Warszawa, 27.01.2016

Seminarium naukowe: ***„Terapie przełomowe w onkologii i hematoonkologii a dostępność do leczenia w Polsce na tle Europy”***

Terapie dla kobiet z zaawansowanym rakiem piersi w Polsce

Dr n. med. Agnieszka Jagiełło-Gruszfeld

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Zaawansowany rak piersi – cele leczenia

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Opóźnić czas do progresji

- Maksymalna kontrola objawów
- Utrzymanie lub poprawa jakości życia
- Zapobiec poważnym powikłaniom

Ostatecznym celem jest wydłużenie czasu przeżycia i utrzymanie jakości życia

Leczenie chorej na uogólnionego raka piersi

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- Najbardziej istotną rolę w leczeniu chorych na uogólnionego rak piersi odgrywa terapia systemowa;
  - W wyborze sposobu leczenia należy kierować się przede wszystkim możliwościami wykorzystania leczenia celowanego:
    - Terapia hormonalna w przypadku chorych na raka hormonozależnego
    - Terapia biologiczna (nakierowana na receptor HER2) w przypadku chorych na raka ze zwiększoną ekspresją receptora HER2
    - Chemioterapia

Cardoso F, Castiglione M on behalf the ESMO Guidelines Working Group
Locally recurrrent or metastatic breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

Informacje niezbędne do podjęcia decyzji o sposobie leczenia w momencie stwierdzenia przerzutów odległych

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Czynniki związane z chorobą	Czynniki związane z pacjentem
Czas wolny od choroby	Preferencje pacjenta
Wcześniejsze leczenie (ew. odpowiedź na leczenie)	Wiek biologiczny
Status receptorowy	Status menopauzalny
Lokalizacja i liczba przerzutów	Choroby towarzyszące i stan ogólny chorego
Kontrola objawów choroby, szybkość narastania objawów	Czynniki socjoekonomiczne i psychologiczne
Dostępność do określonych terapii	

Cardoso F, Castiglione M on behalf the ESMO Guidelines Working Group
Locally recurrrent or metastatic breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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Biologiczne podtypy raka piersi

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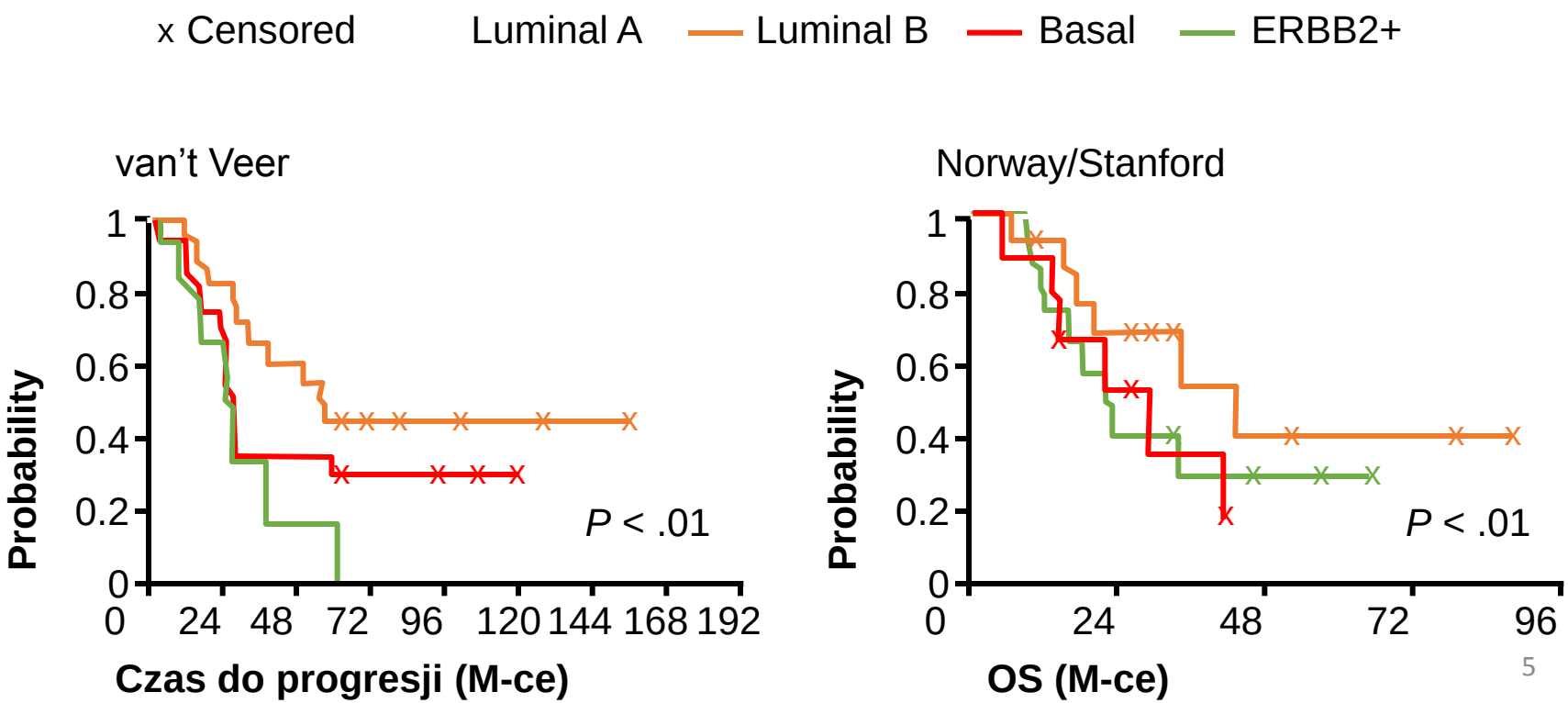

Sørlie T, et al. PNAS. 2003;100:8418-8423.

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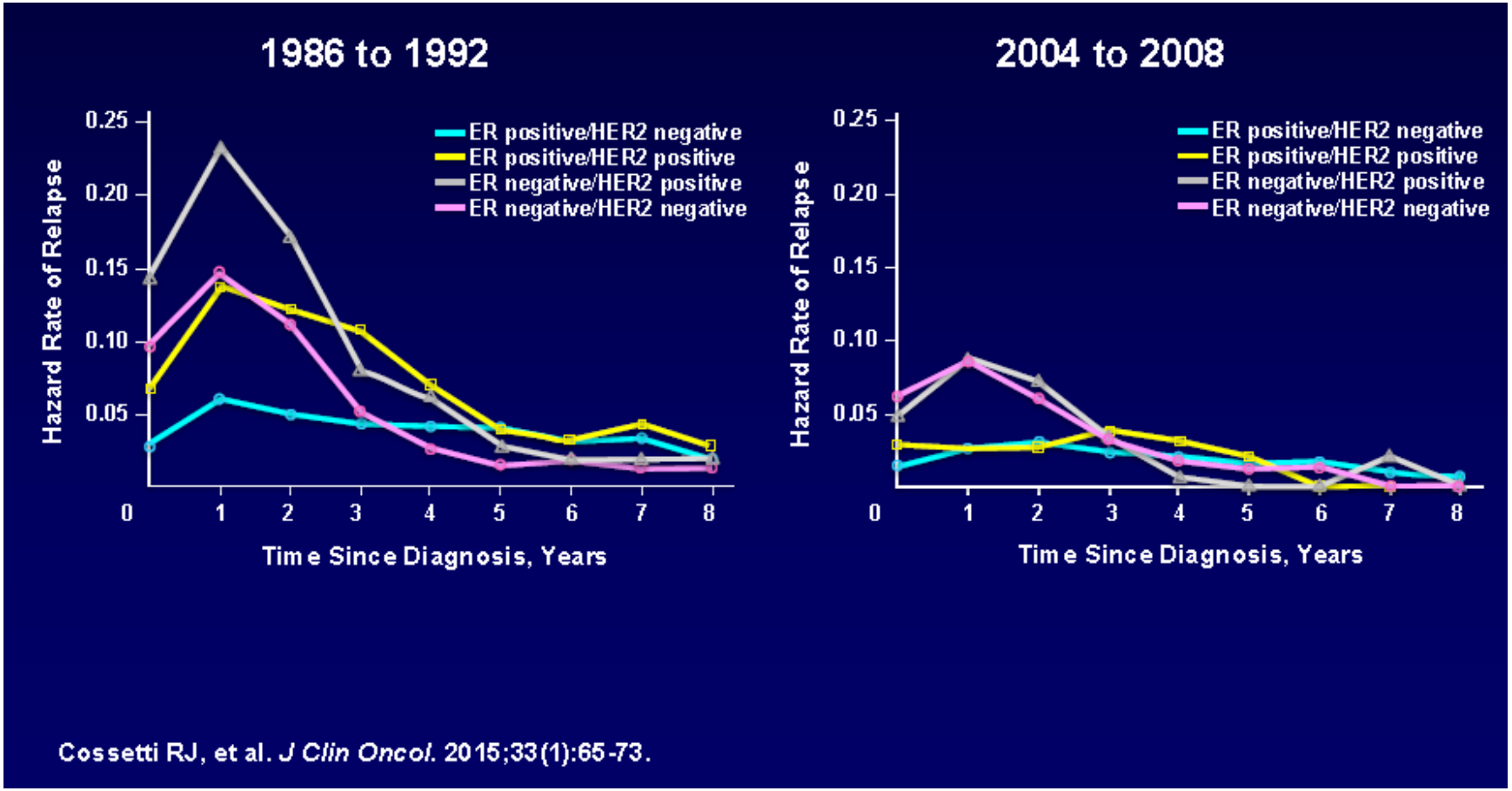
Prawdopodobieństwo nawrotu raka piersi w zależności od podtypu molekularnego



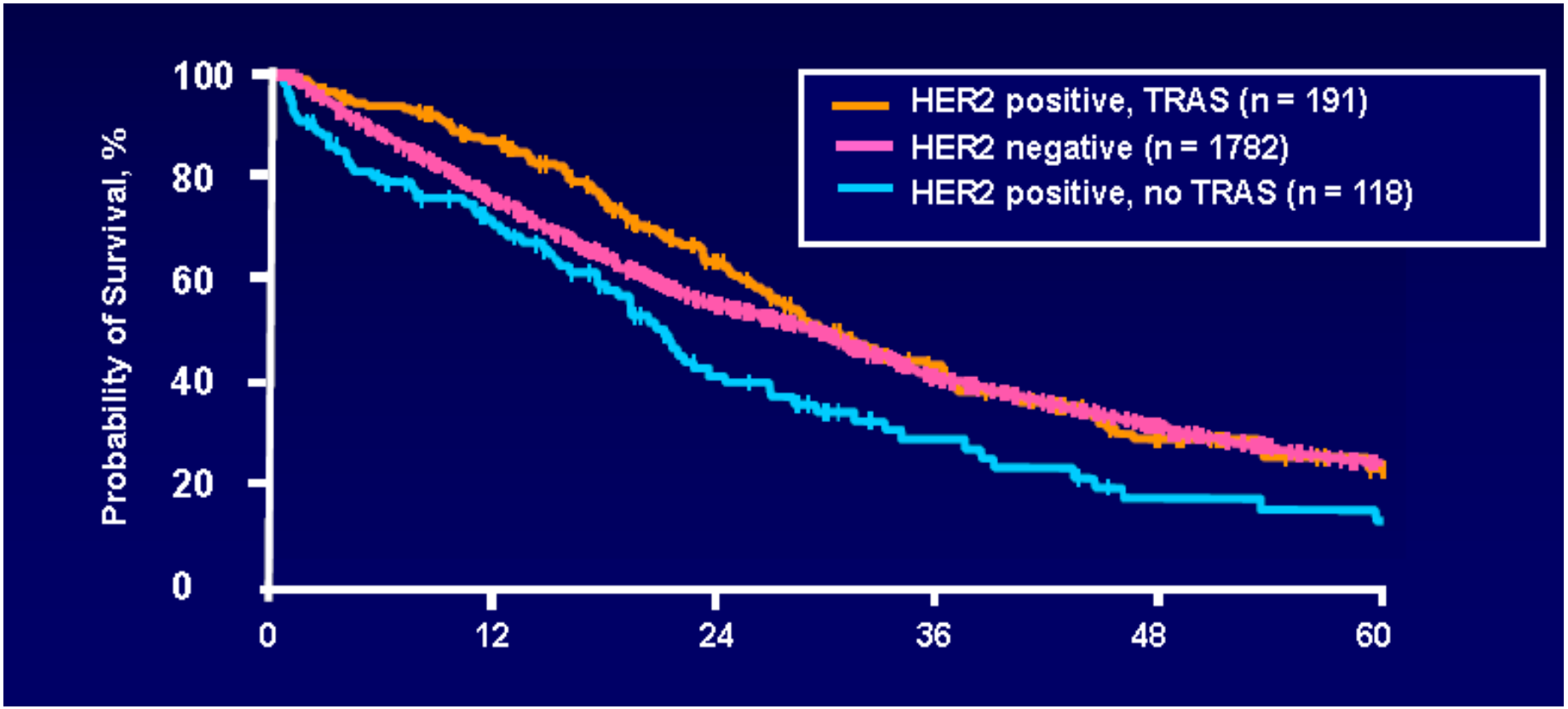
Rak piersi – podtyp HER2 pos

Rak piersi – podtypy Luminal A i Luminal B (hormonozależny)

Rak piersi – podtyp trójnegatytny

Leczenie wspomagające

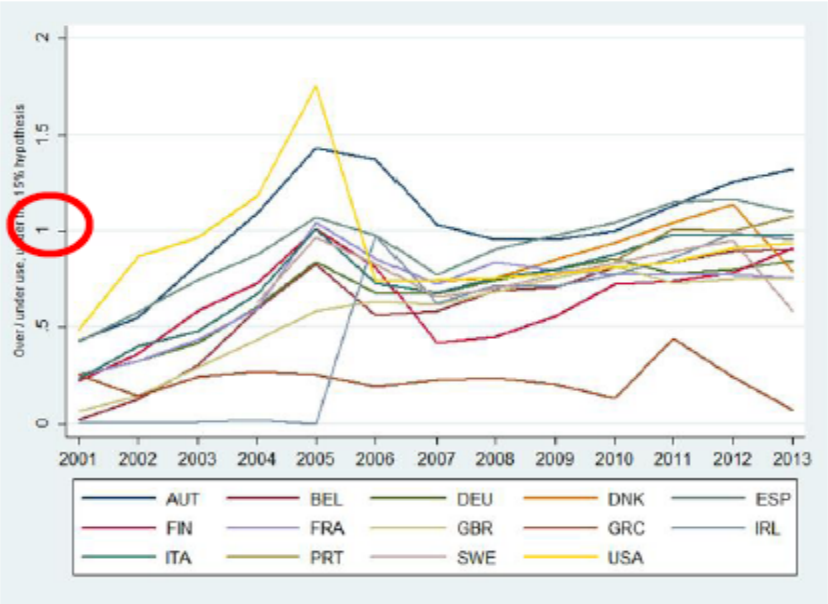
Trastuzumab zmienił naturalny przebieg choroby u chorych na HER2 pos raka piersi

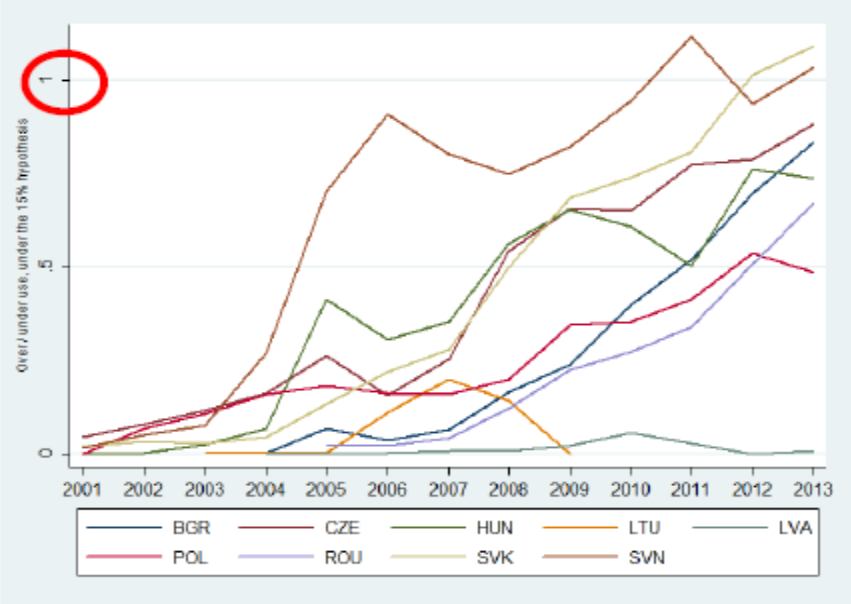


Dawood S, et al. *J Clin Oncol*. 2010;28(1):92-98.

Wykorzystanie trastuzumabu u chorych na HER2 pos raka piersi

15% HER2+ scenario





Cleopatra
MA31

BOLERO-1

Badanie CLOPATRA: pertuzumab + trastuzumab + docetaxel w 1-szej linii terapii

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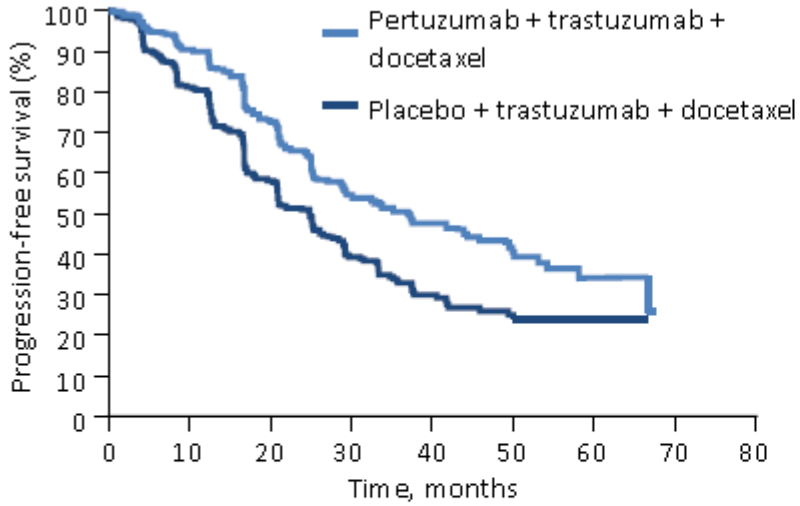
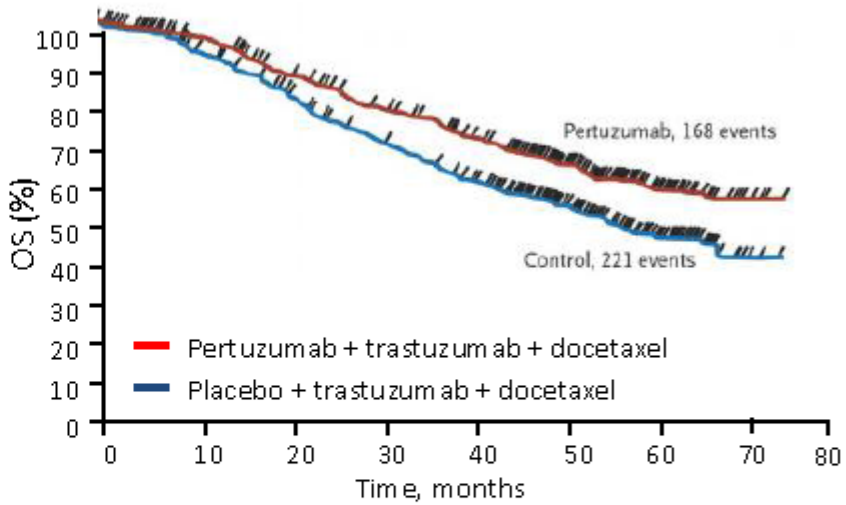
Progression-free survival[1]



Overall survival[2]



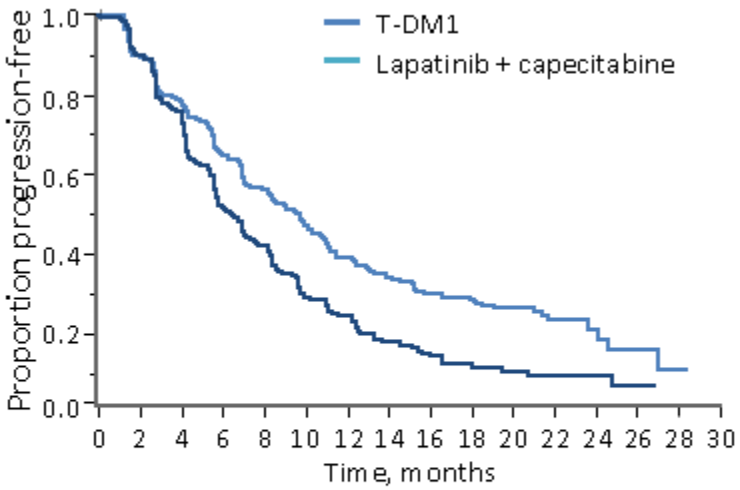
	Pertuzumab + trastuzumab + docetaxel	Placebo + trastuzumab + docetaxel	Hazard ratio	*P* value
ORR[1]	80.2%	69.3%		.0001
PFS[1]	18.7 months	12.4 months	0.69	<.0001
OS[2]	56.5 months	40.8 months	0.66	.0001

Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. 2. Swain SM, et al. *N Engl J Med*. 2015;372(8):724-734.

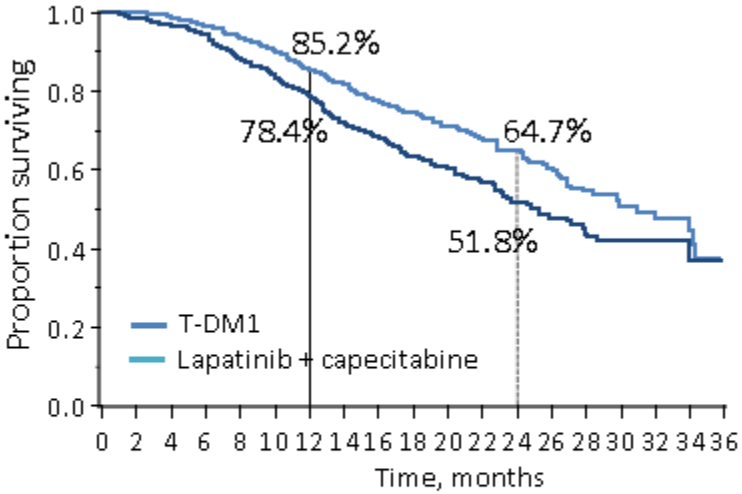
Badanie EMILIA – 2-ga linia terapii

WWW.COI.PL

Progression-free survival



Overall survival



	T-DM1	Lapatinib + capecitabine	Hazard ratio	*P* value
PFS	9.6 months	6.4 months	0.65	<.001
OS	30.9 months	25.1 months	0.68	<.001

Verma S, et al. *N Engl J Med.* 2012;367:1783-1791.

Badanie TH3RESA

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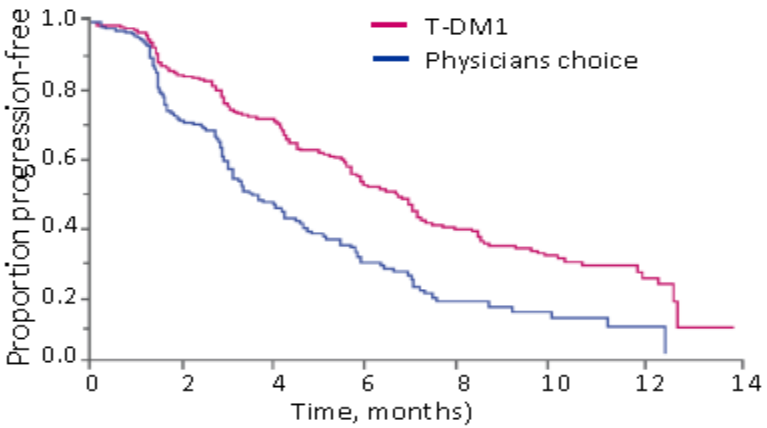
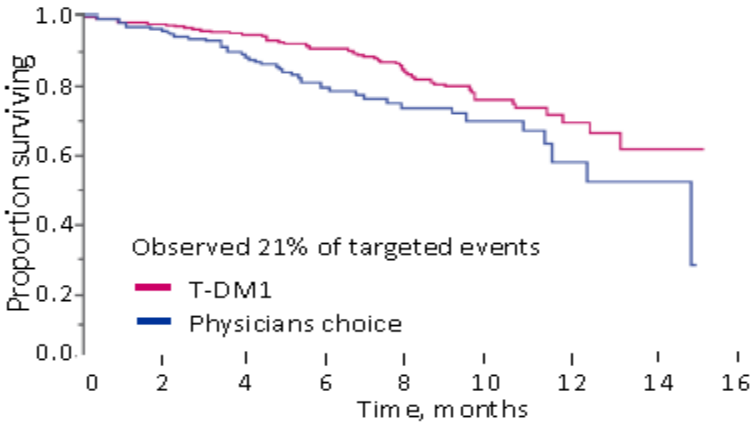
PFS by investigator assessment



First interim OS analysis



	T-DM1	Physicians' choice *	Hazard ratio	*P* value
PFS	6.2 months	3.3 months	0.53	<.0001
OS	NE	14.9 months	0.55	.0034

Krop IE, et al. *Lancet Oncol.* 2014;15:689-699.

Kolejne linie terapii – badanie EGF104900

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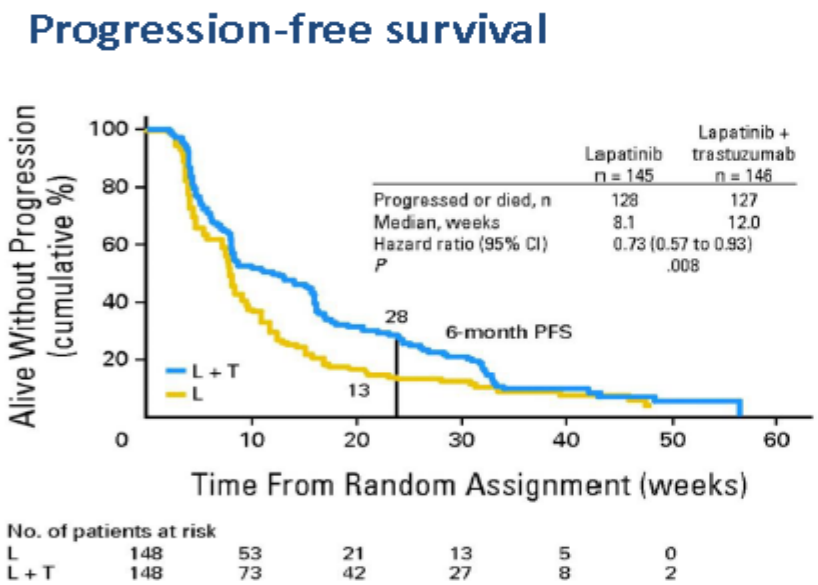

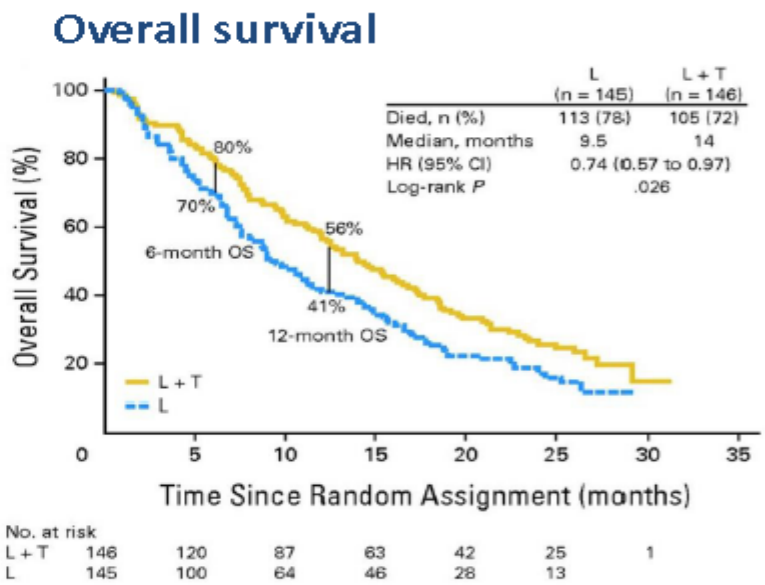

	Lapatinib + trastuzumab	Lapatinib*	Hazard ratio (95% CI)
PFS	11.1 weeks	8.1 weeks	0.74 (0.58, 0.94)
OS	14 months	9.5 months	0.74 (0.57, 0.97)

Blackwell KL, et al. *J Clin Oncol*. 2010;28(7):1124-1130. 2. Blackwell KL, et al. *J Clin Oncol*. 2012;30(21):2585-2592.

Annals of Oncology Advance Access published September 18, 2014

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special article

Annals of Oncology 00: 1–18, 2014
doi:10.1093/annonc/mdu385

ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

F. Cardoso[1*], A. Costa[2,3], L. Norton[4], E. Senkus[5], M. Aapro[6], F. André[7], C. H. Barrios[8], J. Bergh[9], L. Biganzoli[10], K. L. Blackwell[11], M. J. Cardoso[12], T. Cufer[13], N. El Saghir[14], L. Fallowfield[15], D. Fenech[16], P. Francis[17], K. Gelmon[18], S. H. Giordano[19], J. Gligorov[20], A. Goldhirsch[21], N. Harbeck[22], N. Houssami[23], C. Hudis[24], B. Kaufman[25], I. Krop[26], S. Kyriakides[27], U. N. Lin[26], M. Mayer[28], S. D. Merjaver[29], E. B. Nordström[30], O. Pagani[31], A. Partridge[32], F. Penault-Llorca[33], M. J. Piccart[34], H. Rugo[35], G. Sledge[36], C. Thomssen[37], L. van't Veer[38], D. Vorobiof[39], C. Vrieling[40], N. West[41], B. Xu[42] & E. Winer[26]

HER-2-positive ABC

Anti-HER-2 therapy should be offered *early* to all patients with HER-2+ MBC, except in the presence of contraindications to the use of such therapy.	IA	91% (30) yes 3% (1) abstain (33 voters)
For patients with ER+/HER-2+ MBC for whom ET was chosen over CT, anti-HER-2 therapy + ET should be considered with the initiation of ET (provided that further anti-HER-2 therapy is available) since anti-HER-2 therapy (either trastuzumab or lapatinib) in combination with ET has shown substantial progression-free survival (PFS) benefit (i.e. 'time without CT') compared with ET alone. The addition of anti-HER-2 therapy in this setting has not led to a survival benefit.	IA	90% (27) yes 10% (3) abstain (30 voters)
Patients whose tumours progress on an anti-HER-2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER-2 therapy with subsequent treatment since it is beneficial to continue suppression of the HER-2 pathway. The optimal duration of anti-HER-2 therapy for MBC (i.e. when to stop these agents) is currently unknown.	IB	97% (29) yes 0% (0) abstain (30 voters)

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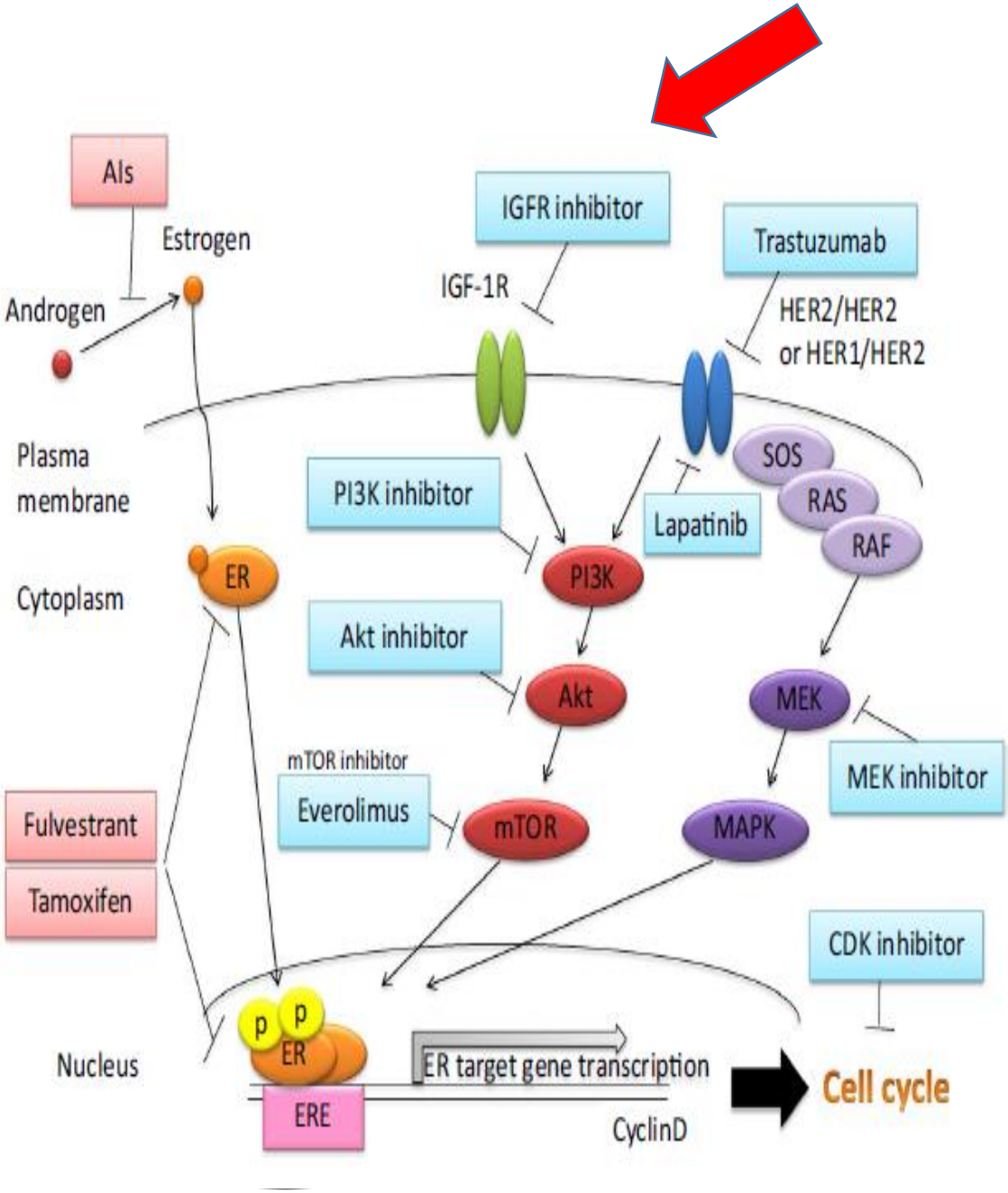
Rak piersi – podtyp HER2 pos

Rak piersi – podtypy Luminal A i Luminal B (hormonozależny)

Rak piersi – podtyp trójnegatytny

Leczenie wspomagające

Fig. 4 Therapeutic molecular targets in ER-positive breast cancer



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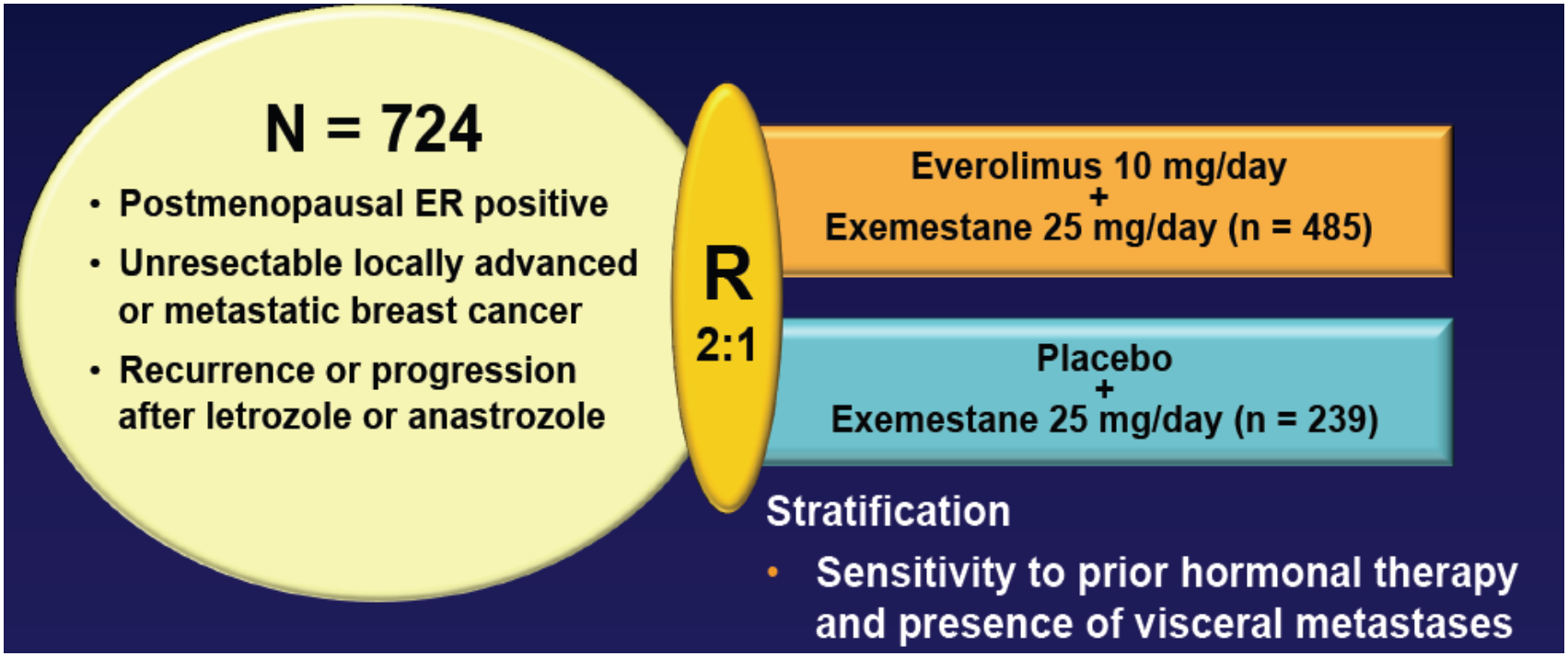
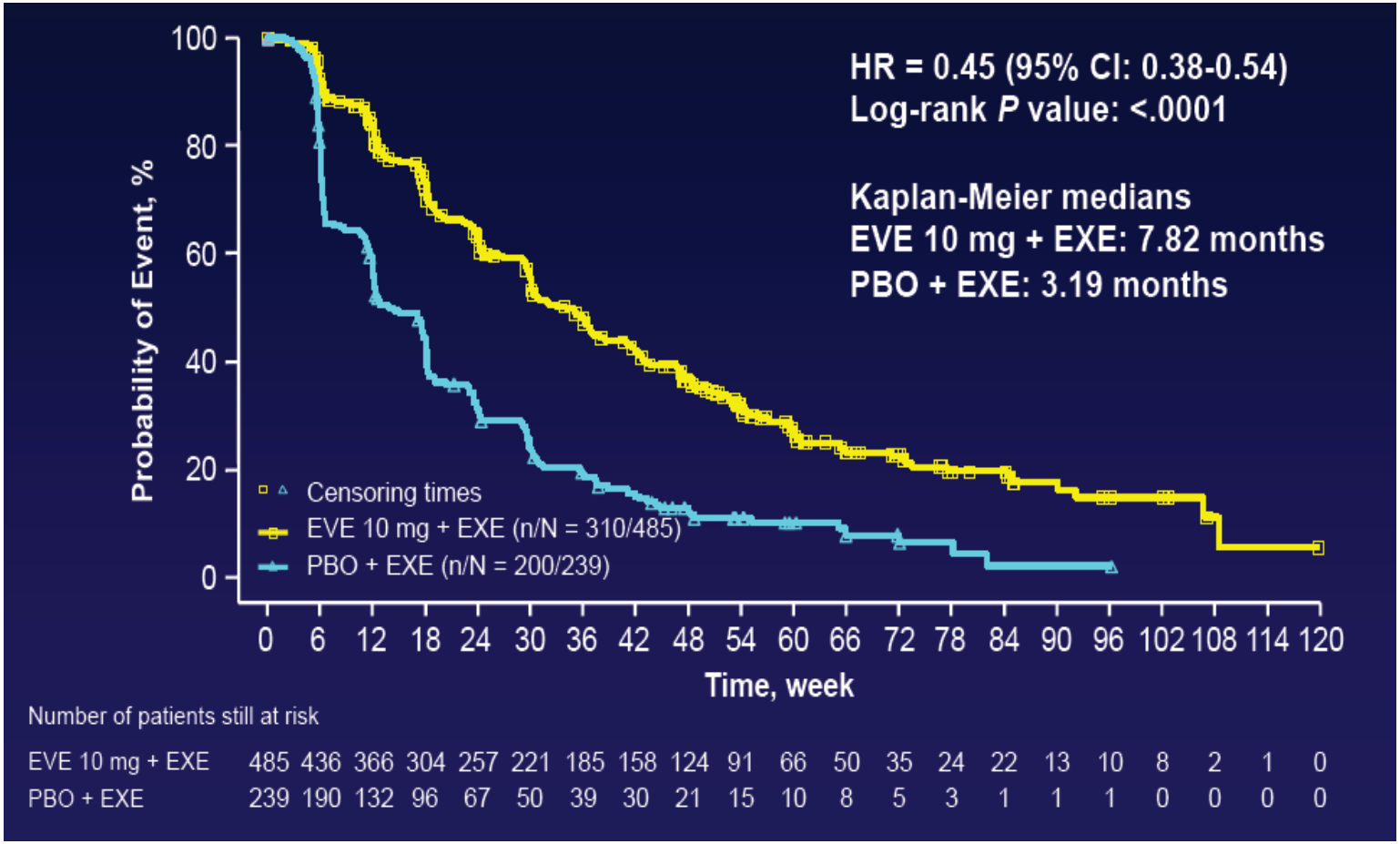
BOLERO-2 (exe + eve; HR pos, MBC)

Punkty końcowe: 1. – PFS
2. OS, ORR, QoL, bezpieczeństwo, biomarkery, PK



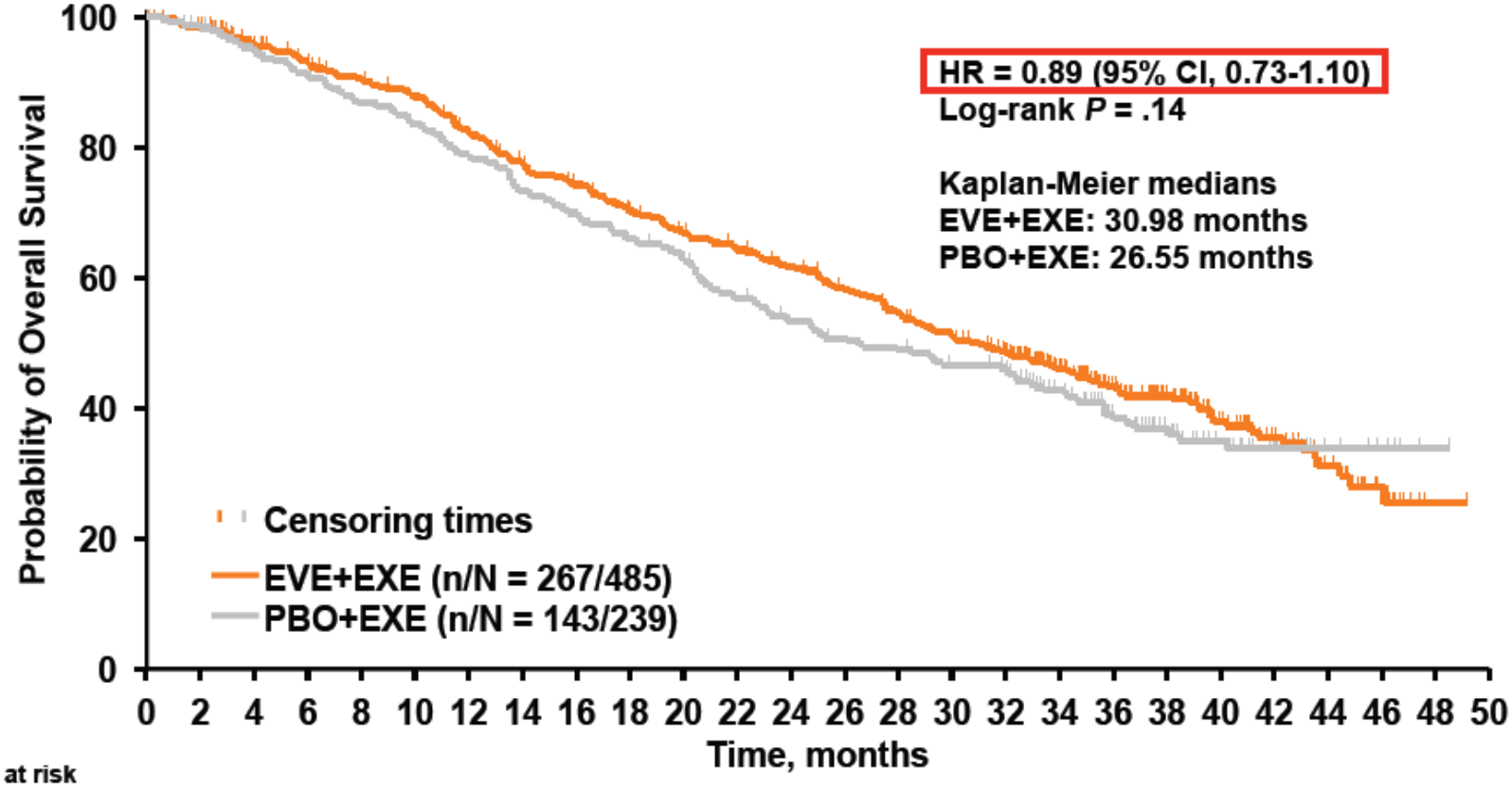
Baselga J, et al. *N Engl J Med.* 2012;366(6):520-529.

BOLERO-2, PFS, Fu – 18 m-cy



Piccart MJ, et al. *J Clin Oncol.* 2012;30(suppl): Abstract 559.

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



No. at risk

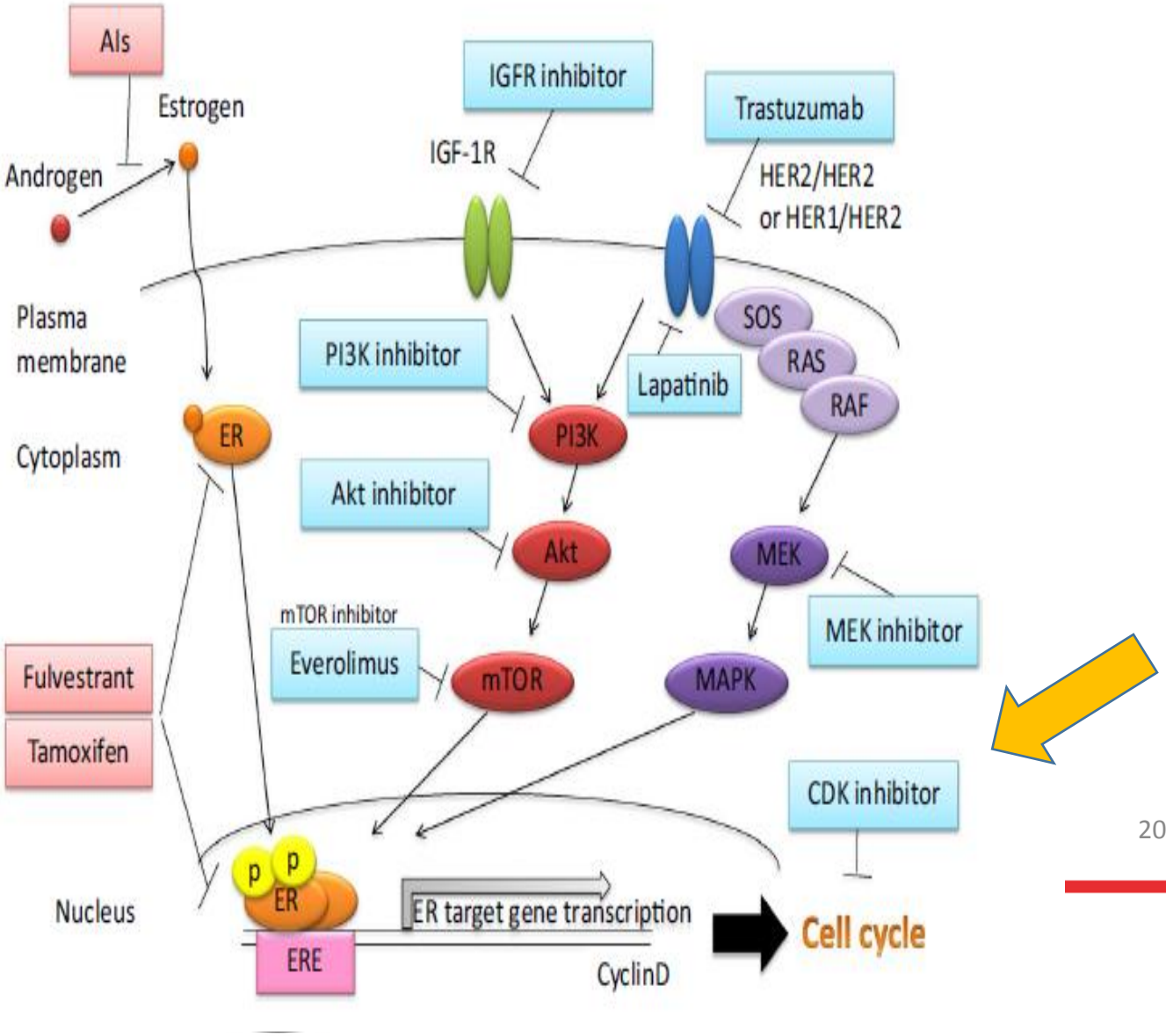
EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

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

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

Piccart M, et al. Presented at: 9th European Breast Cancer Conference; March 19-21 2014; Glasgow, United Kingdom. Abstract 1.

Fig. 4 Therapeutic molecular targets in ER-positive breast cancer



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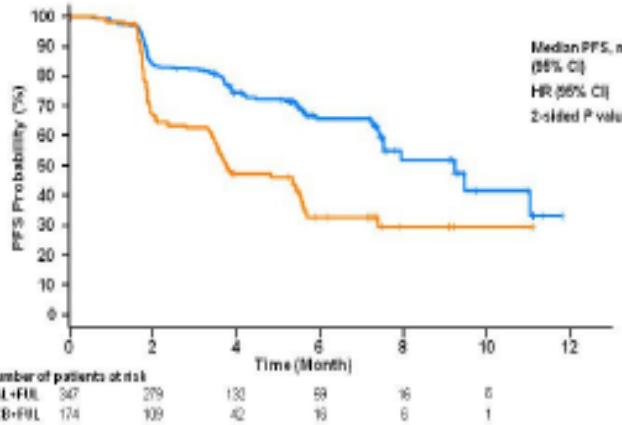
Badanie PALOMA3: fulv +/- palbociclib (CDK 4/6 inhibitor)

Primary Endpoint: PFS (ITT Population)



	Palbociclib + Fulvestrant n=347	Placebo + Fulvestrant n=174
Median PFS, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.422 (0.318, 0.560)	
2-sided P value	<0.000001	

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.

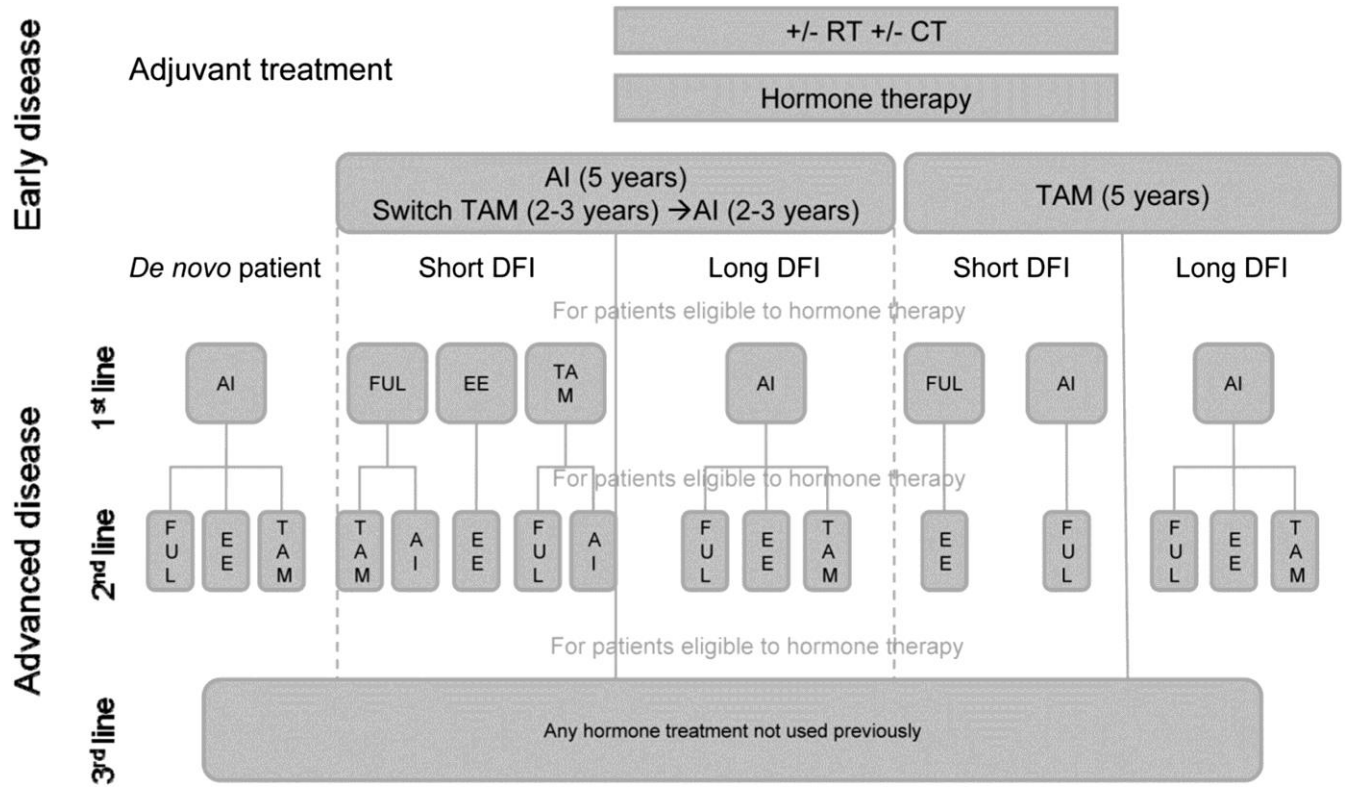
Major PFS benefit

Very little toxicity (asymptomatic neutropenia)

FDA approval

Subgroup	n (%)	Hazard Ratio and 95% CI	*P* value for Interaction
All randomized patients (ITT)	521 (100)		
Age			0.480
<65 Years	392 (75.2)		
≥65 Years	129 (24.8)		

NEJM 2015 Turner et al



The therapeutic role of fulvestrant in the management of patients with hormone receptor-positive breast cancer

http://dx.doi.org/10.1016/j.breast.2014.01.016

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ELSEVIER

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Annals of Oncology Advance Access published September 18, 2014

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special article

Annals of Oncology 00: 1–18, 2014
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ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

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ER+/HER-2-negative ABC

ET is the preferred option for hormone receptor-positive disease, *even in the presence of visceral disease*, unless there is concern or proof of endocrine resistance, or there is disease needing a fast response.	IA	100% (29) yes 0% (0) abstain (29 voters)
For premenopausal women, ovarian suppression/ablation combined with additional ET is the first choice.	IA	97% (29) yes 0% (0) abstain (30 voters)
The additional endocrine agent should be tamoxifen unless tamoxifen resistance is proved. An aromatase inhibitor is also a viable option, but absolutely mandates the use of ovarian suppression/ablation. Fulvestrant has not been adequately studied in premenopausal women.	IB	97% (29) yes 0% (0) abstain (30 voters)
Optimal post-aromatase inhibitor treatment is uncertain. Available options include, but are not limited to, tamoxifen, another aromatase inhibitor (with a different mechanism of action), fulvestrant HD, megestrol acetate, and everolimus + aromatase inhibitor.	IA	97% (30) yes 3% (1) abstain (31 voters)
Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, although this approach has not been assessed in randomized trials.	IC	88% (28) yes 9% (3) abstain (32 voters)

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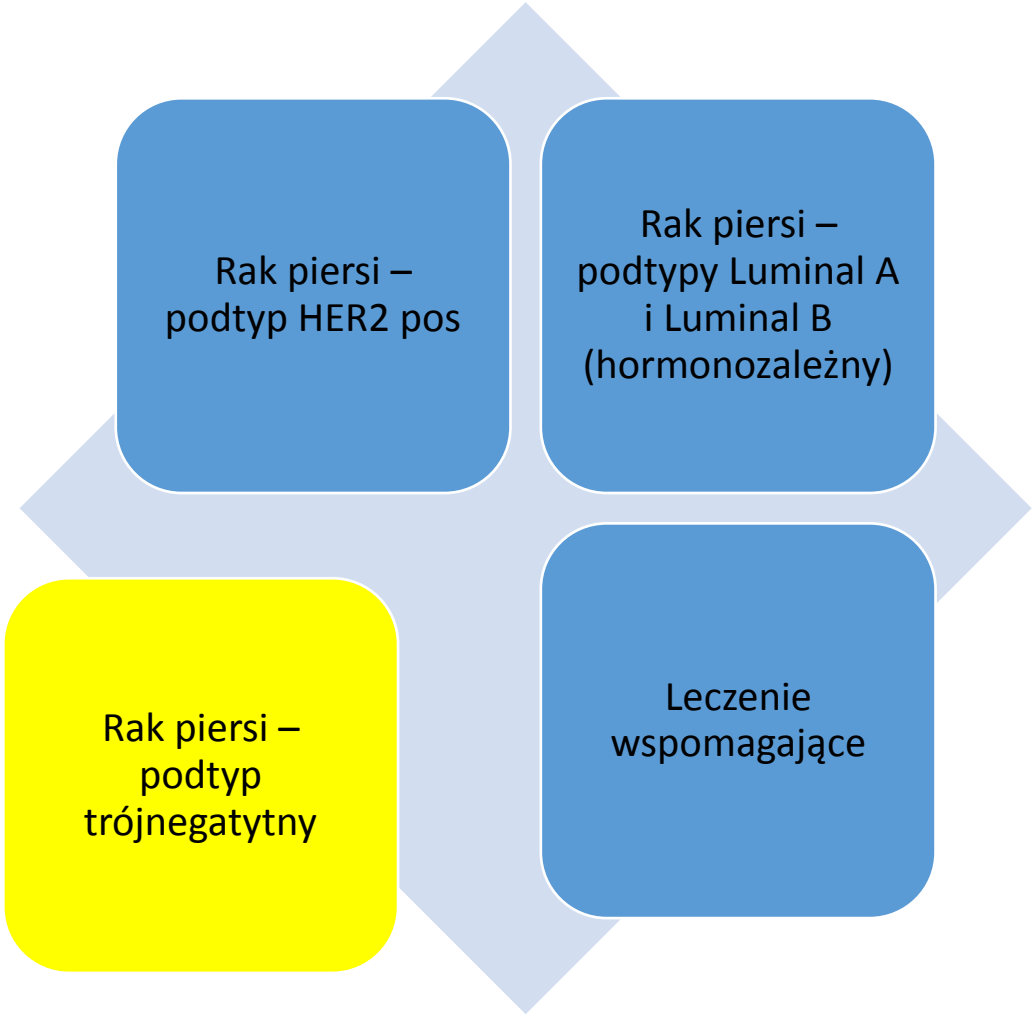
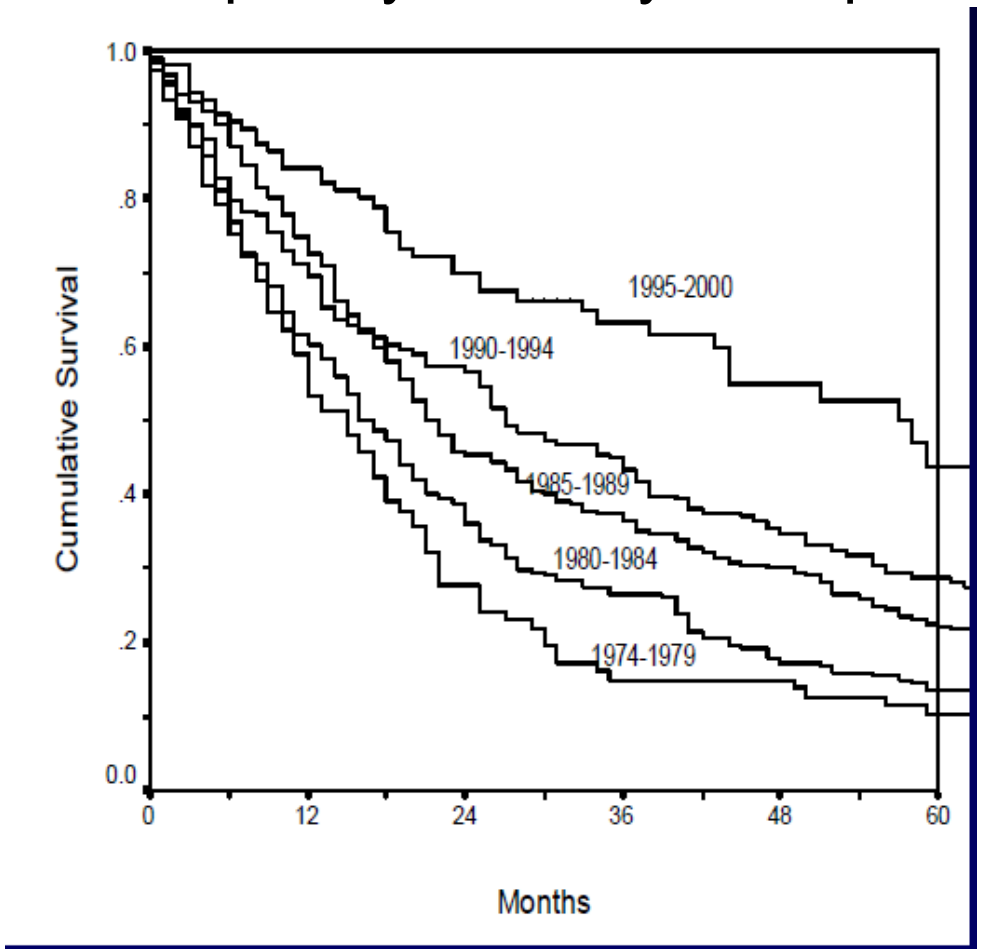

Rak piersi – podtyp HER2 pos
Rak piersi – podtypy Luminal A i Luminal B (hormonozależny)
Rak piersi – podtyp trójnegatytny
Leczenie wspomagające

Rola badań klinicznych w onkologii

- Postęp w leczeniu nowotworów
  - Poszukiwanie nowych cząstek
  - Wybór optymalnych schematów
  - Ograniczenie toksyczności
  - Zapewnienie bezpieczeństwa leczenia
  - Dostęp do bardziej „przyjaznych” form podawania cytostatyków
  - Poszukiwanie możliwości leczenia celowanego molekularnie wraz z poszukiwaniem czynników predykcyjnych tych terapii
  - Racjonalizacji leczenia

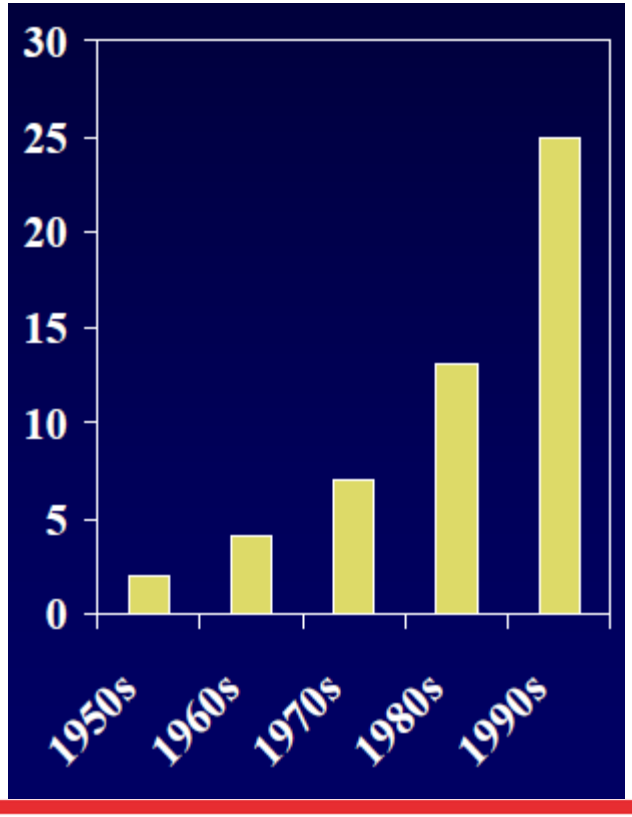
- Nie ma postępu w medycynie bez badań klinicznych
- Możliwość prowadzenia badań korzystnie wpływa na postępowanie w codziennej praktyce

Czas przeżycia chorych na przerzutowego raka piersi



Giordano SH et al. Cancer 2004;100(1): 44-52

Dostęp do nowych leków



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Rak piersi – podtyp HER2 pos
Rak piersi – podtypy Luminal A i Luminal B (hormonozależny)
Rak piersi – podtyp trójnegatytny
Leczenie wspomagające

Denosumab for the treatment of bone metastases in breast cancer: evidence and opinion

Ther Adv Med Oncol
|2011| 3|5| 233–243
DOI: 10.1177/
1758834011412656

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Guenther G. Steger and Rupert Bartsch

	Denosumab	Zoledronic acid
Type of substance	Monoclonal antibody	Chemical agent
Mode of action	Inhibition of osteoclast differentiation	Induction of osteoclast apoptosis
Application	Subcutaneous	Intravenous
Direct antitumour effect	Possible, not yet observed	Suggested from preclinical and inconsistent clinical data
Inhibition of T-cell function	Suggested from *in vitro* data; increased infection rate not fully excluded	Not observed
Osteonecrosis of the jaw	Relevant side effect in patients receiving denosumab for bone metastases. Not observed in patients treated for osteoporosis	Relevant side effect in patients receiving zoledronic acide for bone metastases and osteoporosis
Renal toxicity	Not observed	Relevant side effects

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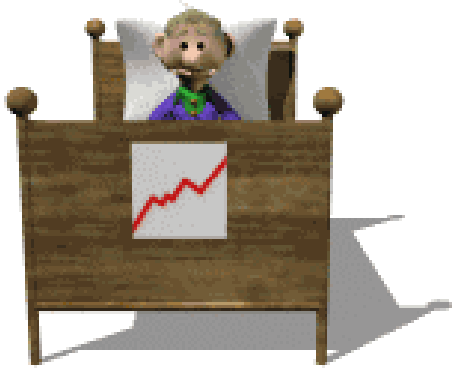
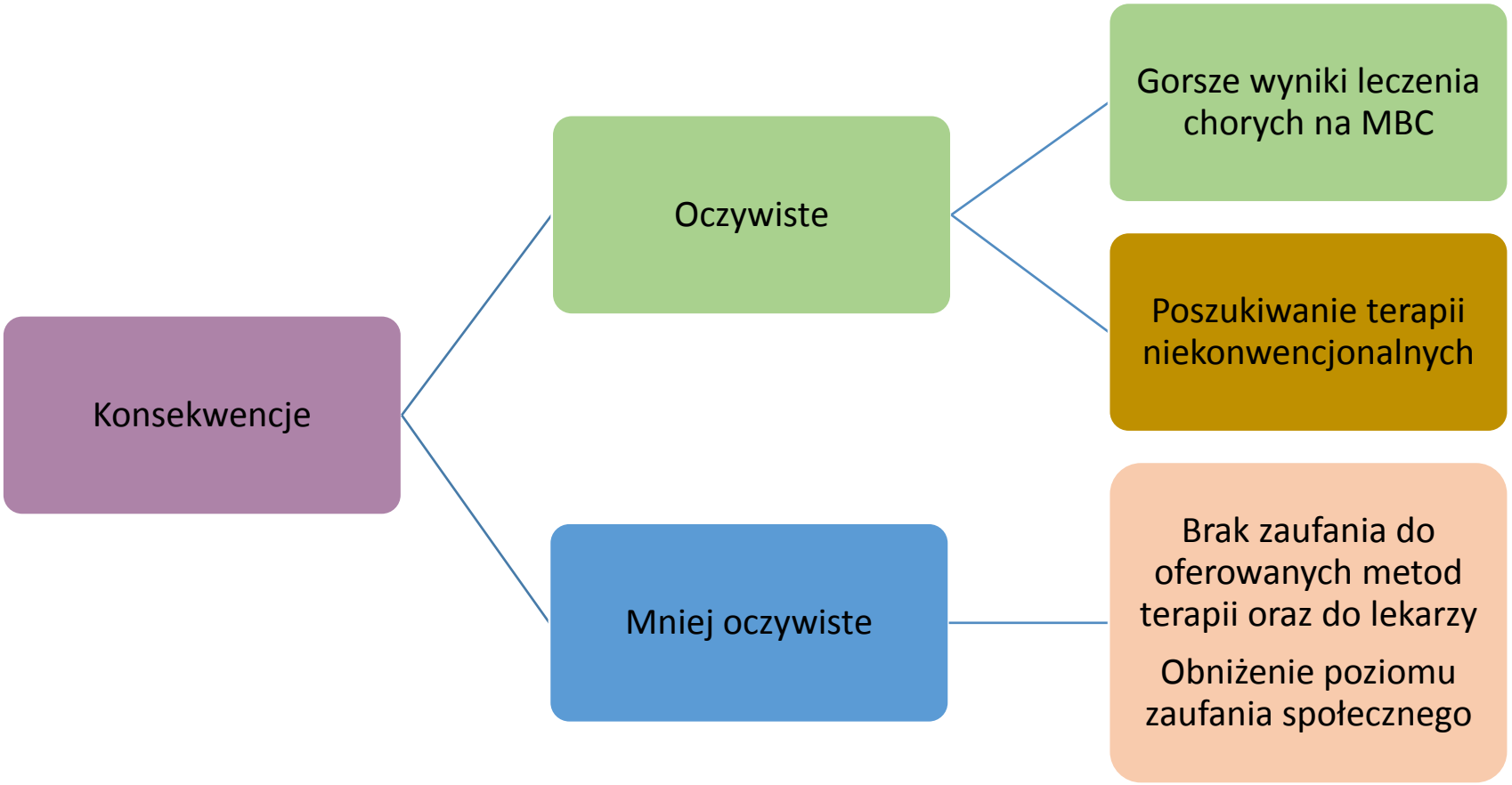
CENTRUM ONKOLOGII – INSTYTUT
IM. MARII SKŁODOWSKIEJ-CURIE

Podsumowanie

- Brak możliwości optymalnego leczenia chorych na HER2 – pos MBC
- Brak niektórych możliwości optymalnego leczenia chorych na hormonozależnego MBC oraz leczenia wspomagającego
- Znaczący spadek dostępności do badań klinicznych w onkologii dla chorych z MBC




Konsekwencje
Oczywiste
Mniej oczywiste
Gorsze wyniki leczenia chorych na MBC
Poszukiwanie terapii niekonwencjonalnych
Brak zaufania do oferowanych metod terapii oraz do lekarzy
Obniżenie poziomu zaufania społecznego