Breast cancer update

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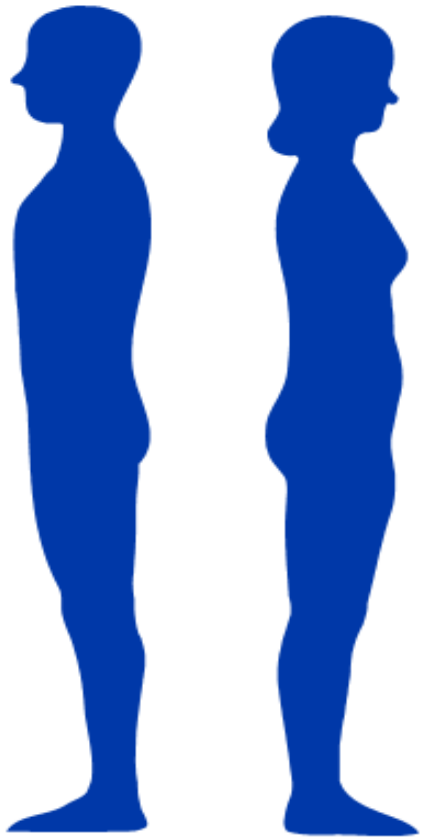
Estimated New Cancer Cases* in the US in 2014

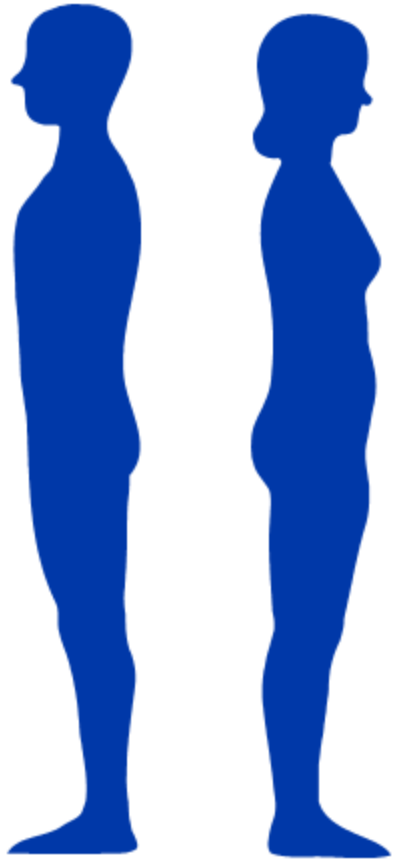


Men		Women	
Prostate	27%	29%	Breast
Lung & bronchus	14%	13%	Lung & bronchus
Colon & rectum	8%	8%	Colon & rectum
Urinary bladder	7%	6%	Uterine corpus
Melanoma of skin	5%	6%	Thyroid
Kidney & renal pelvis	5%	4%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	4%	4%	Melanoma of skin
Oral cavity & pharynx	4%	3%	Kidney & renal pelvis
Leukemia	4%	3%	Pancreas
Liver & intrahepatic bile duct	3%	3%	Leukemia
All other sites	20%	21%	All other sites

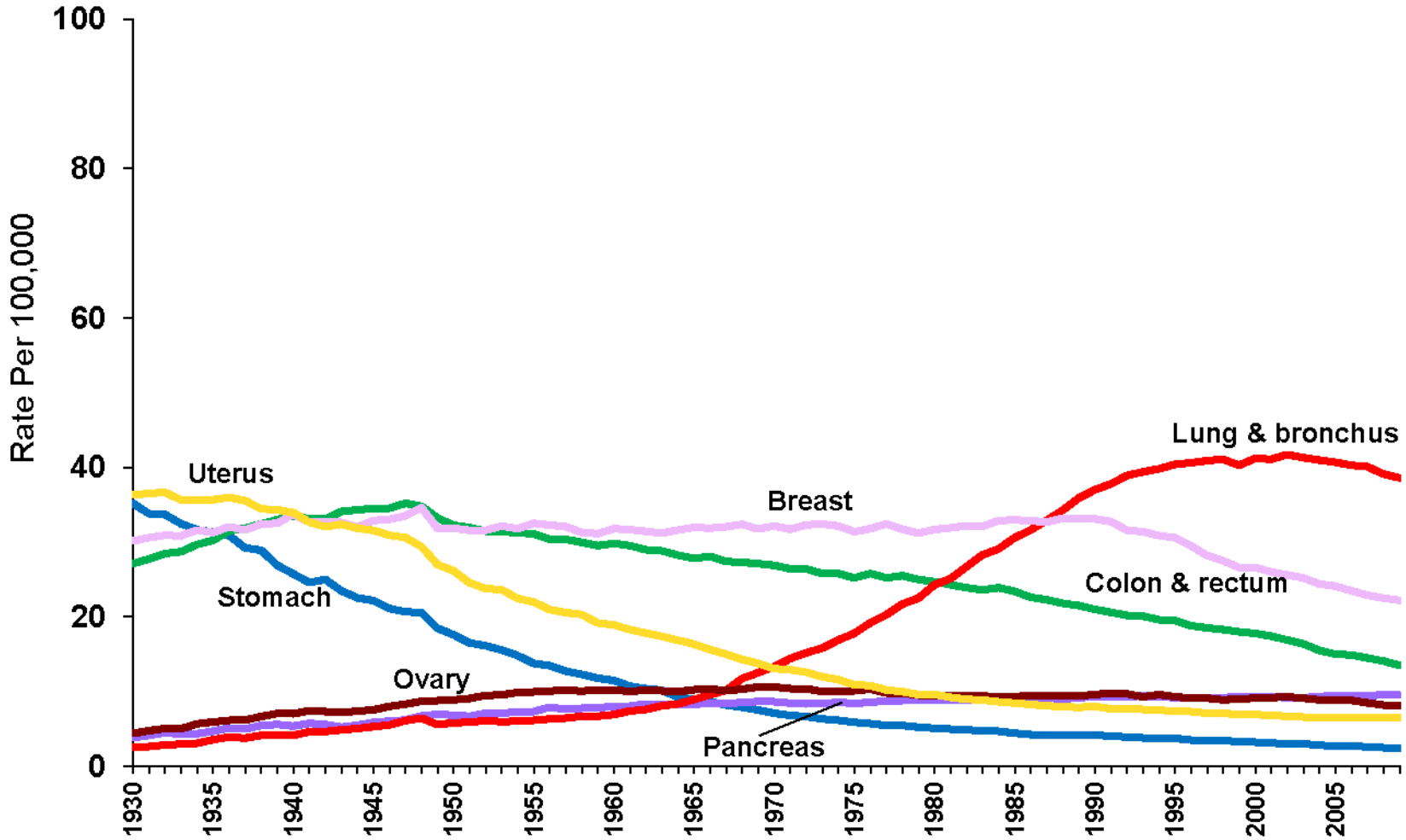
*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Estimated Cancer Deaths in the US in 2014

Men 310,010		Women 275,710	
Lung & bronchus	28%	26%	Lung & bronchus
Prostate	10%	15%	Breast
Colon & rectum	8%	9%	Colon & rectum
Pancreas	7%	7%	Pancreas
Liver & intrahepatic bile duct	5%	5%	Ovary
Leukemia	5%	4%	Leukemia
Esophagus	4%	3%	Uterine corpus
Urinary bladder	4%	3%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	3%	3%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain & other nervous system
All other sites	24%	23%	All other sites

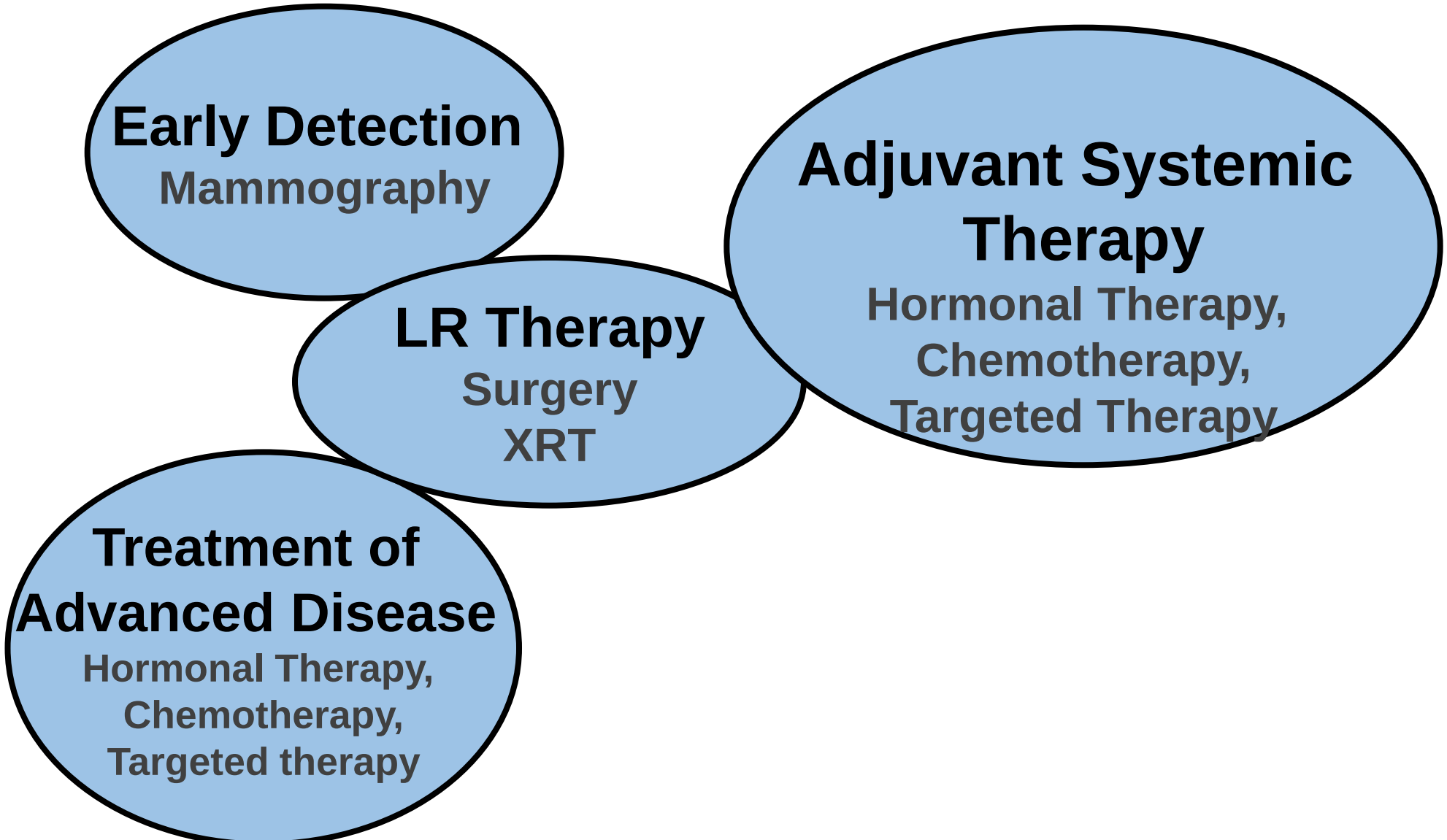


Cancer Death Rates* Among Women, US,1930-2009



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2009, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention.

Factors Associated with Reduction In Breast Cancer Mortality



Treatment of Advanced Disease

- Hormone receptor positive (Estrogen/Progesteron Receptor)
- HER2 positive

Endocrine Receptor-Positive Breast Cancer

- Most common type of breast cancer(70%)-responsive to hormonal therapy
- Incurable when diagnosed in advanced stage (survival – several years)
- Endocrine therapy is preferable less toxic option
- Resistance eventually develops to endocrine therapies

Endocrine therapy in metastatic breast cancer

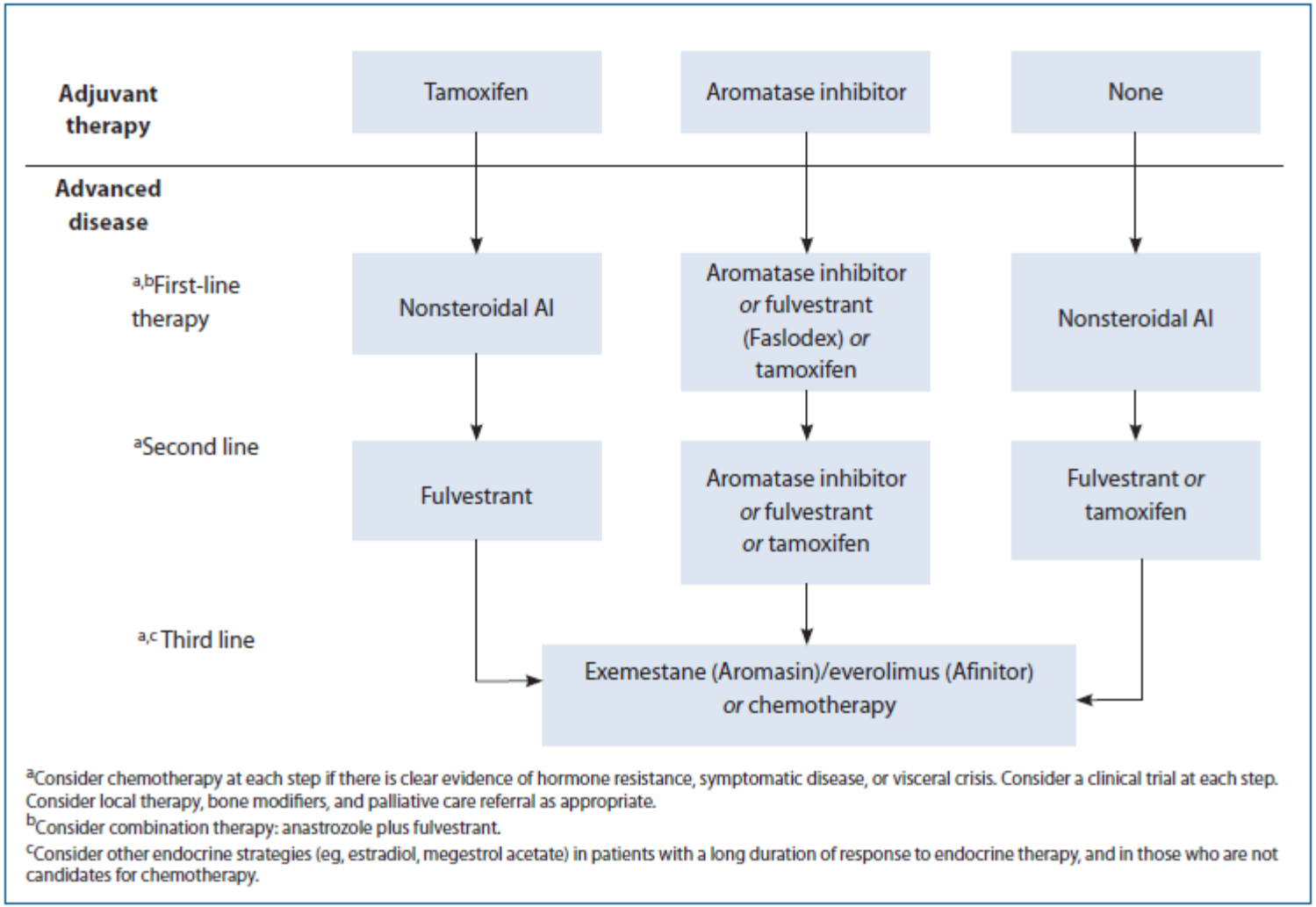
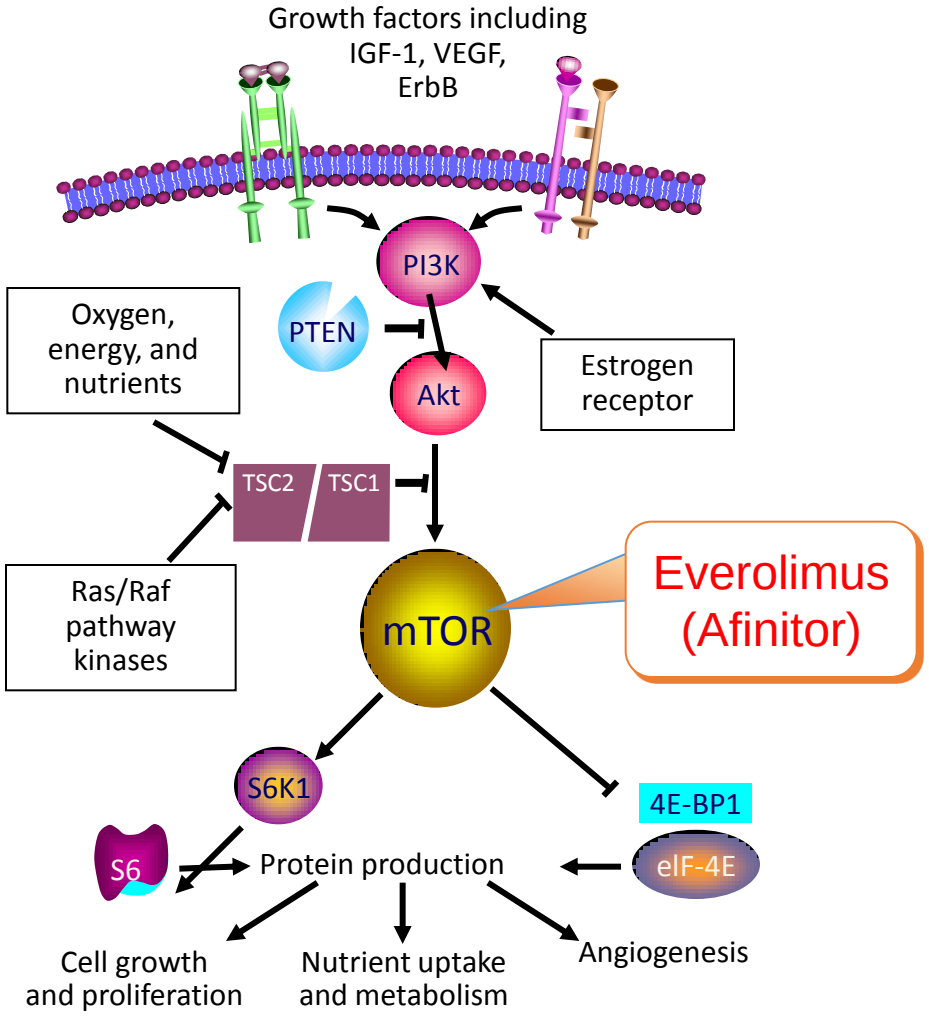


Figure: Suggested Sequencing of Endocrine Therapy in Patients With Advanced Breast Cancer.

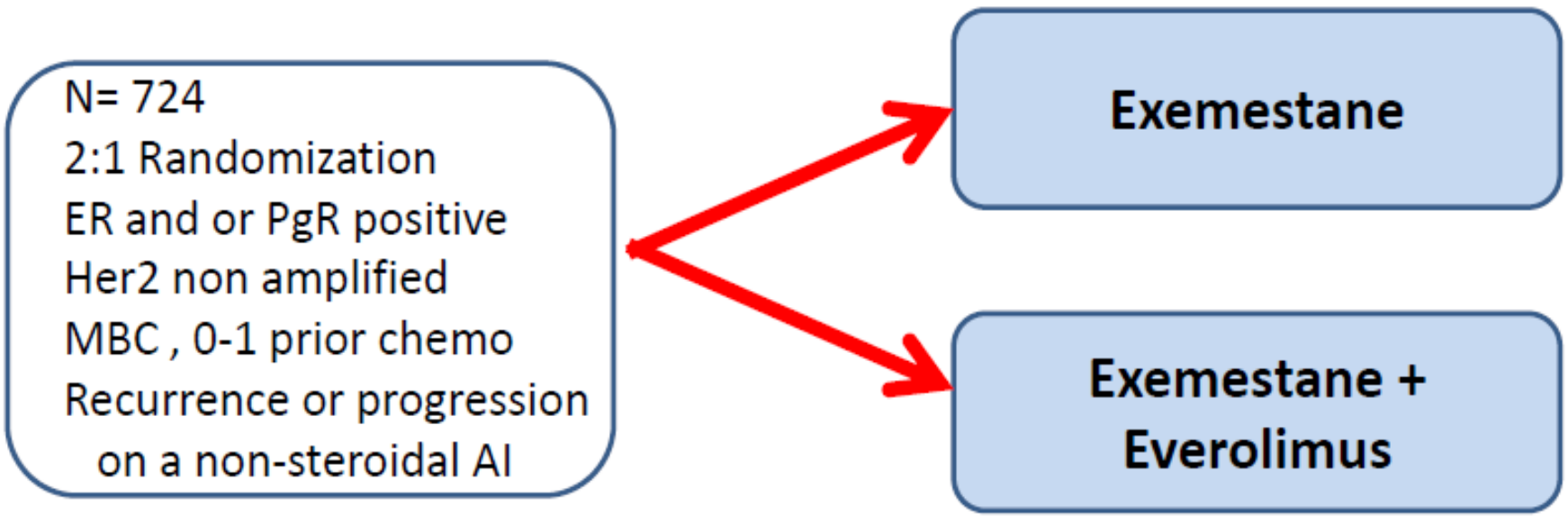
Everolimus(Afinitor): Targeting the PI3K / AKT / mTOR



- Everolimus (RAD001) is a novel oral inhibitor of the Ser/Thr kinase, mTOR
- Blocking mTOR leads to inhibition of cellular growth / proliferation, cellular metabolism, and angiogenesis
- Broad clinical activity demonstrated in multiple tumor types (RCC, NET)

1. Bjornsti MA, Houghton PJ. *Nat Rev Cancer*. 2004;34(5):335-348.
2. Crespo JL, Hall MN.*Microbiol Mol Biol Rev*. 2002;66(4):579-591.
3. Huang S, *et al*. *Cancer Biol Ther*. 2003;2(3):222-232.
4. Mita MM, *et al*. *Clin Breast Cancer* 2003;4(2):126-137.
5. Wullschleger S, *et al*. Cell 2006;124(3):471-484.

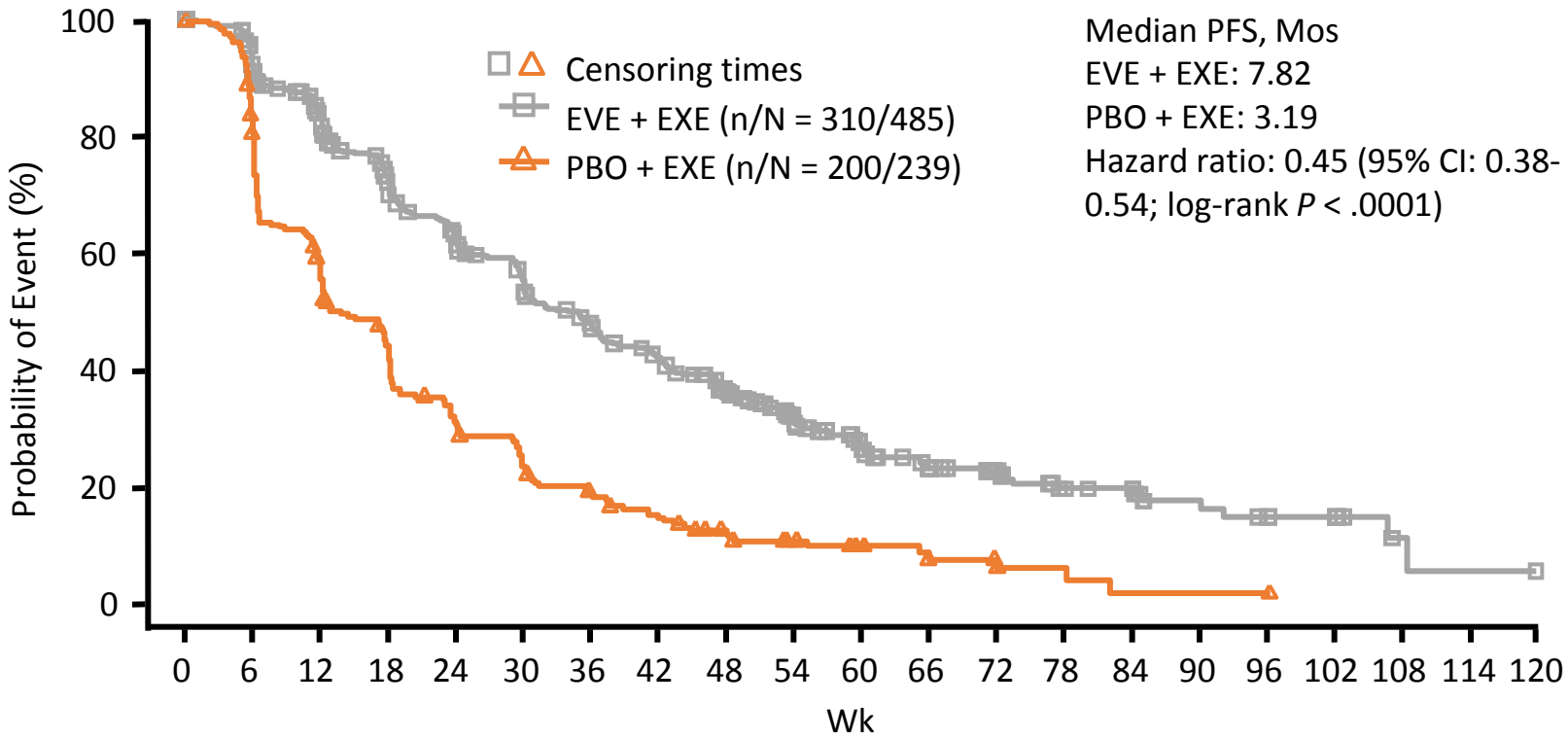
Phase III Trial Evaluating Whether Everolimus Adds To Exemestane (Bolero-2)



Exemestane: 25 mg P0 QD; Everolimus 10 mg PO QD

Baselga, et al. N Engl J Med 2012;366:520-9.

BOLERO-2: PFS at 18-Mo Follow-up



Patients at Risk, n

EVE + EXE	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
PBO + EXE	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

28. Piccart-Gebhart M, et al. ASCO 2012. Abstract 559.

BOLERO -2: Overall Survival

	7-month follow-up	12-month follow-up	18-month follow-up
Cut-off date	11 Feb 2011	8 Jul 2011	15 Dec 2011
OS events (EVE vs PBO)	83 (10.7 vs 13.0%)	137 (17.3 vs 22.7%)	200 (25.4 *vs* 32.2%)
Δ OS events	2.3%	5.4%	6.8%

BOLERO-2: Most Common Adverse Events

Most Common Adverse Events (Reported in ≥25% of Patients)										
	EVE+EXE (n=482), %					PBO+EXE (n=238), %				
		Grade					Grade			
AE (Preferred Term)	All	1	2	3	4	All	1	2	3	4
Any AE	100	7	40	44	9	91	26	36	23	5
Stomatitis	59	29	22	8	0	12	9	2	<1	0
Rash	39	29	9	1	0	7	5	2	0	0
Fatigue	37	18	14	4	<1	27	16	10	1	0
Diarrhea	34	26	6	2	<1	19	14	4	<1	0
Nausea	31	21	9	<1	<1	29	21	7	1	0
Decreased appetite	31	19	10	1	0	13	8	4	1	0
Weight decreased	28	10	16	2	0	7	3	5	0	0
Cough	26	21	4	1	0	12	8	3	0	0
Pneumonitis*	16	7	6	3	0	0	0	0	0	0
Hyperglycemia*	14	4	5	5	<1	2	1	1	<1	0

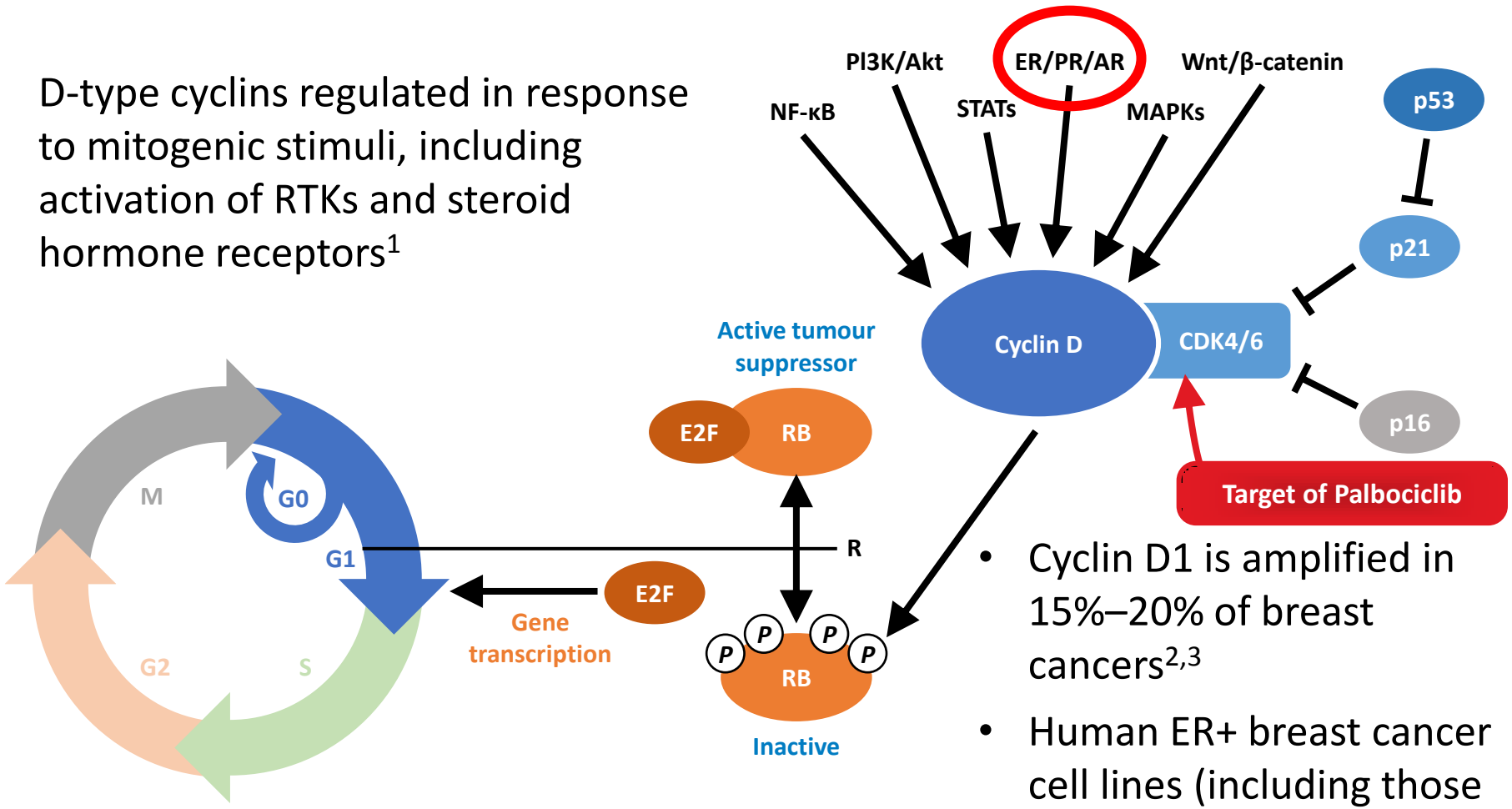
[a] Adverse events of special interest.

Piccart-Gebhart M, et al. *J Clin Oncol.* 2012;30(suppl; abstr 559)(poster).

Palbociclib
CDK4/6 inhibitor

Regulation of the G1/S Checkpoint in Breast Cancer

D-type cyclins regulated in response to mitogenic stimuli, including activation of RTKs and steroid hormone receptors[1]



- Cyclin D1 is amplified in 15%–20% of breast cancers[2,3]
- Human ER+ breast cancer cell lines (including those with HER2 amplification) sensitive to G0/G1 arrest[4]

Lange, et al. *Endocr Rel Cancer.* 2011;18:C19-C24; 1. Caldon CE, et al. *J Cell Biochem.* 2006;97:261-274; 2. Buckley MF, et al. *Oncogene*. 1993;8:2127-2133; 3. Dickson C, et al. *Cancer Lett.* 1995;90:43-50; 4. Finn RS, et al. *Breast Cancer Res.* 2009;11:R77.

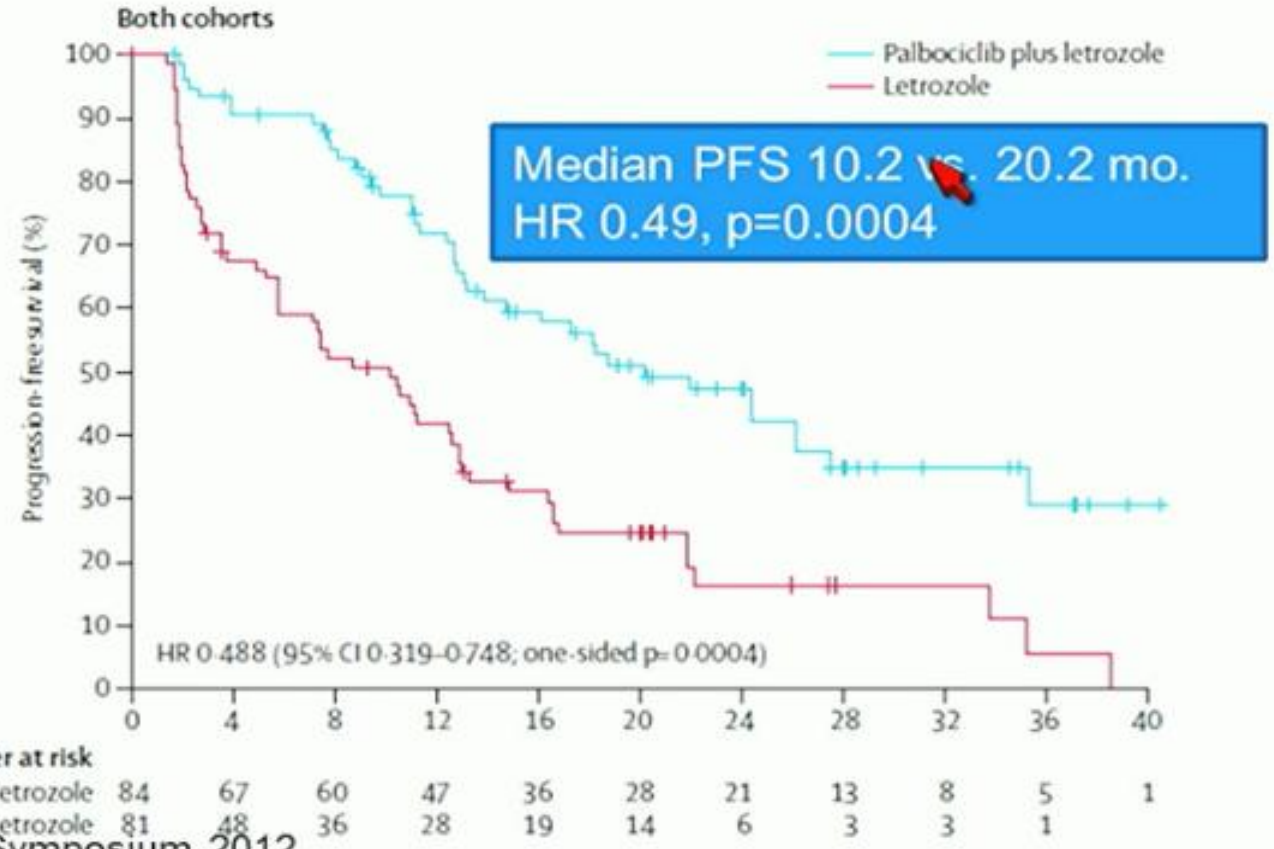
PALOMA-1: Randomized open-label phase II trial

Letrozole plus Palbociclib

R

- HR+, HER2– ABC

Letrozole

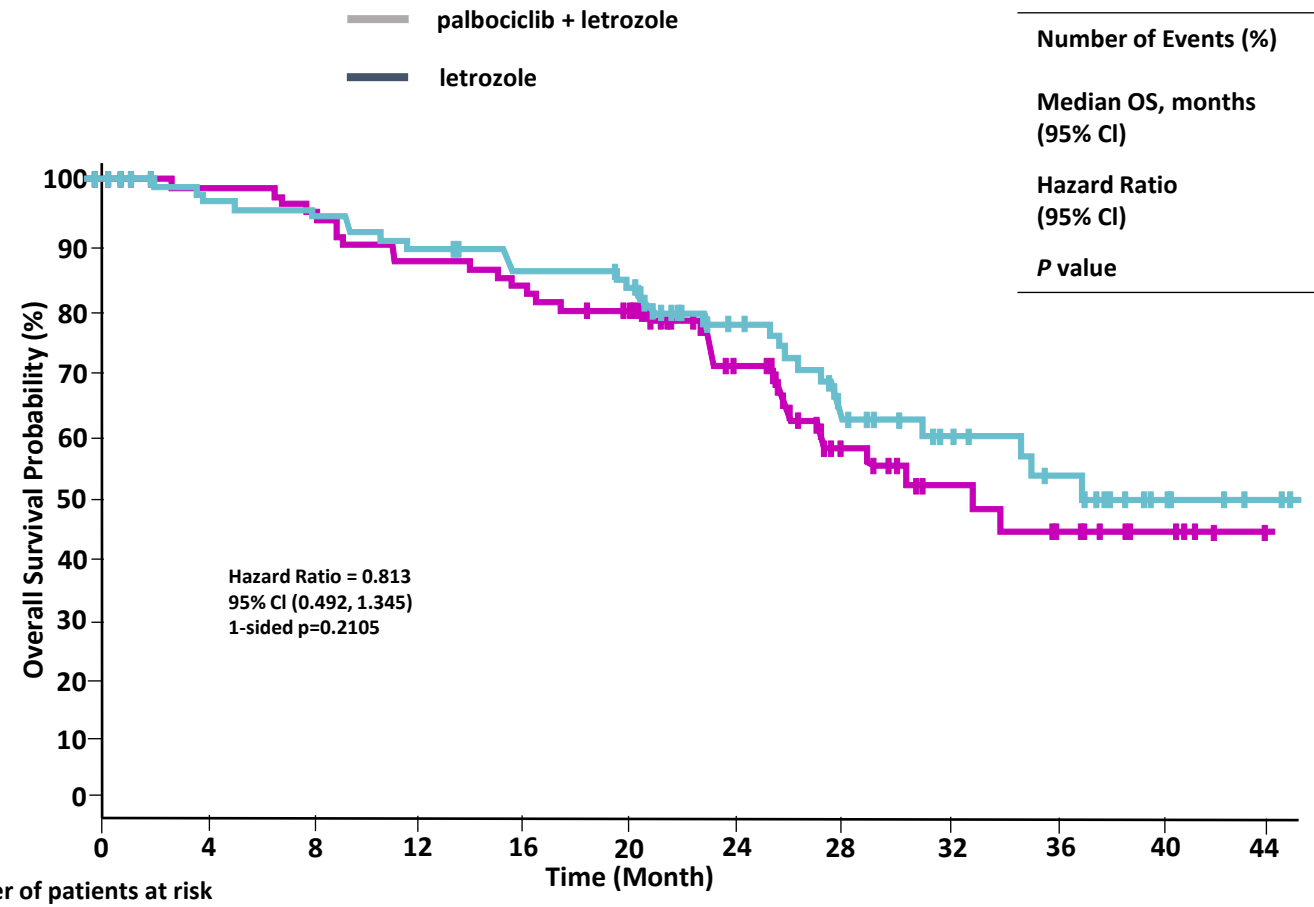


Finn et al. San Antonio Breast Cancer Symposium, 2012
Finn et al. AACR, 2014; Finn et al. Lancet Oncol, 2015

PRESENTED AT: ASCO Annual '15 Meeting

Overall Survival (ITT) at Time of Final PFS Analysis

	PAL + LET (N = 84)	LET (N = 81)
Number of Events (%)	30 (36)	31 (38)
Median OS, months (95% CI)	37.5 (28.4, NR)	33.3 (26.4, NR)
Hazard Ratio (95% CI)	0.813 (0.492, 1.345)	
P value	.2105	



Number of patients at risk

PAL + LET	84	80	78	73	68	65	47	35	22	17	7	2
LET	81	76	74	67	64	59	37	23	14	12	5	1

Finn RS, et al: AACR Annual Meeting. Abstract CT 101 presented April 6, 2014.

Most Common Treatment-Related AEs ≥10% (AT)

	PAL + LET (N = 83)			LET (N = 77)		
	G1/2 (%)	G3 (%)	G4 (%)	G1/2 (%)	G3 (%)	G4 (%)
Neutropenia	19	48	6	1	1	0
Leukopenia	23	18	0	0	0	0
Anaemia	23	4	1	0	0	0
Fatigue	22	2	0	14	0	0
Alopecia	22	0	0	3	0	0
Hot flush	18	0	0	10	0	0
Arthralgia	17	0	0	9	1	0
Thrombocytopenia	14	2	0	0	0	0
Nausea	14	1	0	1	0	0
Decreased appetite	8	1	0	0	0	0
Stomatitis	10	0	0	0	0	0

- Neutropenia was self-limited and not associated with infectious complications

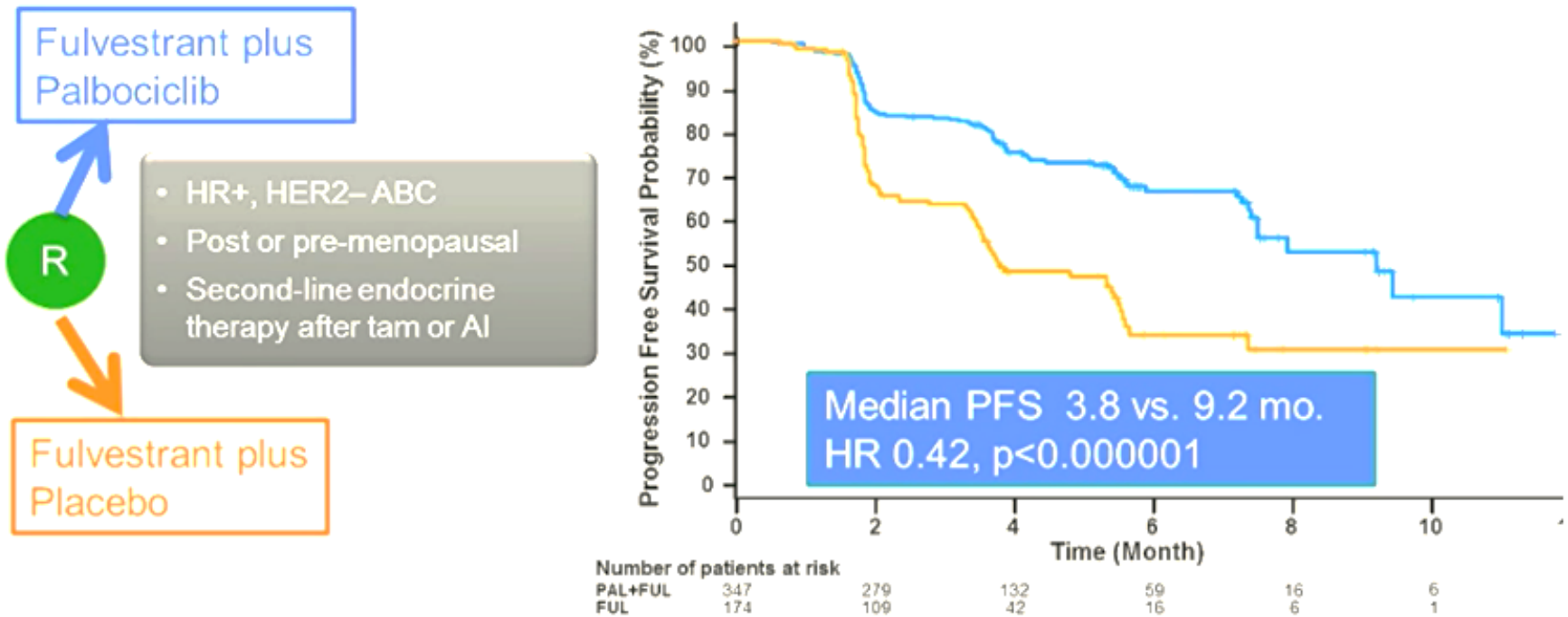
Finn RS, et al: AACR Annual Meeting. Abstract CT 101 presented April 6, 2014.

Palbociclib

- Palbociclib, a first-in-class CDK 4/6 inhibitor, in combination with letrozole, significantly improves median PFS in patients with advanced ER+/HER2– breast cancer in the first-line setting
  - PFS: 20.2 vs 10.2 months; HR = 0.488; *P* = .0004
- Beneficial effect is consistently observed in secondary measures of efficacy (ORR and CBR) and in all clinical subgroups
- OS analysis at the time of final PFS analysis demonstrates a positive trend in favor of the combination
- The safety profile of the combination is acceptable and manageable with uncomplicated neutropenia as the most frequently reported AE

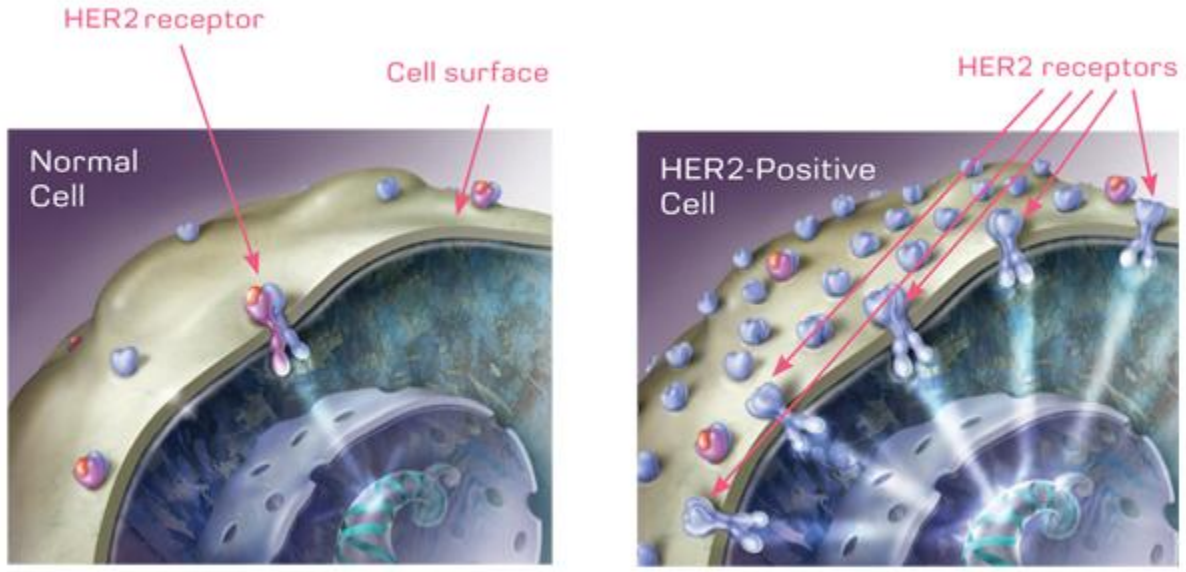
FDA approval (2015)

PALOMA3 Primary Endpoint: PFS (Investigator-Assessed) ITT Population



CI=confidence interval; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.

HER 2 positive Breast Cancer



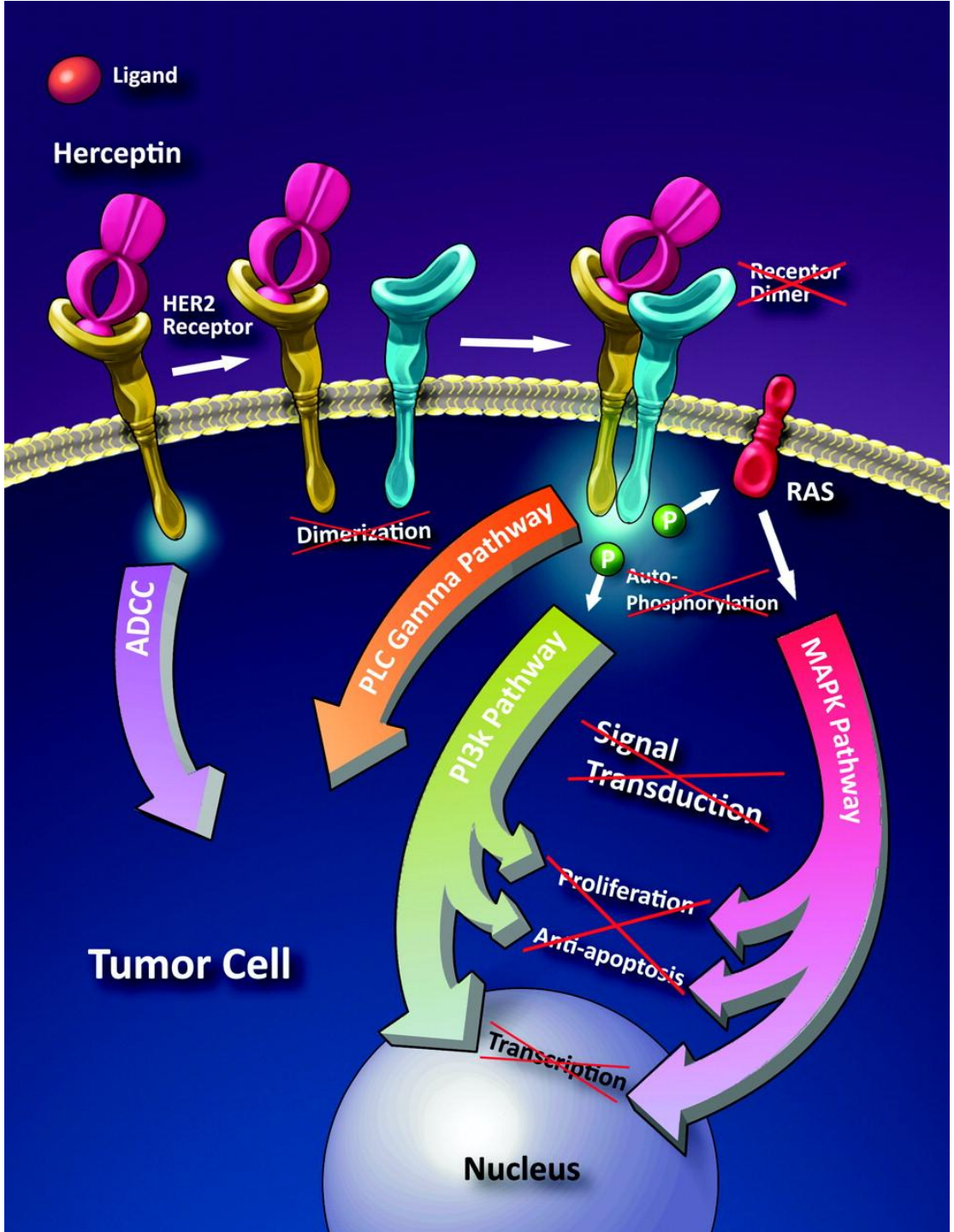
20-25% of breast cancers

Increased risk of disease recurrence and death

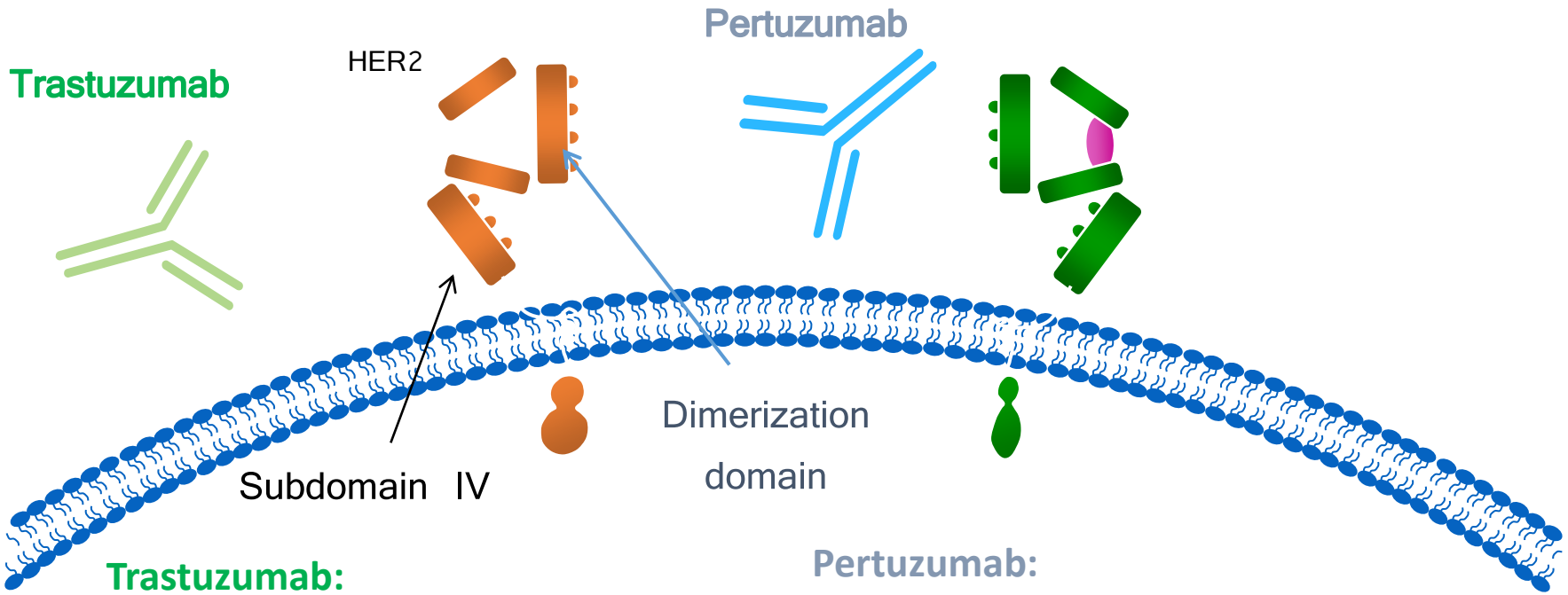
Herceptin

Monoclonal antibody

Significantly improved outcome in both early stage and metastatic disease



Pertuzumab and trastuzumab have complementary mechanisms of action



Trastuzumab:

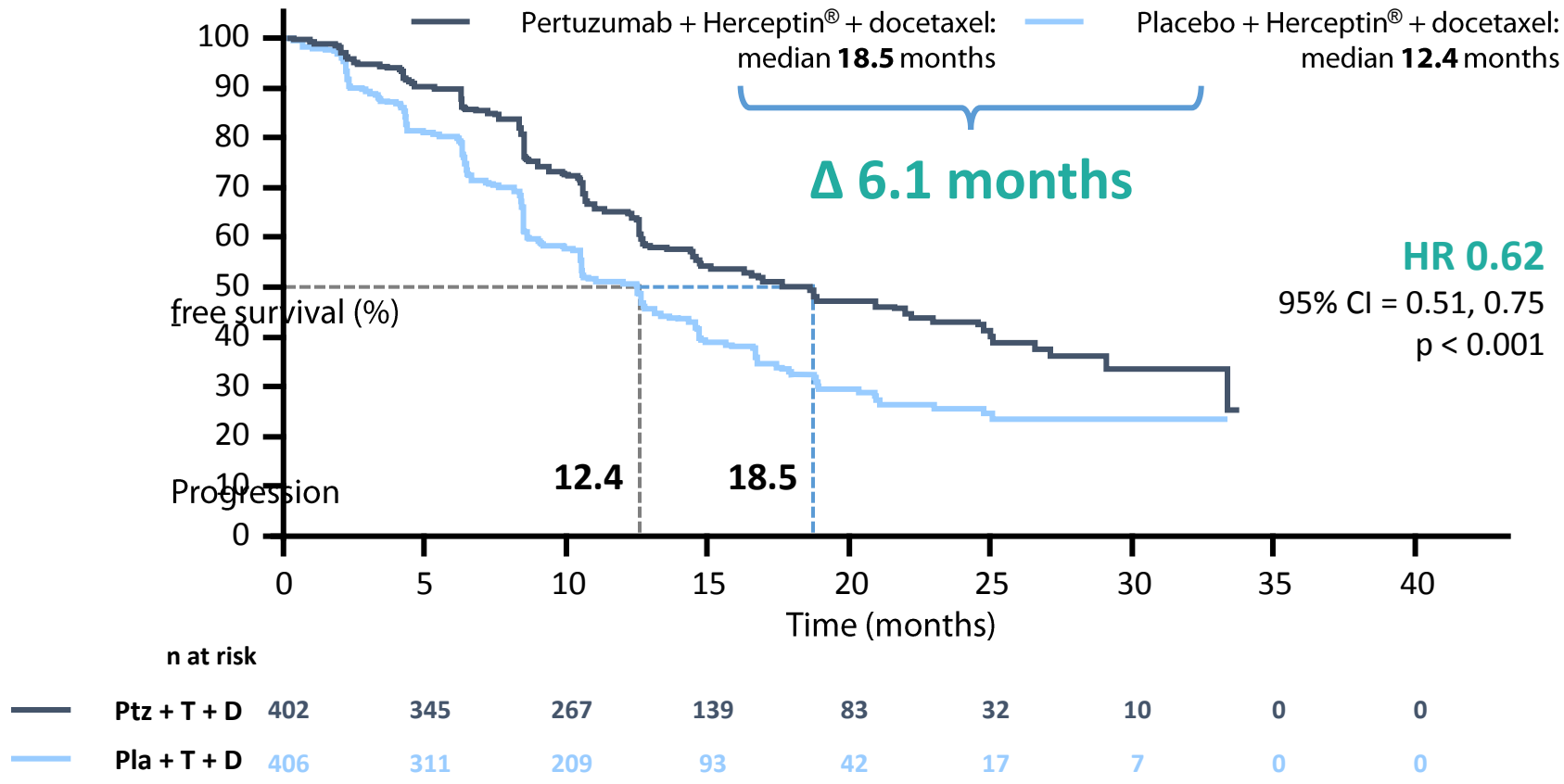
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Pertuzumab:

- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

Pertuzumab-based regimen significantly extends PFS in patients with HER2-positive first-line MBC

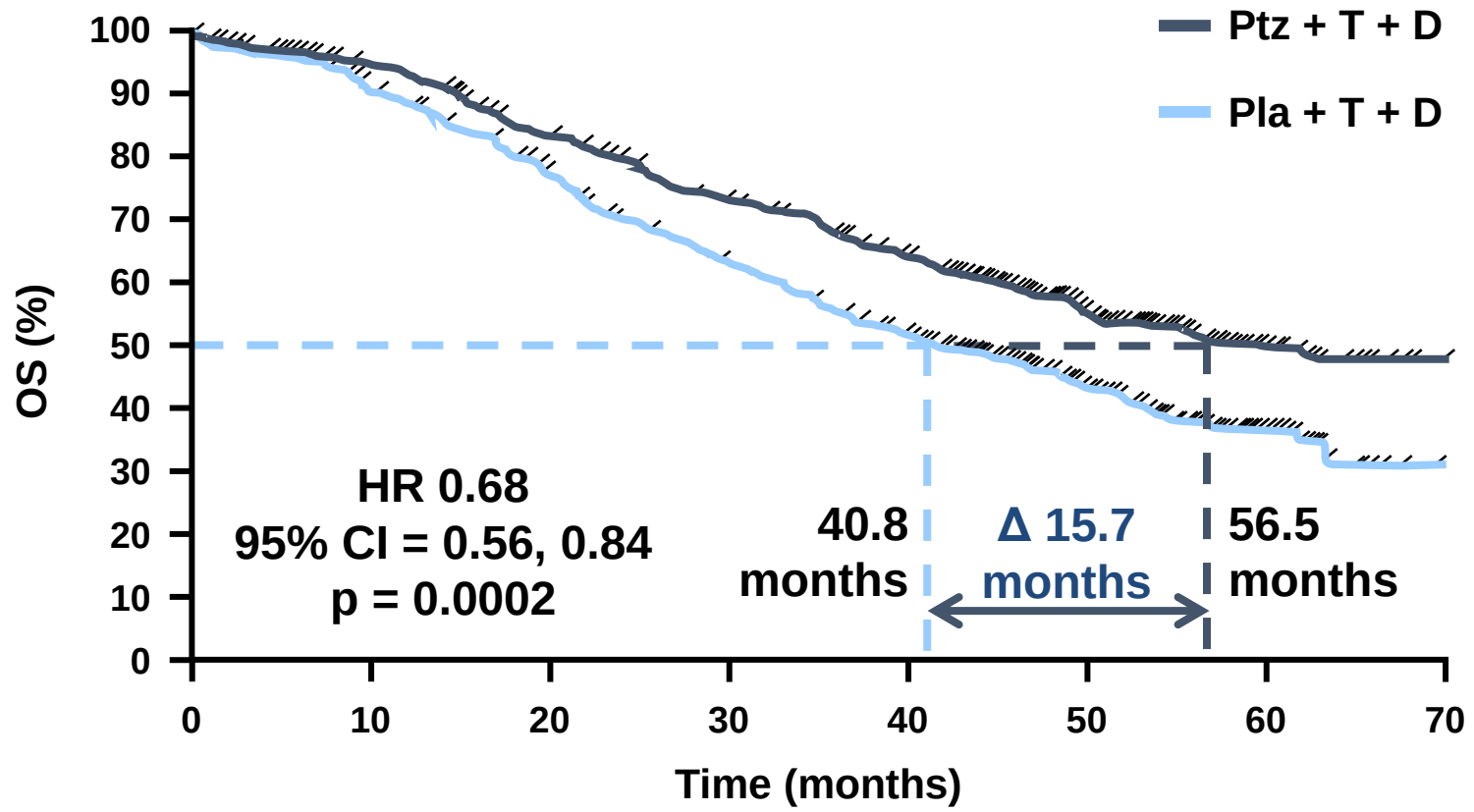
Median follow-up: 19.3 months



- Baselga J, *et al. N Engl J Med* 2012.

Final OS Analysis

Median follow-up 50 months (range 0–70 months)



n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

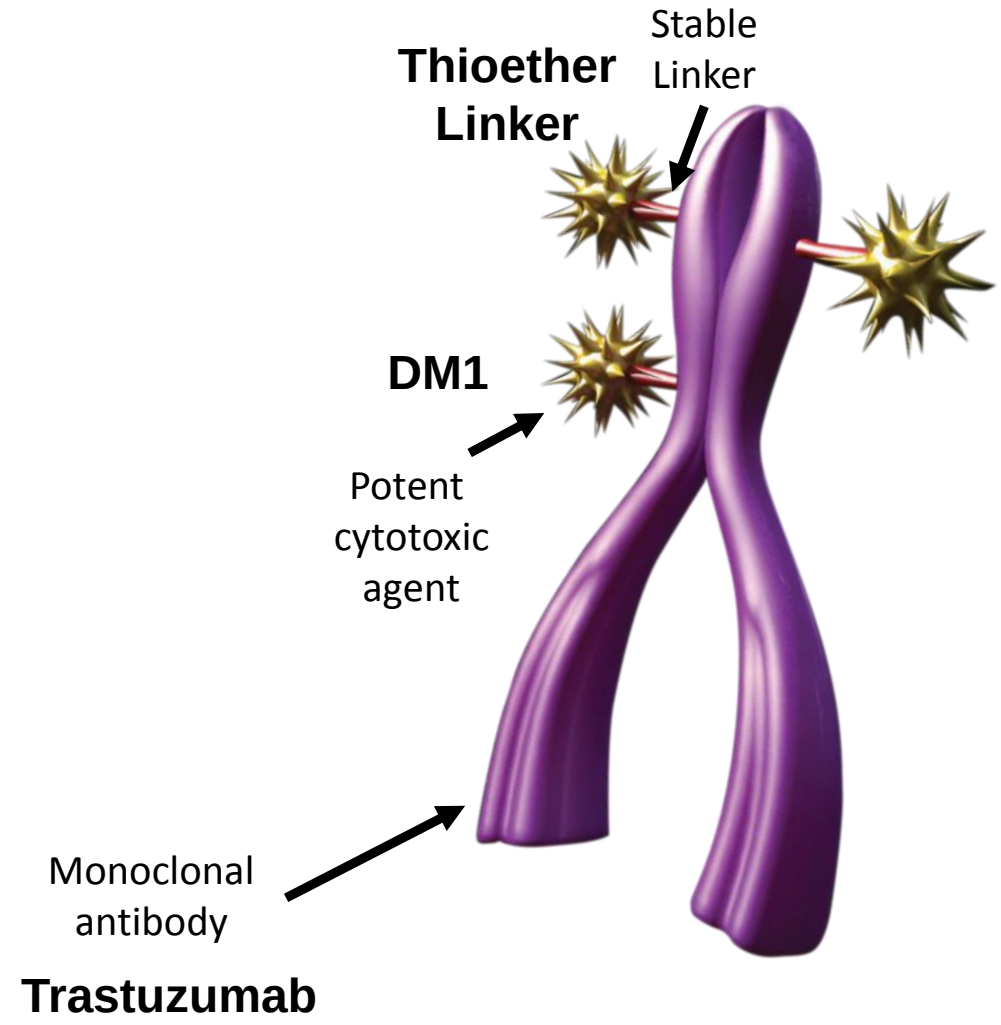
25

Adverse events (all grades)

Adverse event, n (%)	Placebo + trastuzumab + docetaxel (n = 397)	Pertuzumab + trastuzumab + docetaxel (n = 407)
Diarrhea	**184 (46.3)**	**272 (66.8)**
Alopecia	**240 (60.5)**	**248 (60.9)**
Neutropenia	197 (49.6)	215 (52.8)
Nausea	165 (41.6)	172 (42.3)
Fatigue	146 (36.8)	153 (37.6)
Rash	**96 (24.2)**	**137 (33.7)**
Decreased appetite	105 (26.4)	119 (29.2)
Mucosal inflammation	**79 (19.9)**	**113 (27.8)**
Asthenia	120 (30.2)	106 (26.0)
Peripheral edema	119 (30.0)	94 (23.1)
Constipation	99 (24.9)	61 (15.0)
Febrile neutropenia	**30 (7.6)**	**56 (13.8)**
Dry skin	**17 (4.3)**	**43 (10.6)**

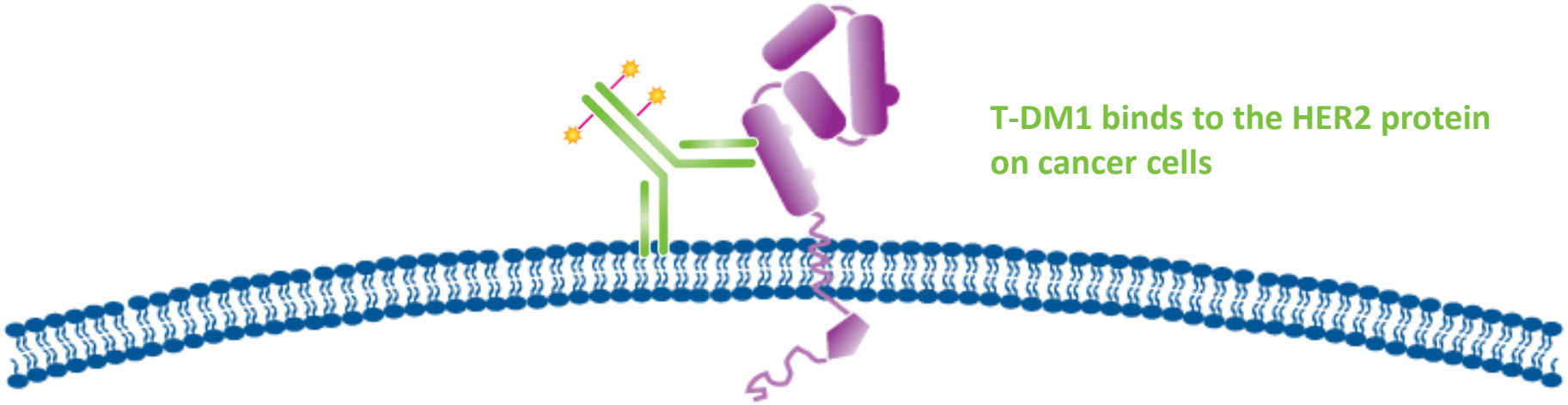
Antibody–drug conjugates
TDM-1 (Kadcyla)

- An ADC is a unique combination of:
  - A targeted monoclonal antibody (mAb)
  - A stable linker
  - A potent cytotoxic
- ADCs are designed to target cancer cells while minimizing effects on normal tissue



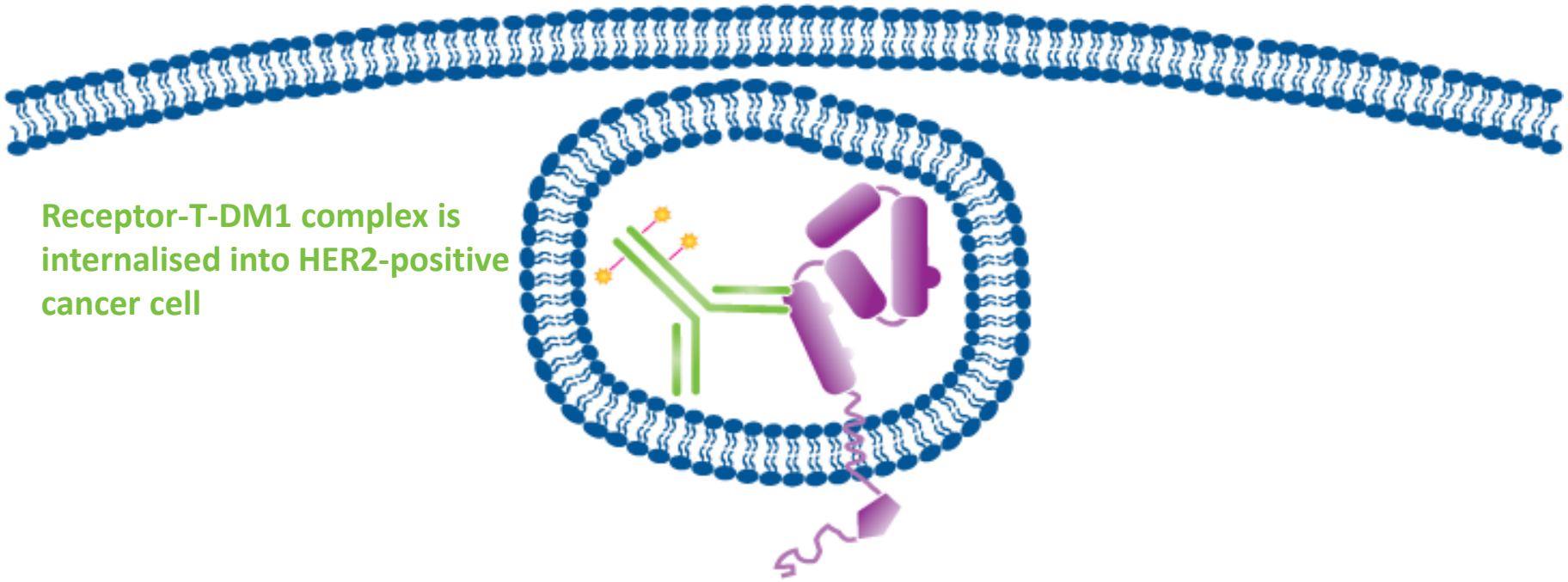
Gerber et al. *mAbs* 2009

T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells



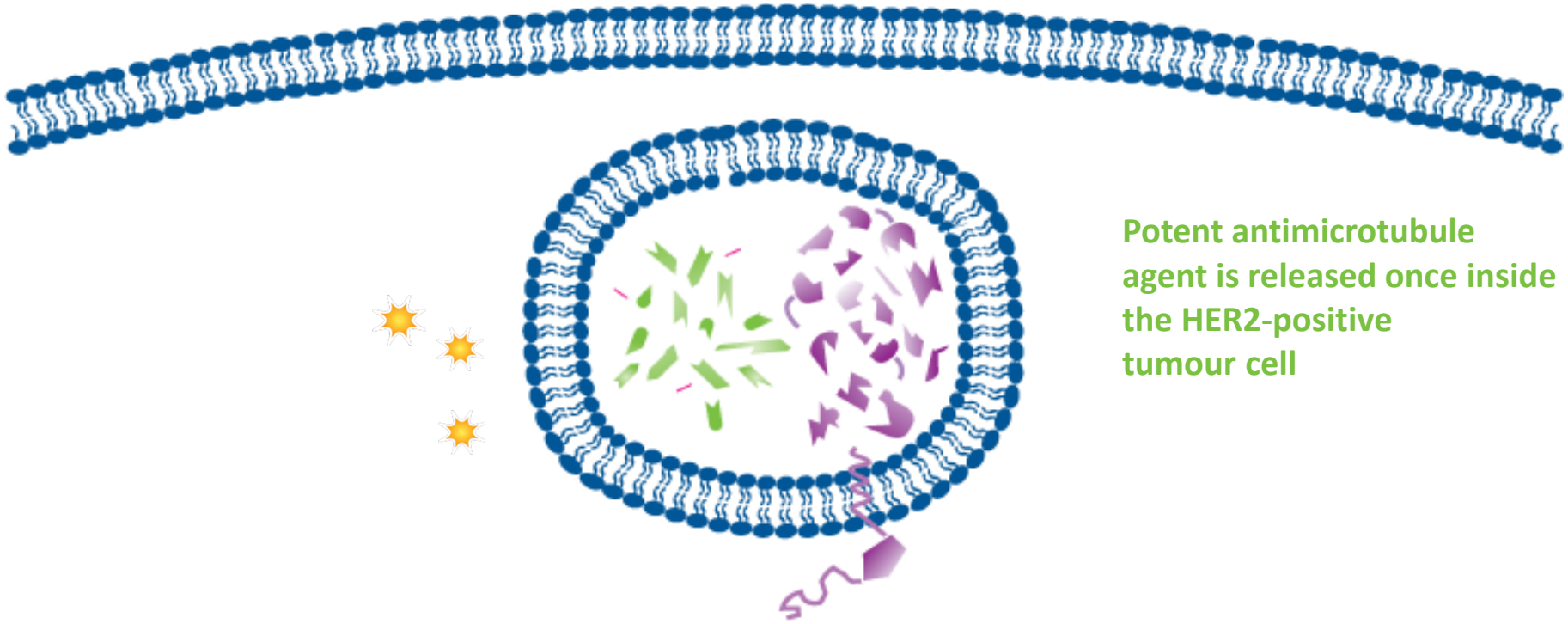
T-DM1 binds to the HER2 protein on cancer cells

T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells



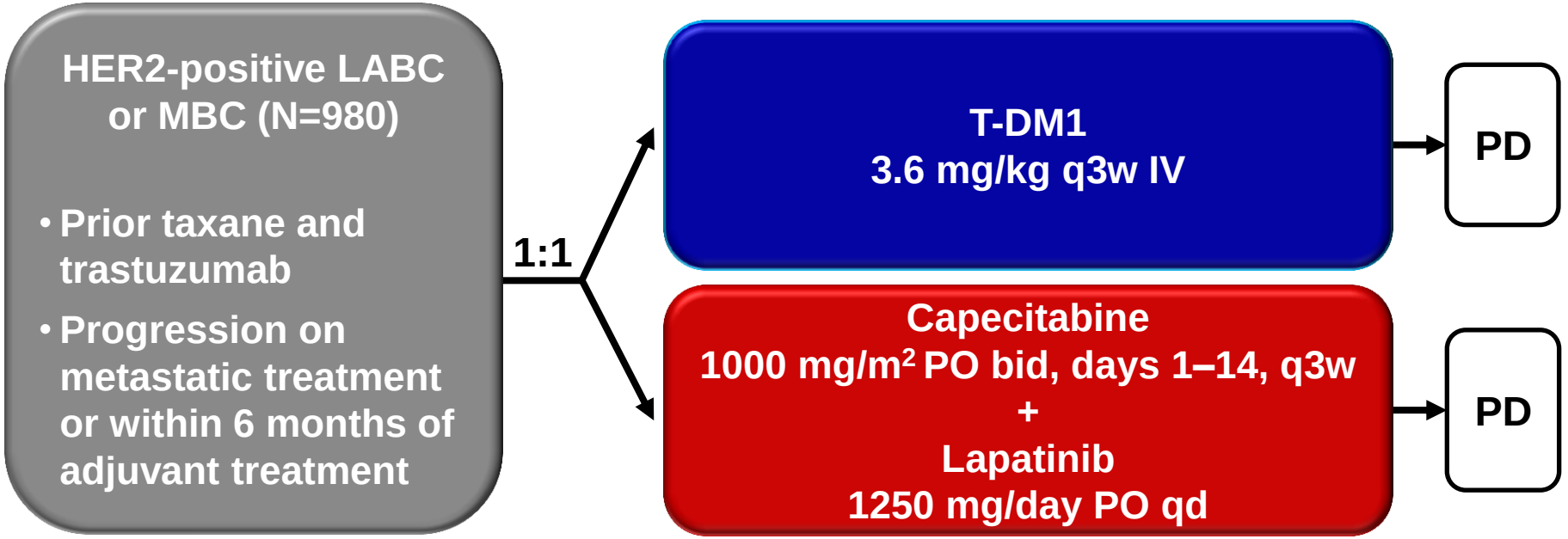
Receptor-T-DM1 complex is internalised into HER2-positive cancer cell

T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells



Potent antimicrotubule agent is released once inside the HER2-positive tumour cell

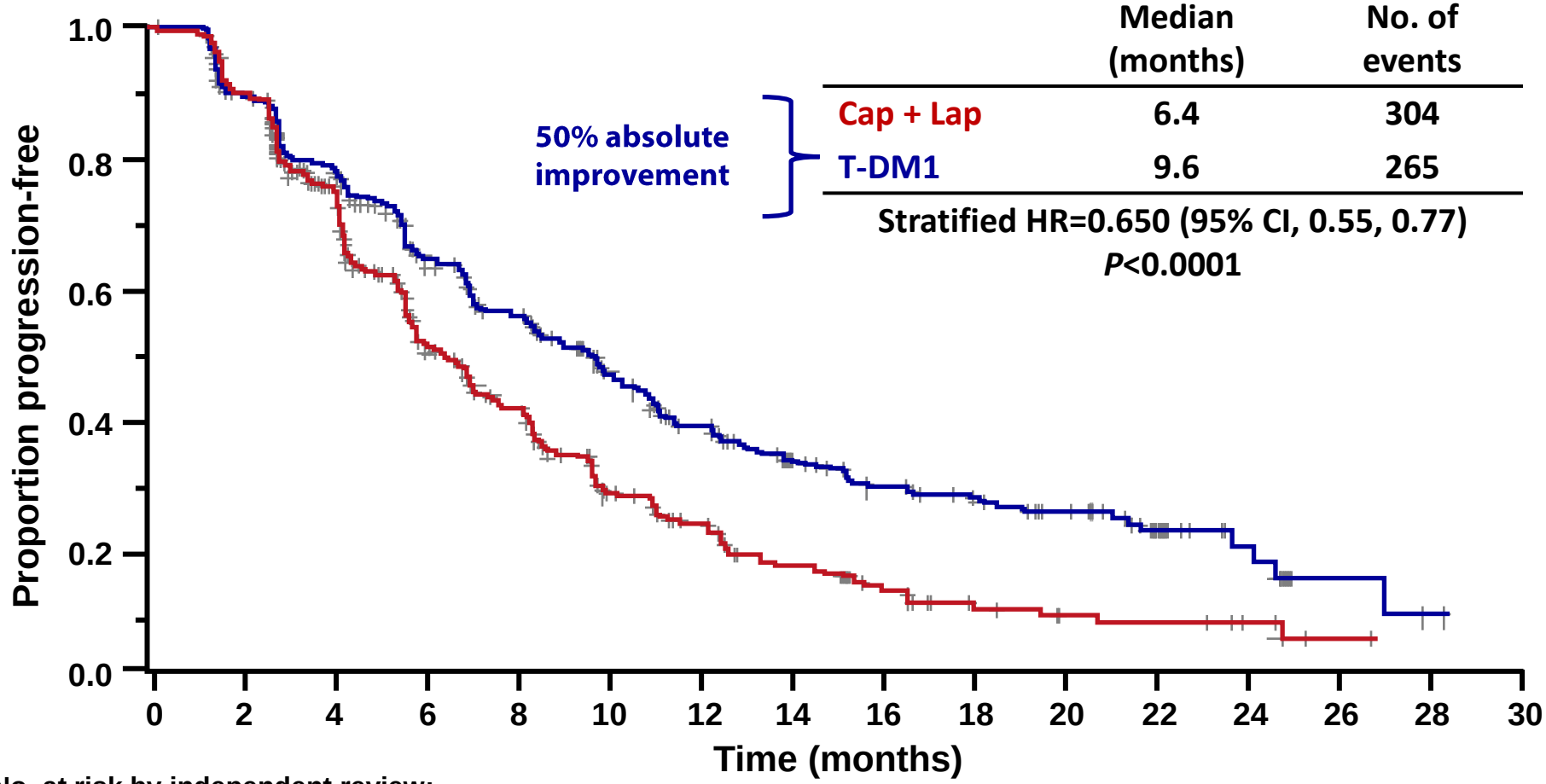
EMILIA Study Design



Primary endpoints: PFS by independent review, OS, and safety

Patients previously treated with taxanes, antracyclines, trastuzumab

Progression-Free Survival



	Median (months)	No. of events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)
P<0.0001

No. at risk by independent review:

Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

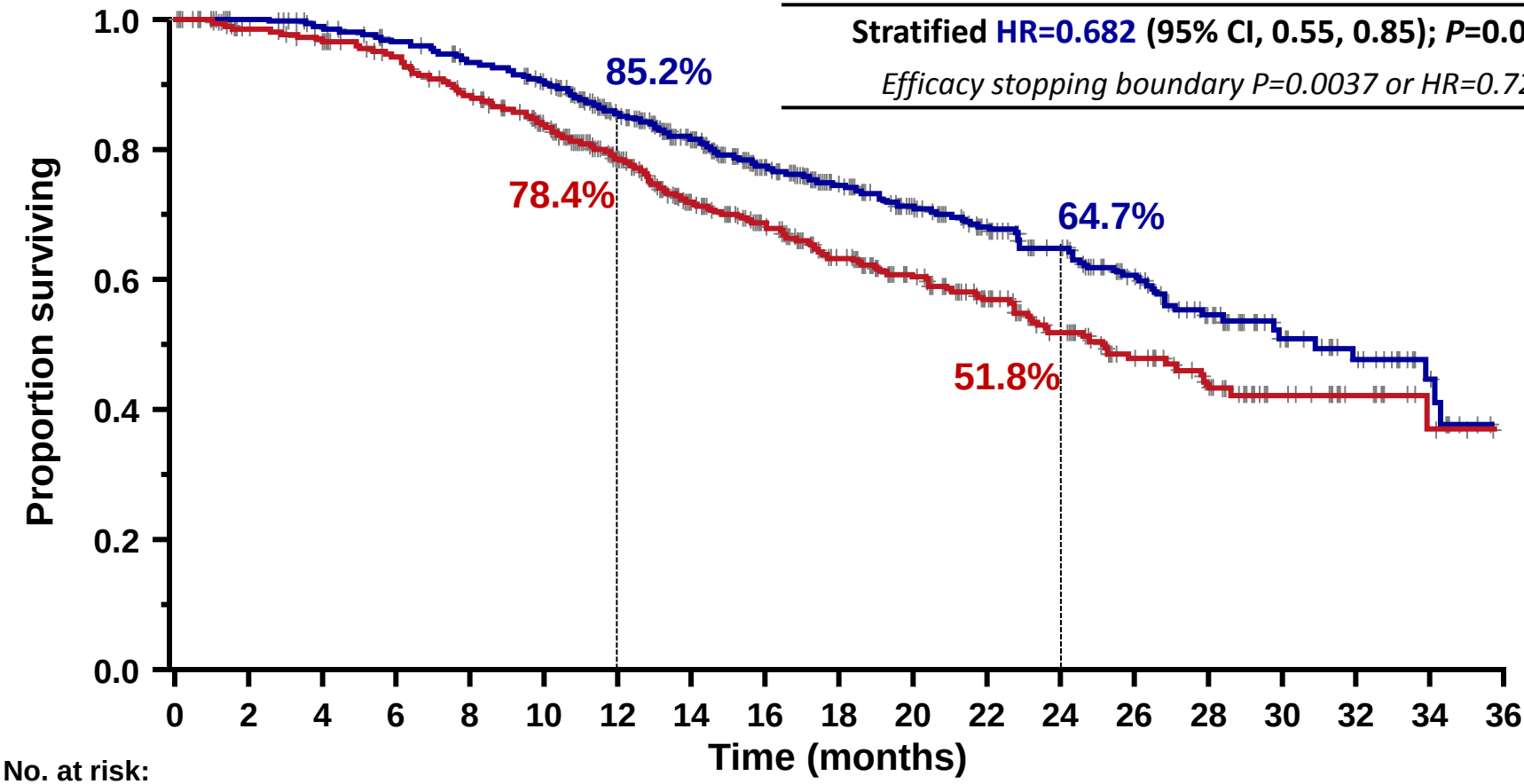
Unstratified HR=0.66 (*P*<0.0001).

Overall Survival

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727



No. at risk:

Cap + Lap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

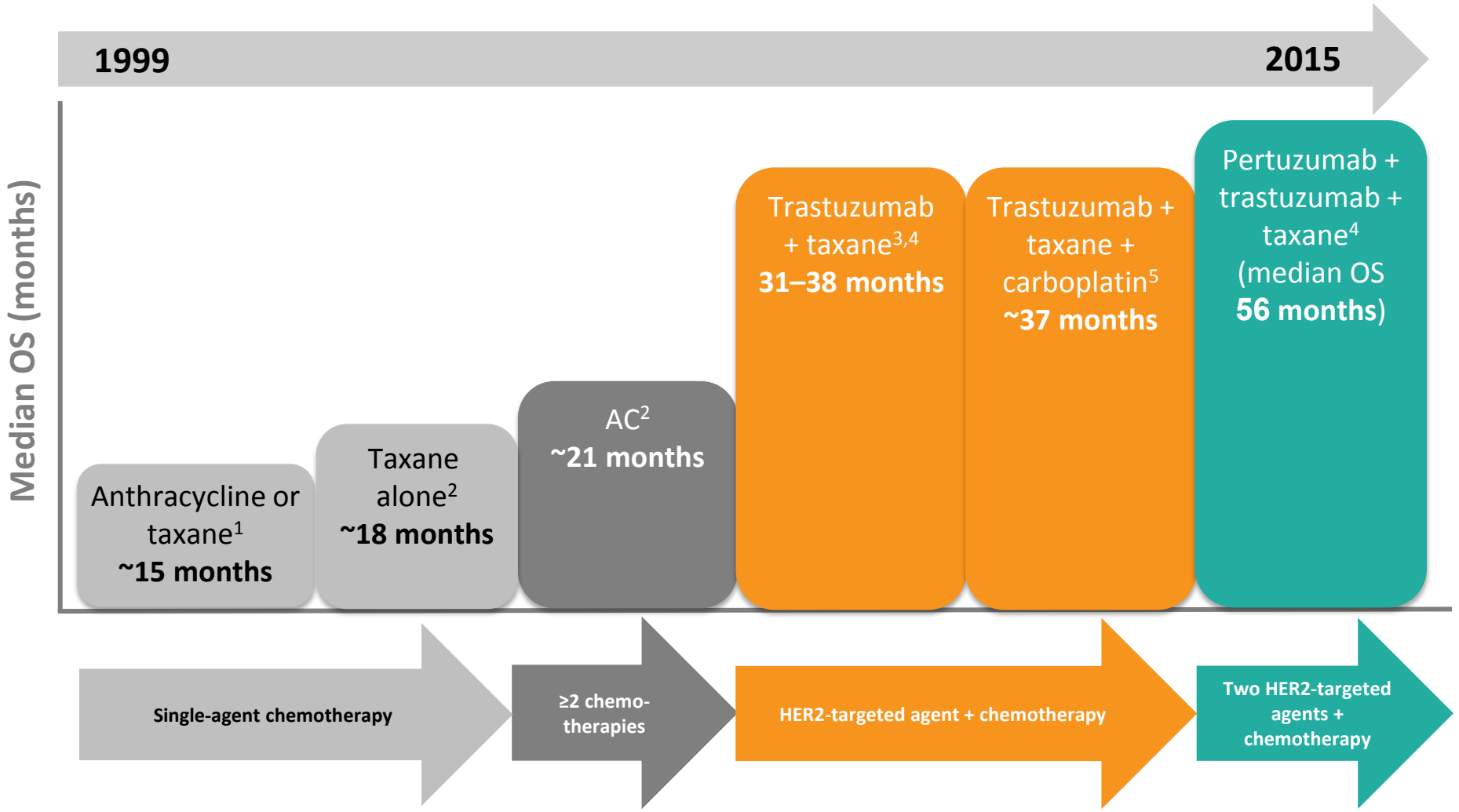
Adverse Events

Grade ≥3 AEs With Incidence ≥2%

	Cap + Lap (n=488)		T-DM1 (n=490)	
Adverse Event	**All Grades, %**	**Grade ≥3, %**	**All Grades, %**	**Grade ≥3, %**
Diarrhea	79.7	**20.7**	23.3	1.6
Hand-foot syndrome	58.0	**16.4**	1.2	0.0
Vomiting	29.3	**4.5**	19.0	0.8
Neutropenia	8.6	**4.3**	5.9	2.0
Hypokalemia	8.6	**4.1**	8.6	2.2
Fatigue	27.9	**3.5**	35.1	2.4
Nausea	44.7	**2.5**	39.2	0.8
Mucosal inflammation	19.1	**2.3**	6.7	0.2
Thrombocytopenia	2.5	0.2	28.0	**12.9**
Increased AST	9.4	0.8	22.4	**4.3**
Increased ALT	8.8	1.4	16.9	**2.9**
Anemia	8.0	1.6	10.4	**2.7**

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Improvement in overall survival with anti-HER2 therapy



Thank you