

# Cílená léčba v onkologii

Vladimír Rak

# Prerekvizity ...

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- 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!

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

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- 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?

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- Standardní léčba:
  - Nevyléčí 100% lidí
  - Toxická

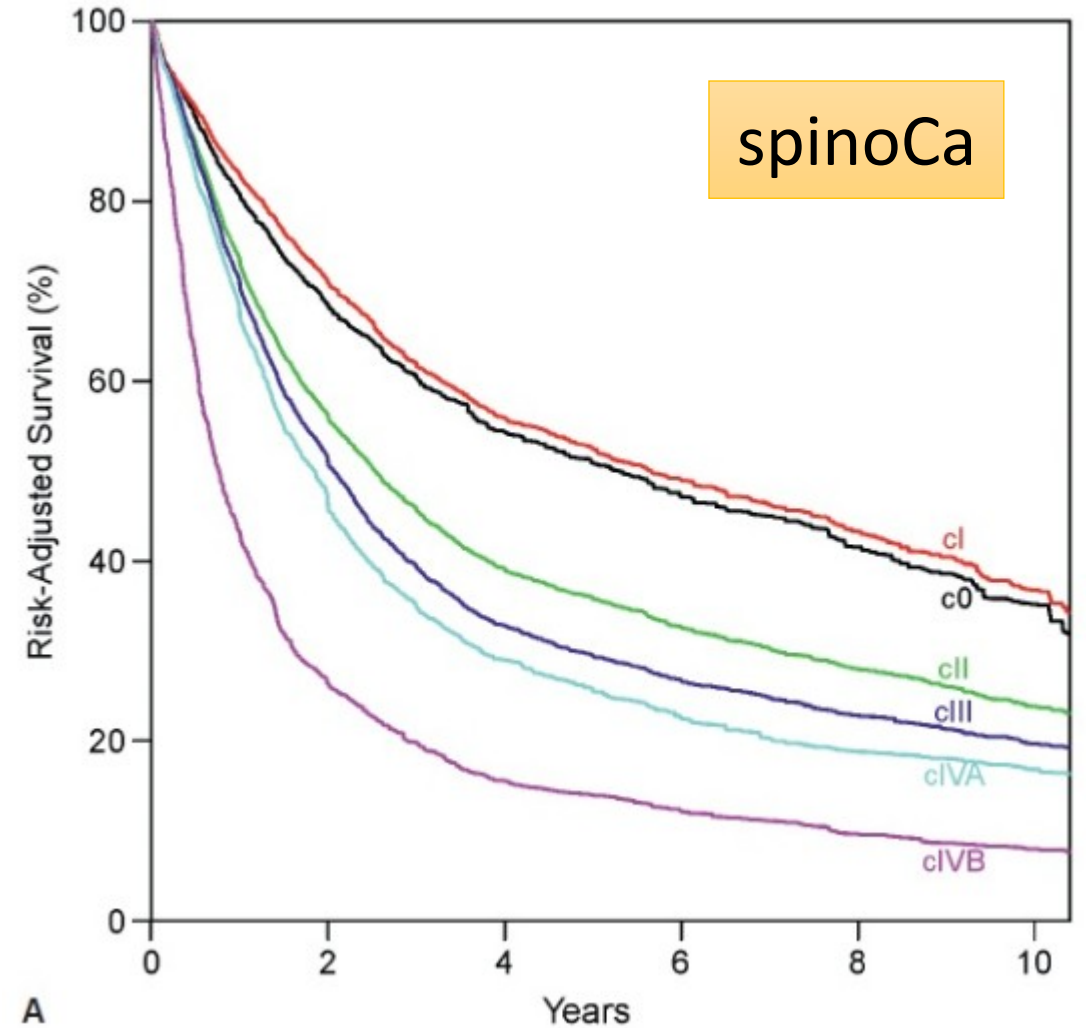
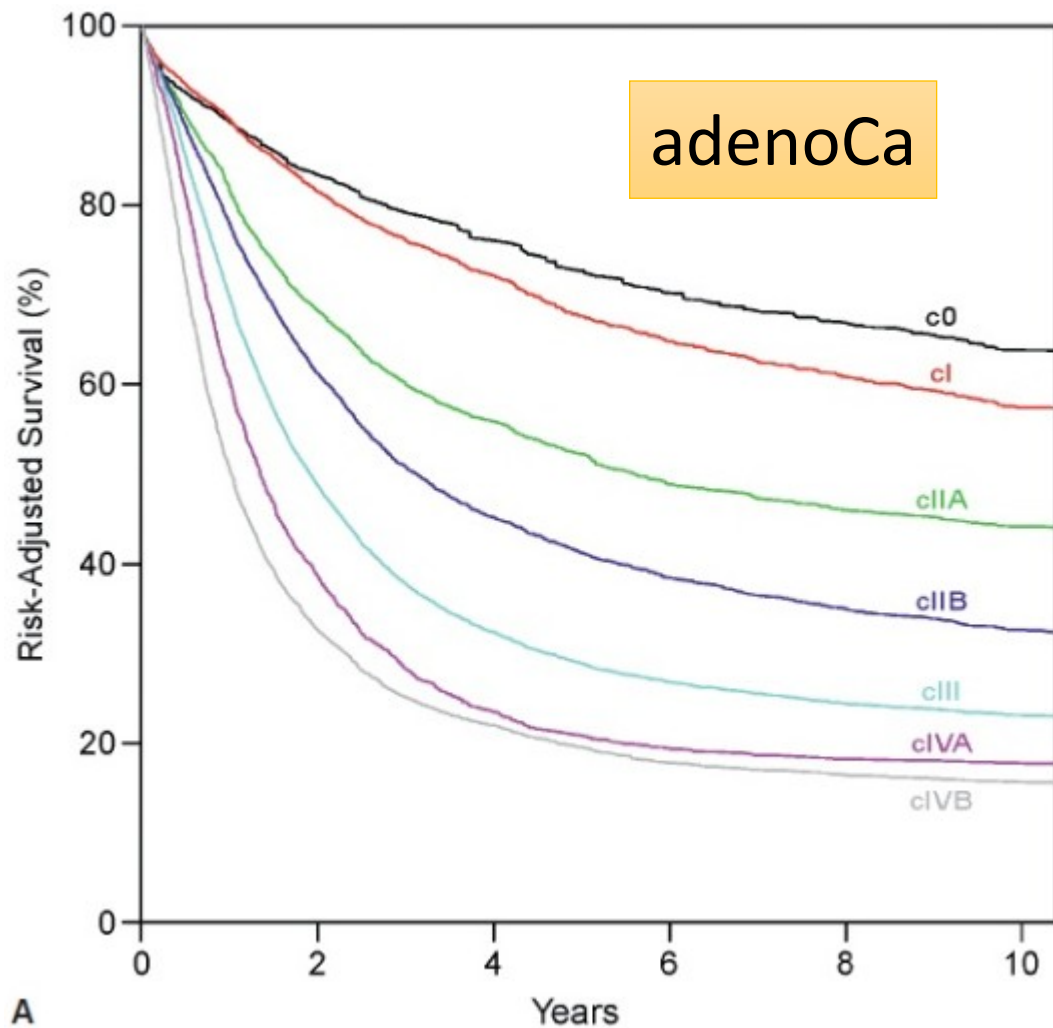
# Proč vůbec potřeba?

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

# Proč vůbec potřeba?

- Nevyléčí 100% lidí – **jícen**

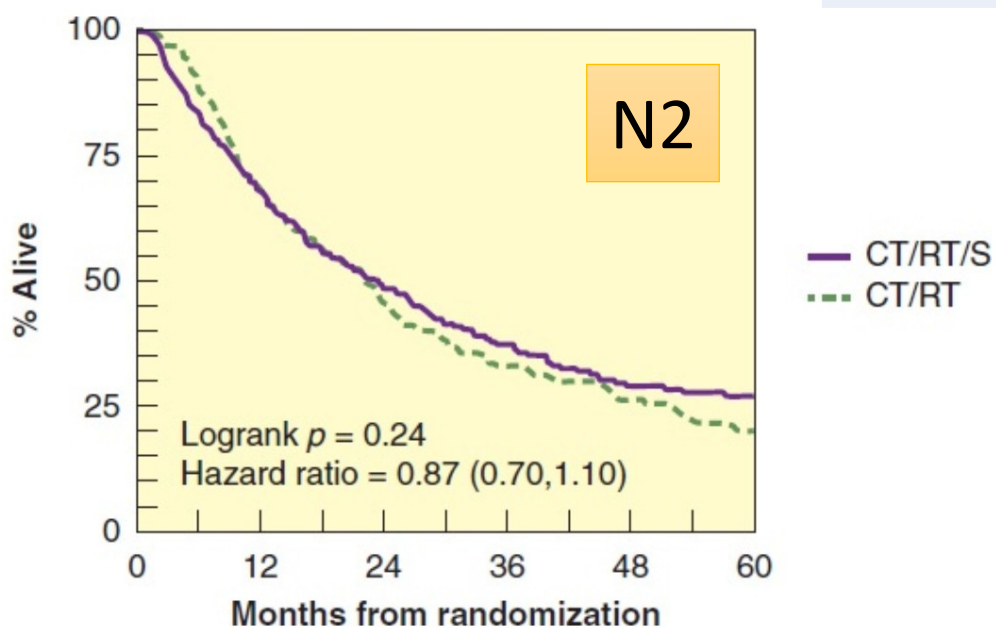


# Proč vůbec potřeba?

- 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 $\leq 1$	IA1	IIB	IIIA	IIIB
	T1b $>1-2$	IA2	IIB	IIIA	IIIB
	T1b $>2-3$	IA3	IIB	IIIA	IIIB
T2	T2a <i>Cent, Yisc PI</i>	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 <i>Inv</i>	IIB	IIIA	IIIB	IIIC
	T3 <i>Satell</i>	IIB	IIIA	IIIB	IIIC
T4	T4 $>7$	IIIA	IIIA	IIIB	IIIC
	T4 <i>Inv</i>	IIIA	IIIA	IIIB	IIIC
	T4 <i>Ipsi Nod</i>	IIIA	IIIA	IIIB	IIIC
M1	M1a <i>Contr Nod</i>	IVA	IVA	IVA	IVA
	M1a <i>PI Dissem</i>	IVA	IVA	IVA	IVA
	M1b <i>Single</i>	IVA	IVA	IVA	IVA
	M1c <i>Multi</i>	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**

<b>T: Primary Tumor</b>		<b>Five-Year Survival (%)</b>
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1a	Tumor $\leq 4$ cm and confined to the kidney	90–100
T1b	Tumor $>4$ cm and $\leq 7$ cm and confined to the kidney	80–90
T2a	Tumor $>7$ cm and $\leq 10$ 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
<b>N: Regional Lymph Nodes</b>		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph nodes metastasis	
N1	Metastasis in regional lymph node(s)	0–20
<b>M: Distant Metastases</b>		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis present	0–10

# Proč vůbec potřeba?

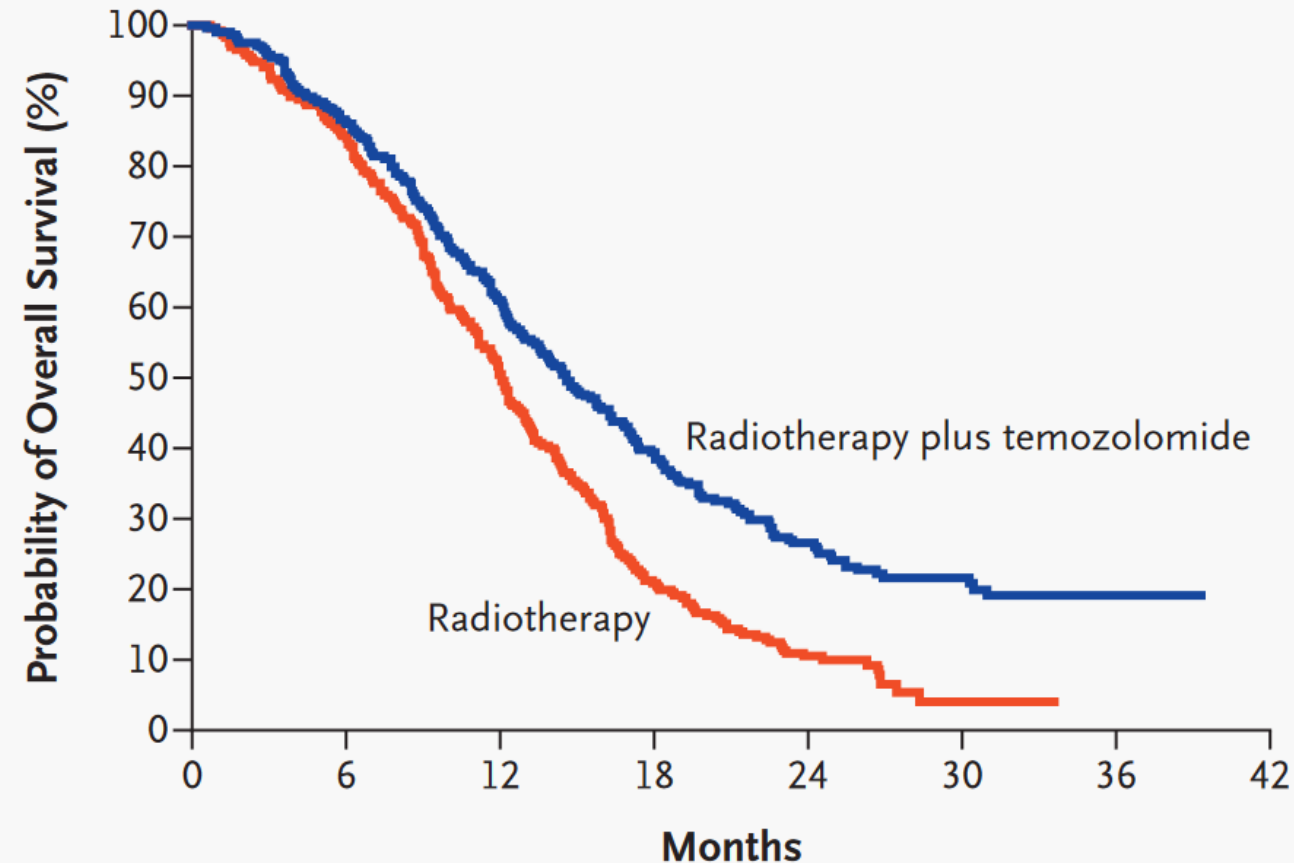
- Nevyléčí 100% lidí – **CNS (GBM)**

*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?

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- 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. <sup>213</sup>	1992	368	S	6.5	7.6
Lieberman et al. <sup>214</sup>	1995	258	A/S	5	27
Adam et al. <sup>212</sup>	1996	597	A/S	6.9	16.3
Sharpe and Moghissi <sup>210</sup>	1996	562	A/S	9	18
Bosset et al. <sup>215</sup>	1997	139	S	3.6	26
Ellis <sup>211</sup>	1999	455	A/S	3.3	24.7

A, adenocarcinoma; S, squamous cell carcinoma.

# Proč vůbec potřeba?

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

Akutní / pozdní

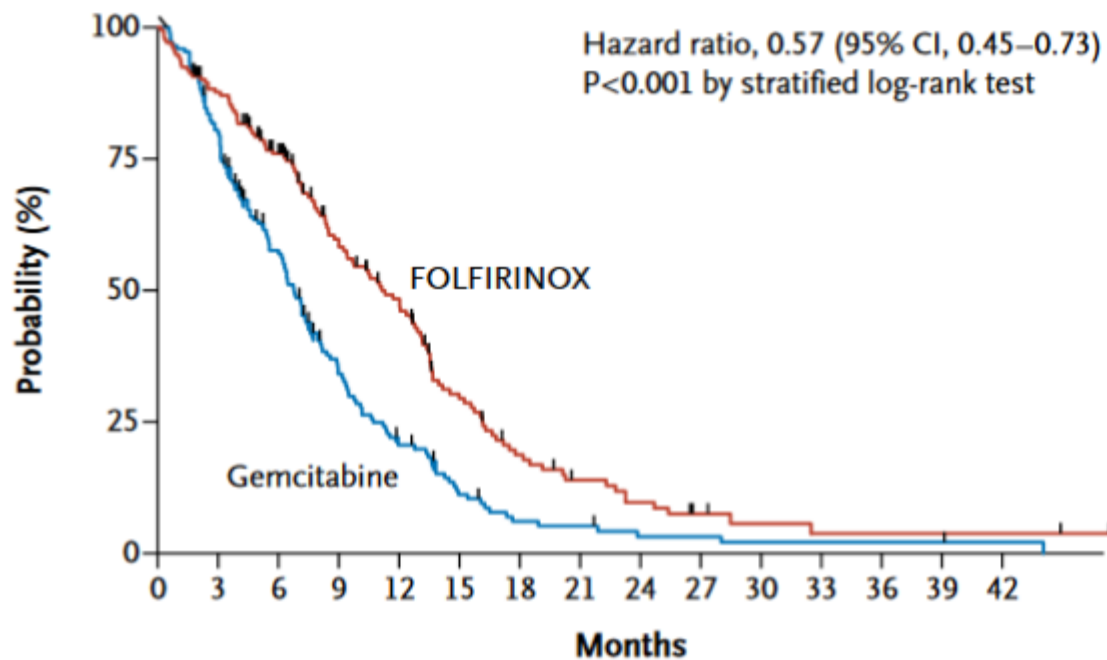


# Proč vůbec potřeba?

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

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

A Overall Survival



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2	2

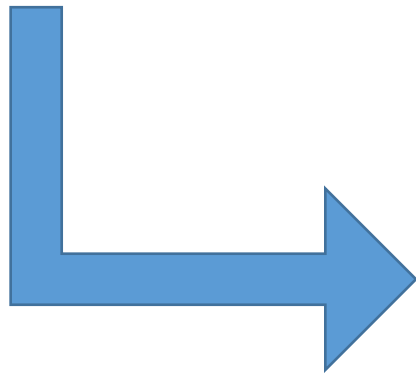
**Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.\***

Event	FOLFIRINOX (N=171) <i>no. of patients/total no. (%)</i>	Gemcitabine (N=171) <i>no. of patients/total no. (%)</i>	P Value
<b>Hematologic</b>			
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
<b>Nonhematologic</b>			
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“?

MAY 28, 2001 [www.time.com](http://www.time.com) AOL Keyword: TIME

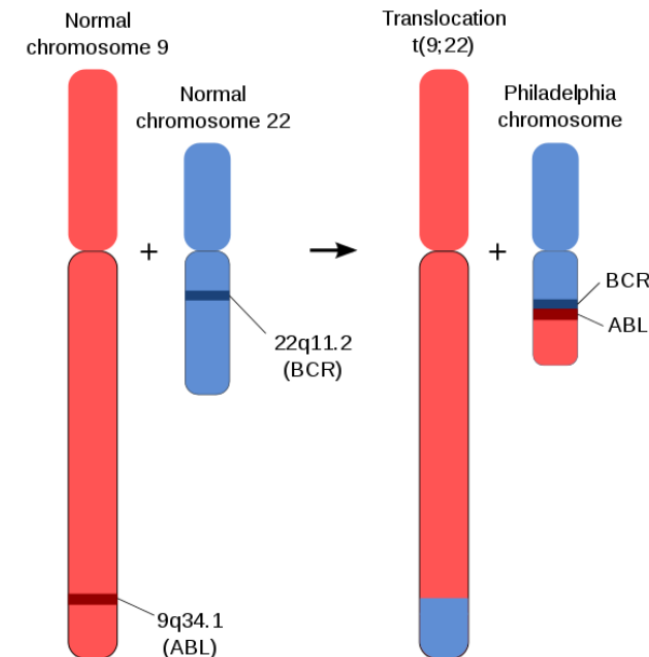
# TIME

THERE IS NEW **AMMUNITION**  
IN THE WAR AGAINST  
**CANCER.**  
**THESE ARE THE BULLETS.**

Revolutionary new pills like **GLEEVEC** combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

# První krůčky

- Chronická myeloidní leukemie
  - U těchto nádorů je častá specifická translokace mezi 9. a 22. chromozomem
    - Vzniká fúzní 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 fúzního genu



# První krůčky

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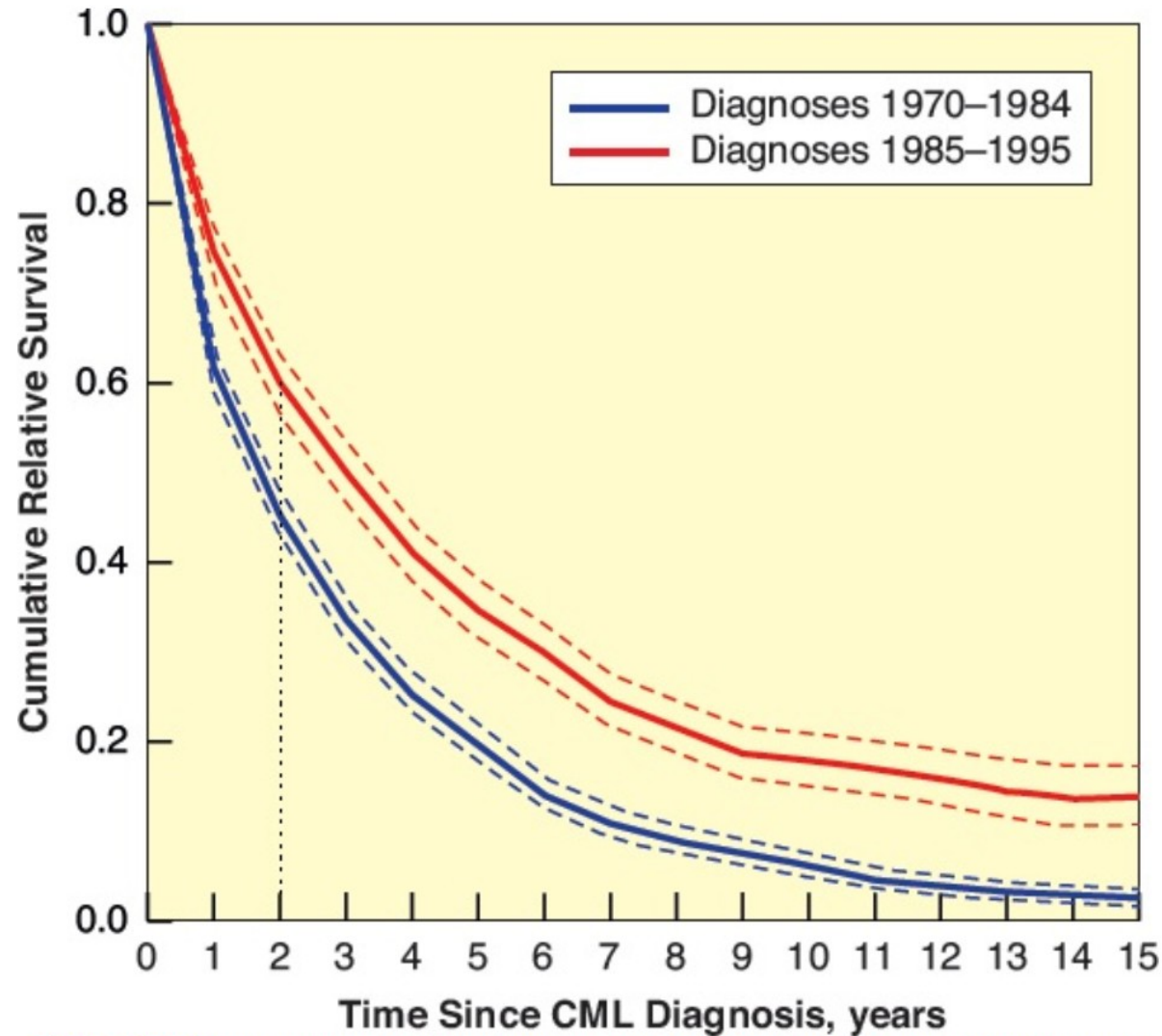
- Ovlivňuje

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

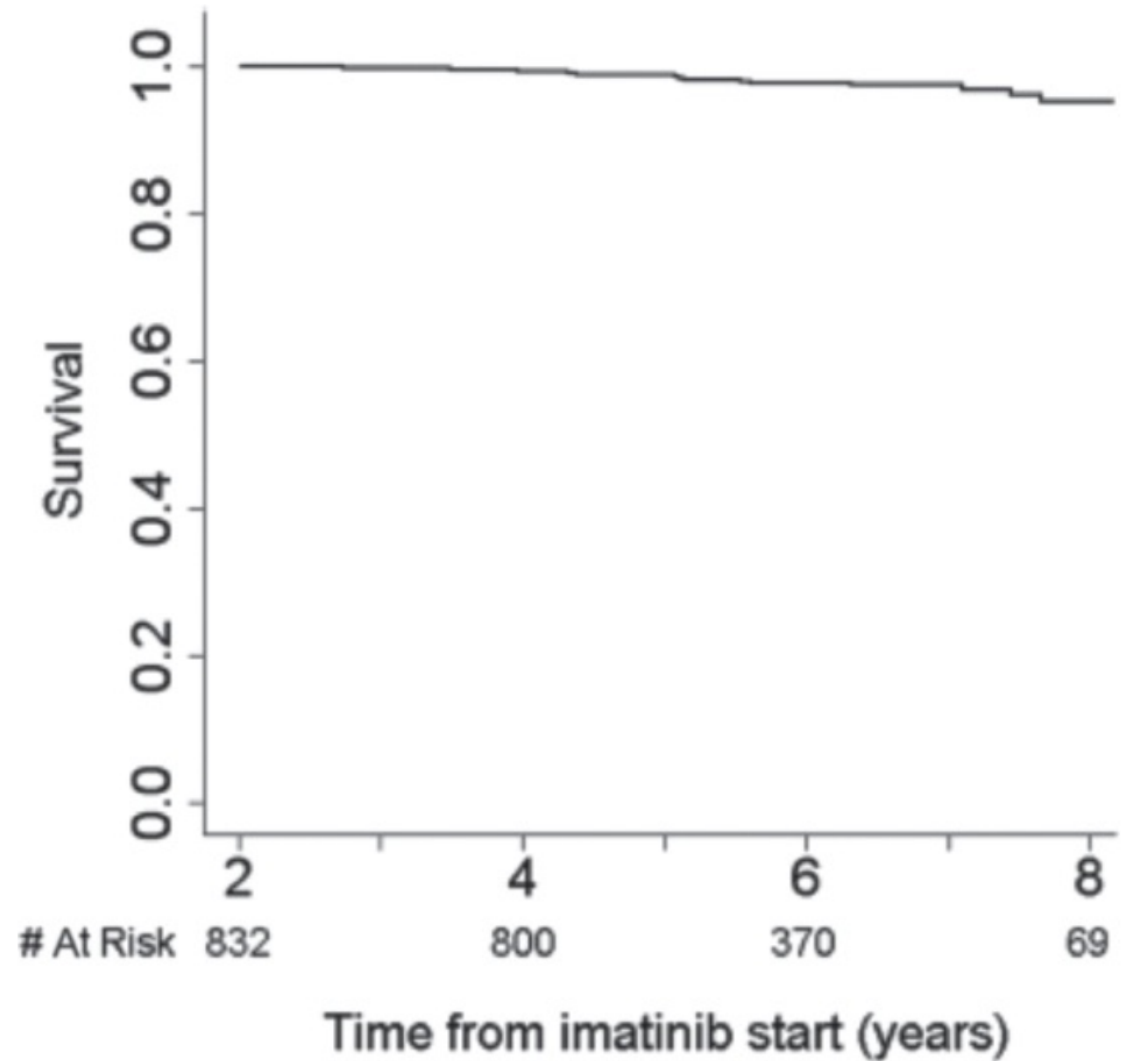
Skoro vše

- Pokud ale porušíme tyrosin kinázovou funkci → ztráta maligního chování
- První cílený lék – imatinib mesylate (gleevec)
  - Vážená 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 Reborá 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

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- relativně specifický – inaktivuje 4 TK

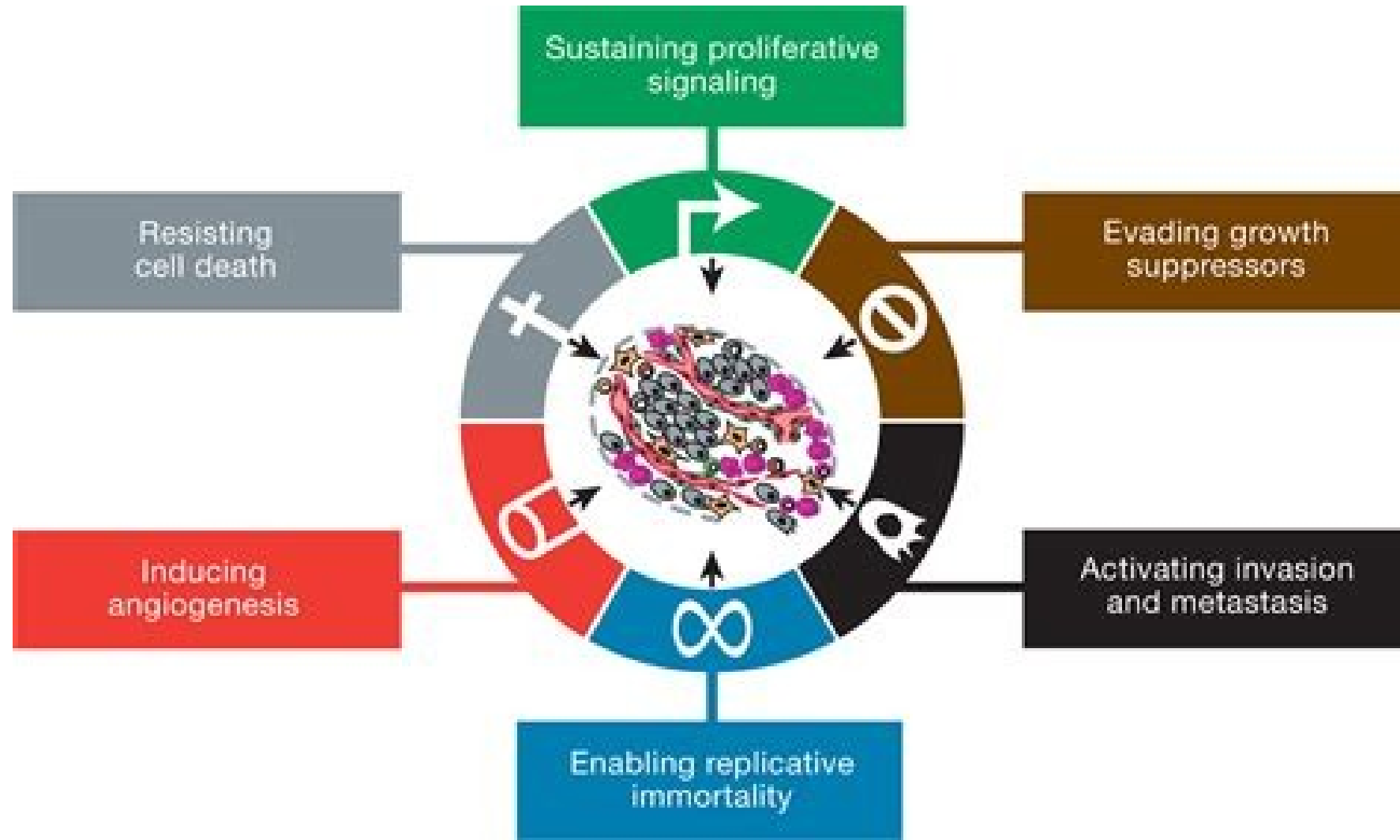
Další je Kit

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

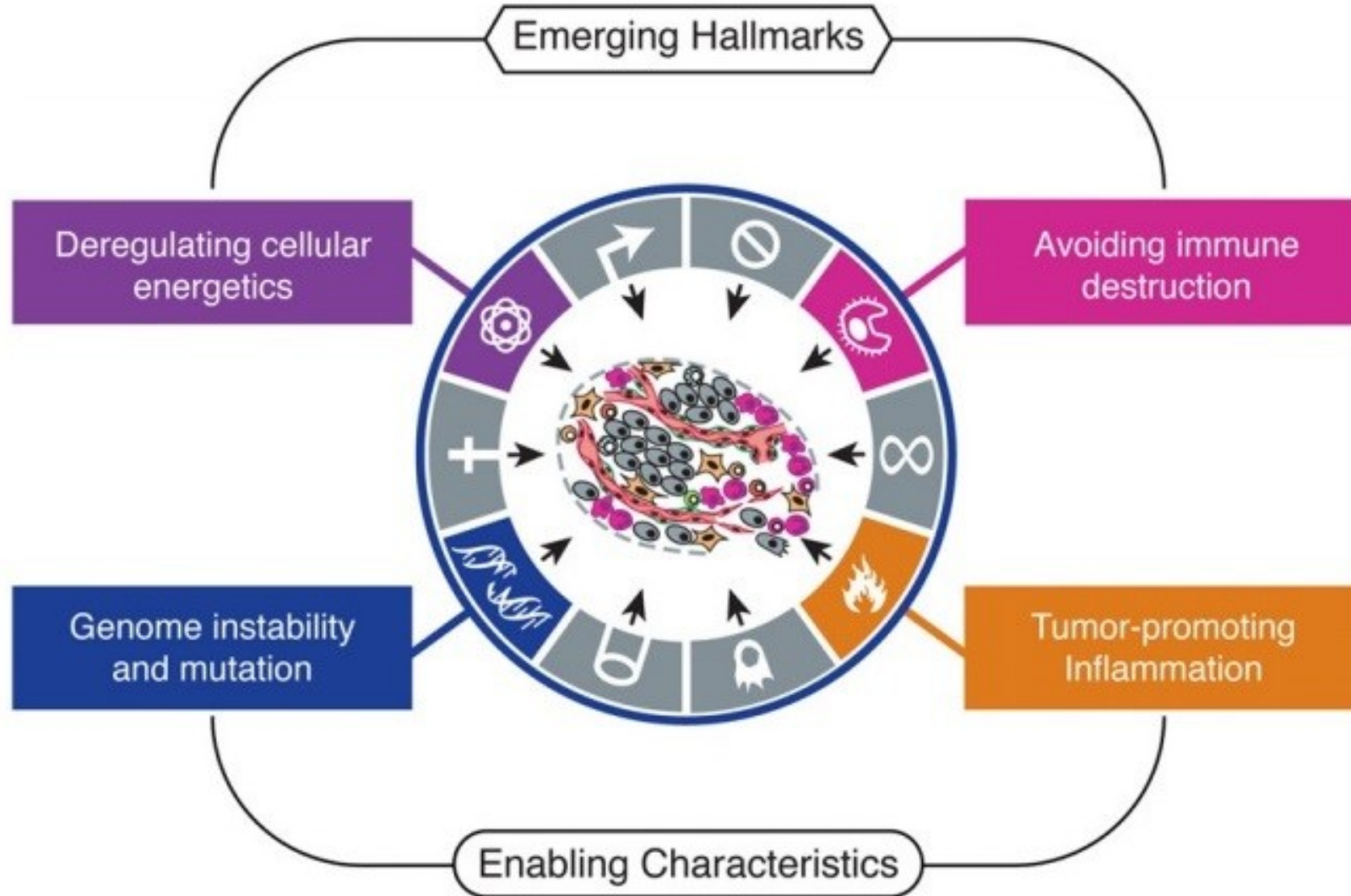


# Hallmarks

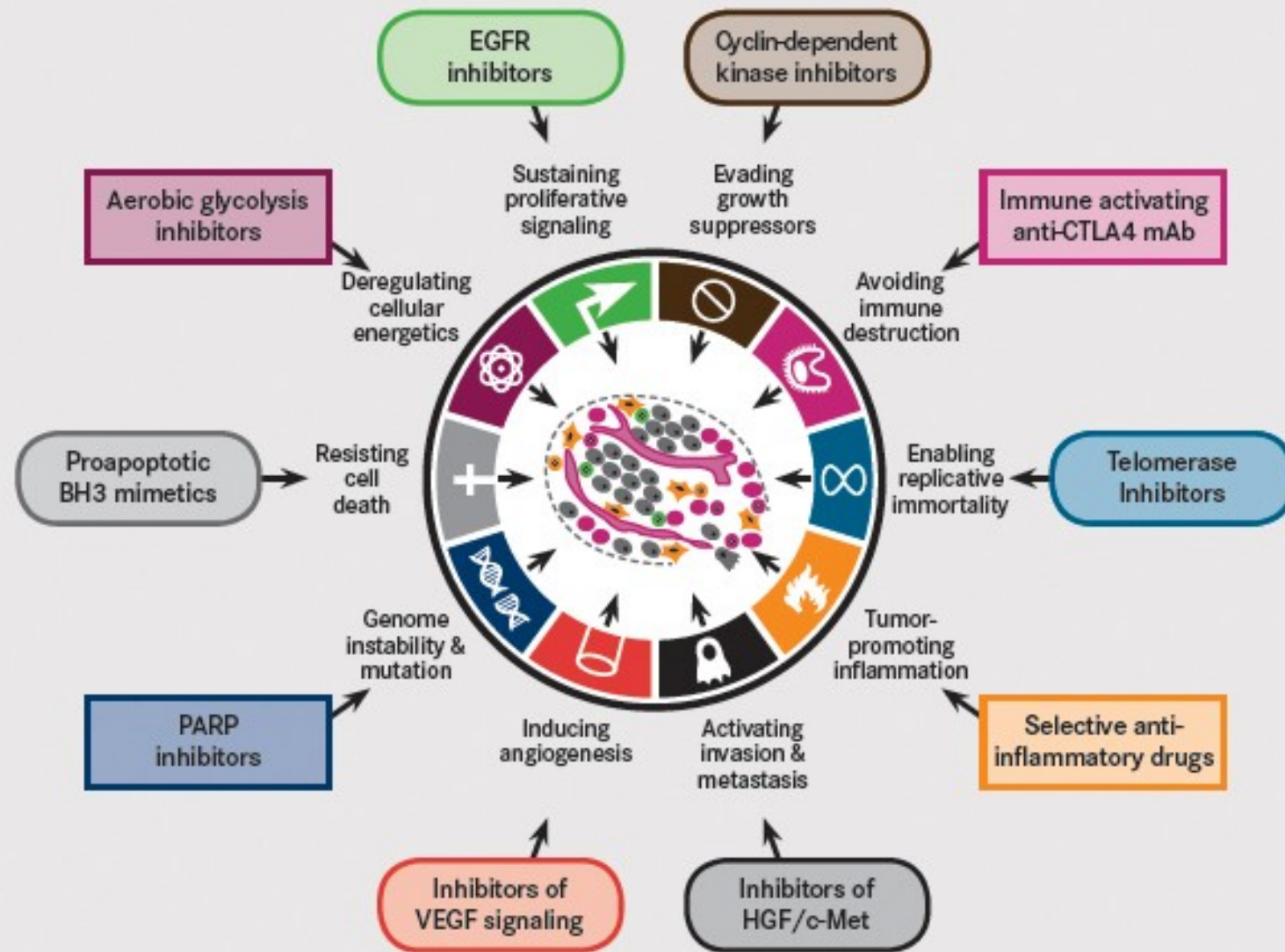
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# Hallmarks



# 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.

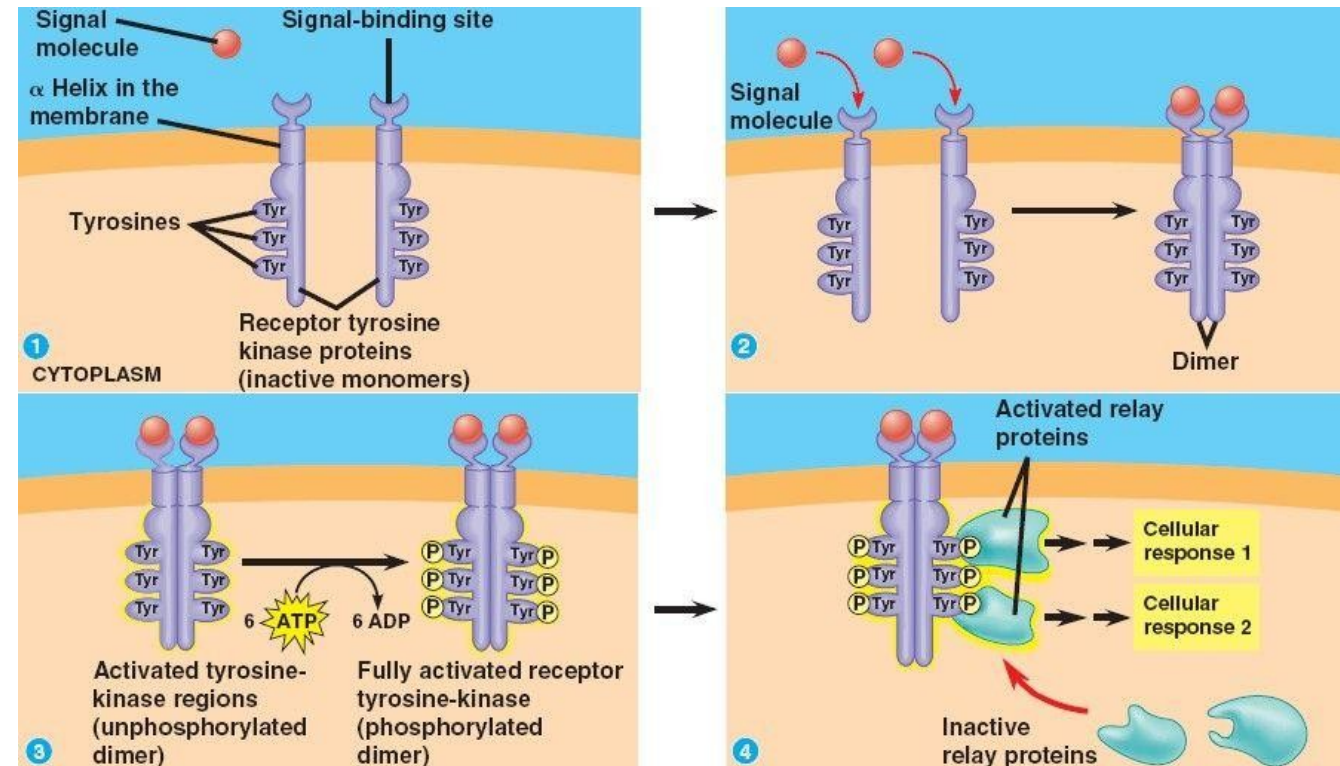
# Typy léků

	Small molecule	Antibody
Target	tyrosine kinase domain	receptor ectodomain
Specificity	+++	++++
Binding	most are rapidly reversible	receptor internalized, only slowly regenerated
Dosing	oral daily	intravenous, $\leq$ 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



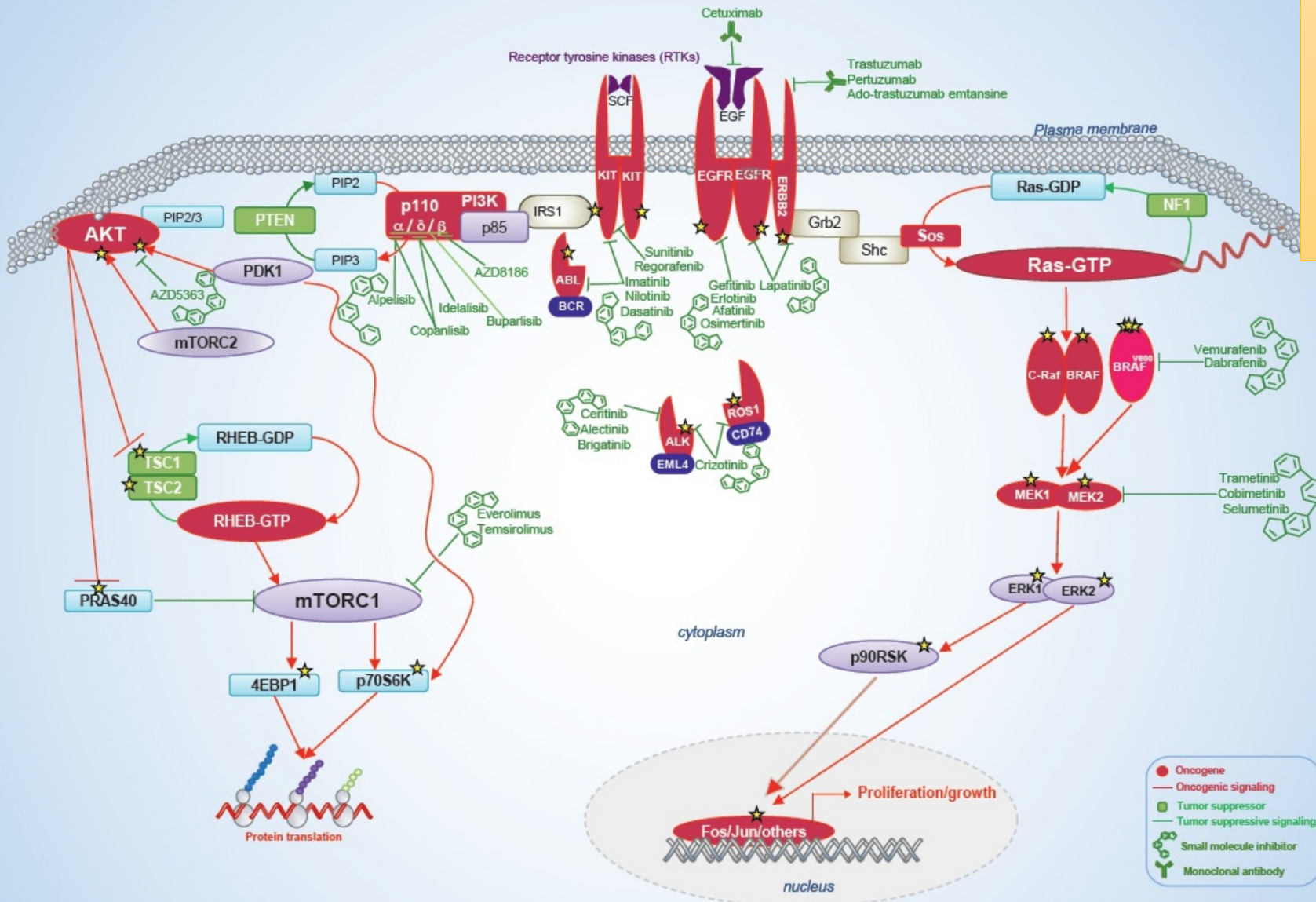
*... intrinsic and acquired resistance are major clinical challenges that limit the effectiveness of this drug class:*

- 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-PDGFR	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.

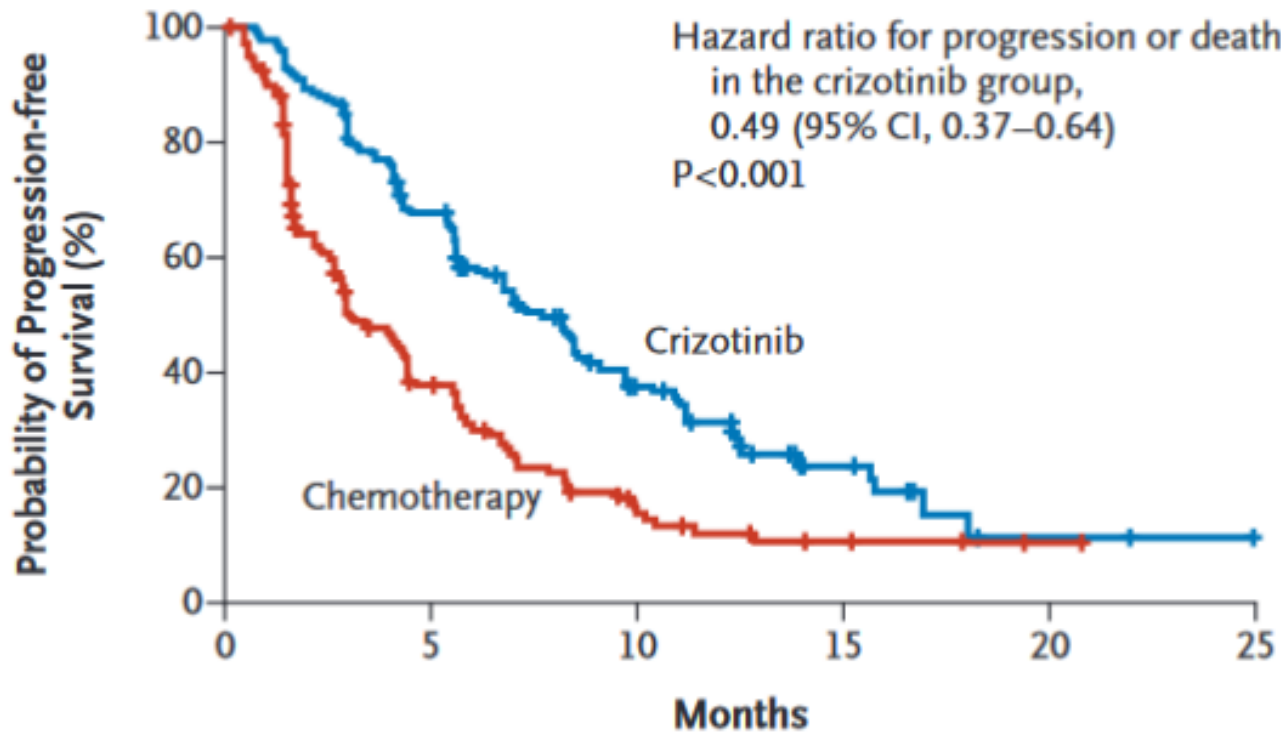
*We conducted a phase 3, open-label trial comparing crizotinib with chemotherapy in 347 patients with locally advanced or metastatic ALK-positive lung cancer...*



# 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)

A Progression-free Survival



## Ceritinib in ALK-Rearranged Non-Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Raneer 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**

No. at Risk

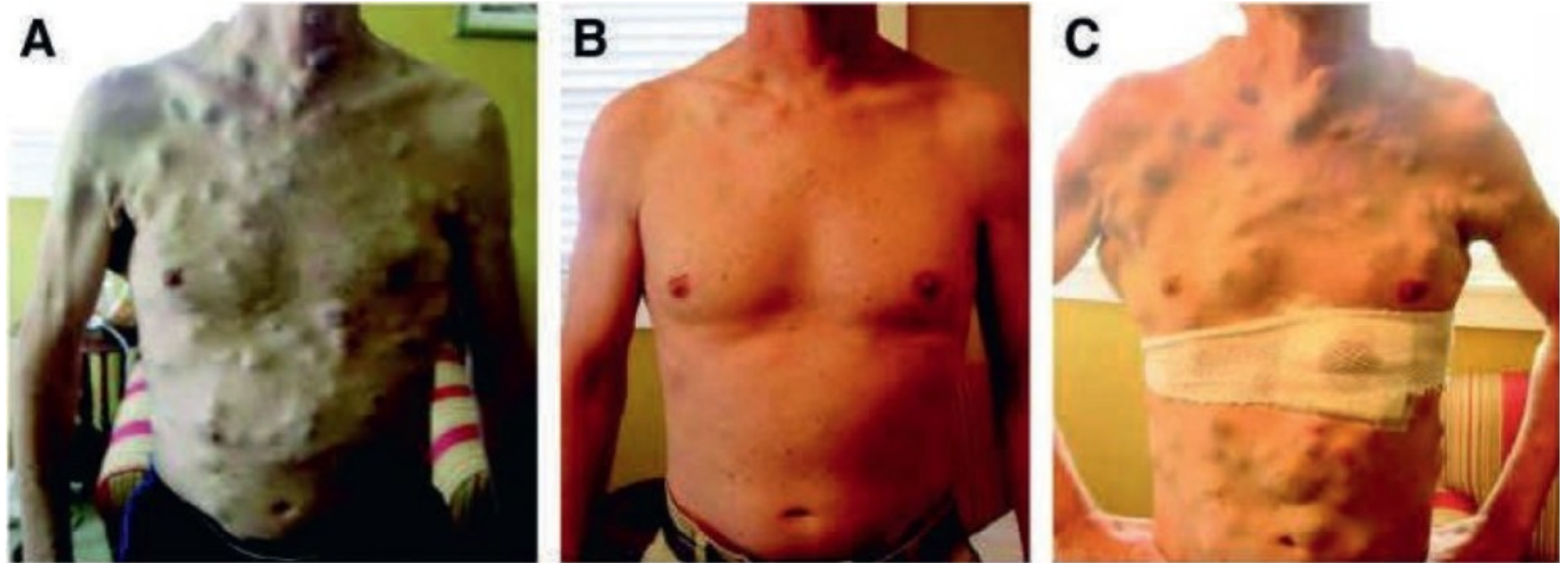
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

# TKIs – BRAF V600E (vemurafenib, dabrafenib)

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- Mutace přítomná u  $\approx$ 50 - 60% melanomů
- Nebývá při mutaci Ras (stejný efekt)
- Pokud RAF wt  $\rightarrow$  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.

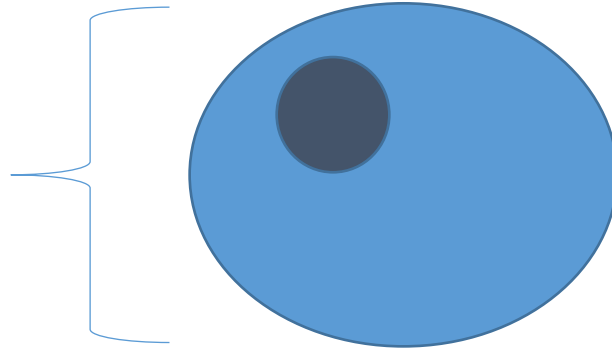
**B:** **After 15 weeks** of therapy with vemurafenib.

**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?

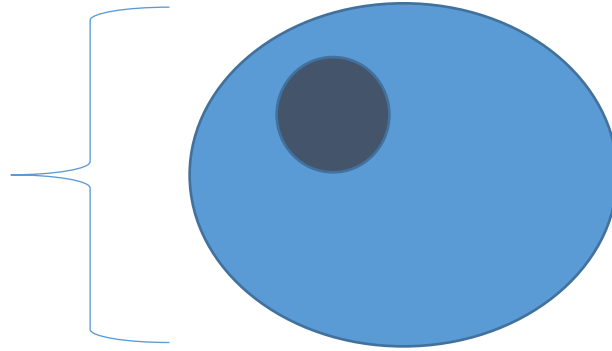
- Jak moc je v nádoru buněk?

- 1buňka  $\approx 10 \mu\text{m}$



- Jak moc je v nádoru buněk?

- 1 buňka  $\approx 10 \mu\text{m}$

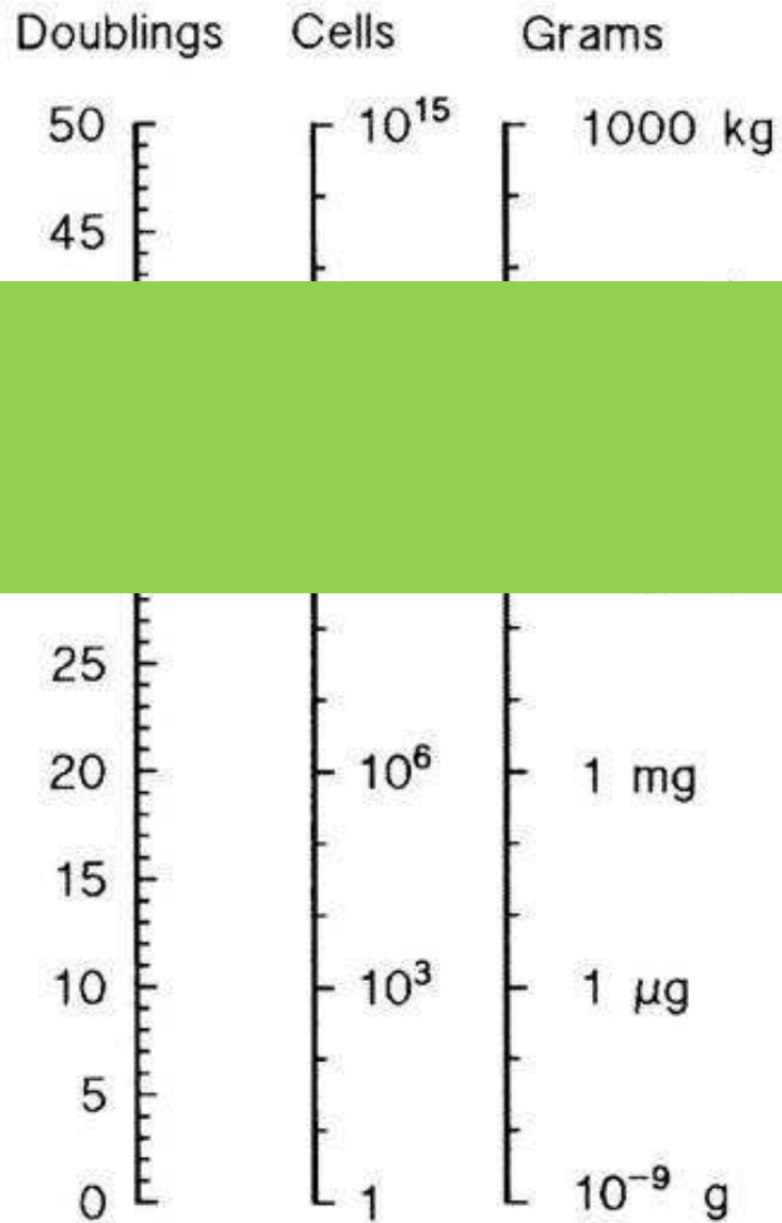


- $1 \text{ mm}^3 = 100 \times 100 \times 100 \text{ buněk} = 10^6 \text{ buněk}$

- $1 \text{ cm}^3 = 10^9 \text{ buněk}$

- 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

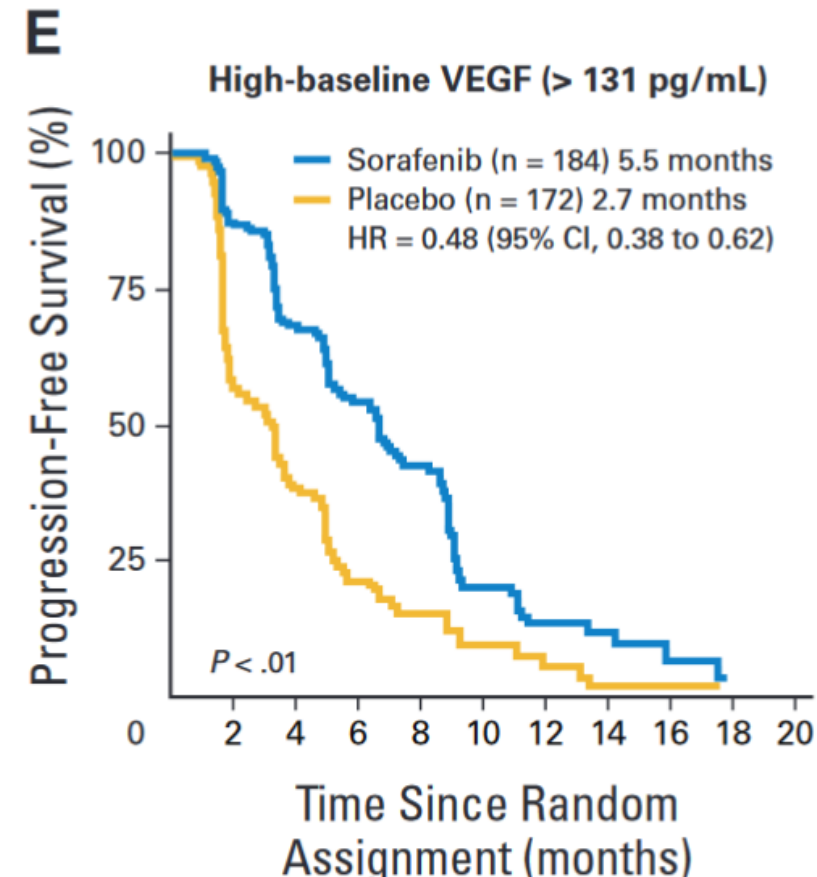
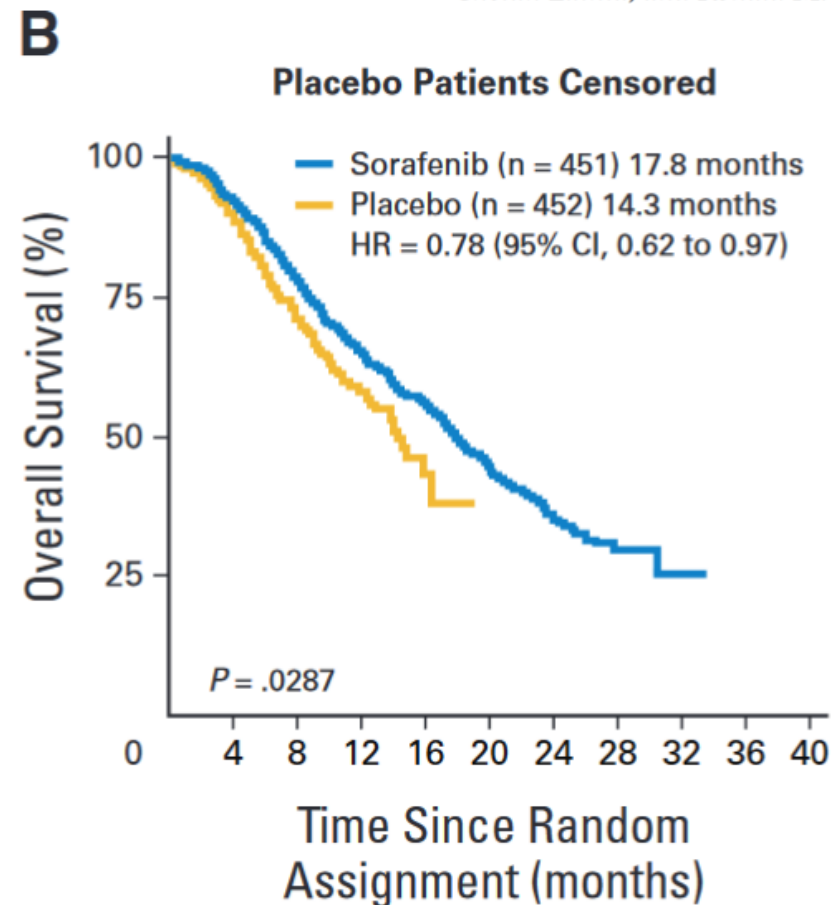
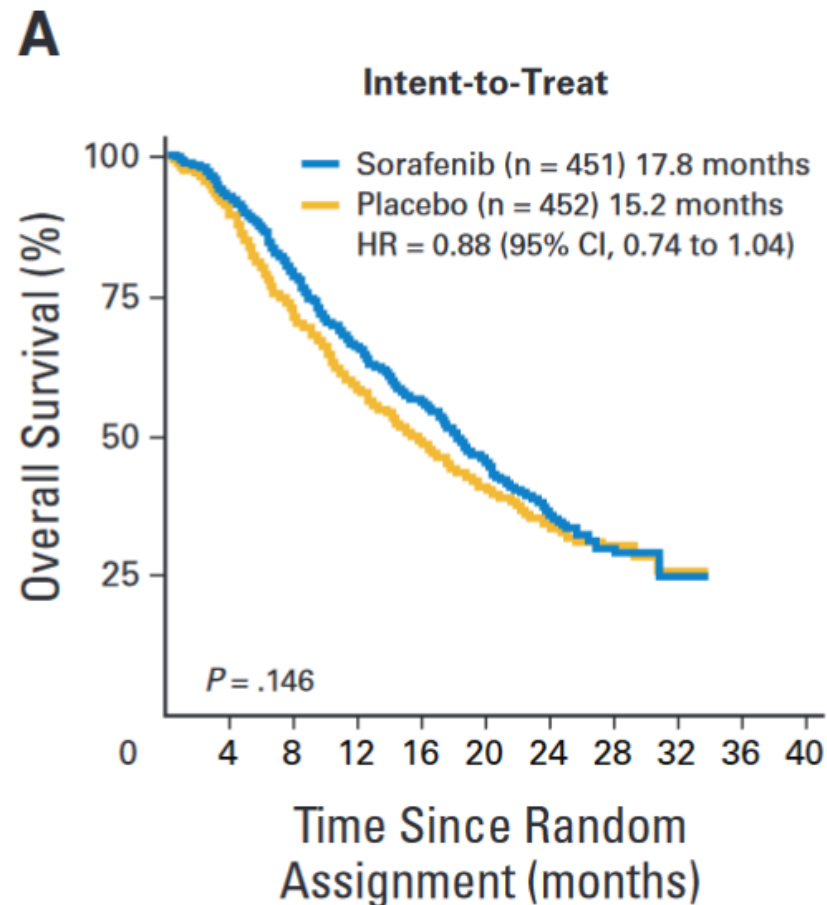
99,9999999% cell death: Complete remission, Local control, Cure if no metastasis

# 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





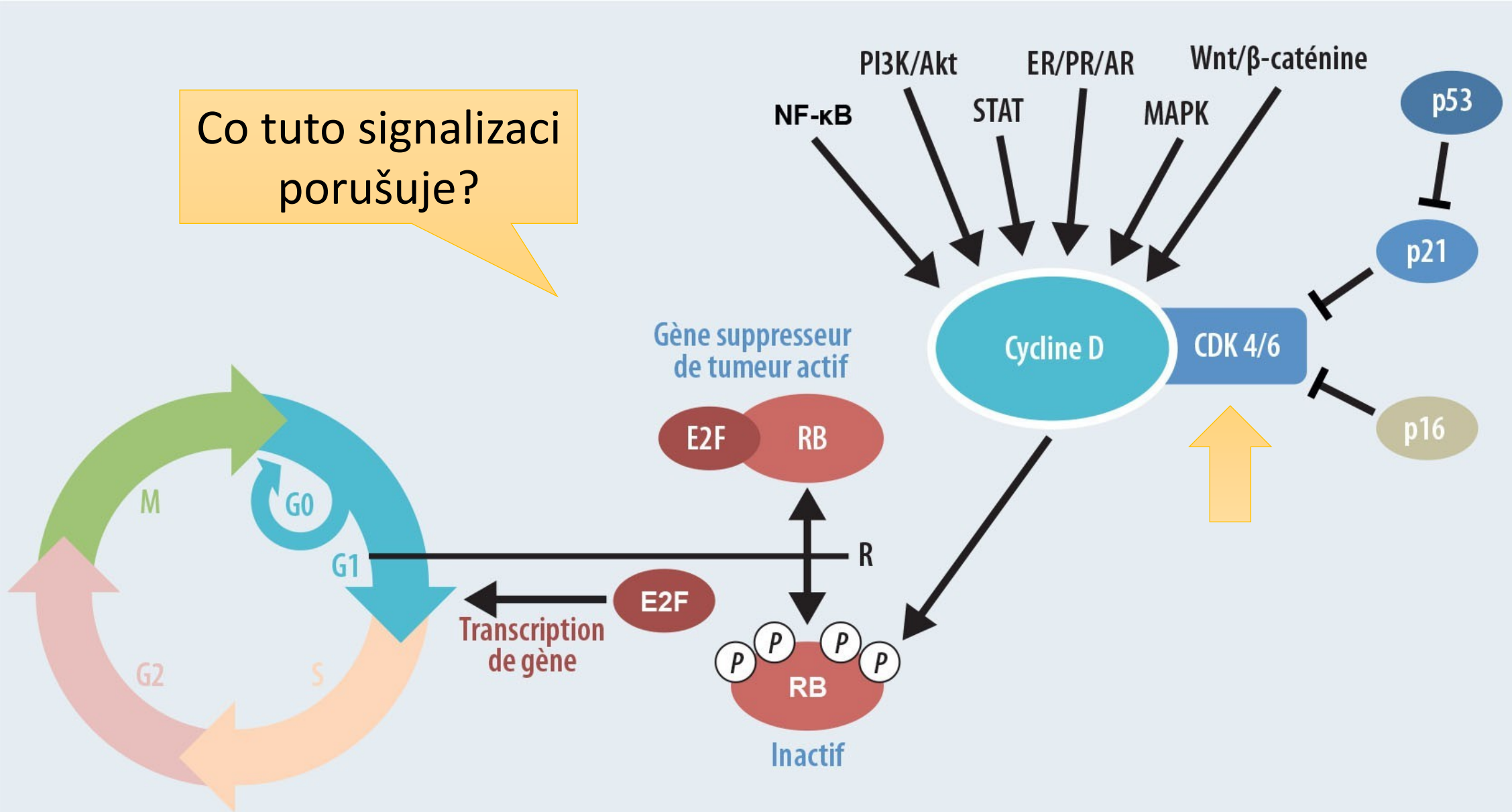
# Multi TKIs – sorafenib, sunitinib

---

- 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)

Co tuto signalizaci porušuje?



# CDK4/6 TKIs (palbociclib, ribociclib, abemaciclib)

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 17, 2016

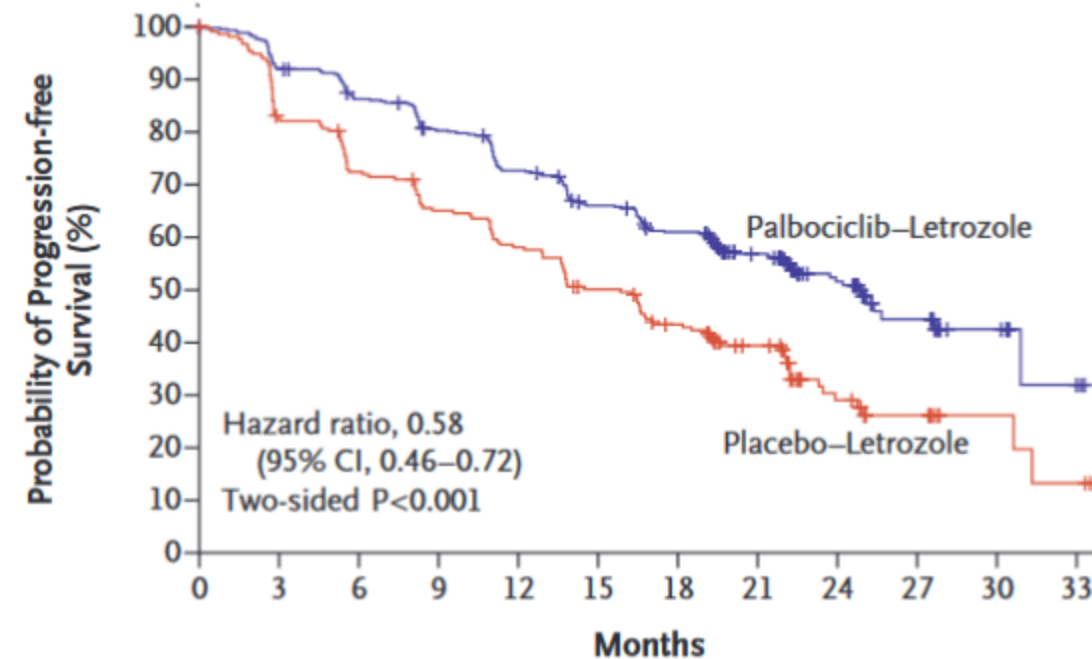
VOL. 375 NO. 20

## 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.

### A Investigator Assessment



#### 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

Gene A   Gene B   Cell survival?

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

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

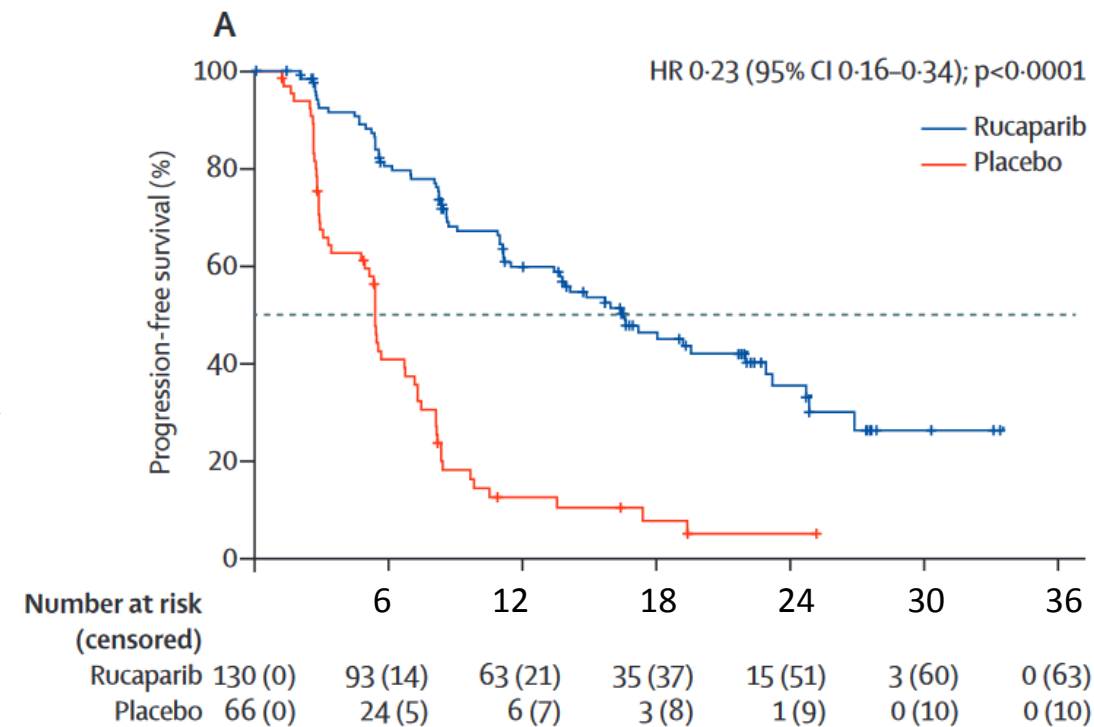
## Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial

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)

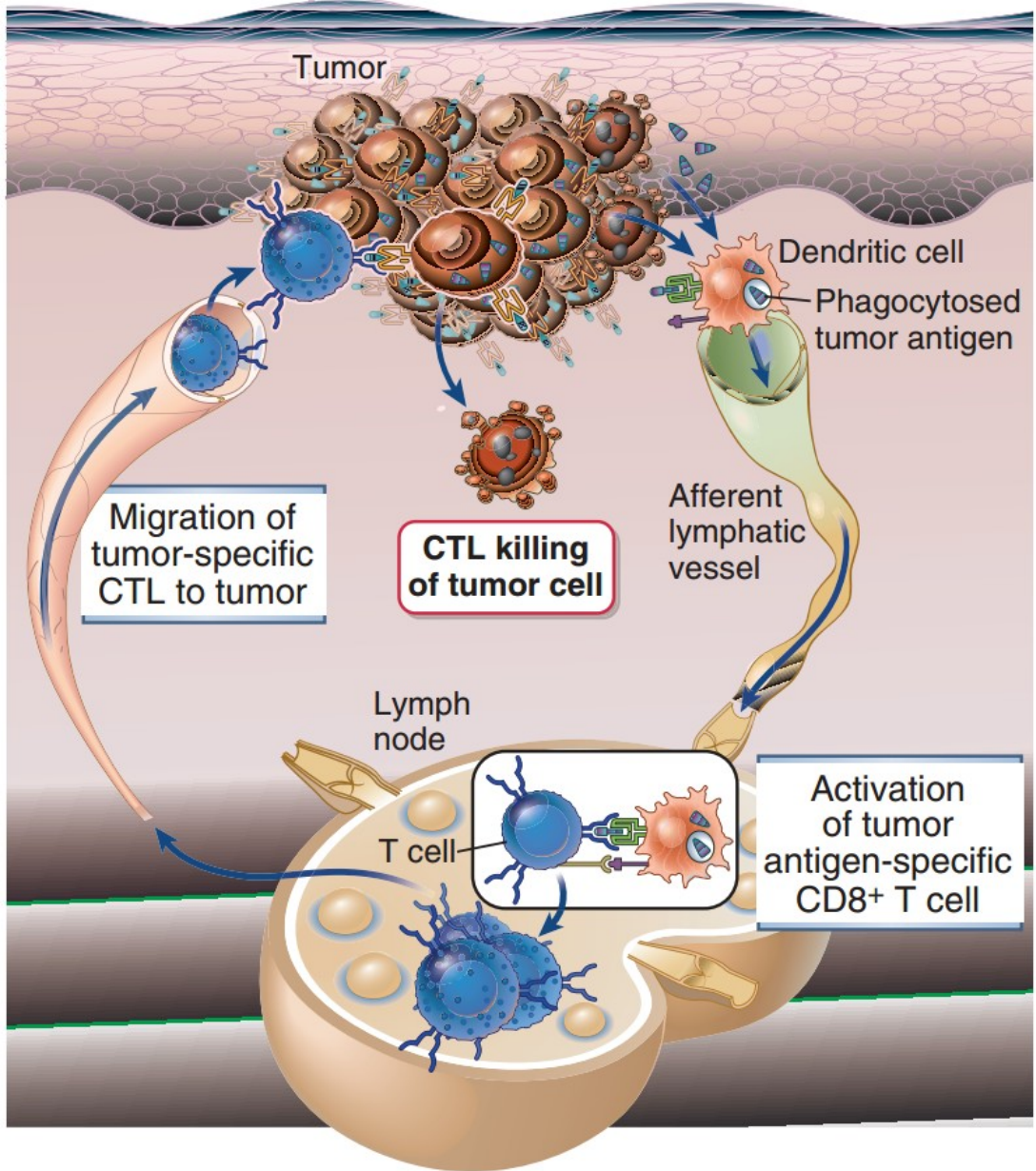
CEA

T lymfocyty = CD8+ CTLs

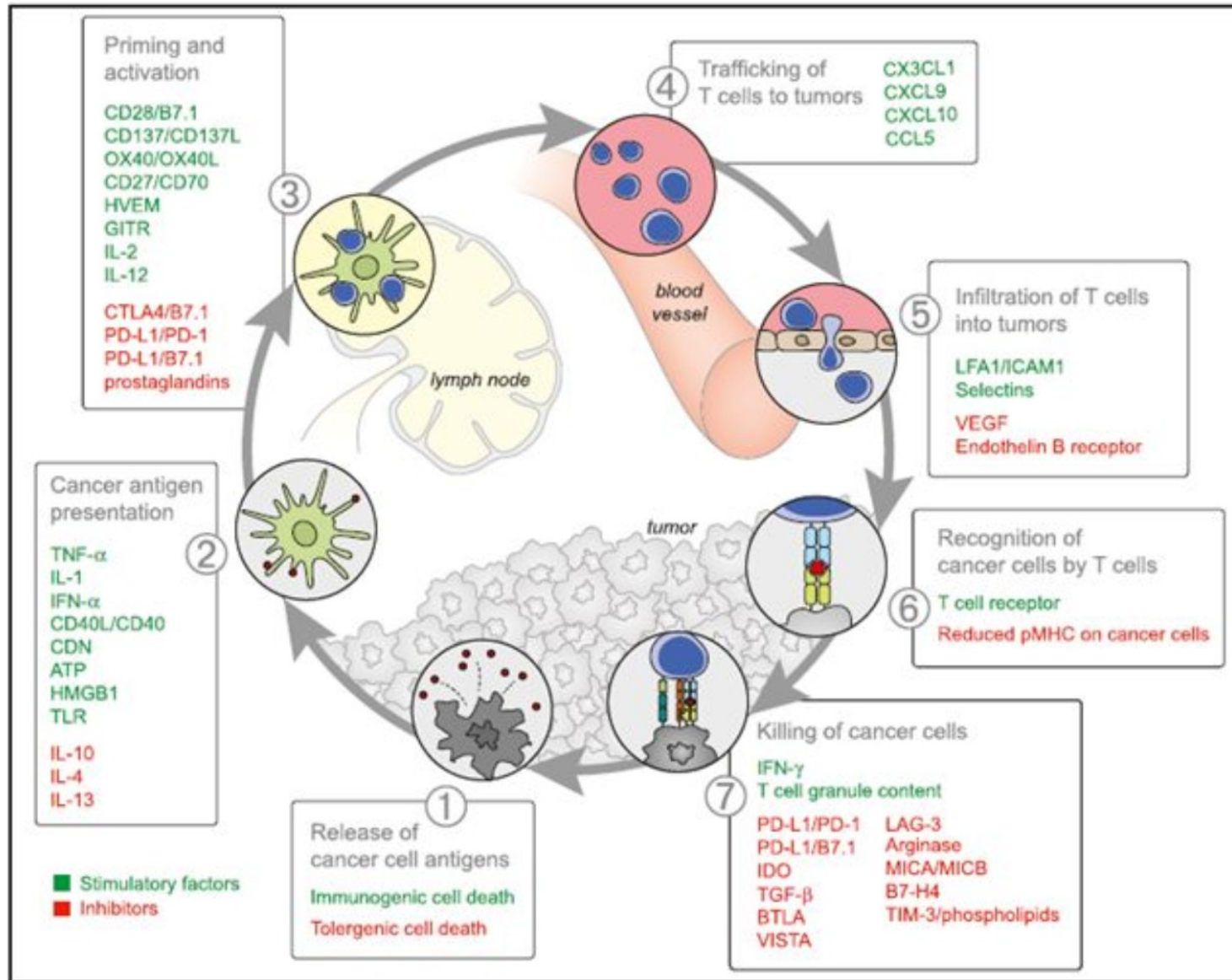




# Imunitní systém

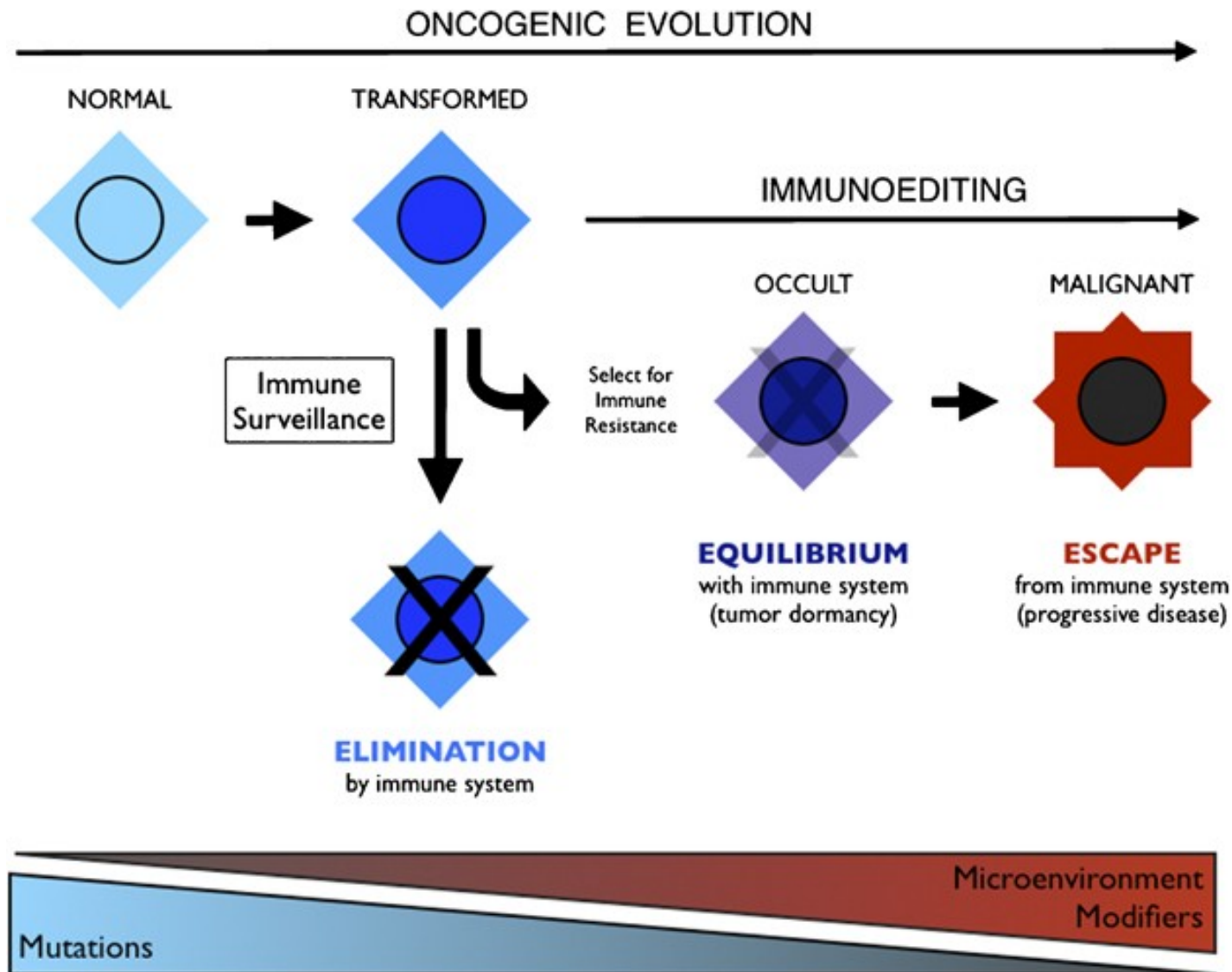


# Imunitní systém



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

# Imunitní systém

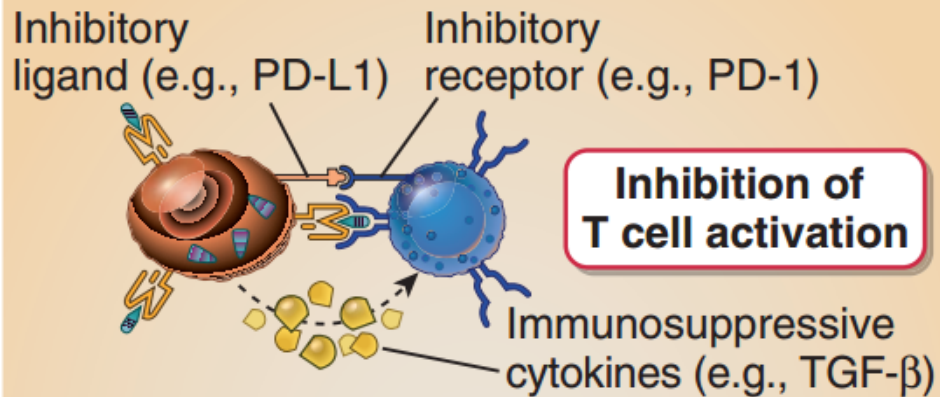


Makroskopické nádory se už imunitě úspěšně vyhly



# Imunitní systém – obrana nádorů

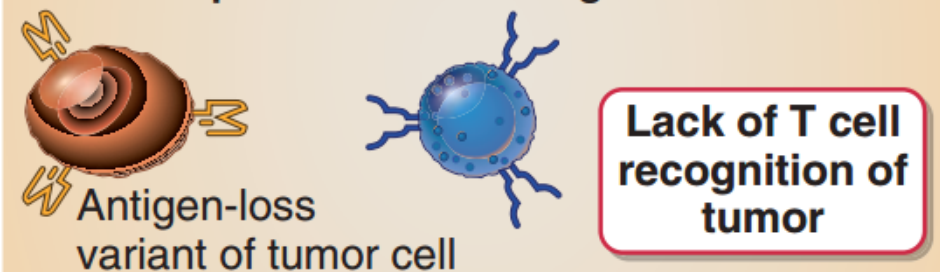
Production of immunosuppressive proteins or expression of inhibitory cell surface proteins



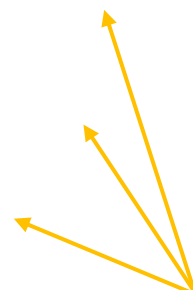
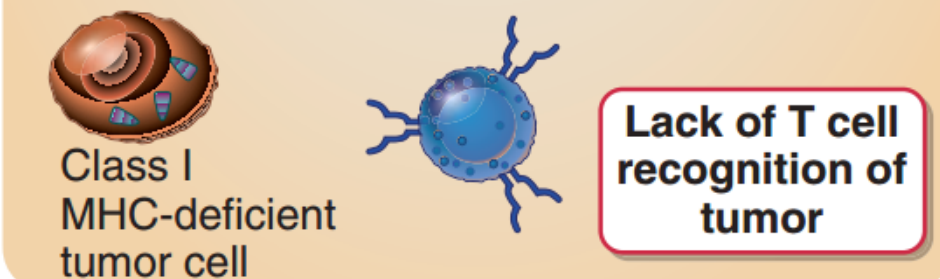
CTLA-4  
PD-1

Blokují  
aktivaci CTLs

Failure to produce tumor antigen



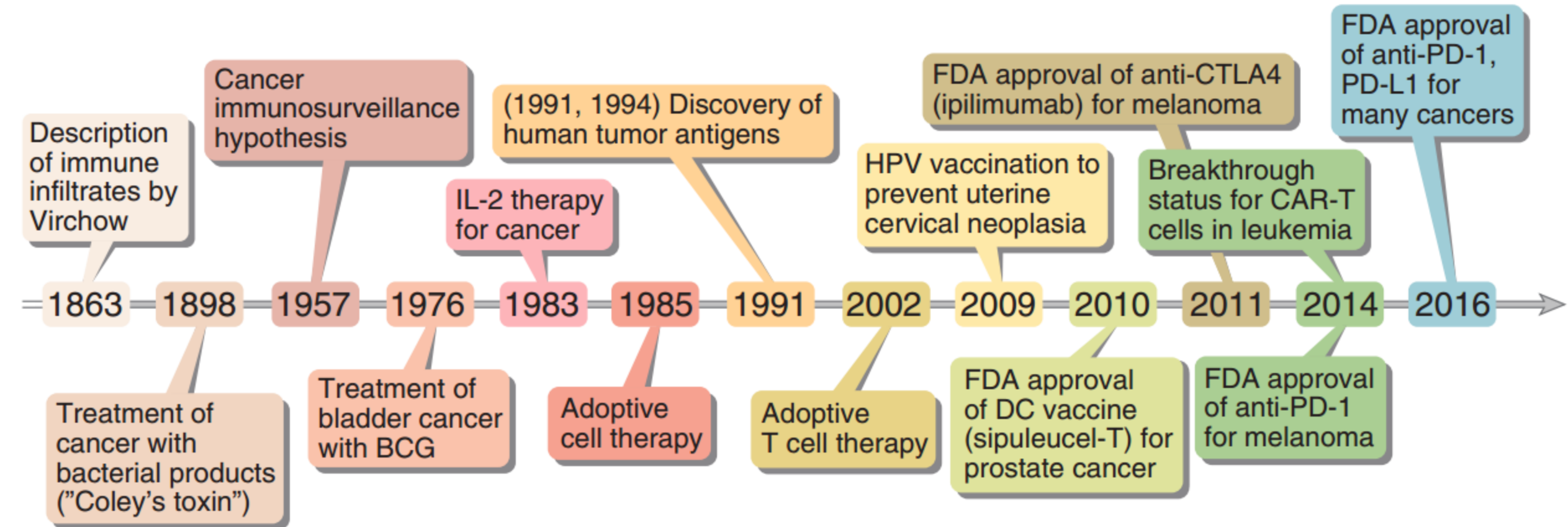
Mutations in MHC genes or genes needed for antigen processing



Nenastává u myši s poruchou adaptivní imunity

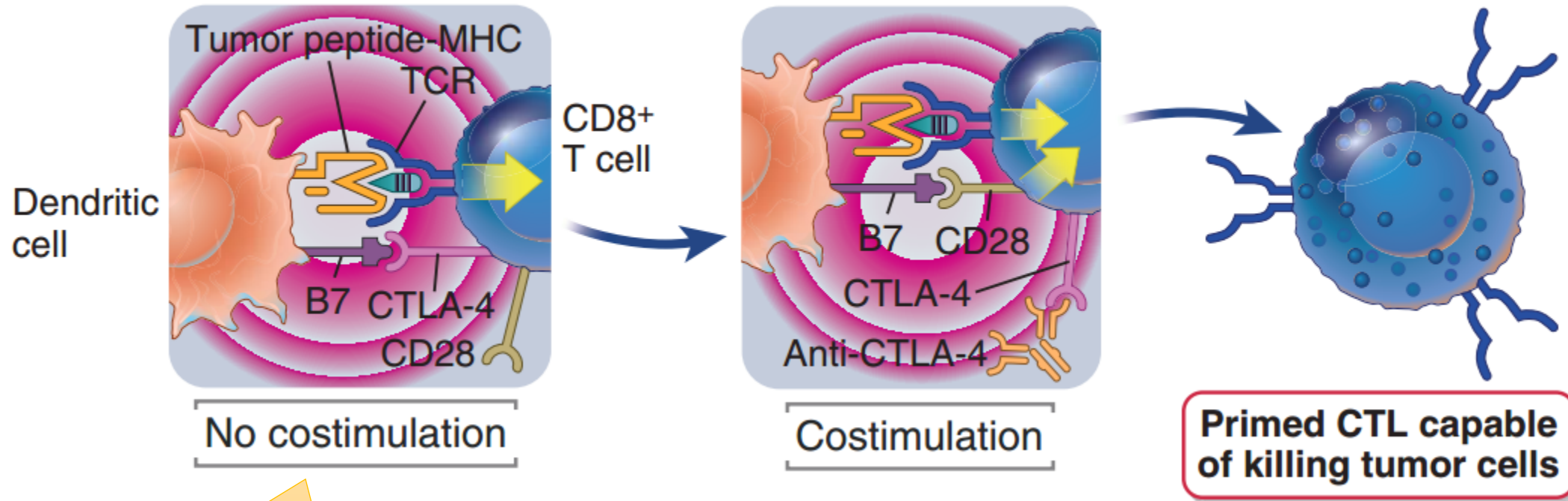


# Imunitní systém



# Blokování CTLs

## A Induction of antitumor immune response in lymph node



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

Funkce: limitace imunitní reakce

„Checkpoint 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

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AUGUST 19, 2010

VOL. 363 NO. 8

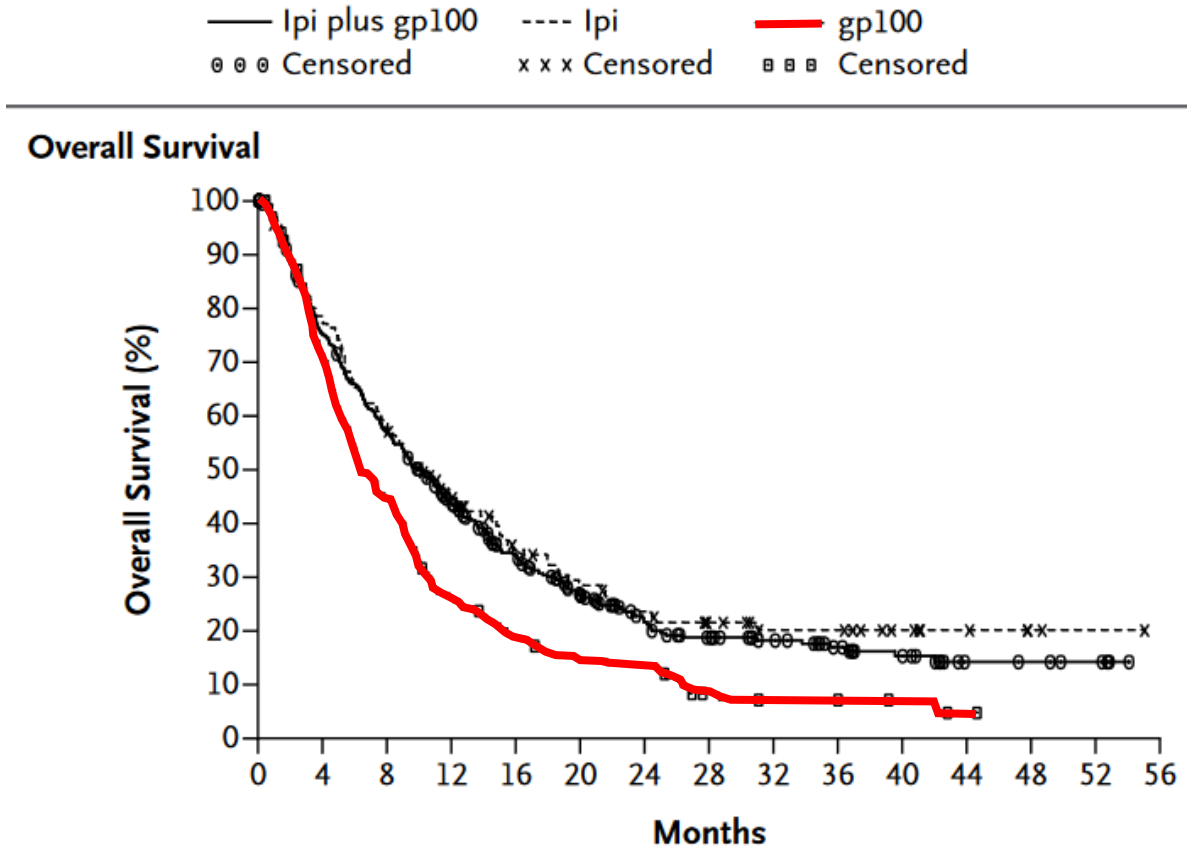
### Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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 Qirt, 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. Urban, 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;  $P < 0.001$ )



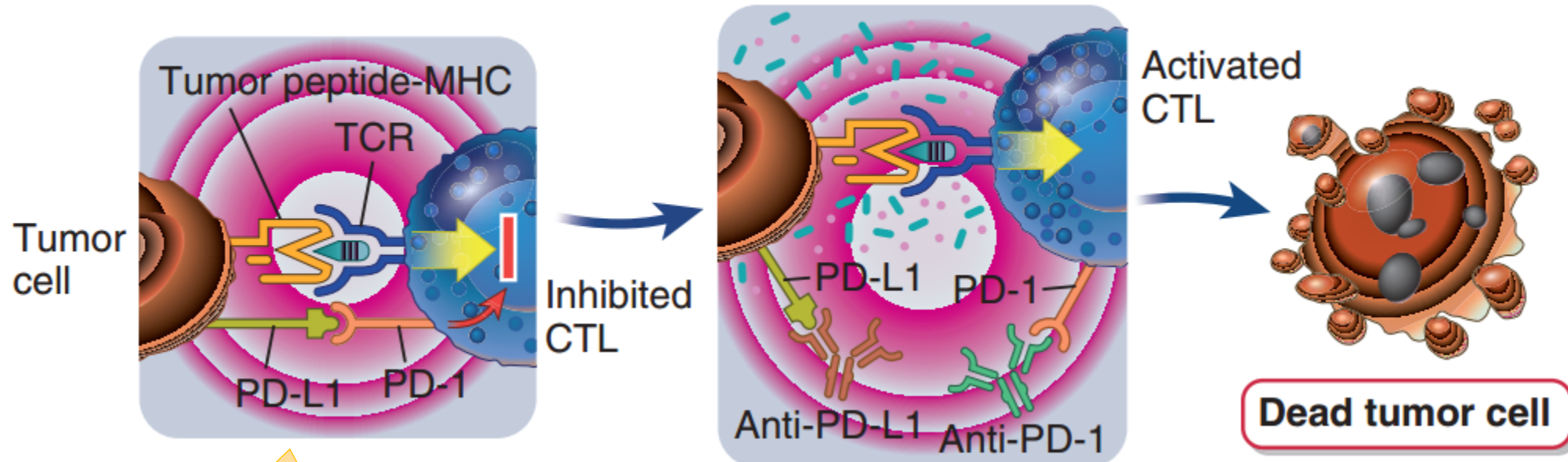
## No. at Risk

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

## B CTL-mediated killing of tumor cells



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

„Checkpoint inhibitory“  
(„matoucí“ termín)

# Protilátky proti PD-1 / PD-L1

Target	Agent	Year Approved	Tumor	Stage	Indication
PD-1	Nivolumab	2014	Melanoma	<ul style="list-style-type: none"> <li>Unresectable</li> <li>Metastatic</li> </ul>	
		2015	NSCLC	<ul style="list-style-type: none"> <li>Metastatic</li> </ul>	Progressing after PC, EGFR-TKI, ALK-TKI
		2015	Renal cell carcinoma	<ul style="list-style-type: none"> <li>Metastatic</li> </ul>	
		2016	Classical Hodgkin lymphoma	<ul style="list-style-type: none"> <li>Relapsed</li> <li>Refractory</li> </ul>	<ul style="list-style-type: none"> <li>Adults</li> <li>Progressing after ASCT + brentuximab vedotin</li> <li>Progressing after ≥3 lines of therapy, including ASCT</li> </ul>
		2016	HNSCC	<ul style="list-style-type: none"> <li>Recurrent</li> <li>Metastatic</li> </ul>	Progressing after PC
		2017	dMMR or MSI-H colorectal cancer	<ul style="list-style-type: none"> <li>Metastatic</li> </ul>	Progressing after chemotherapy: 5-FU, oxaliplatin, irinotecan
		2017	Urothelial carcinoma	<ul style="list-style-type: none"> <li>Locally advanced</li> <li>Metastatic</li> </ul>	Progressing after PC
		2017	Hepatocellular carcinoma	<ul style="list-style-type: none"> <li>Unresectable</li> <li>Metastatic</li> </ul>	Progressing after sorafenib
		2017	Melanoma	<ul style="list-style-type: none"> <li>Completely resected</li> <li>Lymph node involvement</li> <li>Metastatic</li> </ul>	Adjuvant

# Protilátky proti PD-1 / PD-L1

Target	Agent	Year Approved	Tumor	Stage	Indication
PD-1	Pembrolizumab	2014	Melanoma	<ul style="list-style-type: none"> <li>■ Unresectable</li> <li>■ Metastatic</li> </ul>	
		2015	NSCLC	<ul style="list-style-type: none"> <li>■ Advanced</li> <li>■ Metastatic <i>and</i> PD-L1 &gt;1%</li> </ul>	Progressing after PC
		2016	NSCLC	<ul style="list-style-type: none"> <li>■ Metastatic <i>and</i> PD-L1 &gt;50%</li> </ul>	First line
		2016	HNSCC	<ul style="list-style-type: none"> <li>■ Recurrent</li> <li>■ Metastatic</li> </ul>	Heavily pretreated
		2017	NSCLC	<ul style="list-style-type: none"> <li>■ Advanced</li> <li>■ Metastatic</li> <li>■ Any PD-L1 expression level</li> </ul>	First line <i>in combination with</i> carboplatin + pemetrexed chemotherapy
		2017	Classical Hodgkin lymphoma	<ul style="list-style-type: none"> <li>■ Relapsed</li> <li>■ Refractory</li> </ul>	<ul style="list-style-type: none"> <li>■ Adults, children</li> <li>■ Progressing after ≥3 lines of therapy</li> </ul>
		2017	Any dMMR or MSI-H cancers	<ul style="list-style-type: none"> <li>■ Unresectable</li> <li>■ Metastatic</li> </ul>	Progressing after all standard therapy
		2017	Urothelial carcinoma	<ul style="list-style-type: none"> <li>■ Locally advanced</li> <li>■ Metastatic</li> </ul>	
		2017	Gastric/GEJ adenocarcinoma	<ul style="list-style-type: none"> <li>■ Recurrent</li> <li>■ Locally advanced</li> <li>■ Metastatic</li> </ul>	<ul style="list-style-type: none"> <li>■ CPS ≥1</li> <li>■ Progressing after ≥2 lines of 5-FU, PC, anti-HER2/neu</li> </ul>
		2018	Cervical cancer	<ul style="list-style-type: none"> <li>■ Recurrent</li> <li>■ Metastatic</li> </ul>	<ul style="list-style-type: none"> <li>■ CPS ≥1</li> <li>■ Progressing after ≥1 line of chemotherapy</li> </ul>
		2018	PMBCL	<ul style="list-style-type: none"> <li>■ Relapsed</li> <li>■ Refractory</li> </ul>	<ul style="list-style-type: none"> <li>■ Adults, children</li> <li>■ Progressing after ≥3 lines of therapy</li> </ul>

# Protilátky proti PD-1 / PD-L1

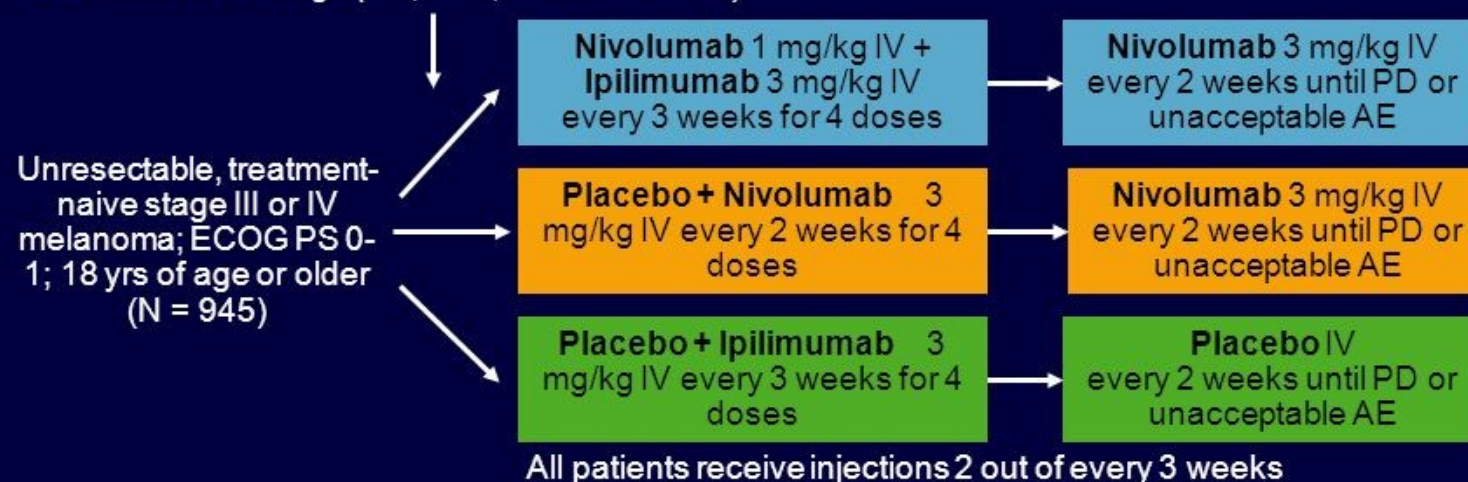
Target	Agent	Year Approved	Tumor	Stage	Indication
PD-L1	Atezolizumab	2016	NSCLC	<ul style="list-style-type: none"> <li>Metastatic</li> </ul>	Progressing after PC
		2016	Urothelial carcinoma	<ul style="list-style-type: none"> <li>Locally advanced</li> <li>Metastatic</li> </ul>	Progressing after PC
		2017	Urothelial carcinoma	<ul style="list-style-type: none"> <li>Locally advanced</li> <li>Metastatic</li> </ul>	<ul style="list-style-type: none"> <li>First line: ineligible for cisplatin-based chemotherapy</li> <li>Second line: progressing after PC</li> </ul>
PD-L1	Durvalumab	2017	Urothelial carcinoma	<ul style="list-style-type: none"> <li>Locally advanced</li> <li>Metastatic</li> </ul>	Progressing after PC
		2018	NSCLC	<ul style="list-style-type: none"> <li>Unresectable stage III</li> </ul>	<ul style="list-style-type: none"> <li>Consolidation</li> <li>No progression after chemoradiation</li> </ul>
PD-L1	Avelumab	2017	Urothelial carcinoma	<ul style="list-style-type: none"> <li>Locally advanced</li> <li>Metastatic</li> </ul>	Progressing after PC
		2017	Merkel cell carcinoma	<ul style="list-style-type: none"> <li>Metastatic</li> </ul>	<ul style="list-style-type: none"> <li>Adults, children &gt;12 y old</li> </ul>

# Protilátky proti PD-1 / PD-L1

## Checkmate-067: Nivo + Ipi vs Nivo vs Ipi for First-line Treatment of Melanoma

- A randomized, double-blind phase III study

*Stratified by tumor PD-L1 status (positive vs negative/indeterminate), BRAF mutation status (V600 mutation–positive vs wild-type), and AJCC metastasis stage (M0, M1a, or M1b vs. M1c)*

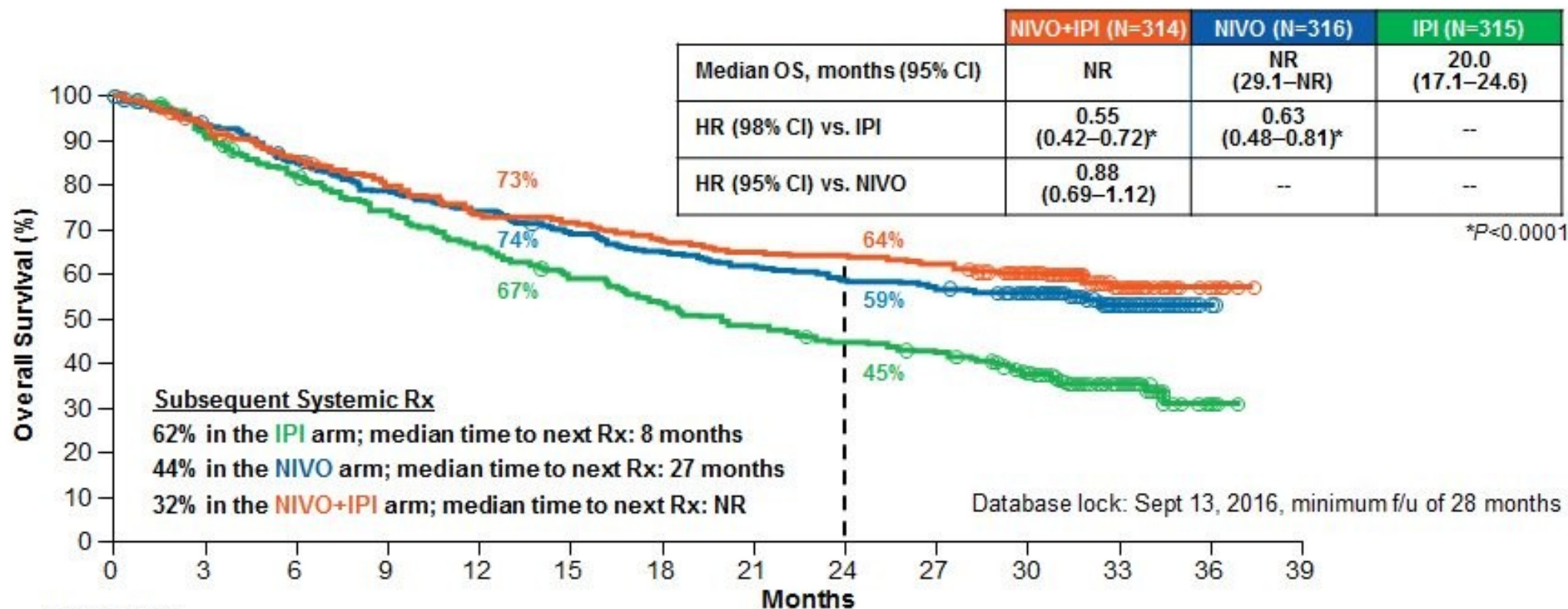


- Primary endpoint: OS, PFS
- Secondary endpoint: ORR, OS by PD-L1, Safety



# Protilátky proti PD-1 / PD-L1

## Overall Survival (Co-Primary Endpoint)



Patients at risk:

	0	3	6	9	12	15	18	21	24	27	30	33	36	39
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%)<sup>1</sup> and the phase CheckMate 066 trial of NIVO monotherapy (58%)<sup>2</sup>



# Imunoterapie

## The Nobel Prize in Physiology or Medicine 2018



© Nobel Media AB. Photo: A. Mahmoud

**James P. Allison**

Prize share: 1/2

CTLA-4



© Nobel Media AB. Photo: A. Mahmoud

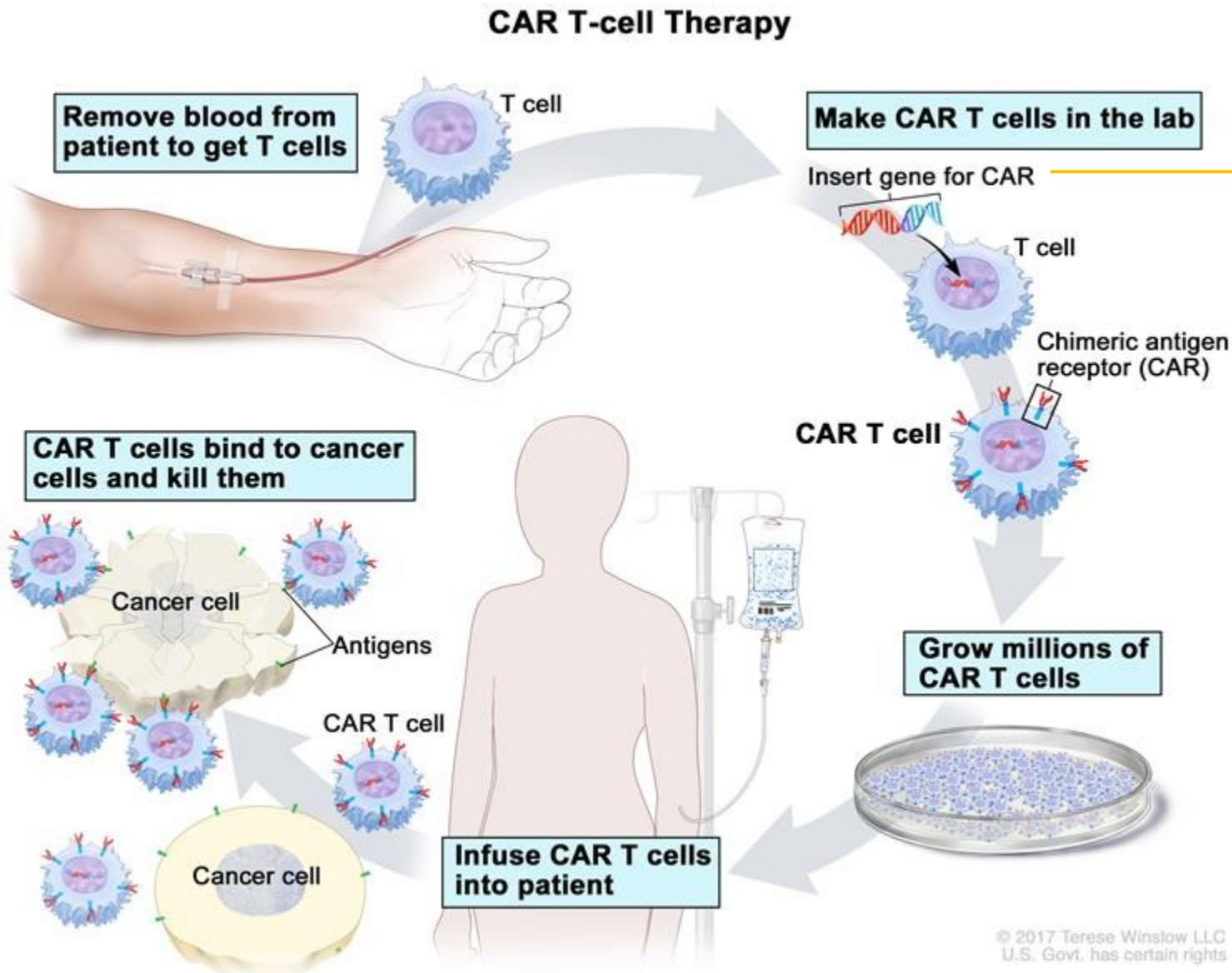
**Tasuku Honjo**

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

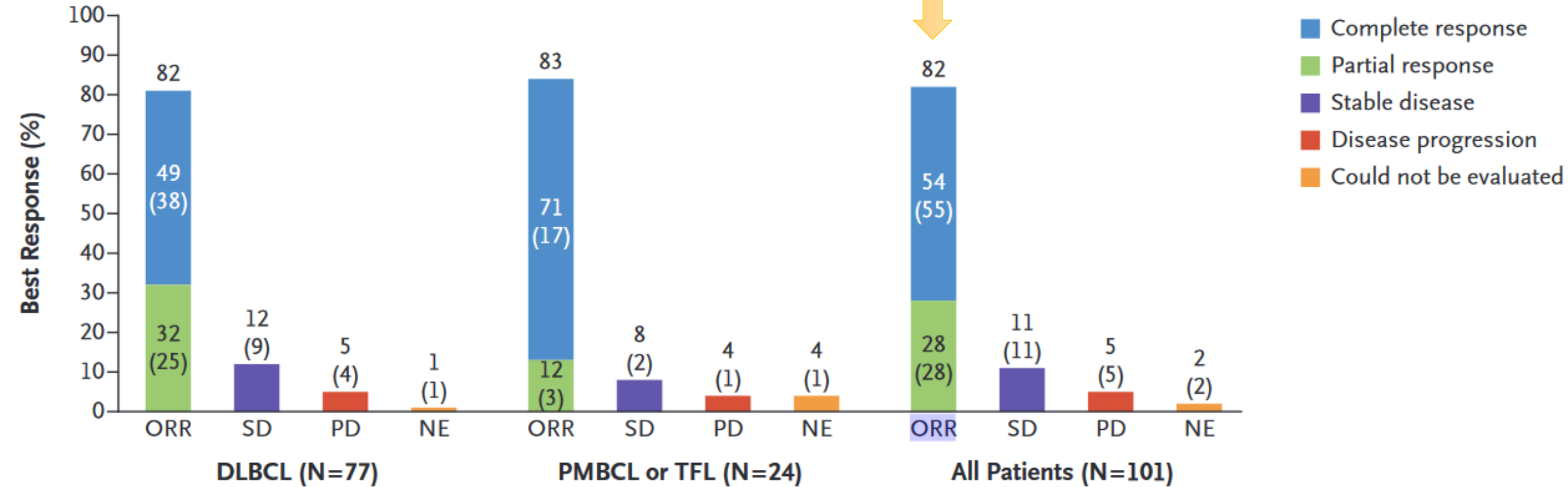
## Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

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. Wieszorek, 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)

## A Objective Response Rate

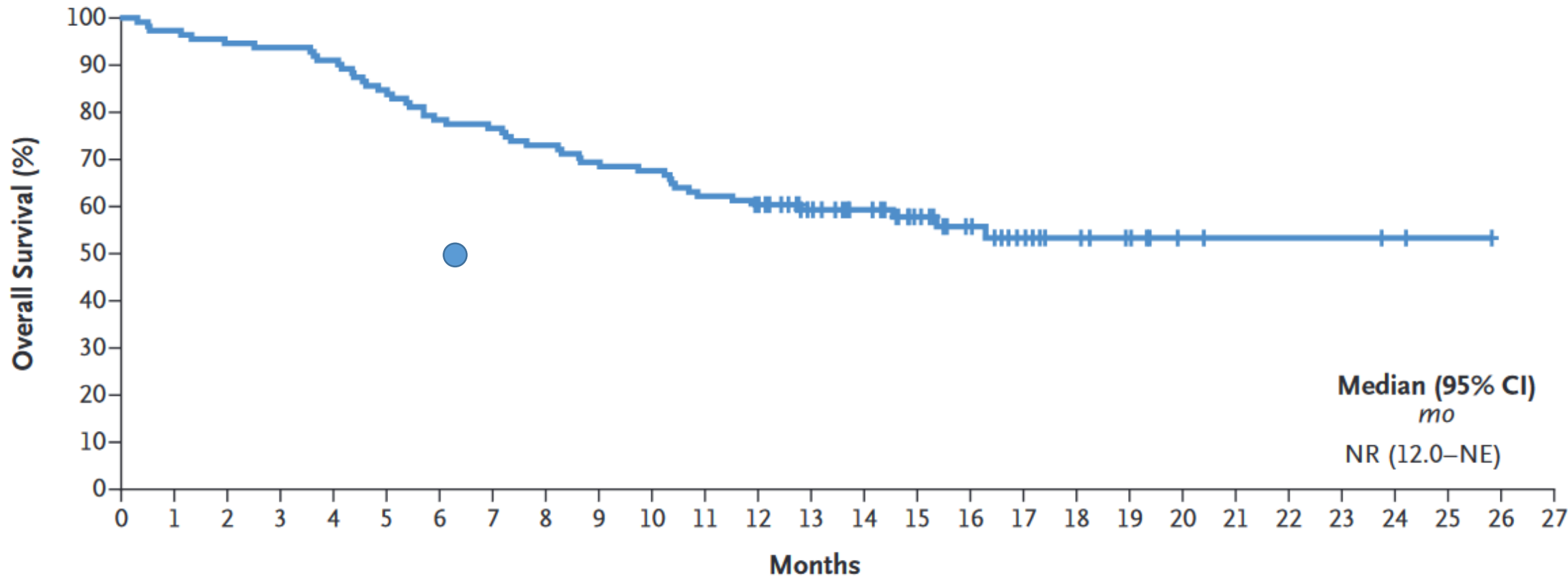


...objective response rate of 26%, a complete response rate of 7%...

# CAR-T cells (Chimeric Antigen Receptor)

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

C Overall Survival



No. at Risk 108 105 102 101 98 91 84 82 78 74 72 66 63 51 40 30 23 16 11 8 4 3 3 3 2 1 0



# 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

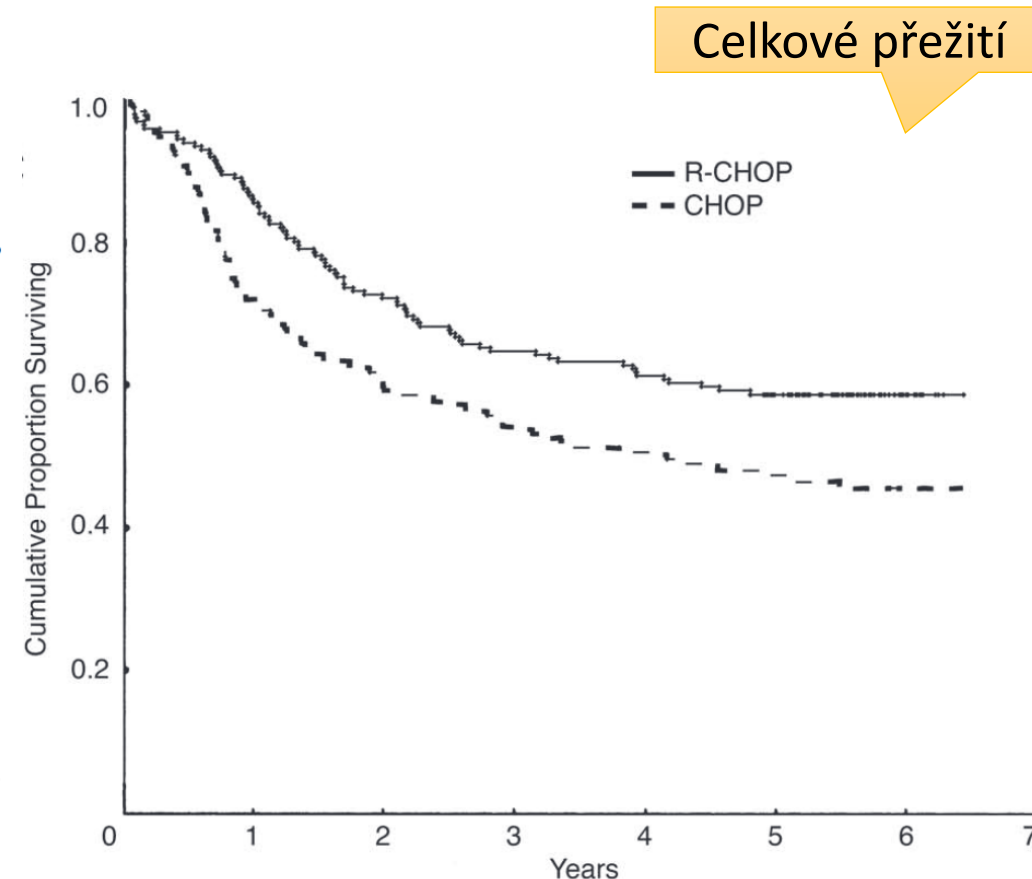
*„**CD20 function is not fully understood**, although **it is known to be involved in the calcium flux**. Recent studies suggested that raft-associated CD20 constitutes a component of a store-operated calcium entry pathway activated by BCR“*

(2015)

## 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/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, vincristine 1.4 mg/m<sup>2</sup>, and prednisone 40 mg/m<sup>2</sup> for 5 days) every 3 weeks.
- In R-CHOP, rituximab 375 mg/m<sup>2</sup> was administered the same day as CHOP. Survivals were analyzed using the intent-to-treat principle.



# MABs

Generic Name (Trade Name)	Origin	Isotype (Conjugate)	Indication	Target	Initial Approval
<i>Unconjugated MABs</i>					
Rituximab (Rituxan)	Chimeric	IgG1	NHL	CD20	1997
Trastuzumab (Herceptin)	Humanized	IgG1	BrCa	HER2	1998
Alemtuzumab (Campath-1H)	Humanized	IgG1	CLL	CD52	2001
Cetuximab (Erbix)	Chimeric	IgG1	CRC, SCCHN	EGFR	2004
Bevacizumab (Avastin)	Humanized	IgG1	CRC, NSCLC, RCC, GBM	VEGF	2004
Panitumumab (Vectibix)	Human (XenoMouse)	IgG2	CRC	EGFR	2006
Ofatumumab (Arzerra)	Human (XenoMouse)	IgG1	CLL	CD20	2009
Denosumab (Prolia/Xgeva)	Human	IgG2	Metastasis-related SREs, ADT/AI-associated osteoporosis, GCT	RANKL	2010
Pertuzumab (Perjeta)	Humanized	IgG1	BrCa	HER2	2012
Obinutuzumab (Gazyva)	Humanized	IgG1	CLL, FL	CD20	2013
Blinatumomab (Blincyto)	Murine	BiTE	ALL	CD3/CD19	2014
Ramucirumab (Cyramza)	Human	IgG1	Gastric, colorectal, lung	VEGFR2	2014–

# MABs

Daratumumab (Darzalex)	Human	IgG1	MM	CD38	2015
Elotuzumab (Empliciti)	Humanized	IgG1	MM	SLAMF7	2015
Necitumumab (Portrazza)	Human	IgG1	NSCLC	EGFR	2015
Dinutuximab (Unituxin)	Chimeric	IgG1	Neuroblastoma	GD2	2015
Olaratumab (Latruvo)	Human	IgG1	PDGFR $\alpha$	Sarcoma	2016

## *Immunoconjugates*

Gemtuzumab ozogamicin (Mylotarg)	Humanized	IgG4 (calicheamicin)	AML	CD33	2000 <sup>a</sup>
Ibritumomab tiuxetan (Zevalin)	Murine	IgG1 ( <sup>90</sup> Y)	NHL	CD20	2002
Tositumomab (Bexxar)	Murine	IgG2A ( <sup>131</sup> I)	NHL	CD20	2003
Brentuximab vedotin (Adcetris)	Chimeric	IgG1 (MMAE)	HL, sALCL	CD30	2011
Ado-trastuzumab emtansine (Kadcyla)	Humanized	IgG1 (DM1)	BrCa	HER2	2013
Inotuzumab ozogamicin (Besponsa)	Humanized	IgG4 (calicheamicin)	ALL	CD22	2017

# MABs

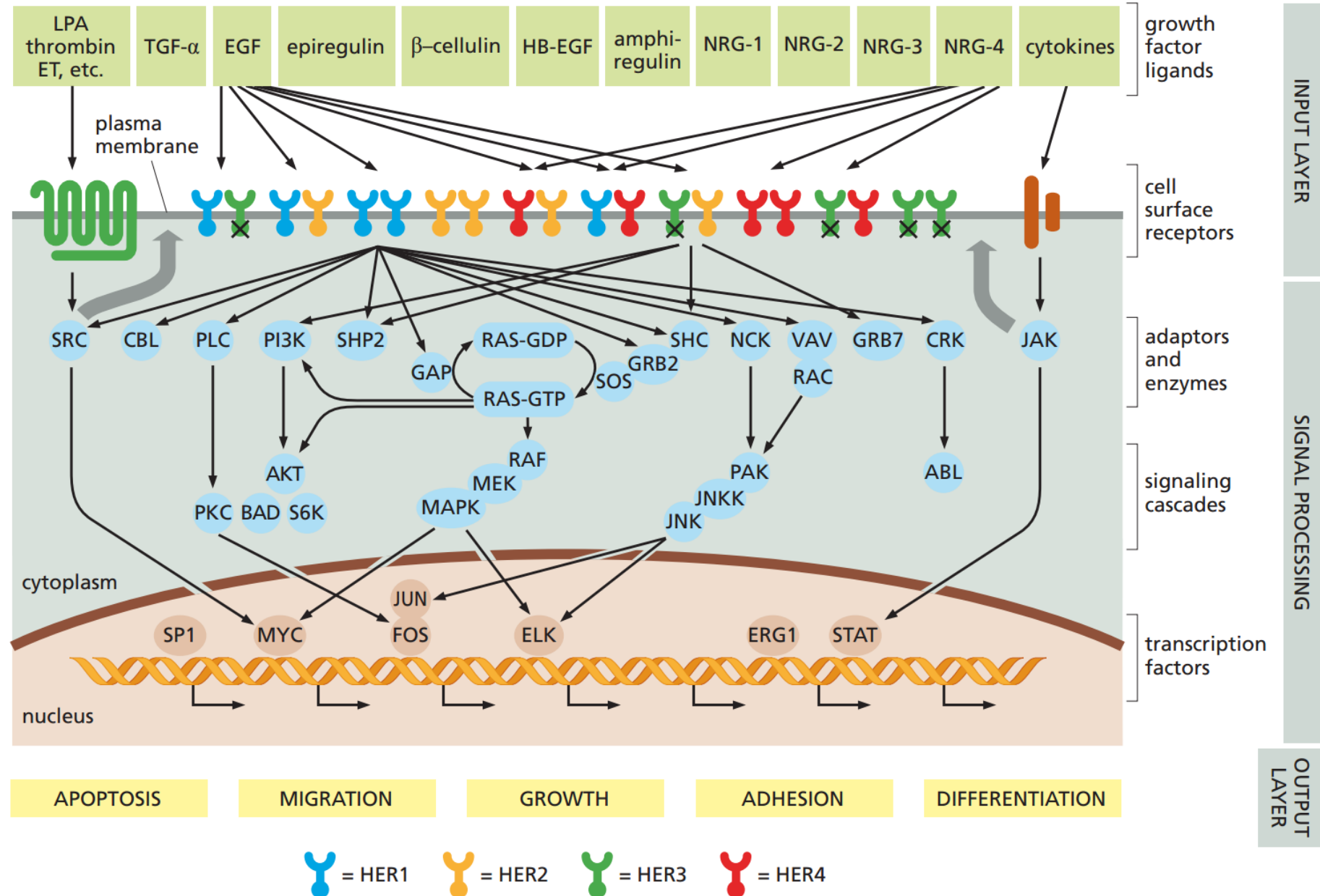


## **Substem Indication of the Species on Which the Immunoglobulin Sequence Is Based**

- o- Mouse
- xi- Chimeric
- zu- Humanized
- xizu- Chimeric/humanized
- u- Human

# ErbB rodina

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





# HER2

První klinicky  
používaný MAB

- Receptor na povrchu buněk, součástí ErbB rodiny
- Tyrozin-kináza
  
- Trastuzumab, pertuzumab, ...

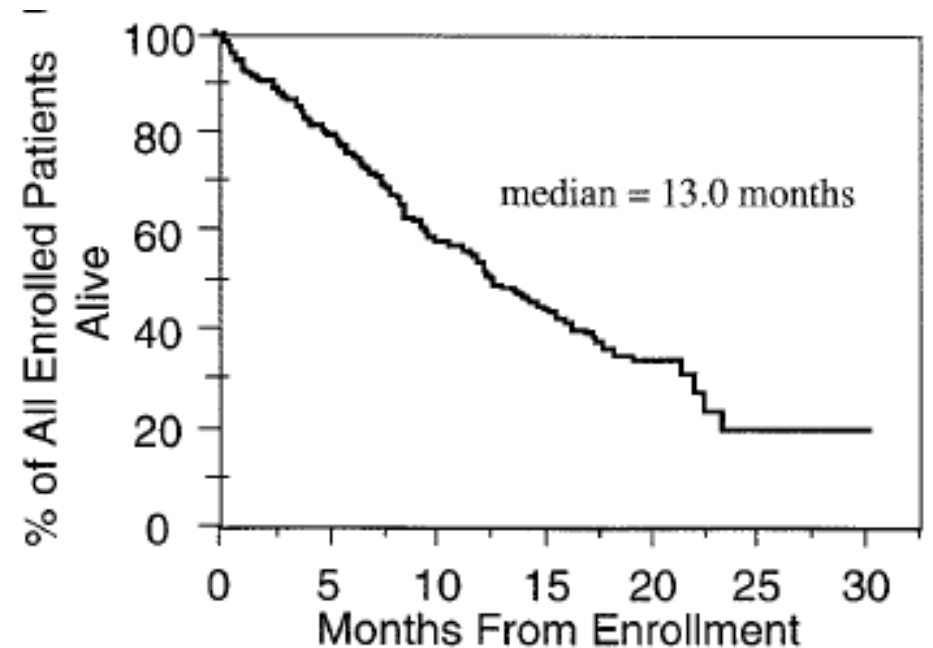
*In 1987, **amplification** of the ERBB2 gene, which encodes the HER2 transmembrane receptor tyrosine kinase, was identified in a subset of breast cancers*

# HER2

## Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer That Has Progressed After Chemotherapy for Metastatic Disease

By Melody A. Cobleigh, Charles L. Vogel, Debu Tripathy, Nicholas J. Robert, Susy Scholl, Louis Fehrenbacher, Janet M. Wolter, Virginia Paton, Steven Shak, Gracie Lieberman, and Dennis J. Slamon

**Results:** Study patients had **advanced metastatic disease** and had received extensive prior therapy. A blinded, independent response evaluation committee identified eight complete and 26 partial responses, for an **objective response rate of 15%** in the intent-to-treat population (95% confidence interval, 11% to 21%). The median duration of response was 9.1 months; the median duration of survival was 13 months.



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## Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

Martine J. Piccart-Gebhart, M.D., Ph.D., Marion Procter, M.Sci., Brian Leyland-Jones, M.D., Ph.D., Aron Goldhirsch, M.D., Michael Untch, M.D., Ian Smith, M.D., Luca Gianni, M.D., Jose Baselga, M.D., Richard Bell, M.D., Christian Jackisch, M.D., David Cameron, M.D., Mitch Dowsett, Ph.D., Carlos H. Barrios, M.D., Günther Steger, M.D., Chiun-Shen Huang, M.D., Ph.D., M.P.H., Michael Andersson, M.D., Dr.Med.Sci., Moshe Inbar, M.D., Mikhail Lichinitser, M.D., István Láng, M.D., Ulrike Nitz, M.D., Hiroji Iwata, M.D., Christoph Thomssen, M.D., Caroline Lohrich, M.D., Thomas M. Suter, M.D., Josef Rüschoff, M.D., Tamás Sütő, M.D., Ph.D., Victoria Greatorex, M.Sc., Carol Ward, M.Sc., Carolyn Strahle, Ph.D., Eleanor McFadden, M.A., M. Stella Dolci, and Richard D. Gelber, Ph.D., for the Herceptin Adjuvant (HERA) Trial Study Team

# HER2

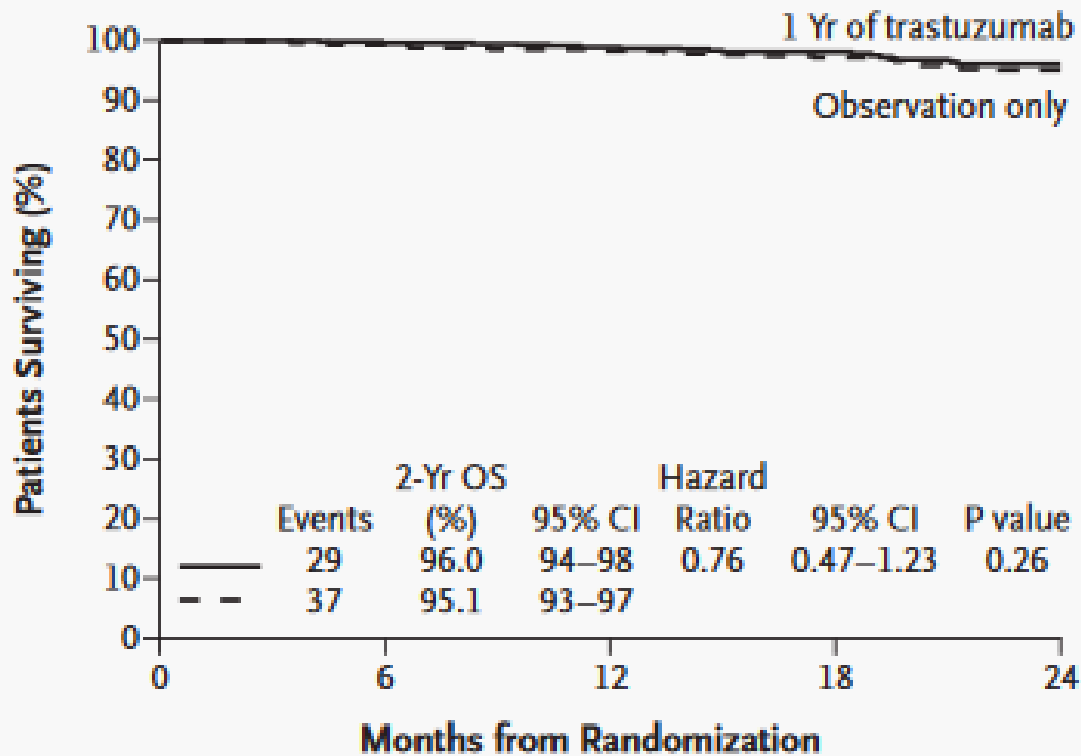


Methods: This international, multicenter, randomized trial compared one or two years of trastuzumab given every three weeks with observation in patients with HER2-positive and either node-negative or node-positive breast cancer who had completed locoregional therapy and at least four cycles of neoadjuvant or adjuvant chemotherapy.

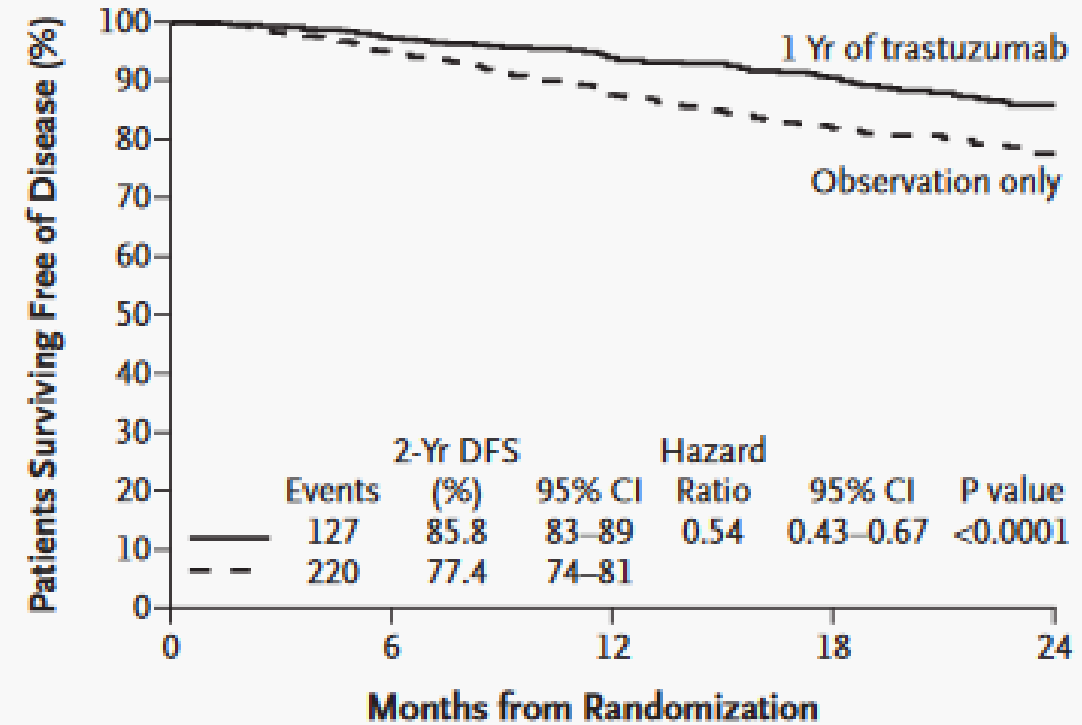
At the first planned interim analysis (median follow-up of one year), 347 events (recurrence of breast cancer, contralateral breast cancer, second nonbreast malignant disease, or death) were observed: 127 events in the trastuzumab group and 220 in the observation group. The unadjusted hazard ratio for an event in the trastuzumab group, as compared with the observation group, was 0.54

# HER2

Methods: This international, multicenter, randomized trial compared one or two years of trastuzumab given every three weeks with observation in patients with HER2-positive and either node-negative or node-positive breast cancer who had completed locoregional therapy and at least four cycles of neoadjuvant or adjuvant chemotherapy.



No. at Risk							
1 Yr of trastuzumab	1694	1195	920	560	284	1 Yr of trastuzumab	1694
Observation only	1693	1160	832	485	242	Observation only	1693



No. at Risk							
1 Yr of trastuzumab	1694	1172	885	532	268	1 Yr of trastuzumab	1694
Observation only	1693	1108	767	445	224	Observation only	1693

# EGFR

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- Standardní léčba:
  - Nevyléčí 100% lidí
  - Toxická



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. <sup>74,a</sup>	79	SCC–POD on CDDP based	CDDP based + cetuximab	6%–20%	2.0–3.0	4.3–6.1
Baselga et al. <sup>73,a</sup>	96	SCC–POD on platin based	CDDP based + cetuximab	10%–11%	2.4–2.8	4.9–6.0
Trigo et al. <sup>75</sup>	103	SCC–POD on platin based	Cetuximab	13%	2.3	5.9
Burtness et al. <sup>76,b</sup>	117	SCC No chemo for R/M	CDDP CDDP + cetuximab	10% 26%	2.7 4.2	8.0 9.2

<sup>a</sup>Range related to how POD was defined in different subgroups.

<sup>b</sup>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.

# Proč vůbec potřeba?

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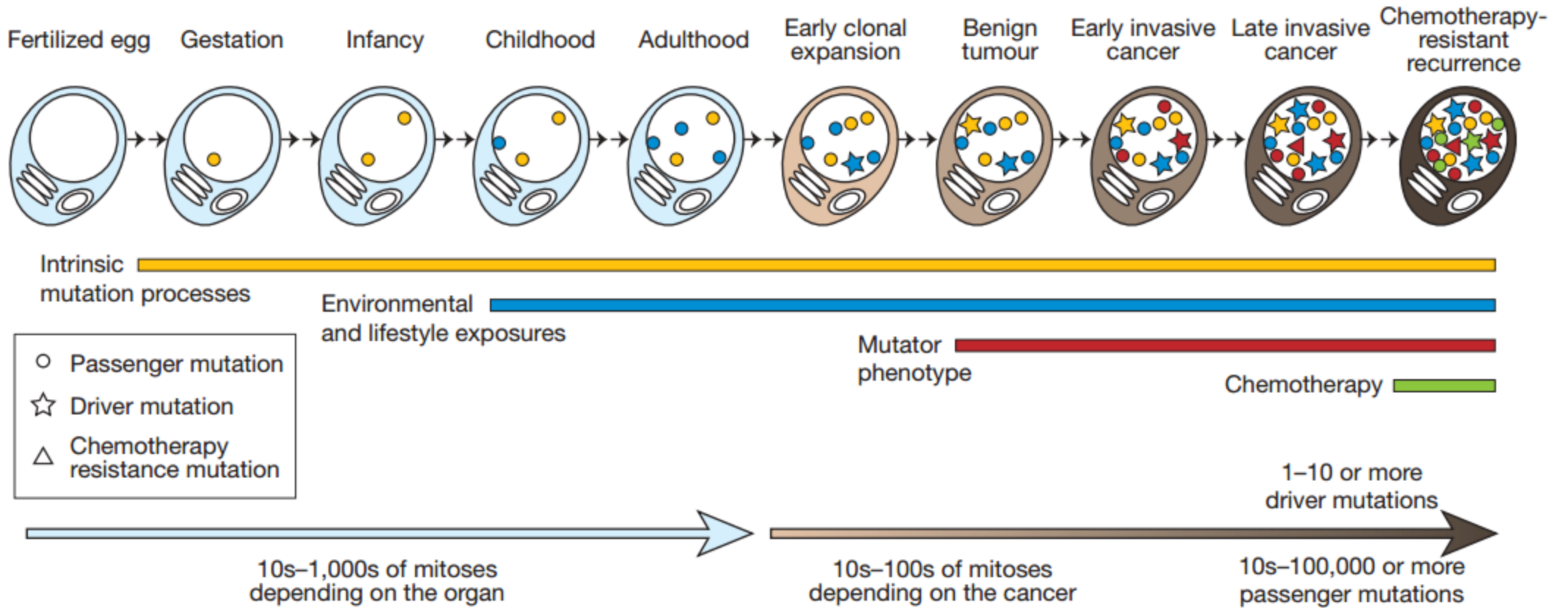
- Standardní léčba:
  - Nevyléčí 100% lidí
  - Toxická

# Problémy

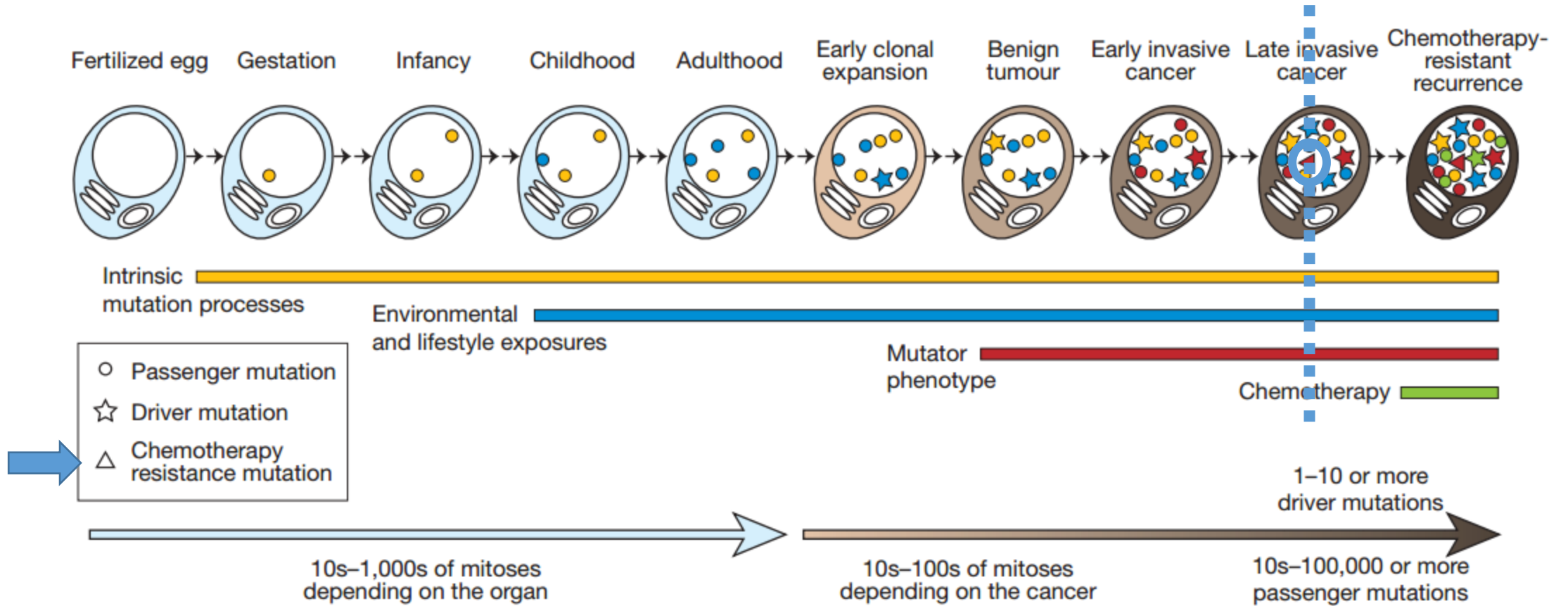
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- Resistance
  - Genetická instabilita
  - Intranádorová heterogenita – obrázek prso geny
- Limitace cílů

# Problémy



# Problémy



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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.





IT'S IMPORTANT TO KNOW THE INTERNATIONAL WARNING SYMBOL FOR RADIOACTIVE HIGH-VOLTAGE LASER-EMITTING BIOHAZARDS THAT COAT THE FLOOR AND MAKE IT SLIPPERY.