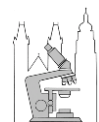


Nové prediktory imunoterapie – pohled do budoucnosti

A. Ryška

Fingerlandův ústav patologie LF UK a FN, Hradec Králové





„Dělat předpovědi je těžké, zvláště pokud se týkají budoucnosti.“



Prediktivní biomarkery

vědecky/biologicky zajímavé, uchopitelné

x

klinicky využitelné

x

regulátory vyžadované

Prediktivní biomarkery

vědecky/biologicky zajímavé, uchopitelné

x

klinicky využitelné

x

regulátory vyžadované

Prediktivní biomarkery

vědecky/biologicky zajímavé, uchopitelné

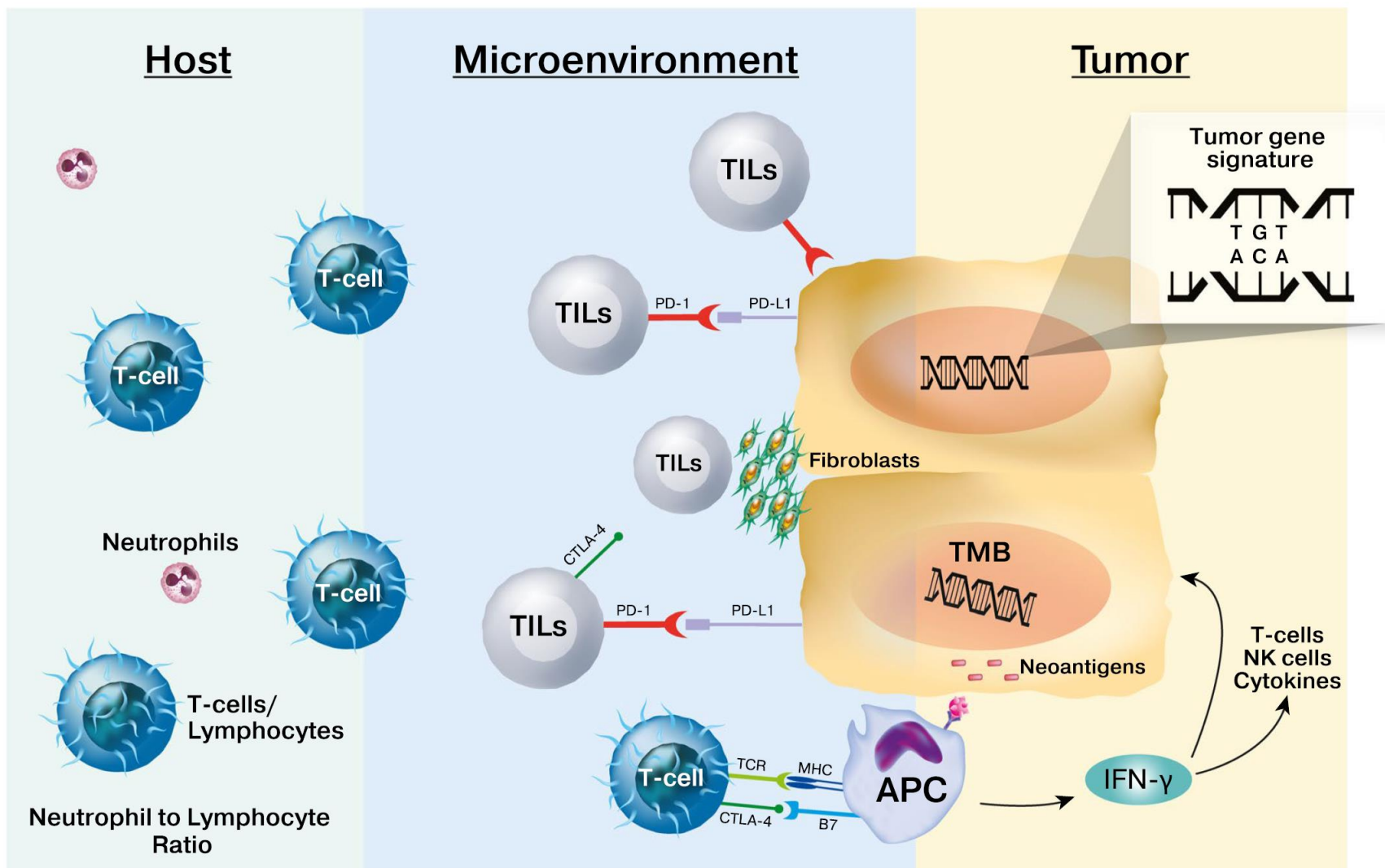
X

klinicky využitelné

X

regulátory vyžadované

Faktory ovlivňující interakci nádoru s imunitním systémem



Faktory ovlivňující interakci nádoru s imunitním systémem

Mikroprostředí

- specifické vlastnosti
- DDR1, 2
- Thrombospondin-1
- TIL

Antigenicita tu bb.

- TNB (tumor neoantigen burden)
- TMB (tumor mutation burden)

Příčiny - vrozené x získané

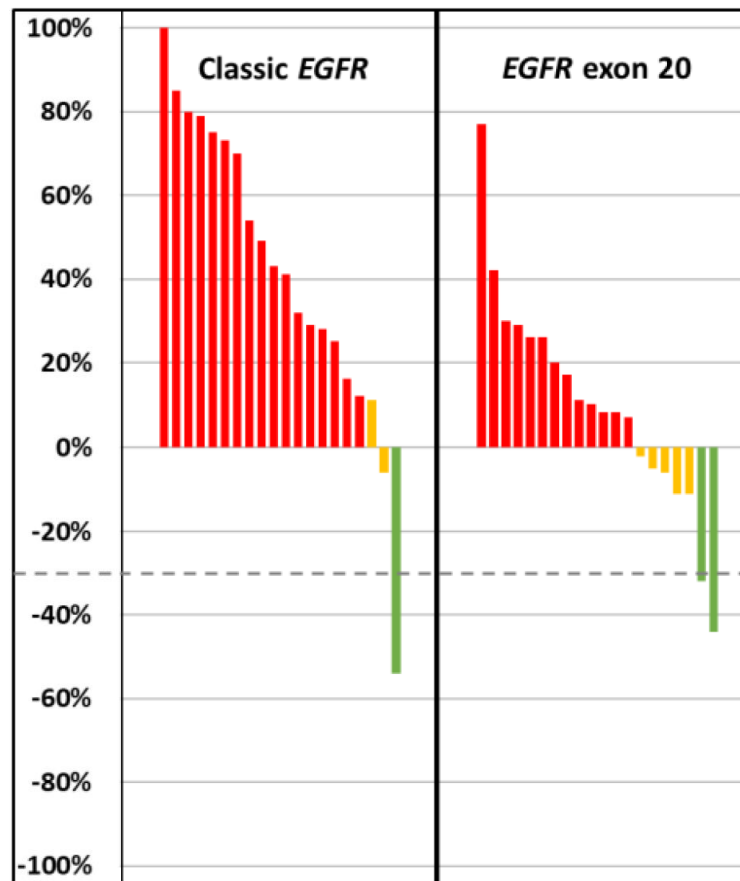
- HRD (zejm. BRCA 1/2)
- dMMR (MSI)
- POLE
- kouření, chemické látky
- viry (HPV, EBV, PV)
- protinádorová léčba

Schopnost "ošálit" imunitu

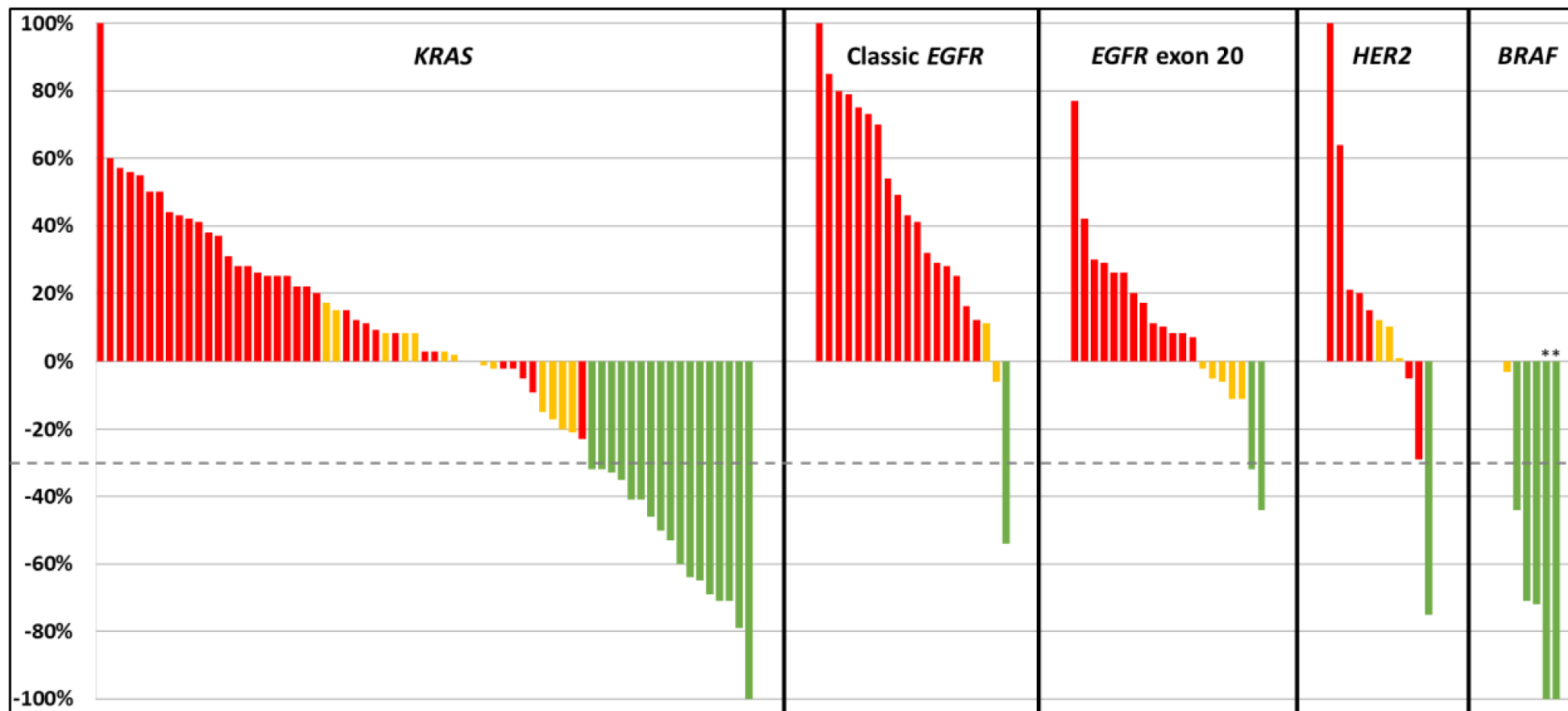
- PD-L1 exprese
- INF gamma gene signature
- STK11
- KEAP1

V různých nádorech hrají jednotlivé faktory různou roli!

Role driver mutací není černobílá!

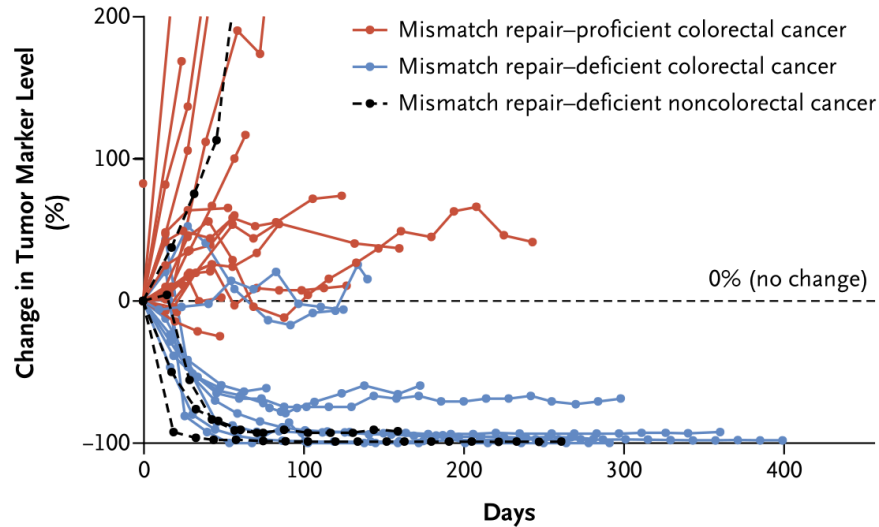


Role driver mutací není černobílá!

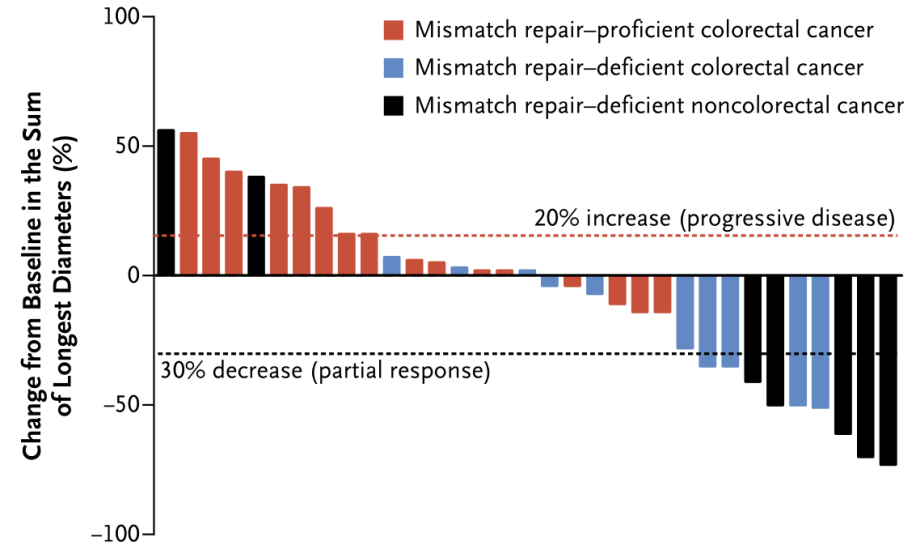


PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

A Biochemical Response

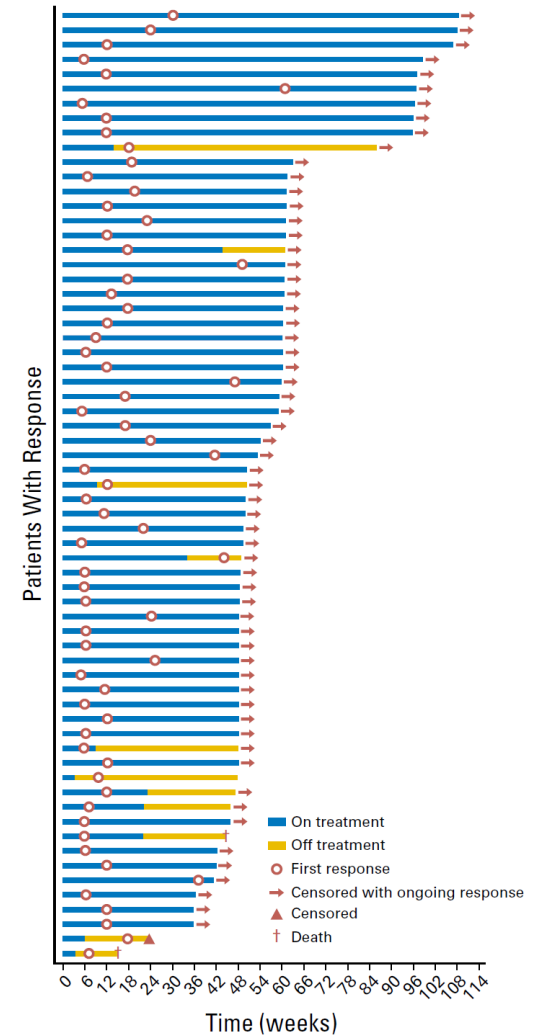
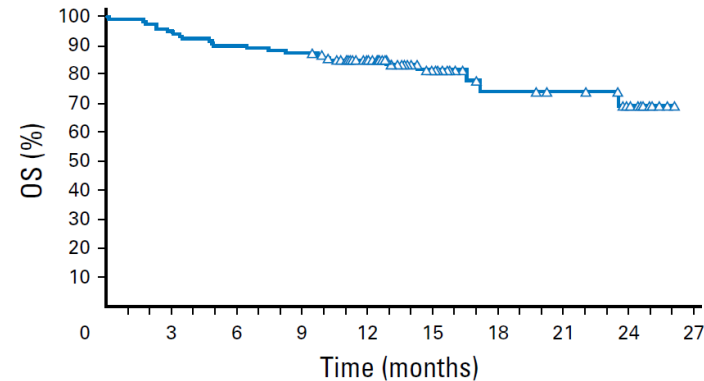
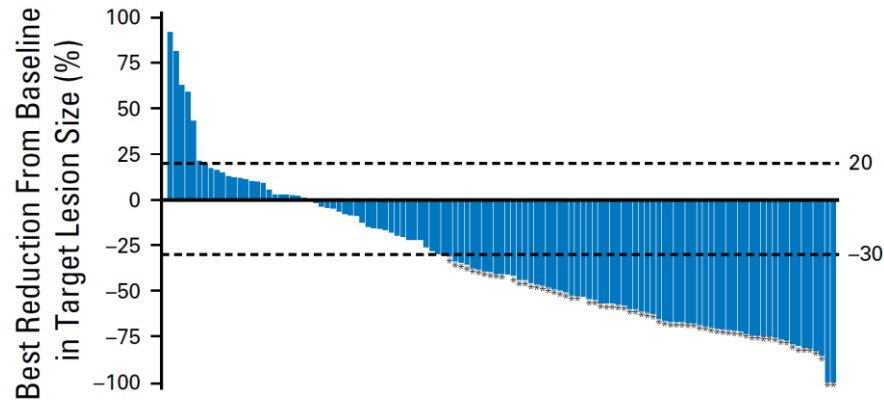


B Radiographic Response

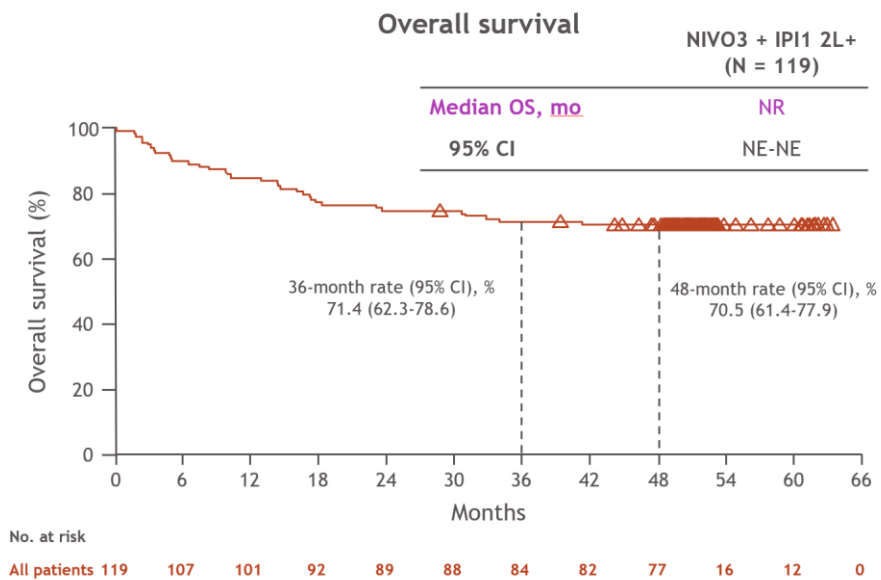
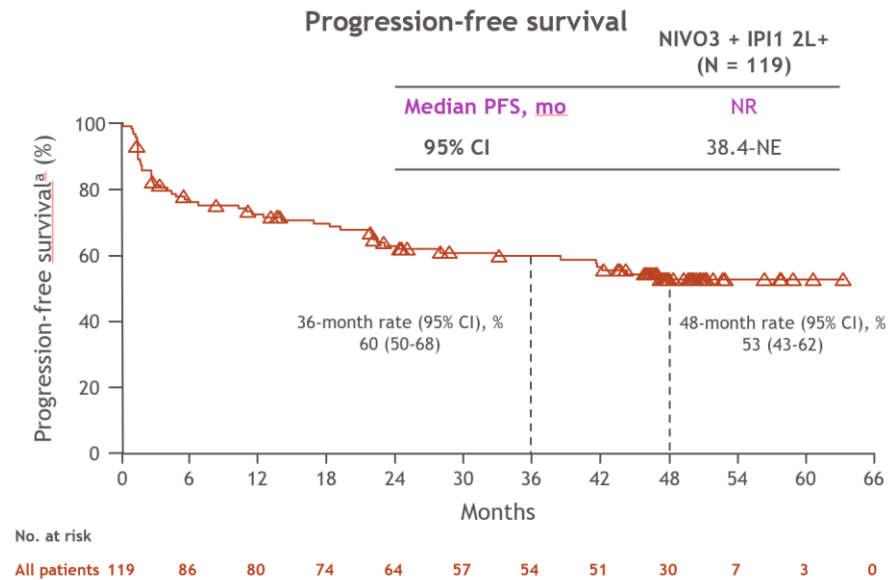
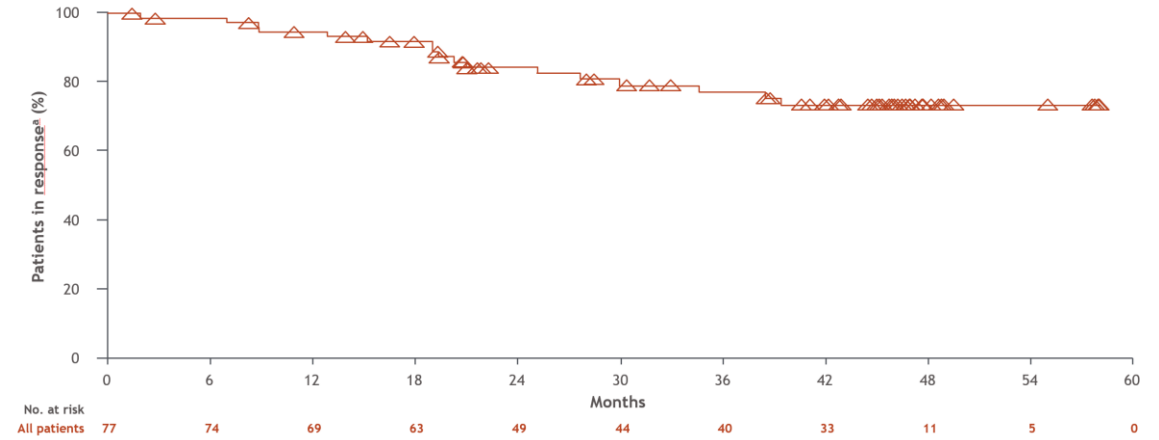
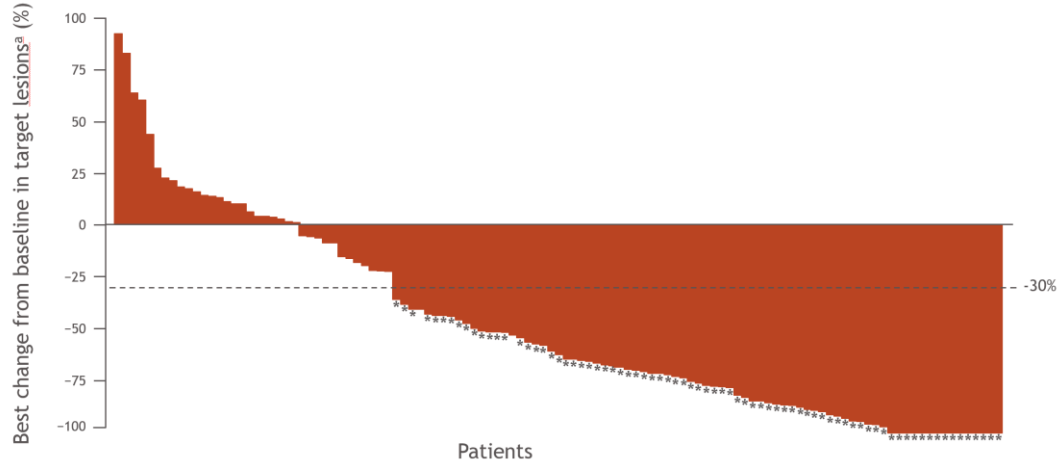


Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

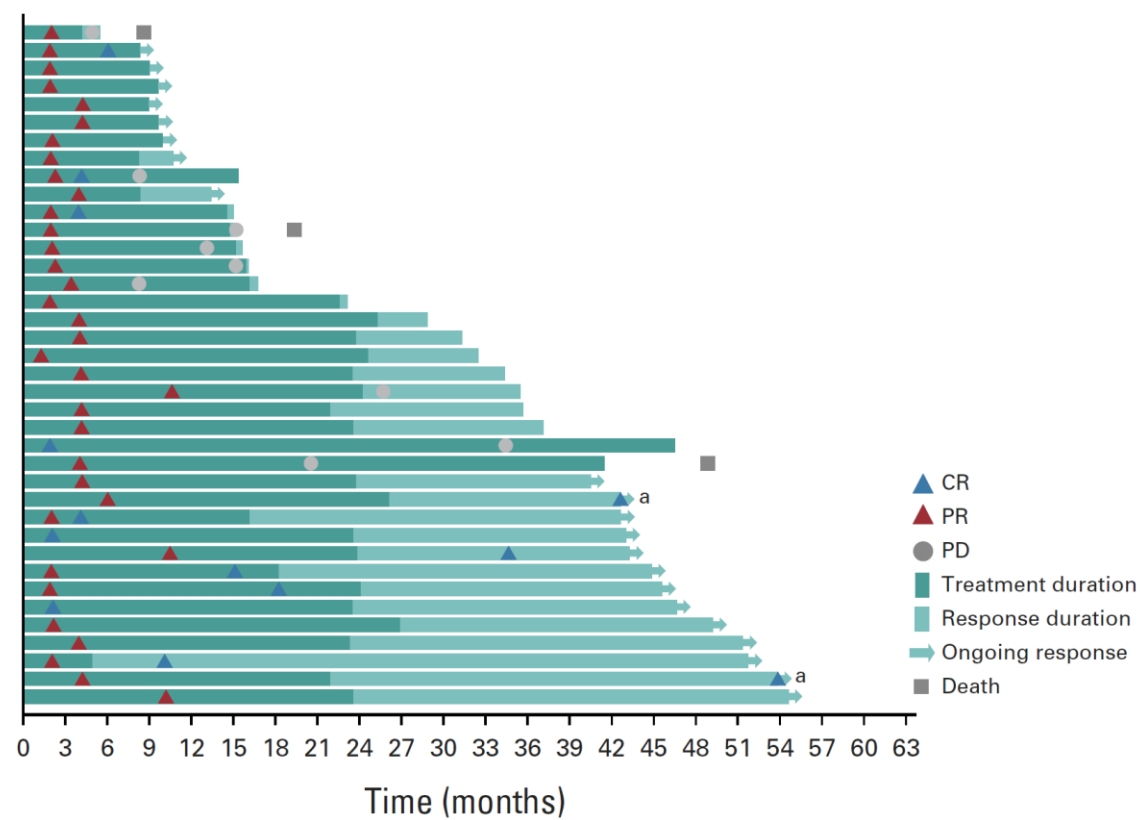
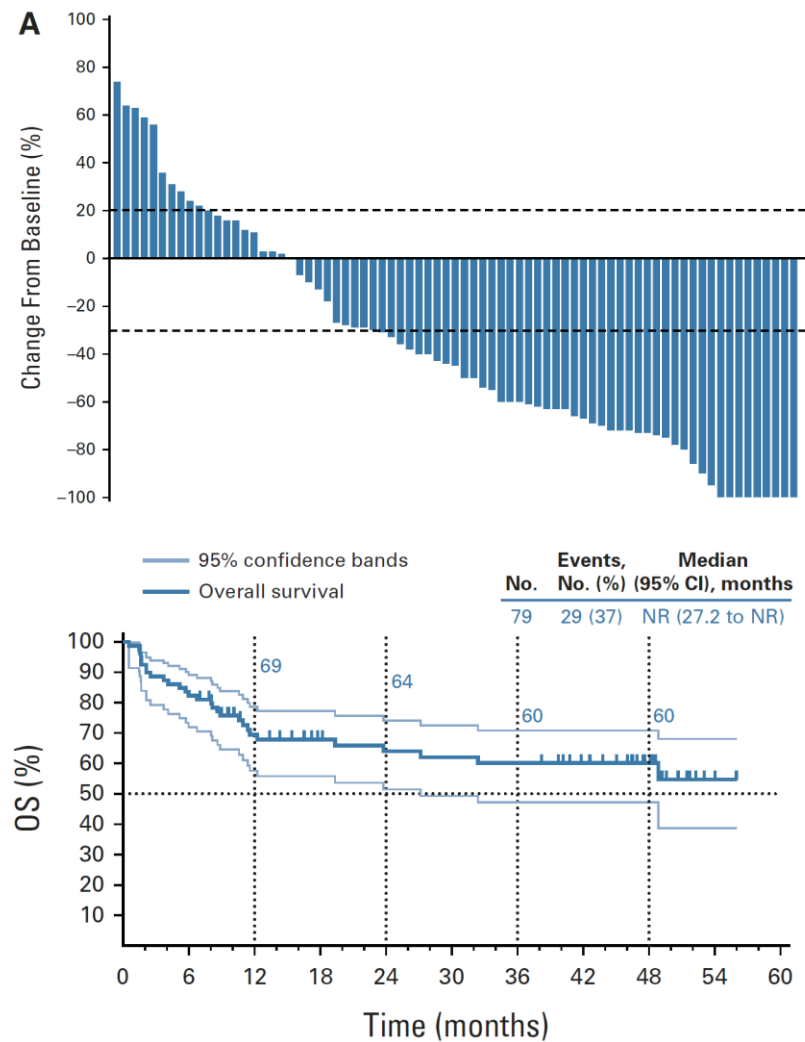


CHECKMATE 142 – follow up 4 roky



André T et al. ESMO WCGC 2021, abstr. SO-27

MSI-H endometroidní ca (KN 158)



HRD – poruchy homologní rekombinace

- Nefunguje oprava dvoušroubovicových zlomů DNA
- BRCA1, BRCA2, další HR geny
(*53BP1, ATM, ATR, ATRIP, BARD1, BLM, BRIP1, DMC1, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RIF1, RMI1, RMI2, RPA1, TOP3A, TOPBP1, XRCC2, XRCC3*)

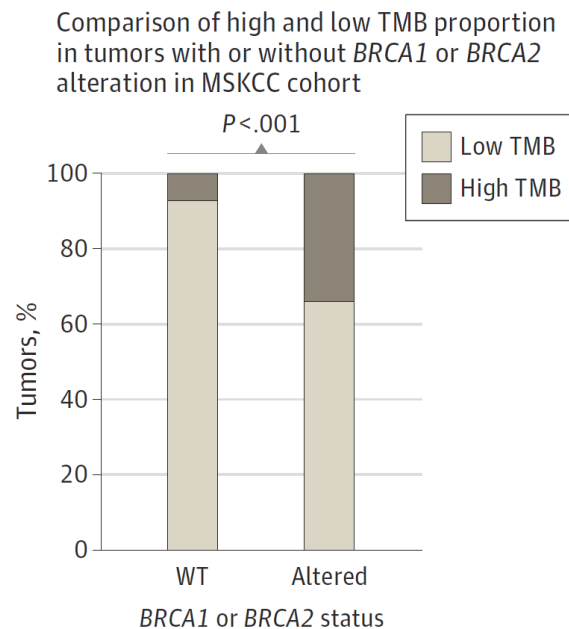
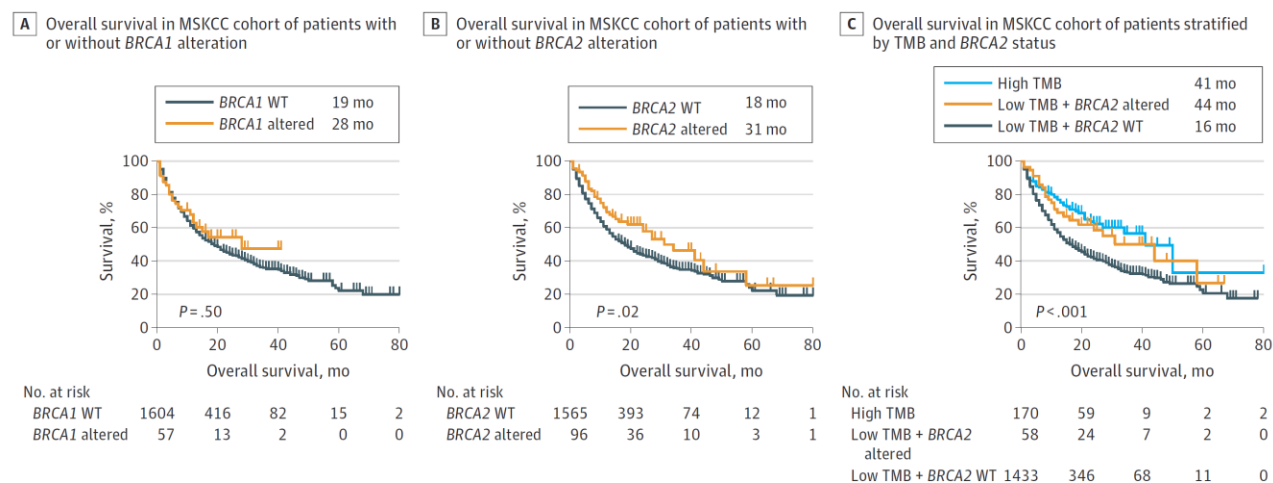
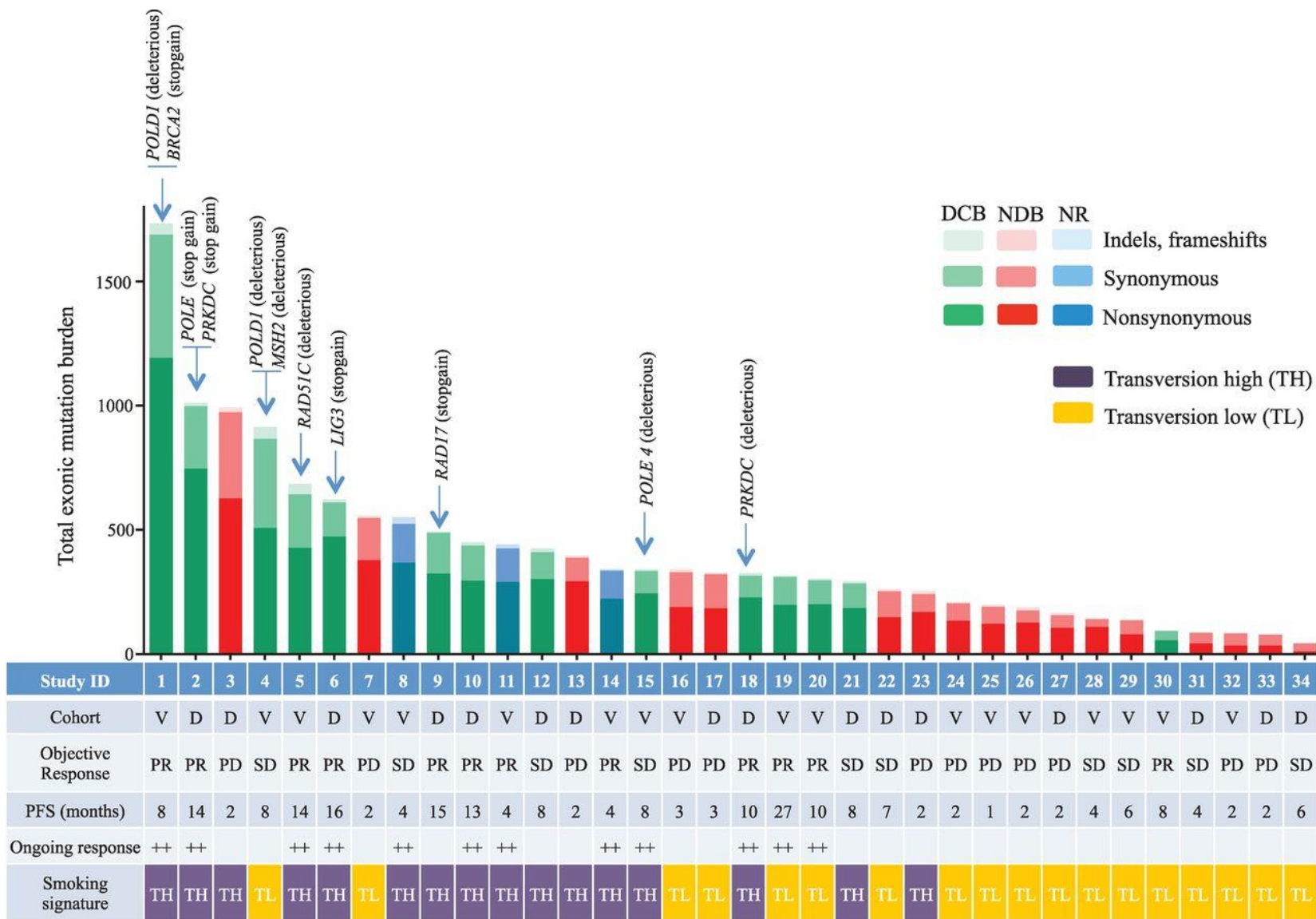


Figure 2. Prognostic Association of Tumor Mutation Burden (TMB) and *BRCA1/2* Alteration in Patients Receiving Immune Checkpoint Inhibitors



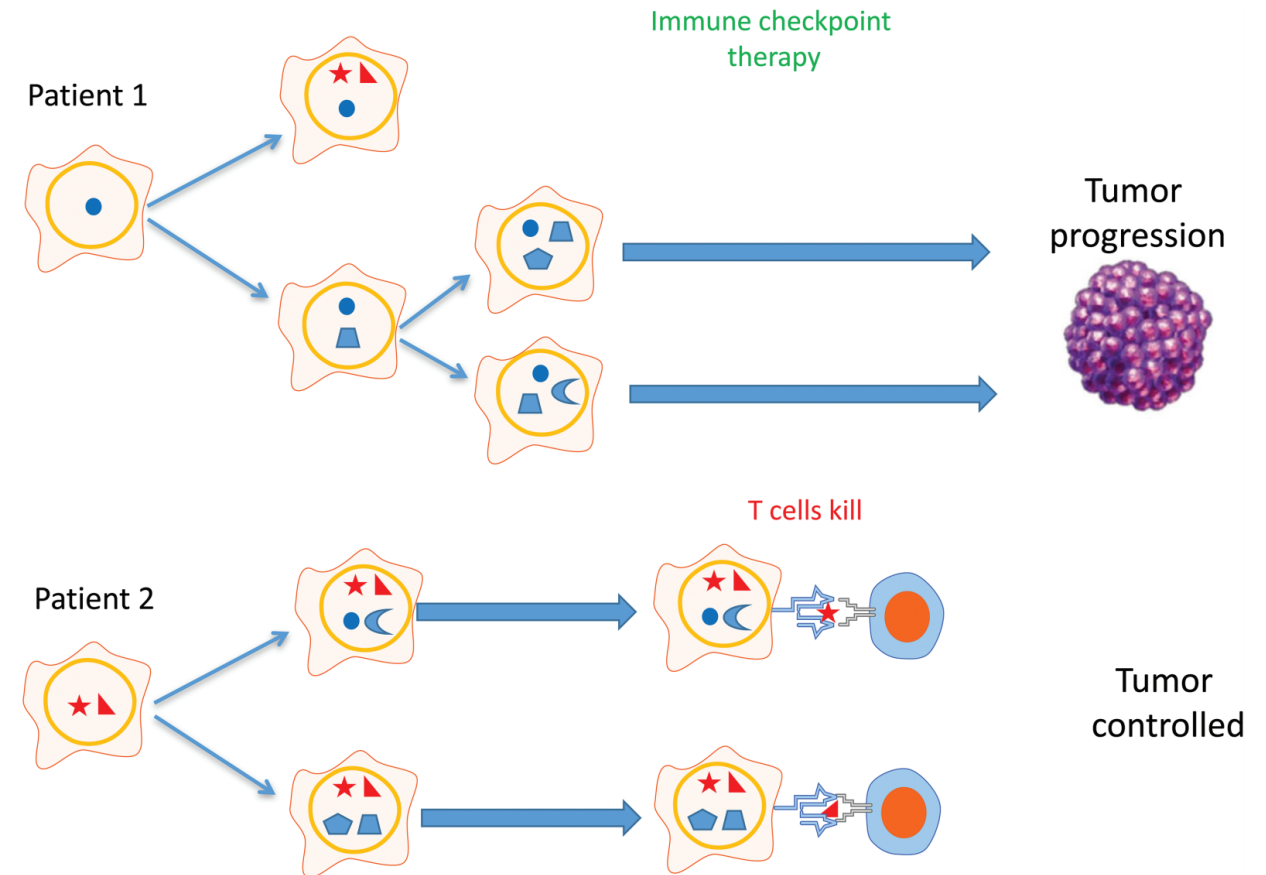
MSKCC indicates Memorial Sloan Kettering Cancer Center; WT, wild type.

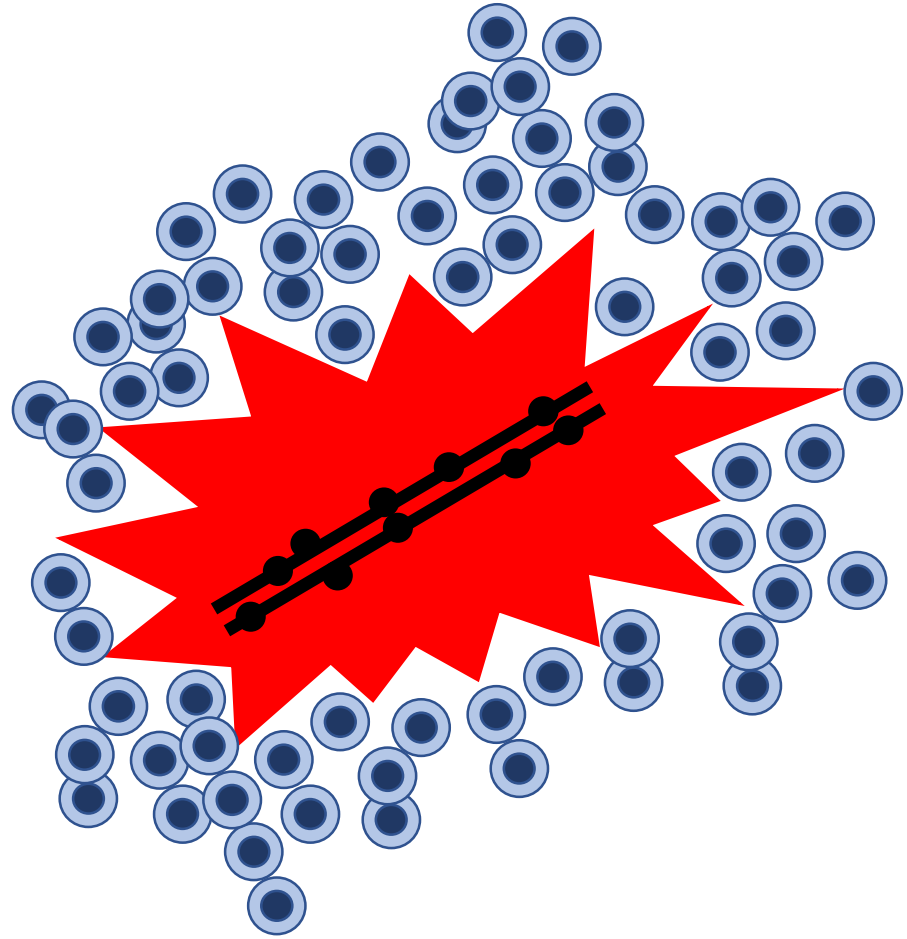
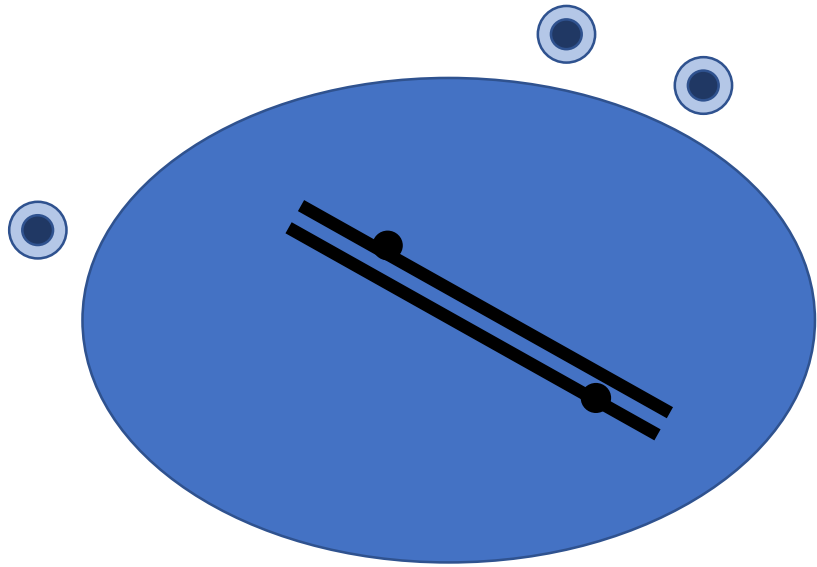
Mutační nálož u NSCLC a faktory k ní přispívající

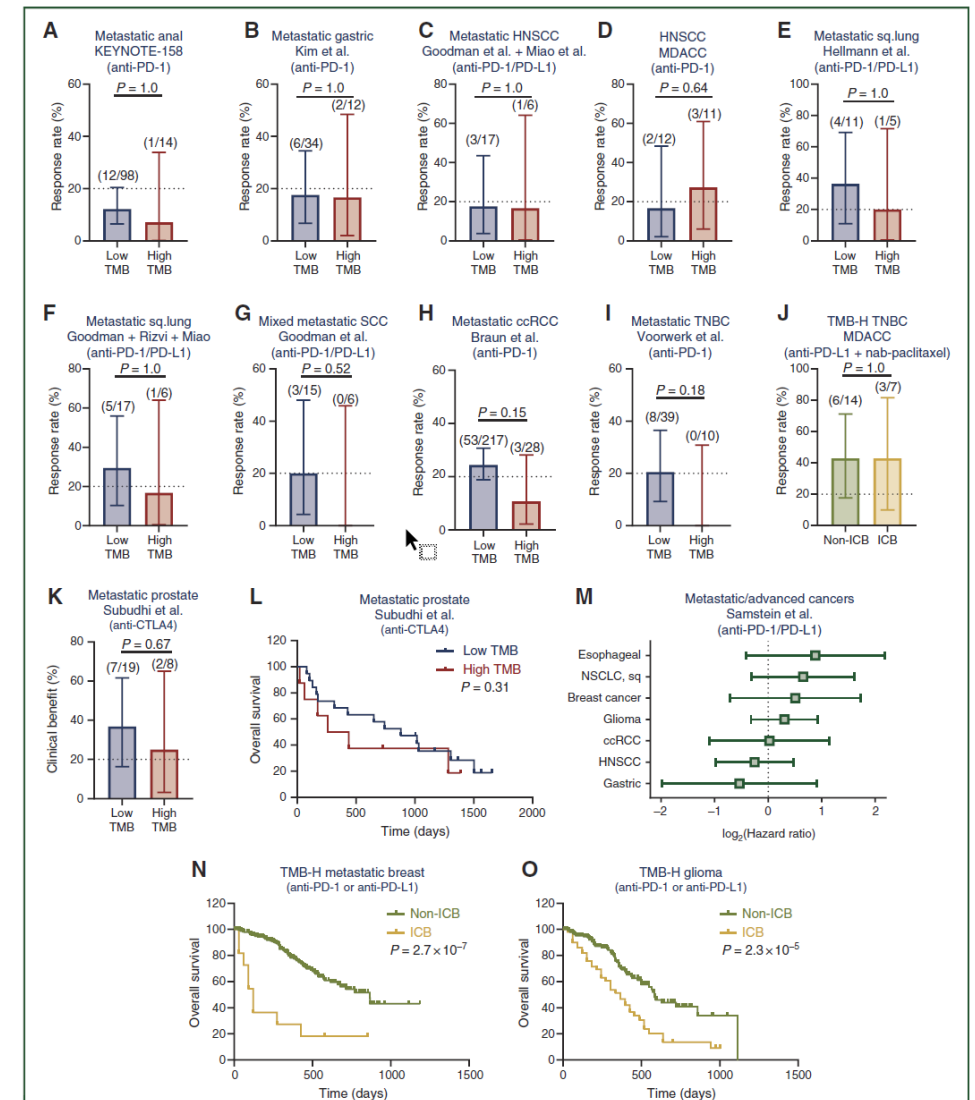
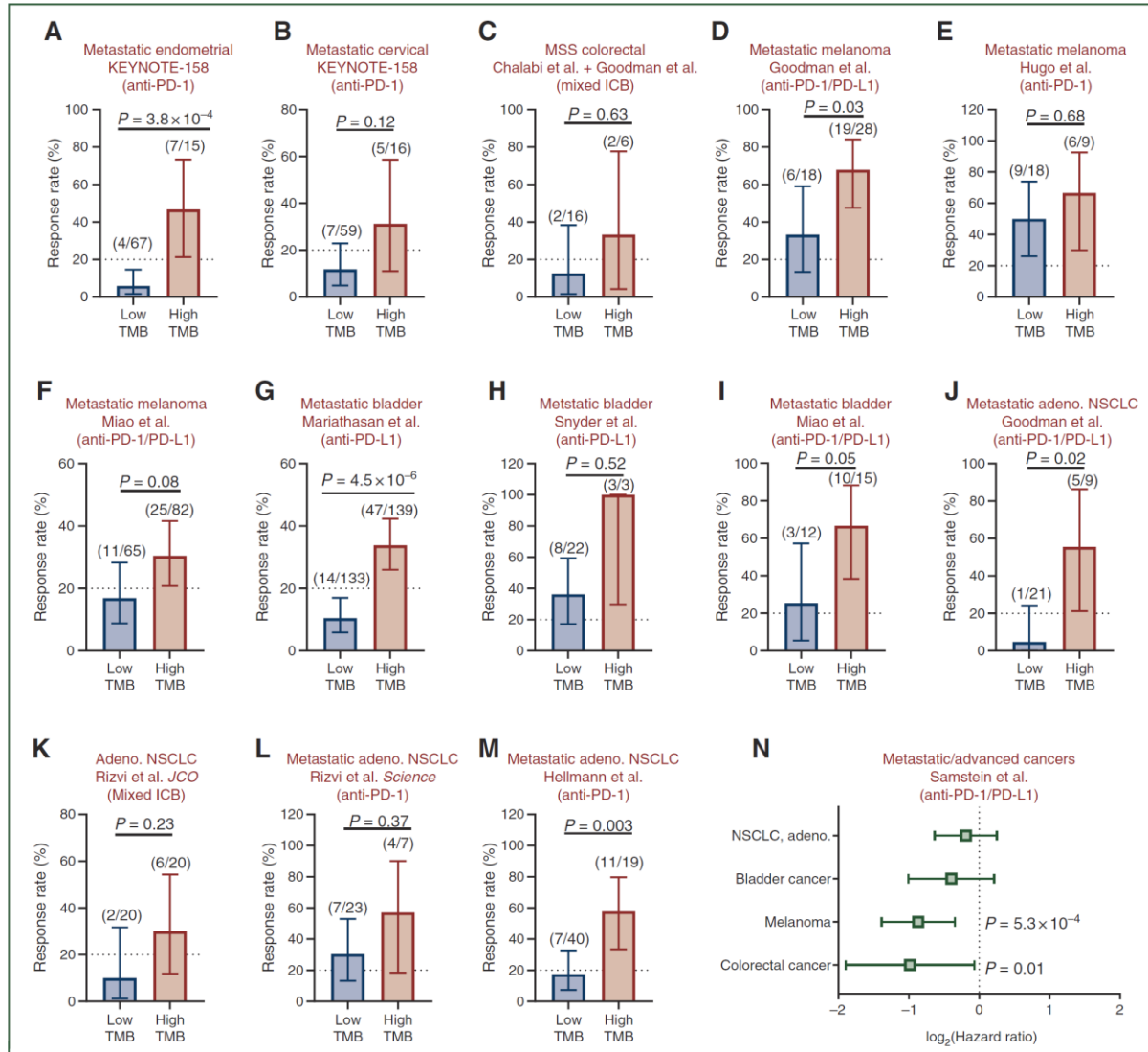


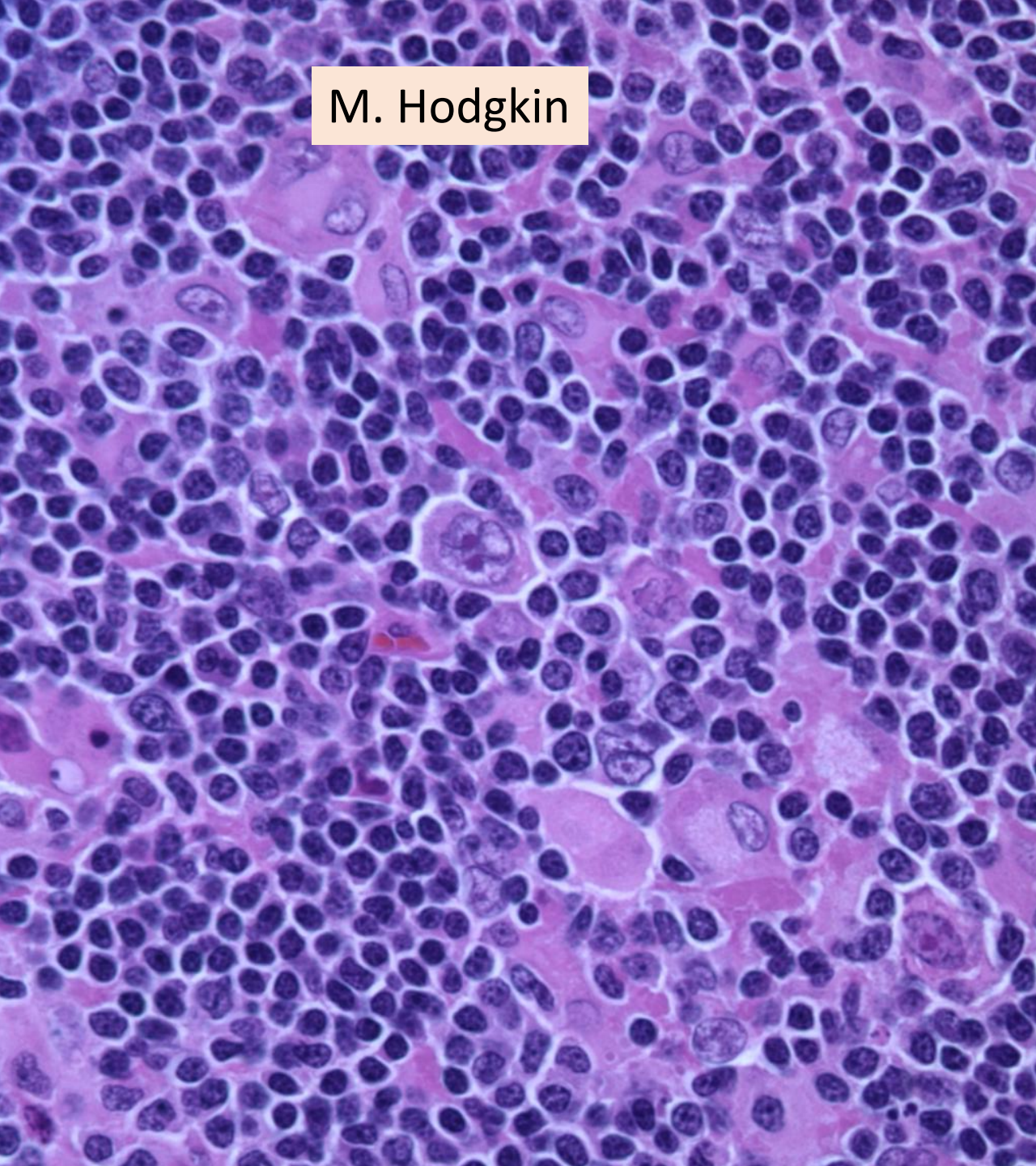
Antigenicita nádoru – komplexní záležitost

- Ne každá passenger mutace vede ke vzniku neoantigenu (TMB \neq TNB)
- Ne každý neoantigen je imunogenní (TNB \neq TIL)
- Záleží na fázi kancerogeneze, kdy imunogenní neoantigen vznikne (TIL \neq OR)






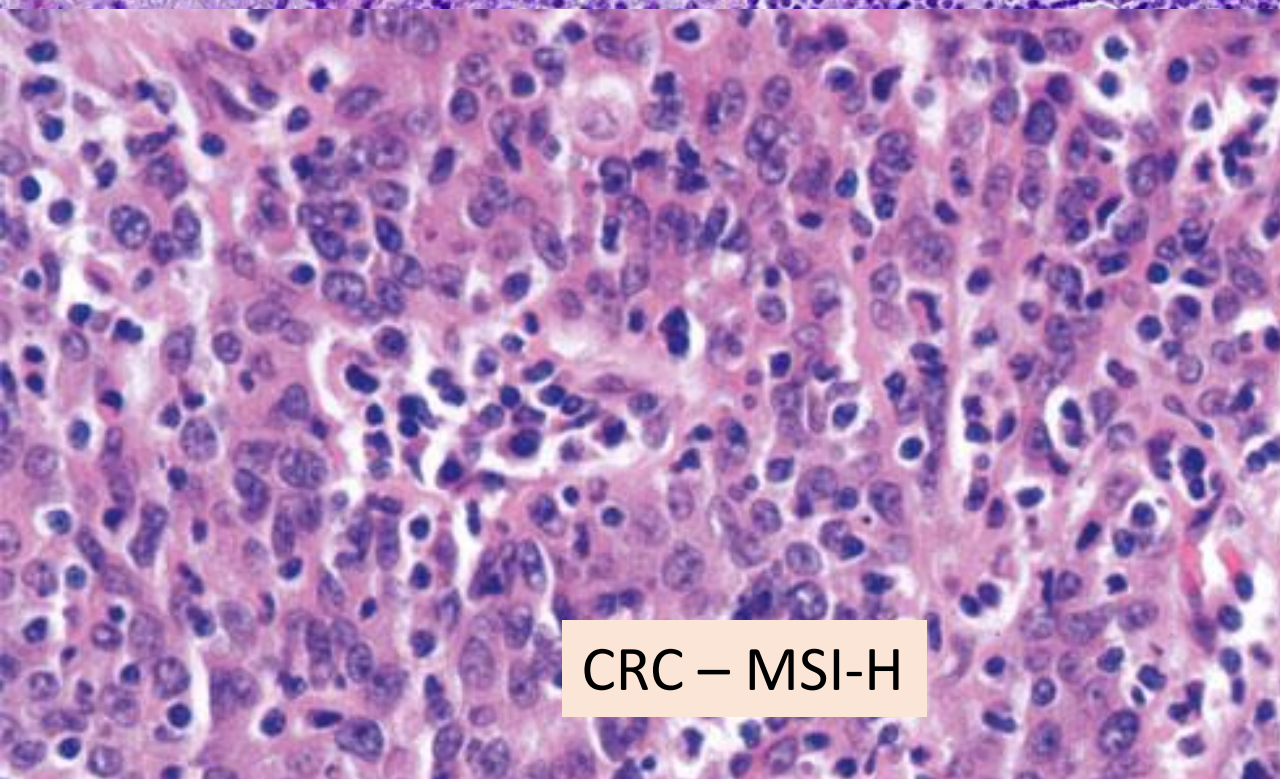




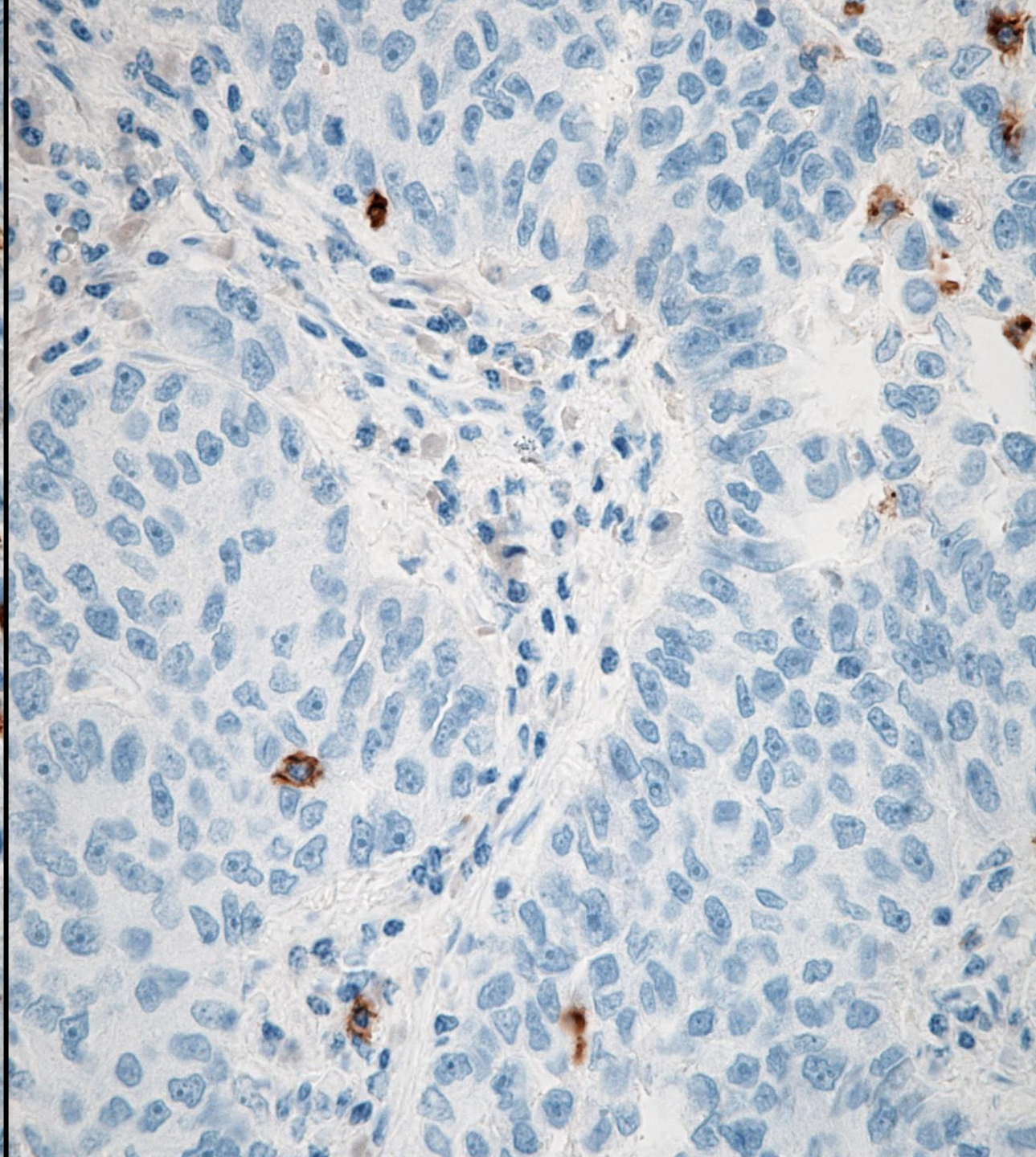
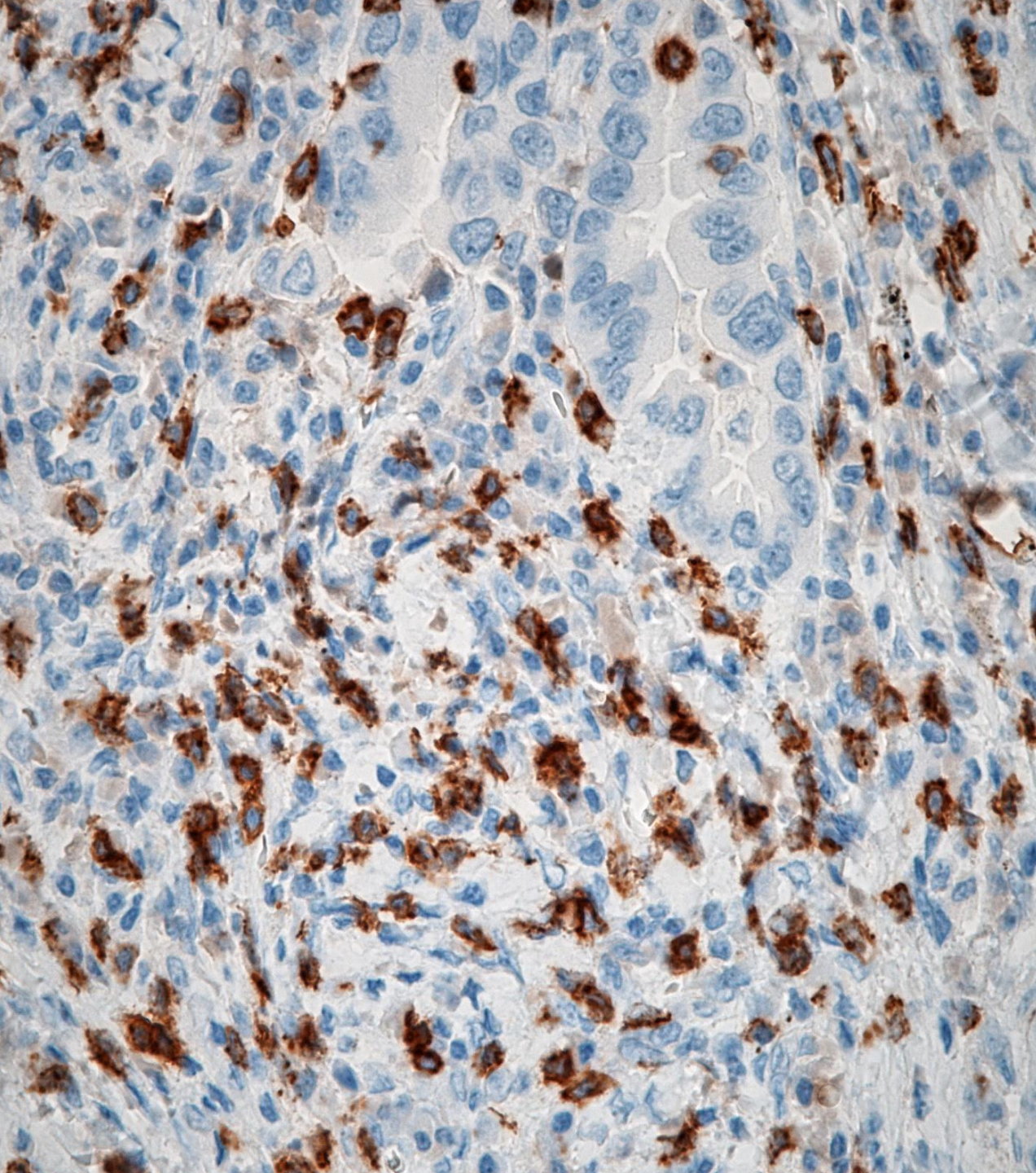
M. Hodgkin



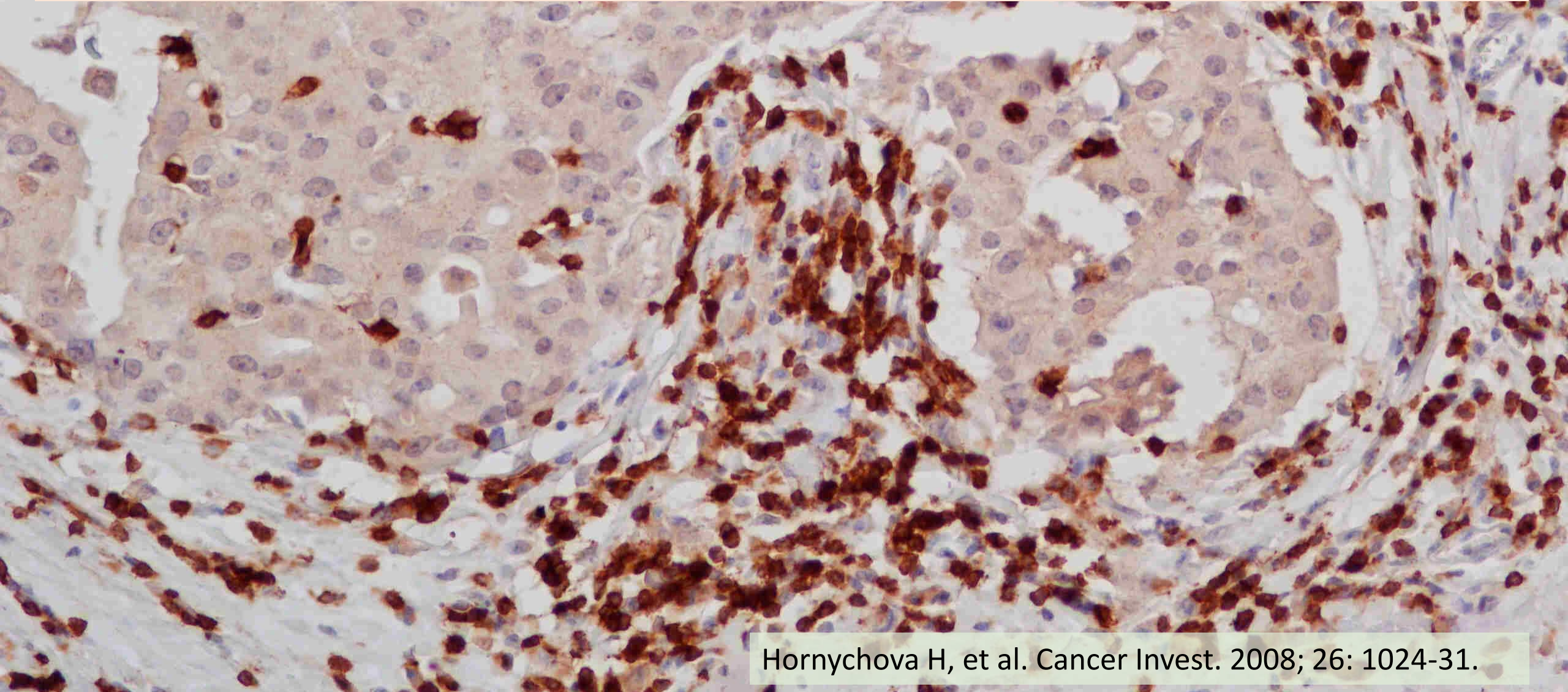
Karcinom prsu
s medulárními rysy



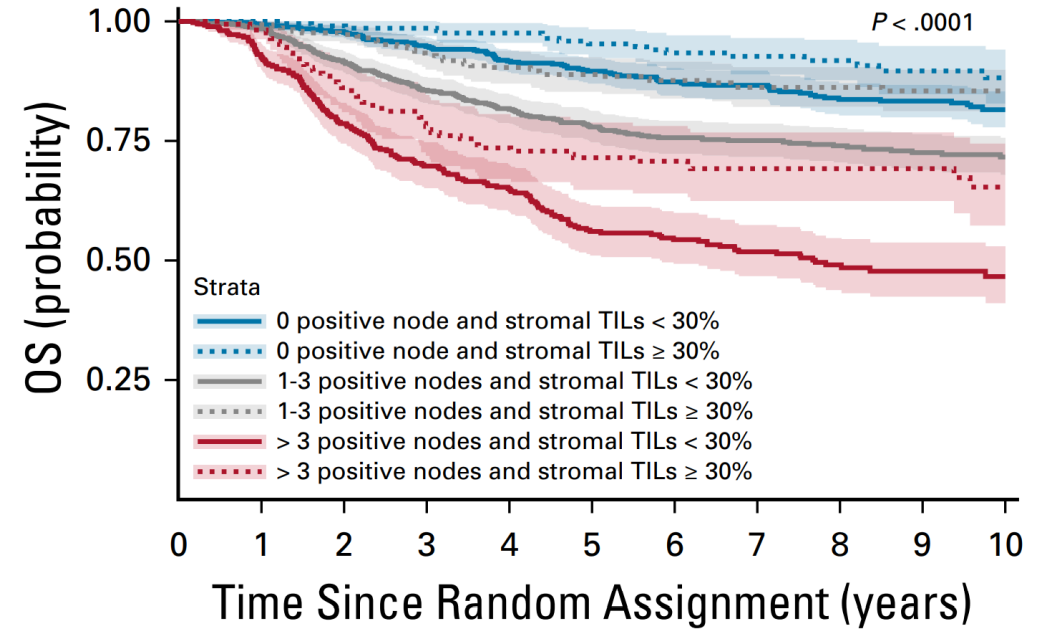
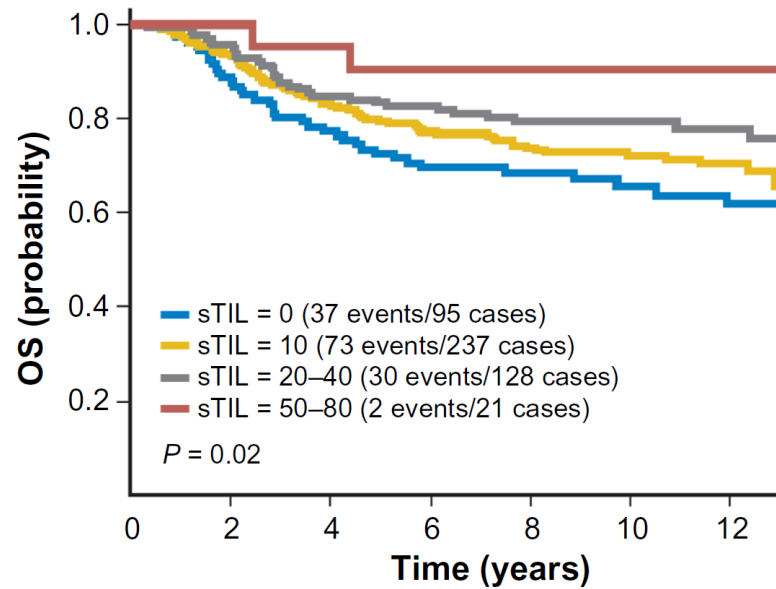
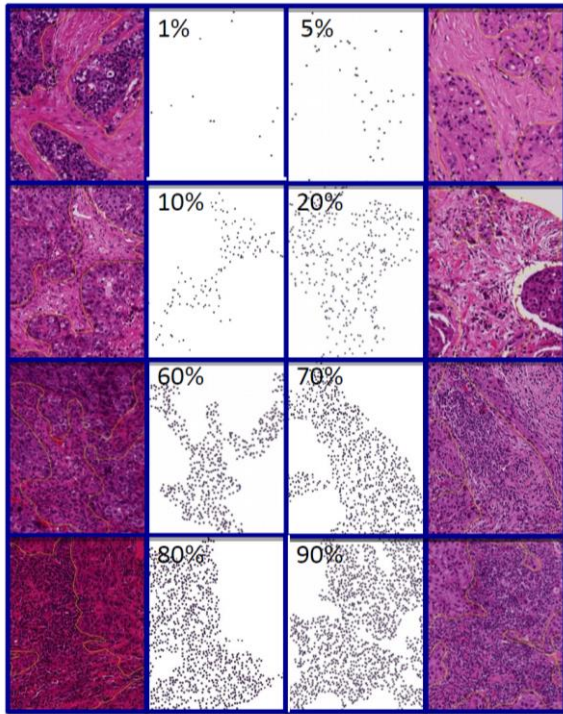
CRC – MSI-H



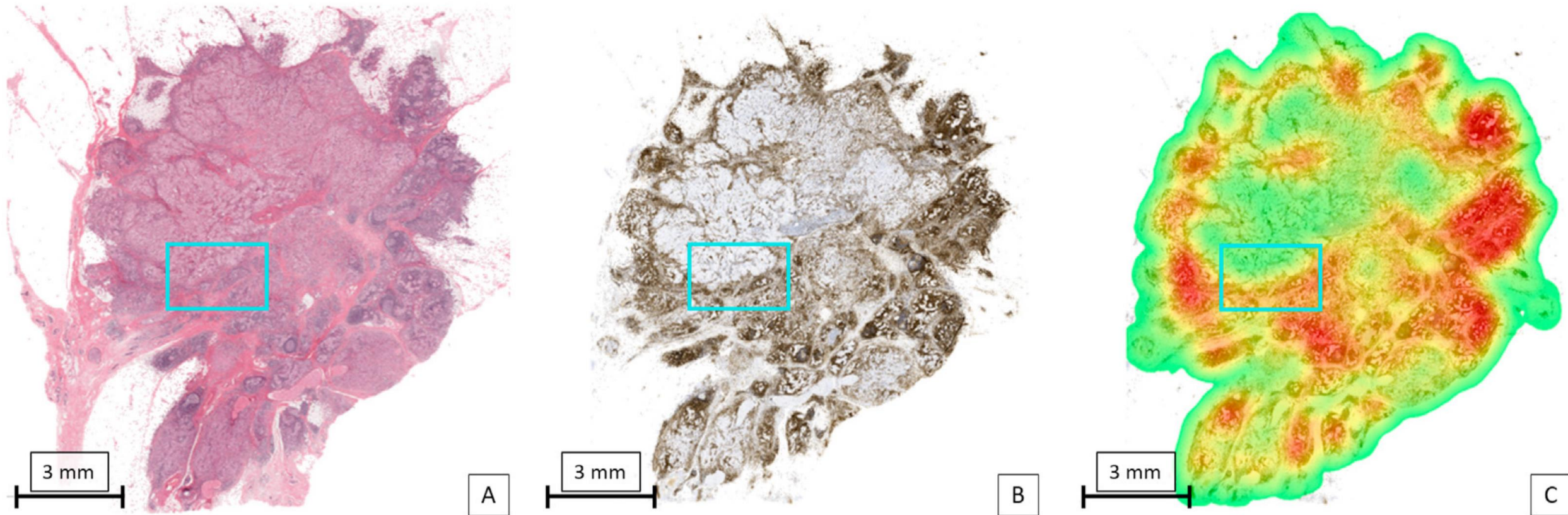
**Tumor infiltrující lymfocyty –
prognostický a/nebo prediktivní marker u TNBC?**



Standardizace hodnocení TIL u ca prsu












TIL – slibný marker se zásadními limitacemi

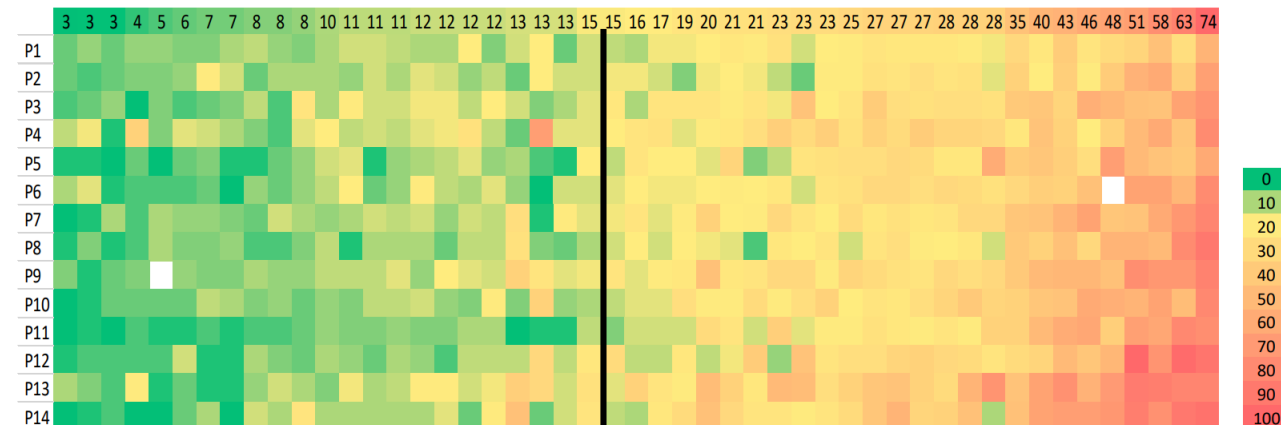
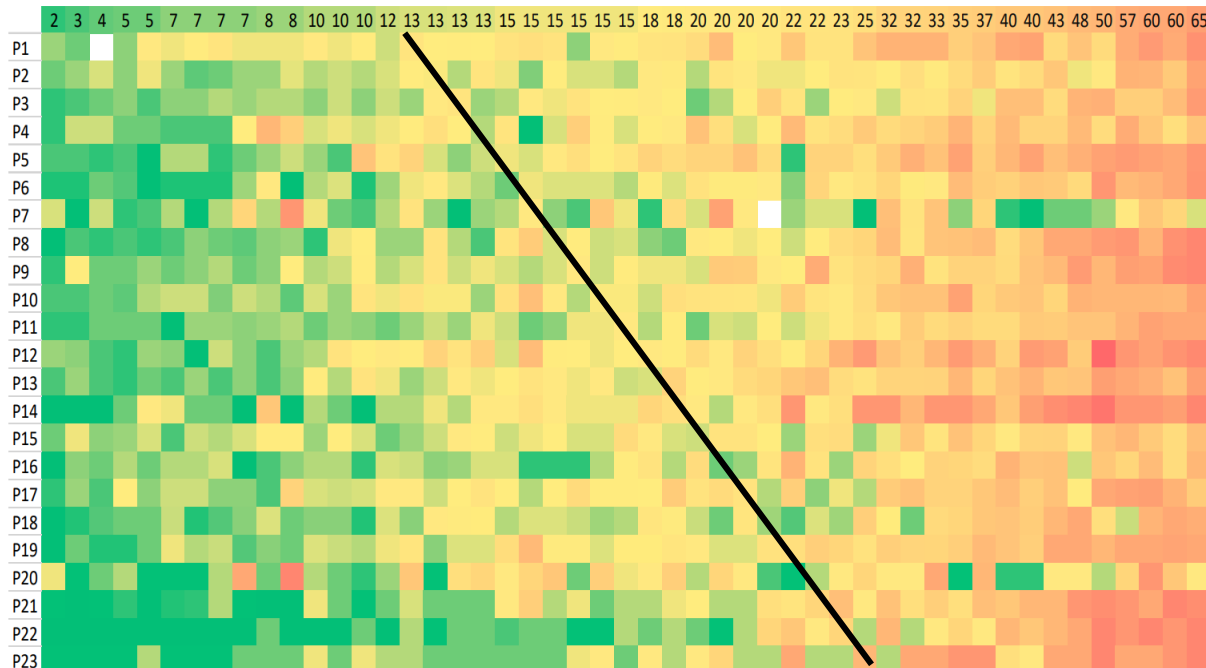


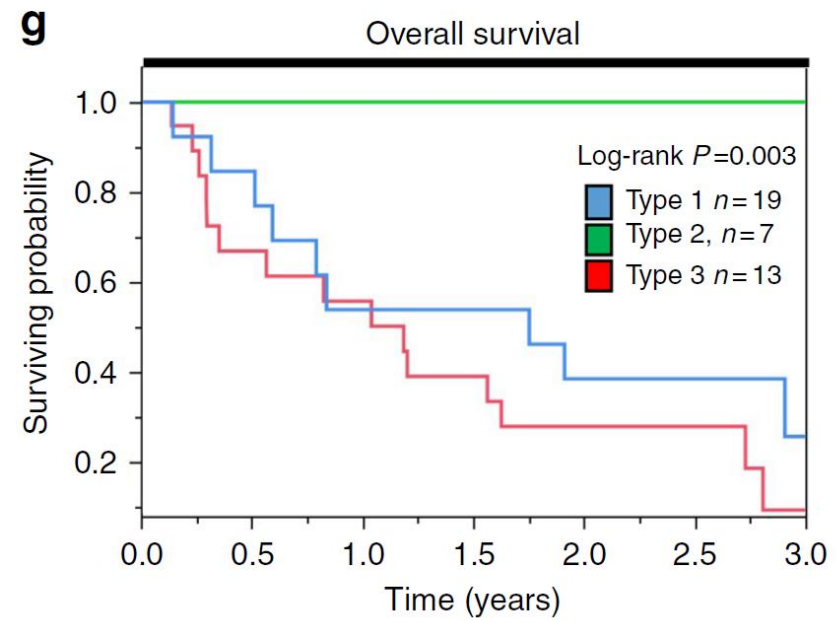
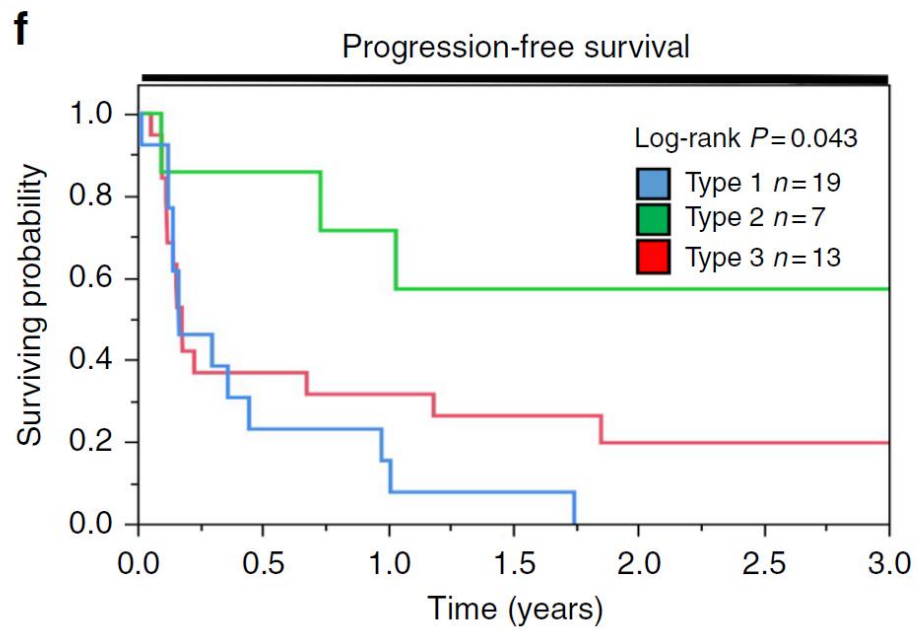
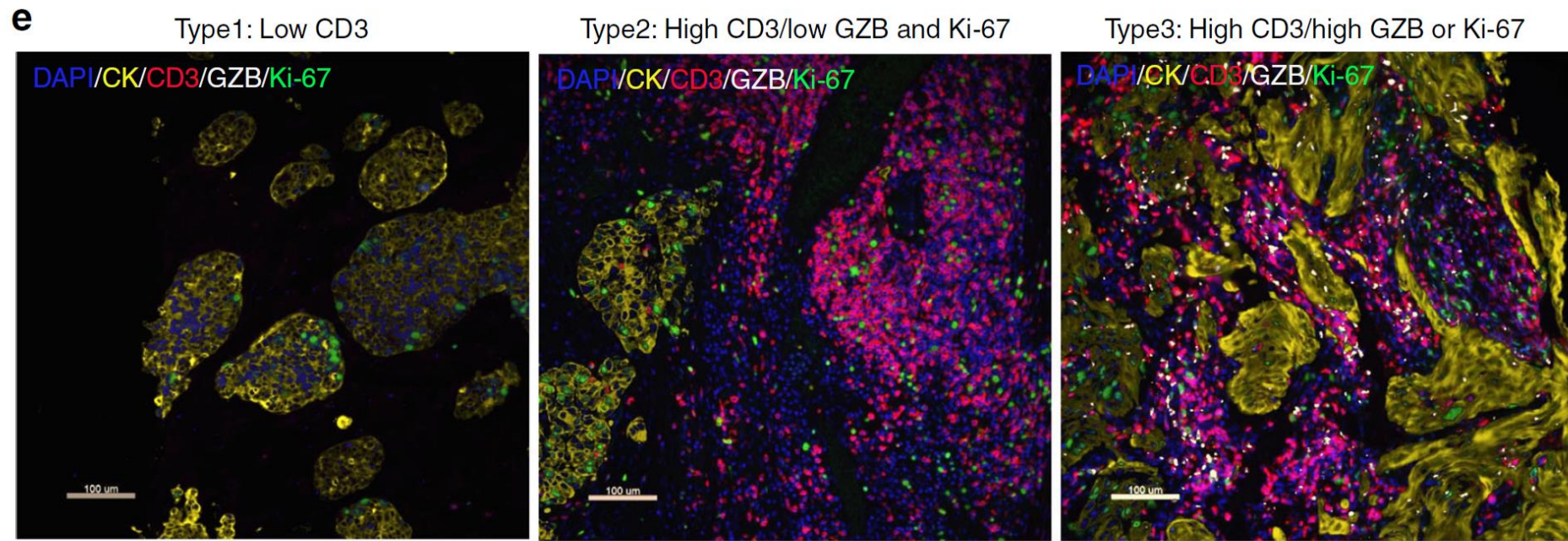
Article

Intra-Tumour Heterogeneity Is One of the Main Sources of Inter-Observer Variation in Scoring Stromal Tumour Infiltrating Lymphocytes in Triple Negative Breast Cancer

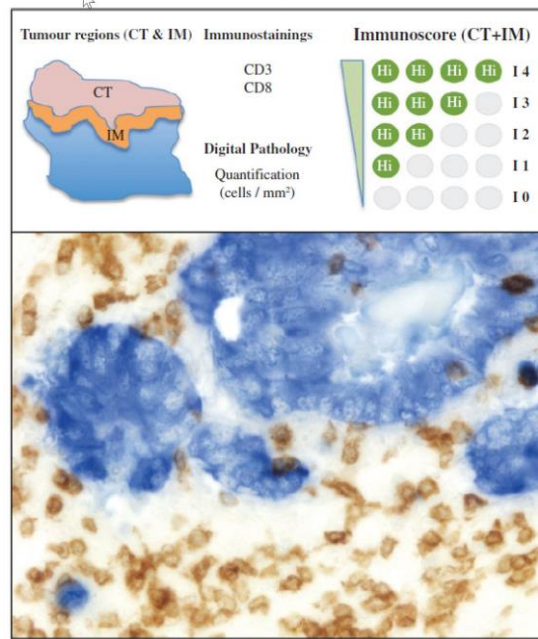
Darren Kilmartin ¹, Mark O’Loughlin ¹, Xavier Andreu ², Zsuzsanna Bagó-Horváth ³, Simonetta Bianchi ⁴ , Ewa Chmielik ⁵, Gábor Cserni ^{6,†} , Paulo Figueiredo ⁷, Giuseppe Floris ⁸, Maria Pia Foschini ⁹ , Anikó Kovács ¹⁰, Päivi Heikkilä ¹¹, Janina Kulka ¹², Anne-Vibeke Laenkholm ¹³, Inta Liepniece-Karele ¹⁴, Caterina Marchiò ^{15,16} , Elena Provenzano ^{17,18}, Peter Regitnig ¹⁹ , Angelika Reiner ²⁰, Aleš Ryška ²¹, Anna Sapino ^{15,16} , Elisabeth Specht Stovgaard ²² , Cecily Quinn ^{23,24}, Vasiliki Zolota ²⁵, Mark Webber ¹, Davood Roshan ²⁶ , Sharon A. Glynn ¹  and Grace Callagy ^{1,*}

- Tréninkem lze významně zlepšit interindividuální shodu
- Heterogenita zůstává zdrojem variability

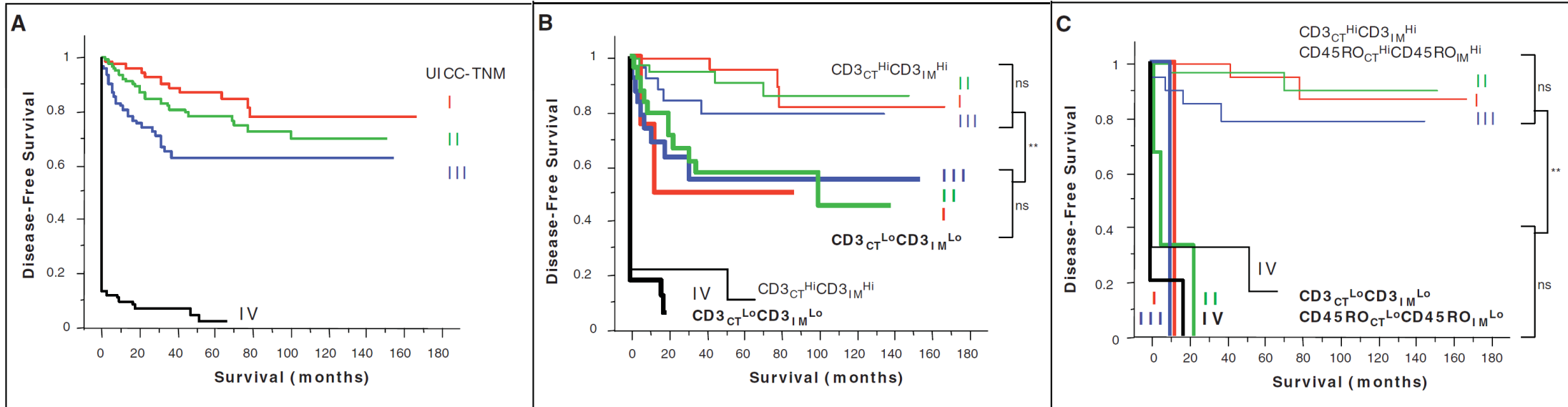




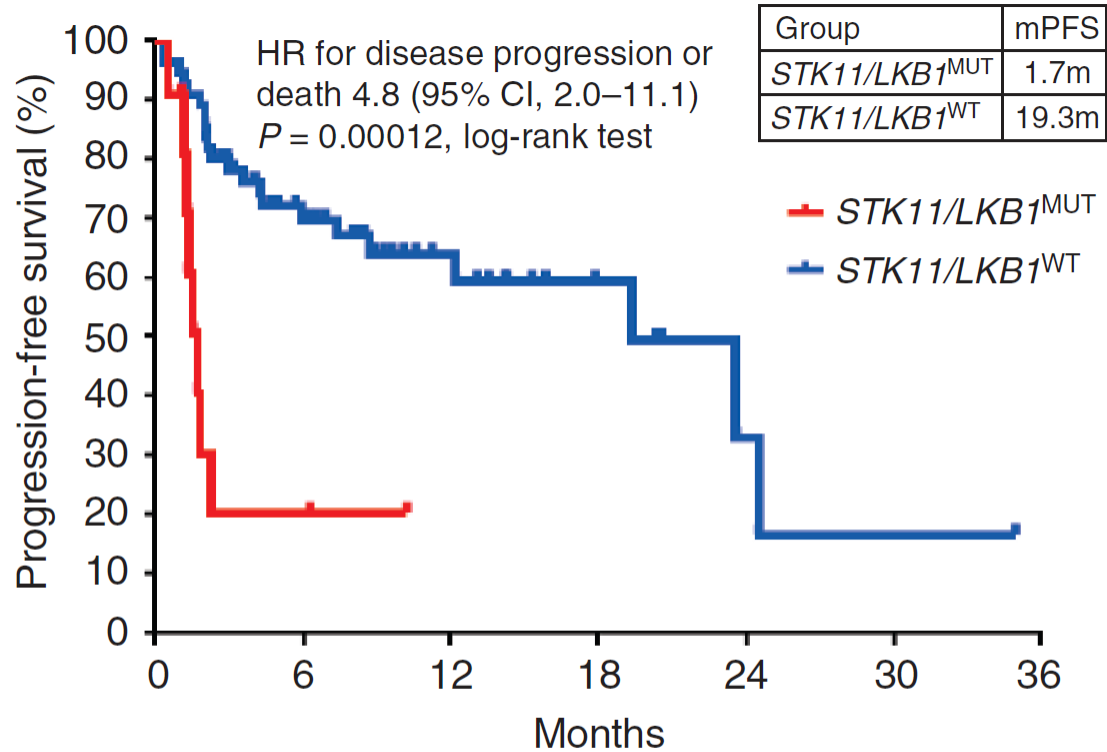
TIL – využití v rutinní praxi?



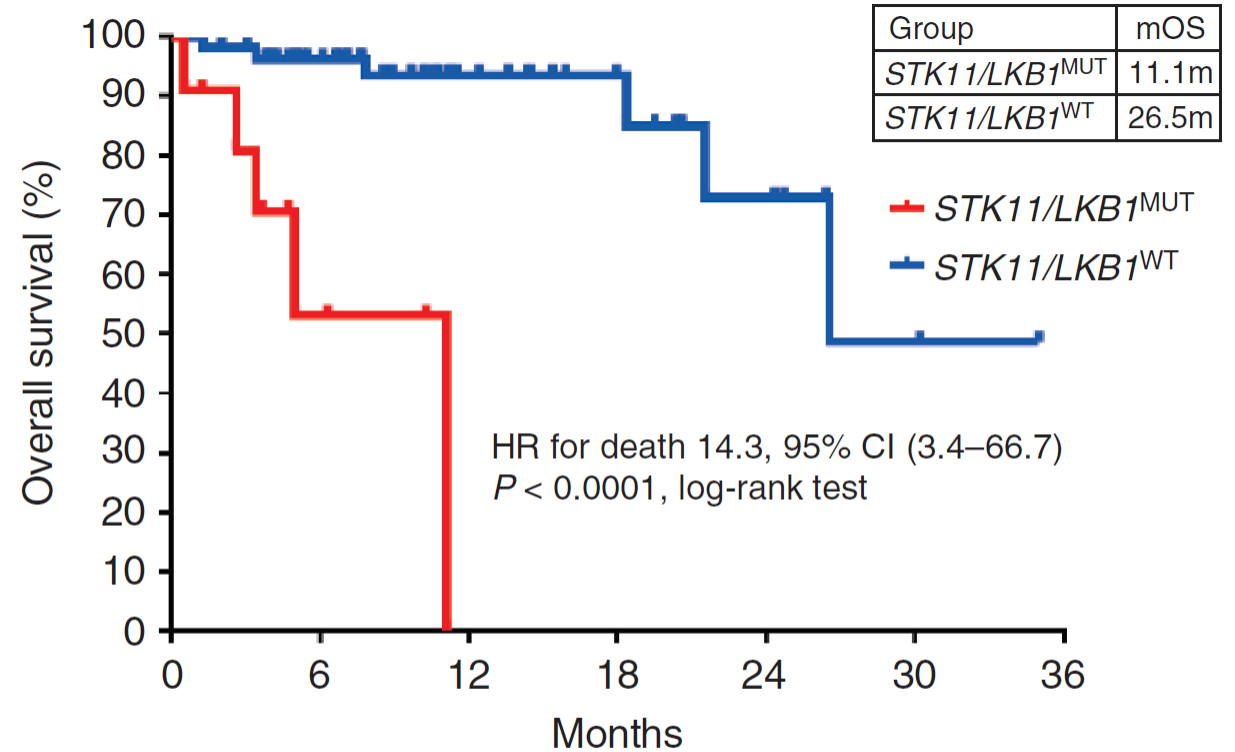
Immune contexture		Immunoscore
Type	CD3, CD8, CD45RO	
Density	Cells/mm ²	
Location	Centre, Margin	
Orientation	Th1, cytotoxic, chemokines, adhesion	



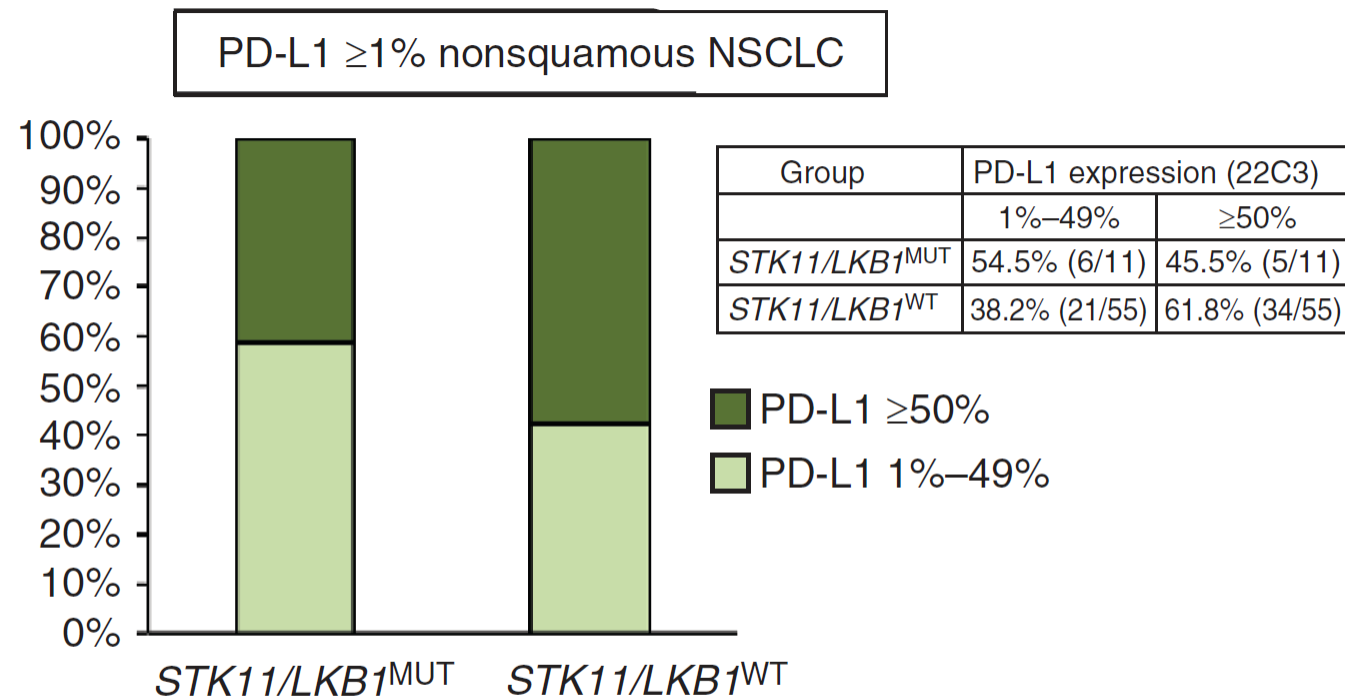
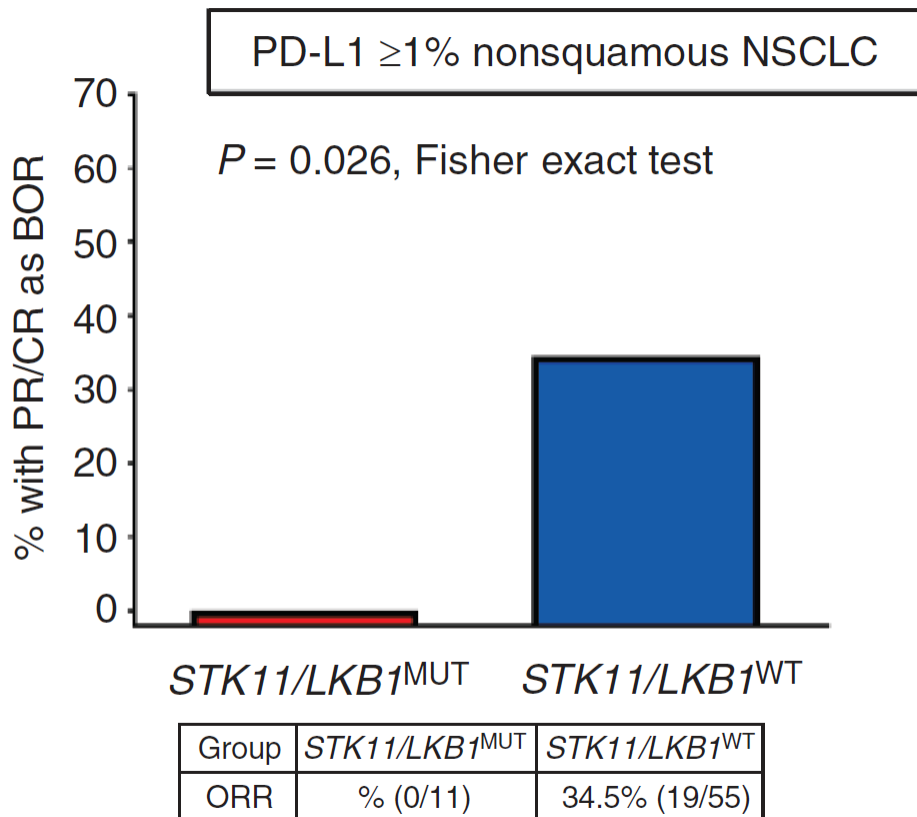
Komutace STK11 – prediktor selhání IO

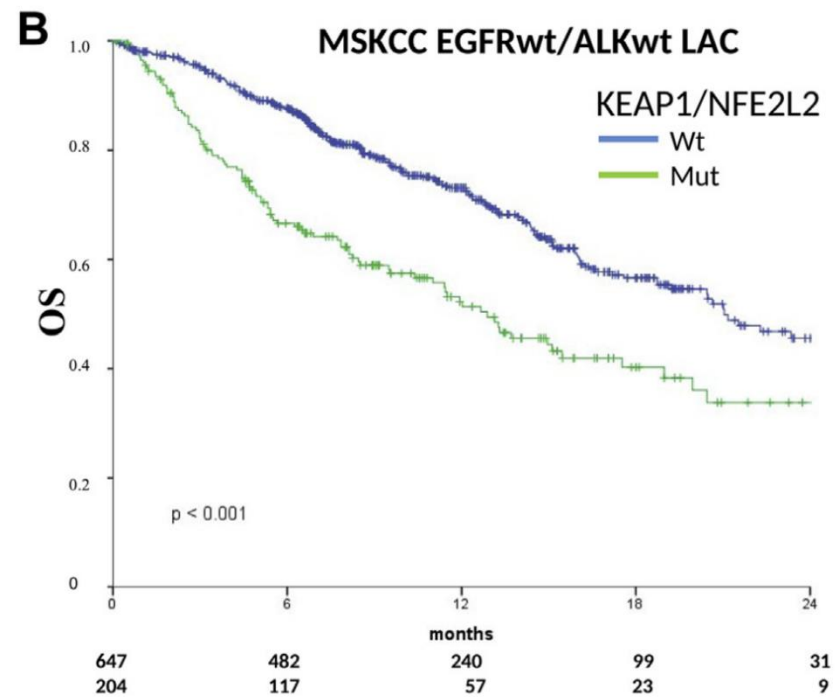
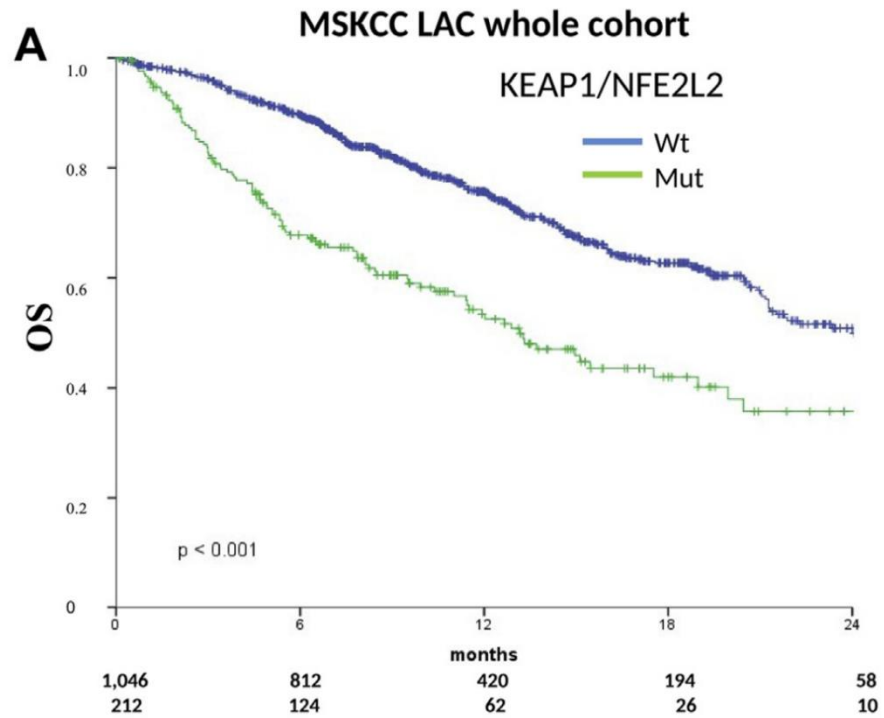
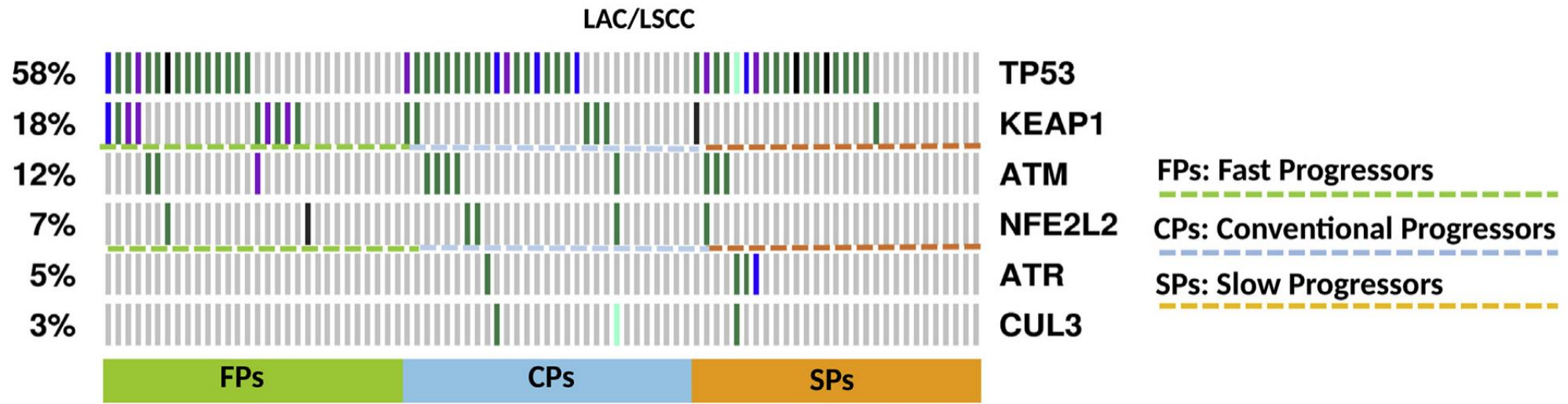


	11(0)	2(1)	0(3)	0(3)	0(3)	0(3)	0(3)
	55(0)	30(9)	14(23)	6(30)	2(32)	1(32)	0(33)



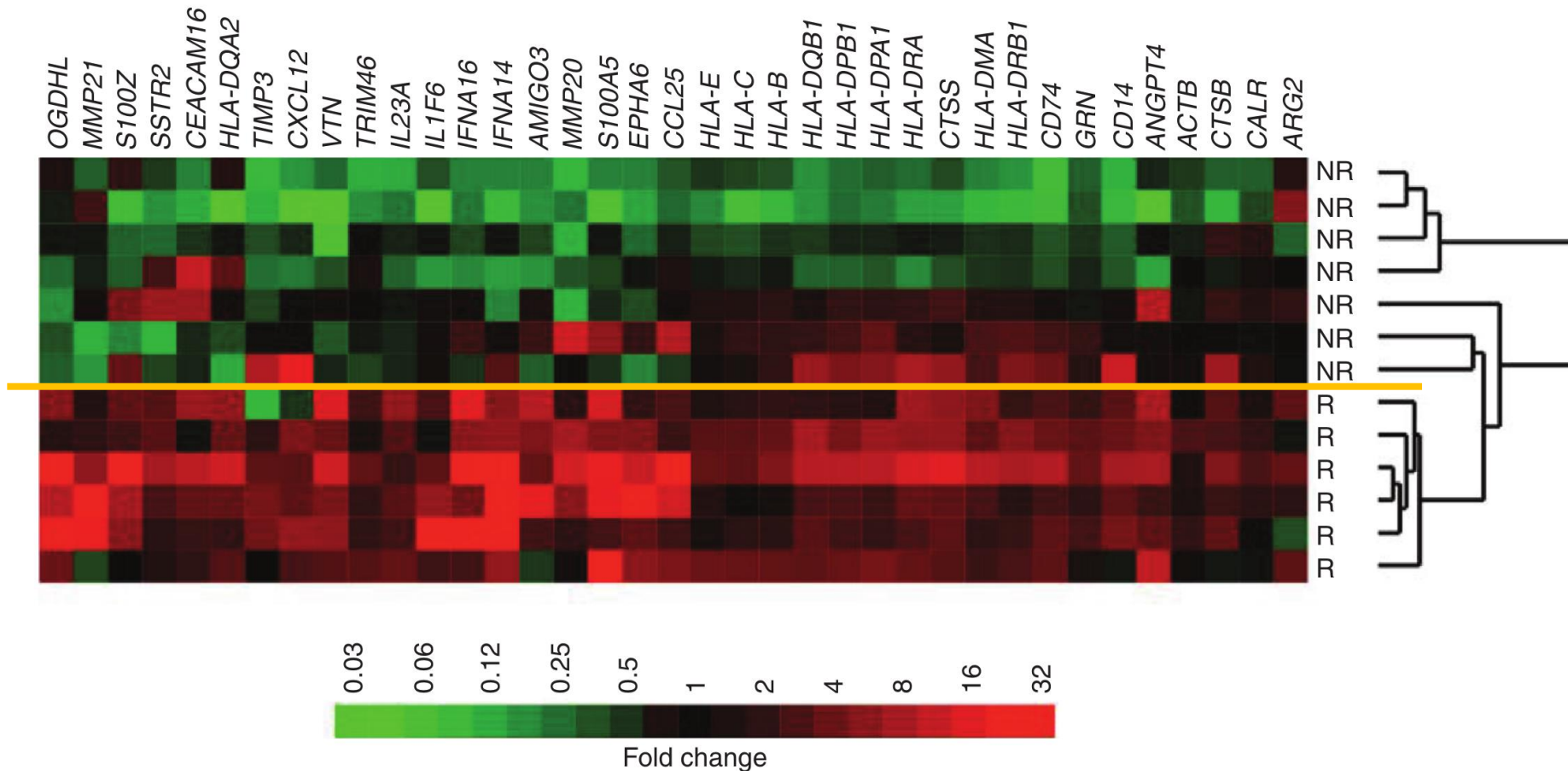
	11(0)	3(4)	0(6)	0(6)	0(6)	0(6)	0(6)
	55(0)	42(11)	20(32)	11(41)	6(44)	2(47)	0(49)



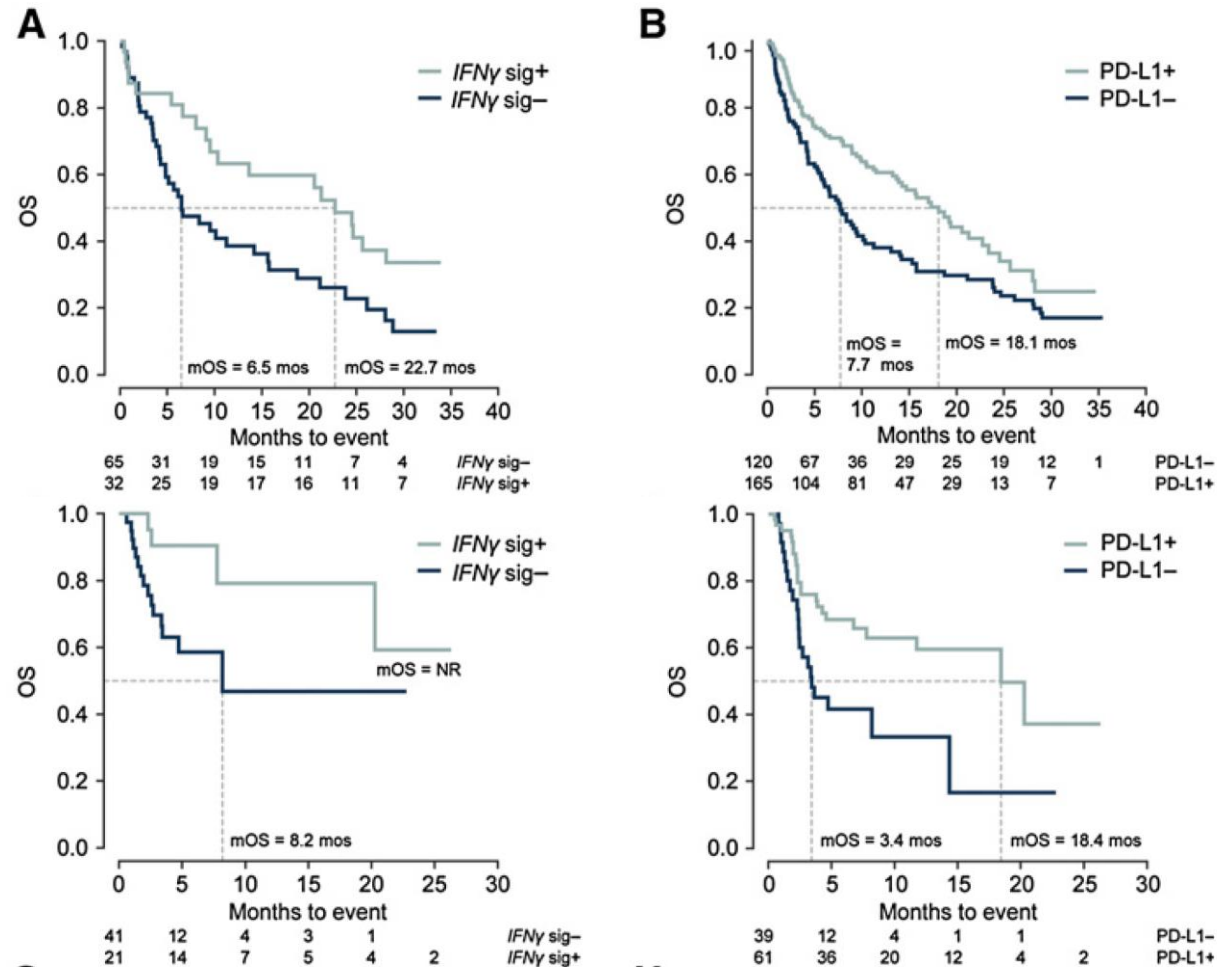


Analýza „Immune Signatures“

54 pacientů s maligním melanomem



Prediktivní význam PD-L1 a INFy signatury

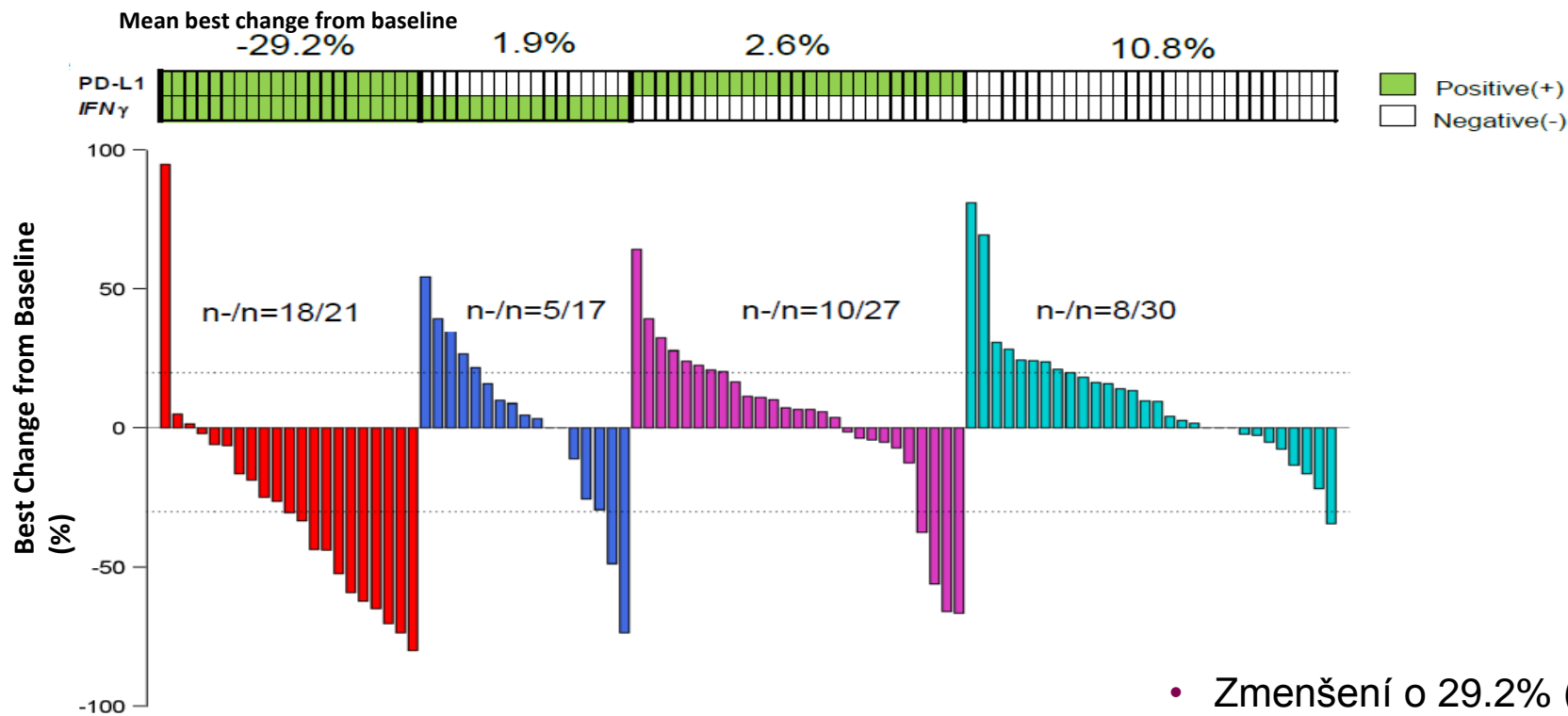


NSCLC

UC

Kombinace stanovení PD-L1 a IFN- γ signatury u pacientů s NSCLC predikuje odpověď na monoterapii durvalumabem

Best change in tumor size from baseline by pretreatment IFN- γ mRNA/PD-L1 status

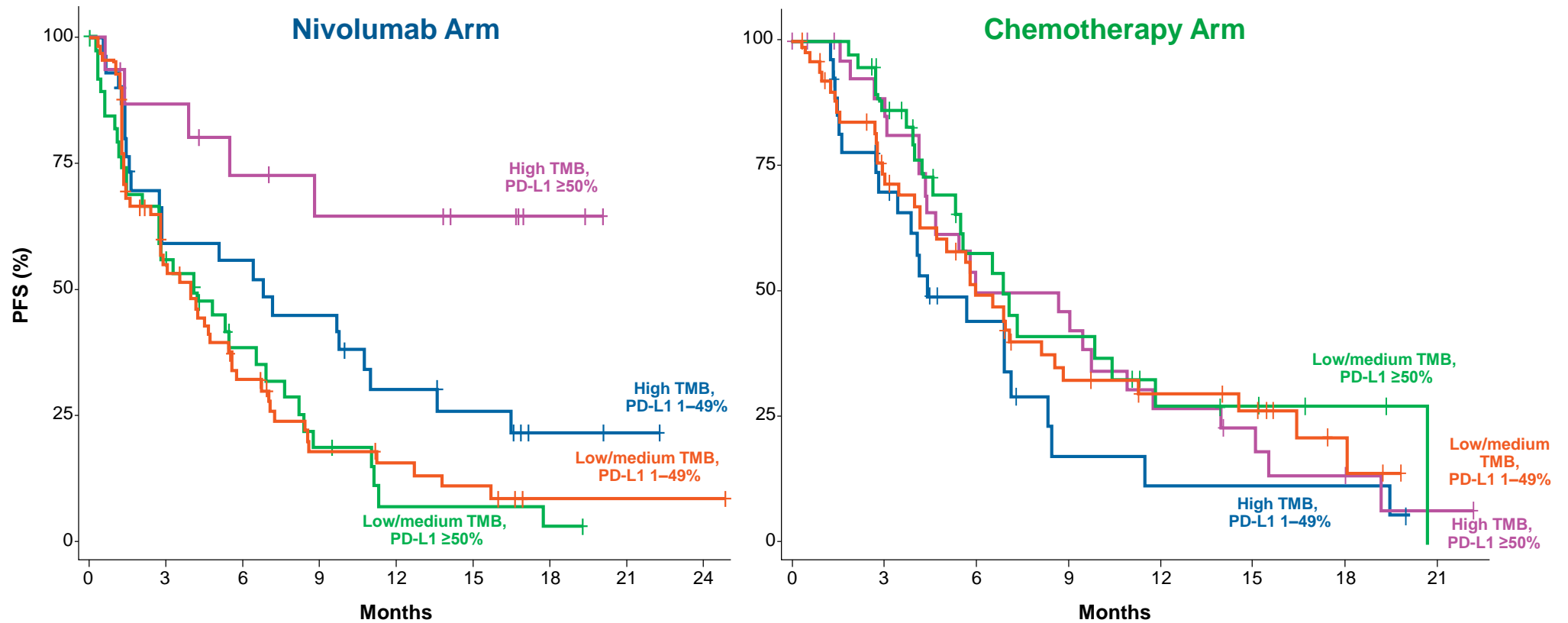


- Zmenšení o 29.2% (double positive)
- Zvětšení o 10.8% (double negative)

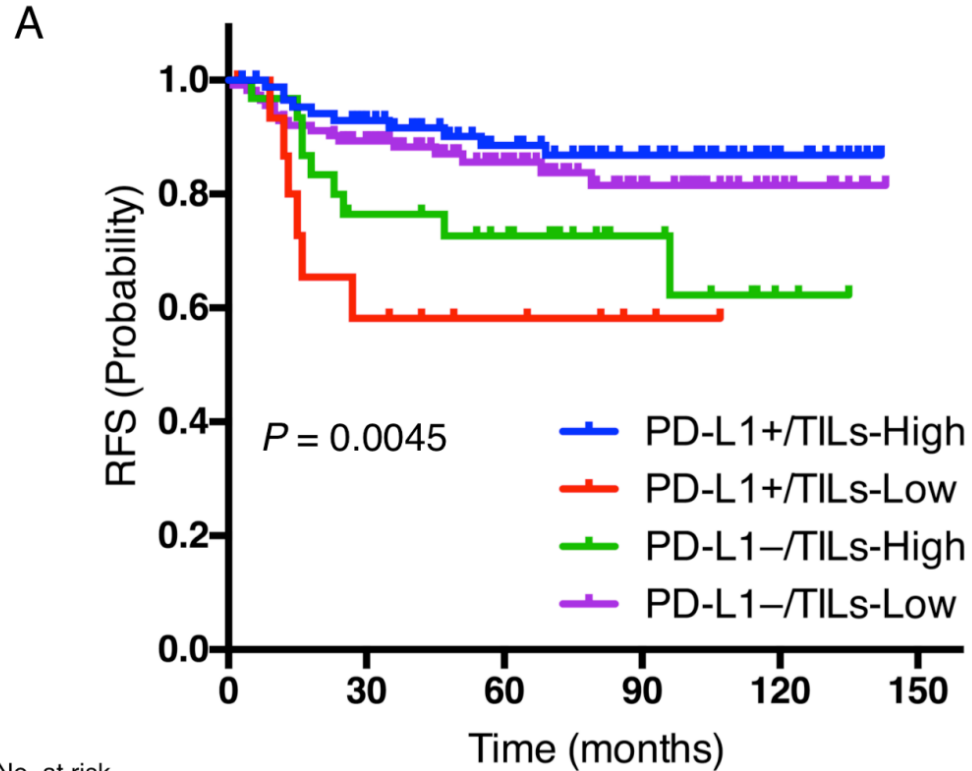
n=all patients with baseline and ≥ 1 follow-up scan; n-=number of patients with tumor shrinkage.
 Higgs BW et al. ECC 2015. Abstract 15LBA.

PFS by TMB Subgroup and PD-L1 Expression

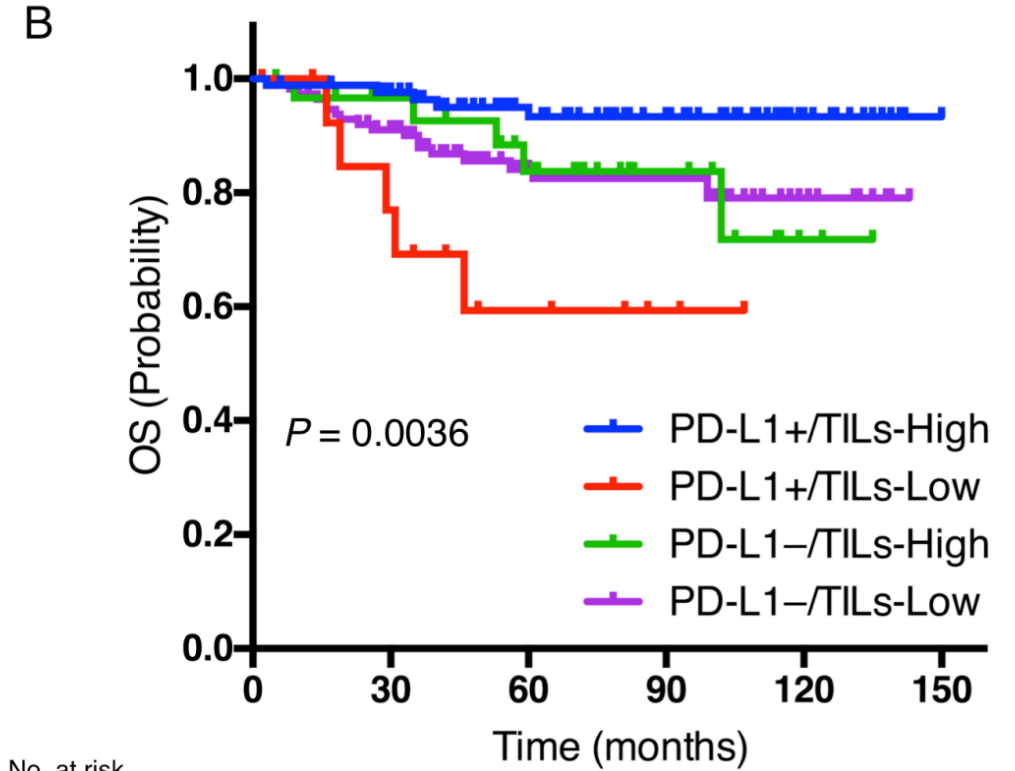
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



Kombinace hodnocení PD-L1 a TIL u TNBC



No. at risk	0	30	60	90	120	150
PD-L1+/TILs-High	87	81	78	77	77	77
PD-L1+/TILs-Low	16	10	10	10	10	10
PD-L1-/TILs-High	31	24	23	23	22	22
PD-L1-/TILs-Low	114	102	99	97	97	97



No. at risk	0	30	60	90	120	150
PD-L1+/TILs-High	87	85	82	82	82	82
PD-L1+/TILs-Low	16	13	11	11	11	11
PD-L1-/TILs-High	31	30	27	27	26	26
PD-L1-/TILs-Low	114	104	98	97	96	96

Kombinace GEP a TMB u TNBC

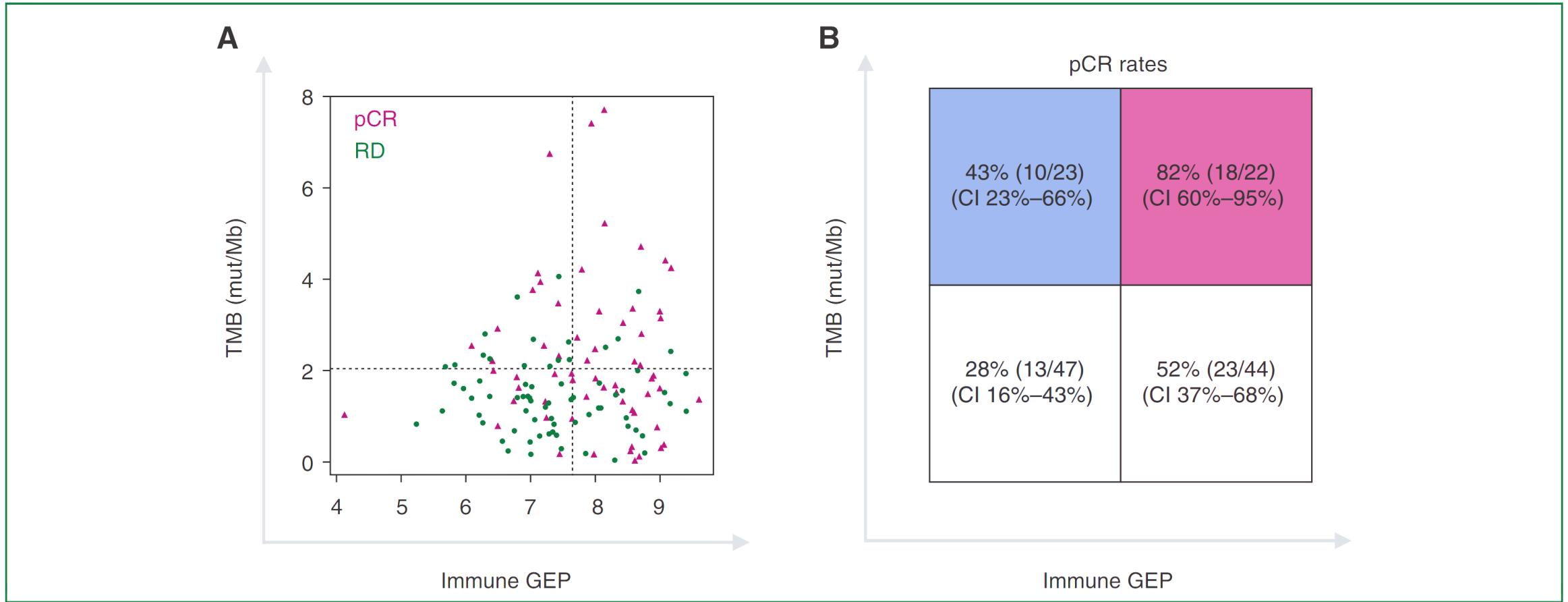
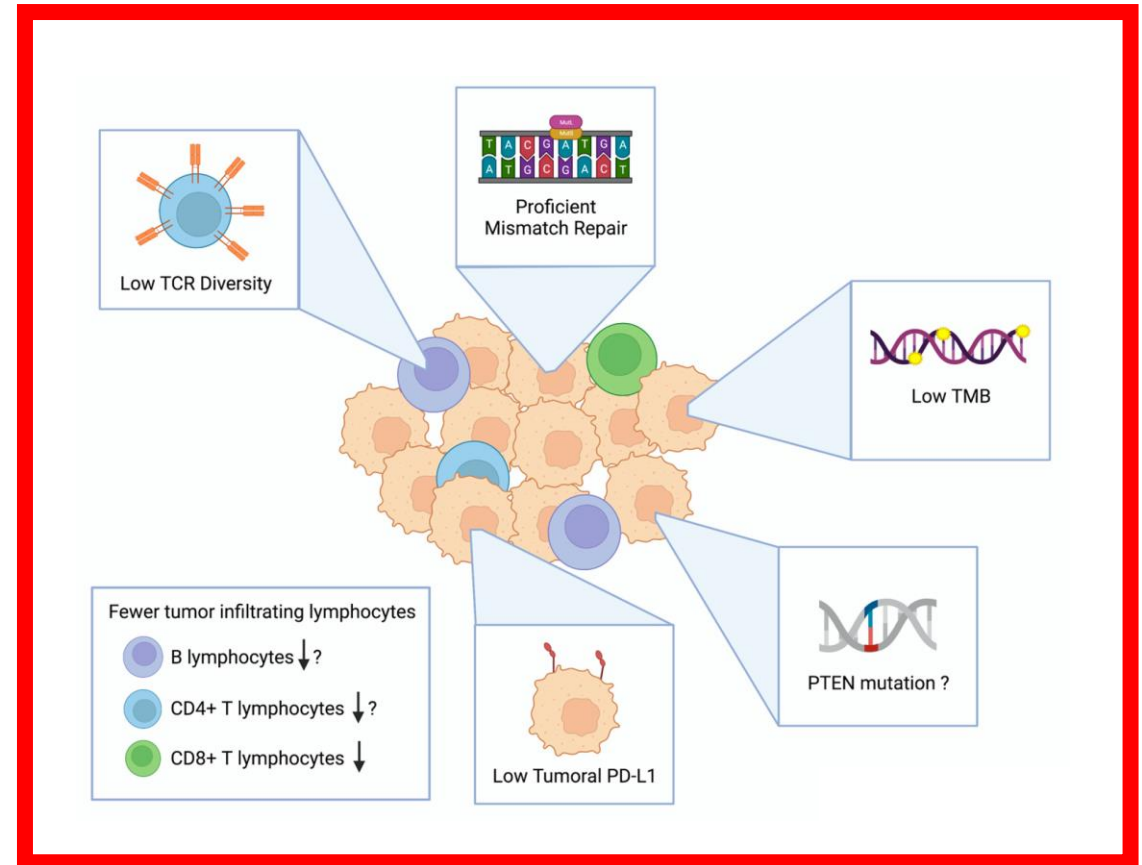
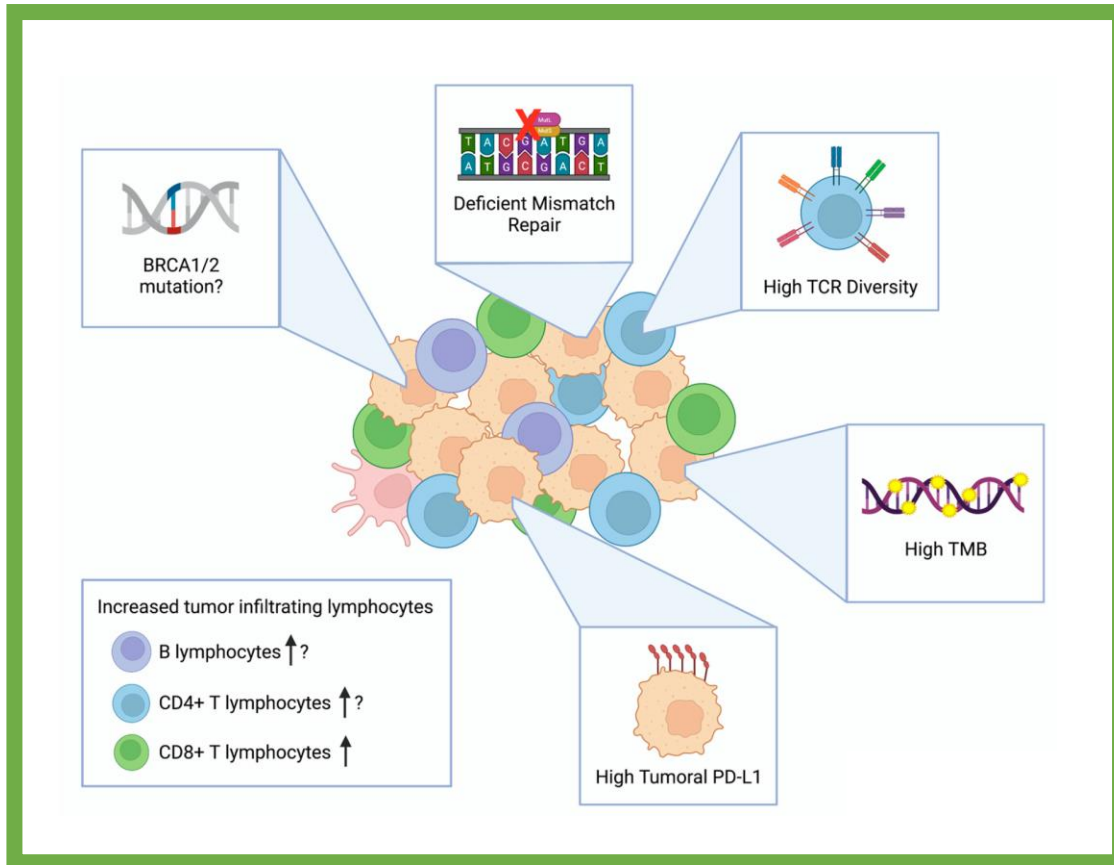
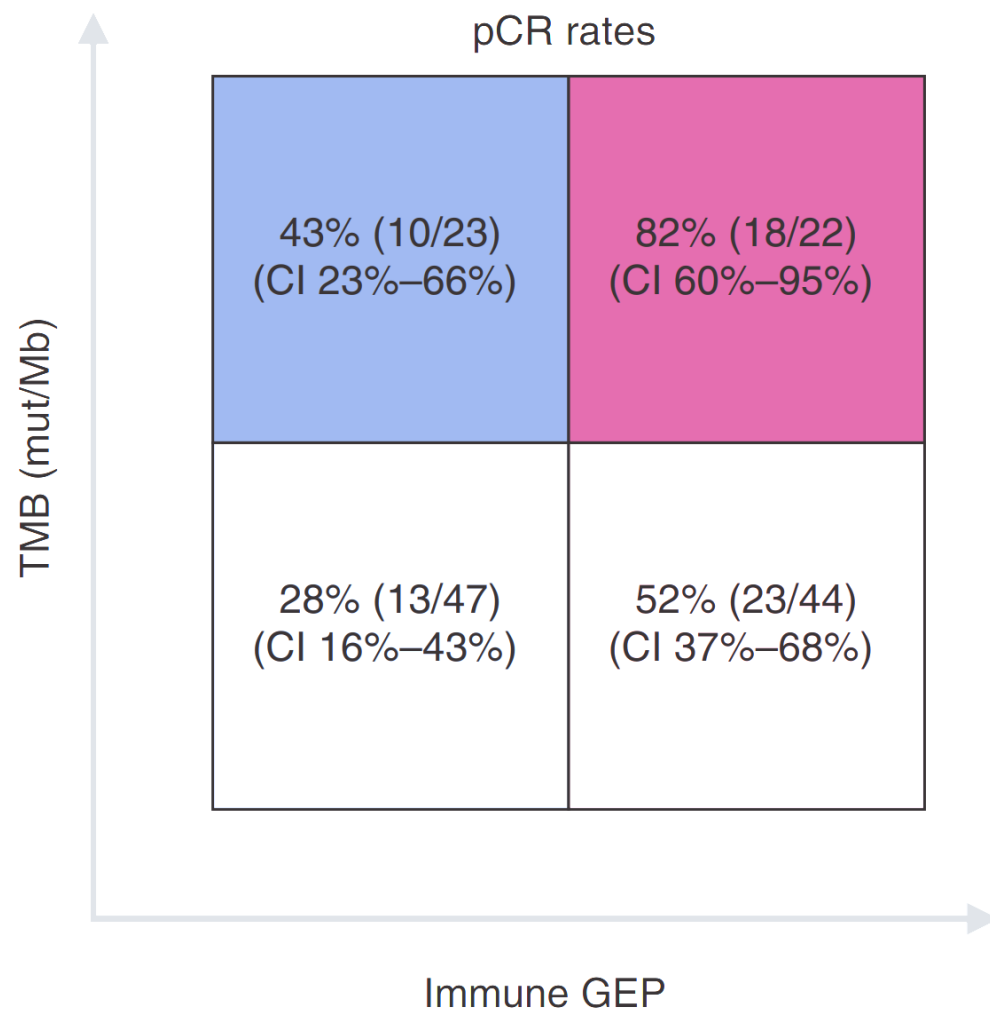


Figure 2. Joint relationship of tumor mutational burden (TMB) and immune gene expression profile (GEP) with pCR in GeparNuevo.

Pozitivní a negativní prediktory IO



Využití prediktivních markerů – etické dilema



Take home message

- v nejbližší budoucnosti nelze čekat nový "magický" biomarker pro IO
- kombinace několika markerů zvyšuje pozitivní prediktivní hodnotu - vysoká cena
- zatím lze využívat "staré známé" - PD-L1, MSI
- u PD-L1 - v blízké budoucnosti podpora AI?
- TMB - řada limitací (metodické, finanční)
- nové markery v rámci panelového sekvenování (STK11, KEAP1)
- nové markery - HRD, INFy, TIL - biologicky velmi slibné, nasazení v reálné praxi obtížnější
- zásadní bude úloha MDT/MTB

