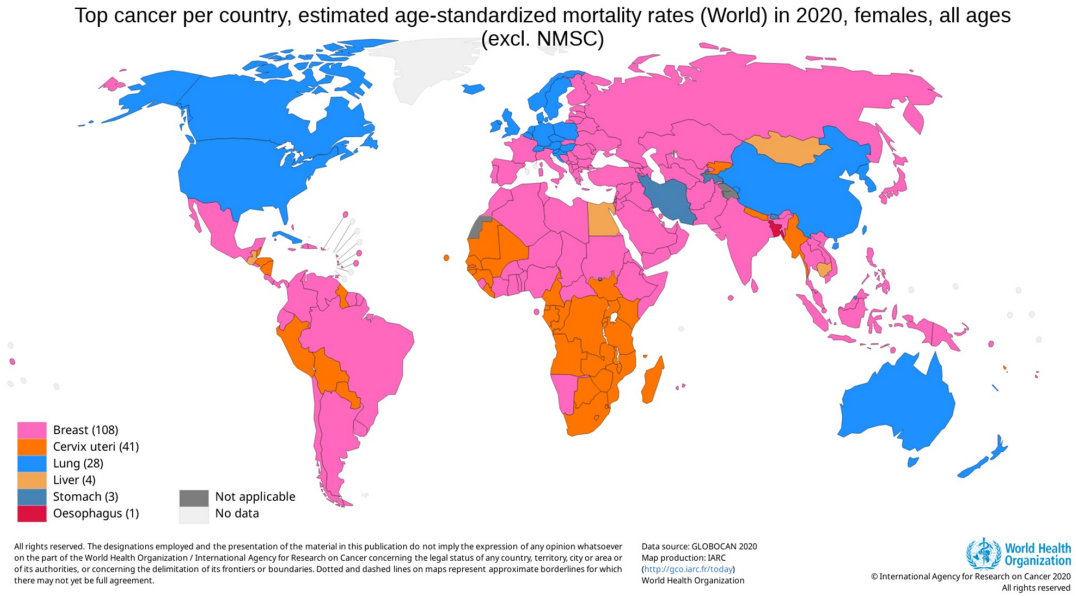


Nuevas Terapias dirigidas en cáncer de mama metastásico como paradigma.

Dra. Ingiborg Araya Calero

Introducción

- Representa la principal causa de mortalidad por cáncer en la mujer a nivel mundial.
- Entre un 5 a 6% de las pacientes debutan con enfermedad metastásica al diagnóstico.
- A pesar de los avances en el tratamiento y seguimiento de las pacientes, un 30% presenta recurrencia a distancia.
  - Largo periodo de recurrencia (5-20 años)
- La recurrencia a distancia o el debut como enfermedad metastásica está relacionada con el subtipo de cáncer de mama.
  - Predictivo y pronóstico

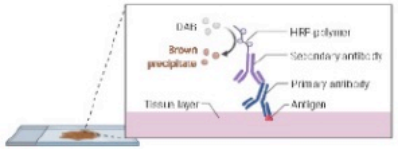


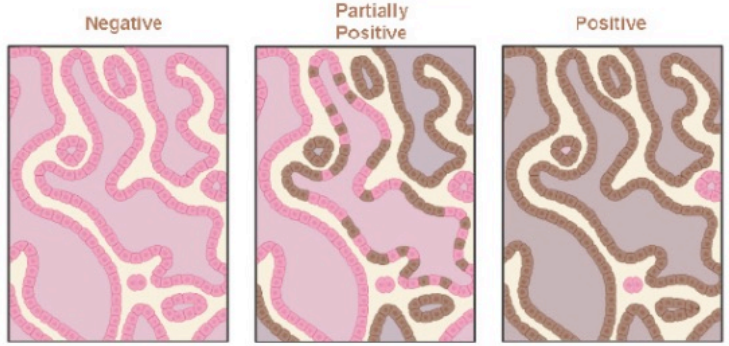
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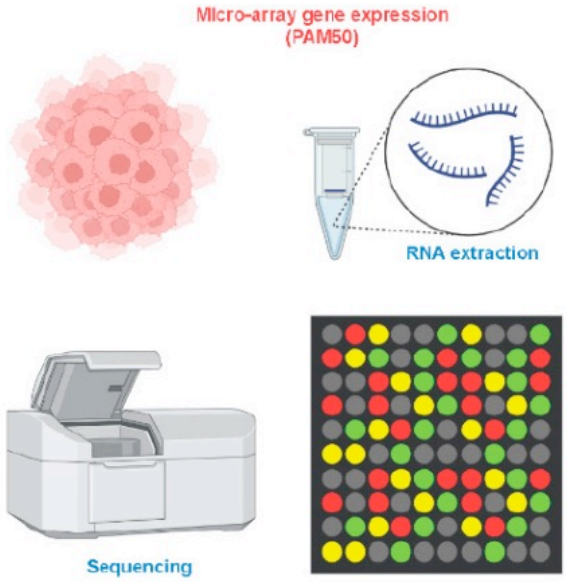
Histological characteristics

Immunohistological Markers
ER
PR
HER2
EGFR
Ki67
CK5/6

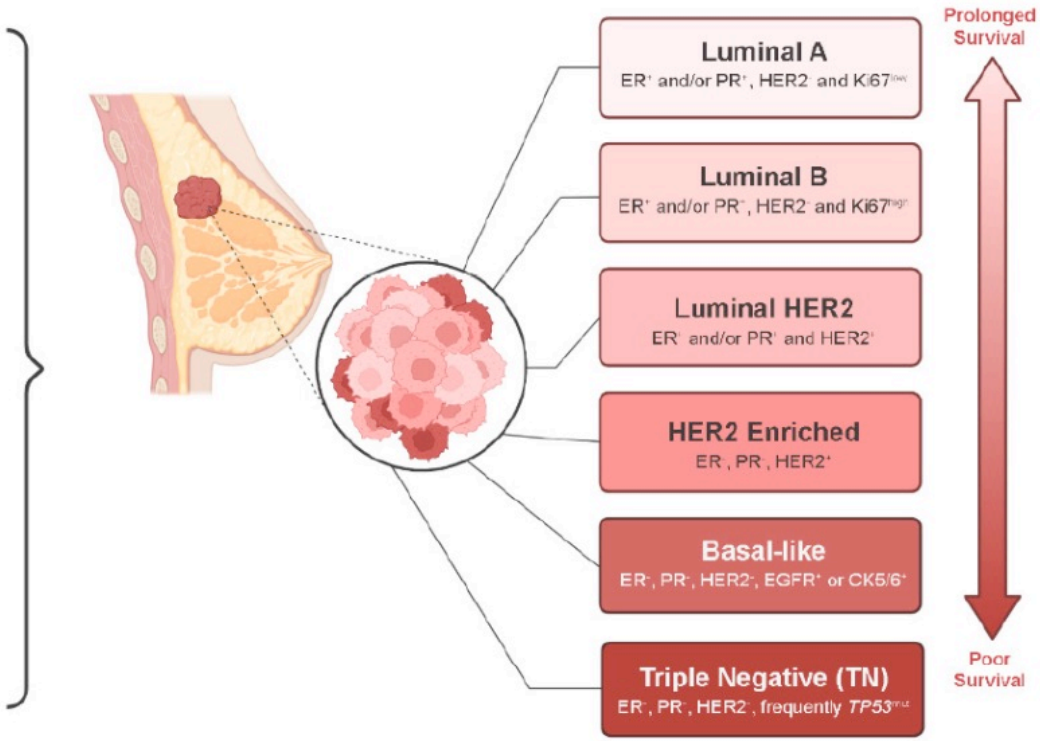




Transcriptomic profiling



Breast Cancer Subtypes



Cancer. J. Clin. Med. 2022, 11, 5891

Table 1. Prevalence, Prognosis, and Therapeutic Options for the 3 Breast Cancer Subtypes

	Hormone Receptor (HR) +/*ERBB2*−	*ERBB2*+ (HR+ or HR−)	Triple-Negative
Pathological definition	≥1% Of tumor cells stain positive for estrogen receptor or progesterone receptor proteins	Tumor cells stain strongly (3+) for ERBB2 protein or *ERBB2* gene is amplified in tumor cells. Approximately half of *ERBB2*+ tumors are also HR+	Tumor does not meet any pathologic criteria for positivity of estrogen receptor, progesterone receptor, or *ERBB2*
Molecular pathogenesis	Estrogen receptor α (a steroid hormone receptor) activates oncogenic growth pathways	The oncogene *ERBB2*, encoding ERBB2 receptor tyrosine kinase from the epidermal growth factor receptor family, is overactive	Unknown (likely various)
Percentage of breast cancer cases, %[12]	70	15-20	15
Prognosis			
Stage I (5-y breast cancer-specific survival), %[13,a]	≥99	≥94	≥85
Metastatic (median overall survival)[14-16,b]	4-5 y	5 y	10-13 mo

Typical systemic therapies for nonmetastatic disease (agents, route, and duration)	• Endocrine therapy (all patients):
	  • Tamoxifen, letrozole, anastrozole, or exemestane
	  • Oral therapy
	  • 5-10 y
	• Chemotherapy (some patients):
	  • Adriamycin/cyclophosphamide (AC)
	  • Adriamycin/cyclophosphamide/ paclitaxel (AC-T)
	  • Docetaxel/cyclophosphamide (TC)
	  • Intravenous therapy
	  • 12-20 wk
		• Chemotherapy plus ERBB2-targeted therapy (all patients):
		  • Paclitaxel/trastuzumab (TH)
		  • Adriamycin/cyclophosphamide/ paclitaxel/trastuzumab ± pertuzumab (AC-TH±P)
		  • Docetaxel/carboplatin/trastuzumab ± pertuzumab (TCH±P)
		  • Intravenous therapy
		  • 12-20 wk of chemotherapy; 1 y of ERBB2-targeted therapy
		• Endocrine therapy (if also hormone receptor positive)
		  • Tamoxifen, letrozole, anastrozole, or exemestane
		  • Oral therapy
		  • 5-10 y
			• Chemotherapy (all patients):
			  • AC
			  • AC-T
			  • TC
			  • Intravenous therapy
			  • 12-20 wk

[a] Prognosis estimated from nearly 44 000 patients with breast cancer enrolled in the California Cancer Registry (2005-2008); stage I breast cancer defined by the American Joint Committee on Cancer staging manual anatomic staging table, 8th edition. 95% CIs for stage I 5-year breast cancer-specific survival estimates are as follows: 98%-100% for HR+/*ERBB2*−, 83%-100% for *ERBB2*+, and 75%-98% for triple-negative.

[b] Prognosis listed is from time of diagnosis of metastatic breast cancer.

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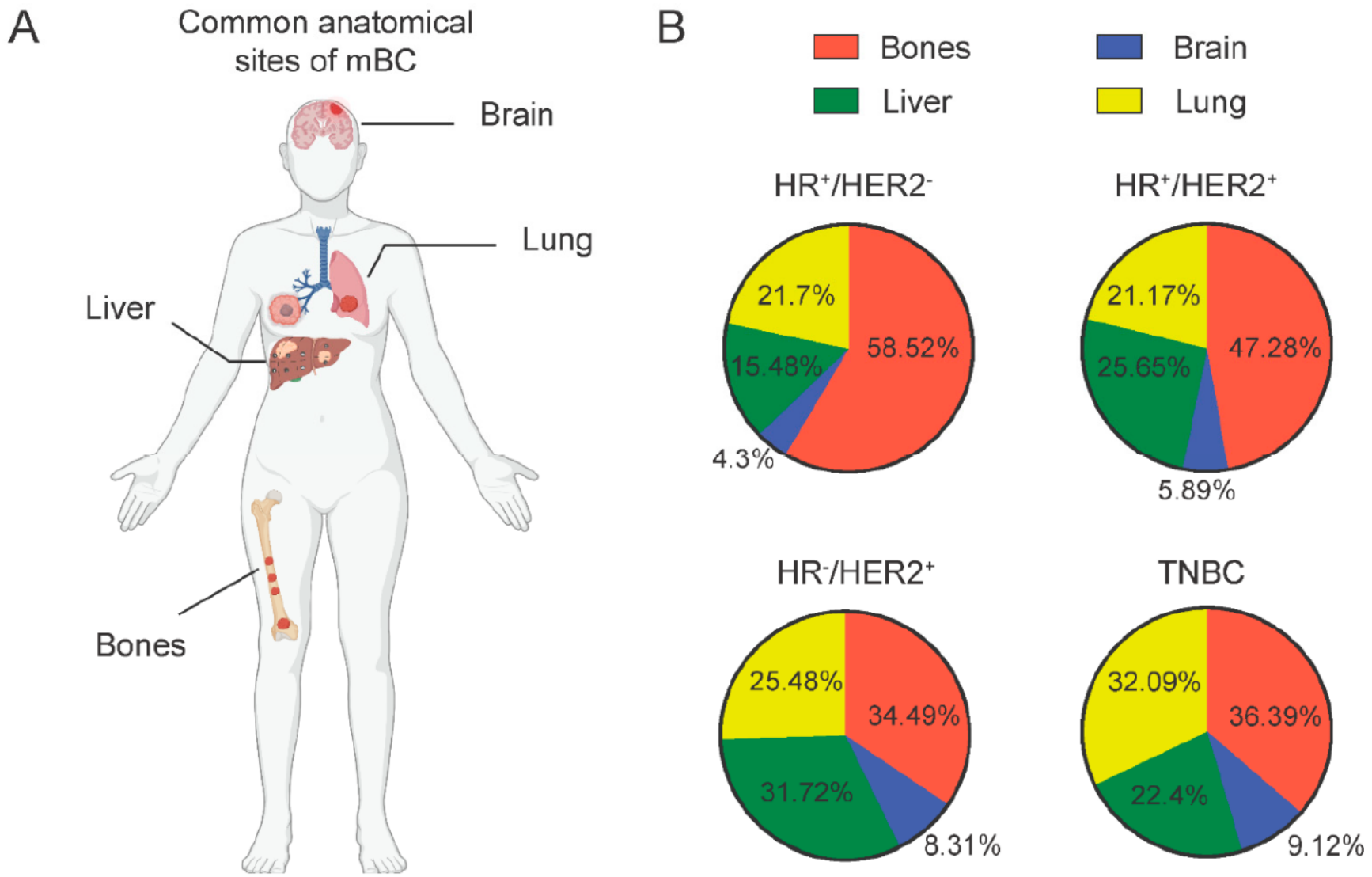


Figure 2. Common metastatic sites of breast cancer subtypes. (**A**) Representation of common metastatic sites in breast cancer patients. (**B**) The frequencies of metastatic sites in breast cancer subtypes, as described previously [22], represented as pie charts.

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Factores pronósticos

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Table 1. Prognostic and Predictive factors for metastatic Breast Cancer.

Prognostic Factors	Details	References
★ Relapse Free interval	≥2 years from primary breast cancer diagnosis is considered more favorable	Swenerton et al. [27] Hortobagyi et al. [28] Clark et al. [29] Harris et al. [30]
Metastatic sites: bones, chest wall, or lymph nodes	May have prolonged-free survival	Swenerton et al. [27] Hortobagyi et al. [28] Robertson et al. [31]
Metastatic sites: hepatic or lymphangitic pulmonary disease	Shorter PFS and OS	Barrios et al. [32]
Hormone receptor status	HR^+: more favorable prognosis, ER^+/PR^+: significantly longer survival than single hormone receptor-positive tumors	Stuart-Harris et al. [33]

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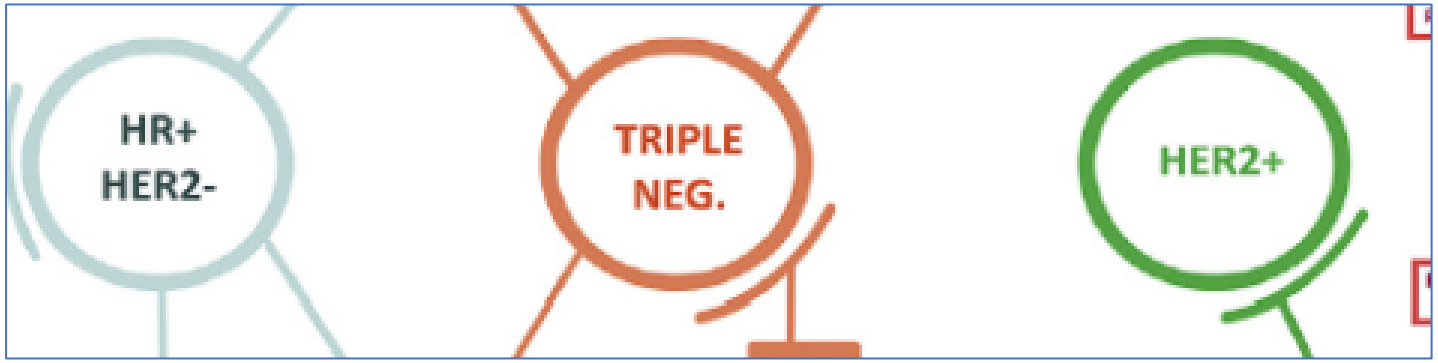
Table 1. *Cont.*

Prognostic Factors	Details	References
HER-2$^+$ or TNBC	Shorter median survival	Clark et al. [29] Emi et al. [34] Ismail-Khan et al. [35]
PS (Performance Status)	Weight loss, high LDH and low PS are poor prognostic features	Swenerton et al. [27] Yamamoto et al. [36]
★ Circulating Tumor Cells (CTC) *	CTC $\geq$ 5/7.5 mL, poor prognosis with shortened PFS and OS	Bidard et al. [37] Smerage et al. [38]
★ Circulating tumor DNA (ctDNA) *	High ctDNA, increased risk of death	Ye et al. [39]

* CTC and ctDNA should not dictate treatment decisions. Abbreviations: PFS: Progression Free Survival; OS: Overall Survival; TNBC: Triple Negative Breast Cancer; LDH: Lactate dehydrogenase

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NUEVAS TERAPIAS EN CÁNCER DE MAMA MESTASTÁSICO (ABC)



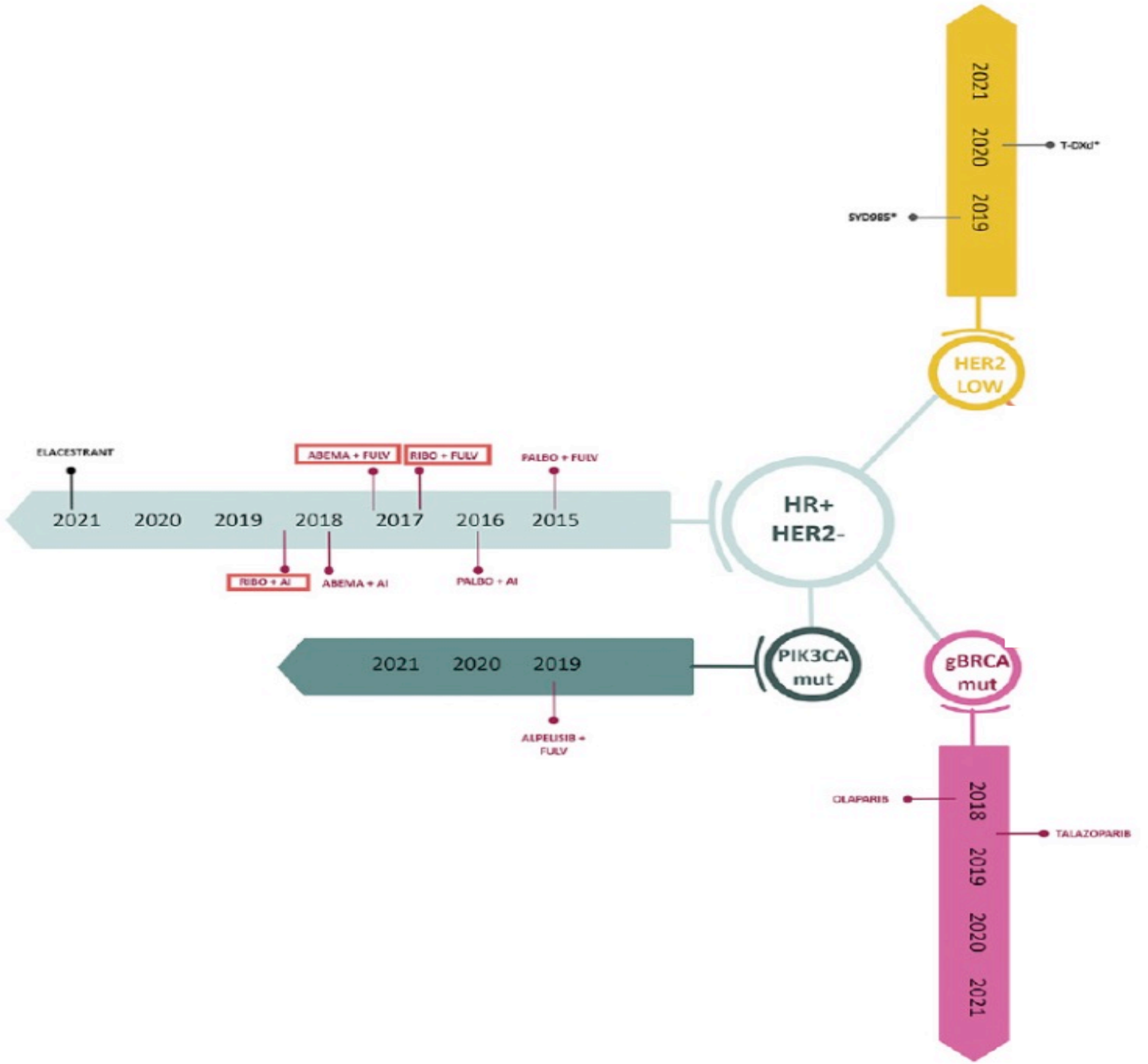
RH(+)HER2(-)

Representa el 70% de todos los cánceres de mama

Tratamiento secuencial

Las primeras líneas del tratamiento son terapias endocrinas.

Quimioterapia reservada para pacientes en crisis visceral.



https://doi.org/10.1016/j.esmoop.2022.100409

Drugs (2021) 81:317–331
https://doi.org/10.1007/s40265-020-01461-2

REVIEW ARTICLE

Inhibiting CDK4/6 in Breast Cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences

C. Louwrens Braal[1] · Elisabeth M. Jongbloed[1] · Saskia M. Wilting[1] · Ron H. J. Mathijssen[1] · Stijn L. W. Koolen[1,2] · Agnes Jager[1]

Accepted: 10 December 2020 / Published online: 28 December 2020
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Abstract
The cyclin-dependent kinase (CDK) 4/6 inhibitors belong to a new class of drugs that interrupt proliferation of malignant cells by inhibiting progression through the cell cycle. Three such inhibitors, palbociclib, ribociclib, and abemaciclib were recently approved for breast cancer treatment in various settings and combination regimens. On the basis of their impressive efficacy, all three CDK4/6 inhibitors now play an important role in the treatment of patients with HR+, HER2− breast cancer; however, their optimal use still needs to be established. The three drugs have many similarities in both pharmacokinetics and pharmacodynamics. However, there are some differences on the basis of which the choice for a particular CDK4/6 inhibitor for an individual patient can be important. In this article, the clinical pharmacokinetic and pharmacodynamic profiles of the three CDK4/6 inhibitors are reviewed and important future directions of the clinical applicability of CDK4/6 inhibitors will be discussed.

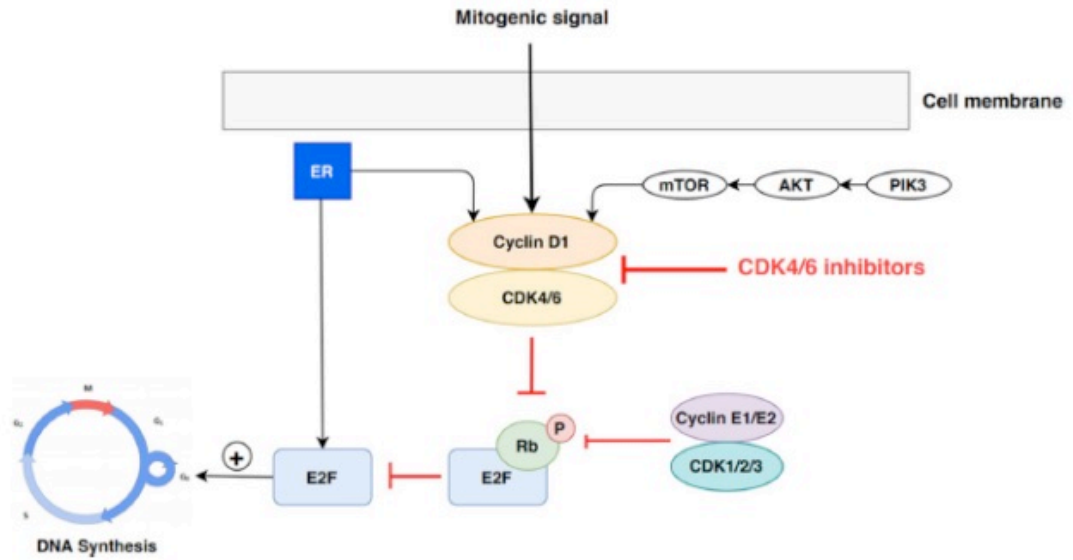
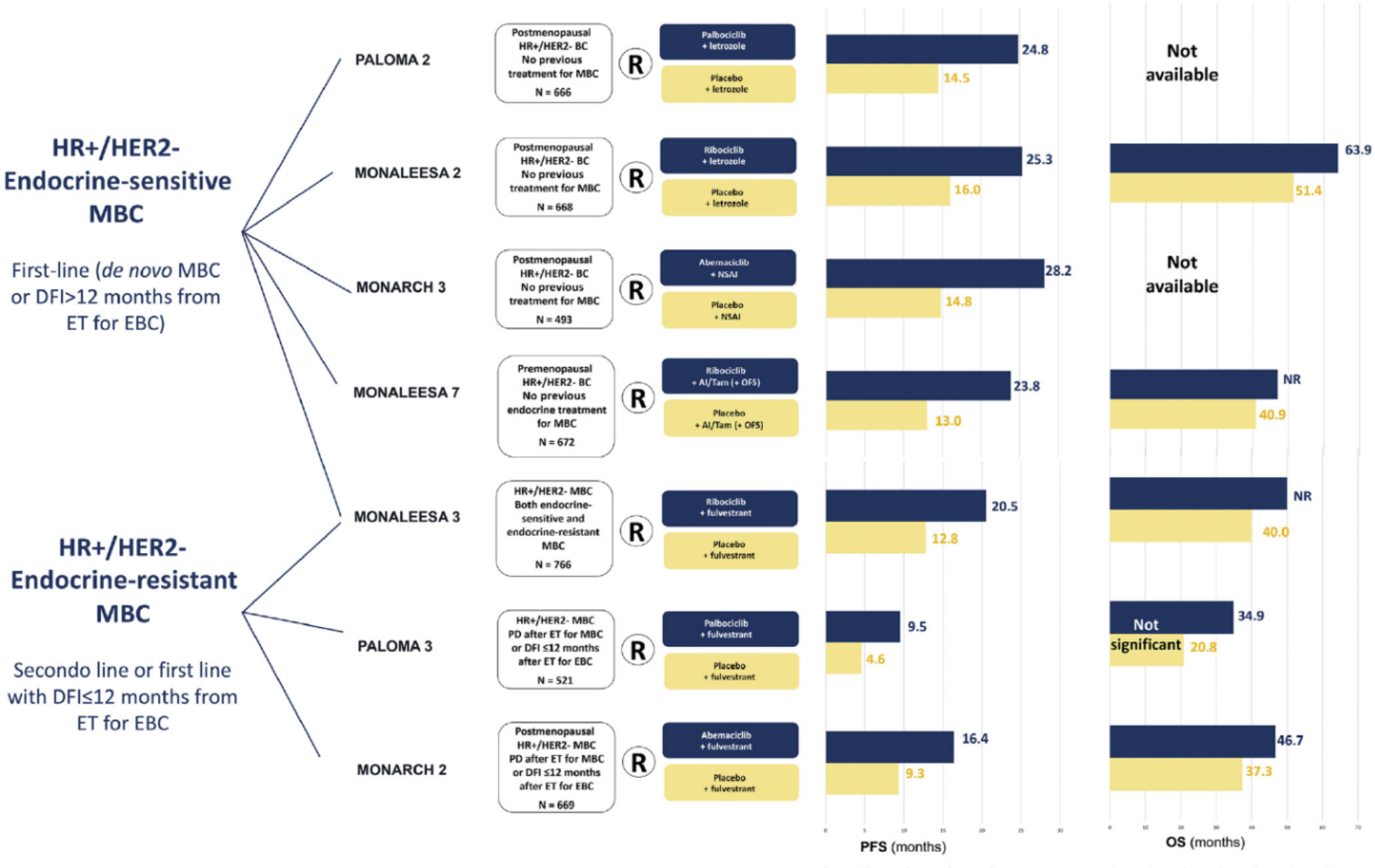


Fig. 1 Mechanism of action of CDK4/6 inhibitors. The CDK4/6-cyclin D1 complex induces phosphorylation of the retinoblastoma (Rb) tumor-suppressor protein. Free transcription factor E2F stimulates cell transition from the G1 to the S phase and cell division. *AKT* protein kinase B, *CDK4/6* cyclin dependent kinase 4 and 6, *ER* estrogen receptor, *E2F* transcription factor family, *HER2* human epidermal growth factor receptor-2, *PIK3* phosphoinositide 3-kinase, *Rb* retinoblastoma tumor suppressor protein, *mTOR* mammalian target of rapamycin

Table 1. Main breakthrough therapies across BC subtypes in the advanced setting and their value according to ESMO-Magnitude of Clinical Benefit Scale

Treatment class	Subtype	Treatment strategy		Phase III Clinical Trials	Significant results ([a] if primary endpoint)		Practice changing	Current clinical positioning	ESMO MCBS
					PFS	OS			
CDK 4/6 inhibitors	HR+/HER2−	CDK 4/6 inhibitors + AI	Palbociclib + letrozole	PALOMA-2[3]	Yes[a]	N.A.	Yes	First-line treatment for endocrine-sensitive HR+/HER2− MBC with postmenopausal status.	3
			Ribociclib + letrozole	MONALEESA-2[4,5]	Yes[a]	Yes	Yes	First-line treatment for endocrine-sensitive HR+/HER2− MBC with postmenopausal status.	3
			Abemaciclib + NSAI	MONARCH-3[6]	Yes[a]	N.A.	Yes	First-line treatment for endocrine-sensitive HR+/HER2− MBC with postmenopausal status.	3
	HR+/HER2−	CDK 4/6 inhibitors + endocrine therapy	Ribociclib + AI/Tam	MONALEESA-7[7,8]	Yes[a]	Yes	Yes	First-line treatment for endocrine-sensitive HR+/HER2− MBC with premenopausal status.	5
	HR+/HER2−	CDK 4/6 inhibitors + fulvestrant	Palbociclib + fulvestrant	PALOMA-3[9]	Yes[a]	No	Yes	Second- or first-line treatment (DFI ≤12 months from ET for EBC) for endocrine-resistant HR+/HER2− MBC	4
			Ribociclib + fulvestrant	MONALEESA-3[10,11]	Yes[a]	Yes	Yes	Second- or first-line treatment (DFI ≤12 months from ET for EBC) for endocrine-resistant HR+/HER2− MBC and first-line treatment for endocrine-sensitive HR+/HER2− MBC	4
			Abemaciclib + fulvestrant	MONARCH-2[12,13]	Yes[a]	Yes	Yes	Second- or first-line treatment (DFI ≤12 months from ET for EBC) for endocrine-resistant HR+/HER2− MBC	4
PI3K inhibitors	HR+/HER2−	Alpelisib + fulvestrant		SOLAR-1[14]	Yes[a] (in PIK3CA-mutant cohort)	No	Yes	Treatment for endocrine-resistant HR+/HER2− MBC (EMA: no prior CDK 4/6)	3
Oral SERDs	HR+/HER2−	Elacestrant		EMERALD[15]	Yes[a] (in ITT and ESR1-mutant cohort)	No (immature)	Potentially	Treatment for endocrine-resistant HR+/HER2− MBC	N.A.
mTOR inhibitors	HR+/HER2−	Everolimus + exemestane		BOLERO-2[16,17]	Yes[a]	No	Yes	Treatment for HR+/HER2− MBC progressing to AI	2

https://doi.org/10.1016/j.esmoop.2022.100409


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
PALOMA 2
Postmenopausal HR+/HER2- BC No previous treatment for MBC N = 666
R
Palbociclib + letrozole
Placebo + letrozole
24.8
14.5
Not available
MONALEESA 2
Postmenopausal HR+/HER2- BC No previous treatment for MBC N = 668
R
Ribociclib + letrozole
Placebo + letrozole
25.3
16.0
63.9
51.4
MONARCH 3
Postmenopausal HR+/HER2- BC No previous treatment for MBC N = 493
R
Abemaciclib + NSAI
Placebo + NSAI
28.2
14.8
Not available
MONALEESA 7
Premenopausal HR+/HER2- BC No previous endocrine treatment for MBC N = 672
R
Ribociclib + AI/Tam (+ OFS)
Placebo + AI/Tam (+ OFS)
23.8
13.0
NR
40.9
MONALEESA 3
HR+/HER2- MBC Both endocrine-sensitive and endocrine-resistant MBC N = 766
R
Ribociclib + fulvestrant
Placebo + fulvestrant
20.5
12.8
NR
40.0
PALOMA 3
HR+/HER2- MBC PD after ET for MBC or DFI ≤12 months after ET for EBC N = 521
R
Palbociclib + fulvestrant
Placebo + fulvestrant
9.5
4.6
34.9
Not significant
20.8
MONARCH 2
Postmenopausal HR+/HER2- MBC PD after ET for MBC or DFI ≤12 months after ET for EBC N = 669
R
Abemaciclib + fulvestrant
Placebo + fulvestrant
16.4
9.3
46.7
37.3
0 5 10 15 20 25 30
PFS (months)
0 10 20 30 40 50 60 70
OS (months)

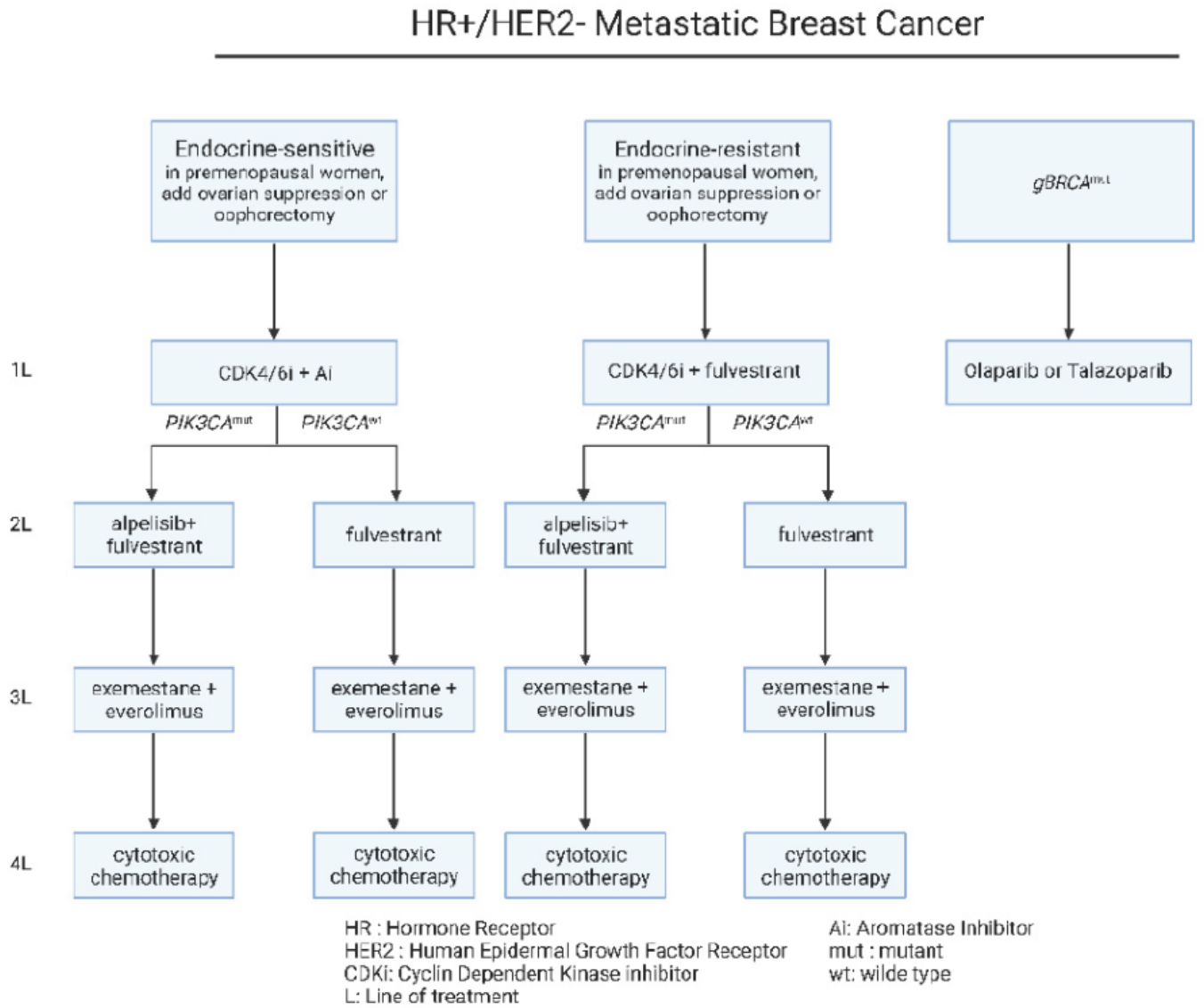


Figure 3. Current therapeutic algorithm for the management of HR$^+$/HER-2$^-$ mBC. Proposed therapeutic algorithm for patients with HR$^+$/HER-2$^-$ metastatic breast cancer [39]. The abbreviations of the terms used in the figure are outlined in the lower part of the algorithm.

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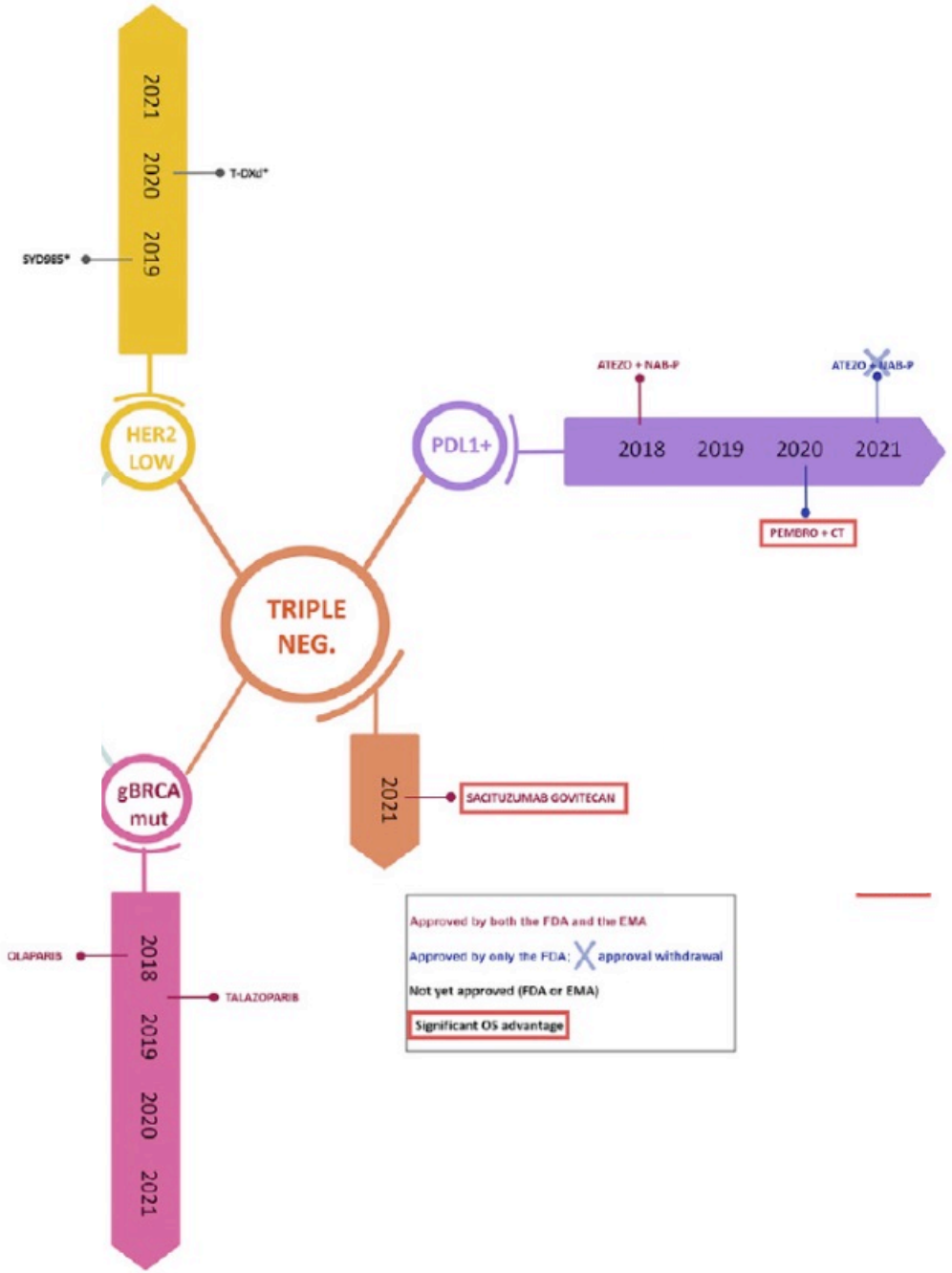
RH(-) Her2(-)

Representa el 15% de todos los cánceres de mama

Quimioterapia

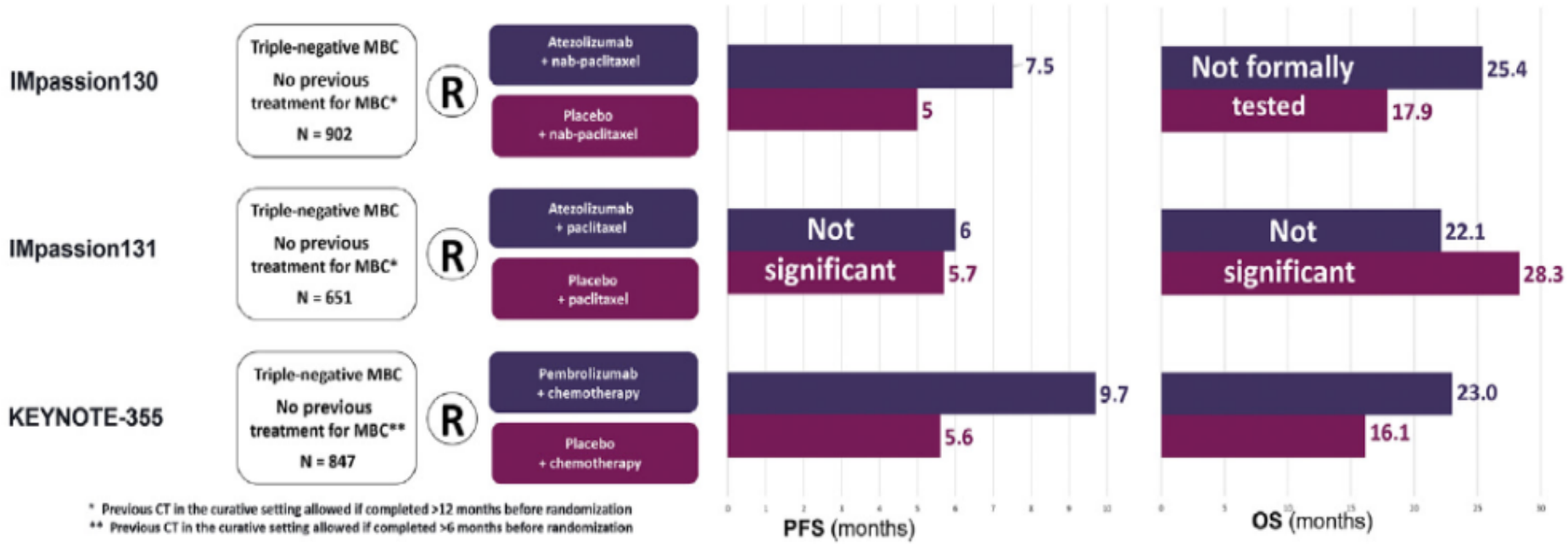
Tratamiento secuencial monodroga

Mayor probabilidad de suspensión de tratamiento por toxicidad.



https://doi.org/10.1016/j.esmoop.2022.100409

Triple-negative PD-L1+ MBC



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TNBC

abstracts

LBA16 **KEYNOTE-355: Final results from a randomized, double-blind phase III study of first-line pembrolizumab + chemotherapy vs placebo + chemotherapy for metastatic TNBC**

J. Cortés[1], D.W. Cescon[2], H.S. Rugo[3], S-A. Im[4], M. Md Yusof[5], C. Gallardo[6], O. Lipatov[7], C.H. Barrios[8], J. Perez-Garcia[9], H. Iwata[10], N. Masuda[11], M. Torregroza Otero[12], E. Gokmen[13], S. Loi[14], Z. Guo[15], X. Zhou[15], V. Karantza[15], W. Pan[15], P. Schmid[16]

Table: LBA16

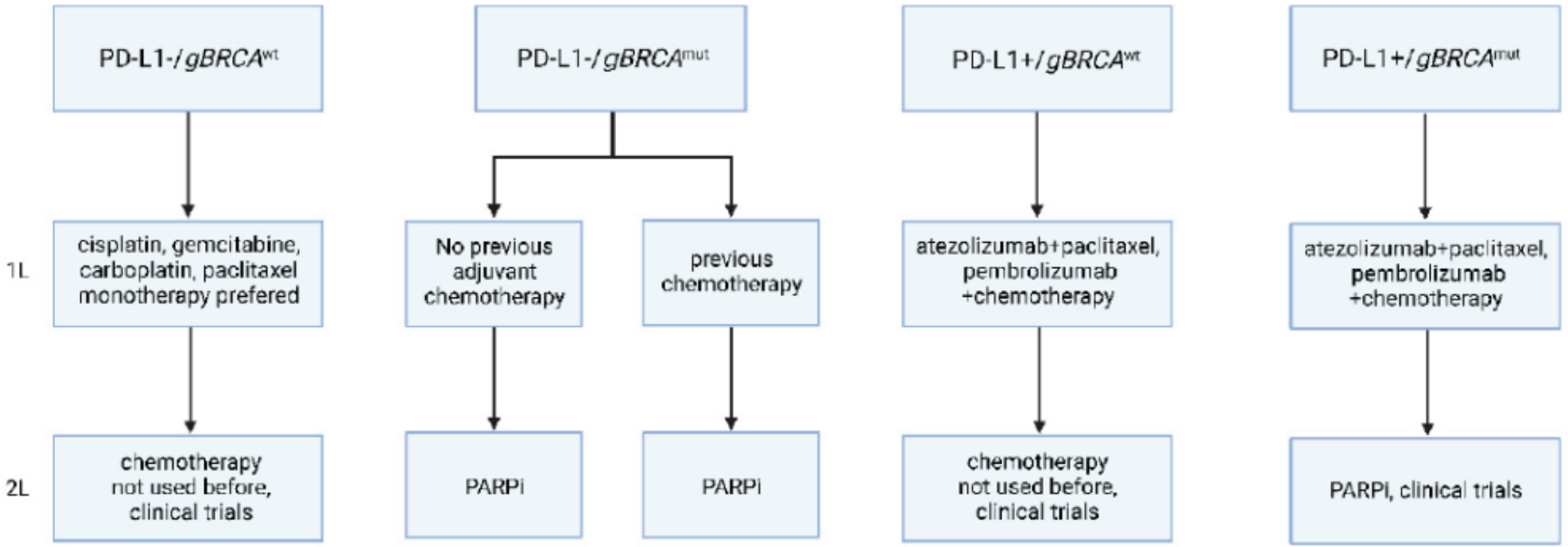
	CPS ≥10		CPS ≥1		ITT	
	P + C n = 220	C n = 103	P + C n = 425	C n = 211	P + C n = 566	C n = 281
OS, mo, median[a] (95% CI)	23.0 (19.0 – 26.3)	16.1 (12.6 – 18.8)	17.6 (15.5 – 19.5)	16.0 (12.8 – 17.4)	17.2 (15.3 – 19.0)	15.5 (13.9 – 17.2)
OS, HR[b] (95% CI)	0.73[c] (0.55 – 0.95)		0.86[d] (0.72 – 1.04)		0.89 (0.76 – 1.05)	
PFS, mo, median[a] (95% CI)	9.7 (7.6 – 11.3)	5.6 (5.3 – 7.5)	7.6 (6.6 – 8.0)	5.6 (5.4 – 7.4)	7.5 (6.3 – 7.7)	5.6 (5.4 – 7.2)
PFS, HR[b] (95% CI)	0.66 (0.50 – 0.88)		0.75 0.62 – 0.91		0.82 0.70 – 0.98	
ORR, % (95% CI)	52.7 (45.9 – 59.5)	40.8 (31.2 – 50.9)	44.9 (40.1 – 49.8)	38.9 (32.2 – 45.8)	40.8 (36.7 – 45.0)	37.0 (31.4 – 42.9)

[a]From Kaplan-Meier method.
[b]From a stratified Cox model.
[c]P=0.0093; boundary of P=0.0113 met.
[d]P=0.0563; boundary of P=0.0172 not met.

Treatment class	Subtype	Treatment strategy	Phase III Clinical Trials	Significant results ([a] if primary endpoint)		Practice changing	Current clinical positioning	ESMO MCBS
				PFS	OS			
Anti-PD-1/PD-L1 agents	TN—PD-L1+	Atezolizumab + nab-paclitaxel	IMPASSION130[29,30]	Yes[a] (in ITT)	No[a] (in ITT not significant → PD-L1+ not tested)	Yes	First-line treatment for TN and PD-L1+ MBC (atezolizumab marketing authorization withdrawn in the United States)	3
	TN—PD-L1+	Pembrolizumab + CT	KEYNOTE355[31]	Yes[a] (in PD-L1+ CPS ≥10 → PD-L1+ CPS ≥1 → ITT)	Yes[a] (in PD-L1+ CPS ≥10 → PD-L1+ CPS ≥1 not significant → ITT not tested)	Yes	First-line treatment for TN and PD-L1+ MBC	3
Anti-TROP2 ADC	TN	Sacituzumab govitecan	ASCENT[32]	Yes[a] (in patients without brain metastases)	Yes	Yes	Treatment for TN MBC with two or more prior lines (at least one for MBC)	4
PARP inhibitors	gBRCA+ HER2−	Olaparib	OlympiAD[33,34]	Yes[a]	No	Yes	Treatment for gBRCA+ TN MBC with prior chemotherapy	4
	gBRCA+ HER2−	Talazoparib	EMBRACA[35,36]	Yes[a]	No	Yes	Treatment for gBRCA+ TN MBC with prior chemotherapy	4

https://doi.org/10.1016/j.esmoop.2022.100409

TNBC Metastatic Breast Cancer



TNBC : Triple Negative Breast Cancer
L: Line of treatment
PD-L1 : Program Death-Ligand 1
gBRCA : germline BRCA mutation
wt : wild type

BRCA: Breast Cancer Gene
mut : mutated
PARPi : Poly Adenosine Diphosphate-Ribose Polymerase inhibitor

Figure 5. Current therapeutic algorithm for the management of TNBC mBC. Proposed therapeutic algorithm for patients with Triple Negative metastatic breast cancer [79,80]. The abbreviations of the terms used in the figure are outlined in the lower part of the algorithm.

Cancer. J. Clin. Med. 2022, 11, 5891

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HER2(+)

Representa el 20% de todos los cánceres de mama

Puede expresar RH (+)

Terapia target que ha mejorado PFS y OS

50% de las pacientes tendrán compromiso cerebral



https://doi.org/10.1016/j.esmoop.2022.100409

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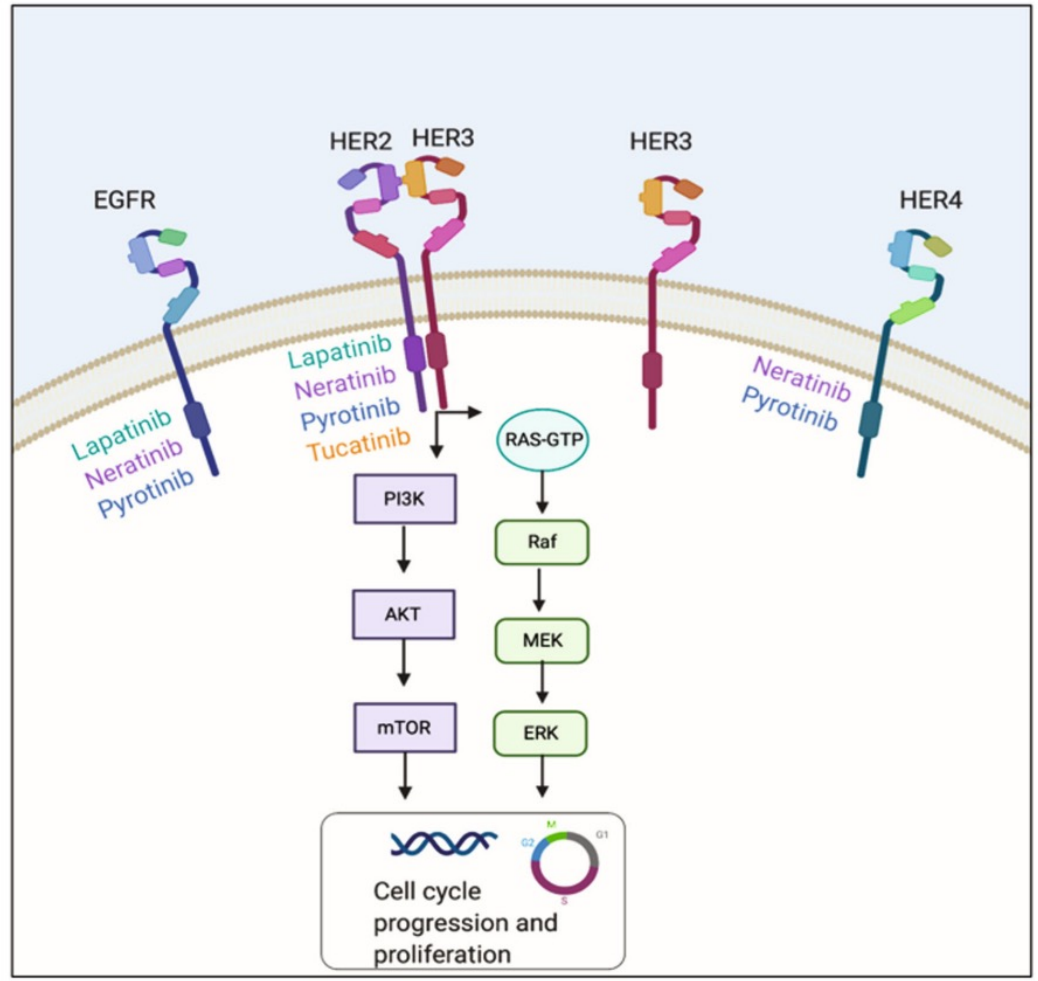


Fig. 1 Mechanism of action of HER2 tyrosine kinase inhibitors. There are four members of the HER2 receptor family, these are the targets of lapatinib, neratinib, pyrotinib and tucatinib. The HER2 extracellular domain has no known ligand and is activated by the formation of homo or heterodimers (exemplified by a HER2-HER3 heterodimer in the figure). These dimers lead to phosphorylation of tyrosine kinase residues in the cytoplasmic domain which function as docking sites for proteins that activate the PI3K and MAPK signaling pathways downstream leading to cell cycle progression and proliferation.

Treatment class	Subtype	Treatment strategy	Phase III Clinical Trials	Significant results ([a] if primary endpoint)		Practice changing	Current clinical positioning	ESMO MCBS
				PFS	OS			
Dual HER2 blockade with anti-HER2 MABS	HER2+	Pertuzumab + trastuzumab + CT	CLEOPATRA[18,19]	Yes[a]	Yes	Yes	First-line treatment for HER2+ MBC	4
Anti-HER2 ADCS	HER2+	T-DM1	EMILIA[20,21]	Yes[a]	Yes[a]	Yes	Second-line treatment for HER2+ MBC or first line if DFI ≤6 months after completion of adjuvant trastuzumab	4
	HER2+	T-DXd	DESTINY-Breast03[22]	Yes[a]	No (immature)	Yes	Upcoming second-line treatment for HER2+ MBC with ≥1 prior anti-HER2-based lines.	2 (based on DESTINY-Breast01)
	HER2+	Trastuzumab duocarmazine	TULIP[23]	Yes[a]	No	Uncertain	Treatment as third-line or higher setting	NA
Anti-HER2 TKIs	HER2+	Tucatinib + trastuzumab + capecitabine	HER2CLIMB[24,25]	Yes[a]	Yes	Yes	Treatment for HER2+ MBC HER2+ MBC with two or more prior anti-HER2-based lines (second line or higher for the FDA; third line or higher for the EMA)	3
Novel anti-HER2 MAB	HER2+	Margetuximab + trastuzumab + CT	SOPHIA[26]	Yes[a]	No[a]	Yes	Treatment for HER2+ MBC HER2+ MBC with two or more prior anti-HER2-based lines (at least one for MBC)	2
PAN-HER TKIs	HER2+	Neratinib + capecitabine	NALA[27]	Yes[a]	No[a]	Yes	Treatment for HER2+ MBC HER2+ MBC with two or more prior anti-HER2-based lines	1
	HER2+	Pyrotinib + capecitabine	PHOEBE[28]	Yes[a]	No	Not outside China	Treatment in patients with one or more prior line	N.A.

https://doi.org/10.1016/j.esmoop.2022.100409

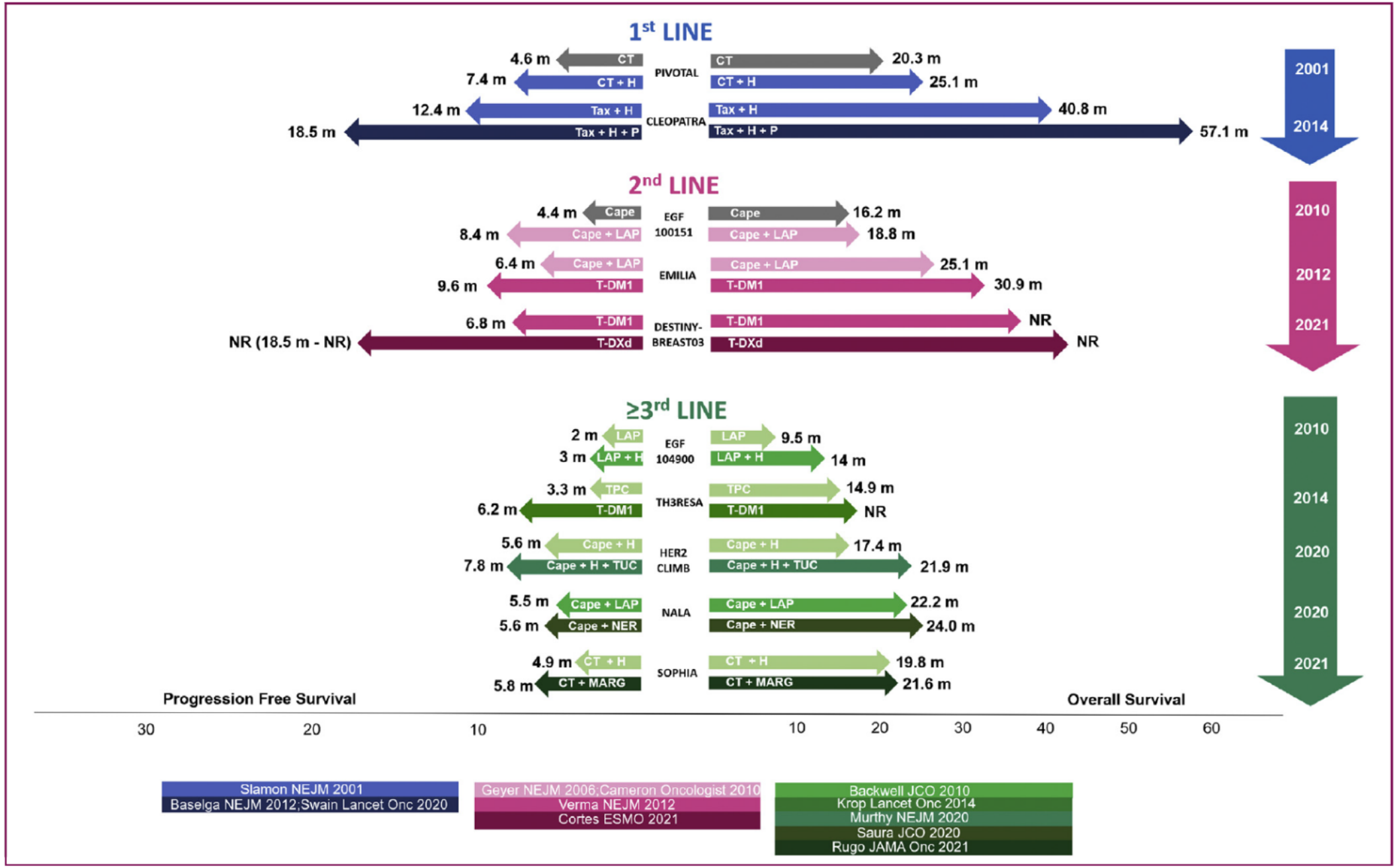


Figure 3. Progression-free survival (PFS) and overall survival (OS) results from major randomized clinical trials testing anti-HER2 strategies according to treatment line.[18-20,22,25-27,70-74]

Enfermedad Her2 positivo

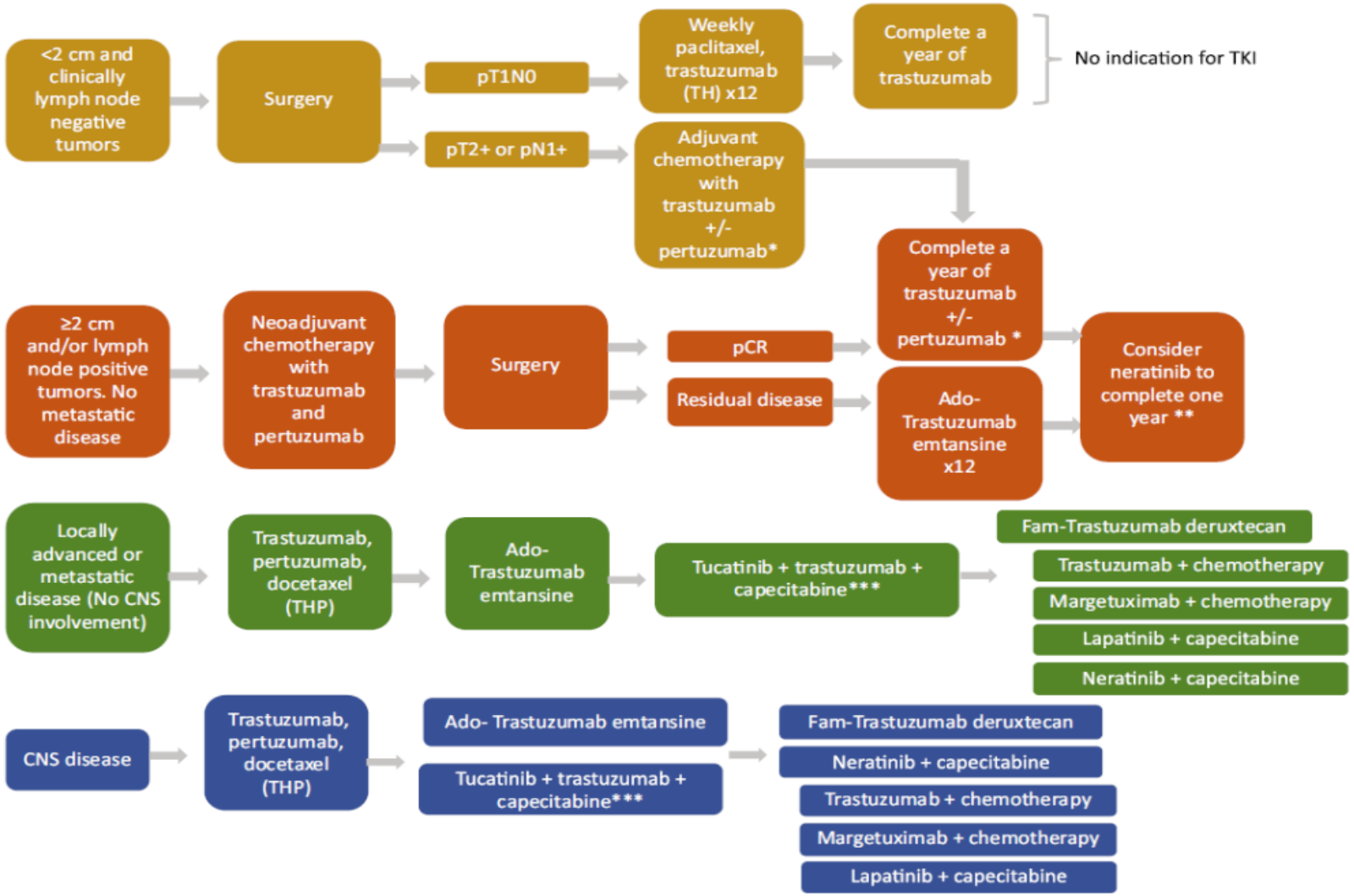


Fig. 3 Proposed treatment algorithm for HER2+Breast Cancer. This is a suggested treatment algorithm for early stage and advanced human epidermal growth factor 2 positive BC, based on the current United States Food and Drug Administration approvals. Radiation therapy and endocrine therapy should be incorporated when appropriate. There are multiple options for metastatic disease beyond second line, tucatinib can be considered in the third line setting based on the results of the phase 3 HER2CLIMB study. Other agents can be considered as fourth line or beyond, based on prior therapies, toxicity profile and comorbidities. *Subgroup analysis of APHINITY showed that patients with node positive disease have a greater benefit from adjuvant dual HER2 blockade. **Benefit seen in patients with hormone receptor positive and HER2 positive disease. There are no data about the use of neratinib after treatment with pertuzumab and/or ado-trastuzumab emtansine. ***Tucatinib is FDA approved in the second line setting after treatment with trastuzumab, pertuzumab and ado-trastuzumab emtansine. Can be considered for patients with CNS involvement.

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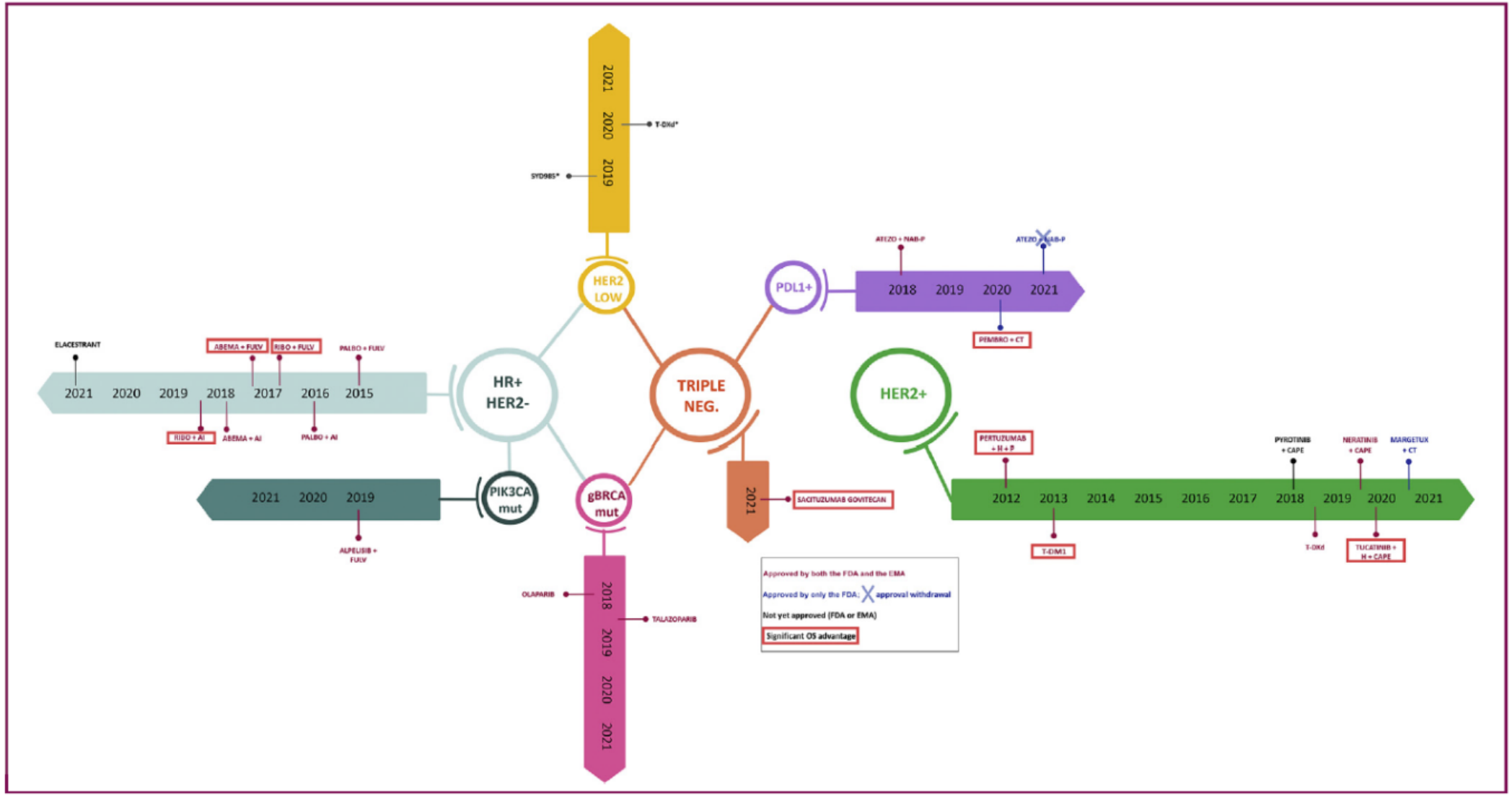


Figure 1. Timeline of main breakthrough therapies across breast cancer (BC) subtypes.

HR, hormone receptor; PALBO, palbociclib; FULV, fulvestrant; AI, aromatase inhibitor; RIBO, ribociclib; ABEMA, abemaciclib; mut, mutated; gBRCA, BRCA germline mutation; neg, negative; PDL1, Programmed death-ligand 1; ATEZO, atezolizumab; NAB-P, nab-paclitaxel; PEMBRO, pembrolizumab, CT, chemotherapy; H, trastuzumab; P, docetaxel; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; CAPE, capecitabine; MARGETUX, margetuximab; FDA, Food and Drug Administration; EMA, European Medicines Agency; OS, overall survival.

*phase I trials.

https://doi.org/10.1016/j.esmoop.2022.100409

Conclusiones

- Los subtipos de cáncer de mama predicen respuesta a determinados tratamientos.
- Los nuevos tratamientos tienen como objetivo prolongar la sobrevida con la menor toxicidad posible y con el mayor respeto a la calidad de vida.
- Debemos buscar transformar al cáncer de mama metastásico de una enfermedad mortal a una enfermedad crónica.
- Seguiremos expectantes al desarrollo de los futuros tratamientos que logren este último objetivo.


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