Les défis des patients guéris, les défits des malades chroniques

Cancer du sein

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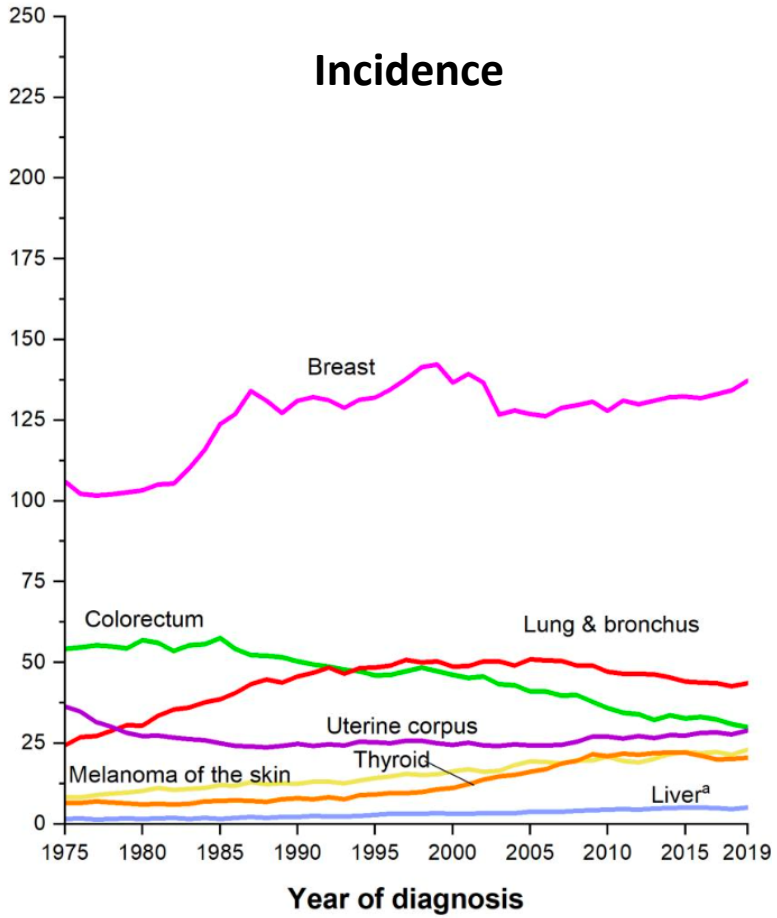
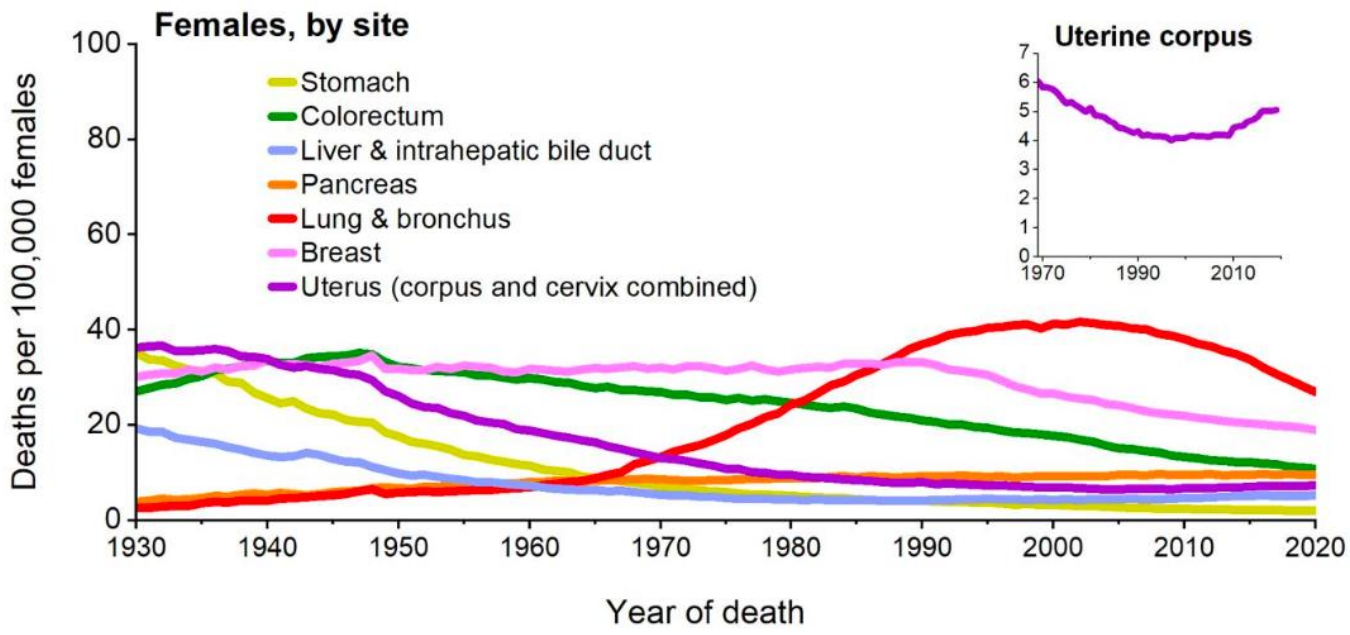
Cancer statistics

Incidence

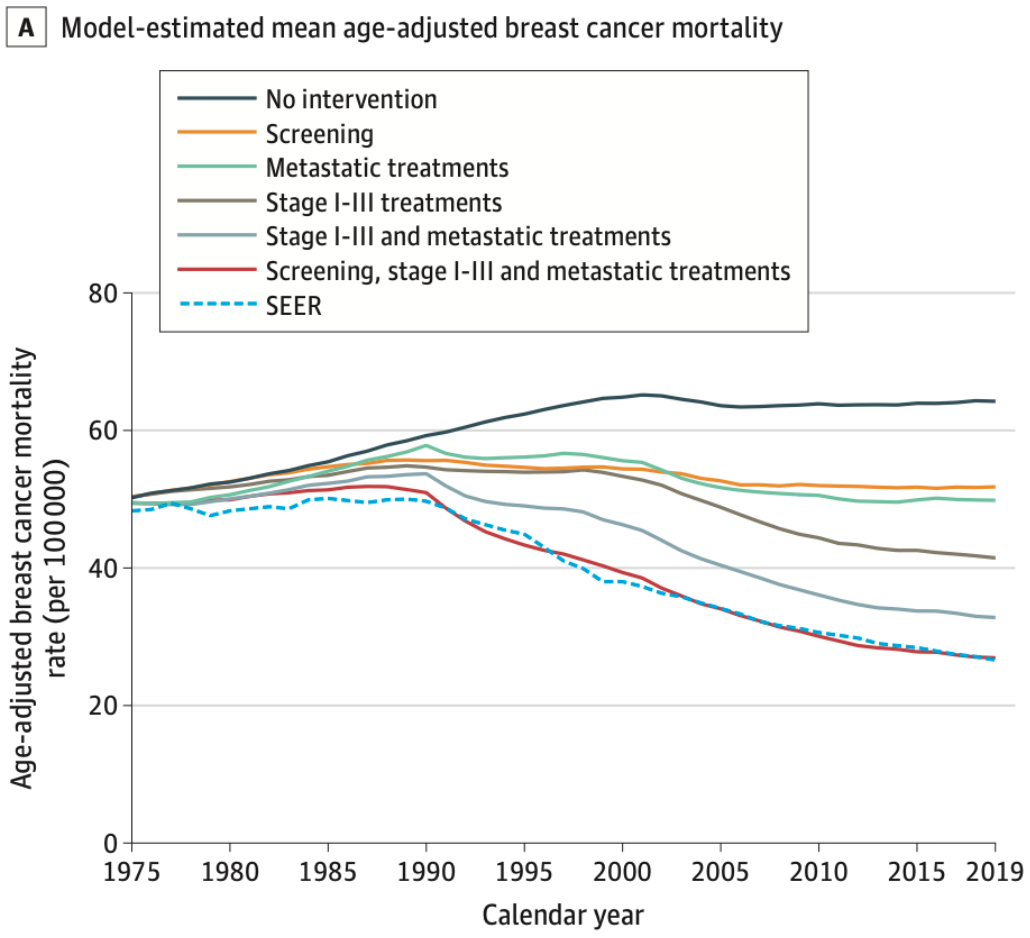


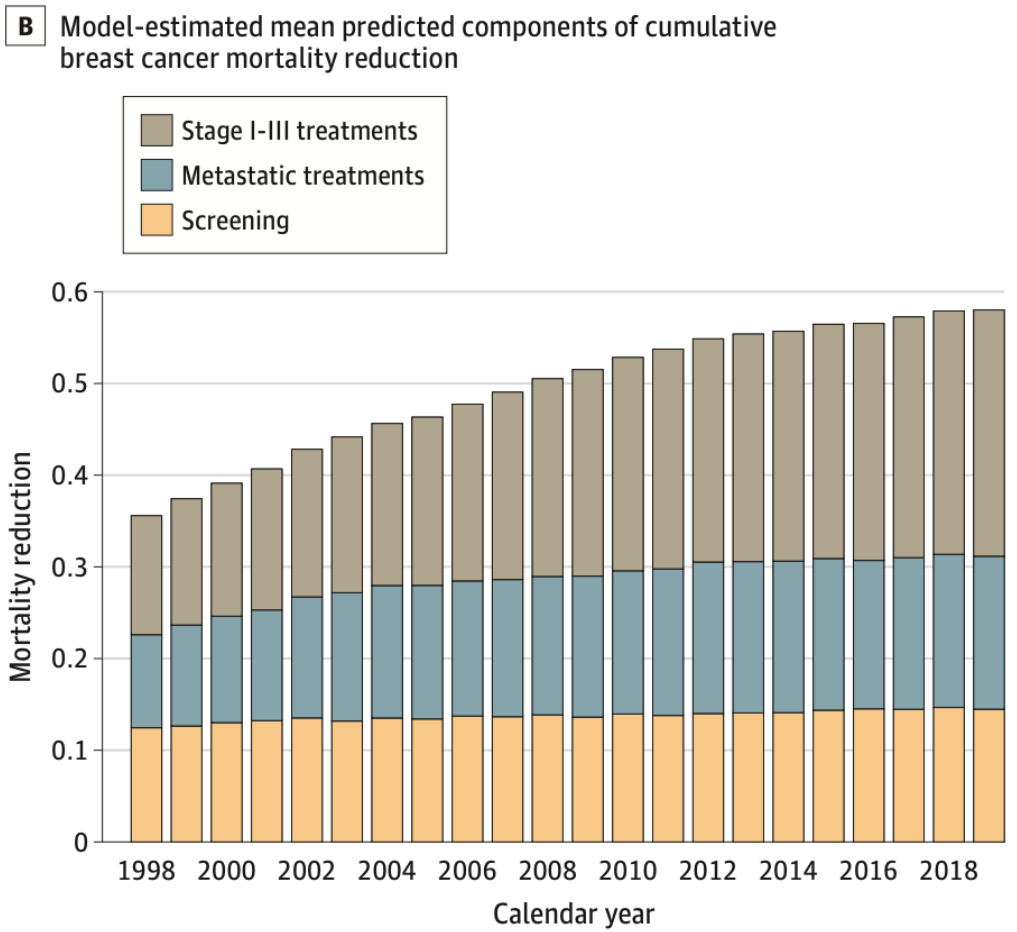
Mortality



Siegel RL et al. CA Cancer J Clin 2023

Analysis of Breast Cancer Mortality in the US—1975 to 2019





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

Breast cancer numbers in Switzerland

Stage of breast cancer

Breast cancer death per year

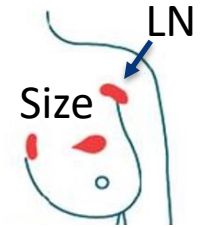
	New cases				Deaths			
Cancer	Number	Rank	(%)	Cum.risk	Number	Rank	(%)	Cum.risk
Breast	7 292	1	12.1	9.84	1 506	3	7.9	1.48

Bouchardy et al., Schweizer Krebsbulletin Nr. 2/2015: 152; WHO, Globocan 2020

Cancer mammaire stade précoce

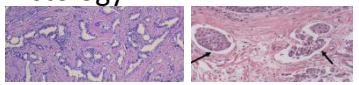
Adjuvant systemic treatments overview

Stage

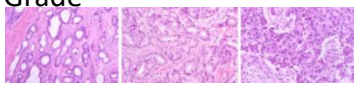


Biology

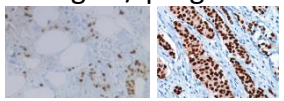
Histology LVI



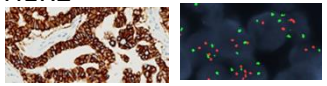
Grade



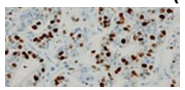
Estrogen / progesterone rec.

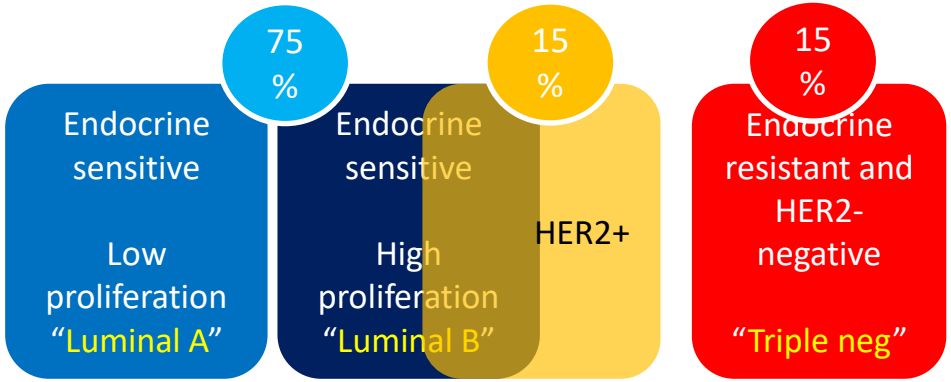


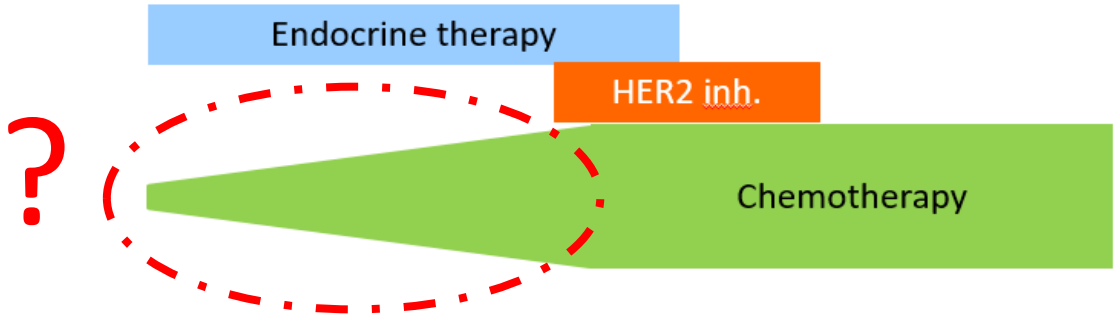
HER2



Proliferation (Ki67)



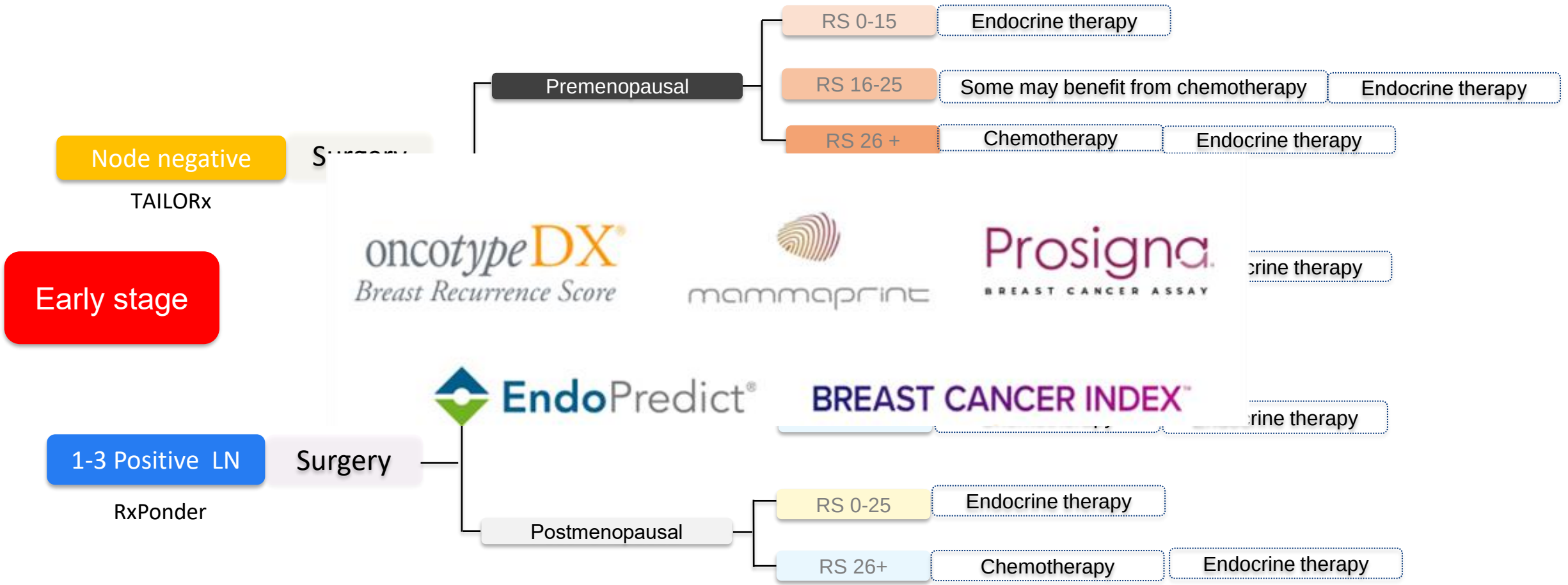




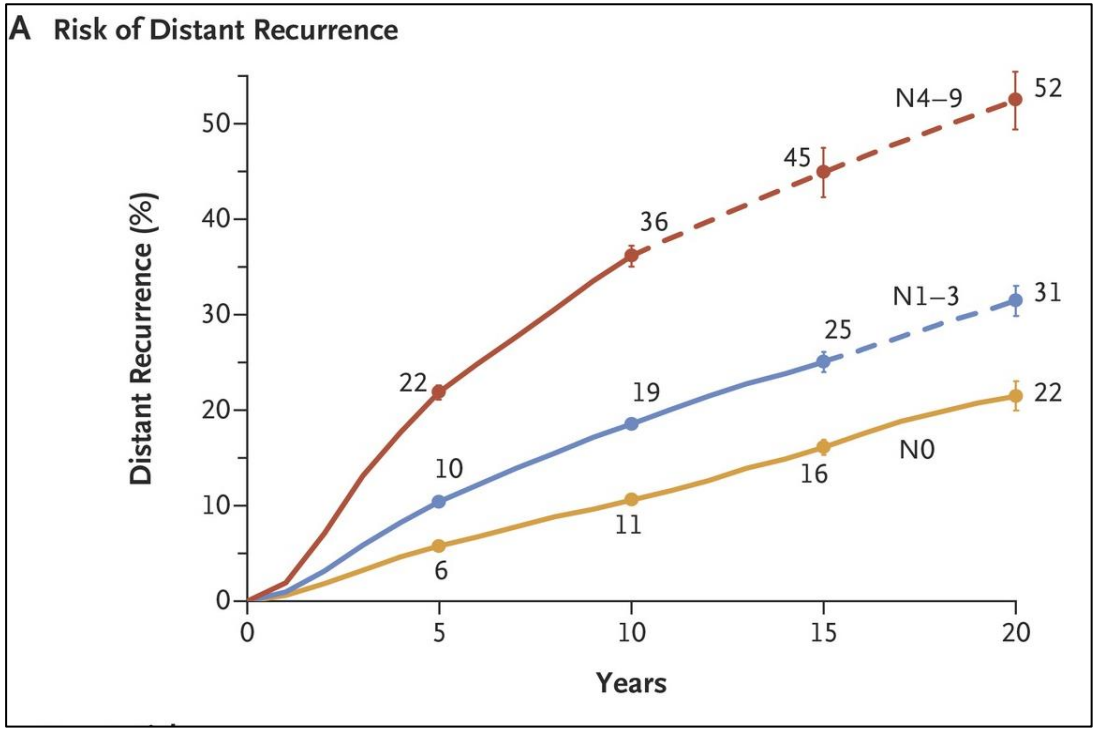
LN= lymph nodes; LVI= lymphovascular invasion

Lancet 2015; 386: 1341–52 / Lancet Oncol 2021; 22: 1139–50 / Lancet 2012; 379: 432–44

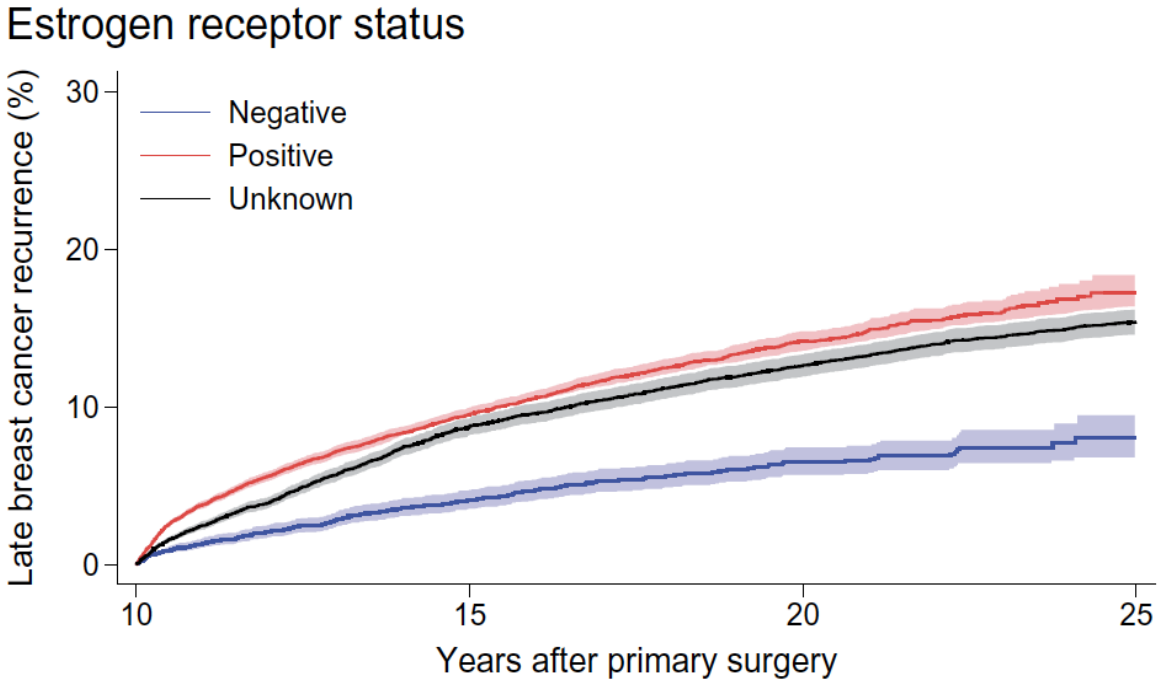
Current standard of care in eBC HR+/HER2-



Late Recurrence: Scope of the Clinical Challenge

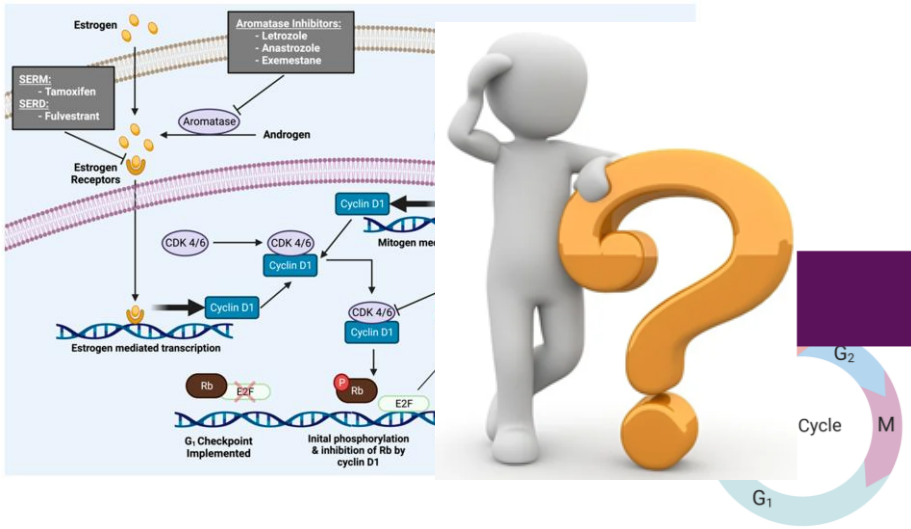


Pan H et al. *NEJM* 2017



Pedersen RN, et al JNCI 2021

Phase III trials: CDK4/6 inhibitors in HR+/HER2- Advanced stage BC



Consider adjuvant CDK4/6i?

HR+/HER2- Endocrine-sensitive MBC

First-line (*de novo* MBC or DFI>12 months from ET for EBC)

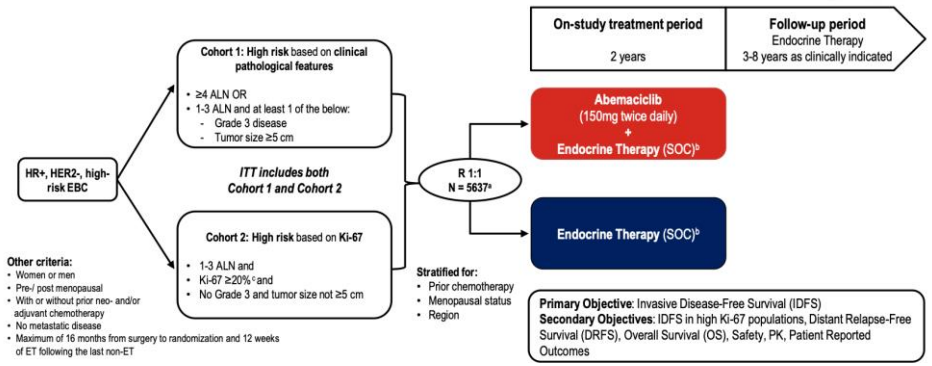
HR+/HER2- Endocrine-resistant MBC

Secondo line or first line with DFI≤12 months from ET for EBC

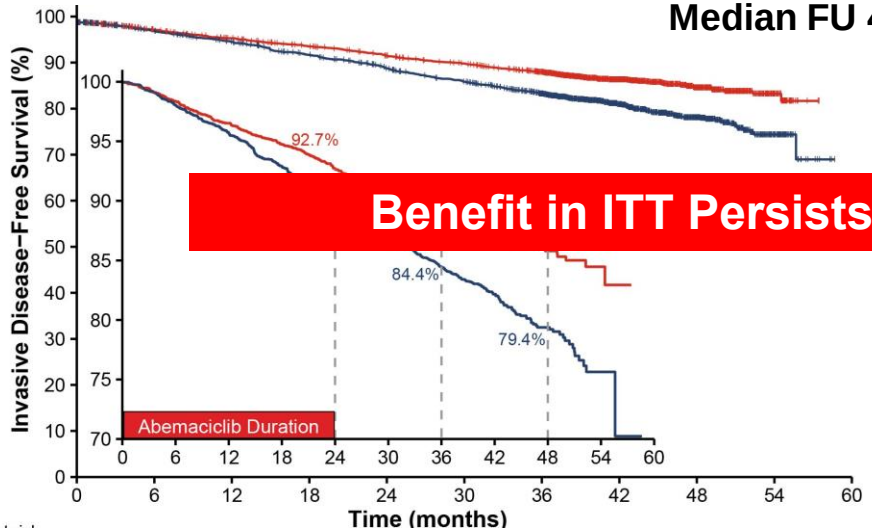
HR: 0.46 to 0.59

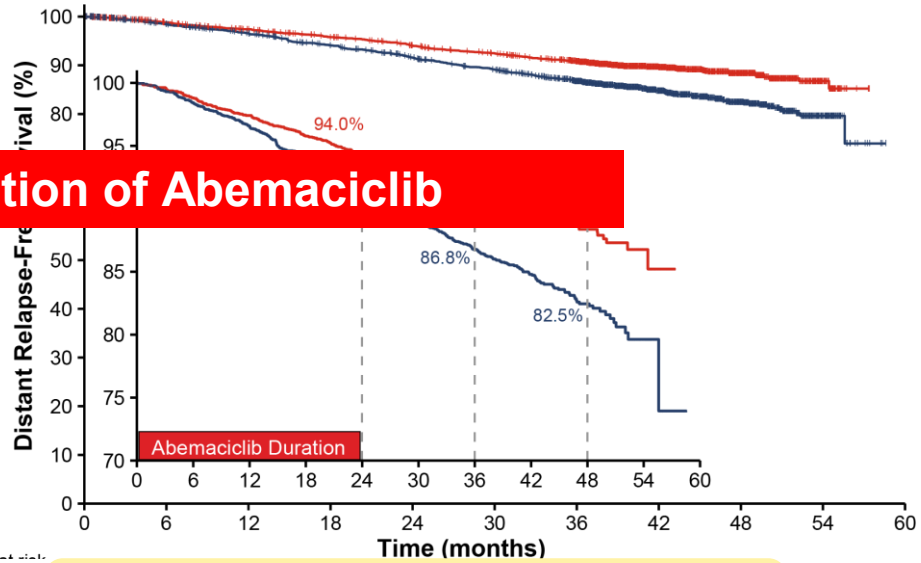
Abdelmalak M et al. Cancers 2022 ; Miglietta F et al. ESMO Open 2022

MonarchE trial



Median FU 42m (>99% off ttt)





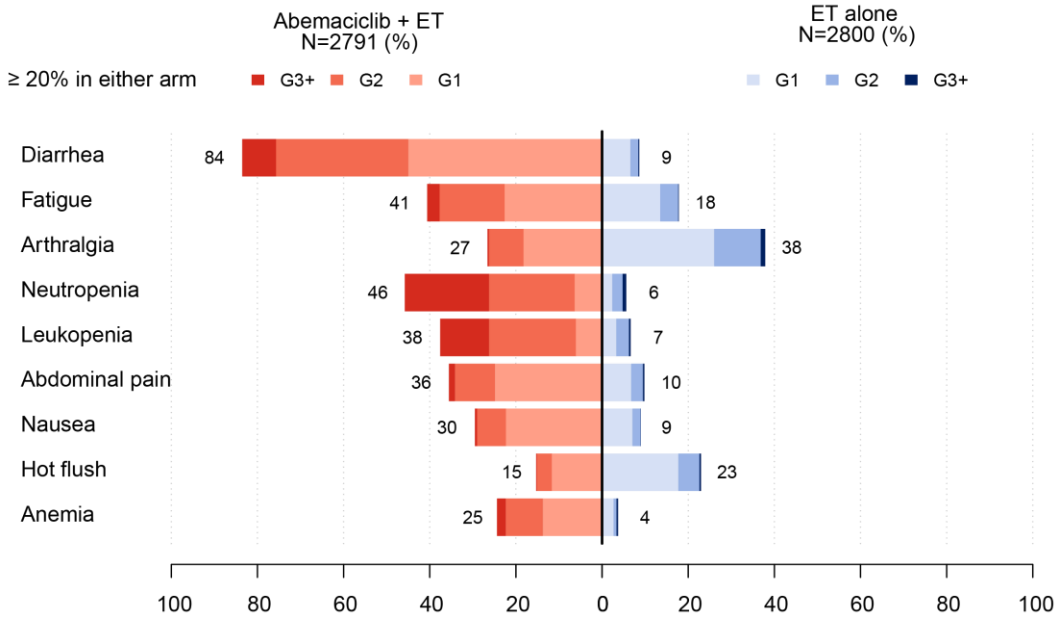
Benefit in ITT Persists Beyond Completion of Abemaciclib

33.6% reduction in the risk of developing an IDFS event

34.1% reduction in the risk of developing a DRFS event

Johnston SRD et al 2023. Lancet Oncol :24(01):77-90

monarchE: toxicity profile

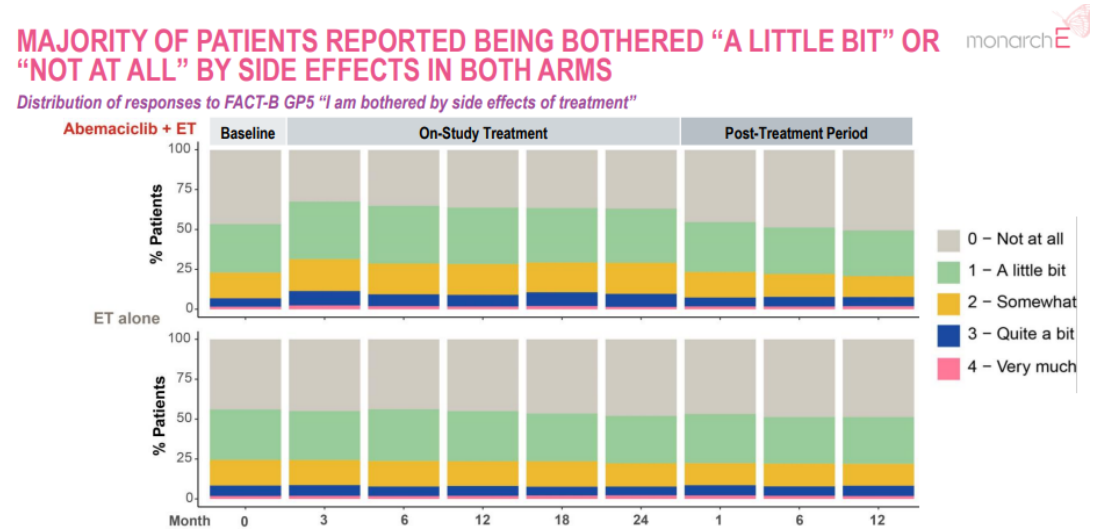


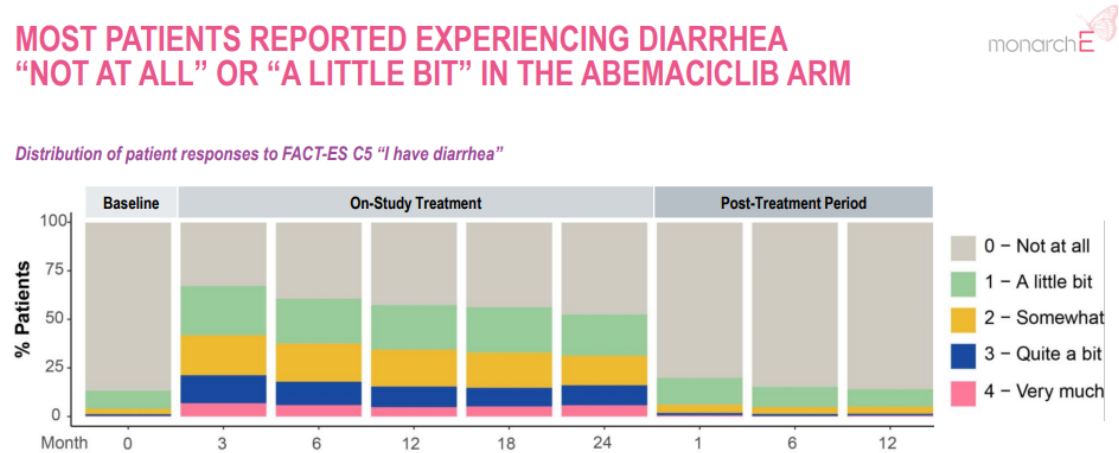
Median duration of abemaciclib: 23.7 months

Other events of interest, any gradec	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

Johnston SRD et al 2023. Lancet Oncol :24(01):77-90

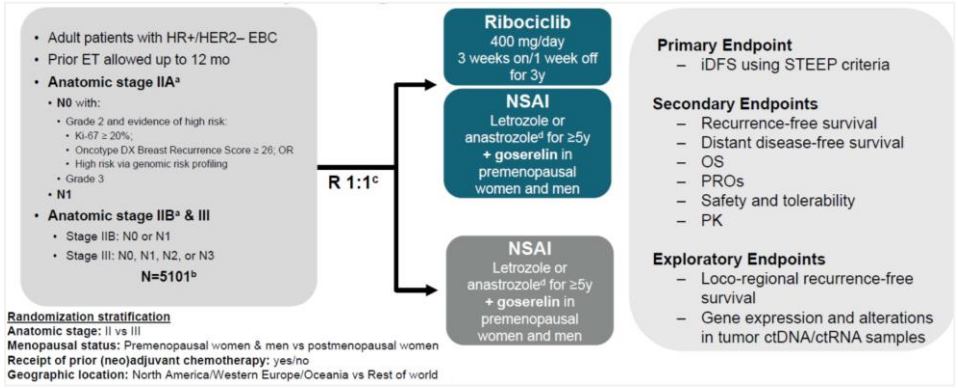
PROs

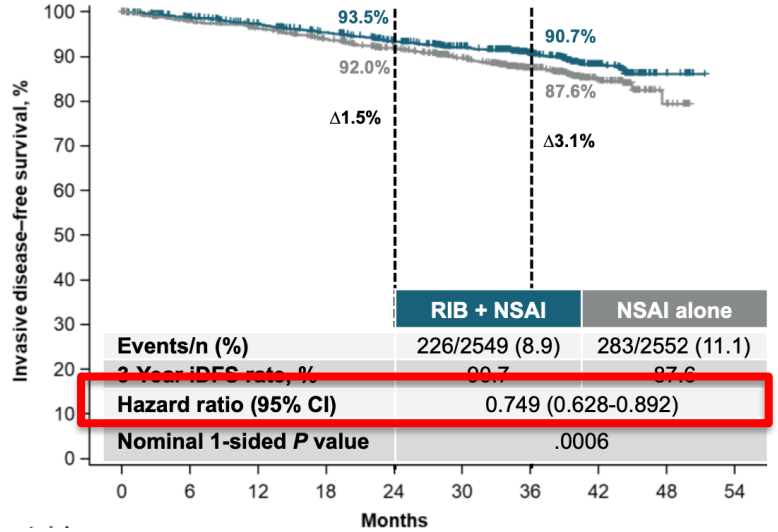


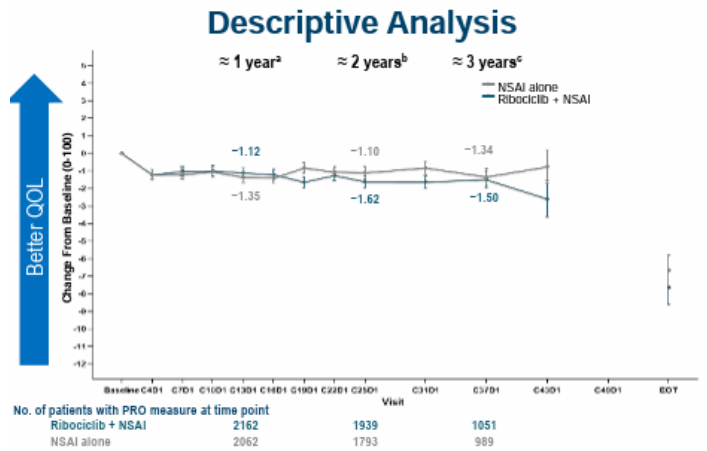


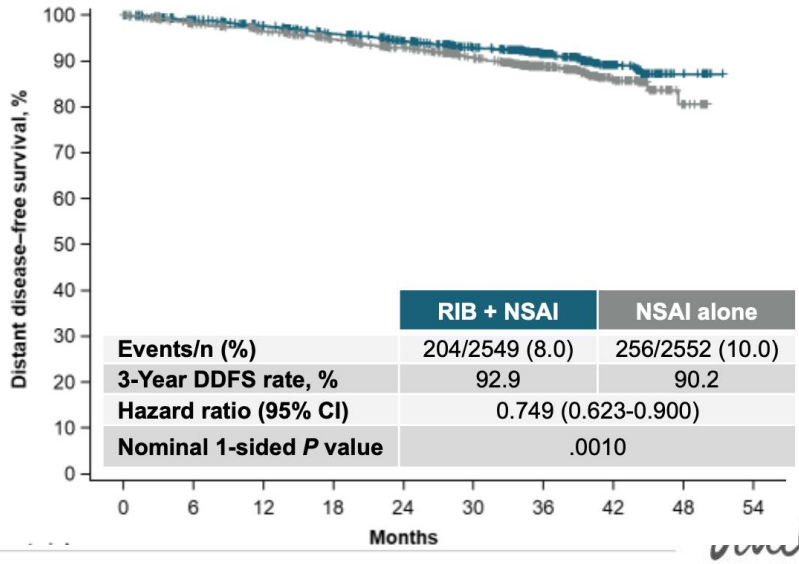
Harberck N et al. ESMO Breast 2023

NATALEE trial





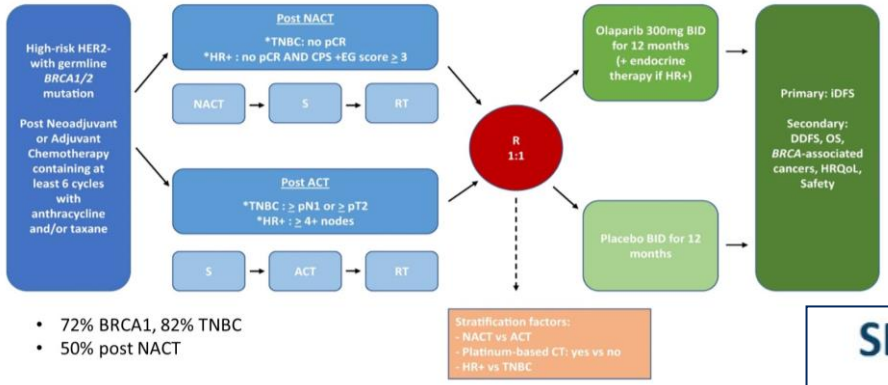




The risk of distant disease was reduced by 25.1% with Ribo+NSAI vs NSAI alone

Hortobagyi G. N. et al. Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2– Early Breast Cancer: Final Invasive Disease–Free Survival Analysis From the NATALEE Trial. SABCS 2023 (GS03-03)

OlympiA: Adjuvant Olaparib for gBRCA1/2

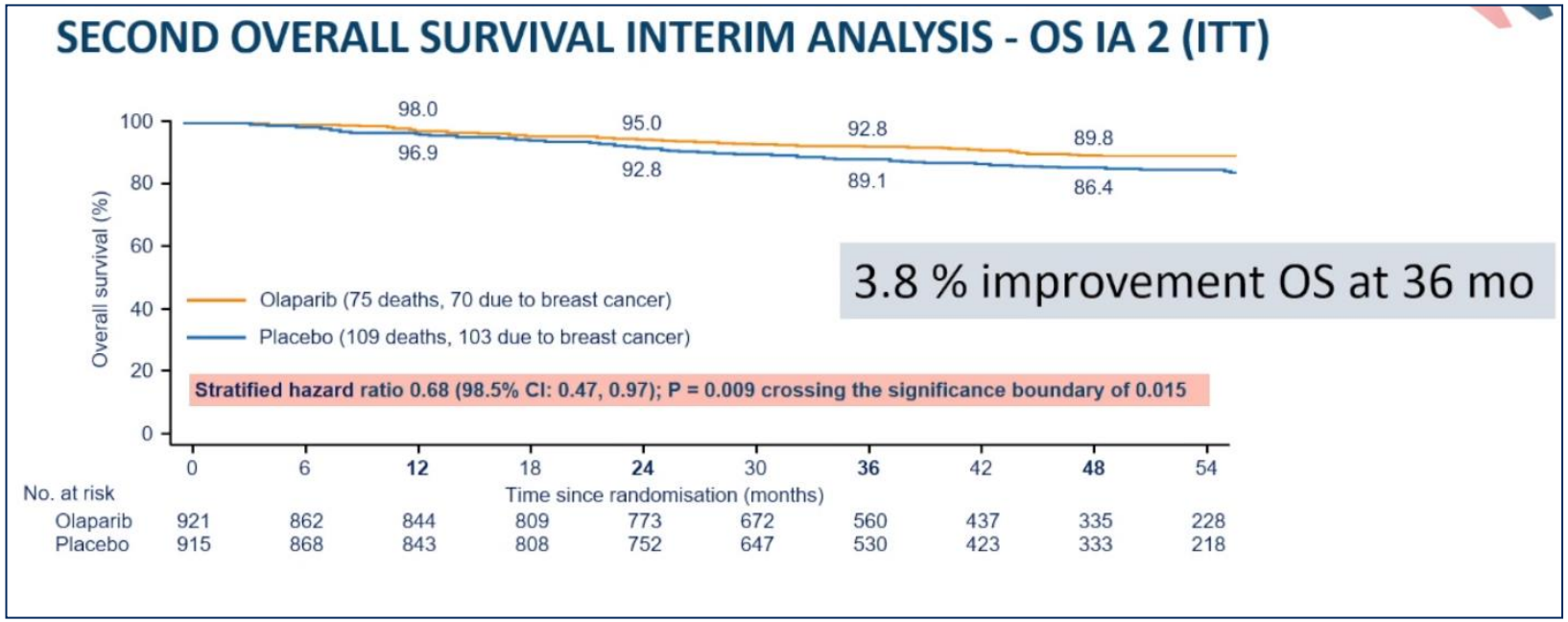


- 72% BRCA1, 82% TNBC
- 50% post NACT

ER and/or PgR positive/HER2 negative patients must have residual **invasive** cancer in the breast or the resected lymph nodes (non pCR) **AND CSP&EG score ≥ 3**

Add the points for Clinical Stage + Pathologic Stage + ER status + Nuclear grade to derive a sum (CPS&EG score) between 0 and 6.

- No increase in MDS/AML compared to placebo
- Most toxicity grade 1/2; nausea most common
- Grade 3: Anemia 9%, fatigue 2%, neutropenia 5%



Tutt et al. NEJM 2021; Tung N NPJ Breast Cancer 2022

Preoperative or Postoperative Chemotherapy in eTNBC?

RCTs confirm same outcome with adj/neo-adjuvant therapy (eg NSABP 18&27)

Adjuvant treatment

OP → Chemo

Historically if operable

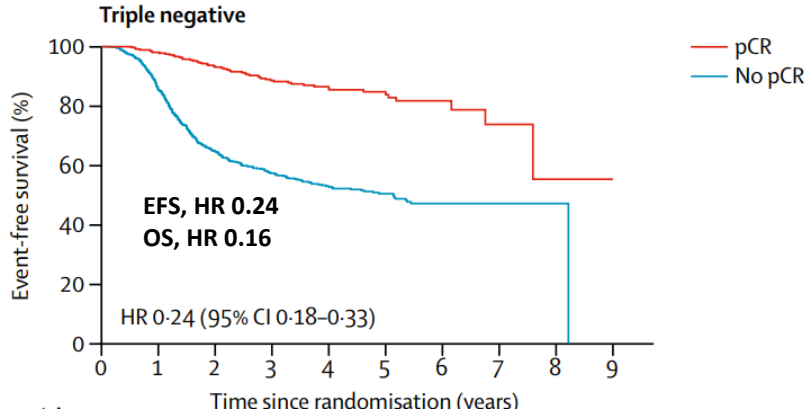
Chemo → OP

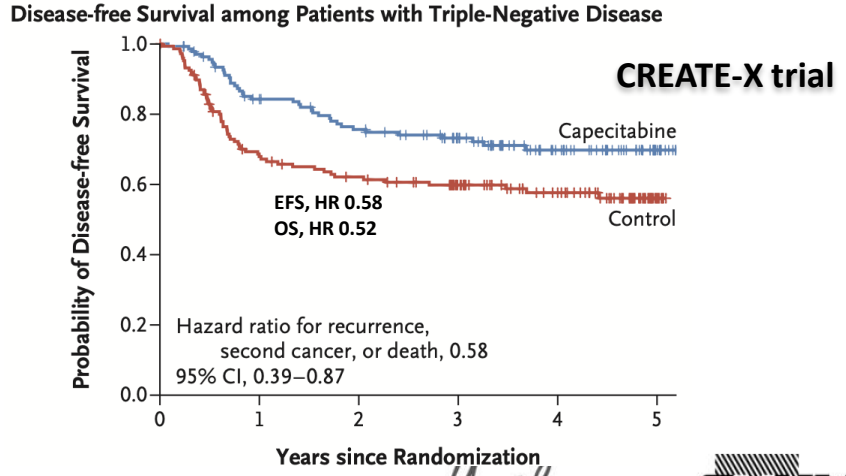
Neo-adjuvant treatment

Dowstaging facilitates less invasive surgery

Path CR ypT0/is ypN0

Residual disease





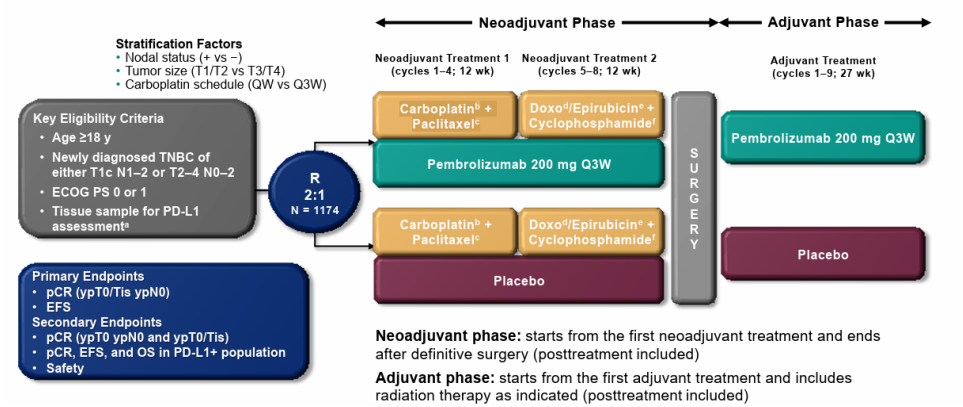
TNBC= 33% (n=390)
DFS 5y TNBC: 69.8% vs 56.1%
HR0.58
OS 5y TNBC: 78.8% vs 70.3%
HR0.52

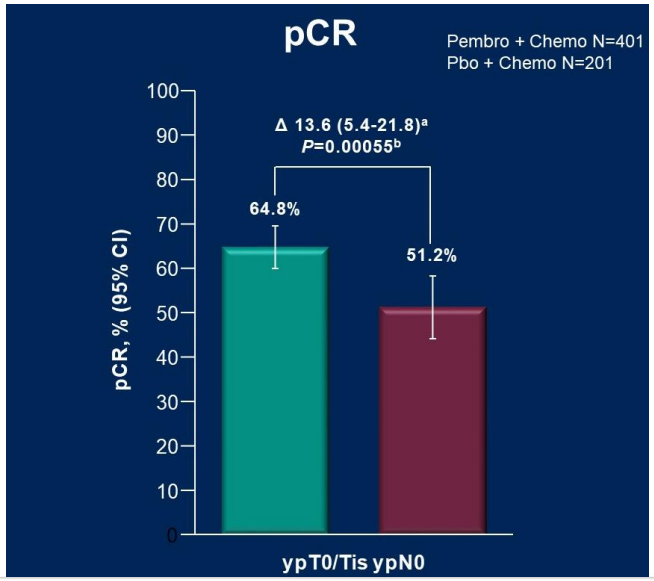
Cortazar P et al. Lancet 2014; 384:164-72; Masuda N et al. NEJM 376:2147-59, 2017

Early TNBC: how can we increase response to NACT?

Addition of PD-L1/PD1 inhibitors

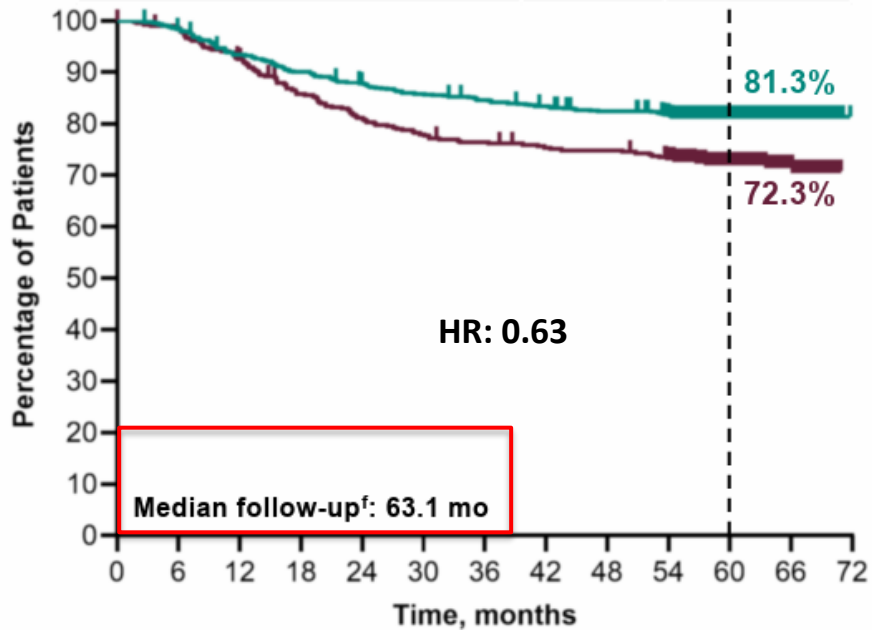
KEYNOTE 522: updated EFS





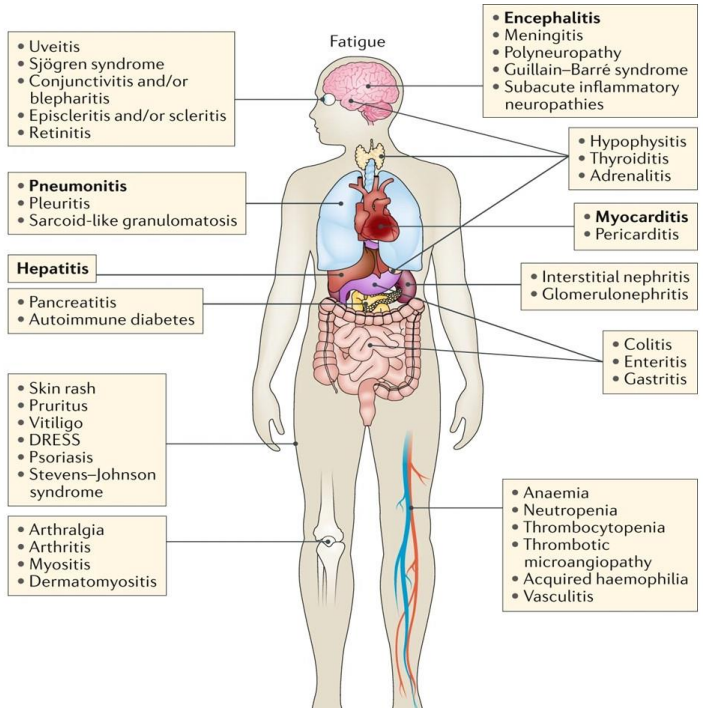
EFS at IA6

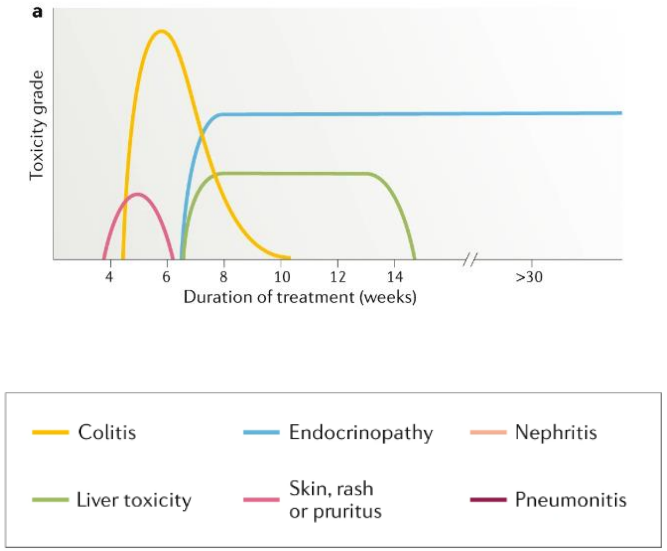
IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	



Schmid P et al. SABCS 2023

Adverse events of immune checkpoint inhibitors



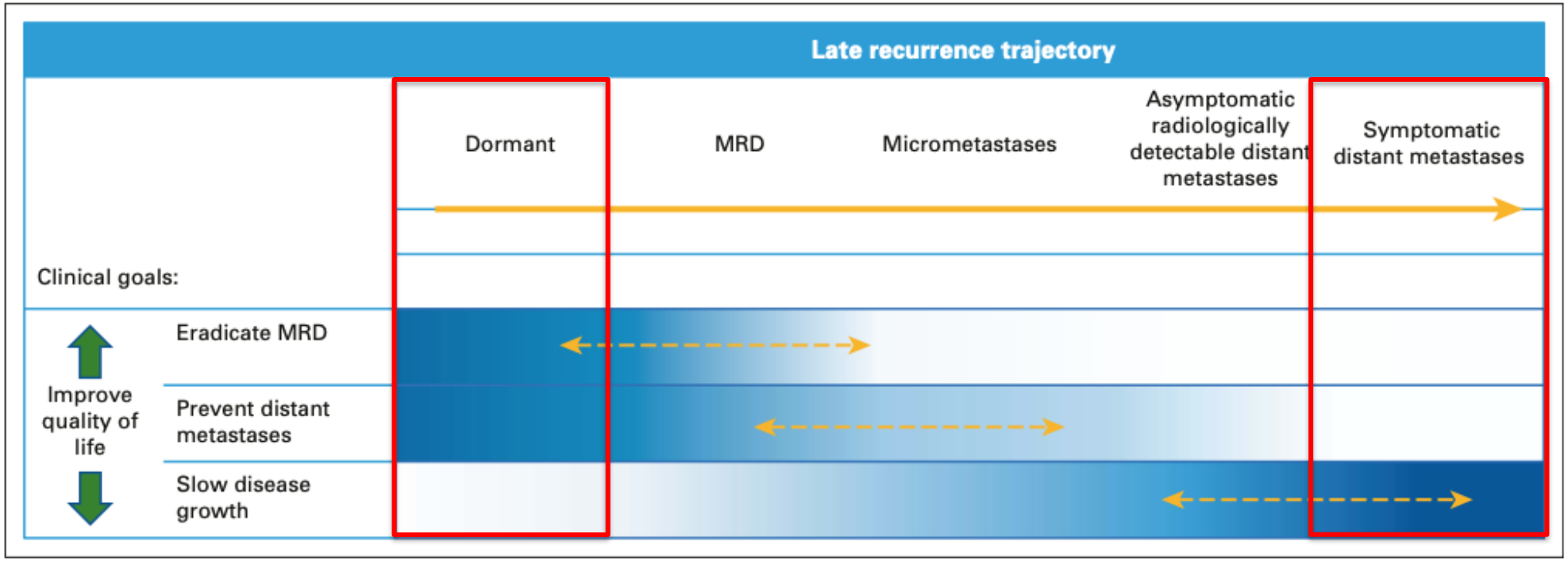


KEYNOTE 522: Immune related Aes

ADVERSE EVENT	PEMBROLIZUMAB-CHEMOTHERAPY	PLACEBO-CHEMOTHERAPY	PEMBROLIZUMAB-CHEMOTHERAPY	PLACEBO-CHEMOTHERAPY
	ANY GRADE		GRADE 3 OR ABOVE	
Hypothyroidism	13.7 %	3.3 %	0.4 %	0 %
Hyperthyroidism	4.6%	1 %	0.3 %	0 %
Severe Skin reactions	4.4%	1%	3.8 %	0.3 %
Adrenal insufficiency	2.3%	0 %	1.3 %	0 %
Fatigue	41.1 %	37.8 %	3.5 %	1.5 %
Diarrhea	29.4%	23.7 %	2.2 %	1.3 %
Rash	21.8 %	15.2 %	0.9 %	0.3 %
Infusion reaction	16.9 %	11.1 %	2.6 %	1.0 %
Elevated Alanine aminotransferase level	25.5 %	24.7 %	5.2 %	2.3 %

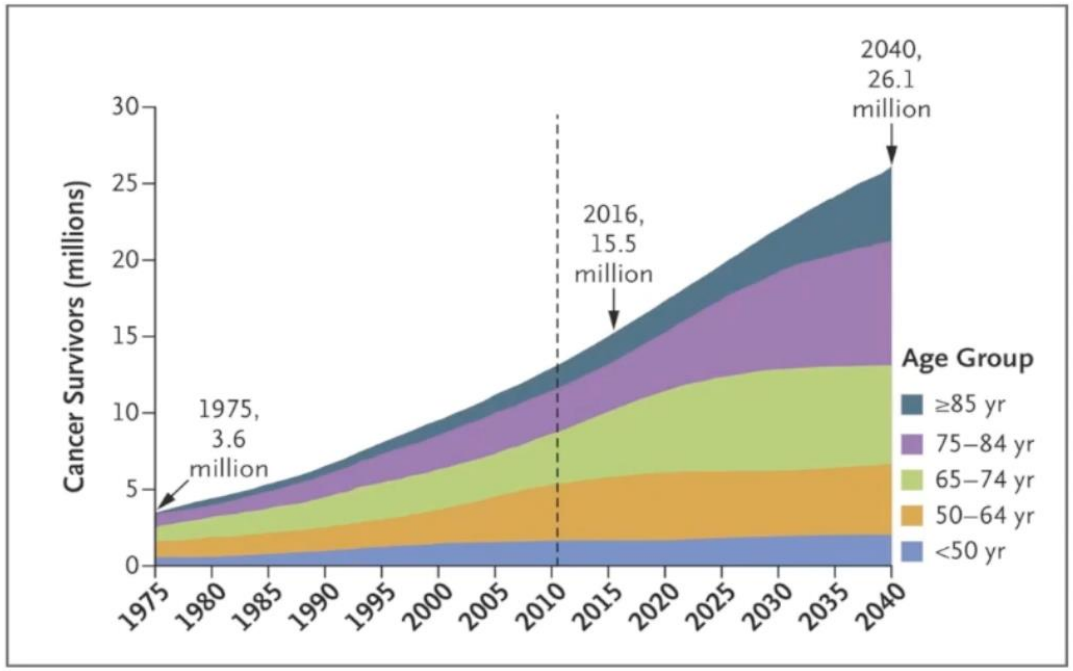
Martins F et al. Nat Rev Clin Oncol 2019; Schmid P et al. NEJM 2022

Treatment landscape of eBC



Thomas A et al. JCO 2022

An increasing number of cancer survivors



Cancer survivors worldwide, by age group 1975-2040

- Currently, over **17 million** individuals diagnosed with cancer every year
- By 2040, estimated over **26+ million**
- **Breast cancer:** as of 01/2022, ~4 million women with a history of breast cancer in the US
- Survival rates **exceeding 80% at 10 years** after diagnosis of early-stage breast cancer

Shapiro CL, NEJM 2018

Current practice parterns and gaps in guideline concordant BC survivorship care

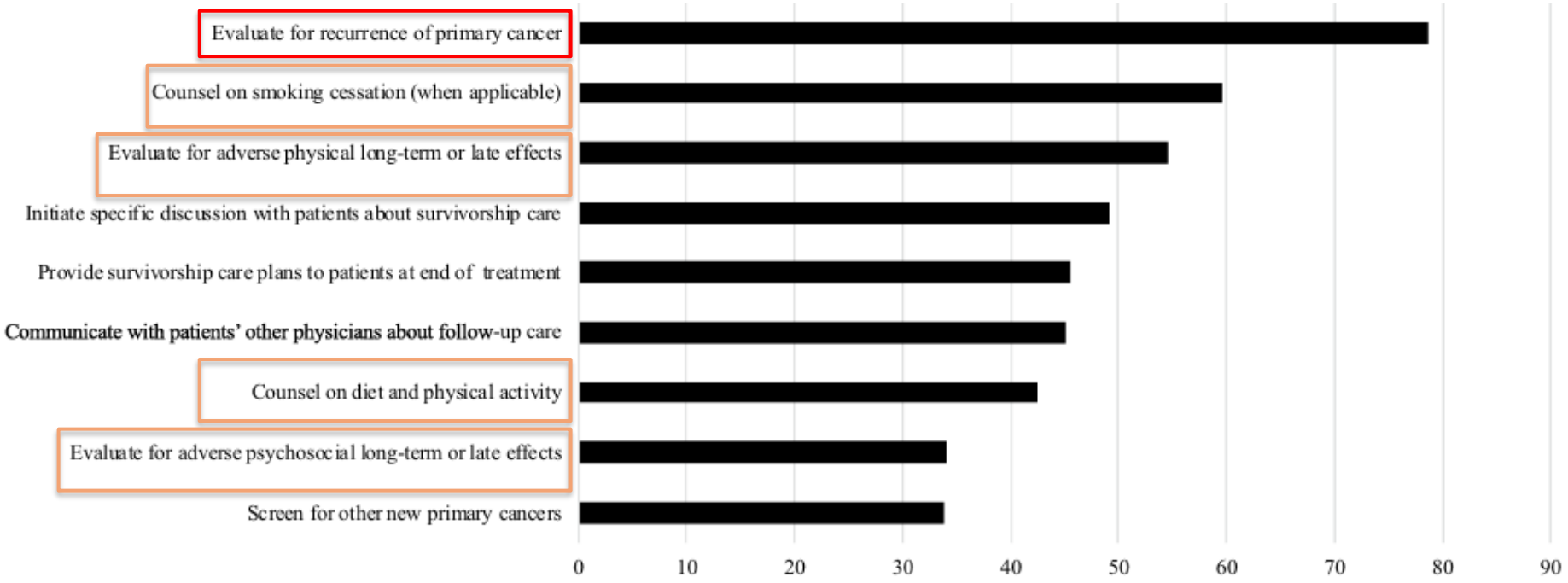
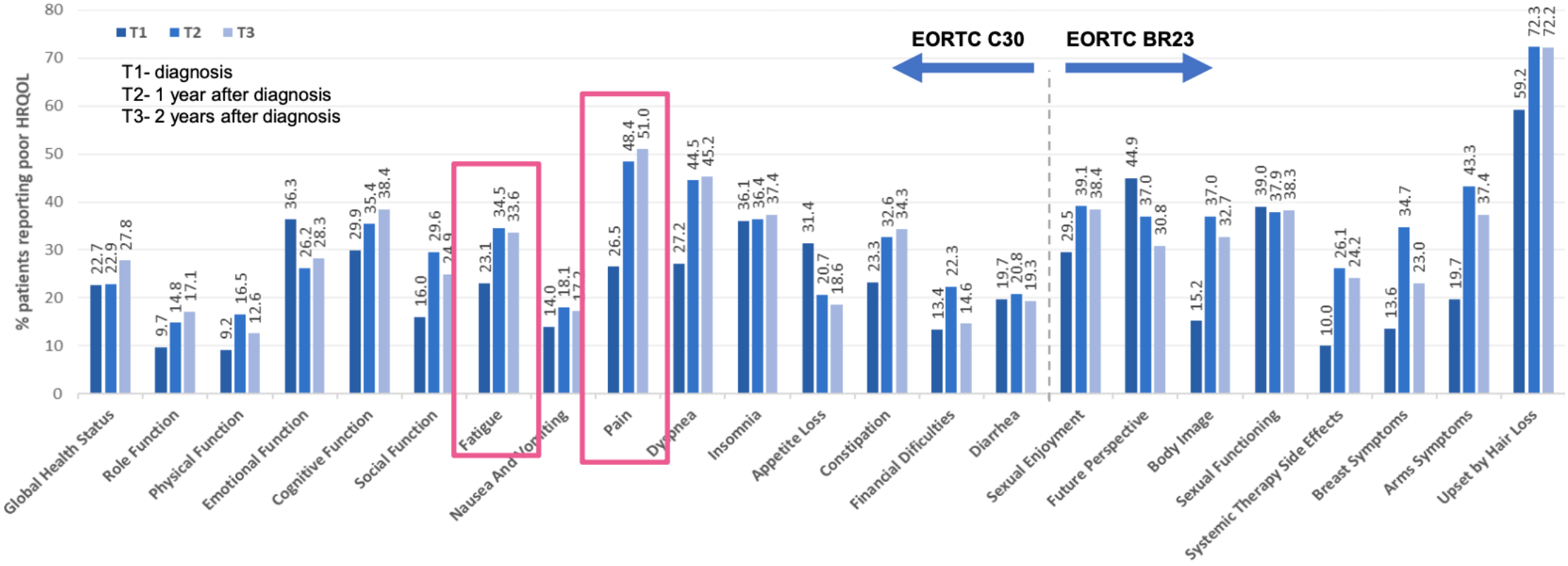


Fig. 2 Frequency of high engagement in core survivorship services

Brauer R, J Cancer Surviv 2021

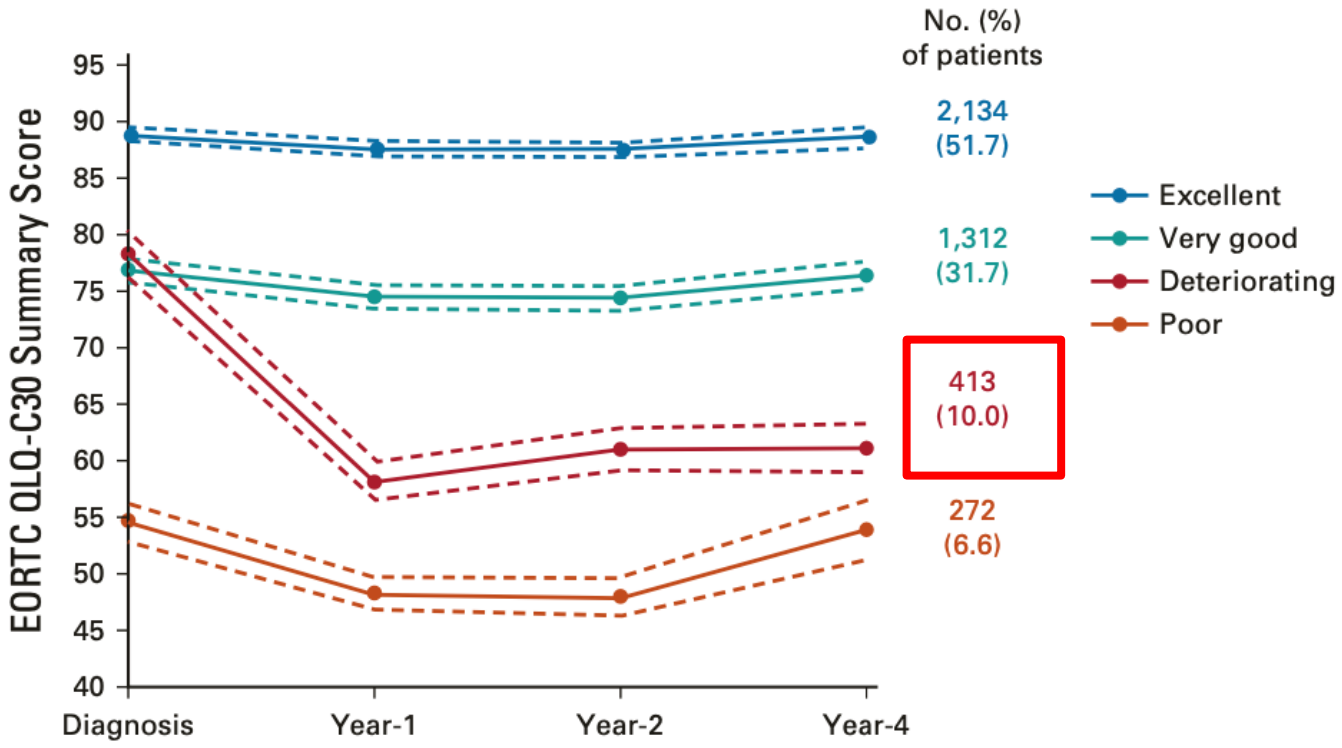
Post-diagnosis QoL among survivors of early-stage BC



- Increasing proportion of patients reporting a severe dysfunction or severe symptom after diagnosis, CANTO data

Ferreira AR, Di Meglio A, Vaz-Luis I, Ann Oncol 2019

Risk stratification: clustering techniques among BC survivors



Group-based trajectory analysis of EORTC QLQ-C30 summary score among women receiving adjuvant BC chemotherapy (N=4131, FU 4y)

Clinical: younger/comorbidities
Social: lower income
Treatment-related: take hormonal therapy
Behavioral: Smokers, higher BMI

Di Meglio A, J Clin Oncol 2022

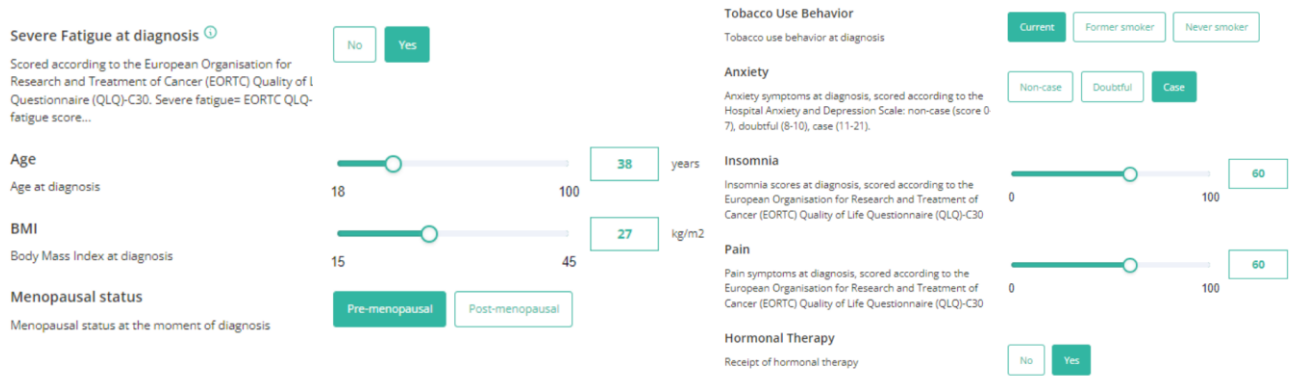
Fatigue: Individual risk prediction among BC survivors

TABLE 2. 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)		

TABLE 3. Exploratory Predictive Model of the Risk of Severe Fatigue at 4 Years After Diagnosis

Variable	OR	95% CI	β Coefficient	95% CI	*P*
Severe pretreatment fatigue,[a] yes versus no	2.480	2.022 to 3.042	0.908	0.704 to 1.112	< .0001
Menopausal status, pre- versus postmenopausal	1.325	1.123 to 1.563	0.281	0.116 to 0.446	.0009
Hormonal therapy, yes versus no	1.448	1.165 to 1.799	0.370	0.153 to 0.587	.0008
Anxiety,[b] doubtful case versus noncase	1.137	0.924 to 1.398	0.128	–0.079 to 0.335	.225
Anxiety,[b] case versus noncase	1.460	1.196 to 1.781	0.378	0.179 to 0.577	.0002
Insomnia,[a] continuous (for unit increment)	1.004	1.001 to 1.007	0.004	0.0013 to 0.007	.003
Pain,[a] continuous (for unit increment)	1.016	1.012 to 1.021	0.016	0.012 to 0.020	< .0001
Intercept			–2.018	–2.273 to –1.763	< .0001
AUC (95% CI)			0.71 (0.70 to 0.72)		



Risk of severe fatigue: Year-2: 83.2% Year-4: 75.8%

Di Meglio, JCO 2022

original reports

Long-Term Longitudinal Patterns of Patient-Reported Fatigue After Breast Cancer: A Group-Based Trajectory Analysis

Ines Vaz-Luis, MD, PhD[1,2]; Antonio Di Meglio, MD, PhD[1,2]; Julie Havas, MSc[2]; Mayssam El-Mouhebb, MSc[2]; Pietro Lapidari, MD[2]; Daniele Presti, MD[2]; Davide Soldato, MD[2]; Barbara Pistilli, MD[1,2]; Agnes Dumas, PhD[3]; Gwenn Menvielle, PhD[4]; Cecile Charles, PhD[5]; Sibille Everhard, PhD[6]; Anne-Laure Martin, PharmD[6]; Paul H. Cottu, MD[7]; Florence Lerebours, MD[8]; Charles Coutant, MD[9]; Sarah Dauchy, PhD[5]; Suzette Delaloge, MD[1]; Nancy U. Lin, MD[10]; Patricia A. Ganz, MD[11]; Ann H. Partridge, MD[10]; Fabrice André, MD, PhD[1,2]; and Stefan Michiels, PhD[12,13]

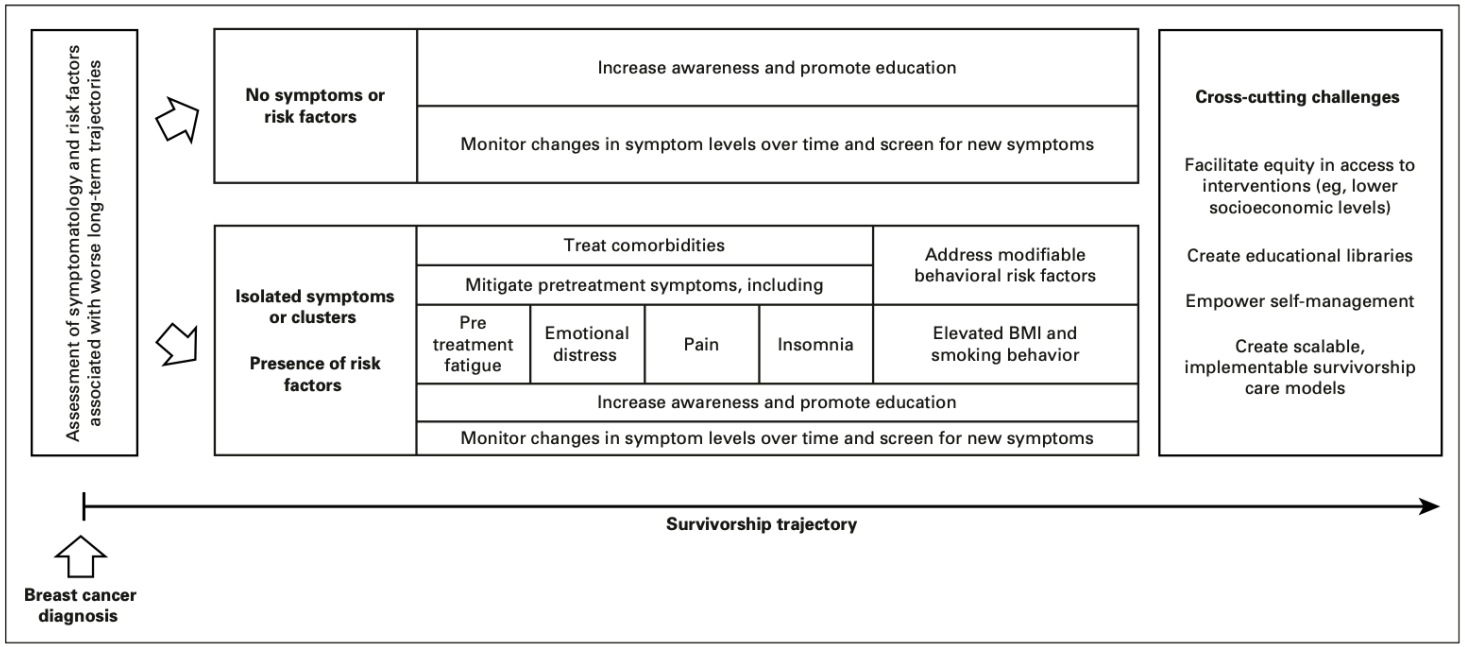


FIG 2. A comprehensive patient-centered survivorship care model building on predicted longitudinal symptom patterns to avoid long-term deterioration. BMI, body mass index.

Understanding of the impact of cancer beyond symptoms

original reports

Impact of Breast Cancer Treatment on Employment: Results of a Multicenter Prospective Cohort Study (CANTO)

Agnes Dumas, PhD[1,2]; Ines Vaz Luis, MD, PhD[3,4]; Thomas Bovagnet, MSc[5]; Mayssam El Mouhebb, MSc[2,4]; Antonio Di Meglio, MD[4]; Sandrine Pinto, MSc[5]; Cecile Charles, PhD[6,7]; Sarah Dauchy, MD[6]; Suzette Delaloge, MD, PhD[3]; Patrick Arveux, MD, PhD[8,9]; Charles Coutant, MD, PhD[8]; Paul Cottu, MD, PhD[10]; Anne Lesur, MD[11]; Florence Lerebours, MD, PhD[12]; Olivier Tredan, MD, PhD[13]; Laurence Vanlemmens, MD[14]; Christelle Levy, MD[15]; Jerome Lemonnier, PhD[16]; Christelle Mesleard, MSc[16]; Fabrice Andre, MD, PhD[3,4]; and Gwenn Menvielle, PhD[5]

- **2 years after diagnosis, 21% of p had not returned to work**

- Stage III
- Mastectomy +ALND
- Chemotherapy and trastuzumab (iv administration)
- Grade 3 toxicity and morbidity
- Age > 50y
- Manual work, low income
- Part-time employment
- Emotional fatigue
- **Depression**

Dumas, JCO 2019

Work and BC

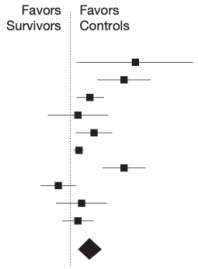
CLINICAL REVIEW

CLINICIAN'S CORNER

Cancer Survivors and Unemployment
A Meta-analysis and Meta-regression

Figure 2. Meta-analysis of Cancer Survivors vs Control Participants and Employment Outcomes

Source	Cancer Survivors No.	Cancer Survivors Total No.	Healthy Control Participants No.	Healthy Control Participants Total No.	Weight, %	I^2, %	RR (Random) (95% CI)
Breast cancer							
Weitzner et al,[46] 1997	13	48	10	85	1.58		2.30 (1.09-4.85)
Dorval et al,[45] 1998	34	54	36	114	2.88		1.99 (1.42-2.80)
Bradley et al,[41] 2002	72	156	2083	5818	3.42		1.29 (1.08-1.53)
Servaes et al,[40] 2002	53	150	25	78	2.69		1.10 (0.75-1.63)
Maunsell et al,[37] 2004	113	567	131	890	3.26		1.35 (1.08-1.70)
Taskila-Abrandt et al,[36] 2004	1598	4098	1434	4098	3.64		1.11 (1.05-1.18)
Bradley et al,[32] 2005	140	445	59	372	3.12		1.98 (1.51-2.60)
Helgeson and Tomich,[31] 2005	100	267	82	187	3.27		0.85 (0.68-1.07)
Gudbergson et al,[26] 2007	53	269	65	382	2.92		1.16 (0.83-1.61)
Farley Short et al,[25] 2008	83	289	514	1969	3.36		1.10 (0.90-1.34)
Subtotal	2259	6343	9439	13993	30.14	77.9	1.28 (1.11-1.49)



De Boer et al. JAMA 2009

Supportive Care in Cancer (2020) 28:4435–4443
https://doi.org/10.1007/s00520-019-05189-y

ORIGINAL ARTICLE

Check for updates

The positive effect of workplace accommodations on the continued employment of cancer survivors five years after diagnosis

Caroline Alleaume[1] · Alain Paraponaris[2,3] · Marc-Karim Bendiane[1] · Patrick Peretti-Watel[3,4] · Anne-Déborah Bouhnik[1]

Receipt of workplace accommodations appeared to improve the continued employment rate 5 years after cancer diagnosis from **77.8% to 95.0%.**

Journal of Cancer Survivorship (2023) 17:694–705
https://doi.org/10.1007/s11764-022-01197-w

Check for updates

Change in the value of work after breast cancer: evidence from a prospective cohort

Elsa Caumette[1,2] · Antonio Di Meglio[3,4] · Inès Vaz-Luis[3,4] · Cécile Charles[5] · Julie Havas[3,4,6] · Garazi Ruiz de Azua[1] · Elise Martin[3] · Laurence Vanlemmens[7] · Suzette Delaloge[3] · Sibille Everhard[8] · Anne-Laure Martin[8] · Asma Dhaini Merimeche[9] · Olivier Rigal[10] · Charles Coutant[11] · Marion Fournier[12] · Christelle Jouannaud[13] · Patrick Soulie[14] · Paul-Henri Cottu[15] · Olivier Tredan[16] · Gwenn Menvielle[1] · Agnès Dumas[17]

46% of women had reordered their life priorities toward private life 2 years after diagnosis

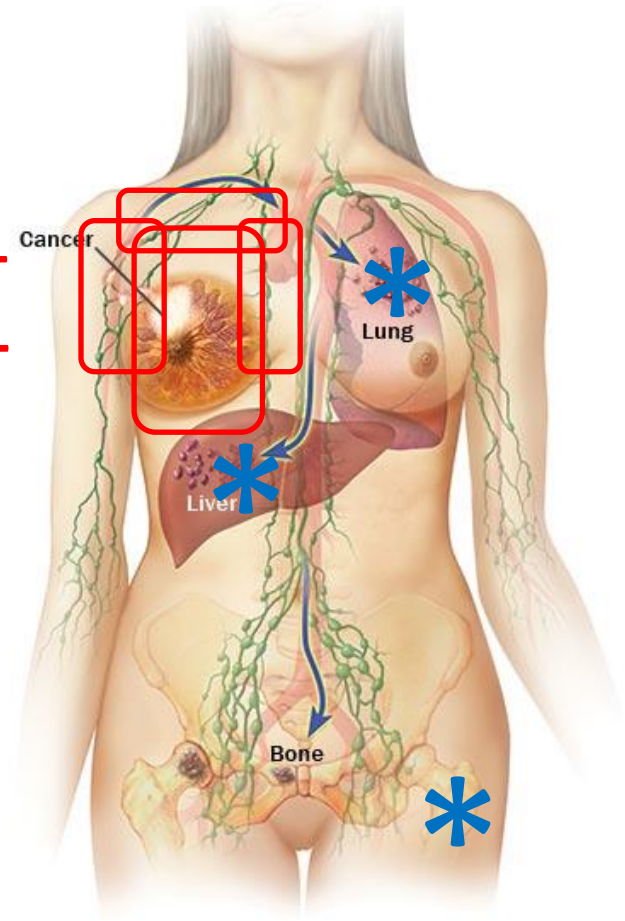
Cancer mammaire métastatique

Early versus advanced stage breast cancer

*

Breast
Chest
Regional skin or lymph nodes

LOCO-REGIONAL

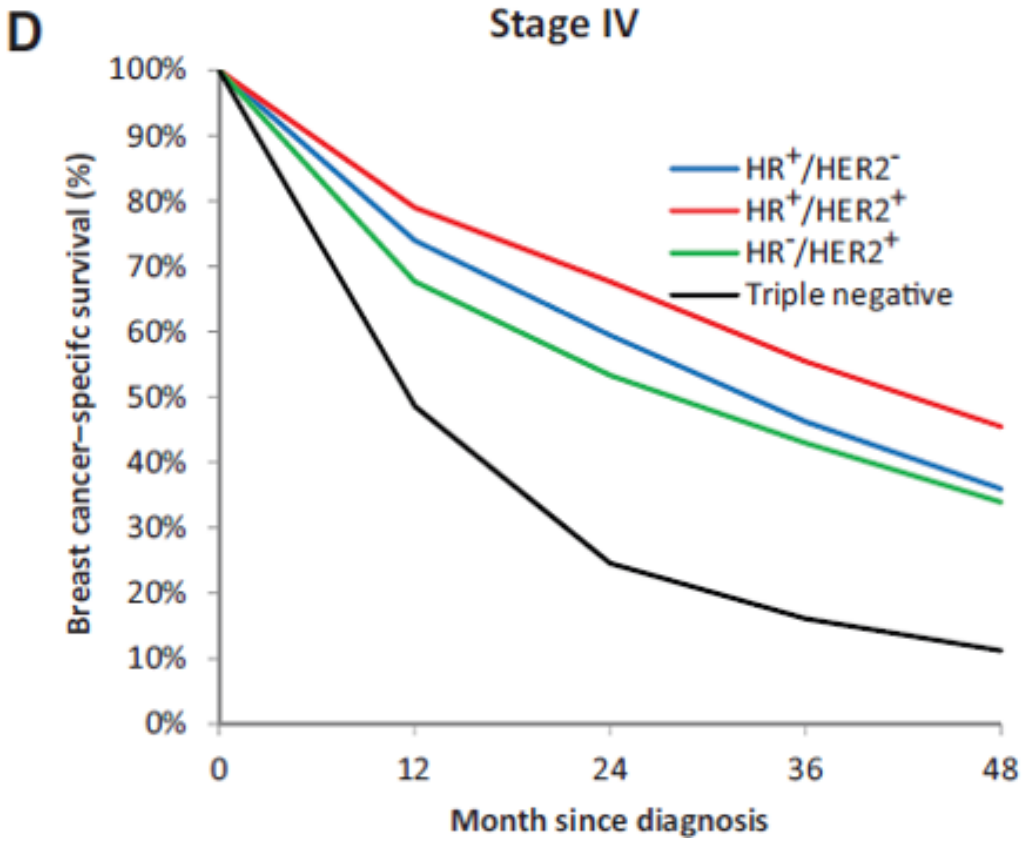


DISTANT METASTASES
(+ non operable loco-regional)

Bone-only	39.80%
Multiple metastasis	33.07%
Lung metastasis	10.94% Liver
metastasis	7.34% Brain
metastasis	1.51%
Other metastasis	7.34%

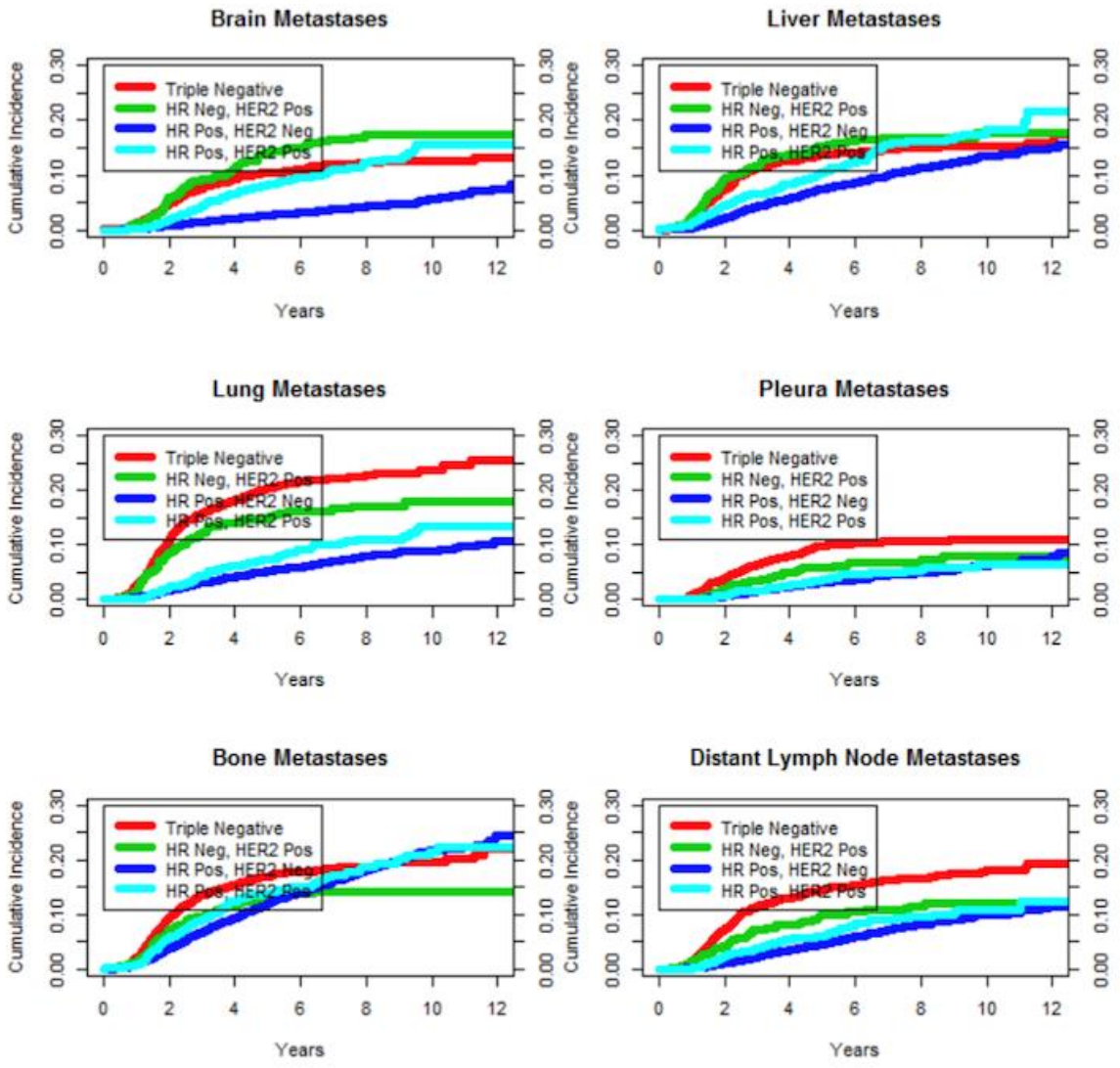
Pictire from Mayo Foundation for Medical Education and Research; Wang et al. BMC Cancer (2019) 19:1091

Metastatic breast cancer



Cancer Epidemiol Biomarkers Prev 2018,27(6):1–8

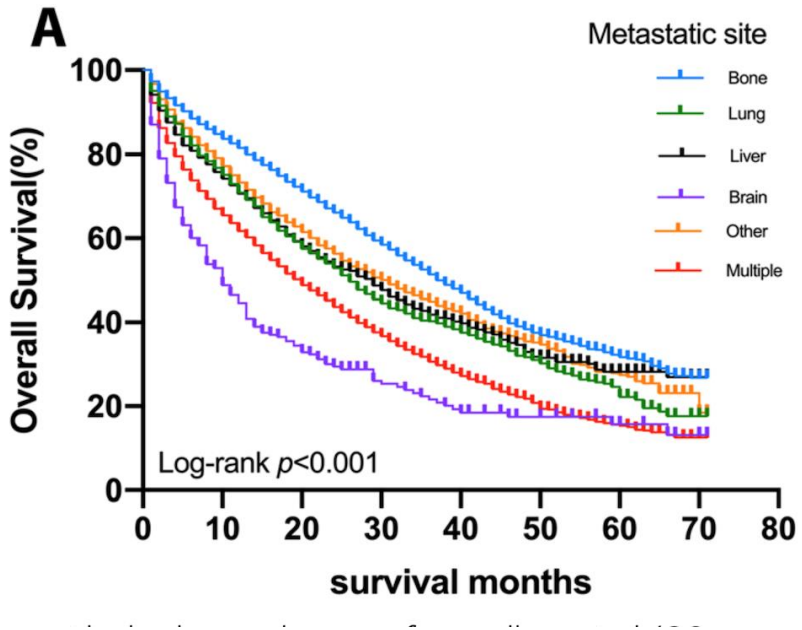
Pattern of relapse according to the biology of the cancer

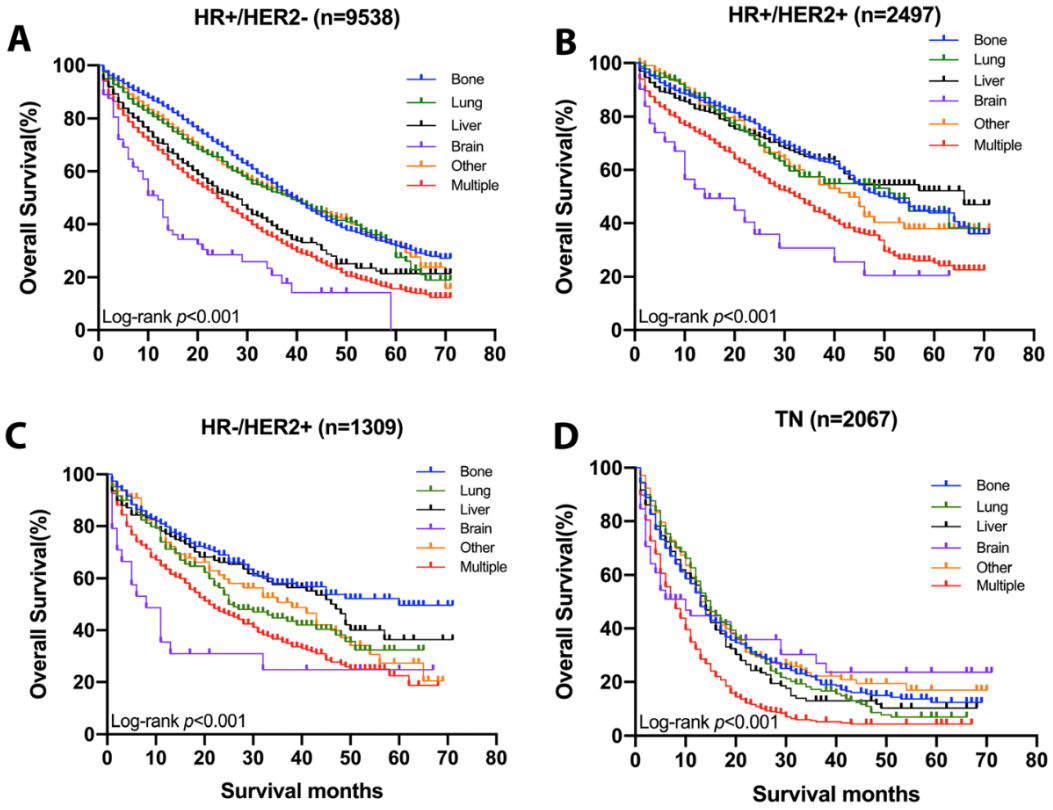


Breast Cancer Res Treat 2013;137

Outcome and metastatic site

Surveillance, Epidemiology and End Results database (2010 to 2015) 18,322 patients





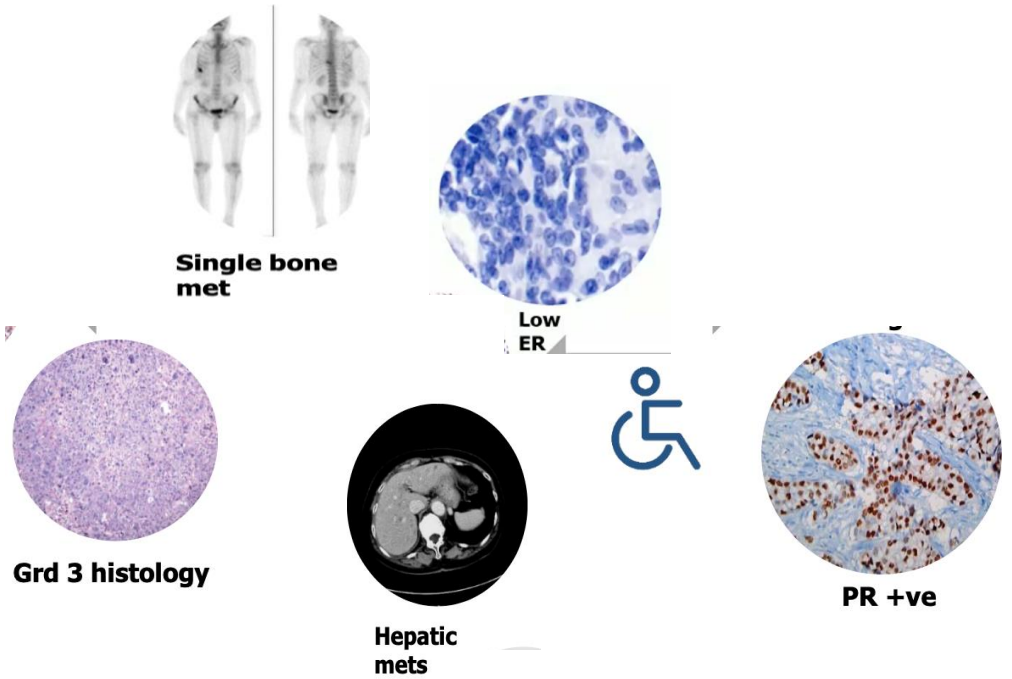
TNBC: All locations are bad!

Wang et al. BMC Cancer 2019;19:1091

Current treatment approach for mBC

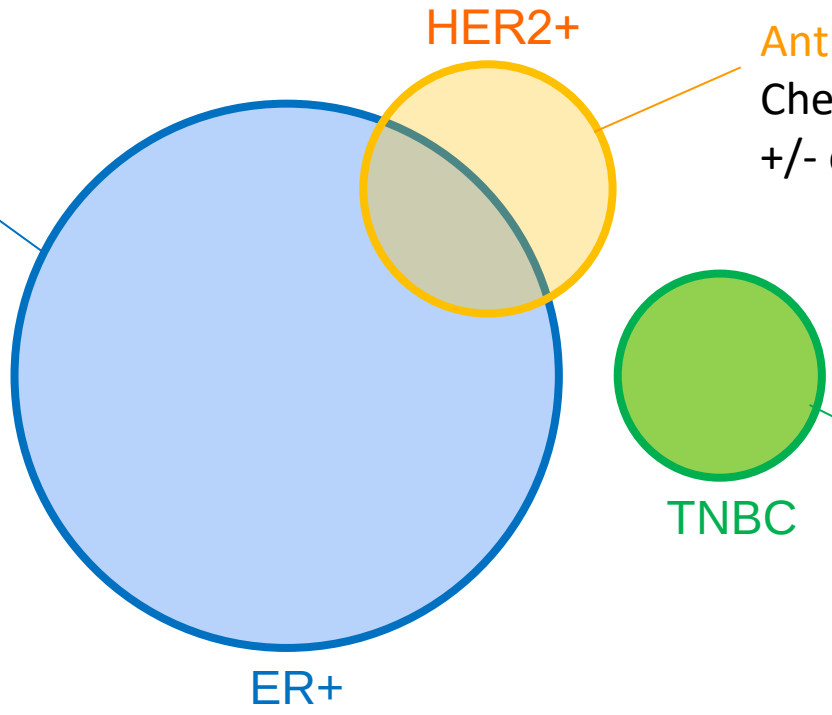
- Lengthening median survival whilst maintaining quality of life
- Sequential therapy, with switches at disease progression
- Combination endocrine therapy
- Single agent chemotherapy

Treatment choice in ER+mBC influenced by a number of factors



Metastatic breast cancer

mOS:~ 58.7 – 63.9 months ←
Endocrine therapy
Pathways inhibitors
New endocrine therapies
Chemotherapy

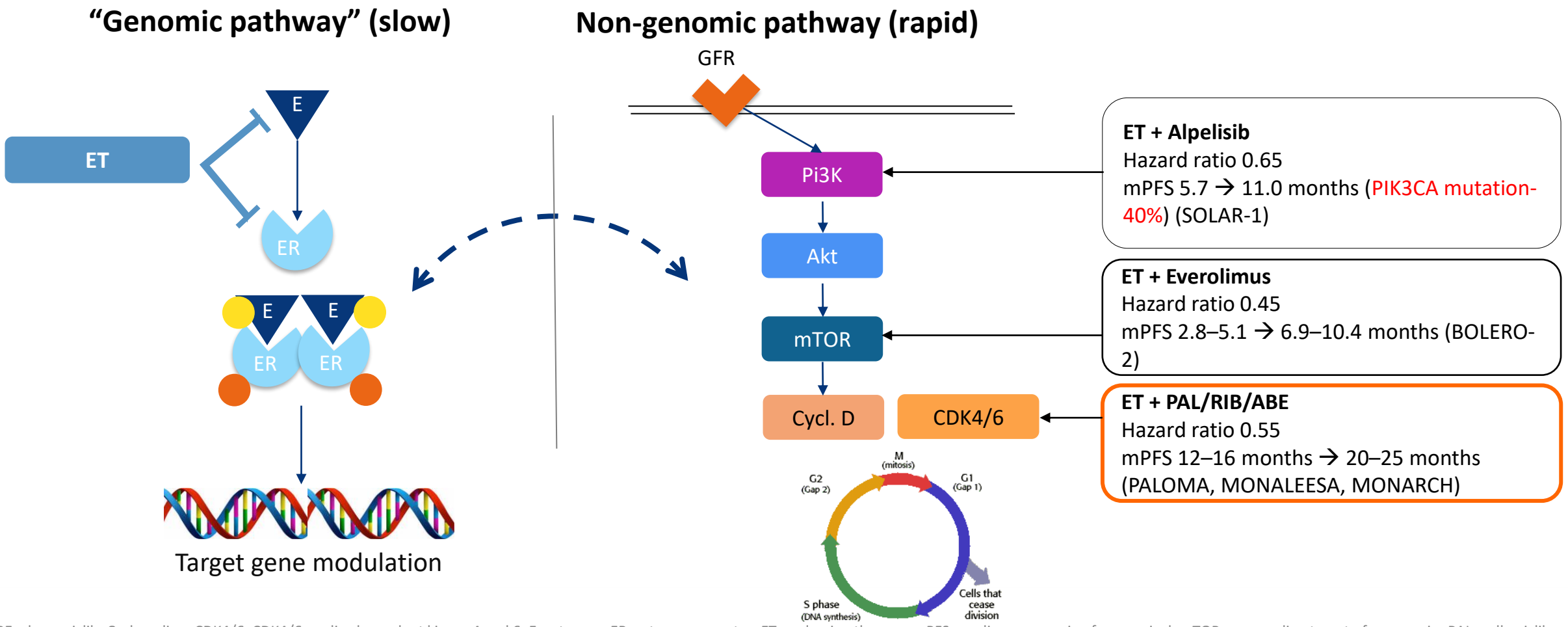


→ mOS:~ 57.1 months
Anti-HER2 therapies
Chemotherapy
+/- endocrine therapy

→ mOS: ~ 18-25.4 months
Chemotherapy
Immunotherapy
Antibody drug conjugates

Emens, Ann Oncol 2021 / Rugo, ESMO 2021, LBA16 / Lancet Oncol 2020; 21: 519–30 / Hortobagyi, ESMO 2021 / Tripathy, SABCS 2020, PD2-04

Resistance to endocrine therapy: pathways



ABE, abemaciclib; Cycl, cycline; CDK4/6, CDK4/6, cyclin-dependent kinase 4 and 6; E, estrogen; ER, estrogen receptor; ET, endocrine therapy; mPFS, median progression free survival; mTOR, mammalian target of rapamycin; PAL, palbociclib; PI3K, phosphoinositide 3-kinase; RIB, ribociclib.

Smith IA, Dowsett M. N Engl J Med. 2003;348:2431-42. Chia S, et al. J Clin Oncol. 2008;26:1664-70. Di Leo A, et al. J Clin Oncol. 2010;28:4594-600. Robertson JFR, et al. Lancet. 2016;388:2997-3005. Kaufman B, et al. J Clin Oncol. 2009;27:5529-37. Johnston S, et al. J Clin Oncol. 2009;27:5538-46. Krop IE, et al. Lancet Oncol. 2016;17:811-21. Baselga J, et al. Oral presentation at SABCS 2015; abstract S6-01. Di Leo A, et al. Poster presented at SABCS 2017; abstract S4-07. Baselga J, et al. N Engl J Med. 2012;366:520-9. Bachelot T, et al. J Clin Oncol. 2012;30:2718-24. Hortobagyi GN, et al. N Engl J Med. 2016;375:1738-48. Finn RS, et al. Poster presented at ASCO 2016; abstract 507. Cristofanilli M, et al. Lancet Oncol. 2016;17:425-39. Cardoso F, et al. Poster presented at ASCO 2017; abstract 1010. Sledge GW, et al. J Clin Oncol. 2017;35:2875-84.

Endocrine sensitive HR+/HER2- mBC

- HR+, HER2 – mBC
- Postmenopausal
- No prior systemic therapy in this setting
- If NA or adjuvant ET administered, a disease free interval of >12 months since completion of ET

N=666

2:1 Randomization

Palbociclib + AI

Placebo + AI

PALOMA-2

No OS benefit

bociclib + AI

lacebo + AI

MONALEESA-2

OS benefit

2:1 Randomization

Abemaciclib + AI

Placebo + AI

MONARCH-3

Interim OS analysis: OS benefit
No OS benefit

Primary endpoint:
Investigator-assessed PFS

Finn RS et al. NEJM 2016; Hortobagy G et al. NEJM 2016, Di Leo et al. JCO 2017

CDK4/6i: Effets secondaires

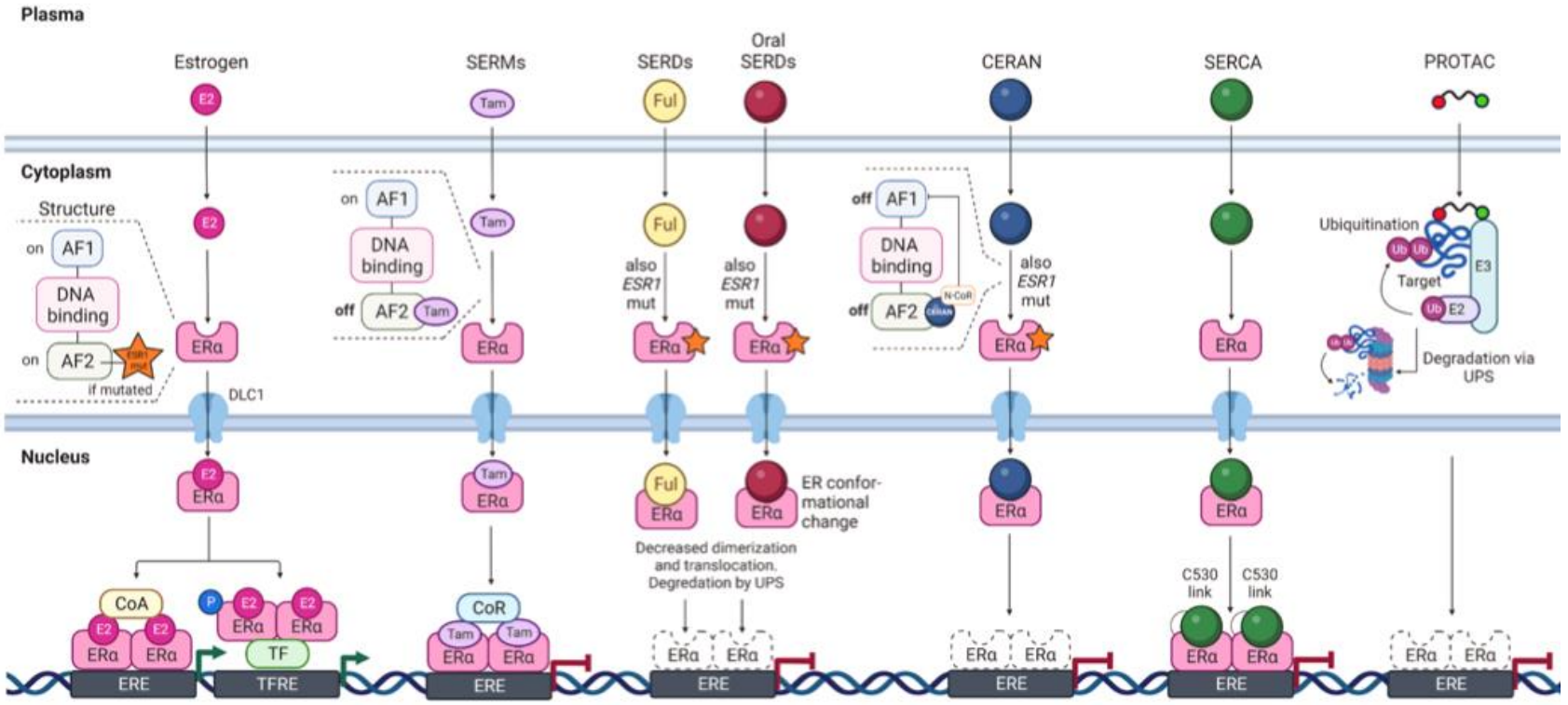
	MONALEESA-2 [1-3] (N=668)	MONALLESA-3 [1,4] (N=726)	MONALEESA-7 [1,5] (N=672)	MONARCH-2 [6,7] (N=669)	MONARCH-3 [6,8] (N=493)	PALOMA-2 [9,10] (N=666)	PALOMA-3 [11,12] (N=521)
Treatment arm	RIBO+LET (n=334)	RIBO+FUL (n=483)	RIBO+ET+GOS (n=335)	ABE+FUL (n=446)	ABE+NSAI (n=327)	PAL+LET (n=444)	PAL+FUL (n=345)
Most common AEs (≥30%, all grade)	Neutropenia,leukopenia,nausea,fatigue, alopecia diarrhea,	Neutropenia, nausea, fatigue	Neutropenia, leukopenia, nausea, hot flash	Diarrhea, neutropenia, nausea, fatigue, abdominal pain	Diarrhea, neutropenia, nausea, fatigue	Neutropenia, leukopenia, fatigue, nausea, alopecia, stomatitis	Neutropenia, leukopenia, thrombocytopenia, infections, fatigue, nausea
Grade 3-4 neutropenia (%)	207(62)	258(53.6)	203(60.6)	117 (26.5)	78 (23.9)	295 (66.4)	214 (62.0)
Diarrhea	8 (2.4)	3(0.6)	5(1)	381 (86.4)	269 (82.3)	6 (1.4)	0 (0)
AES of interest							
Thromboembolic events	Overall : NR PE:2(0.6)	NR	NR	Overall: 9 (2.0) PE: 4 (0.9)	Overall: 16 (4.9)	Overall: NR PE: 0.9%	Overall: 6 (1.7) PE: 3 (0.9) DVT: 1 (0.3)
QTcF prolongation	12(3.6)	27 (5.6)	23 (7)	3 (0.7)	1 (0.3)	0/77 (0)	1 (<1)

Neutropénie
Diarrhées
Evénements thromboemboliques
Allongement du QT

QTcF >480ms; NR: not reported, PE: pulmonary embolism, DVT: deep vein thrombosis

1.Burris et al. SABCS 2018 P6-18-15;2.Hortobagyi GN et al.NEJM 2016;3. Hortobagyi GN et al. Ann Oncol 2018; 4. Slamon DJ et al JCO 2018; 5.Tripathy GN et al. Lancet Oncol 2018; 6. Rugo HS et al. ESMO 2018; 7. Sledge GW et al. JCO 2017; 8. Goetz MP et al. JCO 2017; 9. Finn RS et al. NEJM 2016; 10. Durairaj C et al. Anticancer Drugs 2018; 11. Turner NC et al. NEJM 2015;12. Cristofanilli M et al Lancet Oncol 2016

Novel endocrine therapies: What is next in HR+/HER2- mBC



Oral SERDs: Selective estrogen receptors degraders

Novel SERMs: Selective estrogen receptors modulators

SERCA : Selective estrogen receptor covalent antagonist degraders

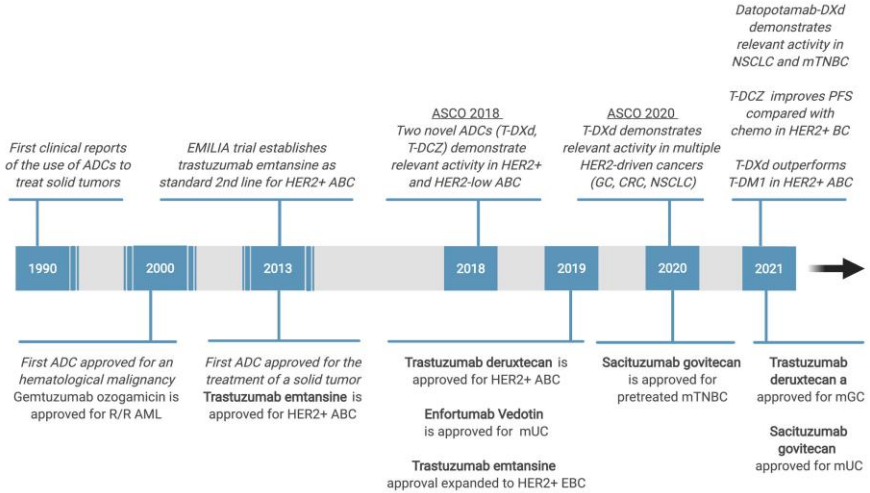
PROTAC: Proteolysis targeting chimera

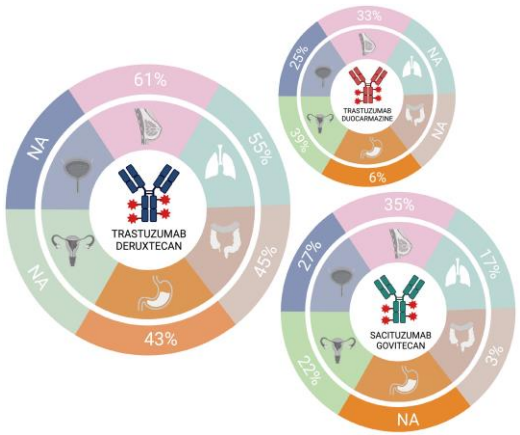
CERAN: Complete estrogen receptor antagonist

Corti C et al. Cancer Treat Rev 2023

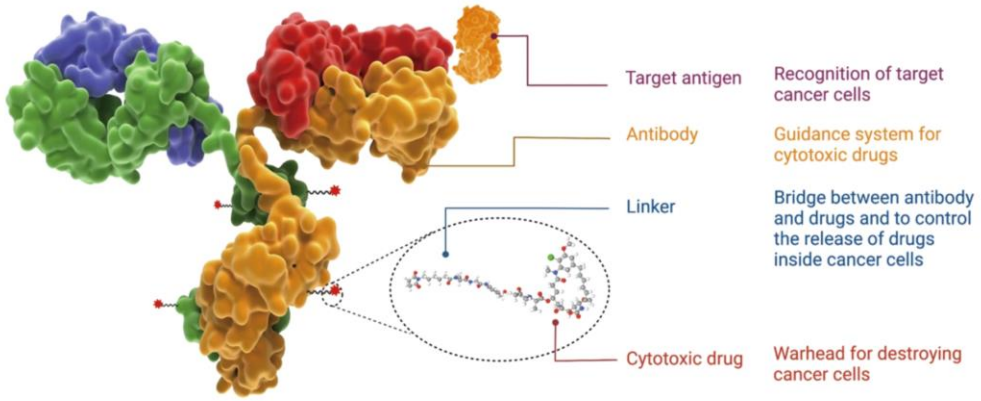
ADC in mBC

Antibody drug conjugates have transformed the therapeutic landscape of BC



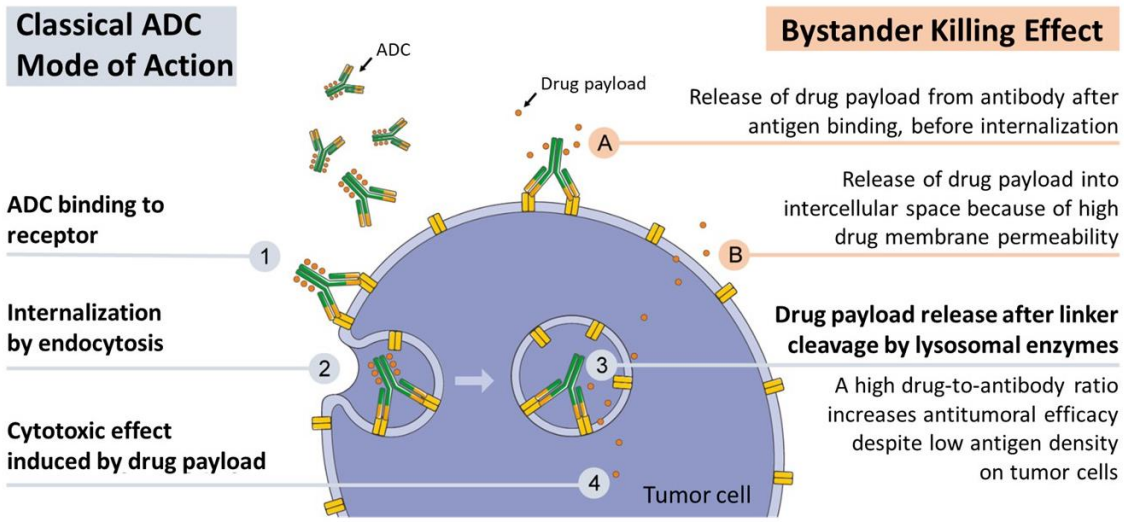


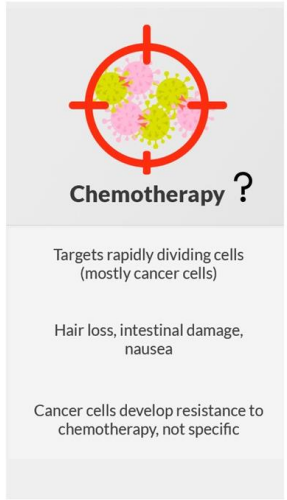
Tarantino P et al. CA A Cancer J Clinicians 2022

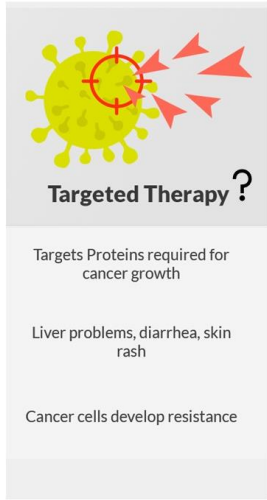


Chau el at. Lancet 2019; 394(10200)
Fu et al. Signal Transduction and Targeted Therapy 2022; 7(93)

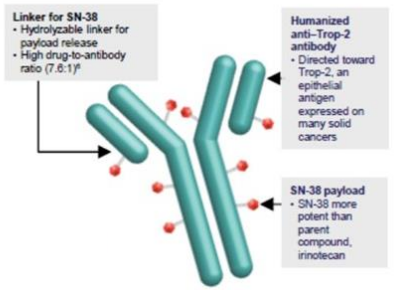
How do these drugs truly work

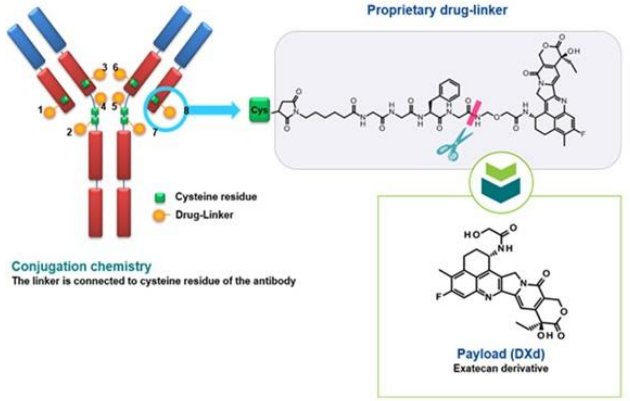






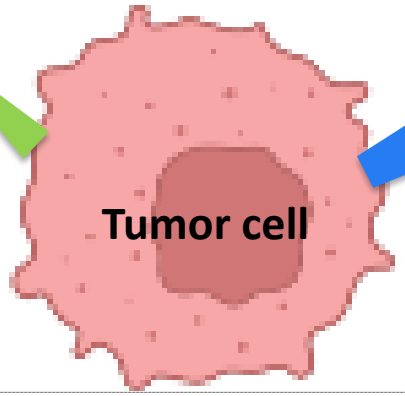
ADCs in mBC





Trop-2

Sacituzumab govitecan
TROPiCs-02 in HR+/HER2- mBC
ASCENT in TNBC



HER2

Trastuzumab deruxtecan
Destiny Breast 03 HER2+ mBC
Destiny Breast 04 in HER2 low mBC

Payload: topo-I inhibitor SN38 and DXD exatecan

HER2 positive mBC

DESTINY-Breast02

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- **Previously treated with T-DM1**

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine
(n = 202)

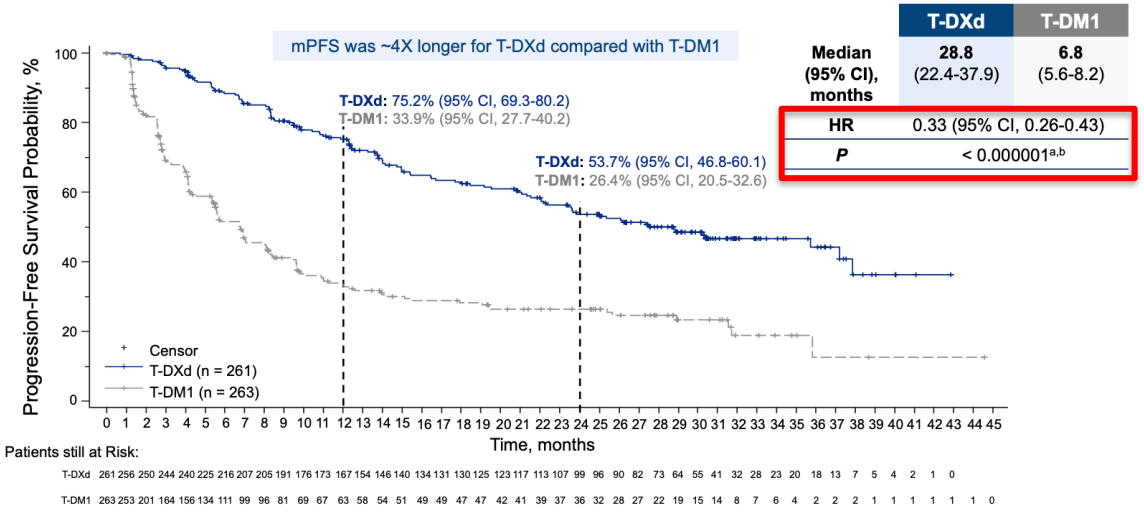
Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

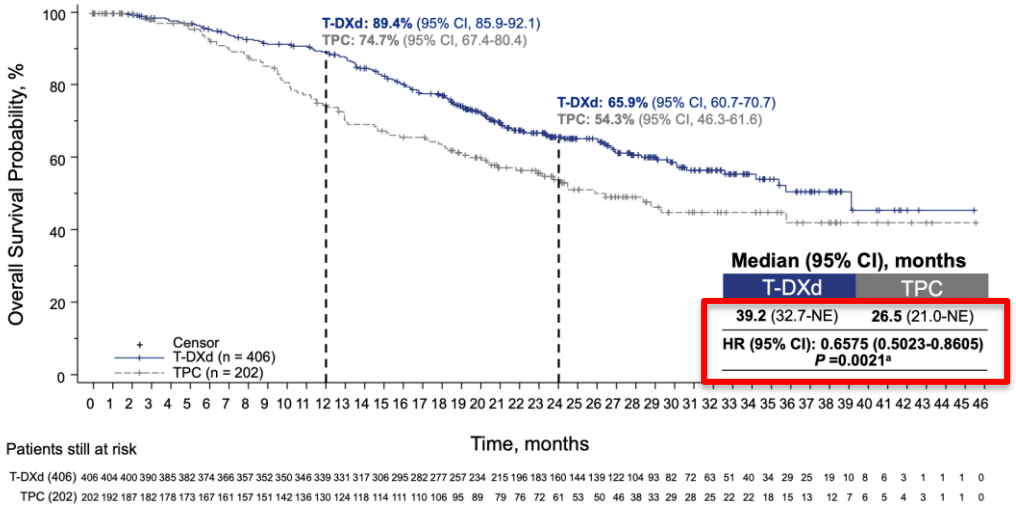
Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

Updated Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
Median (95% CI), months	28.8 (22.4-37.9)	6.8 (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Key Secondary Endpoint: OS



HER2 positive mBC

DESTINY-Breast03

Patients
- Unresectable or metastatic HER2-positive breast cancer
- **Previously treated with trastuzumab and taxane in advanced/metastatic setting**
- Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

R 1:1

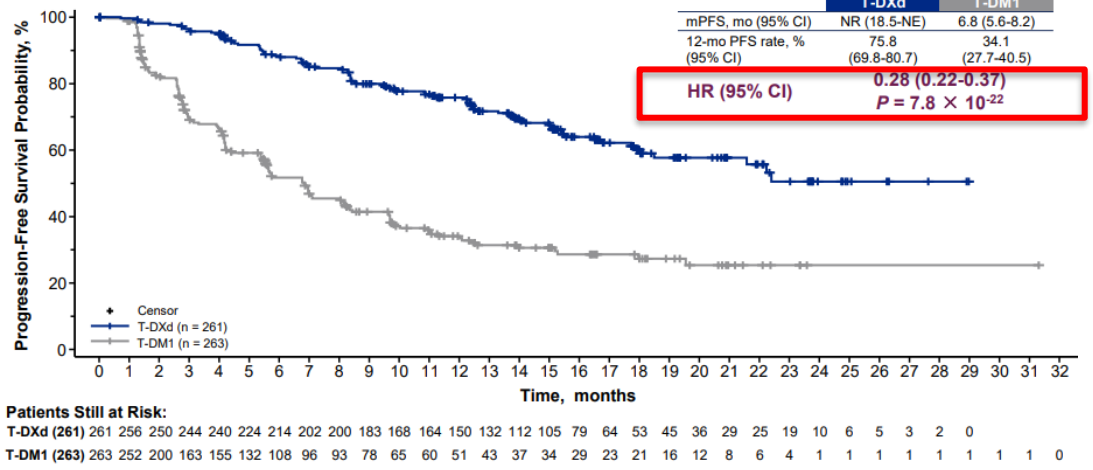
- **T-DXd** 5.4 mg/kg Q3W (n = 261)
- **T-DM1** 3.6 mg/kg Q3W (n = 263)

Primary endpoint
- PFS (BICR)

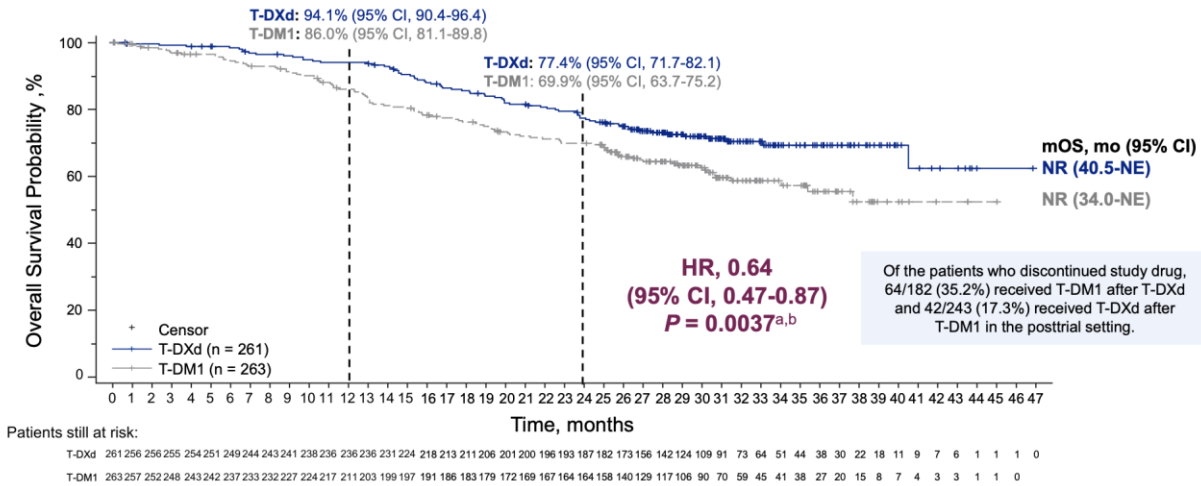
Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Primary Endpoint: PFS by BICR

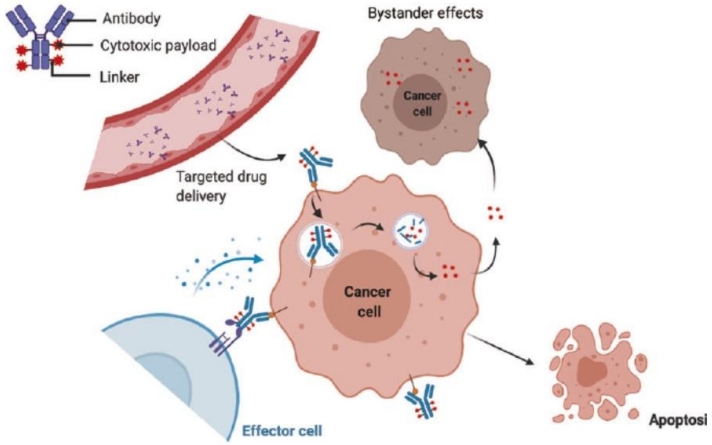


OS

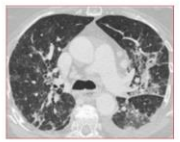


Hurvitz S, SABCS 2022

Third generation ADC: bystander effect



- High potency
- **BUT** « off target » toxicities
- **Interstitial Lung Disease (ILD)**



Appropriate strategies for the management in clinical practice

Clinical Review & Education

JAMA Oncology | Review

Interstitial Lung Disease Induced by Anti-ERBB2 Antibody-Drug Conjugates
A Review

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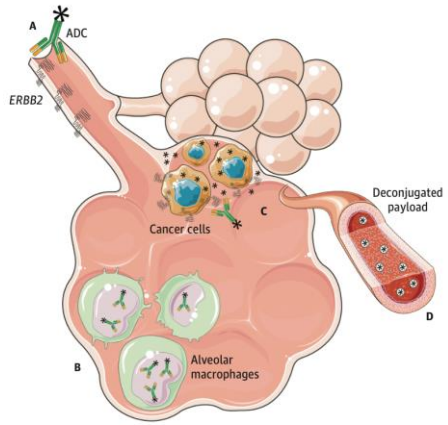
Figure 1. Possible Mechanisms of Anti-ERBB2 Antibody-Drug Conjugate (ADC)–Induced Lung Toxic Effects



A, ERBB2-dependent uptake of the ADC (asterisk). B, ERBB2-independent uptake of the ADC in intra-alveolar immune cells. C, Bystander killing by free payload released from targeted cancer cells. D, Deconjugated payload circulating in the bloodstream. This image was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License.[32]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

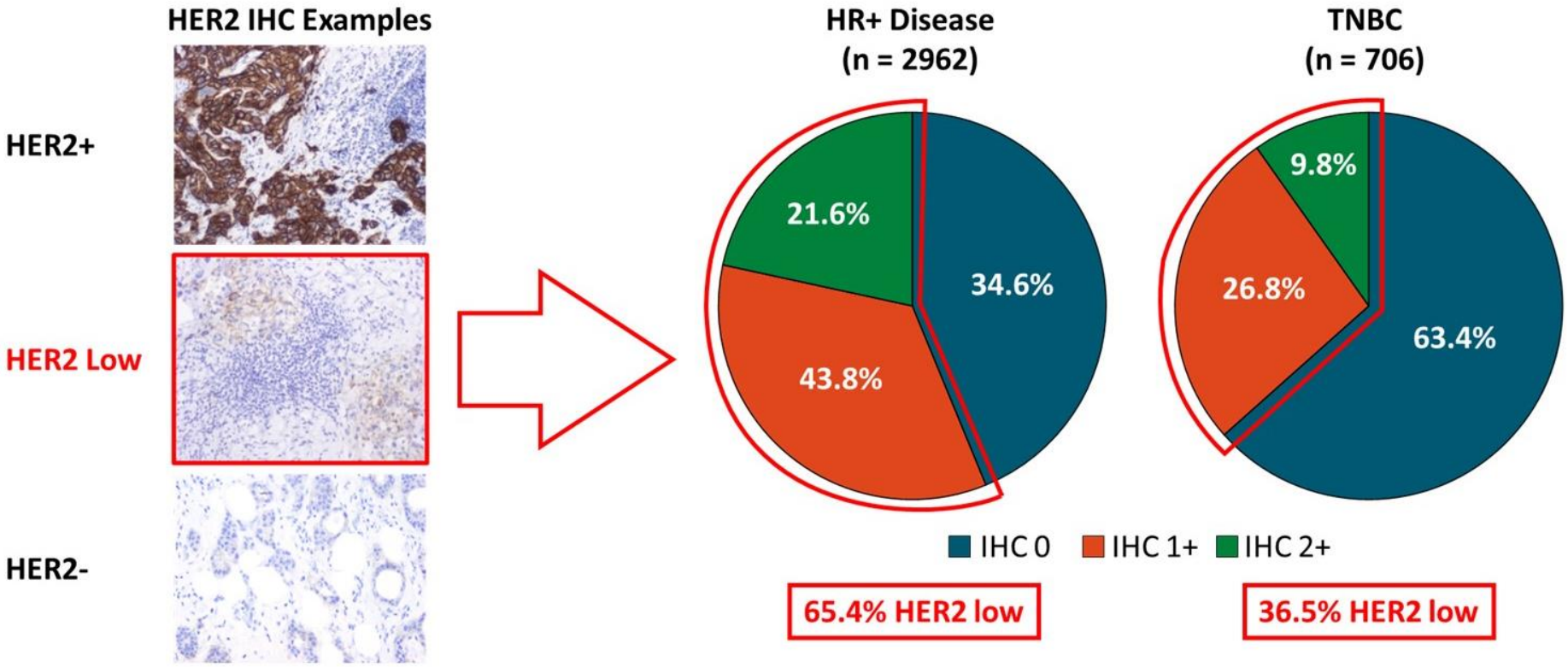
ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

REVIEW

Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer

H. S. Rugo[1*], G. Bianchini[2,3], J. Cortes[4,5,6,7], J.-W. Henning[8] & M. Untch[9]

Prevalence of HER2-Low by HR Status: Many with MBC Eligible for Multiple ADCs



Schettini et al. NPJ Breast Cancer 2021; Scherrini et al. Breast 2021

DESTINY-Breast 04

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

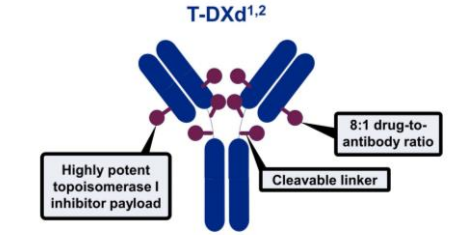
TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

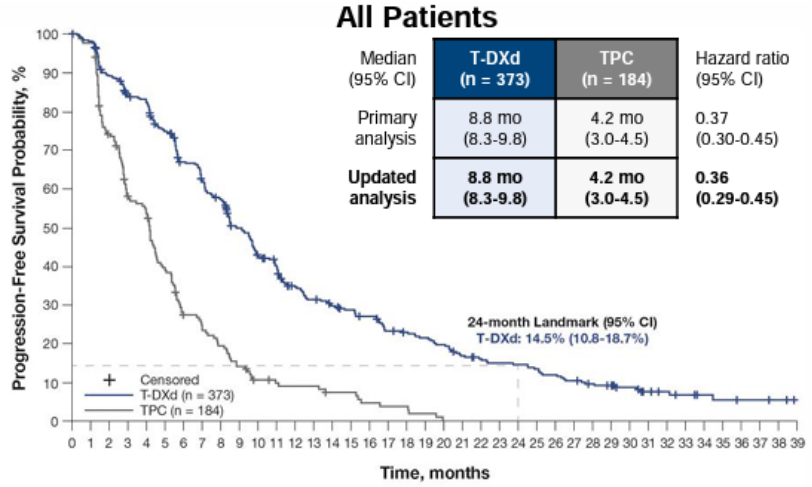
- 3 lines of prior therapy
- 70% CDK4/6i

Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy



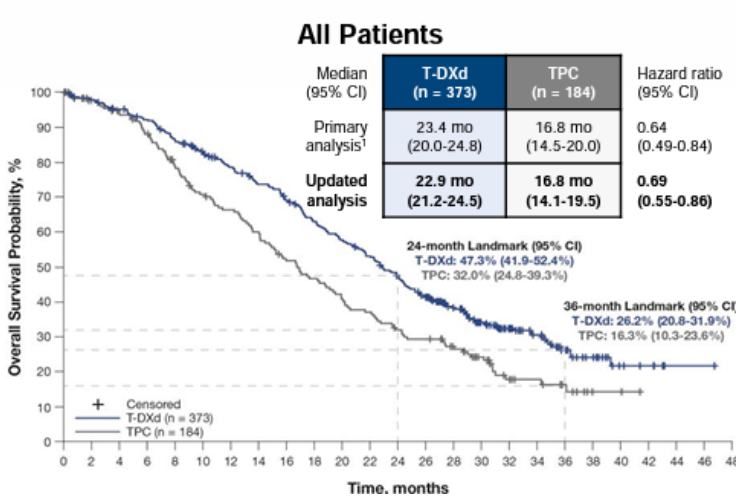
Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]

PFS



Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**

OS



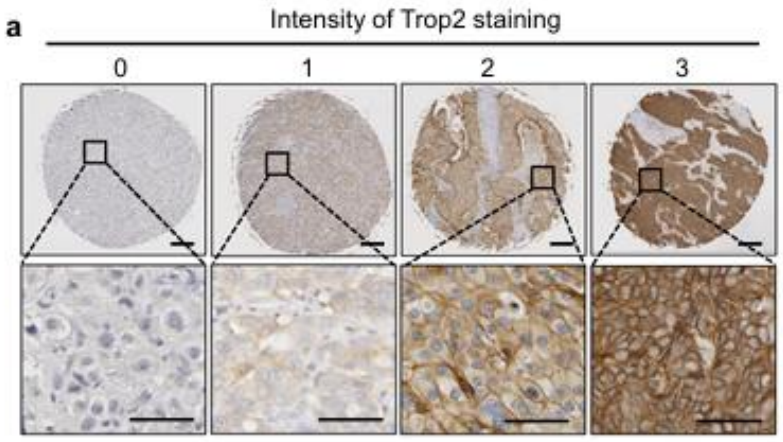
Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**

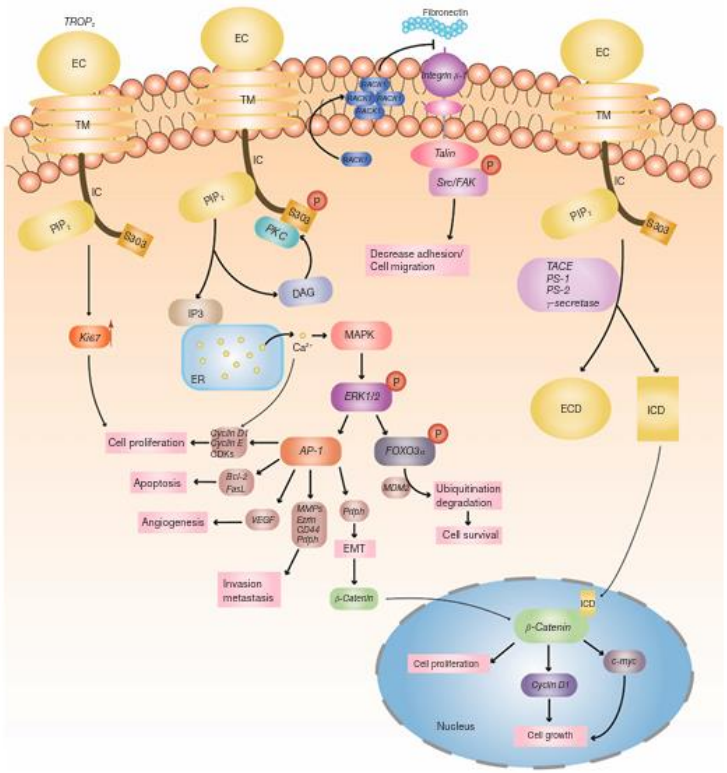
Results from the 32-month median follow-up for DESTINY-Breast 04 confirm the sustained clinically meaningful improvement for T-DXd vs TCP, regardless of HR+ status

Modi et al. ASCO 2022

Trophoblast-Cell surface Antigen 2: Trop-2

- Type I transmembrane glycoprotein/intracellular calcium signal transducer, encoded by TACSTD2
- Highly expressed in various epithelial cancers, including breast, GU and lung cancers
- Not expressed in many normal tissues
- Plays a regulatory role in cell proliferation and transformation, by regulating calcium signaling pathway, cyclin expression, nuclear oncogene transcription and fibronectin adhesion

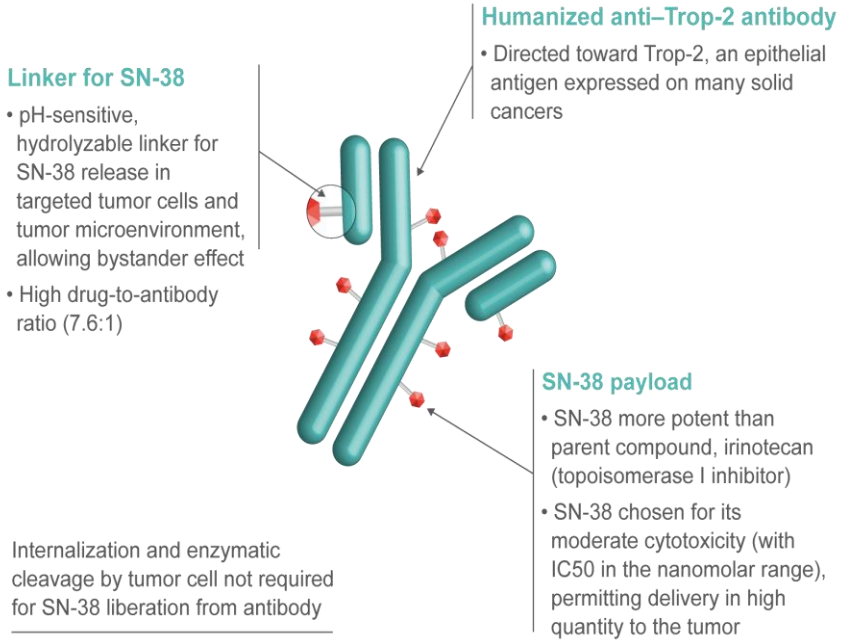




Wen Y et al. Ann Transl Med 2022;10:1403

Shvartsur A et al. Genes Cancer 2015;6:84-105;Wang J et al. Mol Cancer Ther 2008;7:280-285;Ohmachi T et al. Clin Cancer Res 2006;12:3075-3063

Sacituzumab govitecan is a first in class Trop-2 directed antibody drug conjugate



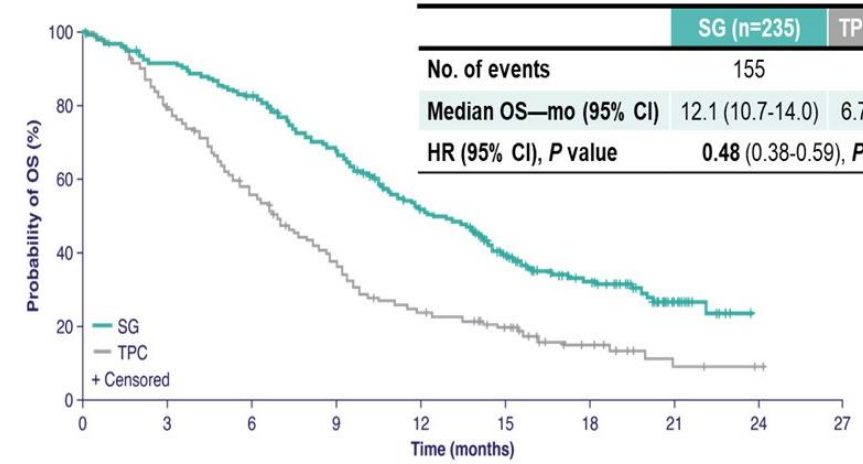
Trop-2 is an epithelial antigen that is highly expressed in ~85-90% of all subtypes of breast cancer, including HR+ breast cancer[6]

SG is approved for patients with mTNBC with ≥2 prior therapies (≥1 in the metastatic setting)

mTNBC

ASCENT

	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	**0.48** (0.38-0.59), ***P*** **<.0001**	



Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2− Locally Recurrent Inoperable or Metastatic Breast Cancer

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan 10 mg/kg IV days 1 and 8, every 21 days n=272

Treatment of physician's choice[b] (capecitabine, vinorelbine, gemcitabine, or eribulin) n=271

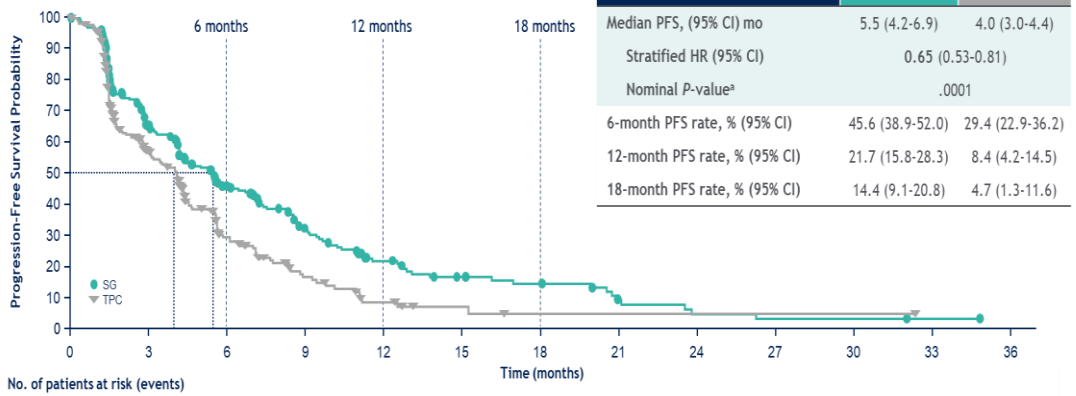
Endpoints

Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

Stratification
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

Progression-Free Survival

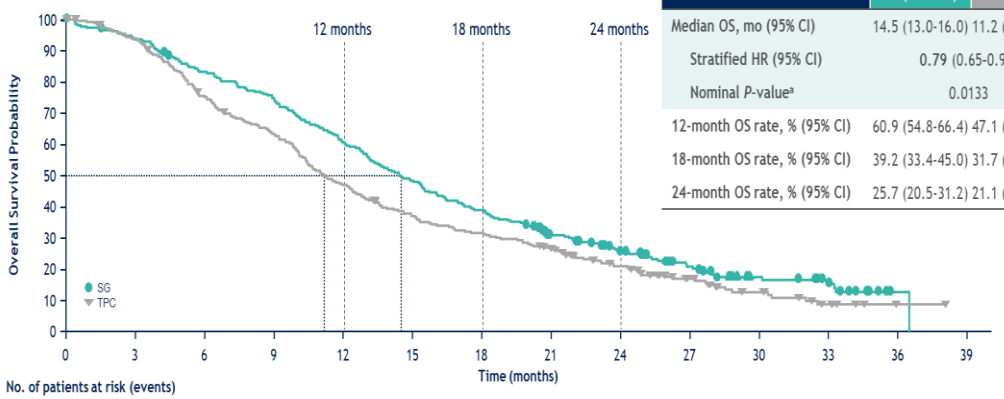


BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
Nominal *P*-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

No. of patients at risk (events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

Overall Survival



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	0.79 (0.65-0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

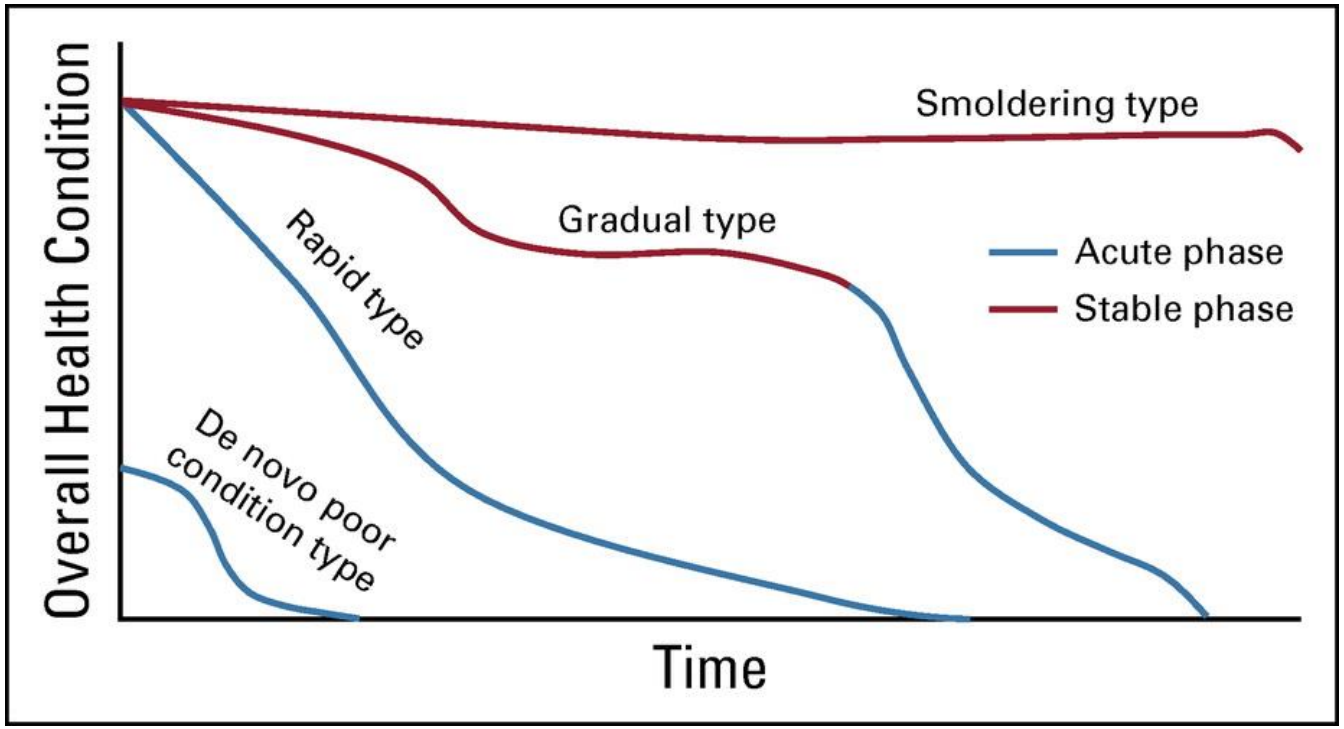
No. of patients at risk (events)

SG	272 (0)	253 (17)	223 (45)	200 (68)	163 (105)	130 (138)	105 (163)	71 (184)	52 (196)	33 (204)	19 (209)	13 (211)	1 (213)	0 (214)
TPC	271 (0)	251 (16)	199 (66)	167 (97)	124 (140)	96 (166)	82 (180)	66 (193)	46 (206)	27 (214)	15 (220)	7 (224)	1 (224)	0 (224)

Rugo H, SABCS 2022

Considerations in metastatic breast cancer

- Heterogeneity in disease presentations
- Variable disease trajectories
- Variability in breast cancer prognosis
- Substantial improvements in survival in recent years



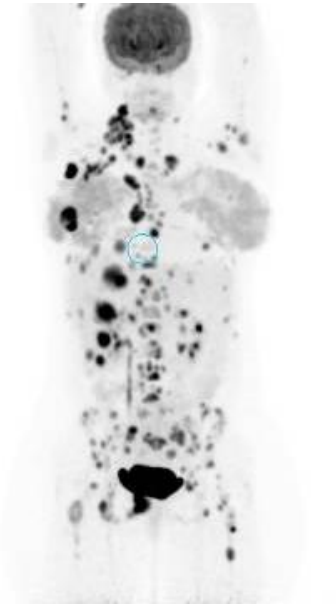
Kida et al. JCO Oncology Practice 2021;17:177-183

BL 31 ans

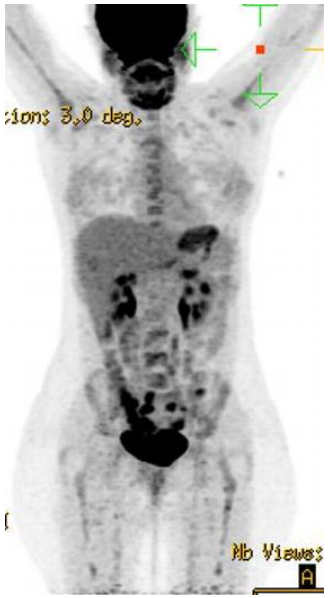
09.2022: Carcinome mammaire bilatéral synchrone d'emblée métastatique diagnostiqué après son accouchement

•Sein droit : NST de la jonction du quadrant externe, grade 3, classé cT2 (35 mm) cN3 cM1 (métastases osseuses, hépatiques, péritonéales et ganglionnaires), stade IV, ER 1%, PR 0%, Mib-1 70%, HER2 négatif (2+ en IHC), PD-L1 négatif,

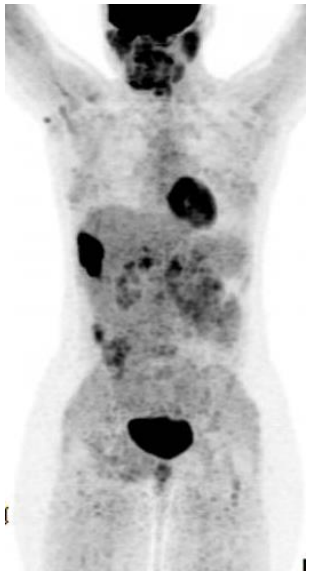
•Sein gauche : NST du quadrant supéro-interne, grade 3, classé cT1b (9 mm) cN0 cM1 (métastases osseuses, hépatiques, péritonéales et ganglionnaires), stade IV, ER 1%, PR 0%, Mib-1 70%, HER2 négatif (2+ en IHC), PD-L1 négatif

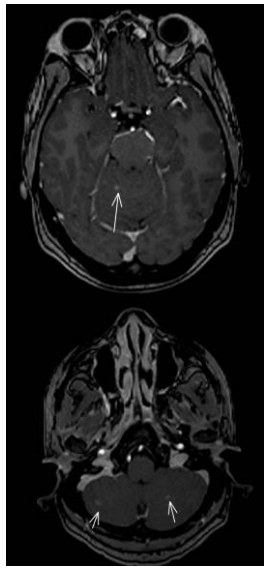


09.2022

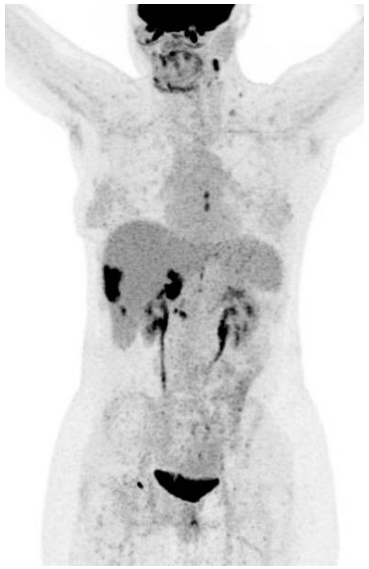


28.12.2022



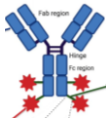


29.03.2024



06.2023

08.2023

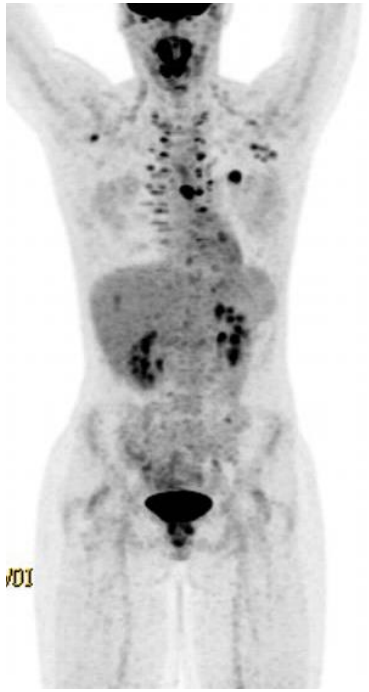


F-D C, 26ans

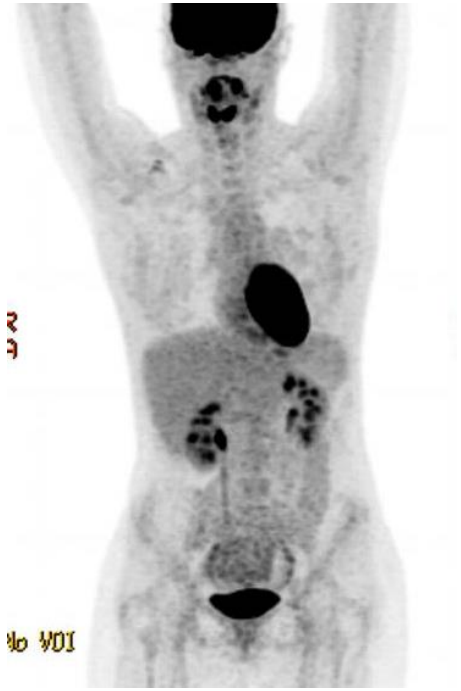
11.03.2014: Carcinome invasif NST du quadrant supéro-interne du sein gauche, grade 2, ER 0%, PR 0%, HER2 positif (IHC score 3+), MIB1 hétérogène, >30% en périphérie du carcinome invasif, cT1c cN3 (axillaire et mammaire interne) cM1 avec multiples métastases osseuses et hépatiques, stade IV :

10.04.2014 au 16.07.2014 : 4 cycles de paclitaxel, trastuzumab et pertuzumab dans le cadre de l'étude SAKK 22/10.

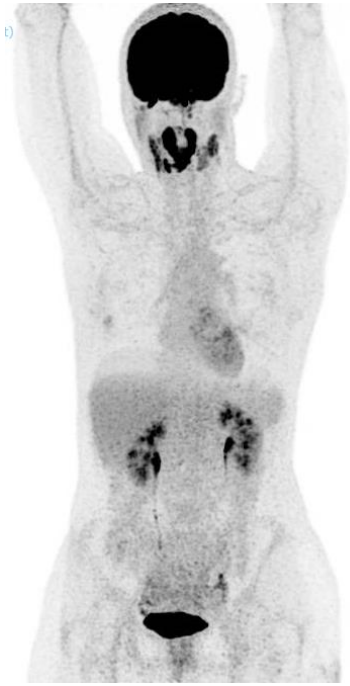
Depuis le 23.07.2014 : maintenance par Trastuzumab et Pertuzumab.



04.2014

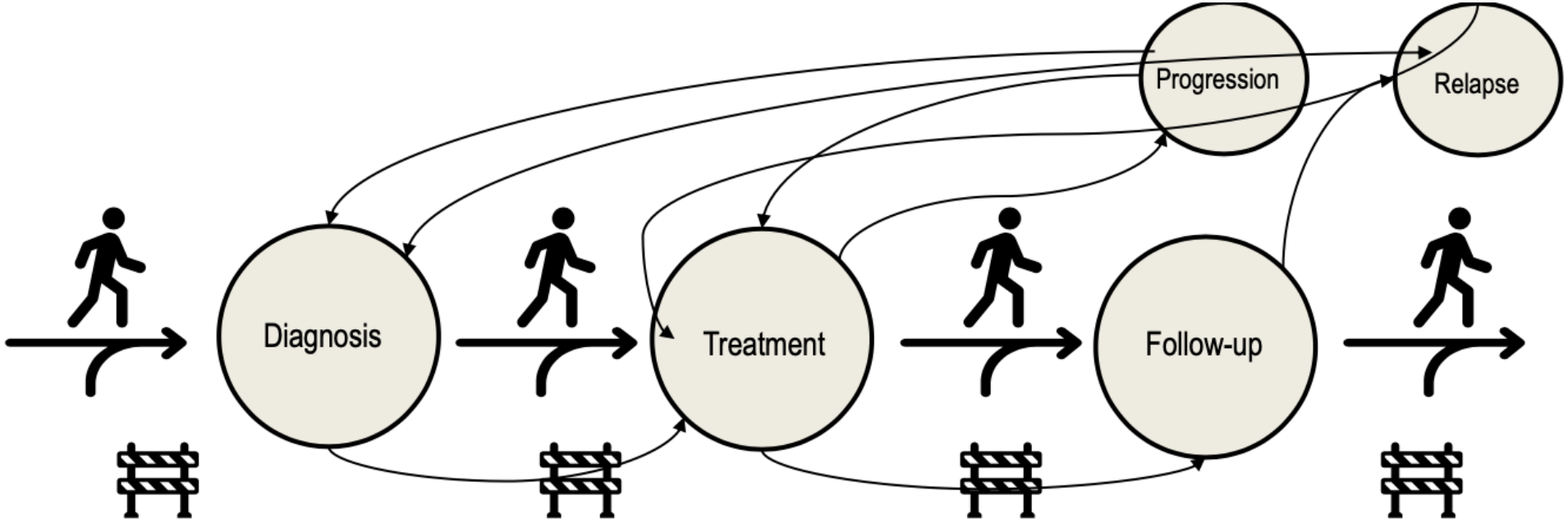


06.2014

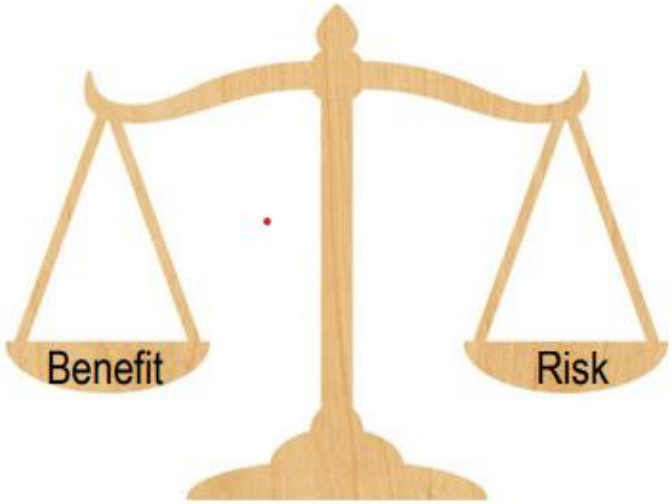


09.2023

Expanding the concept of pathway and individual complexity



When expanding options means prolonging survival



Thank you for your attention

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