XXIV SPOTKANIE Po ASCO

Rak piersi
Omówienie

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w Warszawie

Spotkanie Po ASCO; Edycja XXIV; 27-28 czerwca 2025 r. Gdańsk

Driving Knowledge to Action: Building a Better Future

ASCO 2025!

Wczesny rak piersi

1. **De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP): A multicentre, open-label, randomised, phase 3 trial.**
2. **Predicting pathologic complete response (pCR) from clinicopathologic variables and HER2DX genomic test in stage II/III HER2+ breast cancer treated with taxane, trastuzumab, and pertuzumab (THP): Secondary results from the EA1181/CompassHER2 pCR trial.**
3. **Prediction of survival after de-escalated neoadjuvant therapy in HER2+ early breast cancer: A pooled analysis of three WSG trials.**
4. **Prospective randomized phase II trial to assess the efficacy and safety of neo-adjuvant olaparib/carboplatin (OC) in comparison to docetaxel/epirubicin/cyclophosphamide (TAC) in patients with early triple-negative breast cancer (TNBC) with homologous recombination deficiency (HRD): Primary results from the ABCSG 45 trial.**
5. A phase 2 study of response-guided neoadjuvant sacituzumab govitecan and pembrolizumab (SG/P) in patients with early-stage triple-negative breast cancer: Results from the **NeoSTAR trial**.
6. 15-year outcomes for women with premenopausal hormone receptor-positive early breast cancer (BC) in the **SOFT and TEXT** trials assessing benefits from adjuvant exemestane (E) + ovarian function suppression (OFS) or tamoxifen (T)+OFS.
7. **Efficacy and safety of elinzanetant for vasomotor symptoms associated with adjuvant endocrine therapy: Phase 3 OASIS 4 trial.**
8. Efficacy and safety of ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in **NATALEE**: Analysis across menopausal status and age.
9. The **TRADE** study: A phase 2 trial to assess the tolerability of abemaciclib dose escalation in early-stage HR+/HER2- breast cancer.

Zaawansowany rak piersi

1. **Abstrakt LBA 1008 Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for first-line (1L) treatment of patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) advanced/metastatic breast cancer (a/mBC): Interim results from DESTINY-Breast09.**
2. **Abstrakt LBA 4 Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the treatment of emergent ESR1 mutations during first-line (1L) endocrine-based therapy (ET) and ahead of disease progression in patients (pts) with HR+/HER2- advanced breast cancer (ABC): Phase 3, double-blind ctDNA-guided SERENA-6 trial.**
3. **Abstrakt 1001- Patient-reported outcomes (PROs) in patients with ER+, HER2- advanced breast cancer (ABC) treated with imlunestrant, investigator's choice standard endocrine therapy, or imlunestrant + abemaciclib: Results from the phase III EMBER-3 trial.**
4. Abstrakt LBA 1000- Vepdegestrant, a PROTAC estrogen receptor (ER) degrader, vs fulvestrant in ER-positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer: Results of the global, randomized, phase 3 **VERITAC-2** study.
5. Abstrakt 1003 **INAVO120**: Phase III trial final overall survival (OS) analysis of first-line inavolisib (INAVO)/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with PIK3CA-mutated, hormone receptor-positive (HR+), HER2-negative (HER2–), endocrine-resistant advanced breast cancer (aBC).
6. **Abstrakt 1005 A double-blind placebo controlled randomized phase III trial of fulvestrant and ipatasertib as treatment for advanced HER2-negative and estrogen receptor positive (ER+) breast cancer following progression on first line CDK 4/6 inhibitor and aromatase inhibitor: The CCTG/BCT MA.40/FINER study (NCT04650581).**
7. **Abstrakt LBA 109 Sacituzumab govitecan (SG) + pembrolizumab (pembro) vs chemotherapy (chemo) + pembro in previously untreated PD-L1-positive advanced triple-negative breast cancer (TNBC): Primary results from the randomized phase 3 ASCENT-04/KEYNOTE-D19 study.**
8. Abstrakt 1019 Sacituzumab tirumotecan (sac-TMT) as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): Initial results from the phase II **OptiTROP-Breast05** study.

Wczesny HER2-dodatni rak piersi

Czy możemy odstąpić od pochodnych platyny w schematach NAT (opartych o taksoid i podwójną blokadę anty-HER2: trastuzumab/pertuzumab; THP)?

NAT, neoadjuvant therapy

Przesłanki do skojarzenia taksoidu, trastuzumabu i pochodnych platyny

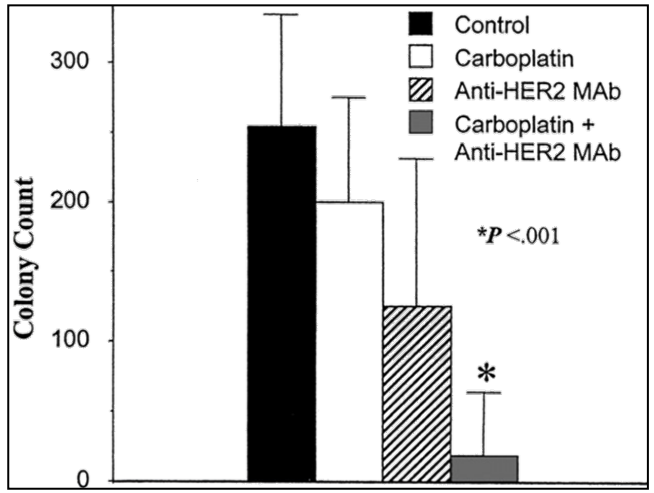


Table 2. Study drug administration for patients enrolled in open-label phase II trials of docetaxel, platinum salts, and trastuzumab*

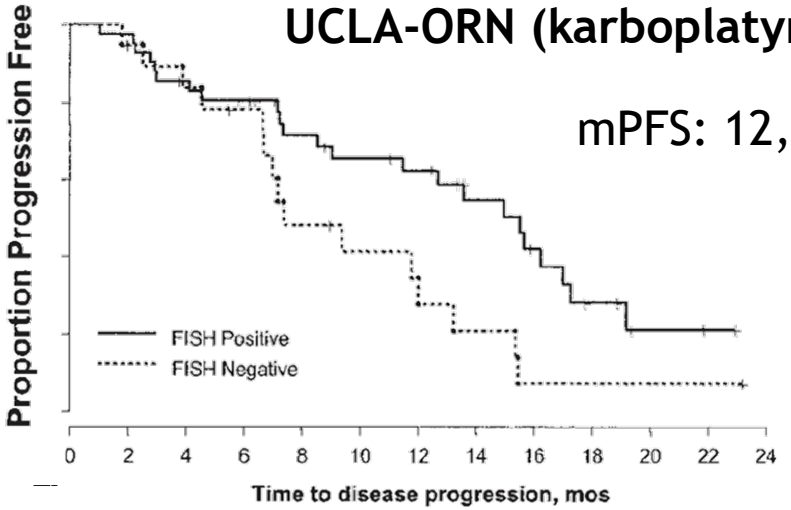
	BCIRG 101 (N = 62)	UCLA-ORN (N = 62)
Chemotherapy cycles		
Total number of cycles	389	385
Median number of cycles (range)	6 (3–8)	6 (2–13)
No. of cycles requiring dose reduction (%)	46 (12)	77 (20)
No. of patients treated with G-CSF/GM-CSF (%)	10 (16)	42 (68)
Total number of trastuzumab infusions	2503	2520
During chemotherapy	1160	1242
Median (range)	18 (7–25)	18 (4–57)
Following chemotherapy	1343	1278
Median (range)	25 (1–75)	24 (1–87)

Table 5. Clinical objective responses to treatment among patients enrolled in open-label, phase II trials (N = 62 for each) of docetaxel, platinum salts, and trastuzumab*

	BCIRG 101	UCLA-ORN
No. of evaluable patients (%)	62 (100)	59 (95)
Complete response, No. (%)†	3 (5)	12 (20)
Partial response, No. (%)	46 (74)	22 (37)
Stable disease, No. (%)	12 (19)	13 (22)
Disease progression, No. (%)	1 (2)	12 (20)
Overall objective response, No. (%)	49/62 (79)	34/59 (58)
Overall response rate by FISH status‡	N = 54	N = 57
Positive, No. (%)	27/35 (77)	25/40 (63)
Negative, No. (%)	16/19 (84)	7/17 (41)

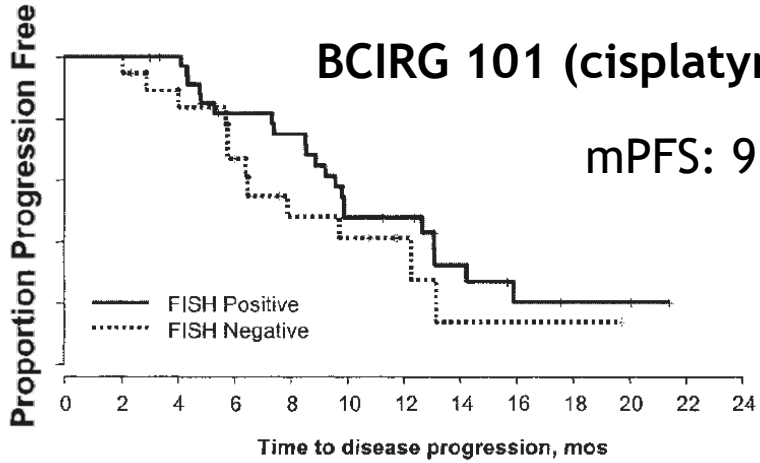
UCLA-ORN (karboplatyna)

mPFS: 12,7 m



BCIRG 101 (cisplatyna)

mPFS: 9,9 m



Pegram MD, JNCI 2004

pCR i parametry przeżycia w kluczowych badaniach klinicznych

Fenotyp	Badanie Faza	Schemat neoadiuwantowy	**pCR %**	EFS/DFS %	OS%	Piśmiennictwo
HER2+	NeoSphere 2	THP	**46**	5-DFS 84	BD	Gianni L, i wsp. Lancet Oncol. 2012; Lancet Oncol. 2016
	TRYPHAENA 2	TCbHP	**64**	3-DFS 90	3-OS 95	Schneeweiss A, i wsp. Ann Oncol 2013; Eur J Cancer. 2018
	BERENICE 2	AC_Xdd→PXLHP FEC_x→THP	**62** **61**	BD	BD	Swain SM, i wsp. Ann Oncol 2018
	TRAIN-2 3	PXLCbHP	**68**	3-EFS 94	3-OS 98	van der Voort A, i wsp. JAMA Oncol 2021

T, docetaksel; H, trastuuzmab; P, pertuzumab; Cb, karboplatyna; A, doksorubicyna; C_x, cyklofosfamid; dd, dose-dence; PXL, paklitaksel; F, fluorouracyl; E, epirubicyna; BD, brak danych

neoCARHP Study Design (NCT04858529)

Aged ≥18, untreated, staged II-III , HER2-positive breast cancer

Stratification
- Hormone status
- Nodal status

R (1:1) N=774

THP×6 Q3W (n=387) (Investigator-selected taxane* + Trastuzumab IV 6 mg/kg, loading dose 8 mg/kg + Pertuzumab IV 420 mg, loading dose 840mg)

TCbHP×6 Q3W (n=387) (Investigator-selected taxane* + Carboplatin IV AUC 6 mg/mL/min + Trastuzumab IV 6 mg/kg, loading dose 8 mg/kg + Pertuzumab IV 420 mg, loading dose 840mg)

Surgery

- Primary endpoint: pCR (ypT0/is ypN0)
- Secondary endpoints: Safety, clinical response during neoadjuvant therapy, EFS, DFS, OS

* Docetaxel, Paclitaxel or Nab-paclitaxel

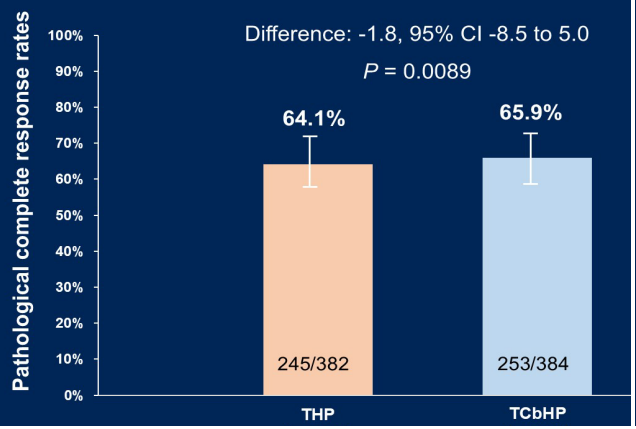
Baseline Patients Characteristics

	THP (n=382)	TCbHP (n=384)
Age (median [IQR], years)	52 (45-58)	51 (44-56)
Menopausal status, n (%)		
Premenopausal	191 (50.0%)	200 (52.1%)
Postmenopausal	191 (50.0%)	184 (47.9%)
T stage, n (%)		
T1-2	311 (81.4%)	302 (78.6%)
T3-4	71 (18.6%)	82 (21.4%)
Nodal status, n (%)		
Negative	137 (35.9%)	138 (35.9%)
Positive	245 (64.1%)	246 (64.1%)
Disease stage, n (%)		
Stage II	294 (77.0%)	275 (71.6%)
Stage III	88 (23.0%)	109 (28.4%)
Histological type, n (%)		
Ductal	375 (98.2%)	376 (97.9%)
Lobular	1 (0.3%)	2 (0.5%)
Others	6 (1.6%)	6 (1.6%)

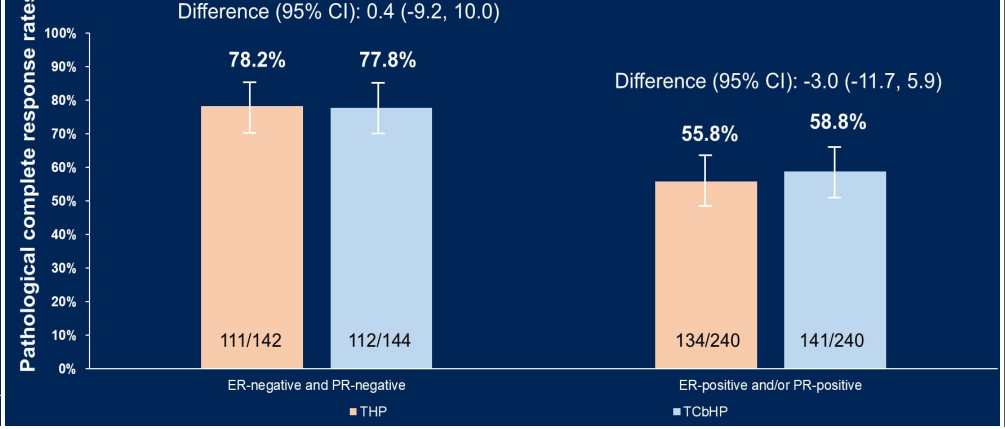
	THP (n=382)	TCbHP (n=384)
Hormone receptor status, n (%)		
ER-negative andPR-negative	142 (37.2%)	144 (37.5%)
ER-positive and/orPR-positive	240 (62.8%)	240 (62.5%)
HER2 status, n (%)		
Immunohistochemistry 3+	338 (88.5%)	348 (90.6%)
Immunohistochemistry 2+ and ISH-positive	44 (11.5%)	36 (9.4%)
Ki67, n (%)		
≤30%	163 (42.7%)	172 (44.8%)
>30%	219 (57.3%)	212 (55.2%)
Taxane therapy, n (%)		
Nab-paclitaxel	170 (44.5%)	171 (44.5%)
Docetaxel	137 (35.9%)	141 (36.7%)
Paclitaxel	75 (19.6%)	72 (18.8%)

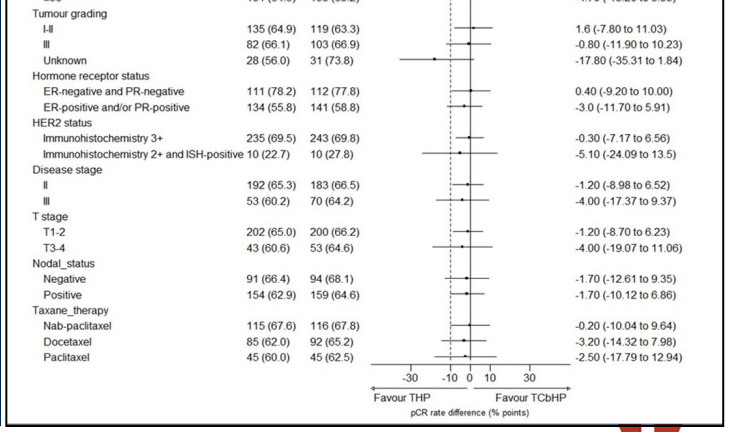
THP was considered non-inferior if the lower bound of the two-sided 95% CI (Newcombe-Wilson score method) for the pCR difference exceeded the prespecified - 10% non-inferiority margin

Efficacy Analysis: pCR



Efficacy Analysis: pCR by hormone receptor status





Gao HF, J Clin Oncol 43, 2025 (suppl 17; abstr LBA500)

neoCARHT: działania niepożądane

	THP (n=382) n (%)			TCbHP (n=384) n (%)		
AE term	**Grade 3**	**Grade 4**	**Total**	**Grade 3**	**Grade 4**	**Total**
Neutropenia	14 (3.7%)	12 (3.1%)	**26 (6.8%)**	35 (9.1%)	28 (7.3%)	**63 (16.4%)**
Febrile neutropenia	5 (1.3%)	0	**5 (1.3%)**	10 (2.6%)	0	**10 (2.6%)**
Leucopenia	14 (3.7%)	7 (1.8%)	**21 (5.5%)**	45 (11.7%)	12 (3.1%)	**57 (14.8%)**
Thrombocytopenia	1 (0.3%)	0	**1 (0.3%)**	10 (2.6%)	6 (1.6%)	**16 (4.2%)**
Anaemia	8 (2.1%)	0	**8 (2.1%)**	24 (6.3%)	1 (0.3%)	**25 (6.6%)**

	THP (n=382) n (%)		TCbHP (n=384) n (%)	
AE term	**Grade 1–2**	**Grade ≥3**	**Grade 1–2**	**Grade ≥3**
Neuropathy	166（43.5）	1（0.3）	186（48.4）	2（0.5）
Nausea	102（26.7）	0	166（43.2）	1（0.3）
Vomiting	66（17.3）	0	112（29.2）	3（0.8）
Fatigue	158（41.4）	2（0.5）	167（43.5）	3（0.8）
Increased creatinine	10（2.6）	0	63（16.4）	5（1.3）

Gao HF, J Clin Oncol 43, 2025 (suppl 17; abstr LBA500)

neoCARHP w odniesieniu do obecnego standardu

Badanie	Schemat	pCR (ogółem)	pCR (ER dodatni)	pCR (ER ujemny)
neoCARHP	6x TCbHP	66%	59%	78%
neoCARHP	6x THP	64%	56%	78%
TRYPHAENA	6x TCbHP	64%	50%	84%
TRAIN-2	9x PXLCbHP	68%	55%	84%

T, docetaksel (co 3 tygodnie); H, trastuzumab; P, pertuzumab; Cb, karboplatyna; PXL, paklitaksel (co tydzień)

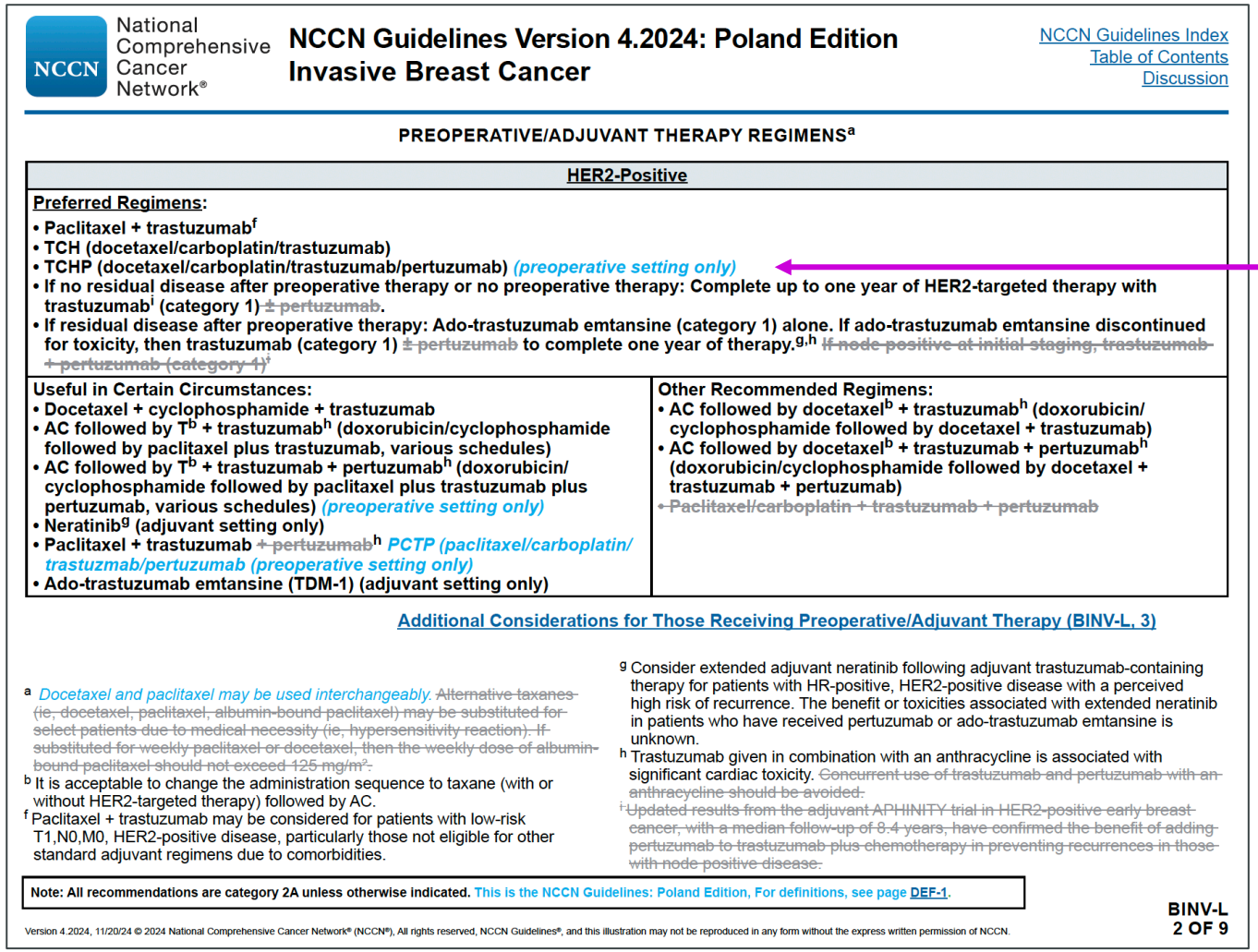
neoCARHP:

- **większość chorych ponad 70 % w stopniu II, luminalym HER2-dodatnim ponad 62%;**
- **dane dotyczące EFS, DFS, OS niedojrzałe;**
- **brak wytarczających danych dla schematu (nab)paklitaksel co 3 tyg.**
- **poszukiwanie biomarkerów wrażliwości na karboplatynę?**

Schneeweiss A, i wsp. Ann Oncol 2013; Eur J Cancer. 2018; van der Voort A, i wsp. JAMA Oncol 2021

Wczesny HER2-dodatni rak piersi

Czy możemy odstąpić od pochodnych platyny w schematach NAT (opartych o taksoid i podwójną blokadę anty-HER2: trastuzumab/pertuzumab; THP)?



National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024: Poland Edition
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive

Preferred Regimens:

- **Paclitaxel + trastuzumab[f]**
- **TCH (docetaxel/carboplatin/trastuzumab)**
- **TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)** ***(preoperative setting only)***
- **If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[i] (category 1)** ~~**± pertuzumab**~~**.**
- **If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1)** ~~**± pertuzumab**~~ **to complete one year of therapy.[g,h]** ~~**If node-positive at initial staging, trastuzumab + pertuzumab (category 1)[i]**~~

Useful in Certain Circumstances:

- **Docetaxel + cyclophosphamide + trastuzumab**
- **AC followed by T[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)**
- **AC followed by T[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules)** ***(preoperative setting only)***
- **Neratinib[g] (adjuvant setting only)**
- **Paclitaxel + trastuzumab** ~~**+ pertuzumab**~~**[h]** ***PCTP (paclitaxel/carboplatin/trastuzumab/pertuzumab (preoperative setting only)***
- **Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)**

Other Recommended Regimens:

- **AC followed by docetaxel[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab)**
- **AC followed by docetaxel[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)**
- ~~**Paclitaxel/carboplatin + trastuzumab + pertuzumab**~~

Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

[a] *Docetaxel and paclitaxel may be used interchangeably.* ~~Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m².~~

[b] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.

[f] Paclitaxel + trastuzumab may be considered for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

[g] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.

[h] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. ~~Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.~~

[i] ~~Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences in those with node positive disease.~~

Note: All recommendations are category 2A unless otherwise indicated. This is the NCCN Guidelines: Poland Edition, For definitions, see page DEF-1.

BINV-L
2 OF 9

TAK!
w wybranej grupie chorych
Stopień II

NAT, neoadjuvant therapy

Czy możemy de-eskalować schematy NAT:

↓liczby cykli do 4?
(12 vs 18-24 tygodni?)

NAT, neoadjuvant therapy

De-eskalacja poprzez ↓liczby cykli NAT do 4?

ADAPT-HR-/HER2+ (n=134)

4× T + P vs
4× T + P + paclitaxel q1w

pCR: 34% vs 91%[1]
5y iDFS: 87% vs 98%[2]

ADAPT-HR+/HER2+ (n=375)

4× T-DM1 ± ET vs
4× T + ET

pCR: pCR: 41-42% vs 15%[3]
5y iDFS: 85-89% vs 85%[4]

TP-II (n=207)

4× T + P + ET vs
4× T + P + paclitaxel q1w

pCR: 24% vs 56%[5]
5y iDFS: 92% vs 95%[6]

Keyriched-1 (n=43)

HER2-enriched (by PAM50)

4× T + P + pembrolizumab

pCR: 47%[7]

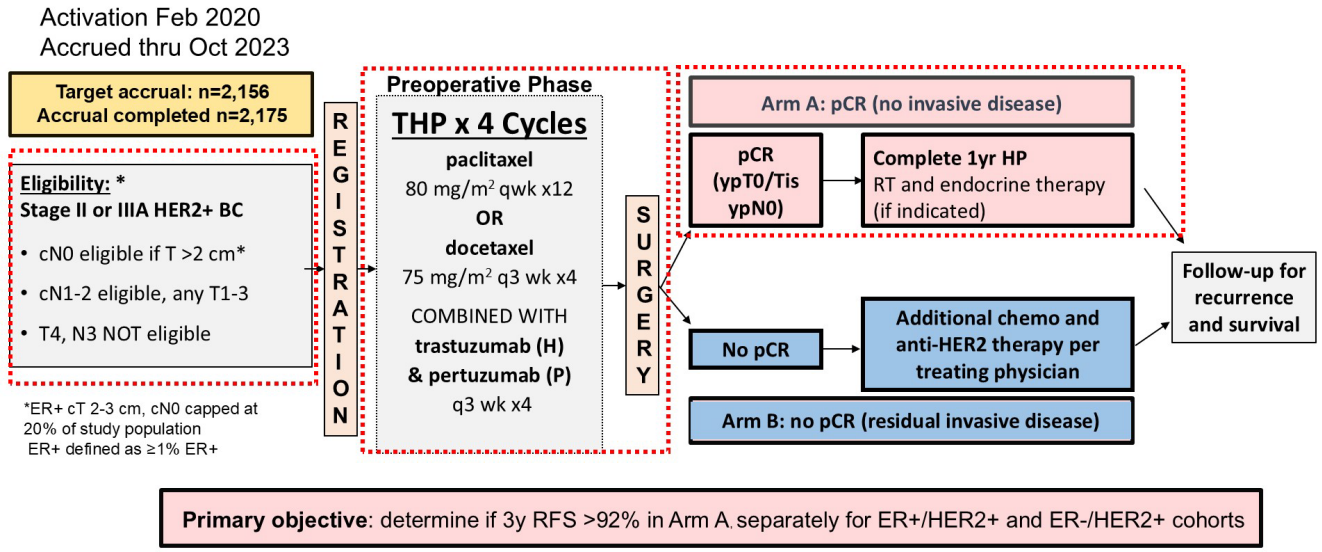
Ongoing: HER2-IV (n=402)

4-6× T-DXd vs
4-6× T + P + paclitaxel ± carboplatin

ET, endocrine therapy, iDFS, invasive disease-free survival; pCR, pathological complete response (ypT0/is ypN0); P, pertuzumab; T, trastuzumab; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Nitz UA et al. Ann Oncol 2017; 2. Nitz UA et al. Lancet Oncol 2022; 3. Harbeck N et al. J Clin Oncol 2017; 4. Harbeck N et al. J Clin Oncol 2023; 5. Gluz O et al. JAMA Oncol 2023; 6. Gluz O et al. presented at ESMO Congress 2024; 7. Kuemmel S et al. Lancet Oncol 2025.

EA1181 CompassHER2 pCR: Study design

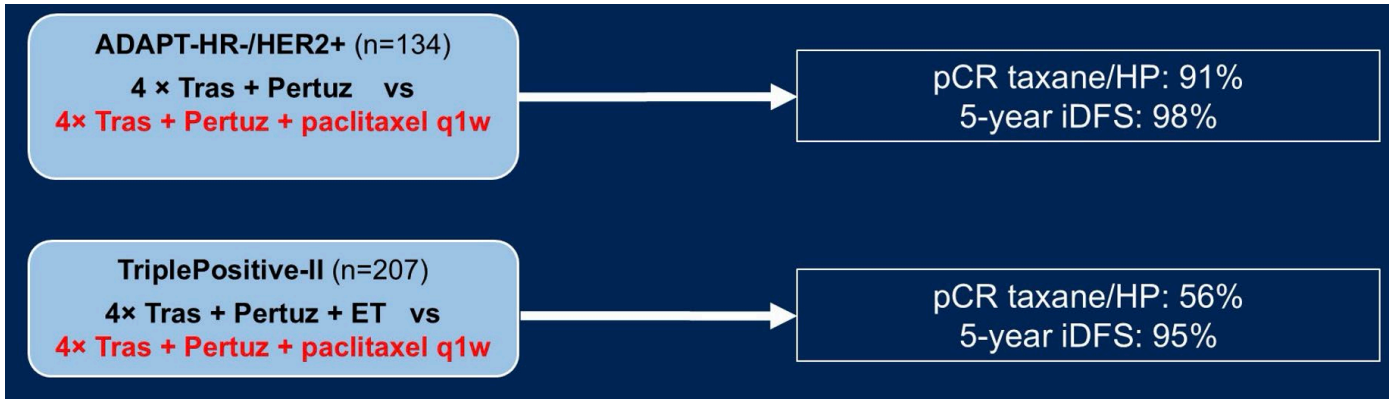


Primary objective: determine if 3y RFS >92% in Arm A separately for ER+/HER2+ and ER-/HER2+ cohorts

Graeser MK, J Clin Oncol 43, 2025 (suppl 16; abstr 502); Tung N, J Clin Oncol 43, 2025 (suppl 16; abstr 501)

De-eskalacja poprzez ↓liczby cykli NAT do 4?

West Germany Group



Łącznie:
- paklitaksel, trastuzumab, pertuzumab N=149
- bez pochodnych platyny
- **75% w stopniu I**
- 72% HR+

H, trastuzumab; P, pertuzumab

EA1181 CompassHER2

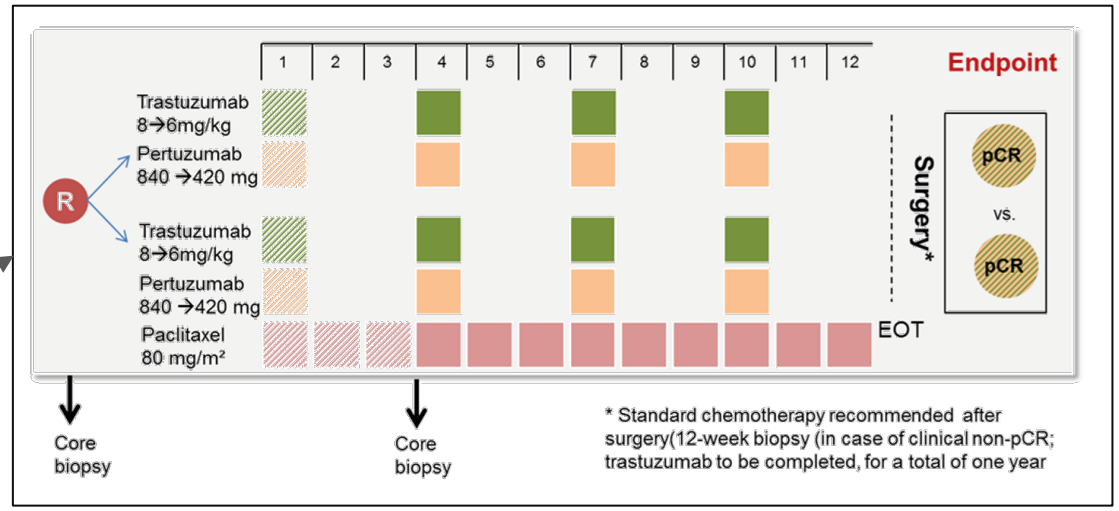
Łącznie: N = 2175
- 63% paklitaksel i HP (N = 1367)
  34% docetaksel i HP
- bez pochodnych platyny
- **58% w stopniu IIA**
- **8% w stopniu IIIA**
- 2/3 chorych HR+ (ER ≥70%)
- ER (-) 36%
- częściej HER2 3+ IHC i G3

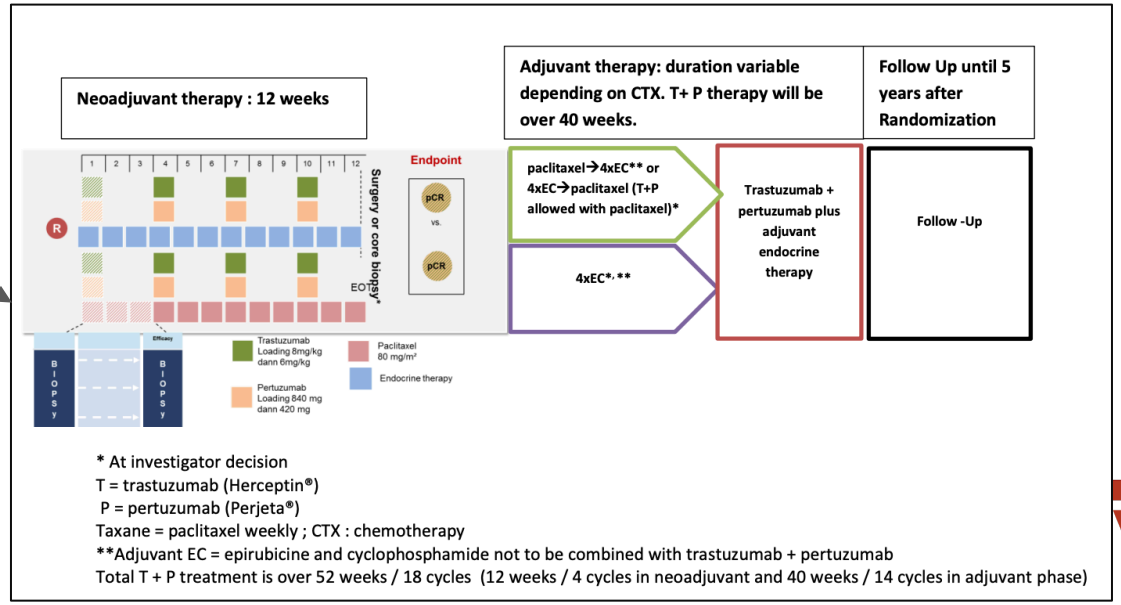
Graeser MK, J Clin Oncol 43, 2025 (suppl 16; abstr 502); Tung N, J Clin Oncol 43, 2025 (suppl 16; abstr 501)

Badania West Germany Group

ADAPT-HR-/HER2+ (n = 134)
4x Tras + Pertuz vs
4x Tras + Pertuz + paclitaxel q1w

TriplePositive-II (n = 207)
4x Tras + Pertuz + ET vs
4x Tras + Pertuz + paclitaxel q1w





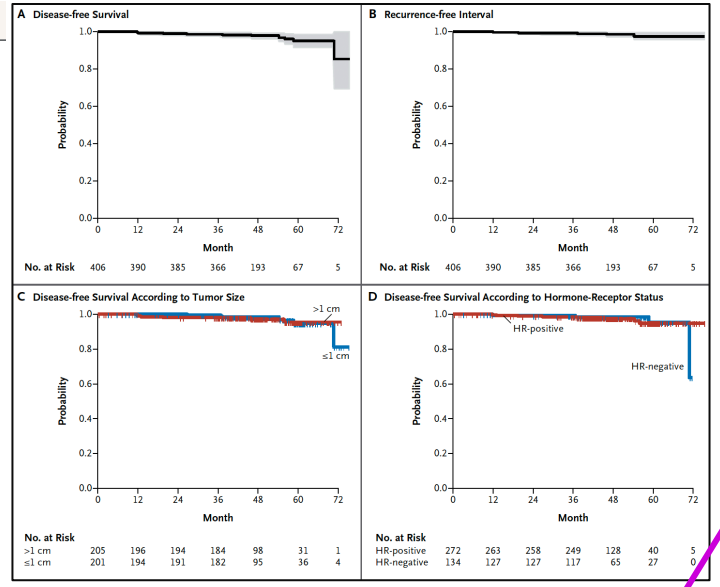
Tras, trastuzumab; Pertuz, pertuzumab

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients (N = 406)
Primary tumor	*no. (%)*
Size	
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0 cm	36 (8.9)
Nodal status	
N0	400 (98.5)
N1mic	6 (1.5)
Histologic grade	
I: well-differentiated	44 (10.8)
II: moderately differentiated	131 (32.3)
III: poorly differentiated	228 (56.2)
Unknown	3 (0.7)
HER2-positive status	406 (100)
Estrogen-receptor status	
Positive	260 (64.0)
Negative	141 (34.7)
Borderline	5 (1.2)
Progesterone-receptor status	
Positive	201 (49.9)
Negative	196 (48.3)
Borderline	8 (2.0)
Unknown	1 (0.2)
Hormone-receptor status	
Positive	272 (67.0)
Negative	134 (33.0)



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024: Poland Edition
Invasive Breast Cancer

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive

Preferred Regimens:
- **Paclitaxel + trastuzumab[f]**
- **TCH (docetaxel/carboplatin/trastuzumab)**
- **TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)** *(preoperative setting only)*
- **If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[i] (category 1)** ~~**± pertuzumab**~~**.**
- **If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1)** ~~**± pertuzumab**~~ **to complete one year of therapy.[g,h]** ~~**If node-positive at initial staging, trastuzumab + pertuzumab (category 1)[i]**~~

Useful in Certain Circumstances:
- **Docetaxel + cyclophosphamide + trastuzumab**
- **AC followed by T[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)**
- **AC followed by T[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules)** *(preoperative setting only)*
- **Neratinib[g] (adjuvant setting only)**
- **Paclitaxel + trastuzumab** ~~**+ pertuzumab**~~**[h]** *PCTP (paclitaxel/carboplatin/ trastuzumab/pertuzumab (preoperative setting only)*
- **Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)**

Other Recommended Regimens:
- **AC followed by docetaxel[b] + trastuzumab[h] (doxorubicin/ cyclophosphamide followed by docetaxel + trastuzumab)**
- **AC followed by docetaxel[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)**
- ~~**Paclitaxel/carboplatin + trastuzumab + pertuzumab**~~

Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

[a] *Docetaxel and paclitaxel may be used interchangeably.* ~~Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m².~~

[b] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.

[f] Paclitaxel + trastuzumab may be considered for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

[g] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.

[h] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. ~~Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.~~

[i] ~~Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences in those with node-positive disease.~~

Stage		Tumor subtype
		HER2 positive
Stage I Typically as adjuvant therapy	T1a	TH—case by case (with ET therapy if HR positive)
	T1b	TH
	T1c	TH
Stage II Neoadjuvant therapy preferred		AC/TH or TCH, with addition of P if neoadjuvant and/or node-positive
Stage III Neoadjuvant therapy preferred		AC/THP or TCHP[c]
Residual invasive cancer after neoadjuvant therapy		Trastuzumab emtansine (T-DM1) for 14 cycles

Tolaney S, N Engl J Med 2015; nccn.org; Curigliano G, Ann Oncol. 2023

Zestawienie dotychczasowych badań↓liczby cykli NAT

Regimen/ Study	N	pCR all	pCR HR-	pCR HR+
Docetaxel + (trastuzumab/pertuzumab (HP) x 6 cycles PREDIX[1]	99	46%	67%	36%
Docetaxel + HP x 4 cycles NeoSphere[2]	107	39%	63%	26%
Docetaxel q3 weeks x 4 + HP EA1181 CompassHER2[3]	774	39%	56%	30%
Paclitaxel x 12 weeks + HP WSG-ADAPT-HR-/HER2+[4]	42	91%	91%	-
Paclitaxel x 12 weeks + HP WSG-Triple Positive II[5]	101	56%	-	56%
Paclitaxel x 12 weeks + HP DAPHNE[6]	98	57%	42%	85%
Paclitaxel x 12 weeks + HP EA1181 CompassHER2[3]	1367	47%	69%	34%

[1]Hatschek T, JAMA Oncol 2021; [2]Gianni L, Lancet Oncol 2012; Lancet Oncol 2016; [3]Tung N, ASCO 2025; [4]Nitz UA, Ann Oncol 2014; [5]Gluz O, JAMA Oncol 2023; [6]Waks AG, npj Breast Cancer 2022

Omówienie Hurvitz SA, ASCO 2025

Poszukiwanie biomarkerów dla pCR; HER2DX®
Badanie EA1181 CompassHER2

HER2DX® included in the Spanish Society of Medical Oncologists (SEOM) guidelines.

CLINICAL GUIDES IN ONCOLOGY | Open Access | Published: 16 June 2023

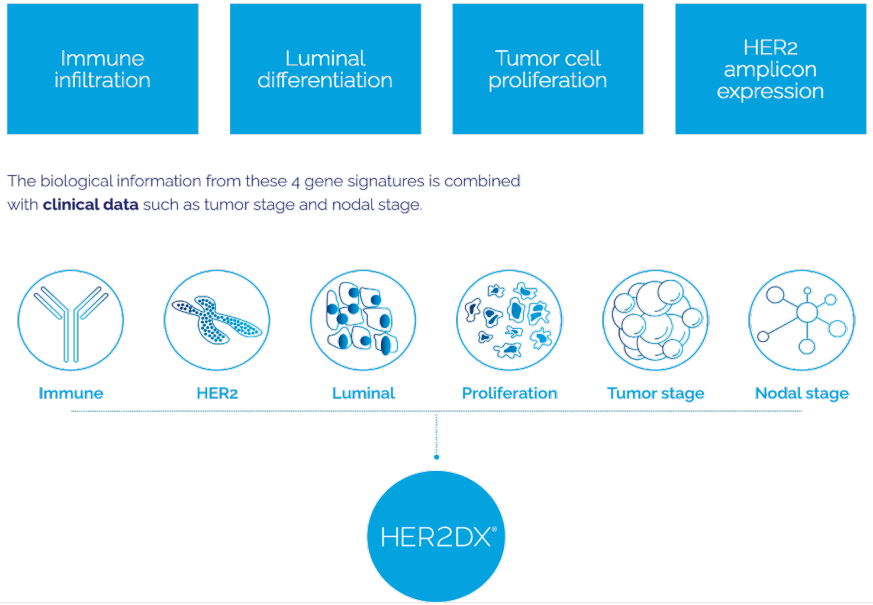
SEOM-GEICAM-SOLTI clinical guidelines for early-stage breast cancer (2022)

Francisco Ayala de la Peña, Silvia Antolín Novoa, Joaquín Gavilá Gregori, Lucía González Cortijo, Fernando Henao Carrasco, María Teresa Martínez Martínez, Cristina Morales Estévez, Agostina Stradella, María Jesús Vidal Losada & Eva Ciruelos

Based on a systematic **review of** relevant studies **and on** the consensus **of experts** from **GEICAM**, **SOLTI,** and **SEOM**.

"In HER2-positive disease, the HER2DX 27-gene test has recently emerged as a useful clinical tool [22-25]. The HER2DX test provides two independent scores indicating prognosis when treated with -based CT (HER2DXrisk-score),and the probability of achieving a pathological complete response following trastuzumab based therapy(HER2DX pCR-score). Thus, HER2DX can help to identify suitable candidates for escalation and deescalation treatment strategies in some clinical situations, even when this tool needs additional validation (II, B)."

Pomiar ekspresji 27 genów;
materiał bloczek parafinowy



https://www.reveal-genomics.com

Badanie EA1181 CompassHER2 analiza wieloczynnikowa: pCR i biologia!

Clinical Factor		OR for pCR (95% CI)	# patients (n=569)
HER2Dx pCR score			
	Low	1.0	226
	Medium	**4.12 (2.33-7.28)**	161
	High	**2.75 (1.36-5.56)**	182
ER	ER+ >70%	1.0	244
	ER+ 11-70%	**2.37 (1.22-4.63)**	64
	ER+ 1-10%	**3.12 (1.18-8.19)**	31
	ER- 0%	**3.70 (2.01-6.81)**	230
HER2 IHC *			
	2+/ISH+	1.0	85
	3+	**7.46 (3.39-16.42)**	461
Taxane^			
	docetaxel	1.0	188
	paclitaxel	**1.58 (1.03-2.43)**	368

Clinical Factor/Biomarker		OR for pCR (95% CI)	# patients
ERBB2 mRNA level			
	ERBB2/10 units	**1.33 (1.16-1.51)**	569
Intrinsic subtype			
	non-HER2E	1.0	216
	HER2E	**2.69 (1.63-4.42)**	353
IgG			
	IgG/10 units	**1.09 (1.02-1.16)**	569
ER	ER+ >70%	1.0	244
	ER 11-70%	**2.71 (1.39-5.27)**	64
	ER 1-10%	**2.89 (1.14-7.33)**	31
	ER-	**4.21 (2.57-6.91)**	230
HER2 IHC			
	2+/ISH+	1.0	85
	3+	**2.74 (1.14-6.59)**	461
Taxane			
	docetaxel	1.0	188
	paclitaxel	**1.76 (1.12-2.75)**	368

Czynniki związane z pCR: niska ekspresja ER; wysoka: HER2 3+IHC, ↑ERBB2 mRNA, HER2E sygnatura; HER2DX ale brak prospektywnych badań

Bez wpływu na pCR: T, N, zaawansowanie kliniczne, wiek, rasa, ECOG PS, typ histologiczny, cecha G

Czy dysponujemy narzędziami (biomarkerami), które pozwalą podjąć decyzję o de-eskalacji leczenia?
Jesteśmy blisko!

Wczesny HER2-dodatni rak piersi

Czy możemy de-eskalować schematy: ↓liczbę cykli NAT w schematach z podwójną blokadę anty-HER2?

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DOSING: PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Positive[l,m]

Paclitaxel + trastuzumab[21]
- Paclitaxel 80 mg/m² IV weekly for 12 weeks
  - ◊ With:
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel
  - ◊ Followed by:
- Trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 year of trastuzumab treatment.

TCH[22]
- Docetaxel 75 mg/m² IV day 1
- Carboplatin AUC 6 IV day 1
  - ◊ Cycled every 21 days for 6 cycles
  - ◊ With:
- Trastuzumab 4 mg/kg IV week 1
  - ◊ Followed by:
- Trastuzumab 2 mg/kg IV for 17 weeks
  - ◊ Followed by:
- Trastuzumab 6 mg/kg IV
  - ◊ Cycled every 21 days to complete 1 year of therapy[n]

OR
- Trastuzumab 8 mg/kg IV week 1
  - ◊ Followed by:
- Trastuzumab 6 mg/kg IV
  - ◊ Cycled every 21 days to complete 1 year of therapy[n]

TCH + pertuzumab[23]
- Docetaxel 75 mg/m² IV day 1
- Carboplatin AUC 6 IV day 1
  - ◊ Cycled every 21 days for 6 cycles

With:
- Trastuzumab 8 mg/kg IV day 1
- Pertuzumab 840 mg IV day 1
  - ◊ Followed by:
- Trastuzumab 6 mg/kg IV on day
- Pertuzumab 420 mg IV day 1
  - ◊ Cycled every 21 days to complete 1 year of therapy[n]

TDM-1
- 3.6 mg/kg day 1
  - ◊ Cycled every 21 days for 14 cycles

NAT, neoadjuvant therapy

TAK!
w wybranej grupie chorych stopień II (I)
4 kursy NAT

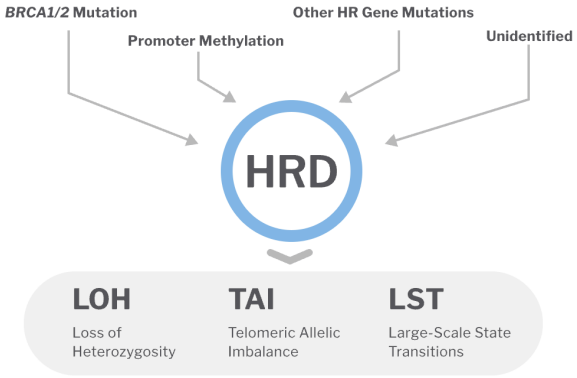
(oczekiwanie na EFS, DFS, OS w badaniu CompassHER2)

Ocena HRD w guzach litych - rak jajnika

MyChoice determines HRD status in multiple ways for comprehensive results

MyChoice examines ovarian cancer tumors using two methods (*BRCA1/2* mutation and genomic instability) to determine a patient's HRD status.

***BRCA1* & *BRCA2* status**	**Sequence variants + Large rearrangements** • Detection and classification of sequence variants and large rearrangements • Identification of somatic and germline variants present in the tumor
Genomic instability status	**LOH + TAI + LST** • Comprehensive assessment of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and large-scale state transitions (LST) across the entire genome

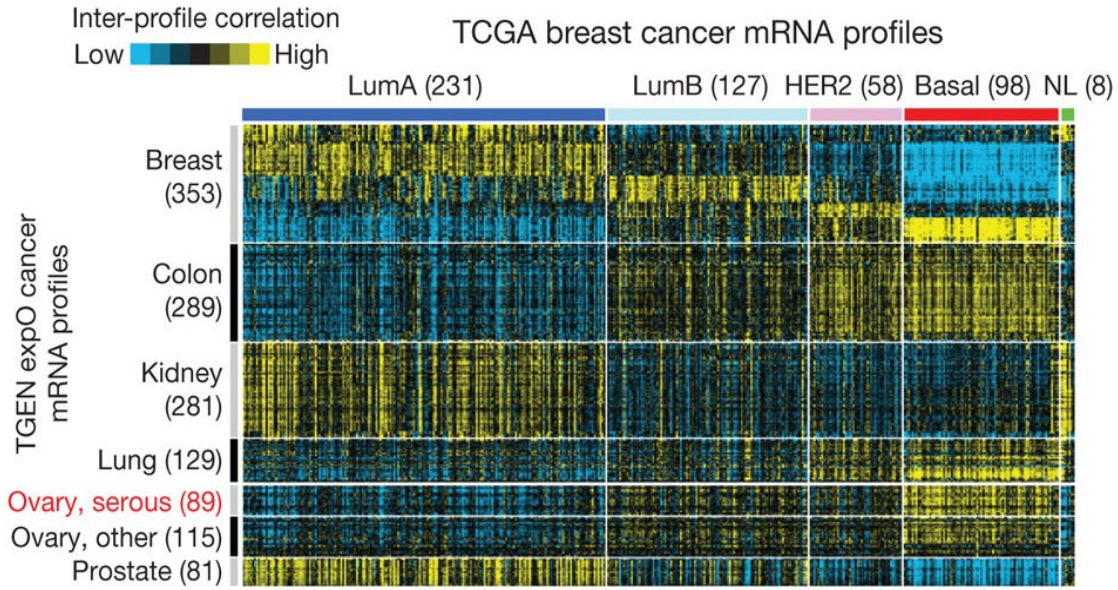


Overcoming the limitations of less sensitive tests in HRD detection

There is a critical need for integrated germline and tumor genomic testing in oncology, as **up to 10% of germline mutations are missed through tumor testing alone.**[2]

Determining HRD status through gene sequencing alone can miss critical causes, such as epigenetic events like *BRCA1* promoter methylation and other measures of genomic instability.[3,4] These limitations highlight the need for a more comprehensive approach to HRD assessment.

Niskozróżnicowany, surowiczy rak jajnika a fenotyp raka piersi

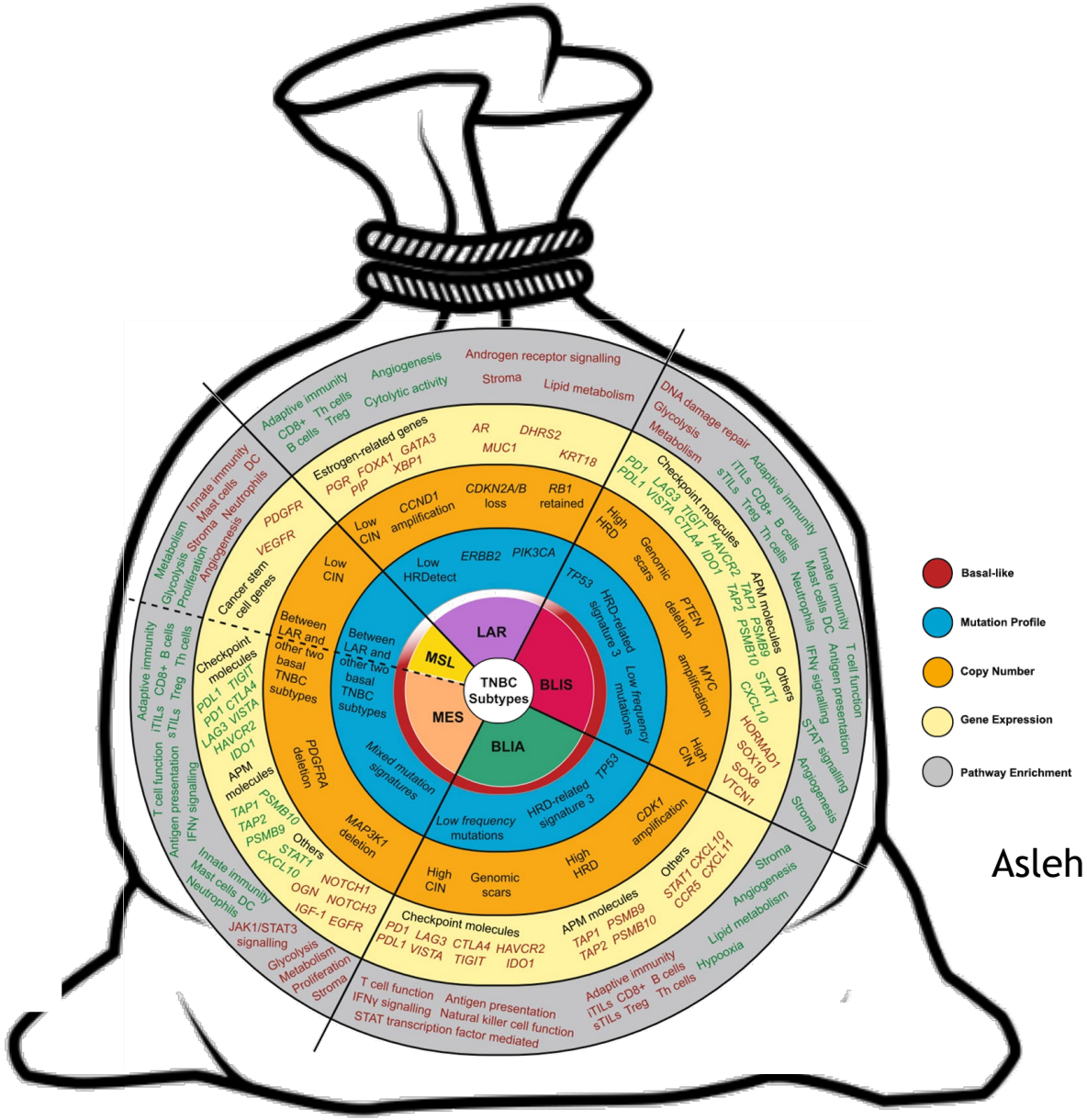


HRD, *Homologous Recombination Deficiency*

https://myriad.com/genetic-tests/mychoicecdx-tumor-test/

The Cancer Genome Atlas Research Network; Nature, 2012

Heterogenność potrójnie ujemnego raka piersi



Asleh K, J Exp Clin Cancer Res 2022

HRD i pCR u chorych leczonych neoadiuwantowo
Schematy z karboplatyną; badanie GeparSixto

All Tumors (pCR = ypT0 N0)	Paclitaxel/Liposomal Doxorubicin (PM)	PM + Carboplatin	p-Value
myChoice HRD® Positive[1]	33.9 (n=62)	63.5 (n=74)	<0.001
myChoice HRD® Negative[2]	20.0 (n=30)	29.6 (n=27)	0.54
p-Value	0.22	0.003	

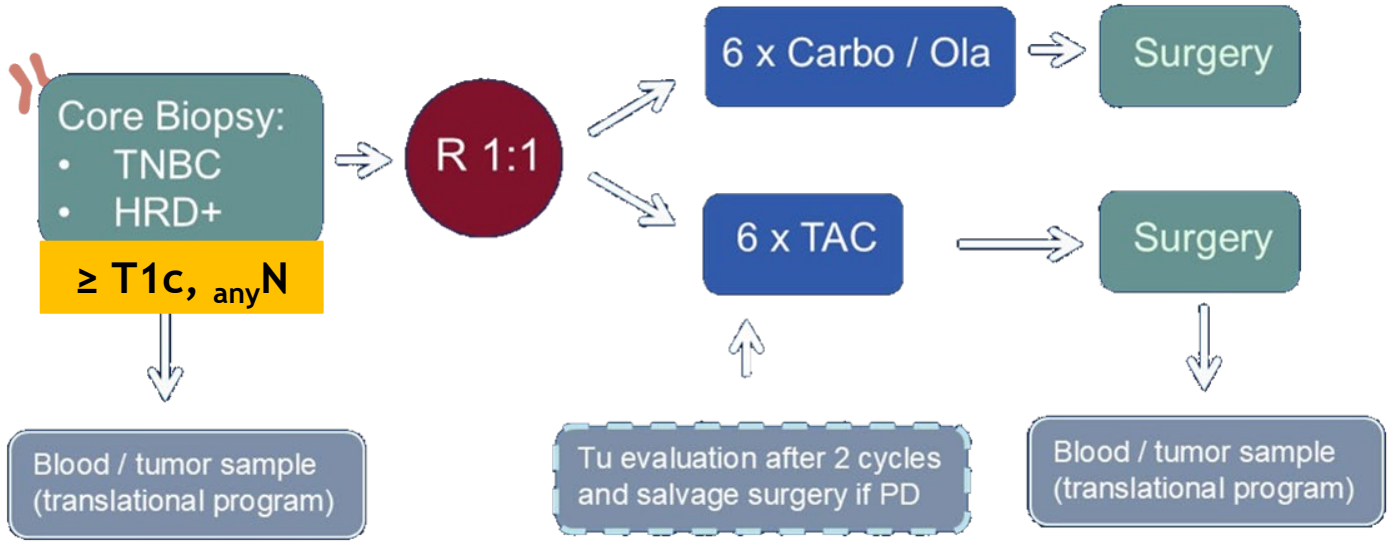
myChoice HRD® Positive[1] (pCR = ypT0 N0)	Paclitaxel/Liposomal Doxorubicin (PM)	PM + Carboplatin	p-Value
Positive HRD score with no tumor *BRCA1/2* mutation	31.7 (n=41)	63.2 (n=38)	0.005
Tumor *BRCA1/2* mutation	38.1 (n=21)	69.7 (n=33)	0.022

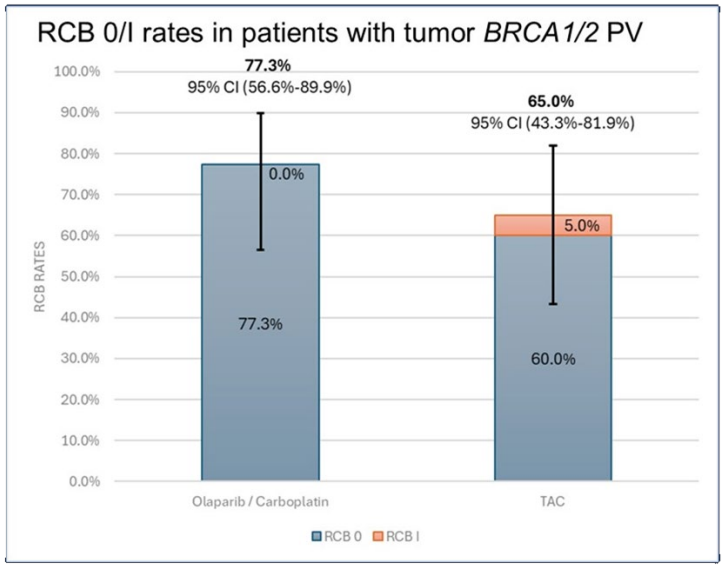
HRD w kawlifikacji do leczenia z udziałem pochodnych platyny nieokreślona rola

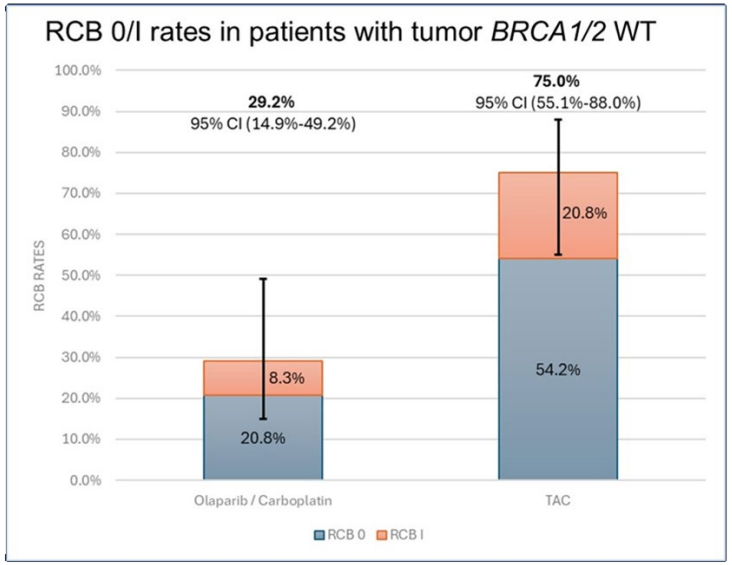
[1]myChoice HRD positive = homologous recombination deficiency as measured by the combination of loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions and/ or tumor mutation in the *BRCA1/2* genes; [2]myChoice HRD negative = intact homologous recombination pathway.

von Minckwitz G, J Clin Oncol 2015. 33, 2015 (suppl; abstr 1004), ASCO 2015

Badanie ABCSG-45; faza 2, N = 90







Carbo/Ola: 6x karboplatyna AUC 5 co 3 tyg. + olaparyb ≥ 100 mg bid (4-19 dzień)
TAC: 6x docetaksel 75 mg, epirubicyna 50 mg/m²; cyklofosfamid 500 mg/m² co 3 tyg.

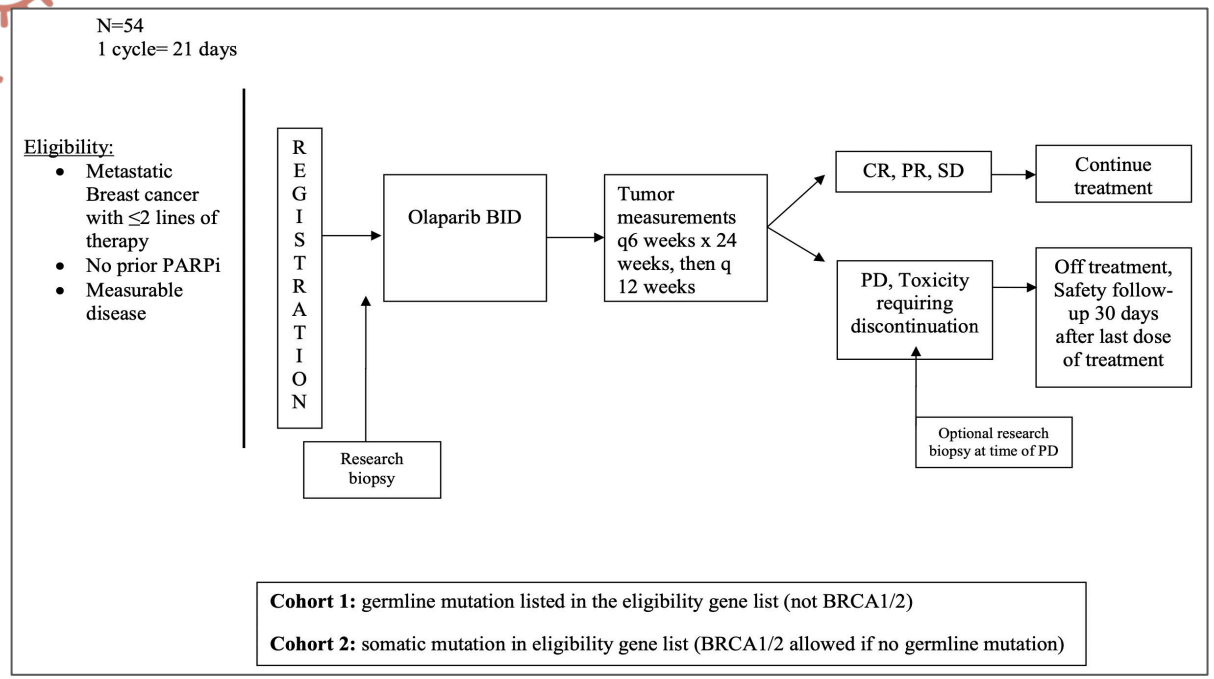
- HRD+ (*BRCA1/2* PV w guzie lub Genomic Instability Score ≥42)
- Stratyfikacja ocena *BRCA1/2* w guzie; stan menopuazy
- Pierwszorzędowy punkt końcowy: Residual Cancer Burden 0/I;
- Drugorzędowy punkt końcowy: pCR, bezpieczeństwo i tolerancja, QoL

	Carbo/Ola (n=46)	TAC (n=44)	Total (n=90)
Age, mean (SD)	50.2 (12.7)	51.6 (12.5)	**50.9** (12.5)
Menopausal status			
pre- and peri-menopausal	23 (50.0%)	23 (52.3%)	46 (51.1%)
postmenopausal	23 (50.0%)	21 (47.7%)	44 (**48.9%**)
Tumor *BRCA1/2* PV status			
negative	24 (52.2%)	24 (54.5%)	48 (53.3%)
positive	22 (47.8%)	20 (45.5%)	42 (**46.7%**)
Genomic Instability Status			
positive	42 (91.3%)	41 (93.2%)	83 (**92.2%**)
negative	1 (2.2%)	2 (4.5%)	3 (3.3%)
missing	3 (6.5%)	1 (2.3%)	4 (4.4%)

TNBC HRD+ u około 50% somatyczna *BRCA1/2* PV

Singer C, J Clin Oncol 43, 2025 (suppl 16; abstr 510)

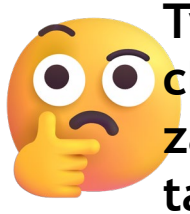
Badanie TBCRC 048; faza II



Clinical/ Molecular factor	Total # response/ total
Tumor subtype (primary) TNBC ER+/HER2- HER2+	 7/10 (70%) 12/33 (36%) 0/3 (0%)
BRCA1 *BRCA2*	8/22 (36%) 10/24 (42%)
1L met RX > 1L metastatic Rx	12/17 (71%) 7/29 (24%)
Prior platinum No prior platinum	1/4 (25%) 18/42 (43%)
Method of dx s*BRCA*m cfDNA Tumor bx	 1/10 (10%) 18/36 (50%)
PV/LPV* Single *BRCA* copy loss Biallelic *BRCA* copy loss	16/39 (41%) 1/5 (20%) 2/2 (100%)

g*PALB2* N=24	
Best Response	Responses (rate, %)
Complete Response (CR)	1 (4%)
Partial Response (PR)	17 (71%)
Stable Disease (SD)	5 (21%)
Progressive Disease (PD)	1 (4%)
ORR = 75% (18/24, 80%-CI: 60%-86%)	
CBR (18 wks) = 83% (20/24, 90%-CI: 66%-94%)	

s*BRCA1/2* N=30	
Best Response	Responses, (rate, %)
Complete Response (CR)	1 (3%)
Partial Response (PR)^	10 (33%)
Stable Disease (SD)	13 (43%)
Progressive Disease (PD)	6 (20%)
ORR = 37% (11/30, 80%-CI: 25%-50%)	
CBR (18 wks) = 53% (16/30, 90%-CI: 37%-69%)	

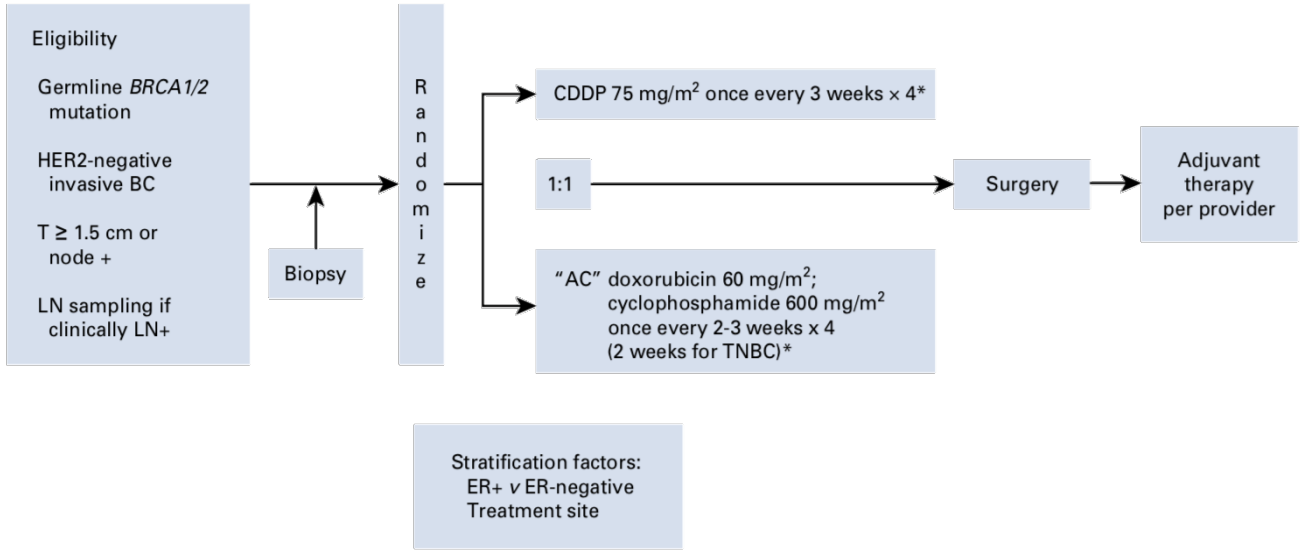


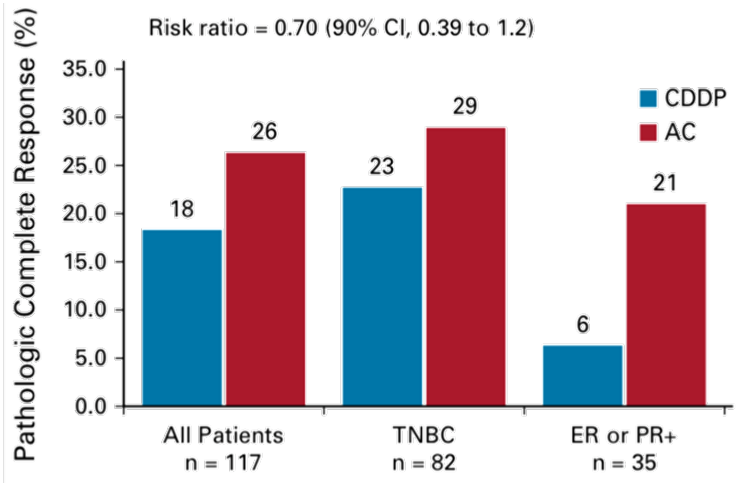
Warto o tym pomyśleć!?
Tymczasem brak rejestracji dla iPARP u chorych z g*PALB2 i sBRCA1/2*, chociaż w zaleceniach międzynarodowych jest taka opcja (kategoria 2B)

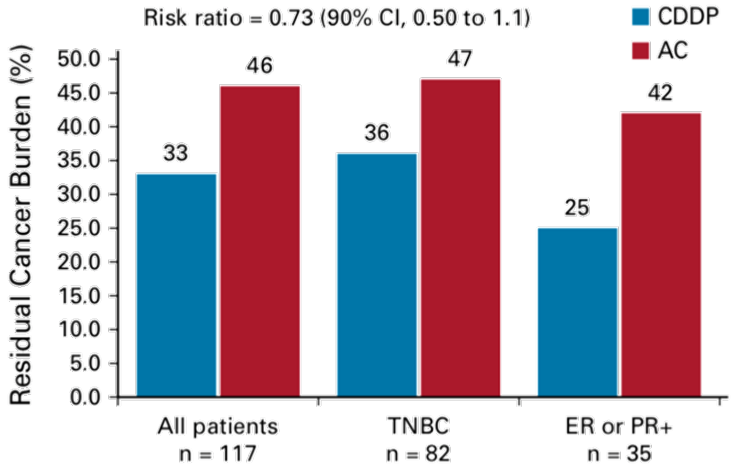
Tung NM, J Clin Oncol 2020
Tung NM, J Clin Oncol 42, 2024 (suppl 16; abstr 1021)

TBCRC 031: A randomized phase II study of preoperative cisplatin (CDDP) vs doxorubicin, cyclophosphamide (AC) in germline *BRCA* mutation carriers with newly diagnosed breast cancer (the INFORM trial)

	All patients N=118	CDDP N=60	AC N=58
ER/PR status (≤ or ≥ 10%)			
TNBC	70%	73%	67%
ER or PR >10%	30%	27%	33%







Badanie INFORM:

- Wynik spójny z badaniem TBCRC 030, Geparsixto i BrighTNess

Tung i wsp. SABCS 2019, GS6-03; Tung i wsp. J Clin Onco 2020

XXIV SPOTKANIE Po ASCO

Co można “taniej” oznaczyć: mutacje somatyczną *BRCA1/2* czy HRD?

Grupa wysokiego ryzyka TNBC → do NACT

XXIV SPOTKANIE Po ASCO

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

The regimens listed in the table for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.

HER2-Negative	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[b] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[b] • TC (docetaxel and cyclophosphamide) • ~~Olaparib, if germline *BRCA1/2* mutations[c,d]~~ • **High-risk[e] TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab** • ~~TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy[d]: Capecitabine~~	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[b] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[b] *or AC followed by weekly paclitaxel[b]* • EC (epirubicin/cyclophosphamide) *(useful in certain circumstances)* • ~~TAC (docetaxel/doxorubicin/cyclophosphamide)~~ • For TNBC: ▸ Paclitaxel + carboplatin (various schedules) (category 2A) ▸ Docetaxel + carboplatin (category 2A)

Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

[a] *Docetaxel and paclitaxel may be used interchangeably.* ~~Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m².~~

[b] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.

[c] Consider addition of adjuvant olaparib for 1 y for those with germline *BRCA1/2* mutations and:
- TNBC, if 1) ≥pT2 or ≥pN1 disease after adjuvant chemotherapy, or 2) residual disease after preoperative chemotherapy
- HR-positive, HER2-negative tumors, if 1) ≥4 positive lymph nodes after adjuvant chemotherapy (category 2A), or 2) residual disease after preoperative therapy and a clinical stage, pathologic stage, ER status, and tumor grade (CPS+EG) score ≥3.

Adjuvant olaparib can be used concurrently with endocrine therapy.

[d] ~~Patients in the OlympiA trial did not receive capecitabine; thus, there are no data on sequencing or to guide selection of one agent over the other.~~

[e] High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.

Note: All recommendations are category 2A unless otherwise indicated. This is the NCCN Guidelines: Poland Edition, For definitions, see page DEF-1.

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Discussion

PREOPERATIVE/ADJUVANT THERAPY[a,b]

The regimens listed in the table are all category 1 (except where indicated) when used in the adjuvant setting. See BINV-M, 1 for Considerations for Those Receiving Preoperative/Adjuvant Systemic Therapy.

HR-Negative, HER2-Negative	
Preferred Regimens: **Stage I** **Preoperative or adjuvant setting:** • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[c,e] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[c,e] • TC (docetaxel and cyclophosphamide)[e] **Stage II–III** **Preoperative followed by adjuvant:** • **Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab (category 1)** **Stages I–III** **Adjuvant setting only:** • If residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy[d,e]: Capecitabine • Germline *BRCA1/2* mutations[d]: Olaparib	
Useful in Certain Circumstances: **Preoperative only:** • Docetaxel/carboplatin/pembrolizumab **Preoperative or adjuvant:** • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • ~~AC followed by weekly paclitaxel[c]~~ • **AC (doxorubicin/cyclophosphamide) followed or preceded by carboplatin + taxane (paclitaxel or docetaxel)[c]** **Maintenance therapy after adjuvant chemotherapy:** • Capecitabine	**Other Recommended Regimens:** **Preoperative or adjuvant setting:** • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Paclitaxel + carboplatin (various schedules) (category 2A) • Docetaxel + carboplatin[†] (category 2A) • **Regimens listed as "Preferred" for stage I, may be considered for patients with Stage II–III disease who are not eligible for pembrolizumab.**

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m².

[b] Principles of Preoperative Systemic Therapy (BINV-L).

[c] It is acceptable to change the administration sequence to taxane followed by AC.

[d] Patients in the OlympiA trial did not receive capecitabine; thus, there are no data on sequencing or to guide selection of one agent over the other. In patients eligible for both adjuvant olaparib and abemaciclib, the optimal sequence is not known. See BINV-K, 2.

[e] For patients with stage II–III disease who are not eligible for pembrolizumab, the regimens listed as "preferred" for stage 1 could be considered as other recommended options.

Note: All recommendations are category 2A unless otherwise indicated.

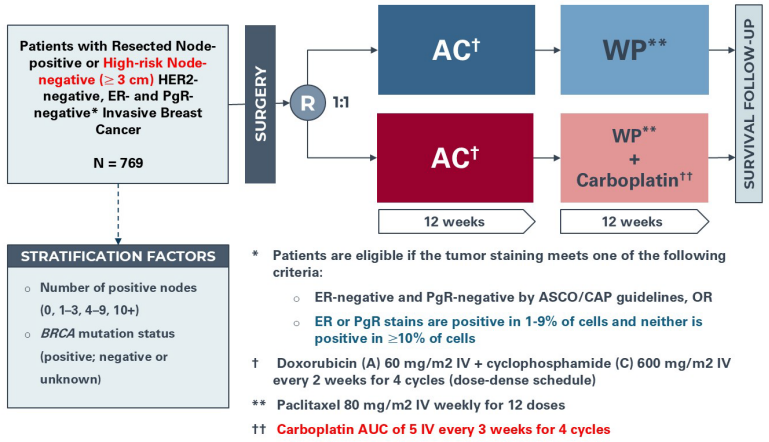
References on BINV-M 10 of 10

XXIV SPOTKANIE Po ASCO

Korzyść z karboplatyny w TNBC …

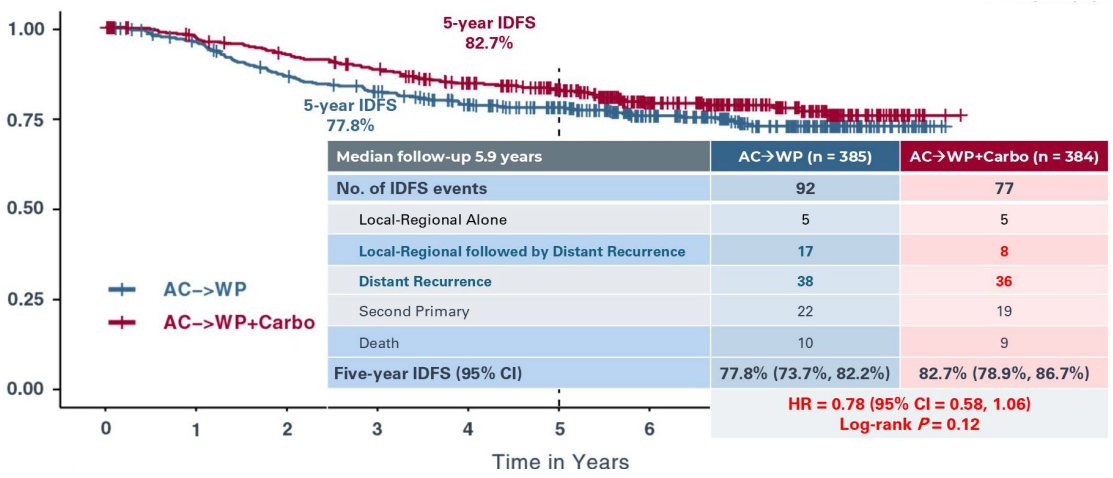
The Never Ending Story…

Badanie NRG-BR003; 3 faza

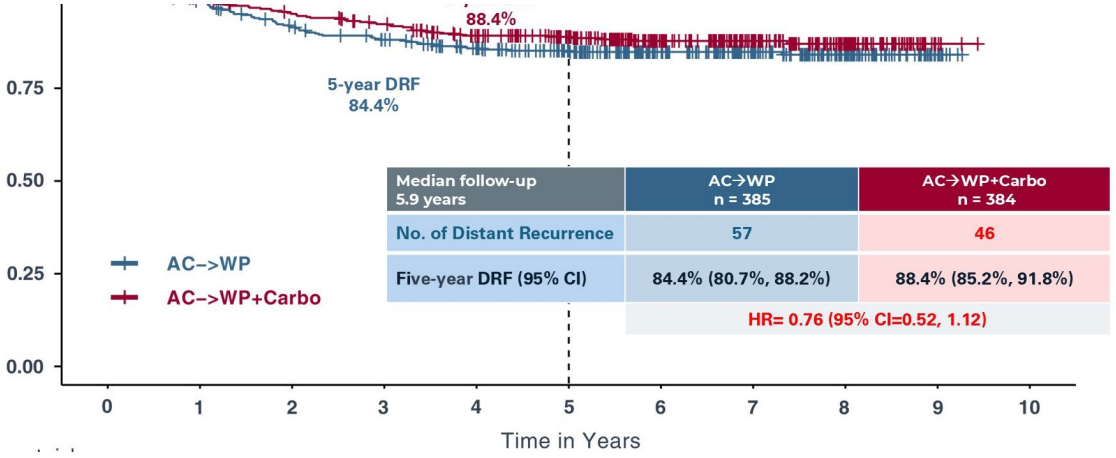


Primary Endpoint:
- Invasive disease-free survival (IDFS)

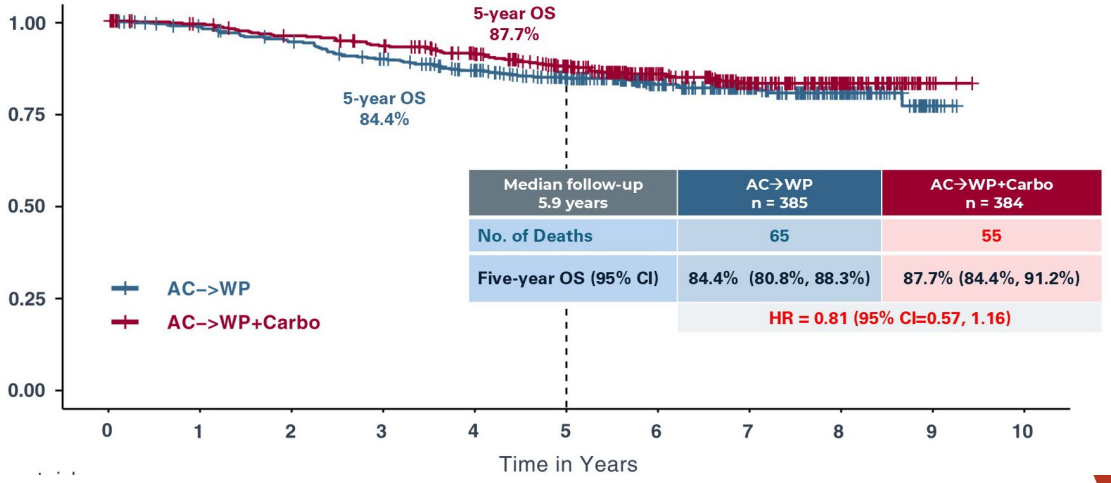
Secondary Endpoints:
- Overall survival (OS)
- Breast cancer-free survival (BCFS)
- Recurrence-free interval (RFI)
- Distant recurrence-free interval (DRFI)
- Frequencies of adverse events categorized using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0)



Median follow-up 5.9 years	AC→WP (n = 385)	AC→WP+Carbo (n = 384)
No. of IDFS events	92	77
Local-Regional Alone	5	5
Local-Regional followed by Distant Recurrence	17	8
Distant Recurrence	38	36
Second Primary	22	19
Death	10	9
Five-year IDFS (95% CI)	77.8% (73.7%, 82.2%)	82.7% (78.9%, 86.7%)
	HR = 0.78 (95% CI = 0.58, 1.06) Log-rank *P* = 0.12	



Median follow-up 5.9 years	AC→WP n = 385	AC→WP+Carbo n = 384
No. of Distant Recurrence	57	46
Five-year DRF (95% CI)	84.4% (80.7%, 88.2%)	88.4% (85.2%, 91.8%)
	HR= 0.76 (95% CI=0.52, 1.12)	

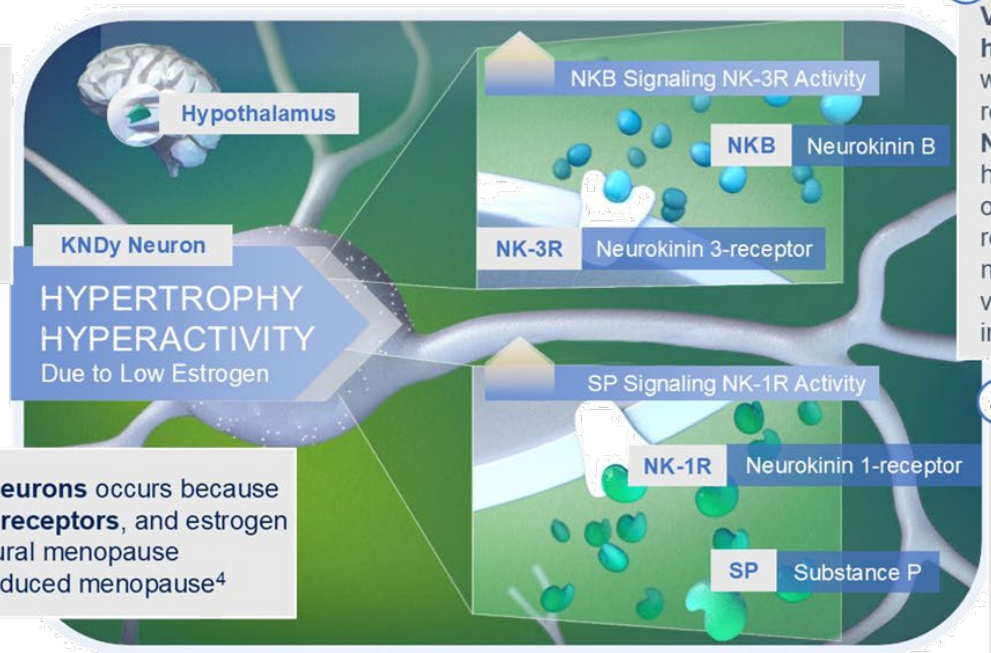


Median follow-up 5.9 years	AC→WP n = 385	AC→WP+Carbo n = 384
No. of Deaths	65	55
Five-year OS (95% CI)	84.4% (80.8%, 88.3%)	87.7% (84.4%, 91.2%)
	HR = 0.81 (95% CI=0.57, 1.16)	

Valero V, J Clin Oncol 43, 2025 (suppl 17; abstr LBA509)

Objawy naczynioruchowe (VMS) w okresie menopauzy (uderzenia gorąca i nocne poty) - patomechanizm

1. Specific neurons called **KNDy neurons**, located in the **hypothalamus**, are thought to play a **key role in thermoregulation and sleep**[1-3]



2. **VMS are thought to be caused by hyperactivity of KNDy neurons**, in which several neuropeptides and receptors are upregulated, including **NK-1 and NK-3 receptors**. This hyperactivity leads to dysregulation of the thermoregulatory center resulting in VMS.[4-11] NK-1 receptors may have a role in peripheral vasodilatation and primary insomnia.[12]

3. Hyperactivity of **KNDy neurons** occurs because they **express estrogen receptors**, and estrogen levels decline in the natural menopause transition or as part of induced menopause[4]

4. Targeted **dual antagonism of NK-1 and NK-3 receptors decreases the frequency and severity of VMS** and **sleep disturbances**[12]

ŁAGODNE

Uczucie ciepła bez pocenia się

UMIARKOWANE

Uczucie ciepła z poceniem się

CIĘŻKIE

Uczucie ciepła z poceniem się oraz upośledzeniem aktywności

Uderzenia gorąca należą do najczęściej zgłaszanych objawów menopauzy, według prognoz dotknie 1,2 miliarda kobiet na całym świecie do 2030 roku. Wykazano również, że uderzenia gorąca mają negatywny wpływ na jakość życia kobiet i są jedną z głównych przyczyn, dla których kobiety zgłaszają się do lekarza.
https://www.bayer.com/en/us/news-stories/new-drug-application-to-us-fda-for-elinzanetant

VMS, vasomotor symptoms

Dotychczasowe leczenie VMS u chorych na raka piersi SSRI i SNRI, akupunktura…

SSRI (***selective serotonin reuptake inhibitor***)	**SNRI** (***serotonin-norepinephrine reuptake inhibitor***)
Paroksetyna	Wenlafaksyna (Effexor)[1-3]
Fluoksetyna	
Citalopram	
Escitalopram	
Sertralina	

Najczęstsze działania niepożądane:

- SSRI i SNRI: nudności i zaparcia (większości ustępują w 1 tygodniu leczenia)
- SNRI: ↑RR; ostrożnie u kobiet z nadciśnieniem tętniczym.

Przy przepisywaniu SSRI leczonych HTH rozsądne jest unikanie silnych i średnio silnych inhibitorów CYP2D6, w szczególności paroksetyny i fluoksetyny, jeśli istnieje odpowiednia alternatywa.

[1]Loprinzi CL, Lancet. 2000; [2]Boekhout AH, J Clin Oncol. 2011; [3]Bordeleau L, J Clin Oncol. 2010

Potrzeba “Oazy”…

Elinzanetant (ELIN), pierwszy podwójny antagonista receptorów neurokininy-1 i 3 (NK-1 i 3); niehormonalne leczenie umiarkowanych do ciężkich VMS związanych z menopauzą.

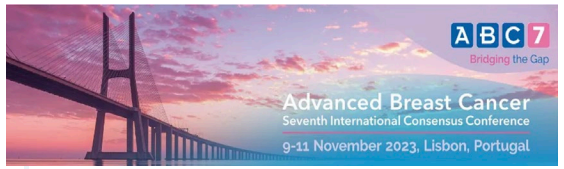
Badanie 3 fazy	N	Grupa badana	Schemat badania	Wyniki	Działania niepożądane
OASIS 1/2	396/400	K; umiarkowane, ciężkie VMS; 40 - 65 r.ż.	ELIN 120 mg/d. 26 tyg.; Grupa kontrolna PLB 12 tyg. →120 mg ELIN 14 tyg.	↓częstotliwości i nasilenia VMS. ↓zaburzenia snu i ↑ jakości życia	bóle głowy i zmęczenie
OASIS 3	628		ELIN 120 mg/d. 52 tyg.	↓ 1,6 VMS dziennie w 12 tyg. ↑PROMIS SD SF i MENQOL	
OASIS 4	474	18-70 r.ż.; HR+ BC lub wysokie ryzyko zachorowania BC; HTH; uderzenia gorąca **≥35** umiarkowanych lub ciężkich w tygodniu z uwzględnieniem epizodów nocnych	ELIN 120 mg/d. 52 tyg,; Grupa kontrolna PLB 12 tyg. →120 mg ELIN 40 tyg. do 52 tyg. Kontynucja do 2 lat.	↓ częstości i nasilenia VMS ↑PROMIS SD SF i MENQOL	ból głowy, zmęczenie i senność

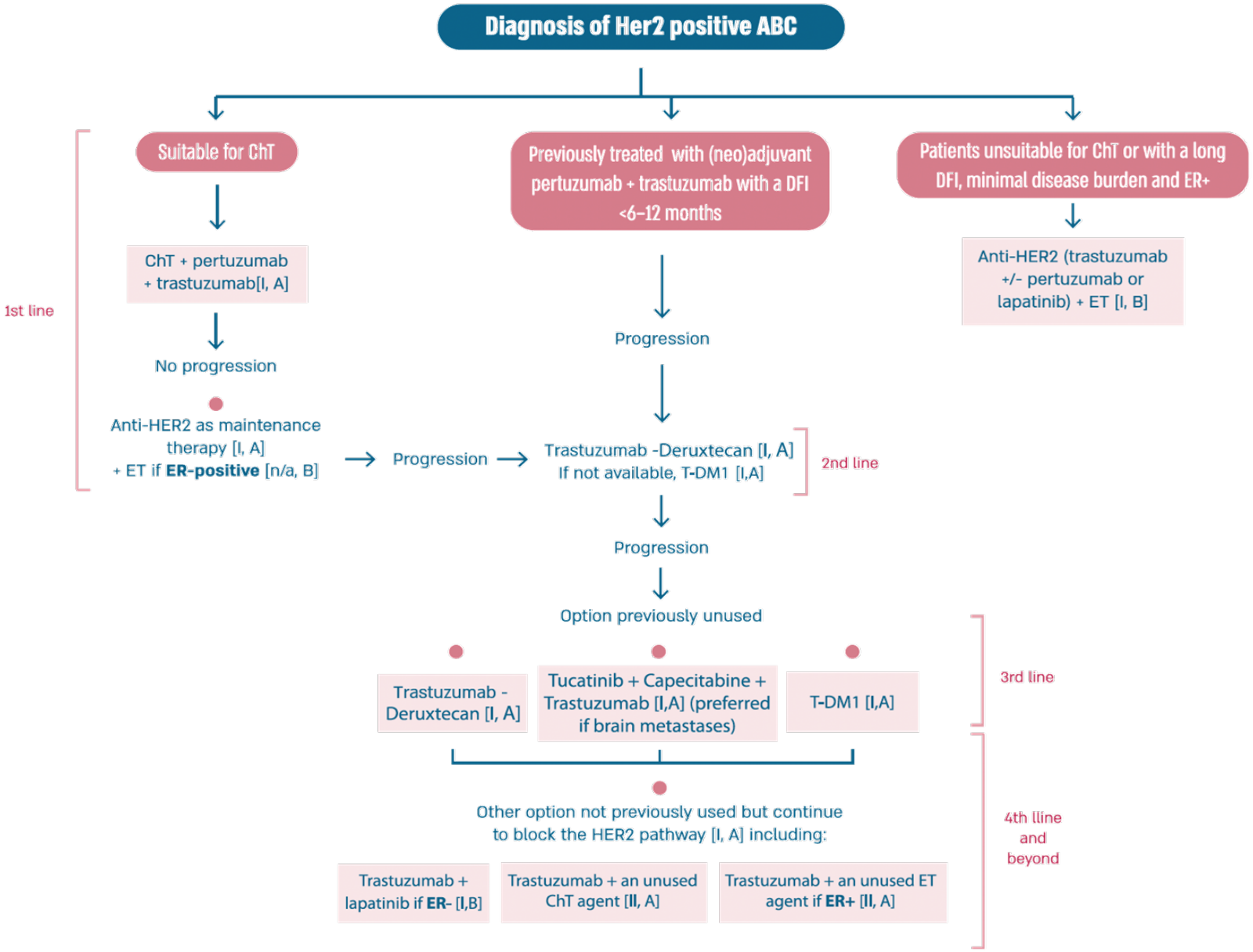
ELIN, Elinzanetant; d, na dobę; PLB, placebo; ŚCZ, średnia częstotliwość; VMS, vasomotor symptoms; PROMIS SD SF (Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form); MENQOL (Menopause-Specific Quality of Life)

Cardoso F, J Clin Oncol 43, 2025 (suppl 16; abstr 508)

U.S. Food and Drug Administration (FDA) accepts New Drug Application for elinzanetant. Bayer. October 9, 2024. Accessed October 9, 2024. https://www.bayer.com/media/en-us/us-food-and-drug-administration-fda-accepts-new-drug-application-for-elinzanetant/; Elinzanetant significantly reduces frequency and severity of moderate to severe hot flashes associated with menopause. Bayer. May 16, 2024. Accessed October 9, 2024.https://www.bayer.com/en/us/news-stories/elinzanetant; Panay N, Joffe H, Maki P, et al. Efficacy and long-term safety of elinzanetant for the treatment of VMS associated with menopause:A phase 3 randomized trial (OASIS 3). Presented at the 2024 Annual Meeting of The Menopause Society. Chicago, Illinois. September 10-14, 2024.

Choroba zaawansowana



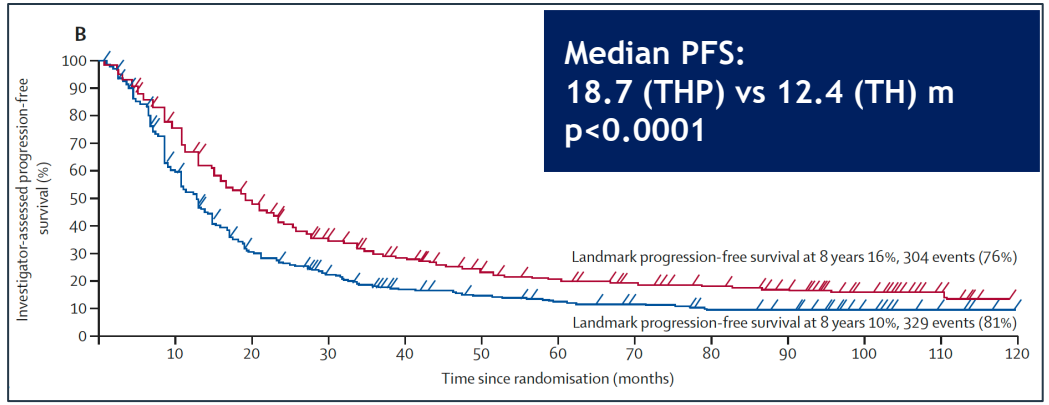


Legend: ABC, advanced breast cancer; ChT, chemotherapy; DFI, disease-free interval; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab-emtansine.

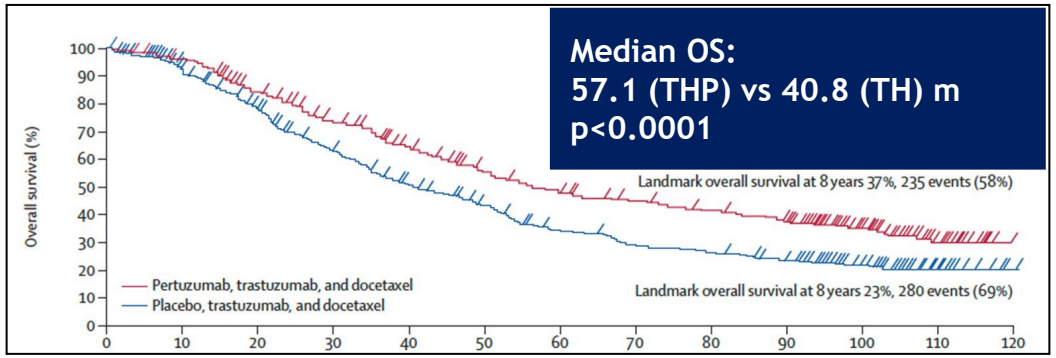
Cardoso F, i wsp. ABC guidelines 6 and 7. Breast 2024.

CLEOPATRA; 1 linia

≥12 miesięcy po leczeniu okołooperacyjnym; bez przerzutów do OUN



Median PFS:
18.7 (THP) vs 12.4 (TH) m
p<0.0001

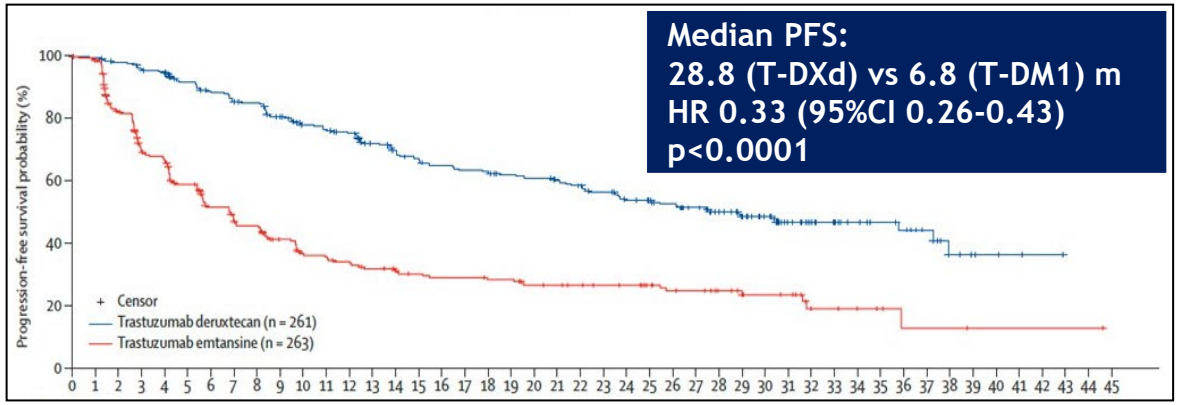


Median OS:
57.1 (THP) vs 40.8 (TH) m
p<0.0001

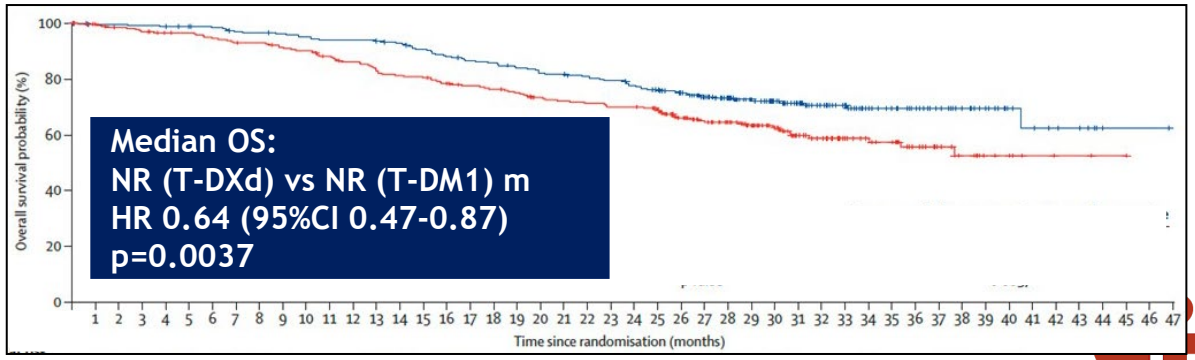
Swain S, i wsp. N Engl J Med 2015; Swain S, i wsp. Lancet Oncol 2020

DESTINY-Breast03; 2 linia

+ w ciągu 6 miesięcy po leczeniu neoadiuwantowym lub adiuwantowym z udziałem trastuzumabu, taksanu



Median PFS:
28.8 (T-DXd) vs 6.8 (T-DM1) m
HR 0.33 (95%CI 0.26-0.43)
p<0.0001



Median OS:
NR (T-DXd) vs NR (T-DM1) m
HR 0.64 (95%CI 0.47-0.87)
p=0.0037

Cortes, NEJM 2022; Hurvitz, Lancet 2023

Badanie AFT-38 PATINA; 3 fazy

Registration
- Histologically confirmed HR+,HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

Key eligibility criteria
- Completion of induction chemotherapy and no evidence of disease progression (i.e., CR, PR, or SD)

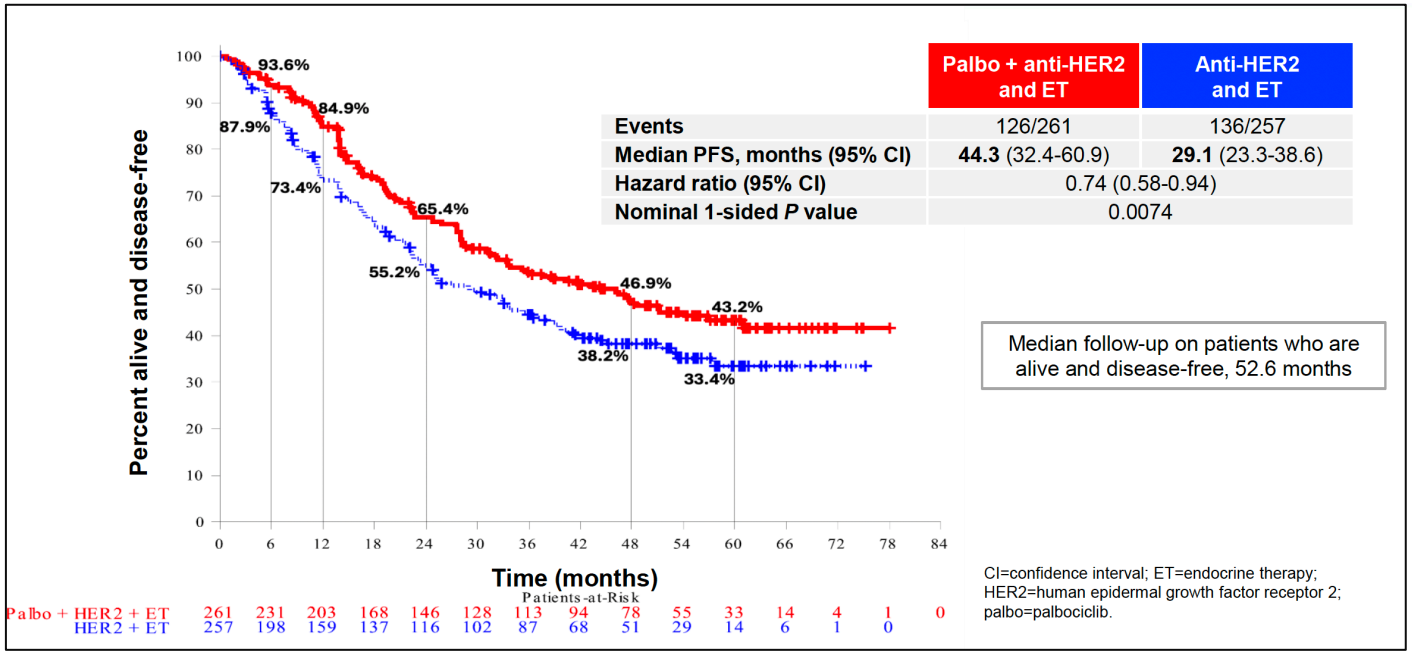
N=518

R 1:1

- Palbociclib (125 mg PO QD D1-D21) Trastuzumab ± pertuzumab + endocrine therapy*
- Trastuzumab ± pertuzumab + endocrine therapy*

Until PD or toxicity

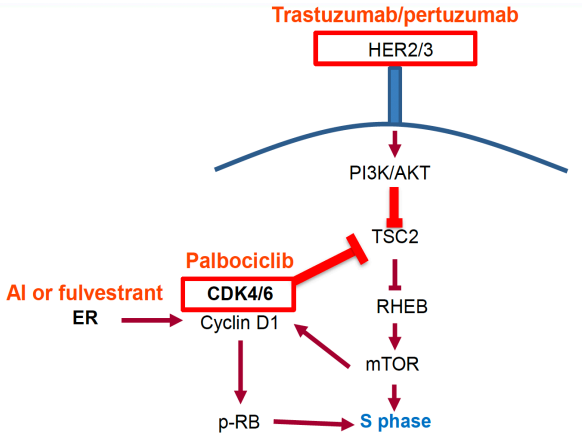
SURVIVAL FOLLOW-UP



	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Median follow-up on patients who are alive and disease-free, 52.6 months

CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.



The HER2 and CDK4/6 pathways converge at the tumor suppressor protein TSC2

When CDK4/6 and HER2 inhibitors are combined, potent suppression of RB phosphorylation and mTORC1 activity, enhancing anti-proliferative effects in tumor cells

Otto Metzger, SABCS 2024; GS2-12

DESTINY-Breast09 study design

A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

Eligibility criteria
- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**

Stratification factors
- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)

R 1:1:1

- n=387: T-DXd‡ + placebo
- n=383: T-DXd‡ + pertuzumab§
- n=387: THP — Taxane (paclitaxel or docetaxel)¶ + trastuzumab‖ + pertuzumab§

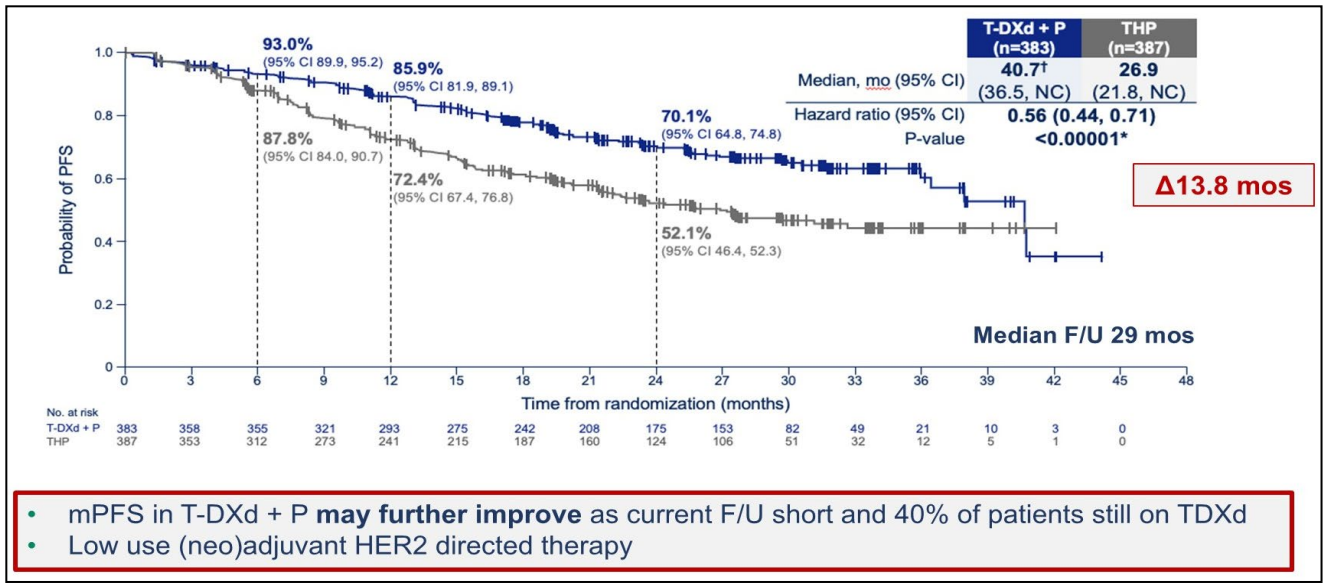
Endpoints

Primary
- PFS (BICR)

Key secondary
- OS

Secondary
- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

- If T-DXd was discontinued due to AEs (except Grade >2 ILD), patients could switch to trastuzumab**
- Concurrent use of ET (AI or tamoxifen) was allowed for those with HR+ disease after six cycles of T-DXd or discontinuation of taxane in THP arm



- mPFS in T-DXd + P **may further improve** as current F/U short and 40% of patients still on TDXd
- Low use (neo)adjuvant HER2 directed therapy

PFS2; T-DXd+P vs THP; HR = 0,60 (95%CI 0,45-0,79), p=0,00038; mediana NC vs 36.5 m (95%CI 26.1-NC)

Charakterystyka chorych:
- 51% *de novo* mBC; 54% HR+; ~82% IHC 3+
- ~80-85% (neo)adiuwant) CHT,~58% trastuzumab, ~15% pertuzumab; 2% T-DM1
- HTH jednocześnie u chorych HR+: 13,5% T-DXd+P; 38,3% THP

- **T-DXd do nietolerancji lub PD, mediana czasu leczenia 20 m.;**
- **THP: mediana 16,9 m: docetaksel 5,5 m. (8 cykli); paklitaksel 4,4 m (6 cykli)**
- 10,1% z PD w ramieniu THP otrzymało T-DXd
- 30% z PD w ramieniu THP i 40% w ramieniu T-DXd+P nie otrzymało żadnej kolejnej linii leczenia
- 27,6% w ramieniu THP PD w 1. roku

Tolaney S, J Clin Oncol 43, 2025 (suppl 17; abstr LBA1008)

The Death of Cleopatra, Juan Luna, Museo del Prado in Madrid

DESTINY-Breast09 wnioski na dzisiaj

- T-DXd + P bardzo skuteczne 1. linia leczenia w chorobie uogólnionej; bez nowych sygnałów w zakresie toksyczności; dane dotyczące OS niedojrzałe; *dane dla ramienia T-DXd+placebo nie przedstawiono*;

- Optymalna sekwencja 1. linii wymaga uwzględnienia szeregu czynników:
  - klinicznych: wczesna progresja po leczeniu okołooperacyjnym, obecność przerzutów do mózgu, obciążenie chorobą
  - biologii raka piersi: obecność mutacji *PIK3CA*, aktywność szlaku HER2 (test HER2DX?)
  - ustalenia roli krążących biomarkerów np. ctDNA
  - preferencji pacjenta;

- Rola indukcji z udziałem T-DXd+P (6 cykli) → HP ± HT nieokreślona (badanie DEMETHER)

- Nowe badania: poszukiwanie czynników klinicznych i biologicznych wrażliwości w grupie HR+ i HR-, m.in. PATINA, HER2CLIMB-05, INAVO122.

Algorytm leczenia zaawansowanego HR+/HER2- raka piersi

		mPFS m.
1 L	**IA lub fulwestrant + iCDK4/6** Inawolisyb (GDC-007)+PALBO+FUL z *mPIK3CA* z nawrotem w trakcie lub w ciagu 12 miesięcy od zakończenia adiuwantowej hormonoterapii (1 L.); mPFS 17,2 vs 7,3 m.; HR 0,42; p < 0,0001); mOS 34 vs 27 m HR 0,67; p=0,019[11]	25-28[1-3]
2 L	*PI3K i ESR1 WT*: IA lub FUL ± ewerolimus; IA lub FUL ± abemacyklib *mESR1*: Elacestrant (iCDK >12 m) *PI3K zaburzenia szlaku* (*mPIK3CA*, *AKT1/PTEN$_{alt}$*): FUL + kapiwasertyb; IA lub FUL ± alpelisyb (*mPIK3CA*)	Po iCDK4/6 HT i T: 5,5[4] HT: 2-3[4,5]
3 L	IA lub FUL lub TAM ± T; Elacestrant (*mESR1*); Olaparyb, talazoparyb (*mBRCA*); T-DXd (HER2 low i ultralow); CT (PXL, CAP)	CT: 6-7[6-8] T-DXd: 10[9]
4+ L	CT (PXL, CAP, ERI); Olaparyb, talazoparyb (*mBRCA*); T-DXd (HER2 low i ultralow); Sacituzumab gowitekan (≥2 CT); Pozytywne biomarkery[10]	

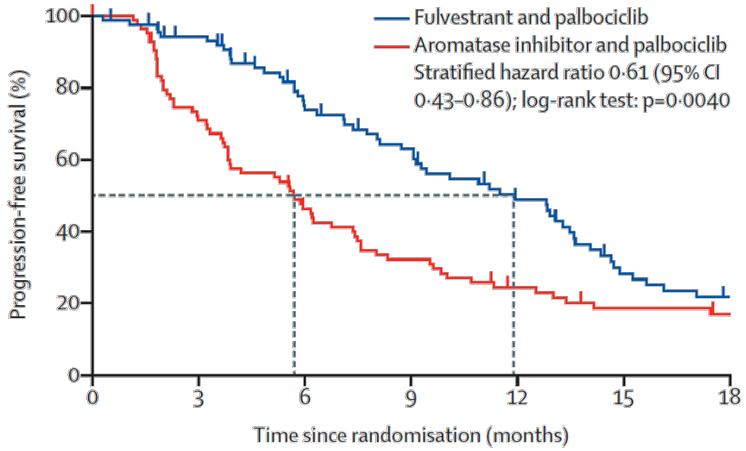
IA, inhibitor aromatazy; FUL, fulwestrant; T, terapie ukierunkowane molekularnie; CT, chemioterapia; PXL, paklitaksel; CAP, kapecytabina; ERI, erybulina; [1]Finn, *NEJM* 2016; [2]Hortobagyi, *Ann Oncol* 2018; [3]Johnston, *Breast Cancer* 2019; [4]Turner, *NEJM* 2023; [5]Bidard, *JCO* 2022; [6]O'Shaughnessy, *JAMA Netw Open* 2021; [7]O'Shaughnessy, *Cancer Res* 2021; [8]Robert, *JCO* 2011; [9]Modi, *NEJM* 2022; [10]TMB-H: pembrolizumab; MSI-H: pembrolizumab, dostarlimab; *NTRK* fuzja: larotrektynib, entrektynib; *RET* fuzja: selperkatynib; [11]Turner, ASCO 2025; abst 1003; Jhaveri, NEJM 2025

ASCO 2024/2025

Schematy ukierunkowane na m*ESR1*

PADA-1; 3 faza
IA+PALBO→ctDNA *mESR1*→ IA+PALBO lub FUL+ PALBO

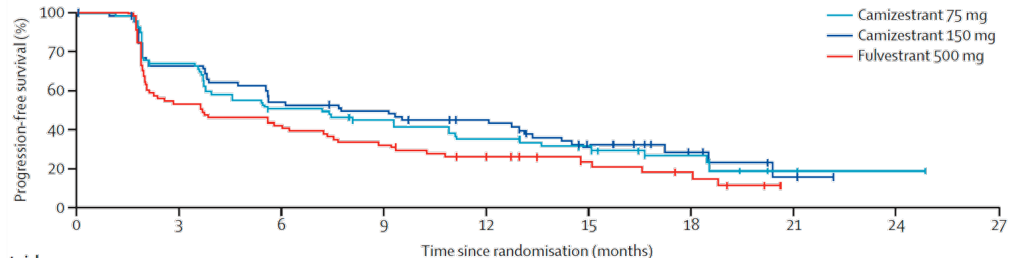
1 linia mBC HR+/HER2-; IA wrażliwe



mPFS 11,9 m. FUL/PALBO vs 5,7 m. IA+PALBO
HR 0,61; 0,43-0,86; p=0,0040

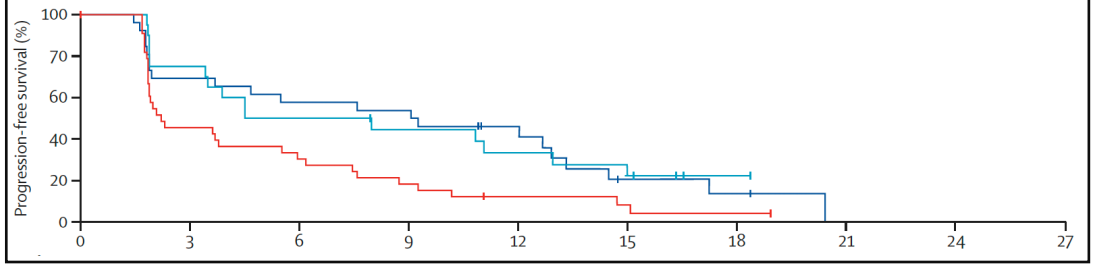
SERENA-2; 2 faza
Progresja na 1. linii HTH mBC

mPFS 7,2 m. kamizestrant 75 mg; 7,7 m. 150 mg vs 3,7 m. FUL
HR 0,59; 0,42-0,82; p=0,017; HR=0,64 (0,46-0,89); p=0,009



E *ESR1* mutations detectable at baseline

	Camizestrant 75 mg (n=22)	Camizestrant 150 mg (n=26)	Fulvestrant 500 mg (n=35)
Patients with events (%)	15 (68%)	21 (81%)	31 (89%)
Median progression-free survival (90% CI), months	6·3 (3·4–12·9)	9·2 (3·7–12·9)	2·2 (1·9–3·8)
HR (90% CI)*	0·33 (0·18–0·58)	0·52 (0·31–0·86)	..



Bidard FC, Lancet Oncol. 2022; Oliveira M, Lancet Oncol. 2024

Modyfikacja leczenia w oparciu o biomarkery molekularne ctDNA *ESR1m* (i nie tylko)…

SERENA-6 study design

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1, N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Continuing AI (anastrozole/letrozole) + CDK4/6i + placebo for camizestrant

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Stratification factors

- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

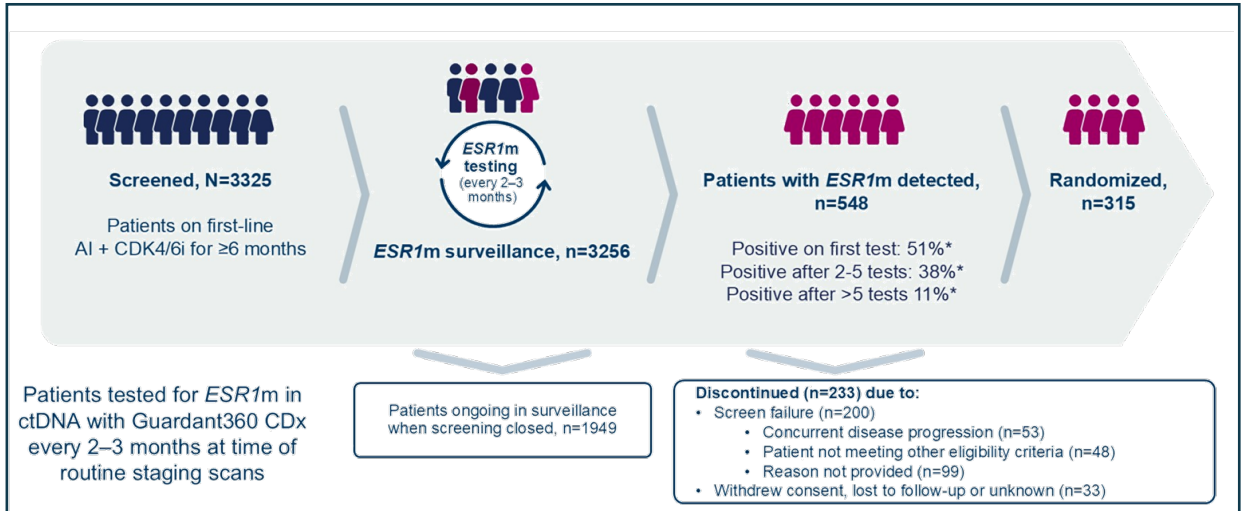
Primary endpoint

PFS by investigator assessment (RECIST v1.1)

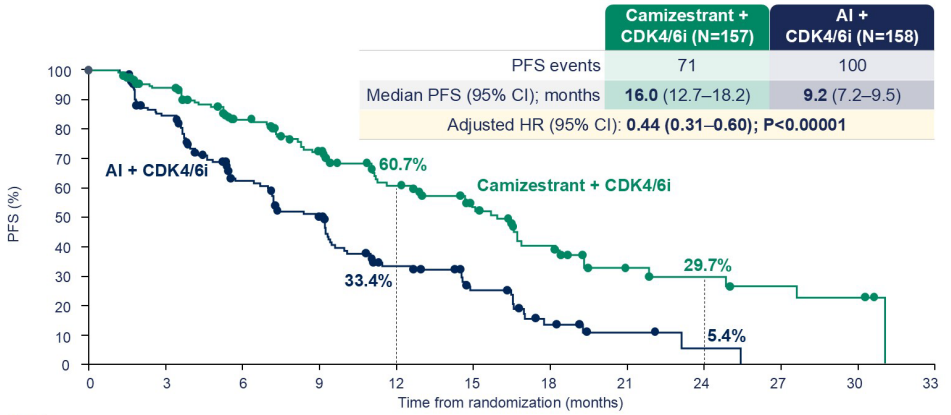
Secondary endpoints

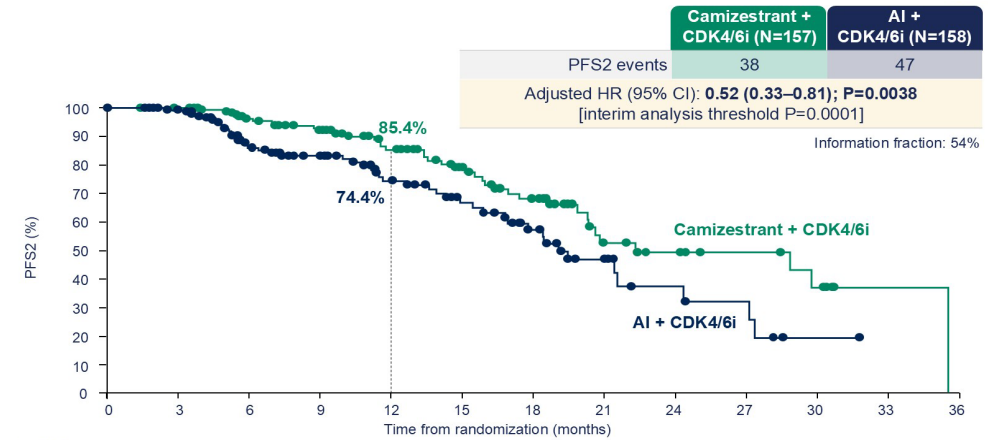
- PFS2**
- OS**
- Safety
- Patient-reported outcomes

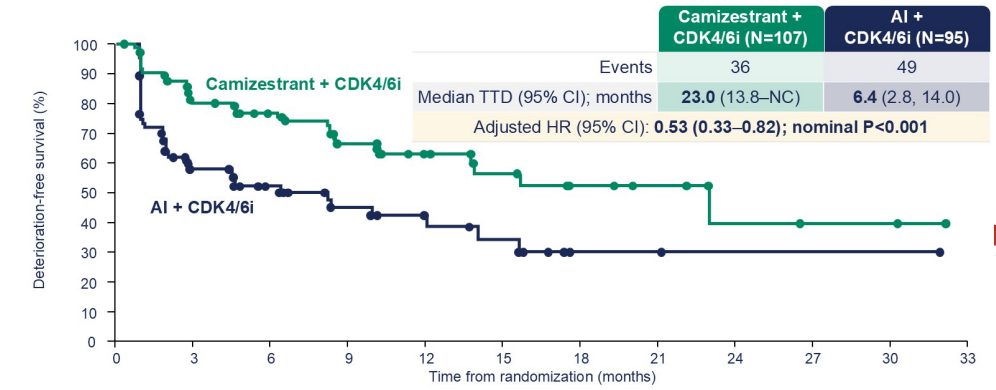
*Pre- or perimenopausal women, and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. **Key secondary endpoint.
OS, overall survival; PFS2, second progression-free survival; qd, once daily dose; R, randomized; RECIST, response evaluation criteria in solid tumors.



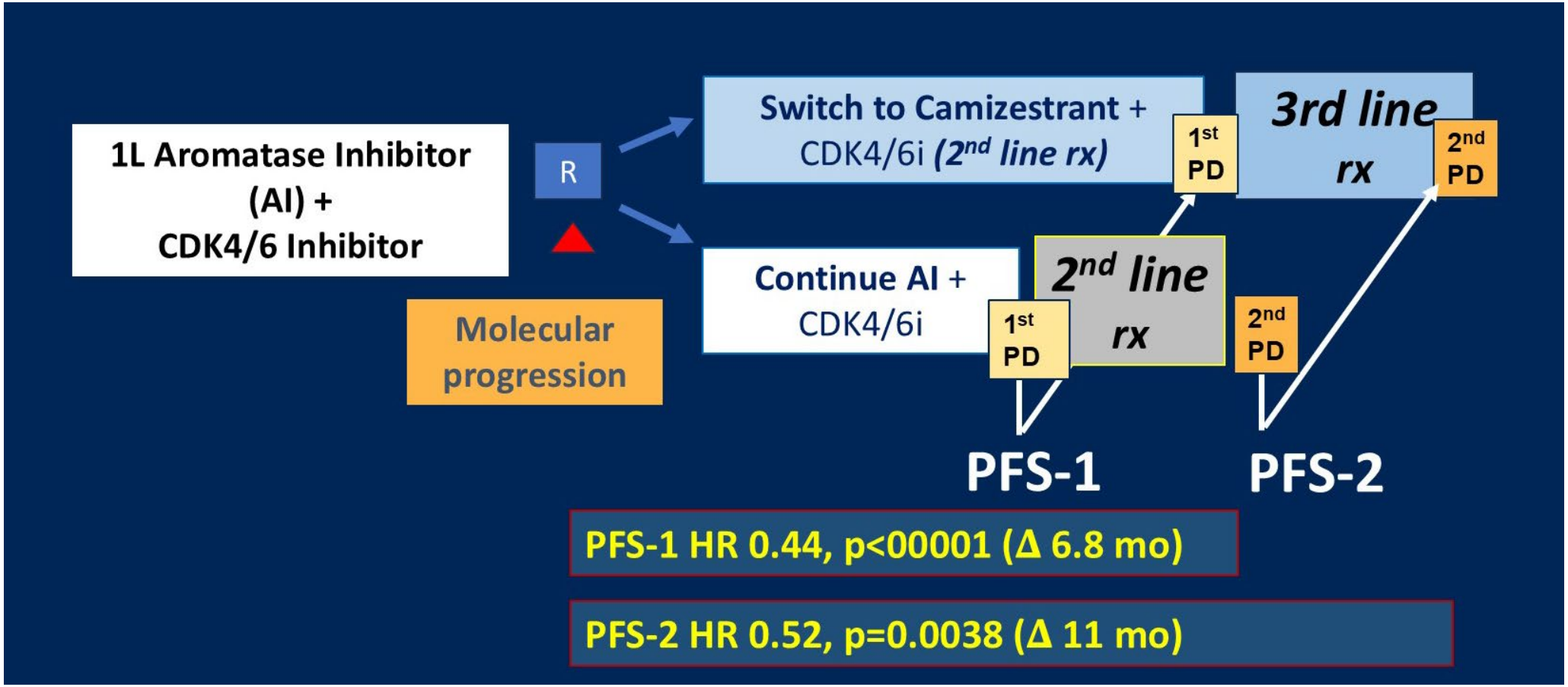
Turner N, J Clin Oncol 43, 2025 (suppl 17; abstr LBA4)







PFS-2 w badaniu SERENA-6



Omówienie DeMichele A, ASCO 2025

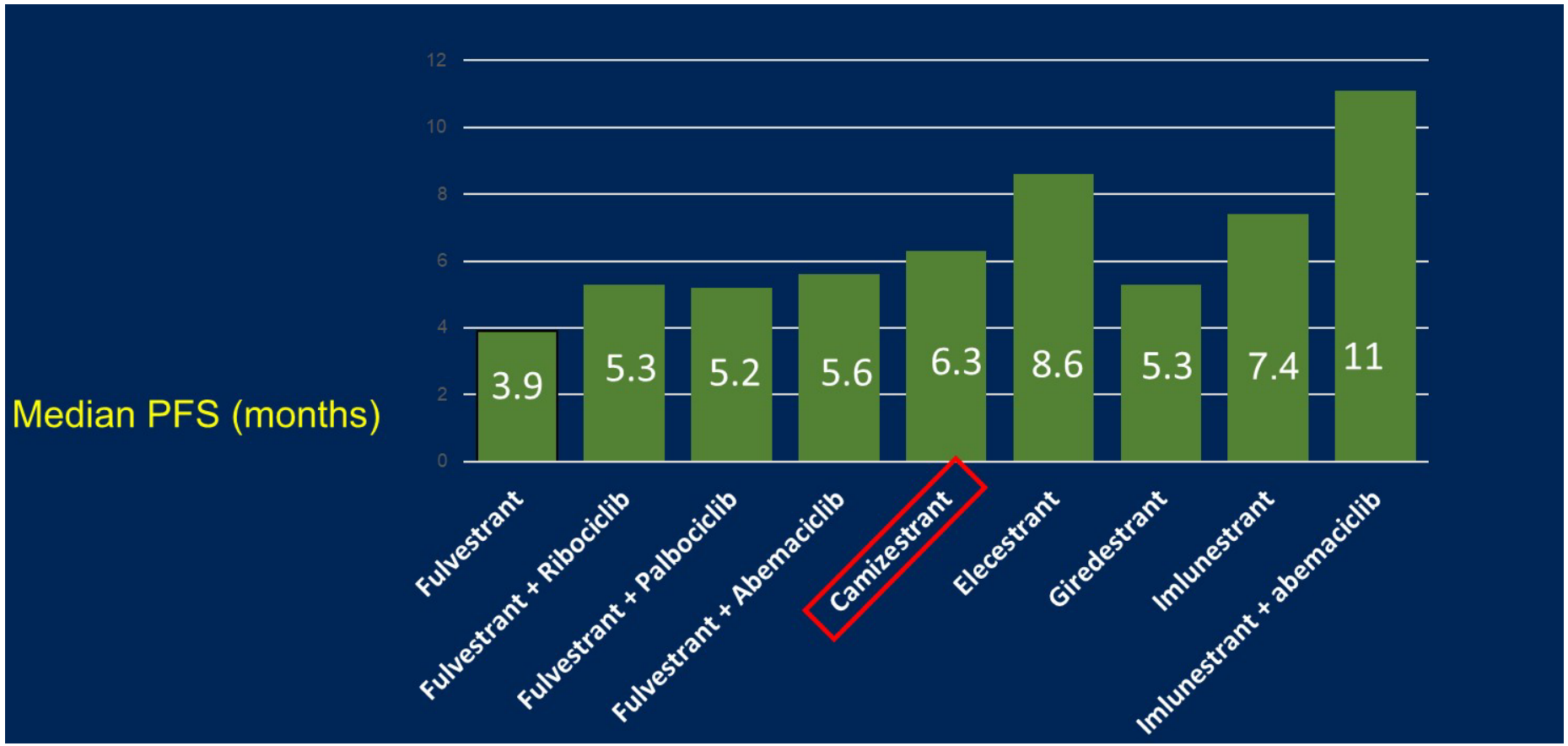
Badanie SERENA-6 wnioski na dzisiaj

- Kamizestrant nie ma jeszcze rejestracji (z pewnością wkrótce rejestracja w oparciu o PFS i QoL) ale
  cyt. *"Is more time on this treatment worth going thougth the testing process if its doesn't help you live longer?"* ale
- zmiana leczenia na podstawie progresji molekularnej (pomiar ctDNA) pozwala wydłużyć PFS-1, odstąpić od kontynuacji nieskutecznego leczenia i uniknąć związanych z nim powikłań, i
- akceptowalny profil bezpieczeństwa.

Dodatkowe czynniki zanim ocena progresji molekularnej zaistnieje w praktyce klinicznnej

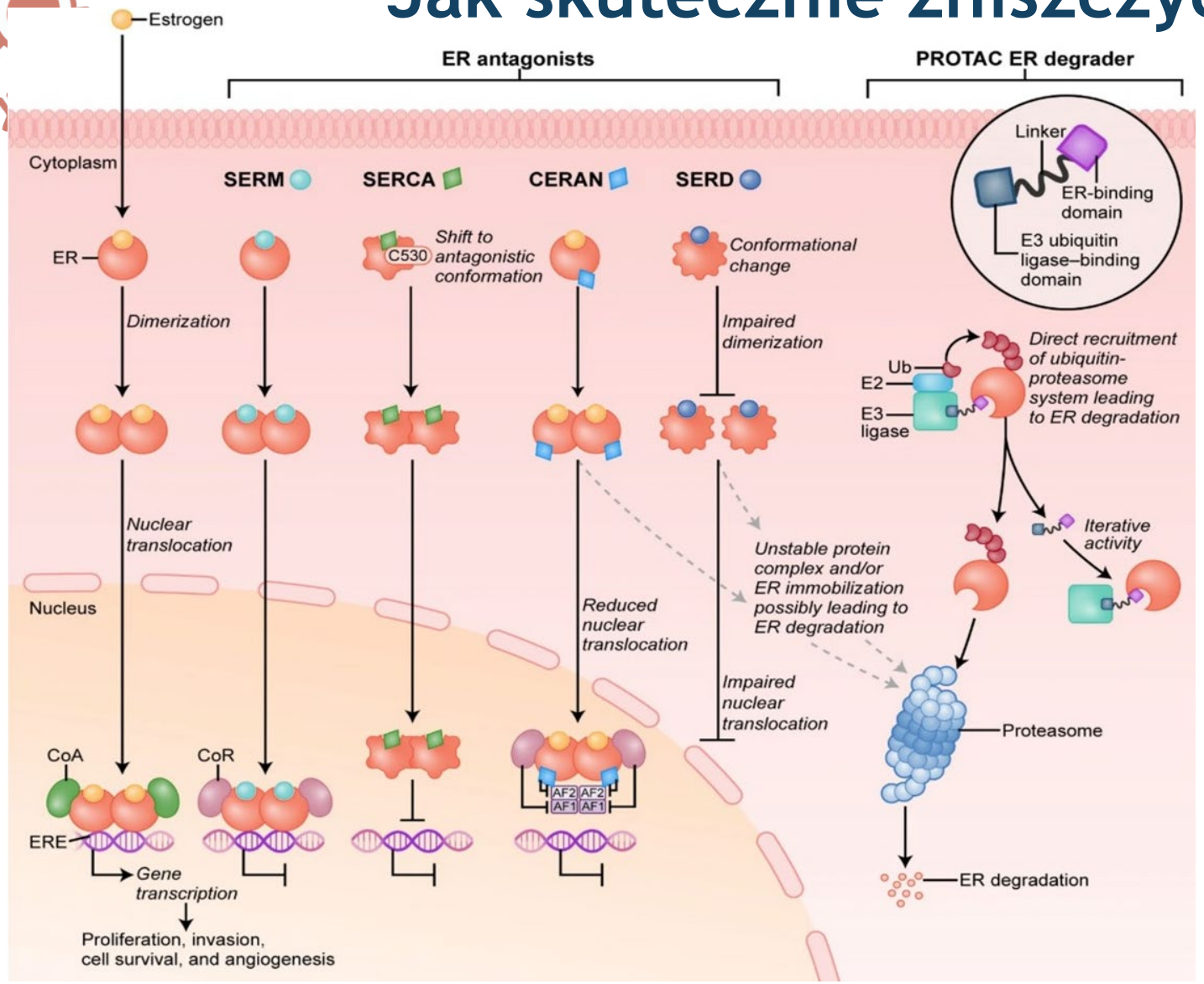
- za wcześnie na ocenę PFS-2 i OS,
- pomiar ctDNA wyzwanie dla praktyki klinicznej, konieczne określenie standardu postępowania u chorych mBC,
- chore dłużej na chemioterapii w związku z wcześniejszym zakończeniem HT (coraz większa rola dla koniugatów); ale możliwe ↓ lub opóźnienie np. w rozwoju przerzutów do mózgu – konieczne dalsze obserwacje,
- wyzwania finansowe i psychologiczne.

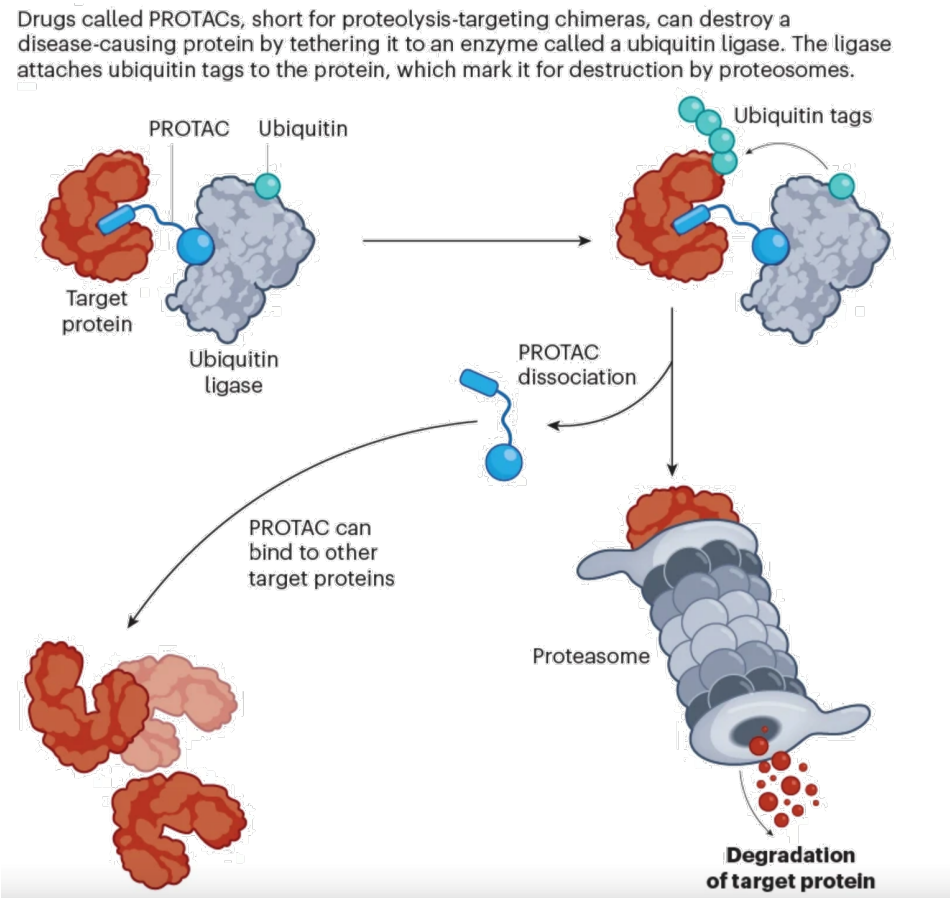
PFS SERDs w 2. linii leczenia *ESR1m* ER+ mBC



Turner, CCR 2020; Kalinsky, JCO 2023; Mayer, JCO 2024; Kalinsky JCO 2024; Oliveira, Lancet Oncology2024; Bidard, JCO 2022; Martin, JCO 2024; Jhaveri, NEJM 2025

Jak skutecznie zniszczyć receptor ER!





Garber K, How protein-slayer drugs could beat some of the cruellest cancers. Nature 2025

Leki z grupy PROTAC w 2. linii

VERITAC-2; 3 faza
Vepdegestrant vs fulvestarnt (po iCDK4/6 30% w całej grupie; z mutacją *ESR1* 74%)

Key Eligibility Criteria
- Age ≥18 years old
- ER+/HER2- advanced or metastatic breast cancer
- Prior therapy:
  - 1 line of CDK4/6i + ET
  - ≤1 additional ET
  - Most recent ET for ≥6 months
  - No prior SERD (eg, fulvestrant, elacestrant)
  - No prior chemotherapy for advanced or metastatic disease
- Radiological progression during or after the last line of therapy

Randomization (1:1)

28-day Treatment Cycles

Vepdegestrant (n=313)
200 mg orally (once daily)

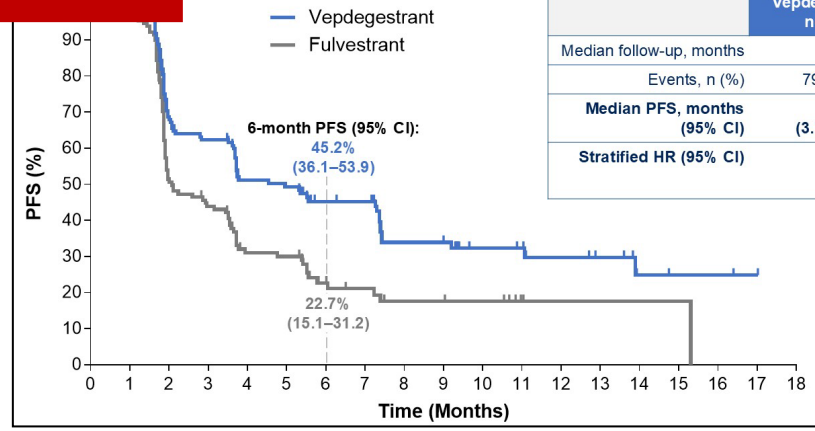
Fulvestrant (n=311)
500 mg IM
(days 1 and 15 of cycle 1; day 1 of subsequent cycles)

Primary Endpoint:
- PFS by BICR in
  - *ESR1*m population
  - All patients

Secondary Endpoints:
- OS (key secondary)
- CBR and ORR by BICR
- AEs

Stratification Factors:
- *ESR1* mutation[a] (yes vs no)
- Visceral disease (yes vs no)

mESR1



	Vepdegestrant n=136	Fulvestrant n=134
Median follow-up, months	7.4	6.0
Events, n (%)	79 (58)	95 (71)
Median PFS, months (95% CI)	**5.0 (3.7–7.4)**	**2.1 (1.9–3.5)**
Stratified HR (95% CI)	**0.57 (0.42–0.77)**	
	2-sided *P*<0.001	

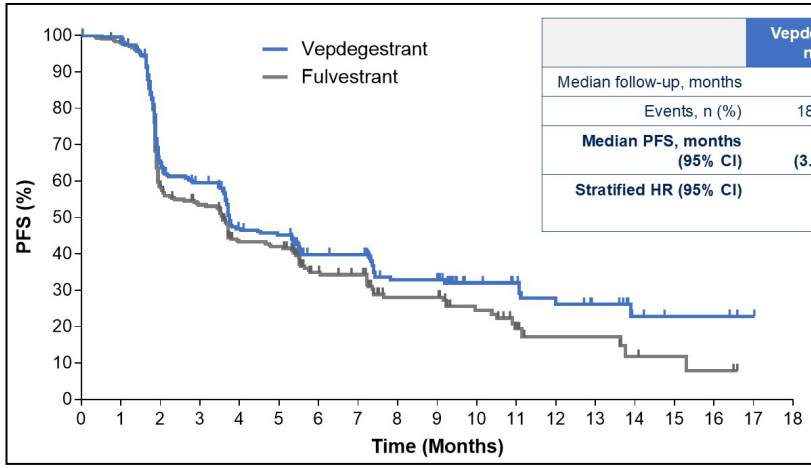
Overview

TEAEs, %	Vepdegestrant (n=312)	Fulvestrant (n=307)
Any grade	87	81
Grade ≥3	23	18
Serious	10	9
Leading to treatment discontinuation	3	1
Leading to dose reduction	2	NA
TRAEs, %		
Any grade	57	40
Grade ≥3	8	3

QT prolongation
- TEAEs: vepdegestrant,10%; fulvestrant, 1%
- A QT interval sub-study (n=88) confirmed a mild increase (11.1 ms) from baseline in mean QTcF, with upper 90% CI (13.7 ms) <20 ms,[f] **indicating no large QT-prolonging effect**

TEAEs in >10% of Patients in Either Group

TEAE, %	Vepdegestrant (n = 312) Any Grade	Vepdegestrant (n = 312) Grade 3/4	Fulvestrant (n = 307) Any Grade	Fulvestrant (n = 307) Grade 3/4
Fatigue[a]	27	1	16	1
ALT increased[b]	14	1	10	1
AST increased[b]	14	1	10	3
Nausea	13	0	9	1
Anemia[b, c]	12	2	8	3
Neutropenia[d]	12	2[e]	5	1[e]
Back pain	11	1	7	<1
Arthralgia	11	1	11	0
Decreased appetite	11	<1	5	0



	Vepdegestrant n=313	Fulvestrant n=311
Median follow-up, months	7.4	7.2
Events, n (%)	186 (59)	198 (64)
Median PFS, months (95% CI)	**3.7 (3.6–5.3)**	**3.6 (2.2–3.8)**
Stratified HR (95% CI)	**0.83 (0.68–1.02)**	
	2-sided *P*=0.07	

Hamilton E, J Clin Oncol 43, 2025 (suppl 17; abstr LBA1000)

Schematy w 2. linii po ±iCDK4/6; brak rejestracji

EMBER-3; 3 faza

Key Eligibility Criteria

- Men and Pre[a]/Postmenopausal women with ER+, HER2- ABC
- Prior adjuvant therapy: recurrence on or within 12 mo of completion of AI ± CDK4/6i
- Prior therapy for ABC: progression on first-line AI ± CDK4/6i
- No other therapy for ABC

(N = 874)

R 1:1:1[b]

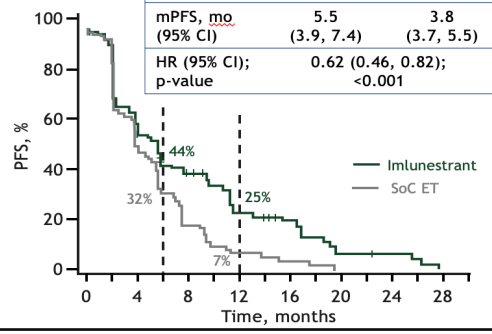
- **Arm A** Imlunestrant 400 mg QD
- **Arm B** SOC ET[b] (IC: fulvestrant or exemestane)
- **Arm C[c]** Imlunestrant 400 mg QD + abemaciclib[b]

- **Primary endpoint: investigator-assessed PFS**
  - Arms A vs B in patients with *ESR1*m[e]
  - Arms A vs B in all patients
  - Arms C vs A in all[f] patients

mESR 1

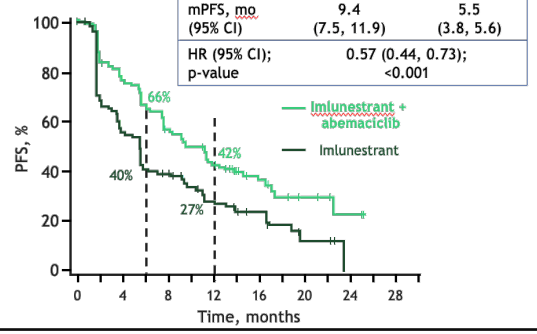
Ramie A vs B

	Imlunestrant (n=138)	SoC ET (n=118)
Events, n	109	102
mPFS, mo (95% CI)	5.5 (3.9, 7.4)	3.8 (3.7, 5.5)
HR (95% CI); p-value	0.62 (0.46, 0.82); <0.001	



Ramie C vs A

	Imlunestrant + abemaciclib n=213	Imlunestrant (n=213)
Events, n	114	149
mPFS, mo (95% CI)	9.4 (7.5, 11.9)	5.5 (3.8, 5.6)
HR (95% CI); p-value	0.57 (0.44, 0.73); <0.001	



MA.40 FINER, 3 faza

Study population:

- Stage IV ER+/HER-2 negative breast cancer
- Prior line of systemic treatment with CDK 4/6i and AI
- ECOG PS 0–1
- Measurable or evaluable disease

CDK 4/6i and AI progression → randomization ≦ 4 weeks

cfDNA for Stratification *(FoundationOne®Liquid CDx)*

N=250

R 1:1

- **Ipatasertib + Fulvestrant** 400 mg PO day 1-21
- **Placebo + Fulvestrant** Placebo PO day 1-21

Stratification

- *PIK3CA/PTEN/AKT* altered vs wild type/unknown
- Primary versus secondary endocrine resistance

Primary endpoint

- PFS by RECIST v1.1 in intent to treat (ITT) population

Key secondary endpoints

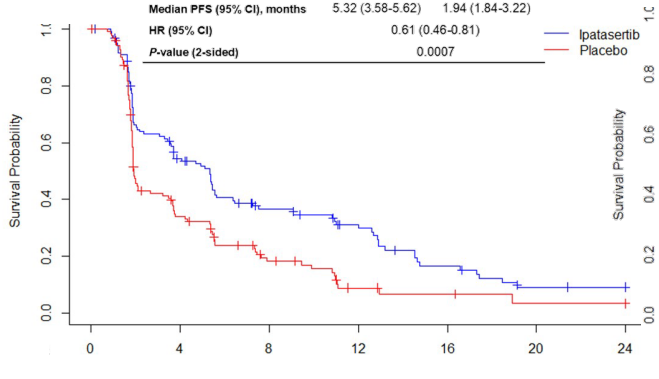
- PFS
  - by BICR in ITT
  - in AKT pathway altered cohort
- OS
- AEs
- QoL
- Health Economics
- Correlative

Today, we will present the final PFS analysis from ITT and biomarker altered cohort

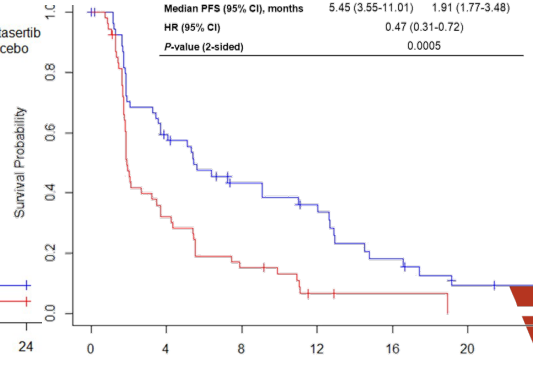
Fulvestrant 500 mg IM days 1 and 14 and 28 then q28 days

AKT$_{alt}$

	IPAT arm n=125	PBO arm n=125
Median follow-up: 15.2 months		
Median PFS (95% CI), months	5.32 (3.58-5.62)	1.94 (1.84-3.22)
HR (95% CI)	0.61 (0.46-0.81)	
P-value (2-sided)	0.0007	



	IPAT arm n=57	PBO arm n=54
Median follow-up: 15.2 months		
Median PFS (95% CI), months	5.45 (3.55-11.01)	1.91 (1.77-3.48)
HR (95% CI)	0.47 (0.31-0.72)	
P-value (2-sided)	0.0005	



Jhaveri K, NEJM 2024; Curigliano G, J Clin Oncol 43, 2025 (suppl 16; abstr 1001); Chia S, J Clin Oncol 43, 2025 (suppl 17; abstr LBA1005)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

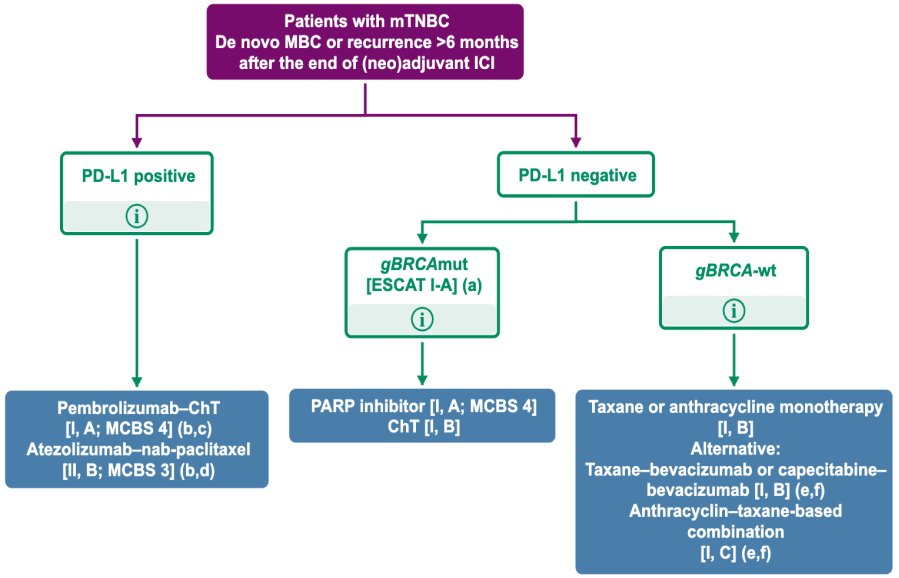
Search for abstracts, Guidelines, Meetings | Search

ESMO Living Guideline

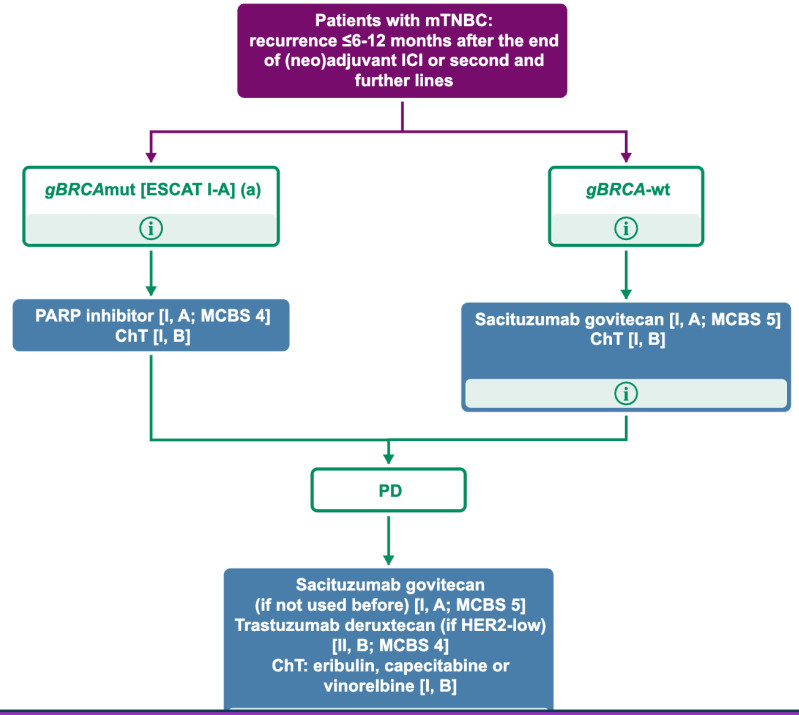
Metastatic Breast Cancer

ESMO-MCBS and ESCAT | Glossary

De Novo MBC or Recurrence >6-12 Months After the End of (Neo)Adjuvant ICI



Recurrence ≤6-12 Months After the End of (Neo)Adjuvant ICI or Second and Further Lines



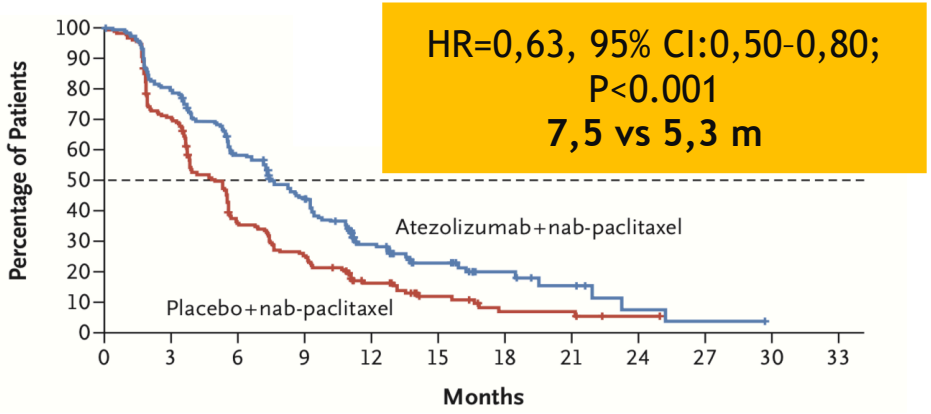
49% nie otrzymuje 2. linii leczenia; 34% umiera przed 2. linią leczenia (dane RWE)

https://www.esmo.org/guidelines/living-guidelines; Punie, The Oncologist 2025

Immunoterapia i chemioterapia

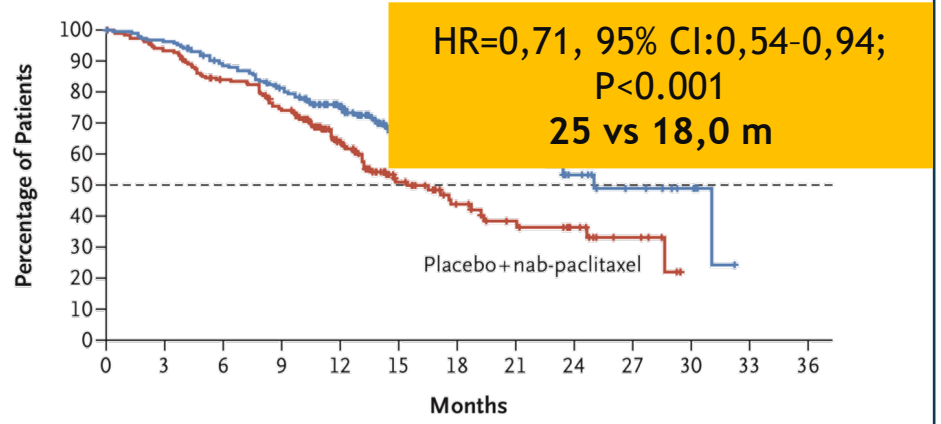
IMpassion130; faza III (atezolizumab + nab-P vs placebo + nab-P)

PFS



HR=0,63, 95% CI:0,50-0,80; P<0.001
7,5 vs 5,3 m

OS

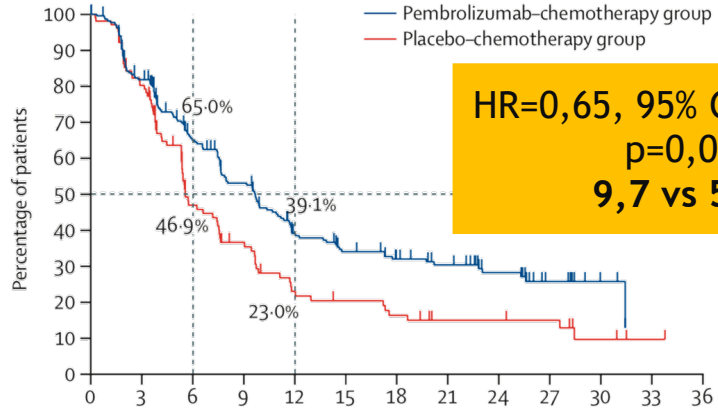


HR=0,71, 95% CI:0,54-0,94; P<0.001
25 vs 18,0 m

In case of PD-L1 immune cell positivity (Ventana SP142), atezolizumab [ESMO-MCBS v1.1 score: 3; EMA approved, not FDA approved] when the disease-free interval is ≥12 months in countries where this indication is approved [II, B].

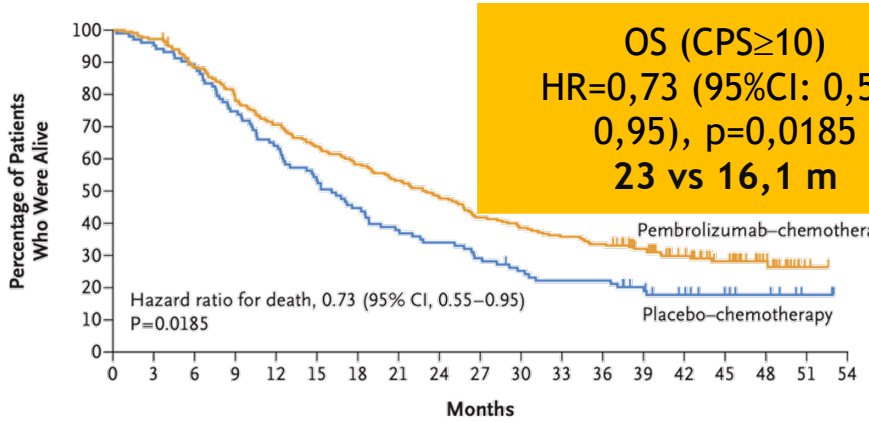
KEYNOTE-355; faza III (pembrolizumab + CHT vs placebo + CHT)

PFS



HR=0,65, 95% CI:0,49-0,86; p=0,0012
9,7 vs 5,6 m

OS



OS (CPS≥10)
HR=0,73 (95%CI: 0,55-0,95), p=0,0185
23 vs 16,1 m

In case of combined positive score ≥10, pembrolizumab [ESMO-MCBS v1.1 score: 4] plus paclitaxel, nab-paclitaxel or carboplatin-gemcitabine when the disease-free interval is ≥6 months [I, A].

Cortes J, Lancet 2020; Cortes J, NEJM 2022; Cescon DW, J Natl Cancer Inst 2023; Schmid P, NEJM 2018; Schmid P, Lancet Oncol 2020; Adams S, Ann Oncol 2020

Badanie ASCENT-04/KEYNOTE-D19; faza 3

Previously untreated, locally advanced unresectable, or metastatic TNBC[a]:

- PD-L1-positive (CPS ≥ 10 by the 22C3 assay[b])
- ≥ 6 months since treatment in curative setting (prior anti-PD-[L]1 use allowed)

N = 443

R 1:1

SG + pembro[d]
(SG 10 mg/kg IV, days 1 and 8 of 21-day cycles; pembro 200 mg, day 1 of 21-day cycles)
n = 221

Chemo* + pembro[d]
(paclitaxel 90 mg/m² OR nab-paclitaxel 100 mg/m² on days 1, 8, & 15 of 28-day cycles, OR gemcitabine 1000 mg/m² + carboplatin AUC 2 on days 1 & 8 of 21-day cycles; pembro 200 mg on day 1 of 21-day cycles)
n = 222

**Eligible patients who experienced BICR-verified disease progression were offered to cross-over to receive 2L SG monotherapy*

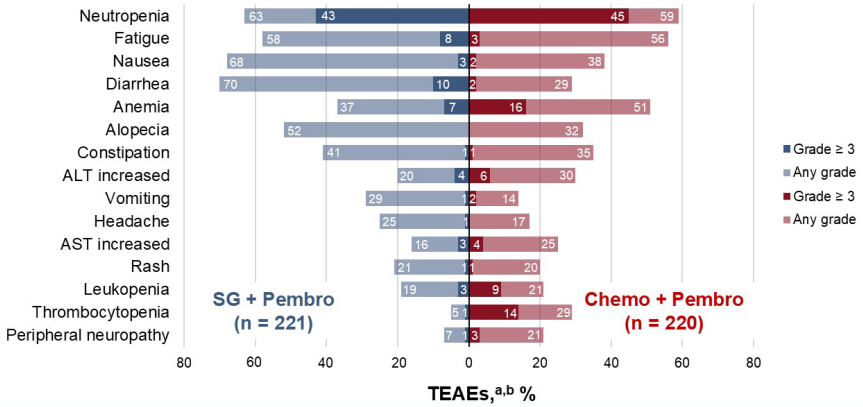
All treatment, including SG or chemo, was continued until BICR-verified disease progression or unacceptable toxicity

End points

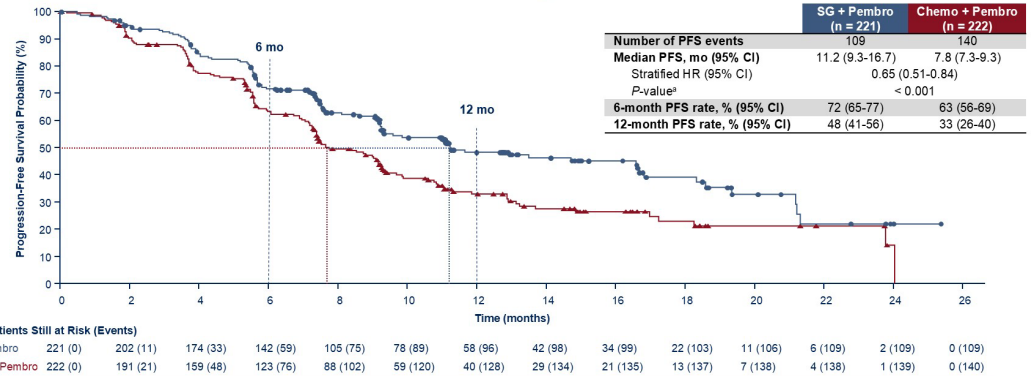
Primary
- PFS by BICR[e]

Secondary
- OS
- ORR, DOR by BICR[e]
- Safety
- QoL

Stratification factors:
- De novo mTNBC[c] vs recurrent within 6 to 12 months from completion of treatment in curative setting vs recurrent > 12 months from completion of treatment in curative setting
- US/Canada/Western Europe vs the rest of the world
- Prior exposure to anti-PD-(L)1 (yes vs no)

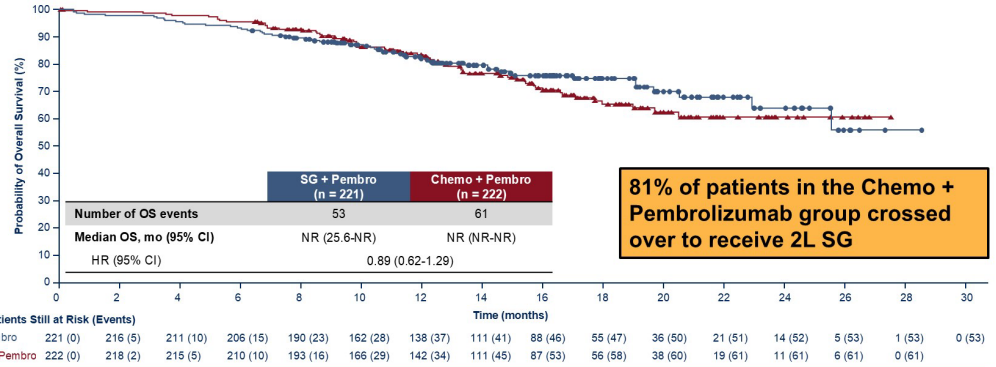


- Safety profiles consistent with known safety profiles of each drug
- No new safety signals
- Lower rates of TEAEs leading to treatment discontinuation or dose reduction



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	109	140
Median PFS, mo (95% CI)	11.2 (9.3-16.7)	7.8 (7.3-9.3)
Stratified HR (95% CI)	0.65 (0.51-0.84)	
P-value[a]	< 0.001	
6-month PFS rate, % (95% CI)	72 (65-77)	63 (56-69)
12-month PFS rate, % (95% CI)	48 (41-56)	33 (26-40)

SG + pembro demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo + pembro by BICR analysis, with a 35% reduction in risk of disease progression or death



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of OS events	53	61
Median OS, mo (95% CI)	NR (25.6-NR)	NR (NR-NR)
HR (95% CI)	0.89 (0.62-1.29)	

81% of patients in the Chemo + Pembrolizumab group crossed over to receive 2L SG

OS data were immature (maturity rate, 26%), however, a positive trend in improvement was observed for SG + pembro vs chemo + pembro, despite the high cross-over rate

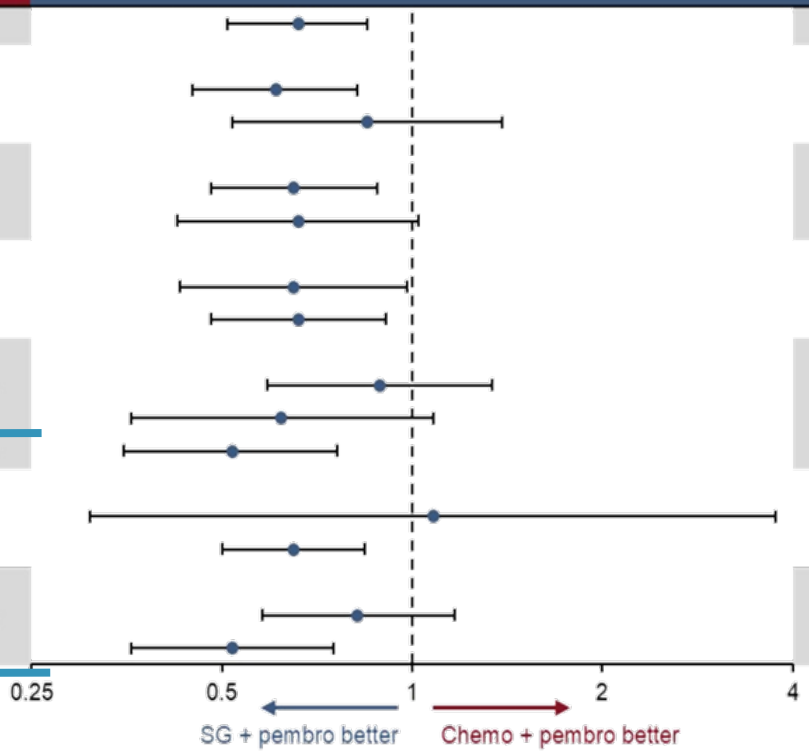
Tolaney S, J Clin Oncol 43, 2025 (suppl 17; abstr LBA109)

Potencjalnie nowa 1. linia leczenia ale dane dla OS niedojrzałe

Badanie ASCENT-04/KEYNOTE-D19; PFS BICR

Co mnie martwi co mnie cieszy…

	SG + Pembro		Chemo + Pembro		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	n	Median PFS, mo (95% CI)	n	Median PFS, mo (95% CI)		
ITT population	221	**11.2** (9.3-16.7)	222	**7.8** (7.3-9.3)		0.66 (0.51-0.85)
Age group						
< 65 yr	163	**11.3** (9.3-16.8)	165	**7.5** (7.0-9.2)		0.61 (0.45-0.82)
≥ 65 yr	58	**11.1** (7.5-NR)	57	**9.3** (7.3-13.2)		0.85 (0.52-1.39)
ECOG PS						
0	156	**12.9** (9.3-16.8)	154	**8.7** (7.3-9.9)		0.65 (0.48-0.88)
≥ 1	65	**9.2** (7.5-18.3)	67	**7.5** (5.6-9.3)		0.66 (0.43-1.03)
Geographic region						
US/Canada/Western Europe	85	**11.7** (7.5-19.4)	85	**7.4** (5.7-9.9)		0.65 (0.43-0.98)
Rest of the world	136	**11.2** (9.3-16.7)	137	**8.4** (7.4-9.3)		0.66 (0.48-0.91)
Curative treatment-free interval						
De novo	75	**8.1** (7.3-18.6)	75	**7.7** (6.1-11.9)		0.89 (0.59-1.34)
Recurrent 6-12 mo	40	**9.9** (5.7-16.8)	40	**7.2** (4.4-9.1)		0.62 (0.36-1.08)
Recurrent > 12 mo	106	**16.6** (11.0-NR)	107	**8.7** (7.3-10.8)		0.52 (0.35-0.76)
Prior (neo)adjuvant anti-PD-(L)1 therapy						
Yes	9	**7.5** (0.9-NR)	11	**6.6** (2.1-NR)		1.08 (0.31-3.75)
No	212	**11.7** (9.3-16.8)	211	**7.8** (7.4-9.3)		0.65 (0.50-0.84)
Chemo selected prior to randomization						
Taxane	116	**11.1** (8.6-16.7)	114	**9.2** (7.2-12.9)		0.82 (0.58-1.17)
Gemcitabine/Carboplatin	105	**11.3** (9.2-21.2)	108	**7.4** (6.9-9.0)		0.52 (0.36-0.75)

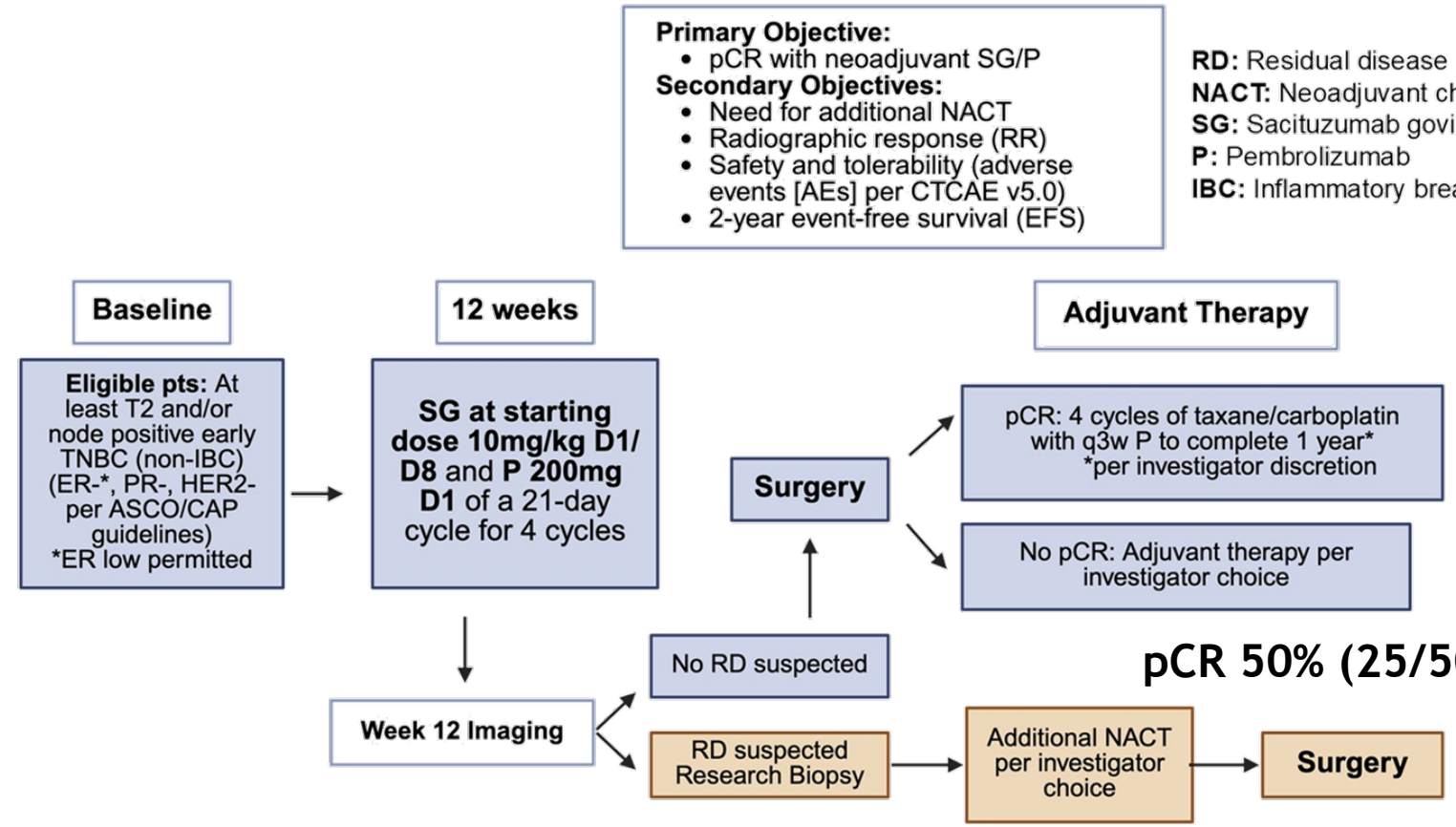


PFS benefit was observed for SG + pembro vs chemo + pembro across prespecified subgroups

Tolaney S, J Clin Oncol 43, 202abstr LBA109)

Bdanie NeoSTAR (ramię A2)[1]

Wczesny rak piersi!



pCR 32% (16/50) SG+P

pCR 50% (25/50) NACT głównie Cb i T)

[1]Ramię A1 4xSG pCR 30%: Sping Ann Oncol 2024

XXIV SPOTKANIE Po ASCO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer

F. Cardoso,[1,2] S. Parke,[3] D.J. Brennan,[4] P. Briggs,[5] G. Donders,[6,7] N. Panay,[8] N. Haseli-Mashhadi,[9] M. Block,[10] C. Caetano,[11] M. Francuski,[3] C. Haberland,[3] K. Laapas,[12] C. Seitz,[3,13] and L. Zuurman[11]

ORIGINAL ARTICLE

First-Line Camizestrant for Emerging *ESR1*-Mutated Advanced Breast Cancer

F.-C. Bidard,[1] E.L. Mayer,[2] Y.H. Park,[3] W. Janni,[4] C. Ma,[5] M. Cristofanilli,[6] G. Bianchini,[7] K. Kalinsky,[8] H. Iwata,[9] S. Chia,[10] P.A. Fasching,[11] A. Brufsky,[12] Z. Nowecki,[13] J. Pascual,[14] L. Moreau,[15] S.-C. Chen,[16] N. Karadurmus,[17] E.N. Gal-Yam,[18] K.H. Jung,[19] S. Pernas,[20] S. McClain,[21] W. He,[22] T. Klinowska,[23] C. Huang-Bartlett,[21] and N.C. Turner,[24] for the SERENA-6 Study Group*

ORIGINAL ARTICLE

Vepdegestrant, a PROTAC Estrogen Receptor Degrader, in Advanced Breast Cancer

M. Campone,[1] M. De Laurentiis,[2] K. Jhaveri,[3,4] X. Hu,[5] S. Ladoire,[6] A. Patsouris,[7] C. Zamagni,[8] J. Cui,[9] M. Cazzaniga,[10] T. Cil,[11] K.J. Jerzak,[12] C. Fuentes,[13] T. Yoshinami,[14] A. Rodriguez-Lescure,[15] A. Sezer,[16] A. Fontana,[17] V. Guarneri,[18,19] A. Molckovsky,[20] M.-A. Mouret-Reynier,[21] U. Demirci,[22] Y. Zhang,[23] O. Valota,[24] D.R Lu,[25] M. Martignoni,[24] J. Parameswaran,[26] X. Zhi,[26] and E.P. Hamilton,[27] for the VERITAC-2 Study Group*

Miłego letniego wypoczynku!