Cílená léčba v onkologii

Vladimír Rak

Prerekvizity ...

- Organizmy z buněk
- Chování určené proteiny
- Proteiny určené geny (DNA)

- Nádory z buněk
- Změněné chování oproti normálním somatickým buňkám
- Změny v DNA (mutace) → nádory

Specifické!

Prerekvizity ...

Nádorové buňky jsou trochu jiné než ostatní somatické buňky protože mají specifické změny v DNA

„Cancers don't invent new things, they co-opt processes, functions that are used in development in normal homeostasis, but they subvert them for their own purposes"

- Douglas Hanahan

Myšlenka dne

- Možná kdybychom ovlivnili specificky ty funkce, kterými se nádorové buňky liší od normálních buněk, tak vyléčíme nádor a nepoškodíme člověka

Proč to dělat?

Proč vůbec potřeba?

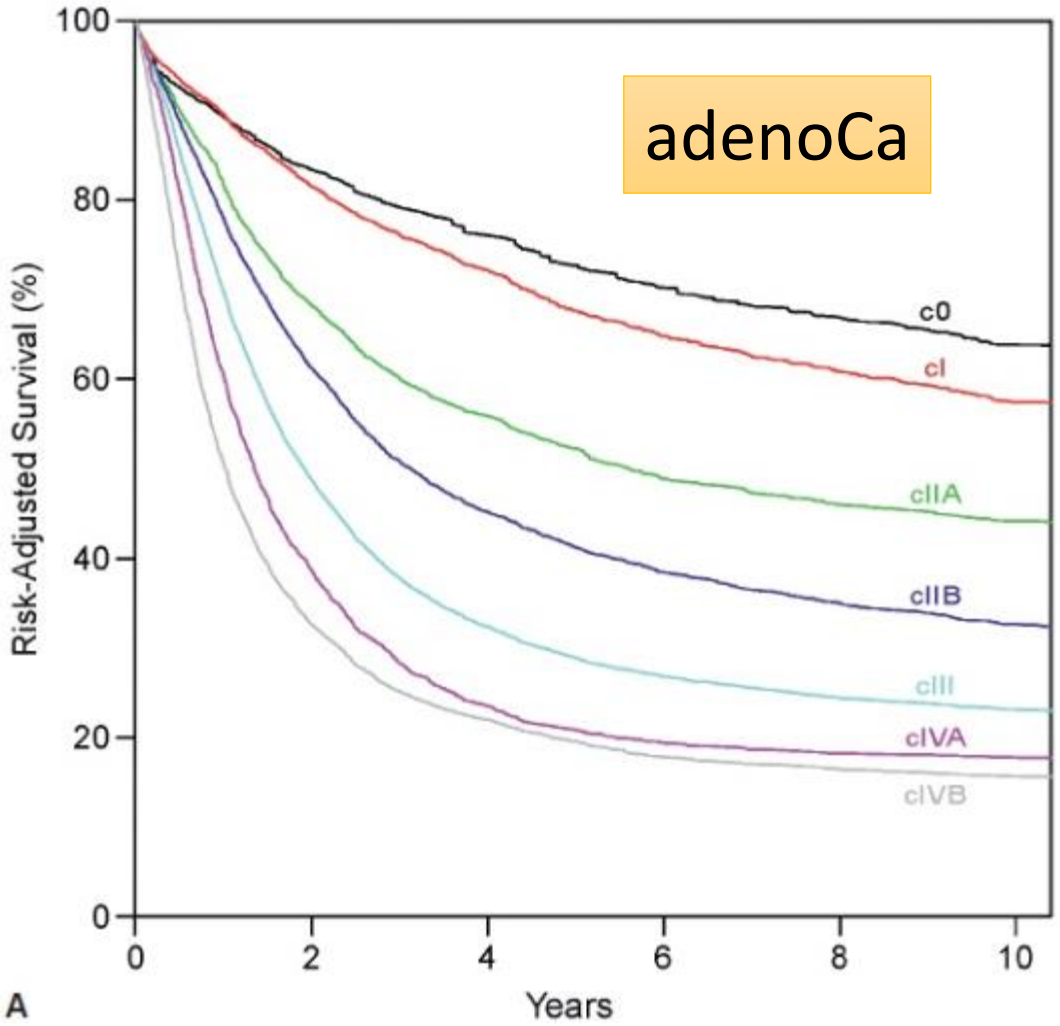
- Standardní léčba:
  - Nevyléčí 100% lidí
  - Toxická

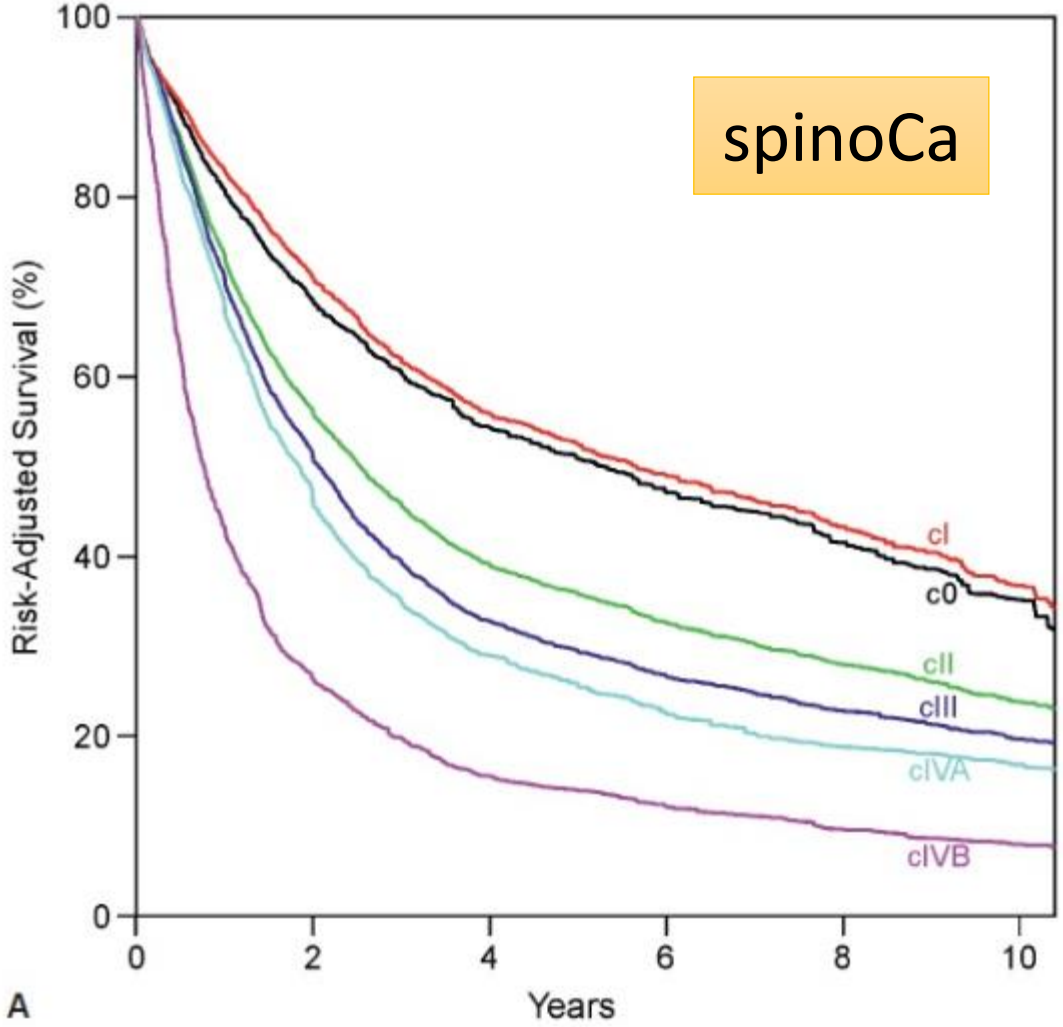
Proč vůbec potřeba?

- Standardní léčba:
  - **Nevyléčí 100% lidí**
  - Toxická

Proč vůbec potřeba?

- Nevyléčí 100% lidí – **jícen**



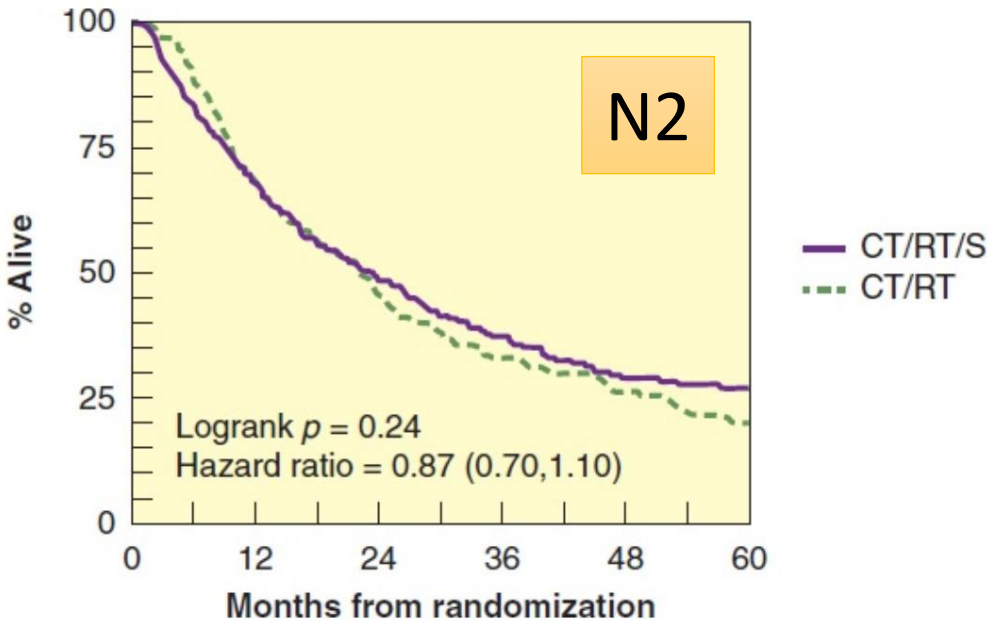


Proč vůbec potřeba?

- Nevyléčí 100% lidí – **plíce**

Stádium		Median OS
IV	CHT	9-10 měs.
	Cíl. léčba	≈ 25 měs.*

Stádium	5-leté přežití
IA1	92%
IA2	83%
IA3	77%
IB	68%
IIA	60%
IIB	53%



T/M	Label	N0	N1	N2	N3
T1	T1a ≤1	IA1	IIB	IIIA	IIIB
	T1b >1-2	IA2	IIB	IIIA	IIIB
	T1b >2-3	IA3	IIB	IIIA	IIIB
T2	T2a Cent, Visc Pl	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T2 Inv	IIB	IIIA	IIIB	IIIC
	T3 Satell	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC
M1	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1a Pl Dissem	IVA	IVA	IVA	IVA
	M1b Single	IVA	IVA	IVA	IVA
	M1c Multi	IVB	IVB	IVB	IVB

Figure 48.4 Stage classification: stage groups of lung cancer in the eighth edition of the TNM classification of malignant tumors. (Reproduced with permission from Detterbeck FC, Boffa DJ, Kim AW, et al. The eighth edition lung cancer stage classification. *Chest* 2017;151[1]:193–203.)

Proč vůbec potřeba?

- Nevyléčí 100% lidí – **krk - tonzila**

TABLE 45.13

Tonsillar Region: 5-Year Outcomes After Definitive Radiotherapy at the University of Florida (531 Patients)

Stage	No. of Patients	Local–Regional Control	Distant Metastasis-Free Survival	Cause-Specific Survival	Survival
I	19	75%	100%	94%	68%
II	71	80%	97%	88%	66%
III	90	86%	95%	87%	68%
IVA	264	81%	87%	75%	61%
IVB	87	69%	64%	52%	39%

From Kennedy WR, Herman MP, Deraniyagala RL, et al. Radiotherapy alone or combined with chemotherapy as definitive treatment for squamous cell carcinoma of the tonsil. *Eur Arch Otorhinolaryngol* 2016;273(8):2117–2125.

The **length of time** from either the date of diagnosis or the start of treatment for a disease, such as cancer, **to the date of death from the disease**. Patients who die from causes unrelated to the disease are not counted in this measurement. In a clinical trial, measuring the cause-specific survival is one way to see how well a new treatment works. Also called CSS.

Proč vůbec potřeba?

- Nevyléčí 100% lidí – **ledvina**

T: Primary Tumor		**Five-Year Survival (%)**
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1a	Tumor ≤4 cm and confined to the kidney	90–100
T1b	Tumor >4 cm and ≤7 cm and confined to the kidney	80–90
T2a	Tumor >7 cm and ≤10 cm and confined to the kidney	65–80
T2b	Tumor >10 cm and confined to the kidney	50–70
T3a	Tumor extends into the renal vein or its segmental veins, or tumor invades perirenal fat, renal sinus fat, and/or the pelvicalyceal system	40–65
T3b	Tumor grossly extends into the vena cava below the diaphragm	30–50
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava	20–40
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)	0–20
N: Regional Lymph Nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph nodes metastasis	
N1	Metastasis in regional lymph node(s)	0–20
M: Distant Metastases		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis present	0–10

Proč vůbec potřeba?

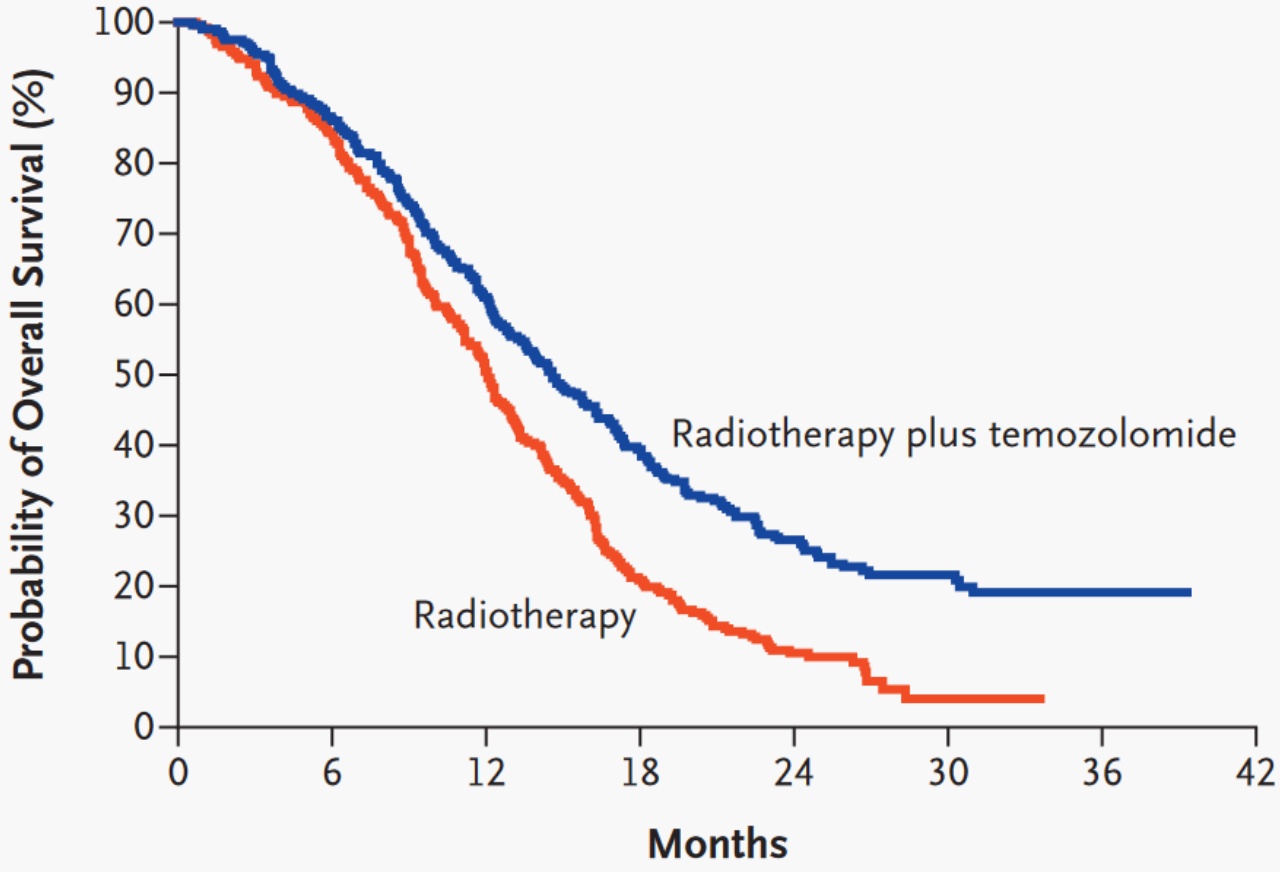
- Nevyléčí 100% lidí – **CNS (GBM)**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

Proč vůbec potřeba?

- Standardní léčba:
  - Nevyléčí 100% lidí
  - **Toxická**
    - Chirurgie
    - Radioterapie
    - Chemoterapie

Proč vůbec potřeba?

- Toxická
  - **Chirurgie**
  - Radioterapie
  - Chemoterapie

+ CNS, pankreaty, HNSCC, ...

TABLE 52.5

Results of Transthoracic Esophagectomy for Esophageal Cancer

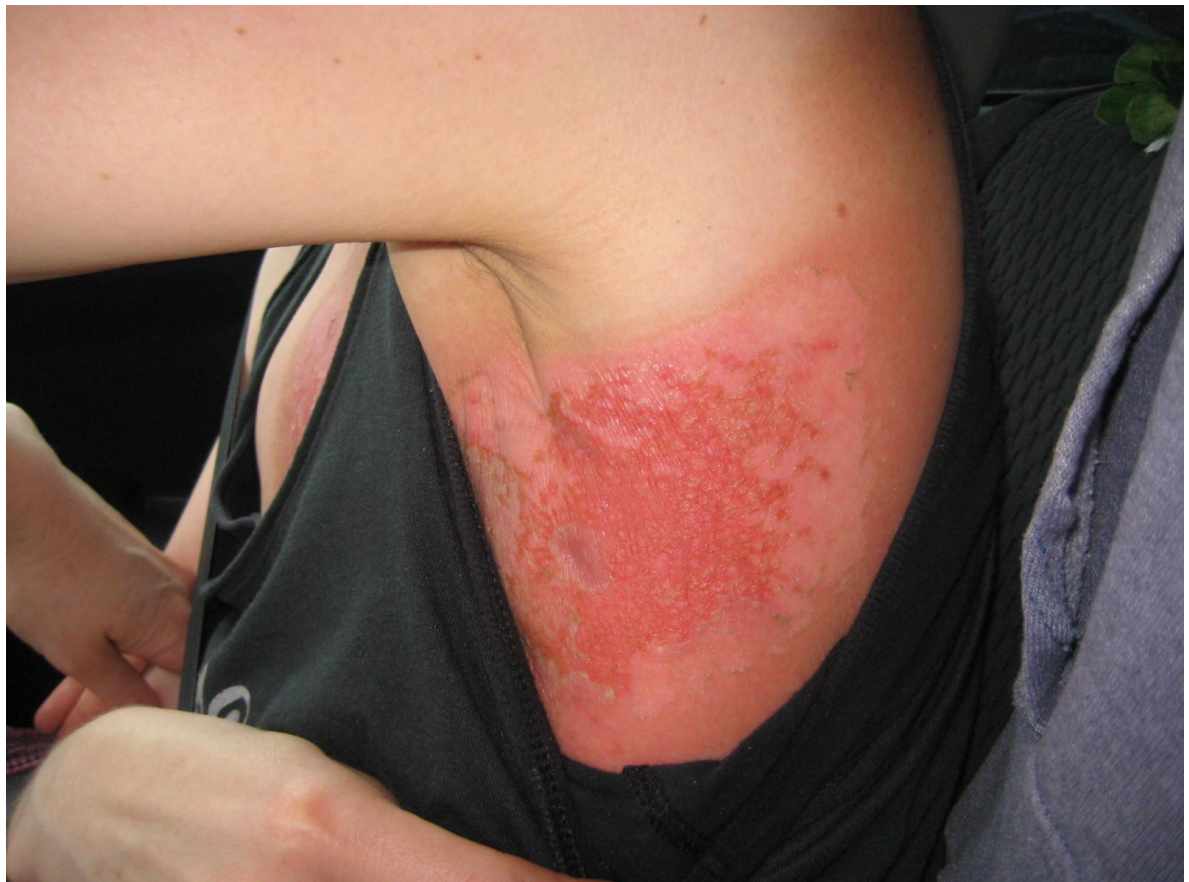
Study (Ref.)	Year	No. of Patients (N)	Histologic Type	Perioperative Mortality (%)	Five-Year Survival (%)
Wang et al.[213]	1992	368	S	6.5	7.6
Lieberman et al.[214]	1995	258	A/S	5	27
Adam et al.[212]	1996	597	A/S	6.9	16.3
Sharpe and Moghissi[210]	1996	562	A/S	9	18
Bosset et al.[215]	1997	139	S	3.6	26
Ellis[211]	1999	455	A/S	3.3	24.7

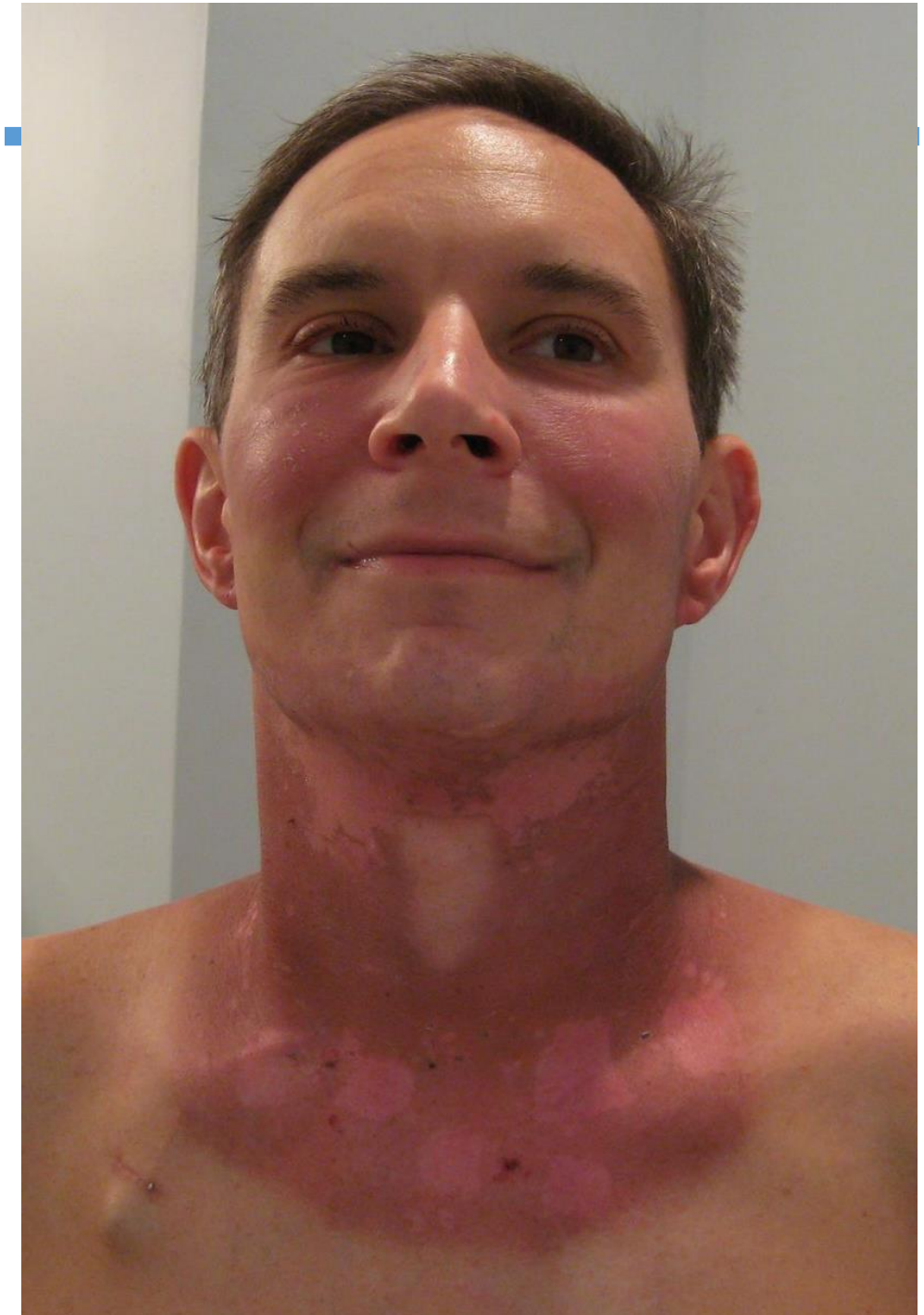
A, adenocarcinoma; S, squamous cell carcinoma.

Proč vůbec potřeba?

- Toxická
  - Chirurgie
  - **Radioterapie**
  - Chemoterapie

Akutní / pozdní





Proč vůbec potřeba?

- Toxická
  - Chirurgie
  - Radioterapie
  - **Chemoterapie**

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

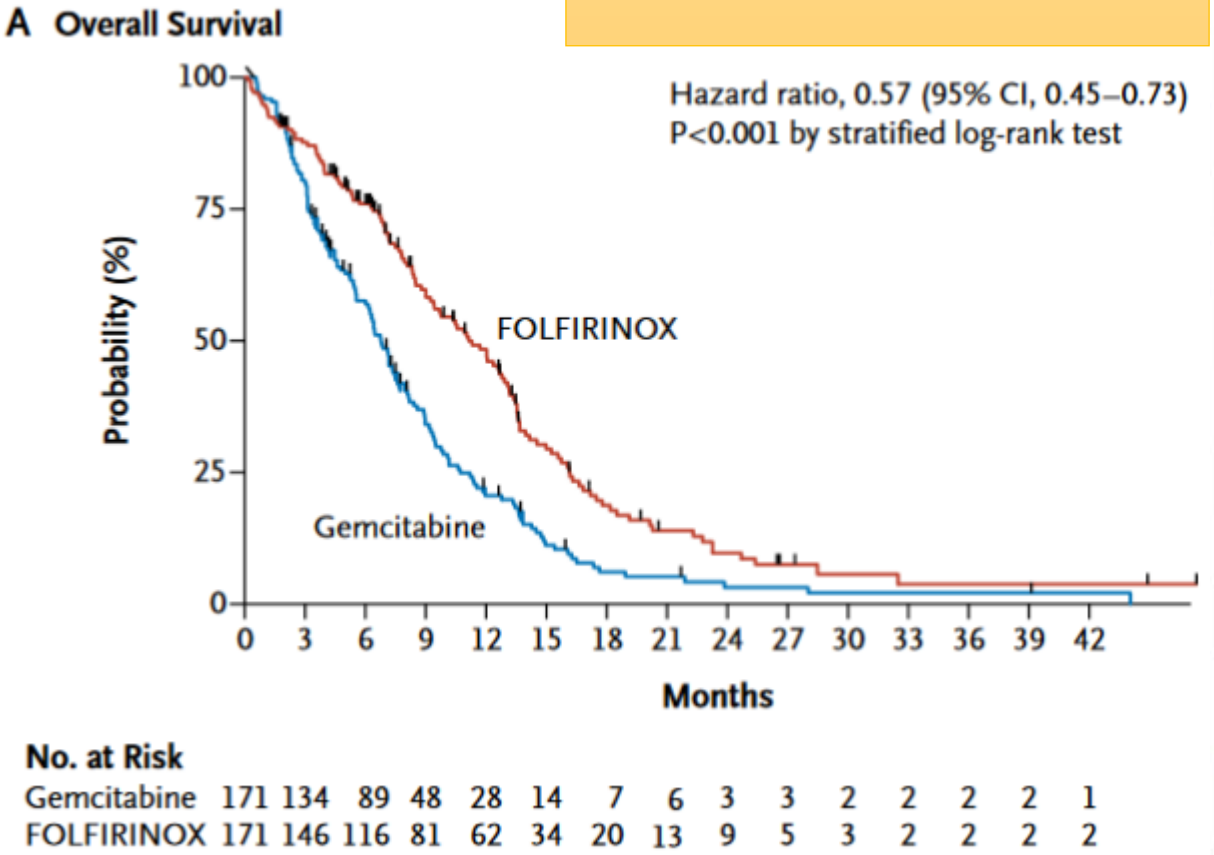


Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

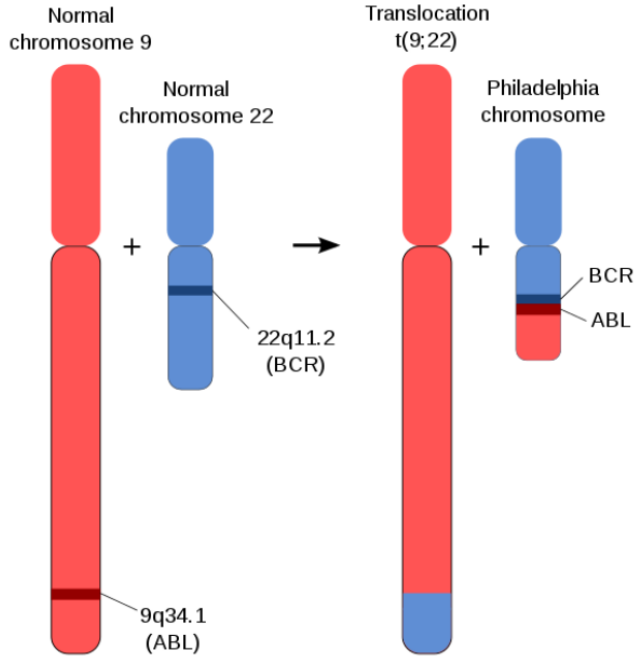
„klasická“ léčba

- Toxická
- Nedostatečně účinná

Čas ji zahodit a začít používat něco „modernějšího“?

První krůčky

- Chronická myeloidní leukemie
  - U těcho nádorů je častá specifická translokace mezi 9. a 22. chromozomem
    - Vzniká fůzní gen bcr-abl
  - Je to příčina tohoto onemocnění
    - cDNA → retrovirus → myš → CML
  - ABL – protoonkogen
    - Tyrosin kináza, buněčná diferenciace, dělení, adheze, odpověď na stres
  - Pokud spojený s BCR (breakpoint cluster region)
    - Zvýšená aktivita fůzního genu



První krůčky

- Ovlivňuje
  - RAS
  - PI3k – Akt/PKB
  - Jak-STAT
  - Jun, Myc, ...
  - ...

Skoro vše

- Pokud ale porušíme tyrosin kinázovou funkci → ztráta maligního chování

- První cílený lék – imatinib mesylate (gleevec)
  - Vážena se na a inaktivuje Bcr - Abl
  - (relativně specifický – inaktivuje 4 TK)

První krůčky

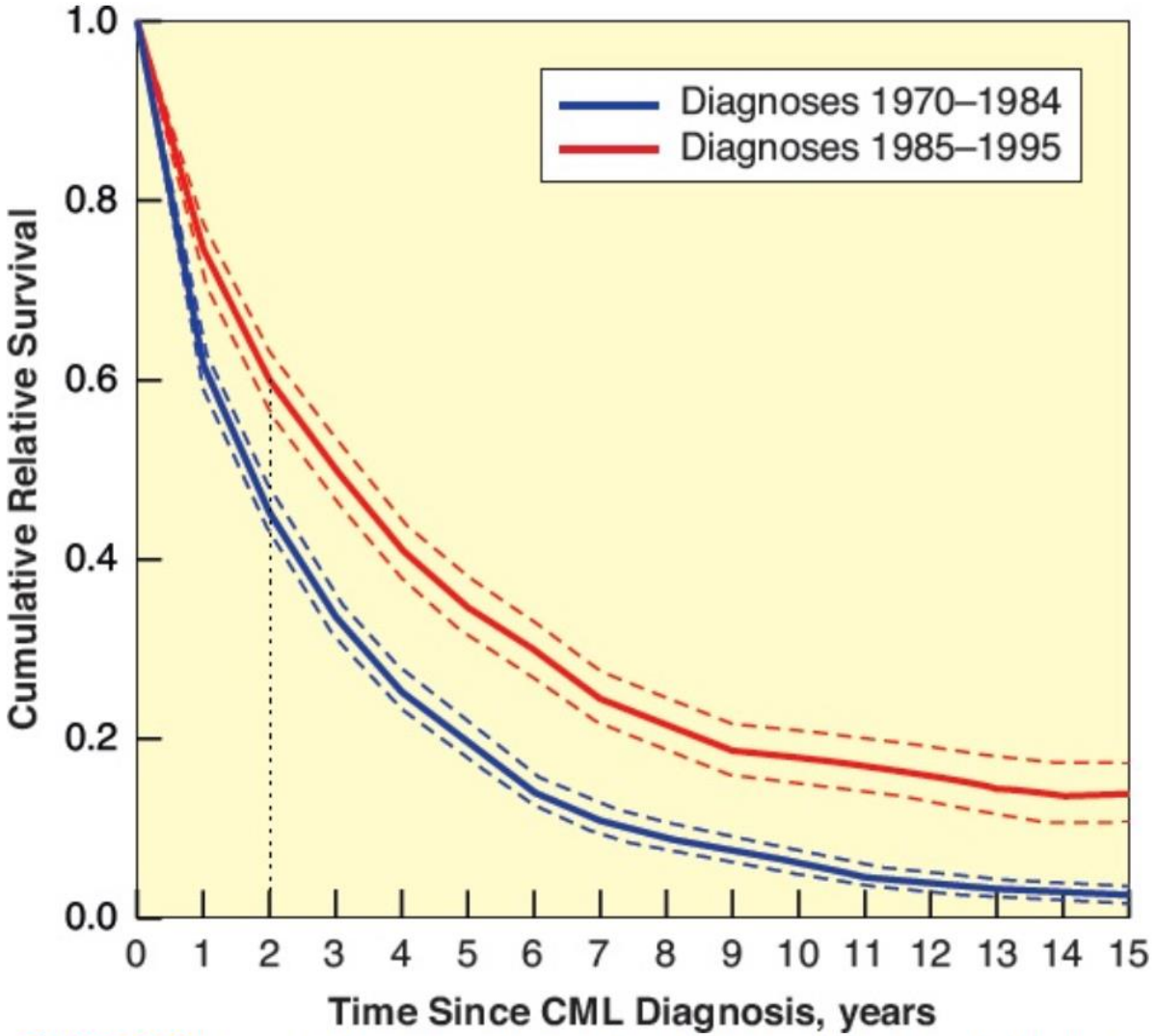


Figure 104.2 Estimated relative survival curves of newly diagnosed chronic myeloid leukemia patients being diagnosed between 1970 and 1984 versus 1985 and 1995. CML, chronic myeloid leukemia. (From Rebora P, Czene K, Antolini L, et al. Are chronic myeloid leukemia patients more at risk for second malignancies? A population-based study. *Am J Epidemiol* 2010;172[9]:1028–1033.)

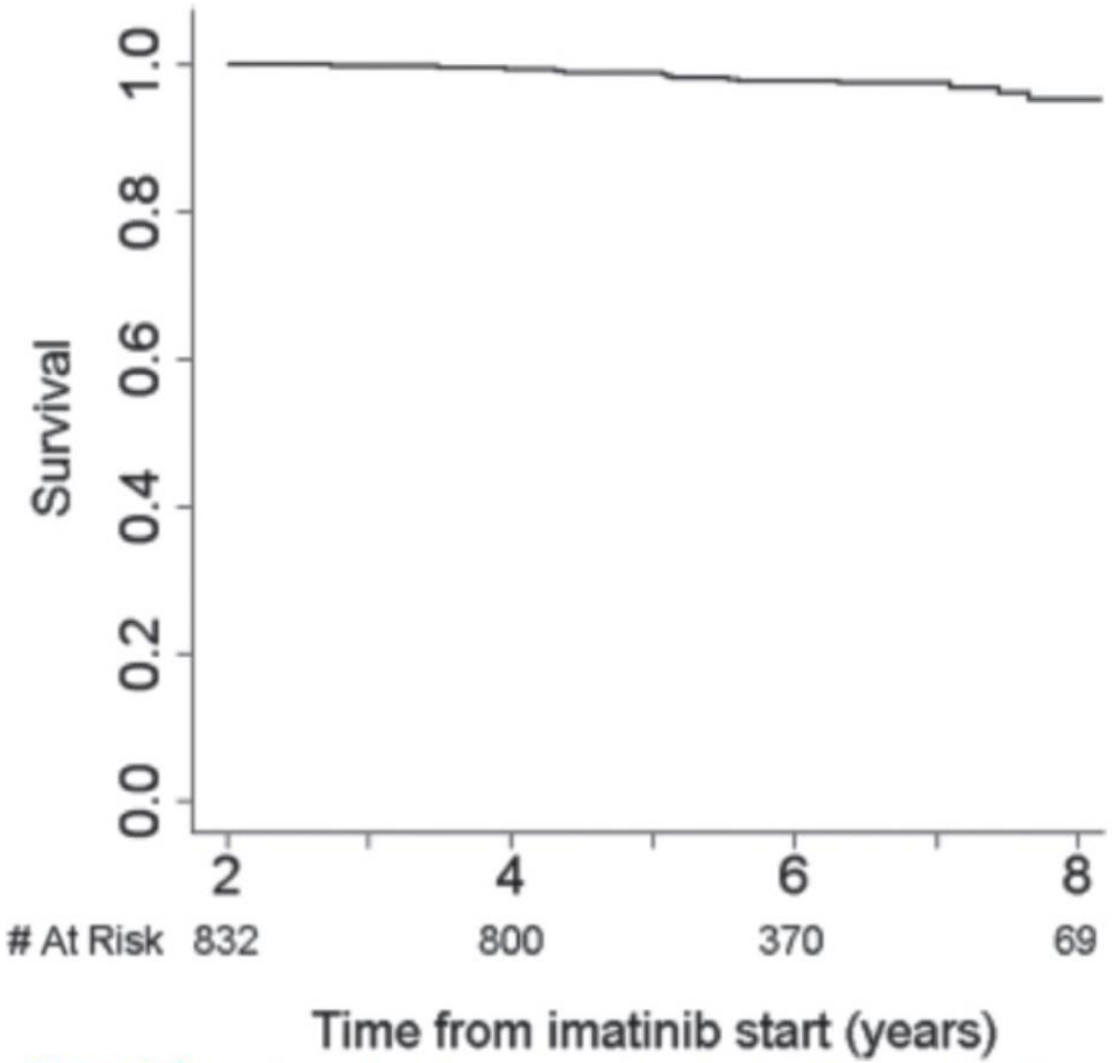


Figure 104.3 Overall survival for 832 patients entered worldwide in the Imatinib Long Term Effects study; mortality at 8 years was 5%, of which only 1% caused by chronic myeloid leukemia. (From Gambacorti-Passerini C, Antolini L, Mahon FX, et al. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. *J Natl Cancer Inst* 2011;103[7]:553–561.)

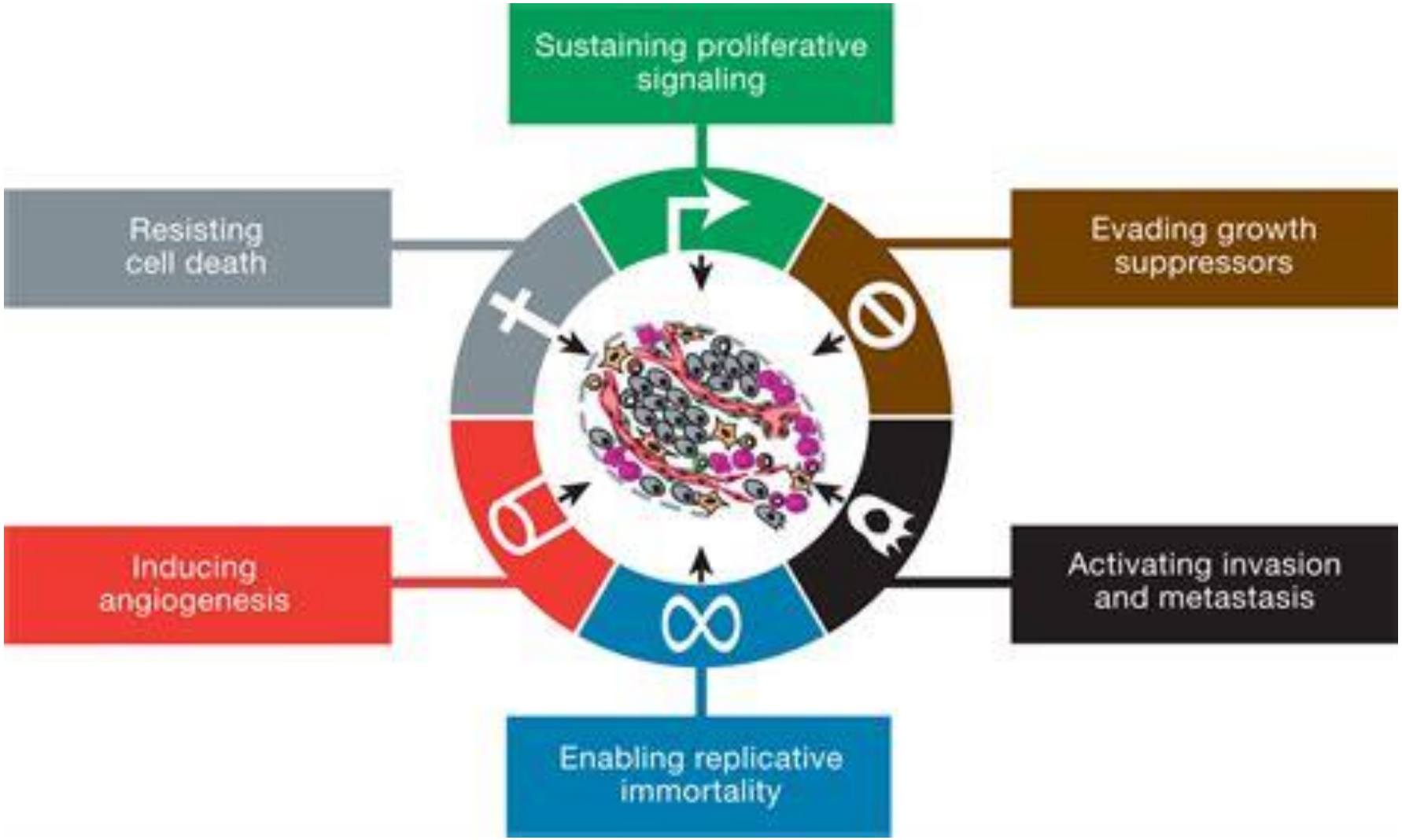
První krůčky

- relativně specifický – inaktivuje 4 TK

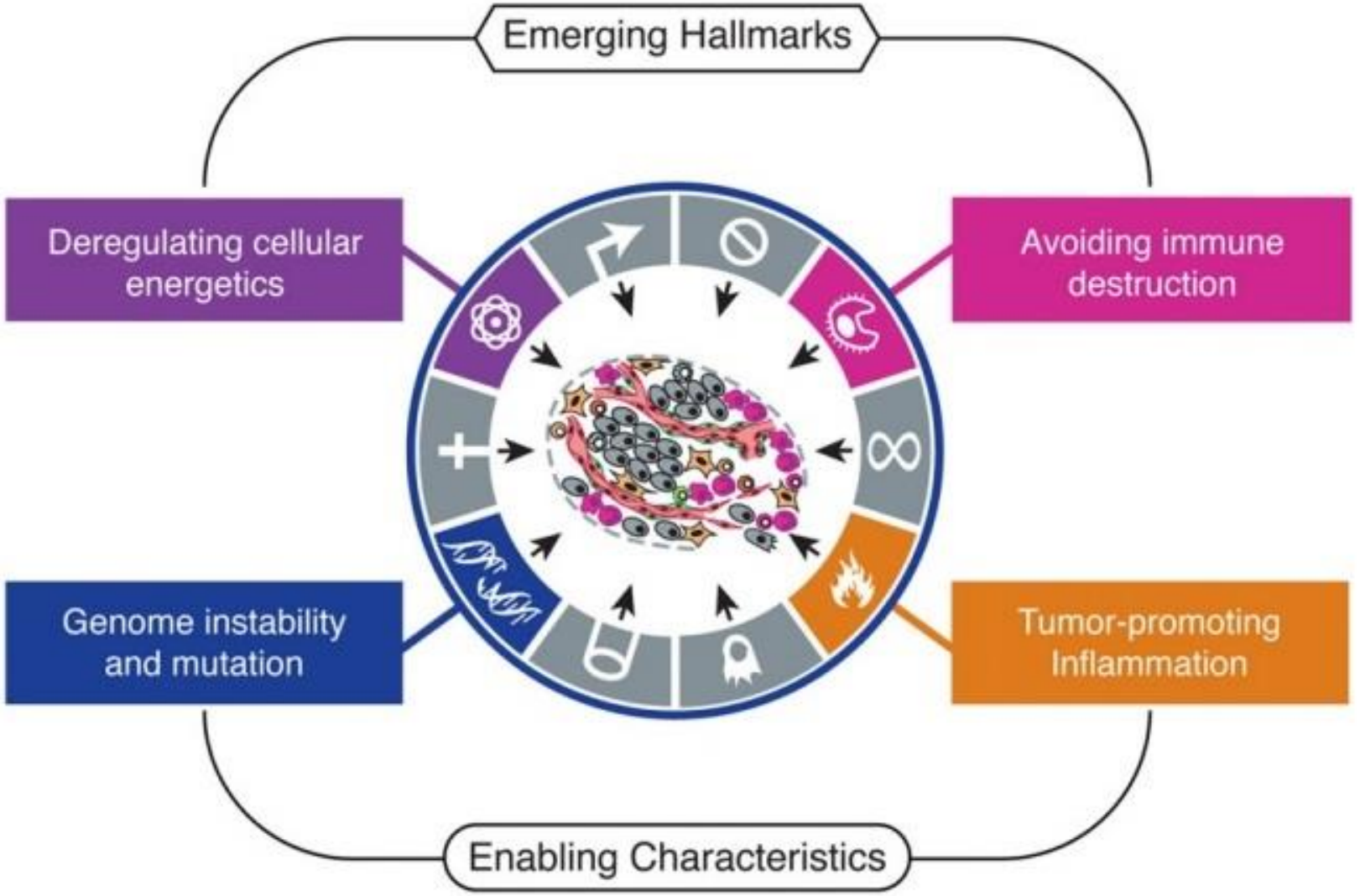
Další je Kit

- Kit se vyskytuje u přibližně % GIST
- Solidní nádor – horší výsledky (větší genetická heterogenita?)

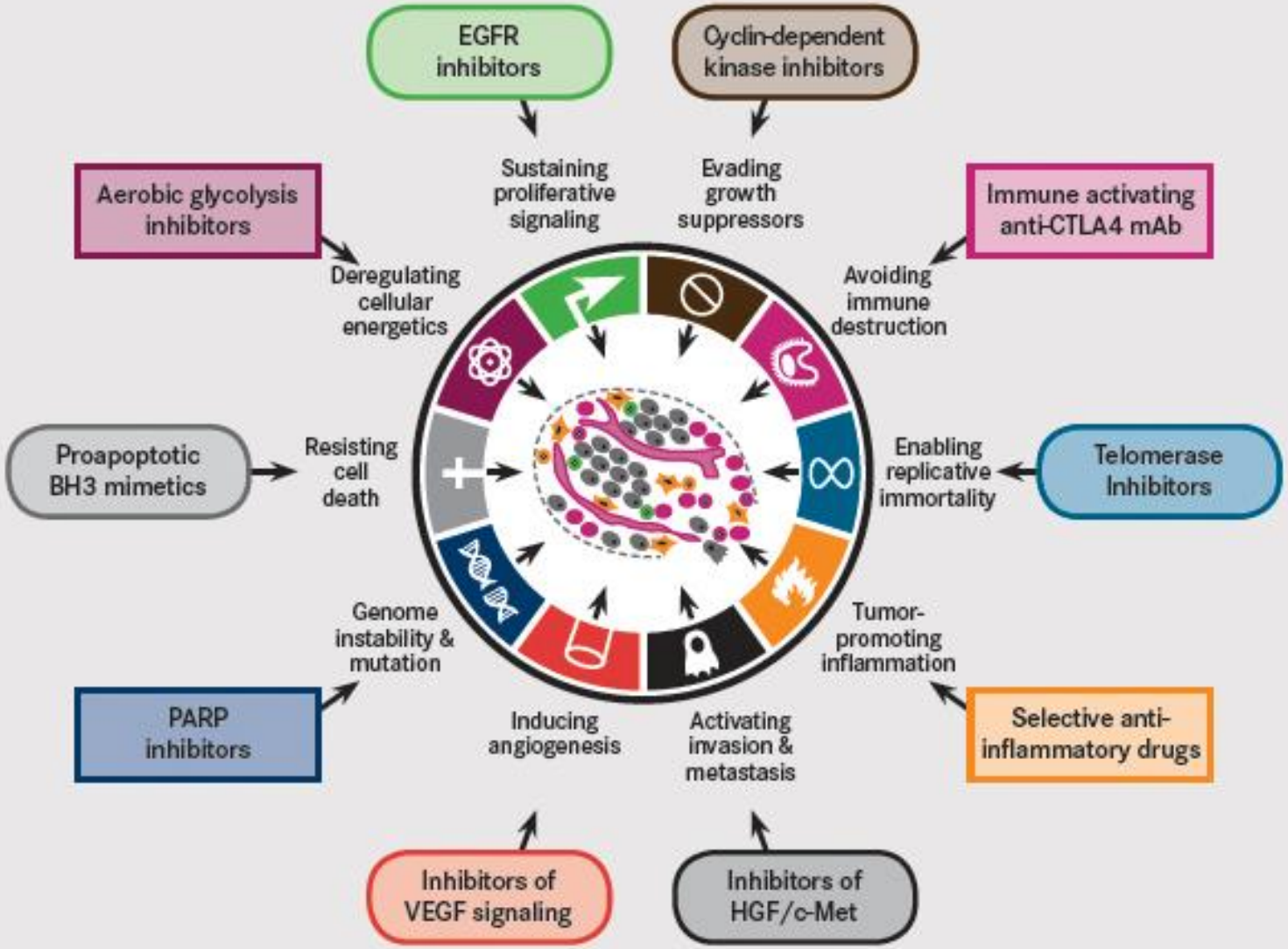
Hallmarks


Sustaining proliferative signaling
Evading growth suppressors
Activating invasion and metastasis
Enabling replicative immortality
Inducing angiogenesis
Resisting cell death

Hallmarks


Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation
Enabling Characteristics

Hallmarks



This figure illustrates some of the many approaches employed in developing therapeutics targeted to the known and emerging hallmarks of cancer.

EGFR indicates epidermal growth factor receptor; CTLA4, cytotoxic T lymphocyte-associated antigen 4; mAb, monoclonal antibody; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; PARP, poly-(ADP ribose) polymerase.

Source: Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144:646-674. Reprinted with permission.

Typy léků

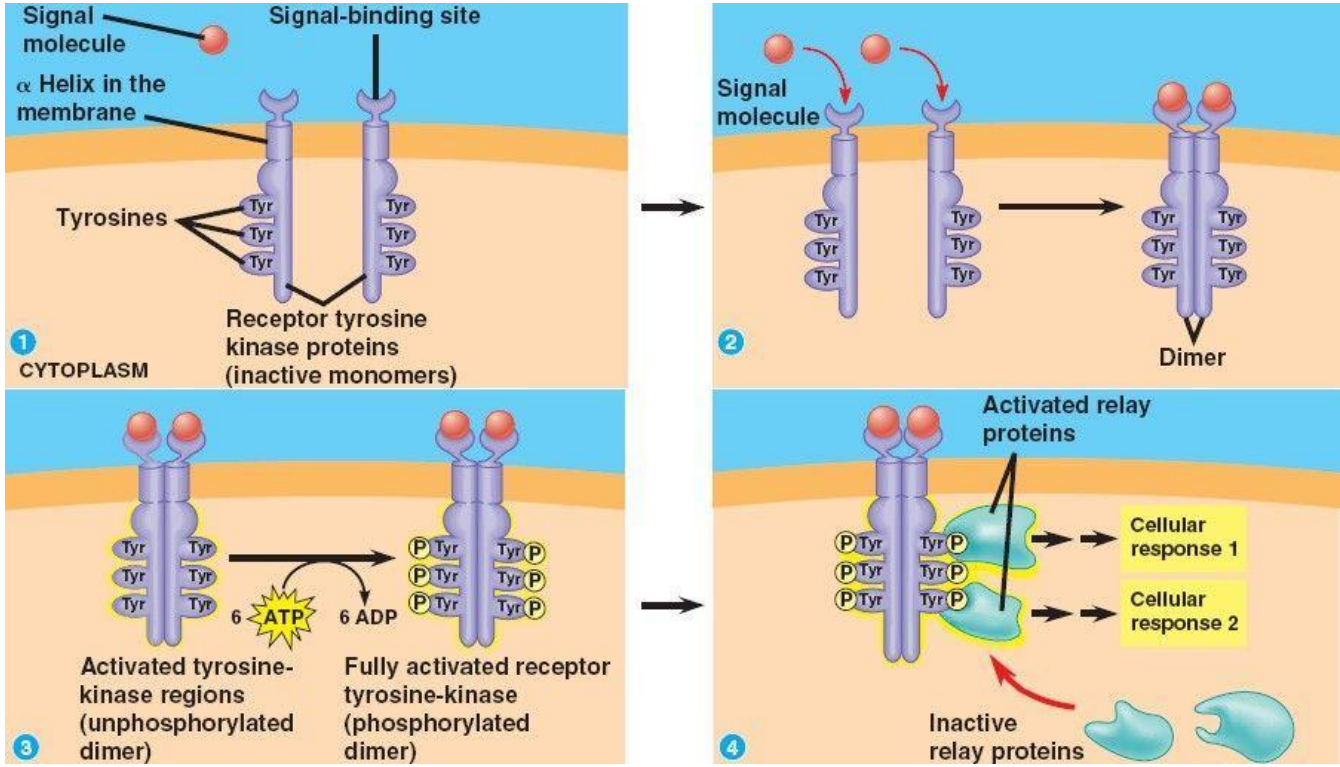
	Small molecule	Antibody
Target	tyrosine kinase domain	receptor ectodomain
Specificity	+++	++++
Binding	most are rapidly reversible	receptor internalized, only slowly regenerated
Dosing	oral daily	intravenous, ≤ weekly
Distribution in tissues	more complete	less complete
Toxicity	rash, diarrhea, pulmonary	rash, allergy
Antibody-dependent cellular cytotoxicity	no	possibly

Courtesy of N.J. Meropol and from N. Damjanov and N. Meropol, *Oncol. (Huntington)* 18:479–488, 2004.

TKIs

- Pozice TKs:
  - Na povrchu (EGFR,)
  - V cytoplazmě (Raf,)
  - Uvnitř jádra

- Cíle TKs:
  - Serin/threonin
  - Tyrozin

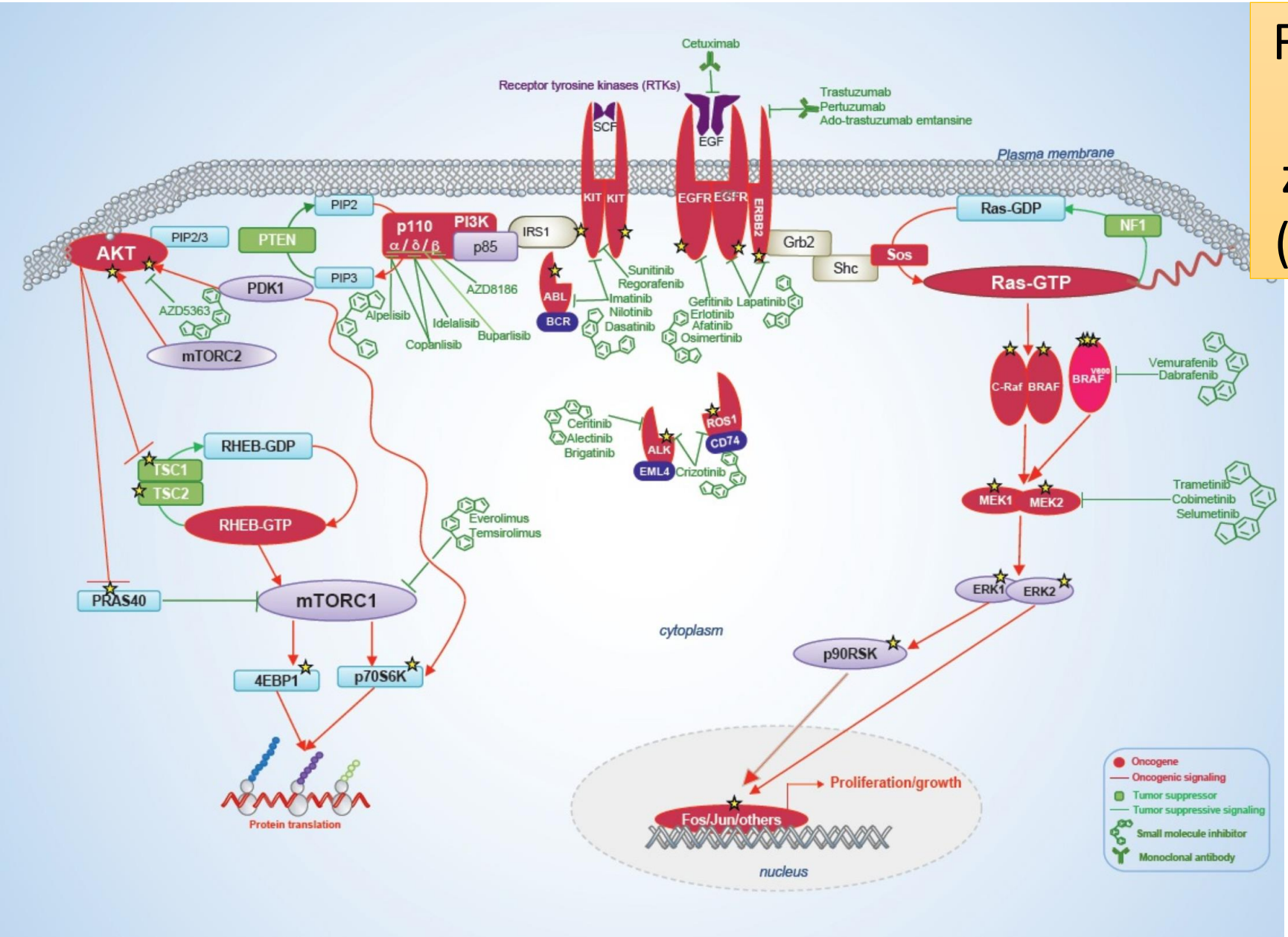


... intrinsic and acquired resistance are major clinical challenges that limit the effectiveness of this drug class:

- secondary **mutations** in the kinase that **prevent or alter drug binding**
- co-mutations or adaptive **changes** involving parallel signaling pathways **that reduce dependence on the target kinase**

TKIs

Funguje pouze u nádorů co mají danou mutaci / jsou závislé na určité signalizaci (crizotinib, vemurafenib ...)



The mitogen-activated protein kinase and phosphatidylinositol 3-kinase (PI3K) signaling pathways. Major signaling nodes are shown as well as select kinase inhibitors and antireceptor antibodies.

TKIs

OncoKB level 1 mutations represent established FDA-recognized biomarkers of response to an FDA-approved drug being used in the FDA-approved cancer indication

Gene	Alteration(s)	Cancer Type(s)	Drug(s)
ABL1	BCR-ABL1 fusion	ALL, CML	Imatinib, nilotinib, dasatinib
ALK	Fusions	NSCLC	Crizotinib, ceritinib, alectinib, brigatinib
BRAF	V600 mutations	Melanoma	Vemurafenib, dabrafenib, trametinib, dabrafenib + trametinib, cobimetinib + vemurafenib
BRCA1	Inactivating mutations	Ovarian cancer	Rucaparib, niraparib
BRCA2	Inactivating mutations	Ovarian cancer	Rucaparib, niraparib
EGFR	Exon 19 deletions, L858R, G719, S768I, Exon 19 insertions, L861Q/R, E709K, L833V, L747P, A763_Y764insFQEA E709_T710delinsD EGFR-KDD	NSCLC	Erlotinib, afatinib, gefitinib
EGFR	T790M	NSCLC	Osimertinib
ERBB2	Amplification	Breast cancer	Trastuzumab, ado-trastuzumab emtansine, pertuzumab, lapatinib
ERBB2	Amplification	Esophagogastric cancer	Trastuzumab
IDH2	Oncogenic mutations	AML	Enasidenib
KIT	Exon 9, 11, 17 mutations, T670I, V654A	GIST	Imatinib, sunitinib, regorafenib
MMR-d	MSI+	Solid tumors	Pembrolizumab
PDGFRA	FIP1L1-PDGFRA	Leukemia	Imatinib
PDGFRA	Fusions	MDS/MPN	Imatinib
PDGFRB	Fusions	MDS/MPN	Imatinib
PDGFRB	Fusions	DFSP	Imatinib
ROS1	Fusions	NSCLC	Crizotinib

+sorafenib, sunitinib

TKIs – ALK (anaplastic lymphoma kinase)

- Orphan receptor (*insuline kinase family*)
- Role při vývoje nervového systému
- Fúze z jinými geny (EML4) → ligand-nezávislá signalizace
- **U přibližně 4-5% NSCLC** (mladší muži nekuřáci adenoCa)
- Nebývá zároveň s EGFR nebo KRAS mu

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

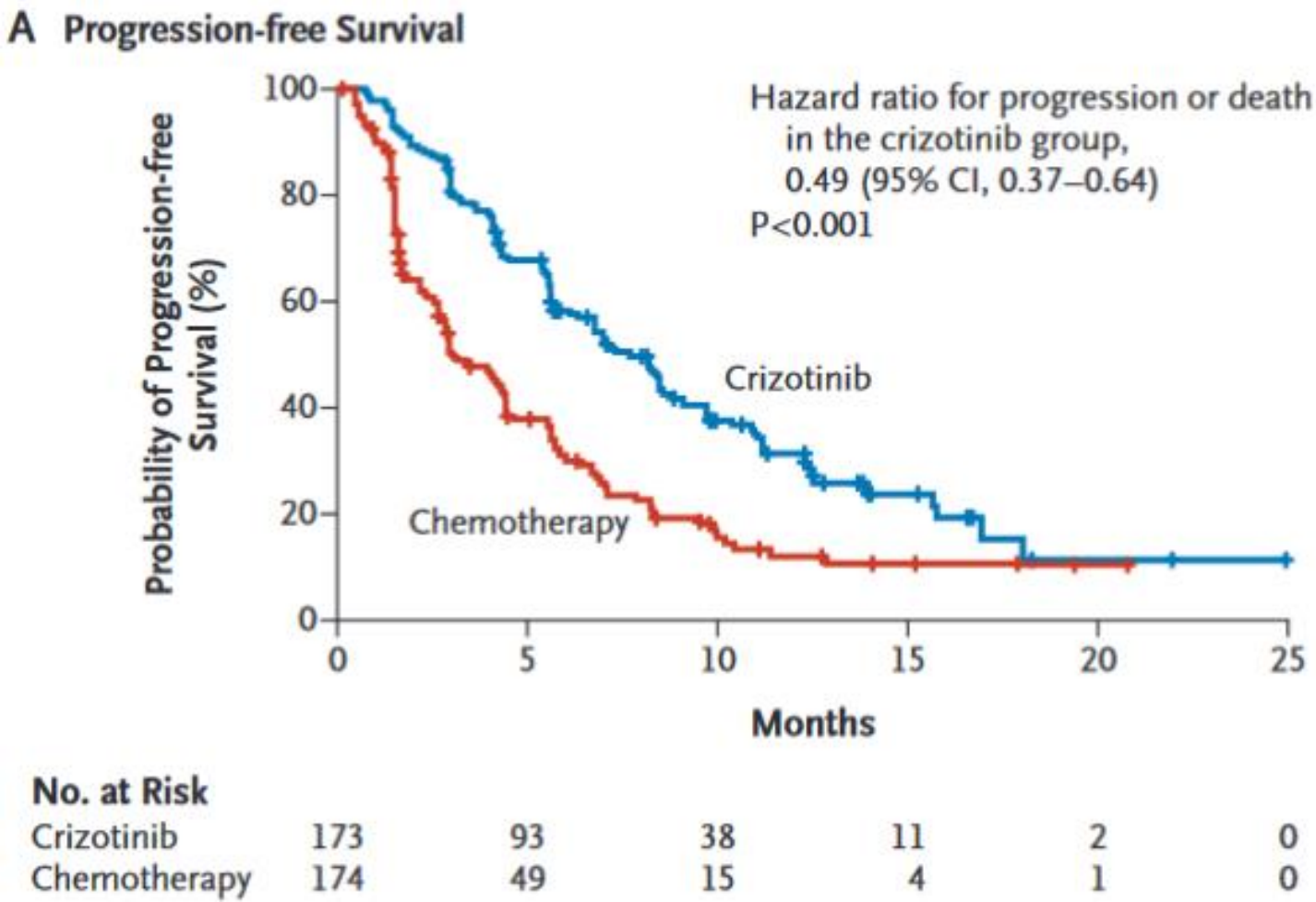
Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D., Tommaso De Pas, M.D., Benjamin Besse, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Fiona Blackhall, M.D., Ph.D., Yi-Long Wu, M.D., Michael Thomas, M.D., Kenneth J. O'Byrne, M.D., Denis Moro-Sibilot, M.D., D. Ross Camidge, M.D., Ph.D., Tony Mok, M.D., Vera Hirsh, M.D., Gregory J. Riely, M.D., Ph.D., Shrividya Iyer, Ph.D., Vanessa Tassell, B.S., Anna Polli, B.S., Keith D. Wilner, Ph.D., and Pasi A. Jänne, M.D., Ph.D.

We conducted a phase 3, open-label trial comparing crizotinib with chemotherapy in 347 patients with locally advanced or metastatic ALK-positive lung cancer...

TKIs – ALK (anaplastic lymphoma kinase)

- The median progression-free survival was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (hazard ratio for progression or death with crizotinib, 0.49; 95% confidence interval [CI], 0.37 to 0.64; P<0.001)



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ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

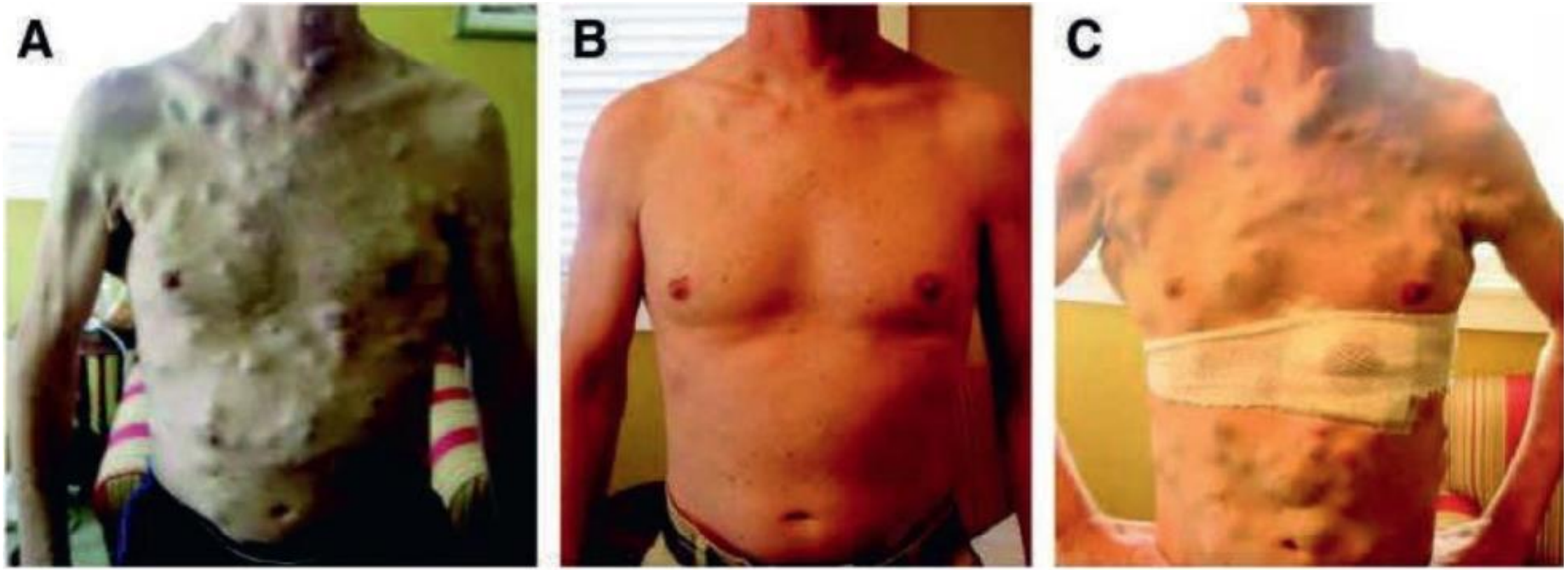
Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

Among 80 patients who had received crizotinib previously, the response rate was 56% (95% CI, 45 to 67). **Responses were observed in patients with various resistance mutations in ALK** and in patients without detectable mutations. Among patients with NSCLC who received at least 400 mg of ceritinib per day, the **median progression-free survival was 7.0 months**

TKIs – BRAF V600E (vemurafenib, dabrafenib)

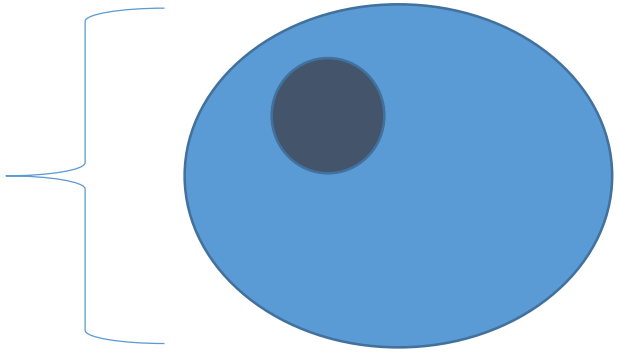
- Mutace přítomná u ≈50 - 60% melanomů
- Nebývá při mutaci Ras (stejný efekt)
- Pokud RAF wt → TKI **aktivují** (místo inhibice) downstream ERK signální dráhu

RAF TKI (vemurafenib, dabrafenib)



A 38-year-old man with BRAF-mutant advanced melanoma with widespread subcutaneous tumor nodules.
A: Prior to initiation with vemurafenib.
B: **After 15 weeks** of therapy with vemurafenib.
C: At progression, **after 23 weeks** of therapy. A post-progression biopsy was sequenced and revealed a BRAF V600E mutation and a concomitant MEK1 C121S activating resistance mutation. (Reproduced from Wagle N, Emery C, Berger MF, et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. *J Clin Oncol* 2011;29[22]:3085–3096.)

- Jak moc je v nádoru buněk?
- 1buňka ≈10 µm



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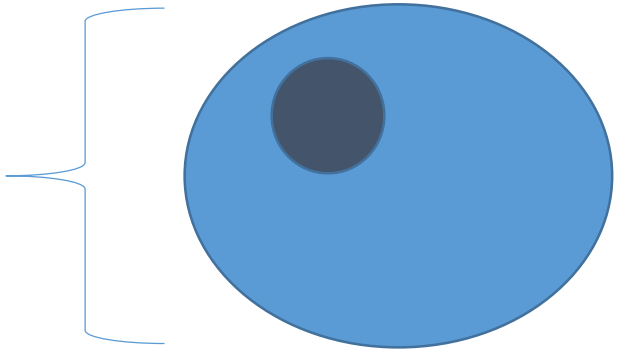
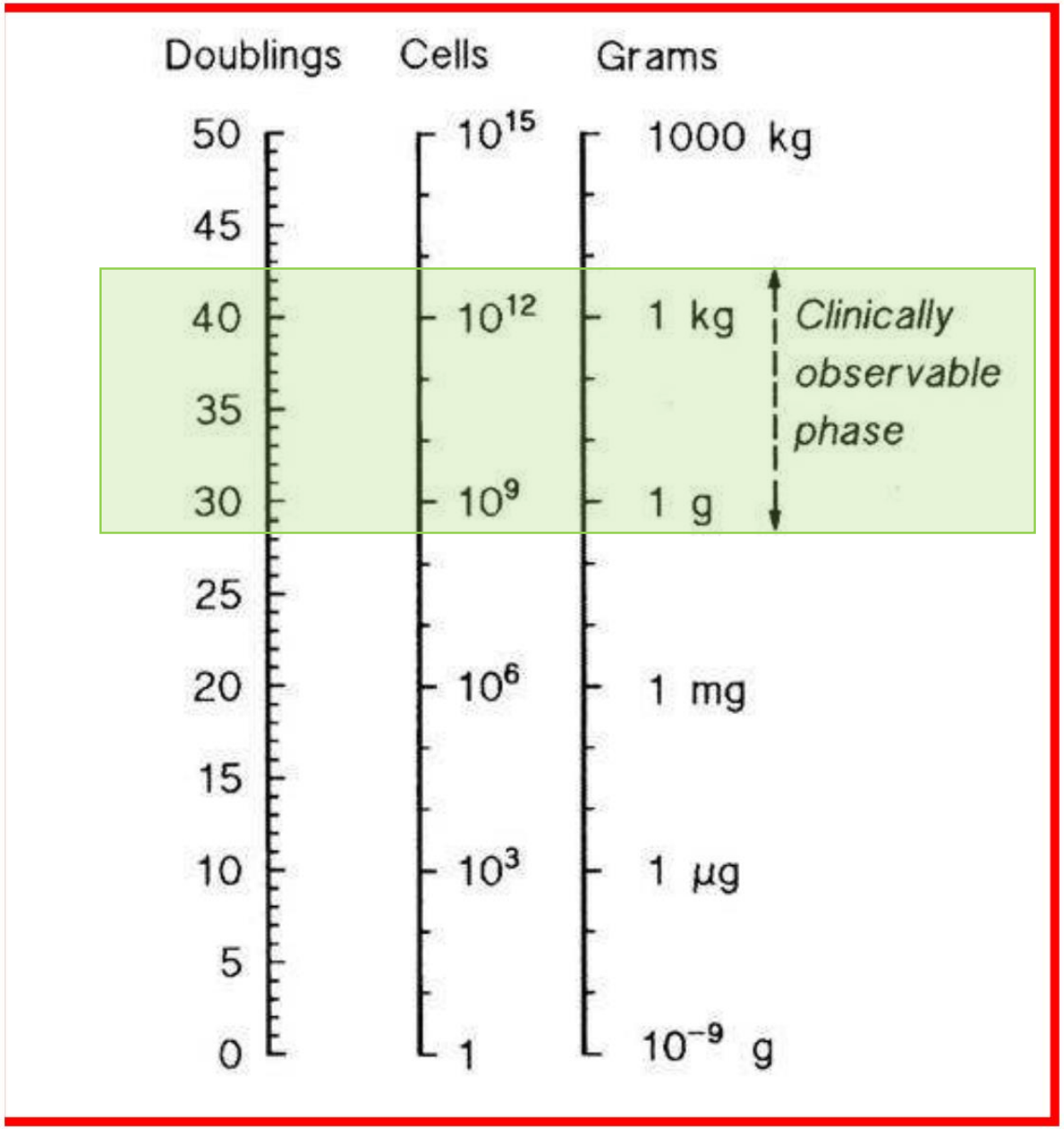


- 1 mm^3 = 100x100x100 buněk = 10^6 buněk
- 1 cm^3 = 10^9 buněk

- Rozlišovací mez zobrazovacích metod je v rámci milimetrů
- To že po léčbě není nikde vidět žádný nádor znamená, že v těle může být něco mezi 0 a asi 10^7 buněk



90% cell death: Partial Remission, no cure

99,9% cell death: Complete remission, no cure

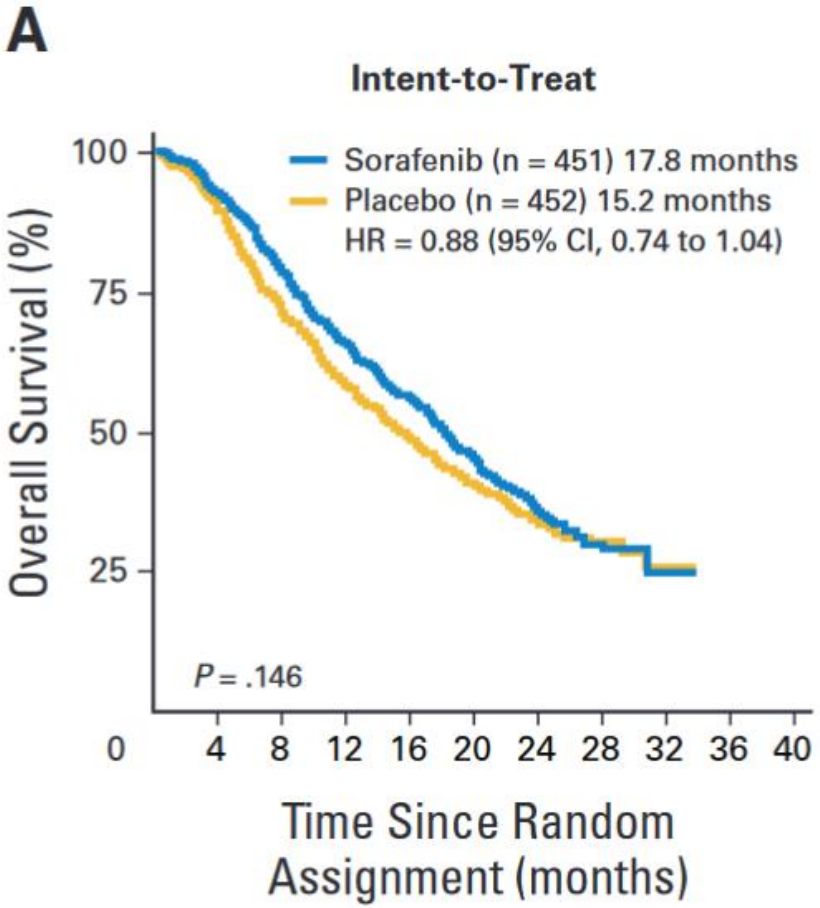
99,9999999% cell death: Complete remission, Local control, Cure if no metastasis

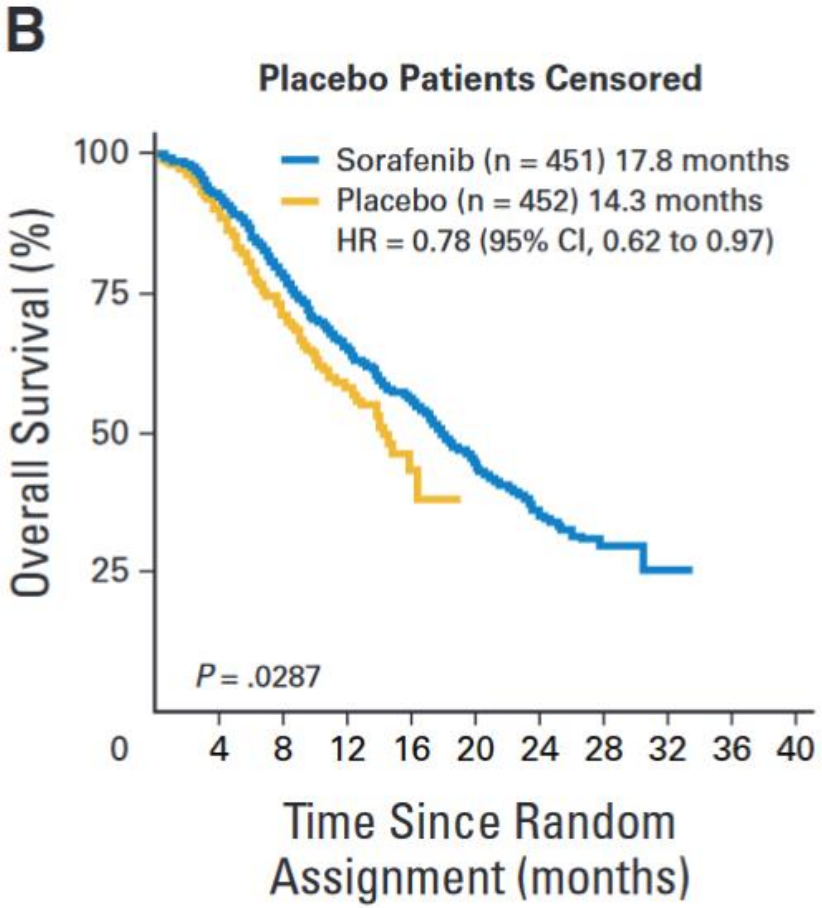
Multi TKIs – sorafenib, sunitinib

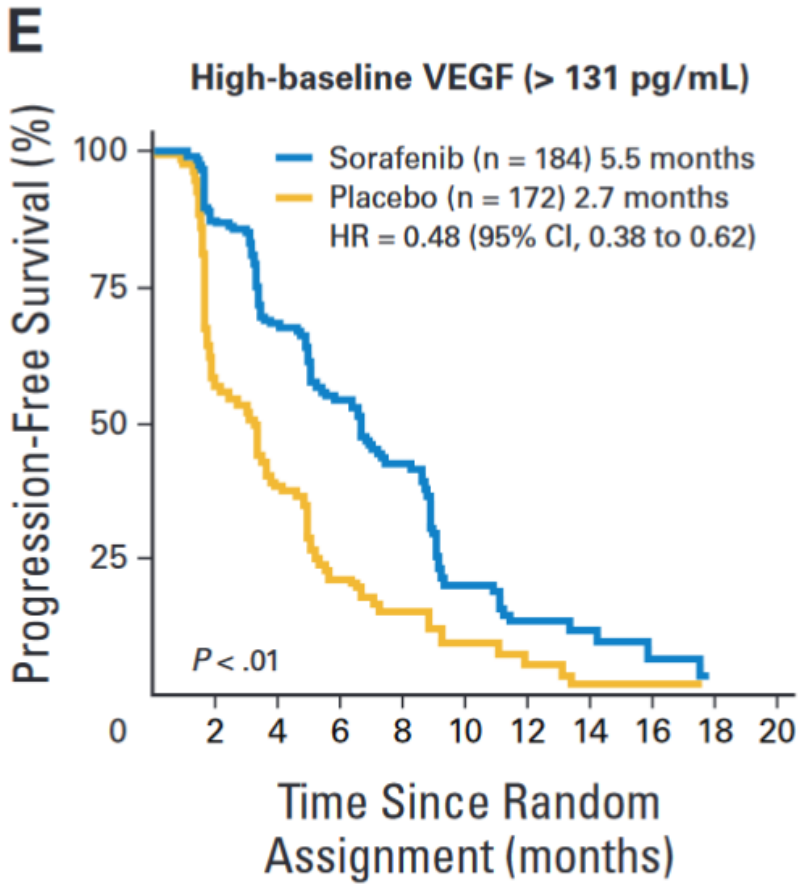
- Sorafenib
  - VEGFR, PDGFR, RAF, FLT3, KIT, RET inhibitor

Sorafenib for Treatment of Renal Cell Carcinoma: Final Efficacy and Safety Results of the Phase III Treatment Approaches in Renal Cancer Global Evaluation Trial

Bernard Escudier, Tim Eisen, Walter M. Stadler, Cezary Szczylik, Stéphane Oudard, Michael Staehler, Sylvie Negrier, Christine Chevreau, Apurva A. Desai, Frédéric Rolland, Tomasz Demkow, Thomas E. Hutson, Martin Gore, Sibyl Anderson, Gloria Hofilena, Minghua Shan, Carol Pena, Chetan Lathia, and Ronald M. Bukowski



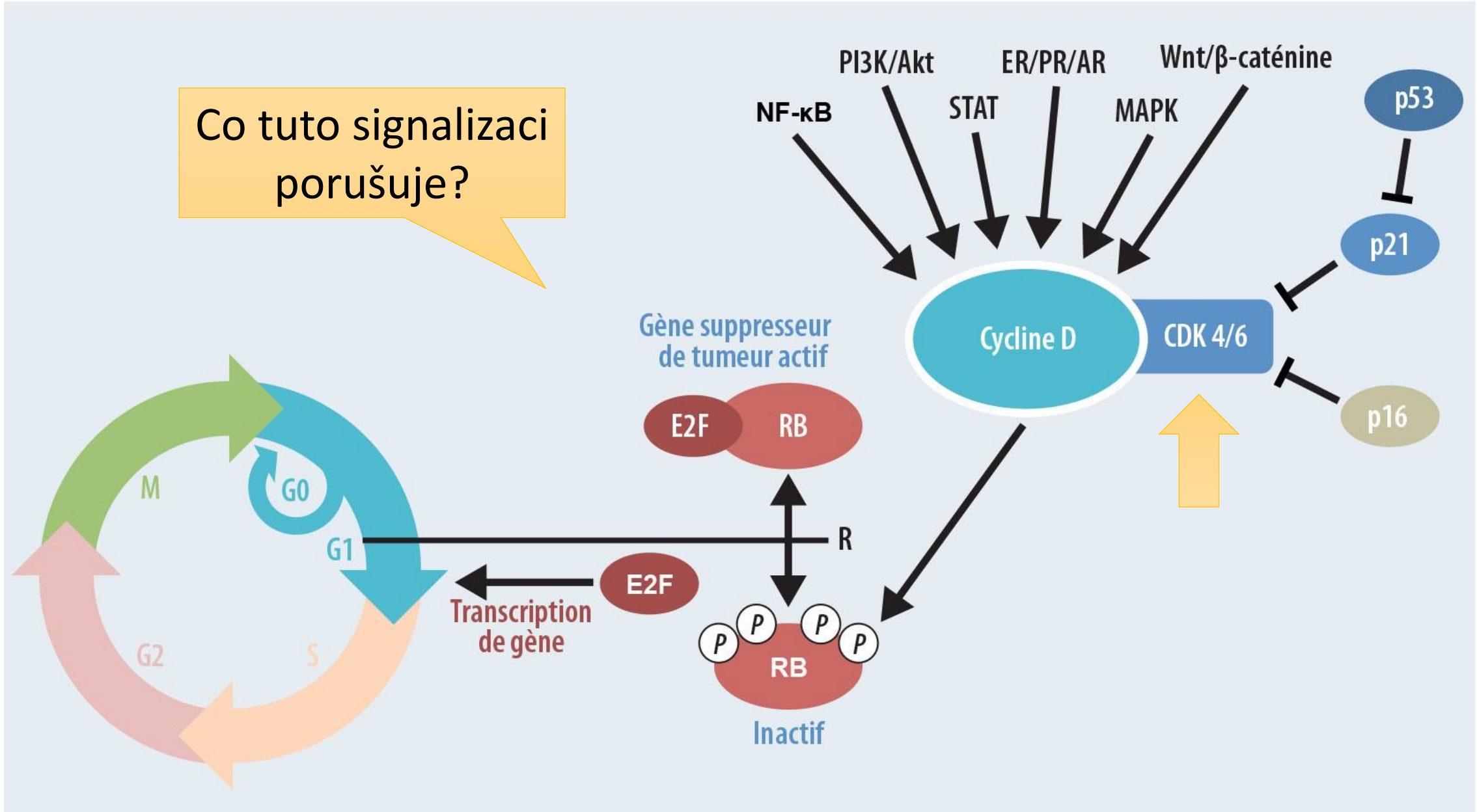




Multi TKIs – sorafenib, sunitinib

- Sunitinib
  - VEGFR, PDGFR, FGFR, FLT3, KIT, RAF, FMS
- Pazopanib
  - VEGFR, PDGFR, KIT
- Cabozantinib
  - VEGFR, AXL, MET, KIT, TIE2, FLT3, RET

CDK4/6 TKIs (palbociclib, ribociclib, abemaciclib)



CDK4/6 TKIs (palbociclib, ribociclib, abemaciclib)

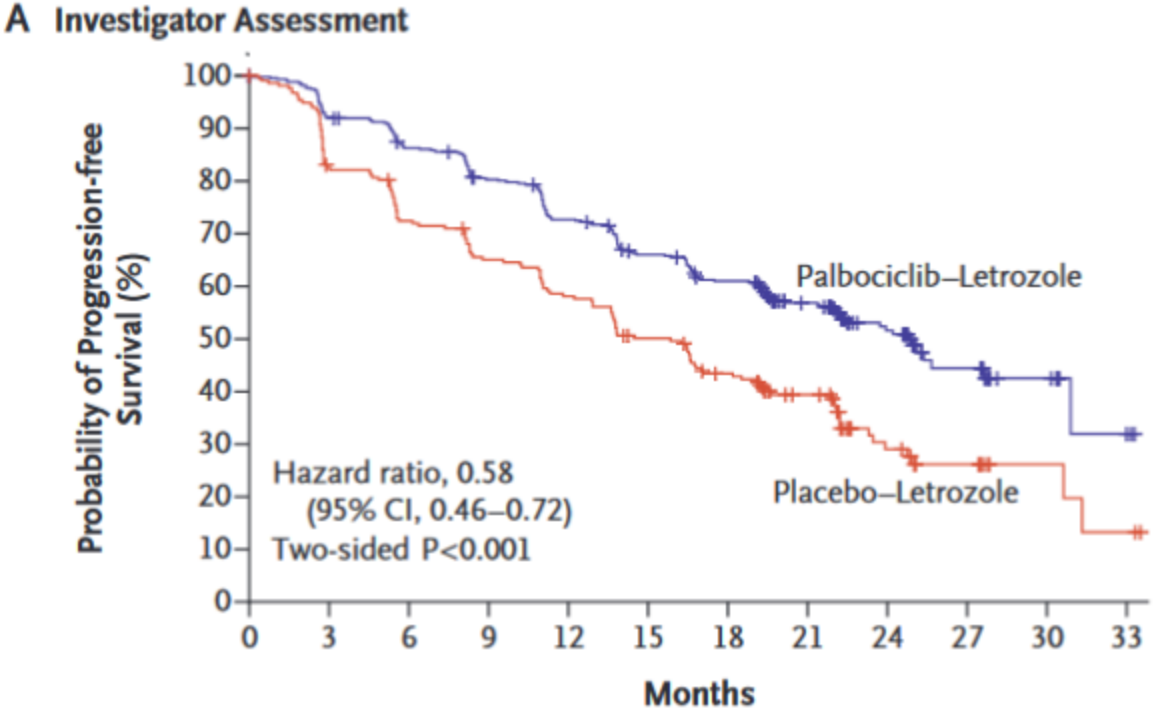
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 17, 2016 VOL. 375 NO. 20

Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D., Karen Gelmon, M.D., Nadia Harbeck, M.D., Ph.D., Oleg N. Lipatov, M.D., Janice M. Walshe, M.D., Stacy Moulder, M.D., Eric Gauthier, Pharm.D., Ph.D., Dongrui R. Lu, M.Sc., Sophia Randolph, M.D., Ph.D., Véronique Diéras, M.D., and Dennis J. Slamon, M.D., Ph.D.

In this double-blind study, we randomly assigned, in a 2:1 ratio, 666 postmenopausal women with **ER-positive**, **HER2-negative breast cancer**, who **had not had prior treatment for advanced disease**, to receive palbociclib plus letrozole or placebo plus letrozole.



No. at Risk												
Palbociclib–Letrozole	444	395	360	328	295	263	238	154	69	29	10	2
Placebo–Letrozole	222	171	148	131	116	98	81	54	22	12	4	2

mTOR inhibitory .....

- Součást PIK3, reguluje především růst a přežití buněk
- Serin / threonin kináza
- Everolimus, sirolimus, ...

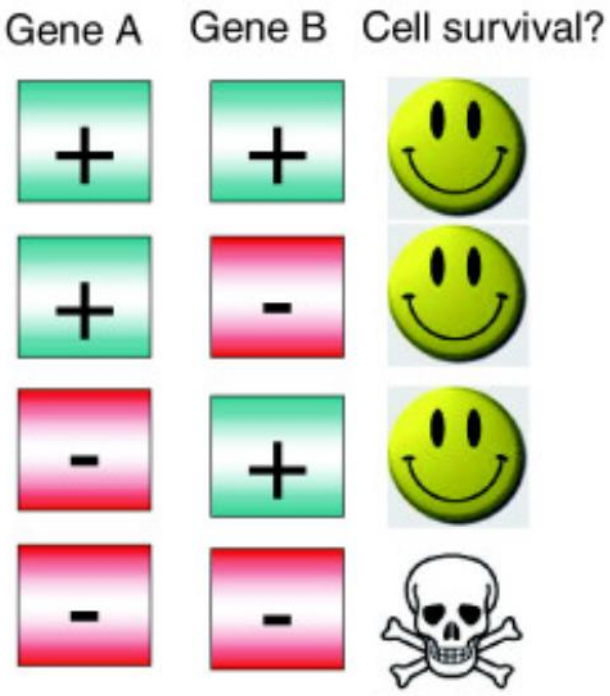
TKIs závěr

- DeVita 2018:

Although often effective initially, *both intrinsic and acquired* ***resistance to kinase inhibitors is the rule rather than the exception****. In many cases, resistance is the result of selection for cells with a co-mutation in a second targetable kinase. In others, "adaptive" resistance due to activation of parallel kinase pathways is the basis for treatment failure.* ***Achieving the promise of precision oncology will thus require the development of combination therapies that can prevent or delay the emergence of drug resistance.*** *Such combinations have been* ***difficult to develop to date due to the diversity of co-mutation patterns*** *observed in lung cancer, melanoma, and other common cancer types. The* ***additive toxicity associated with the use of multiple agents is also a hurdle*** *in the development of effective combination regimens. One can, however, envision a future in which broad prospective tumor molecular profiling and the availability of more selective inhibitors will allow for the personalized selection of kinase inhibitor combinations. Achieving this vision will require close collaboration between clinical and laboratory researchers focused on identifying the biologic basis for drug response in parallel with the development of less toxic, more selective kinase inhibitors.*

PARPi (olaparib, veliparib, rucaparib, ...)

- Oprava SSBs
- Pokud porucha DSBs opravy a nárůst SSBs → problém
- *„BRCAness“*
- Syntetická letalita



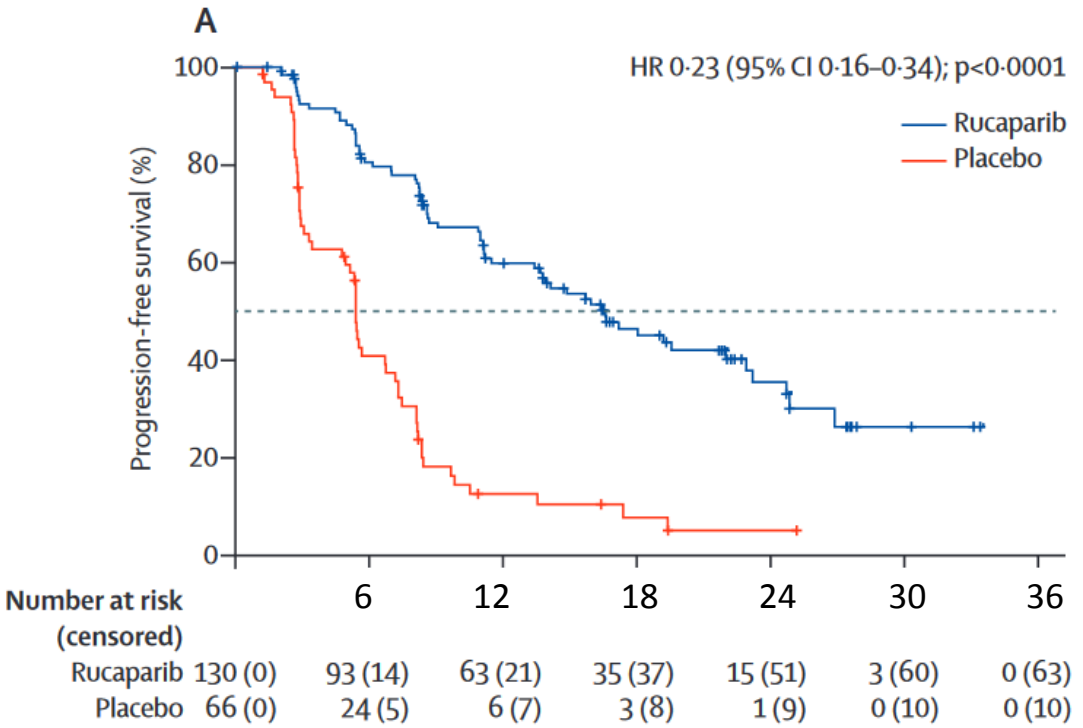
Potenciální otázky:
Proč dojde ke smrti buňky, když NHEJ je pořád funkční? A je NHEJ opravdu tak špatné?

PARPi (olaparib, veliparib, rucaparib, ...)

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial

Robert L Coleman, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Jesus Garcia-Donas, Elizabeth M Swisher, Anne Floquet, Gottfried E Konecny, Iain A McNeish, Clare L Scott, Terri Cameron, Lara Maloney, Jeff Isaacson, Sandra Goble, Caroline Grace, Thomas C Harding, Mitch Raponi, James Sun, Kevin K Lin, Heidi Giordano, Jonathan A Ledermann*, on behalf of the ARIEL3 investigators†*

Lancet 2017; 390: 1949–61



Between April 7, 2014, and July 19, 2016, **we randomly allocated 564 patients: 375 (66%) to rucaparib and 189 (34%) to placebo**

Eligible patients were aged 18 years or older, had a **platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma**, had received at least two previous platinum-based chemotherapy regimens, had achieved complete or partial response to their last platinum-based regimen, had a cancer antigen 125 concentration of less than the upper limit of normal, had a performance status of 0–1, and had adequate organ function.

Imunitní systém

- Nádory mají neoantigeny (mutované geny), které imunitní systém bere jako cizí

Většinou
passenger mutace

- Imunitní dohled – především **T lymfocyty** a NK buňky

„cizí“ epitopy na MHC-1

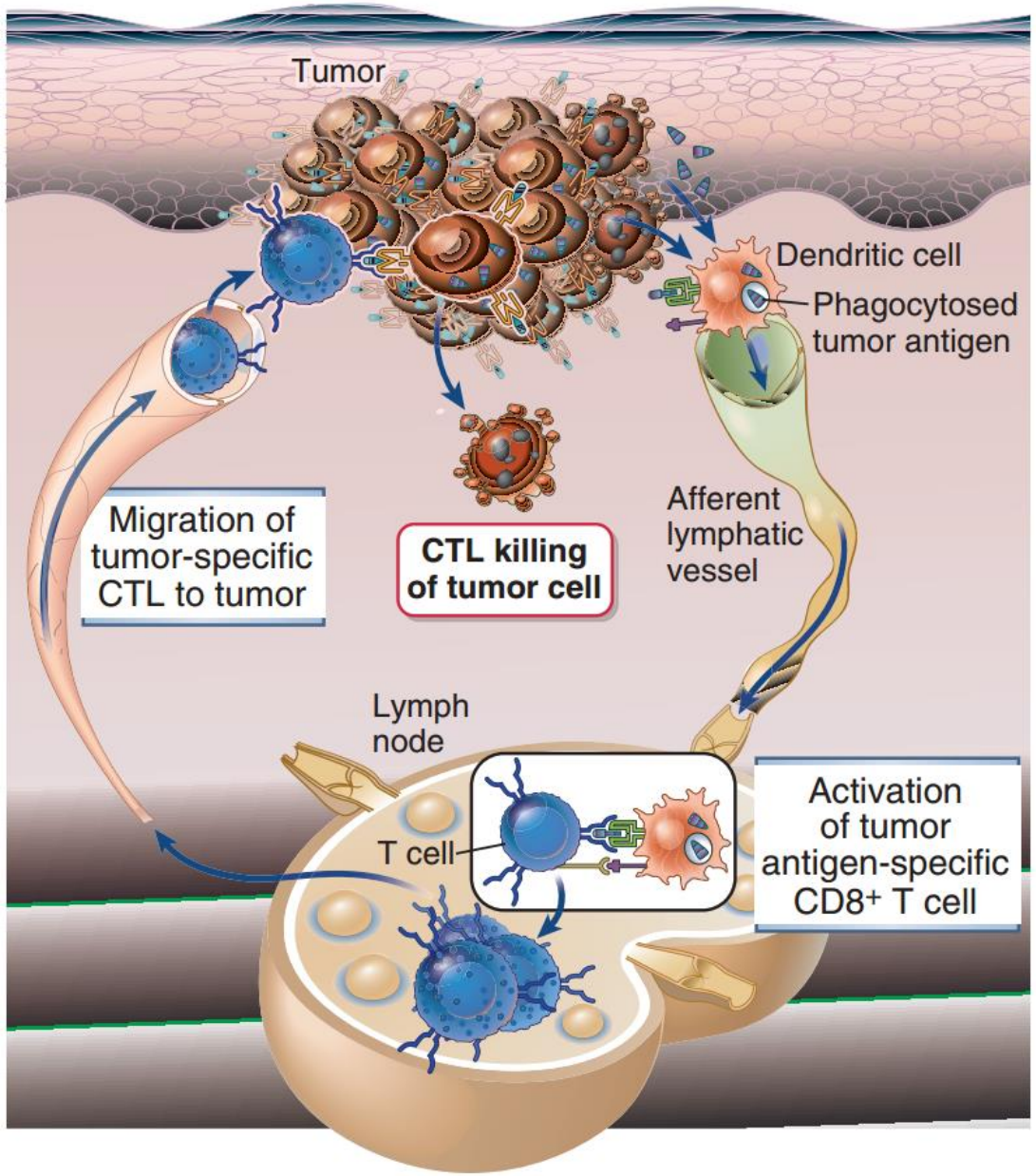
Málo MHC-1

Neoantigeny
Fetální antigeny
Antigeny ze specif. míst (testis)

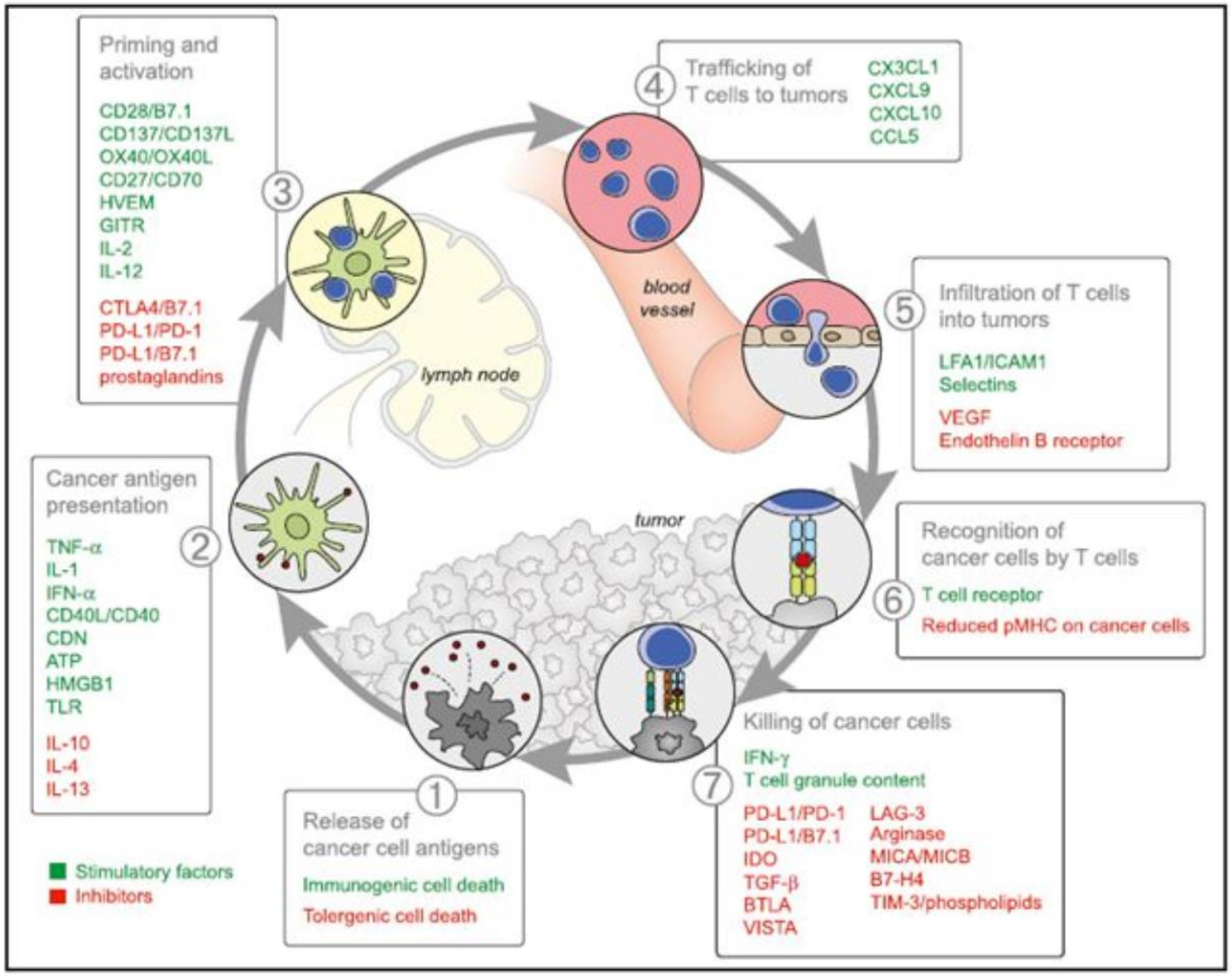
CEA

T lymfocyty = CD8+ CTLs

Imunitní systém



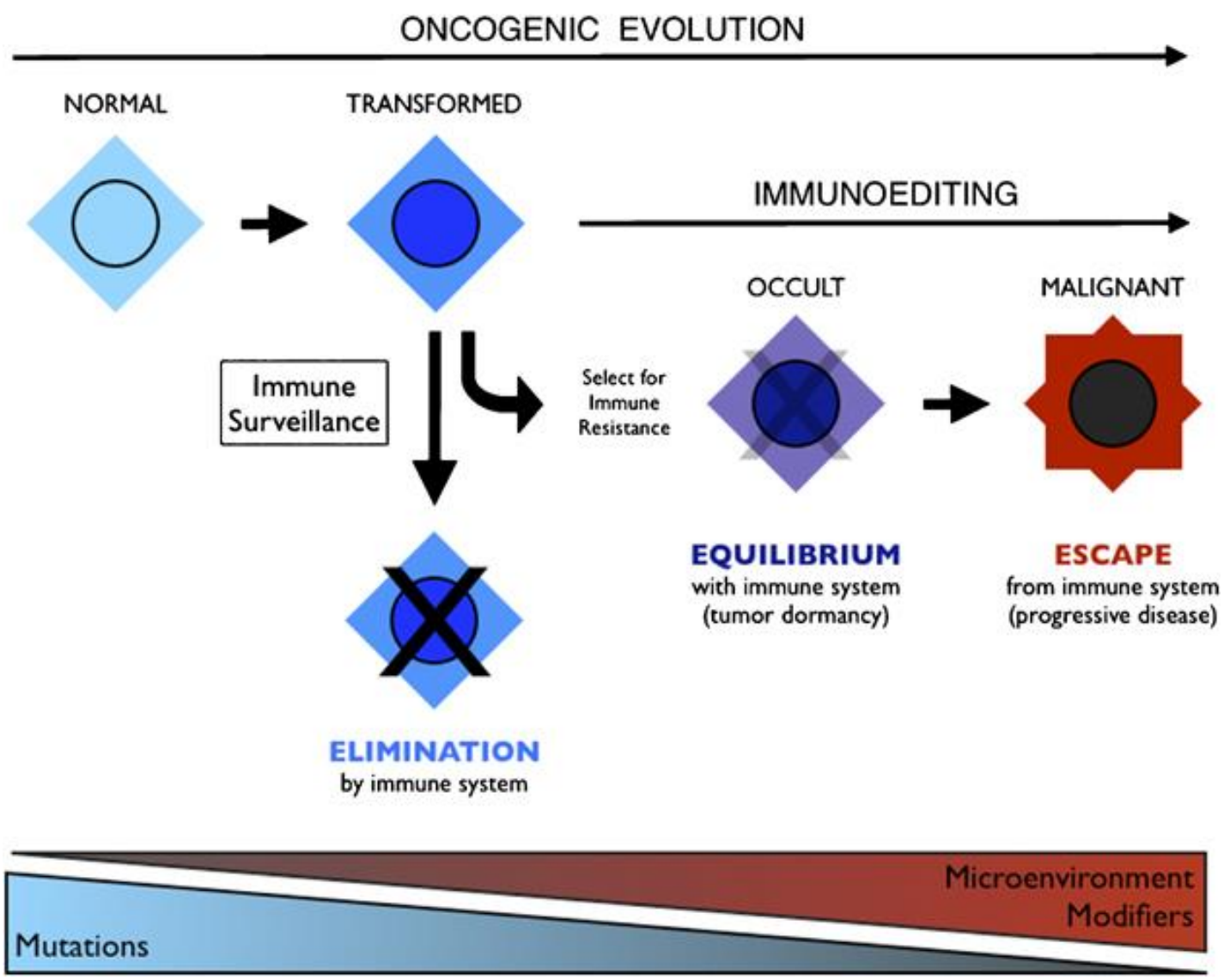
Imunitní systém



Immunity 39, July 25, 2013

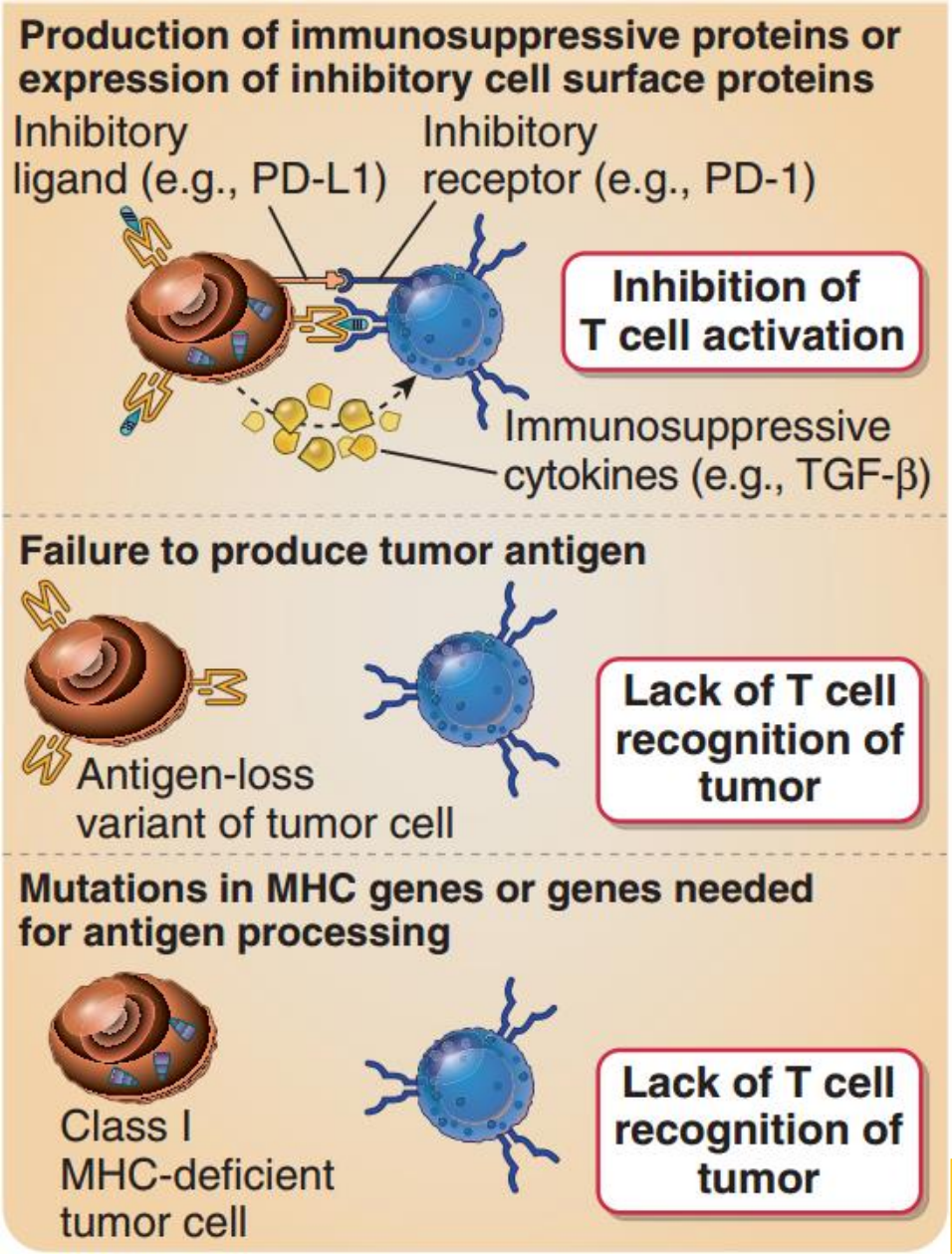
„...Immune response in cancer reflects a series of carefully regulated events that may be **optimally addressed not singly but as a group**.“

Imunitní systém



Makroskopické nádory se už imunitě úspěšně vyhly

Imunitní systém – obrana nádorů

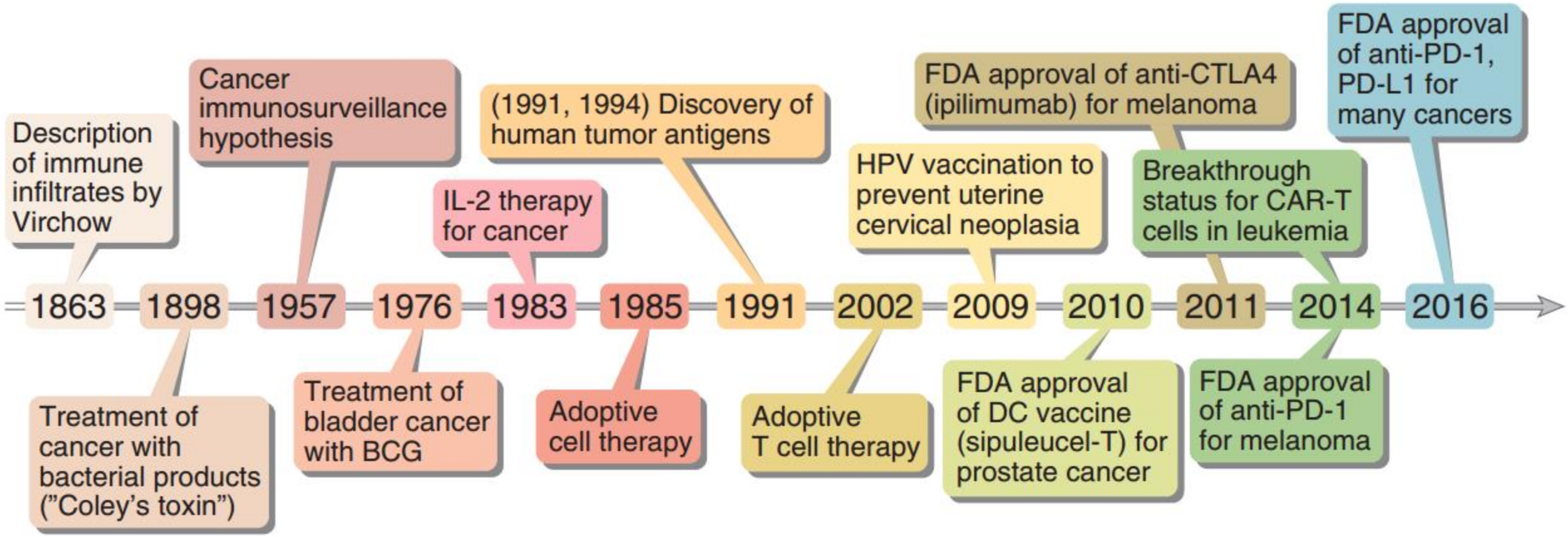


CTLA-4
PD-1

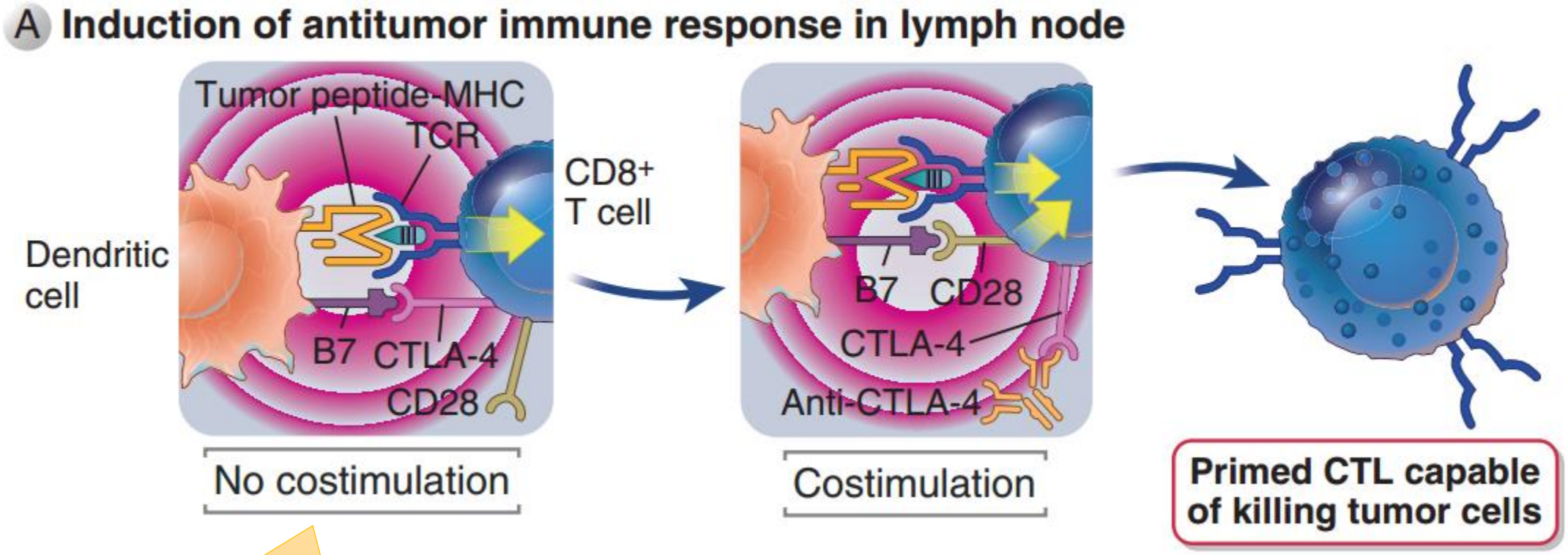
Blokují aktivaci CTLs

Nenastává u myší s poruchou adaptivní imunity

Imunitní systém



Blokování CTLs



CTLA-4 je **inhibiční** receptor na povrchu T lymfocytů

Funkce: limitace imunitní reakce

„Chechpoint inhibitory“ („matoucí“ termín)

Protilátky proti CTLA-4 (ipilimumab)

Target	Agent	Year Approved	Tumor	Stage	Indication
CTLA-4	Ipilimumab	2011	Melanoma	▪ Unresectable ▪ Metastatic	
		2015	Melanoma	▪ Stage III	Adjuvant therapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

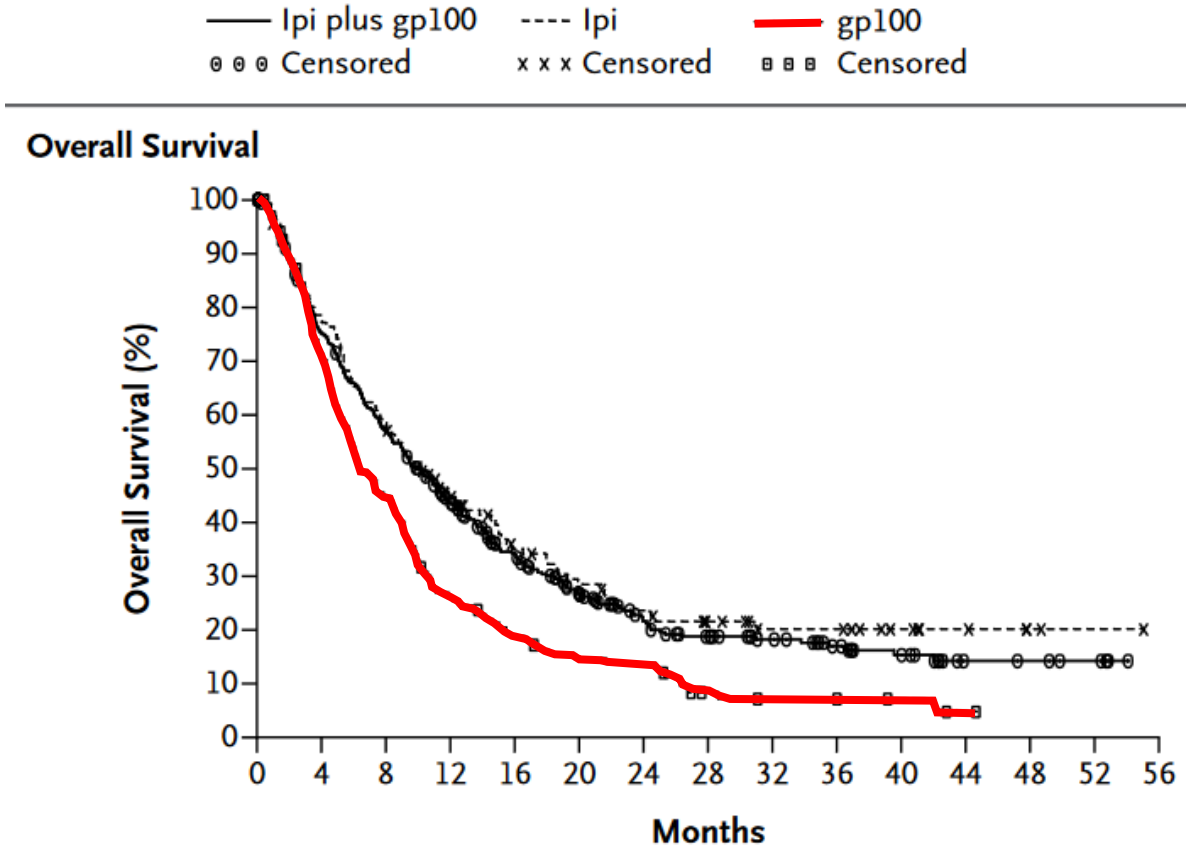
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

Protilátky proti CTLA-4 (ipilimumab)

A total of 676 patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned to ....

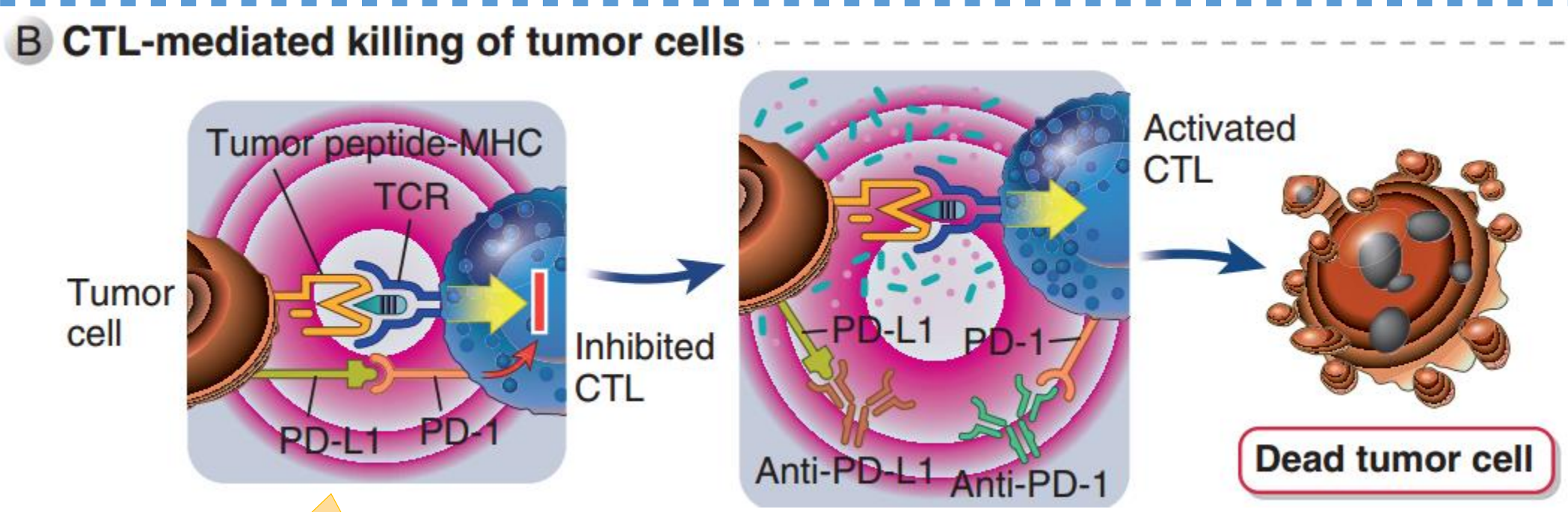
The **median overall survival** was **10.0 months** among patients receiving ipilimumab plus gp100, as **compared with 6.4 months** among patients receiving gp100 alone (hazard ratio for death, 0.68; P<0.001)



No. at Risk

Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

Blokování CTLs



PD-1 je **inhibiční** receptor na povrchu T lymfocytů

„Chechpoint inhibitory“ („matoucí“ termín)

Protilátky proti PD-1 / PD-L1

Target	Agent	Year Approved	Tumor	Stage	Indication
PD-1	Nivolumab	2014	Melanoma	▪ Unresectable ▪ Metastatic	
		2015	NSCLC	▪ Metastatic	Progressing after PC, EGFR-TKI, ALK-TKI
		2015	Renal cell carcinoma	▪ Metastatic	
		2016	Classical Hodgkin lymphoma	▪ Relapsed ▪ Refractory	▪ Adults ▪ Progressing after ASCT + brentuximab vedotin ▪ Progressing after ≥3 lines of therapy, including ASCT
		2016	HNSCC	▪ Recurrent ▪ Metastatic	Progressing after PC
		2017	dMMR or MSI-H colorectal cancer	▪ Metastatic	Progressing after chemotherapy: 5-FU, oxaliplatin, irinotecan
		2017	Urothelial carcinoma	▪ Locally advanced ▪ Metastatic	Progressing after PC
		2017	Hepatocellular carcinoma	▪ Unresectable ▪ Metastatic	Progressing after sorafenib
		2017	Melanoma	▪ Completely resected ▪ Lymph node involvement ▪ Metastatic	Adjuvant

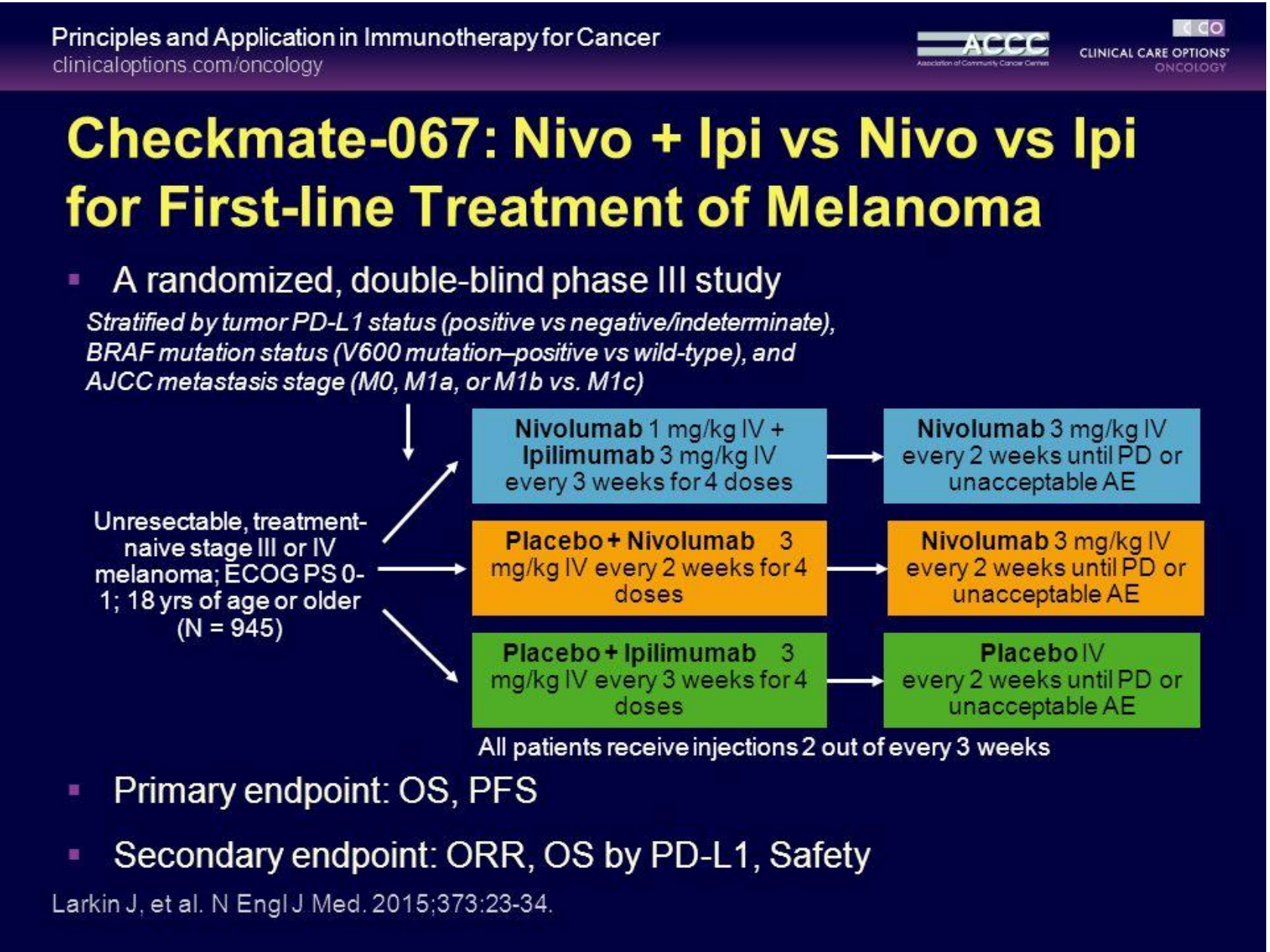
Protilátky proti PD-1 / PD-L1

Target	Agent	Year Approved	Tumor	Stage	Indication
PD-1	Pembrolizumab	2014	Melanoma	▪ Unresectable ▪ Metastatic	
		2015	NSCLC	▪ Advanced ▪ Metastatic *and* PD-L1 >1%	Progressing after PC
		2016	NSCLC	▪ Metastatic *and* PD-L1 >50%	First line
		2016	HNSCC	▪ Recurrent ▪ Metastatic	Heavily pretreated
		2017	NSCLC	▪ Advanced ▪ Metastatic ▪ Any PD-L1 expression level	First line *in combination with* carboplatin + pemetrexed chemotherapy
		2017	Classical Hodgkin lymphoma	▪ Relapsed ▪ Refractory	▪ Adults, children ▪ Progressing after ≥3 lines of therapy
		2017	Any dMMR or MSI-H cancers	▪ Unresectable ▪ Metastatic	Progressing after all standard therapy
		2017	Urothelial carcinoma	▪ Locally advanced ▪ Metastatic	
		2017	Gastric/GEJ adenocarcinoma	▪ Recurrent ▪ Locally advanced ▪ Metastatic	▪ CPS ≥1 ▪ Progressing after ≥2 lines of 5-FU, PC, anti-HER2/neu
		2018	Cervical cancer	▪ Recurrent ▪ Metastatic	▪ CPS ≥1 ▪ Progressing after ≥1 line of chemotherapy
		2018	PMBCL	▪ Relapsed ▪ Refractory	▪ Adults, children ▪ Progressing after ≥3 lines of therapy

Protilátky proti PD-1 / PD-L1

Target	Agent	Year Approved	Tumor	Stage	Indication
PD-L1	Atezolizumab	2016	NSCLC	▪ Metastatic	Progressing after PC
		2016	Urothelial carcinoma	▪ Locally advanced ▪ Metastatic	Progressing after PC
		2017	Urothelial carcinoma	▪ Locally advanced ▪ Metastatic	▪ First line: ineligible for cisplatin-based chemotherapy ▪ Second line: progressing after PC
PD-L1	Durvalumab	2017	Urothelial carcinoma	▪ Locally advanced ▪ Metastatic	Progressing after PC
		2018	NSCLC	▪ Unresectable stage III	▪ Consolidation ▪ No progression after chemoradiation
PD-L1	Avelumab	2017	Urothelial carcinoma	▪ Locally advanced ▪ Metastatic	Progressing after PC
		2017	Merkel cell carcinoma	▪ Metastatic	▪ Adults, children >12 y old

Protilátky proti PD-1 / PD-L1

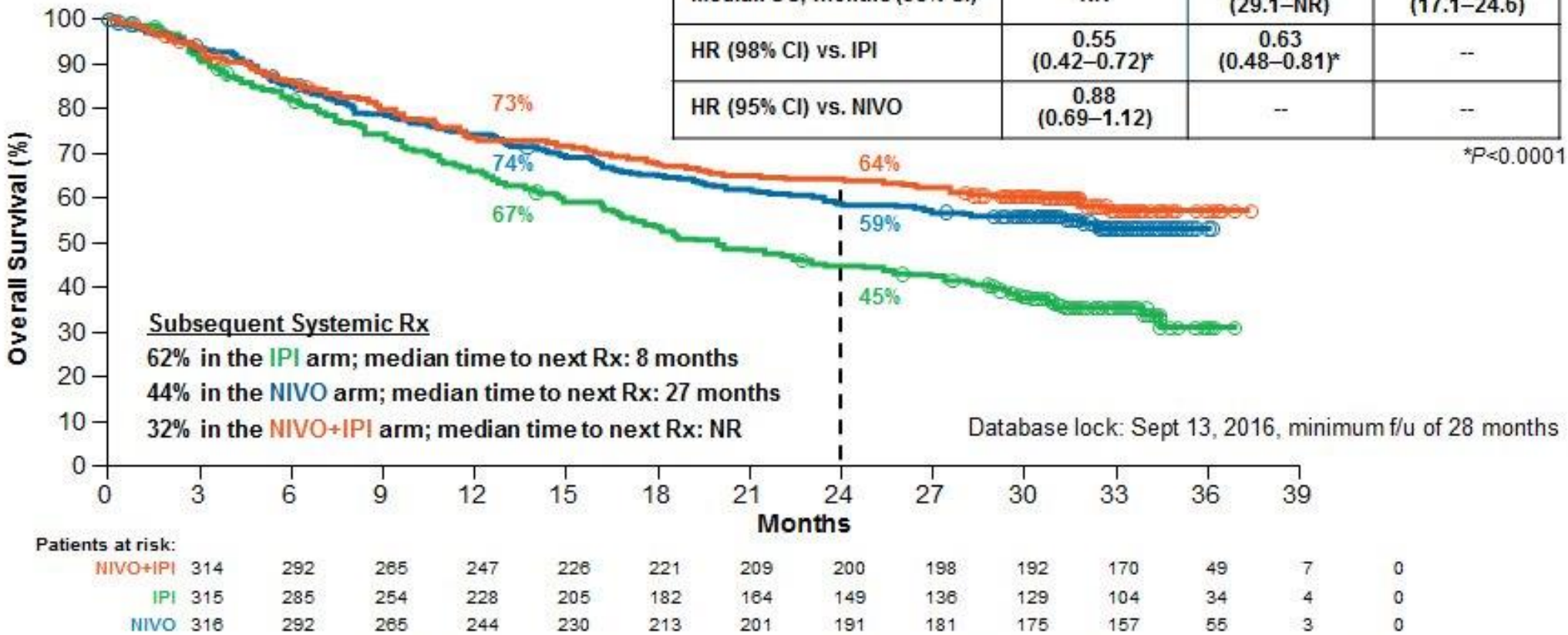


Protilátky proti PD-1 / PD-L1

Overall Survival (Co-Primary Endpoint)

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, months (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0

- 2-year OS rates were similar to results from the phase II CheckMate 069 trial of NIVO+IPI (64%)[1] and the phase CheckMate 066 trial of NIVO monotherapy (58%)[2]

1. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress; 2. Hodi FS, et al. *Lancet Oncol* 2016;17:1558–68.

Imunoterapie

The Nobel Prize in Physiology or Medicine 2018

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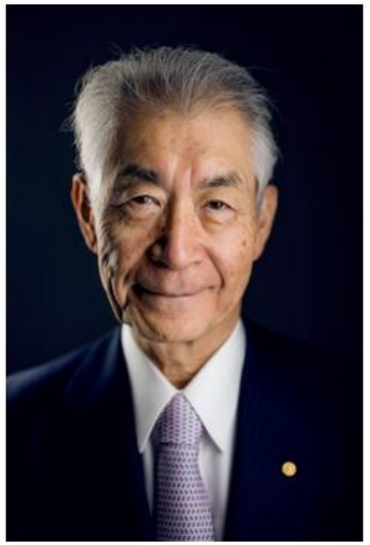
James P. Allison

Prize share: 1/2

CTLA-4



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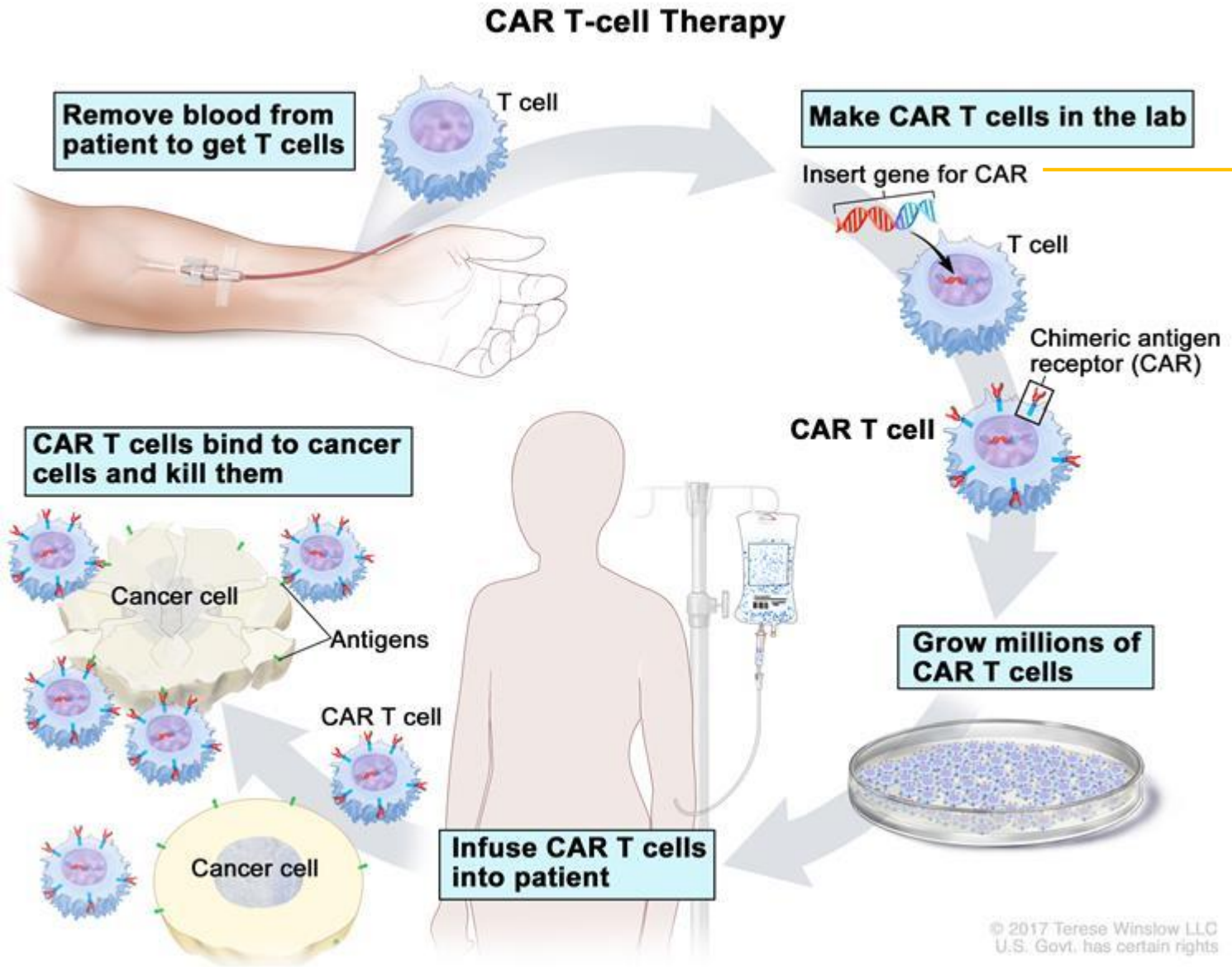
Tasuku Honjo

Prize share: 1/2

PD-1

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."

CAR-T cells (Chimeric Antigen Receptor)



...Upon encountering the antigen of interest, **all necessary costimulation occurs and the T cell can eliminate the encountered cell**...

„**Choosing the most appropriate antigen is extremely critical**, as CARs will essentially kill any cell expressing its target antigen.“

CAR-T cells (Chimeric Antigen Receptor)

Vhodný antigen?

- **CD19 (B-cell ALL a B lymfomy)**
- BCMA (mnohočetný myelom)
- CD30 (Hodgkin lymphoma)
- FLT3 (AML)

„**Choosing the most appropriate antigen is extremely critical**, as CARs will essentially kill any cell expressing its target antigen.“

„human epidermal growth factor receptor 2 **(HER2)-targeted CAR that caused fatal pulmonary toxicity**, potentially due to low levels of HER2 expression in the lungs“

CAR-T cells (Chimeric Antigen Receptor)

The NEW ENGLAND JOURNAL of MEDICINE

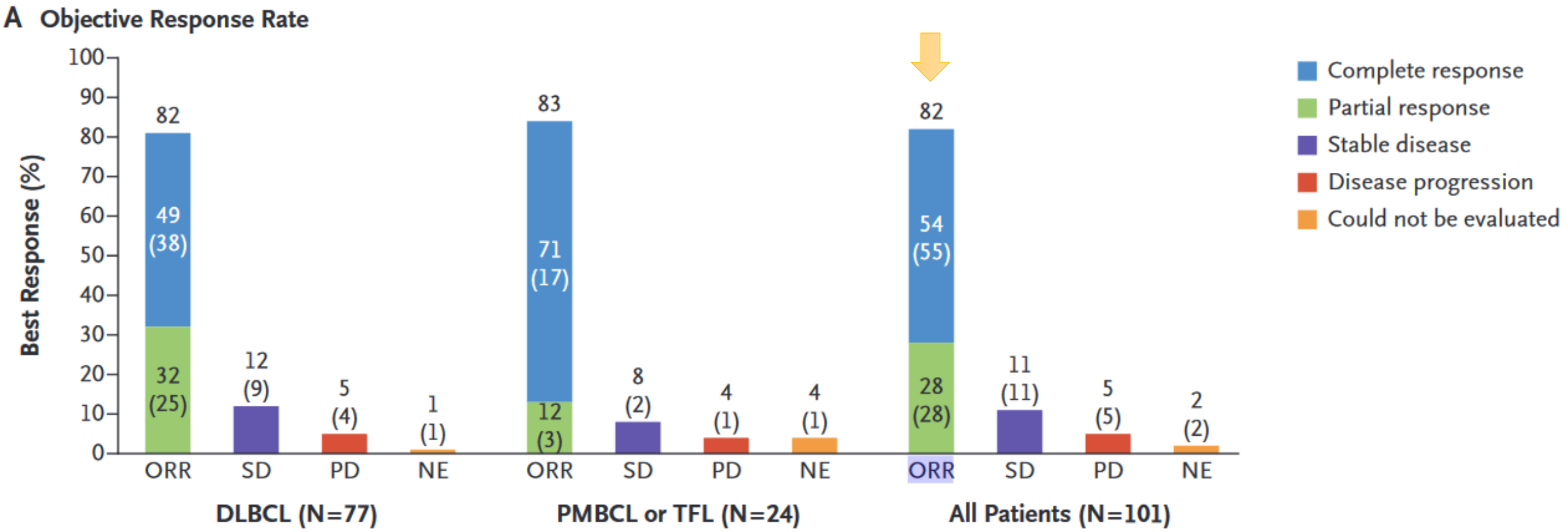
ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

Large B-cell lymphomas, including diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma, are **treated with combination chemoimmunotherapy** at diagnosis. **Patients who have a relapse** with chemotherapy-sensitive disease **may be treated with** high-dose chemotherapy followed by **autologous stem-cell transplantation**. However, **patients who have disease that is resistant to primary or salvage chemoimmunotherapy or who have had a relapse after transplantation have an extremely poor prognosis**. Recently, in a large, international, retrospective research study involving patients with non-Hodgkin's lymphoma (SCHOLAR-1), investigators found an **objective response rate of 26%**, a **complete response rate of 7%**, and a **median overall survival of 6.3 months** with existing therapies among patients who had aggressive B-cell lymphoma that was resistant to chemotherapy or who had a relapse within 12 months after autologous stem-cell transplantation.

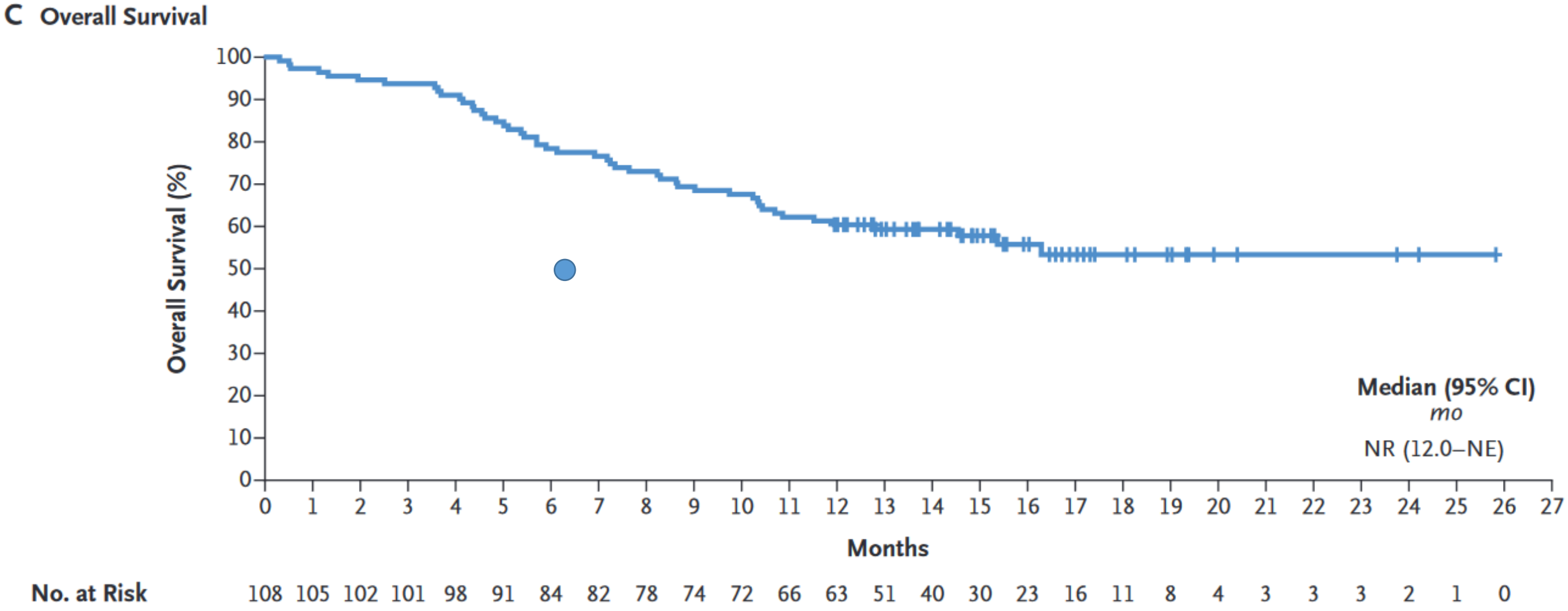
CAR-T cells (Chimeric Antigen Receptor)



...objective response rate of 26%, a **complete response rate of 7%...**

CAR-T cells (Chimeric Antigen Receptor)

...median overall survival of 6.3 months...



CD20

- Receptor na povrchu B-lymfomů
- Rituximab
- induces lymphoma cell lysis through:
  - complement-mediated cytolysis
  - Antibody dependent cell cytotoxicity
  - induction of apoptosis
- acts synergistically with chemotherapy

Vývoj a dozrávání B lymfocytů

*„**CD20 function is not fully understood**, although **it is known to be involved in the calcium flux**. Recent studies suggested that raft-associated CD20 constitutes a component of a store-operated calcium entry pathway activated by BCR“*

(2015)

CD20 (rituximab)

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JOURNAL OF CLINICAL ONCOLOGY

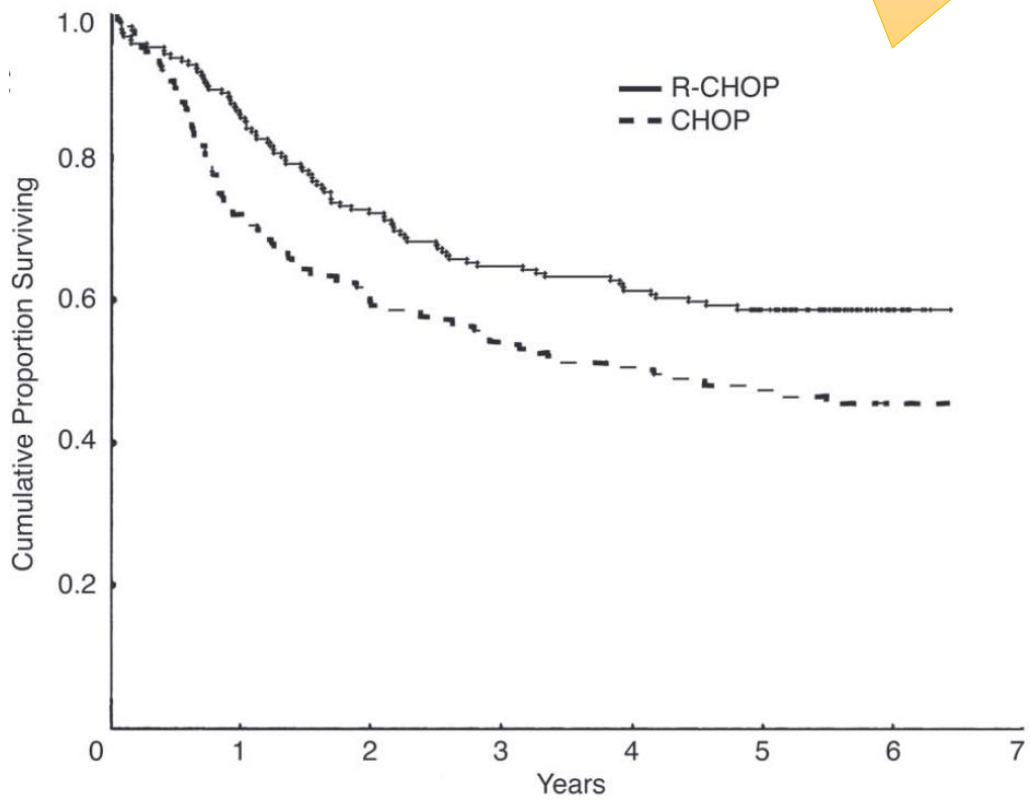
ORIGINAL REPORT

Long-Term Results of the R-CHOP Study in the Treatment of Elderly Patients With Diffuse Large B-Cell Lymphoma: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

P. Feugier, A. Van Hoof, C. Sebban, P. Solal-Celigny, R. Bouabdallah, C. Fermé, B. Christian, E. Lepage, H. Tilly, F. Morschhauser, P. Gaulard, G. Salles, A. Bosly, C. Gisselbrecht, F. Reyes, and B. Coiffier

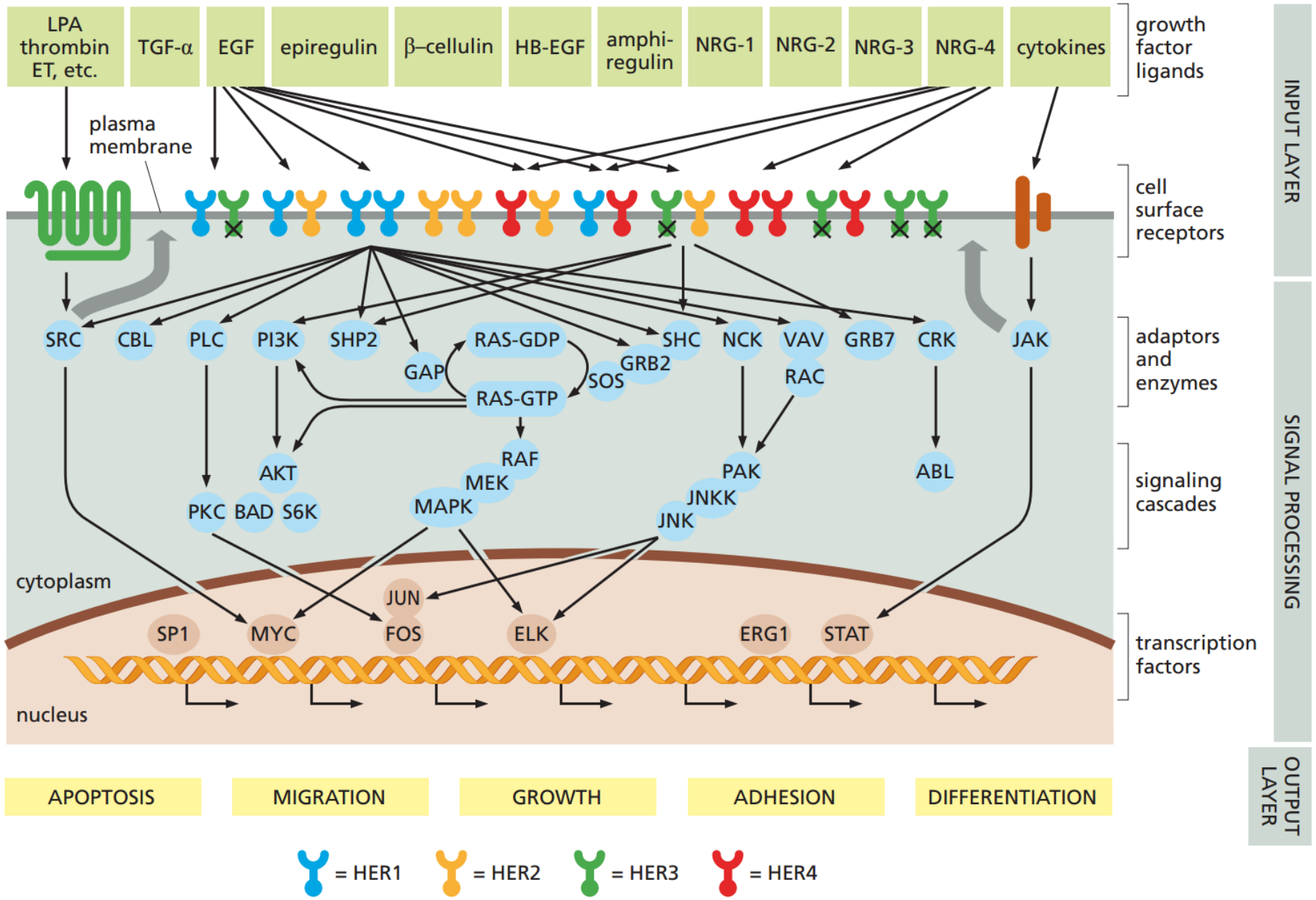
- 399 previously untreated patients, age 60 to 80 years, with diffuse large B-cell lymphoma.
- Patients received eight cycles of classical CHOP (cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2, vincristine 1.4 mg/m2, and prednisone40 mg/m2 for 5 days) every 3 weeks.
- In R-CHOP, rituximab 375 mg/m2was administered the same day as CHOP. Survivals were analyzed using the intent-to-treat principle.

Celkové přežití



ErbB rodina

- Receptory na povrchu buněk
- Přenos signálu přes buněčnou membránu
- Tyrozin-kinázová funkce
- Protoonkogeny



HER2

- Receptor na povrchu buněk, součástí ErbB rodiny
- Tyrozin-kináza

*In 1987, **amplification** of the ERBB2 gene, which encodes the HER2 transmembrane receptor tyrosine kinase, was identified in a subset of breast cancers*

- Trastuzumab, pertuzumab, ...

TABLE 45.7

Cetuximab for Recurrent or Metastatic Head and Neck Cancer: Selected Studies

Author	No. of Patients	Cancer	Chemotherapy	RR	Median PFS (mo)	Median OS (mo)
Herbst et al.[74,a]	79	SCC–POD on CDDP based	CDDP based + cetuximab	6%–20%	2.0–3.0	4.3–6.1
Baselga et al.[73,a]	96	SCC–POD on platin based	CDDP based + cetuximab	10%–11%	2.4–2.8	4.9–6.0
Trigo et al.[75]	103	SCC–POD on platin based	Cetuximab	13%	2.3	5.9
Burtness et al.[76,b]	117	SCC No chemo for R/M	CDDP CDDP + cetuximab	10% 26%	2.7 4.2	8.0 9.2

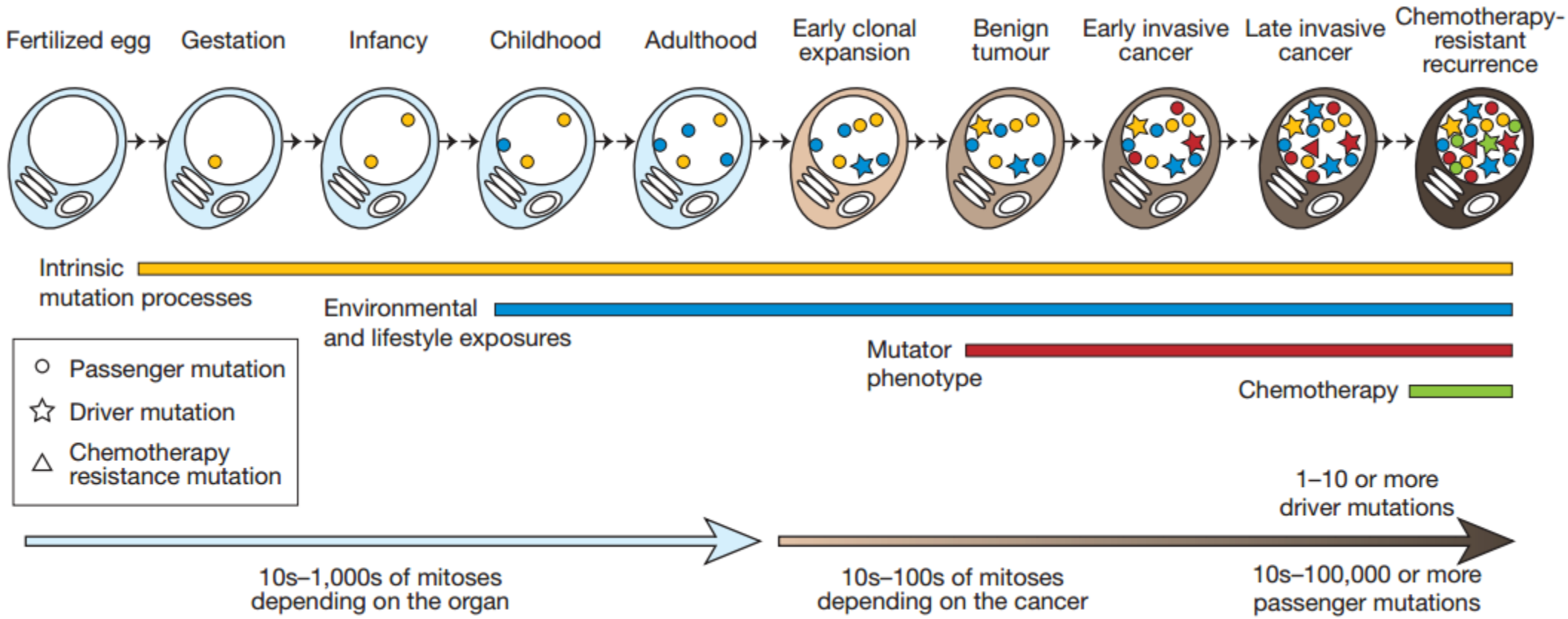
[a]Range related to how POD was defined in different subgroups.
[b]Response rates were significantly different ($P = .03$): PFS ($P = .09$) and OS ($P = .21$) did not reach statistical significance.
RR, response rate; PFS, progression-free survival; OS, overall survival; SCC, squamous cell cancer; POD, progression of disease; CDDP = cisplatin; R/M = recurrent or metastatic disease.

Problémy

- Resistence
  - Genetická instabilita
  - Intranádorová heterogenita – obrázek prso geny

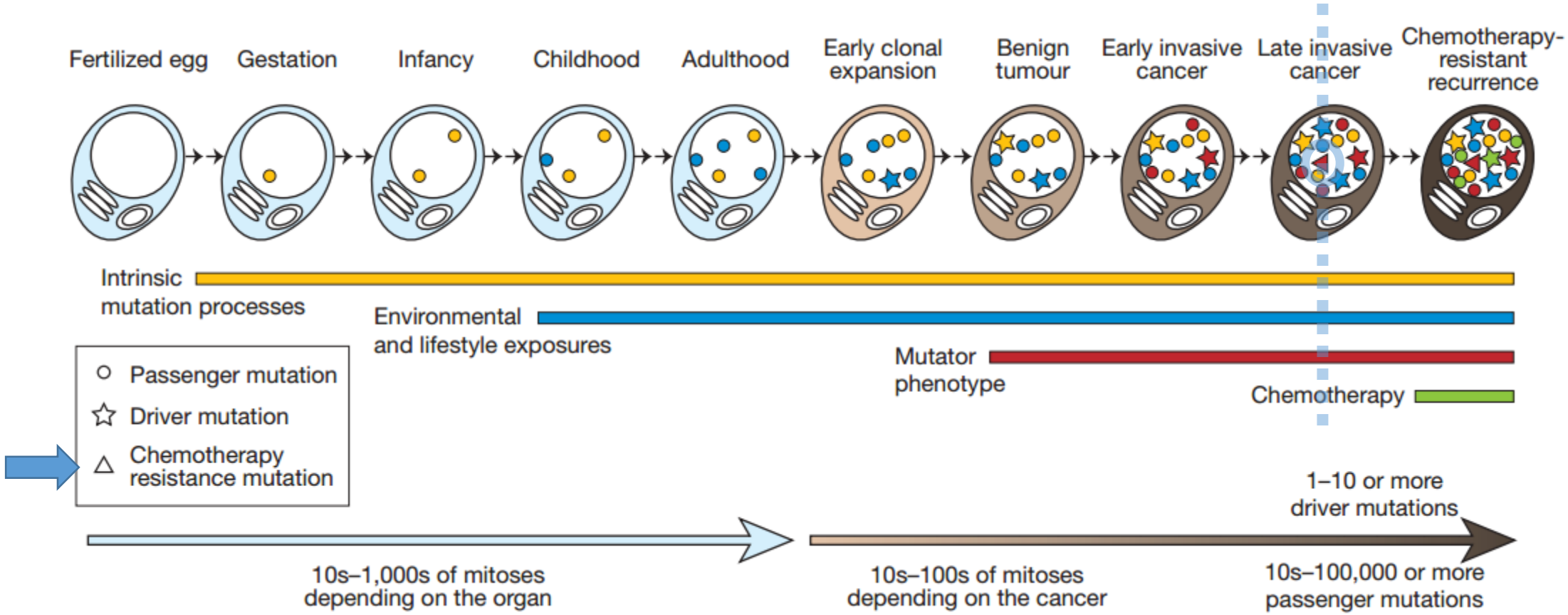
- Limitace cílů

Problémy



Nature - Vol 458j9 April 2009 doi:10.1038/nature07943

Problémy



Nature - Vol 458j9 April 2009 doi:10.1038/nature07943

The advent of molecularly targeted agents, as discussed in the following sections, has not changed a **widespread consensus among drug developers: monotherapies** involving either low–molecular-weight drugs or biological molecules **are unlikely to cure most types of cancer**, and effective **multi-agent therapies must be devised if definitive, durable clinical responses are to be achieved** in the future.

Biology of cancer 2014, weinberg