The Landscape of Systemic Cancer Therapy in Africa

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Disclaimer

- I have no conflicts of interest to declare.
- I have not practiced in other African countries, my presentation is based predominately on the South African experience and on contact I have had with African colleagues at loco-regional meetings and advisory board meetings.

Overview

- Incidence of Cancer
- Resource Considerations and Challenges
- Systemic Breast Cancer treatments
- Systemic Colon Cancer Treatments
- Conclusions

Incidence of Cancer

- In areas across the continent where infectious diseases, infant mortality, maternal mortality, civil war and violence have a major impact on life expectancy - cancer incidence associated with an aging population is not the greatest health care focus or concern.
- South African data is quite similar to international age specific data on the incidence of cancer that is biased towards a much higher incidence in later years.
- In South Africa, and elsewhere in Africa, the incidence of cancer has been steadily increasing as the populations urbanize and adopt different lifestyles and diets.

Incidence of Cancer

- South Africa is faced with the grave reality that life expectancies across racial groups still differ dramatically and therefore, if we are to factor in age related cancer, so too is the likely cancer incidence among specific groups.
- The black community in South Africa has by far the shortest life expectancy at birth. In addition, the age structure differs substantially among the race groups.

Potential Effects of Better access to care

- Improvements in general medical outcomes, resulting in increased life expectancy implies an ageing population.
- This would result in increasing incidence of cancer and the need for cancer care and resources.
- So paradoxically.. We can (hopefully) expect a dramatic increase in cancer incidence with age in South Africa and Africa as a whole as health care to the wider population improves and we work towards less disparity in health care.
- An article in The Lancet indicated experience elsewhere in the world where perceived cancer incidence increased dramatically, from similar levels to South Africa's, following the introduction of proper diagnostic facilities such as a screening program.

Incidence and Screening

- True screening is not available through most of Africa within the public health structures tasked with the care of the vast majority of Africa's population.
- Even within South Africa there is a huge disparity across the various regions, in urban areas the density and penetration of screening programs is starting to make inroads, however in peripheral and rural areas this is not the case.
- The dire scenario of only 3 mammogram units for a neighbouring country can in no way begin to offer screening to a population, rather an attempt to facilitate the diagnosis of already advanced disease.
- Poorer outcomes are unfortunately the consequence.
- It is only within the affluent and insured minority of patients in Africa that anything approaching a screening program is seen.
- There is currently a big push by the South African department of Health to formulate a white paper with protocols for screening and up referral for breast and cervical cancer that is a vast step in the right direction to improve health care.

Incidence of Cancer

- The Medical Research Council (MRC) gives a total cancer incidence of cancer as:
  148.9/100,000 in males and
  134.9/100,000 in females,
- BUT it finds dramatically different incidence rates between the race groups.
  - White South Africans have cancer incidence of 277 and 230/100,000 for males and females,
  - Black South Africans have cancer incidence of only 97.1 and 103.7/100,000 for males and females

Incidence of Cancer

- HOWEVER International experience has shown that when similar levels of care are available there is not such a significant difference in incidence between race groups.

Breast Cancer Incidence

- In South Africa and in developed countries, breast cancer is the most common cancer of women having overtaken cervical cancer.
- Worldwide, breast cancer is the cause of more than 500,000 deaths annually.
- Based on incidence in 2007 the calculated lifetime risk of Breast Cancer in females in South Africa is 1:35
- In developed countries, the lifetime risk of breast cancer is approximately 1:10
- While the reduction (both relative and real) in cervical cancer incidence can in part be ascribed to some penetrance of screening programs at local clinics. As yet the impact of HPV vaccination is not a contributing factor.

Resources

- In South Africa < 16% of the population is covered by medical insurance

  - Of which < 50% of these have access to upper end funding models which would include cover monoclonal antibodies, tyrosine kinase inhibitors and immunotherapy
  - The public sector is required to care for around 84% of population

- Our public sector under the current model would not be ideal to manage an increasing incidence of cancer BUT effective planning and retention of expertise can increase the capacity.


SPECIAL REPORT
TIME
BAYER
WHY MEDICAL BILLS
ARE KILLING US

Rising Cost in USA

- From 1990 to 2008, overall costs of treating cancer more than tripled in nominal dollars and more than doubled in inflation-adjusted dollars
- Cancer treatment in the US cost more than $90 billion in 2006
  - Just under 5% of total US spending on medical care

Challenges:

- Identify drivers of cost
- Identify how we can reduce costs?
- Identify how we can maintain or improve quality?
- And still meet demand?

Challenge: Understanding What Drives the Cost of Cancer Care

- Demographics
- Behaviour
  - Tobacco, obesity, adherence to screening
- Novel Interventions
  - Drugs,
  - Genetic Tests,
  - Radiation Therapy,
  - Imaging
- Over-Utilization
  - Lack of Evidence based practice,
  - Incentive structure,
  - Defensive medicine,
  - Lack of communication/care delivery inconsistent with patients preferences

Reasons for increasing costs of cancer treatment

- Overall increase in spending for cancer care reflects increases in both price and quantity of care
  - Between 1991 and 2002, the proportion of breast cancer patients receiving chemotherapy and the average cost of the chemotherapy both roughly doubled. Similar trends have been observed for other types of cancer.
- The increases in price and quantity reflect the introduction of new medical technology
  - Newer cancer therapies are more expensive than the prior standard of care;
  - Newer drugs expand the pool of treatment candidates (e.g. because of broader indications, reduced side effects).
  - Drug spending has been growing faster than costs for physicians' services or hospital care
    - Kaiser Family Foundation, Prescription Drug Trends, September 2008, www.kff.org/rxdrugs/upload/3057_07.pdf

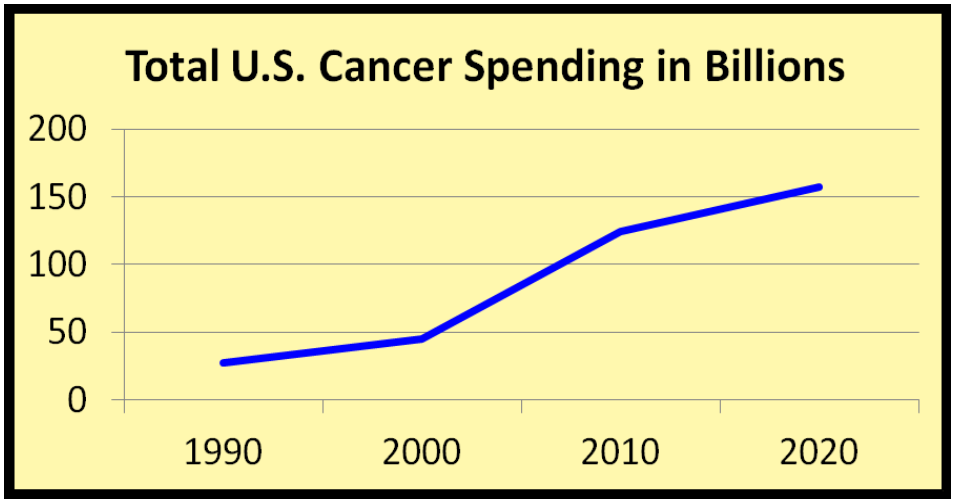
What drives increased spending on pharmaceuticals?

- Number of prescriptions dispensed (42%)
  - Average prescriptions per capita increased from 7.9 to 12.4 between 1994 and 2006
- Types of prescriptions (34%)
  - newer, higher-priced drugs replacing older, less-expensive drugs
- Manufacturer price increases for existing drugs (25%)

Kaiser Family Foundation, Prescription Drug Trends. May 2007 and October 2004, http://www.kff.org/rxdrugs/upload/3057_06.pdf; http://www.kff.org/rxdrugs/upload/Prescription-Drug-Trends-October-2004-UPDATE.pdf

Rising Cancer Care Costs

- **Most Expensive Cancers in U.S. in 2010**
  - Breast $16.5 billion
  - Colorectal $14.1 billion
  - Lymphoma $12.1 billion
  - Lung $12.1 billion
  - Prostate $11.9 billion
- 600% Increase in spending over 30 years….



Mariotto et al. JNCI 2011

BREAST CANCER SYSTEMIC TREATMENT

Adjuvant Chemotherapy

- EBCTCG meta-analysis of 47 trials comparing combination chemotherapy to no chemotherapy showed a significant reduction in mortality in patients receiving chemotherapy regardless of nodal status, ER status or whether tamoxifen was given.
- Benefit of chemotherapy varied with age
  - < 50yrs 10yr survival improved from 71 to 78% in node negative pts and 42 to 53% node positive
  - 50-69 yrs 10yr survival improved from 67 to 69% in node negative pts and 46 to 49% in node positive pts

Risk Stratification to Define Rx

	Low risk (has all listed factors)	Intermediate risk (risk classified between the other 2 categories)	High risk (has at least 1 listed factor)
Tumor size	</=1cm	1-2cm	>2cm
ER or PR Status	Positive	Positive	Negative
Tumor grade	Grade 1	Grade 1-2	Grade 2-3
Her2 neu	Negative	Negative	Positive
S phase proliferation	Low fraction	Intermediate fraction	High fraction
Nodes positive	No	No	Yes

Adjuvant Systemic Treatment Risk Models

- Magee Score
  - In a study from University of Pittsburgh standard histopathologic factors and immunohistochemical markers can be used to estimate the recurrence score validated on a separate set of over 200 cases, sent for clinical onco*type* DX®. Multiple linear regression analysis was performed to model the prediction of the onco*type* DX® RS by Nottingham Score, Ki-67 labelling index (0-100), tumor size (in cm.), H-scores (range: 0-300) for ER and PR, and HER2 status (negative, equivocal or positive).

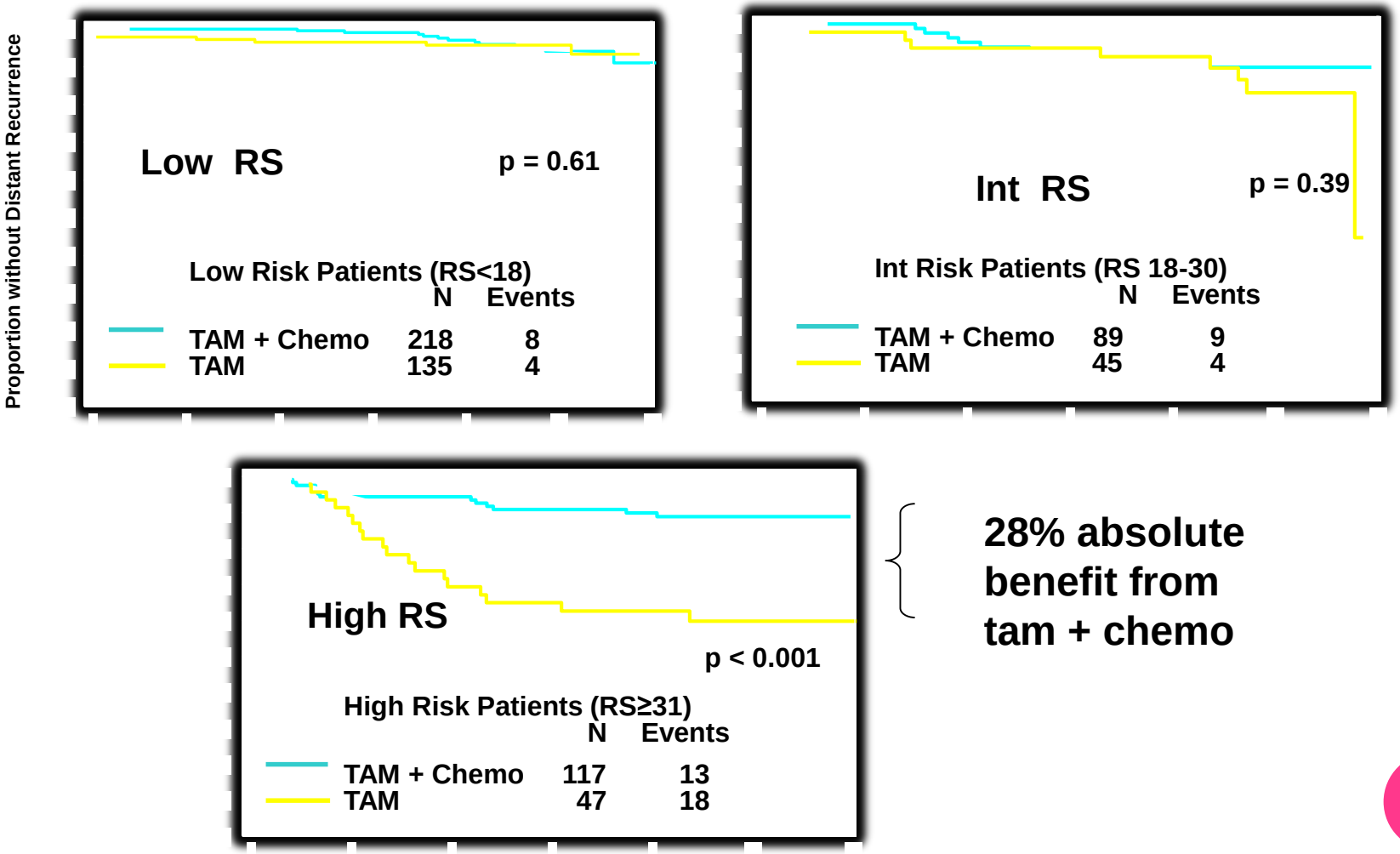
- Adjuvant Online
  - Adjuvant! Online is a web-based application designed to provide 10 years survival probability of patients with breast cancer. However, this model is currently unavailable as it is being upgraded.

- Predict Tool
  - An online prognostication and treatment benefit tool. The survival estimates are presented both with and without adjuvant therapy (hormone therapy, chemotherapy and trastuzumab), and provided for 5 and 10 years following surgery. Development of the model was a collaborative project between the Cambridge Breast Unit, University of Cambridge Department of Oncology and the Eastern Cancer Information and Registration Centre (ECRIC) and was supported by an unrestricted educational grant from Pfizer Limited.

Adjuvant Systemic Treatment Risk Models

- Mammaprint®
  - 70-gene signature test that among women with early-stage breast cancer who were at high clinical risk and low genomic risk for recurrence, the receipt of no chemotherapy on the basis of the 70-gene signature led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points lower than the rate with chemotherapy.
- Oncotype®
  - Oncotype DX looks at the expression of a panel of 21 genes within a tumour to determine a Recurrence Score. The Recurrence Score is a number between 0 and 100 that corresponds to a specific likelihood of breast cancer recurrence within 10 years of the initial diagnosis.

B-20 Results: Tam vs Tam + Chemo



28% absolute benefit from tam + chemo

Paik et al. *J Clin Oncol.* 2006.

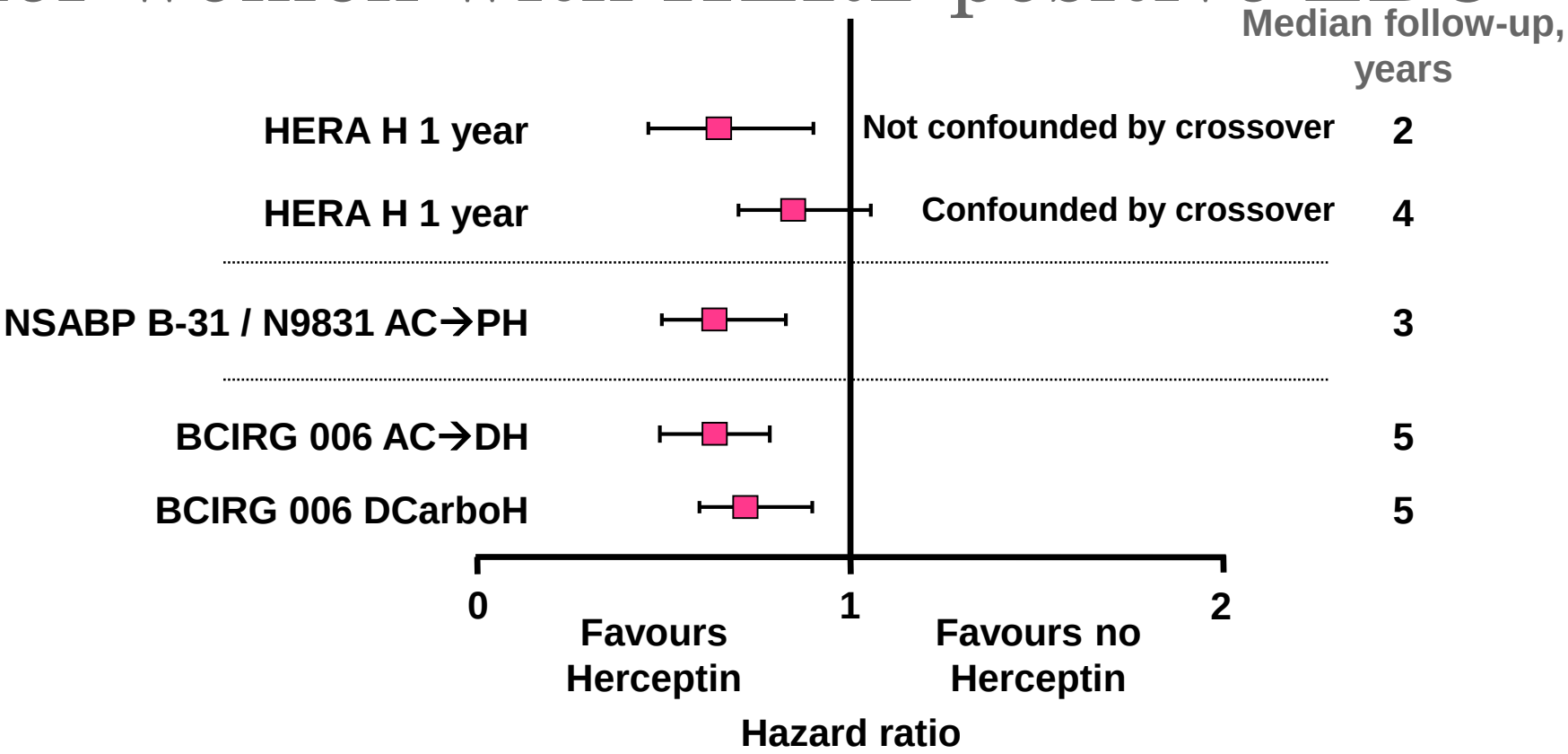
Adjuvant Chemotherapy

- First-generation regimens
  - First-generation regimens are considered less effective than second- or third-generation regimens , however CMF is a reasonable alternative for patients who have contraindications to anthracycline and taxane therapy.
  - CMF
  - AC for four cycles
- Second-generation regimens
  - Second-generation regimens are more effective than first-generation protocols.
  - FAC for six cycles
  - FEC for six cycles
  - Dose-dense AC-Paclitaxel with colony-stimulating factor (CSF) support
  - TC for four cycles shown to be more effective than AC
- Third-generation regimens
  - Third-generation regimens are more effective than some second-generation regimens and include anthracyclines and taxanes.
  - 4AC-Paclitaxel weekly for 12 wk
  - TAC six cycles with granulocyte CSF support
  - 3FEC-3Docetaxel
  - 4FEC-Paclitaxel weekly for eight cycles

Adjuvant Trastuzumab

- Trastuzumab is a humanized monoclonal antibody targeting tumor cells overexpressing Her2/neu
- 15-20% of pts with breast cancer overexpress Her2/neu marking for poorer prognosis more aggressive disease.
- 4 studies have addressed the merit of Trastuzumab in the adjuvant setting. All published in NEJM
- These 4 trials enrolled over 11 000 pts
    - HERA
    - Combined B31 & N9831 analysis
    - BCIRG006

Trastuzumab for 1 year improves OS for women with HER2-positive EBC



OS, overall survival; Carbo, carboplatin

Perez et al 2007; Smith at al 2007; Gianni et al 2009; Slamon et al 2009

Adjuvant Trastuzumab

- Adjuvant Chemotherapy protocols with Trastuzumab
- 4AC-Paclitaxel weekly for 12 weeks **or** 3 weekly for four cycles given concurrently with trastuzumab for a 1-y total duration of trastuzumab therapy.
- 4AC-4Docetaxel plus trastuzumab 1 y of trastuzumab.
- 6TC with trastuzumab to complete 1-y total duration of trastuzumab therapy
- Of Note: The PHARE comparing 6 months to 12 months of adjuvant Herceptin was unable to show non-inferiority of the 6month protocol

Neoadjuvant Systemic treatment

Neoadjuvant Chemotherapy Protocols

- 4AC-Paclitaxel weekly for 12 wk
- TAC six cycles with granulocyte CSF support
- 3FEC-3Docetaxel
- 4FEC-Paclitaxel weekly for eight cycles
- Dose-dense AC-Paclitaxel with colony-stimulating factor (CSF) support
- TC for four cycles

Neoadjuvant Chemotherapy Protocols with Trastuzumab

- 4AC-Paclitaxel weekly **or** 3 weekly for four cycles given concurrently with trastuzumab for a 1-y total duration of trastuzumab therapy.
- 4AC-4Docetaxel plus trastuzumab 1 y of trastuzumab.
- 6TC with trastuzumab to complete 1-y total duration of trastuzumab therapy
- ? Plus Pertuzumab or Lapatinib
- Remember to always consider clinical trials.

Treatment Principles

- Patients with hormone receptor-positive advanced breast cancer are appropriate candidates for endocrine therapy if they have no or little symptoms related to their disease.
- Patients who present with any of the following disease characteristics are optimal candidates for endocrine therapy:
    - No or limited visceral metastases
    - Bone-only metastatic disease
    - Slowly progressive disease

First Line Treatment ABC

- Depends if this is the initial presentation.
- If not the initial presentation depends on what treatment the patient had in the adjuvant setting.
- Depends if the patient is premenopausal or postmenopausal.

Hormone RECEPTOR POSITIVE HER 2 Negative

Adjuvant Hormone treatment

Options include:

- Ovarian suppression or ablation for premenopausal women
- Selective estrogen receptor modulator (SERM)
- Combination treatment (tamoxifen/AIs ± ovarian suppression)
- A choice between them is based on patient and physicians preferences.
- All the above options are available in the public and private sector

2ND LINE PREMENOPAUSAL

- For patients with disease progression following first-line endocrine therapy, second-line hormonal treatment is a reasonable option, provided they are not symptomatic and their disease continues to be slowly progressive.
- Patients who develop symptoms due to disease progression and those with rapidly progressive metastatic disease should be treated with chemotherapy.

3RD LINE PREMENOPAUSAL

- Clinical trial needs to be considered,
- All lines of chemotherapy can be considered once hormonal therapies have been exhausted.

POSTMENOPAUSAL

- Fulvestrant is an estrogen receptor antagonist used in the treatment of postmenopausal women. Fulvestrant blocks ER dimerization and DNA binding, increases ER turnover, and inhibits nuclear uptake of the receptor.
- One trial suggests that fulvestrant has equivalent efficacy to anastrozole. In the FIRST (First-Line Study Comparing Endocrine Treatments) trial, when compared with anastrozole, fulvestrant resulted in:
    - A similar ORR (36 percent in both arms)
    - A longer time to progression (median, 23 versus 13 months, HR 0.66; 95% CI 0.47-0.92)
- Overall survival was not reported for this trial.
- At this time, fulvestrant is probably not the first option in the first-line setting in SA if one is to consider cost and that it is not available in the state sector.

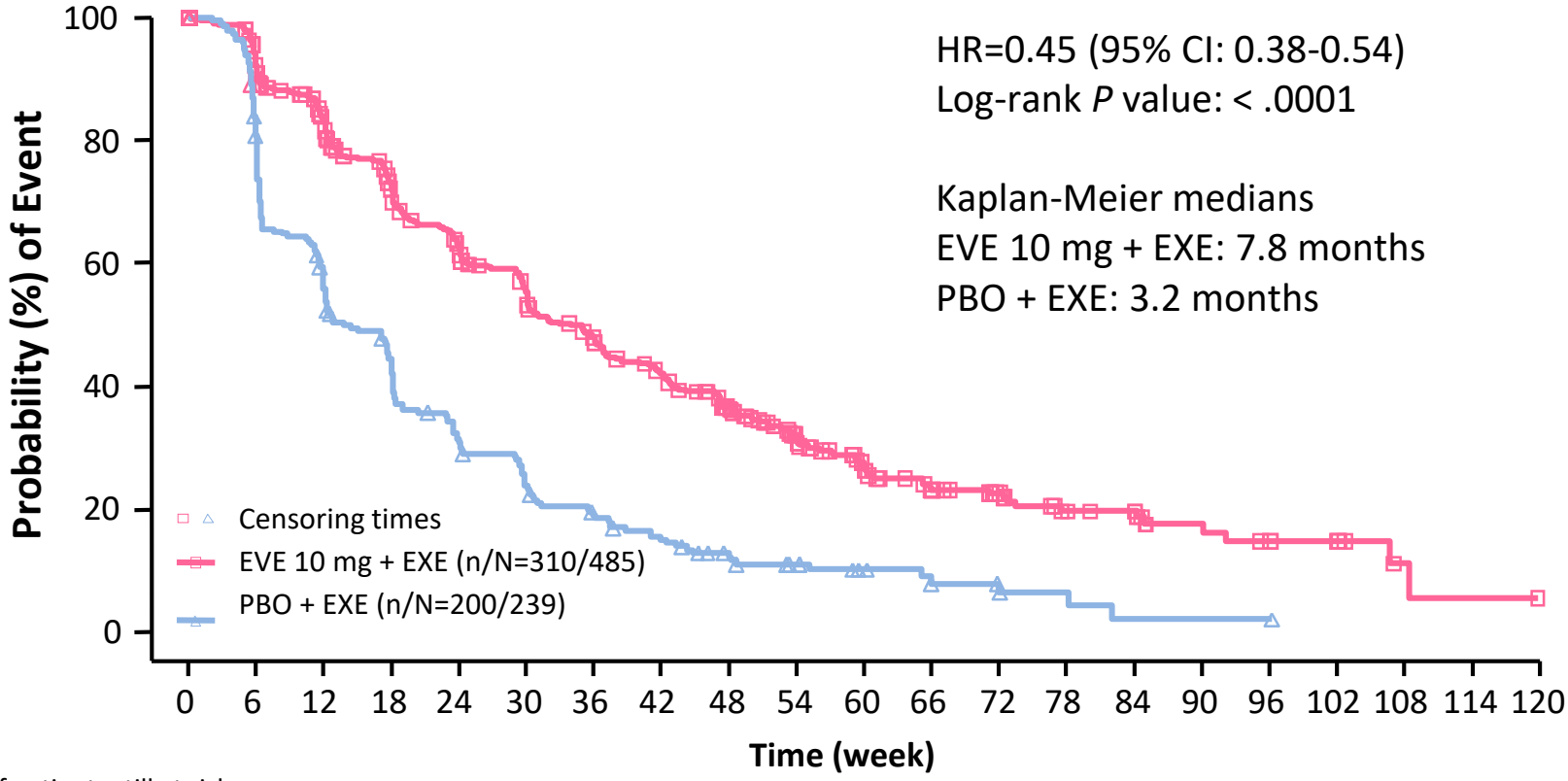
2ND LINE POSTMENOPAUSAL

- There is a lack of clinical trials to address the optimal sequence of therapy from the first to the second-line setting.
- The available options include:
  - tamoxifen,
  - a non-cross-resistant AI,
  - fulvestrant,
  - endocrine therapy plus the mammalian target of rapamycin (mTOR) inhibitor, everolimus, in the second-line setting.
  - A choice between them should be individualized based on prior treatment received and a patients co-morbidities.

2ND LINE POSTMENOPAUSAL

- The benefit of everolimus plus the steroidal AI, exemestane versus exemestane alone, was shown in the Breast Cancer Trials of Oral Everolimus (BOLERO-2) trial
- The combination of exemestane and everolimus resulted in:
  - An improvement in PFS (median, 7 versus 3 months; HR for mortality 0.43, 95% CI 0.35-0.54)
  - Higher ORR (9.5 versus 0.4 percent)

BOLERO-2: Primary Endpoint, PFS (18-Month Follow-up, Local Assessment)

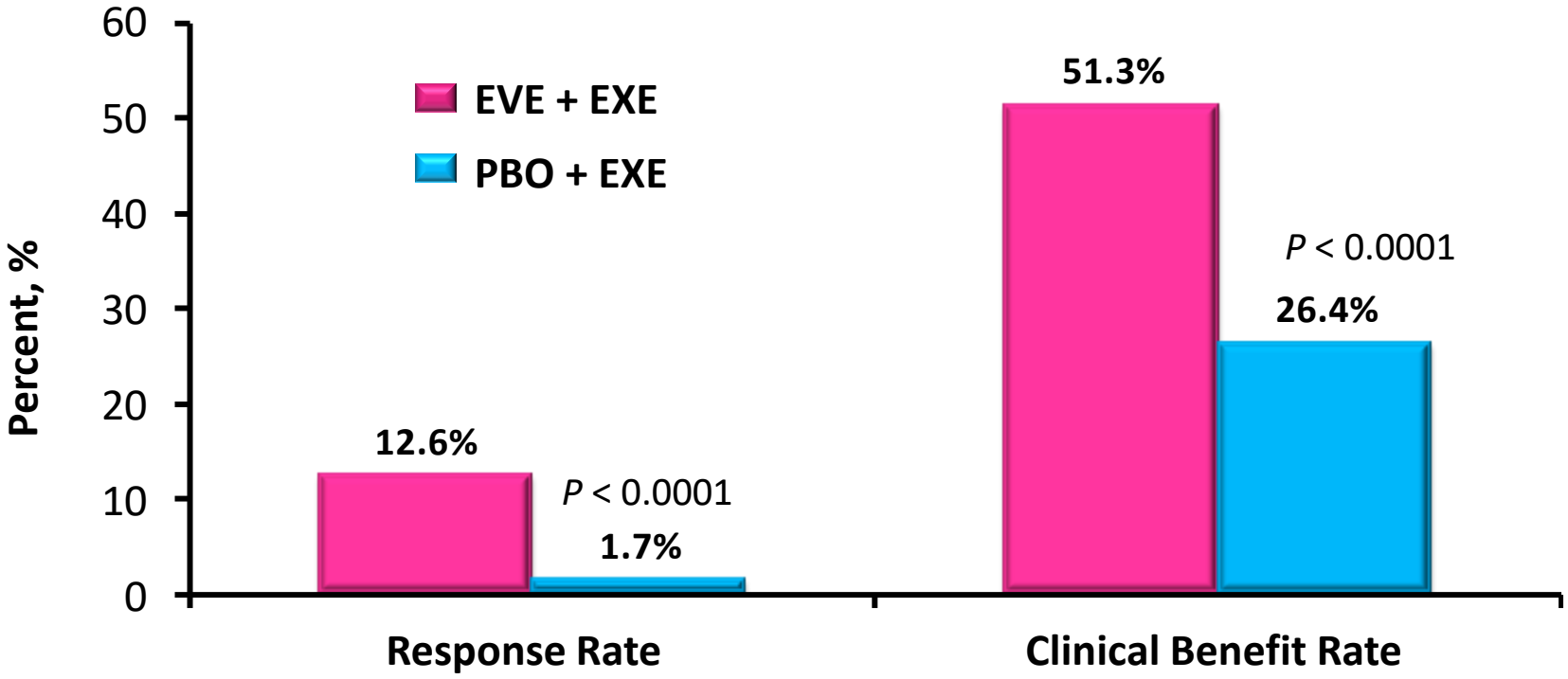


Number of patients still at risk

EVE 10 mg + EXE	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
PBO + EXE	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.
Piccart M, et al. Presented at: ASCO 2012. Abstract 559 (poster).

BOLERO-2: ORR and CBR (18-Month Follow-up, Local Assessment)

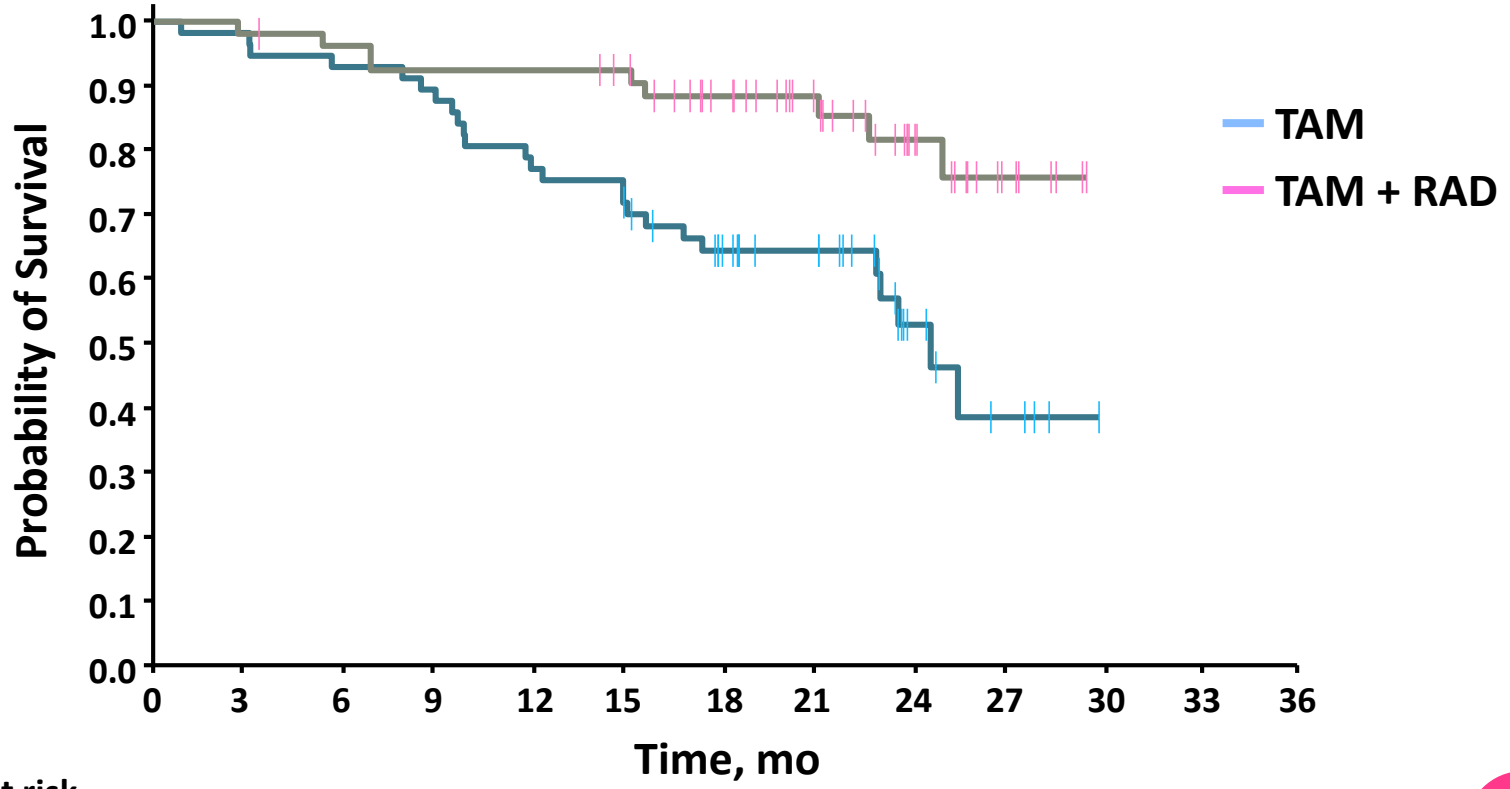


CBR, clinical benefit rate; EVE, everolimus; EXE, exemestane; PBO, placebo; ORR, overall response rate.
Piccart M, et al. Presented at: ASCO 2012. Abstract 559 (poster).

Overall Survival (October 2010)

Hazard ratio = 0.32; 95% CI 0.15-0.68

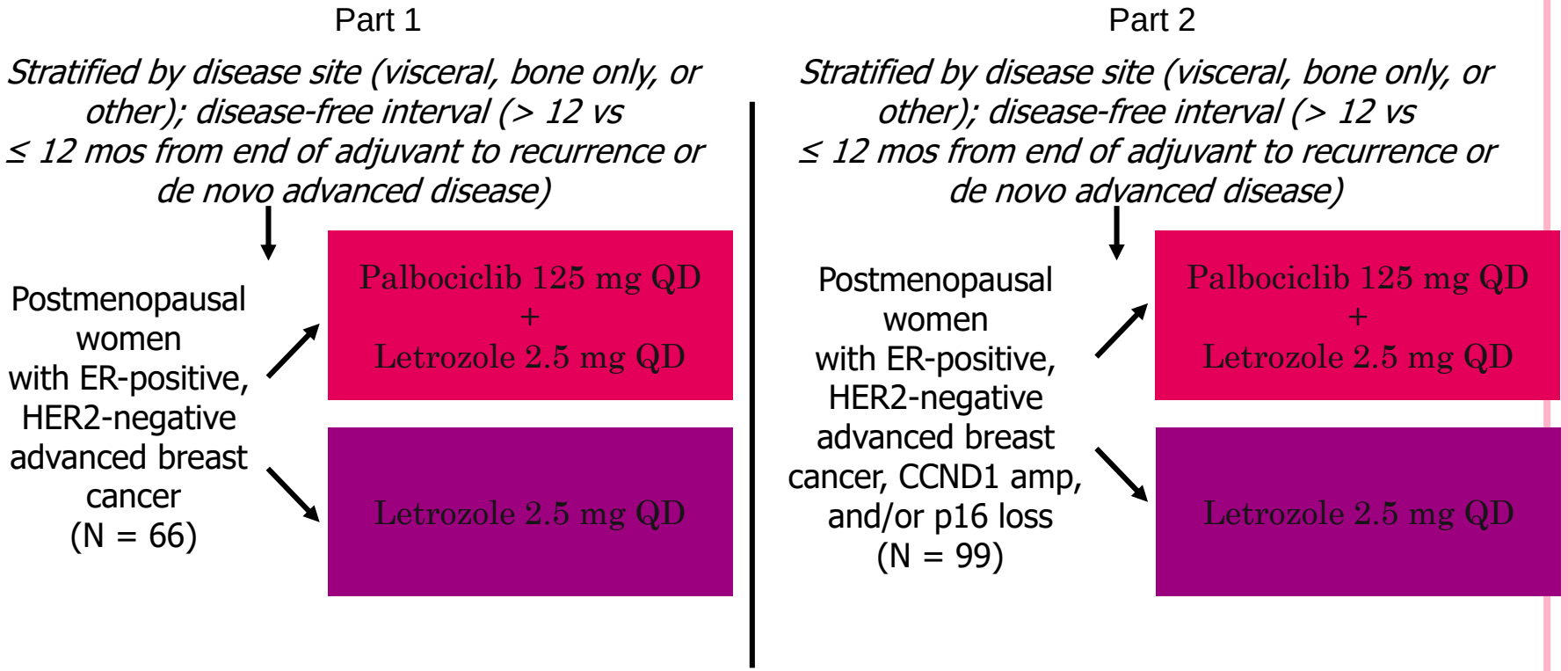
Exploratory log-rank: *P*=.0019



Patients at risk											
TAM + RAD: n =	54	53	51	49	49	45	38	26	14	6	0
TAM: n =	57	55	53	50	44	38	30	22	9	4	0

Bachelot T, et al. *Breast Cancer Res Treat.* 2010;100 suppl 1; SABCS 2010, abstract S1-6.

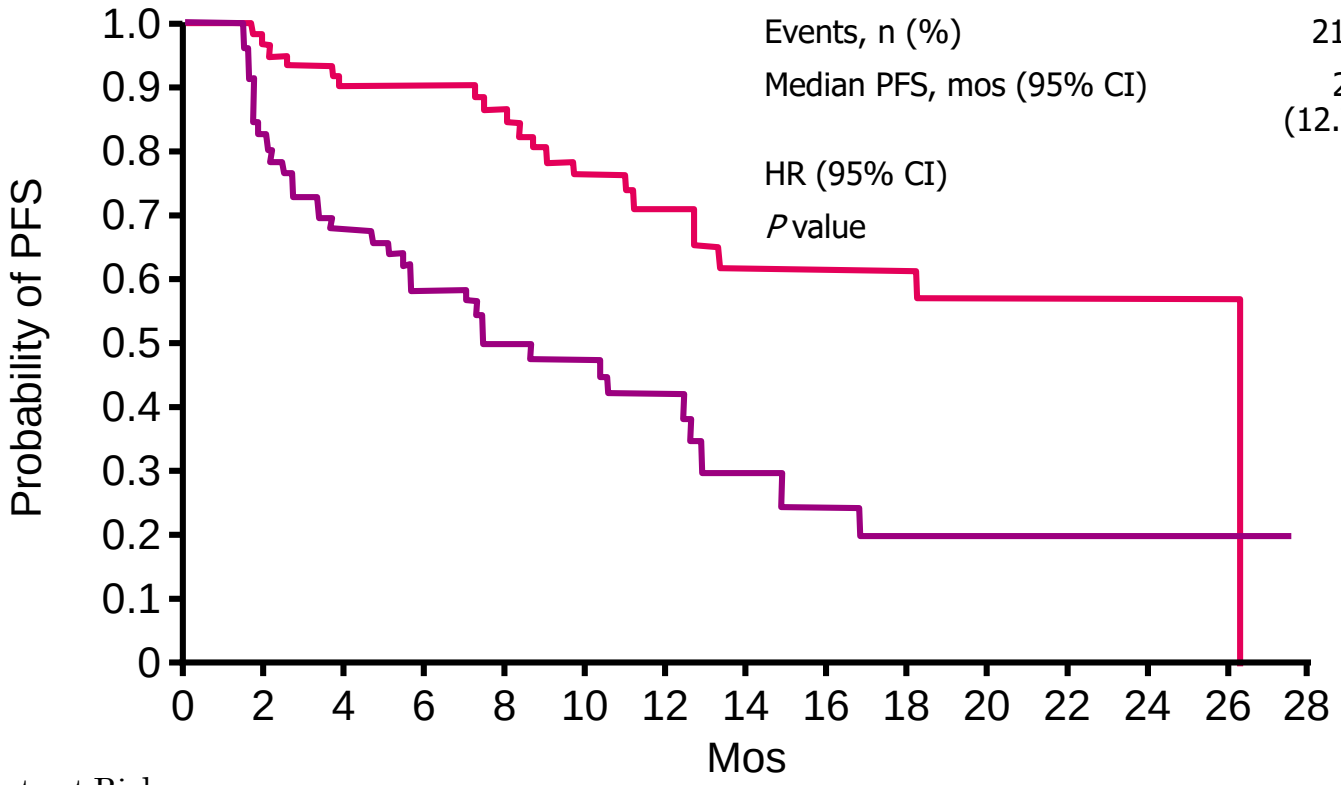
Phase II Study of Letrozole ± Palbociclib (PD-0332991) in ER+, HER2- MBC



All patients continued assigned treatment until disease progression, withdrawal of consent, or unacceptable toxicity with follow-up tumor assessment every

Finn RS, et al. SABCS 2012. Abstract S1-S6.

Letrozole ± Palbociclib in ER+, HER2- MBC: PFS



	Palb + LET (n = 84)	LET (n = 81)
Events, n (%)	21 (25)	40 (49)
Median PFS, mos (95% CI)	26.1 (12.7-26.1)	7.5 (5.6-12.6)
HR (95% CI)	0.37 (0.21-0.63)	
P value	< .001	

Patients at Risk, n

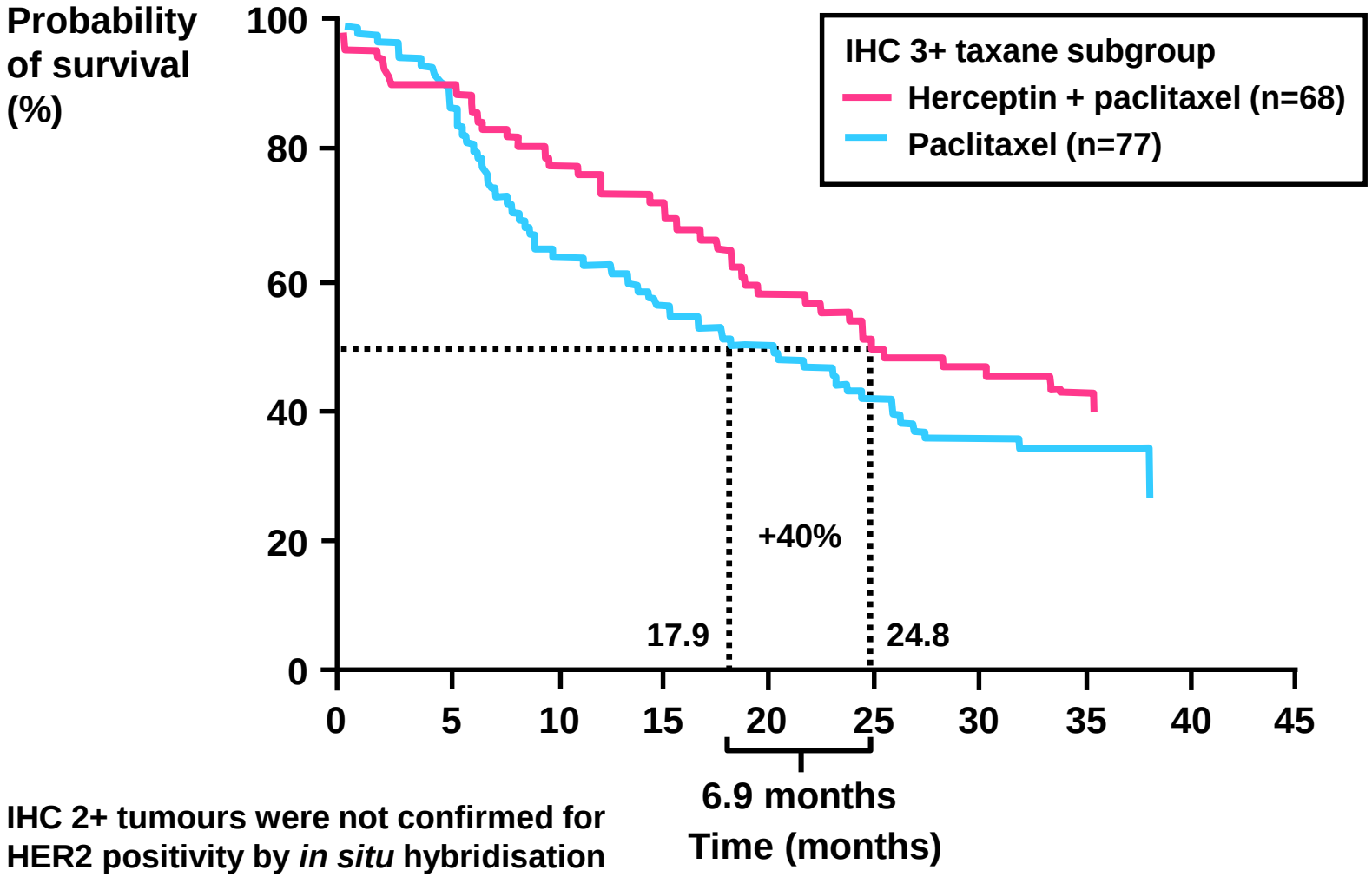
Palb + LET	84	75	60	53	43	35	25	18	15	14	9	5	3	1
LET	81	57	33	29	22	17	11	6	5	4	3	3	1	1

Finn RS, et al. SABCS 2012. Abstract S1-6.

HER 2 POSITIVE PATIENTS

1st Line Treatment

H0648g pivotal trial confirmed predictive value of HER2

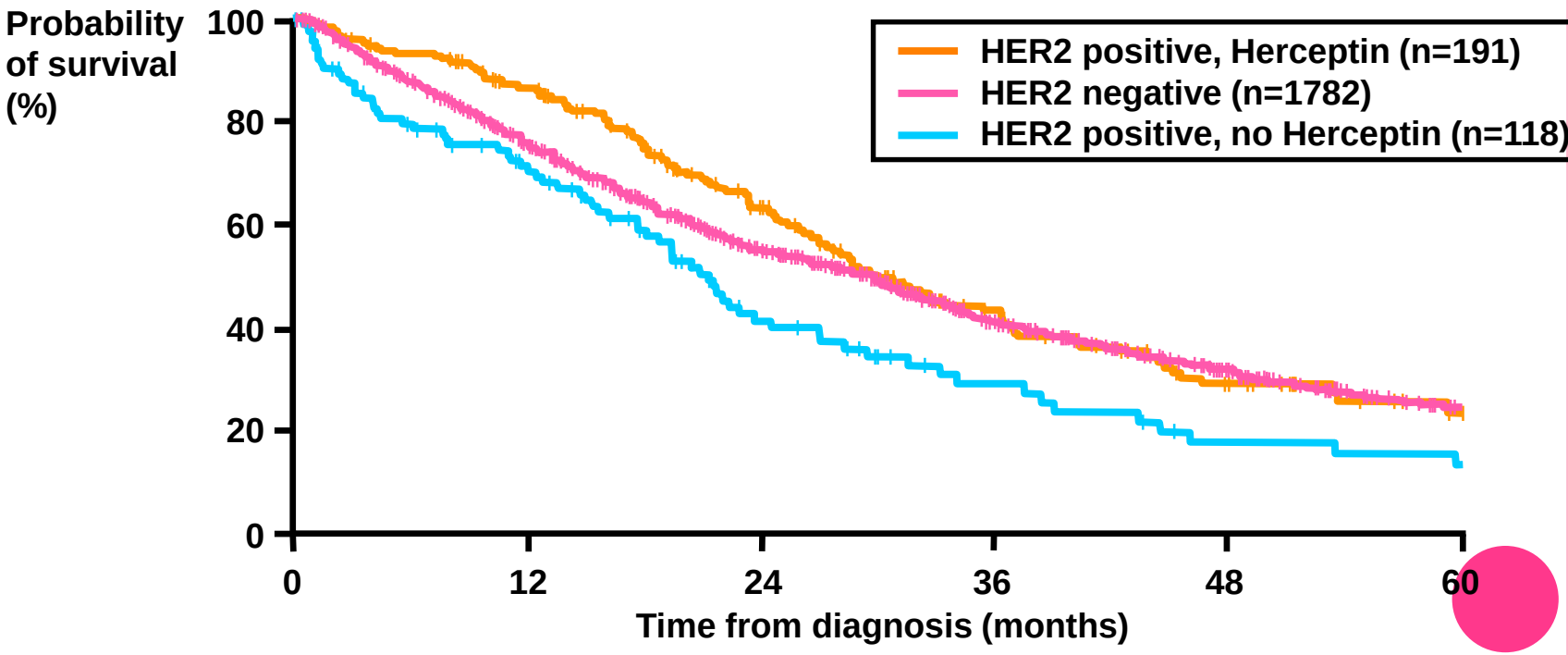


IHC 2+ tumours were not confirmed for HER2 positivity by *in situ* hybridisation
Subgroup analysis, p value not reported

Smith 2001

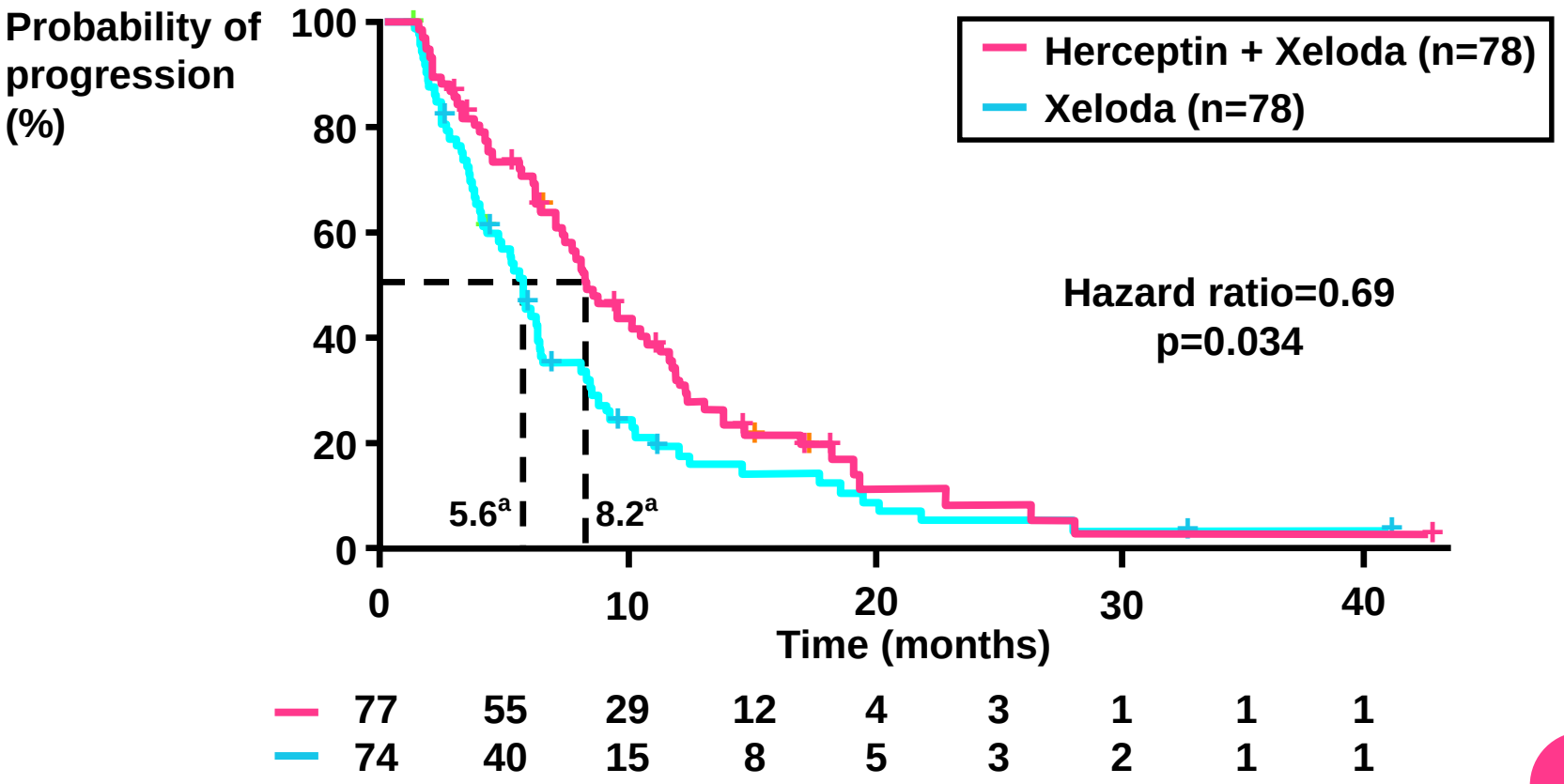
Trastuzumab has changed the natural history of HER2-positive disease

- Patients with HER2-positive MBC now have comparable outcomes with HER2-negative MBC



Dawood et al 2010

GBG-26: continuation of Trastuzumab beyond progression provides benefit BUT probably not "value"



[a]Median TTP in months (time between randomisation and documented disease progression or disease-related death)
Median follow-up: 15.6 months

Not within EMEA-approved indication for Herceptin

von Minckwitz et al 2009

TRIPLE NEGATIVE BREAST CANCER

1ST LINE TREATMENT

- Consider a clinical trial if available.
- Possible Trials with checkpoint inhibitors if PDL1 positive
- Consider testing for Androgen Receptor

Hormonal Anti-androgen Treatment

- Endocrine therapy is ineffective in breast cancer patients with classic hormone receptor-negative disease.
- However, in ER- and PR-negative disease there is a subset with the AR expression that is predictive to respond to antiandrogen therapies.
- Unfortunately, the role of anti-AR targeted drugs is limited. TNBC represents 20 % of the disease, and 10 % of that is AR positive, so only 2 % of overall breast cancer cases may benefit from this form of treatment.

- A phase II study explored bicalutamide in the subset of AR-positive metastatic disease. In this study, AR was tested by IHC and considered positive if the nuclear staining was greater than 10 %.
- Patients were treated with bicalutamide at a dose of 150 mg daily. The primary endpoint of this study was defined as the total number of patients who showed a CR, PR, or stable disease (SD) after 6 months.
- The percentage of patients showing clinical benefit (CR, PR, and SD) was 19 % (95 % CI 7–39 %) for bicalutamide.
- The median PFS was 12 weeks (95 % CI 11–22 weeks).
- Bicalutamide was well tolerated with moderate activity in patients with ER- and PR-negative, AR-positive breast cancer.

COLORECTAL CANCER SYSTEMIC TREATMENT

Rising Cost

Table. Estimated Drug Costs for Eight Weeks of Treatment for Metastatic Colorectal Cancer.

Regimen	Drugs and Schedule of Administration	Drug Costs*
		$
Regimens containing fluorouracil		
Mayo Clinic	Monthly bolus of fluorouracil plus leucovorin	63
Roswell Park	Weekly bolus of fluorouracil plus leucovorin	304
LV5FU2	Biweekly fluorouracil plus leucovorin in a 48-hr infusion	263
Regimens containing irinotecan or oxaliplatin		
Irinotecan alone	Weekly bolus	9,497
IFL	Weekly bolus of fluorouracil plus irinotecan	9,539
FOLFIRI	LV5FU2 with biweekly irinotecan	9,381
FOLFOX	LV5FU2 with biweekly oxaliplatin	11,889
Regimens containing bevacizumab or cetuximab		
FOLFIRI with bevacizumab	FOLFIRI with fortnightly bevacizumab	21,399
FOLFOX with bevacizumab	FOLFOX with biweekly bevacizumab	21,033
Irinotecan with cetuximab	Weekly irinotecan plus cetuximab	30,790
FOLFIRI with cetuximab	FOLFIRI and weekly cetuximab	30,675

* Costs represent 95 percent of the average wholesale price in May 2004.

Rising Cost

- Ziv-Aflibercept Met CRC
  Median OS 1m> placebo
  (13 vs. 12months)
- Regorafinib Met CRC Median
  OS 1.4m>placebo
  (6.4 vs. 5months)

Addressing some drivers of Cost other than direct drug costs: ASCO's TOP 5

- For patients with advanced solid-tumour cancers who have a poor performance status and are unlikely to benefit, do not provide unnecessary anticancer therapy, such as chemotherapy, but instead focus on symptom relief and palliative care.
- Do not use PET, CT and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.
- Do not use PET, CT and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.
- For individuals who have completed curative breast cancer treatment and have no physical symptoms of cancer recurrence, routine blood tests for biomarkers and advanced imaging tests should not be used to screen for cancer recurrences.
- Avoid administering colony stimulating factors (CSFs) to patients undergoing chemotherapy who have less than a 20 percent risk for febrile neutropenia

Reality Check For Systemic Treatment

- Except for the Haematological Malignancies and GIST Tyrosine kinase inhibitors are not available to the majority of patients.
- Except for the Haematological Malignancies Monoclonal antibodies are not available to the majority of patients.
- Outside of clinical studies none of our patients in the public sector are likely to access newer cancer therapies

Existing Strategies to Limit Costs of Oncology Drugs

- More choices within therapeutic class
- Tiered formularies
- Step edits
- Prior authorization
- Quantity limits
- Cost transparency

Deborah Schrag MD MPH
Dana-Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts USA

Strengths Current Models:

- Structures that are essentially not for profit.
- Academically minded treatment guidelines and clear treatment exit criteria.
- Multidisciplinary review included in guideline criteria.
- Quality peer review and appeals process.
- Ethos of patient care and quality treatment.
- Broader access to quality cancer care through like minded role players coming together to increase patient access to QUALITY care, used RATIONALLY and in the most APPROPRIATE setting.
- Systems with outcomes driven to benefit patients and funders.

Conclusion

- The dichotomy of healthcare access across our continent is pronounced, it is the comfort of the adequately insured and discomfort of those who are not.
- The inequality of the haves versus the have-nots.
- The will of some of those in positions of power as opposed to the apathy of others.

Conclusion

- “It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair.”
  — Charles Dickens, A Tale of Two Cities

Thank you