Újabb eredmények a tüdőrák kezelésében

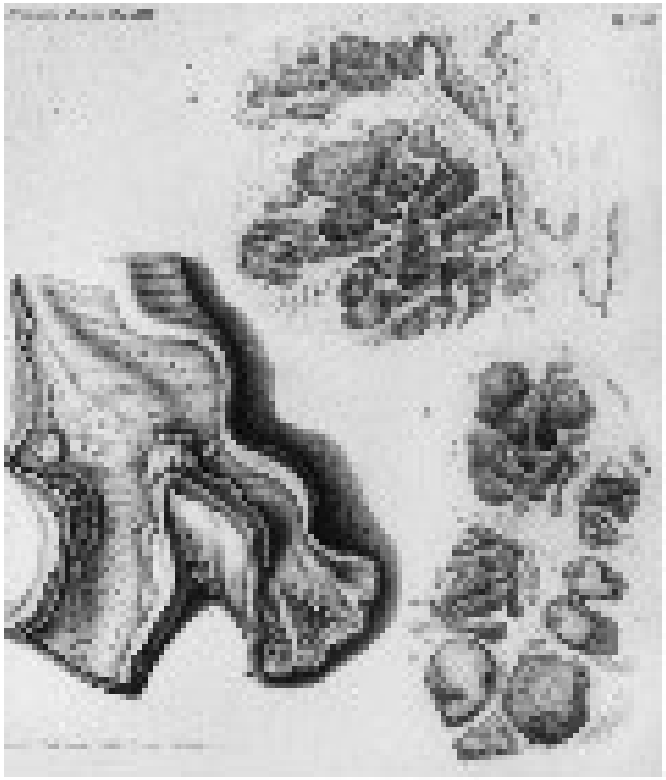
Ostoros Gyula
Országos Korányi Pulmonológiai Intézet
Budapest

Mióta ismerjük?

Up to the mid 19 (th) century primary bronchial carcinoma was unknown. Primary tumours and metastases of malignant lung tumours were often not distinguished one from the other. Only in 1871, Theodor Langhans from Marburg reported the first certain observation of bronchial carcinoma.

1871

Pneumologie 2004; 58(9): 680-685
DOI: 10.1055/s-2004-818417
Historisches Kaleidoskop

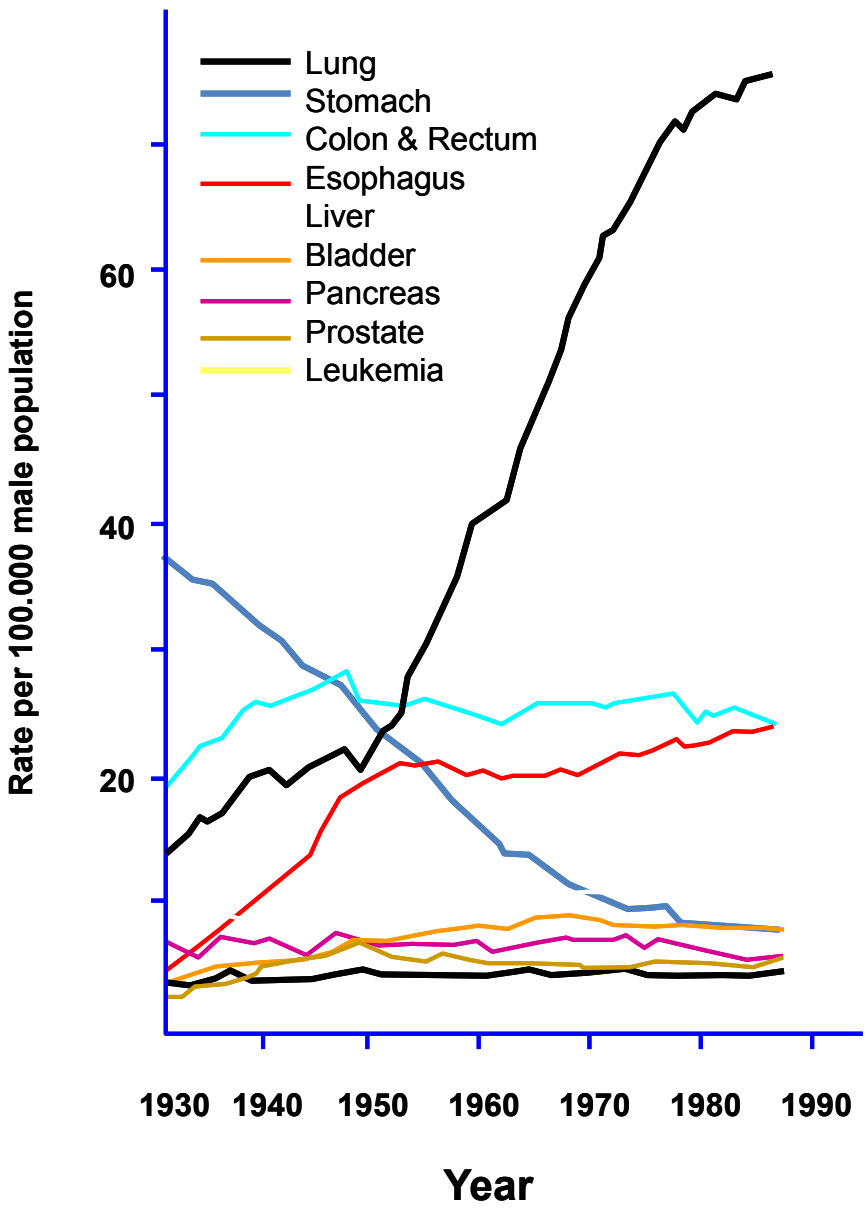


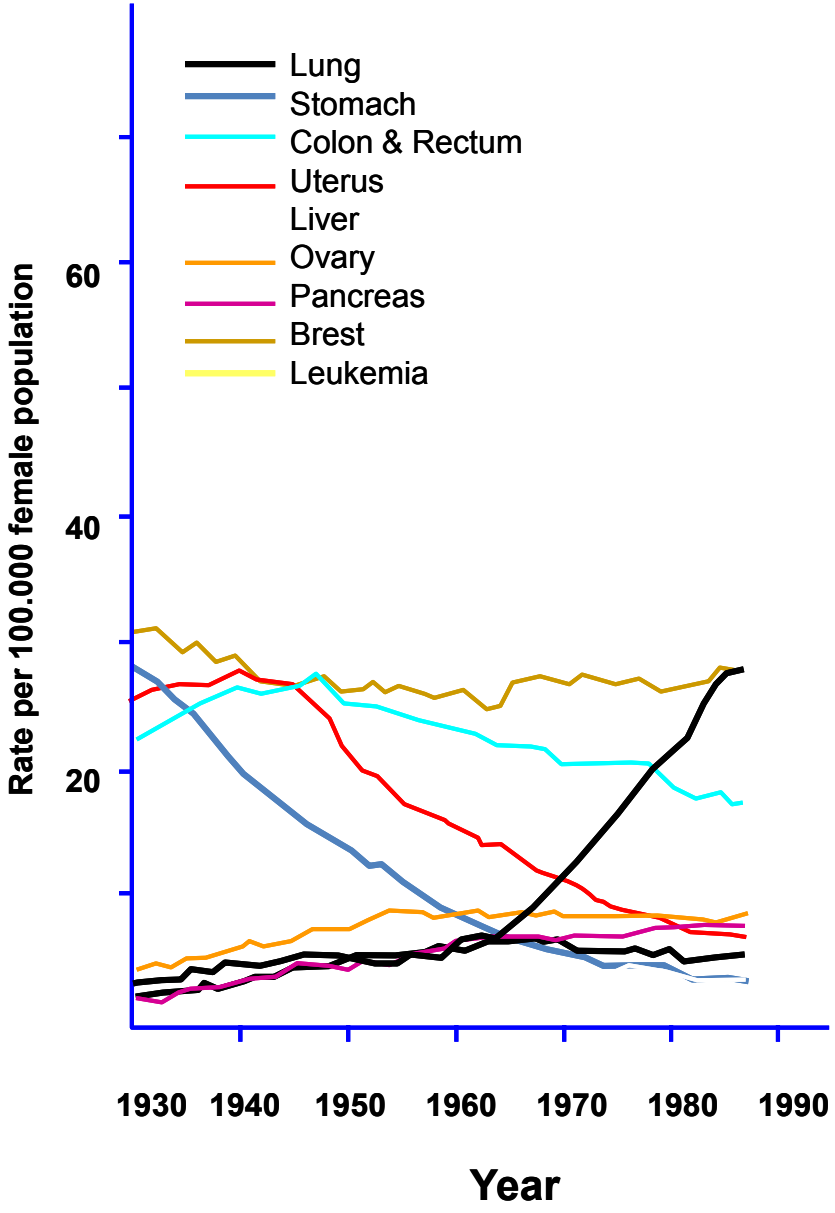
1912-ig

312 esetleírás van

Pneumologie 2004; 58(9): 680-685
DOI: 10.1055/s-2004-818417
Historisches Kaleidoskop

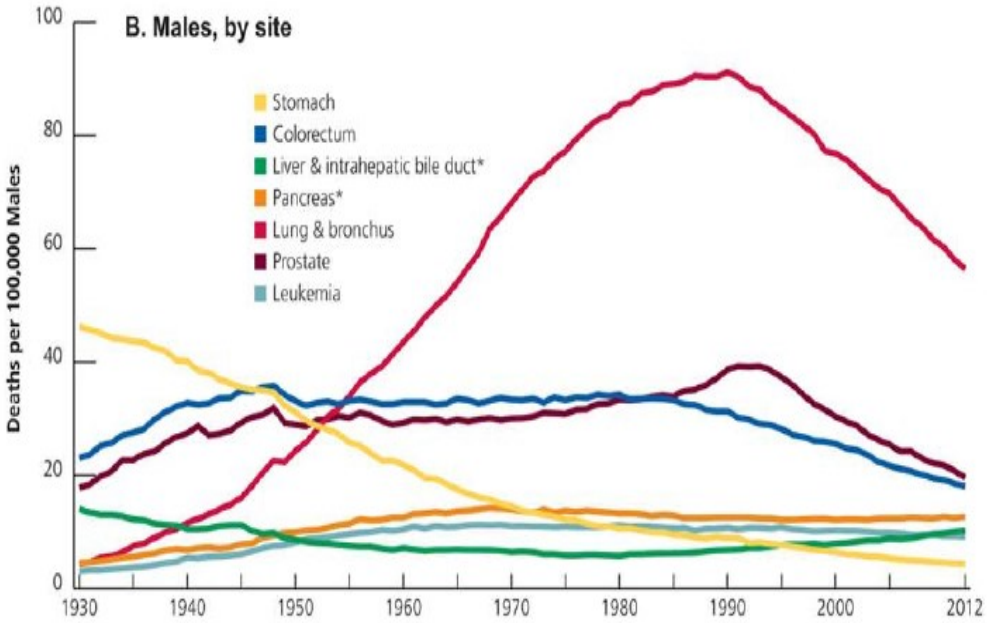
A tüdőrák mortalitása a huszadik században

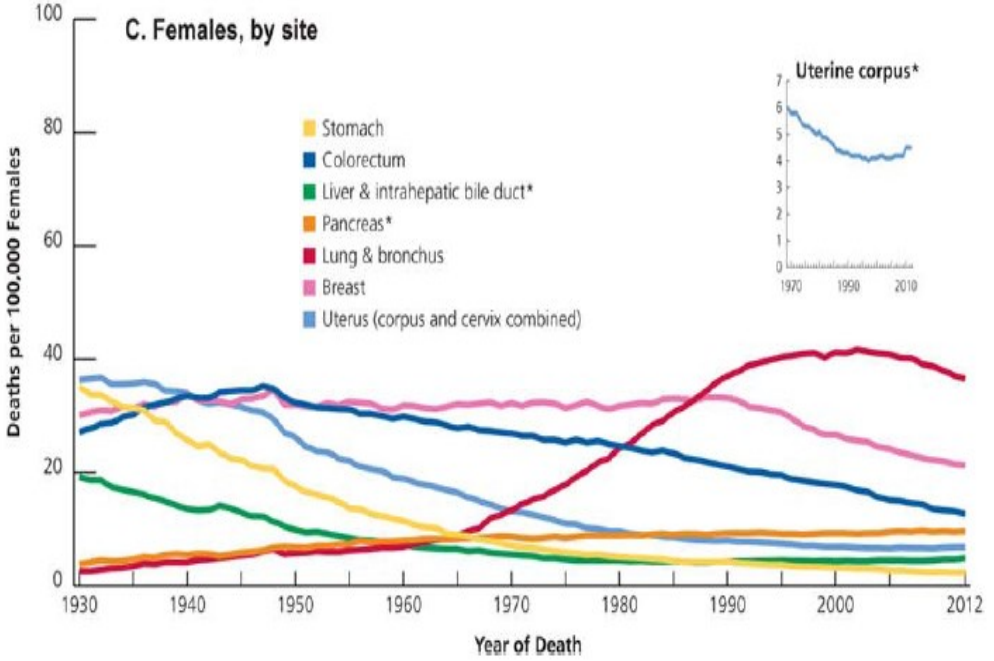




A tüdőrák mortalitás:

Átmenet a huszadik századból a huszonegyedik századba.

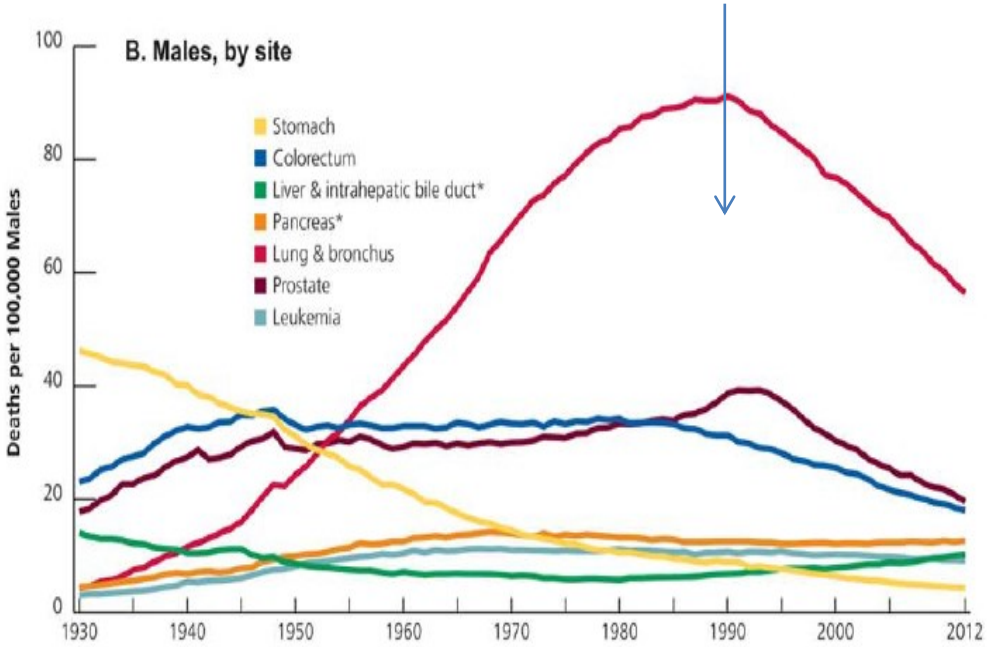


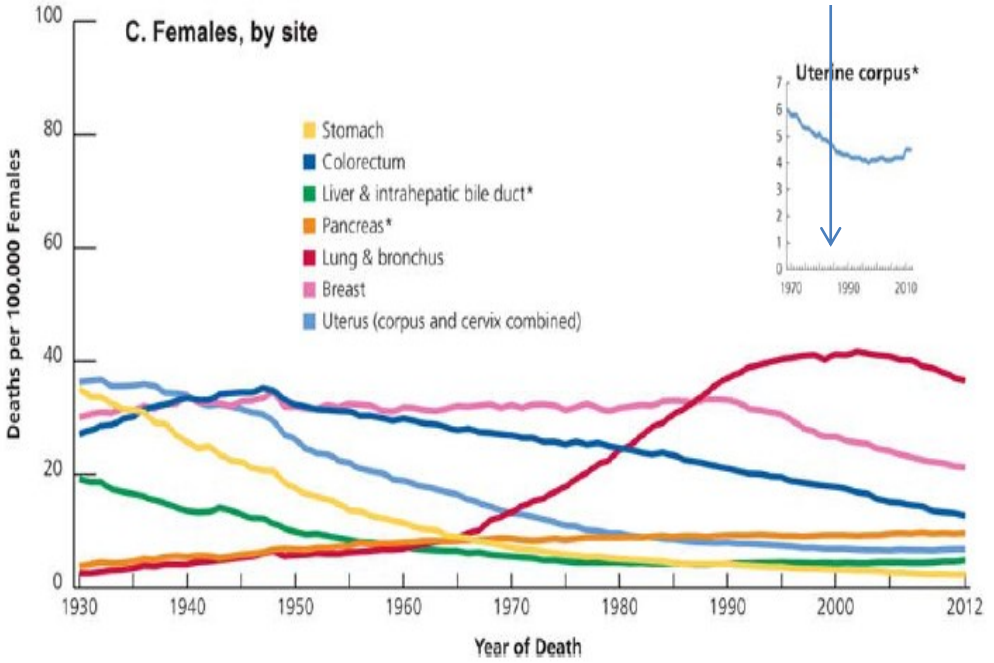


Siegel et al, CA Cancer J Clin 2016;66:7-30.

A tüdőrák mortalitás:

Átmenet a huszadik századból a huszonegyedik századba.

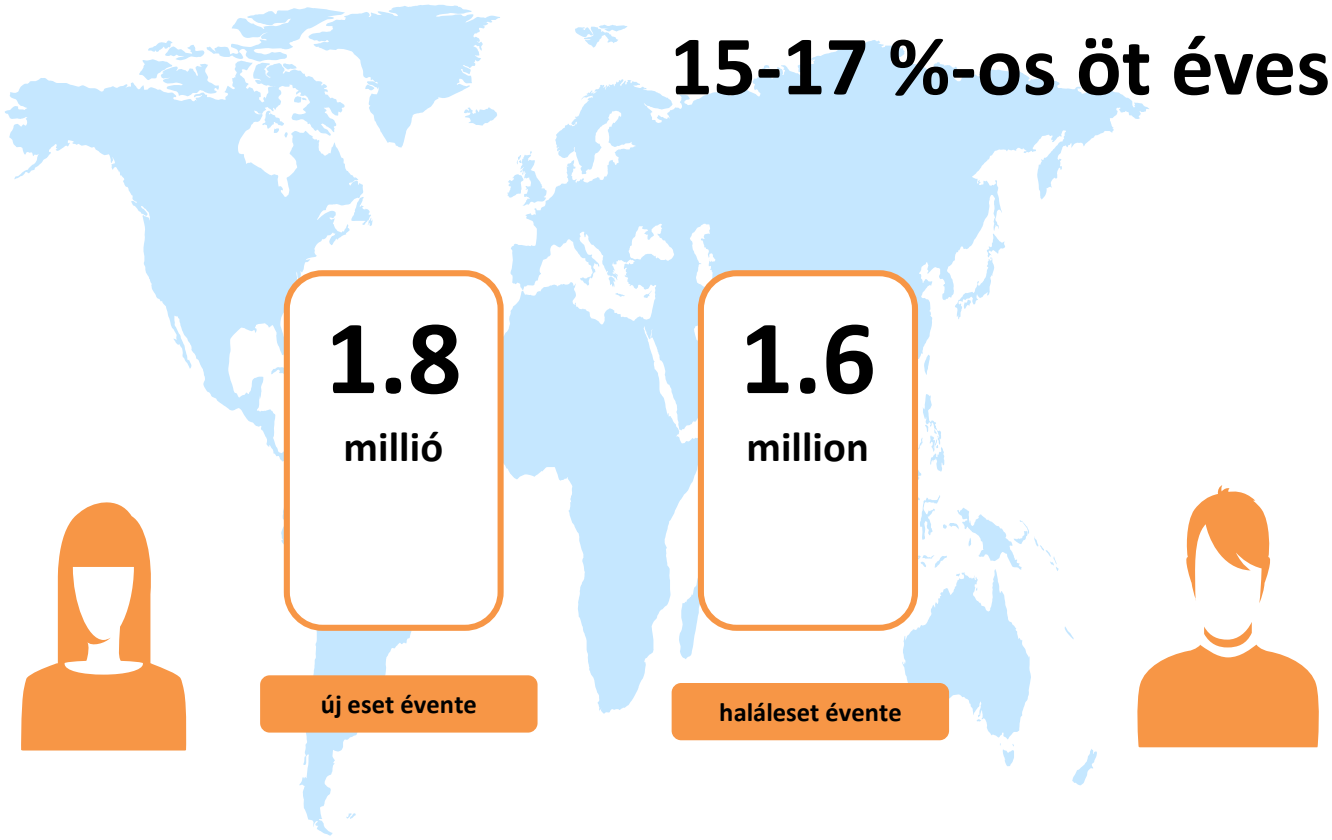




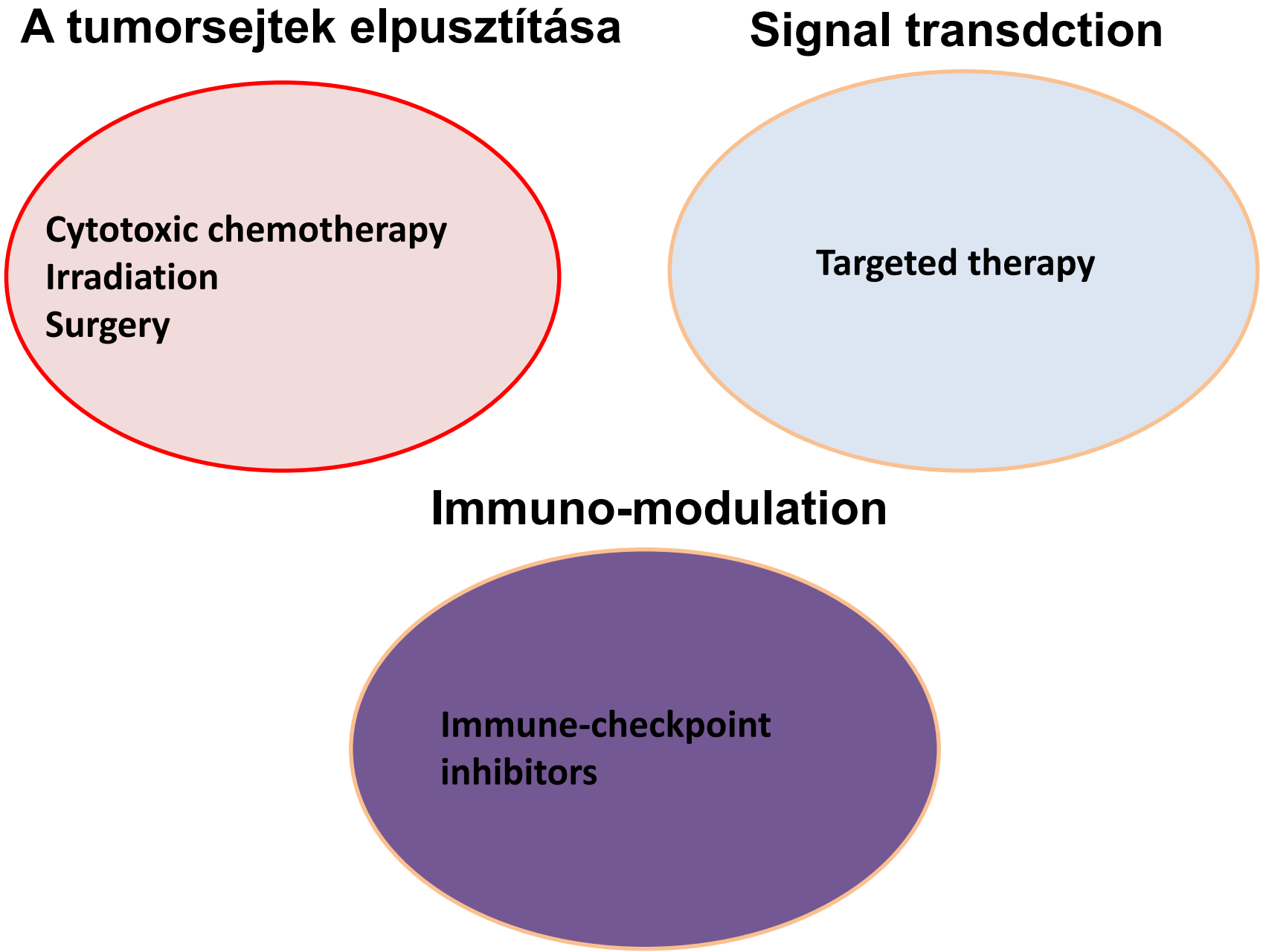
Siegel et al, CA Cancer J Clin 2016;66:7-30.

A tüdőrák világszinten jelentős egészségügyi probléma

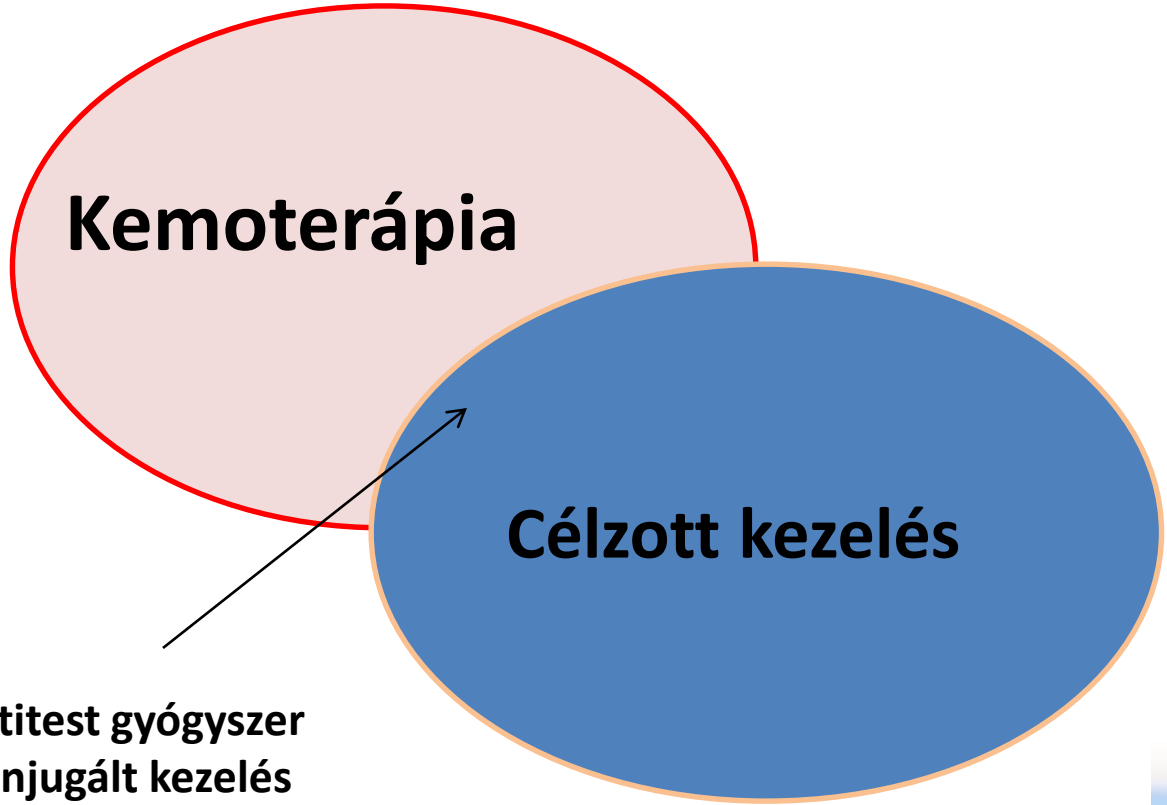
A tüdőrák világszerte a leggyakoribb daganat és vezeti a daganattal összefüggő halálozási staisztikát.



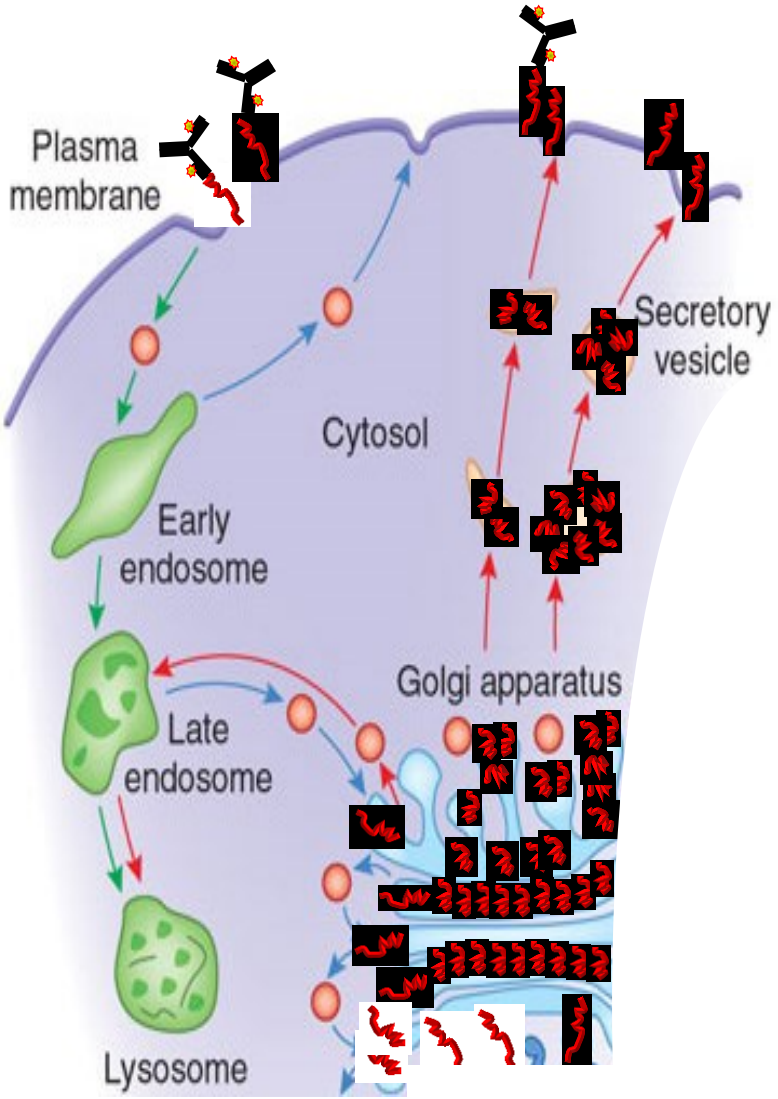
Ferlay J, et al. GLOBOCAN 2012 v1.0; http://globocan.iarc.fr, accessed on 12/02/2015


A tumorsejtek elpusztítása
Cytotoxic chemotherapy
Irradiation
Surgery
Signal transdction
Targeted therapy
Immuno-modulation
Immune-checkpoint
inhibitors

Az antitest gyógyszer konjugált terápia (ADC), mely „drónok” segítségével támadja a tumort



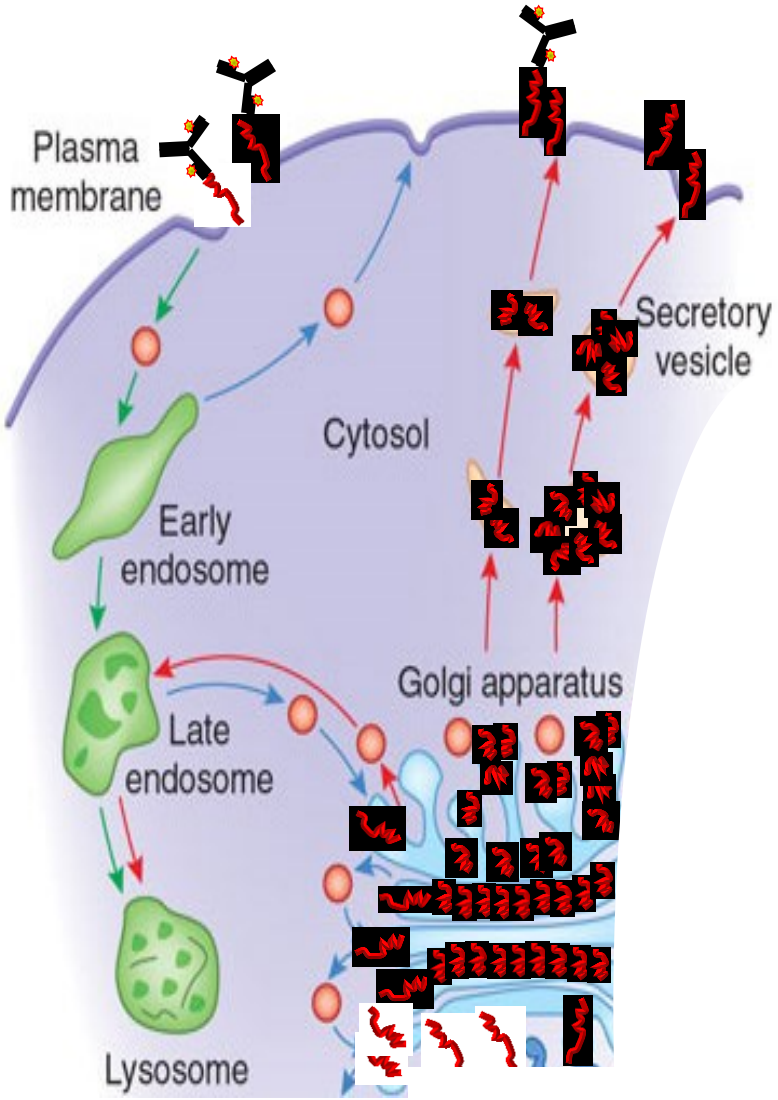
Rova-T Leverages Surface DLL3 to Deliver PBD Toxin



= DLL3

Rova-T (SC16LD6.5)

Rova-T Leverages Surface DLL3 to Deliver PBD Toxin

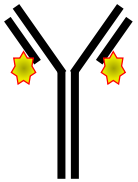


= DLL3

Rova-T (SC16LD6.5)

PBD Dimer Toxin Mediates Tumor Cell Killing

= DLL3



Rova-T (SC16LD6.5)

Rova-T Clinical Development Program in SCLC

1L Therapy

SCRX001-004
Phase 1: Rova-T ± cisplatin & etoposide vs cisplatin & etoposide in 1L DLL3+ SCLC

Maintenance Therapy

MERU
Phase 3: Rova-T versus placebo as maintenance following platinum-based therapy

2L Therapy

SCRX16-001
Phase 1/2: Rova-T monotherapy in recurrent SCLC

M16-300
Phase 1/2: Rova-T + nivolumab ± ipilimumab in 2L+ SCLC

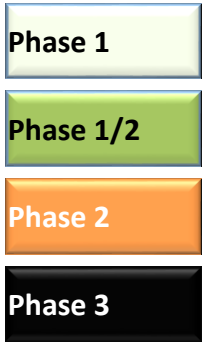
TAHOE
Phase 3: Rova-T versus topotecan in 2L DLL3 high SCLC

3L+ Therapy

SCRX16-001
Phase 1/2: Rova-T monotherapy in recurrent SCLC

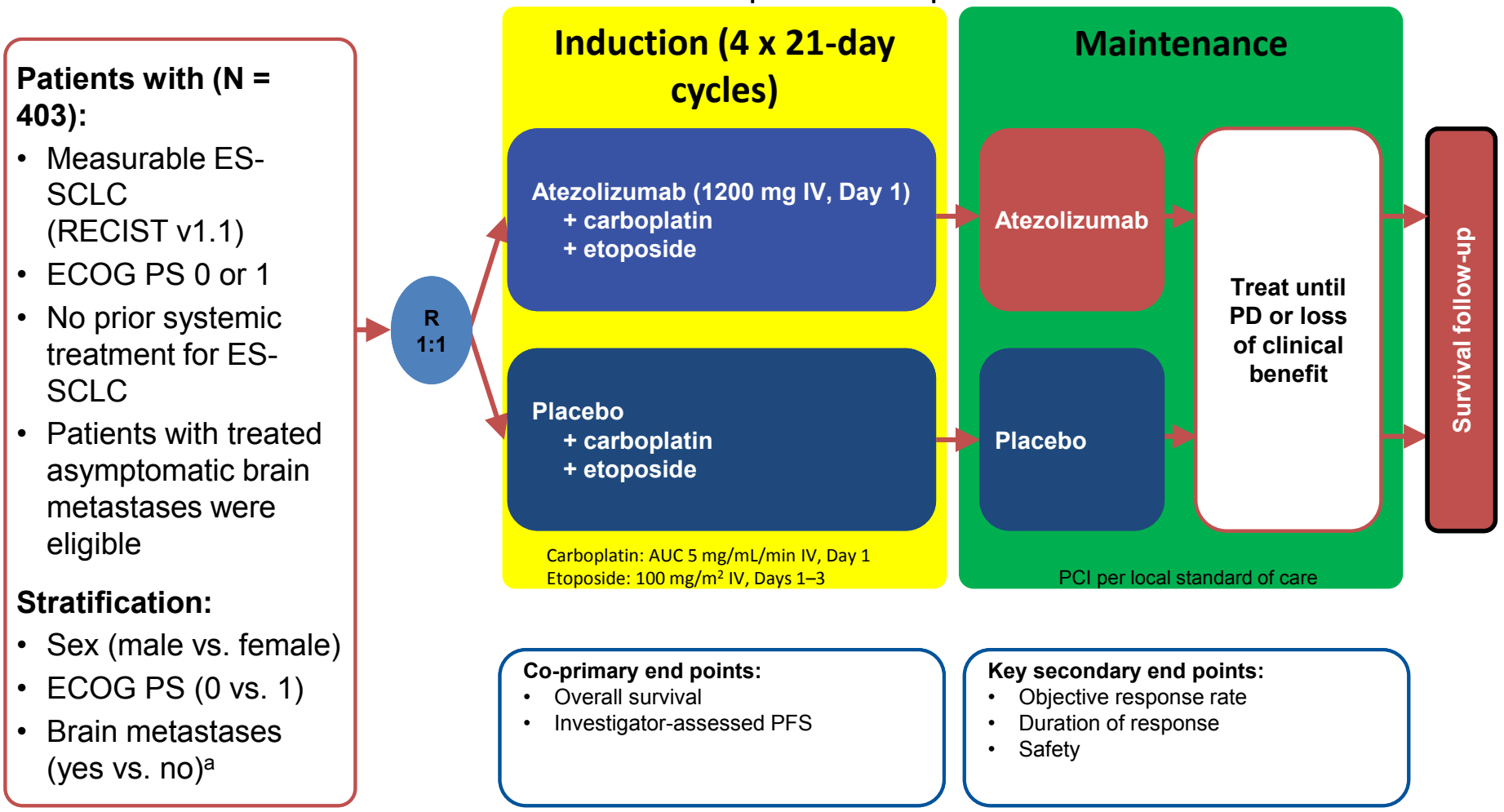
M16-300
Phase 1/2: Rova-T + nivolumab ± ipilimumab in 2L+ SCLC

TRINITY
Phase 2: Rova-T monotherapy in 3L+ DLL3-positive R/R SCLC



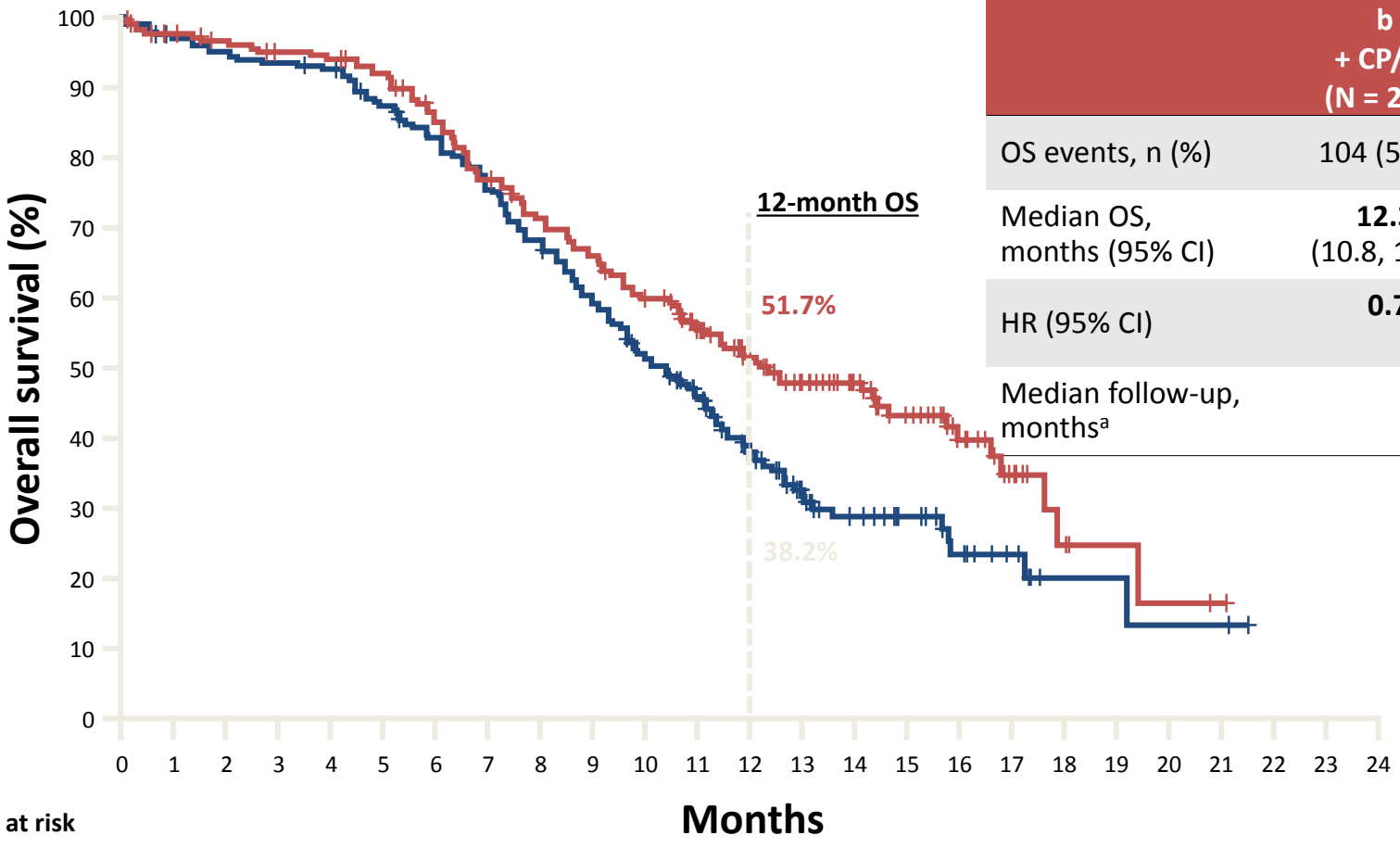
SCLC=Small Cell Lung Cancer.
ClinicalTrials.gov. https://clinicaltrials.gov. Accessed August 2017.

IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC



[a] Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors.

Teljes túlélés



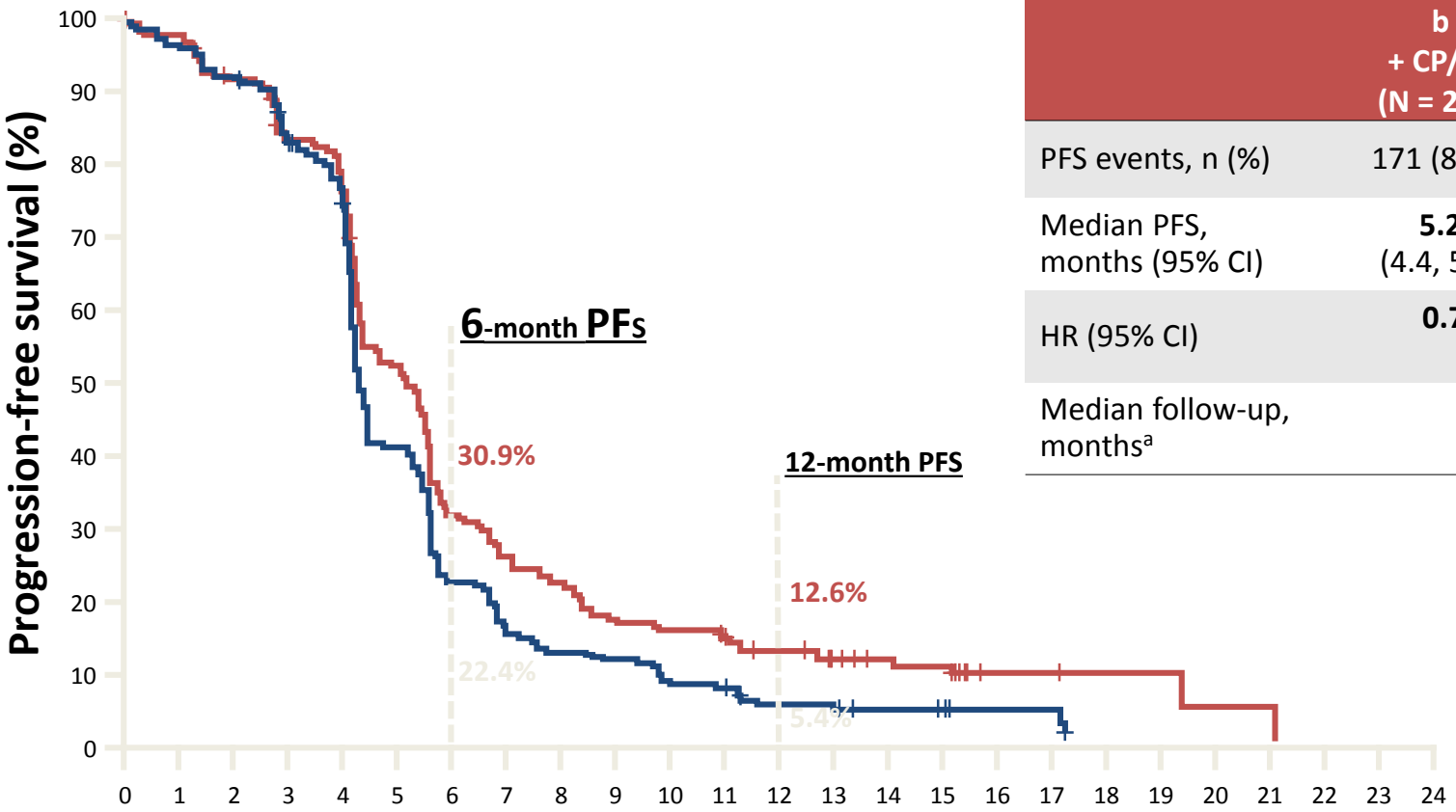
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

No. at risk

Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Progresszió mentes túlélés



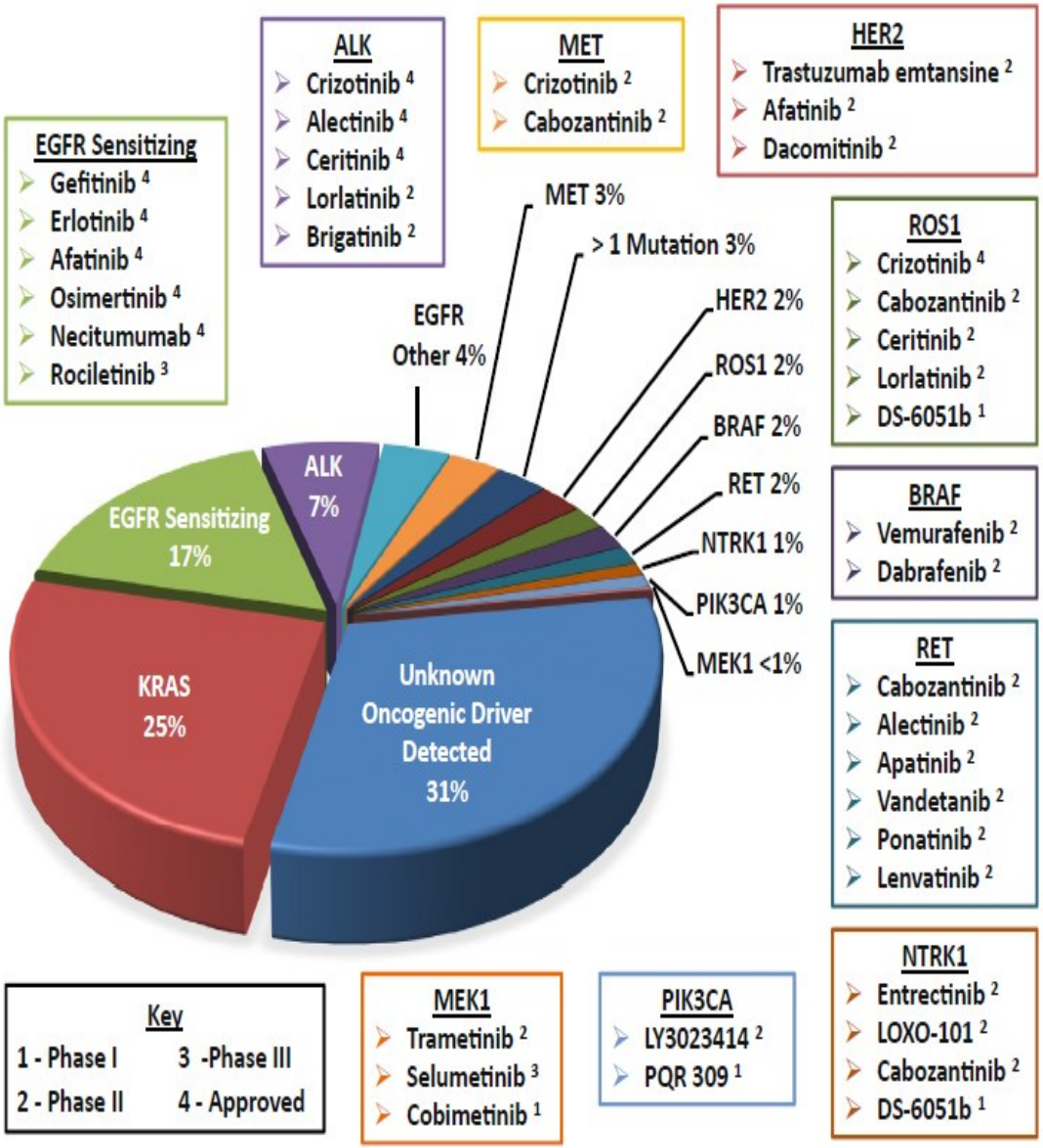
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

No. at risk																						
Atezolizumab	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1
Placebo	202	193	184	167	147	80	44	30	25	23	16	15	9	9	6	5	3	3				

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Adenocarcinoma. Heterogenitás.

Gefitnib
Erlotinib
Osmertinib
Necitumumab
Crizotinib
Alectinib
Afatinib



1-3: nem törzskönyvezett készítmények
Tsao et alJ Thorac Oncol. 2016 May;11(5):613-38

EGFR aktiváló mutáció felfedezése

The Boston Globe

A drug that works — for some

Researchers try to solve mystery of lung cancer medicine

By Raja Mishra
GLOBE STAFF

CONCORD — Early last year, Kate Robbins started her death journal. It was meant to guide her two children after lung cancer killed her. Robbins poured out advice: on dating, on morality, on family. The things a mother explains to her teens.

She also memorialized quiet, poignant moments. One rainy day, watching 10-year-old Hillary board the school bus, Robbins began weeping. She wrote simply, "You looked really pretty today." The kids would read the journal years later, she hoped, and feel their mother's love.

Advanced lung cancer patients rarely live one year. Robbins had months left. Then, last autumn, she began taking an experimental drug called Iressa, as did hundreds of other patients in the United States. Most continued to worsen.

But a small group, including Robbins, thrived.

Progress in Lung Cancer Research

1930s 1940s 1950s 1960s 1970s 1980s 1990s — 1930-1993

1933
Dr. Evarts Graham reported the first successful resection in lung cancer using a single-stage pneumonectomy

1950
Cigarette smoking definitively linked to lung cancer

1960s
Chemotherapy found to prolong survival for patients with lung cancer

1964-1969
Surgeon General's Report on Smoking and Health, public health warnings issued

The Surgeon General's Report definitively stated that cigarette smoking is causally related to lung cancer. The report led to the Federal Cigarette Labeling and Advertising Act of 1965, which required a health warning to appear on cigarette packages sold in the United States. This warning was modified by the Public Health Smoking Act of 1969 to be more explicit

1980s
Systemic chemotherapy with or without chest irradiation found to be curative for a small subset of patients with SCLC

1992
Combined-modality therapy became the standard of care for limited-stage SCLC

1993-present
Secondhand smoke identified as causative for lung cancer in adult nonsmokers

The Environmental Protection Agency (EPA) released a report in 1993, "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders." The EPA concluded that secondhand smoke causes lung cancer in adult nonsmokers. The EPA report classified secondhand smoke as a Group A carcinogen, a designation that means that there is sufficient evidence that secondhand smoke causes cancer in humans. This has led to widespread bans on indoor smoking in public buildings in the United States and around the world.

15 éve

1990s 2000s 2010s — 1994-2014

2004
***EGFR* mutations were discovered in patients who demonstrated dramatic responses to the EGFR-TKIs erlotinib and gefitinib**

2006
Bevacizumab plus paclitaxel and carboplatin linked to improved overall survival for a subset of patients with nonsquamous NSCLC

These data led to the subsequent approval of the agent later that year for initial systemic treatment of patients with unresectable, locally advanced recurrent, or metastatic, nonsquamous NSCLC.

2007
Chromosomal rearrangements of *ALK* were discovered in a subset of NSCLC

2009-2013
EGFR-TKIs gefitinib, erlotinib, and afatinib approved for previously untreated NSCLC and EGFR-sensitizing mutations

In several studies, patients with *EGFR*-mutated NSCLC were treated with either platinum-based chemotherapy or with one of the EGFR-TKIs (gefitinib, erlotinib, or afatinib). Results showed increased response rates, prolongation of progression-free survival, and improvements in symptom control for those treated with the EGFR-TKI compared with those treated with chemotherapy.

2010
Standard of care for patients with NSCLC with resected stage IB or patients with stage II or III NSCLC shifted to cisplatin-based adjuvant chemotherapy

2010
Annual low-dose spiral CT found to reduce the risk of death from lung cancer by 20%, compared with chest x-ray in current and heavy former smokers

2011
Crizotinib approved for *ALK*-positive NSCLC

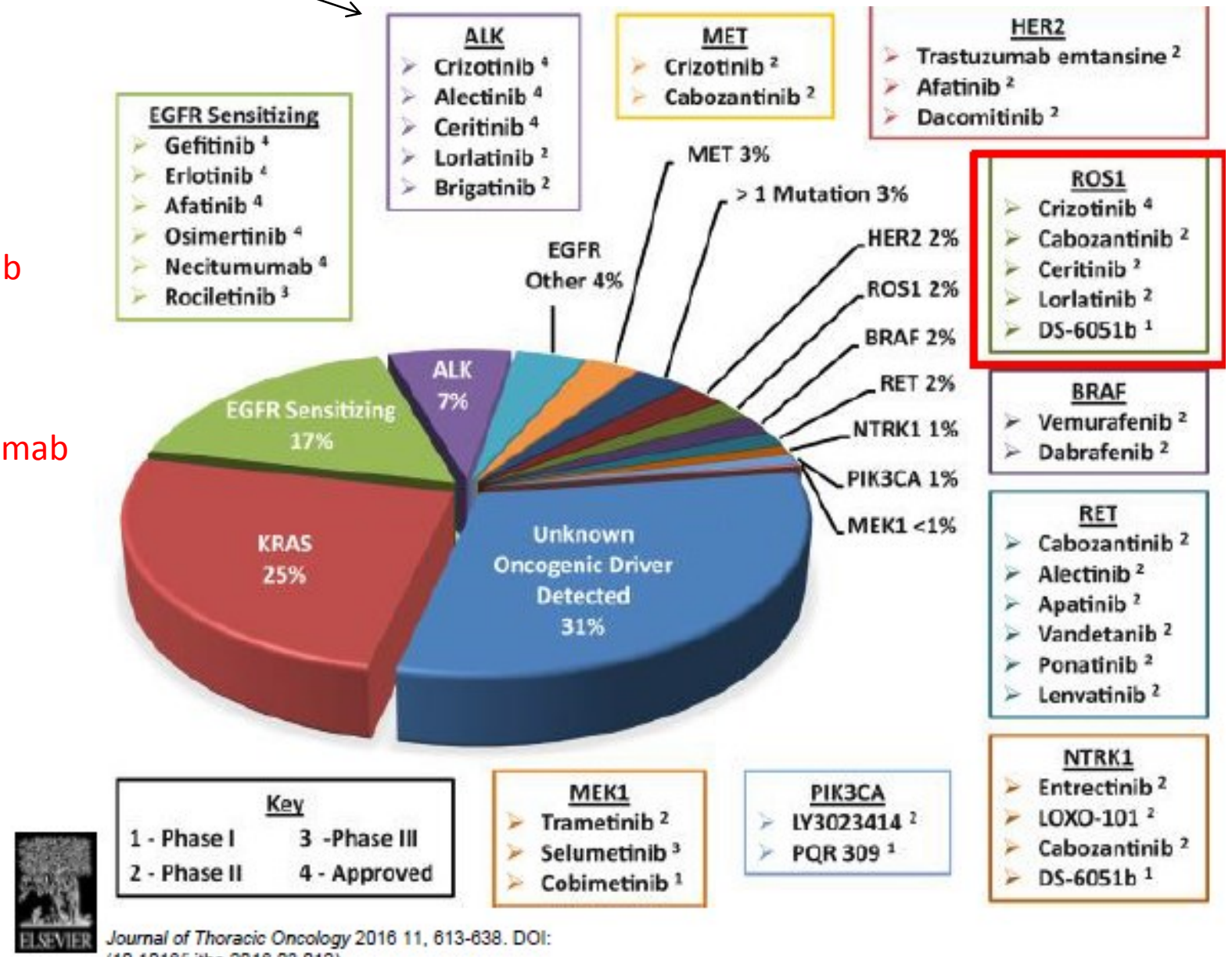
Response rates for crizotinib were found to be 3-fold higher and progression-free survival was prolonged by 2-fold when compared with standard chemotherapy.

2013
The U.S. Preventive Services Taks Force (USPSTF) recommends low-dose spiral CT

The USPSTF adopted the recommendation for annual screening for lung cancer with low-dose CT in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.

ALK gátlás

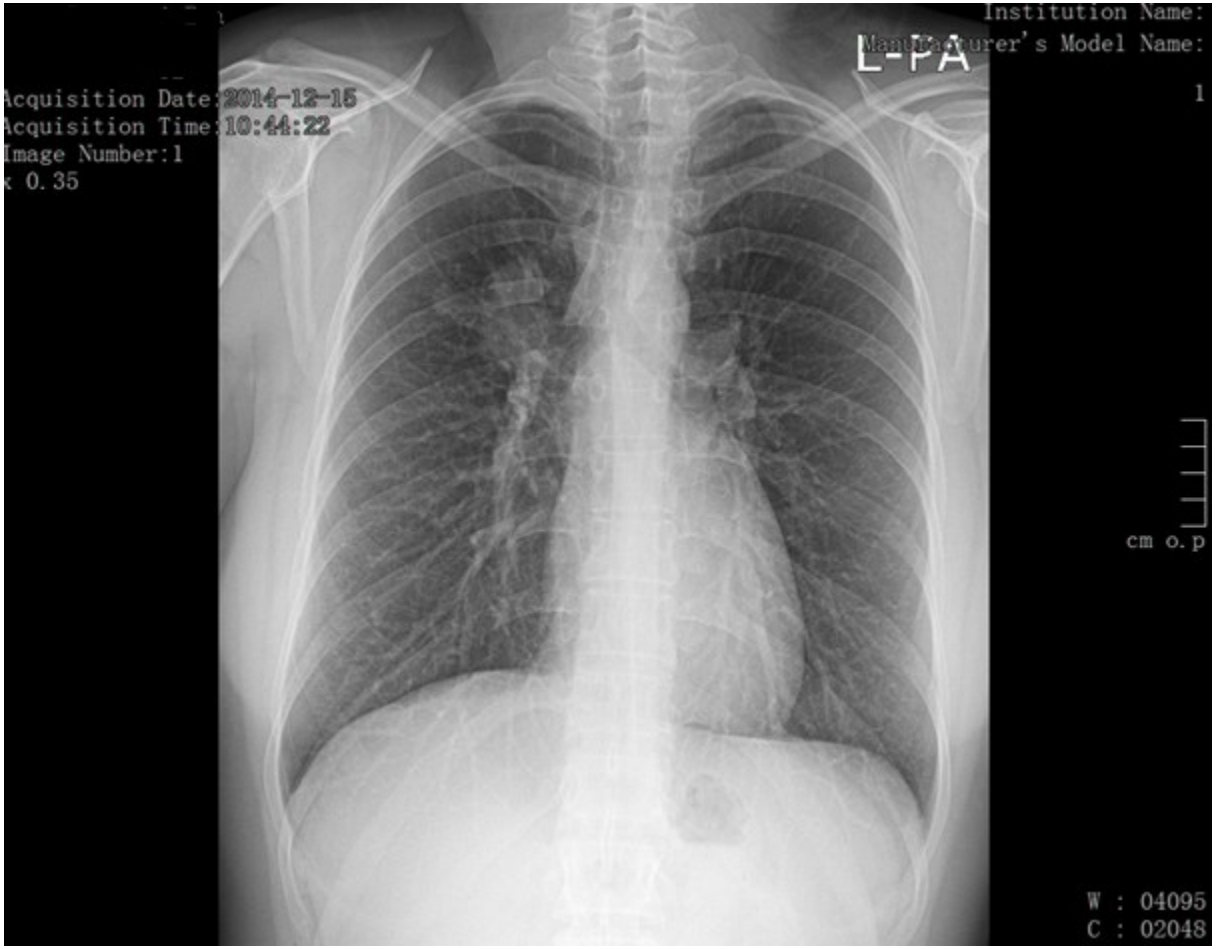
Gefitnib
Erlotinib
Afatinib
Osmertinib
Crizotinib
Alectinib
Ceritinib
Necitumumab



Journal of Thoracic Oncology 2016 11, 613-638. DOI: (10.1016/j.jtho.2016.03.012)

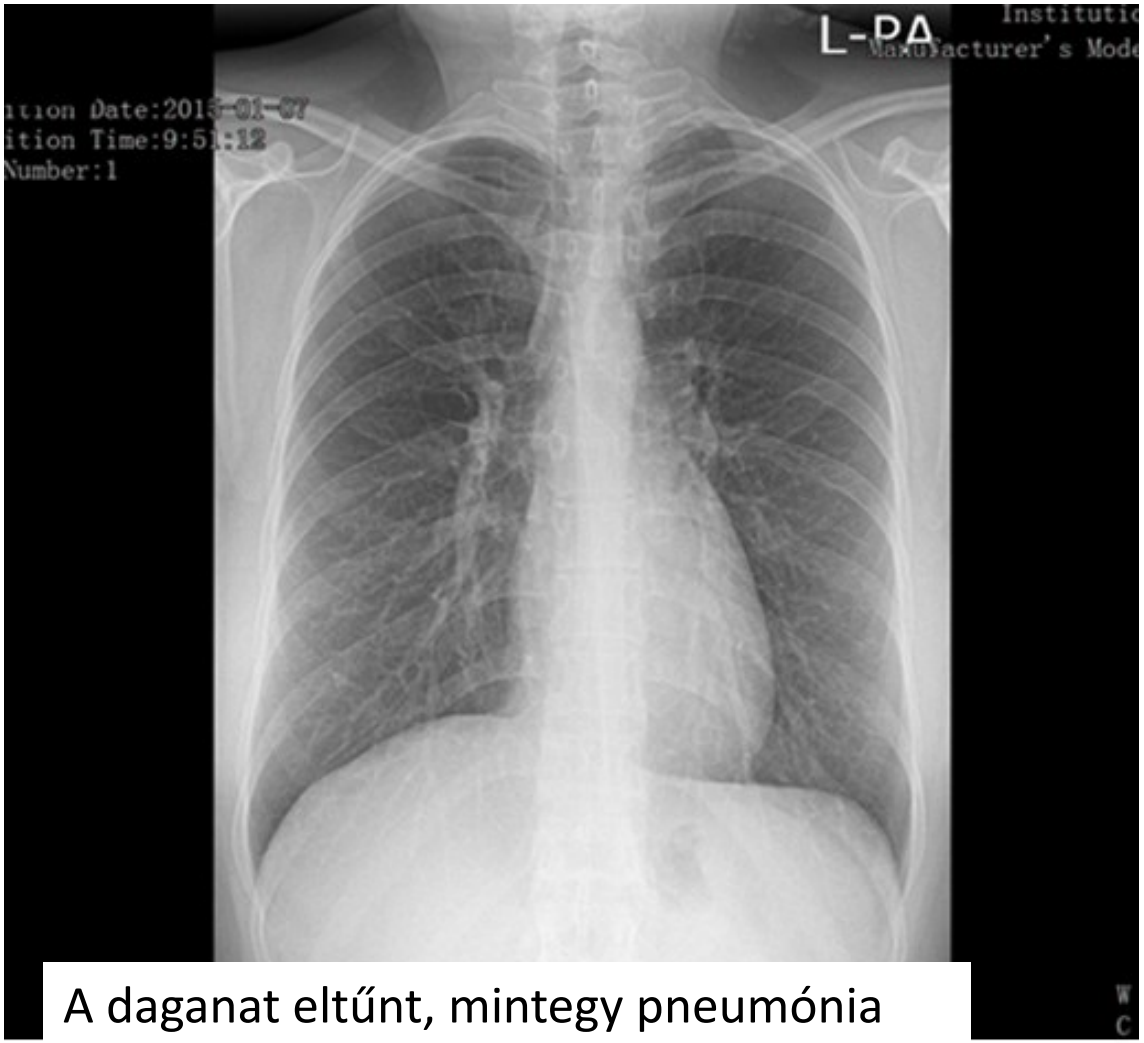
Mellkas rtg a krizotinib kezelés előtt

2014 december 15.



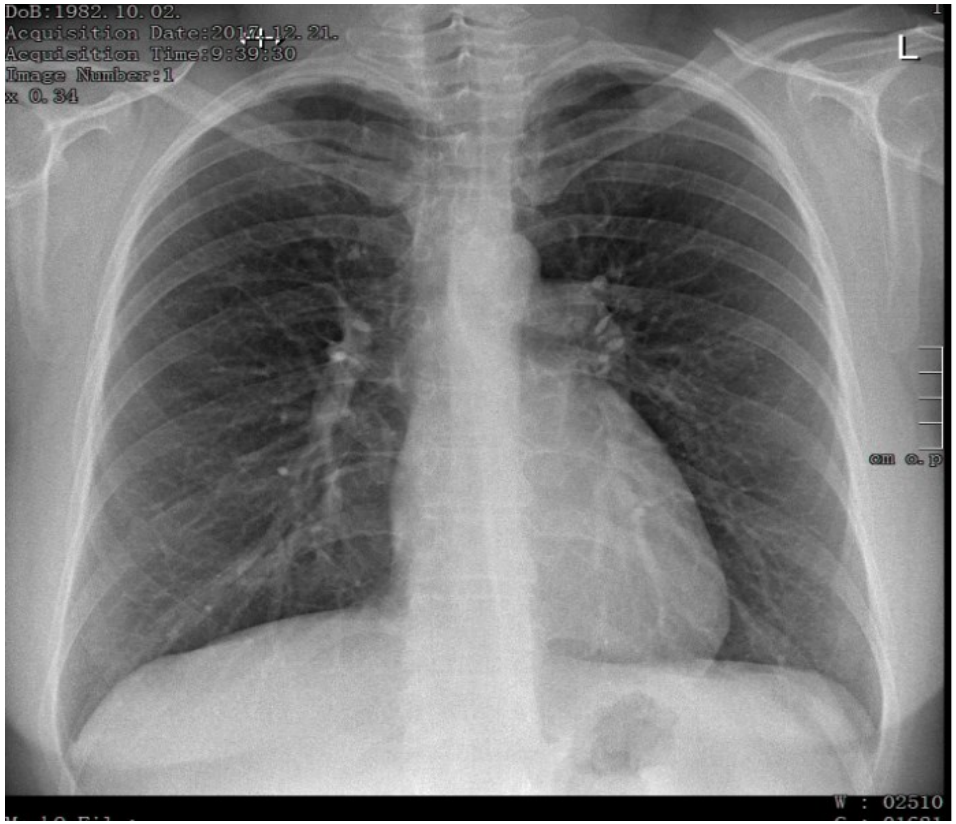
Mellkas rtg. Két héttel a krizotinib kezelés elkezdése után

2015 január 7.



A daganat eltűnt, mintegy pneumónia

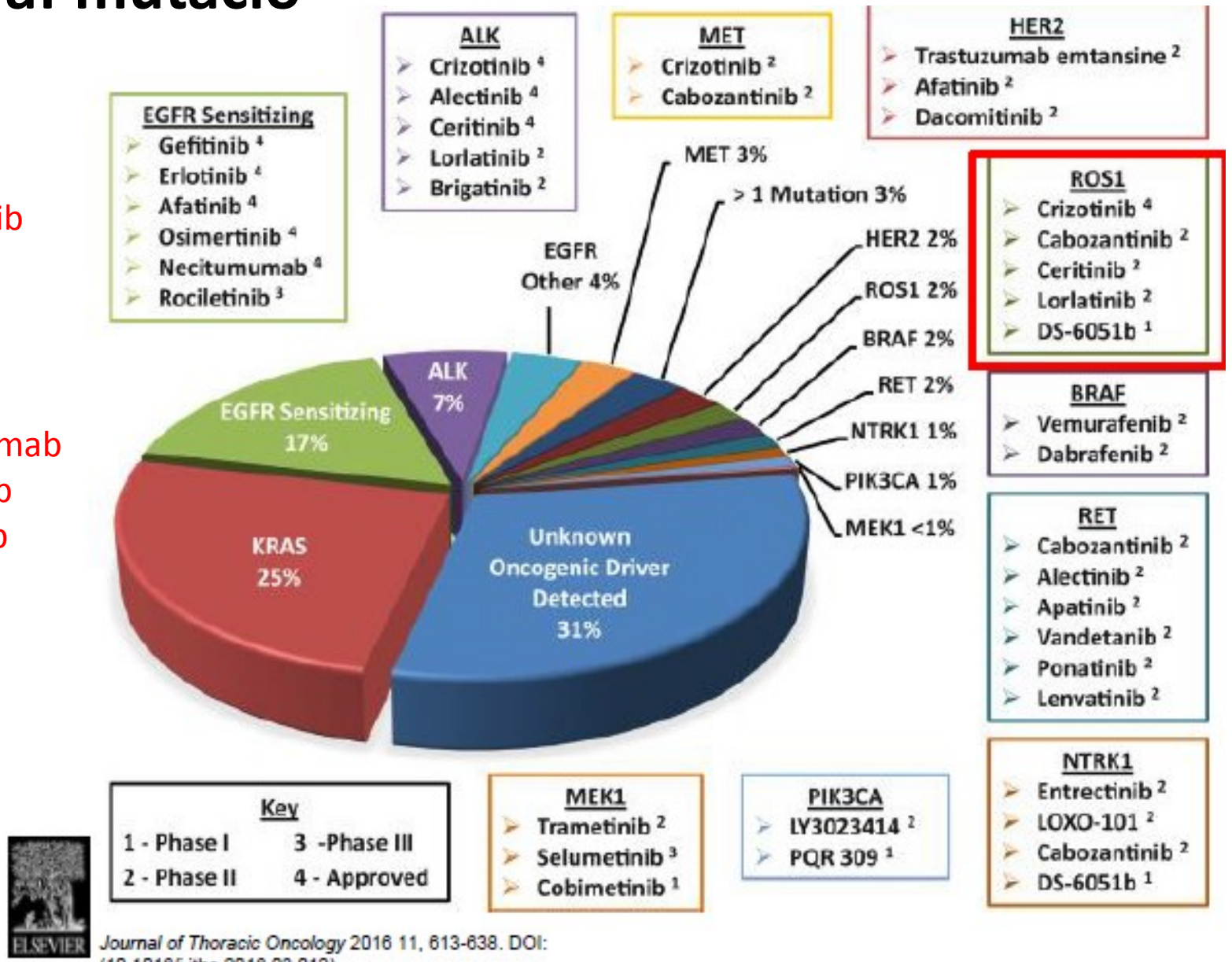
Mellkas rtg. 4 év után



Négy éves progresszió mentes túlélés eddig, folyamata csaknem komplett remisszióban.
Gyakorlatilag tünet és panaszmentes.

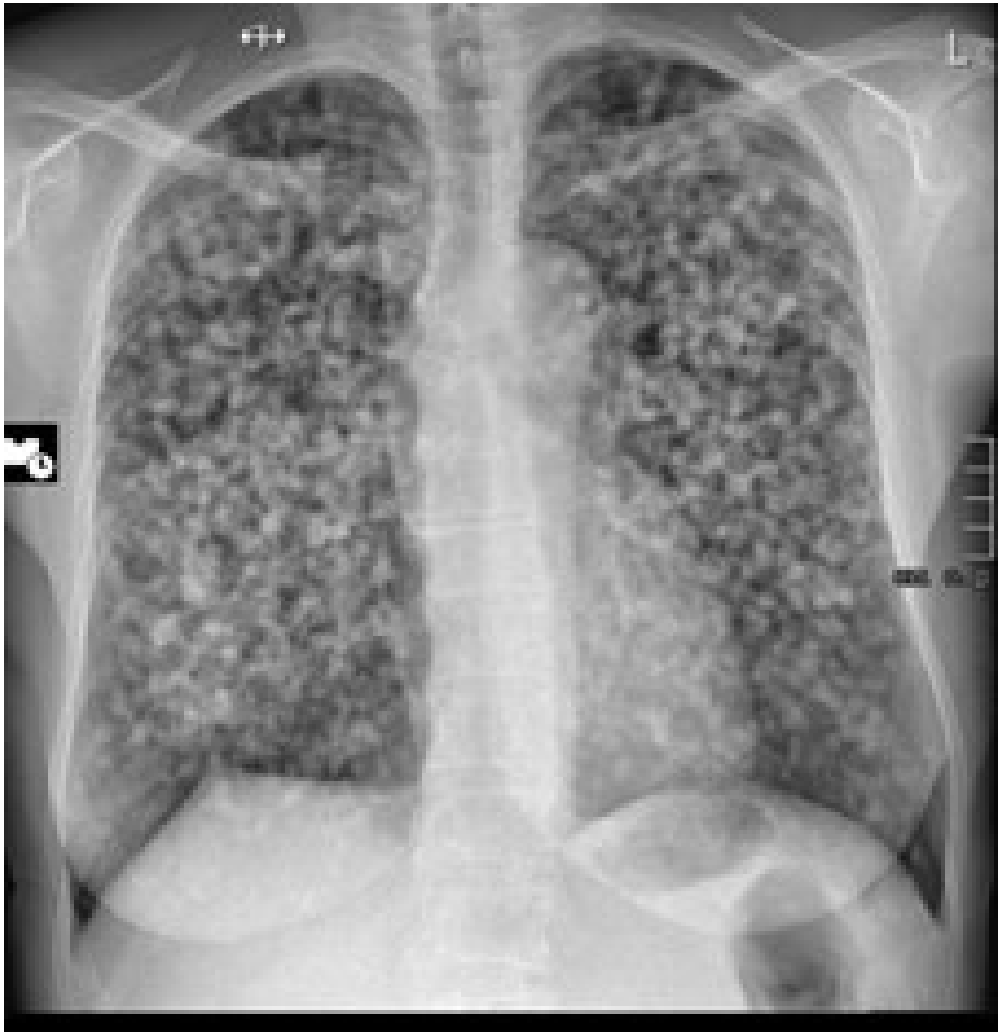
Braf mutáció

Gefitinib
Erlotinib
Afatinib
Osimertinib
Crizotinib
Alectinib
Ceritinib
Brigatinib
Necitumumab
Dabrafenib
Trametinib

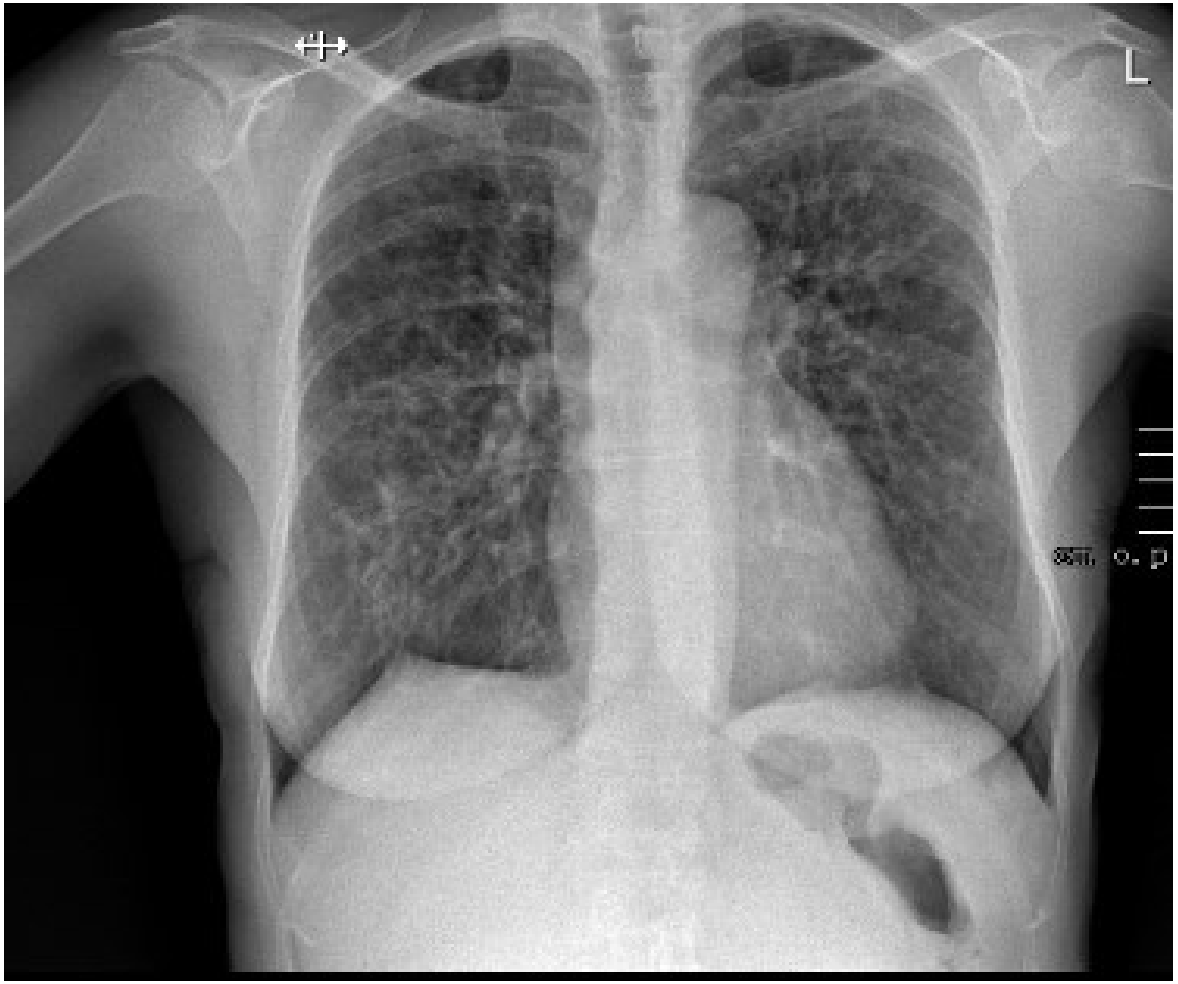


Journal of Thoracic Oncology 2016 11, 613-638. DOI: (10.1016/j.jtho.2016.03.012)

Dabrafenib Trametinib kezelés előtt



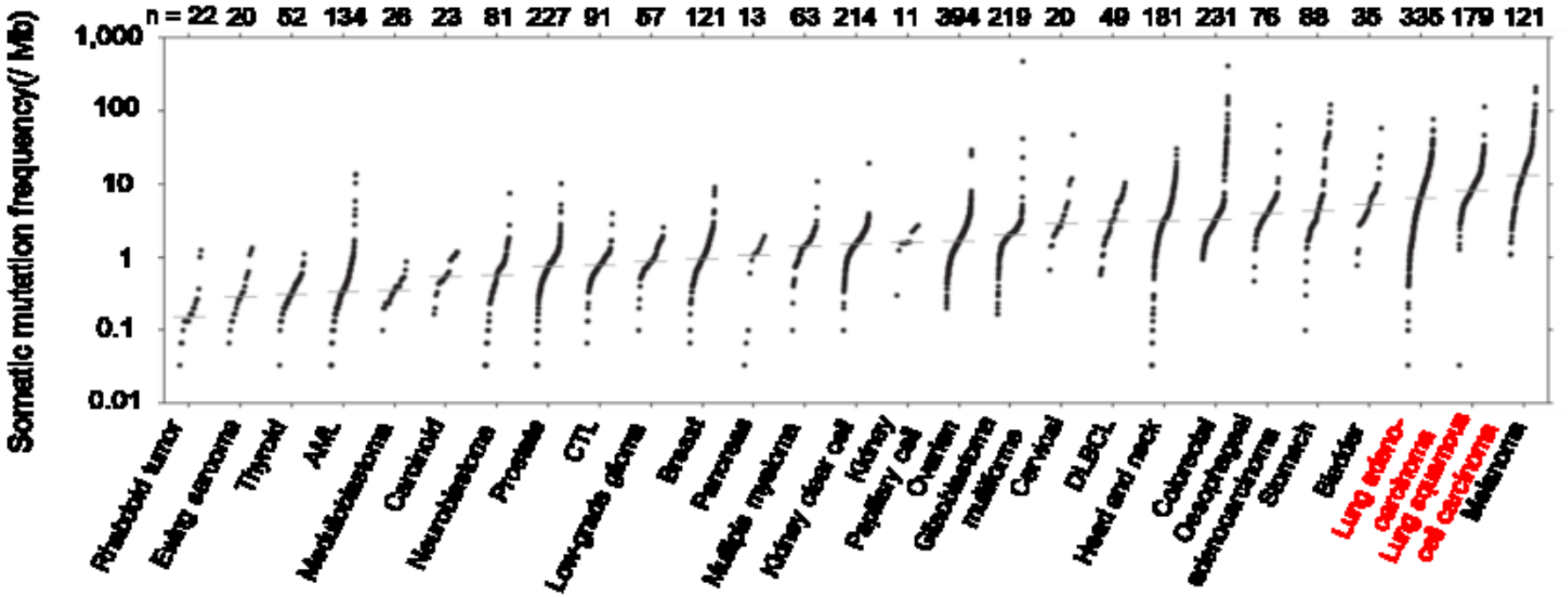
Dabrafenib Trametinib kezelés után 6 héttel



BRAF mutáció meghatározás

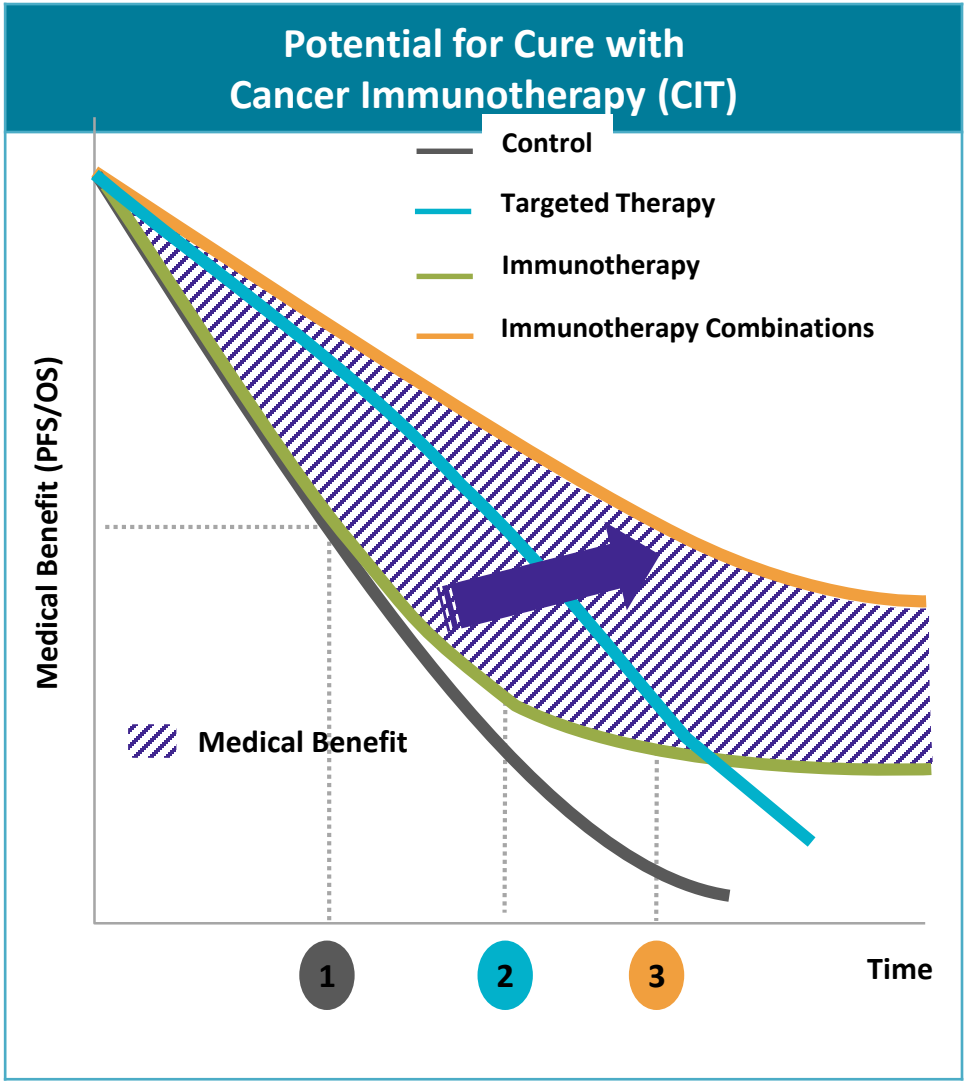
Magas mutációs arány a tüdőrákban

Somatic mutation frequencies observed in exomes from 3083 tumour-normal pairs



Immunonkológia

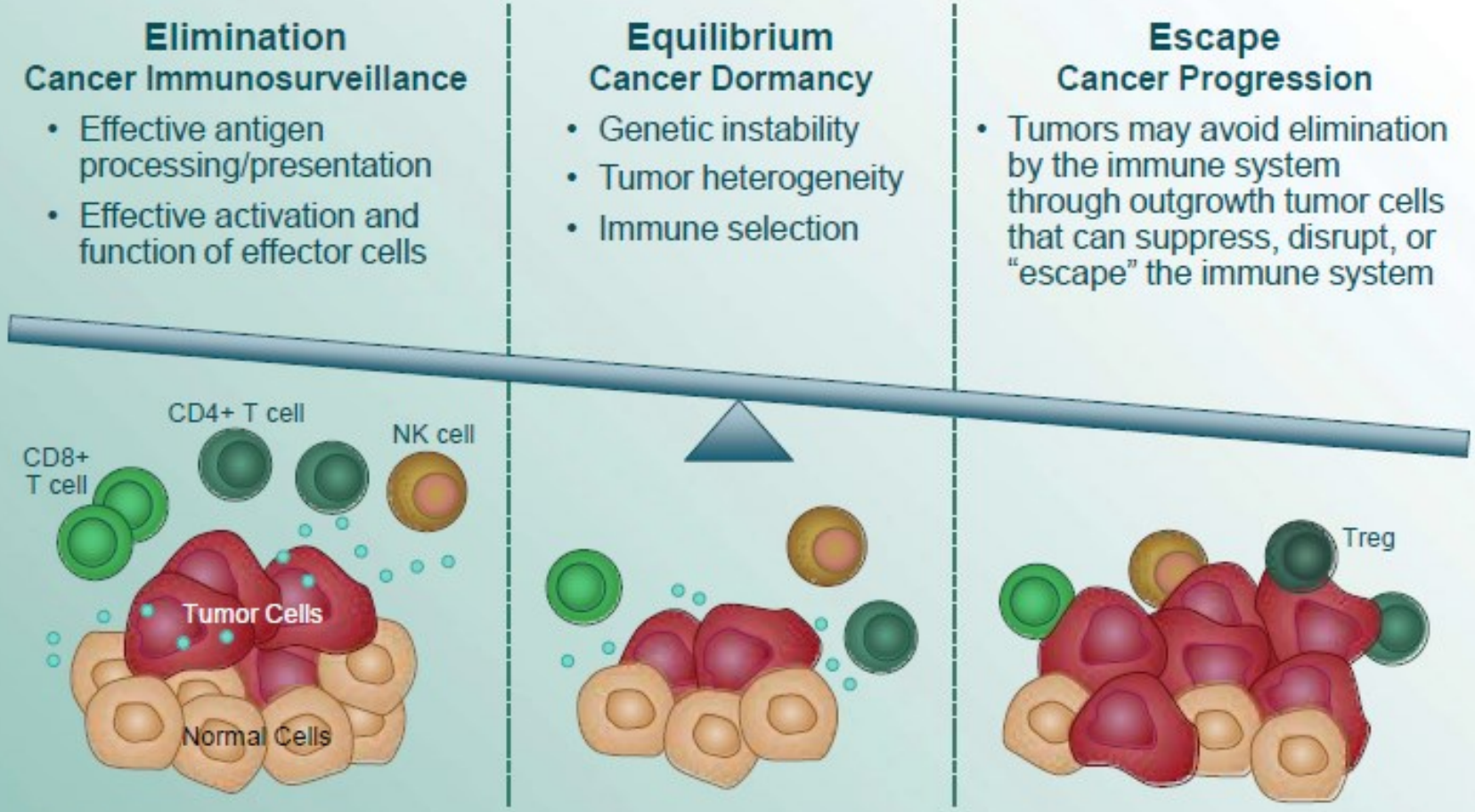
Esély a hosszú távú túlélésre



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

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

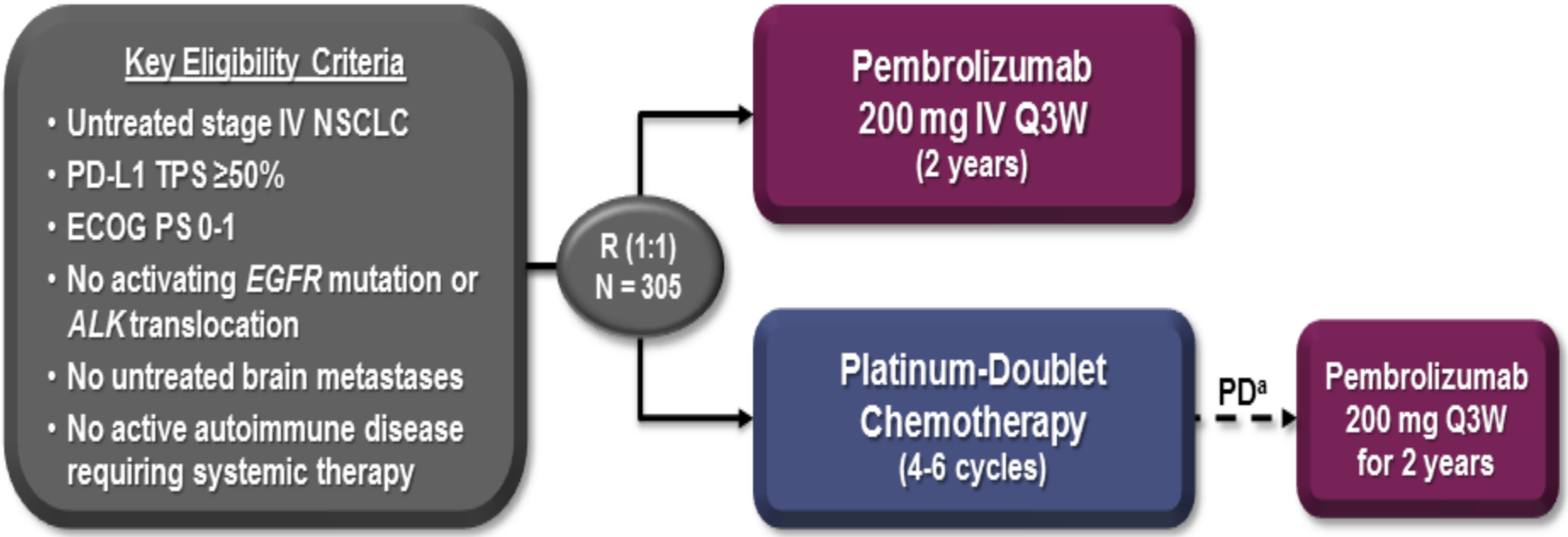
- **The three E's of cancer immunoediting describe the immune system's role in protecting against tumor development and promoting tumor growth**



NK=natural killer; Treg=regulatory T cell.

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

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Előbb immunellenőrző pont gátló kezelés, majd kemoterápia PDL1-et magasan expresszáló nem kissejtes tüdőrák esetén.

Megjegyzések:

10

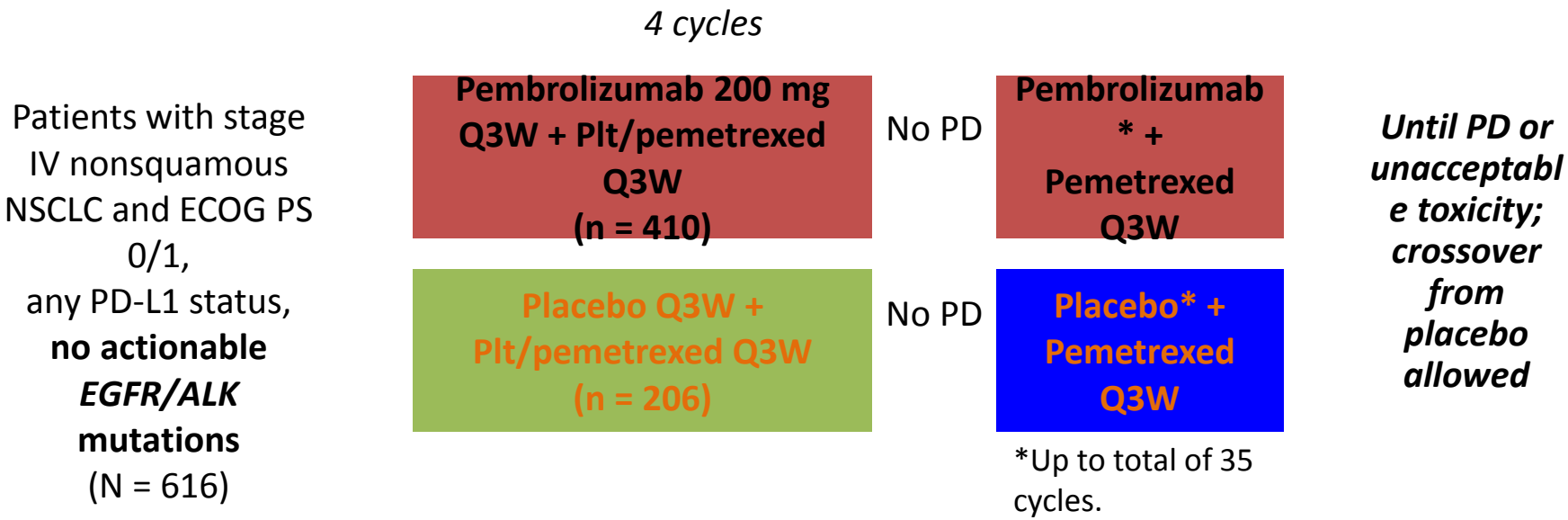
Szuperszelektált betegek:

- PDL1 expr. 50 % felett
- PS 0-1
- EGFR ALK kizárva
- Agyi áttét
- Aktív autoimmun betegség

1-2

KEYNOTE-189: Pembrolizumab+ CT vs CT
IV-es stádiumú nem laphámsejtes tüdőrák

- Randomizált, dupla vak fázis III-as vizsgálat

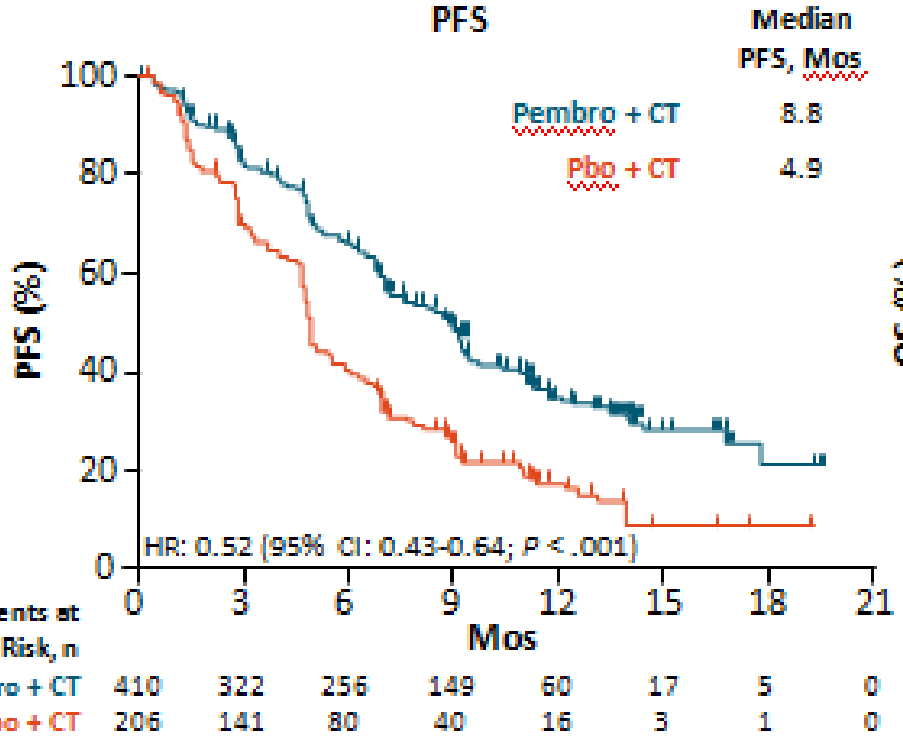


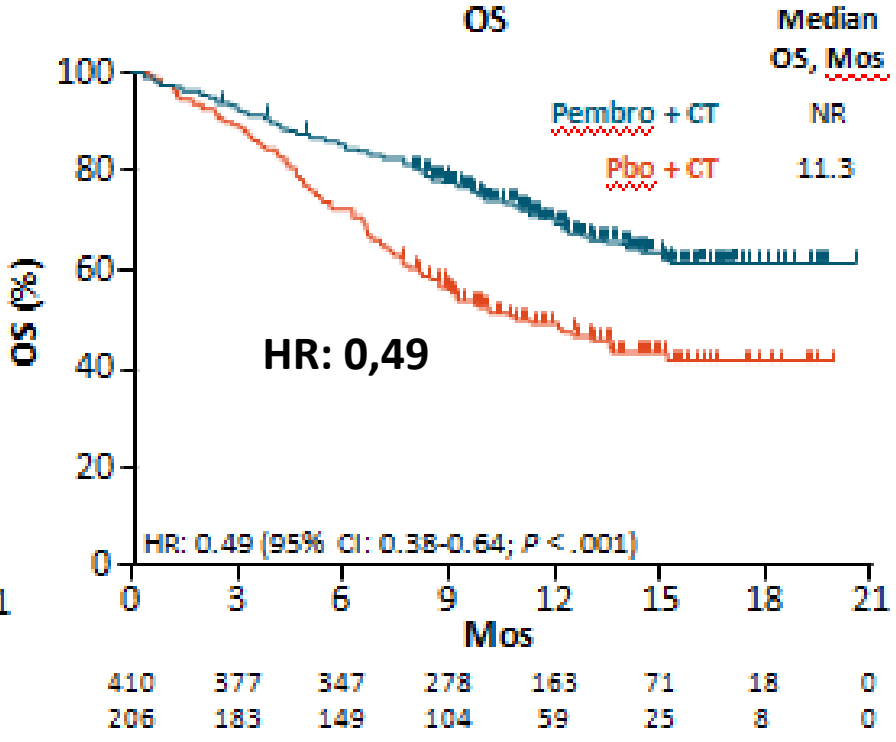
- Primary endpoints: OS, PFS by BICR
- Secondary endpoints: ORR, DoR, safety

Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print]. ClinicalTrials.gov. NCT02578680.

AACR 2018.

Keynote 189 Túlélés





Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

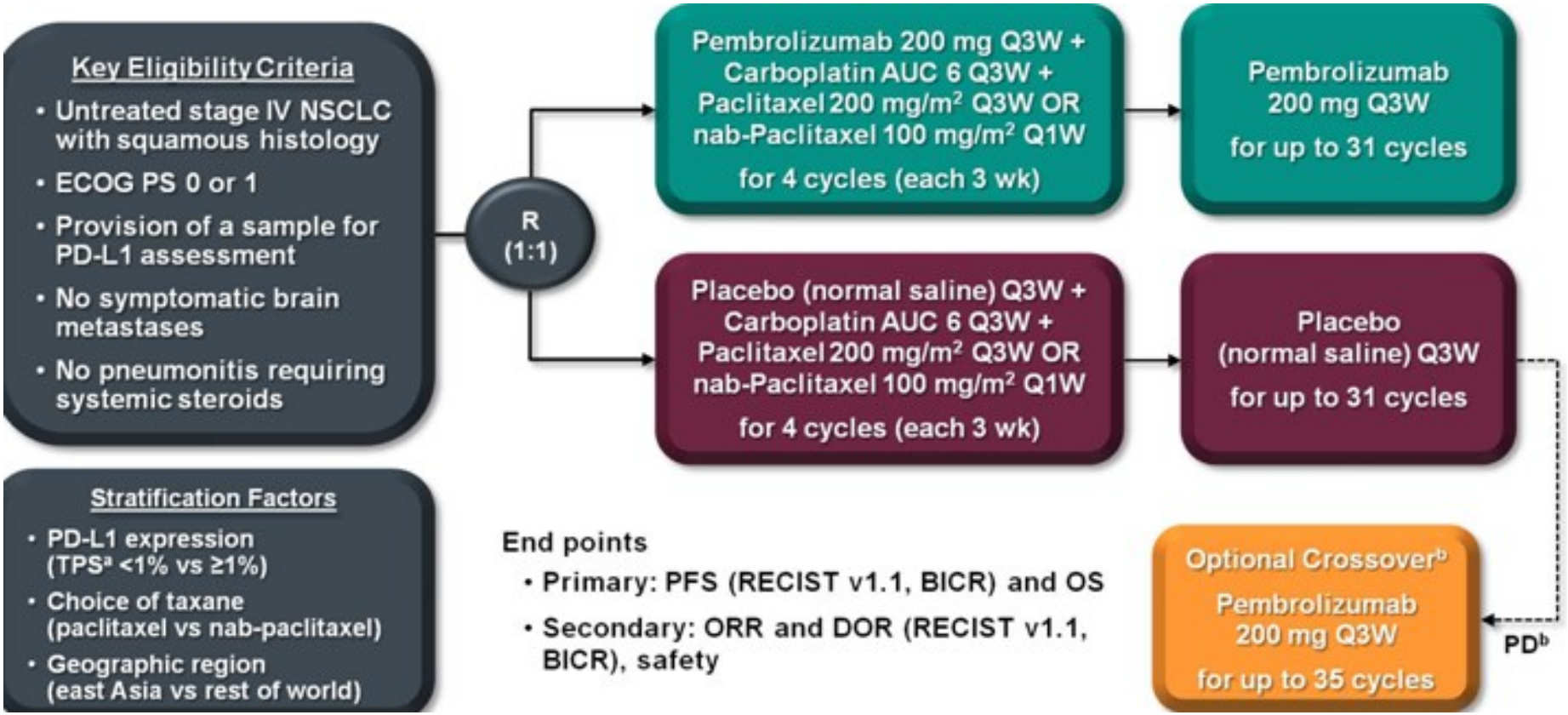
KEYNOTE-189: Következtetések

- IV-es stádiumú nem laphámsejtes tüdőrák esetén, a pembrolizumab + kemoterápiás kombináció, összevetve a platina bázisú kemoterápiával szignifikánsan megnöveli a PFS és az OS értékeket azoknál a betegeknél, akiknél nem mutatkozik driver mutáció
- PDL1 expressziótól független hatékonyság

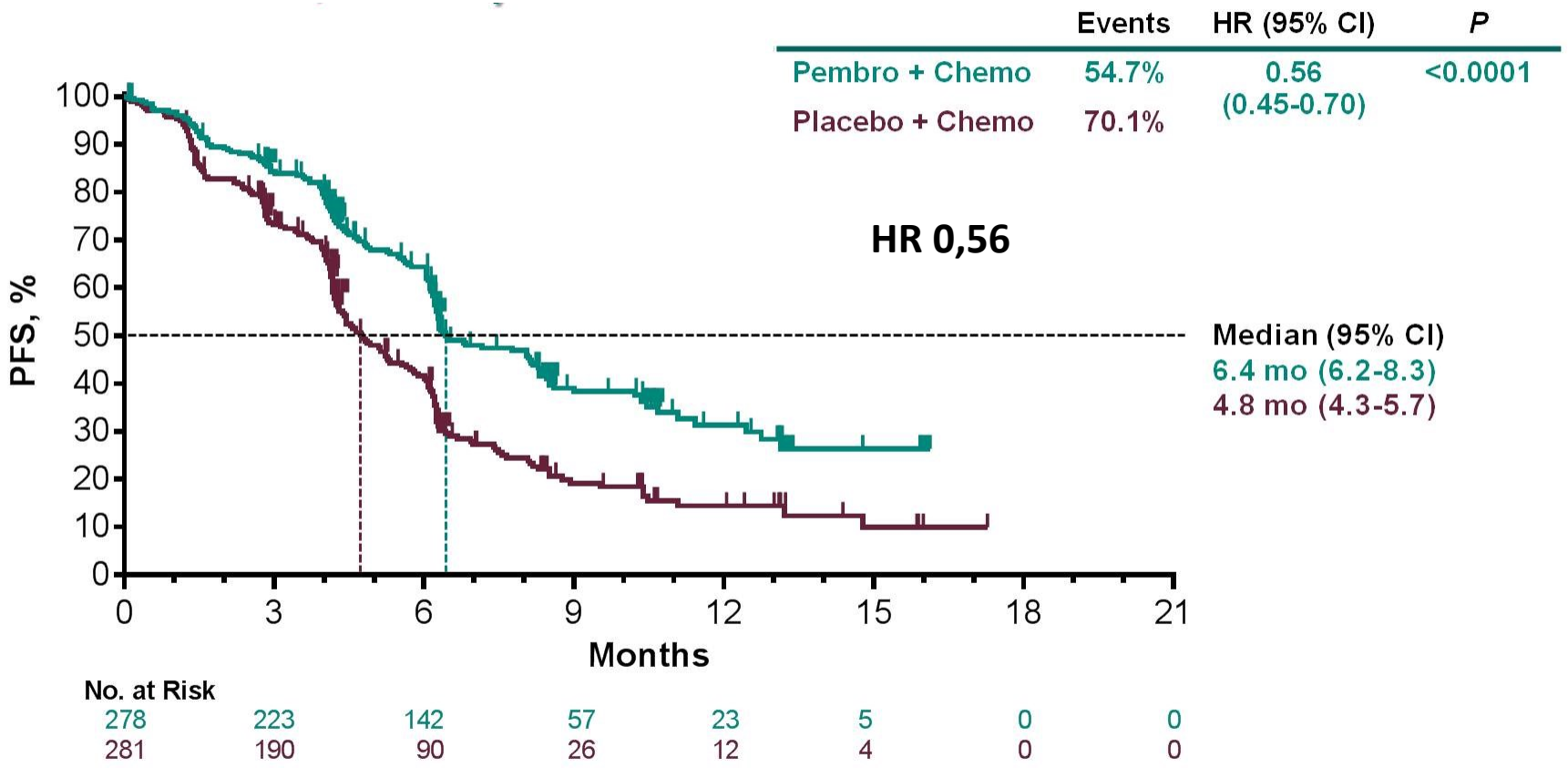
A pembrolizumab + platina + pemetrexed kombinációs kezelés, majd a fenntartó pemetrexed+pembrolizumab terápia új elsővonalbeli standard kezelés a IV-es stádiumú nem laphámsejtes tüdőrákban

Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print].

KEYNOTE 407: Fázis III-as vizsgálat Paclitaxel/carboplatin. Pembrolizmabbal, vagy anélkül IV-es stádiumú laphámsejtes tüdőrákban



Progresszómentes túlélés

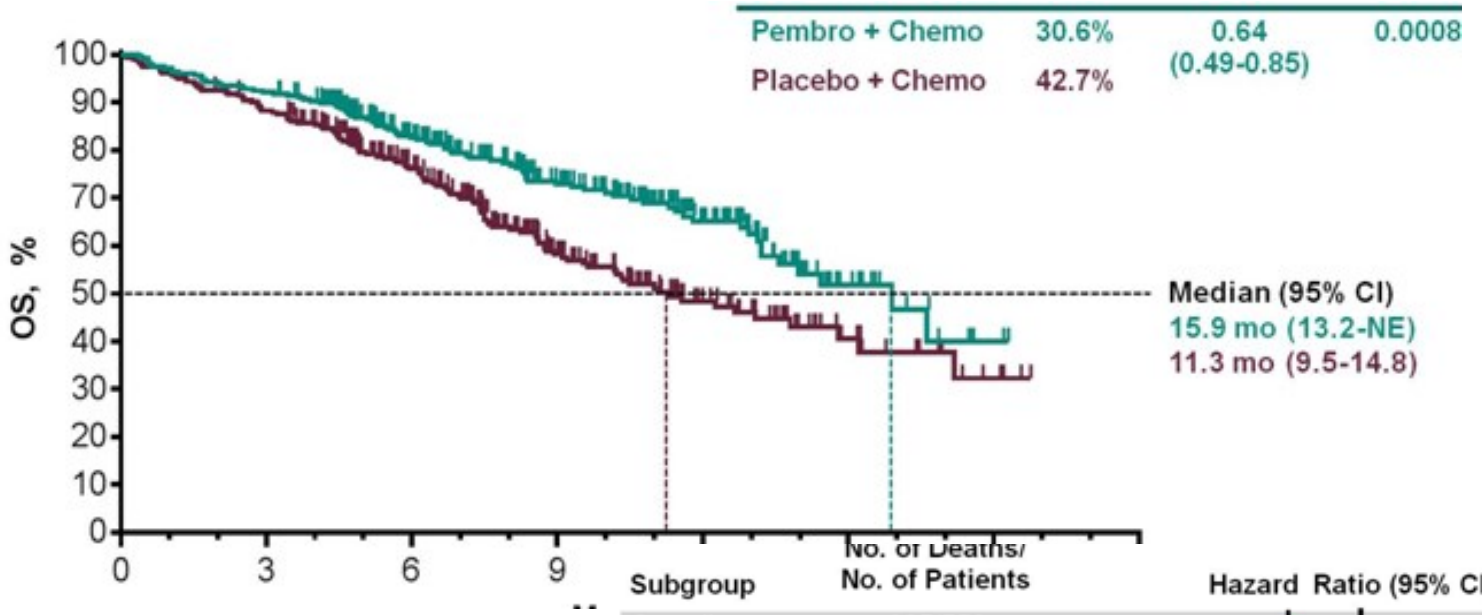


BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

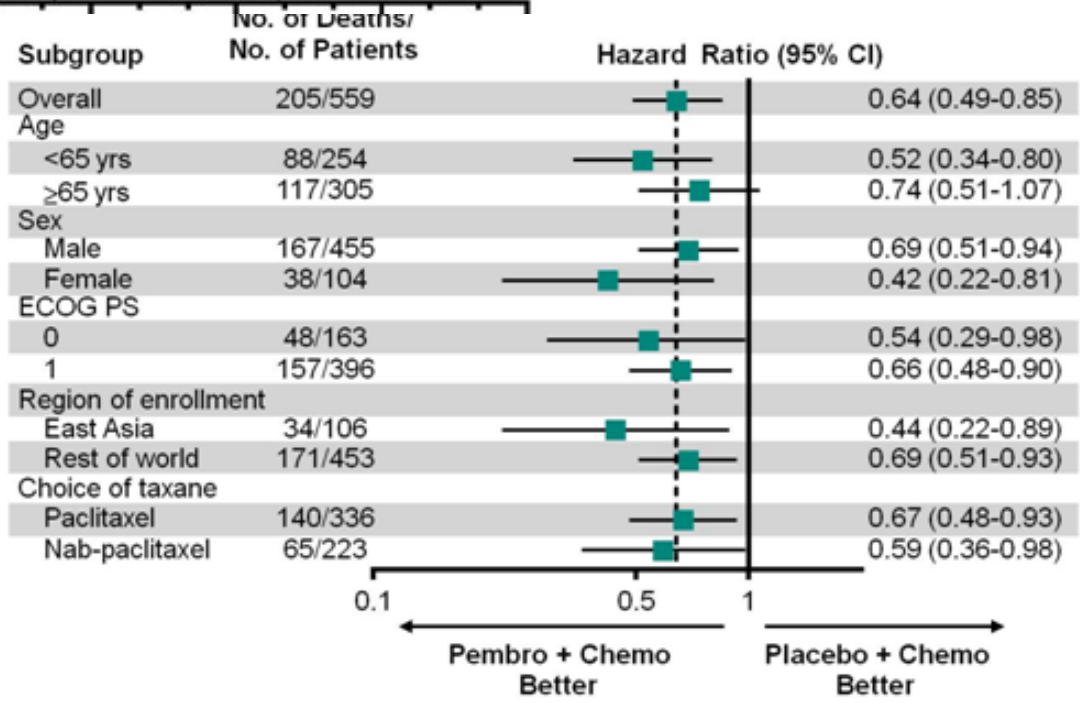
Presented By Luis Paz-Ares at 2018 ASCO Annual Meeting

Eredmények

Medián túlélés:



Minden nézett alcsoportban jobb a kemo+pembro kar



Következtetés:

Data suggest pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel should become a new standard-of-care for first-line treatment of metastatic squamous NSCLC, irrespective of PD-L1 expression

Pembrolizumab plusz carboplatin/paclitaxel kezelés, fenntartó pembrolizumab terápiával új terápiás standard a IV-es stádiumú laphámsejtes nem kissejtes tüdőrák esetén a PDL1 expressziótól függetlenül.

PACIFIC vizsgálat:

Phase 3, randomized, double-blind, placebo-controlled, multi-center, global study[1,2]

Treatments of patients with stage III unresectable NSCLC who have not progressed following platinum-based concurrent chemoradiation
Patients randomized = 713

Randomization 2:1
1–42 days post-cCRT

Durvalumab IV 10 mg/kg q2w up to 12 months (N=476)

Placebo IV q2w (N=237)

Co-primary Endpoints	Secondary Endpoints	
• OS • PFS*	• OS24 • DoR (per BICR) • ORR (per BICR) • APF12 and APF18	• TTDM • Safety and tolerability • Health-related QoL • PK and immunogenicity

* Response Evaluation Criteria In Solid Tumors v1.1

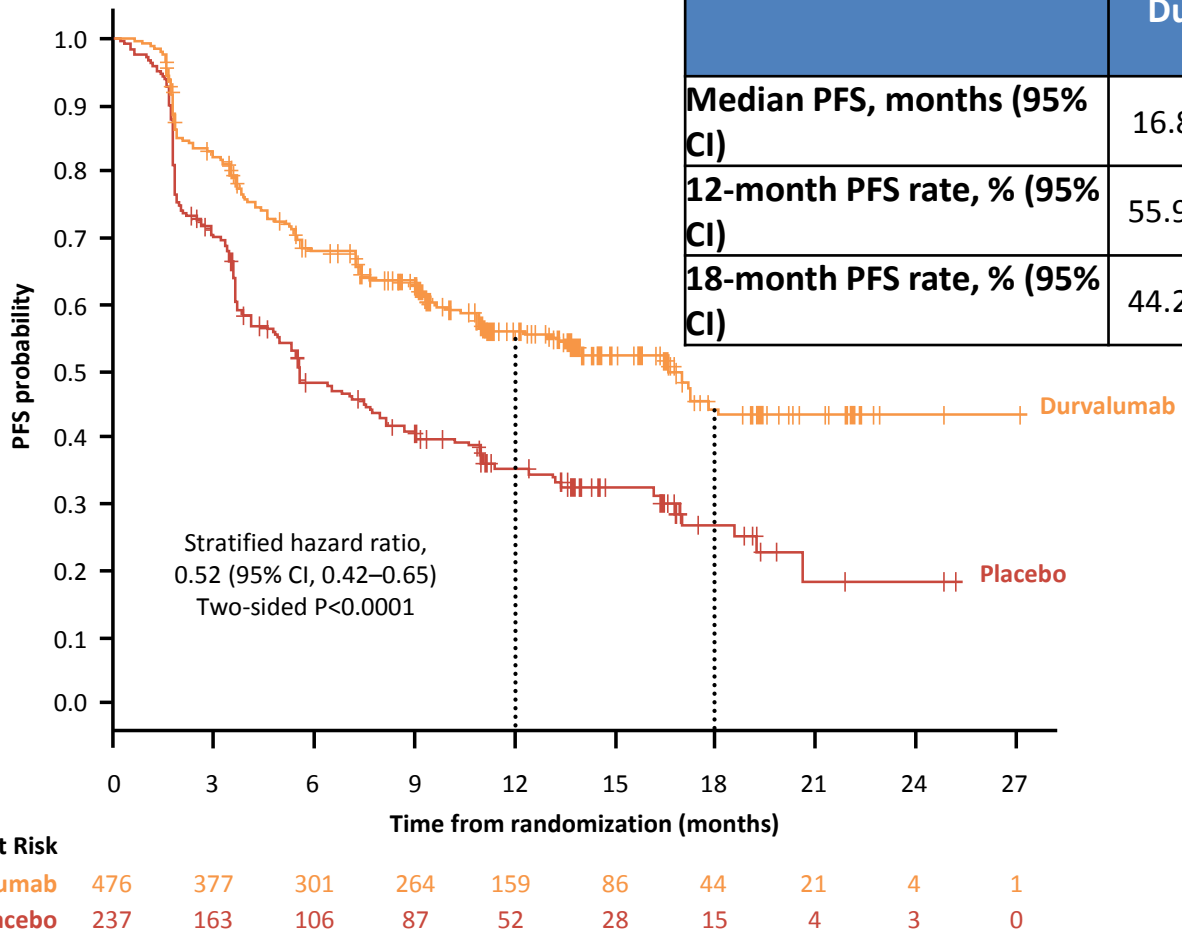
Stratification factors

1. **Age at randomization** (<65 vs ≥65 years of age)
2. **Sex** (male vs female)
3. **Smoking history** (smoker vs non-smoker)

APF12 = proportion of patients alive and progression-free at 12 months; BICR = blinded independent central review; DoR = duration of response; IV = intravenously; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; OS24 = number (%) of patients who are alive at 24 months; PFS = progression-free survival; PK = pharmacokinetics; QoL = quality of life; q2w = every 2 weeks; SoC = standard of care; TTDM = time to death or distant metastasis.

1. US National Institutes of Health. https://www.clinicaltrials.gov/ct2/show/NCT02125461. **2.** Paz-Arez A et al. Poster presented at: ESMO Annual Meeting, September 8-12, 2017; Madrid, Spain.

PACIFIC Study – PFS by BICR



	Durvalumab (N=476)	Placebo (N=237)
Median PFS, months (95% CI)	16.8 (13.0–18.1)	5.6 (4.6–7.8)
12-month PFS rate, % (95% CI)	55.9 (51.0–60.4)	35.3 (29.0–41.7)
18-month PFS rate, % (95% CI)	44.2 (37.7–50.5)	27.0 (19.9–34.5)

3 X

BICR = blinded independent central review; PFS = progression-free survival.

1. Paz-Arez A et al. Poster presented at: ESMO Annual Meeting, September 8-12, 2017; Madrid, Spain.

A tüdőrák immunterápiája teljesen átformálja a kezelési stratégiát

Amennyiben nincs onkogén driver mutáció

- Első vonalban IV-es stádiumú megbetegedés esetén
- Második fonalban IV-es stádiumú megbetegedés esetén
- Fenntartó terápiában lokálisan kiterjedt nem kissejtes tüdőrák esetén

Kísérleti stádium:

- Neoadjuváns kezelés
- Aduváns kezelés
- Onkogén driver mutáció esetén

CLLA4 gátlás

2018		James P. Allison	USA	"A a rák elleni modern immunterápia kifejlesztéséért"[
		Hondzso Taszuku	Japán	

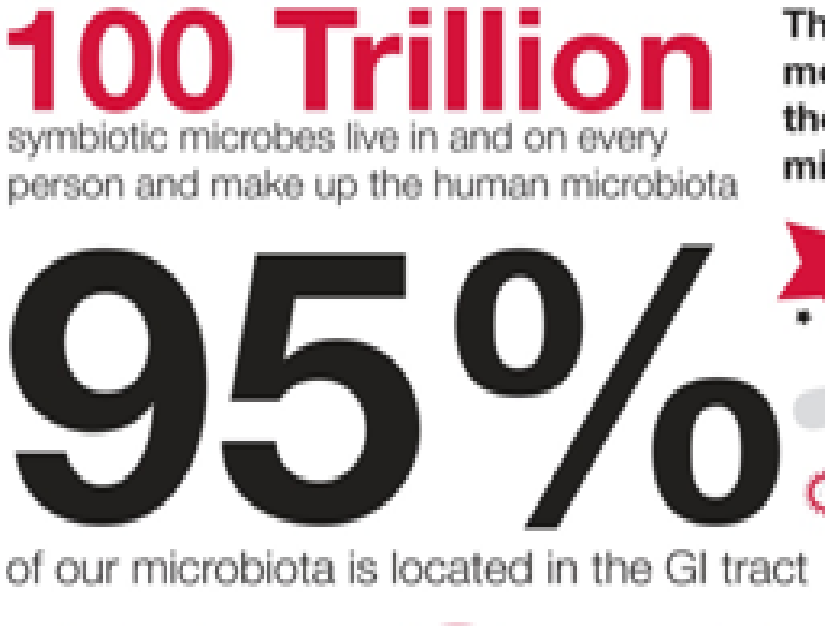
PD axis gátlás

Mikrobiom és a Tüdőrák

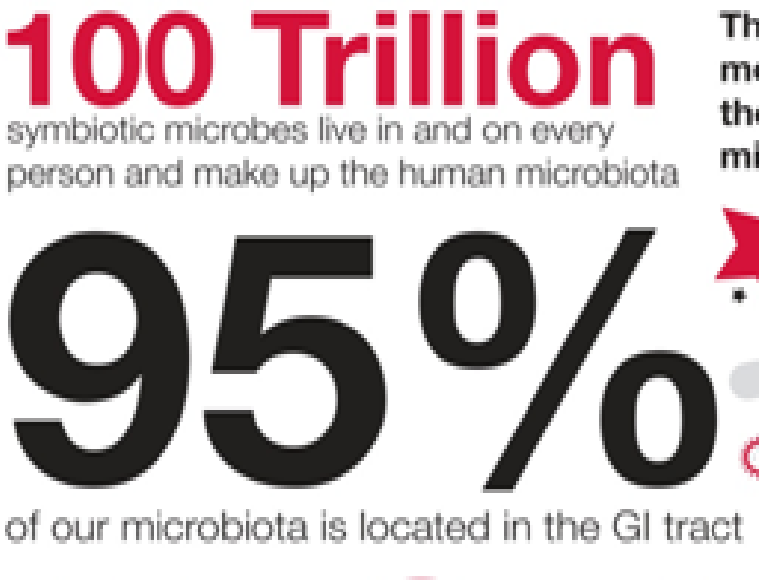
A mikrobiom a bennünk élő szimbionta és patogén mikroorganizmusok ökológiai rendszere.

The microbiome is the ecological community of commensal, symbiotic, and pathogenic microroganisms that literally share our body space.

Joshua Lederberg (2001)



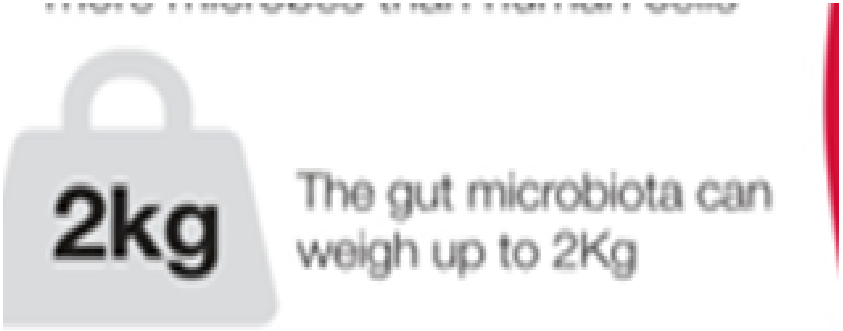
80 – 100 milliárd mikroorganizmus



A Tejút csillagainál is többen élnek velünk

Több a velünk együtt élő mikroorganizmusok száma, mint a testünket alkotó sejtek száma

Több, mint 10 000 fajta



Ujjlenyomat

Mikrobiom kutatás

- Anna Karenina effektus

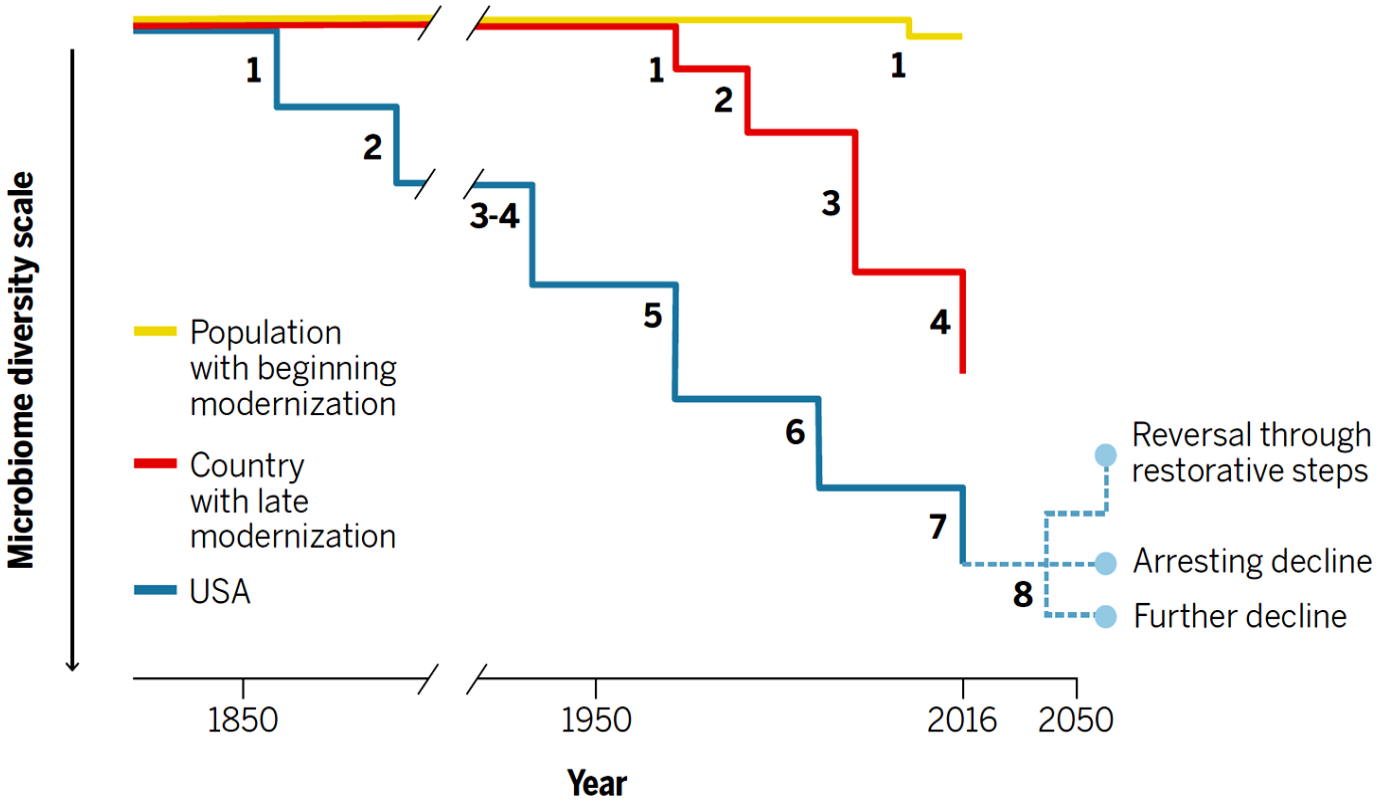
- „A boldog családok mind hasonlóak egymáshoz, minden boldogtalan család a maga módján az”
- „Happy families are all alike; every unhappy family is unhappy in its own way.”

- Velünk élő élőlények.
- Mikrobiom egyensúly megbomlás egyedi
- Hatása az immunterápiára (antibiotikumok, probiotikumok)

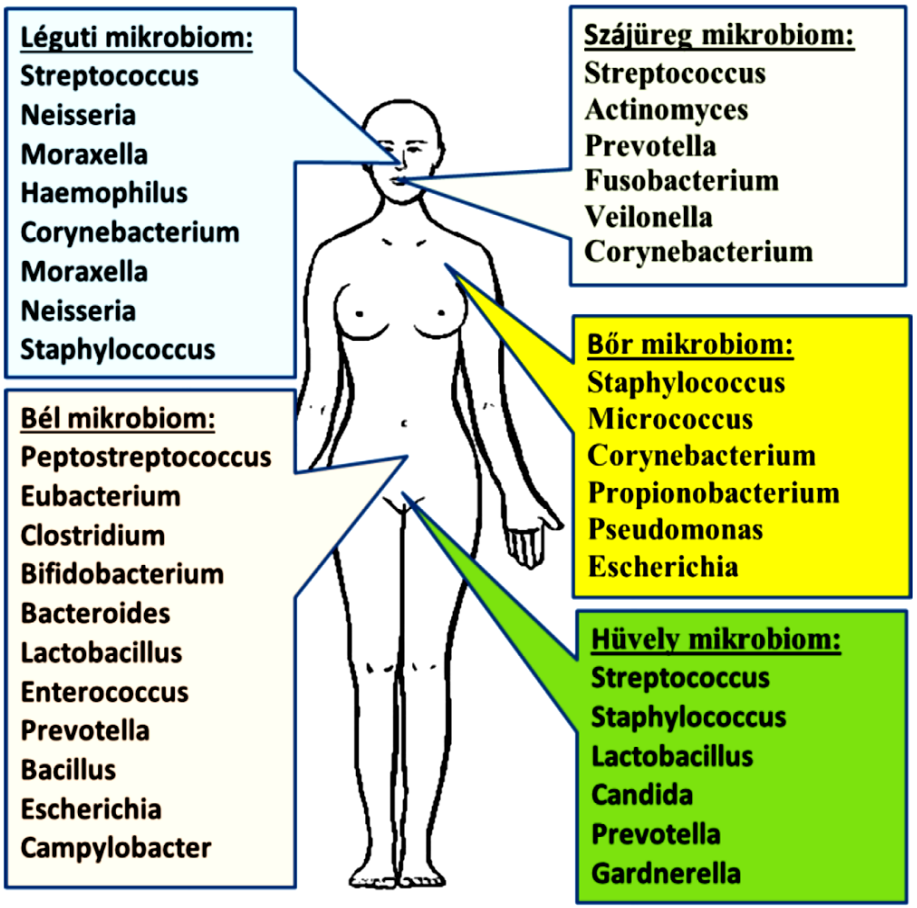
J Zaneveld et al. Nature Microbiology 2017.

Mikrobiom sokféleségének változása

Blaser MJ: Antibiotic use and its consequences for the normal microbiome.
Science 2016: 352: 545-546.



A mikrobiom eloszlása



Négy élű kard

Antibiotikumok

Négy élű kard

Antibiotikumok

Egy: infekciók kezelése

Kettő: prevenció

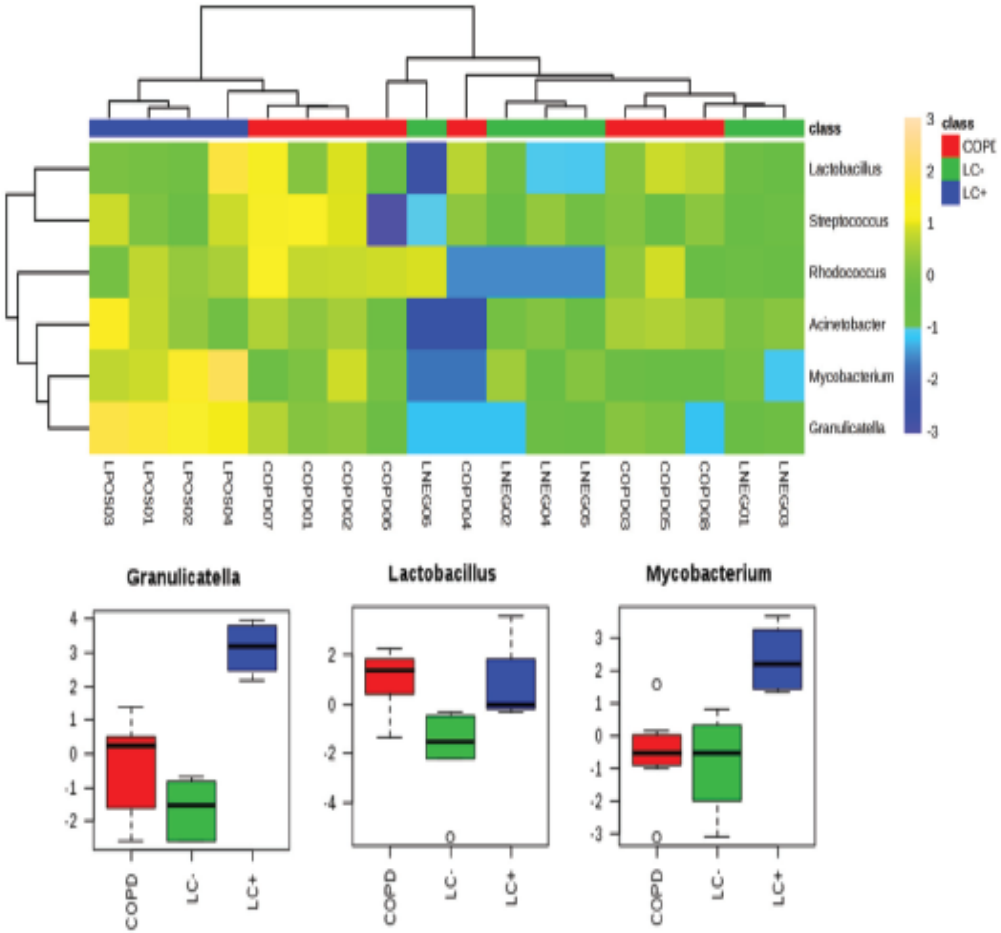
Három: rezisztencia

Négy: hatása a mikrobiomra

Lung cancer: a new frontier for microbiome research and clinical translation

Luis AJ Mur[1], Sharon A Huws[2], Simon JS Cameron[3], Paul D Lewis[4] and Keir E Lewis[5,6]

ecancer 2018, 12:866 https://doi.org/10.3332/ecancer.2018.866

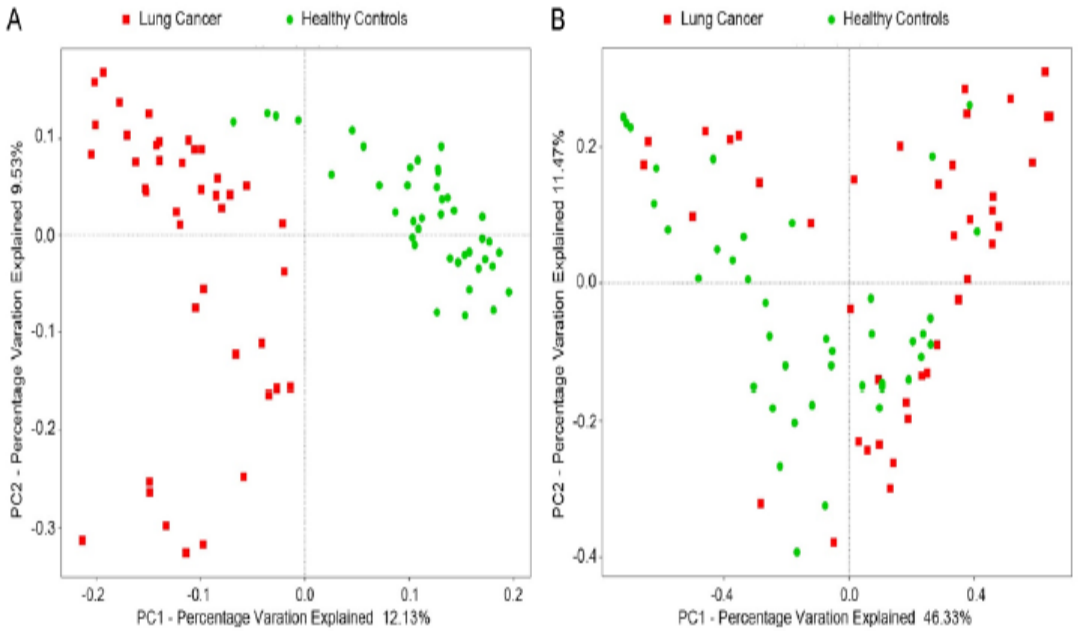


Köpet és bronchoalveolaris lavage vizsgálatok alapján új tüdőrák szűrési metódus lehetősége

Alterations of fecal bacterial communities in patients with lung cancer

Wei-Quan Zhang[1,2], Shu-Kang Zhao[1,2], Jun-Wen Luo[1,2], Xiao-Peng Dong[1], Ying-Tao Hao[1], Hui Li[3], Lei Shan[1], Yong Zhou[4], Hu-Bo Shi[5], Zai-Yun Zhang[4], Chuan-Liang Peng[1], Xiao-Gang Zhao[1]

Am J Transl Res 2018;10(10):3171-3185
www.ajtr.org /ISSN:1943-8141/AJTR0077798



A széklet mikrobiom összetétele jellemző lehet a tüdőrákos betegségre

Alterations of fecal bacterial communities in patients with lung cancer

Wei-Quan Zhang[1,2], Shu-Kang Zhao[1,2], Jun-Wen Luo[1,2], Xiao-Peng Dong[1], Ying-Tao Hao[1], Hui Li[3], Lei Shan[1], Yong Zhou[4], Hu-Bo Shi[5], Zai-Yun Zhang[4], Chuan-Liang Peng[1], Xiao-Gang Zhao[1]

Am J Transl Res 2018;10(10):3171-3185
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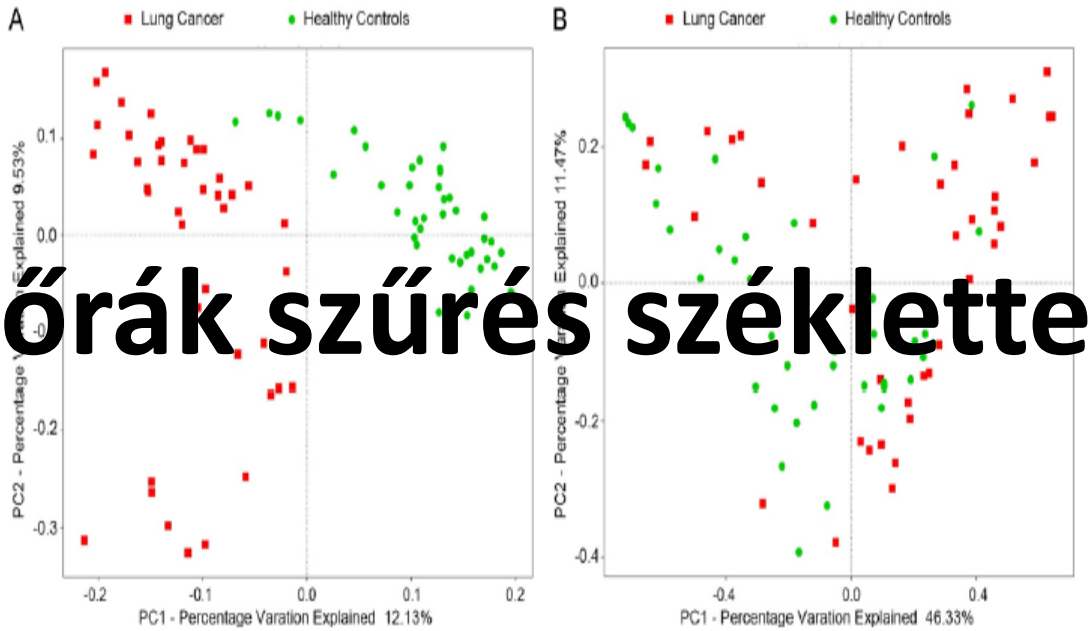
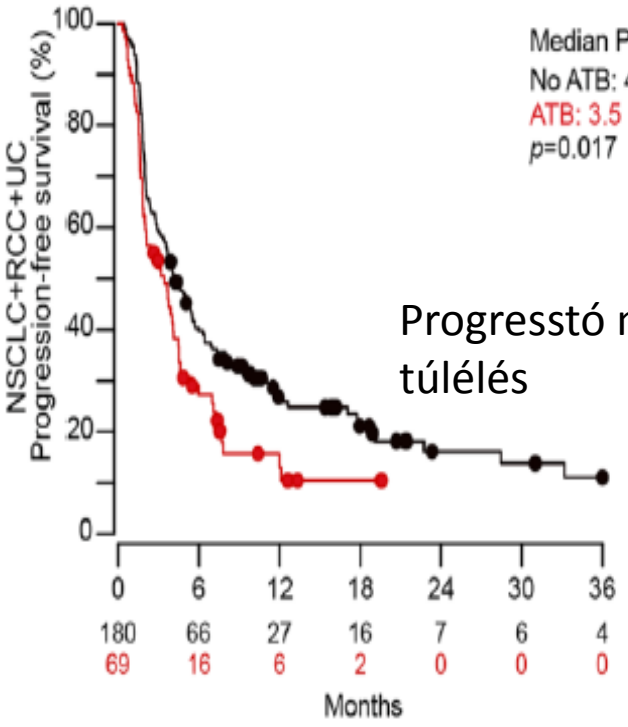


Tüdőrák szűrés széklettel ??

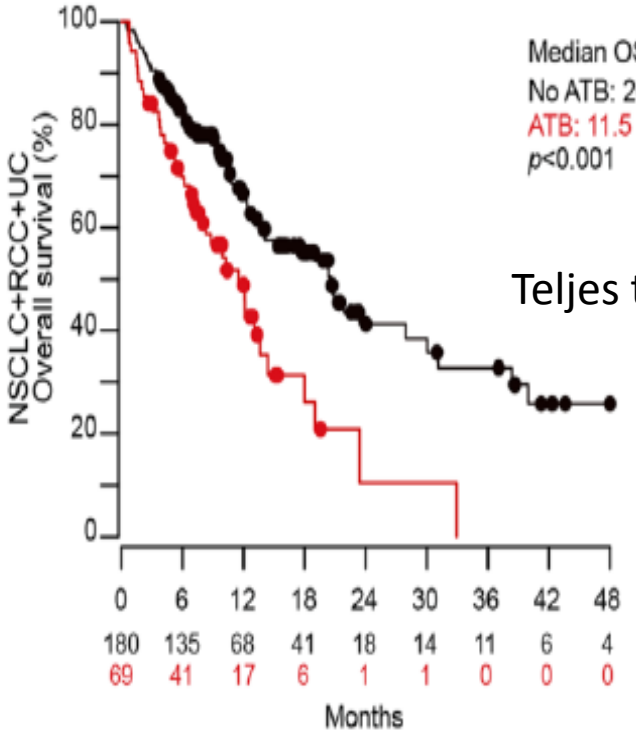
A széklet mikrobiom összetétele jellemző lehet a tüdőrákos Betegségre

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5]



Progresstó mentes túlélés

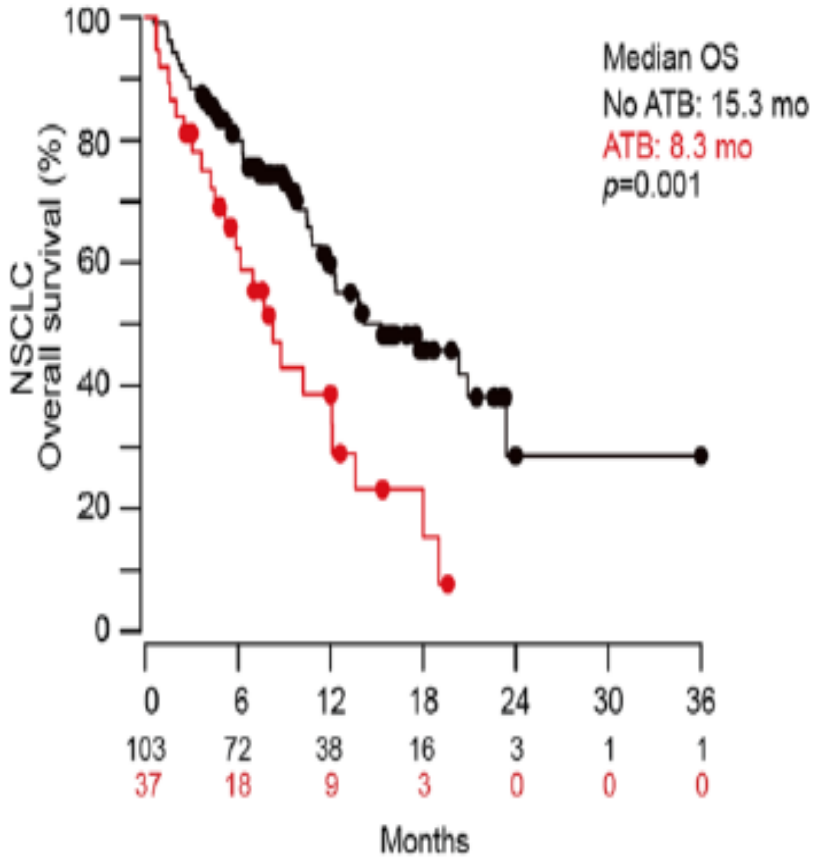


Teljes túlélés

Tüdőrákos, vesedaganatos és urotheliális rákos betegek

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

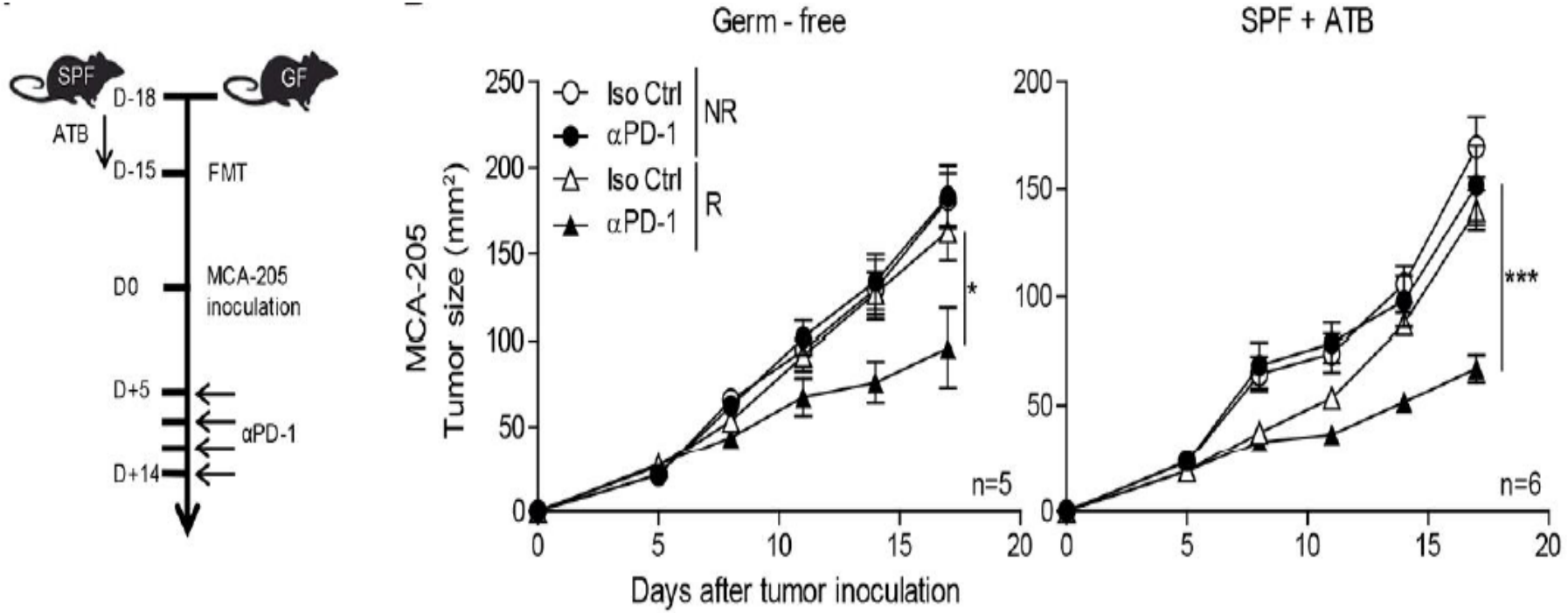
Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5]



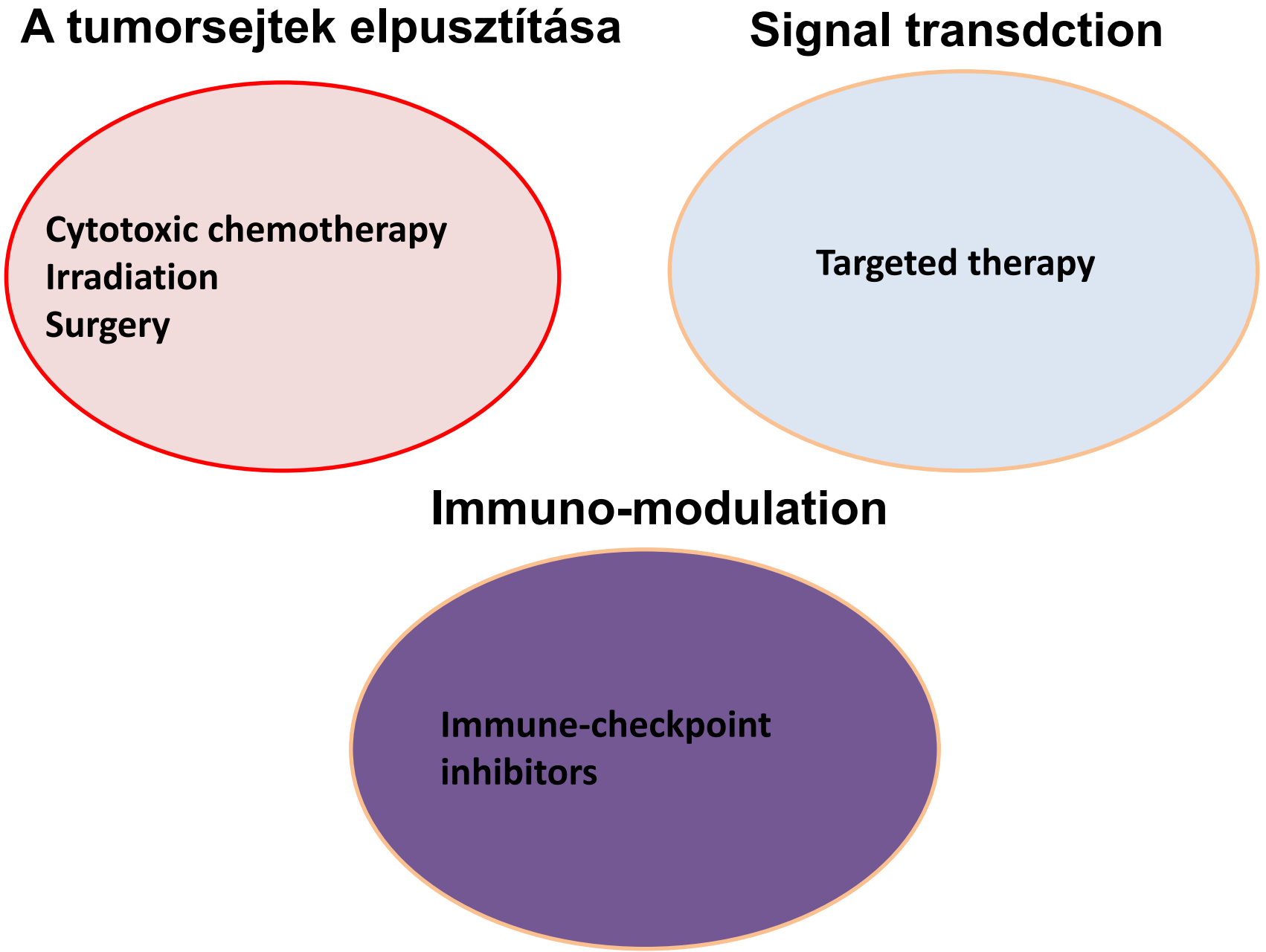
Az antibiotikus kezelés alkalmazása negatív irányba befolyásolta az Immunellenőrző pont gátló kezelések hatékonyságát

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5]



Széklet átültetés daganatos betegekből akik reagáltak és akik nem az immunkezelésre, illetőleg antibiotikus kezelés + immunkezelés hatékonysága


A tumorsejtek elpusztítása
Cytotoxic chemotherapy
Irradiation
Surgery
Signal transdction
Targeted therapy
Immuno-modulation
Immune-checkpoint
inhibitors

Együttműködés:

Pulmonológus
Klinikai onkológus
Sebész
Patológus
Képalkotó diagnoszta
Immunológus
Endokrinológus