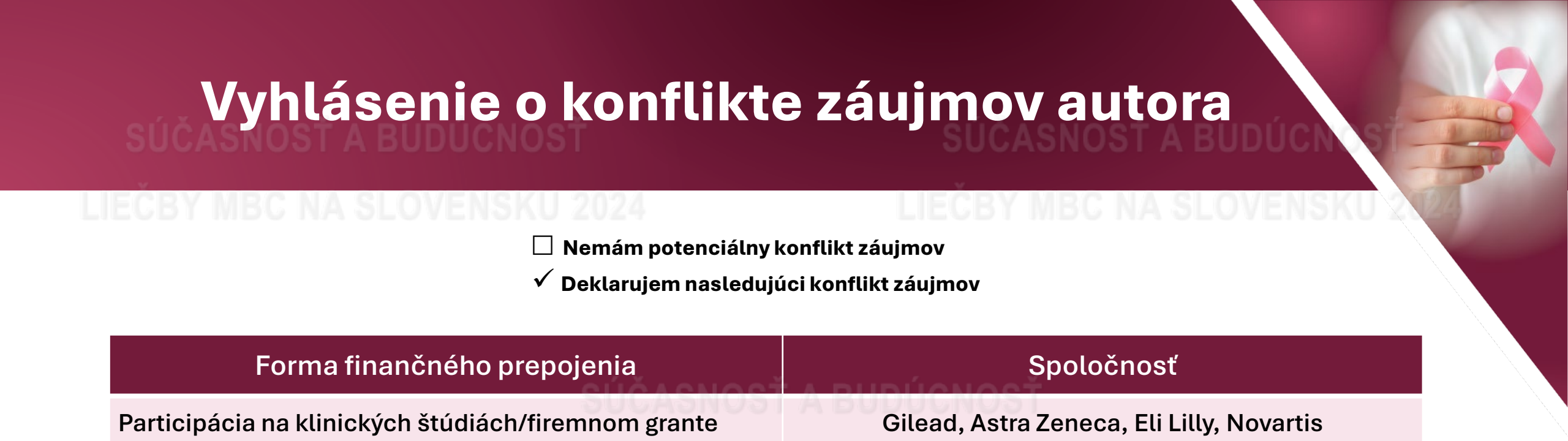
Systémová léčba mozkových metastáz karcinomu prsu

MUDr. Miloš Holánek, Ph.D.
Klinika komplexní onkologické péče
Masarykův onkologický ústav, Brno

Vyhlásenie o konflikte záujmov autora



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

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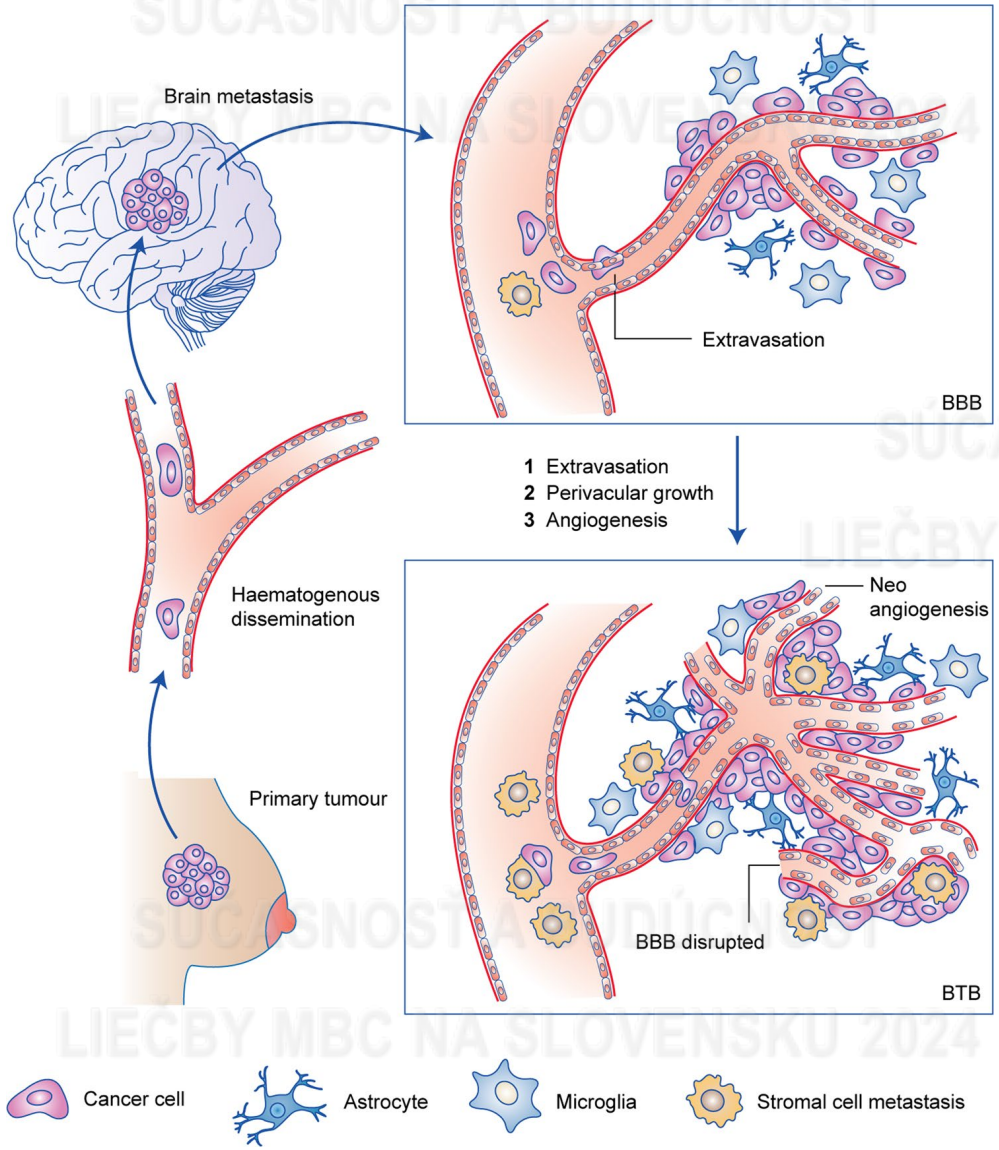
Úvod

- Časté místo MTS postižení u karcinomu prsu - **20 – 40 % pacientek**[1]
- **Špatná prognóza** onemocnění, limitace v léčebných možnostech
- Zvláště agresivní subtypy onemocnění
  - **HER2+** - 35 – 50 %, avšak lepší prognóza než HER2-[2]
  - **TNBC** – 35 %, špatná prognóza[3], častá asociace s *gBRCA*m, kde také vyšší riziko vzniku MTS CNS[4]
- **Kombinace více léčebných modalit!**
- Rozšiřující se možnosti systémové léčby → lepší efektivita → změna guidelines

Vznik mozkového MTS postižení[5,6]



- Epiteliálně mezenchymální tranzice
- Hematogenní diseminace
- Přechod do CNS přes HEB
- Mezenchymálně epiteliální tranzice
- Perivaskulární růst
- Stimulace mikroprostředí v CNS → proliferace MTS
- Poškození HEB

Úskalí léčby mozkových metastáz v klinické praxi

- Celkový stav pacienta, špatná prognóza MTS CNS
- Nutnost rychlého řešení
- Dlouhodobě absence dat vycházejících z klinických studií
  - mozkové MTS postižení jako vylučující kritérium k zařazení do klinických studií
- Omezená efektivita systémové léčby v CNS x NÚL terapie

Konzultace v rámci MDT!!!

Otázky z klinické praxe

- **Diagnostika – kdy a jaké vyšetření?**
  - Asymptomatické pacientky?
  - CT x MRI?
- **Pokud MTS CNS – volba optimálního léčebného postupu a sekvence?**
  - Operační výkon
  - Operační výkon → SBRT
  - SBRT
  - WBRT
  - Systémová léčba – volba konkrétního preparátu
  - V případě lokální terapie CNS a efektu extrakrtaniálně – pokračovat stejným preparátem nebo změna?
- **Dosažení nejlepšího léčebného efektu**
  - Celkový stav pacientky
  - Subtyp onemocnění
  - Rozsah postižení v CNS a extrakraniální
  - Předcházející léčba a její efekt
  - Jaké mám další možnosti léčby, sekvence
  - Preference pacientky

Možnosti systémové léčby MTS CNS

- Omezená účinnost klasických cytostatik, bez dopadu na OS
- Obtížné hodnocení vlastní efektivity – většina pacientů po RT
- Přechod přes HEB – lepší přechod po provedení RT (porušení HEB)
- Standardní cytostatika
  - Kapecitabin – cca 20 % RR v CNS
  - Temozolomid – do 5 % RR v CNS
  - Platinové deriváty +/- kapecitabin – cca 50 % RR v CNS
  - CBDCA + gemcitabin
- HER2+ karcinom – antiHER2 terapie, TKI, ADC – jednoznačný benefit v dlouhodobých parametrech léčebné odpovědi - **změna léčebného algoritmu**
- TNBC/luminální karcinomy – klinické studie, ADC, IO, HT+CDK4/6i…

Léčebná doporučení[7,8,9]

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Brain Metastases

NCCN Guidelines Index
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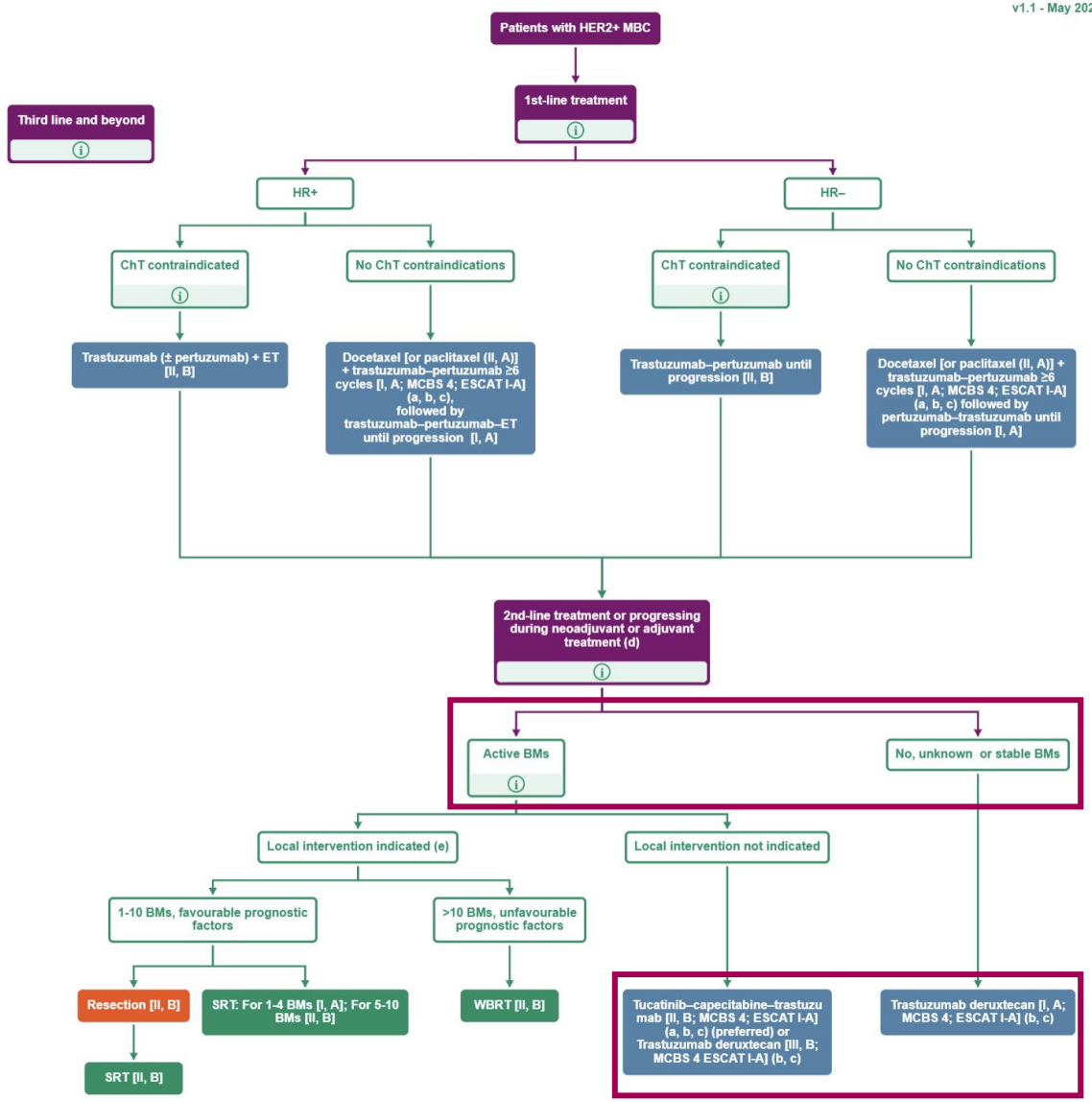
Note: All recommendations are category 2A unless otherwise indicated.



HER2+ karcinom prsu

- Trastuzumab proniká do CNS lépe při porušené HEB, např. po RT
  - udržovací terapie trastuzumabem po RT – kontrola intra a extrakraniálního postižení[10]
- Trastuzumab v monoterapii i kombinace s pertuzumabem – benefit v přežití u pacientek s MTS CNS[11,12]
- Změna preparátu při PD – oligometastatické postižení – prodloužení OS a PFS mimo CNS, ale nesignifikantně[13]
- T-DM1 – velká molekulová hmotnost, obtížný průnik do CNS, pouze při porušené HEB[14], nesignifikantní prodloužení OS v podskupině pacientek s MTS CNS (THERESA[15]), RR v CNS 25 %[16]
- Lapatinib – průnik do CNS, ORR V CNS a prodloužení PFS[17,18]
- **Tucatinib** – signifikantní ORR a OS benefit u pacientek s MTS CNS[19-22]
- **T-DXd** – signifikantní benefit u pacientek s MTS CNS – aktivní i neaktivní postižení – ESMO2024[23]

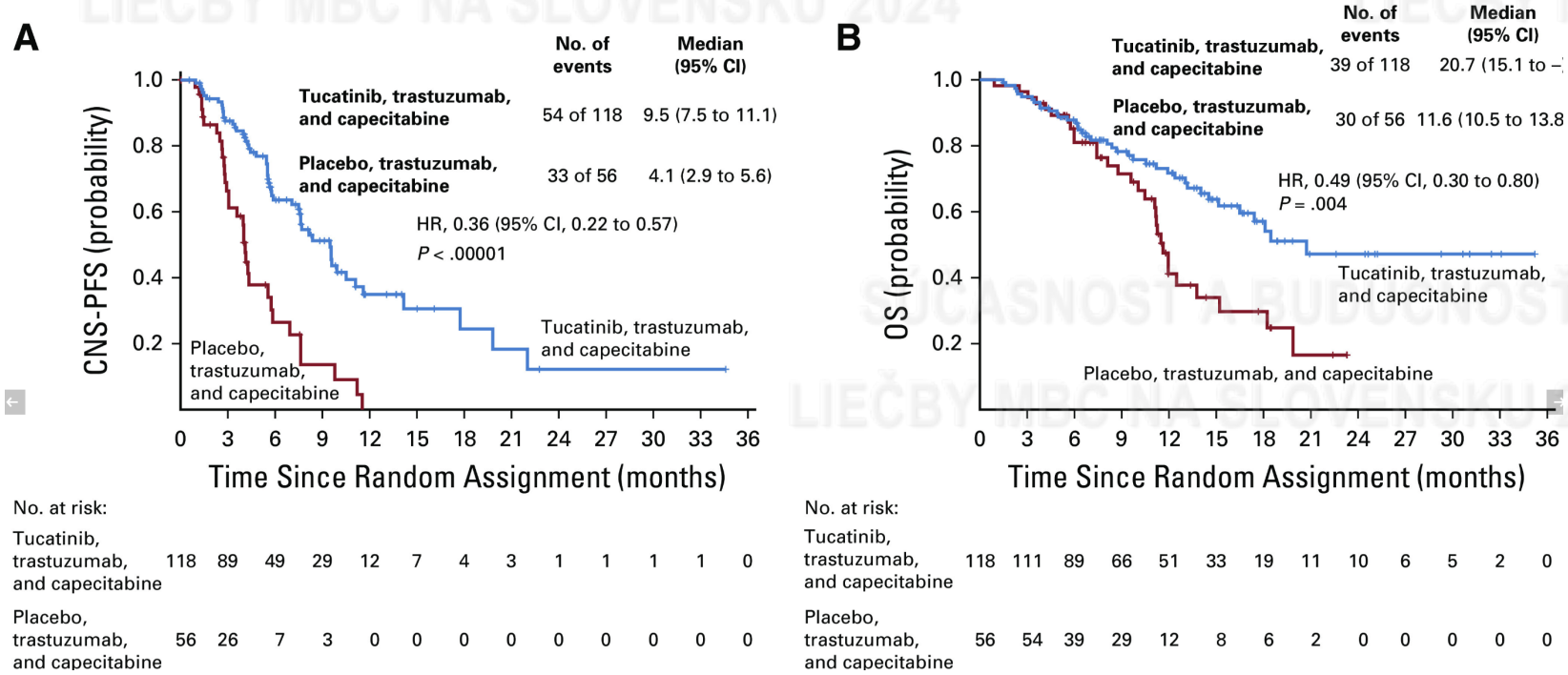
HER2+ karcinom prsu:

Přehled publikovaných studií pro MTS CNS[24]

Trastuzumab treatment beyond brain progression	Park et al[83]	Trastuzumab maintenance therapy in patients with BMs and extracranial responsive metastases	Significantly longer median OS (13.6 months [95% CI, 9.0 to 18.2]) compared with those without trastuzumab (5.5 months [95% CI, 0.0 to 13.6])
Dual HER2 blockade for breast cancer brain metastases	Bergen et al[84]	Trastuzumab + pertuzumab *v* other systemic therapies as first-line treatment after BM diagnosis	Significantly longer OS (44 months) compared with other HER2-targeted therapies, including trastuzumab alone, trastuzumab + lapatinib, lapatinib alone, T-DM1 (17 months), or no HER2-targeted therapy (3 months; *P* < .001)
Changing systemic therapy in relapsed breast cancer with BMs	Alhalabi et al[85]	Systemic therapy (not specified) changed when applicable per treating physician's discretion for patients with 1-3 BMs	Longer median OS (20.1 *v* 15.1 months) and extracranial PFS (14.9 *v* 11.6 months) in patients treated with changing systemic therapy
T-DM1 activity in HER2-positive breast cancer brain metastases	Bartsch et al[86]	T-DM1 *v* physician's choice	Median OS improvement with T-DM1 vs physician's choice in patients with baseline BMs (17.3 *v* 12.6 months)
TH3RESA trial comparing T-DM1 with physician's choice	Krop et al[87]	T-DM1 *v* physician's choice (subgroup analysis of patients with *v* without BM)	No statistically significant difference in OS between T-DM1 and physician's choice (95% CI, not provided)
T-DM1 and brain metastases in a real-world study	Fabi et al[135]	T-DM1	Median PFS and OS of 7 and 14 months in patients with BMs. OR in 24.5% (N = 13), with CR in 3.8% (N = 2) and stable disease in 30.1% (N = 16)
Lapatinib access into normal brain and metastases	Saleem et al[89]	Radiolabeled lapatinib and PET scans before and after oral lapatinib (8 days) in patients with or without 1 or more 1-cm BM	PET demonstrated lapatinib's ability to penetrate BBB and shrink HER2-positive BMs
Lapatinib in patients with brain metastases	Lin et al[90]	Lapatinib in patients with CNS progression after previous trastuzumab and cranial radiotherapy	Objective CNS response in 20% of patients
Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE)	Bachelot et al[91]	Lapatinib + capecitabine for previously untreated BMs	Patients with >50% reduction of CNS volume had longer median PFS than patients with <50% reduction (3.38 *v* 2.07 months)
CEREBEL study (EGF111438)	Pivot et al[136]	Trastuzumab + capecitabine *v* lapatinib + capecitabine in patients without baseline CNS metastases	No difference in the incidence of BMs between the two treatment groups
NEfERT-T trial	Awada et al[93]	Neratinib + trastuzumab *v* trastuzumab + paclitaxel	Comparable PFS between the two treatment groups, but symptomatic or progressive CNS recurrences were more frequent in the trastuzumab + paclitaxel group (17% *v* 8%, *P* = .002)
Phase III NALA trial	Saura et al[94]	Neratinib + capecitabine *v* lapatinib + capecitabine in patients with metastatic disease previously treated with ≥2 HER2-directed regimens	Superior PFS (HR, 0.76 [95% CI, 0.63 to 0.93]; *P* = .0059) and fewer interventions for CNS disease (cumulative incidence, 22.8% *v* 29.2%; *P* = .043) occurred with neratinib + capecitabine
Phase III ExteNET trial, Efficacy of neratinib in early-stage HER2-positive breast cancer	Holmes et al[95]	Neratinib *v* placebo 1 year after definitive primary surgery in women with early-stage disease who had completed neoadjuvant or adjuvant trastuzumab + chemotherapy	Improved 5-year distant disease-free survival of 7% and 10-year OS of 9.1% with neratinib in patients without pathologic CR to neoadjuvant treatment
Phase Ib study of tucatinib and T-DM1 in *ERBB2*-positive breast cancer	Borges et al[96]	Tucatinib + T-DM1 in patients with previously treated ERBB2/HER2-positive metastatic breast cancer, both with and without BMs	Acceptable toxicity and signs of antitumor activity. Median PFS of 6.7 months (95% CI, 4.1 to 10.2) and OR duration of 6.9 months (95% CI, 1.45 to 19.48) in patients with BMs
HER2CLIMB study	Murthy et al[97]	Tucatinib + capecitabine + trastuzumab	42% of patients with BMs achieved brain-specific OR
HER2CLIMB study comparing tucatinib with placebo	Murthy et al[98]	Tucatinib + capecitabine + trastuzumab *v* placebo + capecitabine + trastuzumab (subgroup analysis of patients with BMs at baseline)	Among patients with baseline BMs, those in the tucatinib combination group, vs the placebo combination group, had better median PFS (7.6 *v* 5.4 months), OS (HR, 0.58 [95% CI, 0.40 to 0.85]), and PFS (HR, 0.48 [95% CI, 0.34 to 0.69])
Trastuzumab deruxtecan in HER2-low advanced breast cancer	Modi et al[137]	Trastuzumab deruxtecan (DS8201)	PFS for patients with stable BMs was 18.1 months, and OS was not reached

T-DXd nebo kombinace tucatinib + kape + trastu?

Analýza HER2CLIMB[22]

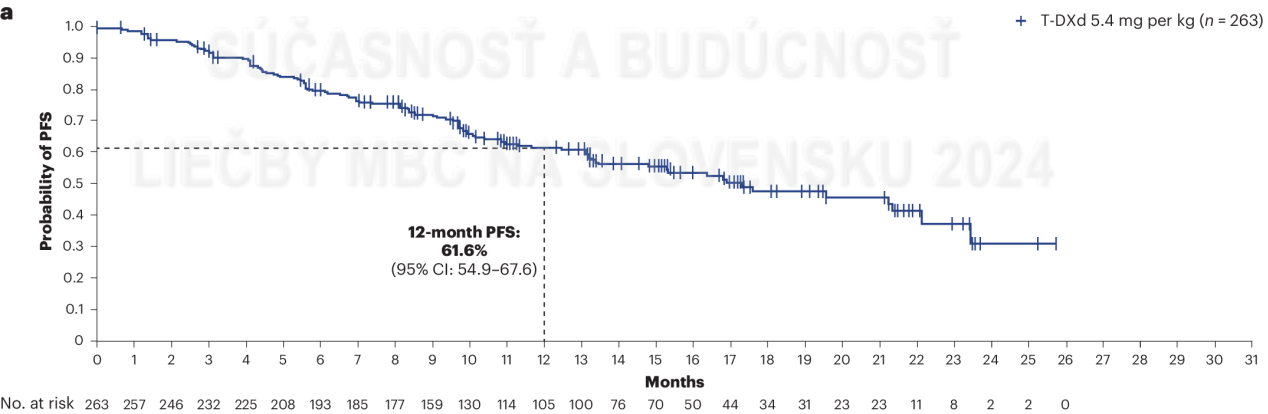


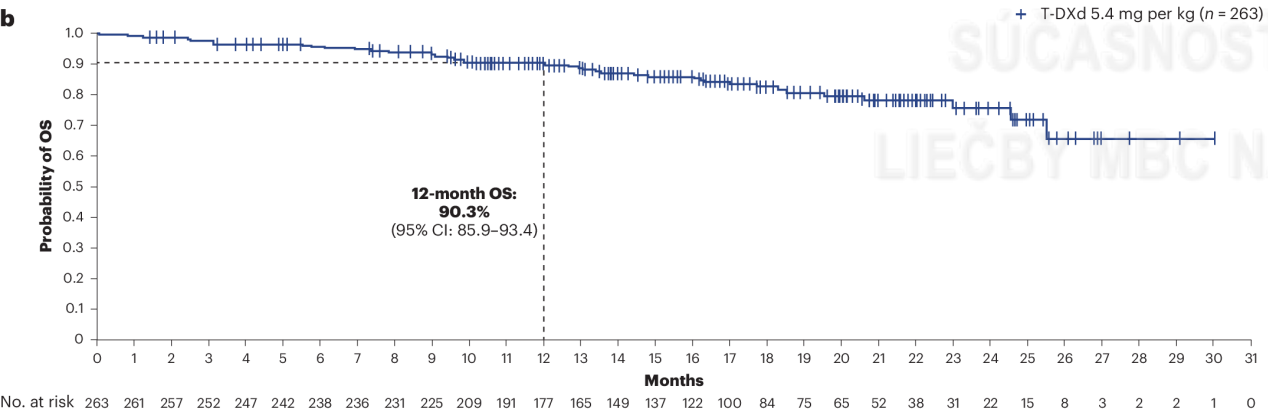
- Trastuzumab + kapecitabin +/- tucatinib
- **291**/612 pac. MTS CNS při zahájení léčby
- **174**/291 aktivní mozkové MTS

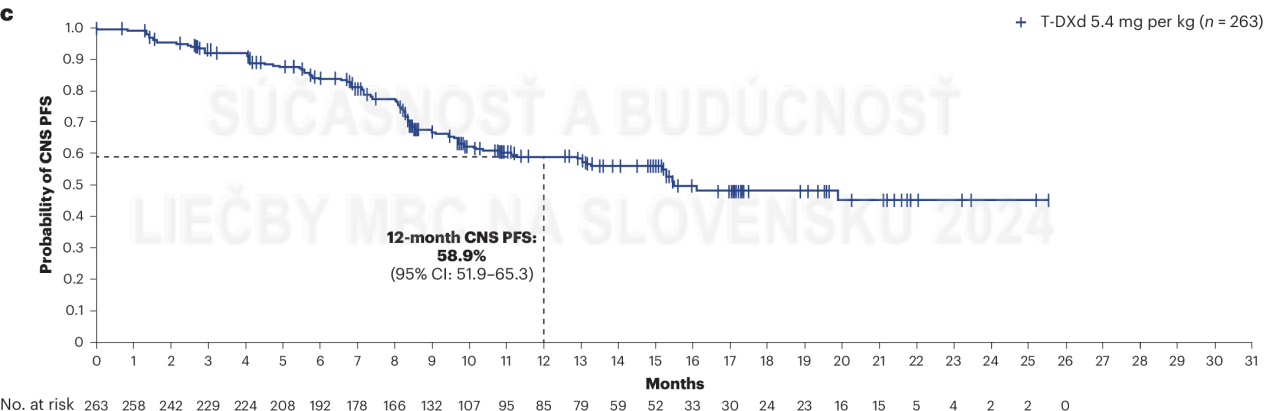
- The risk of intracranial progression or death was reduced by 68% (hazard ratio [HR], 0.32; 95% CI, 0.22 to 0.48; *P* < .0001)
- Median CNS-PFS was 9.9 months in the tucatinib arm versus 4.2 months in the control arm.
- Risk of death was reduced by 42% (OS HR, 0.58; 95% CI, 0.40 to 0.85; *P* = .005)
- Median OS was 18.1 versus 12.0 months
- ORR-IC was higher in the tucatinib arm (47.3%; 95% CI, 33.7% to 61.2%) versus the control arm (20.0%; 95% CI, 5.7% to 43.7%; *P* = .03)

T-DXd nebo kombinace tucatinib + kape + trastu?

Analýza DESTINY-Breast12[23]





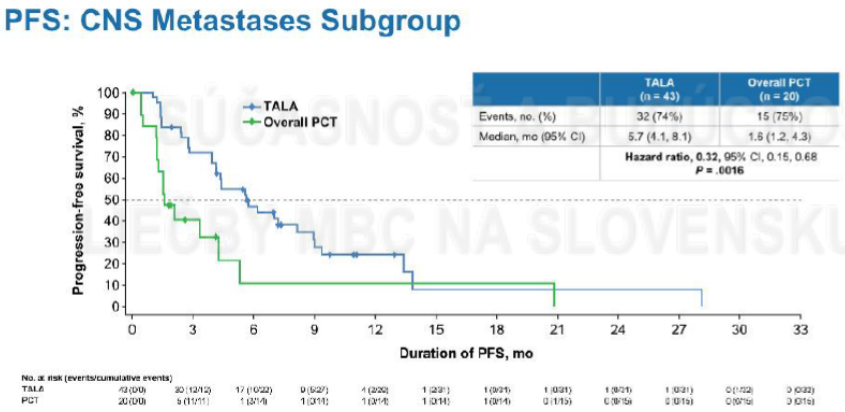


- DESTINY-Breast12
- Studie fáze 3b/4
- T-DXd u HER2+ MBC s MTS CNS
- Pacientky s MTS CNS (stable/active BMs (*n* = 263) a bez MTS CNS (*n* = 241))
- Předléčeny jednou nebo více liniemi anti-HER2 terapie
- Podáván T-DXd (5.4 mg/kg)
- Primární cíle PFS; BMs cohort a ORR (non-BMs cohort)
- Sekundární cíle: (CNS) PFS, ORR, time to second progression, CNS ORR (BMs cohort), incidence of new symptomatic CNS metastases (non-BMs cohort), time to progression, duration of response, overall survival and safety (both cohorts)
- **BMs cohort, 12-month PFS 61.6%** (95% confidence interval (CI): 54.9–67.6), a**12-month CNS PFS 58.9%** (95% CI: 51.9–65.3)
- Non-BMs cohort, ORR was 62.7% (95% CI: 56.5–68.8)
- Grade 3 or higher adverse events 51% (BMs cohort) and 49% (non-BMs cohort) of patients
- Investigator-reported interstitial lung disease/pneumonitis in 16% (grade ≥3: 3%) of patients with BMs and 13% (grade ≥3: 1%) of patients without BMs
- These data show **substantial and durable overall and intracranial activity for T-DXd, supporting its use in previously treated patients with HER2⁺ mBC irrespective of stable/active baseline BMs.**

Změna guidelines

HER2- / TNBC

- Luminální HER2- karcinomy - 14 % MTS CNS[25], TNBC – 35 %, špatná prognóza[3], častá asociace s *gBRCA*m, kde také vyšší riziko vzniku MTS CNS[4]
- Systémová terapie – HT, kombinace HT+CDK4/6i, CHT, ADC, **klinické studie!!!**
- Kombinace více modalit – lokální terapie MTS CNS, není takový benefit systémové terapie jako u HER2+
- Nejdříve snaha o lokální kontrolu (operace, SBRT) a následně systémová terapie – kontrola onemocnění v CNS a kontrola extrakraniálního postižení
- Luminální karcinomy
  - kombinace HT+CDK4/6i – abemaciklib proniká v dostatečné koncentraci do CNS, iCBR 24 %, koncentrace v CNS dostatečné na inhibici CDK4/6[26]
  - Elacestrant (*ESR1*m, SR+/HER2-), elacestrant + abemaciklib (ELECTRA) – probíhá
- Protinádorové konjugáty – T-DXd HER2-low a SG HER2 0 – při stabilizaci mozkového MTS postižení
- PARPi – intrakraniální aktivita talazoparibu (EMRACA[27]) a olaparibu (OlympiAD[28])



	Olaparib	Placebo
Distant recurrence	88 (8.9%)	136 (14.9%)
CNS recurrence	24 (2.8%)	38 (3.9%)
Distant recurrence (without CNS)	64 (6.9%)	98 (10.7%)

Závěr

- Mozkové postižení u karcinomu prsu je časté a je projevem agresivního chování onemocnění
- I přes pokroky v diagnostice a léčbě je spojeno se špatnou prognózou
- Výrazného pokroku bylo dosaženo u HER2+ onemocnění
- TNBC a HER2- onemocnění – lokální terapie a následně systémové léčba v případě stabilizace
- HER2+ onemocnění – preference systémové terapie, lokální terapie pouze některých ložisek?
- Pokud je plánována další léčba, v rámci lokální terapie jednoznačná preference operace/SBRT, odklon od WBRT
- **Diskuze v rámci MDT – multidisciplinární a individuální přístup**

Slovenská onkologická spoločnosť

SÚČASNOSŤ A BUDÚCNOSŤ
LIEČBY MBC NA SLOVENSKU

26.-27.09.2024 HOTEL PARTIZÁN, TÁLE

Ďakujem za pozornosť

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