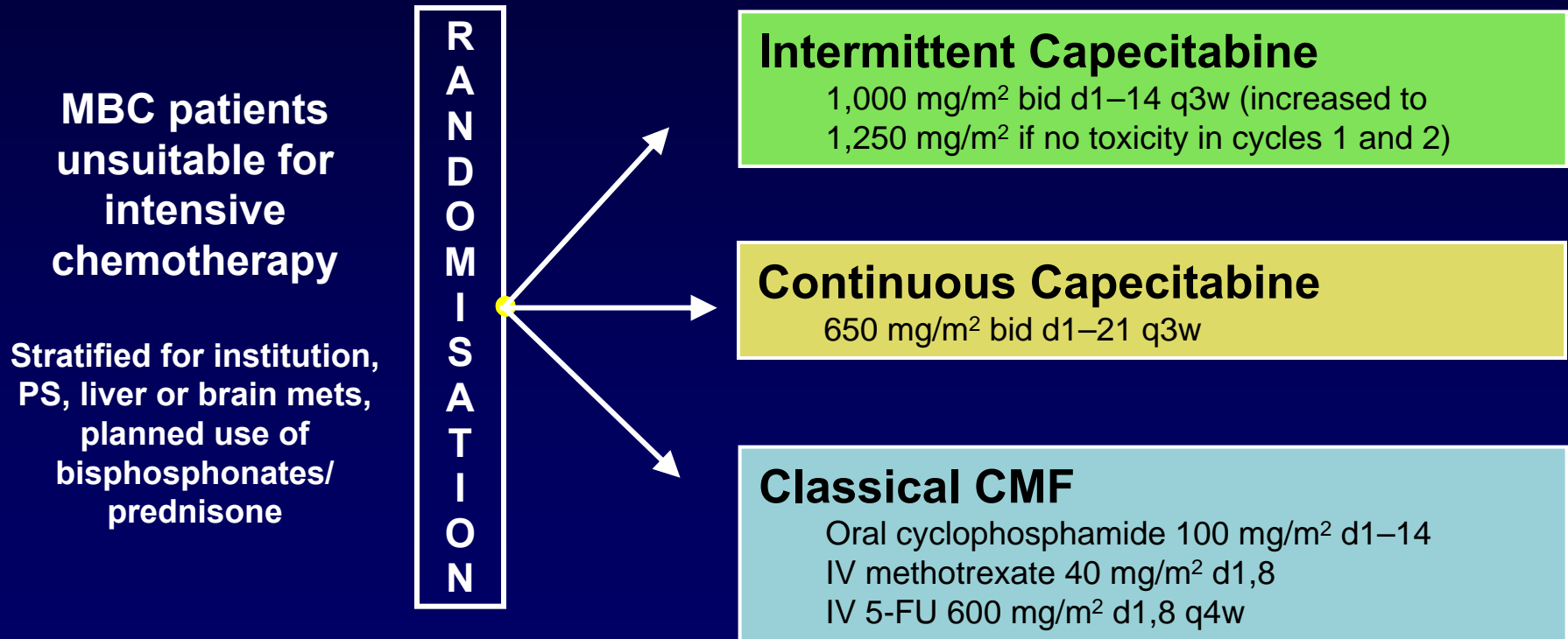
Safety of capecitabine 1000 mg/m² twice daily in patients ≥65 years

Patients (%; n=43)



- Grade 3/4 diarrhoea: 13% with 1250mg/m², 2% with 1000mg/m²
- Efficacy of the two starting doses was similar (n=73)

Capecitabine vs CMF in First-line MBC



- **Primary endpoints: PFS**
- **Secondary endpoints: RR, health-related QoL, OS and safety**

Capecitabine vs CMF

- **Similar PFS**
 - 6 vs 7 months
- **Improved OS**
 - 22 vs 18 months, $p=0.02$
- **Capecitabine associated with more HFS, less bone marrow suppression**

Vinorelbine: First-line Efficacy (IV data; also available PO)

Reference	Vinorelbine mg/m ²	Patients N	OR (%)	TTP (months)
Fumoleau	30	145	41	3
Bonadonna	30	27	59	-
Bruno	30	63	44	-
Garcia-Conde	30	50	50	5
Romero	30	44	41	6
Twelves	25	34	50	4.5
Weber	30	65	40	-

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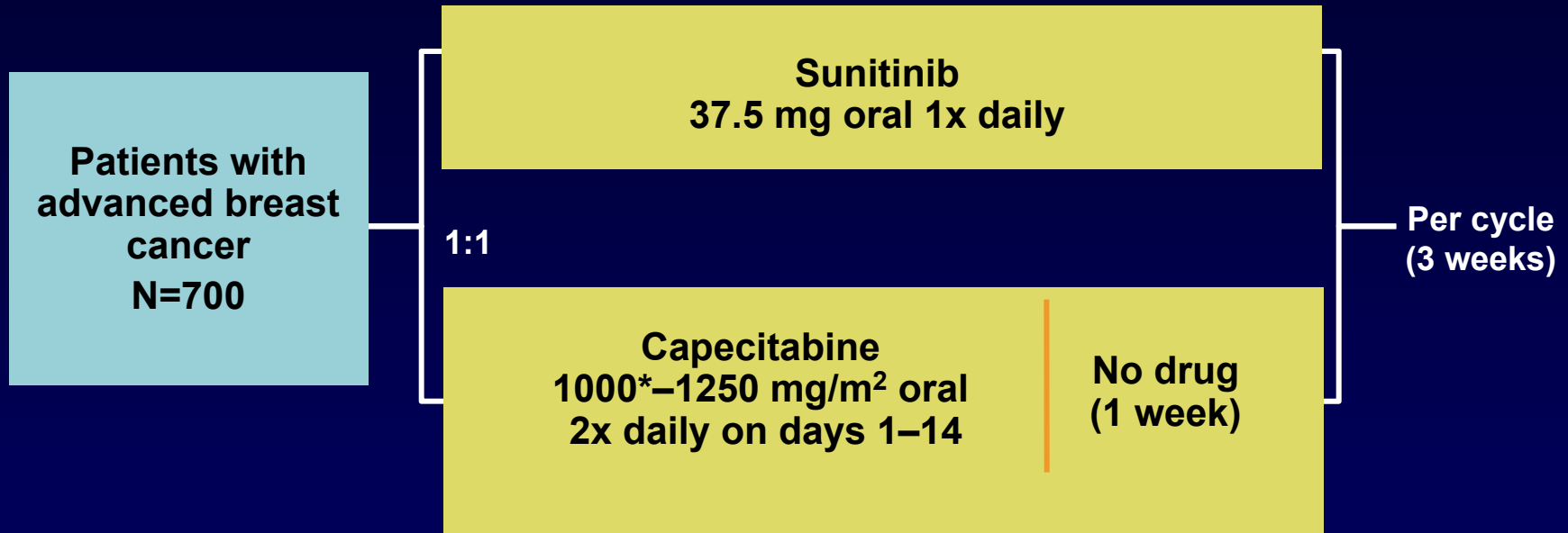
Need or not an immediate response?

MOSG: combination vs sequential capecitabine and taxane therapy

RANDOMISATION	n=345	RR (%)	Median PFS (months)	Median OS (months)
	C ₈₂₅ T ₇₅	74	8.1	24+
	C ₈₂₅ P ₁₇₅	65	6.7	24+
	C _{1,250} → PD: T or P	46	8.4	24+

C = capecitabine; T = docetaxel; P = paclitaxel
PD = progression of disease

SUN 1107: Sunitinib vs. Capecitabine 1st/2nd-line in Advanced Breast Cancer



Trial design	Endpoints	Study sites	Indication
Multinational, multicenter, randomized, [†] open-label	Primary: PFS Secondary: TTP, ORR, DR, TTR, OS, PRO, safety	EU, Canada, Latin America, Asia Pacific	1st line met breast

*Patients >65 years of age will receive 1000 mg/m²

[†]Randomization stratified based on visceral/nonvisceral disease, taxane refractory/sensitive, ER and PgR status, and country



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Review

Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology



Hans Wildiers, Ian Kunkler, Laura Biganzoli, Jacques Fracheboud, George Vlastos, Chantal Bernard-Marty, Arti Hurria, Martine Extermann, Véronique Girre, Etienne Brain, Riccardo A Audisio, Harry Bartelink, Mary Barton, Sharon H Giordano, Hyman Muss, Matti Aapro

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer mortality in women worldwide. *Lancet Oncol* 2007; 8: 1101-15
Elderly individuals make up a large part of the breast cancer population, and there are important specific Department of General Medical

Adjuvant Therapy in the Elderly: Making the Right Decision

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A B S T R A C T

Adjuvant chemotherapy has led to improvements in relapse-free and overall survival in patients with breast, colon, and non-small-cell lung cancer, yet many older patients are not offered these potentially life-saving treatments. Moreover, older patients have been either excluded or underrepresented in most adjuvant trials, limiting the generalizability of these treatments to older populations. Limited data in elders suggest that older patients derive significant benefits from adjuvant therapies provided they have life expectancies exceeding 5 years. Making treatment decisions in elders is challenging. Many have major comorbidities that may substantially limit life expectancy and minimize or negate the benefits of adjuvant chemotherapy. In this review, we discuss the potential benefits of adjuvant treatment in older patients with solid tumors with a focus on general principles involved in the selection of adjuvant therapy for patients with breast, colon, and non-small-cell lung cancer. In addition, we discuss the role of comorbidity and how it factors in treatment decisions. Finally, we discuss future research directions and funding for elders with cancer.

J Clin Oncol 25:1870-1875. © 2007 by American Society of Clinical Oncology

Breast Cancer in the Elderly

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A B S T R A C T

Screening and adjuvant postoperative therapies have increased survival among women with breast cancer. These tools are seldom applied in elderly patients, although the usually reported incidence of breast cancer is close to 50% in women 65 years or older, reaching 47% after 70 years in the updated Surveillance, Epidemiology, and End Results (SEER) database. Elderly breast cancer patients, even if in good medical health, were frequently excluded from adjuvant clinical trials. Women age 70 years who are fit actually have a median life expectancy of 15.5 years, ie, half of them will live much longer and will remain exposed for enough time to the potentially preventable risks of a relapse and specific death. In the last few years, a new concern about this issue has developed. Treatment now faces two major end points, as in younger women: to improve disease-free survival in the early stages, and to palliate symptoms in advanced disease. However, in both settings, the absolute benefit of treatment is critical because protecting quality of life and all its related aspects (especially functional status and independence), is crucial in older persons who have more limited life expectancy. Furthermore, the new hormonal compounds (aromatase inhibitors) and chemotherapeutic drugs (capecitabine, liposomal doxorubicin), are potentially less toxic than and equally as effective as older more established therapies. These new treatments bring new challenges including higher cost, and defining their benefit in elderly breast cancer must include an analysis of the cost/benefit ratio. These issues emphasize the urgent need to develop and support clinical trials for this older population of breast cancer patients both in the adjuvant and metastatic settings, a move that will take us from a prejudiced, age-based medicine to an evidence-based medicine.

What Would I Do?

- Older patient, hormone resistant, chemotherapy naïve metastatic breast cancer
- Keep patient's goals in mind!
- I would use single agent chemotherapy
 - First choices
 - capecitabine or vinorelbine (oral) or liposomal doxorubicin (anthracycline naïve)

SIOG in BERLIN OCTOBER 15-17, 2009



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Geriatric Oncology:
Cancer in Senior Adults