Innowacyjne metody farmakoterapii niedrobnokomórkowego raka płuca dzisiaj i jutro

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Centrum Onkologii – Instytut w Warszawie
Warszawa, 20. 03. 2014

Zasady celowania

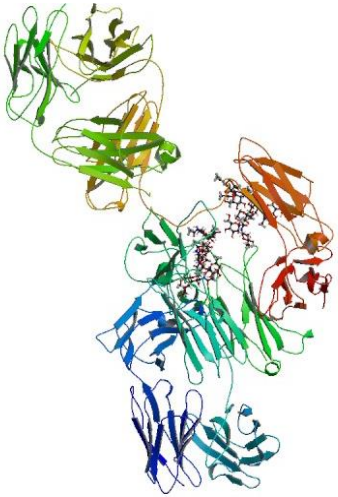
Wybór leczenia

Plan prezentacji

- Co było, a nie jest
- Co jest
- Co będzie
- Czego się nie spodziewasz

PAST

Rodzina Receptorów HER



Hereguliny

NRG2
NRG3
Hereguliny
b-cellulina

Domeny bogato-cysteinowe

Domena kinazy tyrozynowej

C-terminus

ErbB-1
Her1
EGFR

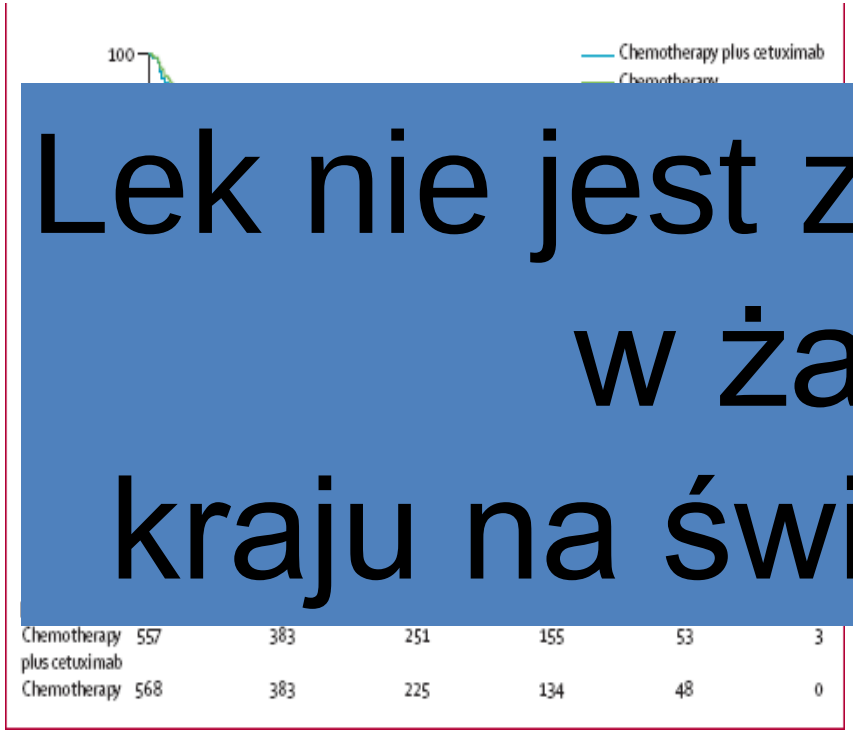
ErbB-2
Her2
neu

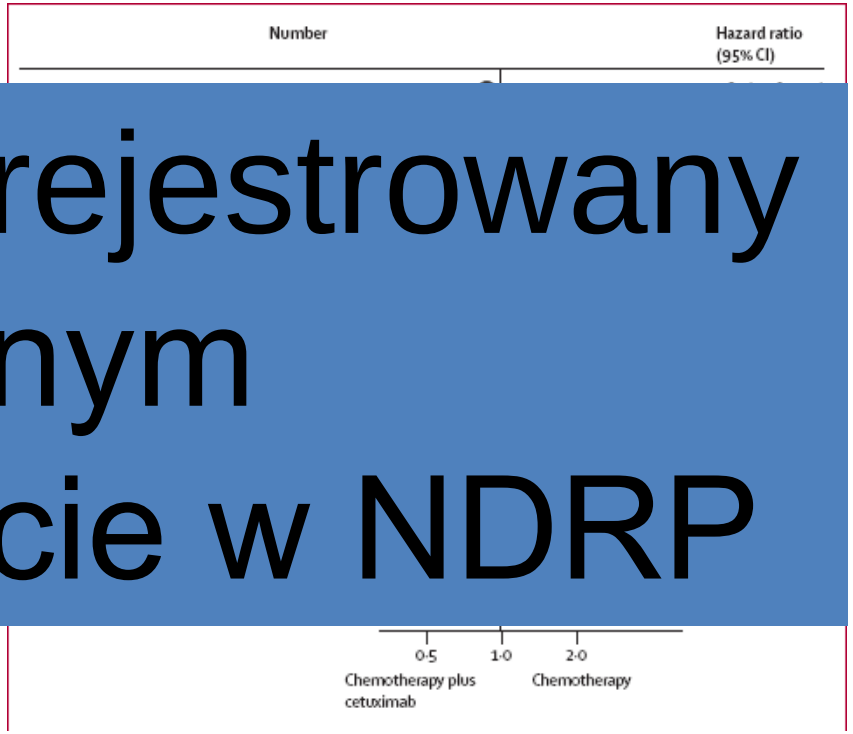
ErbB-3
Her3

ErbB-4
Her4

Leczenie anty EGFR - cetuksymab

FLEX Trial

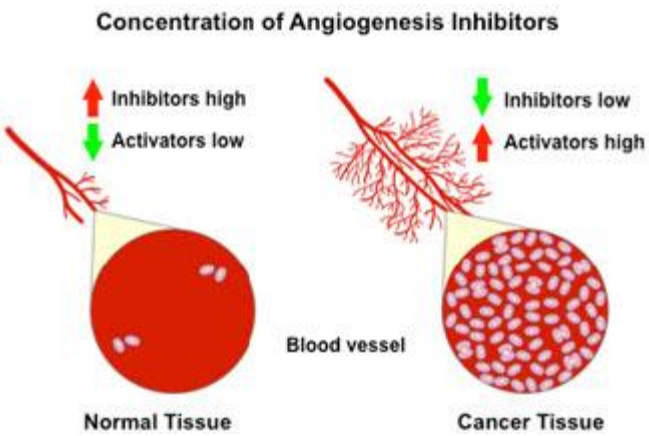


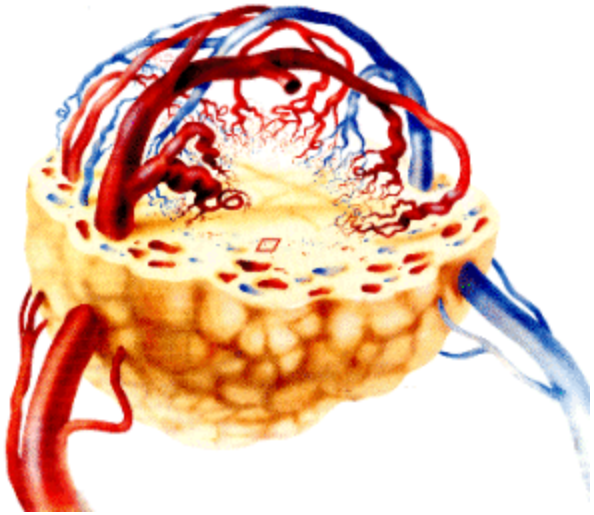


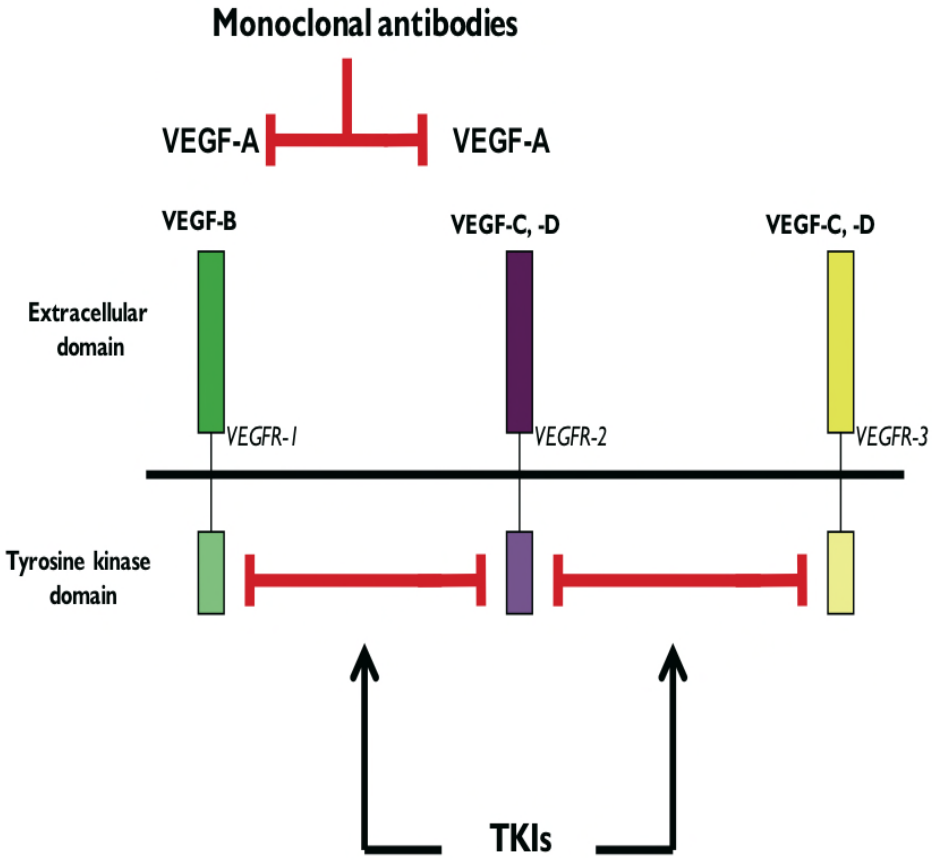
Lek nie jest zarejestrowany w żadnym kraju na świecie w NDRP

Pirker R i wsp. Lancet 2009; 373: 1525-1531

Leki antyangiogenne







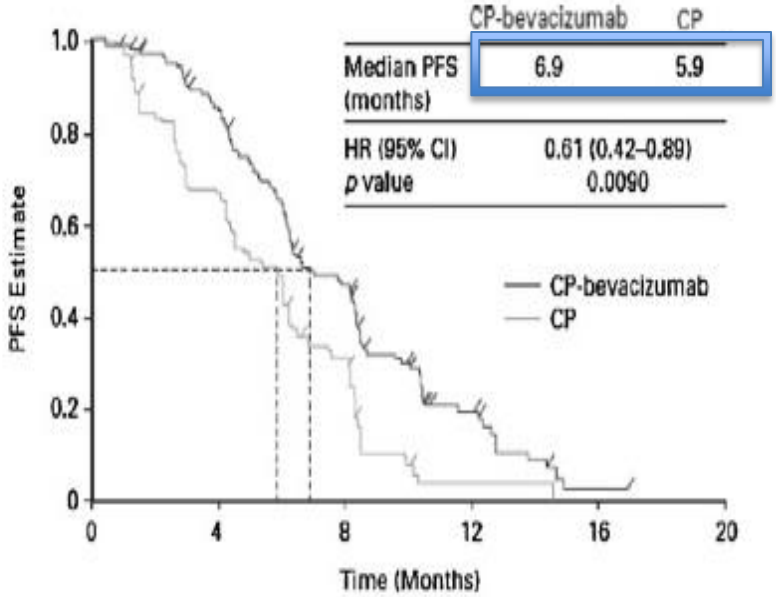
Valdés i wsp. Reproductive Biology and Endocrinology 2008; 6:13
Kalluri R i wsp. Nature Reviews Cancer 2012; 3, 422-433

Bewacyzumab w NDRP nie SCC

	ECOG4599		AVAiL		
	PCB	PC	PGB (7,5)	PGB (15)	PG
RR (%)	35	15	34,1	30,4	20,1
P value	<0.001		<0.0001 dla 7,5 mg <0.0023 dla 15 mg		
PFS miesiące	6,2	4,5	6,7	6,5	6,1
HR (p value)	0.66 (<0.001)		0.75 (0.003) dla 7,5 mg 0.82 (0.03) dla 15 mg		
OS miesiace	12,3	10,3	13,6	13,4	13,1
HR (p value)	0.79 (0.003)		0.93 (NS) dla 7,5 mg 1.03 (NS) dla 15 mg		

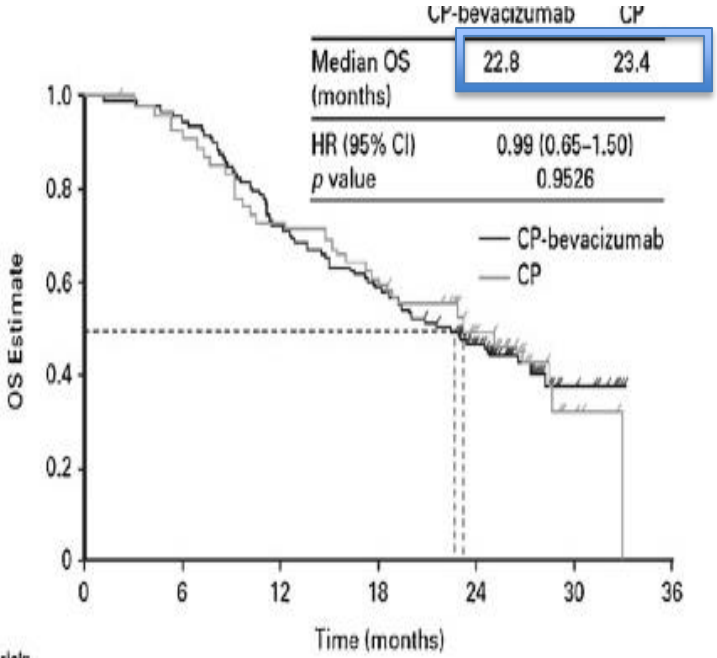
Bewacyzumab – JAPAN STUDY

PFS



Patients at risk:						
CP-bevacizumab	117	94	49	14	1	0
CP	58	35	15	1	0	0

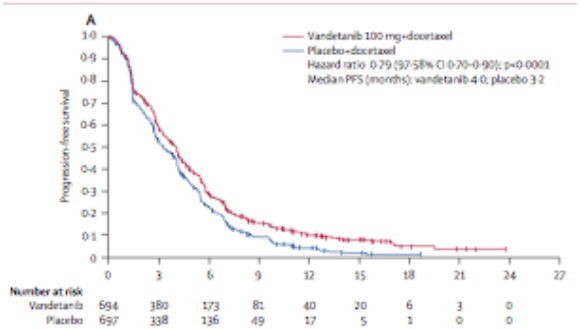
OS

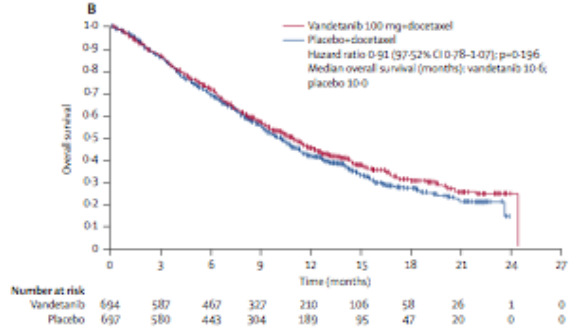


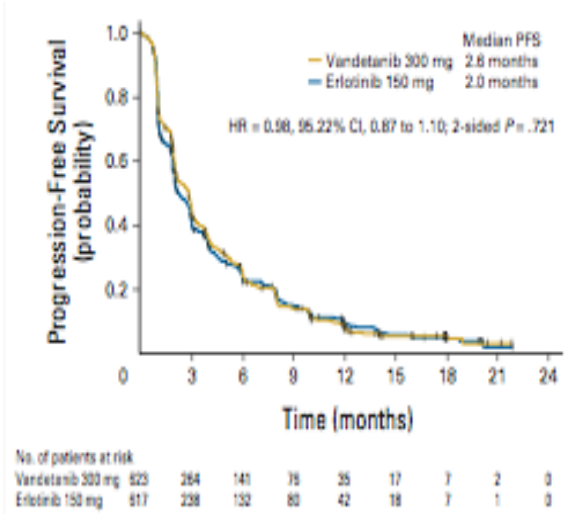
Patients at risk:							
CP-bevacizumab	117	111	85	69	46	9	0
CP	58	52	42	35	20	4	0

Niho S i wsp. Lung Cancer 2013 in press

Wandetanib – badania III fazy







ZEPHYR

Wandetanib wobec Placebo

ZEST

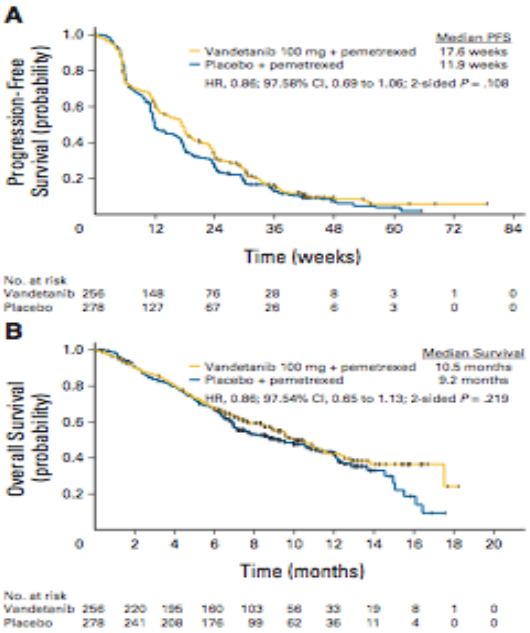
Wandetanib wobec Erlotynib

ZODIAC

Wandetanib + DXL wobec DXL

ZEAL

Wandetanib + PMX wobec PMX



Herbst RS i wsp. Lancet Oncol 2010; 11: 619-626
De Boer RH i wsp. J Clin Oncol 2011; 29 (8): 1067-1074
Natale RB i wsp. J Clin Oncol 2011; 29 (8): 1059-1066

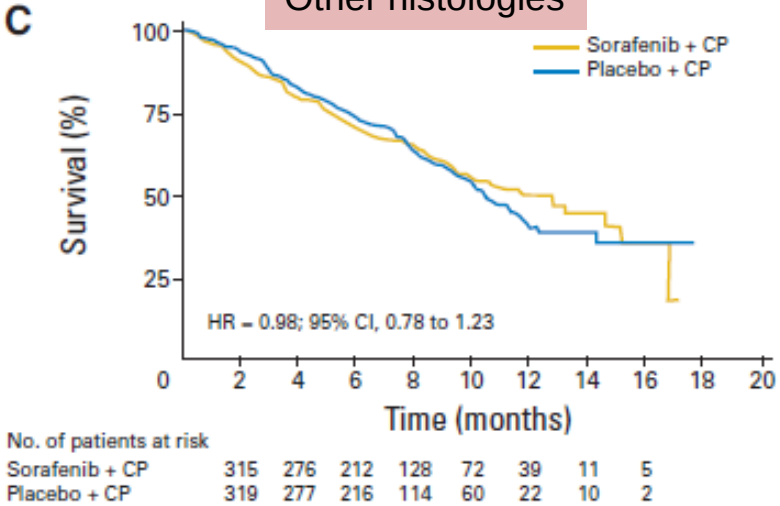
ESCAPE: OS

Table 1. Baseline Patient Demographics and Clinical Characteristics

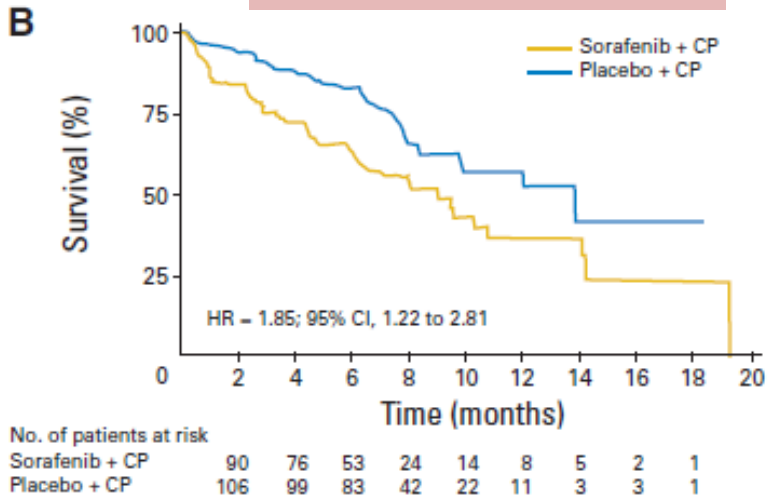
Demographic or Clinical Characteristic	Arm A: Sorafenib Plus CP (n = 464) No. of Patients	%	Arm B: CP Alone (n = 462) No. of Patients	%
Age, years				
Median	62.0		63.0	
Range	34-86		34-82	
≥ 65	185	40	196	42
Male	293	63	288	62
Race				
White	406	88	396	86
Black	18	4	13	3
Asian	21	5	21	5
Hispanic	11	2	21	5
Other	7	2	11	2
ECOG PS				
0	190	41	188	41
1	274	59	274	59
Past or present smoker	388	84	397	86
Stage at study entry				
IIIB	44	9	47	10
IV	420	91	415	90
Histology				
Adenocarcinoma	263	57	271	59
Large-cell carcinoma	23	5	30	6
Squamous cell carcinoma	109	23	114	25
Other*	69	15	47	10

Abbreviations: CP, carboplatin/paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status.
*Includes bronchoalveolar, undifferentiated, and neuroendocrine carcinoma and unspecified histology.

Other histologies



Squamous cell carcinoma



Scagliotti G i wsp. J Clin Oncol 2010; 28: 1835 – 1842

Leki nowe – badania II i III fazy

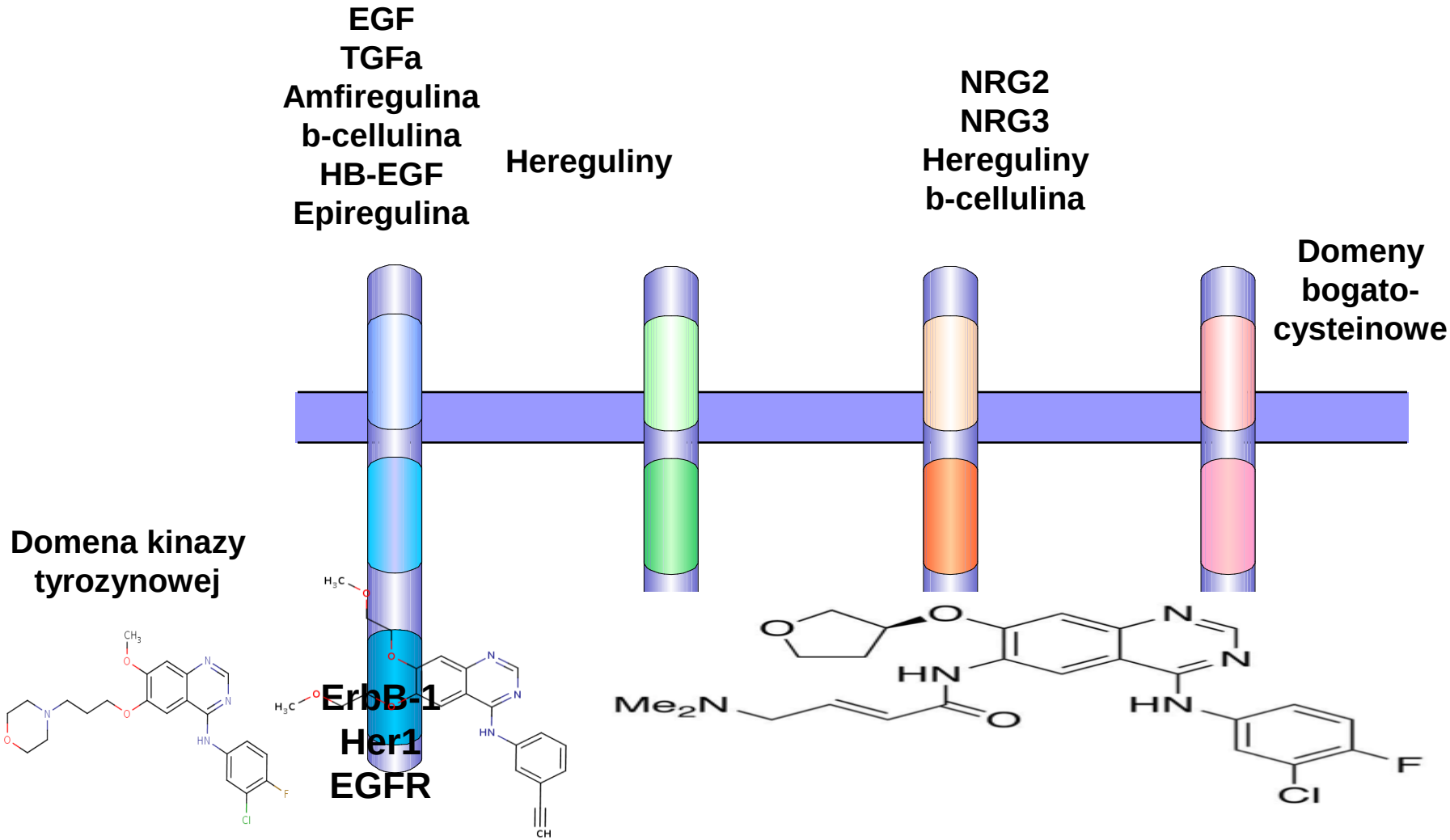
Preparat	Linia leczenia	Status
CEDYRANIB	I	zakończone
Aksytynib	I	zakończono
Sorafenib, Sunitynib	I, II	różny stan

Czynniki predykcyjne

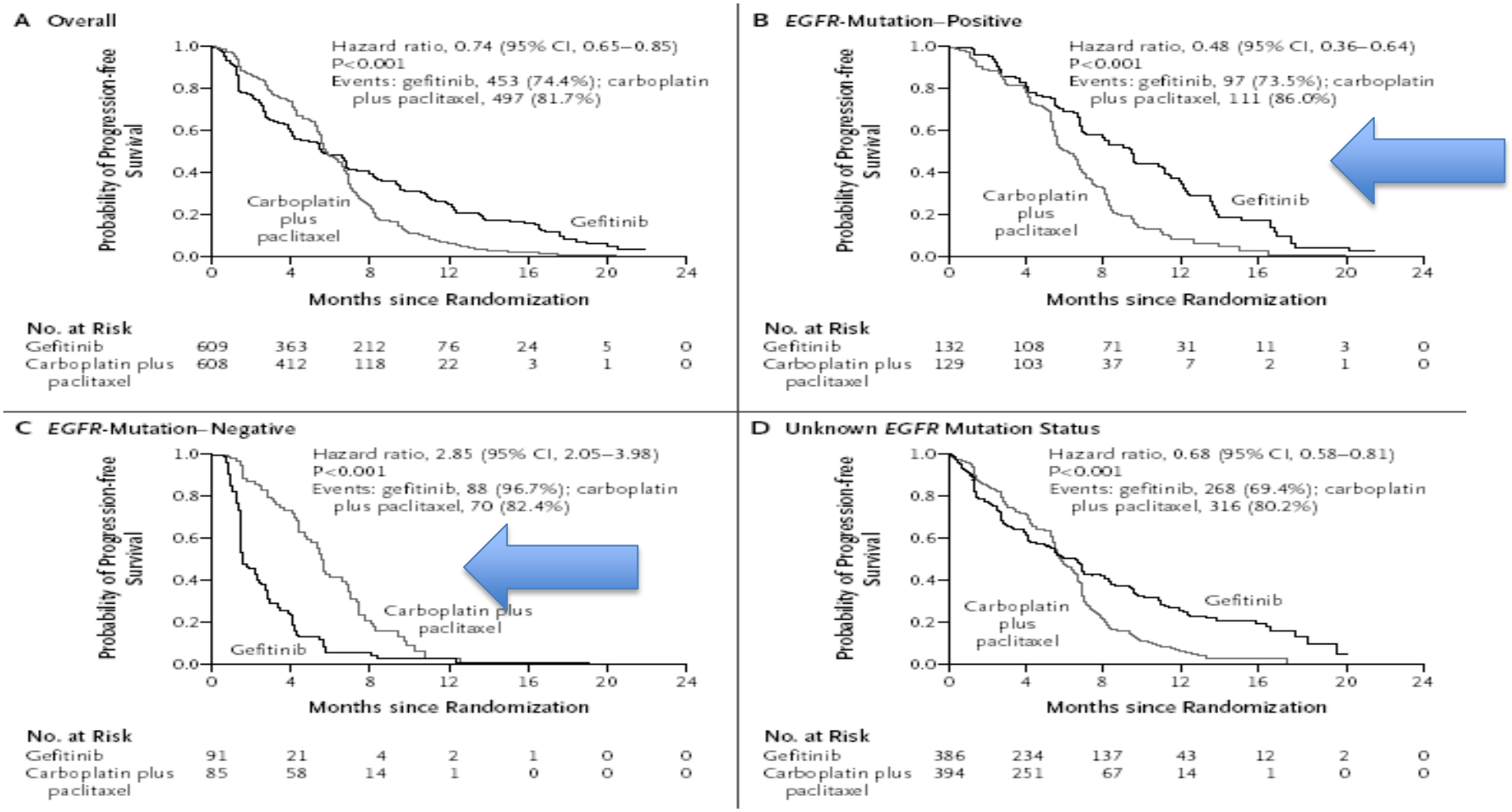
Aggarwal C i wsp. Cancer Biol Ther 2012; 13: 247-263

PRESENT

Rodzina Receptorów HER

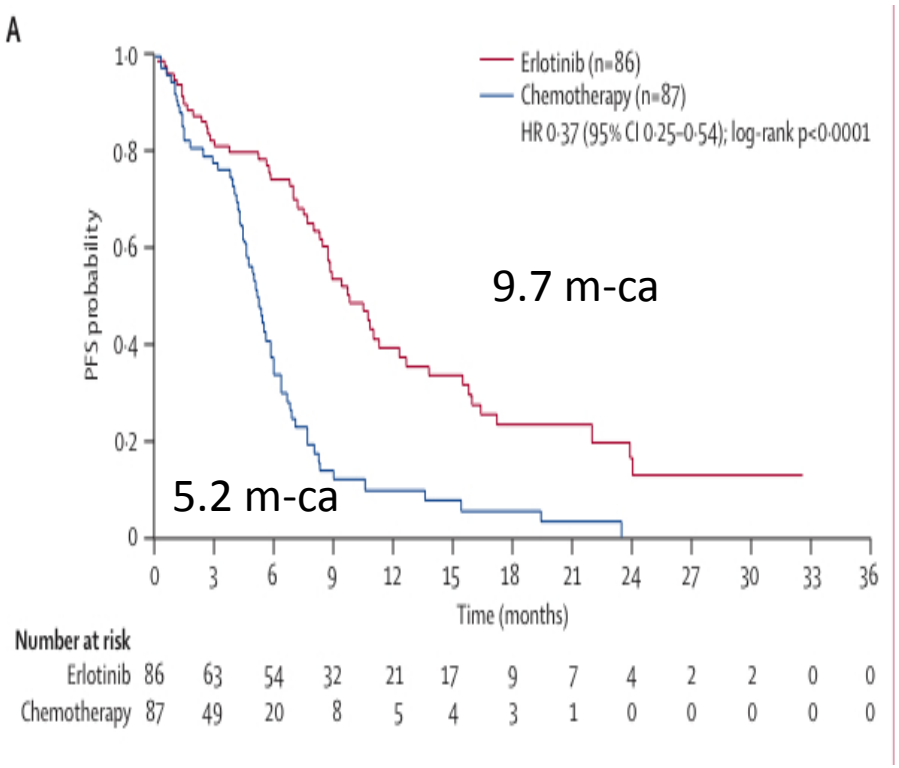


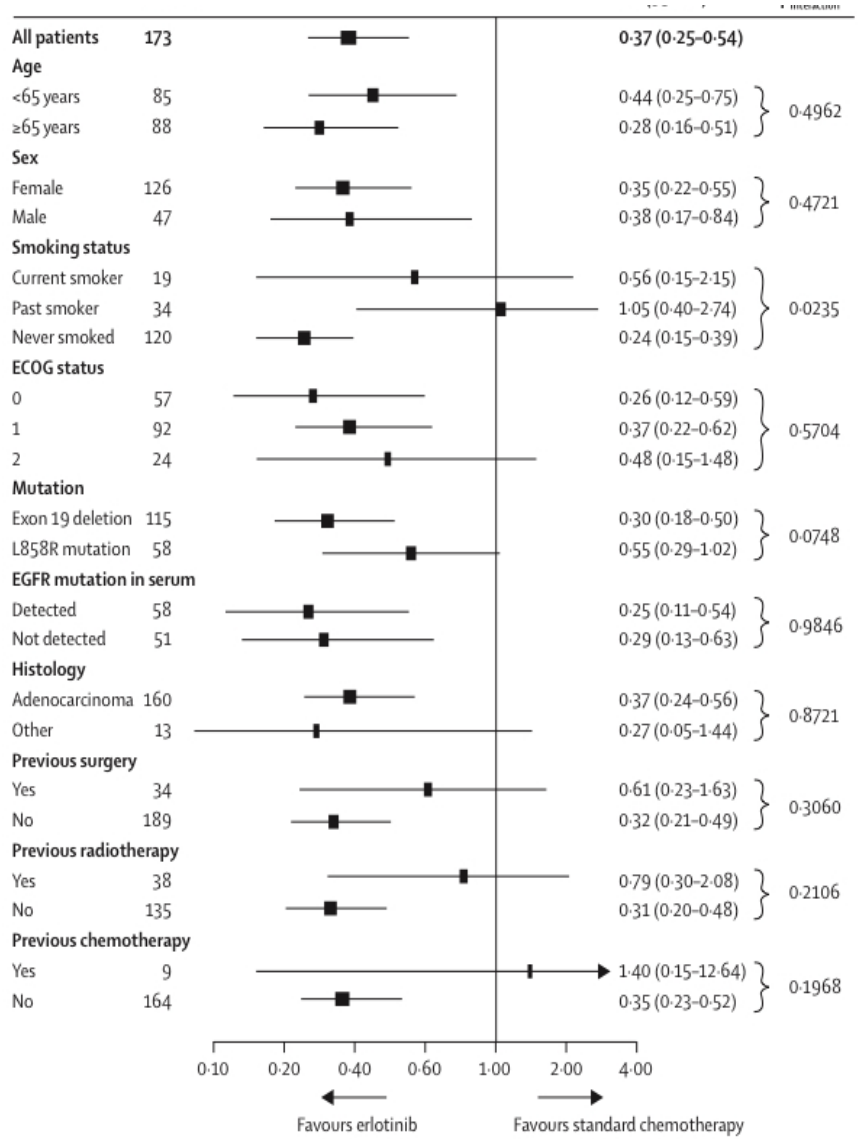
Gefitynib



Mok TS i wsp. N Engl J Med. 2009; 36: 1-11

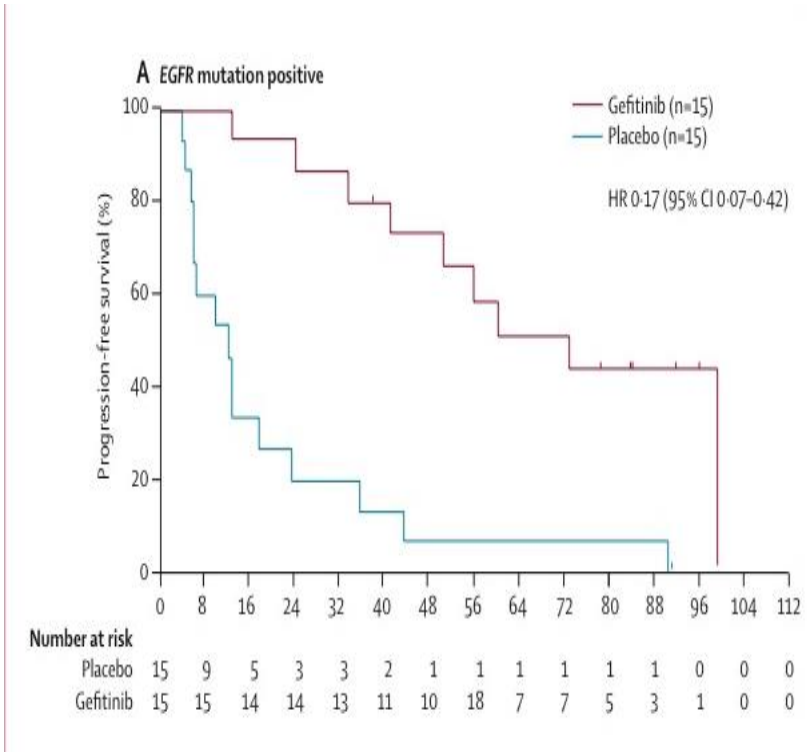
EURTAC - Czas wolny od progresji - PFS

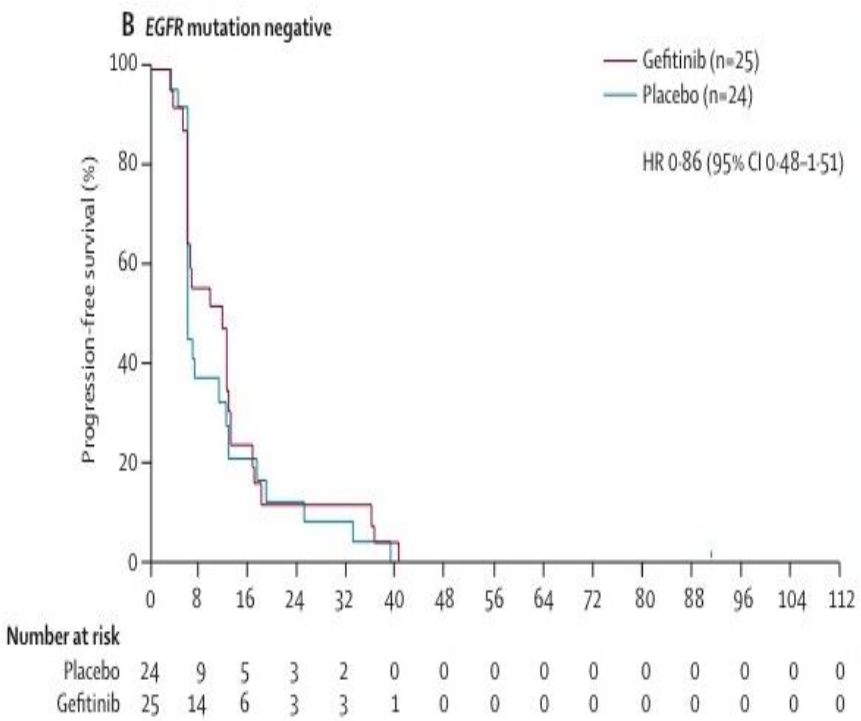




Rosell R i wsp. Lancet Oncol 2012; 13: 239-246

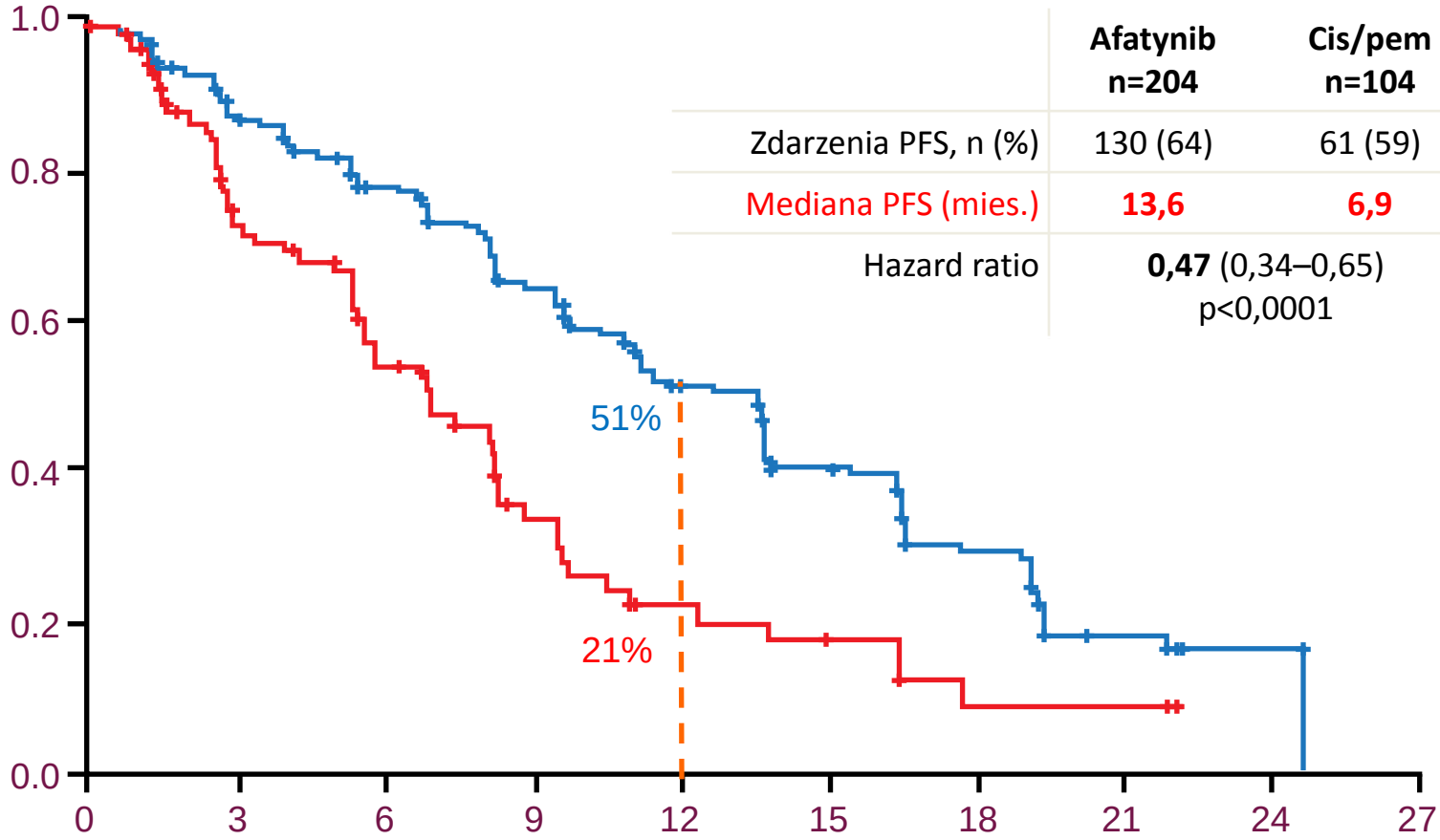
INFORM – stan mutacji EGFR





Zhang L i wsp. Lancet Oncol 2012; 13 (5): 466-475

LUX LUNG III - PFS: Połączone mutacje (Del19/L858R)
Ocena niezależna – chorzy z Del19/L858R (n=308)



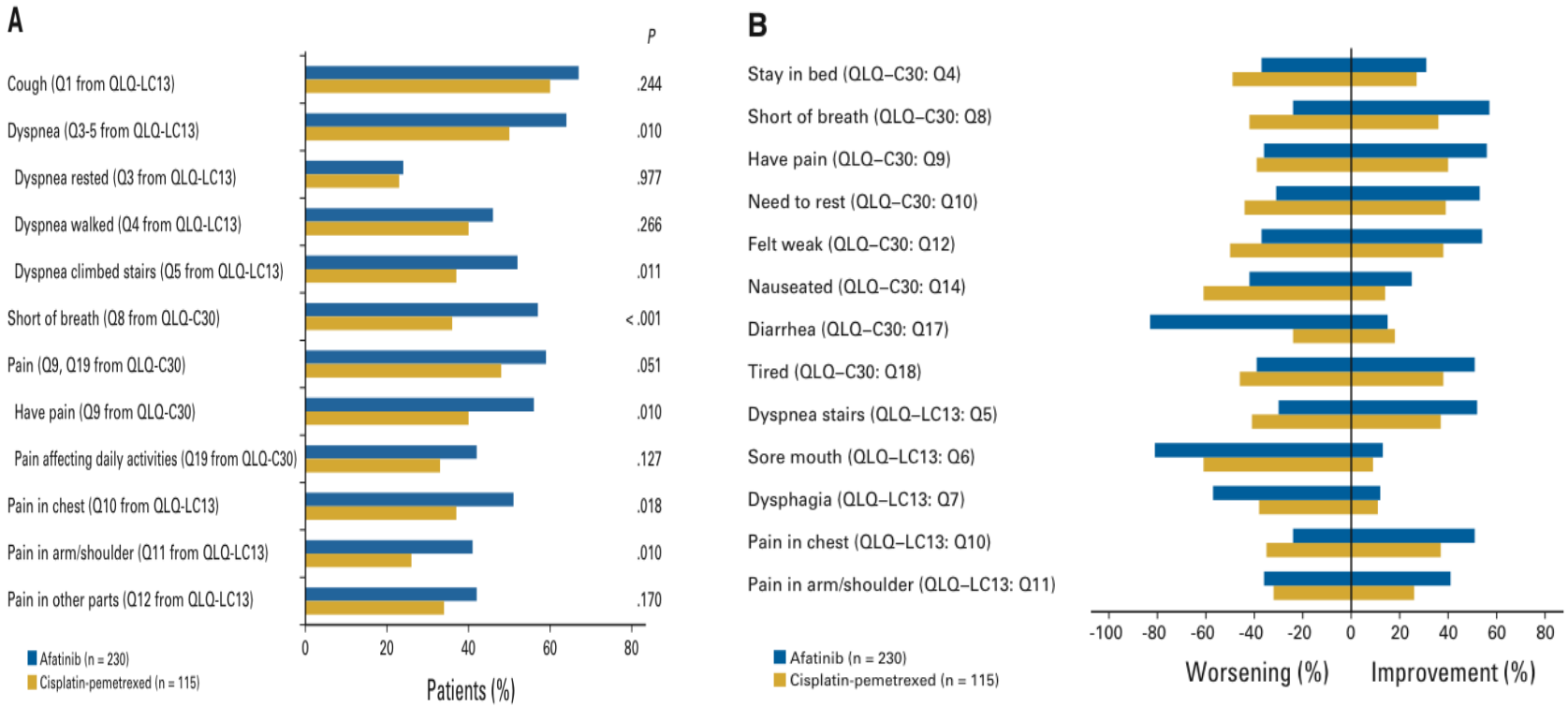
	Afatynib n=204	Cis/pem n=104
Zdarzenia PFS, n (%)	130 (64)	61 (59)
Mediana PFS (mies.)	**13,6**	**6,9**
Hazard ratio	**0,47** (0,34–0,65) p<0,0001	

Liczba chorych z ryzykiem

Afatynib	204	169	143	115	75	49	30	10	3	0
Cis/Pem	104	62	35	17	9	6	2	2	0	0

Sequist LV i wsp. J Clin Oncol 2013; 31: 3327-3334

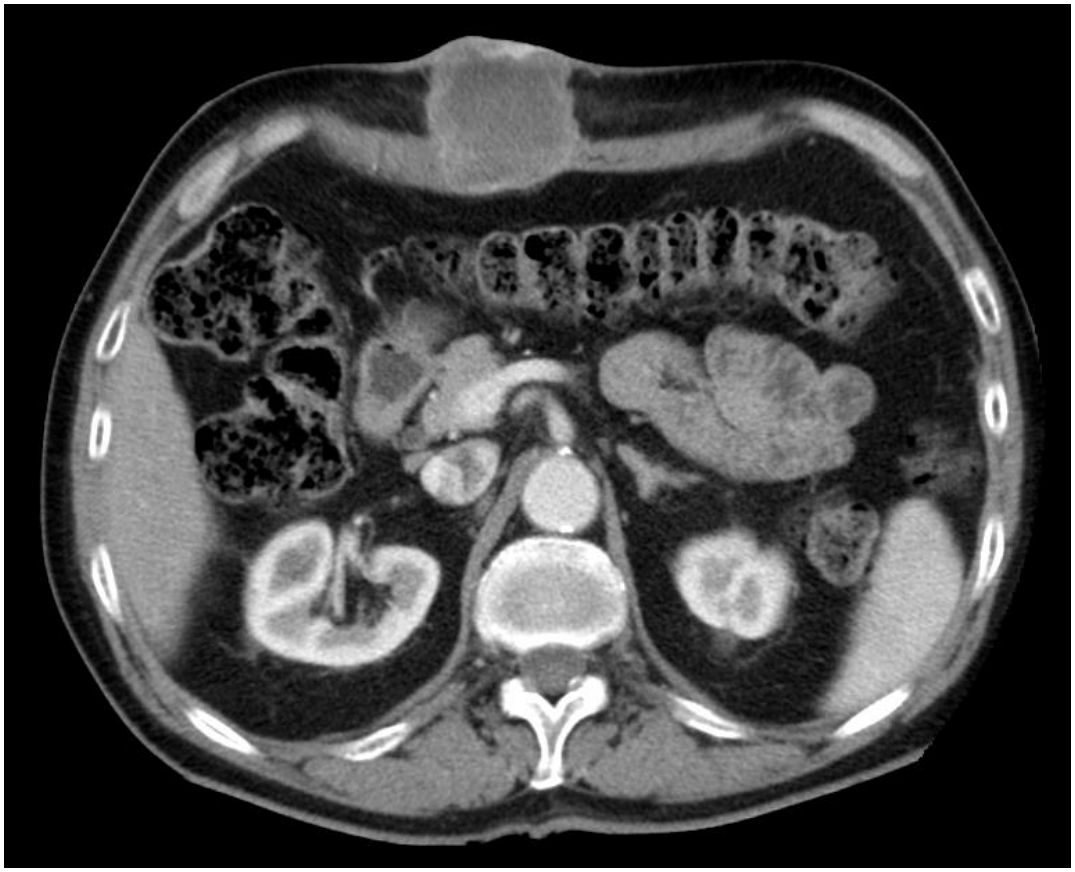
LUX LUNG III – QoL



Yang JCH i wsp. J Clin Oncol 2013; 31: 3342-3350

Ocena odpowiedzi na erlotynib

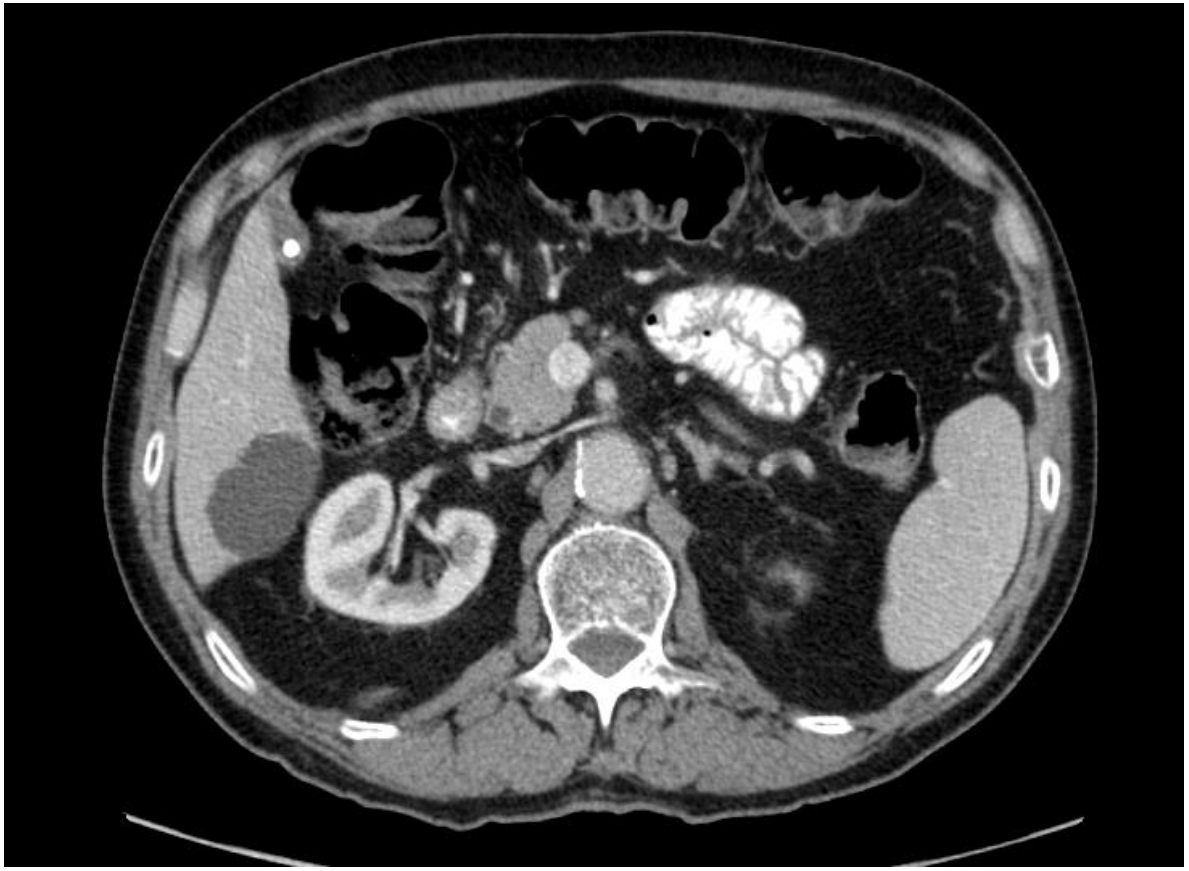
01. 06. 2008



Kowalski DM Materiał COI

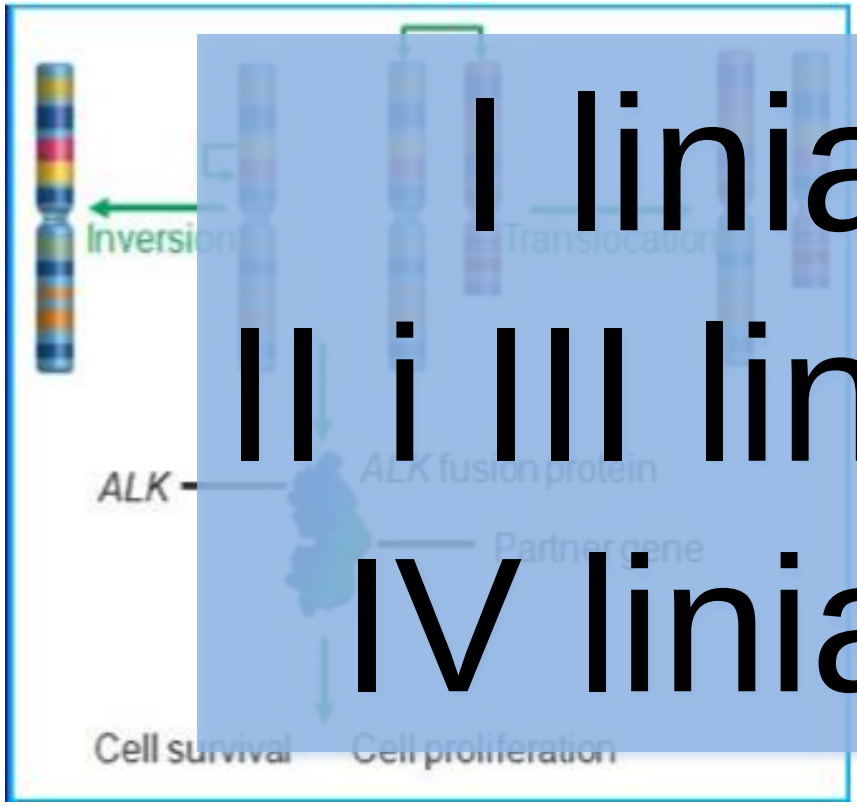
Ocena odpowiedzi na erlotynib

06. 05. 2011



Kowalski DM Materiał COI

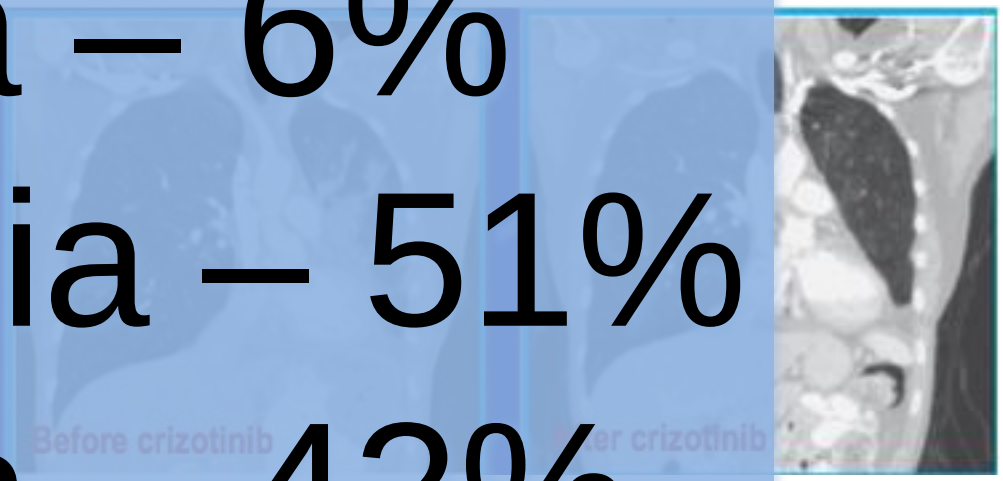
Szlak ALK



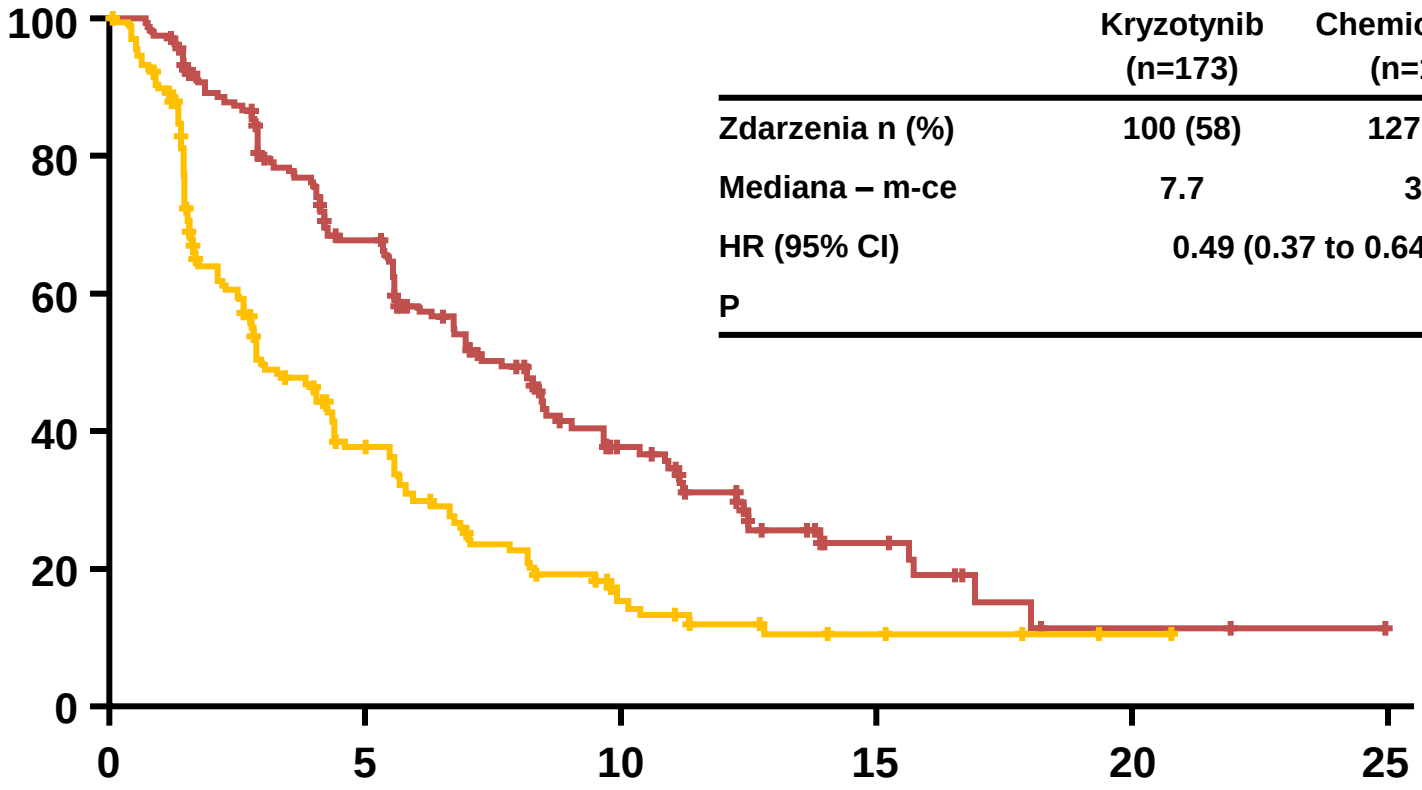
I linia – 6%

II i III linia – 51%

IV linia – 42%



PROFILE 1007 - PFS – ocena niezależna



	Kryzotynib (n=173)	Chemioterapia (n=174)
Zdarzenia n (%)	100 (58)	127 (73)
Mediana – m-ce	7.7	3.0
HR (95% CI)	0.49 (0.37 to 0.64)	
P		

PROFILE 1007: NCT00932893

PROFILE 1014 – badanie III fazy I linia

Trial design

- Worldwide
- Multicenter
- Randomized
- Open-label
- Focused screening

Endpoints

- *Primary*: PFS
- *Secondary*: 12-month, 18-month, and overall OS; ORR; DR; Safety; HRQoL; Lung cancer-specific sy
Biom

Stratification

- ECOG PS (0/1 vs 2)
- Ethnicity (Asian vs non-Asian)
- Brain metastases

Accrual completed in June 2013

Key entry criteria

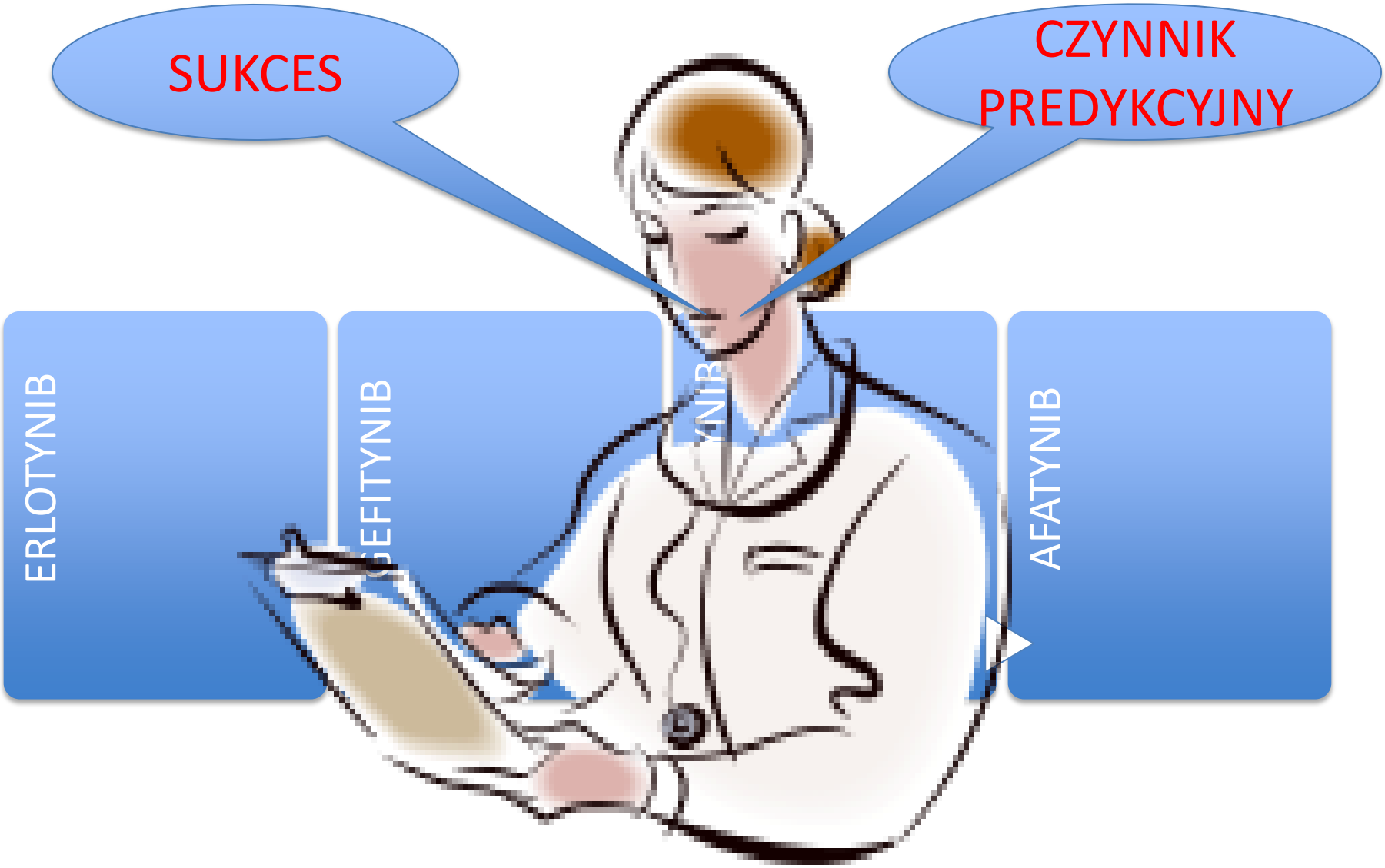
- Diagnosis of locally advanced/metastatic non-squamous NSCLC
- ECOG 0-2
- Positive for *EML4-ALK*
- No prior treatment for advanced disease
- Brain metastases allowed

RANDOMIZE

(n=167): Crizotinib 250 mg BID administered on a continuous dosing schedule

Arm B (n=167): Pemetrexed/cisplatin or pemetrexed/carboplatin Day 1 of a 21-day cycle for 6 cycles

TKI

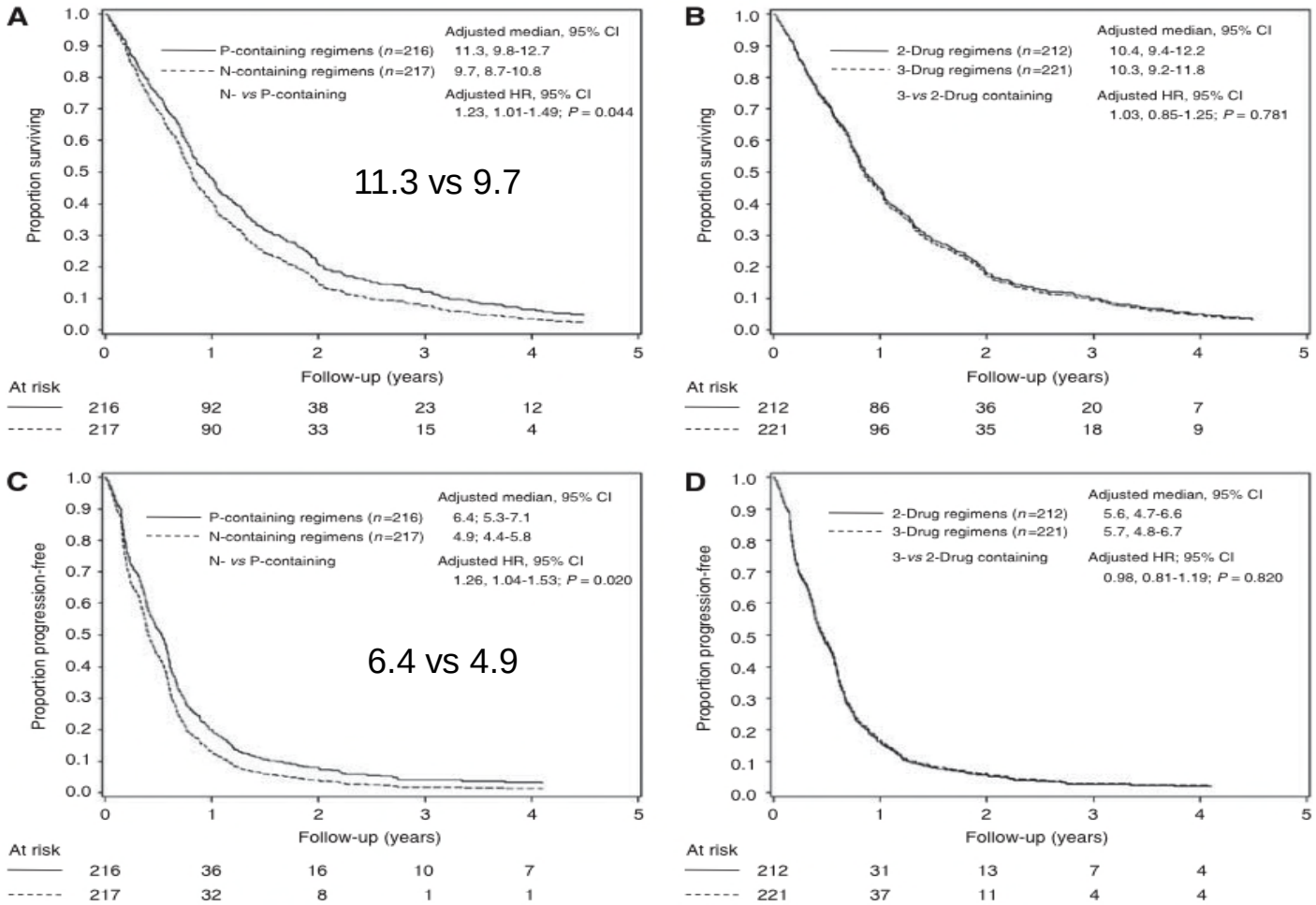

SUKCES
CZYNNIK PREDYKCYJNY
ERLOTYNIB
GEFITYNIB
AFATYNIB

NDRP – Liczba leków 2 wobec 3

N=443

OS

PFS



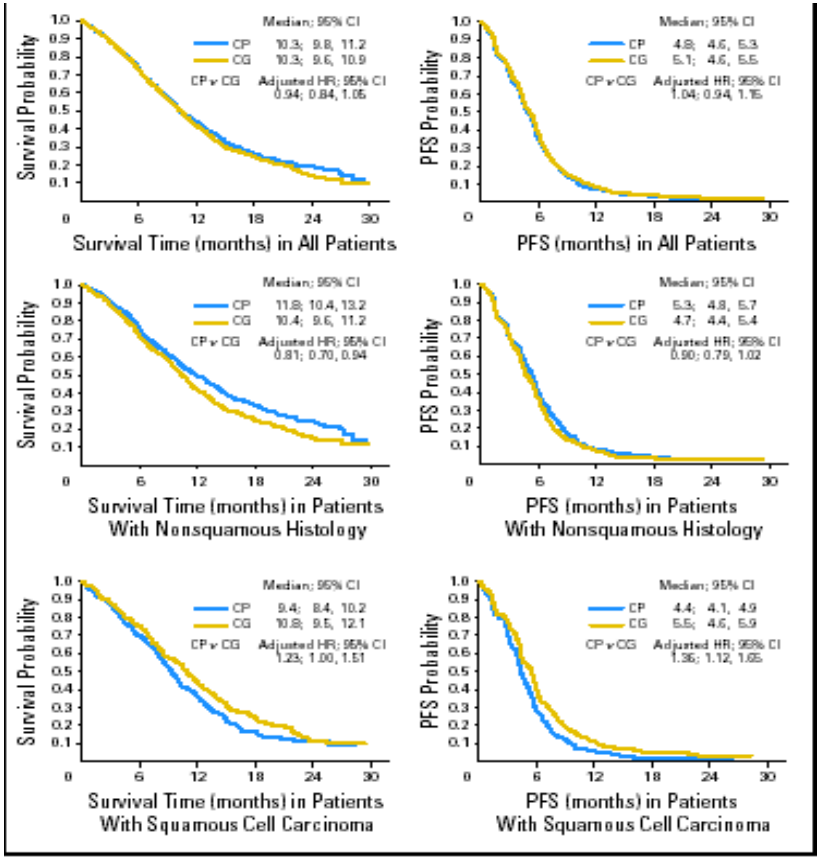
Boni C i wsp. Br J Cancer 2012; 106: 658-665

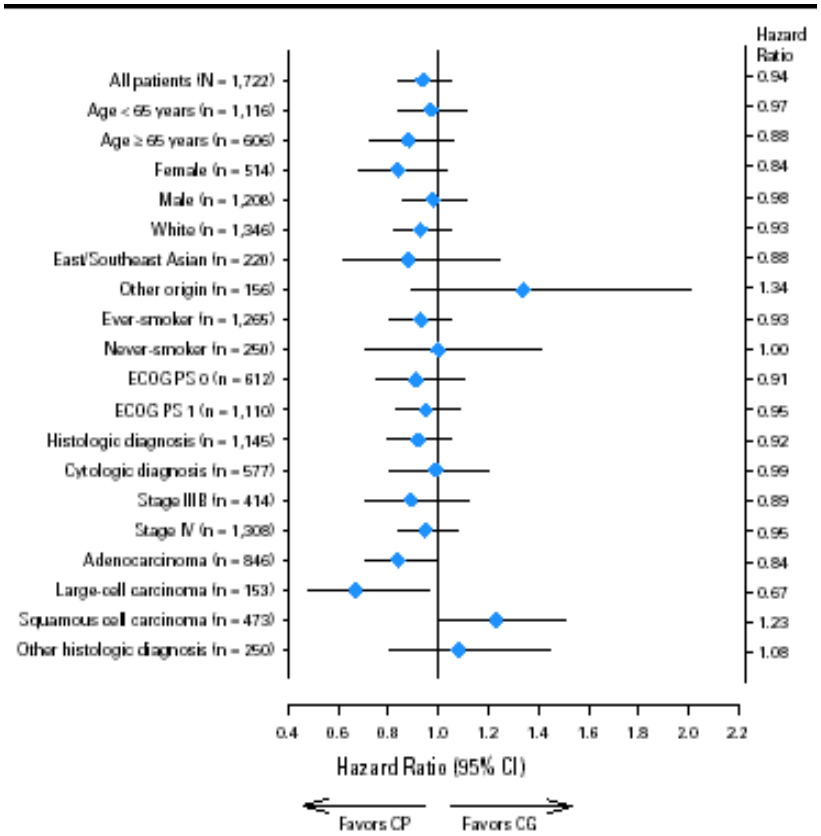
Schemat leczenia i histologia

10.3 vs 10.3 m-ca

AC 12.7 vs 10.9 m-ca
LC 10.4 vs 6.7 m-ca

SCC 10.8 vs 9.4 m-ca

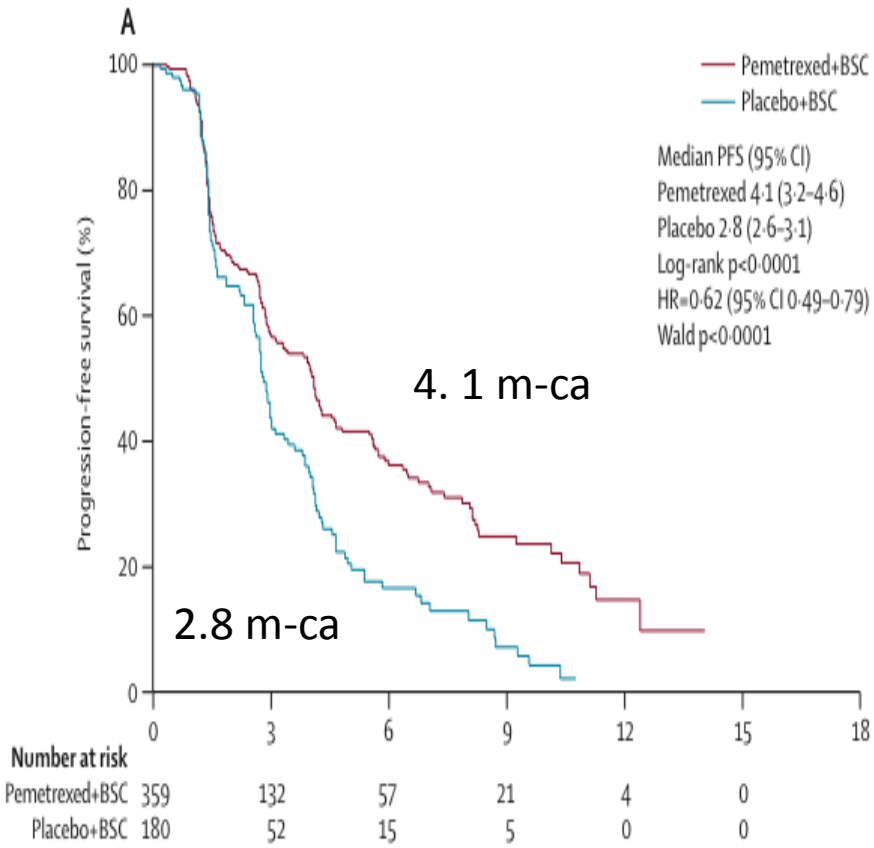




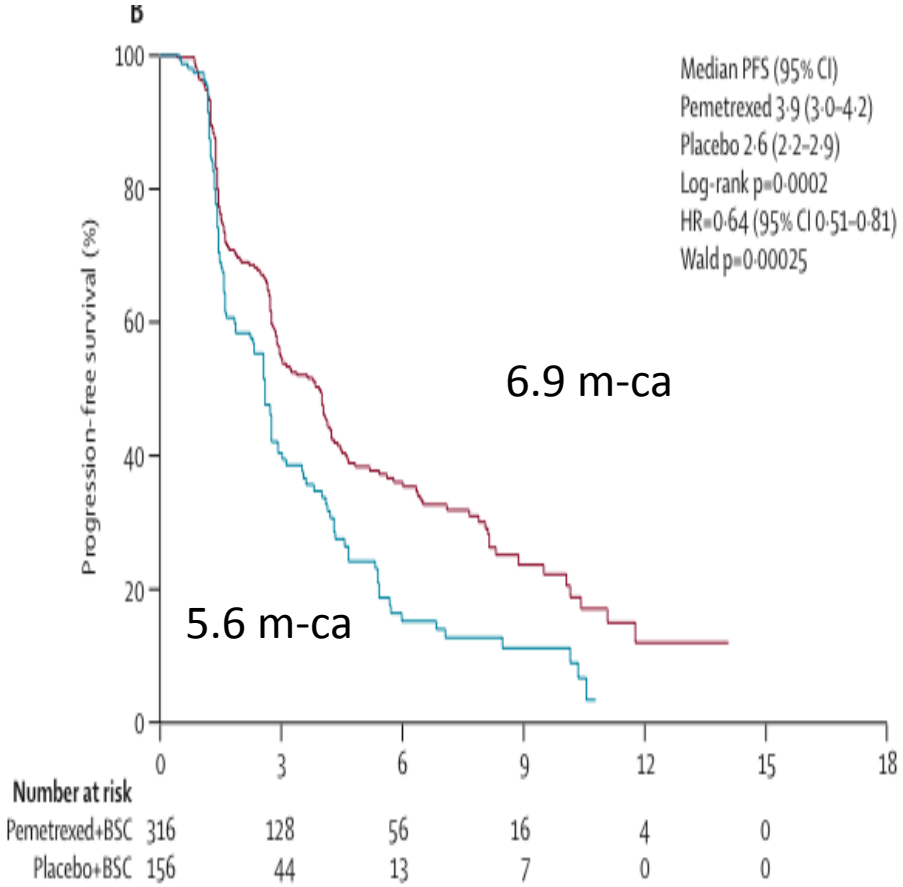
Scagliotti GV i wsp. J Clin Oncol 2008; 21: 1-11

PARAMOUNT – PMX po DDP+PMX

PFS od randomizacji

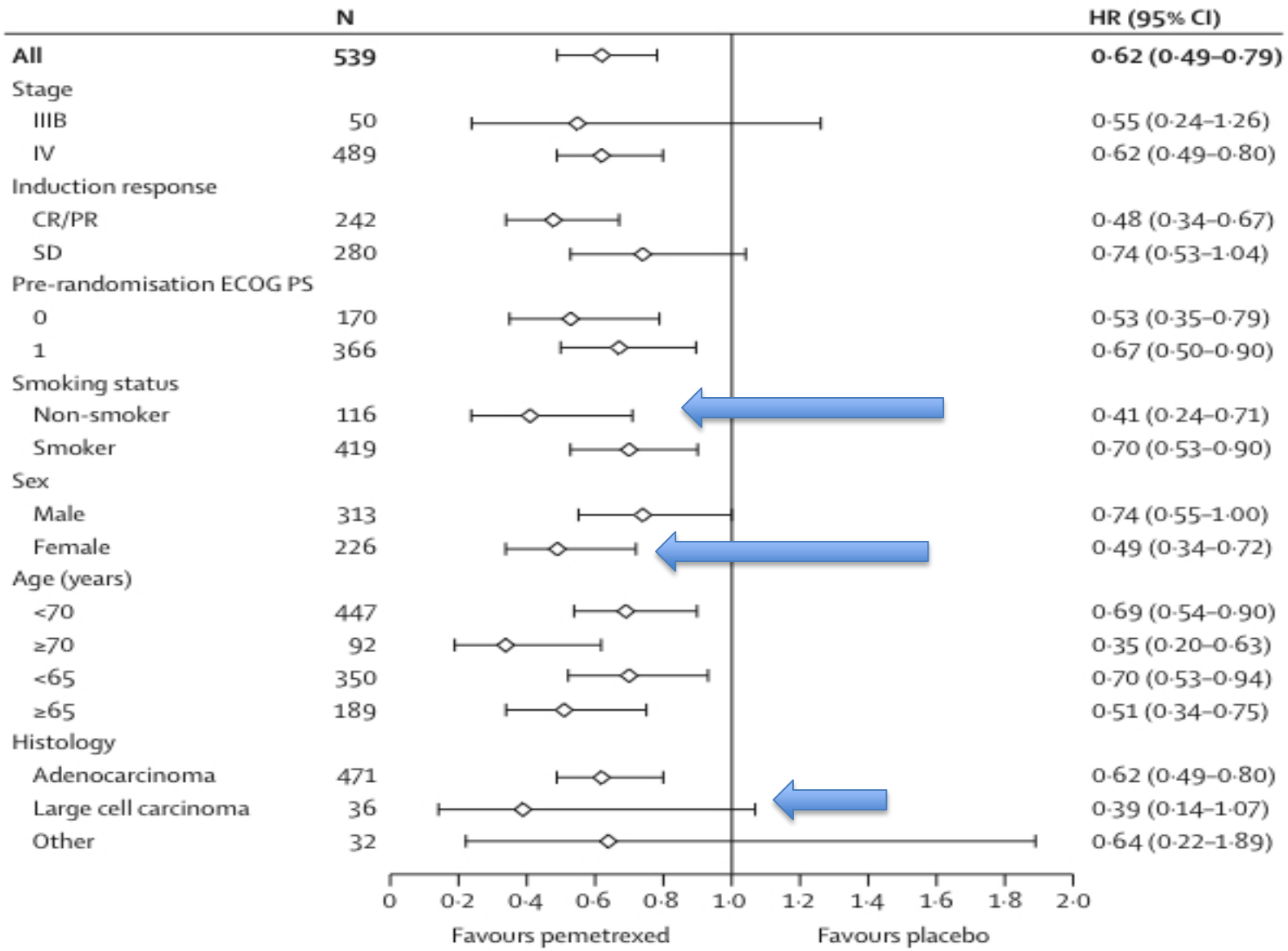


PFS od start CTH



Paz-Ares L i wsp. Lancet Oncol 2012; 12: 247-255

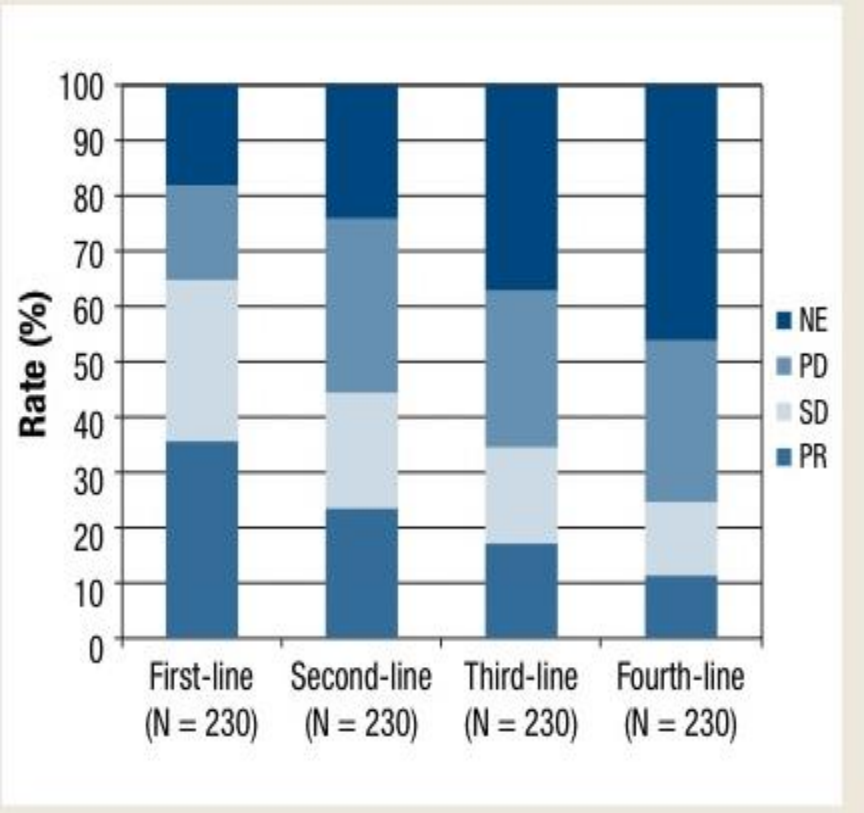
PARAMOUNT – analiza podgrup



Paz-Ares L i wsp. Lancet Oncol 2012; 12: 247-255

I, II Linia – co dalej – CTH?

69.33% i 38.4% i 17.7% i 6.0%



MOS

1 linia – 15.3 m-ca

2 linia – 12.8 m-ca

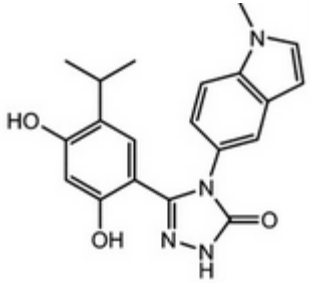
3 linia 12.0 m-ca

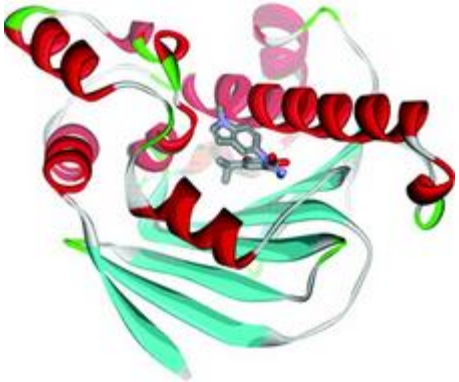
4 linia – 9.9 m-ca

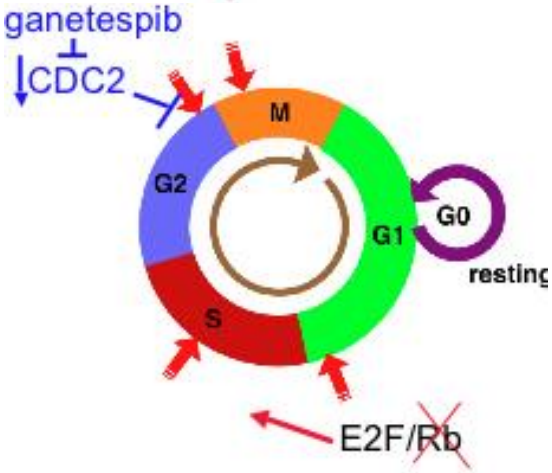
Asahina H i wsp. Clin Lung Cancer 2012; 13: 39-43

FUTURE

Ganetespib







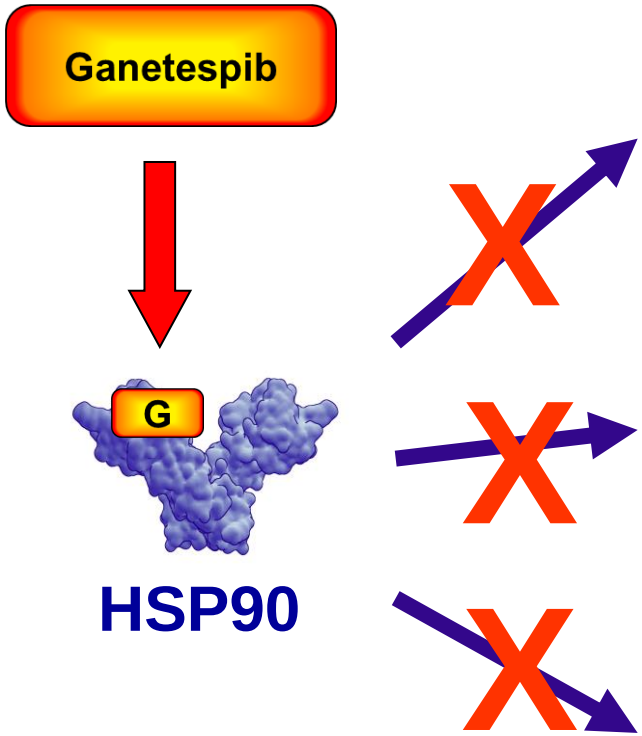
Nowy selektywny bloker HSP 90

Synergizm z taksanami

Hamowanie angiogenezy

Aktywność w NDRP

Ganetespib - potencjalne możliwości



Hamowanie aktywności onkogenów

- ALK, EGFR, HER2, szlak KRAS (RAF, MEK, ERK), AR, ER, JAK2

Hamowanie przerzutowania i angiogenezy

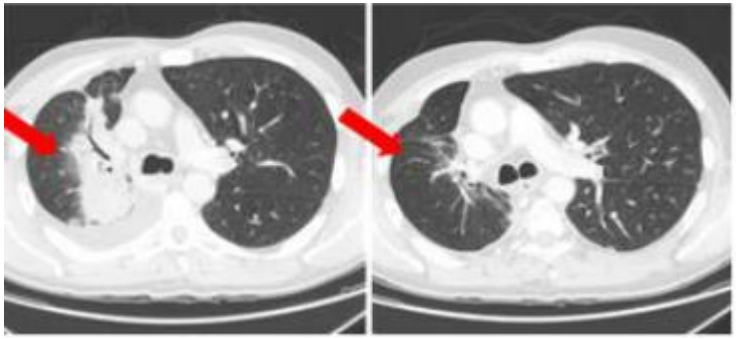
- Angiogeneza: HIF-1α, VEGFR, PDFGR, VEGF
- Przerzutowanie: MET, RAF, AKT, MMPs, HIF-1α, IGF-1R

Synergizm z CTH i LUM

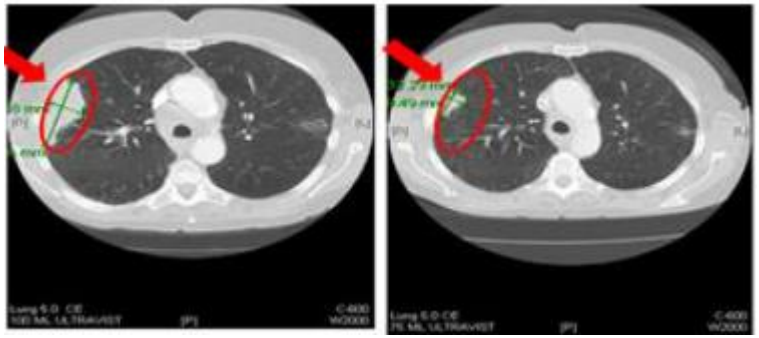
- DNA naprawa, antyapoptoza, punkty kontroli cyklu komórkowego: ATR, BRCA1/2, BCL2, CDK1/4, CHK1, surwiwin, WEE1, HIF-1α

Ganetespib

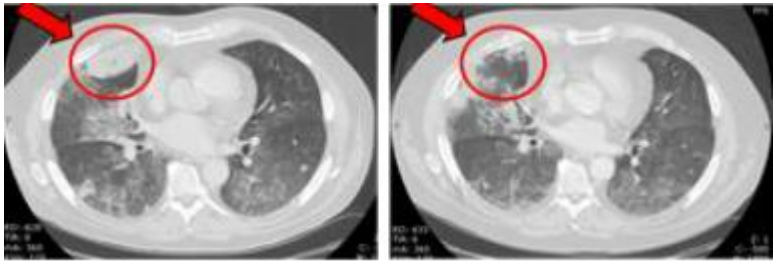
ALK /+/ NDRP



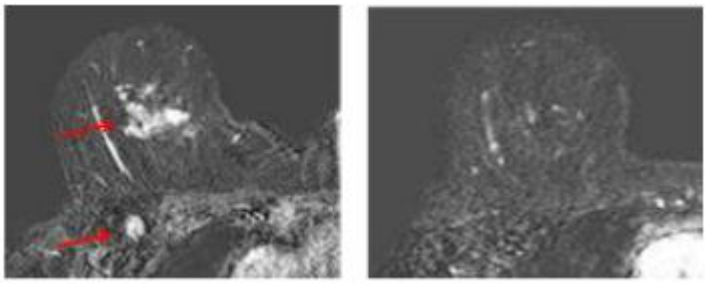
Żołądek



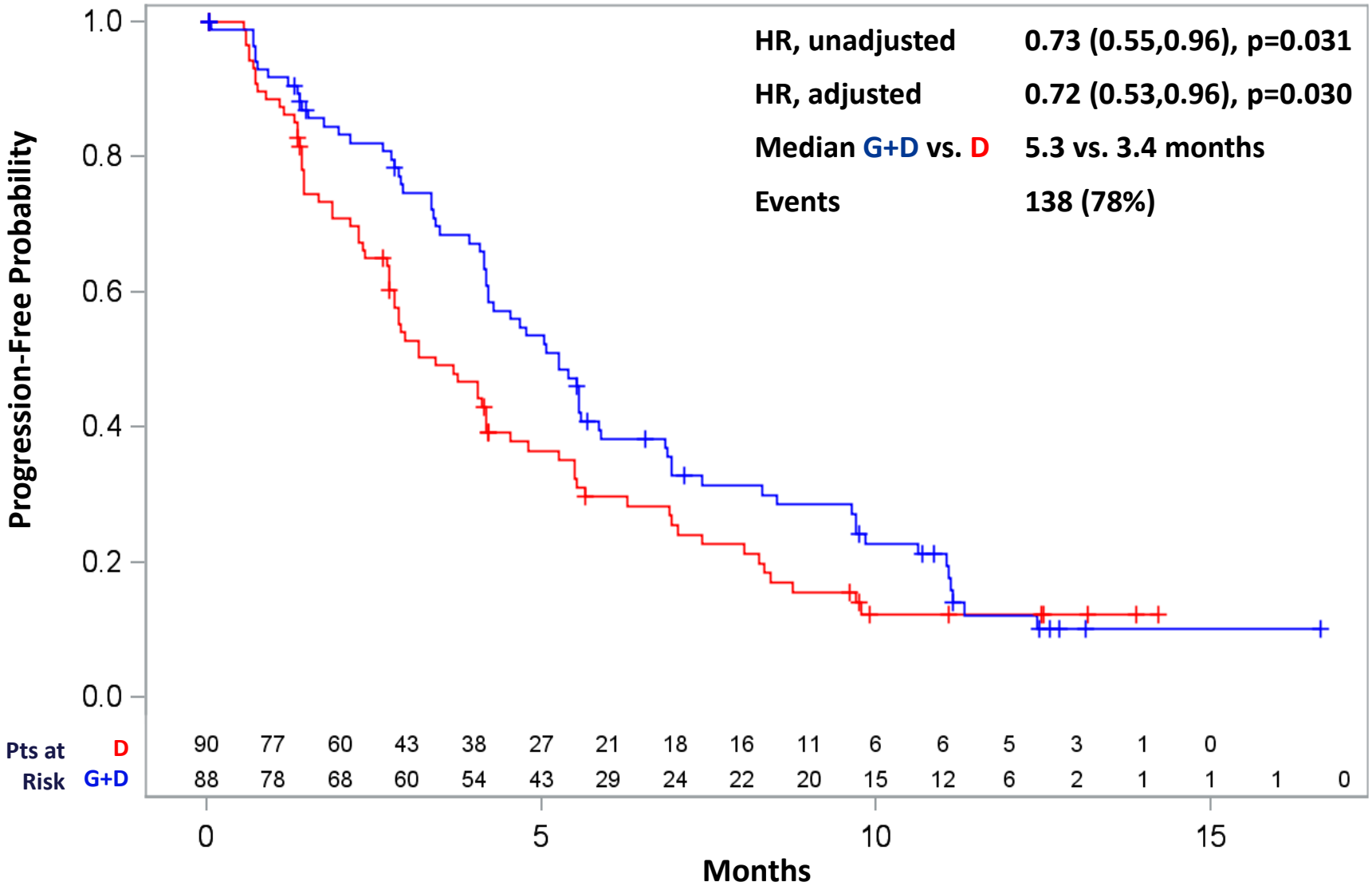
BRAF /+/ NDRP



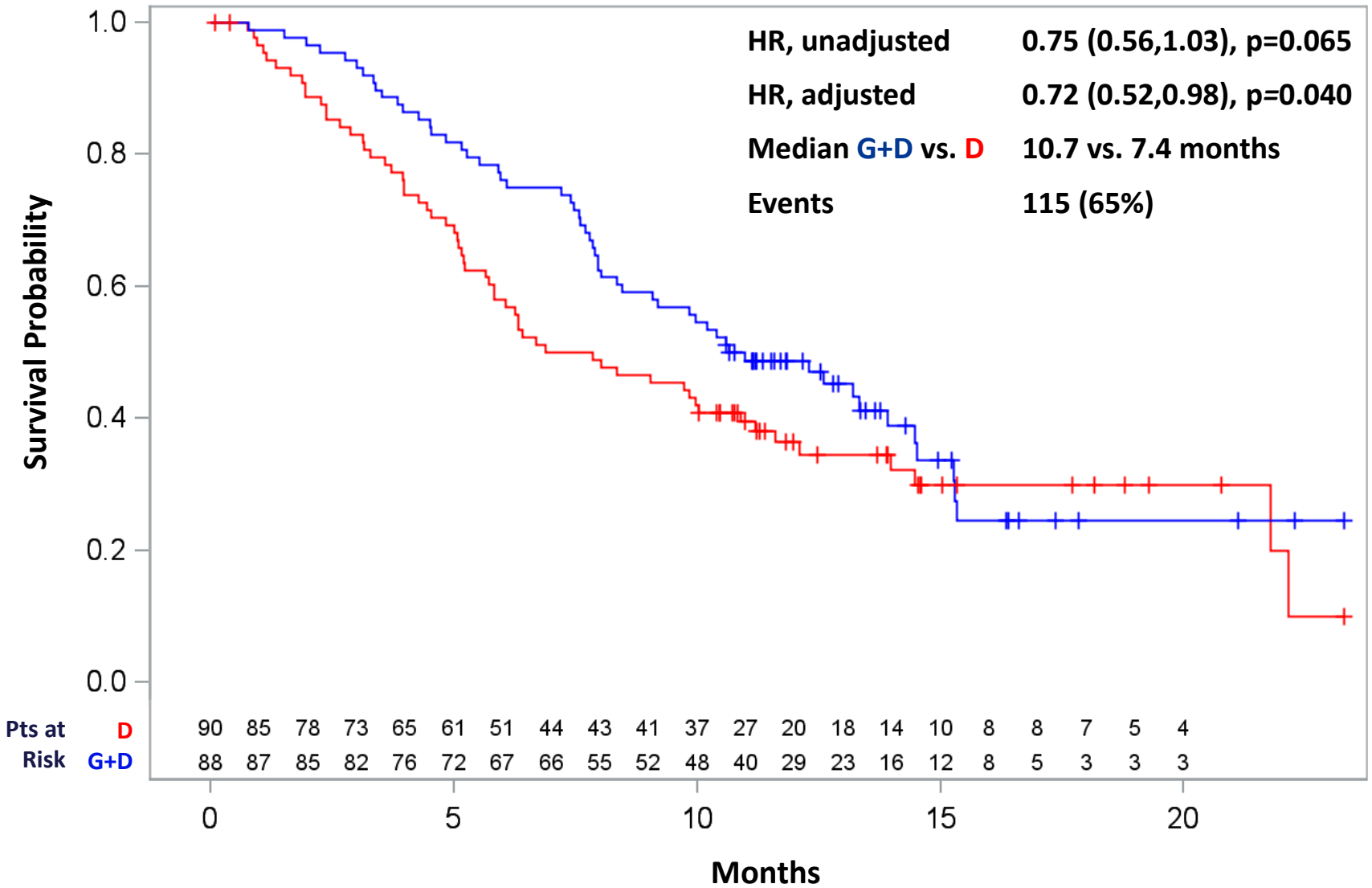
Pierś



Ganetespib - PFS



Ganetespib - OS



GALAXY-2 – Schemat badania III fazy

Zaawansowany NDRP-AC
- PD po 1 CTH
- ECOG PS 0/1
- Rozpoznanie > 6 miesięcy

RANDOMZACJA 1:1

Ganetespib + Docetaksel

G: 150 mg/m^2 d 1,15 q3w
D: 75 mg/m^2 d 1 q3w

Docetaksel

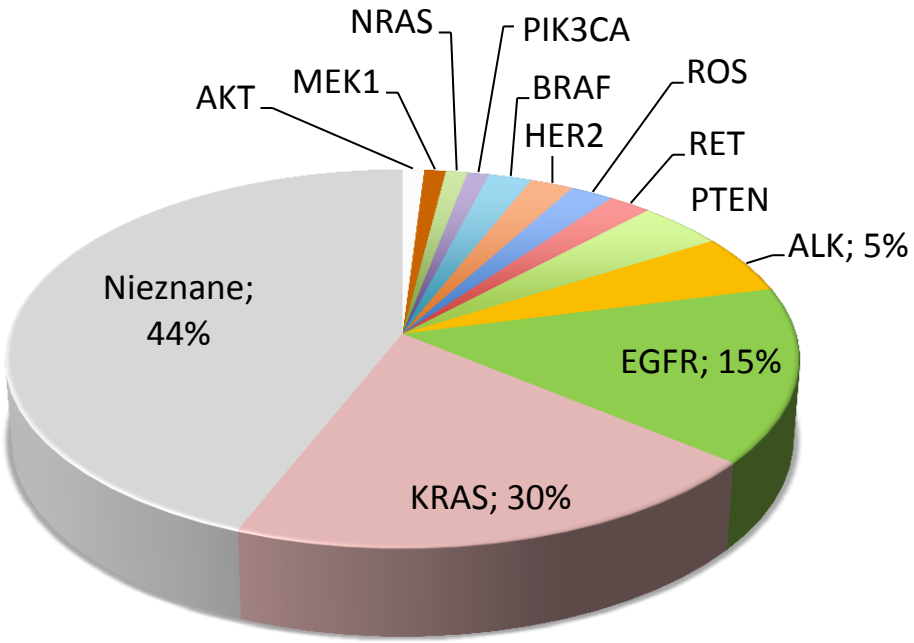
D: 75 mg/m^2 d 1 q3w

N=500

Pierwszorzędowy punkt końcowy: OS

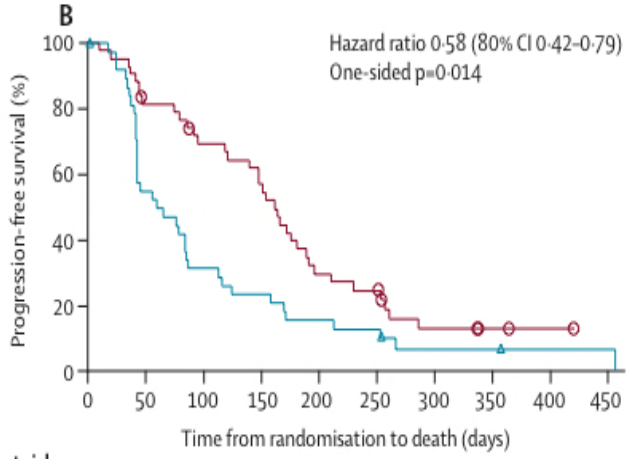
Badanie w trakcie rekrutacji; 15 państw; >100 ośrodków

Leki nowe


NRAS
PIK3CA
AKT
MEK1
BRAF
ROS
HER2
RET
PTEN
ALK; 5%
Nieznane; 44%
EGFR; 15%
KRAS; 30%

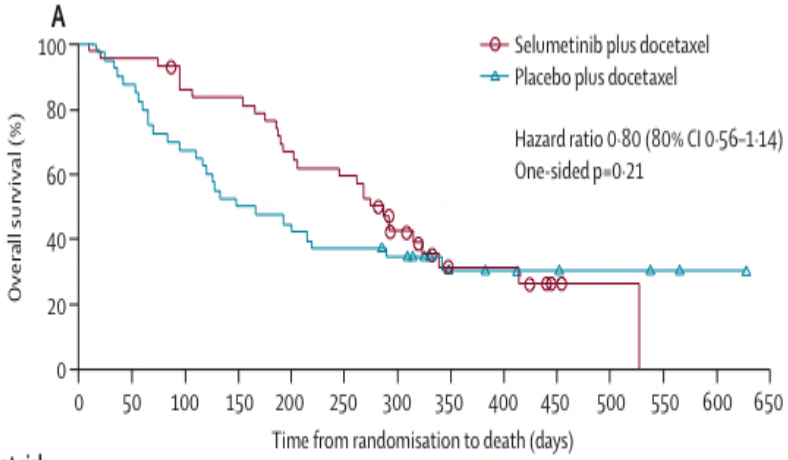
Selumetynib + DXL wobec DXL

PFS 5,5 wobec 2,1 m-ca



Number at risk										
Selumetinib plus docetaxel	43	34	28	23	12	10	4	2	1	
Placebo plus docetaxel	40	21	12	9	6	5	2	2	1	1

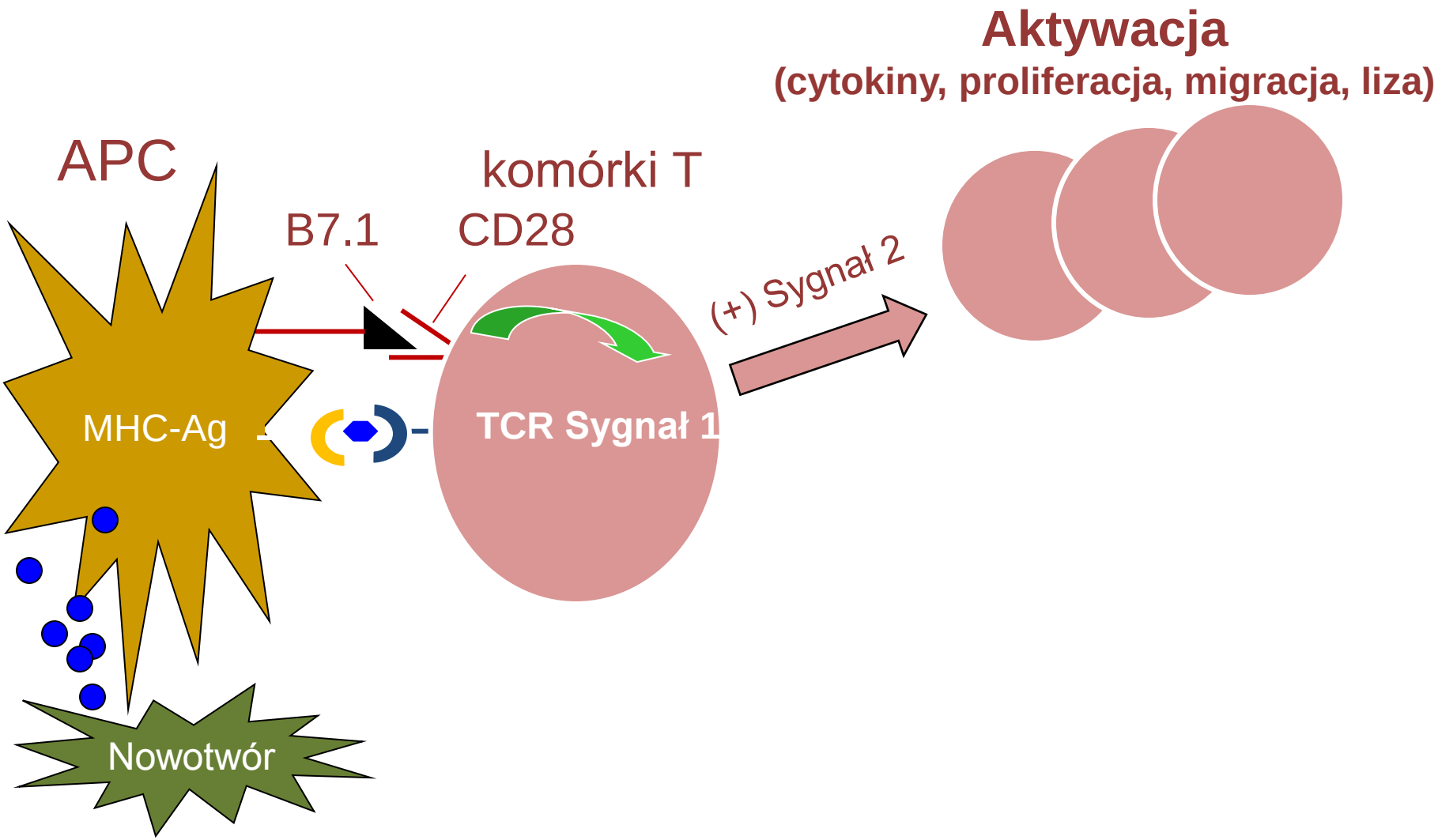
OS 9,4 wobec 5,2 m-ca



Number at risk												
Selumetinib plus docetaxel	43	41	36	35	28	25	14	6	6	2	1	
Placebo plus docetaxel	40	35	27	20	18	15	13	6	5	4	3	2	1

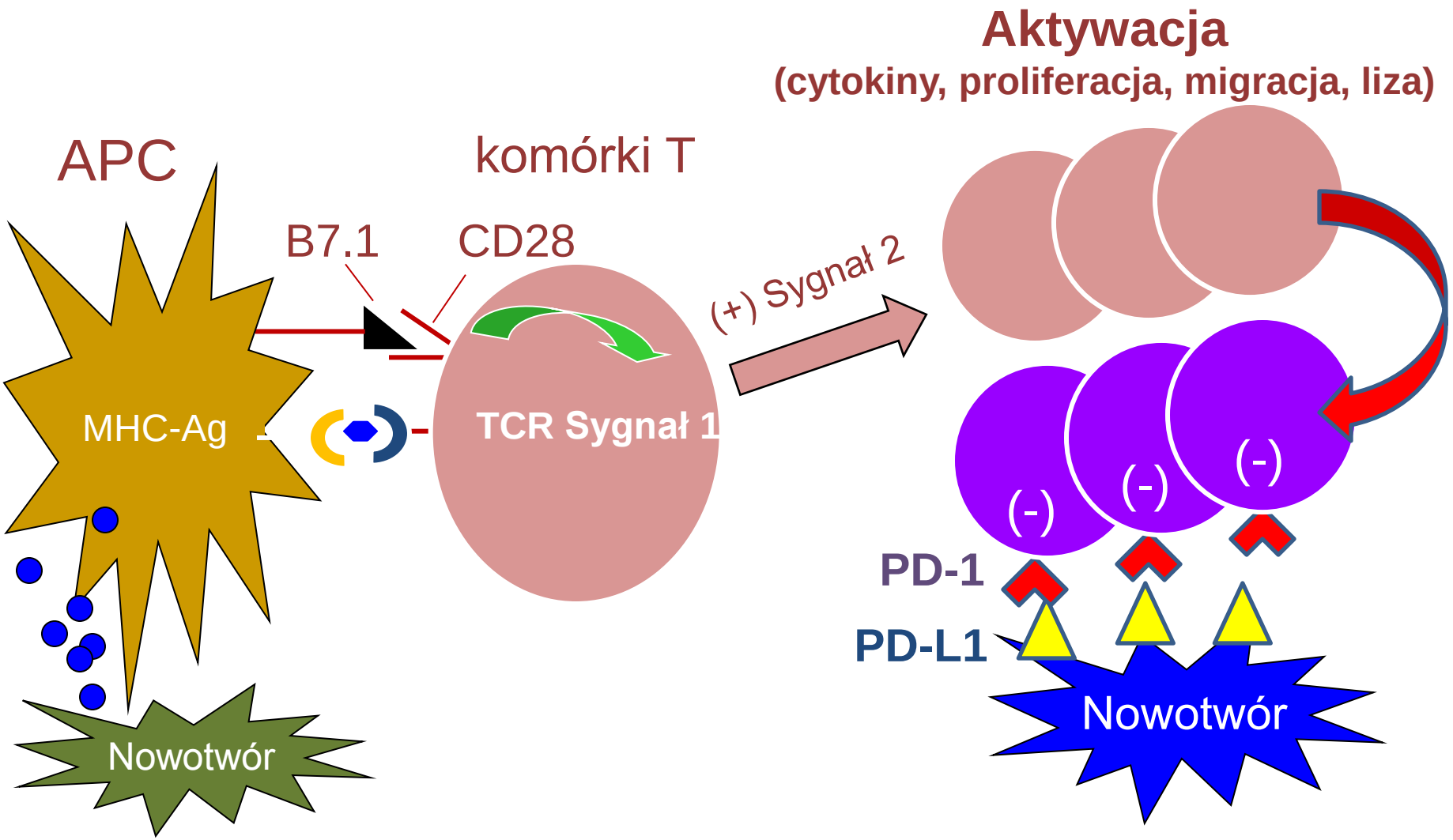
Jane PA i wsp. Lancet Oncol 2013; 14: 38-47

Rola of PD-1 w hamowaniu odpowiedzi immunologicznej (“Tumor Cell Defense”)



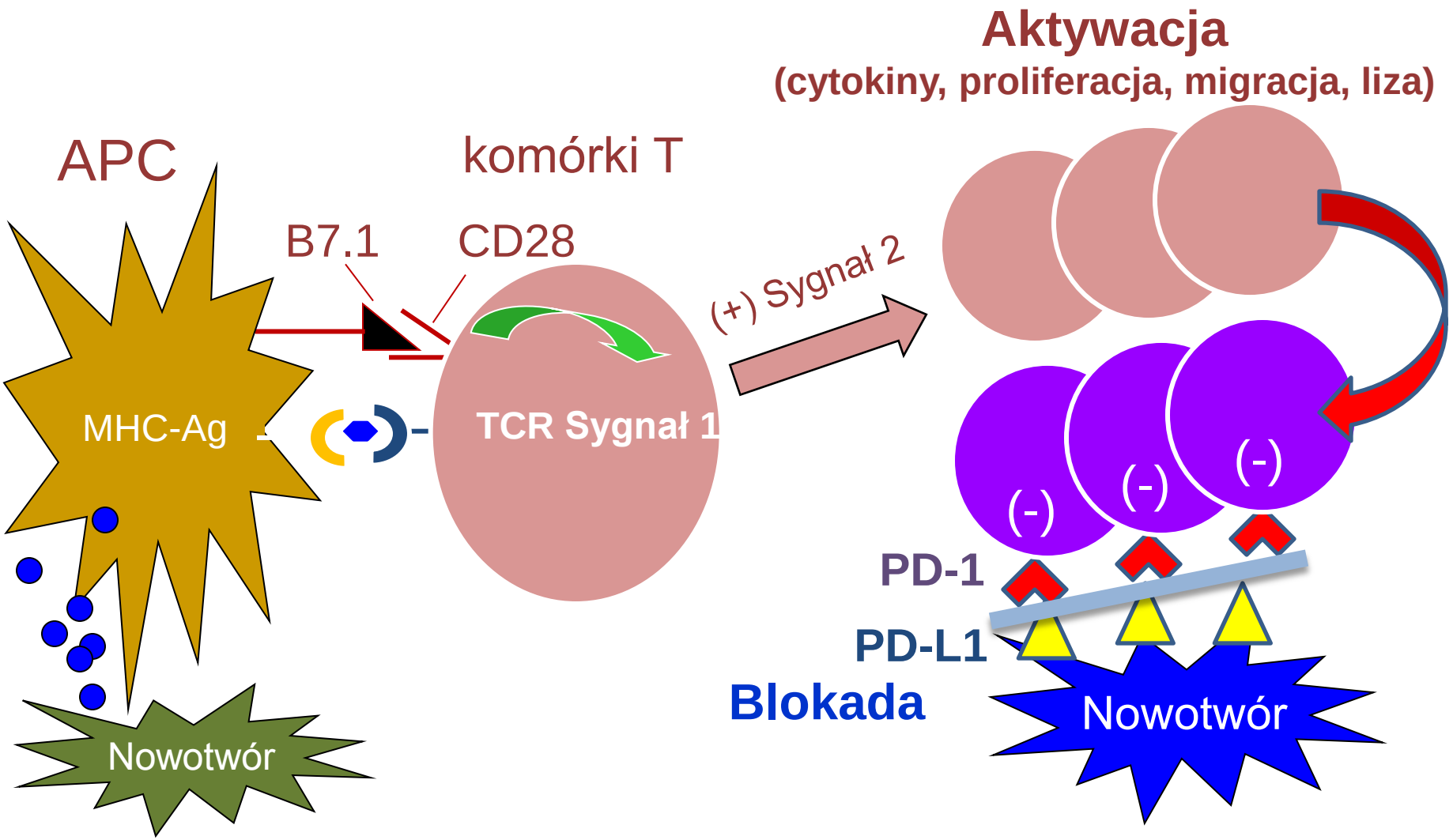
Keir ME I wsp., Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

Rola of PD-1 w hamowaniu odpowiedzi immunologicznej (“Tumor Cell Defense”)



Keir ME i wsp. Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

Rola of PD-1 w hamowaniu odpowiedzi immunologicznej (“Tumor Cell Defense”)

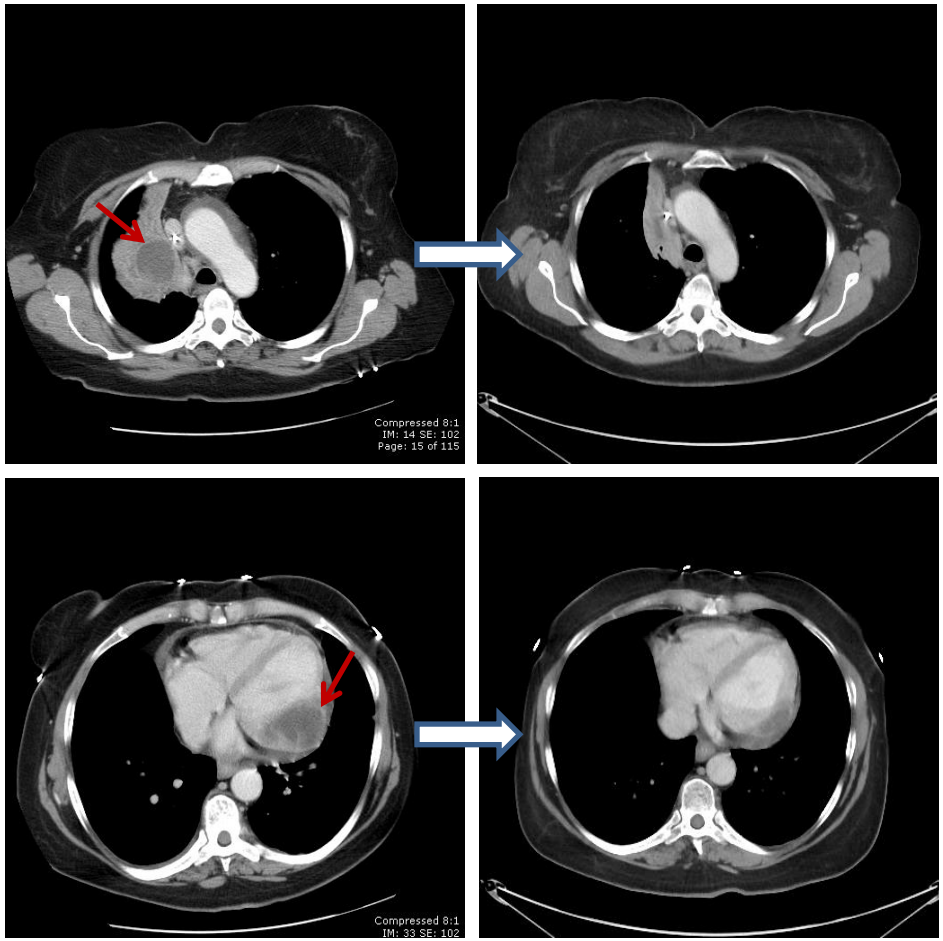


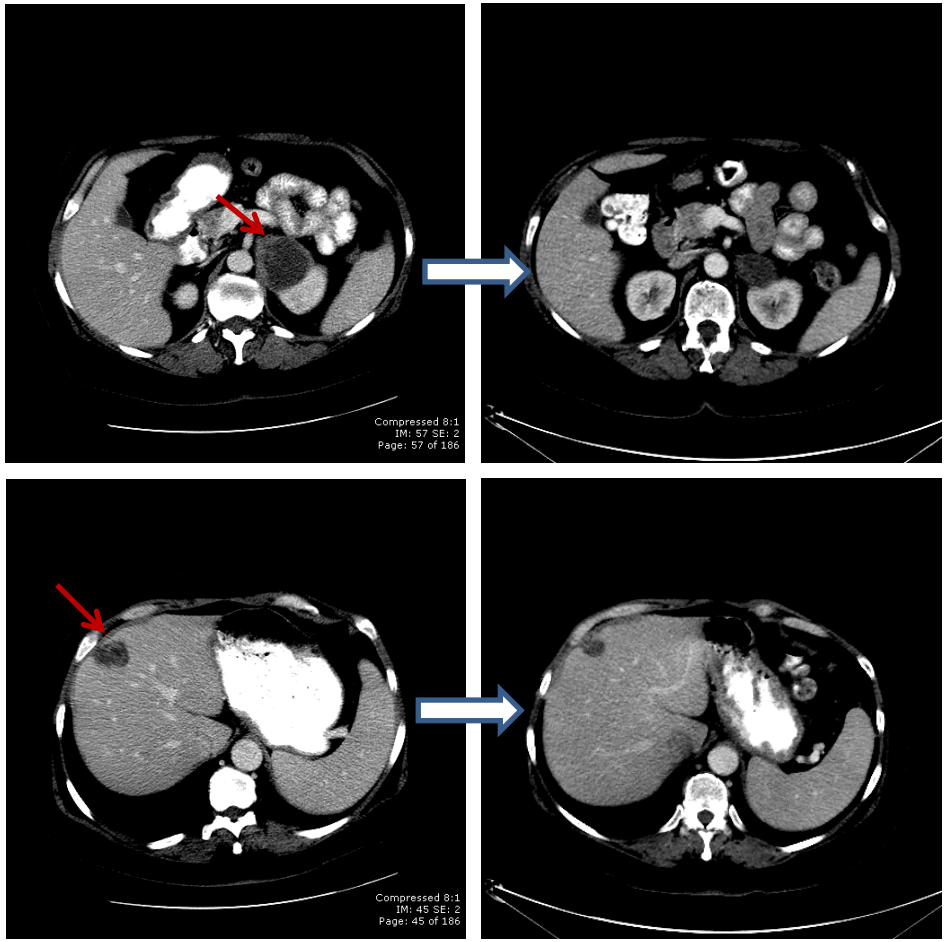
Keir ME i wsp. Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

Ocena aktywności anty-PD-1

Pts	Dawka (mg/kg)	Pts n	ORR n (%)	Czas trwania RR (m-ce)	SD ≥24 tyg. n (%)	PFSR 24 tyg. (%)
NDRP	1-10	76	14 (18)	1.9+ to 30.8+	5 (7)	26
NDRP	1	18	1 (6)	9.2+	1 (6)	16
	3	19	6 (32)	1.9+ to 30.8+	2 (11)	41
	10	39	7 (18)	3.7 to 14.8+	2 (5)	24

Przed/Po Anty-PD





- 58 lat były palacz NDRP - SCC
- po 4 liniach CTH

Afatynib – mutacje „inne”

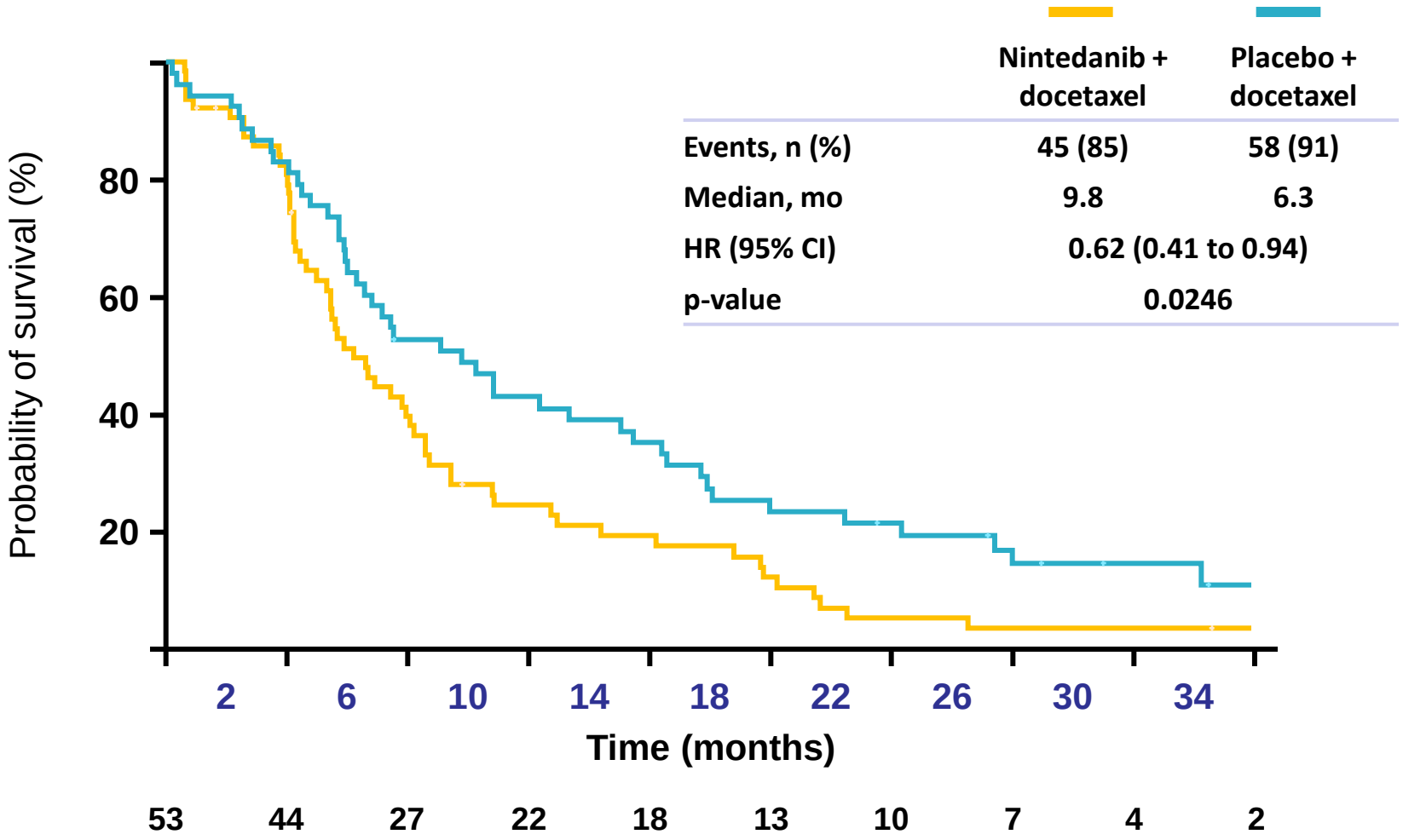
	De novo T790M N=14	Ekson 20 insercja N=23	Inne=38
Mediana PFS miesiące (zakres)	2,9 (0,3 – 13,8)	2,7 (0,4 – 11,9)	10,7 (0+ - 35,8+)
Mediana OS miesiące (zakres)	14,9 (1,5 – 30,5)	9,4 (0,4 – 32,2+)	18,6 (0+ - 51,3+)

T790M + L858R, n=6		
Patient	**PFS**	**OS**
1	0.8	8.7
2	2.6	24.9
3	6.7	13.2
4	8.3	30.5
5	9.6*	24.4*
6	11.0	20.8
Median	**7.5**	**22.9**

T790M + Del19, n=3		
Patient	**PFS**	**OS**
1	0.3	8.1
2	1.2	7.5
3	3.0	24.6
Median	**1.2**	**8.1**

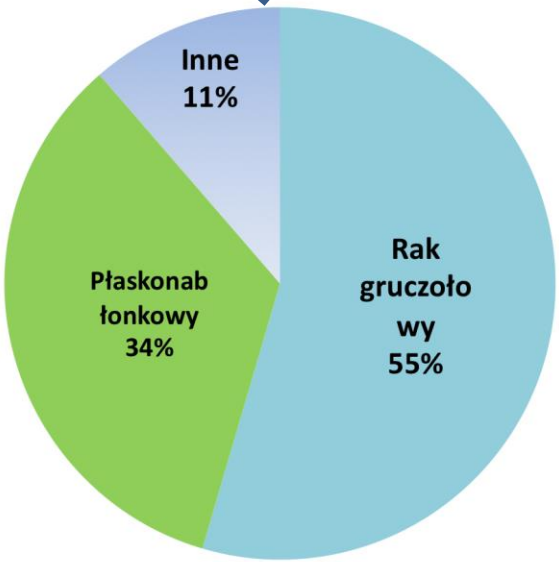
Yang JCH i wsp. WCLC 2013

LUME LUNG 1 - OS chorzy z AC i RR PD



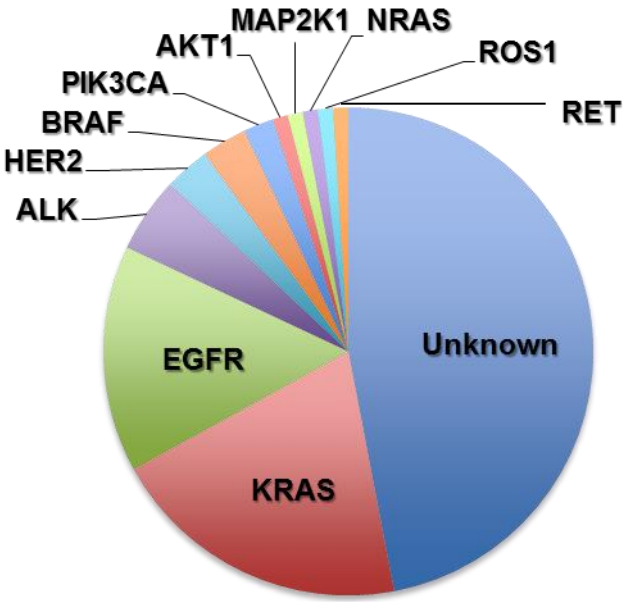
Podsumowanie

NDRP
(jedna jednostka)

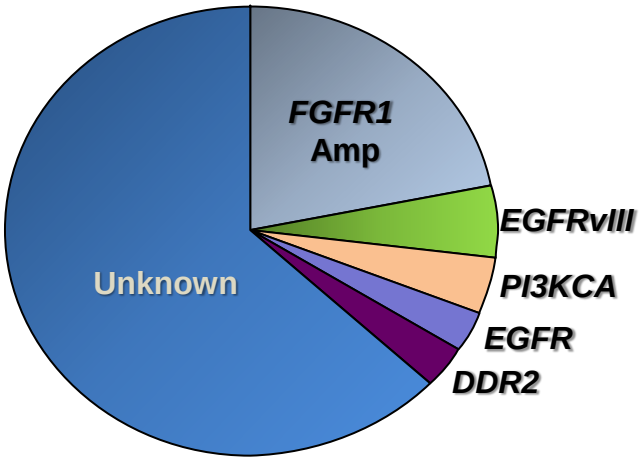


Typy histologiczne

Rak gruczołowy



Rak płaskonabłonkowy



Dziękuję za uwagę