Effects of capecitabine as part of neo-/adjuvant chemotherapy

A meta-analysis of individual patient data from 12 randomized trials including 15,457 patients

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Disclosures

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Background

Study	Eligibility	Design	Patients (N)
GeparQuattro	>cT2 (>1cm sono), HR pos, cN+ or pNsln+	EC-D vs EC-DX vs EC-D-X	1421
ICE	>65 years of age, pN+ or pN- and pT>2 or G2/3, HRneg	X vs nil	1358
FinXX	pN+, >pT2 and pN0 and PR neg	D-CEF vs DX-CEX	1495
USON 01062	pN+, >pT2 and pN0, >pT1b and HR neg,	AC-D vs AC-DX	2611
NSABP B-40	cT2-3, cN0, 1 and 2a	D-AC vs DX-AC +/- Bev	773
CreateX	>ypTis, HER2 neg	Post NAC X vs nil	887
CIBOMA/2004-01	pN+ or -, tumor >1cm, TNBC	X vs nil post adjuvant	876
GeparTRIO	>cT2	DAC-DAC vs DAC-NX	622
GAIN	pN+	EPC vs EC-PX	3023
ICE II	>65years, pT1/2, pN0/1, Her2 pos, HR neg, G3 and any pT3/4 and pN2/3	EC or CMF vs NabPX	391
CALGB 49907	>=65 years of age, tumor size >1cm	AC or CMF vs X	616
GEICAM/2003-10	pT1-3, pN1-3	EC-D vs ED-X	1384

E: Epirubicin, C: Cyclophosphamide, D: Docetaxel, X: Capecitabine, F: Fluorouracil, A: Doxorubicin, Bev: Bevacizumab, N: Vinorelbine, P: Paclitaxel, M: Methotrexate, NabP: Nab-paclitaxel, NAC: neoadjuvant chemotherapy

Objectives

Primary objective

- Examine the effect of capecitabine on disease-free survival (DFS)

Secondary objectives

- Examine the effect of capecitabine on overall survival (OS)
- Test if there is an interaction of occurrence of capecitabine-specific toxicity and treatment effect

Methods

- **Bivariable Cox proportional hazards models including log-normal distributed random effects of studies were used for analyses of DFS and OS**
- **The interaction with toxicity was assessed by including an interaction term into Cox proportional hazards models**
- **Subsets:**
  - Capecitabine (X) is given **in addition** to another therapy
  - Capecitabine (X) is given **instead** of another therapy
- **Median follow up was 79 months (0-193)**

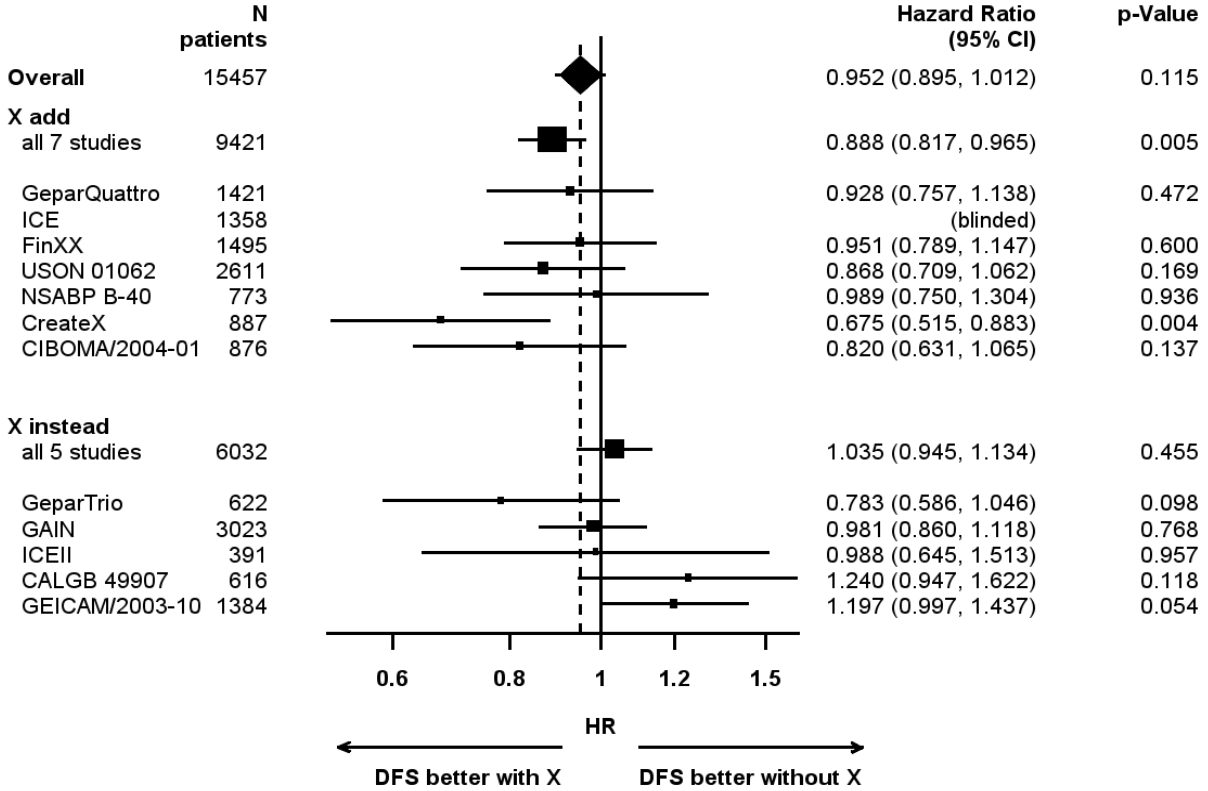
Number of Patients and Events Overall and per Study

Study		With Capecitabine		Without Capecitabine		Overall	
		Patients (N)	DFS events	Patients (N)	DFS events	Patients (N)	DFS events
X addition	GeparQuattro	950	263	471	143	1421	406
	ICE	677	blinded	681	blinded	1358	387
	FinXX	751	217	744	221	1495	438
	USON 01062	1307	177	1304	200	2611	377
	NSABP B-40	389	101	384	100	773	201
	CreateX	443	91	444	126	887	217
	CIBOMA/2004-01	448	105	428	120	876	225
X instead	GeparTRIO	301	83	321	102	622	185
	GAIN	1509	447	1514	452	3023	899
	ICE II	193	40	198	45	391	85
	CALGB 49907	300	110	316	103	616	213
	GEICAM/2003-10	715	254	669	210	1384	464
Overall		7983		7474		15457	4097

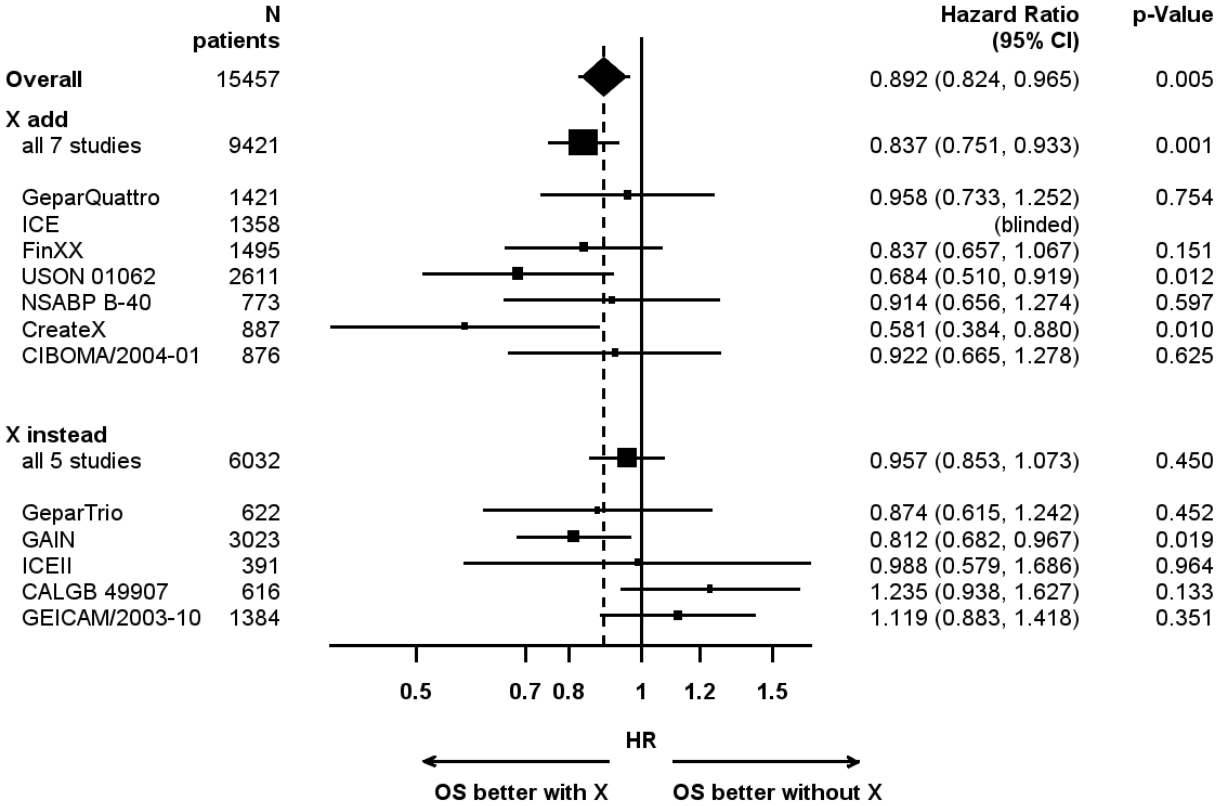
Patient and Tumor Characteristics

		With Capecitabine N(%) N=7983	Without Capecitabine N(%) N=7474	Overall N(%) N=15457
Age at primary diagnosis	Median, (Min,Max), yrs	53 (20, 90)	53 (20, 88)	53 (20,90)
Tumor stage	T0/1	2217 (28.2)	2273 (30.9)	4490 (29.5)
	T2	4463 (56.7)	4086 (55.5)	8549 (56.1)
	T3/4	1191 (15.0)	1000 (13.6)	2191 (14,4)
Nodal stage	N0	2093 (26.6)	1823 (24.8)	3916 (25.7)
	N+	5772 (73.5)	5526 (75.2)	11298 (74.3)
Hormone receptor status	Both ER and PgR negative	2525 (31.7)	2351 (31.6)	4876 (31.7)
	ER and/or PgR positive	5436 (68.3)	5091 (68.4)	10527 (68.3)
HER2 status	negative	6491 (85.2)	6032 (84.7)	12523 (85.0)
	positive	1128 (14.8)	1090 (15.3)	2218 (15.0)
Tumor grading	G1/2	4241 (55.1)	3831 (53.3)	8072 (54.3)
	G3	3457 (44.9)	3352 (46.7)	6809 (45.8)
Ki67 at baseline	<=20%	473 (44.6)	440 (43.1)	913 (43.9)
	>20%	587 (55.4)	582 (56.9)	1169 (56.1)
Treatment setting	neoadjuvant	1640 (20.5)	1176 (15.7)	2816 (18.2)
	adjuvant	6343 (79.5)	6298 (84.3)	12641 (81.8)

HR for Disease-Free Survival

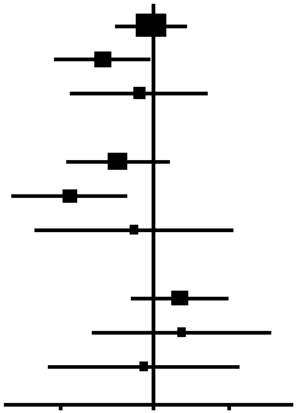


HR for Overall Survival

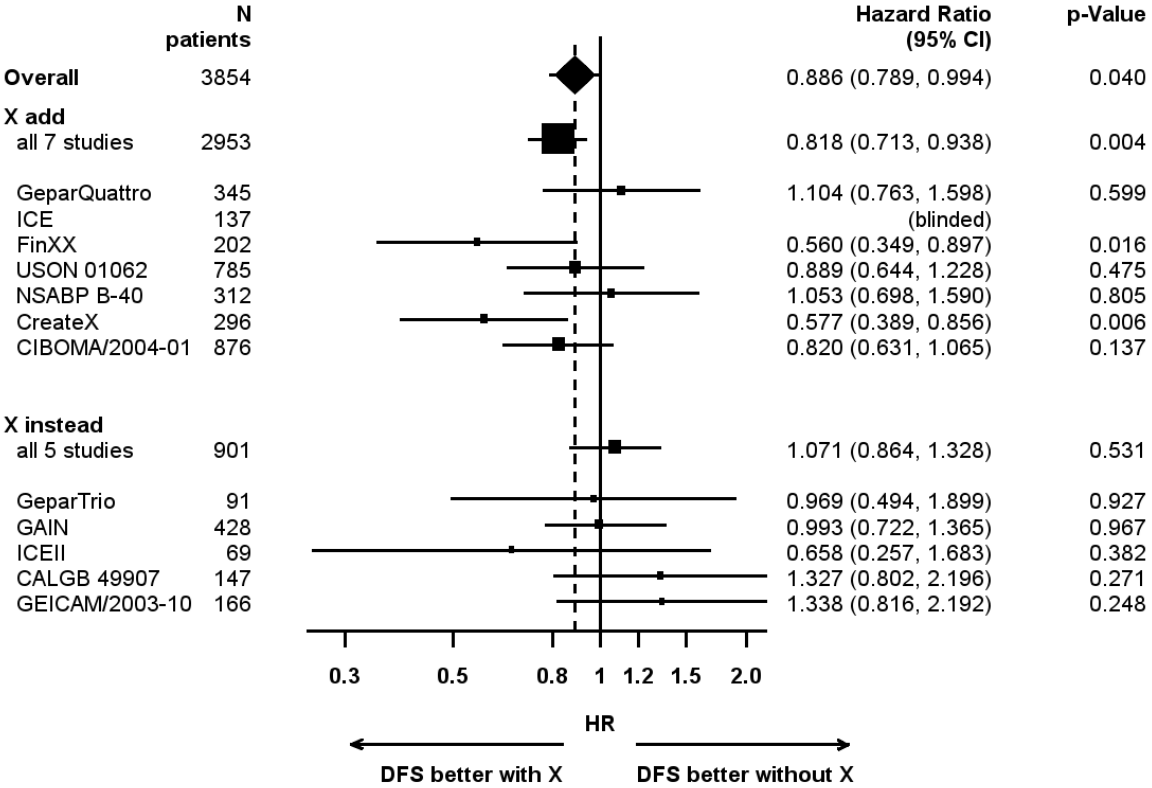


Disease-Free Survival according to Subtype

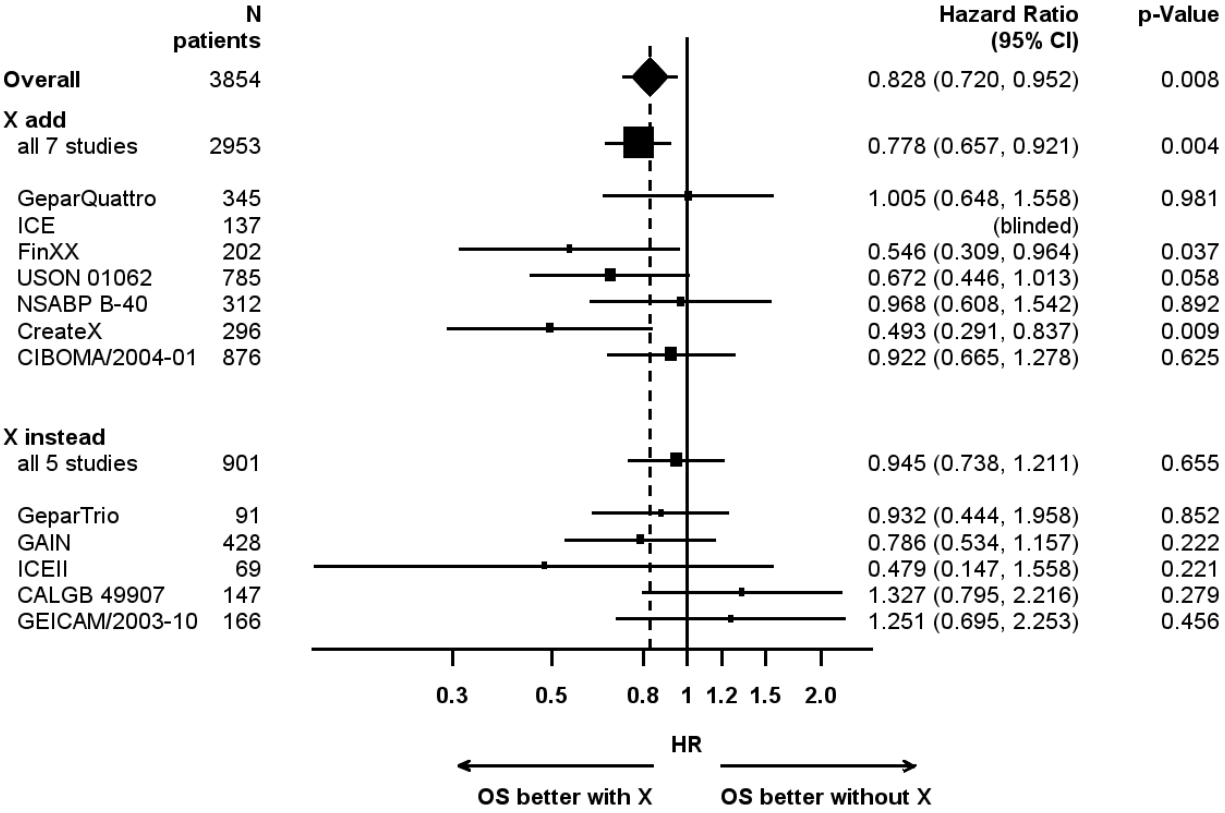
	N patients	Hazard Ratio (95% CI)	p-Value
Overall	15457		
All trials			
HR+/HER2-	8635	0.995 (0.914, 1.084)	0.914
TNBC	3854	0.886 (0.789, 0.994)	0.040
HER2+	2218	0.967 (0.820, 1.140)	0.687
X add			
HR+/HER2-	4874	0.919 (0.812, 1.041)	0.184
TNBC	2953	0.818 (0.713, 0.938)	0.004
HER2+	1163	0.955 (0.753, 1.211)	0.701
X instead			
HR+/HER2-	3761	1.067 (0.949, 1.199)	0.278
TNBC	901	1.071 (0.864, 1.328)	0.531
HER2+	1055	0.979 (0.778, 1.231)	0.854



Disease-Free Survival in Patients with TNBC

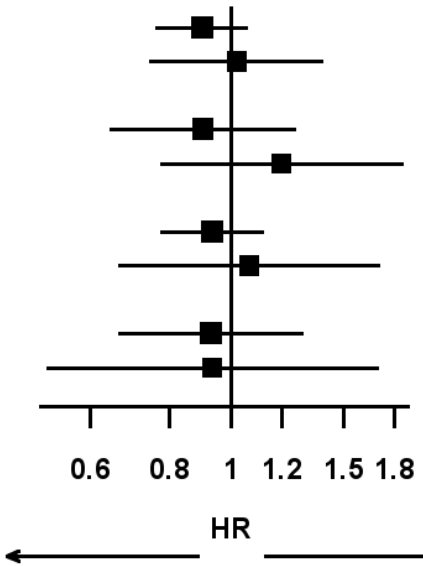


Overall Survival in Patients with TNBC



Toxicity as potential Predictor of Disease-Free Survival

	N patients	Hazard Ratio (95% CI)	p-Value	Test for Interaction
Overall	7780			
Any toxicity grade 3-4				0.655
with X		0.898 (0.760, 1.060)	0.204	
without X		1.017 (0.743, 1.393)	0.916	
Mucositis grade 3-4				0.416
with X		0.901 (0.643, 1.263)	0.547	
without X		1.199 (0.773, 1.858)	0.418	
Hand-foot syndrome grade 3				0.714
with X		0.932 (0.773, 1.124)	0.464	
without X		1.067 (0.666, 1.712)	0.787	
Diarrhea grade 3-4				0.923
with X		0.928 (0.664, 1.296)	0.660	
without X		0.933 (0.512, 1.698)	0.819	



Summary

- Overall Capecitabine did not alter DFS in this meta-analysis, but when administered in addition to other systemic treatment an improvement in DFS could be observed
- OS was improved by Capecitabine treatment in the overall cohort and when given in addition
- Only TNBC patients benefited from treatment with Capecitabine overall and in addition to other systemic therapy in terms of DFS and OS
- All effects were small, the largest was observed for OS in patients with TNBC who received Capecitabine in addition (HR 0.78, 95%CI [0.66, 0.92])
- There was no evidence supporting a predictive value of Capecitabine-specific adverse events on patient outcome

Conclusions

- The addition of Capecitabine to other systemic treatment may be recommended for TNBC patients
- The two trials driving the results were CreateX and FinXX although different Capecitabine doses were applied
- To date there exist no data comparing the effect of Capecitabine with Carboplatin in TNBC patients, however, there is one trial recruiting in the post-neoadjuvant setting (NCT02445391)
- The effect of the addition of Capecitabine to other systemic treatment including Carboplatin in TNBC remains to be investigated

Acknowledgement

- All patients and their families
- All participating sites
- Slides will be available on www.gbg.de

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