Az onkopulmonológia legújabb eredményei

Ostoros Gyula
Országos Korányi Intézet
Budapest
2016. január 29.

Komplex gyógyszeres terápia

- Hagyományos citotoxikus kemoterápia
- Molekuláris (célzott) kezelés
- Immunterápia

E terápiás modalitások személyre szabott kombinálása

TERANOSZTIKA

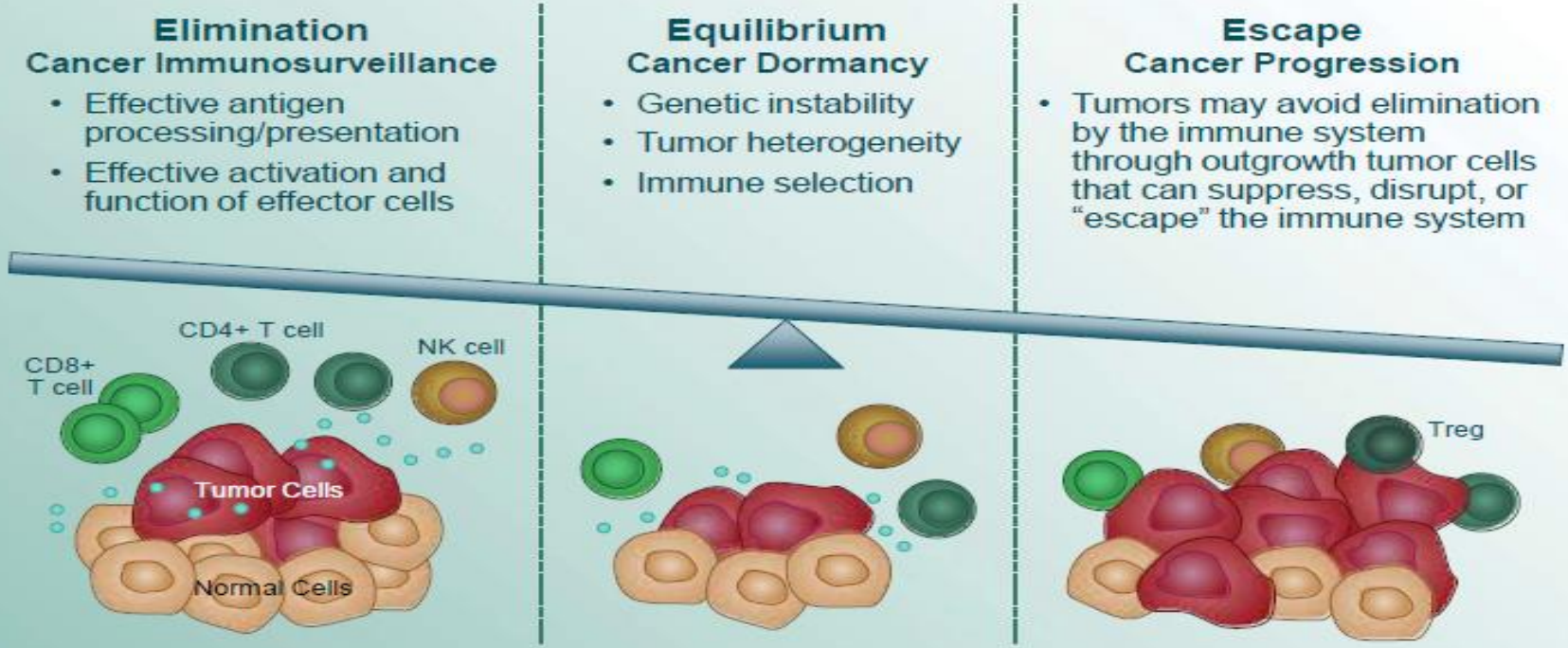
Immunellenörző-pont gátlás

Célzott kezelések

Komplex kezelés

The Role of the Immune System in Cancer and Process of Immunoediting

- **The three E's of cancer immunoediting describe the immune system's role in protecting against tumor development and promoting tumor growth**

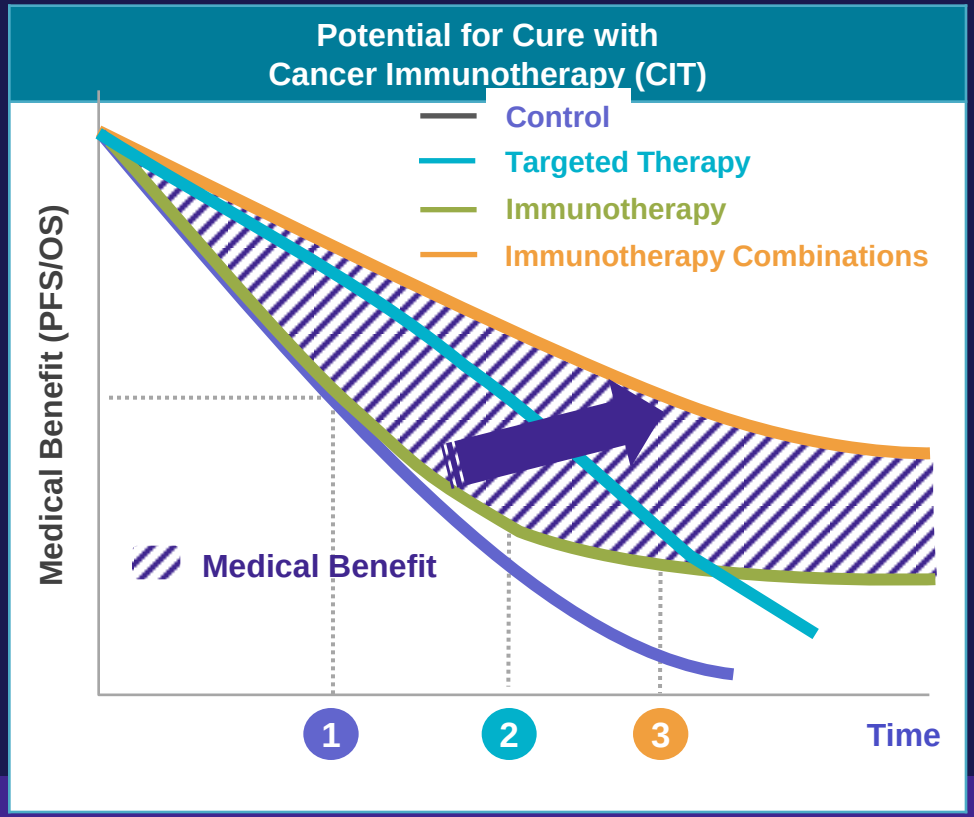


NK=natural killer; Treg=regulatory T cell.

Vesely MD et al. *Ann Rev Immunol.* 2011;29:235-271.

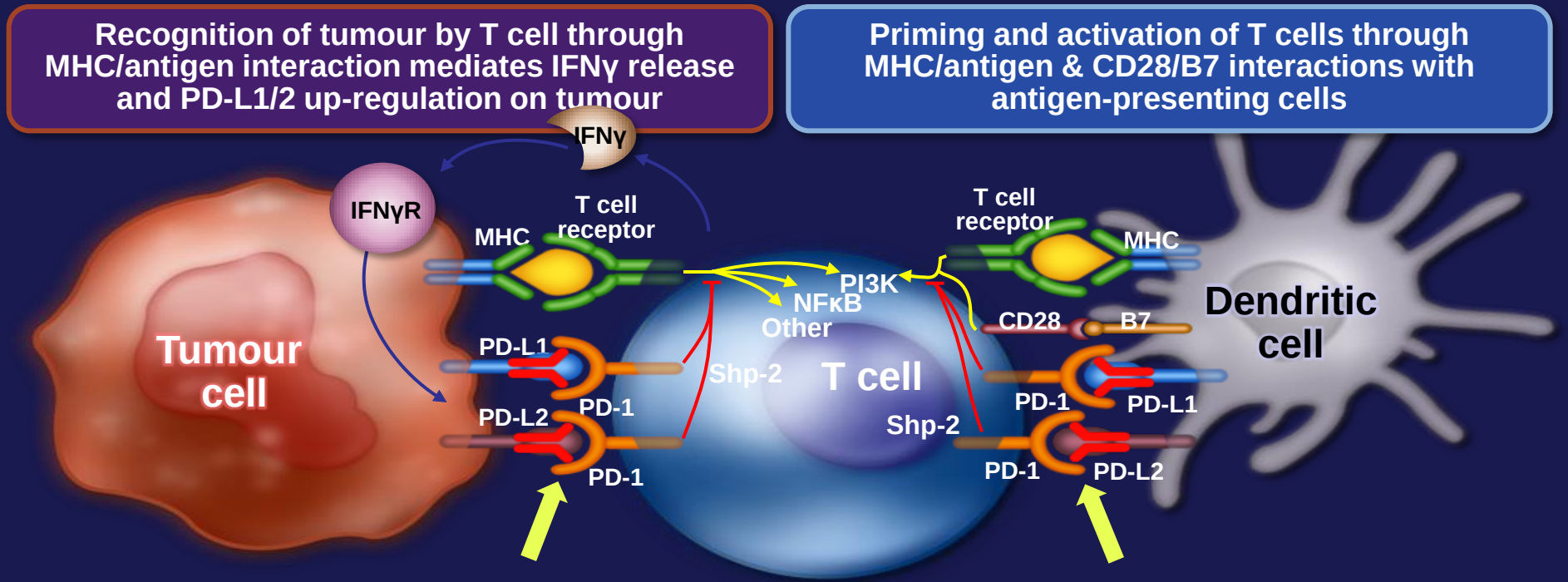
Immunonkológia

Esély a hosszú távú túlélésre



* Sehn, L. H. et al. J Clin Oncol; 23:5027-5033 2005

PD-1, PDL-1 gátlás hatásmechanizmusa:



Adapted from Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Anti-PD-1 Nivolumab

Phase	Indication(s)	N	Comparator
3	Advanced/metastatic squamous NSCLC, second-line (CA209-017)	264	Docetaxel
3	Advanced/metastatic non-squamous NSCLC, second line (CA209-057)	574	Docetaxel
3	First-line Advanced/Recurrent /Metastatic PDL1+ positive NSCLC (CheckMate 026)	495	Investigator's choice 1st line chemotherapy

Anti-PD-1, Pembrolizumab

2/3	Previously treated PD-L1 positive NSCLC	920	Docetaxel
2	Post Chemoradiation inoperable Stage IIIA/IIIB	93	None
3	First-line PD-L1-positive Advanced or Metastatic Non-small Cell Lung Cancer	1240	Platinum-based chemotherapy

www.clinicaltrials.gov accessed May 20, 2015

Anti-PDL1 - MPDL3280A

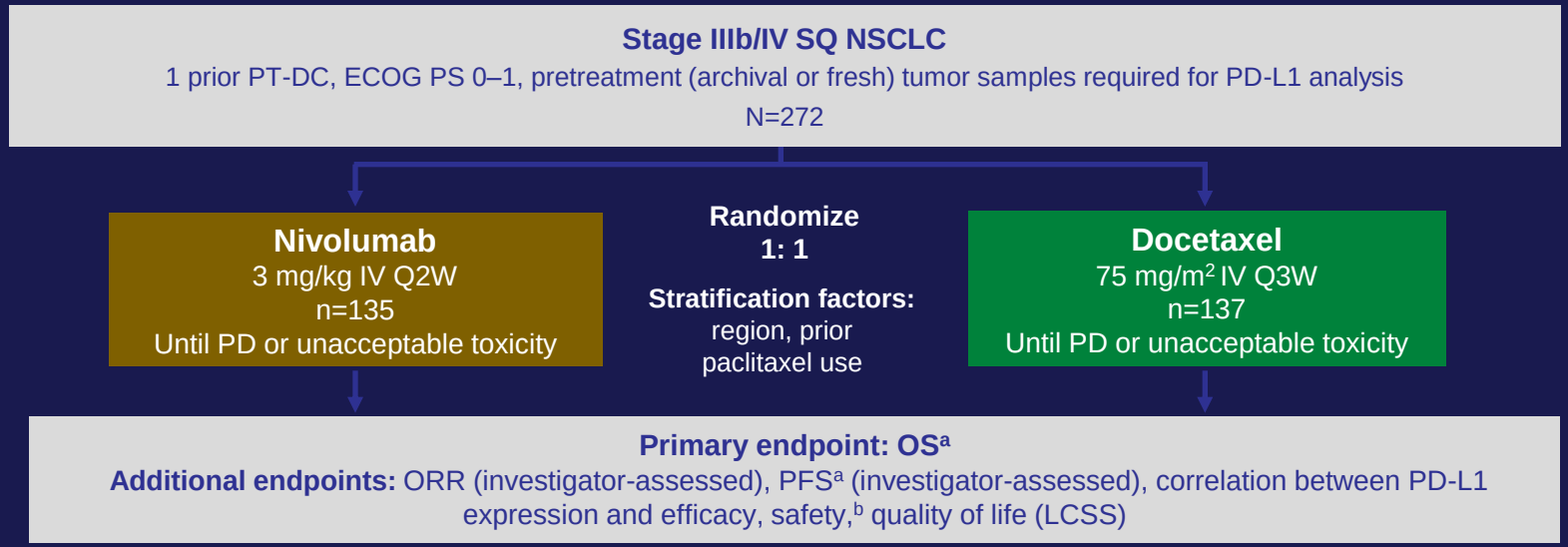
Phase	Indication(s)	N	Comparator
2	PD-L1-positive stage IIIB/IV or recurrent NSCLC (FIR)	130	None
2	PD-L1-positive stage IIIB/IV or recurrent NSCLC (BIRCH)	300	None
2	Locally advanced or metastatic NSCLC, PD following prior platinum-containing regimen (POPLAR)	287	Docetaxel
3	Locally advanced or metastatic NSCLC, PD following prior platinum-containing regimen (OAK)	850	Docetaxel

Anti-PDL1 - MEDI4736

Phase	Indication(s)	N	Comparator
2	Advanced/Metastatic NSCLC – after at least 2 prior systemic therapy regimens (ATLANTIC)	210	None
3	Post Chemoradiation in unresectable Stage III (PACIFIC)	720	None
3	Adjuvant in Completely Resected	1100	Placebo
3	Monotherapy or in combination with Tremelimumab by PDL1 expression status – after 2 prior regimens (ARCTIC)	900	SOC chemotherapy gemcitabine, vinorelbine, erlotinib)

www.clinicaltrials.gov accessed May 20, 2015

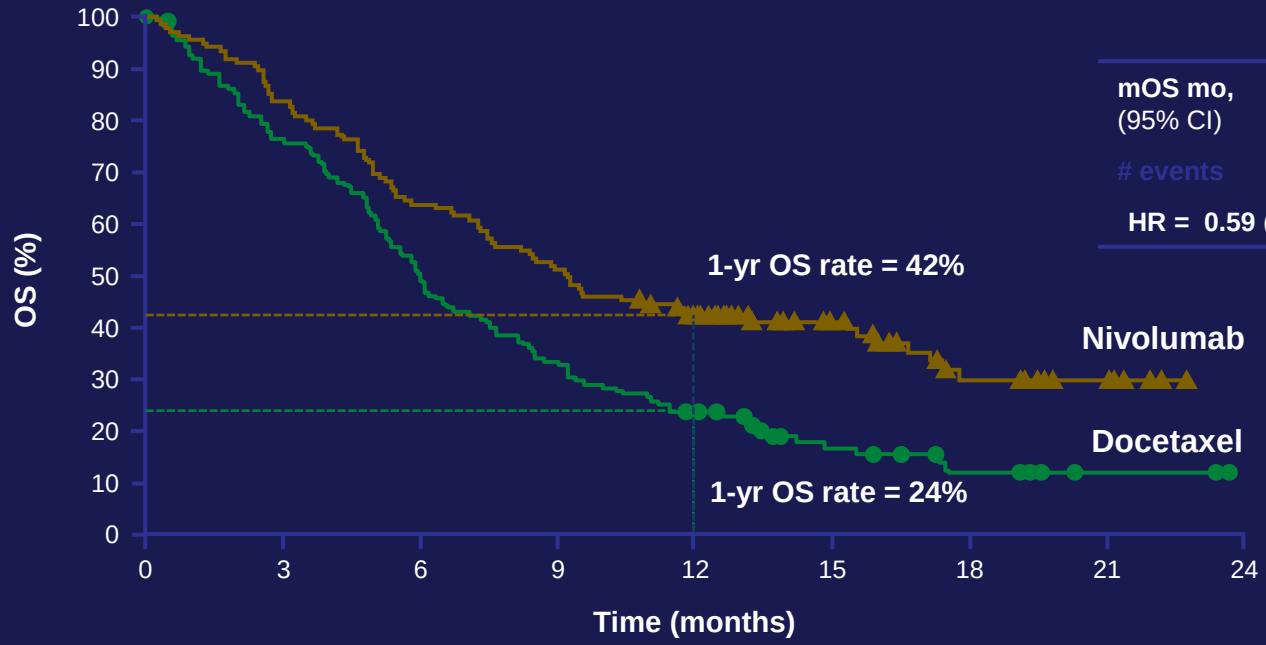
CheckMate 017 (NCT01642004) — Vizsgálat felépítése



- Updated safety and longer-term survival (18 months) are reported here
- At the time of analysis, 13% of patients in the nivolumab arm were continuing treatment vs no patients in the docetaxel arm

[a]Updated based on August 2015 database lock (DBL). [b]Updated based on June 2015 DBL

Teljes túlélés



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), ***P* = 0.00025**

Number of Patients at Risk

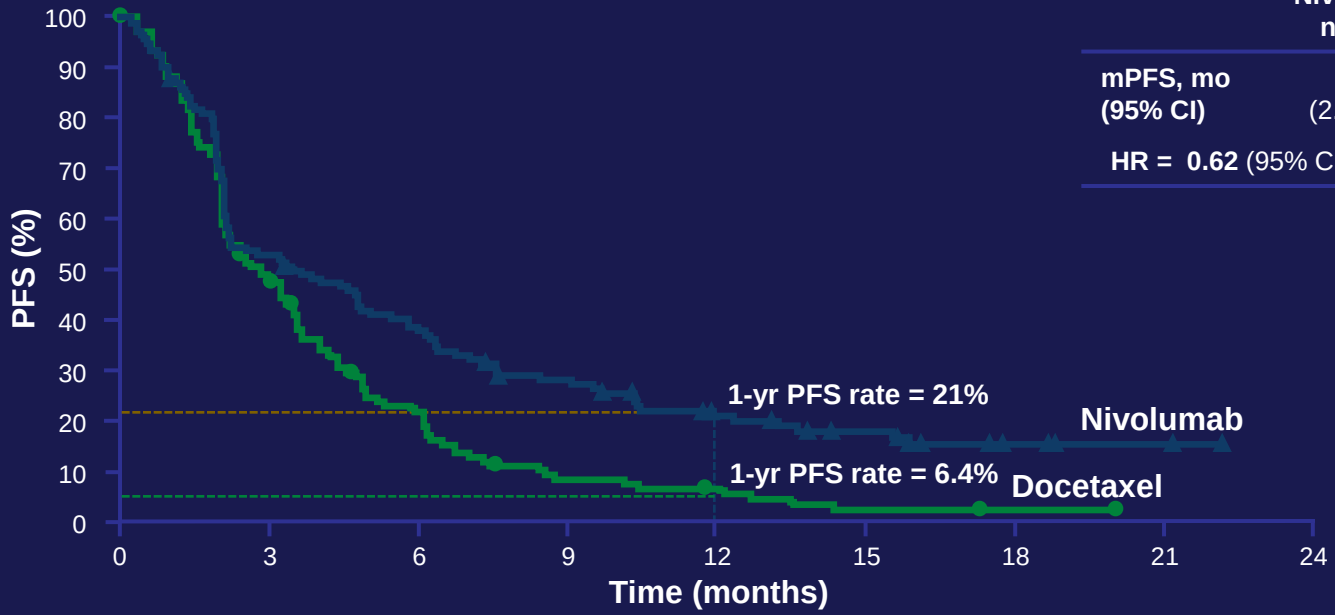
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

Progresszió mentes túlélés

	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	**3.5** (2.1, 4.9)	**2.8** (2.1, 3.5)

HR = 0.62 (95% CI: 0.47, 0.81); ***P* = 0.0004**



Number of Patients at Risk									
Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

PFS per investigator.

Teljes túlélési arány 18 hónap múlva:

	Nivolumab n=135	Docetaxel n=137
mOS, mos (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR=0.62 (0.48, 0.81); *P*=0.0004		

Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	3	1	0

Minimum follow-up for survival: 18 months

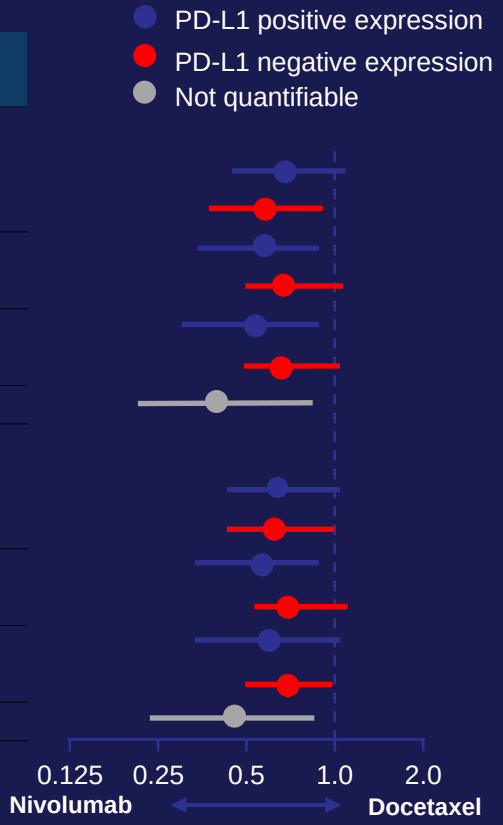
Based on August 2015 DBL.
Symbols refer to censored observations.

Based on August 2015 DBL.
Symbols refer to censored observations.

OS és a PFS a PD-L1 expresszió függvényében

- Survival benefit with nivolumab was independent of PD-L1 expression level

PD-L1 expression	Patients, n Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	63	56	0.69 (0.45, 1.05)	**0.56**
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	**0.47**
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	**0.41**
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
≥1%	63	56	0.67 (0.44, 1.01)	**0.70**
<1%	54	52	0.66 (0.43, 1.00)	
≥5%	42	39	0.54 (0.32, 0.90)	**0.16**
<5%	75	69	0.75 (0.52, 1.08)	
≥10%	36	33	0.58 (0.33, 1.02)	**0.35**
<10%	81	75	0.70 (0.49, 0.99)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	

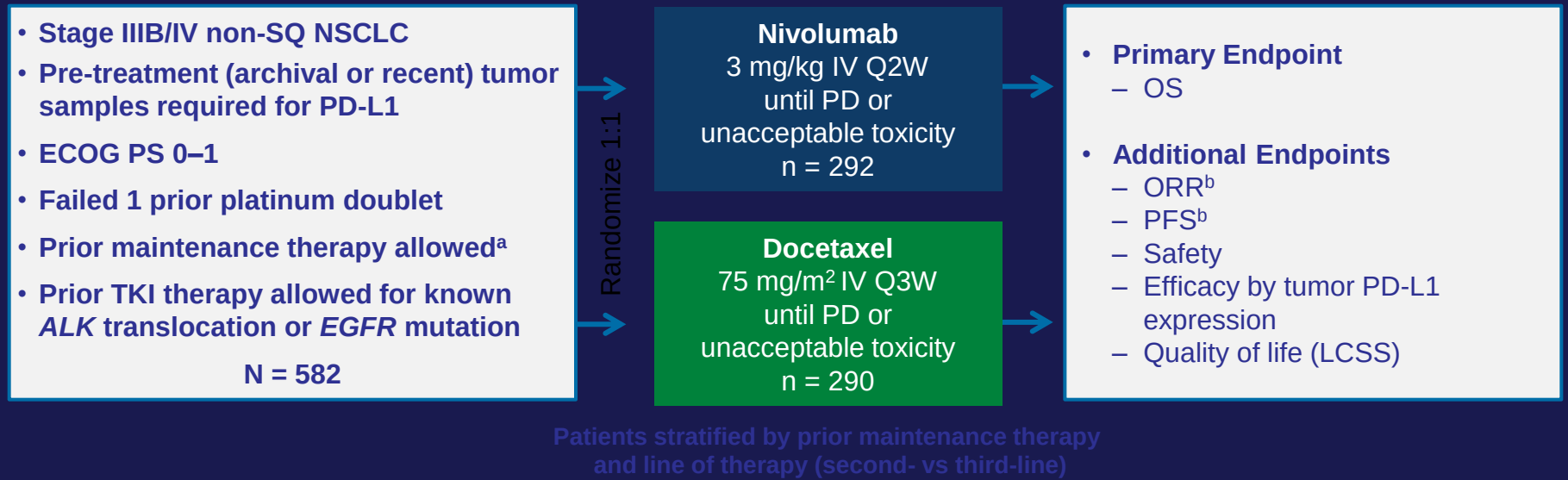


- PD-L1 expression was measured in pre-treatment tumor biopsies (DAKO automated IHC assay)[15]

Összefoglalás

- Nivolumab az első PD-1 inhibitor, mely túlélési előnyt mutatott a standard-of-care docetaxellel összevetve, megelőzően kezelt előrehaladott tüdő laphámcc. esetén.
- 41% - al csökkentette a halál valószínűségét (HR 0.59; *P* = 0.00025)
  - 1-y éves OS: 42% vs 24% 1,5 évest OS: 28% vs. 18%
  - mOS: 9.2 vs 6.0 hónap
- Teljesültek a vizsgálat másodlagos végpontjai is:
  - ORR: 20% vs 9% (*P* = 0.0083)
  - 1- évnél PFS: 21% vs 6.4%; mPFS: 3.5 vs 2.8 hó (HR 0.62; *P* = 0.0004)
- Nivolumab hatékonysága független volt a PD-L1 expressziótól
- Nivolumab jobb toxicitási profil
- FDA approval az USA-ban 2015 március 4-től.

CheckMate 057 (NCT01673867) vizsgálat felépítése:



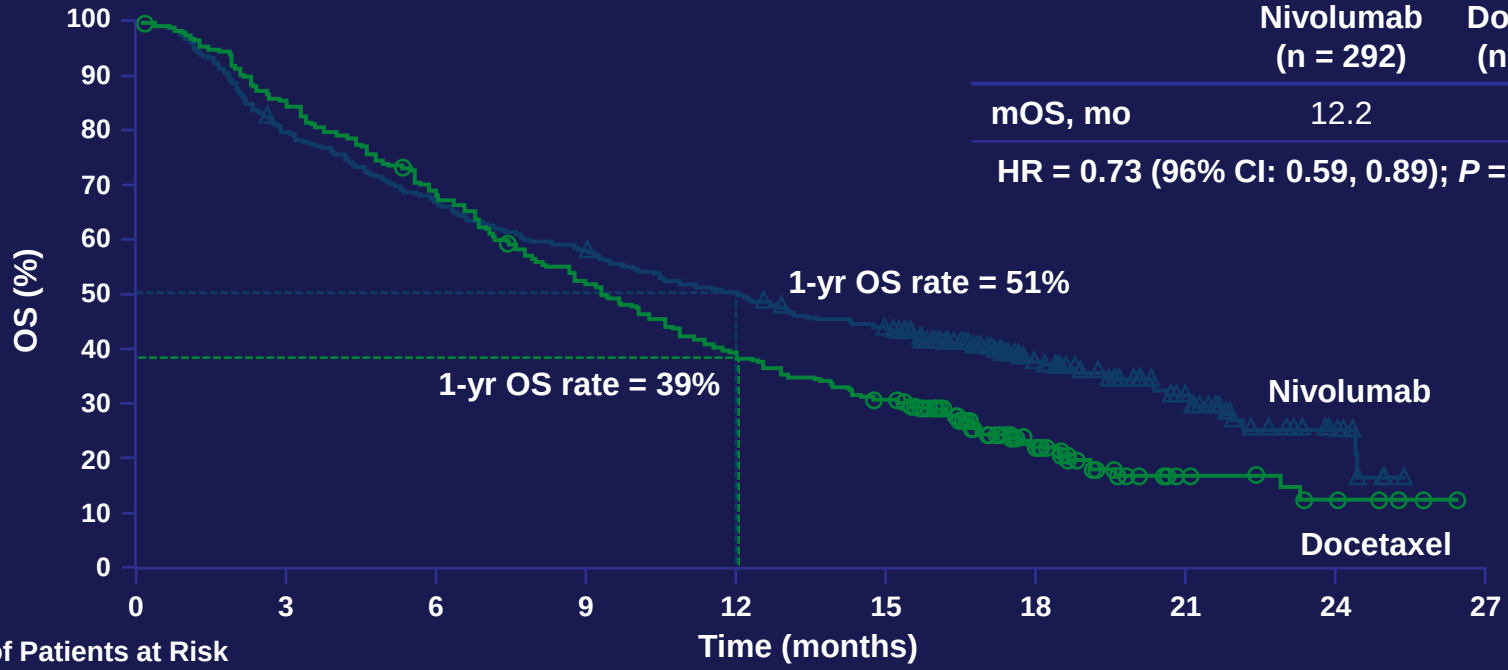
- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

Teljes túlélés

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015



Number of Patients at Risk

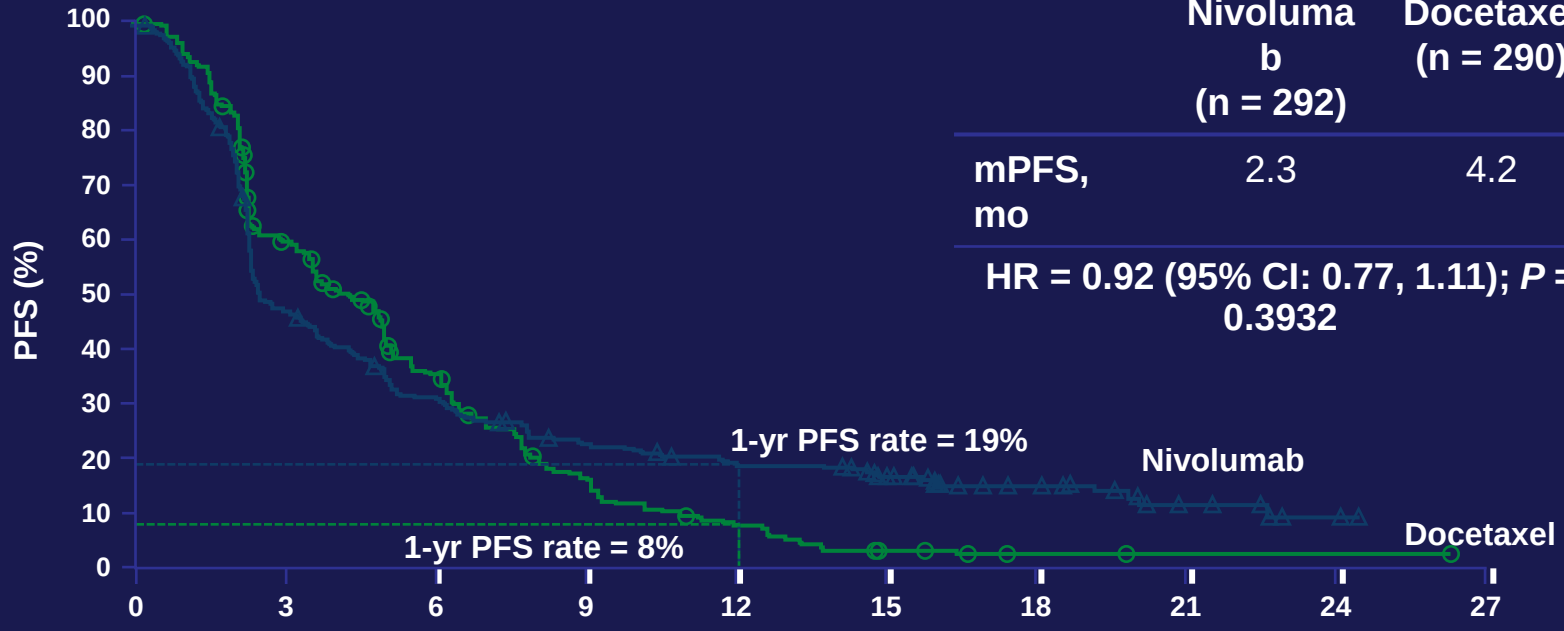
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

Progresszió mentes túlélés:

	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

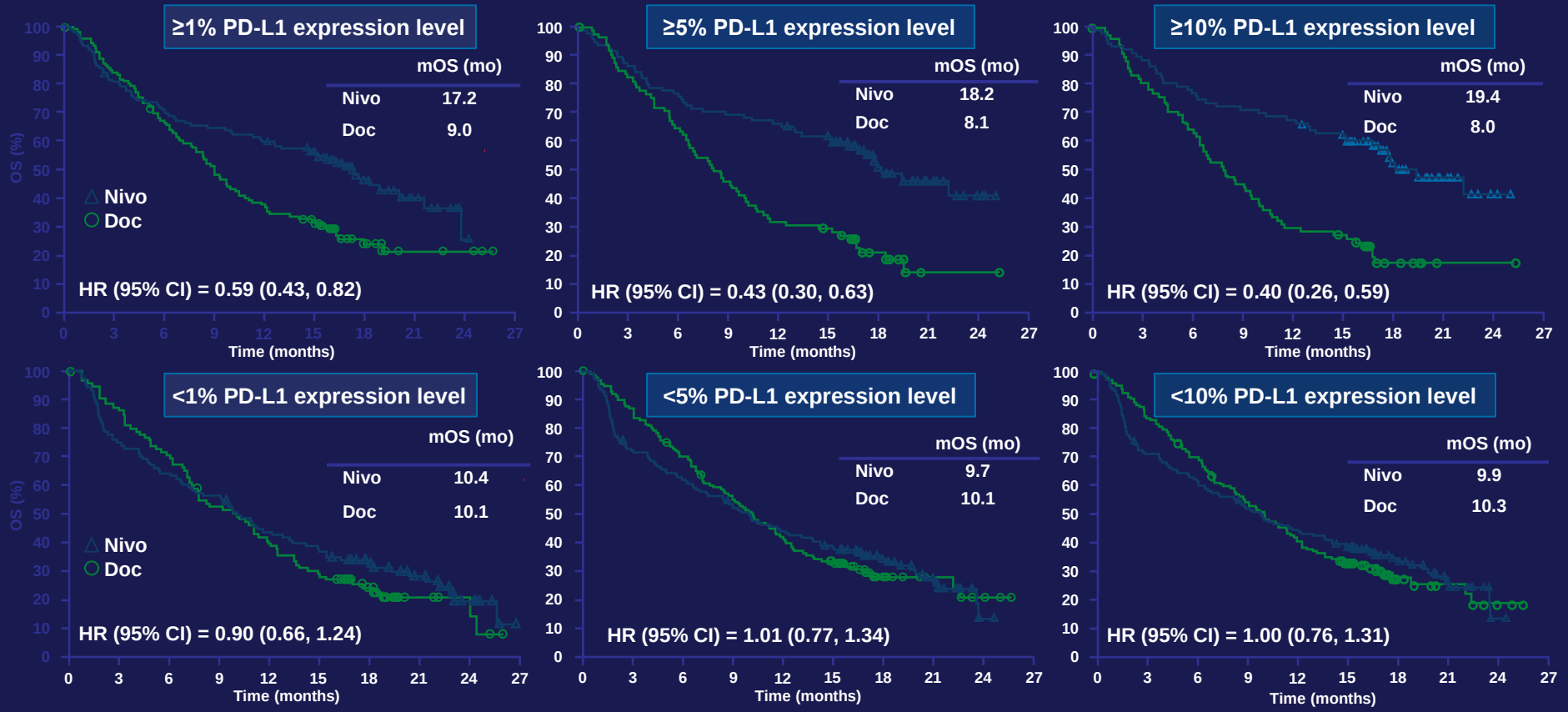
HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932



Number of Patients at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

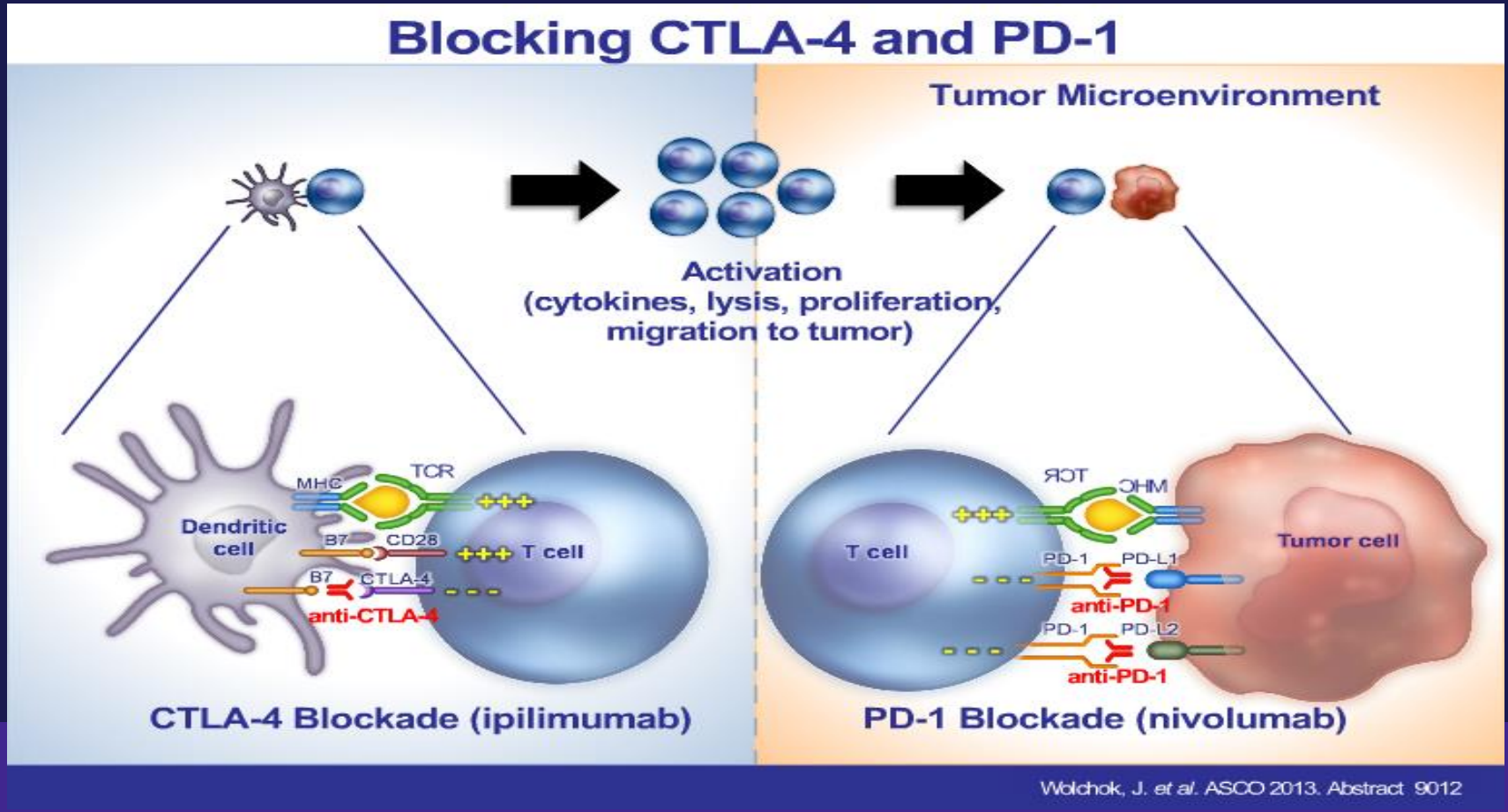
Symbols represent censored observations.

OS a PD-L1 expresszió függvényében:



Symbols represent censored observations.

Kettős immunológiai gátlás



Phase 1 Study of Pembrolizumab Plus Ipilimumab as Second-Line Therapy for Advanced Non-Small Cell Lung Cancer: KEYNOTE-021 Cohort D

Amita Patnaik,[1] Mark A. Socinski,[2] Matthew Gubens,[3]
Leena Gandhi,[4] James Stevenson,[5] Robert D. Bachman,[6]
Jennifer Bourque,[6] Joy Yang Ge,[6] Harry Raftopoulos,[6]
Ellie Im,[6] Shirish M. Gadgeel[7]

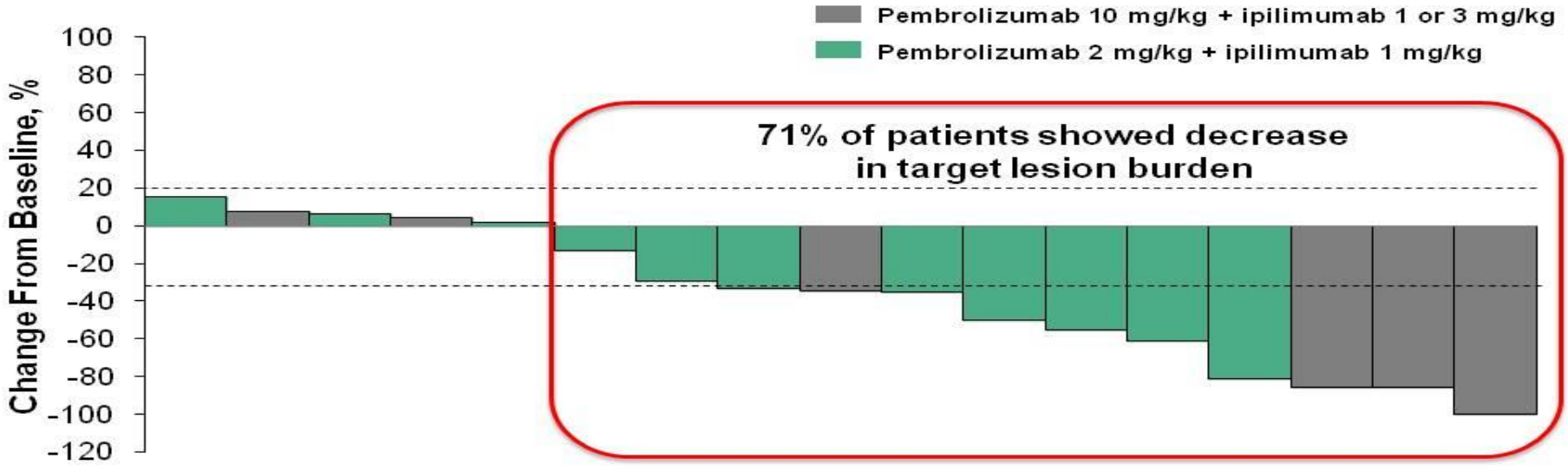
[1]South Texas Accelerated Research Therapeutics, San Antonio, TX; [2]University of Pittsburgh Cancer Center, Pittsburgh, PA; [3]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [4]Dana Farber Cancer Institute, Boston, MA; [5]Cleveland Clinic, Cleveland, OH; [6]Merck & Co., Inc., Kenilworth, NJ; [7]Barbara Ann Karmanos Cancer Center, Detroit, MI

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Amita Patnaik at 2015 ASCO Annual Meeting

A terápiás válasz a betegek 71 %-nál volt megfigyelhető

Change From Baseline in Tumor Size
(RECIST v1.1, Investigator Review)



Change from baseline was evaluated in patients with ≥1 postbaseline tumor assessment.
Analysis cutoff date: March 31, 2015.

PRESENTED AT: ASCO Annual '15 Meeting

Az első evidencián alapuló eredmények a tüdőrák kezelésében

A terápiás gyakorlatot megváltoztató adatok !

CO® DAILY NEWS

SUNDAY · MAY 31, 2015

Nivolumab Considered Practice Changing in Refractory, Advanced Nonsquamous NSCLC

Having recently been approved for second-line treatment of squamous non–small cell lung cancer (NSCLC), nivolumab demonstrated a significant overall survival (OS) benefit for patients with nonsquamous (NSQ) NSCLC based on data from the CheckMate 057 trial (Abstract LBA109) reported during "Immunotherapy for Every Patient: Check Your Enthusiasm," on Saturday, May 30. "Checkmate 057 is the second phase III trial to demonstrate superior survival with nivolumab over docetaxel

NSCLC for whom platinum-based doublet chemotherapy had failed. Patients were randomly assigned to receive the PD-1 immune checkpoint inhibitor nivolumab at a dose of 3 mg/kg every 2 weeks (292 patients) or docetaxel at a dose of 75 mg/m² every 3 weeks (290 patients) until disease progression or discontinuation because of toxicity or other reasons. "The confirmed prespecified boundary for overall survival was crossed, and an Independent Data Monitoring Committee was unanimous in declaring superiority in OS for

fore, at a 27% reduce
death. One-year OS w
the nivolumab group
to 39% for the docet
Survival benefits we
all subgroups of p
cept those whose
EGFR mutations.

Objective respon
was also significan
patients receivin
19% for the niv
versus 12% for
group (p = 0.02
no significant
progression-free

Jövőkép:

Első vonalban való alkalmazás

Adjuváns vizsgálatok

EGFR, ALK pozitivitás esetén hatékonysága

Kissejtes tüdőrák

Biomarkerek

Kombinációk

269 vizsgálat

CÉLZOTT TERÁPIA

EGFR mutáns tüdőrák

EGFR mutáns tüdőrák

EGFR Mutated NSCLC: Targeted Therapy

			RR (%)		Median PFS (mo)		Median OS (mo)	
Country	Trial	Agent	TKI	Chemo	TKI	Chemo	TKI	Chemo
	IPASS Mut +	gefitinib	71.2	47.3	9.5	6.3	21.6	21.9
	First-SIGNAL Mut +	gefitinib	84.6	37.5	8.4	6.7	30.6	26.5
	WJTOG	gefitinib	62.1	32.2	9.2	6.3	30.9	NR
	NEJ002	gefitinb	73.7	30.7	10.8	5.4	27.7	26.6
	OPTIMAL	erlotinib	83	36	13.7	4.6	22.6	28.8
	EURTAC	erlotinib	58	15	9.7	5.2	19.3	19.5
	LUX-Lung 3	afatinib	56.1	22.6	11.1	6.9	NR	NR
	LUX-Lung 6	afatinib	66.9	23.0	11.0	5.6	NR	NR

A CEETAC vizsgálat felépítése

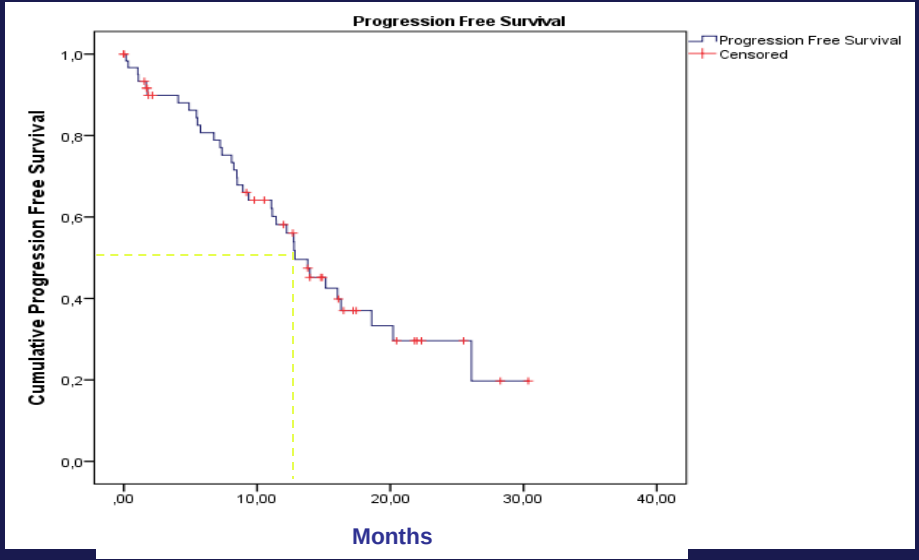
- **Kemonaiv**
- **St. IIIB/IV adenokarcinóma**
- ***EGFR* mut+**
  - **Exon 19 deléció vagy**
  - **Exon 21 pontmutáció***
- **ECOG PS 0–2**
- **n=60**

- **Nyílt, nem randomizált, multicentrikus, fázis IV-es klinikai vizsgálat**
- Regionális részvétel (kezelő ctr.): Magyarország (10), Törökország (5), Lettország (2)
- Beválasztás: 2012 március – 2014 január
- Utolsó beteg utolsó vizitje: 2015 január
- Adatzárás: 2015 június

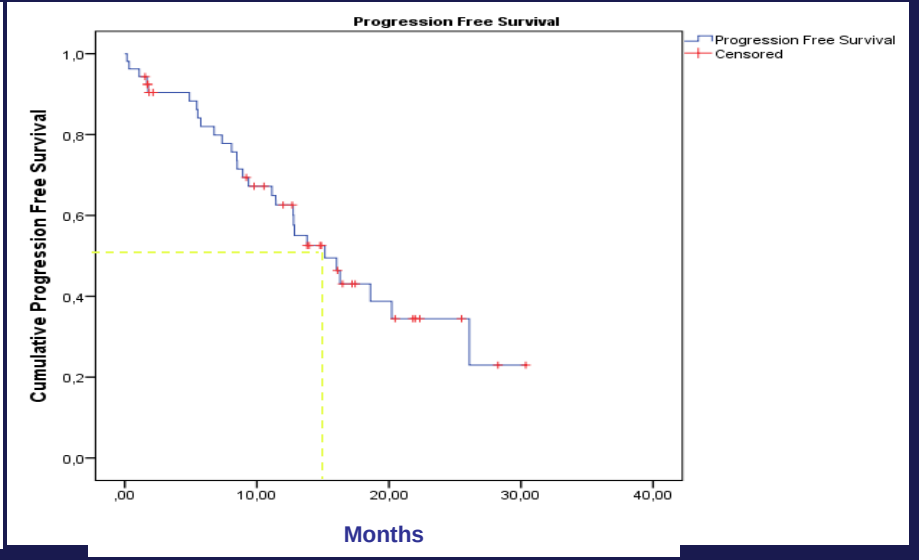
- **Elsődleges végpont**
  - Progressziómentes túlélés (**PFS**)
- **Másodlagos végpontok**
  - Objektív válaszráta (ORR)
  - 1-éves túlélési arány
  - Biztonságosság

Elsődleges végpont: PFS

Medián PFS: **12,846 hónap**
(95% CI: 9,901-15,791)
az ITT populációban (N=62)



Medián PFS: **15,146 hónap**
(95% CI: 10,832-19,459)
a PP populációban (N=53)



Másodlagos végpont: Válaszráták az ITT populációban

- **Legjobb válasz**:

Legjobb válasz	ITT populáció	
	N	%
Teljes válasz (CR)	1	1.8%
Részleges válasz (PR)	36	**64.3%**
Stabil betegség (SD)	18	32.1%
Progresszív betegség (PD)	1	1.8%
Összes:	56	100%

- Objektív válaszráta (**ORR** = CR + PR): **66,1%**
- Klinikai haszonráta (**CBR** = CR + PR + SD): **98,2%**

ORR = Objective Response Rates; CBR = Clinical Benefit rate; CR = Complete Response; PR = Partial Response; SD = Stable Disease

LUX Lung 7 vizsgálat:

- **Stage IIIB/IV adenocarcinoma of the lung**
- ***EGFR* mutation (Del19 and/or L858R) in the tumor tissue***
- **No prior treatment for advanced/ metastatic disease**
- **ECOG PS 0/1**

1:1

Afatinib 40 mg once daily†

Stratified by
- Mutation type (Del19/L858R)
- Brain metastases (present/absent)

Gefitinib 250 mg once daily

Primary endpoints:
- PFS (independent)
- TTF
- OS

Secondary endpoints:
- ORR
- Time to response
- Duration of response
- Duration of disease control
- Tumor shrinkage
- HRQoL
- Safety

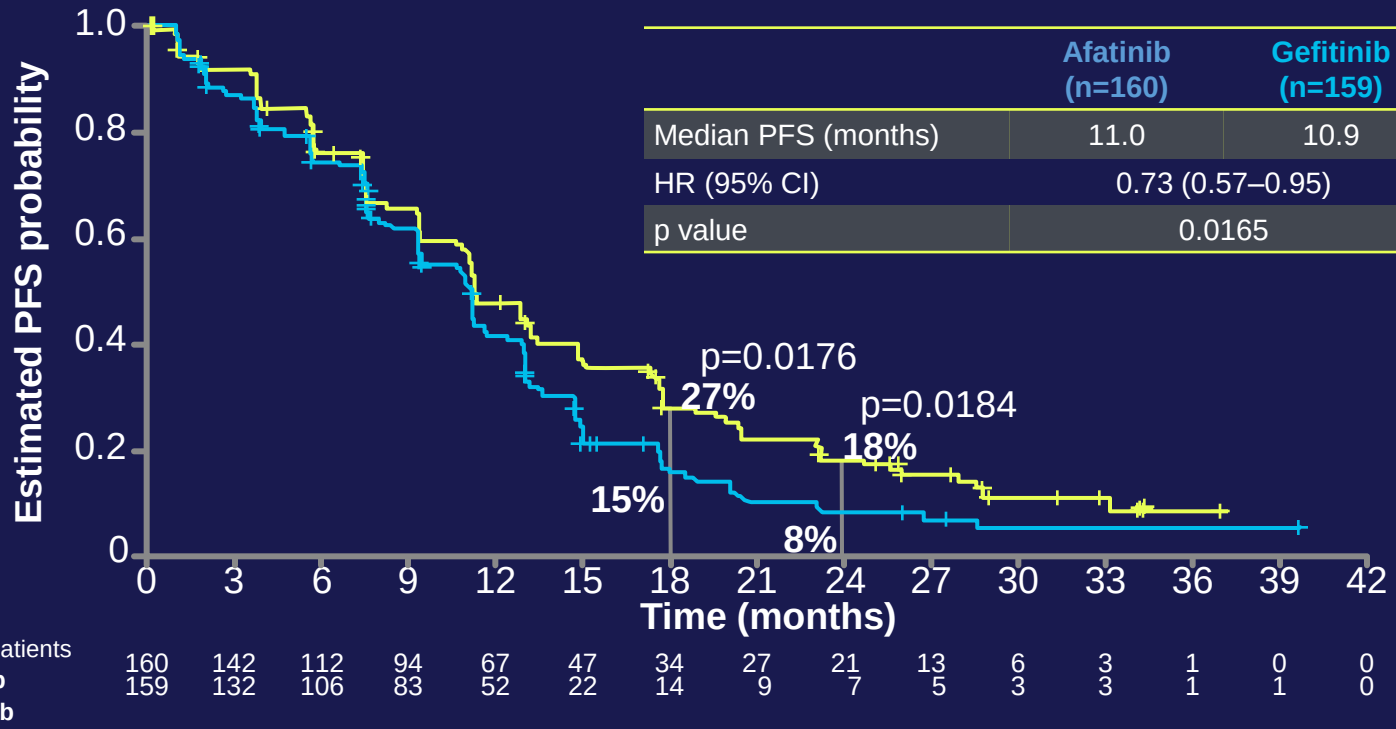
- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter

ECOG PS, Eastern Oncology Cooperative Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTF, time to treatment failure

*Central or local test

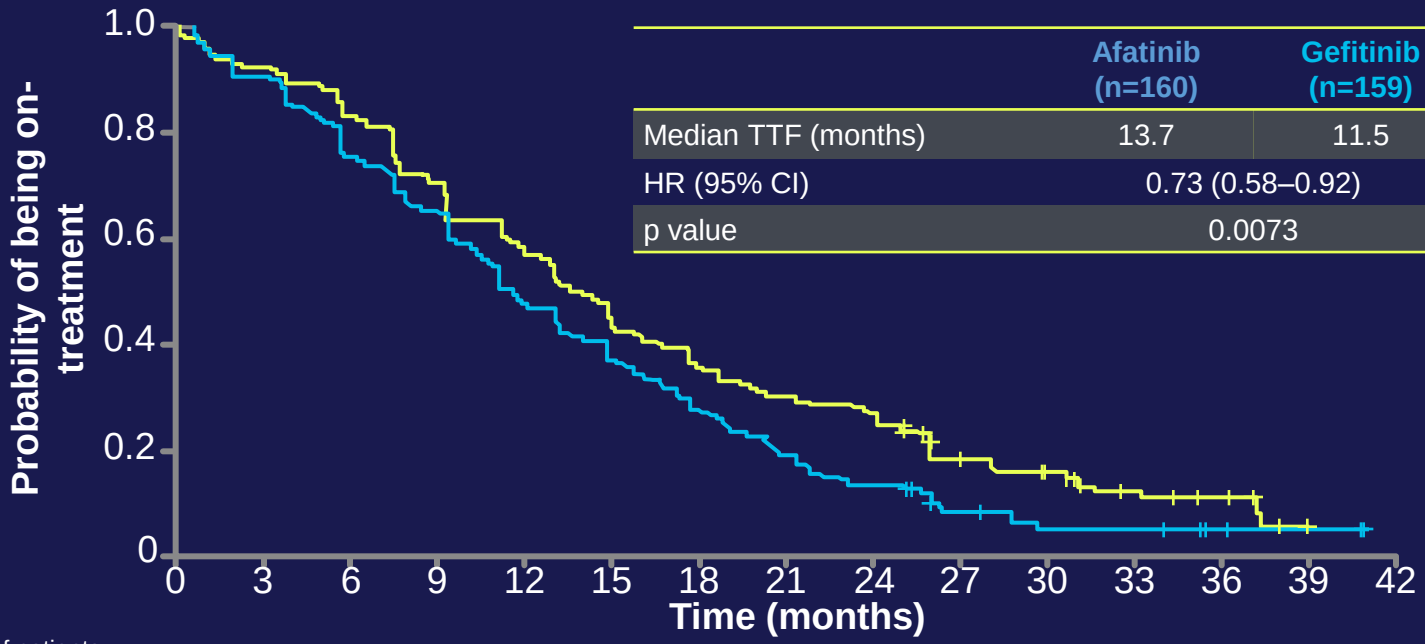
†Dose modification to 50, 30, 20 mg permitted in line with prescribing information

PFS by independent review



	Afatinib (n=160)	Gefitinib (n=159)
Median PFS (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	

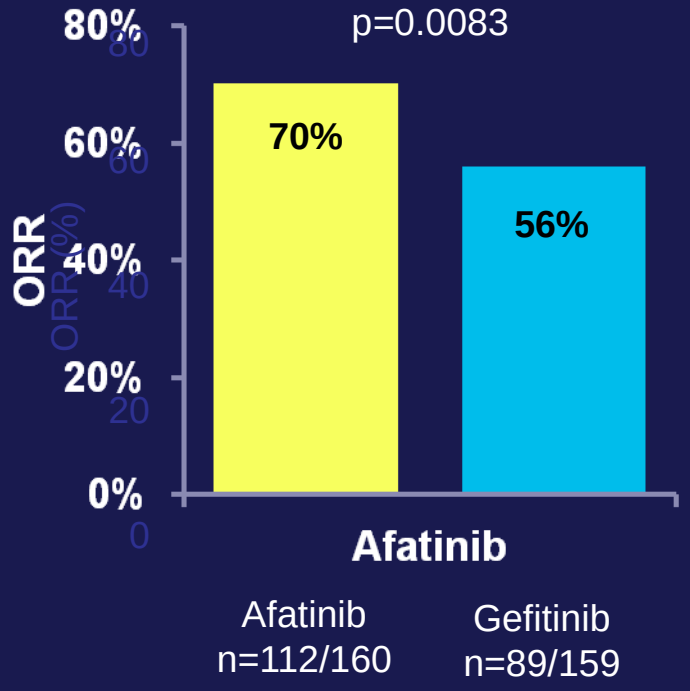
Time to treatment failure



	Afatinib (n=160)	Gefitinib (n=159)
Median TTF (months)	13.7	11.5
HR (95% CI)	0.73 (0.58–0.92)	
p value	0.0073	

No. of patients														
Afatinib	160	148	133	113	91	68	56	48	40	25	18	9	5	0	0
Gefitinib	159	144	120	103	74	59	43	30	21	11	6	6	2	2	0

Objective response and duration of response (independent review)



	Afatinib (n=112)	Gefitinib (n=89)
Median DoR (months)	10 .1	8.4
95% CI	(7.8–11.1)	(7.4–10.9)

DoR, duration of response

A vizsgálat értékelése

- Afatinib significantly improved PFS of patients with *EGFR*m+ NSCLC relative to gefitinib. Results are consistent across subgroups
- Afatinib treatment was associated with a significant improvement in response rate and TTF
- The improvement in efficacy was observed in both Del19 and L858R populations
- OS data immature (current HR: 0.87, 95%CI: 0.66–1.15)
- AEs in both groups were consistent with previous experience, and were manageable leading to equally low rates of treatment discontinuation
- LUX-Lung 7 confirms the benefit of irreversible ErbB blockade with afatinib over reversible EGFR inhibition with gefitinib in treatment of *EGFR*m+ NSCLC

LUX-Lung 3 és 6 vizsgálatok felépítése:

- **Stage IIIB/IV adenocarcinoma of the lung**
- **Presence of *EGFR* mutation in the tumor tissue***
- **No prior treatment with chemotherapy for advanced/metastatic disease or EGFR inhibitors**
- **ECOG PS 0 or 1**

Randomization

2:1

Stratification by EGFR mutation type: Del19/L858R/other
and by race (LUX-Lung 3 only): Asian/non-Asian

Afatinib
40 mg orally once daily

LUX-Lung 3[1]:
Cisplatin + pemetrexed
up to 6 cycles

LUX-Lung 6[2]:
Cisplatin + gemcitabine
up to 6 cycles

Primary endpoint: PFS (independent review)
Secondary end points: ORR, DCR, OS, PRO, safety

*EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213.

LUX-Lung 3 és 6: progresszió mentes túlélés

- Szignifikánsan megnövelte a PFS-t az afatinibes csoportban a platina kettős kezeléshez képest (elsődleges végpont)[1,2]

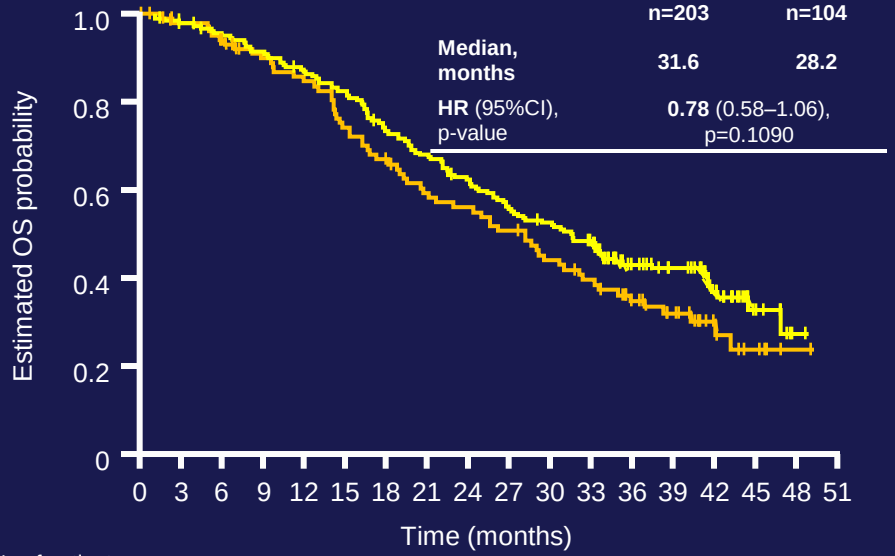
Common mutations (Del19/L858R)

	LUX-Lung 3 (n=307)		**LUX-Lung 6** (n=324)	
	Afatinib	Pem/Cis	Afatinib	Gem/Cis
Median PFS, mo	**13.6**	**6.9**	**11.0**	**5.6**
HR, p-value	**HR=0.47,** p<0.0001		**HR=0.25,** p<0.0001	

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213; 3. Yang et al. *J Thorac Oncol*. 2013;8:suppl 2 (O03.05); 4. Sequist et al. *J Thorac Oncol*. 2013;8:suppl 2 (P3.11-023).

LUX-Lung 3 és 6: teljes túlélés

LUX-Lung 3

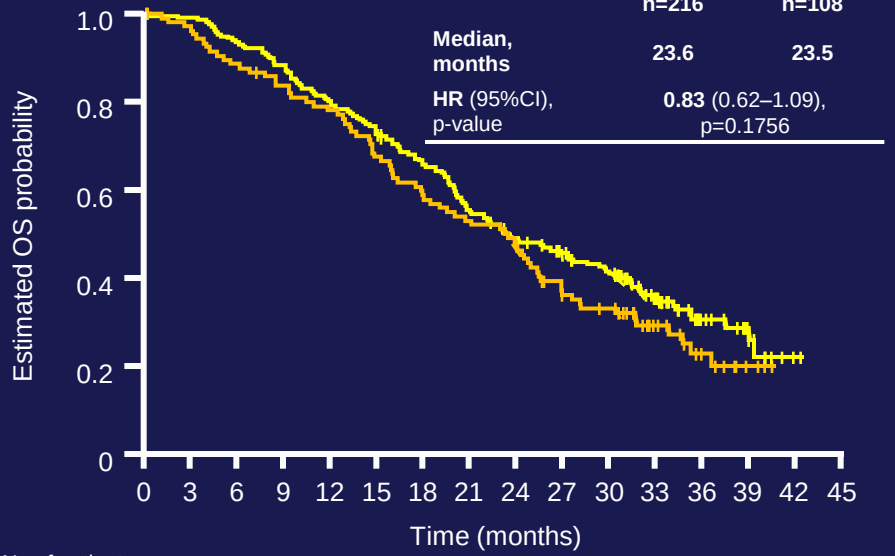


	Afatinib n=203	Pem/Cis n=104
Median, months	31.6	28.2
HR (95%CI), p-value	0.78 (0.58–1.06), p=0.1090	

No of patients

Afatinib	203	197	188	181	171	162	143	133	121	108	101	90	58	49	32	9	1	0
Pem/Cis	104	98	92	86	81	71	63	55	52	47	40	35	26	20	10	5	1	0

LUX-Lung 6

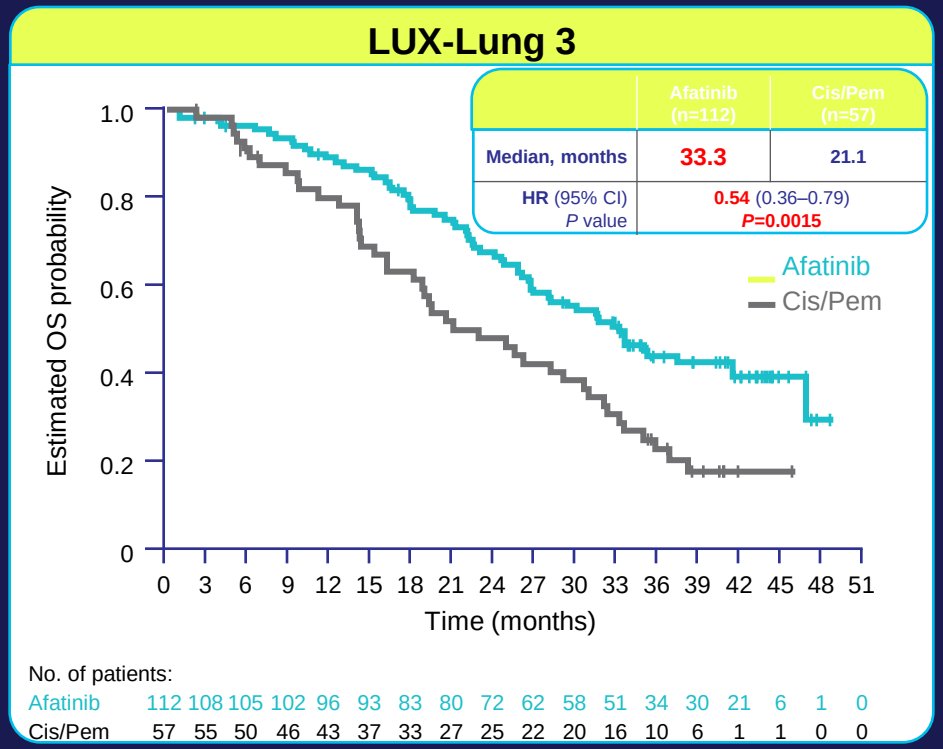


	Afatinib n=216	Gem/Cis n=108
Median, months	23.6	23.5
HR (95%CI), p-value	0.83 (0.62–1.09), p=0.1756	

No of patients

Afatinib	216	214	202	190	172	158	141	118	104	93	80	51	19	9	1	0	
Gem/Cis	108	101	93	87	81	70	61	55	49	36	30	17	8	3	0	0	

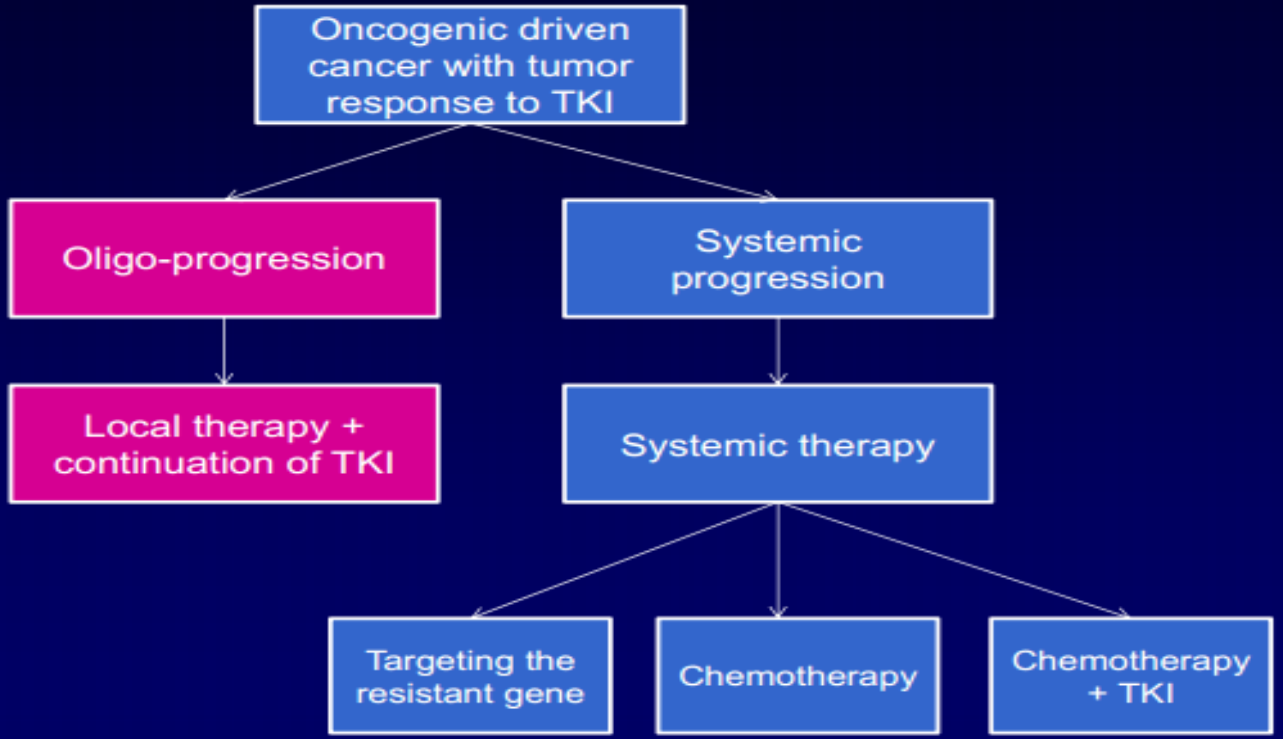
Szignifikáns afatinib OS előny Del19-es EGFR mutációban



Afatinib: Szignifikáns OS többlet del19-ben!
A különbség cisz/pem-hez képest mediánban 1 év.

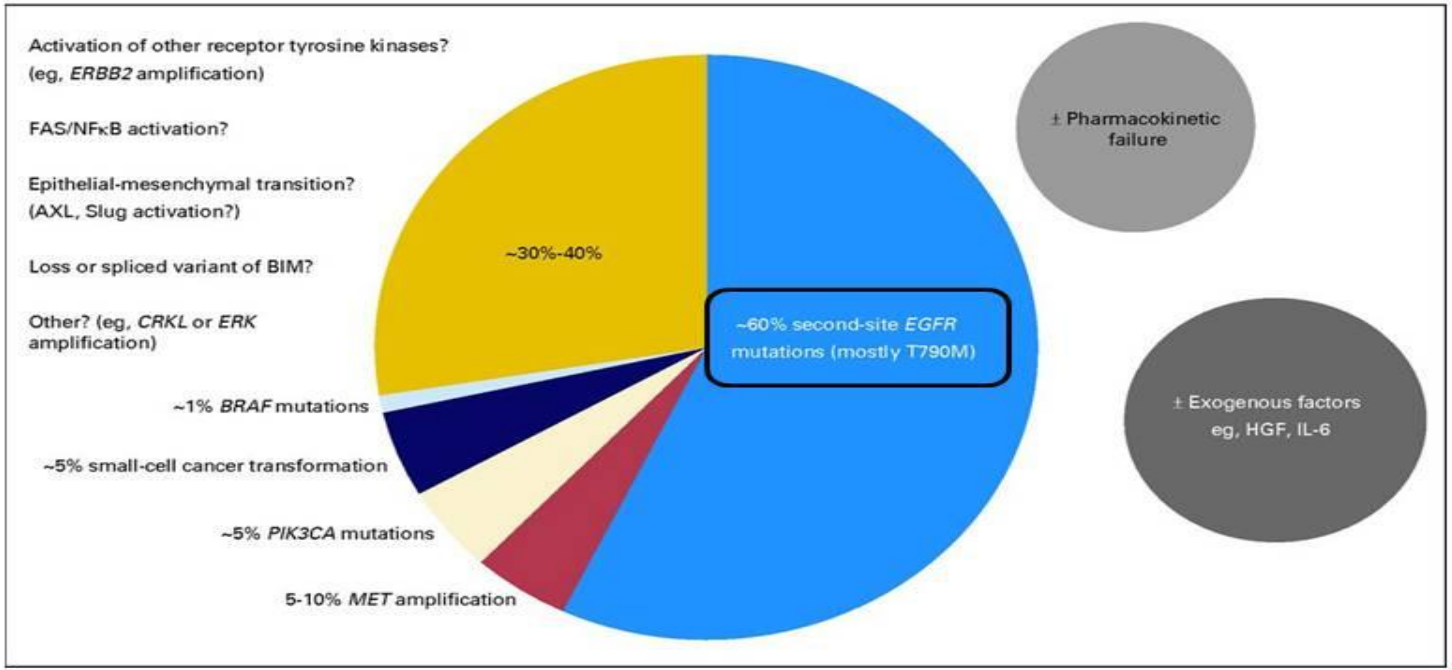
Presented by Yang et al. ASCO 2014. Abstract 8004.

Treatment of TKI Resistance



A megelőző EGFRTKI kezelés során kialakult rezisztencia

Acquired resistance to EGFR inhibition



Ref: Ohashi, K Journal of Clinical Oncology 2013

Harmadik generációs EGFR TKI vegyületek

Third Generation (mutant specific) EGFR TKIs

- A (relatively) new class of drugs irreversibly inhibits mutant EGFR, in particular EGFR T790M, with much less activity against wild-type EGFR.
- Effective in preclinical tumor models with both EGFR-TKI-sensitizing and T790M resistance mutations.

	Drug	Target	Reversible/ Irreversible	Company
3rd generation (mutant specific)	AP26113	EGFR/ALK	Reversible	Ariad
	CO-1686	Mutant EGFR	Irreversible	Clovis
	AZD9291	Mutant EGFR	Irreversible	Astra Zeneca
	EGF816	Mutant EGFR	Irreversible	Novartis
	ASP8273	Mutant EGFR	Irreversible	Astellas

Ref: Yu, Riely, and Lovly Clinical Cancer Research 2014

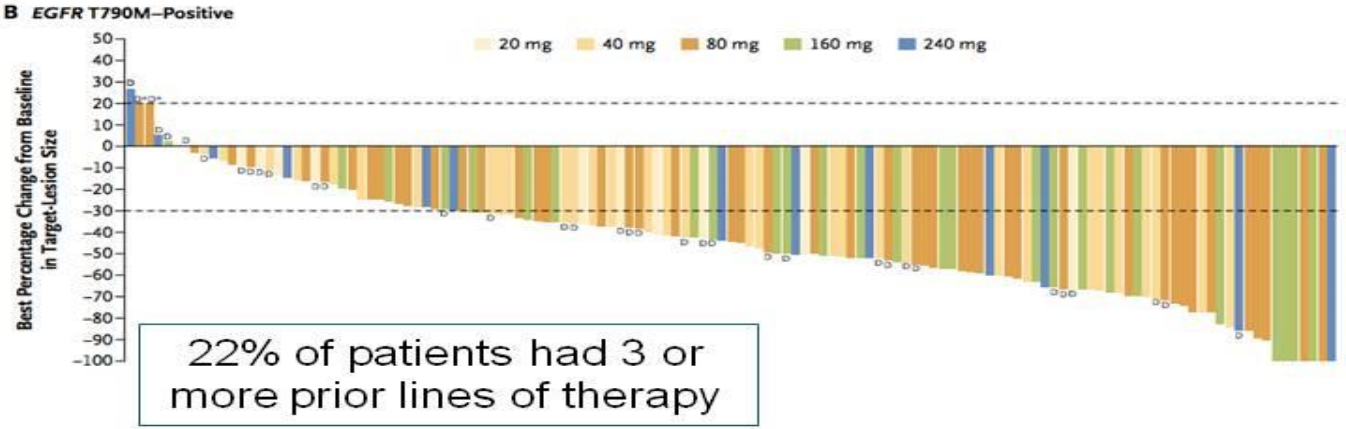
Presented By Christine Lovly at 2015 ASCO Annual Meeting

AZD9291 (osimertinib)-TAGRISSO hatékony T790M mutáció esetén

AZD9291 in *EGFR* T790M-positive

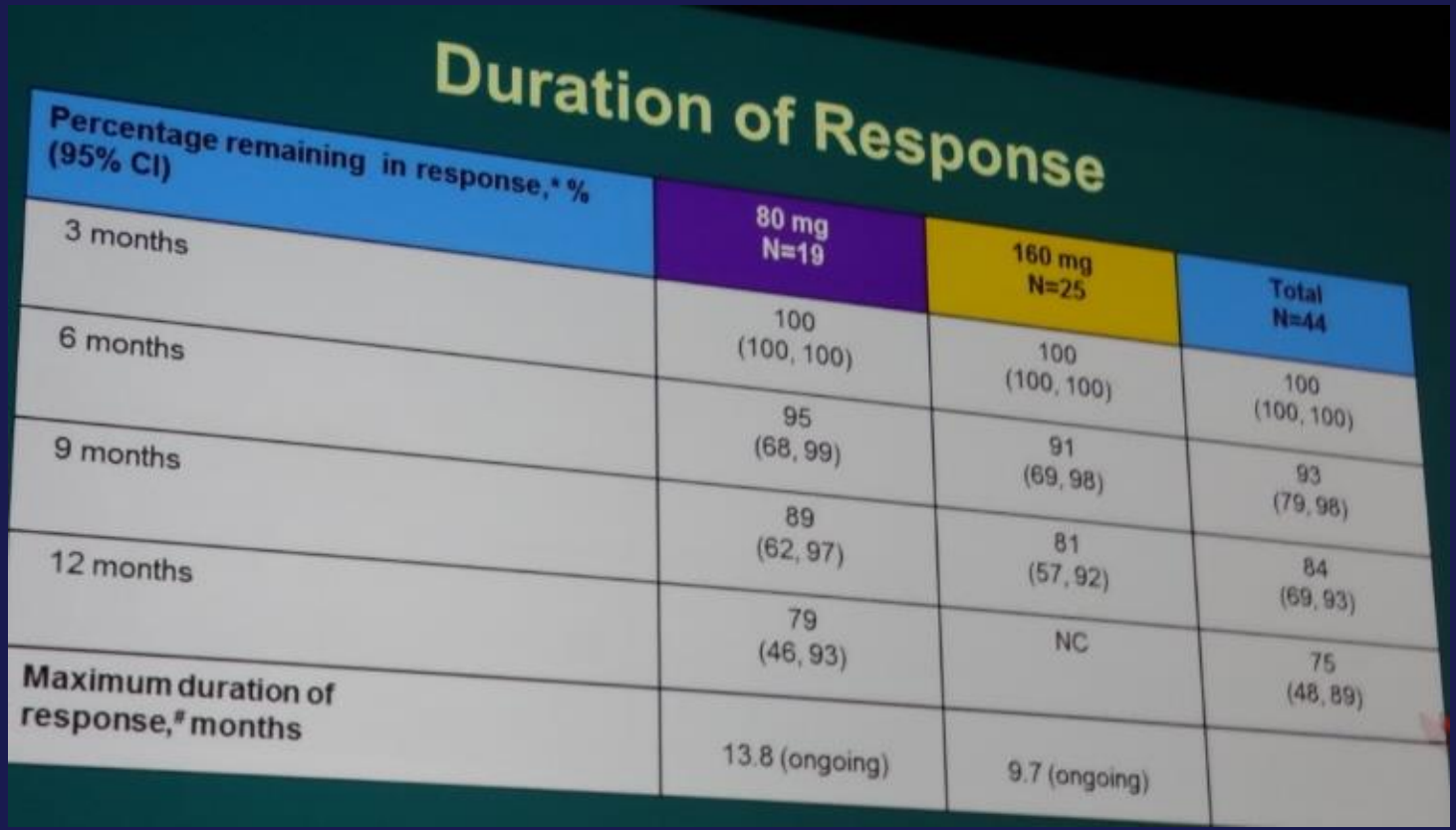
Prior Cytotoxic Regimens

	Total N = 253
Median number of regimens (range)	2 (0–9)
Number of regimens, n	
0	51
1	65
2	70
3	38
4	13
5	6
6	3
7	1
8	3
9	1
Unknown	2



Janne et al, NEJM 2015

A terápiás válasz időtartama:



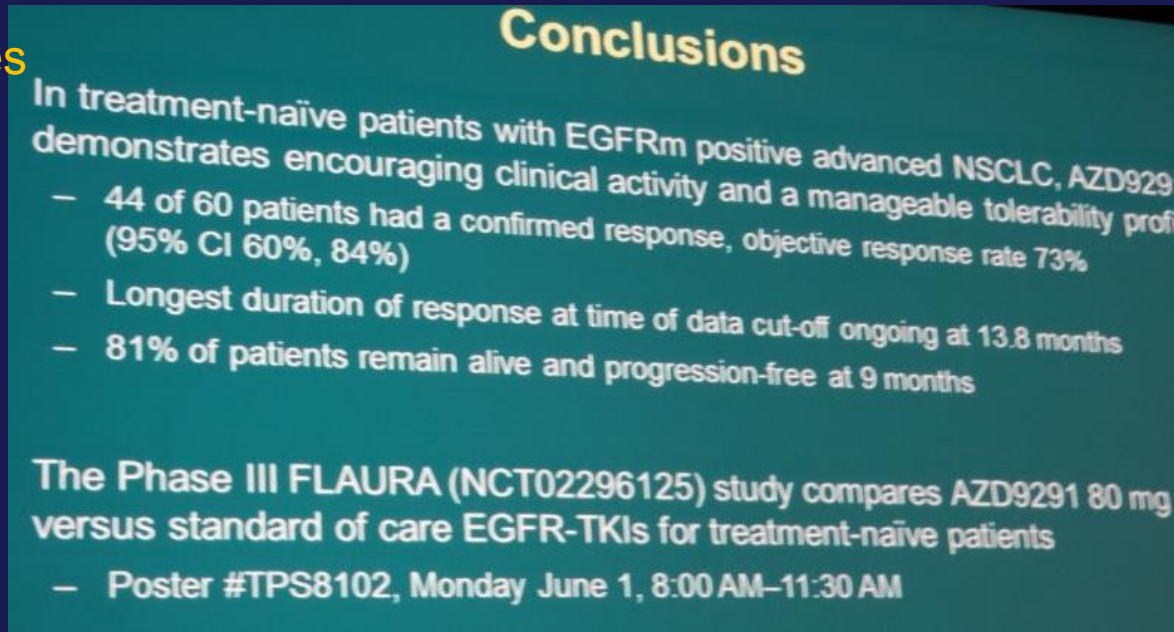
Duration of Response

Percentage remaining in response,* % (95% CI)	80 mg N=19	160 mg N=25	Total N=44
3 months	100 (100, 100)	100 (100, 100)	100 (100, 100)
6 months	95 (68, 99)	91 (69, 98)	93 (79, 98)
9 months	89 (62, 97)	81 (57, 92)	84 (69, 93)
12 months	79 (46, 93)	NC	75 (48, 89)
Maximum duration of response,# months	13.8 (ongoing)	9.7 (ongoing)	

Biztató eredmények- FLAURA VIZSGÁLAT

RR: 73 %

A betegek 83 % progressziómentes 9 hónap után !

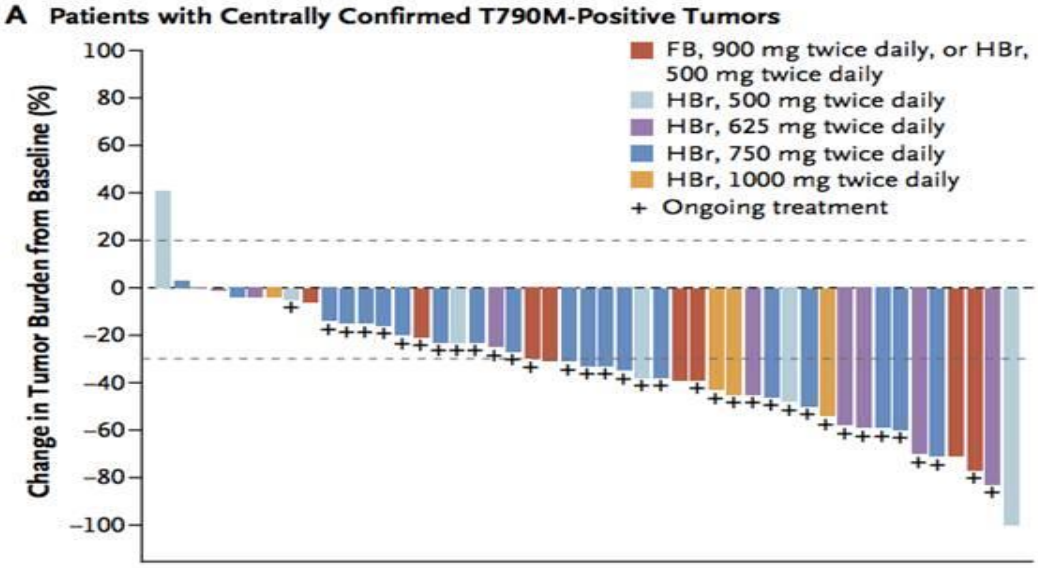


Rociletinib hatékonysága T790M mutáció esetén

Rociletinib in *EGFR* T790M-positive

Table 1. Baseline Characteristics of the Patients.

Characteristic	Any Dose of Rociletinib (N = 130)
Median age — yr	60.0
Female sex — no. (%)	100 (77)
Asian race — no. (%)*	19 (15)
ECOG performance-status score of 0 — no. (%)†	35 (27)
History of brain metastases — no. (%)	57 (44)
≥3 Metastatic sites — no. (%)	65 (50)
History of diabetes or impaired glucose tolerance — no. (%)	12 (9)
Previous lines of therapy — median	4
Previous EGFR inhibitor ongoing at study consent — no. (%)	94 (72)
Previous lines of therapy containing an EGFR inhibitor — median	2
Previous use of erlotinib — no. (%)	120 (92)
Previous use of gefitinib — no. (%)	13 (10)
Previous use of afatinib — no. (%)	23 (18)
Initial activating EGFR mutation — no. (%)	
Del19	74 (57)
L858R	42 (32)
Other	11 (8)
Unknown	3 (2)

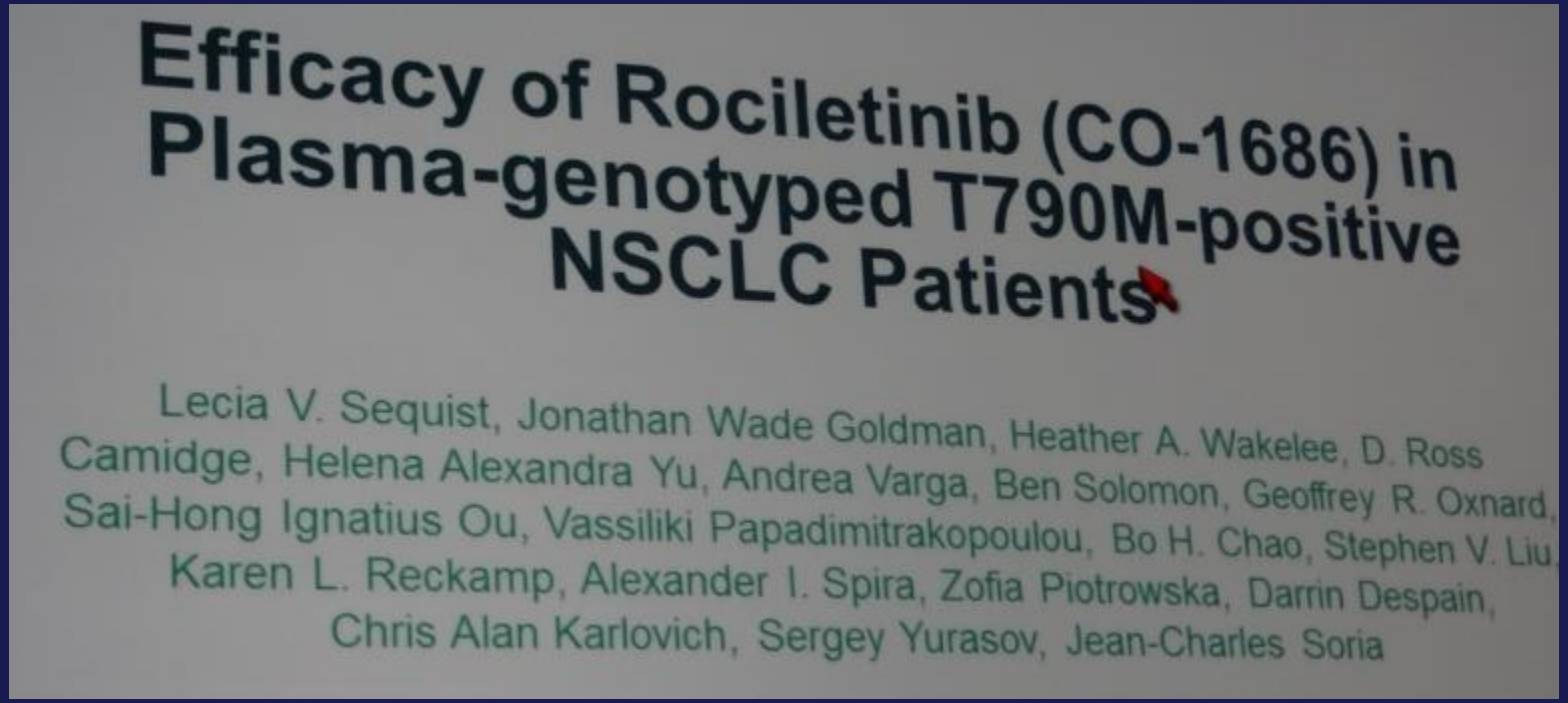


Sequist et al, NEJM 2015

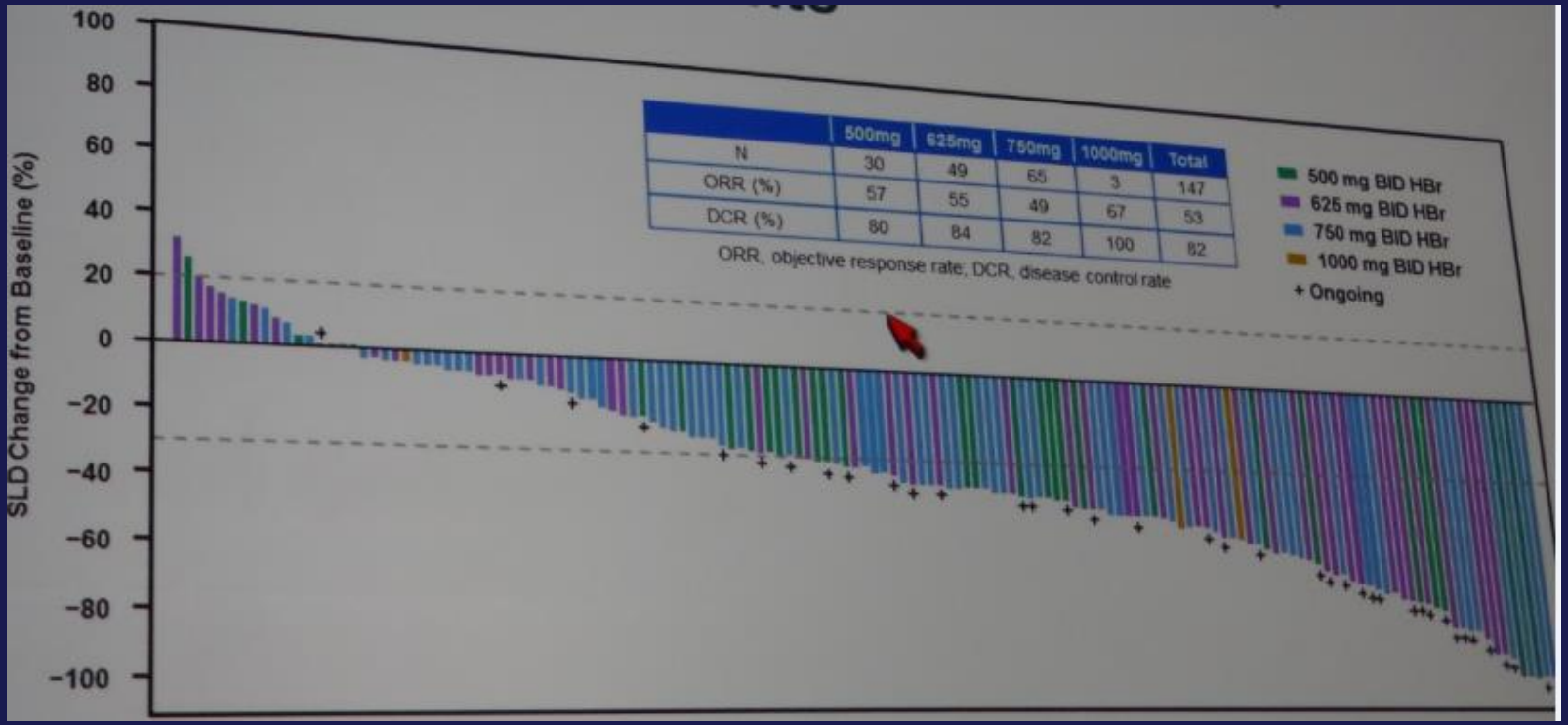
PRESENTED AT: ASCO Annual '15 Meeting

Presented By Gregory Riely at 2015 ASCO Annual Meeting

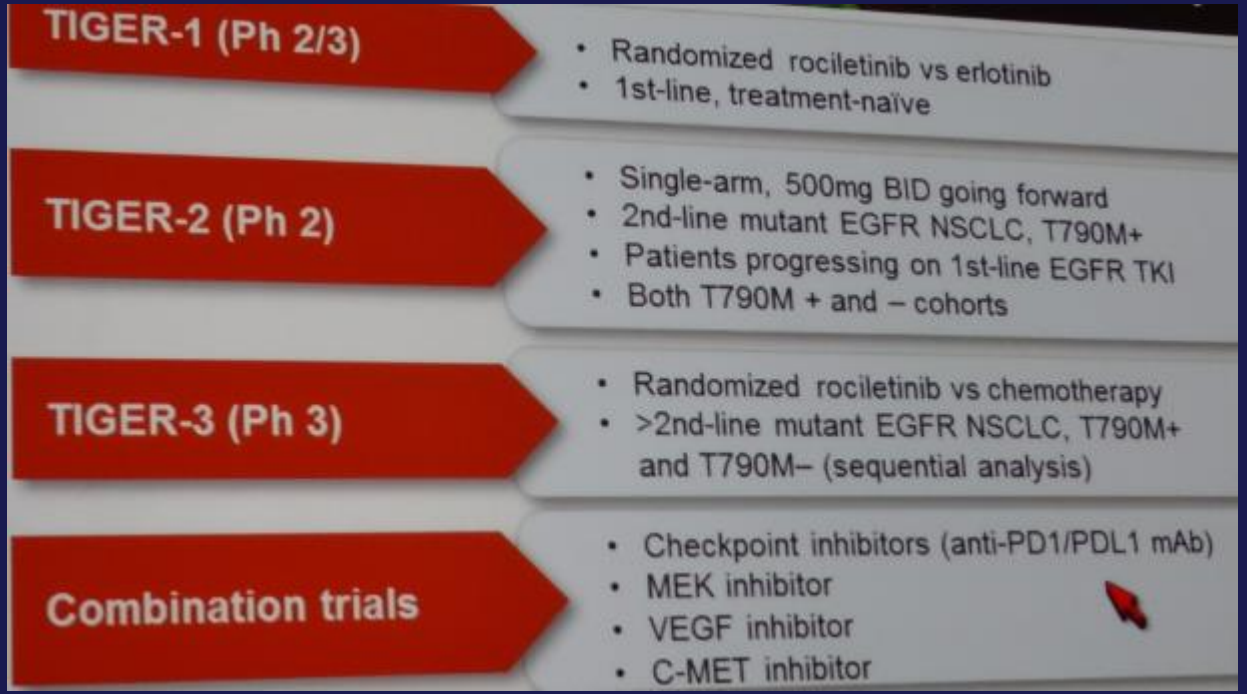
CO-1686 hatékonyság, liquid biopsia összefüggései (Ph 1-2)



Hasonló eredmények plazma T790 M+ poz. esetén



CO-1686 vizsgálati tervek:



EGFR GÁTLÓK, MELYIKET VÁLASSZAM ?

EGFR inhibitors

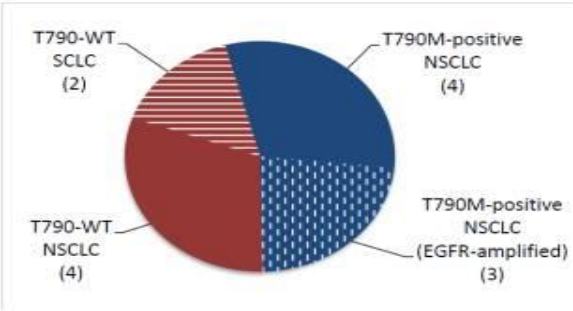
	Gefitinib	Erlotinib	Afatinib	Rociletinib	AZD9291
Highly active	Yes	Yes	Yes	Yes	Yes
Tolerability	Good	Good	Moderate	Moderate	Good
Therapeutic range	Moderate	Wide	Moderate	Moderate	Wide
Predictive biomarker	Yes	Yes	Yes	Probably	Probably
Off target activity	Wildtype	Wildtype	Wildtype, HER2	IGFR1	Minimal
CNS activity	Yes	Yes	Probably?	Maybe?	Maybe?

Harmadik gen. EGFRTKI kezelés során kialakult rezisztencia genetikai háttere

Acquired resistance to 3rd generation EGFR inhibitors

Acquired resistance to rocelitinib

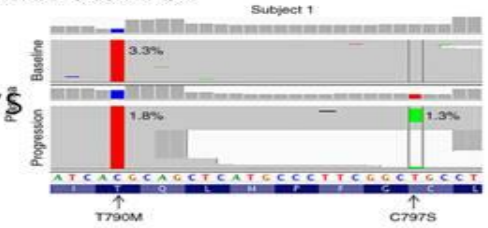
- 12 patients with T790M+ tumors at start of rocelitinib
- 13 biopsy samples
- 7 tumors retained T790M at the time of rocelitinib resistance
  - 3 tumors gained *EGFR* amplification
- 6 had loss of T790M at the time of rocelitinib resistance
  - Tumors became T790 wild type
  - 2 T790 wild-type tumors has conversion to SCLC histology

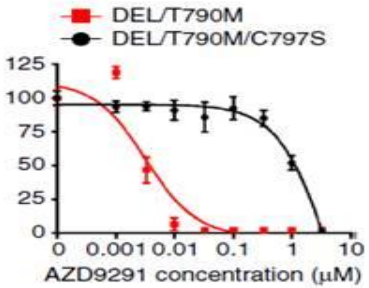


Piotrowska et al Cancer Discov 2015

Acquired resistance to AZD9291

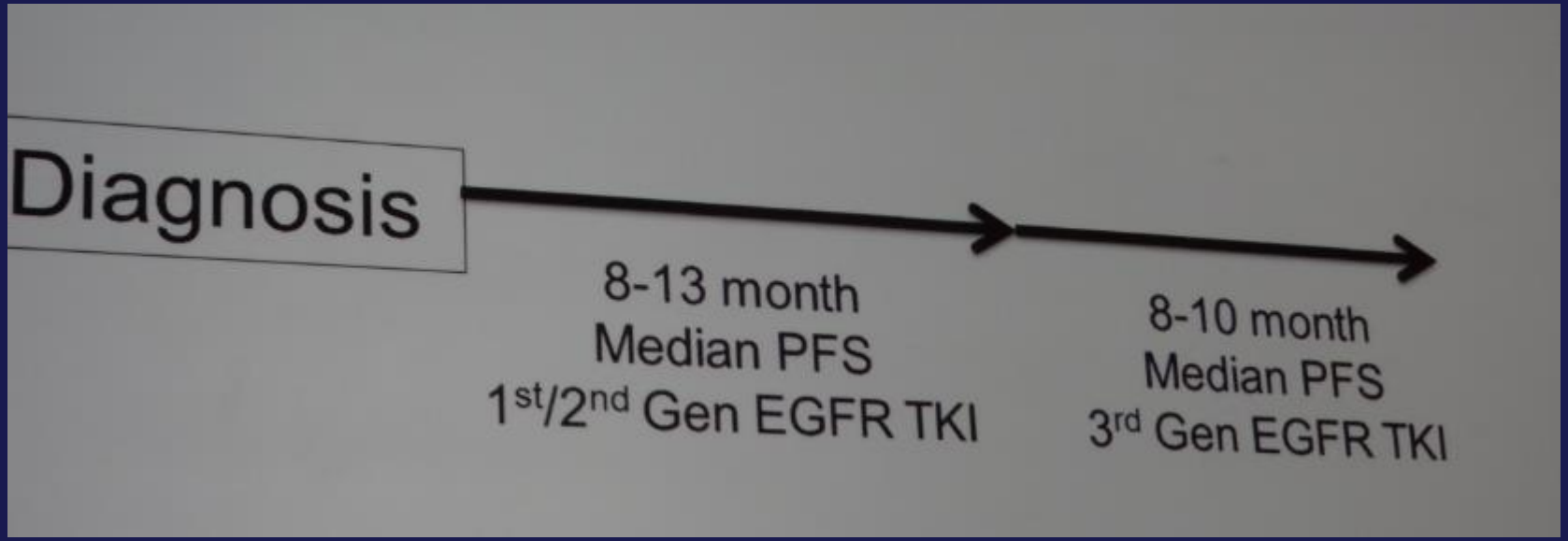
- Study of cell free plasma DNA (cfDNA) from 15 patients with acquired resistance to AZD9291 (all had T790M at the start of AZD9291).
- 6/15 cases: acquired C797S mutation
  - genotype: *EGFR* exon19 del, T790M, C797S
- 5/15 cases: maintained T790M; no C797S
  - genotype: *EGFR* exon19 del, T790M
- 4/15 cases: lost T790M mutation
  - genotype: *EGFR* exon19 del





Thress et al Nature Medicine 2015

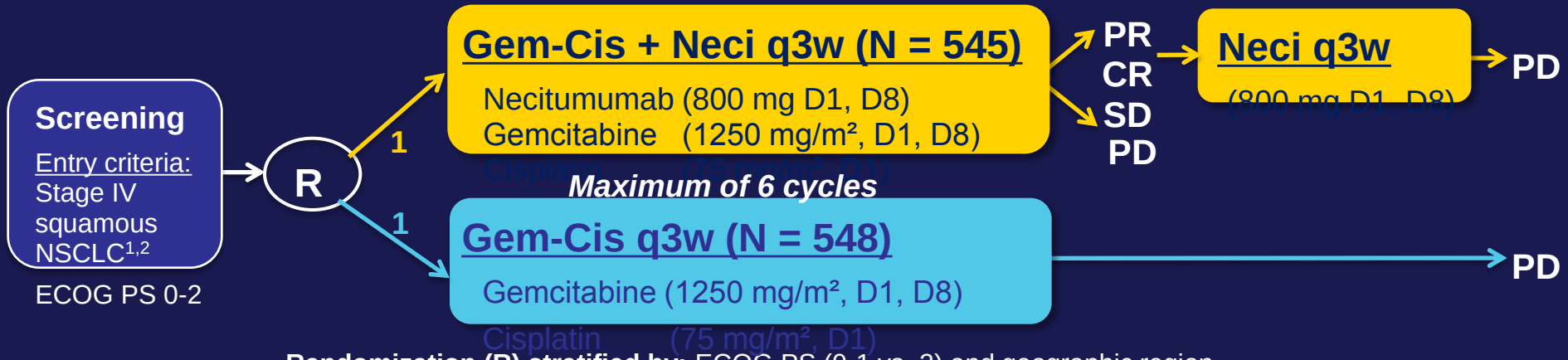
EGFR mutáns betegek kezelése



További generációs EGFRTKI vegyületek fejlesztése , harmadik generációs vegyületek rezisztenciájának vizsgálata

Laphámsejtes karcinóma

A vizsgálat felépítése:



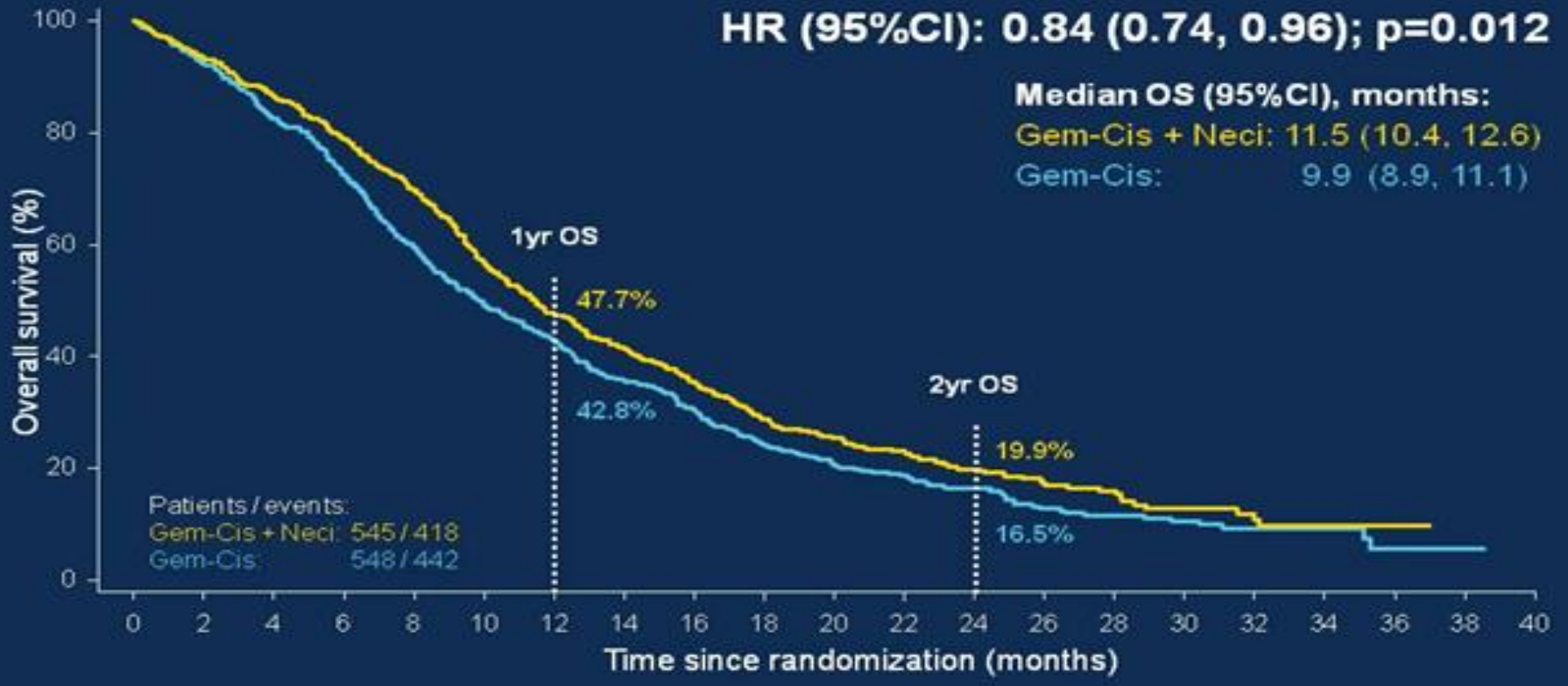
Randomization (R) stratified by: ECOG PS (0-1 vs. 2) and geographic region (North America, Europe and Australia; vs. South America, South Africa and India; vs. Eastern Asia)

Patient selection not based on EGFR protein expression

Radiographic tumor assessment (investigator read): at baseline and every 6 weeks until PD

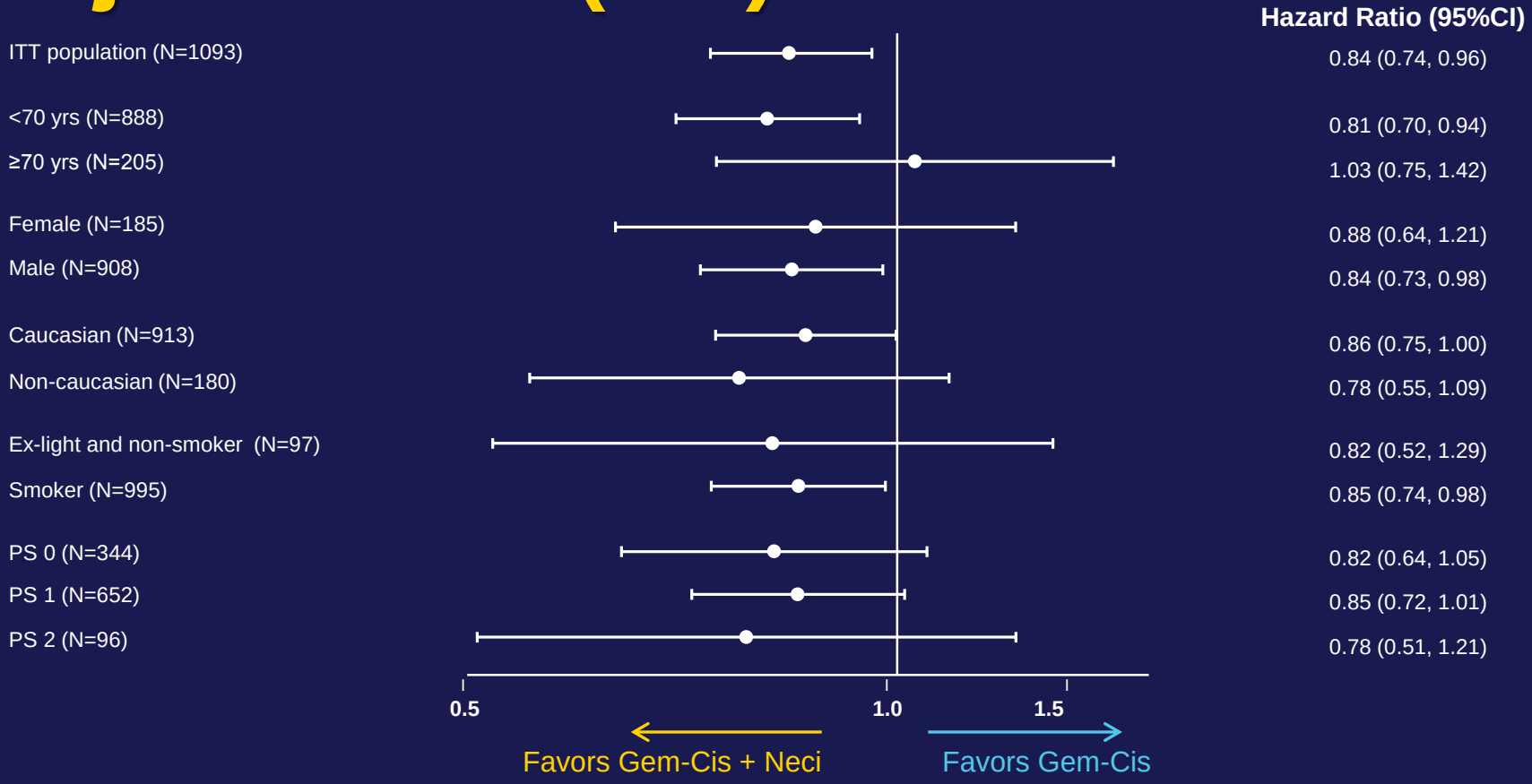
Mandatory tissue collection

Elsődleges végpont: teljes túlélés



Follow-up time (median): Gem-Cis + Neci: 25.2 months; Gem-Cis: 24.8 months

Teljes túlélés (ITT) :



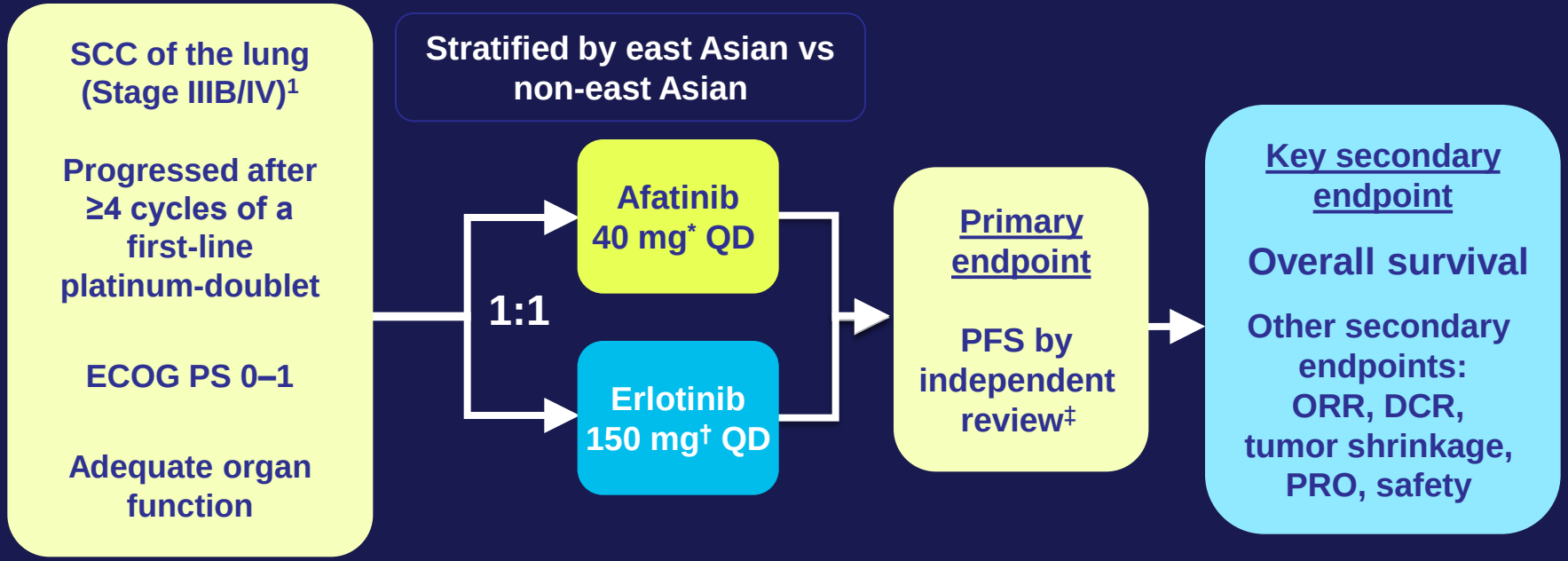
Presented by: Nick Thatcher

Következtetések:

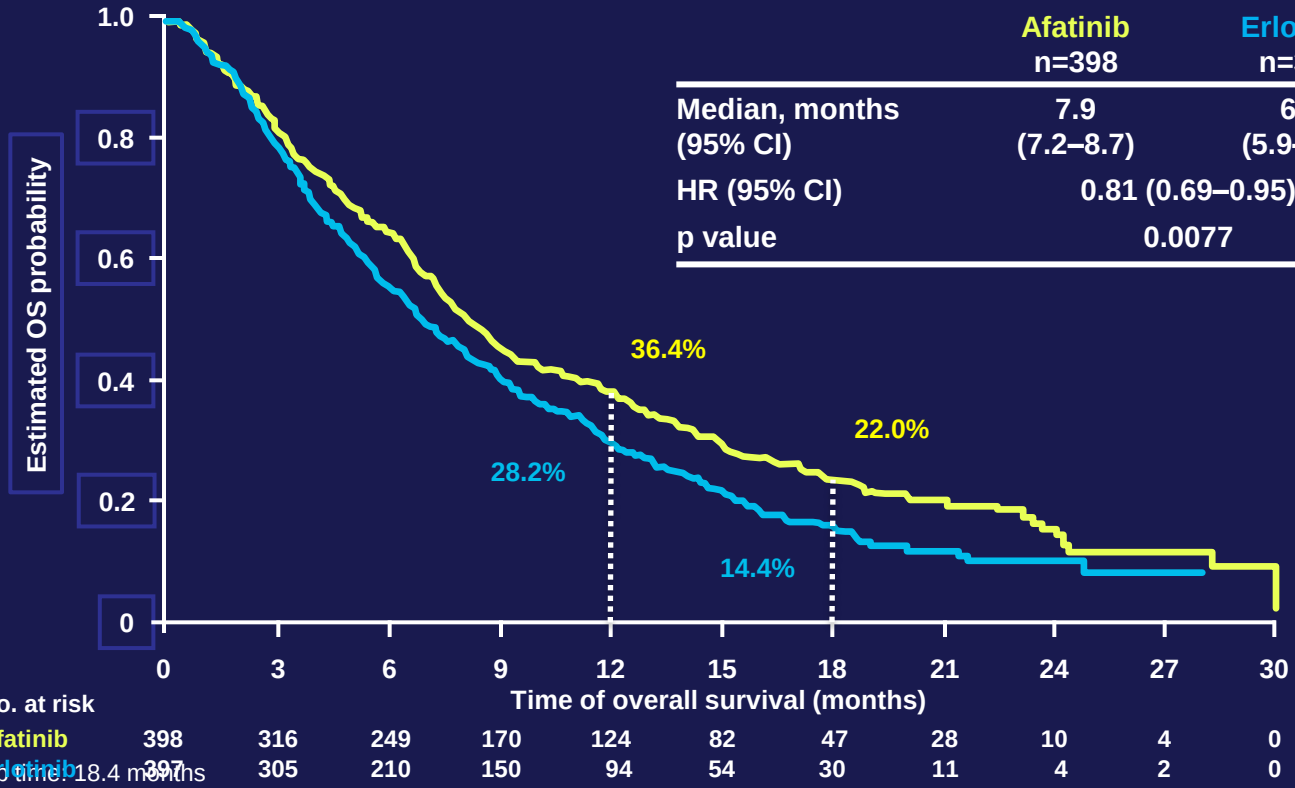
- SQUIRE is the largest randomized Phase 3 trial in the first line treatment for metastatic squamous NSCLC
- The study met its primary endpoint by showing a statistically significant improvement in OS
- Results were consistent across endpoints and pre-specified subgroups, including ECOG PS 2 patients
- Necitumumab combined with Gem-Cis showed an acceptable safety profile

PORTRAZZA

A vizsgálat felépítées:



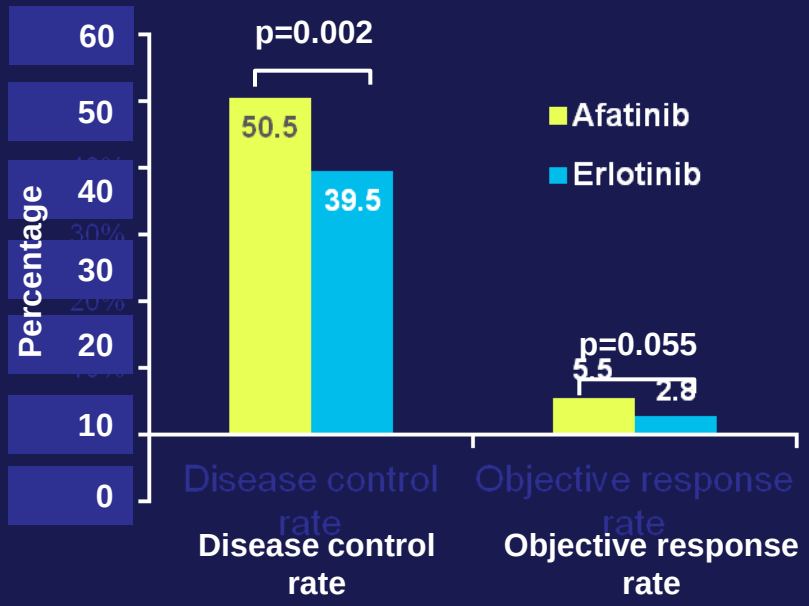
Teljes túlélés (n=795):



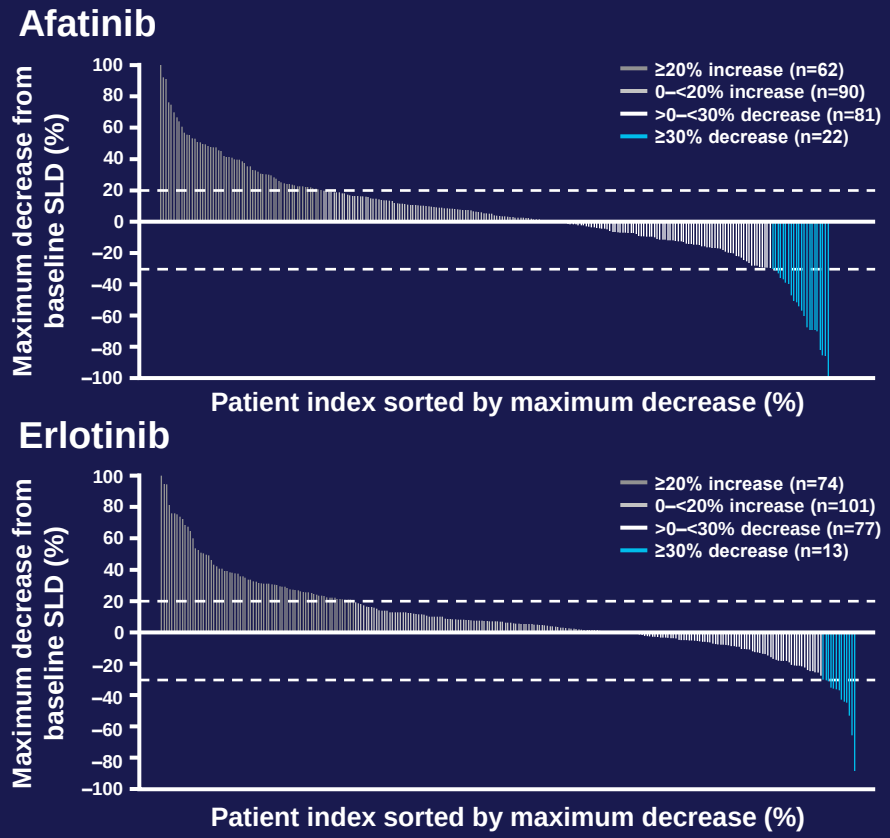
	Afatinib n=398	Erlotinib n=397
Median, months (95% CI)	7.9 (7.2–8.7)	6.8 (5.9–7.8)
HR (95% CI)	0.81 (0.69–0.95)	
p value	0.0077	

- Median follow-up time: 18.4 months

Objective response and tumor shrinkage



- Duration of response was 7.29 months for afatinib and 3.71 months for erlotinib



Összefoglalás:

- LUX-Lung 8 a legnagyobb fázis II-as vizsgálat
- A halálozás valószínűsége szignifikánsan csökkent az afatinibes csoportban
- A vizsgálat végpontjai teljesültek
- Jobb az életminőség a kérdőívek szerint
- Adverz események száma megegyezik

Afatinib should be the TKI of choice in second-line treatment of patients with SCC of the lung

REVEL: A vizsgálat felépítése

- Stage IV NSCLC after one platinum-based chemo +/- maintenance
- Prior Bev allowed
- All histologies
- PS 0 or 1

1:1

RANDOMIZE

Ramucirumab 10 mg/kg
+
Docetaxel 75 mg/m^2 q3wks
N=628

Placebo
+
Docetaxel 75 mg/m^2 q3wks
N=625

Treatment until disease progression or unacceptable toxicity

Stratification factors:

- ECOG PS 0 *vs* 1
- Gender
- Prior maintenance
- East-Asia vs. ROW

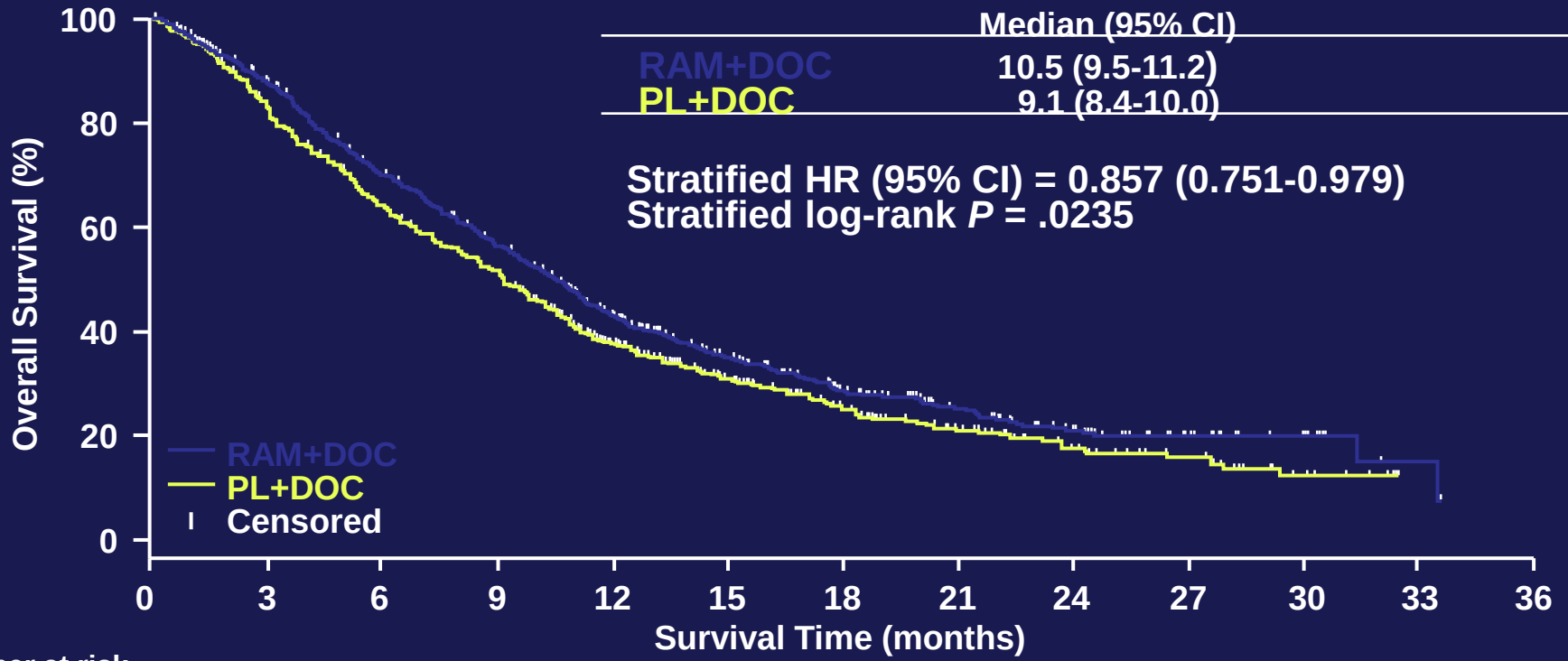
Primary endpoint: **Overall Survival**

Secondary endpoints:
PFS, ORR, safety, patient-reported outcomes

Abbreviations: Bev=bevacizumab; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=objective response rate; PFS=progression-free survival; ROW=rest of the world; q3wks=every 3 weeks

Teljes túlélés:

ITT Population



Number at risk

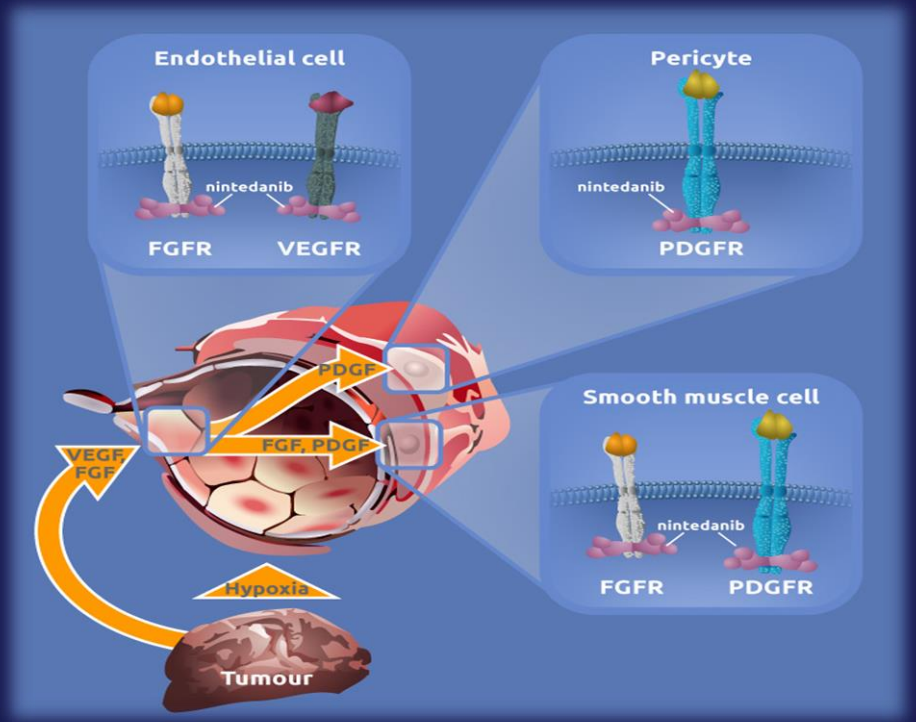
RAM+DOC	628	527	415	329	231	156	103	70	45	23	11	2	0
PL+DOC	625	501	386	306	197	129	86	56	36	23	9	0	0

REVEL: Következtetések

- REVEL met its primary endpoint of OS improvement.
- RAM+DOC showed statistically significant improvement in PFS and ORR compared to PL+DOC.
- OS and PFS improvement were consistent in most major subgroups, including squamous and nonsquamous histology.

Cyramza

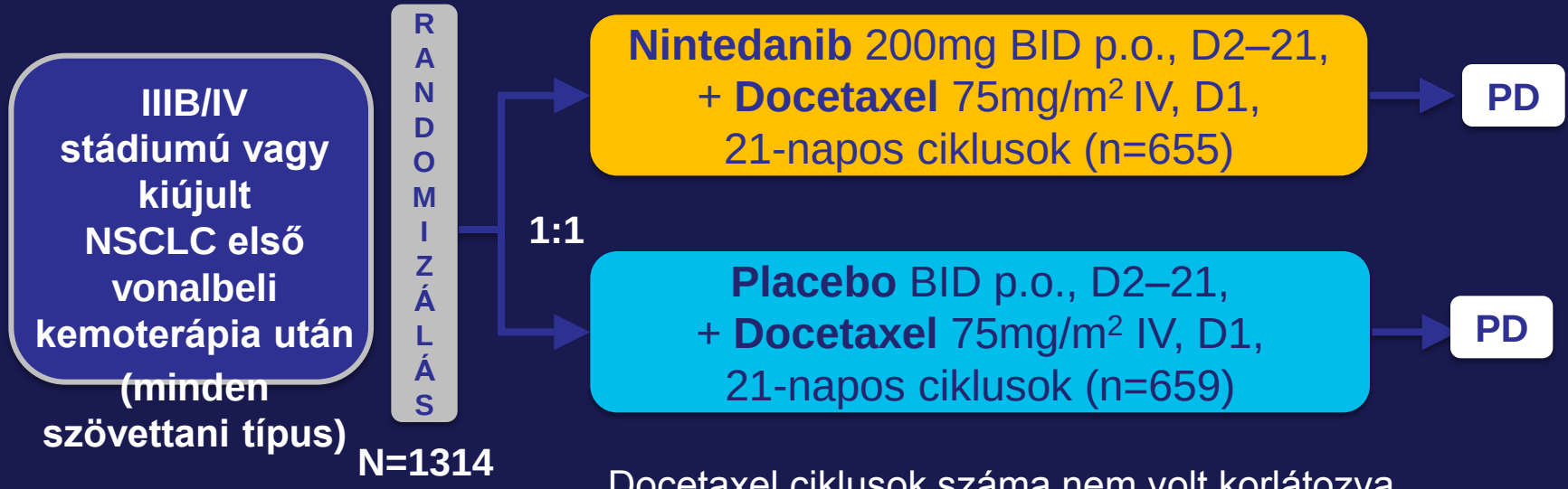
A nintedanib hatásmechanizmusa



- Orális angiokinase inhibitor
- Célozza a VEGFR 1–3, FGFR 1–3, and PDGFR α/β és RET útvonalat
- Jól kombinálható:
  - Docetaxel
  - Pemetrexed
  - Paclitaxel/carboplatin
  - Gemcitabine/cisplatin
  - Afatinib
- Nintedanib hatékony a fázis II –es vizsgálatokban NSCLC esetén

1. Hilberg F, et al. Cancer Res 2008;68:4774–8; 2. Data on File; 3. Stopfer P, et al. Xenobiotica 2011;41:297–311; 4. Bousquet G, et al. Br J Cancer 2011;105:1640–5; 5. Ellis PM, et al. Clin Cancer Res 2010;16:2881–9; 6. Doebele RC, et al. Ann Oncol 2012;23:2094–102; Data on File (clinicaltrials.gov NCT01346540); 7. Soria J-C, et al. Ann Oncol 2012;23(Suppl.9): abs 979;

A LUME Lung 1 klinikai vizsgálat felépítése



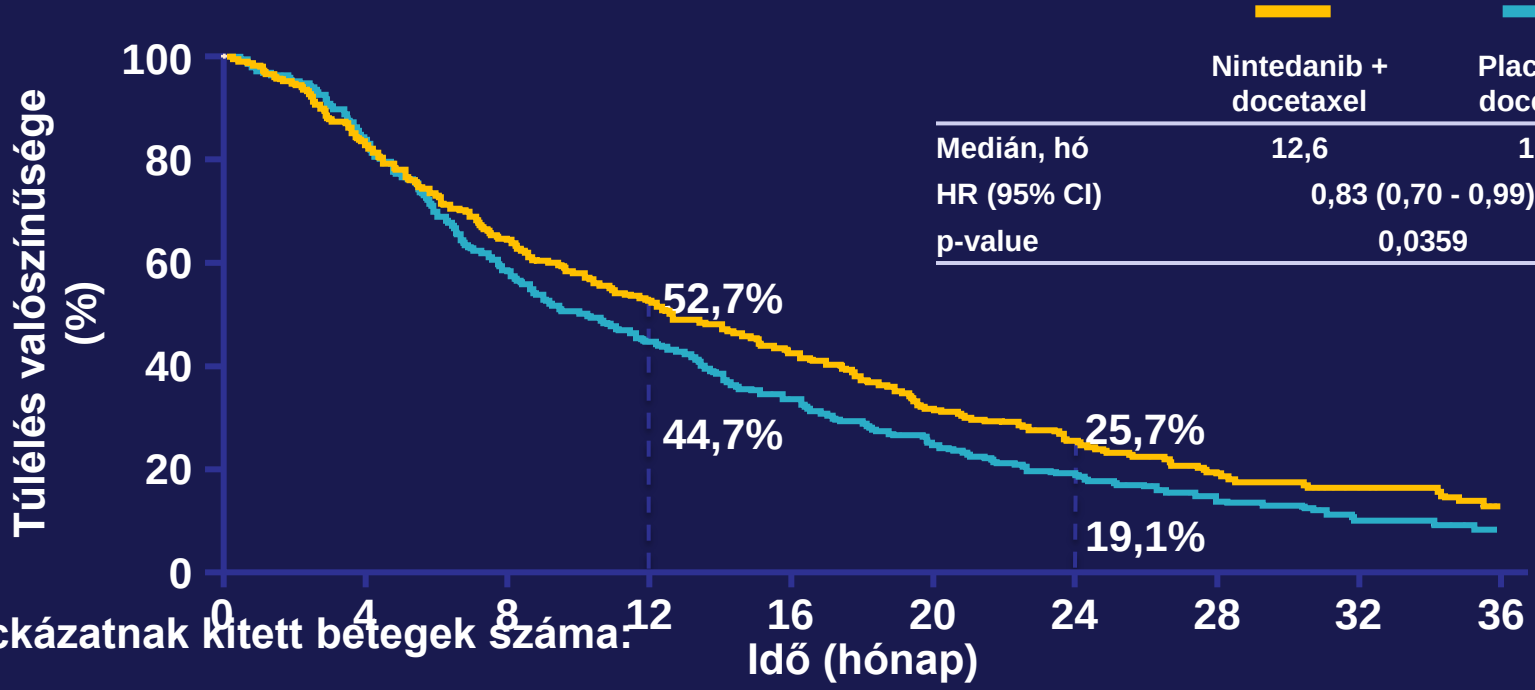
Docetaxel ciklusok száma nem volt korlátozva
Legalább 4 cicklus kombinált kezelés

Régiók: Európa / Ázsia / Dél-Afrika

Stratifikáció: ECOG PS (0 vs 1)
Megelőző bevacizumab (igen vs nem)
Hisztológy (squamous vs non-squamous)

Reck M, et al. Ann Oncol 2011;22:1374-81

Teljes túlélés - Adenocarcinoma



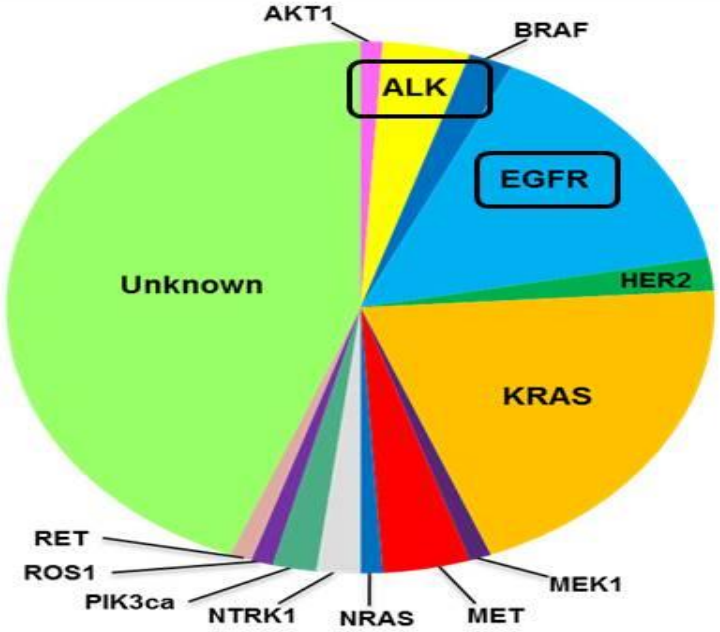
Kockázatnak kitett betegek száma:

Nintedanib	322	263	203	163	131	96	72	46	25	10
Placebo	336	269	184	139	101	73	55	33	15	7

Reck M. et al. Ann Oncol 2011;22:1374–81.

Adenocarcinoma heterogenitása

Molecular Subsets of Lung Adenocarcinoma Defined by 'Driver' Mutations



Frequency of driver mutations in NSCLC	
AKT1	1%
ALK	3-7%
BRAF	1-3%
EGFR	10-35%
HER2	2-4%
KRAS	15-25%
MEK1	1%
MET	~4%
NRAS	1%
NTRK1	~3%
PIK3CA	1-3%
RET	1-2%
ROS1	1-2%

PRESENTED AT: ASCO Annual '15 Meeting

ALK gátlás

PROFILE 1007

A vizsgálat felépítése:

Bevonási kritériumok:

- *ALK*+ by central FISH testing[a]
- Stage IIIB/IV NSCLC
- 1 prior chemotherapy (platinum-based)
- ECOG PS 0–2
- Értékelhető léziók
- Agyi áttét megengedett

RANDOMIZE[b]

N [illegible]8

Crizotinib 250 mg BID PO, 21-day cycle (n=159)

Pemetrexed 500 mg/m² or Docetaxel 75 mg/m² IV, day 1, 21-day cycle (n=159)

CROSSOVER TO CRIZOTINIB ON PROFILE 1005

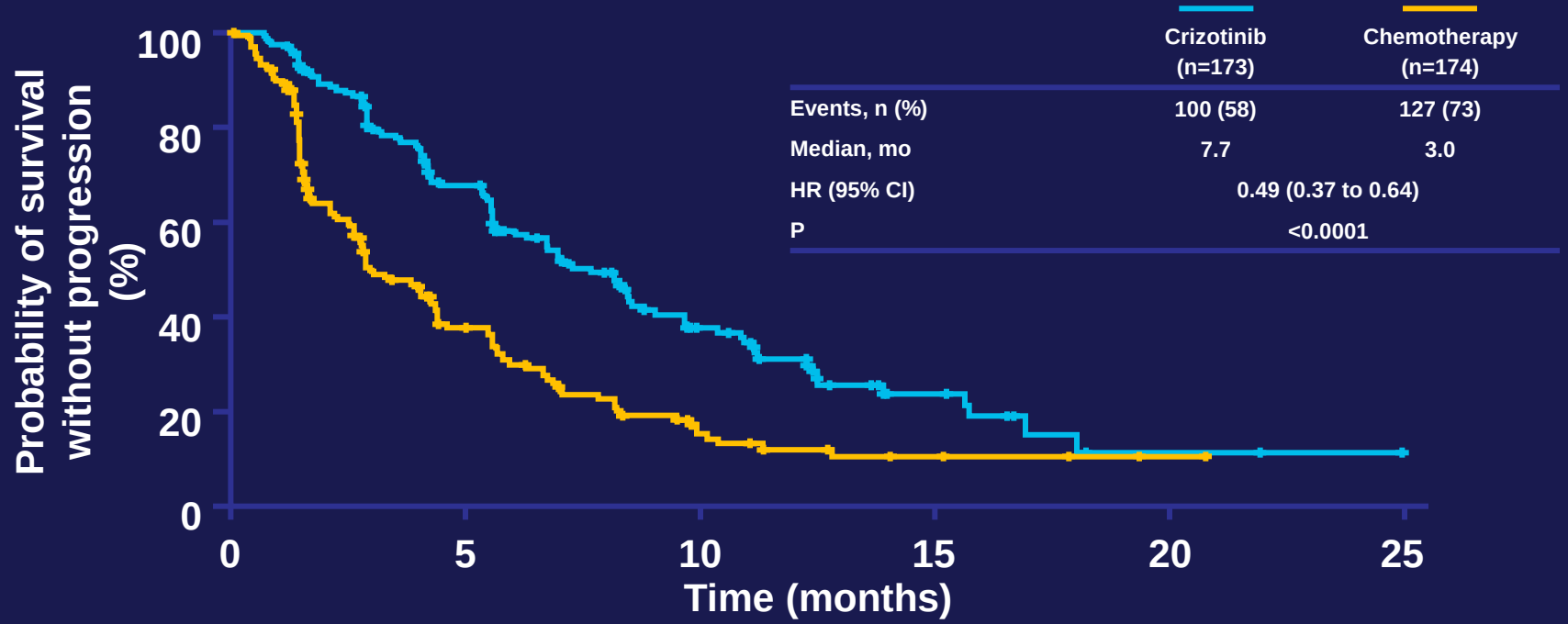
Endpoints

- Primary
  - PFS (RECIST 1.1), independent radiology review)
- Secondary
  - ORR, DCR,
  - OS
  - Safety
  - Patient reported outcomes (EORTC QLQ-C30, LC13)

[a]*ALK* status determined using standard *ALK* break-apart FISH assay
[b]Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

PROFILE 1007: NCT00932893

PFS (független értékelés)



No. at risk						
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Phase 3 vizsgálat első vonalban *ALK*-positive NSCLC: PROFILE 1014

Bevonási kritériumok;
N=334

- *ALK*-positive locally adv/metastatic non-squamous NSCLC

RANDOMIZE

N=167 **Crizotinib 250 mg BID**

Crossover on PD

N=167 **Pemetrexed/ cisplatin vagy pemetrexed/ carboplatin (Day 1/21)**

Vizsgálat felépítése:	Végpontok:	Stratifikáció:
Worldwide Multicenter Randomized Open-label Focused screening Read-out: Sept-Oct 2013	**Primary: PFS*** Secondary: OS, ORR*, DR, safety, QoL, Lung cancer-specific symptoms	ECOG PS (0/1 vs 2) Ethnicity (Asian vs non-Asian) Brain metastases

*Based on RECIST v 1.1 and confirmed by independent radiology review

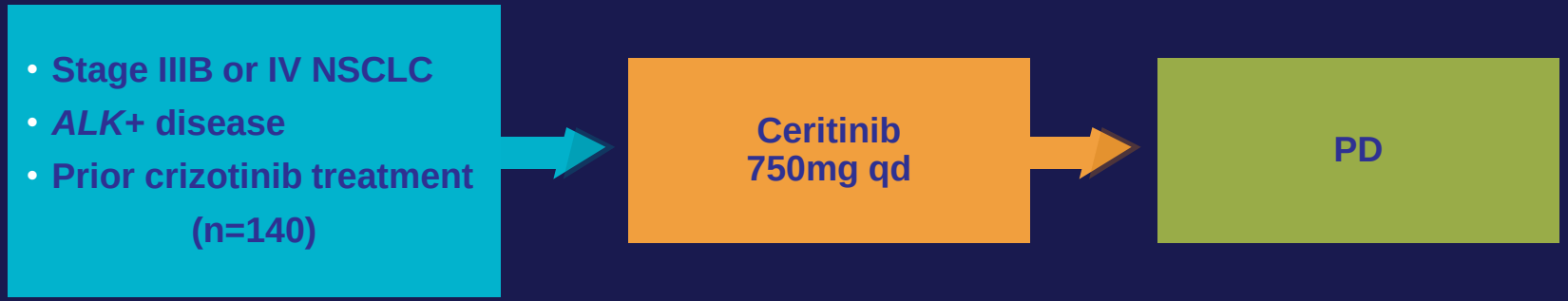
ALK gátlás, újabb szerek

'SECOND-GENERATION' ALK INHIBITORS

TKI	COMPANY	REFERENCE
CH5424802 (alectinib)	Chugai Pharmaceutical	Seto, T. et al. Lancet Oncol 2013; S1470-2045 (13)70142-6. Sakamoto, H et al. Cancer Cell 2011;19:679–90.
AP26113	Ariad Pharmaceuticals	Katayama, R et al. PNAS 2011;108: 7535–40.
X-396	Xcovery Inc.	Lovly, C et al. Cancer Research 2011;71:4920–31. Horn, L et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8030^)
ASP3026	Astellas Pharma US, Inc.	Kuromitsu, S. Molecular Cancer Therapeutics 2011;10(11 Suppl.). Abstract A227.
GSK1838705	GlaxoSmithKlein	Sabbatini, P. et al. Molecular Cancer Therapeutics 2009;8:2811–20.
CEP-28122	Cephalon, Inc.	Cheng, M. Molecular Cancer Therapy 2012;11:67–9.
LDK378 (ceritinib)	Novartis, Inc.	Mehra, R. Journal of Clinical Oncology 2012; 30(suppl; abstract 3007).

Presented By Christine Lovly at 2015 ASCO Annual Meeting

Ceritinib (ZYKADIA) hatékonysága: ASCEND-2 vizsgálat



1 Primary endpoint	2 Secondary endpoints
• ORR by investigator	• DoR • DCR • ORR by BIRC • PFS

Median duration of follow-up: 11.3 months

Mok, et al. ASCO 2015 (Abs 8059)
BIRC = Blinded Imaging Review Committee; OIRR = overall intracranial response rate

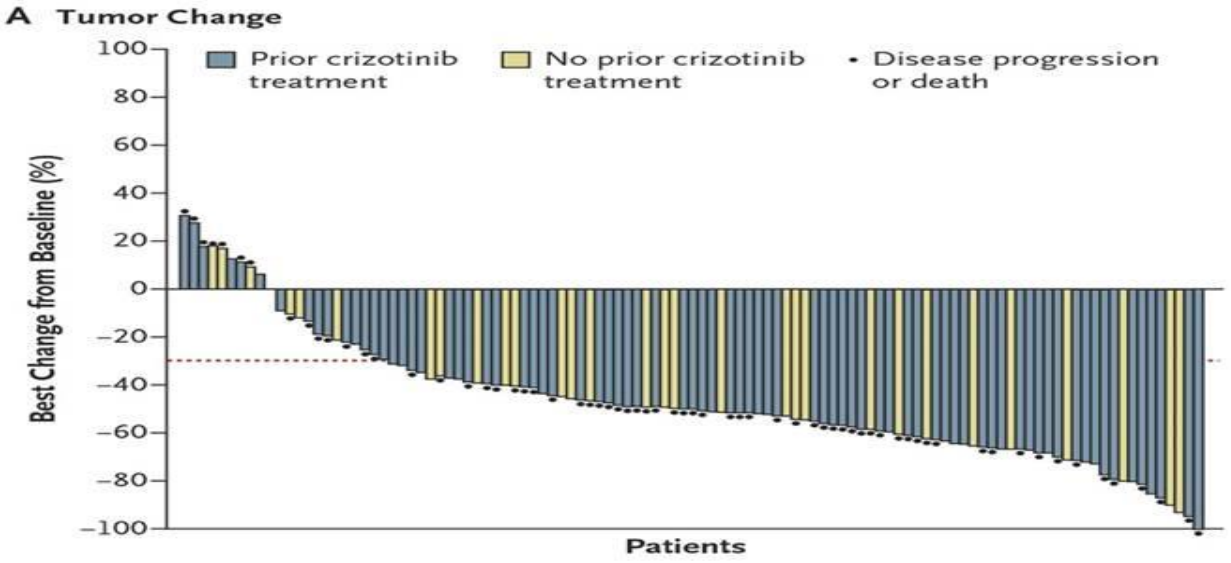
ASCEND-2: Hatékonyság

	ASCEND-2 n=140
ORR by investigator, %	38.6
Response by IRC, %	–
ORR	**–**
DCR	**–**
mPFS, months	5.7
CNS response in patients with measurable disease at baseline	
CNS response by IRC, %	–
ORR	–
DCR	**–**
CNS response by investigator, %	n=20
ORR	–
DCR	**80.0**

*16 patients did not have measurable disease per IRC read and were not included in IRC response evaluable population; Cut-off 8 Jan 2015
Mok, et al. ASCO 2015 (Abs 8059)

Ceritinib hatékony mind az ALK gátló kezelésben korábban nem részesültek, mind pedig korábban ALK gátló kezelésben részesültek esetén is

Ceritinib in *ALK*-rearranged lung cancer



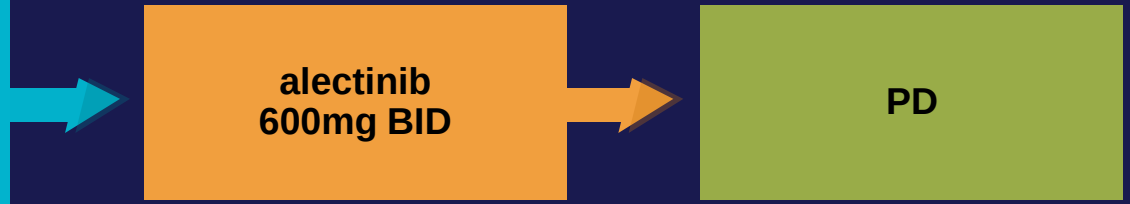
ORR (CR + PR): 56% in crizotinib-treated patients
ORR (CR + PR): 58% in crizotinib-naïve patients

Shaw et al NEJM 2014

Presented By Christine Lovly at 2015 ASCO Annual Meeting

Fázis II vizsgálat alectinib hatékonysága crizotinib kezelés során kialakult progressziókor

- **Locally advanced or metastatic NSCLC**
- ***ALK*+ disease**
- **Prior crizotinib treatment**
- **ECOG PS 0–2**



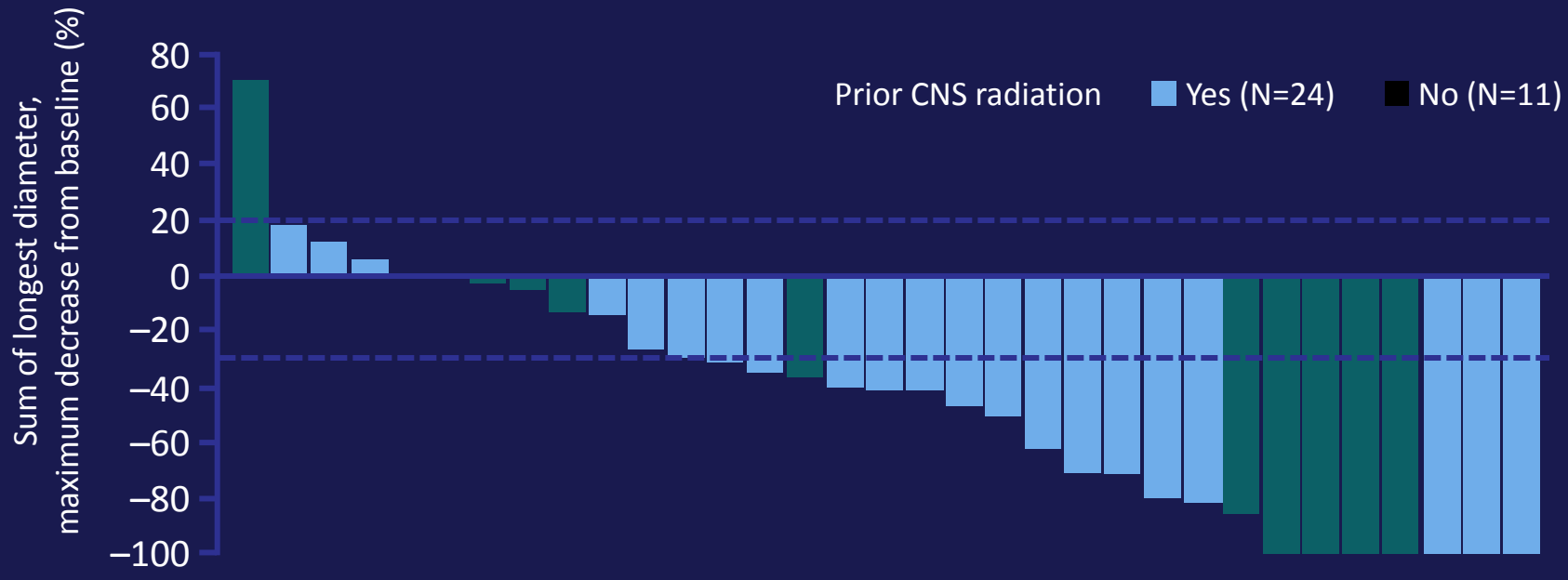
NP28673 (global) n=138

1 Primary endpoints	2 Secondary endpoints
•ORR by IRC	•CNS ORR •CNS DoR •PFS •DCR •Safety

Ou, et al ASCO 2015 (Abs 8008); Gandhi, et al ASCO 2015 (Abs 8019)

BID = twice a day; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IRC = Independent Review Committee; ORR = Objective Response Rate; OS = overall survival; PD = pharmacodynamics; PFS = progression-free survival; QoL = quality of life

Agyi áttét esetén is hatékony



27% CR agyi áttét esetén

*Patients with measurable CNS metastases at baseline

Updated analysis cut-off 8 Jan 2015

Alectinib hatékony megelőző crizotinib kezelés során kialakult rezisztencia esetén

Alectinib in *ALK*-rearranged lung cancer

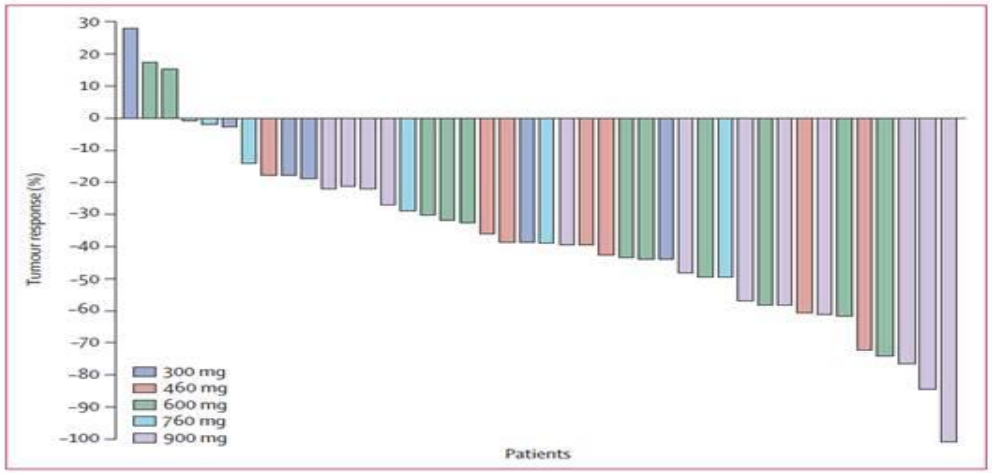
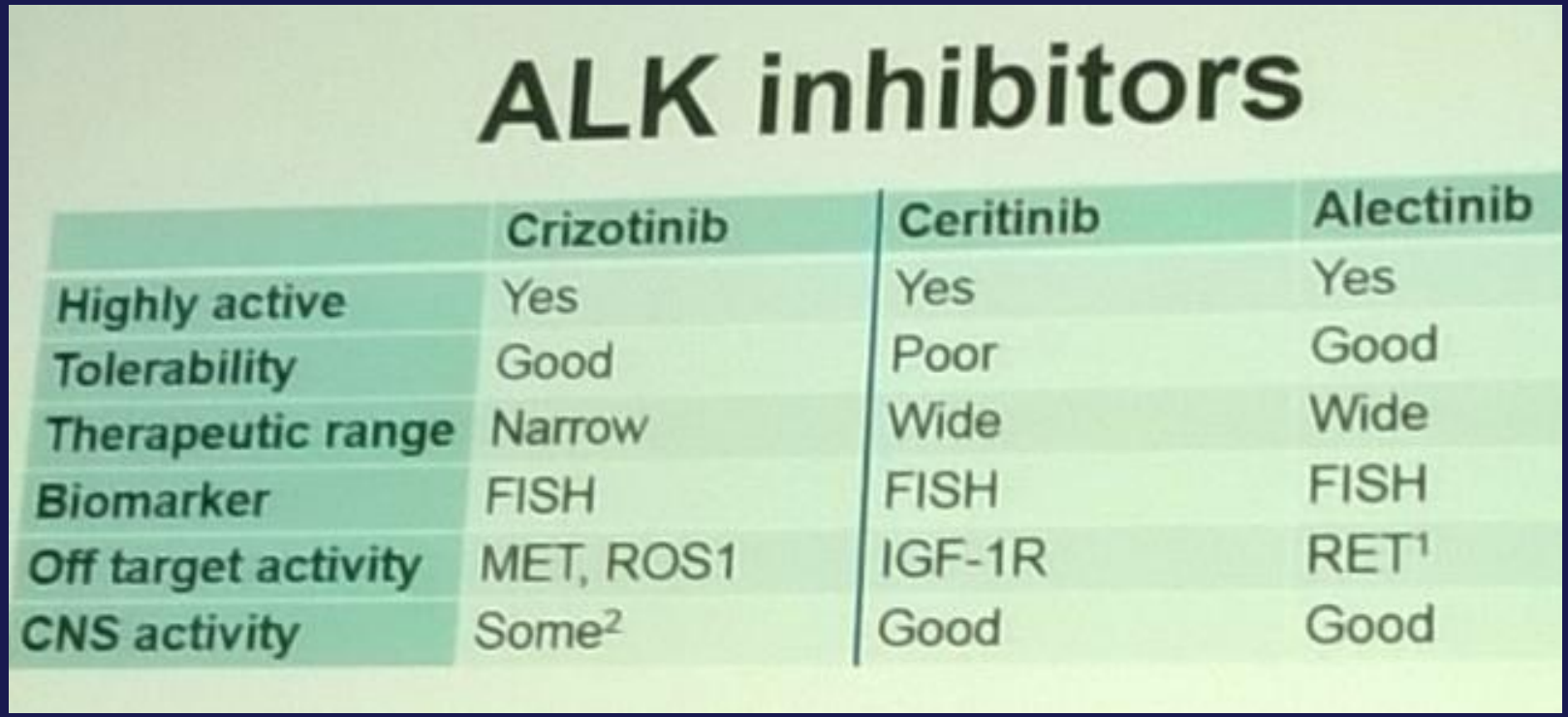


***Figure 3*: Waterfall plot of best tumour response**
Response was measured as the largest post-baseline percentage reduction in the sum of longest diameters of target lesions for all assessable patients with a radiographic post-baseline assessment (n=42).

47 patients with ALK+ lung cancer enrolled.
44 patients assessed.
All patients has prior crizotinib.
ORR (CR + PR): 55%
CNS RR: 52%

Ref: Gadgeel et al Lancet Oncology 2014

ALK GÁTLÓK, MELYIKET VÁLASSZAM ?



ALK inhibitors

	Crizotinib	Ceritinib	Alectinib
Highly active	Yes	Yes	Yes
Tolerability	Good	Poor	Good
Therapeutic range	Narrow	Wide	Wide
Biomarker	FISH	FISH	FISH
Off target activity	MET, ROS1	IGF-1R	RET[1]
CNS activity	Some[2]	Good	Good

Új eredmények

Nivolumab (Opdivo) új kezelési standard másodvonalban mind a laphámsejtes, mind pedig a nem laphámsejtes nem kissejtes tüdőrák esetén.

Afatinib (Giotrif) jobb hatékonyságú a gefitinibbel összevetve EGFR mutáns tüdő adenokarcinomában

Afatinib jobb hatékonyságú másodvonalban laphámsejtes tüdőrákban az erlotinibnél

A necitumumab (PORTRAZZA) jobb hatékonyságú első vonalbeli kezelésben laphámsejtes tüdőrákban

A ramicurumab (ZYRAMZA) (docetaxellel kombinálva) jobb hatékonyságú, mint a docetaxel, monoterápia másodvonalban NSCLC esetén.

A ceritinib (ZYKADIA) új kezelési standard ALK pozitív tüdőrák esetén a crizotinib kezelés során kialakult progresszió esetén.

Az osimertinib (Tagrissao, ZD 9291) T790M zerzett mutáció esetén új terápiás lehetőség első, vagy második generációs EGFRTKI kezelés után.

Új szerek

- Opdivo, Keytruda
- Portrazza
- Vargatef
- Cyramza
- Tagrisso
- Zykadia

- Giotrif
- Xalkori

Köszönöm a figyelmet !