每月乳癌教育講座

主題:乳癌新攻略

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乳癌新攻略

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23/3/2019 (六)

何謂「新」?

- 「新」的定義
- 循証醫學 **Evidence based Medicine**
  - 從早期乳癌治療「輔助」性質去談
  - 從公費醫療 (大眾負擔) 去談
- 「証據」的評級，「方針」的訂立 **(FDA, NICE, EMA)**

Level of evidence	
I	Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity
II	Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts' opinions

基本認知(一)

「第幾期」對治療的影響

- 「早期」：第一至三期治療的方向
- 「晚期」：第四期治療的方向

乳癌的分期

乳癌分期			
0期	Tis	N0	M0
ⅠA期	T1	N0	M0
ⅠB期	T0-1	N1mi	M0
ⅡA期	T0-1	N1	M0
	T2	N0	M0
ⅡB期	T2	N1	M0
	T3	N0	M0
ⅢA期	T0-3	N2	M0
	T3	N1	M0
ⅢB期	T4	N0-2	M0
ⅢC期	Any T	N3	M0
Ⅳ期	Any T	Any N	M1

- **零期(原位癌)**：癌細胞指侷限在乳腺管內或小葉內
- **第Ⅰ期**：腫瘤小於2公分，沒有腋窩淋巴結的轉移，或僅有淋巴結顯微轉移
- **第Ⅱ期**：腫瘤大小在2至5公分之間(不論有無腋窩淋巴結有轉移)；或腫瘤小於2公分，但腋窩淋巴結有1-3顆轉移。
- **第Ⅲ期**：局部廣泛性乳癌：（1）腫瘤大於5公分的浸潤癌且腋窩淋巴結有任何癌轉移；（2）有胸壁或皮膚的浸潤乳癌；（3）同側鎖骨下、內乳淋巴結或鎖骨上淋巴結轉移；（4）腋窩淋巴結4顆以上有轉移。
- **第Ⅳ期**：已轉移到身體其他器官

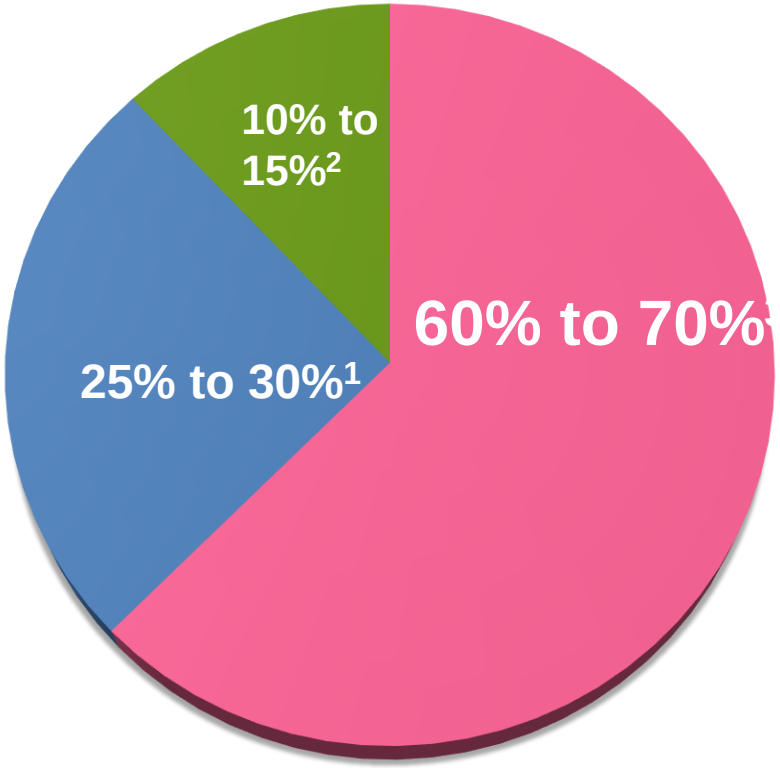
基本認知(二)

四種乳癌的思迷

- HR+ Luminal A (管狀A型)
- HR+ Luminal B (管狀B型)
- HER 2 陽性
- Basal-like三陰乳癌

乳癌的分類

- HR + 荷爾蒙受體
- HER2 + 陽性
- Triple Negative 三陰性



	Luminal A	Luminal B	Her-2	Basal-like	Normal-like
賀爾蒙ER/PR受體	+++	+/++	+/-	-	+/-
HER-2受體	-	+/-	+	-	+/-

[1]Slamon DJ, et al. *New Eng J Med*. 2001; 344:783-792; [2]Dawood S, et al. *J Clin Oncol.* 2009;27:220-226; [3] Bedard PL, et al. *Breast Cancer Res Treat*. 2008;108:307–317.

基本認知(三)

局部治療

- 手術
- 放射治療

藥物治療

- 荷爾蒙治療
- 化學治療
- 標靶治療
- 免疫治療

治療新法一覽

1.手術前先作藥物治療趨勢

2.手術後輔助治療

- 較常用 / 新用化療方案
- HER 2型乳癌新用標靶藥
- 荷爾蒙治療
- 放射治療技術的選擇

3.擴散性乳癌治療

1

賀爾蒙治療
+
標靶治療

2

HER 2型
乳癌治療

3

三陰性乳癌：
免疫治療的
運用

4

單/少數基因測試

基因排序檢查 -
次世代基因測試
(NGS)

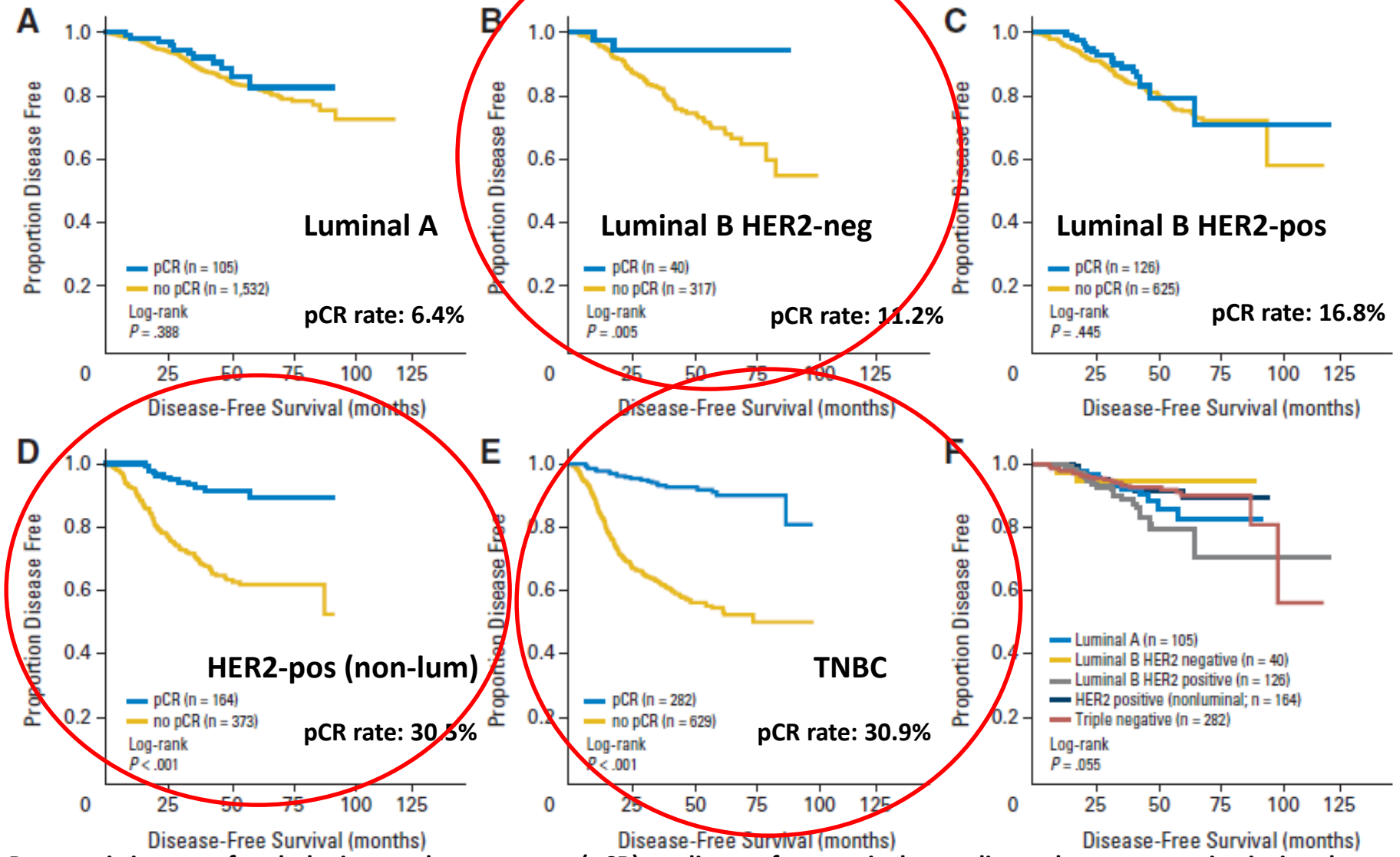
手術前先用藥治療方法 (NEOADJUVANT THERAPY)

- 早於二,三十年前開始採用
- 用於局部嚴重主瘤，增加手術在腫瘤經藥物治療後縮減
- 臨床研究用於早期腫瘤沒有存活率的好處，所以不是常用
- 後來發覺不同種類的乳癌對不同藥物有不同反應，現時若正確地使用，已經漸成常規治療方法

pCR Rates by Subtype

von Minckwitz G et al., SABCS 2011

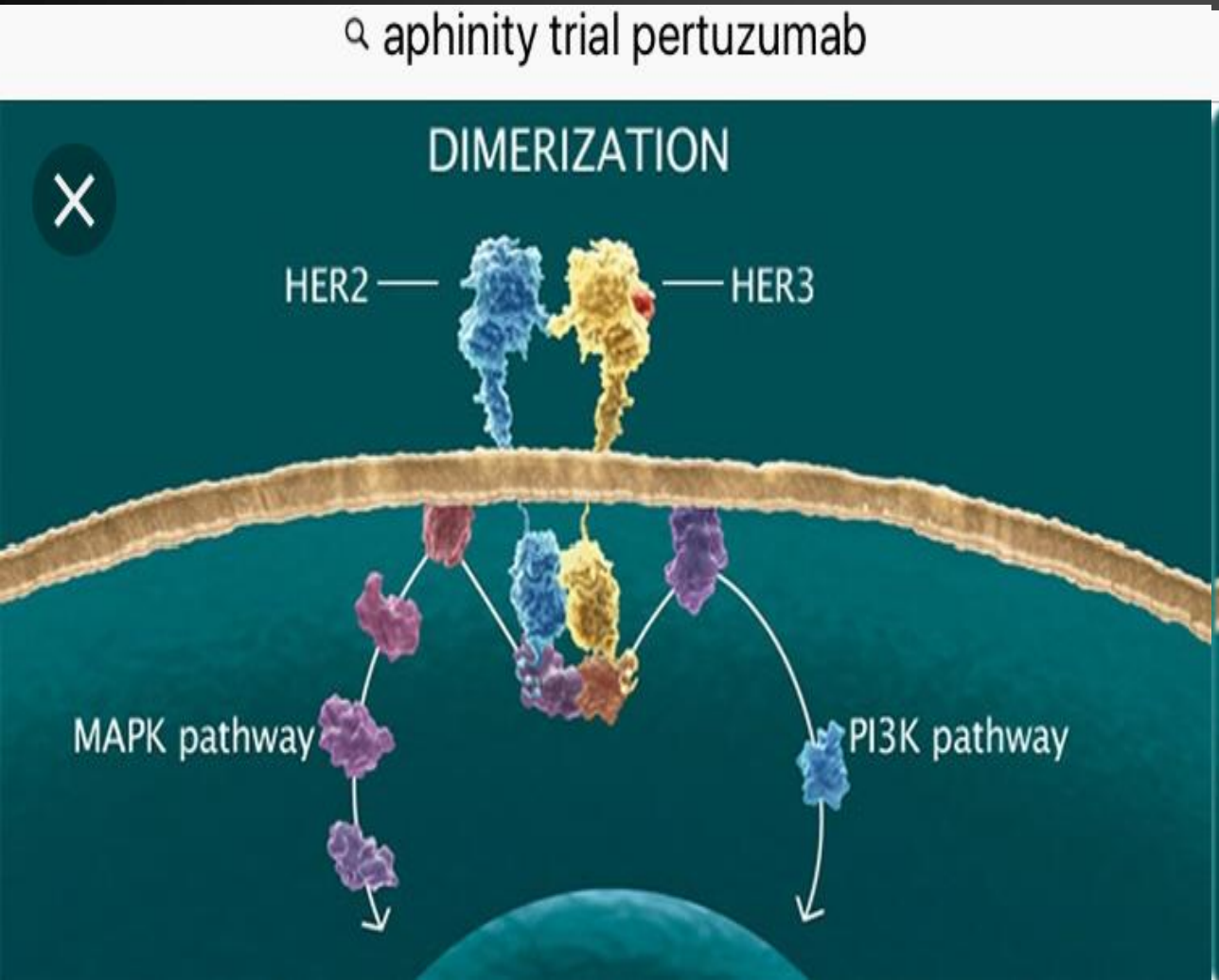
pCR as surrogate of Survival
– Differences among the subtypes (N = 4193)

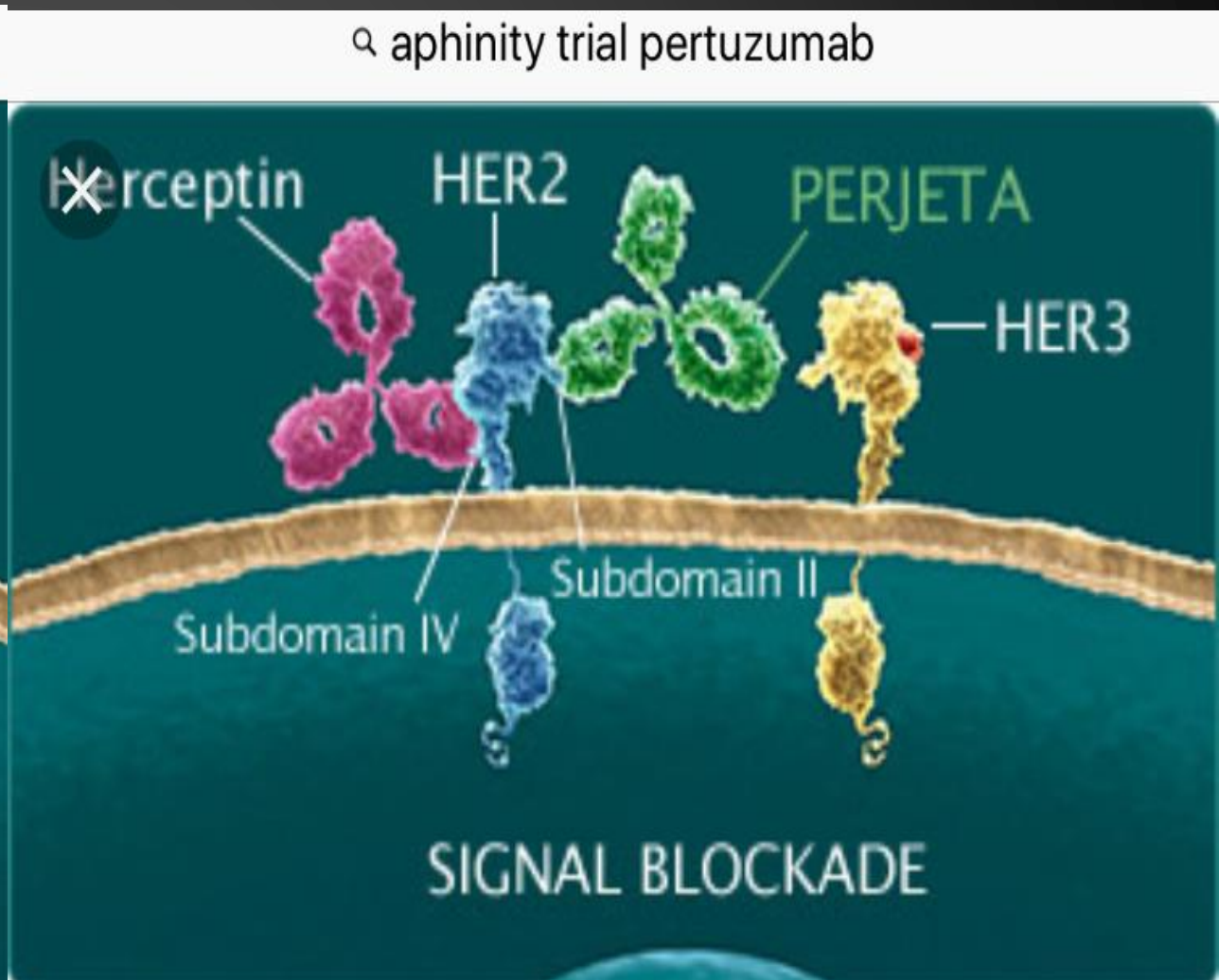


Prognostic impact of pathologic complete response (pCR) on disease-free survival according to breast cancer intrinsic subtype

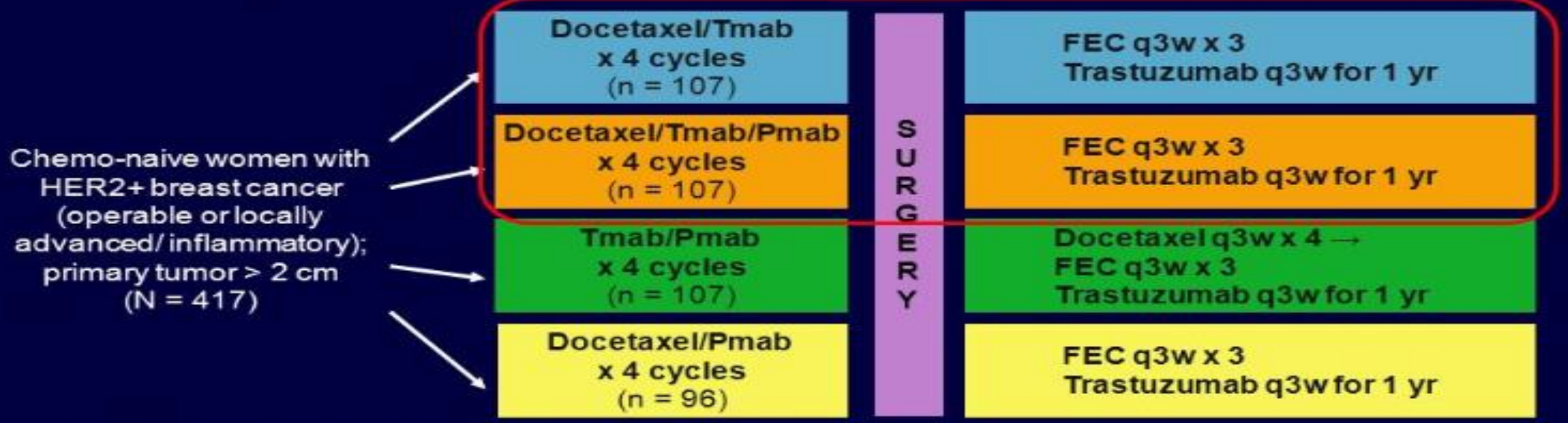
Von Minckwitz G, et al. J Clin Oncol 2012;30:1796-1804

MECHANISM OF SYNERGY BETWEEN TRASTUZUMAB & PERTUZUMAB





Open-Label Phase II NeoSphere Study: Neoadjuvant Pertuzumab/Trastuzumab



- Primary endpoint: pCR in breast (ITT pop)
- pCR defined as absence of invasive neoplastic cells at microscopic examination of the primary tumor at surgery

Trastuzumab 8 mg/kg loading dose, then 6 mg/kg q3w; pertuzumab 840 mg loading dose, then 420 mg q3w; docetaxel 75 mg/m^2 escalating, if tolerated, to 100 mg/m^2 q3w

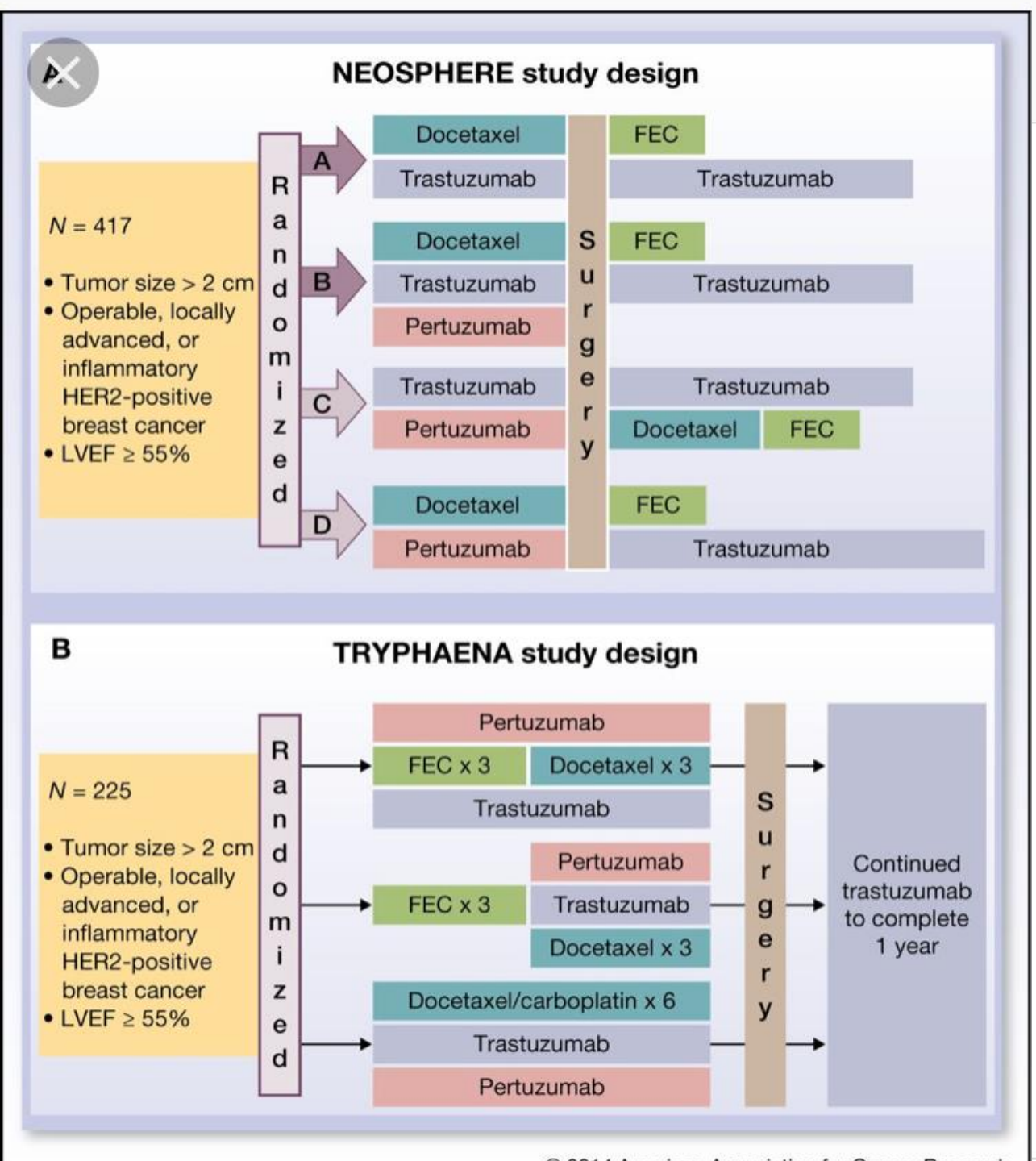
Gianni L, et al. Lancet Oncol. 2012;13:25-32.

pertuzumab neoadjuvant trial

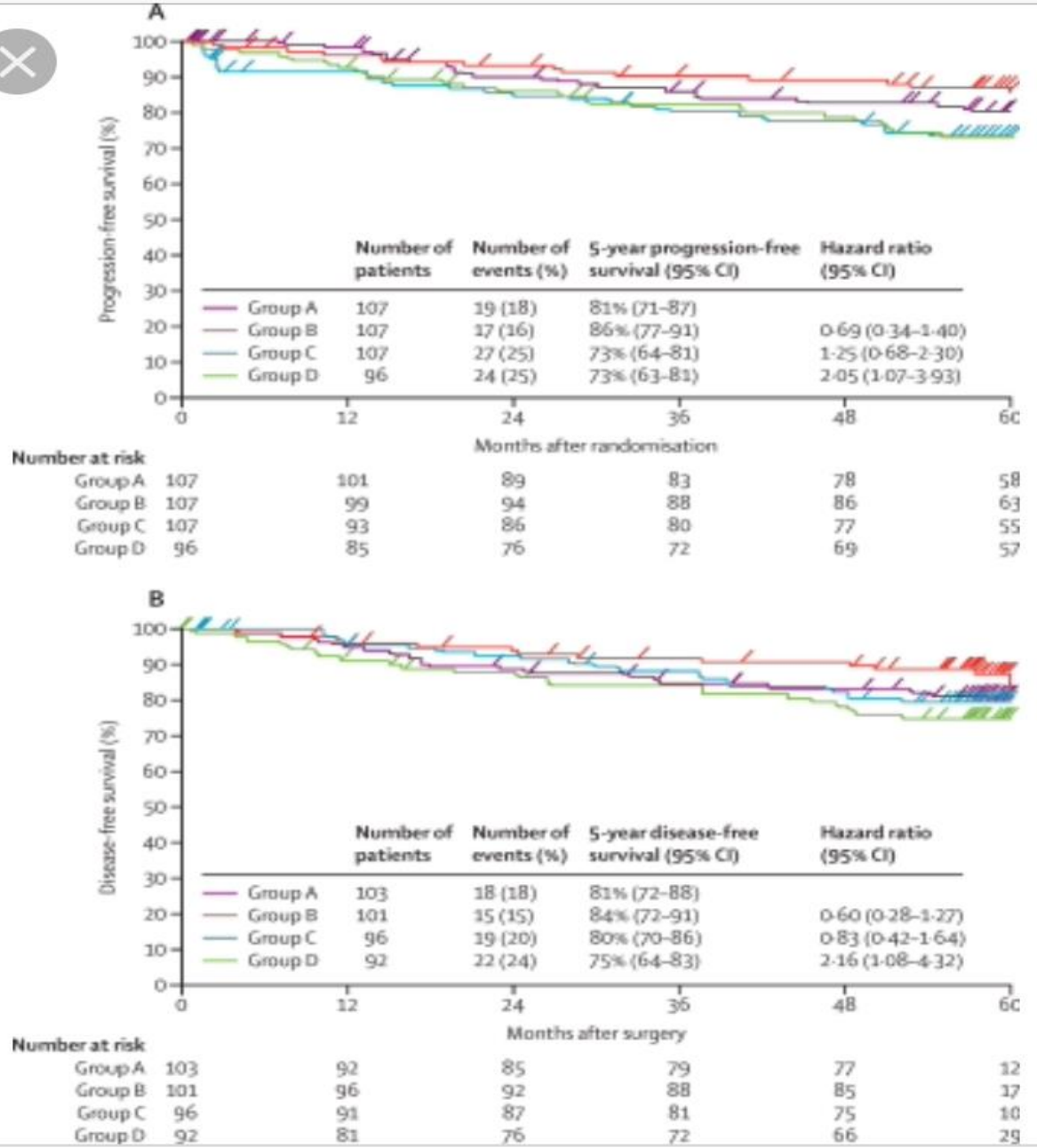
Percentage of patients in subgroups who achieved pCR[1]

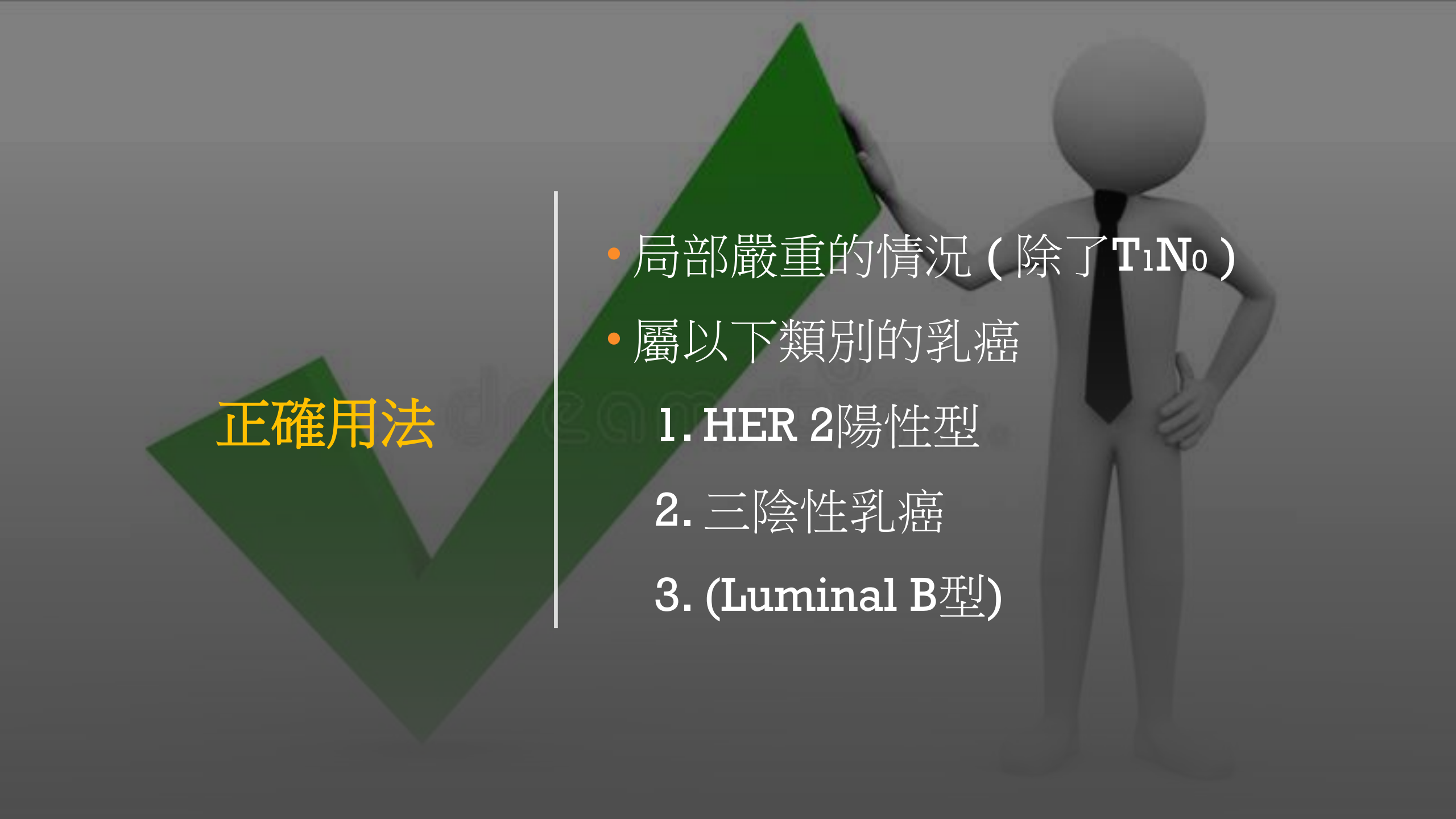
	PERJETA + Herceptin + docetaxel (n=50)	Herceptin + docetaxel (n=50)	PERJETA + Herceptin (n=51[†])	PERJETA + docetaxel (n=46)
ER+ and/or PR+	22% 95% CI: 11.5-36.0	12% 95% CI: 4.5-24.3	2.0% 95% CI: 0.1-10.5	8.7% 95% CI: 2.4-20.8

	PERJETA + Herceptin + docetaxel (n=57)	Herceptin + docetaxel (n=57)	PERJETA + Herceptin (n=55[†])	PERJETA + docetaxel (n=50)
ER– and PR–	54.4% 95% CI: 40.7-67.6	29.8% 95% CI: 18.4-43.4	20.0% 95% CI: 10.4-33.0[†]	26.0% 95% CI: 14.6-40.3



pertuzumab neoadjuvant trial





正確用法

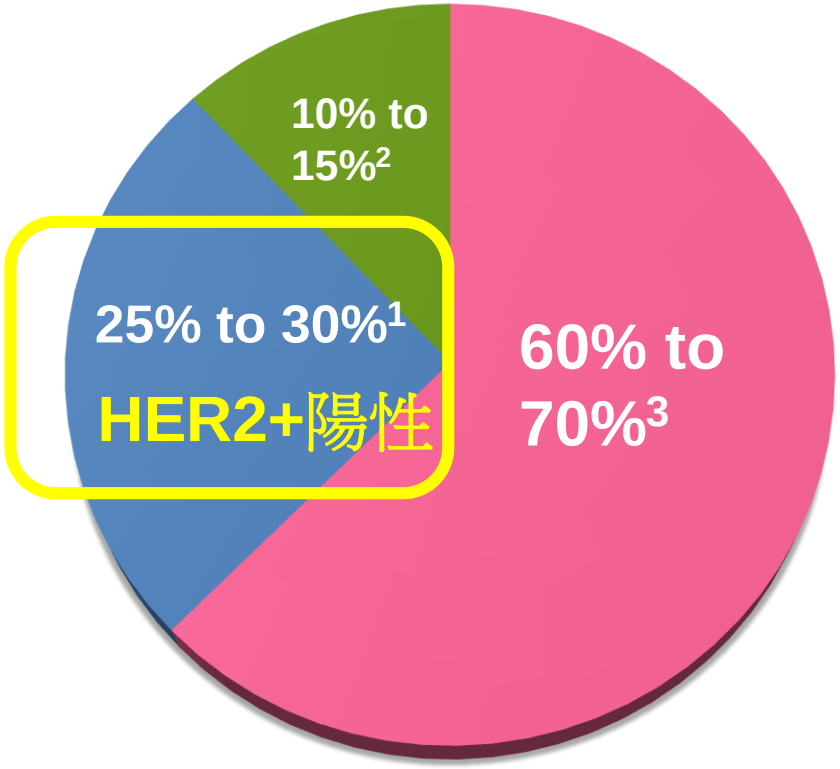
- 局部嚴重的情況 (除了T_1N_0)
- 屬以下類別的乳癌
  1. HER 2陽性型
  2. 三陰性乳癌
  3. (Luminal B型)

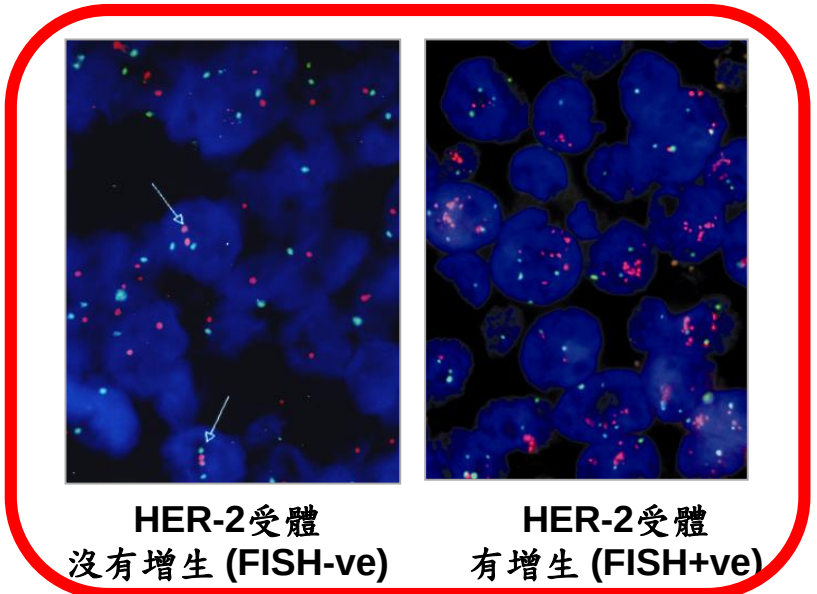
術後治療概要

- 參考資料,病理報告:
  - 主瘤 / 淋巴期數 TN
  - 荷爾蒙特性
  - HER 2 陰/陽性
  - 腫瘤惡性情況：Grade / Ki 67

乳癌的分類

- HR + 荷爾蒙受體
- HER2 + 陽性
- Triple Negative 三陰性

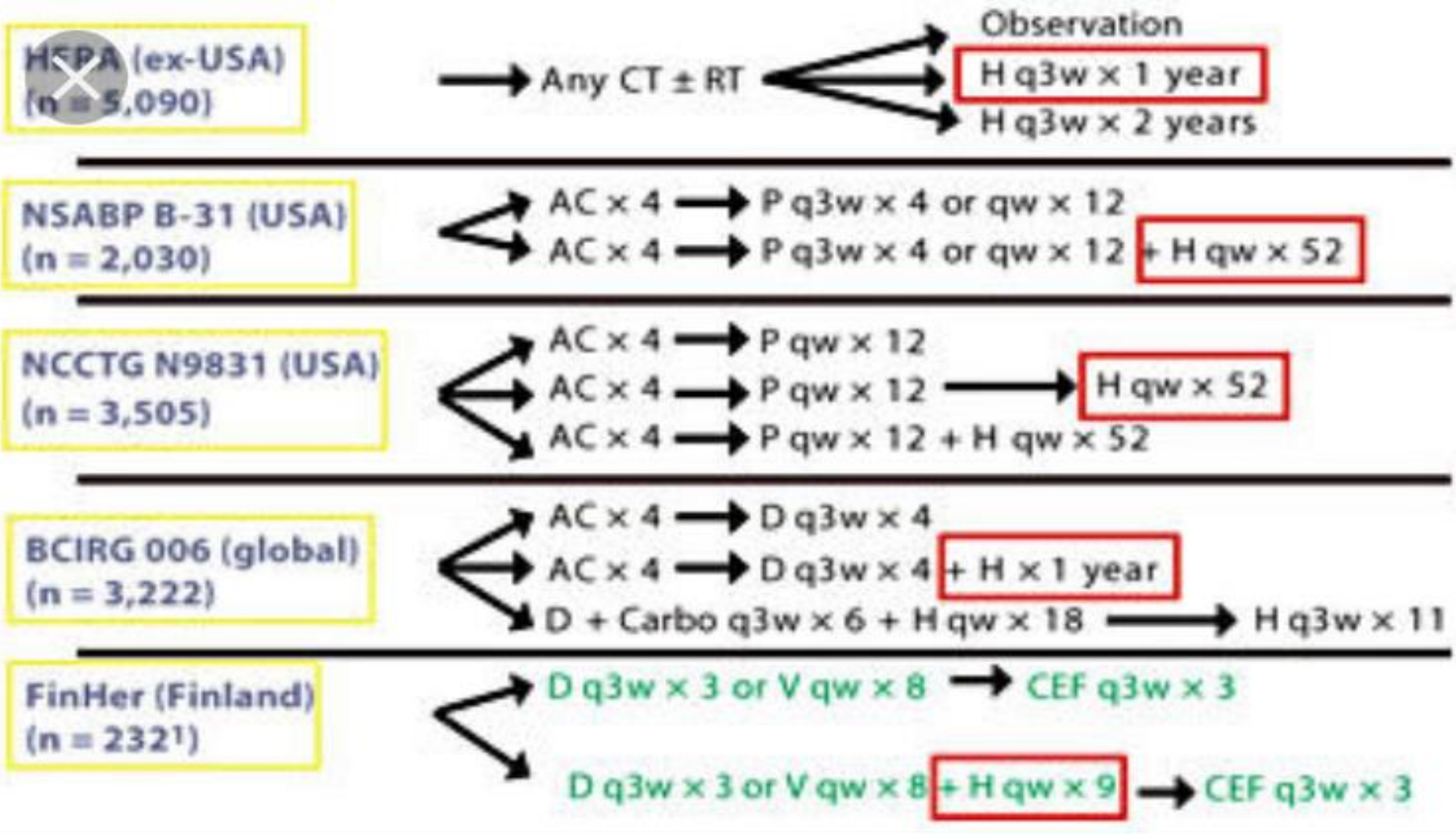




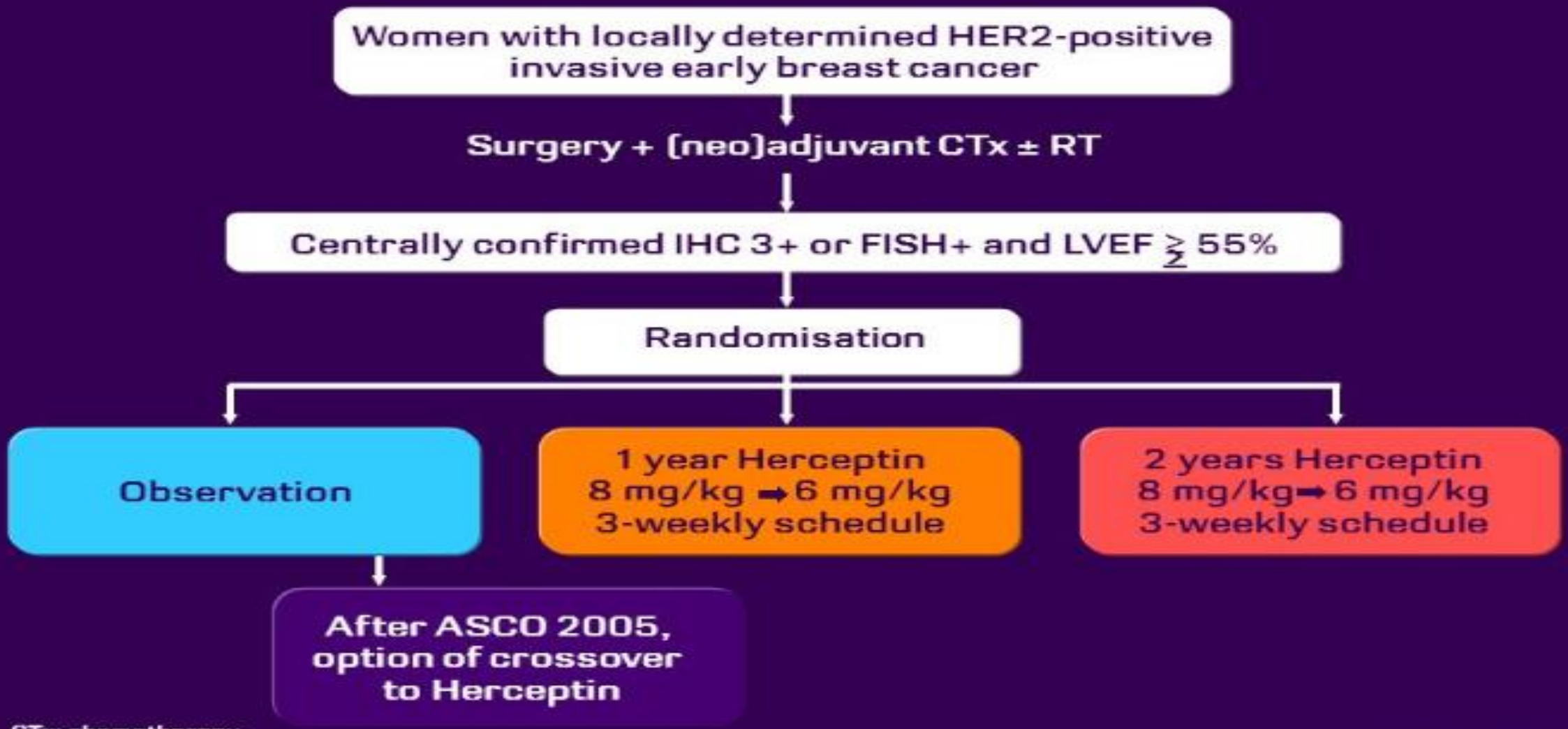
[1]Slamon DJ, et al. *New Eng J Med*. 2001; 344:783-792; [2]Dawood S, et al. *J Clin Oncol*. 2009;27:220-226; [3] Bedard PL, et al. *Breast Cancer Res Treat*. 2008;108:307–317.

HER 2 乳癌術後治療

- 什麼情況可免術後藥物治療？pT1a？
- 常用方案：TCH , TC x 4 + H , ACTH
- 特殊情況：Taxol + H , 每週一次 x 12
- 比較嚴重個案：+ Pertuzumab 的數據


HERA (ex-USA)
(n = 5,090)
Any CT ± RT
Observation
H q3w × 1 year
H q3w × 2 years
NSABP B-31 (USA)
(n = 2,030)
AC × 4 → P q3w × 4 or qw × 12
AC × 4 → P q3w × 4 or qw × 12 + H qw × 52
NCCTG N9831 (USA)
(n = 3,505)
AC × 4 → P qw × 12
AC × 4 → P qw × 12 → H qw × 52
AC × 4 → P qw × 12 + H qw × 52
BCIRG 006 (global)
(n = 3,222)
AC × 4 → D q3w × 4
AC × 4 → D q3w × 4 + H × 1 year
D + Carbo q3w × 6 + H qw × 18 → H q3w × 11
FinHer (Finland)
(n = 232[1])
D q3w × 3 or V qw × 8 → CEF q3w × 3
D q3w × 3 or V qw × 8 + H qw × 9 → CEF q3w × 3

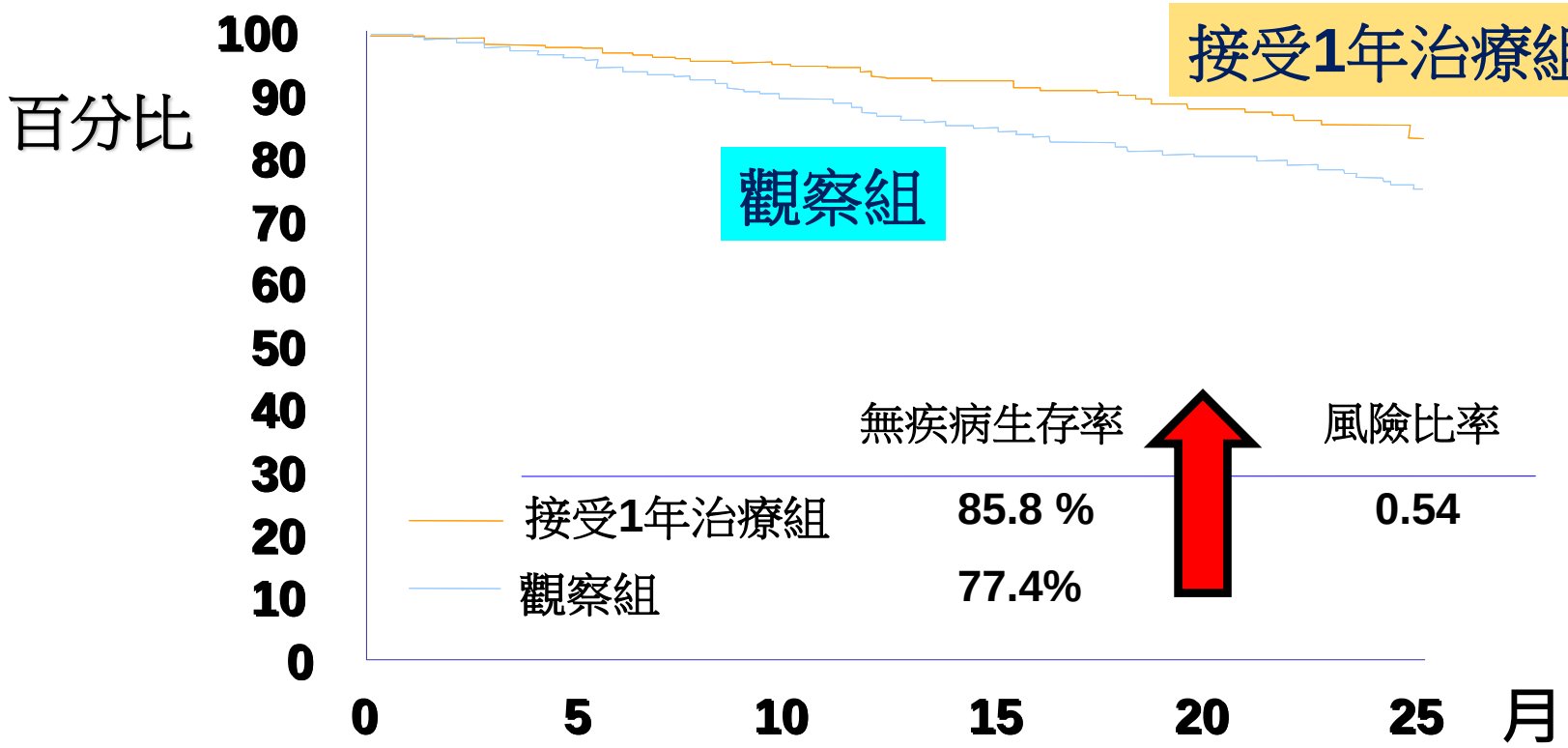
HERA study design



CTx: chemotherapy
RT: radiotherapy

Gianni 2009

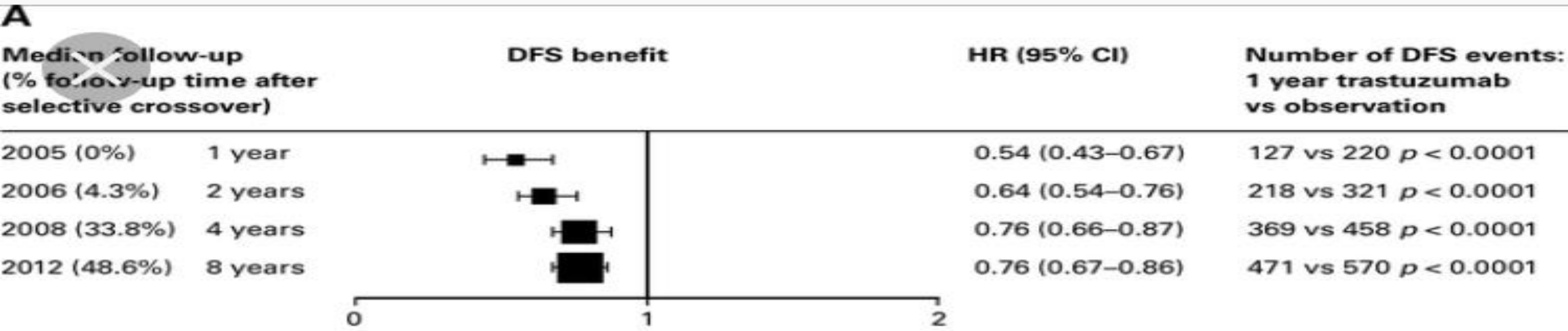
於2005年發布的中期報告:
輔助性標靶治療，患者復發風險降低接近一半



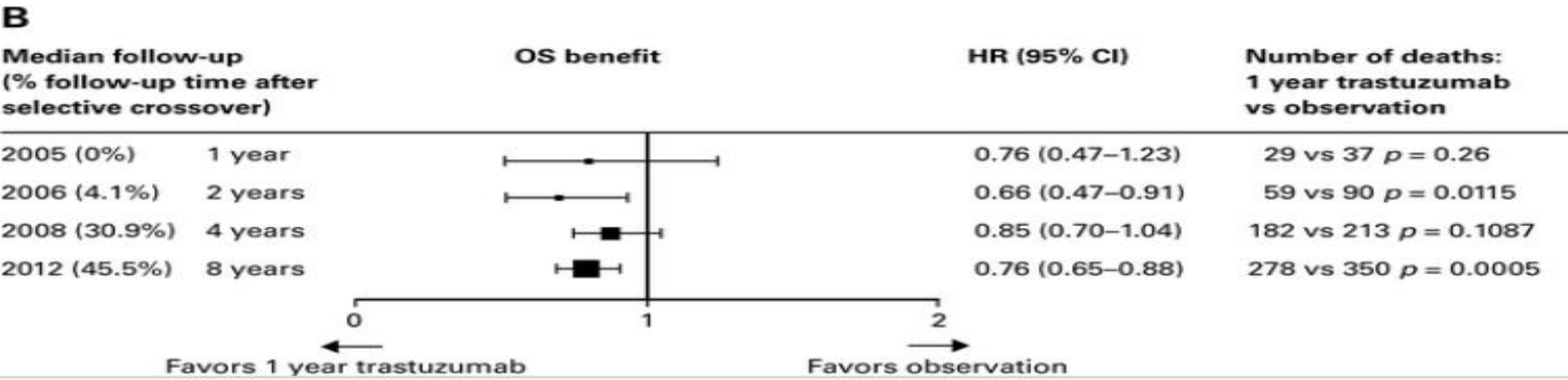
1年Herceptin®治療組比觀察組的
復發風險能減低約一半 (46%)

long term survival benefits here

A

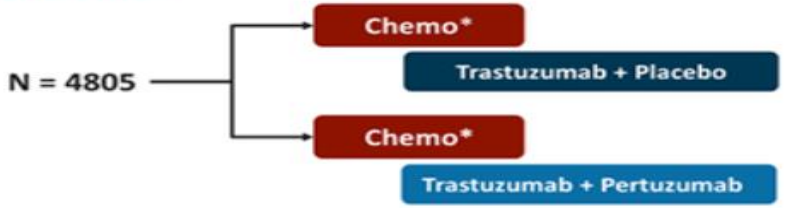


B



APHINITY TRIAL

APHINITY
Study Schema

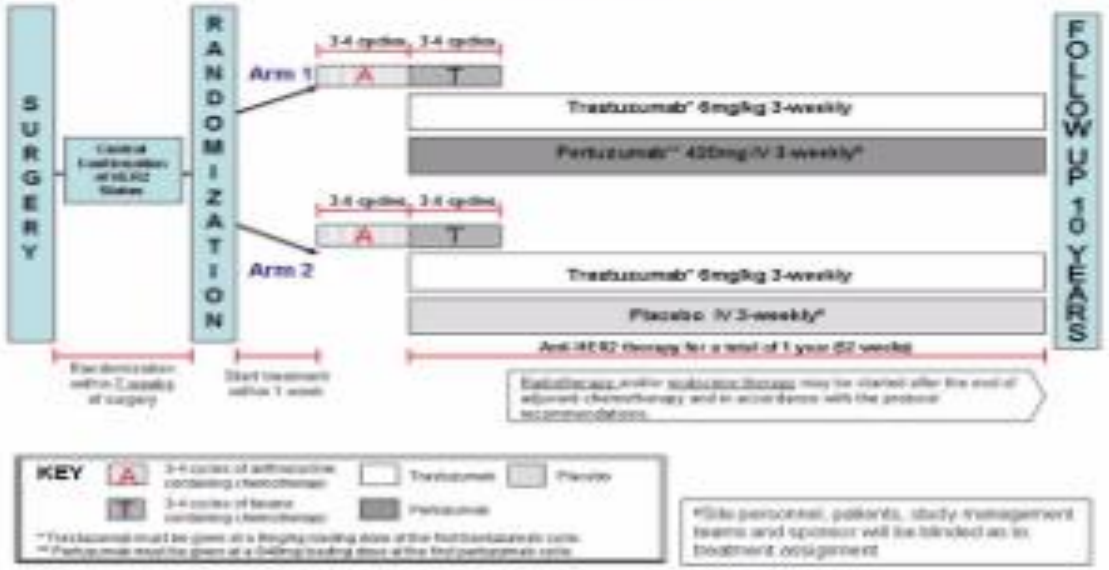


- HER2+ *centrally confirmed*
  - Node + or node – (tumor >1 cm or 0.5-1 cm with high risk feature)
- Stratification factors:
  - Nodal status, ER/PR ±; geographic region;
  - Anthracycline vs non-anthracycline regimen

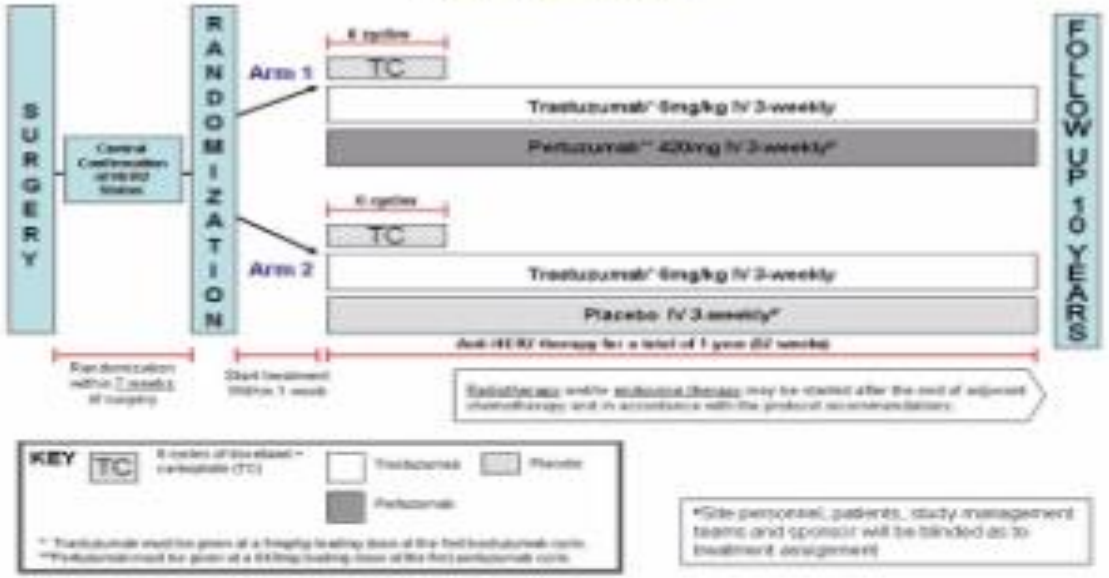
***Chemo: FEC or FAC x 3 or 4 →TH x 3-4 OR AC x 4 → TH x 4 OR TCH x 6**

Clinicaltrials.gov.

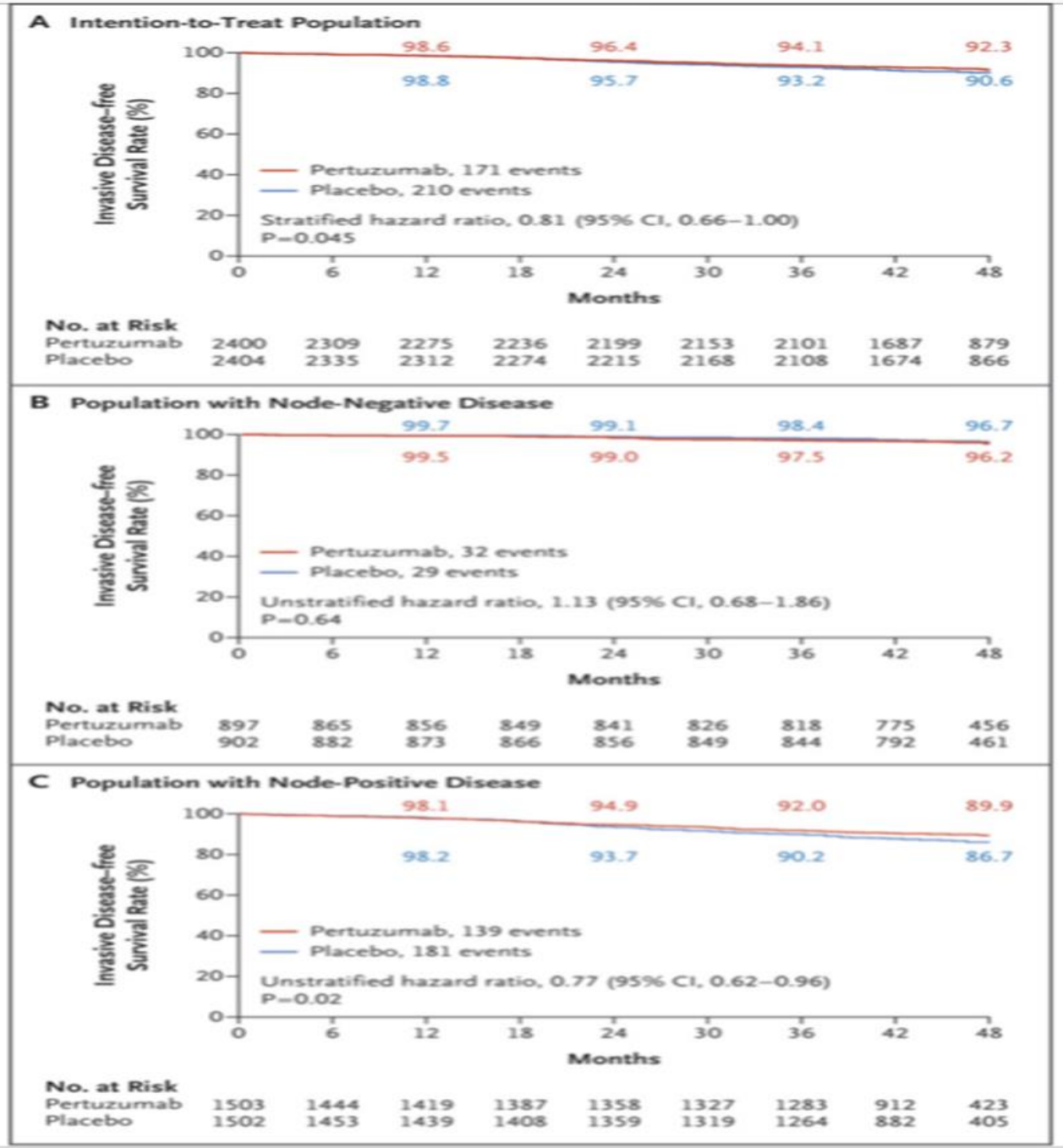
ANTHRACYCLINE BASED CHEMOTHERAPY



NON-ANTHRACYCLINE BASED CHEMOTHERAPY



aphinity trial pertuzumab



aphinity trial pertuzumab

TABLE 1: APHINITY Trial: Primary and Secondary Endpoints

3-Year Endpoint	Pertuzumab	Placebo	Hazard Ratio	*P* Value
IDFS	94.1%	93.2%	0.81	.045
IDFS including second primary non–breast cancer events	93.5%	92.5%	0.82	.043
Disease-free interval	93.4%	92.3%	0.81	.033
Recurrence-free interval	95.2%	94.3%	0.79	.043
Distant recurrence-free interval	95.7%	95.1%	0.82	.101
Overall survival (first interim analysis)	97.7%	97.7%	0.89	.467

IDFS = invasive disease-free survival

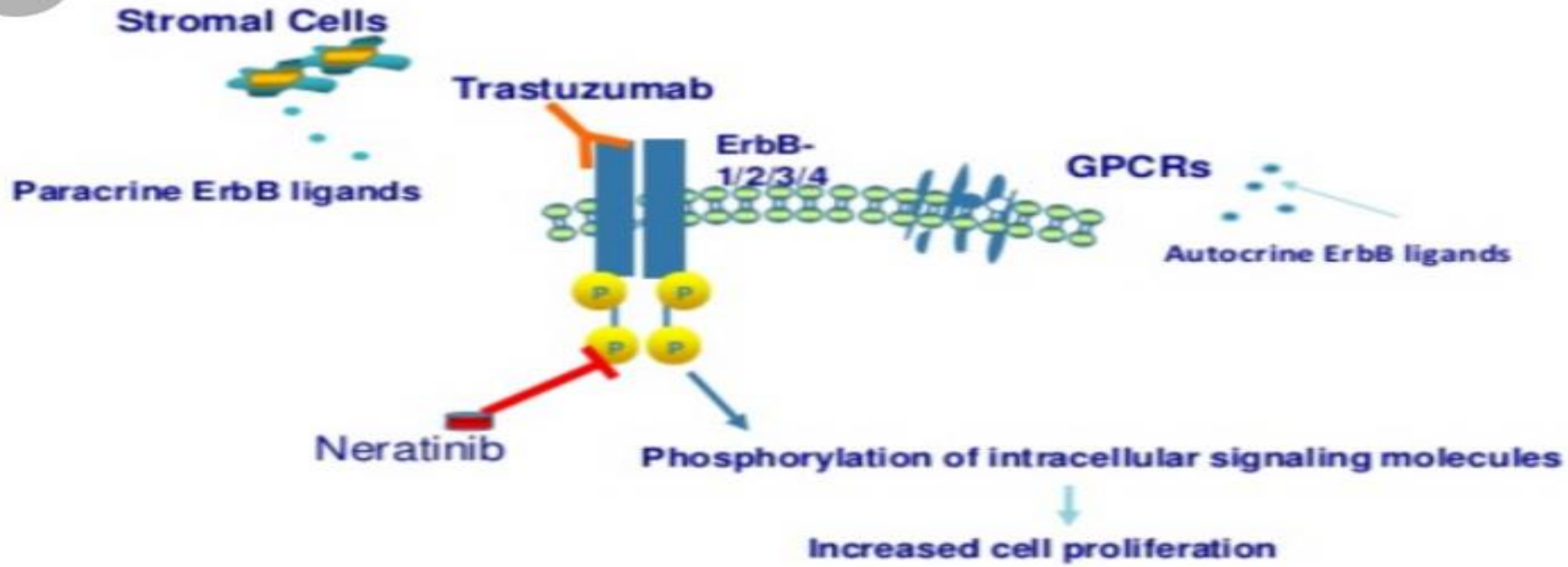
Positive Results for APHINITY, bu...

ascopost.com

Most common (≥5%) severe (Grade 3 or higher) AEs		
Neutropenia *Decrease in a certain type of white blood cell*	16.3%	15.7%
Febrile neutropenia *Fever associated with decrease in a certain type of white blood cell*	12.1%	11.1%
Diarrhoea	9.8%	3.7%
Diarrhoea *Onset after chemotherapy, during targeted therapy*	0.5%	0.2%
Neutrophil count decreased *Decrease in a certain type of white blood cell*	9.6%	9.6%
Anaemia *Decrease in red blood cells or haemoglobin*	6.9%	4.7%

Roche APHINITY study shows

Neratinib (HKI-272)

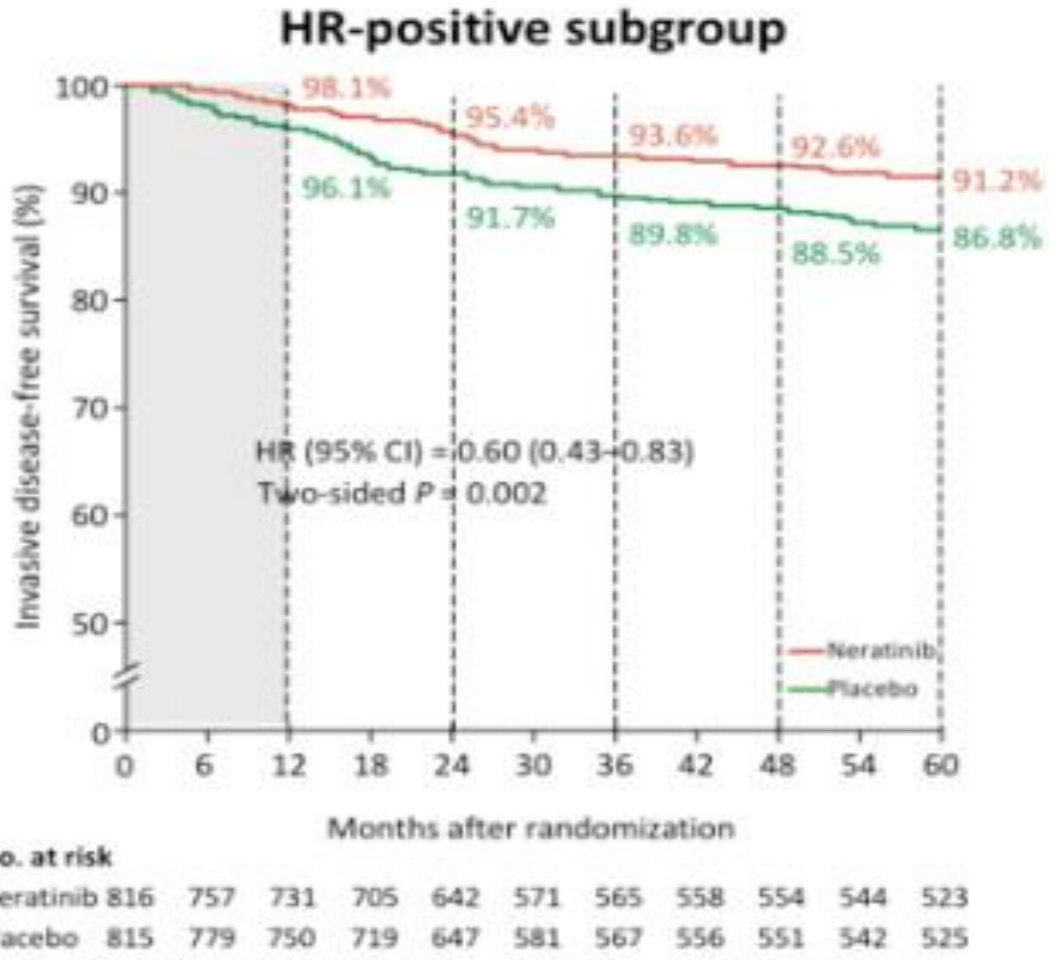


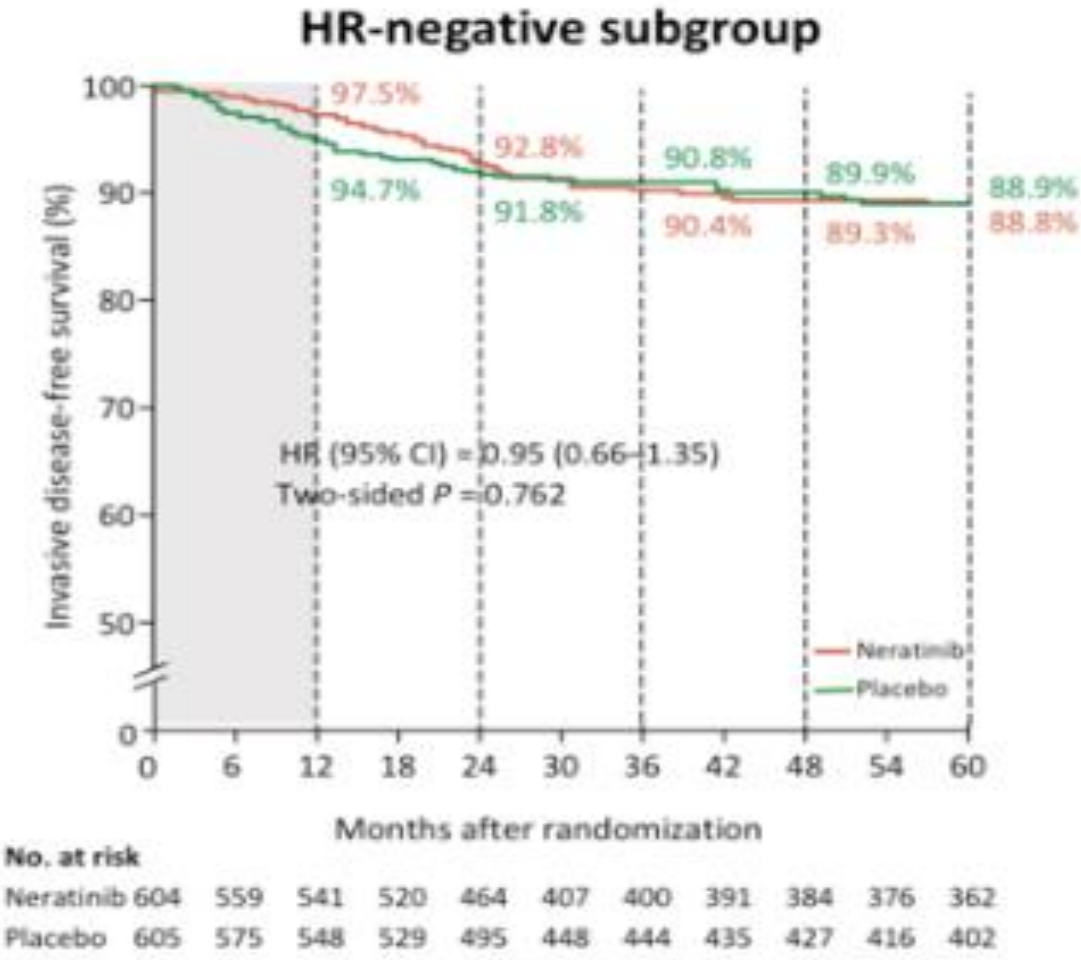
- **Potent, low molecular weight, orally administered irreversible pan-HER tyrosine kinase inhibitor (HER-1, -2, -4).**
- **Binds covalently to the intracellular TK domain and inhibits auto-phosphorylation and subsequent downstream signaling.**
- **Preclinical studies show increased potency over lapatinib**

Cortés-Funes H, et al. *Breast Cancer Res.* 2009; Suppl 1:S19.

neratinib adjuvant breast cancer

ExteNET: iDFS by hormone receptor status





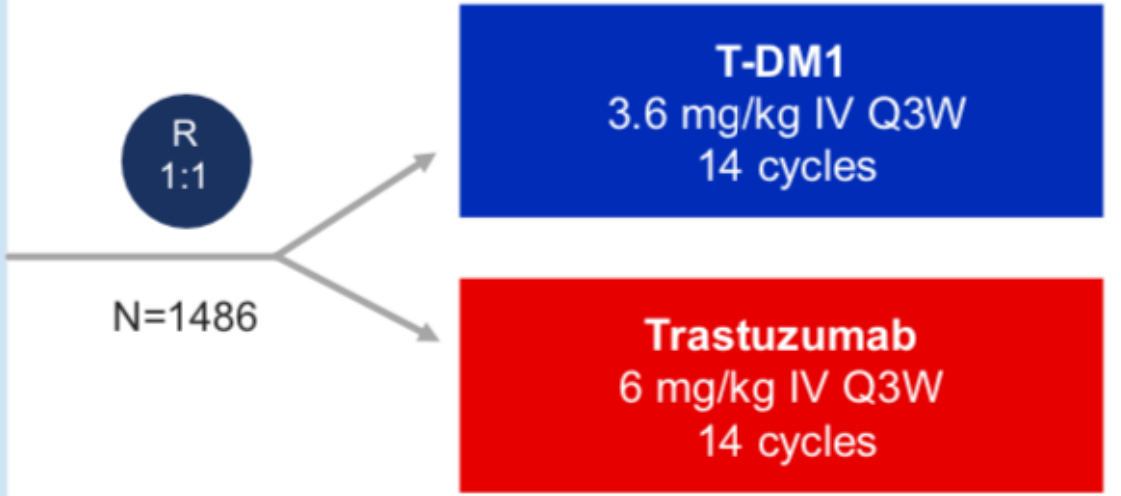
Intention-to-treat population. Cut-off date: March 1, 2017

Neratinib in HER2-Positive Breast Cancer

- The phase III ExteNET trial evaluated 1 year of treatment with the tyrosine kinase inhibitor neratinib, following chemotherapy and trastuzumab, in patients with early-stage HER2-positive breast cancer.
- The study met its primary endpoint, showing improved invasive disease–free survival with neratinib, which translated to an absolute benefit of 2.3% at 2 years.
- In the predefined, hormone receptor–positive subset, patients receiving neratinib derived an even greater benefit, with a 49% risk reduction of an invasive event (2.2% absolute benefit).
- Grade 3 diarrhea was a problem for nearly 40% of patients treated with neratinib, but intensive prophylaxis with loperamide reduced the frequency of this side effect.

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

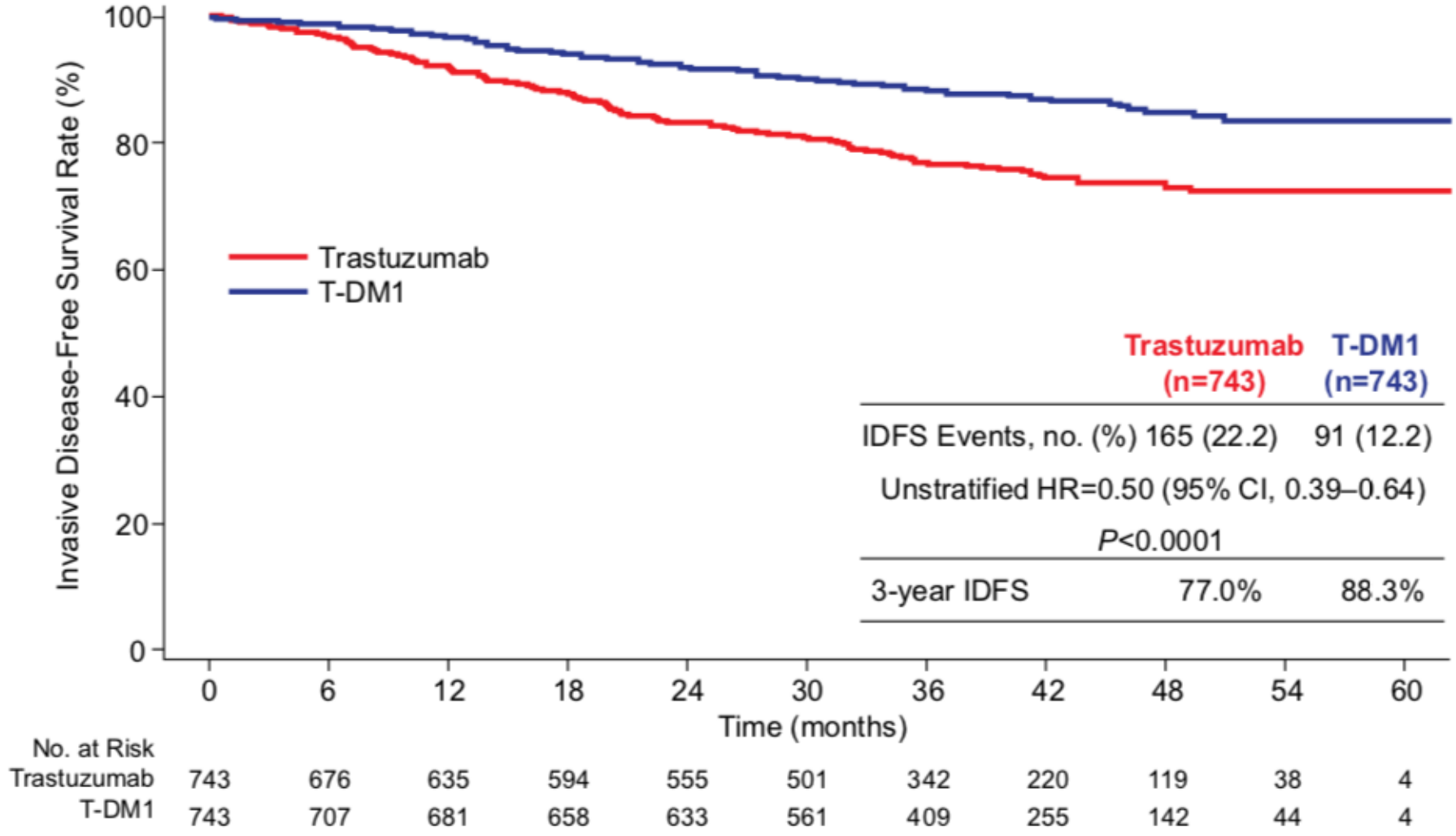


Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

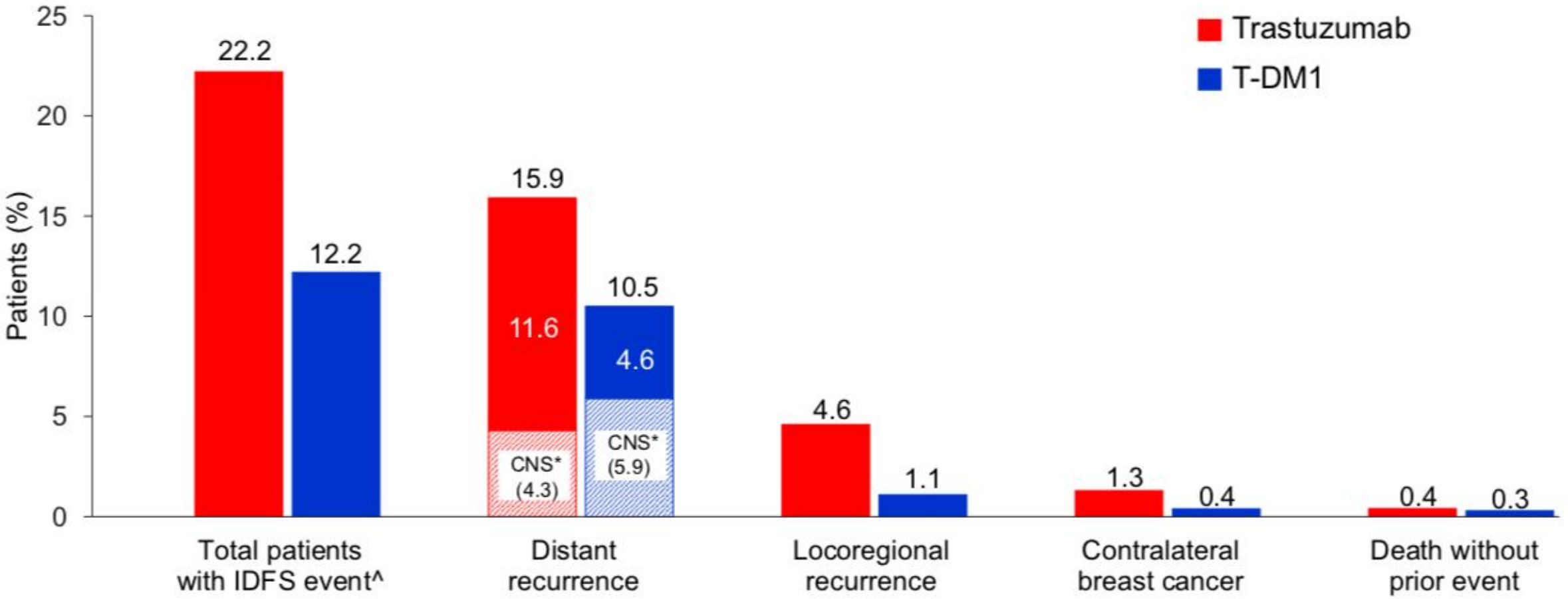
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Invasive Disease-Free Survival



	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64)		
P<0.0001		
3-year IDFS	77.0%	88.3%

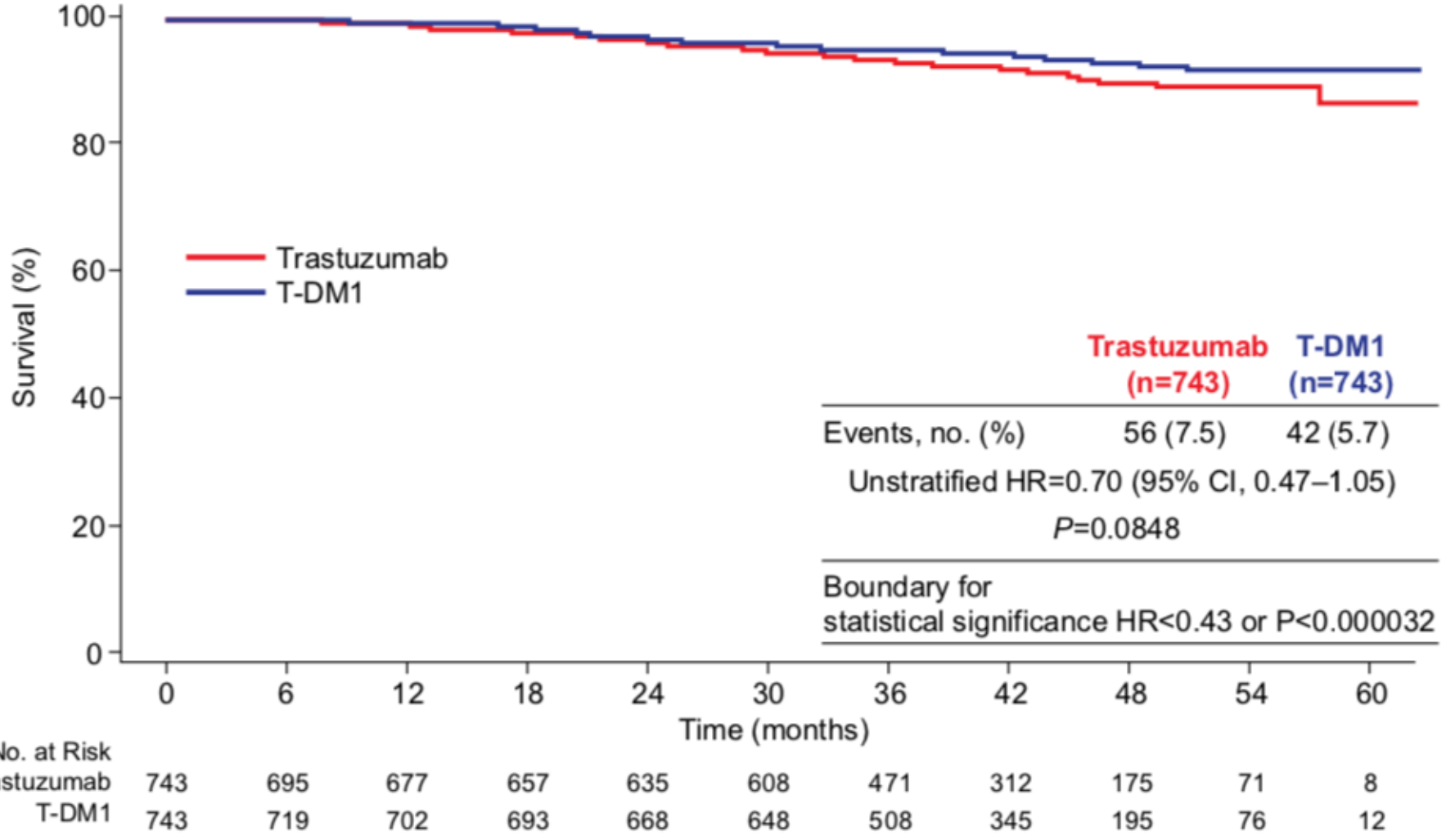
First IDFS Events



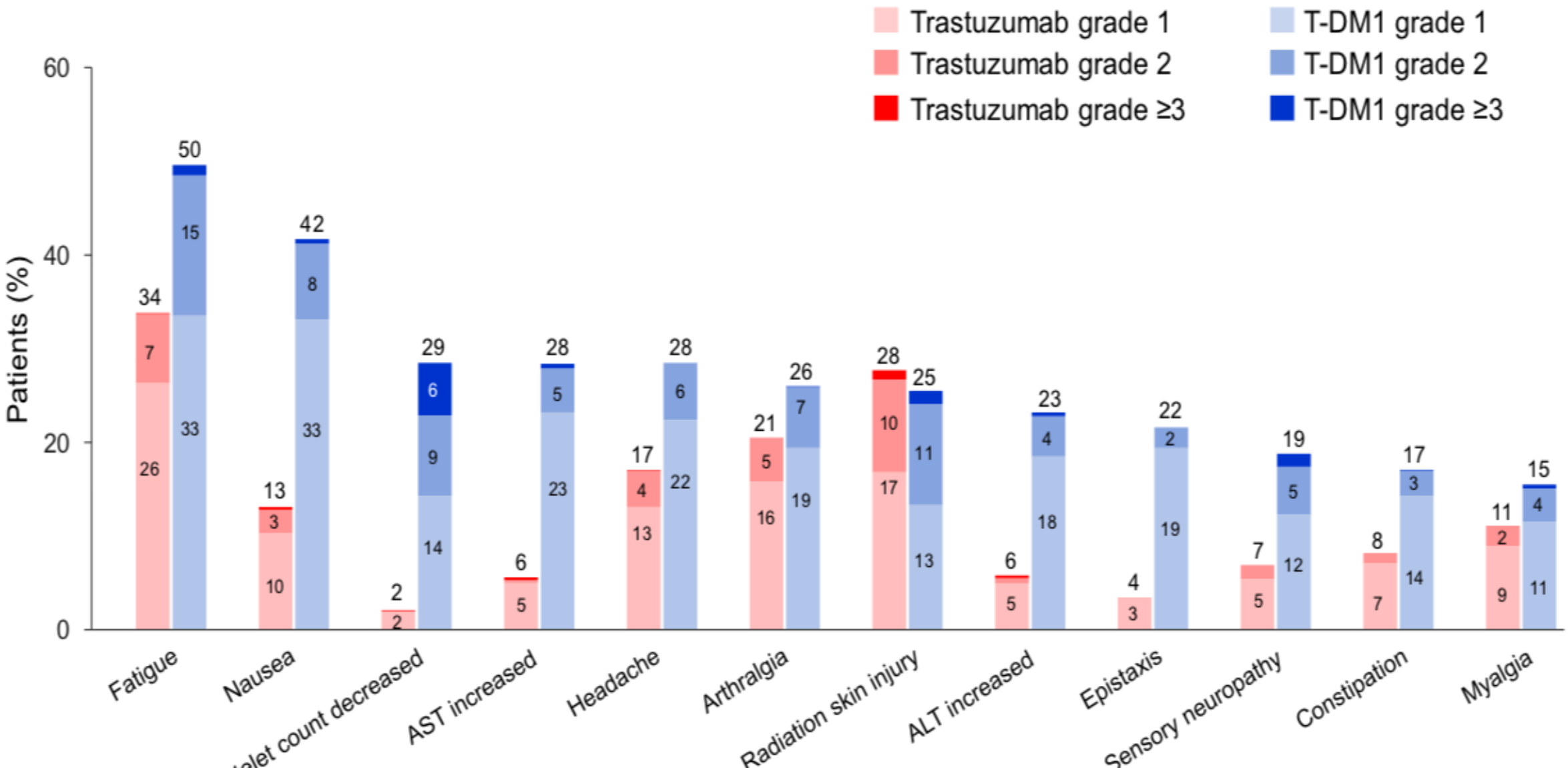
^Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.

***CNS metastases as component of distant recurrence (isolated or with other sites).** **Trastuzumab** **T-DM1**

Overall Survival



All Grade AEs ≥15% Incidence in Either Arm

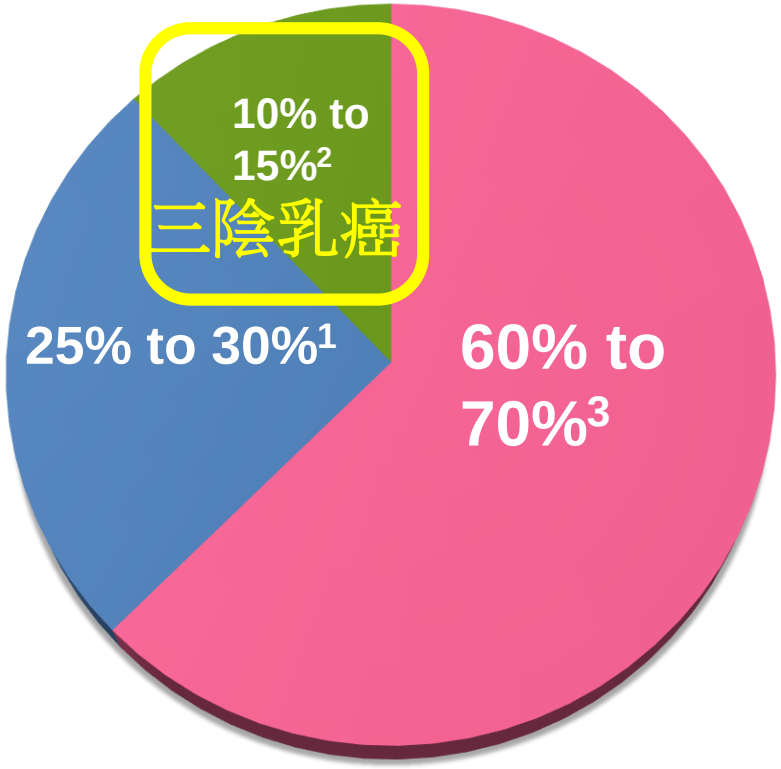


KATHERINE Summary and Conclusions

- Adjuvant T-DM1 demonstrated both a statistically significant and clinically meaningful improvement in IDFS compared with trastuzumab
  - Unstratified HR=0.50; 95% CI 0.39–0.64; *P*<0.0001
  - 3-year IDFS rate improved from 77.0% to 88.3% (difference=11.3%)
- Benefit of T-DM1 was consistent across all key subgroups including HR status, extent of residual invasive disease, and single or dual HER2-targeted neoadjuvant therapy
- The safety data were consistent with the known manageable toxicities of T-DM1, with expected increases in AEs associated with T-DM1 compared to trastuzumab
- Additional follow-up will be necessary to evaluate the effect of T-DM1 on OS
- The KATHERINE data will likely form the foundation of a new standard of care in this population and increase the use of neoadjuvant therapy in HER2-positive EBC

乳癌的分類

- HR + 荷爾蒙受體
- HER2 + 陽性
- Triple Negative 三陰性



[1]Slamon DJ, et al. *New Eng J Med*. 2001; 344:783-792; [2]Dawood S, et al. *J Clin Oncol.* 2009;27:220-226; [3] Bedard PL, et al. *Breast Cancer Res Treat*. 2008;108:307–317.

化學治療 (Chemotherapy)

- **原理:** 由於癌細胞的增殖快於正常細胞，化療藥物的作用通常是阻斷細胞分裂的機制以抑制癌細胞的生長

- **輔助化學治療**通常需要4至6個療程，每個療程2至3星期。(一般需要3至4月)

目標：

→ 減低乳癌復發率

→ 延長性命

輔助化療藥物

組合治療

- Anthracycline (俗稱”紅針”)
- Taxol (紫杉醇)，Taxotere (多西紫杉醇
- Cyclophosphamide
- Carboplatin

(AC x 4) , TC x 4 , Weekly Taxol

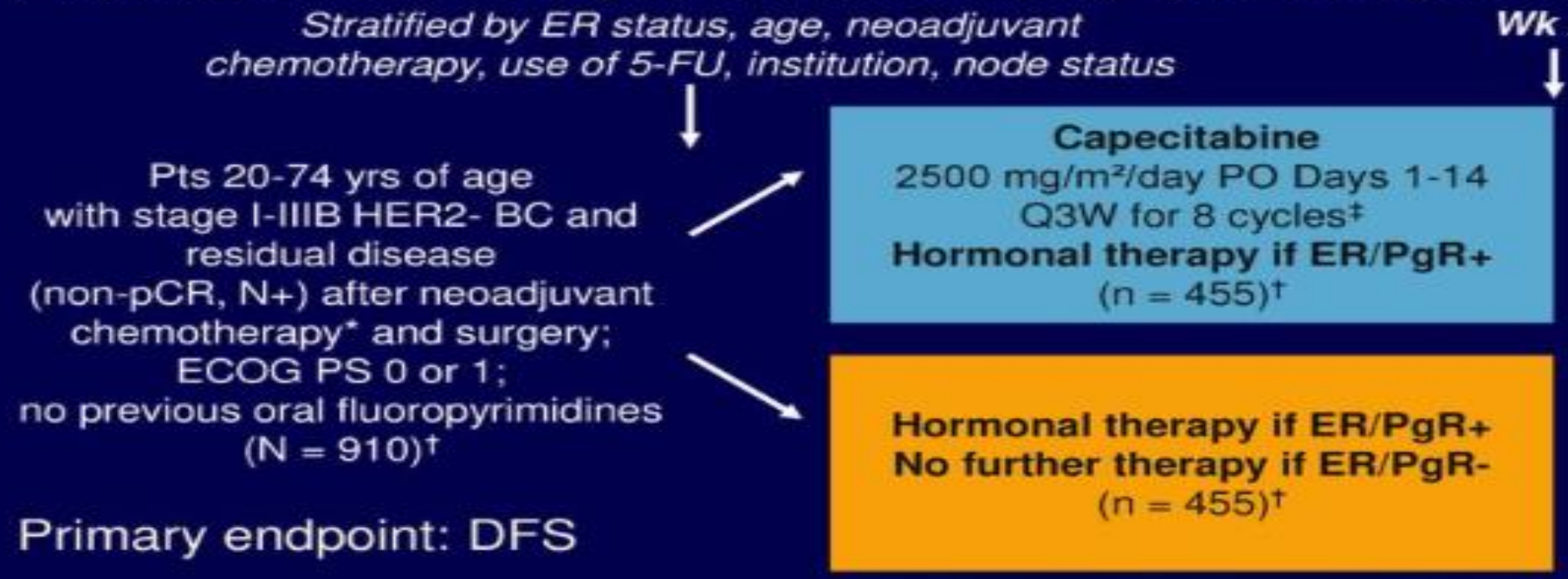
(FAC) , AC + T

FEC100 + T , DDAC + T(J) , (TAC)

手術後化療趨勢

CREATE-X: Study Design

- Preplanned interim analysis of a randomized, open-label phase III study[1]

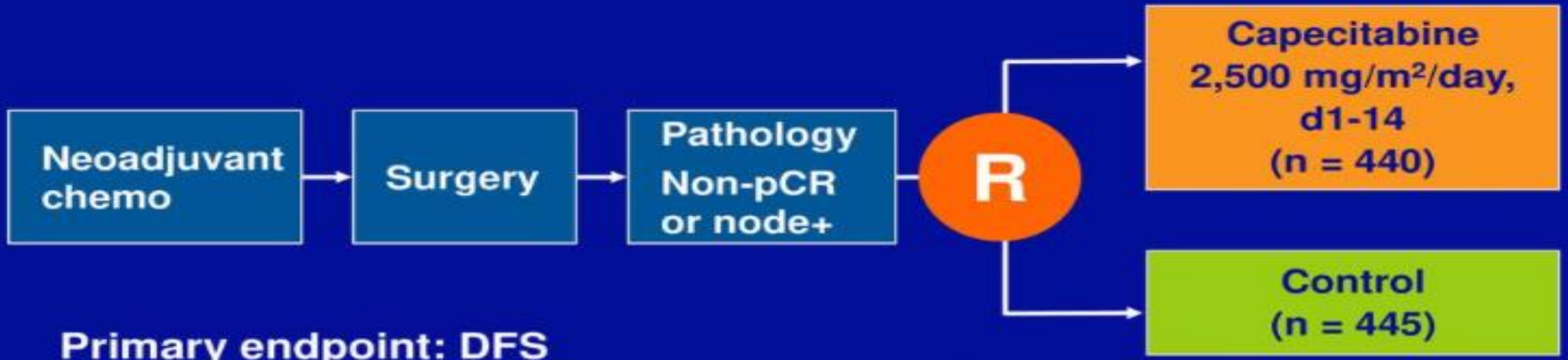


- Primary endpoint: DFS
- Secondary endpoints: OS, time from first day of preoperative chemotherapy to recurrence or death, safety, cost-effectiveness

*Anthracycline/taxane, anthracycline containing, or docetaxel/cyclophosphamide.
†25 pts were removed from treatment (n = 10) and control (n = 15) arms due to failure to meet eligibility criteria.
‡IDMC recommended extension to 8 cycles following interim safety analysis of first 50 pts receiving 6 cycles.[2]

1. Toi M, et al. SABCS 2015. Abstract S1-07.
2. Ohtani S, et al. SABCS 2013. Abstract P3-12-03.

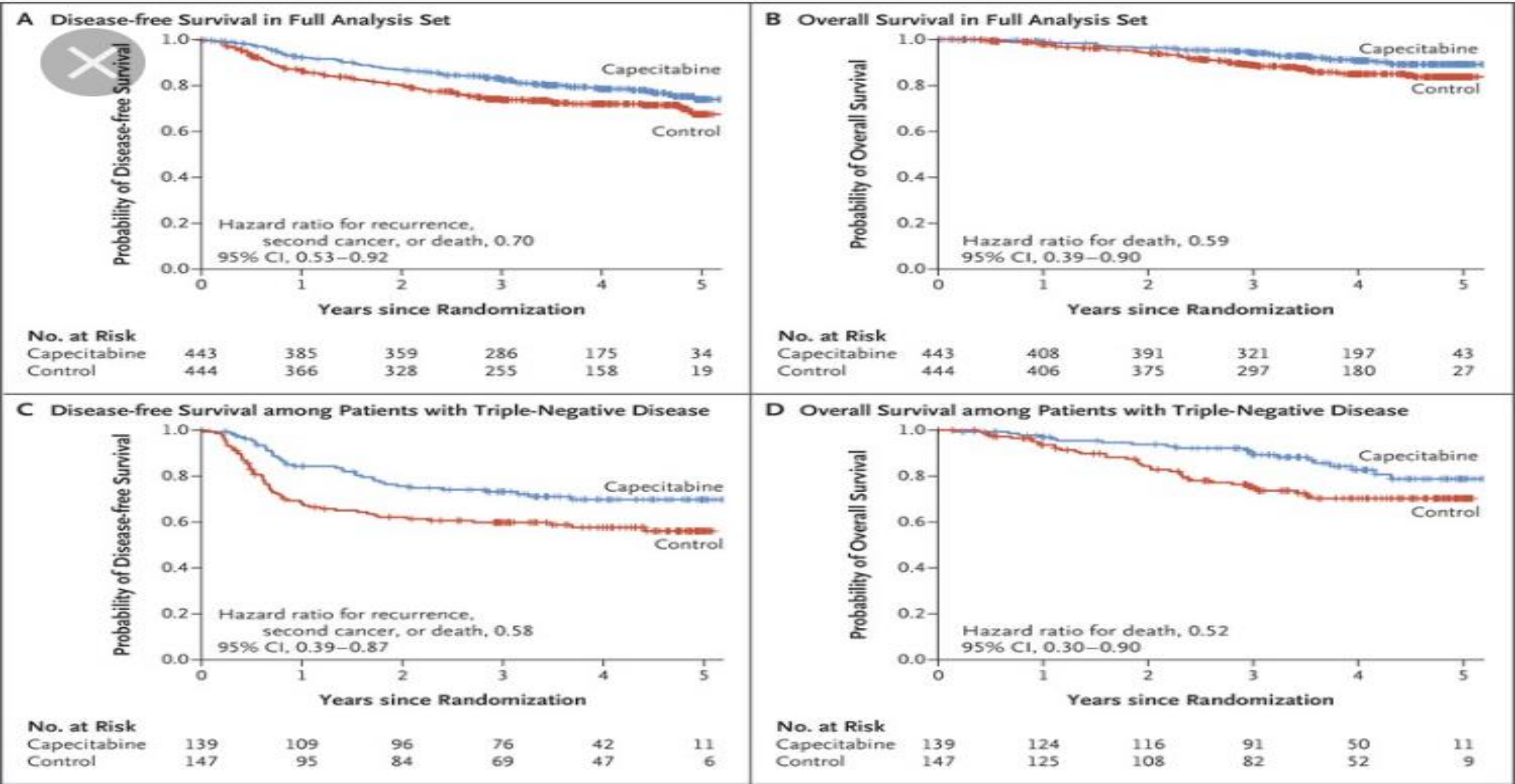
CREATE-X: A Phase III Trial of Adjuvant Capecitabine for HER2-Negative Stage I-IIIB Breast Cancer



Primary endpoint: DFS

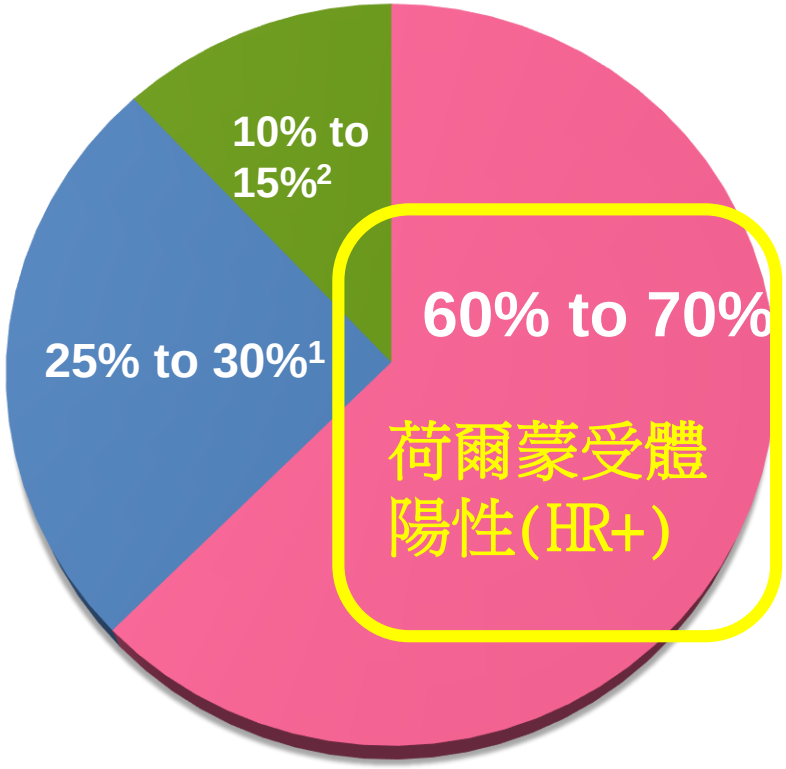
Outcome	Capecitabine (n = 440)	Control (n = 445)	HR	*p*-value
5-year DFS	74.1%	67.7%	0.70	0.00524
5-year OS	89.2%	83.9%	0.60	0.01

Subgroup analysis of DFS for pts with HR-negative disease (n = 296): HR = 0.58

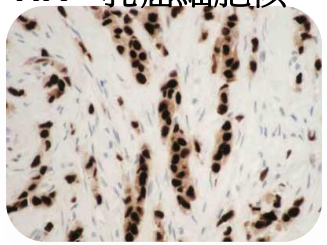


乳癌的分類

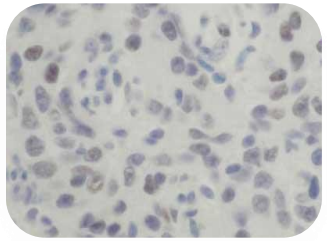
- HR + 荷爾蒙受體
- HER2 + 陽性
- Triple Negative 三陰性



免疫組織化學法下染色的 **HR+** 乳癌細胞核



A. 深色的細胞核染色代表廣泛的HR表現 (Allred 分數 = 8)



B. 淺色的細胞核染色代表低度至中度的 HR 表現 (Allred 分數 = 4)

[1]Slamon DJ, et al. *New Eng J Med*. 2001; 344:783-792; [2]Dawood S, et al. *J Clin Oncol.* 2009;27:220-226; [3] Bedard PL, et al. *Breast Cancer Res Treat*. 2008;108:307–317.

ONCOTYPE DX & TAILOR-X TRIAL

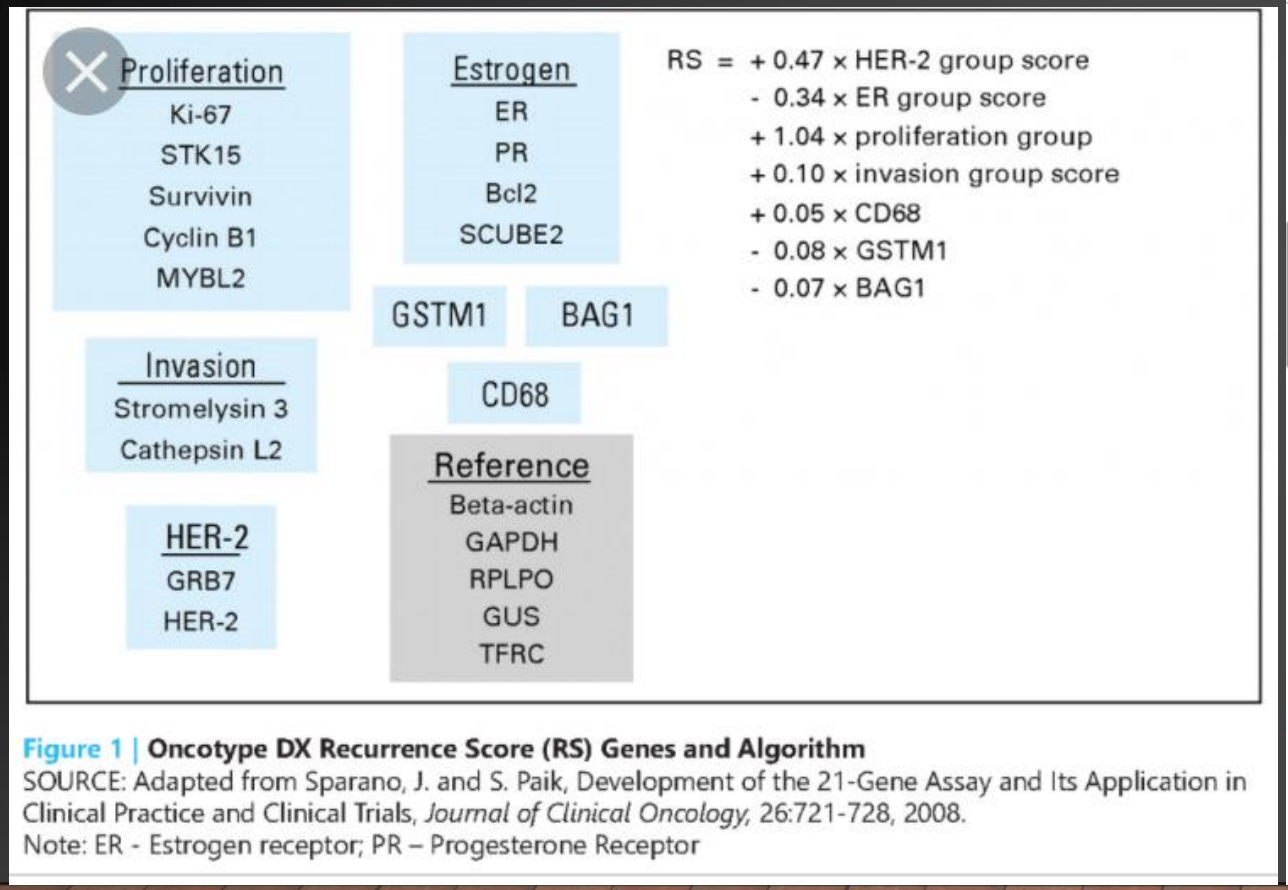
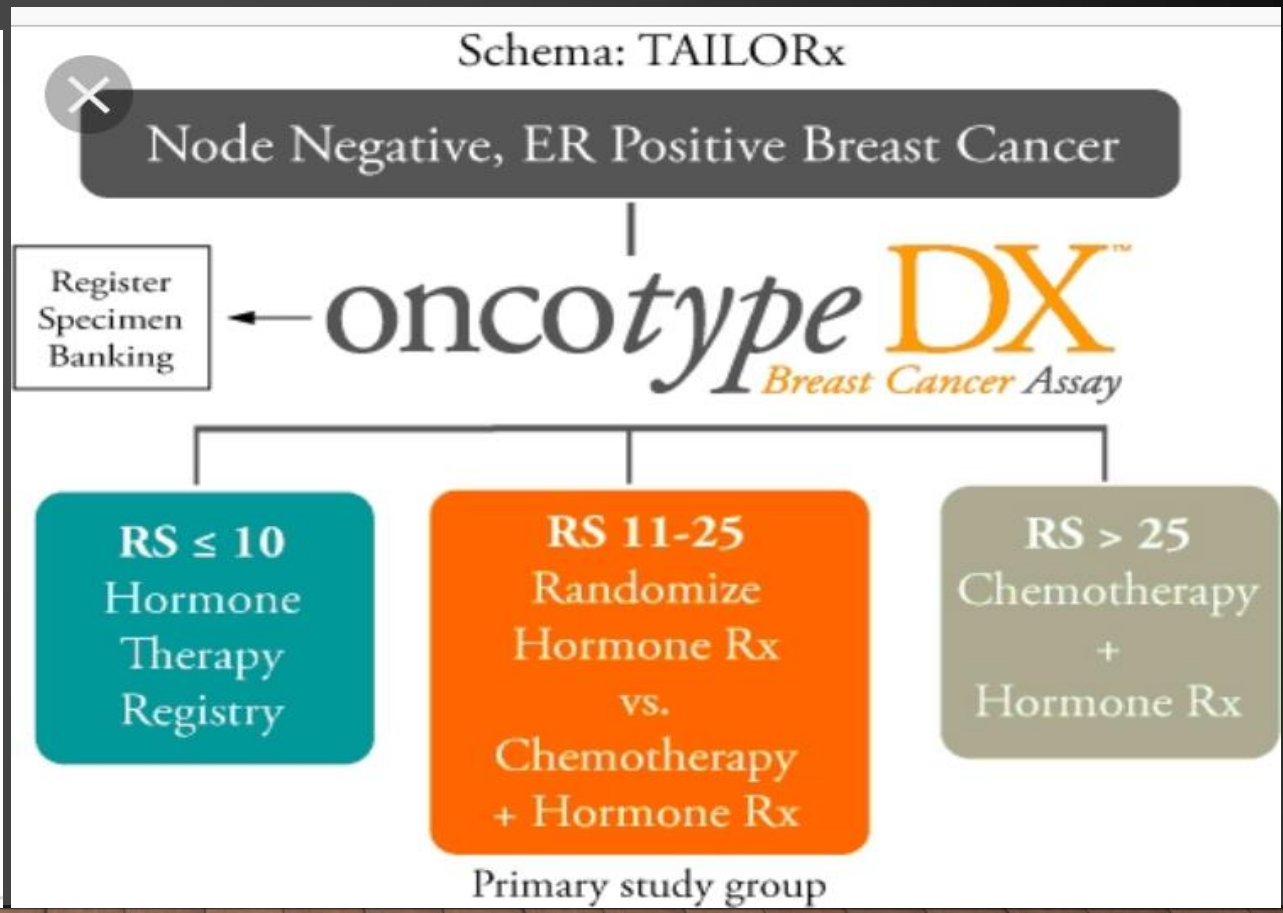


Figure 1 | Oncotype DX Recurrence Score (RS) Genes and Algorithm
SOURCE: Adapted from Sparano, J. and S. Paik, Development of the 21-Gene Assay and Its Application in Clinical Practice and Clinical Trials, *Journal of Clinical Oncology*, 26:721-728, 2008.
Note: ER - Estrogen receptor; PR – Progesterone Receptor



TAILORx: Design

- Female 18-75
- ER and / or PR +ve
- HER2-ve
- 1.1 – 5.0 cm and any grade
- 0.6-1.0 cm and grade 2/3
- Node-negative

ONCOTYPE DX

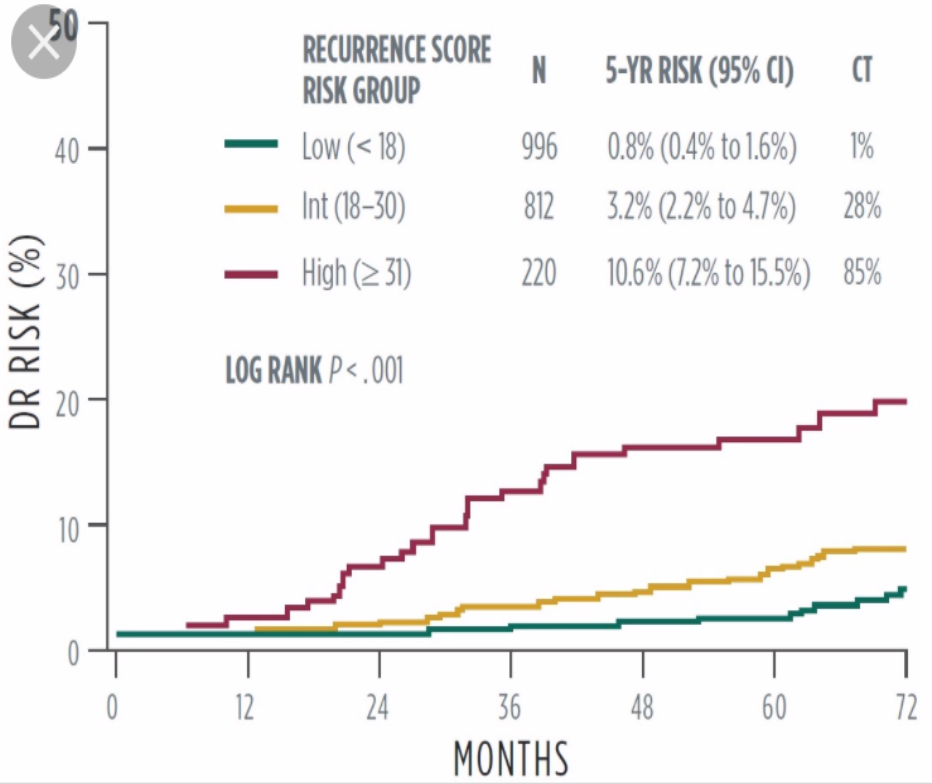
RS >25 → CT+ET

RS 11-25 → R → CT+ET / ET

RS 0-10 → ET

- primary endpoint – IDFS
- sample size based on non-inferiority of ET versus CT+ET in the 11-25 RS population

tailorx trial result of intermediate oncotype recurrence sc



Oncotype DX

Clinical Evidence | Oncoytpe DX Breast Recurrence Score ...

Data further showed that greater than 95% of patients with micromets or 1 positive node and Recurrence Score results <18 were distant recurrence free at 5 ...

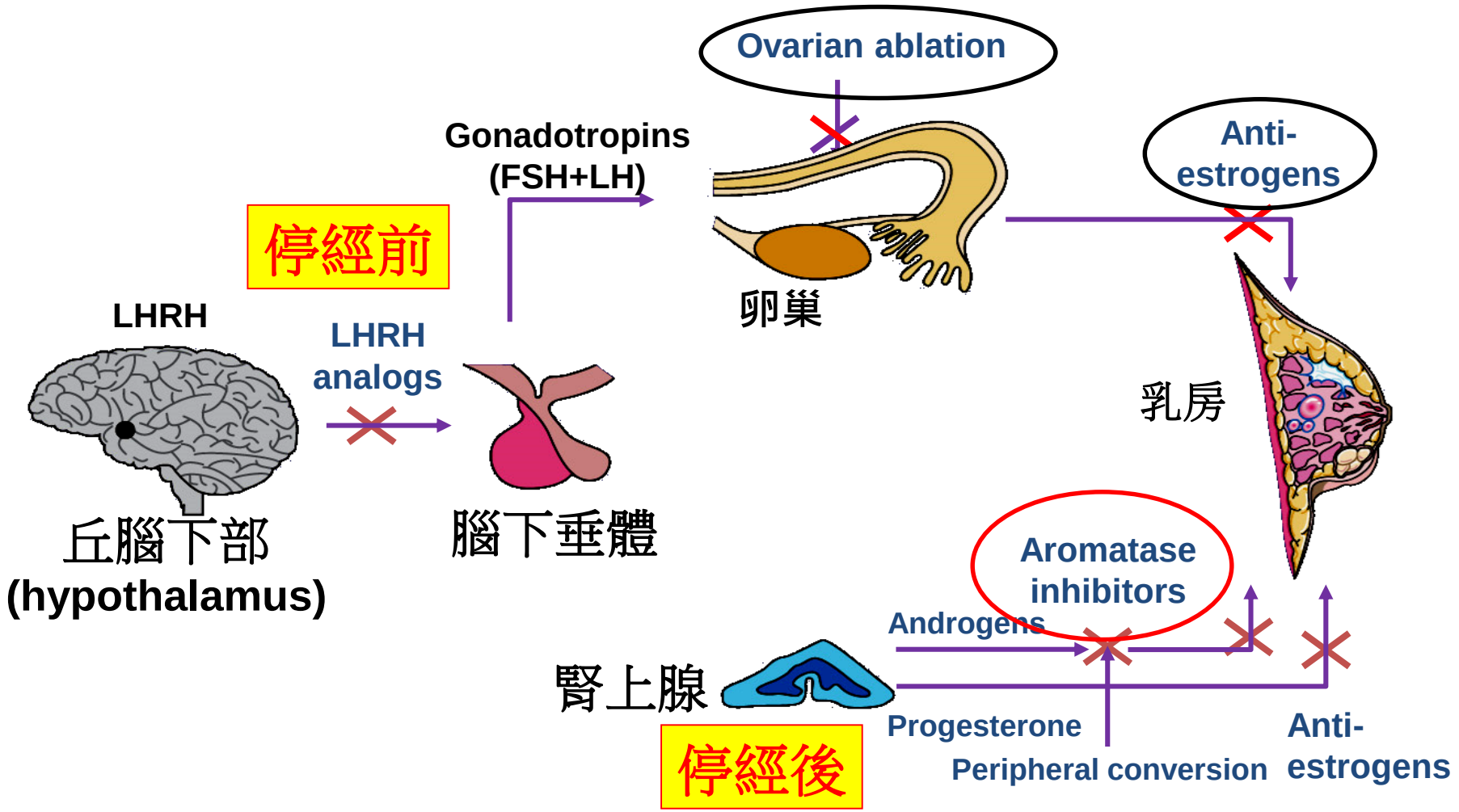
荷爾蒙治療

- 雌激素對乳房有刺激作用
- 適用於荷爾蒙受體 (ER/PR) 呈陽性反應之腫瘤

- **傳統藥物:** 抗雌激素藥 Tamoxifen (他莫昔芬, 三苯氧胺)
  - 副作用: 增加子宮內膜增生、血管栓塞（亞洲人罕見）

- **新一類藥物:** 芳香酶抑制劑 Aromatase Inhibitors (A.I.)
  - ❖ 能抑制身體內雌激素製造，進一步減低復發機會，或令乳癌細胞不能生長
  - ❖ 只適用於**停經後**的乳癌患者
  - ❖ 副作用: 熱潮、肌肉及關節痛、骨質疏鬆、心血管病等

雌激素對乳房之刺激作用



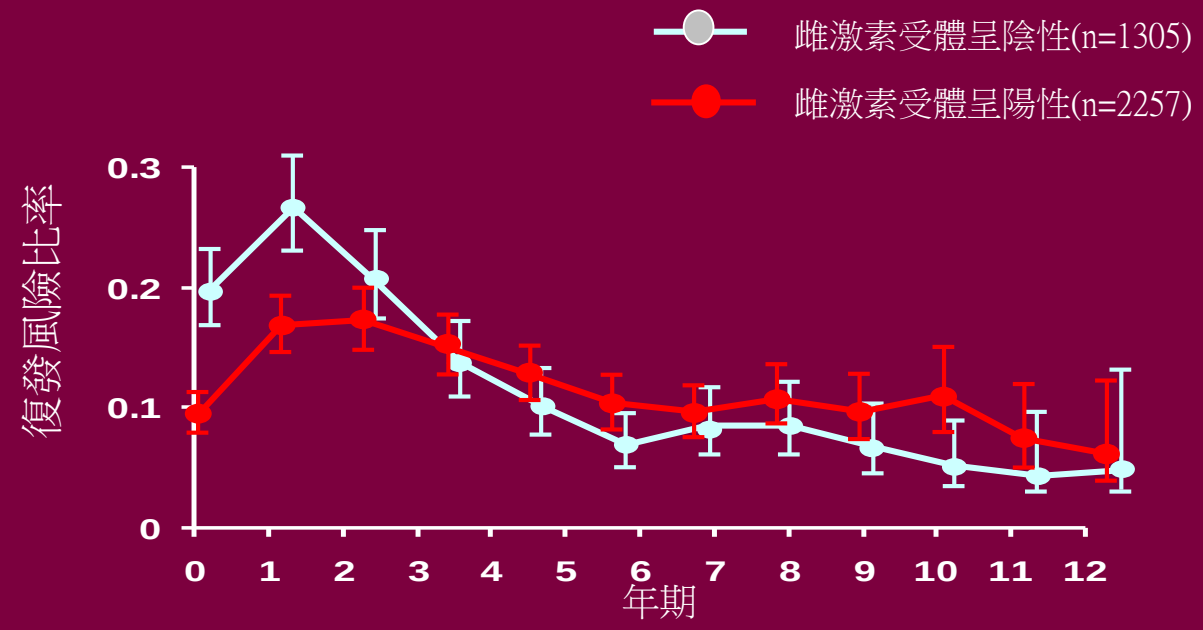
FSH = follicle-stimulating hormone; LHRH = luteinizing hormone-releasing hormone

手術後荷爾蒙治療
現今標準

- Tamoxifen 10年 (5年 ??)
- A.I. 5年
- Switch Tamoxifen 5年+A.I. 5年
- A.I. – Zometa Infusion

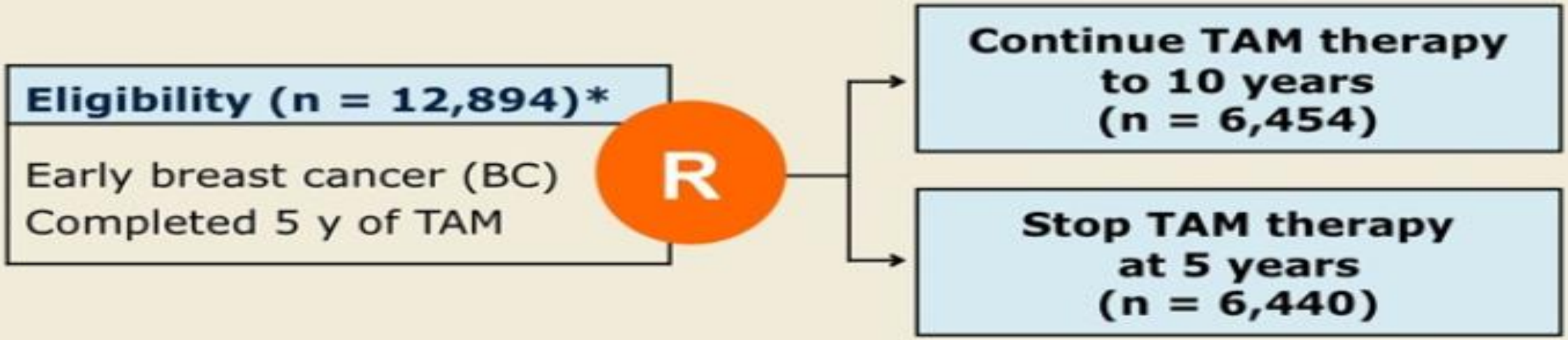
乳癌復發

- 即使手術後10年仍有復發的風險:
  - 手術後首兩年復發的風險最高
  - 手術後5至6年，復發風險會降低



1. Saphner et al. *J Clin Oncol*. 1996;14:2738.
2. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;351:1451.
3. Update of Houghton. *J Clin Oncol*. 2005;23(16S):24s. Abstract 582.

ATLAS Trial Design



* Of the study's entire population, ER-positive BC: 6,846 (53%); ER-negative BC: 1,248 (10%); unknown ER status: 4,800 (37%)

- Yearly follow-up forms sent by central organizers recorded recurrence, incidence of second cancer, hospital admission or death.
- Besides duration of TAM therapy, disease management was at physician's discretion.
- Recurrence was defined as first recurrence of any form of BC after ATLAS entry.

Davies C et al. *Lancet* 2012;[Epub ahead of print].

Event Rate Ratios in ER-Positive Disease from Time of Diagnosis in Meta-Analysis and ATLAS Trial

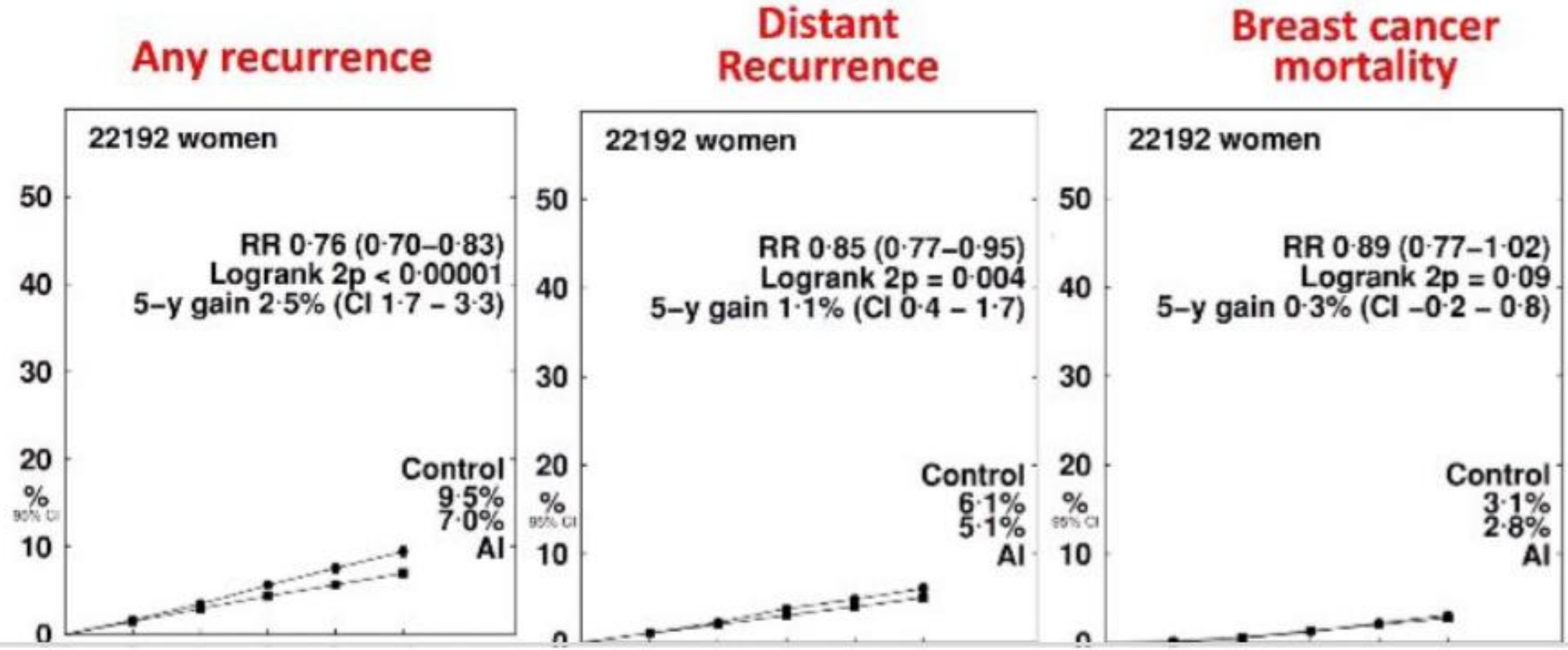
	5 y TAM vs none: Meta-analysis	10 y TAM vs 5 y: ATLAS	10 y TAM vs none*
Breast cancer recurrence ≥10 y	0.94	0.75	0.70
Breast cancer mortality ≥10 y	0.73	0.71	0.52

* Product of rate ratios, estimated effect

"Taken together with the results from trials of 5 years of tamoxifen versus none, the results from ATLAS show that 10 years of effective endocrine therapy can approximately halve breast cancer mortality during years 10-14 after diagnosis."

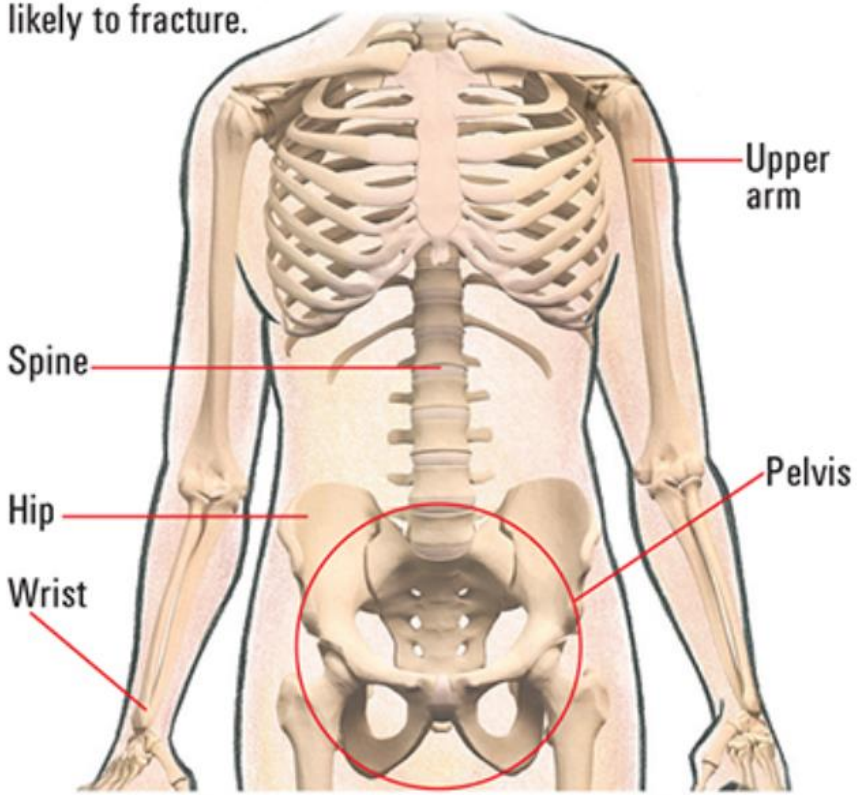
Davies C et al. *Lancet* 2012;[Epub ahead of print].

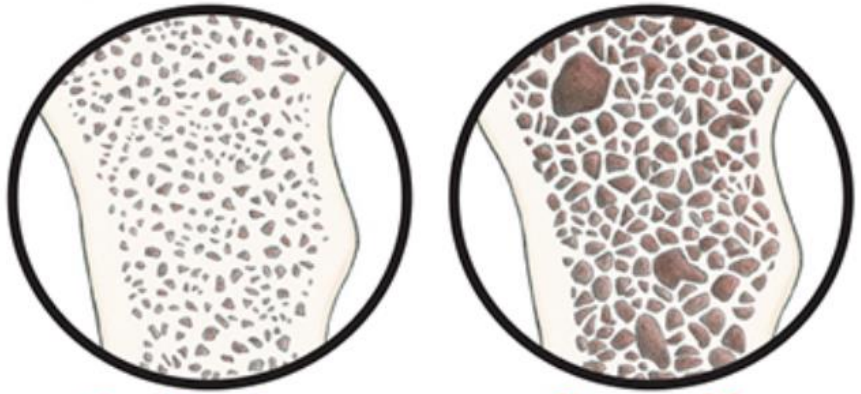
Combined results from all trials of Extended AI following 5-10 years of any prior endocrine therapy



COMMON SITES OF OSTEOPOROSIS

In men with osteoporosis, these bones are most likely to fracture.





Healthy bone

Bone with osteoporosis

zometa adjvant breast bmd

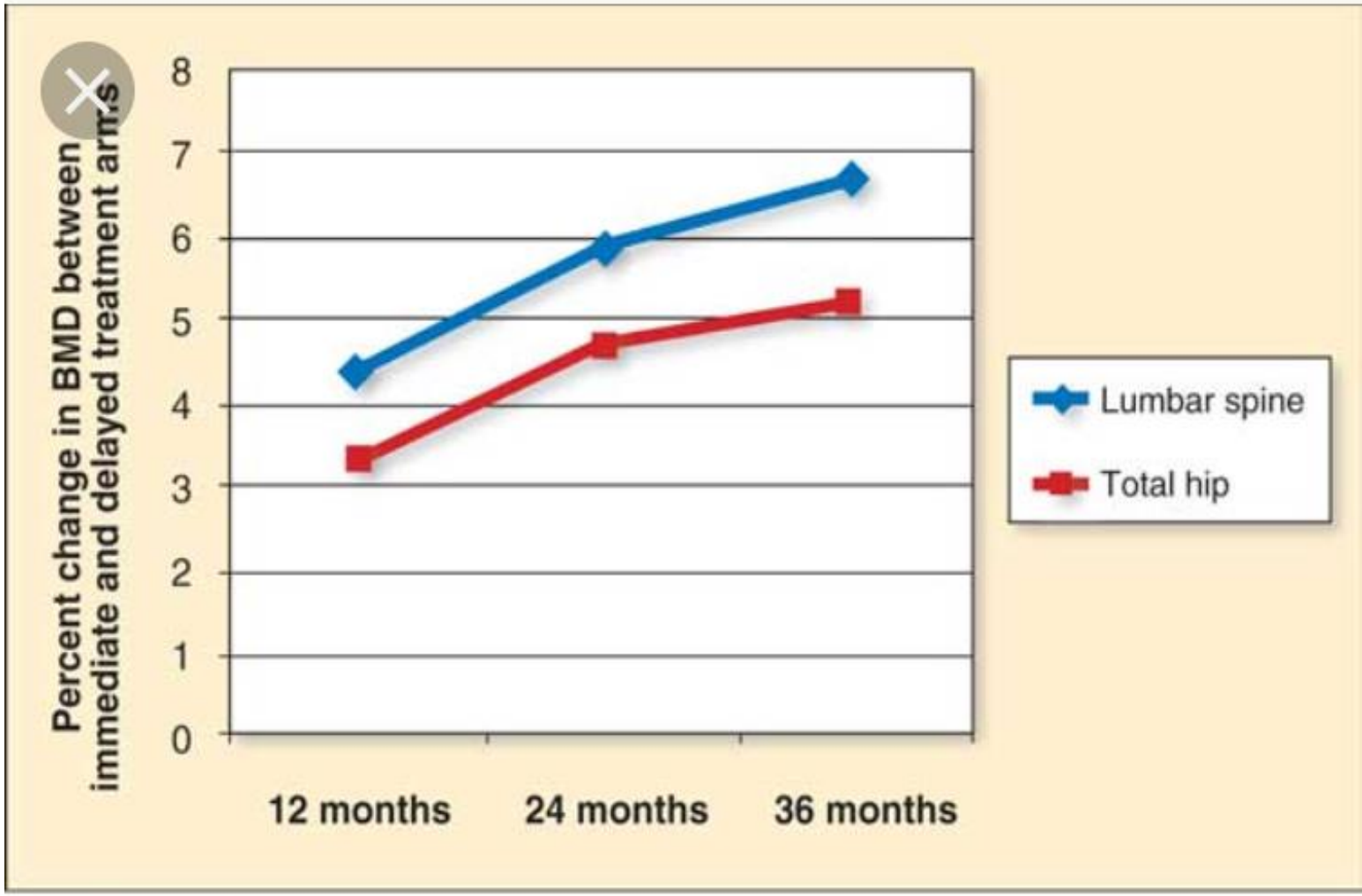


Figure 3: Zoledronic acid increased BMD at the lumbar spine and total hip in the Zometa-Femara Adjuvant Synergy Trial (Z-FAST)—This graph shows that the total percent change in bone mineral density (BMD) between the immediate-treatment arm and the delayed-treatment arm continued to increase over time. Adapted with permission from data in Brufsky A et al: *Clin Breast Cancer* 9:77-85, 2009.[36]

ebctcg meta-analysis bisphosphonates

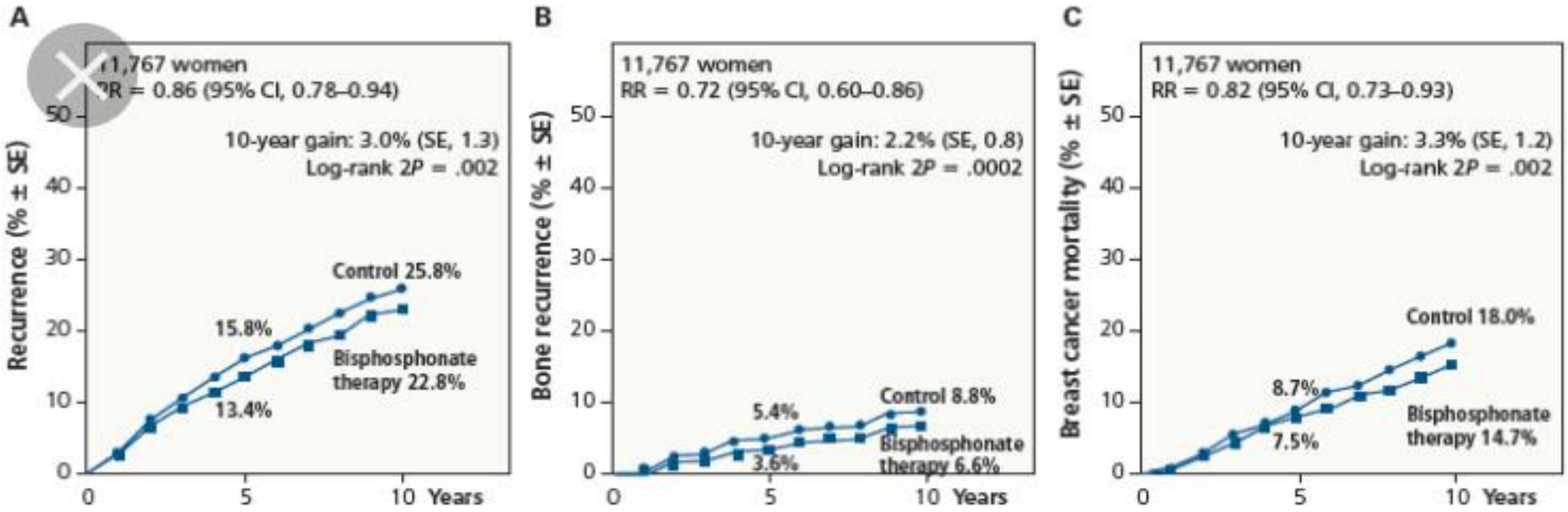


Figure 2. Results From the EBCTCG Meta-Analysis of Treatment With Adjuvant Bisphosphonates. Data are for postmenopausal women and show **(A)** breast cancer recurrence, **(B)** bone recurrence, and **(C)** breast cancer mortality.[22] EBCTCG = Early Breast Cancer Trialists' Collaborative Group; RR = relative risk; SE = standard error. Figure reprinted from Early Breast Cancer Trialists' Collaborative Group et al. Lancet. 2015.[22] Published under a Creative Commons License [https://creativecommons.org/license]. DOI: http://dx.doi.org/10.1016/S0140-6736(15)60908-4. Open access funded by Cancer Research UK.

放射治療: 手術後治療的選擇 (一)

必要做放射治療的情況：

1. 保留乳房

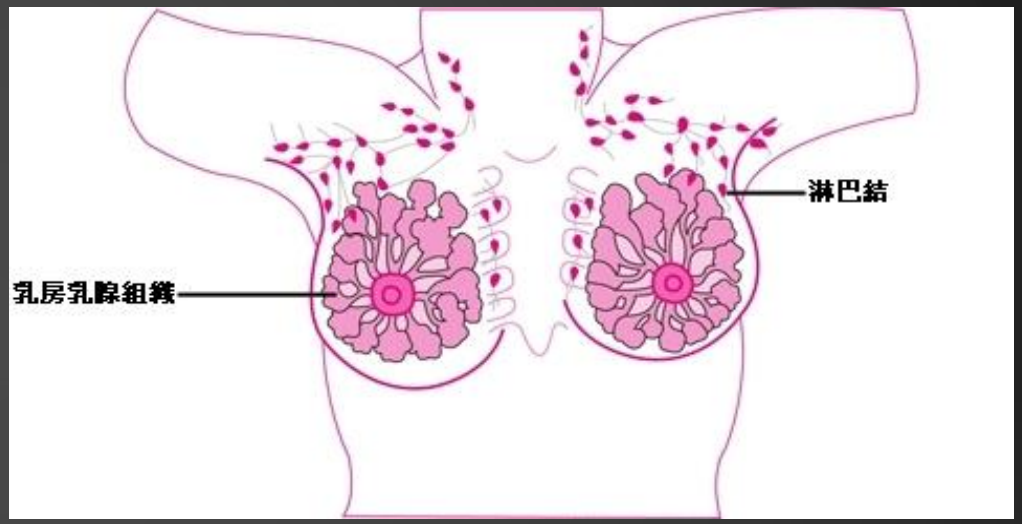
2. 全乳切除 - 主瘤 > 3 - 5公分
- 切割口近或穿破主瘤
- 腋下 > 3 顆淋巴核影響

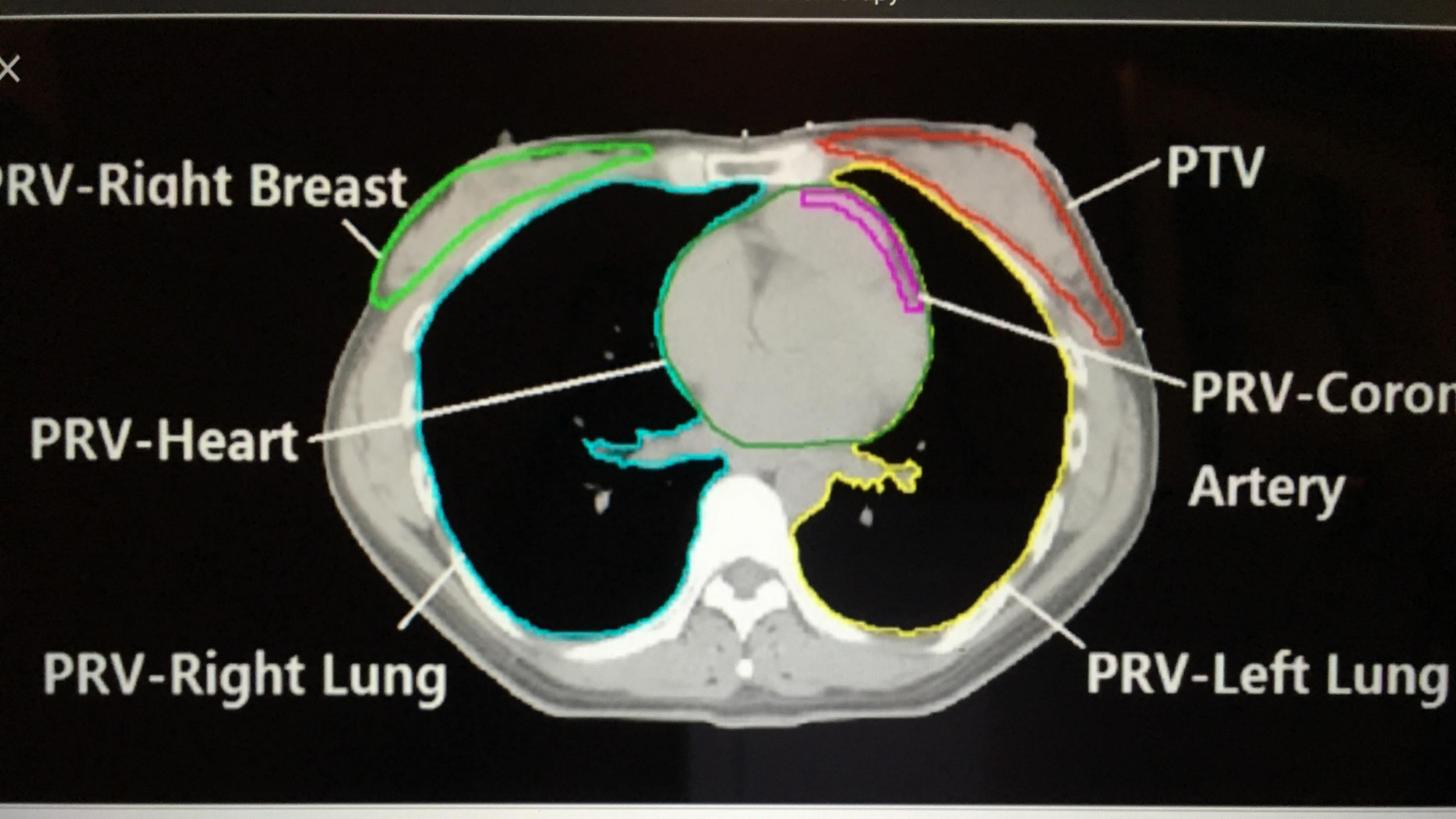
3. 灰色地帶 - 1-3顆腋下淋巴核 / 血管侵佔
- 高惡性、生長活躍主瘤
- 不利的主瘤位置

放射治療: 手術後治療的選擇 (一)

治療目標：

- 主瘤 – 主瘤盤地 、全乳 / 胸口
- 淋巴區域 – 腋下第一、二、三區
  - 內乳房淋巴區
  - 鎖骨上 (下頸)區
- 可能受影響的正常組織 – 肺、心、淋巴回流、臂叢神經
  - 肝、胃



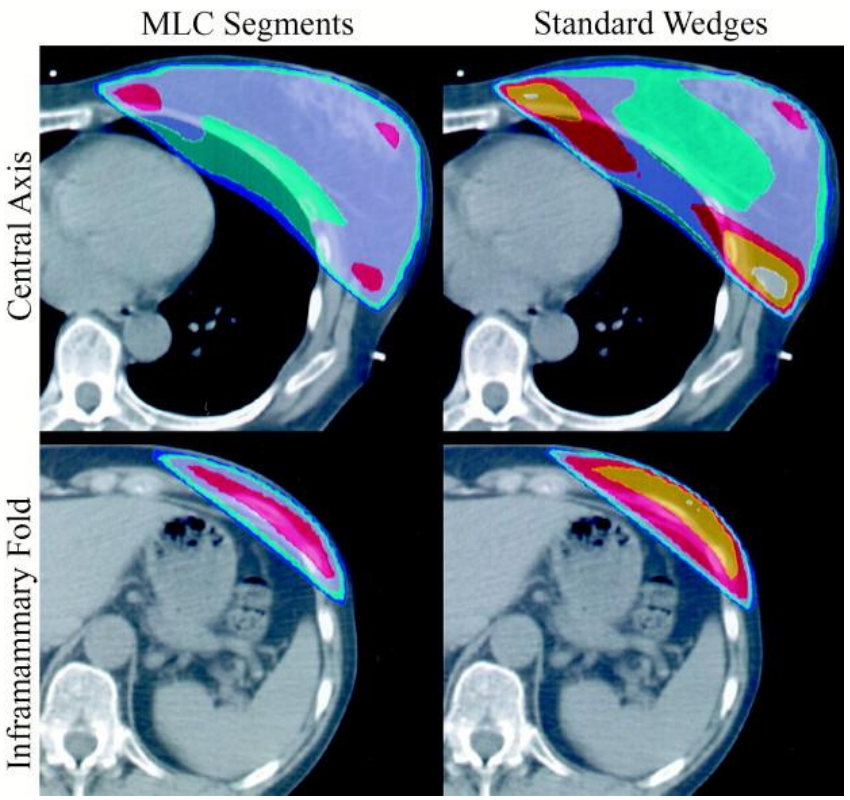

PRV-Right Breast
PTV
PRV-Heart
PRV-Coron
Artery
PRV-Right Lung
PRV-Left Lung

手術後治療的選擇 (三)

放射治療技術分類 ：

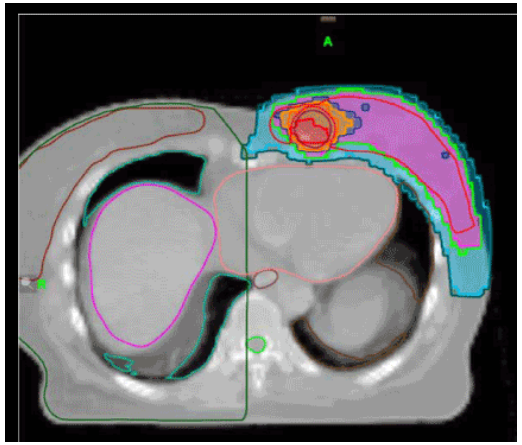
- 3D-Conformal (三維適形放射技術)
- IMRT- RapidArc (容積弧形調強放射技術)
- Tomotherapy (螺旋斷層放射治療技術)
- Active Breath Control – ABC
  (主動式呼吸調控技術)

放射治療 (Radiotherapy)



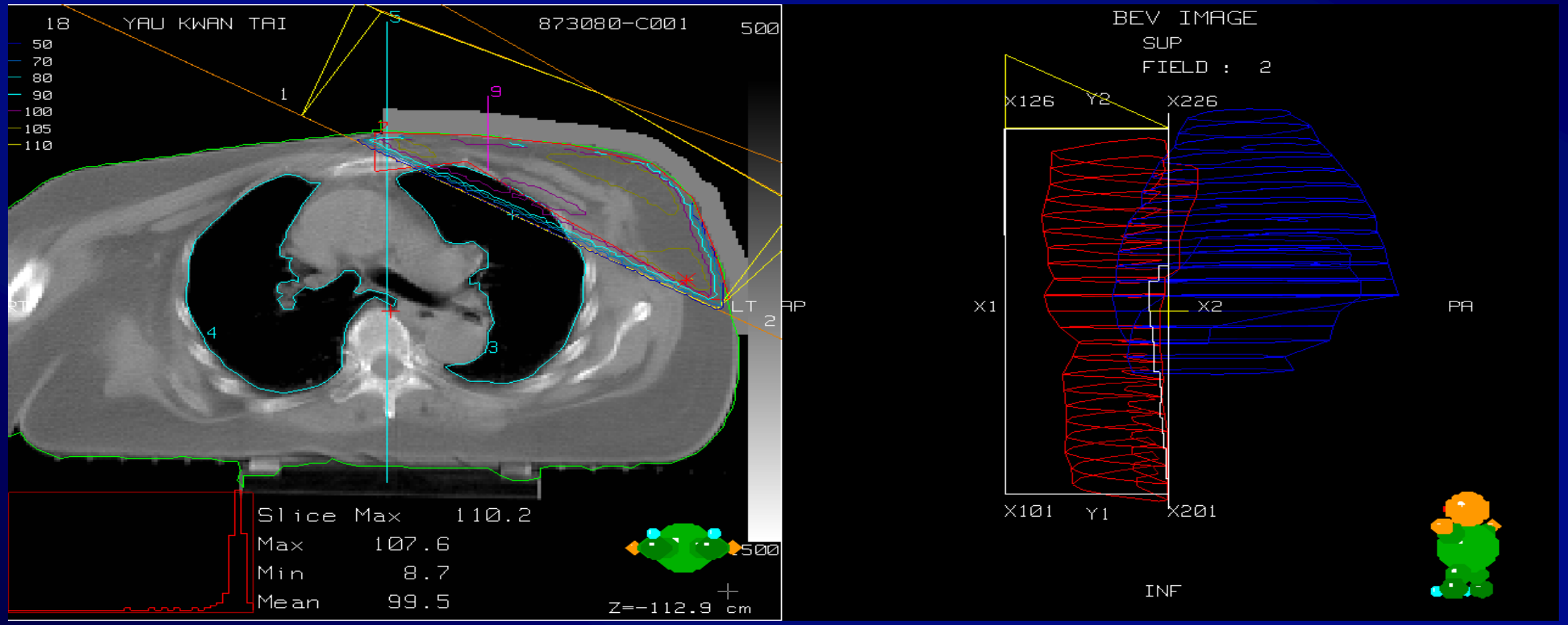
3D傳統電療法

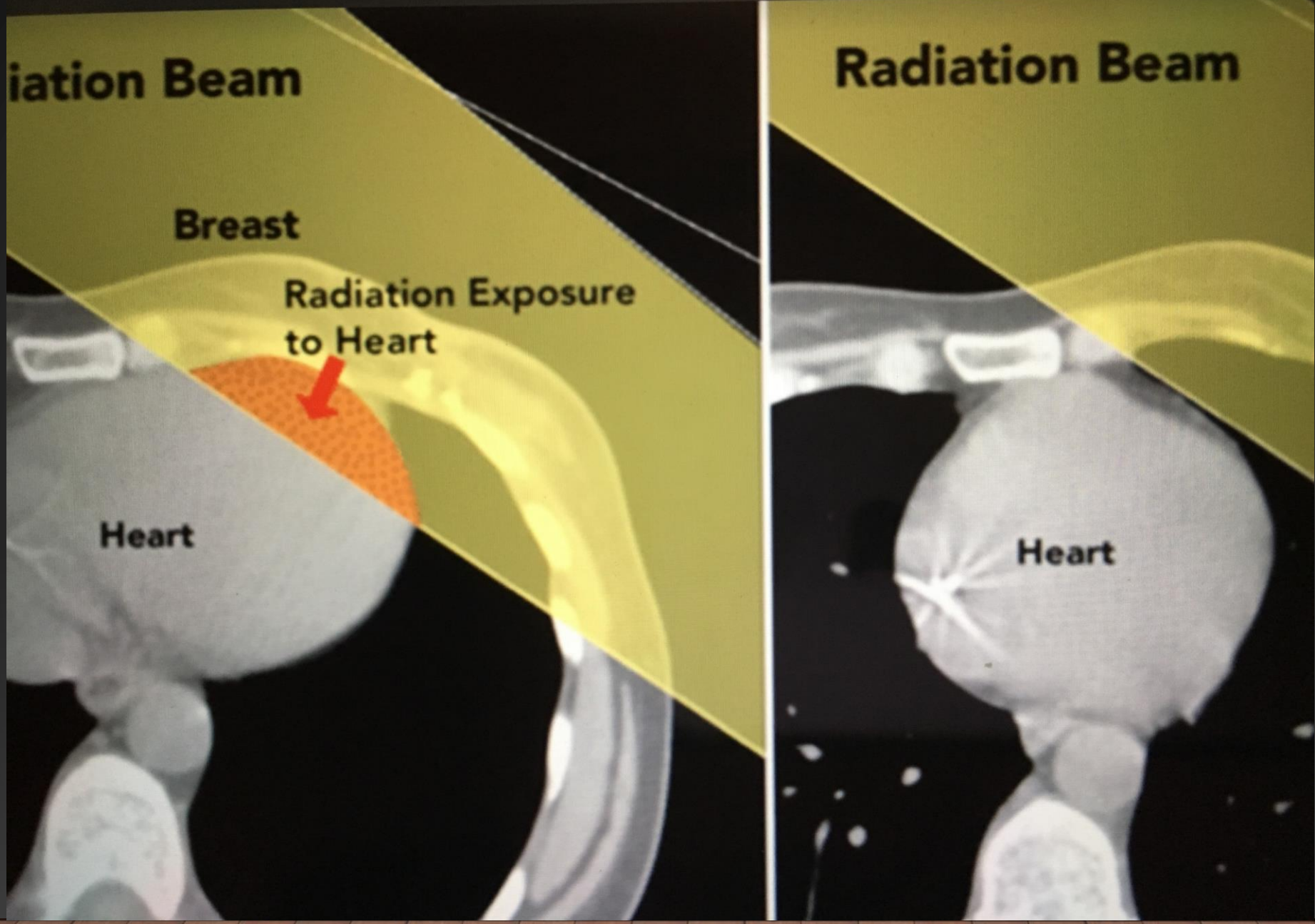
IMRT/RapidArc

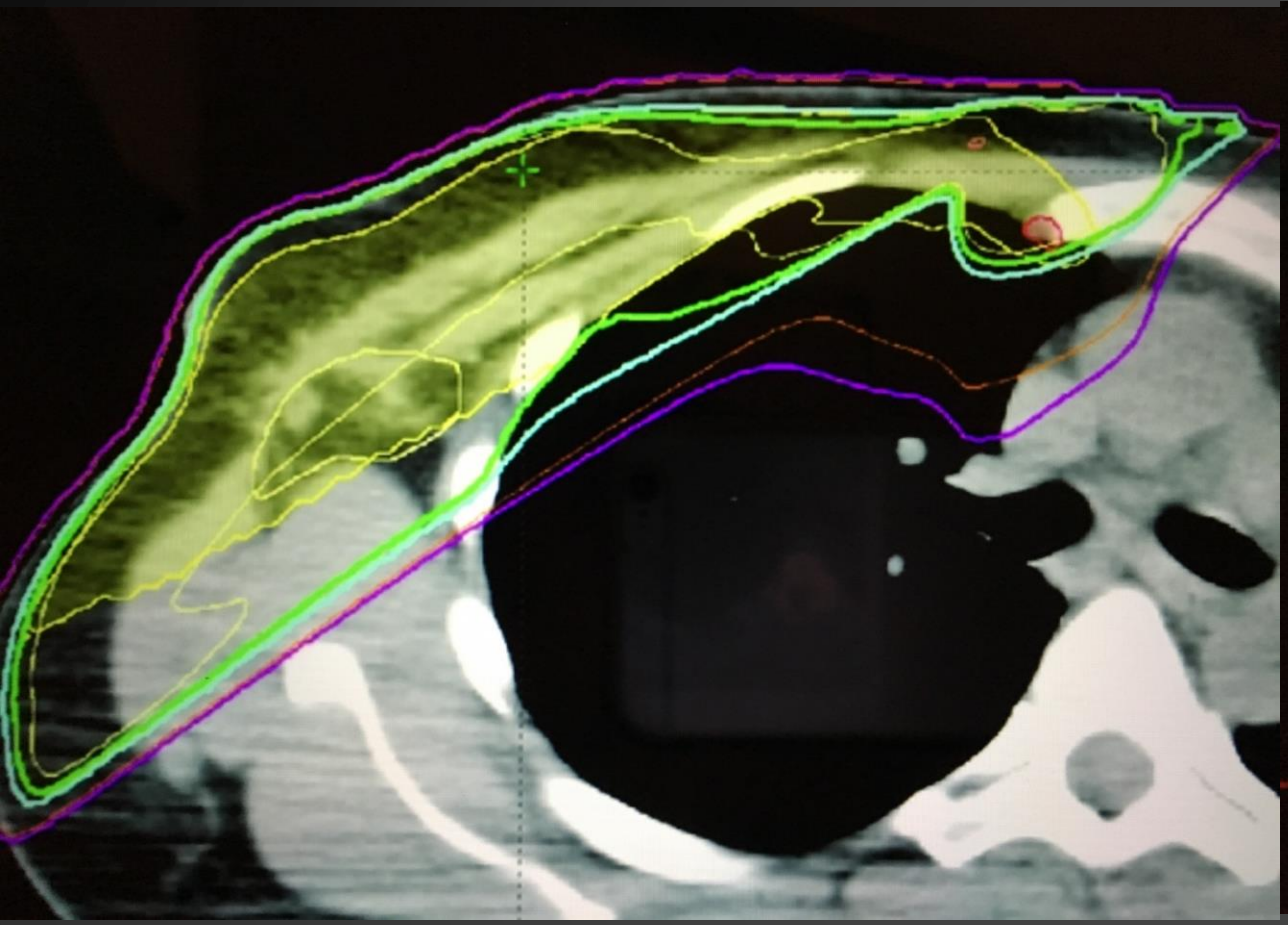


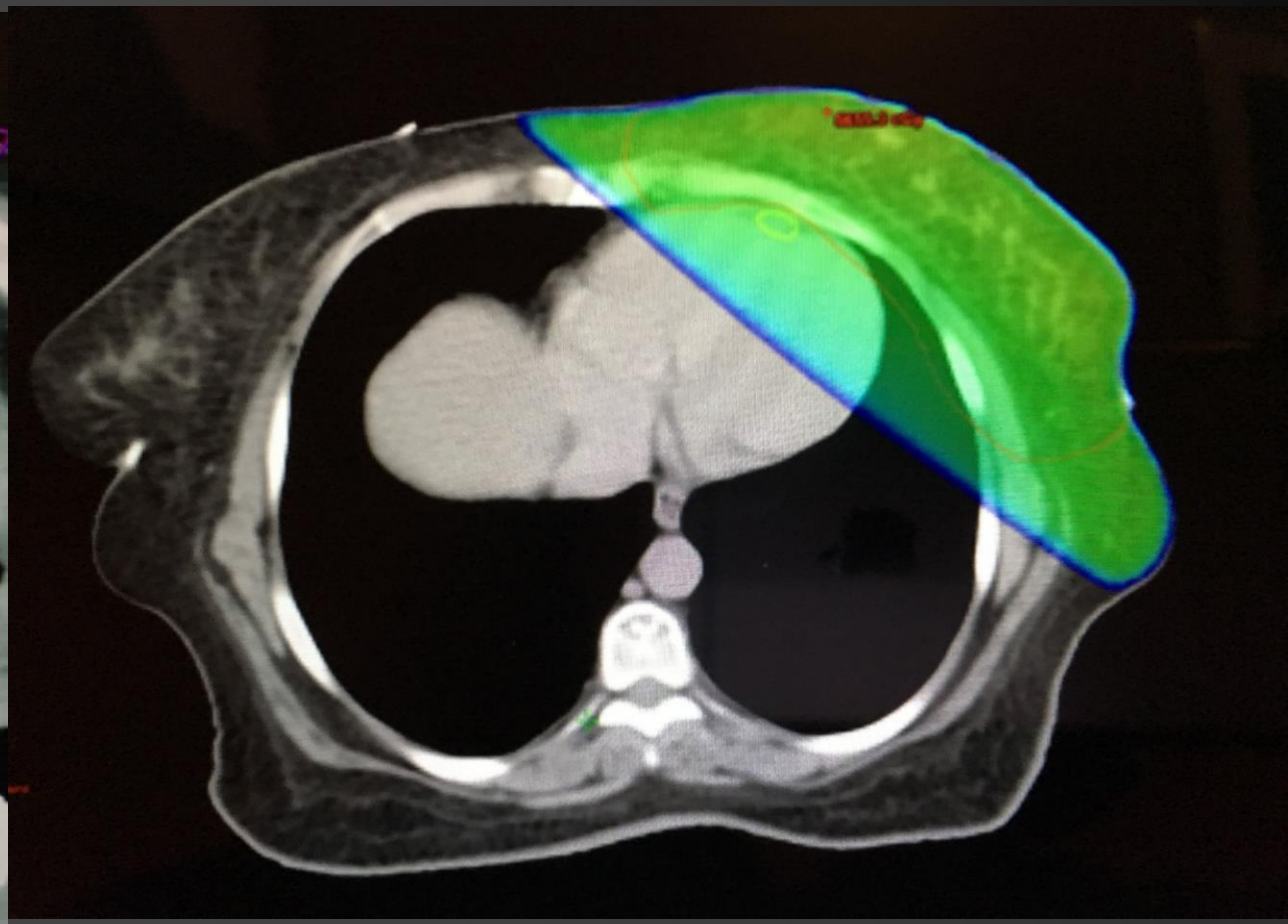
Tomotherapy
螺旋電療機器

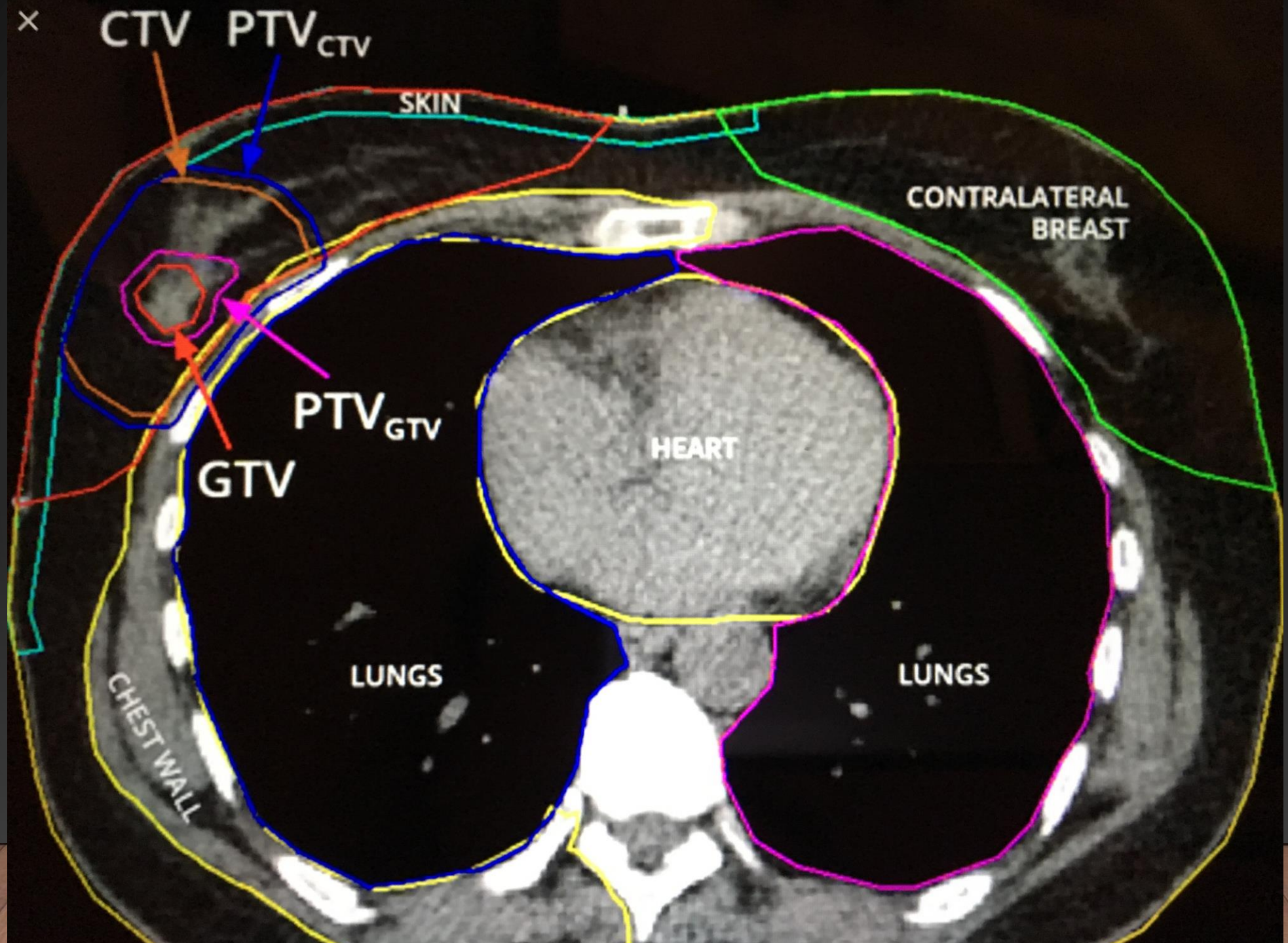
3D -電腦素描設計放射治療
- 減低對肺部的損害




iation Beam
Breast
Radiation Exposure
to Heart
Heart
Radiation Beam
Heart



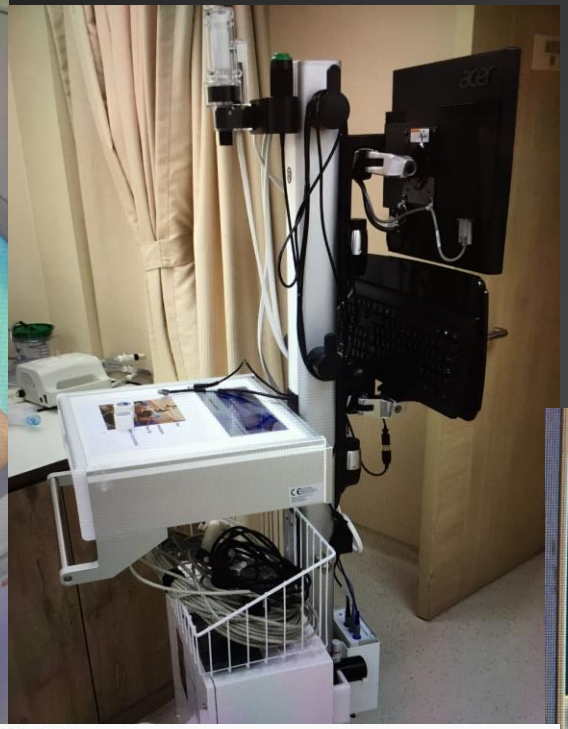



CTV
PTV$_{CTV}$
SKIN
CONTRALATERAL BREAST
PTV$_{GTV}$
GTV
HEART
LUNGS
LUNGS
CHEST WALL

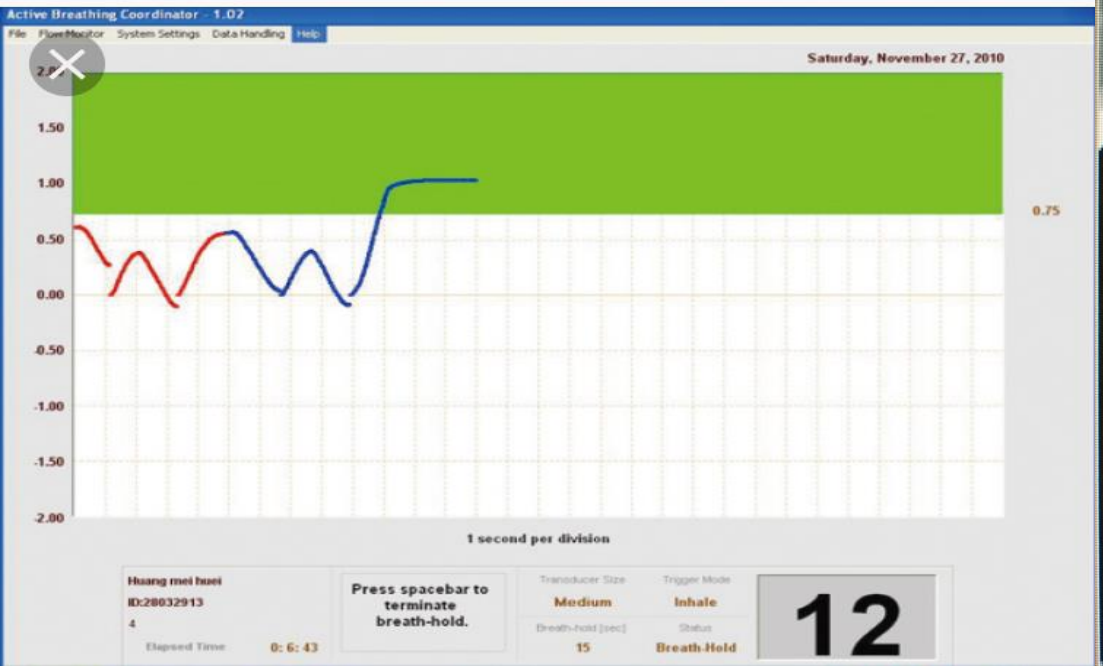
速狐 / 調強放射治療技術

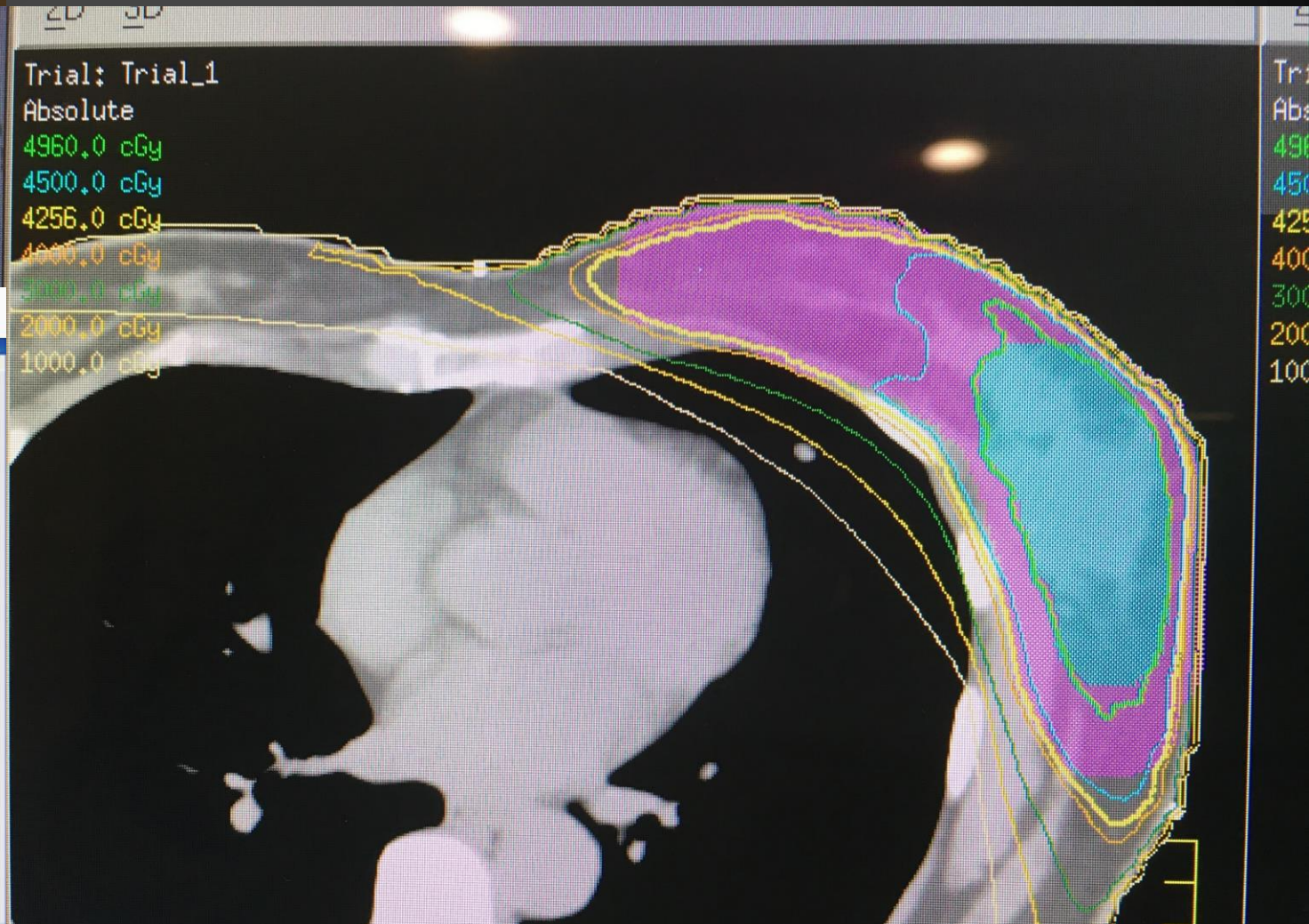
Tomotherapy

ACTIVE BREATH CONTROL
ABC （主動式呼吸調控技術)

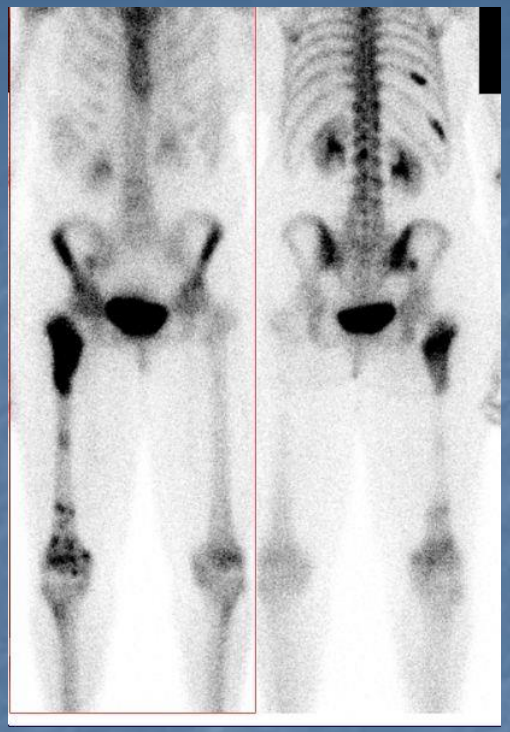


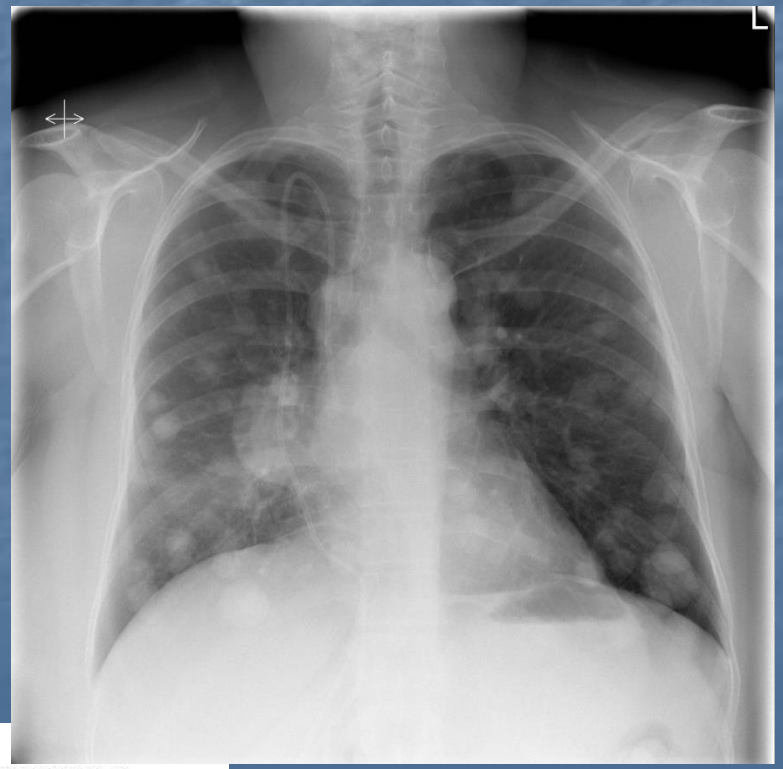
abc radiotherapy

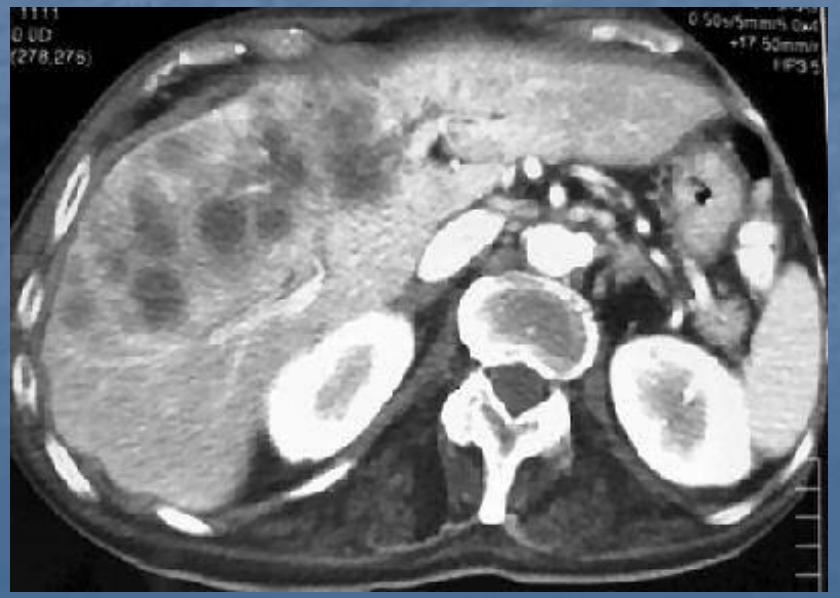




擴散乳癌



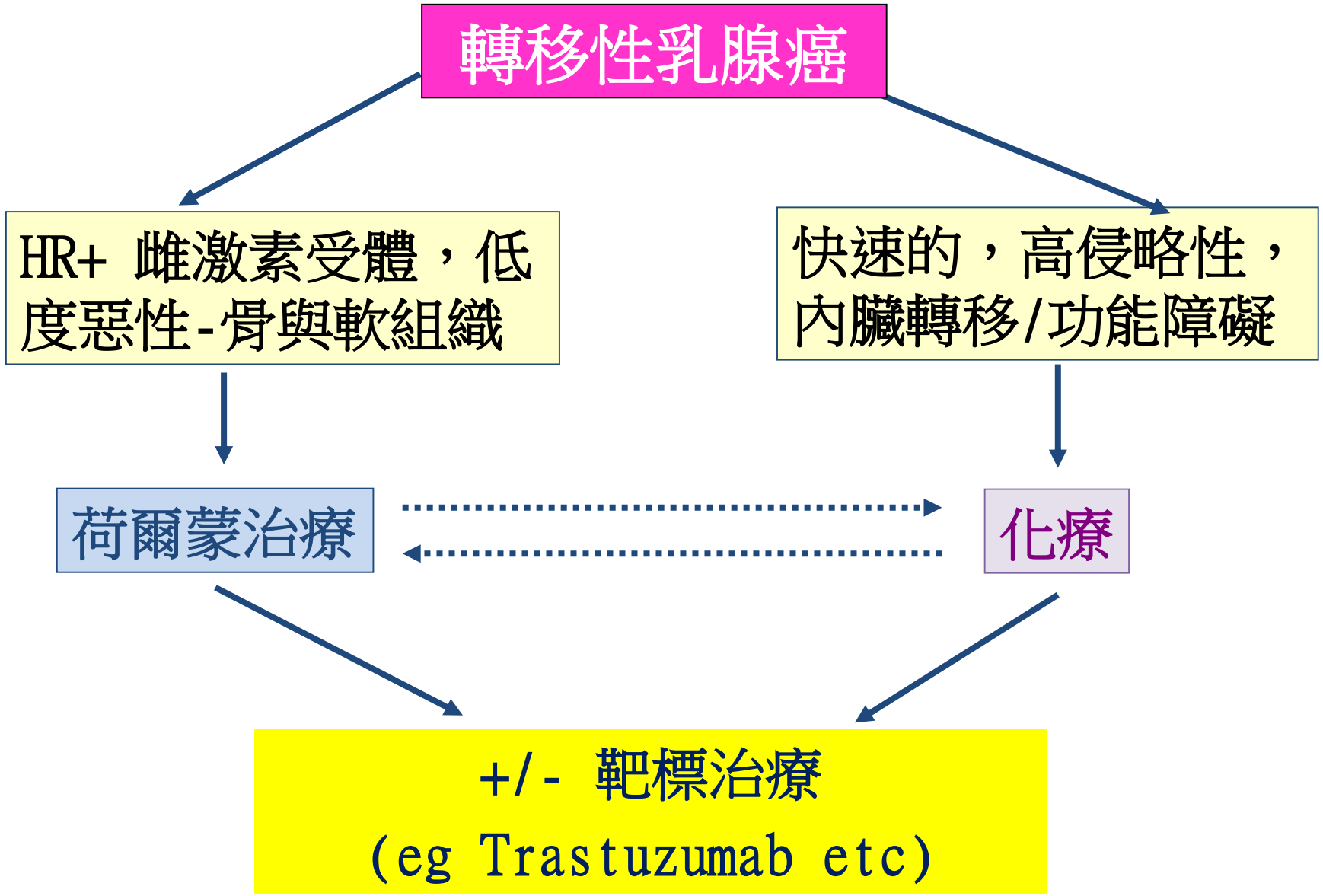




全身治療在MBC個案的目的

- 在考慮到病人身體可接受下用藥
- 使病人身上的癌腫縮小
- 延長病人(無病徵)的壽命和增加存活率
- 個別腫瘤細胞負荷少的病人，腫瘤或可進入多年睡眠狀態或可痊癒

轉移性乳腺癌的治療


轉移性乳腺癌
HR+ 雌激素受體，低度惡性-骨與軟組織
快速的，高侵略性，內臟轉移/功能障礙
荷爾蒙治療
化療
+/- 靶標治療
(eg Trastuzumab etc)

HER2+標靶治療

新一代抗癌藥物，能針對癌細胞的特別生長基因和它們所產生的蛋白(即癌細胞的生物標記)，抑制癌細胞的生長或殺死癌細胞，它們通常副作用較少，一般稱為標靶藥物。

類別	核准的藥品	副作用
上皮細胞生長因子受體抑制劑 (EGFR inhibitor)	曲妥珠單 (Trastuzumab)	腹瀉、刺激注射部位皮膚發红、反胃、嘔吐、口腔潰瘍、肚子痛、心臟功能受損
	拉帕替尼 (Lapatinib)	腹瀉、胃部不適、皮疹、口腔潰瘍
	T-DM1 (Trastuzumab emtansine)	疲倦反胃、肌肉骨骼痛、頭痛、便秘
HER2聚化抑制劑的單克隆抗體	帕妥珠單抗 (Pertuzumab)	心臟問題、腹瀉、反胃、嘔吐、疲倦、食欲不振、暫時性脫髮

擴散乳癌HER-2+治療

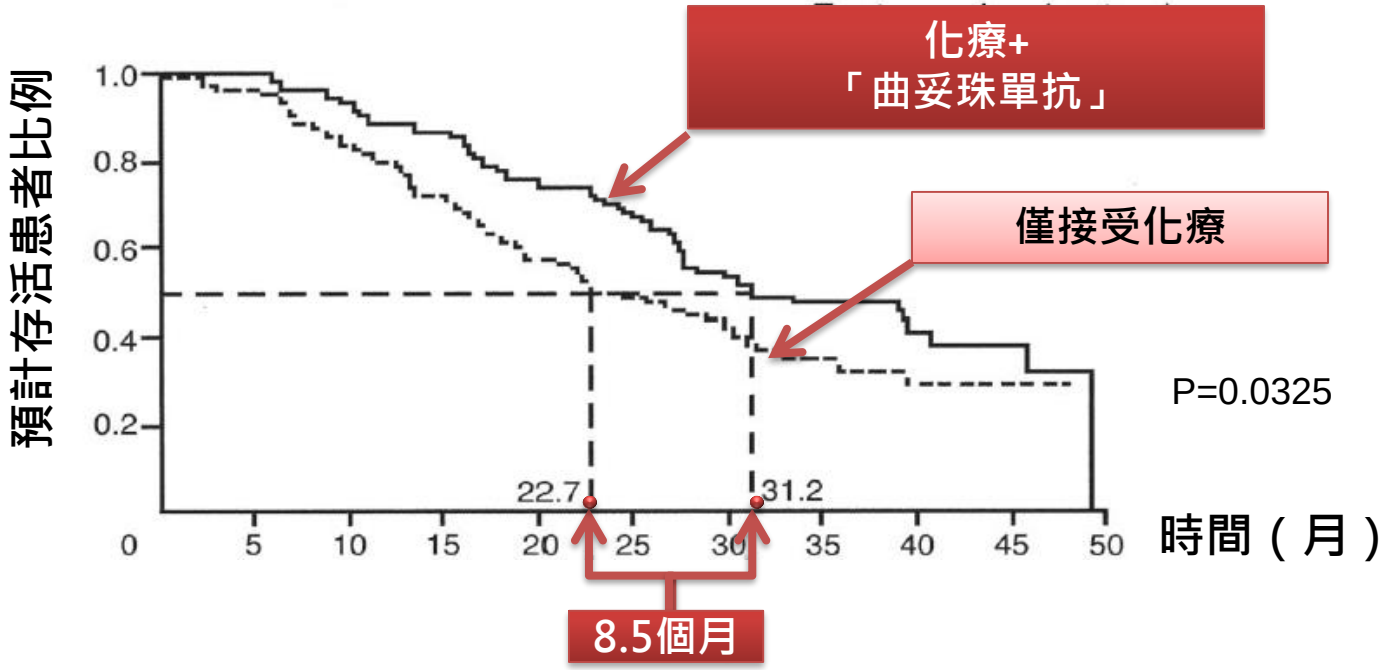
1ST Line : H + P + Chemo

2nd Line : TDM-1 (Kadcyla)

3rd Line : Lapatinib +Capecitabine

*要注意腦轉移的發生

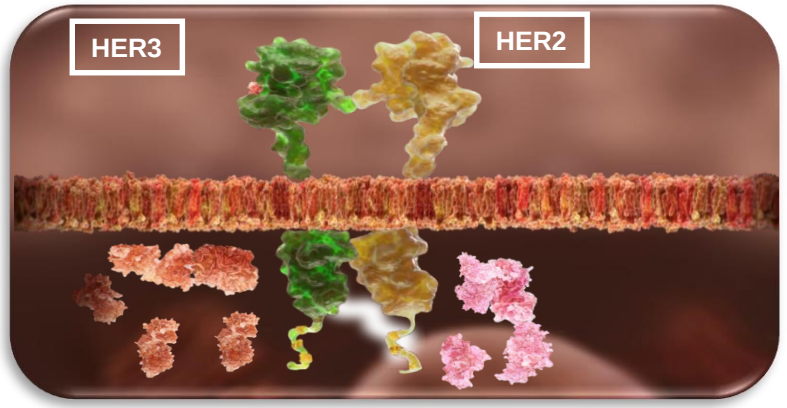
Trastuzumab「曲妥珠單抗」用於轉移性HER2型乳癌的一線治療



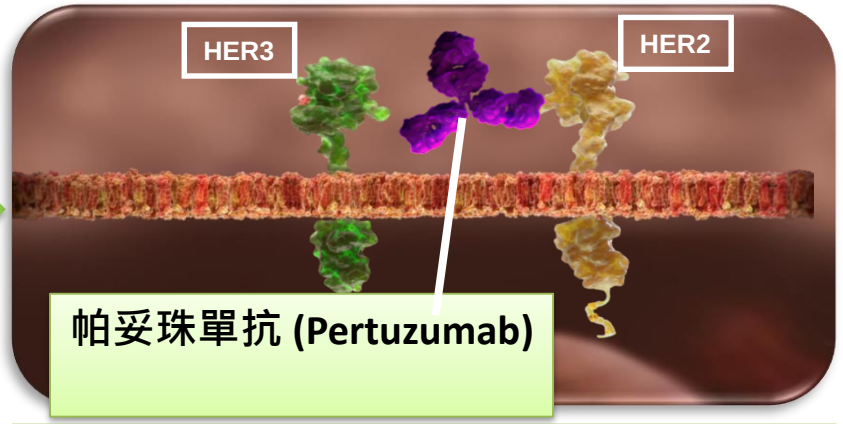
●在轉移性HER2型乳癌患者中，在化療同時加入「曲妥珠單抗」治療，將患者整體存活期中位數由22.7個月延長至31.2個月，延長了8.5個月。

Marty M et al., J Clin Oncol. 2005 Jul 1;23(19):4265-74.

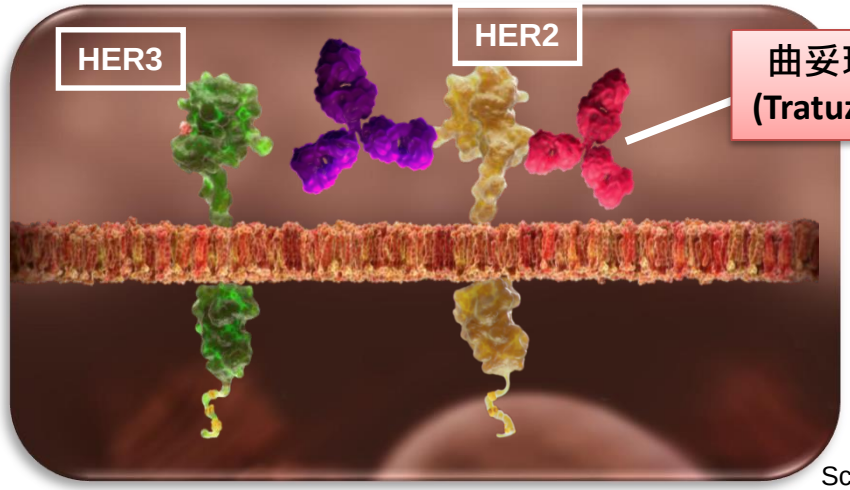
HER2型乳癌—嶄新標靶治療
「帕妥珠單抗」（Pertuzumab）



HER2受體超量表達會產生訊號，令到癌細胞增生及分裂。HER2受體會跟其他HER受體配對起來(二聚作用)，並產生這些增生及分裂訊號



當帕妥珠單抗 (Pertuzumab) 進入人體，與HER2受體的聚合處，並抑制它與其他HER受體相聚合，阻斷訊號傳遞

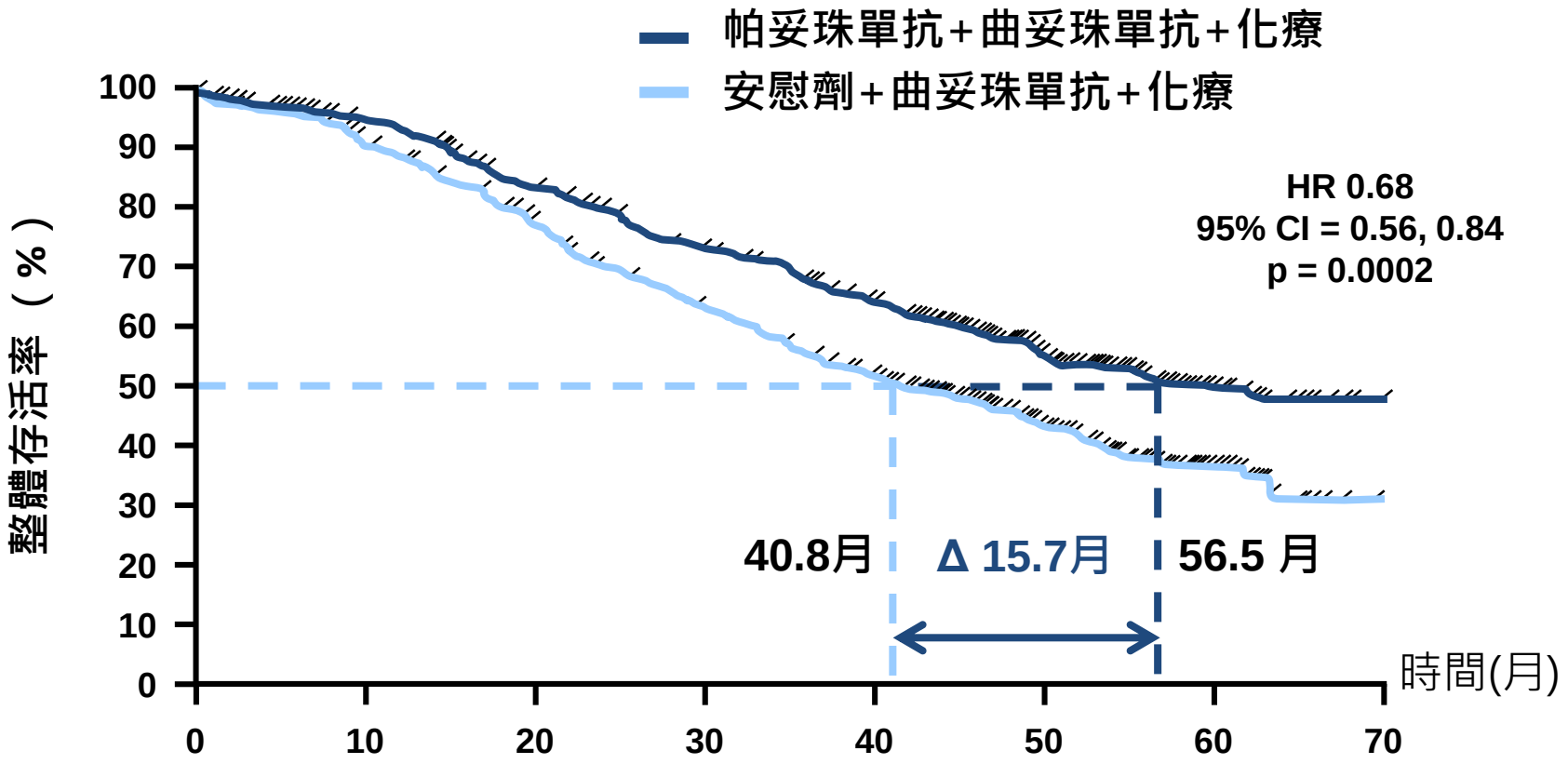


而曲妥珠單抗(Tratuzumab) 會與HER2受體的另一部分結合，阻截HER2訊號路徑

曲妥珠單抗與帕妥珠單抗同時使用，可更有效封鎖HER2訊號傳遞路徑，並控制癌細胞生長

Schulz R. et al., Cell Death and Disease (2014) 5, e980; doi:10.1038/cddis.2013.50
Scheuer W., et al., *Cancer Res* 2009;69:9330-9336
Nahta R, et al. Cancer Res 2004:64, 2342-2346

「帕妥珠單抗」提高患者存活率

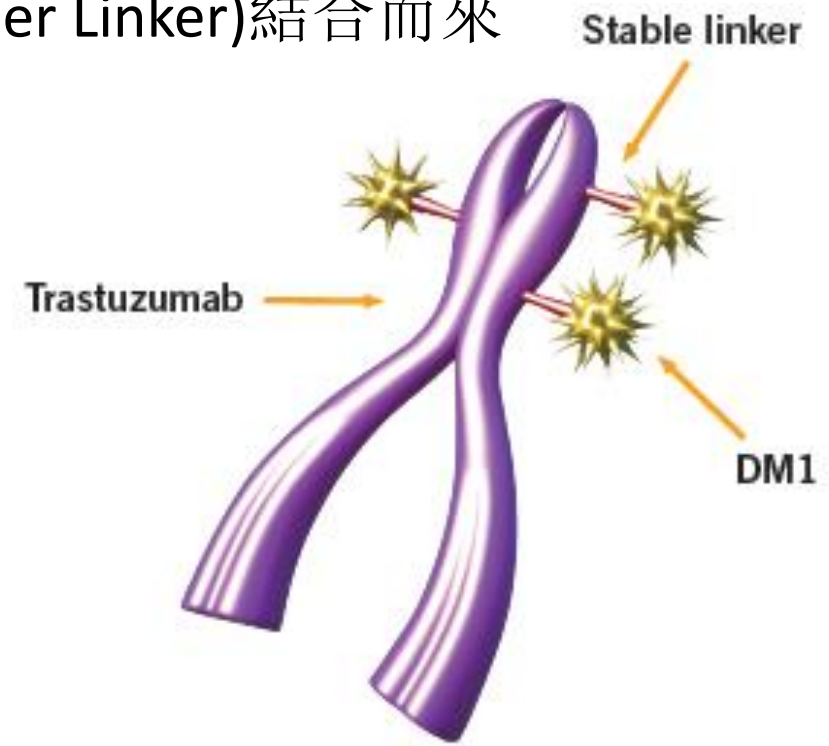


研究結果顯示，在提高晚期HER2型乳癌患者存活率方面，接受「帕妥珠單抗 + 曲妥珠單抗 + 化療」的治療組比接受「安慰劑+曲妥珠單抗 + 化療」治療可延長多15.7個月

Swain SM, et al. ESMO 2014, Madrid, Spain (Abstract 350O_PR)

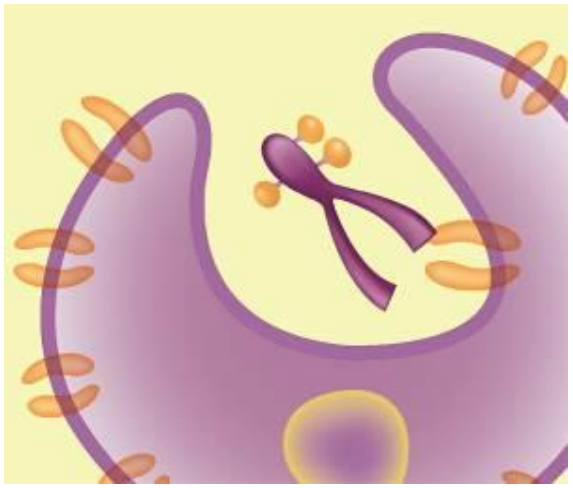
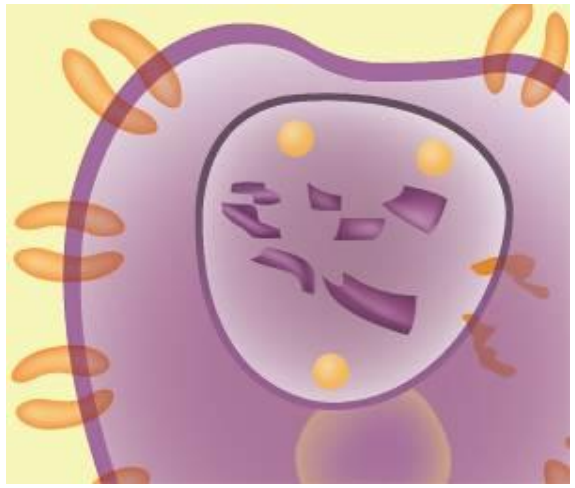
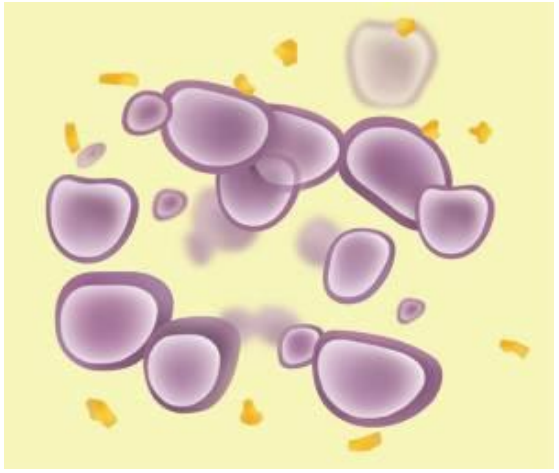
T-DM1 (Kadcyla) 的結構與運作[2]

- 是一種HER2型乳癌的抗體-藥物偶聯物(Antibody-drug Conjugate)，可以黏附於癌細胞的HER2蛋白上，由以下兩種藥物結合而成：
- 單克隆抗體，用於治療擴散性HER2型乳癌
- 化療藥物DM1
- 並通過穩定的連接物(Thioether Linker)結合而來



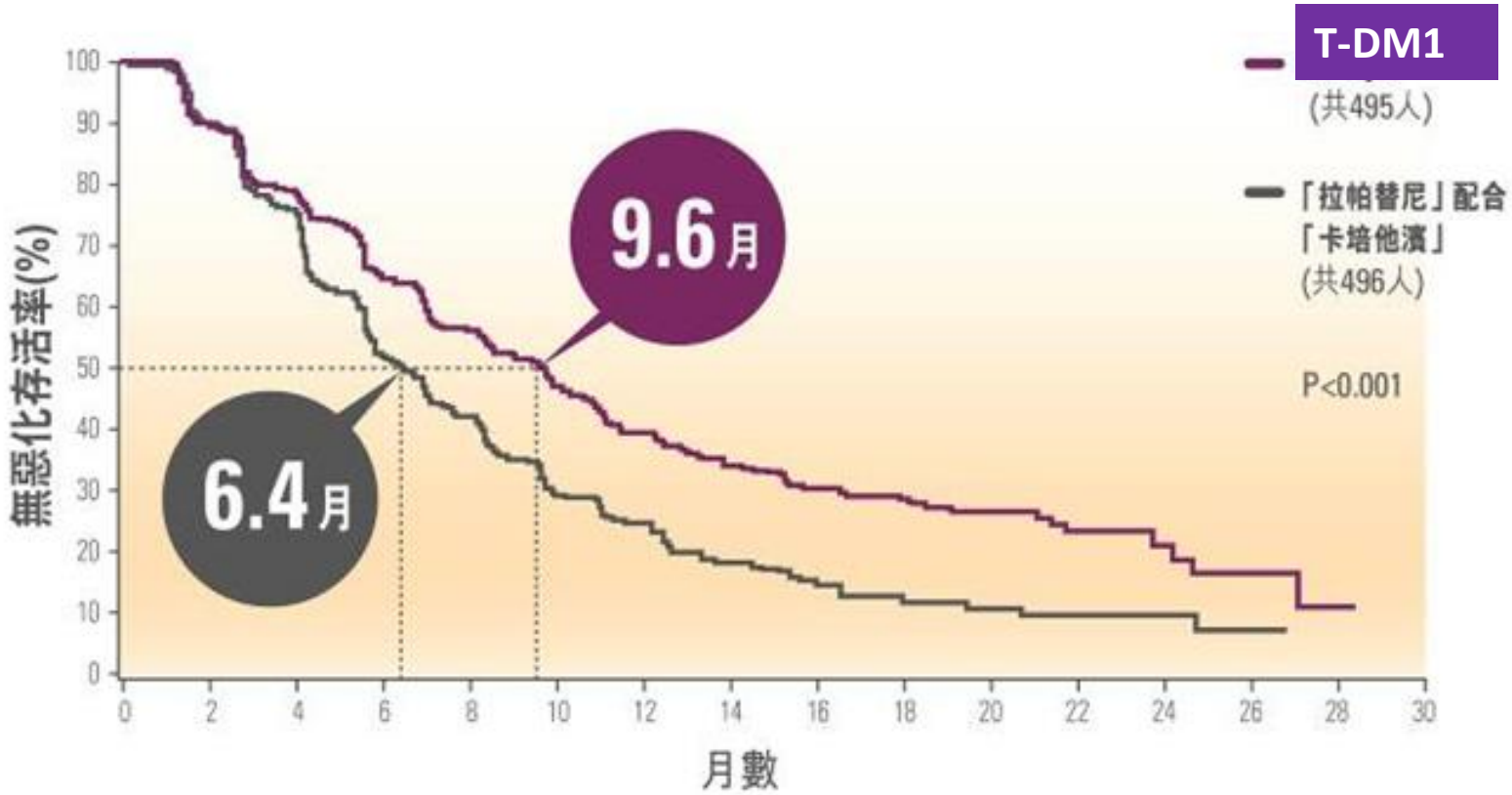
T-DM1的運作

- 在單克隆抗體的作用下，T-DM1透過黏附於HER2受體來識別HER2型癌細胞。
- 當T-DM1黏附於HER2型癌細胞上，它可能會令癌細胞的生長減慢或停止，甚至可能會造成細胞凋亡。
- 其後T-DM1會進入癌細胞之內，釋放化療藥物DM1

T-DM1-藥效

- 無惡化存活期中位數延長至9.6個月，提升了50%[4]



T-DM1的治療對象[2]

- 當乳癌患者符合以下條件，便可考慮接受T-DM1治療
- 經病理檢測證實癌細胞為HER2陽性
- 曾單獨或混合使用「曲妥株單抗」及紫杉醇類化療藥物(如太平洋紫杉醇或多西紫杉醇)作治療
- 癌細胞已擴散至乳房以外的組織

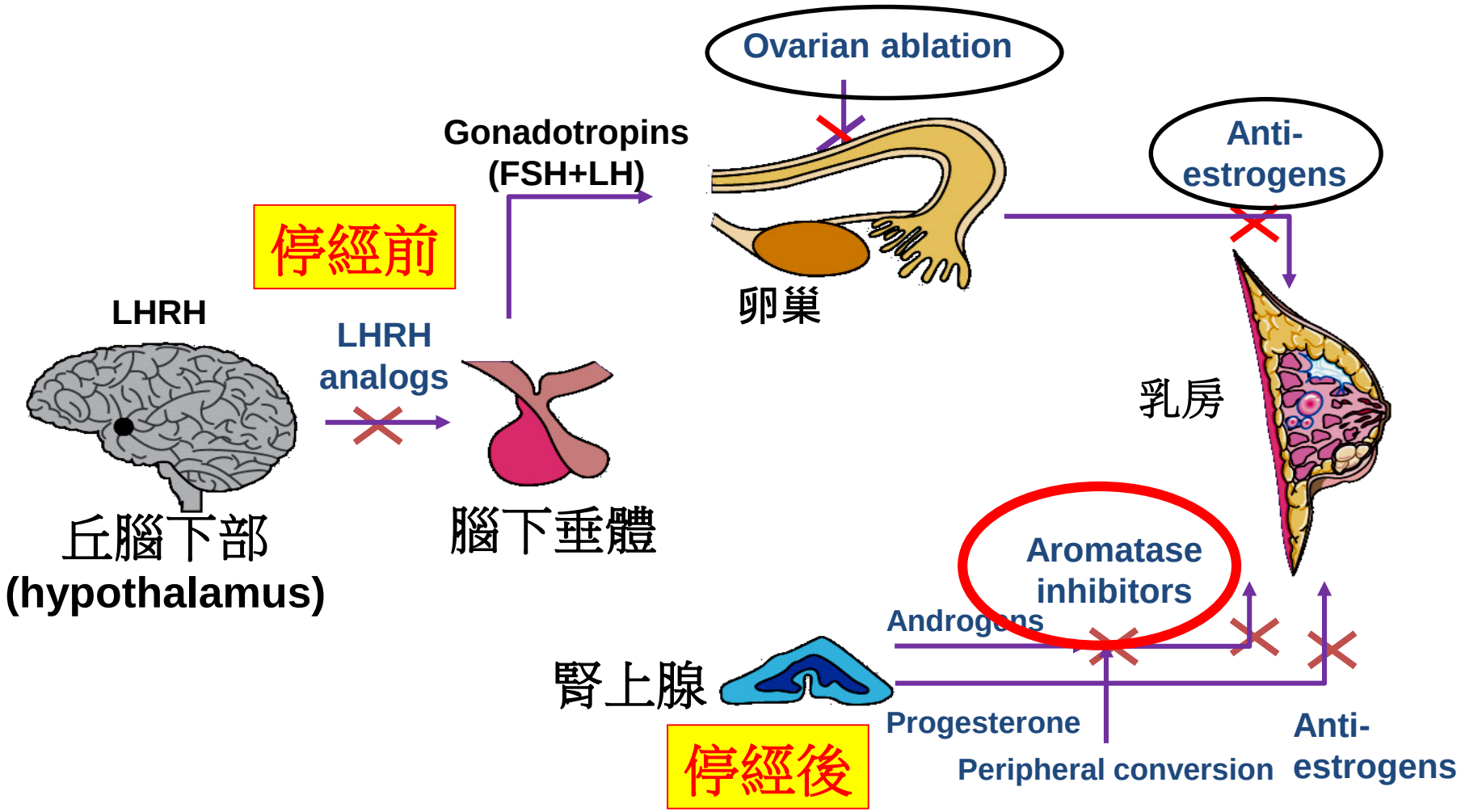
治療轉移性HR+乳腺癌

- ✓ 減少腫瘤體積 → 緩解症狀
- ✓ 延長治療效果及腫瘤惡化時間
- ✓ 延遲化學治療
- ✓ 延長患者的壽命
- ✓ 改善或保持生活質素

荷爾蒙治療

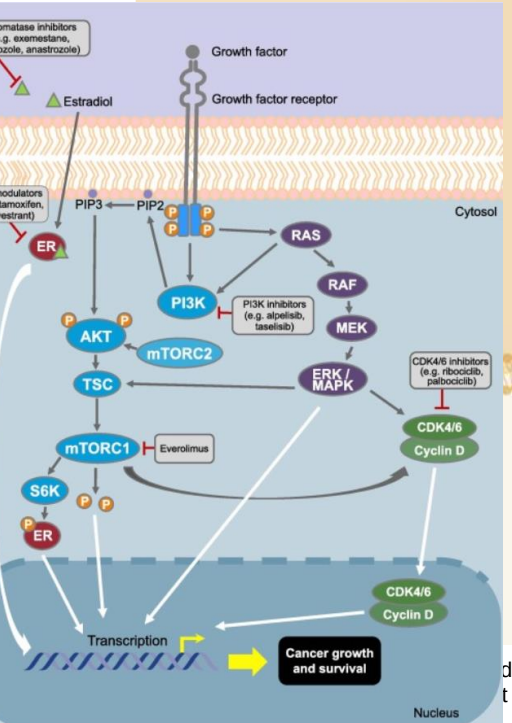
類別	核准的藥品	副作用
選擇性雌激素受器調節因子 Selective estrogen receptor modulators (SERMs)	Tamoxifen	熱潮紅、陰道分泌物或出血、月經不規則、子宮癌風險增加、血塊
芳香酶抑制劑 Aromatase inhibitors (AI)	Letrozole Anastrozole Exemestane	肌肉痛、關節僵硬、骨骼變薄、骨質疏鬆、骨折
雌激素受器調低因子 Estrogen receptor downregulators (ERDs)	Fulvestrant	熱潮紅、反胃、疲倦

雌激素對乳房之刺激作用



FSH = follicle-stimulating hormone; LHRH = luteinizing hormone-releasing hormone

HR+(荷爾蒙)受體陽性乳癌標靶藥物



dley DA, et al. ASCO BC 2011, Abstract 268; 2. Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247; 3. Yamnik RL, et al. *J Biol Chem.* 2009;284(10):6361-6369;
t al. *Nat Rev Clin Oncol*. 2013;10(4):191-210; 5. Infante JR, ASCO 2014, Abstract 2528.

晚期HR+乳癌患者出現抗藥性的原因

正常細胞中，細胞外胰島素，生長因子IGF-1、IGF-2等多種信號

激活

mTOR 蛋白

刺激

細胞內蛋白質合成

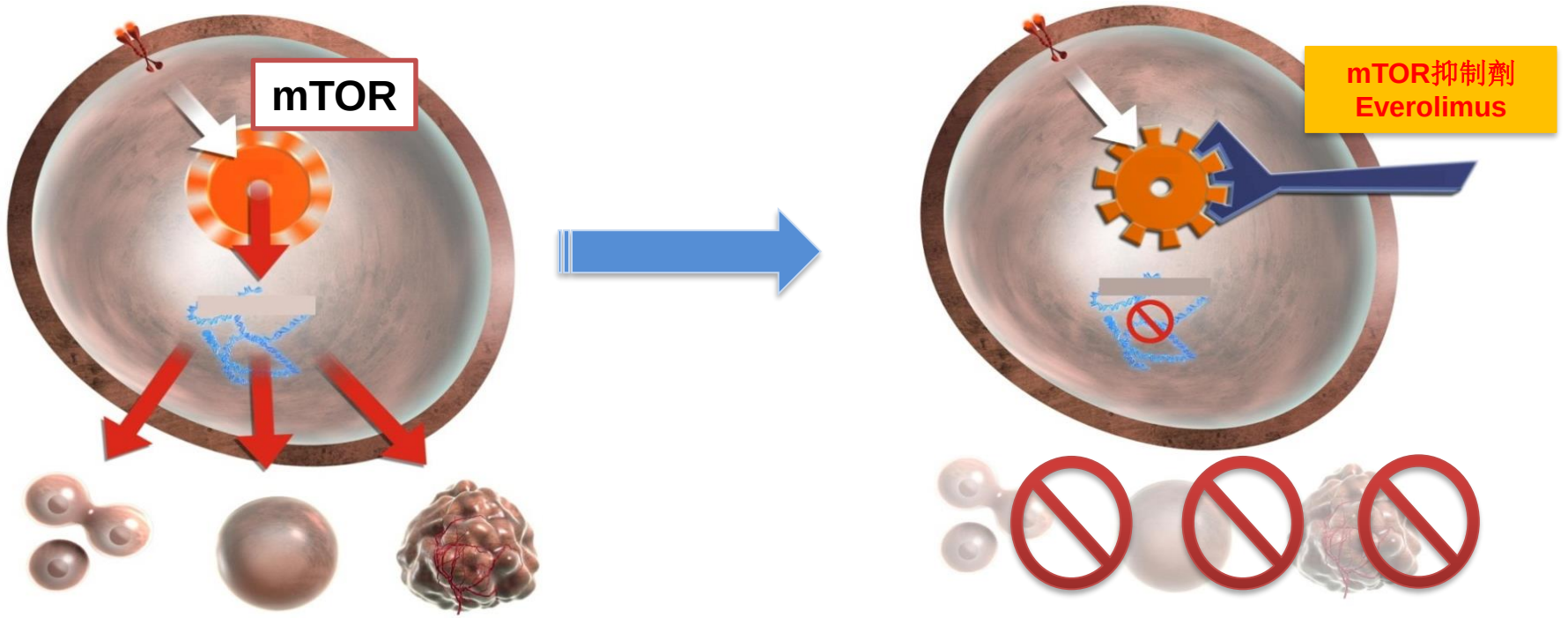
生長分裂 細胞代謝 血管增生

產生抗藥性的癌細胞，mTOR被異常激活

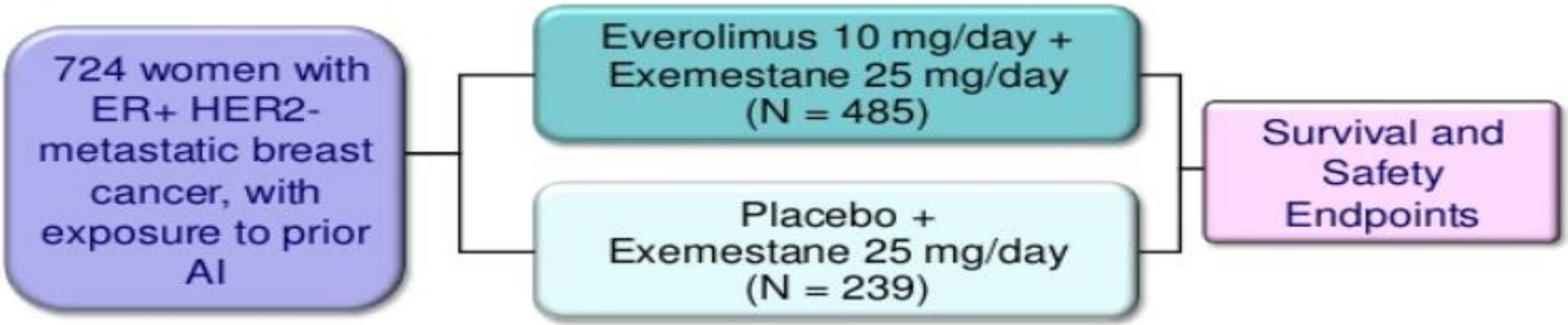
癌細胞生長、分裂
血管增生，
令病情惡化

“新的”標靶藥對抗復發乳癌

口服 mTOR 激酶抑制劑標靶藥物 Everolimus，能阻截抗藥性 HR+ 癌細胞的生長訊息傳遞

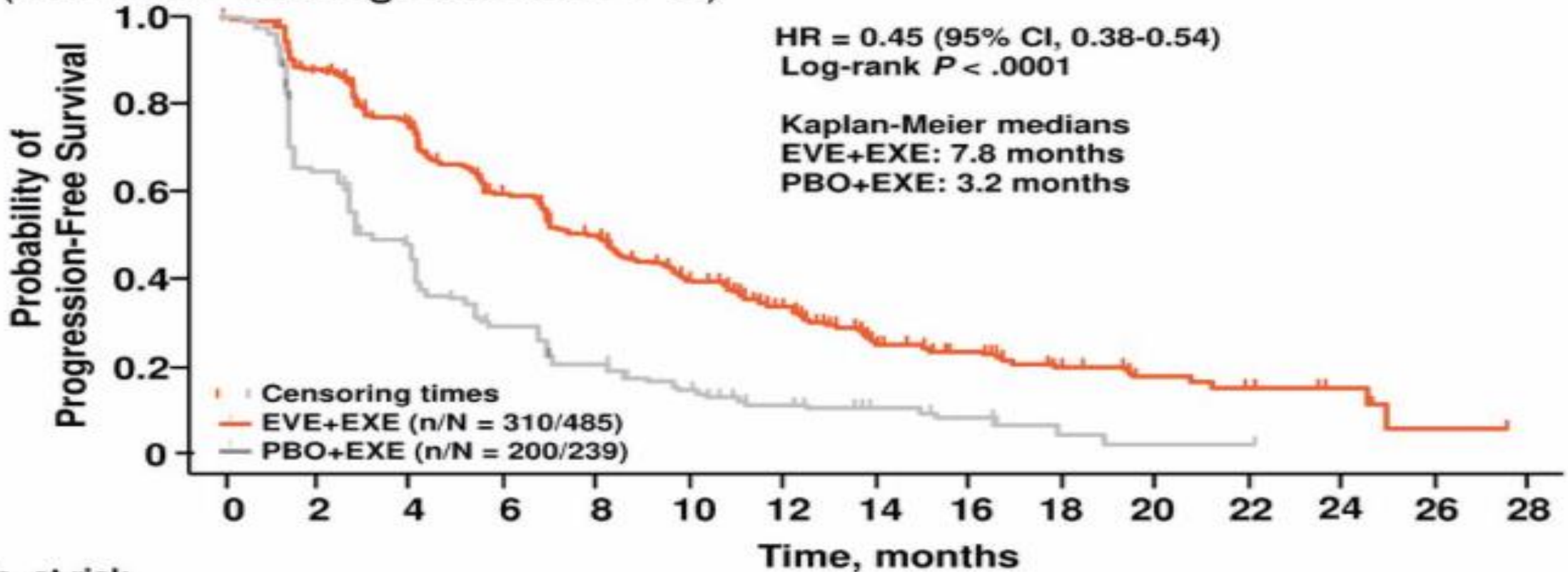


BOLERO-2: A Trial of Everolimus in HR+ Breast Cancer



Baselga et al. NEJM 2012

BOLERO-2 (18-mo): Final PFS Analysis Based on Local Assessment—Met Primary Endpoint (4.6-mo Prolongation of PFS)

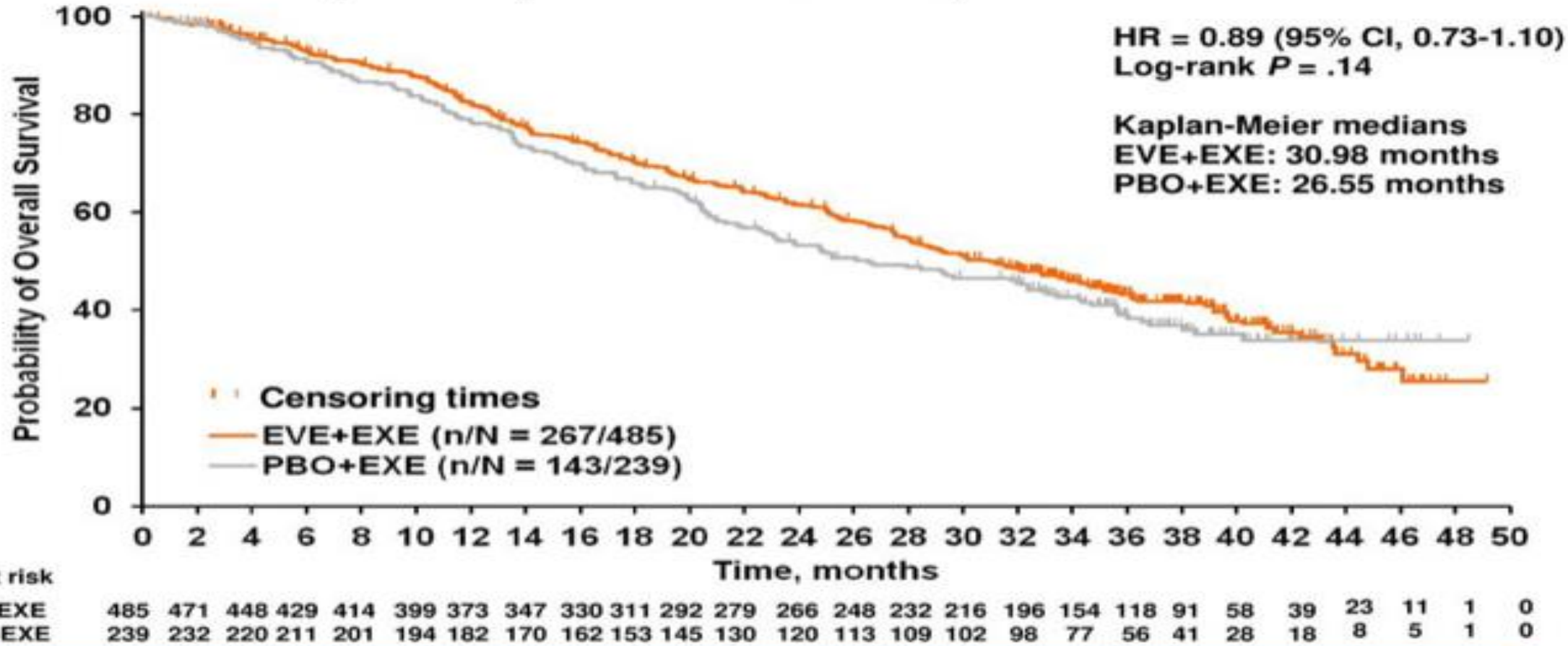


No. at risk															
EVE+EXE	485	394	318	236	194	147	99	57	42	23	13	10	4	1	0
PBO+EXE	239	146	103	61	42	27	17	9	6	2	1	1	0	0	0

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

Yardley DA, et al. *Adv Ther*. 2013;30(10):870-884.

BOLERO-2 (39-mo): Final OS Analysis



No. at risk

EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

At 39 months' median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013)
- 267 deaths (55%) in the EVE+EXE arm vs 143 deaths (60%) in the PBO+EXE arm

One-sided *P* value was obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS®.
Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; IXRS®, Interactive Voice and Web Response System; PBO, placebo.

Piccart et al. presented at EBCC-9; 19–21 March 2014; Glasgow, Scotland. Abstract 1LBA.

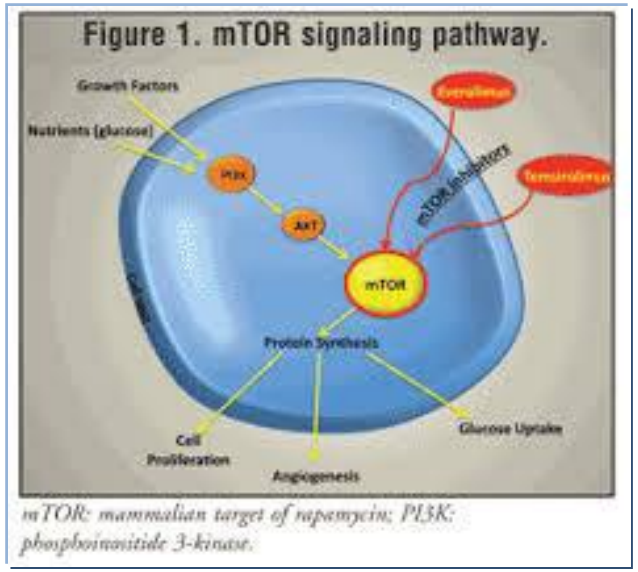
BOLERO-2 研究: 結論

- **Everolimus** 是第一種能夠增強激素治療效益的藥物
  - √ 反轉內分泌抗藥性
  - √ 延長疾病的穩定和腫瘤控制

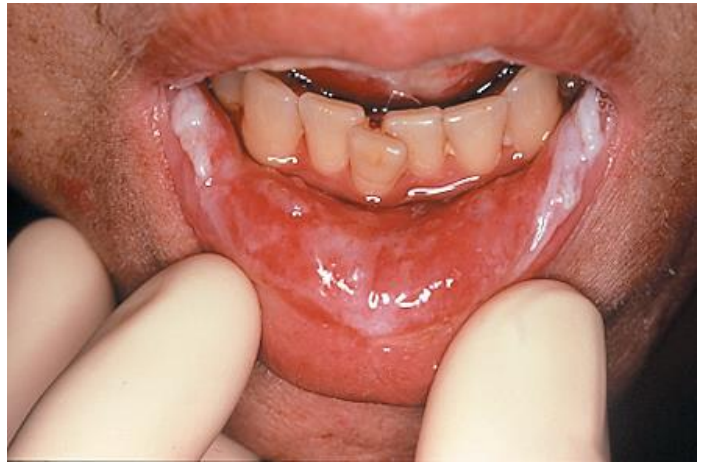
- 對末期乳癌病患，**Everolimus+**內分泌治療可以幫助：
  - √ 延長內分泌治療效益的持續時間
  - √ 提供全口服的治療方式，對病患相當方便
  - √ 延後需要化學治療的時間

Everolimus 可能出現的副作用

口腔炎
紅疹
疲倦
腹瀉
噁心
食慾降低
非感染性的肺間質炎
高血糖



mTOR: mammalian target of rapamycin; PI3K: phosphoinositide 3-kinase.



口腔炎

- 潰瘍融合或形成假膜
- 症狀在開始治療後頭兩個星期出現
- 適當預防及處理能減輕嚴重性或痊癒
- 治療後兩個月新個案不常見

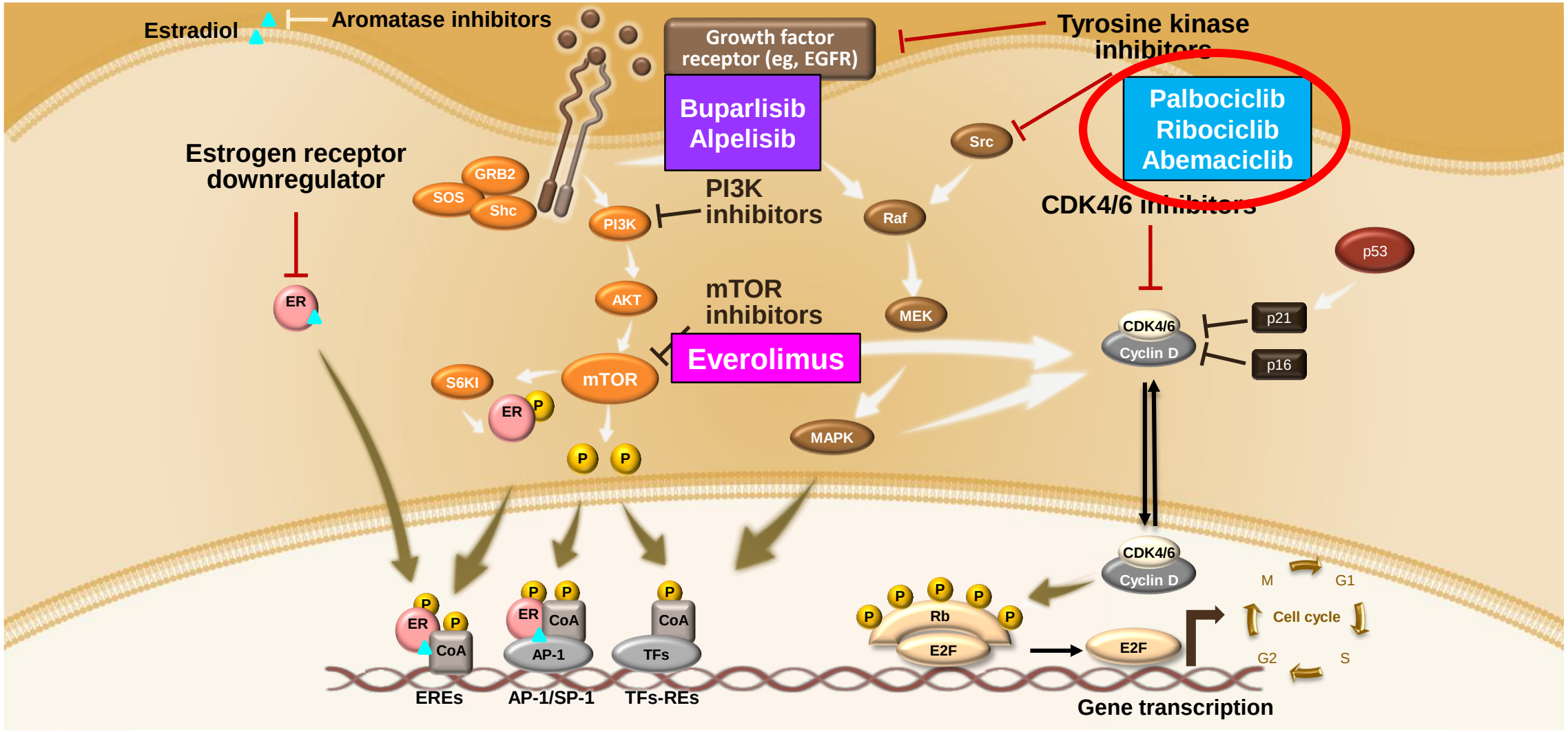
口腔潰瘍或口瘡

紓緩小貼士[4,5]

- 使用柔軟的牙刷刷牙
- 使用不含酒精的漱口水
- 避免進食太硬的食物（如多士、堅果）
- 避免進食一些會再次引起口腔潰瘍的食物（如朱古力、咖啡）
- 適當紓緩壓力（如運動、瑜珈）

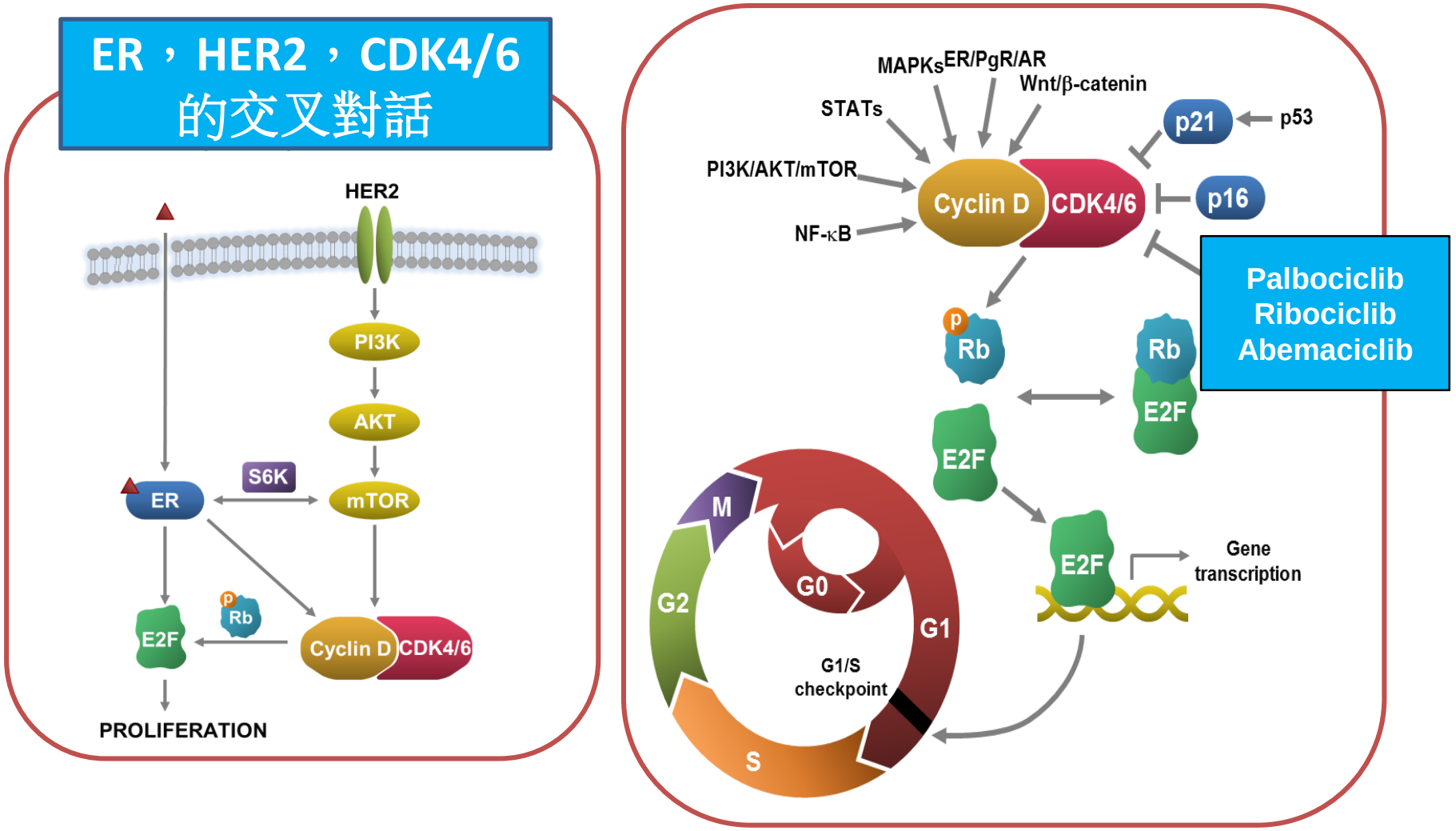
在一些嚴重情況下，醫生或會處方藥物，加速傷口癒合。

發展中的HR+(荷爾蒙)受體陽性乳癌標靶藥物



Data from 1. Yardley DA, et al. ASCO BC 2011, Abstract 268; 2. Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247; 3. Yamnik RL, et al. *J Biol Chem.* 2009;284(10):6361-6369; 4. Zardavas D, et al. *Nat Rev Clin Oncol*. 2013;10(4):191-210; 5. Infante JR, ASCO 2014, Abstract 2528.

CDK4/6 抑制劑



Kim S, *et al. AACR-NCI-EORTC* 2013; Abstract B264; Rader J, *et al. Clin Cancer Res* 2013;19:6173–6182; Finn RS, *et al. Breast Cancer Res* 2009;11:R77; Thangavel C, *et al. Endocr Relat Cancer* 2011;18:333–345.

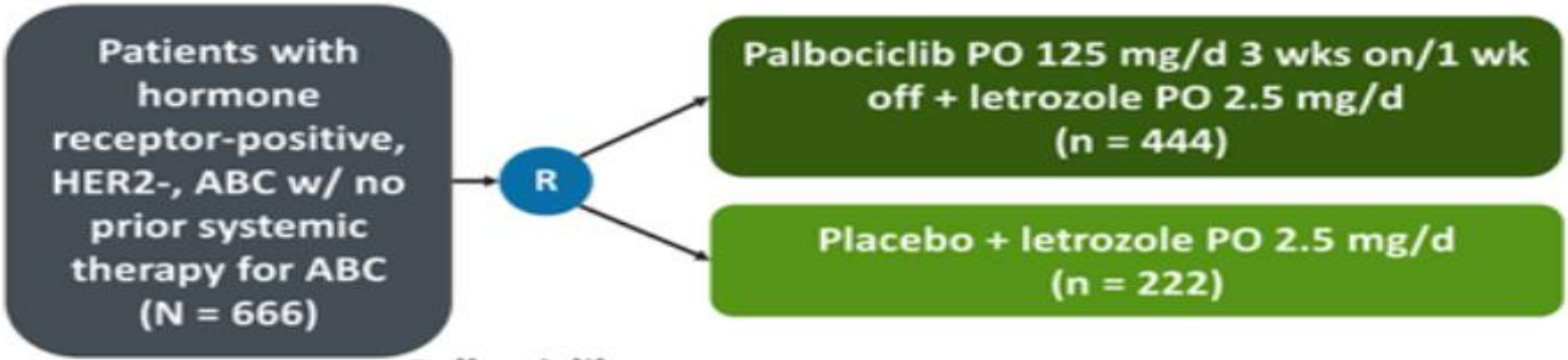
Table 1. Summary of Clinical Trial Data for CDK4/6 Inhibitors for HR+/HER2– Advanced Breast Cancer

	Study	Phase	Arms	Description	Median PFS Hazard Ratio (95% CI)	ORR	Median OS Hazard Ratio (95% CI)
First-line	PALOMA-1/ TRIO-18	II	2	Palbociclib/letrozole vs letrozole	20.2 vs 10.2 mo 0.488 (0.319–0.748)	55.0% vs 39.0%	37.5 vs 34.5 mo 0.897 (0.623–1.294)
	PALOMA-2	III	2	Palbociclib/letrozole vs placebo/letrozole	24.8 vs 14.5 mo 0.58 (0.46–0.72)	55.3% vs 44.4%	Pending
	MONALEESA-2	III	2	Ribociclib/letrozole vs placebo/letrozole	25.3 vs 16.0 mo 0.568 (0.457–0.704)	52.7% vs 37.1%	Pending
	MONALEESA-7	III	2	Ribociclib/OFS/AI or tamoxifen vs placebo/OFS/AI or tamoxifen	23.8 vs 13.0 mo 0.553 (0.441–0.694)	51.0% vs 36.0%	Pending
	MONARCH-3	III	2	Abemaciclib/AI vs placebo/AI	NR vs 14.7 mo 0.543 (0.409–0.723)	59.0% vs 44.0%	Pending
Second-line	PALOMA-3	III	2	Palbociclib/fulvestrant vs placebo/fulvestrant	9.5 vs 4.6 mo 0.46 (0.36–0.59)	24.6% vs 15.0%	Unknown
	MONARCH-2	III	2	Abemaciclib/fulvestrant vs placebo/fulvestrant	16.4 vs 9.3 mo 0.553 (0.449–0.681)	48.1% vs 21.3%	Pending
Later-line	MONARCH-1	II	1	Abemaciclib	6.0 mo	19.7%	17.7 mo

AI = aromatase inhibitor; CDK4/6 = cyclin-dependent kinase 4 and 6; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; OFS = ovarian function suppression; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Palbociclib + Letrozole in First-Line MBC: PALOMA-2 Trial

- Randomized, double-blind, phase 3 trial



	Palbociclib + Letrozole	Letrozole	HR (95% CI)	*P* Value
Median PFS, mo	24.8	14.5	0.58 (0.46, 0.72)	<.000001

Most common grade 3/4 AEs with palbociclib + letrozole:

- Neutropenia, leukopenia

Finn RS, et al. ASCO 2016. Abstract 507.

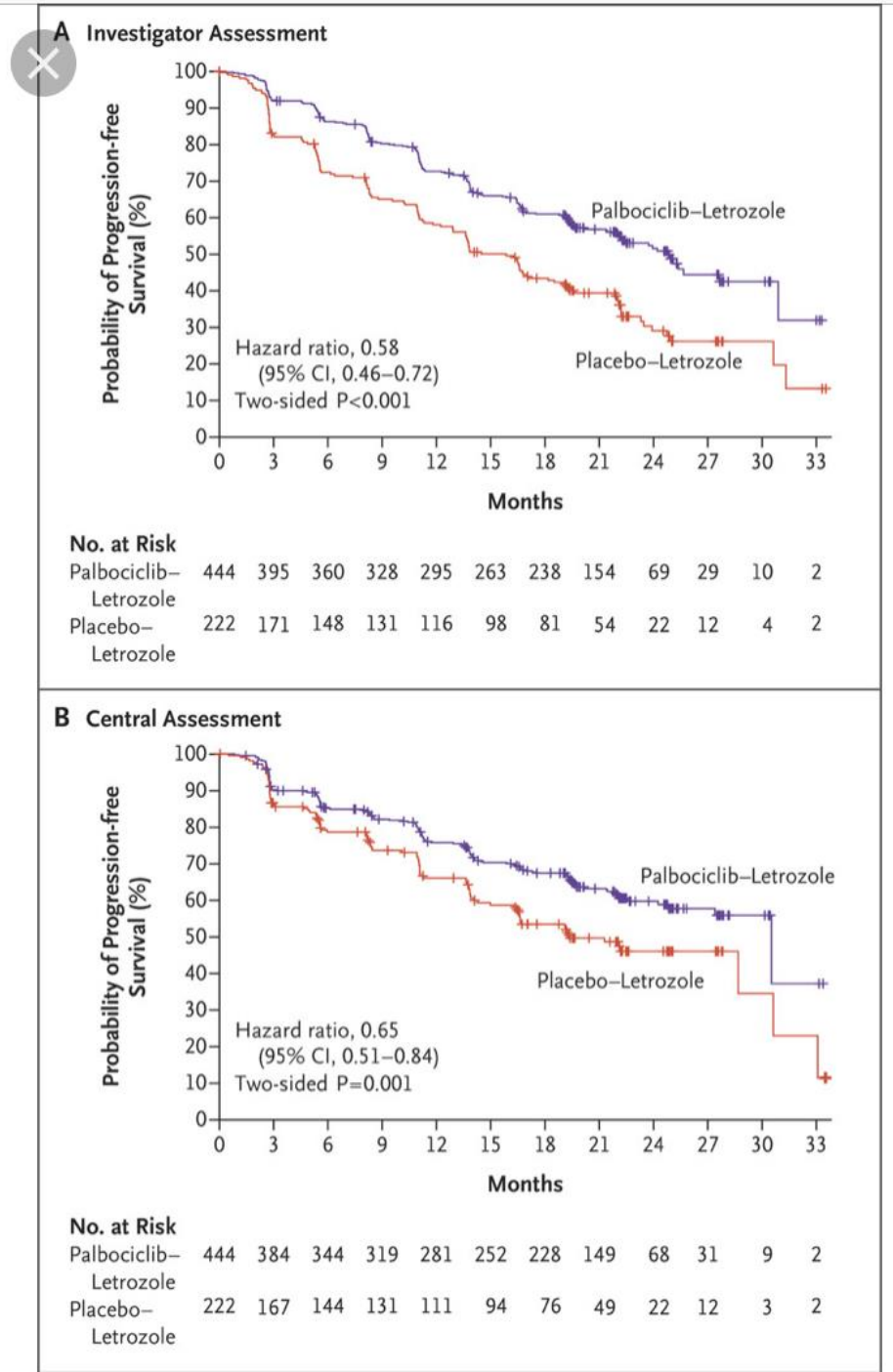
PALOMA-2: A Phase III Trial of First-Line Palbociclib with Letrozole

	Palbociclib + letrozole (n = 444)	Placebo + letrozole (n = 222)	HR (*p*-value)
Median PFS	24.8 mo	14.5 mo	0.58 (<0.000001)

Hematologic AEs, %	Palbociclib + letrozole (n = 444)			Placebo + letrozole (n = 222)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Neutropenia	80	56	10	6	1	<1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0

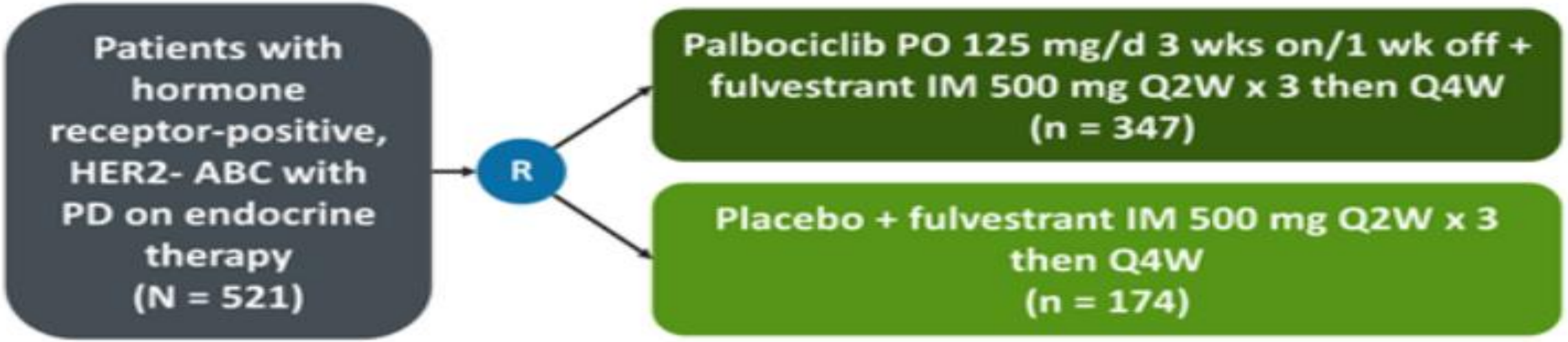
Finn RS et al. *Proc ASCO* 2016;Abstract 507.

paloma 2 trial



Palbociclib + Fulvestrant in Previously Treated ABC: PALOMA-3 Trial

- Randomized, double-blind, phase 3 trial



	Palbociclib + Fulvestrant	Placebo + Fulvestrant	HR (95% CI)	*P* Value
Median PFS, mo	9.2	3.8	0.42 (0.32, 0.56)	<.001

Most common grade 3/4 AEs with palbociclib + fulvestrant:

- Neutropenia, leukopenia, anemia, thrombocytopenia, fatigue

Turner NC, et al. *N Engl J Med.* 2015;373:209-219.

Palbociclib Plus Fulvestrant in Previously Treated ABC: PALOMA-3 Trial

Patients with hormone receptor-positive, HER2- ABC with PD on ET (N = 521)

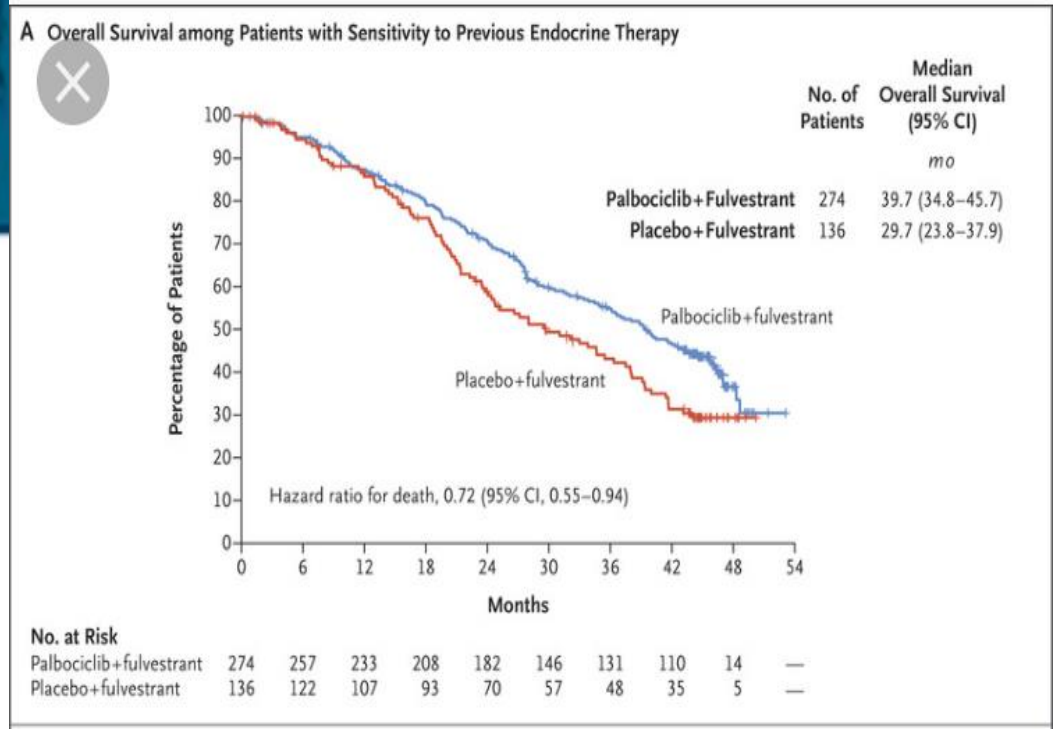
R

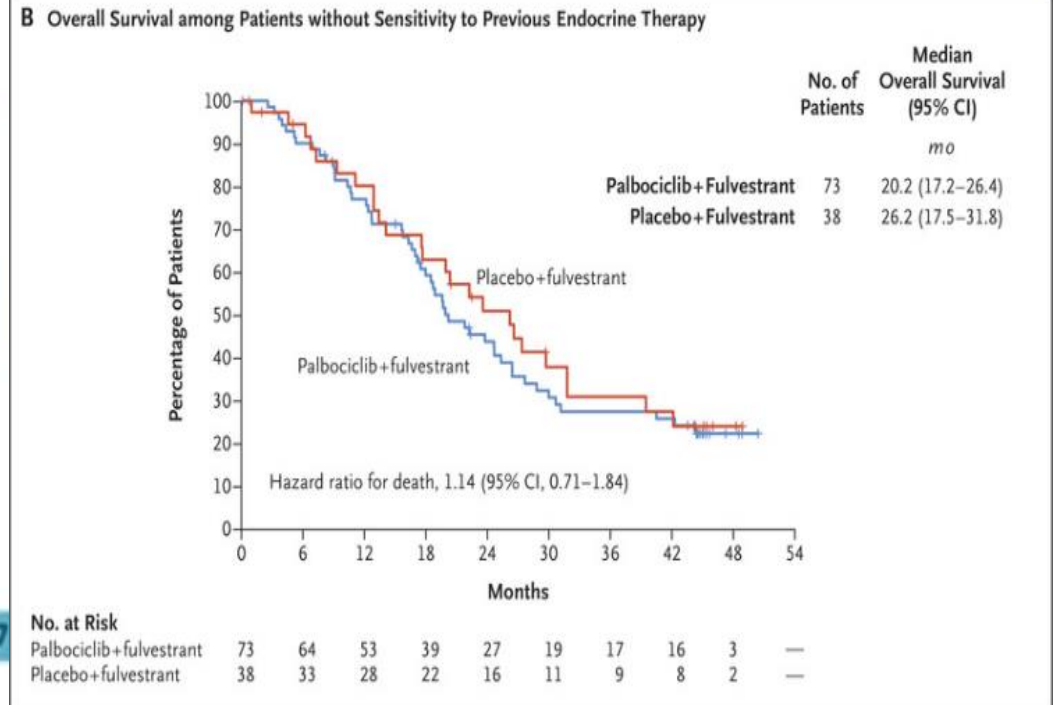
- Palbociclib PO 125 mg/d 3 wk on/1 wk off + fulvestrant IM 500 mg Q2W x 3 then Q4W (n = 347)
- Placebo + fulvestrant IM 500 mg Q2W x 3 then Q4W (n = 174)

	Palbociclib + Fulvestrant	Placebo + Fulvestrant	Hazard ratio (95% CI)	*P* Value
Median PFS, mo	9.2	3.8	0.42 (0.32, 0.56)	< .001

- Randomized, double-blind, phase 3 trial
- Most common grade 3/4 AEs with palbociclib plus fulvestrant:
  - Neutropenia, leukopenia, anemia, thrombocytopenia, fatigue

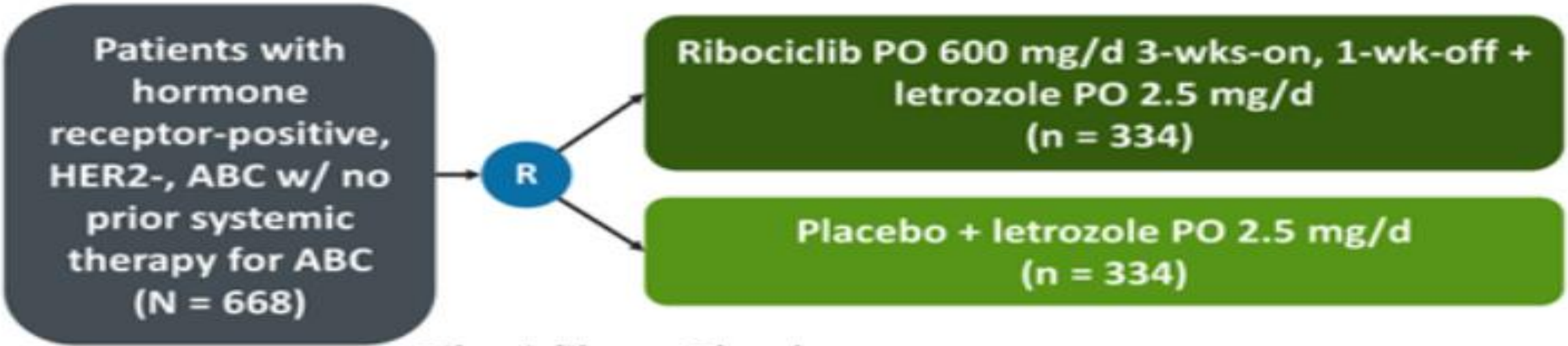
Turner NC, et al. *N Engl J Med*. 2015;373:209-219.





Ribociclib + Letrozole in First-Line MBC: MONALEESA-2 Trial

- Randomized, double-blind, phase 3 trial



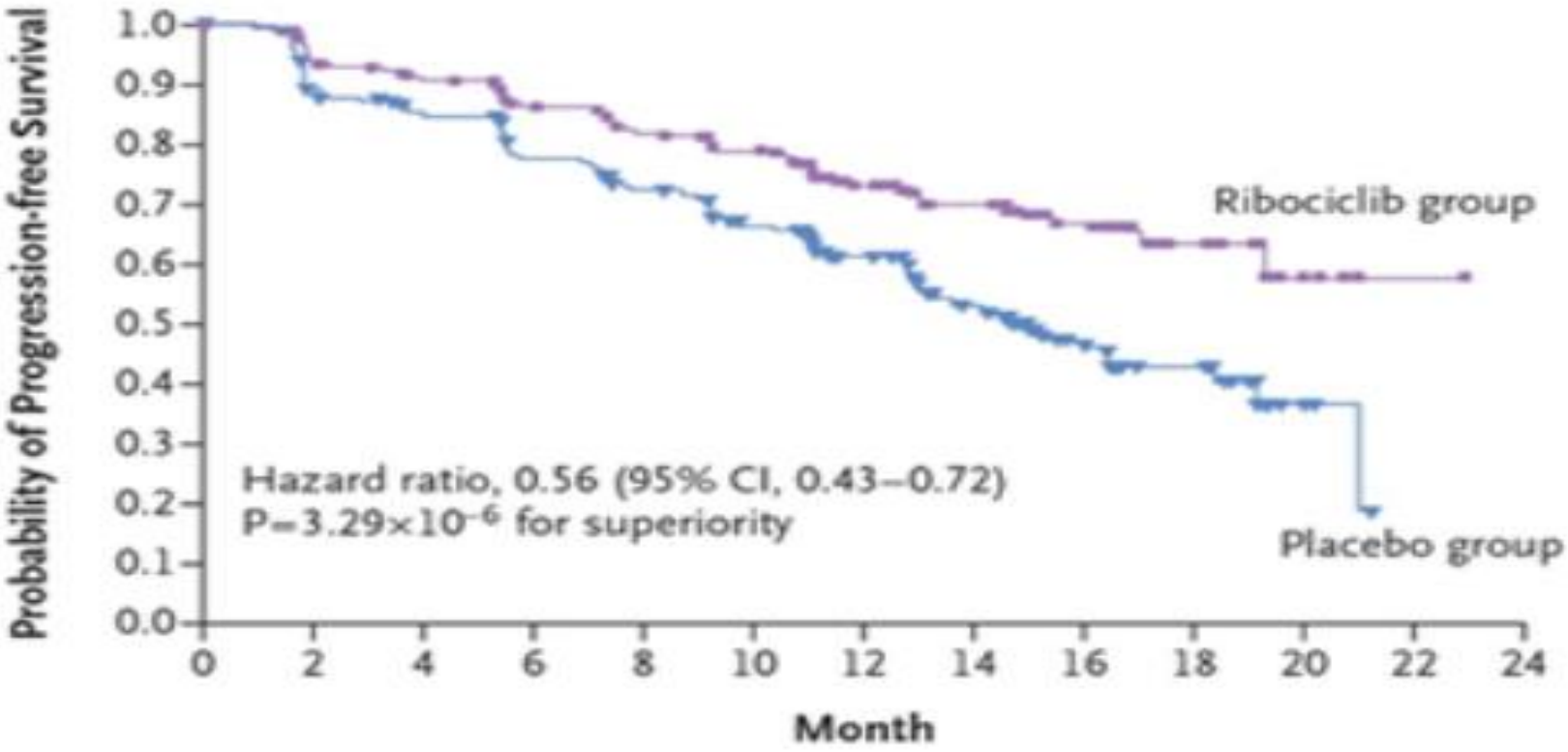
	Ribociclib + Letrozole	Placebo + Letrozole	HR (95% CI)	*P* Value
Median PFS, mo	Not reached	14.7	0.56 (0.43, 0.72)	3.29×10^{-6}

Most common grade 3/4 AEs with ribociclib + letrozole:

- Neutropenia, leukopenia, anemia, thrombocytopenia

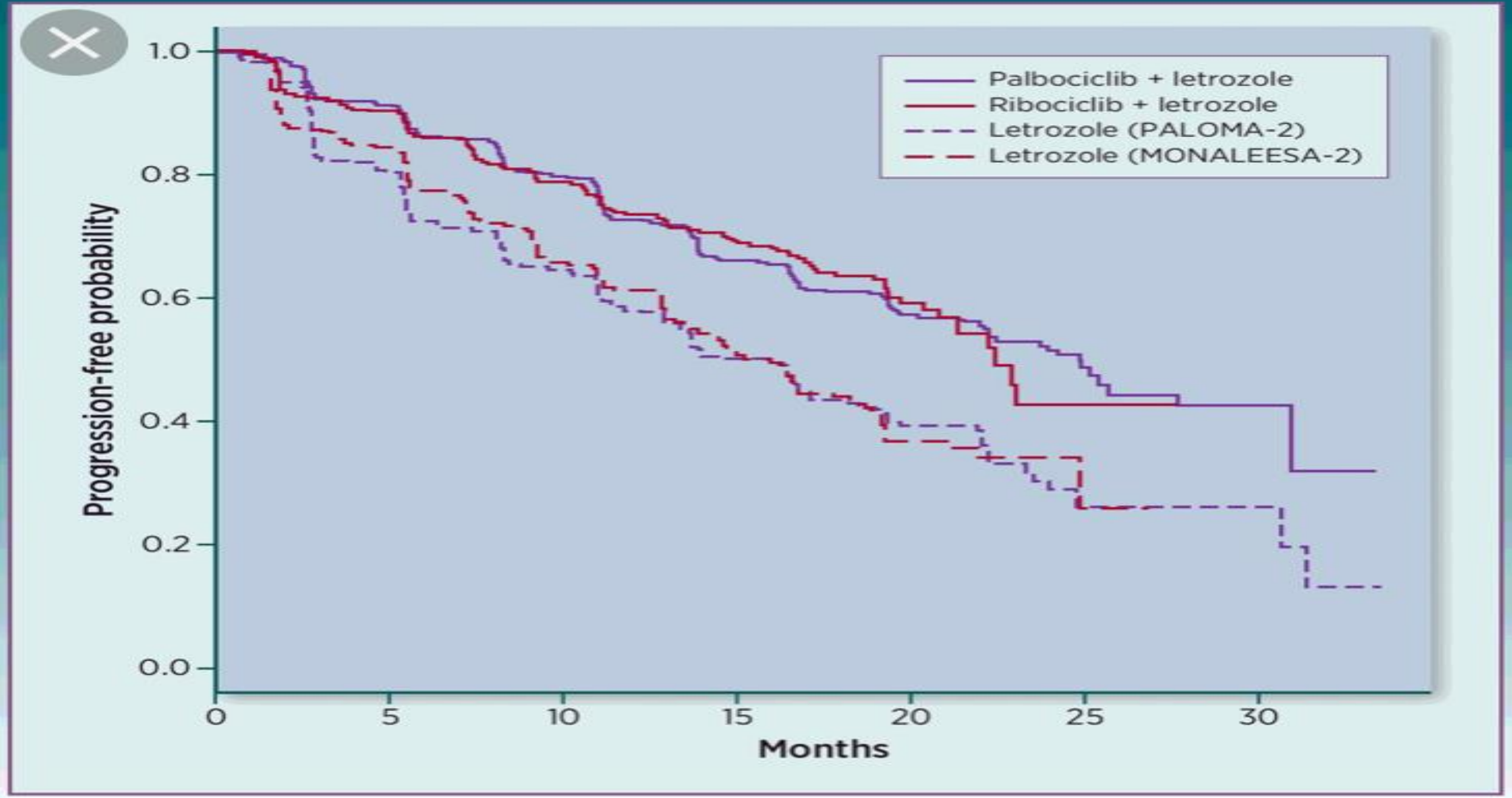
Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748.

PFS in MONALEESA-2



No. at Risk													
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

From *N Engl J Med*, Hortobagyi GN, et al., Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer, 375., 1738-1748. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.



PALOMA-2 and MONALEESA-2 Trials
Adverse Events

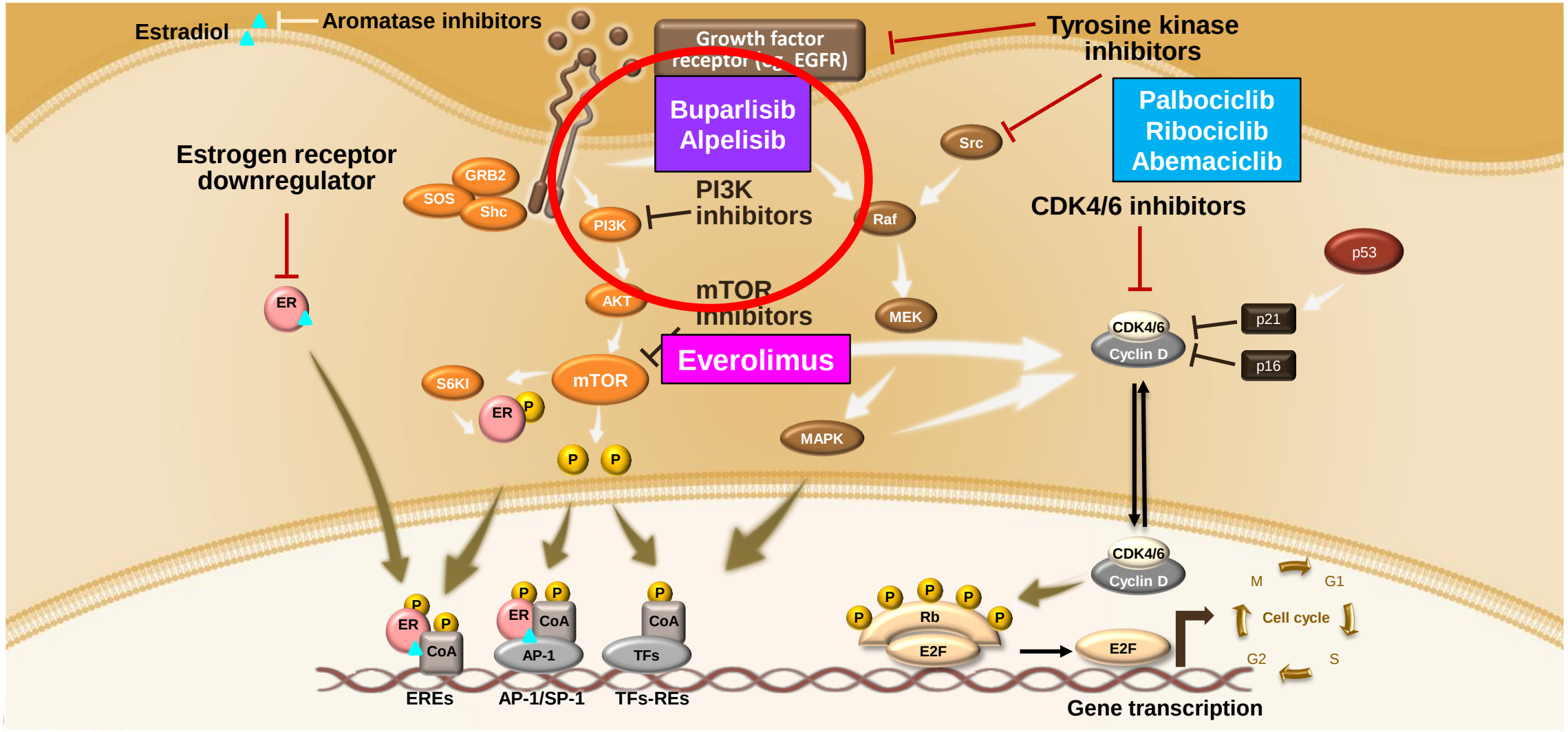
AEs occurring in ≥ 35% of patients in PALOMA-2 and MONALEESA-2 trials

	Ribociclib[a]			
	Ribociclib + Letrozole n = 334		Placebo + Letrozole n = 330	
AE, %	All grade	Grade 3/4	All grade	Grade 3/4
Neutropenia	74	59	5	1
Nausea	52	2	29	1
Infections	50	4	42	2
Fatigue	37	2	30	1
Diarrhea	35	1	22	1

	Palbociclib[b]			
	Palbociclib + Letrozole n = 444		Placebo + Letrozole n = 222	
AE, %	All grade	Grade 3/4	All grade	Grade 3/4
Neutropenia	80	66	6	2
Infections	60	7	42	3
Leukopenia	39	25	2	0
Fatigue	37	2	28	1
Nausea	35	<1	26	2

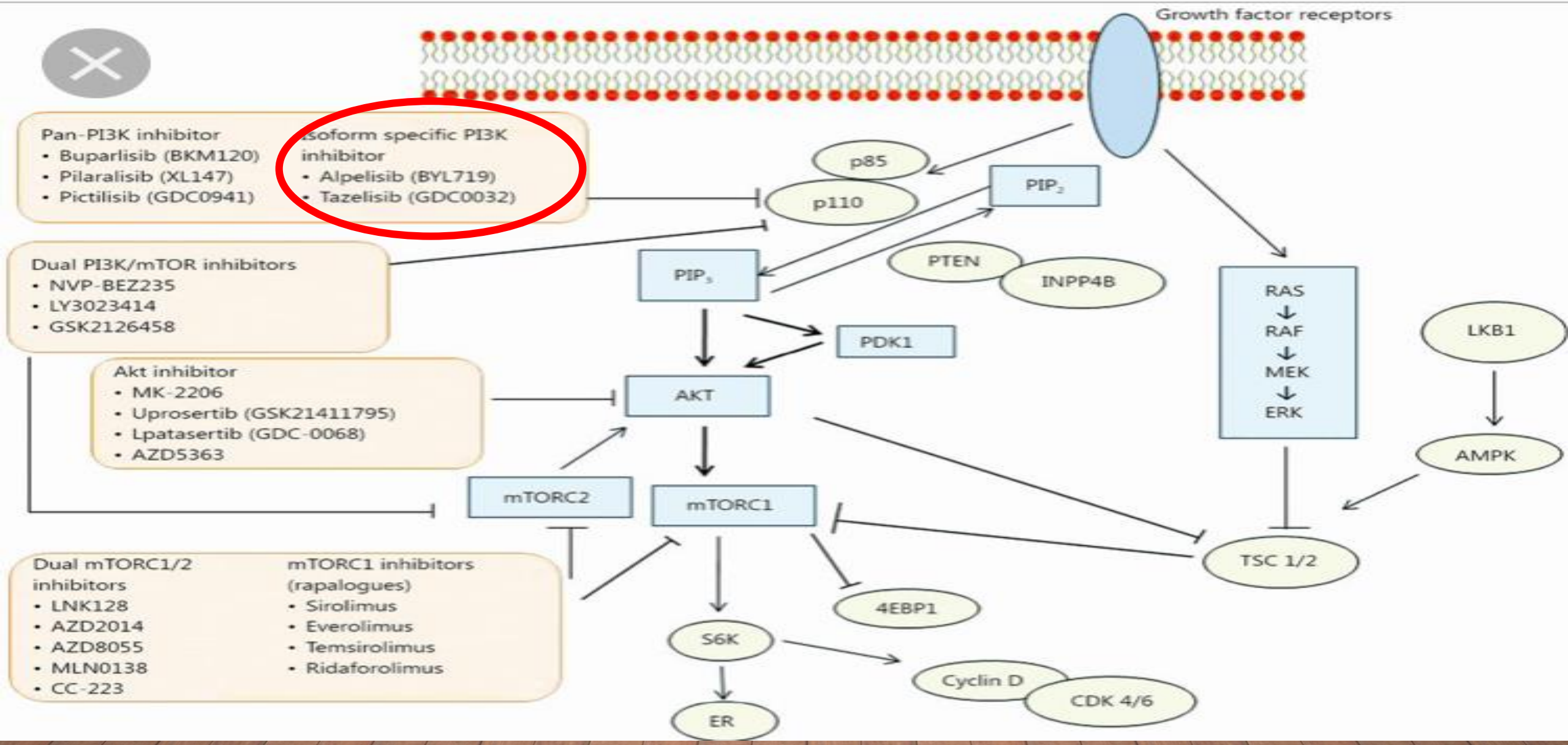
a. Janni W, et al. *J Clin Oncol*. 2017;35. Abstract 1047; b. IBRANCE® PI 2017.

發展中的HR+(荷爾蒙)受體陽性乳癌標靶藥物



Data from 1. Yardley DA, et al. ASCO BC 2011, Abstract 268; 2. Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247; 3. Yamnik RL, et al. *J Biol Chem.* 2009;284(10):6361-6369; 4. Zardavas D, et al. *Nat Rev Clin Oncol*. 2013;10(4):191-210; 5. Infante JR, ASCO 2014, Abstract 2528.

pi3k inhibitor breast cancer



Agent (industry developer)	Study Description	Phase (ClinicalTrials.gov identifier)
Alpelisib (BYL719) (Novartis)	• SOLAR-1: fulvestrant + alpelisib or placebo in hormone receptor–positive, HER2-negative progressive advanced BC	III (NCT02437318)[a]
	• BYLieve: alpelisib + fulvestrant or letrozole in hormone receptor–positive, HER2-negative recurrent advanced/metastatic BC with *PIK3CA* mutations	II (NCT03056755)
	• Apelisib + LSZ102[b] in progressive advanced/metastatic ER-positive BC	I (NCT02734615)
Buparlisib (Novartis)	• BELLE-2: fulvestrant + buparlisib or placebo in hormone receptor–positive, HER2-negative recurrent advanced/metastatic BC	III (NCT01610284)
Copanlisib (Aliqopa) (Bayer)	• Copanlisib with letrozole +/- palbociclib as neoadjuvant therapy in hormone receptor–positive, HER2-negative stage I to IV BC	I/II (NCT03128619)
GDC-0077 (Genentech)	• GDC-0077 as a single agent OR combined with palbociclib + letrozole, letrozole, or fulvestrant in hormone receptor–positive, HER2-negative advanced/metastatic BC with *PIK3CA* mutations	I (NCT03006172)
IPI-549 (Infinity)	• IPI-549 + nivolumab in TNBC	I (NCT02637531)
Gedatolisib[c] (PF-05212384) (Pfizer)	• Gedatolisib + palbociclib with letrozole OR palbociclib with fulvestrant in MBC	I (NCT02684032)
	• Gedatolisib + docetaxel, cisplatin, or dacomitinib in TNBC	I (NCT01920061)
LY3023414 (Eli Lilly)	• LY3023414 + abemaciclib with fulvestrant in MBC	I (NCT02057133)

擴散三陰乳癌的治療

化療 ，+/- Bevacizumab

檢測BRCA Germline 情況，

若有變異 → **PARP抑制劑** (Olaparib/Talazoparib)

免疫治療的運用

– Pembrolizumab

- Atezolizumab (Impassion 130 study)

化療藥物

- Anthracycline (俗稱”紅針”)
- Taxol (紫杉醇)，Taxotere (多西紫杉醇)
- Abraxane (白蛋白结合型紫杉醇)
- Gemzar (健擇)
- Xeloda (希羅達) (口服)
- Eribulin (艾日布林)
- Vinorelbine (長春瑞賓) (靜脈注射及口服)

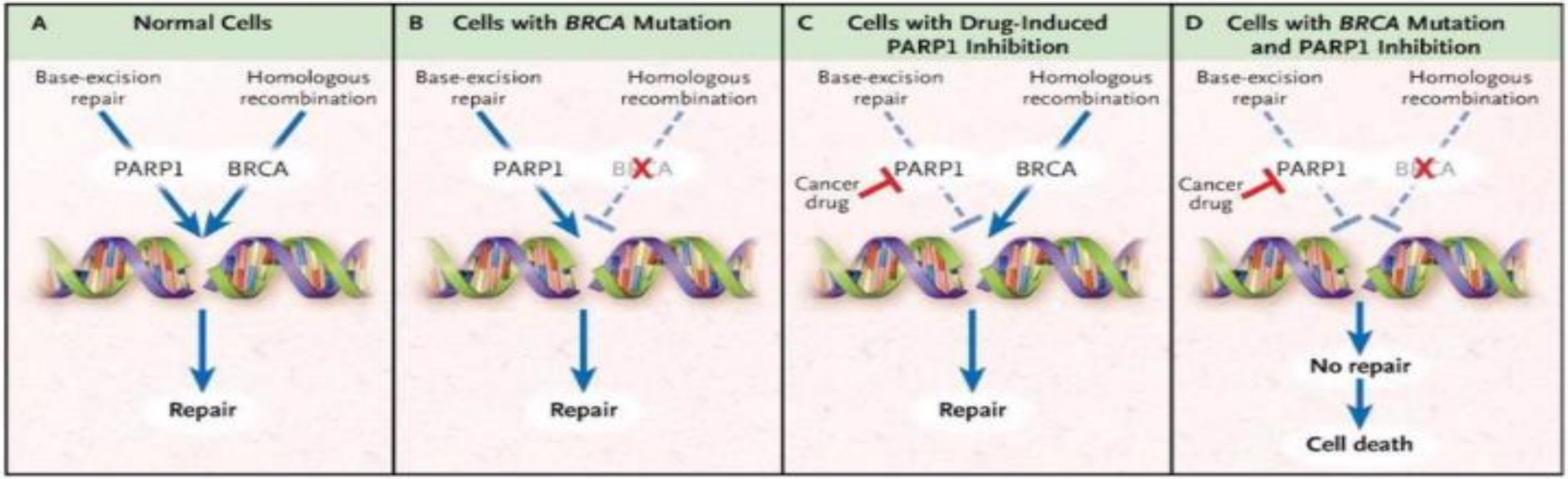
能使用於單藥治療或組合治療

PARP i FDA indication in Breast

PARP inhibitors	FDA Breast indication
Olaparib	Indicated for deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, in patients who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy
Talazoparib	Indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (*gBRCAm*) HER2-negative locally advanced or metastatic breast cancer.

PARP Inhibition in BRCA-deficient Tumors

- Accumulation of double strand breaks, in the absence of an alternative DNA repair mechanism, leads to cell death



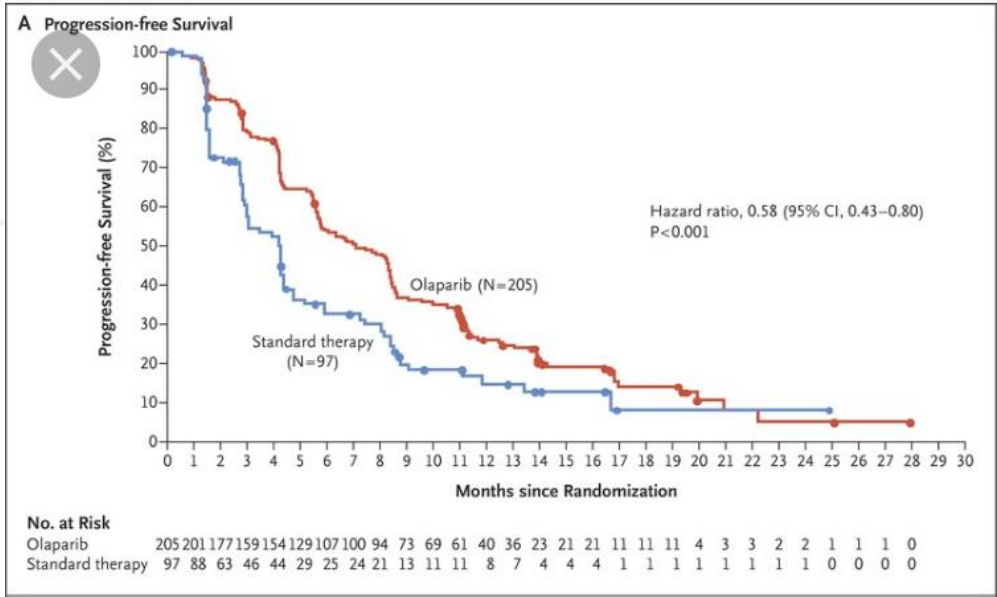
Iglehart et al. NEJM 2009, Bryant et al. Nature 2005 , Farmer et al. Nature 2005

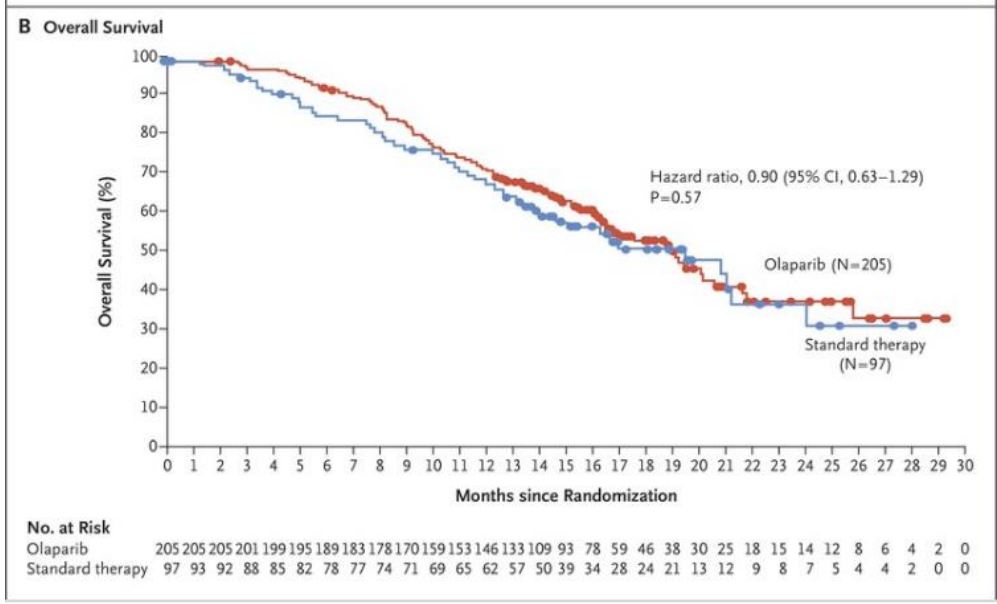
AstraZeneca

LYNPARZA® (olaparib) approved by US FDA in germline BRCA-mutated metastatic breast cancer

PUBLISHED

12 January 2018

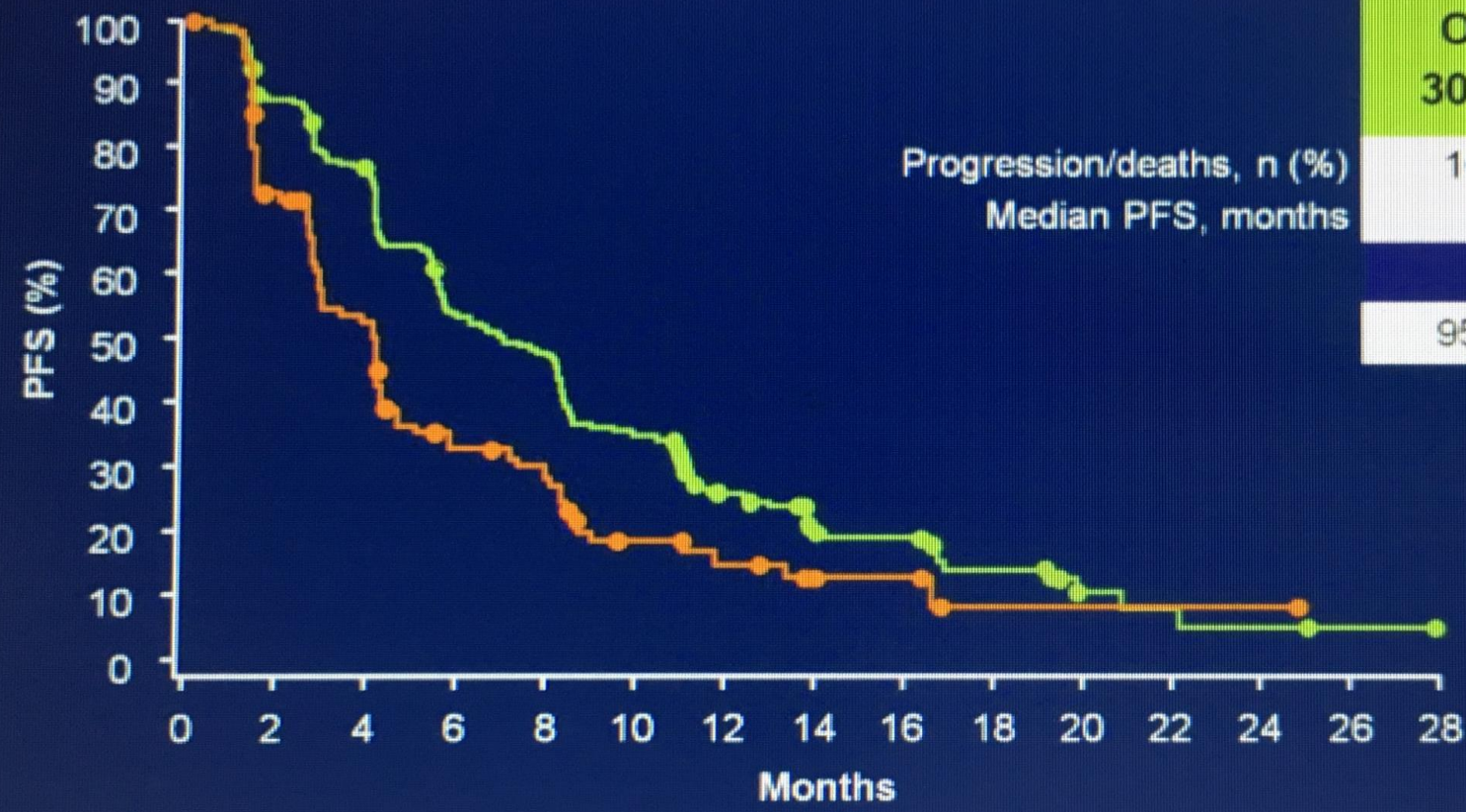




The New England Journal of…

Olaparib for Metastatic Breast

Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2

HR 0.58

95% CI 0.43 to 0.80; *P*=0.0009

At risk, n																
Olaparib 300 mg bd	205	177	154	107	94	69	40	23	21	11	4	3	2	1	0	
Chemotherapy TPC	97	63	44	25	21	11	8	4	4	1	1	1	1	0	0	

OlympiAD

Study Design: EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

R 2:1

Talazoparib
1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

Phase 3, international, open-label study randomized
431 patients in 16 countries and 145 sites

Primary endpoint

- Progression-free survival by RECIST by blinded central review

Key secondary efficacy endpoints

- Overall survival (OS)
- ORR by investigator
- Safety

Exploratory endpoints

- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os); QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; TNBC, triple-negative breast cancer.

*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated. †HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.

www.clinicaltrials.gov (NCT01945775)

Background

- Talazoparib (TALA) is a highly potent dual-mechanism PARP inhibitor[1-3]
  - Inhibits the PARP enzyme
  - Traps PARP on single-stranded DNA breaks[4]
  - Prevents repair of DNA damage, resulting in cell death
- Phase 1 trial established a tolerable dose of 1 mg/day for continuous dosing (fed or fasting)[5]
  - Single-agent activity in other tumor types (prostate, ovarian, SCLC)
- The phase 2 ABRAZO trial showed encouraging efficacy and safety in patients with germline *BRCA1/2* mutations and prior platinum therapy or at least 3 prior cytotoxic regimens[6]

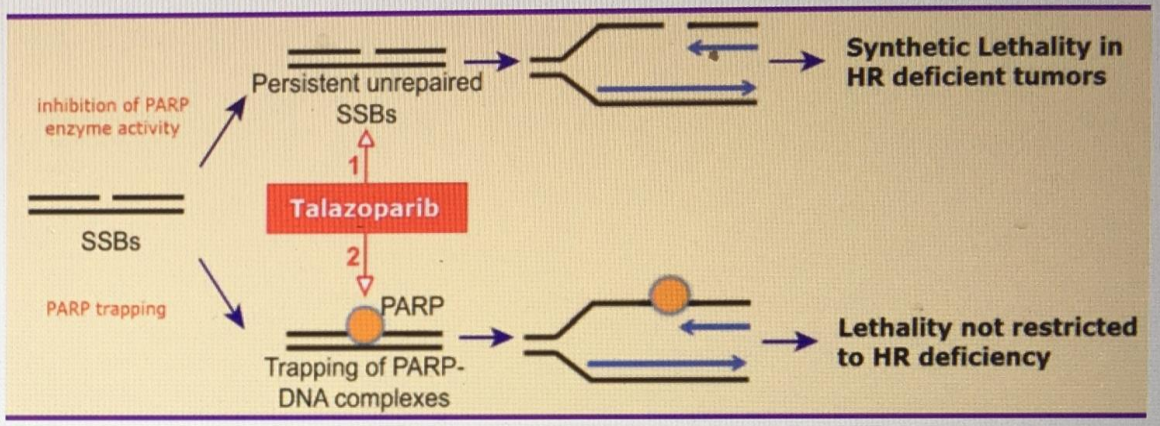


Figure adapted from Murai J et al. *Cancer Res*. 2012;72:5588-5599, with permission from AACR.

		ABRAZO	
	Phase 1 (n = 14)[a]	Prior Platinum (n = 48)	≥ 3 Lines, No Platinum (n = 35)
Confirmed ORR, % (95% CI)	50%	21% (10, 35)	37% (22, 55)
PFS, mo (95% CI)	7.5	4.0 (2.8, 5.4)	5.6 (5.5, 7.8)
CBR24, % (95% CI)	86%	38% (24, 53)	66% (48, 81)

[a]Data shown for the phase 1 study is only in breast cancer patients.

Abbreviations: CI, confidence interval; CBR24, clinical benefit rate at 24 weeks; HR, homologous recombination; PARP, poly(ADP-ribose) polymerase; ORR, objective response rate; PFS, progression-free survival; SCLC, small cell lung cancer; SSB, single-strand break.

1. Ashworth A. *J Clin Oncol*. 2008;26:3785-3790. 2. Jalve M, Curtin NJ. *Ther Adv Med Oncol*. 20113:257-267. 3. Helleday T. *Mol Oncol*. 2011;5:387-393. 4. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158. 5. de Bono J et al. *Cancer Discov*. 2017;7:620-629. 6. Turner NC et al. Presented at ASCO; June 3, 2017; Chicago, IL. Abstract 1007.

Baseline Characteristics (ITT Population)

	TALA (n = 287)	Overall PCT (n = 144)
Age, median (range), y	45 (27.0-84.0)	50 (24.0-88.0)
<50 y, no. %	182 (63.4%)	67 (46.5%)
Gender, % female	98.6%	97.9%
ECOG = 0 / 1 / 2, %	53.0% / 44.0% / 2.0%	58.0% / 40.0% / 1.0%
Measurable disease by investigator, no. (%)	219 (76.3%)	114 (79.2%)
History of CNS metastasis, no. (%)	43 (15.0%)	20 (13.9%)
Visceral disease, no. (%)	200 (69.7%)	103 (71.5%)
Hormone receptor status, no. (%)		
TNBC	130 (45.3%)	60 (41.7%)
HR+	157 (54.7%)	84 (58.3%)
BRCA status, no. (%)		
BRCA1+	133 (46.3%)	63 (43.8%)
BRCA2+	154 (53.7%)	81 (56.3%)
Disease free interval (initial diagnosis to aBC) <12 months	108 (37.6%)	42 (29.2%)

Abbreviations: aBC, advanced breast cancer; ITT, intent to treat.

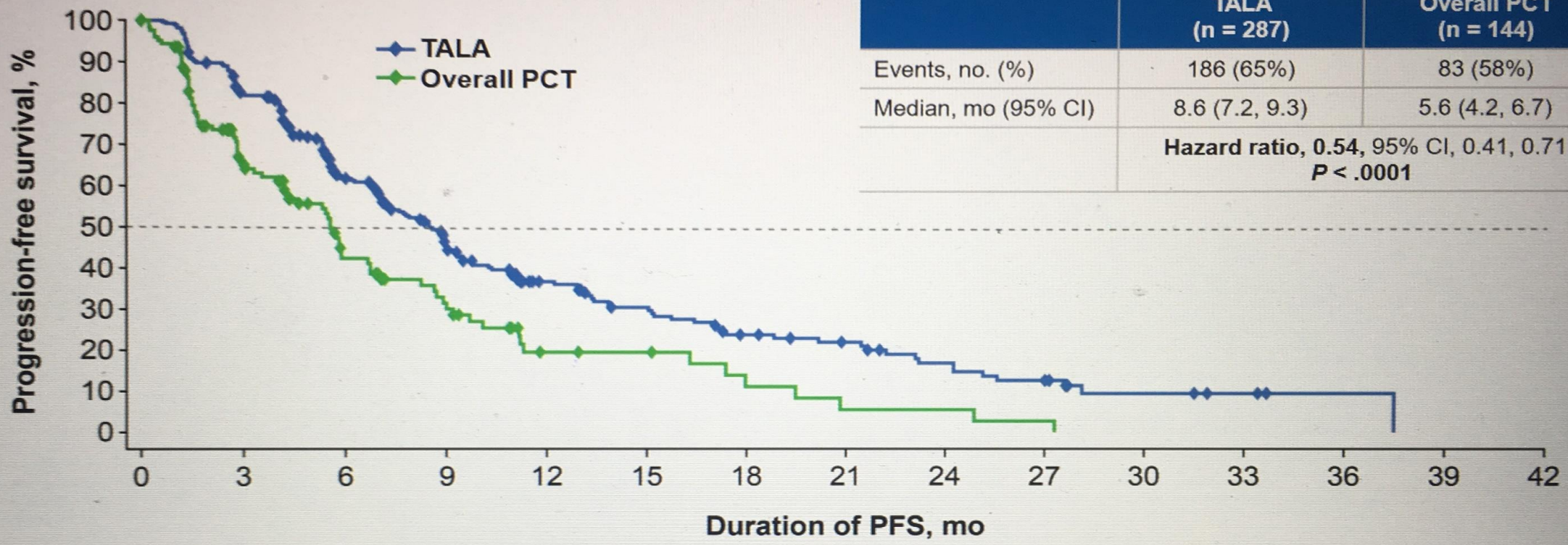
Abbreviations: aBC, advanced breast cancer; ITT, intent to treat.

n Antonio Breast Cancer Symposium, December 5-9, 2017

Prior Therapies for Advanced Breast Cancer

	TALA (n = 287)	Overall PCT (n = 144)
Prior adjuvant/neoadjuvant therapy, no. (%)	238 (82.9%)	121 (84.0%)
Prior hormonal therapy, no. (%)	161 (56.1%)	77 (53.5%)
Prior platinum therapy, no. (%)	46 (16.0%)	30 (21.0%)
No. of prior cytotoxic regimens for aBC, no. (%)		
0	111 (38.7%)	54 (37.5%)
1	107 (37.3%)	54 (37.5%)
2	57 (19.9%)	28 (19.4%)
≥ 3	12 (4.2%)	8 (5.6%)

Primary Endpoint: PFS by Blinded Central Review



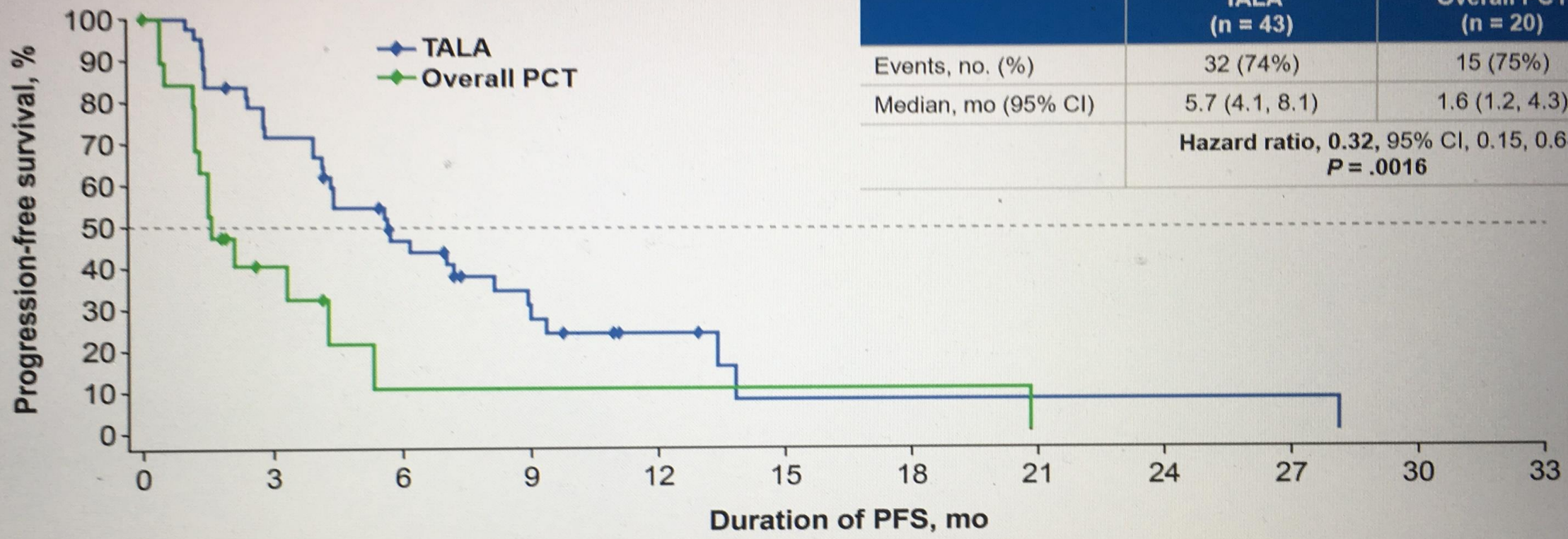
	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

No. at risk (events/cumulative events)														
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

PFS: CNS Metastases Subgroup

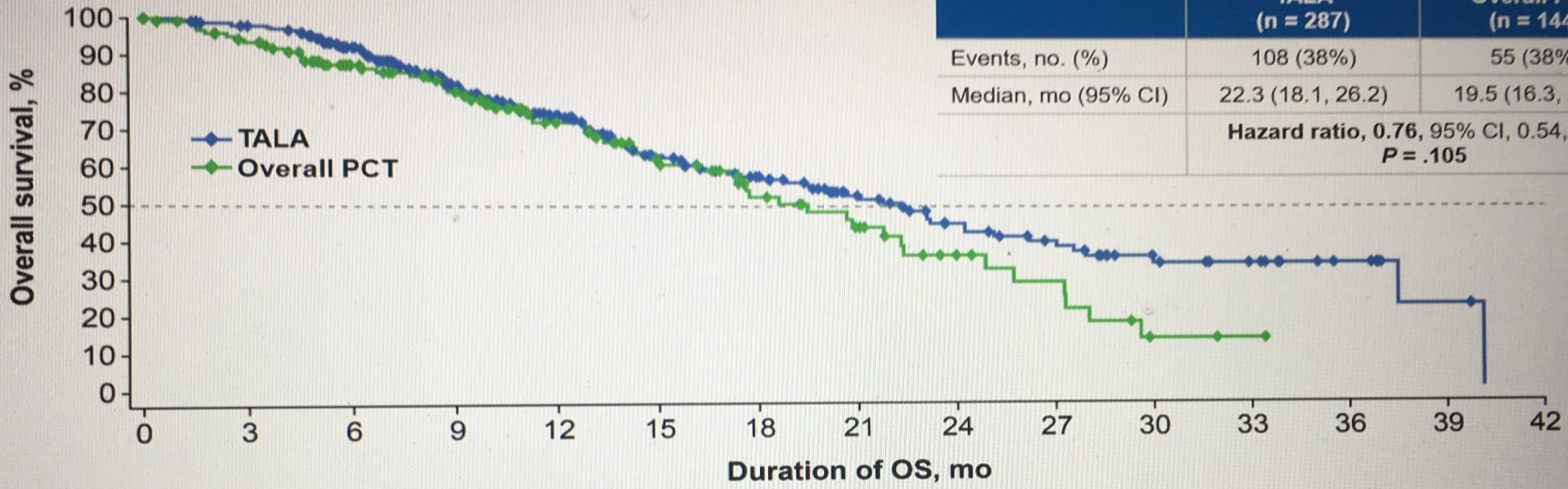
	TALA (n = 43)	Overall PCT (n = 20)
Events, no. (%)	32 (74%)	15 (75%)
Median, mo (95% CI)	5.7 (4.1, 8.1)	1.6 (1.2, 4.3)
	Hazard ratio, 0.32, 95% CI, 0.15, 0.68 ***P* = .0016**	



No. at risk (events/cumulative events)												
TALA	43 (0/0)	30 (12/12)	17 (10/22)	9 (5/27)	4 (2/29)	1 (2/31)	1 (0/31)	1 (0/31)	1 (0/31)	1 (0/31)	0 (1/32)	0 (0/32)
PCT	20 (0/0)	5 (11/11)	1 (3/14)	1 (0/14)	1 (0/14)	1 (0/14)	1 (0/14)	0 (1/15)	0 (0/15)	0 (0/15)	0 (0/15)	0 (0/15)

Interim OS Analysis: Secondary Endpoint

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	108 (38%)	55 (38%)
Median, mo (95% CI)	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
	Hazard ratio, 0.76, 95% CI, 0.54, 1.06 ***P* = .105**	



No. at risk (events/cumulative events)													
TALA	287 (0/0)	278 (5/5)	236 (15/20)	179 (24/44)	132 (16/60)	91 (17/77)	74 (8/85)	52 (6/91)	38 (7/98)	30 (4/102)	18 (4/106)	14 (0/106)	8 (0/106)	2 (1/107)	0 (1/108)
PCT	144 (0/0)	119 (8/8)	92 (7/15)	78 (7/22)	55 (7/29)	41 (7/36)	28 (6/42)	20 (4/46)	11 (3/49)	8 (2/51)	2 (4/55)	1 (0/55)	0 (0/55)	0 (0/55)	0 (0/55)

Survival Probability at:	TALA (n = 287)	Overall PCT (n = 144)
Month 24, % (95% CI)	45% (36.7-53.5)	37% (24.1-49.1)
Month 36, % (95% CI)	34% (25.3-43.7)	0%

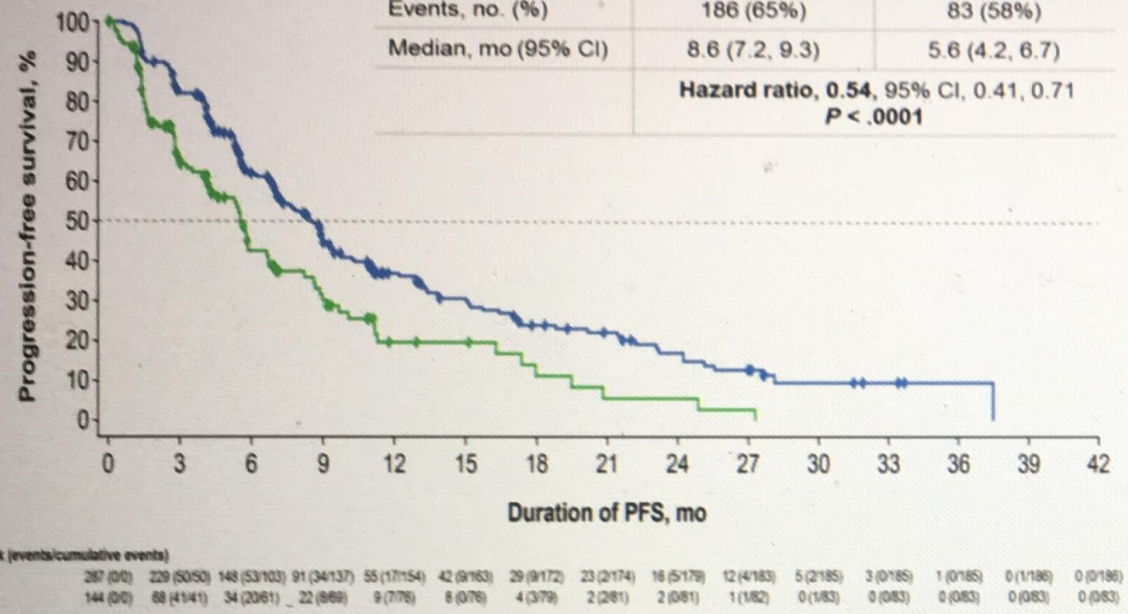
Secondary/Exploratory Endpoints

	TALA	Overall PCT
Best overall response [measurable disease]*	**n = 219**	**n = 114**
Complete response, no. (%)	12 (5.5%)	0
Partial response, no. (%)	125 (57.1%)	31 (27.2%)
Stable disease, no. (%)	46 (21.0%)	36 (31.6%)
Non-evaluable, no. (%)	4 (1.8%)	19 (16.7%)
Objective response by investigator [measurable disease]*	**n = 219**	**n = 114**
ORR, % (95% CI)	62.6 (55.8-69.0)	27.2 (19.3-36.3)
Odds ratio (95% CI); 2-sided *P* value**	**4.99 (2.9-8.8); *P* < .0001**	
Clinical benefit rate at 24 weeks [ITT]	**n = 287**	**n = 144**
CBR24, % (95% CI)	68.6 (62.9-74.0)	36.1 (28.3-44.5)
Odds ratio (95% CI); 2-sided *P* value**	**4.28 (2.70-6.83); *P* < .0001**	
DOR by investigator [subgroup with objective response]	**n = 137**	**n = 31**
Median (IQR), mo	5.4 (2.8-11.2)	3.1 (2.4-6.7)

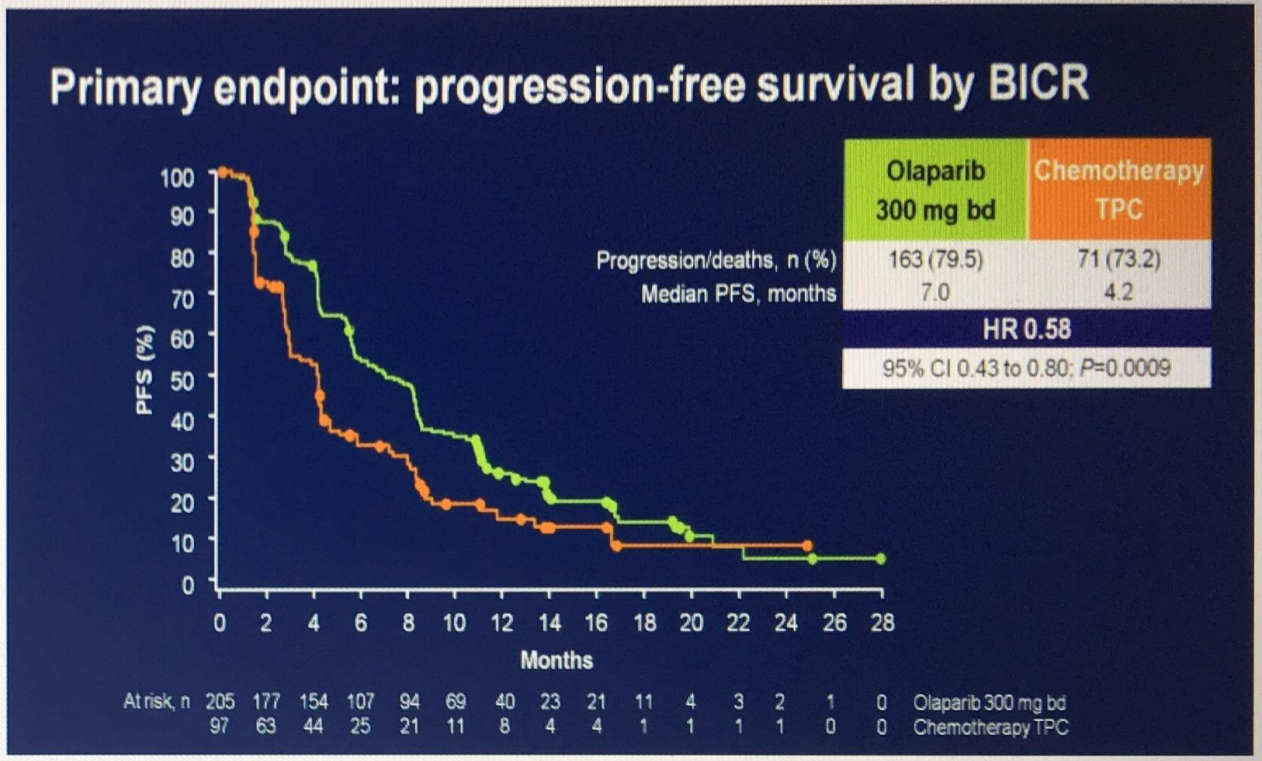
Abbreviation: IQR, interquartile range.
*Per RECIST version 1.1, confirmation of complete response or partial response was not required. **CMH=Cochran-Mantel-Haenszel.

EMBRACA vs. OlympiAD

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 *P* < .0001	



EMBRACA



OlympiAD

Adverse Events: Hematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
No. of patients with ≥ 1 AE, no. (%)	194 (67.8%)	140 (49.0%)	17 (5.9%)	63 (50.0%)	29 (23.0%)	19 (15.1%)
Anemia	151 (52.8%)	110 (38.5%)	2 (0.7%)	23 (18.3%)	5 (4.0%)	1 (0.8%)
Neutropenia	99 (34.6%)	51 (17.8%)	9 (3.1%)	54 (42.9%)	25 (19.8%)	19 (15.1%)
Thrombocytopenia	77 (26.9%)	32 (11.2%)	10 (3.5%)	9 (7.1%)	2 (1.6%)	0
Lymphopenia	21 (7.3%)	9 (3.1%)	0	4 (3.2%)	0	1 (0.8%)
Febrile neutropenia	1 (0.3%)	0	1 (0.3%)	1 (0.8%)	0	1 (0.8%)

MDS / AML: none reported in the TALA arm; 1 patient on capecitabine

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

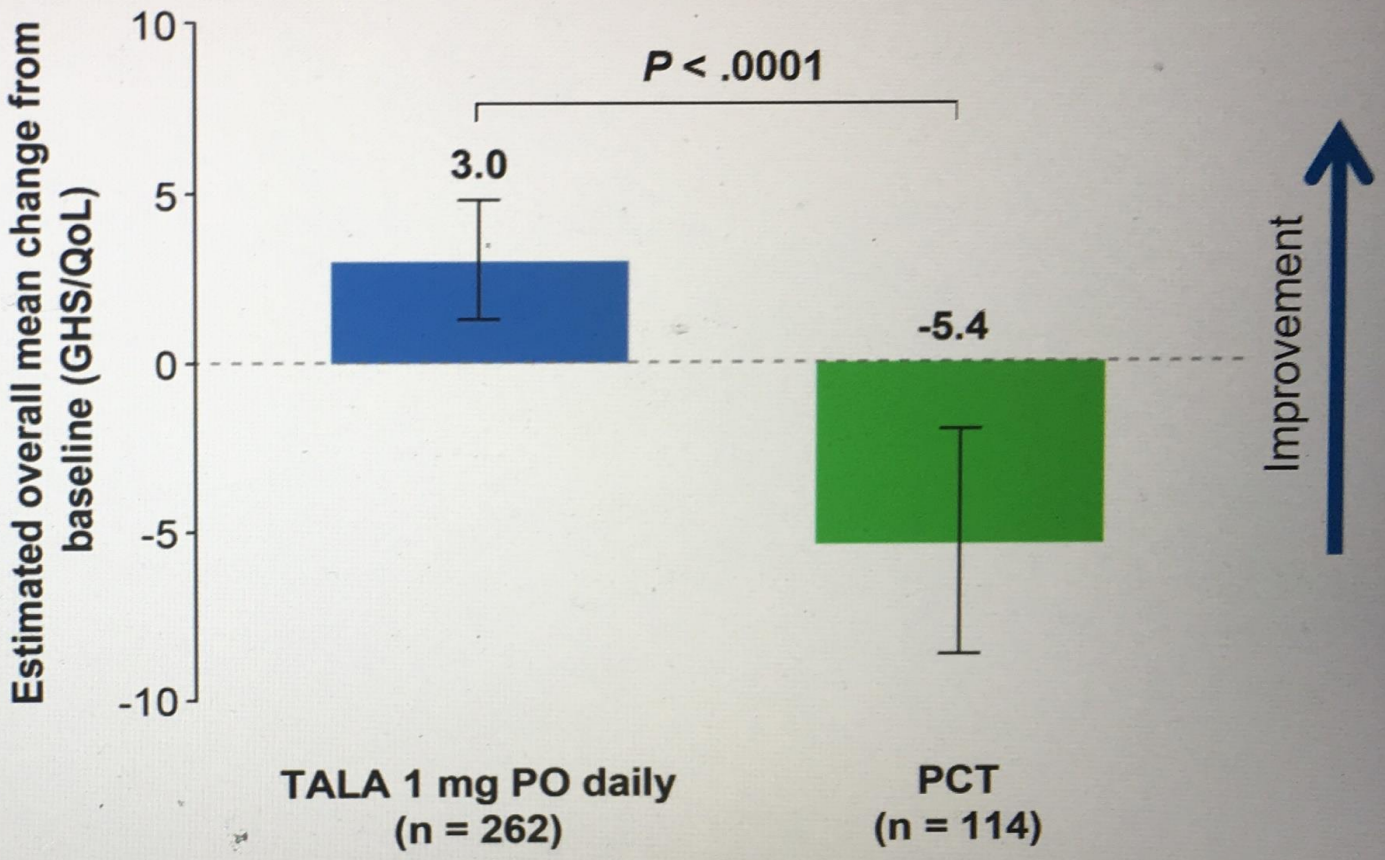
Adverse Events: Nonhematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
No. of patients with ≥ 1 nonhematologic AE, no. (%)	282 (98.6%)	91 (31.8%)		123 (97.6%)	48 (38.1%)	
Fatigue	144 (50.3%)	5 (1.7%)	0	54 (42.9%)	4 (3.2%)	0
Nausea	139 (48.6%)	1 (0.3%)	0	59 (46.8%)	2 (1.6%)	0
Headache	93 (32.5%)	5 (1.7%)	0	28 (22.2%)	1 (0.8%)	0
Alopecia	72 (25.2%)	-	-	35 (27.8%)	-	-
Vomiting	71 (24.8%)	7 (2.4%)	0	29 (23.0%)	2 (1.6%)	0
Diarrhea	63 (22.0%)	2 (0.7%)	0	33 (26.2%)	7 (5.6%)	0
Constipation	63 (22.0%)	1 (0.3%)	0	27 (21.4%)	0	0
Decreased appetite	61 (21.3%)	1 (0.3%)	0	28 (22.2%)	1 (0.8%)	0
Back pain	60 (21.0%)	7 (2.4%)	0	20 (15.9%)	2 (1.6%)	0
Dyspnea	50 (17.5%)	7 (2.4%)	0	19 (15.1%)	3 (2.4%)	0
Palmar-plantar erythrodysesthesia syndrome	4 (1.4%)	1 (0.3%)	0	28 (22.2%)	3 (2.4%)	0
Pleural effusion	6 (2.1%)	5 (1.7%)	0	11 (8.7%)	5 (4.0%)	0

- All adverse events (AEs) in ≥ 20% of patients and grade 3-4 AEs in ≥ 2.4% of patients
- No clinically relevant cardiac or vascular toxicity observed in the TALA arm
- Alopecia: all grade 1 except 2.4% grade 2 in TALA; 7.9% grade 2 in PCT

EORTC QLQ-C30: Patient-Reported Global Health Status (GHS)/QoL

Statistically significant improvement in estimated overall mean change from baseline in GHS/QoL for TALA-treated patients [3.0 (95% CI, 1.2, 4.8)] compared to PCT-treated patients [-5.4 (-8.8, -2.0)]

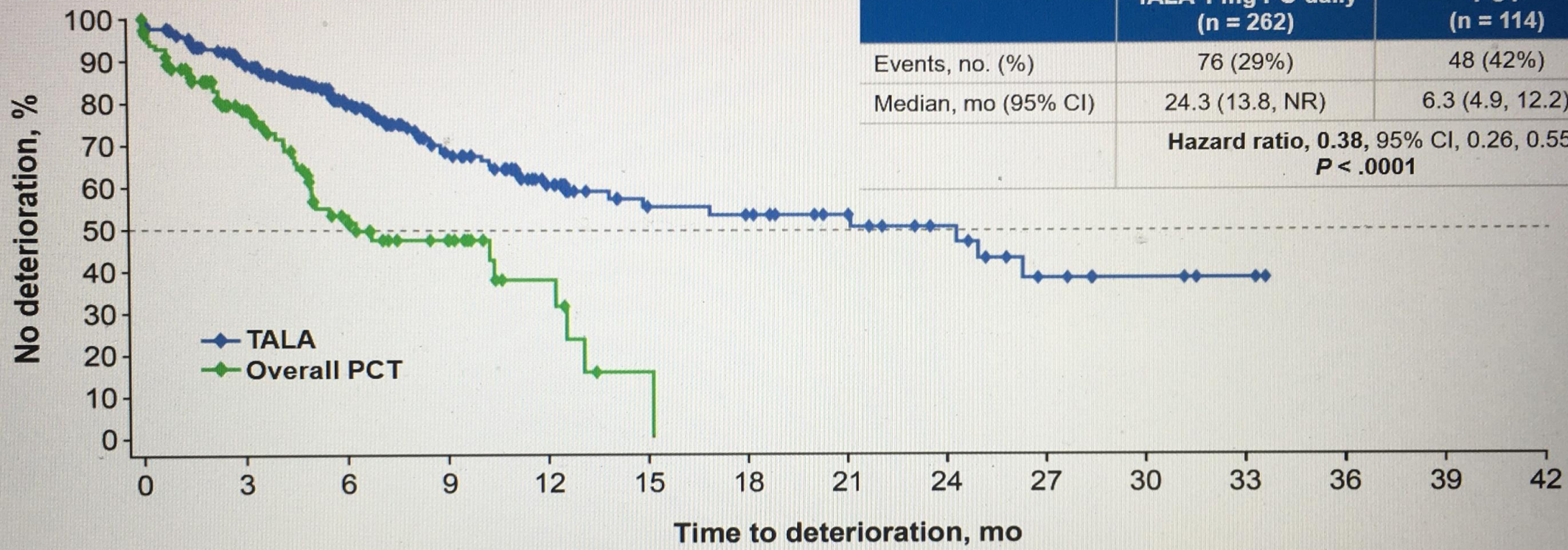


Note: Results from longitudinal repeated measures mixed effects model.

Time to Deterioration in EORTC QLQ-C30: GHS/QoL

Statistically significant delay in the time to clinically meaningful deterioration* in GHS/QoL favoring TALA

	TALA 1 mg PO daily (n = 262)	PCT (n = 114)
Events, no. (%)	76 (29%)	48 (42%)
Median, mo (95% CI)	24.3 (13.8, NR)	6.3 (4.9, 12.2)
	Hazard ratio, 0.38, 95% CI, 0.26, 0.55 ***P* < .0001**	



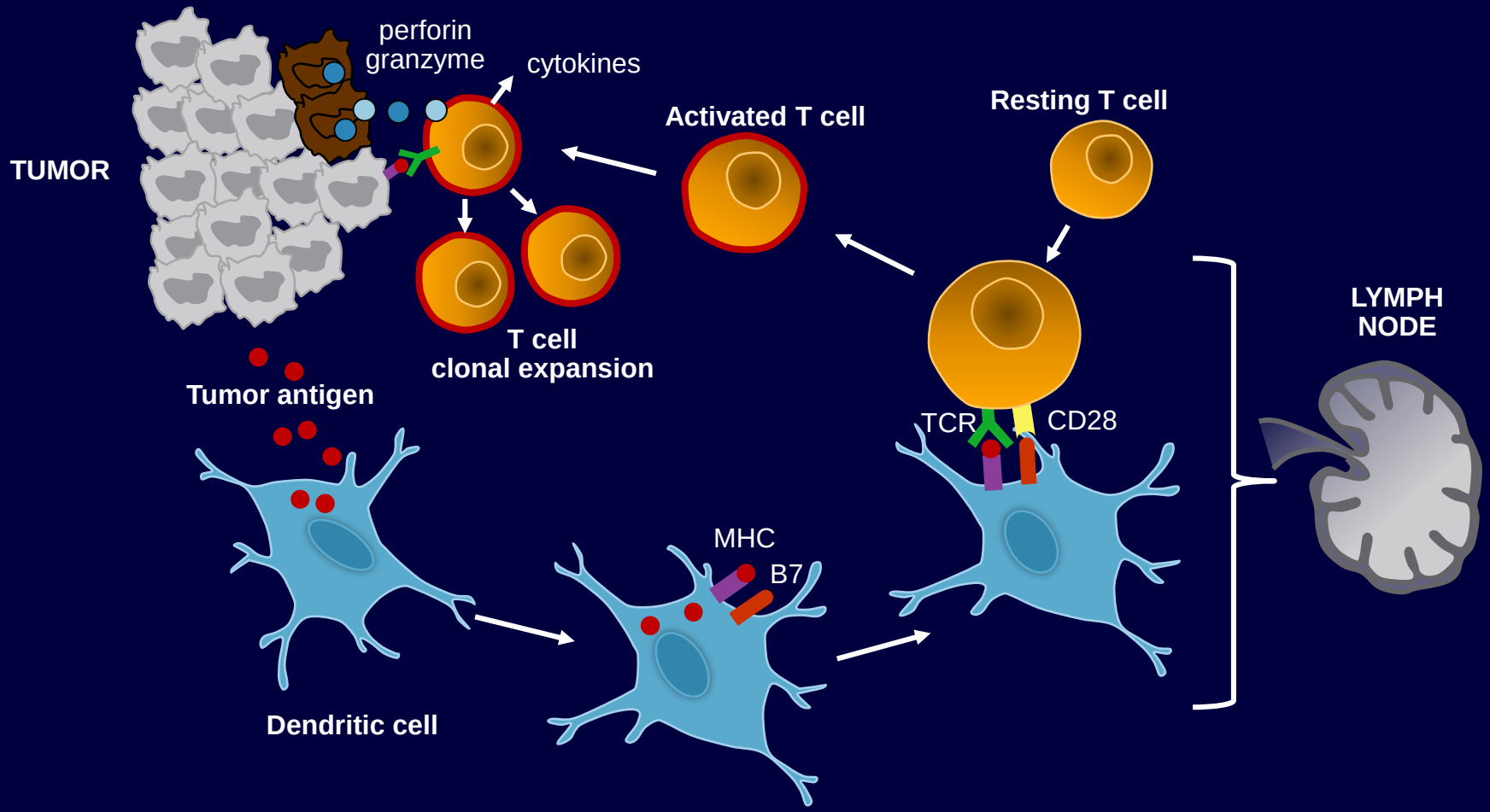
No. at risk (events/cumulative events)													
TALA	262 (0/0)	212 (26/26)	139 (18/44)	78 (17/61)	44 (7/68)	28 (3/71)	26 (1/72)	20 (0/72)	14 (1/73)	7 (3/76)	4 (0/76)	2 (0/76)	0 (0/76)	0 (0/76)	0 (0/76)
PCT	114 (0/0)	64 (22/22)	30 (17/39)	17 (3/42)	6 (2/44)	1 (3/47)	0 (1/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)

Abbreviation: NR, not reached. *≥ 10-point decrease and no subsequent observation with a < 10-point decrease from baseline.

EMBRACA Phase 3 Trial of Talazoparib: Conclusions

- EMBRACA is the largest randomized trial evaluating a PARP inhibitor in patients with advanced breast cancer and a germline *BRCA1/2* mutation
- Talazoparib resulted in prolonged progression-free survival vs physician's choice of therapy by blinded central review
  - HR: 0.54 (95% CI, 0.41, 0.71); $P < .0001$
- All key secondary efficacy endpoints demonstrated benefit with talazoparib
  - Overall survival is immature (51% of projected events); HR: 0.76 (95% CI, 0.54, 1.06); $P = .105$
- Global Health Status/Quality of Life showed overall improvement from baseline and a delay in the time to clinically meaningful deterioration in patients receiving talazoparib
  - HR: 0.38 (95% CI, 0.26, 0.55); $P < .0001$
- Talazoparib was generally well tolerated, with minimal nonhematologic toxicity and few adverse events resulting in treatment discontinuation

免疫系與癌細胞的關係


perforin
granzyme
cytokines
TUMOR
Activated T cell
Resting T cell
T cell
clonal expansion
Tumor antigen
LYMPH
NODE
TCR
CD28
MHC
B7
Dendritic cell

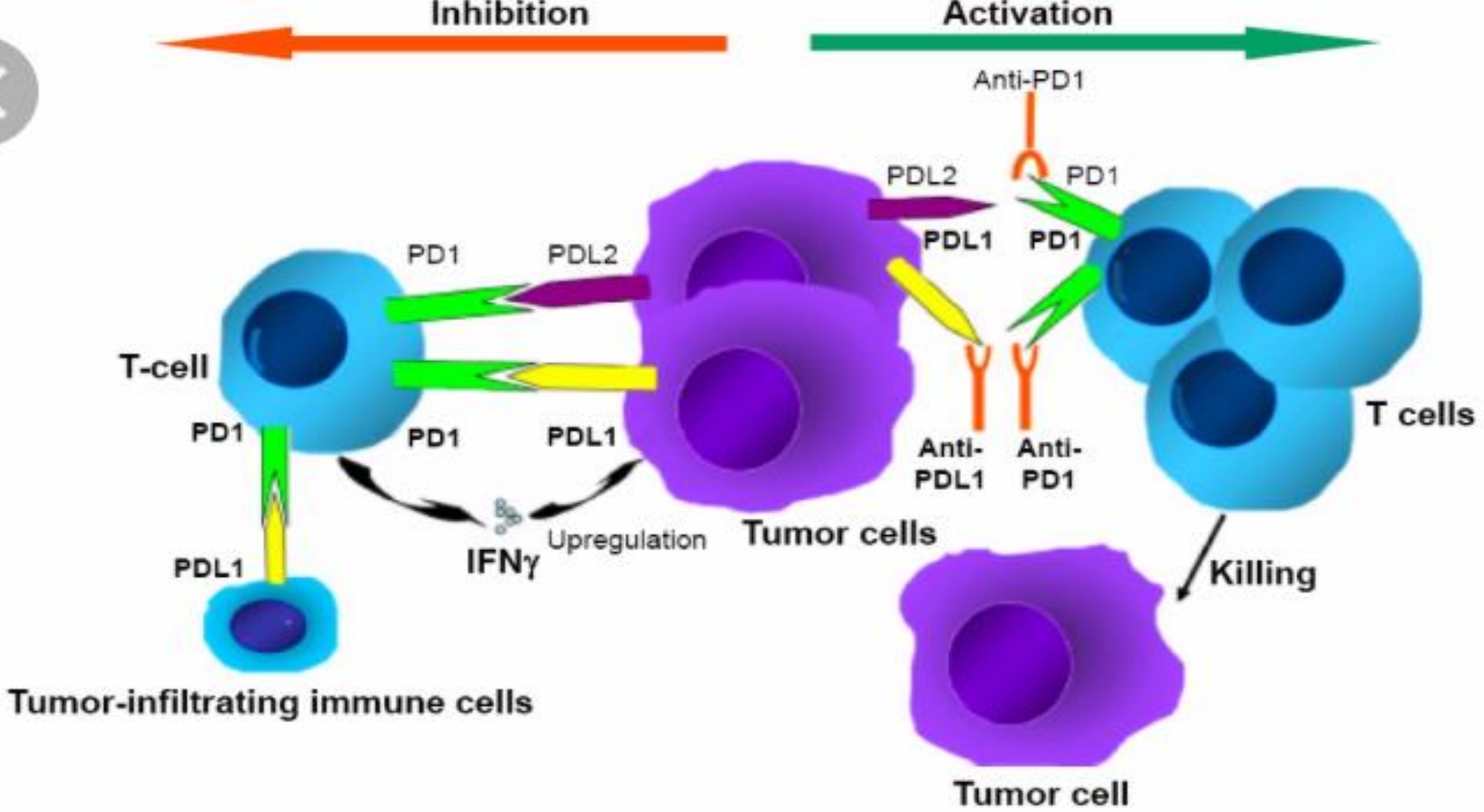
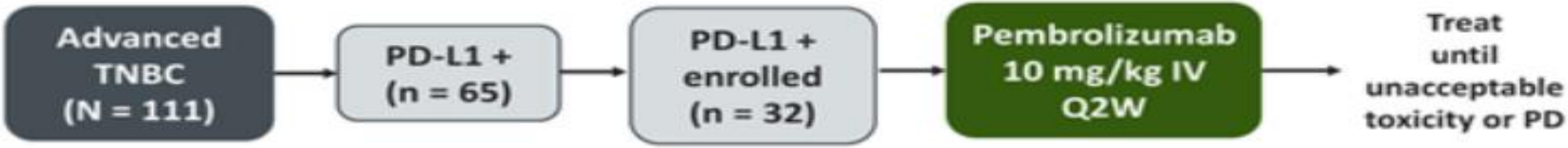


Figure 1 Mechanism of anti-PD1 and anti-PDL1 checkpoint blockades.

Notes: PD1 is expressed by T cells. PDL1 is expressed in tumor cells and tumor-infiltrating immune cells. Combination of PD1 and PDL1/PDL2 contributes to the suppression of T-cell function. Inhibiting the interaction of PD1 and its ligands can significantly enhance T-cell function, resulting in antitumor activity. Reprinted from *Cancer Treat Rev*, 41(10), Meng X, Huang Z, Teng F, Xing L, Yu J, Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy, 868–876, Copyright (2015), with permission from Elsevier.[34]

KEYNOTE-012: Phase 1b Study of Pembrolizumab in Advanced TNBC



Patients evaluable for response (n = 27)

- ORR: 18.5%
- Median time to response: 17.9 wk (range, 7.3 to 32.4 wk)
- Median DoR: not yet reached (range, 15.0 to ≥ 47.3 wk)
- Median OS: 11.2 mo (6-mo OS, 66.7%; 12-mo OS, 43.1%)

Nanda R, et al. *J Clin Oncol.* 2016;34:2460-2467.

Study Design – KEYNOTE-086 Cohort A

Patients

- Age ≥18 y
- Centrally confirmed TNBC[a]
- ≥1 prior systemic treatment for mTNBC with documented PD
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample for PD-L1 evaluation
- No radiographic evidence of CNS metastases
- Measurable disease per RECIST v1.1 by central review

N = 170

Pembrolizumab 200 mg IV Q3W

for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

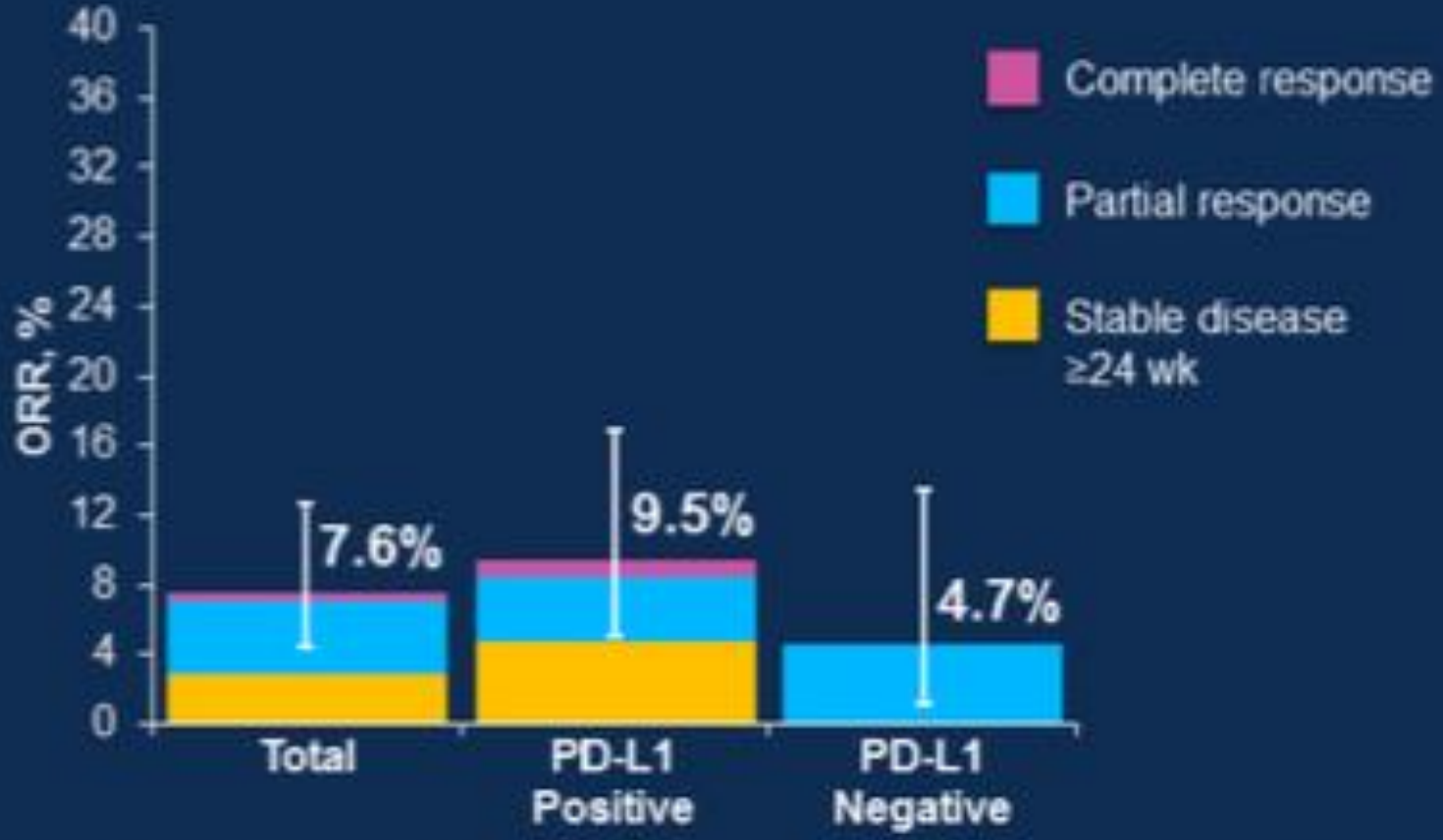
Protocol-specified follow-up

- Primary end points: ORR[b] and safety
- Secondary end points[b]: DOR, DCR,[c] PFS, OS

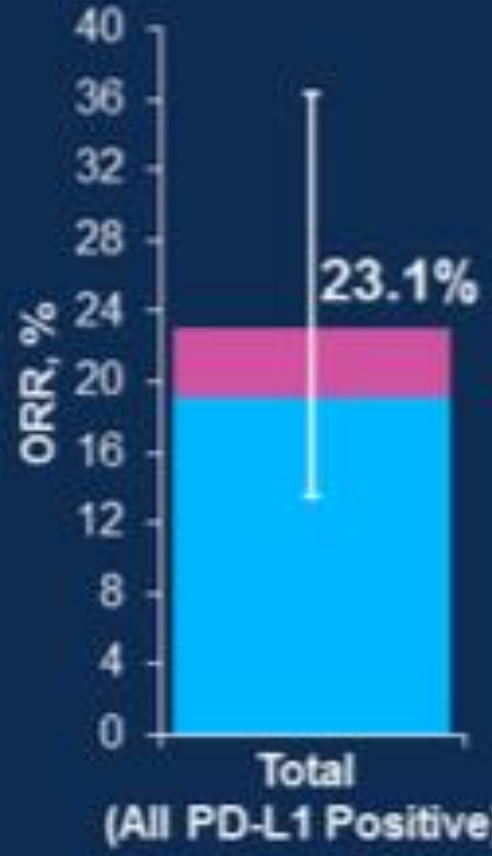
[a]<1% tumor cells positive for ER and PR by IHC, irrespective of intensity, and HER2 IHC 0 or 1+ or FISH negative. [b]Assessed in the total population and in the PD-L1–positive population.

Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC

Cohort A (N = 170): Previously Treated, Regardless of PD-L1 Expression



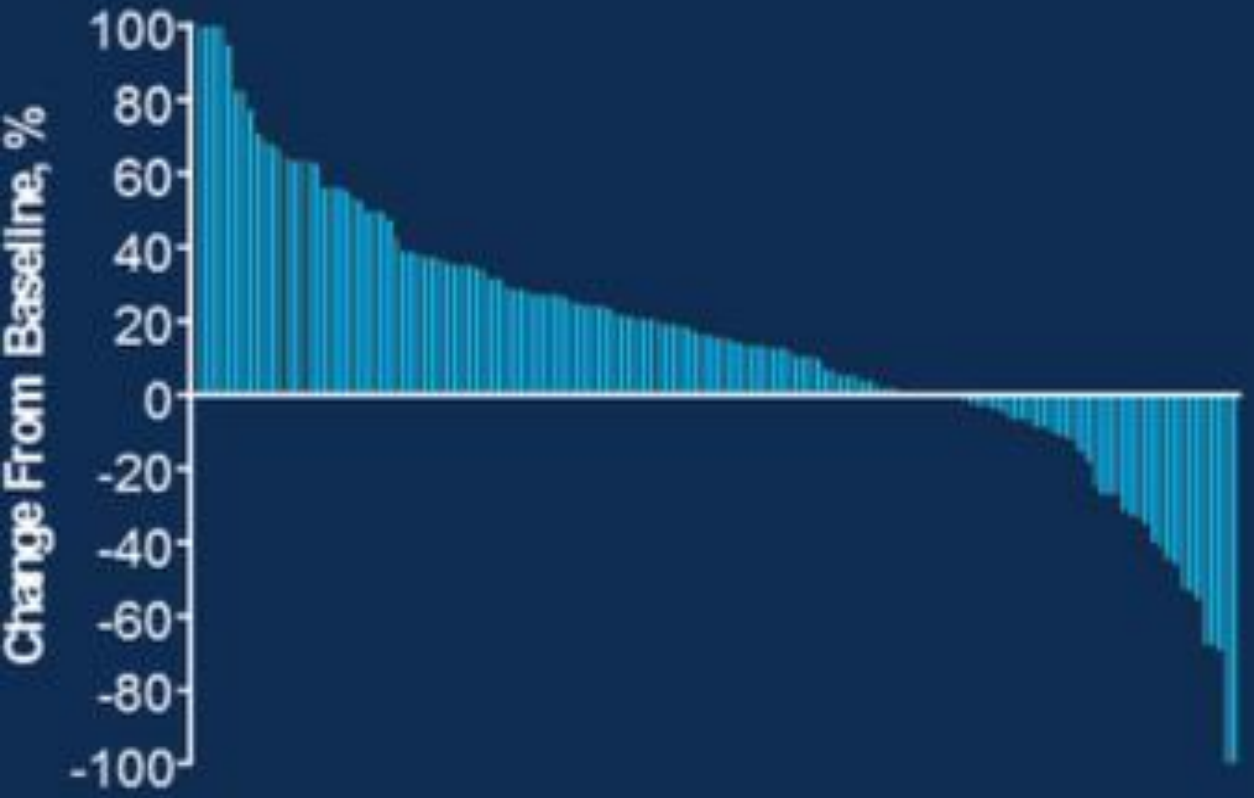
Cohort B (N = 52)[1]: Previously Untreated, PD-L1 Positive



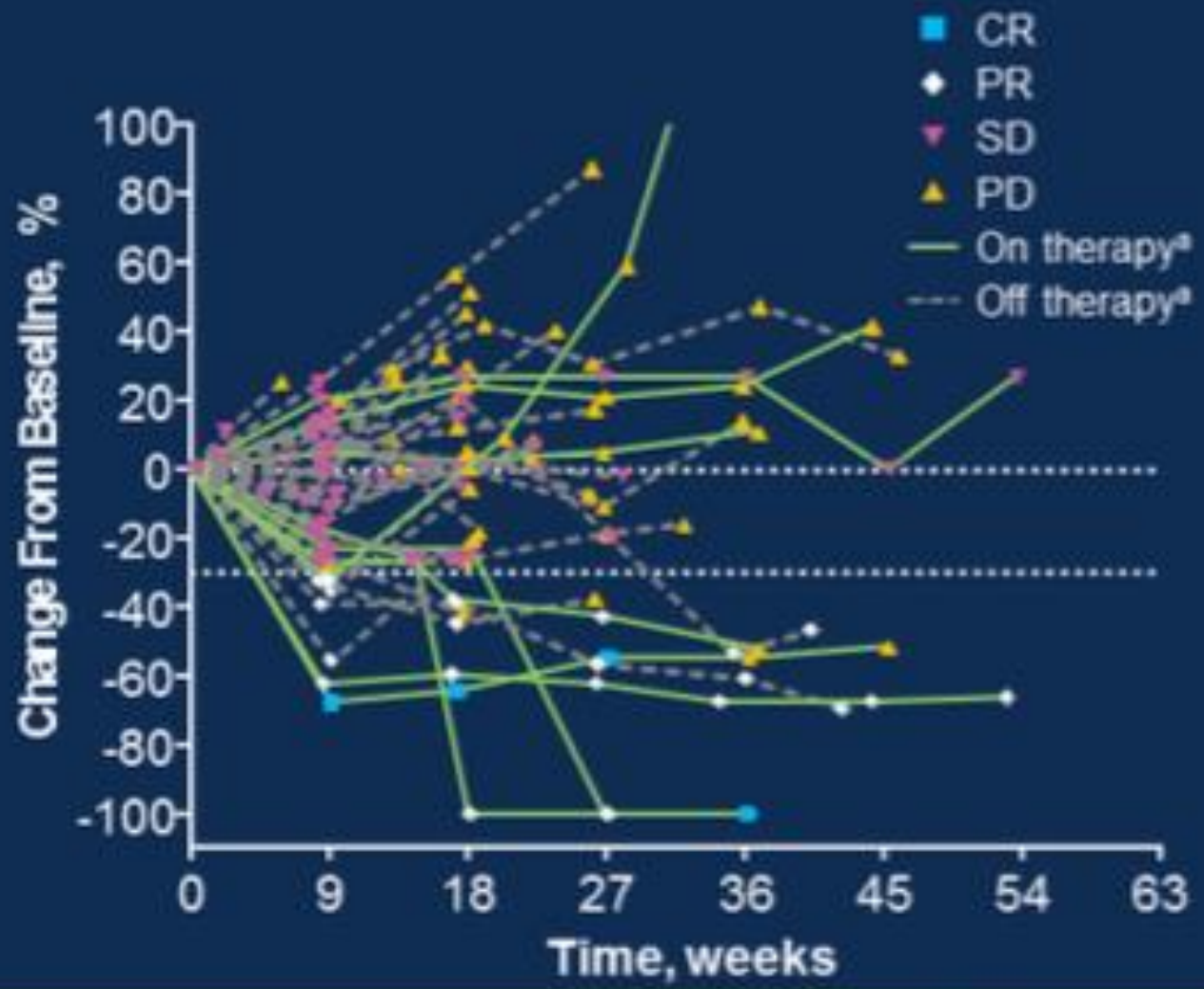
1. Adams S et al. ASCO Annual Meeting; Jun 2-6, 2017; Chicago, IL; abstr 1088;

S. Adams. ASCO 2017.

Best Change From Baseline in Target Lesion Size, All Patients



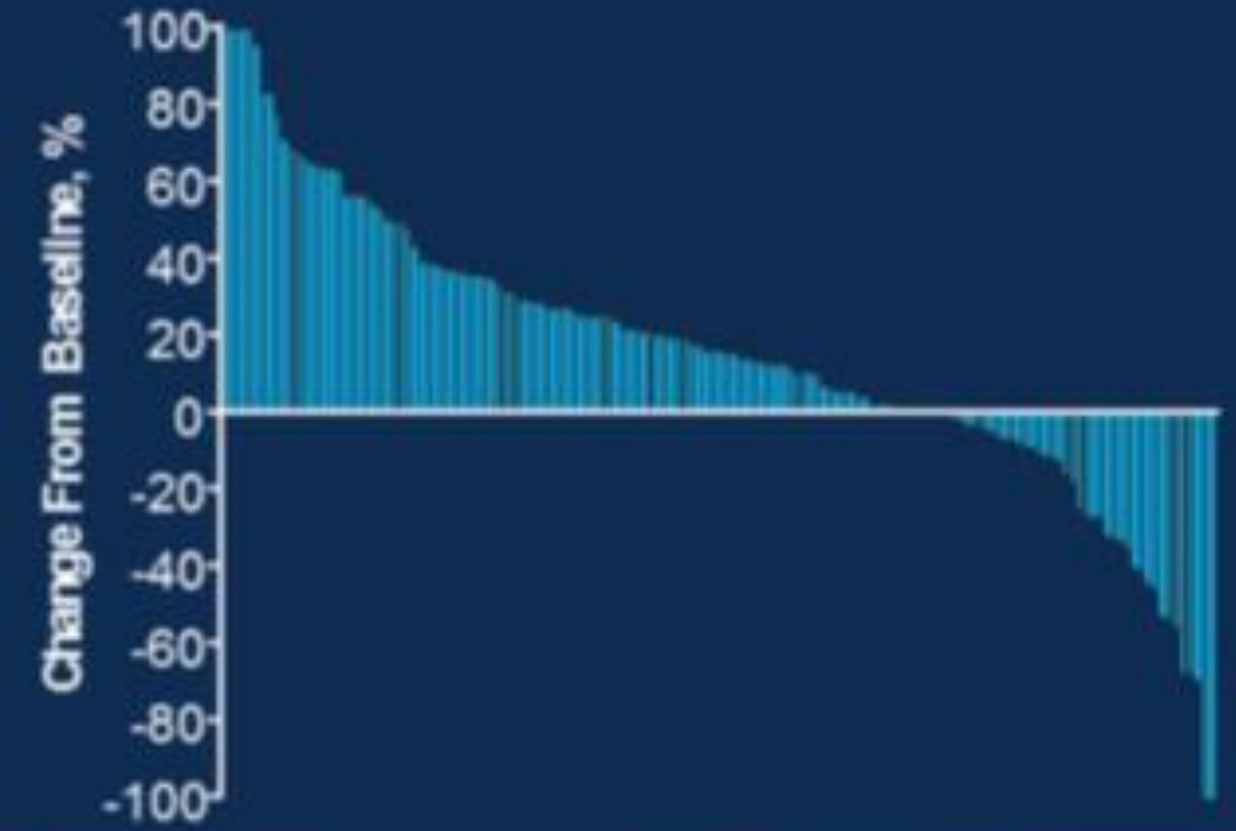
Change From Baseline in Target Lesion Size, Patients With CR, PR, or SD at Any Time Point



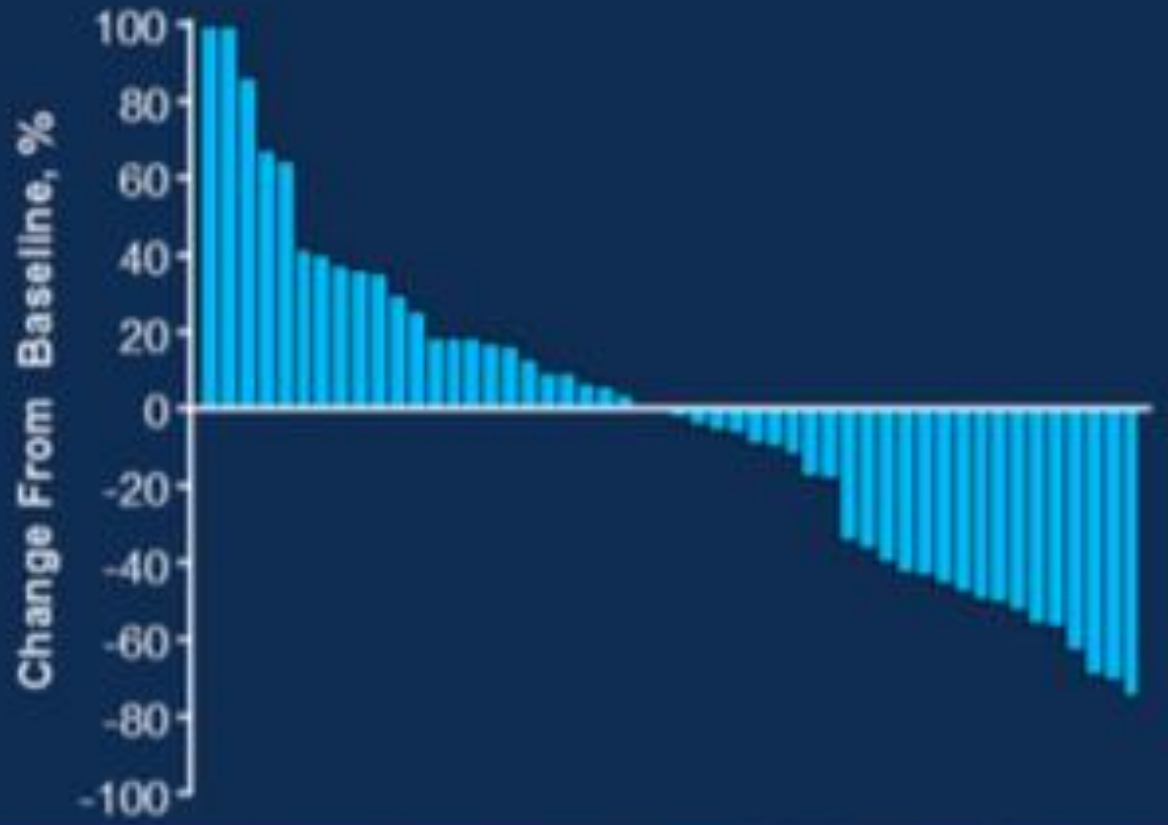
[a]At the time of data cutoff (ie, Nov 20, 2016).
Left panel includes patients with ≥1 evaluable postbaseline assessment (n = 143). Right panel includes patients with CR, PR, and SD at any time point (n = 46).
Response assessed per RECIST v1.1 by central review. Increases >100% truncated at 100%.

Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC

Cohort A (N = 170): Previously Treated, Regardless of PD-L1 Expression



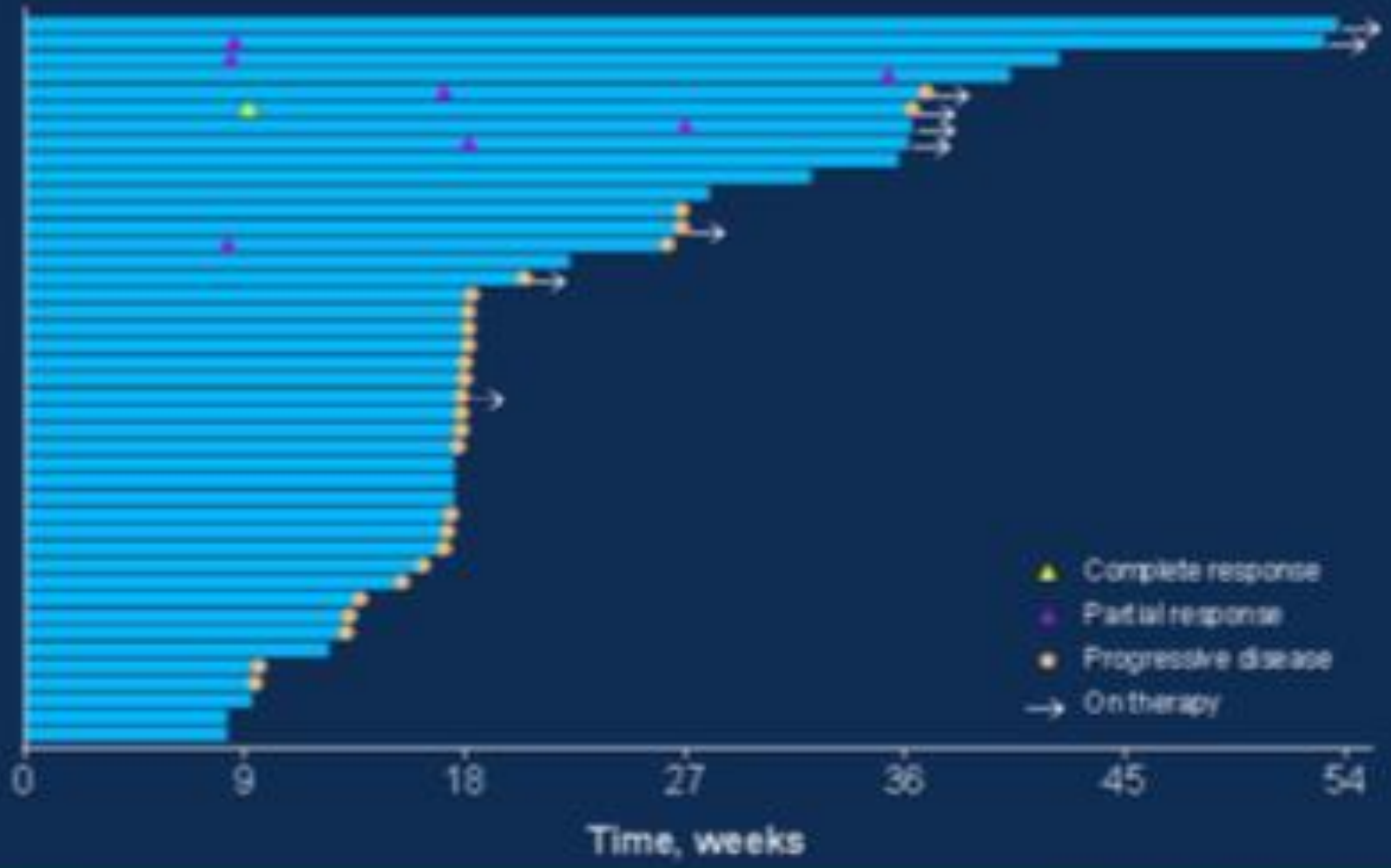
Cohort B (N = 52)[1]: Previously Untreated, PD-L1 Positive



Plots include patients with ≥1 evaluable postbaseline assessment (n = 143 for cohort A, n = 50 for cohort B).

1. Adams S, et al. ASCO Annual Meeting; Jun 2-6, 2017; Chicago, IL; abstr 1008; presented Sunday, Jun 4, from 8:00-11:30 am on poster board #30.

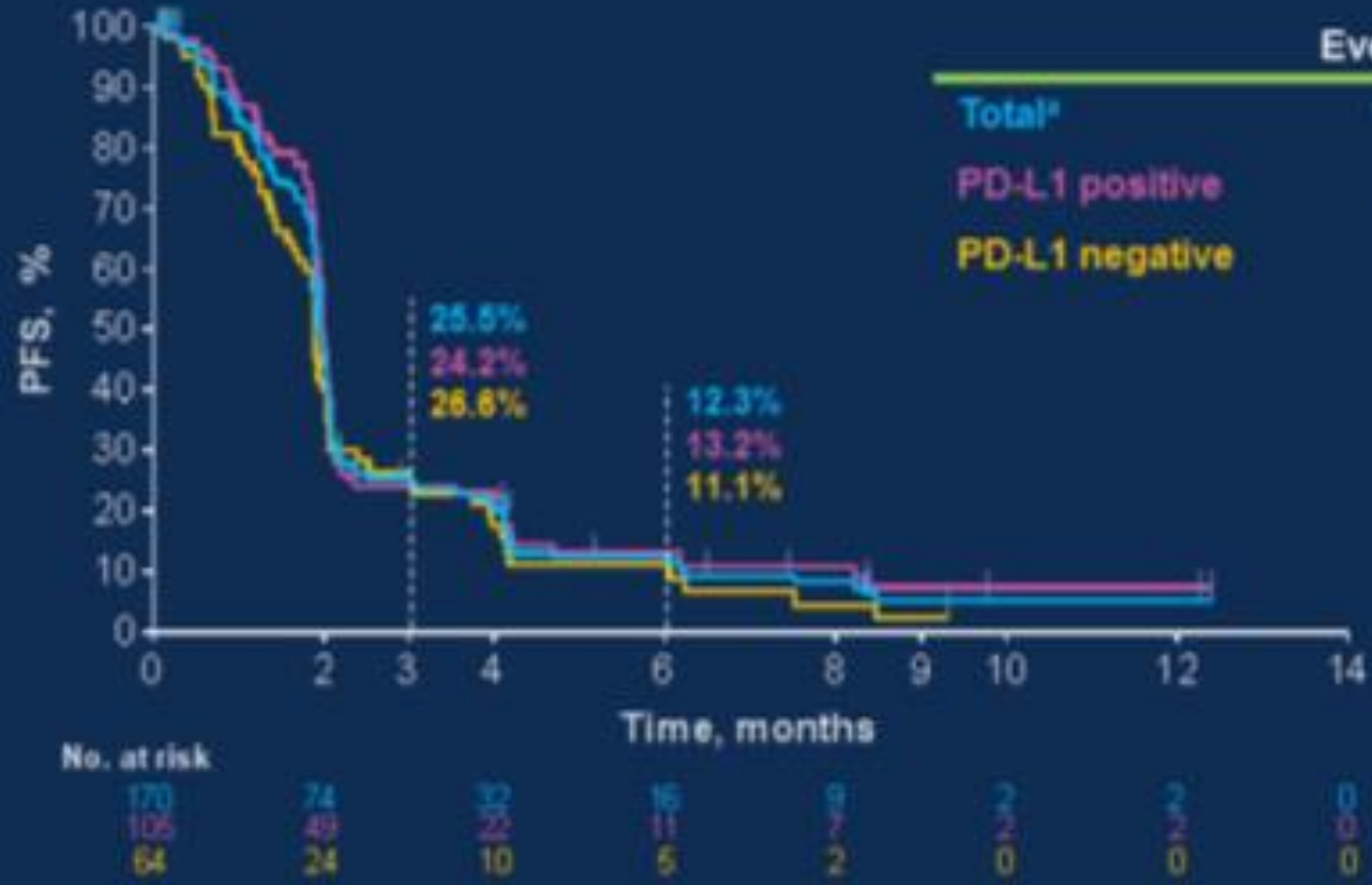
Time to Response and Duration of Response and Stable Disease (RECIST v1.1, Central Review)



- Median TTR: 3.0 mo (range, 1.9-8.1)
- No subsequent progression
  - 0/1 with CR
  - 5/7 with PR
  - 12/35 with SD
- Median DOR: 6.3 mo (range 1.2+ to 10.3+)

Length of the bars represents time to the last imaging assessment. Bars without a symbol for complete or partial response represent patients with best response of stable disease.
Data cutoff date: Nov 10, 2016.

Kaplan-Meier Estimate of PFS
(RECIST v1.1, Central Review)

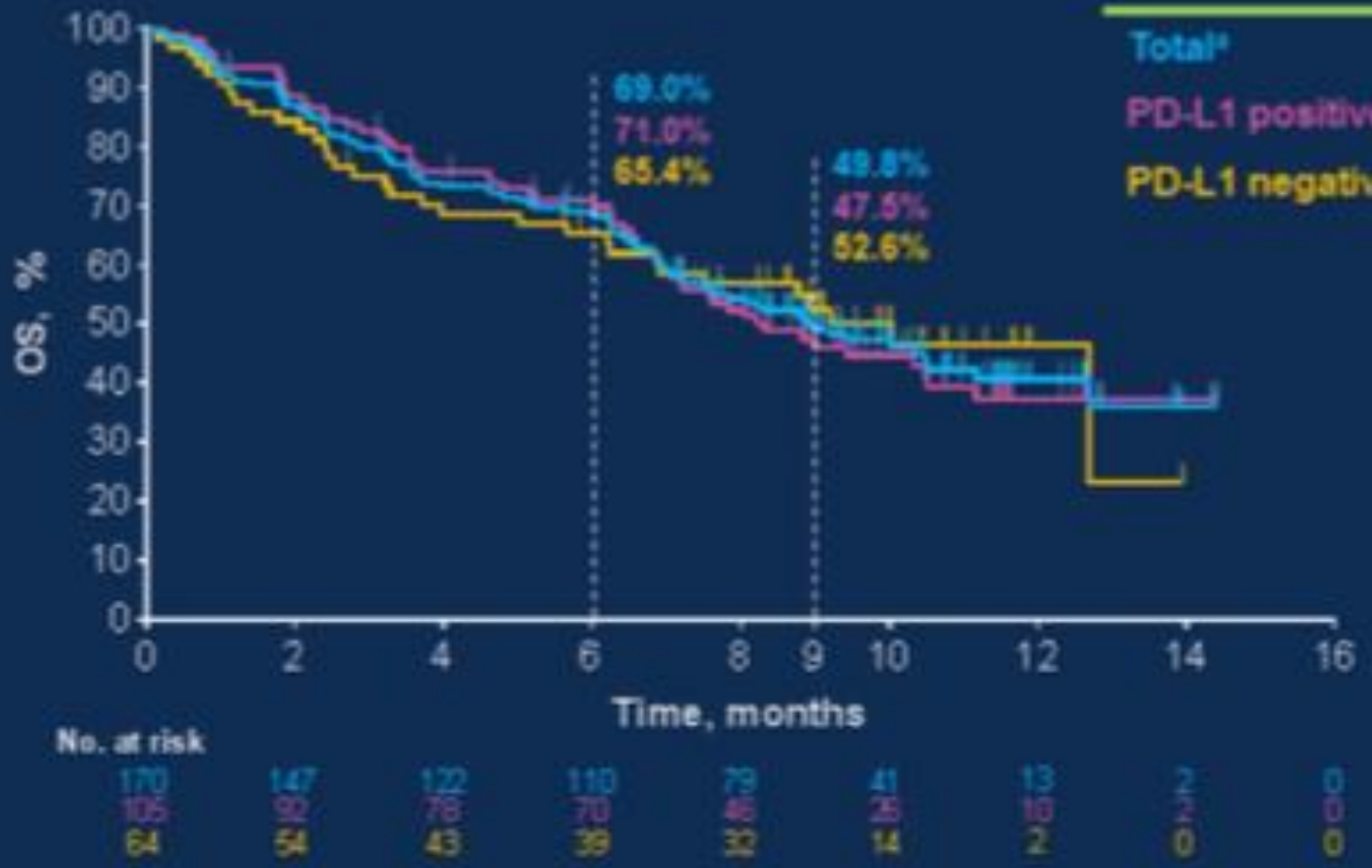


	Events/Pts, n	Median (95% CI)
Total*	148/170	2.0 mo (1.9-2.0)
PD-L1 positive	90/105	2.0 mo (1.9-2.1)
PD-L1 negative	57/64	1.9 mo (1.6-2.0)

*Includes 1 patient with unknown PD-L1 status who experienced PD.
Data cutoff date: Nov 10, 2016

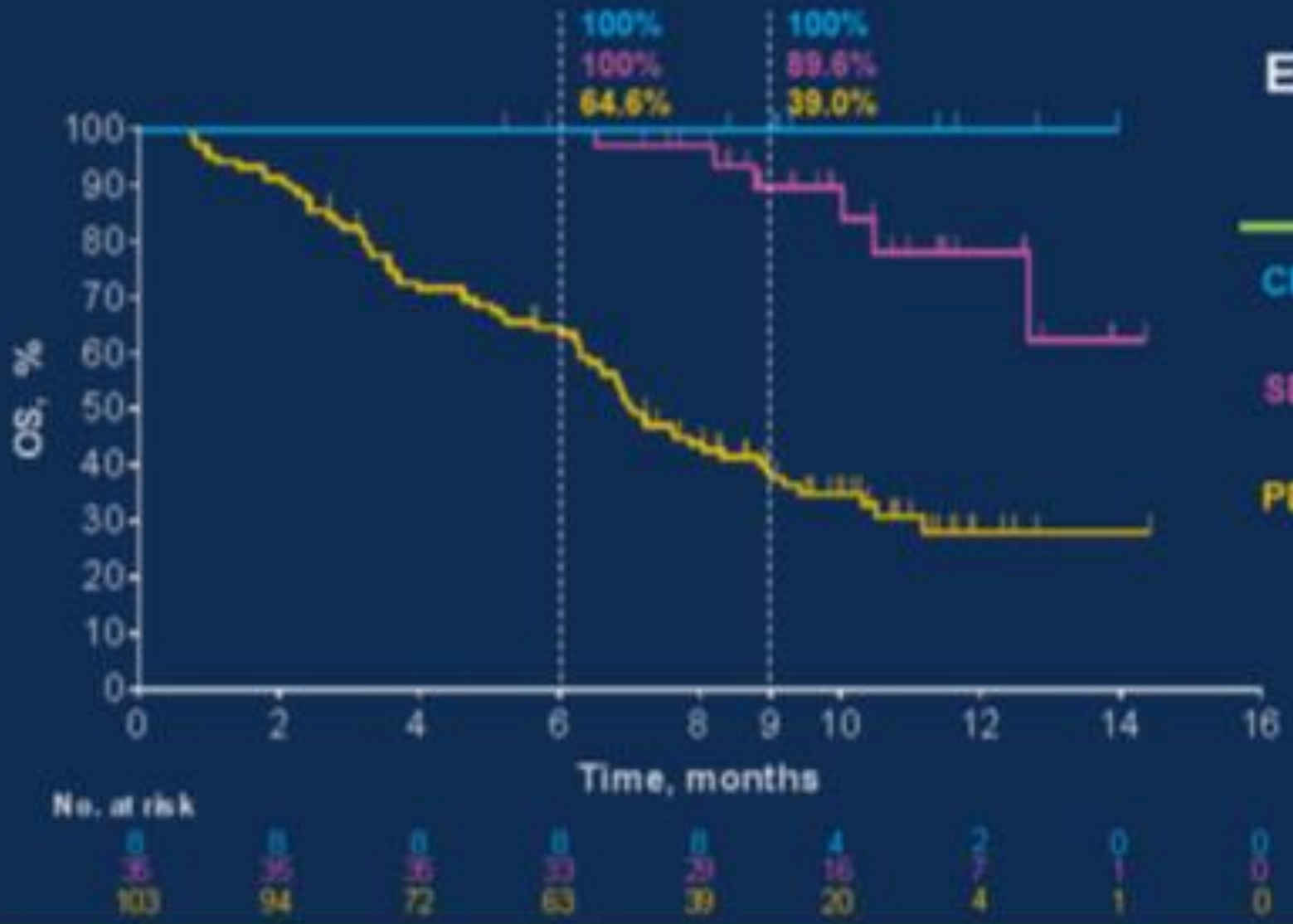
Kaplan-Meier Estimate of OS

	Events/Pts, n	Median (95% CI)
Total[a]	90/170	8.9 mo (7.2-11.2)
PD-L1 positive	58/105	8.3 mo (6.9-10.5)
PD-L1 negative	32/64	10.0 mo (6.2-NR)



NR, not reportable.
[a]Includes 1 patient with unknown PD-L1 status who was alive at data cutoff.
Data cutoff date: Nov 10, 2016.

Overall Survival by Best Overall Response



Exploratory Analysis

	Events/Pts, n	Median (95% CI)
CR or PR	0/8	Not reached (NR-NR)
SD	6/35	Not reached (12.7-NR)
PD	66/103	7.1 mo (6.3-8.8)

NR, not reportable
Patients with response that was nonevaluable (n = 5) or not assessed (n = 19) per RECIST v1.1 by central review are not included. Data cutoff date: Nov 10, 2016

Summary and Conclusions

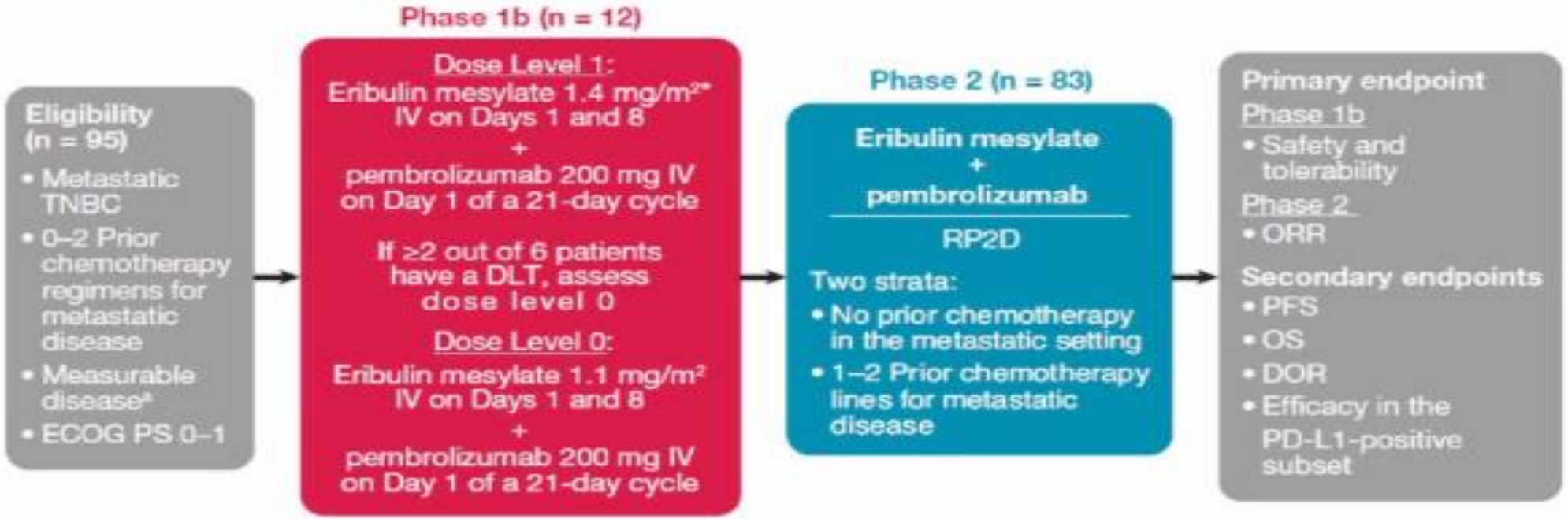
- Pembrolizumab monotherapy showed durable antitumor activity in a subset of patients with heavily pretreated mTNBC
  - Activity appeared independent of tumor PD-L1 expression
  - ORR was numerically lower in patients with poor prognostic factors
  - Survival is promising, particularly in patients with CR, PR, or SD
- Activity may be greater in patients with less heavily pretreated disease
- Analyses of non–PD-L1 biomarkers, including TILs, are ongoing
- Treatment was well tolerated
- Randomized studies of pembrolizumab monotherapy and pembrolizumab-based combination therapy are ongoing for TNBC

Study Desigin

Eribulin + Pembrolizumab Phase1/2

Eribulin in combination with pembrolizumab in patients with TNBC previously treated with 0–2 lines of chemotherapy in the metastatic setting

Figure 1. Study Design

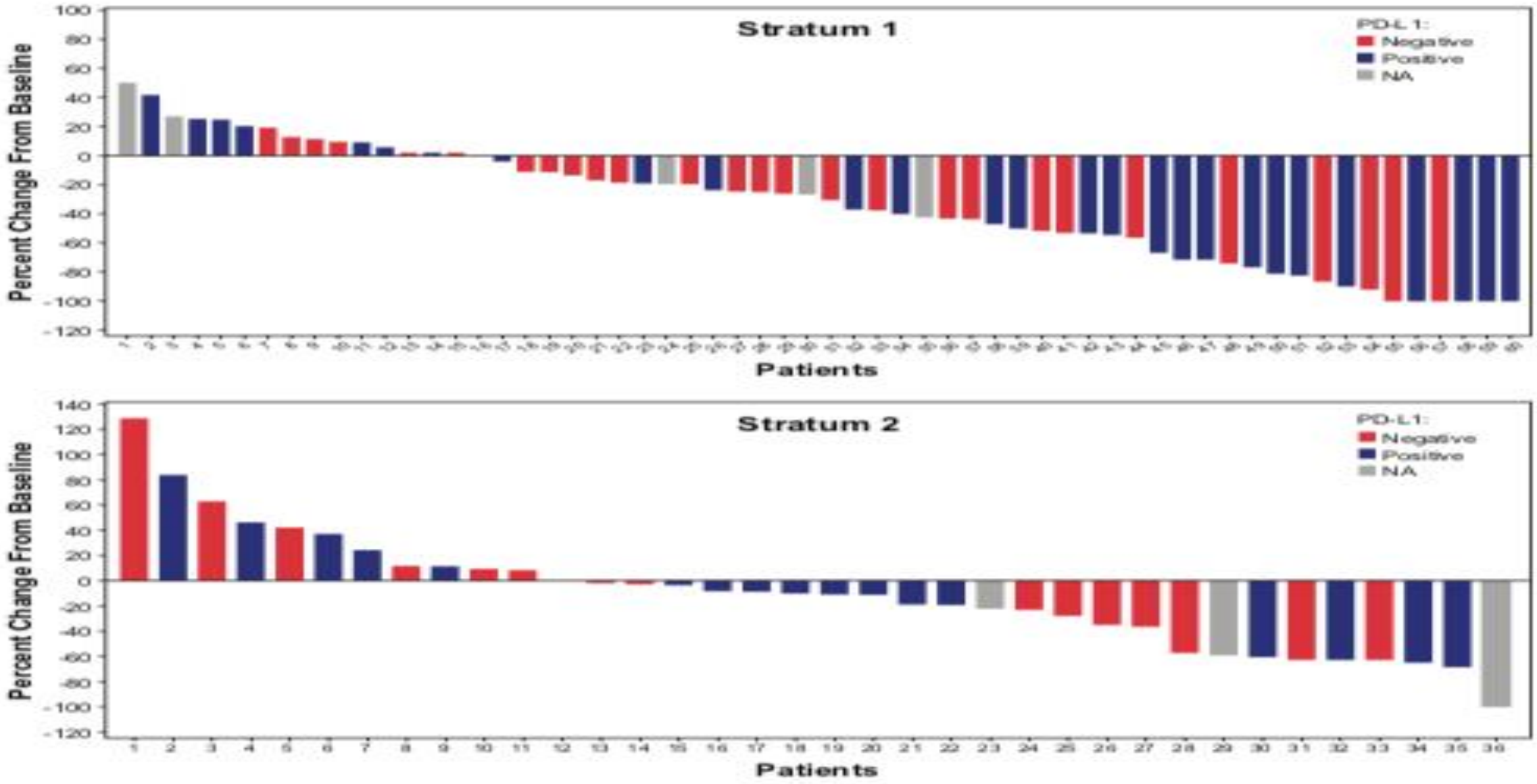


*Equivalent to 1.23 mg/m² eribulin (expressed as free base).

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; RP2D, recommended phase 2 dose; TNBC, triple-negative breast cancer.

Tolaney S et al.: San Antonio Breast Cancer Symposium 2016. P5-15-02

Figure 2. Maximum Percentage Change in Total Sum of Target Lesion Diameters From Baseline per RECIST v1.1

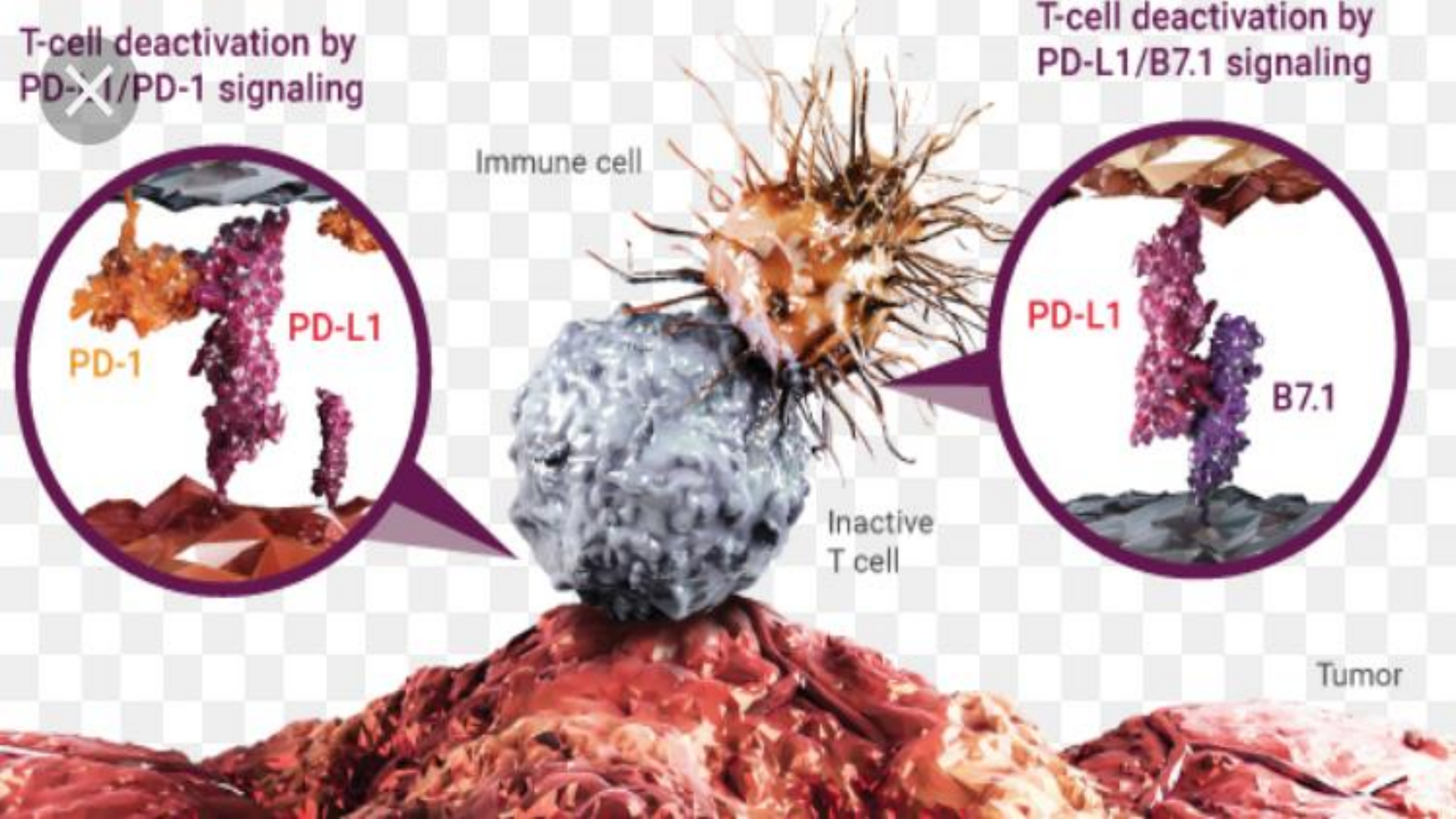


Patients with both baseline and postbaseline target lesion measurements were included.
NA, not available; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria In Solid Tumors.

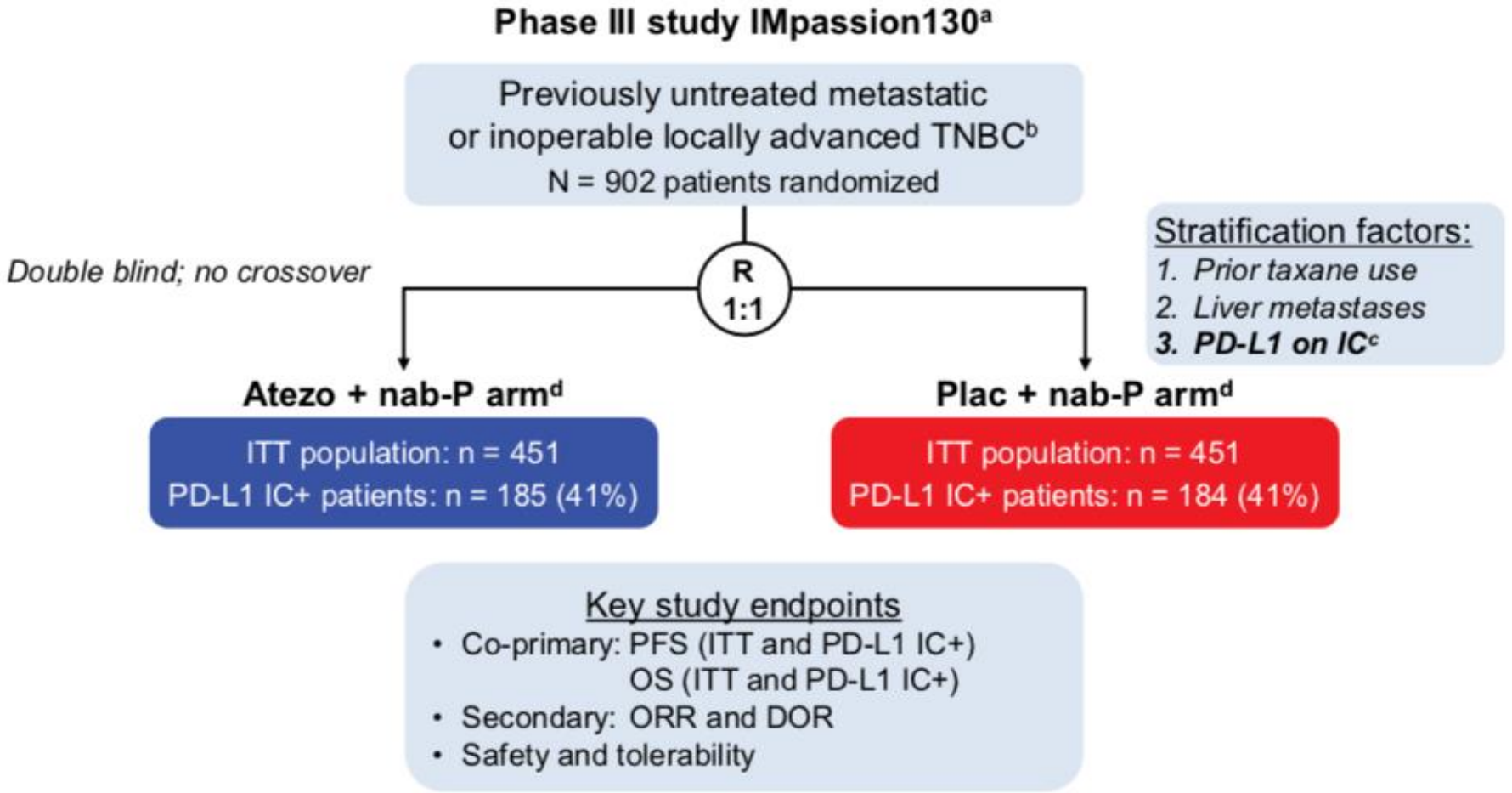
Ongoing Randomized, Phase 3 Trials of Immune Checkpoint Inhibitors for TNBC

Study Identifier	Setting	Study Design
KEYNOTE-119[a]	Second- or third-line	Pembrolizumab vs physicians' choice (capecitabine, eribulin, gemcitabine, or vinorelbine)
KEYNOTE-355[b]	First-line	Chemotherapy (nab-P, paclitaxel, or gemcitabine/carboplatin), +/- pembrolizumab
IMpassion 130[c]	First-line	Nab-paclitaxel +/- atezolizumab

a. ClinicalTrials.gov. NCT02555657.
b. ClinicalTrials.gov. NCT02819518.
c. ClinicalTrials.gov. NCT02425891.


T-cell deactivation by
PD-L1/PD-1 signaling
PD-1
PD-L1
Immune cell
Inactive
T cell
T-cell deactivation by
PD-L1/B7.1 signaling
PD-L1
B7.1
Tumor

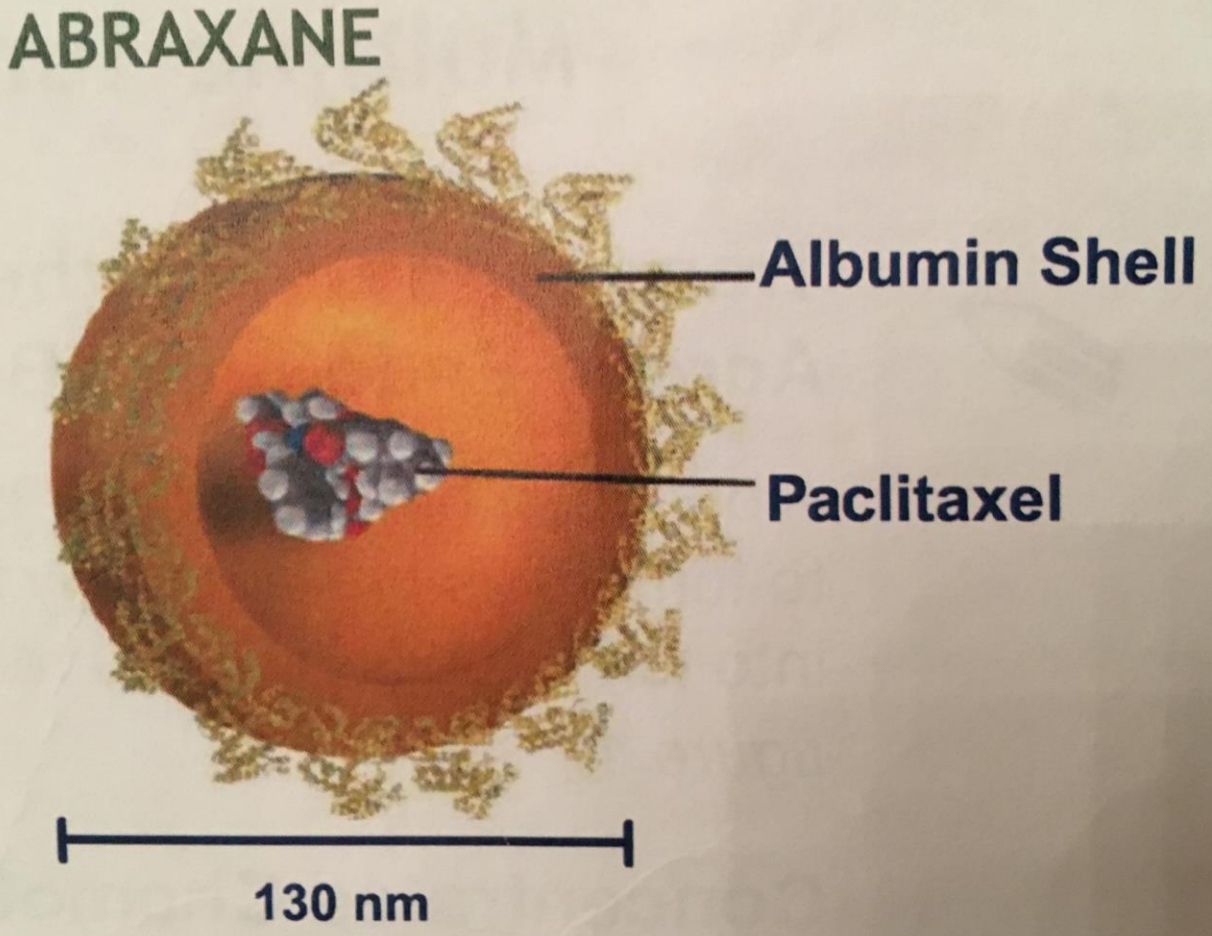
IMpassion130 study design: Prespecified analyses in the ITT and PD-L1 IC+ population



[a] NCT02425891. [b] Locally evaluated per ASCO-CAP guidelines. Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo.
[c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status, PD-L1+: PD-L1 on ≥ 1% of IC). [d] Atezolizumab or placebo 840 mg IV on days 1 and 15 + *nab*-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15 of 28-day cycle until RECIST v1.1 PD. 1. Schmid *N Engl J Med* 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

NAB - PACLITAXEL



NANO-SIZED* PROTEIN (ALBUMIN) SHELLS ENCASE CHEMOTHERAPY AGENTS TO CARRY THEM DIRECTLY INTO THE TUMOR

*100 times smaller than a human blood cell

Multiple Tumor-Targeting Mechanisms

Transports Chemotherapy Across Endothelial Barrier

Albumin, a natural carrier of nutrients to tumors, is *preferentially* transported into tumor cells by gp60 receptors *(See figure 1)*

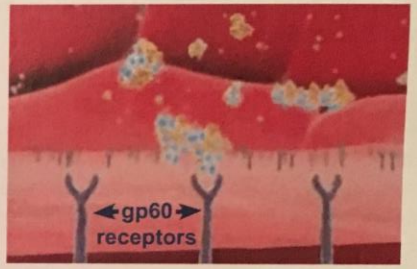


figure 1

Concentrates Chemotherapy Within Tumor Cells Via SPARC

Newly discovered mechanism: tumors secrete a specialized protein called SPARC (Secreted Protein Acidic and Rich in Cysteine), that acts as a highly charged receptor to specifically attract and bind albumin *(See figure 2)*

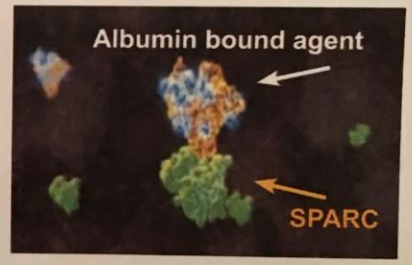


figure 2

Overcomes Insolubility of Many Chemo Agents

- Protein shell (albumin) replaces harsh chemicals and solvents needed to introduce water insoluble cytotoxic agents into the blood stream *(See figure 3)*
- Eliminates solvent-related toxicities and other dose-limiting complications
- Cuts infusion time to just 30 minutes

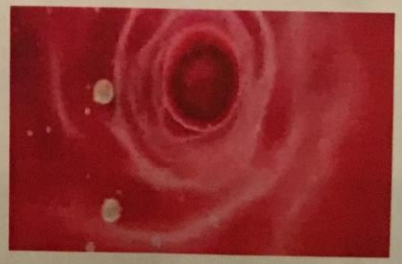
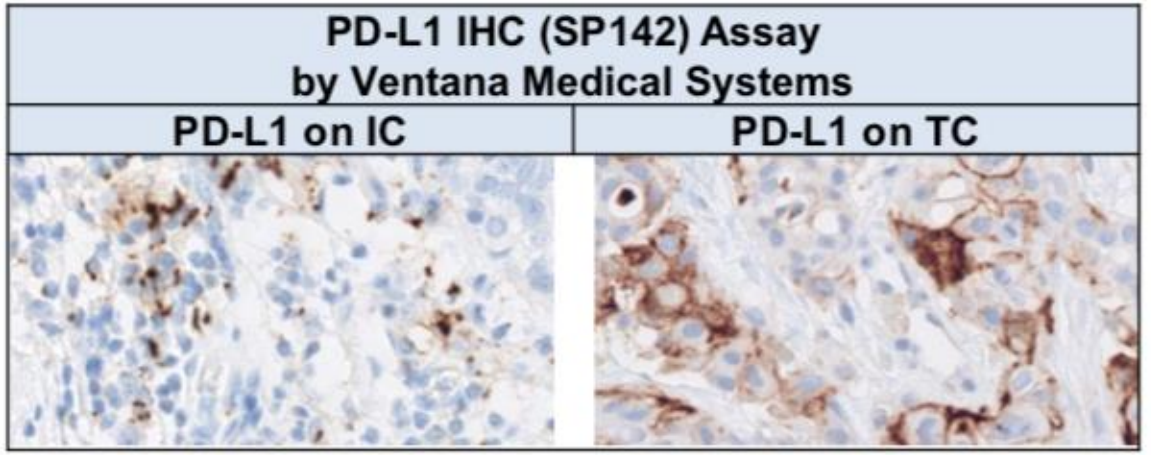


figure 3

IMpassion130 biomarker analyses

- Pre-existing immune biology, including PD-L1 expression on TC, CD8+ T cells and stromal TILs, has also been associated with clinical benefit from anti–PD-L1/PD-1[1,2]
- In this exploratory analysis, we sought to evaluate whether this immune biology and *BRCA1/2* mutation status were associated with clinical benefit from atezolizumab + *nab*-paclitaxel
- Biomarkers were centrally analyzed in pre-treatment biopsies
  - PD-L1 on IC and TC by VENTANA SP142 IHC assay[a]
  - Intratumoral CD8+ T cells by IHC (Dako clone C8/144B) and stromal TILs by H&E[b]
  - *BRCA1/2* mutation status by FoundationOne assay



H&E, hematoxylin and eosin staining; IHC, immunohistochemistry.
[a] PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.
[b] Pre-specified cutoffs for CD8 IHC and stromal TILs are based on references 1 and 2.
1. Adams *JAMA Oncol* 2018. 2. Denkert *Lancet Oncol* 2018.

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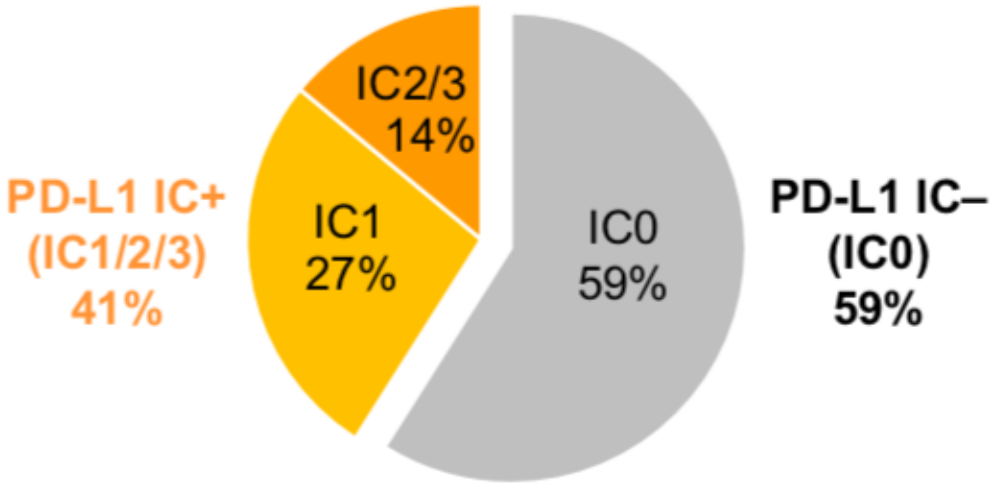
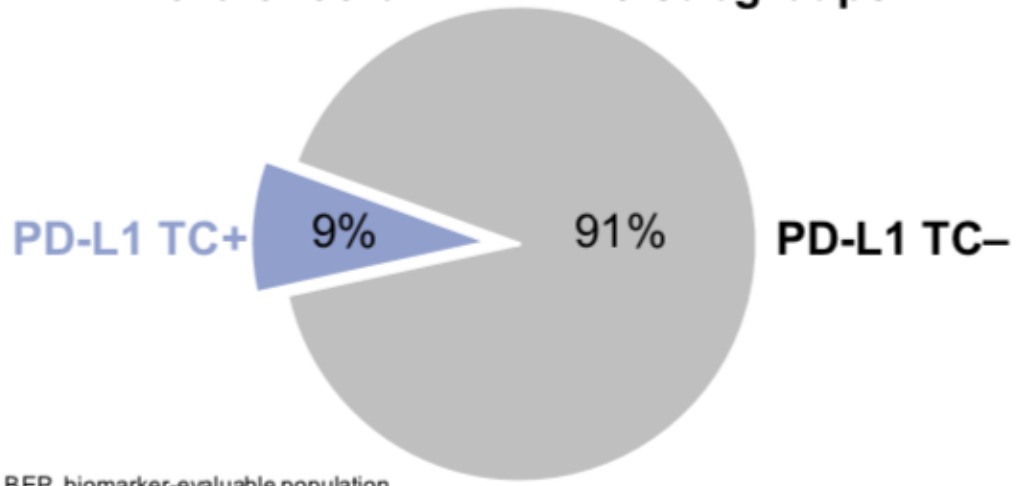
In IMpassion130, PD-L1 in TNBC is expressed mainly on tumor-infiltrating immune cells

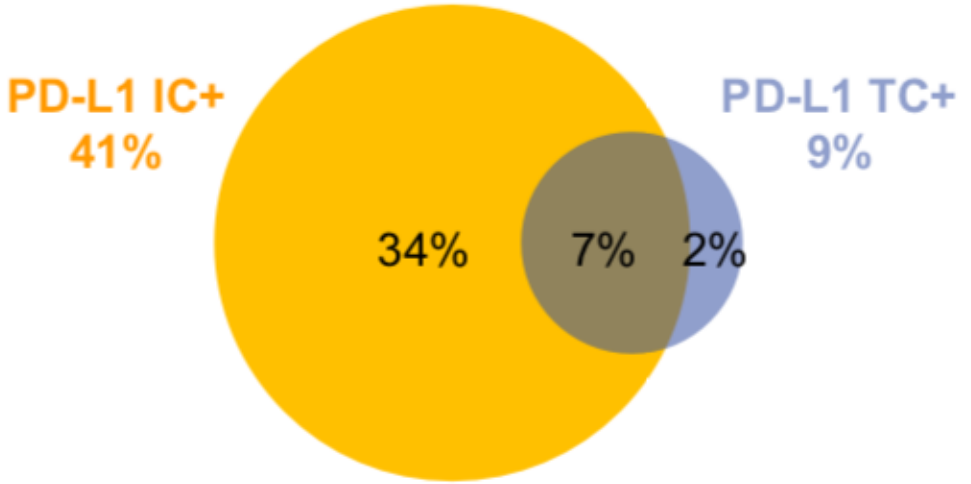
Prevalence of PD-L1 IC subgroups



Prevalence of PD-L1 TC subgroups



The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population



BEP, biomarker-evaluable population.
BEP (TC): n = 900. PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.

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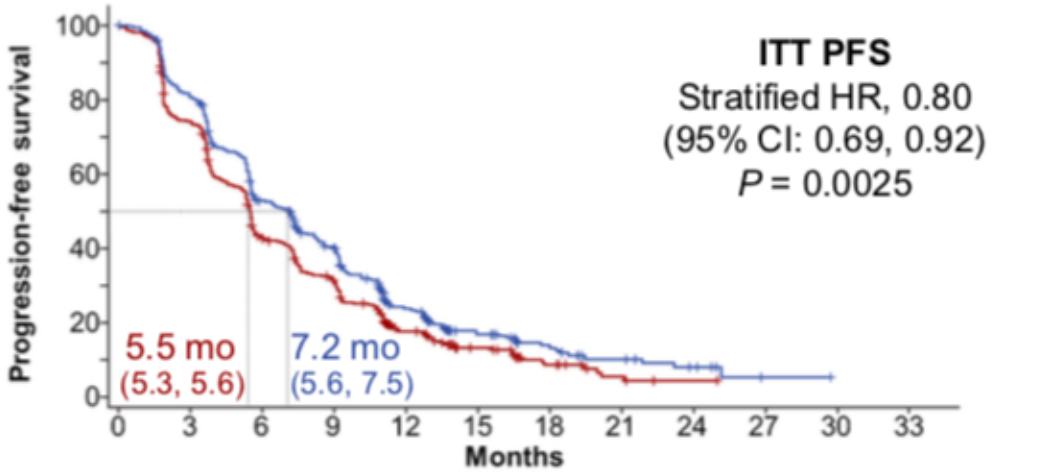
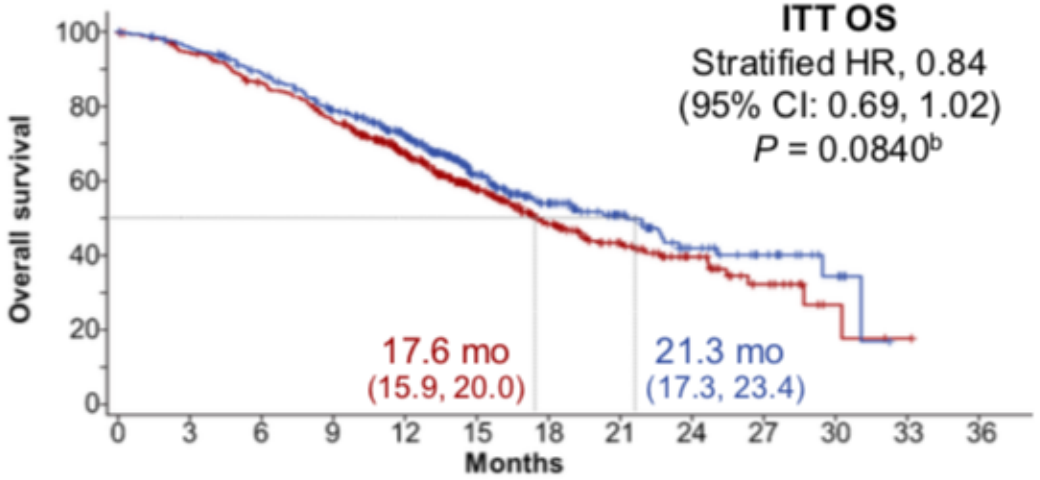
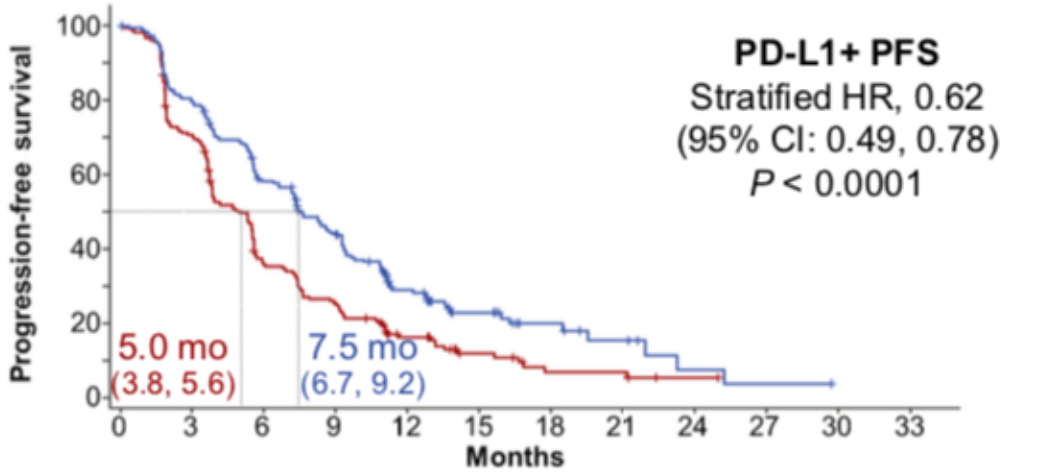
IMpassion130 primary analysis[1,2]: Clinically meaningful PFS and OS benefit in the PD-L1+ population

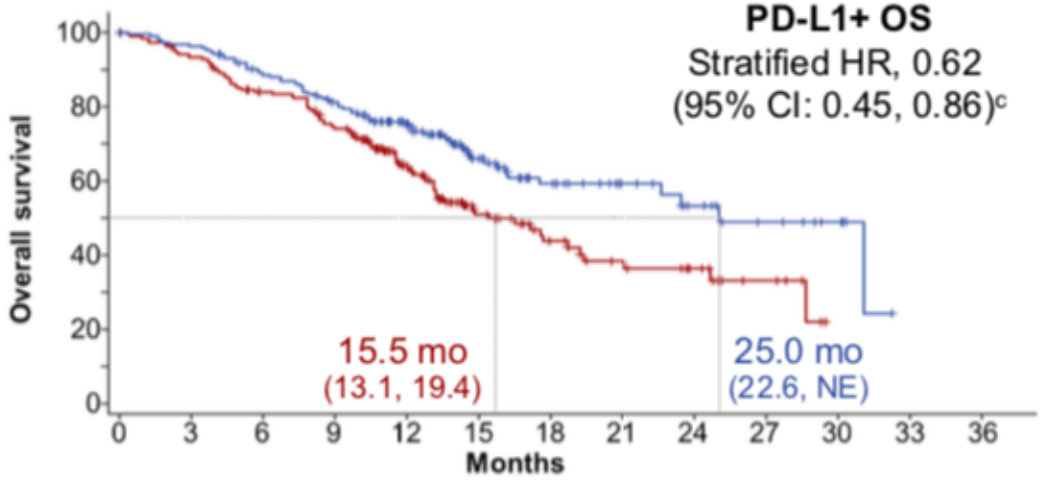
ITT population





PD-L1+ population[a]





NE, not estimable.
Median follow-up (ITT): 12.9 months.
[a] PD-L1+: PD-L1 in ≥ 1% of IC. [b] Not significant. [c] Not formally tested per hierarchical study design.

1. Schmid *N Engl J Med* 2018. 2. Schmid ESMO 2018 [LBA1_PR].

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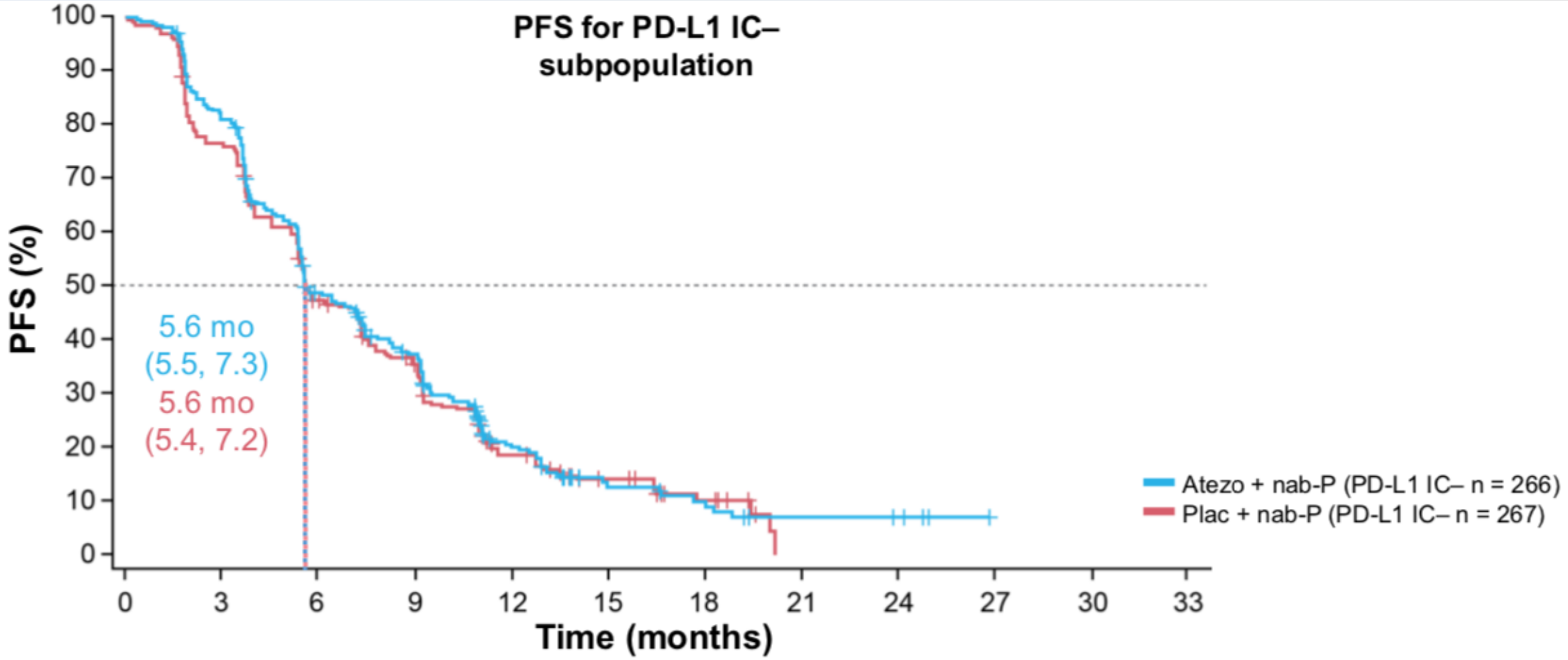
PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + *nab*-paclitaxel



Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values. Data cutoff: April 17, 2018.

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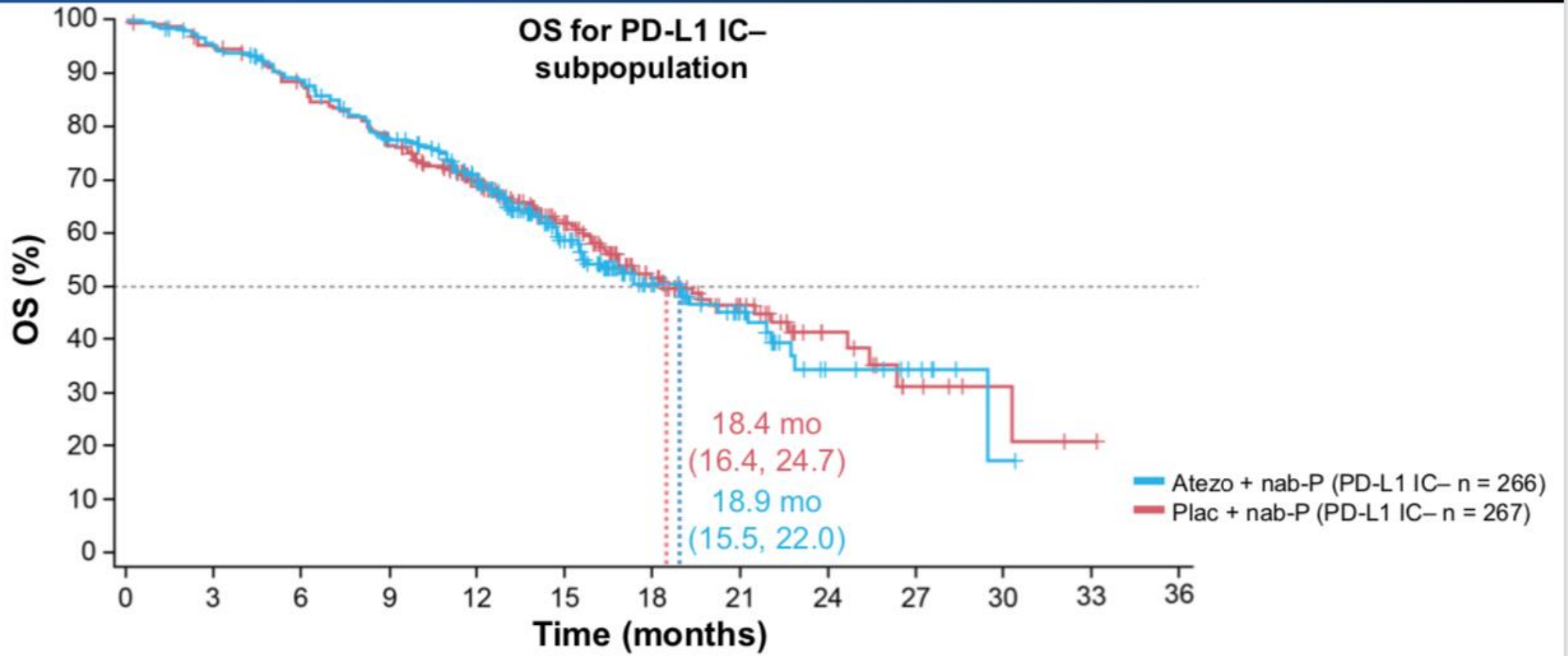
PD-L1 IC status (positive vs negative) predicts OS benefit with atezolizumab + *nab*-paclitaxel



- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values are nominal. Data cutoff: April 17, 2018.

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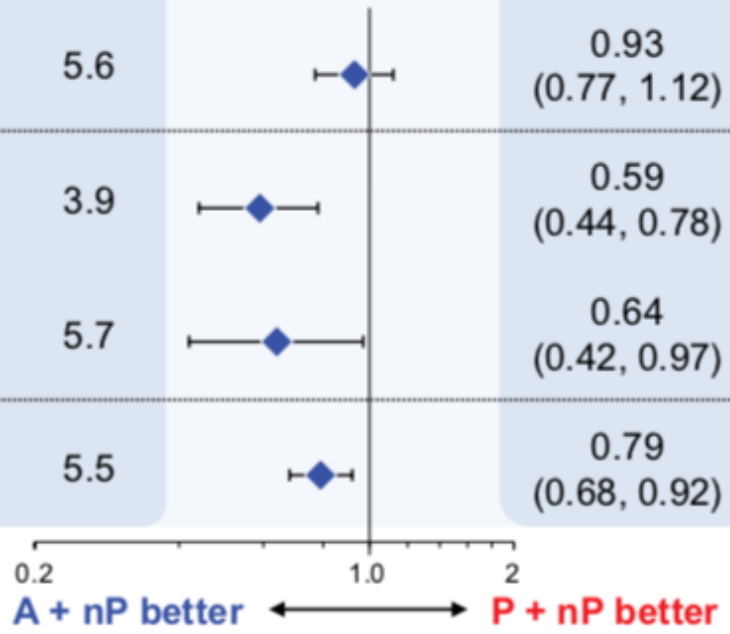
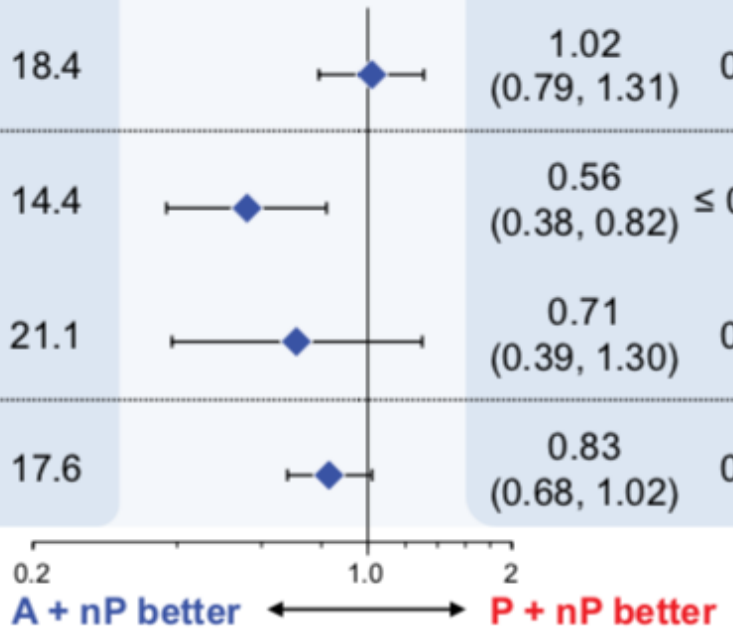
Consistent clinical benefit with atezolizumab + *nab*-paclitaxel was observed across all PD-L1 IC+ subgroups

	PD-L1 IC Status	n	PFS Median, mo A + nP	PFS Median, mo P + nP	PFS HR[a] (95% CI)	PFS *P* value	OS Median, mo A + nP	OS Median, mo P + nP	OS HR[a] (95% CI)	OS *P* value
Neg	IC0	532	5.6	5.6	0.93 (0.77, 1.12)	0.47	18.9	18.4	1.02 (0.79, 1.31)	0.90
Pos	IC1	243	7.4	3.9	0.59 (0.44, 0.78)	≤ 0.005	23.4	14.4	0.56 (0.38, 0.82)	≤ 0.005
Pos	IC2/3	125	9.3	5.7	0.64 (0.42, 0.97)	0.03	25.0	21.1	0.71 (0.39, 1.30)	0.26
	All	900	7.2	5.5	0.79 (0.68, 0.92)	≤ 0.005	21.3	17.6	0.83 (0.68, 1.02)	0.07





[a] Adjusted for prior taxane treatment and liver metastases.
A multivariate analysis was performed to account for imbalances in baseline characteristics between PD-L1 IC–expressing subgroups (IC1, IC2 and IC3).
IC0: < 1% PD-L1; IC1: ≥ 1% and < 5% PD-L1; IC2/3: ≥ 5% PD-L1. All *P* values are nominal. Data cutoff: April 17, 2018.

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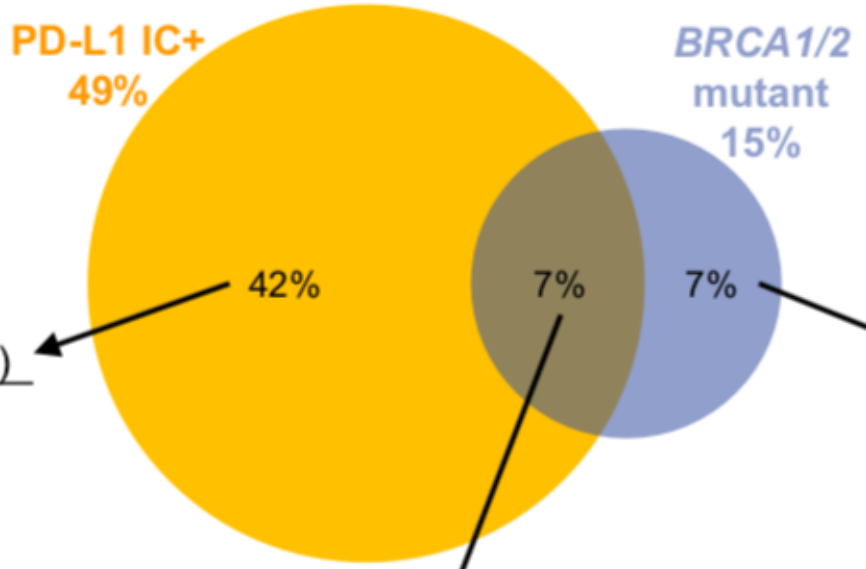
The clinical benefit derived by PD-L1 IC+ patients was independent of their *BRCA1/2* mutation status



***BRCA1/2* non-mut/PD-L1 IC+** (n = 257)

	HR (95% CI)	*P* Value
PFS	0.63 (0.48, 0.83)	≤ 0.005
OS	0.62 (0.43, 0.91)	0.01

***BRCA1/2* mut/PD-L1 IC–** (n = 44)

	HR (95% CI)	*P* Value
PFS	0.77 (0.37, 1.61)	0.49
OS	0.85 (0.29, 2.43)	0.76

***BRCA1/2* mut/PD-L1 IC+** (n = 45)

	HR (95% CI)	*P* Value
PFS	0.45 (0.21, 0.96)	0.04
OS	0.87 (0.26, 2.85)	0.82

- *BRCA1/2* mutants and PD-L1 IC+ are independent from each other (*P* = ns)[a]
- ***Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+[b]***

BEP (BRCA1/2): n = 612. Per FoundationOne *BRCA1/2* testing, *BRCA1/2* mutant: known and likely mutations. All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests. [b] Data interpretation limited by small number of *BRCA1/2*-mutant patients.

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總結(一)

理解治療乳癌新領域要建基於：

- 乳癌的**種類**
- 乳癌的**分期**(早期或後期)

有六種可能應用的治療：

- 局部 / 區域治療：手術 / 放射治療
- 全身治療：荷爾蒙 / 化療 / 標靶治療 / 免疫治療

總結(二)

早期 (一至三期)乳癌

- 術前先化療的趨勢
- HER-2型乳癌 - Pertuzumab新標靶藥 在術前 / 術後
- HR+乳癌 – Luminal A/B 的分別; Oncotype DX
- 三陰乳癌 - 對化療的依賴

總結(三)

四期乳癌

- **HR+型乳癌** - 標靶藥輔助荷爾蒙治療 (CPK4/6,mTOR,P13K抑制劑)
  - 何時要用化療?
- 三陰乳癌 **- BRCA基因陽性 : PARP抑制劑**
  - 免疫治療
- **HER 2型乳癌** - Pertuzumab / TDM-1

TAKE HOME MAINPOINTS

- Neoadjuvant Therapy :
  - HER2: +Pertuzumab; nonpCR: adj TDM-1
  - nonHER2 nonpCR: Ex-Xeloda (esp TNBC)
- Adjuvant:
  - HER2: +Pertuzumab, Ex-Neratinib after Trastuzumab (esp HR+)
  - HR+: 10 years therapy esp N+, chemo or not - Oncotype DX
  - Radiotherapy: RapidArc/Tomo, ABC x left breast/chest wall
- **MBC:**
  - HER2: +P or TDM-1
  - HR+: AI/Fulfest (+CDK4/6 inh; + PI3K inh; + mTOR inh)
  - TNBC: PARP inh (Olaparib, Talazoparib), Immunotherapy (Impassion 130)