

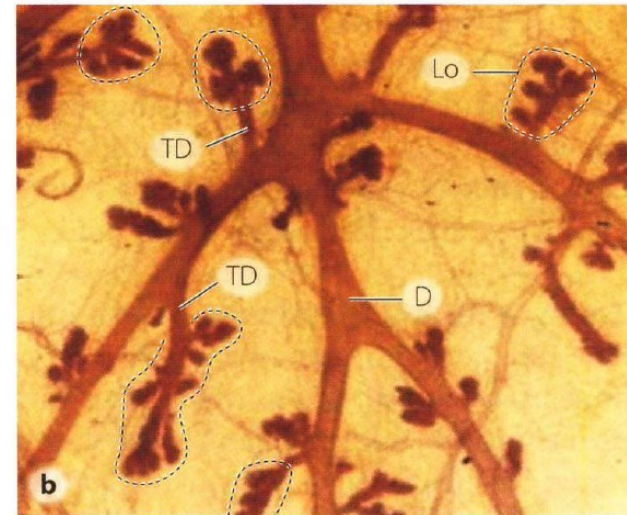
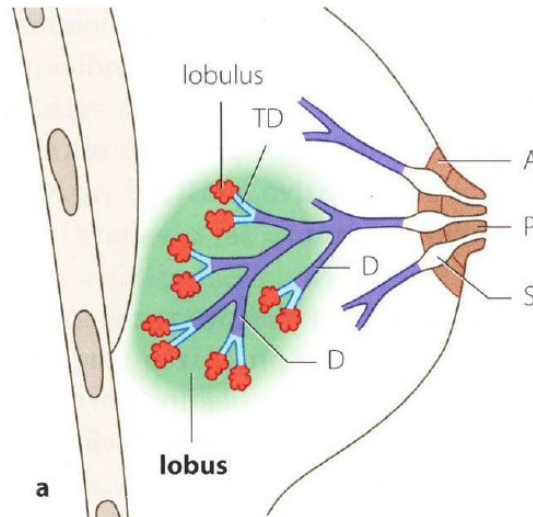
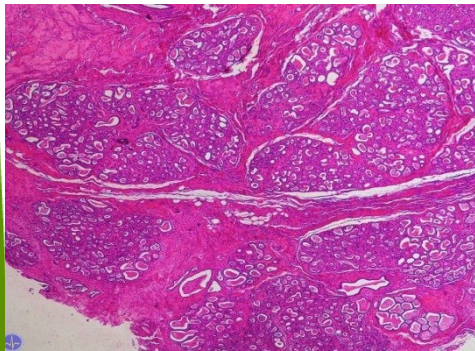
Nádory prostaty a prsu

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MLÉČNÁ ŽLÁZA

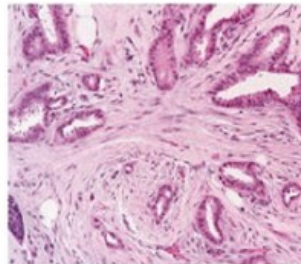
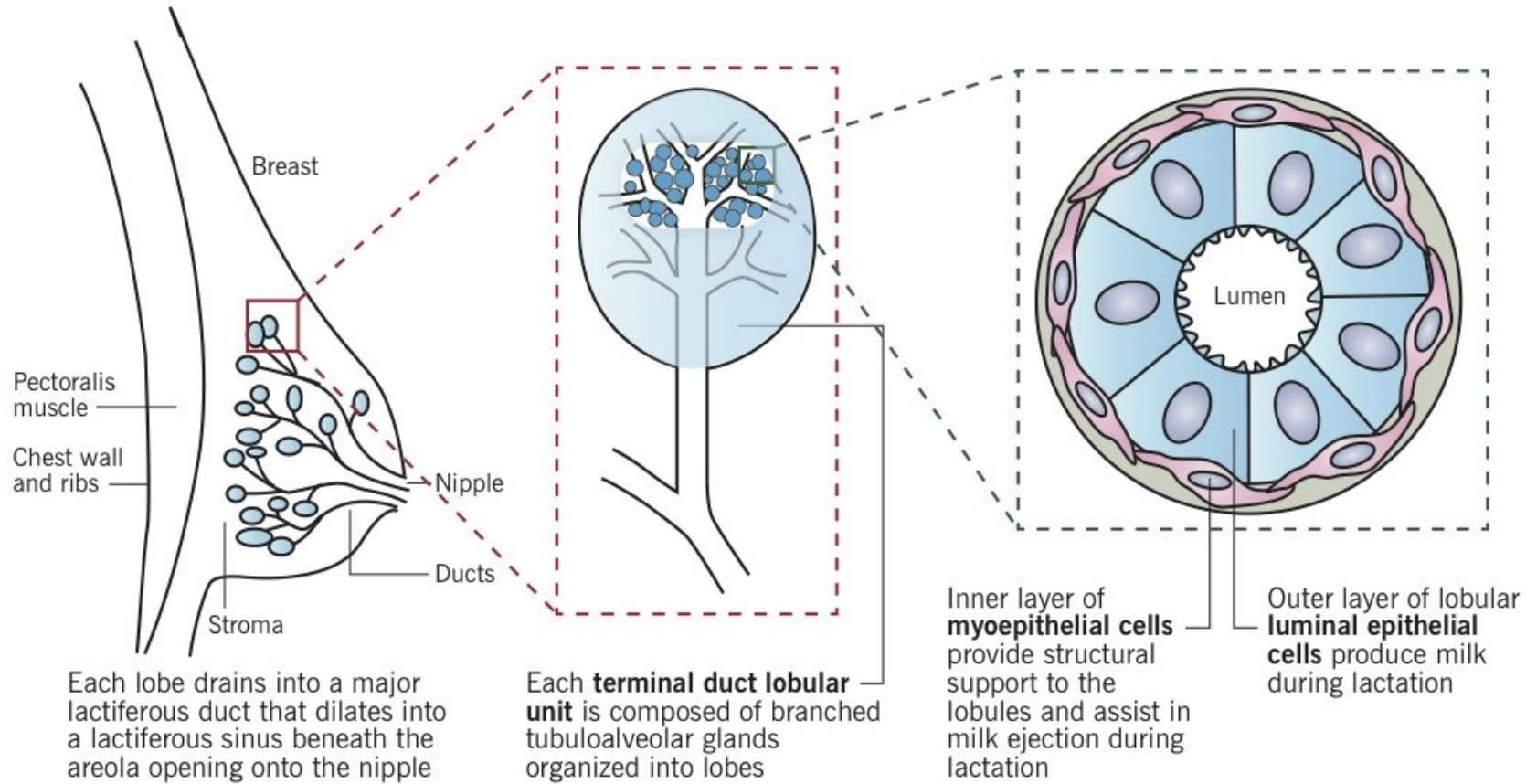
- Soubor 15 – 20 tuboaveolárních žláz tvořící laloky - **lobi**
- Každý vývod se rozvětluje, sekreční oddíly - **lobuly**
- Spolu s tukovou tkání a vazivovým stromatem je podkladem prsu
- K plnému rozvoji dochází v průběhu těhotenství – laktace
 - Intenzivní proliferace **alveolů** na konci interlobulárních vývodů



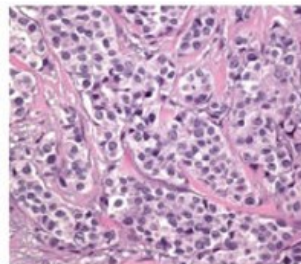
Breast anatomy and histology

Clin Obstet Gynecol. 2011 Mar;54(1):91-5.

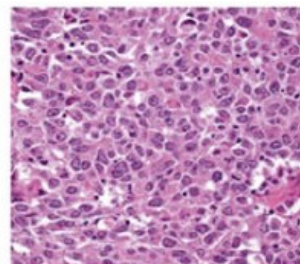
The breast is composed of glandular and stromal tissue. Glandular tissue includes the ducts and lobules. **Stroma** comprises area between lobes.



Grade I



Grade II



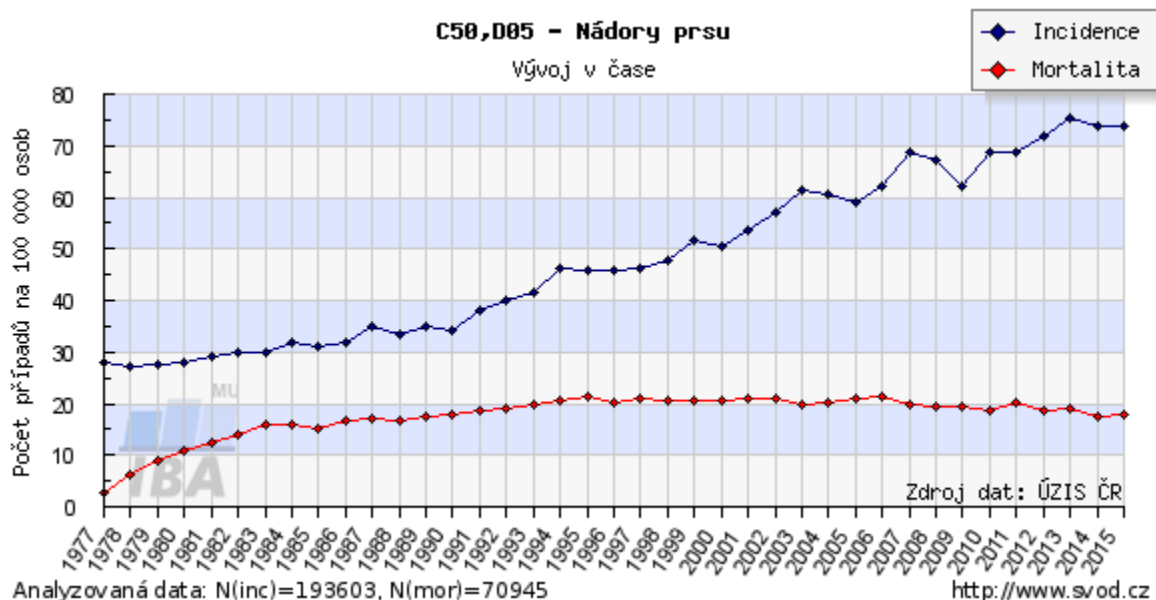
Grade III

Změny mléčné žlázy spojené s věkem

- Prepuberta
 - Základ duktů vytvořen, lobuly zůstávají nevyvinuty
- Puberta
 - Estrogen a progesteron produkovaný ovárii indukují větvení duktů a vývoj lobulů
- Těhotenství
 - Progesteron a prolaktin indukují kompletní maturaci prsní žlázy
 - Zvýšení počtu a velikosti lobulů
 - Oxytocin indukuje proliferaci a diferenciaci myoepiteliálních buněk
 - Po ukončení laktace dochází k apoptóze epitelu a atrofii lobulů
- Menopauza
 - Lobulární a duktální atrofie
 - Zvýšení množství interlobulárního stromatu, fibrózní a tukové tkáně

Karcinom prsu

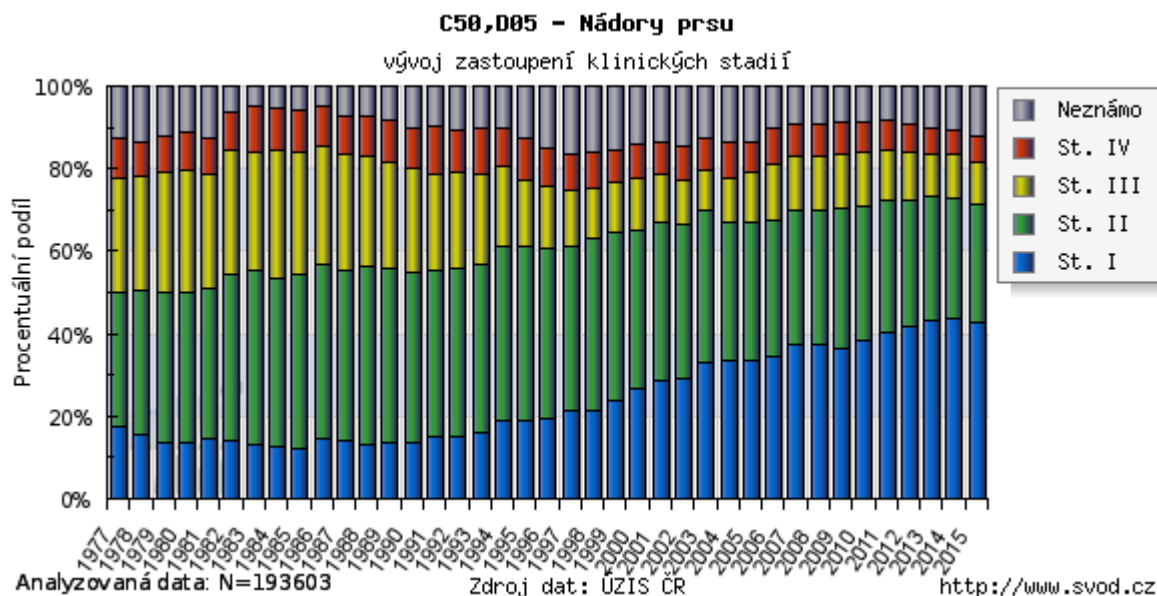
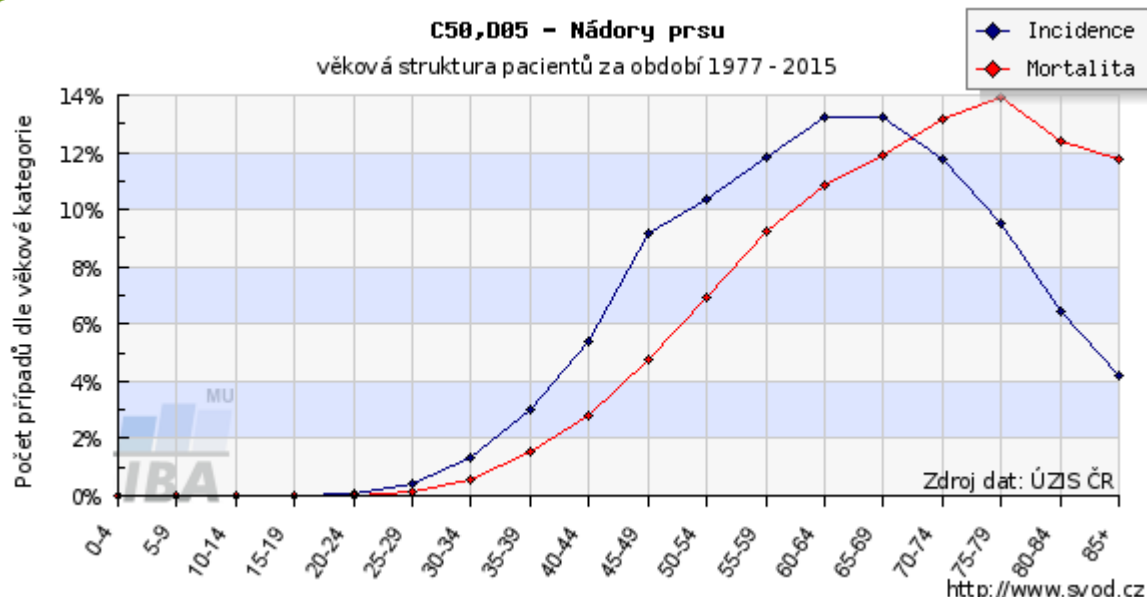
► Druhé nejčastější maligní onemocnění u žen



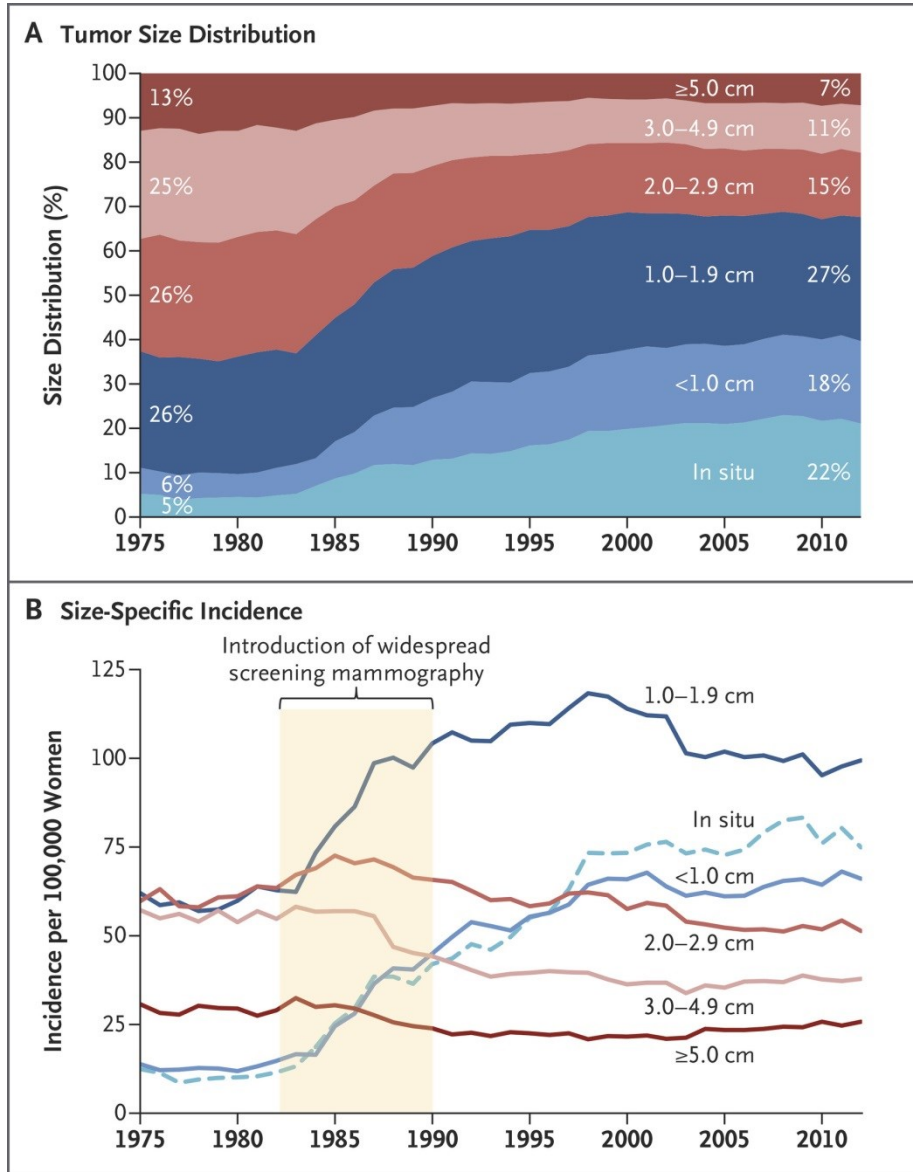
► TNM klasifikace

- TX – primární nádor nelze hodnotit
- T0 – bez známek primárního nádoru
- Tis – Kacinom in situ
- T1 – nádor ≤ 2 cm
- T2 – nádor > 2cm, ≤ 5cm
- T3 – nádor > 5cm
- T4 – nádor jakékoliv velikosti s přímým šířením do stěny hrudní nebo kůže

Karcinom prsu – věková struktura a zastoupení klinických stádií



Breast-Cancer Tumor-Size Distribution and Size-Specific Incidence among Women 40 Years of Age or Older in the United States, 1975–2012.



Karcinom prsu – rizikové faktory



Age

It's the strongest risk factor for breast cancer, and aging increases your risk.



Genetic alterations

Inherited changes in certain genes (including BRCA and PTEN) affect your risk.



Family history

A breast cancer diagnosis in your mother, sister and/or daughter, especially before age 50.



Dense breast tissue

A high percentage of dense breast tissue can make it more difficult to detect an abnormality on a mammogram.



Reproductive and menstrual history

Having your first menstrual period before age 12, going through menopause after age 55, or having your first full-term pregnancy after age 30 raises your risk.



Body weight

The chance of getting breast cancer is higher for postmenopausal women who are overweight or obese.



Radiation therapy

Undergoing radiation therapy to the chest before age 30 puts you at increased risk.



Menopausal hormonal therapy

Long term combined estrogen and progestin menopausal hormone therapy raises your breast cancer risk.

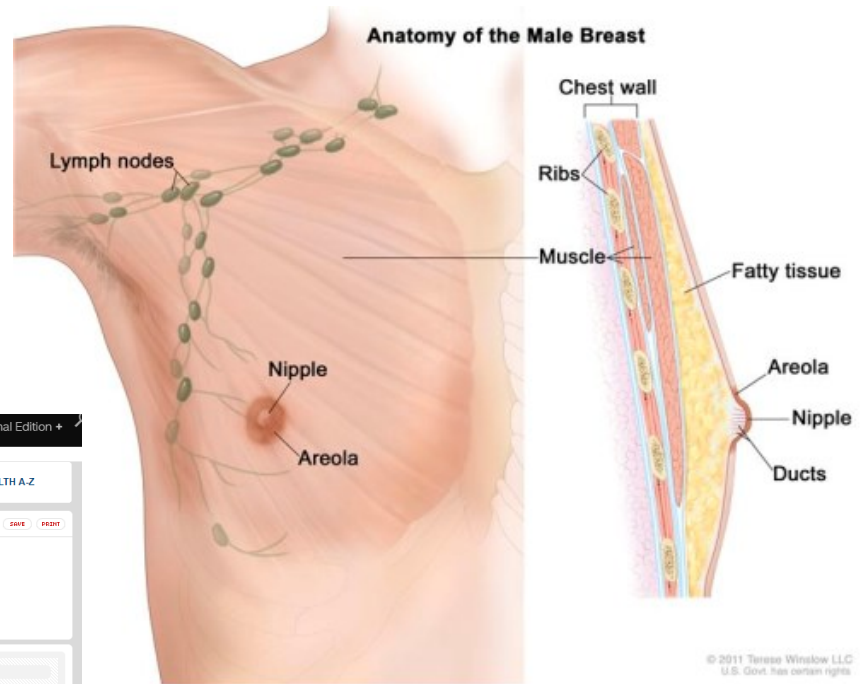


Alcohol

Drinking alcohol frequently may increase breast cancer risk.

Karcinom prsu – rizikové faktory

- Hlavní rizikový faktor – pohlaví
- 1 z 8-mi žen onemocnění invazivním adenokarcinomem prsu (USA, ~ 12%)
- 1 z 1000 mužů



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Male breast cancer patients blame water at Marine base

September 24, 2009 – Updated 2150 GMT (0550 HKT)

STORY HIGHLIGHTS

- 20 people, all Marines or sons of Marines, have had male breast cancer
- Each lived at Camp Lejeune between the 1960s and 1980s
- "We all at some point in our lives drank the water at Camp Lejeune," one says
- Marine Corps says two studies found no link to "adverse health effects"

Next Article in Health »

From Abbie Doubrau and Scott Bronstein
CNN Special Investigations Unit

Editor's note: This is part one of a two-part series.

Jim Fortella was based at Camp Lejeune in 1966 and 1967. He was diagnosed with breast cancer in 1995.

TAMPA, Florida (CNN) -- The sick men are Marines, or sons of Marines. All 20 of them were based at or lived at Camp Lejeune, the U.S. Marine Corps' training base in North Carolina, between the 1960s and the 1980s.

They all have had breast cancer, a disease that strikes fewer than 2,000 men in the United States a year, compared with about 200,000 women. Each has had part of his chest removed as part of his treatment, along with chemotherapy, radiation or both.

And they blame their time at Camp Lejeune, where government records show drinking water was contaminated with high levels of toxic chemicals for three decades, for their illnesses.

"We come from all walks of life," said Mike Partain, the son and grandson of Marines, who was born on the base 40 years ago. "And some of us have college degrees, some of us have blue-collar jobs. We are all over the country. And what is our commonality? Our commonality is that we all at some point in our lives drank the water at Camp Lejeune. Go figure."

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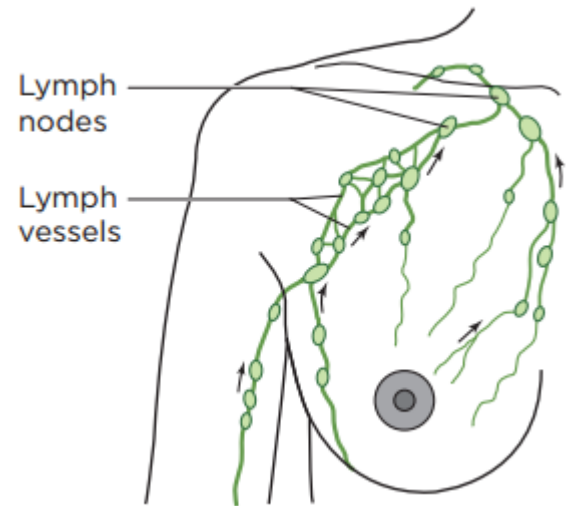
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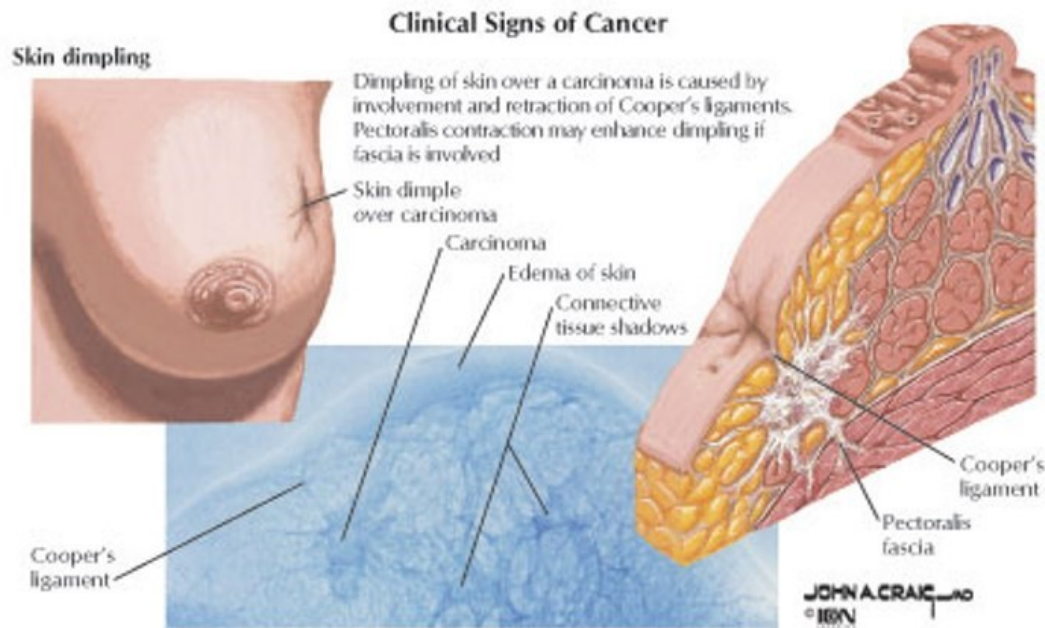
Karcinom prsu – prognostické faktory

- Exprese hormonálních receptorů v nádoru
- Věk
- Klinické stádium
- Postižení axilárních uzlin
- Exprese onkogenu HER2/Neu
- Velikost primárního nádoru
- Histologický typ nádoru a jeho *grade*
- Vaskulární a lymfatická invaze
- Molekulárně genetický profil nádoru
 - Oncotype (21 genů)
 - Mammaprint (70 genů)
 - PAM50 (Prosigna, 50 genů)



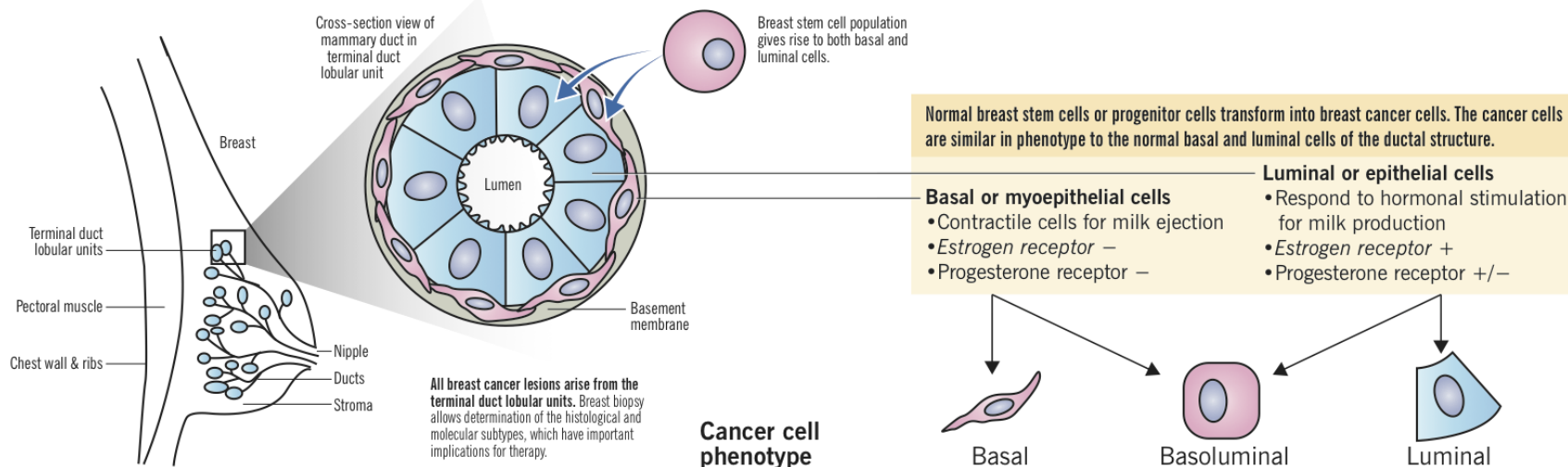
Klinické příznaky

- Primární nádor může být zcela asymptomatický, jindy vede ke změnám prsu
- Nejčastějším příznakem je hmatná rezistence v prsu nebo podpaží
- Metastázování – plíce, játra, kosti



Breast cancer pathogenesis and histologic vs. molecular subtypes

Eric Wong and Jenna Rebelo



Histological subtypes	Ductal	Lobular
Preinvasive cancer 25% Cells limited to basement membrane	Ductal carcinoma in situ (DCIS) 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cadherin loss 1% progress per year Can be bilateral
Invasive cancer 75% Extension beyond the basement membrane	Invasive ductal carcinoma (IDC) 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	Invasive lobular carcinoma (ILC) 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+

Curr Treat Options Oncol. 2000 Aug;1(3):199-209.
Clin Transl Oncol. 2008 Dec;10(12):777-85.

Nat Clin Pract Oncol. 2007 Sep;4(9):516-25.
Robbins 8E

Molecular subtypes	Triple negative	HER2+	Luminal B	Luminal A
	ER-, PR-, HER2-			
% of breast cancers	15-20%	10-15%	20%	40%
Receptor expression		HER2		ER+/PR+
Histologic grade Level of cell differentiation	High (grade III)			Low (grade I)
Prognosis Correlates to histologic grade	Poor			Good
Response to medical therapy	Chemotherapy	Trastuzumab		Endocrine

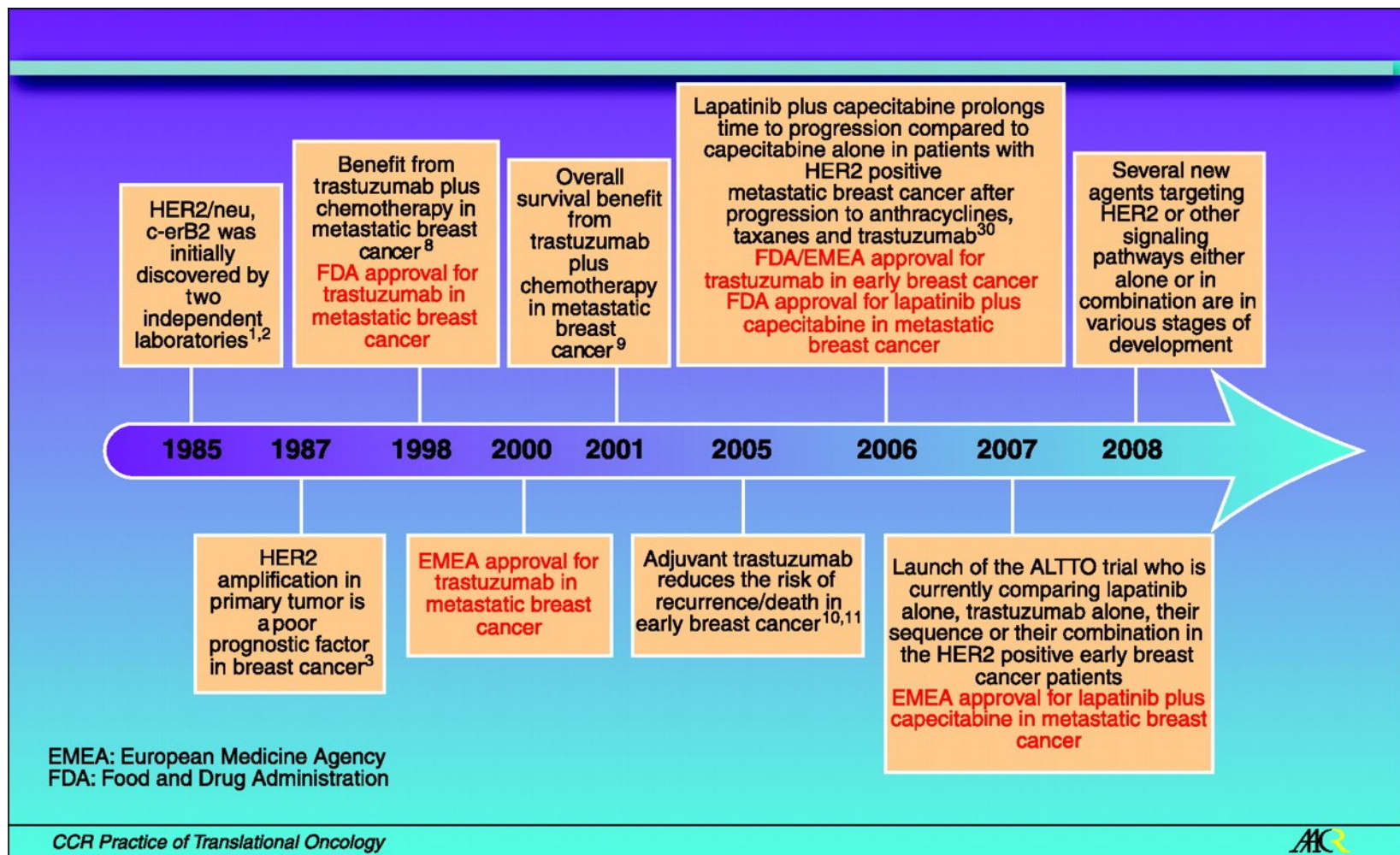
Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.

Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.

Léčebný postup

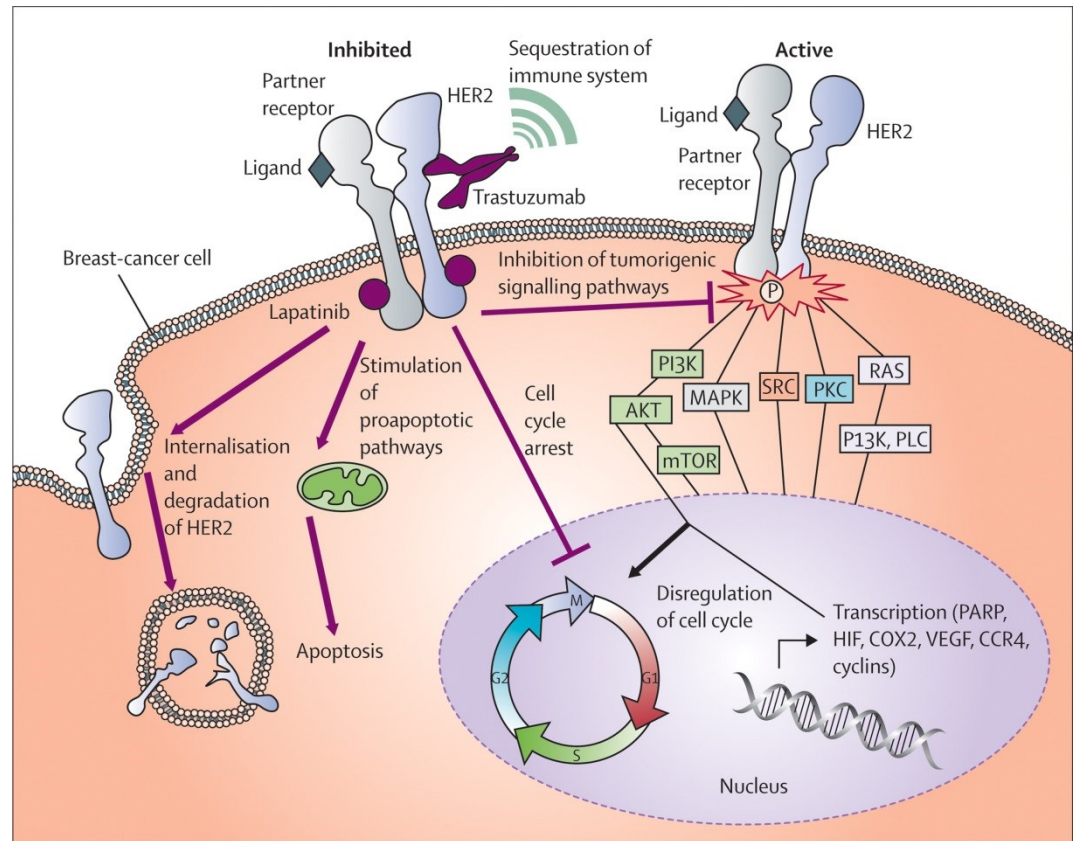
- Chirurgický výkon
- Pooperační systémová léčba
 - **Hormonální adjuvantní léčba**
 - Premenopauzální pacientky
 - Analoga Luteinizing-hormone-releasing hormone, LHRH
 - Tamoxifen (nesteroidní antiestrogen)
 - Postmenopauzální pacientky
 - Tamoxifen
 - Inhibitory aromatáz
 - **Adjuvantní chemoterapie**
 - Antracyklíny (doxorubicin, epirubicin), taxany (docetaxel)
 - **Adjuvantní biologická léčba**
 - Transtuzumab – pacientky pozitivní na HER2
 - Vedlejší účinky – neuregulin-1 – vliv na cardiomyocyty - cardiopatie
- Pooperační radioterapie

HER2 jako cíl protinádorové léčby

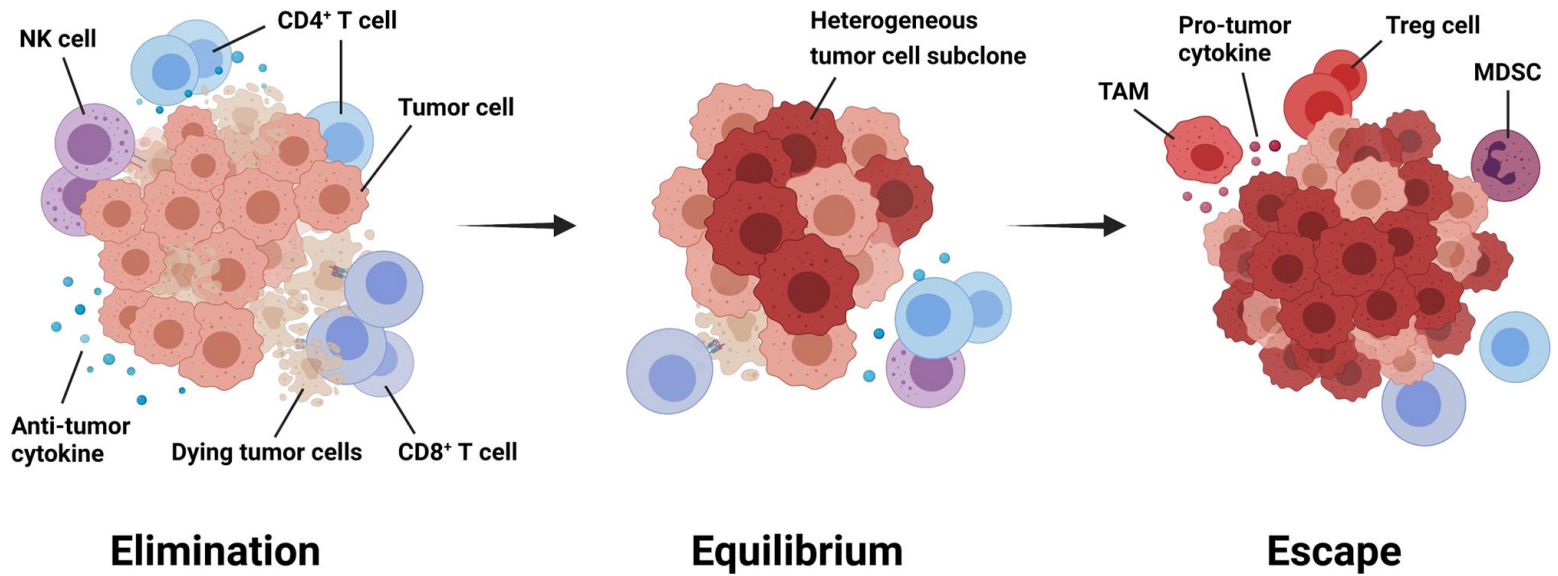


HER2/neu

- Receptor tyrosine-protein kinase erbB-2, CD340
- Rodina epidermal growth factor receptor
- Amplifikace u ~ 30% nádorů prsu

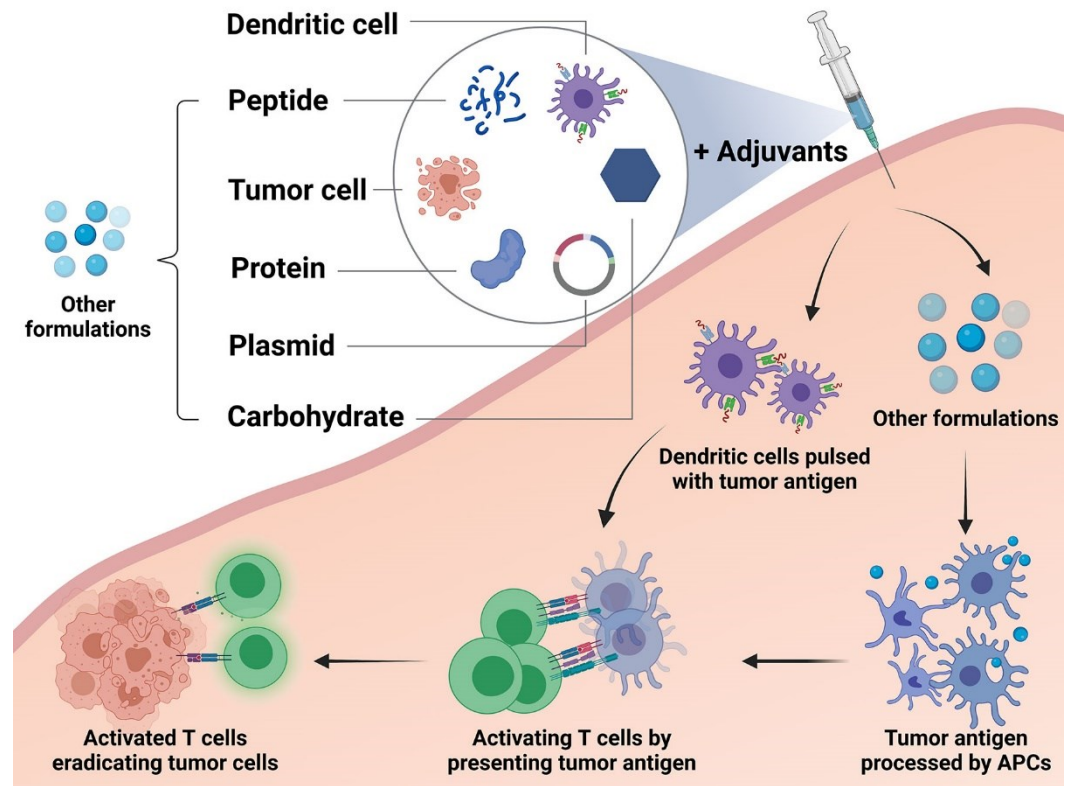


Imunoeditace v průběhu nádorového bujení a progresu.



Imunoterapie v léčbě karcinomu prsu

- NeuVax – HER2-derived peptide E75
- INO 1400 - virus-like replicon particle (VRP)-HER2
- hTERT DNA



Hlavní klinické studie vakcín proti rakovině prsu zaměřených na antigeny související s HER2.

Clinical Trial Reference	Trial Phase	Setting	Targeted Tumor Antigen	Design and Arms	Breast Cancer Subtype	Primary Objectives	Outcomes
PRESENT Trial NCT01479244 (102)	III	Adjuvant	HER2-derived peptide E75	Vaccination Arm: E75 + GM-CSF (N=376) Control Arm: Placebo + GM-CSF (N=382)	HLA-A2/A3+, HER2 low-expressing (IHC 1/2+), node-positive	DFS	RR at 16.8 months interim analysis: 9.8% (vaccinated group) versus 6.3% (control group) (P = 0.07). Based on these data, the study was terminated for futility.
US Military Cancer Institute Clinical Trials Group Study I-01 and I-02 (103)	III	Adjuvant	HER2-derived peptide E75	Vaccination Arm: E75 + GM-CSF of different doses (N=108) Control Arm: Observation (N=79)	HLA-A2/A3+, HER2-expressing, node-positive or high-risk node-negative	Safety, optimal dosing of immune response	Five-year DFS: 89.7% (vaccinated group) versus 80.2% (control group) (P = 0.08). Toxicities were minimal.
NCT01570036 (104)	II	Adjuvant	HER2-derived peptide E75	Vaccination Arm: E75 + GM-CSF + trastuzumab (N=136) Control Arm: Placebo + GM-CSF + trastuzumab (N=139)	HLA-A2/A3+, HER2 low-expressing (IHC 1/2+), node-positive	DFS	The estimated 24-month DFS: 89.8% (vaccinated group) versus 83.8% (control group) (P= 0.18).
NCT00524277 (105, 106)	II	Adjuvant	HER2-derived peptide GP2	Vaccination Arm: GP2 + GM-CSF (N=89) Control Arm: GM-CSF alone (N=91)	HLA-A2+, HER2-expressing, node-positive or high-risk node-negative	DFS, RR	The estimated 5-year DFS: 88% (vaccinated group) versus 81% (control group) (P = 0.43); 100% (HER2 3+ vaccinated patients) versus 89% (HER2 3+ placebo patients) (P=0.03).
US Military Cancer Institute Clinical Trials Group Study I-04 (84)	I	Adjuvant	HER2-derived peptide GP2	Single arm: GP2 + GM-CSF of different doses (N=18)	HLA-A2+, HER2-expressing, node-negative	Safety, immune response	Immune response was induced in all the enrolled patients. Toxicities were minimal.
NCT00524277 (107)	II	Adjuvant	HER2-derived peptide AE37	Vaccination Arm: AE37 + GM-CSF (N=153) Control Arm: GM-CSF alone (N=145)	HLA-A2+, HER2-expressing, node-positive or high-risk node-negative	RR	RR at 25-month median follow-up: 12.4% (vaccinated group) versus 13.8% (control group) (P=0.70).
US Military Cancer Institute Clinical Trials Group Study I-03 (85)	I	Adjuvant	HER2-derived peptide AE37	Single arm: AE37 + GM-CSF of different doses (N=15)	HLA-A2+, HER2-expressing, node-negative	Safety, immune response	Immune response was induced in all the enrolled patients. Toxicities were minimal.
NCT00399529 (108)	II	Metastatic	HER2	Single arm: HER2 GM-CSF-secreting tumor cell vaccine + cyclophosphamide + trastuzumab (N=20)	Stage IV, HER2-expressing	Safety, CBR	CBR at 6 months and 1 year was 55% and 40%, respectively. Toxicities were minimal.
NCT00140738 (109)	III	Metastatic	HER2	Single arm: recombinant HER2 protein + AS15 (N=40)	Stage IV, HER2-expressing	Safety, CBR	Clinical activity was observed with 2/40 objective responses and prolonged stable disease for 10/40 patients. Immunization was associated with minimal toxicity.
NCT02061332 (110)	II	Neoadjuvant	HER2	Single arm: HER2 dendritic cell vaccine with different routes (N=27)	HER2-expressing DCIS or early invasive breast cancer	Safety, immune and clinical response	Vaccination by all injection routes was well tolerated. There was no significant difference in immune response rates by vaccination route.

CBR, clinical benefit rate; DCIS, ductal carcinoma in situ; DFS, disease-free survival; GM-CSF, granulocyte-macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HI A, human leukocyte antigen; IHC, immunohistochemistry; RR, recurrence rate.

Hlavní klinické studie vakcín proti rakovině prsu zaměřené na antigeny nesouvisející s HER2.

Clinical Trial Reference	Trial Phase	Setting	Targeted Tumor Antigen	Breast Cancer Subtype	Primary Objectives	Outcomes
NCT00003638 (101)	III	Metastatic	STn	Stage IV	TTP, OS	TTP: 3.4 months (treatment group) versus 3.0 months (control group) (P=0.35). Median OS: 23.1 months (treatment group) versus 22.3 months (control group) (P=0.91).
Miles DW, et al. (111)	II	Metastatic	STn	Stage IV	Safety, immune and clinical response	Clinical activity was observed with 2/18 minor responses and stable disease for 5/18 patients. Toxicities were minimal.
NCT00179309 (112)	II	Metastatic	Mucin-1, CEA	Stage IV	PFS	Median PFS: 7.9 months (vaccinated arm) versus 3.9 months (control arm) (P=0.09).
Svane IM, et al. (113)	II	Metastatic	p53	Stage IV HLA-A2+	Safety, immune and clinical response	Clinical activity was observed with 8/19 stable disease or minor regression with 11/19 progressive disease. Toxicities were minimal.
Domchek SM, et al. (114)	I	Metastatic	hTERT	Stage IV HLA-A2+	Immune response	High immune response was observed in 9/16 patients and non/low response was seen in 7/16 patients.
NCT00807781 (99)	I	Metastatic	Mammaglobin-A	Stage IV HLA-A2/A3+	Safety, immune response	No serious adverse events and a significant increase in the frequency of MAM-A specific CD8 ⁺ T cells after vaccination (0.9% vs. 3.8%, P<0.001) was observed.
Avigan D, et al. (115)	I	Metastatic	Multiple antigens	Stage IV	Safety, clinical response	No significant toxicity or autoimmunity. Clinical activity was observed with 2/10 disease regression and 1/10 disease stabilization.

CEA, carcino-embryonic antigen; HLA, human leukocyte antigen; hTERT, human telomerase reverse transcriptase; OS, overall survival; PFS, progression-free survival; STn, Sialyl-Tn; TTP, time to progression.

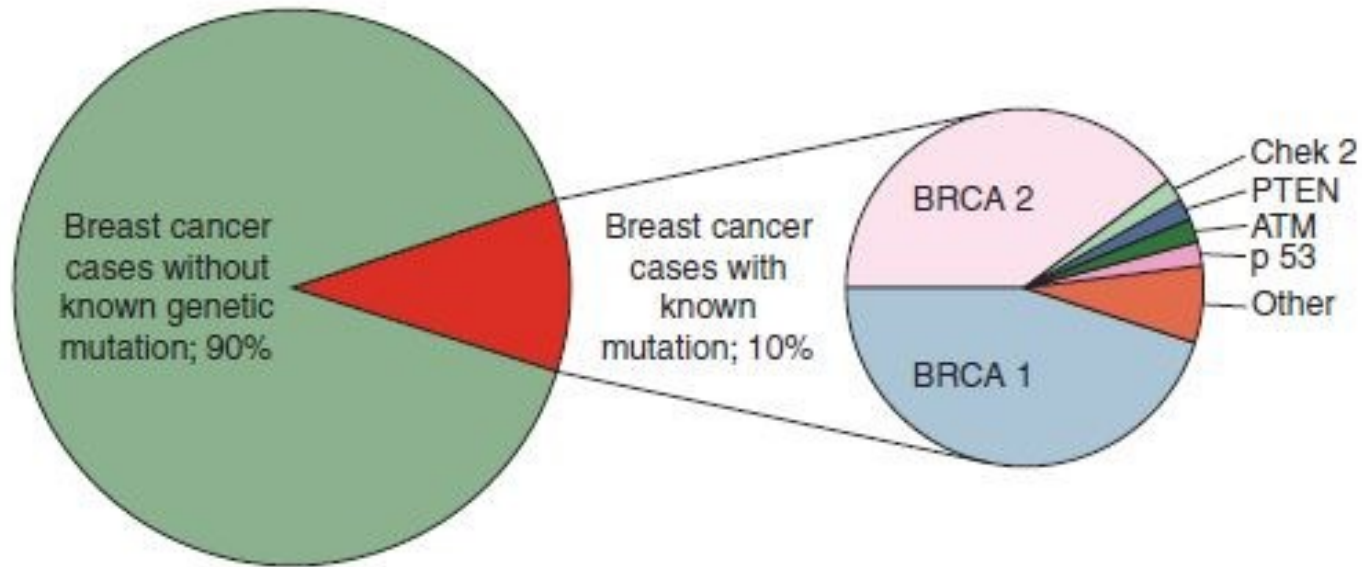


FIGURE 8-2 Percentage of breast cancer cases with a genetic mutation.

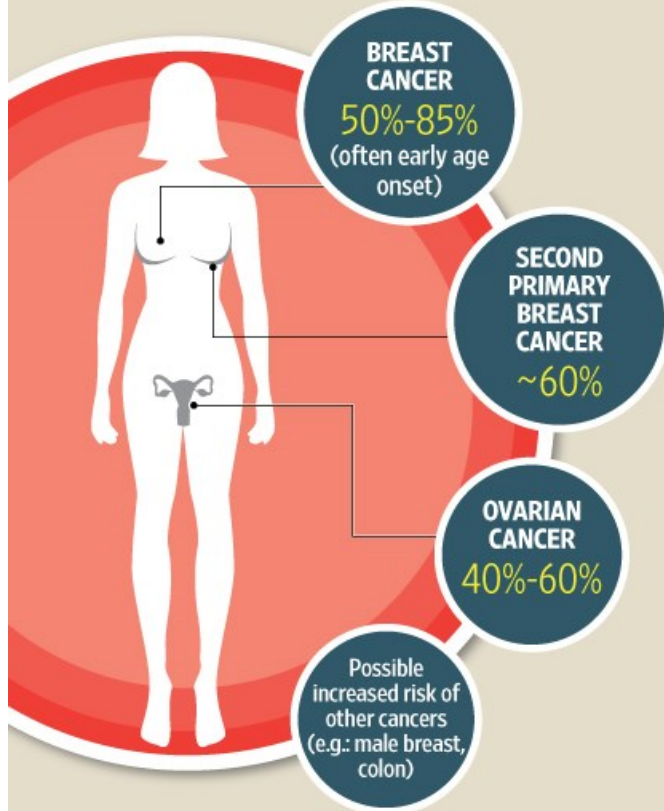
Table 9.1 Inherited risk factors: genes that influence breast cancer risk

Classification	Examples	Magnitude of risk
High penetrance	BRCA1, BRCA2, TP53, PTEN, STK11, LKB1, CDH1	25–85 % lifetime
Intermediate penetrance	CHEK2, ATM, BRIP1, BALB2	Two to threefold increased
Low penetrance	Numerous SNPs from GWAS studies	1.5-fold increased or less

UNDERSTANDING BRCA MUTATIONS

A BRCA gene mutation means a change in either of the two genes—BRCA1 or BRCA2—that prevents that gene from working properly. When the gene is damaged by mutation, it can increase the risk of cancer

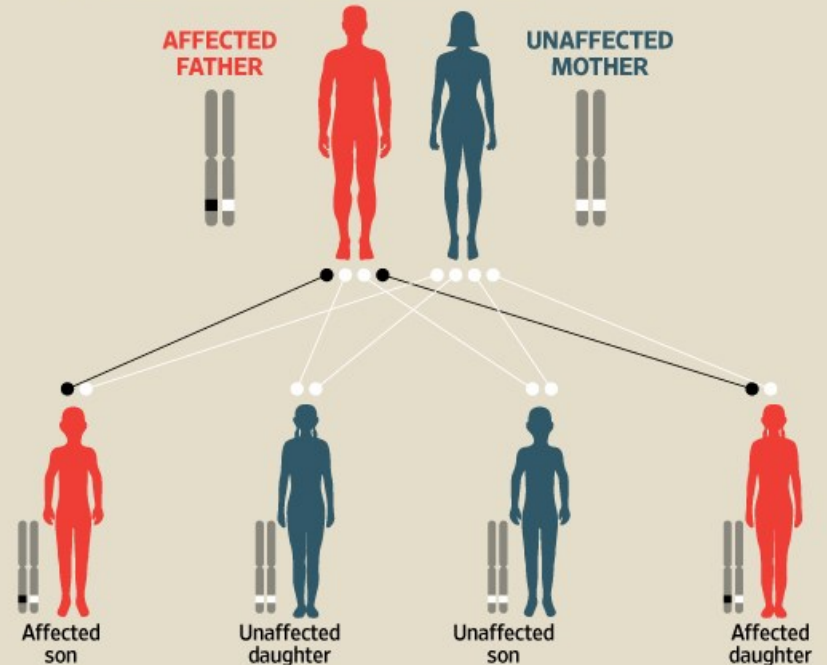
BRCA1- ASSOCIATED CANCERS: **LIFETIME RISK**



AUTOSOMAL DOMINANT INHERITANCE

Each child inherits a normal copy from his/her mother and either a normal or a defective copy from the father

- Chromosome with normal copy of gene
- Chromosome with defective copy of gene



BRCA

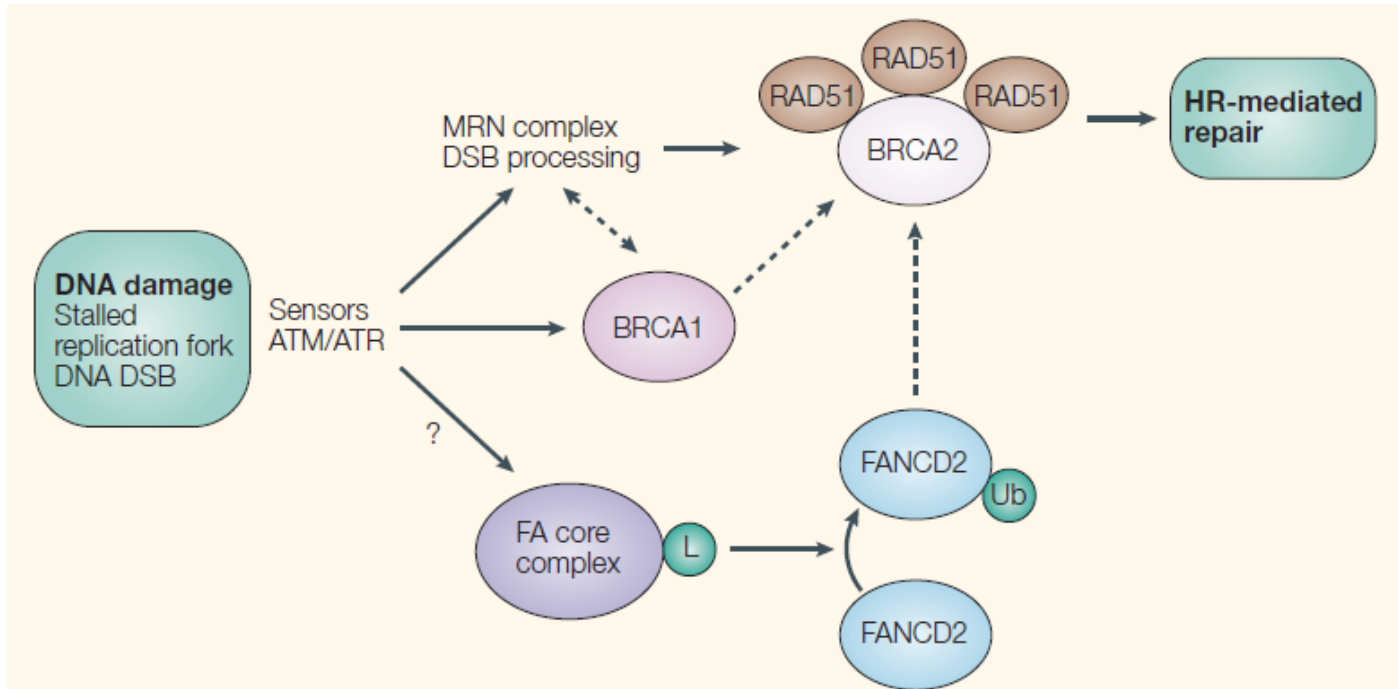


Figure 1 | **The BRCA/Fanconi anaemia DNA-repair pathways.** The BRCA and Fanconi anaemia (FA) proteins function in pathways that repair DNA double-strand breaks (DSBs), stalled replication forks and DNA crosslinks. DNA damage is sensed by protein kinases such as ataxia telangiectasia and Rad3 related (ATR), and ataxia telangiectasia mutated (ATM) that activate the pathways. Five FA proteins (FANCA, FANCC, FANCE, FANCF and FANCG) form a nuclear complex⁵, which interacts with FANCL in response to DNA damage leading to mono-ubiquitylation of FANCD2 (REF. 62). Ubiquitylated FANCD2 subsequently co-localizes with both BRCA1 (REF. 63) and BRCA2 (REF. 64) in nuclear foci. Interestingly, homozygous mutations in *BRCA2* also cause FA; BRCA2 is also known as FANCD1 (REF. 54). BRCA2 regulates the RAD51 recombinase that mediates strand invasion and homology-directed repair. For further information, see recent reviews of the mechanistic aspects of these pathways^{4,5}. MRN; MRE11–RAD50–NBS1.

Syntetická letalita

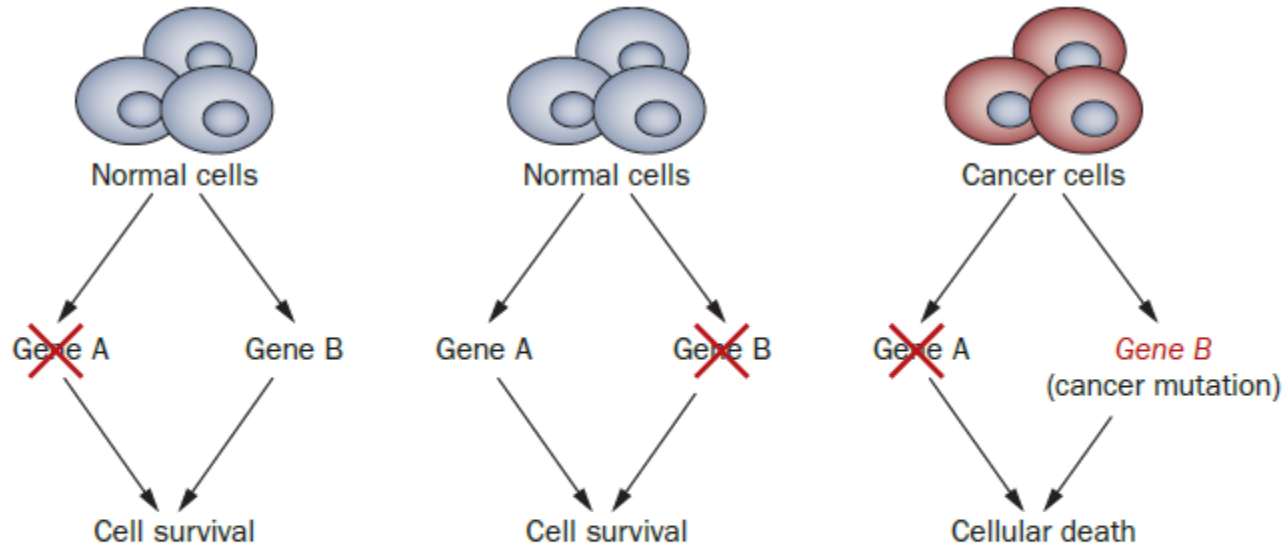


Figure 1 | Synthetic lethality. Loss of either gene A or gene B in normal cells is compensated by the action of the remaining gene. In tumor cells, however, a mutation in one of these genes leaves the cell vulnerable to loss of the other gene by drug inhibition. This approach is the basis of drugs that target synthetic lethal relationships. By contrast, normal tissues are spared any toxic effects.

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Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

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Poly(ADP-ribose) polymerase (PARP1) facilitates DNA repair by binding to DNA breaks and attracting DNA repair proteins to the site of damage^{1–3}. Nevertheless, PARP1^{-/-} mice are viable, fertile and do not develop early onset tumours⁴. Here, we show that PARP inhibitors trigger γ -H2AX and RAD51 foci formation. We

propose that, in the absence of PARP1, spontaneous single-strand breaks collapse replication forks and trigger homologous recombination for repair. Furthermore, we show that BRCA2-deficient cells, as a result of their deficiency in homologous recombination, are acutely sensitive to PARP inhibitors, presumably because resultant collapsed replication forks are no longer repaired. Thus, PARP1 activity is essential in homologous recombination-deficient BRCA2 mutant cells. We exploit this requirement in order to kill BRCA2-deficient tumours by PARP inhibition alone. Treatment with PARP inhibitors is likely to be highly tumour specific, because only the tumours (which are BRCA2^{-/-}) in BRCA2^{+/-} patients are defective in homologous recombination. The use of an inhibitor of a DNA repair enzyme alone to selectively kill a tumour, in the absence of an exogenous DNA-damaging agent, represents a new concept in cancer treatment.

Despite its important role in the cellular response to genotoxic stress, PARP1 is not required for survival in the absence of such an insult, and PARP1^{-/-} mice are viable and fertile^{5,6}. These mice do not develop early onset tumours and tumour latency is increased in PARP1 knockout mice that are deficient for p53 (ref. 4). Nevertheless, it is generally accepted that loss of PARP1 activity is important in maintaining genetic stability, because PARP1^{-/-} mice exhibit defective DNA single-strand break (SSB) repair and an increase in homologous recombination, sister chromatid exchange and micronuclei formation^{1,2,5,7}. However, the elevated homologous recombination levels in PARP1^{-/-} mice represent an error-free repair pathway, which may explain why the genetic instability in PARP1-deficient or inhibited cells is not associated with any accumulation of mutations or cancer.

PARP1 does not seem to be directly involved in homologous recombination, as RAD51 foci form normally in PARP1-deficient cells and homologous recombination-mediated repair of a DNA double-strand break (DSB) is unaffected by inhibition or loss of

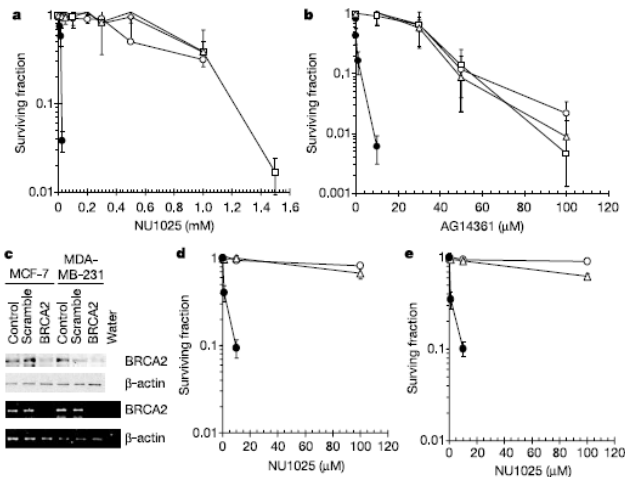
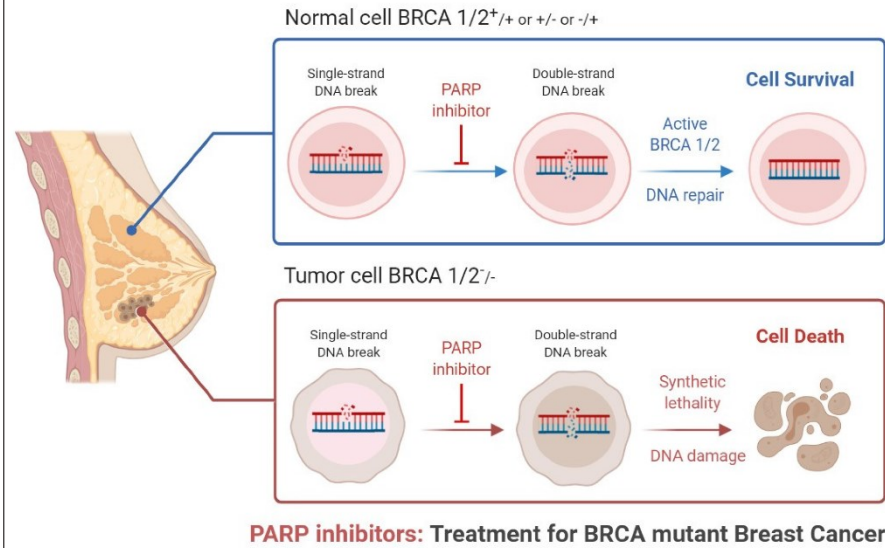


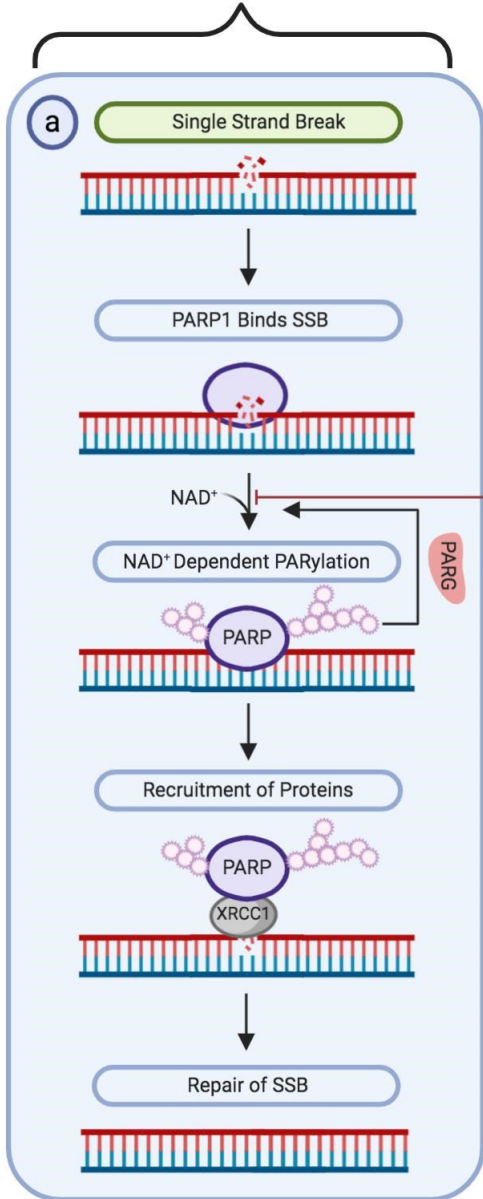
Figure 1 BRCA2-deficient cells are hypersensitive to inhibitors of PARP. **a**, **b**, Colony outgrowth of V79 (wild type; open circles), V-C8 (BRCA2-deficient¹⁴; filled circles), V-C8+B2 (V-C8 complemented with BRCA2 on human chromosome 13 (ref. 14); squares) and V-C8+B2 (V-C8 complemented with BRCA2 on an expression vector¹⁴; triangles) cells upon continuous exposure to the PARP inhibitor NU1025 (**a**) or after a 24-h treatment with AG14361 (**b**). **c**, Western blot and RT-PCR analysis of protein and RNA lysates

isolated from MCF-7 (p53^{WT}) or MDA-MB-231 (p53^{MDM2}) breast cancer cells after 48-h transfection with siRNA. **d**, **e**, Clonogenic survival of siRNA-treated MCF-7 cells (**d**) or MDA-MB-231 cells (**e**) after exposure to the PARP inhibitor NU1025. Open circles, control; triangles, scramble siRNA; filled circles, BRCA2 siRNA. The means and standard deviation of at least three experiments are shown.



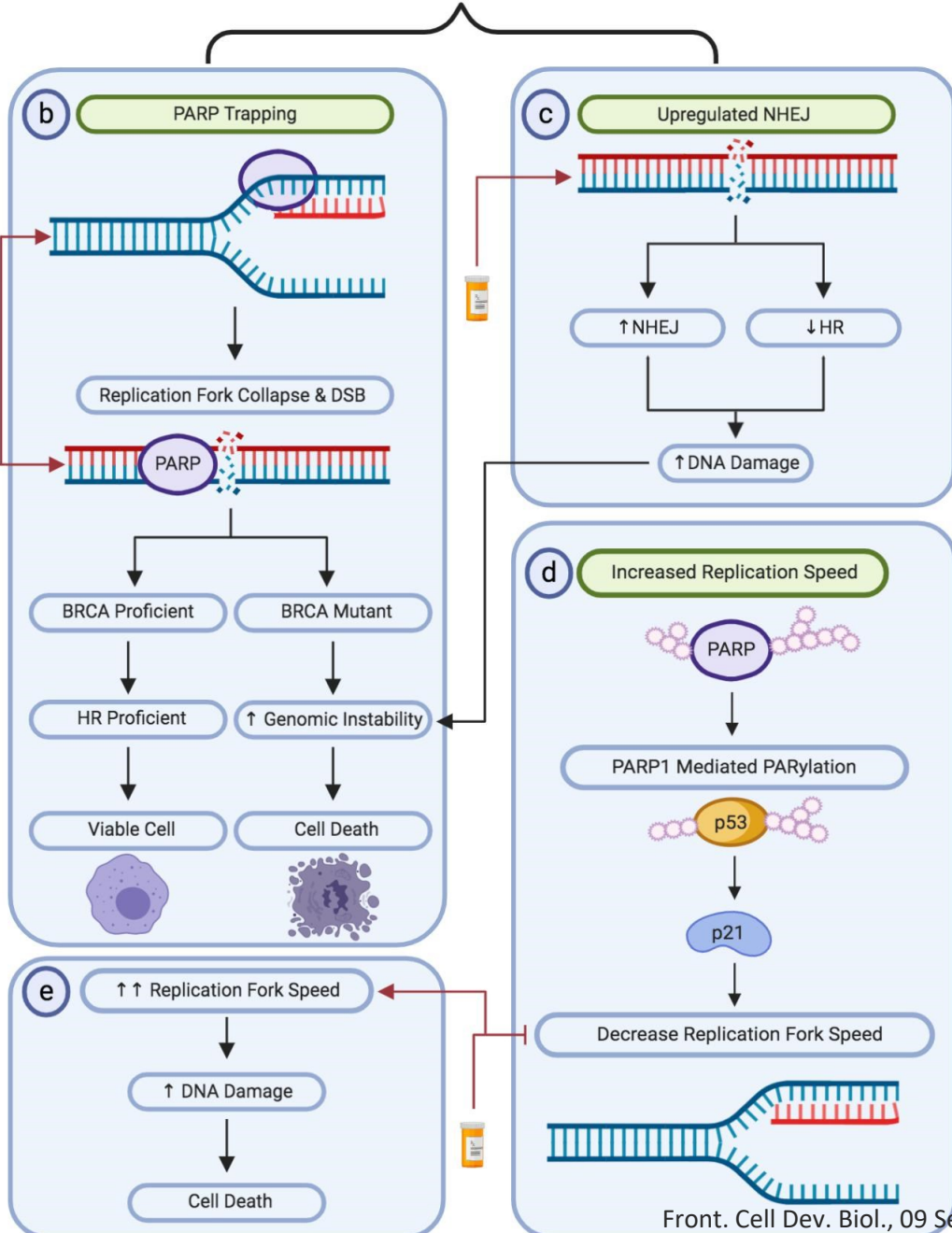
PARP inhibitors: Treatment for BRCA mutant Breast Cancer

Normal PARP1 Function



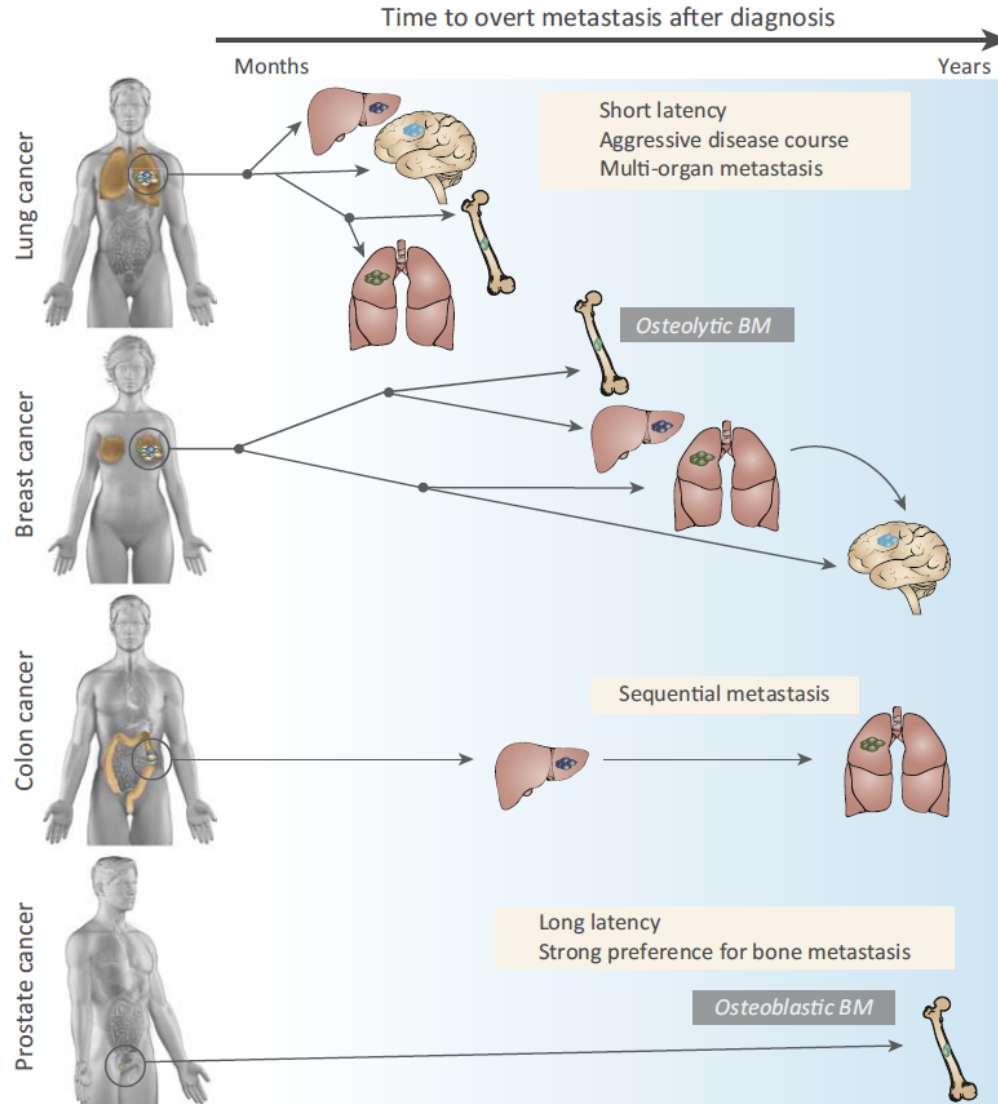
PARP Inhibitor

Proposed PARPi Mechanisms of Action



PARP inhibitor	Approving organization	Year of approval	Indication	Mutational requirement	Relevant studies
Olaparib	FDA and EMA	2014	Advanced ovarian carcinoma	Germline BRCA1/2 Mutation	NCT0107662 (Kaufman et al., 2015)
	FDA and EMA	2017	Reoccurring ovarian, fallopian and primary peritoneal carcinoma	Independent of BRCA1/2 Mutational Status	SOLO-2 (Pujade-Lauraine et al., 2017) and Study 19 (Friedlander et al., 2018)
	FDA EMA	2018 2019	HER-2 negative breast cancer	BRCA1/2 Mutated	OlympiAD (Robson et al., 2017)
	FDA EMA	2018 2019	First-line treatment of advanced ovarian, fallopian and primary peritoneal carcinoma	Germline BRCA1/2 Mutation Complete or partial chemotherapy response.	SOLO-1 (Moore et al., 2018)
	FDA	2019	Metastatic pancreatic cancer	BRCA1/2 Mutated	POLO (Golan et al., 2019)
	FDA	2020	First-line treatment of advanced ovarian, fallopian and primary peritoneal carcinoma in combination with Bevacizumab	HRD-Positive Complete or partial chemotherapy response.	PAOLA-1 (Ray-Coquard et al., 2019)
	FDA	2020	Metastatic castration-resistant prostate cancer	HRD-positive	PROfound (de Bono et al., 2020)
Rucaparib	FDA EMA	2016 2018	Advanced ovarian carcinomas, following multiple chemotherapy treatments	BRCA1/2 Mutated	ARIEL2 and Study 10 (Oza et al., 2017)
	FDA EMA	2018 2019	Reoccurring ovarian, fallopian and primary peritoneal carcinoma	Independent of BRCA1/2 Mutational Status	ARIEL3 (Coleman et al., 2017)
	FDA	2020	Metastatic castration-resistant prostate cancer	BRCA1/2 Mutated	TRITON2 (Abida et al., 2019)
Niraparib	FDA and EMA	2017	Reoccurring ovarian, fallopian and primary peritoneal carcinoma	Complete or partial chemotherapy response.	ENGOT-OV16/NOVA Study (Mirza et al., 2016)
	FDA	2019	Reoccurring ovarian, fallopian and primary peritoneal carcinoma	HRD-positive Independent of chemotherapy response	QUADRA Study (Moore et al., 2019)
	FDA and EMA	2020	Advanced ovarian carcinomas and primary peritoneal carcinoma	Independent of biomarker status Complete or partial chemotherapy response.	PRIMA Study (Gonzalez-Martin et al., 2019)
Talazoparib	FDA and EMA	2018	Advanced or metastatic HER2-negative breast cancer	Germline BRCA1/2 Mutated	EMBRACA Study (Ettl et al., 2018)

Diseminace solidních nádorů



Diseminace na nádorů prsu – TNBC vs. non-TNBC

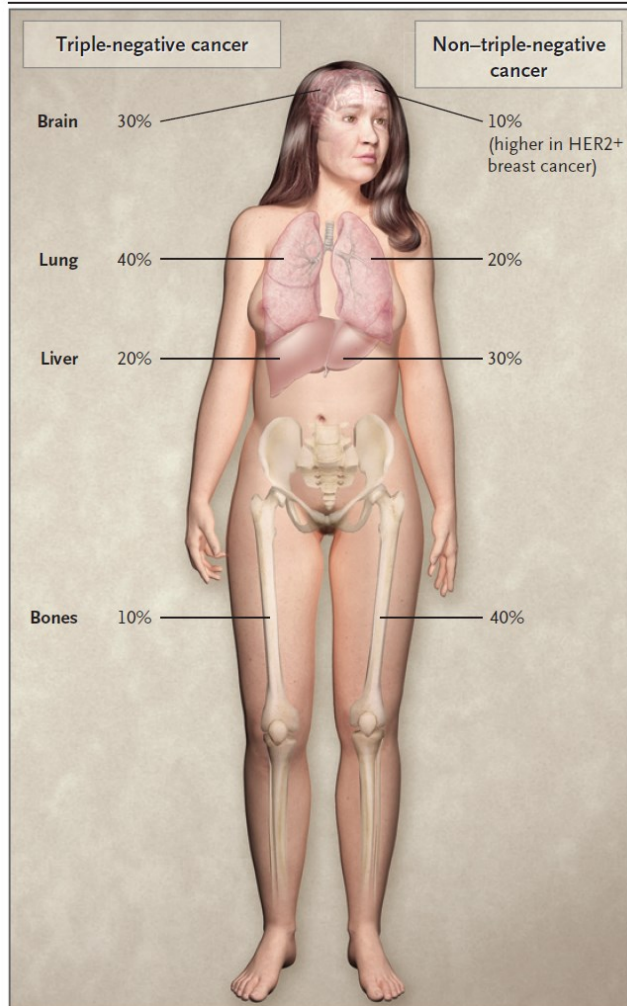
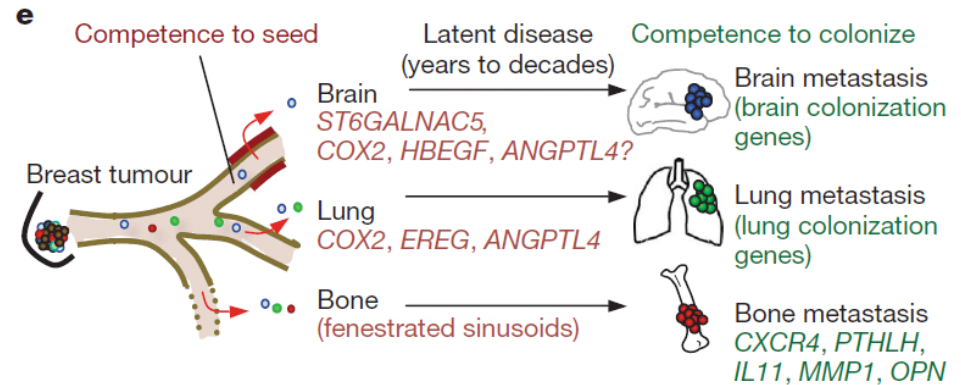


Figure 2. Sites of First Distant Recurrence in Cases of Metastatic Triple-Negative Breast Cancer as Compared with Non-Triple-Negative Breast Cancer. The percentages shown are approximate percentages of women with a first distant recurrence among women in whom metastases develop. Data are from Dent et al.,⁴⁷ Rodríguez-Pinilla et al.,⁴⁸ and Liedtke et al.⁴⁹



Vol 459 | 18 June 2009 | doi:10.1038/nature08021

nature

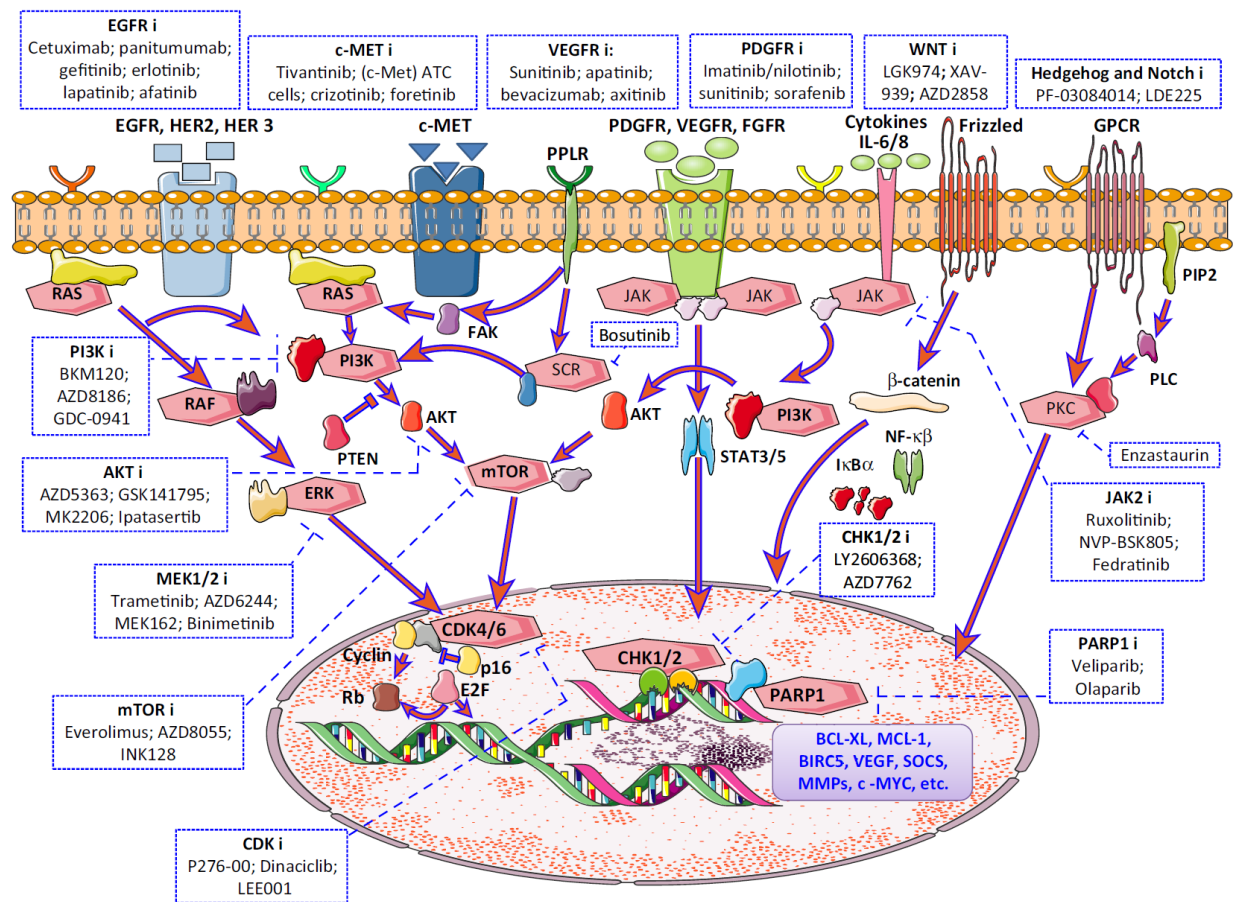
LETTERS

Genes that mediate breast cancer metastasis to the brain

Paula D. Bos¹, Xiang H.-F. Zhang¹, Cristina Nadal^{1†}, Weiping Shu¹, Roger R. Gomis^{1†}, Don X. Nguyen¹, Andy J. Minn², Marc J. van de Vijver³, William L. Gerald⁴, John A. Foekens⁵ & Joan Massagué^{1,6}

TNBC

- 15-20% ze všech diagnostikovaných nádorů prsu
- Heterogenní onemocnění, 4-6 molekulárních subtypů
- Řada uvažovaných cílů pro terapii (proliferace, DDR, buněčný cyklus, přežívání)

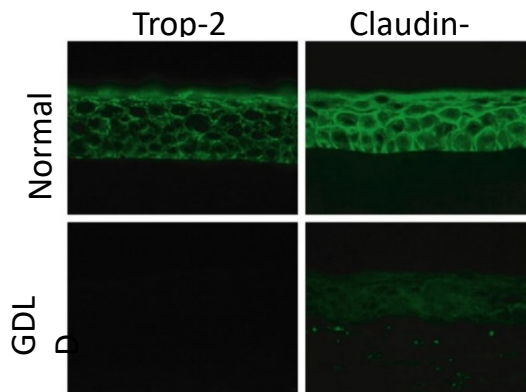


Trop-2 – impact on the tissue organization

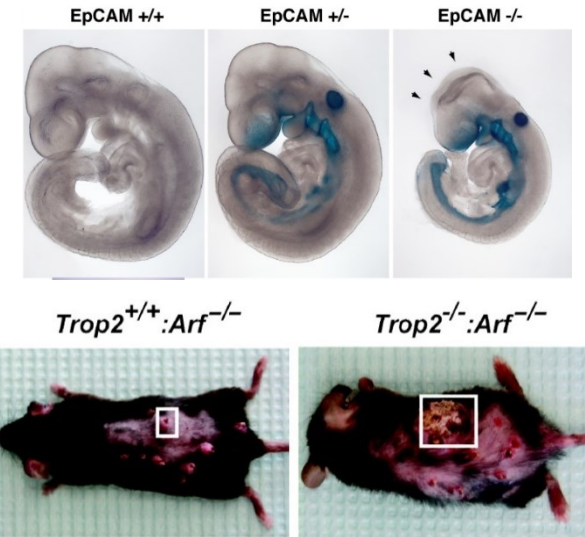
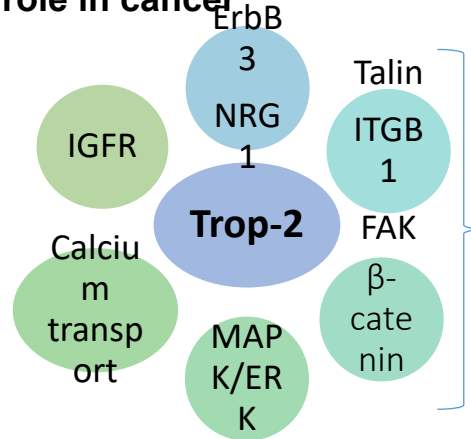
- Homolog of EpCAM
- high Trop-2 and EpCAM - stem cell characteristics, epithelial progenitors
- EpCAM loss - lethal vs Trop-2 loss - tumor promotion
- Involvement in organization of epithelium (proper localization of tight junction proteins Claudins)

Trop-2 mutation

Gelatinous drop-like corneal dystrophy:

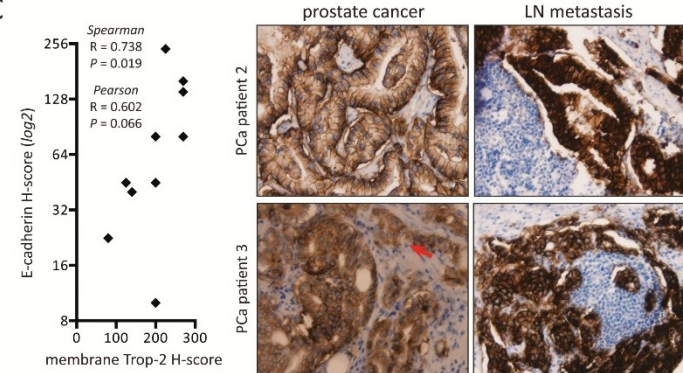
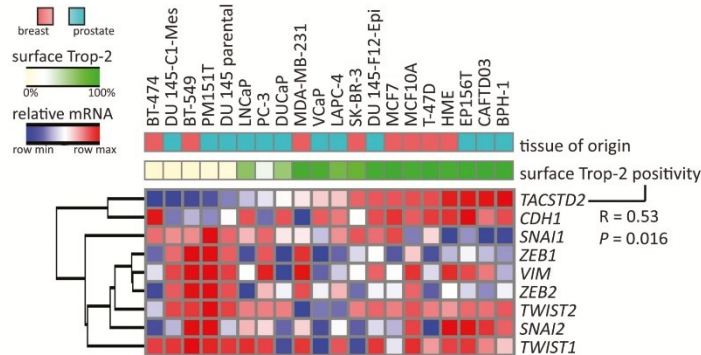


Possible Trop-2 signaling role in cancer

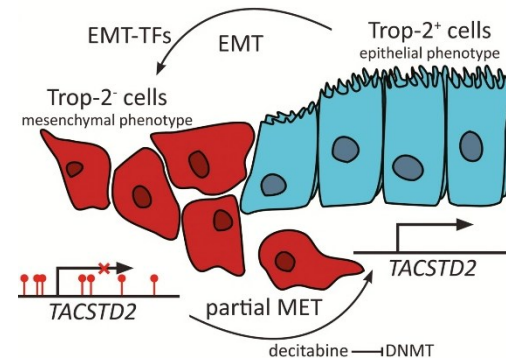
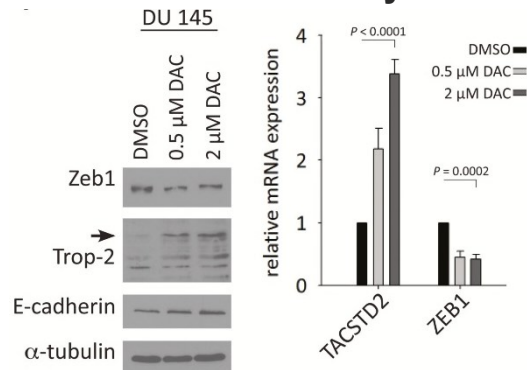


**REPRODUCIBILITY ISSUES
... ROLE OF TROP-2 NEEDS
TO BE CLARIFIED**

Trop2 positively correlates with E-cadherin expression and negatively with the mesenchymal gene signature (breast and prostate cancer cell lines, tumors)



DNA methylation and EMT machinery modulate Trop-2 expression



Trop-2 great target for cancer therapy?

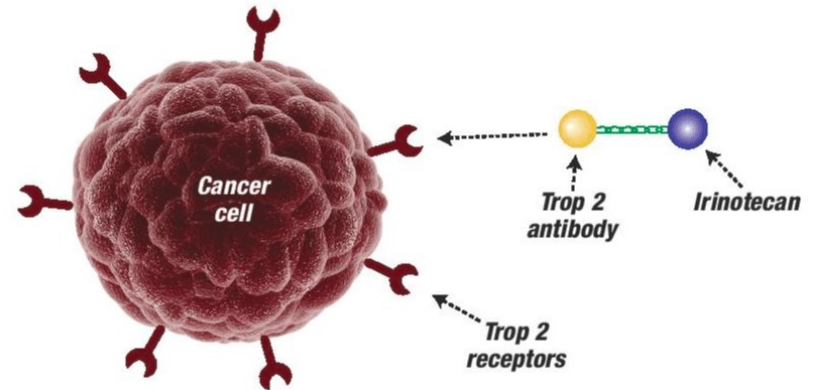
PROS +

- Trop-2 **overexpressed in many cancers** (breast, prostate,...)
- Association with progenitor and stem cells characteristics
- **Trop-2 stimulates tumour growth**
- Trop-2 drives metastasis (reported for prostate cancer)

- **antibody-based cancer therapy** (metastatic triple negative breast cancer)

sacituzumab govitecan

IMMU-132



Trodelvy, SÚKL 3/2022

U.S. FOOD & DRUG ADMINISTRATION

FDA NEWS RELEASE

FDA Approves New Therapy for Triple Negative Breast Cancer That Has Spread, Not Responded to Other Treatments

For Immediate Release: April 22, 2020

Today, the U.S. Food and Drug Administration granted accelerated approval to Trodelvy (sacituzumab govitecan-hydrochloride) for the treatment of adult patients with triple-negative breast cancer that has spread to other parts of the body. Patients must have received at least two prior therapies before taking Trodelvy.

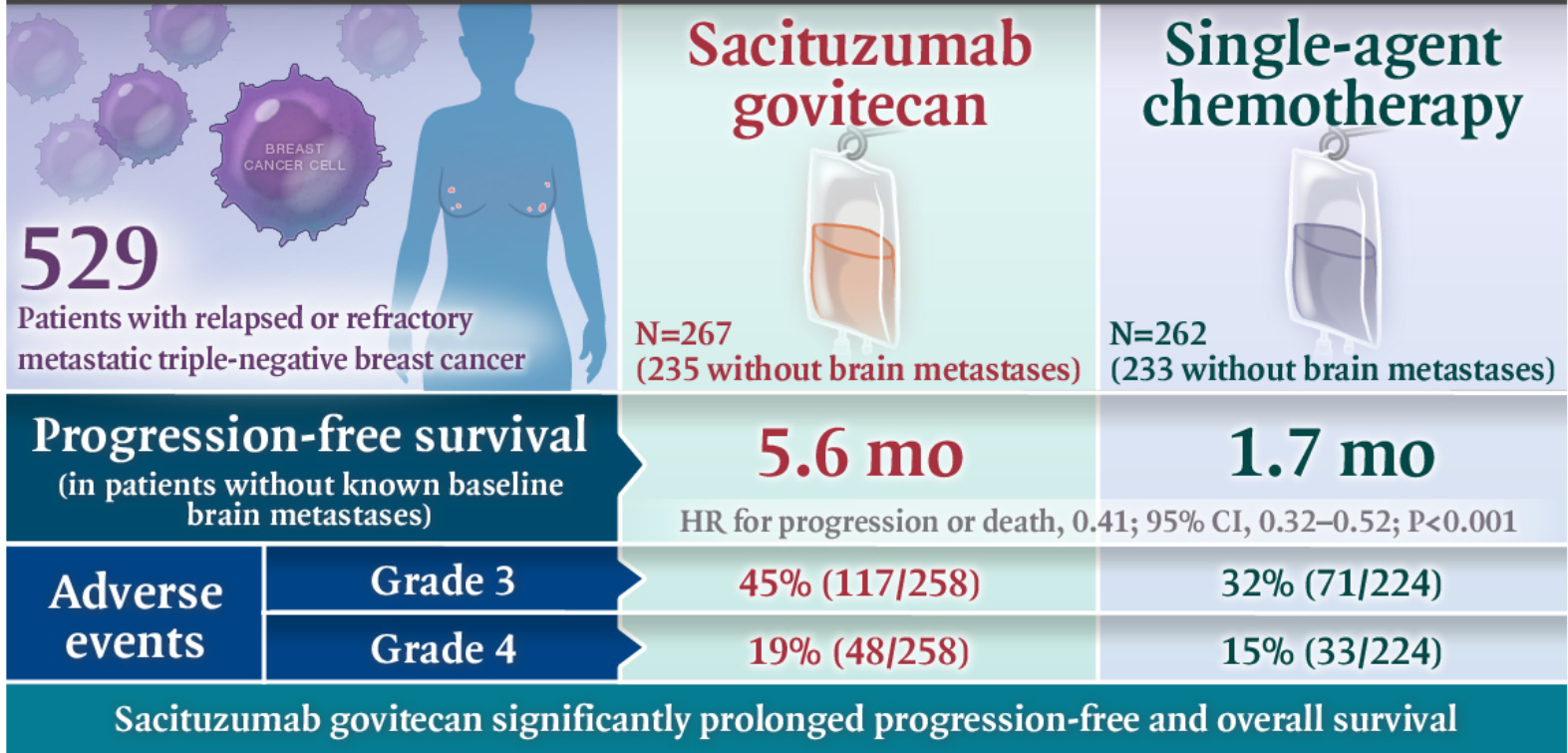
"Metastatic triple-negative breast cancer is an aggressive form of breast cancer with limited treatment options. Chemotherapy has been the mainstay of treatment for triple-negative breast cancer. The approval of Trodelvy today represents a new targeted therapy for patients living with this aggressive malignancy," said Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research. "There is intense interest in finding new modalities to help treat metastatic triple-negative breast cancer. Today's approval provides patients who've already tried two prior therapies with a new option."

Content created on 04/22/2020

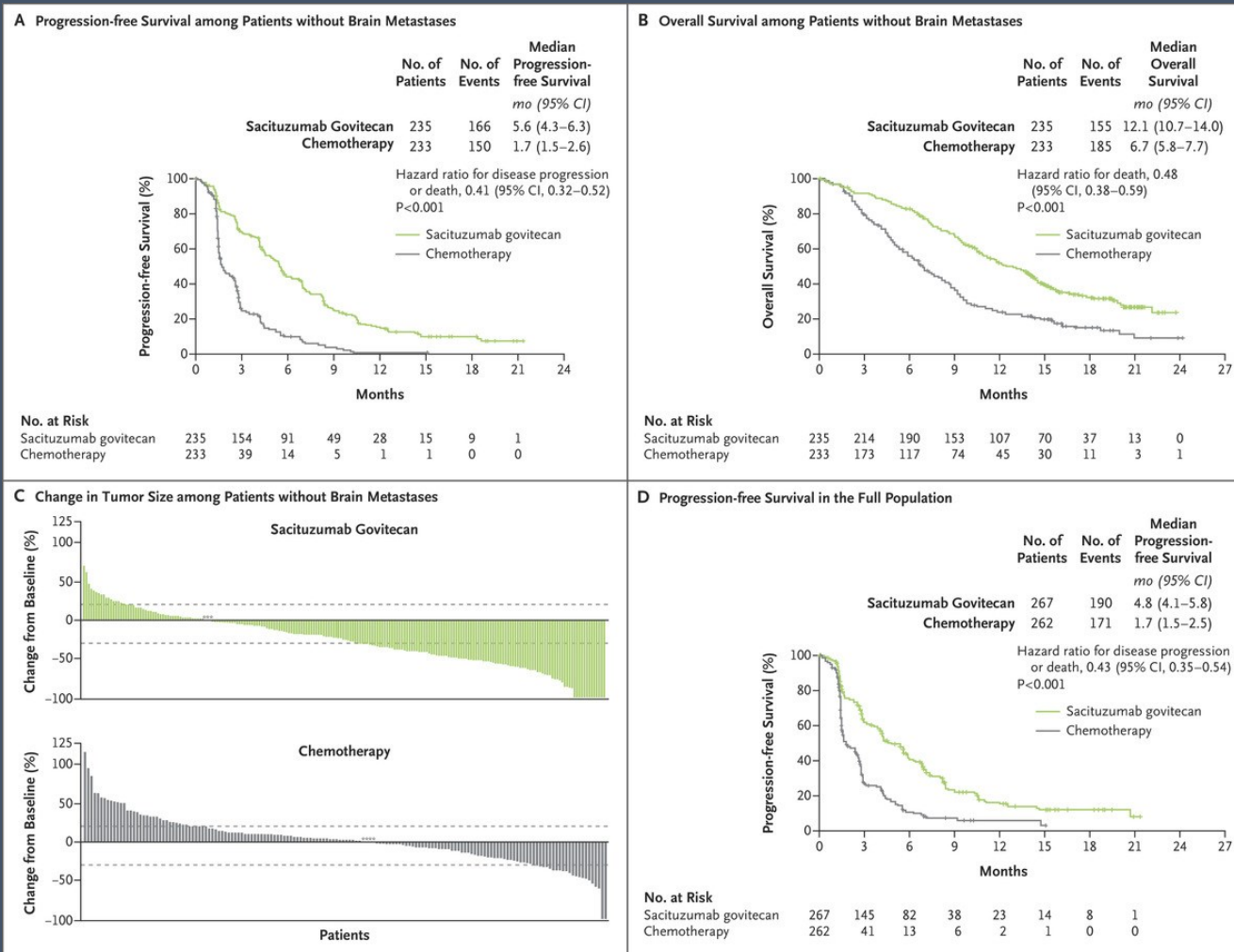
Follow FDA
@FDA
FDA
FDA

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

ASCENT, A PHASE 3, OPEN-LABEL, RANDOMIZED TRIAL



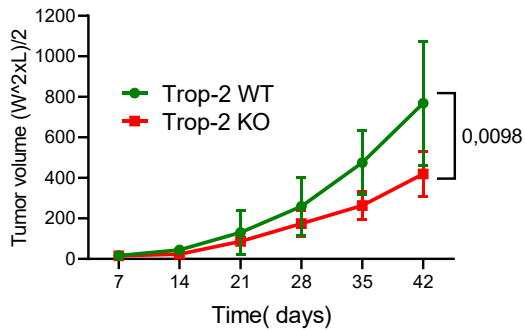
Efficacy Results in Patients without Brain Metastases at Baseline and in the Full Population.



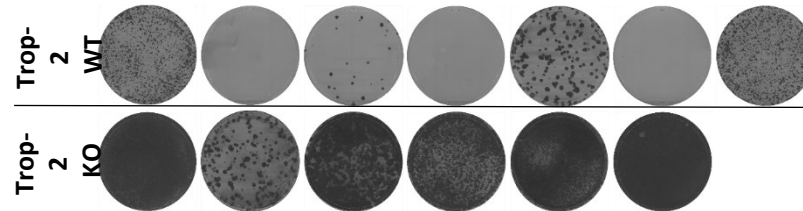
In vivo phenotype of Trop-2 KO breast cancer cells (orthotopic model – spontaneous metastasis)

Growth of primary tumor and spontaneous metastasis of breast cancer models:

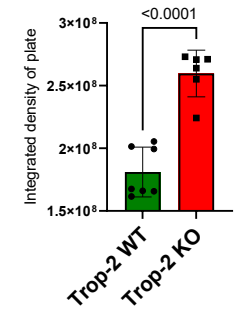
Growth of primary tumor: 4T1 12B luc2



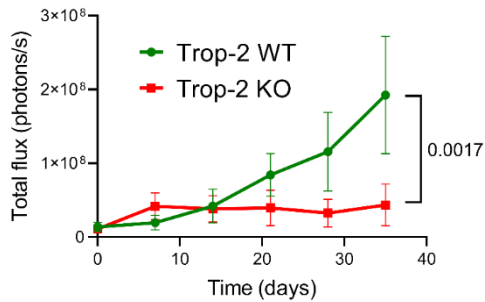
Lung metastasis: 4T1 12B luc2 (clonogenic assay)



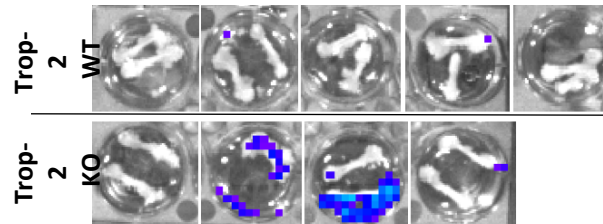
Clonogenic assay quantification



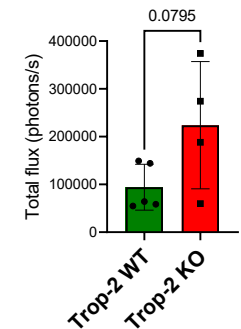
Growth of primary tumor: T-47D



Bone metastasis: T-47D (Ex vivo imaging)



Ex vivo imaging quantification



Trop-2 great target for cancer therapy?

- **antibody-based cancer therapy** (metastatic triple negative breast cancer)

PROS +

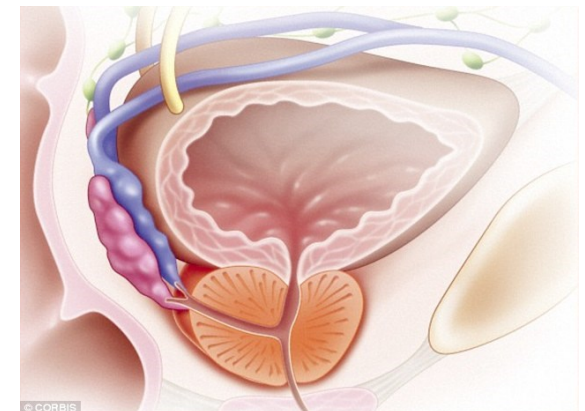
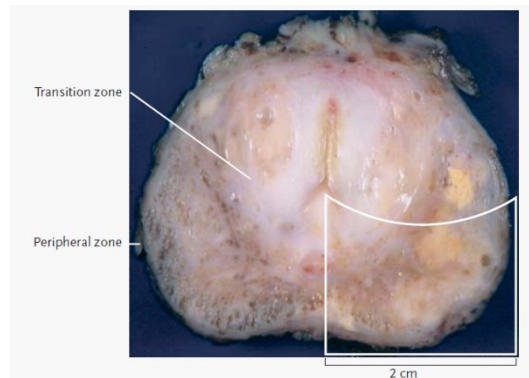
- Trop-2 **overexpressed in many cancers** (breast, prostate,...)
- Association with progenitor and stem cells characteristics
- **Trop-2 stimulates tumour growth**
- Trop-2 drives metastasis (reported for prostate cancer)

CONS -

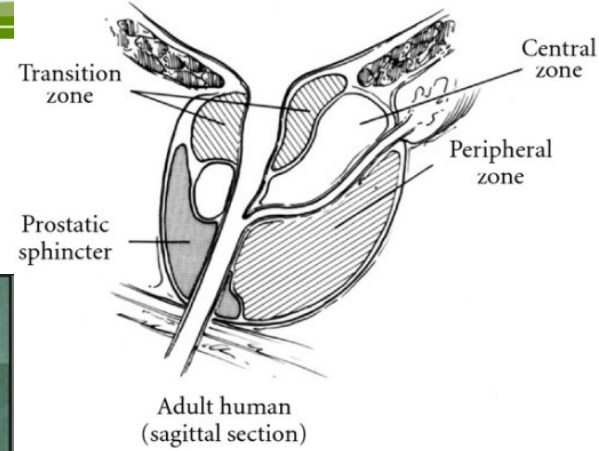
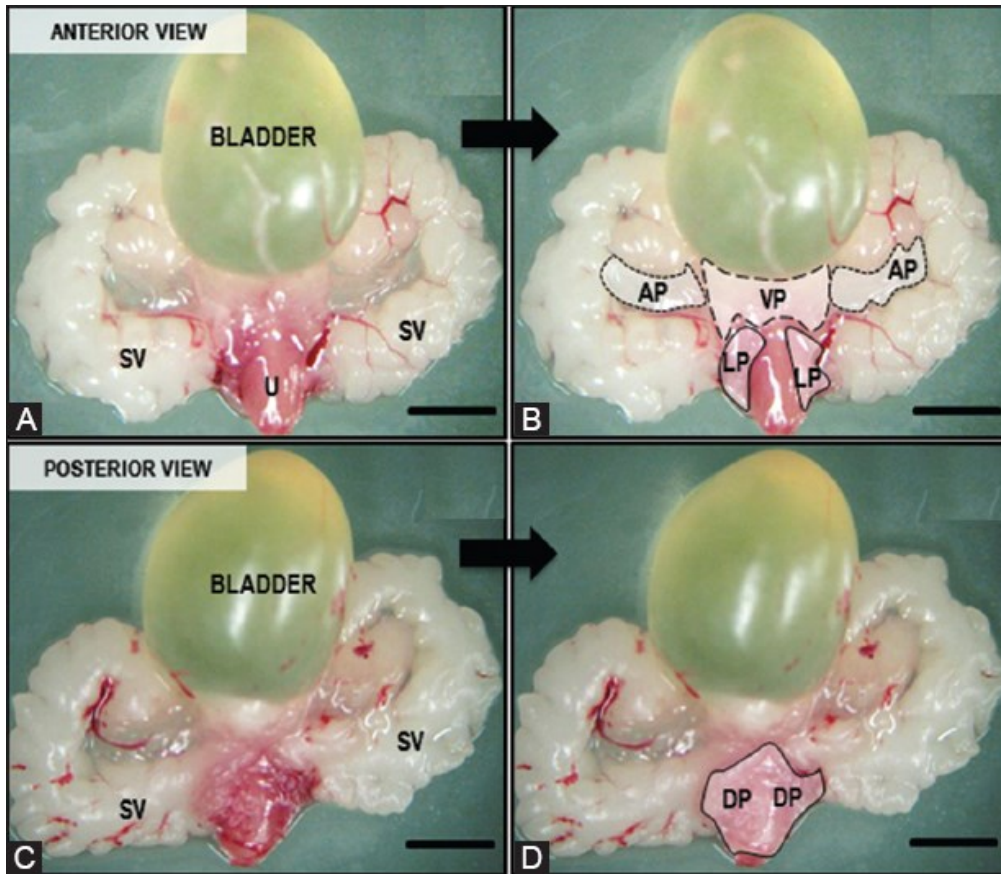
- **Trop-2 KO in mice** – promotion of **solid tumors development**
- Trop-2 connected with an **epithelial phenotype and is suppressed by EMT** transcription factors
- **Intra- and intertumoral heterogeneity** in Trop-2 expression
- **Favourable effect of Trop-2** high expression in some cancer patients datasets

PROSTATA

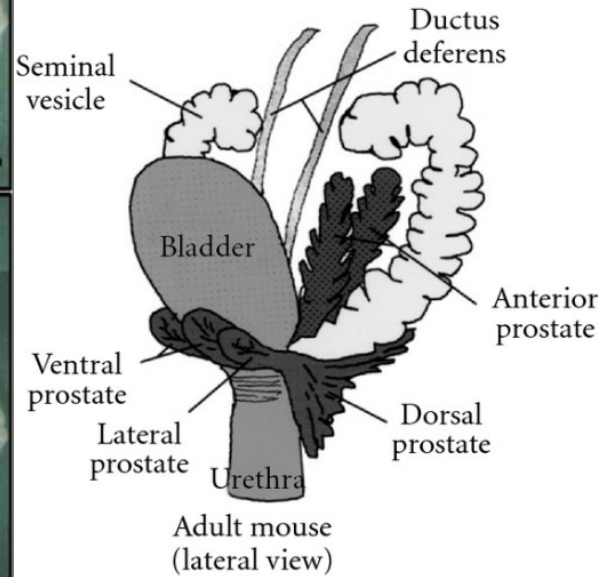
- ▶ parenchymatozní orgán, lumen žlázek je složeno v slizniční řasy (vystlány 1vrst.-dvouřadým kubickým až cyl. epitelem)
- ▶ 30-50 rozvětvených tuboalveolární žlázek uložených ve vazivově-svalovém stromatu; vývody ústí na colliculus seminalis uretry
- ▶ žlázy mají jako podklad **fibromuskulární stroma**
 - ▶ **trojí lokalizace: slizniční , podslizniční, hlavní**
- ▶ **sekret:** hojně bílkovin, kapénky lipidů, kyselá fosfatáza (klin.významná), pH lehce kyselé, kyselina citronová, fibrinolysin, prostaglandiny; ve vyšším věku konkrementy prostaty (corpora amylacea)



Prostata člověk vs. myš

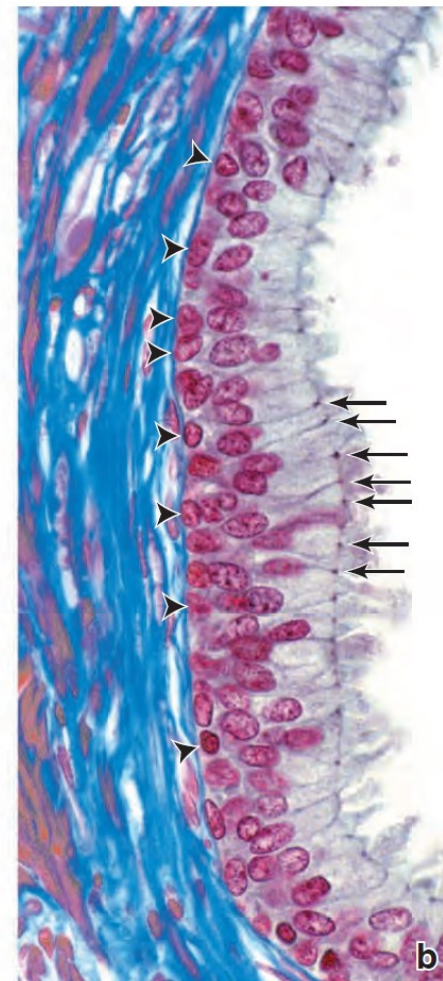
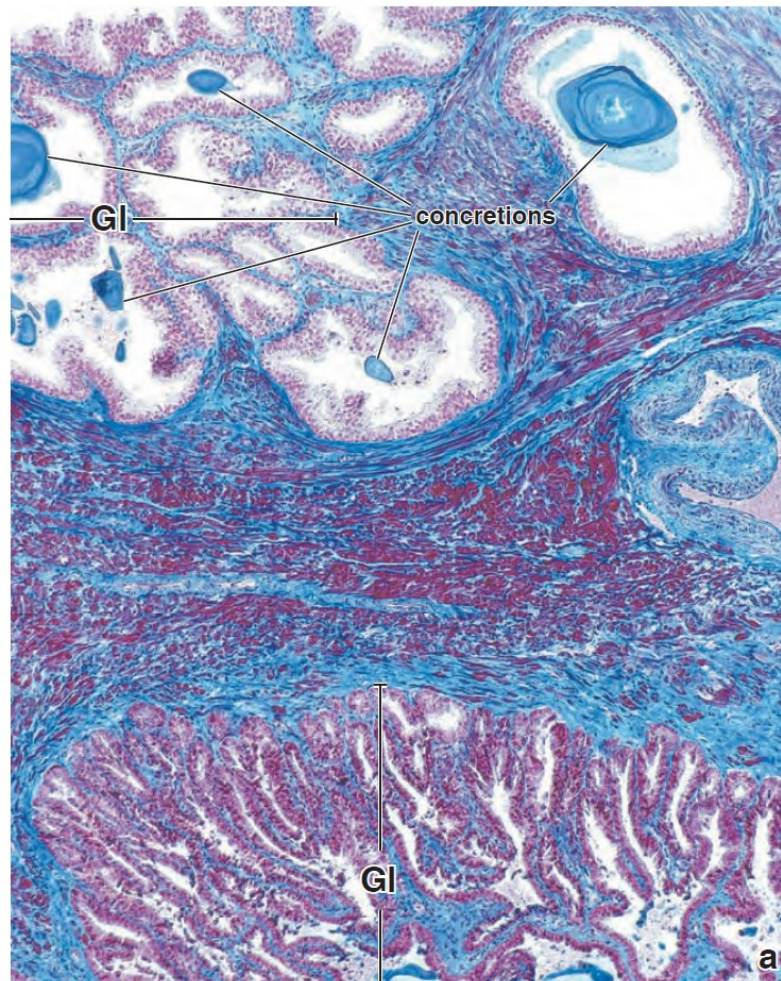


(a)

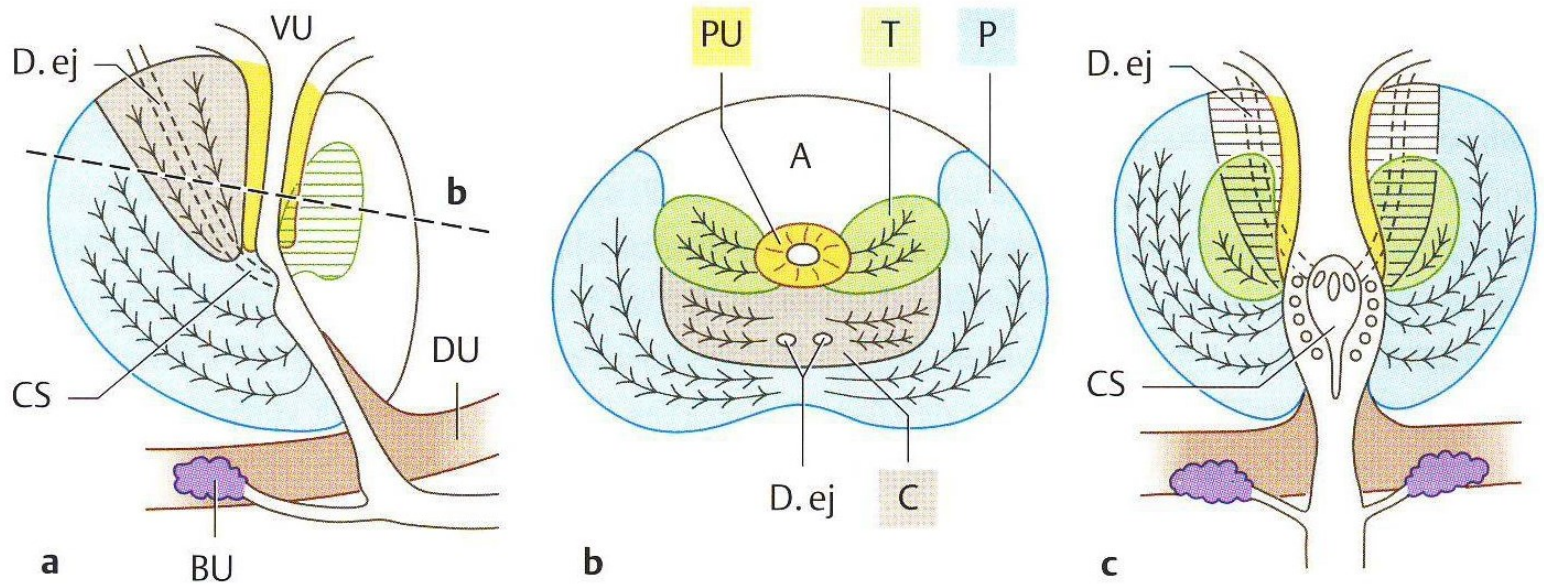


(b)

Prostata - člověk



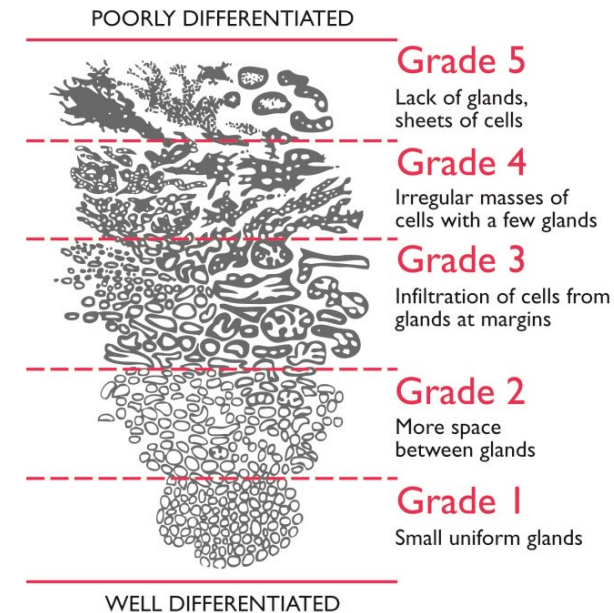
Členění prostaty člověka



- Zóna centrální (C), periferní (P), přechodová (T), periuterální (PU), přední, nežlaznatá (A)

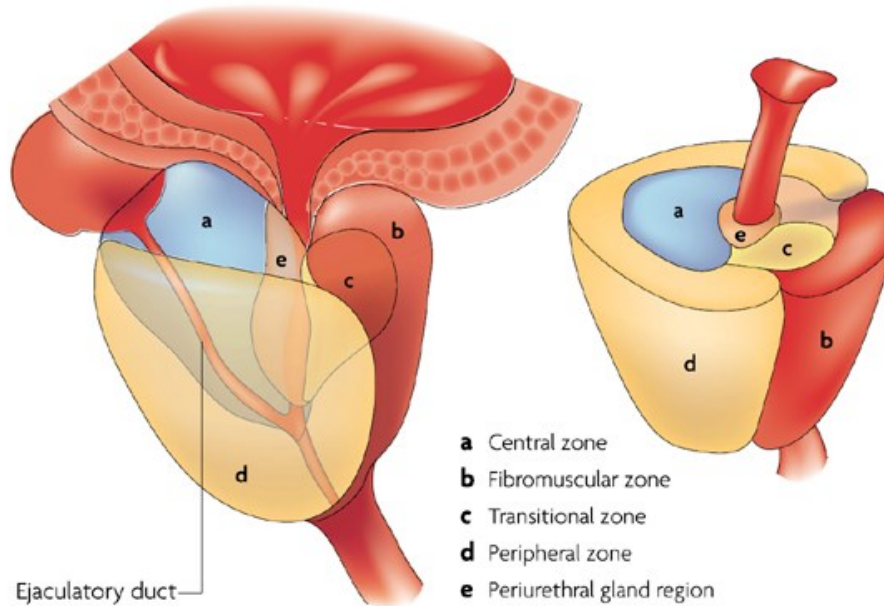
Karcinom prostaty

- Třetí nejčastější nádorové onemocnění u mužů
 - Diagnostikován u 20% mužů, u 3% příčinou úmrtí (USA)
- 95% - adenokarcinom
- Heterogenní, multifokální charakter
 - Gleasonovo skóre – zohledňuje stupeň diference
- TNM klasifikace
 - TX – primární nádor nelze hodnotit
 - T0 – bez známek primárního nádoru
 - T1 – nezjistitelný klinicky, palpačně ani zobrazovací metodou
 - T2 nádor omezený na prostatu
 - T3 nádor se šíří přes pouzdro prostaty
 - NX, N0, N1 – zasažení regionálních mízních uzlin
 - MX, M1 – vzdálené metastázi
 - Stádia - I – IV (př. III – T3 N0 M0)



Zonální predispozice k onemocnění prostaty

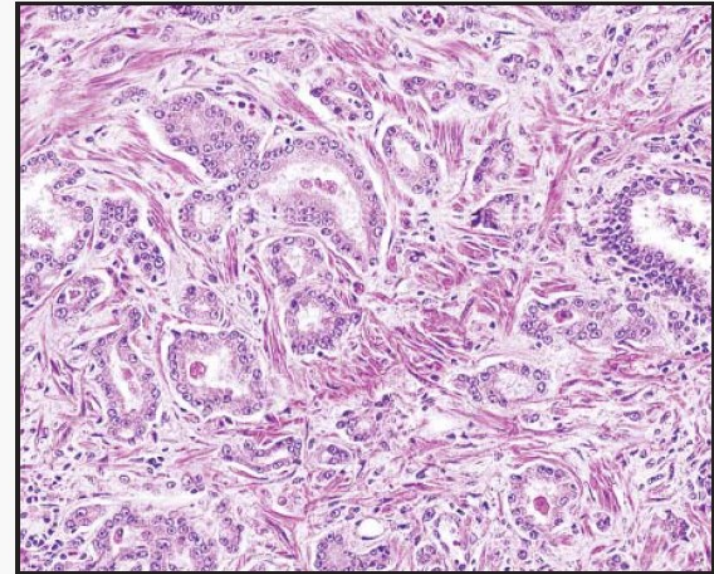
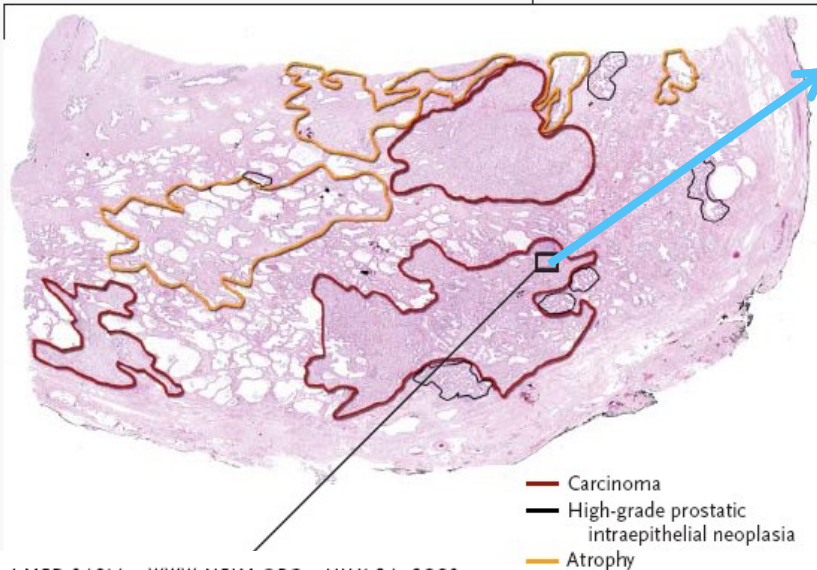
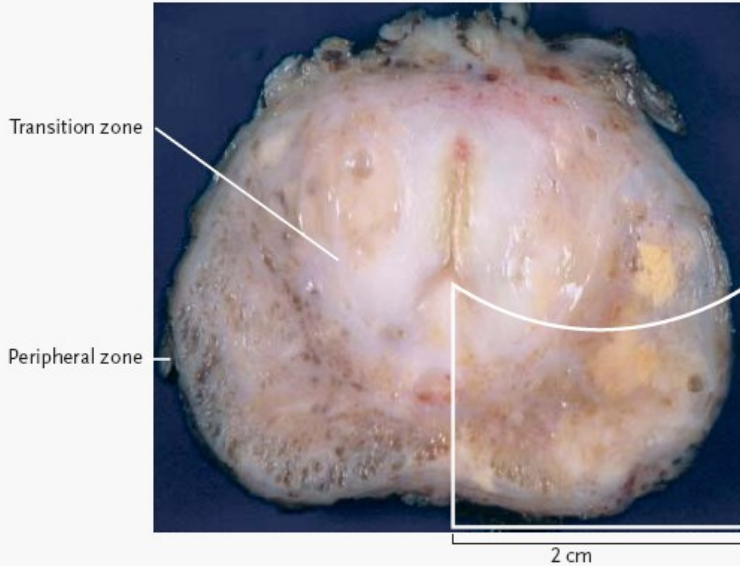
Prostate zones



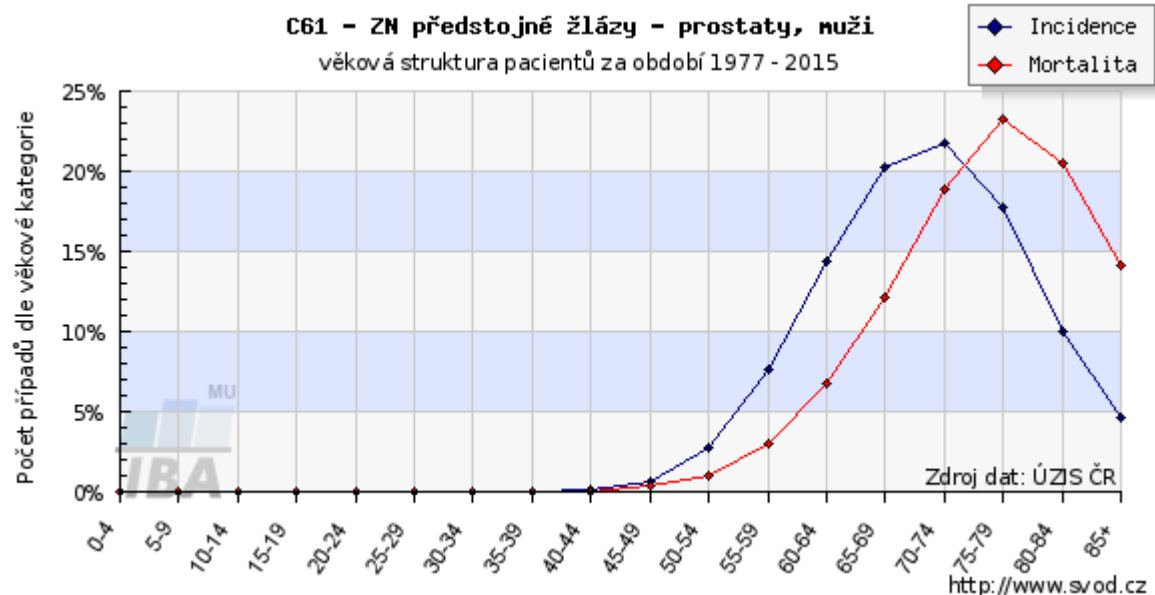
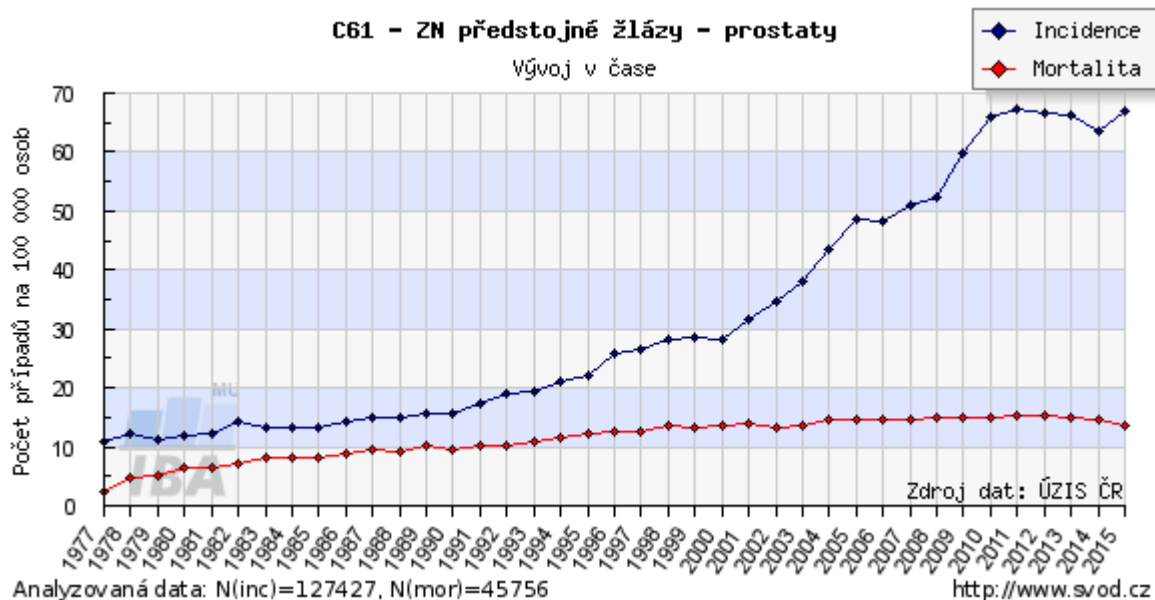
	Prostate zone		
	Peripheral	Transition	Central
Focal atrophy	High prevalence	Medium-high prevalence	Low prevalence
Acute inflammation	Low prevalence	Low prevalence	None
Chronic inflammation	Medium-high prevalence	Medium-high prevalence	Low prevalence
Benign prostatic hyperplasia	None	High prevalence	Low prevalence
High-grade PIN	High prevalence	Medium-high prevalence	Low prevalence
Carcinoma	High prevalence	Medium-high prevalence	Low prevalence

■ High prevalence ■ Low prevalence
■ Medium-high prevalence ■ None

Mechanismy karcinogeneze



Karcinom prostaty - incidence



Karcinom prostaty – rizikové faktory, prognóza

➤ Riziko

- Hladina DHT (etnický původ)
- Věk
- Rodinná anamnéza (15%, mutace BRCA1, BRCA2)
- Stravovací návyky

➤ Prognóza

- TNM, Gleasonovo skóre, Prostate Specific Antigen (PSA)
– nízké < 10ng/ml, vysoké > 20ng/ml

➤ Klinické příznaky

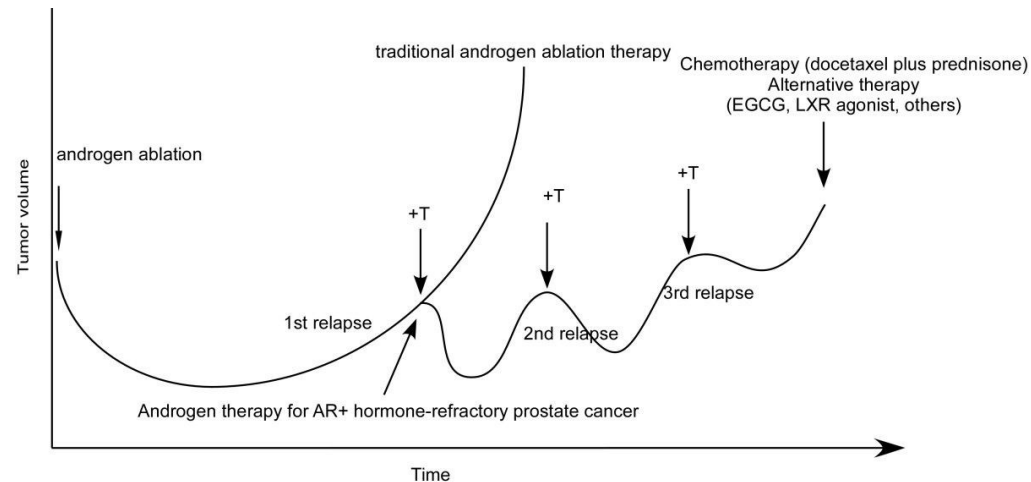
- 75% nádorů bez příznaku, krev v moči a ejakulátu, poruchy močení, metastázování do kostí

➤ Diagnostika

- Biopsie, PSA, sonografie, MRI, scintigrafie skeletu

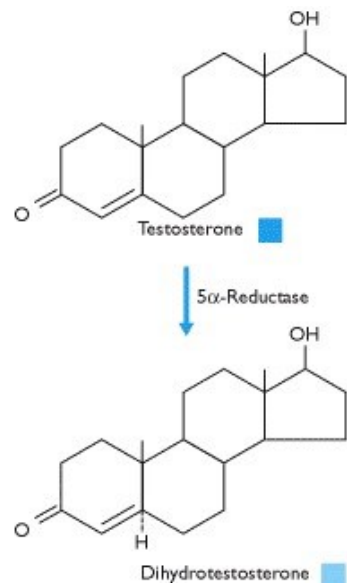
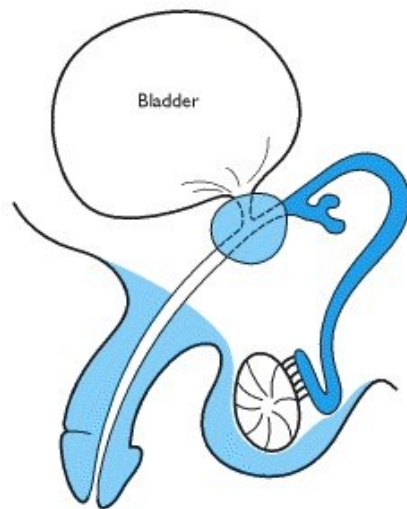
Léčebný postup

- ◆ Nemocní s velmi nízkým rizikem
 - ◆ Terapie v případě výhledu přežití > 20 let
 - ◆ jinak pouze observace
- ◆ Nemocní s nízkým rizikem
 - ◆ v případě výhledu přežití do 10 let
 - ◆ observace
 - ◆ v případě výhledu přežití > 10 let
 - ◆ radikální prostatektomie
 - ◆ Radikální ozáření
- ◆ Nemocní se středním rizikem
 - ◆ v případě výhledu přežití do 10 let
 - ◆ observace
 - ◆ v případě výhledu přežití > 10 let
 - ◆ radikální prostatektomie
 - ◆ Radikální ozáření
 - ◆ Krátkodobá **androgen deprivation therapy (ADT)**
- ◆ Nemocní s vysokým rizikem
 - ◆ v případě výhledu přežití do 5 let
 - ◆ observace
 - ◆ v případě výhledu přežití > 5 let
 - ◆ radikální prostatektomie
 - ◆ Radikální ozáření
 - ◆ androgen deprivation therapy (ADT)

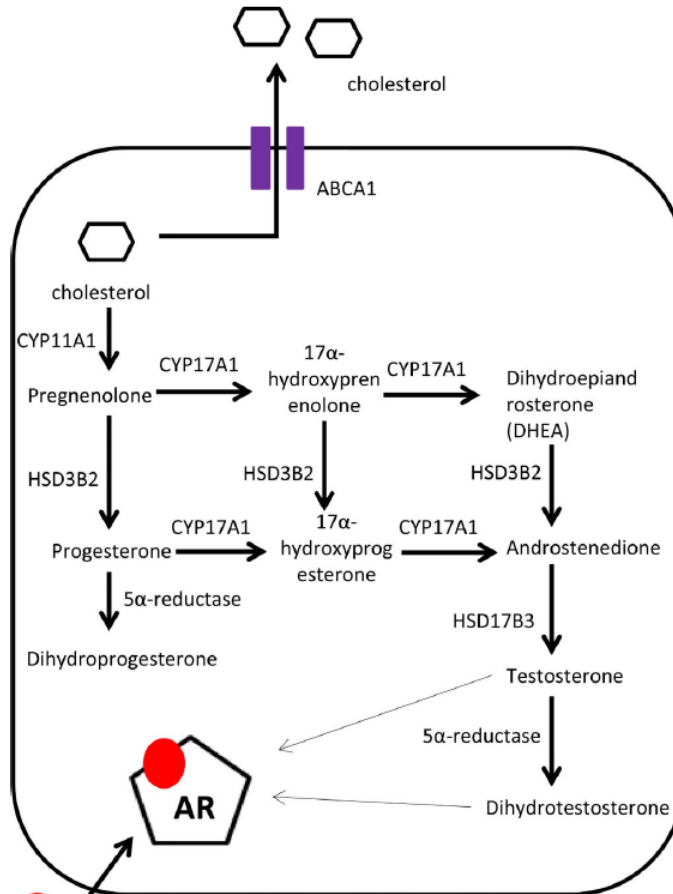


Hlavní místa syntézy mužských pohlavních hormonů:

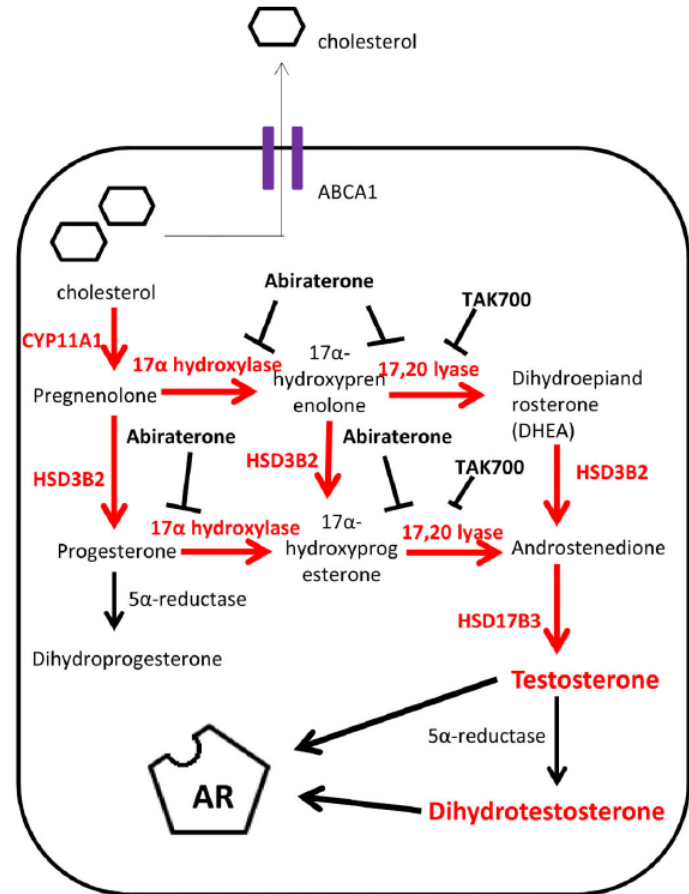
Muž (%)	Varlata	Nadledvinky	Konverze ve tkáních
Testosterone	95	<1	<5
5 α -DHT	20	<1	80
Androstenedione	20	<1	90
DHEA	2	<1	98
DHEA-S	<10	90	-



Biosyntéza androgenů



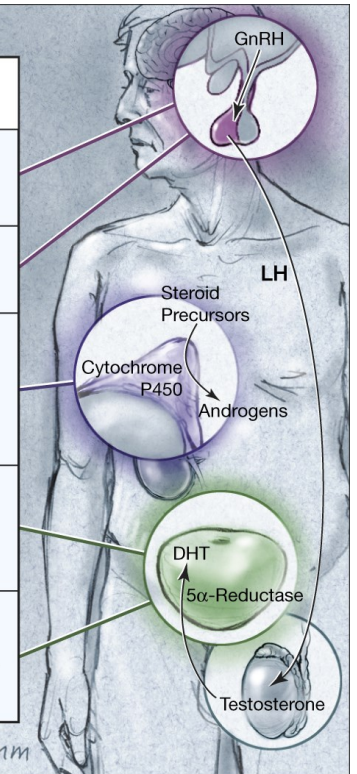
Hormone naïve prostate cancer



Castrate resistant prostate cancer

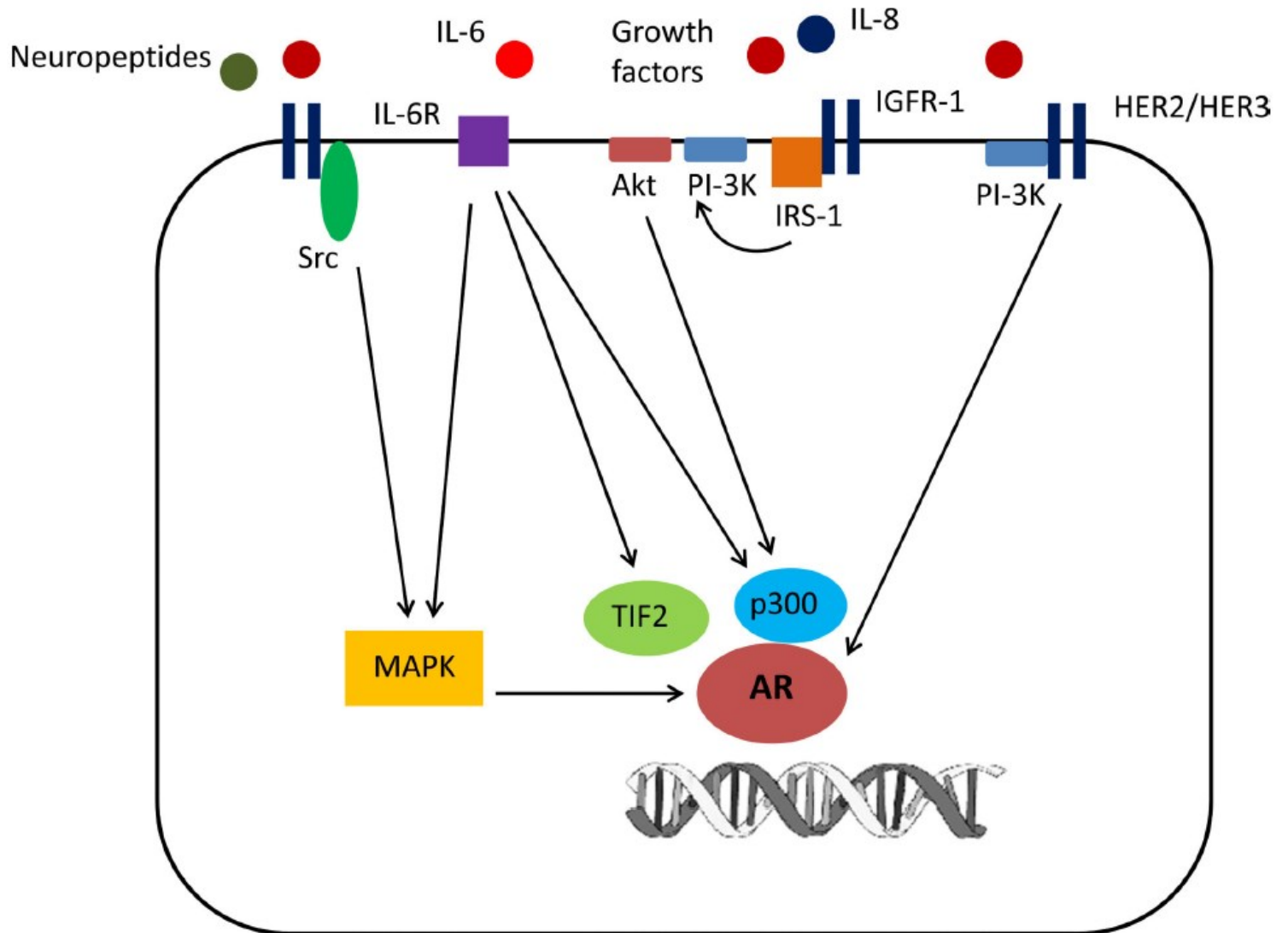
Mechanism of androgenesis

Drug Class	Drugs	Site of Action	Mechanism of Action	Comments/Risks
Gonadotropin-Releasing Hormone (GnRH) Agonists	Leuprolide Goserelin	Anterior Pituitary Gland	Decreases Release of LH Through Down-regulation of GnRH Receptors	Testosterone Surge
GnRH Antagonists	Abarelix*	Anterior Pituitary Gland	Directly Inhibits GnRH Receptors	Anaphylaxis
Adrenal Ablating Drugs	Ketoconazole	Adrenal Gland	Decreases Androgen Synthesis From Steroid Precursors Through Inhibition of Cytochrome P450 Enzymes	Administration Requires Steroid Supplementation to Prevent Adrenal Insufficiency
Androgen Receptor Antagonists	Flutamide Bicalutamide Nilutamide	Prostate Gland	Inhibits Androgen Receptor Ligand-Binding Domain Through Competitive Binding	Gynecomastia, Increased Liver Transaminases, and Mastodynia
5 α -Reductase Inhibitors	Finasteride	Prostate Gland	Decreases Conversion of Testosterone to DHT Through Inhibition of 5 α -Reductase	No Defined Role in Standard Care of Prostate Cancer

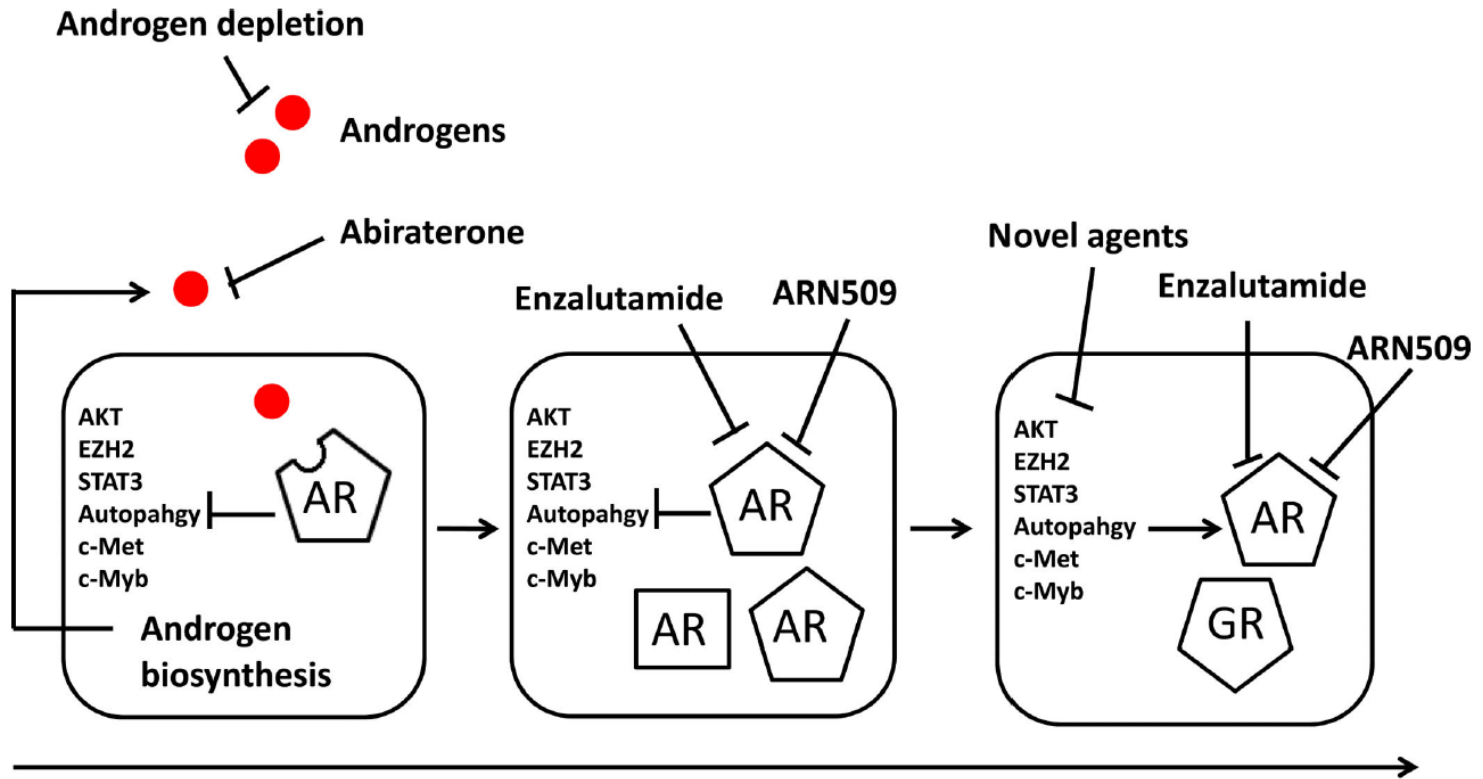


C. Lynn

Alternativní onkogenní dráhy regulující postranlační modifikace AR



Progrese karcinomu prostaty

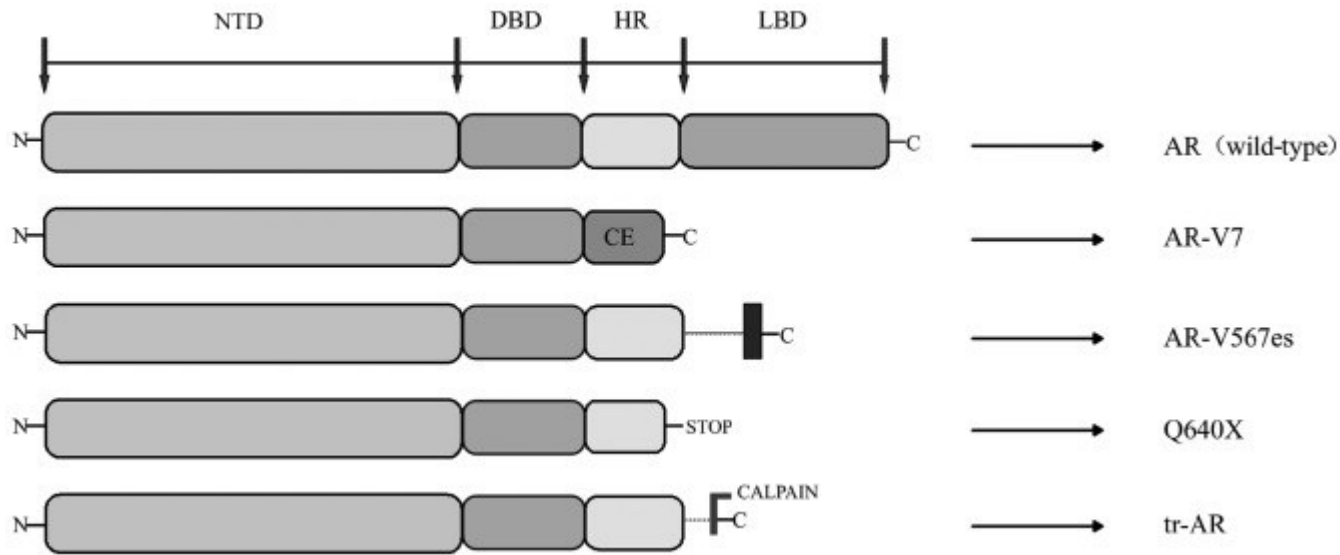


- Androgen biosynthesis at the tumor microenvironment

- AR mutations
- AR amplifications
- AR variants

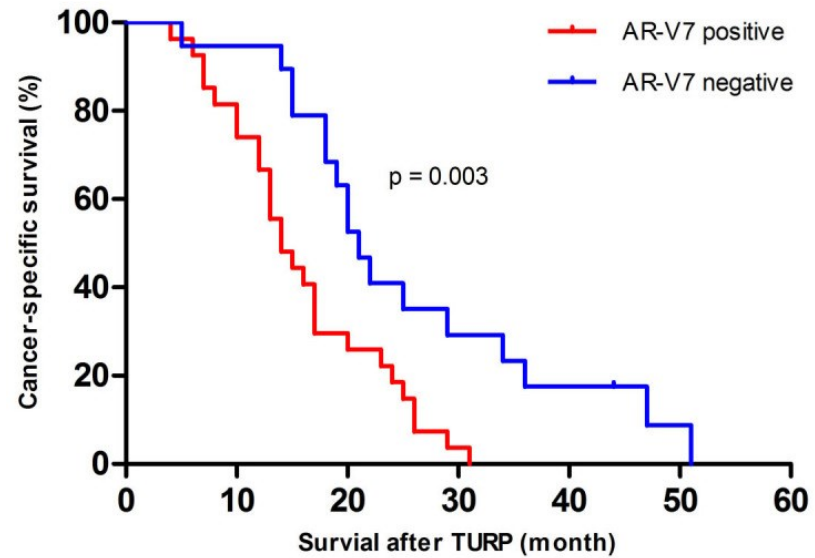
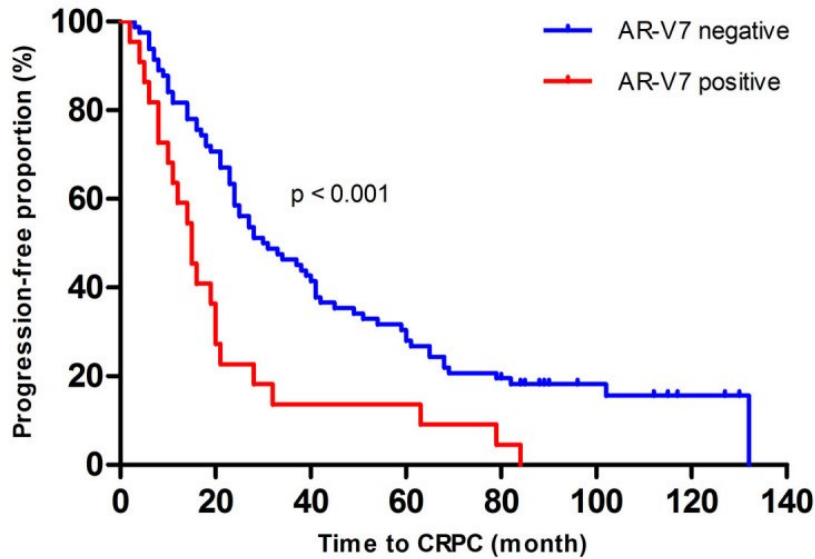
- GR upregulation
- Alternative oncogenic signaling induction

AR a jeho varianty



AR, full length AR wild type; AR-V7, product of alternative splicing, CE; ARv567es, product of altered splicing, exon 5, 6 and 7 skipped during splicing; Q640X, AR with a nonsense mutation leading to a tr-AR of 640 aa; enzymatically cleaved by calpain. AR, androgen receptor; DBD, DNA-binding domain; LBD, ligand-binding domain; PCa, prostate cancer; CE, cryptic exon; tr-AR, truncated AR; AR-V, AR splice variants; NTD, N-terminal domain; HR, hinge region.

Role AR-V7 v rozvoji rezistentního karcinomu prostaty



Vakcína proti karcinomu prostaty

- sipuleucel-T (Provenge) - vakcína pro léčbu karcinomu prostaty (od roku 2010)
- Imunogen – prostatic specific phosphatase
- Využití v terapii pokročilého onemocnění – rezistentního na anti-androgenní léčbu
- 100 000 USD/patient
- Další v testech – např. POSTVAC, rekombinantní poxvirus exprimující PSA

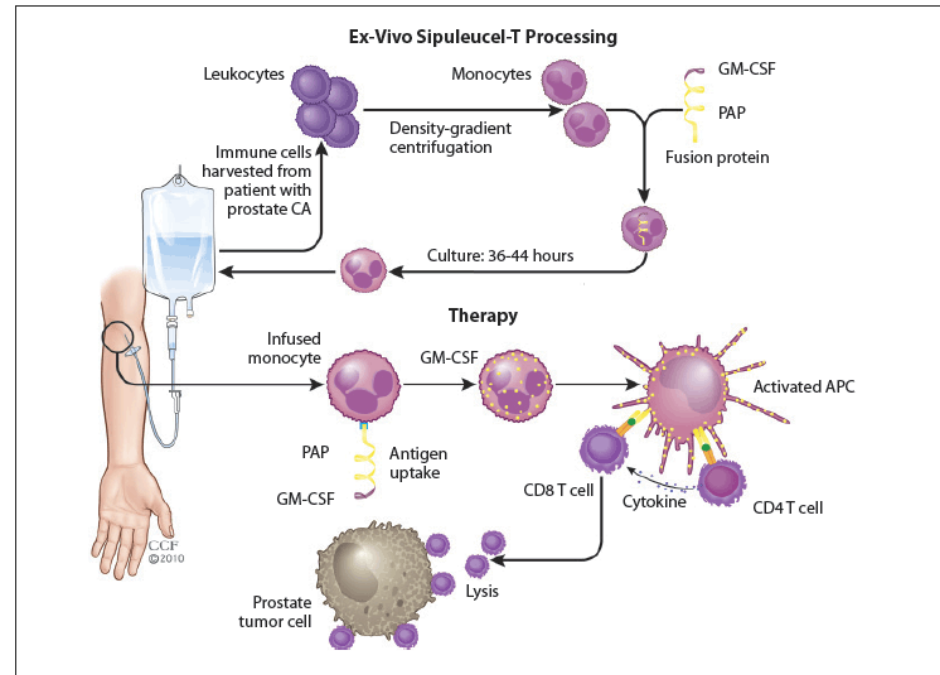
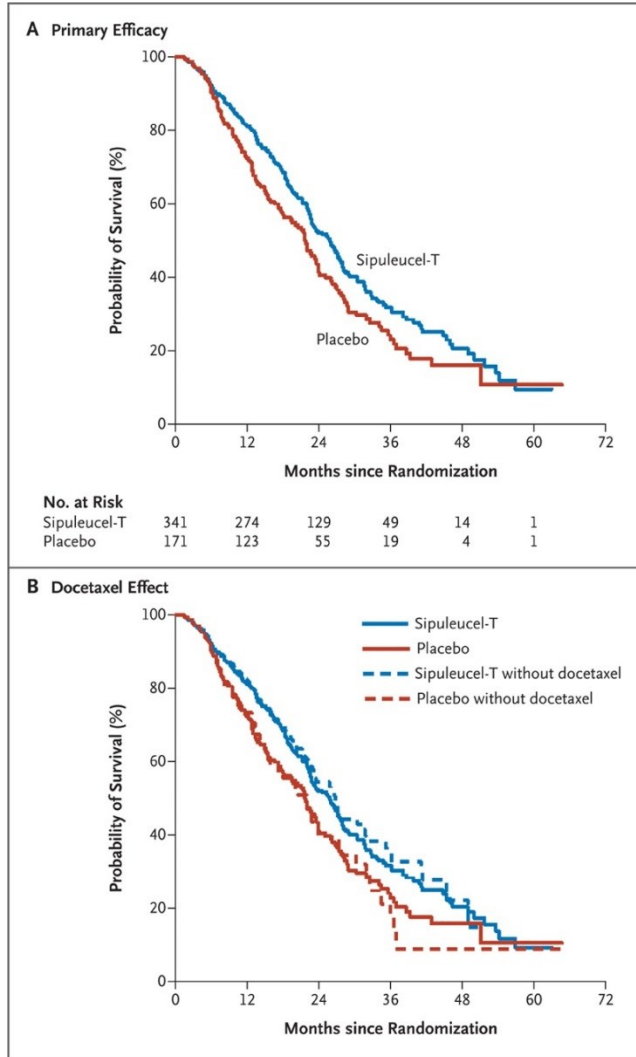


Figure: The diagram illustrates the two steps involved in sipuleucel-T therapy: (1) harvesting the patient's dendritic cells and then pulsing these ex vivo with a recombinant fusion protein made of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF); and (2) infusing the cultured cells into the patient, where the PAP-GM-CSF-loaded antigen-presenting cells induce the proliferation of T-cells that recognize and target prostate tumor cells. APC = antigen-presenting cell.

sipuleucel-T (Provenge)





...se smiřuje s nutností vstupu do NATO



...už pojmy žena a muž nestačí



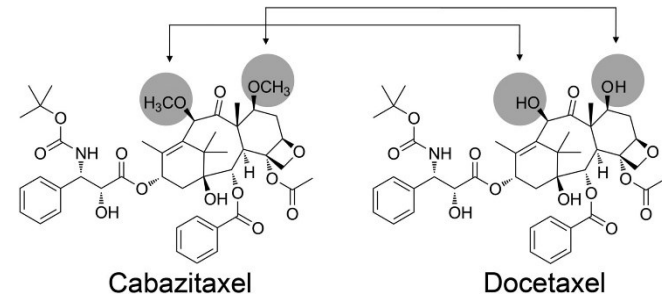
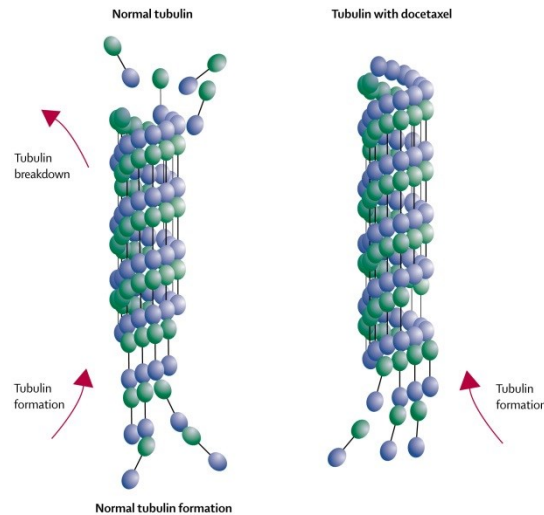
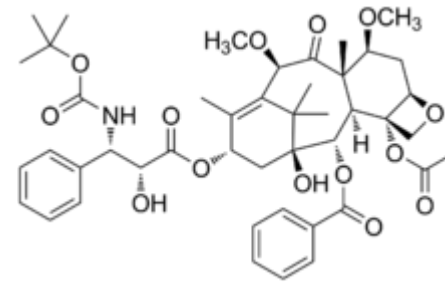
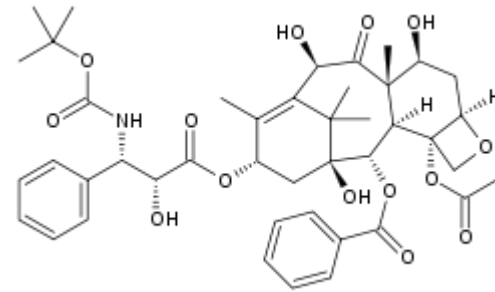
...vlastní kůži. Vouchery do českého TEPfactoru zdarma

Průlomová léčba rakoviny prostaty už se testuje. Zásahu má i česká vědkyně

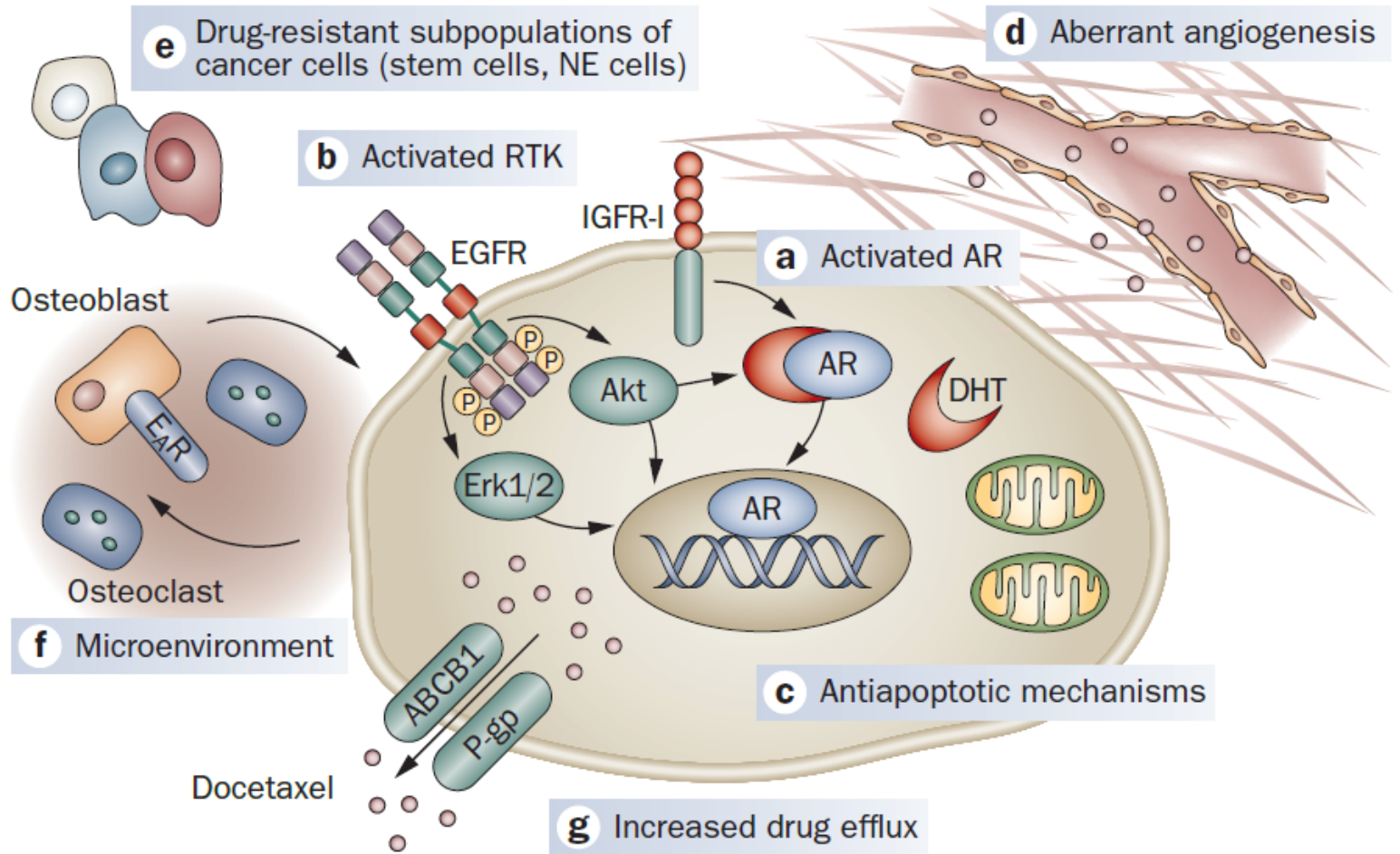


Chemoterapie pokročilého adenokarcinomu prostaty

- Docetaxel (Taxotere)
 - Semi-syntetický analog paclitaxelu
 - Stabilizuje mikrotubuly
 - Benefit ~ 5 měsíců
 - rezistence
- Cabazitaxel (Jevtana)



Mechanismy docetaxelové rezistence



Shrnutí

➤ Nádory prsu

- Hormonálně dependentní – lze relativně šetrně léčit
- TNBC – neexistuje efektivní cílená léčba
- Dlouhé období dormance
- ? mechanismus aktivace a vzniku makrometastáz
- Zásadní otázky:
 - Jaké nádory léčit?
 - Lepší biomarkery a prediktory
 - Koho a jak často vyšetřovat mamogramem?
 - Jaké jsou skutečné možnosti imunoterapie?
 - Jaké jsou faktory rizika?

➤ Nádory prostaty

- Relativně pomalu progredující
- AR cílená terapie končí rozvojem rezistentního, metastazujícího onemocnění
- Zásadní otázky:
 - Co způsobuje nádorové onemocnění prostaty?
 - Je testování hladiny PSA vhodnou metodou pro screening?
 - Je bezpečné neléčit nádory prostaty?
 - Je možná léčba pokročilého karcinomu prostaty?