Metastatický karcinom prsu

J. Novotný

Otázky k léčbě MBC

- Léčba pacientek s hormonálně dependentním MBC
- Léčba pacientek s hormonálně nedependentním MBC
- Léčba starých / mladých / těhotných
- Lokoreg. léčba ve stádiu generalizace
- Léčba pacientů s izolovaným relapsem
- Adjuvantní léčba po resekci recidivy

Strategie léčby

1) **Izolovaný relaps**

Solitární metastáza

- Je-li resekabilní, resekovat?
  - Ano, pokud jde o lokoregionální onemocnění
    - Po SE provedeme ME
    - Reexenterace axily
    - Další adjuvantní léčba? - viz. následující snímky

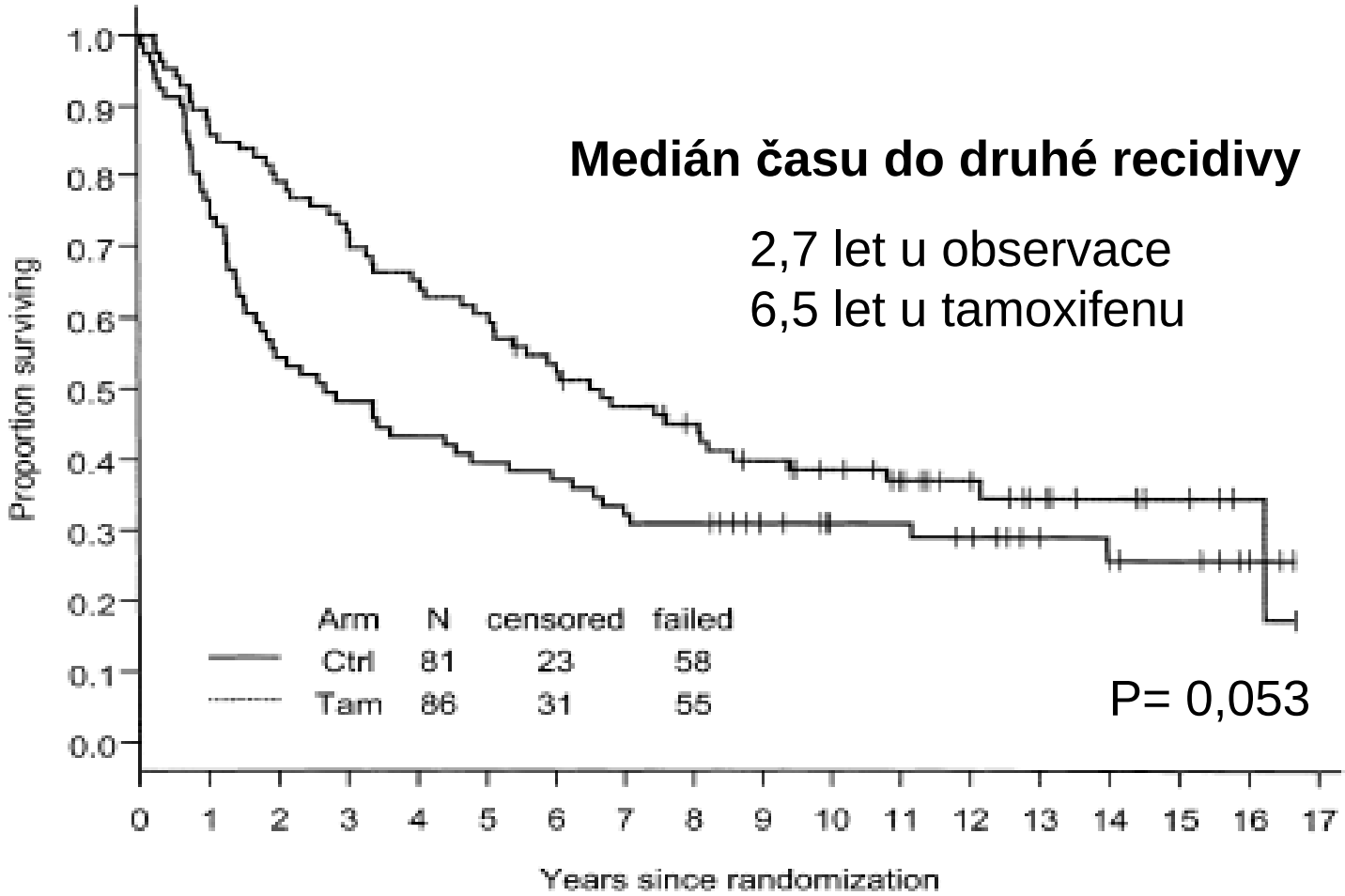
„It is not yet clear whether adding chemotherapy (anti-cancer drugs) to another treatment for a recurrence of breast cancer in the same area improves survival“

Solitární metastáza

- Je-li resekabilní, resekovat?
  - SAKK 23/82:
    - resekce recidivy → RT +/- tamoxifen u HR+ pacientek
    - Medián sledování 11,6 let
    - 187 pacientek

Ann Oncol 2003, 14, 1215

Solitární metastáza



Medián času do druhé recidivy

2,7 let u observace
6,5 let u tamoxifenu

P= 0,053

Figure 1. Disease-free survival by treatment. Ctrl, control; Tam, tamoxifen.

Ann Oncol 2003, 14, 1215

Solitární metastáza

- Je-li resekabilní, resekovat?
  - Ano, pokud jde o metastázu do plic
    - Počet výkonů malý, postižení je obvykle vícečetné
    - Často je solitární plicní nodul duplicitním nádorem
    - Pokud ale opravdu jde o metastázu ca prsu, pak chirurgický výkon s následnou adjuvantní léčbou vede k pětiletému přežívání kolem 36%, což je výsledek jinak nedosažitelný

Solitární metastáza

- Je-li resekabilní, resekovat?
  - Ano, pokud jde o metastázu do jater
    - Mělo by jít o onemocnění izolované na játra, nebo s další generalizací, ovšem ta musí být kontrolována (chirurgicky, medikamentózně)
    - Pětileté přežívání po resekci minimálně 20%
    - Prediktor dobrého efektu:
      - R0 resekce (proveditelná u více než 0% pacientů)
      - Chemosenzitivní onemocnění

Solitární metastáza

TABLE 1. Presentation of Studies Documenting Long-term Outcome Following Hepatic Resection in Patients With Breast Cancer Liver Metastases (Inclusion Criteria >5 Patients Reported)

Author	Year	Dates	n	Postoperative Mortality (%)	Median Survival (mo)	5-Year Survival (%)
Stehlin[24]	1974	—	9	—	28	11
Schneebaum[25]	1994	—	6	—	42	—
Lorenz[26]	1995	—	8	—	15	12
Elias[20]	1995	1986–1994	21	0	26	22
Raab[27]	1998	1983–1993	34	3	27	18
Seifert[22]	1999	1985–1997	15	0	57	18
Kondo[21]	2000	1990–1999	6	0	36	40
Maksan[28]	2000	1984–1998	9	0	—	51
Selzner[29]	2000	1987–1999	17	6	25	22
Yoshimoto[30]	2000	1985–1998	25	—	34	—
Pocard[12]	2001	1988–1999	65	0	47	46*
Carlini[31]	2002	1990–1999	17	0	53	46
Vlastos[13]	2004	1991–2002	31	0	63	61
Sakamoto[14]	2005	1985–2003	34	0	36	21
d'Annibale[32]	2005	1984–1999	18	0	32	30
Ercolani[33]	2005	1990–2003	21	0	42	25

*Four-year survival.

Solitární metastáza

- Je-li resekabilní, resekovat?
  - Ano, pokud jde o metastázu do mozku
    - Metastázy z karcinomu prsu tvoří 15-20% všech mozkových metastáz
    - Chirurgická léčba a/nebo stereotaktická radioterapie je indikována v případě předpokládané lepší prognózy pacienta – viz. následující snímek
    - CHT má stejný RR v CNS jako v jiných lokalizacích

Solitární metastáza

Table 2. Median survival duration according to RPA class for patients treated with WBRT [12]

RPA class	Clinical characteristics	Median survival
1	KPS score ≥70 *and* age <65 *and* controlled primary tumor *and* no extracranial metastases	7.1 months
2	KPS score ≥70 *and* age ≥65 *or* uncontrolled primary tumor *or* extracranial metastases	4.2 months
3	KPS score <70	2.3 months

Abbreviations: KPS, Karnofsky performance status; RPA, recursive partitioning analysis; WBRT, whole brain radiation therapy.

Databáze RTOG

Solitární metastáza

Table 3. Randomized studies comparing surgery or SRS plus WBRT versus WBRT alone

	Treatment group			Comparison group				
Intervention	***n* of brain metastases**	**Sample size**	**Median survival (months)**	**Intervention**	**Sample size**	**Median survival (months)**	***p*-value**	**Study**
WBRT with or without surgery								
Resection + WBRT	1	25	9.2	Biopsy + WBRT	23	3.4	<.01	Patchell et al. [64]
Resection + WBRT	1	32	10.0	WBRT	31	6.0	.04	Vecht et al. [81]
Resection + WBRT	1	41	5.6	WBRT	43	6.3	.24	Mintz et al. [80]
WBRT with or without SRS								
SRS + WBRT	≤3	167	6.5	WBRT	164	5.7	.13[a]	Andrews et al. [58]
SRS + WBRT	2–4	13	11	WBRT	14	7.5	.22	Kondziolka et al. [59]

[a]For a prespecified group of patients with a single brain metastasis, the median survival time was 6.5 versus 4.9 months, $p = .04$.

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy

Solitární metastáza

Table 4. Chemotherapeutic regimens with activity in brain metastases from breast cancer

Chemotherapy	New or recurrent	*n*	Complete response	Partial response	Objective response rate (%)	Median overall survival	Study
Cyclophosphamide, 5-FU, prednisone	New	52	NR	NR	52%	NR	Rosner et al. (1986) [108]
Cyclophosphamide, 5-FU, prednisone, MTX, vincristine	New	35	NR	NR	54%	NR	Rosner et al. (1986) [108]
MTX, vincristine, prednisone	New	7	NR	NR	43%	NR	Rosner et al. (1986) [108]
Cyclophosphamide, doxorubicin	New	6	NR	NR	17%	NR	Rosner et al. (1986) [108]
Cyclophosphamide, 5-FU, MTX[a]	New	22	NR	NR	59%	NR	Boogerd et al. (1992) [91]
Cisplatin, etoposide	New	22	5	7	55%	58 wks	Cocconi et al. (1992) [109]
	New	56	7	14	38%	31 wks	Franciosi et al. (1999) [94]
Topotecan	New	24	1	5	37%	6.25 mos	Oberhoff et al. (2001) [110]
	New	19[b]	0	0	0%	NR	Lorusso et al. (2006) [129]
Bendamustine	New	1	0	1	NA	NR	Zulkowski et al. (2002) [130]
TMZ, cisplatin	Recurrent	15	0	6	40%	5.5 mos[c]	Christodoulou et al. (2005) [112]
TMZ, capecitabine	Both[d]	24	1	3	18%	NR	Rivera et al. (2006) [113]
Capecitabine	Both	4[e]	0	4	NA	NR	Wang et al. (2001) [117] Siegelmann-Danieli et al. (2003) [116] Fabi et al. (2006) [114] Hikino et al. (2006) [115]
Methotrexate	NR	9	0	3	33%	25.4 wks	Lassman et al. (2006) [118]
Lapatinib	Recurrent	39	0	2	5%	NR	Lin et al. (2006) [120]

[a]Cyclophosphamide, 5-FU, and doxorubicin in two patients.
[b]Small cell lung cancer, non-small cell lung cancer, breast cancer, and colon cancer.
[c]For a total of 32 patients (15 breast cancer, 12 lung cancer, 3 melanoma, 2 other).
[d]14 new, 10 recurrent breast cancer patients with multiple brain metastases.
[e]Case reports.
Abbreviations: 5-FU, 5-fluorouracil; MTX, methotrexate; NA, not available; NR, not reported; TMZ, temozolomide.

Solitární metastáza

- Je-li resekabilní, resekovat?
  - Ne, pokud jde o metastázu do skeletu bez rizika postižení CNS

Strategie léčby

2) Systémový relaps

Strategie léčby

2) Systémový relaps

Je onemocnění:

- rychle progredující?

- DFI do jednoho roku?

- jsou postiženy dva či více orgánů?

Strategie léčby

2) Systémový relaps

Je onemocnění:

- rychle progredující?

- DFI do jednoho roku?

- jsou postiženy dva či více orgánů?

Neodkladně CHT bez ohledu na stav HR primárního nádoru

Hormonální terapie MBC

- 1. linie léčby pro MBC:
  - Nepředléčené pacientky
  - Předléčené tamoxifenem
  - Předléčené nesteroidním IA
  - Předléčené tamoxifenem a steroidním IA
  - Předléčené tamoxifenem a nesteroidním IA
- Exprese ERB-B2 ??

Hormonální terapie MBC

- 1. linie léčby pro MBC:
  - Nepředléčené pacientky
    - Obvykle z důvodu primární prezentace MBC
    - Cochrane review
      - 9 416 pacientek: 3. studie IA vs T
      - **Nezařazení IA do léčby zhoršuje přežívání s HR 0,89**
      - CB, RR, PFS stejné pro IA a T

Hormonální terapie MBC

	-	T	T – ns IA	ns IA	T – s IA
1. linie					
2. linie					
3. linie					
4. linie					

Hormonální terapie MBC

	-	T	T – nIA	nIA	T – sIA
1. linie	**T / nIA**				
2. linie					
3. linie					
4. linie					

Hormonální terapie MBC

- 1. linie léčby pro MBC:
  - Tamoxifenem předléčené pacientky
    - Obvykle první relaps MBC
    - Cochrane review
      - 3. studie IA vs G
      - **Nezařazení IA do léčby zhoršuje přežívání s HR 0,78**
      - CB, RR, PFS stejné pro IA a G

Hormonální terapie MBC

	-	T	T – nIA	nIA	T – sIA
1. linie	**T / nIA**	**nIA**			
2. linie					
3. linie					
4. linie					

Hormonální terapie MBC

- 1. linie léčby pro MBC:
  - nIA předléčené pacientky
    - Obvykle první relaps MBC
    - Fulv vs sIA:
      - EFECT: 693 pacientek po léčbě nIA a T
      - TTP 3,7 měsíce; CB 32,2% vs 31,5%
    - Tam po IA
      - Data chybí
      - RR 10,1%, CB 48,7% po sIA

Hormonální terapie MBC

	-	T	T – nIA	nIA	T – sIA
1. linie	**T / nIA**	**nIA**	**sIA / F**	**sIA / F**	
2. linie					
3. linie					
4. linie					

Hormonální terapie MBC

	-	T	T – nIA	nIA	T – sIA
1. linie	**T / nIA**	**nIA**	**sIA / F**	**sIA / F**	**F**
2. linie					
3. linie					
4. linie					

Hormonální terapie MBC

- 2. linie léčby pro MBC:
  - nIA předléčené pacientky
    - Obvykle první relaps MBC
    - Fulv vs sIA:
      - EFECT: 693 pacientek po léčbě nIA a T
      - TTP 3,7 měsíce; CB 32,2% vs 31,5%
    - Tam po IA
      - Data chybí
      - RR 10,1%, CB 48,7% po sIA

Hormonální terapie MBC

	-	T	T – nIA	nIA	T – sIA
1. linie	T / nIA	nIA	sIA / F	sIA / F	F
2. linie	sIA / F	sIA	F / sIA	F / sIA	T
3. linie					
4. linie					

Hormonální terapie MBC

	-	T	T – nIA	nIA	T – sIA
1. linie	T / nIA	nIA	sIA / F	sIA / F	F
2. linie	sIA / F	sIA	F / sIA	F / sIA	T
3. linie	G	F	G	T	G
4. linie					

Hormonální terapie MBC

	-	T	T – nIA	nIA	T – sIA
1. linie	T / nIA	nIA	sIA / F	sIA / F	F
2. linie	sIA / F	sIA	F / sIA	F / sIA	T
3. linie	G	F	G	T	G
4. linie	?	G	?	G	?

Chemoterapie MBC 1. linie

Reindukce antracyklinů?

Reindukce antracyklinů?

- 4 retrospektivní a 1 prospektivní RCT
  - účinnost paliativní léčby není ovlivněna předchozí adjuvantní léčbou, byl-li odstup od ukončení léčby delší než 1 rok

ANO

The Oncologist 2007, 12, 1288

Taxany v 1. linii paliativní CHT?

Table 1. Clinical Trials Included in the Meta-Analysis

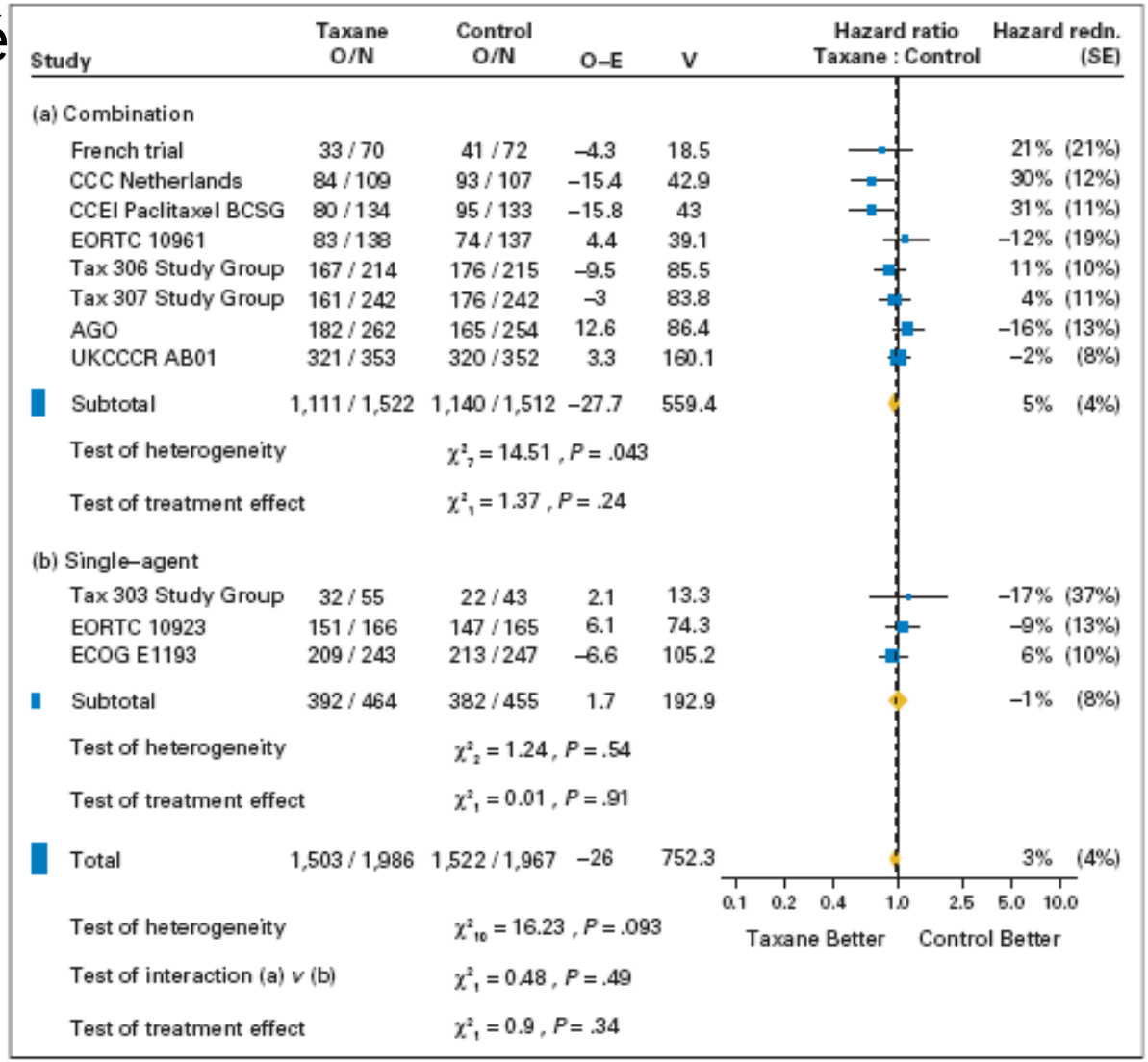
Trial	Dose, Control Arm (mg/m^2)	Dose, Taxane Arm (mg/m^2)	No. of Patients
Combination trials			3,034
Paclitaxel			1,763
UKCCCR AB01[1]	Epi 75 + Cyc 600	Epi 75 + Pac 200	705
AGO[2]	Epi 60 + Cyc 600	Epi 60 + Pac 175	516
EORTC 10961[3]	Dox 60 + Cyc 600	Dox 60 + Pac 175	275
CCEI Paclitaxel BCSG[4]	Flu 500 + Dox 50 + Cyc 500	Dox 50 + Pac 220	267
Docetaxel			1,271
Tax 307 Study Group[5]	Flu 500 + Dox 50 + Cyc 500	Doc 75 + Dox 50 + Cyc 500	484
Tax 306 Study Group[6]	Dox 60 + Cyc 600	Dox 50 + Doc 75	429
CCC Netherlands[7]	Flu 500 + Dox 50 + Cyc 500	Dox 50 + Doc 75	216
French trial[8]	Flu 500 + Epi 75 + Cyc 500	Epi 75 + Doc 75	142
Single-agent trials			919
Paclitaxel			821
ECOG E1193[9]	Dox 60	Pac 175	490
EORTC 10923[10]	Dox 75	Pac 200	331
Docetaxel			98
Tax 303 Study Group[11]	Dox 75	Doc 100	98
All trials			3,953

Abbreviations: dox, doxorubicin; cyc, cyclophosphamide; epi, epirubicin; flu, fluorouracil; pac, paclitaxel; doc, docetaxel; AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; UKCCCR, United Kingdom Committee for Cancer Clinical Research; AB, Advanced Breast; EORTC, European Organisation for Research and Treatment of Cancer; CCEI Paclitaxel BCSG, Central Europe and Israel Paclitaxel Breast Cancer Study Group; CCC, Comprehensive Cancer Centre; ECOG, Eastern Cooperative Oncology Group.

JCO 2008, 26, 1980-1986

Taxany v 1. linii paliativní CHT ?

Vliv taxanů na celkové přežívání pacientek s karcinomem prsu



Study	Taxane O/N	Control O/N	O–E	V	Hazard ratio Taxane : Control	Hazard redn. (SE)
(a) Combination						
French trial	33 / 70	41 / 72	–4.3	18.5		21% (21%)
CCC Netherlands	84 / 109	93 / 107	–15.4	42.9		30% (12%)
CCEI Paclitaxel BCSG	80 / 134	95 / 133	–15.8	43		31% (11%)
EORTC 10961	83 / 138	74 / 137	4.4	39.1		–12% (19%)
Tax 306 Study Group	167 / 214	176 / 215	–9.5	85.5		11% (10%)
Tax 307 Study Group	161 / 242	176 / 242	–3	83.8		4% (11%)
AGO	182 / 262	165 / 254	12.6	86.4		–16% (13%)
UKCCCR AB01	321 / 353	320 / 352	3.3	160.1		–2% (8%)
Subtotal	1,111 / 1,522	1,140 / 1,512	–27.7	559.4		5% (4%)
Test of heterogeneity		$\chi^2_7 = 14.51$, $P = .043$				
Test of treatment effect		$\chi^2_1 = 1.37$, $P = .24$				
(b) Single–agent						
Tax 303 Study Group	32 / 55	22 / 43	2.1	13.3		–17% (37%)
EORTC 10923	151 / 166	147 / 165	6.1	74.3		–9% (13%)
ECOG E1193	209 / 243	213 / 247	–6.6	105.2		6% (10%)
Subtotal	392 / 464	382 / 455	1.7	192.9		–1% (8%)
Test of heterogeneity		$\chi^2_2 = 1.24$, $P = .54$				
Test of treatment effect		$\chi^2_1 = 0.01$, $P = .91$				
Total	1,503 / 1,986	1,522 / 1,967	–26	752.3		3% (4%)
Test of heterogeneity		$\chi^2_{10} = 16.23$, $P = .093$				
Test of interaction (a) *v* (b)		$\chi^2_1 = 0.48$, $P = .49$				
Test of treatment effect		$\chi^2_1 = 0.9$, $P = .34$				

0.1 0.2 0.4 1.0 2.5 5.0 10.0

Taxane Better Control Better

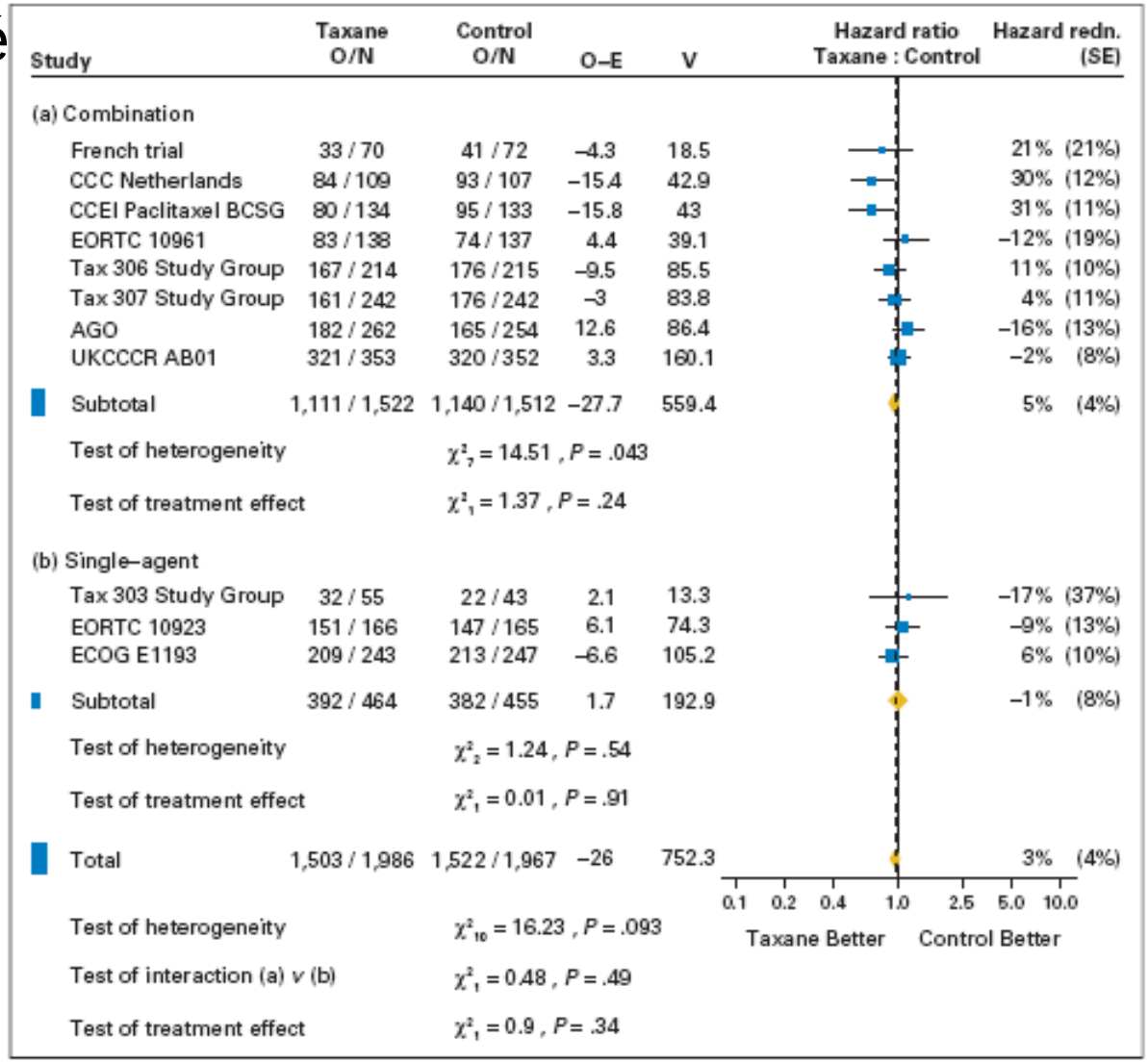
JCO 2008, 26, 1980-1986

Taxany v 1. linii paliativní CHT ?

Vliv taxanů na celkové přežívání pacientek s karcinomem prsu

Žádný pro kombinace

Žádný pro monoterapii

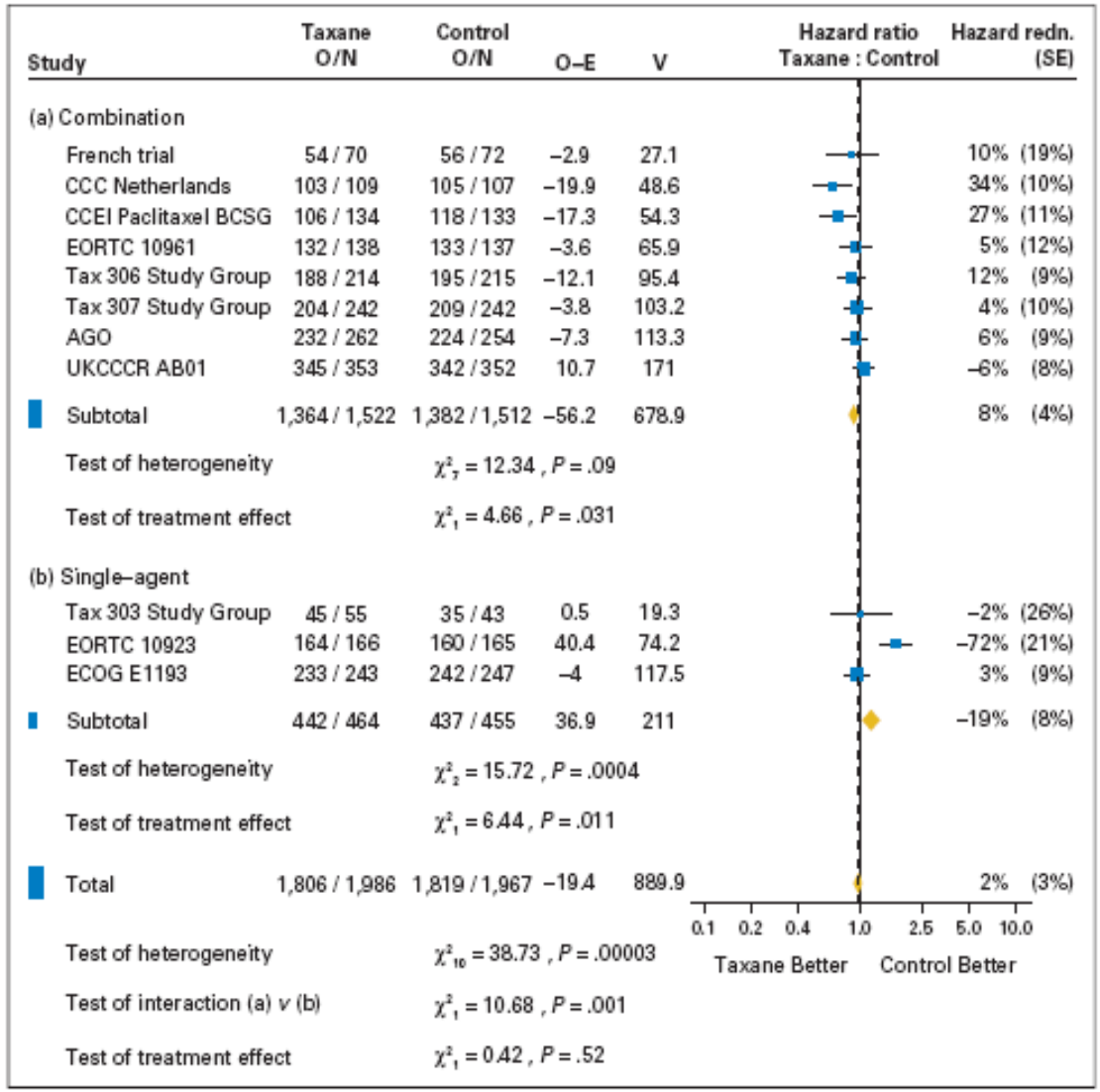


Study	Taxane O/N	Control O/N	O–E	V	Hazard ratio Taxane : Control	Hazard redn. (SE)
(a) Combination						
French trial	33 / 70	41 / 72	–4.3	18.5		21% (21%)
CCC Netherlands	84 / 109	93 / 107	–15.4	42.9		30% (12%)
CCEI Paclitaxel BCSG	80 / 134	95 / 133	–15.8	43		31% (11%)
EORTC 10961	83 / 138	74 / 137	4.4	39.1		–12% (19%)
Tax 306 Study Group	167 / 214	176 / 215	–9.5	85.5		11% (10%)
Tax 307 Study Group	161 / 242	176 / 242	–3	83.8		4% (11%)
AGO	182 / 262	165 / 254	12.6	86.4		–16% (13%)
UKCCCR AB01	321 / 353	320 / 352	3.3	160.1		–2% (8%)
Subtotal	1,111 / 1,522	1,140 / 1,512	–27.7	559.4		5% (4%)
Test of heterogeneity		$\chi^2_7 = 14.51$, $P = .043$				
Test of treatment effect		$\chi^2_1 = 1.37$, $P = .24$				
(b) Single–agent						
Tax 303 Study Group	32 / 55	22 / 43	2.1	13.3		–17% (37%)
EORTC 10923	151 / 166	147 / 165	6.1	74.3		–9% (13%)
ECOG E1193	209 / 243	213 / 247	–6.6	105.2		6% (10%)
Subtotal	392 / 464	382 / 455	1.7	192.9		–1% (8%)
Test of heterogeneity		$\chi^2_2 = 1.24$, $P = .54$				
Test of treatment effect		$\chi^2_1 = 0.01$, $P = .91$				
Total	1,503 / 1,986	1,522 / 1,967	–26	752.3		3% (4%)
Test of heterogeneity		$\chi^2_{10} = 16.23$, $P = .093$				
Test of interaction (a) *v* (b)		$\chi^2_1 = 0.48$, $P = .49$				
Test of treatment effect		$\chi^2_1 = 0.9$, $P = .34$				

JCO 2008, 26, 1980-1986

Taxany v 1. linii paliativní CHT ?

Vliv taxanů na čas do progrese u pacientek s karcinomem prsu

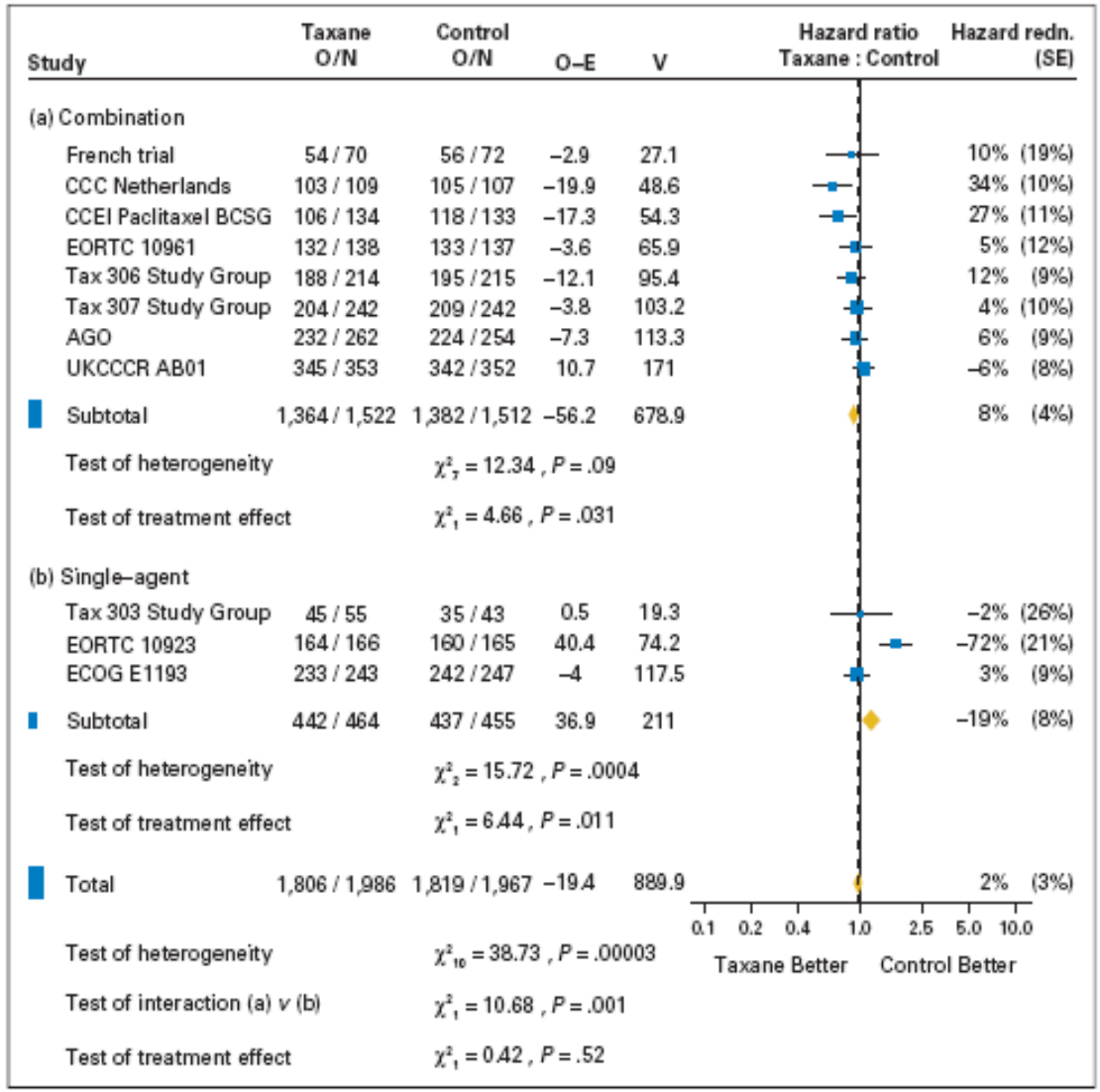


JCO 2008, 26, 1980-1986

Taxany v 1. linii paliativní CHT ?

Vliv taxanů na čas do progrese u pacientek s karcinomem prsu

Taxan lepší v kombinaci



Study	Taxane O/N	Control O/N	O–E	V	Hazard ratio Taxane : Control	Hazard redn. (SE)
(a) Combination						
French trial	54 / 70	56 / 72	–2.9	27.1		10% (19%)
CCC Netherlands	103 / 109	105 / 107	–19.9	48.6		34% (10%)
CCEI Paclitaxel BCSG	106 / 134	118 / 133	–17.3	54.3		27% (11%)
EORTC 10961	132 / 138	133 / 137	–3.6	65.9		5% (12%)
Tax 306 Study Group	188 / 214	195 / 215	–12.1	95.4		12% (9%)
Tax 307 Study Group	204 / 242	209 / 242	–3.8	103.2		4% (10%)
AGO	232 / 262	224 / 254	–7.3	113.3		6% (9%)
UKCCCR AB01	345 / 353	342 / 352	10.7	171		–6% (8%)
Subtotal	1,364 / 1,522	1,382 / 1,512	–56.2	678.9		8% (4%)
Test of heterogeneity		$\chi^2_7 = 12.34$, $P = .09$				
Test of treatment effect		$\chi^2_1 = 4.66$, $P = .031$				
(b) Single–agent						
Tax 303 Study Group	45 / 55	35 / 43	0.5	19.3		–2% (26%)
EORTC 10923	164 / 166	160 / 165	40.4	74.2		–72% (21%)
ECOG E1193	233 / 243	242 / 247	–4	117.5		3% (9%)
Subtotal	442 / 464	437 / 455	36.9	211		–19% (8%)
Test of heterogeneity		$\chi^2_2 = 15.72$, $P = .0004$				
Test of treatment effect		$\chi^2_1 = 6.44$, $P = .011$				
Total	1,806 / 1,986	1,819 / 1,967	–19.4	889.9		2% (3%)
Test of heterogeneity		$\chi^2_{10} = 38.73$, $P = .00003$				
Test of interaction (a) *v* (b)		$\chi^2_1 = 10.68$, $P = .001$				
Test of treatment effect		$\chi^2_1 = 0.42$, $P = .52$				

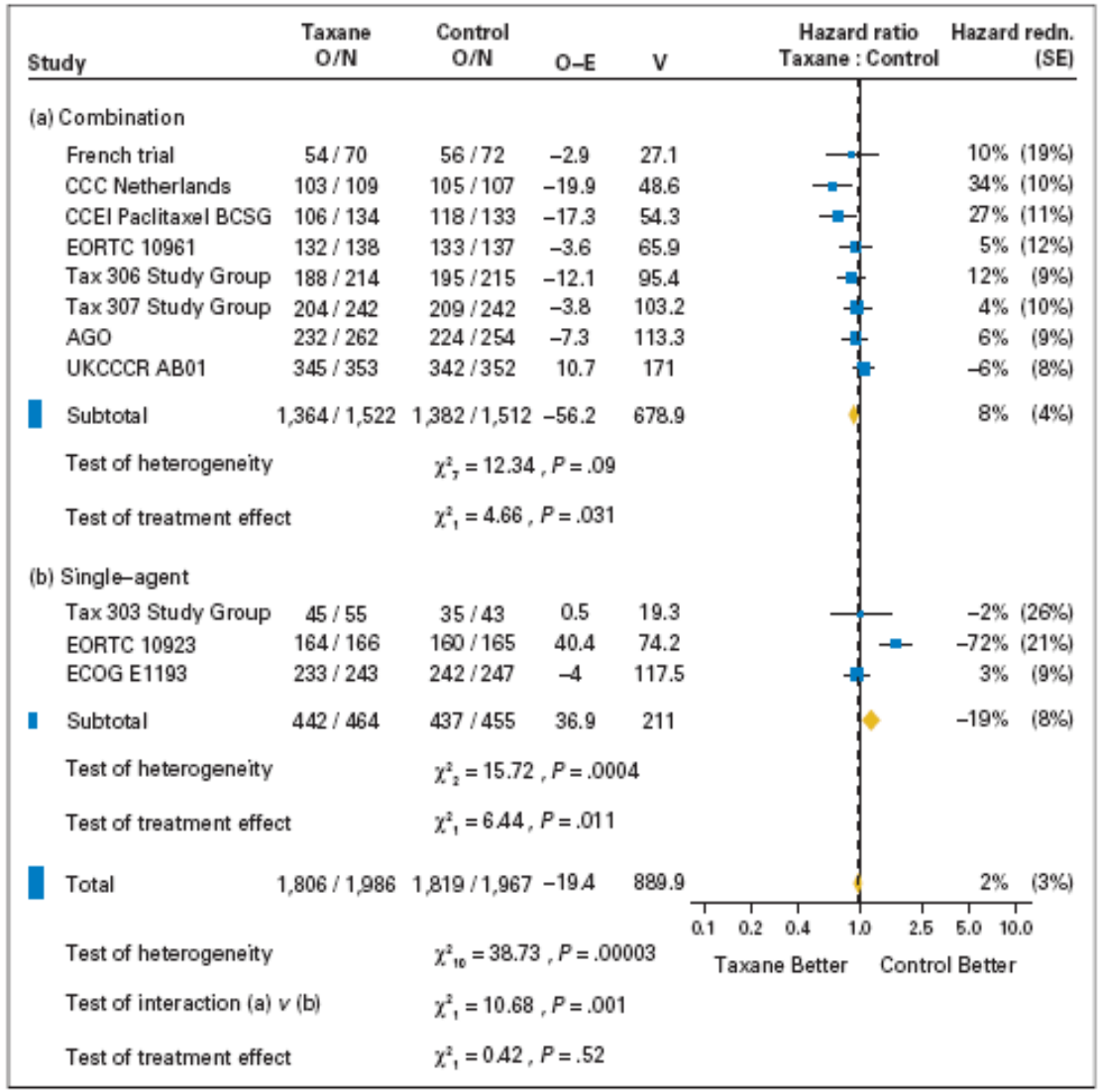
JCO 2008, 26, 1980-1986

Taxany v 1. linii paliativní CHT ?

Vliv taxanů na čas do progrese u pacientek s karcinomem prsu

Taxan lepší v kombinaci

Taxan horší v monoterapii



Study	Taxane O/N	Control O/N	O–E	V	Hazard ratio Taxane : Control	Hazard redn. (SE)
(a) Combination						
French trial	54 / 70	56 / 72	–2.9	27.1		10% (19%)
CCC Netherlands	103 / 109	105 / 107	–19.9	48.6		34% (10%)
CCEI Paclitaxel BCSG	106 / 134	118 / 133	–17.3	54.3		27% (11%)
EORTC 10961	132 / 138	133 / 137	–3.6	65.9		5% (12%)
Tax 306 Study Group	188 / 214	195 / 215	–12.1	95.4		12% (9%)
Tax 307 Study Group	204 / 242	209 / 242	–3.8	103.2		4% (10%)
AGO	232 / 262	224 / 254	–7.3	113.3		6% (9%)
UKCCCR AB01	345 / 353	342 / 352	10.7	171		–6% (8%)
Subtotal	1,364 / 1,522	1,382 / 1,512	–56.2	678.9		8% (4%)
Test of heterogeneity		$\chi^2_7 = 12.34$, $P = .09$				
Test of treatment effect		$\chi^2_1 = 4.66$, $P = .031$				
(b) Single–agent						
Tax 303 Study Group	45 / 55	35 / 43	0.5	19.3		–2% (26%)
EORTC 10923	164 / 166	160 / 165	40.4	74.2		–72% (21%)
ECOG E1193	233 / 243	242 / 247	–4	117.5		3% (9%)
Subtotal	442 / 464	437 / 455	36.9	211		–19% (8%)
Test of heterogeneity		$\chi^2_2 = 15.72$, $P = .0004$				
Test of treatment effect		$\chi^2_1 = 6.44$, $P = .011$				
Total	1,806 / 1,986	1,819 / 1,967	–19.4	889.9		2% (3%)
Test of heterogeneity		$\chi^2_{10} = 38.73$, $P = .00003$				
Test of interaction (a) *v* (b)		$\chi^2_1 = 10.68$, $P = .001$				
Test of treatment effect		$\chi^2_1 = 0.42$, $P = .52$				

JCO 2008, 26, 1980-1986

Taxany v 1. linii paliativní CHT ?

Vliv taxanů na RR u pacientek s karcinomem prsu	Taxany	Kontrola
Taxan lepší v kombinaci	57% (10%)	46% (6%)
Taxan lepší v monoterapii	38%	33%

JCO 2008, 26, 1980-1986

Taxany v 1. linii paliativní CHT ?

- **Ano, ale**
  - výhradně v kombinaci
  - u pacientek s rychle progredujícím onemocněním
  - u pacientek s dobrým výkonnostním stavem

HER2-

Reindukce antracyklinu

Taxan + antracyklin (G)

VNR + kapecitabin

Chemoterapie 2. linie

Table 4. Regimens evaluated in phase III clinical trials dedicated to anthracyclines-pretreated metastatic breast cancer patients

Study	*n* of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)
Nabholtz et al. (1999) [25][b]	392	First and second	Docetaxel (D) versus vinblastine + mitomycin (VM)	11.4,[a] 8.7	4.7,[a] 2.7	30,[a] 11.6
Sjöström et al. (1999) [26][b]	283	First and second	Docetaxel (D) versus methotrexate + fluorouracil (MF)	10.4, 11.1	6.3,[a] 3.0	42,[a] 21
O' Shaughnessy et al. (2002) [35][b]	511	First, second, and third	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30
Albain et al. (2004) [39][b,c]	529	First	Gemcitabine + paclitaxel (GP) versus paclitaxel (P)	18.5,[a] 15.8	5.4,[a] 3.5	39,[a] 25
Jones et al. (2005) [27][b]	449	First and second	Paclitaxel (P) versus docetaxel (D)	12.7, 15.4[a]	3.6, 5.7[a]	25, 31
Chan et al. (2005) [40][b,c]	305	First and second	Gemcitabine + docetaxel (GD) versus capecitabine + docetaxel (CD)	NR	8.1, 8.1	32, 32
Miller et al. (2005) [54][b,c]	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 6.1	28.2,[a] 14.2
Beslija et al. (2006) [37][c]	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,[a] 19	9.3,[a] 7.7	68,[a] 40
Soto et al. (2006) [38][c]	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]
Mavroudis et al. (2006) [47][c]	114	Salvage	Gemcitabine + vinorelbine (GV) versus capecitabine (C)	NR	3.7, 5.8	25.8, 24.1
Pacilio et al. (2006) [10]	51	First	Epirubicin + docetaxel (ED) versus docetaxel (D)	18, 21	9, 11	72, 79
Batist et al. (2006) [22]	68	First	Nonpegylated liposomal doxorubicin (M) versus doxorubicin (A) (pooled data)	16, 15	4.5, 3.4	31,[a] 11
Martin et al. (2007) [46]	252	First, second, and third	Gemcitabine + vinorelbine (GV) versus vinorelbine (V)	NR	6.3,[a] 4.1	37,[a] 25
Vahdat et al. (2007) [49][b,c]	752	Second and third	Ixabepilone + capecitabine (IC) versus capecitabine (C)	NR	5.8,[a] 4.2	35,[a] 14

Table 4. Regimens evaluated in phase III clinical trials dedicated to anthracyclines-pretreated metastatic breast cancer patients

Study	*n* of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)
Nabholtz et al. (1999) [25][b]	392	First and second	Docetaxel (D) versus vinblastine + mitomycin (VM)	11.4,[a] 8.7	4.7,[a] 2.7	30,[a] 11.6
Sjöström et al. (1999) [26][b]	283	First and second	Docetaxel (D) versus methotrexate + fluorouracil (MF)	10.4, 11.1	6.3,[a] 3.0	42,[a] 21
O' Shaughnessy et al. (2002) [35][b]	511	First, second, and third	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30
Albain et al. (2004) [39][b,c]	529	First	Gemcitabine + paclitaxel (GP) versus paclitaxel (P)	18.5,[a] 15.8	5.4,[a] 3.5	39,[a] 25
Jones et al. (2005) [27][b]	449	First and second	Paclitaxel (P) versus docetaxel (D)	12.7, 15.4[a]	3.6, 5.7[a]	25, 31
Chan et al. (2005) [40][b,c]	305	First and second	Gemcitabine + docetaxel (GD) versus capecitabine + docetaxel (CD)	NR	8.1, 8.1	32, 32
Miller et al. (2005) [54][b,c]	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 6.1	28.2,[a] 14.2
Beslija et al. (2006) [37][c]	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,[a] 19	9.3,[a] 7.7	68,[a] 40
Soto et al. (2006) [38][c]	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]
Mavroudis et al. (2006) [47][c]	114	Salvage	Gemcitabine + vinorelbine (GV) versus capecitabine (C)	NR	3.7, 5.8	25.8, 24.1
Pacilio et al. (2006) [10]	51	First	Epirubicin + docetaxel (ED) versus docetaxel (D)	18, 21	9, 11	72, 79
Batist et al. (2006) [22]	68	First	Nonpegylated liposomal doxorubicin (M) versus doxorubicin (A) (pooled data)	16, 15	4.5, 3.4	31,[a] 11
Martin et al. (2007) [46]	252	First, second, and third	Gemcitabine + vinorelbine (GV) versus vinorelbine (V)	NR	6.3,[a] 4.1	37,[a] 25
Vahdat et al. (2007) [49][b,c]	752	Second and third	Ixabepilone + capecitabine (IC) versus capecitabine (C)	NR	5.8,[a] 4.2	35,[a] 14

Table 4. Regimens evaluated in phase III clinical trials dedicated to anthracyclines-pretreated metastatic breast cancer patients

Study	*n* of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)
Nabholtz et al. (1999) [25][b]	392	First and second	Docetaxel (D) versus vinblastine + mitomycin (VM)	11.4,[a] 8.7	4.7,[a] 2.7	30,[a] 11.6
Sjöström et al. (1999) [26][b]	283	First and second	Docetaxel (D) versus methotrexate + fluorouracil (MF)	10.4, 11.1	6.3,[a] 3.0	42,[a] 21
O' Shaughnessy et al. (2002) [35][b]	511	First, second, and third	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30
Albain et al. (2004) [39][b,c]	529	First	Gemcitabine + paclitaxel (GP) versus paclitaxel (P)	18.5,[a] 15.8	5.4,[a] 3.5	39,[a] 25
Jones et al. (2005) [27][b]	449	First and second	Paclitaxel (P) versus docetaxel (D)	12.7, 15.4[a]	3.6, 5.7[a]	25, 31
Chan et al. (2005) [40][b,c]	305	First and second	Gemcitabine + docetaxel (GD) versus capecitabine + docetaxel (CD)	NR	8.1, 8.1	32, 32
Miller et al. (2005) [54][b,c]	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 6.1	28.2,[a] 14.2
Beslija et al. (2006) [37][c]	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,[a] 19	9.3,[a] 7.7	68,[a] 40
Soto et al. (2006) [38][c]	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]
Mavroudis et al. (2006) [47][c]	114	Salvage	Gemcitabine + vinorelbine (GV) versus capecitabine (C)	NR	3.7, 5.8	25.8, 24.1
Pacilio et al. (2006) [10]	51	First	Epirubicin + docetaxel (ED) versus docetaxel (D)	18, 21	9, 11	72, 79
Batist et al. (2006) [22]	68	First	Nonpegylated liposomal doxorubicin (M) versus doxorubicin (A) (pooled data)	16, 15	4.5, 3.4	31,[a] 11
Martin et al. (2007) [46]	252	First, second, and third	Gemcitabine + vinorelbine (GV) versus vinorelbine (V)	NR	6.3,[a] 4.1	37,[a] 25
Vahdat et al. (2007) [49][b,c]	752	Second and third	Ixabepilone + capecitabine (IC) versus capecitabine (C)	NR	5.8,[a] 4.2	35,[a] 14

Table 4. Regimens evaluated in phase III clinical trials dedicated to anthracyclines-pretreated metastatic breast cancer patients

Study	*n* of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)
Nabholtz et al. (1999) [25][b]	392	First and second	Docetaxel (D) versus vinblastine + mitomycin (VM)	11.4,[a] 8.7	4.7,[a] 2.7	30,[a] 11.6
Sjöström et al. (1999) [26][b]	283	First and second	Docetaxel (D) versus methotrexate + fluorouracil (MF)	10.4, 11.1	6.3,[a] 3.0	42,[a] 21
O' Shaughnessy et al. (2002) [35][b]	511	First, second, and third	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30
Albain et al. (2004) [39][b,c]	529	First	Gemcitabine + paclitaxel (GP) versus paclitaxel (P)	18.5,[a] 15.8	5.4,[a] 3.5	39,[a] 25
Jones et al. (2005) [27][b]	449	First and second	Paclitaxel (P) versus docetaxel (D)	12.7, 15.4[a]	3.6, 5.7[a]	25, 31
Chan et al. (2005) [40][b,c]	305	First and second	Gemcitabine + docetaxel (GD) versus capecitabine + docetaxel (CD)	NR	8.1, 8.1	32, 32
Miller et al. (2005) [54][b,c]	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 6.1	28.2,[a] 14.2
Beslija et al. (2006) [37][c]	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,[a] 19	9.3,[a] 7.7	68,[a] 40
Soto et al. (2006) [38][c]	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]
Mavroudis et al. (2006) [47][c]	114	Salvage	Gemcitabine + vinorelbine (GV) versus capecitabine (C)	NR	3.7, 5.8	25.8, 24.1
Pacilio et al. (2006) [10]	51	First	Epirubicin + docetaxel (ED) versus docetaxel (D)	18, 21	9, 11	72, 79
Batist et al. (2006) [22]	68	First	Nonpegylated liposomal doxorubicin (M) versus doxorubicin (A) (pooled data)	16, 15	4.5, 3.4	31,[a] 11
Martin et al. (2007) [46]	252	First, second, and third	Gemcitabine + vinorelbine (GV) versus vinorelbine (V)	NR	6.3,[a] 4.1	37,[a] 25
Vahdat et al. (2007) [49][b,c]	752	Second and third	Ixabepilone + capecitabine (IC) versus capecitabine (C)	NR	5.8,[a] 4.2	35,[a] 14

Table 4. Regimens evaluated in phase III clinical trials dedicated to anthracyclines-pretreated metastatic breast cancer patients

Study	*n* of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)
Nabholtz et al. (1999) [25][b]	392	First and second	Docetaxel (D) versus vinblastine + mitomycin (VM)	11.4,[a] 8.7	4.7,[a] 2.7	30,[a] 11.6
Sjöström et al. (1999) [26][b]	283	First and second	Docetaxel (D) versus methotrexate + fluorouracil (MF)	10.4, 11.1	6.3,[a] 3.0	42,[a] 21
O' Shaughnessy et al. (2002) [35][b]	511	First, second, and third	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30
Albain et al. (2004) [39][b,c]	529	First	Gemcitabine + paclitaxel (GP) versus paclitaxel (P)	18.5,[a] 15.8	5.4,[a] 3.5	39,[a] 25
Jones et al. (2005) [27][b]	449	First and second	Paclitaxel (P) versus docetaxel (D)	12.7, 15.4[a]	3.6, 5.7[a]	25, 31
Chan et al. (2005) [40][b,c]	305	First and second	Gemcitabine + docetaxel (GD) versus capecitabine + docetaxel (CD)	NR	8.1, 8.1	32, 32
Miller et al. (2005) [54][b,c]	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 6.1	28.2,[a] 14.2
Beslija et al. (2006) [37][c]	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,[a] 19	9.3,[a] 7.7	68,[a] 40
Soto et al. (2006) [38][c]	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]
Mavroudis et al. (2006) [47][c]	114	Salvage	Gemcitabine + vinorelbine (GV) versus capecitabine (C)	NR	3.7, 5.8	25.8, 24.1
Pacilio et al. (2006) [10]	51	First	Epirubicin + docetaxel (ED) versus docetaxel (D)	18, 21	9, 11	72, 79
Batist et al. (2006) [22]	68	First	Nonpegylated liposomal doxorubicin (M) versus doxorubicin (A) (pooled data)	16, 15	4.5, 3.4	31,[a] 11
Martin et al. (2007) [46]	252	First and second	Gemcitabine + vinorelbine (GV) versus vinorelbine (V)	NR	6.3,[a] 4.1	37,[a] 25
Vahdat et al. (2007) [49][b,c]	752	Second and third	Ixabepilone + capecitabine (IC) versus capecitabine (C)	NR	5.8,[a] 4.2	35,[a] 14

Table 4. Regimens evaluated in phase III clinical trials dedicated to anthracyclines-pretreated metastatic breast cancer patients

Study	*n* of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)
Nabholtz et al. (1999) [25][b]	392	First and second	Docetaxel (D) versus vinblastine + mitomycin (VM)	11.4,[a] 8.7	4.7,[a] 2.7	30,[a] 11.6
Sjöström et al. (1999) [26][b]	283	First and second	Docetaxel (D) versus methotrexate + fluorouracil (MF)	10.4, 11.1	6.3,[a] 3.0	42,[a] 21
O' Shaughnessy et al. (2002) [35][b]	511	First, second a	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30
Albain et al. (2004) [39][b,c]	529	First	Gemcitabine + paclitaxel (GP) versus paclitaxel (P)	18.5,[a] 15.8	5.4,[a] 3.5	39,[a] 25
Jones et al. (2005) [27][b]	449	First and second	Paclitaxel (P) versus docetaxel (D)	12.7, 15.4[a]	3.6, 5.7[a]	25, 31
Chan et al. (2005) [40][b,c]	305	First and second	Gemcitabine + docetaxel (GD) versus capecitabine + docetaxel (CD)	NR	8.1, 8.1	32, 32
Miller et al. (2005) [54][b,c]	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 6.1	28.2,[a] 14.2
Beslija et al. (2006) [37][c]	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,[a] 19	9.3,[a] 7.7	68,[a] 40
Soto et al. (2006) [38][c]	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]
Mavroudis et al. (2006) [47][c]	114	Salvage	Gemcitabine + vinorelbine (GV) versus capecitabine (C)	NR	3.7, 5.8	25.8, 24.1
Pacilio et al. (2006) [10]	51	First	Epirubicin + docetaxel (ED) versus docetaxel (D)	18, 21	9, 11	72, 79
Batist et al. (2006) [22]	68	First	Nonpegylated liposomal doxorubicin (M) versus doxorubicin (A) (pooled data)	16, 15	4.5, 3.4	31,[a] 11
Martin et al. (2007) [46]	252	F a	Gemcitabine + vinorelbine (GV) versus vinorelbine (V)	NR	6.3,[a] 4.1	37,[a] 25
Vahdat et al. (2007) [49][b,c]	752	Second and third	Ixabepilone + capecitabine (IC) versus capecitabine (C)	NR	5.8,[a] 4.2	35,[a] 14

HER2-

Reindukce antracyklinu

Taxan + antracyklin (G)

VNR + kapecitabin

HER2-

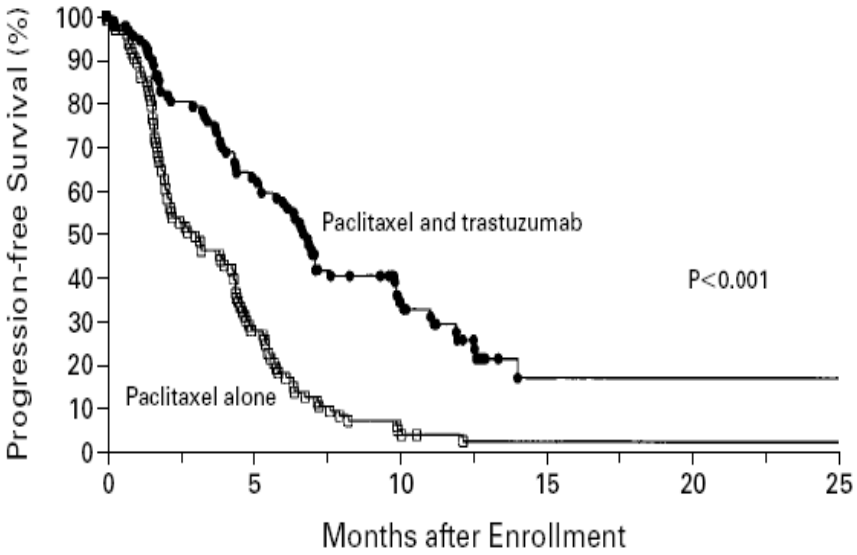
Reindukce antracyklinu	Taxan + antracyklin (G)	VNR + kapecitabin
GD / GP	GV / CV	GD / GP / CV

CV / I / LA / CBDCA / CDDP

Léčba HER2+ MBC

- Léčbu zahajujeme vždy kombinací trastuzumabu s cytostatikem:

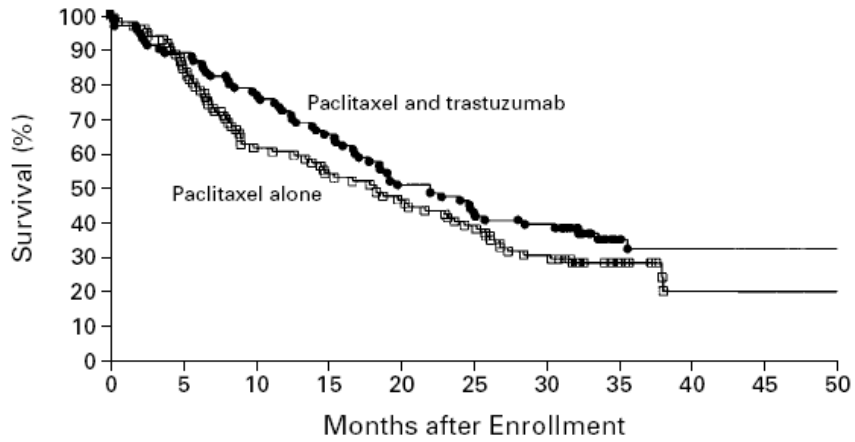
Trastuzumab u HER2+ MBC



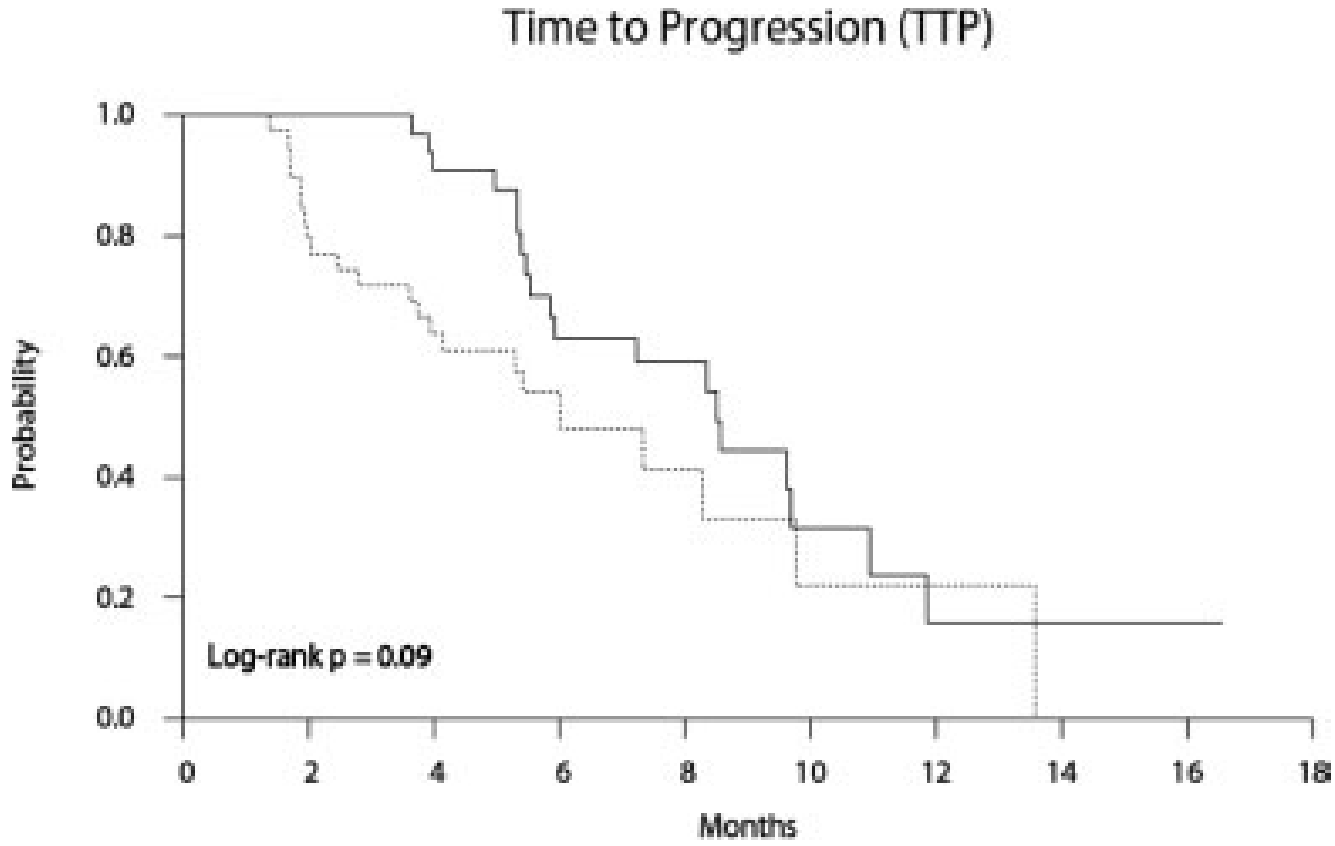
TTP 7,4 vs 4,6 M

MS 25,1 vs 20,3, p=0,046

RR 50 vs 32 %, p<0,001



Trastuzumab u HER2+ MBC



RR VT vs DT: 51 vs 40 %, ns

Trastuzumab u HER2+ MBC

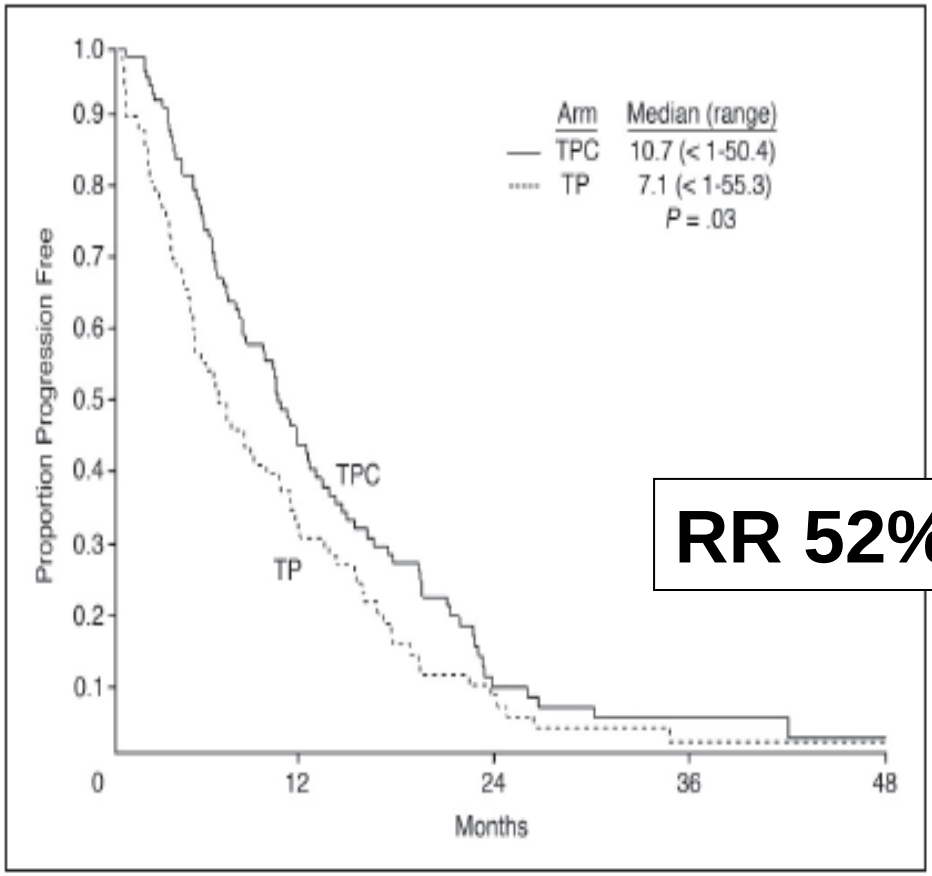


Fig 1. Kaplan-Meier plot of progression-free survival by treatment arm (hazard ratio = 0.66; 95% CI, 0.50 to 0.73). TPC, trastuzumab, paclitaxel, and carboplatin; TP, trastuzumab and paclitaxel.

RR 52% vs 36%, p=0,04

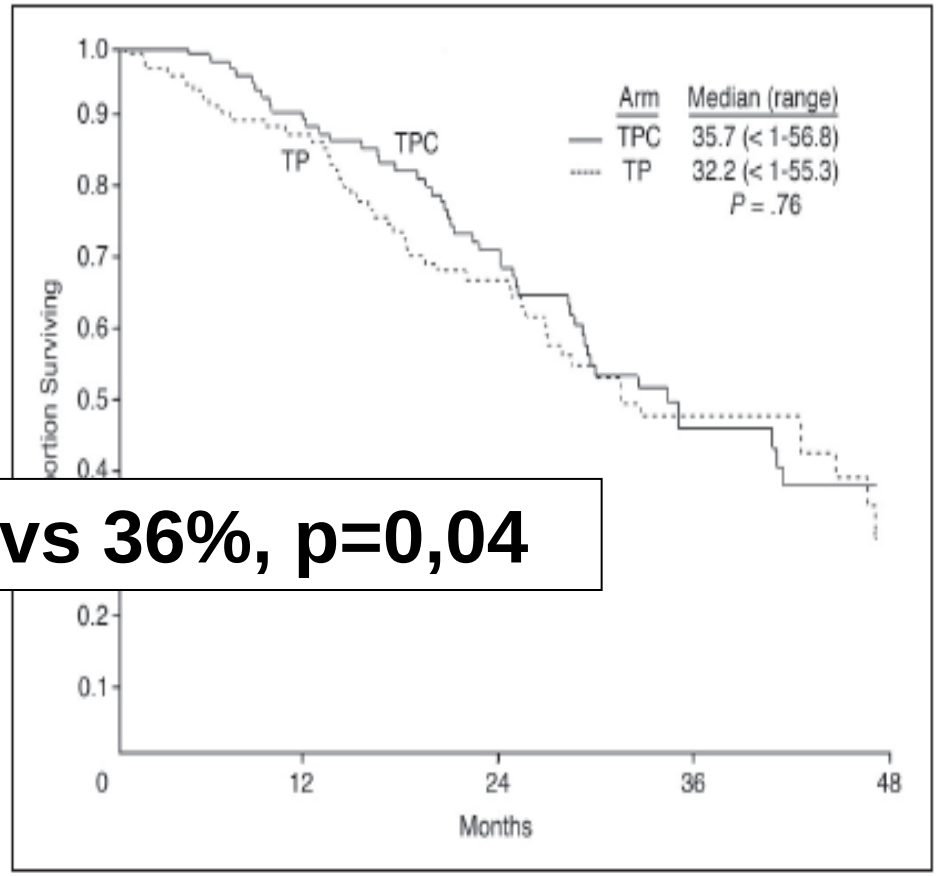
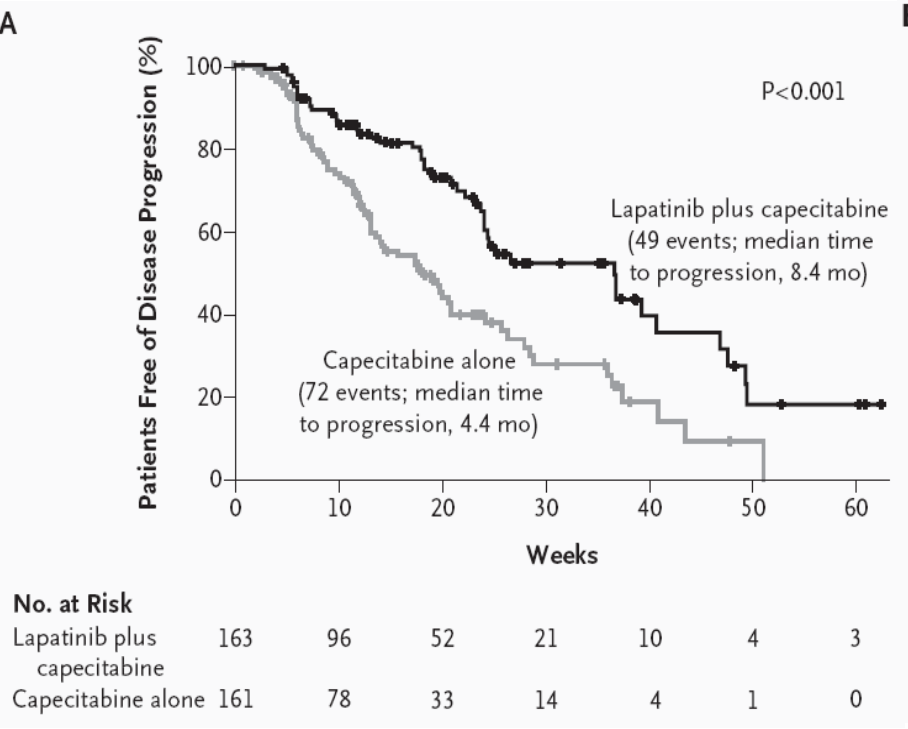
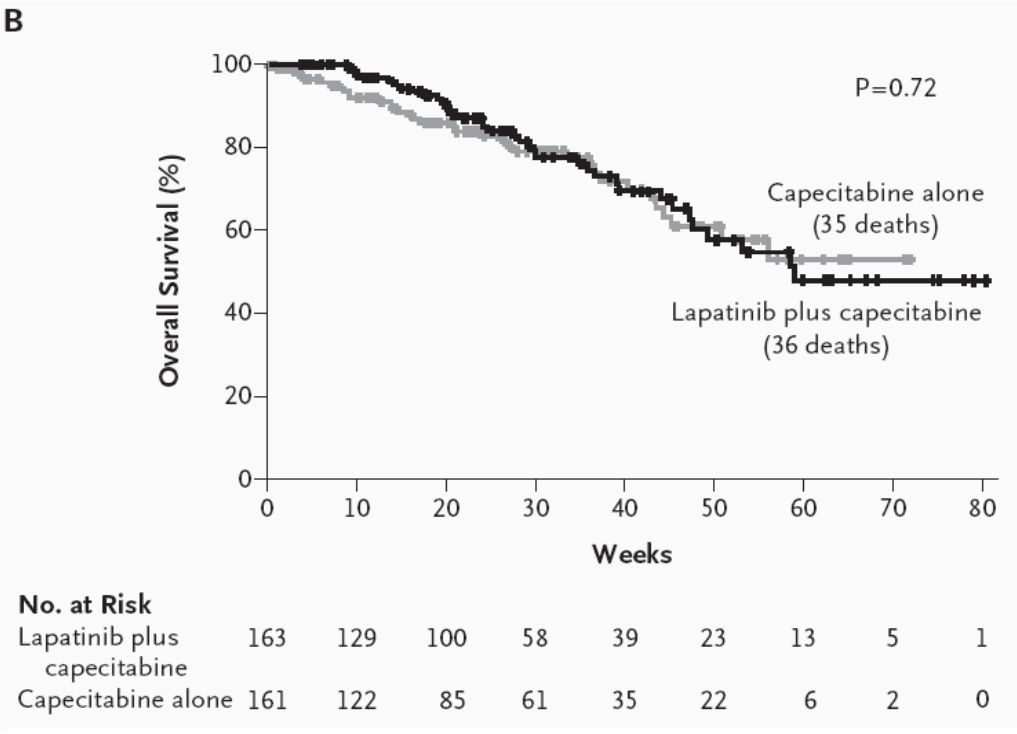


Fig 3. Kaplan-Meier plot of overall survival time by treatment arm (hazard ratio = 0.90; 95% CI, 0.88 to 0.92). TPC, trastuzumab, paclitaxel, and carboplatin; TP, trastuzumab and paclitaxel.

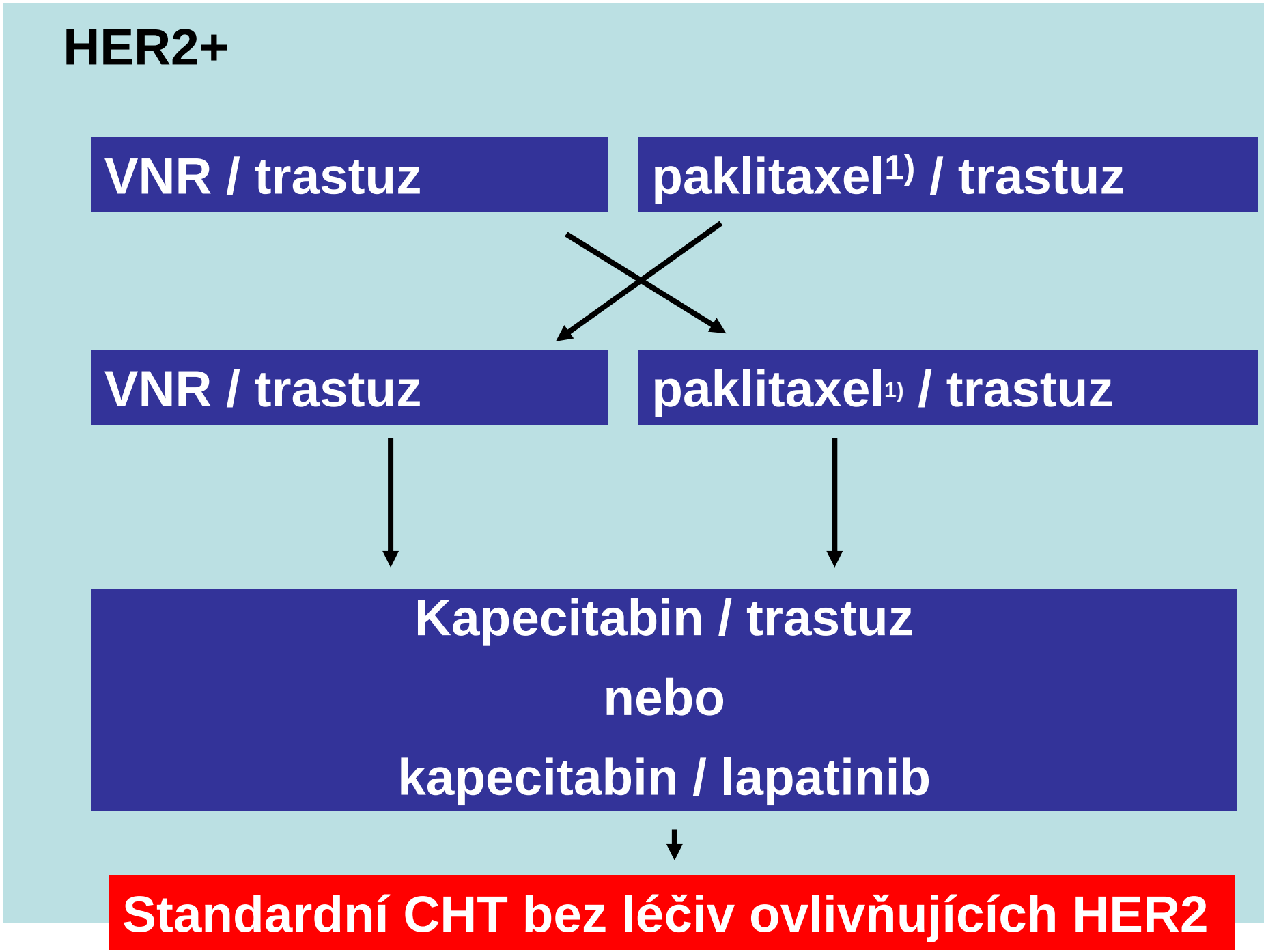
Lapatinib u HER2+ MBC





Pacienti předléčení antracykliny a taxany

RR 22 vs 14 %, ns


HER2+
VNR / trastuz
paklitaxel1) / trastuz
VNR / trastuz
paklitaxel1) / trastuz
Kapecitabin / trastuz
nebo
kapecitabin / lapatinib
Standardní CHT bez léčiv ovlivňujících HER2

Nové postupy

Epothilony

	NCI-0229 [10] (*n* = 37)	CA-163009 [9] (*n* = 49)	CA-163010 [11] (*n* = 61)	CA-163081 [12] (*n* = 113)[a]
Schedule of ixabepilone	6 mg/m^2 for five consecutive days every 3 weeks	40 mg/m^2 every 3 weeks	40 mg/m^2 every 3 weeks	40 mg/m^2 every 3 weeks
Patient population	Taxane resistance	Anthracyline resistance	Taxane resistance	Anthracycline, taxane, and capecitabine resistance
Outcome, *n* (%)				
CR	1 (3)	–	–	–
PR	7 (19)	6 (12)	27 (42)	13 (12)
SD	13 (35)	20 (41)	23 (35)	57 (50)
PD	16 (43)	23 (47)	13 (20)	36 (32)

DLT: neutropenie, slabost

Alternativní formy doxorubicinu

- viz. zvláštní prezetace

Bisfosfonáty

TABLE 3
Skeletal Morbidity Rate for All Skeletal-Related Events (Not Including Hypercalcemia) by Treatment Group for Patients in the Lytic Subgroup versus Patients in the Nonlytic Subgroup

	Skeletal morbidity rate (mean ± SD)			
Subgroup	Zoledronic acid 4 mg (n = 378)	P value[a]	Zoledronic acid 8/4 mg (n = 364)	Pamidronate (n = 388)
Lytic	1.16 ± 2.32	0.008	1.28 ± 2.02	2.36 ± 7.16
Nonlytic	0.81 ± 1.69	0.904	0.86 ± 2.07	0.97 ± 2.47
Total	0.98 ± 2.04	0.073	1.06 ± 2.06	1.55 ± 5.03

MBC u starých osob

- Chemoterapie:
  - Má stejný efekt jako u mladších žen
  - Vhodné volit monoterapii, weekly režimy:
    - Taxany
    - Vinorelbin
    - Lipozomální formy antracyklinů

Děkuji za pozornost