XXIV SPOTKANIE Po ASCO

Zaawansowany rak piersi
ASCO 2025

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Oświadczenie o konflikcie interesów

- Honoraria za udział w komitetach doradczych: Genetech, Lilly, Roche, Novartis, Mylan, Pfizer, Glaxo, AstraZeneca, Gilead
- Honoraria za wykłady: Lilly, Roche, Novartis, Mylan, Pfizer, AstraZeneca, Gilead
- Honoraria za prowadzenie badań klinicznych: Novartis, Lilly, Astra, Roche
- Granty na wyjazdy na konferencje naukowe: Roche, Pfizer, Astra, Gilead

DESTINY-Breast09

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

- 51% de novo MBC, 54% HR+, 82% IHC +3
- Chore z nawrotem: 80-85% NAC: **~58% TZB; ~ 15% PTZ, 2% T-DM1**
- Jednoczesna HT w HR +: 13,5% w ramieniu z T-DxD, 38,3% w ramieniu z THP

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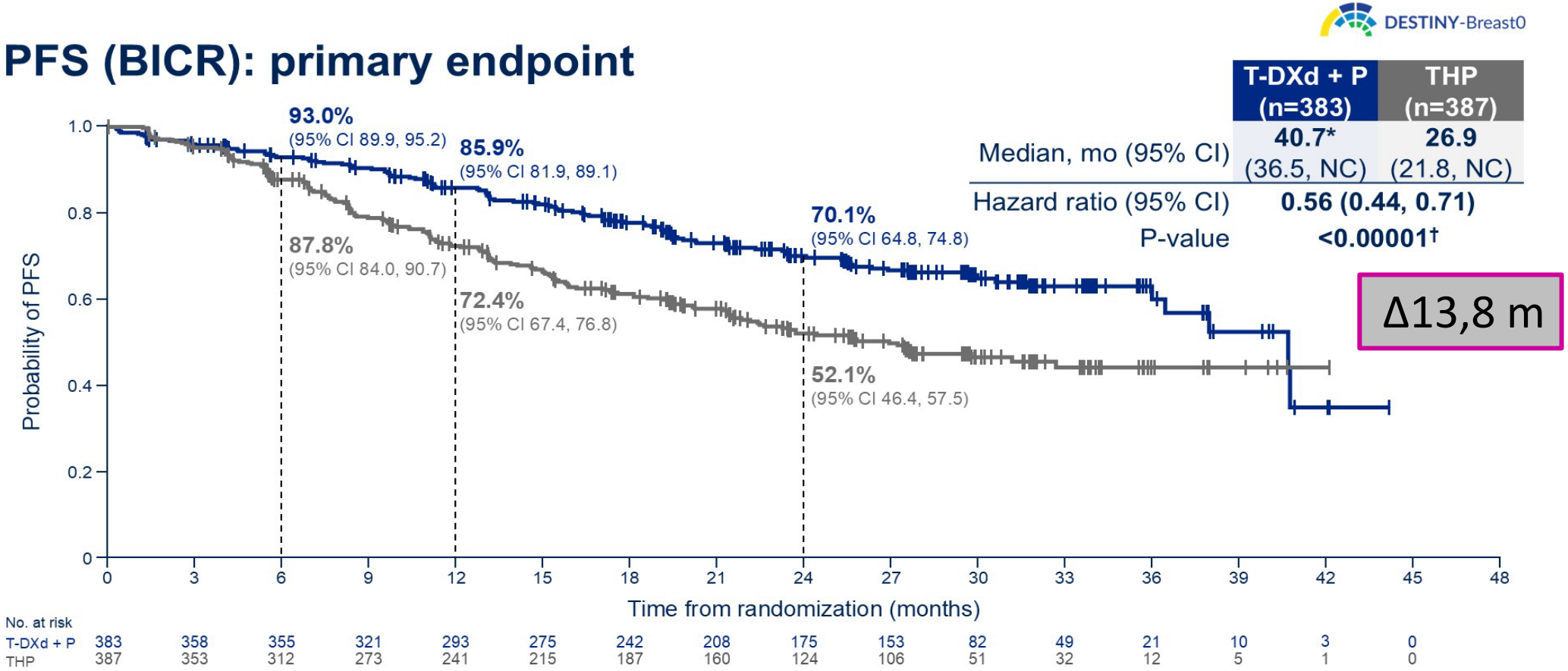

Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

- Prawdopodobne dalsze wydłużenie mPFS w ramieniu z T-DXd + P (40% chorych nadal otrzymuje TDXd
- **Relatywnie niewiele chorych otrzymało w leczeniu okołooperacyjnym anty-HER2**

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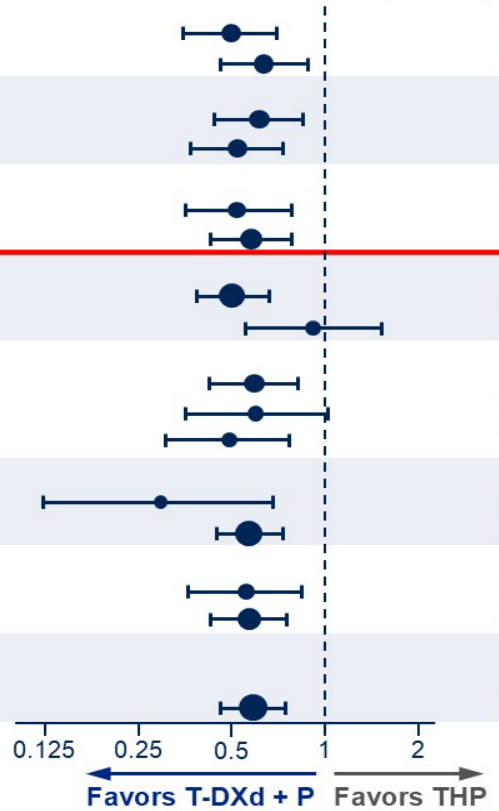
PFS (BICR): subgroup analyses

	No. of events / no. of patients		mPFS, months (95% CI)		Hazard ratio (95% CI)
	T-DXd + P	THP	T-DXd + P	THP	
Prior treatment status					
De novo	52/200	85/200	NC (36.5, NC)	31.2 (23.5, NC)	0.49 (0.35, 0.70)
Recurrent	66/183	87/187	38.0 (26.9, NC)	22.5 (18.1, NC)	0.63 (0.46, 0.87)
HR status					
Positive	65/207	87/209	38.0 (36.0, NC)	27.7 (22.4, NC)	0.61 (0.44, 0.84)
Negative	53/176	85/178	40.7 (40.7, NC)	22.6 (17.3, 32.7)	0.52 (0.37, 0.73)
***PIK3CA* mutation status**					
Detected	41/116	64/121	36.0 (29.7, NC)	18.1 (15.1, 25.6)	0.52 (0.35, 0.77)
Not detected	76/266	108/266	40.7 (38.0, NC)	32.7 (24.4, NC)	0.57 (0.43, 0.77)
Age at randomization					
<65 years	90/315	139/315	40.7 (36.5, NC)	27.4 (22.4, NC)	0.50 (0.38, 0.65)
≥65 years	28/68	33/72	27.6 (14.9, NC)	21.5 (13.9, NC)	0.92 (0.55, 1.51)
Geographical region					
Asia	62/188	87/191	40.7 (36.5, NC)	27.2 (21.5, NC)	0.60 (0.43, 0.83)
Western Europe and North America	27/87	31/78	36.0 (30.6, NC)	31.2 (15.8, NC)	0.60 (0.35, 1.01)
Rest of World	29/108	54/118	NC (38.0, NC)	24.4 (14.8, NC)	0.48 (0.30, 0.76)
Brain metastases at baseline					
Present	10/25	15/22	31.8 (18.5, NC)	9.5 (5.6, 13.3)	0.30 (0.12, 0.68)
Not present	108/358	157/365	40.7 (36.5, NC)	27.6 (22.6, NC)	0.58 (0.45, 0.74)
Prior exposure to anti-HER2 therapies					
Yes	39/115	51/112	38.0 (26.9, NC)	21.5 (15.3, NC)	0.55 (0.36, 0.83)
No	79/268	121/275	40.7 (36.5, NC)	27.6 (22.5, NC)	0.56 (0.42, 0.74)
Prior exposure to pertuzumab					
Yes	5/31	12/26	40.8 (25.4, NC)	19.8 (7.5, NC)	NC
No	113/352	160/361	40.7 (36.0, NC)	27.4 (22.4, NC)	0.61 (0.48, 0.77)



Size of circle is proportional to the number of events
BICR, blinded independent central review;
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor;
NC, not calculable; P, pertuzumab;
(m)PFS, (median) progression-free survival;
T-DXd, trastuzumab deruxtecan;
THP, taxane + trastuzumab + pertuzumab

PFS benefit with T-DXd + P vs THP was consistently observed across prespecified subgroups, including stratification factors

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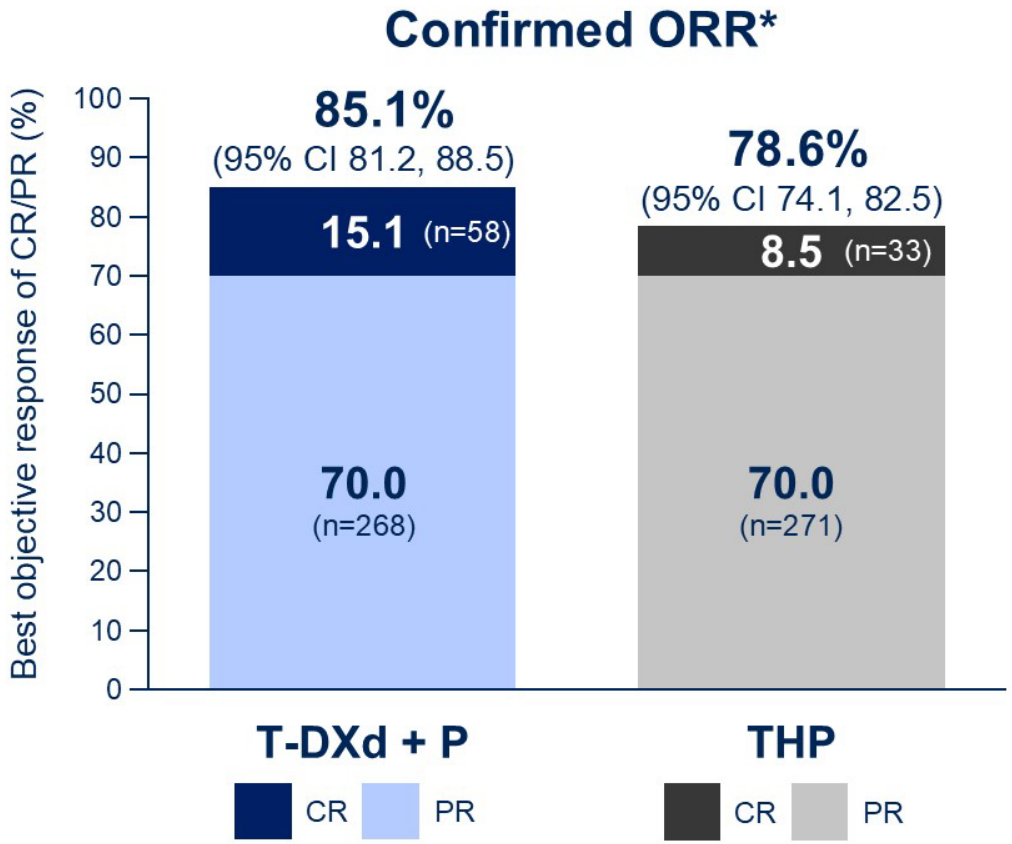
ORR and DOR (BICR)



Δ 6,5 %

Δ 12,8 m

	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

Response rates were greater with T-DXd + P vs THP and were durable

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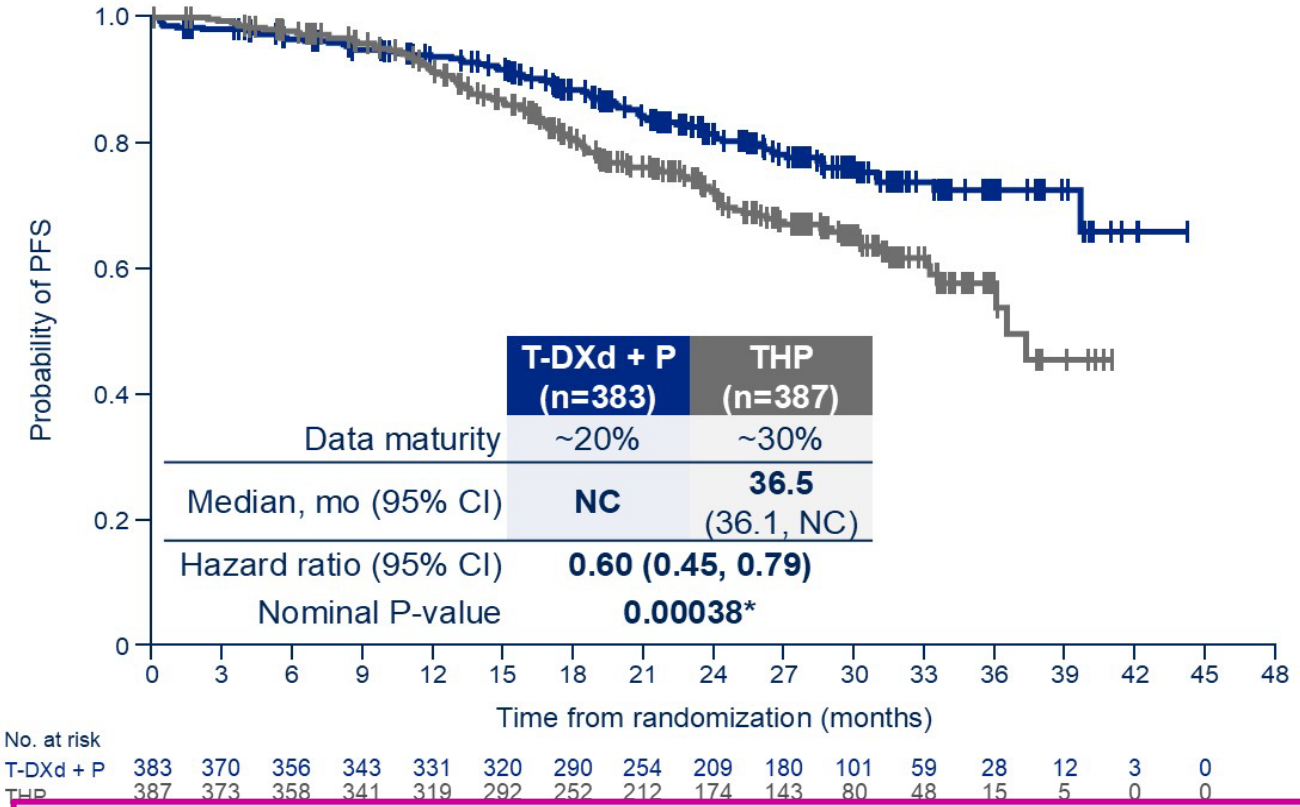
PFS2 (investigator assessment) and post-trial treatments



	T-DXd + P (n=383)	THP (n=387)
Data maturity	~20%	~30%
Median, mo (95% CI)	**NC**	**36.5** (36.1, NC)
Hazard ratio (95% CI)	**0.60 (0.45, 0.79)**	
Nominal P-value	**0.00038***	

	T-DXd + P (n=383)	THP (n=387)
Received post-discontinuation therapy in second line, n (%)†	124 (32.4)	181 (46.8)
Targeted therapy, n (%)†	111 (29.0)	166 (42.9)
T-DXd	6 (1.6)	39 (10.1)
T-DM1	7 (1.8)	47 (12.1)
Trastuzumab-containing regimen‡	78 (20.4)	51 (13.2)
Pertuzumab-containing regimen‡	53 (13.8)	34 (8.8)
Chemotherapy, n (%)†	68 (17.8)	57 (14.7)
Docetaxel	24 (6.3)	8 (2.1)
Paclitaxel	18 (4.7)	4 (1.0)
Capecitabine	24 (6.3)	35 (9.0)
Endocrine therapy, n (%)†	19 (5.0)	13 (3.4)

- Jak dotąd, tylko 10,1% chorych z ramienia THP otrzymało T-DXd w 2. linii
- Wśród chorych z PD z ramienia THP 30% i 40% z ramienia T-DXd + P nie otrzymało leczenia po PD
- Krótki okres obserwacji, ale te dane odpowiadają sytuacji gdy T-DXd chorzy otrzymują **w 1. linii lub NIGDY**

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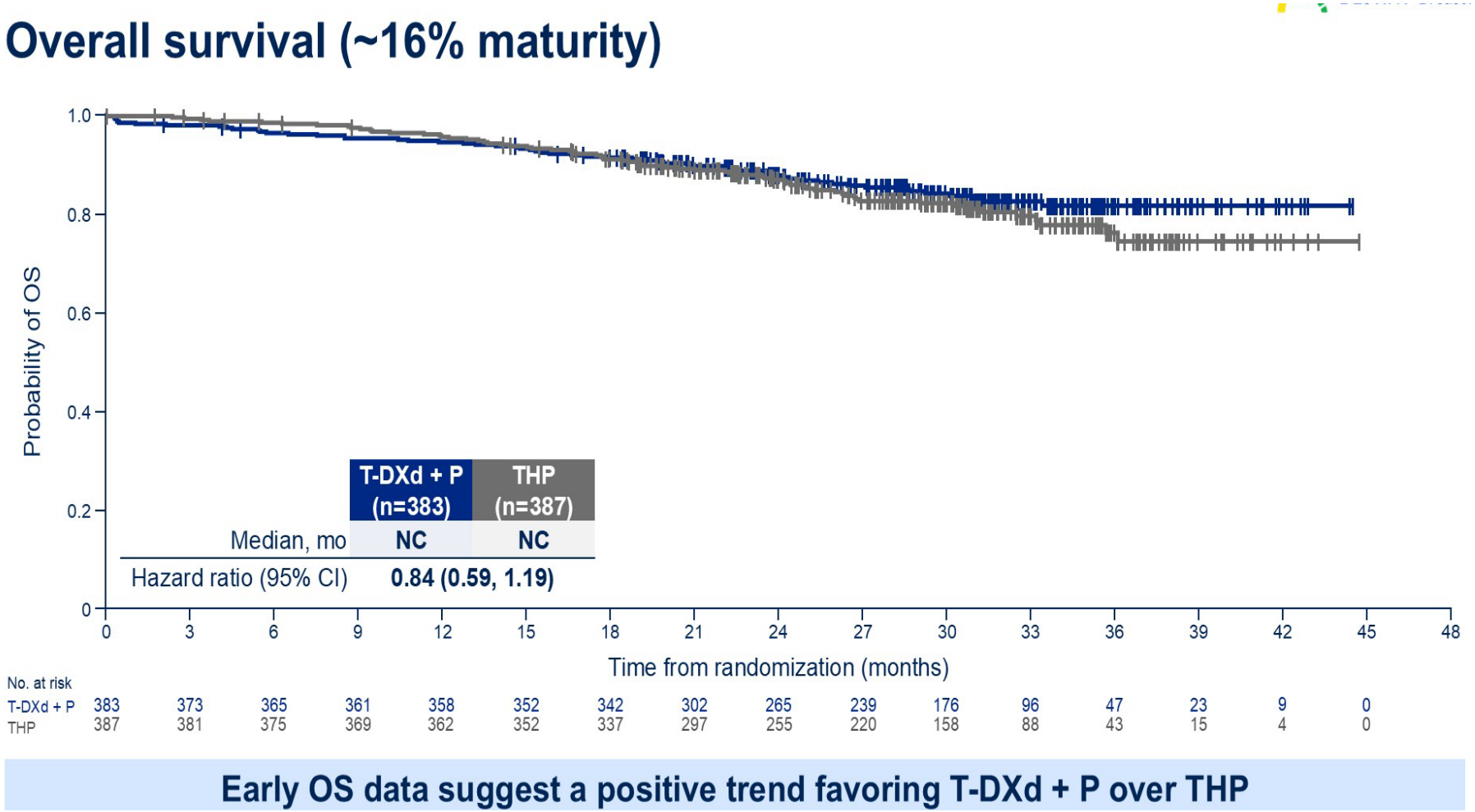

Early OS data suggest a positive trend favoring T-DXd + P over THP

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DESTINY-Breast09

Overall safety summary

	Safety analysis set*	
	T-DXd + P (n=381)	THP (n=382)
Total exposure, patient years	659.7	564.0
Any TEAE, n (%)	380 (99.7)	378 (99.0)
Possibly treatment-related TEAEs (investigator assessed), n (%)	373 (97.9)	369 (96.6)
Grade ≥3	209 (54.9)	200 (52.4)
Serious TEAEs, n (%)	103 (27.0)	96 (25.1)
TEAEs associated with any treatment discontinuation,† n (%)	79 (20.7)	108 (28.3)
TEAEs associated with any dose interruptions,† n (%)	262 (68.8)	187 (49.0)
TEAEs associated with any dose reductions,† n (%)	175 (45.9)	76 (19.9)
TEAEs with outcome of death, n (%)	13 (3.4)	3 (0.8)
Possibly treatment related (investigator assessed)‡	5 (1.3)	1 (0.3)

Median total treatment duration:

- **T-DXd + P: 21.7 mo (range 0.3–44.5)**
  - T-DXd: 20.0 mo§
- **THP: 16.9 mo (range 0.7–41.7)**

Median treatment duration for taxanes:

- Docetaxel: 5.5 mo (range 0.7–37.4)
- Paclitaxel: 4.4 mo (range 0.2–30.7)

Median number of cycles for taxanes:

- Docetaxel: 8 (range 1–51)
- Paclitaxel: 6 (range 1–42)

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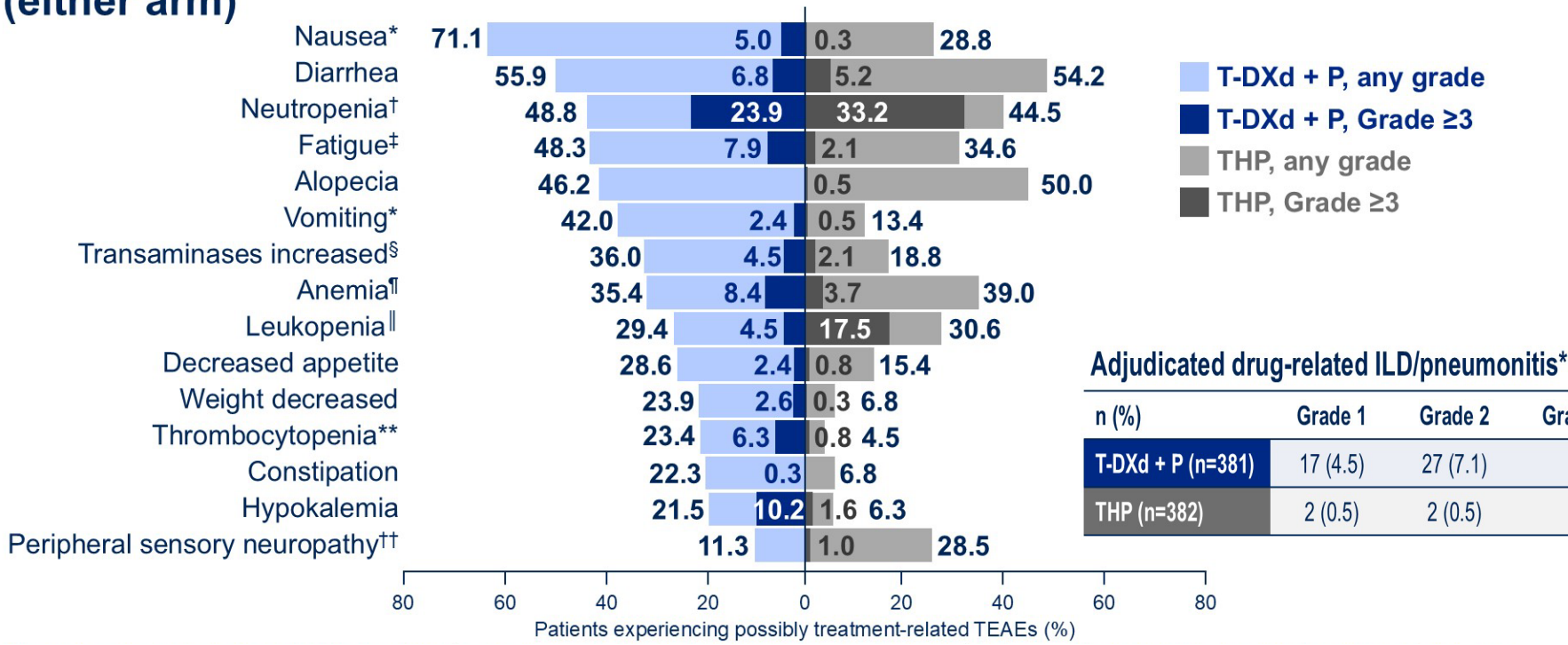
Possibly treatment-related (investigator assessed) TEAEs in ≥20% of patients (either arm)



Adjudicated drug-related ILD/pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	17 (4.5)	27 (7.1)	0	0	2 (0.5)	46 (12.1)
THP (n=382)	2 (0.5)	2 (0.5)	0	0	0	4 (1.0)

- Bez nieoczekiwanych powikłań T-DXd +P: 12,1% ILD w tym 2 zgony, dysfunkcja LV 11 % vs 7,1 w THP
- TEAE, podobna częstość w obu ramionach, więcej redukcji dawek i przerw w leczeniu z T-DXd (60% vs 49%, 46% vs 20%)
- **W CLEOPATRA w fazie podtrzymania niemal bez AE, doskonała QoL. POCZEKAJMY NA OCENĘ QoL w DB-09**

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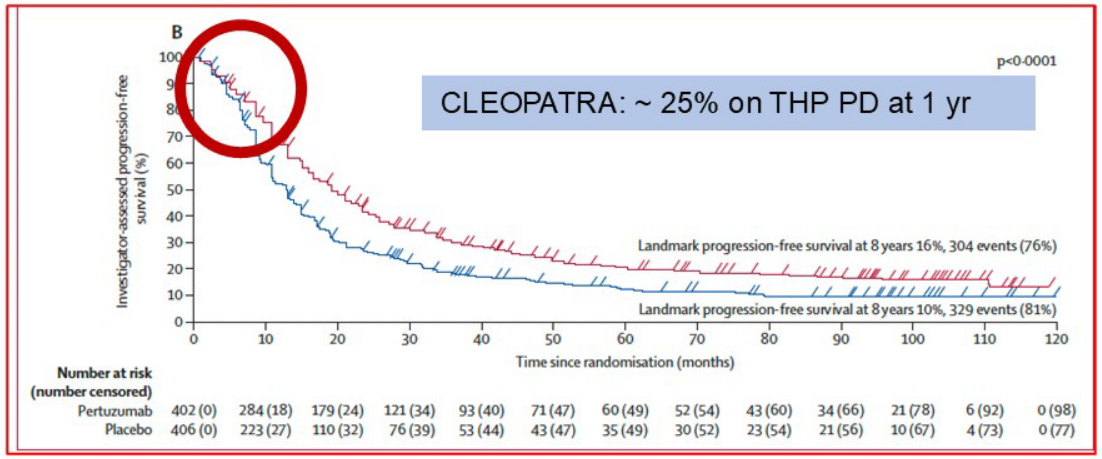
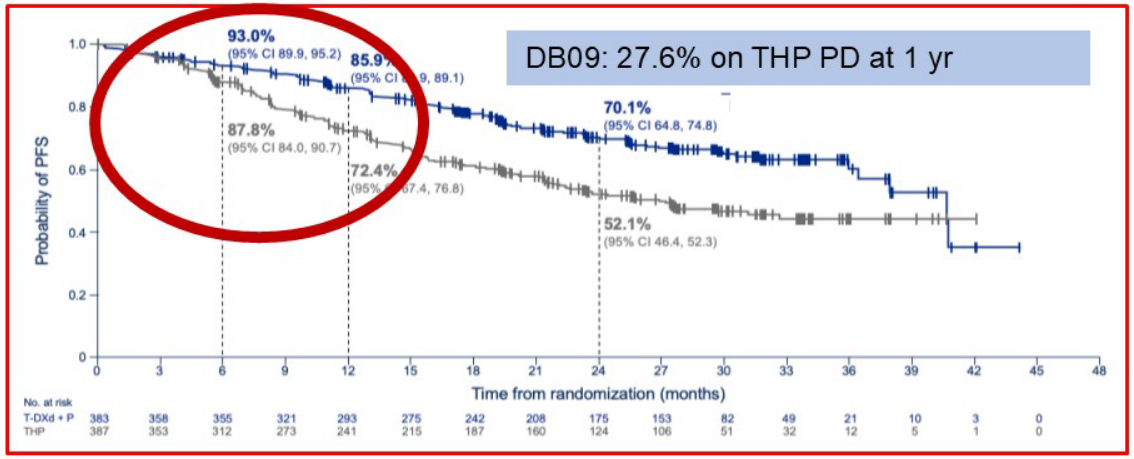
Jak te dane wpłyną na algorytm leczenia ?

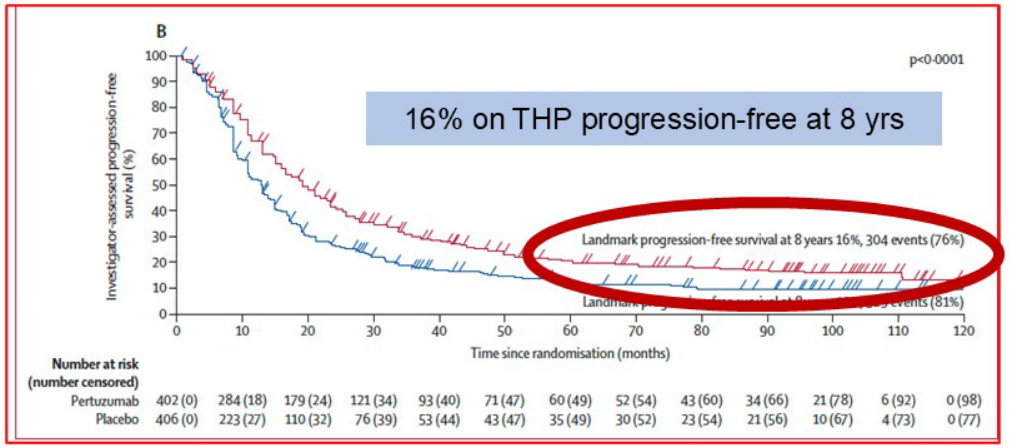
Kluczowe problemy

- Sekwencja
- Czas trwania leczenia : indukcja i faza podtrzymania ?

CLEOPATRA: ramię kontrolne DB-06







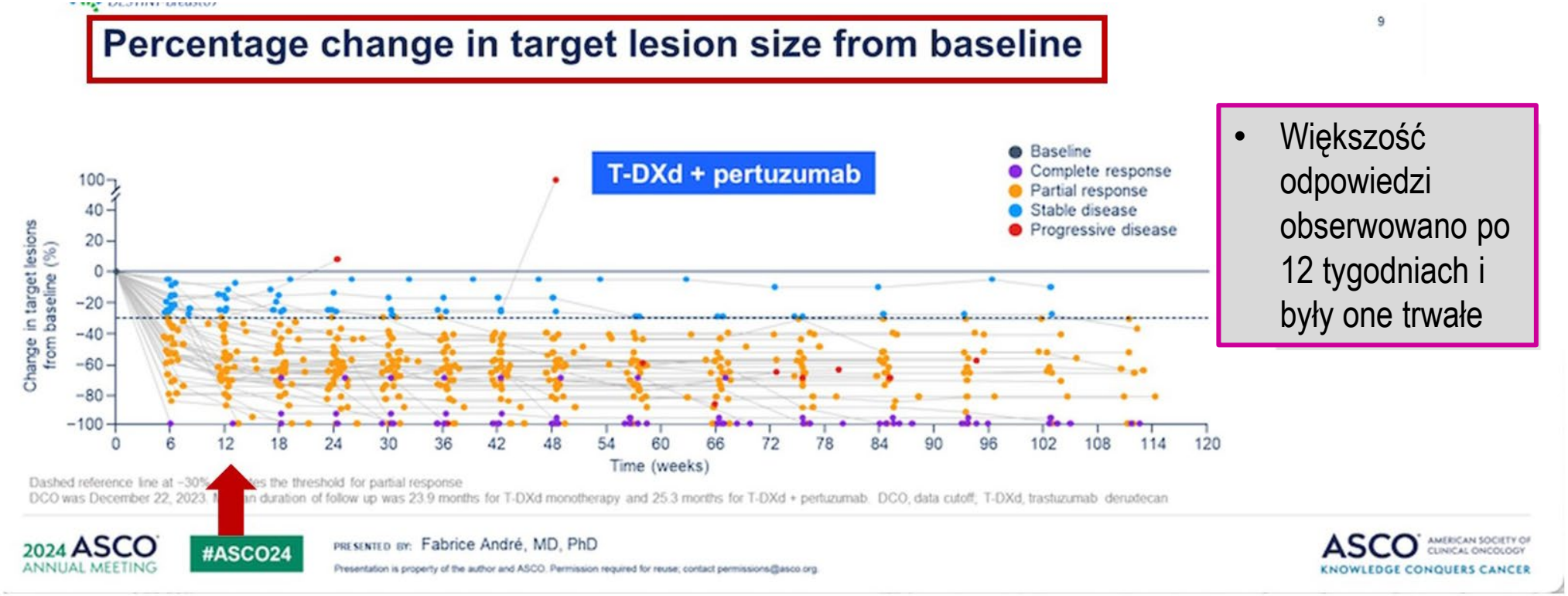
- Kto odnosi długoterminowe korzyści z THP ?
- Czy możemy poczekać, aby tym chorym zaproponować T-DXd w 2. liii

- U kogo dojdzie do wczesnej progresji na THP ?
- Czy te chore odniosą korzyści z eskalacji leczenia(T-DXd 1 linia)

- Długotrwałe odpowiedzi (> 3 lat) częstsze:
  - De novo mBC
  - Dłuższe DFI
  - Bez przerzutów do narządów miąższowych
  - IHC+/wys *HER2* mRNA, niskie HER2 w surowicy
  - *PIK3CAwt*

Swain S I wsp. Lancet 2020.

Czas trwania leczenia leczenia TDXd
A może indukcja TDXd i faza podtrzymująca PH ?



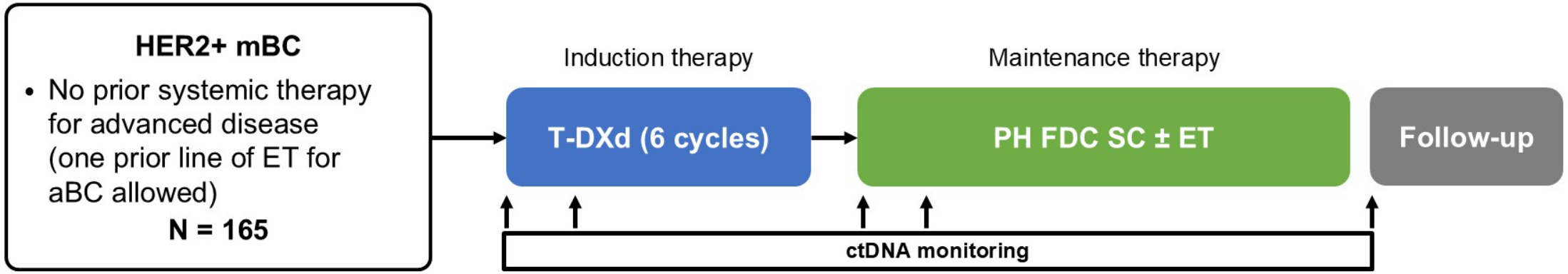
- Większość odpowiedzi obserwowano po 12 tygodniach i były one trwałe

DB-07: Phase 1b/2 of TDXd +/- P 1L mBC

Fabrice Andre i wsp. ASCO 2024.

Czas trwania leczenia leczenia TDXd
A może indukcja TDXd i faza podtrzymująca PH ?

DEMETHER: Phase II study of 1L T-DXd induction followed by maintenance PH FDC SC[1]



Primary endpoints
- 1-year PFS, 3-year OS

- Ograniczeniem jednoramienny projekt badania, brak grupy kontrolnej
- W DB-09 8,7% chorych z ramienia T-DXd +P zmieniło leczenie na HP z powodu AE

Cortes J i wsp. SABCS 2024.

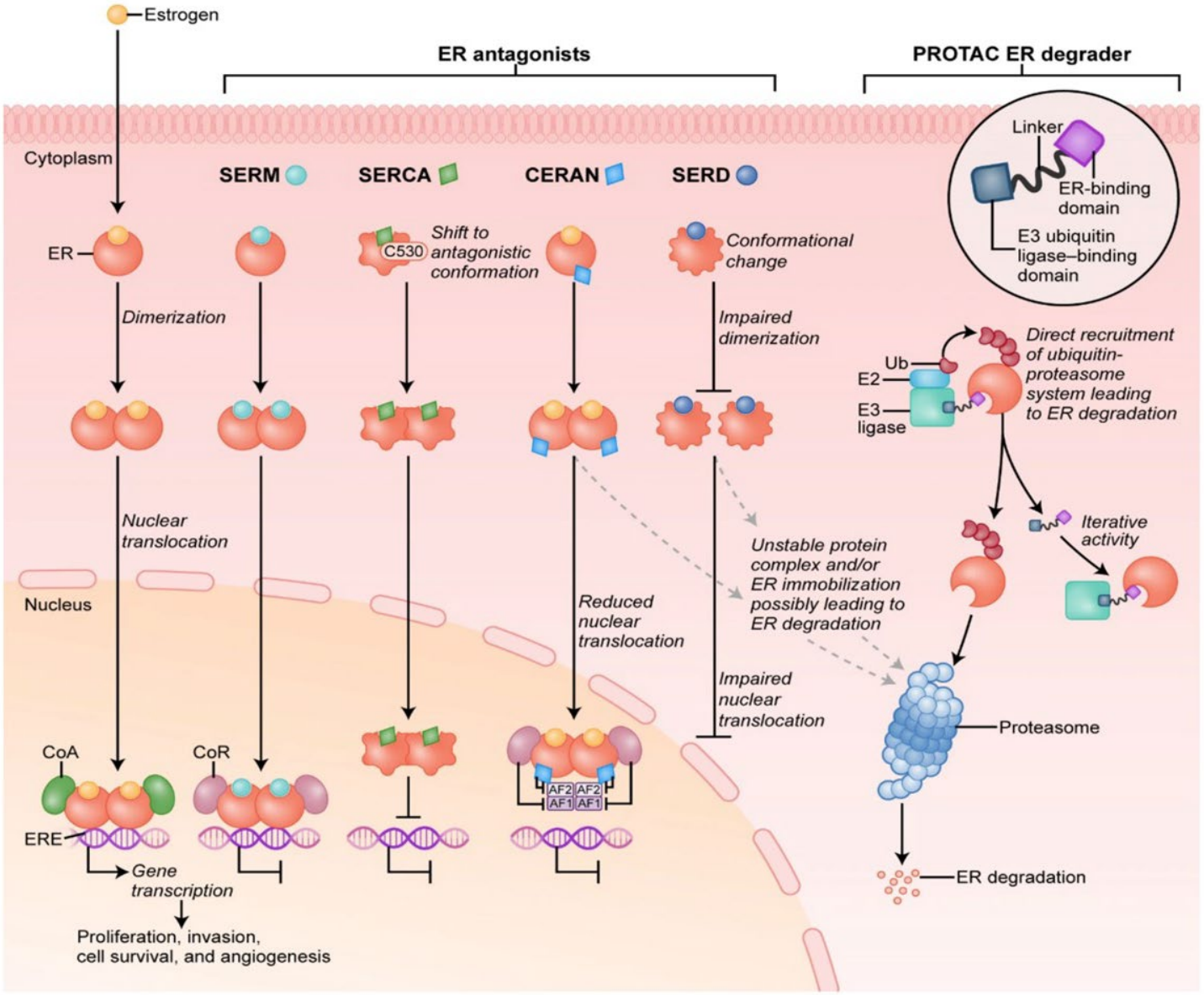
NIE ULEGA WĄTPLIWOŚCI

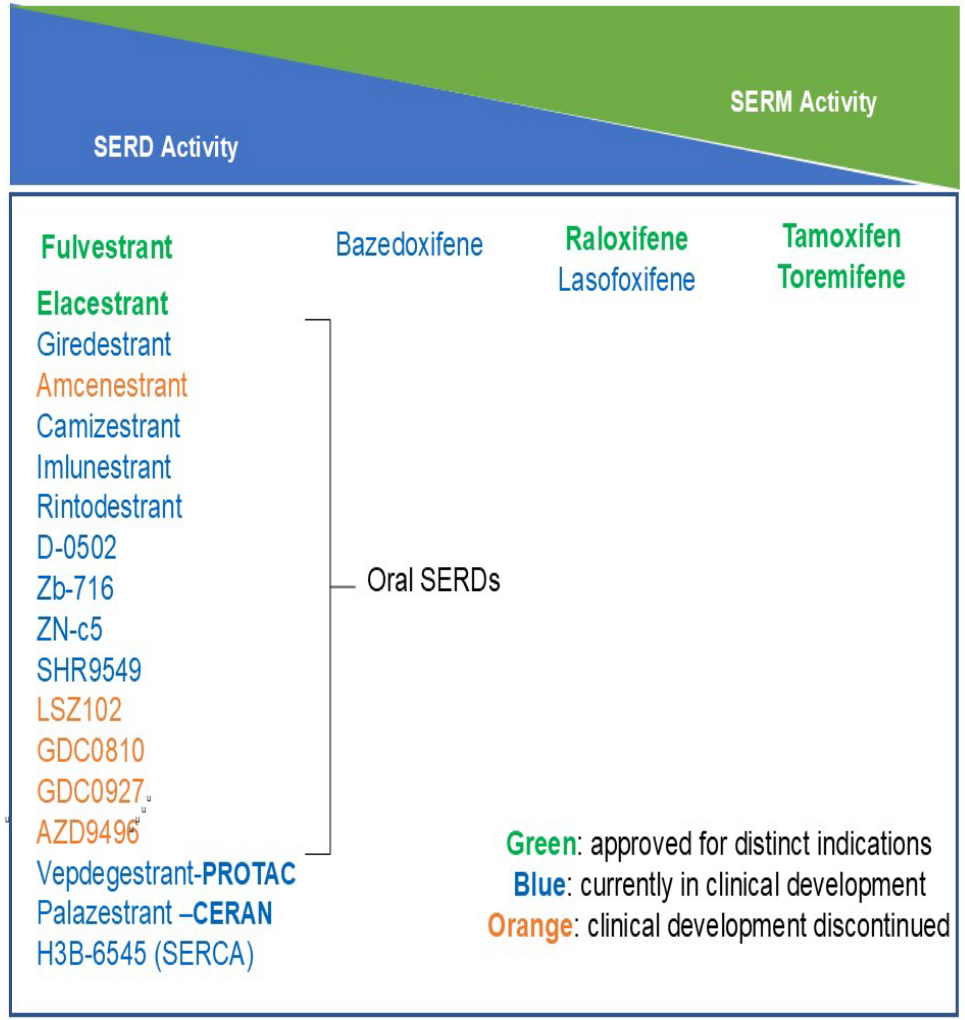
- T-DXd +P ma znaczną skuteczność w 1. linii

WĄTPLIWOŚCI

- Optymalna sekwencja pozostaje niejasna
  - Potencjalne czynniki doboru leczenia
    - **Kliniczne**: rozsiew do OUN/trzewny, krótki DFI
    - **Biologiczne**: wskaźniki wczesnej PD (PIK3CAmut), HER2DXlow/med. Wskaźnik ERBB2 , markery dynamiczne (brak wczesnego spadku ctDNA)
    - **Wola chorych**
- Może porównywalne korzyści można osiągnąć z indukcji T-DXd +P do optymalnej odpowiedzi z następową fazą podtrzymującą HP?(BRAK DANYCH)
  - A może faza podtrzymująca z HT w ER+ (PATINA)

HT w raku piersi, coraz rzadziej samodzielna…

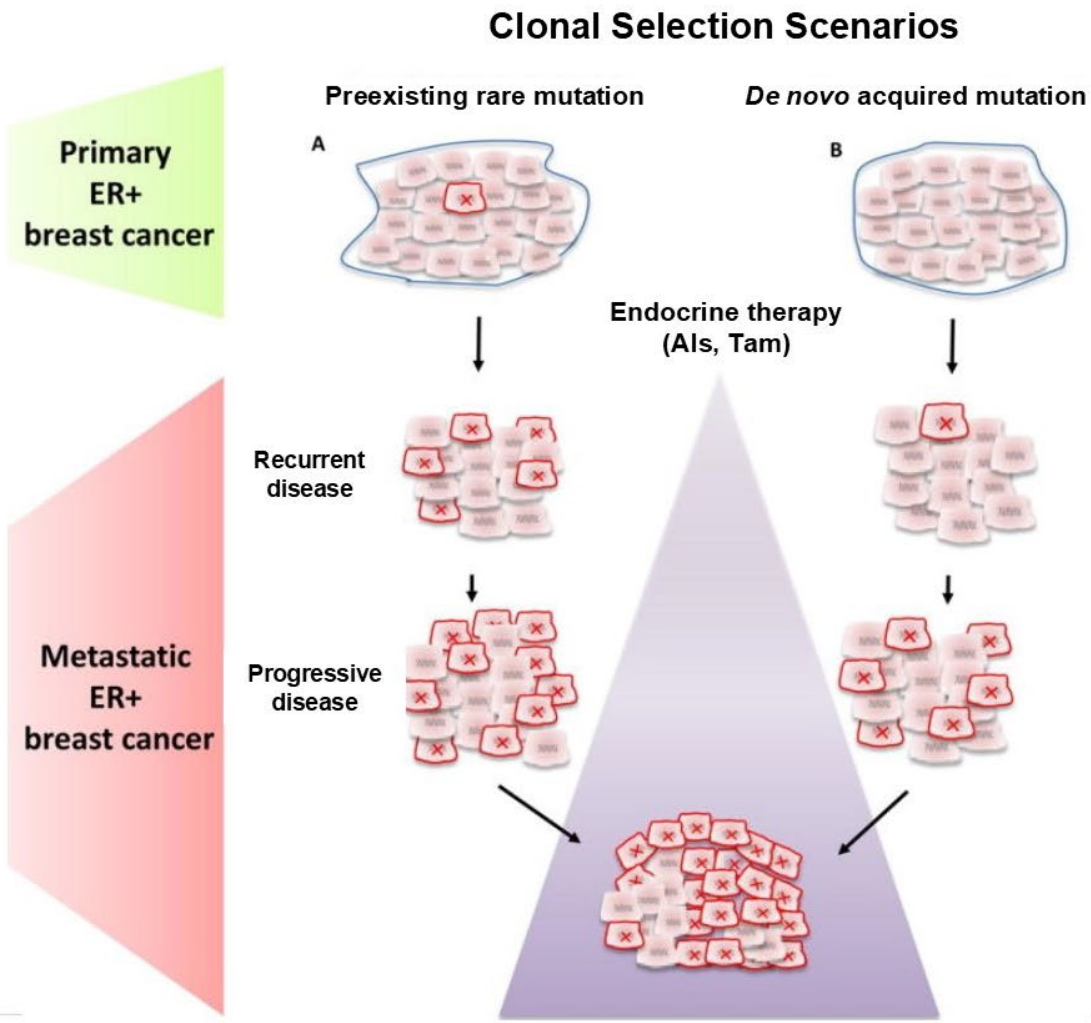




McDonnell DP et al. *J Clin Oncol*. 2021;39:1383-1388. 2. Ferraro E et al. *Cancer Treat Rev*. 2022;109:10

Grandishar W. ASCO 2025

Acquired *ESR1* Mutations



***ESR1* mutations: ~1%**

***ESR1* mutations: 10% to 50%**

Jeselsohn R et al. *Nat Rev Clin Oncol*. 2015;12:573-583.
Zundelevich A et al. *Breast Cancer Res*. 2020;22:16.

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

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

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

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints

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

Characteristic		Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Visceral metastases — n (%)†		66 (42)	71 (45)
Time of *ESR1*m detection — n (%)†	At first test	84 (54)	84 (53)
	At a subsequent test‖	73 (47)	74 (47)
	Median (range) – months	22 (4–95)	22 (6–96)
Time from initiation of AI + CDK4/6i to randomization — n (%)†	≥18 months	97 (62)	100 (63)
	<18 months	60 (38)	58 (37)
	Median (range) – months	23 (7–96)	23 (6–96)
CDK4/6i continued at randomization — n (%)†	Palbociclib	119 (76)	119 (75)
	Ribociclib	24 (15)	23 (15)
	Abemaciclib	14 (9)	16 (10)

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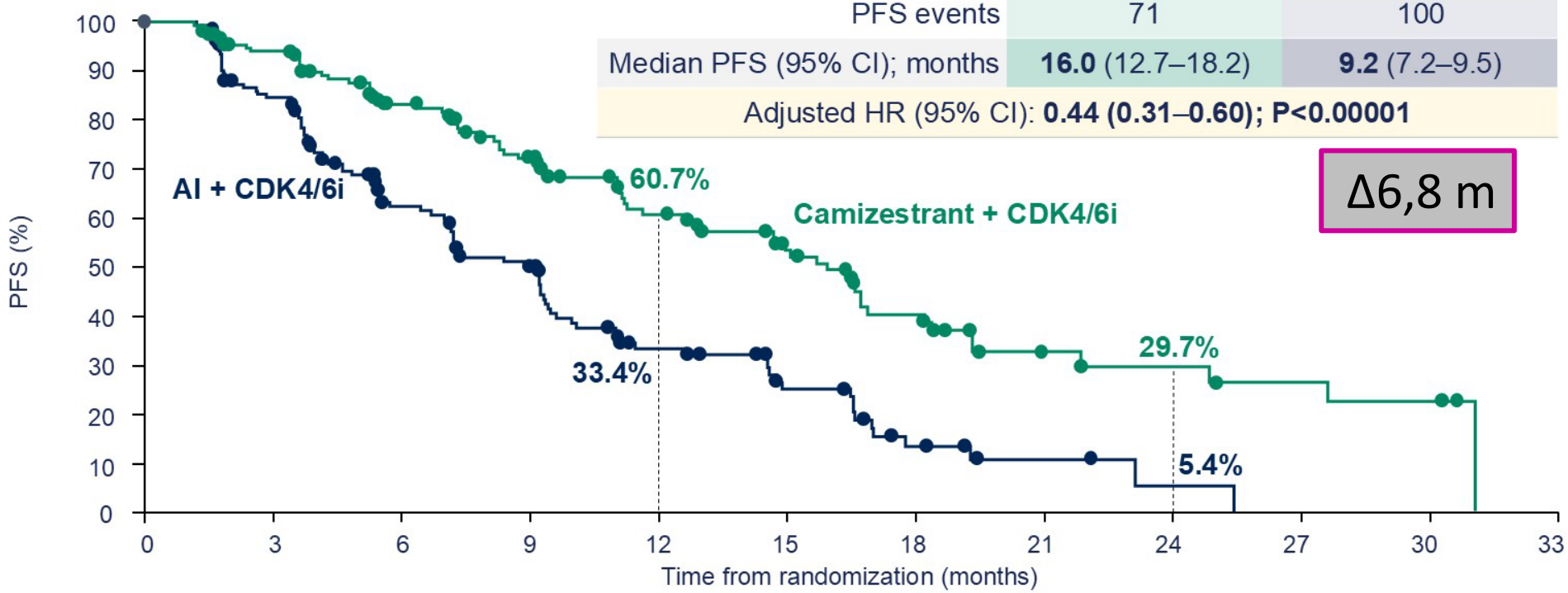
SERENA-6: PFS

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median PFS (95% CI); months	**16.0** (12.7–18.2)	**9.2** (7.2–9.5)
Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001**		



Number of patients at risk

Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

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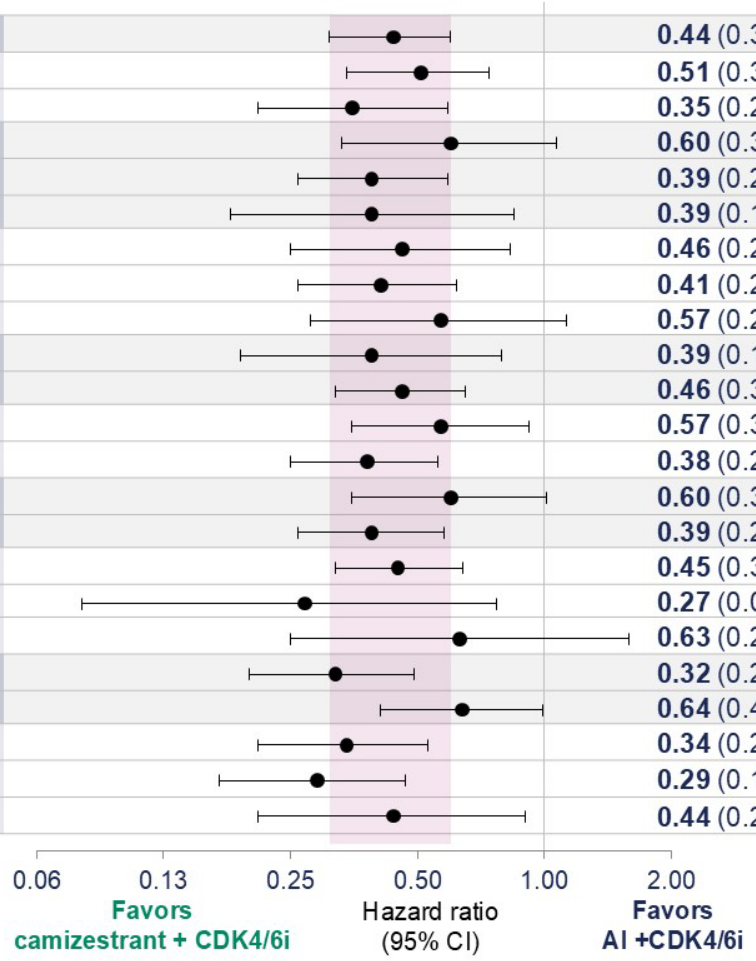
SERENA-6: PFS analiza podgrup

	Subgroup	Camizestrant + CDK4/6i	AI + CDK4/6i	Hazard ratio (95% CI)
		no. of events/total no.		
	All patients	71/157	100/158	**0.44** (0.31–0.60)
Age	<65 years	44/95	67/104	**0.51** (0.34–0.74)
	≥65 years	27/62	33/54	**0.35** (0.21–0.59)
Race	Asian	22/39	25/34	**0.60** (0.33–1.07)
	White	37/97	61/102	**0.39** (0.26–0.59)
	Other	12/21	14/21	**0.39** (0.18–0.85)
Region	Asia	19/40	28/39	**0.46** (0.25–0.83)
	Europe	37/89	54/91	**0.41** (0.26–0.62)
	North America	15/28	18/28	**0.57** (0.28–1.13)
Menopausal status	Pre-/perimenopausal women, and men	14/34	18/31	**0.39** (0.19–0.79)
	Postmenopausal	57/123	82/127	**0.46** (0.32–0.65)
Disease site*	Visceral	32/65	37/64	**0.57** (0.35–0.92)
	Non-visceral	39/92	63/92	**0.38** (0.25–0.56)
Time from initiation of AI + CDK4/6i to randomization*	<18 months	28/50	29/46	**0.60** (0.35–1.01)
	>18 months	43/105	69/110	**0.39** (0.26–0.58)
CDK4/6i*	Palbociclib	57/117	78/118	**0.45** (0.32–0.64)
	Ribociclib	4/23	13/23	**0.27** (0.08–0.77)
	Abemaciclib	10/15	9/15	**0.63** (0.25–1.59)
Time of *ESR1*m detection*	First test	36/82	56/79	**0.32** (0.20–0.49)
	A subsequent test‖	35/75	44/79	**0.64** (0.41–0.99)
Type of *ESR1*m	D538G	29/70	52/82	**0.34** (0.21–0.53)
	Y537S	24/61	46/60	**0.29** (0.17–0.47)
	Y537N	13/29	18/25	**0.44** (0.21–0.90)



*Stratification factors at randomization. ‖Subsequent tests were performed every 2-3 months after the initial test. HRs and 95% CIs were not calculated for subgroups with <20 events, except for the CDK4/6i subgroup. HRs and 95% CIs were calculated from a Cox proportional hazards model with treatment, factor and treatment-by-factor as covariates.

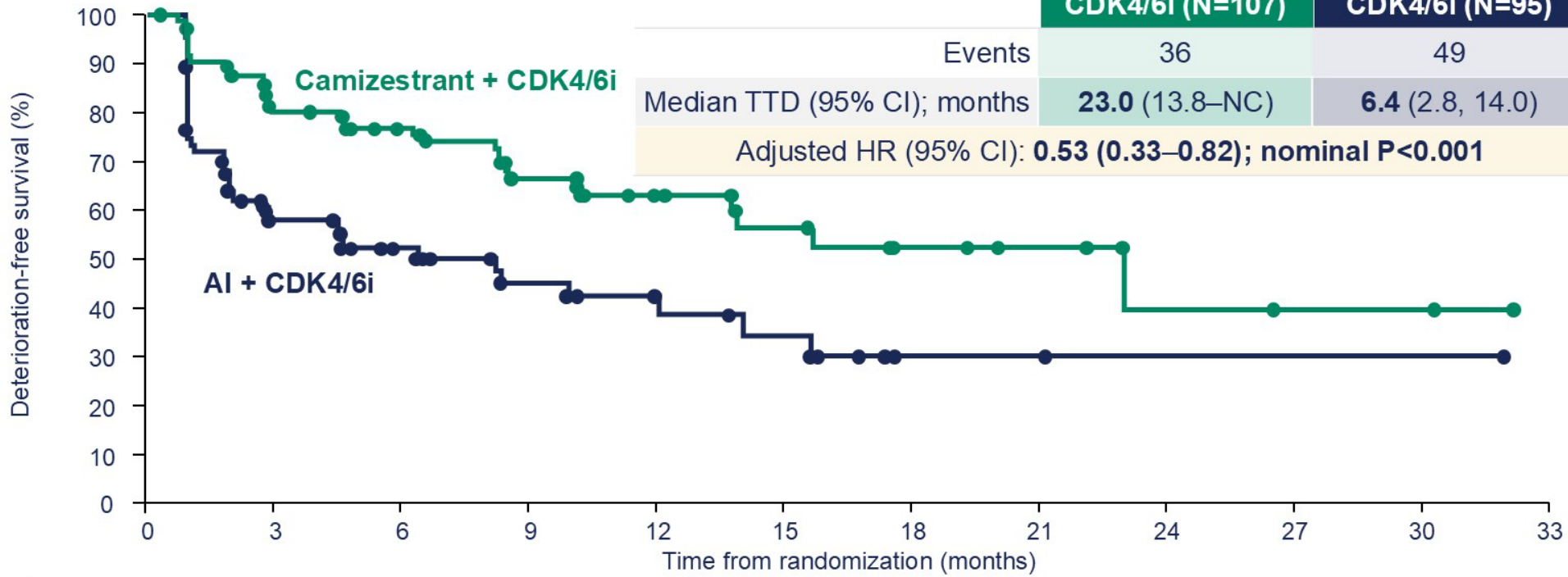
Turner N I wsp. ASCO 2025

SERENA-6: QoL

Time to deterioration in global health status/quality of life

EORTC QLQ-C30

	Camizestrant + CDK4/6i (N=107)	AI + CDK4/6i (N=95)
Events	36	49
Median TTD (95% CI); months	**23.0** (13.8–NC)	**6.4** (2.8, 14.0)
Adjusted HR (95% CI): **0.53 (0.33–0.82); nominal P<0.001**		



Number of patients at risk

Camizestrant + CDK4/6i	107	72	59	40	24	16	9	6	3	2	2	0
AI + CDK4/6i	95	42	26	16	11	8	2	2	1	1	1	0

- Camizestrant + CDK4/6i also delayed the time to deterioration in pain compared with AI + CDK4/6i

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SERENA-6: PFS2

Second progression-free survival (PFS2)

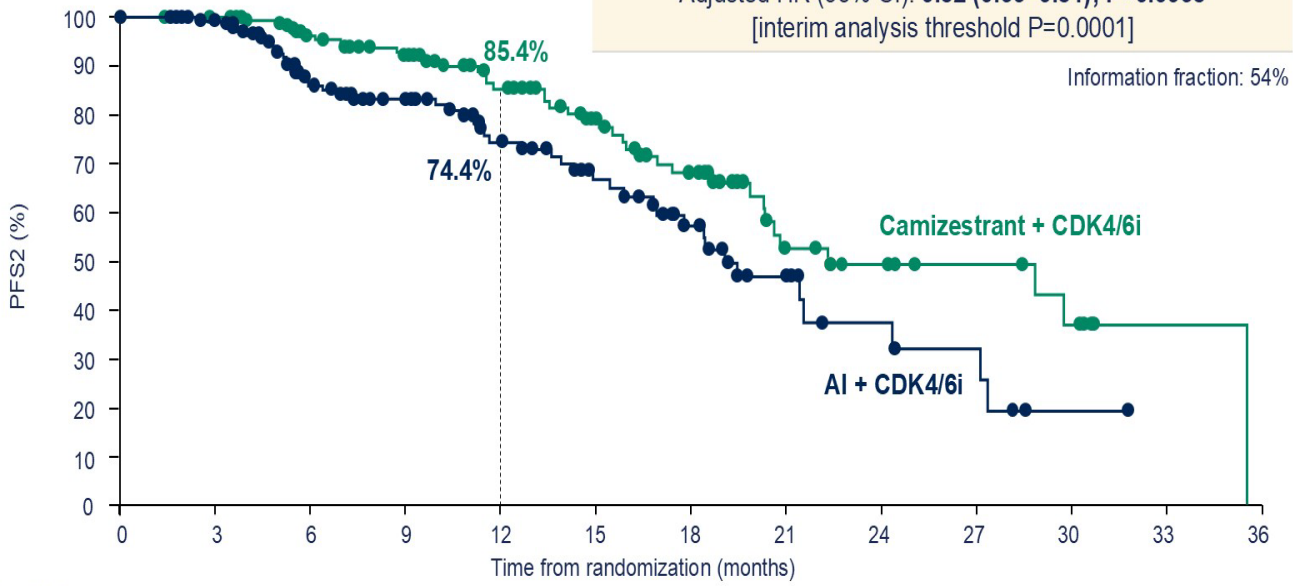
Key secondary endpoint

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events	38	47

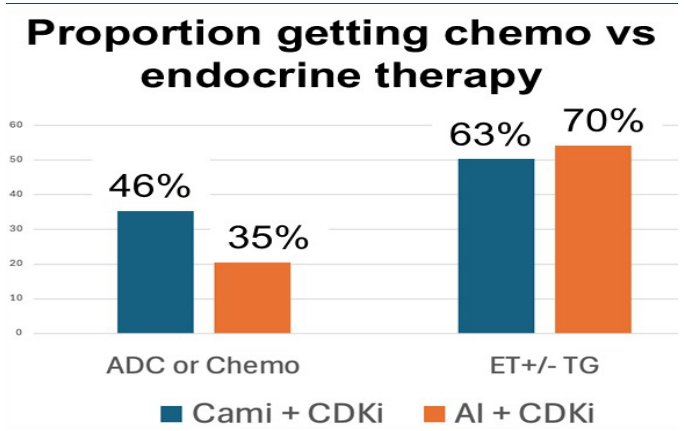
Adjusted HR (95% CI): **0.52 (0.33–0.81); P=0.0038**
[interim analysis threshold P=0.0001]

Information fraction: 54%



Number of patients at risk

Camizestrant + CDK4/6i	157	146	120	103	74	55	39	17	12	9	6	1	0
AI + CDK4/6i	158	144	98	78	55	38	25	12	7	5	1	0	0



Subsequent therapy — n (%)	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Any	57 (36.3)	83 (52.5)
Chemotherapy	26 (45.6)	19 (22.9)
Antibody–drug conjugate	0	10 (12.0)
Endocrine therapy + targeted therapy	21 (36.8)	35 (42.2)
Endocrine monotherapy	14 (24.6)	23 (27.7)
Other*	4 (7.0)	3 (3.6)

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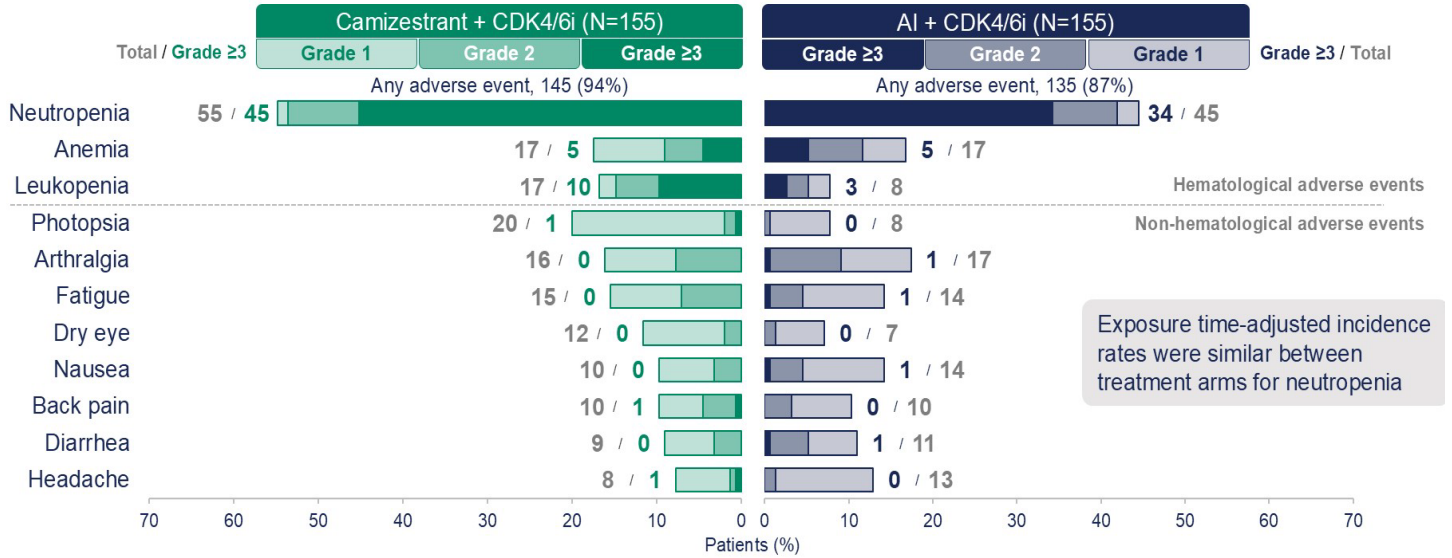
SERENA-6: powikłania

Adverse events (≥10% of patients)



Exposure time-adjusted incidence rates were similar between treatment arms for neutropenia

Photopsia (brief flashes of light in the peripheral vision) did not impact daily activities: If experienced, visual effects had no/minimal impact on daily activities, were typically ≤1 minute, ≤3 days/week, and reversible. There were no structural changes in the eye and no changes in visual acuity

	Camizestrant + CDK4/6i (N=155)	AI + CDK4/6i (N=155)
Any adverse event — n (%)	145 (94)	135 (87)
Grade ≥3	93 (60)	71 (46)
Any serious adverse event — n (%)	16 (10)	19 (12)
Any adverse event leading to discontinuation — n (%)		
Camizestrant/AI	2 (1)	3 (2)
Both camizestrant/AI and CDK4/6i	1 (1)	2 (1)
CDK4/6i	2 (1)	2 (1)

Turner N I wsp. ASCO 2025

NIE ULEGA WĄTPLIWOŚCI

- Zmiana HT na camizestrant, z kontynuacją iCDK4/6 przed anatomiczną PD, na podstawie stwierdzenia ESR1m w ctDNA wydłuża PFS
- Akceptowalna toksyczność
- Wpływ na QoL
- Dłuższy czas do CT
- Wydłużenie czasu do rozwoju bardziej agresywnej postaci choroby

WĄTPLIWOŚCI

- Przedwczesna ocena PFS2 i OS
- Czy aby to dysponujemy wystarczającymi dowodami naukowymi, potwierdzającymi kliniczną użyteczność testowania ctDNA ?

EMBER-3: Imlunestrant ± Abemaciclib vs SOC for ER+, HER2- Advanced Breast Cancer Pretreated With ET

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]

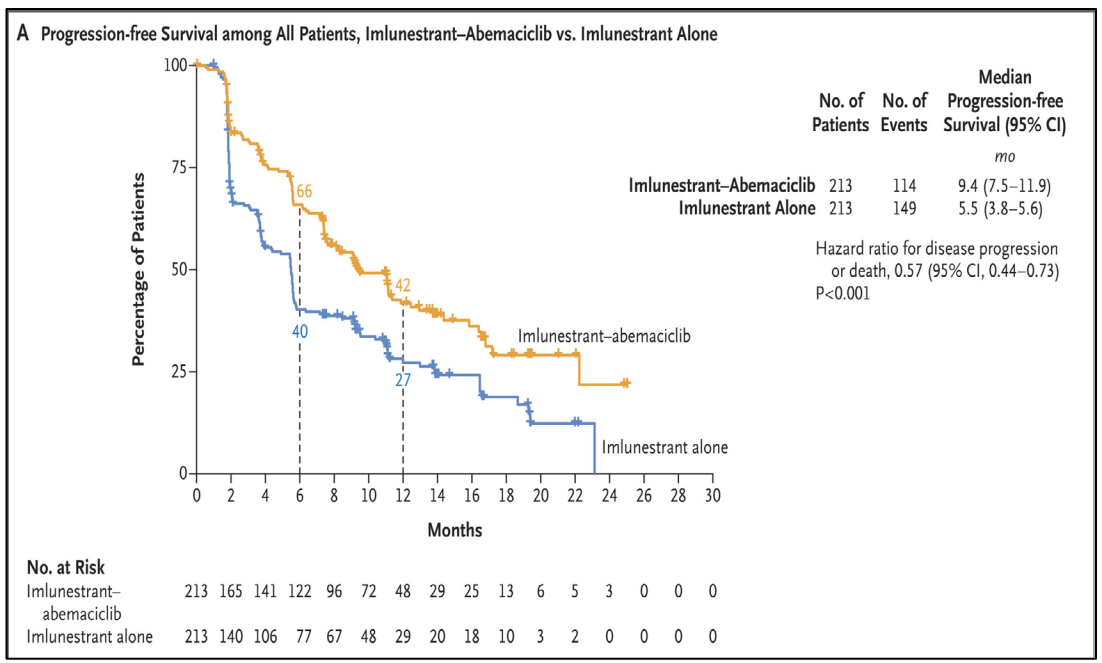
Arm A
Imlunestrant 400 mg QD

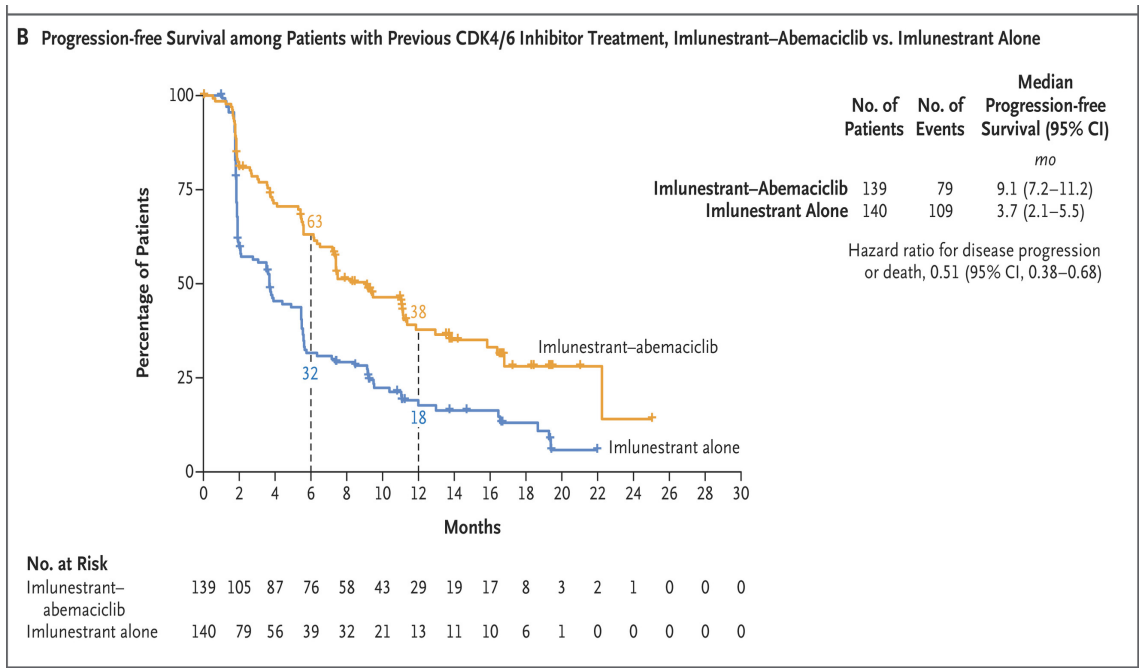
Arm B
SOC ET[b]
(IC: fulvestrant or exemestane)

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

Jhaveri K SABCS 2024: NEJM 2024

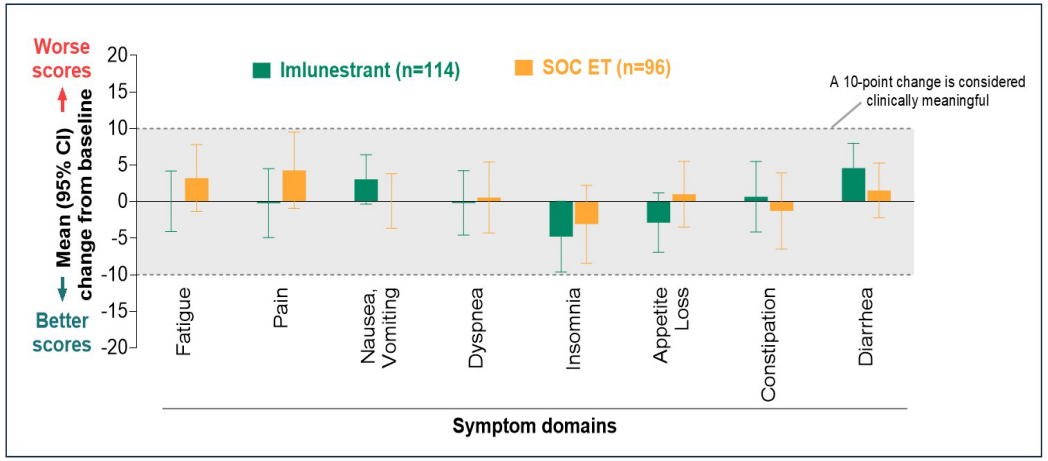




EMBER-3:QoL

EMBER-3:Overall Symptom Domains on Treatment with Imlunestrant vs SOC ET in Patients with *ESR1*m

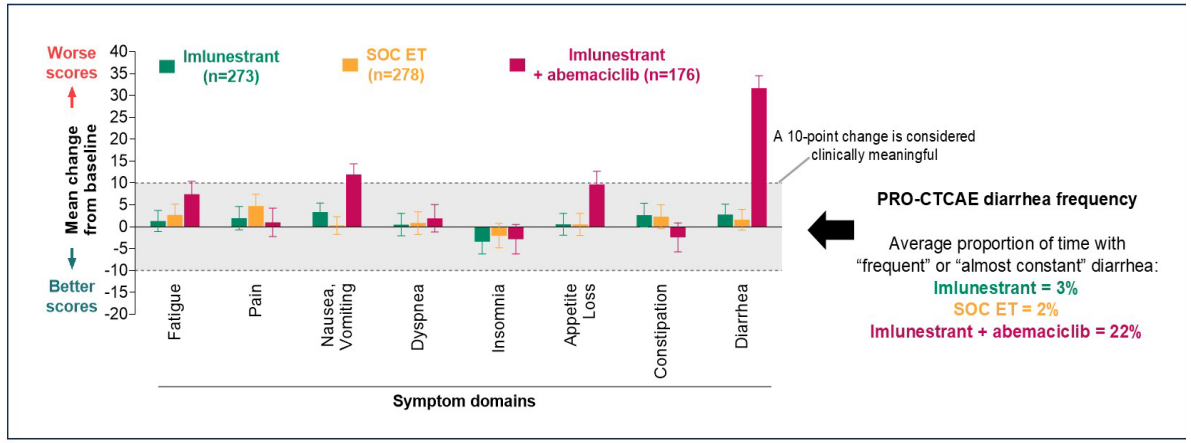
Overall change from baseline in EORTC QLQ-C30 symptom domains
MONOTHERAPY



Symptom domains were broadly similar overall across treatment arms

EMBER-3: Overall Symptom Domains On Treatment with Imlunestrant + Abemaciclib vs Imlunestrant or vs SOC ET in All Patients

Overall change from baseline in EORTC QLQ-C30 symptom domains

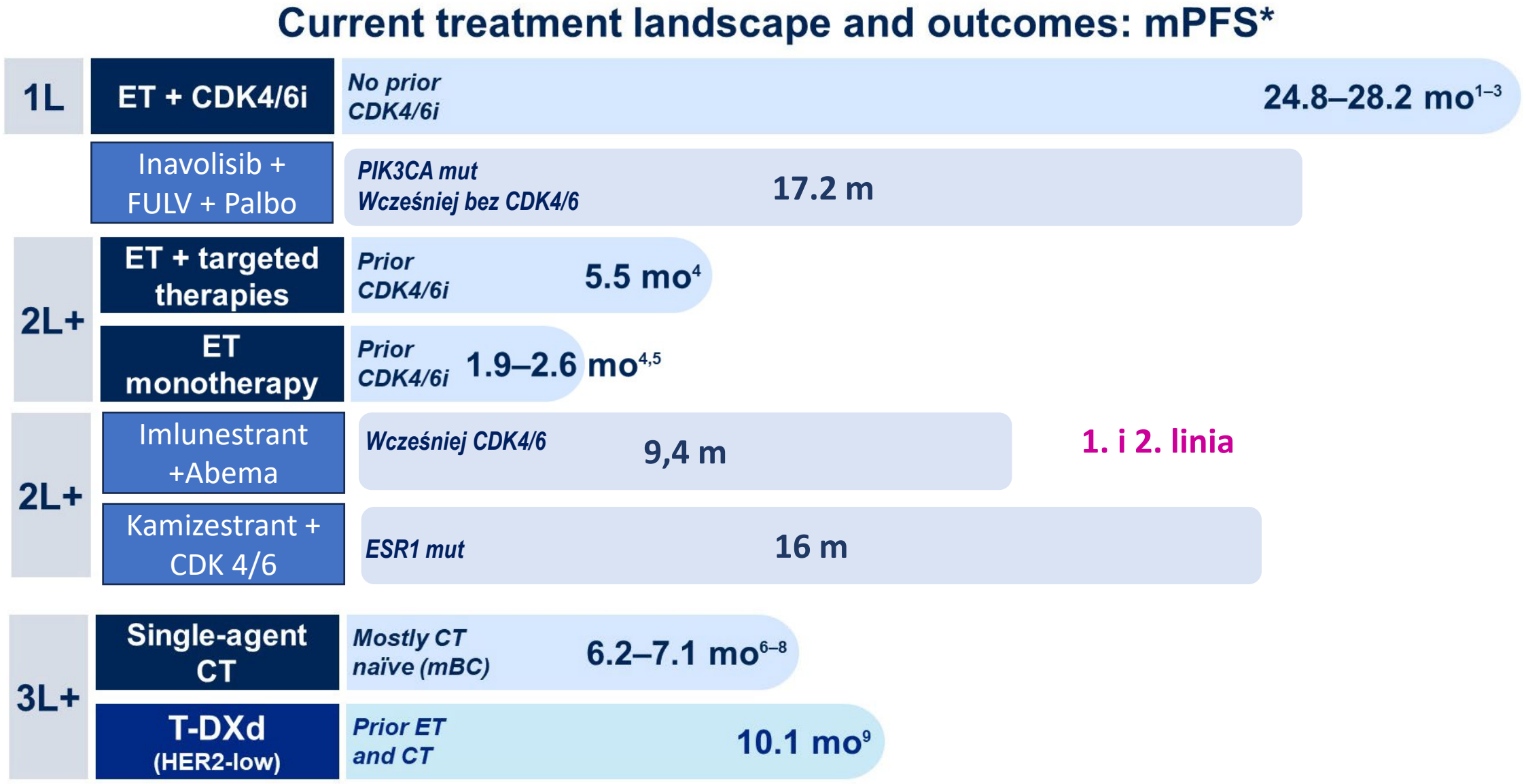


Symptom domains were broadly similar overall across treatment arms, except for expected increased diarrhea and nausea/vomiting with imlunestrant + abemaciclib

EMBER-3 Global Health Status QOL- Δ**9.9 ("≤ 10 *clinically meaningful*")** for monotherapy imlunestrant arm

Curigliano G i wsp. ASCO 2025

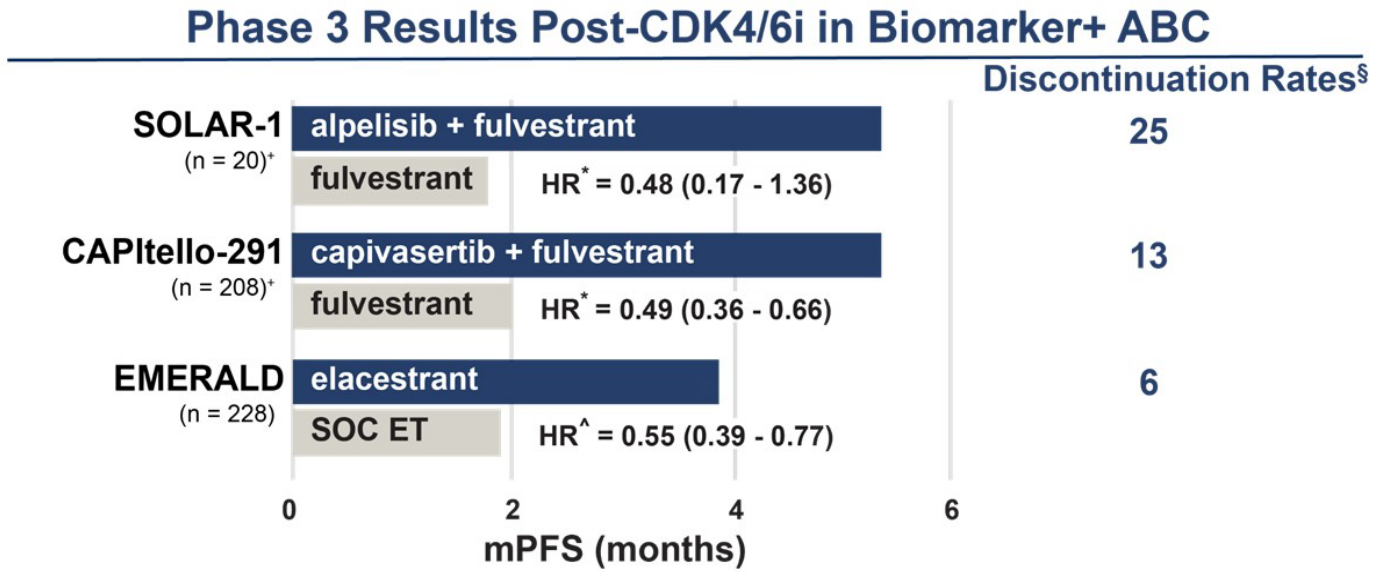
Możliwości leczenia HR+, HER2- mBC



Curigliano G, ASCO 2024.

Opcje leczenia ukierunkowanego molekularnie po 1L CDK4/6i

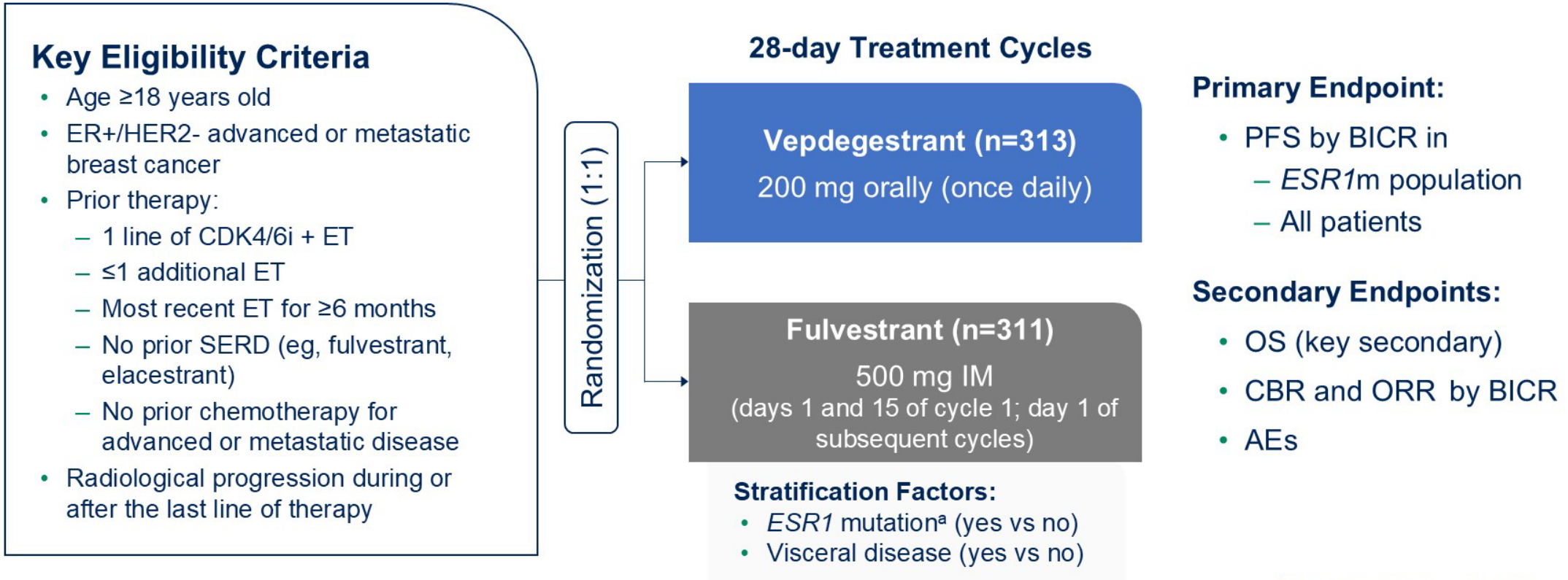
- Dobór leczenia na podstawie biomarkeru (ALP (*PIK* mut), elacestrant (*ESR1* mut)
- PFS po leczeniu z udziałem tych leków < 6 miesięcy, w wielu przypadkach toksyczność problemem



Juric D I wsp. SABCS 2019, Oliviera M i wsp. AnnOncol 2023, Turner N i wsp. NEJM 2023, Bidard F i wsp. JCO 2022

Rozciągamy okres wrażliwości na HTH…

VERITAC -2 : vepdegestrant vs FULV



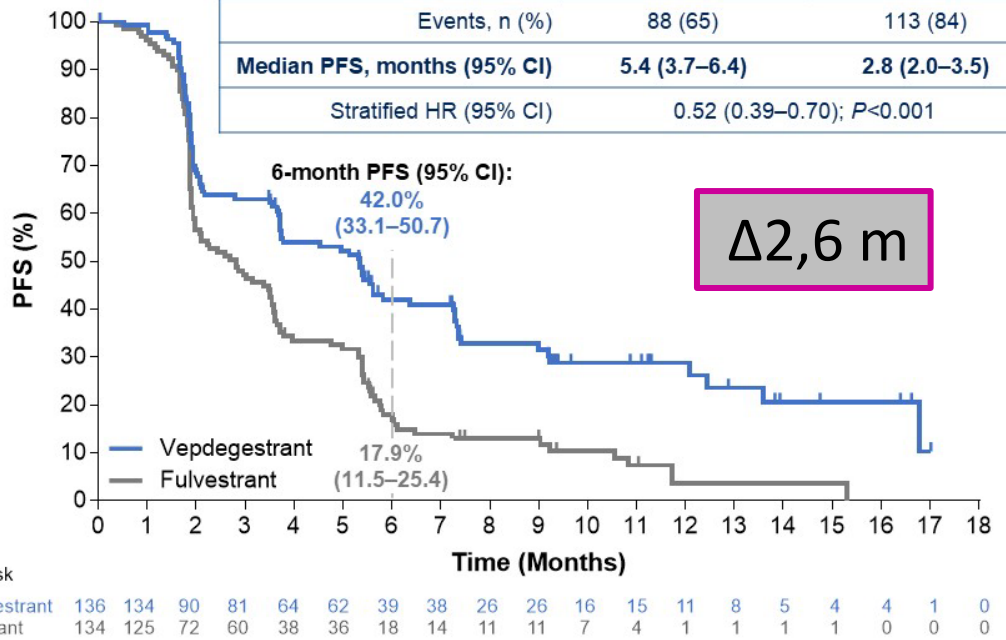
- 43% *ESR1*m
- Wszyscy chorzy wcześniej leczeni iCDK4/6
- 76-82 % : wcześniej 1 linia leczenia, 18-23% 2 linie leczenia

Hamilton E. I wsp. ASCO 2025

VERITAC -2 : PFS

Patients With *ESR1*m

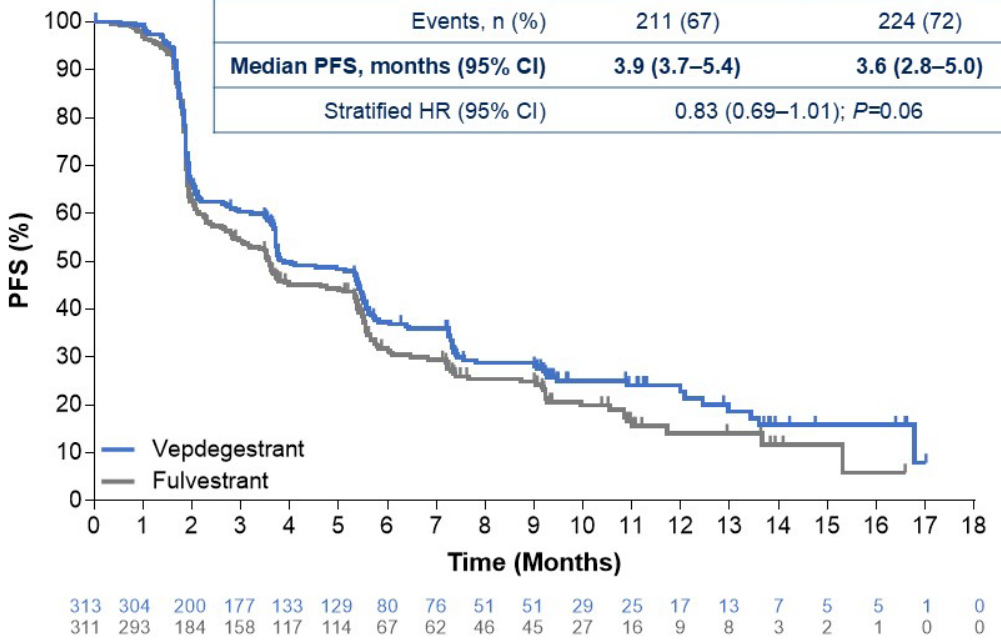
	Vepdegestrant n=136	Fulvestrant n=134
Events, n (%)	88 (65)	113 (84)
Median PFS, months (95% CI)	**5.4 (3.7–6.4)**	**2.8 (2.0–3.5)**
Stratified HR (95% CI)	0.52 (0.39–0.70); *P*<0.001	



Δ2,6 m

All Patients

	Vepdegestrant n=313	Fulvestrant n=311
Events, n (%)	211 (67)	224 (72)
Median PFS, months (95% CI)	**3.9 (3.7–5.4)**	**3.6 (2.8–5.0)**
Stratified HR (95% CI)	0.83 (0.69–1.01); *P*=0.06	

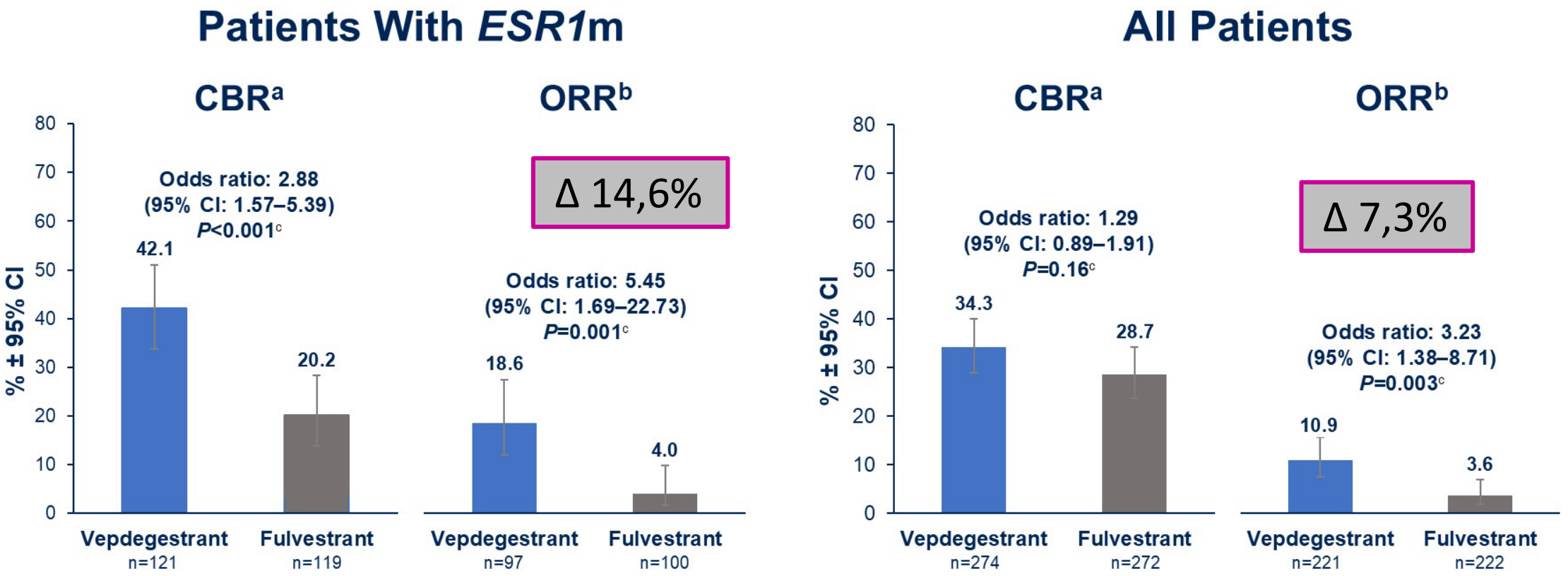


ESR1m=estrogen receptor 1 gene mutation; HR=hazard ratio; PFS=progression-free survival.

- Leczenie dobrze tolerowane
- Najczęściej występującym AE: zmęczenie : 27% (vepdegestrant)
- Tylko 3% przerwało leczenie z powodu AE, u 2% zredukowano dawkę leku

Hamilton E. I wsp. ASCO 2025

VERITAC -2 : CBR i ORR



Hamilton E. I wsp. ASCO 2025

INAVO120 : projekt badania

Key eligibility criteria

Enrichment of patients with poor prognosis:

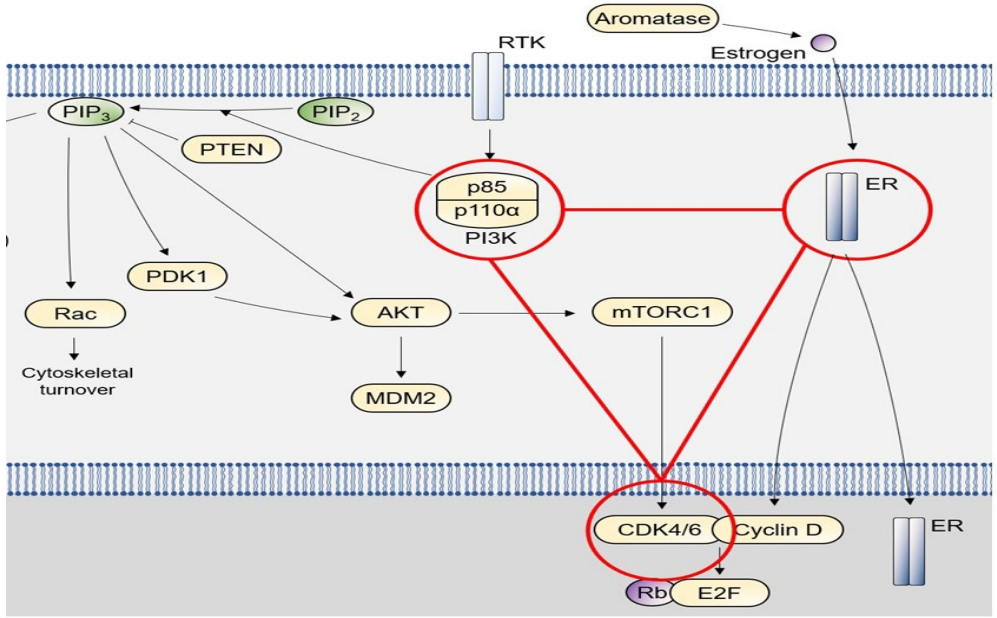
- ***PIK3CA*-mutated, HR+, HER2– LA/mBC** by central ctDNA or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1c <6.0% (< 42 mmol/mol)**

N = 325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)

Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)



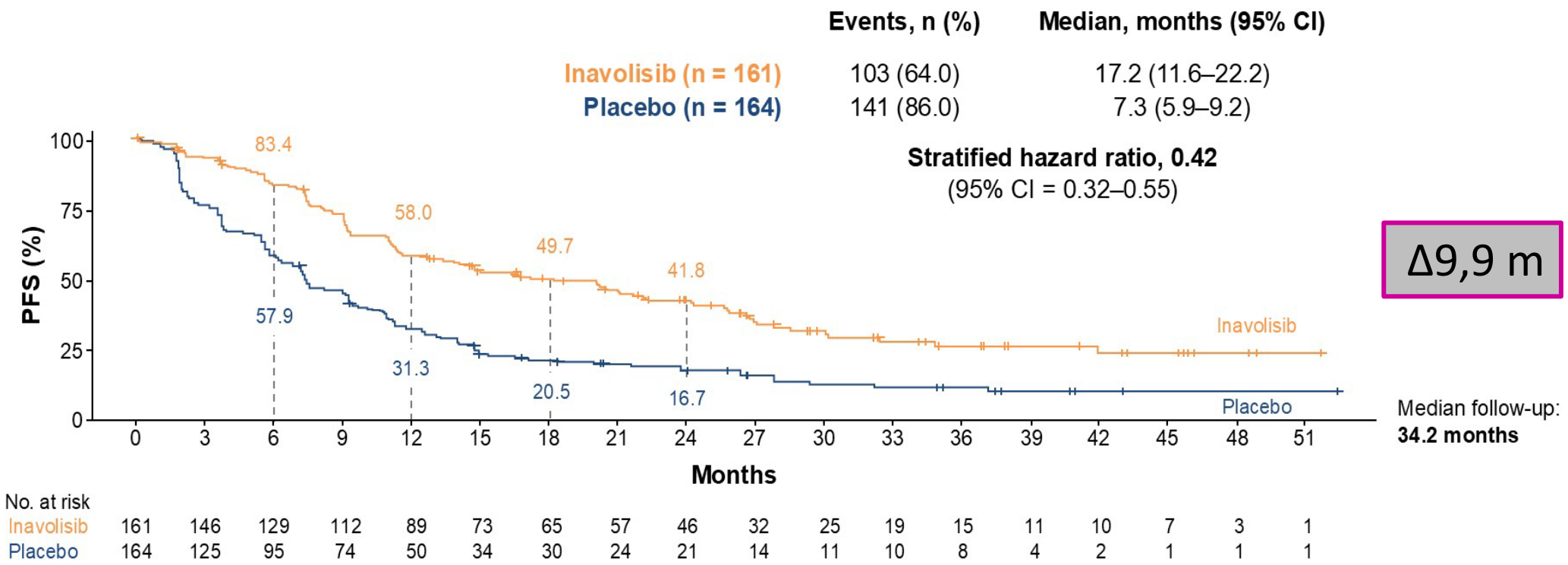
Populacja oporna na HT
Wcześniej nie leczona z powodu MBC

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	132 (82.0)	137 (83.5)
Prior (neo)adjuvant endocrine therapy, n (%)		
Yes	160 (99.4)	163 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)
Tamoxifen only	82 (50.9)	73 (44.5)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)
Prior adjuvant CDK4/6 inhibitor, n (%)		
Yes	3 (1.9)	1 (0.6)

Inavolisib is a highly potent and selective inhibitor of the catalytic alpha isoform subunit (p110α encoded by *PIK3CA*) of the PI3K complex that also promotes the degradation of mutated p110α[7–9]

Abstrakt 1003 Juric i wsp. ASCO 2024.

INAVO120 uaktualniony PFS



Δ9,9 m

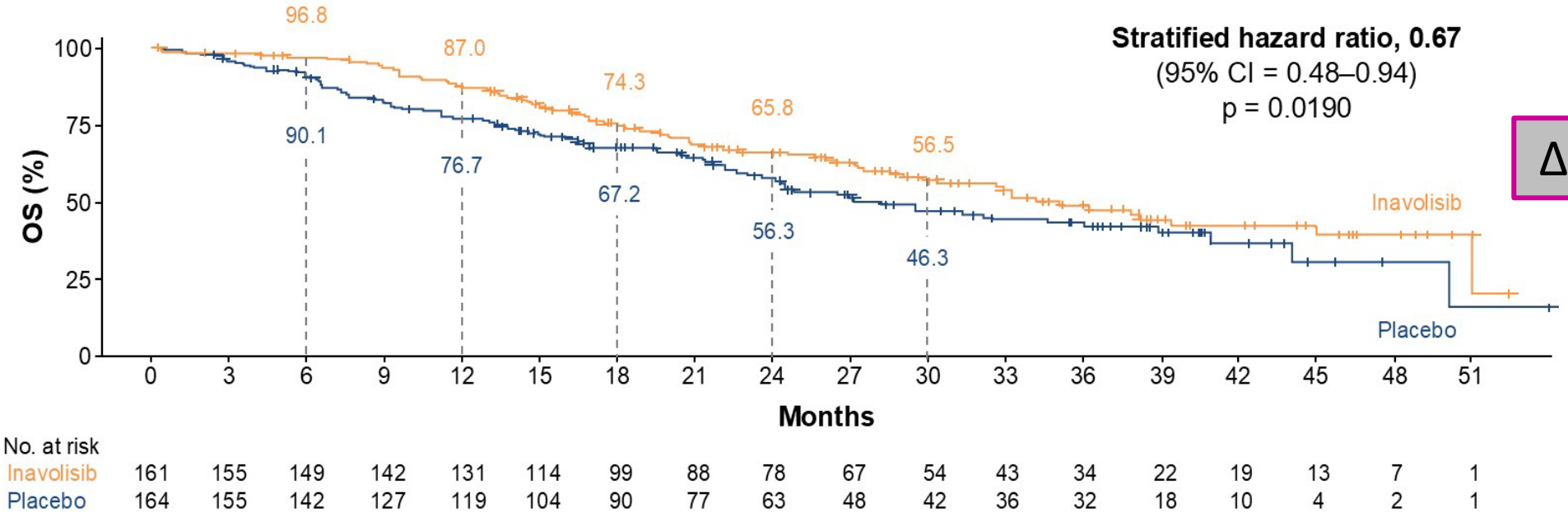
Median follow-up:
34.2 months

The improvement in PFS was maintained during longer follow-up

Turner I wsp. ASCO 2025.

INAVO120 uaktualniony OS

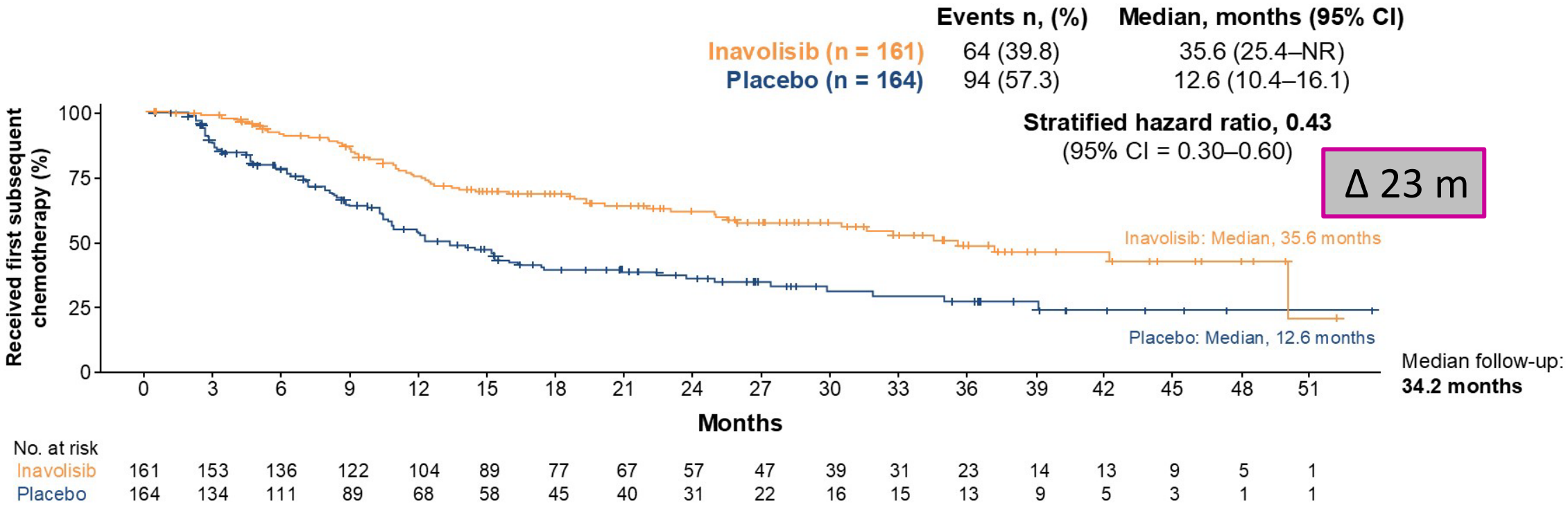
	Deaths, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	72 (44.7)	34.0 (28.4–44.8)
Placebo (n = 164)	82 (50.0)	27.0 (22.8–38.7)



Improvement in median OS: 7 months. The prespecified boundary for statistical significance (p < 0.0469) was crossed

Turner I wsp. ASCO 2025.

INAVO120 : czas do 1. linii CT



Median time to first subsequent chemotherapy was substantially delayed by almost 2 years (23 months)

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INAVO120 : leczenie po progresji

	Inavolisib		Placebo	
Patients, n (%)	**Second line**	**Third line or greater**	**Second line**	**Third line or greater**
Discontinued treatment	111/161 (68.9)		144/164 (87.8)	
No subsequent therapy – death	17/161 (10.6)		22/164 (13.4)	
Received subsequent therapy*	83/111 (74.8)	48/111 (43.2)	109/144 (75.7)†	56/144 (38.9)
Chemotherapy (any)	46/83 (55.4)	41/48 (85.4)	79/109 (72.5)	49/56 (87.5)
Capecitabine	26/83 (31.3)	14/48 (29.2)	37/109 (33.9)	24/56 (42.9)
Paclitaxel	12/83 (14.5)	17/48 (35.4)	20/109 (18.3)	16/56 (28.6)
Eribulin	1/83 (1.2)	11/48 (22.9)	6/109 (5.5)	17/56 (30.4)
Antibody–drug conjugate (any)	1/83 (1.2)	8/48 (16.7)	1/109 (0.9)	20/56 (35.7)
Trastuzumab deruxtecan	0	6/48 (12.5)	1/109 (0.9)	16/56 (28.6)
Sacituzumab govitecan	0	2/48 (4.2)	0	8/56 (14.3)
PI3K inhibitor (any)	5/83 (6.0)	2/48 (4.2)	11/109 (10.1)	3/56 (5.4)
Alpelisib	5/83 (6.0)	2/48 (4.2)	9/109 (8.3)	2/56 (3.6)
mTOR kinase inhibitor (everolimus)	8/83 (9.6)	4/48 (8.3)	10/109 (9.2)	9/56 (16.1)
CDK4/6 inhibitor (any)	8/83 (9.6)	3/48 (6.2)	5/109 (4.6)	3/56 (5.4)
Ribociclib	1/83 (1.2)	1/48 (2.1)	5/109 (4.6)	0
Abemaciclib	2/83 (2.4)	2/48 (4.2)	0	2/56 (3.6)
Other (any)	6/83 (7.2)	0	3/109 (2.8)	5/56 (8.9)

Following treatment discontinuation, fewer patients in the inavolisib group than in the placebo group received chemotherapy in the second line, antibody–drug conjugates in the third line or later, or a PI3K inhibitor in the second line or later

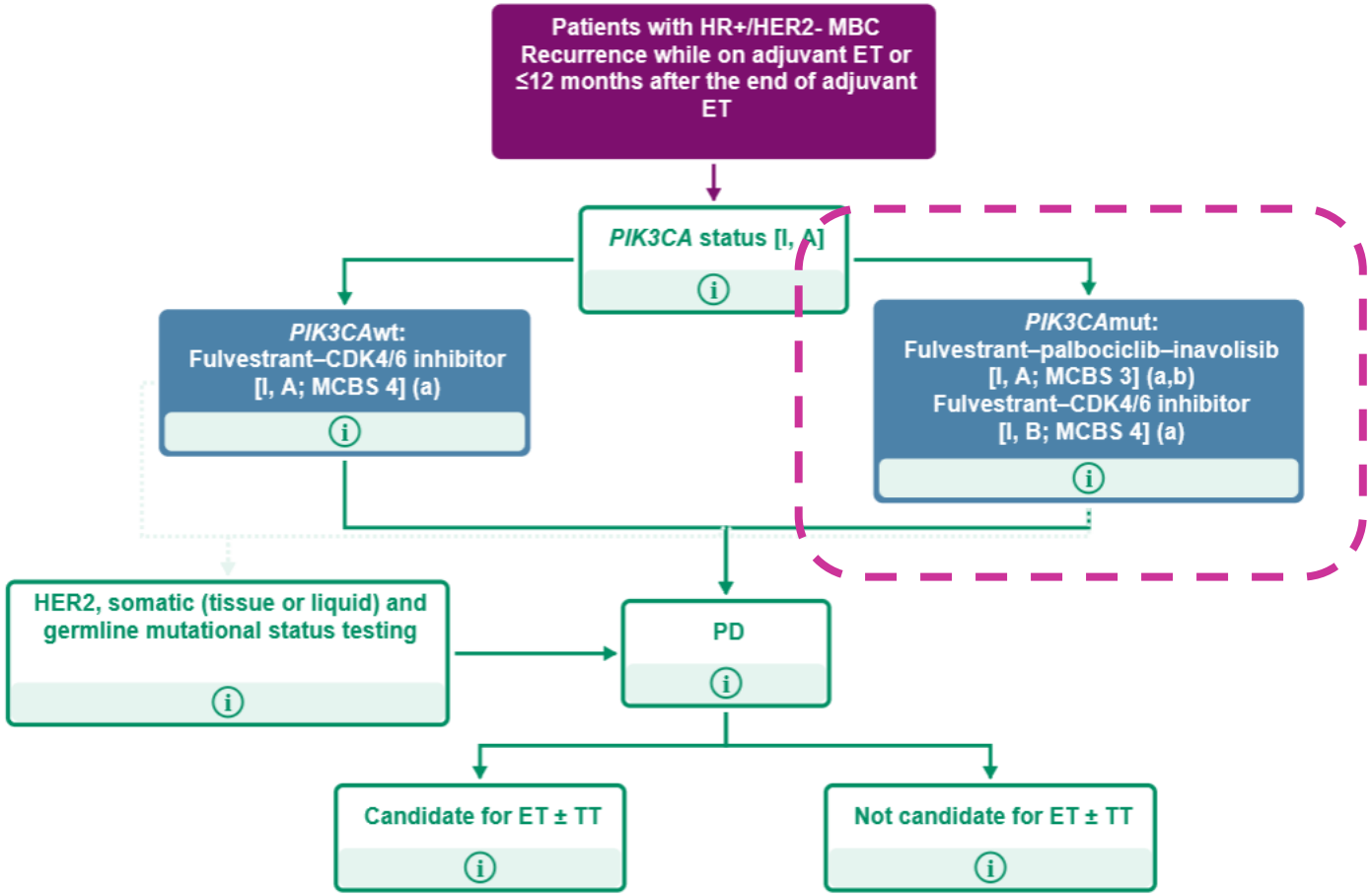
Tylko 15.5% chorych z grupy kontrolnej otrzymało w kolejnych liniach leczenia iPIK3CA
Cross over nie dopuszczony w badaniu

Turner I wsp. ASCO 2025.

ESMO 2025 : zalecenia

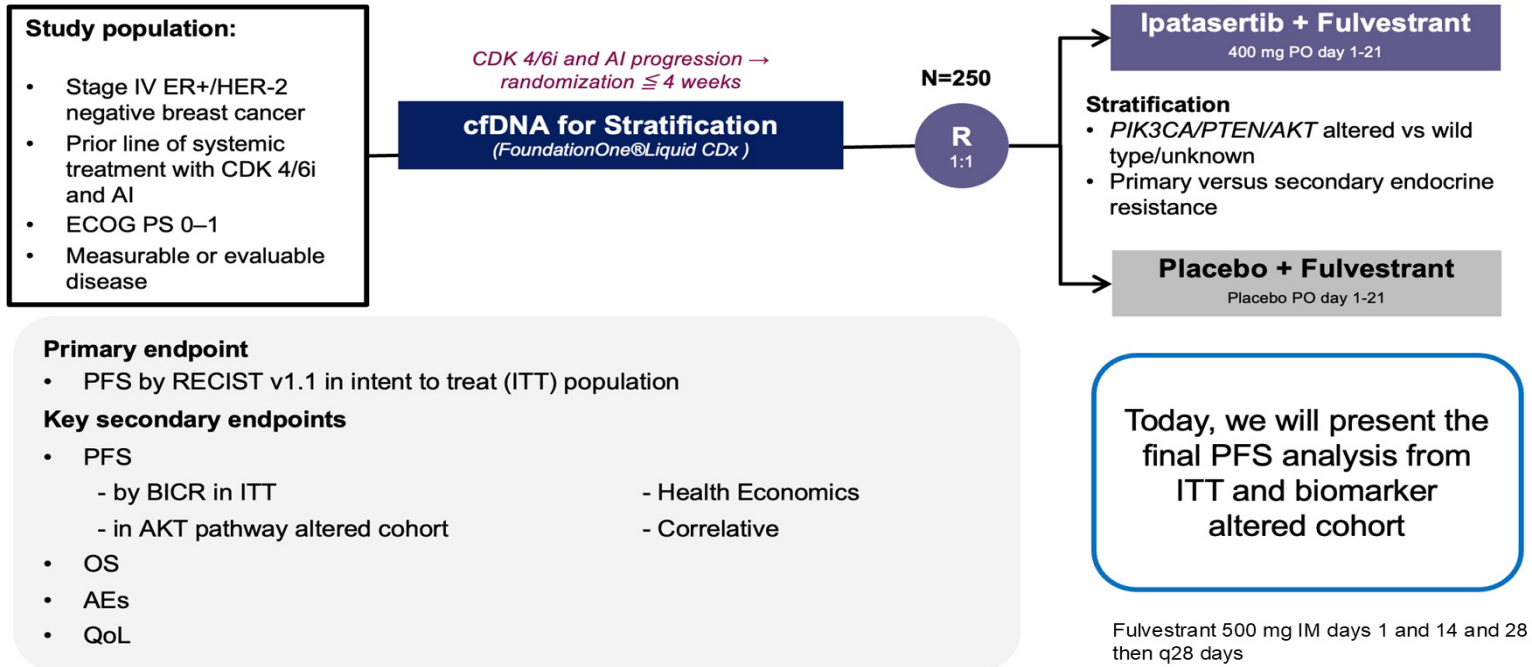
HR+/HER2– MBC: Recurrence While on Adjuvant ET or ≤12 Months After the End of Adjuvant ET (Primary or Secondary ET-Resistance)

v1.2 - April 2025



www. ESMO org

CCTG MA.40/FINER Trial Design

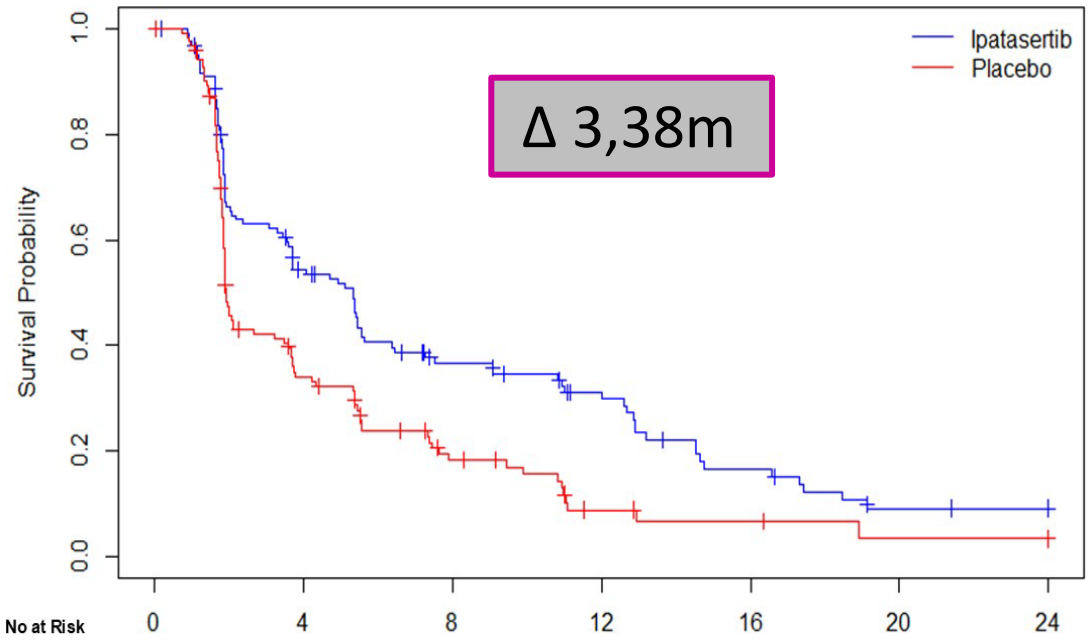


Characteristic	Ipatasertib + Fulvestrant (n=125)	Placebo + Fulvestrant (n=125)	Total Population (n=250)
De novo MBC at presentation	39.2%	40%	39.6%
Sites of disease Bone only Lung and/or liver involvement	 16.8% 66.4%	 16.8% 66.4%	 16.8% 66.4%
Prior duration of CDK 4/6i < 6 months > 6 months	 8% 92%	 4% 96%	 6% 94%
PIK3CA/PTEN/AKT status Wild type/unknown Altered	 54.4% 45.6%	 56.8% 43.2%	 55.6% 44.4%

Chia S . I wsp. ASCO 2025

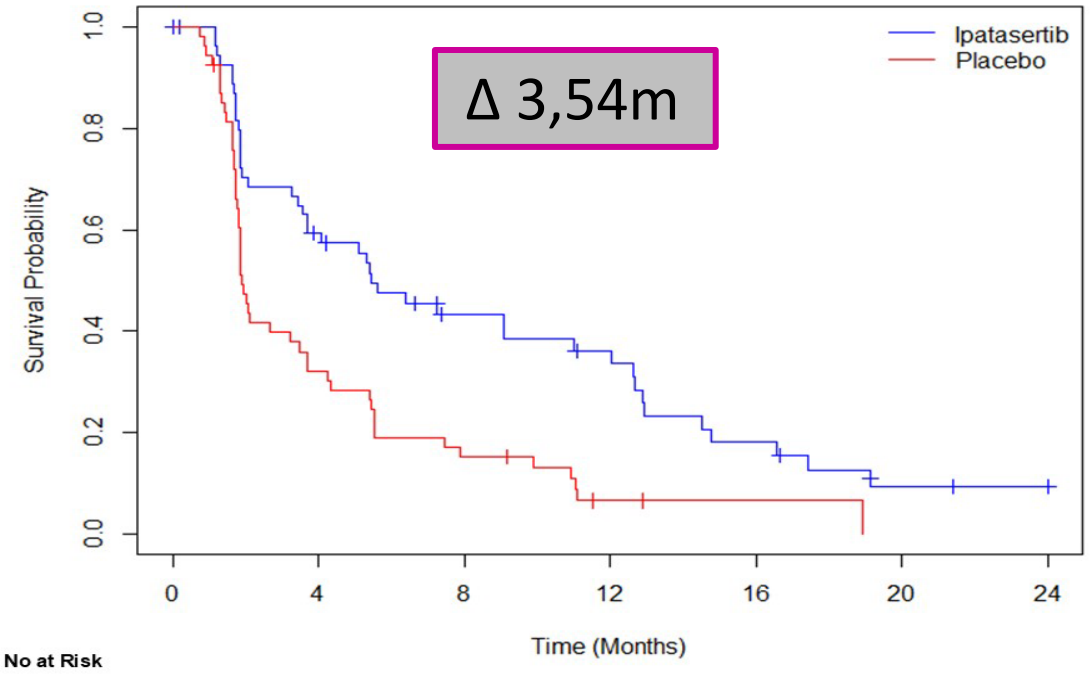
PFS w ITT oraz w populacji z zaburzeniem AKT

ITT



	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	

AKT alt

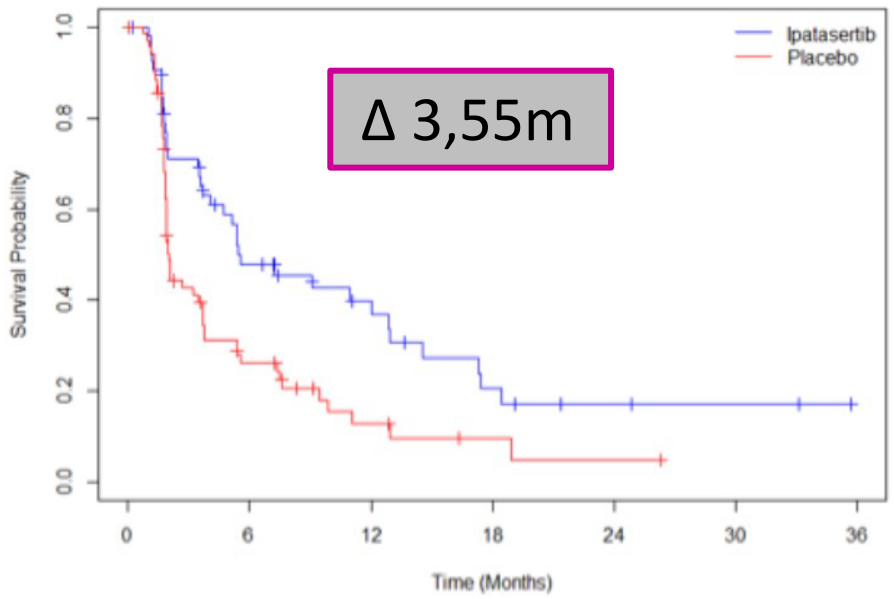


	IPAT arm n=57	PBO arm n=54
Median follow-up: 15.2 months		
Median PFS (95% CI), months	5.45 (3.55-11.01)	1.91 (1.77-3.48)
HR (95% CI)	0.47 (0.31-0.72)	
***P*-value (2-sided)**	0.0005	

Chia S . I wsp. ASCO 2025

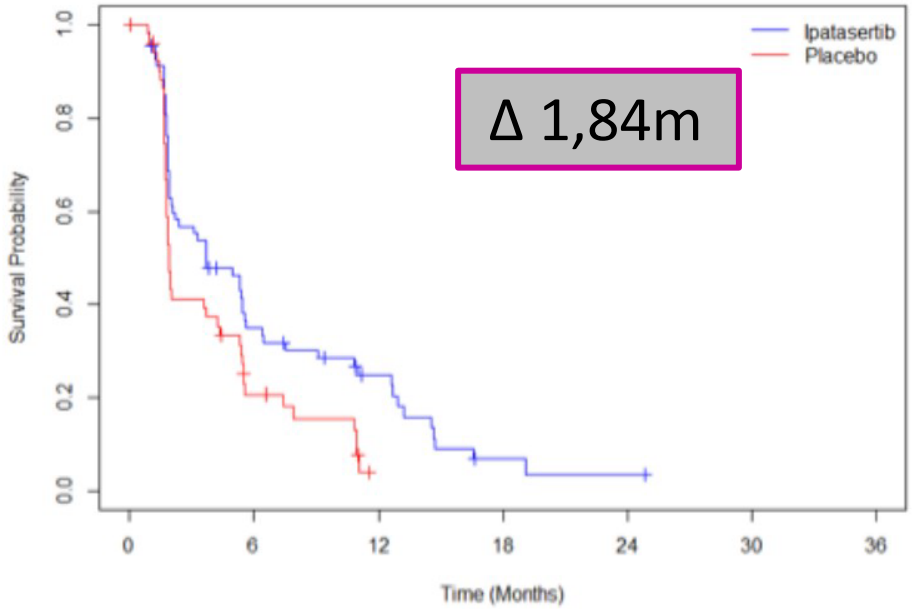
Analiza eksploracyjna PFS w ITT w zależności od stanu ESR1

PFS in *ESR1* wild type cohort (n=128; 51%)



Median PFS
IPAT: 5.55 months 95% CI: (3.71-12.88)
Placebo: 2.00 months 95% CI: (1.84-3.68)
HR 0.54 95% CI (0.36-0.83)

PFS in *ESR1* mutant cohort (n=122; 49%)



Median PFS
IPAT: 3.71 months 95% CI: (2.04-5.45)
Placebo: 1.87 months 95% CI: (1.77-4.24)
HR 0.61 95% CI (0.41-0.91)

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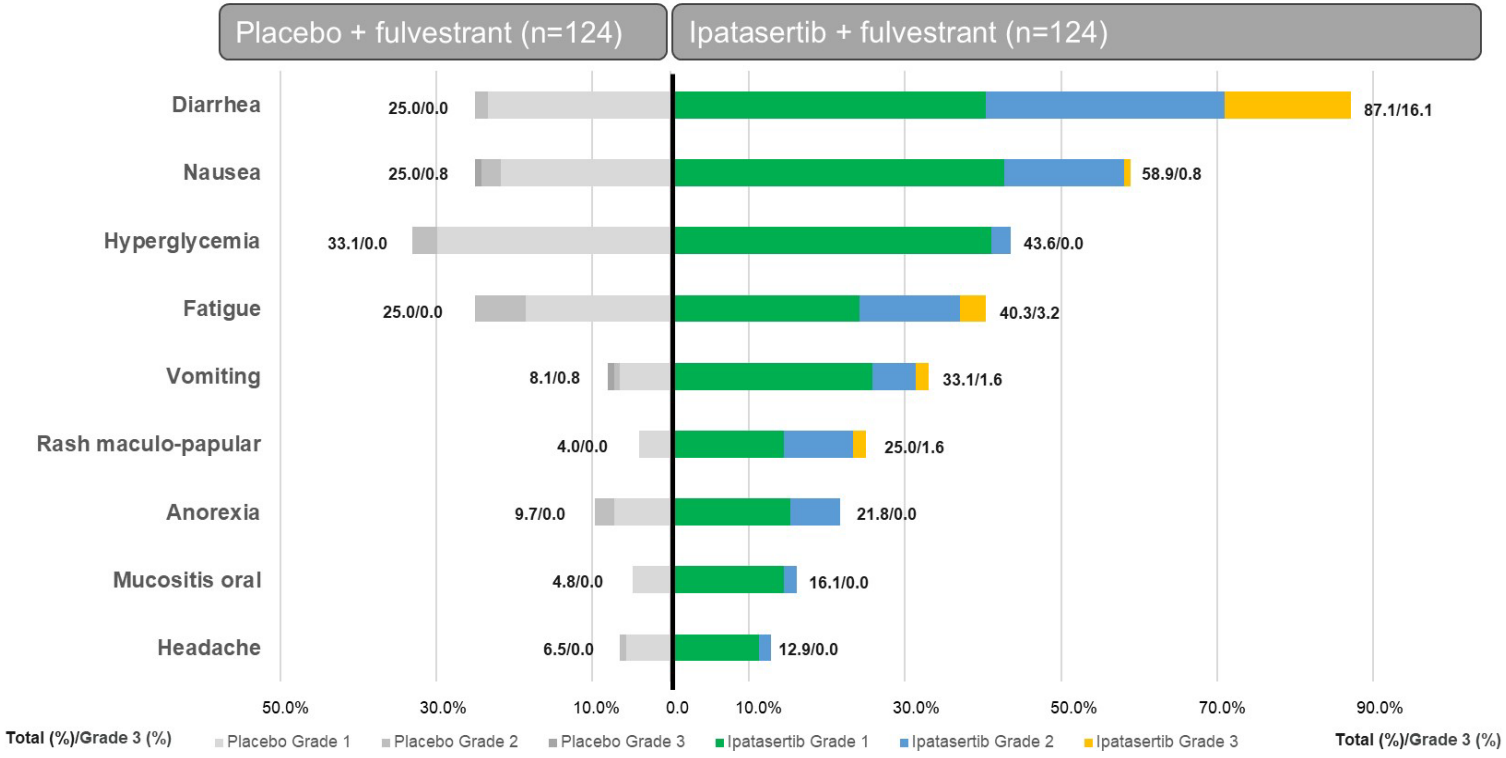
AE związane z ipatasertibem z częstością > 10%



Reason for discontinuation of Ipatasertib / Placebo	Ipatasertib + Fulvestrant (n=124)	Placebo + Fulvestrant (n=124)
Adverse Event - related to protocol treatment	8 (6.5)	1 (0.8)
Progressive disease (Objective)	84 (67.7)	97 (78.2)
Symptomatic progression	5 (4.0)	6 (4.8)
Intercurrent illness - adverse events unrelated to protocol treatment	1 (0.8)	2 (1.6)
Patient refusal (not related to adverse event)	0 (0.0)	4 (3.2)

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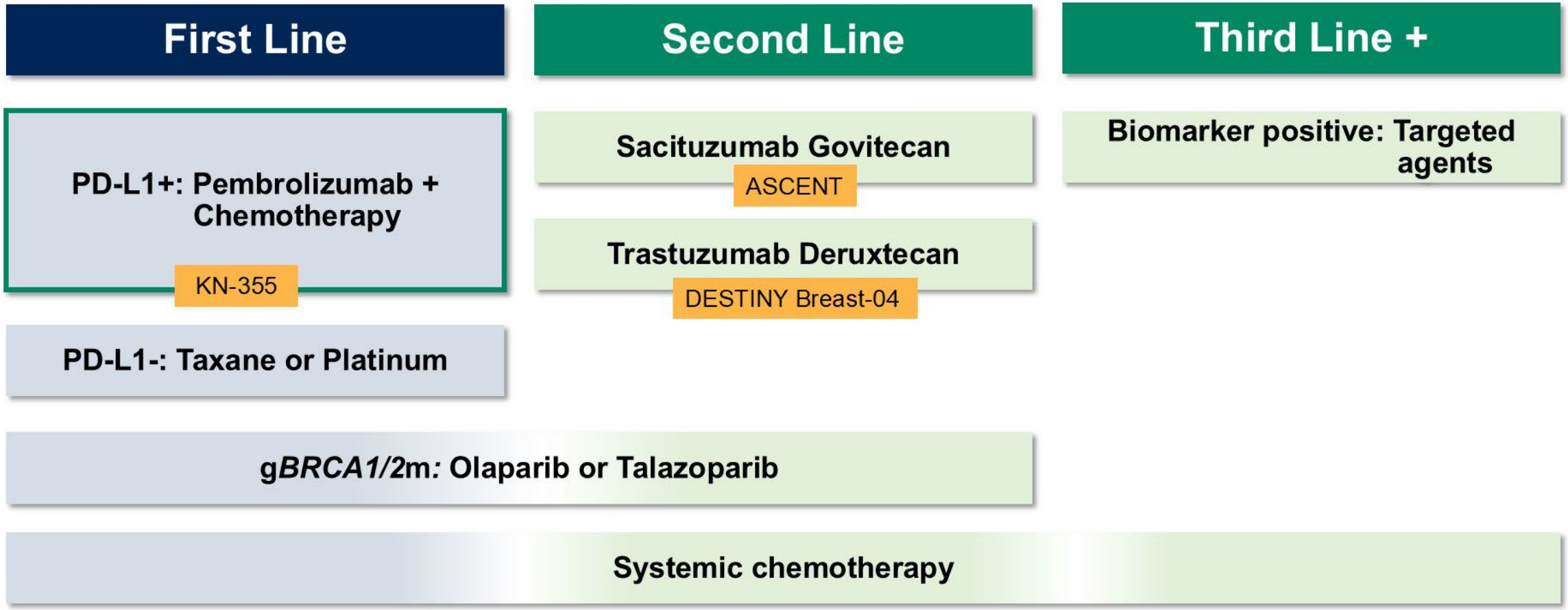
Leczenie mTNBC *anno domini* 2025



NCCN Guidelines. Breast Cancer. v4.2025.

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Wyzwania w leczeniu mTNBC

First Line	Second Line	Third Line +
PD-L1+: Pembrolizumab + Chemotherapy		

- 9.7months Median PFS
- 23 months Median OS[2,3]

- 49% Do **not** receive 2L treatment in the real-world[4]
- 34% **Die** before receiving 2L treatment in the real-world[4]

NCCN Guidelines. Breast Cancer. v4.2025

1. NCCN Guidelines. Breast Cancer. v4.2025
2. Cortes et al. Lancet 2020 3. Cortes et al. NEJM 2022
4. Punie et al. The Oncologist 2025

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ASCENT-05/KEYNOTE- D19- projekt badania

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/m^2 OR nab-paclitaxel 100 mg/m^2 on days 1, 8, & 15 of 28-day cycles, OR gemcitabine 1000 mg/m^2 + 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

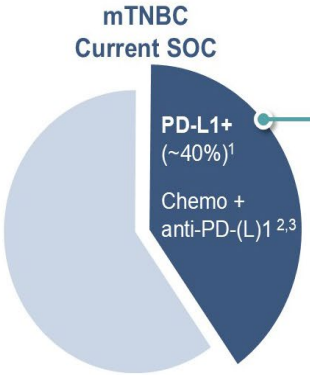
- PFS by BICR[e]

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)



Remaining unmet need

- Median PFS observed in prior studies of chemotherapy in combination with immune checkpoint inhibitors was 7.5-9.7 months[1,4]; most patients still experience disease progression[5-7]
- About half of the patients treated for 1L mTNBC do not receive 2L treatment[5]

Rationale for this study

- SG is the only Trop-2–directed ADC with demonstrated OS benefit in multiple phase 3 studies; it is approved for 2L+ mTNBC and pre-treated HR+/HER2- mBC in multiple countries[8,9]
- Early studies have observed improved anti-tumor effects when immunotherapy is combined with ADCs[10]

ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Curative treatment-free interval, n (%)		
De novo	75 (34)	75 (34)
Recurrent within 6-12 mo	40 (18)	40 (18)
Recurrent > 12 mo	106 (48)	107 (48)
Prior anti-PD-(L)1 therapy,[g] n (%)	9 (4)	11 (5)

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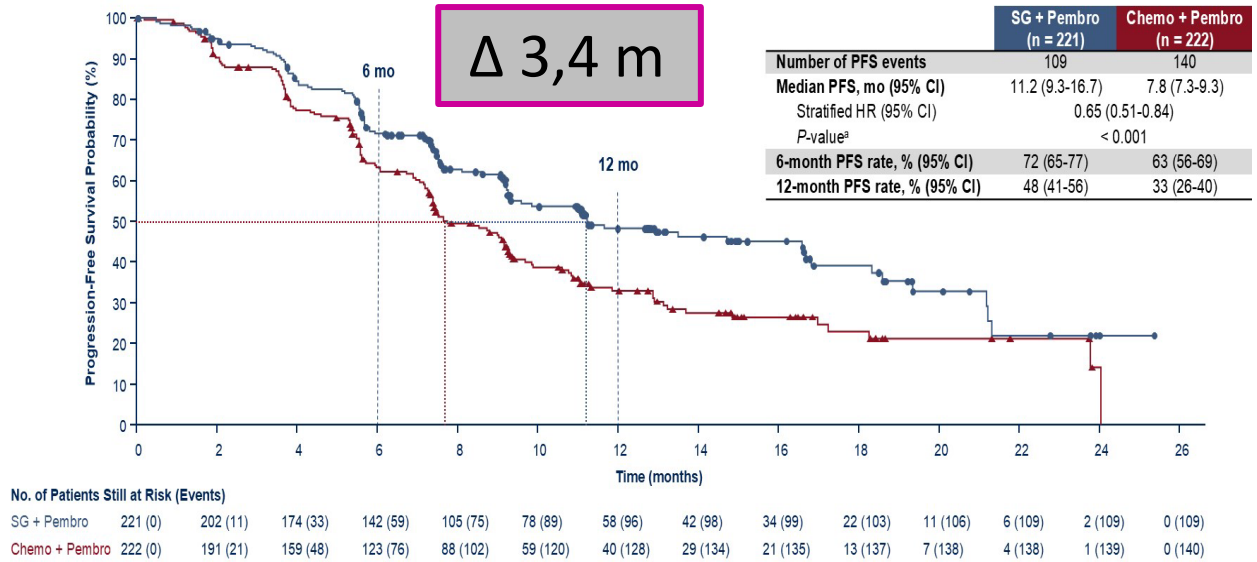
ASCENT-05/KEYNOTE- D19- PFS i OS

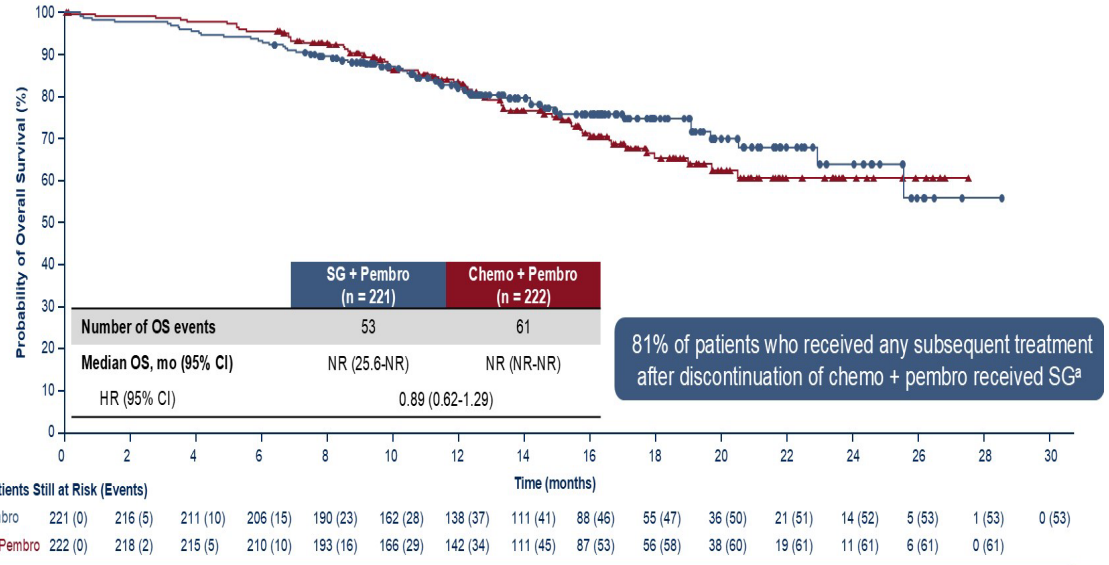
Progression-Free Survival by BICR



	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

Descriptive Overall Survival at Primary Analysis



	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 who received any subsequent treatment after discontinuation of chemo + pembro received SG[a]

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

81% chorych z ramienia CT-Pembro w 2. linii otrzymała SG

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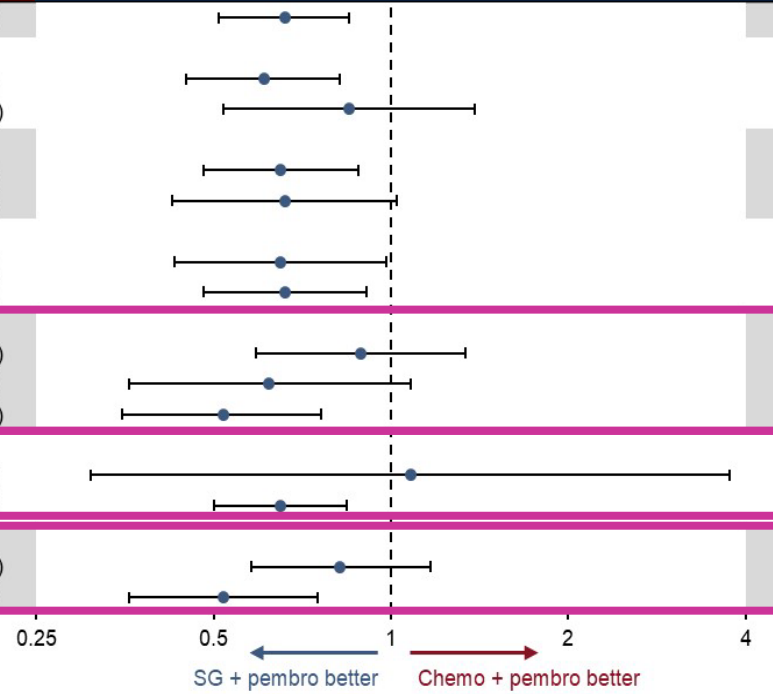
ASCENT-05/KEYNOTE- D19- analiza podgrup dla PFS

	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

Tylko 5% chorych otrzymało ICI w leczeniu okołooperacyjnym

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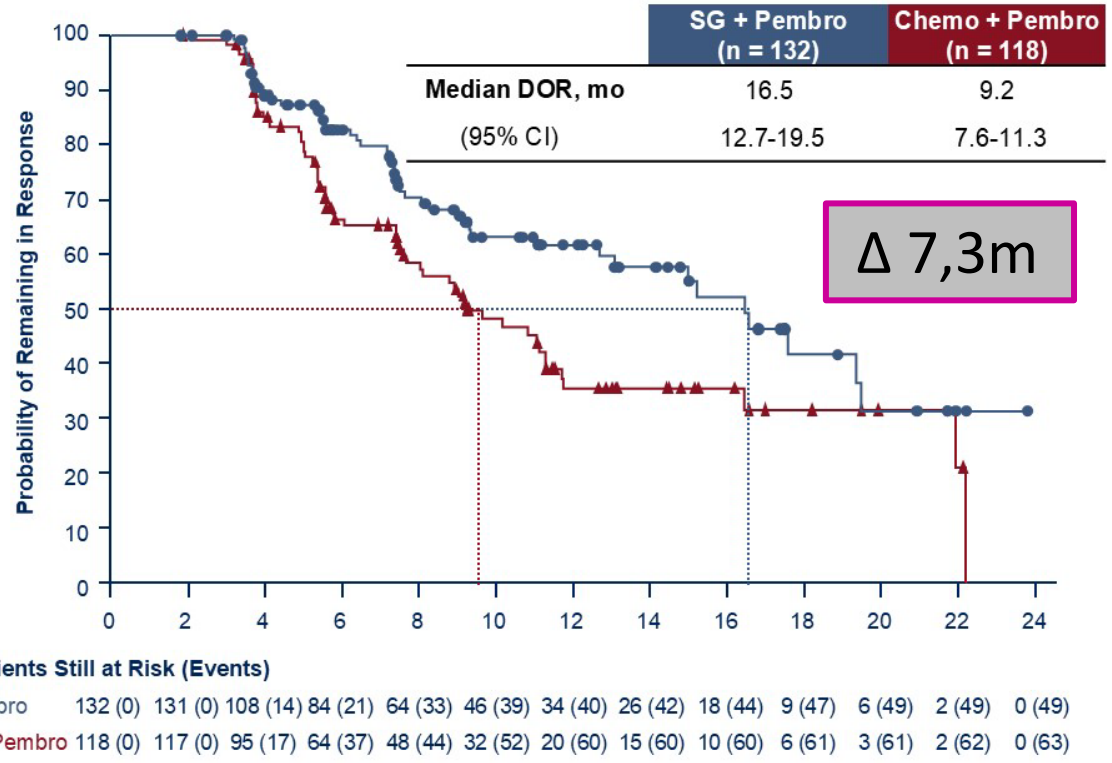
ASCENT-05/KEYNOTE- D19- ORR i czas trwania odpowiedzi

Variable	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Objective response rate[a] (95% CI), %	60 (52.9-66.3)	53 (46.4-59.9)
Stratified odds ratio (95% CI)	1.3 (0.9-1.9)	
Best overall response, n (%)		
Complete response	28 (13)	18 (8)
Partial response	104 (47)	100 (45)
Stable disease	70 (32)	70 (32)
Stable disease ≥ 6 months	23 (10)	29 (13)
Progressive disease	9 (4)	26 (12)
Not evaluable	10 (5)	8 (4)
Time to response,[b] median (range), months	1.9 (1.0-9.3)	1.9 (1.1-11.4)



A substantially longer duration of response and a higher overall response rate (including an increased complete response rate) was observed for SG + pembro vs chemo + pembro

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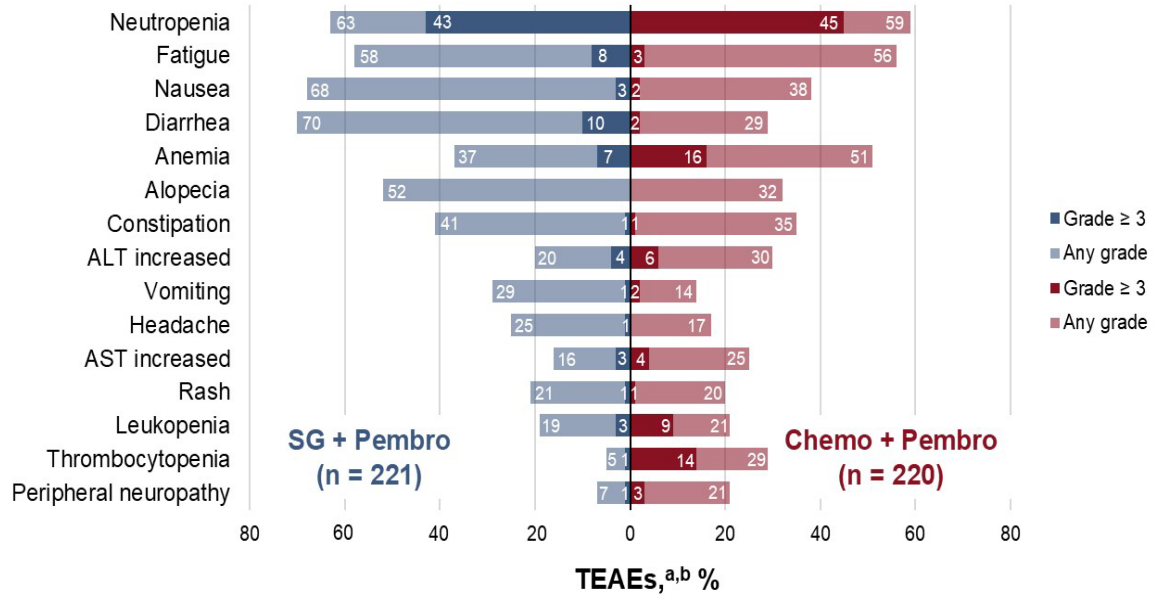
ASCENT-05/KEYNOTE- D19- powikłania

Most Common Adverse Events (≥20% in any group)



n (%)	SG + Pembro (n = 221)	Chemo + Pembro (n = 220)
Any TEAE	220 (> 99)	219 (> 99)
Grade ≥ 3	158 (71)	154 (70)
Treatment-emergent SAE	84 (38)	68 (31)
Treatment-related	61 (28)	42 (19)
TEAEs leading to treatment discontinuation[a]	26 (12)	68 (31)
TEAEs leading to dose interruption	171 (77)	162 (74)
TEAEs leading to dose reduction[b]	78 (35)	96 (44)
TEAEs leading to death[c]	7 (3)	6 (3)
Treatment-related	3 (1)	1 (< 1)

The AEs observed are consistent with the known profiles of both SG and pembro

Despite longer duration of treatment with SG + pembro, rates of grade ≥ 3 AEs were similar for both groups. TEAEs leading to dose reduction or treatment discontinuation were lower with SG + pembro

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OptiTROP- Breast 05- projekt badania

Multicenter, open-label phase II study (NCT05445908)

Key eligibility criteria

- **No prior systemic therapy for a/m TNBC**
- **PD-L1 positive or negative[a]**
- **DFI ≥6 months**
- **ECOG PS 0–1**

→ **Sac-TMT (5 mg/kg Q2W)** → Treatment until disease progression or unacceptable toxicity →

Primary endpoint[b]

- ORR by investigator assessment

Secondary endpoints

- PFS, DOR, DCR, OS
- Safety

Tumor assessment

- Every 6 weeks for the first 18 months and every 12 weeks afterward.

Characteristic	Sac-TMT (N = 41)
Female, n (%)	41 (100)
Median age (range), yr	55 (34, 75)
≥65 years, n (%)	5 (12.2)
ECOG PS, n (%)	
0	23 (56.1)
1	18 (43.9)
Location of metastasis, n (%)	
Visceral sites[a]	25 (61.0)
Lung	19 (46.3)
Bone	8 (19.5)
Liver	6 (14.6)

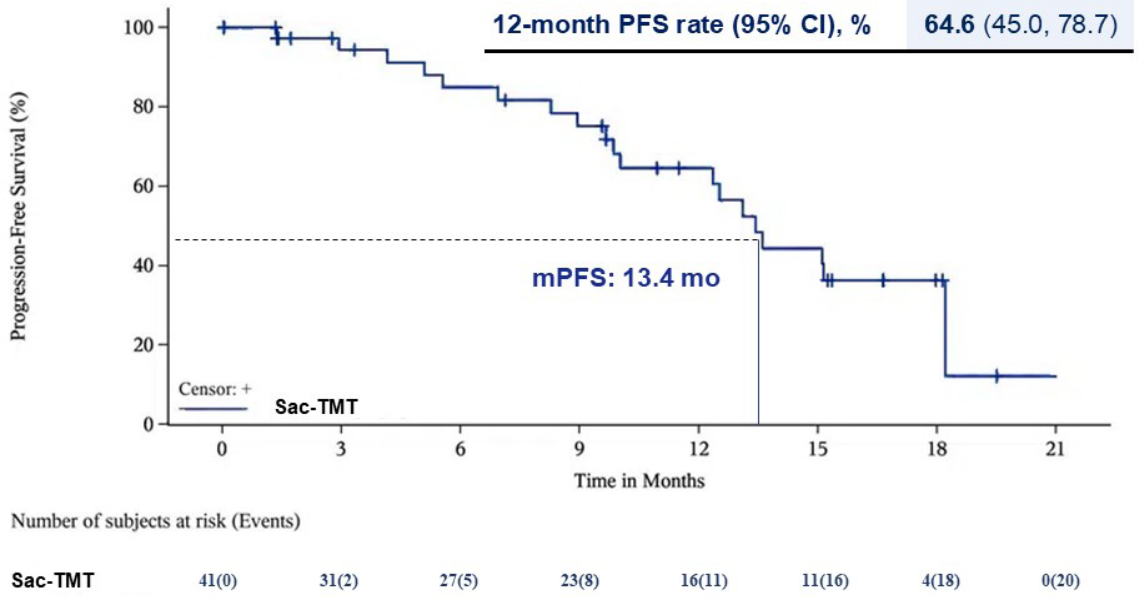
Characteristic	Sac-TMT (N = 41)
Disease-free interval, n (%)	
De novo metastasis	12 (29.3)
6-12 months	8 (19.5)
≥12 months	21 (51.2)
Prior treatments, n (%)	
Radiotherapy	15 (36.6)
Chemotherapy	27 (65.9)
Hormonal therapy	6 (14.6)
PD-L1 expression,[b] n (%)	
CPS <10	32 (78.0)
CPS ≥10	9 (22.0)

Yongmei Yin I wsp. ASCO 2025.

OptiTROP- Breast 05: PFS

PFS benefits were observed regardless of PD-L1 expression.

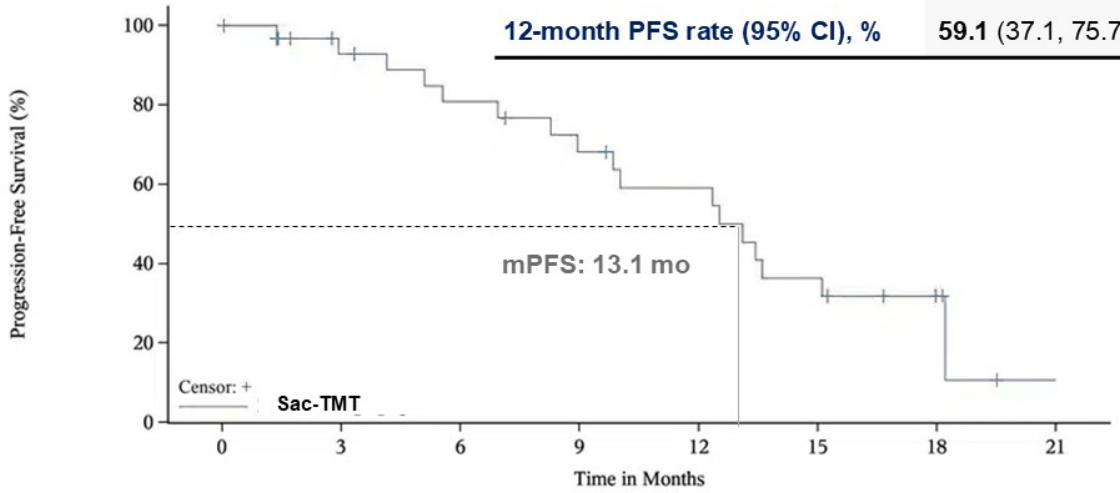
	All patients (N = 41)
PFS events, n (%)	20 (48.8)
Median PFS, months (95% CI)	**13.4** (9.9, 18.2)
12-month PFS rate (95% CI), %	**64.6** (45.0, 78.7)



Number of subjects at risk (Events)

Sac-TMT	41(0)	31(2)	27(5)	23(8)	16(11)	11(16)	4(18)	0(20)

	PD-L1 CPS <10 (N = 32)
PFS events, n (%)	18 (56.3)
Median PFS, months (95% CI)	**13.1** (8.9, 18.2)
12-month PFS rate (95% CI), %	**59.1** (37.1, 75.7)



Number of subjects at risk (Events)

Sac-TMT	32(0)	24(2)	20(5)	16(8)	13(10)	8(15)	4(16)	0(18)

Tylko 7.3% chorych przerwało leczenie z powodu powikłań

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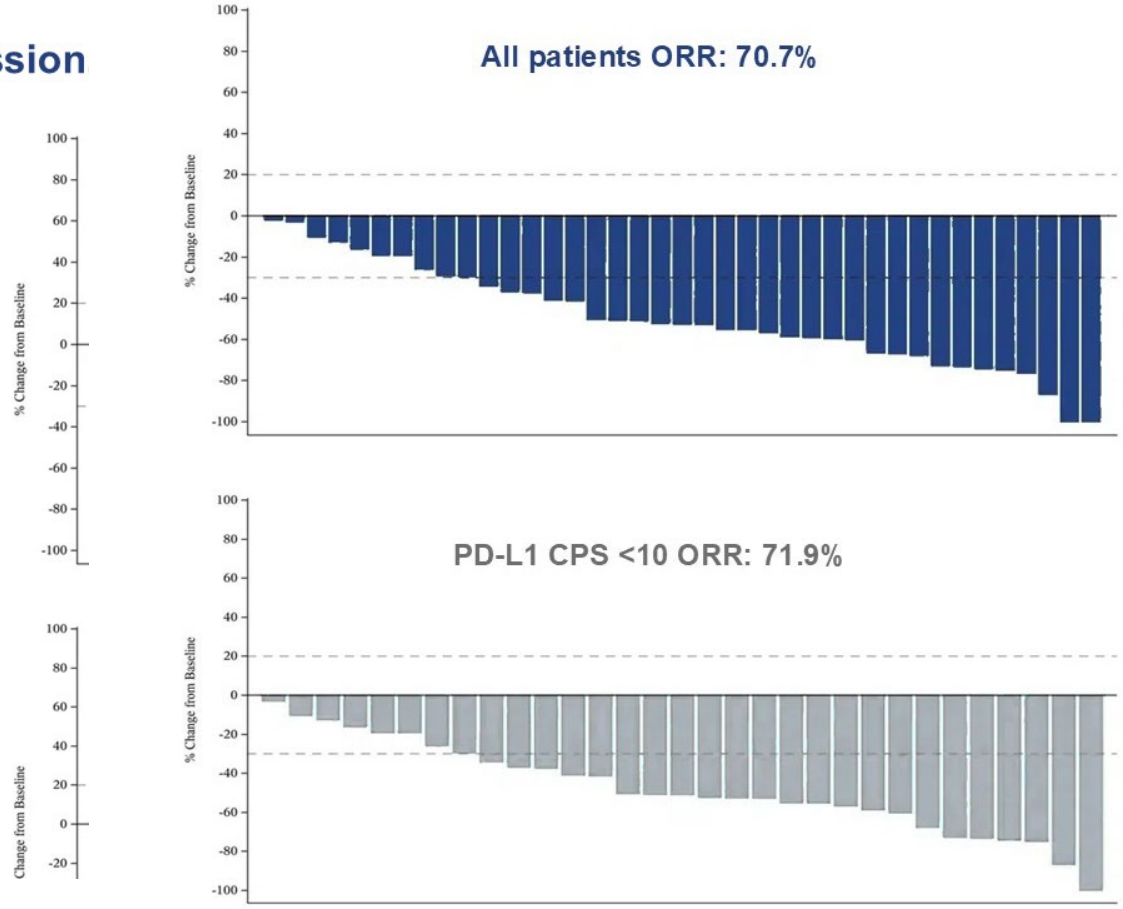
OptiTROP- Breast 05:ORR

Antitumor Responses were observed regardless of PD-L1 expression

	All patients (N = 41)	PD-L1 CPS <10[c] (N = 32)
ORR[a], n (%)	29 (**70.7**)	23 (**71.9**)
(95% CI)	(54.5, 83.9)	(53.3, 86.3)
CR[b], n (%)	2 (4.9)	1 (3.1)
PR, n (%)	27 (65.9)	22 (68.8)
Confirmed PR, n (%)	24 (58.5)	19 (59.4)
SD, n (%)	9 (22.0)	7 (21.9)
DCR, n (%)	38 (**92.7**)	30 (**93.8**)
(95% CI)	(80.1, 98.5)	(79.2, 99.2)



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Pięknych wakacji