Slovenská onkologická spoločnosť

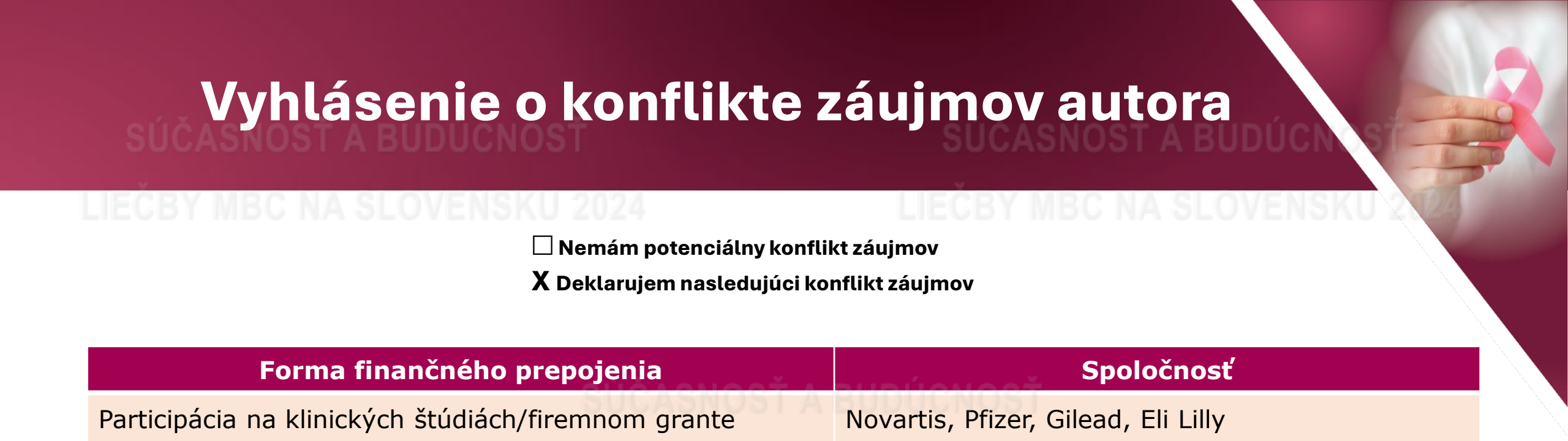
SÚČASNOSŤ A BUDÚCNOSŤ LIEČBY MBC NA SLOVENSKU

26.-27.09.2024 HOTEL PARTIZÁN, TÁLE

# Aplikácia výsledkov vyšetrení a úskalia ich využitia v praxi

MUDr. Bela Mriňáková, PhD, MPH, MHA

# Vyhlásenie o konflikte záujmov autora



☐ **Nemám potenciálny konflikt záujmov**

**X Deklarujem nasledujúci konflikt záujmov**

| Forma finančného prepojenia | Spoločnosť |
|---|---|
| Participácia na klinických štúdiách/firemnom grante | Novartis, Pfizer, Gilead, Eli Lilly |
| Nepeňažné plnenie (v zmysle zákona) | Novartis, Roche, Eli Lilly, AstraZeneca |
| Prednášajúci | Novartis, Pfizer, Eli Lilly, MSD, AstraZeneca |
| Akcionár | |
| Konzultant/odborný poradca | Eli Lilly, Novartis, MSD, Pfizer, Merck |
| Ostatné príjmy (špecifikovať) | |

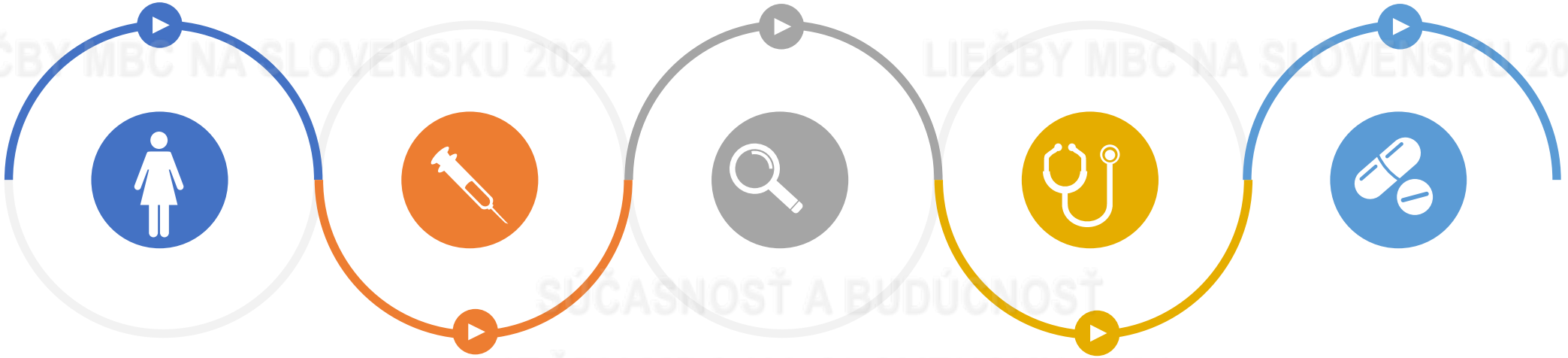
Podľa UEMS (upravené v zmysle slovenskej legislatívy)

**Účelom prednášky nie je reklama liekov. Jej účelom je výlučne zdieľanie výsledkov klinických štúdií, výmena skúseností z klinickej praxe a podpora odbornej medicínskej diskusie.**

# POSUN OD PERSONALIZOVANEJ LIEČBY K PRECÍZNEJ MEDICÍNE

# CIEĽOM SPRÁVNA LIEČBA SPRÁVNEMU PACIENTOVI V SPRÁVNOM ČASE

# VSTUPY PRI ROZHODOVANÍ O LIEČBE



PACIENT | BIOPSIA | PATOLÓGIA | DIAGNOSTIKA | LIEČBA

- Možné vstupy do rozhodovacieho procesu významne narastajú
- Liečba jednotlivých podskupín podľa prognostických a prediktívnych faktor sa stále významnejšie odlišuje
- Nesprávne indikovaná liečba môže mať dopad na prežívanie pacienta
- SR stále limitované dostupnosťou a možnosťou indikácie nových terapeutických možností v úhrade ZP
- Pacienti sú stále viac informovaní o možnostiach precíznej medicíny
- Pacienti veľakrát aj svojvoľne realizujú rôzne vyšetrenia a zvyšujú podiel vstupov v rozhodovacom procese

# CESTA K PERSONALIZOVANEJ LIEČBE KARCINÓMU PRSNÍKA

**1970**

**ER**

**ER sa pôvodne stanovoval pomocou techník závislých na viazaní ligandu[1]**
**Neskôr prebrali úlohu v diagnostike IHC, ktoré sa využívajú dodnes[1]**

**Prvý HER2 IHC test bol schválený FDA v 1998, v tom istom čase sa schválil trastuzumab v liečbe HER2-pozitívneho karcinómu prsníka[2,3]**

**HER2**

**1998**

**V 2019 FDA schválenie kombinácie *nab*-pac + atezolizumab u pacientok s PD-L1 IC+ metastatickým TNBC[4,5]**

**Vyšetrenie VENTANA SP142 IHC assay**

**PD-L1**

**2019**

**súčasnosť**

**NGS**

**ER, estrogénový receptor; IC, tumor-infiltrujúce imunitné bunky; IHC, immunohistochémia; *nab*-pac, *nab*-paclitaxel; PD-L1, ligand programovanej smrti 1; TNBC, triple-negatívny karcinóm prsníka.**

1. Ciocca DR & Elledge R. Endocrine 2000; 2. Perez EA, et al. Cancer Treat Rev 2014;
3. Press MF, et al. J Clin Oncol 2002; 4. Emens LA, et al. SABCS 2018. (Abstract GS1-04);
5. Atezolizumab PI 2019. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761034s018lbl.pdf;
6. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160002S009;
7. Cardoso F, et al. Ann Oncol 2018; 8. NCCN Breast Cancer Guidelines v1 – March 2019.

# S AKÝMI ”NOVÝMI” VSTUPMI SA STRETÁVAME

## VSTUPY Z TAKZVANÉHO “SKUTOČNÉHO SVETA“

RIEŠENIA DIGITÁLNEHO ZDRAVIA
IOT TECHNOLÓGIE
SOCIÁLNE MÉDIA
ELEKTRONICKÉ/LEKÁRSKE ZÁZNAMY
DOTAZNÍKY
PROMs
VYJADRENIA POISŤOVNÍ
DIAGNOSTICKÉ/GENOMICKÉ DATABÁZY
REGISTRÁCIE LIEKOV
PODANIA DOPLNENÍ NÚ
MOŽNOSTI KLINICKÝCH ŠTÚDIÍ
DATABÁZY INTERAKCIÍ
„GENETICKÉ ANALÝZY“ – NGS, transkriptomika, drug resistance, sekvenovaný mikrobióm atď...

Pocit naliehavosti
Skreslené informácie
Investované náklady
Viera vo vyliečenie
Uverenie šarlatánom
Pocit sklamania, že lekár nerobí dosť


PACIENT


LEKÁR

Pocit inkompetencie
Odborná „pýcha“, bagatelizácia nepoznaného
Pocit vyhorenia, nedostatok času
Preťaženie množstvom informácií
Neprehľadnosť akým vyšetreniam dôverovať
Neprehľadnosť odporúčaní ako naložiť s výsledkami

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

## Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

F. Mosele[1], J. Remon[2], J. Mateo[3], C. B. Westphalen[4], F. Barlesi[1], M. P. Lolkema[5], N. Normanno[6], A. Scarpa[7], M. Robson[8], F. Meric-Bernstam[9], N. Wagle[10], A. Stenzinger[11], J. Bonastre[12,13], A. Bayle[1,12,13], S. Michiels[12,13], I. Bièche[14], E. Rouleau[15], S. Jezdic[16], J-Y. Douillard[16], J. S. Reis-Filho[17], R. Dienstmann[18] & F. André[1,19,20*]

- Hodnotenie jednotlivých typov liečby ESCAT škálou (popri známejšej ESMO-MCBS a sile dôkazu) bolo zaradené do **ESMO guidelines**, vrátene **ESMO living guidelines schém**
- Pre metastatický nádor prsníka v r. 2021
- Pre včasný nádor prsníka v r. 2023
- Pre karcinóm prsníka akt. ESCAT IA- pri BRCA

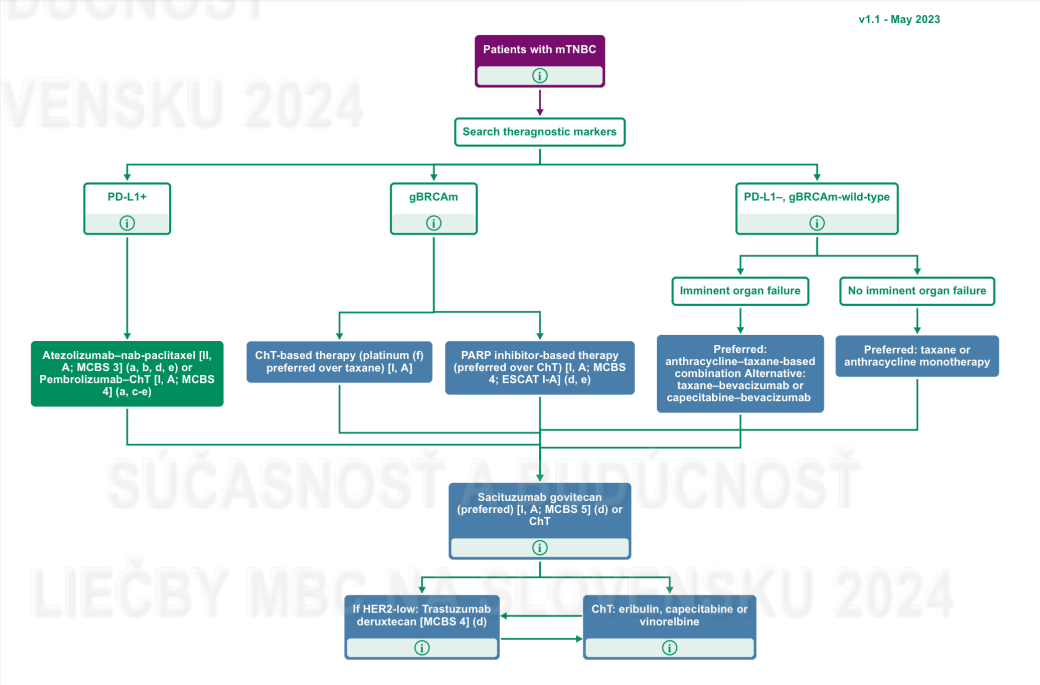



**Table 3. List of genomic alterations level I/II according to ESCAT in advanced breast cancer**

| Gene | Alteration | Estimated prevalence | ESCAT score | Drug class matched | References |
|---|---|---|---|---|---|
| *ERBB2* | Amplifications | 15%-20% | IA | Anti-HER2 monoclonal antibodies<br>HER2 TKIs<br>Anti-HER2 ADCs | Baselga et al., *N Engl J Med* 2012[55]<br>Krop et al., *Lancet Oncol* 2014[56]<br>Lin et al., *J Clin Oncol* 2020[57]<br>Saura et al., *J Clin Oncol* 2020[58]<br>Rugo et al., *JAMA Oncol* 2021[59] |
| | Hotspot mutations | 4% | IIB | Pan-HER TKIs<br>Anti-HER2 ADCs | Hyman et al., *Nature* 2018[51]<br>Smyth et al., *Cancer Discov* 2020[60]<br>Li et al., *Ann Oncol* 2023[61] |
| *PIK3CA* | Hotspot mutations | 30%-40% | IA (ER-positive HER2-negative ABC) | α-specific PI3K inhibitors* | André et al., *N Engl J Med* 2019[62]<br>Rugo et al., *Lancet Oncol* 2021[63]<br>Turner et al, *N Engl J Med* 2023[70] |
| *ESR1* | Mutations | 30%-40% | IA (ER-positive HER2-negative ABC resistant to AI) | SERDs | Bidard et al., *J Clin Oncol* 2022[64]<br>Bardia et al., *Cancer Res* 2023[65] |
| *BRCA1/2* | Germline pathogenic/likely pathogenic variants | 4% | IA | PARP inhibitors | Litton et al., *N Engl J Med* 2018[66]<br>Robson et al., *Eur J Cancer* 2023[67] |
| | Somatic mutations | 3% | IIB | PARP inhibitors | Tung et al., *J Clin Oncol* 2020[68] |
| *PTEN* | Mutations/deletions | 7% | I/II | AKT inhibitors | Schmid et al., *J Clin Oncol* 2020[69]<br>Turner et al., *N Engl J Med* 2023[70] |
| *AKT1* | Mutations (p. E17K) | 5% | I/II | AKT inhibitors | Kalinsky et al., *JAMA Oncol* 2021[71]<br>Turner et al., *N Engl J Med* 2023[70] |
| *PALB2* | Germline pathogenic/likely pathogenic variants | 1% | IIB | PARP inhibitors | Tung et al., *J Clin Oncol* 2020[68]<br>Gruber et al., *Nat Cancer* 2022[72] |

ABC, advanced breast cancer; ADCs, antibody—drug conjugates; AI, aromatase inhibitors; ER, oestrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HER, human epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase; SERDs, selective oestrogen receptor degrader; TKIs, tyrosine kinase inhibitors.
*AKT inhibitors have shown efficacy in patients with PIK3CA mutated ER-positive HER2-negative ABC

Mosele MF, Westphalen CB, Stenzinger A, Barlesi F, Bayle A, Bièche I, Bonastre J, Castro E, Dienstmann R, Krämer A, Czarnecka AM, Meric-Bernstam F, Michiels S, Miller R, Normanno N, Reis-Filho J, Remon J, Robson M, Rouleau E, Scarpa A, Serrano C, Mateo J, André F. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2024 Jul;35(7):588-606.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

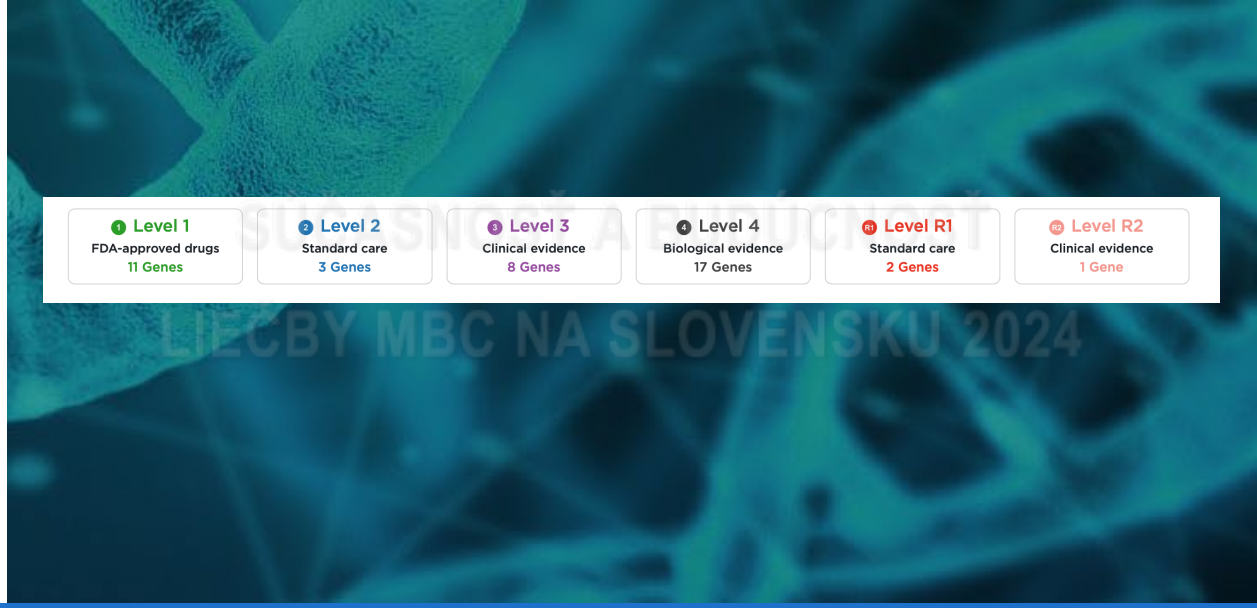
*Annals of Oncology* 29: 1895–1902, 2018
doi:10.1093/annonc/mdy263
Published online 21 August 2018

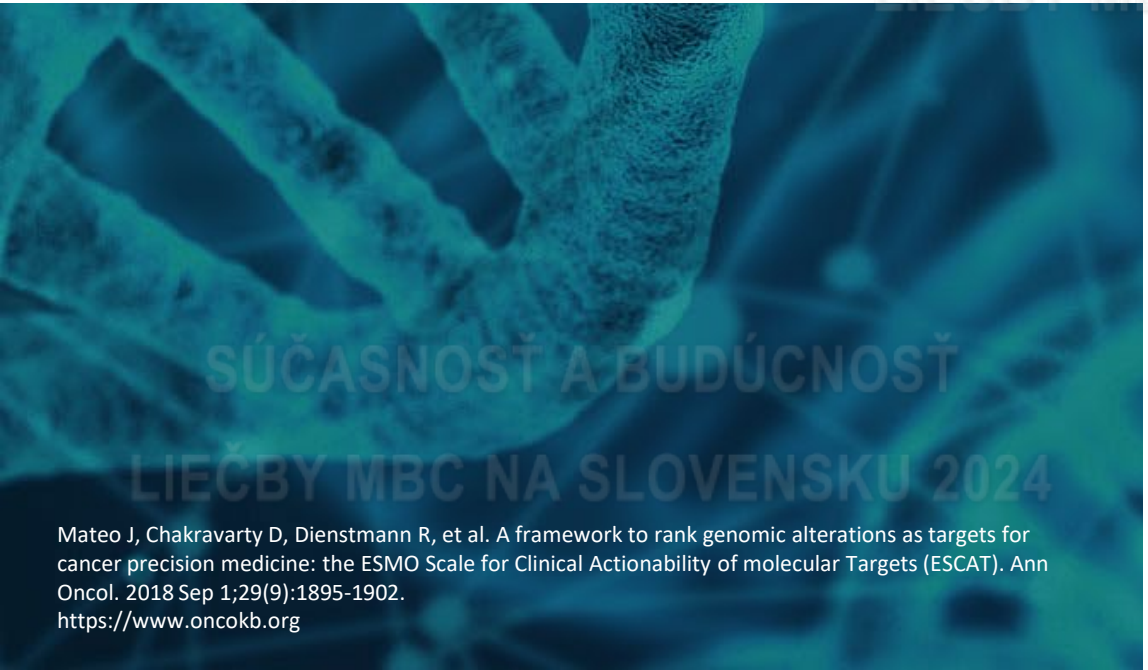
SPECIAL ARTICLE

# A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

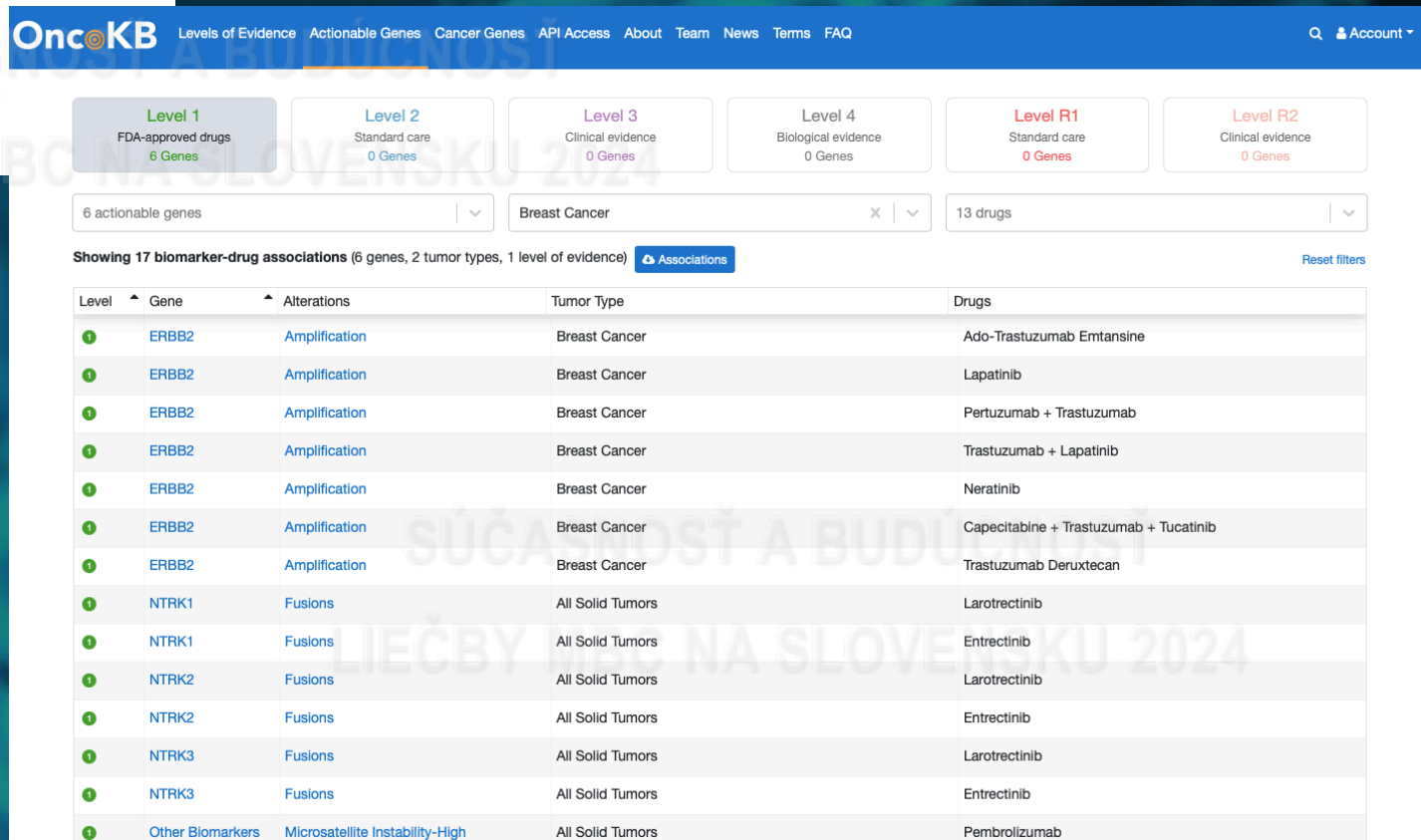
J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J.-Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12*] & L. Pusztai[13]

[1]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Memorial Sloan Kettering Cancer Center, New York, USA; [3]European Society for Medical Oncology, Lugano, Switzerland; [4]Institute for Research in Biomedicine (IRB), Barcelona; [5]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain; [6]University Hospital Basel, Basel, Switzerland; [7]Princess Margaret Cancer Centre, Toronto, ON, Canada; [8]University of Verona, Verona; [9]Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; [10]Harvard Medical School Dana-Farber Cancer Center and Broad Institute, Boston, USA; [11]The Francis Crick Institute, London, UK; [12]Institut Gustave Roussy, Villejuif, France; [13]Yale Cancer Center, New Haven, USA



Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol. 2018 Sep 1;29(9):1895-1902.
https://www.oncokb.org




| Level | Gene | Alterations | Tumor Type | Drugs |
|---|---|---|---|---|
| 1 | ERBB2 | Amplification | Breast Cancer | Ado-Trastuzumab Emtansine |
| 1 | ERBB2 | Amplification | Breast Cancer | Lapatinib |
| 1 | ERBB2 | Amplification | Breast Cancer | Pertuzumab + Trastuzumab |
| 1 | ERBB2 | Amplification | Breast Cancer | Trastuzumab + Lapatinib |
| 1 | ERBB2 | Amplification | Breast Cancer | Neratinib |
| 1 | ERBB2 | Amplification | Breast Cancer | Capecitabine + Trastuzumab + Tucatinib |
| 1 | ERBB2 | Amplification | Breast Cancer | Trastuzumab Deruxtecan |
| 1 | NTRK1 | Fusions | All Solid Tumors | Larotrectinib |
| 1 | NTRK1 | Fusions | All Solid Tumors | Entrectinib |
| 1 | NTRK2 | Fusions | All Solid Tumors | Larotrectinib |
| 1 | NTRK2 | Fusions | All Solid Tumors | Entrectinib |
| 1 | NTRK3 | Fusions | All Solid Tumors | Larotrectinib |
| 1 | NTRK3 | Fusions | All Solid Tumors | Entrectinib |
| 1 | Other Biomarkers | Microsatellite Instability-High | All Solid Tumors | Pembrolizumab |

| | | | | |
|---|---|---|---|---|
| 1 | AKT1 | E17K | Breast Cancer | Capivasertib + Fulvestrant |
| 1 | BRAF | V600E | All Solid Tumors (excluding Colorectal Cancer) | Dabrafenib + Trametinib |
| 1 | ERBB2 | Amplification | Breast Cancer | Ado-Trastuzumab Emtansine |
| 1 | ERBB2 | Amplification | Breast Cancer | Lapatinib + Capecitabine |
| 1 | ERBB2 | Amplification | Breast Cancer | Lapatinib + Letrozole |
| 1 | ERBB2 | Amplification | Breast Cancer | Margetuximab + Chemotherapy |
| 1 | ERBB2 | Amplification | Breast Cancer | Neratinib |
| 1 | ERBB2 | Amplification | Breast Cancer | Neratinib + Capecitabine |
| 1 | ERBB2 | Amplification | Breast Cancer | Trastuzumab |
| 1 | ERBB2 | Amplification | Breast Cancer | Trastuzumab + Chemotherapy |
| 1 | ERBB2 | Amplification | Breast Cancer | Trastuzumab + Pertuzumab + Chemotherapy |
| 1 | ERBB2 | Amplification | Breast Cancer | Trastuzumab + Tucatinib + Capecitabine |
| 1 | ERBB2 | Amplification | Breast Cancer | Trastuzumab Deruxtecan |
| 1 | ESR1 | Oncogenic Ligand-Binding Domain Missense Mutations | Breast Cancer | Elacestrant |
| 1 | NTRK1 | Fusions | All Solid Tumors | Entrectinib |
| 1 | NTRK1 | Fusions | All Solid Tumors | Larotrectinib |
| 1 | NTRK1 | Fusions | All Solid Tumors | Repotrectinib |
| 1 | NTRK2 | Fusions | All Solid Tumors | Entrectinib |
| 1 | NTRK2 | Fusions | All Solid Tumors | Larotrectinib |
| 1 | NTRK2 | Fusions | All Solid Tumors | Repotrectinib |
| 1 | NTRK3 | Fusions | All Solid Tumors | Entrectinib |
| 1 | NTRK3 | Fusions | All Solid Tumors | Larotrectinib |
| 1 | NTRK3 | Fusions | All Solid Tumors | Repotrectinib |
| 1 | Other Biomarkers | Microsatellite Instability-High (MSI-H) | All Solid Tumors | Pembrolizumab |
| 1 | Other Biomarkers | Tumor Mutational Burden-High (TMB-H) | All Solid Tumors | Pembrolizumab |
| 1 | PIK3CA | C420R and 10 other alterations | Breast Cancer | Alpelisib + Fulvestrant |
| 1 | PIK3CA | C420R and 10 other alterations | Breast Cancer | Capivasertib + Fulvestrant |
| 1 | PIK3CA | E545Q and 7 other alterations | Breast Cancer | Capivasertib + Fulvestrant |
| 1 | PTEN | Oncogenic Mutations | Breast Cancer | Capivasertib + Fulvestrant |
| 1 | RET | Fusions | All Solid Tumors | Selpercatinib |

OnkoKB prehľad molekulárnych targetov a FDA registrovaných liečiv, ktoré sa však nemusia zhodovať so štandardom liečby

| | | | | |
|---|---|---|---|---|
| 2 | AKT1 | Oncogenic Mutations (excluding E17K) | Breast Cancer | Capivasertib + Fulvestrant |
| 2 | ESR1 | V422del | Breast Cancer | Elacestrant |
| 2 | PIK3CA | Oncogenic Mutations (excluding C420R, E542K, E545A, E545D, E545G, E545K, Q546E, Q546R, H1047L, H1047R and H1047Y) | Breast Cancer | Alpelisib + Fulvestrant |
| 2 | PIK3CA | Oncogenic Mutations (excluding C420R, E542K, E545A, E545D, E545G, E545K, Q546E, Q546R, H1047L, H1047R, H1047Y, R88Q, N345K, E545Q, Q546K, Q546P, M1043V, M1043I and G1049R) | Breast Cancer | Capivasertib + Fulvestrant |

Tie, ktoré sa považujú za štandard liečby

www.oknokb.org, navštívené sept. 2024

# Nevšedné kombinácie liekov v rámci klinických štúdií

**Aktuálne zvýšený záujem o pacientov s potvrdenými patologickými variatami génov**

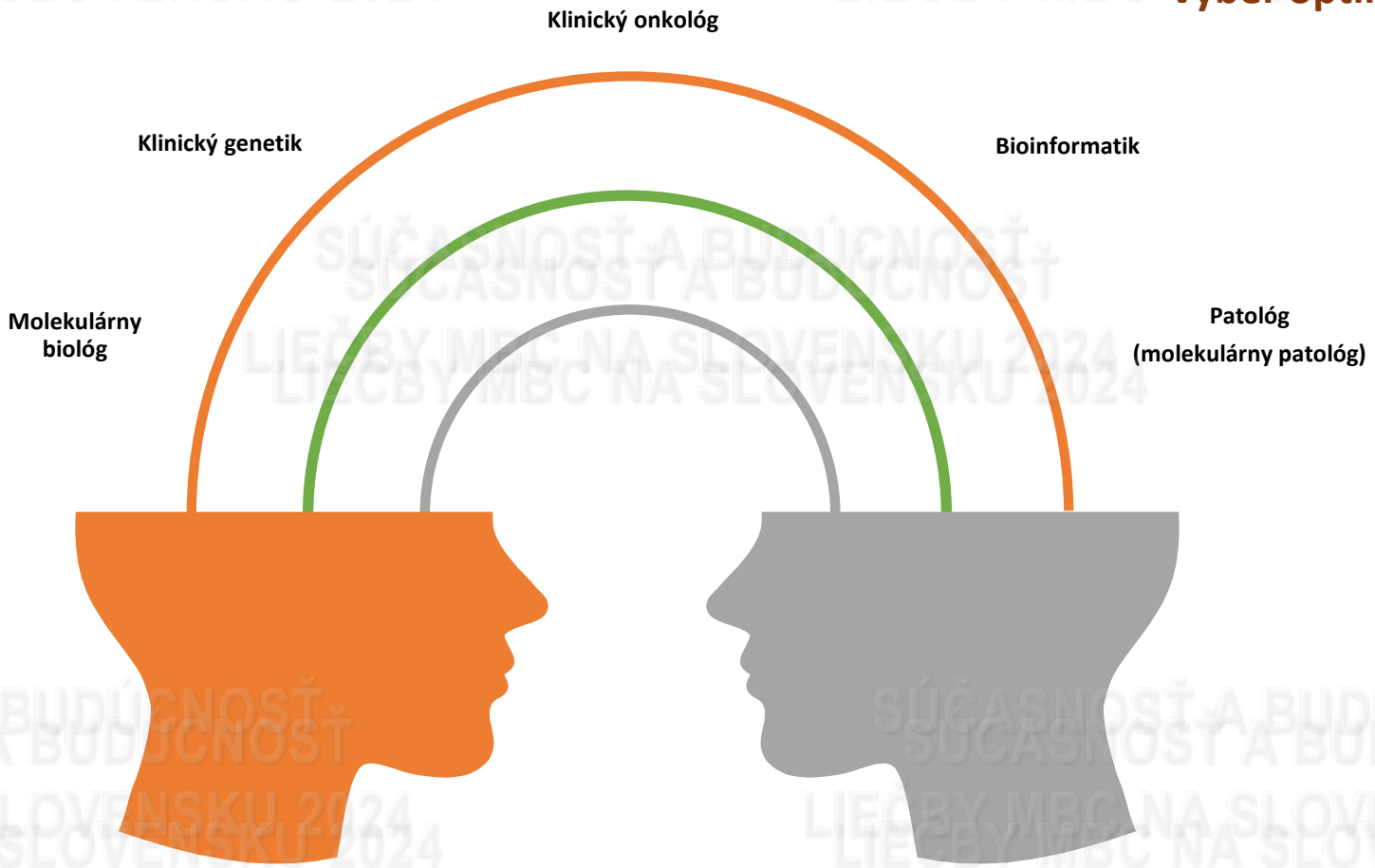
OncoKB Levels of Evidence | Actionable Genes | Cancer Genes | API Access | About | Team | News | Terms | FAQ

| Level | Gene | Alterations | Tumor Type | Drugs |
|---|---|---|---|---|
| 3 | AKT1 | E17K | Breast Cancer | AZD5363 |
| 3 | ERBB2 | Oncogenic Mutations | Breast Cancer | Neratinib |
| 3 | ESR1 | Oncogenic Mutations | Breast Cancer | AZD9496, Fulvestrant |
| 3 | PIK3CA | Oncogenic Mutations | Breast Cancer | GDC-0077 |
| 3 | PIK3CA | Oncogenic Mutations | Breast Cancer | Copanlisib + Fulvestrant |
| 4 | BRAF | L597 | All Solid Tumors | PLX8394 |
| 4 | BRAF | K601 | All Solid Tumors | PLX8394 |
| 4 | BRAF | G464, G469A, G469R, G469V | All Solid Tumors | PLX8394 |
| 4 | CDK12 | Truncating Mutations | All Solid Tumors | Pembrolizumab, Cemiplimab, Nivolumab |
| 4 | CDKN2A | Oncogenic Mutations | All Solid Tumors | Ribociclib, Abemaciclib, Palbociclib |
| 4 | FGFR1 | Oncogenic Mutations | All Solid Tumors | BGJ398, Debio1347, Erdafitinib, AZD4547 |
| 4 | FGFR2 | Oncogenic Mutations | All Solid Tumors | BGJ398, AZD4547, Erdafitinib, Debio1347 |
| 4 | FGFR3 | Oncogenic Mutations | All Solid Tumors | Debio1347, Erdafitinib, AZD4547, BGJ398 |
| 4 | KRAS | Oncogenic Mutations | All Solid Tumors | Trametinib, Binimetinib, Cobimetinib |
| 4 | MET | Fusions | All Solid Tumors | Crizotinib |
| 4 | MTOR | Oncogenic Mutations | All Solid Tumors | Temsirolimus, Everolimus |

https://www.oncokb.org

# Molekulárna multidisciplinárna komisia

**Interpretácia komplexných dát- výber optimálneho klinického riešenia**



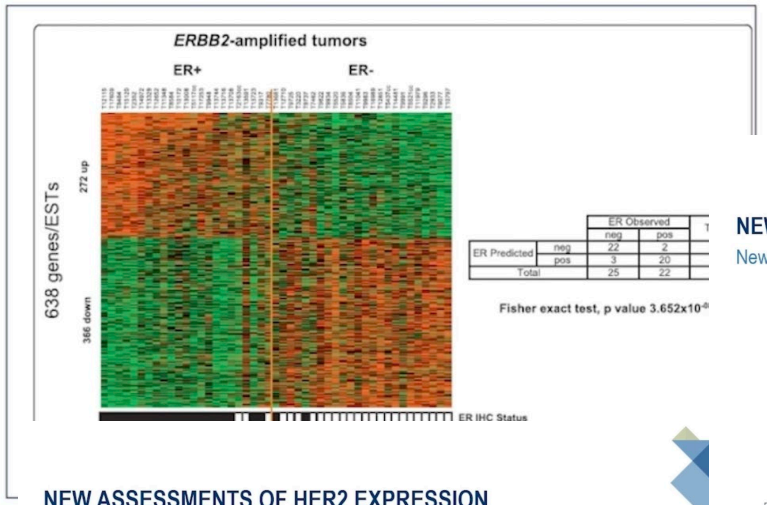

- Uľahčenie interpretácie komplexných dát
- Výber správnej liečby
- Edukácia
- Udržanie kroku s aktuálnymi liečebnými možnosťami GCP

# SMERUJE TO NIEKAM? ÁNO..

- **402 génov je exprimovaných rozdielne pri ER+ s ER-**
- Z toho napríklad GATA3, ESR1, TFF3 a ERBB4 boli upregulované a IGF2R, GATA6, EGFR a TGFA downregulované pri ER+HER2 amplifikovaných nádoroch

## GENOMIC PROFILING OF HER2+ ABC

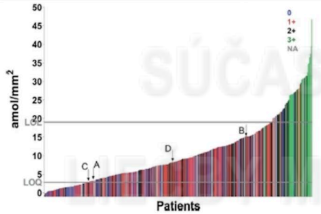
Comparison of ER+ and ER- breast cancer




## NEW ASSESSMENTS OF HER2 EXPRESSION

Do we need new "more quantitative" methods to assess HER2 expression ?

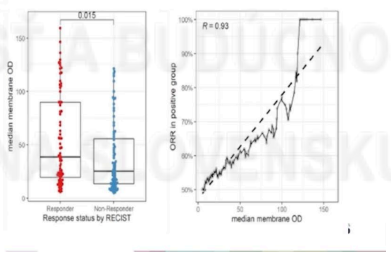
quantitative immunofluorescence coupled with mass spectrometry **to measure absolute amounts of HER2 protein**: 67% of patients had HER2 expression, but would have been considered negative by standard IHC




Moutafi et al, Laboratory Investigations 2022; Kapil et al, Scientific Reports 2024

ESMO DEEP DIVE: BREAST CANCER

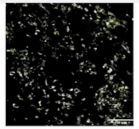
**Quantification of HER2 protein expressi**
optical density (OD) in the membrane and
tumor cell by using deep-learning–based i
digitized tissue sections better predicted re
compared to manual IHC




## NEW ASSESSMENTS OF HER2 EXPRESSION

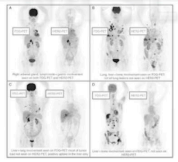
New technologies for capturing intratumor and inter-metastases HER2 heterogeneity

Spatial technologies for multiple protein analysis- AI digital pathology



Better quantification of HER2 expression and characterization of HER2 spatial distribution

Ab-radiolabeled PET scan



Inter-metastases heterogeneity of HER2 expression

Modified from Pistilli, ASCO 2023. Imaging mass cytometry (Hyperion) o

ESMO DEEP DIVE: BREAST CANCER

## NEW ASSESSMENTS OF HER2 EXPRESSION

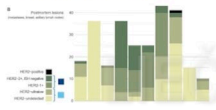
Heterogeneity of HER2 expression can also affect treatment response

INTRA-TUMOR AND INTER-METASTASES HER2 HETEROGENEITY

Cluster with prevalence of HER2-neg areas -> no response to T-DXd

INTRATUMOR TARGET SPATIAL DISTRIBUTION AFFECT RESPONSE TO T-DXd !

8/10 patients: inter-metastasis heterogeneity of HER2 status



DOES IT AFFECT RESPONSE TO T-DXd ?

Modified from Pistilli, ASCO 2023; Mosele et al, Nature Medicine 2023; Geukens et al, EJC 2023

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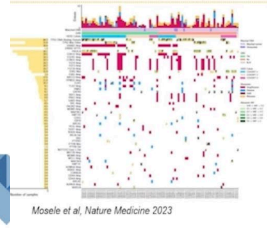
## MECHANISMS OF RESISTANCE TO HER2-DIRECTED THERAPIES TO GUIDE FURTHER TREATMENT CHOICE

Potential mechanisms of resistance to T-DXd

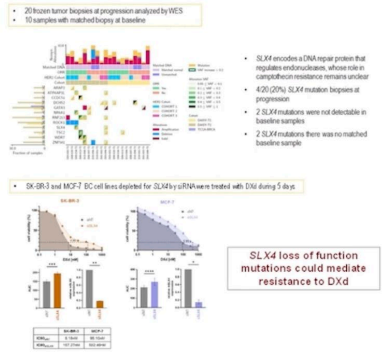
WES at baseline (n=88) and at progression (n=20)
ERBB2 hemizygous deletion was detected in 5 out of 88 (6%) patients at baseline-> no response




Mosele et al, Nature Medicine 2023

No recurrent driver alterations in baseline samples were associated with resistance

- 5/88 (6%) *ERBB2* hemizygous deletion
- 4 of these patients did not response to T-DXd (2 with HER2-low and 2 with HER2-null mBC)



*SLX4* loss of function mutations could mediate resistance to DXd

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Barbara Pistilli- ESMO Deep Dive Webinar, september 2024, www.esmo.org

# AKO MÁM TO TEDA POMÔŽE, KEĎ VIDÍME VÝSLEDKY?

# Príklad 1

## GENOMIC FINDINGS

NOTE: This is a comprehensive list of cancer-related alterations detected in this patient's sample.

| GENE | ALTERATION | HGVS CodingEffect | Chromosomal Position | VAF |
|---|---|---|---|---|
| ATM | p.P1141Lfs*15 | NM_000051.3: c.3422del | chr11:108151740 | 0.13% |
| CCND1 | amplification -equivocal | - | - | - |
| CCNE1 | amplification | - | - | - |
| FGF19 | amplification -equivocal | - | - | - |
| FGF3 | amplification -equivocal | - | - | - |
| FGF4 | amplification -equivocal | - | - | - |
| GNAS | amplification | - | - | - |
| IDH1 | p.R132H | NM_005896.2: c.395G>A | chr2:209113112 | 0.39% |
| IGF1R | amplification | - | - | - |
| KRAS | amplification | - | - | - |
| TP53 | p.R249G | NM_000546.4: c.745A>G | chr17:7577536 | 5.7% |

- **Výsledok prehľadný, odlišuje údaje relevantné pre klinika**
- **Oddelenie údajov o variantoch s neznámym klinickým dopadom**
- **Jasný prehľad o tom, či môžeme analýzu považovať za hodnotiteľnú- najmä v prípade liquid biopsie**

| Biomarker | Result |
|---|---|
| Tumor Mutational Burden | 6.32 mutations-per-megabase |
| Microsatellite Instability Status | Not Evaluable |
| ctDNA Tumor Fraction | High (12%) |

## VARIANTS OF UNKNOWN SIGNIFICANCE

Note: These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes significance unclear. FMI VUS are included here, in the event that they become clinically meaningful in the future.

| GENE | ALTERATION | HGVS CodingEffect | Chromosomal Position | VAF |
|---|---|---|---|---|
| AMER1 (FAM123B or WTX) | p.V184I | NM_152424.3: c.550G>A | chrX:63412617 | 0.32% |
| BRCA1 | p.M1728T | NM_007294.3: c.5183T>C | chr17:41215360 | 0.09% |
| BRCA1 | p.N1102S | NM_007294.3: c.3305A>G | chr17:41244243 | 41.4% |
| BRIP1 | amplification -equivocal | - | - | - |
| CD79B | amplification -equivocal | - | - | - |
| GNA13 | amplification -equivocal | - | - | - |
| GNAS | GNAS rearrangement | - | - | 1.3% |
| GNAS | p.A7D | NM_016592.2: c.20C>A | chr20:57415181 | 1.5% |
| GNAS | p.P147L | NM_016592.2: c.440C>T | chr20:57415601 | 1.6% |
| IGF1R | IGF1R rearrangement | - | - | 0.89% |
| IGF1R | IGF1R-LOC284757 rearrangement | - | - | 1.2% |
| IGF1R | p.D1235H | NM_000875.3: c.3703G>C | chr15:99491918 | 1.7% |
| IGF1R | p.G1169A | NM_000875.3: c.3506G>C | chr15:99486200 | 2.1% |
| IGF1R | p.S1278F | NM_000875.3: c.3833C>T | chr15:99500400 | 0.29% |
| MET | p.V136I | NM_000245.2: c.406G>A | chr7:116339544 | 50.8% |
| PIK3C2G | amplification -equivocal | - | - | - |
| PRDM1 | amplification | - | - | - |
| RAD21 | p.G92S | NM_006265.2: c.274G>A | chr8:117875369 | 0.57% |
| RAD51C | amplification -equivocal | - | - | - |
| RNF43 | amplification -equivocal | - | - | - |
| SRC | SRC rearrangement | - | - | 1% |
| SRC | SRC rearrangement | - | - | 3.6% |
| TSC1 | p.V178I | NM_000368.4: c.532G>A | chr9:135797337 | 49.7% |

Zdroj: výsledky pacientok Mriňáková, OÚSA

# Príklad 2

3. **Dokázané SNV, malé inzercie, malé delécie, indel varianty a zostrihové varianty** – Uvedené sú iba varianty so silným klinickým významom TIER IA a IB a potenciálnym klinickým významom TIER IIC a IID.

| Gén | Referenčná sekvencia | HGVS cDNA zápis | HGVS proteínový zápis | VAF % | Biologický efekt | TIER terapeutická klasifikácia somatických variantov |
|---|---|---|---|---|---|---|
| *PIK3CA* | -- | -- | -- | -- | -- | -- |
| *AKT1* | -- | -- | -- | -- | -- | -- |
| *PTEN* | -- | -- | -- | -- | -- | -- |
| *ESR1* | NM_001122742.2 | c.1610A>C | p.(Y537S) | 5,6 | Patogénny | TIER IA |

**PRÍLOHA1 – OncoDeep™ DNA Kit zoznam vyšetrovaných génov :**
**Vyšetrované gény (638 génov):** *ABL1, ABL2, ACVR1, ACVR1B, ADARB2, AGO1, AGO2, AJUBA, AKT1, AKT2, AKT3, ALB, ALK, ALOX12B, AMER1, ANKRD11, ANKRD26, APC, APLNR, AR, ARAF, ARFRP1, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, ATXN7, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BABAM1, BAP1, BARD1, BBC3, BCL10, BCL2, BCL2L1, BCL2L11, BCL2L2, BCL6, BCOR, BCORL1, BCR, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTG2, BTK, CALR, CARD11, CARM1, CASP8, CBFB, CBL, CCNB3, CCND1, CCND2, CCND3, CCNE1, CD276, CD70, CD74, CD79A, CD79B, CDC42, CDC73, CDH1, CDH4, CDK12, CDK4, CDK6, CDK7, CDK8, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CEBPA, CENPA, CHD2, CHD4, CHEK1, CHEK2, CIC, CMTR2, CNTN4, CREBBP, CRKL, CRLF2, CSDE1, CSF1R, CSF3R, CSNK1A1, CTCF, CTLA4, CTNNA1, CTNNB1, CTR9, CUL3, CUL4A, CUX1, CXCR4, CYLD, CYP17A1, CYP19A1, CYP2C19, CYP2D6, CYSLTR2, DAXX, DCUN1D1, DDR1, DDR2, DDX41, DHX15, DICER1, DIS3, DNAJB1, DNMT1, DNMT3A, DNMT3B, DOT1L, DPYD, DROSHA, DUSP4, E2F3, EED, EGFL7, EGFR, EIF1AX, EIF4A2, EIF4E, ELF3, EML4, EMSY, EP300, EPAS1, EPCAM, EPHA3, EPHA5, EPHA7, EPHB1*

- **Výsledok prehľadný, stručný, ukazuje všetky vyšetrené varianty**
- **Oddelenie údajov s ESCAT potvrdenými cieľmi pre klinického onkológa**
- **Bonus – ESCAT odporúčaná terapia**
- **Uvedené klinické štúdie**
- **Bonus SJ a možnosť konzultácie výsledku**

Zdroj: výsledky pacientok Mriňáková, OÚSA

Vo vzorke DNA izolovanej z nádorového tkaniva sme **DOKÁZALI**:

- prítomnosť somatického **patogénneho** variantu **Y537S** v géne ***ESR1* so silným klinickým významom TIER IA.**

Vo vzorke DNA izolovanej z nádorového tkaniva sme **NEDOKÁZALI:**

- prítomnosť patogénnych/pravdepodobne patogénnych somatických variantov so silným/potenciálnym klinickým významom vrátane génov a variantov: *BRCA1,BRCA2, PIK3CA, AKT1, PTEN a ERBB2 (HER2)*;
- prítomnosť CNV prestavby;

Vo vzorke DNA izolovanej z nádorového tkaniva je:

- **MSI status: MSS** (mikrosatelitovo stabilný)
- **TMB status: nízky**
- **HRD status: negatívny**

***Poznámka:*** *Výsledok analýzy ďalších potenciálne relevantných biomarkerov, vrátane tumor agnostických génov (podľa ESMO odporúčaní 2024), dodáme na vyžiadanie dodatočne.*

**Terapia asociovaná s klinickým benefitom:**

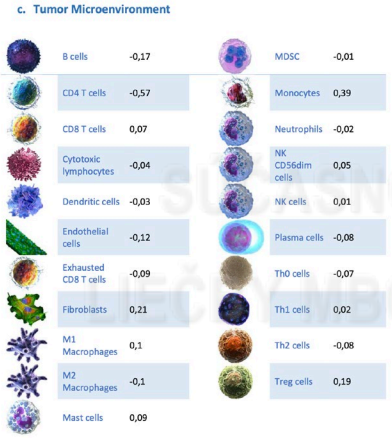
| Názov lieku | Trieda | Status | Indikované na |
|---|---|---|---|
| ***Asociovaný biomarker: ESR1:* p.(Y537S)** | | | |
| Elacestrant | „Estrogen receptor degrader„ | FDA/NCCN/ESMO/EMA schválené | Karcinóm prsníka |

**PRÍLOHA2 – Zoznam klinických štúdií:**

CLINICAL TRIALS

| Name | Phase | Countries | NCT ID |
|---|---|---|---|
| Phase III Study to Assess AZD9833+ CDK4/6 Inhibitor in HR+/HER2-MBC With Detectable ESR1m Before Progression (SERENA-6) | Phase 3 | FR GB HU IL SK AT AU BE BG CA CH DE ES US IT JP KR NO PL PT RU TR TW | NCT04964934 |
| Evaluation of Lasofoxifene Combined With Abemaciclib Compared With Fulvestrant Combined With Abemaciclib in Locally Advanced or Metastatic ER+/HER2- Breast Cancer With an ESR1 Mutation | Phase 3 | FR GB HU IL SG AU BE CA CZ DE ES US IT KR PL RO TR TW | NCT05696626 |
| A Study to Evaluate Efficacy and Safety of Giredestrant Compared With Fulvestrant (Plus a CDK4/6 Inhibitor), in Participants With ER-Positive, HER2-Negative Advanced Breast Cancer Resistant to Adjuvant Endocrine Therapy (pionERA Breast Cancer) | Phase 3 | FR GT HK HU IL IN AR AU BE BR CA CL CN CO CR DE ES US IT KR NZ PL PT TH TW | NCT06065748 |

# Príklad 3

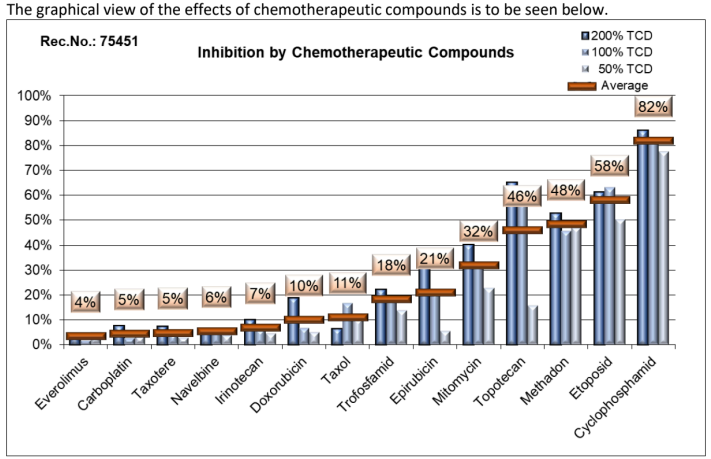



Status: 5 of 9 immune checkpoint related genes overexpressed.

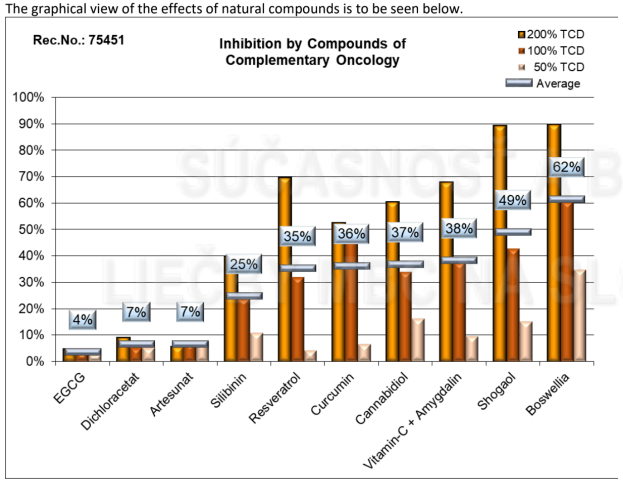
| Gene | Value | Median | Score | Status |
|---|---|---|---|---|
| PDL1 | 271 | 385 | -0,51 | low |
| PDL2 | 628 | 882 | -0,49 | low |
| PD1 | 154 | 64 | 1,27 | overexpressed |
| TIGIT | 293 | 221 | 0,41 | overexpressed |
| HAVCR2/TIM3 | 2644 | 1644 | 0,69 | overexpressed |
| CTLA4 | 373 | 191 | 0,97 | overexpressed |
| IDO1 | 567 | 766 | -0,43 | low |
| LAG3 | 644 | 234 | 1,46 | overexpressed |
| CD40* | 458 | 651 | -0,22 | low |

*Data based on qPCR results, * Data based on RefSeq results*

The graphical view of the effects of chemotherapeutic compounds is to be seen below.




The graphical view of the effects of natural compounds is to be seen below.




- **Výsledok neprehľadný, zahlcujúci**
- **Veľa obrázkov a farieb na upútanie laika**
- **Bez označenia klinickej relevancie**
- **Uvedené, že koncentrácie nekorelujú s hladinami in vivo**

Zdroj: výsledky pacientok Mriňáková, OÚSA

**AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, ERBB2, ERBB4, FBX7, FGFR1, FGFR2, FGFR3, KRAS, MAP2K1, MET, NOTCH1, NRAS, PIK3CA, PTEN, SMAD4, STK11, TP53**

**The following nonsynonymous mutations were detected:**

| Gene | Position* | Mutation | Freq. | Variant effect | Comment |
|---|---|---|---|---|---|
| TP53 | Chr 17<br>7578406<br>C>T | NM_000546.5<br>c.524G>A<br>p.Arg175His | 54% | missense | Pathogenic<br>No therapeutic intervention known for this mutation |

**Reference hg 19*

3. Drug Sensitivity (based on transcriptome data)

| Drug / Drug Class | Drugs | Sensitivty | References |
|---|---|---|---|
| **Anthracyclines** | Doxorubicin, Epirubicin | **PR/R** | [i],[ii] |
| **Platin** | Oxaliplatin | **IS** | |
| **Artemisinin** | Artesunate | **R** | |
| **Aspirin** | Aspirin | **IS/PR** | |
| **Bevacizumab** | Avastin | **PR** | |
| **Capecitabine** | Xeloda | **IS/PR** | |
| **Dichloroacetate** | DCA | **S** | |
| **CBD** | Cannabidiol | **IS/S** | |
| **Gemcitabin/Carboplatin** | Gemzitabine (various brands); Carboplatin | **R** | [iii] |
| **Gemcitabin** | Gemzitabine (various brands) | **IS/PR** | |
| **Carboplatin** | Carboplatin | **IS/PR** | |
| **Glucose Pathway directed** | 2-desoxyglucose (2DG) | **PR** | |
| **Growth factor Pathway directed** | Cetuximab | **R** | |
| **Heat shock protein related** | hyperthermia therapy | **PR/R** | [xxi], [xxii]; [xxiii] |
| **HER2/neu inhibitors** | Herceptin, Tycerb, Nerlynx, Kadcyla, Perjeta | **R** | |
| **Immunotherapy** | mutated neoantigen peptides | **S** | |
| **Melphalan/Busulfan** | | **PR** | |
| **Mitoxantrone** | Novantrone | **IS/S** | [iv] |
| **NFkB inhibitors** | Curcumin, Acurmin, Curcuflex | **S** | [xix], [xx] |
| **Palbociclib** | Ibrance | **PR** | |
| **Platinum derivates** | Cisplatin | **IS/PR** | [v],[vi],[vii] |
| **Pemetrexed** | Alimta | **S** | |
| **Taxanes** | Paclitaxel, Docetaxel | **PR** | [ix],[x],[xi] |
| **Topotecan/Irinotecan** | Hycamtin, Irinotecan | **IS/PR** | [xii],[xiii],[xiv] |
| **Telomerase inhibitors** | medical frankincense and many others | **S** | [xxiv] |
| **Vitamin D** | | **S** | |

The definitive therapeutic decisions are the responsibility of the treating oncologist.

# Príklad 4

| ANALYZED MOLECULAR PROFILE | |
|---|---|
| MUTANT GENES | |
| CHEK2-E239*, CYP2A6-S467*, FBXW7-E134D, KMT2C-C391*, TP53-E204* | |
| WILD TYPE GENES | |
| ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1, ACVR1B, ACVR2A, ADARB2, ADGRA2, ADORA2A, AGO1, AGO2, AIP, AJUBA, AKT1, AKT2, AKT3, ALB, ALK, ALOX12B, AMER1, ANKRD11, ANKRD26, APC, APLNR, AR, ARAF, ARFRP1, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, ATXN7, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BABAM1, BAP1, BARD1, BAX, BBC3, BCL10, BCL2, BCL2L1, BCL2L11, BCL2L2, BCL6, BCOR, BCORL1, BCR, BIRC3, BIRC5, BLM, BMP1, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTG2, BTK, CALR, CARD11, CARM1, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CCN6, CCNB3, CCND1, CCND2, CCND3, CCNE1, CCNQ, CD22, CD274, CD276, CD70, CD74, CD79A, CD79B, CDC42, CDC73, CDH1, CDH4, CDK12, CDK2, CDK4, CDK6, CDK7, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CENPA, CHD1, CHD2, CHD4, CHEK1, CIC, CMTR2, CNTN4, COP1, CREBBP, CRKL, CRLF2, CRTC1, CSDE1, CSF1, CSF1R, CSF2, CSF3R, CSNK1A1, CTC1, CTCF, CTLA4, CTNNA1, CTNNB1, CTR9, CUL3, CUL4A, CUX1, CXCR2, CXCR4, CYLD, CYP17A1, CYP19A1, CYP2B6, CYP2C19, CYP2D6, CYSLTR2, DAXX, DCUN1D1, DDIT3, DDR1, DDR2, DDX11, DDX41, DHX15, DICER1, DIS3, DIS3L2, DNAJB1, DNMT1, DNMT3A, DNMT3B, DOT1L, DPH3, DPYD, DROSHA, DSE, DUSP4, E2F3, EED, EEF1A1, EGFL7, EGFR, EIF1AX, EIF4A2, EIF4E, ELF3, ELOC, EML4, EMSY, EP300, EP400, EPAS1, EPCAM, EPHA2, EPHA3, EPHA5, EPHA7, EPHB1, EPHB4, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, ERF, ERG, ERRFI1, ESR1, ETAA1, ETS1, ETV1, ETV4, ETV5, ETV6, EWSR1, EXO1, EZH1, EZH2, EZR, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FGF1, FGF10, FGF12, FGF14, FGF19, FGF2, FGF23, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLI1, FLT1, FLT3, FLT4, FOXA1, FOXF1, FOXL2, FOXO1, FOXP1, FRS2, FUBP1, FYN, FZD1, FZD10, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD9, GAB1, GAB2, GABRA6, GATA1, GATA2, GATA3, GATA4, GATA6, GEN1, GID4, GLI1, GNAT1, GNA13, GNAQ, GNAS, GNB1, GPC3, GPS2, GREM1, GRIN2A, GRM3, GSK3B, H1-2, H2BC5, H3-3A, H3-3B, H3-4, H3-5, H3C1, H3C10, H3C11, H3C12, H3C13, H3C14, H3C15, H3C2, H3C3, H3C4, H3C6, H3C7, H3C8, HDAC1, HDAC2, HDAC6, HGF, HLA-A, HLA-B, HLA-C, HNF1A, HNRNPK, HOXB13, HRAS, HSD3B1, HSP90AA1, HUWE1, ICOSLG, ID3, IDH1, IDH2, IFNGR1, IGF1, IGF1R, IGF2, IGF2R, IGSF10, IKBKE, IKZF1, IL10, IL6ST, IL7R, INHA, INHBA, INPP4A, INPP4B, INPPL1, INSR, IRF2, IRF4, IRS1, IRS2, JAK1, JAK2, JAK3, JUN, KAT6A, KBTBD4, KDM5A, KDM5C, KDM6A, KDR, KEAP1, KEL, KIF5B, KIT, KLF4, KLF5, KLHL6, KMT2A, KMT2B, KMT2D, KMT5A, KNSTRN, KRAS, LAMP1, LATS1, LATS2, LMO1, LRP1B, LTK, LYN, LZTR1, MAD2L2, MAF, MAGI2, MALT1, MAML1, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K13, MAP3K14, MAP3K4, MAPK1, MAPK3, MAPKAP1, MAX, MCL1, MDC1, MDM2, MDM4, MED12, MEF2B, MEN1, MERTK, MET, MGA, MITF, MKNK1, MLC1, MLH1, MLH3, MLLT1, MLLT3, MPL, MRE11, MSH2, MSH3, MSH6, MSI1, MSI2, MST1, MST1R, MTAP, MTOR, MUTYH, MYB, MYC, MYCL, MYCN, MYD88, MYOD1, NAB2, NADK, NBN, NCOA3, NCOR1, NEGR1, NF1, NF2, NFE2L2, NFKBIA, NKX2-1, NKX3-1, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPM1, NRAS, NRG1, NSD1, NSD2, NSD3, NT5C2, NTHL1, NTRK1, NTRK2, NTRK3, NUF2, NUP93, NUTM1, OPCML, P2RY8, PAK1, PAK3, PAK5, PALB2, PARG, PARP1, PARP2, PARP3, PAX3, PAX5, PAX7, PAX8, PAXIP1, PBRM1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDK1, PDPK1, PGBD5, PGR, PHF6, PHOX2B, PIGA, PIK3C2B, PIK3C2G, PIK3C3, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PIK3R3, PIM1, PLCG2, PLEKHS1, PLK2, PMAIP1, PMS1, PMS2, PNRC1, POLD1, POLE, POLQ, POT1, PPARG, PPM1D, PPP2R1A, PPP2R2A, PPP4R2, PPP6C, PRDM1, PRDM14, PREX2, PRKAR1A, PRKCI, PRKD1, PRKDC, PRKN, PRSS8, PTCH1, PTEN, PTP4A1, PTPN11, PTPN12, PTPRD, PTPRN2, PTPRO, PTPRS, PTPRT, QKI, RAB35, RAC1, RAC2, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RANBP2, RARA, RARG, RASA1, RB1, RBM10, RECQL, RECQL4, RECQL5, REL, REST, RET, REV3L, RFC1, RHEB, RHOA, RICTOR, RIF1, RIT1, RNF43, ROS1, RPA1, RPS6KA3, RPS6KA4, RPS6KB1, RPS6KB2, RPTOR, RRAGC, RRAS, RRAS2, RSPO2, RTEL1, RUNX1, RUNX1T1, RXRA, RYBP, SBDS, SCG5, SDC4, SDHA, SDHAF2, SDHB, SDHC, SDHD, SERPINB3, SERPINB4, SESN1, SESN2, SESN3, SETBP1, SETD2, SETDB1, SF3B1, SGK1, SH2B3, SH2D1A, SHH, SHLD2, SHOC2, SHQ1, SLC22A1, SLC22A2, SLC34A2, SLFN11, SLIT2, SLX4, SMAD2, SMAD3, SMAD4, SMARCA2, SMARCA4, SMARCB1, SMARCD1, SMARCE1, SMC1A, SMC3, SMO, SMYD3, SNCAIP, SNTG2, SOCS1, SOS1, SOX10, SOX17, SOX2, SOX9, SPEN, SPOP, SPRED1, SPRTN, SPTA1, SRC, SRCAP, SRSF2, STAG1, STAG2, STAT3, STAT4, STAT5A, STAT5B, STK11, STK19, STK40, STN1, SUFU, SUZ12, SYK, TAF1, TAP1, TAP2, TBX3, TCF19, TCF3, TCF7L2, TEK, TEN1, TENT5C, TERC, TERT, TET1, TET2, TFE3, TFRC, TGFBR1, TGFBR2, TIPARP, TLR4, TLR7, TLR8, TLR9, TMEM127, TMPRSS2, TNFAIP3, TNFRSF14, TOP1, TOP2A, TP53BP1, TP63, TPMT, TRAF2, TRAF3, TRAF7, TRIP13, TSC1, TSC2, TSHR, TYK2, TYRO3, U2AF1, UGT1A1, UPF1, USP8, VEGFA, VHL, VTCN1, WAS, WEE1, WRN, WT1, WWTR1, XIAP, XPA, XPC, XPO1, XRCC1, XRCC2, XRCC3, XRCC5, XRCC6, YAP1, YES1, ZBTB2, ZBTB7A, ZFHX3, ZNF217, ZNF703, ZNRF3, ZRSR2 | |
| FISH/CNA/IHC POSITIVE GENES | FISH/CNA/IHC NEGATIVE GENES |
| CCNE1 AMPLIFICATION PRESENCE, HER2 PROTEIN LOW EXPRESSION, PDL1 PROTEIN OVEREXPRESSION | ER PROTEIN NORMAL, PR PROTEIN NORMAL |

Line neoadjuvant - 4 cycle chemotherapy - (09/2022-03/2023)
Line adjuvant - 4 cycle capecitabine - (05/2023-08/2023)
Radiotherapy 03/2023
Line: 1 - ERIBULIN - (13/08/2023 - 01/11/2023)
Line: 2 - Trastuzumab Deruxtecan (from 11/2023)

**Triple negative breast cancer - targeted drugs regardless of molecular profile**

According to the scientific literature, 25-35% of triple-negative breast cancers (TNBCs) overexpress androgen receptor (AR), in which case AR inhibitors may be effective [173].

50-70% of triple-negative breast cancers have increased EGFR expression [174,175]. In a randomized phase II study adding cetuximab to cisplatin doubled the objective response rate (ORR) and appeared to prolong progression-free survival (PFS) and overall survival (OS) in a molecularly not selected group of TNBC patients. Cisplatin plus cetuximab resulted in longer median PFS compared with cisplatin alone (3.7 v 1.5 months) [176].

**Tumor-agnostic biomarkers/immunotherapy-related biomarkers:**

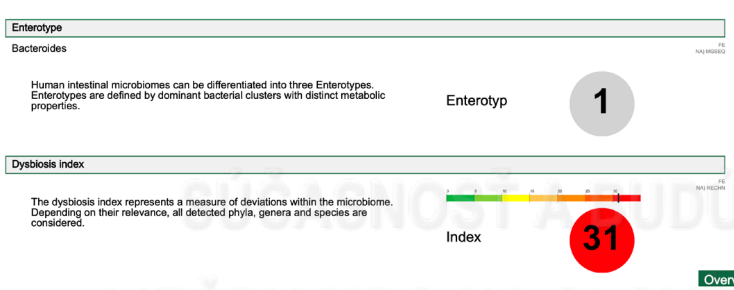
The tumor is **MSS**, **TMB-elevated** (8,655 muts/Mb), and **PD-L1 positive** (CPS 60%, TPS 0%, antibody: 22C3 pharmDx), and PD-L1 negative (CPS 0%, TPS 0%, antibody: SP142).

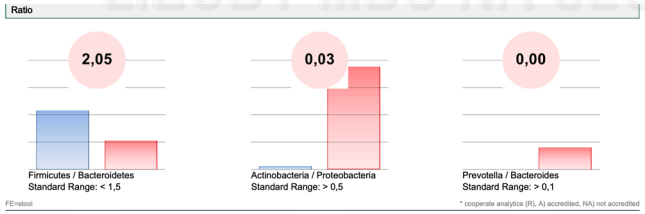
High TMB associates with response to PD-1 and PD-L1 inhibitors in various tumor types.

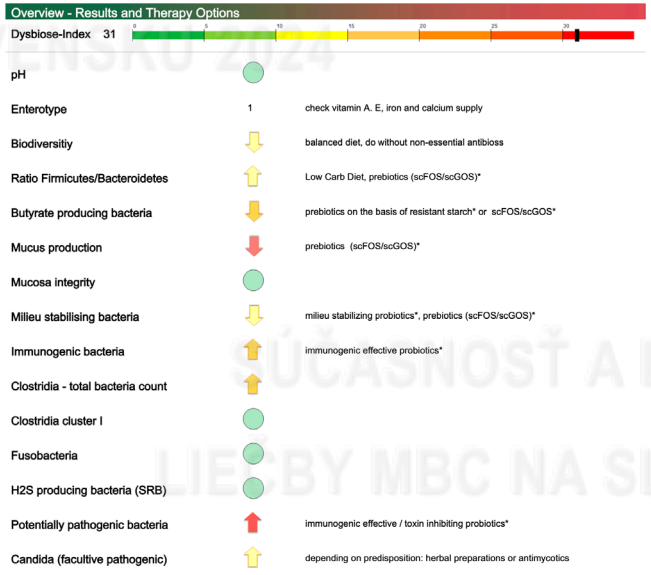
- Výsledok relatívne prehľadný, ale zahlcujúci- 25 strán
- Údaje nesedia s interpretáciou
- Interpretácia založená na publikovaných prácach
- Odporúčaná liečba nad rámec ESCAT aj ESMO odporúčaní- na báze výsledkov FII klinických skúšaní
- Vypísané všetky ESMO odporúčania, zasahovanie do líniovosti liečby nad rámec štandardných odporúčaní- napríklad vyslovene línie liečby bežných cytostatík, odporúčania už podanej liečby o ktorej mali informáciu

Zdroj: výsledky pacientok Mriňáková, OÚSA

# Príklad 5





**Ale nevieme, čo s tým..**

| Bacteria Phyla - most important genera and species | | | |
|---|---|---|---|
| **Actinobacteria** | | | |
| Bifidobacterium | 2,7 x 10^9 CFU/g faeces | > 5,0 x 10^9 | |
| Bifidobacterium longum | 100 % | | |
| **Bacteroidetes** | | | |
| Bacteroides | 2,0 x 10^11 CFU/g faeces | > 1,5 x 10^11 | |
| Prevotella | 1,2 x 10^8 CFU/g faeces | > 1,0 x 10^10 | |
| **Firmicutes** | | | |
| **Butyrate producing bacteria** | | | |
| Total bacteria count | 4,1 x 10^11 CFU/g faeces | > 1,2 x 10^11 | |
| Faecalibacterium prausnitzii | 1,7 x 10^11 CFU/g faeces | > 5,0 x 10^10 | |
| Eubacterium rectale | 9,8 x 10^10 CFU/g faeces | > 1,0 x 10^10 | |
| Eubacterium hallii | 3,7 x 10^9 CFU/g faeces | > 5,0 x 10^9 | |
| Roseburia spp. | 1,1 x 10^11 CFU/g faeces | > 2,0 x 10^10 | |
| Ruminococcus spp. | 2,4 x 10^10 CFU/g faeces | > 3,0 x 10^10 | |
| Coprococcus spp. | 7,4 x 10^9 CFU/g faeces | > 2,0 x 10^10 | |
| Butyrivibrio spp. | 7,9 x 10^8 CFU/g faeces | > 5,0 x 10^9 | |
| **Clostridia** | | | |
| Clostridia total bacteria count | 5,0 x 10^10 CFU/g faeces | < 4,0 x 10^9 | |
| Clostridia Cluster I | 1,0 x 10^5 CFU/g faeces | < 2,0 x 10^9 | |
| **Fusobacteria** | | | |
| Fusobacterium | < 1,0 x 10^5 CFU/g faeces | < 1,0 x 10^7 | |
| **Verrucomicrobia** | | | |
| Akkermansia muciniphila | 1,0 x 10^7 CFU/g faeces | > 5,0 x 10^9 | |
| **Proteobacteria** | | | |
| **Pathogenic or potentially pathogenic bacteria** | | | |
| Haemophilus spp. | 1,7 x 10^8 CFU/g faeces | < 1,0 x 10^9 | |
| Acinetobacter spp. | < 1,0 x 10^5 CFU/g faeces | < 1,0 x 10^6 | |

- Výsledok prehľadný
- Veľa údajov o tom, že mikrobióm môže ovplyvniť vznik nádorového ochorenia, účinnosť terapie aj toleranciu
- Zjavné, že nález nie je dobrý
- Žiadne odporúčania, čo robiť v onkologických guidelinoch

Dať bežné probiotiká a prebiotiká?
Probiotiká na mieru?
Kompletná zmena životného štýlu?
Fekálna transplantácia?

Zdroj: výsledky pacientok Mriňáková, OÚSA

# Záver

- Riadime sa známymi faktami a EBM
- Najvyššiu relevanciu má **ESCAT** hodnotenie – uvádzané aj v rámci **ESMO odporúčaní**
- Nejasné výsledky treba prebrať s **lekárskym genetikom**, prípadne konzultovať cestou MDT, respektíve optimálne **„molecular multidisciplinary board“**
- Pacientku ideálne vopred upozorniť, či je ňou vybraté vyšetrenie validované a bude mať dopad na rozhodnutie o liečbe
- Nebrániť sa dialógu, ale vysvetliť, že mnohé predkladané výsledky nevedia mať dopad na rozhodnutie o liečbe, ak napriek tomu pacient chce užívať odporúčané látky, ktoré nie sú obmedzené indikáciou klinického onkológa – napr. kurkuma, inhibítori COX a ďalšie, **upozorniť na možné interakcie s liečbou**

- **Snažiť sa udržať v strehu a byť zvedavý – budúcnosť toho prinesie VIAC...**

Slovenská onkologická spoločnosť

SÚČASNOSŤ A BUDÚCNOSŤ
LIEČBY MBC NA SLOVENSKU

26.-27.09.2024 HOTEL PARTIZÁN, TÁLE

# Ďakujem za pozornosť

SÚČASNOSŤ A BUDÚCNOSŤ
LIEČBY MBC NA SLOVENSKU 2024