# Úskalia podávania imunoterapie

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# Vyhlásenie o konflikte záujmov autora

☐ **Nemám potenciálny konflikt záujmov**

☐ **Deklarujem nasledujúci konflikt záujmov**

| Forma finančného prepojenia | Spoločnosť |
|---|---|
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| Nepeňažné plnenie (v zmysle zákona) | |
| Prednášajúci | Eli Lilly |
| Akcionár | |
| Konzultant/odborný poradca | |
| Ostatné príjmy (špecifikovať) | |

Podľa UEMS (upravené v zmysle slovenskej legislatívy)

OpenAI. (2024). *A much more distant view of two enormous rocks with a very shallow and narrow path in between* [AI-generated image]. DALL·E.

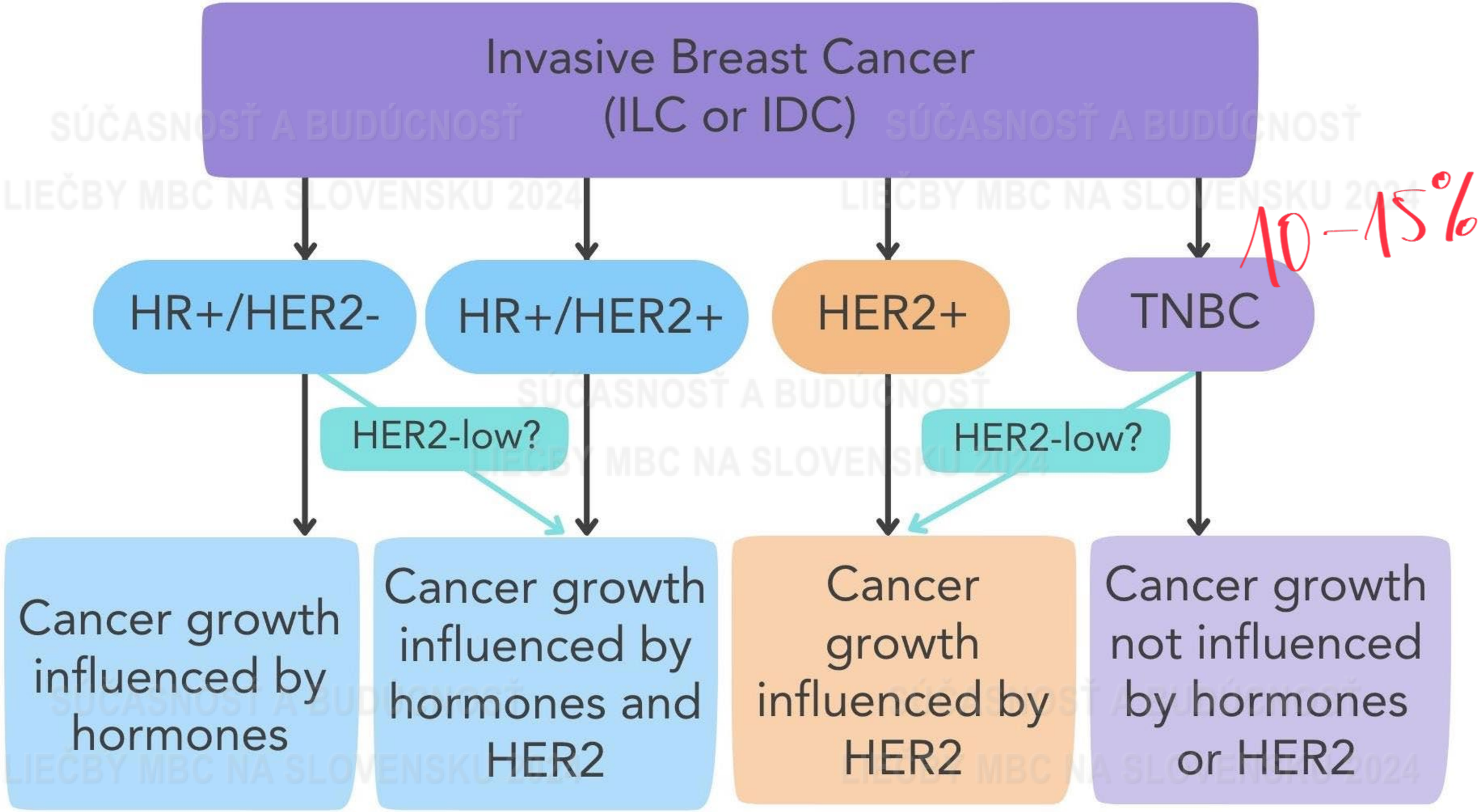
ja s mojou prezentáciou

Predošlé prezentácie

Nasledujúce prezentácie

OpenAI. (2024). *A much more distant view of two enormous rocks with a very shallow and narrow path in between* [AI-generated image]. DALL·E.

# Úskalie prvé: použitie imunoterapie u ABC (na Slovensku)






National Cancer Institute. (2024). *SEER cancer statistics: Triple-negative breast cancer.* SEER. Retrieved [date], from https://seer.cancer.gov/explorer/

Ximena Baez-Navarro, Mieke R. van Bockstal, Eleni-Rosalina Andrinopoulou, Carolien H.M. van Deurzen,HER2-Low Breast Cancer: Incidence, Clinicopathologic Features, and Survival Outcomes From Real-World Data of a Large Nationwide Cohort,Modern Pathology,Volume 36, Issue 4,2023,00087,ISSN 0893-3952,

https://owise.uk/understanding-breast-cancer-diagnosis/

# MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer

Matthew P Goetz [1], Masakazu Toi [1], Mario Campone [1], Joohyuk Sohn [1], Shani Paluch-Shimon [1], Jens Huober [1], In Hae Park [1], Olivier Trédan [1], Shin-Cheh Chen [1], Luis Manso [1], Orit C Freedman [1], Georgina Garnica Jaliffe [1], Tammy Forrester [1], Martin Frenzel [1], Susana Barriga [1], Ian C Smith [1], Nawel Bourayou [1], Angelo Di Leo [1]

HR_PFS 0.54

# Palbociclib and Letrozole in Advanced Breast Cancer

mPFS +10.3m
HR 0.58

**Authors**: Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D., Karen Gelmon, M.D., Nadia Harbeck, M.D., Ph.D., +7, and Dennis J. Slamon, M.D., Ph.D. Author Info & Affiliations

**Published November 17, 2016 | N Engl J Med 2016;375:1925-1936 | DOI: 10.1056/NEJMoa1607303**
**VOL. 375 NO. 20**

# Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

mOS +15.7m
HR 0.68

**Authors**: Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D., Vladimir Semiglazov, M.D., Mario Campone, M.D., Eva Ciruelos, M.D., +7, for the CLEOPATRA Study Group* Author Info & Affiliations

**Published February 19, 2015 | N Engl J Med 2015;372:724-734 | DOI: 10.1056/NEJMoa1413513 | VOL. 372 NO. 8**

# Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

mPFS$_2$ +4.8m
HR 0.64

**Authors**: Shanu Modi, M.D., William Jacot, M.D., Ph.D., Toshinari Yamashita, M.D., Ph.D., Joohyuk Sohn, M.D., Maria Vidal, M.D., Ph.D., Eriko Tokunaga, M.D., Ph.D., Junji Tsurutani, M.D., Ph.D., +31, for the DESTINY-Breast04 Trial Investigators* Author Info & Affiliations

**Published June 5, 2022 | N Engl J Med 2022;387:9-20 | DOI: 10.1056/NEJMoa2203690 | VOL. 387 NO. 1**

# Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

HR_PFS 0.56



**Authors**: Gabriel N. Hortobagyi, M.D., Salomon M. Stemmer, M.D., Howard A. Burris, M.D., Yoon-Sim Yap, M.D., Gabe S. Sonke, M.D., Ph.D., Shani Paluch-Shimon, M.D., Mario Campone, M.D., Ph.D., +29, and Joyce O'Shaughnessy, M.D. Author Info & Affiliations

# Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

HR_PFS 0.28

**Authors**: Javier Cortés, M.D., Ph.D., Sung-Bae Kim, M.D., Ph.D., Wei-Pang Chung, M.D., Seock-Ah Im, M.D., Ph.D., Yeon Hee Park, M.D., Ph.D., Roberto Hegg, M.D., Ph.D., Min Hwan Kim, M.D., Ph.D., +17, for the DESTINY-Breast03 Trial Investigators* Author Info & Affiliations

**Published March 23, 2022 | N Engl J Med 2022;386:1143-1154 | DOI: 10.1056/NEJMoa2115022 | VOL. 386 NO. 12**

# Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

mOS +5.4m
HR 0.48

**Authors**: Aditya Bardia, M.D., Sara A. Hurvitz, M.D., Sara M. Tolaney, M.D., M.P.H., Delphine Loirat, M.D., Ph.D., Kevin Punie, M.D., Mafalda Oliveira, M.D., Ph.D., Adam Brufsky, M.D., Ph.D., +23, for the ASCENT Clinical Trial Investigators* Author Info & Affiliations

Modi, S., Jacot, W., Yamashita, T., Sohn, J., Vidal, M., Tokunaga, E., Tsurutani, J., et al. (2022). Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *The New England Journal of Medicine, 387*(1), 9-20. https://doi.org/10.1056/NEJMoa2203690

Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, Park IH, Trédan O, Chen SC, Manso L, Freedman OC, Garnica Jaliffe G, Forrester T, Frenzel M, Barriga S, Smith IC, Bourayou N, Di Leo A. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol. 2017 Nov 10;35(32):3638-3646. doi: 10.1200/JCO.2017.75.6155. Epub 2017 Oct 2. PMID: 28968163.

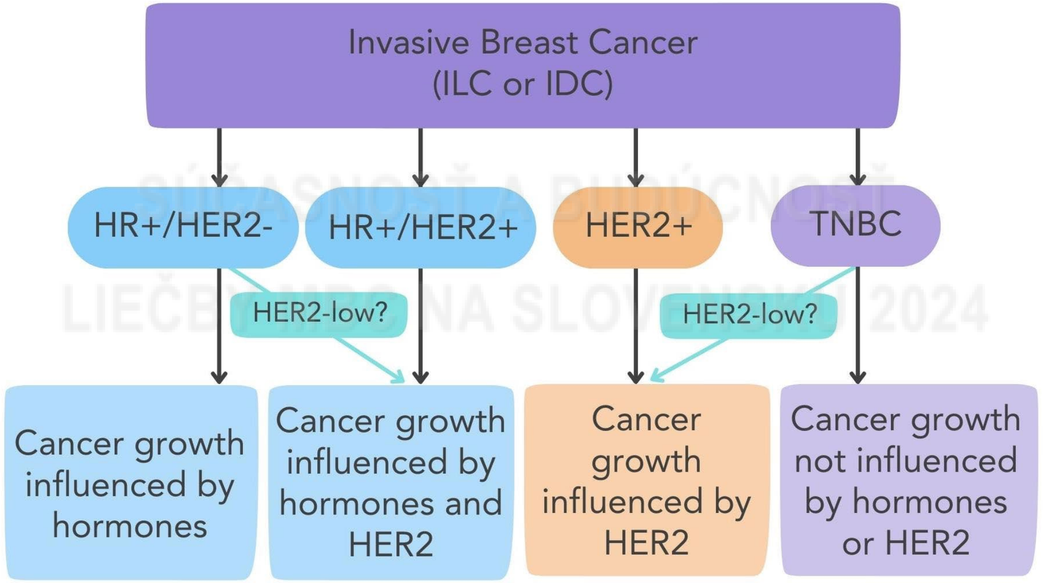
Hortobagyi, G. N., Stemmer, S. M., Burris, H. A., Yap, Y.-S., Sonke, G. S., Paluch-Shimon, S., Campone, M., et al. (2016). Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *The New England Journal of Medicine, 375*(18), 1738-1748. https://doi.org/10.1056/NEJMoa1609709

Finn, R. S., Martin, M., Rugo, H. S., Jones, S., Im, S.-A., Gelmon, K., Harbeck, N., et al. (2016). Palbociclib and letrozole in advanced breast cancer. *The New England Journal of Medicine, 375*(20), 1925-1936. https://doi.org/10.1056/NEJMoa1607303

Swain, S. M., Baselga, J., Kim, S.-B., Ro, J., Semiglazov, V., Campone, M., Ciruelos, E., et al. (2015). Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *The New England Journal of Medicine, 372*(8), 724-734. https://doi.org/10.1056/NEJMoa1413513

Cortés, J., Kim, S.-B., Chung, W.-P., Im, S.-A., Park, Y. H., Hegg, R., Kim, M. H., et al. (2022). Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *The New England Journal of Medicine, 386*(12), 1143-1154. https://doi.org/10.1056/NEJMoa2115022

Bardia, A., Hurvitz, S. A., Tolaney, S. M., Loirat, D., Punie, K., Oliveira, M., & Brufsky, A., et al. (2021). Sacituzumab govitecan in metastatic triple-negative breast cancer. *The New England Journal of Medicine, 384*(16), 1529-1541. https://doi.org/10.1056/NEJMoa2028485




# Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer

**Authors**: Javier Cortes, M.D., Ph.D., Hope S. Rugo, M.D., David W. Cescon, M.D., Ph.D., Seock-Ah Im, M.D., Ph.D., Mastura M. Yusof, M.D., Carlos Gallardo, M.D., Oleg Lipatov, M.D., +12, for the KEYNOTE-355 Investigators* Author Info & Affiliations

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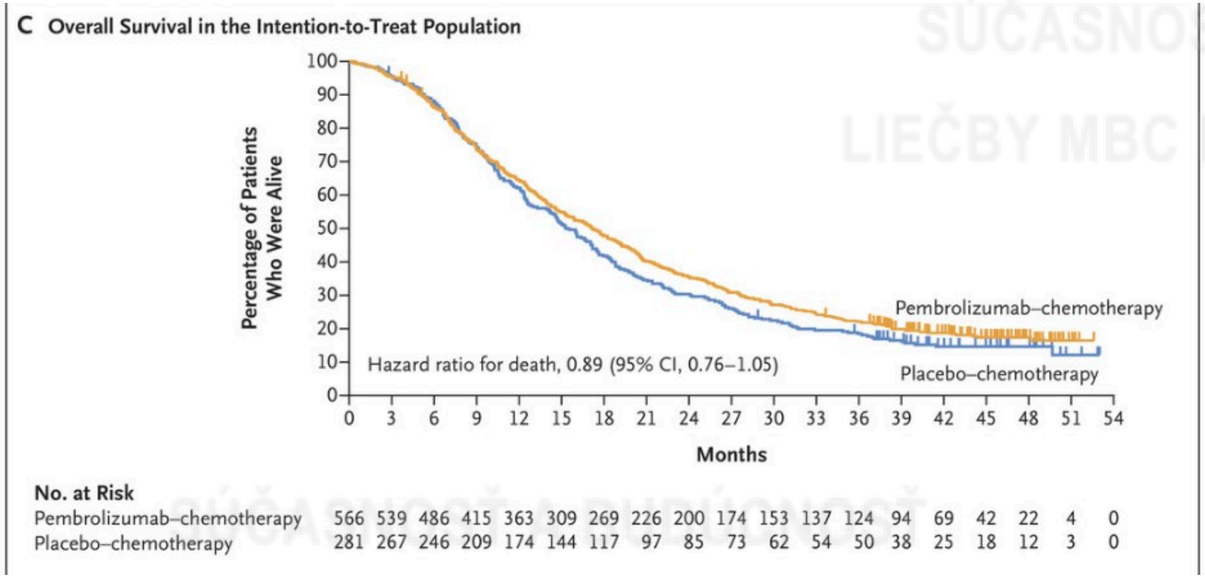
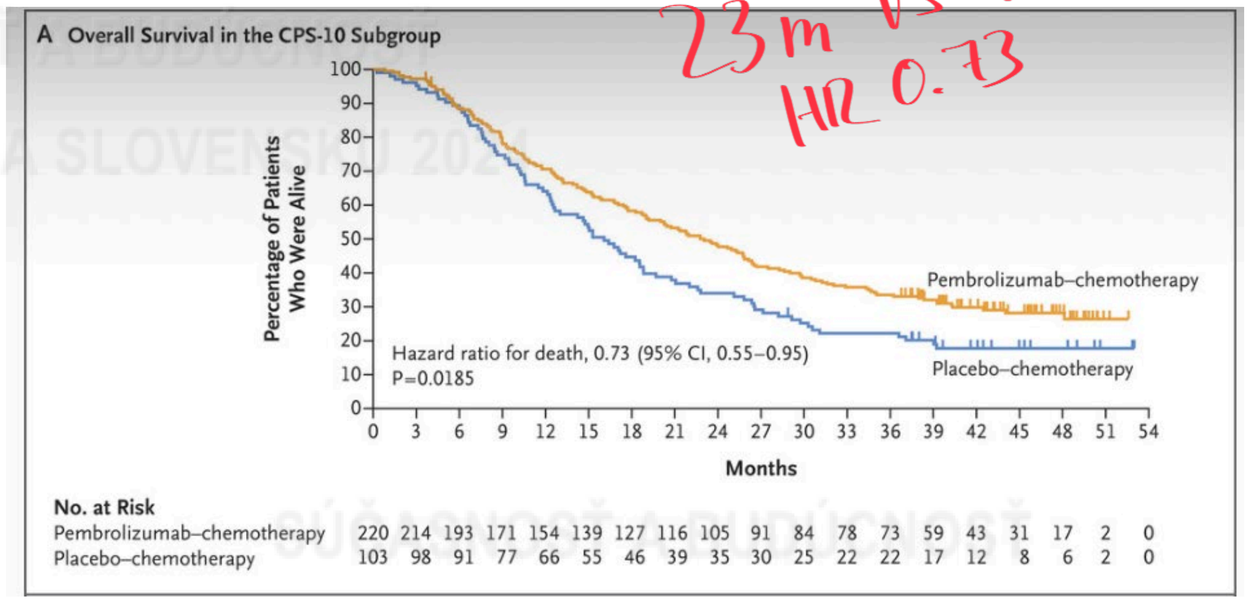
mOS
23m vs 16.1m
HR 0.73

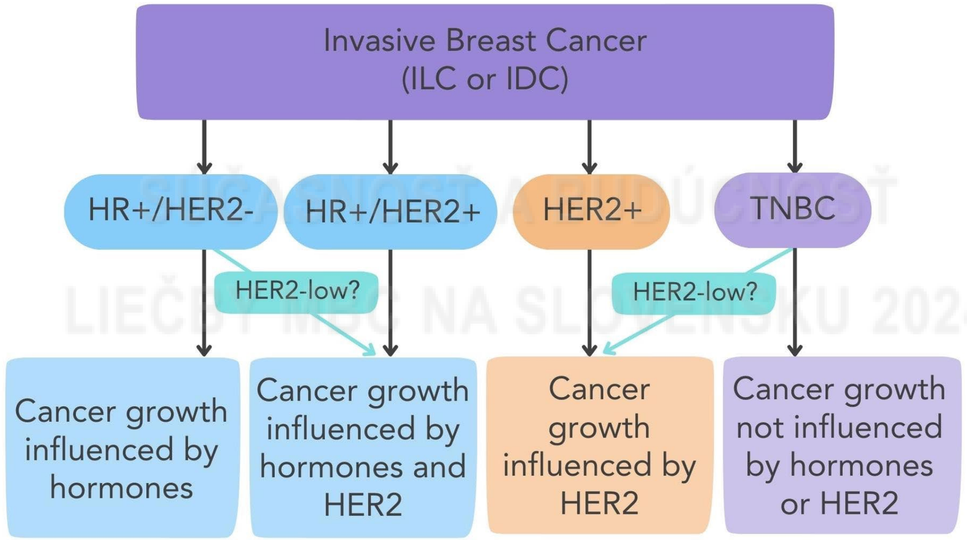





Schmid, P., Cortes, J., Pusztai, L., McArthur, H., Kümmel, S., Bergh, J., Denkert, C., et al. (2020). Pembrolizumab for early triple-negative breast cancer. *The New England Journal of Medicine, 382*(9), 810-821. https://doi.org/10.1056/NEJMoa1910549

https://owise.uk/understanding-breast-cancer-diagnosis/

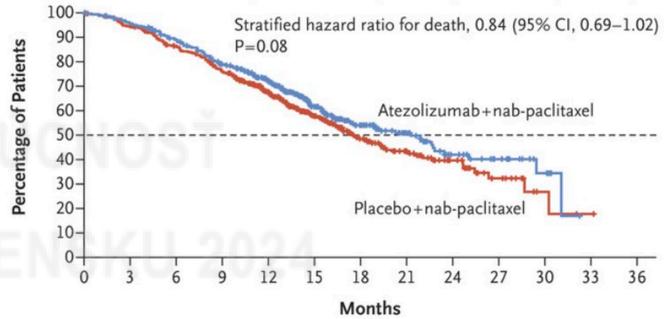



# Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

**Authors**: Peter Schmid, M.D., Ph.D., Sylvia Adams, M.D., Hope S. Rugo, M.D., Andreas Schneeweiss, M.D., Carlos H. Barrios, M.D., Hiroji Iwata, M.D., Ph.D., Véronique Diéras, M.D., +11, for the IMpassion130 Trial Investigators* Author Info & Affiliations

**C** Overall Survival in the Intention-to-Treat Population

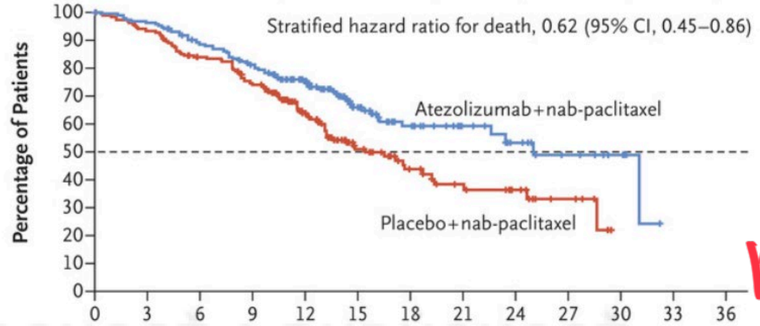
| | No. of Events/ No. of Patients | Median Overall Survival (95% CI) | 2-Yr Rate of Overall Survival (95% CI) |
|---|---|---|---|
| | | *mo* | % |
| Atezolizumab+Nab-Paclitaxel | 181/451 | 21.3 (17.3–23.4) | 42.1 (34.3–49.9) |
| Placebo+Nab-Paclitaxel | 208/451 | 17.6 (15.9–20.0) | 39.7 (33.2–46.3) |




| No. at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab+ nab-paclitaxel | 451 | 426 | 389 | 337 | 271 | 146 | 82 | 48 | 26 | 15 | 6 | NE | NE |
| Placebo+ nab-paclitaxel | 451 | 419 | 375 | 328 | 246 | 145 | 89 | 52 | 27 | 12 | 3 | 1 | NE |

**D** Overall Survival in the PD-L1–Positive Subgroup

| | No. of Events/ No. of Patients | Median Overall Survival (95% CI) | 2-Yr Rate of Overall Survival (95% CI) |
|---|---|---|---|
| | | *mo* | % |
| Atezolizumab+Nab-Paclitaxel | 64/185 | 25.0 (22.6–NE) | 53.5 (42.3–64.6) |
| Placebo+Nab-Paclitaxel | 88/184 | 15.5 (13.1–19.4) | 36.6 (26.4–46.7) |




| No. at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab+ nab-paclitaxel | 185 | 177 | 160 | 142 | 113 | 61 | 36 | 22 | 15 | 9 | 5 | NE | NE |
| Placebo+ nab-paclitaxel | 184 | 170 | 147 | 129 | 89 | 44 | 27 | 19 | 13 | 6 | NE | NE | NE |

mOS PD-L1+
25 vs 15.5m
HR 0.62

Schmid, P., Adams, S., Rugo, H. S., Schneeweiss, A., Barrios, C. H., Iwata, H., Diéras, V., et al. (2018). Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *The New England Journal of Medicine, 379*(22), 2108-2121. https://doi.org/10.1056/NEJMoa1809615

https://owise.uk/understanding-breast-cancer-diagnosis/

## L01FF02 Pembrolizumab parent. 25 mg/ml

## L01FF05 Atezolizumab parent. 1200 mg

d) v kombinácii s chemoterapiou indikovaná ako neoadjuvantná liečba a následne s pokračovaním vo forme monoterapie ako adjuvantná liečba po chirurgickom zákroku dospelým s lokálne pokročilým trojnásobne negatívnym karcinómom prsníka alebo trojnásobne negatívnym karcinómom prsníka v skorom štádiu s vysokým rizikom rekurencie.

Hradená liečba podlieha predchádzajúcemu súhlasu zdravotnej poisťovne.



§88

**Žiadosť o schválenie lieku, ktorého predpísanie schvaľuje zdravotná poisťovňa***

v zmysle § 3 zákona č. 363/2011 Z. z. o rozsahu a podmienkach úhrady liekov, zdravotníckych pomôcok a dietetických potravín na základe verejného zdravotného poistenia v platnom znení

---

**Údaje o poskytovateľovi ZS**

Názov a adresa zdravotníckeho zariadenia: .....

Meno a priezvisko lekára: ..... Kód lekára: .....

**Tel. kontakt**: **..... **fax**: ..... **e-mail**: .....

# Úskalie prvé: použitie imunoterapie u ABC (na Slovensku)

TNBC je ochorenie s agresívnou biológiou

- Imunoterapia predstavuje po dlhej dobe modalitu zlepšujúcu SR u TNBC

- na základe výsledkov RCT - podávanie s chemoterapiou

- benefit iba u selektovanej populácie PD-L1+ resp. CPS > 10

- dostupnosť u aTNBC na Slovensku obmedzená

**DALL·E Image Generation**. (2024). *Rocky Pitfall*. Generated by OpenAI's DALL·E 3 model through the ChatGPT platform.

# Úskalie druhé: podávanie imunoterapie s cytostatickou liečbou

PEMBROLIZUMAB

Trojnásobne negatívny karcinóm prsníka (triple-negative breast cancer, TNBC)

v kombinácii s chemoterapiou indikovaná ako neoadjuvantná liečba a následne s pokračovaním vo forme monoterapie ako adjuvantná liečba po chirurgickom zákroku dospelým s lokálne pokročilým trojnásobne negatívnym karcinómom prsníka alebo trojnásobne negatívnym karcinómom prsníka v skorom štádiu s vysokým rizikom rekurencie (pozri časť 5.1).

v kombinácii s chemoterapiou indikovaná na liečbu lokálne rekurentného neresekovateľného alebo metastatického trojnásobne negatívneho karcinómu prsníka u dospelých, ktorých nádory vykazujú expresiu PD-L1 s CPS ≥ 10 a ktorí v minulosti neboli liečení chemoterapiou pre metastatické ochorenie (pozri časť 5.1).



Trojnásobne negatívny karcinóm prsníka (triple-negative breast cancer, TNBC)

v kombinácii s nab-paklitaxelom je indikovaný na liečbu dospelých pacientov s neresekovateľným lokálne pokročilým alebo metastatickým TNBC, u ktorých je v nádore expresia PD-L1 ≥ 1 %, a ktorí predtým nedostávali chemoterapiu na metastatické ochorenie.

ATEZOLIZUMAB

European Commission. (2020). *Annex I: Summary of product characteristics – Keytruda (pembrolizumab)*. Community Register of medicinal products (No. 20200602147910). https://ec.europa.eu/health/documents/community-register/2020/20200602147910/anx_147910_sk.pdf
European Medicines Agency. (2023). *Tecentriq: Annex I – Summary of product characteristics*. https://ec.europa.eu/health/documents/community-register/2023/20230209158173/anx_158173_sk.pdf

# Toxicity of immunotherapy combinations with chemotherapy across tumor indications: Current knowledge and practical recommendations

Layal Rached [a], Ariane Laparra [b], Madona Sakkal [a], François-Xavier Danlos [a], Fabrice Barlesi [c], Franck Carbonnel [d], Eleonora De Martin [e], Michel Ducreux [c], Caroline Even [c], Jerome Le Pavec [f,g], Jean-Marie Michot [a], Joana M. Ribeiro [c], Florian Scotte [b], Santiago Ponce Aix [a], Olivier Lambotte [h], Capucine Baldini [a], Stéphane Champiat [a,*]

All grade
RR 1.11
n = 14 980
0 excess mortality

**Table 3**
Risk ratio of grade 3–4 adverse events in patients treated with chemotherapy + immunotherapy combinations.

| ADVERSE EVENTS (grade 3–4) | Number of analyzed studies | Number of patients presenting the AE | RISK RATIO (95 % CI) | Chi$^2$ (p value) | $I^2$ | Overall Effect Z (p value) |
|---|---|---|---|---|---|---|
| Anemia | 20 | 2198 | 1.07 [0.94; 1.21] | 43.56 (p = 0.001) | 56 % | 0.99 (p = 0.32) |
| Diarrhea | 19 | 395 | 1.42 [1.09; 1.87] | 25.55 (p = 0.11) | 30 % | 2.55 (p = 0.01) |
| Dyspnea | 14 | 217 | 1.87 [1.37; 2.55] | 12.54 (p = 0.40) | 4 % | 3.96 (p < 0.0001) |
| Elevated Liver Enzymes | 18 | 482 | 1.56 [1.22; 2.01] | 23.87 (p = 0.12) | 29 % | 3.54 (p = 0.0004) |
| Fatigue | 20 | 605 | 1.32 [1.05; 1.66] | 33.09 (p = 0.02) | 43 % | 2.39 (p = 0.02) |
| Nausea | 19 | 360 | 0.88 [0.65; 1.20] | 31.80 (p = 0.02) | 43 % | 0.79 (p = 0.43) |
| Neutropenia | 20 | 3035 | 1.08 [0.99; 1.17] | 29.98 (p = 0.05) | 37 % | 1.74 (p = 0.08) |
| Peripheral neuropathy | 12 | 216 | 1.15 [0.88; 1.50] | 6.27 (p = 0.85) | 0 % | 1.00 (p = 0.32) |
| Rash | 17 | 117 | 2.58 [1.21; 5.52] | 29.48 (p = 0.02) | 46 % | 2.44 (p = 0.01) |
| Thrombocytopenia | 18 | 1039 | 1.11 [0.89; 1.25] | 14.32 (p = 0.64) | 0 % | 1.67 (p = 0.09) |
| Vomiting | 19 | 323 | 1.11 [0.89; 1.39] | 11.76 (p = 0.86) | 0 % | 0.94 (p = 0.35) |

# Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer

**Authors**: Javier Cortes, M.D., Ph.D. , Hope S. Rugo, M.D., David W. Cescon, M.D., Ph.D., Seock-Ah Im, M.D., Ph.D., Mastura M. Yusof, M.D., Carlos Gallardo, M.D., Oleg Lipatov, M.D., +12 , for the KEYNOTE-355 Investigators* Author Info & Affiliations

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**Table 1. Adverse Events.***

| Event | Pembrolizumab–Chemotherapy (N=562) | | Placebo–Chemotherapy (N=281) | |
|---|---|---|---|---|
| | Any Grade | Grade 3, 4, or 5 | Any Grade | Grade 3, 4, or 5 |
| | *number of patients (percent)* | | | |
| Any adverse event | 554 (98.6) | 438 (77.9) | 276 (98.2) | 207 (73.7) |
| Adverse events that were attributed to the trial regimen† | 541 (96.3) | 383 (68.1) | 267 (95.0) | 188 (66.9) |
| Anemia | 276 (49.1) | 93 (16.5) | 129 (45.9) | 41 (14.6) |
| Neutropenia | 231 (41.1) | 167 (29.7) | 107 (38.1) | 84 (29.9) |
| Nausea | 221 (39.3) | 9 (1.6) | 116 (41.3) | 4 (1.4) |
| Alopecia | 186 (33.1) | 5 (0.9) | 94 (33.5) | 3 (1.1) |
| Fatigue | 161 (28.6) | 16 (2.8) | 84 (29.9) | 7 (2.5) |
| Neutrophil count decreased | 126 (22.4) | 98 (17.4) | 74 (26.3) | 57 (20.3) |
| Alanine aminotransferase increased | 115 (20.5) | 34 (6.0) | 46 (16.4) | 13 (4.6) |
| Immune-mediated adverse events‡ | 149 (26.5) | 30 (5.3) | 18 (6.4) | 0 |
| Hypothyroidism | 89 (15.8) | 2 (0.4) | 9 (3.2) | 0 |
| Hyperthyroidism | 24 (4.3) | 1 (0.2) | 3 (1.1) | 0 |
| Pneumonitis | 14 (2.5) | 6 (1.1) | 0 | 0 |
| Colitis | 10 (1.8) | 2 (0.4) | 4 (1.4) | 0 |
| Severe skin reactions | 10 (1.8) | 10 (1.8)§ | 1 (0.4) | 0 |

# Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

**Table 3. Key Adverse Events.***

| Event | Atezolizumab + Nab-Paclitaxel (N=452) | | Placebo + Nab-Paclitaxel (N=438) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| | *number of patients with event (percent)* | | | |
| Alopecia | 255 (56.4) | 3 (0.7) | 252 (57.5) | 1 (0.2) |
| Nausea | 208 (46.0) | 5 (1.1) | 167 (38.1) | 8 (1.8) |
| Cough | 112 (24.8) | 0 | 83 (18.9) | 0 |
| Peripheral neuropathy | 98 (21.7) | 25 (5.5) | 97 (22.1) | 12 (2.7) |
| Neutropenia | 94 (20.8) | 37 (8.2) | 67 (15.3) | 36 (8.2) |
| Pyrexia | 85 (18.8) | 3 (0.7) | 47 (10.7) | 0 |
| Hypothyroidism | 62 (13.7) | 0 | 15 (3.4) | 0 |



Schmid, P., Cortes, J., Pusztai, L., McArthur, H., Kümmel, S., Bergh, J., Denkert, C., et al. (2020). Pembrolizumab for early triple-negative breast cancer. *The New England Journal of Medicine, 382*(9), 810-821. https://doi.org/10.1056/NEJMoa1910549

Schmid, P., Adams, S., Rugo, H. S., Schneeweiss, A., Barrios, C. H., Iwata, H., Diéras, V., et al. (2018). Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *The New England Journal of Medicine, 379*(22), 2108-2121. https://doi.org/10.1056/NEJMoa1809615

# A čo premedikácia u I/O + ChT?

## Antiemetics: ASCO Guideline Update

nonpalliative indications had comparable survival as patients not receiving corticosteroids.[8] A systematic review of the literature was reported in 2017 assessing clinical outcomes of patients with cancer treated with CPIs and concomitant corticosteroids.[36] No clear evidence of a poorer clinical outcome was noted in the reviewed populations.

## Recommendations

There is no evidence from clinical trials in adults to warrant omitting dexamethasone from guideline-compliant prophylactic antiemetic regimens when CPIs are administered in combination with chemotherapy. CPIs administered alone or in combination with another CPI are minimally emetogenic in adults and do not require routine use of a prophylactic antiemetic.



Hesketh, P. J., Kris, M. G., Basch, E., Bohlke, K., Barbour, S. Y., Clark-Snow, R. A., Danso, M. A., … & Lyman, G. H. (2020). Antiemetics: ASCO guideline update. *Journal of Clinical Oncology, 38*(24), 2782–2797. https://doi.org/10.1200/JCO.20.01296

OpenAI. (2024). *Nurse administering premedication to a patient* [AI-generated image].

# U aTNBC sa podávajú taxány alebo CBDCA/gemcitabín...

**BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Pembrolizumab with PACLitaxel**

| | |
|---|---|
| ***Protocol Code:*** | *BRAVPP* |
| ***Tumour Group:*** | *Breast* |
| ***Contact Physician:*** | *Dr. Nathalie LeVasseur* |

DXM 10mg + AH

pri IRR

DXM 20mg 12-6-0h

+AH

+redukcia na 10mg!

**BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Pembrolizumab and PACLitaxel NAB (ABRAXANE)**

primárna profylaxia:
NIČ!
sekundárna (pembro)
AH + paracetamol

**BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Pembrolizumab, Gemcitabine, and CARBOplatin**

DXN 8-12mg
+ 5-HT-A
+/- olanzapin



BC Cancer. (2024.). *Chemotherapy protocols*. BC Cancer. http://www.bccancer.bc.ca/health-professionals/clinical-resources/chemotherapy-protocols

# Úskalie druhé: podávanie imunoterapie s cytostatickou liečbou

- oba schválené I/O lieky-  podávanie s CHT

- kombinácia I/O a CHT: iba mierne zvýš. F toxicity v meta-analýze

- v RCT - ešte nižšia miera toxicity z kombinácie

- pacienti s I/O a CHt by mali dostať štandardnú premedikáciu

- vzhľadom na relatívne nízky emetogénny potenciál používanej chemo- premed. max 10mg Dexametazonu

**DALL·E Image Generation**. (2024). *Challenge*. Generated by OpenAI's DALL·E 3 model through the ChatGPT platform.

# Úskalie tretie: infúzne reakcie počas podávania imunoterapie

# Management of infusion-related reactions in cancer therapy: strategies and challenges

**A. Barroso[1], F. Estevinho[2], V. Hespanhol[3,4], E. Teixeira[5], J. Ramalho-Carvalho[6] & A. Araújo[7,8]***

[1]Multidisciplinary Unit of Thoracic Tumours, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia; [2]Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos; [3]Departamento de Medicina Faculty of Medicine, University of Porto, Porto; [4]Department of Pulmonology, Centro Hospitalar de São João, Porto; [5]Lung Cancer Unit, CUF Descobertas, Lisboa; [6]Janssen-Cilag Farmacêutica, Porto Salvo; [7]Medical Oncology Department, Centro Hospitalar Universitário do Porto, Porto; [8]Oncology Research Unit, UMIB-Unit for Multidisciplinary Research in Biomedicine, ICBAS-School of Medicine and Biomedical Sciences, Universidade do Porto, Porto, Portugal

Veľmi zriedkavé

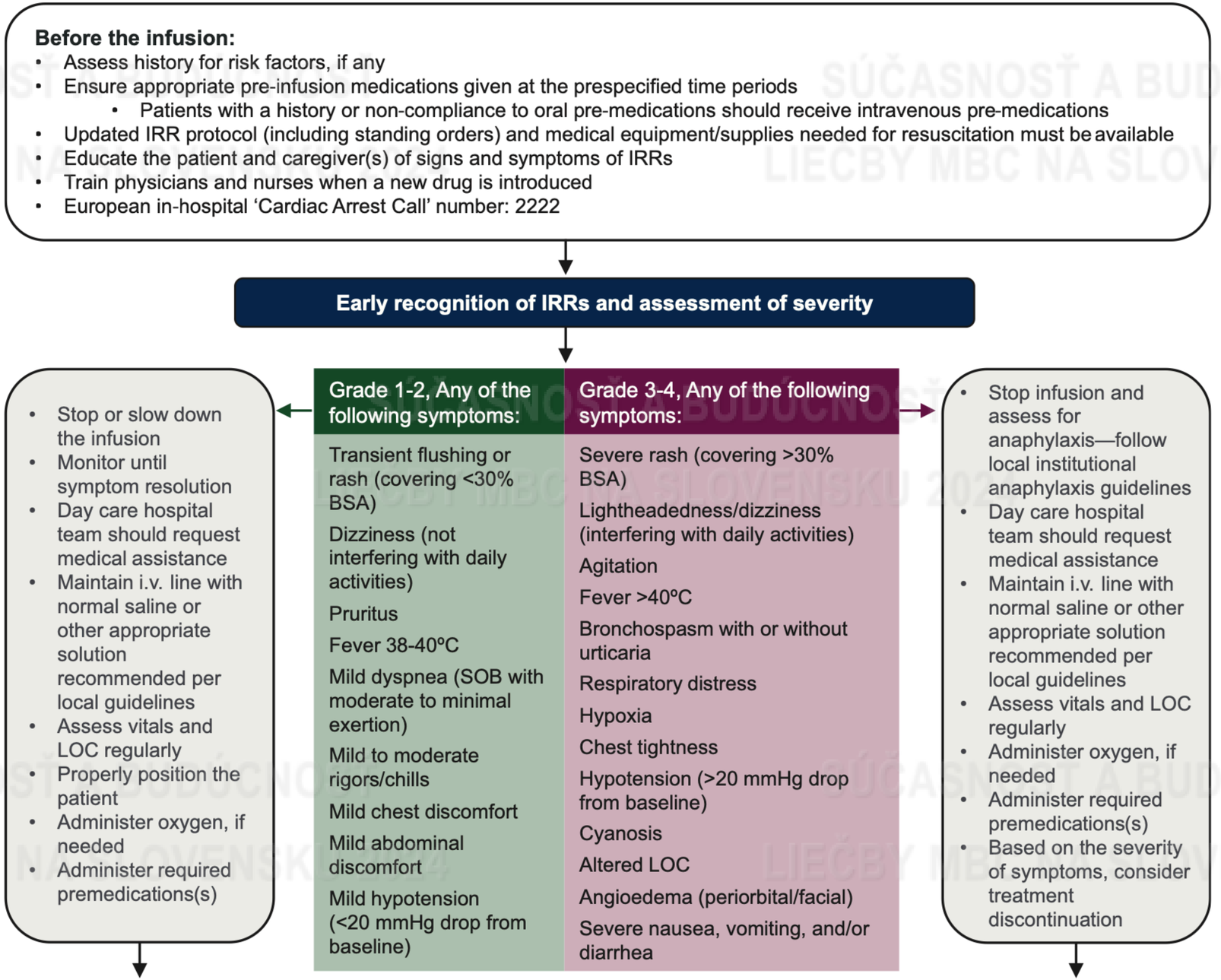
Sekundárna profylaxia

| | | | | | |
|---|---|---|---|---|---|
| Immunotherapy | | | | | |
| Pembrolizumab[131-135] | 3%<br><1% grade ≥3<br>0.2% (of 2799 patients) severe or life-threatening (hypersensitivity, anaphylaxis). | | Pyrexia, chills. | Antipyretics and antihistamines can be considered. | Grade 1/2: stop or slow the infusion rate with close monitoring + symptomatic treatment.<br>Grade 3/4: stop and permanently discontinue treatment. |
| Atezolizumab[148-153] | 1%-2%<br>1.3%-1.7% severe | Only reports of single cases: 10 min into the first infusion; after second lifetime exposure. | Dizziness, numbness, lack of consciousness, severe hypotension, chills, itching or rash, swelling of face or lips, flushing, shortness of breath, swelling, dyspnea or wheezing, fever, back or neck pain, anaphylaxis. | Antipyretics and antihistamines can be considered. | Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Treatment may be resumed with close monitoring when the event is resolved.<br>Grade 3/4: stop the infusion + aggressive symptomatic treatment.<br>Permanently discontinue treatment. |



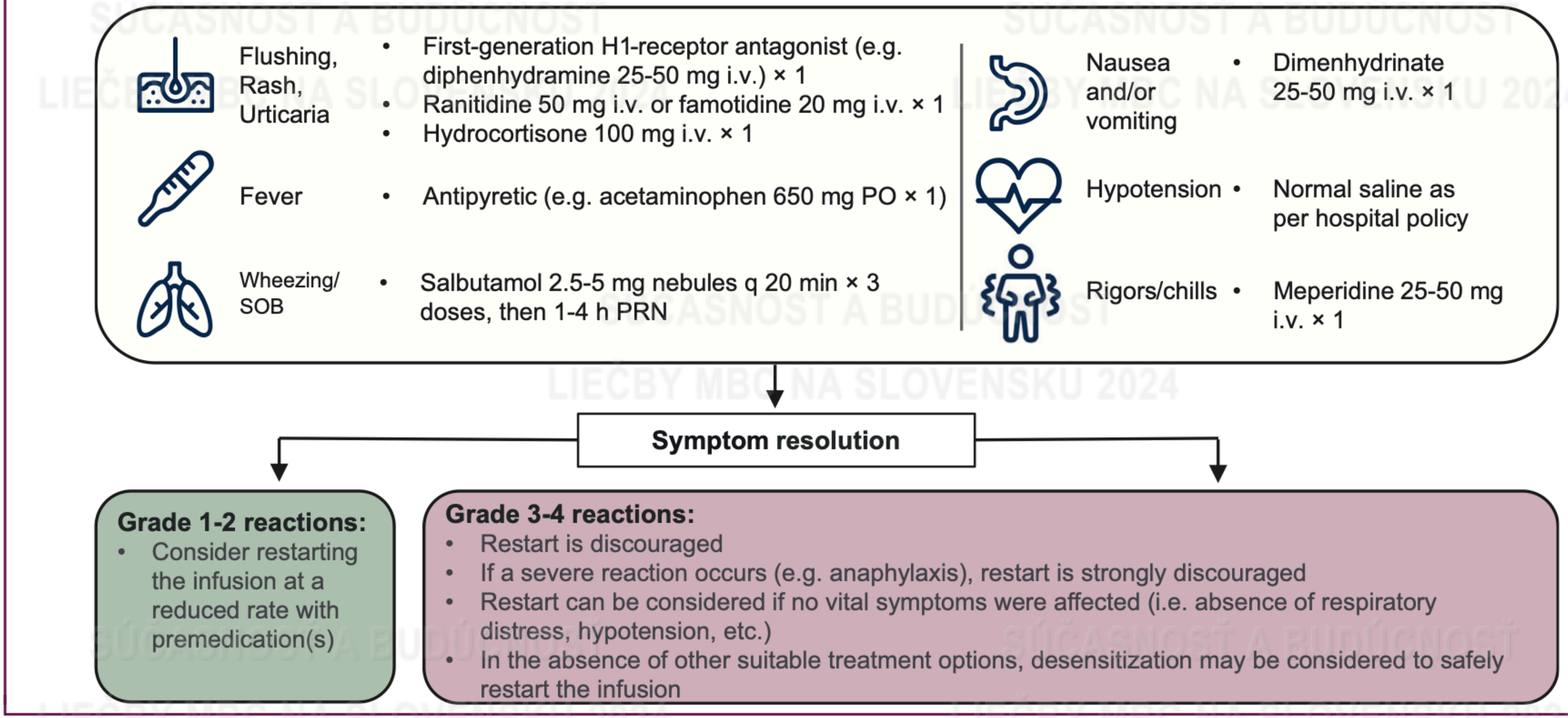
Roselló, S., Blasco, I., García Fabregat, L., Cervantes, A., & Jordan, K. (2017). Management of infusion reactions to systemic anticancer therapy: ESMO clinical practice guidelines. *Annals of Oncology, 28*(suppl 4), iv100–iv118. https://doi.org/10.1093/annonc/mdx216

# Management of infusion-related reactions






Roselló, S., Blasco, I., García Fabregat, L., Cervantes, A., & Jordan, K. (2017). Management of infusion reactions to systemic anticancer therapy: ESMO clinical practice guidelines. *Annals of Oncology, 28*(suppl 4), iv100–iv118. https://doi.org/10.1093/annonc/mdx216






Roselló, S., Blasco, I., García Fabregat, L., Cervantes, A., & Jordan, K. (2017). Management of infusion reactions to systemic anticancer therapy: ESMO clinical practice guidelines. *Annals of Oncology, 28*(suppl 4), iv100–iv118. https://doi.org/10.1093/annonc/mdx216

Anafylaxia:
-adrenalín
-kortikoidy
-antihistaminiká
-Calcium
-vazopresory
-kortikoidy →

**Table 1. Suggested guidance for the management of anaphylaxis (based and adapted from Roselló et al. 2017[3] and Cancer Care Ontario 2019[22])**

| If yes → suspected anaphylaxis | If no → suspected cytokine-release syndrome/hypersensitivity reaction |
|---|---|
| 1. Immediately administer epinephrine (adrenaline) at a dose of 0.01 mg/kg (1 mg/ml dilution, to a maximum total dose of 0.5 ml) intramuscularly into the lateral thigh muscle. | 1. Assess the grade of the reaction:<br>If grade 1—slow down the infusion rate<br>If grade 2—slow down the infusion rate or suspend the infusion for short term |
| 2. Repeat every 5-15 min, if necessary. | 2. Treat with:<br>Antihistamines: 50 mg of i.v. diphenhydramine plus 50 mg of i.v. ranitidine (clemastine can also be also an option)<br>Corticosteroids: equivalent dose to 1-2 mg/kg of i.v. (methyl) prednisolone every 6 h<br>After symptom resolution, restart the infusion at half the rate and titrate until tolerated |
| 3. Administer i.v. epinephrine in cases of failure of a prompt response, with severe hypotension or cardiac arrest. | If grade 3/4—stop the infusion |
| 4. Provide fluid resuscitation in the form of a rapid infusion of 1-2 l of normal saline at a rate of 5-10 ml/kg in the first 5 min. Provide crystalloids or colloids in boluses of 20 ml/kg, followed by slow infusion. | Treat with:<br>Antihistamines: 50 mg of i.v. diphenhydramine plus 50 mg of i.v. ranitidine<br>Corticosteroids dose equivalent to 1-2 mg/kg of i.v. (methyl) prednisolone every 6 h |
| 5. Administer diphenhydramine (1-2 mg/kg or 25-50 mg) slowly via i.v. infusion in combination with ranitidine (50 mg diluted in 5% dextrose water to a total volume of 20 ml) injected i.v. over 5 min. | Do not restart (not recommended in severe reactions) |
| 6. Treat bradycardia with 600 mg of i.v. atropine. | |
| 7. Treat refractory cardiovascular effects in patients receiving $\beta$-blockers with 1-5 mg of i.v. glucagon infusion over 5 min, followed by an infusion (5-15 mg/min) titrated to clinical response. | |
| 8. Treat hypotension that is unresponsive to epinephrine and fluid resuscitation with:<br>a. Dopamine (400 mg in 500 ml of 5% dextrose water) administered at 2-20 mg/kg/min and titrated to increase systolic blood pressure.<br>b. Vasopressin 25 units (U) in 250 ml of 5% dextrose water or normal saline (0.1 U/ml), with a dose range of 0.01-0.04 U/min. | |
| 9. Provide corticosteroids for preventing biphasic reactions in the equivalent to 1-2 mg/kg of i.v. (methyl)prednisolone every 6 h (note that methylprednisolone is slightly stronger than prednisone, so caution should be exercised about the dose to use) | |

i.v., intravenous.



Roselló, S., Blasco, I., García Fabregat, L., Cervantes, A., & Jordan, K. (2017). Management of infusion reactions to systemic anticancer therapy: ESMO clinical practice guidelines. *Annals of Oncology, 28*(suppl 4), iv100–iv118. https://doi.org/10.1093/annonc/mdx216

# Úskalie tretie: infúzne reakcie počas podávania imunoterapie

- pembrolizumab aj atezolizumab majú veľmi nízku prevalenciu IRR

- premedikácia iba v sekundárnej profylaxii -AH + paracetamol

- prípadné IRR sa liečia podľa protokolu z medzinárodných guidelines pre IRR

**DALL·E Image Generation**. (2024). *Stumbling Rock*. Generated by OpenAI's DALL·E 3 model through the ChatGPT platform.

# Úskalie štvrté: imunoterapia u pacientov s preexistujúcimi autoimunitnými ochoreniami

# Immunotherapy in patients with autoimmune disease

Sagar Rakshit, Julian R. Molina

Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA

**Table 2** Retrospective studies using PD-1/PD-L1 inhibitors in patients with pre-existing AID

| ICI | Patients | Tumor types | G3–4 irAEs | ORR | Author |
|---|---|---|---|---|---|
| PD-1/PD-L1 | 52 | Melanoma | 29% | 33% | Menzies (17) |
| PD-1/PD-L1 | 19 | Melanoma | 16% | 32% | Gutzmer (18) |
| PD-1/PD-L1 | 56 | NSCLC | 38% | 22% | Leonardi (19) |
| CTLA-4, PD-1, PD-L1 | 16 | Melanoma, NSCLC, other malignancies | 38% | Not available | Ritchter (20) |
| PD-1/PD-L1 | 45 | Melanoma, NSCLC, other malignancies | 22.5% | 38% | Danlos (21) |
| CTLA-4, PD-1, PD-L1 | 112 | Melanoma, NSCLC, other malignancies | 38% | 48–54% | Tison (22) |
| CTLA-4, PD-1, PD-L1 | 102 | Melanoma, NSCLC, other malignancies | 41% | 48% | Abu-Sbeih (23) |
| PD-1/PD-L1 | 85 | Renal cell carcinoma, urothelial cancer | 9.4% | 38.1% | Cortellini (24) |

PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; AID, autoimmune disease; ICI, immune checkpoint inhibitor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; NSCLC, non-small cell lung cancer; ORR, overall response rate; irAEs, immune-related adverse events.

Flare:
Reumatoc: 52%
Psoriasis: 50%
pre IBD → 21%
63-64

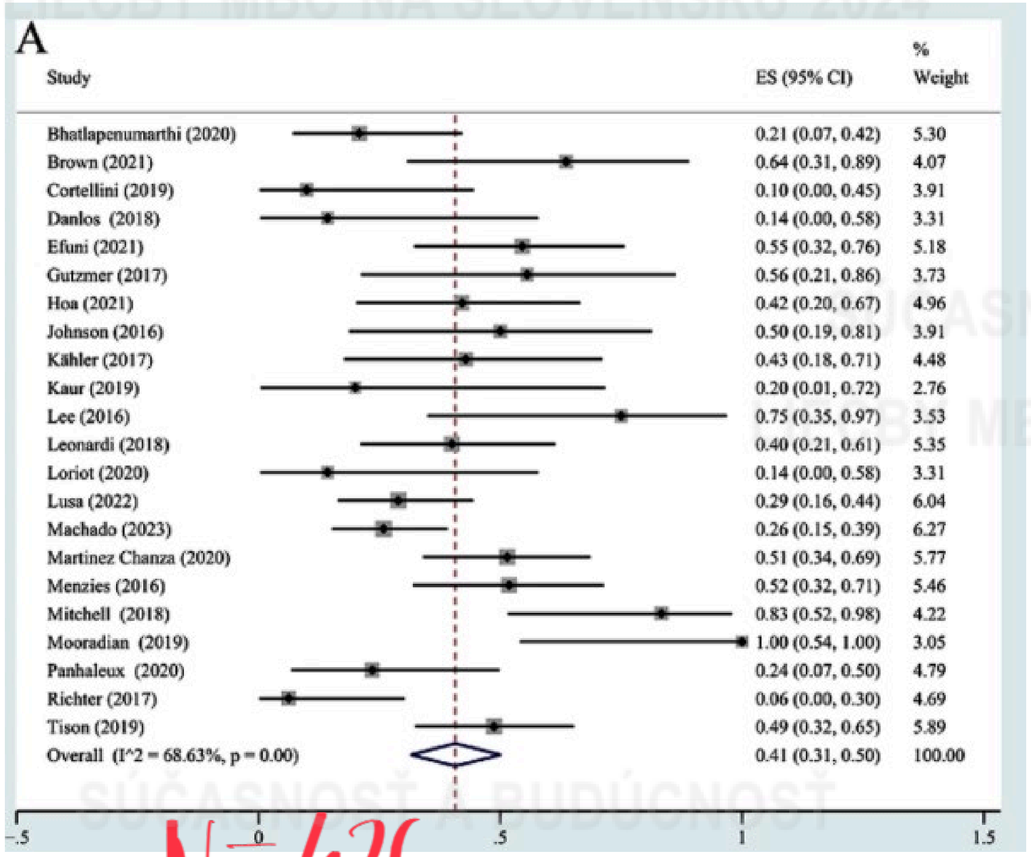
## Summary

Other Section

Although the evidence available for the use of ICI in patients with pre-existing AID is limited to retrospective analysis, for most AID, the use of ICI may not only be safe but also effective. Therefore, we recommend considering treatments with ICI for most patients with pre-existing AID including those with an active AID. Special considerations should be given to patients with neurologic AID, such as myasthenia gravis as the risk for a flare of the underlying condition may result in a life-threatening event. We also recommend for patients with other active or

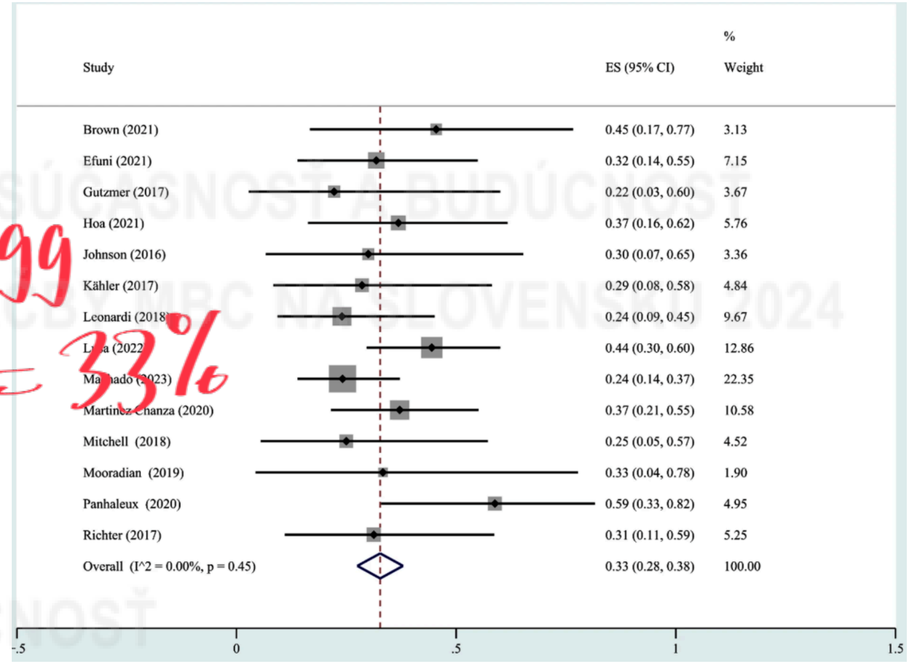
# Immune checkpoint inhibitors in Cancer patients with rheumatologic preexisting autoimmune diseases: a systematic review and meta-analysis

Xin Liu, Su Li, Liyuan Ke & Hongxia Cui



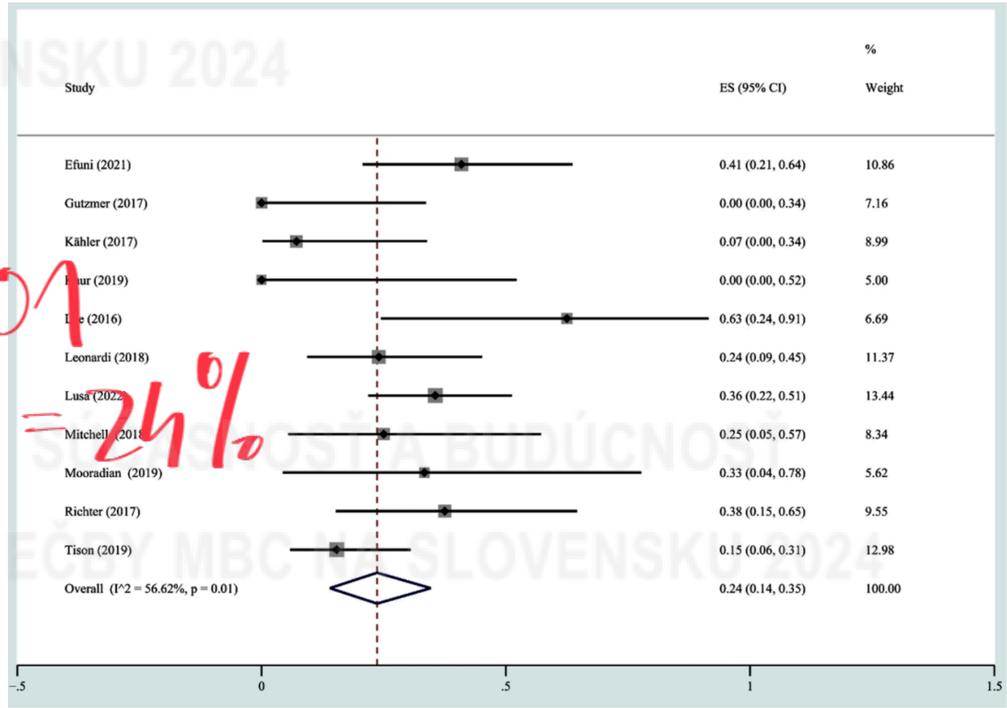

N = 426

any-grade flares = 41%




N = 299

new IRAEs = 33%




N = 201

disc. ICI = 24%

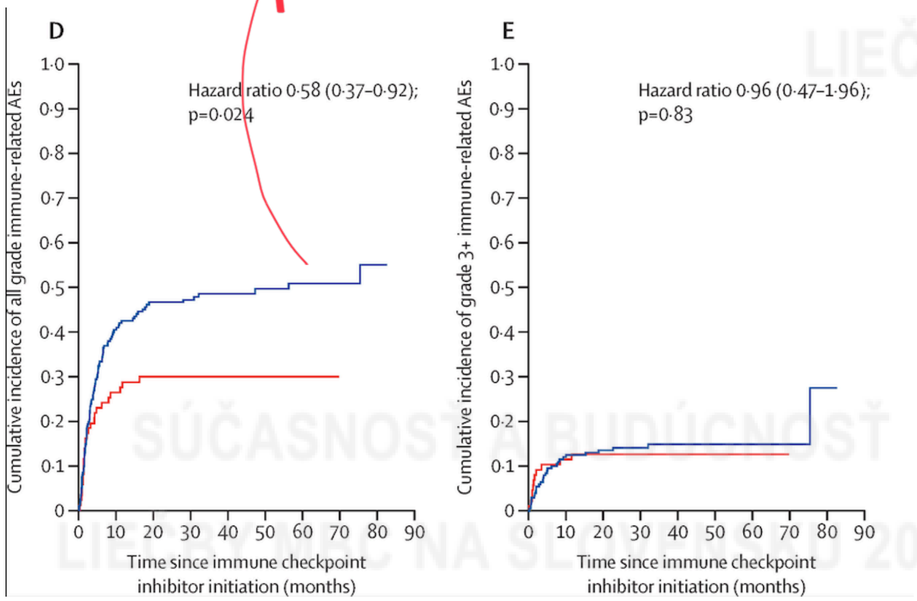
Liu, X., Li, S., Ke, L. *et al.* Immune checkpoint inhibitors in Cancer patients with rheumatologic preexisting autoimmune diseases: a systematic review and meta-analysis. *BMC Cancer* **24**, 490 (2024). https://doi.org/10.1186/s12885-024-12256-z

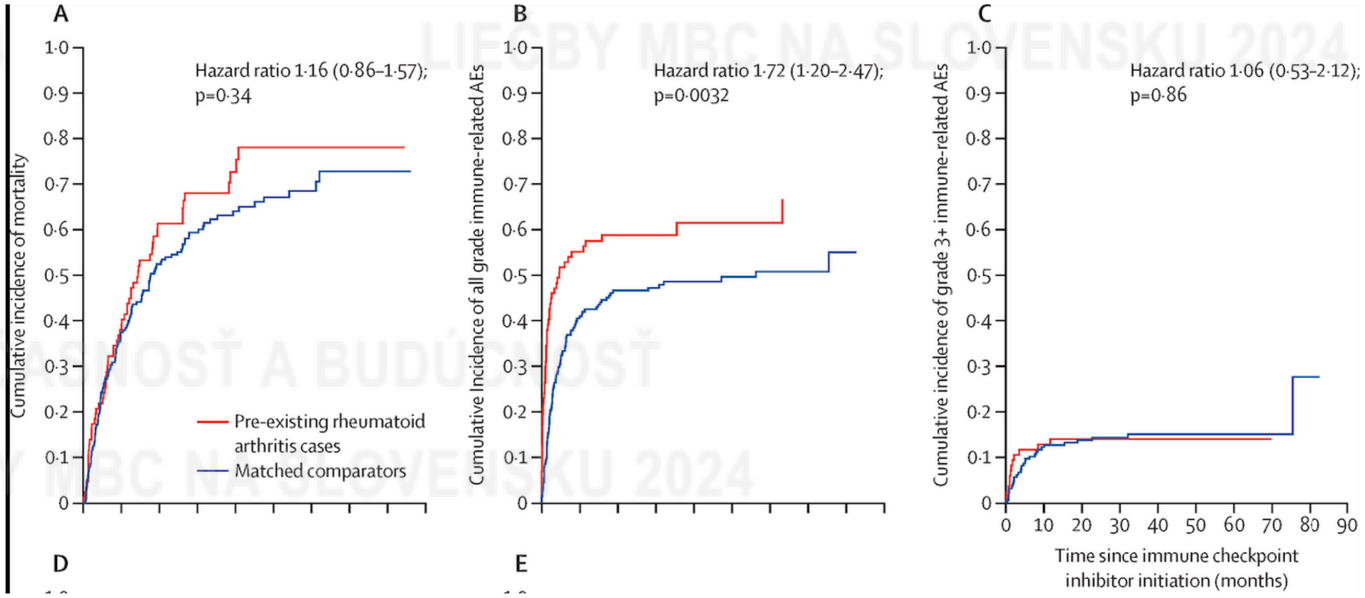
# Mortality and immune-related adverse events after immune checkpoint inhibitor initiation for cancer among patients with pre-existing rheumatoid arthritis: a retrospective, comparative, cohort study

Kaitlin R McCarter, MD [a,d] · Taylor Wolfgang, MD [a,b,d] · Senada Arabelovic, DO [a,b,d] · Xiaosong Wang, MSc [a,d] · Kazuki Yoshida, ScD [a,b,d] · Emily P Banasiak, BA [a,b] · et al. Show more



rozdiel pre flare RA



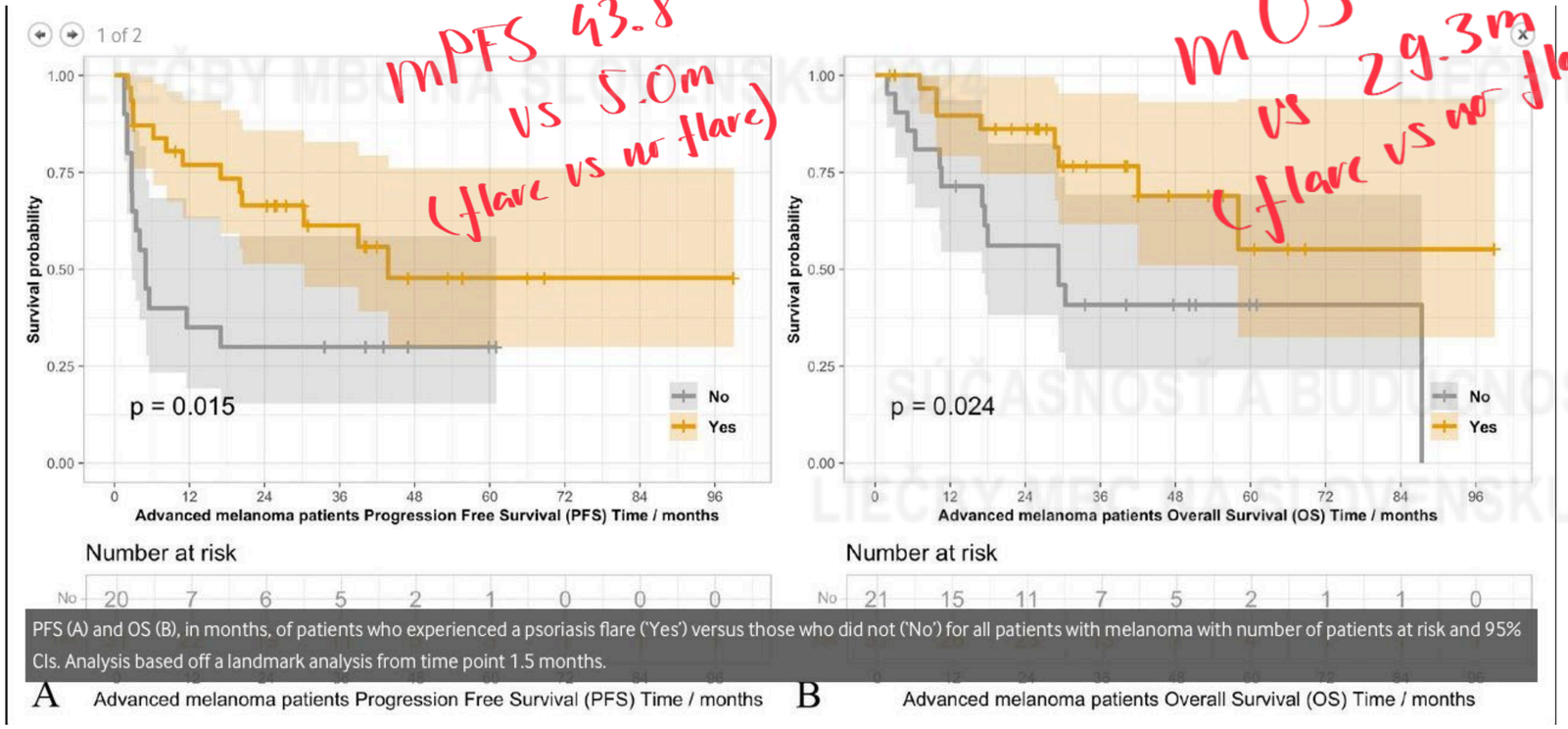




## Interpretation

Patients with pre-existing rheumatoid arthritis initiating immune checkpoint inhibitors had similar risk of mortality and severe immune-related AEs as matched comparators. Although patients with pre-existing rheumatoid arthritis were more likely to have immune-related AEs, this finding was mostly due to mild rheumatoid arthritis flares. These results suggest that this patient population can safely receive immune checkpoint inhibitors for cancer treatment.

McCarter, K. R., Wolfgang, T., & Arabelovic, S et al. (2023). Mortality and immune-related adverse events after immune checkpoint inhibitor initiation for cancer among patients with pre-existing rheumatoid arthritis: A retrospective, comparative, cohort study. *The Lancet Rheumatology, 5*(5), e274–e283. https:

# Immune checkpoint inhibitors in patients with pre-existing psoriasis: safety and efficacy




PFS (A) and OS (B), in months, of patients who experienced a psoriasis flare ('Yes') versus those who did not ('No') for all patients with melanoma with number of patients at risk and 95% CIs. Analysis based off a landmark analysis from time point 1.5 months.

mPFS 43.8 vs 5.0m (flare vs no flare)

mOS NR vs 29.3m (flare vs no flare)

N = 76 pts (psoriasis)

flare = 57% (43)

median TTF = 44d

lok. liečba 53% (23)

sys. liečba 21% (16)

discont. 7% (5)

Inc' IRAE 59% (45)

IRAE G3/G4 22% (17)

**Conclusions** In this multicenter study, ICI therapy was associated with frequent psoriasis exacerbation, although flares were manageable with standard psoriasis treatments and few required ICI discontinuation. Patients who experienced disease exacerbation performed at least as well as those who did not. Thus, pre-existing psoriasis should not prevent patients from receiving ICIs for treatment of malignancy.

Halle BR, Betof Warner A, Zaman FY, et al Immune checkpoint inhibitors in patients with pre-existing psoriasis: safety and efficacy Journal for ImmunoTherapy of Cancer 2021;9:e003066. doi: 10.1136/jitc-2021-003066

ABSTRACTS | IMMUNOTHERAPY OF CANCER · Volume 29, Supplement 8, VIII427, October 2018 · Open Archive

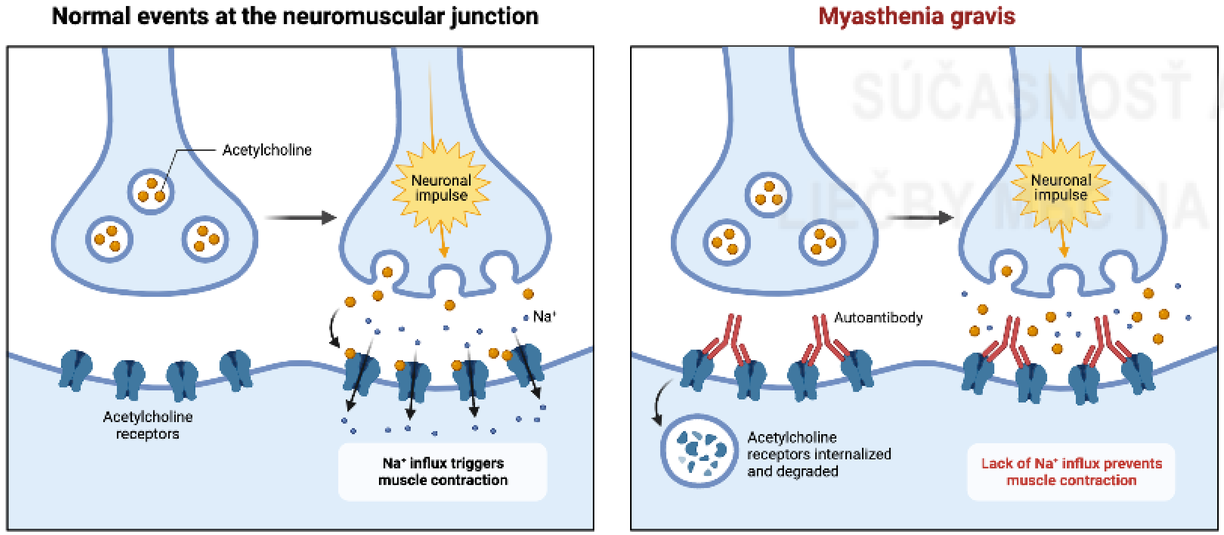
# Use of immune checkpoint inhibitors (CPI) in patients with cancer and concomitant myasthenia gravis (MG)

H. Safa [1] · N. Abdel-Wahab [2] · V.A. Trinh [1] · ... · T.E. Rodgers [1] · M. Suarez-Almazor [2] · A. Diab [1] ... Show more

Al

## Myasthenia Gravis

Autoantibodies Against Receptors Cause Disease by Blocking Receptor Function




**Conclusions:** CPI seems to be associated with serious consequences and high rate of death in pts with MG. Further studies are needed to establish the risk-benefit profile in this population.

N = 39 pts

prior 23%

after ICI 77%

38% (!) – RF!

↳ 8 pts intubation

15% (myocarditis, GBS, myositis ...)

87% – discont.

HD – cort. – 90%

IVIG – 45%

plasmaf. – 42%

11% + RF

# Preexisting Autoimmune Disease: Implications for Immune Checkpoint Inhibitor Therapy in Solid Tumors

JNCCN NCCN National Comprehensive Cancer Network®
OFFICIAL JOURNAL OF THE NATIONAL COMPREHENSIVE CANCER NETWORK

Laura C. Kennedy, MD, PhD[a,b]; Shailender Bhatia, MD[a,b]; John A. Thompson, MD[a,b]; and Petros Grivas, MD, PhD[a,b]

**Table 3. Patients With Preexisting Autoimmune Disease and Cancer**

| ICIs May Be Considered | Avoid ICIs |
|---|---|
| 1. Consult with appropriate autoimmune subspecialist | 1. Autoimmune neurologic or neuromuscular disease |
| 2. Low level of or no immunosuppression with good control of underlying autoimmune disorder | 2. Life-threatening autoimmune disease |
| 3. Patient informed consent | 3. Patients with poor control of autoimmune disease OR requiring high doses of immunosuppressants for control |

frequency of moderate to severe irAEs.[44,47] We also recommend avoiding dual blockade with a combination of PD-(L)1/CTLA-4 agents or high-dose (10 mg/kg) ipilimumab because of much higher rates of toxicity in the general patient population (Table 1). The patient's untreating malignancy for each individual patient. The risk/benefit ratio of ICI therapy in patients with autoimmunity may be less favorable in the adjuvant setting.[53,55,56]

Kennedy, L. C., Bhatia, S., Thompson, J. A., & Grivas, P. (2019). Preexisting autoimmune disease: Implications for immune checkpoint inhibitor therapy in solid tumors. *JNCCN—Journal of the National Comprehensive Cancer Network, 17*(6), 750–757. https://doi.org/10.6004/jnccn.2019.7310

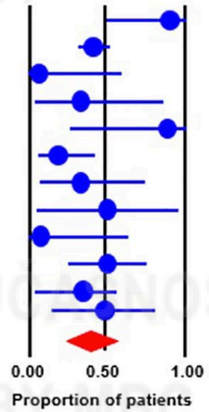
# Safety and Tolerability of Immune Checkpoint Inhibitors in Patients with Pre-existing Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis

Joseph Meserve,[1] Antonio Facciorusso,[2] Ariela K. Holmer,[1] Vito Annese,[3] William J. Sandborn,[1] and Siddharth Singh[1,4]

## Risk of Relapse of IBD with Checkpoint Inhibitors

| Study name | Event rate | Lower limit | Upper limit | Events/ Total |
|---|---|---|---|---|
| Abdel | 0.889 | 0.518 | 0.997 | 8 / 9 |
| AbuSbeih | 0.412 | 0.315 | 0.514 | 42 / 102 |
| Leonardi | 0.000 | 0.000 | 0.459 | 0 / 6 |
| Kahler | 0.333 | 0.043 | 0.906 | 1 / 3 |
| Cortellini | 1.000 | 0.292 | 1.000 | 3 / 3 |
| Grover | 0.190 | 0.054 | 0.419 | 4 / 21 |
| Johnson | 0.333 | 0.043 | 0.777 | 2 / 6 |
| Kaur | 0.500 | 0.013 | 0.987 | 1 / 2 |
| Menzies | 0.000 | 0.000 | 0.522 | 0 / 5 |
| Tison | 0.500 | 0.230 | 0.770 | 7 / 14 |
| Braga Neto | 0.308 | 0.091 | 0.614 | 4 / 13 |
| Brown | 0.556 | 0.212 | 0.863 | 5 / 9 |
| IBD RELAPSE | 0.398 | 0.261 | 0.545 | 77 / 193 |

Event rate and 95% CI

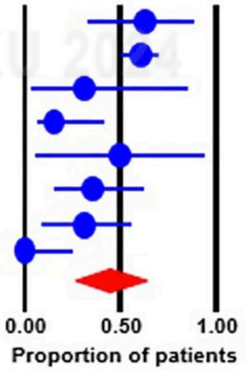



N = 193 (12 trials)
IBD relaps = 39.8%

## Need to Discontinue Checkpoint Inhibitors

| Study name | Event rate | Lower limit | Upper limit | Events/ Total |
|---|---|---|---|---|
| Abdel | 0.667 | 0.299 | 0.925 | 6 / 9 |
| AbuSbeih | 0.608 | 0.506 | 0.703 | 62 / 102 |
| Kahler | 0.333 | 0.008 | 0.906 | 1 / 3 |
| Grover | 0.190 | 0.054 | 0.419 | 4 / 21 |
| Kaur | 0.500 | 0.013 | 0.987 | 1 / 2 |
| Tison | 0.357 | 0.128 | 0.987 | 5 / 14 |
| Brown | 0.333 | 0.075 | 0.648 | 3 / 9 |
| Braga Neto | 0.000 | 0.000 | 0.247 | 0 / 13 |
| DISCONTINUED ICIs | 0.354 | 0.168 | 0.567 | 82 / 173 |

Event rate and 95% CI

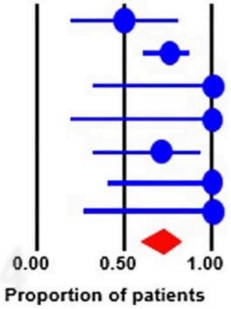



N = 173
disc - 35.4%

## Needed Corticosteroids for IBD Flare

| Study name | Event rate | Lower limit | Upper limit | Events/ Total |
|---|---|---|---|---|
| Abdel | 0.500 | 0.157 | 0.843 | 4 / 8 |
| AbuSbeih | 0.762 | 0.605 | 0.879 | 32 / 42 |
| Grover | 1.000 | 0.398 | 1.000 | 4 / 4 |
| Johnson | 1.000 | 0.158 | 1.000 | 2 / 2 |
| Tison | 0.714 | 0.290 | 0.963 | 5 / 7 |
| Braga Neto | 1.000 | 0.397 | 1.000 | 4 / 4 |
| Kahler | 1.000 | 0.025 | 1.000 | 1 / 1 |
| NEEDED CORTICOSTEROIDS | 0.761 | 0.654 | 0.854 | 52 / 68 |

Event rate and 95% CI

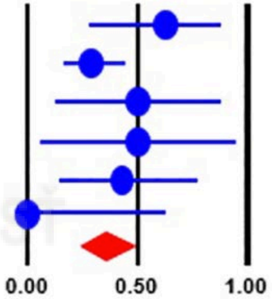



N = 68
kortikoidy 76.1%

## Needed Biologic Therapy for IBD Flare

| Study name | Event rate | Lower limit | Upper limit | Events/ Total |
|---|---|---|---|---|
| Abdel | 0.625 | 0.245 | 0.915 | 5 / 8 |
| AbuSbeih | 0.288 | 0.157 | 0.446 | 12 / 42 |
| Grover | 0.500 | 0.068 | 0.932 | 2 / 4 |
| Johnson | 0.500 | 0.013 | 0.987 | 1 / 2 |
| Tison | 0.429 | 0.099 | 0.816 | 3 / 7 |
| Braga Neto | 0.000 | 0.000 | 0.602 | 0 / 4 |
| NEEDED BIOLOGICS | 0.366 | 0.219 | 0.527 | 23 / 67 |

Event rate and 95% CI




N = 67 biol. agens 36.6%



Meserve J, Facciorusso A, Holmer AK, Annese V, Sandborn WJ, Singh S. Systematic review with meta-analysis: safety and tolerability of immune checkpoint inhibitors in patients with pre-existing inflammatory bowel diseases. Aliment Pharmacol Ther. 20

Position Paper

# Management of immune checkpoint inhibitor in patients with cancer and pre-existing inflammatory bowel disease: Recommendations from the GETAID ☆

Aurelien Amiot [a b], David Laharie [c], Georgia Malamut [d], Melanie Serrero [e], Florian Poullenot [c]
the educational committee of the GETAID[1]


1. **IBD + ICI**: Väčšina pacientov s IBD v remisii môže dostať ICI, relaps IBD alebo hnačka/kolitída u 39,8 %.
2. **Riziko IMDC**: Najvyššie riziko pri anti-CTLA-4 a kombinácii s anti-PD-1/PD-L1. Vyhnúť sa kombinácii, uprednostniť monoterapiu.
3. **Pred liečbou**: Vyhodnotiť aktivitu IBD pomocou CRP, fekálneho kalprotektínu, endoskopie, diagnostických zobrazovacích metód.
4. **Aktívna IBD**: ICI kontraindikovaná, kým sa nedosiahne remisia, okrem život ohrozujúcich prípadov.
5. **Vyšetrenia pri tráviacich ťažkostiach**: Kultúry stolice, testy na *C. difficile*, CRP a krvné testy.
6. **Endoskopia**: Povinná pri CTCAE stupni 3–4, alebo pretrvávajúcich symptómoch.
7. **Liečba**: Závisí od závažnosti; ICI prerušiť pri CTCAE 3–4.
8. **Kortikosteroidy**: Pri CTCAE 1–2 perorálne, pri 3–4 intravenózne.
9. **Biologická liečba**: Infliximab/vedolizumab pri zlyhaní kortikosteroidov.
10. **Dlhodobá liečba**: Individuálne posúdenie pokračovania biologickej liečby po remisii.



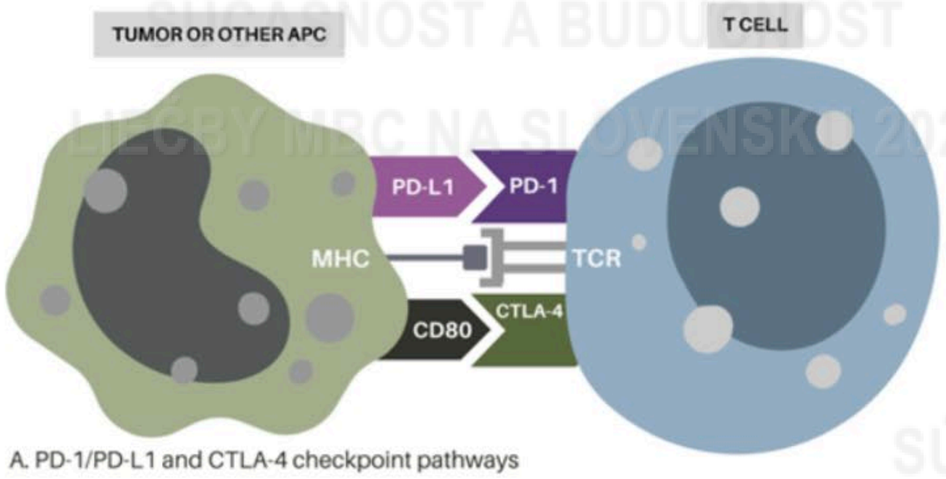
Amiot, A., Laharie, D., Malamut, G. R et al (2022). Management of immune checkpoint inhibitor in patients with cancer and pre-existing inflammatory bowel disease: Recommendations from the GETAID. *Digestive and Liver Disease, 54*(9), 1162-1167. https://doi.org/10.1016/j.dld.2022.05.022

# Úskalie štvrté: imunoterapia u pacientov s preexistujúcimi autoimunitnými ochoreniami

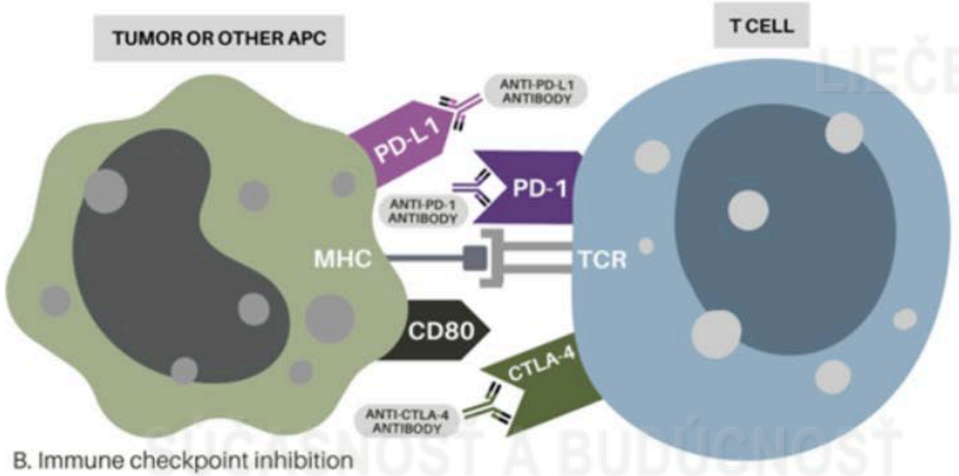
- AID ochorenia predstavujú potenciálnu prekážku v I/O
- preex. AID- častý flare po zahájení I/O
- u život- ohrozujúcich AID I/O kontraindikované
- u dobre kontrolovaných AID- I/O môže byť so súhlasom pacienta použitá
- dáta získané z iných indikácii I/O

**DALL·E Image Generation**. (2024). *Danger on a Rocky Mountain*. Generated by OpenAI's DALL·E 3 model through the ChatGPT pl

# Úskalie piate: imunoterapia u pacientov liečených kortikoidmi a/alebo imunosupresívami




A. PD-1/PD-L1 and CTLA-4 checkpoint pathways




B. Immune checkpoint inhibition

**TUMOR IMMUNE EVASION**

- Inhibition of effector T-cell activity
- Self-tolerance - prevents immune responses against self-antigens and autoimmunity

**UPREGULATION OF IMMUNE RESPONSE**

- Increased effector T-cell activity
- Autoimmunity (irAEs)

| Immunotherapy | Corticosteroids |
|---|---|
| Increased activation and proliferation of tumor-reactive CD8+ T cells | Reduced memory CD8+ T cells |
| Increased immune cells | Decreased monocytes, macrophages, lymphocytes, eosinophils, and basophils. |
| Increased pro-inflammatory cytokines (IFN-gamma, TNF, IL-17) | Suppression of pro-inflammatory cytokines (IL-2, IL-6, TNF-alpha) and prostaglandins. |
| Reduced regulatory T cells<br>• Decreased anti-inflammatory cytokines (TGF-beta, IL-10) | Increased regulatory T cells<br>• increased anti-inflammatory cytokines (TGF-beta, IL-10) |

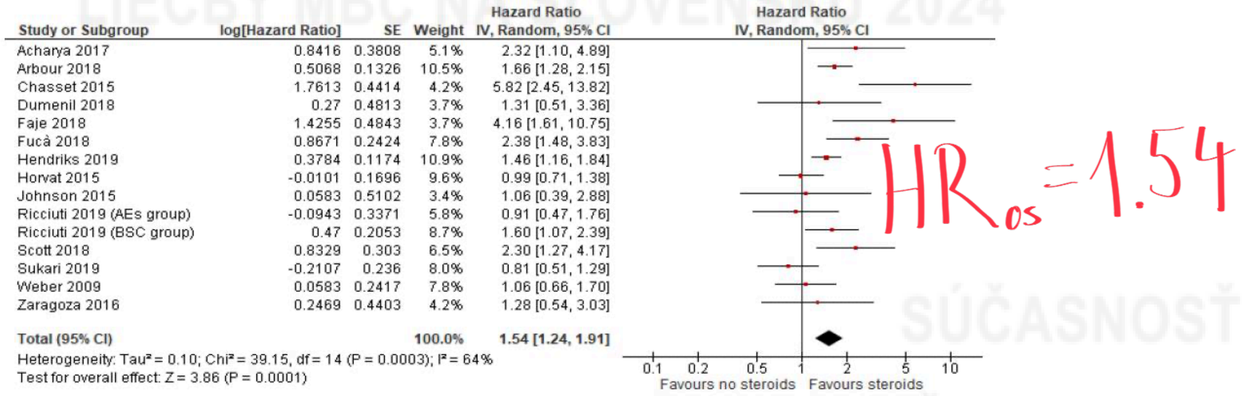
C. ICIs and corticosteroids produce antagonistic effects on the immune system.



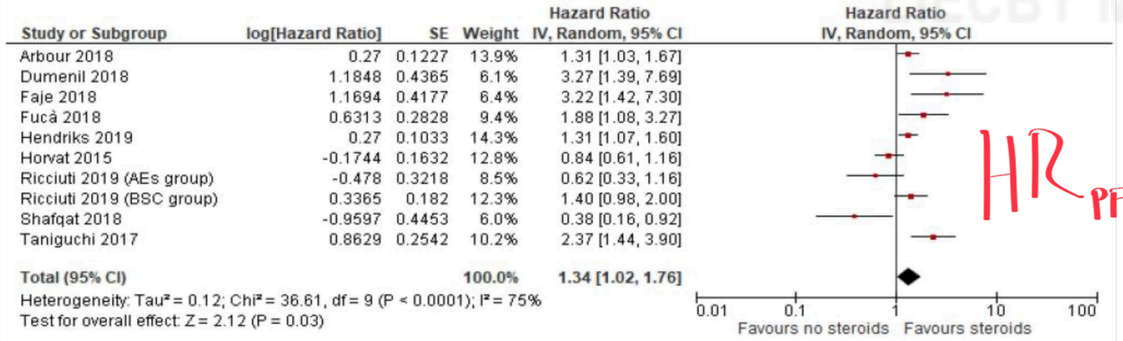
Goodman RS, Johnson DB, Balko JM. Corticosteroids and Cancer Immunotherapy. Clin Cancer Res. 2023 Jul 14;29(14):2580-2587. doi: 10.1158/1078-0432.CCR-22-3181. PMID: 36648402; PMCID: PMC10349688.

# Association of Steroids Use with Survival in Patients Treated with Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis

Fausto Petrelli,[1,*†] Diego Signorelli,[2,†] Michele Ghidini,[3] Antonio Ghidini,[4] Elio Gregory Pizzutilo,[5] Lorenzo Ruggieri,[5] Mary Cabiddu,[1] Karen Borgonovo,[1] Giuseppina Dognini,[6] Matteo Brighenti,[7] Alessandro De Toma,[2] Erika Rijavec,[3] Marina Chiara Garassino,[2] Francesco Grossi,[3] and Gianluca Tomasello[5]




$HR_{OS} = 1.54$

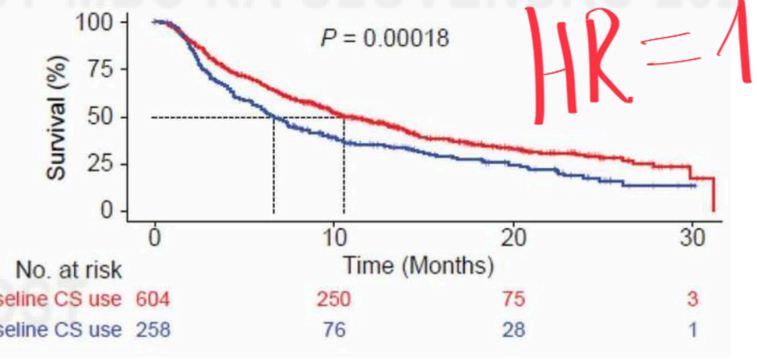



$HR_{PFS} = 1.34$

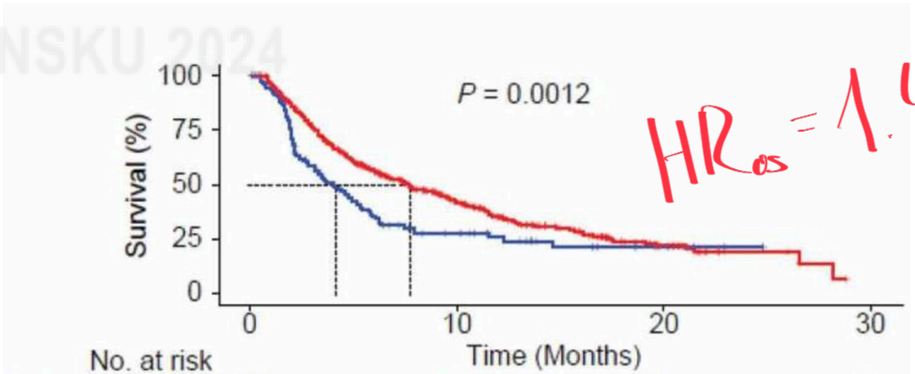
| | | | | |
|---|---|---|---|---|
| Reason for steroid use | 3/836 | 2.5 (1.41–4.43) | <0.01 | 76% |
| • BSC | 3/1164 | 1.51 (1.22–1.87) | <0.01 | 49% |
| • BMs | 9/926 | 1.08 (0.79–1.49) | 0.62 | 48% |
| • AEs | | | | |

# Association of baseline systemic corticosteroid use with overall survival and time to next treatment in patients receiving immune checkpoint inhibitor therapy in real-world US oncology practice for advanced non-small cell lung cancer, melanoma, or urothelial carcinoma

Alexandra Drakaki,[a] Preet K Dhillon,[b] Heather Wakelee,[c] Stephen Y Chui,[d] Jinjoo Shim,[e] Matthew Kent,[f] Viraj Degaonkar,[d] Tien Hoang,[d] Virginia McNally,[g] Patricia Luhn,[b] and Ralf Gutzmer[h]




$HR = 1.34$




$HR_{OS} = 1.44$

CAVE! MULTIVARIAČNÁ ANALÝZA!



Drakaki A, Dhillon PK, Wakelee H, Chui SY, Shim J, Kent M, Degaonkar V, Hoang T, McNally V, Luhn P, Gutzmer R. Association of baseline systemic corticosteroid use with overall survival and time to next treatment in patients receiving immune checkpoint inhibitor therapy in real-world US oncology practice for advanced non-small cell lung cancer, melanoma, or urothelial carcinoma. Oncoimmunology. 2020 Oct 5;9(1):1824645.

Petrelli, F., Signorelli, D., Ghidini, M., et al. (2020). Association of steroid use with survival in patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis. *Cancers (Basel), 12*(3), 546. https://doi.org/10.3390/cancers12030546

# Impact of Baseline Corticosteroids on Immunotherapy Efficacy in Patients With Advanced Melanoma

Kartolo, Adi[*,†]; Deluce, Jasna[‡,§]; Holstead, Ryan[*,†]; Hopman, Wilma[‖]; Lenehan, John[‡,§]; Baetz, Tara[*,†]

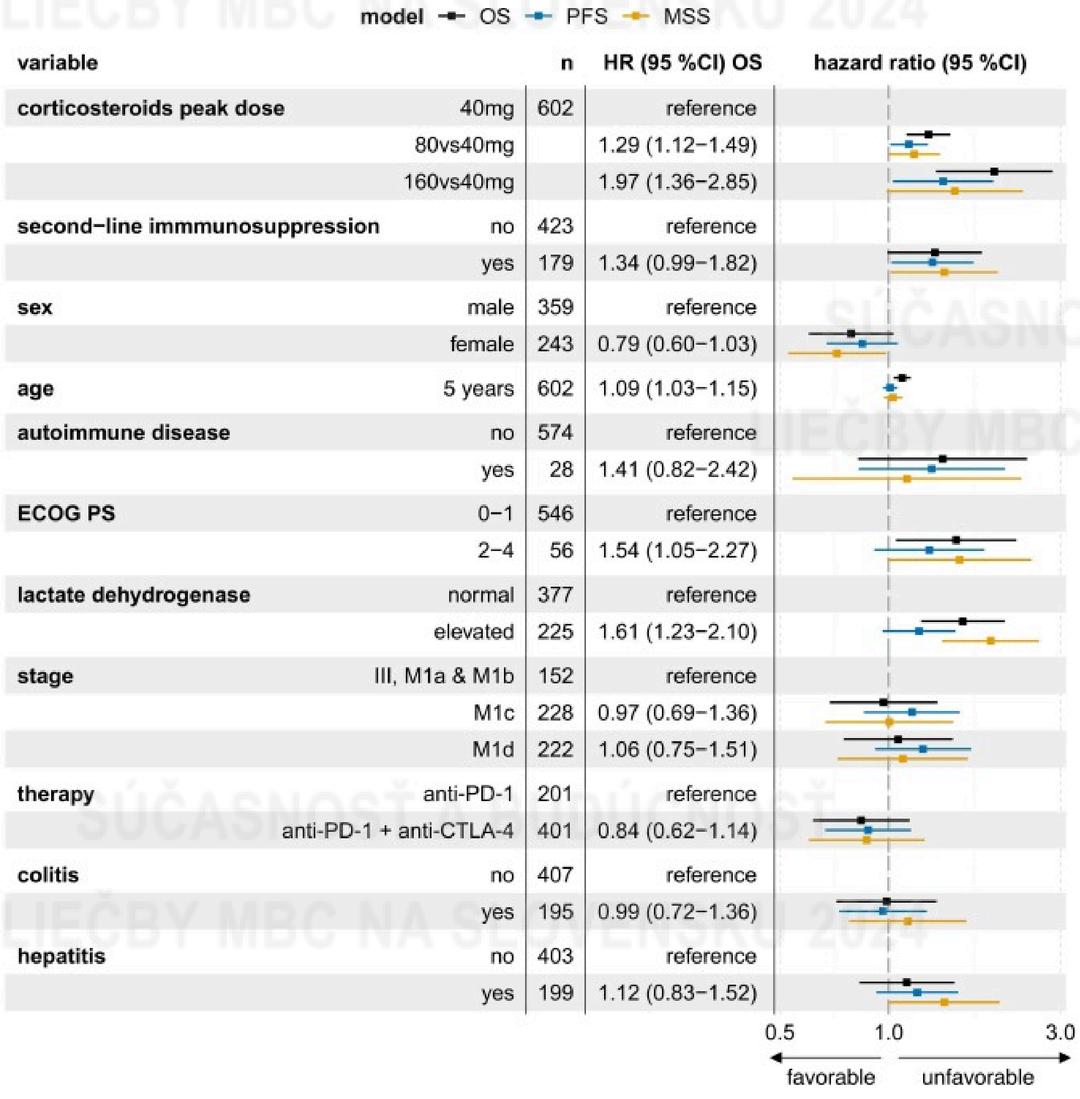
- **Cieľ štúdie**: Hodnotiť vplyv užívania kortikosteroidov na účinnosť imunoterapie u pacientov s pokročilým melanómom.
- **Počet pacientov**: 166 pacientov s pokročilým melanómom, 25 z nich užívalo kortikosteroidy pri začatí liečby PD-1 inhibítormi.
- **Definícia užívania kortikosteroidov**: Kortikosteroidy vo forme prednizónu ≥10 mg/deň v období do 30 dní pred začatím imunoterapie.
- **Výsledky**:
  - Prednizón v dávke ≥10 mg nemal významný vplyv na celkové prežívanie (HR=1,590; 95% CI: 0,773–3,270; P=0,208).
  - Prednizón v dávke ≥50 mg bol nezávisle spojený s horším celkovým prežívaním (HR=2,313; 95% CI: 1,103–4,830; P=0,026).
- **Záver**: Vyššie dávky kortikosteroidov (≥50 mg) sú spojené s horšou prognózou, a preto by sa malo zvážiť zníženie ich používania pred začatím liečby PD-1 inhibítormi.

Kartolo, Adi[*,†]; Deluce, Jasna[‡,§]; Holstead, Ryan[*,†]; Hopman, Wilma[‖]; Lenehan, John[‡,§]; Baetz, Tara[*,†]. Impact of Baseline Corticosteroids on Immunotherapy Efficacy in Patients With Advanced Melanoma. Journal of Immunotherapy 44(4):p 167-174, May 2021. | DOI: 10.1097/CJI.0000000000000360

# Corticosteroids and other immunosuppressants for immune-related adverse events and checkpoint inhibitor effectiveness in melanoma

Rik J. Verheijden [a,b] · Femke H. Burgers [c] · Josephine C. Janssen [d] · ... · John B.A.G. Haanen [c,i,w] · Anne M. May [b] · Karijn P.M. Suijkerbuijk [a] ✉... Show more






HR OS NS

| | | |
|---|---|---|
| All patients | n = 532 | n = 602 |
| 80 vs 40 mg prednisolone eq | 1.14 (1.01-1.29) | 1.29 (1.12-1.49) |
| 160 vs 40 mg prednisolone eq | 1.42 (1.03-1.95) | 1.97 (1.36-2.85) |
| Second-line immunosuppression | 1.32 (1.02-1.72) | 1.34 (0.99-1.82) |

HR PFS 1.32

TNF inhibition

Mycophenolate mofetyl

Tacrolimus

IVIg

Vedolizumab

Methotrexate

# Úskalie piate: imunoterapia u pacientov liečených kortikoidmi a/alebo imunosupresívami

- liečba kortikoidmi (najmä dlhodobá) potenciálne znižuje účinnosť I/O

- kortikoidy do ekv. Prednisonu 50mg denne by nemali mať výrazný vplyv na SR

- snaha o čo možno najnižšiu dávku KS (+/- ekv 10mg Prednisonu denne?)

- nedostatok dát o iných ISD

- dáta získané z iných indikácii I/O

**DALL·E Image Generation**. (2024). *Pitfall in a natural environment*. Generated by OpenAI's DALL·E 3 model through the ChatGPT platform.

# Úskalie šieste: pacienti po transplantácii, pacienti s CLL, vírusové hepatitídy a HIV+

# How about transplant patients?

**A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant.**

**Retrospective cohort study (2010-2020)**

- International Multi-center (23 institutions)
- Kidney transplant recipients (n=69)
- ICI therapy for advanced cancer (aPD-1, aPD-L1, aCTLA-4)

**Safety**

| Acute rejection | Time to rejection | Graft loss |
|---|---|---|
| **42%** | **24 days** | **65%** of rejection |

**Efficacy: Tumor response to ICI therapy (complete response + partial response)**

| Skin squamous cell carcinoma (n=24) | Melanoma (n=22) |
|---|---|
| **36%** | **40%** |

**CONCLUSION:**

Immune checkpoint inhibitors are associated with high acute rejection rate but result in reasonable tumor response.

kidney INTERNATIONAL ISN

Murakami et al, 2020

BARCELONA 2024 ESMO congress

Mathilde Jalving, MD, PhD



Murakami et al. 2020, presented at ESMO Congress 2024

# The Safety and Efficacy of Checkpoint Inhibitors in Transplant Recipients: A Case Series and Systematic Review of Literature

Vivek Kumar, [1] Atul B. Shinagare, [2] Helmut G. Rennke, [3] Sandeep Ghai, [4] Jochen H. Lorch, [1] Patrick A. Ott, [1] and Osama E. Rahma [1]

Characteristics of patients with organ transplant who received treatment with an ICI

| Characteristics | Total, $n = 64$ (100%) | No rejection, $n = 38$ (59%) | Rejection, $n = 26$ (41%) | $p$ value |
|---|---|---|---|---|
| Gender | | | | |
| Female | 16 | 10 (63) | 6 (37) | .74 |
| Male | 48 | 28 (58) | 20 (42) | |
| Median age (range), years | 63.8 (14–85) | 65.5 (35–77) | 63 (14–85) | .48 |
| Time to immunotherapy since transplant, median (range), years | 8 (0.75–32) | 8 (0.75–32) | 6 (0.75–27.6) | .74 |
| Solid organs | | | | |
| Kidneys | 39 | 21 (54) | 18 (46) | .34 |
| Liver | 19 | 13 (68) | 6 (32) | |
| Heart | 5 | 4 (80) | 1 (20) | |
| Cornea | 1 | 0 (0) | 1 (100) | |
| Type of immunotherapy | | | | |
| CTLA-4 inhibitor | 13 | 10 (77) | 3 (23) | .45 |
| PD-1/PD-L1 inhibitors | 43 | 23 (53) | 20 (47) | |
| Sequential ICIs | 8 | 5 (62.5) | 3 (37.5) | |
| Response to therapy | | | | |
| Yes | 25 | 16 (62.5) | 9 (37.5) | .8 |
| CTLA-4 inhibitors | 7 | 6 (86) | 1 (14) | |
| PD-1/PD-L1 inhibitors | 15 | 9 (60) | 6 (40) | |
| Both | 3 | 1 (33) | 2 (66) | |
| No | 31 | 20 (64.5) | 11 (35.5) | |
| CTLA-4 inhibitors | 6 | 4 (67) | 2 (33) | |
| PD-1/PD-L1 inhibitors | 20 | 12 (60) | 8 (40) | |
| Both | 5 | 4 (80) | 1 (20) | |

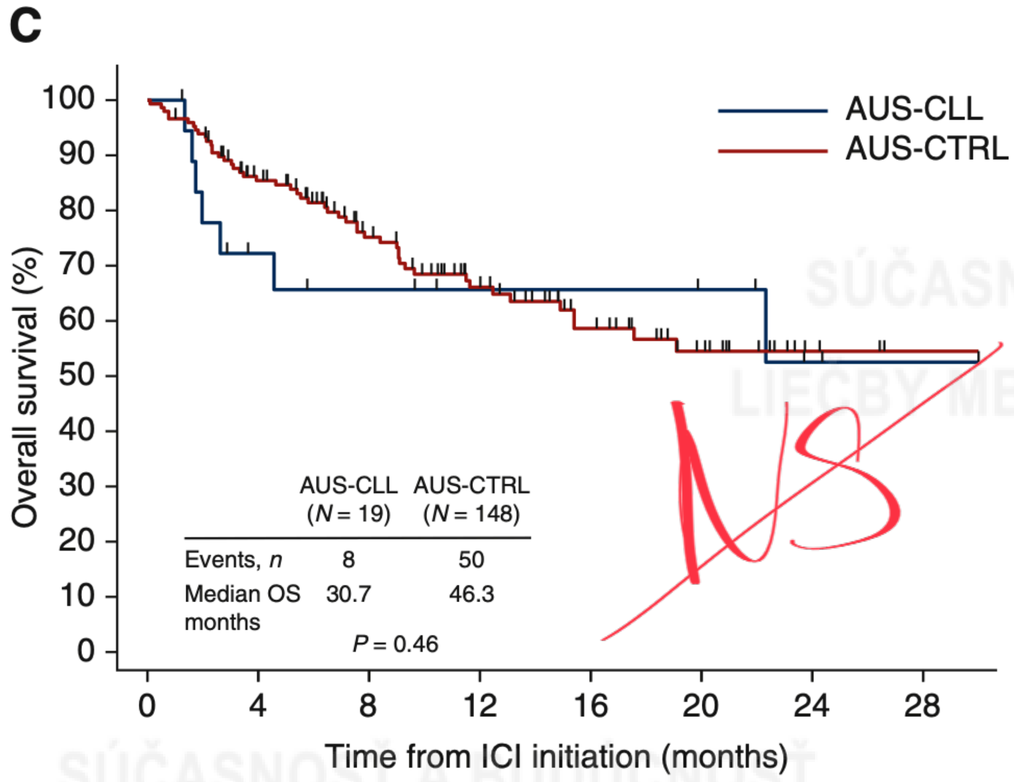
Callout: Our pooled analysis reaffirms previous observations of high rates (~40%) of allograft rejection in cancer patients who were treated with an ICIs leading to organ failure in 71% of the patients who experienced rejection.

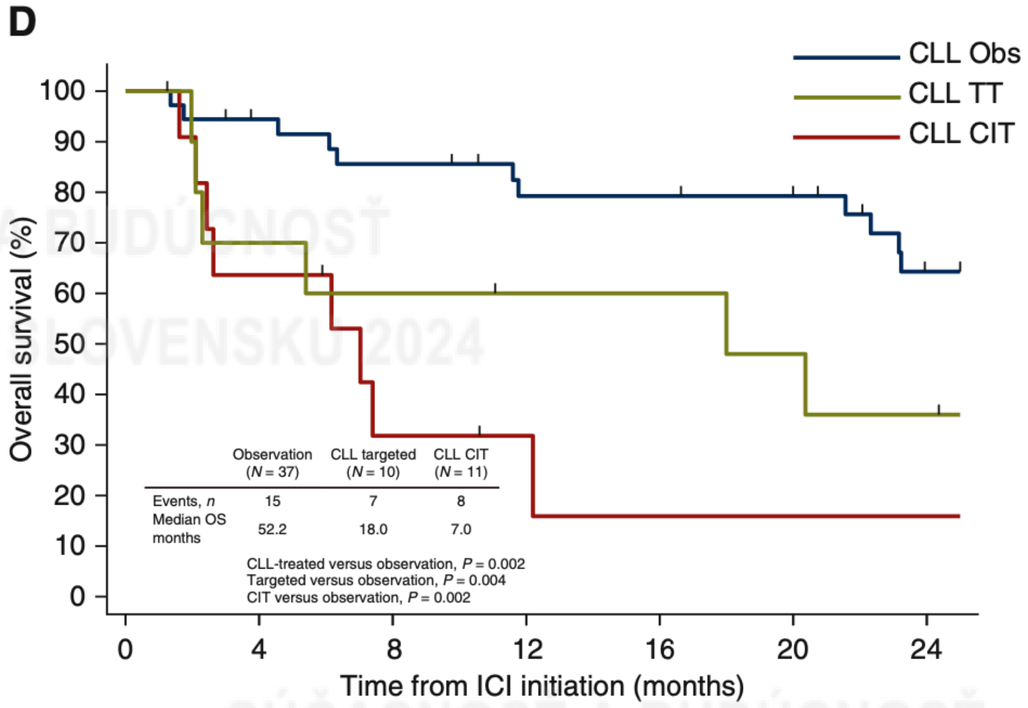
Callout 2: Although the majority of graft rejections happened after 1-2 doses of ICIs, we did not find any association between number of doses of ICIs or time from transplant to commencement of ICI treatment and rate of rejection. This could be due to small number of patients, but it is also possible that the loss of immunotolerance secondary to ICI is dose and time independent.

Kumar V, Shinagare AB, Rennke HG, Ghai S, Lorch JH, Ott PA, Rahma OE. The Safety and Efficacy of Checkpoint Inhibitors in Transplant Recipients: A Case Series and Systematic Review of Literature. Oncologist. 2020 Jun;25(6):505-514. doi: 10.1634/theoncologist.2019-0659. Epub 2020 Feb 11. PMID: 32043699; PMCID: PMC7288631.

# Efficacy of immune checkpoint inhibitors for the treatment of advanced melanoma in patients with concomitant chronic lymphocytic leukemia

S. H. Cass[1], J. W. D. Tobin[2,3], Y. D. Seo[1], G. Gener-Ricos[4], E. Z. Keung[1], E. M. Burton[5], M. A. Davies[5], J. L. McQuade[5], A. J. Lazar[6], R. Mason[7], M. Millward[8], S. Sandhu[9], C. Khoo[9], L. Warburton[10,11,12], V. Guerra[4], A. Haydon[13], H. Dearden[14], A. M. Menzies[14,15,16,17], M. S. Carlino[14,18], J. L. Smith[18], P. Mollee[2,3], M. Burgess[2,3], S. Mapp[2,3], C. Keane[2,3], V. Atkinson[2,3], S. A. Parikh[19], S. N. Markovic[19], W. Ding[19], T. G. Call[19], P. J. Hampel[19], G. V. Long[14,15,16,17], J. A. Wargo[1*] & A. Ferrajoli[4]




**Conclusions:** Our case series of patients with concomitant CLL and melanoma demonstrate frequent, durable clinical responses to ICI. However, those with prior chemoimmunotherapy treatment for CLL had significantly worse outcomes. We found that CLL disease course is largely unchanged by treatment with ICI.

Efficacy of immune checkpoint inhibitors for the treatment of advanced melanoma in patients with concomitant chronic lymphocytic leukemia
Cass, S.H. et al.
Annals of Oncology, Volume 34, Issue 9, 796 - 805

# Iné lymfoproliferatívne ochorenia a myeloproliferatívne ochorenia s I/O?

**DALL·E Image Generation**. (2024). *Mysterious scene with a question mark in a foggy forest*. Generated by OpenAI's DALL·E 3 model through the ChatGPT platform.

# Management of Hepatitis B Virus and Hepatitis C Virus Infections in Patients with Cancer Receiving Immune Checkpoint Inhibitors

Khalis Mustafayev; Vincent Mallet; Harrys A. Torres

*Journal of Immunotherapy and Precision Oncology* (2024) 7 (2): 111–121.

https://doi.org/10.36401/JIPO-23-28 **Article history**

Khalis Mustafayev, Vincent Mallet, Harrys A. Torres; Management of Hepatitis B Virus and Hepatitis C Virus Infections in Patients with Cancer Receiving Immune Checkpoint Inhibitors. Journal of Immunotherapy and Precision Oncology 1 May 2024; 7 (2): 111–121. doi: https://doi.org/10.36401/JIPO-23-28

## Keypoints:

- **HBV and ICI therapy**:
  - 28 studies reviewed (prospective trials, cohort studies, case series, and reports).
  - Overall HBV reactivation rate: 1.4% (38/2799 cases).
  - Reactivation rate in chronic HBV: 2% (35/1667 cases).
  - Reactivation rate in past HBV: 0.3% (3/1132 cases).
  - **Higher risk without antiviral prophylaxis**: 17% reactivation in chronic HBV without antivirals vs. 1% with antivirals ($p < 0.05$).
- **HCV and ICI therapy**:
  - 11 studies reviewed (clinical trials, retrospective studies, and an observational study).
  - Overall HCV reactivation rate: 0.5% (2/387 cases).
  - **Reactivation mainly in patients** receiving immunosuppressants for ICI-related toxicity.

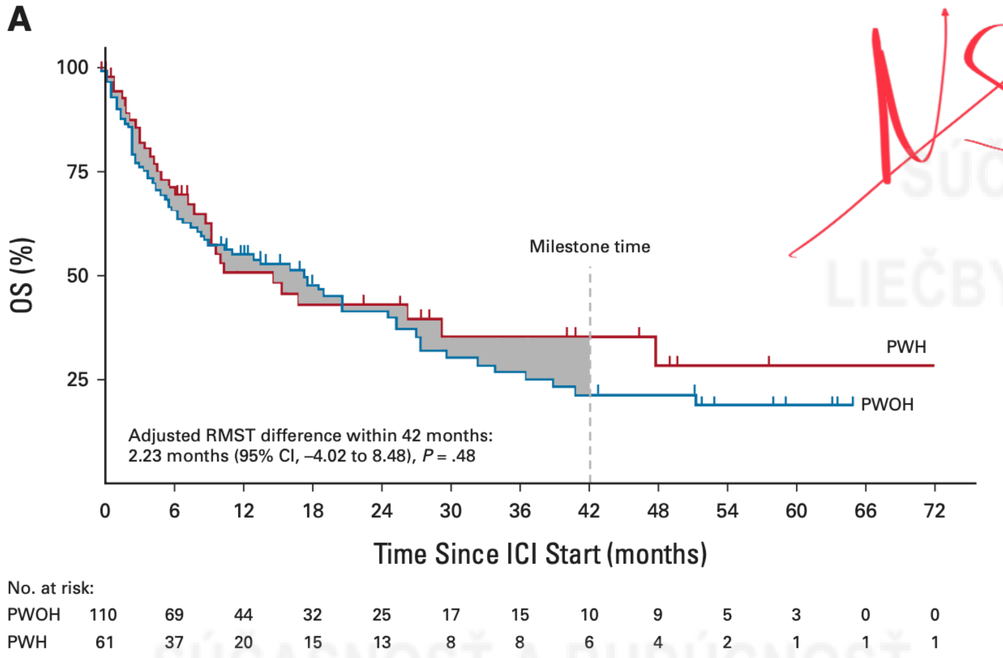
1.4%

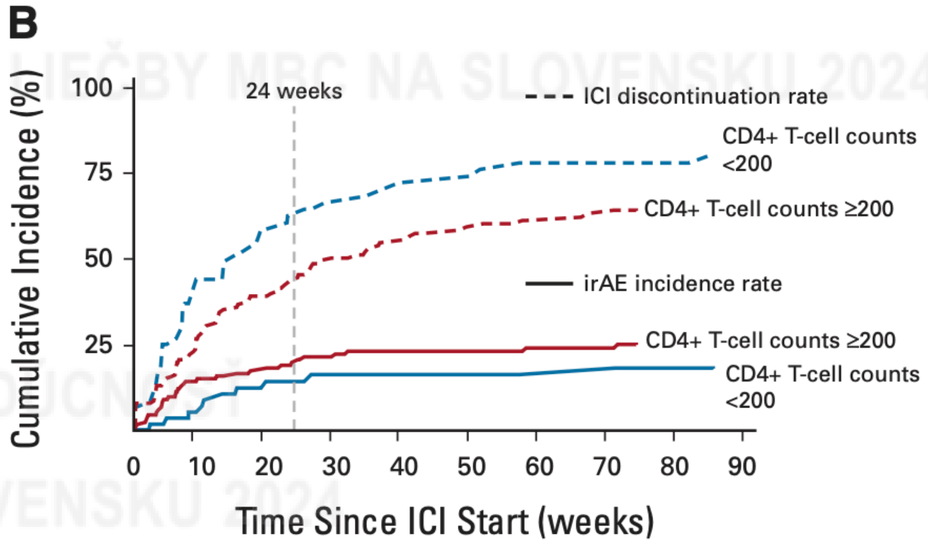
0.5%

## Conclusions

Chronic HBV or HCV infection should not be considered a contraindication for ICI therapy. Specific risk assessment, monitoring, and management strategies are necessary to reduce the risk of ICI-related liver injury in patients with cancer and chronic HBV or HCV infection.

# Safety and Activity of Immune Checkpoint Inhibitors in People Living With HIV and Cancer: A Real-World Report From the Cancer Therapy Using Checkpoint Inhibitors in People Living With HIV-International (CATCH-IT) Consortium




## CONTEXT

**Key Objective**

Determine safety and activity of immune checkpoint inhibitors (ICIs) among people living with HIV (PWH) and cancer.

**Knowledge Generated**

Three hundred and ninety PWH received ICIs while on antiretroviral therapy (ART), including 30% PWH with baseline CD4+ T-cell counts <200 cells/μL. ICIs were deemed safe and had differential activity across tumor types. Among PWH with non–small-cell lung cancer (NSCLC), clinical outcomes were not generally influenced by CD4+ T-cell counts or ART regimens. In a subset of PWH with metastatic NSCLC, the safety and activity of ICIs were comparable with a matched cohort of people living without HIV after matching for relevant clinical variables at the same institution.

**Relevance *(G.K. Schwartz)***

General concerns have persisted on the safety of ICIs in patients with cancer and HIV. This study should reassure physicians that the use of ICIs is safe and effective in this patient population, even for those on ART.*



Zarif, Talal & Nassar, et al (2023). Safety and Activity of Immune Checkpoint Inhibitors in People Living With HIV and Cancer: A Real-World Report From the Cancer Therapy Using Checkpoint Inhibitors in People Living With HIV-International (CATCH-IT) Consortium. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 41. JCO2202459. 10.1200/JCO.22.02459.

# Úskalie šieste: pacienti po transplantácii, pacienti s CLL, vírusové hepatitídy a HIV+

- liečba I/O po transplantácii je zaťažená vysokou mierou rejekcie (+/- 40%)

- I/O sú účinné aj po transplantácii

- CLL nie je KI pre I/O, pacienti predliečení immunoCht- horšia prognóza

- HBV +, HCV+, HIV+ nie sú kontraindikácie pre I/O

# Ďakujem za pozornosť!

**DALL·E Image Generation**. (2024). *Wooden puppet-like character bowing in front of an audience*. Generated by OpenAI's DALL·E 3 model through the ChatGPT platform.