Breast Cancer in Older Patients
What is new?

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EORTC
The future of cancer therapy

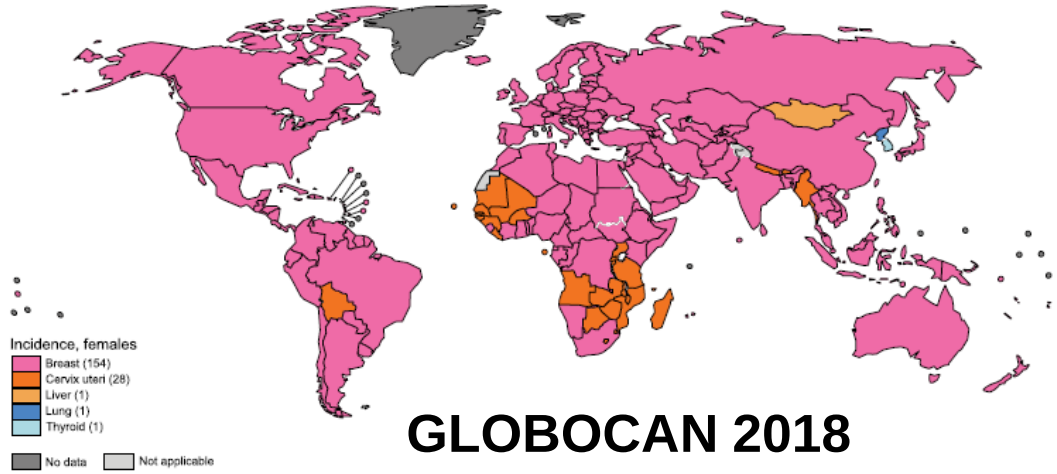
Conflicts of interest

- Receipt of grants/research supports
  - TEVA (Cephalon), HalioDX (Qiagen/Ipsogen), Amgen

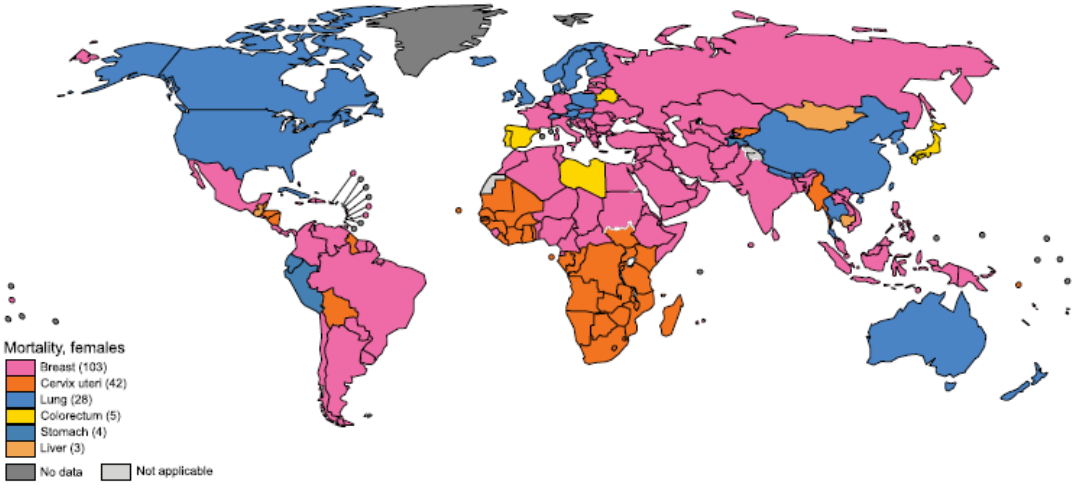
- Receipt of honoraria or consultation fees
  - AstraZeneca, BMS, Celgene, Clinigen, Hospira, Janssen, Mylan, OBI Pharma, Pfizer, Puma, Roche, Samsung

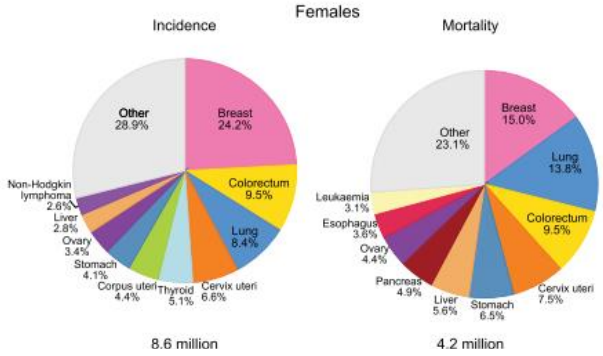
Highlights since 2017

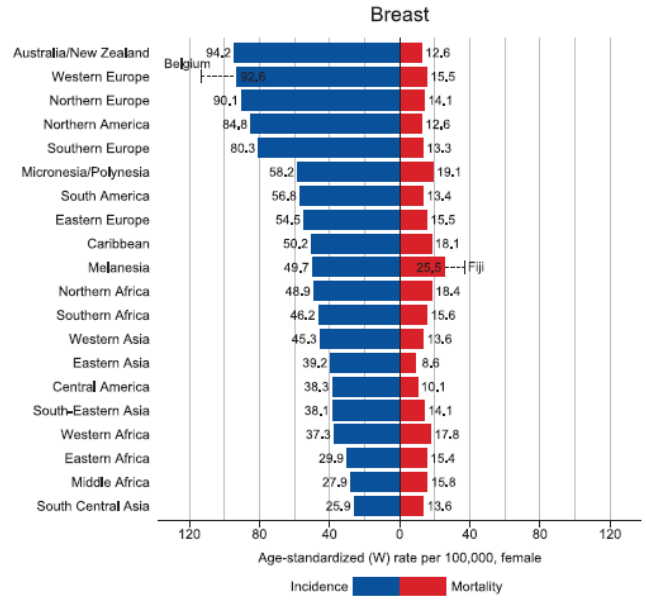
- Numbers and factfulness!
- Targeted treatments
- Prediction
- Some thoughts



GLOBOCAN 2018







Bray CA: A Cancer Journal for Clinicians 2018

- *Most common shortcut in statistics*

"1 in 8 women will develop BC in their lifetime"

instead of

"If everyone lived beyond the age of 70, 1 in 8 of those women would get or have had BC"

- *Since BC risk increases w/ age, lifetime risk changes depending on age*
  - *Age 20-29 1 in 2,000*
  - *Age 30-39 1 in 229*
  - *Age 40-49 1 in 68*
  - *Age 50-59 1 in 37*
  - *Age 60-69 1 in 26*
  - *Ever 1 in 8*

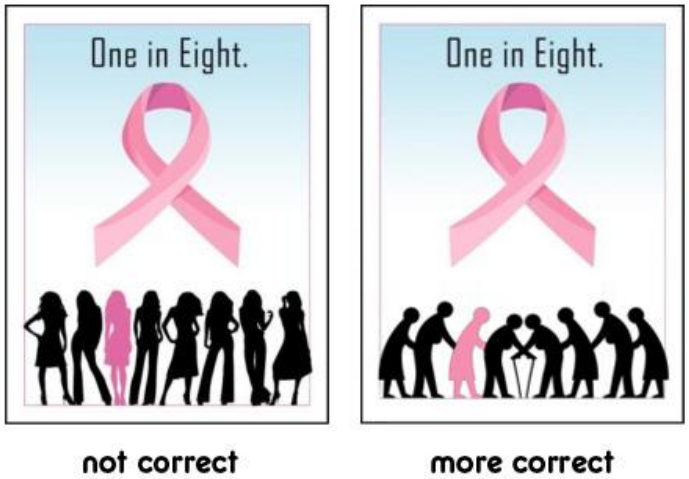


Table 2. Estimated Number of US Cancer Survivors as of January 1, 2014, by Sex and Age at Prevalance

	Male and Female			Male			Female		
	Number	Percent	Cumulative Percent	Number	Percent	Cumulative Percent	Number	Percent	Cumulative Percent
All ages	14,483,830			6,876,600			7,607,230		
0-14	60,620	<1%	<1%	38,210	1%	1%	22,410	<1%	<1%
15-19	48,690	<1%	1%	24,950	<1%	1%	23,740	<1%	1%
20-29	185,500	1%	2%	77,470	1%	2%	108,030	1%	2%
30-39	399,720	3%	5%	140,770	2%	4%	258,950	3%	5%
40-49	985,470	7%	12%	347,780	5%	9%	637,690	8%	14%
50-59	2,388,540	16%	28%	971,660	14%	23%	1,416,880	19%	32%
60-69	3,811,640	26%	54%	1,858,250	27%	50%	1,953,390	26%	58%
70-79	3,762,310	26%	80%	2,026,380	29%	80%	1,735,930	23%	81%
80+	2,841,340	20%	100%	1,391,130	20%	100%	1,450,210	19%	100%

Note: Percentages do not sum to 100% due to rounding.

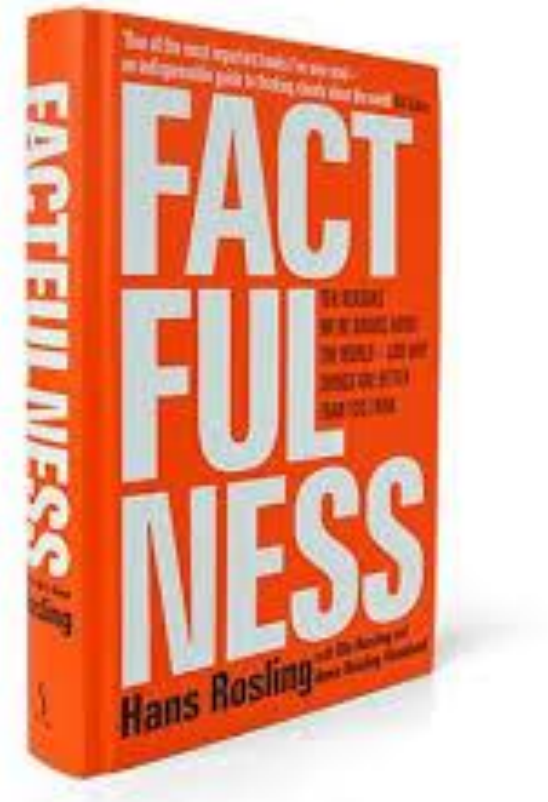
Source: Data Modeling Branch, Division of Cancer Control and Population Sciences, National Cancer Institute.

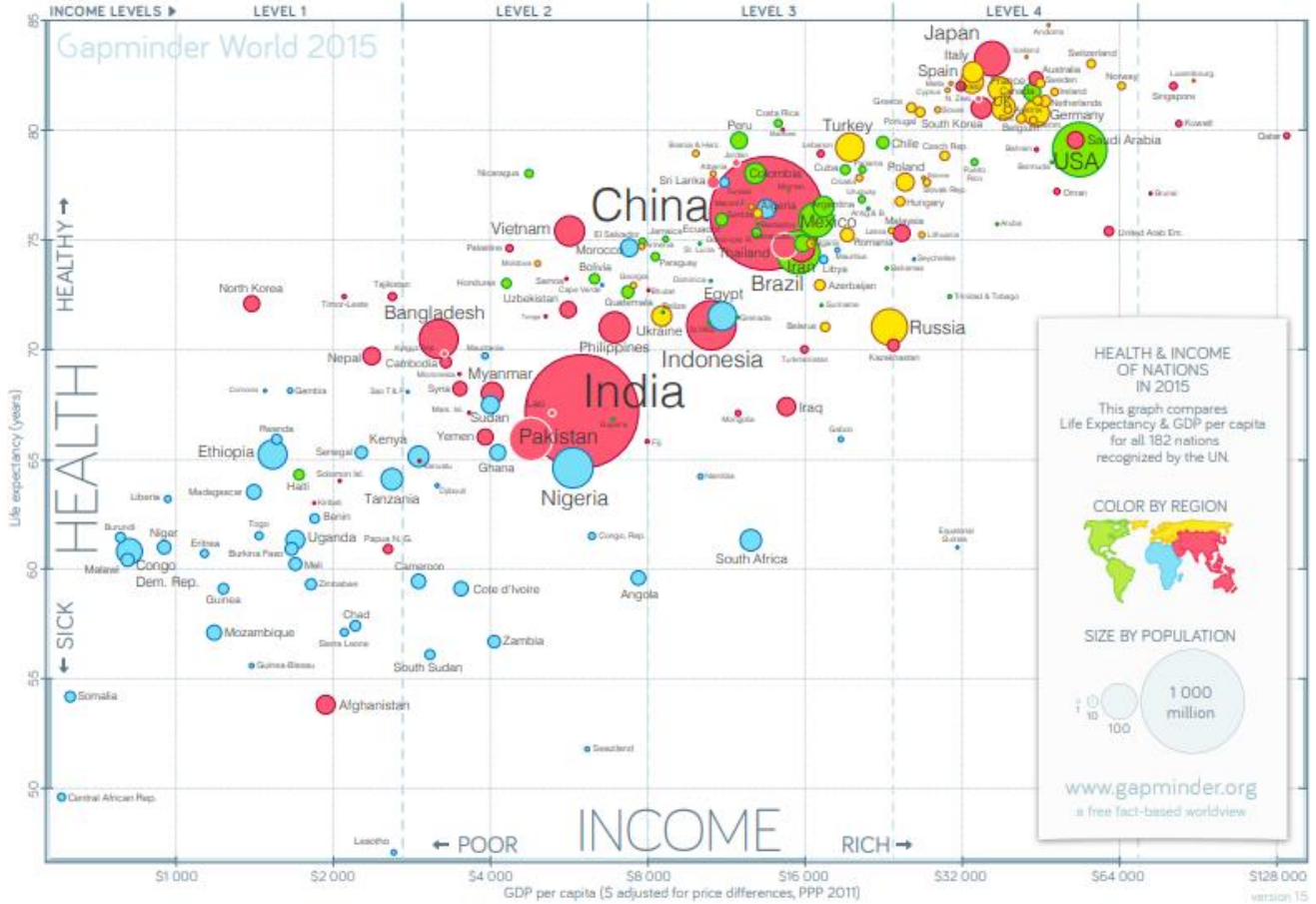
46% of cancer survivors are ≥ 70 yo

All adult oncologists are geriatric oncologists..

They just do not know it yet!

Trendalyzer



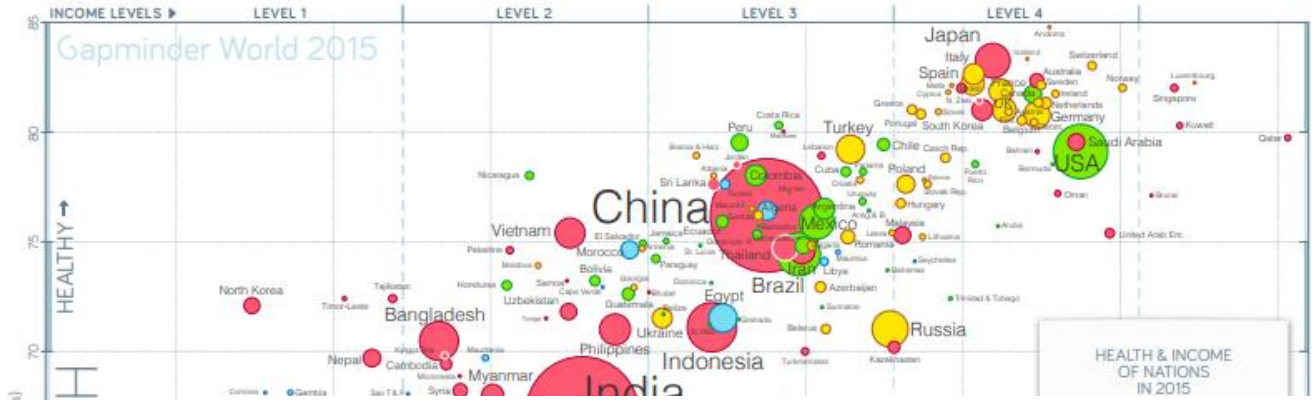


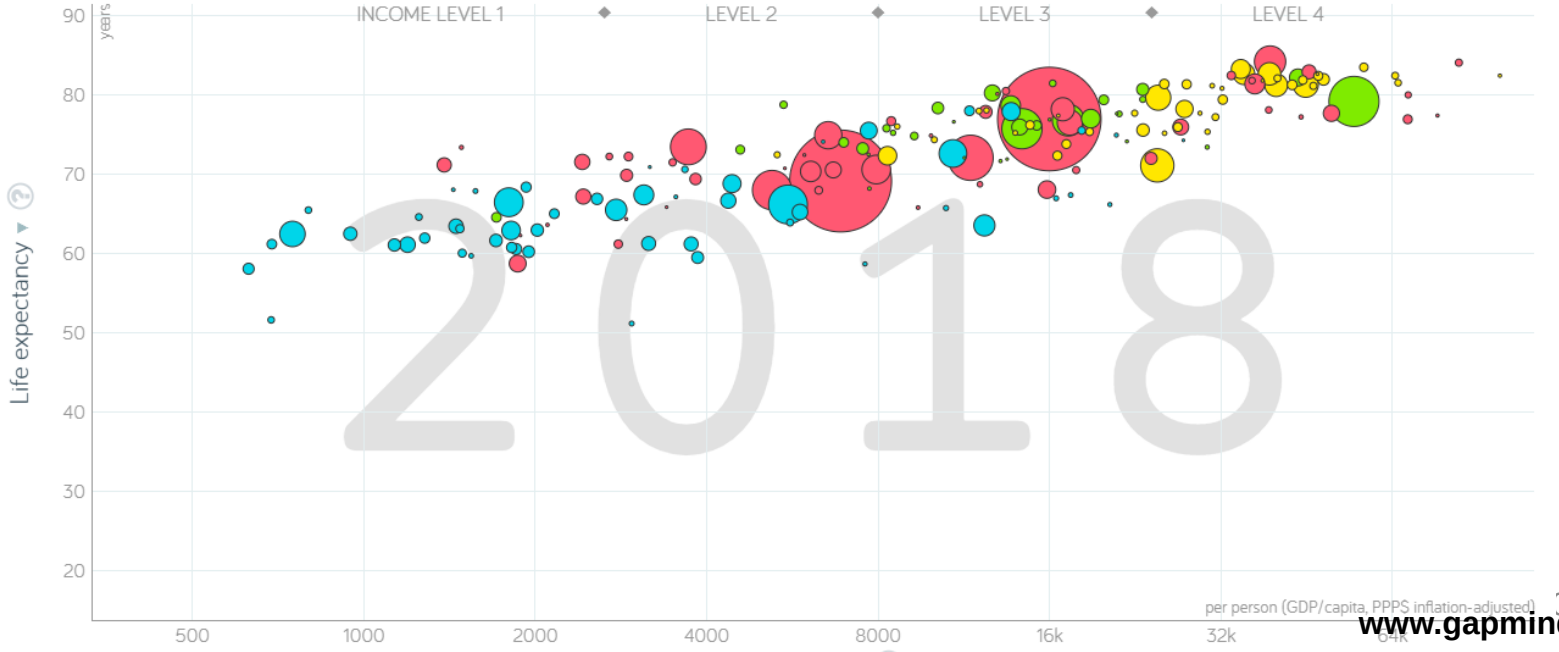
2015 Life Expectancy & Income

182 nations
bubble/country
size/population
color/region

www.gapminder.org

No simple dichotomy but 4 income levels
No country on level 4 has really short LE nor on level 1 has long LE
Most people in the middle, on levels 2 and 3 w/ huge ≠ in LE, depending on how income is used


INCOME LEVELS
LEVEL 1
LEVEL 2
LEVEL 3
LEVEL 4
Gapminder World 2015
HEALTHY
HEALTH
SICK
Life expectancy (years)
Japan
Italy
Spain
Germany
Turkey
Peru
Chile
Poland
Hungary
South Korea
Saudi Arabia
USA
China
Vietnam
Mexico
Brazil
Iran
Egypt
Russia
Indonesia
India
Bangladesh
Philippines
Ukraine
Nepal
Cambodia
Myanmar
Uzbekistan
North Korea
Somalia
Central African Rep.
Congo Dem. Rep.
Niger
Burundi
Malawi
$1 000
HEALTH & INCOME OF NATIONS IN 2015


INCOME LEVEL 1
LEVEL 2
LEVEL 3
LEVEL 4
years
Life expectancy
2018
per person (GDP/capita, PPPS inflation-adjusted)
500
1000
2000
4000
8000
16k
32k
www.gapminder.org

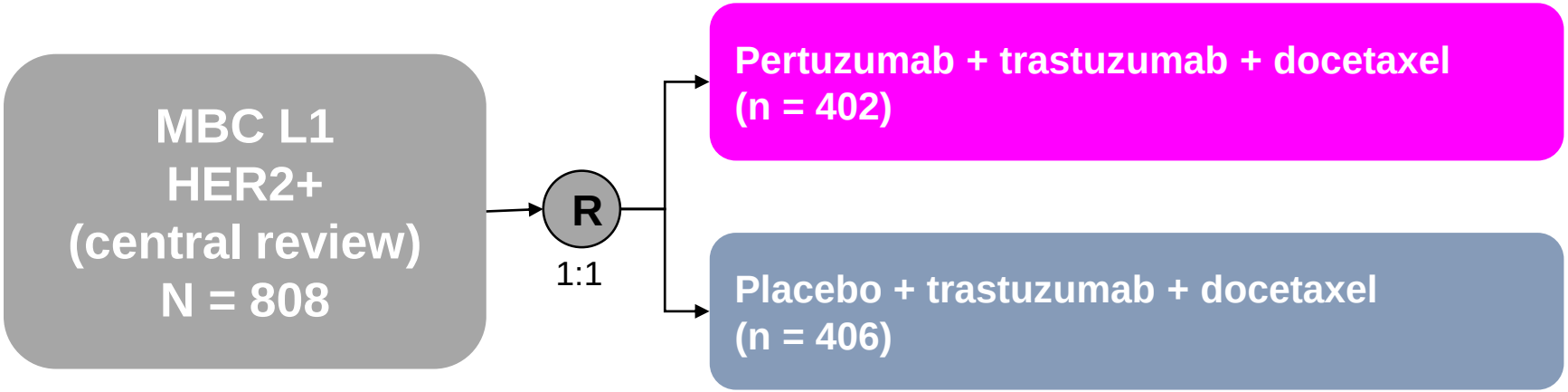
Few older adults included in registration studies! Breast cancer as an example

Agent Name	Approval	N	Age ≥ 65	N	Age ≥ 75
Palbociclib	2/2015	37	44%	8	10%
		86	25%		--
Everolimus	7/2012	290	40%	109	15%
Pertuzumab	6/2012	60	15%	5	1%
Eribulin mesylate	11/2010	121	15%	17	2%
Lapatinib	1/2010	34	17%	2	1%
		282	44%	77	12%
Ixabepilone	10/2007	45	10%	3	<1%
		32	13%	6	2.5%

Package Insert, "Geriatric Usage" section

Courtesy to Arti Hurria (adapted)

Cleopatra double-blinded phase III trial



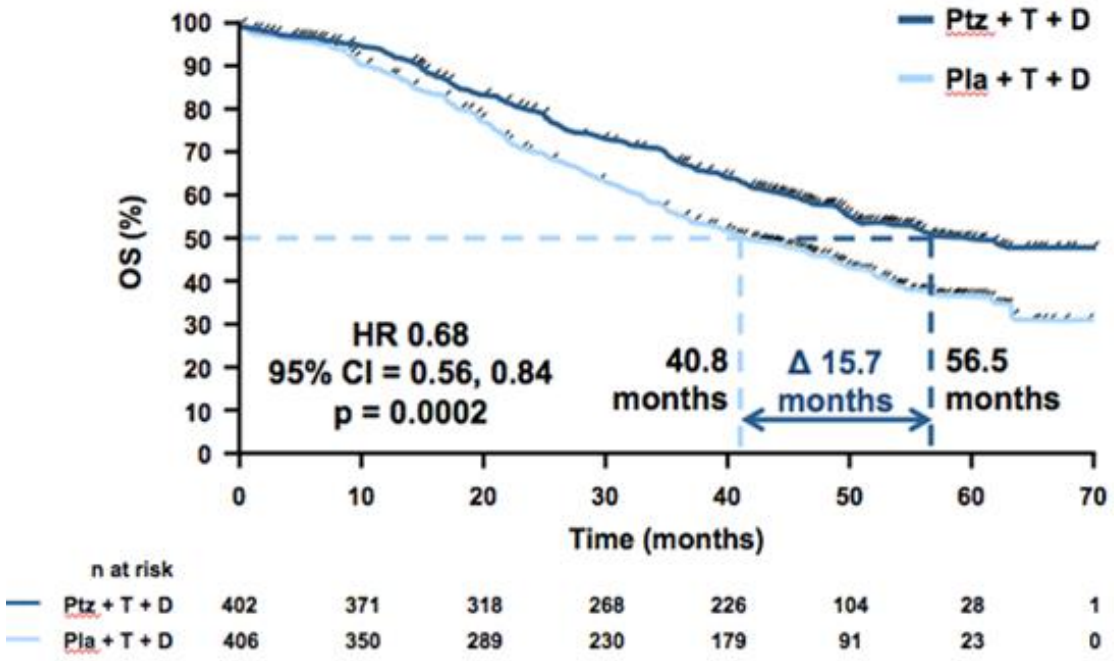
- Pertuzumab: 840 mg loading dose → 420 mg
- Trastuzumab: 8 mg/kg loading dose → 6 mg/kg
- Docetaxel: 75 mg/m^2 → 100 mg/m^2 depending on tolerance
- Primary objective: PFS
- Secondary objectives: OS, ORR, tolerance
- Stratification: geography, (neo)adjuvant treatment

Baselga N Engl J Med 2012

Cleopatra

Final OS Analysis

Median follow-up 50 months (range 0–70 months)

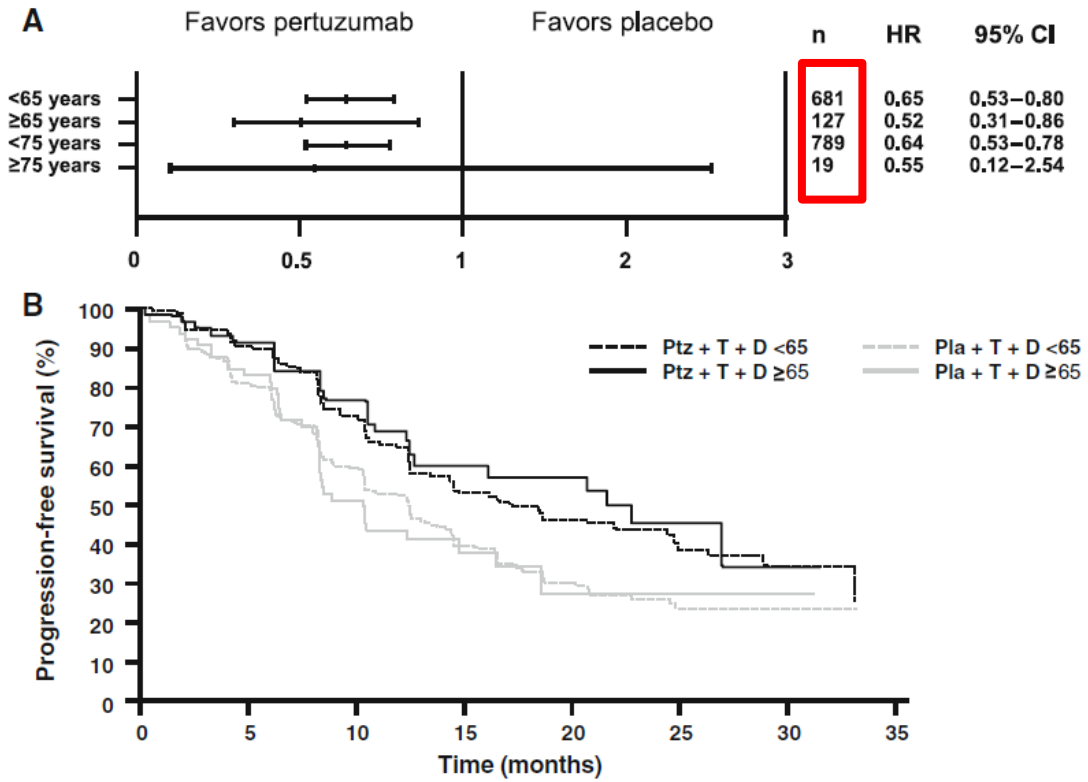


ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

CI, confidence interval; D, docetaxel; HR, hazard ratio; OS, overall survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab.

Swain ESMO 2014; Swain NEJM 2015

Pertuzumab



CLEOPATRA

808 patients

→ 127 (16%) 65+

→ 19 (2%) 75+

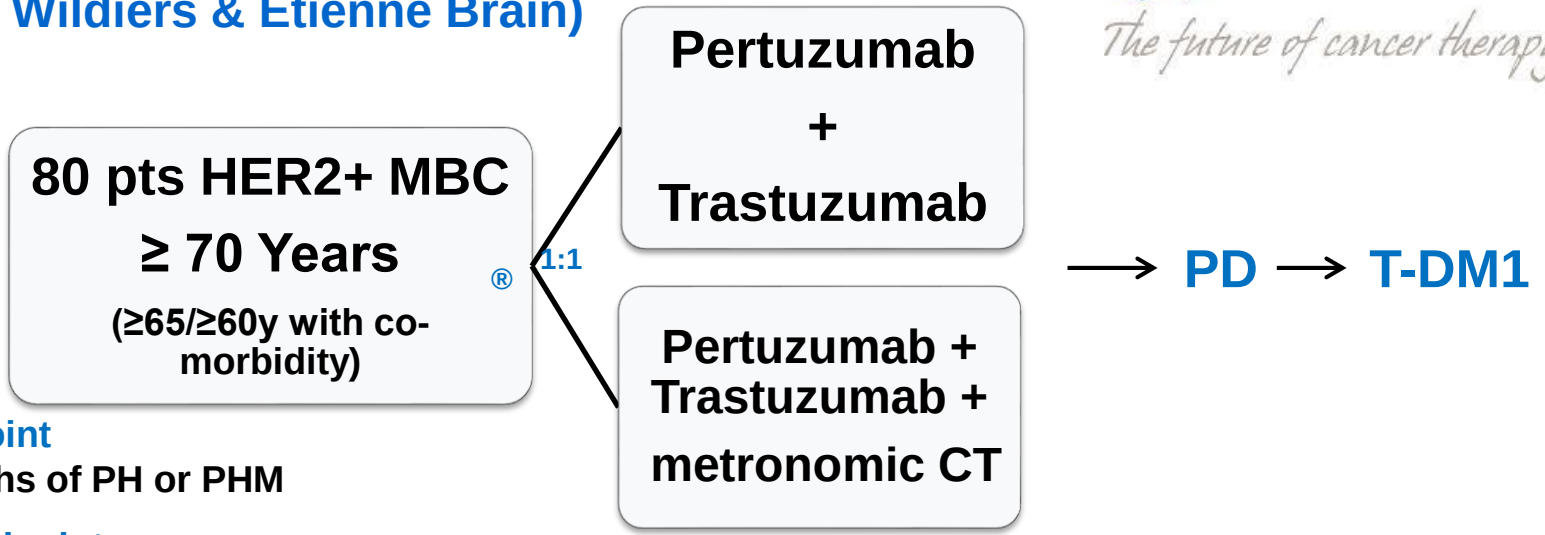
More frequent in elderly patients

- **Any grade**: diarrhea, asthenia, fatigue, anorexia, vomiting and dysgueusia
- **Grade 3**: diarrhea, peripheral neuropathy
- **Dose intensity**: 12% dose escalation , 31% dose reduction, 20-30% G-CSF

Miles Breast Cancer Res Treat 2013

EORTC 75111-10114

(Co-PI Hans Wildiers & Etienne Brain)



Primary endpoint

PFS at 6 months of PH or PHM

Secondary endpoints

OS, BCSS, toxicity, RR (RECIST v1.1), HRQoL, evolution of GA during treatment

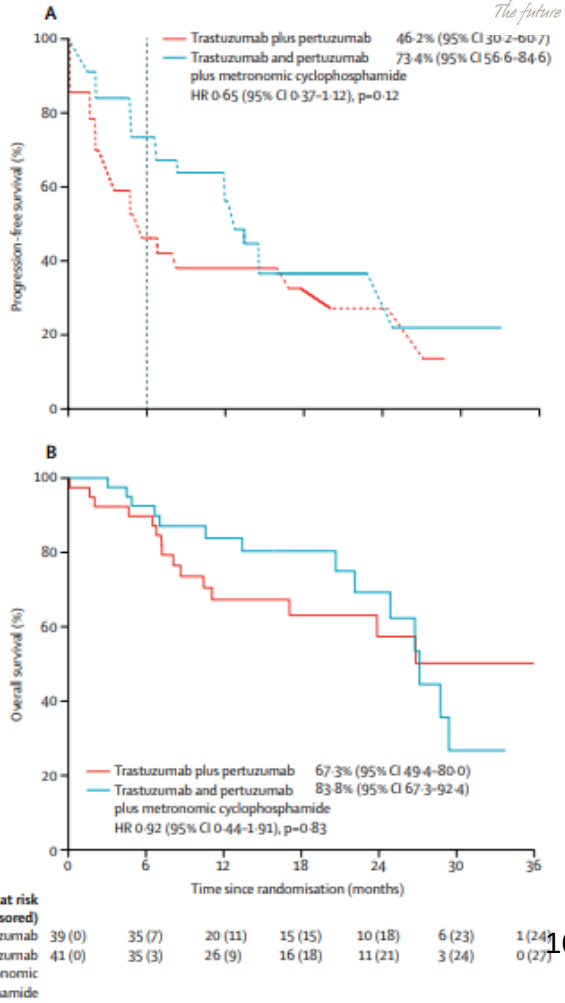
Stratification: ER/PgR, previous HER2 treatment, G8

Pertuzumab	**840 mg loading dose, further 420 mg q3w iv**
Trastuzumab	**8 mg/kg loading dose, further 6 mg/kg q3w iv**
Chemotherapy	**Metronomic chemotherapy: cyclophosphamide 50 mg/d po continuously**
On progression	**Option to have T-DM1** *(3.6 mg/kg iv q3w)* **till progression**

Wildiers Lancet Oncol 2018

Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group

Hans Wildiers, Konstantinos Tryfonidis, Lissandra Dal Lago, Peter Vuylsteke, Giuseppe Curigliano, Simon Waters, Barbara Brouwers, Sevilay Altintas, Nathan Touati, Fatima Cardoso, Etienne Brain



Elderly/frail HER2+ MBC population

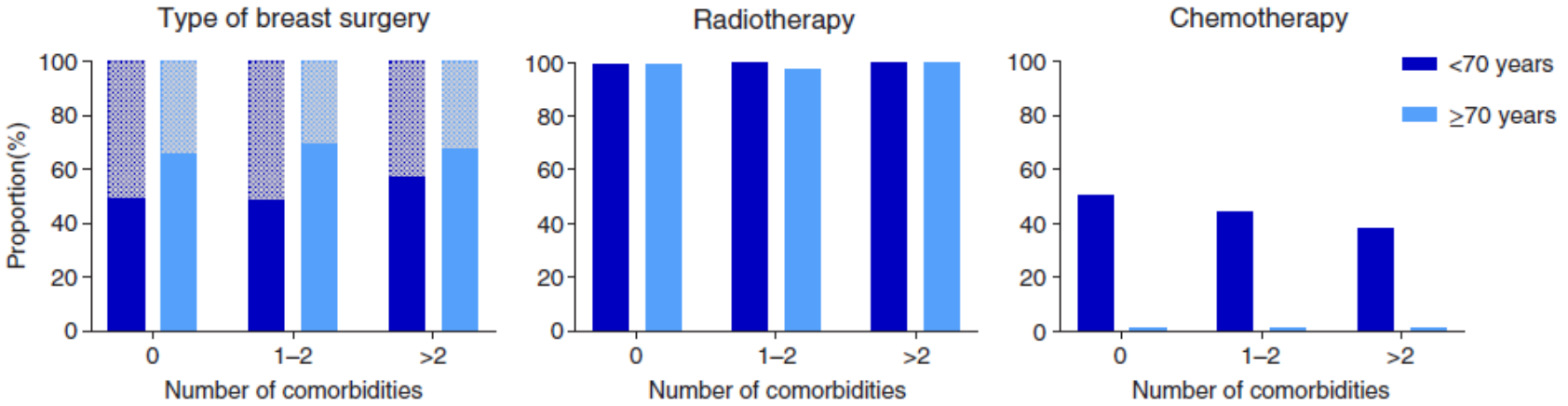
TP + metronomic CT > TP
(7-month longer median PFS: 12.7 vs 5.6)

Acceptable safety profile

T-DM1 at progression active

Wildiers Lancet Oncol 2018

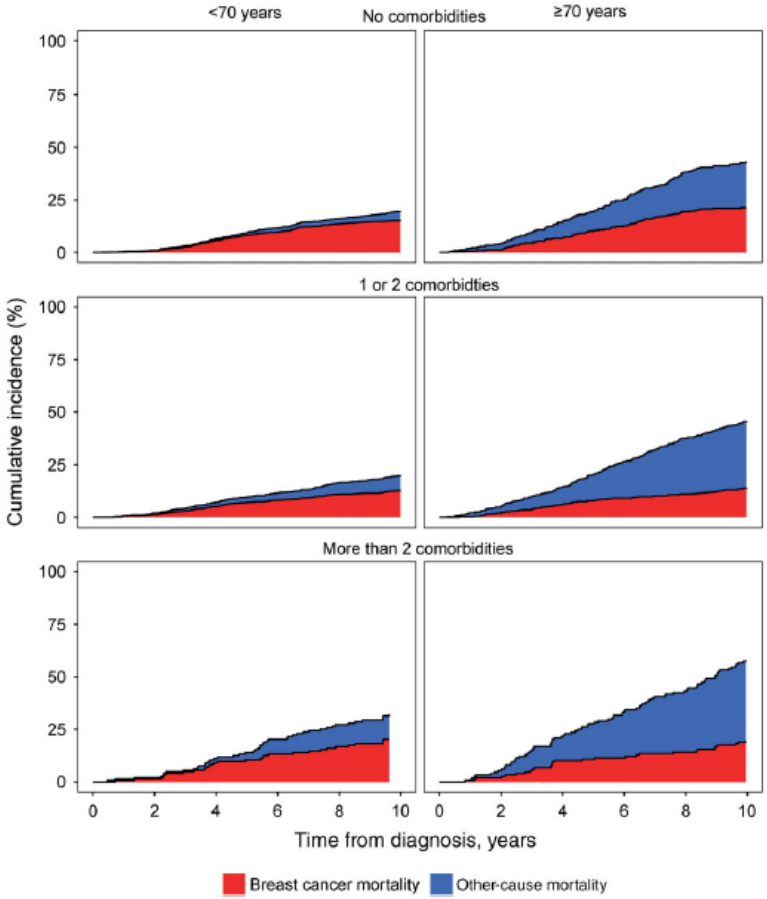
Competing risks for mortality



Dutch & Belgian postmenopausal pts w/ EBC ER+ in the TEAM trial (2001-2006) exemestane vs sequential tamoxifen → exemestane 5 yr

3,159 pts (70% <70 yr); median FU 10 yr; cumulative incidence of BC mortality

Competing risks for mortality

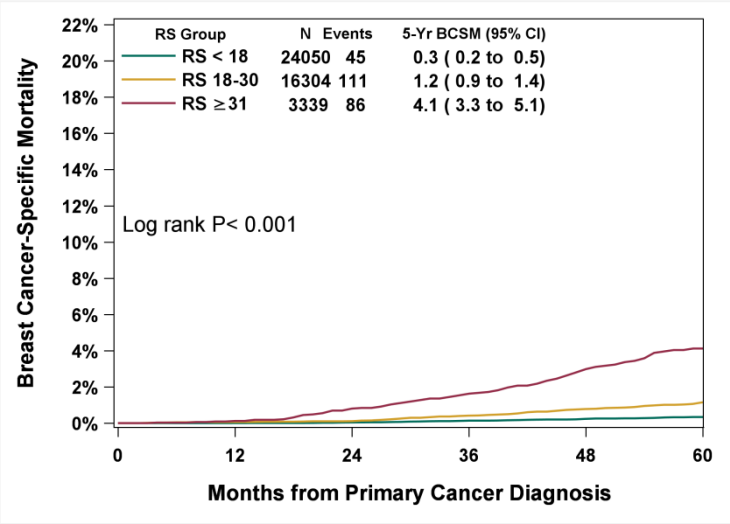


≥70 yr & no comorbidity (33%)
→ higher BC mortality

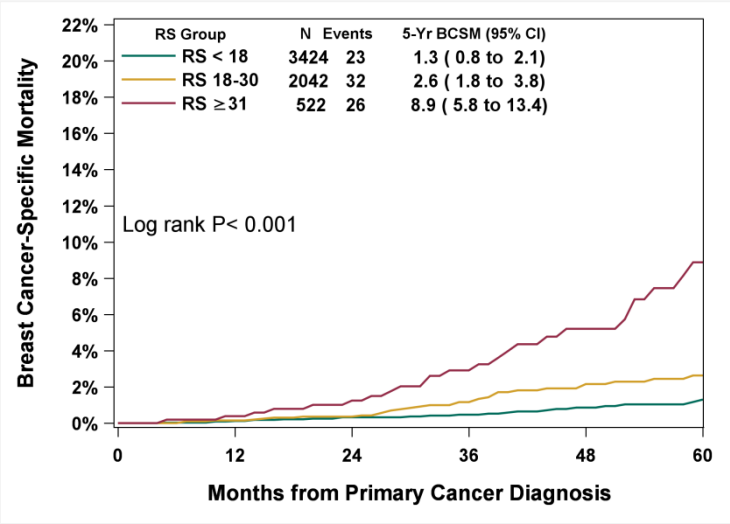
22.2%, 95% CI, 17.5–26.9 vs 15.6%, 95% CI, 13.6–17.7
sHR 1.49, 95% CI, 1.12–1.97, p = .005

5-year BCSM by Age and RS Group

Age <70 y



Age ≥70 y



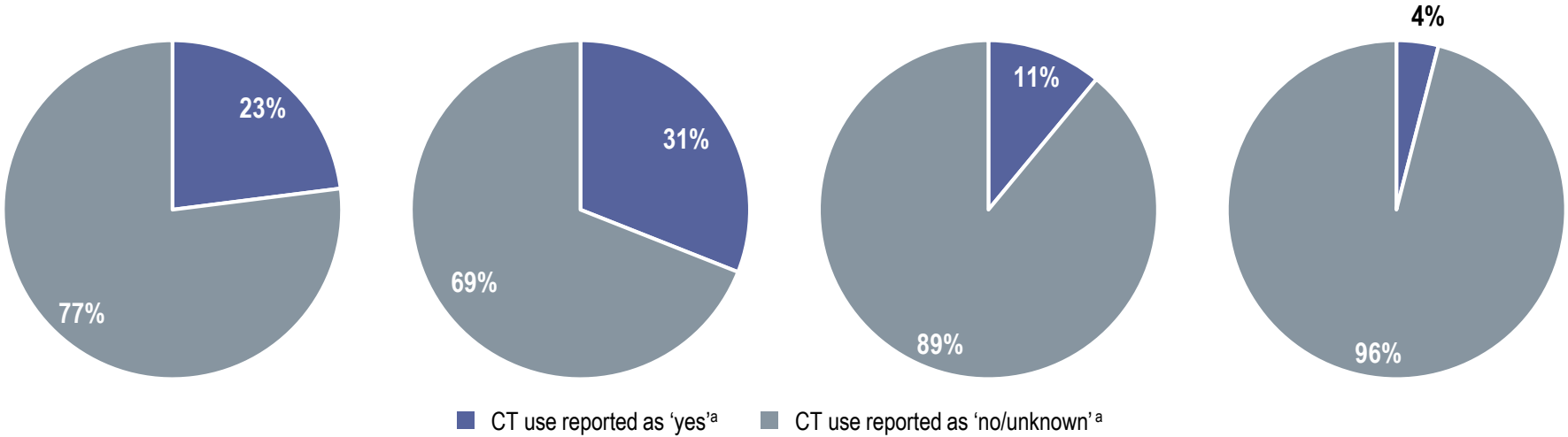
- RS predicts BCSM in both age groups (p<0.001)
- Low 5-y BCSM was observed with RS <18 in both age groups
- Higher 5-y BCSM was observed with RS 18-30 and RS ≥31 in older patients

COPENHAGEN 2016 ESMO congress

Shak ESMO 2016

Reported Chemotherapy (CT) Use

Age <70 years		Age ≥70 years	
Tested (N=43,693)	Not Tested (N=100,519)	Tested (N=5,988)	Not Tested (N=57,120)

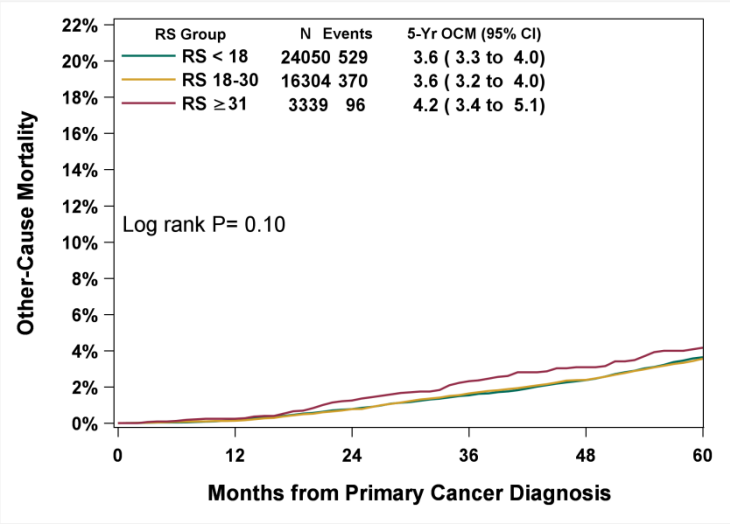


- CT use was lower in patients ≥70 years, in both RS-tested and untested cohorts

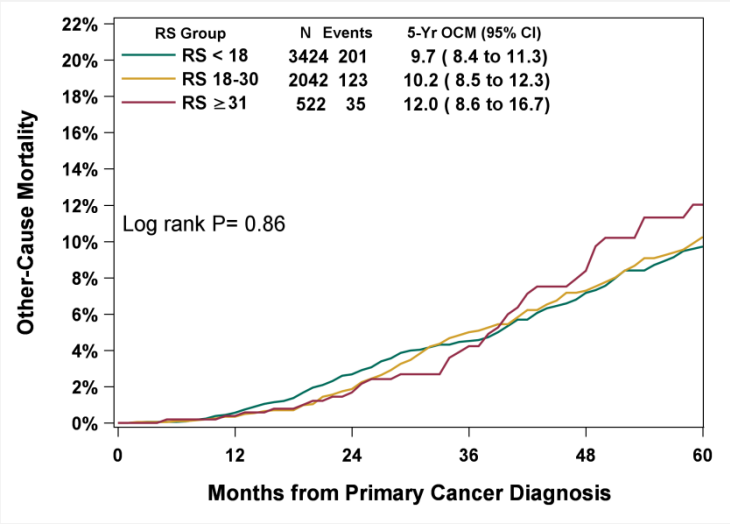
a. Chemotherapy use is known to be under-reported to SEER

5-year Other-Cause Mortality by Age and RS Group

Age <70 y



Age ≥70 y



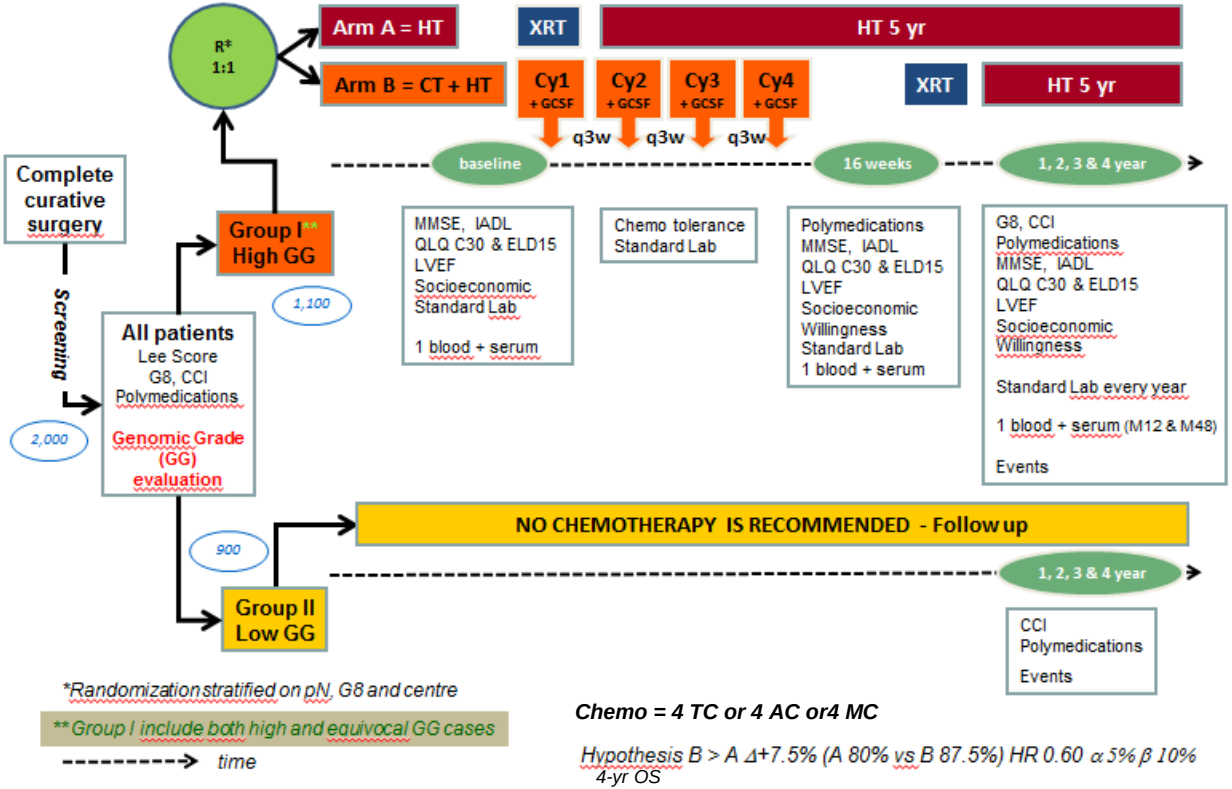
- As expected, RS group does not predict other-cause mortality (p=NS)
- As expected, higher other-cause mortality was observed in older patients

COPENHAGEN 2016 ESMO congress

Shak ESMO 2016

ASTER 70s (EUDRACT N° 2011-004744-22, PHRC national 2011, NCT01564056)

Adjuvant chemotherapy for ER+ HER2- BC in 70+ patients

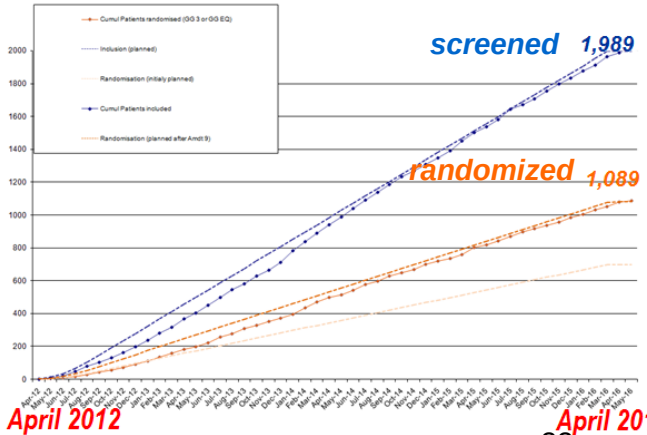


CGA

Microarray qRT-PCR

UNICANCER

GERICO



Chemo = 4 TC or 4 AC or4 MC

Hypothesis B > A Δ+7.5% (A 80% vs B 87.5%) HR 0.60 α 5% β 10%
4-yr OS

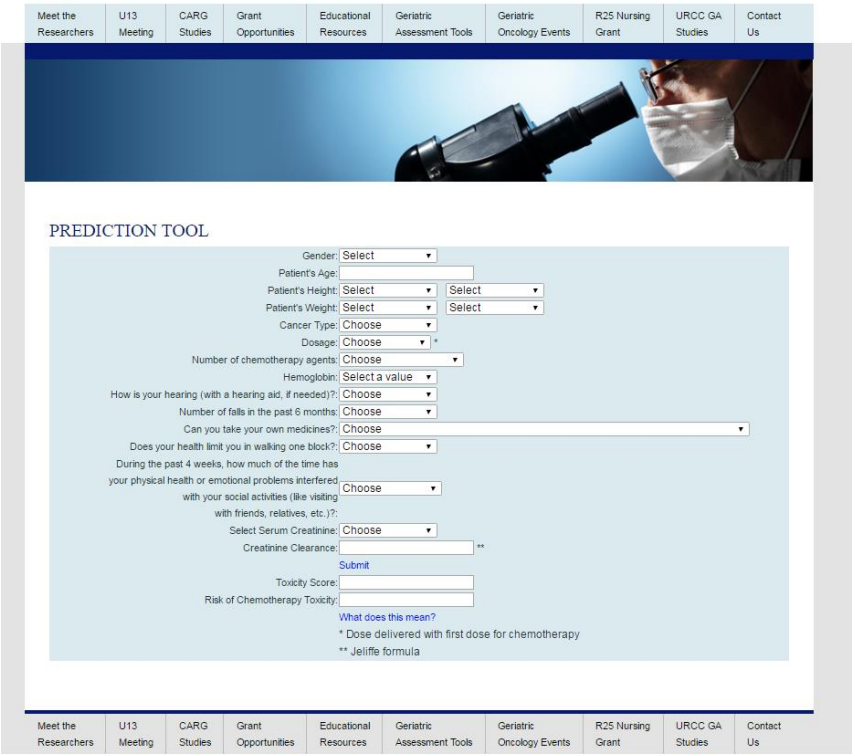
VOLUME 34 · NUMBER 20 · JULY 10, 2016
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

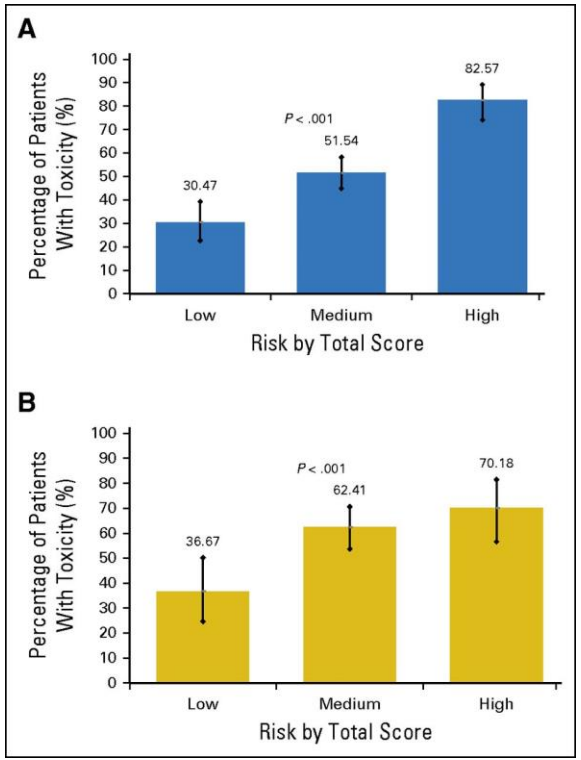
A true predictive model for chemo-related grade 3-5 toxicity

Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer

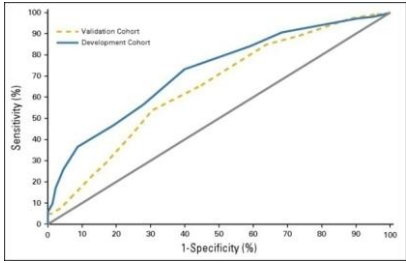
Arti Hurria, Supriya Mohile, Ajeet Gajra, Heidi Klepin, Hyman Muss, Andrew Chapman, Tao Feng, David Smith, Can-Lan Sun, Nienke De Glas, Harvey Jay Cohen, Vani Katheria, Caroline Doan, Laura Zavala, Abrahm Levi, Chie Akiba, and William P. Tew

CARG
CANCER & AGING RESEARCH GROUP





1. 58% grade ≥ 3 toxicity
2. Risk increased w/ increasing risk score
3. AUC/ROC 0.65 (95%CI 0.58-0.71) ~ development cohort 0.72 (95%CI 0.68-0.77) (*P* = .09)
4. No association between PS and chemo toxicity (*P* = .25)



Hurria J Clin Oncol 2016

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Arti Hurria
City of Hope
Duarte, USA
November 2018

CARG-BC

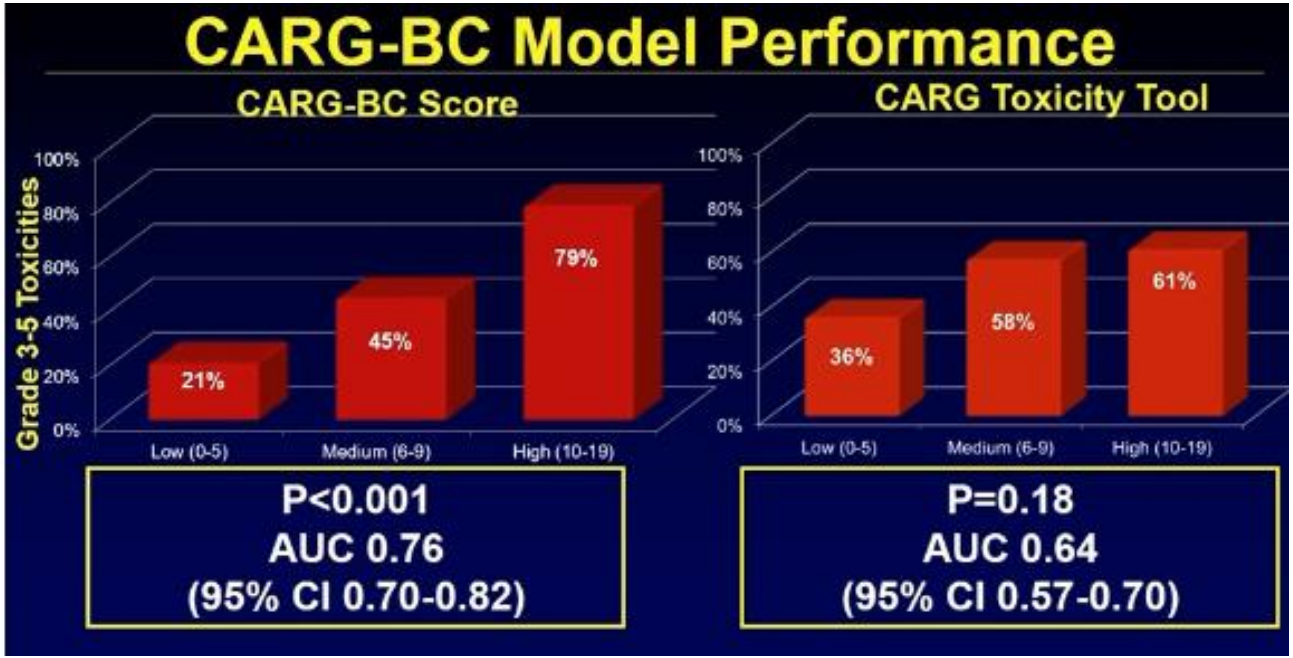
473 pts evaluable/501
- 283 development
- 190 validation

CARG-BC Risk Score

Risk factors for Gr. 3-5 Toxicity	OR (95% CI)	Score
CARG Score: Medium Risk High Risk	2.47 (1.35-4.51) 2.26 (0.70-7.35)	3
Anthracycline	1.37 (0.65-2.85)	1
Stage II/III	1.79 (1.00-3.23)	2
Duration of tx > 3 months	2.98 (1.46-6.09)	4
Abnormal liver function	2.21 (0.90-5.47)	3
Limited in walking a mile	2.22 (1.21-4.05)	3
Lack of someone to provide advice	2.34 (0.99-5.58)	3

Median age 70 (65-85)
Stage I/II/III 39%/41%/20%
TNBC/ER+/HER2+ER+/HER2+ER- 24%/48%/10%/17%
Grade 3-5 AEs 46% (Heme 25%/Non-Heme 36%)

CARG-BC



CARG-BC score → prediction of grade 3-5 toxicity better than CARG or KPS

But also: dose reduction, delay, reduced RDI, hospitalization

Adjuvant palbociclib as an alternative to chemotherapy for older patients with high risk luminal early breast cancer

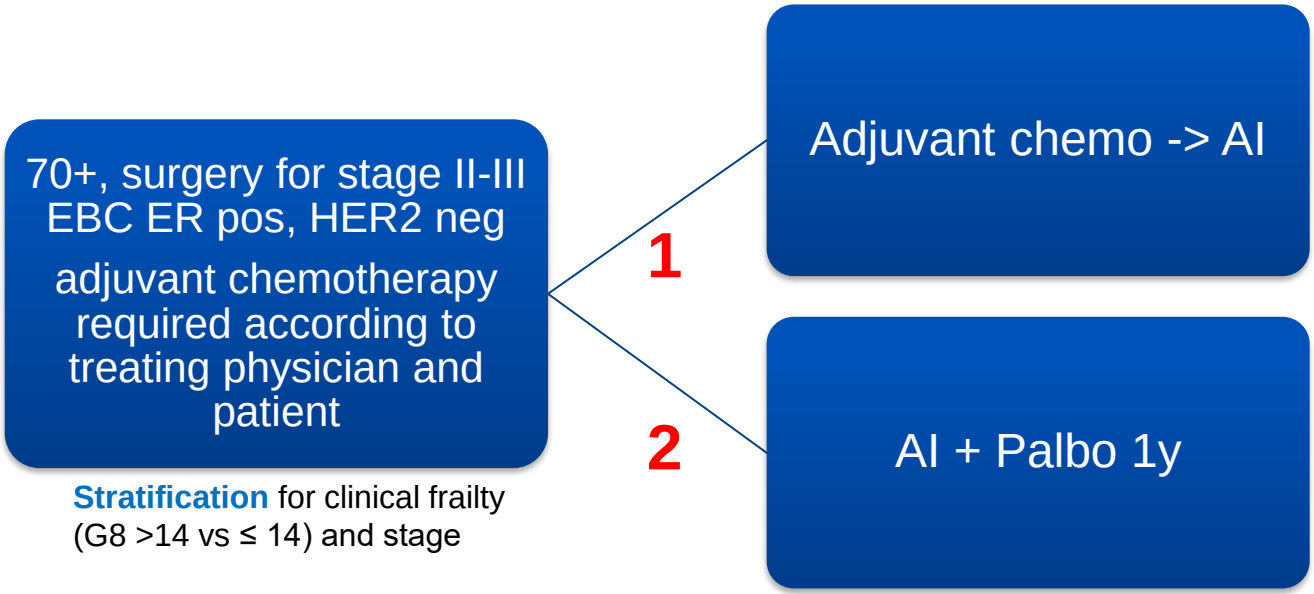
EORTC–ETF-BCG Study 1745 (APPALACHES)

Hans Wildiers & Etienne Brain

EORTC
The future of cancer therapy

BIG
Breast International Group

Non-comparative randomized (2:1) phase II study



Stratification for clinical frailty (G8 >14 vs ≤ 14) and stage

366 patients required (244:122)
Accrual 2y
80 centres required

Pros:
- Easy endpoint, clinically relevant
- Feasible numbers
- Similar endpoint in 1 arm was used in Mindact and Tolaney study (both NEJM)
- If study is + (88% not included in CI), the conclusion and consequences can be similar as for Mindact and Tolaney study: new standard
- QoL and OS/BCSS can be compared to chemo as secondary

Cons:
- No formal comparison w/ chemo group for primary endpoint
- Less data on QoL/OS/BCSS versus chemo

Adjuvant chemo choice:
- 4 TC + G-CSF
- 4 EC or AC + G-CSF
- 12 taxol weekly

Primary endpoint
3y DRFI *(distant metastases or death from breast cancer)* for AI+Palbo arm
- 3-year DRFI of <88% is unacceptable.
- 3-year DRFI of ≥93% is success

EORTC The future of cancer therapy
BIG Breast International Group

Tumour extent
TNM

General health status
Geriatric assessment
Life expectancy
Treatment toxicity

Tumour biology
Luminal A/B
HER2 & TNBC
Gene expression profile

Patient preference & acceptability

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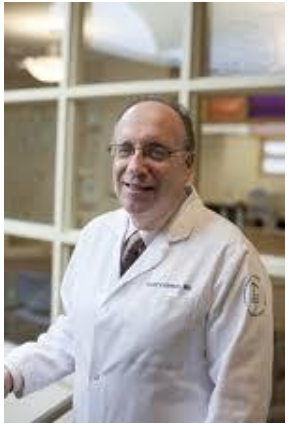

Stuart Licthman
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Key persons: *Matti Aapro, Lodovico Balducci*

SIOG Global Policy Meeting 14th November (UN venue)
SIOG Annual Conference 15th-16th November (International Conference Centre Geneva CICG)

Optimising treatment in older cancer patients is precision medicine too!

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GERIATRIC ONCOLOGY
ADVANCED COURSE
TREVISO, ITALY
JUNE 27-30, 2018

UNIVERSITÀ CATTOLICA del Sacro Cuore

6th edition
26-29/06/2019