Таргетная терапия немелкоклеточного рака лёгких

Трушин Александр Юрьевич

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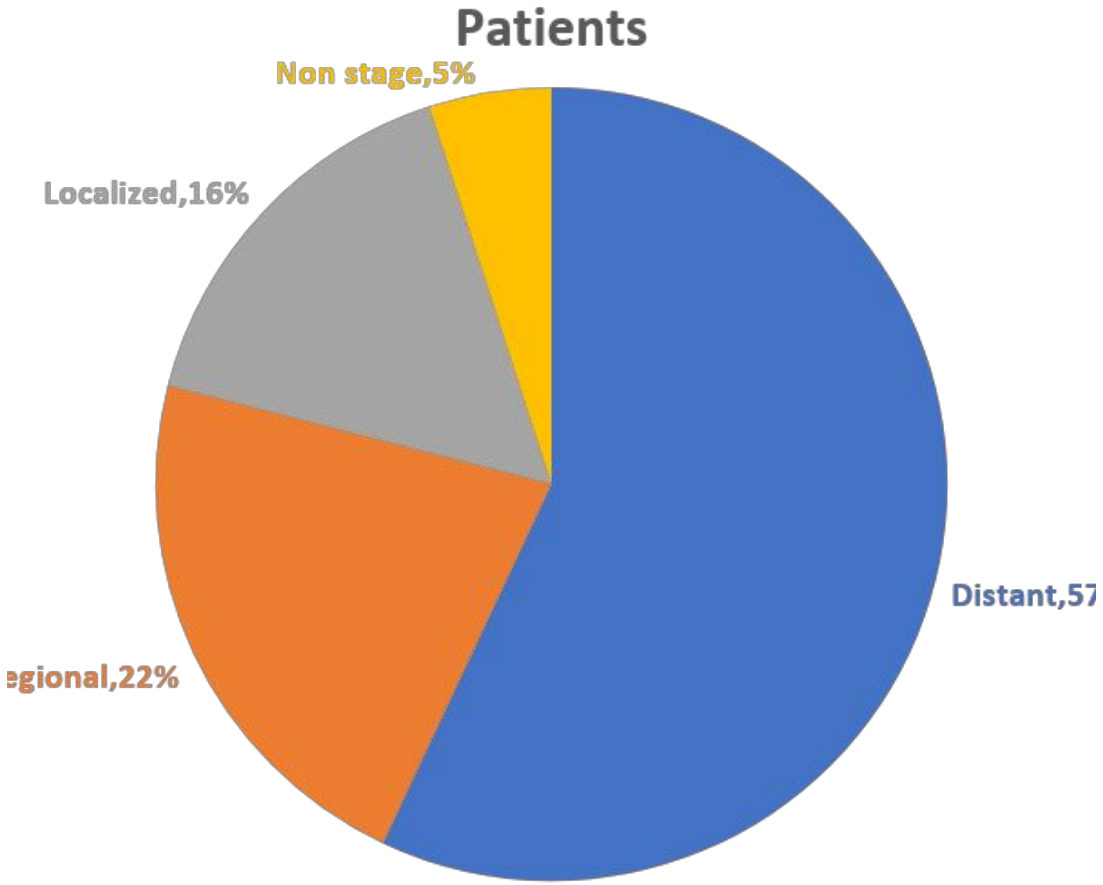
НМРЛ — одно из наиболее распространённых онкологических заболеваний, для которого характерен высокий уровень смертности



Estimated New Cases

			Males	Females			
Prostate	161,360	19%			Breast	252,710	30%
Lung & bronchus	116,990	14%			Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%			Colon & rectum	64,010	8%
Urinary bladder	60,490	7%			Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%			Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%			Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%			Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%			Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%			Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%			Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**			**All Sites**	**852,630**	**100%**

Estimated Deaths

			Males	Females			
Lung & bronchus	84,590	27%			Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%			Breast	40,610	14%
Prostate	26,730	8%			Colon & rectum	23,110	8%
Pancreas	22,300	7%			Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%			Ovary	14,080	5%
Leukemia	14,300	4%			Uterine corpus	10,920	4%
Esophagus	12,720	4%			Leukemia	10,200	4%
Urinary bladder	12,240	4%			Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%			Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%			Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**			**All Sites**	**282,500**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017.
Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Cancer Statistics 2017;

Rebecca L. Siegel, MPH; Kimberly D. Miller, MPH; Ahmedin Jemal, DVM, PhD

CA Cancer J Clin 2017;67:7–30. doi: 10.3322/caac.21387

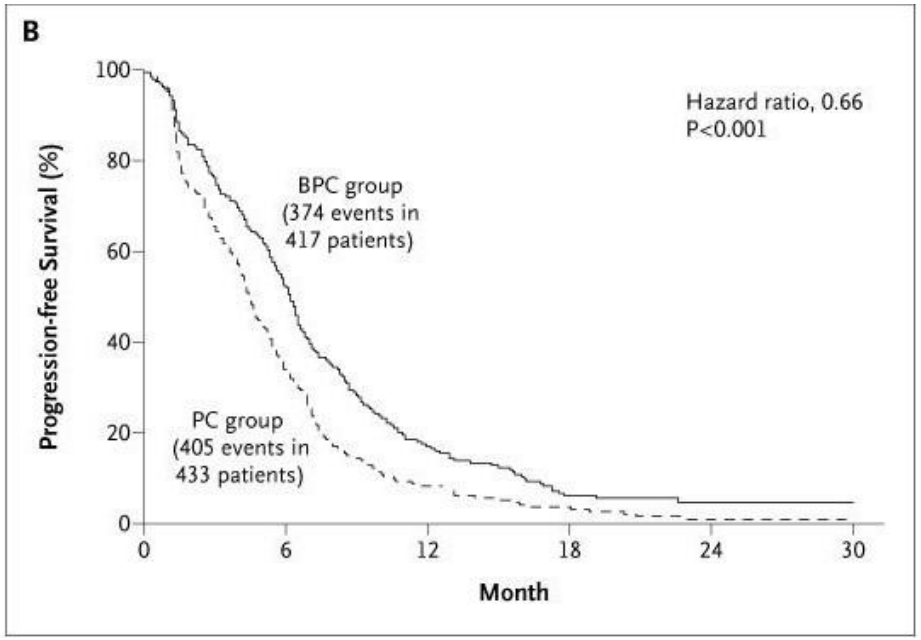
ORIGINAL ARTICLE

Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer

Alan Sandler, M.D., Robert Gray, Ph.D., Michael C. Perry, M.D., Julie Brahmer, M.D., Joan H. Schiller, M.D., Afshin Dowlati, M.D., Rogerio Lilenbaum, M.D., and David H. Johnson, M.D.

Группа	ЧОО %	Медиана ВБП (мес.)	Медиана ОВ (мес.)
Паклитаксел + Карбоплатин	15	4.5	10.3
Паклитаксел + Карбоплатин + Бевацизумаб	35	6.2	12.3

2006



New Engl J Med 2006; 355:2542-2550
DOI: 10.1056/NEJMoa061884

Таргетная терапия

https://www.celgene.com/getting-personal/aml-targeted-therapy/

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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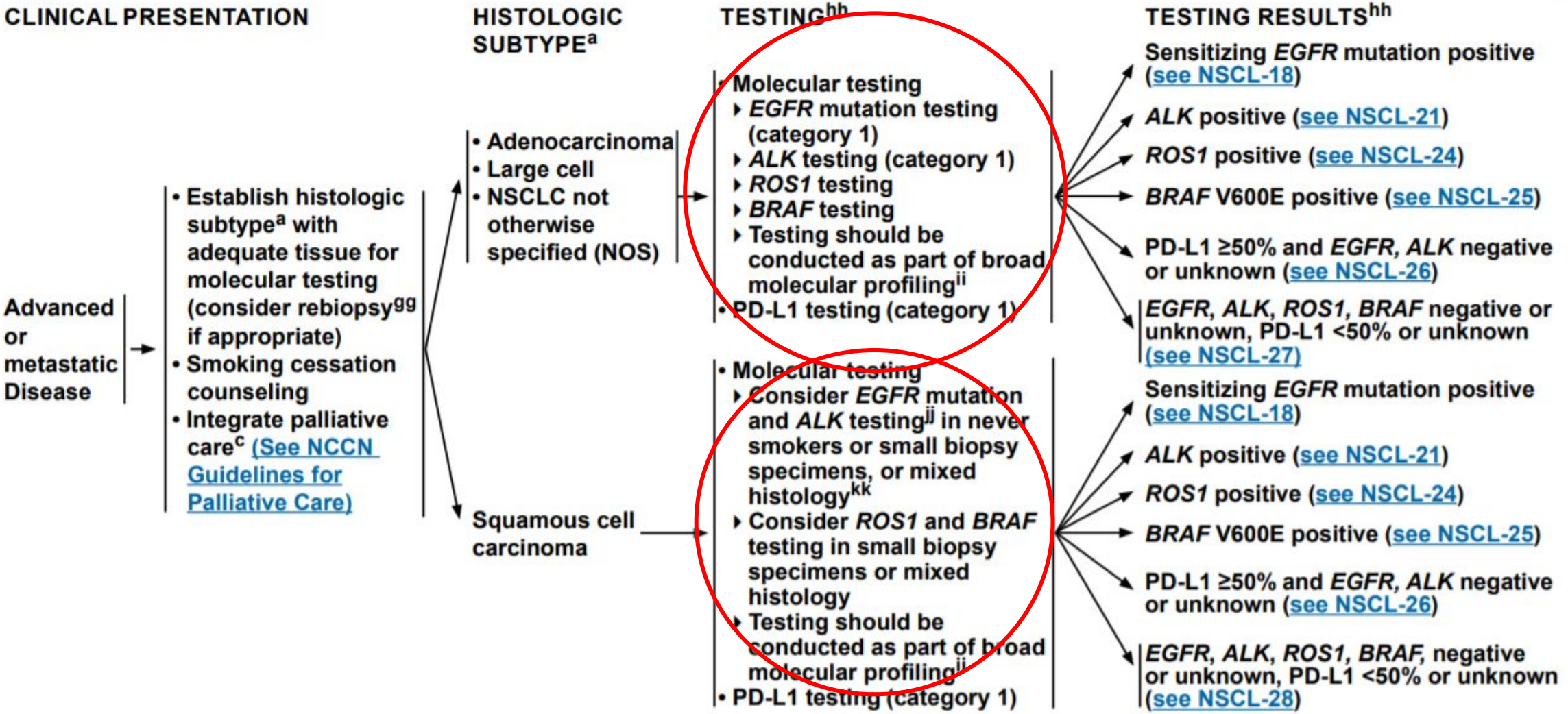
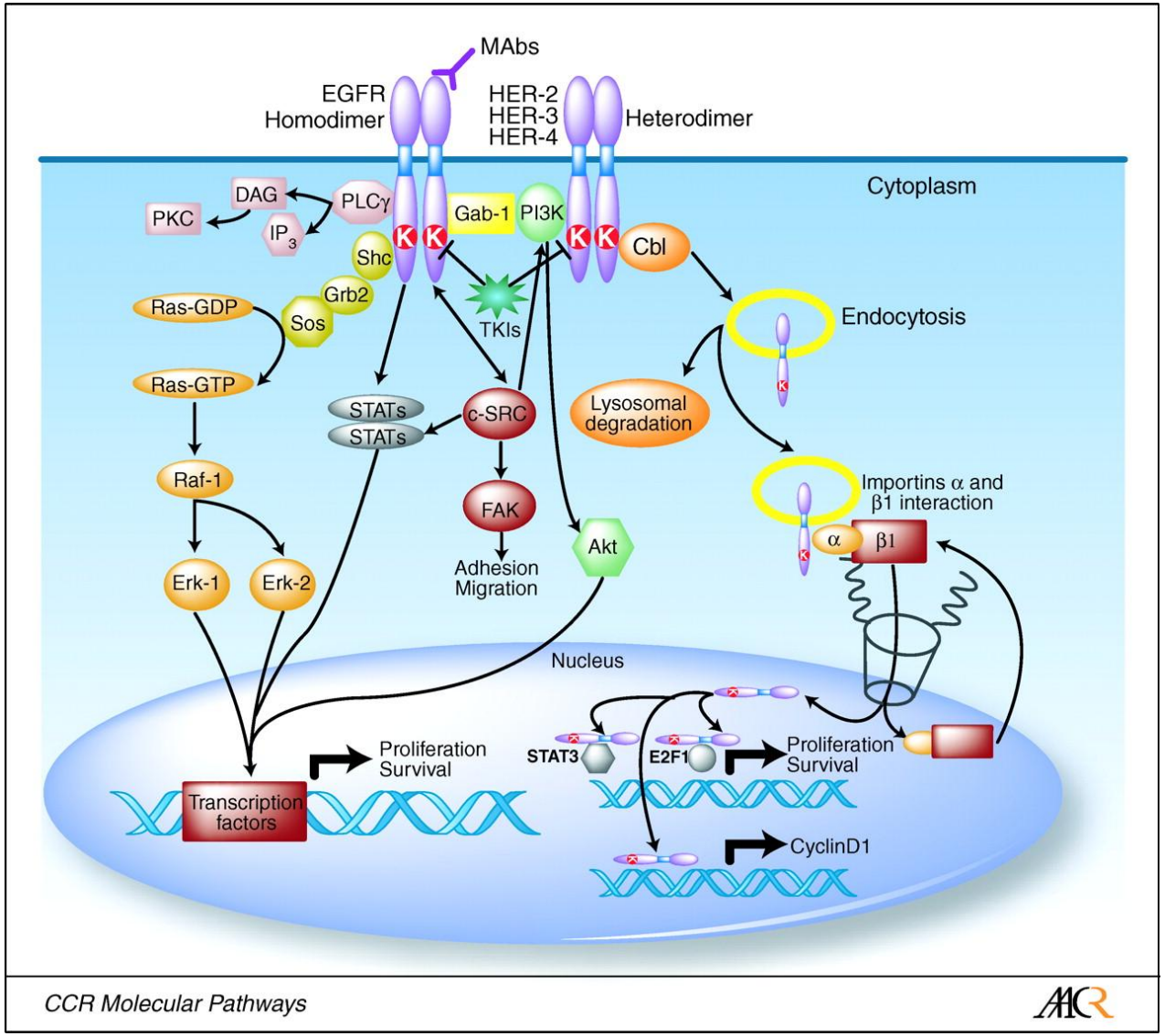
Discussion



Семейство ErbB

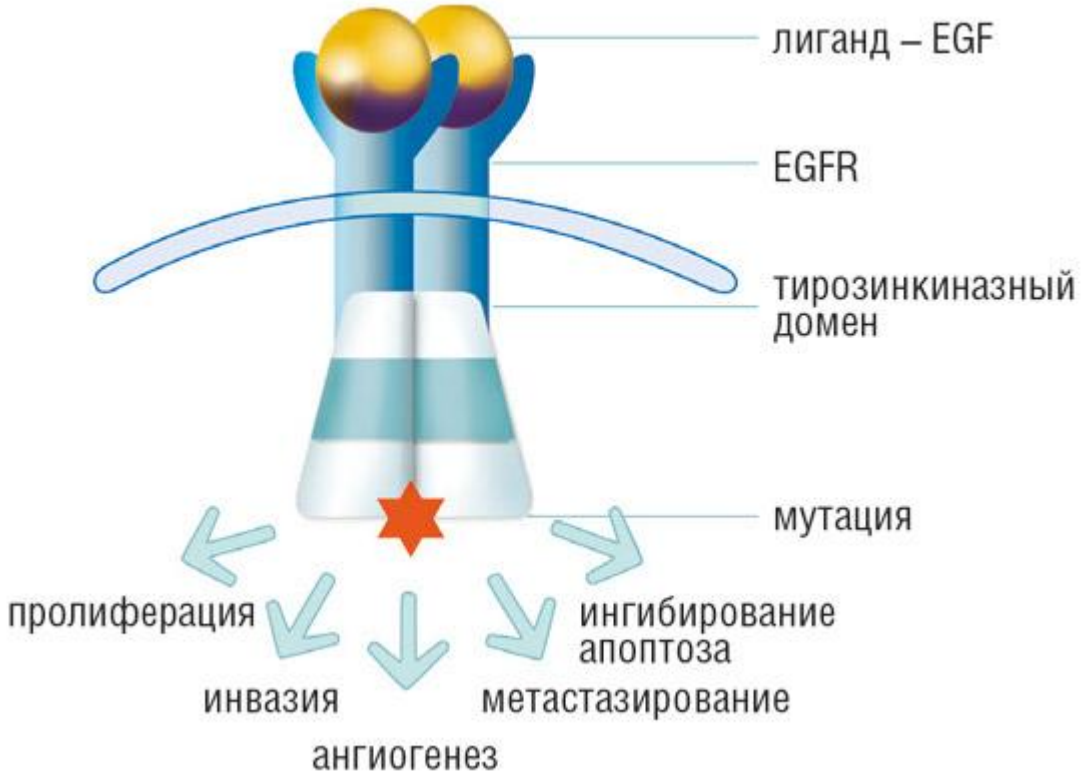
- EGFR (ErbB-1)
- HER2 / neu (ErbB-2)
- Her 3 (ErbB-3)
- Her 4 (ErbB-4)



- Wieduwilt MJ, Moasser MM. The epidermal growth factor receptor family: biology driving targeted therapeutics. Cell Mol Life Sci. 2008;65(10):1566-84
- Hongtao Zhang, … , Ramachandran Murali, Mark I. Greene. ErbB receptors: from oncogenes to targeted cancer therapies Published August 1, 2007 Citation Information: J Clin Invest. 2007;117(8):2051-2058. https://doi.org/10.1172/JCI32278

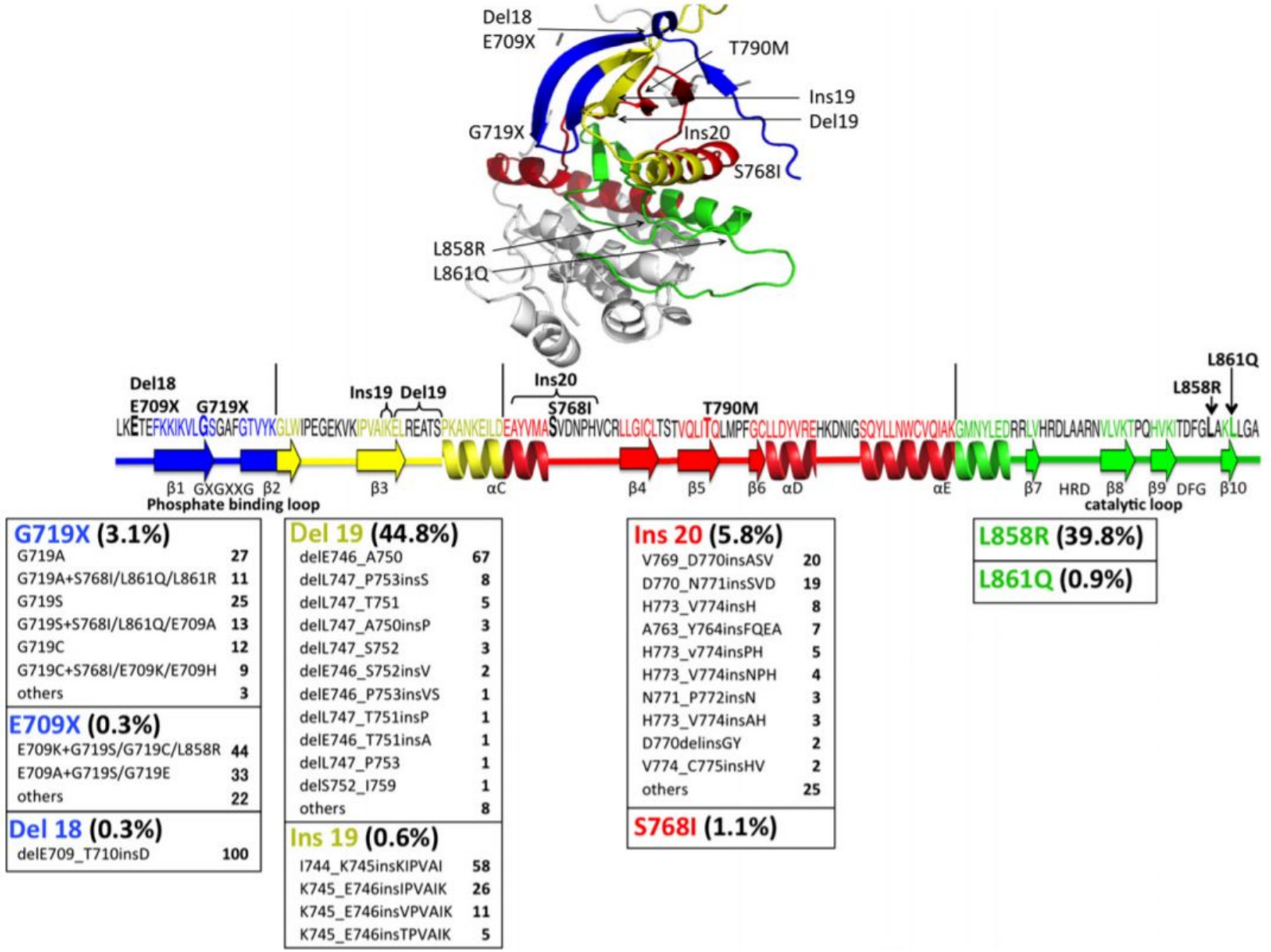
Рецептор эпидермального фактора роста (EGFR)

- EGFR – трансмембранный белок
- Мутация
- Неконтролируемая активация EGFR внутри клетки запускается каскад биохимических реакций, приводящих к повышению пролиферации опухолевых клеток, росту опухоли, стимуляции процессов инвазии, патологического ангиогенеза и метастазирования.



- Wadhwa R, Yaguchi M, Matsui MS. The epidermal growth factor receptor family: biology driving targeted therapeutics. Cell Mol Life Sci. 2008;65(10):1566-84
- http://www.cancergenome.ru/mutations/EGFR/

EGFR ген



G719X (3.1%)	
G719A	27
G719A+S768I/L861Q/L861R	11
G719S	25
G719S+S768I/L861Q/E709A	13
G719C	12
G719C+S768I/E709K/E709H	9
others	3

E709X (0.3%)	
E709K+G719S/G719C/L858R	44
E709A+G719S/G719E	33
others	22

Del 18 (0.3%)	
delE709_T710insD	100

Del 19 (44.8%)	
delE746_A750	67
delL747_P753insS	8
delL747_T751	5
delL747_A750insP	3
delL747_S752	3
delE746_S752insV	2
delE746_P753insVS	1
delL747_T751insP	1
delE746_T751insA	1
delL747_P753	1
delS752_I759	1
others	8

Ins 19 (0.6%)	
I744_K745insKIPVAI	58
K745_E746insIPVAIK	26
K745_E746insVPVAIK	11
K745_E746insTPVAIK	5

Ins 20 (5.8%)	
V769_D770insASV	20
D770_N771insSVD	19
H773_V774insH	8
A763_Y764insFQEA	7
H773_v774insPH	5
H773_V774insNPH	4
N771_P772insN	3
H773_V774insAH	3
D770delinsGY	2
V774_C775insHV	2
others	25

S768I (1.1%)

L858R (39.8%)
L861Q (0.9%)

Kobayashi, Y., & Mitsudomi, T. (2016). Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. Cancer Science, 107(9), 1179–1186. doi:10.1111/cas.12996

VOLUME 29 · NUMBER 21 · JULY 20 2011

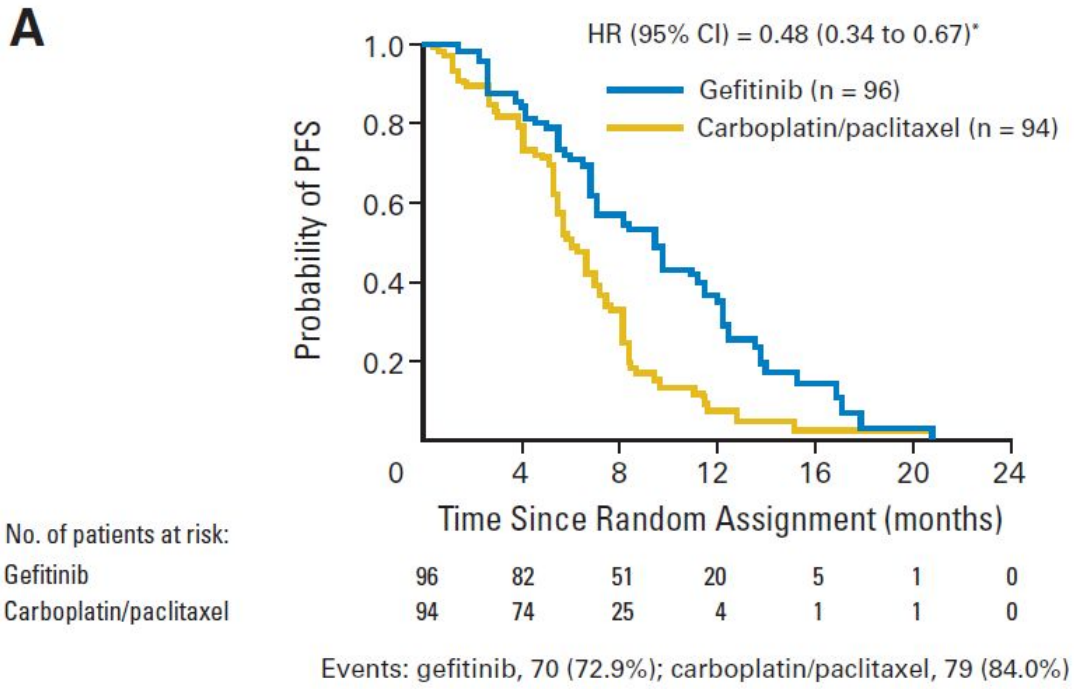
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

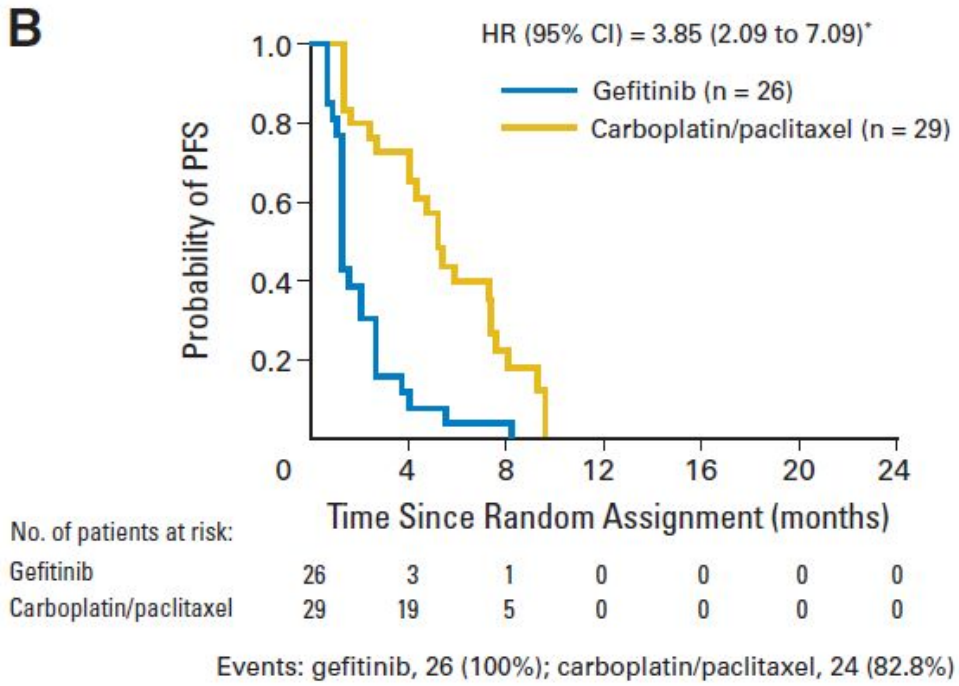
Biomarker Analyses and Final Overall Survival Results From a Phase III, Randomized, Open-Label, First-Line Study of Gefitinib Versus Carboplatin/Paclitaxel in Clinically Selected Patients With Advanced Non–Small-Cell Lung Cancer in Asia (IPASS)

Masahiro Fukuoka, Yi-Long Wu, Sumitra Thongprasert, Patrapim Sunpaweravong, Swan-Swan Leong, Virote Sriuranpong, Tsu-Yi Chao, Kazuhiko Nakagawa, Da-Tong Chu, Nagahiro Saijo, Emma L. Duffield, Yuri Rukazenkov, Georgina Speake, Haiyi Jiang, Alison A. Armour, Ka-Fai To, James Chih-Hsin Yang, and Tony S.K. Mok

EGFR позитивные



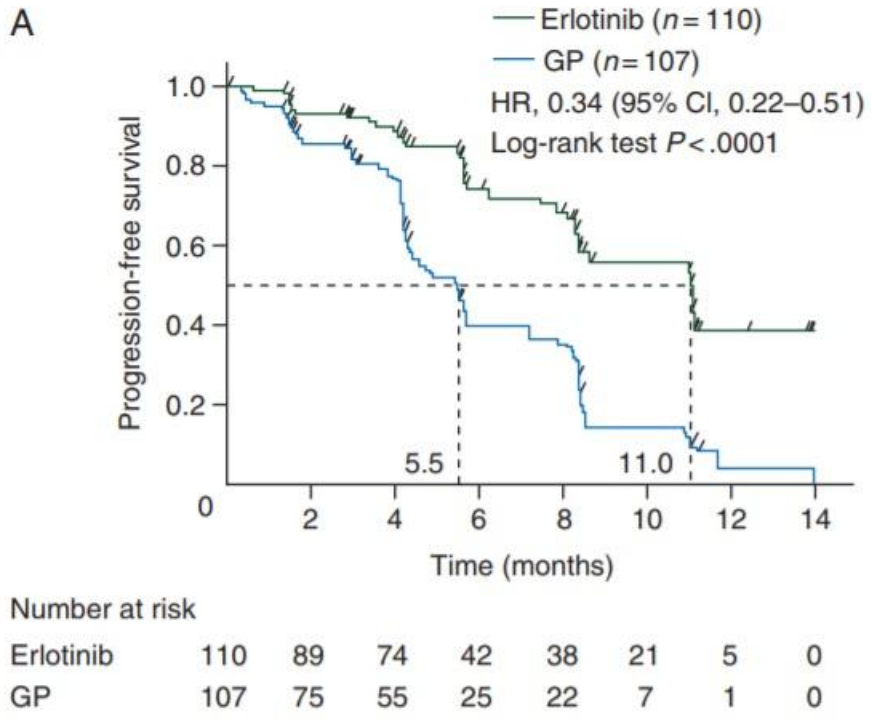
EGFR негативные



First-line erlotinib versus gemcitabine/cisplatin in patients with advanced *EGFR* mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study†

Y.-L. Wu[1*], C. Zhou[2], C.-K. Liam[3], G. Wu[4], X. Liu[5], Z. Zhong[6], S. Lu[7], Y. Cheng[8], B. Han[7], L. Chen[9], C. Huang[10], S. Qin[11], Y. Zhu[12], H. Pan[13], H. Liang[14], E. Li[15], G. Jiang[16], S. H. How[17], M. C. L. Fernando[18], Y. Zhang[19], F. Xia[19] & Y. Zuo[19]

ANNALS OF ONCOLOGY

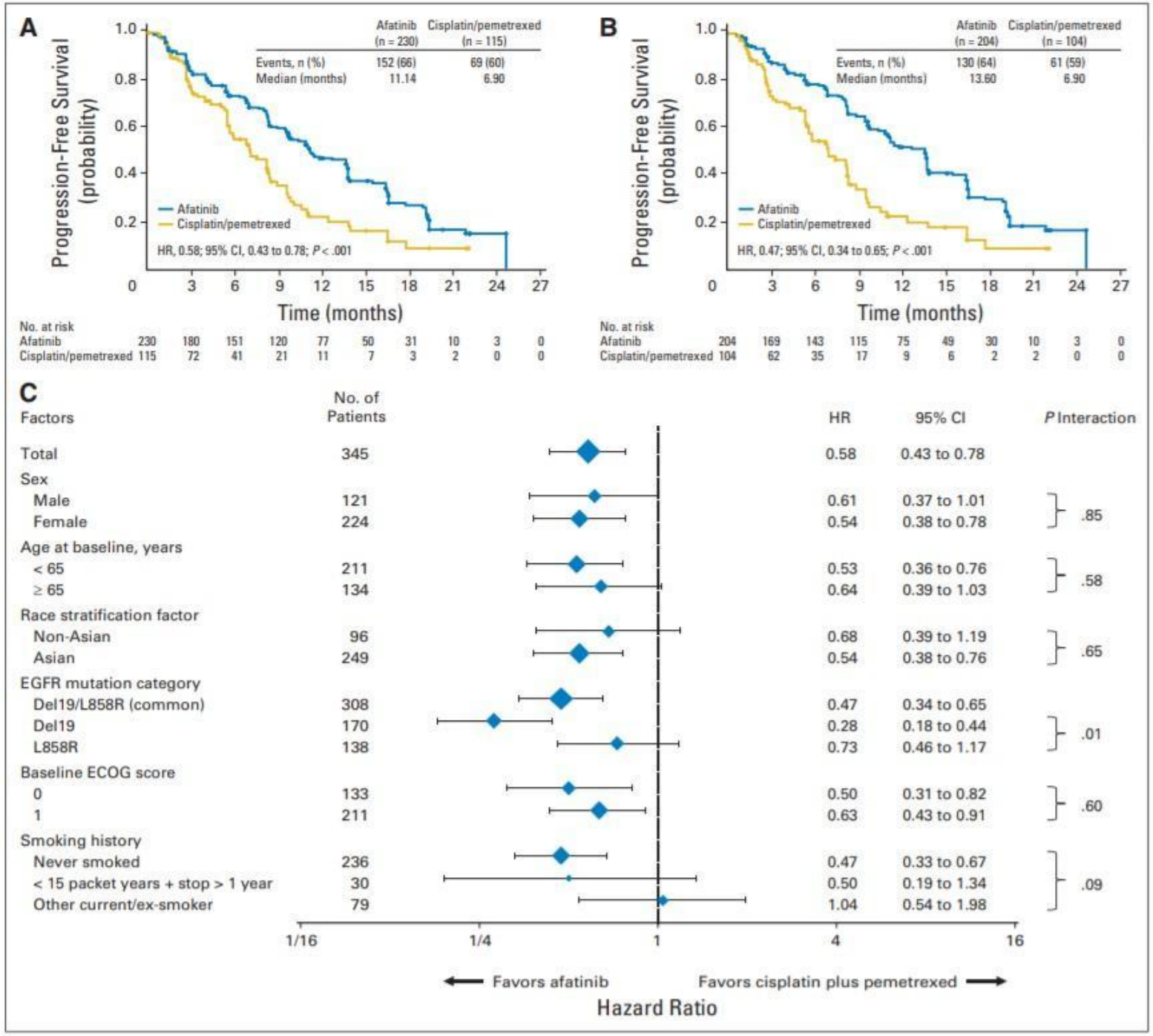


Группы	ЧОО %	Медиана ВБП (мес.)	Медиана ОВ (мес.)	НеЯв. (3-4)
Эрлотиниб	62.7	11.0	26.3	2.7 %
Гемцитабин + цисплатин	33.6	5.5	25.5	10.6%

LUX–lung 3

- ВБП – 11 мес.
  Афатиниб
- ВПБ – 6.9 мес.
  Цисплатин/
  Пеметрексед

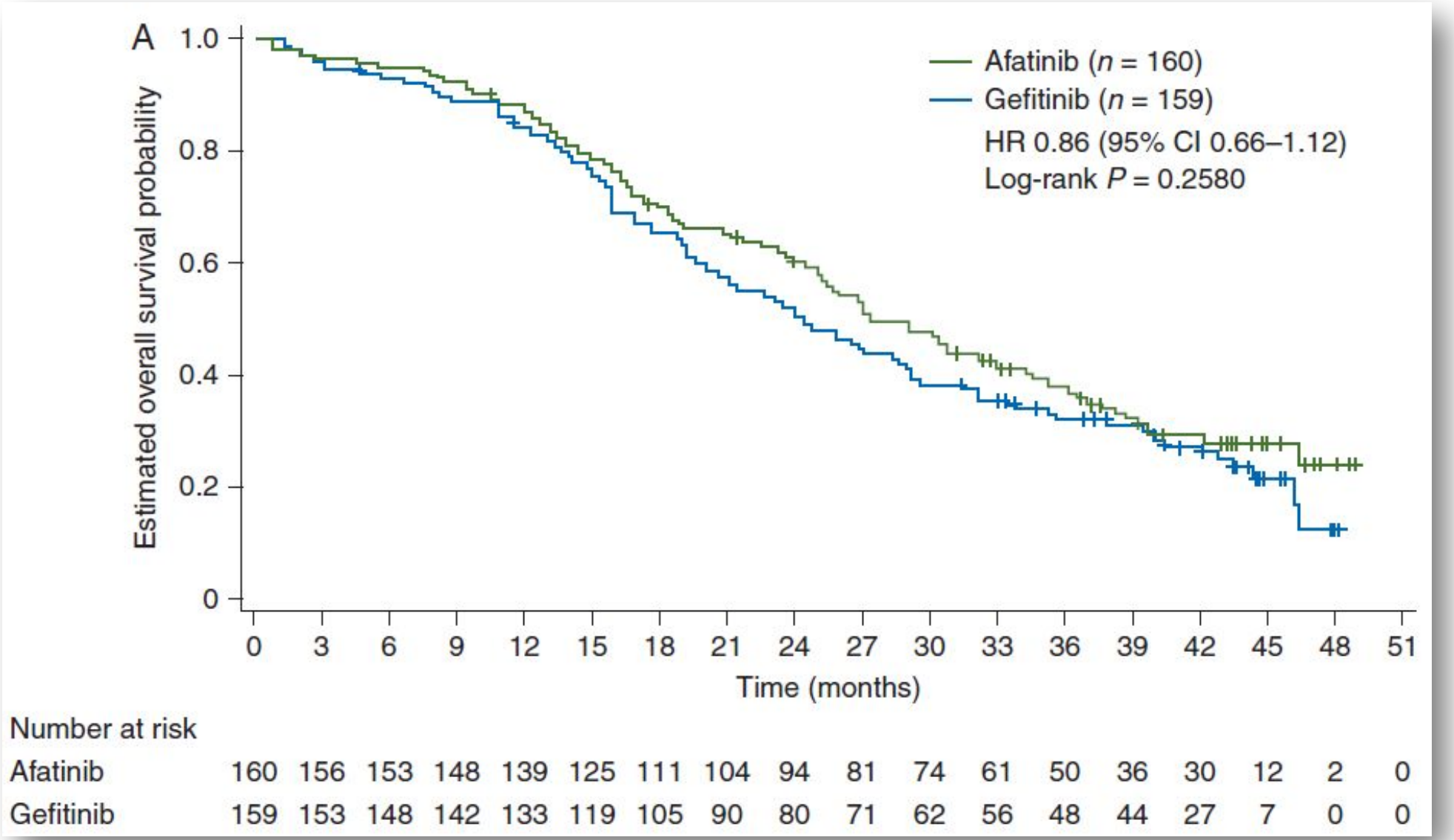
Lecia V. Sequist et al.
DOI:10.1200/JCO.2012.44.2806 Journal of Clinical Oncology 31, no. 27 (September 2013) 3327-3334.



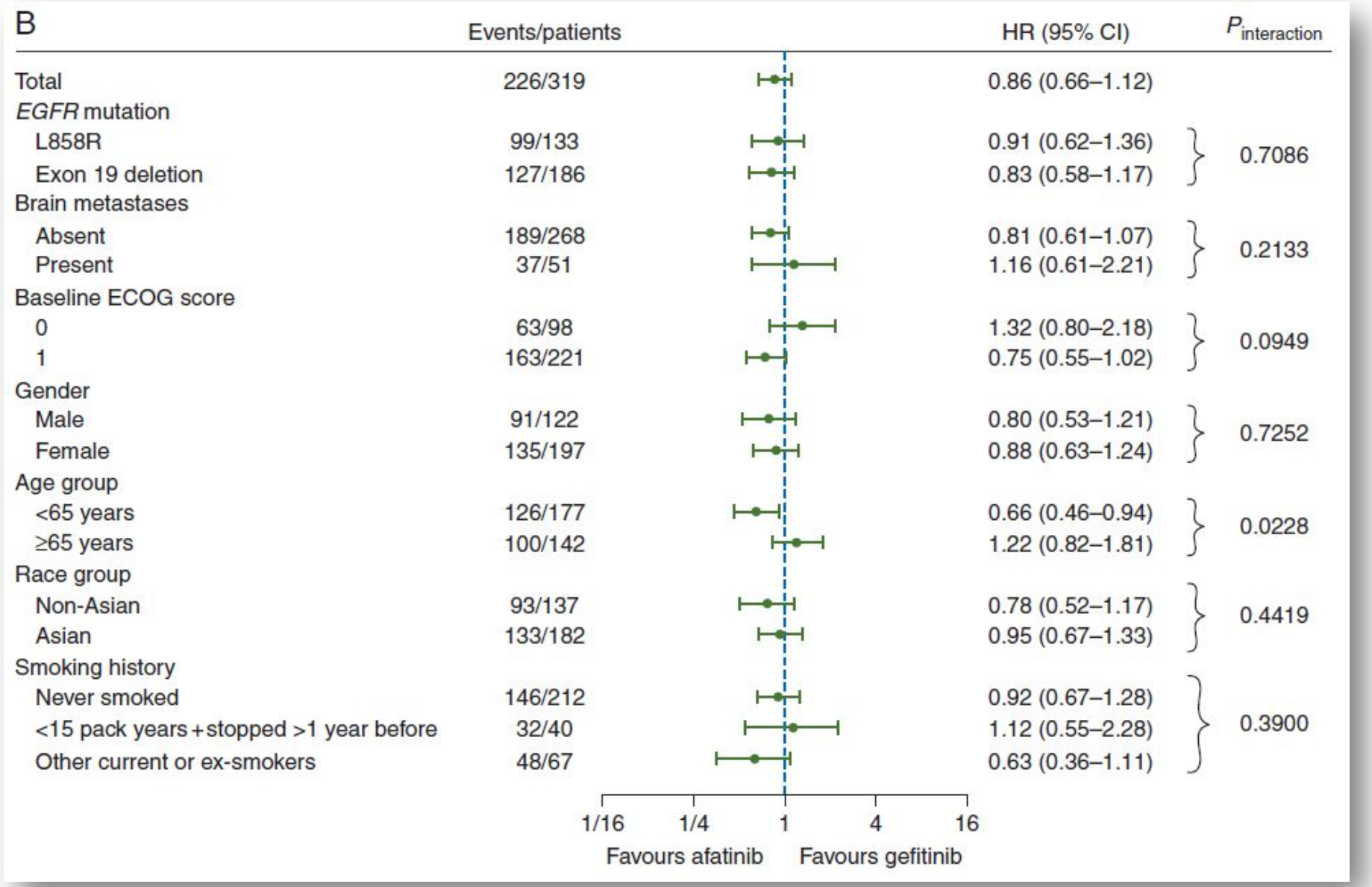
Афатиниб против гефитиниба

Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial

Paz-Ares, L., Tan, E.-H., O'Byrne, K., Zhang, L., Hirsh, V., Boyer, M., … Park, K. (2017). Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Annals of Oncology, 28(2), 270–277. doi:10.1093/annonc/mdw611

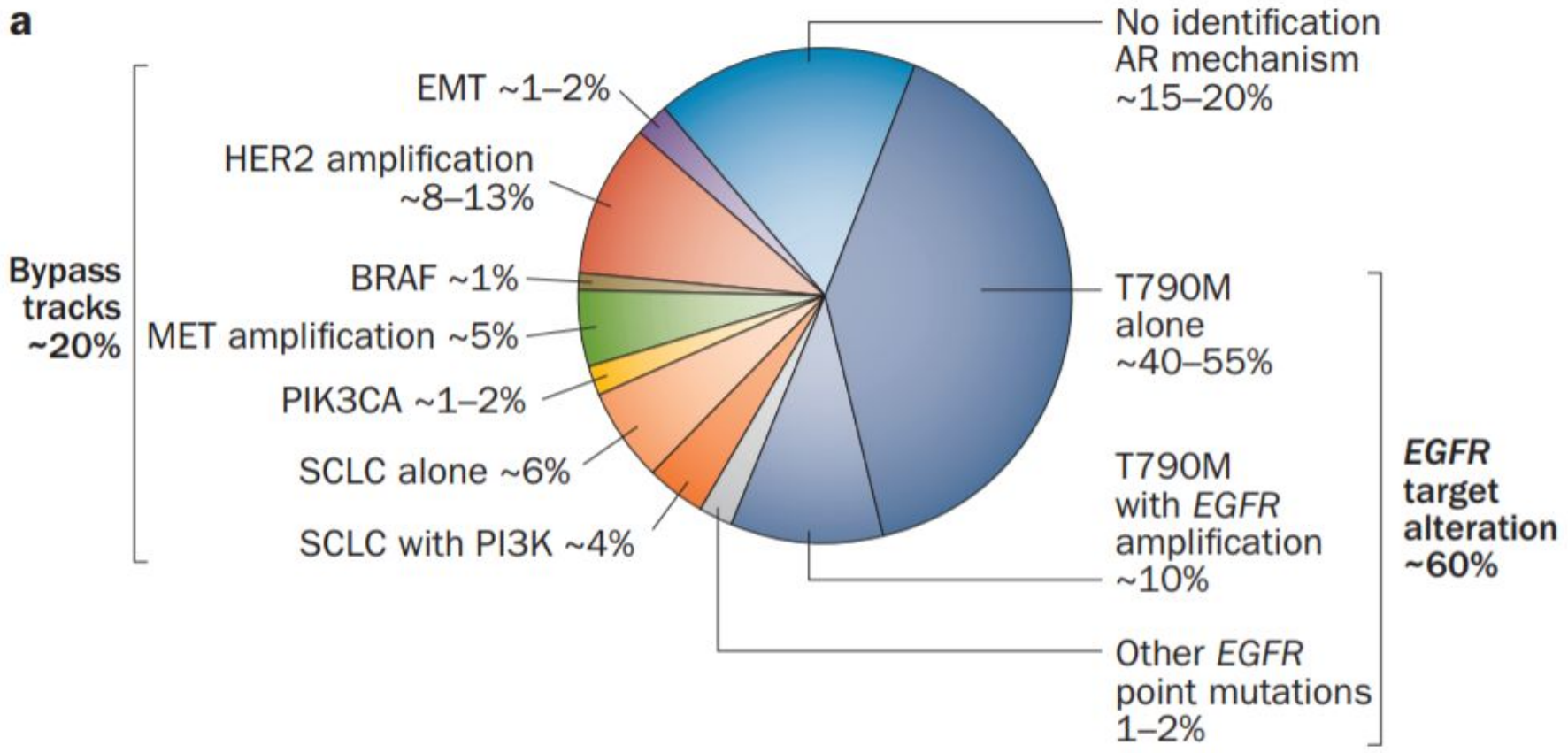


Paz-Ares, L., Tan, E.-H., O'Byrne, K., Zhang, L., Hirsh, V., Boyer, M., … Park, K. (2017). Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Annals of Oncology, 28(2), 270–277. doi:10.1093/annonc/mdw611



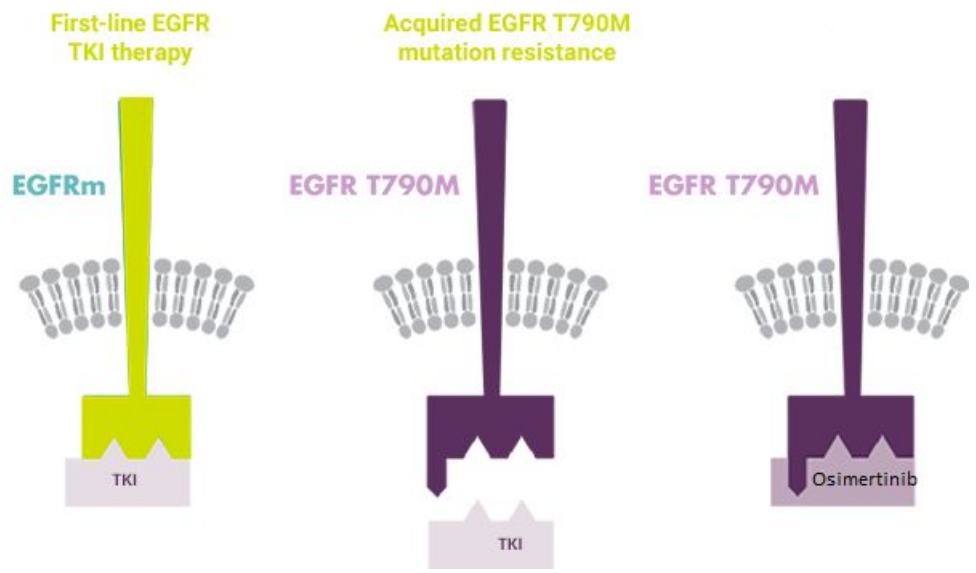
Paz-Ares, L., Tan, E.-H., O'Byrne, K., Zhang, L., Hirsh, V., Boyer, M., … Park, K. (2017). Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Annals of Oncology, 28(2), 270–277. doi:10.1093/annonc/mdw611

Механизмы резистентности



Camidge, D. R., Pao, W., & Sequist, L. V. (2014). Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nature Reviews Clinical Oncology, 11(8), 473–481. doi:10.1038/nrclinonc.2014.104

Мутация T 790 m – около 60 % случаев



- Происходит изменение конфигурации рецептора EGFR
- Ингибиторы тирозинкиназы 1 и 2 поколения не могут взаимодействовать
- Разработан новый препарат – Osimertinib

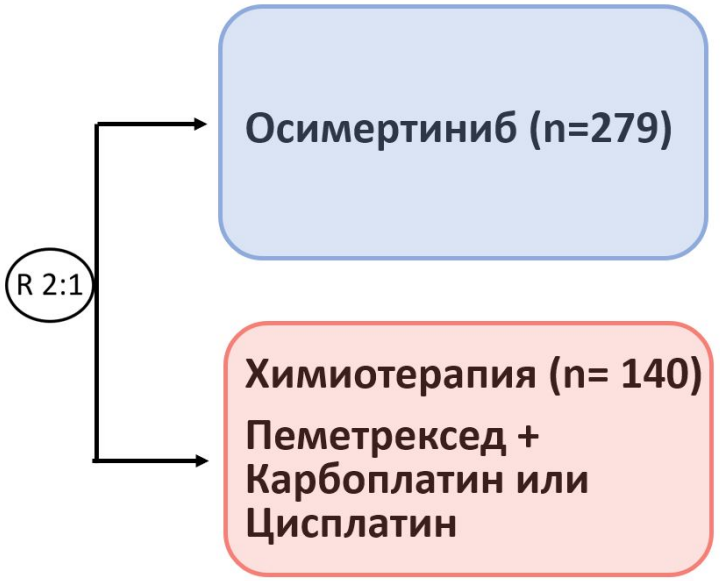
When patients with EGFRm NSCLC have progressed due to the T790M mutation, TAGRISSO offers powerful efficacy and consistent tolerability

Осимертиниб vs Химиотерапия (2 линия)

AURA 3

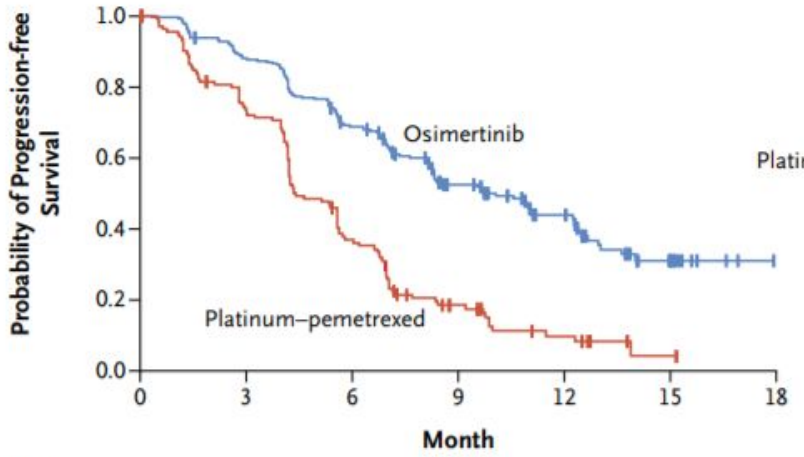
Критерии включения в исследование

- Старше 18 лет
- ECOG 0-1
- Местнораспространённый или метастатический НМРЛ
- Прогрессирование после 1 линии терапии ИТК
- Подтверждена мутация T 790м
- В исследование включались пациенты со стабильными, бессимптомными метастазами в ЦНС



Mok, T. S., Wu, Y.-L., Ahn, M.-J., Garassino, M. C., Kim, H. R., Ramalingam, S. S., … Papadimitrakopoulou, V. A. (2017). Osimertinib or Platinum–Pemetrexed in EGFR T790M–Positive Lung Cancer. New England Journal of Medicine, 376(7), 629–640. doi:10.1056/nejmoa1612674

A Patients in Intention-to-Treat Population

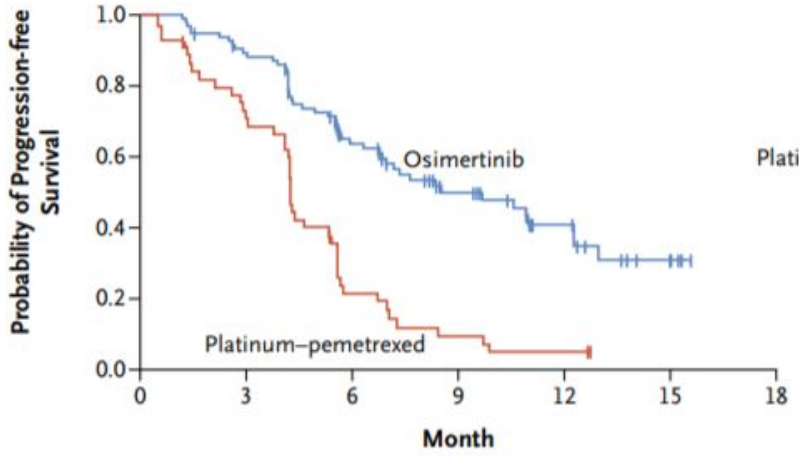


	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

B Patients with CNS Metastases



	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	93	8.5 (6.8–12.3)
Platinum–pemetrexed	51	4.2 (4.1–5.4)

Hazard ratio for disease progression or death, 0.32 (95% CI, 0.21–0.49)

No. at Risk							
Osimertinib	93	80	46	27	14	4	0
Platinum–pemetrexed	51	32	9	4	2	0	0

Осимертиниб во 2-й линии:

- Медиана ВБП – 10.1 мес.
- Медиана ВБП – 8.5 мес. у пациентов с метастазами в ЦНС

- Рандомизированное двойное слепое исследование 3 фазы **FLAURA** (Osimertinib в 1-й линии)
- 556 пациентов
- EGFR + (делеция в 19 экзоне или L858R)
- Местнораспространённый и метастатический НМРЛ
- Рандомизация 1:1
- Первичная конечная точка - PFS

ORIGINAL ARTICLE

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

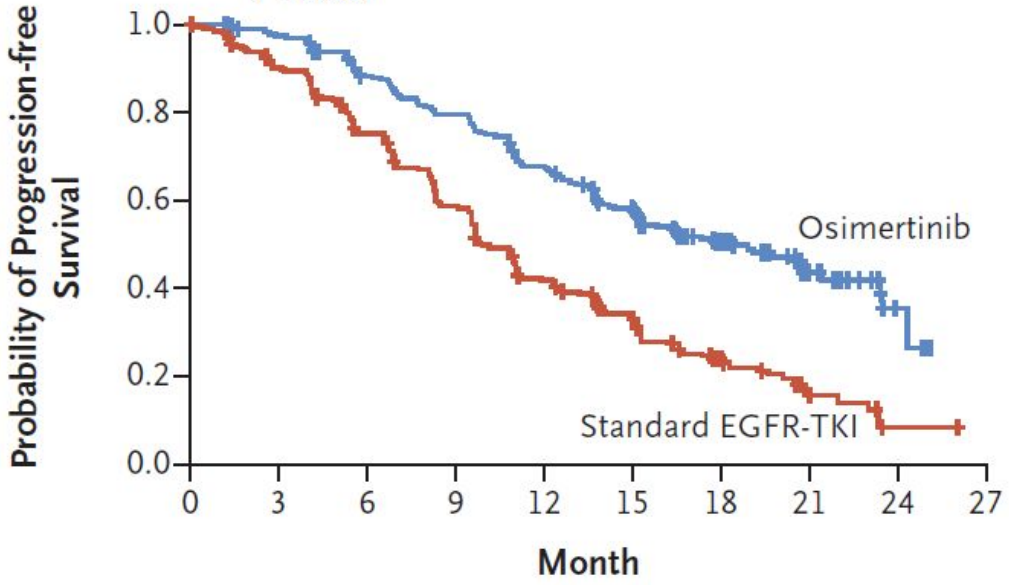
J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

Потрясающие результаты!

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

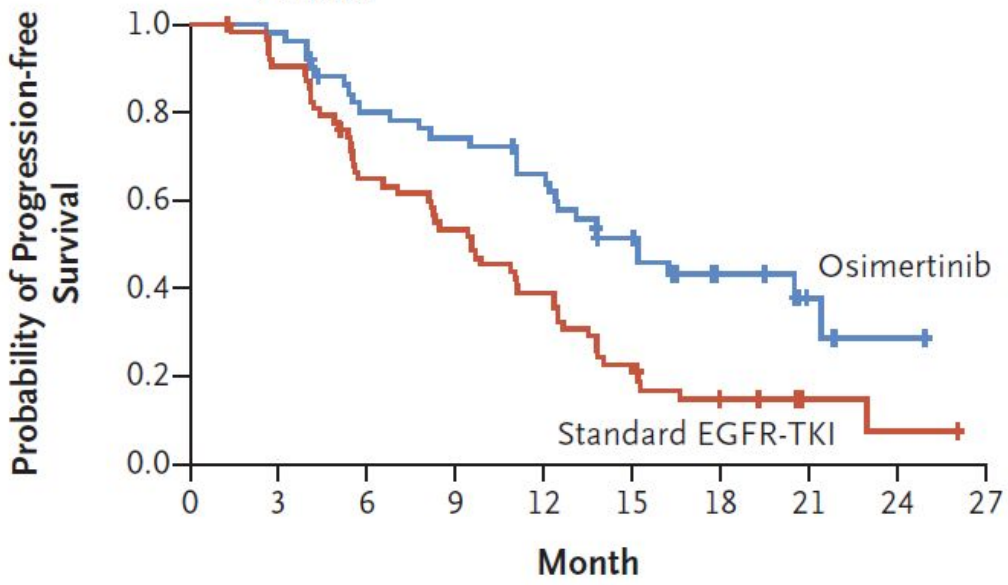


No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

B Progression-free Survival in Patients with CNS Metastases

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	53	15.2 (12.1–21.4)
Standard EGFR-TKI	63	9.6 (7.0–12.4)

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)
P<0.001



No. at Risk										
Osimertinib	53	51	40	37	32	22	9	4	1	0
Standard EGFR-TKI	63	57	40	33	24	13	6	2	1	0

Сложный выбор

- Erlotinib
- Gefitinib
- Afatinib
- Osimertinib

Park, K., Tan, E.-H., O'Byrne, K., Zhang, L., Boyer, M., Mok, T., … Paz-Ares, L. (2016). Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. The Lancet Oncology, 17(5), 577–589. doi:10.1016/s1470-2045(16)30033-x

Soria, J.-C., Ohe, Y., Vansteenkiste, J., Reungwetwattana, T., Chewaskulyong, B., Lee, K. H., … Ramalingam, S. S. (2018). Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. New England Journal of Medicine, 378(2), 113–125. doi:10.1056/nejmoa1713137

ARCHER 1050: Study Design

- Phase 3 randomized open-label study to evaluate dacomitinib as an alternative first-line treatment for patients with advanced NSCLC with an *EGFR*-activating mutation

- Advanced NSCLC with *EGFR*-activating mutation(s)
- No prior systemic treatment of advanced NSCLC
- No CNS metastases
- No prior EGFR TKI or other TKI
- ECOG PS of 0 or 1

N = 452

R
1:1

Dacomitinib 45 mg
PO QD
(n = 227)

Gefitinib 250 mg
PO QD
(n = 225)

Primary endpoint

PFS by blinded independent review (IR)

- Target HR ≤0.667 (50%↑)
- 90% power
- 1-sided α = 0.025
- Assumed median PFS: 14.3 vs 9.5 months

Stratification factors

Race (including Asian vs non-Asian)

EGFR mutation type (exon 19 vs 21)

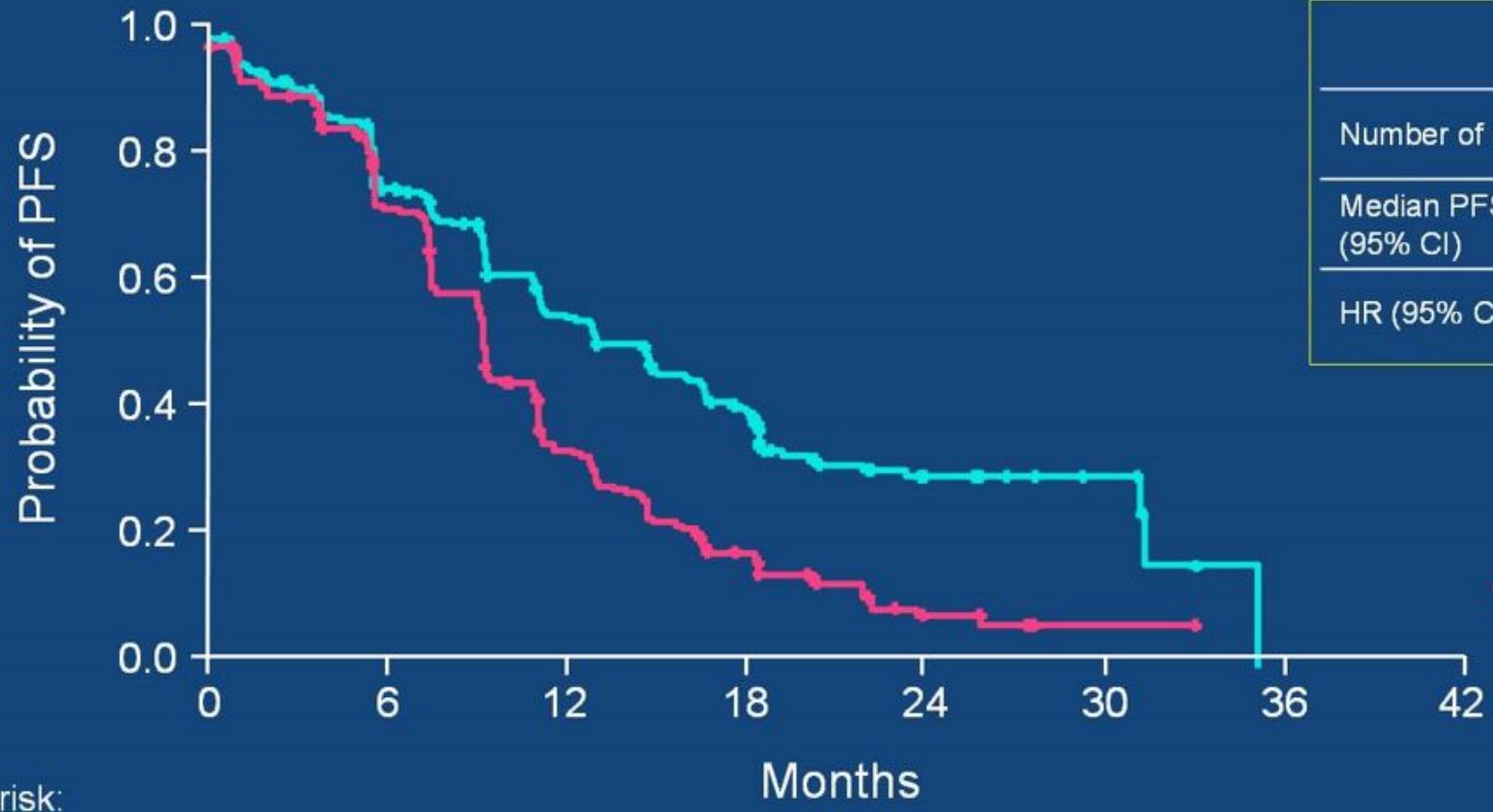
Secondary endpoints

OS

PFS (investigator assessed), ORR, DOR, TTF, Safety, PROs

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01774721.
CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PO, orally; PROs, patient-reported outcomes; PS, performance status; QD, once daily; R, randomized; TTF, time to treatment failure.

PFS: Blinded Independent Review
(Intention-to-Treat Population)



	Dacomitinib (n = 227)	Gefitinib (n = 225)
Number of events, n (%)	136 (59.9)	179 (79.6)
Median PFS, months (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI)	0.59 (0.47, 0.74) *P* < 0.0001	

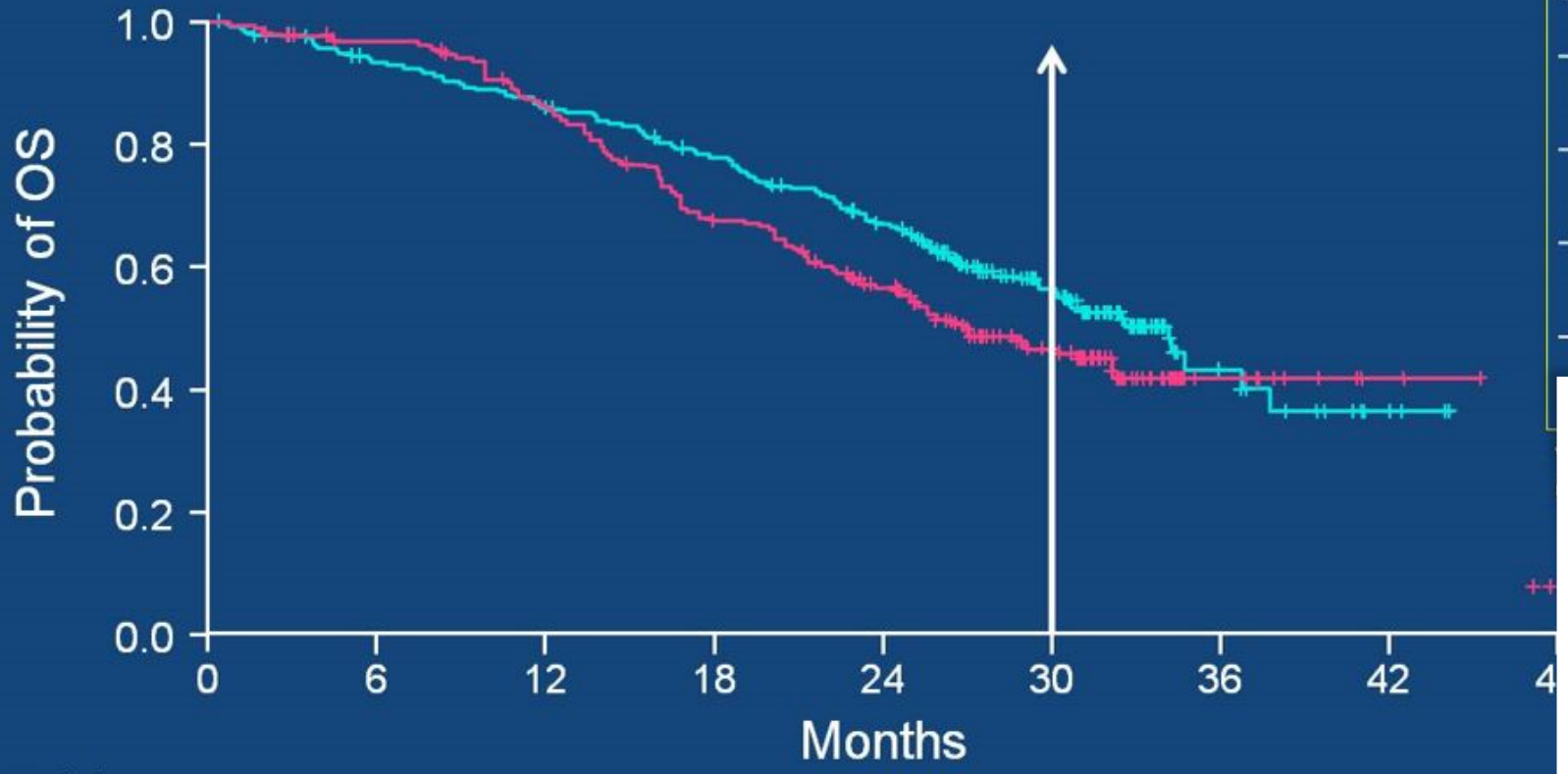
Data cutoff date: July 29, 2016

No. at risk:

Dacomitinib	227	154	106	73	20	6	0	0
Gefitinib	225	155	69	34	7	1	0	0

Wu YL, et al. *Lancet Oncol* 2017;18(11):1454–1466

Final OS (Primary Analysis)



	Dacomitinib (n = 227)	Gefitinib (n = 225)
Number of deaths, n (%)	103 (45.4)	117 (52.0)
Median OS, months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR* (95% CI)	0.760 (0.582, 0.993) 2-sided *P** = 0.0438	
OS probability at 30 months, %	56.2	46.3
CNS metastases at		

No. at risk:

Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

ALK и другие…

PROFILE 1014

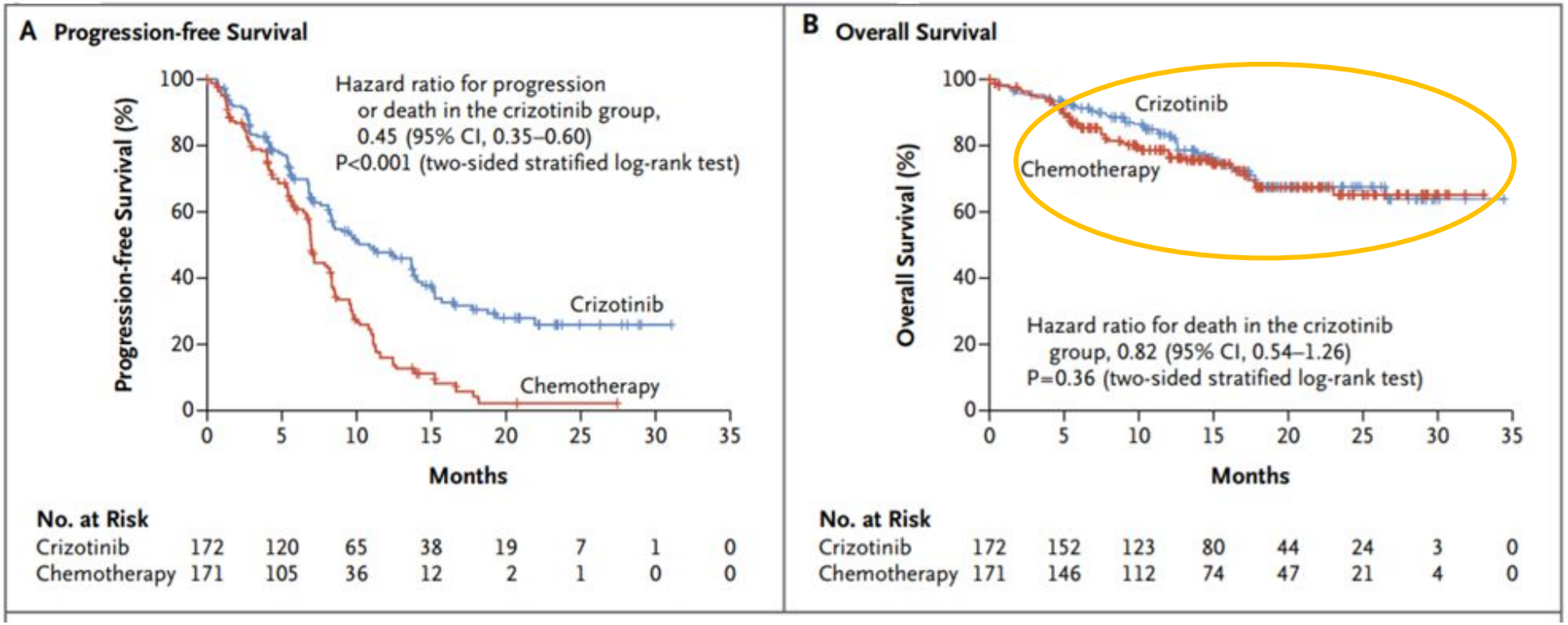
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators*

- 343 пациента с ALK +, местнораспространённый или метастатический НМРЛ, ECOG 0-2
- Рандомизация 1:1
- Кризотиниб vs Пеметрексед + карбоплатин или цисплатин
- Первичная конечная точка ВБП



Кризотиниб

- ЧОО = 74%
- Медиана ВПБ = 10.9 мес.

- **Химиотерапия**
- ЧОО = 45%
- Медиана ВПБ = 7.0 мес.

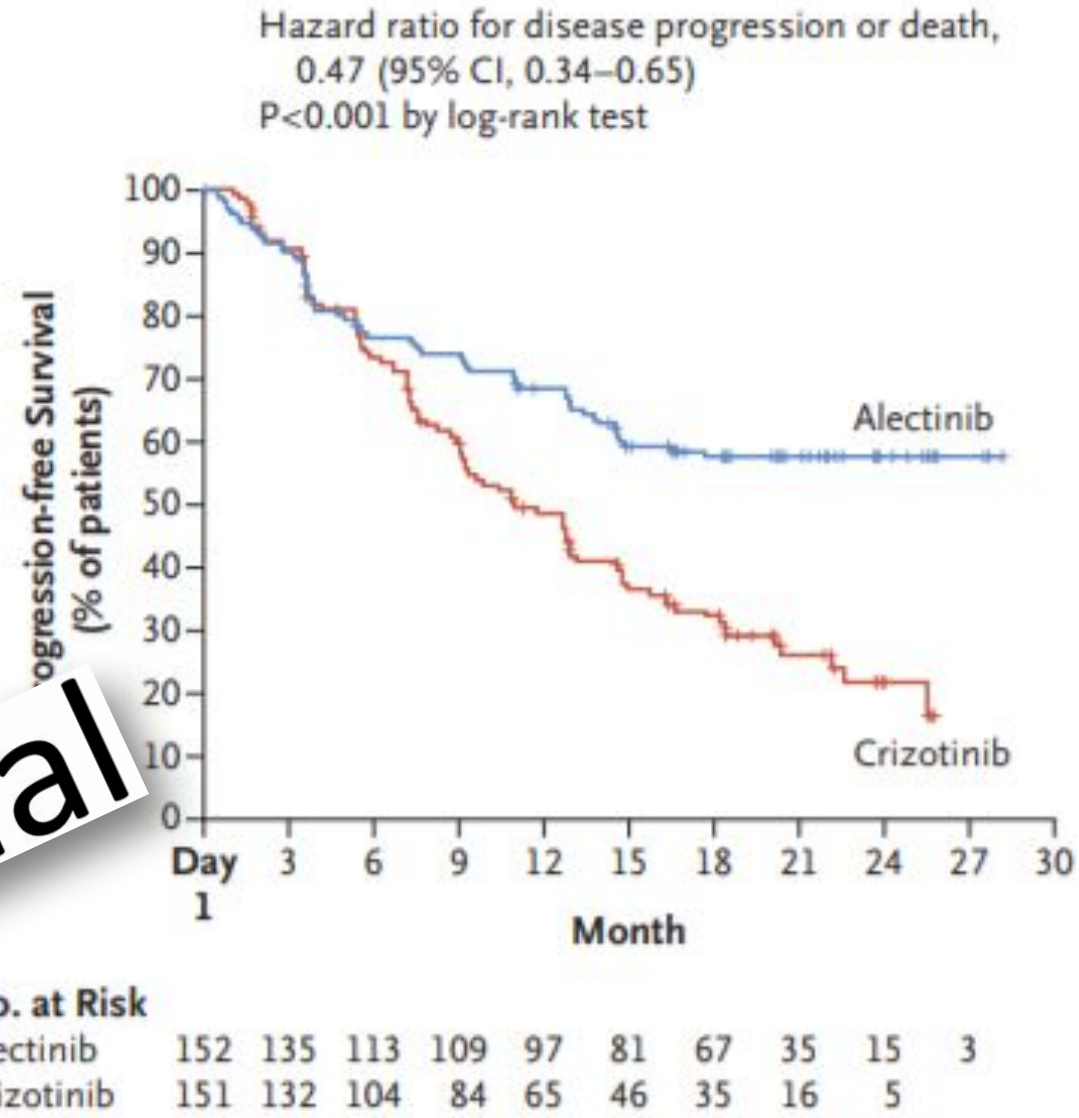
NSCLC ALK +

Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer

Peters, M.D., et al. August 31, 2017

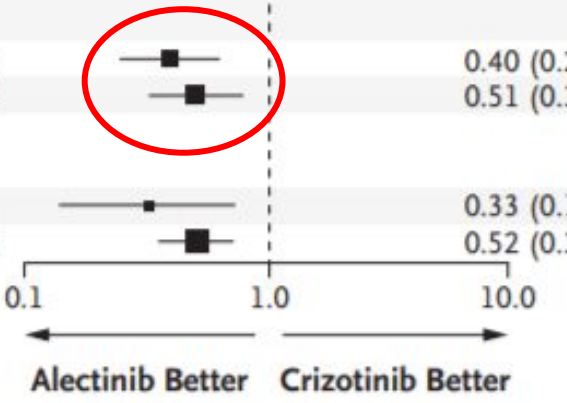
N Engl J Med 2017; 377:829-838 DOI: 10.1056/NEJMoa1704795

ALEX trial



B Subgroup Analysis

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	164/303	0.48 (0.35–0.66)
Age		
<65 yr	125/233	0.48 (0.34–0.70)
≥65 yr	39/70	0.45 (0.24–0.87)
Sex		
Female	91/171	0.39 (0.25–0.60)
Male	73/132	0.61 (0.38–0.98)
Race		
Asian	72/138	0.46 (0.28–0.75)
Non-Asian	92/165	0.49 (0.32–0.75)
Smoking status		
Active smoker	12/17	1.16 (0.35–3.90)
Nonsmoker	103/190	0.44 (0.29–0.66)
Former smoker	49/96	0.42 (0.23–0.77)
ECOG performance status		
0	44/97	0.40 (0.21–0.77)
1	105/186	0.48 (0.32–0.71)
2	15/20	0.74 (0.25–2.15)
CNS metastases at baseline		
Yes	78/122	0.40 (0.25–0.64)
No	86/181	0.51 (0.33–0.80)
Previous brain radiation		
Yes	26/47	0.33 (0.14–0.74)
No	138/256	0.52 (0.36–0.73)

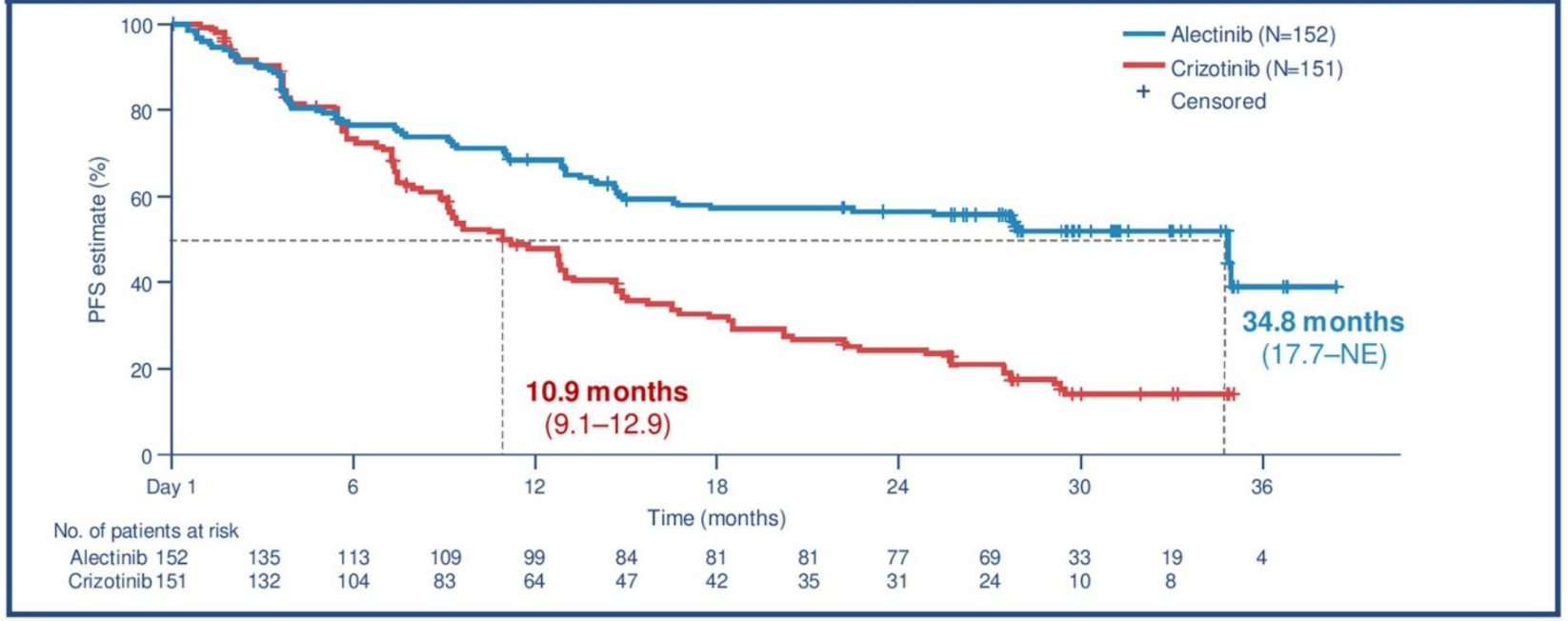


Алектиниб хорошо проникает через гематоэнцефалический барьер, что актуально для пациентов с метастазами в ЦНС.

Alectinib - обновлённые даннь

2018 ASCO ANNUAL MEETING
DELIVERING DISCOVERIES: EXPANDING THE REACH OF PRECISION MEDICINE

Figure 1. Investigator-assessed PFS.

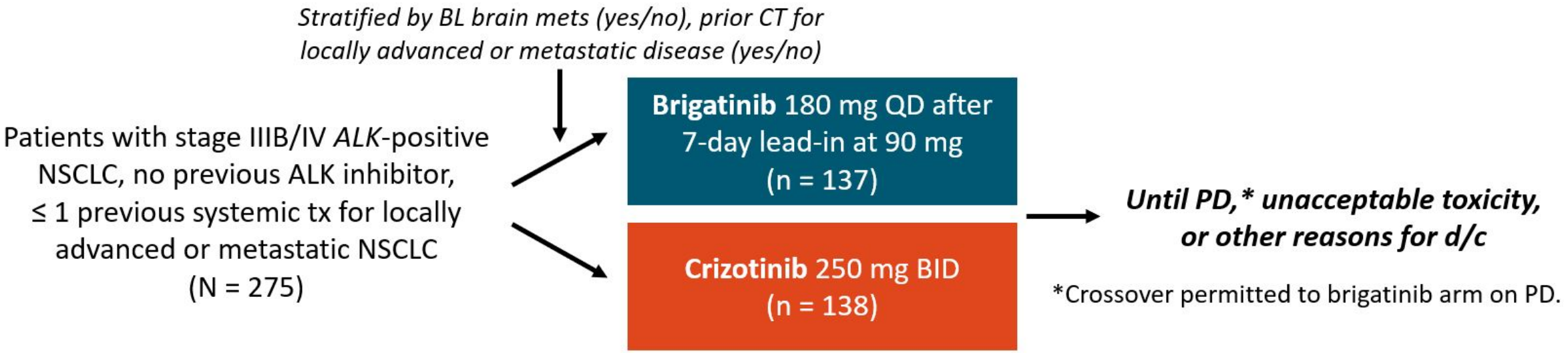


Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced ALK+ NSCLC.

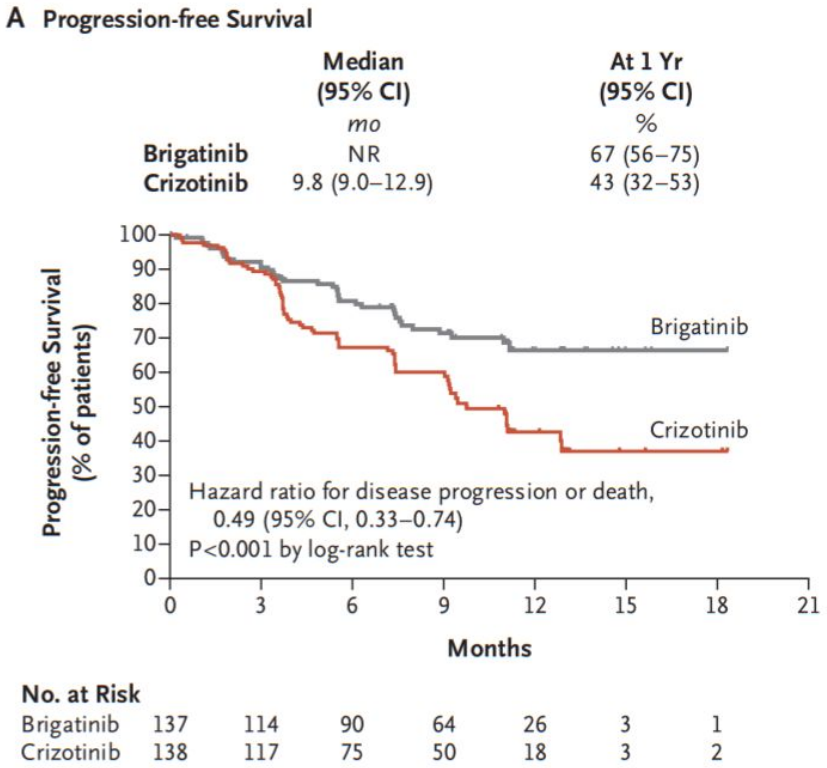
D. Ross Camidge, Solange Peters, Tony Mok, Shirish M. Gadgeel and al.

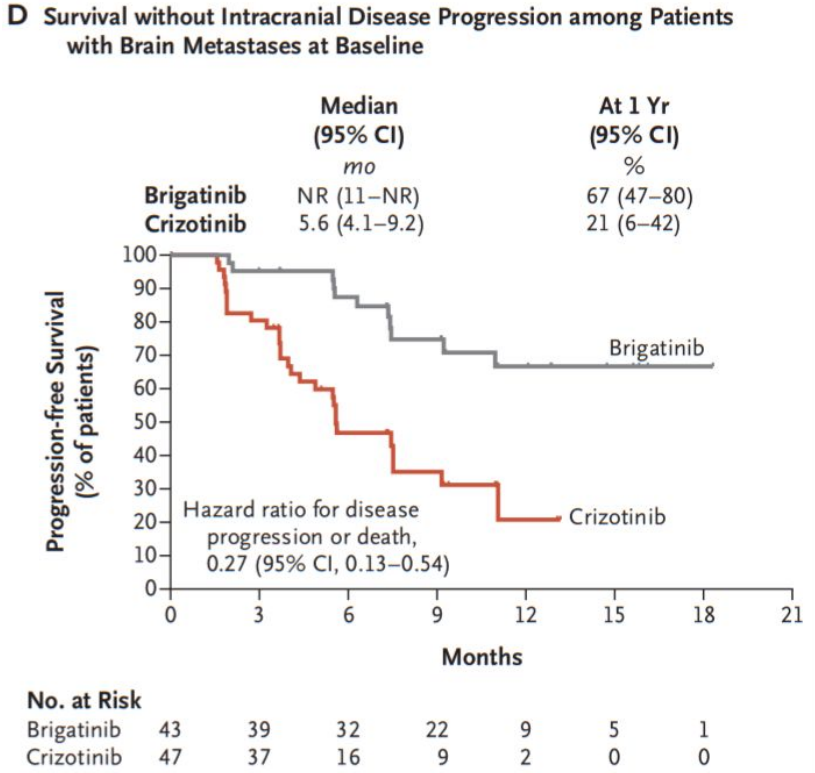
2018 ASCO Meeting Abstract #9043

ALTA-1L первые результаты



Camidge, D. R., Kim, H. R., Ahn, M.-J., Yang, J. C.-H., Han, J.-Y., Lee, J.-S., … Popat, S. (2018). Brigatinib versus Crizotinib in ALK-Positive Non–Small-Cell Lung Cancer. New England Journal of Medicine. doi:10.1056/nejmoa1810171



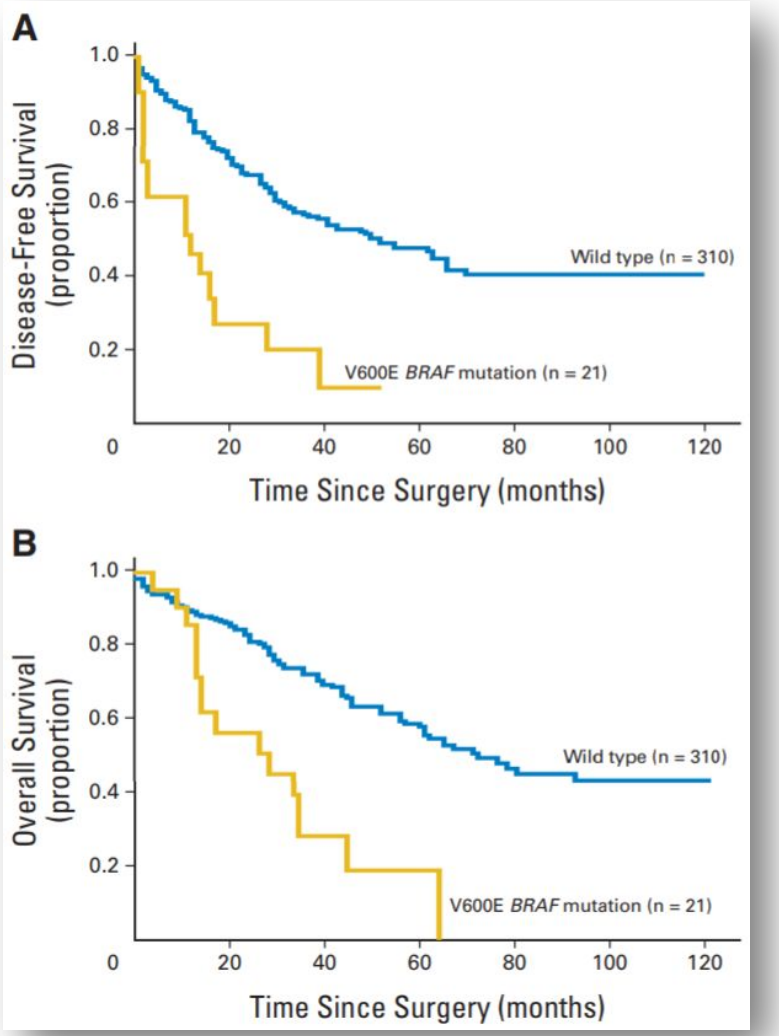


Бригатиниб лучше Кризотиниба

Camidge, D. R., Kim, H. R., Ahn, M.-J., Yang, J. C.-H., Han, J.-Y., Lee, J.-S., … Popat, S. (2018). Brigatinib versus Crizotinib in ALK-Positive Non–Small-Cell Lung Cancer. New England Journal of Medicine. doi:10.1056/nejmoa1810171

BRAF мутация

- По сравнению с меланомой, где мутация BRAF является наиболее встречаемой, при НМРЛ это всего около 2% случаев.
- Распространённый НМРЛ с мутацией BRAF V600 обладает гистологическими характеристиками агрессивной опухоли, а так же ассоциируется с худшей выживаемостью пациентов (если пациентам проводили стандартные режимы химиотерапии).



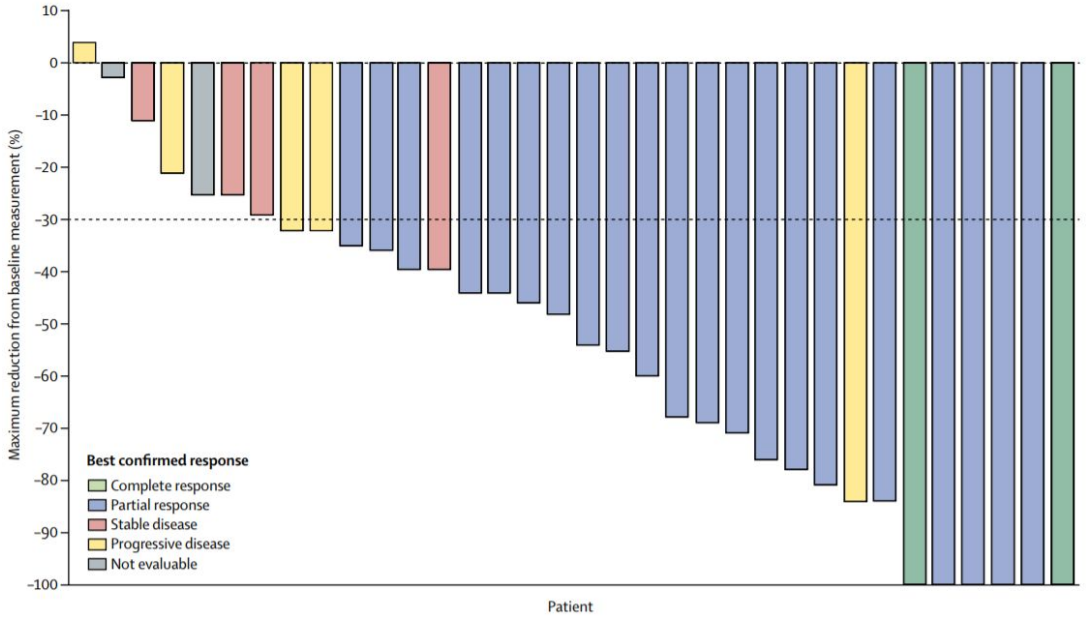
Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations.Marchetti et allJ Clin Oncol. 2011 Sep 10;29(26):3574-9. doi: 10.1200/JCO.2011.35.9638

Дабрафениб + траметиниб

В исследование включились пациенты с IV стадией НМРЛ, наличием мутации BRAF V600E, общее состояние по шкале ECOG 0-2, предшествующее прогрессирование заболевания после использования системной химиотерапии по поводу распространённого и/или метастатического НМРЛ

N=78	• Ранее получавшие лечение (≥ 1 линии) • Дабрафениб
N=57	• Ранее получавшие лечение (≥ 1 линии) • Дабрафениб + Траметиниб
N=36	• Без предшествующего лечения • Дабрафениб + Траметиниб

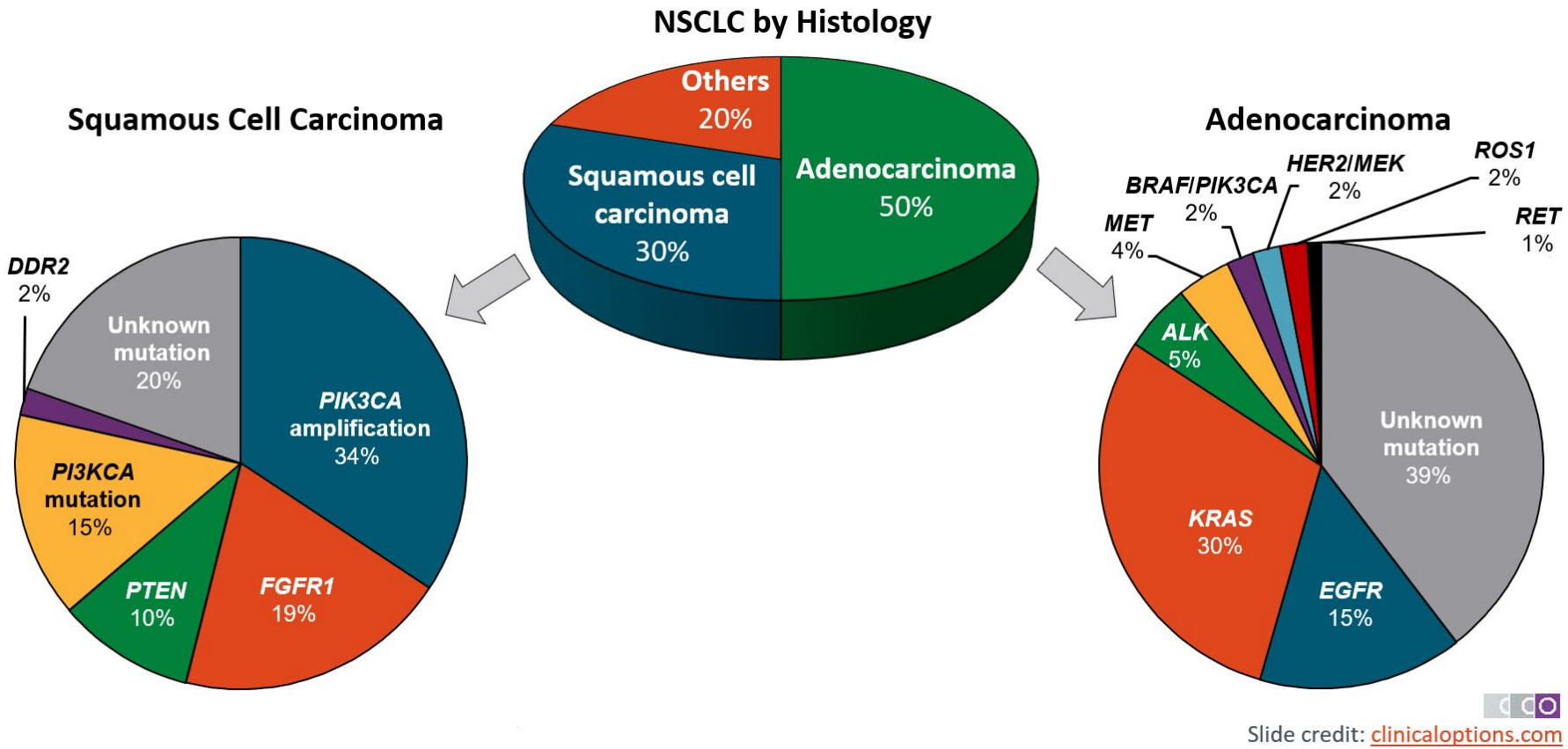
Planchard, D., Smit, E. F., Groen, H. J. M., Mazieres, J., Besse, B., Helland, Å., … Johnson, B. E. (2017). Dabrafenib plus trametinib in patients with previously untreated BRAF V600E -mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. The Lancet Oncology, 18(10), 1307–1316. doi:10.1016/s1470-2045(17)30679-4



В когорте пациентов без предшествующего лечения у 2 человек достижение полного ответа, у 21 человека — частичного ответа.

	Дабрафениб	Дабрафениб + Траметиниб	
Лечение	Ранее получавшие лечение	Ранее получавшие лечение	Без предшествующего лечения
ЧОО	33%	66%	64%
Медиана ВБП (месяцев)	5.5	10.2	14.6
Медиана ОВ (месяцев)	12.7	18.2	24.6

Будущее таргетной терапии



Slide credit: clinicaloptions.com

Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Cancer Res. 2015 Feb;4(1):36-54. doi: 10.3978/j.issn.2218-6751.2014.05.01.

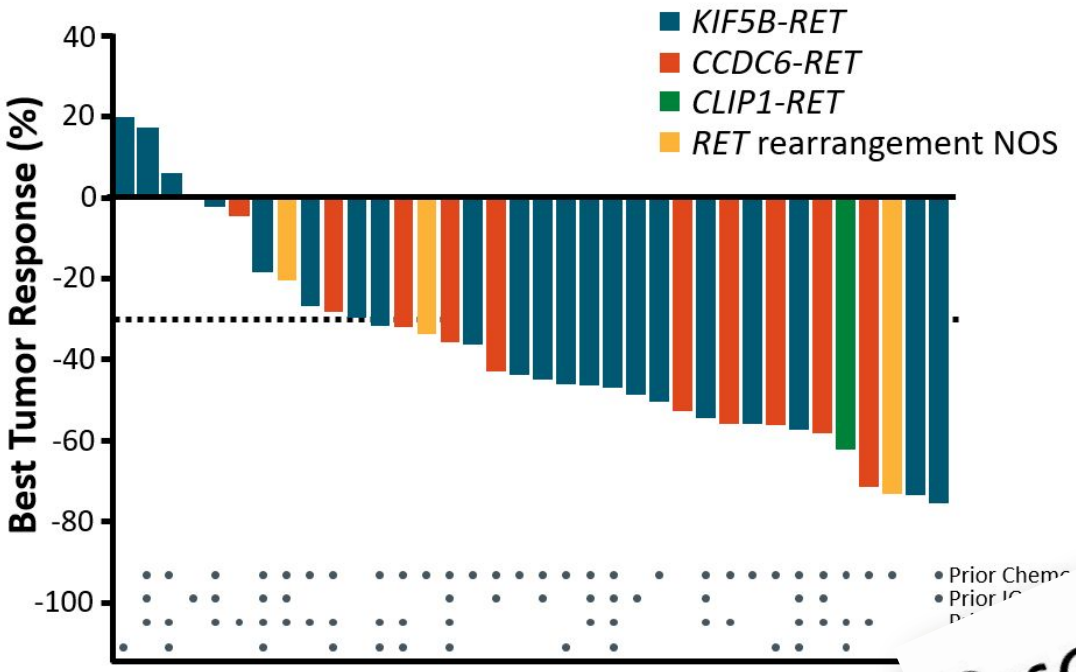
Скоро…

- Ado-Trastuzumab Emtansine
- Tepotinib (MET amplification)
- Entrectinib (ROS1+)
- Lorlatinib (ALK +)
- LOXO-292 (RET+)

- Li BT, Shen R et al. Ado-Trastuzumab Emtansine for Patients With HER2-Mutant Lung Cancers: Results From a Phase II Basket Trial. J Clin Oncol. 2018 Aug 20;36(24):2532-2537. doi: 10.1200/JCO.2018.77.9777. Epub 2018 Jul 10.
- Hotta K, Aoe K et al. A Phase II Study of Trastuzumab Emtansine in HER2-Positive Non-Small Cell Lung Cancer. J Thorac Oncol. 2018 Feb;13(2):273-279. doi: 10.1016/j.jtho.2017.10.032. Epub 2017 Dec 5.
- Drilon, A., Rekhtman, N., Arcila, M., Wang, L., Ni, A., Albano, M., … Kris, M. G. (2016). Cabozantinib in patients with advanced RET -rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. The Lancet Oncology, 17(12), 1653–1660. doi:10.1016/s1470-2045(16)30562-9
- Paik, P. K., Drilon, A., Fan, P.-D., Yu, H., Rekhtman, N., Ginsberg, M. S., … Ladanyi, M. (2015). Response to MET Inhibitors in Patients with Stage IV Lung Adenocarcinomas Harboring MET Mutations Causing Exon 14 Skipping. Cancer Discovery, 5(8), 842–849. doi:10.1158/2159-8290.cd-14-1467
- Felip E et al. Phase II Data for the MET Inhibitor Tepotinib in Patients with Advanced NSCLC and MET Exon 14-Skipping Mutations J Thorac Oncol 2018;13(suppl):Abstr OA12.01
- Doebele RC, et al. WCLC 2018. Abstract OA02.01.

LIBRETTO-001 (фаза 1)

- ORR: 68% (95% CI: 51% to 83%)



LOXO 292

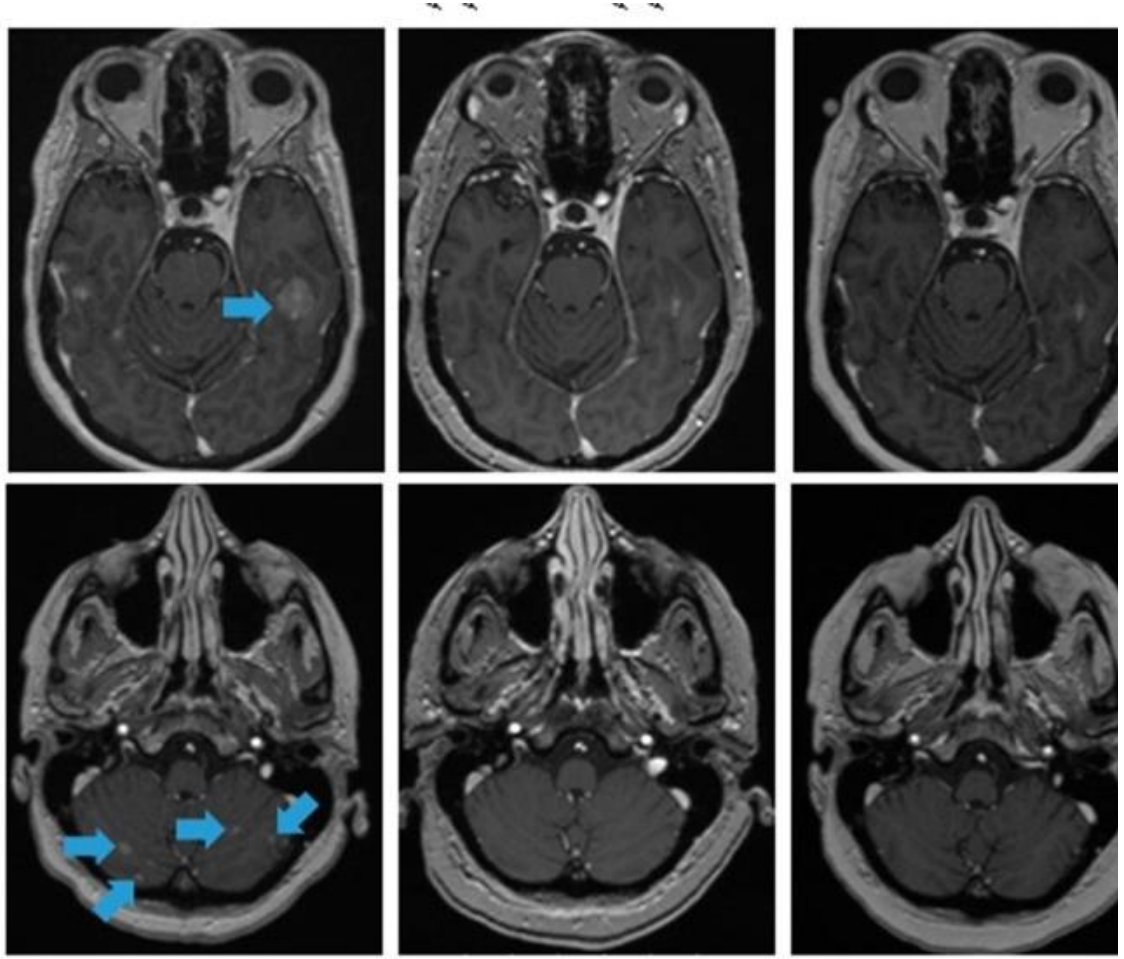
Breakthrough therapy

Oxnard GR, et al. WCLC 2018. Abstract OA12.07.

https://www.onclive.com/web-exclusives/fda-grants-loxo292-breakthrough-designation-for-nsclc-mtc

LOXO-292

Subbiah V, Velcheti V, Tuch BB, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol. 2018;29(8):1869-1876.



Baseline	2 Mo.	5 Mo.
↓ Target Lesions (RANO-BM)	-89% (PR)	-100% (cPR)

EGFR +, PD-L1 >50%

A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC

A. Lisberg, MD, A. Cummings, MD, J. W. Goldman, MD, K. Bornazyan, BS, N. Reese, MD, T. Wang, MD, P. Coluzzi, MD, B. Ledezma, MSN NP, M. Mendenhall, MSN NP, J. Hunt, BS, B. Wolf, BS, B. Jones, BS, J. Madrigal, BS, J. Horton, BS, M. Spiegel, BS, J. Carroll, BS, J. Gukasyan, BS, T. Williams, BS, L. Sauer, BS, C. Wells, BS, A. Hardy, BS, P. Linares, BS, C. Lim, BS, L. Ma, BS, C. Adame, BS, Edward B. Garon, MD, MS*

David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, California

Received 2 March 2018; accepted 25 March 2018
Available online - 1 June 2018

IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

- Пациенты с **EGFR +, PD-L1 >50%** без предшествующего лечения получали Pembrolizumab
- Исследование прекратилось из-за отсутствия эффективности после лечения 11 из 25 планируемых пациентов
- Только у 1 пациента был объективный ответ – ошибка (**EGFR -**)
- Pembrolizumab не является подходящим терапевтическим выбором в этой ситуации

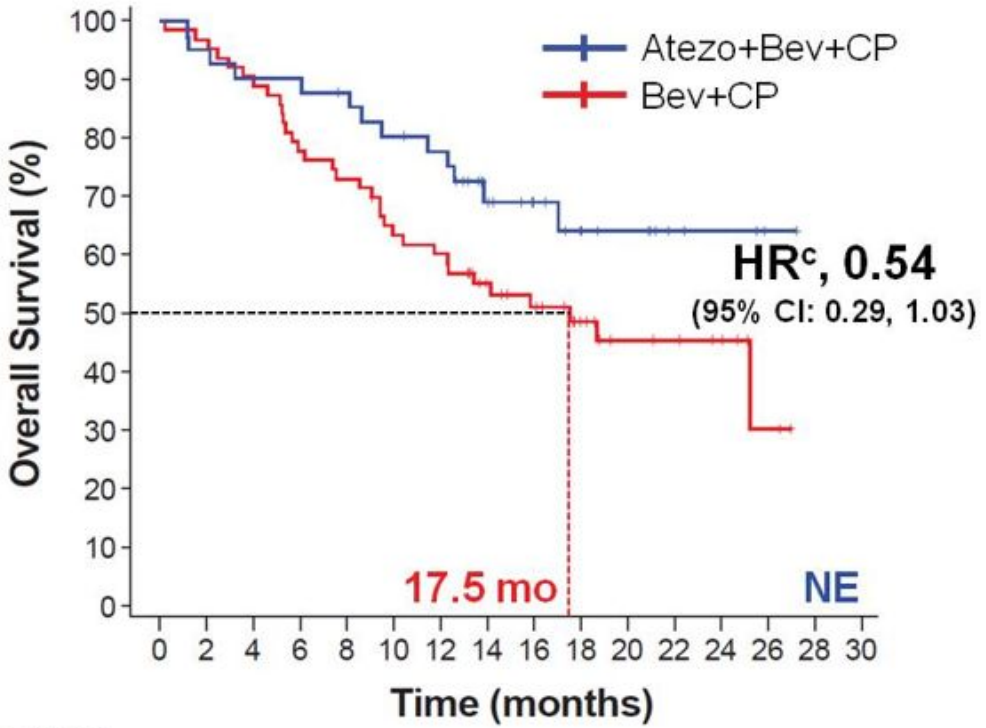
Ретроспектив НО

	PD-L1 >50%	PD-L1 49% -1%	PD-L1 <1%	p-value
ORR (TKI 1st line)	35.7%	63.2%	67.3%	0.002
Median PFS	3.8 m	6.0 m	9.5 m	<0.001

Su, S., Dong, Z.-Y., Xie, Z., Yan, L.-X., Li, Y.-F., Su, J., … Wu, Y.-L. (2018). Strong PD-L1 expression predicts poor response and de novo resistance to EGFR TKIs among non-small cell lung cancer patients with EGFR mutation. Journal of Thoracic Oncology. doi:10.1016/j.jtho.2018.07.016

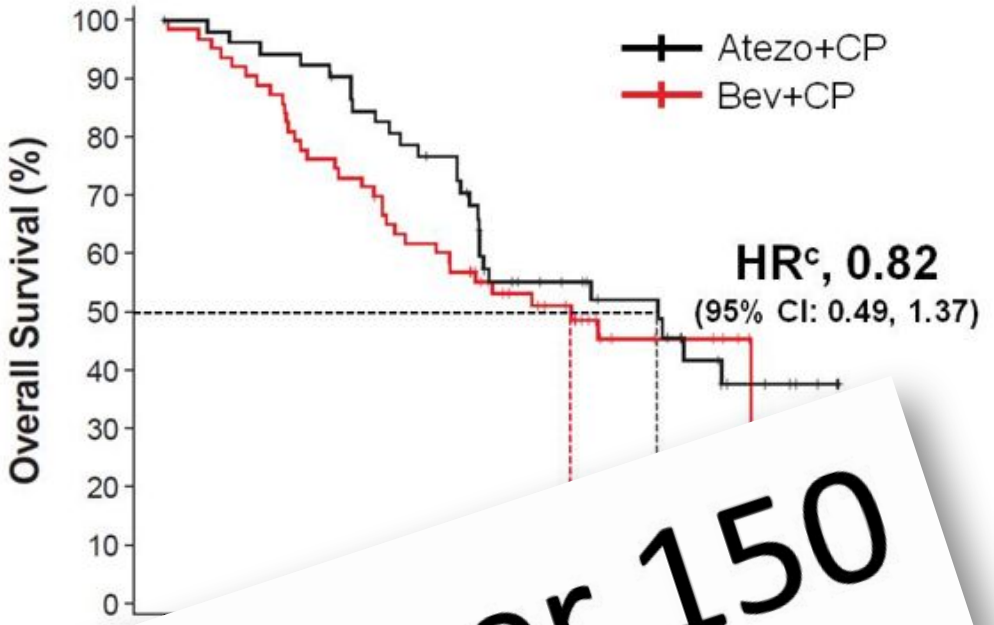
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients[a]

Arm B[b] vs Arm C



No. at Risk														
Atezo+Bev+CP	41	39	37	37	35	32	30	20	15	11	9	5	4	2
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

Arm A vs Arm C



Atezo+CP										20	16	13	8	6	4
Bev+CP										28	24	17	12	11	7	2

IMpower 150

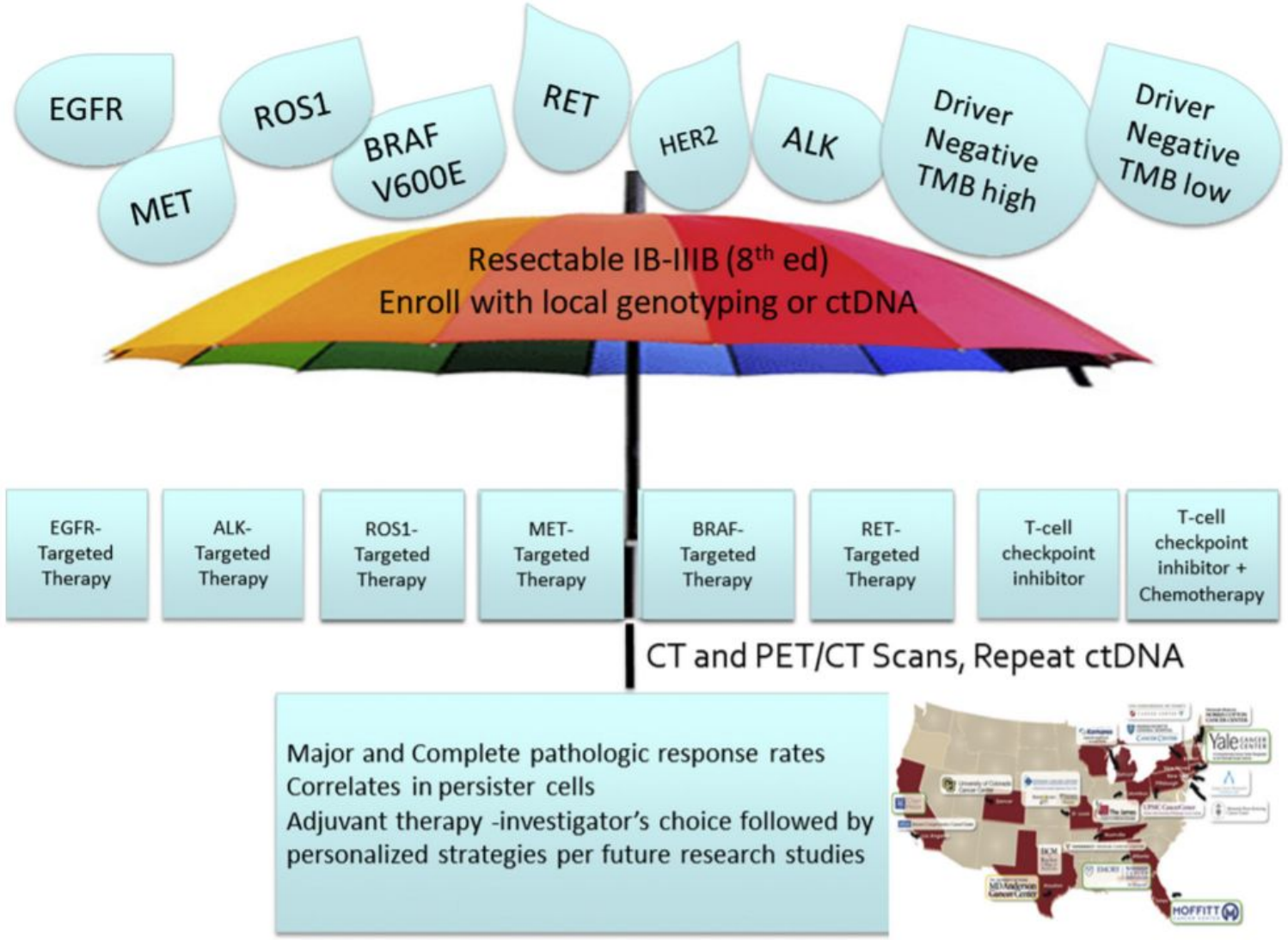
[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of … more approved targeted therapies.
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [c] Unstratified HR.
Data cutoff: January 22, 2018

Адъювантная и неоадъювантная терапия

	Исследование	Препарат
Neo	CTONG 1103	Erlotinib
Adj	RADIANT	Erlotinib
Adj	ADJUVANT/CTONG 1104	Gefitinib
Adj	SELECT	Erlotinib

- W-Z Zhong, et al. CTONG 1103: Erlotinib versus gemcitabine plus cisplatin as neo-adjuvant treatment for stage IIIA-N2 EGFR-mutation non-small cell lung cancer (EMERGING): A randomised study. (LBA48_PR) Annals of Oncology, Volume 29, Issue suppl_8, 1 October 2018, mdy424.058, https://doi.org/10.1093/annonc/mdy424.058
- Kelly, K., Altorki, N. K., Eberhardt, W. E. E., O'Brien, M. E. R., Spigel, D. R., Crinò, L., … Shepherd, F. A. (2015). Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non–Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. Journal of Clinical Oncology, 33(34), 4007–4014. doi:10.1200/jco.2015.61.8918
- Zhong, W.-Z., Wang, Q., Mao, W.-M., Xu, S.-T., Wu, L., Shen, Y., … Xu, L. (2018). Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) EGFR -mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. The Lancet Oncology, 19(1), 139–148. doi:10.1016/s1470-2045(17)30729-5
- Pennell NA et al. SELECT: A Phase II Trial of Adjuvant Erlotinib in Patients With Resected Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer. J Clin Oncol. 2018 Nov 16:JCO1800131. doi: 10.1200/JCO.18.00131. [Epub ahead of print]

PROMISE

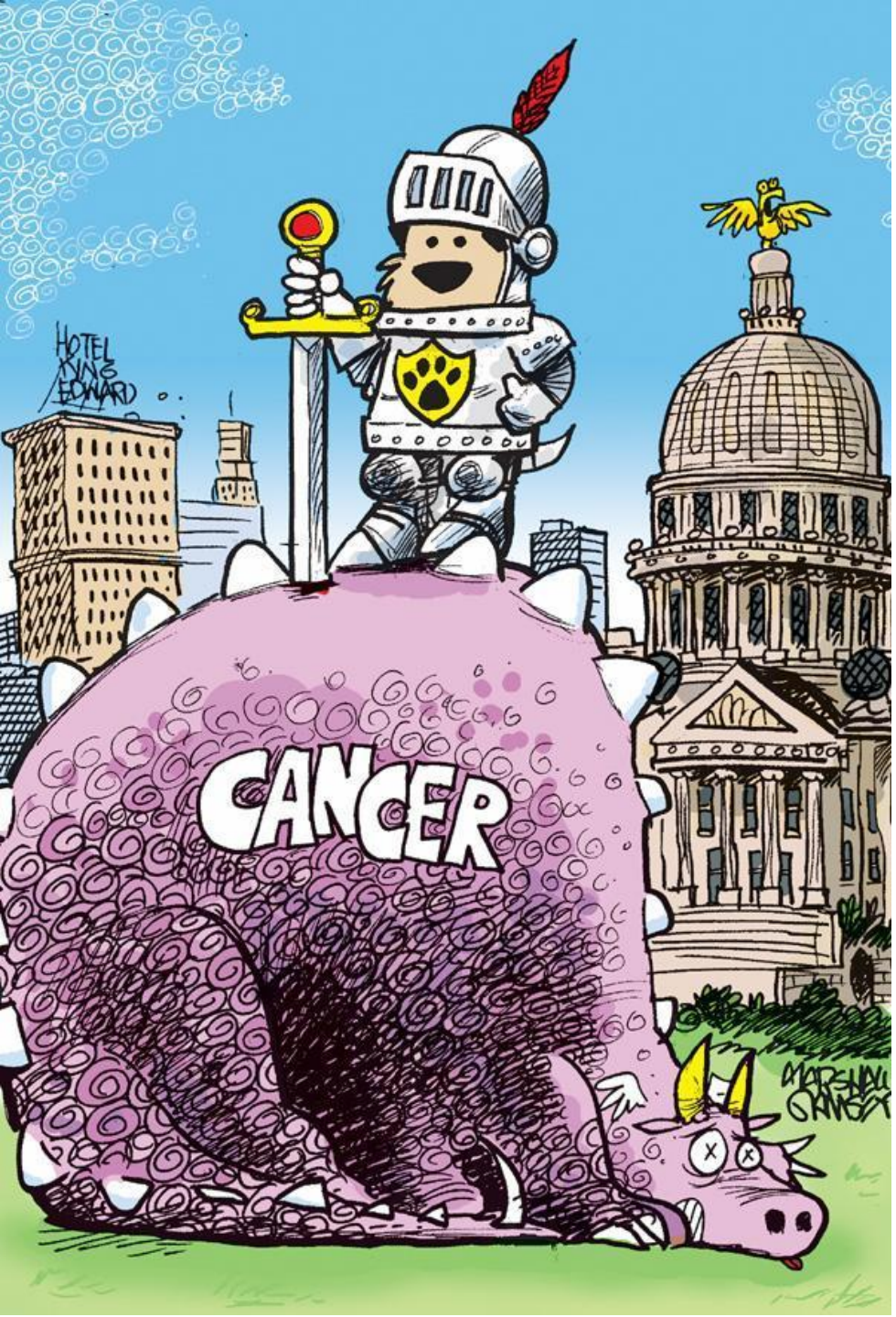


Blumenthal, G. M., Bunn, P. A., Chaft, J. E., McCoach, C. E., Perez, E. A., Scagliotti, G. V., … Kris, M. G. (2018). Current Status and Future Perspectives on Neoadjuvant Therapy in Lung Cancer. Journal of Thoracic Oncology. doi:10.1016/j.jtho.2018.09.017

Выводы

- Разделение пациентов на группы, в основе которого лежат молекулярно-генетические тесты, позволяет добиваться гораздо лучших результатов в лечении
- Выполнение тестов на EGFR, ALK, ROS1, BRAF должно проводиться всем пациента с не плоскоклеточным НМРЛ, а в некоторых случаях и с плоскоклеточным
- Тест на уровень экспрессии PD-L1 должно проводиться всем пациентам с нерезектабельным и метастатическим НМРЛ
- В будущем: поиск новых предикторов ответа, особенно для плоскоклеточного НМРЛ поможет достичь полной индивидуализации лечения


LUNG
CANCER
AWARENESS
MONTH
WE HONOR
AND
REMEMBER
American
Cancer
Society®



Благодарю за внимание!