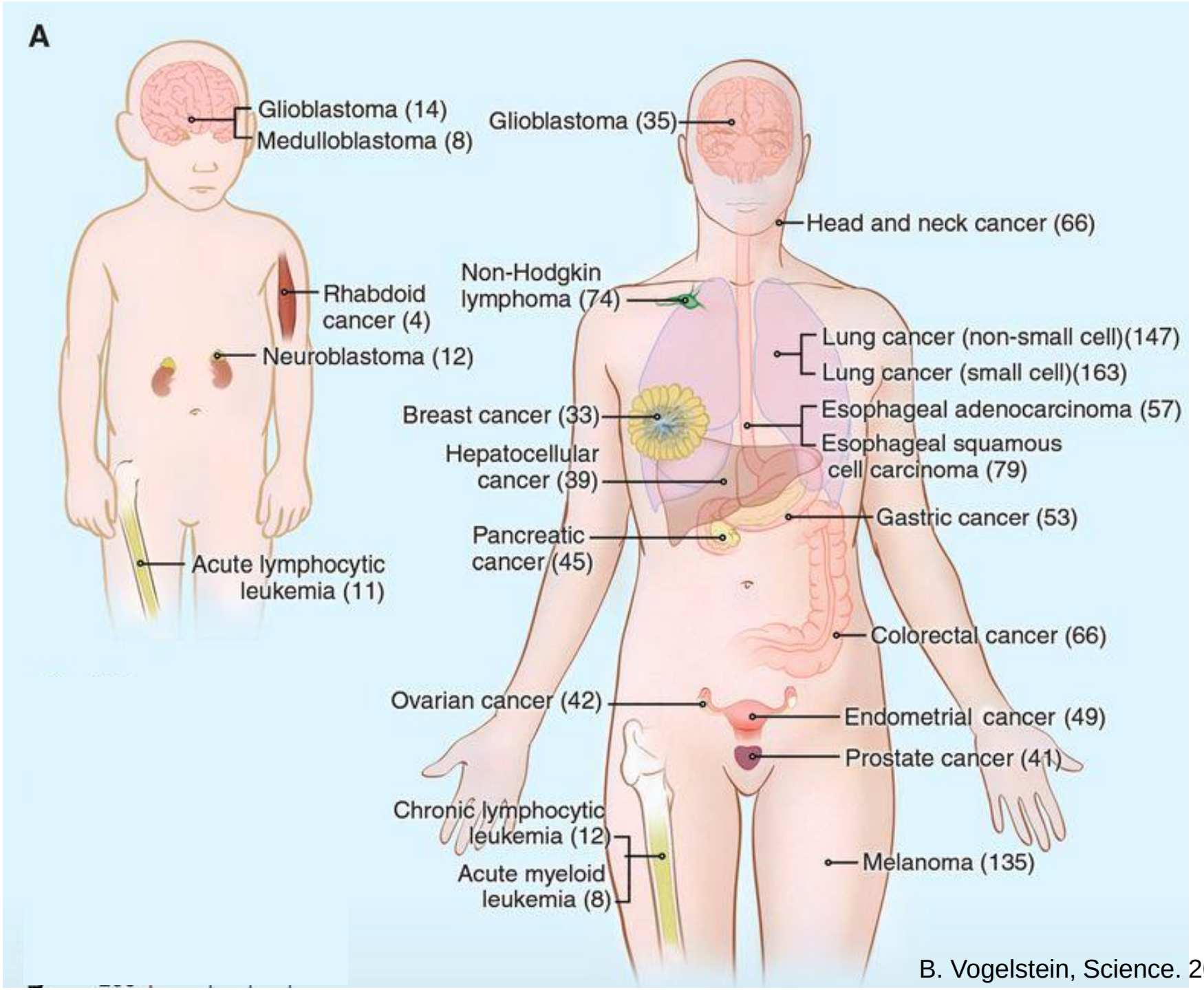
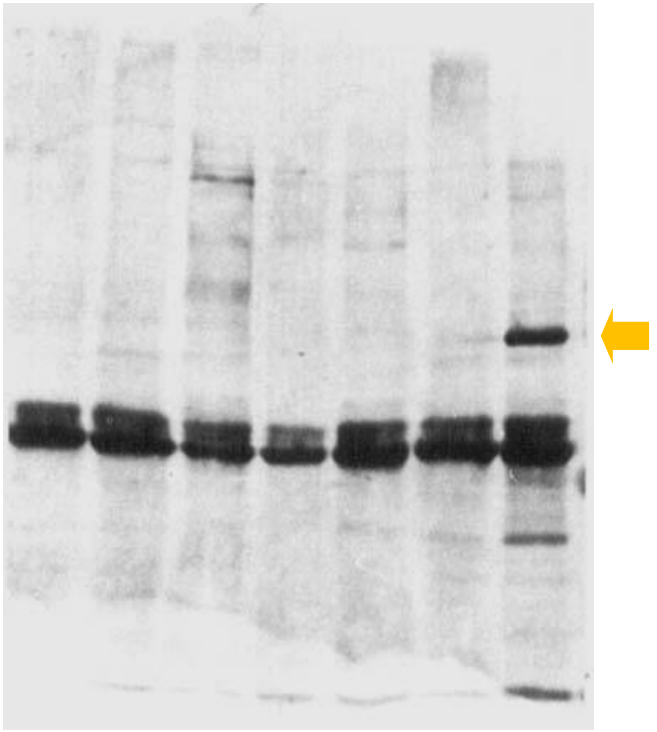
Nowe trendy w chemioterapii i leczeniu celowanym raka płuca



B. Vogelstein, Science. 2013

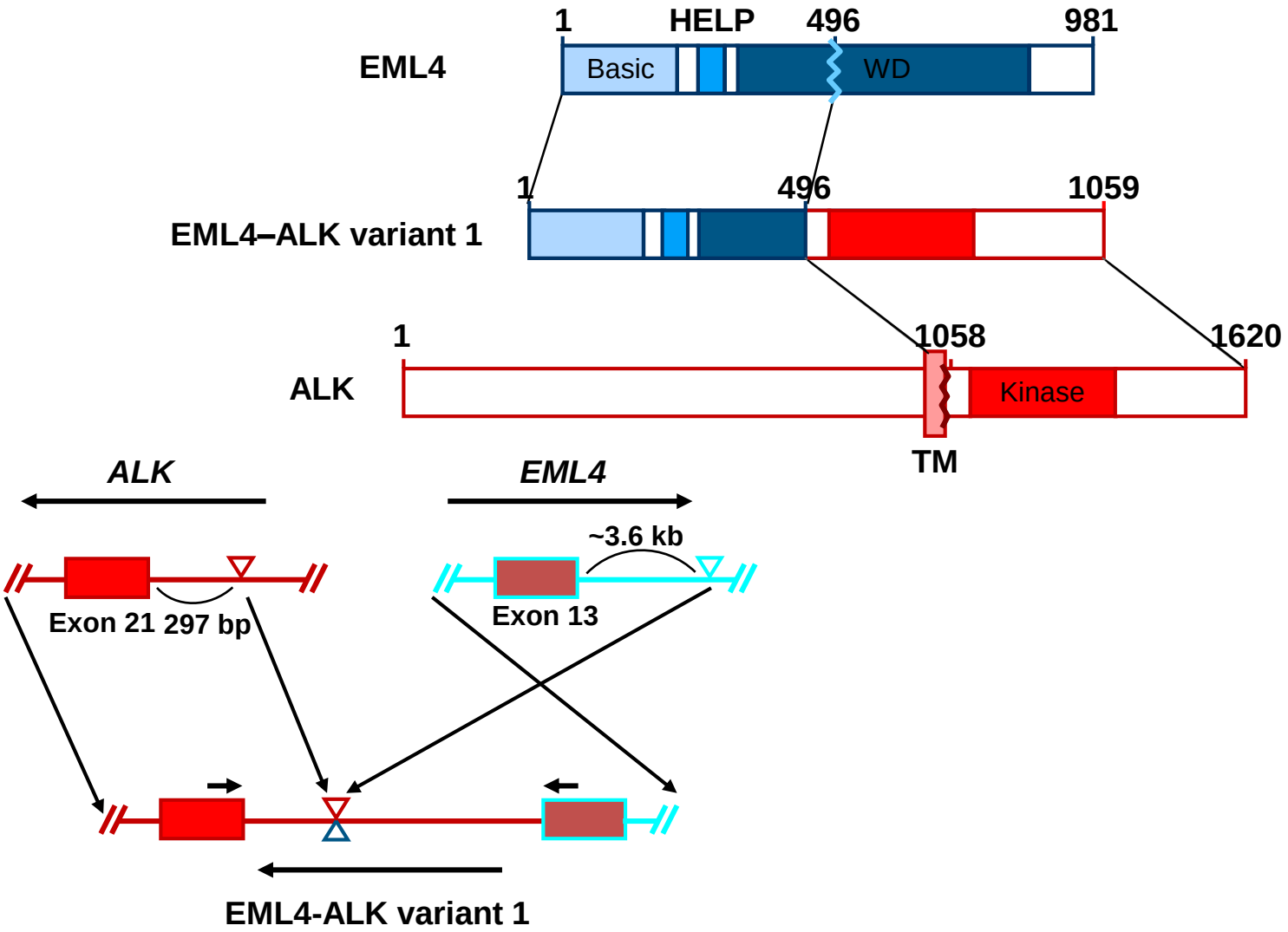
Kinaza anaplastycznego chłoniaka z komórek T (ALCL)

- Translokacja(2;5)
- Geny *ALK* i *NPM*



[1]Shiota M & Mori S. *Leuk Lymphoma.* 1996;23:25–32. [2]Pulford K, et al. *J Cell Physiol.* 2004;199:330–58.
[3]Palmer, et al. *Biochem J*. 2009;420:345–61. [4]Mano. *Cancer Sci.* 2008;99:2349–55.

Gen fuzyjny *EML4-ALK* w raku płuca



EML, echinoderm microtubule-associated protein-like 4;
HELP, hydrophobic echinoderm mizroxbule-associated protein-like protein

Soda M, et al. *Nature.* 2007;448:561–67.

Semin Oncol. 2009 Apr;36(2 Suppl 1):S27-35. doi: 10.1053/j.seminoncol.2009.02.007.

Anaplastic lymphoma kinase (ALK)-induced malignancies: novel mechanisms of cell transformation and potential therapeutic approaches.

Wasik MA[1], Zhang Q, Marzec M, Kasprzycka M, Wang HY, Liu X.

Author information

[1]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA. wasik@mail.med.upenn.edu

Abstract

Among the many oncogenic variants of the anaplastic lymphoma kinase (ALK), nucleophosmin 1 (NPM)/ALK fusion protein expressed in the subset of T-cell lymphoma (ALK(+)TCL) is currently the best characterized. NPM/ALK activates several signal transduction pathways, including PI3K/AKT, MEK/ERK, mTORC1, STAT3, and STAT5b. In turn, the pathways modulate expression and function of many genes and proteins involved in the key cellular functions such as proliferation, growth, survival, metabolism, and angiogenesis. Recent data indicate that NPM/ALK also promotes immune evasion of the ALK(+)TCL by inducing through STAT3 activation the expression of immunosuppressive cytokines interleukin-10 (IL-10) and transforming growth factor-beta (TGFss) and cell surface protein CD274 (PD-L1, B7-H1). In addition, NPM/ALK protects its own expression by mediating via STAT3 and at least one member of the DNA methyltransferase family DNMT1 epigenetic silencing of the SHP-1 and STAT5a genes. In ALK+TCL cells, SHP-1 and STAT5a proteins act as potent tumor suppressors by promoting degradation of the NPM/ALK protein and inhibiting expression of the NPM/ALK gene, respectively. These findings provide further rationale to therapeutically target ALK and its effector proteins, foremost STAT3. They also suggest that immunotherapeutic approaches to ALK(+)TCL and, possibly, other ALK-driven malignancies may require inhibition of ALK and STAT3 to achieve the optimal clinical efficacy.

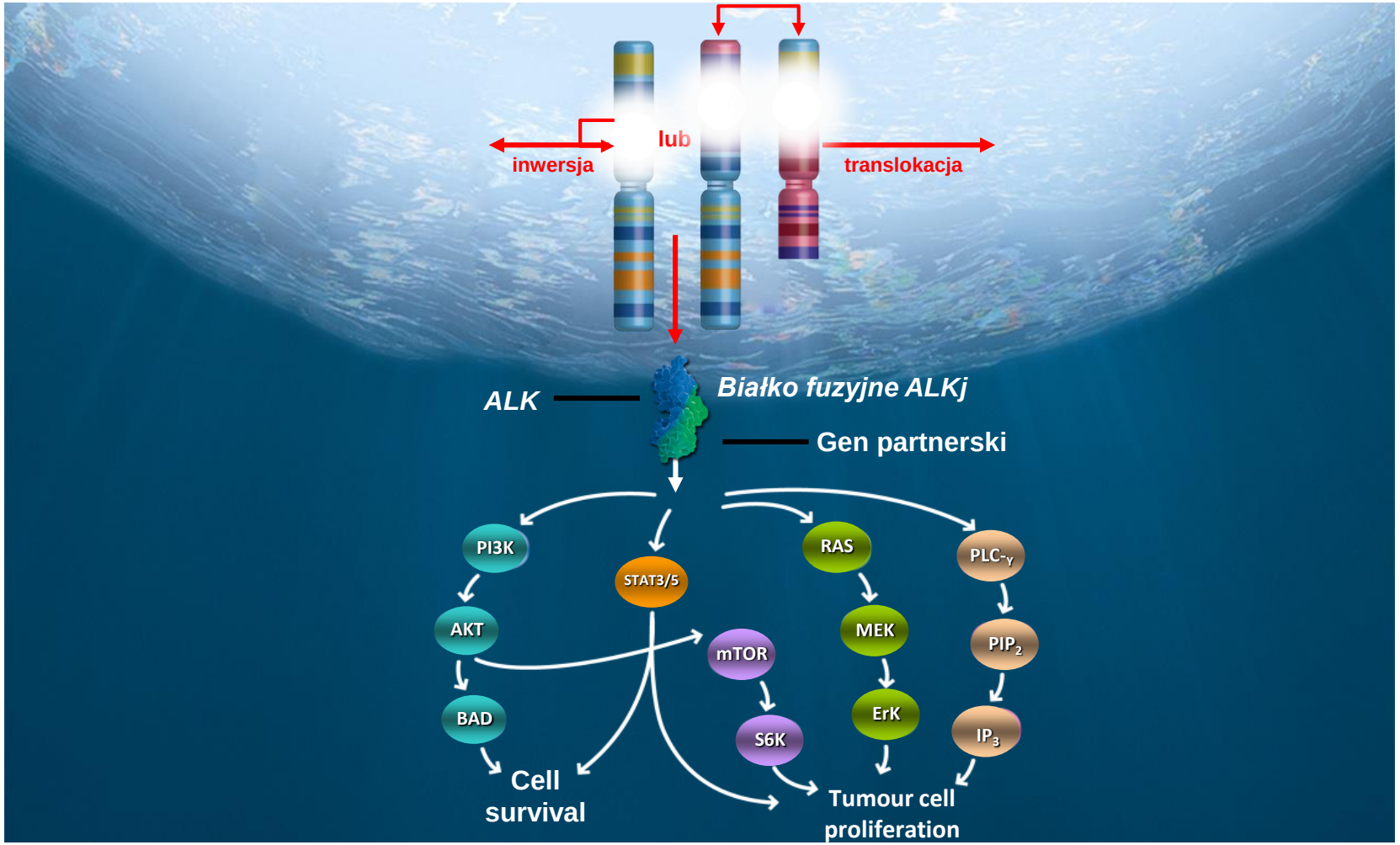
Cancer Therapeutics Insights

Molecular Cancer Therapeutics

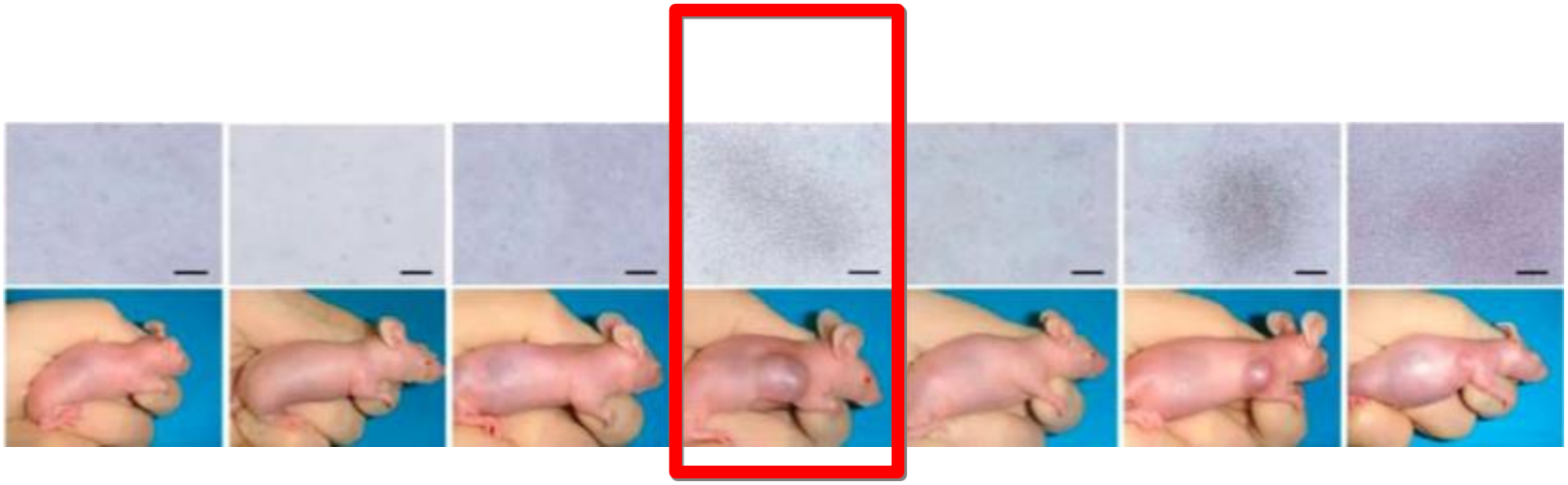
ALK Inhibitor PF02341066 (Crizotinib) Increases Sensitivity to Radiation in Non–Small Cell Lung Cancer Expressing EML4-ALK

Yunguang Sun[1], Kamila A. Nowak[1], Nicholas G. Zaorsky[1], Chia-Lin Winchester[1], Kunal Dalal[1], Nicholas J. Giacalone[3], Ningbo Liu[1], Maria Werner-Wasik[1], Mariusz A. Wasik[2], Adam P. Dicker[1], and Bo Lu[1]

Szlak *ALK*


inwersja
lub
translokacja
ALK
Białko fuzyjne ALKj
Gen partnerski
PI3K
AKT
BAD
STAT3/5
mTOR
S6K
RAS
MEK
ErK
PLC-γ
PIP2
IP3
Cell survival
Tumour cell proliferation

EML4–ALK – potencjał onkogenny



- Inne geny partnerskie dla fuzji: *NPM*, *EML4, TPM3, ATIC, TFG, CARS*, *CLTC*[2]

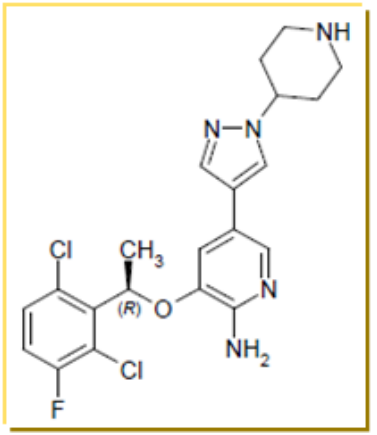
[1]Soda M, et al. *Nature.* 2007;448:561–67.
[2]Zhang, et al. *Mol Cancer.* 2010;9:188.

Kryzotynib: selektywny inhibitor ALK i MET

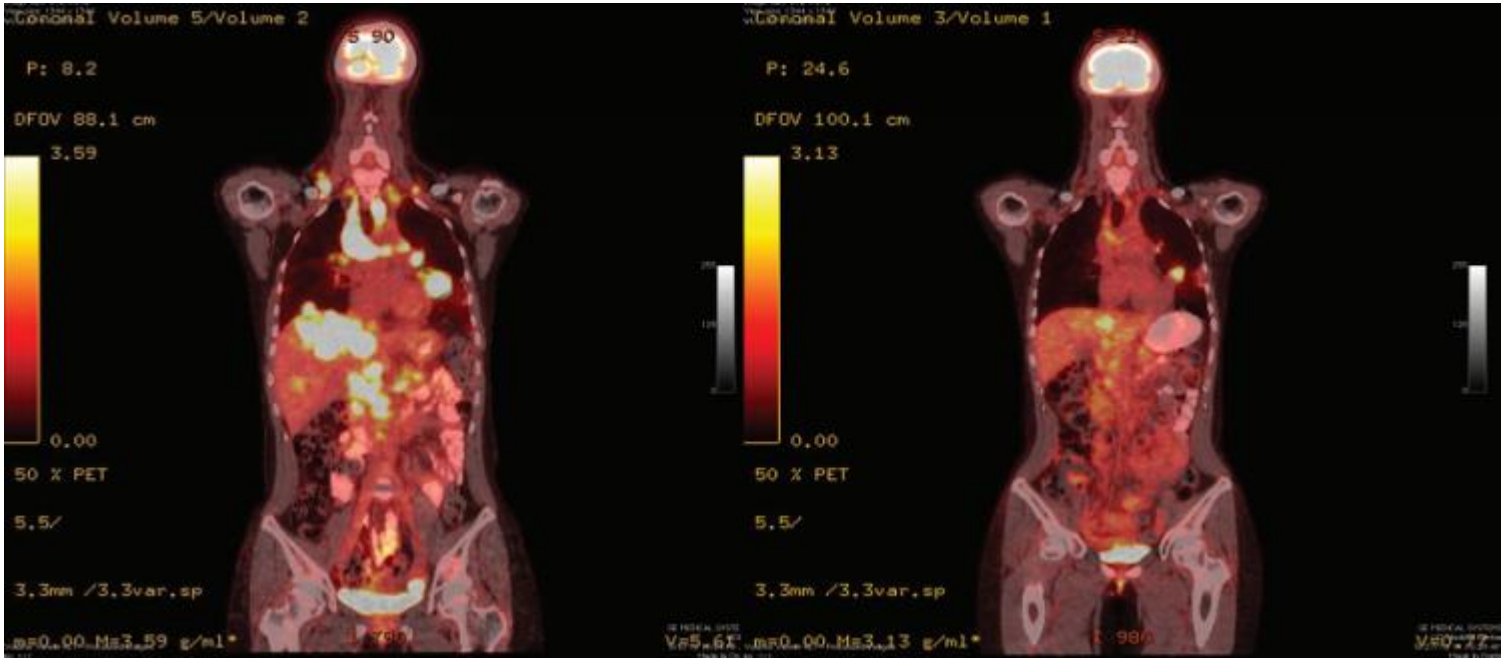
Kinase	% Inhibition
Met(h)	94
Tie2(h)	103
TrkA(h)	102
ALK(h)	100
TrkB(h)	100
Abl(T315I)(h)	98
Yes(h)	96
Lck(h)	95
Rse(h) [SKY]	94
Axl(h)	93
Fes(h)	93
Lyn(h)	93
Arg(m)	91
Ros(h)	90
CDK2/cyclinE(h)	87
Fms(h)	84
EphB4(h)	80
Btk(h)	79
EphB2(h)	77
Fgr(h)	73
Fyn(h)	68
Ron(h)	64
CDK7/cyclinH/MAT1(h)	58
cSRC(h)	58
IGF-1R(h)	56
Aurora-A(h)	54
Syk(h)	52
FGFR3(h)	50
PKCμ(h)	50
Itk(h)	35
CDK1/cyclinB(h)	25
p70S6K(h)	24
PRK2(h)	22
PAR-1Bα(h)	21
PKBβ(h)	21
Ret(h)	21
GSK3β(h)	18
FGR(h)	17
MAPK1(h)	17
ZAP-70(h)	17
Abl(h)	16
c-RAF(h)	16
PKD2(h)	15
ROCK-II(h)	14
Rsk3(h)	14
GSK3α(h)	11
CDK5/p35(h)	10
PDGFRα(h)	10
Rsk1(h)	7
SGK(h)	6
CHK1(h)	5
ErbB4(h)	5
Rsk2(h)	5
JNK1α1(h)	4
PKBα(h)	4
Blk(m)	3
CDK3/cyclinE(h)	3
PKCι(h)	3
PKCθ(h)	3
CDK2/cyclinA(h)	2
PAK2(h)	2
PKCδ(h)	2
Pim-1(h)	1
PKCα(h)	1
SAPK4(h)	1
CaMKII(r)	0
MKK7δ(h)	0
CaMKIV(h)	-1
CHK2(h)	-1
CK2(h)	-1
JNK2α2(h)	-1
MKK6(h)	-1
CK1δ(h)	-2
PKCα(h)	-2
MAPK2(h)	-3
MEK1(h)	-3
PKCδ(h)	-3
PKCε(h)	-3
Pyk2(h)	-3
PKCδ(h)	-5
MSK1(h)	-6
PDGFRδ(h)	-6
PKCζ(h)	-6
SAPK3(h)	-6
MAPKAP-K2(h)	-7
PKA(h)	-7
AMPK(r)	-9
CDK6/cyclinD3(h)	-9
CSK(h)	-9
SAPK2a(h)	-9
JNK3(h)	-10
PKBγ(h)	-10
IKKα(h)	-11
NEK2(h)	-11

13 kinaz
<100X

Kinase	IC50 (nM) mean*	Selectivity ratio
c-Met	8	–
ALK	20	2X
RON	298	34X
	189	22X
Axl	294	34X
	322	37X
Tie2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1000X
VEGFR2	>10,000	>1000X
PDGFRβ	>10,000	>1000X

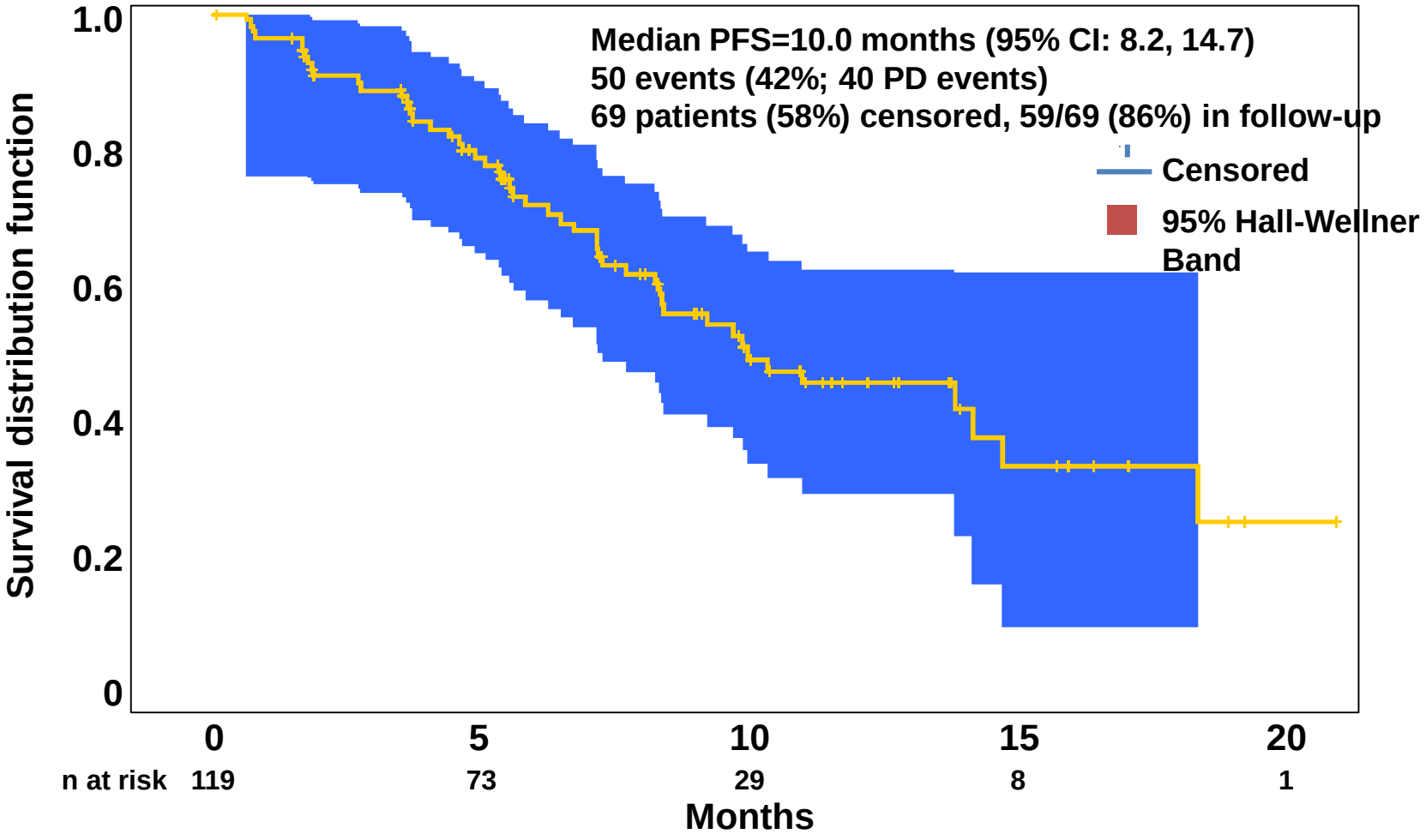


Kryzotynib (A8081001): szybkie odpowiedzi



Symptoms at study entry	Improvement in symptoms
Cough	Significant improvement at day 3, completely resolved by week 2
Daily low-grade fevers	Resolved by day 3
Anorexia	Gained 1.5 kg of weight by week 2
Right neck pain due to tumour invasion	Resolved by day 3

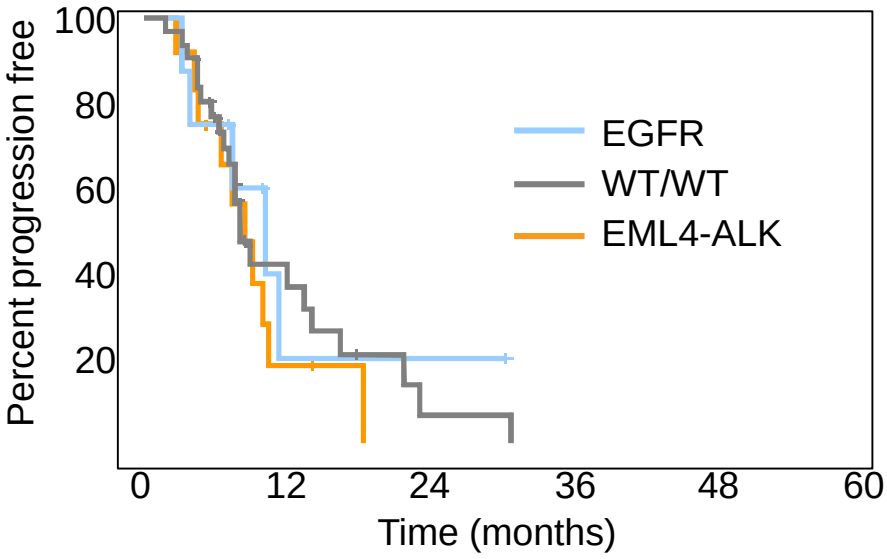
A8081001: PFS (N=119)



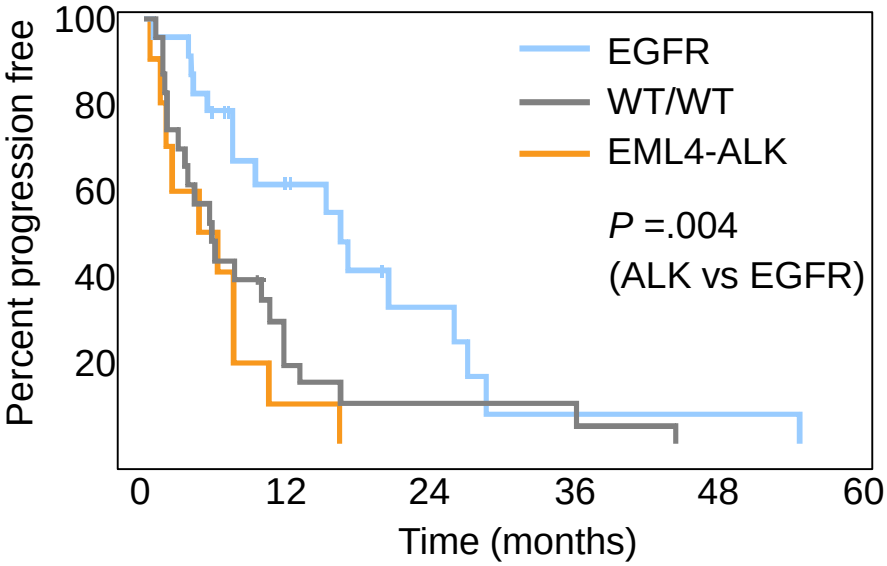
Camidge DR, et al. Presented at ASCO 2011; Abstract 2501.

Gruczolakorak płuca z rearanżacją ALK: gorsze rokowanie na terapii anty-EGFR

TTP on platinum-based chemotherapy

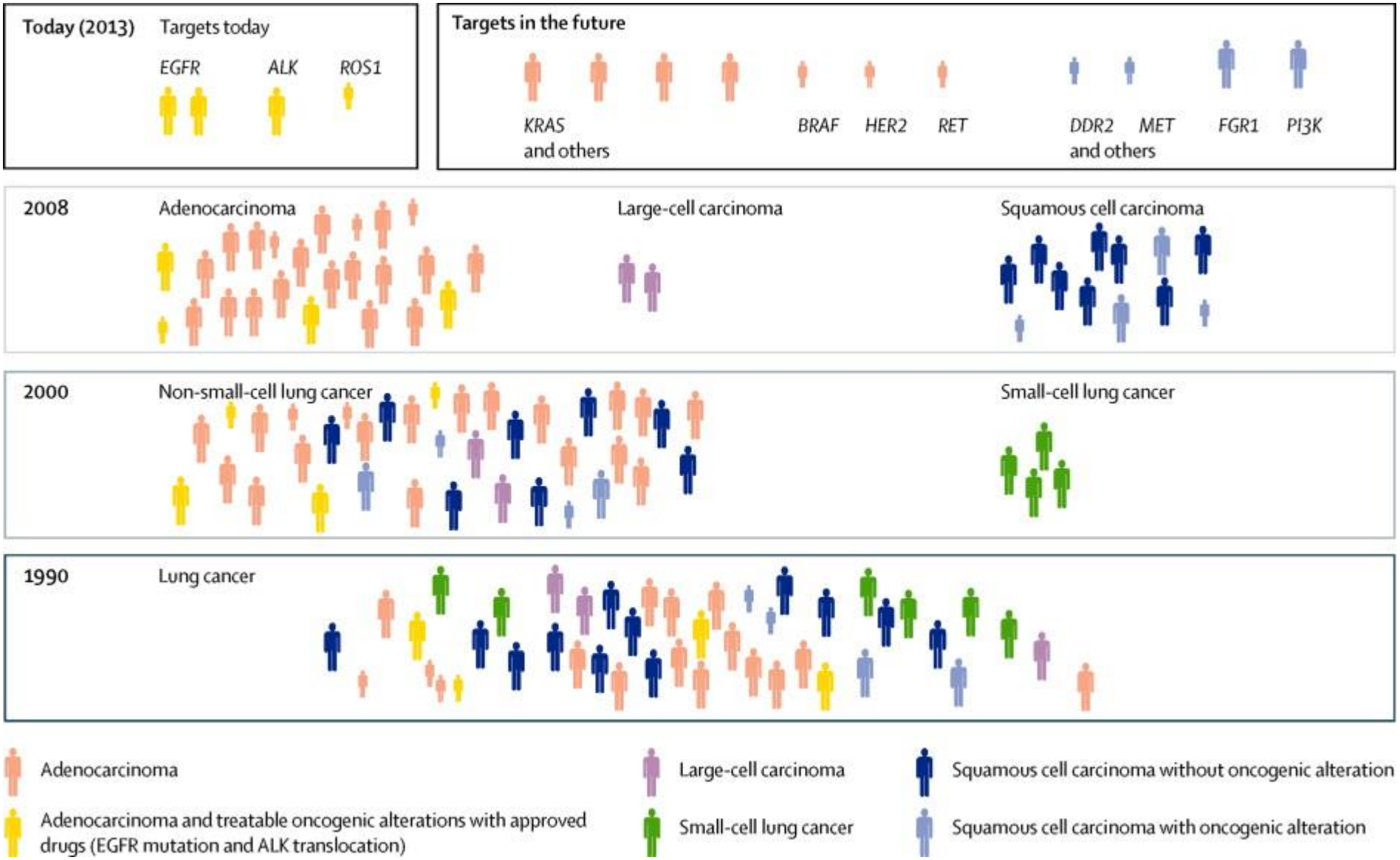


TTP on EGFR-TKI monotherapy
***ALK* may predict sensitivity to *EML4–ALK* inhibition but resistance to *EGFR* TKIs**

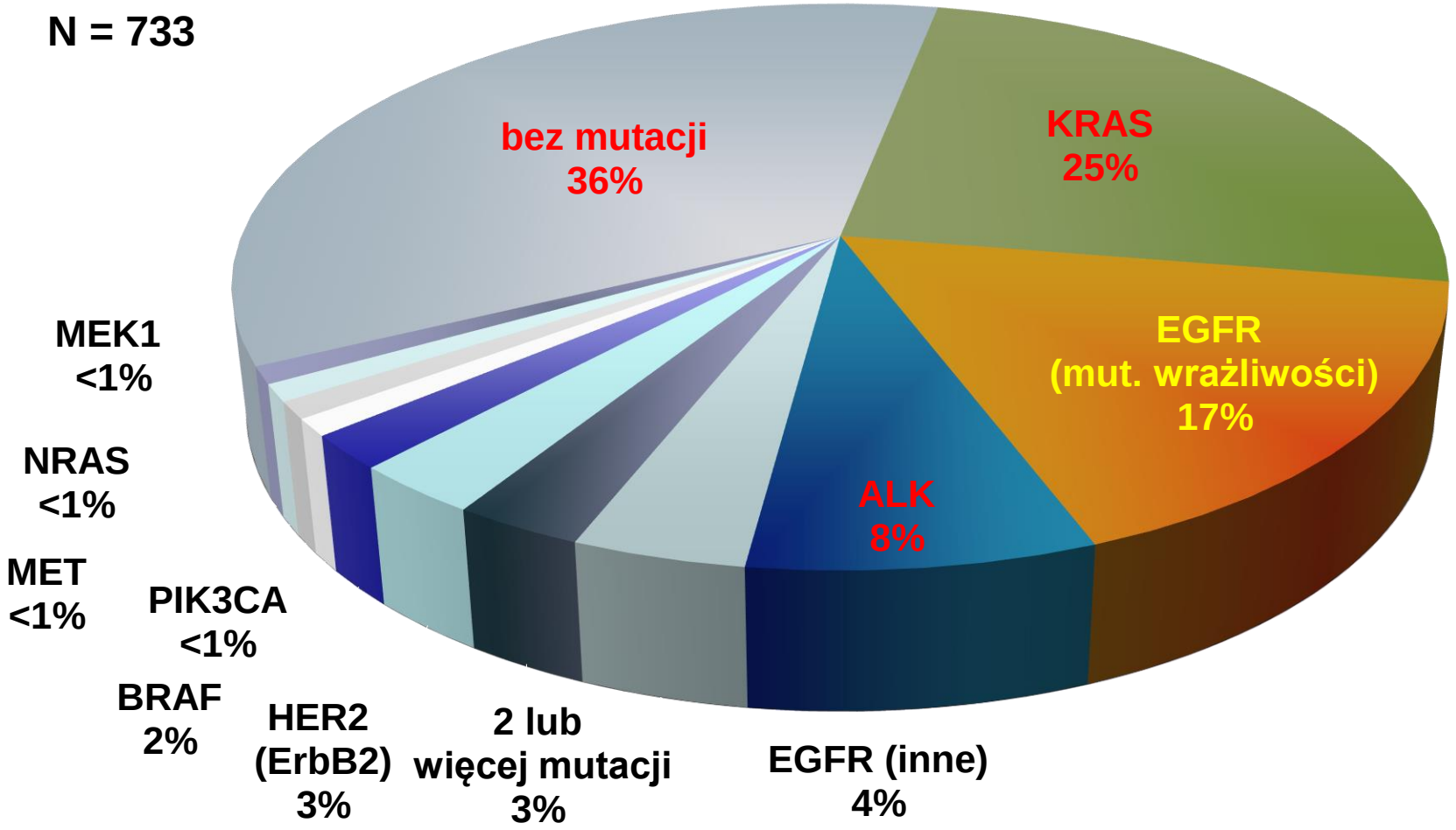


Patients with *ALK*-positive disease (n=15): 5 months
Patients with *EGFR*-positive disease (n=25): 16 months
Patients with *EGFR WT/WT* disease (n=49): 6 months

[1]Shaw AT, et al. *J Clin Oncol.* 2009;27:4247–53.


Today (2013)
Targets today
EGFR
ALK
ROS1
Targets in the future
KRAS and others
BRAF
HER2
RET
DDR2 and others
MET
FGR1
PI3K
2008
Adenocarcinoma
Large-cell carcinoma
Squamous cell carcinoma
2000
Non-small-cell lung cancer
Small-cell lung cancer
1990
Lung cancer
Adenocarcinoma
Adenocarcinoma and treatable oncogenic alterations with approved drugs (EGFR mutation and ALK translocation)
Large-cell carcinoma
Small-cell lung cancer
Squamous cell carcinoma without oncogenic alteration
Squamous cell carcinoma with oncogenic alteration

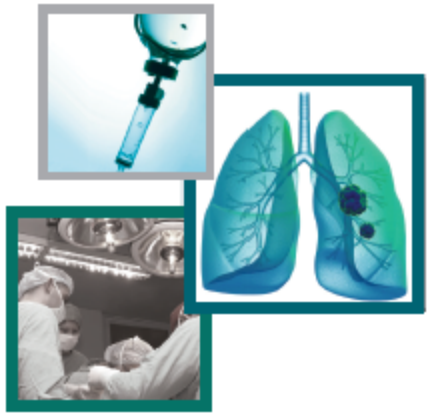
Pojedyncze mutacje indukujące w przerzutowym raku gruczołowym płuca



Kris MG et al. JAMA 2014;311(19):1998-2006.

REVIEW

Lung Cancer Management



Targeted therapy for lung cancer: reviewing the cost and its effect on treatment decisions

Charles Lim[1,2], Melissa Sergi[1,2] & Natasha B Leighl*[,1,2]

Koszt testowania dla rearanżacji ALK: zaporowo wysoki

Table 3. Summary of *ALK*-targeted agents.

TKI agent	Comparison regimen	Cost reporting	Cost (native currency)	Estimated cost (US$)	Study (year)	Notes	Ref.
Crizotinib (cost of treatment not included)	Not specified	Screening cost per QALY gained	US$46,144 (FISH)	$46,144 (FISH)	Atherly *et al.* (2012)	Based on molecular testing methodologies for *ALK* analysis, excluding the cost of treatment	[46]
			US$24,720 (IHC)	$24,720 (IHC)			
Crizotinib	Cisplatin/ gemcitabine	ICER (per QALY gained)	CAD$255,970	$232,700	Djalalov *et al.* (2014)	Compared to standard care with no testing and no crizotinib treatment	[23]

Currency conversion is estimated based on the historical exchange rate provided based on the period average from the month of publication of the article. Estimates are rounded to the nearest US$100.

ICER: Incremental cost–effectiveness ratio; IHC: Immunohistochemistry: QALY: Quality-adjusted life year.

Data taken from [60].

Table 1. Summary of EGF receptor-targeted agents in *EGFR* mutation-positive patients.

Country	TKI agent	Comparison regimen	Cost reporting	Cost (native currency)	Estimated cost	Study (year)	Notes	Ref.
First-line treatment in* EGFR *mutation-positive patients								
UK	GEF	Carboplatin/paclitaxel	ICER (per QALY gained)	GB£35,700	US$56,600	Brown *et al.* (2010)		[24]
UK	GEF	Cisplatin/paclitaxel	ICER (per QALY gained)	GB£57,440	US$87,200	Brown *et al.* (2013)	Based on British National Formulary prices	
	GEF	Carboplatin/paclitaxel		GB£85,848	US$130,300		Based on mean NHS negotiated prices	[26]
China	ERL	Carboplatin/gemcitabine	ICER (per QALY gained)	US$85,927	US$85,927	Wang *et al.* (2013)		[28]
USA	ERL	Carboplatin/paclitaxel	ICER (per QALY gained)	US$122,234	US$122,234	Handorf *et al.* (2012)	Based on rebiopsy strategy for obtaining tissue for molecular diagnostics	[15]
		Carboplatin/pemetrexed		US$103,132	US$103,132			
		Carboplatin/pemetrexed/ bevacizumab		US$44,036	US$44,036			
Second-line treatment in* EGFR *mutation-positive patients								
Canada	GEF	DOC	ICER (per QALY gained)	CAD$43,825 for GEF	US$44,600 for GEF	Horgan *et al.* (2011)		[29]
				CAD$30,764 for DOC	US$31,300 for DOC			
Canada	ERL	Best supportive care	ICER (per life year gained)	CAD$138,168	US$134,800	Bradbury *et al.* (2010)		[33]

Currency conversion is estimated based on the historical exchange rate provided based on the period average from the month of publication of the article. Estimates in US$ are rounded to the nearest 100.

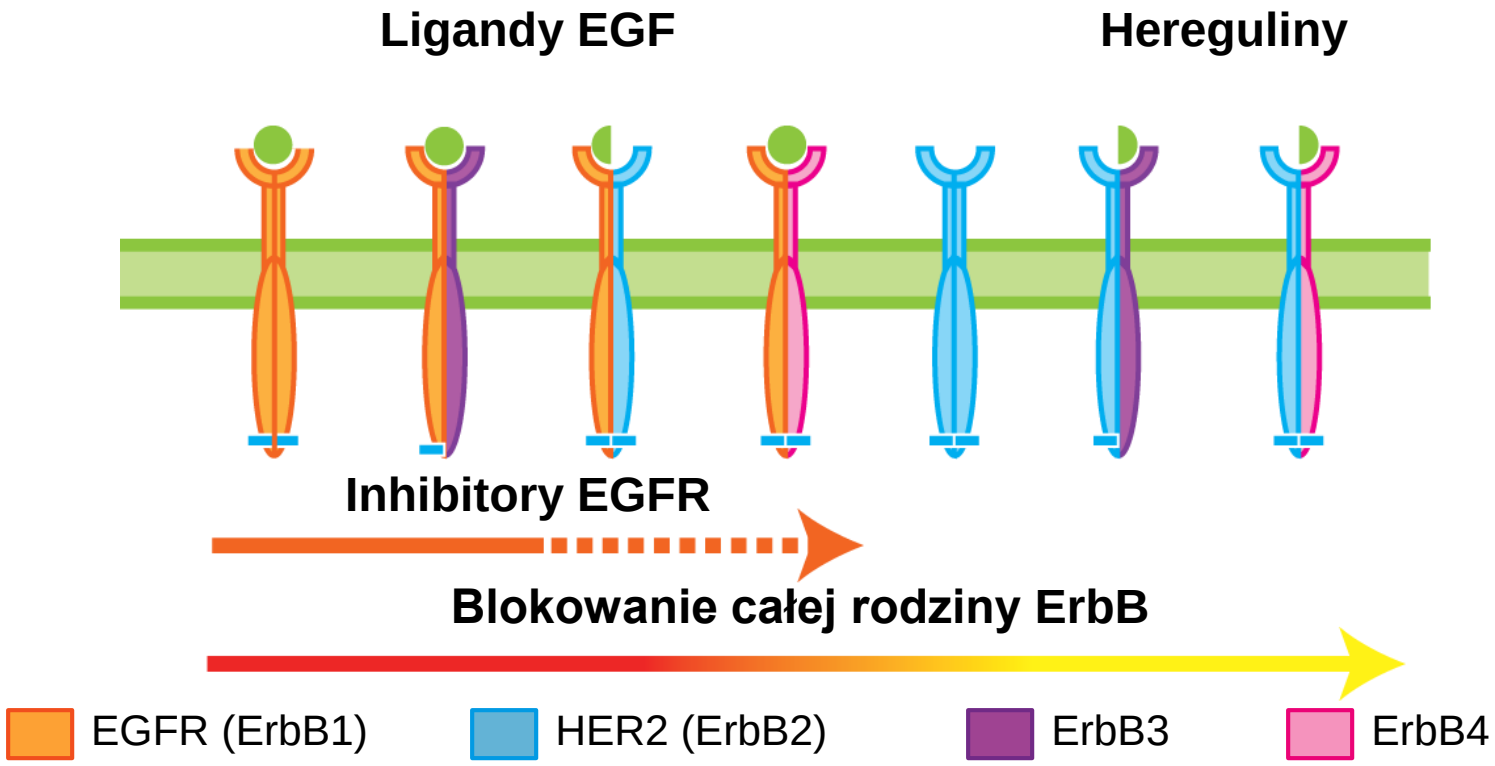
CAD: Canadian dollars; DOC: Docetaxel; EGFR: EGF receptor; ERL: Erlotinib; GEF: Gefitinib; ICER: Incremental cost–effectiveness ratio; NHS: National Health Service; QALY: Quality-adjusted life year; TKI: Tyrosine kinase inhibitor.

Data taken from [60].

Ceritinib (LDK378) Induces Responses in the Majority of Crizotinib-Resistant Patients

- A total of 114 patients with NSCLC received at least 400 mg of ceritinib daily
- Overall response rate (ORR) was 58%
- Confirmed complete response: 1(1%)
- Confirmed partial response: 65 (57%)
- The majority of patients with NSCLC who received ceritinib had previously received crizotinib: 83/122 (68%)
- Among patients who previously received crizotinib, ORR = 56%
- Among patients who had not received crizotinib previously and who received ceritinib at ≥400 mg daily, ORR = 21/34 (62%)

Shaw AT et al. *N Engl J Med* 2014;370(13):1189-97.


Ligandy EGF
Hereguliny
Inhibitory EGFR
Blokowanie całej rodziny ErbB
EGFR (ErbB1)
HER2 (ErbB2)
ErbB3
ErbB4

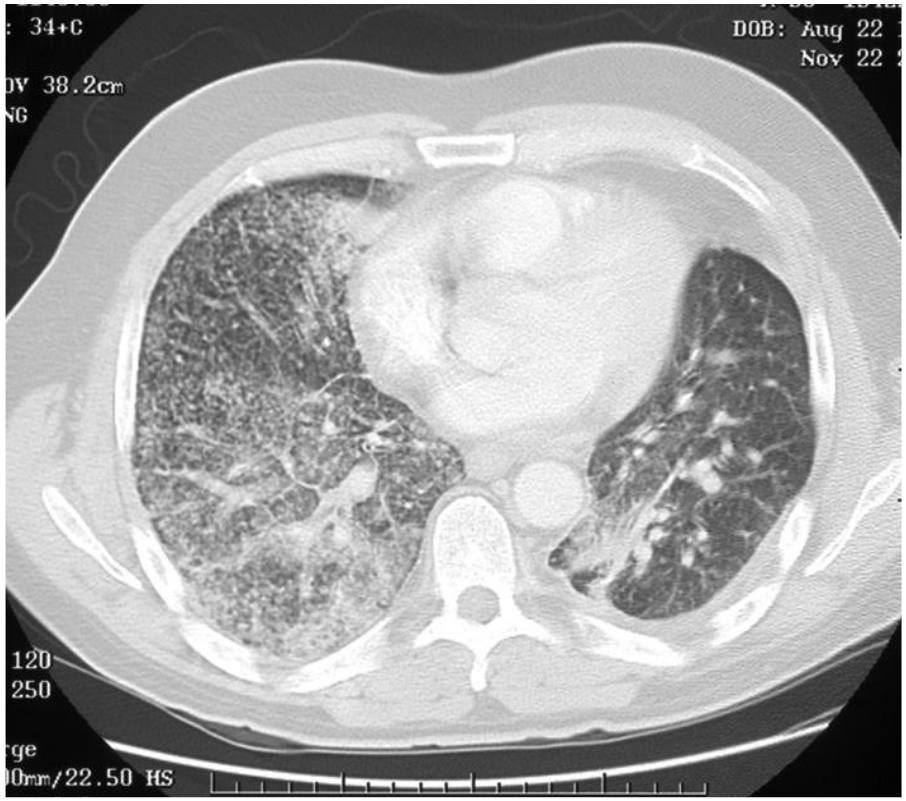
Mutacje EGFR

- **10 % - 15% wszystkich chorych na raka płuca, w Polsce 10-20% chorych z rakiem gruczołowym, 85% chorych wrażliwych na inhibitory EGFR**
- **Częstsze u niepalących, kobiet i Azjatów (>50% raka gruczołowego)**

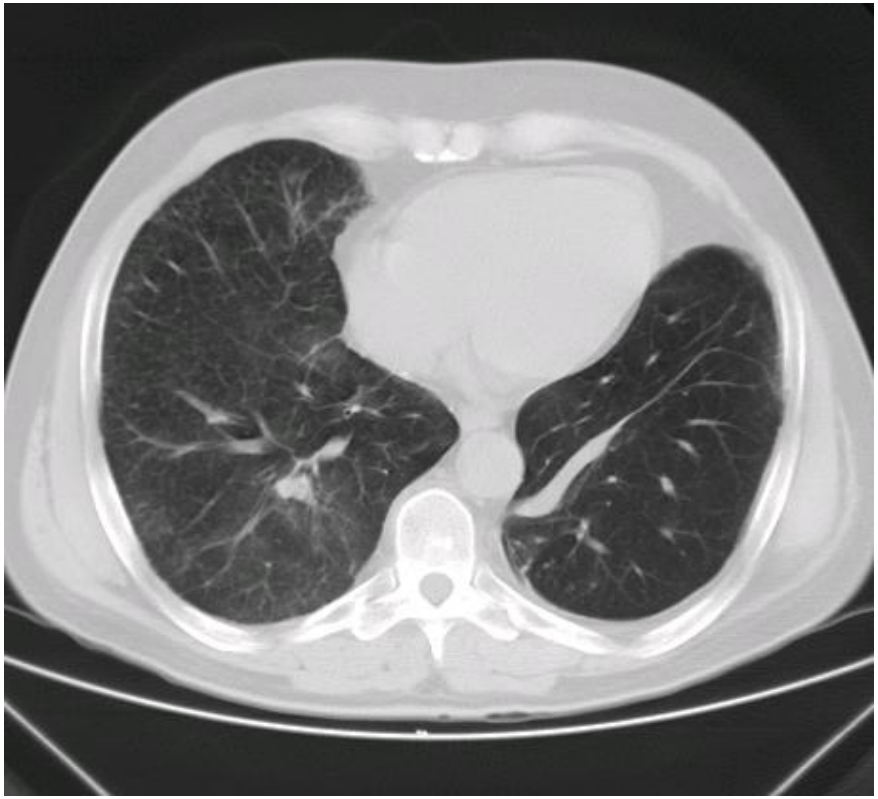
- **Nie wszyskie są mutacjami wrażliwymi na leczenie. Główna mutacja oporności to T790M**

- **85% mutacji to delecje eksonu 19 lub mutacja eksonu 21 L858**

EGFR: delecja w eksonie 19
erlotynib

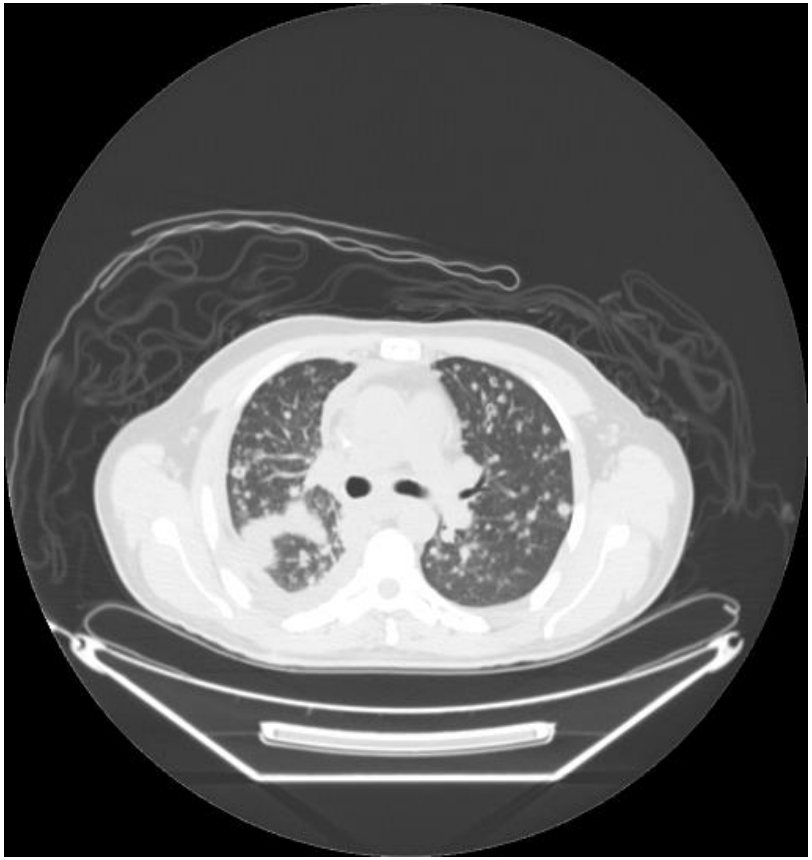


12-00

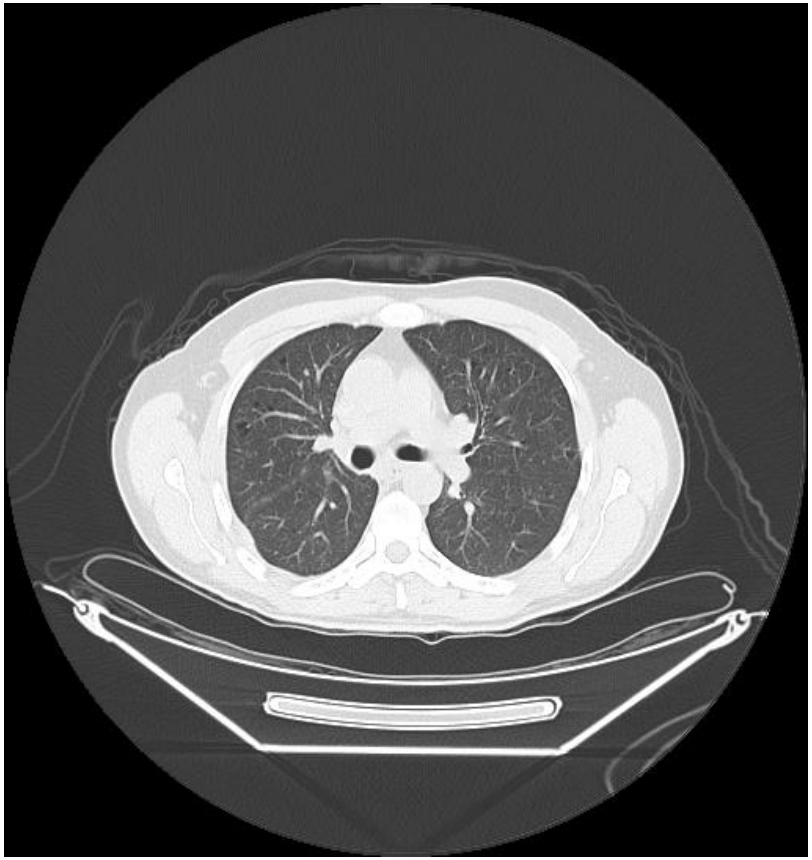


12-02

EGFR: ekson 21 858
erlotynib

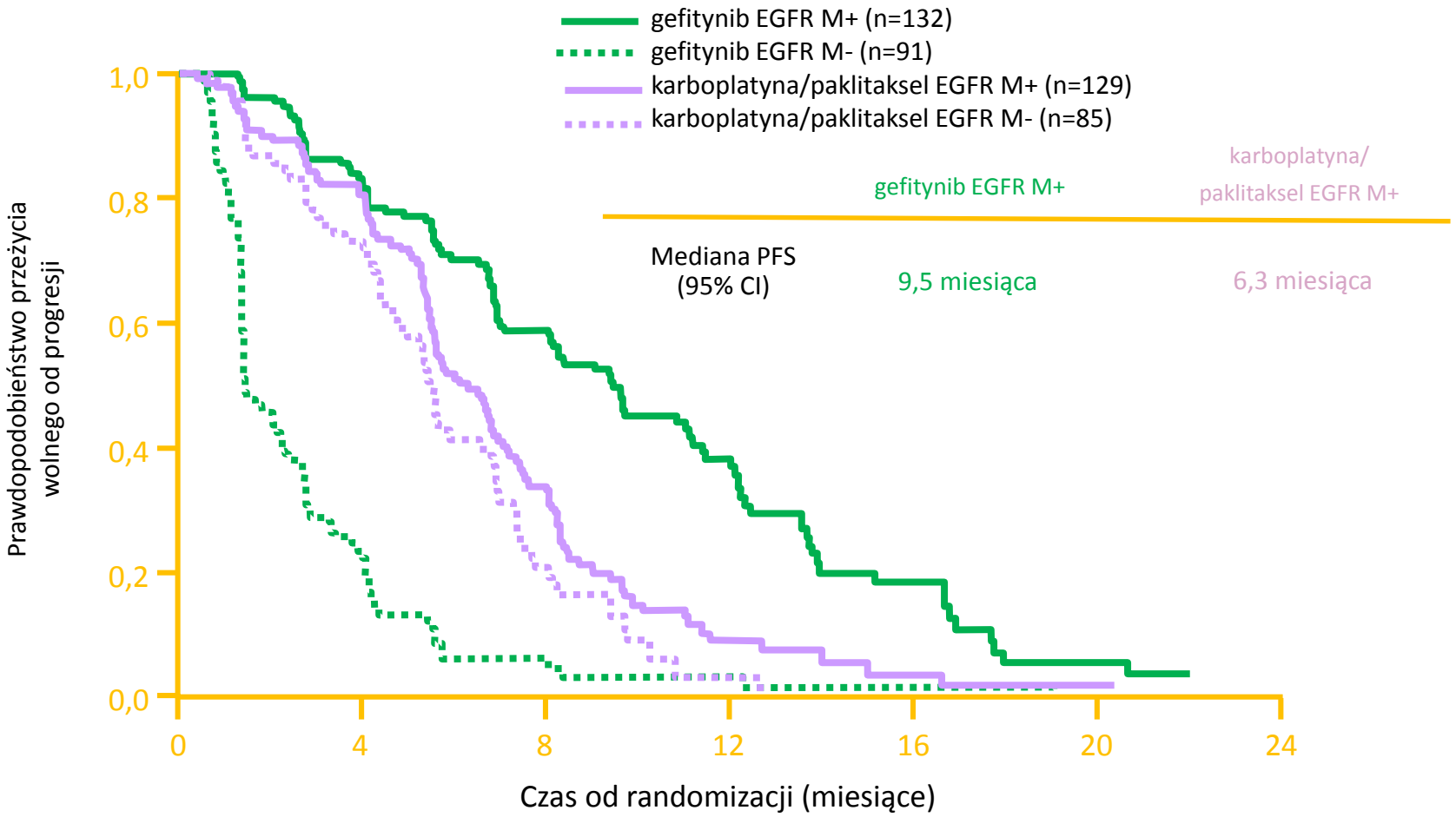


Newly diagnosed
3-16-07



3 months of erlotinib
6-18-07

IPASS: gefitynib vs karboplatyna-paklitaksel w nieselekcjonowanej populacji chorych



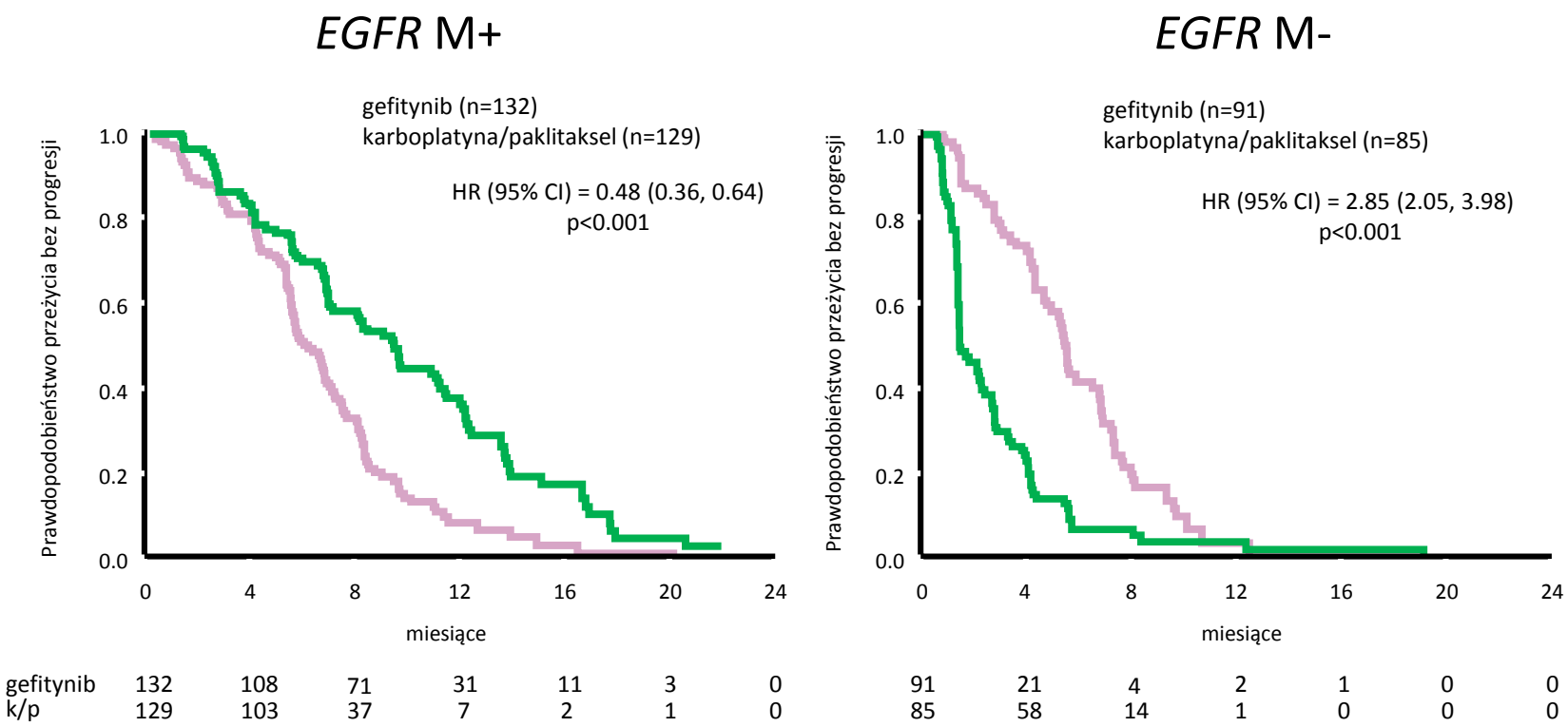
EGFR – receptor naskórkowego czynnika wzrostu

EGFR M+ - mutacja w genie kodującym receptor naskórkowego czynnika wzrostu

EGFR M- - typ dziki genu kodującego receptor naskórkowego czynnika wzrostu

Mok TS i wsp. N Engl J Med 2009;361:947-957

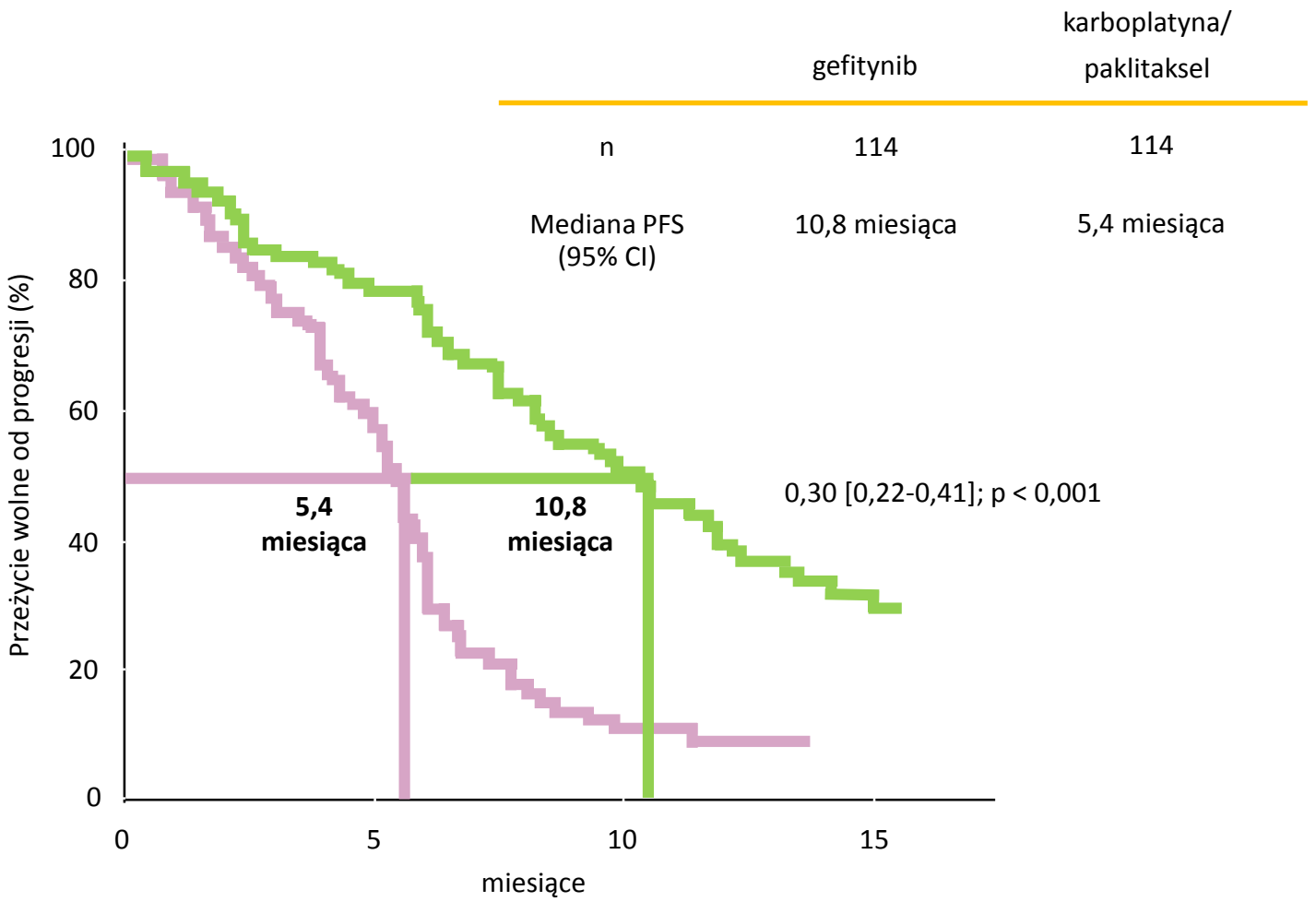
IPASS: gefitynib vs karboplatyna-paklitaksel w nieselekcjonowanej populacji chorych



Mok TS i wsp. N Engl J Med 2009;361:947-957

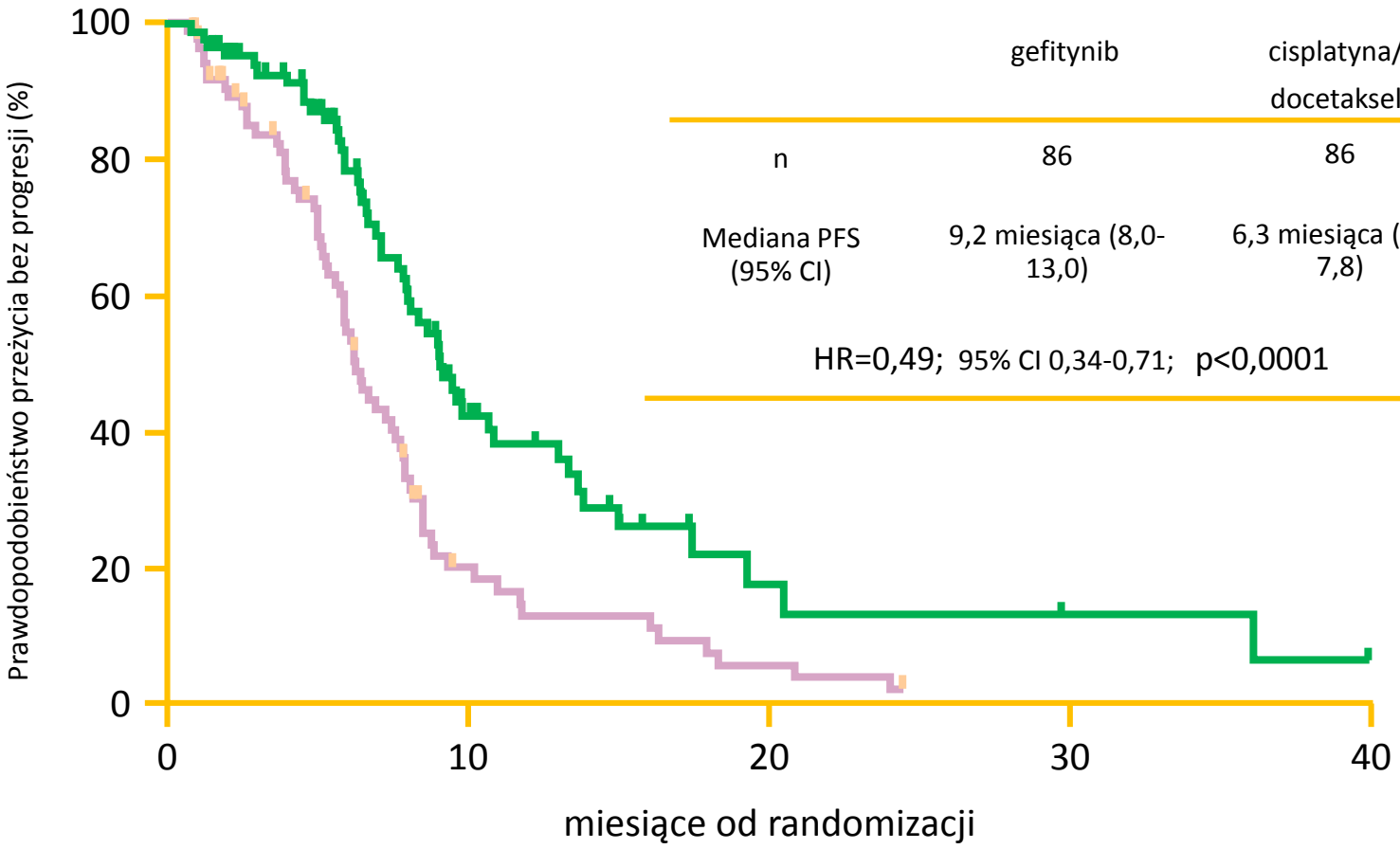
NEJ002: gefitynib vs karboplatyna-paklitaksel

Znaczące wydłużenie mediany przeżycia wolnego od progresji



Maemondo M i wsp. N Engl J Med 2010;362:2380-2388

WJTOG3405: gefitynib vs cisplatyna/docetaksel



	gefitynib	cisplatyna/ docetaksel
n	86	86
Mediana PFS (95% CI)	9,2 miesiąca (8,0-13,0)	6,3 miesiąca (5,8-7,8)

HR=0,49; 95% CI 0,34-0,71; p<0,0001

Mitsudomi T. i wsp Lancet Oncol 2010;11:121–128

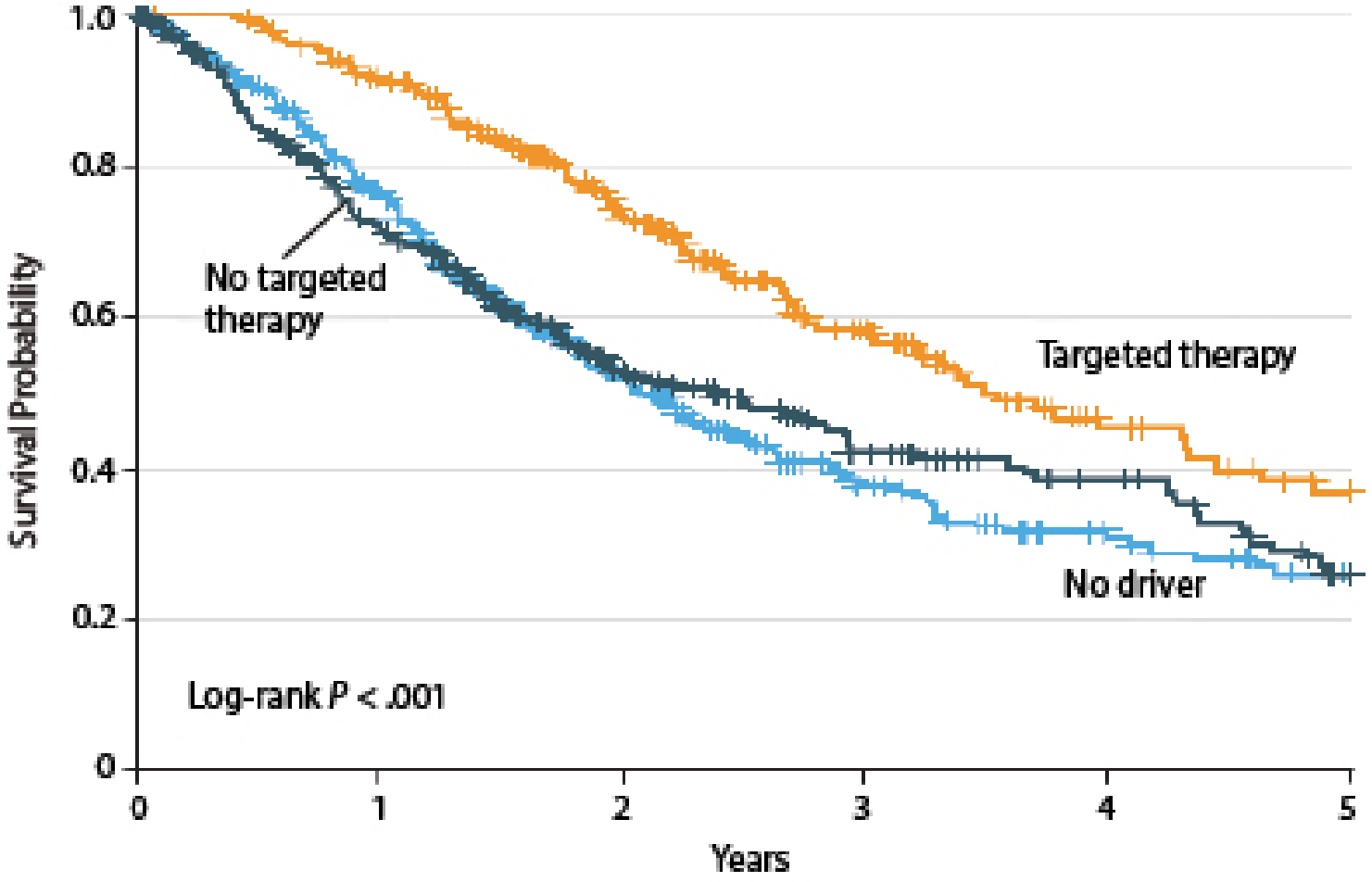
PFS (*Progression-free survival)* – czas przeżycia wolny od progresji choroby
CI *(confidence interval)* – przedział ufności
HR *(hazard ratio)* – współczynnik ryzyka

Badania w 1 linii leczenia chorych z mutacją vs chemioterapia

Badanie	Schemat	N	RR, %	PFS, mies.
IPASS[1,2]	Gefitinib vs Carbo/pac	261	71.2 vs 47.3	**9.5 vs 6.3**
NEJ002[3]	Gefitinib vs Carbo/pac	230	73.7 vs 30.7	**10.8 vs 5.4**
OPTIMAL[4,5]	Erlotinib vs Carbo/gem	165	83 vs 36	**13.1 vs 4.6**
EURTAC[6]	Erlotinib vs Platinum-based chemo	174	58 vs 15	**9.7 vs 5.2**

[1] Mok TS et al. *N Engl J Med* 2009;361(10):947–57. [2] Fukuoka M et al. *J Clin Oncol* 2011;29(21):2866–74. [3] Maemondo M et al. *N Engl J Med* 2010;362(25):2380–8. [4] Zhou C et al. *Lancet Oncol* 2011;12(8):735–42. [5] Zhou C et al. *Proc ASCO* 2012;Abstract LBA7520. [6] Rosell R et al. *Lancet Oncol* 2012;13(3):239–46.

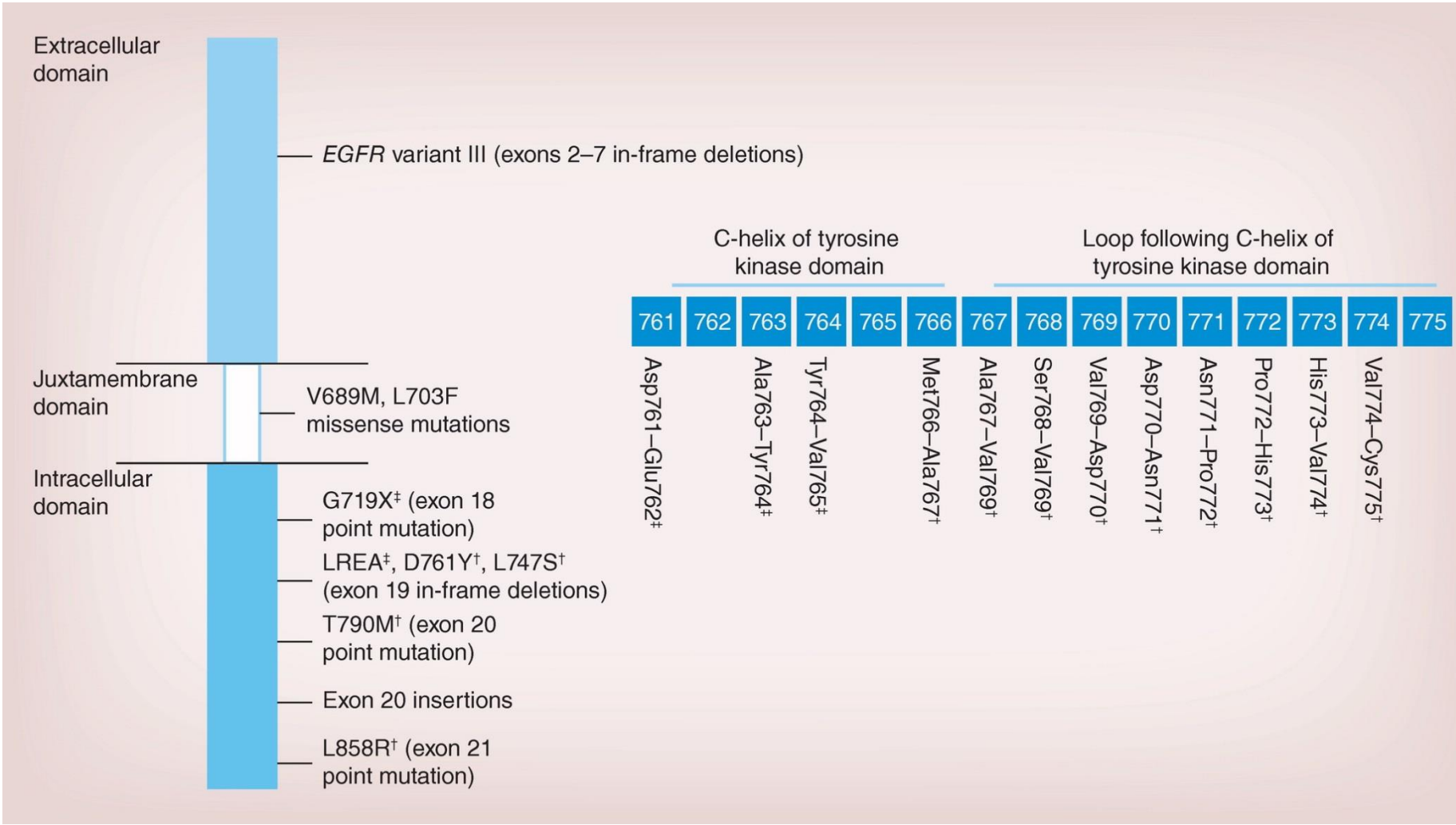
Porównanie skuteczności terapii celowanej do postępowania standardowego (analiza populacyjna)



Badania w 1 linii leczenia chorych z mutacją vs chemioterapia

Badanie	Schemat	N	RR, %	PFS, mies.	OS, mies.
IPASS[1,2]	Gefitinib vs Carbo/pac	261	71.2 vs 47.3	**9.5 vs 6.3**	21.6 vs 21.9
NEJ002[3]	Gefitinib vs Carbo/pac	230	73.7 vs 30.7	**10.8 vs 5.4**	30.5 vs 23.6
OPTIMAL[4,5]	Erlotinib vs Carbo/gem	165	83 vs 36	**13.1 vs 4.6**	22.7 vs 28.9
EURTAC[6]	Erlotinib vs Platinum-based chemo	174	58 vs 15	**9.7 vs 5.2**	19.3 vs 19.5

[1] Mok TS et al. *N Engl J Med* 2009;361(10):947–57. [2] Fukuoka M et al. *J Clin Oncol* 2011;29(21):2866–74. [3] Maemondo M et al. *N Engl J Med* 2010;362(25):2380–8. [4] Zhou C et al. *Lancet Oncol* 2011;12(8):735–42. [5] Zhou C et al. *Proc ASCO* 2012;Abstract LBA7520. [6] Rosell R et al. *Lancet Oncol* 2012;13(3):239–46.

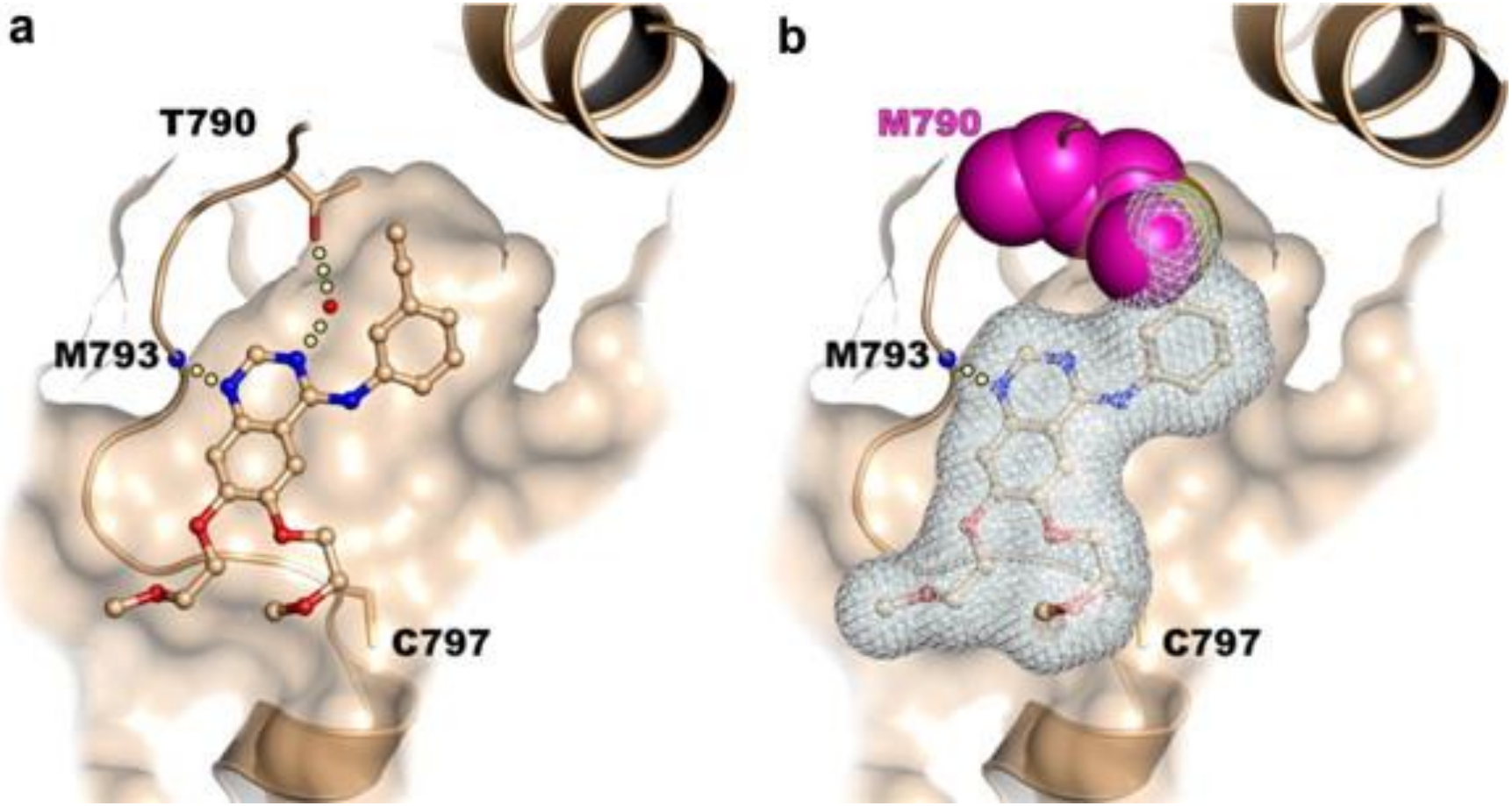

Extracellular domain
EGFR variant III (exons 2–7 in-frame deletions)
Juxtamembrane domain
V689M, L703F missense mutations
Intracellular domain
G719X‡ (exon 18 point mutation)
LREA‡, D761Y†, L747S† (exon 19 in-frame deletions)
T790M† (exon 20 point mutation)
Exon 20 insertions
L858R† (exon 21 point mutation)
C-helix of tyrosine kinase domain
Loop following C-helix of tyrosine kinase domain
761 762 763 764 765 766 767 768 769 770 771 772 773 774 775
Asp761–Glu762‡
Ala763–Tyr764‡
Tyr764–Val765‡
Met766–Ala767†
Ala767–Val769†
Ser768–Val769†
Val769–Asp770†
Asp770–Asn771†
Asn771–Pro772†
Pro772–His773†
His773–Val774†
Val774–Cys775†

EGFR T790M: mutacja nabytej oporności

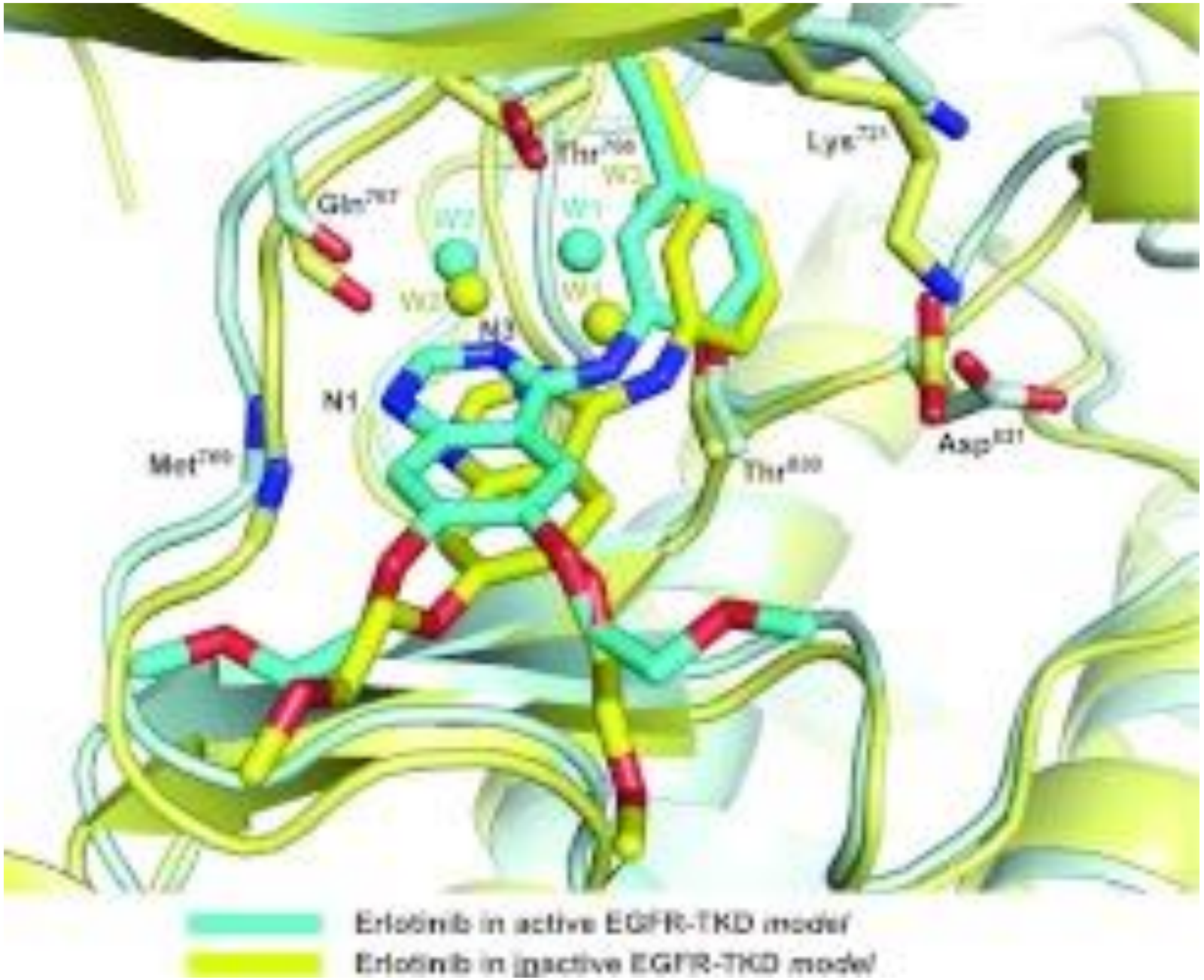
Patient	Sex	Smoking	Drug	Duration	Prior chemo	Prior RT	Sites Examined for Acquired Resistance	Primary Mutation	Secondary Mutation	*EGFR* copy number
1[a,b]	F	Never	E	19	Y	N	Lung, spine	del L747-E749;A750P	T790M	5.7
2	M	Never	G	13	Y	Y	Lung	del L747-S752	T790M	nd
3	M	Oligo	G	11	Y	Y	Omentum	del E746-A750	T790M	5.1 → 6.3
4	F	Never	G	15	Y	N	Lung, pericardial fluid	del L747-P753insS	T790M	9.6 → 11
5	F	Never	E	10	N	N	Pleural fluid	del E746-T751insA	T790M	nd
6	F	Oligo	G→E[c]	n/a	Y	N	Lung	del E746-A750	T790M[f]	nd
7[a]	F	Never	G	10	Y	N	Pleural fluid	L858R	T790M	nd
8	F	Never	G	15	N	N	Lung	L858R	T790M	nd
9	F	Never	G	13	N	N	Lung	L858R	T790M[e]	nd
10	F	Never	G	13	Y	Y	Brain	L858R	D761Y	6.0
11[a,b]	F	Never	E	16	N	Nd	Lung	del L747-P753insQ	None[g]	7.1
12[a]	F	Former	G	11	Y	N	Lung	del L747-E749;A750P	None	nd
13[a]	M	Never	G	11	Y	Nd	Pleural fluid, ascites	del E746-A750	None	2.9 → 6.1
14	F	Oligo	G	19	Y	N	Ascites	del E746-A750	None	nd
15	F	Never	G	8	N	N	Pleura	del E746-A750	None	8.4
16	F	Never	E	10	Y	N	Lung	del E746-A750	None	5.7
17	M	Never	E	9	N	N	Pleural fluid	del E746-A750	None	7.2
18	F	Oligo	G	7	Y	N	Cervix	del[e]	None	nd
19	M	Former	G	12	Y	Y	Inguinal lymph node	del[e]	None	nd
20	F	Oligo	G	28	N	N	Lung	del[e]	None	nd
21	M	Never	G→E	19	Y	Y	Pleural fluid	L858R	None	nd

Pao W, et al. PLoS Med. 2005;2:e73; Balak MN, et al. Clin Cancer Res. 2006;12:6494-6501.

T790M blokuje wiązanie erlotynibu



Michalczyk et al. Bioorganic & Medicinal Chemistry 16 (7): 3482; April 2008


Thr790
Lys721
Gln767
W2
W1
W3
N1
Met790
Thr830
Asp831
Erlotinib in active EGFR-TKD model
Erlotinib in inactive EGFR-TKD model

RODZAJE WIĄZAŃ CHEMICZNYCH

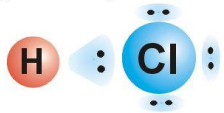
wiązanie kowalencyjne (atomowe)

schematycznie:

H–H

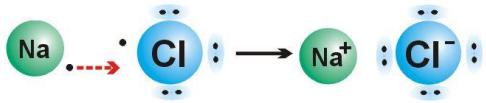
jest to wiązanie utworzone przez wspólną parę elektronową
występuje pomiędzy atomami o niskiej różnicy elektroujemności (0 - 0,4)

wiązanie kowalencyjne spolaryzowane



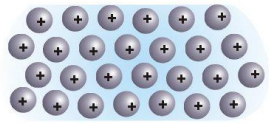
jest to wiązanie kowalencyjne w którym wspólna para elektronowa jest silnie przesunięta w stronę jednego atomu (różnica elektroujemności: 0,4 - 1,7)

wiązanie jonowe



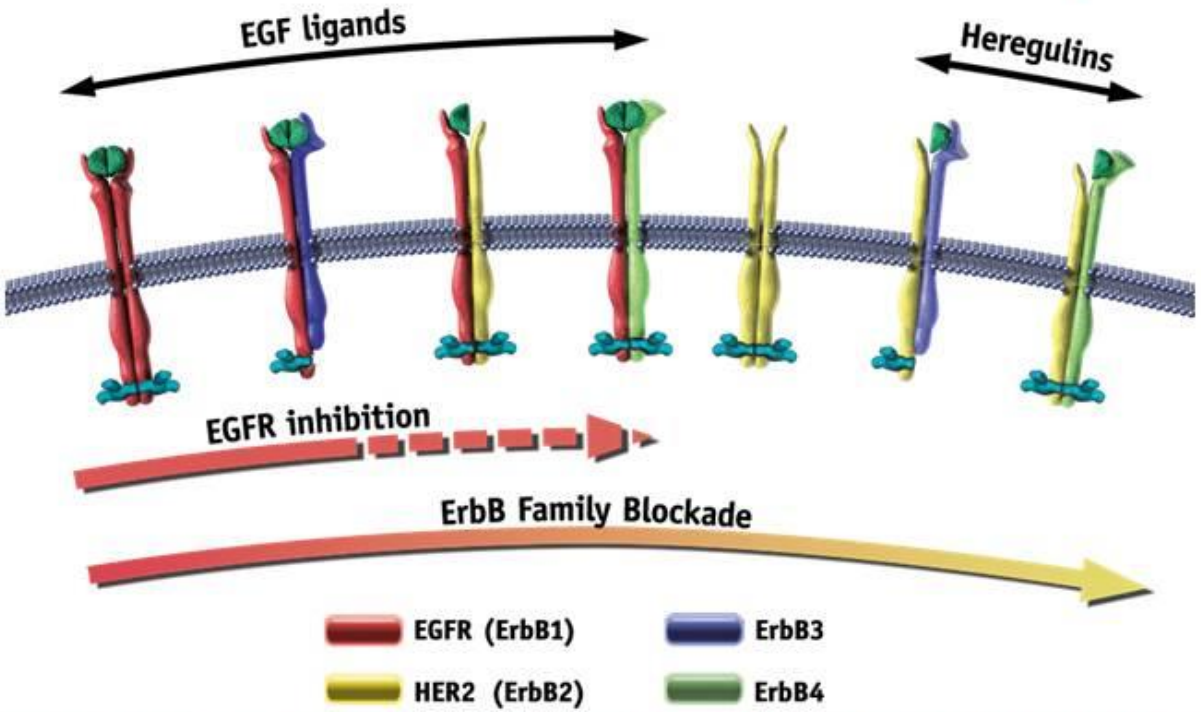
wiązanie powstaje pomiędzy atomami o dużej różnicy elektroujemności (powyżej 1,7)
jeden z atomów oddaje elektron drugiemu, powstają kation i anion, które oddziaływują ze sobą elektrostatycznie

wiązanie metaliczne



jest to wiązanie charakterystyczne dla metali i ich stopów, kationy metalu tworzą strukturę krystaliczną, pomiędzy nimi wolne elektrony tworzą tzw. gaz elektronowy

Afatinib: an irreversible ErbB Family Blocker

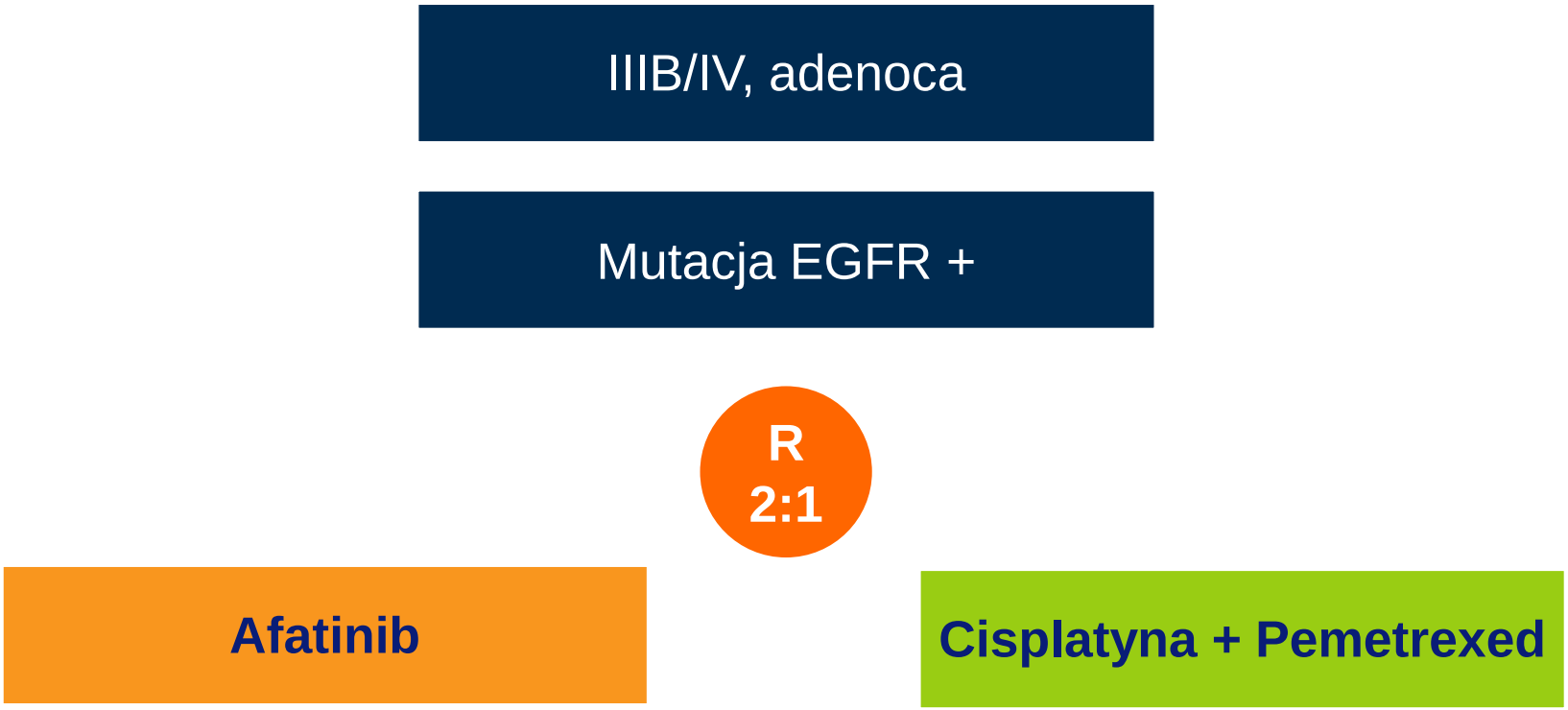


- Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential
  - Inhibition of ErbB Family receptor heterodimerization
  - *In vitro* activity against EGFR-resistant T790M mutation

Li D, et al. *Oncogene* 2008;27:4702–11.

Yang et al. ASCO 2012 Abstract LBA7500

Badanie fazy III LUX-Lung 3



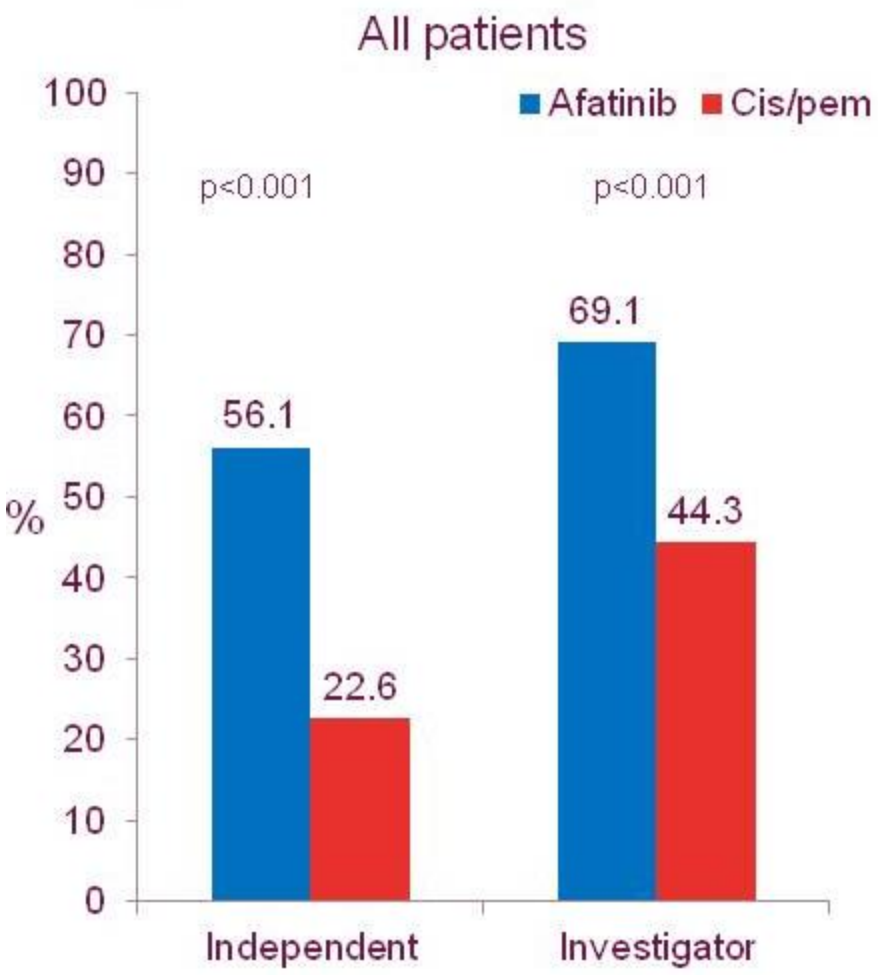
1269 screened, 452 EGFR mutation (+) => 345 randomized

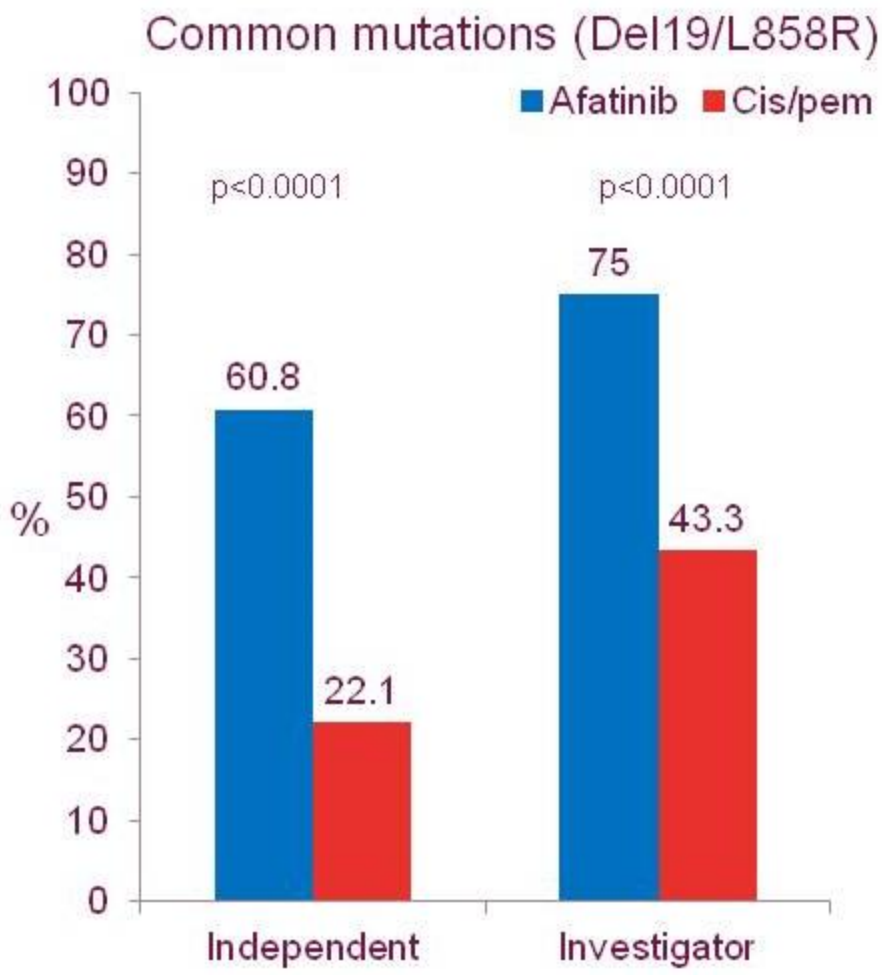
Yang et al. ASCO 2012 Abstract LBA7500

LUX-Lung 3

	Afatinib (n = 230)	Cis/pem (n = 115)
Odsetek odpowiedzi	56%	23%
Mediana PFS	11.1 mieś.	6.9 mieś.

ORR

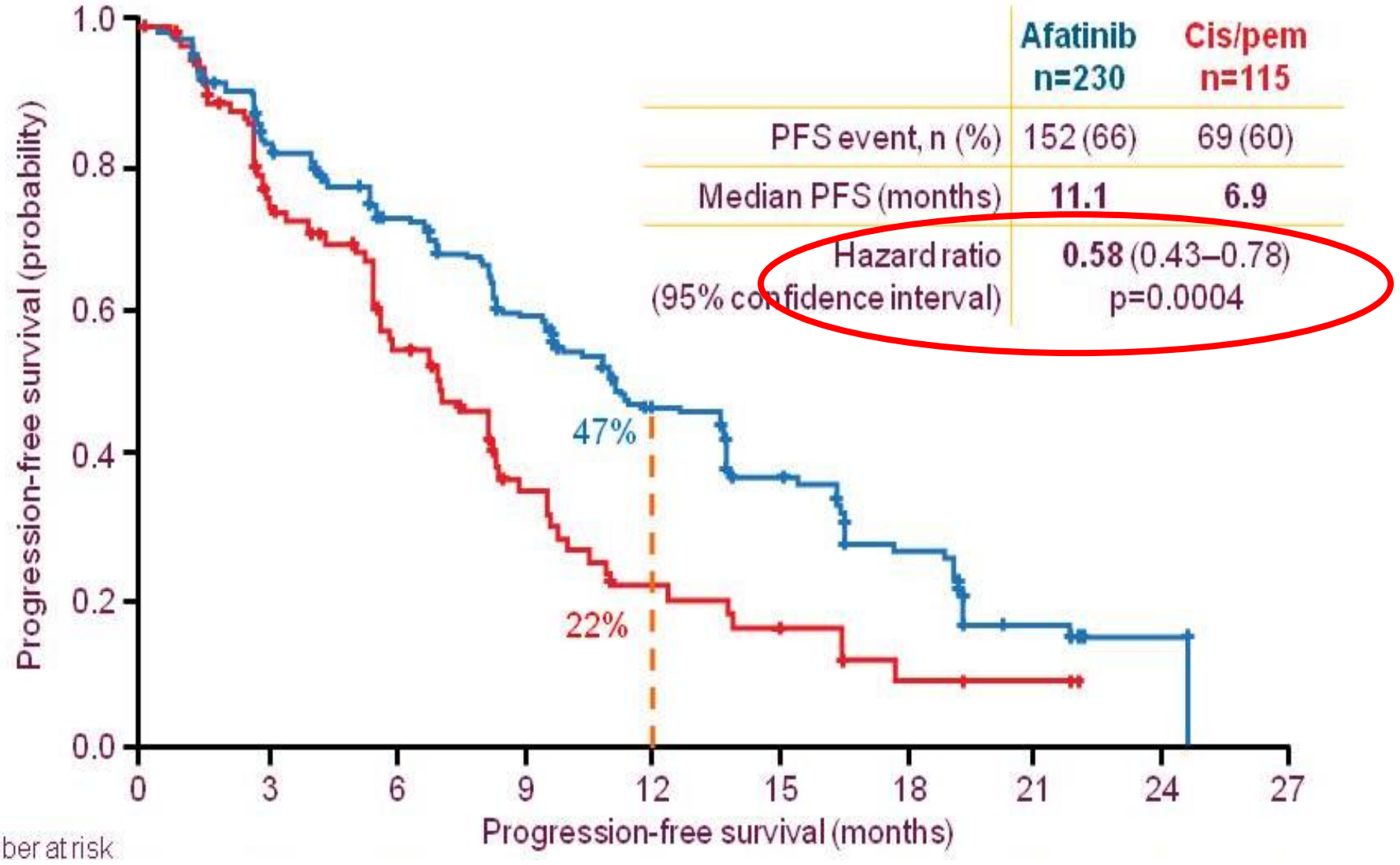




Median duration of response: 11.1 vs. 5.5 months (all patients; independent review)

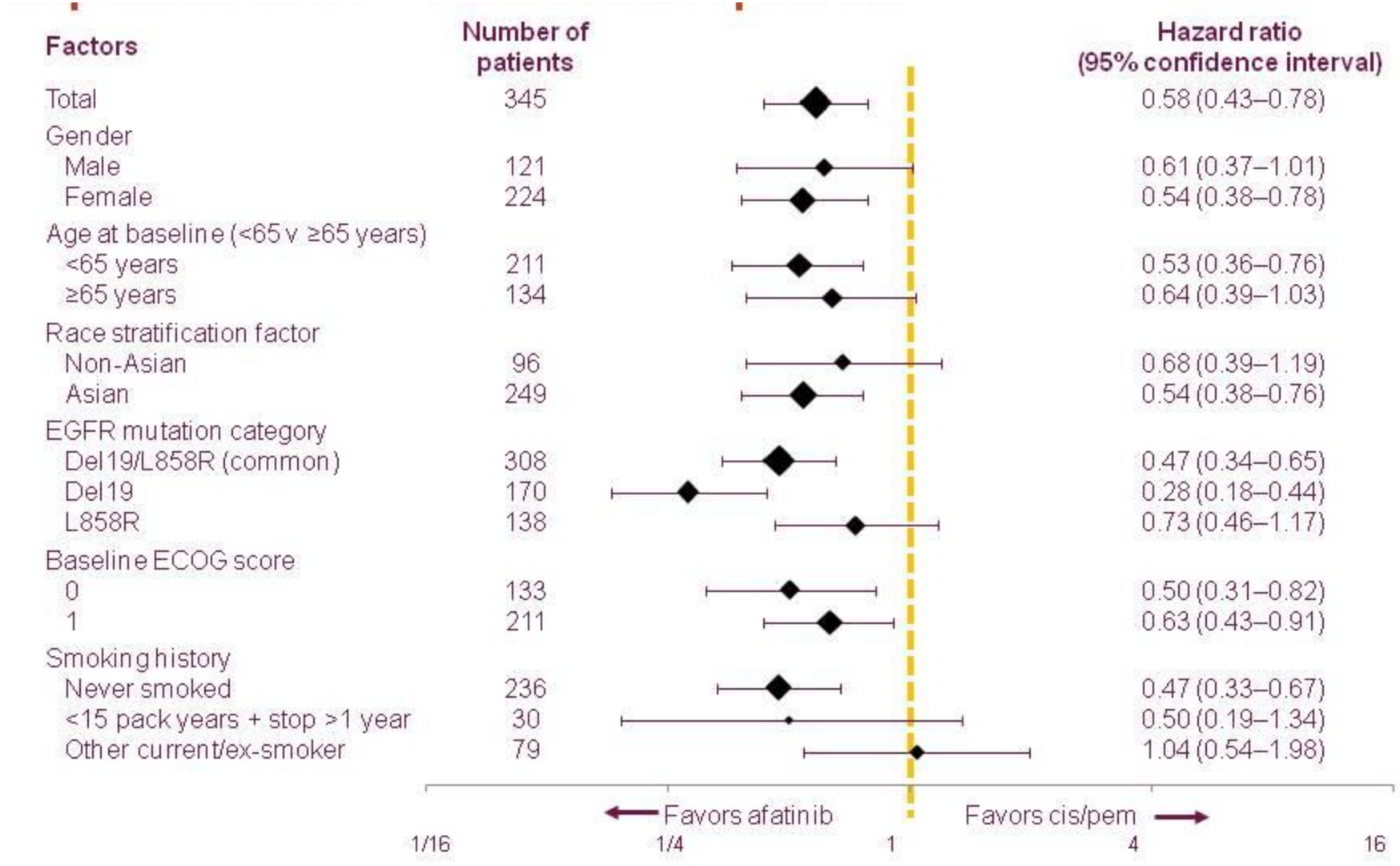
Yang et al. ASCO 2012 Abstract LBA7500

PFS



Yang et al. ASCO 2012 Abstract LBA7500

PFS Independent Review Subgroup Analysis



Yang et al. ASCO 2012 Abstract LBA7500

Badanie	Terapia	RR (%)	Mediana PFS (miesiące)	Mediana OS (miesiące)	Grupa
EURTAC	Erlotinib	58	9.7	19.3	NSCLC with EGFR exon 19 deletion or L858R mutation in exon 21. First-line treatment
	Cisplatin/carboplatin + docetaxel/gemcitabine	15; p < 0.001	5.2; p < 0.001	19.5	
OPTIMAL	Erlotinib	83	13.1	22.6	Chemotherapy-naive Asian patients with advanced NSCLC and EGFR exon 19 deletion or L858R mutation in exon 21. First-line treatment
	Carboplatin + gemcitabine	36; p < 0.001	4.6; p < 0.001	28.8	
NEJ-02	Gefitinib	74	10.8	27.7	Advanced NSCLC with EGFR mutation. First-line treatment
	Carboplatin + paclitaxel	31; p < 0.001	5.4; p < 0.001	26.6	
WJTOG 3405	Gefitinib	62	9.2	35.5	Advanced NSCLC with EGFR exon 19 deletion or L858R mutation in exon 21. First-line treatment
	Cisplatin + docetaxel	32; p < 0.001	6.3; p < 0.001	38.8	
IPASS†	Gefitinib	71.2	9.5	22	Chemotherapy-naive Asian patients (nonsmokers or light smokers) with advanced NSCLC. Study enrolled patients independent of EGFR mutation status
	Carboplatin + paclitaxel	47.3; p < 0.001	6.3; p < 0.001	22	
	Gefitinib	55	9.2	17.5	Advanced NSCLC with EGFR mutation. First-line treatment
	Erlotinib	70.6	14	27	Advanced NSCLC with EGFR exon 19 deletion or L858R mutation in exon 21.
	Gefitinib	76.4	9.7	24.3	Advanced NSCLC Asian patients with EGFR mutation treated with gefitinib.
LUX-Lung 3	Afatinib	56	11.1	16.6	Advanced NSCLC harboring EGFR-activating mutation (exon 19 deletion, L858R, or other). First-line treatment
	Cisplatin + pemetrexed	23; p = 0.001	6.9; p = 0.001	14.8	
LUX-Lung 6	Afatinib	67	11	22.1	Advanced NSCLC harboring EGFR-activating mutation (exon 19 deletion, L858R mutation). First-line treatment
	Cisplatin + gemcitabine	23; p < 0.001	5.6; p < 0.001	22.2	
ENSURE	Erlotinib	63	11	NR	Advanced NSCLC harboring EGFR-activating mutations (exon 19 deletion, L858R mutation). First-line treatment
	Cisplatin + gemcitabine	34; p = 0.0001	5.6§ 5.5¶; p < 0.0001	NR	

Table 1 Studies of EGFR TKIs versus chemotherapy as first-line therapy in NSCLC with typical *EGFR* mutations

Study	EGFR TKI	n	Median PFS in TKI arm (months)	P value	HR
OPTIMAL (11)	Erlotinib	154	13.1	<0.0001	0.16
First Signal (8)	Gefitinib	42	8.4	0.084	0.61
IPASS (4)	Gefitinib	261	9.5	<0.0001	0.48
WJTOG 3405 (9)	Gefitinib	177	9.2	<0.001	0.48
NEJSG 002 (10)	Gefitinib	200	10.8	<0.001	0.36
EURTAC (5)	Erlotinib	174	9.4	<0.0001	0.42
LUX-3 (12)	Afatinib	308	13.6	<0.0001	0.47

Table 2 Main criticisms reported with first-generation EGFR-TKIs

(I)	No response in near 30% of NSCLC with classical exon 19-21 mutation
(II)	No clear benefit in presence of uncommon mutations
(III)	Toxicity
(IV)	No patient is cured: median duration of response 9-12 months
(V)	Lack of efficacy in presence of "acquired" T790M mutation

Table 3 Comparison of best reported phase II results for EGFR TKIs in patients with *EGFR*-Mutant lung cancers (Exon 19 and Exon 21)

	Pts Enrolled, N	RR, %	mPFS, mos	mOS, mos
Dacomitinib (57)	46	74	17	NR
Afatinib (53)	129*	66	15	32-39
Erlotinib (61)	33	70	14	31
Gefitinib (62)	27	59	9.2	17.5

*51 treated first-line

Afatinib

Afatinib (BIBW2992) – nieodwracalny inhibitor EGFR, HER2, HER4, w tym EGFR T790M

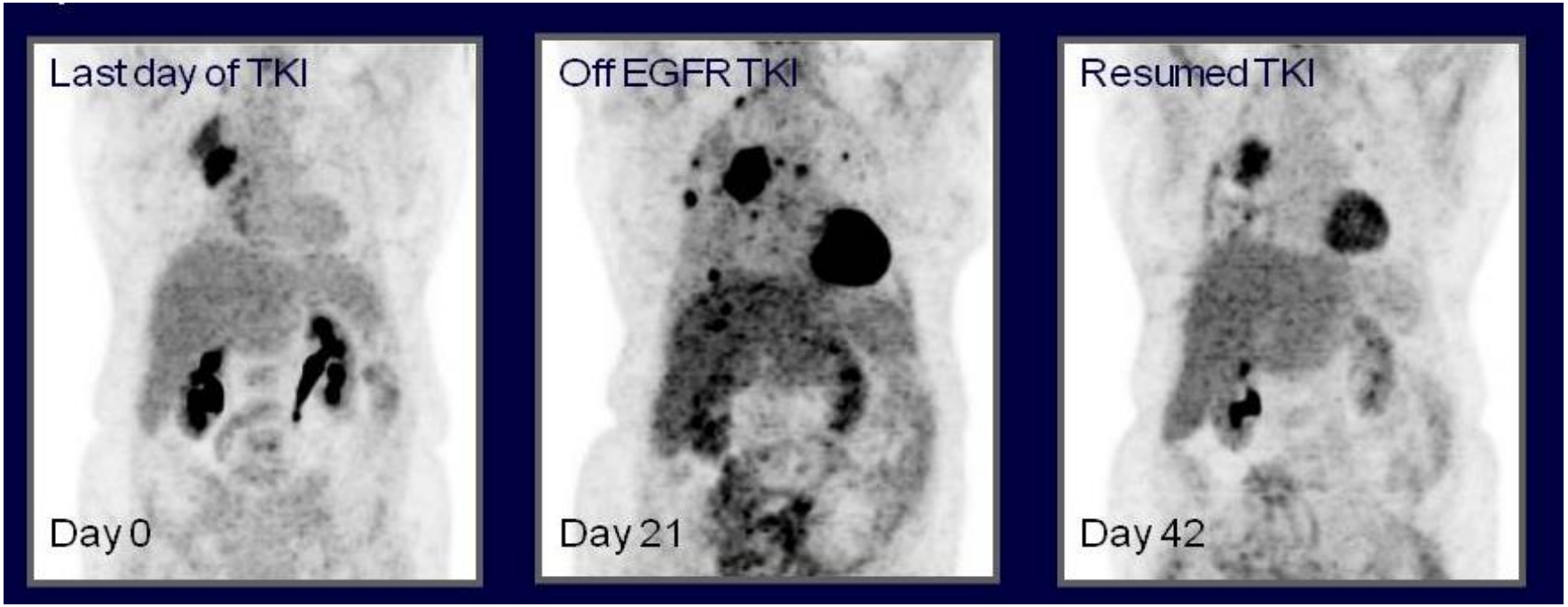
Dacomitinib

Dacomitinib (PF0299804) - nieodwracalny inhibitor EGFR, HER2 and HER4

Neratinib

Neratinib (HKI-272) - nieodwracalny inhibitor EGFR, HER2 and HER4

Progresja nowotworu po odstawieniu TKI (flare)



Szybka progresja choroby po odstawieniu: 23% (n=14)

Riely et al. Clinical Cancer Research 2007, Chaft et al. CCR 17 (19): 6298-6303, 2011

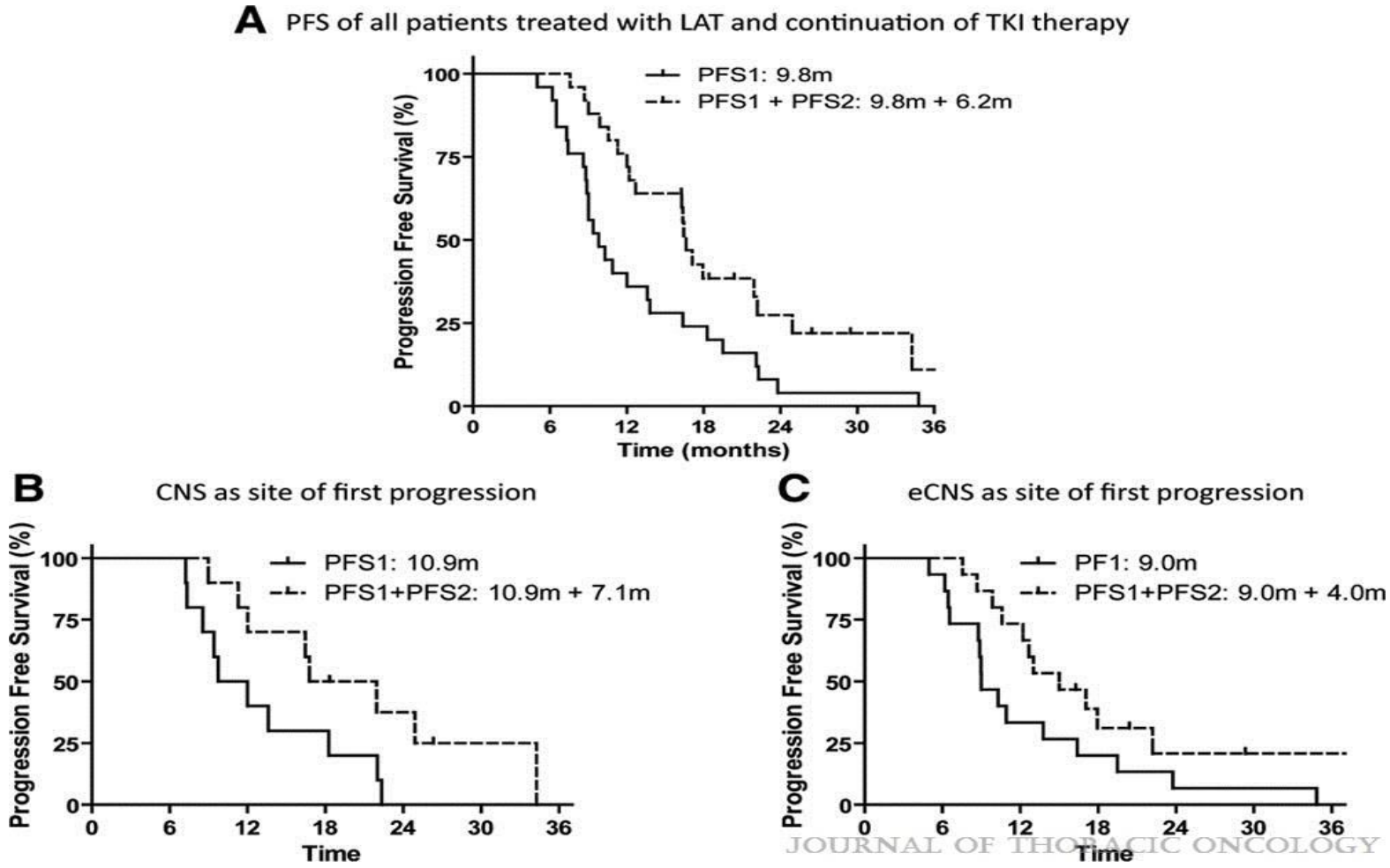
W trakcie terapii TKI rozwija się oligometastatyczna choroba oporna na TKI

- Kontynuować TKI?
- Radioterapia / Resekcja ognisk opornych ?
- Wnikliwe monitorowanie ?

- Czy da się w ten sposób
  wydłużyć PFS (6.2-10 miesiąca ?) i OS (41 miesięcy?)

Weickhardt et al. JTO 7: 1807-1814, 2012; Yu et al. ASCO 2012 abstract 7527, JCO 30 , 2012

EGFR mutation and ALK mutation patients with oligo-progressive disease + local therapy have PFS benefit



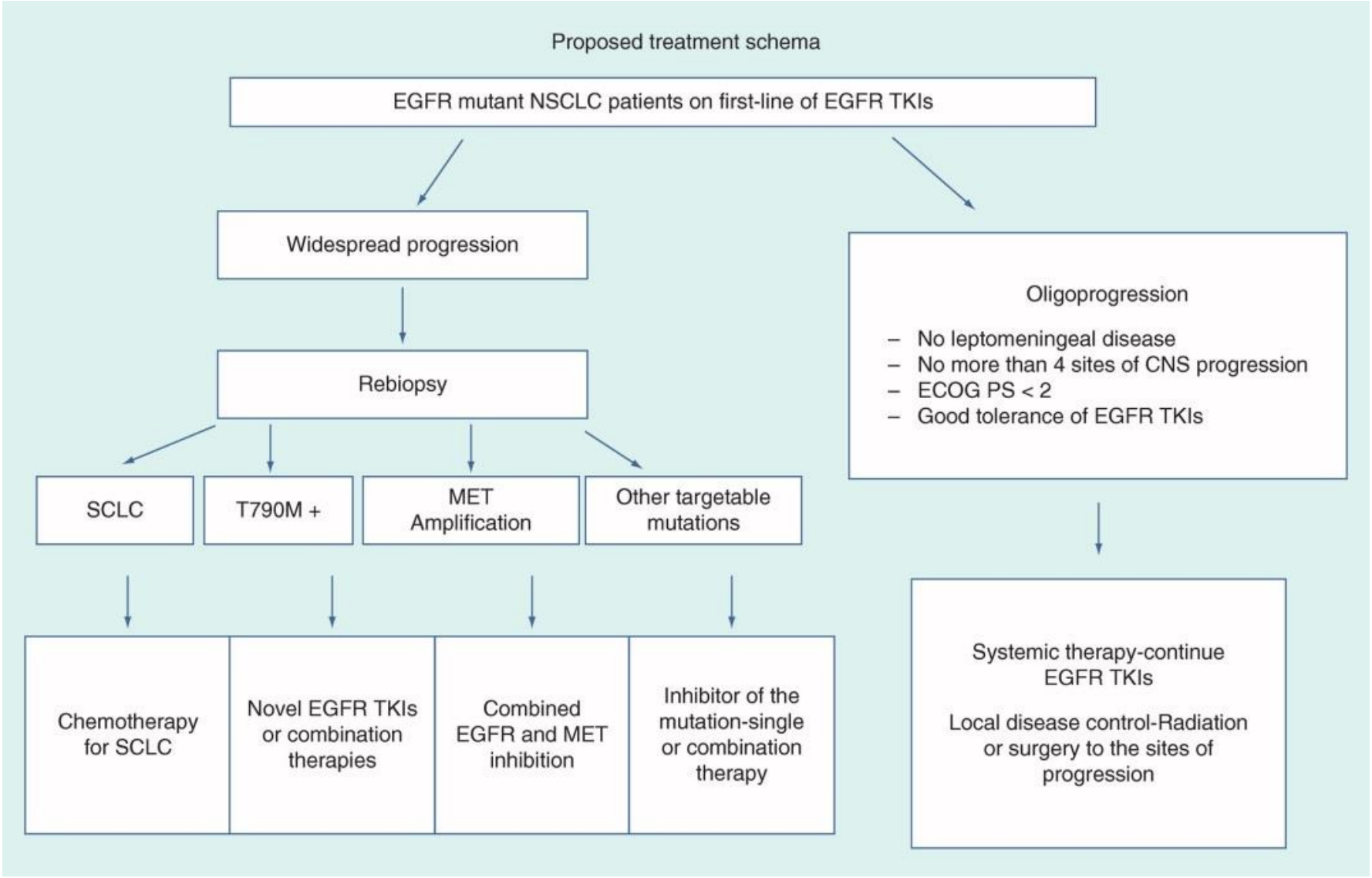
Weickhardt et al. JTO 7: 1807-1814, 2012

Tsao Conclusions on Clinical Management for EGFR mutation patients with Acquired Resistance

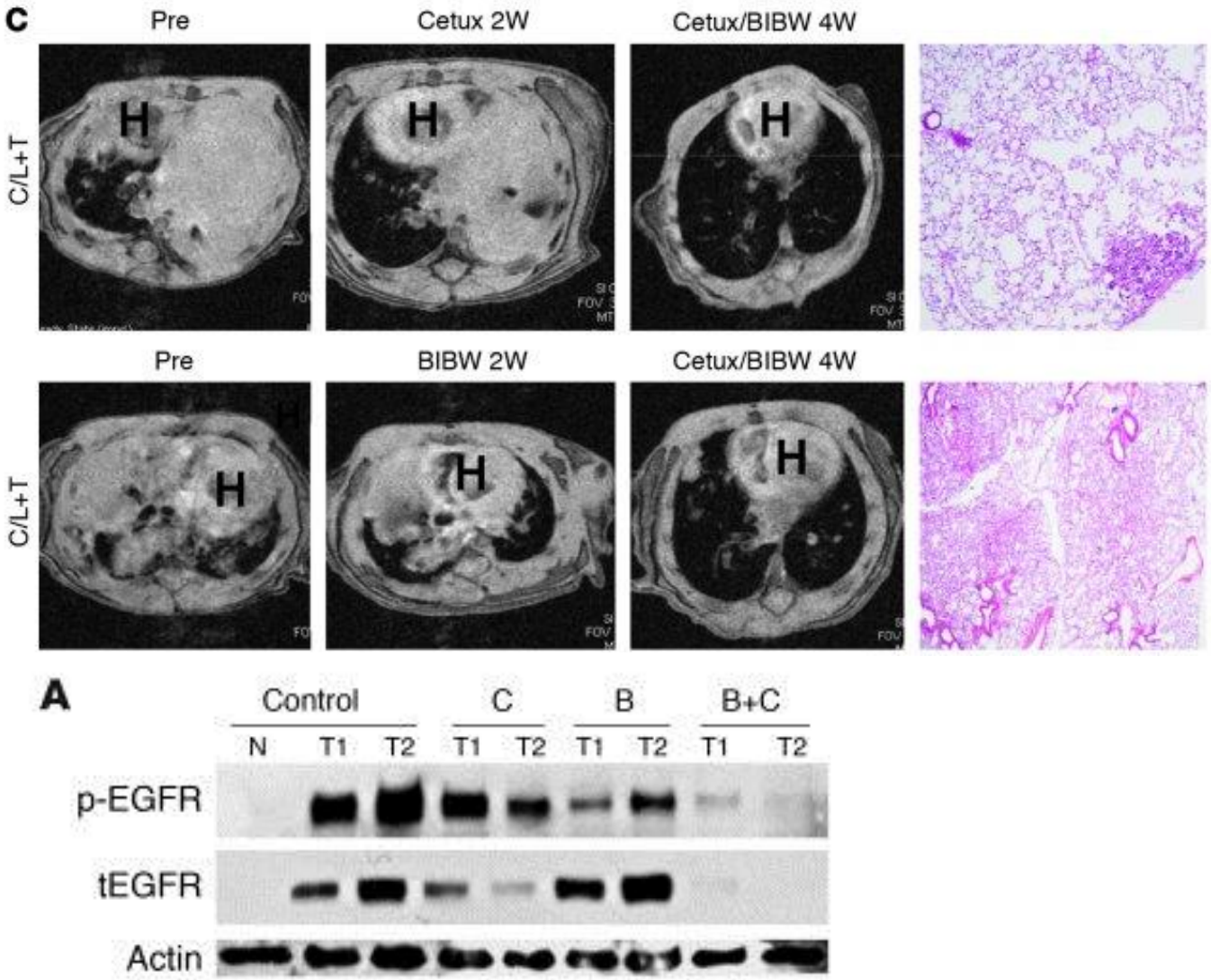
Oligo-PD → **Continue EGFR TKI + localized therapy**

Global PD →

- **Chemo**
- **Chemo then EGFR TKI**
- **Chemo + EGFR TKI**
- **Chemo intercalated with EGFR TKI**

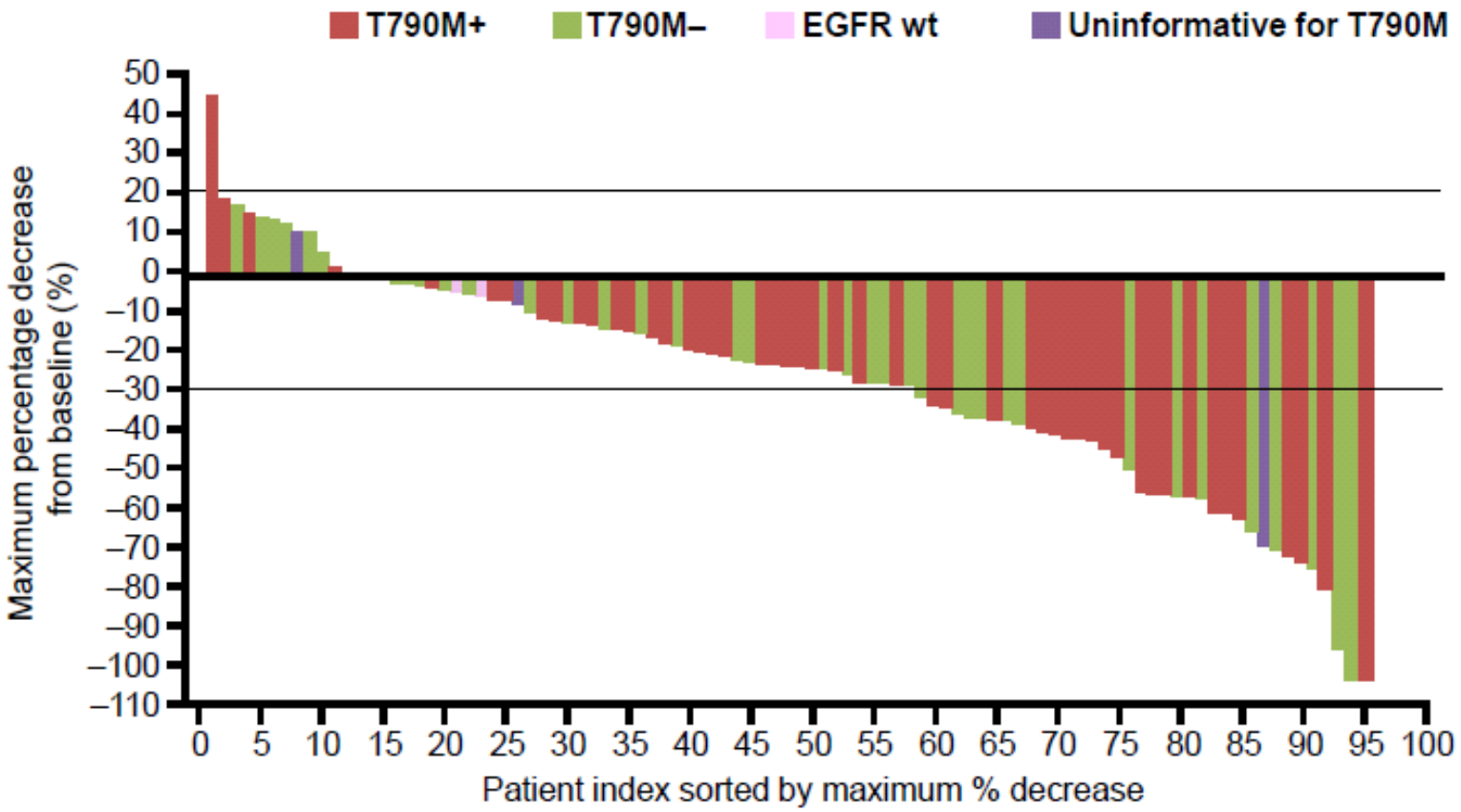

Proposed treatment schema
EGFR mutant NSCLC patients on first-line of EGFR TKIs
Widespread progression
Rebiopsy
SCLC
T790M +
MET Amplification
Other targetable mutations
Chemotherapy for SCLC
Novel EGFR TKIs or combination therapies
Combined EGFR and MET inhibition
Inhibitor of the mutation-single or combination therapy
Oligoprogression
– No leptomeningeal disease
– No more than 4 sites of CNS progression
– ECOG PS < 2
– Good tolerance of EGFR TKIs
Systemic therapy-continue EGFR TKIs
Local disease control-Radiation or surgery to the sites of progression

Kombinacja afatynibu z cetuksymabem: EGFR T790M

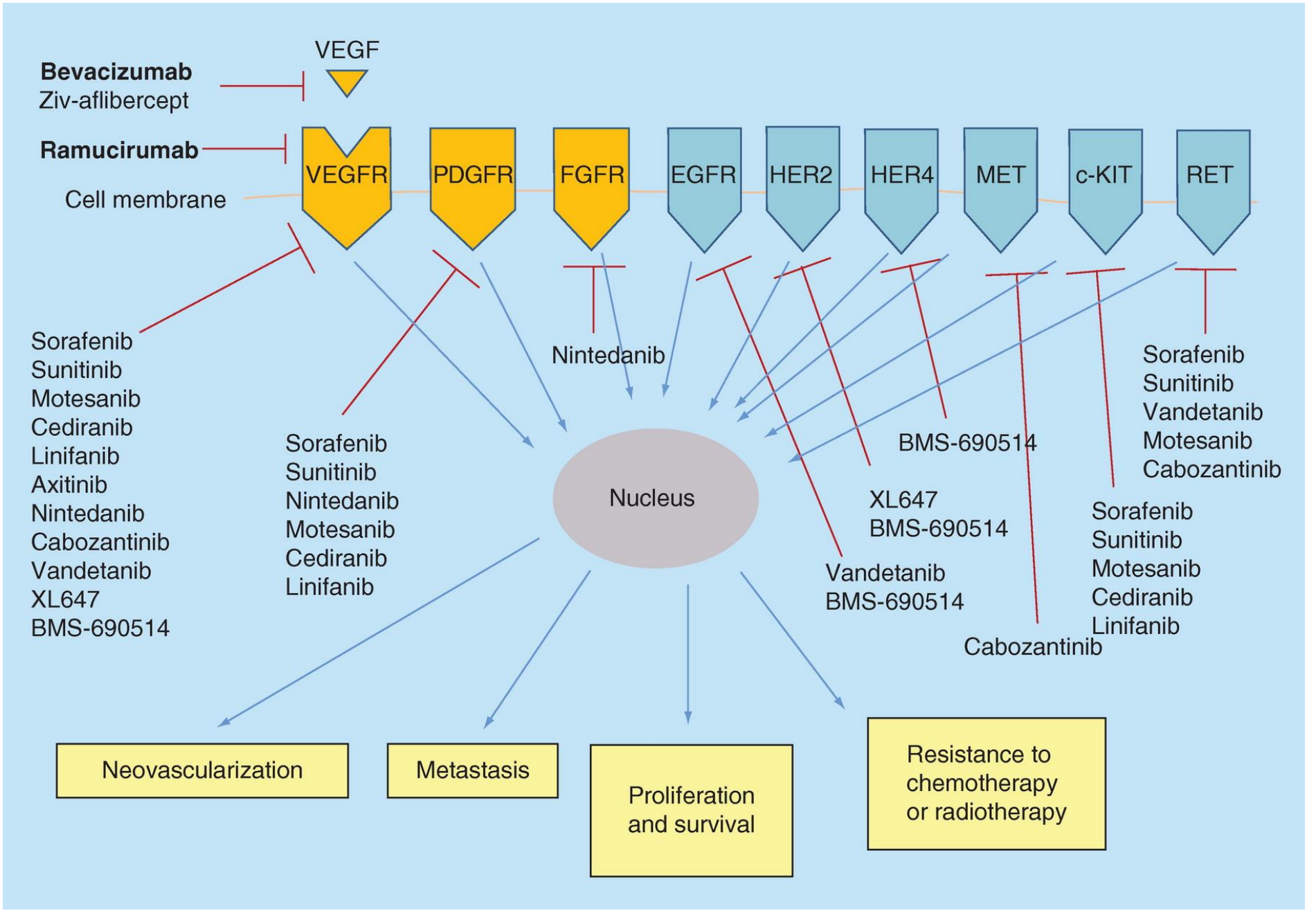


Regales et al. JCI 2009

Kombinacja afatynibu z cetuksymabem



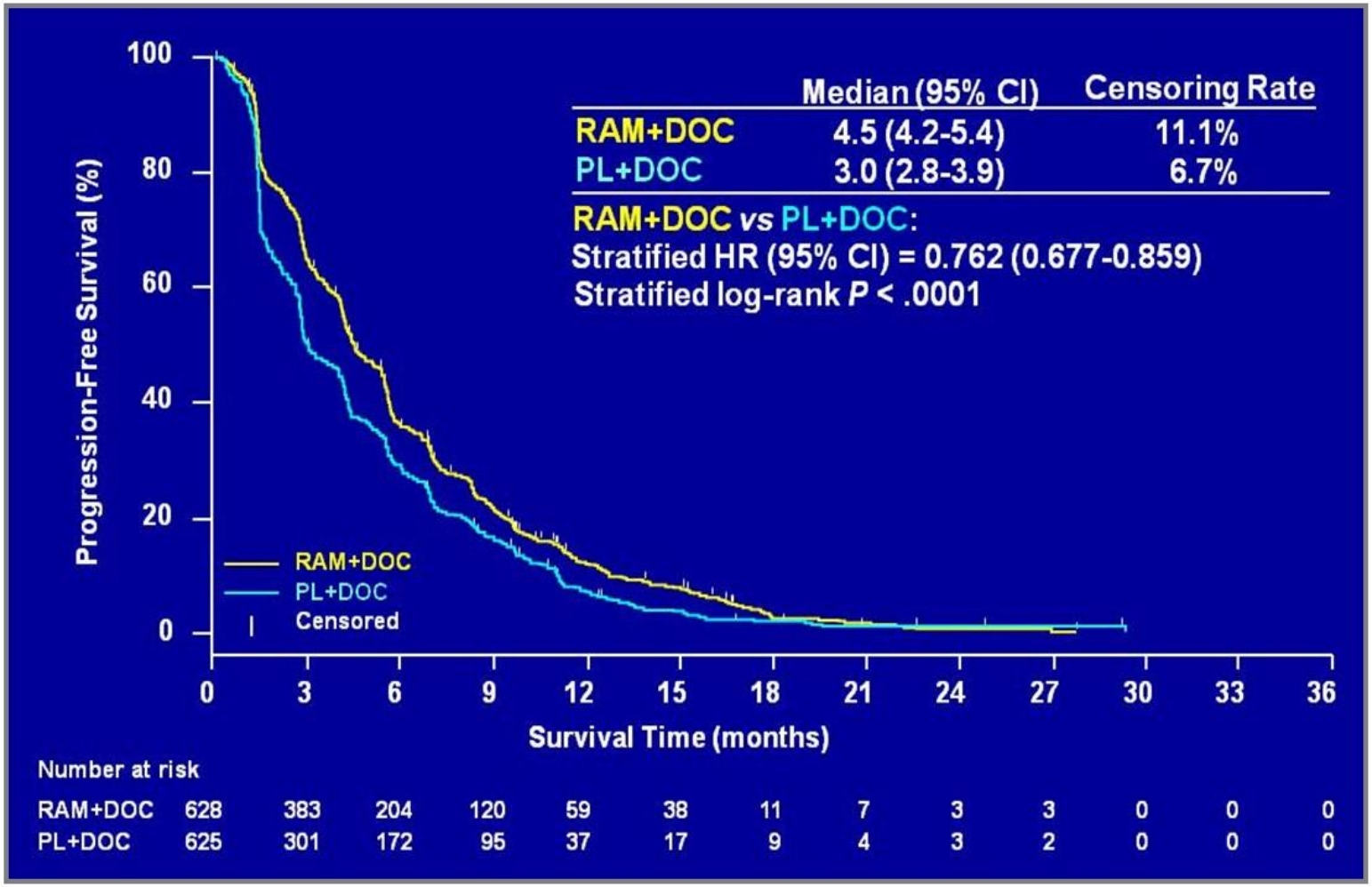
Lynch, T. IASLC Targeted Therapies Meeting Feb 2013; Janjigian, et al. ESMO 2012


VEGF
Bevacizumab
Ziv-aflibercept
Ramucirumab
Cell membrane
VEGFR
PDGFR
FGFR
EGFR
HER2
HER4
MET
c-KIT
RET
Sorafenib
Sunitinib
Motesanib
Cediranib
Linifanib
Axitinib
Nintedanib
Cabozantinib
Vandetanib
XL647
BMS-690514
Sorafenib
Sunitinib
Nintedanib
Motesanib
Cediranib
Linifanib
Nintedanib
Nucleus
BMS-690514
XL647
BMS-690514
Vandetanib
BMS-690514
Cabozantinib
Sorafenib
Sunitinib
Motesanib
Cediranib
Linifanib
Sorafenib
Sunitinib
Vandetanib
Motesanib
Cabozantinib
Neovascularization
Metastasis
Proliferation
and survival
Resistance to
chemotherapy
or radiotherapy

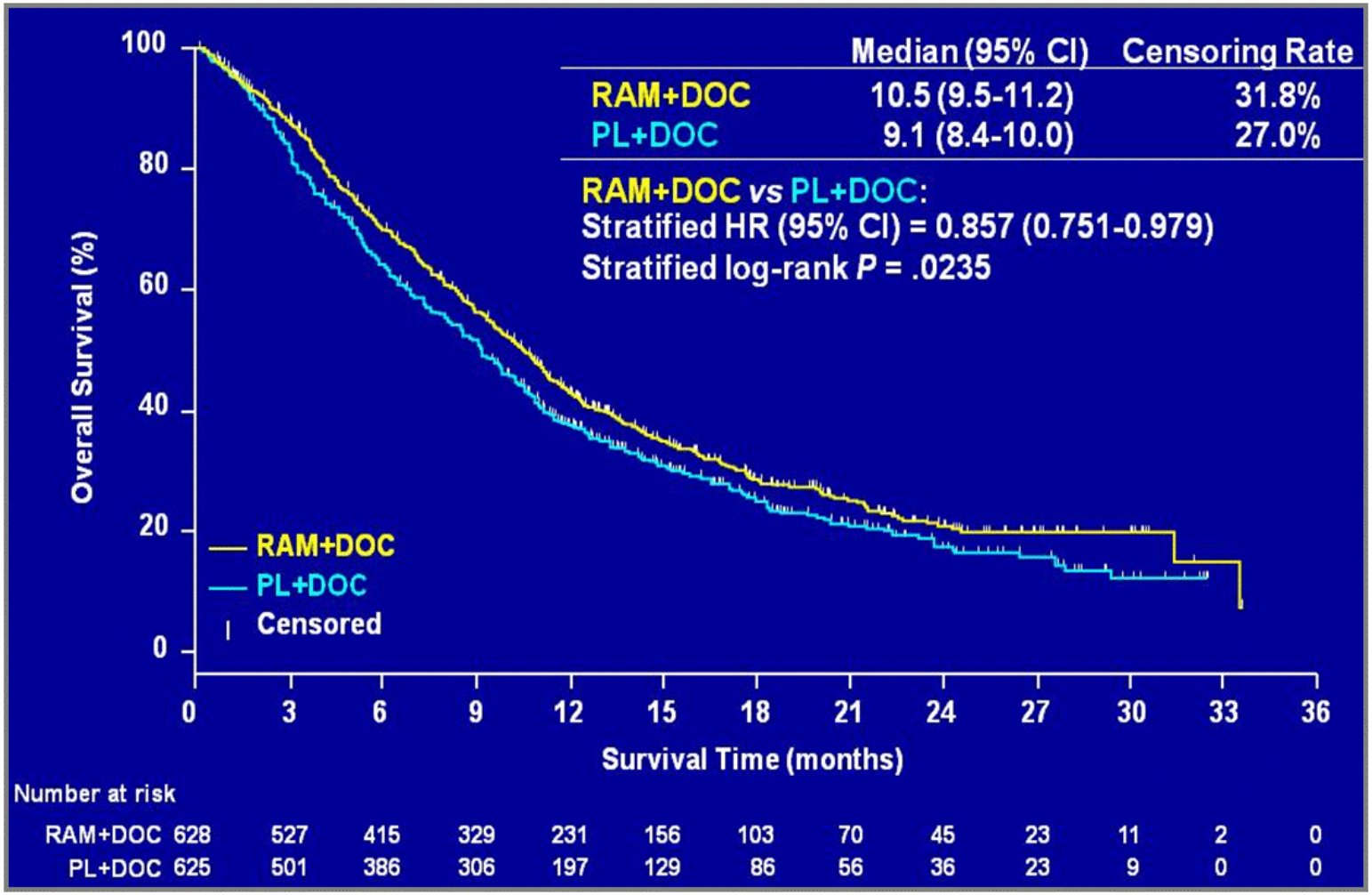
ECOG-E4599: bewacyzumab raku płuca innym niż płaskonabłonkowy

	paklitaksel/karboplatyna +bewacyzumab (n = 443)	paklitaksel/karboplatyna (n = 444)
Mediana PFS	6.2 mieś.	4.5 mieś.
Mediana OS	12.3 mieś.	10.3 mieś.

Taxotere (Docetaxel) +/- Cyramza (Ramucirimab): Progression-Free Survival



Taxotere (Docetaxel) +/- Cyramza (Ramucirimab): Overall Survival



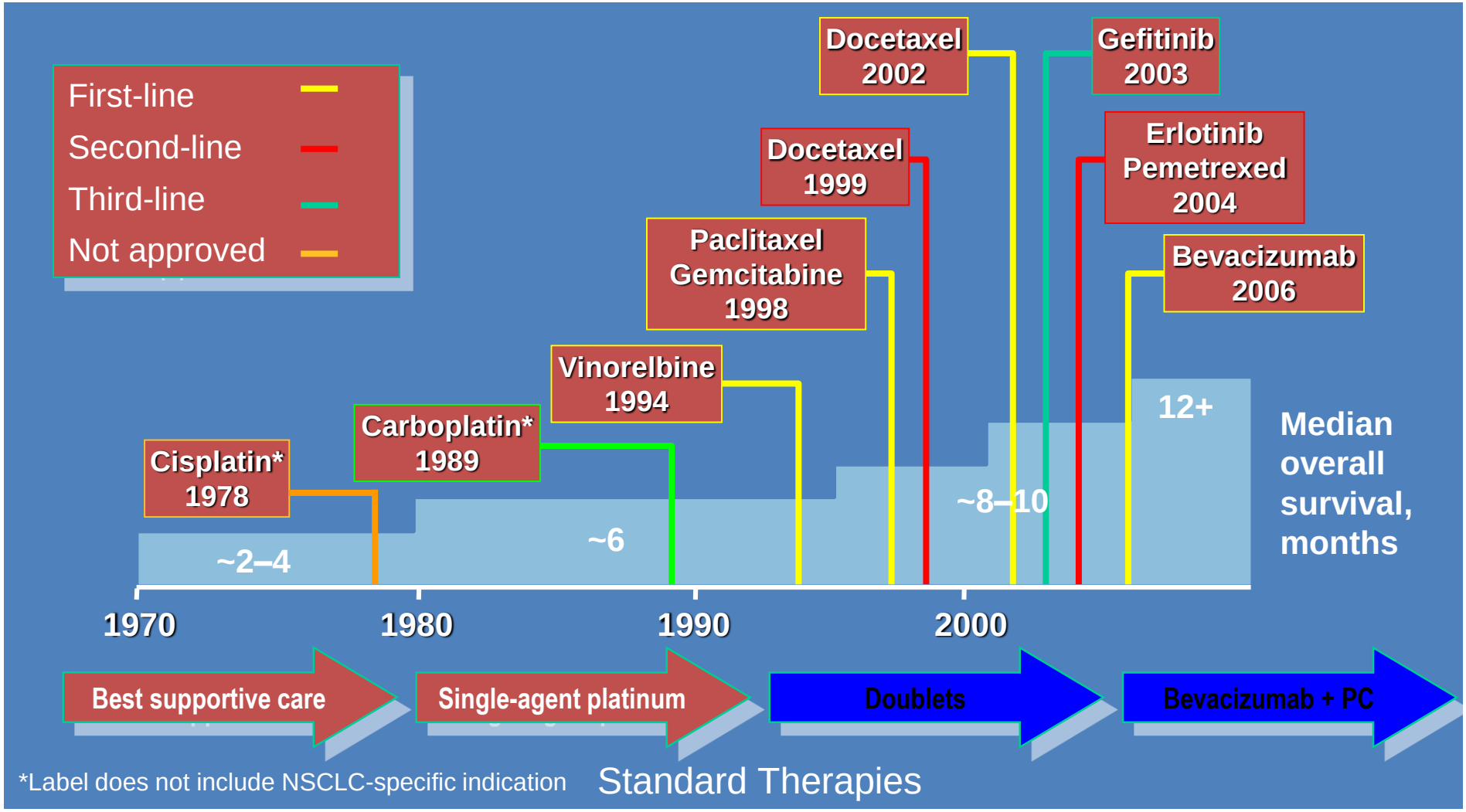
Lek ma w Europie rejestrację w raku żołądka

Podsumowanie cz. 1.

- Erlotynib, gefitynib, afatynib – podstawa terapii 1 rzutu u chorych na raka płuca w IV st. zaawansowania z obecnością mutacji wrażliwości w genie EGFR
- Każdy chory w IV st. zaawansowania z rozpoznaniem raka gruczołowego lub mieszanego winien być badany w kierunku mutacji wrażliwości EGFR
- Opcje terapii antyangiogennej: bewacyzumab (Avastin, 1 rzut) i ramucirimab (Cyramza, 2 rzut) w skojarzeniu z chemioterapią nie są zarejestrowane w Europie

Chorzy bez mutacji ?

60-90% raka gruczołowego
100% raka płaskonabłonkowego


First-line
Second-line
Third-line
Not approved
Cisplatin* 1978
Carboplatin* 1989
Vinorelbine 1994
Paclitaxel Gemcitabine 1998
Docetaxel 1999
Docetaxel 2002
Gefitinib 2003
Erlotinib Pemetrexed 2004
Bevacizumab 2006
~2–4
~6
~8–10
12+
Median overall survival, months
1970
1980
1990
2000
Best supportive care
Single-agent platinum
Doublets
Bevacizumab + PC
*Label does not include NSCLC-specific indication
Standard Therapies

cis-Platinum (DDP) and VP 16-213 (etoposide) combination chemotherapy for advanced non-small cell lung cancer. A phase II clinical trial.

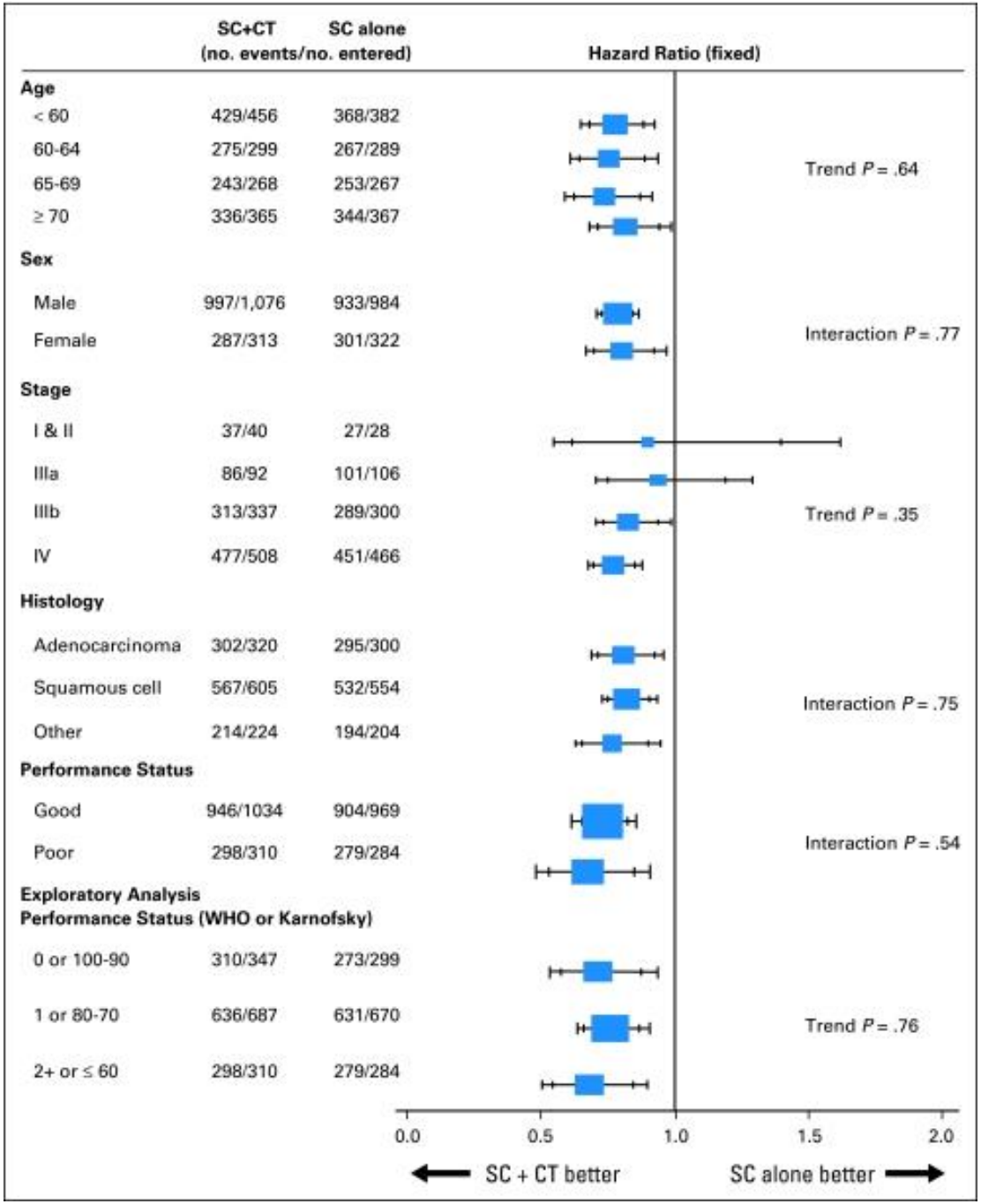
Mitrou PS, Graubner M, Berdel WE, Mende S, Gropp C, Diehl V, Klippstein TH.

Eur J Cancer Clin Oncol. 1984 Mar;20(3):347-51.

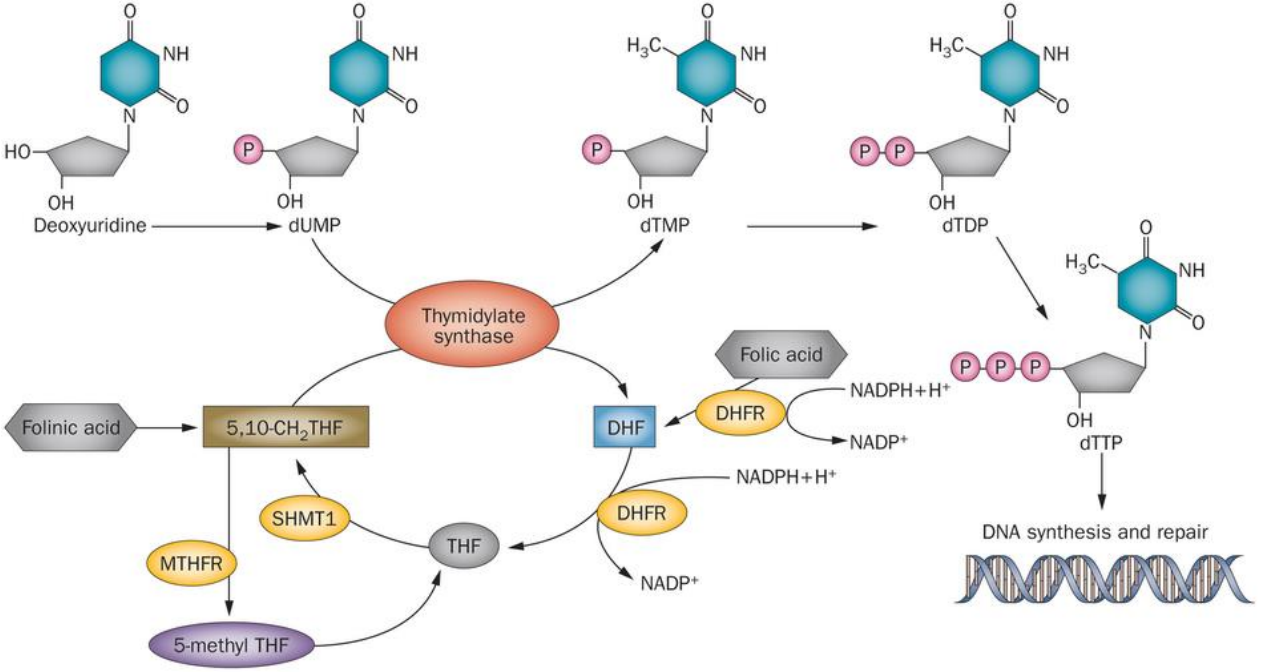
Forty-six patients with non-small cell lung cancer were treated with a combination of cis-platinum, 90 mg/m2 i.v. on day 1 and VP 16-213, 100 mg/m2 i.v. on days 1, 3 and 5. The overall remission rate was 22%, with a median duration of 7 months. Squamous cell and large cell undifferentiated carcinomas responded in 27 and 22% of patients, and seven patients with adenocarcinoma did not respond to chemotherapy. Survival was 7 months for all patients, 11.5 months for responders (7-27+), 8.5 months for patients with stable disease (3-27+) and 5 months for progressive tumours (1-9). **Prognosis was adversely influenced by a performance status of less than 80%, a weight loss of more than 10 kg during the last 3 months before start of treatment** and a radiologically demonstrable 'major' atelectasis (collapse of at least one superior or inferior lobe of the lung). **Only one out of 31 patients with one or more poor prognostic factors came into remission.** In contrast, nine out of 15 patients without poor prognostic factors showed objective tumour regression (60% remission rate). Stage and age did not affect the results. Haemotologic and renal toxicity were mild, but poor subjective tolerance (nausea, vomiting, loss of appetite) was prominent

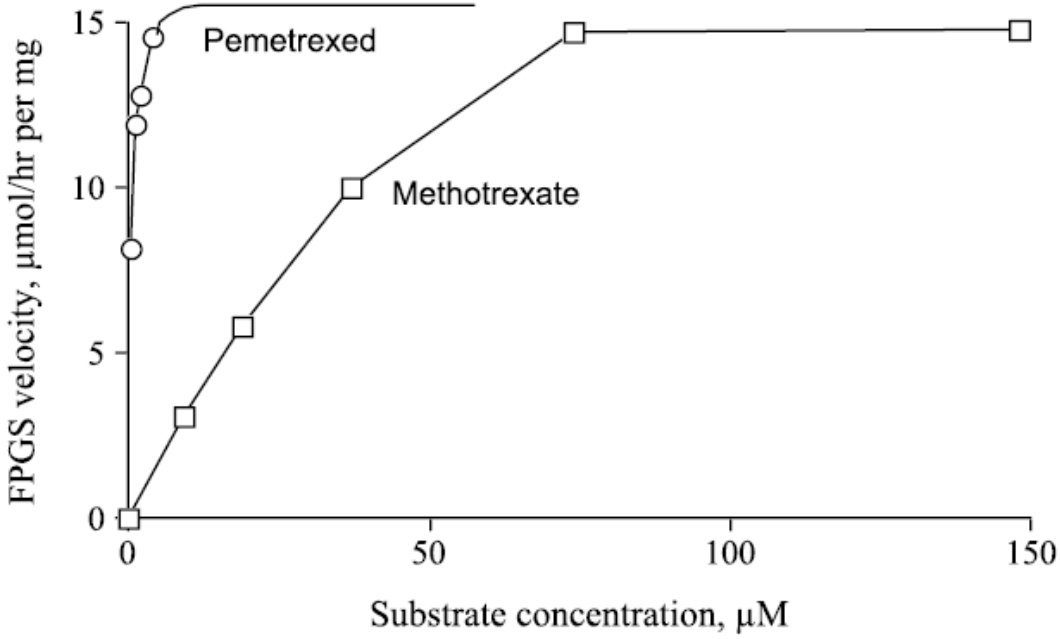
„Zastosowanie paliatywnej CTH u chorych na NDRP w IV stopniu zaawansowania klinicznego jest możliwe przy spełnieniu następujących warunków:
— bardzo dobry lub dobry stan sprawności (0 lub 1 w skali Zubroda-WHO lub przynajmniej 70 w skali Karnofsky'ego);
— prawidłowa masa ciała lub jej ubytek nie większy niż 10% w ciągu 3 miesięcy przed rozpoczęciem leczenia;
— brak poważnych chorób współwystępujących i/lub następstw przebytego wcześniej leczenia;
— wydolność układu krwiotwórczego, wątroby, nerek oraz układu sercowo-naczyniowego i oddechowego;
— możliwość obiektywnej oceny odpowiedzi na leczenie, przy czym zalecane są kryteria klasyfikacji RECIST (*response evaluation criteria in solid tumours*) w wersji 1.1."

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	**Ambulatory and capable of all selfcare** but unable to carry out any work activities. **Up and about** more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40		
Severly disabled. Hospitalisation indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

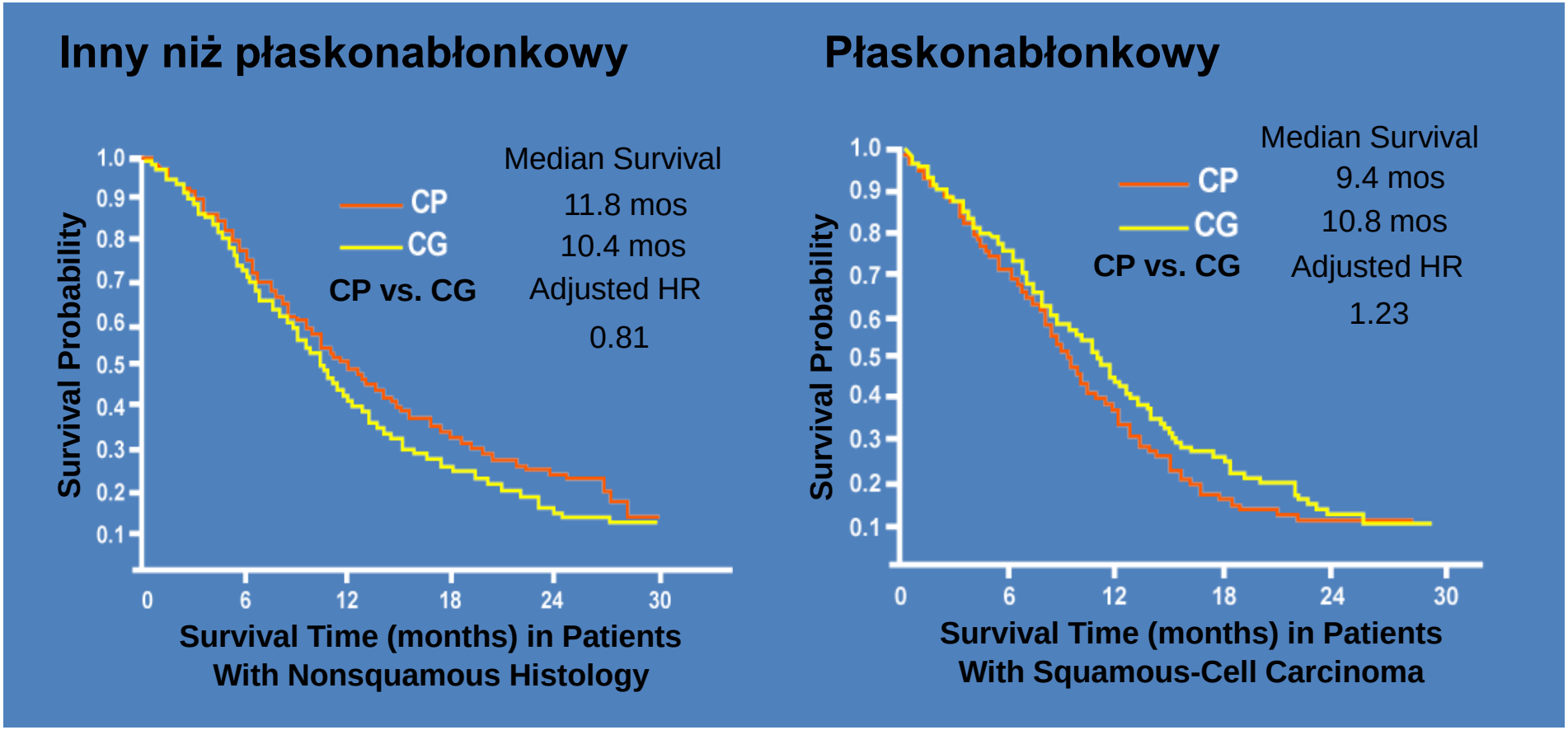

SC+CT (no. events/no. entered)
SC alone (no. events/no. entered)
Hazard Ratio (fixed)
Age
< 60 429/456 368/382
60-64 275/299 267/289
65-69 243/268 253/267
≥ 70 336/365 344/367
Trend P = .64
Sex
Male 997/1,076 933/984
Female 287/313 301/322
Interaction P = .77
Stage
I & II 37/40 27/28
IIIa 86/92 101/106
IIIb 313/337 289/300
IV 477/508 451/466
Trend P = .35
Histology
Adenocarcinoma 302/320 295/300
Squamous cell 567/605 532/554
Other 214/224 194/204
Interaction P = .75
Performance Status
Good 946/1034 904/969
Poor 298/310 279/284
Interaction P = .54
Exploratory Analysis
Performance Status (WHO or Karnofsky)
0 or 100-90 310/347 273/299
1 or 80-70 636/687 631/670
2+ or ≤ 60 298/310 279/284
Trend P = .76
0.0
0.5
1.0
1.5
2.0
SC + CT better
SC alone better

Carboplatin/Paclitaxel	Paclitaxel 225 mg/m2 over 3 hours Carboplatin AUC 6 mg/mL/min	Every 3 weeks	J Clin Oncol 2005; 23:190
	Paclitaxel 100 mg/m2 Carboplatin AUC 2 mg/mL/min	Weekly	Clin Lung Cancer 2006; 7:338
Cisplatin/Etoposide	Cisplatin 100 mg/m2 Etoposide 100 mg/m2 days 1, 2, 3	Every 3 weeks	Ann Oncol 1997; 8:525
Cisplatin/Vinorelbine	Cisplatin 100 mg/m2 day 1 Vinorelbine 25 mg/m2 days 1, 8, 15, 22	Every 4 weeks	J Clin Oncol 1998; 16:2459
Cisplatin/Paclitaxel	Cisplatin 75 mg/m2 Paclitaxel 135 mg/m2	Every 3 weeks	J Clin Oncol 2000; 18:623
Cisplatin/Docetaxel	Cisplatin 75 mg/m2 Docetaxel 75 mg/m2	Every 3 weeks	J Clin Oncol 2003; 21:3016
Carboplatin/Docetaxel	Carboplatin AUC 6 mg/mL/min Docetaxel 75 mg/m2	Every 3 weeks	J Clin Oncol 2003; 21:3016
Cisplatin/Gemcitabine	Cisplatin 100 mg/m2 day 1 Gemcitabine 1000 mg/m2 days 1, 8, 15	Every 4 weeks	J Clin Oncol 2000; 18:122
Cisplatin/Pemetrexed	Cisplatin 75 mg/m2 day 1 Pemetrexed 500 mg/m2 day 1	Every 3 weeks	Scagliotti, G. J Clin Oncol 2008
Carboplatin/Gemcitabine	Carboplatin AUC 5 mg/mL/min Gemcitabine 1200 mg/m2 days 1, 8	Every 3 weeks	Lung Cancer 2003; 41:321
Cisplatin/Irinotecan	Cisplatin 80 mg/m2 day 1 Irinotecan 60 mg/m2 days 1, 8, 15	Every 4 weeks	Proc Am Soc Clin Oncol 2004; 22:618s
Carboplatin/Paclitaxel/Bevacizumab	Carboplatin AUC 6 mg/mL/min day 1 Paclitaxel 200 mg/m2 day 1 Bevacizumab 15 mg/kg day 1	Every 3 weeks*	N Engl J Med 2006; 355:2542
Carboplatin/Pemetrexed	Carboplatin AUC 5 mg/mL/min day 1 Pemetrexed 500 mg/m2 day 1	Every 3 weeks	J Clin Oncol 2007; 25:388s
Carboplatin/Vinorelbine	Carboplatin AUC 4 day 1 Vinorelbine 25 mg/m2 day 1	Every 3 weeks	Br J Cancer 2007; 97:283


Deoxyuridine
dUMP
dTMP
dTDP
dTTP
Thymidylate synthase
Folic acid
DHFR
NADPH+H+
NADP+
DHF
Folinic acid
5,10-CH2THF
SHMT1
THF
MTHFR
5-methyl THF
DNA synthesis and repair


Pemetrexed
Methotrexate
FPGS velocity, µmol/hr per mg
Substrate concentration, µM
0
5
10
15
0
50
100
150

cisplatyna/pemetreksed vs. cisplatyna/gemcytabina



Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26(21):3543-3551.

Podsumowanie cz. 2

- Chorzy w stanie sprawności PS0, PS1 i PS2 zdolni do samoobsługi są kandydatami do chemioterapii
- Pemetreksed + cisplatyna jako optymalna opcja dla chorych na raka gruczołowego (PT)
- Cisplatyna+winorelbina, cisplatyna+gemcytabina jako racjonalne opcje terapii 1 rzutu u innych chorych
- Karboplatyna + paklitaksel jako opcja dla chorych z przeciwwskazaniami do terapii cisplatyną
- Chemioterapia bez pochodnych platyny, w tym doustna, jako opcja dla pozostałych chorych

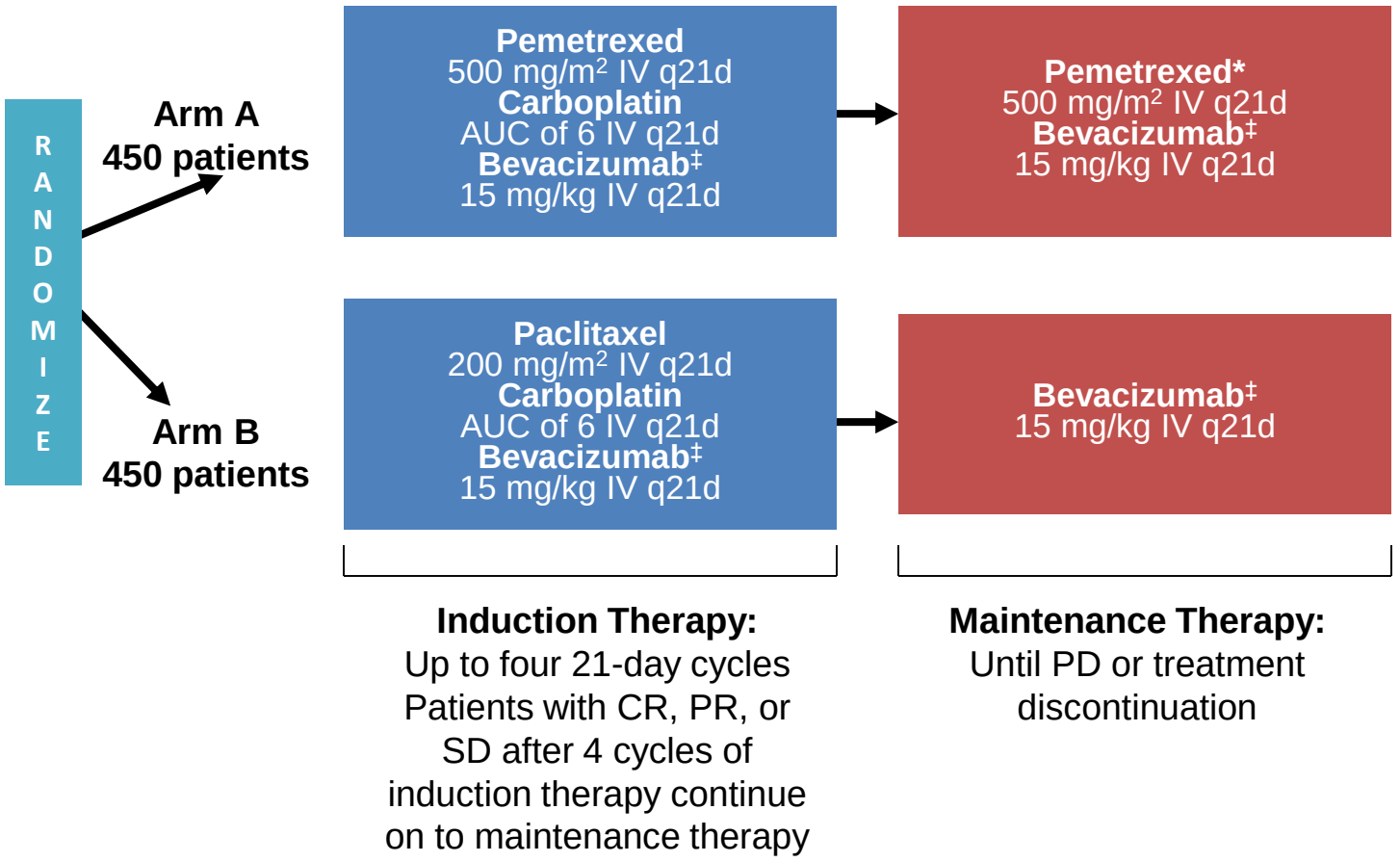
- Oligometastatyczny rozsiew raka płuca (pojedyncza zmiana w nadnerczu, pojedyncza zmiana w mózgowiu)
  – rozważyć terapiię z założeniem radykalnym

PointBreak: badanie III fazy

Inclusion Criteria:
Stage IIIB/IV NSCLC
ECOG PS 0-1
No prior systemic Rx for lung cancer

Exclusion Criteria:
Peripheral neuropathy ≥ grade 1
Uncontrolled pleural effusions

*Investigational



Induction Therapy:
Up to four 21-day cycles
Patients with CR, PR, or SD after 4 cycles of induction therapy continue on to maintenance therapy

Maintenance Therapy:
Until PD or treatment discontinuation

Reprinted with permission from Patel JD, Bonomi P, Socinski MA, et al. Treatment rationale and study design for the pointbreak study: a randomized, open-label phase III study of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *Clin Lung Cancer.* 2009;10(4):252-256.

ECOG-E5508: badanie fazy III

Eligibility

- Stage IIIB/IV nonsquamous NSCLC
- No brain metastases
- Stable or better response after 4 courses of carbo, paclitaxel and bev

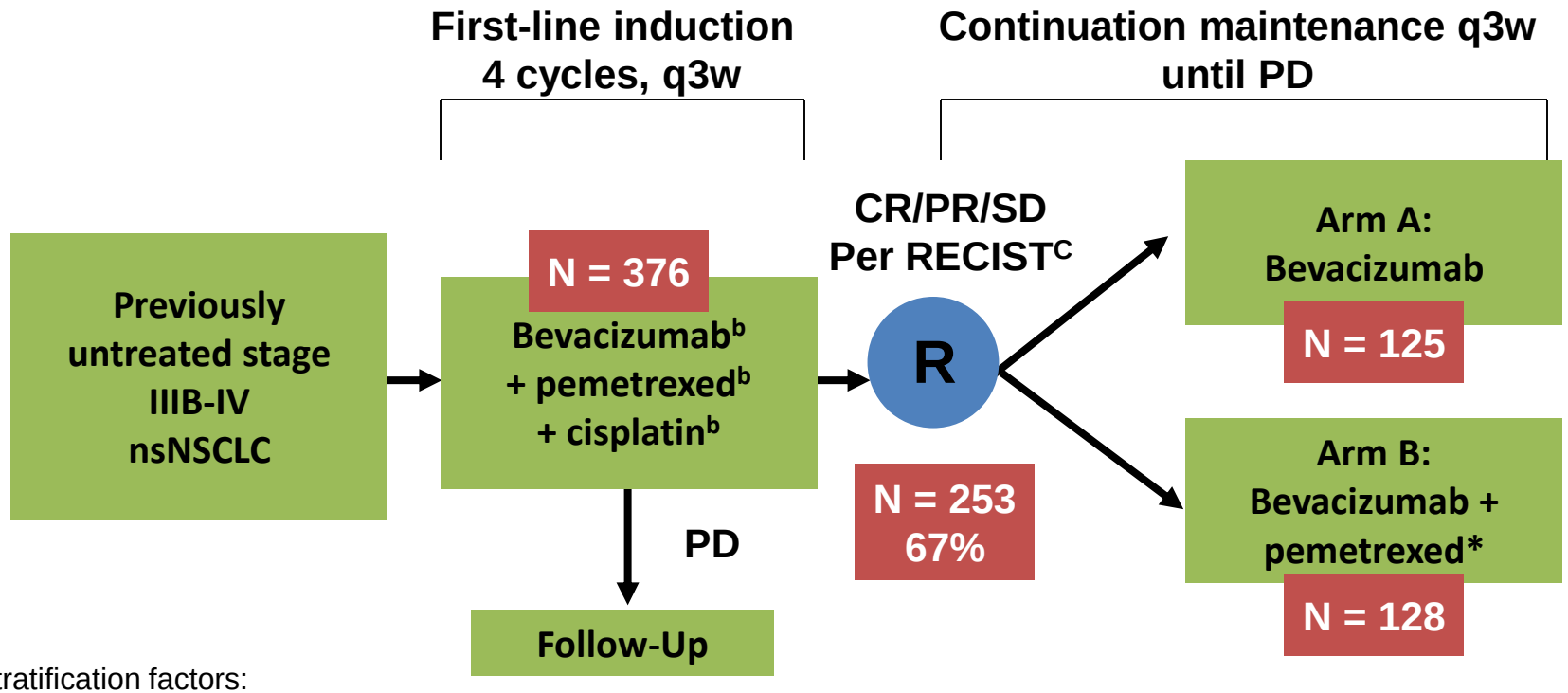
R

Bevacizumab

Pemetrexed

Bevacizumab + Pemetrexed

AVAPERL



Stratification factors:
- Gender
- Smoking status
- Response at randomization

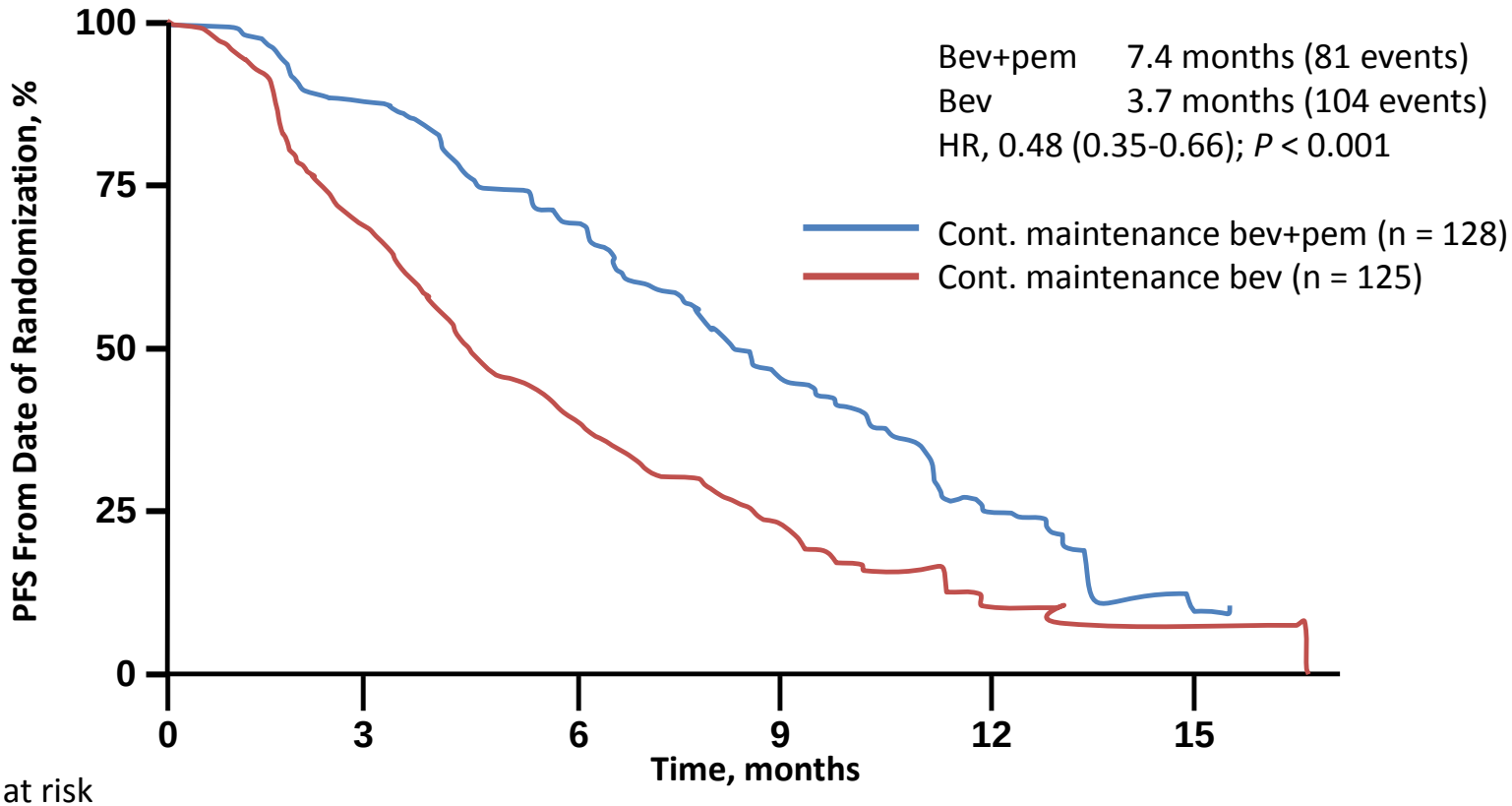
Primary objective: PFS
Secondary objectives: OS, response rate, DCR, duration of response, duration disease control, safety, QOL

[a]Randomized open-label phase 3 study
[b]Dose of bevacizumab = 7.5 mg/kg; dose of pemetrexed = 500 mg/m^2; dose of cisplatin = 75 mg/m^2.
RECIST-related end points measured from the preinduction phase

*Investigational

Barlesi F, et al. ESMO 2011.[Abstract 34LBA].
Slide courtesy of F Barlesi.

AVAPERL: PFS



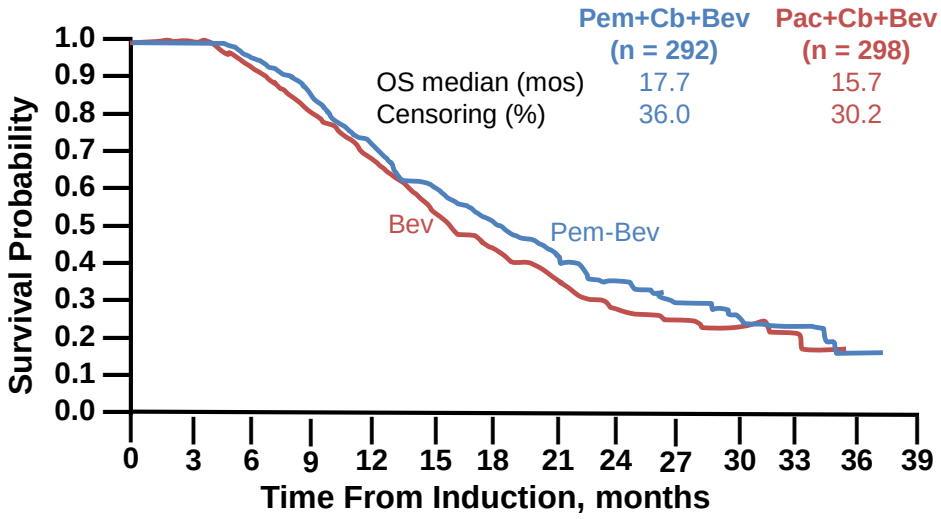
Patients at risk						
Bev+pem	128	104	67	25	4	0
Bev	125	73	36	13	2	0

Median follow-up time in ITT population (excluding induction): 8.28 months (bev+pem arm), 7.95 months (bev arm)

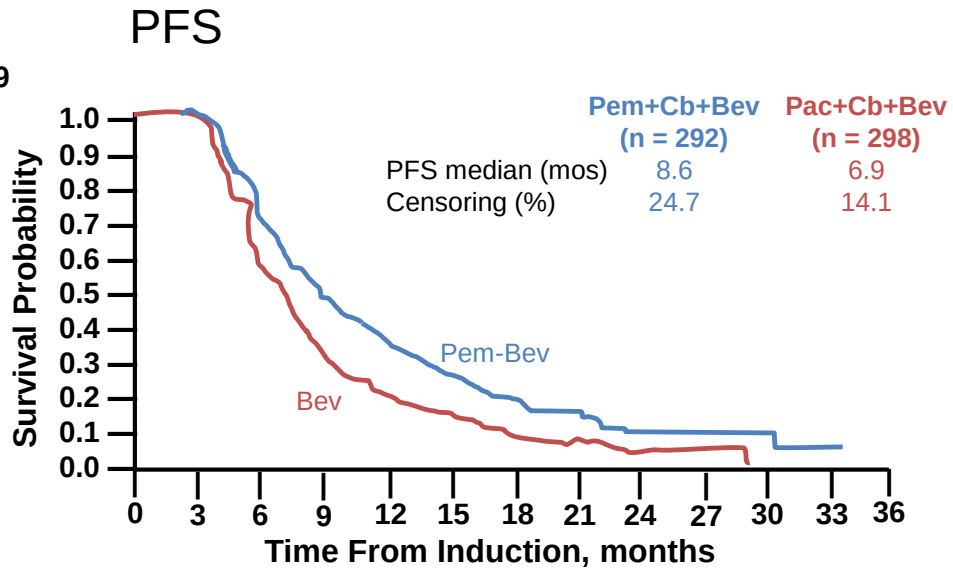
Barlesi F, et al. ESMO 2011.[Abstract 34LBA].
Slide courtesy of F Barlesi.

PointBreak: grupa terapii podtrzymującej

OS



PFS



Prespecified exploratory non-comparative subgroup analyses