bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

7-8 MARZO 2025
NAPOLI
Hotel Royal Continental
Via Partenope, 38

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Introduzione e place in therapy best papers

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SSD Ricerca Clinica e Traslazionale in Senologia
Incarico di Alta Specializzazione « Terapie Sperimentali e sviluppo di nuovi protocolli nel tumore mammario»
IRCCS Fondazione Giovanni Pascale, Napoli

Disclosure

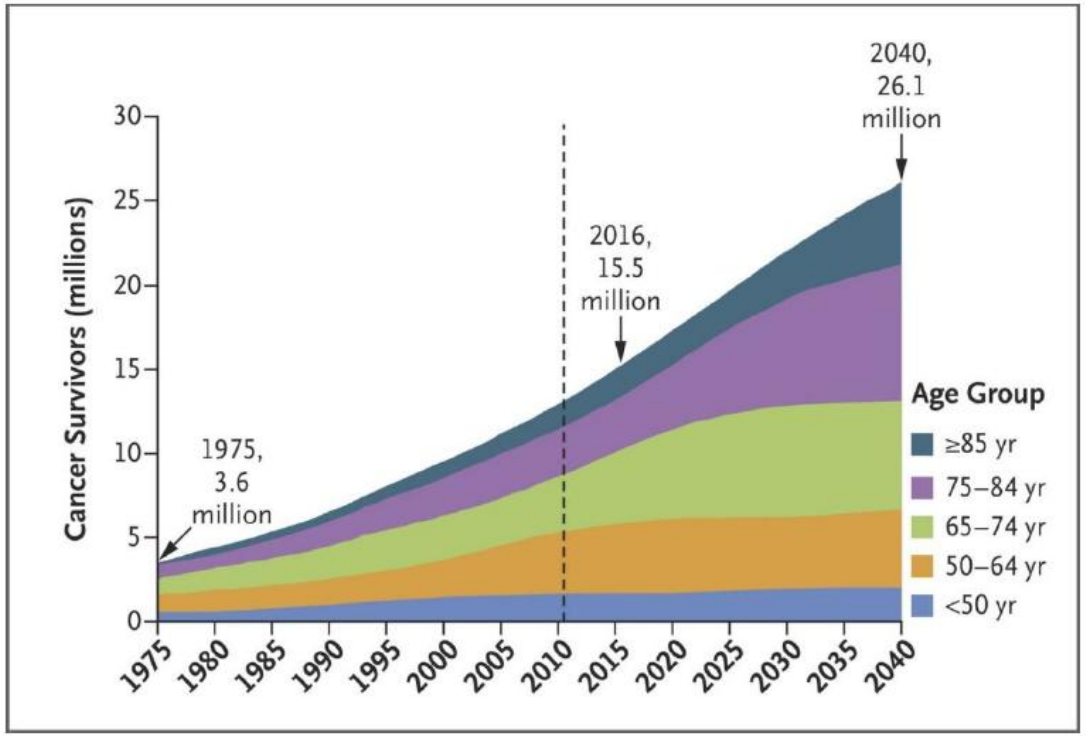
- ✓ Consulting/Advisor: Roche, AstraZeneca, Lilly, Daichii Sankyo, Novartis, Seagen, MSD, Gilead, Pfizer, Pierre-Fabre, Menarini
- ✓ Honoraria: Novartis, Lilly, AstraZeneca, Daichii Sankyo, Veracyte, Pfizer, Gilead, MSD,Gentili, EllevaPharma
- ✓ Research funding to the Institution: Gilead
- ✓ Travel, accommodation, expenses: Lilly, Novartis, Gilead, Accord

Best Papers Under 40

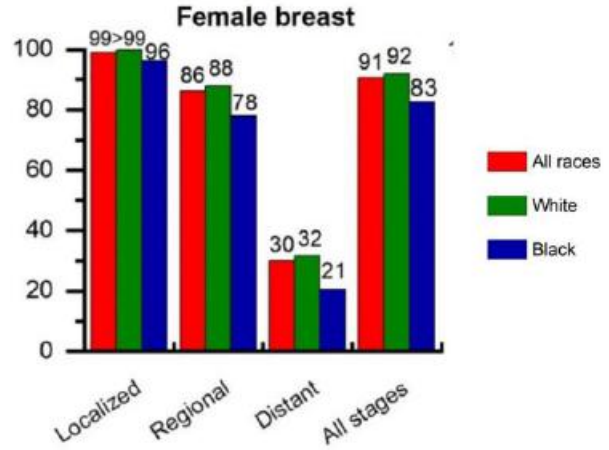
Long-term behavioral symptom clusters among survivors of early-stage breast cancer. Development and validation of a predictive model.
Martina Pagliuca et al.

Clinico-pathological predictors of radiologic complete response to first-line anti-HER2 therapy in metastatic breast cancer
Linda Cucciniello et al.

An Increasing Number Of Cancer Survivors



Cancer Survivors worldwide, by age group 1975-2040

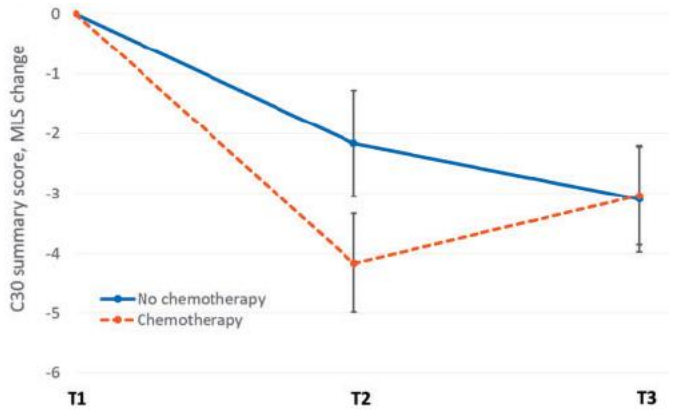


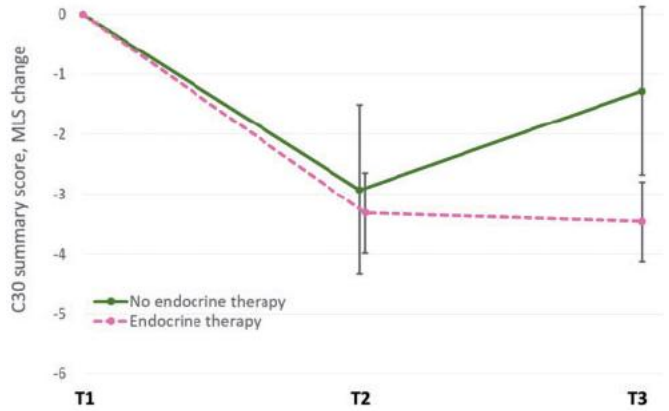
5 year survival, US, SEER

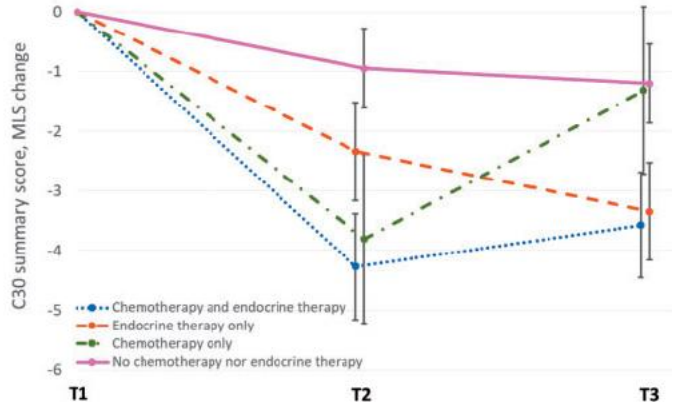
Miller KD, CA Cancer J Clin 2022; Shapiro CL, NEJM 2018, Siegel CA Clinicians, 2023.

Differential impact of ET and CT on QOL of breast cancer survivors

- The overall QoL was negatively impacted 2 years after diagnosis in the general population (C30-SumSc,P<0.001).
- Only ET was associated with deteriorated C30-SumSc 2-years after diagnosis (P= 0.004) that persisted over time . In contrast,after a transient deterioration, there was no detrimental effect of CT on C30-SumSc at 2 years (P= 0.924)

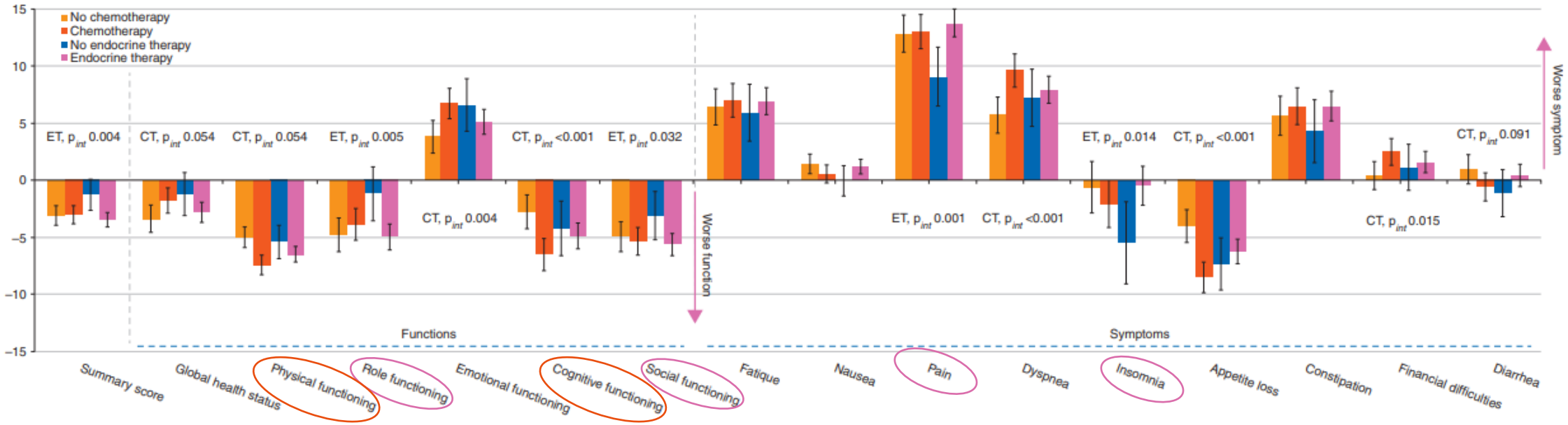






Ferreira, Annals of Oncology 2019

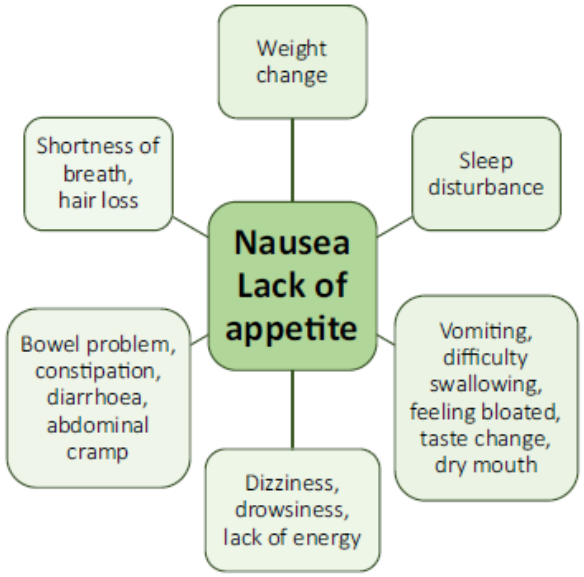
QOL Among Survivors with Early-Stage BC



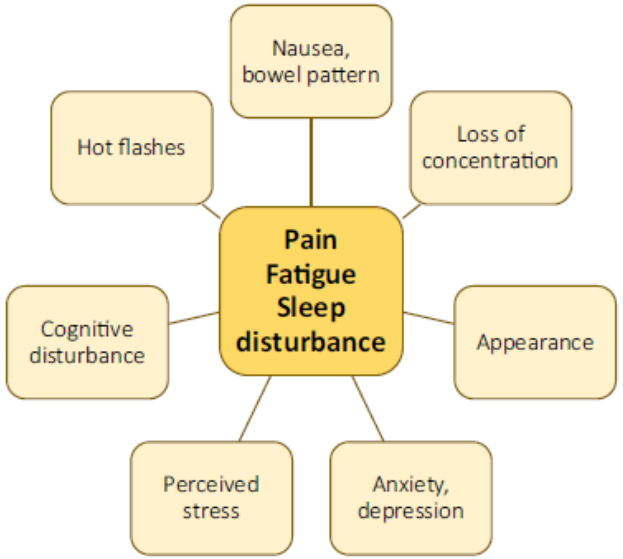
Ferreira, Annals of Oncology 2019

Long-term symptom burden among survivors

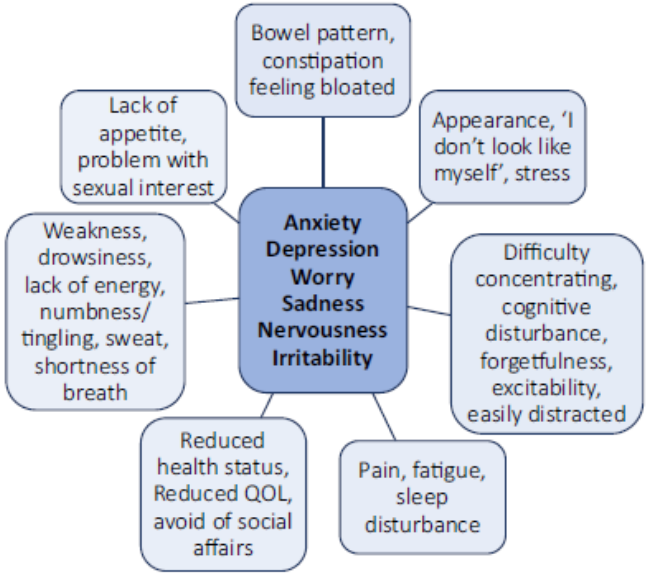
CLUSTERS: A Sets of 3 or more concurrently present and inter-related symptoms



The Gastrointestinal Cluster



Pain-fatigue-sleep disturbance

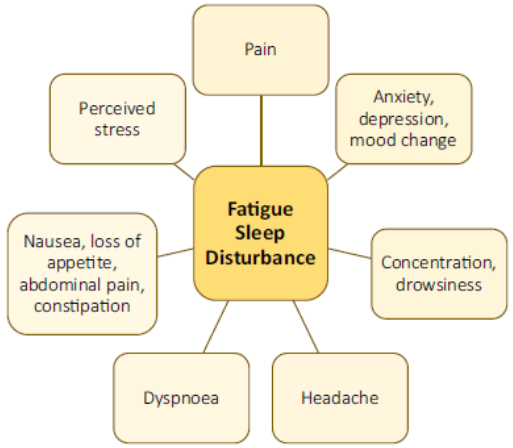


The Psychological Cluster

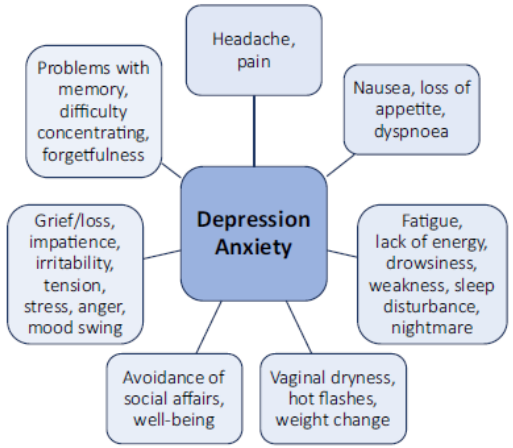
During Treatment

Winnie K. W. So et al, Cancer Medicine 2021

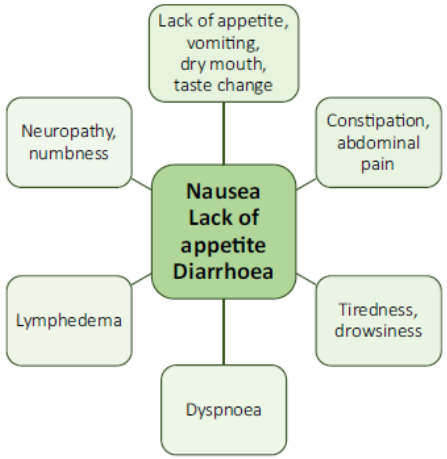
Long-term symptom burden among survivors



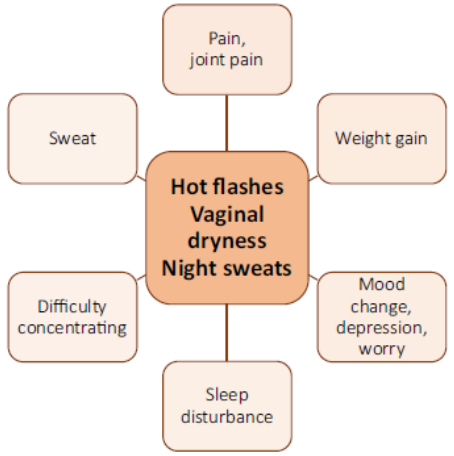
Fatigue-sleep disturbance



The Psychological Cluster



The Gastrointestinal Cluster



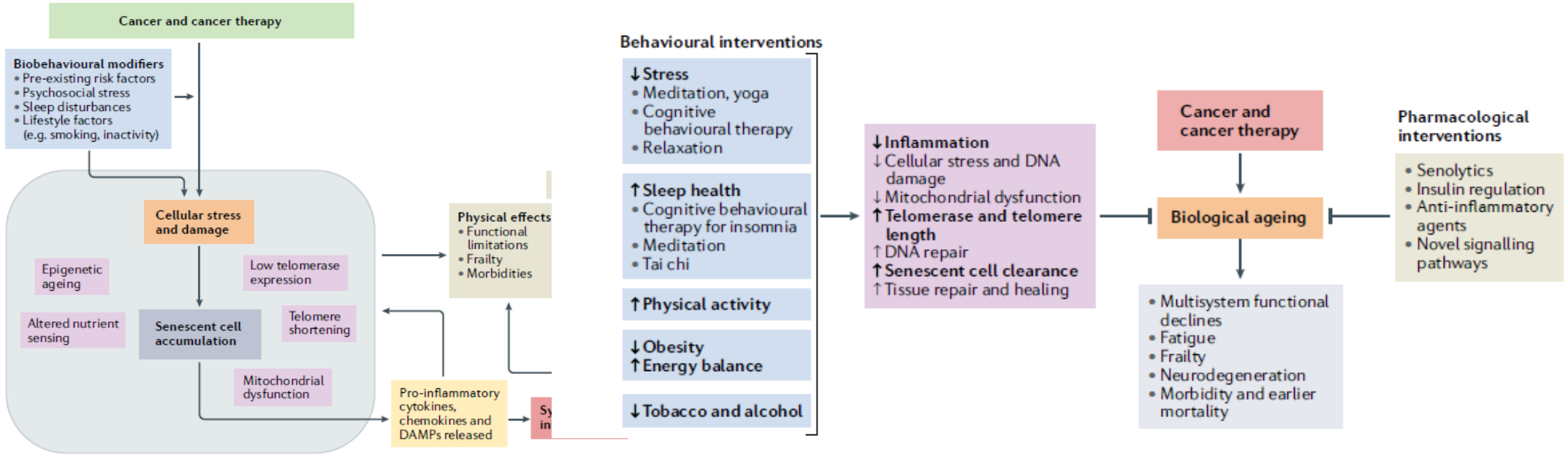
The Menopausal Cluster

After Treatment

Winnie K. W. So et al, Cancer Medicine 2021

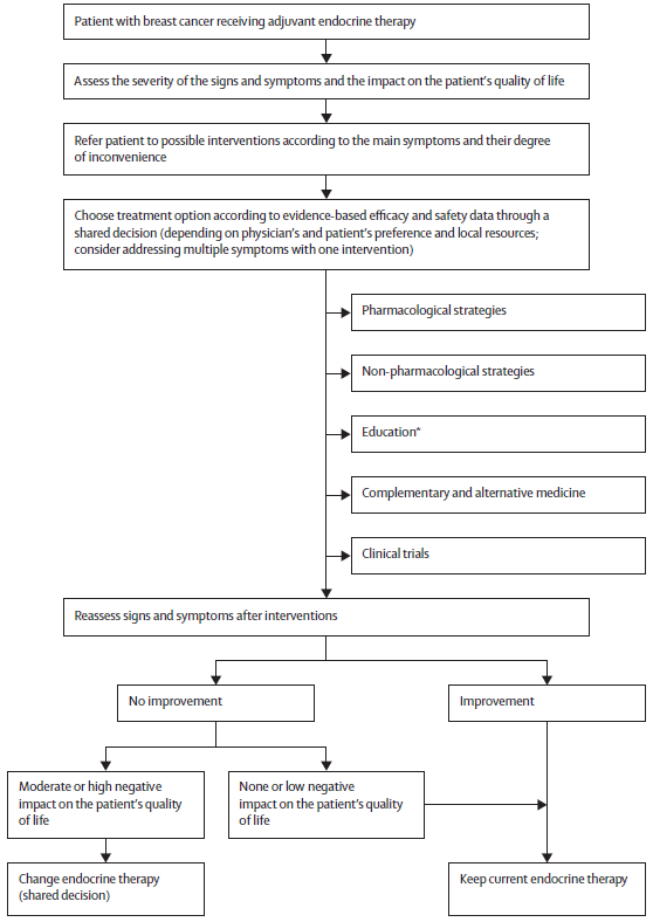
Cancer- related accelerated ageing and biobehavioural modifiers

Cancer-related behavioral symptoms are reported as moderate to severe by as many as 50% to 70% of pts after breast cancer treatment, greatly impairing daily functioning



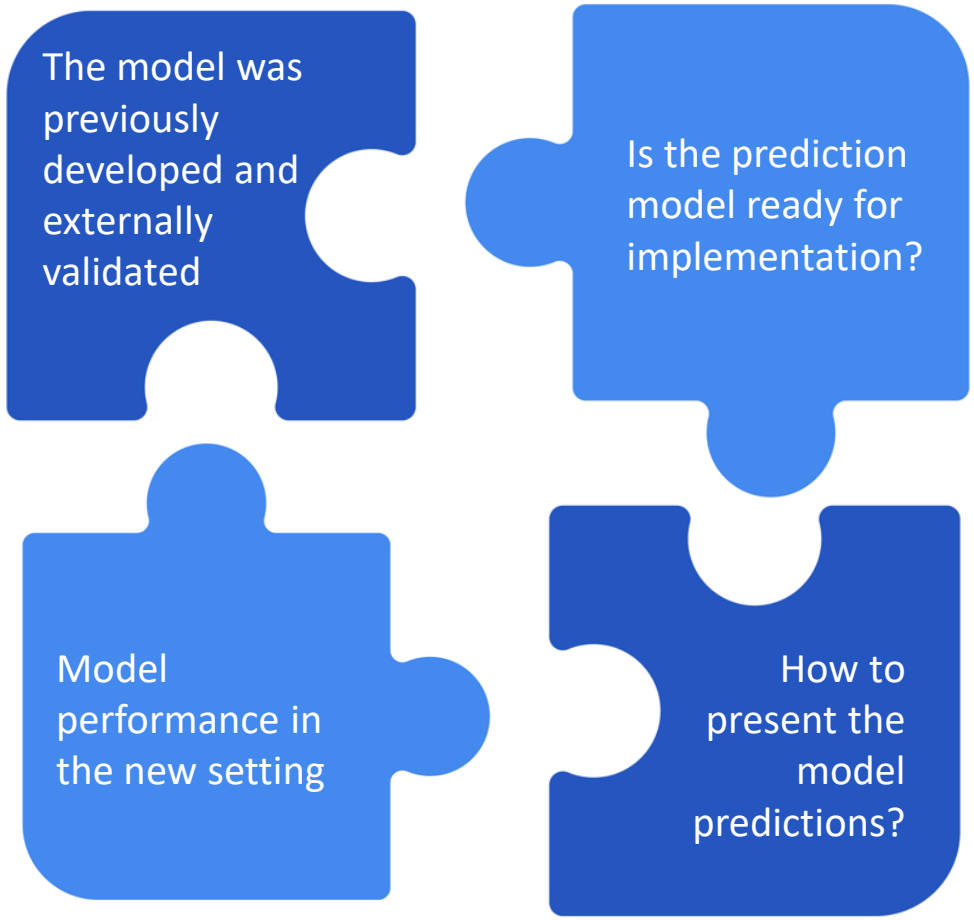
Judith Carroll et al. Nature Reviews 2022

Ensure Supportive Care Delivery



Franzoi M.A. et al. Lancet of Oncology 2021

Evaluating the impact of prediction model

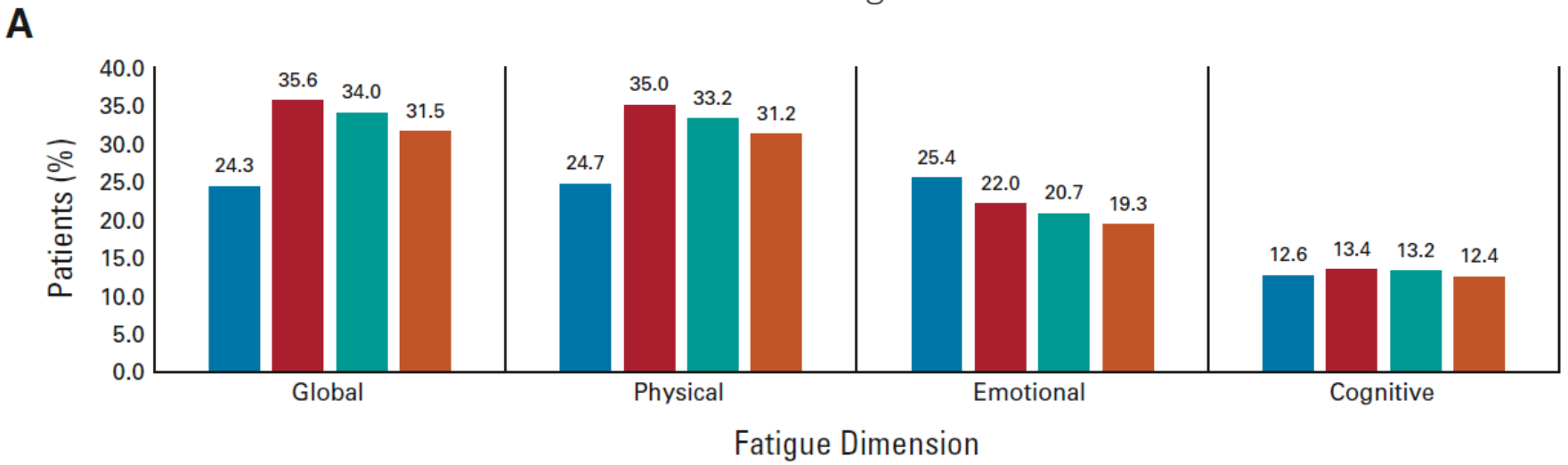


Facilitators: features that increase the ease of use of a prediction model

- ✓ Add a decision recommendation to the predicted probabilities
- ✓ Automatic calculation and presentation of the model's probability within the physician's workflow

Predictive risk models, a case-study: cancer-related fatigue (CRF)

Prevalence of severe CRF among breast cancer survivors



Global, No.		
Time Point	Severe	Nonsevere
Baseline	1,384	4,308
T1	2,006	3,634
T2	1,700	3,300
T3	1,073	2,327

Physical, No.		
Time Point	Severe	Nonsevere
Baseline	1,387	4,217
T1	1,968	3,659
T2	1,661	3,337
T3	1,061	2,337

Emotional, No.		
Time Point	Severe	Nonsevere
Baseline	1,420	4,165
T1	1,231	4,375
T2	1,032	3,961
T3	650	2,727

Cognitive, No.		
Time Point	Severe	Nonsevere
Baseline	705	4,894
T1	751	4,874
T2	658	4,344
T3	420	2,976

Baseline: diagnosis (dx)
T1: year-1 post-dx
T2: year-2 post-dx
T3: year-4 post-dx

Di Meglio A et al, J Clin Oncol 2022

Predictive risk models, a case-study: cancer-related fatigue (CRF)

Predictive Model of the Risk of Severe Fatigue at 2 Years After Diagnosis

Variable	OR	95% CI	β Coefficient	95% CI	*P*
Severe pretreatment fatigue,[a] yes versus no	3.191	2.704 to 3.767	1.160	0.995 to 1.326	< .0001
Age, continuous (for 1-year decrement)	1.015	1.009 to 1.022	–0.015	–0.021 to –0.0088	< .0001
BMI, continuous (for unit increment)	1.025	1.012 to 1.038	0.025	0.012 to 0.038	.0001
Tobacco use behavior, former versus never	1.243	1.055 to 1.463	0.217	0.053 to 0.381	.009
Tobacco use behavior, current versus never	1.552	1.291 to 1.866	0.440	0.256 to 0.624	< .0001
Anxiety,[b] doubtful case versus noncase	1.063	0.895 to 1.262	0.061	–0.110 to 0.233	.485
Anxiety,[b] case versus noncase	1.265	1.073 to 1.492	0.235	0.070 to 0.400	.005
Insomnia,[a] continuous (for unit increment)	1.005	1.003 to 1.007	0.0048	0.0026 to 0.0070	< .0001
Pain,[a] continuous (for unit increment)	1.014	1.010 to 1.017	0.014	0.010 to 0.017	< .0001
Intercept			–1.445	–1.912 to –0.978	< .0001
AUC (95% CI)			0.73 (0.72 to 0.75)		

Di Meglio A, J Clin Oncol 2022

Advancing predictive risk models: a step forward

- Moving from predicting individual symptoms to symptom cluster to offer a more comprehensive understanding of patient experiences
- Development of a parsimonious, pragmatic, and accurate model: a streamlined yet highly effective approach to accurately predict long-term behavioral symptom burden, with a strong focus on real-world applicability
- Intercept patients at high risk of frailty at the time of early-stage breast cancer diagnosis enabling earlier intervention
- Utilizing risk prediction tools to inform personalized care pathways, ensuring that survivors are stratified based on their individual risk profiles facilitating targeted behavioral interventions.

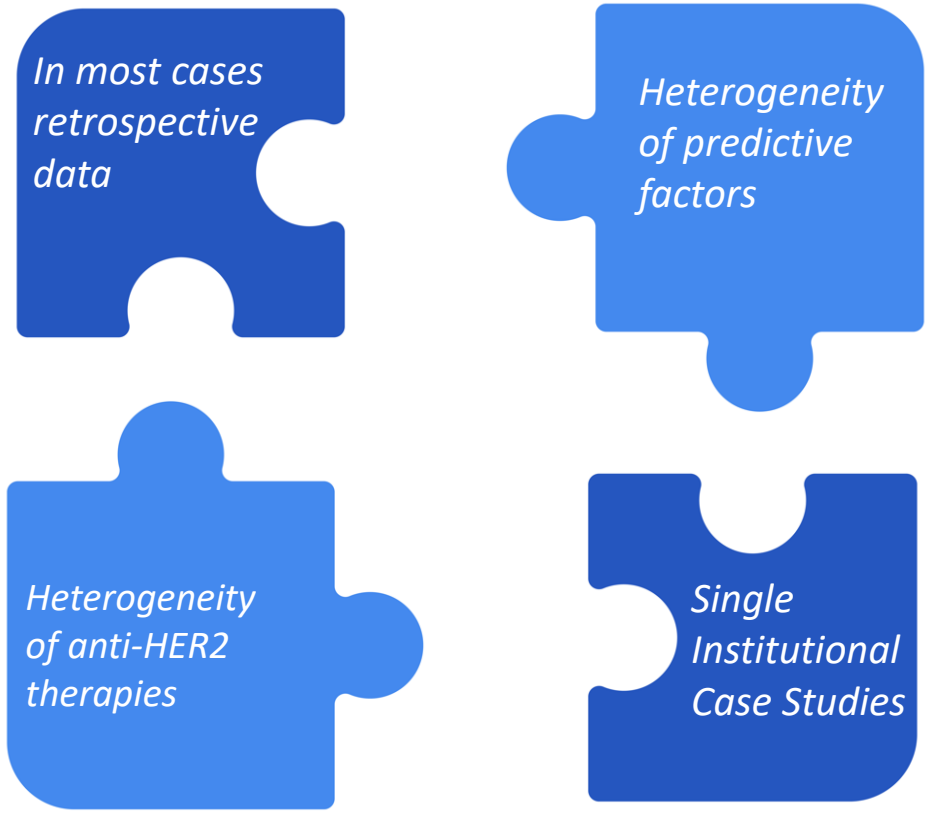
Best Papers Under 40

Long-term behavioral symptom clusters among survivors of early-stage breast cancer. Development and validation of a predictive model.
Martina Pagliuca et al.

Clinico-pathological predictors of radiologic complete response to first-line anti-HER2 therapy in metastatic breast cancer
Linda Cucciniello et al.

Let’s change setting and topic

There is limited data regarding which factors could be predictive of a CR to anti-HER2 therapies and that might inform future de-escalation strategies in the maintenance setting



Clinico-pathological predictors of radiologic complete response to first-line anti-HER2 therapy in metastatic breast cancer

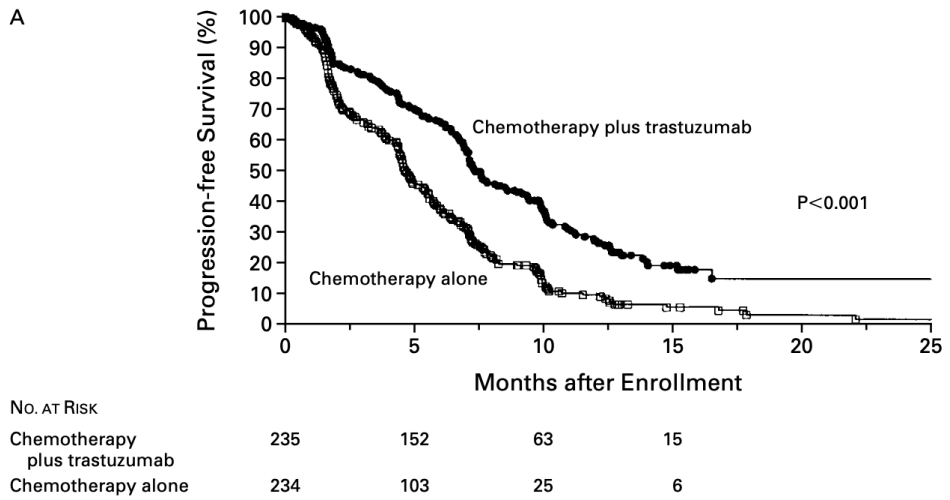
METHODS

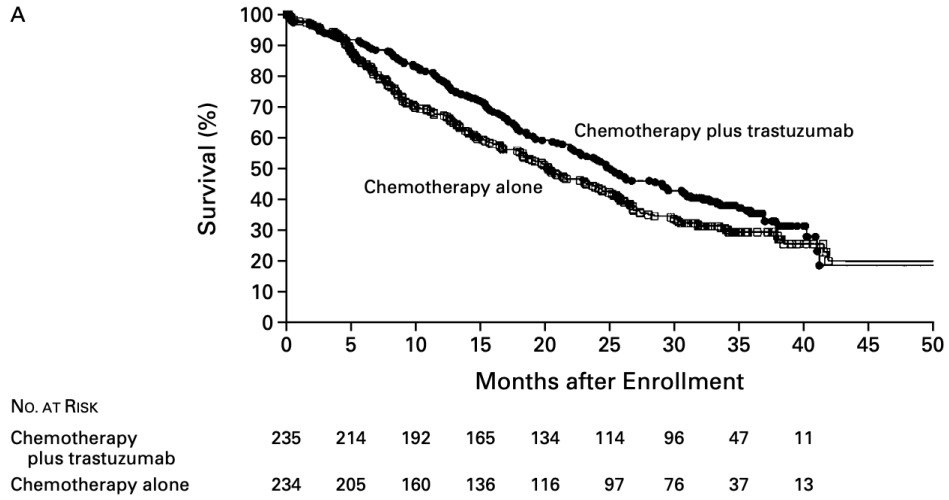
- ✓ Exploratory analysis of **GIM14 BIO-META Study**
- ✓ Patients with HER2-positive MBC treated with first-line anti-HER2 therapy from year 2000 to 2021
- ✓ Patients were classified according to the best radiologic response and the time-to-treatment- discontinuation (TTD)
- ✓ Radiologic complete response (rCR)was defined as a complete response with TTD > 3months
- ✓ Data about the best radiological response were available for **545 patients**, which were included in the final analysis

AIM

- ✓ Identify **clinico-pathological characteristics predictive** of achieving a radiologicalCR(rCR) to a first-line anti-HER2 therapy and to assess the impact of rCR on overall survival (OS)

Trastuzumab has changed the natural history of HER2 positive metastatic breast cancer





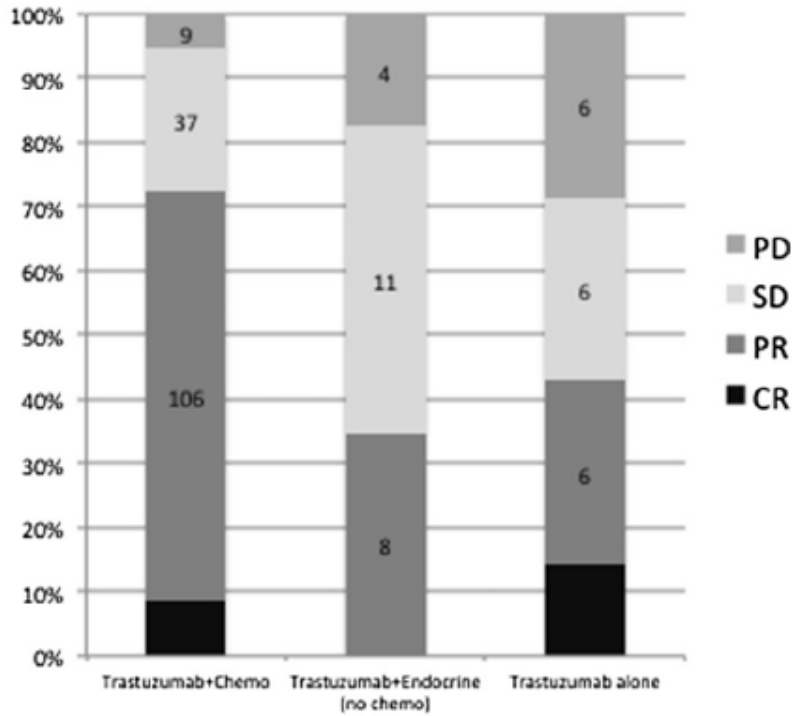
significant PFS and OS benefit by adding Trastuzumab to CT in HER2-positive MBC

Slamon DJ et al. N Engl J Med 2001;344:783–92

Long-term outcome of HER2+ mBC pts treated with first-line trastuzumab

CLINICO-PATHOLOGICAL CHARACTERISTICS

- ✓ **215 pts with HER2+ mBC**
- ✓ **52% ER+, 20% de novo disease**
- ✓ **79% pts treated with Tastuzumab + CT**
- ✓ mPFS (all pts): 12 months
- ✓ 48% remission beyond 1y
- ✓ 12% remission beyond 5y
- ✓ mOS (all pts): 2,6 years
- ✓ ORR: 65% (with 17 (8%) CR and 120 (57%) PR



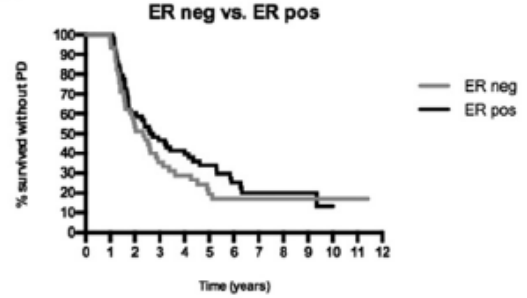
	N	CR	PR	SD	PD	ORR (CR+PR)
Total patients	210*	17 (8)	120 (57)	54 (26)	19 (9)	137 (65)
Trastuzumab + chemotherapy	166	14	106	37	9	130
Trastuzumab + endocrine (no chemo)	23	0	8	11	4	8
Trastuzumab alone	21	3	6	6	6	9

B. Yeo 754 et al. / The Breast 24 (2015) 751e757

Predicting long-term responders to trastuzumab

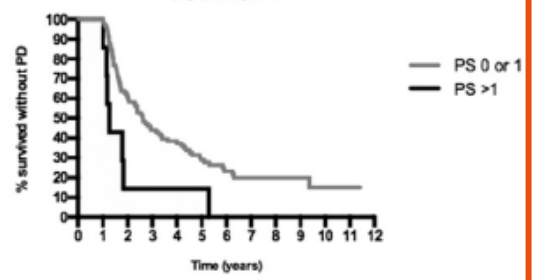
For patients who continued on trastuzumab beyond two years without progression (27%) at a median follow up of 6 years, the median **PFS was 4.9 years** and the **median OS was 7.8 years**

A



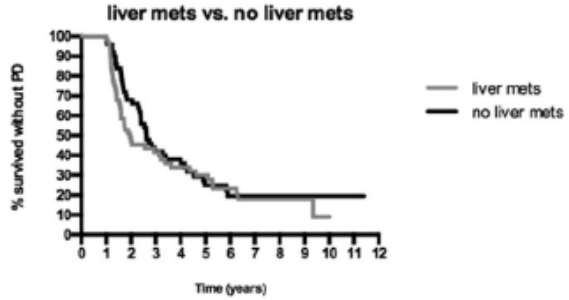
HR 1.254 (95%CI: 0.8107-1.965; p=0.3046)

B



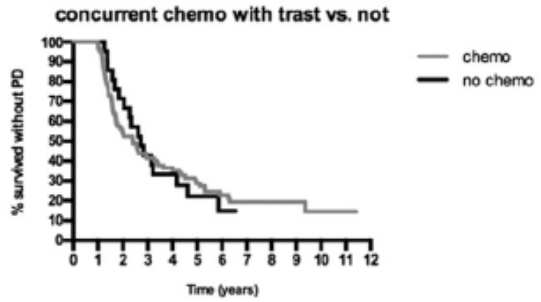
HR 0.36 (95%CI: 0.054-0.623; p=0.0068)

D



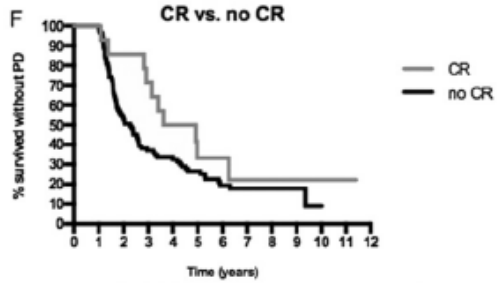
HR 1.186 (95%CI: 0.770-1.831; p=0.4390)

E



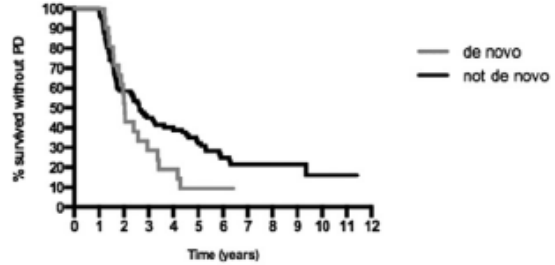
HR 1.024 (95%CI: 0.6028-1.741; p=0.9294)

F



HR 0.6021 (95%CI: 0.3706-1.124; p=0.065)

G



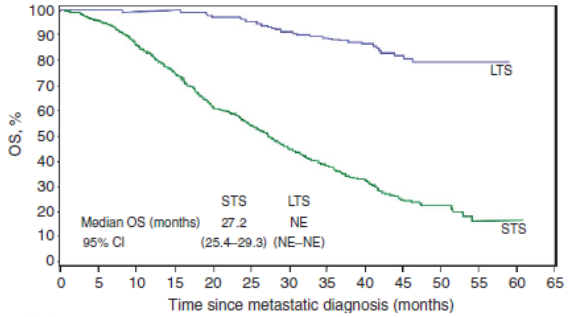
HR 1.491 (95%CI: 0.8952-2.848;

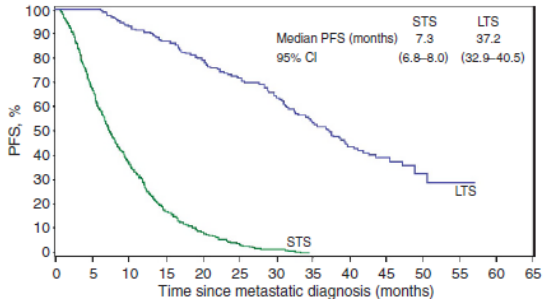
B. Yeo 754 et al. / The Breast 24 (2015) 751e757

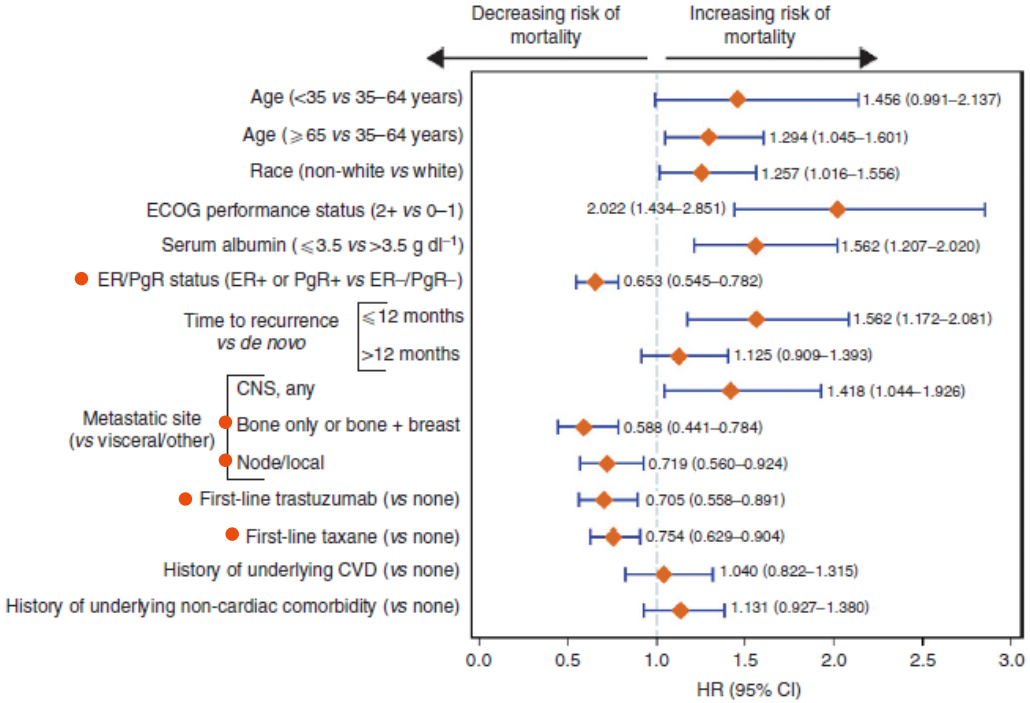
Long-Term Survivors in registHER study data

LCM was used to identify one or more distinct homogeneous LTS group(s) and one or more STS group(s), based on a simultaneous analysis of complete first-line tumour response,PFS, and OS.

- ✓ Long-Term Survivors (LTS): 244 pts (24,4%) of 1001 pts (70,9% CR)
- ✓ Short- Term Survivors (STS): 757 pts (75,6%) of 1001 pts (0,3 % CR)







D A Yardley et al. – BJC 2014

CLEOPATRA Trial

CLINICO-PATHOLOGICAL CHARACTERISTICS

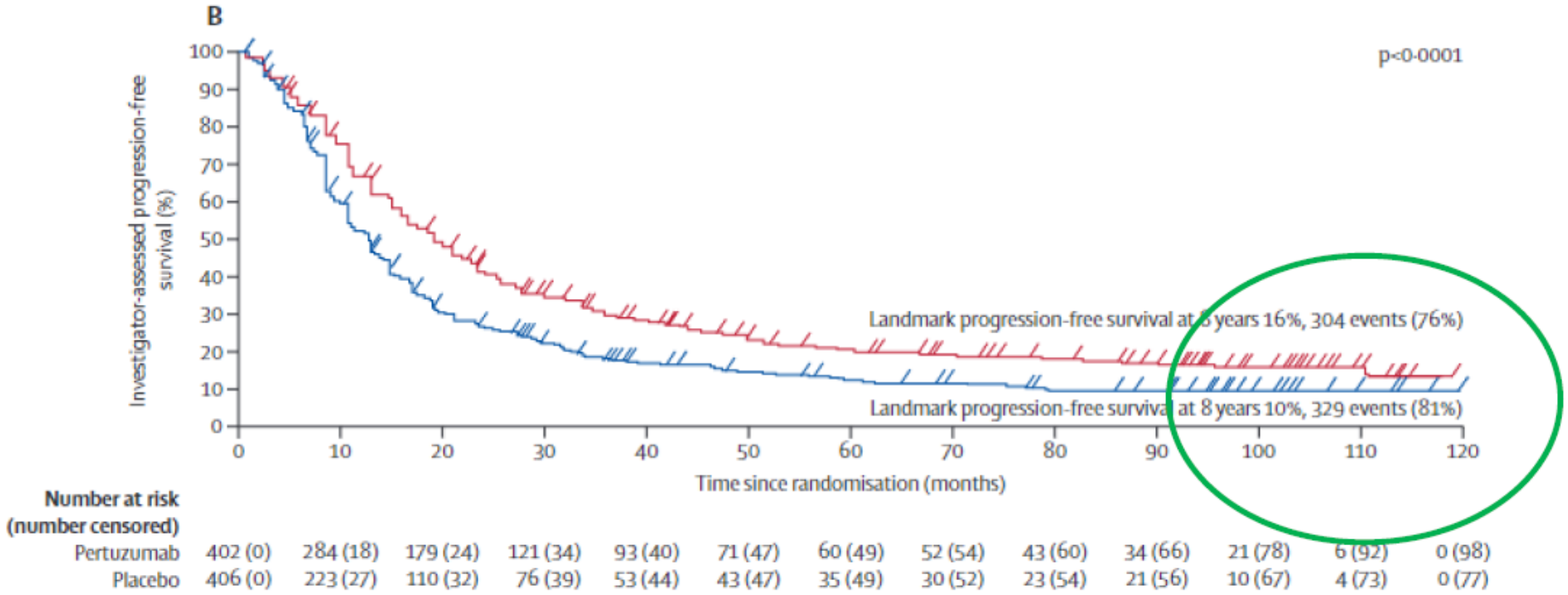
- ✓ Age: 54
- ✓ ECOG 0 : 65%
- ✓ Visceral Disease:78%
- ✓ ER+ or PR+ : 48%
- ✓ HER2 3+: 91%
- ✓ Type of neo/adjuvant therapy:
  - Anthracycline 39%
  - Hormone 25%
  - Taxane 23%
  - Trastuzumab 11%

BEST RESPONSE OUTCOME

Response	Placebo plus Trastuzumab plus Docetaxel (N=336)	Pertuzumab plus Trastuzumab plus Docetaxel (N=343)
	number (percent)	
Objective response	233 (69.3)	275 (80.2)
Complete response	14 (4.2)	19 (5.5)
Partial response	219 (65.2)	256 (74.6)
Stable disease	70 (20.8)	50 (14.6)
Progressive disease	28 (8.3)	13 (3.8)
Not assessable	2 (0.6)	2 (0.6)
No assessment performed	3 (0.9)	3 (0.9)

Baselga J et al. N ENGL J MED 2012

Exceptional Responders: CLEOPATRA



Swain SM, et al., Lancet Oncol. 2020; 21(4):519-530.

Characteristics of Long-Term Responders

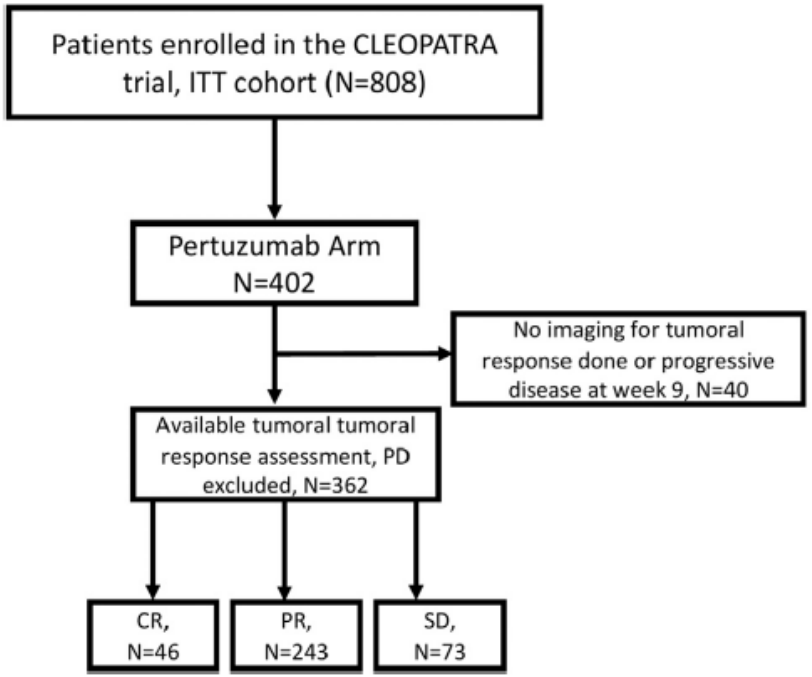
	Pertuzumab, trastuzumab, and docetaxel group		Placebo, trastuzumab, and docetaxel group	
	Long-term responders (n=99)	Non-long-term responders (n=235)	Long-term responders (n=53)	Non-long-term responders (n=286)
Disease type				
Measurable disease	85 (86%)	220 (94%)	48 (91%)	262 (92%)
Non-measurable disease	14 (14%)	15 (6%)	5 (9%)	24 (8%)
Visceral or non-visceral lesions				
Visceral disease	72 (73%)	191 (81%)	38 (72%)	233 (81%)
Non-visceral disease	27 (27%)	44 (19%)	15 (28%)	53 (19%)
Bone only	4 (4%)	6 (3%)	3 (6%)	16 (6%)
Bone and other	8 (8%)	19 (8%)	4 (8%)	17 (6%)
No bone	15 (15%)	19 (8%)	8 (15%)	20 (7%)
Progesterone receptor status				
Positive	35 (35%)	60 (26%)	21 (40%)	95 (33%)
Negative	64 (65%)	172 (73%)	32 (60%)	179 (63%)
HER2 immunohistochemistry status				
0 or 1+	1 (1%)	3 (1%)	0	2 (1%)
2+	2 (2%)	37 (16%)	1 (2%)	29 (10%)
3+	95 (97%)	195 (83%)	52 (98%)	255 (89%)
Oestrogen and progesterone receptor status				
Positive	48 (48%)	110 (47%)	28 (53%)	142 (50%)
Negative	51 (52%)	124 (53%)	25 (47%)	135 (47%)
Mean time from first histological diagnosis to metastatic disease, months	33·2 (n=86) SD 36·9	27·6 (n=212) SD 40·2	30·7 (n=46) SD 44·2	29·9 (n=264) SD 41·0

- ✓ High RNA mRNA expression
- ✓ Low serum HER2 extracellular domain
- ✓ PIK3CA wild-type
- ✓ Higher TILs value (each 10% ↑ stromal TILS → benefit in OS, HR 0.89, p=0.0014)

Swain SM, et al., Lancet Oncol. 2020; 21(4):519-530.

The Impact of Initial Tumor Response on Survival Outcomes of Patients With HER2-PositimBC

An Exploratory Analysis of the Cleopatra Trial



	All Patients $N = 362$	Distribution According to Tumor Response			
		CR $N = 46$ (12.7%)	PR $N = 243$ (67.1%)	SD $N = 73$ (20.2%)	*P*-Value
Median age, years (range)	54 (22-82)	53 (22-82)	54 (22-80)	54 (27-73)	.528
Menopausal status					.981
Premenopausal	87 (24.0%)	9 (19.6%)	60 (24.7%)	18 (24.7%)	
Postmenopausal	235 (64.9%)	27 (58.7%)	161 (66.3%)	47 (64.4%)	
Others/unknown	40 (11.1%)	10 (21.7%)	22 (9.0%)	8 (10.9%)	
ECOG PS					.576
0	258 (71.3%)	35 (76.1%)	174 (71.6%)	49 (67.1%)	
1	101 (27.9%)	11 (23.9%)	67 (27.6%)	23 (31.5%)	
≥ 2	3 (0.8%)	0 (0.0%)	2 (0.8%)	1 (1.4%)	
BMI					.513
< 25kg/m^2	169 (46.7%)	18 (39.1%)	115 (47.3%)	36 (49.3%)	
≥ 25kg/m^2	193 (53.3%)	28 (60.9%)	128 (52.7%)	37 (50.7%)	
Type of metastatic disease					**.015**
De novo	203 (56.1%)	22 (47.8%)	149 (61.3%)	32 (43.8%)	
Recurrent	159 (43.9%)	24 (52.2%)	94 (38.7%)	41 (56.2%)	
Site of metastatic disease					**.005**
Visceral	283 (78.2%)	32 (69.6%)	202 (83.1%)	49 (67.1%)	
Nonvisceral	79 (21.8%)	14 (30.4%)	41 (16.9%)	24 (32.9%)	
HER2 status					.053
HER2 2+	40 (11.2%)	1 (2.2%)	28 (11.6%)	11 (15.71)	
HER2 3+	317 (88.8%)	45 (97.8%)	213 (88.4%)	59(84.3%)	
Unknown	5 (1.4%)	0 (0.0%)	2 (0.8%)	3 (4.3%)	
Hormone receptor status					.455
ER and/or PR positive	171 (47.2%)	18 (39.1%)	116 (47.7%)	37 (50.7%)	
ER and PR negative	190 (52.5%)	28 (60.9%)	126 (51.9%)	36 (49.3%)	
Unknown	1 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	

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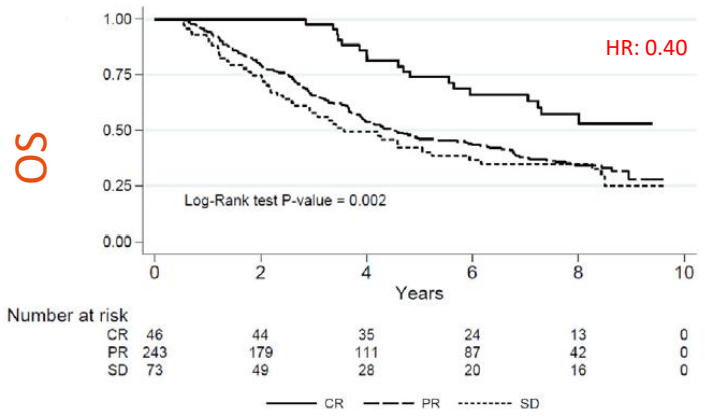
Results

OS



PFS

OS - HER2 status subgroup

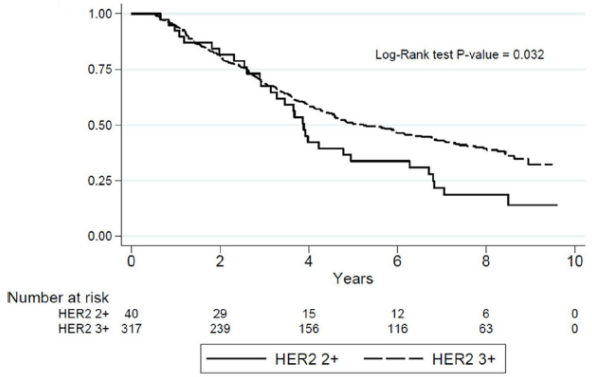


Table 2 Multivariate Analysis for Overall Survival in the Entire Cohort

Variables	HR (95% CI)	*P*-Value
Age	1.00 (0.98-1.01)	0.700
BMI	0.98 (0.96-1.01)	0.212
ECOG PS		0.167
0	Ref.	
≥ 1	1.24 (0.91-1.68)	
Disease site		0.536
Nonvisceral	Ref.	
Visceral	1.11 (0.79-1.57)	
Hormone receptors status		0.767
ER and PR neg.	Ref.	
ER and/or PR pos.	0.96 (0.73-1.26)	
Tumour response		***0.002***
SD	Ref.	
PR	0.85 (0.60-1.20)	
CR	0.40 (0.23-0.70)	

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Univariate and Multivariate Analysis for Overall Survival Per Subgroup

Variable	CR			
	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	0.99 (0.95-1.02)	.475	0.99 (0.94-1.03)	.531
BMI	1.01 (0.94-1.09)	.744	1.03 (0.95-1.13)	.458
Menopausal status				
Postmenopausal	Ref.			
Premenopausal	1.78 (0.68-4.67)	.483		
ECOG PS				
0	Ref.			
≥ 1	1.72 (0.73-4.04)	.212		
Disease site				
Nonvisceral	Ref.		Ref.	
Visceral	0.63 (0.27-1.45)	.275	0.68 (0.27-1.72)	.416
Disease type (de novo vs recurrent)				
De novo	Ref.			
Recurrent	0.84 (0.37-1.88)	.669		
Hormone receptors status				
ER and PR neg.	Ref.		Ref.	
ER and/or PR pos.	1.68 (0.74-3.80)	.215	1.73 (0.68-4.37)	.250
PIK3CA mutation				
No	Ref.		Ref.	
Yes	0.37 (0.08-1.66)	.329	0.42 (0.09-1.91)	.464

In the multivariate analysis per response subgroup, no variable appeared to affect survival in the CR subgroup

- ✓ Pts who achieve a CR after 9 weeks of study treatment have an excellent OS rate compared to those who experience a PR or SD
- ✓ Achieving a radiological CR at the first disease re-evaluation is associated with longer survival

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But…. The research goes on

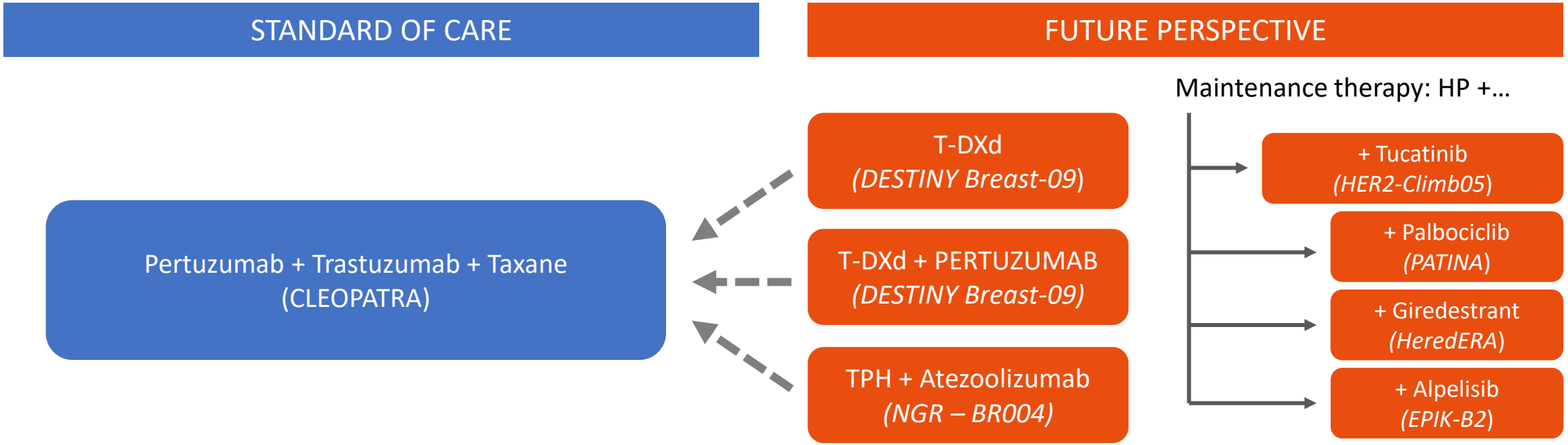
Real World Data, patients enrolled from multiple institutions

Sample Size (more than 500 pts included)

80 pts rCR with TTD > 3 months

56 pts rCR with TTD> 18 months

The future evolution of 1° Line



Thanks for your attention