Carcinoma mammario metastatico

La sopravvivenza globale negli studi clinici e di real-world

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Potential conflicts of interest*

- Amgen
- Astrazeneca**
- Daichii Sankyo
- Celgene
- Eisai**
- Eli Lilly
- Exact Sciences
- Gilead
- GSK
- Ipsen
- Menarini
- MSD
- Novartis
- Pierre-Fabre
- Pfizer
- Roche**
- Seagen
- Takeda
- Viatris

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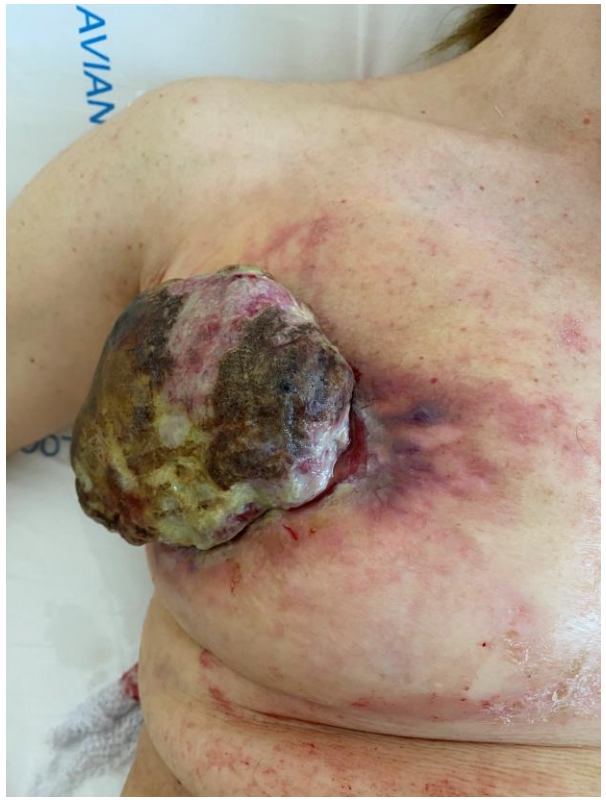
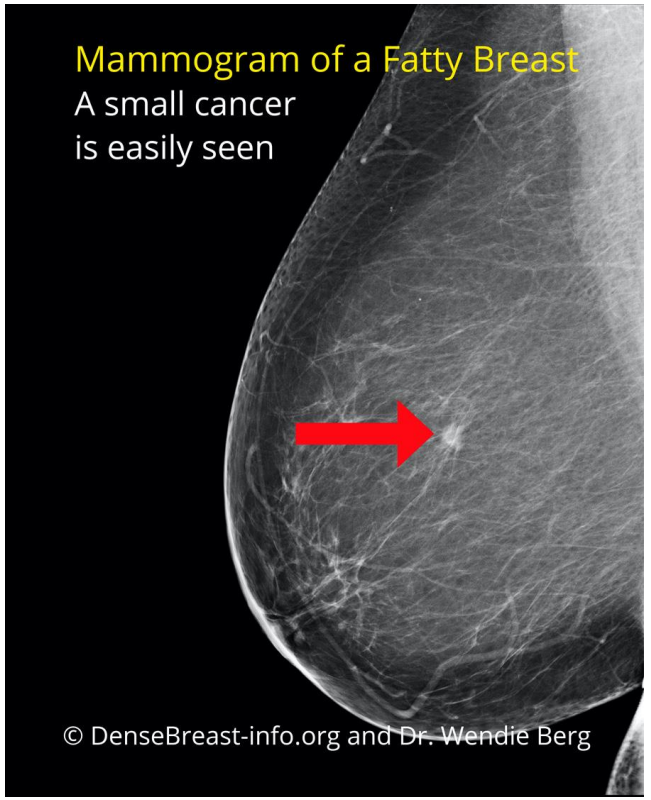
*honoraria for advisory boards, activities as a speaker, travel grants, research grants
**research funding

Views are my own, and do not necessarily represent opinions or positions of University of Udine, or IRCCS National Cancer Institute, Centro di riferimento Oncologico, Aviano.

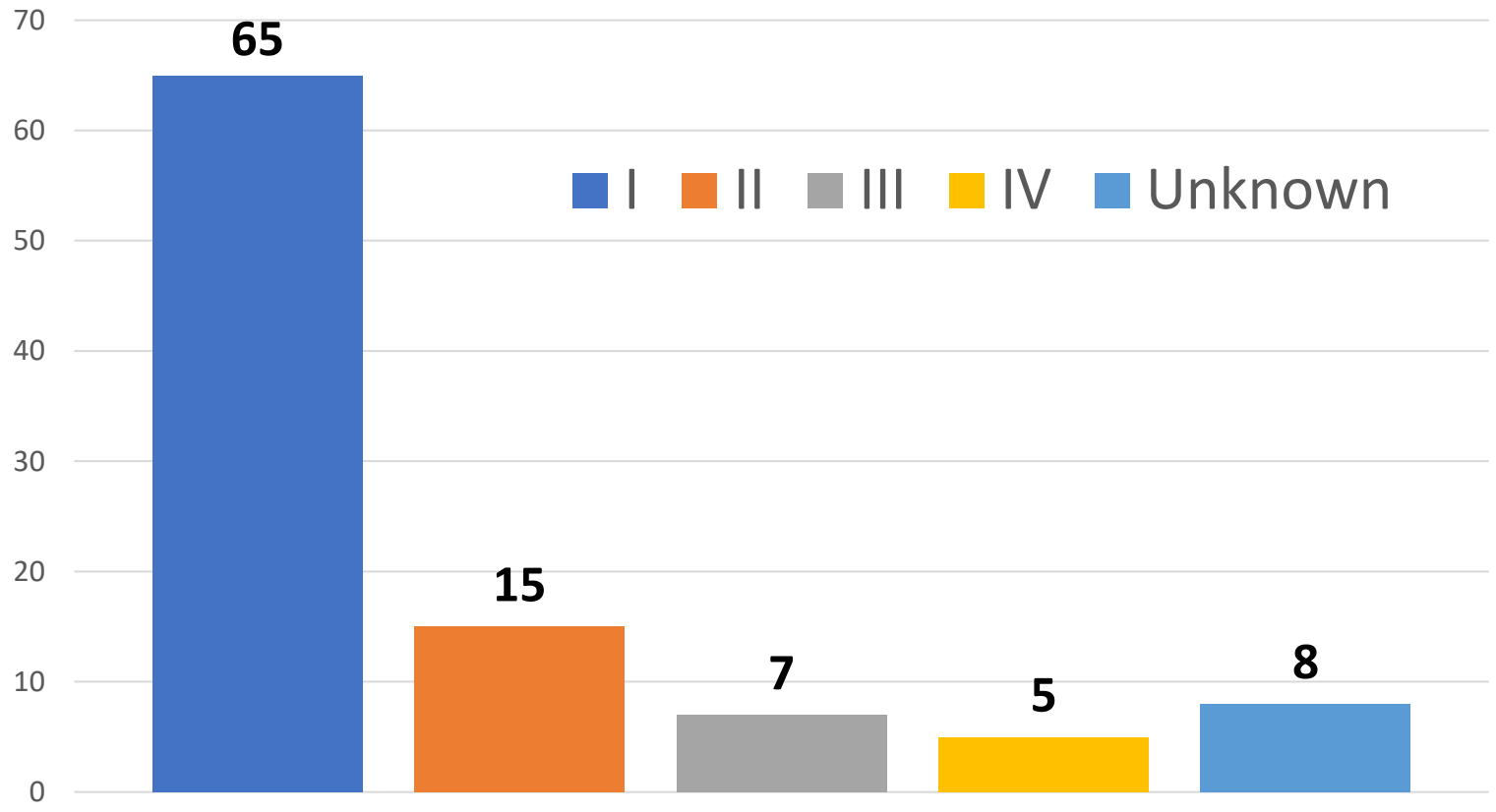




What do these two images share?

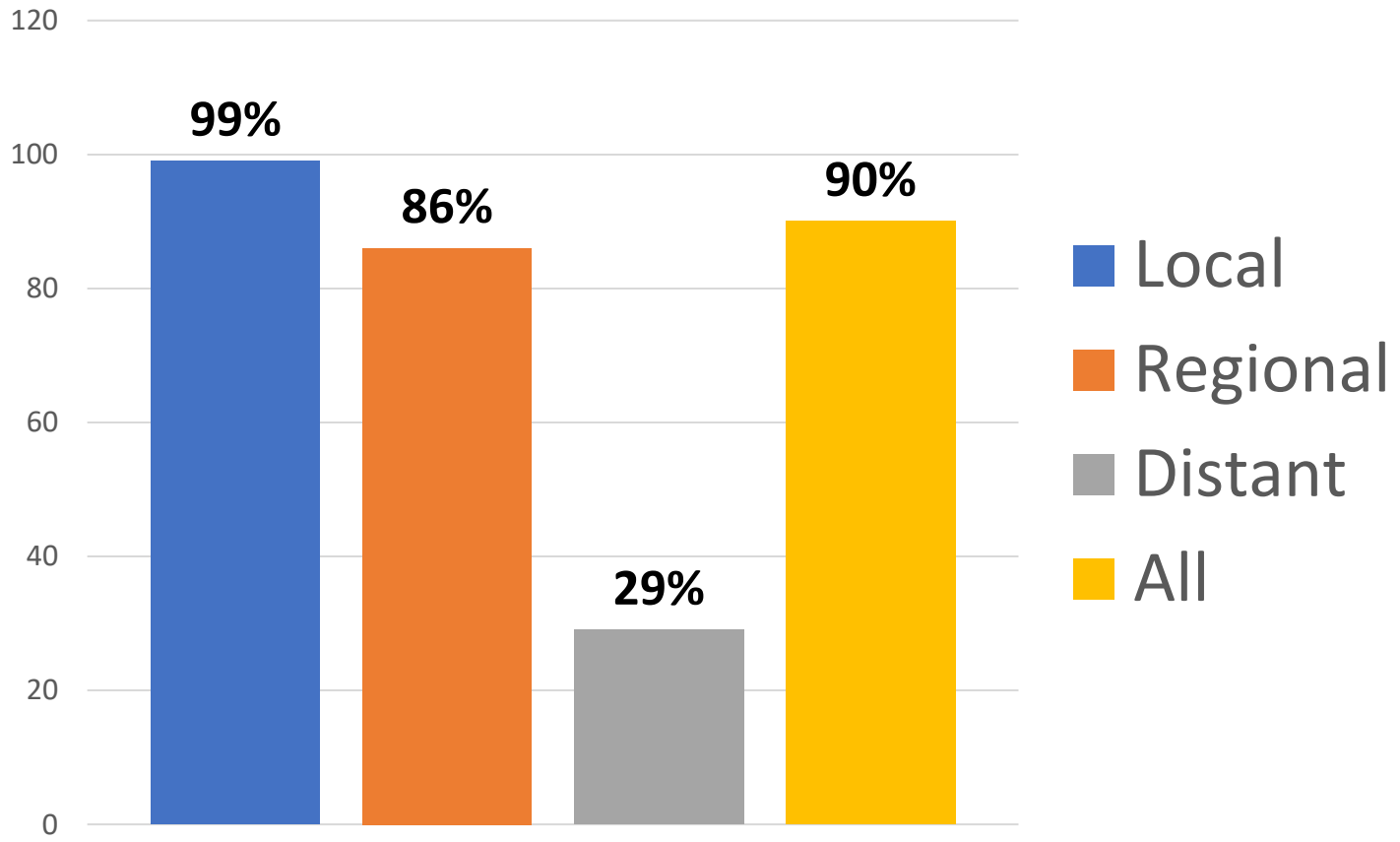
The best care starts with 'early' diagnosis (screening)

Breast Cancer: Stage Distribution (US, 2018)



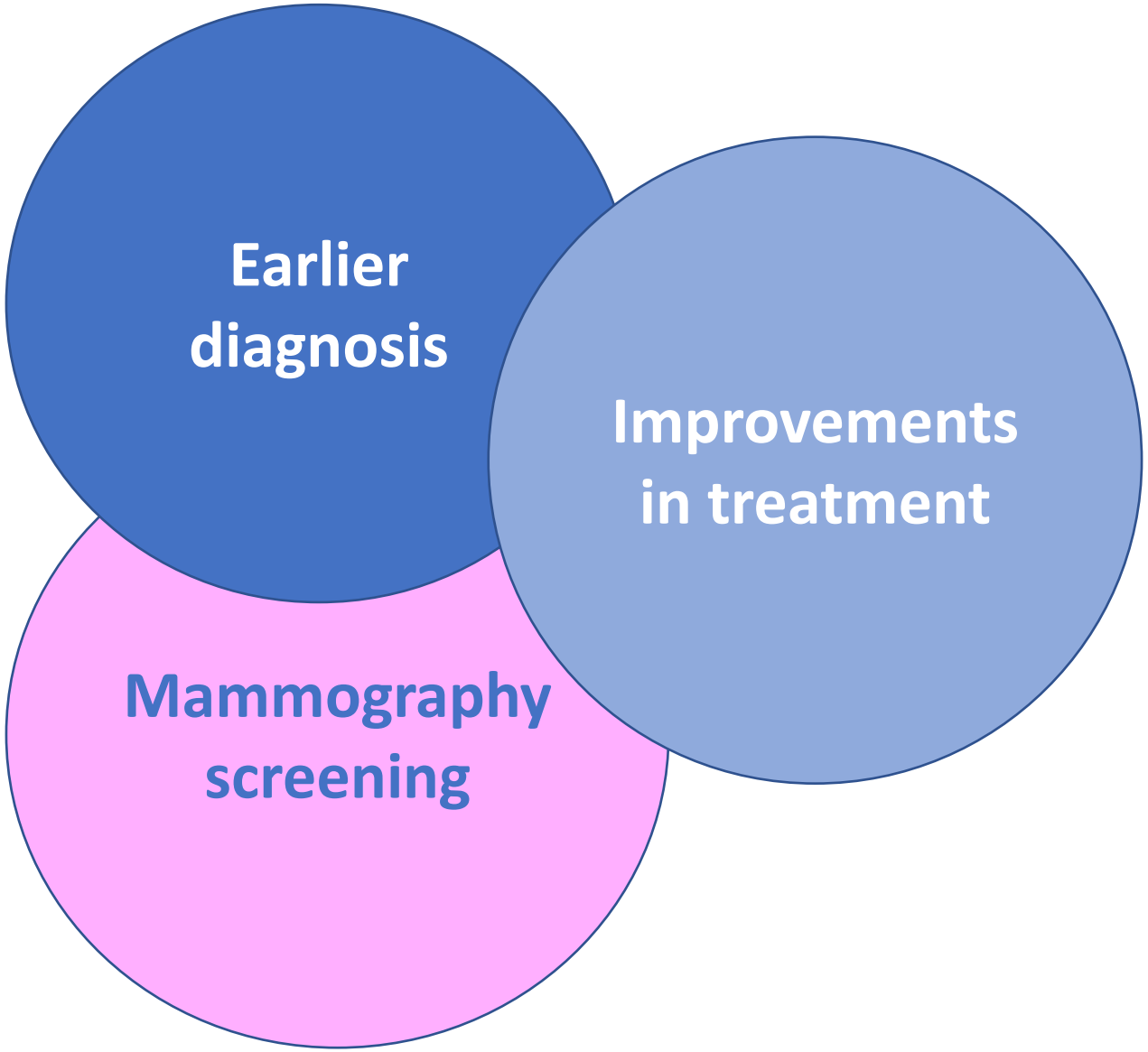
Miller KD, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin 2022;72(5):409-436.

5-year relative survival for BC (US, 2011 to 2017)



Siegel RL, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72(1):7-33.

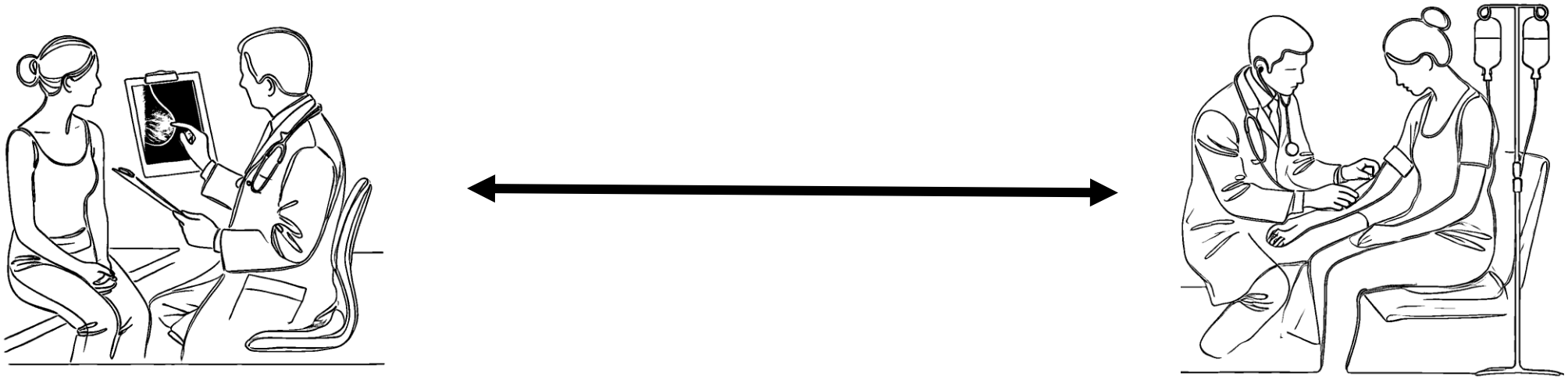
Female breast cancer mortality peaked in 1989 and has since decreased by 43% through 2020



Giaquinto AN, et al. Breast Cancer Statistics, 2022. CA Cancer J Clin 2022 Oct 3. doi: 10.3322/caac.21754.

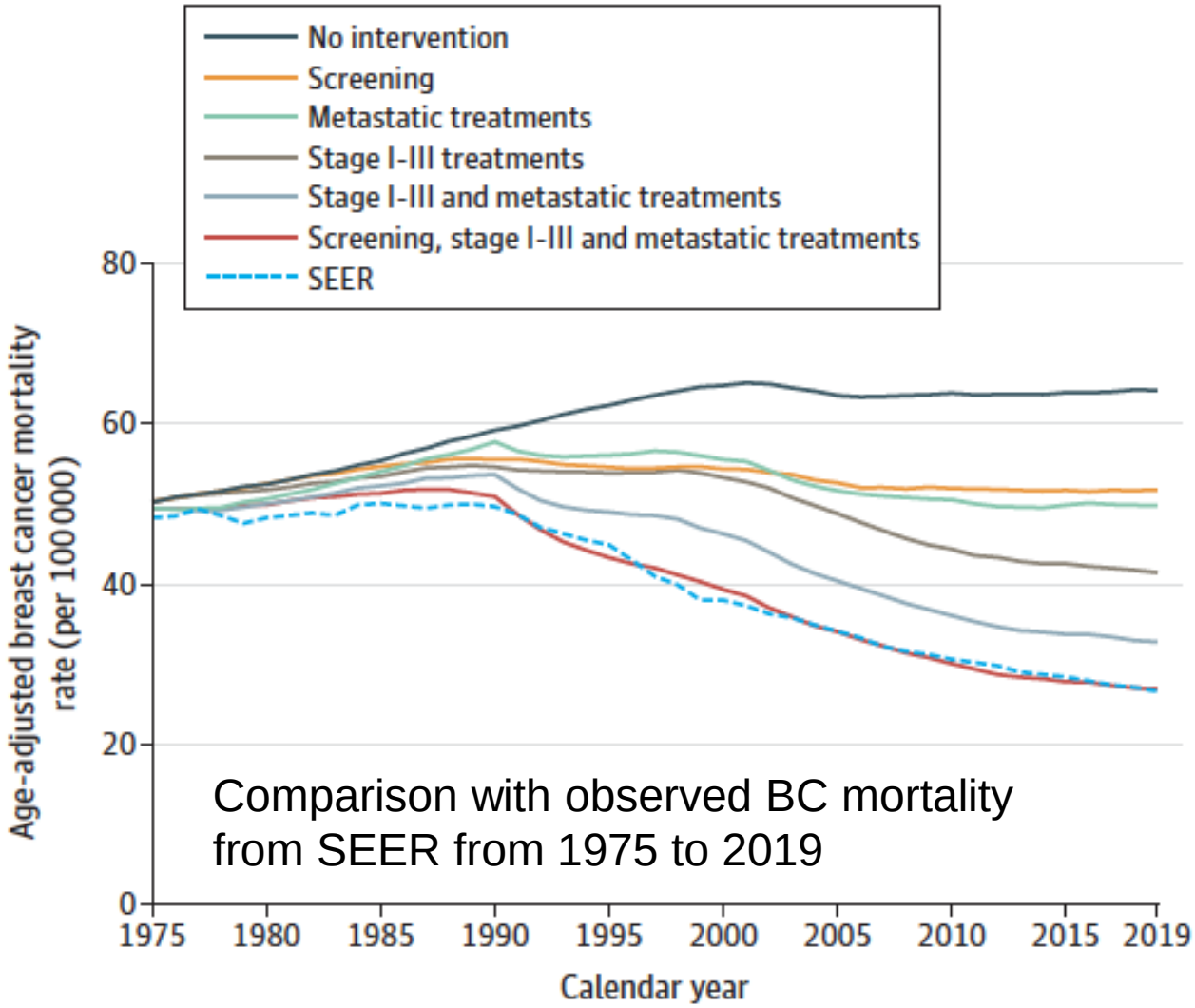
Breast Cancer Mortality Reduction - US (1975-2019)

What are the relative contributions of breast cancer screening, treatment for stage I-III breast cancer, and treatment for metastatic breast cancer in reducing breast cancer mortality in the US from 1975 to 2019?



Caswell-Jin JL, et al. JAMA 2024;331(3):233-241. doi: 10.1001/jama.2023.25881.

Model-estimated mean age-adjusted breast cancer mortality among women aged 30 to 79 years under various scenarios



Caswell-Jin JL, et al. JAMA 2024;331(3):233-241.

Breast Cancer Mortality: Simulation models

Advancements in screening and treatment since 1975 have led to a **58% reduction in breast cancer mortality** by 2019.

- Without interventions
  - Estimated mortality would be **64 per 100,000 women** (age-adjusted).
- With interventions
  - Reduced to **27 per 100,000 women**.

Contributions to Mortality Reduction

- Treatments for Stage I-III: 47%
- Treatments for MBC: 29%
- Screening Mammography: 25%

Caswell-Jin JL, et al. JAMA 2024;331(3):233-241.

Breast Cancer Mortality Reduction and Relative Contributions in 2019 by ER/ERBB2 Status and Model

Models:

- Dana-Farber Cancer Institute
- MD Anderson Cancer Center
- Stanford University
- University of Wisconsin–Harvard

Caswell-Jin JL, et al. JAMA 2024;331(3):233-241.

	Combined mortality reduction, %	Relative contribution to combined mortality reduction, %[a]		
		Screening	Stage I-III treatment	Metastatic treatment
Overall				
Model D[b]	59.0	32.5	34.6	32.9
Model M[c]	54.6	20.9	60.1	19.0
Model S[d]	57.3	25.4	44.1	30.5
Model W[e]	61.2	20.9	47.2	31.8
Mean	58.0	24.9	46.5	28.6
ER+/*ERBB2*−				
Model D	60.4	33.1	32.1	34.8
Model M	56.1	20.6	61.2	18.2
Model S	59.2	25.0	42.7	32.2
Model W	61.9	19.4	46.7	33.9
Mean	59.4	24.5	45.7	29.8
ER+/*ERBB2*+				
Model D	69.0	23.9	45.4	30.7
Model M	67.9	16.5	56.3	27.2
Model S	71.6	20.0	51.9	28.1
Model W	76.1	16.3	55.1	28.6
Mean	71.2	19.2	52.2	28.6
ER−/*ERBB2*+				
Model D	64.9	26.0	39.1	34.9
Model M	52.7	21.0	59.4	19.6
Model S	57.3	25.6	43.1	31.3
Model W	65.7	23.4	45.5	31.1
Mean	60.1	24.0	46.8	29.2
ER−/*ERBB2*−				
Model D	40.3	48.8	30.5	20.7
Model M	38.3	32.5	61.1	6.4
Model S	34.8	40.6	38.0	21.5
Model W	41.7	37.1	36.5	26.4
Mean	38.8	39.8	41.5	18.7

Change in treatment over time

	Stage I-III therapy		Therapy after metastasis			
		Subtype	First line	Second line	Third line	Fourth line
Pre-1975	None, chemotherapy, or endocrine therapy per Plevritis et al[3]	All	Chemotherapy			
1976		ER+	Tamoxifen	Chemotherapy		
		ER-	Chemotherapy			
1991		ER+	Tamoxifen	Chemotherapy * taxane		
		ER-	Chemotherapy * taxane			
1995		ER+	Tamoxifen * AI	Chemotherapy * taxane		
		ER-	Chemotherapy * taxane			
1998		ER+	Tamoxifen * AI	Chemotherapy * taxane	Capecitabine	
		ER-	Chemotherapy * taxane	Capecitabine		
2001		ER+/*ERBB2*-	Tamoxifen * AI	Chemotherapy * taxane	Capecitabine	
		ER+/*ERBB2*+	Chemotherapy * taxane * trastuzumab	Tamoxifen * AI	Capecitabine	
		ER-/*ERBB2*+	Chemotherapy * taxane * trastuzumab	Capecitabine		
		ER-/*ERBB2*-	Chemotherapy * taxane	Capecitabine		
2002		ER+/*ERBB2*-	Tamoxifen * AI * fulvestrant	Chemotherapy * taxane	Capecitabine	
		ER+/*ERBB2*+	Chemotherapy * taxane * trastuzumab	Tamoxifen * AI * fulvestrant	Capecitabine	
		ER-/*ERBB2*+	Chemotherapy * taxane * trastuzumab	Capecitabine		
		ER-/*ERBB2*-	Chemotherapy * taxane	Capecitabine		
2005	Addition of trastuzumab (*ERBB2*+)					

Caswell-Jin JL, et al. JAMA 2024;331(3):233-241. doi: 10.1001/jama.2023.25881.

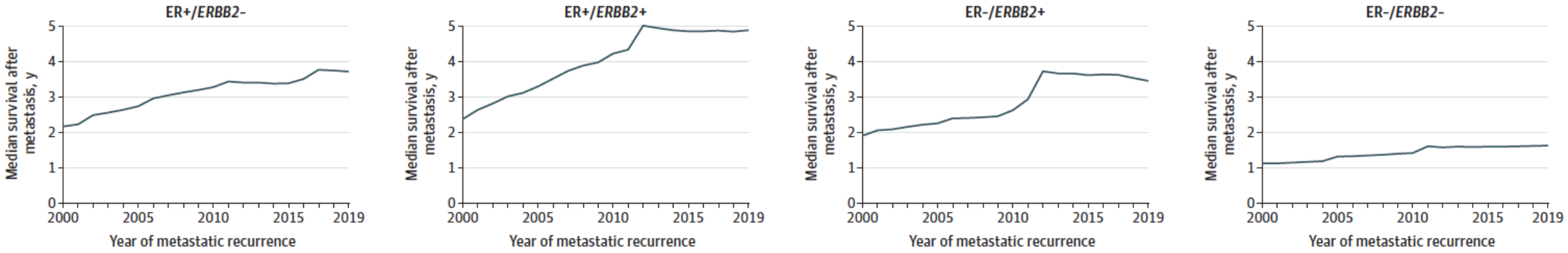
Change in treatment over time

	Stage I-III therapy		Therapy after metastasis			
		Subtype	First line	Second line	Third line	Fourth line
2011		ER+/*ERBB2*-	Tamoxifen * AI * fulvestrant	Chemotherapy * taxane	Capecitabine	Eribulin
		ER+/*ERBB2*+	Chemotherapy * taxane * trastuzumab	Tamoxifen * AI * fulvestrant	Capecitabine	Eribulin
		ER-/*ERBB2*+	Chemotherapy * taxane * trastuzumab	Capecitabine	Eribulin	
		ER-/*ERBB2*-	Chemotherapy * taxane	Capecitabine	Eribulin	
2012		ER+/*ERBB2*-	Tamoxifen * AI * fulvestrant	Chemotherapy * taxane	Capecitabine	Eribulin
		ER+/*ERBB2*+	Chemotherapy * taxane * trastuzumab * pertuzumab	T-DM1 * capecitabine	Tamoxifen * AI * fulvestrant	Eribulin
		ER-/*ERBB2*+	Chemotherapy * taxane * trastuzumab * pertuzumab	T-DM1 * capecitabine	Eribulin	
2014	Addition of ovarian suppression (ER+)	ER-/*ERBB2*-	Chemotherapy * taxane	Capecitabine	Eribulin	
2017	Addition of pertuzumab (*ERBB2*+), neratinib (*ERBB2*+), capecitabine (ER-/*ERBB2*-)	ER+/*ERBB2*-	Tamoxifen * AI * fulvestrant * CDK4/6	Chemotherapy * taxane	Capecitabine	Eribulin
		ER+/*ERBB2*+	Chemotherapy * taxane * trastuzumab * Pertuzumab	T-DM1 * capecitabine	Tamoxifen * AI * fulvestrant	Eribulin
		ER-/*ERBB2*+	Chemotherapy * taxane * trastuzumab * pertuzumab	T-DM1 * capecitabine	Eribulin	
		ER-/*ERBB2*-	Chemotherapy * taxane	Capecitabine	Eribulin	

Caswell-Jin JL, et al. JAMA 2024;331(3):233-241. doi: 10.1001/jama.2023.25881.

Estimated BCSS After Metastatic Recurrence

Change over time (2000 → 2019)



ER+/HER2- 2 → 3.5 (Δ = 1.5) | **ER+/HER2+** 2.3 → 4.8 (Δ = 2.5) | **ER-/HER2+** 2.2 → 3.9 (Δ = 1.7) | **TNBC** 1.2 → 1.8 (Δ = 0.6)

Pertuzumab and T-DM1 were introduced for HER2+ subtypes in 2012

Caswell-Jin JL, et al. JAMA 2024;331(3):233-241. doi: 10.1001/jama.2023.25881.

Trends in Breast Cancer-Specific Mortality by Stage at Diagnosis

- **Context**: Breast cancer mortality decreased by >40% since 2000 due to effective systemic therapies.
- **Key Question**: Has breast cancer-specific (BCS) mortality shifted among stages in response to advancements in early detection and therapy?
- **Objective**: Examine trends in BCS mortality across stages I-IV at diagnosis.
- **Data Source**: SEER database (972,763 patients, 2000-2017).

Marczyk M, et al. J Natl Cancer Inst 2024 (Epub ahead of print)

Trends in Breast Cancer-Specific Mortality by Stage at Diagnosis: Key findings

- **Stage I and II**: Significant increase in BCS mortality
  - Stage I: 16.2% → 23.1%, Stage II: 30.7% → 39.5%, $p < 0.001$.
- **Stage III and IV**: Decline in BCS mortality
  - Stage III: 36.4% → 30.3%, Stage IV: 16.7% → 7.1%, $p < 0.001$.
- **Survival Trends**:
  - 5-year BCSS stable for Stage I, improved for Stages II-IV.
  - HR-positive tumors: Dominant in 2017 BCS mortality (72.3%), indicating long-term recurrence risk.
  - HR-negative tumors: BCS mortality reduced from 33.2% (2000) to 15.2% (2017).

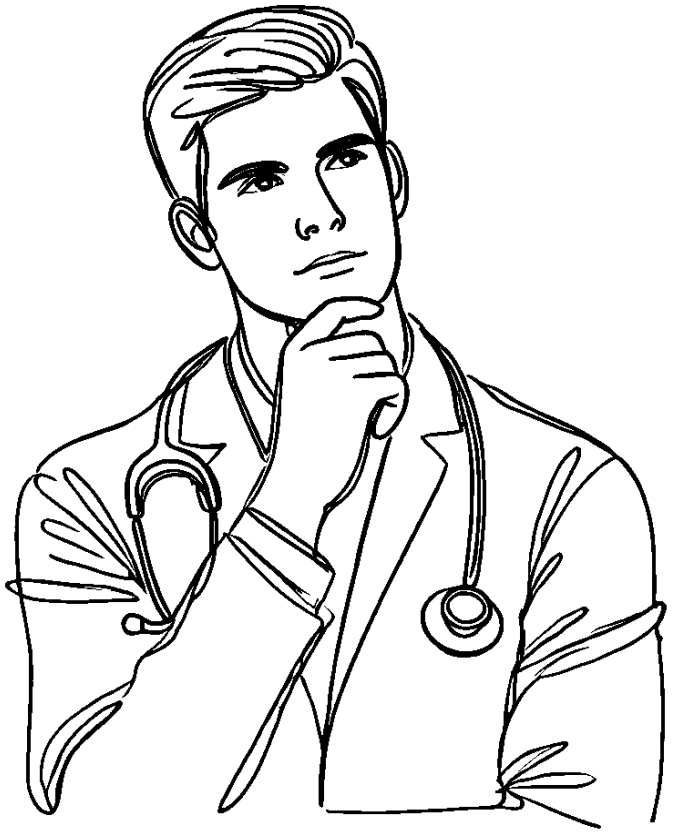
Marczyk M, et al. J Natl Cancer Inst 2024 (Epub ahead of print)

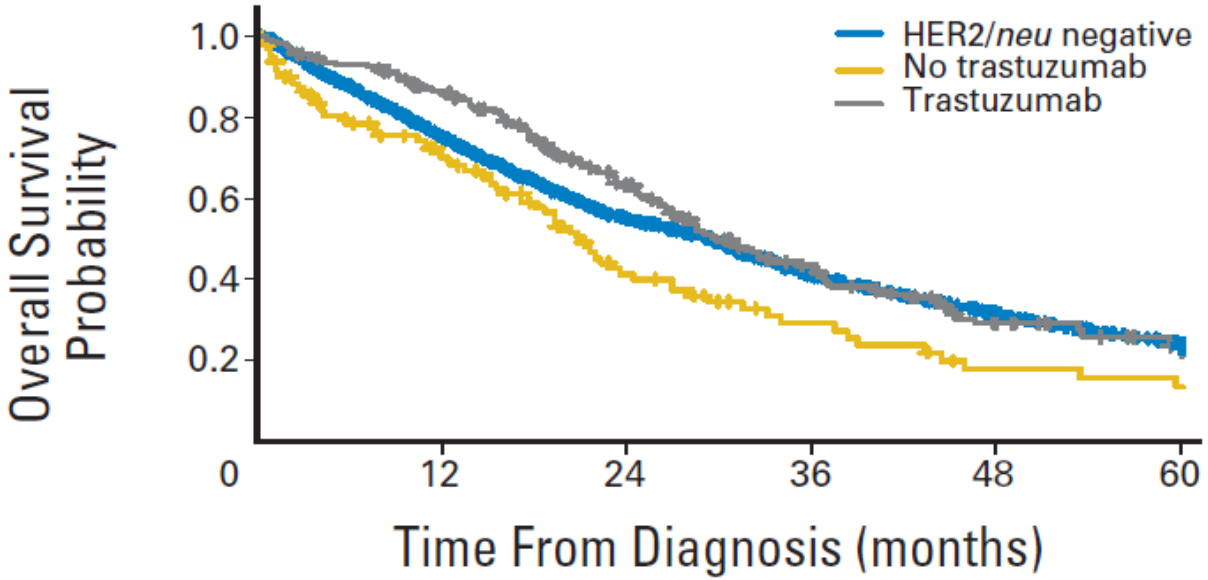
Trends in Breast Cancer-Specific Mortality by Stage at Diagnosis: Implications and Clinical Insights

- **Shift in Mortality Burden**: Early-stage cancers now contribute >60% of BCS mortality.
- **Challenges**:
  - **Risk Stratification**: Need advanced molecular monitoring (e.g., ctDNA) for better risk assessment.
  - **Treatment Balance**: Minimize overtreatment in low-risk patients, while identifying higher-risk patients within early stages.
- **Clinical Message**: Enhanced long-term monitoring and adherence to endocrine therapy for HR-positive, early-stage patients may reduce BCS mortality further.

Marczyk M, et al. J Natl Cancer Inst 2024 (Epub ahead of print)

Trastuzumab is a transformative drug for the treatment of HER2-positive BC



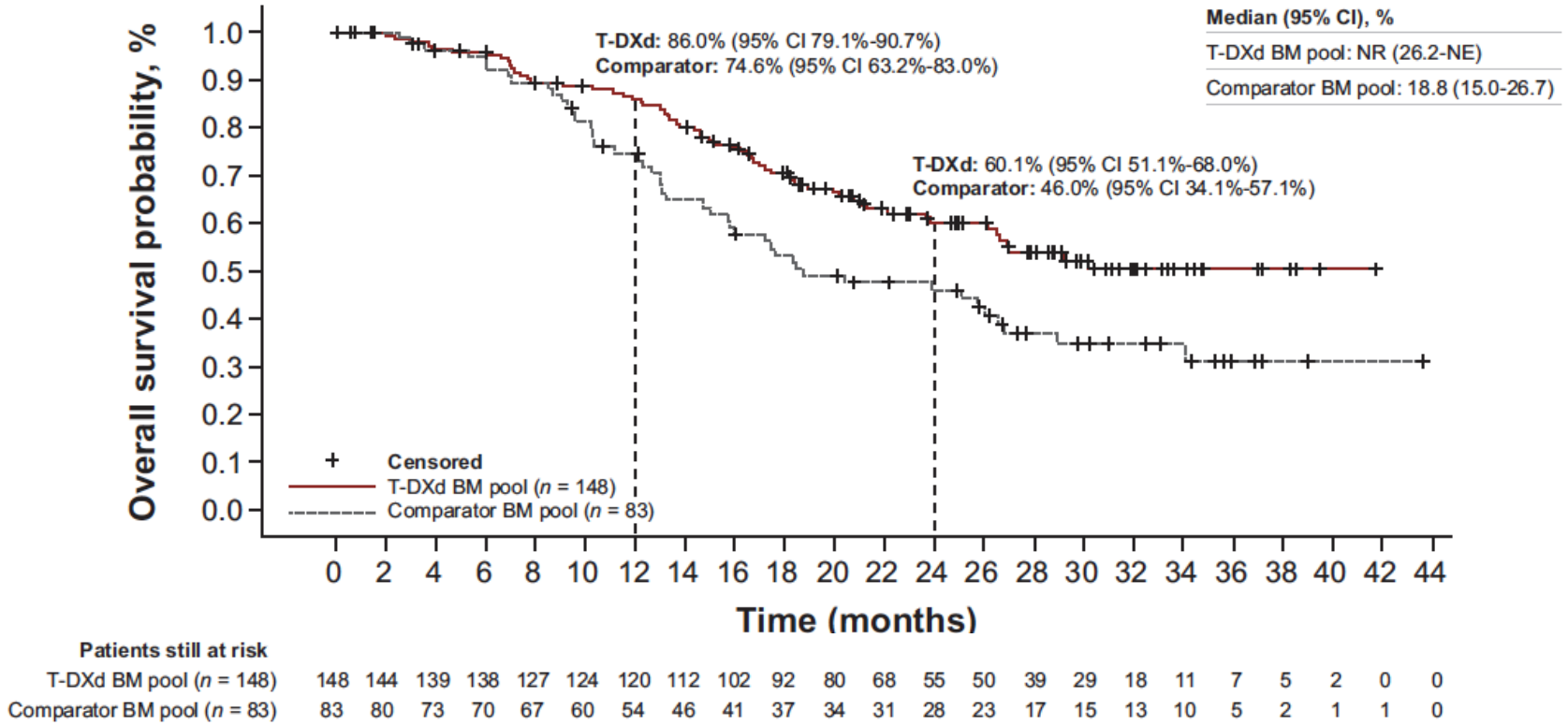


No. of patients at risk

HER2/*neu* negative	1,782	1,060	633	348	211	120
No trastuzumab	118	65	31	16	8	6
Trastuzumab	191	155	94	51	25	10

Dawood S, et al. J Clin Oncol 2010;28:92-8.

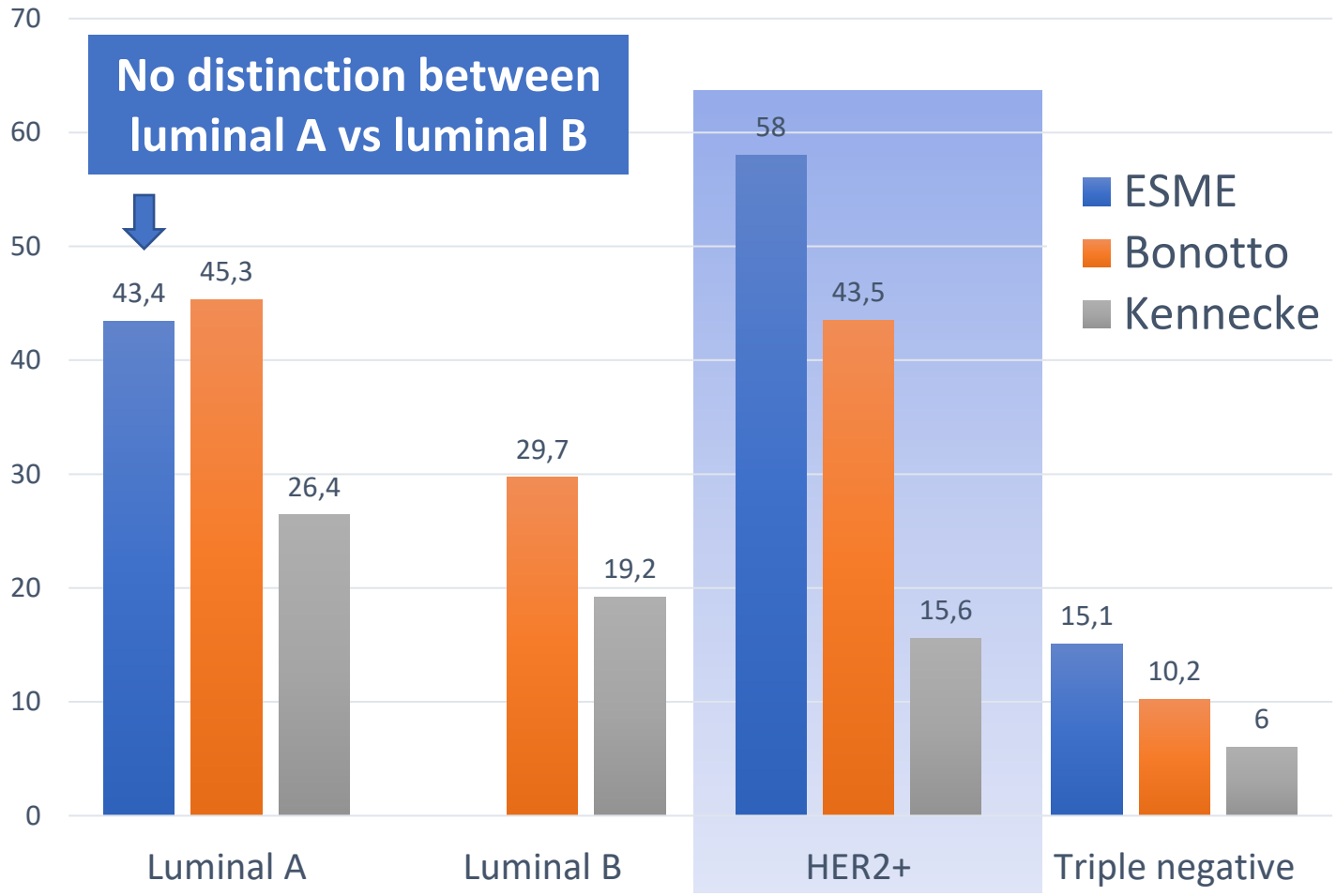
T-DXd is a transformative drug for the treatment of HER2-positive BC: OS in pts with brain metastases



Data Source: DB-01, DB-02, and DB-03 trials.

André F, et al Ann Oncol 2024 doi:10.1016/j.annonc.2024.08.2347.

Overall survival overtime: HER2-positive MBC



OS for 2013 (year of diagnosis) → 2008 → 2017

OS for the whole cohort → 2004 → 2012

1986 → 1992

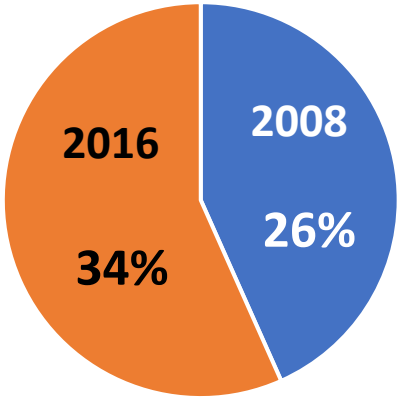
French ESME cohort. ESMO Open 2021; 6:100114.

Bonotto M, et al. Oncologist 2014;19:608-15.

Kennecke H, et al. J Clin Oncol 2010;28:3271-7.

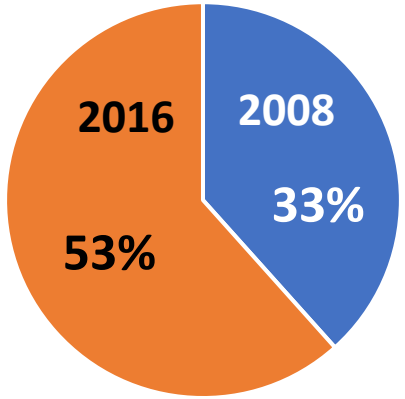
Increase of *de novo* MBC from 2008 to 2016
ESME cohort

HR+/HER2-



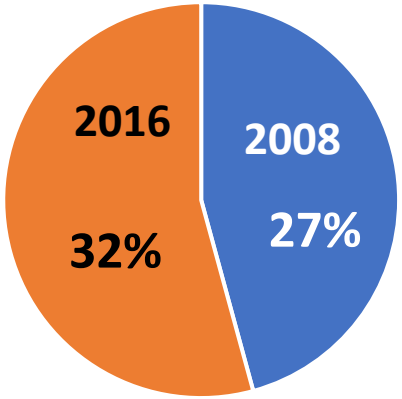
2008-2016: 8%

HER2+



2008-2016: 20%

TNBC

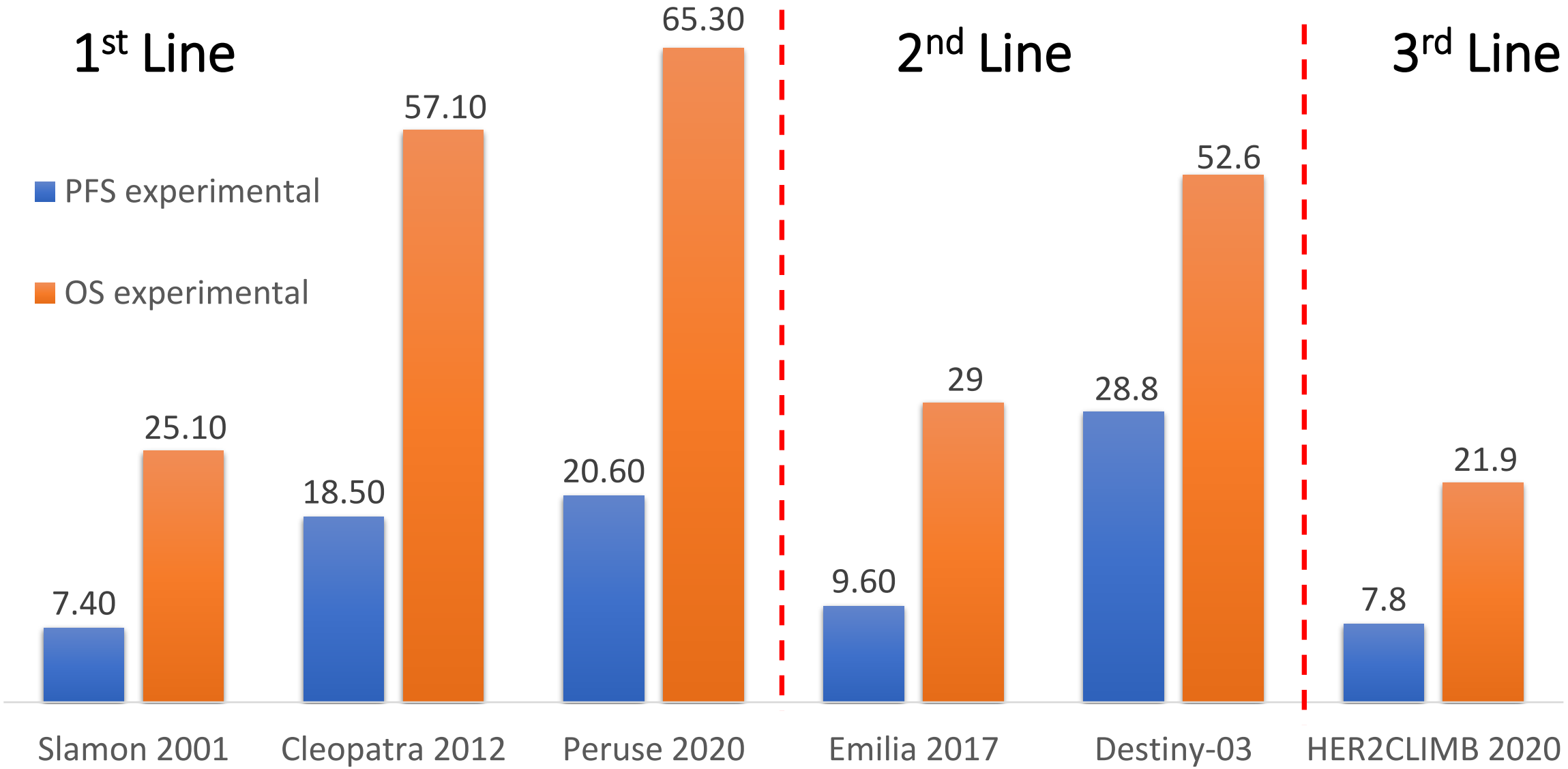


2008-2016: 5%

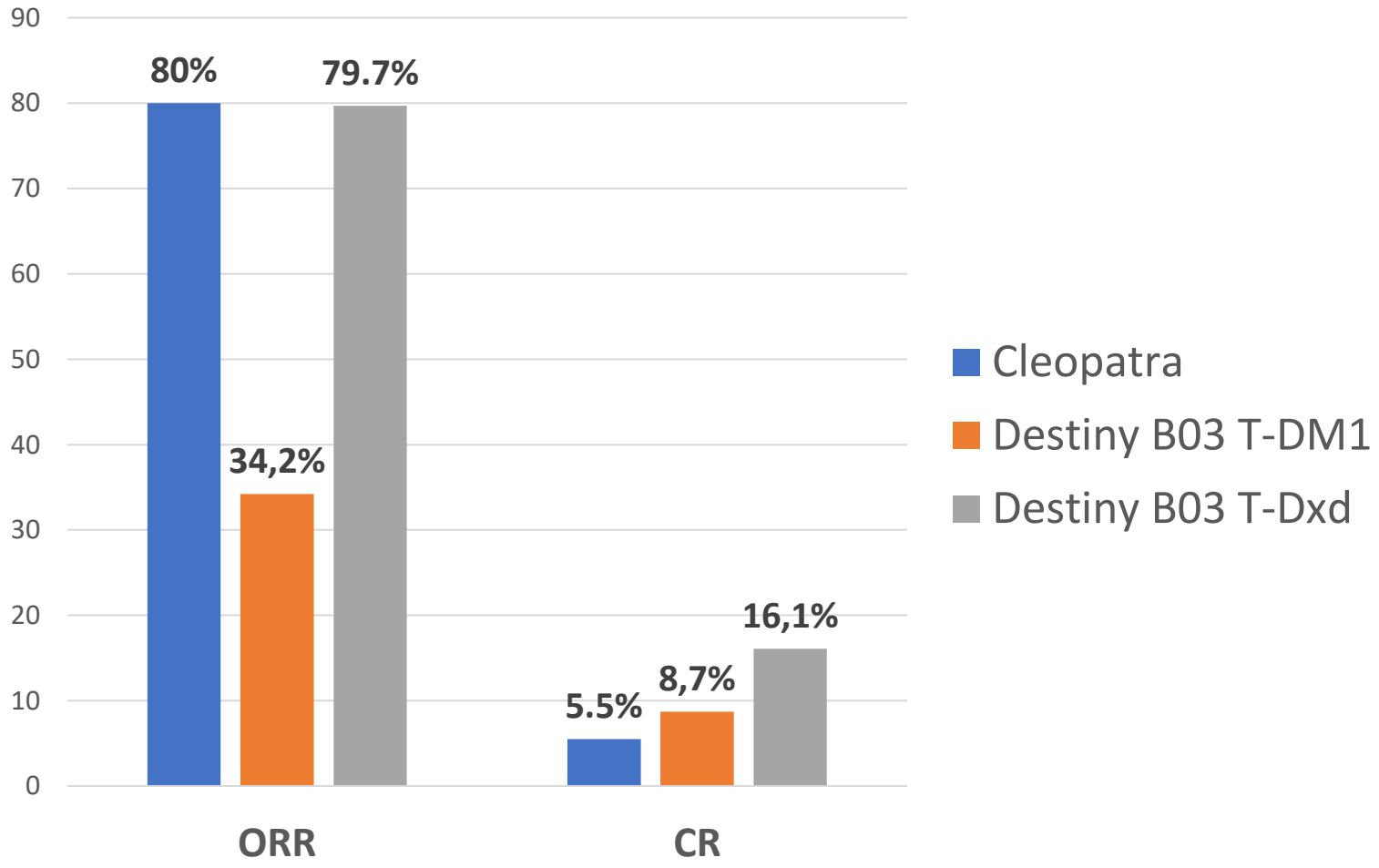
Multivariable analysis of OS in HER2-positive disease			
<6 mos (de novo)	1		
[6-24] mos	2.44	(1.98 - 3.02)	<0.001
>24 mos	1.42	(1.22 - 1.66)	<0.001

ESMO Open 2021; 6:100114.

Outcome (PFS and OS, in months) in landmark trials and overtime

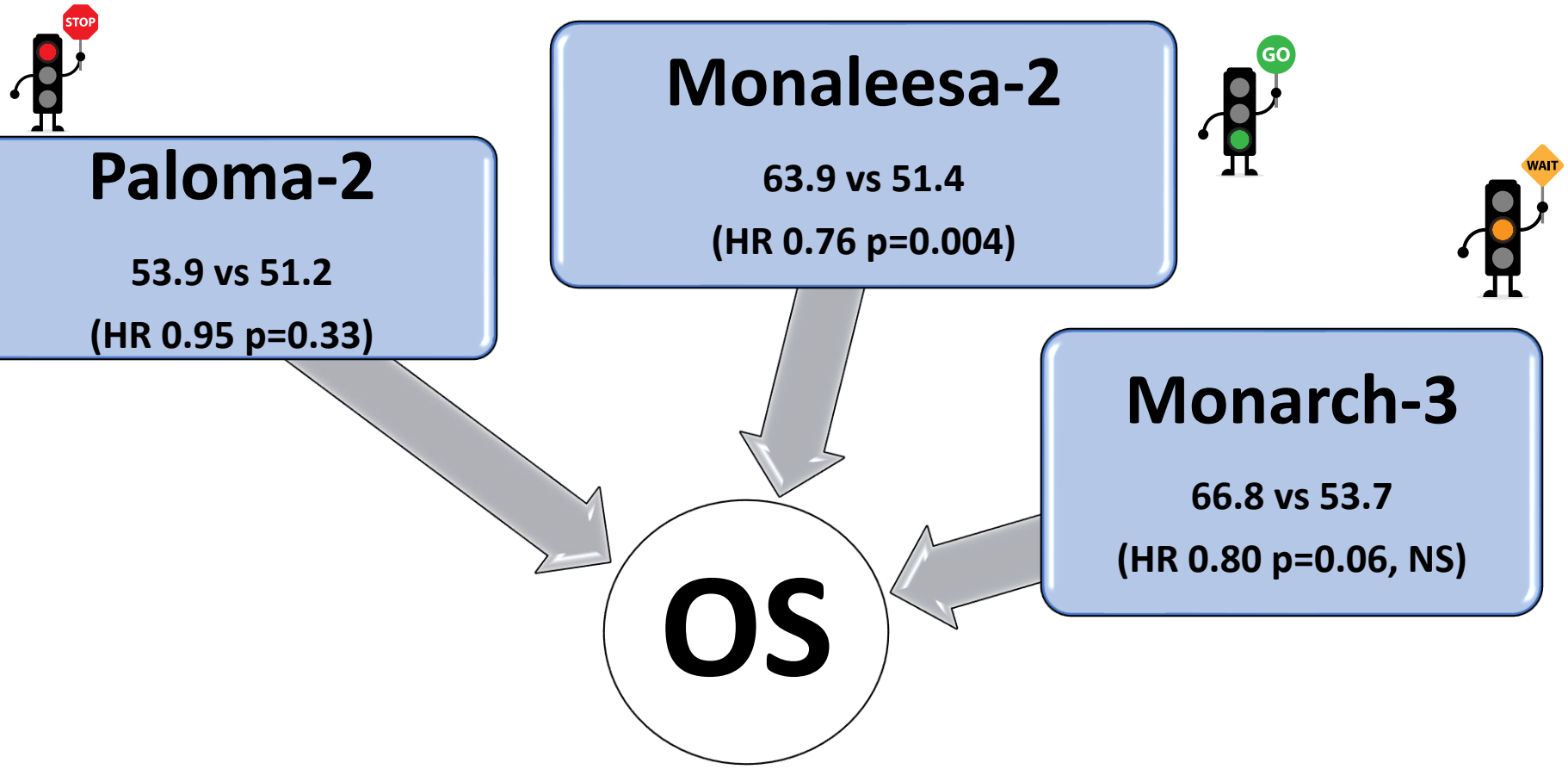


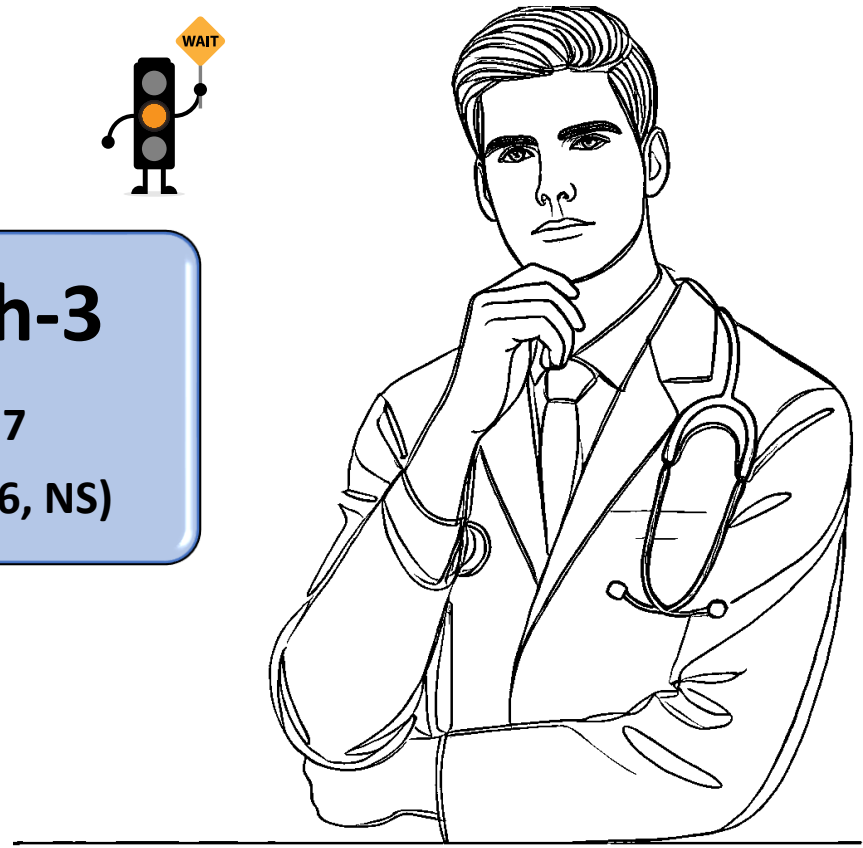
CR rate with modern anti-HER2 systemic therapy



Baselga J, et al. N Engl J Med 2012;366(2):109-19; Cortés J, et al. N Engl J Med 2022;386(12):1143-1154.

CDK 4/6 inhibitors are transformative drugs for the treatment of HR-positive HER2-negative BC

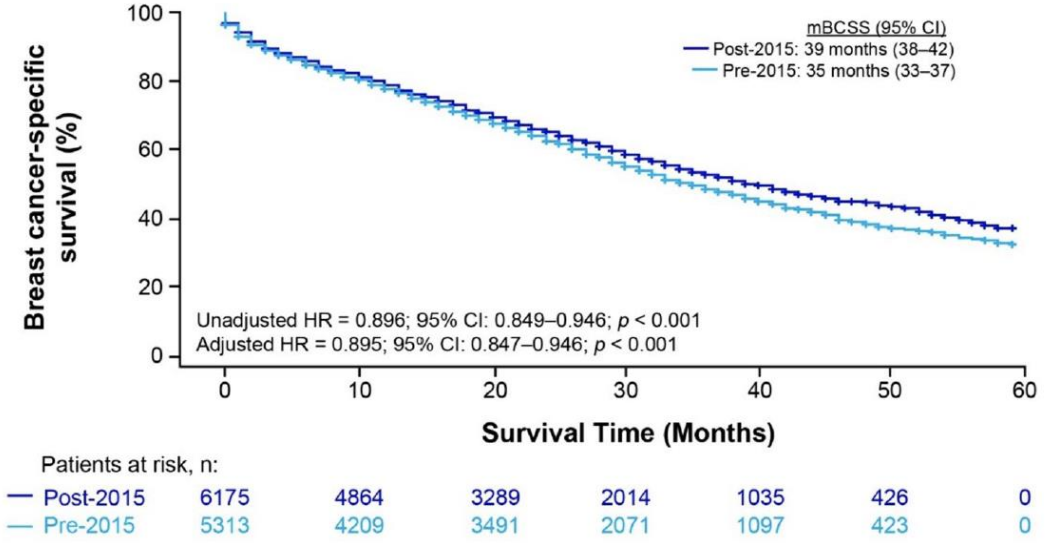




Trends in HR+ MBC survival before and after CDK4/6i introduction in the US

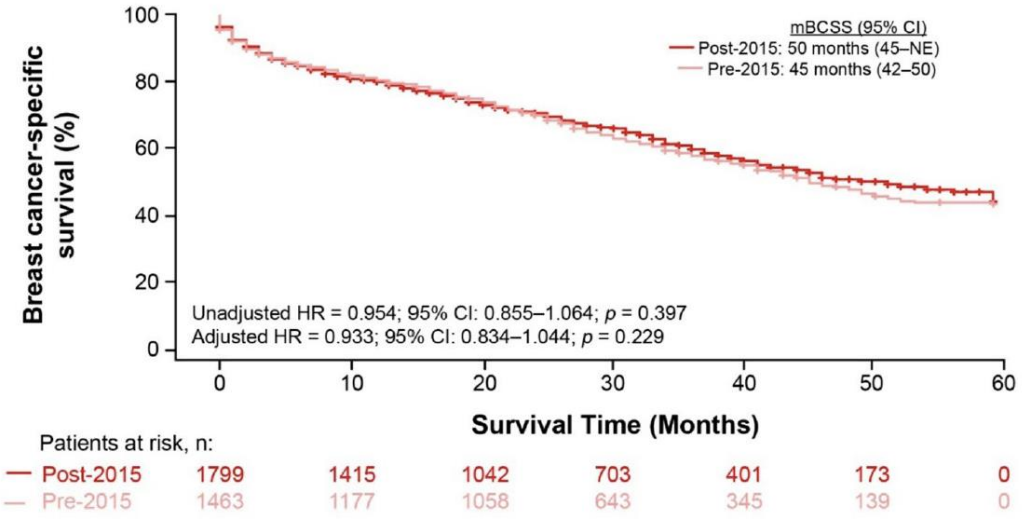
- SEER registry analysis:
  - 11,467 women with HR+/HER2- de novo MBC and 3260 women with de novo HR+/HER2+ MBC were included

HR+/HER2- *de novo* MBC



10% reduction in risk of BC-specific death (post-2015 versus pre-2015)

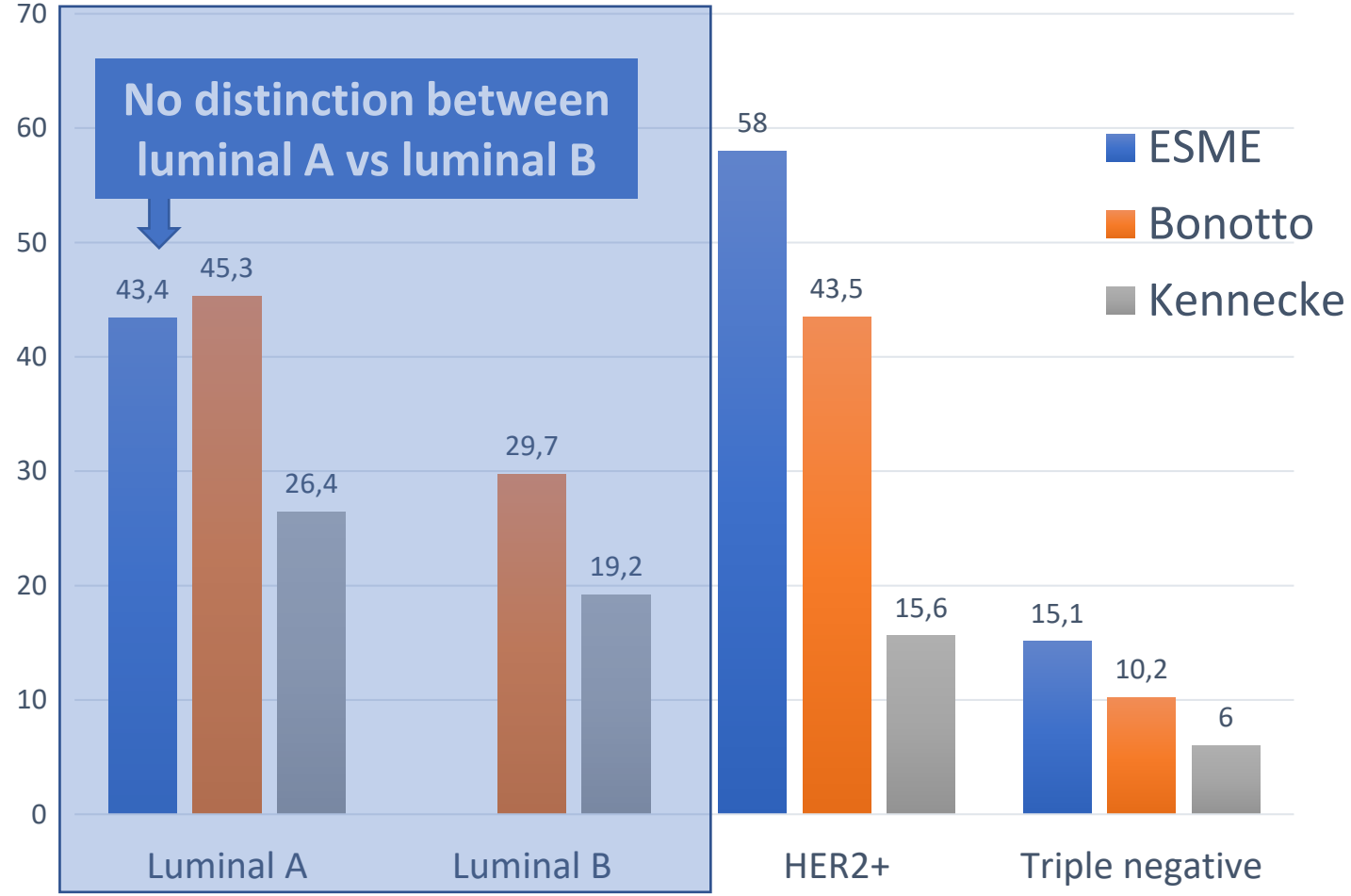
HR+/HER2+ *de novo* MBC



no significant change in BCSS (post-2015 versus pre-2015)

Brufsky A, et al. Breast Cancer Res Treat 2024;208(2):223-235.

Overall survival overtime

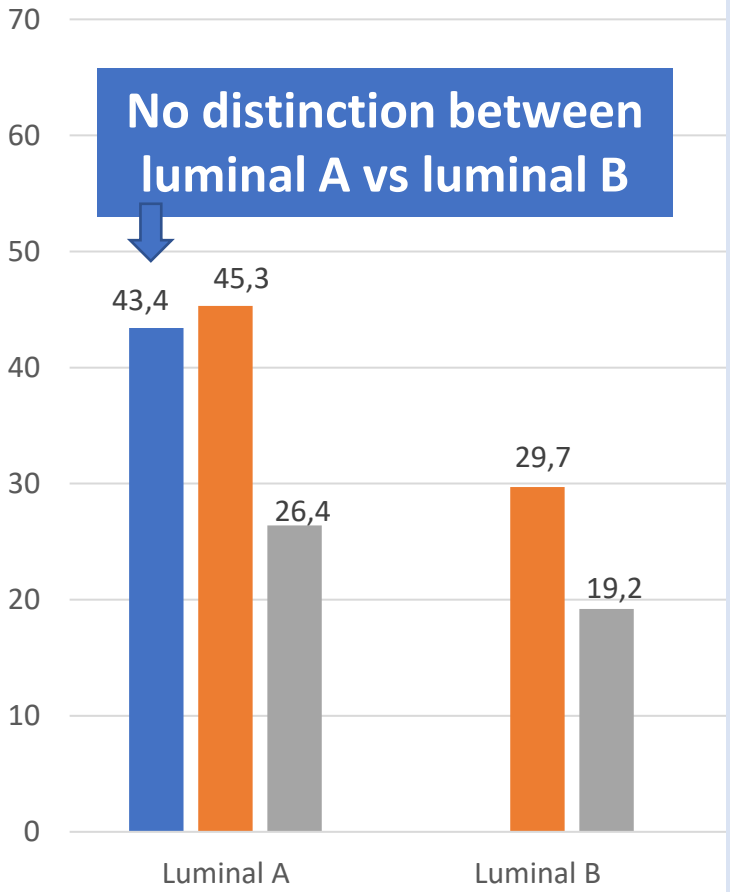


OS for 2013 (year of diagnosis) → 2008 → 2017 — French ESME cohort. ESMO Open 2021; 6:100114.

OS for the whole cohort → 2004 → 2012 — Bonotto M, et al. Oncologist 2014;19:608-15.

1986 → 1992 — Kennecke H, et al. J Clin Oncol 2010;28:3271-7.

OS: A new renaissance is upon us



Luminal A and B

First line (OS, months)

- MONALEESA-2: 63.9
- MONALEESA-7: not reached
- PALOMA-2: 53.9 (not significant)
- MONARCH-3: 66.8 (NS)

First and second line (OS, months)

- MONALEESA-3: 53.7

OS for 2013 (year of diagnosis) → 2008 → 2017 — French ESME cohort. ESMO Open 2021; 6:100114.

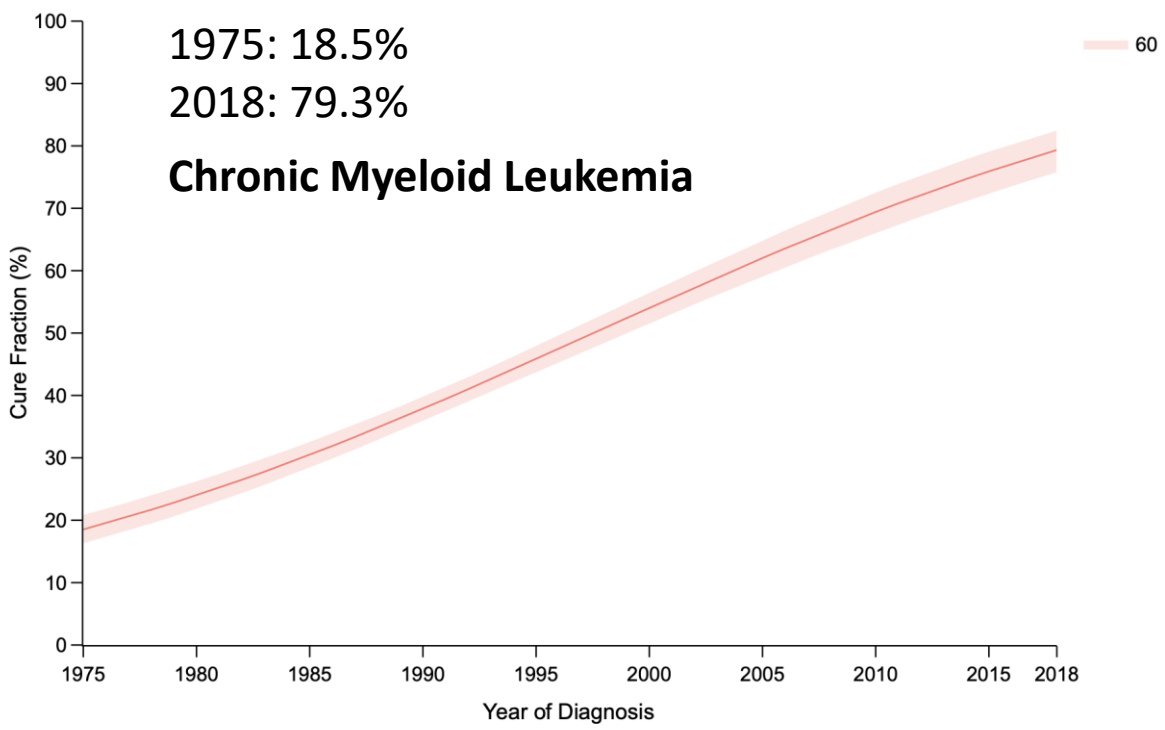
OS for the whole cohort → 2004 → 2012 — Bonotto M, et al. Oncologist 2014;19:608-15.

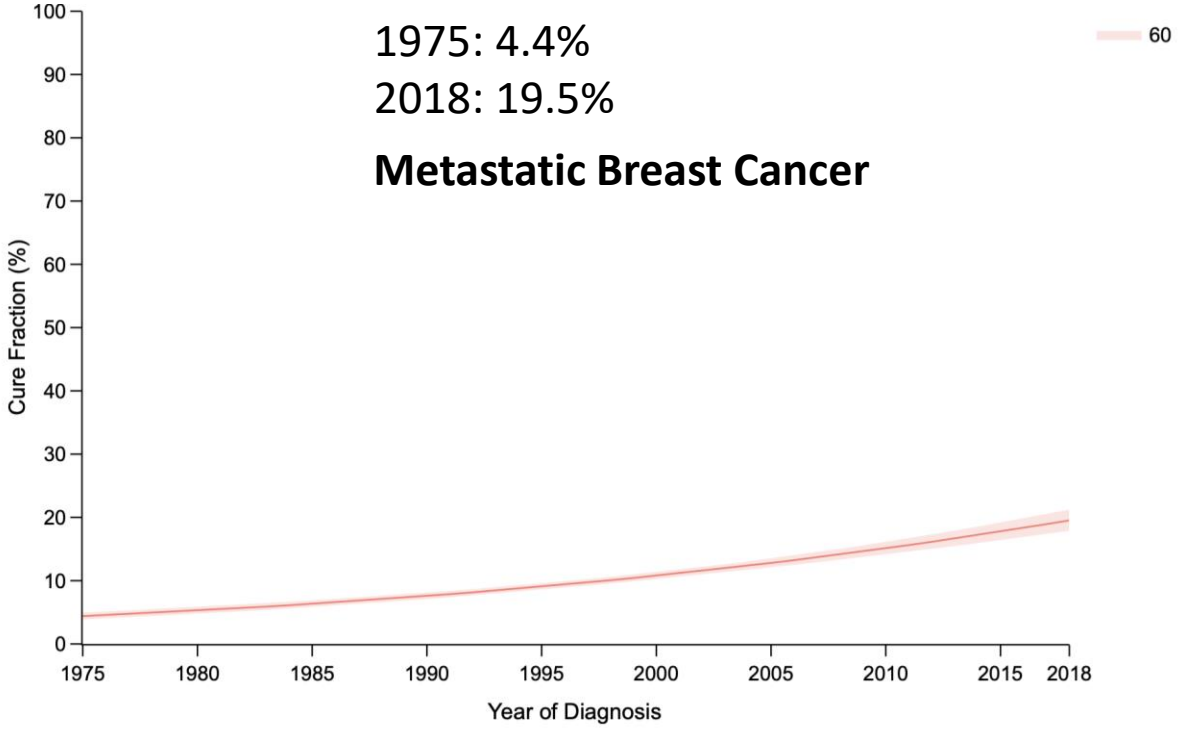
1986 → 1992 — Kennecke H, et al. J Clin Oncol 2010;28:3271-7.

There is is an everyday practical query in the clinic

“Doc, am I now cured?”

Trends in Cure Fraction



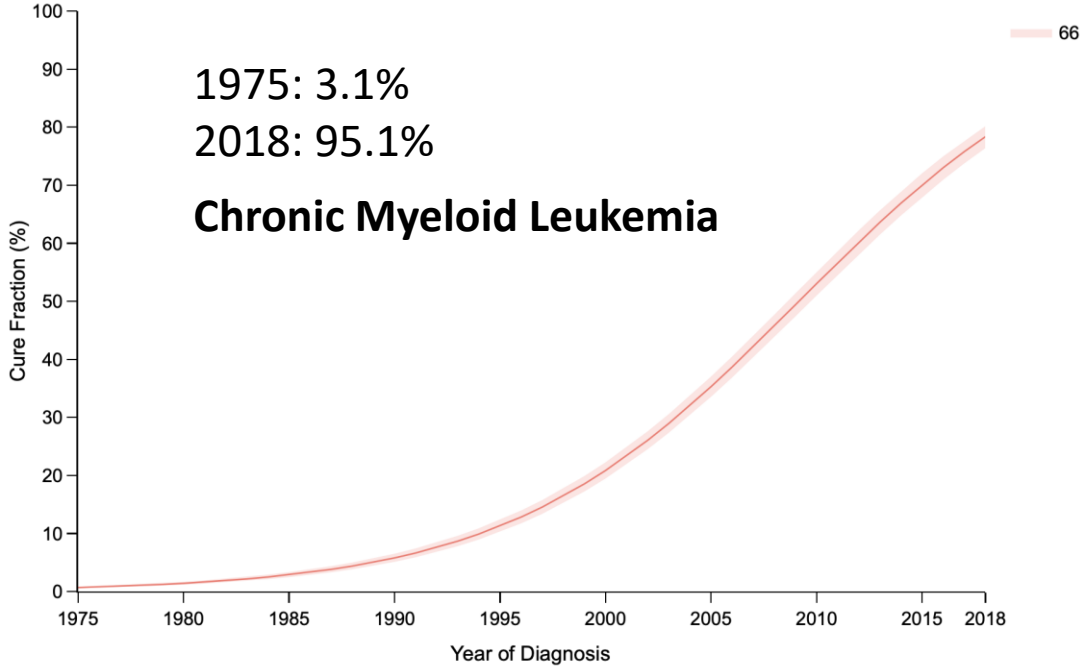


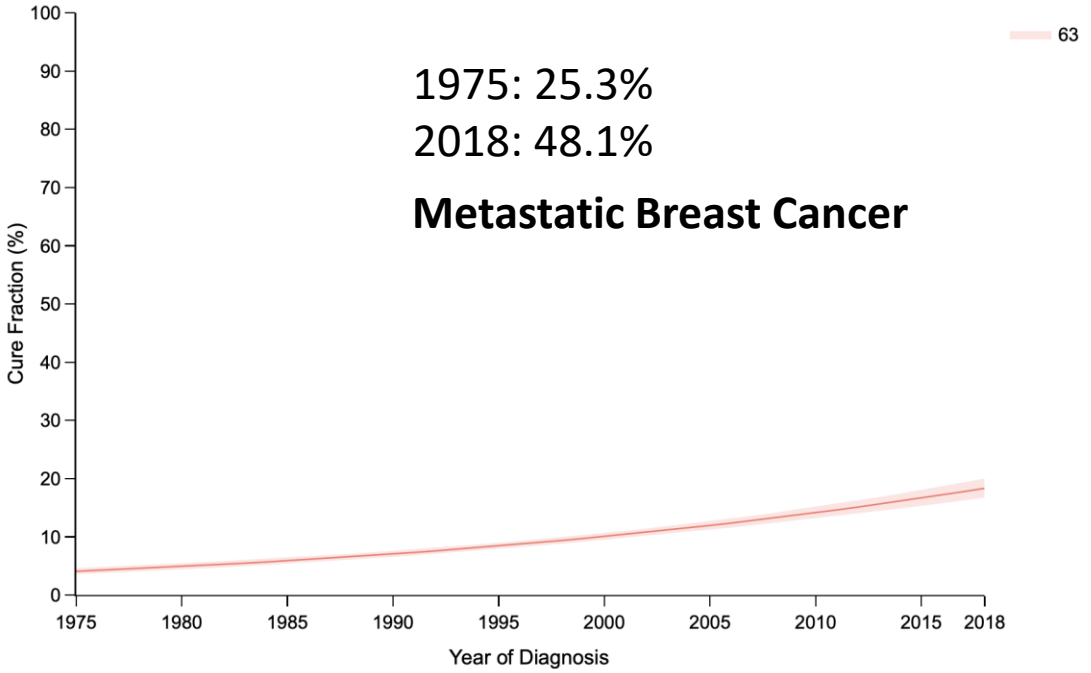
Cure fraction: The proportion of cancer patients expected to have no excess mortality compared with general population

http://cxia.cc/cancure/

Xia C, et al. Int J Cancer 2022

Trends in 5-Year Cure Probability





5-year cure probability: The probability of being cured at five years since cancer diagnosis.

http://cxia.cc/cancure/

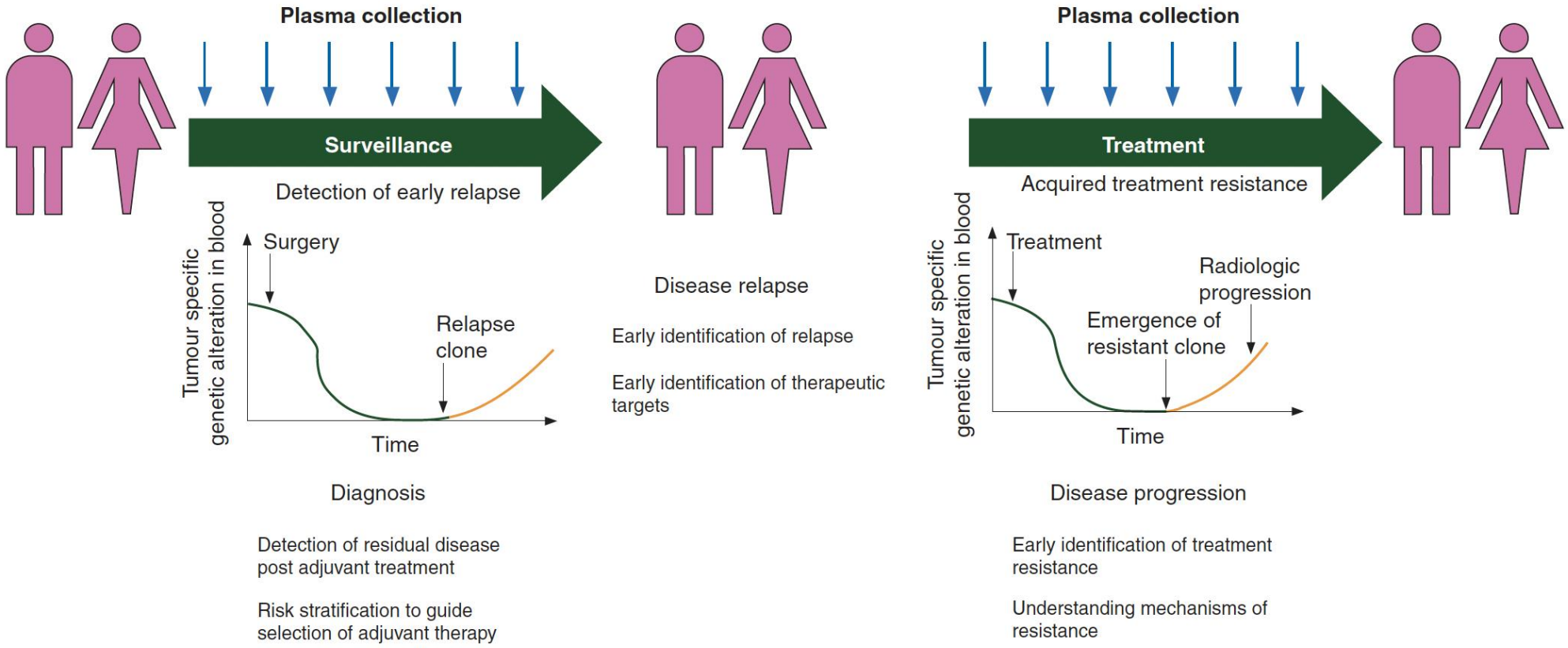
Xia C, et al. Int J Cancer 2022

“Can we consider the patient cured?”

To inform about the prognosis

To identify which patients can safely stop treatment

Potential clinical applications of ctDNA analysis



Ignatiadis M, Dawson SJ. Ann Oncol 2014;25(12):2304-2313.


MISSION
IMPOSSIBLE