Advances in Systemic Treatment of Early-Stage Breast Cancer

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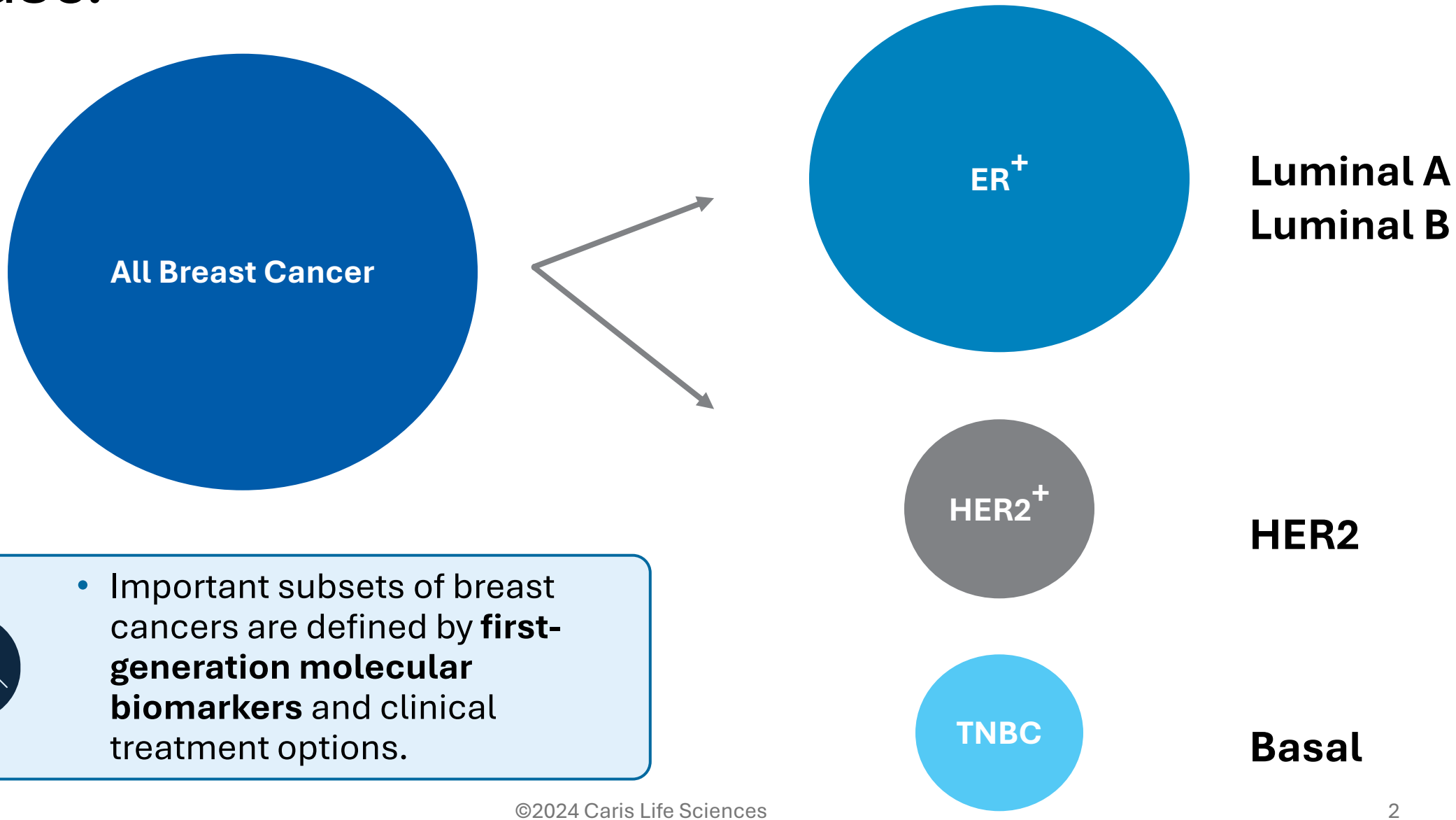
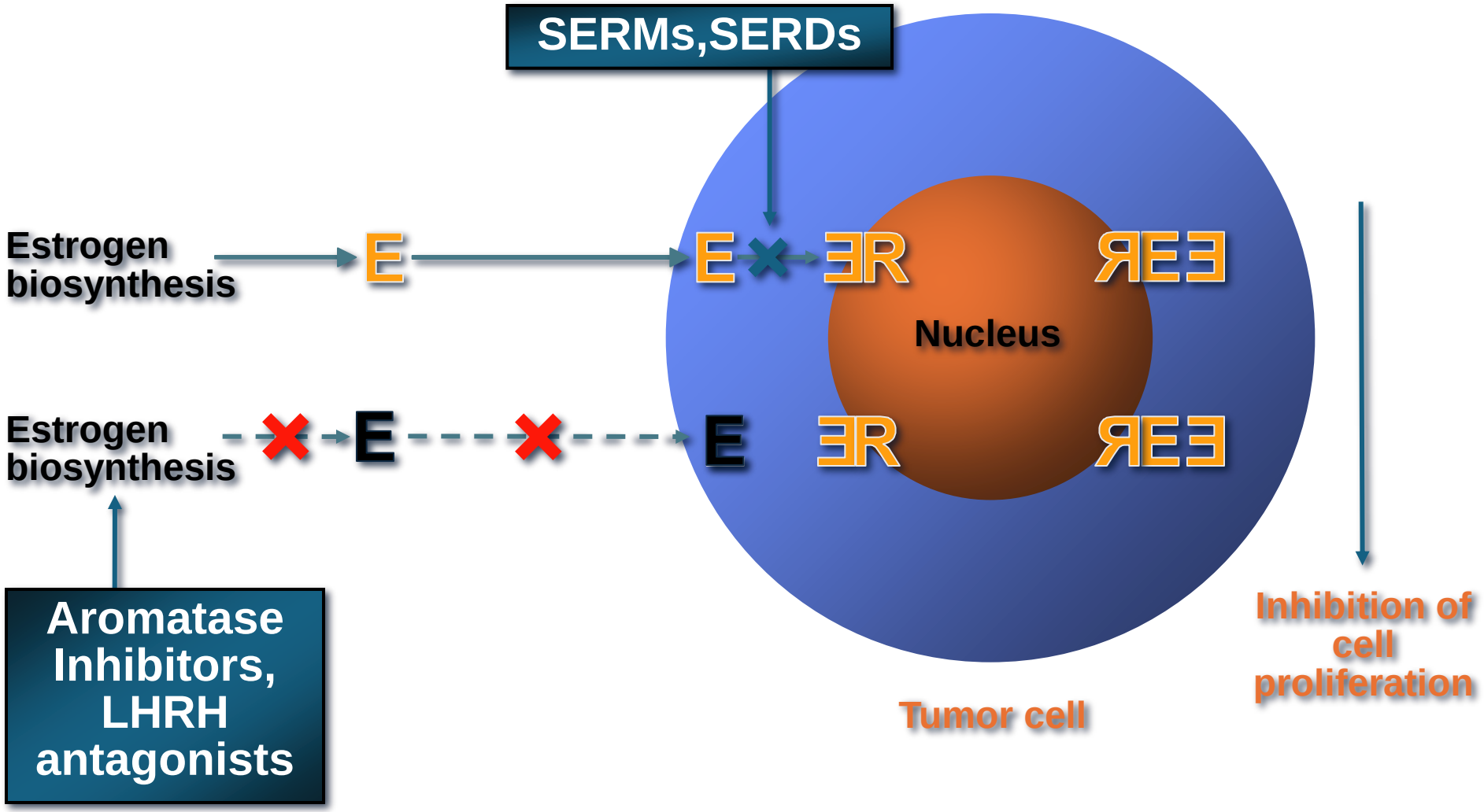
Breast Cancer is a Family of Diseases, Not One Disease.



- Important subsets of breast cancers are defined by **first-generation molecular biomarkers** and clinical treatment options.

Uncontrolled Growth is the Philosophy of Cancer Cells: How Do We Stop Cancer Cell Division?

Inhibition of Estrogen-Dependent Growth



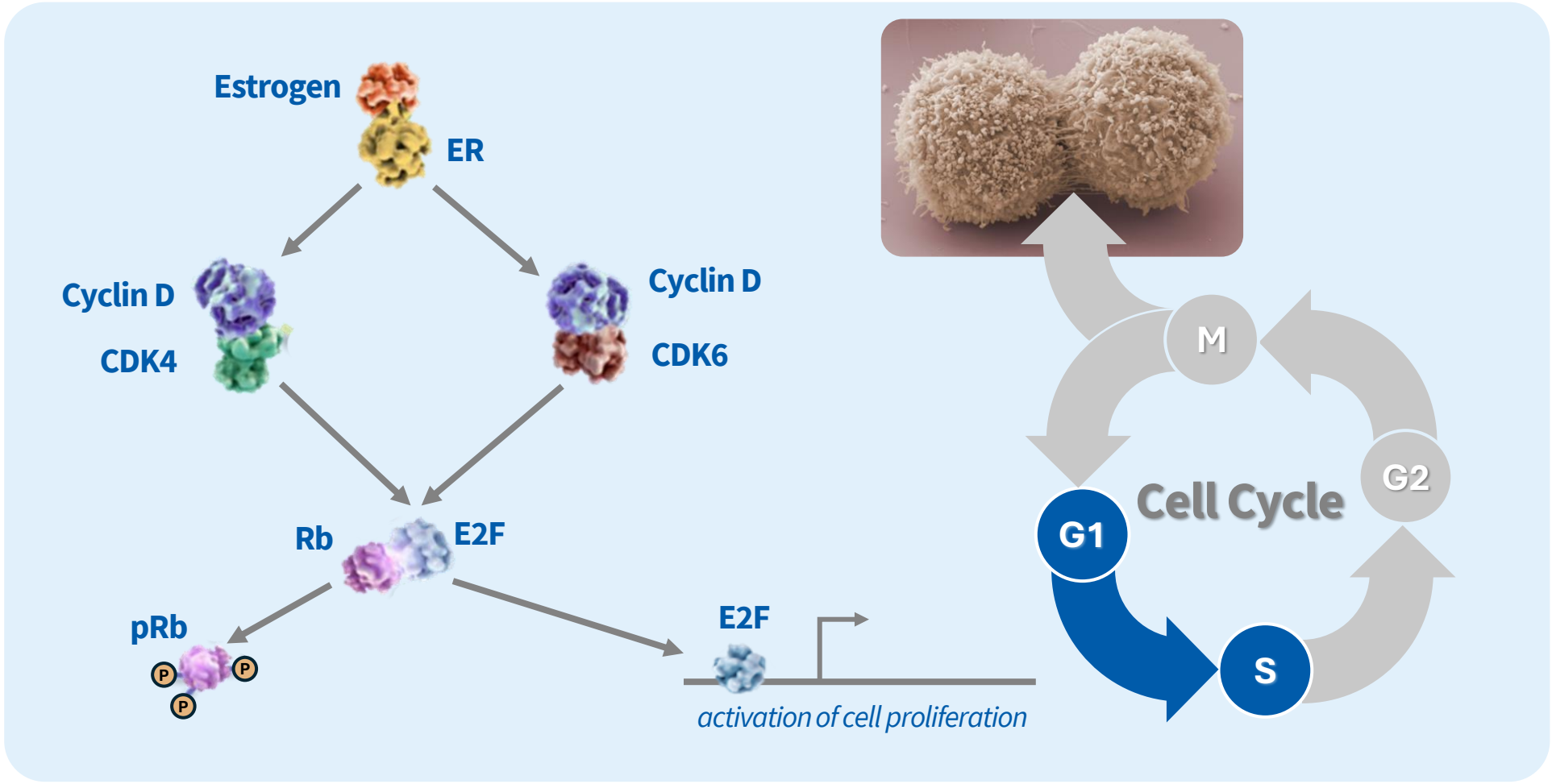
Adjuvant Endocrine Therapy: A Very Brief History

	5 years of tamoxifen vs none: EBCTCG previous meta-analysis[1] (n=10 645)		5 years of aromatase inhibitor vs 5 years of tamoxifen: present meta-analyses* (n=34 882)		5 years of aromatase inhibitor vs none: estimated effects (product of two RRs†)	
	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
Breast cancer recurrence						
During years 0–4	0·53 (0·48–0·57)	2p<0·0001	0·70 (0·64–0·77)	2p<0·0001	0·37 (0·33–0·42)	2p<0·0001
During years 5–9	0·68 (0·60–0·78)	2p<0·0001	0·92 (0·83–1·01)	2p=0·082	0·63 (0·53–0·74)	2p<0·0001
Breast cancer mortality						
During years 0–4	0·71 (0·62–0·80)	2p<0·0001	0·79 (0·67–0·92)	2p=0·002	0·56 (0·46–0·68)	2p<0·0001
During years 5–9	0·66 (0·58–0·75)	2p=0·0001	0·91 (0·80–1·02)	2p=0·12	0·60 (0·50–0·72)	2p<0·0001

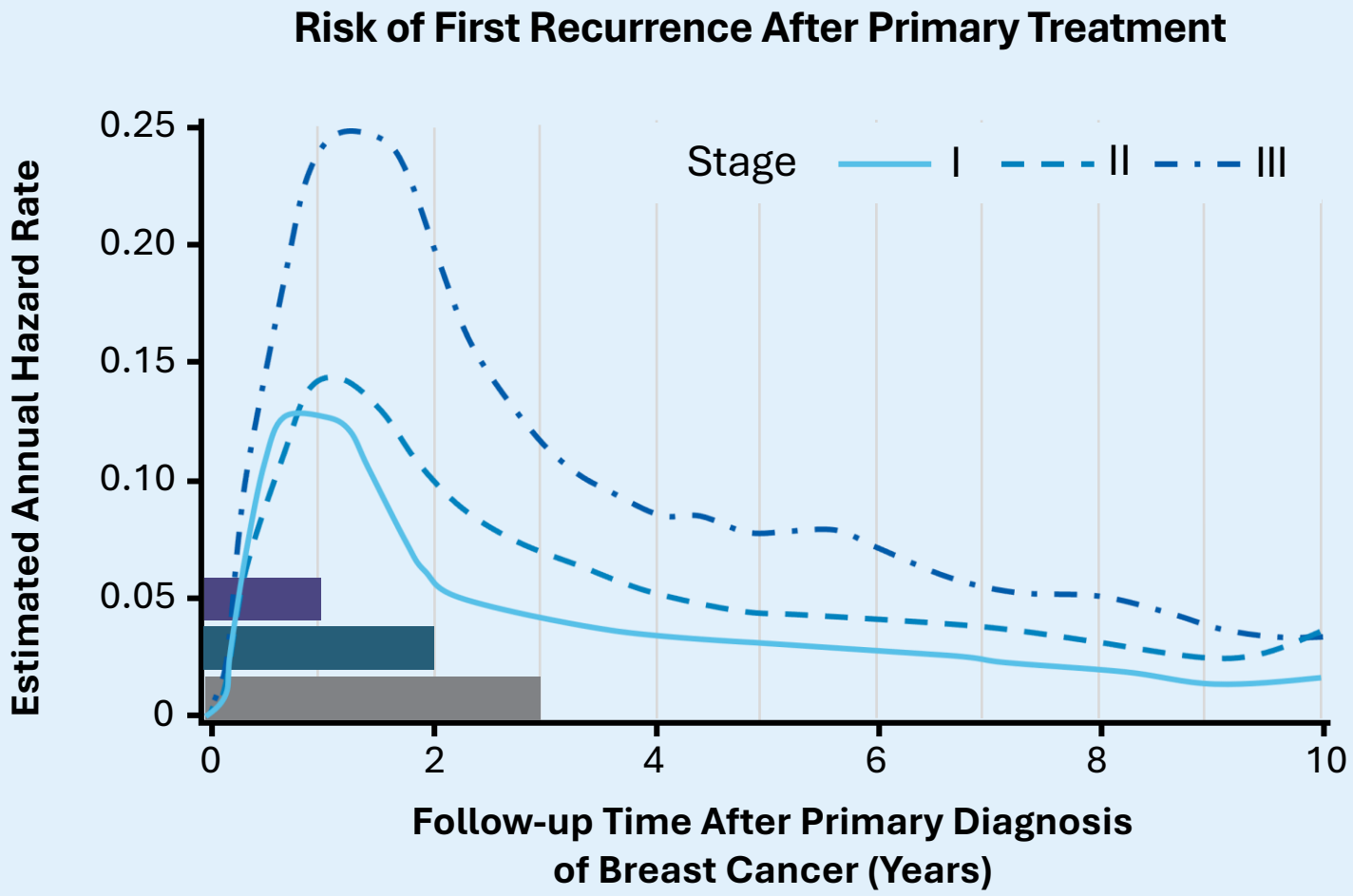
"5 years of an aromatase inhibitor reduces 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen, hence by about 40% (proportionally) compared with no endocrine treatment."

Early Breast Cancer Trialists' Collaborative Group, Lancet 2015; 386: 1341-52

CDK 4/6 Inhibition: Basic Biology



Is There a Role for CDK4/6 Inhibition in Early-Stage HR+ Disease?



1-year follow-up

PENELOPE-B
Palbociclib
After neoadjuvant, high risk

2-year follow-up

monarchE
Abemaciclib
High-risk CPR factors, Ki67

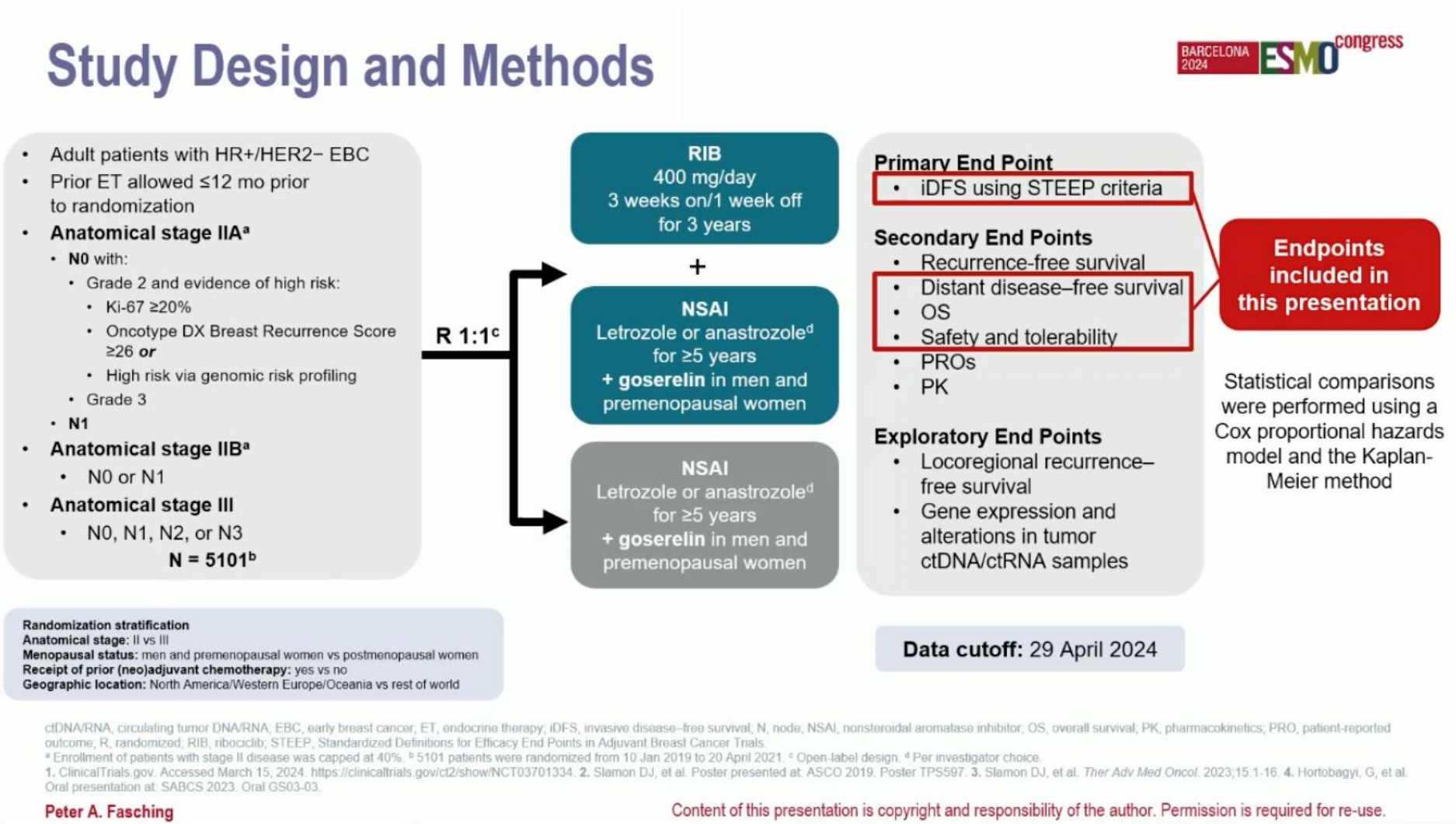
PALLAS
Palbociclib
Stage II, III

3-year follow-up

NATALEE
Ribociclib
Stage II, III

Cheng L, *et al*. (2012) *Cancer Epidemiol Biomarkers Prev* 21, 800-809.

Adjuvant Ribociclib: NATALEE



ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.

1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. 2. Slamon DJ, et al. Poster presented at: ASCO 2019. Poster TPS597. 3. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:1-16. 4. Hortobagyi, G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

Adjuvant Ribociclib: NATALEE

iDFS in ITT Population

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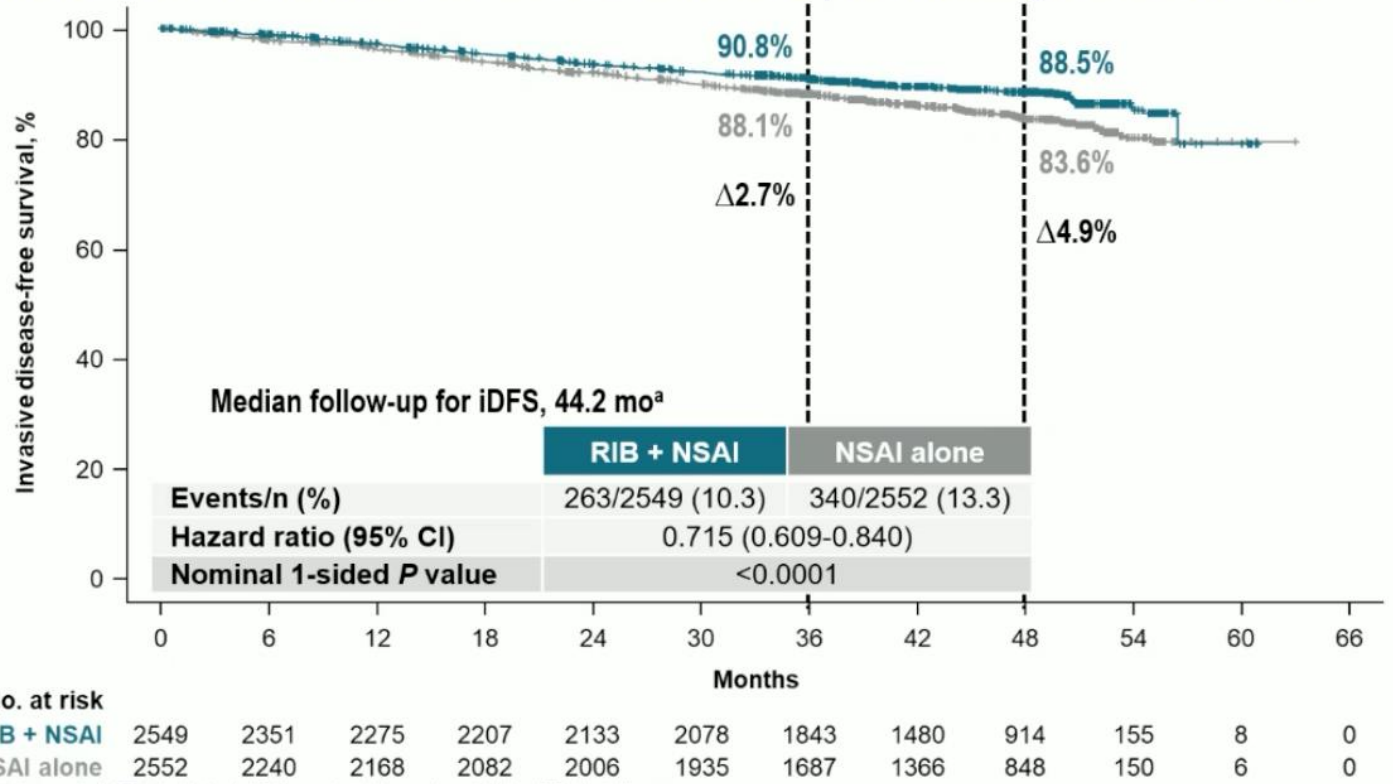
Significant iDFS benefit with RIB + NSAI after the planned 3-year treatment



Median follow-up for iDFS, 44.2 mo[a]

	RIB + NSAI	NSAI alone
Events/n (%)	263/2549 (10.3)	340/2552 (13.3)
Hazard ratio (95% CI)	0.715 (0.609-0.840)	
Nominal 1-sided *P* value	<0.0001	

No. at risk

RIB + NSAI	2549	2351	2275	2207	2133	2078	1843	1480	914	155	8	0
NSAI alone	2552	2240	2168	2082	2006	1935	1687	1366	848	150	6	0

iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

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Adjuvant Ribociclib: DDFS and OS Results

Key Secondary Efficacy Endpoints

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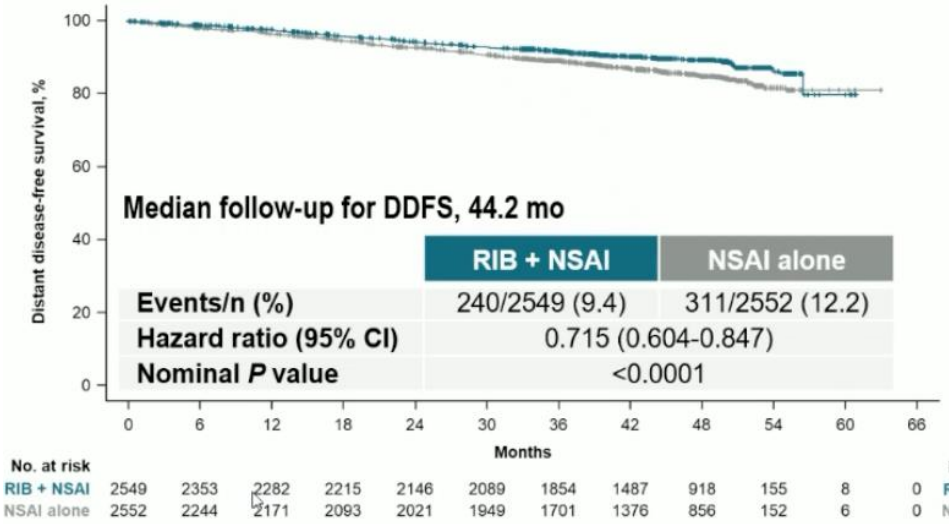
RIB + NSAI continued to improve DDFS and showed a positive trend for OS

DDFS

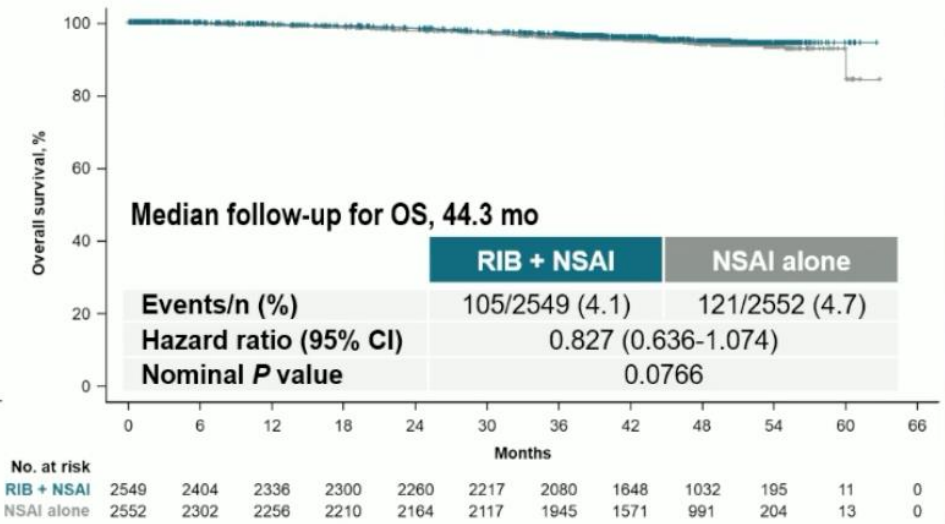


Median follow-up for DDFS, 44.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	240/2549 (9.4)	311/2552 (12.2)
Hazard ratio (95% CI)	0.715 (0.604-0.847)	
Nominal *P* value	<0.0001	

No. at risk												
RIB + NSAI	2549	2353	2282	2215	2146	2089	1854	1487	918	155	8	0
NSAI alone	2552	2244	2171	2093	2021	1949	1701	1376	856	152	6	0

OS



Median follow-up for OS, 44.3 mo

	RIB + NSAI	NSAI alone
Events/n (%)	105/2549 (4.1)	121/2552 (4.7)
Hazard ratio (95% CI)	0.827 (0.636-1.074)	
Nominal *P* value	0.0766	

No. at risk												
RIB + NSAI	2549	2404	2336	2300	2260	2217	2080	1648	1032	195	11	0
NSAI alone	2552	2302	2256	2210	2164	2117	1945	1571	991	204	13	0

DDFS, distant disease–free survival; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

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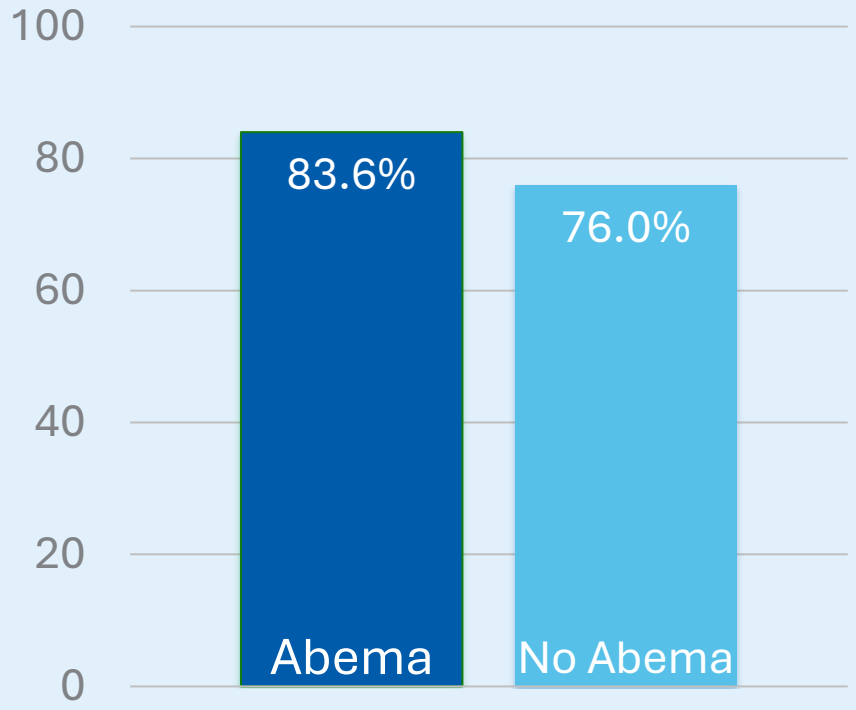
monarchE and NATALEE: Invasive Disease-Free Survival (IDFS)

monarchE: 5-Year IDFS (n=5,607)

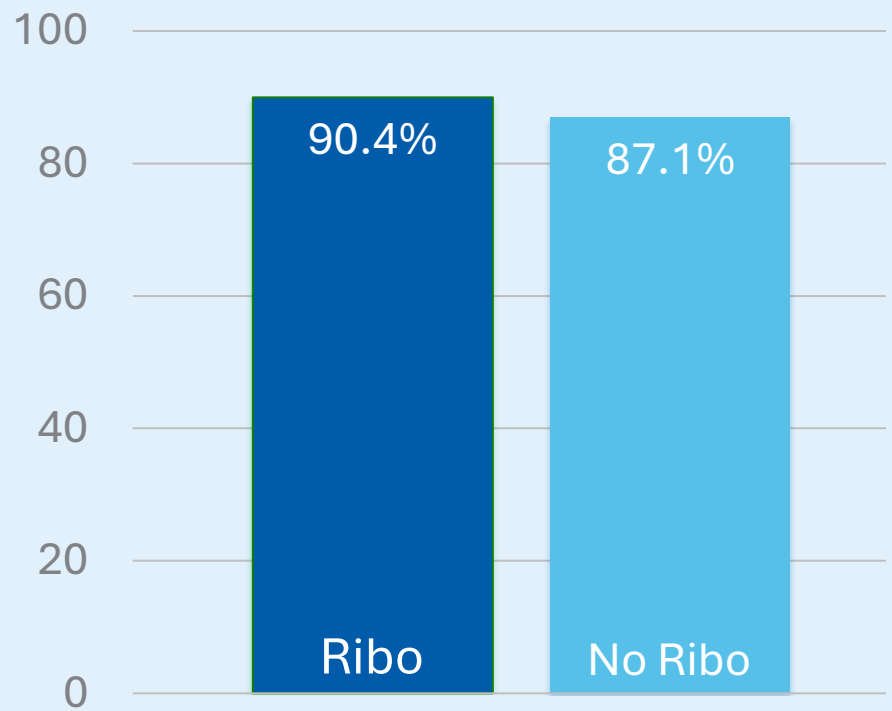


Δ 7.6% (HR: 0.68, 0.60-0.77, p<0.001)

5-Year DRFS: Δ 6.7%

Johnston SRD, *et al*. (2023) *Lancet Oncol* 24, 77-90. NCT03155997.

NATALEE: 3-Year IDFS (n=5,101)



Δ 3.3% (HR: 0.75, 0.62-0.91, p=0.0014)

3-Year DRFS: Δ 2.2%

Slamon DJ, *et al*. (2023) *Ther Adv Med Oncol* 15, 17588359231178125. NCT03701334.

DRFS = Distant Relapse-Free Survival

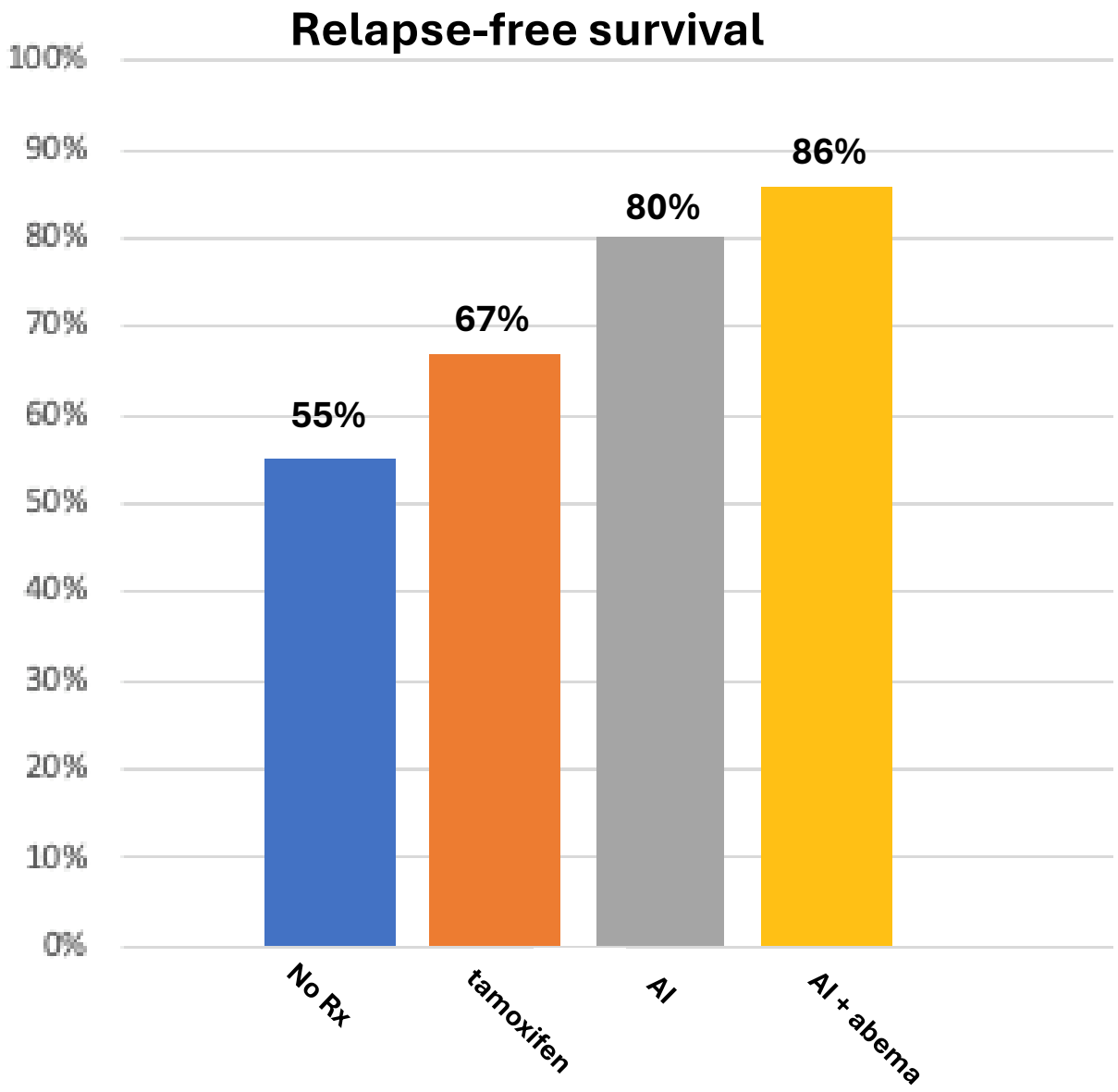
monarchE and NATALEE: Tolerability

≥ Grade 3 AE	monarchE		NATALEE	
	Abema	No Abema	Ribo	No Ribo
Neutropenia	19.7%	0.8%	43.8%	0.8%
Liver-Related AE	1.8-2.6%	0.5-0.7%	8.3%	1.5%
QTC interval Prolongation	N/A	N/A	1.0%	0.5%
Diarrhea	7.8%	0.2%	0.6%	0.1%
Fatigue	2.9%	0.1%	0.7%	0.2%
VTE	1.3%	0.3%	0.6%	0.2%

Discontinued due to AE:	Abemaciclib: 18.5%	Ribociclib: 19%
Similar discontinuation rate due to AEs…but for different AEs.		
QOL tools did not capture any significant difference in QOL compared to ET alone.		

Johnston SRD, *et al*. (2023) *Lancet Oncol* 24, 77-90. NCT03155997.
Slamon DJ, *et al*. (2023) *Ther Adv Med Oncol* 15, 17588359231178125. NCT03701334.

Impact in EBC of Incrementally Improved Endocrine Therapy

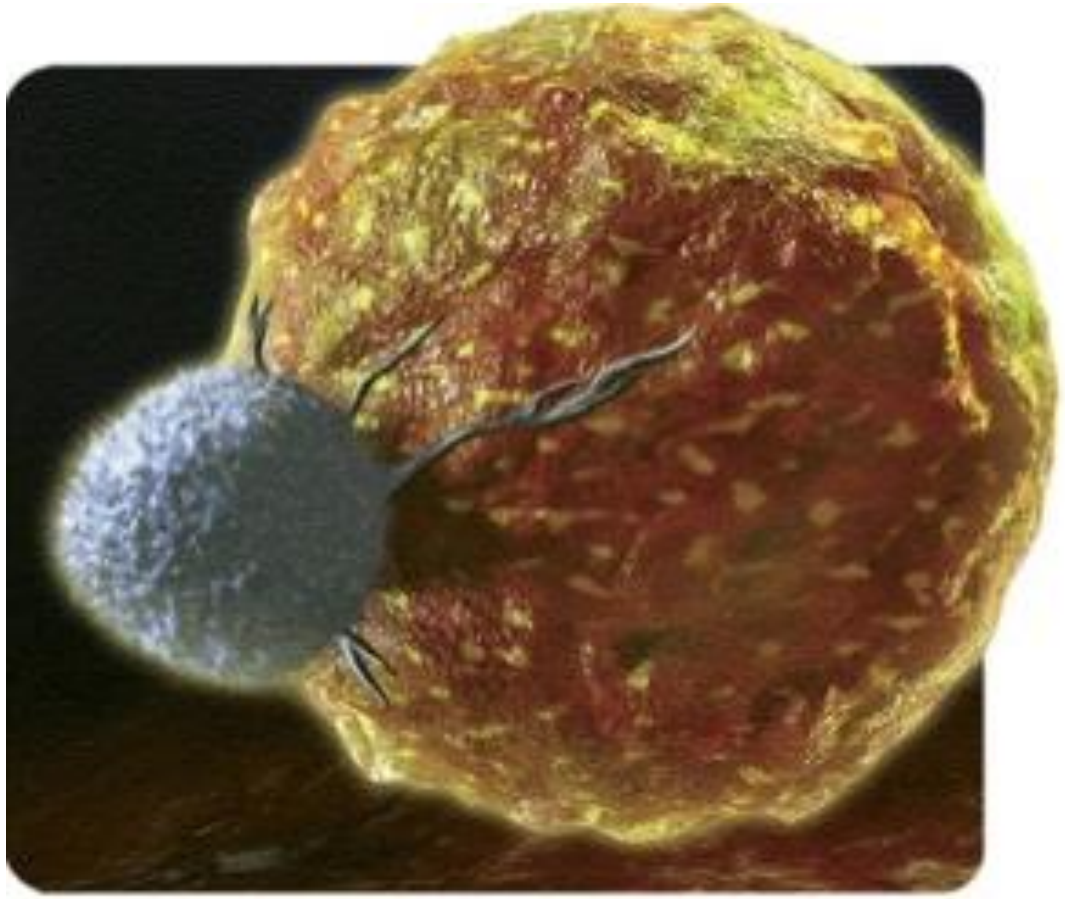


- **ET duration is 5-10y (2y for abemaciclib, 3y for ribociclib)**
- **Toxicity an issue, e.g. abemaciclib - low white cells, diarrhea, ET – musculoskeletal, menopausal**

<u>Beyond ER, we do not have a predictive biomarker for tam, AI, or CDK4/6i.</u>

We escalate on clinical features, and have little opportunity to de-escalate ET.

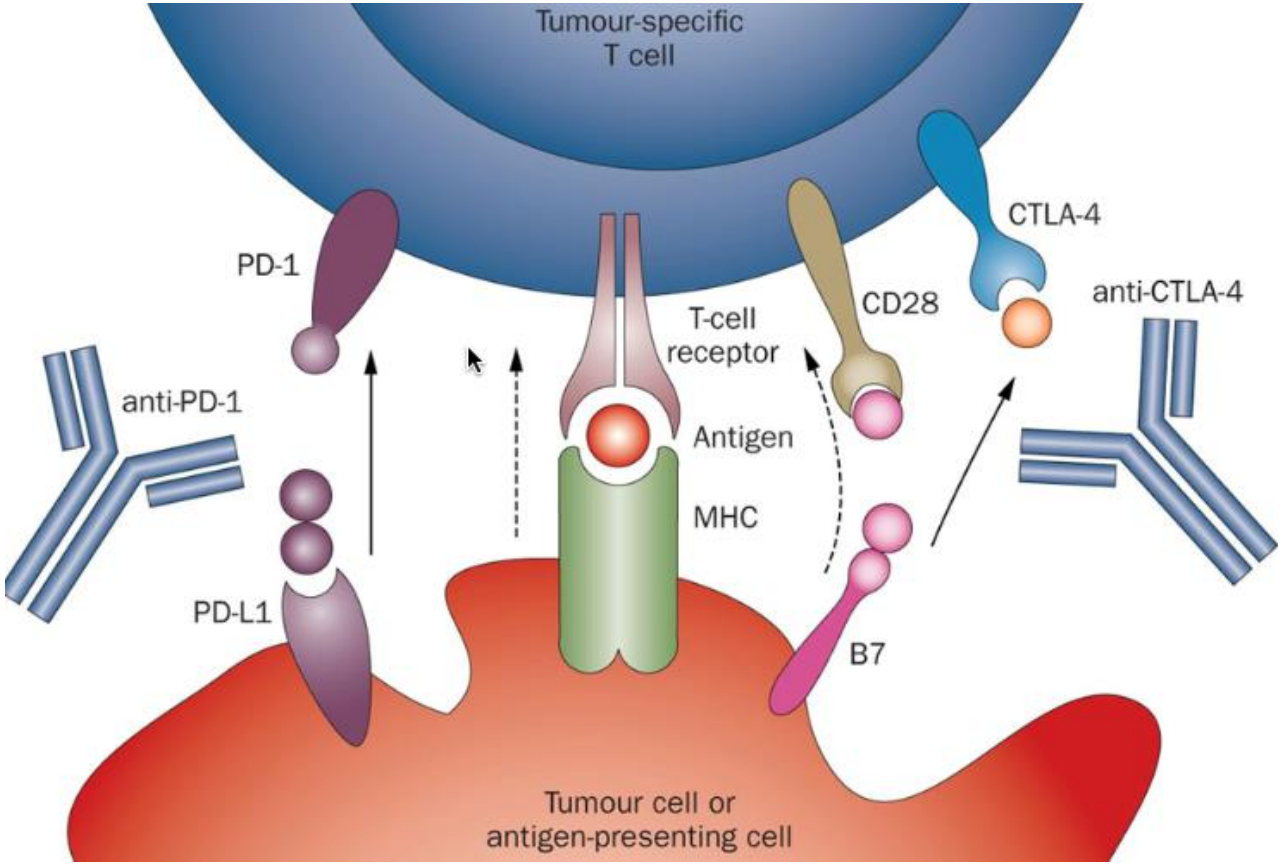
T Cell Attacking a Cancer Cell



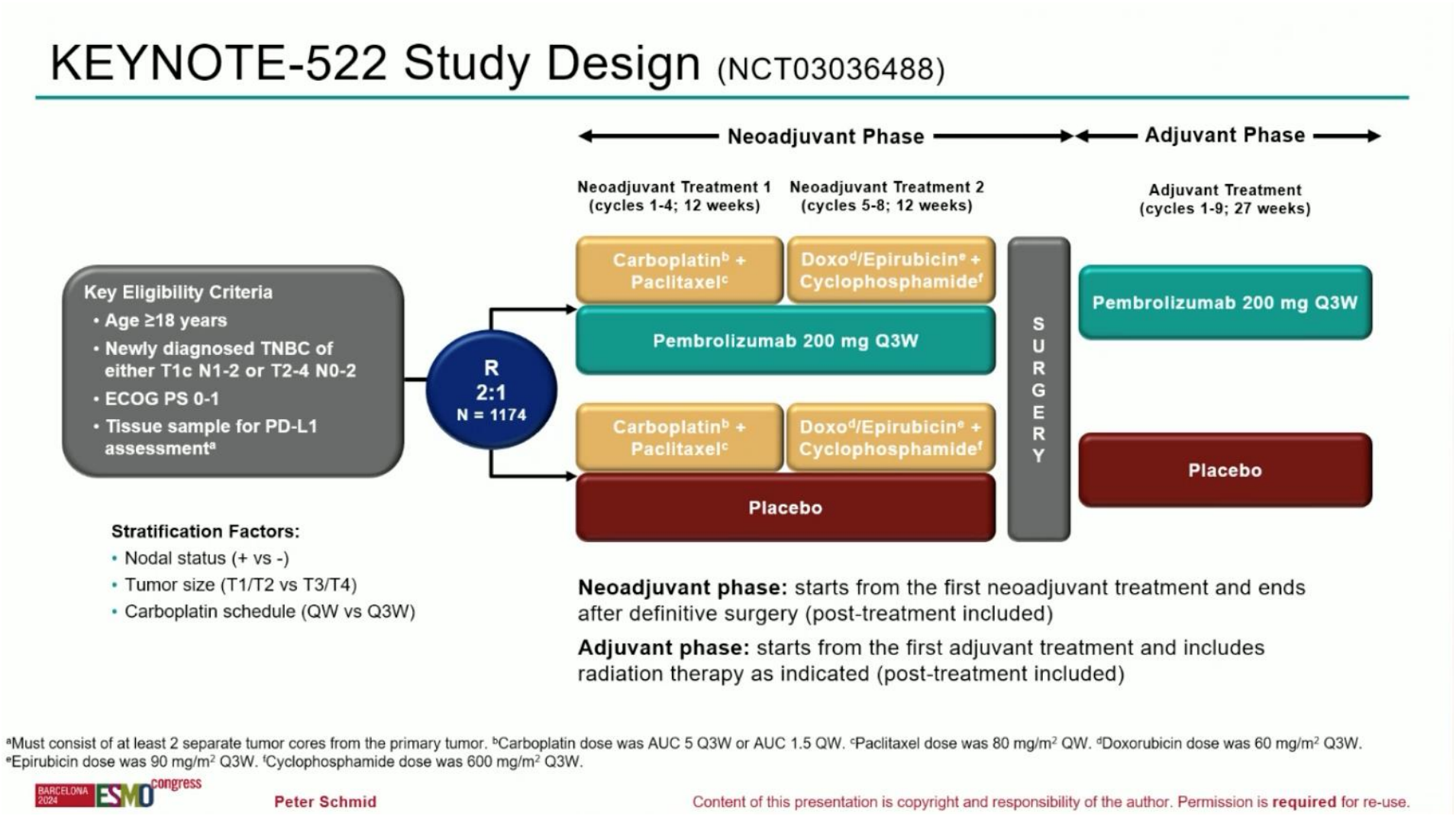
Why Doesn’t the Immune System do it’s Job?

What Cancer Cells Do To T Cells:
These aren’t the droids you’re looking for

Checkpoint Inhibition: These ARE the droids you're looking for



Neoadjuvant Checkpoint Inhibition in Triple-Negative Breast Cancer



[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

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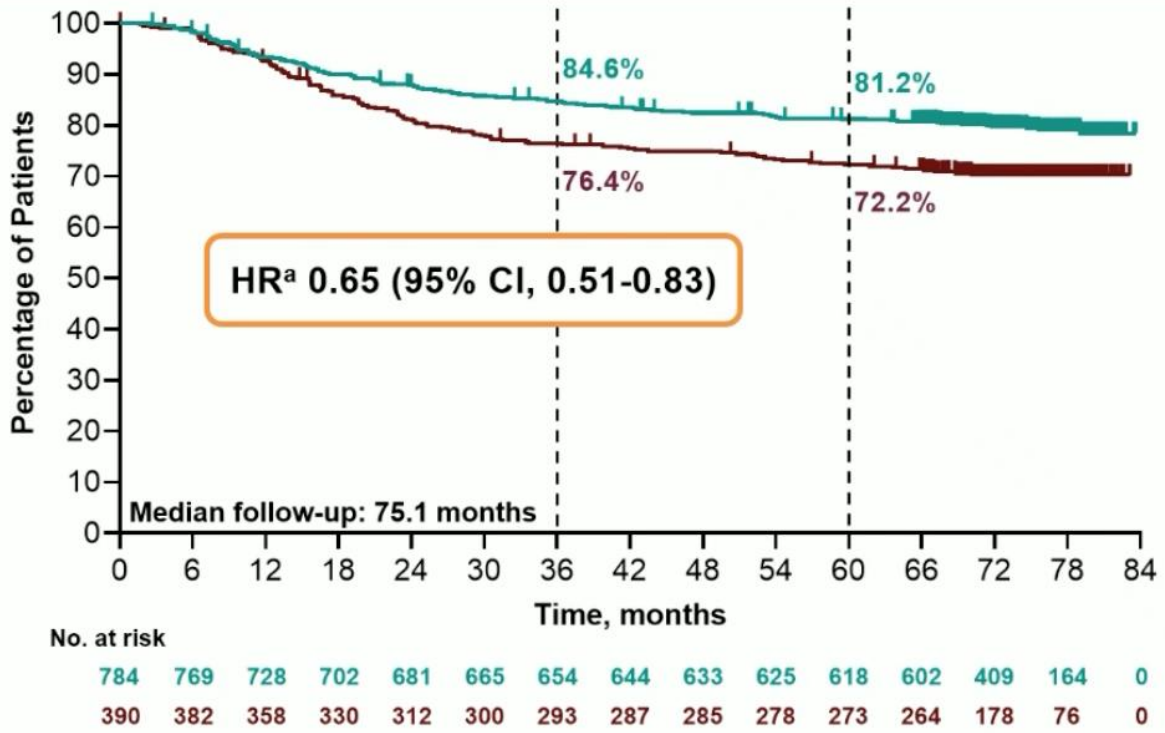
Neoadjuvant Checkpoint Inhibition in Triple-Negative Breast Cancer

Updated Event-Free Survival

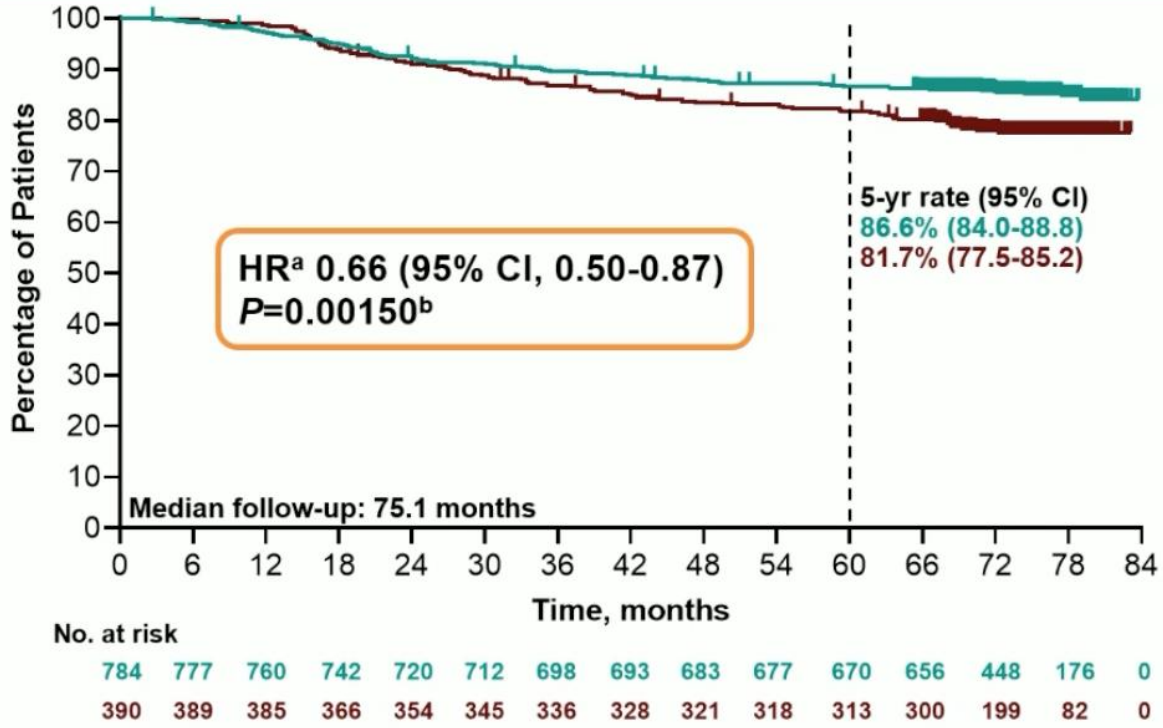


	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 22, 2024.

Neoadjuvant Checkpoint Inhibition in Triple-Negative Breast Cancer

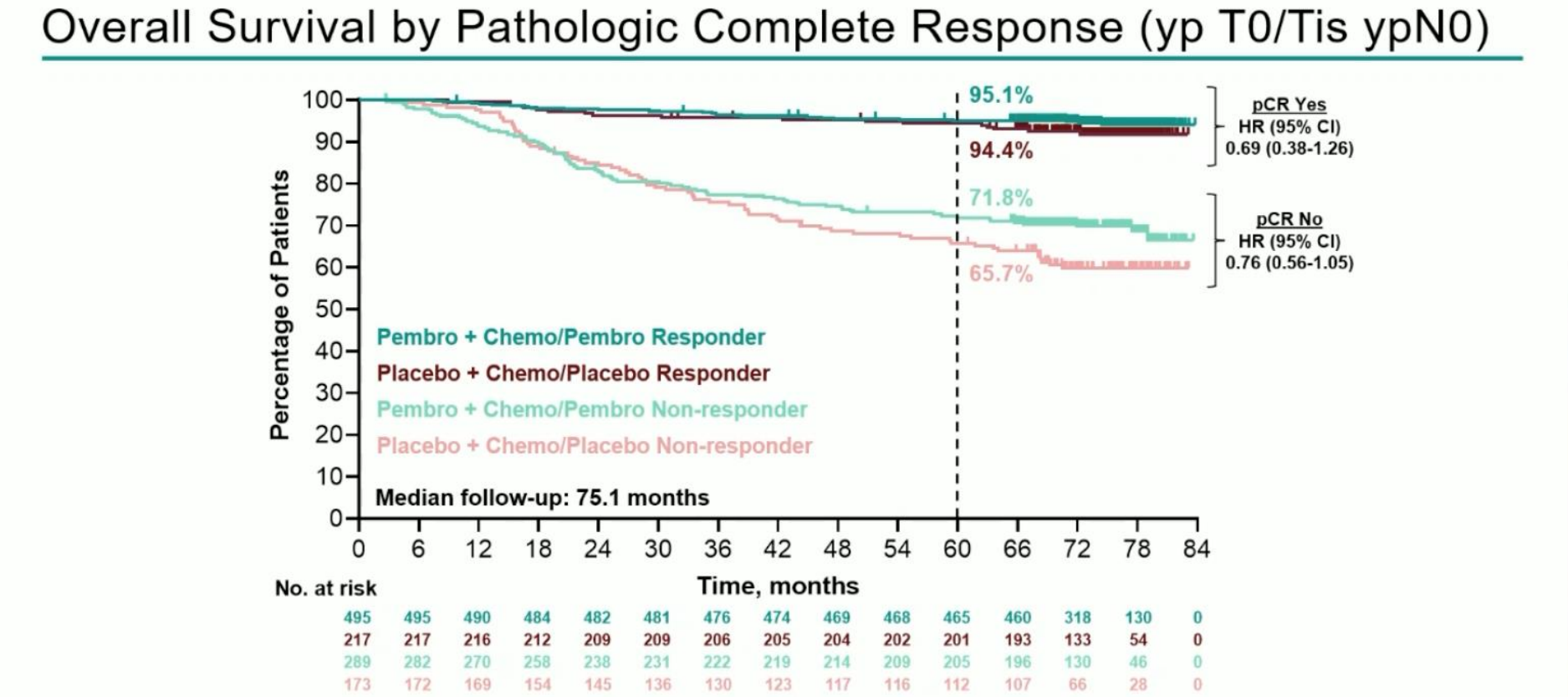
Key Secondary Endpoint: Overall Survival



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

[a]The unstratified piecewise HR was 0.87 (95% CI, 0.57-1.32) before the 2-year follow-up and 0.51 (95% CI, 0.35-0.75) afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis.
Data cutoff date: March 22, 2024.

Neoadjuvant Checkpoint Inhibition in Triple-Negative Breast Cancer



This is a non-randomized subgroup analysis based on the post-treatment outcome of pCR and HRs should therefore be interpreted with caution. Data cutoff date: March 22, 2024.

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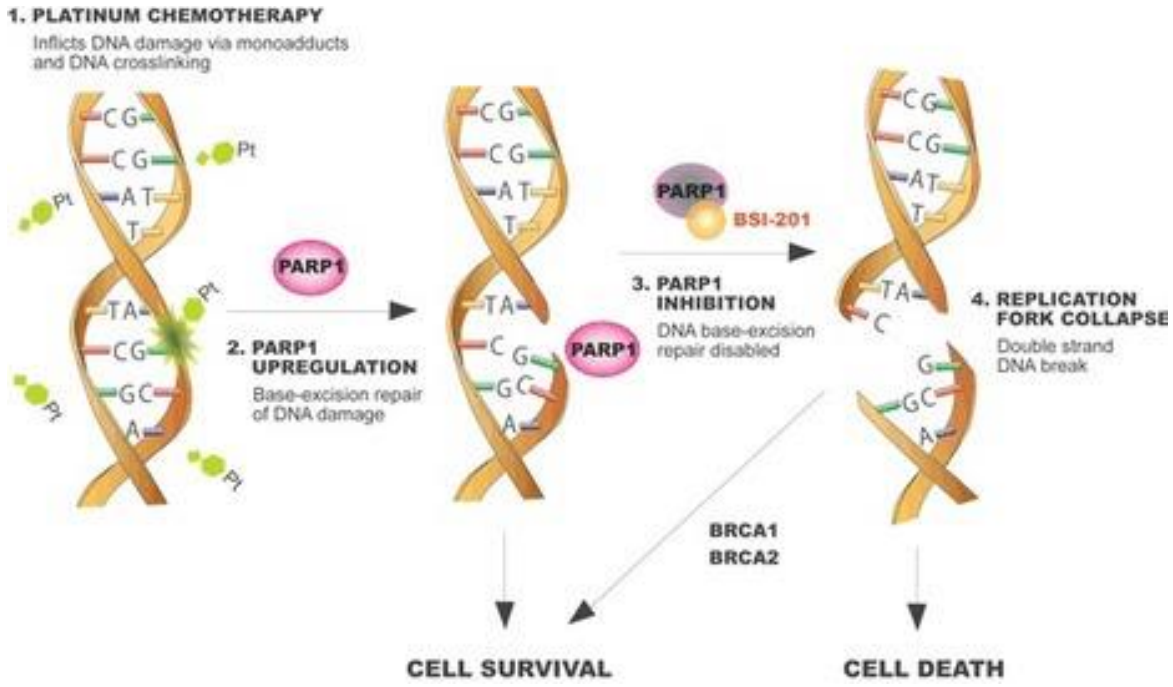
PARP Inhibition for BRCA-mutant cancers



OlympiA: Adjuvant Olaparib Trial Schema

- Local genetic testing or on-study central screening
  (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles Adjuvant Chemotherapy** → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

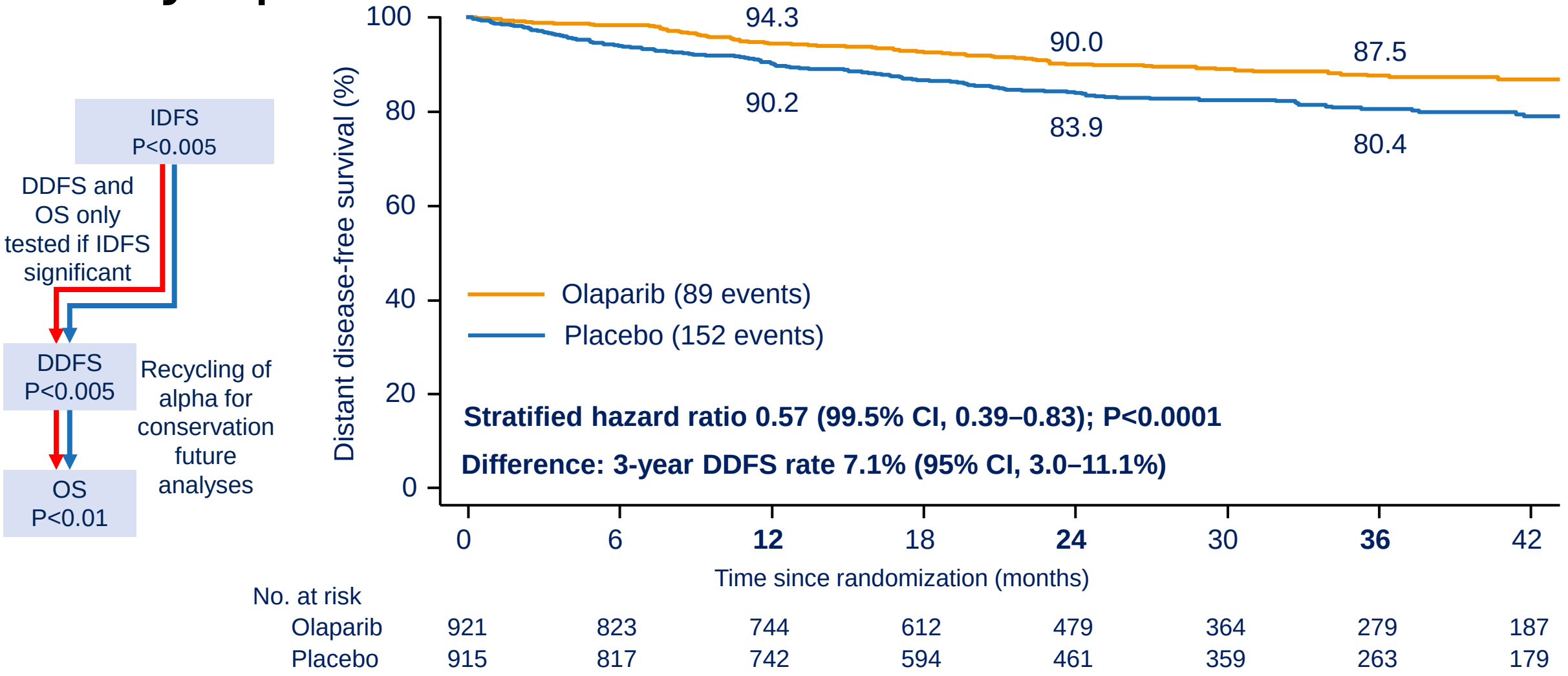
Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

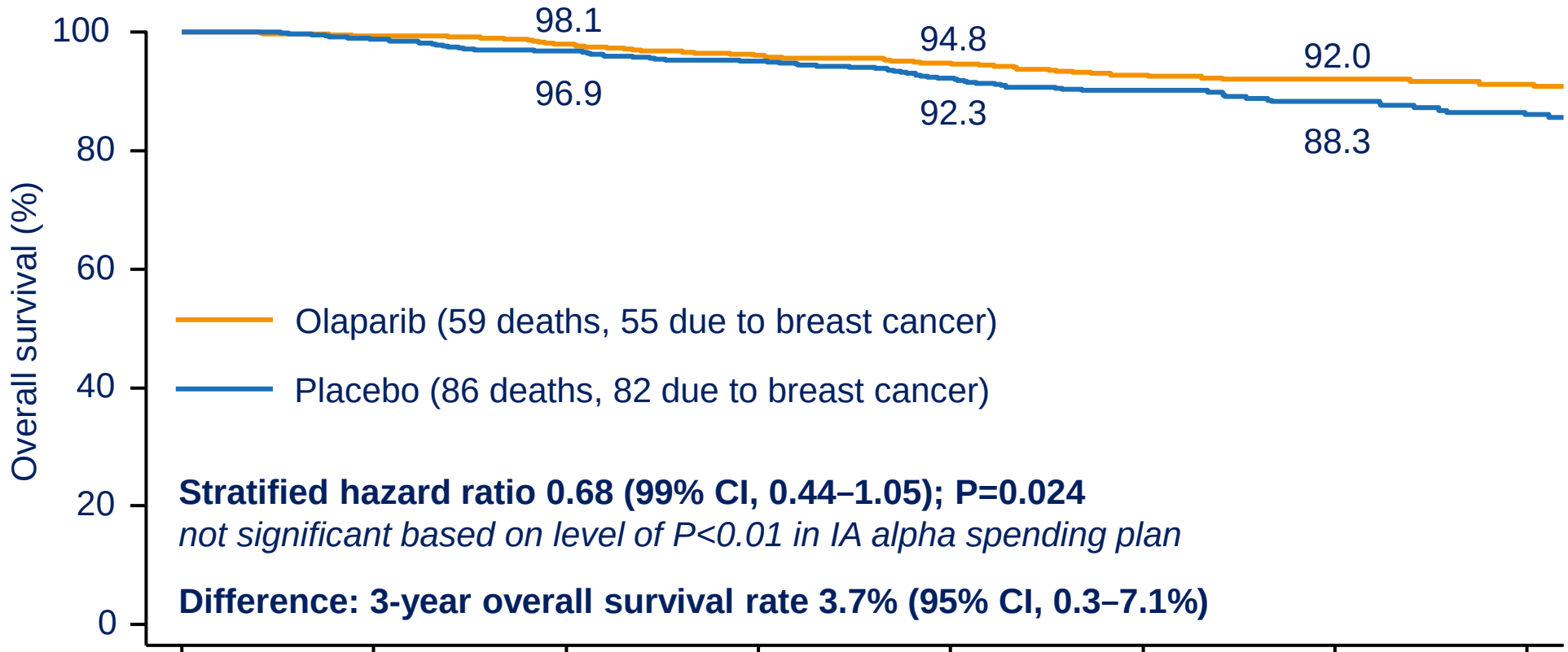
Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

OlympiA: Distant Disease-Free Survival

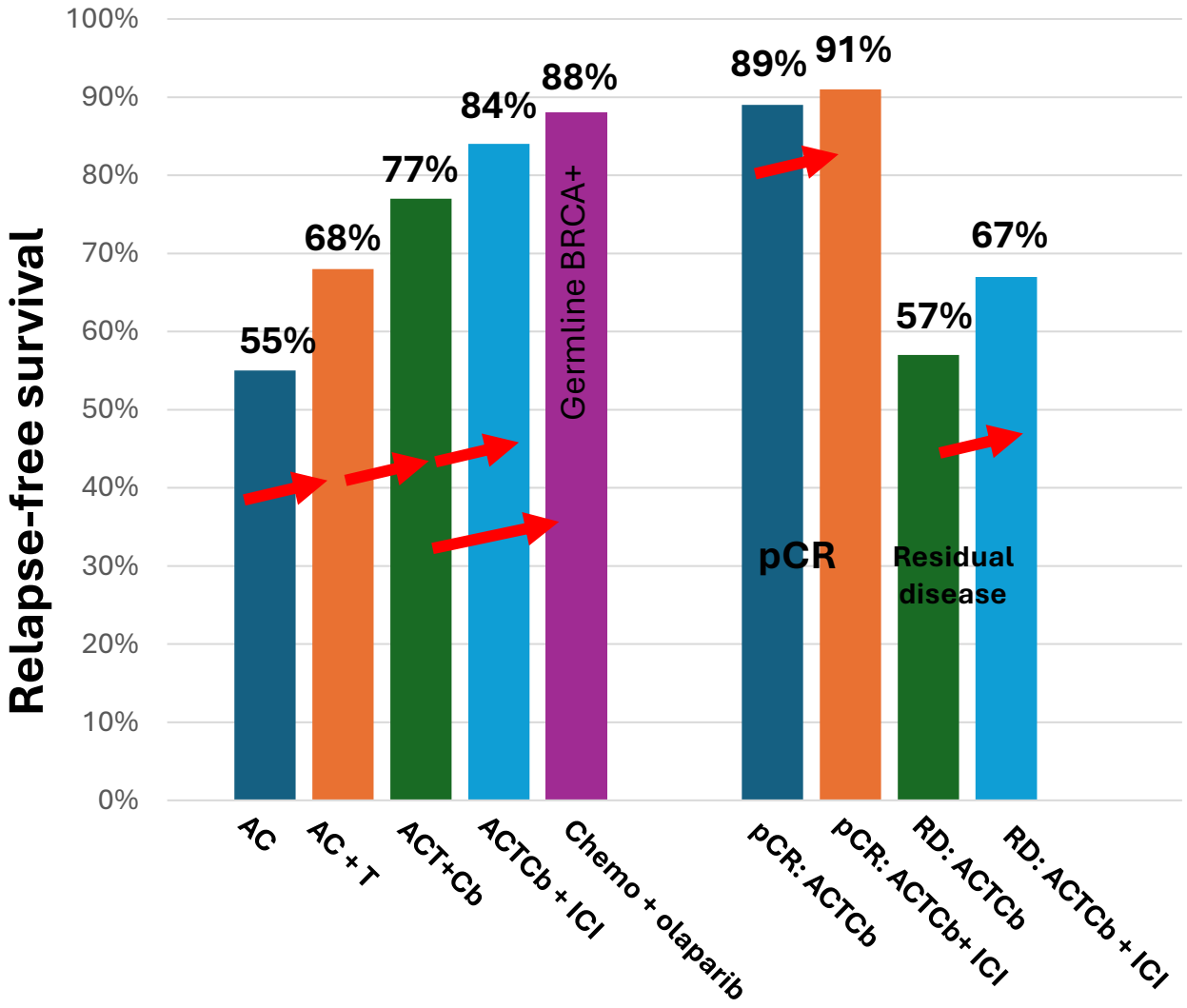


OlympiA: Overall Survival



No. at risk								
Olaparib	921	856	801	659	531	400	310	205
Placebo	915	865	801	659	516	397	292	199

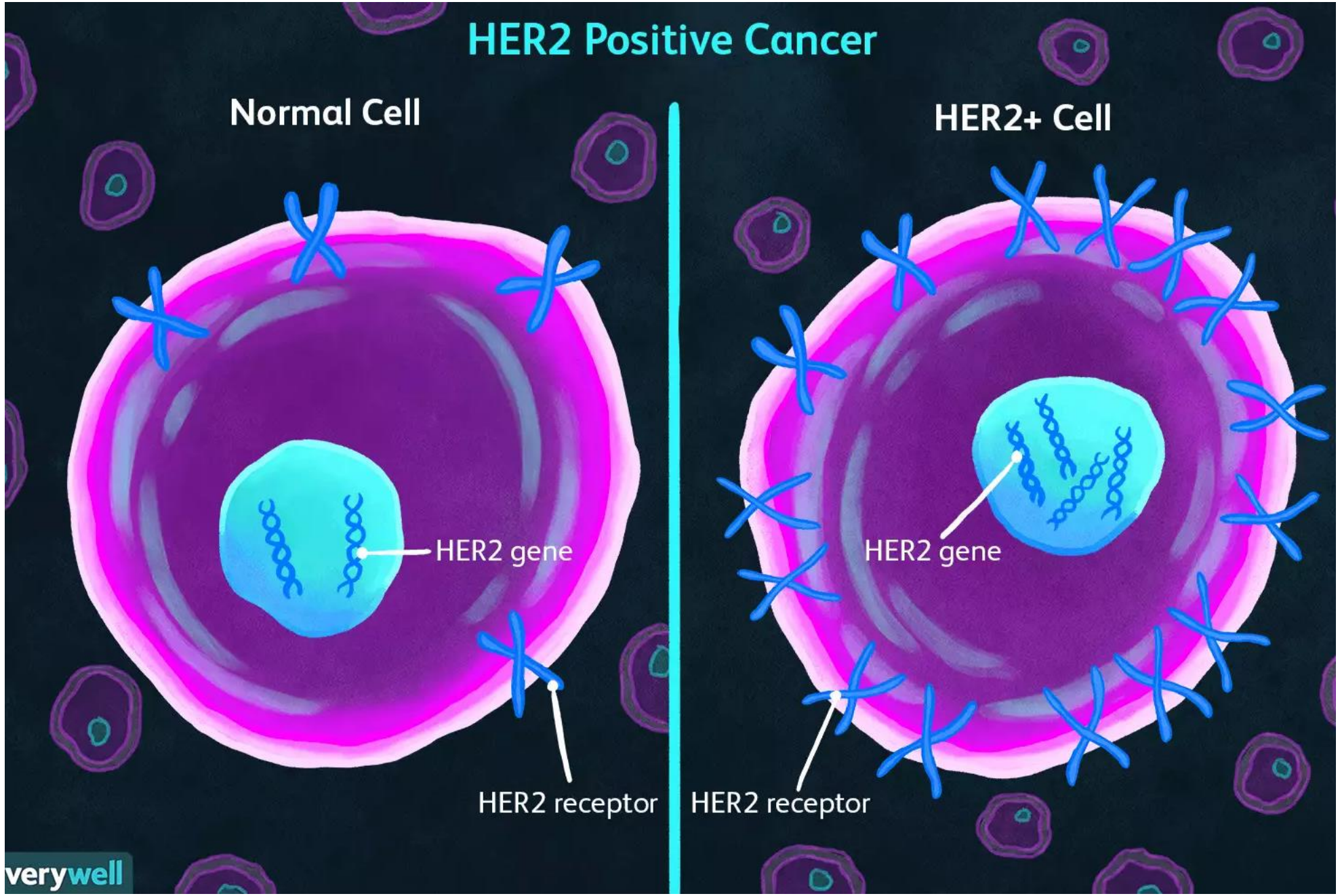
Impact of EBC Therapy in TNBC



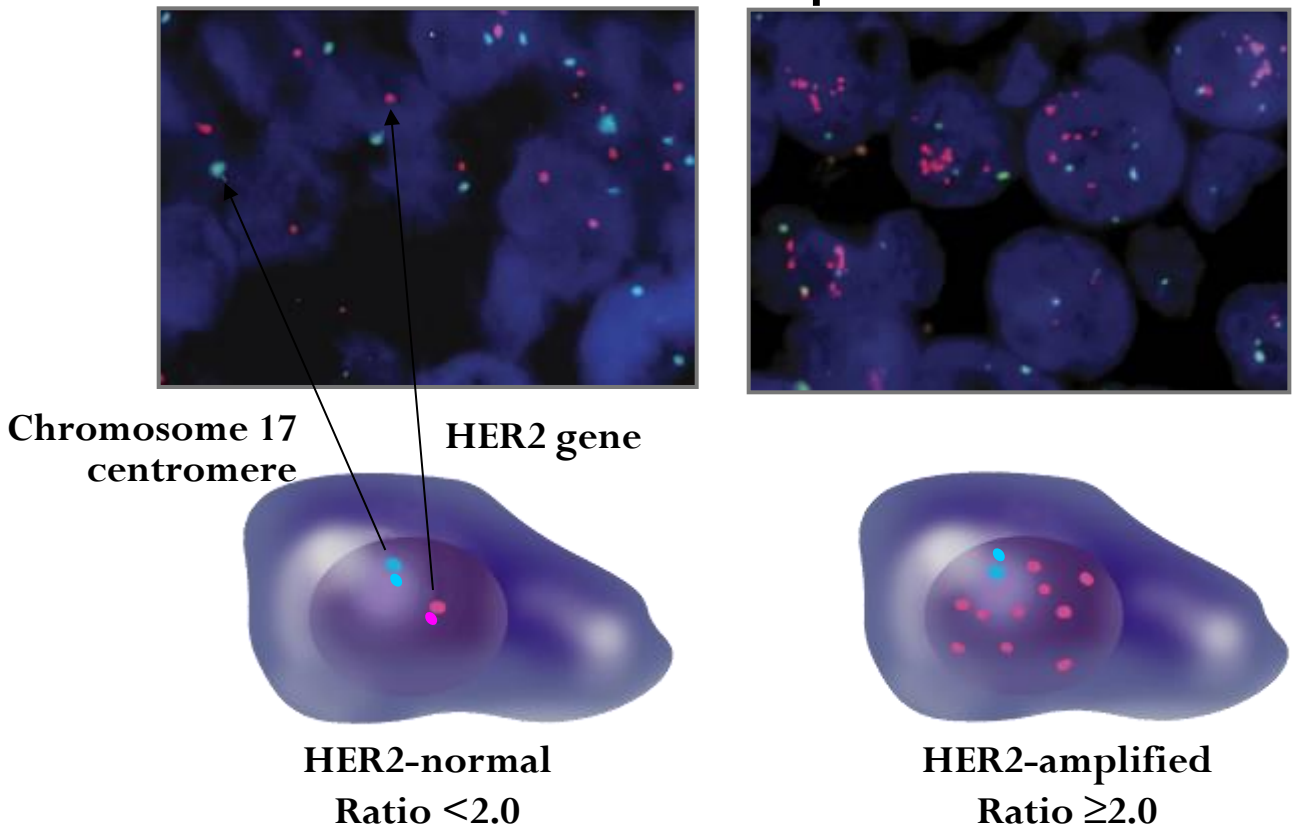
- **Serial chemotherapy addition – now 4 drugs given to nearly all TNBC**
- **Immune checkpoint inhibitor (ICI) for 1 year**
- **PARP inhibition if germline BRCA+**
- **Toxicity is a major issue both short and long-term**

<u>Beyond BRCA, we do not have biomarkers for less chemotherapy, nor for ICI.</u>

EBCTCG, Lancet 2005; Hayes DF, NEJM 2007; Metzger O, Ann Oncol 2022; Schmid P, NEJM 2022


HER2 Positive Cancer
Normal Cell
HER2+ Cell
HER2 gene
HER2 receptor
HER2 gene
HER2 receptor
verywell

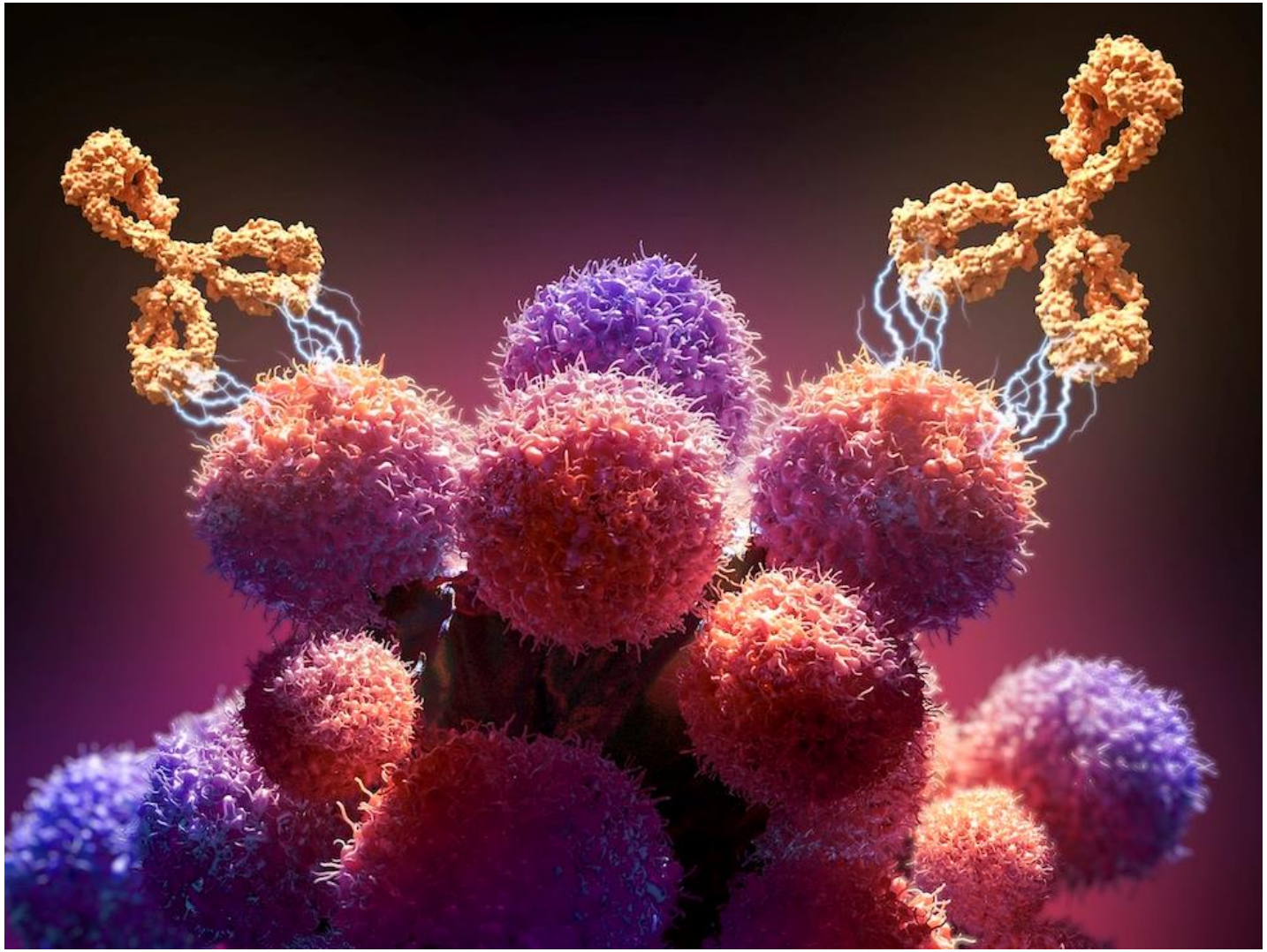
Fluorescence In Situ Hybridization Test Measures HER2 Gene Amplification



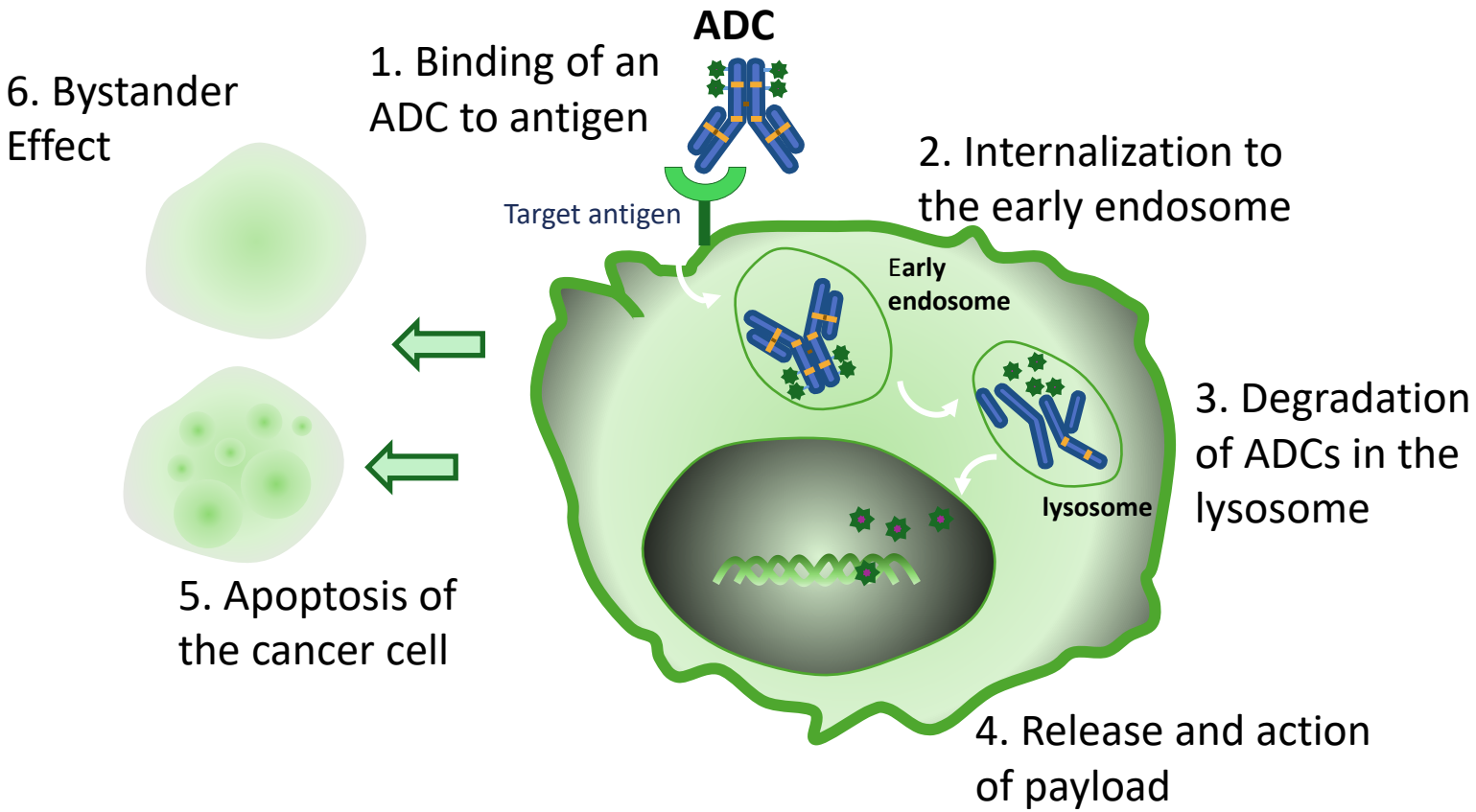
- FISH tests are designed to detect amplification of the HER2 gene

PathVysion® PI. Revised May 2004.

Harnessing the Immune System: Monoclonal Antibodies

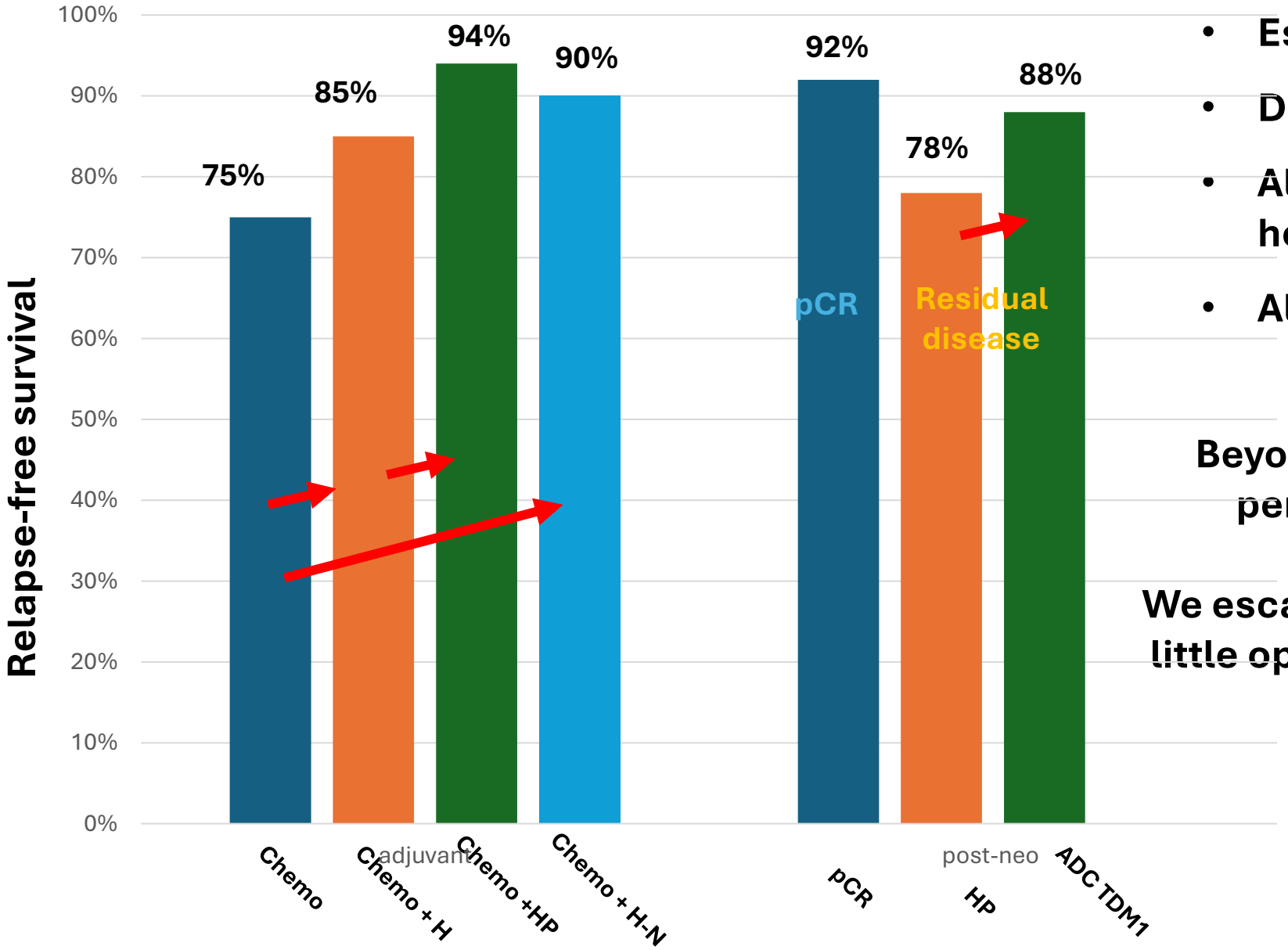


Antibody Drug Conjugates:
Selective Delivery of Toxic Payload and Bystander Effect



Nagayama. Target Oncol. 2017;12:719.

Impact of anti-HER2 Therapy in EBC (beginning in 2005)



- **Escalation of anti-HER2 Rx**
- **Duration 1-2y, mostly intravenous**
- **All involve chemo (we don't know how to exclude yet)**
- **All very expensive**

Beyond HER2, no good biomarker for pertuzumab, neratinib, or T-DM1

We escalate on clinical features, and have little opportunity to de-escalate HER2 Rx.

Sound familiar?

Conclusions

- Targeting cell division has significantly improved outcomes in early-stage breast cancer:
  - Endocrine therapy for ER-positive breast cancer
  - CDK 4/6 inhibition for ER-positive breast cancer
  - PARP inhibition for BRCA-mutant breast cancer
  - HER2-targeted therapy for HER-2 positive breast cancer
- Mobilizing the immune system is improving outcomes in early-stage triple negative breast cancer
  - Checkpoint inhibitor therapy for triple-negative breast cancer


THANK YOU