Zastosowanie inhibitorów kinaz zależnych od cyklin u młodych chorych z zaawansowanym hormonozależnym rakiem piersi

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UNIWERSYTET MEDYCZNY IM. KAROLA MARCINKOWSKIEGO W POZNANIU

Rak piersi jako choroba nieuleczalna

- Zaawansowany rak piersi to:
  - choroba **miejscowo zaawansowana**, która nie kwalifikuje się do terapii miejscowej (chirurgii, radioterapii)
  - choroba **rozsiana** do innych narządów

- Średni czas przeżycia wynosi ok. 3 lata

- 25% chorych przeżywa ponad 5 lat

Real World Data on OS in MBC

	Year of Diagnosis					
OS (m)	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
HR + HER2- (N=9.908)	43.7 (40.2 – 46.6)	42.0 (38.9 – 44.6)	40.9 (38.0 – 43.4)	42.0 (39.2 – 45.0)	44.5 (41.8 – 47.3)	40.3 (37.8 – ND)
HER2+ (N=2.861)	38.6 (33.6 – 44.6)	42.3 (38.3 – 50.8)	40.1 (35.2 – 45.6)	42.3 (36.5 – 49.8)	51.1 (46.5 – ND)	Not Reached
HR- HER2- (N=2.317)	15.1 (12.7 – 16.4)	15.1 (13.0 – 17.4)	14.7 (13.2 – 17.0)	14.0 (11.4 – 15.9)	13.9 (11.4 – 15.9)	14.1 (12.5 – 15.5)

Delaloge S, et al. ASCO 2017

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Delaloge S, et al. ASCO 2017

Every ABC patient should:

- Have access to the most up-to-date treatments and to innovative therapies at accessible Breast Units/Centres. — Expert opinion/ A — 100%
- Be treated in Specialist Breast Units/ Centres/Services (SBUs) by a specialised multidisciplinary team including specialised side effects management and a nurse experienced in the treatment of ABC. — I/A

ABC4 2018

Czy młode chore z rakiem piersi wymagają odmiennego postępowania??

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The age of the patient should not be the sole reason to withhold effective therapy (in elderly patients) nor to overtreat (in young patients). Age alone should not determine the intensity of treatment.	I/E	100%

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ABC4 2018

- Młode chore z rakiem piersi to kobiety do 40r.ż.

- Zachorowania u młodych stanowią ok. 7% spośród wszystkich zachorowań na raka piersi
  - w niektórych krajach nawet do 20%

  (czynniki genetyczne, środowiskowe, późny wiek posiadania potomstwa)

- Rak piersi jest jednym z najczęstszych nowotworów litych u młodych kobiet i pierwszą przyczyną zgonu

- Młody wiek NIE pogarsza rokowania, ale...
  - częściej diagnozowane są bardziej agresywne podtypy biologiczne raka piersi (trójujemny, HER2 dodatni)
  - częściej choroba jest bardziej zaawansowana w chwili rozpoznania (często trudności diagnostyczne)

- Gorsze rokowanie może wynikać z:
  - suboptymalnej terapii
  - braku *compliance* ze strony chorych (co piąta chora nie kontynuuje hormonoterapii z powodu pogorszenia jakości życia)

MŁODE KOBIETY

Chore przed menopauzą

Chore po menopauzie

- po usunięciu jajników
- wiek ≥60 lat
- wiek <60 lat i brak miesiączki >12 m. bez innych przyczyn
- w trakcie terapii tamoksyfenem pomenopauzalny poziom FSH i estradiolu

Many trials in ER-positive ABC have not included **PRE-MENOPAUSAL** women. Despite this, we recommend that young women with ER-positive ABC should have adequate OFS/OFA and then be treated in the same way as post-menopausal women, with endocrine agents and with or without targeted therapies.	Expert opinion/ A	95%

ABC4 2018

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Leczenie choroby zaawansowanej:

- Wydłużenie przeżycia (czasami do kilku/kilkunastu lat)
- Wydłużenie czasu do progresji choroby
- Wydłużenie czasu do włączenia chemioterapii
- Poprawa jakości życia

ABC4 2018

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- Poprawa jakości życia

- Uszanowanie woli pacjentki!!!!

ABC4 2018

The addition of a CDK 4/6 inhibitor to an AI, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is, therefore, one of the preferred treatment options for pre- and peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women. Patients relapsing <12	I/A	90%

The addition of a CDK 4/6 inhibitor to fulvestrant, in patients previously exposed to ET, provided significant improvement in median PFS (6–7 months) as well as improvement in QoL, and is one of the preferred treatment options, if a CDK 4/6 inhibitor was not previously used, for pre- and peri-menopausal women with OFS/OFA and post-menopausal women and men. OS results are awaited.	I/A	90%

ABC4 2018

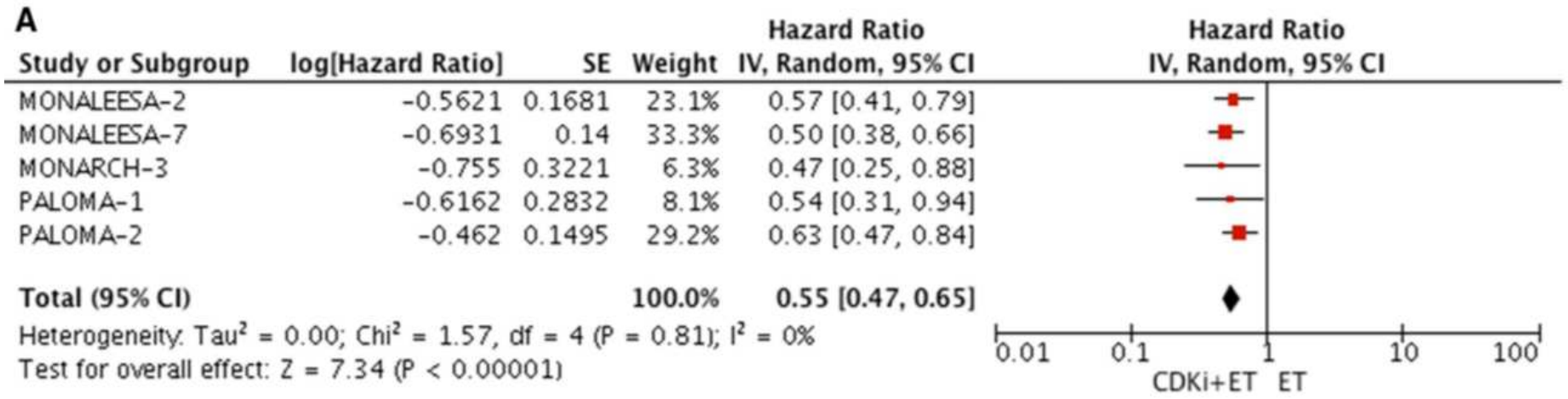
Młode chore w badaniach klinicznych z inhibitorami kinaz zależnych od cyklin

Trial	Design	Population characteristics	Setting	Primary endpoint	PFS
Paloma 1 [7]	Open label, randomized, phase II, palbociclib + letrozole versus letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.49 (95% CI 0.32–0.75)
Paloma 2 [8]	Double blind, randomized (2:1), phase III, palbociclib + letrozole versus placebo + letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.58 (95% CI 0.46–0.72)
Monaleesa 2 [9]	Double blind, randomized (1:1), phase III trial, ribociclib + letrozole vs placebo + letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.56 (95% CI 0.43–0.72)
Monarch 3 [12]	Double blind, randomized (2:1), phase III, abemaciclib + AI (letrozole or anastrozole) versus abemaciclib + AI	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.54 (95% CI 0.41–0.72)

Messina 2018

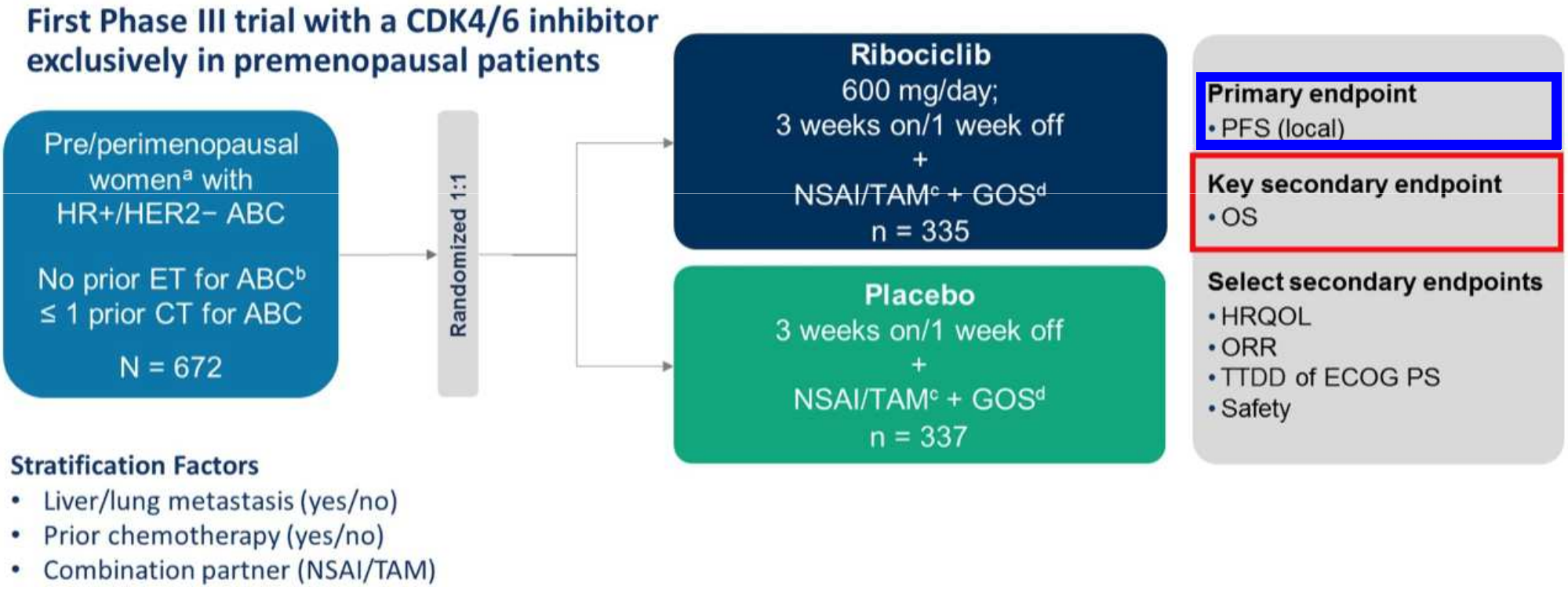
Monaleesa 3 [14]	Double blind, randomized (2:1), phase III, ribociclib + fulvestrant versus placebo + fulvestrant	HR+ HER2−, postmenopausal pts, newly diagnosed or relapse > 12 months from (neo)-adjuvant ET, or progressed after one line of ET	1°and 2°line	PFS	HR 0.59 (95% CI 0.48–0.73)
Monaleesa 7 [13]	Double blind, randomized (1:1), phase III, ribociclib + tamoxifen or AI versus placebo + tamoxifen or AI	HR+ HER2−, premenopausal or perimenopausal pts, progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	1° line	PFS	HR 0.55 (95% CI 0.44–0.69)

PFS



Messina 2018

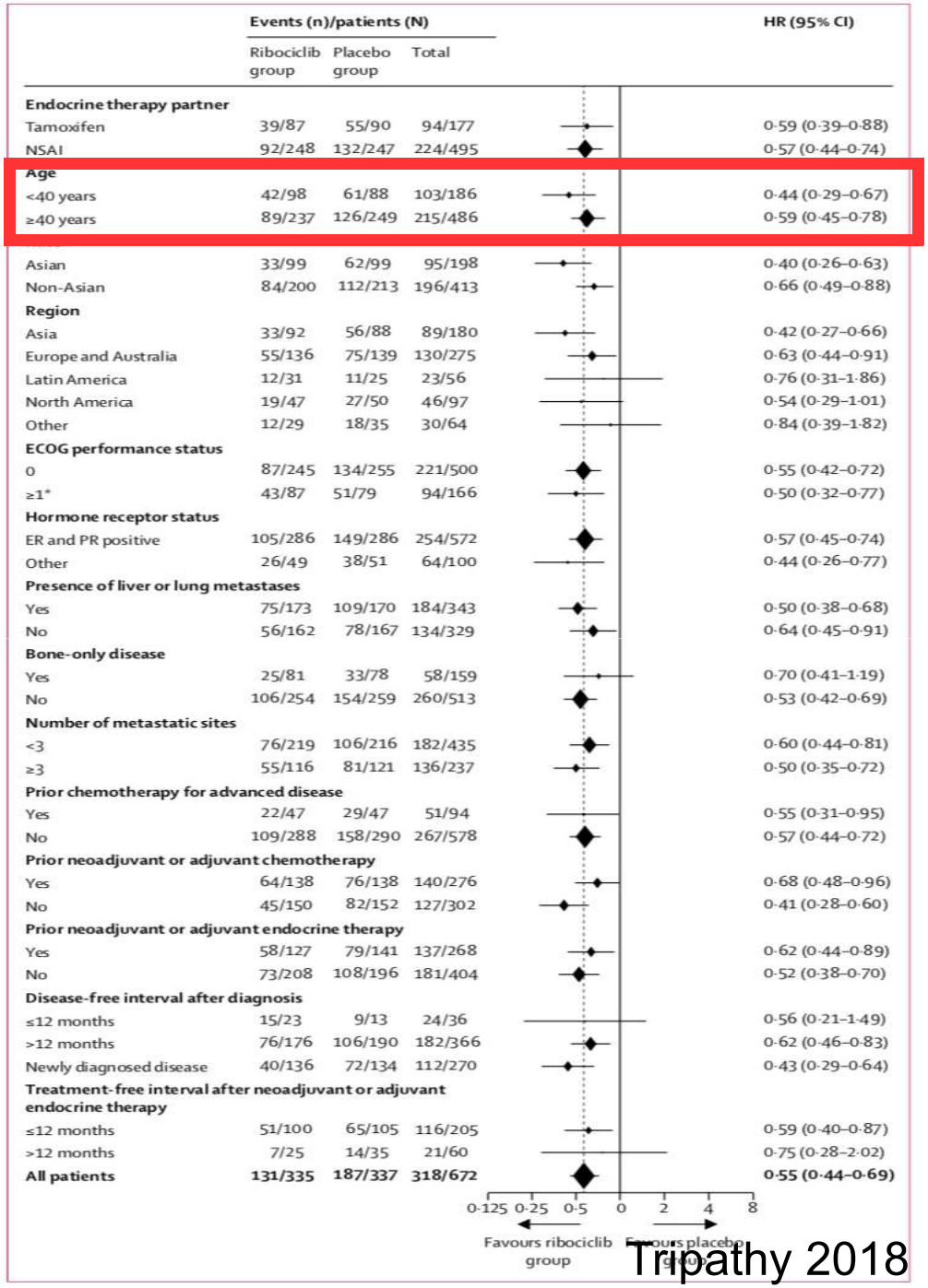
Monaleesa 7 – badanie III fazy



Tripathy 2018

	Ribociclib group (n=335)	Placebo group (n=337)
Age, years	43 (25–58)	45 (29–58)
Race		
White	187 (56%)	201 (60%)
Asian	99 (30%)	99 (29%)
Black	10 (3%)	9 (3%)
Other or unknown	39 (12%)	28 (8%)
ECOG performance status		
0	245 (73%)	255 (76%)
1	87 (26%)	78 (23%)
2	0	1 (<1%)
Missing	3 (1%)	3 (1%)
Disease status at study entry		
Locally advanced	1 (<1%)	1 (<1%)
Metastatic	334 (100%)	336 (100%)
Hormone receptor status		
Oestrogen receptor positive	331 (99%)	335 (99%)
Progesterone receptor positive	290 (87%)	288 (85%)
Disease-free interval*		
Newly diagnosed disease	136 (41%)	134 (40%)
Existing disease	199 (59%)	203 (60%)
≤12 months	23 (7%)	13 (4%)
>12 months	176 (53%)	190 (56%)
Previous neoadjuvant or adjuvant endocrine therapy		
No	208 (62%)	196 (58%)
Yes	127 (38%)	141 (42%)
Progression ≤12 months after endocrine therapy	100 (30%)	105 (31%)
Progression >12 months after endocrine therapy	25 (7%)	35 (10%)
Data missing	2 (1%)	1 (<1%)

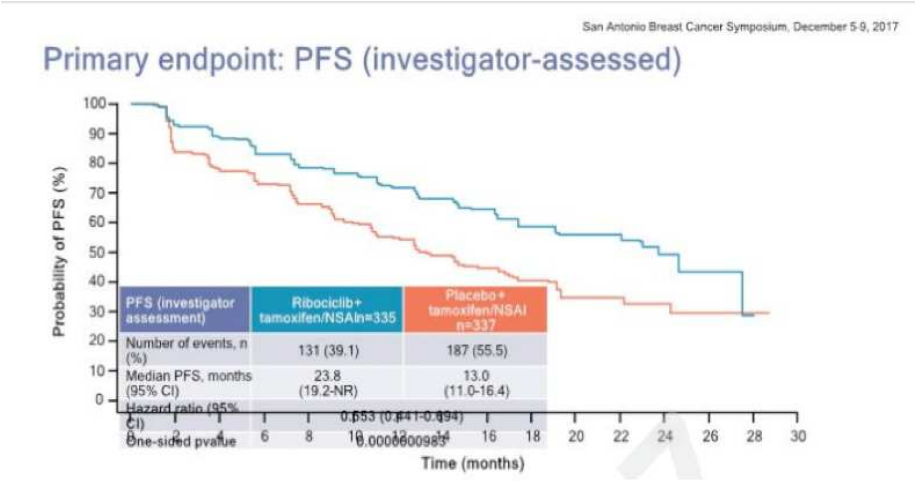
(Table 1 continues in next column)



Tripathy 2018

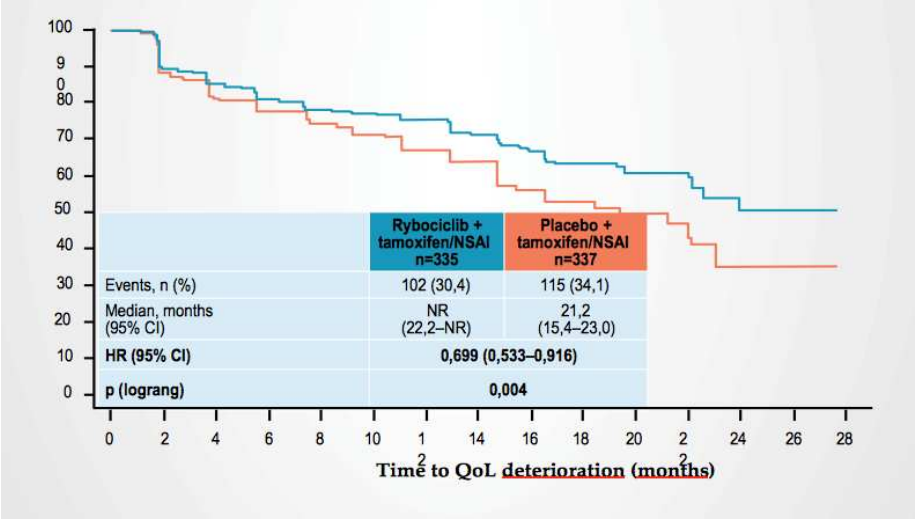
Wydłużenie PFS w grupie leczonej rybocyklibem

- 23.8 m. vs. 13 m. (HR 0.55; 95%CI 0.44-0.69; p<0.0001)

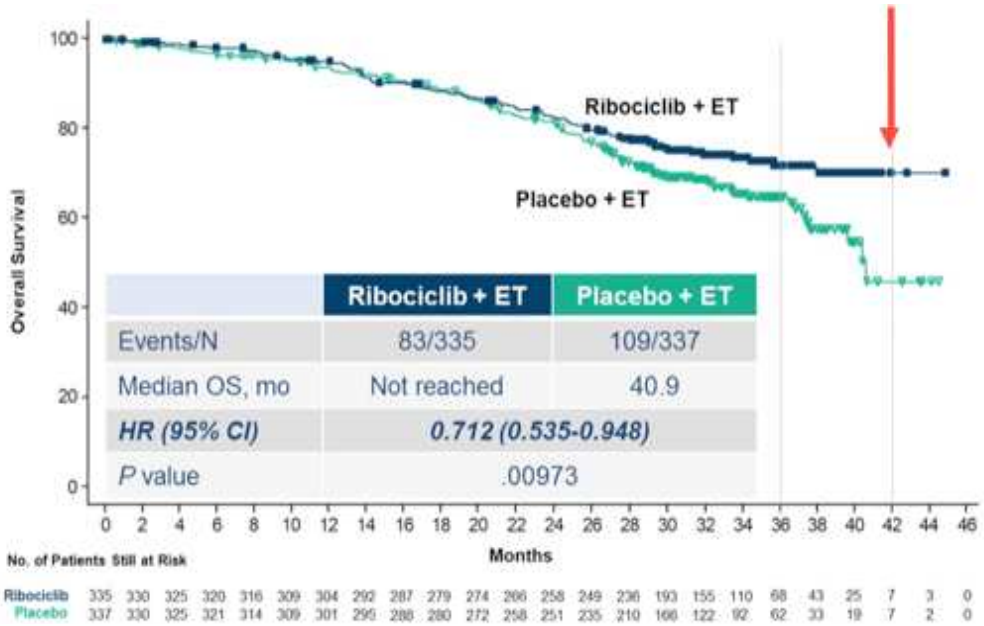


Wydłużenie czasu do pogorszenia jakości życia w grupie leczonej rybocyklibem

- NR vs. 21.2 m. (HR 0.699; 95%CI 0.533-0.916; p<0.0004)



Tripathy 2018

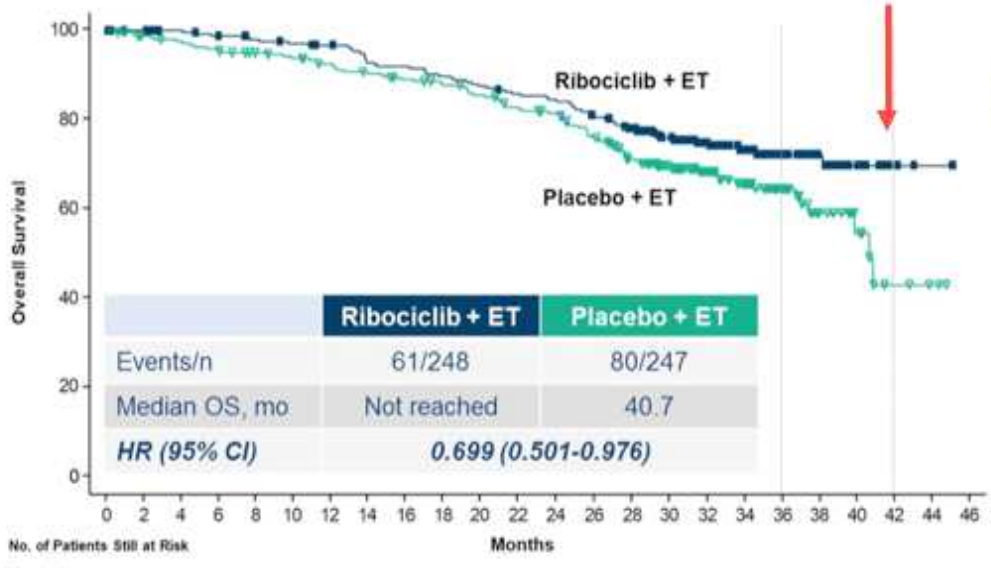


	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

OS w całej populacji

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***



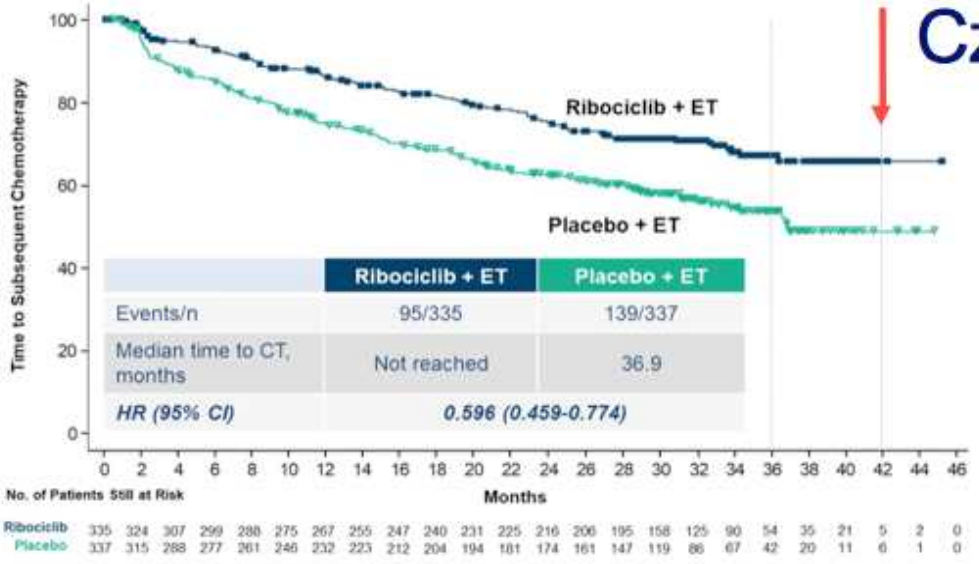
	Ribociclib + ET	Placebo + ET
Events/n	61/248	80/247
Median OS, mo	Not reached	40.7
HR (95% CI)	***0.699 (0.501-0.976)***	

OS w populacji leczonej IA

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	72.2%	64.6%
42 months	69.7%	43.0%

Tripathy 2018



Czas do rozpoczęcia chth po progresji

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	67.2%	53.8%
42 months	65.8%	49.0%

- Średni czas terapii w grupie Rybocyklib+ET wynosił **2 lata,** w grupie placebo+ET - **1 rok**

- Działania niepożądane 3. i 4. stopnia:
  - neutropenia 63.5% vs. 4.5%
  - toksyczność wątrobowa 11% vs. 6.8%
  - wydłużony QT 1.8% vs. 1.2%

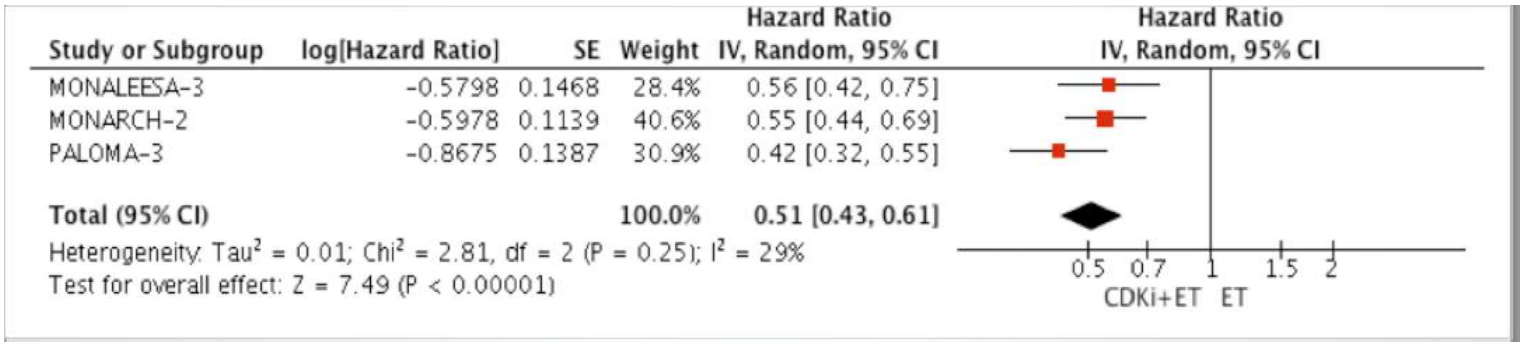
Tripathy 2018

- Rybocyklib + hormonoterapia zmniejsza względne ryzyko zgonu o ok. 30%

- Monaleesa 7 to pierwsze badanie, w którym potwierdzono znamienne wydłużenie OS u pacjentów leczonych inhibitorami CDK4/6 w połączeniu z ET

Trial	Design	Population characteristics	Setting	Primary endpoint	PFS
Paloma 3 [10]	Double blind, randomized (2:1), phase III, palbo + ful vs palbo + fulvestrant	HR+ HER2−, postmenopausal pts or pre-peri menopausal, pts progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	2° line	PFS	HR 0.42 (95% CI 0.32–0.56)
Monarch 2 [11]	Double blind, randomized (2:1), phase III, abemaciclib + fulvestrant versus placebo + fulvestrant	HR+ HER2−, postmenopausal pts or pre-peri menopausal, pts progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	2° line	PFS	HR 0.55 (95% CI 0.45–0.68)

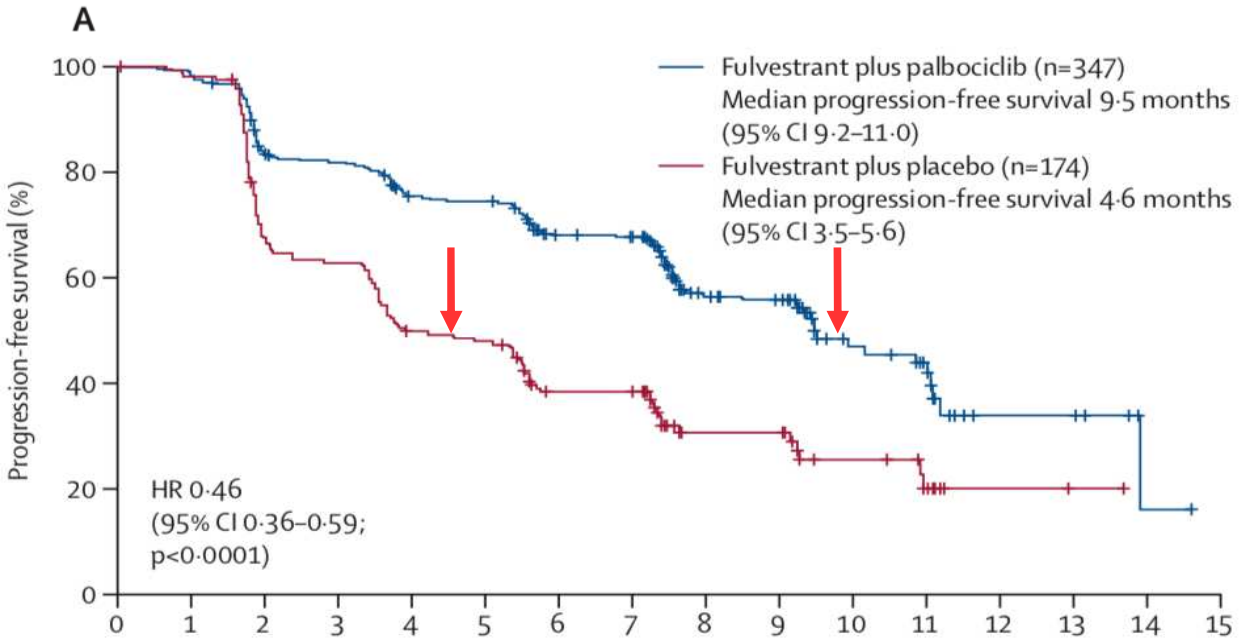
PFS



Messina 2018

Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial

Massimo Cristofanilli, Nicholas C Turner*, Igor Bondarenko, Jungsil Ro, Seock-Ah Im, Norikazu Masuda, Marco Colleoni, Angela DeMichele, Sherene Loi, Sunil Verma, Hiroji Iwata, Nadia Harbeck, Ke Zhang, Kathy Puyana Theall, Yuqiu Jiang, Cynthia Huang Bartlett, Maria Koehler, Dennis Slamon*



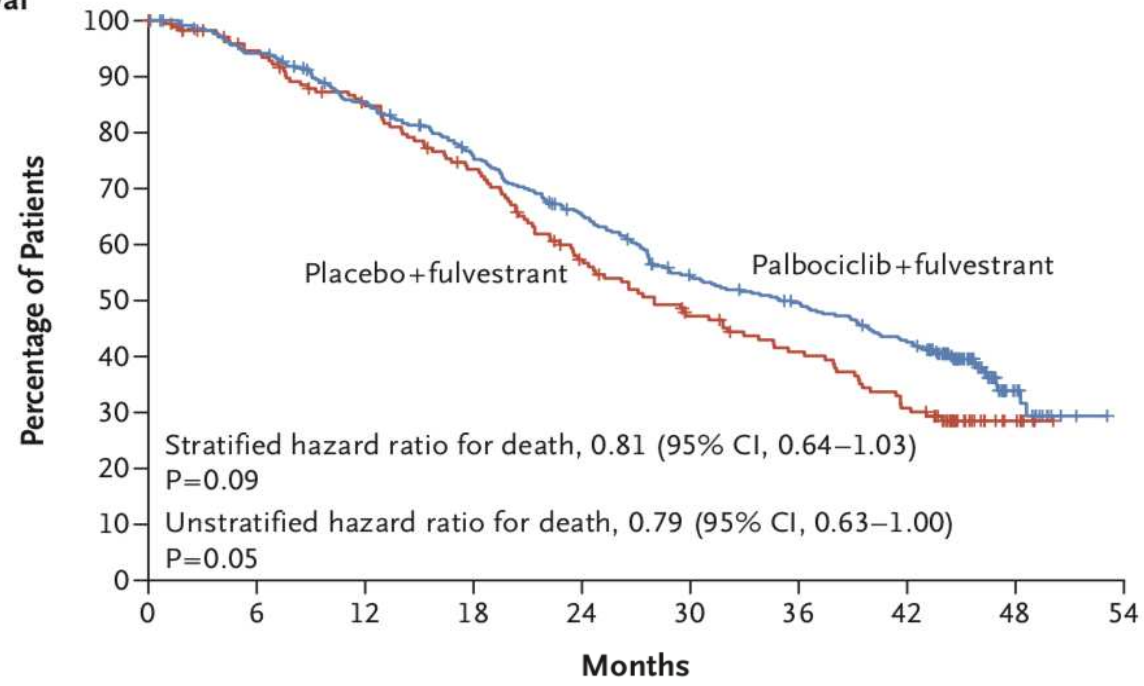
Cristofanilli 2016

	Intention-to-treat population	
	Fulvestrant plus palbociclib (n=347)	Fulvestrant plus placebo (n=174)
Median age, years (range)	57 (30–88)	56 (29–80)
Self-reported race		
White	252 (73%)	133 (76%)
Asian	74 (21%)	31 (18%)
Black and others	21 (6%)	10 (6%)
ECOG performance status		
0	206 (59%)	116 (67%)
1	141 (41%)	58 (33%)
Menopausal status		
Premenopausal or perimenopausal	72 (21%)	36 (21%)
Postmenopausal	275 (79%)	138 (79%)
Non-measurable disease		
Bone	75 (22%)	36 (21%)
Others	4 (1%)	0
Measurable disease		
Any measurable disease	268 (77%)	138 (79%)
Visceral disease*	206 (59%)	105 (60%)
Lung involvement	100 (29%)	45 (26%)
Liver involvement	127 (37%)	81 (47%)

	Fulvestrant plus palbociclib (n=345)				Fulvestrant plus placebo (n=172)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological								
Neutropenia	56 (16%)	189 (55%)	34 (10%)	0	5 (3%)	0	1 (1%)	0
Anaemia	86 (25%)	10 (3%)	0	0	16 (9%)	3 (2%)	0	0
Leucopenia	76 (22%)	93 (27%)	2 (1%)	0	5 (3%)	1 (1%)	1 (1%)	0
Thrombocytopenia	65 (19%)	6 (2%)	2 (1%)	0	0	0	0	0
Lymphopenia	4 (1%)	1 (<1%)	1 (<1%)	0	1 (1%)	1 (1%)	0	0

Cristofanilli 2016

Overall Survival

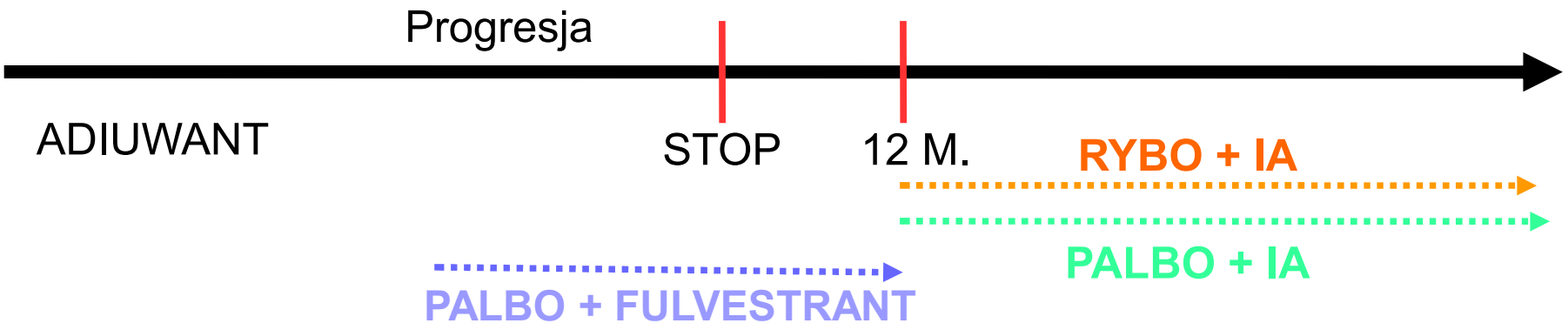


	No. of Patients	Median Overall Survival (95% CI)
		mo
Palbociclib+ Fulvestrant	347	34.9 (28.8–40.0)
Placebo+ Fulvestrant	174	28.0 (23.6–34.6)

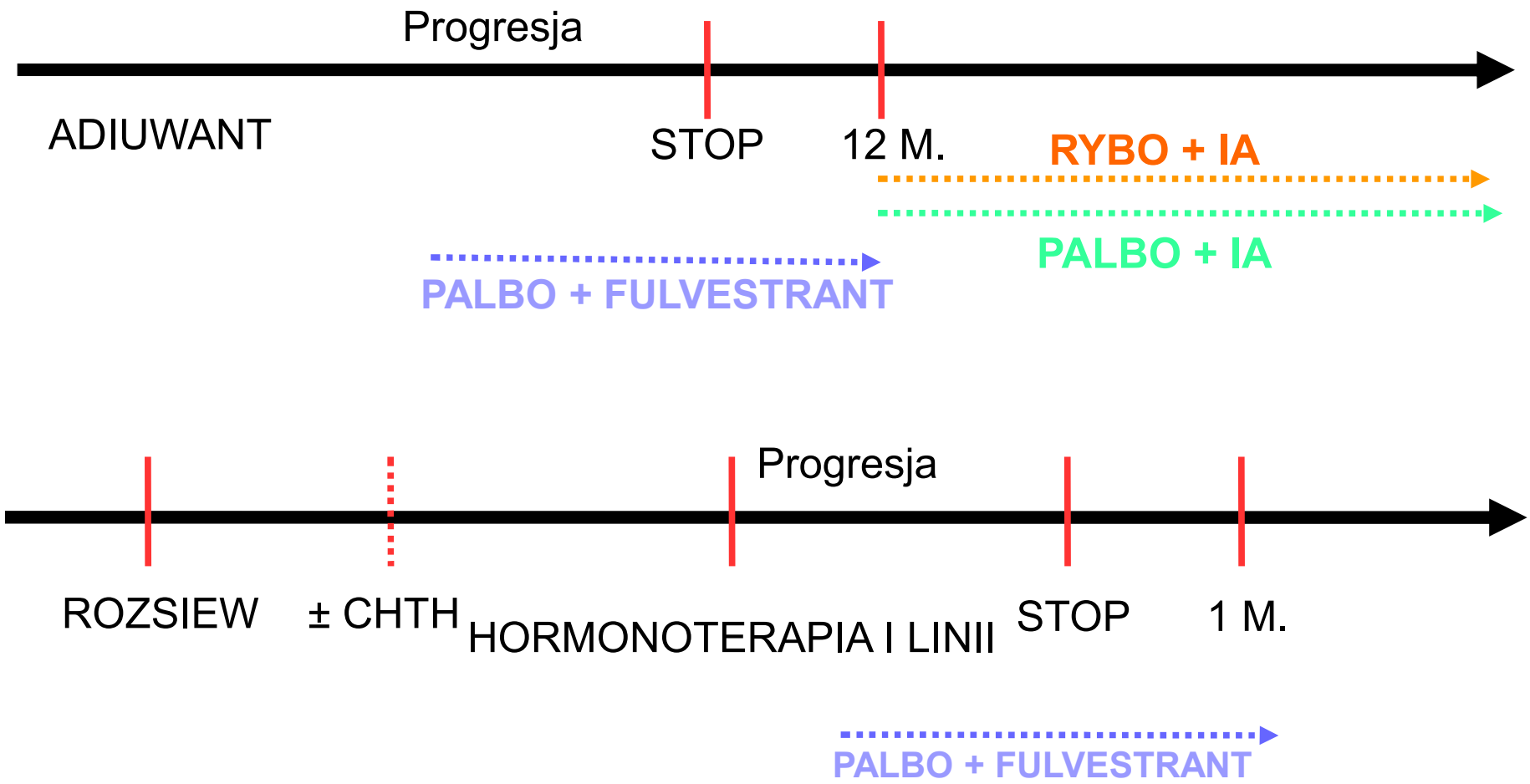
All patients					
Stratified analysis	521 (100)	0.81 (0.64–1.03)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Unstratified analysis	521 (100)	0.79 (0.63–1.00)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Sensitivity to previous hormonal therapy					0.12
Yes	410 (79)	0.72 (0.55–0.94)	39.7 (34.8–45.7)	29.7 (23.8–37.9)	
No	111 (21)	1.14 (0.71–1.84)	20.2 (17.2–26.4)	26.2 (17.5–31.8)	
Site of metastatic disease					0.44
Visceral	311 (60)	0.85 (0.64–1.13)	27.6 (24.4–31.2)	24.7 (20.8–31.8)	
Nonvisceral	210 (40)	0.69 (0.46–1.04)	46.9 (39.3–NE)	35.4 (24.6–NE)	
Menopausal status at study entry					0.25
Postmenopausal	413 (79)	0.73 (0.57–0.95)	34.8 (28.8–40.1)	27.1 (22.8–32.1)	
Premenopausal or perimenopausal	108 (21)	1.07 (0.61–1.86)	38.0 (24.4–NE)	38.0 (22.2–NE)	
Age					0.04
<65 yr	392 (75)	0.91 (0.70–1.20)	31.4 (27.4–39.3)	29.7 (24.0–38.0)	
≥65 yr	129 (25)	0.52 (0.33–0.82)	39.7 (30.7–47.0)	23.8 (20.0–33.8)	

Turner 2018

Młode chore w codziennej praktyce klinicznej



Młode chore w codziennej praktyce klinicznej



Dziękuję za uwagę!!!

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Rak Piersi u Młodych Kobiet

17 lutego 2020, Poznań

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