Updates in Metastatic Breast Cancer treatment

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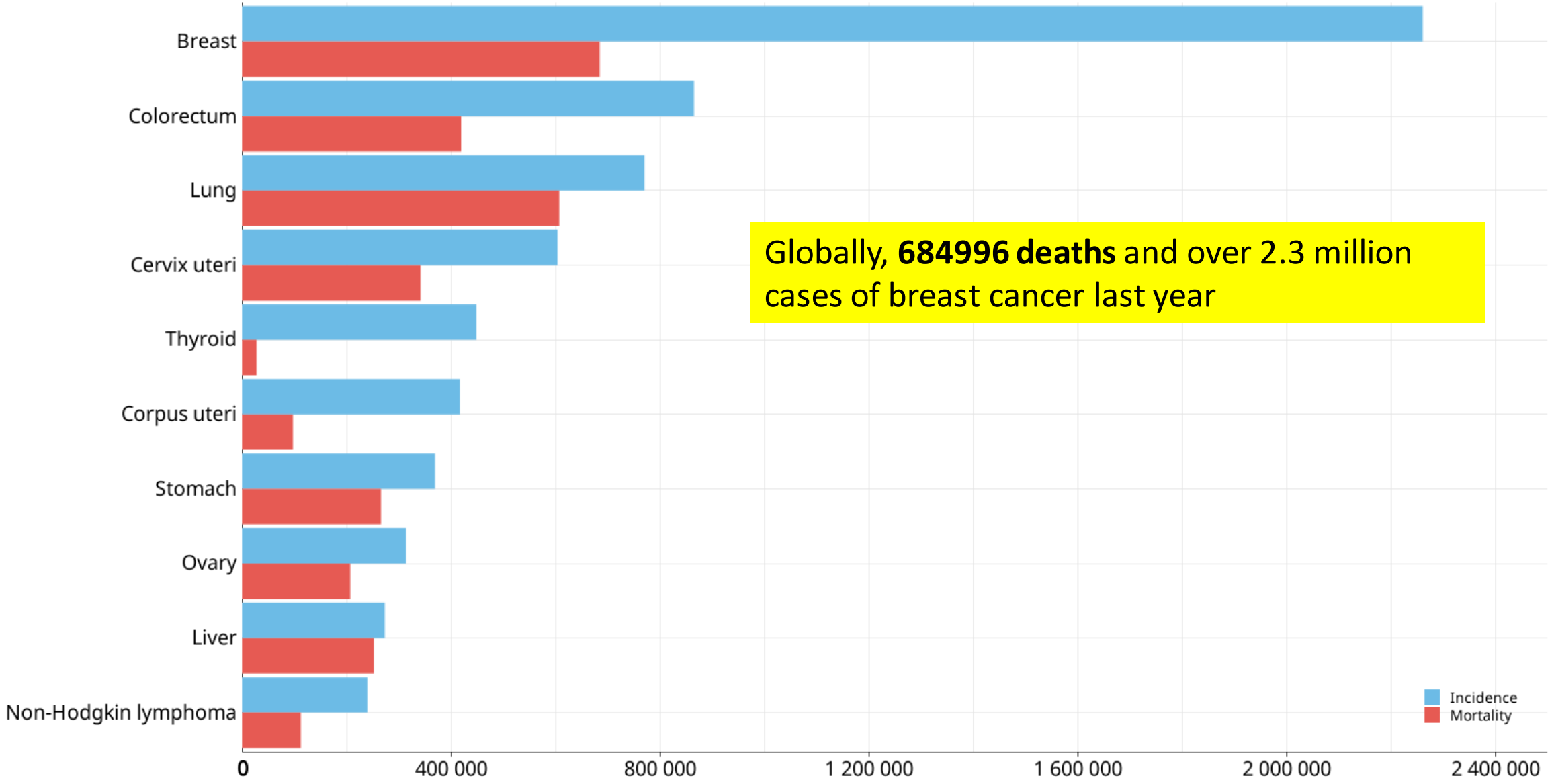
Disclosures

Advisory Board/Consulting

- Gilead 4/2023
- Biotheranostics 5/2023

Estimated number of incident cases and deaths World, females, all ages (excl. NMSC)

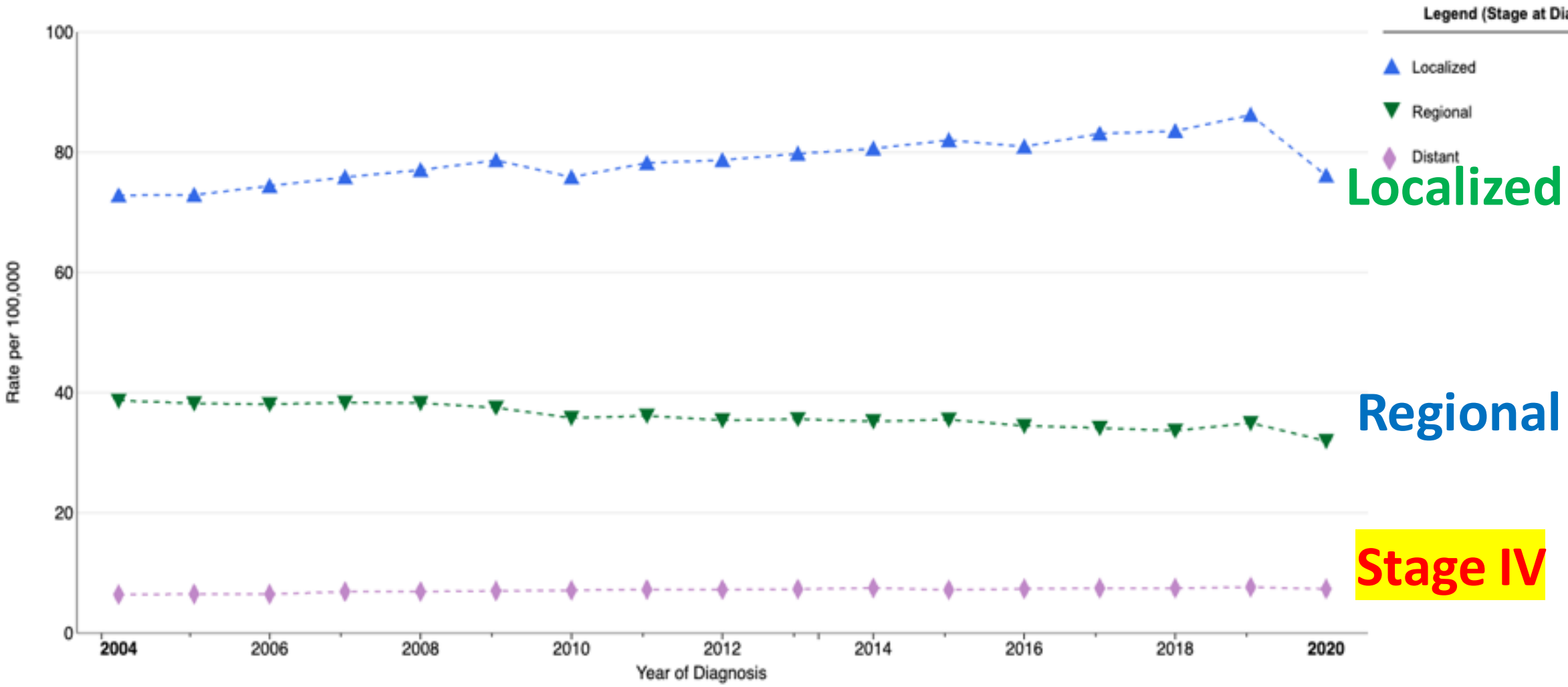


Globally, **684996 deaths** and over 2.3 million cases of breast cancer last year

Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

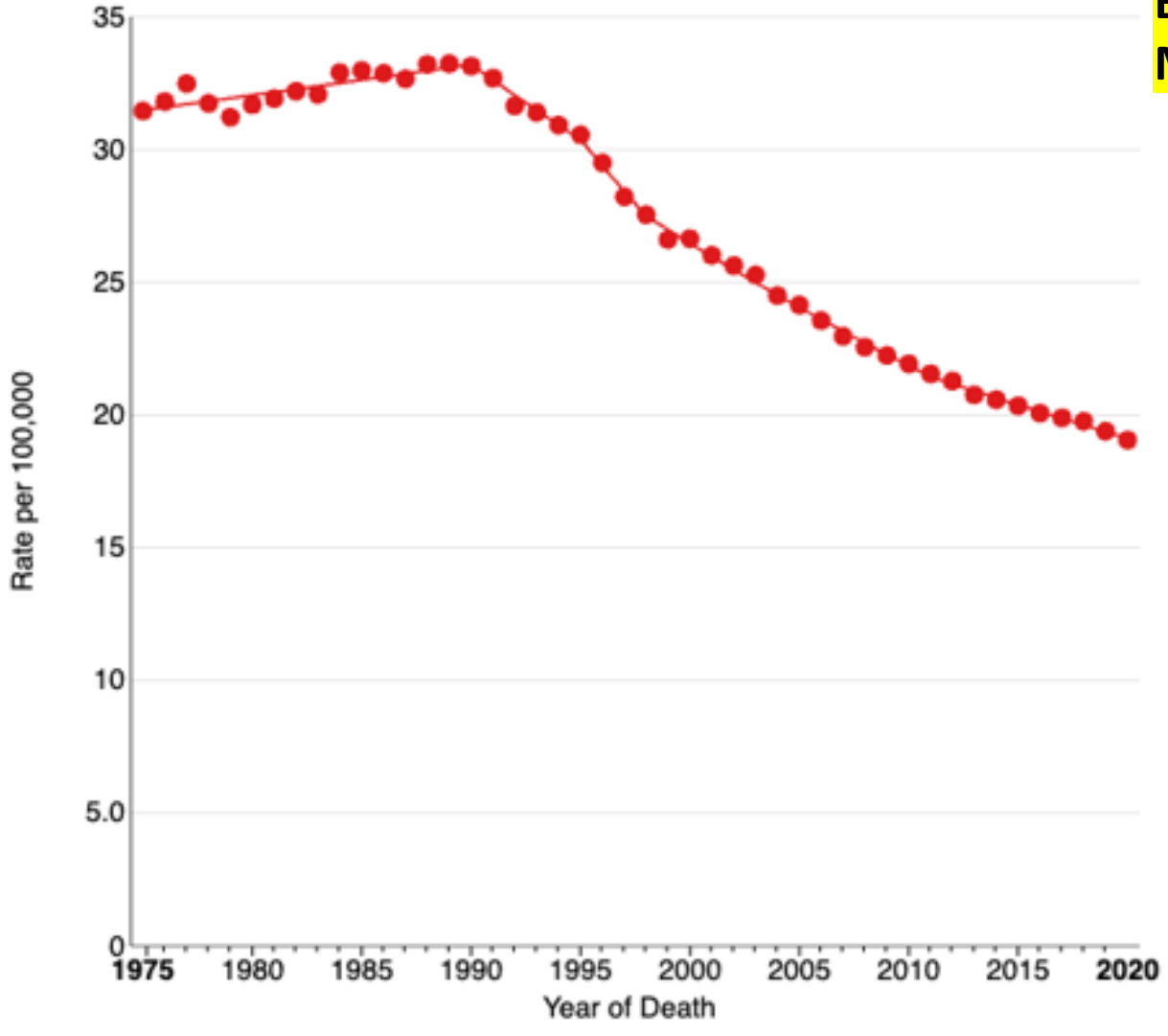
Breast
Recent Trends in SEER Age-Adjusted Incidence Rates, 2004-2020
Observed SEER Incidence Rate By Stage at Diagnosis, Female, All Races / Ethnicities, All Ages



Data Source:
• SEER Incidence Data, November 2022 Submission (1975-2020), SEER 22 registries [https://seer.cancer.gov/registries/terms.html].

Breast
Long-Term Trends in U.S. Age-Adjusted Mortality Rates, 1975-2020
By Sex, All Races / Ethnicities, All Ages

Breast Cancer Mortality



Data Source:
• U.S. Mortality Data (1969-2020), National Center for Health Statistics, CDC.
Methodology:
• Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

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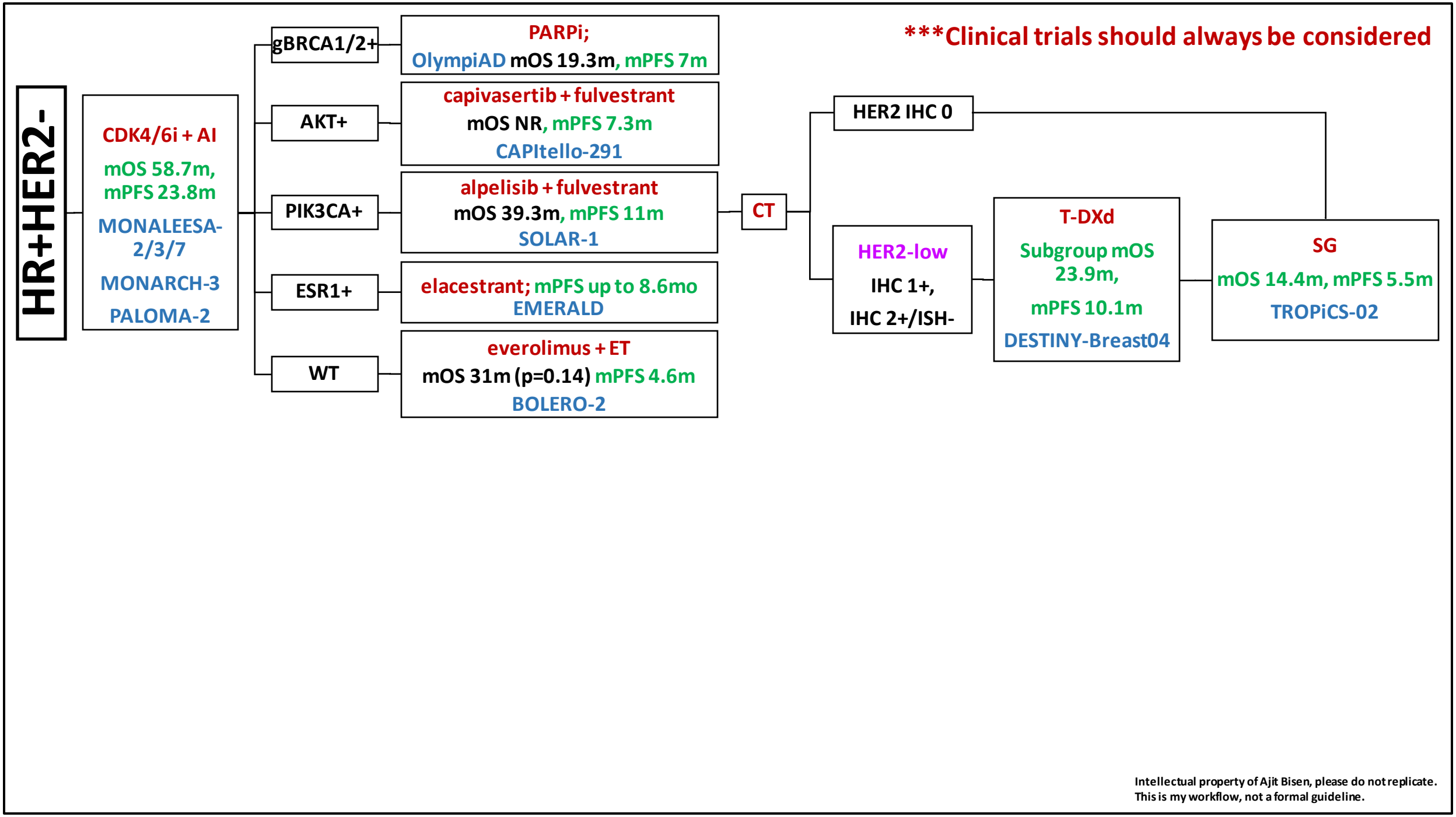
2023

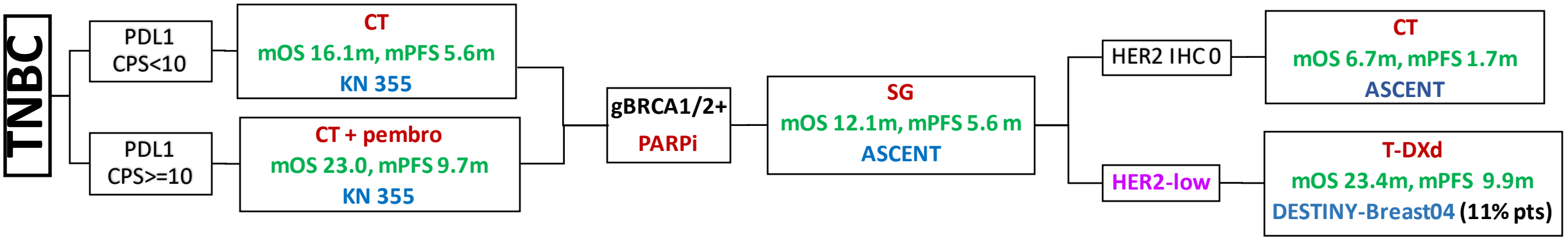
In the United States, **6%** of women have metastatic breast cancer when they are first diagnosed.

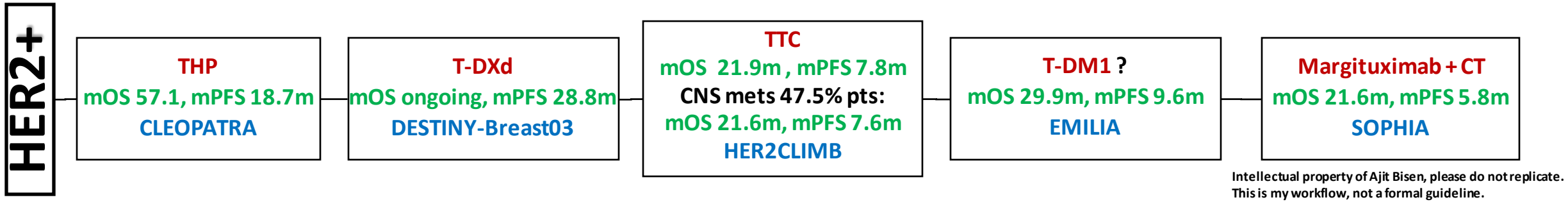
The 5-year survival rate for women with metastatic breast cancer in the U.S. is 30%.

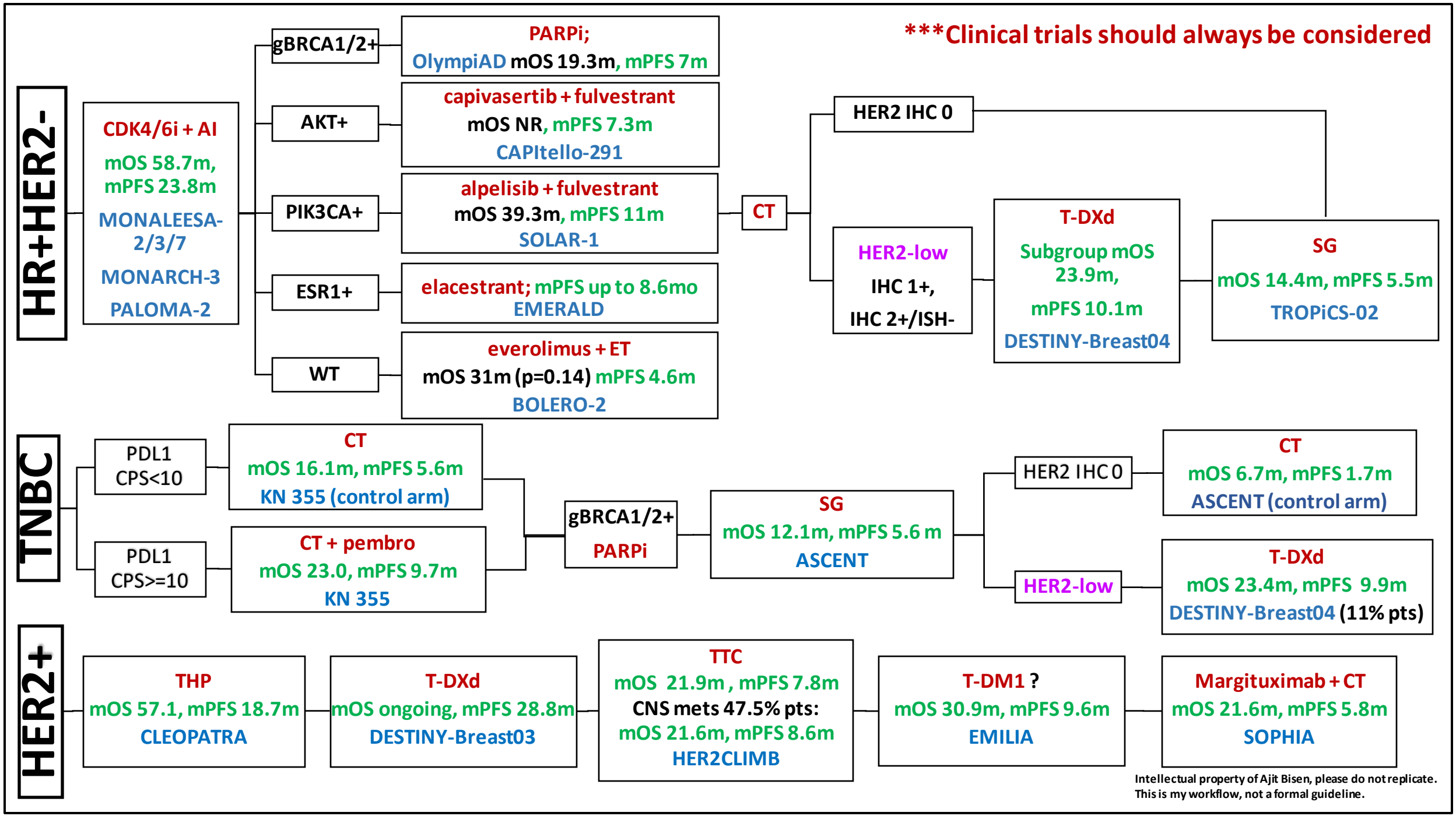
The 5-year survival rate for men with metastatic breast cancer is 19%

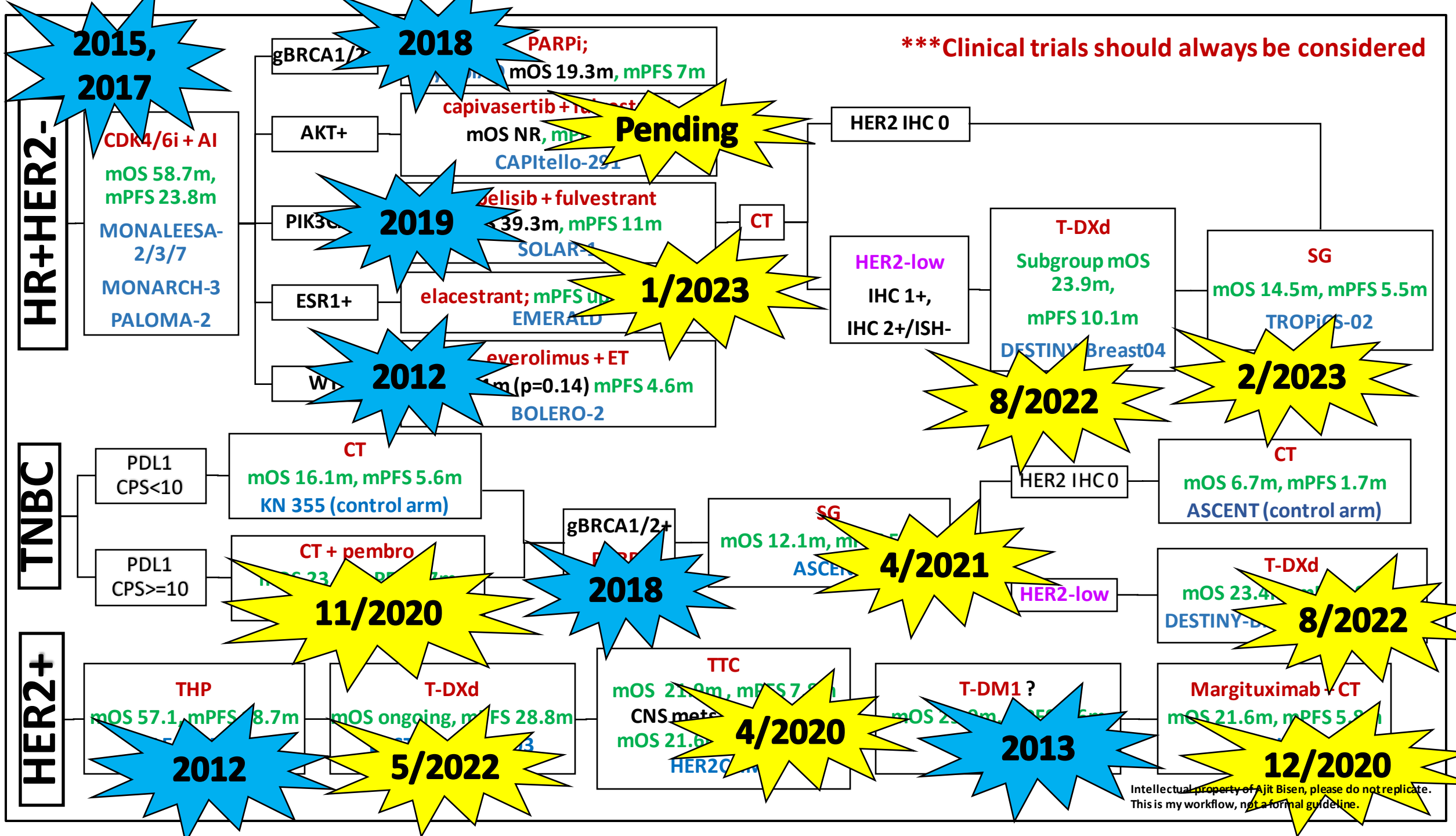
My approach to treating Stage IV Breast cancer and sequencing therapies…










***Clinical trials should always be considered
HR+HER2-
2015, 2017
CDK4/6i + AI
mOS 58.7m, mPFS 23.8m
MONALEESA-2/3/7
MONARCH-3
PALOMA-2
2018
gBRCA1/2+
PARPi;
mOS 19.3m, mPFS 7m
AKT+
capivasertib + fulvestrant
mOS NR, mPFS
CAPItello-291
Pending
PIK3CA+
alpelisib + fulvestrant
mOS 39.3m, mPFS 11m
SOLAR-1
2019
CT
ESR1+
elacestrant; mPFS up
EMERALD
1/2023
WT
everolimus + ET
mOS 1m (p=0.14) mPFS 4.6m
BOLERO-2
2012
HER2 IHC 0
HER2-low
IHC 1+,
IHC 2+/ISH-
T-DXd
Subgroup mOS 23.9m,
mPFS 10.1m
DESTINY-Breast04
8/2022
SG
mOS 14.5m, mPFS 5.5m
TROPiCS-02
2/2023
TNBC
PDL1 CPS<10
CT
mOS 16.1m, mPFS 5.6m
KN 355 (control arm)
PDL1 CPS>=10
CT + pembro
11/2020
gBRCA1/2+
2018
SG
mOS 12.1m, m
ASCE
4/2021
HER2 IHC 0
CT
mOS 6.7m, mPFS 1.7m
ASCENT (control arm)
HER2-low
T-DXd
mOS 23.4
DESTINY-B
8/2022
HER2+
THP
mOS 57.1, mPFS 8.7m
2012
T-DXd
mOS ongoing, mPFS 28.8m
5/2022
TTC
mOS 21.9m, mPFS 7.9m
CNS mets
mOS 21.6
HER2C
4/2020
T-DM1 ?
mOS 2
2013
Margituximab + CT
mOS 21.6m, mPFS 5.9m
12/2020
Intellectual property of Ajit Bisen, please do not replicate.
This is my workflow, not a formal guideline.

HR+HER2-

CDK4/6i + AI

mOS 58.7m, mPFS 23.8m

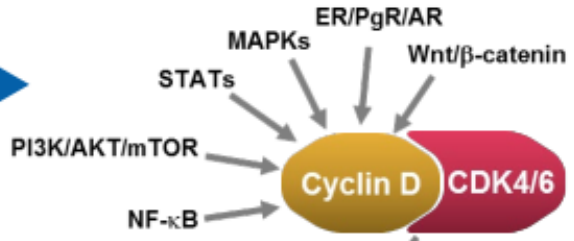
MONALEESA-2/3/7

MONARCH-3

PALOMA-2

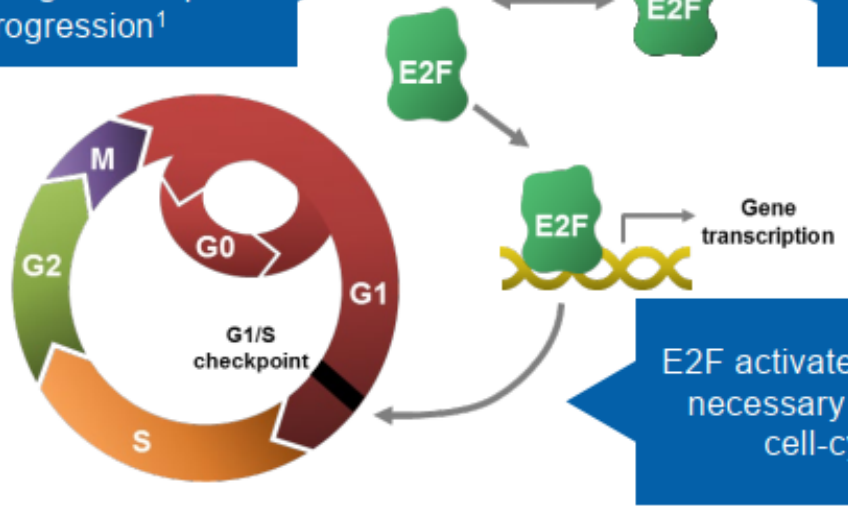
CDK4/6 controls cell-cycle progression from G1 to S phase by regulating the activity of Rb

Synthesis of D-type cyclins (cyclins D1, D2, and D3) and association with CDK4/6 is initiated in response to mitogenic signaling pathways[1]



Active cyclin D-CDK4/6 phosphorylates Rb, decoupling Rb from E2F and allowing transcription of genes required for cell-cycle progression[1]

Rb inhibits E2F-mediated transcription by binding to and sequestering E2F[2]



E2F activates transcription of genes necessary for S-phase entry and cell-cycle progression[2]

AKT, protein kinase B; AR, androgen receptor; CDK, cyclin-dependent kinase; E2F, E2 transcription factor; ER, estrogen receptor; G, gap phase; M, mitotic phase; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NF, nuclear factor; PgR, progesterone receptor; PI3K, phosphoinositide 3-kinase; Rb, retinoblastoma protein; S, synthesis phase; STAT, signal transducer and activator of transcription protein.

References: 1. Lange CA, Yee D. *Endocr Relat Cancer*. 2011;18(4):C19-C24. 2. Rader J, et al. *Clin Cancer Res*. 2013;19(22):6173-6182.

Figure adapted from Lange CA, Yee D.[1] With permission from the Society for Endocrinology.

HR+HER2-

CDK4/6i + AI

mOS 58.7m, mPFS 23.8m

MONALEESA-2/3/7

MONARCH-3

PALOMA-2

Results for Pivotal CDK 4/6 Inhibitor Trials

8

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical significance
PALOMA-2	Palbociclib	1st Line/AI	Post	0.56	Yes	NR	NR
MONALEESA-2	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	0.70	Yes
MONARCH-3	Abemaciclib	1st line/AI	Post	0.54	Yes	NR	NR
PALOMA-3	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	0.78	Yes
MONALEESA-3	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	0.72	Yes

HR+HER2-

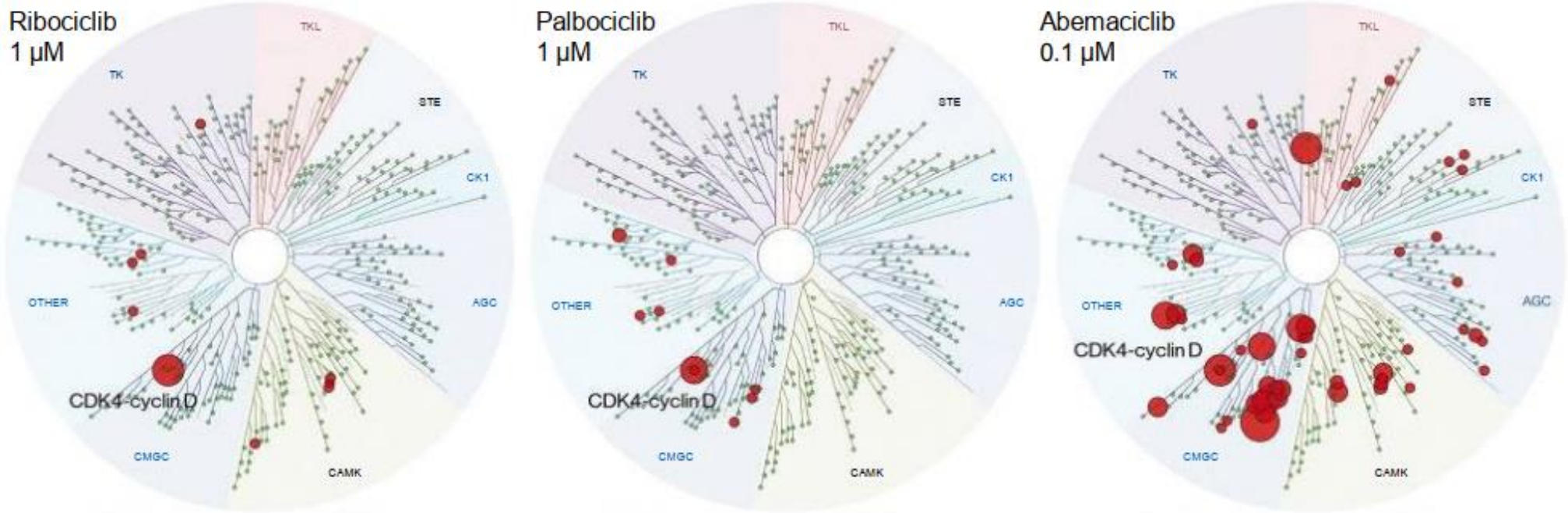
CDK4/6i + AI

mOS 58.7m, mPFS 23.8m

MONALEESA-2/3/7

MONARCH-3

PALOMA-2



TREEspot view of a KINOMEscan. Kinases that bind are marked with red circles if <35% of the recombinant kinase remained captured on the immobilized ligand in the presence of the indicated concentration of CDK4/6 inhibitor relative to the DMSO control.

Preclinical activity does not necessarily correlate with clinical outcomes.

AGC, cAMP-dependent, cGMP-dependent, and protein kinase C; CAMK, Ca2+/calmodulin-dependent protein kinase; CDK, cyclin-dependent kinase; CK, creatine kinase; CMGC, cyclin-dependent, mitogen-activated glycogen synthase and CDK-like kinase; DMSO, dimethyl sulfoxide; STE, yeast sterile kinase; TK, thymidine kinase; TKL, tyrosine kinase-like.

Reference: Kim S, et al. *Oncotarget.* 2018;9(81):35226-35240.

HR+HER2-

CDK4/6i + AI

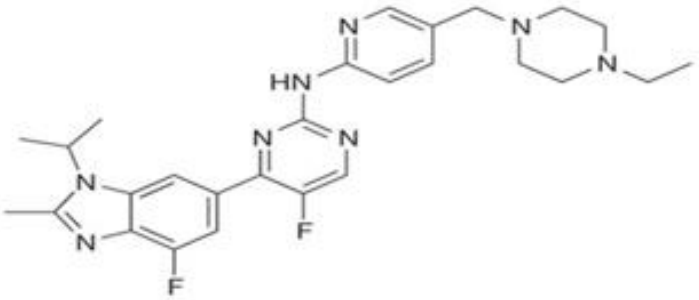
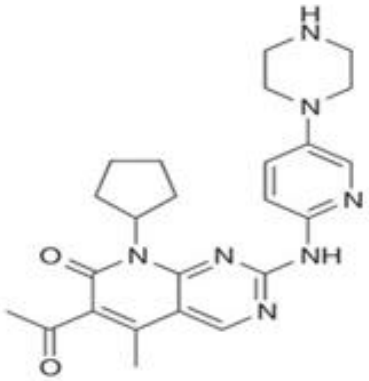
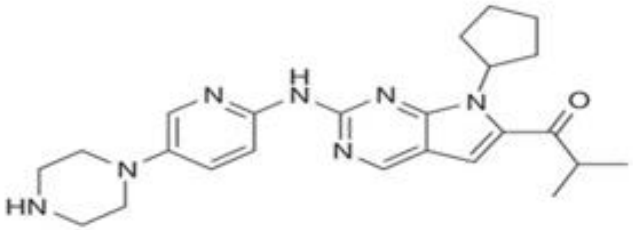
mOS 58.7m, mPFS 23.8m

MONALEESA-2/3/7

MONARCH-3

PALOMA-2

Selective CDK4/6 Inhibitors - tolerability

Abemaciclib	Palbociclib	Ribociclib
		
Less Neutropenia	More Neutropenia	More Neutropenia
More diarrhoea		More hepatotoxicity
Small risk of DVT		Small risk QTc prolongation
All small long-term risk of pneumonitis / ILD		

O'Leary *et al* Nat Rev Clin Oncol 2016

HR+HER2-

CDK4/6i + AI

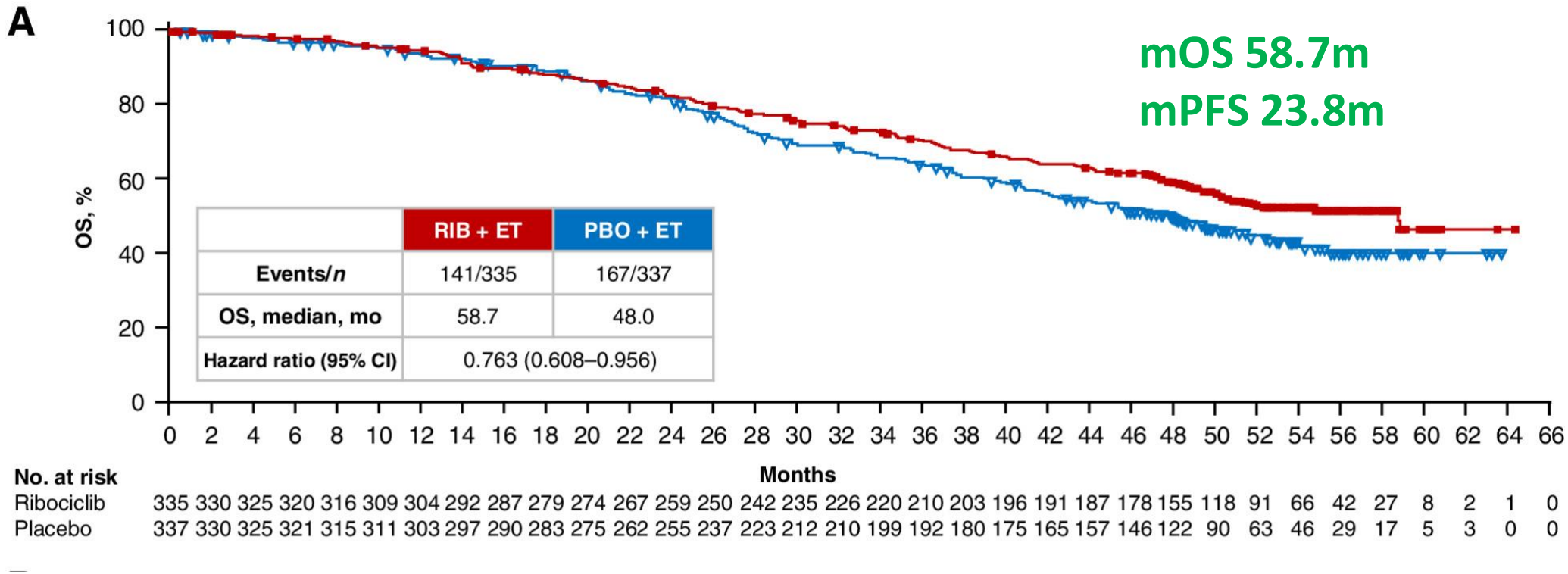
mOS 58.7m, mPFS 23.8m

MONALEESA-2/3/7

MONARCH-3

PALOMA-2

Updated Overall Survival of Ribociclib plus Endocrine Therapy versus Endocrine Therapy Alone in Pre- and Perimenopausal Patients with HR$^+$/HER2$^-$ Advanced Breast Cancer in MONALEESA-7: A Phase III Randomized Clinical Trial



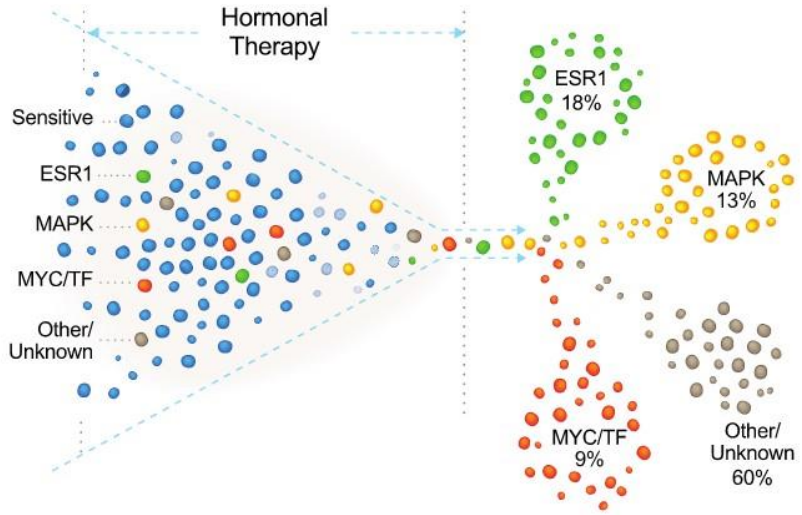
mOS 58.7m

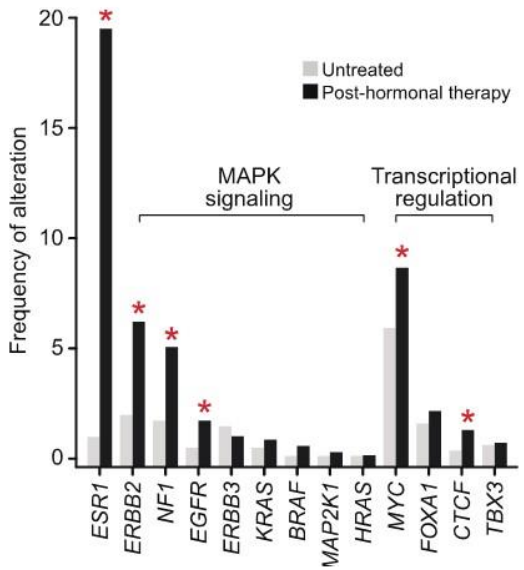
mPFS 23.8m

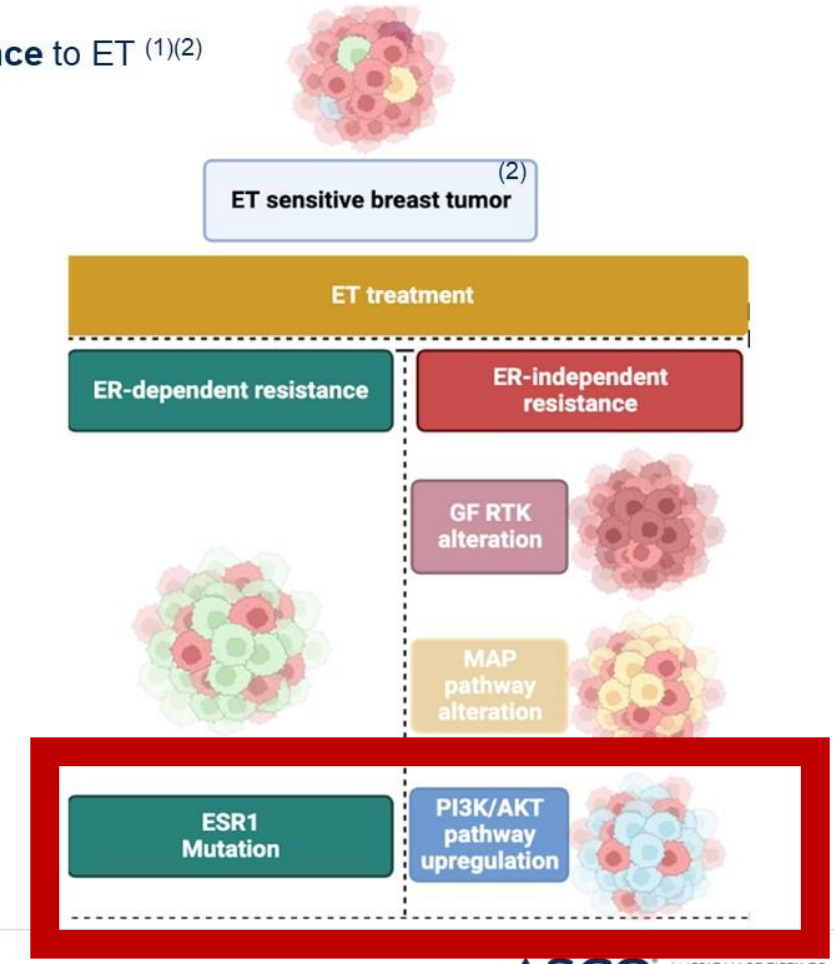
Clin Cancer Res. 2022;28(5):851-859. doi:10.1158/1078-0432.CCR-21-3032

ENDOCRINE THERAPY RESISTANCE

- **Molecular pathways** involved in ER functionality and evolving **mechanisms of resistance** to ET [1][2]
  - **Genomic landscape** of **endocrine resistance after treatment** [1]

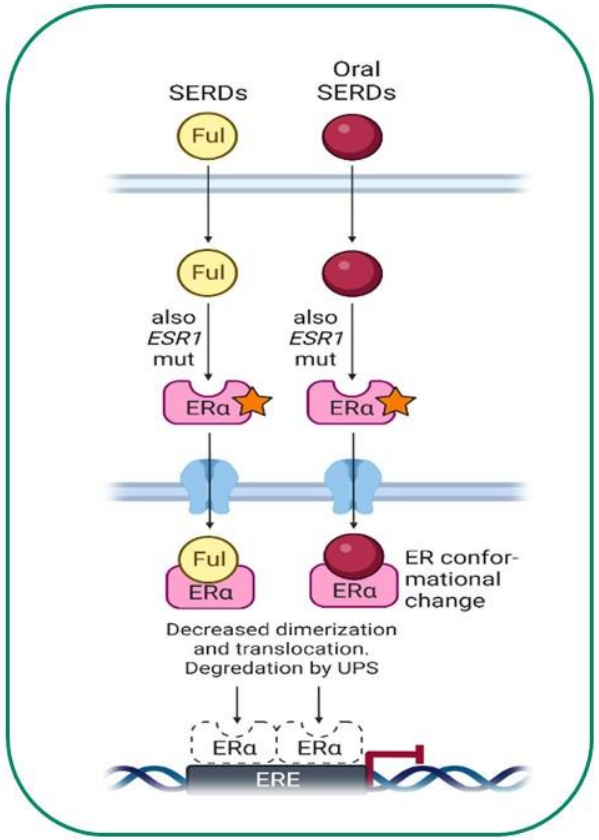






(1) Razavi P *Cancer Cell*. 2018;34(3):427-438.e6
(2) Adapted from Lloyd MR *Therapeutic Advances in Medical Oncology*. 2022;14

NEW ORAL SERDs



- **Non-steroidal** analogues
- **Side chain**
  - Acrylic acid (Rintodestrant)
  - Basic amino acid (elacestrant, giredestrant, imlunestrant, amcenestrant, camizestrant)
- **Oral** availability
- **High potency**
- Active **against *ESR1*** – mut (Y537S)

Adapted from Chiara Corti Cancer Treatment Reviews, 2023, 102569

Hancker A. Cancer Cell 2020
Pagliuca M Crit Rev Onc Hem 2022

EMERALD TRIAL

HR+HER2-

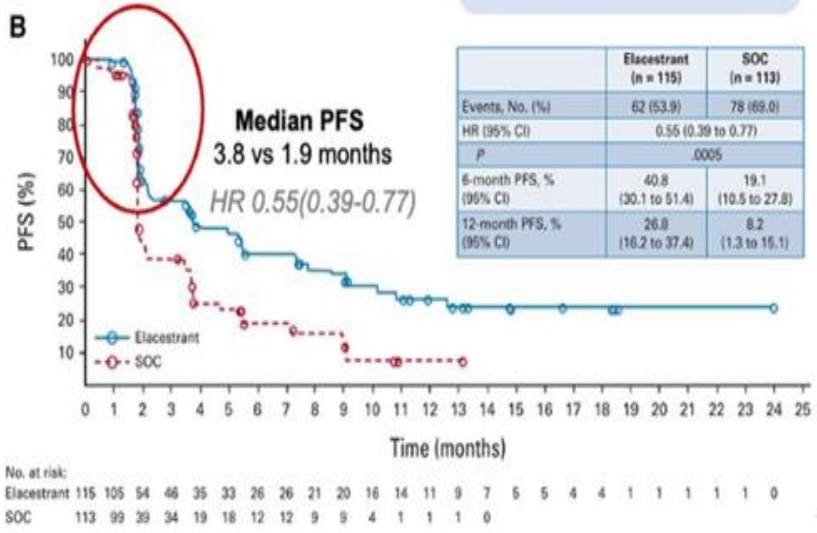
- **CDK4/6i + AI**
  - mOS 58.7m, mPFS 23.8m
  - MONALEESA-2/3/7
  - MONARCH-3
  - PALOMA-2
- **AKT+** → capivasertib + fulvestrant; mOS NR, mPFS 7.3m; CAPItello-291
- **PIK3CA+** → alpelisib + fulvestrant; mOS 39.3m, mPFS 11m; SOLAR-1
- **ESR1+** → elacestrant; mPFS up to 8.6mo; EMERALD

OS at interim analysis currently not statistically significant.

mPFS up to 8.6mo with at least 18 mo CDK4/6i

PFS Patients with tumors harboring *ESR1*-mut

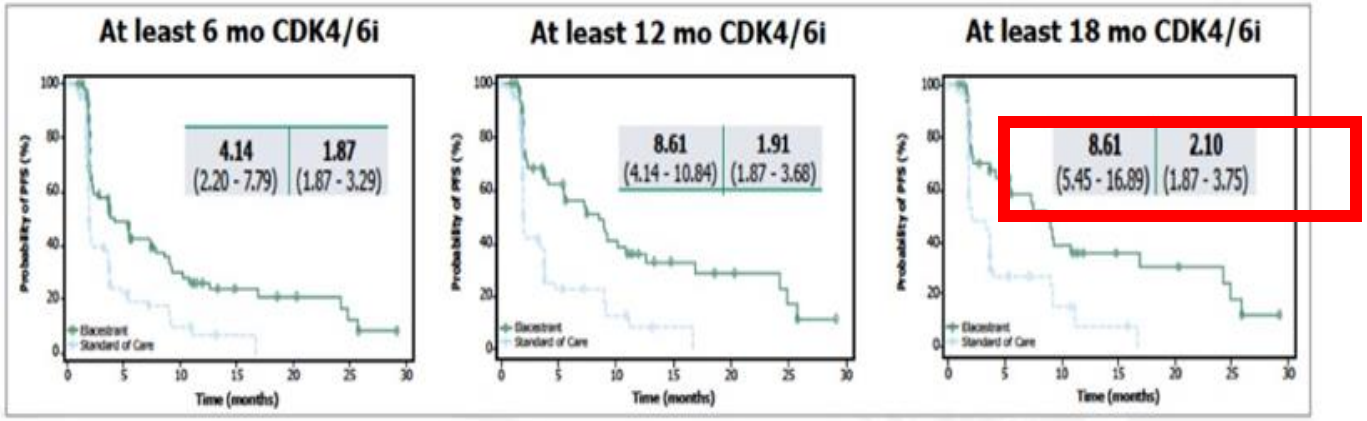
45% reduction risk of progression or death in *ESR1*-mut patients



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

PFS by duration of CDK 4/6i: *ESR1*-mut

Benefit was more marked in the *ESR1*-mut population



Bidard FC J Clin Oncol 2022;40:3246-3256
Kaklamani V SABCS 2022

SOLAR-1

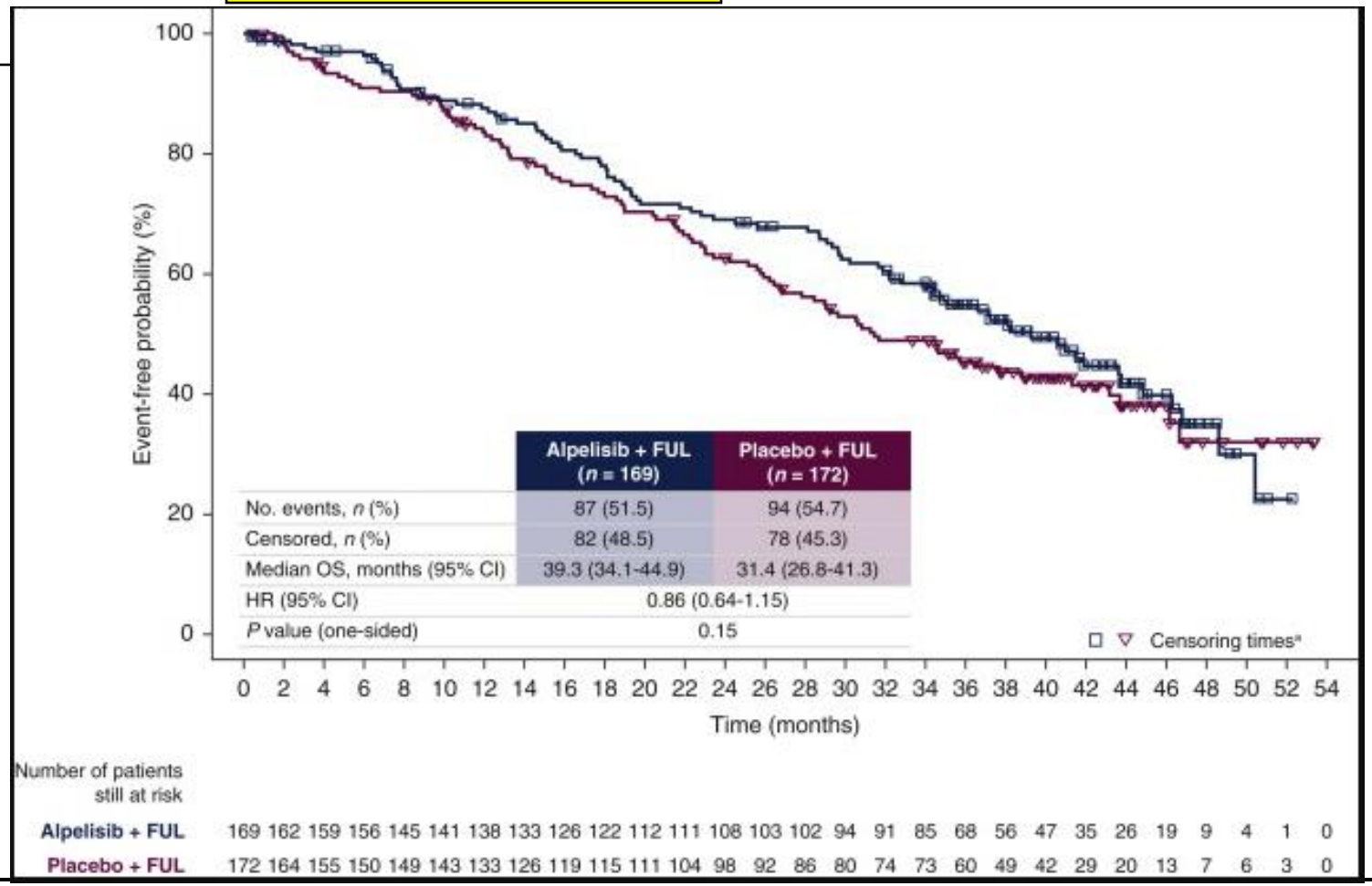
HR+HER2-

CDK4/6i + AI
mOS 58.7m, mPFS 23.8m
MONALEESA-7
MONARCH-3
PALOMA-2

AKT+
capivasertib + fulvestrant
mOS NR, mPFS 7.3m
CAPItello-291

PIK3CA+
alpelisib + fulvestrant
mOS 39.3m (P=0.15), mPFS 11m
SOLAR-1

-mOS 39.3 mo vs 31.4 m
-7.9 m numeric improvement but not statistically significant



Andre et al, NEJM 2019

CAPItello-291

HR+HER2-

CDK4/6i + AI

mOS 58.7m, mPFS 23.8m

MONALEESA-7

MONARCH-3

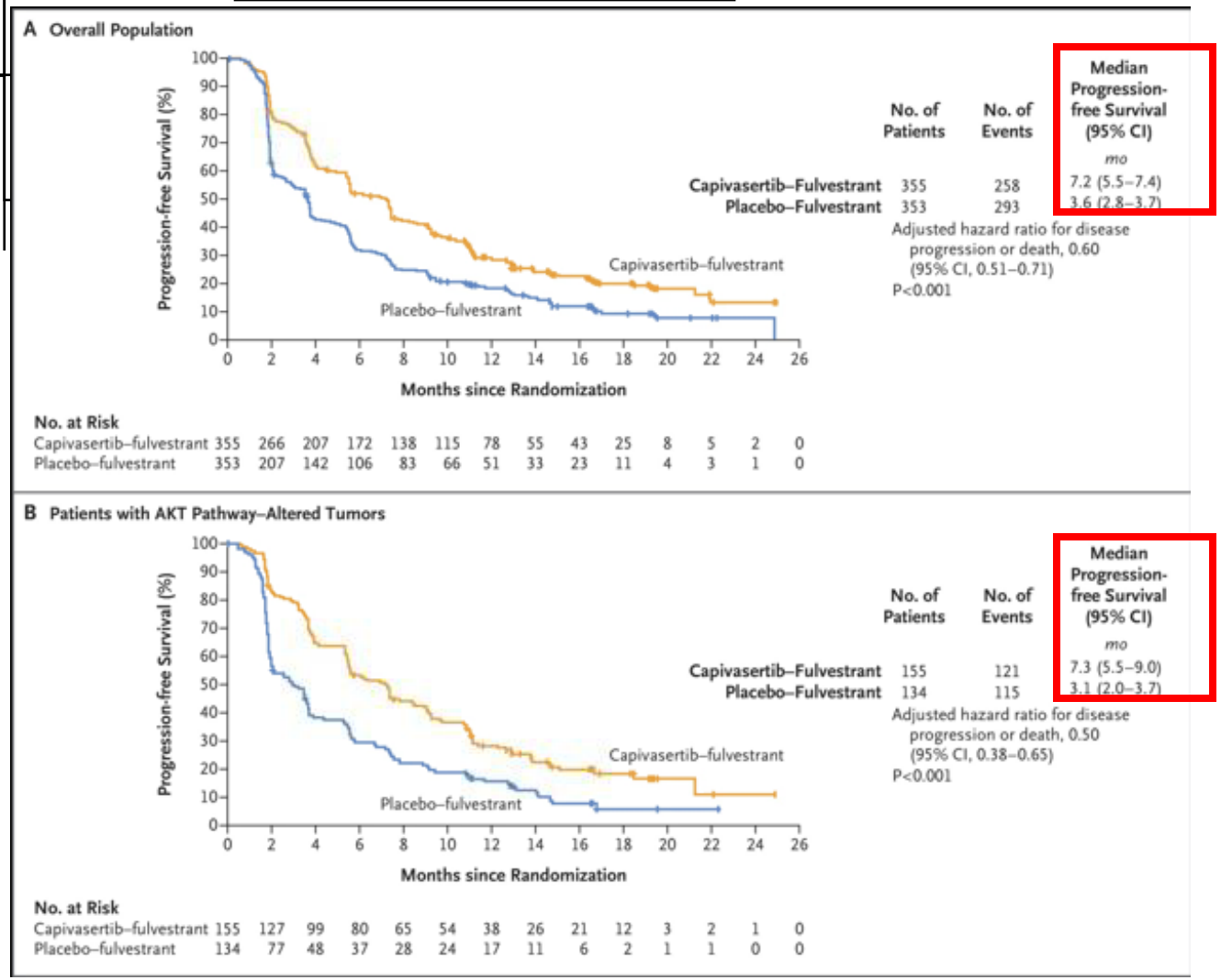
PALOMA-2

AKT+

capivasertib + fulvestrant

mOS NR, mPFS 7.3m

CAPItello-291



CAPItello-291

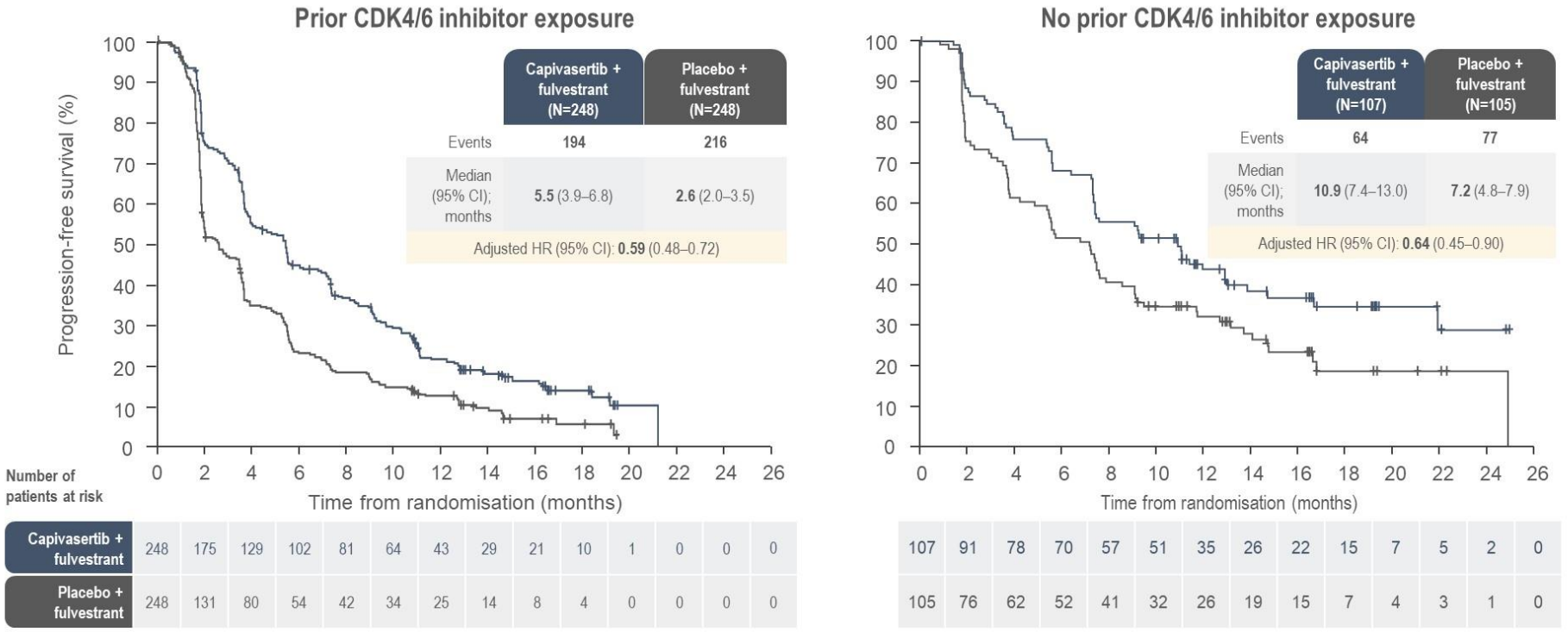
HR+HER2-

CDK4/6i + AI
mOS 58.7m, mPFS 23.8m
MONALEESA-7
MONARCH-3
PALOMA-2

AKT+

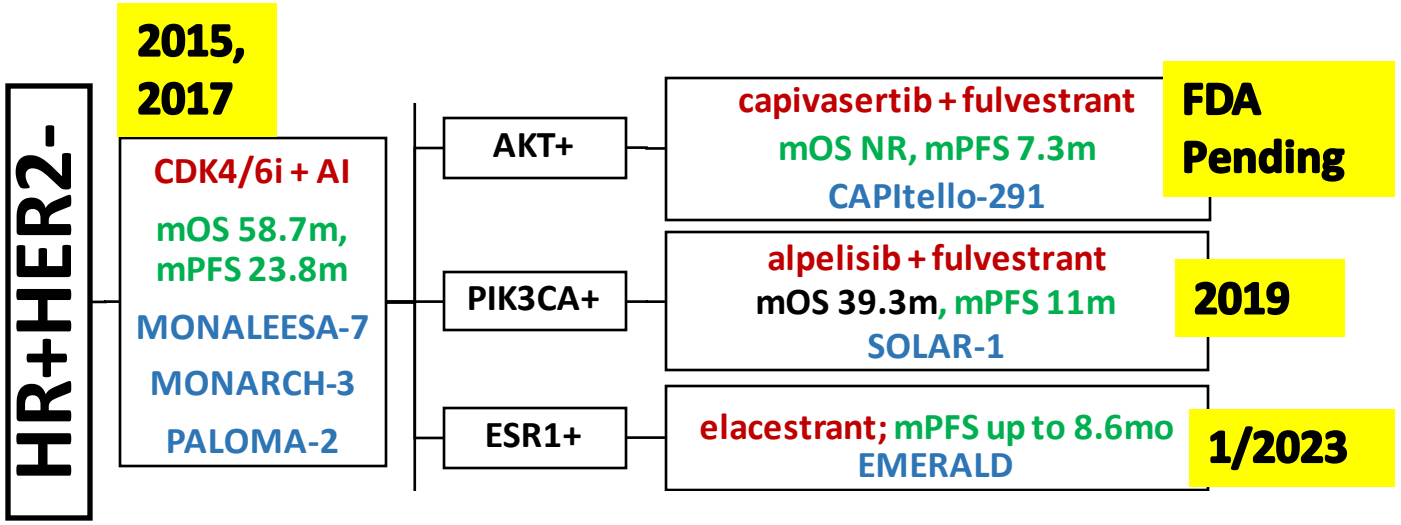
capivasertib + fulvestrant
mOS NR, mPFS 7.3m
CAPItello-291

Post CDK4/6 therapy – capivasertib AKT inhibitor



NOT CURRENTLY LICENSED

Mafalda *et al* ESMO Breast 2023
Turner *et al* NEJM 2023



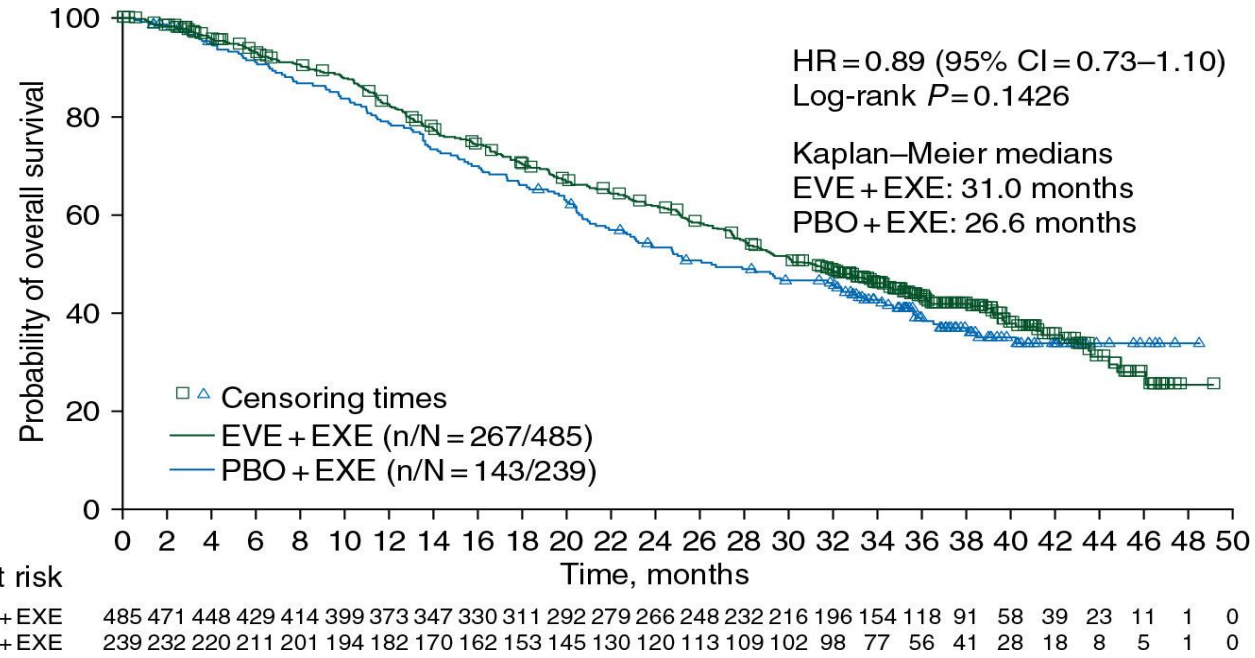
HR+HER2-

- **CDK4/6i + AI**
  - mOS 58.7m, mPFS 23.8m
  - MONALEESA-7
  - MONARCH-3
  - PALOMA-2
- **WT**
  - **everolimus + ET**
    - mOS 31m (p=0.14) mPFS 4.6m
    - BOLERO-2

FDA approved 2012

BOLERO-2

mOS 31m (p=0.14) mPFS 4.6m

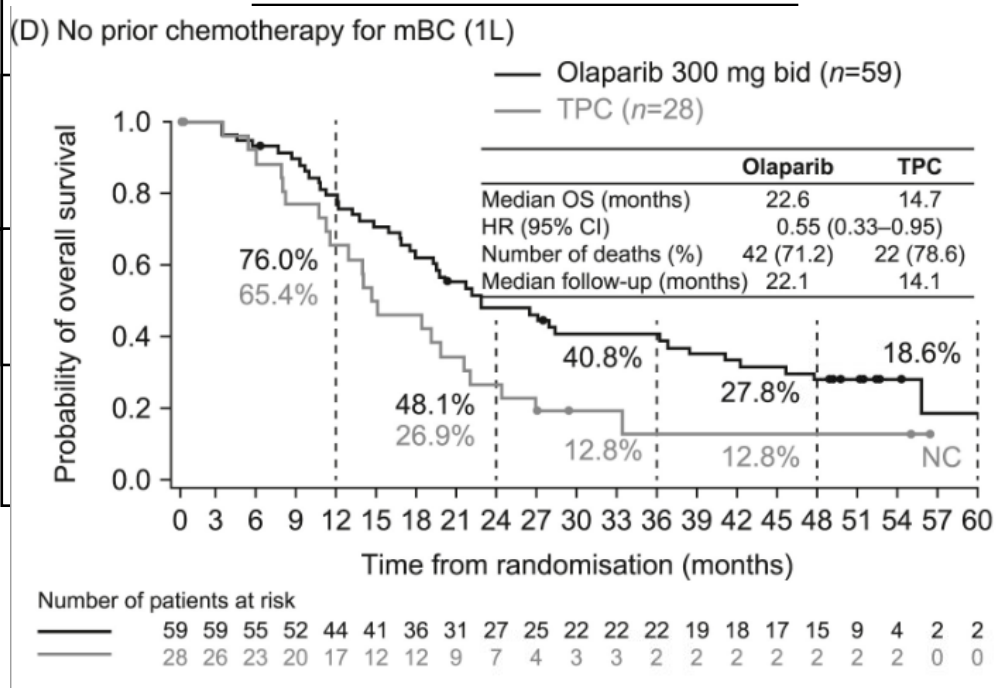


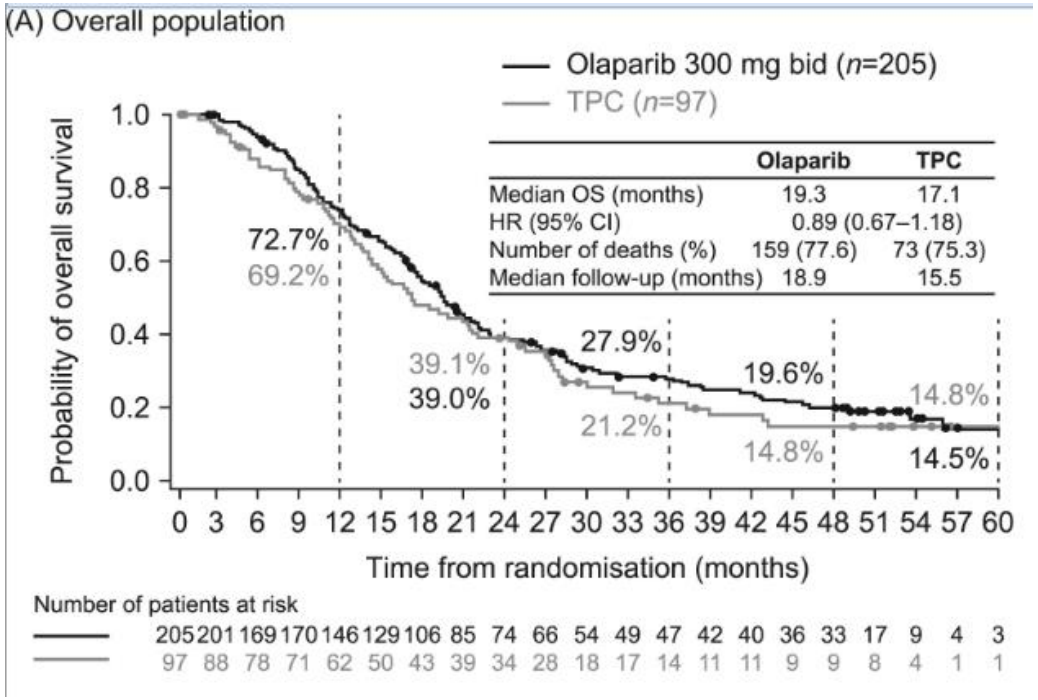
Baselga et al, *Annals of Oncology* 2014 252357-2362DOI: (10.1093/annonc/mdu456)

OlympiAD

HR+HER2-

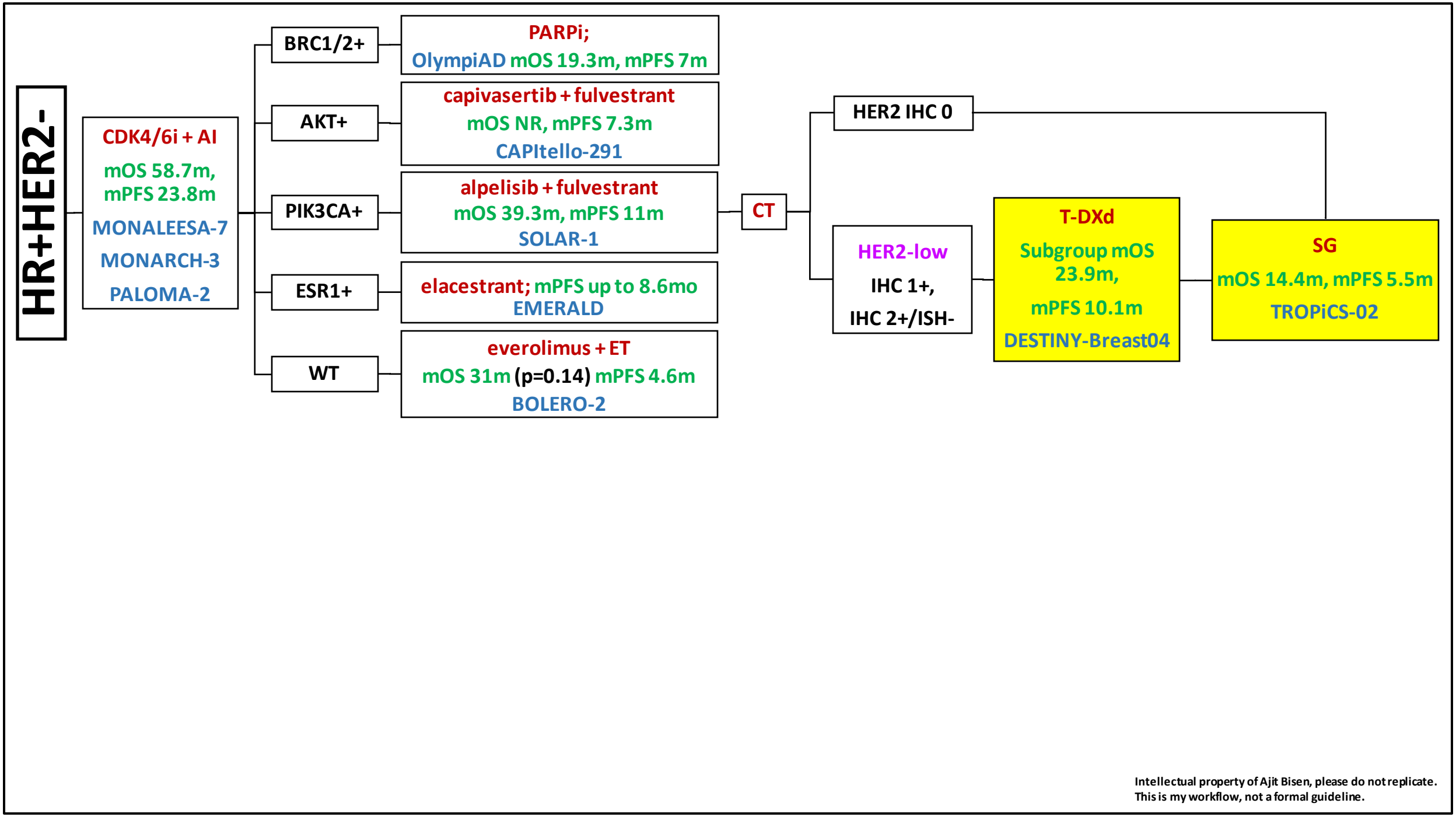
- **CDK4/6i + AI**
  - mOS 58.7m, mPFS 23.8m
  - MONALEESA-7
  - MONARCH-3
  - PALOMA-2
- **gBRC1/2+** → **PARPi;** OlympiAD mOS **19.3m**, mPFS 7m



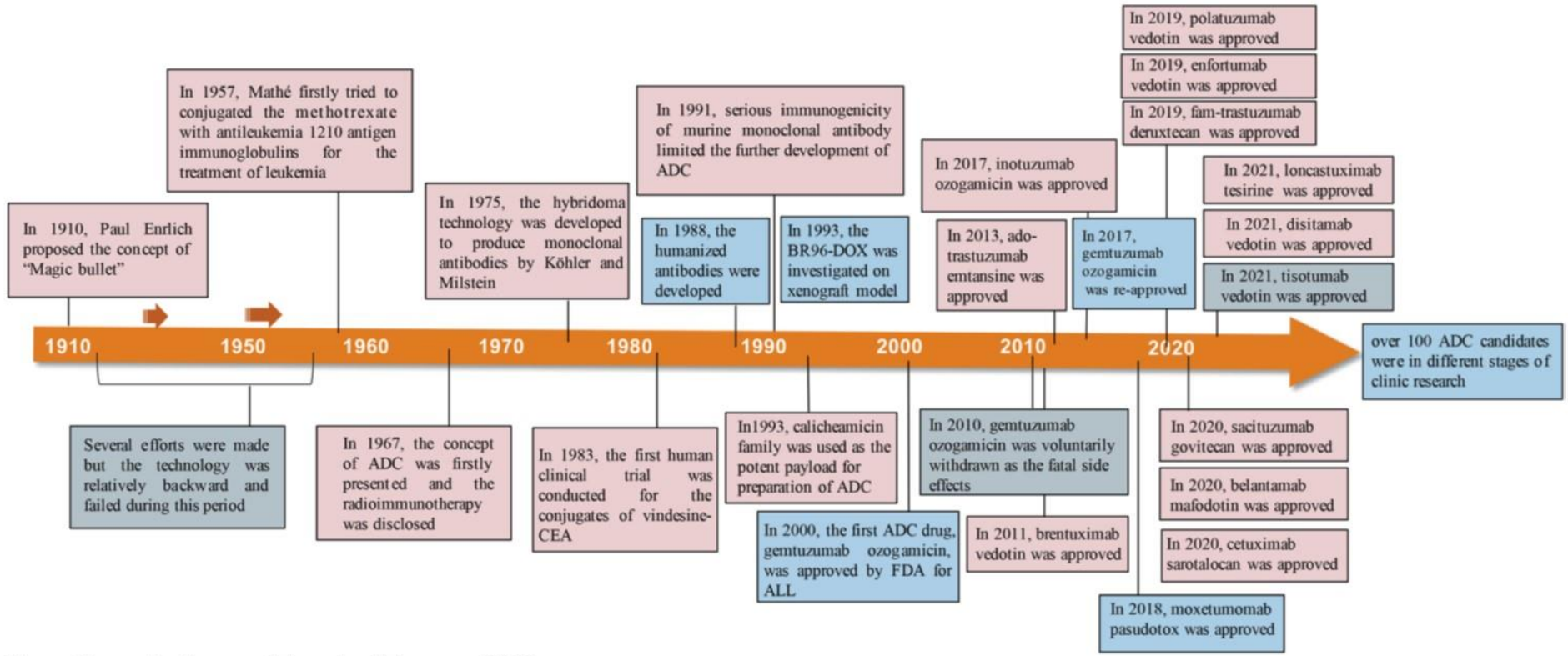


"While there was no statistically significant improvement in OS, there was the possibility of meaningful OS benefit among patients who had not received chemotherapy for metastatic disease."

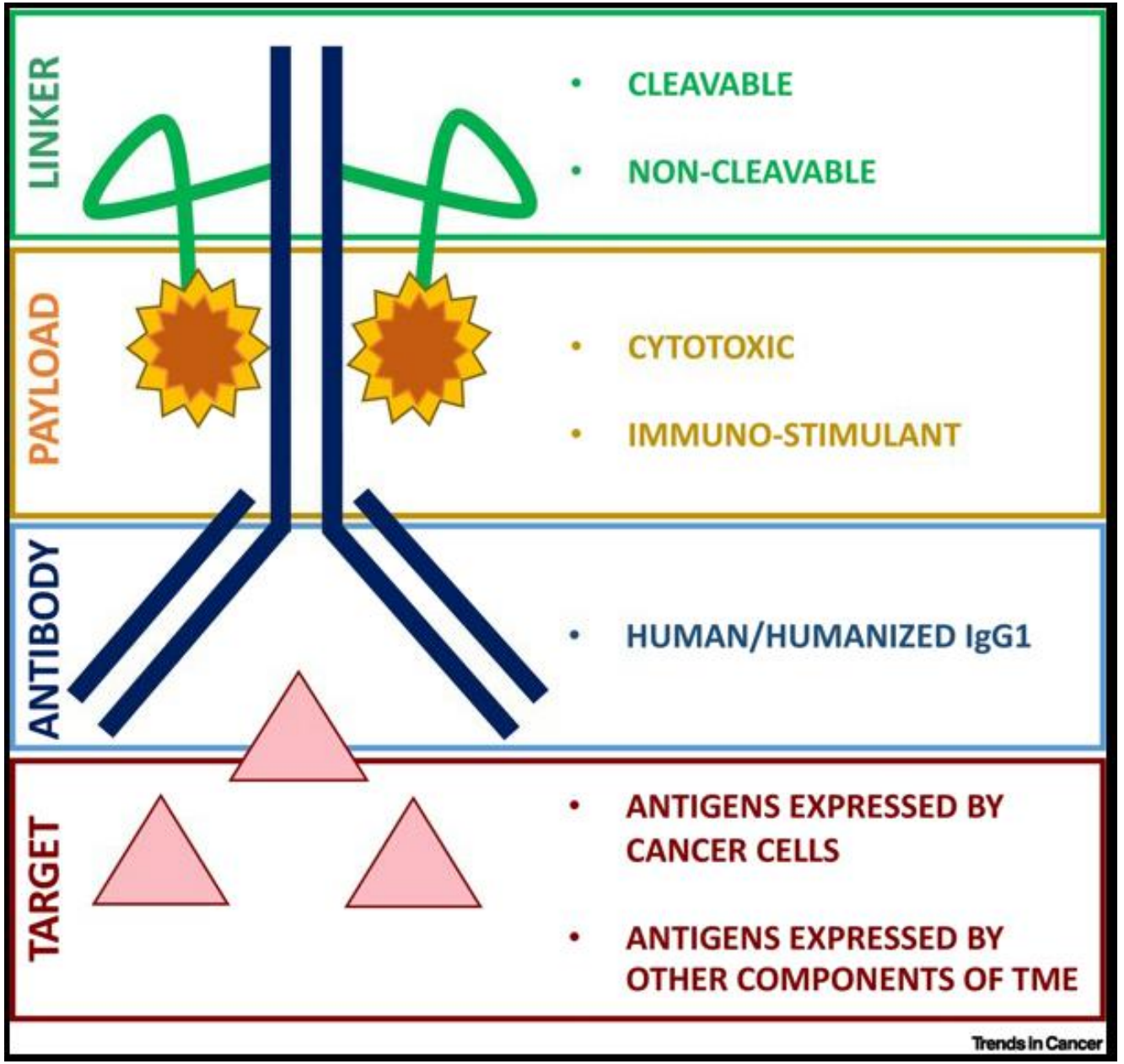
Robson et al. Ann of Oncol 2019.



Antibody Drug Conjugates have Transformed the Therapeutic Landscape of Breast Cancer

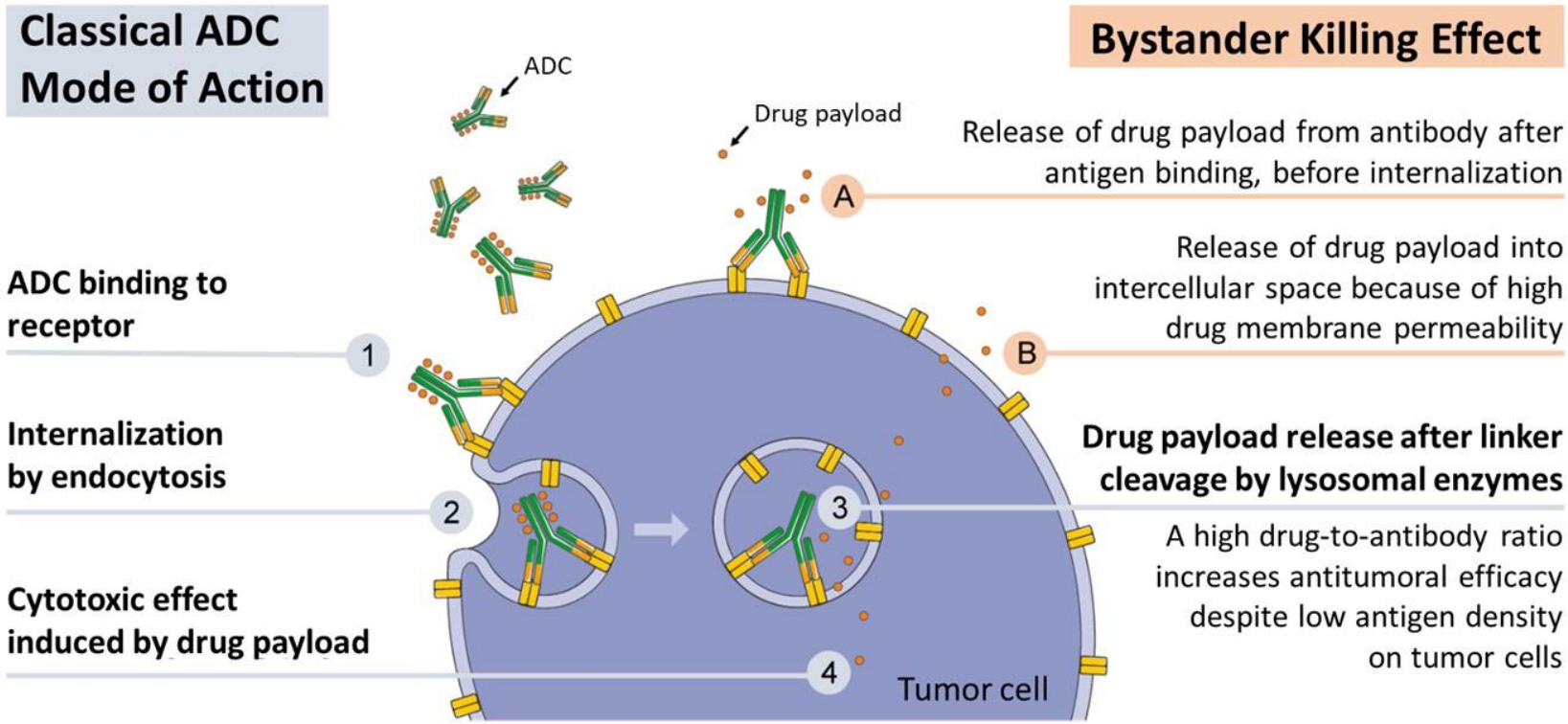


Fu et al, Signal Transduction and Targeted Therapy 2022



Trends in Cancer 2023 9339-354DOI: (10.1016/j.trecan.2023.01.003)

Antibody Drug Conjugates and the Bystander Effect



Rinnerthaler et al, Int J Mol Sci 2019

DESTINY-Breast04

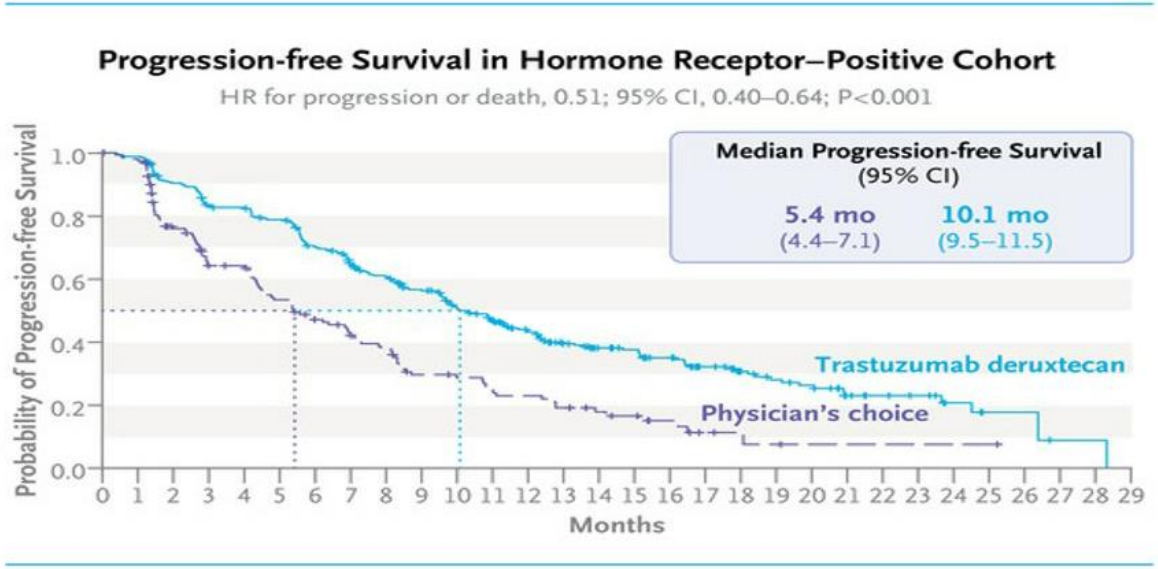
HR+HER2-

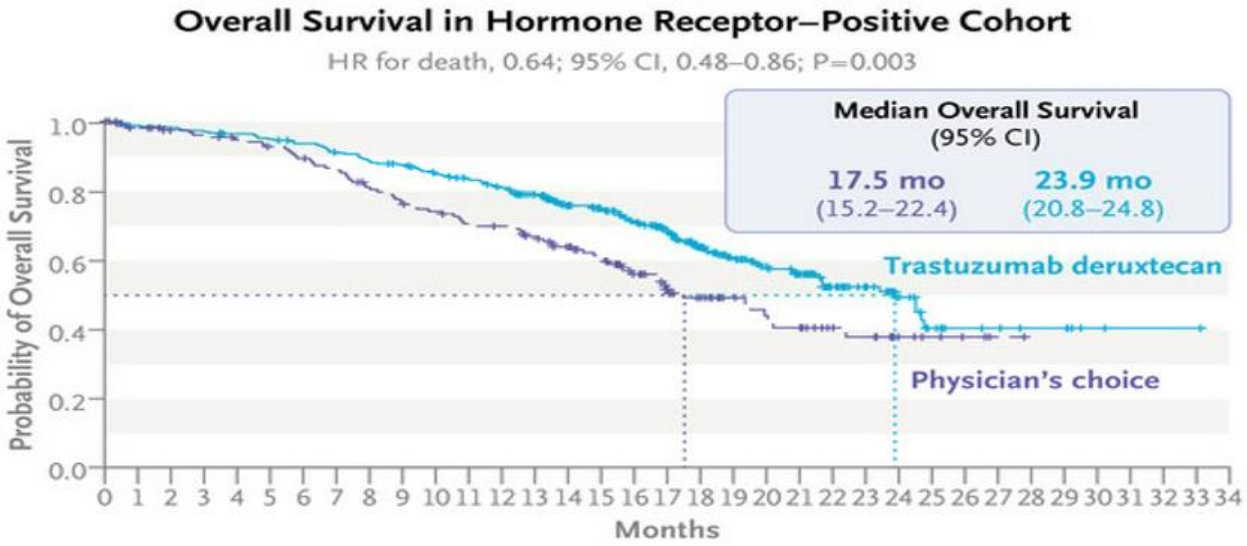
- CDK4/6i + AI
  - mOS 58.7m, mPFS 23.8m
  - MONALEESA-7
  - MONARCH-3
  - PALOMA-2
- BRC1/2+ → PARPi; OlympiAD mOS 19.3m, mPFS 7m
- AKT+ → capivasertib + fulvestrant; mOS NR, mPFS 7.3m; CAPItello-291
- PIK3CA+ → alpelisib + fulvestrant; mOS 39.3m, mPFS 11m; SOLAR-1
- ESR1+ → elacestrant; mPFS up to 8.6mo; EMERALD
- WT → everolimus + ET; mOS 31m (p=0.14) mPFS 4.6m; BOLERO-2

CT

- HER2 IHC 0
- HER2-low IHC 1+, IHC 2+/ISH- → T-DXd; Subgroup mOS 23.9m, mPFS 10.1m; DESTINY-Breast04

SG; mOS 14.4m, mPFS 5.5m; TROPiCS-02





TROPiCS-02

HR+HER2-

CDK4/6i + AI
mOS 58.7m, mPFS 23.8m
MONALEESA-7
MONARCH-3
PALOMA-2

- **BRC1/2+** → **PARPi;** OlympiAD mOS 19.3m, mPFS 7m
- **AKT+** → capivasertib + fulvestrant; mOS NR, mPFS 7.3m; CAPItello-291
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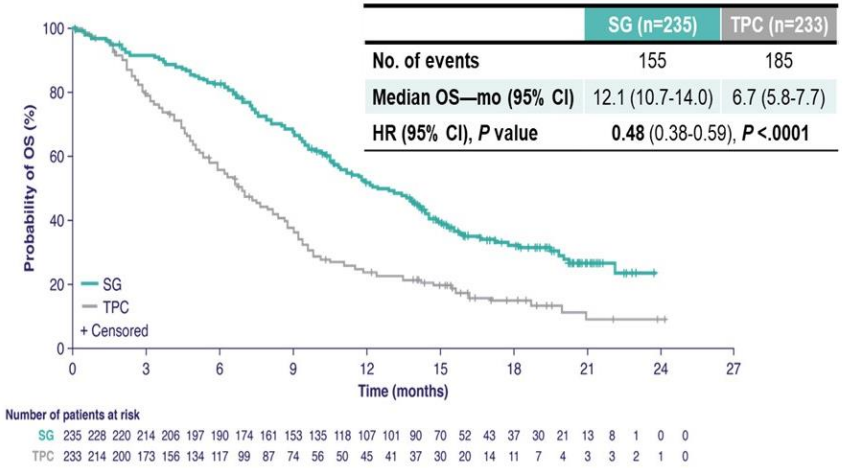
- **ESR1+** → elacestrant; mPFS up to 8.6mo; EMERALD

CT

- **HER2 IHC 0**
- **HER2-low** IHC 1+, IHC 2+/ISH- → **T-DXd** Subgroup mOS 23.9m, mPFS 10.1m; DESTINY-Breast04

SG mOS 14.4m, mPFS 5.5m; TROPiCS-02

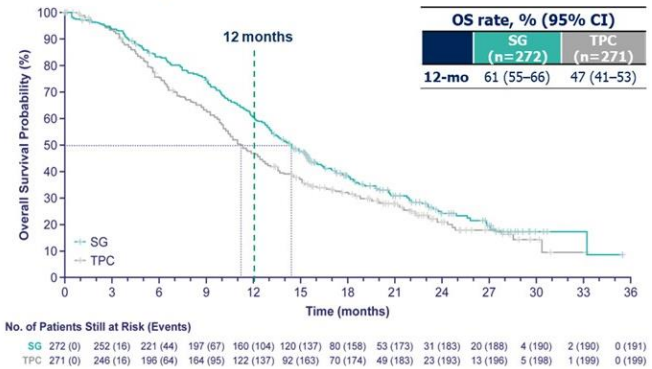
ASCENT



	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	

TROPiCS-02

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	0.79 (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	



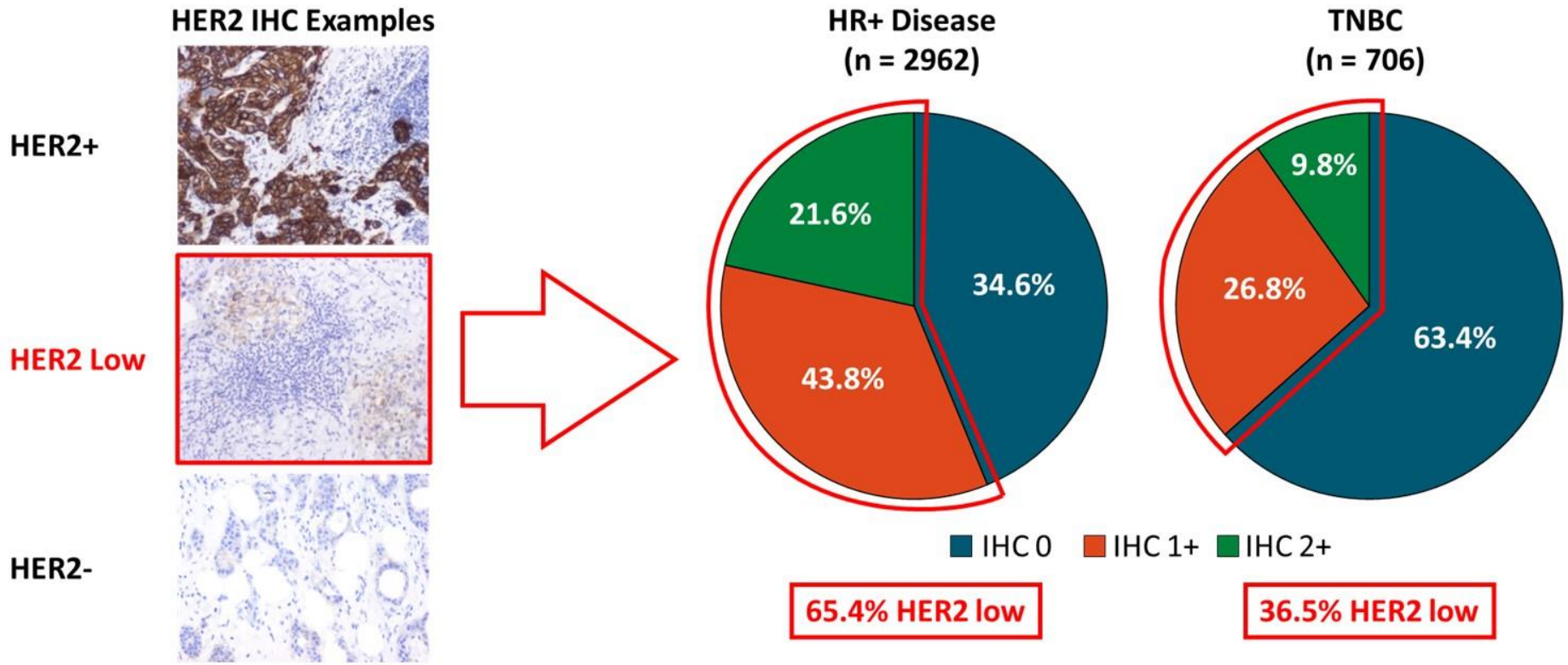
OS rate, % (95% CI)

	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

- Sacituzumab govitecan is FDA approved for both TN (Apr 2021) and HR+/HER2- (Feb 2023) MBC
- Trop-2 expressed in most TN and HR+; **Trop-2 expression not required for use**

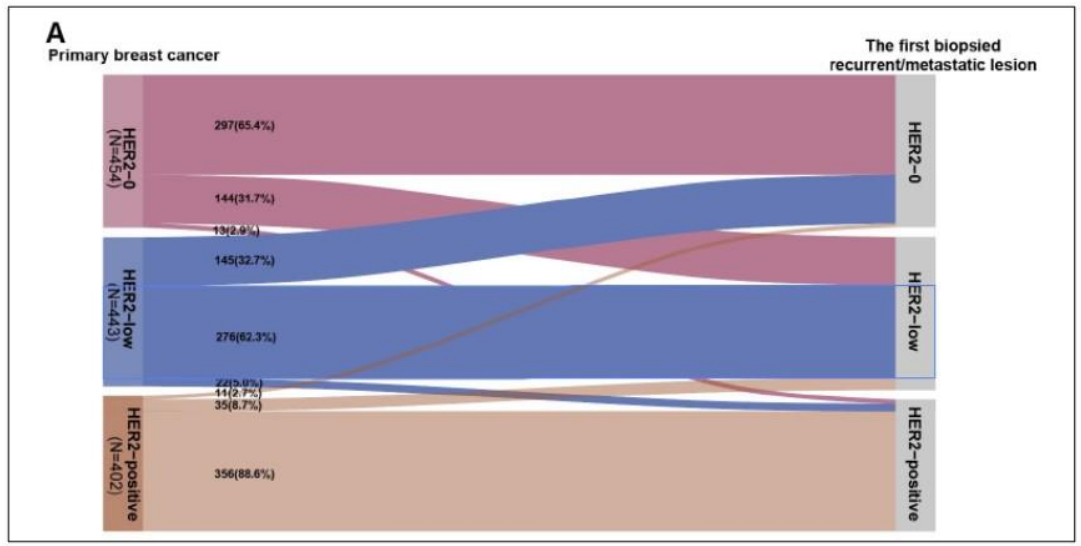
Bardia et al, NEJM 2021; Rugo et al, SABCS 2022

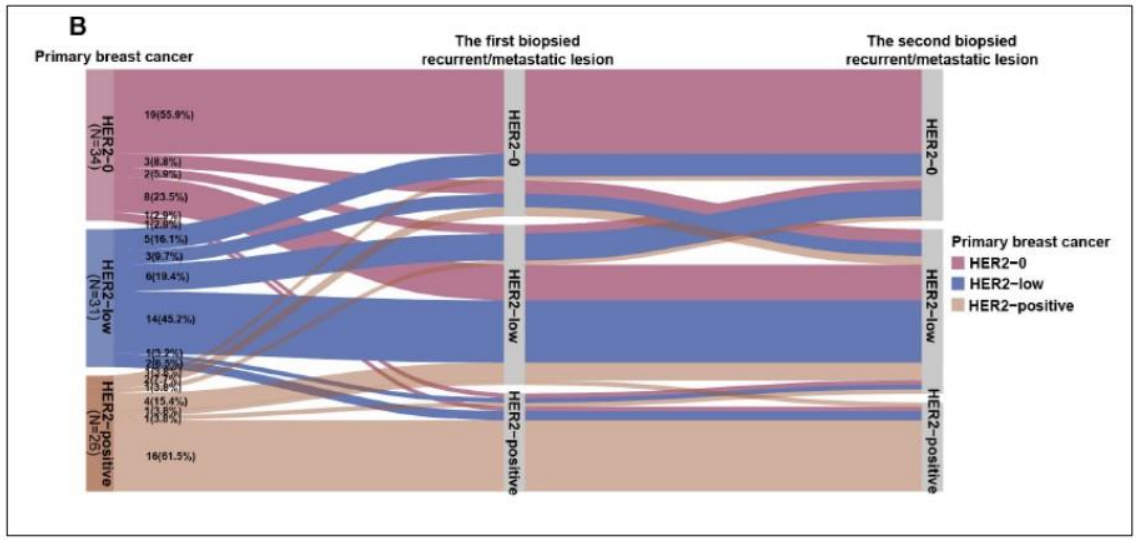
Prevalence of HER2-Low by HR Status: Many with MBC Eligible for Multiple ADCs



Schettini et al, NPJ Breast Cancer 2021; Schettini et al, Breast 2021

Abstract #1021: HER2 Expression Heterogeneity



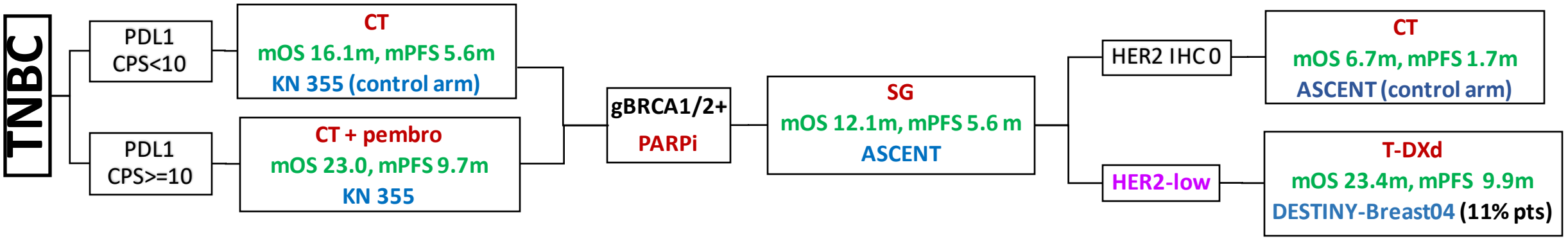


- 28.5% experienced primary to metastatic heterogeneity
- ~17% experienced spatial and temporal heterogeneity
- **HER2 expression changes from primary to met and over time**

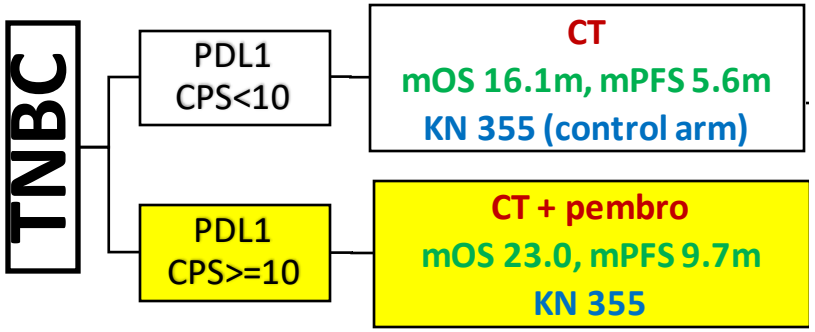
Gaps in Knowledge

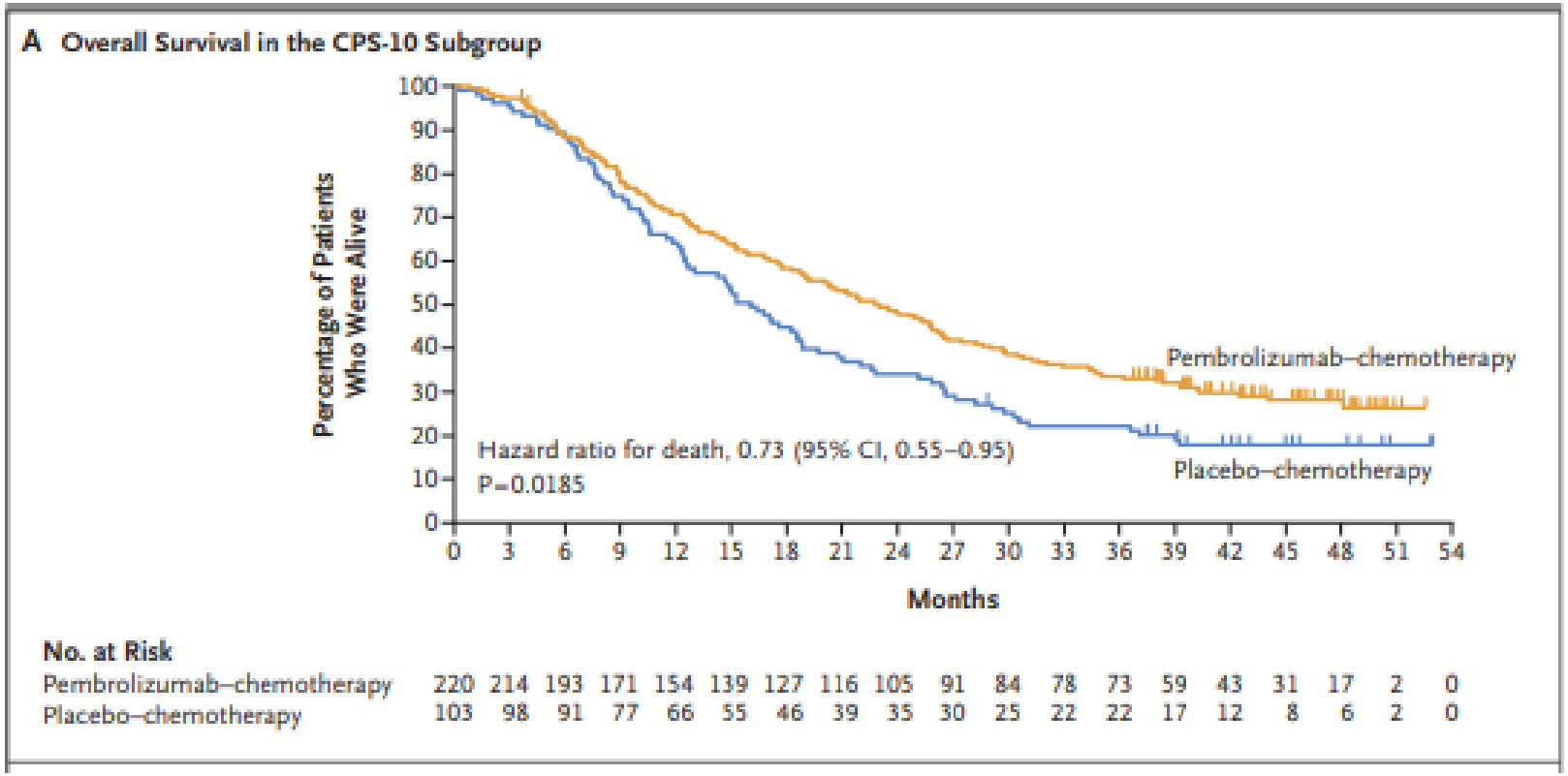
- Biomarkers in HER2-Low
  - Mutations predictive of benefit/resistance
  - HER2 heterogeneity-implications for T-DXd use
- Sequencing of ADCs
  - Multiple ADCs approved or nearing approval
  - Efficacy for one ADC after another
  - How best to sequence them

Reference

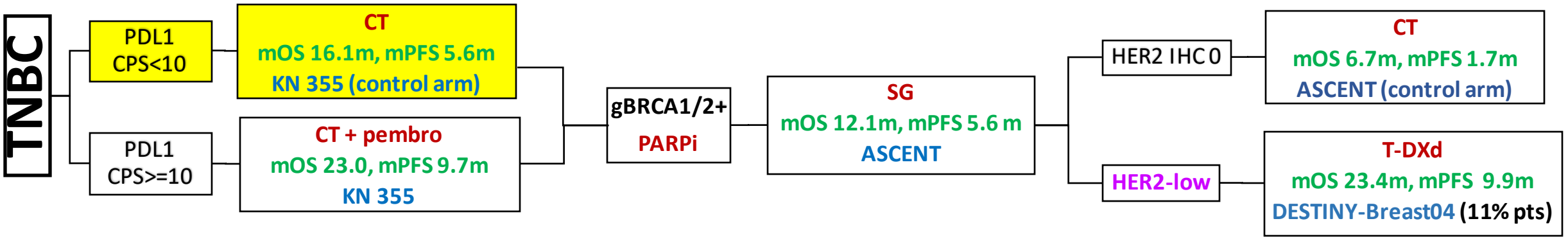


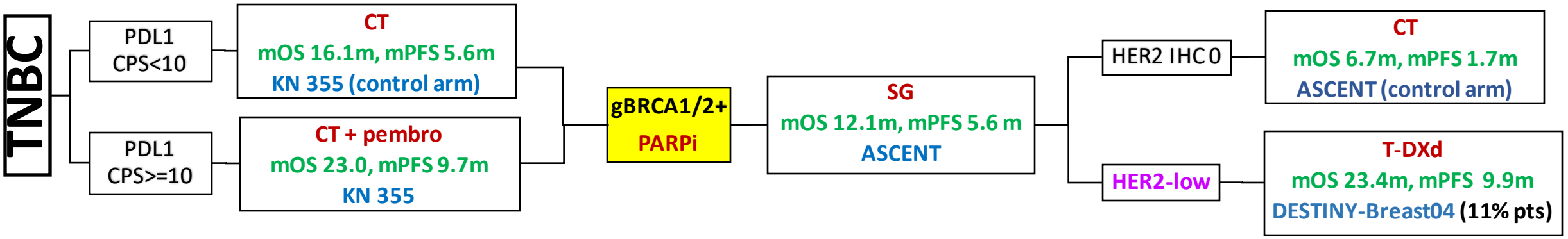
- The median follow-up was 44.1 months. In the CPS-10 subgroup, the median
- overall survival was 23.0 months in the pembrolizumab–chemotherapy group.
- 16.1 months in the placebo–chemotherapy group (hazard ratio for death, 0.73;
- 95% confidence interval [CI], 0.55 to 0.95.



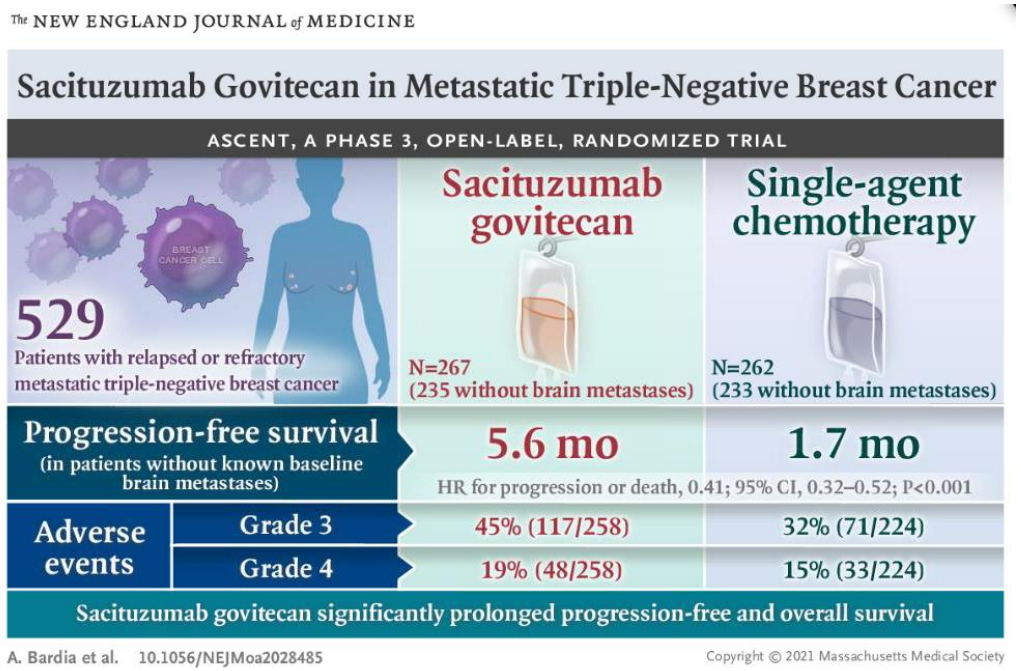


Cortes et al, KEYNOTE-355, NEJM 2022





ASCENT



TNBC

- PDL1 CPS<10 → **CT** mOS 16.1m, mPFS 5.6m, KN 355 (control arm)
- PDL1 CPS>=10 → **CT + pembro** mOS 23.0, mPFS 9.7m, KN 355

→ gBRCA1/2+ PARPi → **SG** mOS 12.1m, mPFS 5.6 m, ASCENT

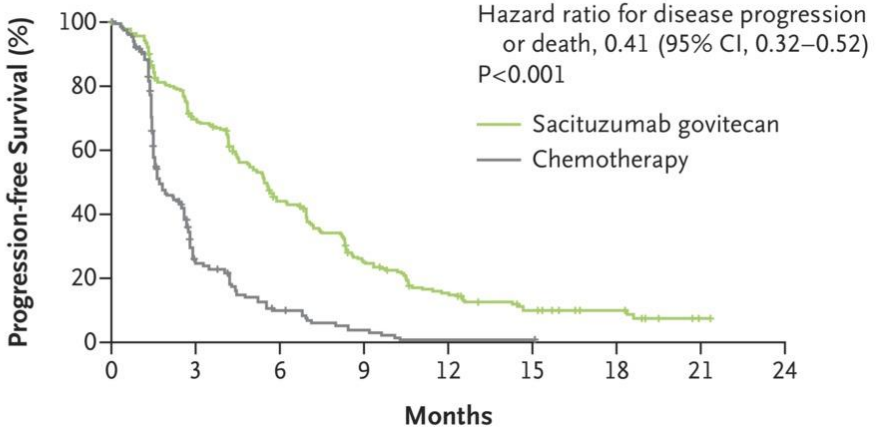
- HER2 IHC 0 → **CT** mOS 6.7m, mPFS 1.7m, ASCENT (control arm)
- HER2-low → **T-DXd** mOS 23.4m, mPFS 9.9m, DESTINY-Breast04 (11% pts)

ASCENT

A Progression-free Survival among Patients without Brain Metastases

mPFS 5.6 m

	No. of Patients	No. of Events	Median Progression-free Survival (mo (95% CI))
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)

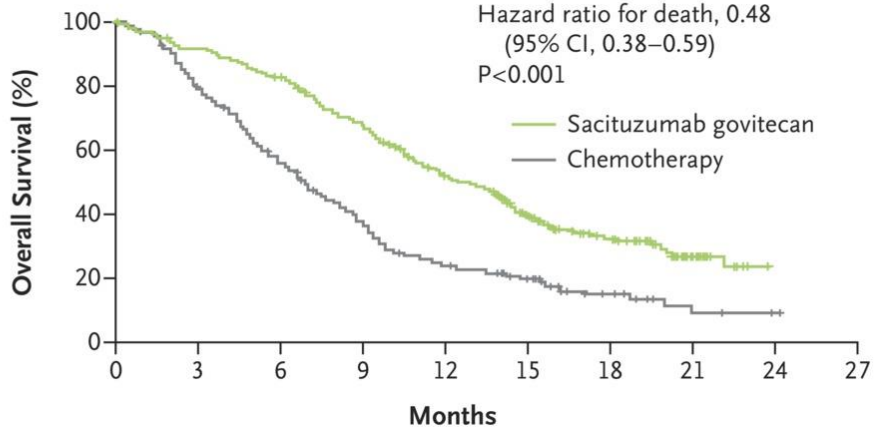


No. at Risk								
Sacituzumab govitecan	235	154	91	49	28	15	9	1
Chemotherapy	233	39	14	5	1	1	0	0

B Overall Survival among Patients without Brain Metastases

mOS 12.1m

	No. of Patients	No. of Events	Median Overall Survival (mo (95% CI))
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)

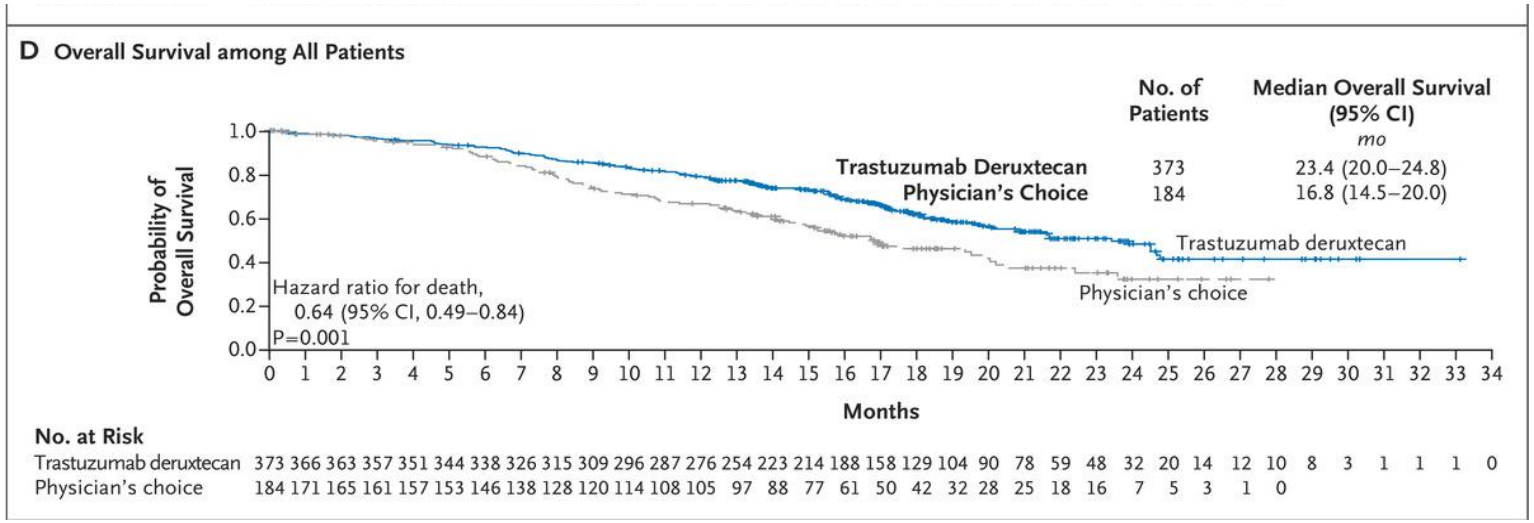


No. at Risk									
Sacituzumab govitecan	235	214	190	153	107	70	37	13	0
Chemotherapy	233	173	117	74	45	30	11	3	1

- Progression-free and overall survival were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with metastatic triple-negative breast cancer.
- Myelosuppression and diarrhea were more frequent with sacituzumab govitecan.

Bardia A et al. N Engl J Med 2021;384:1529-1541

DESTINY-Breast04



TNBC

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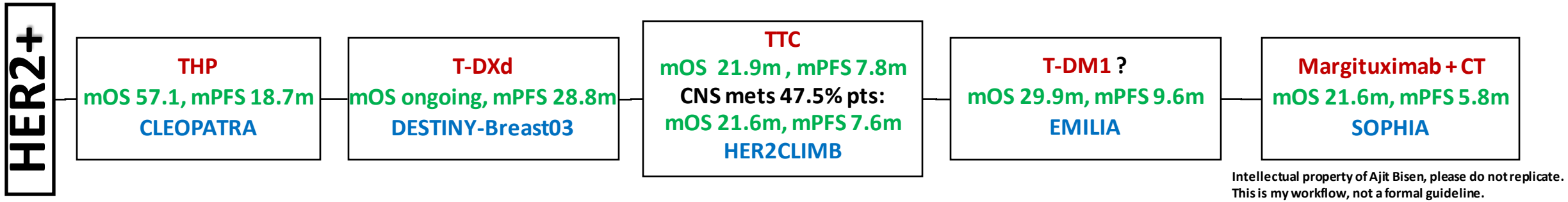
→ **gBRCA1/2+** — PARPi → **SG** — mOS 12.1m, mPFS 5.6 m — ASCENT

- HER2 IHC 0 → **CT** — mOS 6.7m, mPFS 1.7m — ASCENT (control arm)
- HER2-low → **T-DXd** — mOS 23.4m, mPFS 9.9m — DESTINY-Breast04 (11% pts)

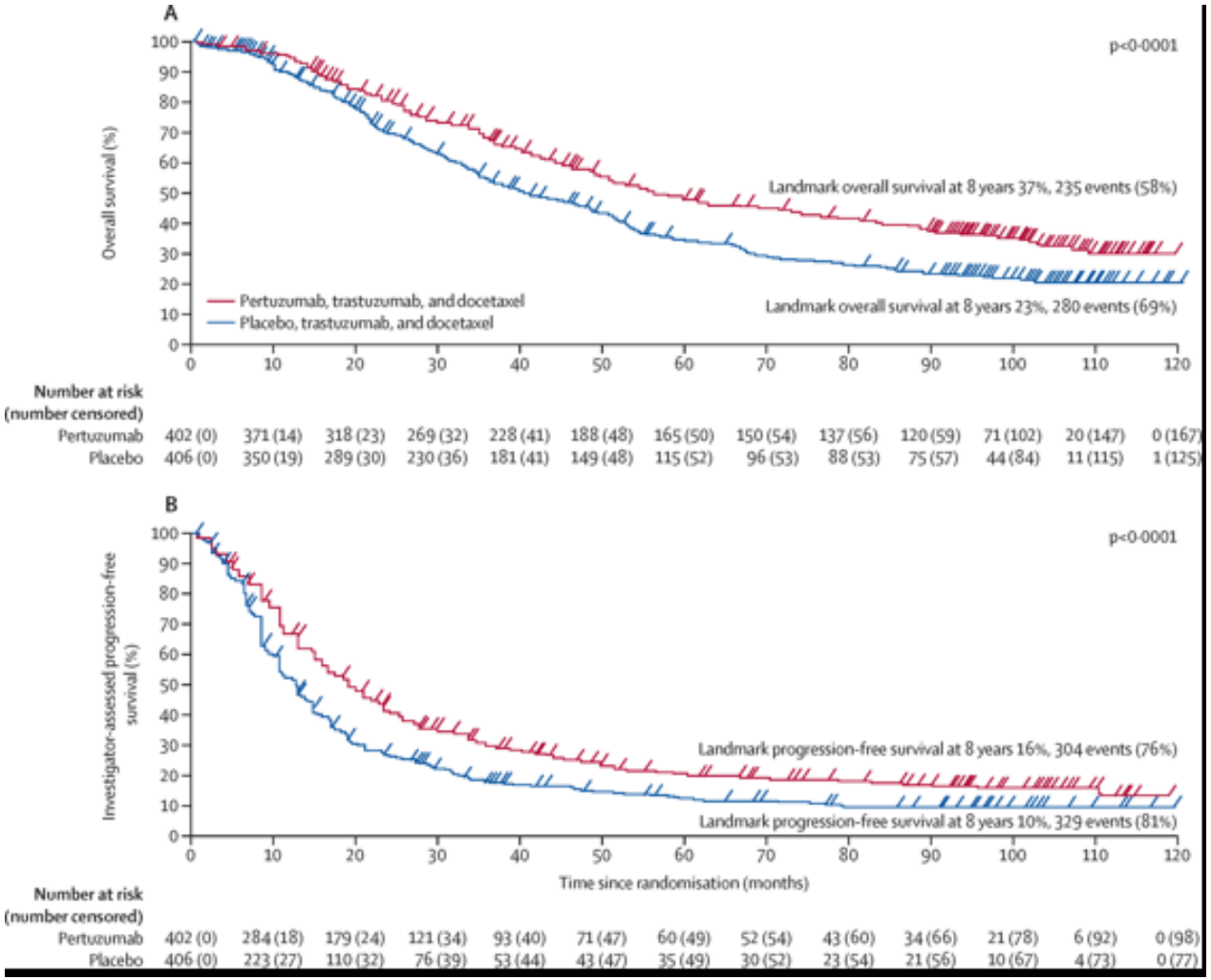


2015

2023

T-DXd = trastuzumab deruxtecan
TTC = tucatinib, trastuzumab, capecitabine
T-DM1 = trastuzumab emtansine

CLEOPATRA



The Lancet Oncology 2020 21519-530DOI: (10.1016/S1470-2045(19)30863-0

HER2+

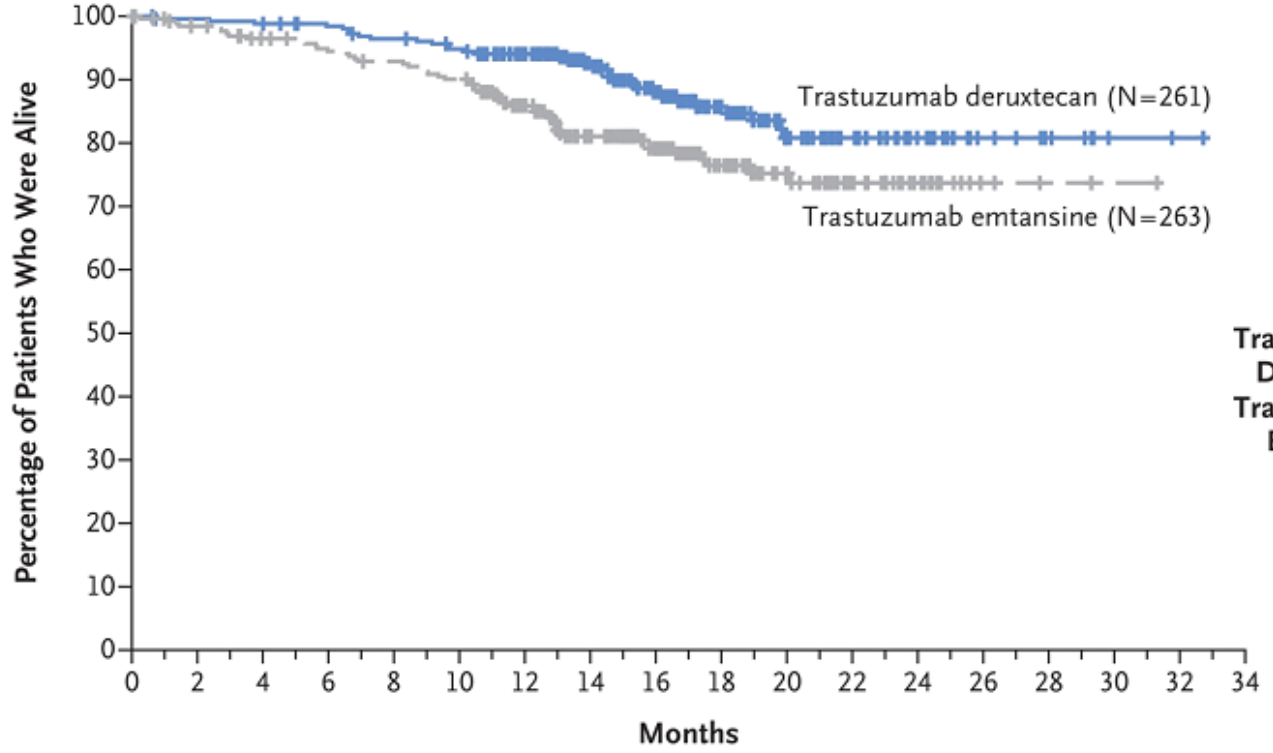
THP
mOS 57.1, mPFS 18.7m
CLEOPATRA

T-DXd
mOS ongoing, mPFS 28.8m
DESTINY-Breast03

TTC
mOS 21.9m , mPFS 7.8m
CNS mets 47.5% pts:
mOS 21.6m, mPFS 7.6m
HER2CLIMB

T-DM1 ?
mOS 29.9m, mPFS 9.6m
EMILIA

Margituximab + CT
mOS 21.6m, mPFS 5.8m
SOPHIA



No. at Risk

Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55 (95% CI, 0.36–0.86)
P=0.007

Cortés J et al. N Engl J Med 2022;386:1143-1154

DESTINY-Breast03

HER2+

THP
mOS 57.1, mPFS 18.7m
CLEOPATRA

T-DXd
mOS ongoing, mPFS 28.8m
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HER2CLIMB

T-DM1 ?
mOS 29.9m, mPFS 9.6m
EMILIA

Margituximab + CT
mOS 21.6m, mPFS 5.8m
SOPHIA

Table 2. Most Common Drug-Related Adverse Events and Adjudicated Drug-Related Interstitial Lung Disease or Pneumonitis.

Event	Trastuzumab Deruxtecan (N=257)		Trastuzumab Emtansine (N=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

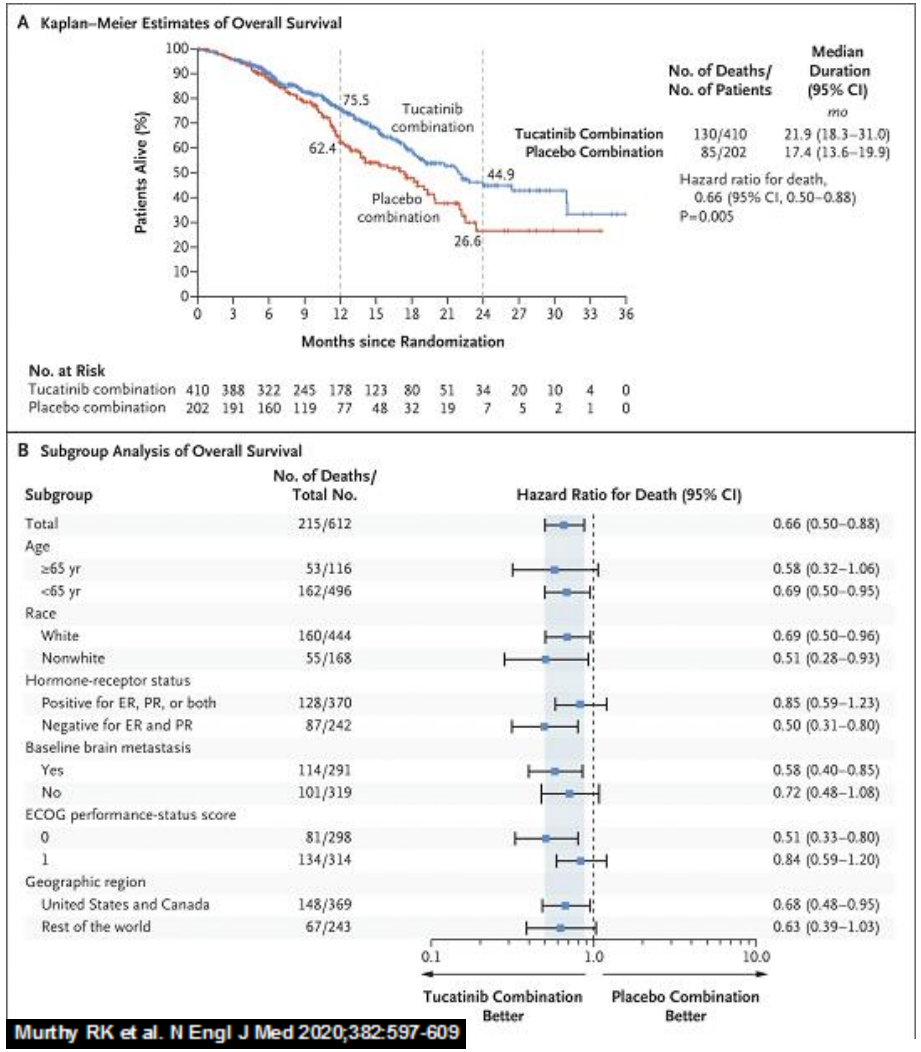
DESTINY-Breast03

Cortés J et al. N Engl J Med 2022;386:1143-1154

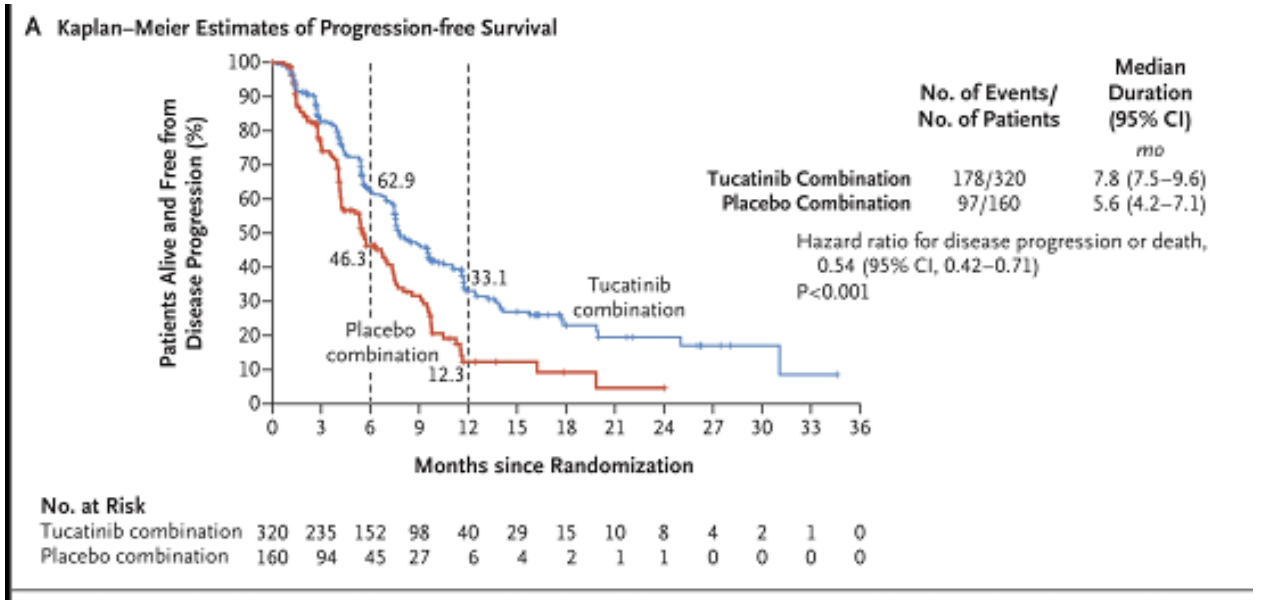
HER2+

- **THP**
  mOS 57.1, mPFS 18.7m
  CLEOPATRA
- **T-DXd**
  mOS ongoing, mPFS 28.8m
  DESTINY-Breast03
- **TTC**
  mOS 21.9m , mPFS 7.8m
  CNS mets 47.5% pts:
  mOS 21.6m, mPFS 7.6m
  HER2CLIMB
- **T-DM1 ?**
  mOS 29.9m, mPFS 9.6m
  EMILIA
- **Margituximab + CT**
  mOS 21.6m, mPFS 5.8m
  SOPHIA

HER2CLIMB



Murthy RK et al. N Engl J Med 2020;382:597-609



Murthy RK et al. N Engl J Med 2020;382:597-609

HER2+

- **THP** — mOS 57.1, mPFS 18.7m — CLEOPATRA
- **T-DXd** — mOS ongoing, mPFS 28.8m — DESTINY-Breast03
- **TTC** — mOS 21.9m, mPFS 7.8m — CNS mets 47.5% pts: mOS 21.6m, mPFS 7.6m — HER2CLIMB
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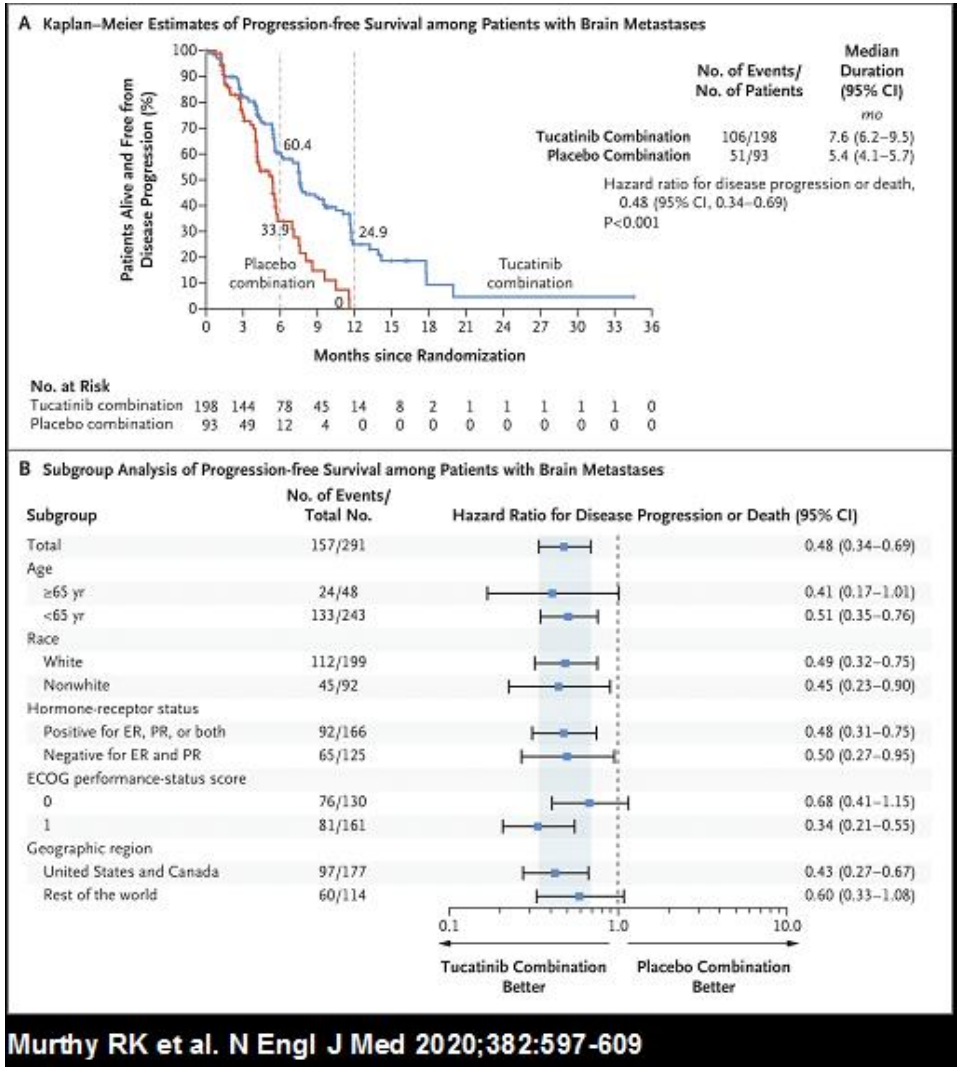
HER2CLIMB



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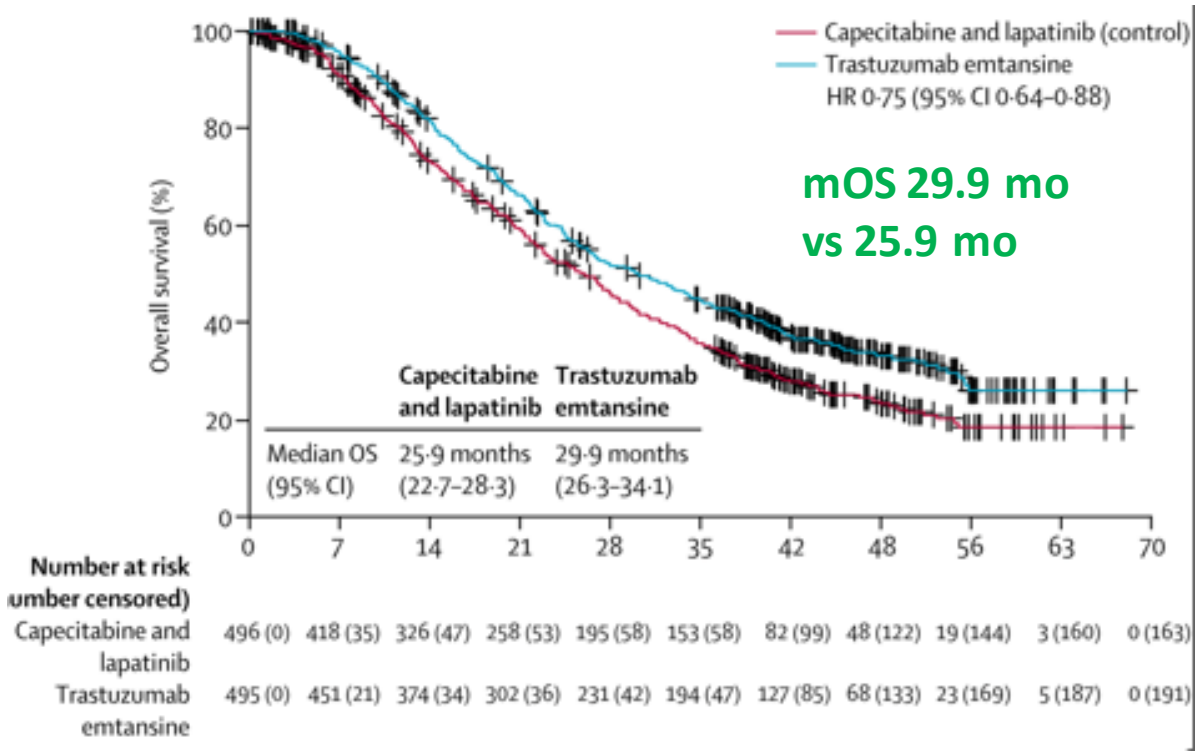
EMILIA



The Lancet Oncology 2017 18732-742DOI: (10.1016/S1470-2045(17)30312-1)

HER2+

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SOPHIA

SOPHIA

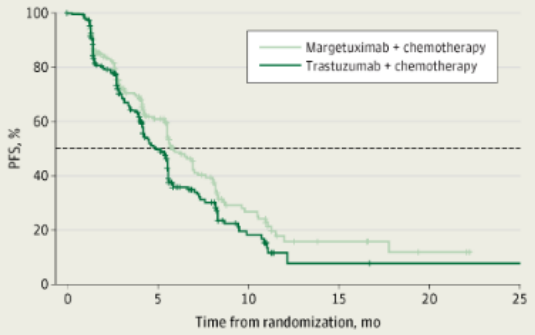
JAMA Oncology

Rugo et al, Journal of Clinical Oncology 2023

RCT: Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer

FINDINGS

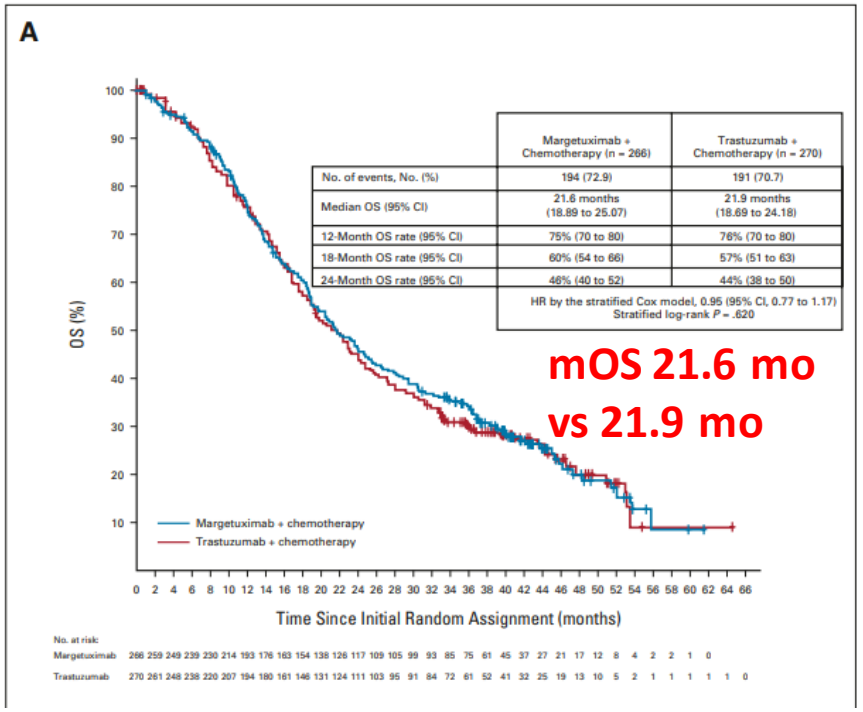
Margetuximab improved blinded primary PFS over trastuzumab, with a 24% relative risk reduction (hazard ratio, 0.76; 95% CI, 0.59-0.98; *P* = .03)



Median PFS:

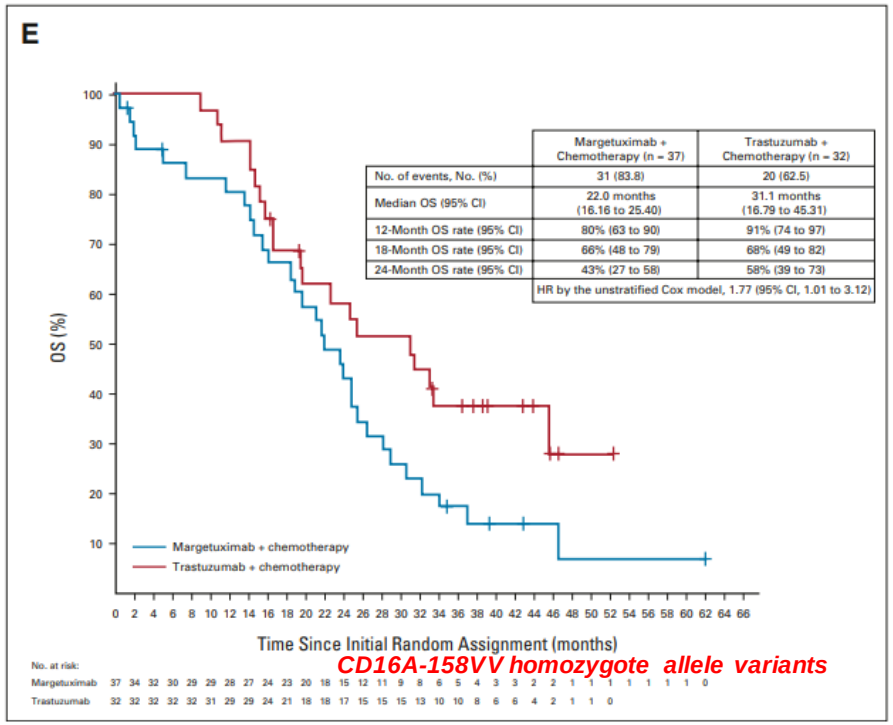
Margetuximab: 5.8 (95% CI, 5.5-7.0) mo

Trastuzumab: 4.9 (95% CI, 4.2-5.6) mo



	Margetuximab + Chemotherapy (n = 266)	Trastuzumab + Chemotherapy (n = 270)
No. of events, No. (%)	194 (72.9)	191 (70.7)
Median OS (95% CI)	21.6 months (18.89 to 25.07)	21.9 months (18.69 to 24.18)
12-Month OS rate (95% CI)	75% (70 to 80)	76% (70 to 80)
18-Month OS rate (95% CI)	60% (54 to 66)	57% (51 to 63)
24-Month OS rate (95% CI)	46% (40 to 52)	44% (38 to 50)
HR by the stratified Cox model, 0.95 (95% CI, 0.77 to 1.17) Stratified log-rank *P* = .620		

mOS 21.6 mo vs 21.9 mo



	Margetuximab + Chemotherapy (n = 37)	Trastuzumab + Chemotherapy (n = 32)
No. of events, No. (%)	31 (83.8)	20 (62.5)
Median OS (95% CI)	22.0 months (16.16 to 25.40)	31.1 months (16.79 to 45.31)
12-Month OS rate (95% CI)	80% (63 to 90)	91% (74 to 97)
18-Month OS rate (95% CI)	66% (48 to 79)	68% (49 to 82)
24-Month OS rate (95% CI)	43% (27 to 58)	58% (39 to 73)
HR by the unstratified Cox model, 1.77 (95% CI, 1.01 to 3.12)		

CD16A-158VV homozygote allele variants

HER2+

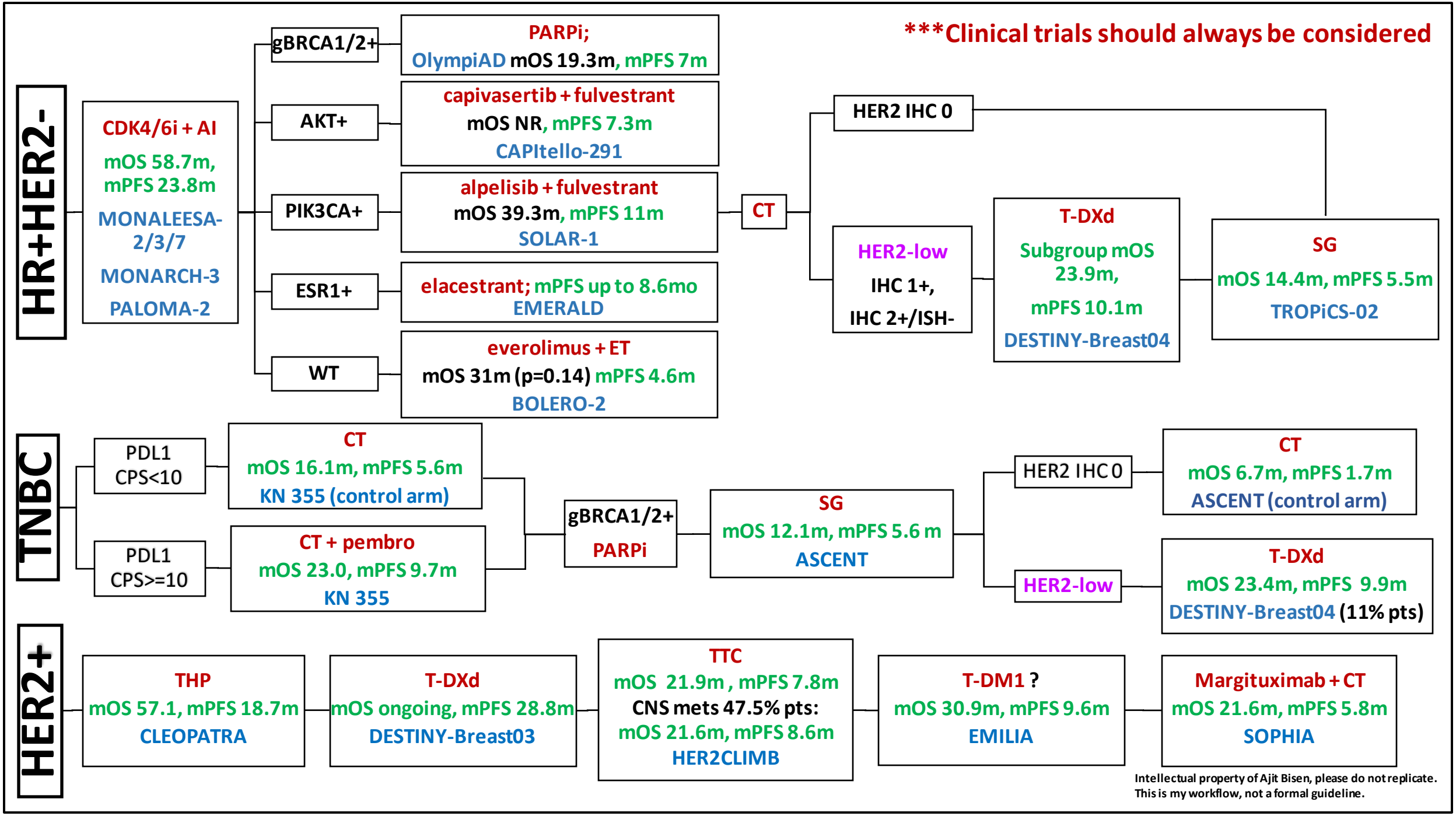
THP
mOS 57.1, mPFS 18.7m
CLEOPATRA

T-DXd
mOS ongoing, mPFS 28.8m
DESTINY-Breast03

TTC
mOS 21.9m , mPFS 7.8m
CNS mets 47.5% pts:
mOS 21.6m, mPFS 7.6m
HER2CLIMB

T-DM1 ?
mOS 29.9m, mPFS 9.6m
EMILIA

Margituximab + CT
mOS 21.6m, mPFS 5.8m
SOPHIA



Summary

- In general, treatment for advanced breast cancer consists of endocrine therapy, targeted therapy, chemotherapy, immunotherapy and/or antibody drug conjugates depending on the subtype of breast cancer.
- Breast cancer treatment landscape continues to advance rapidly.
- Clinical trials should be encouraged at every step.

Acknowledgements

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- TxSCO board