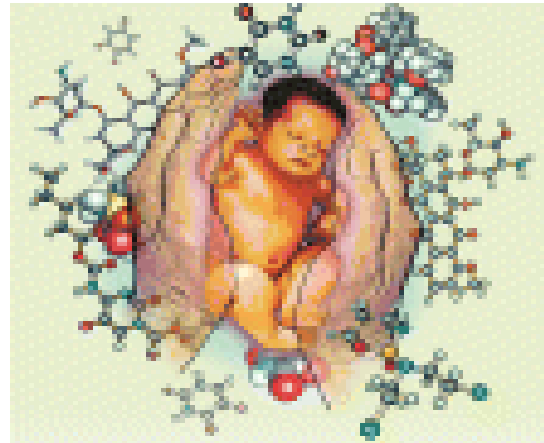# Breast cancer in the very young and pregnant patient

Prof. Sibylle Loibl

**Co-Chair German Breast Group
Sana Klinikum Offenbach**

HEILUNG DURCH INNOVATION, KOMPETENZ UND PARTNERSCHAFT

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Position Paper

The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer
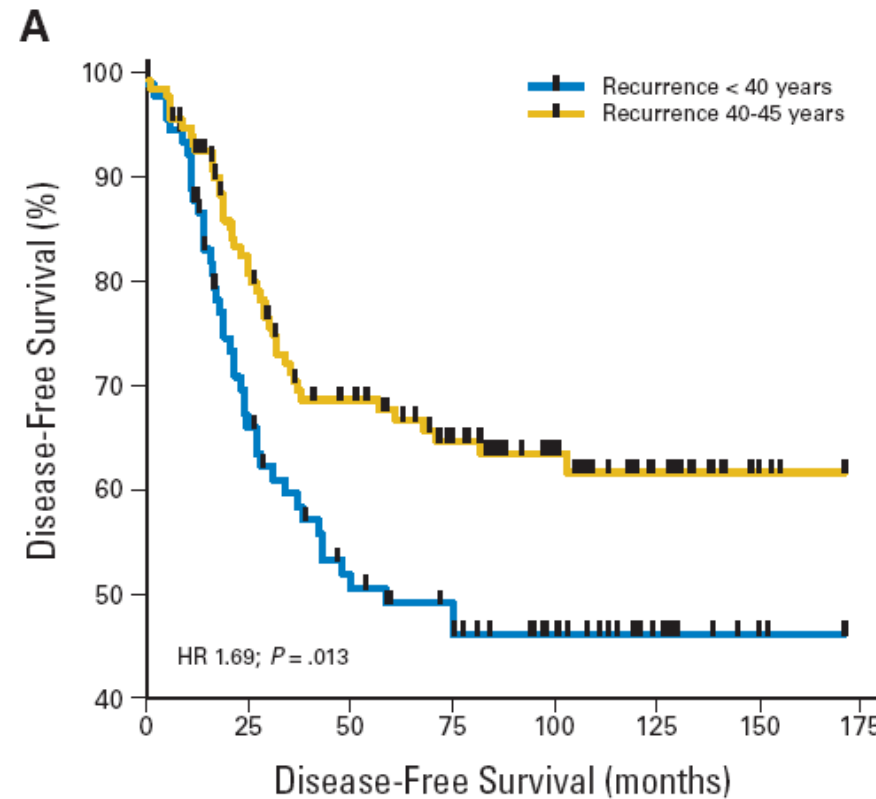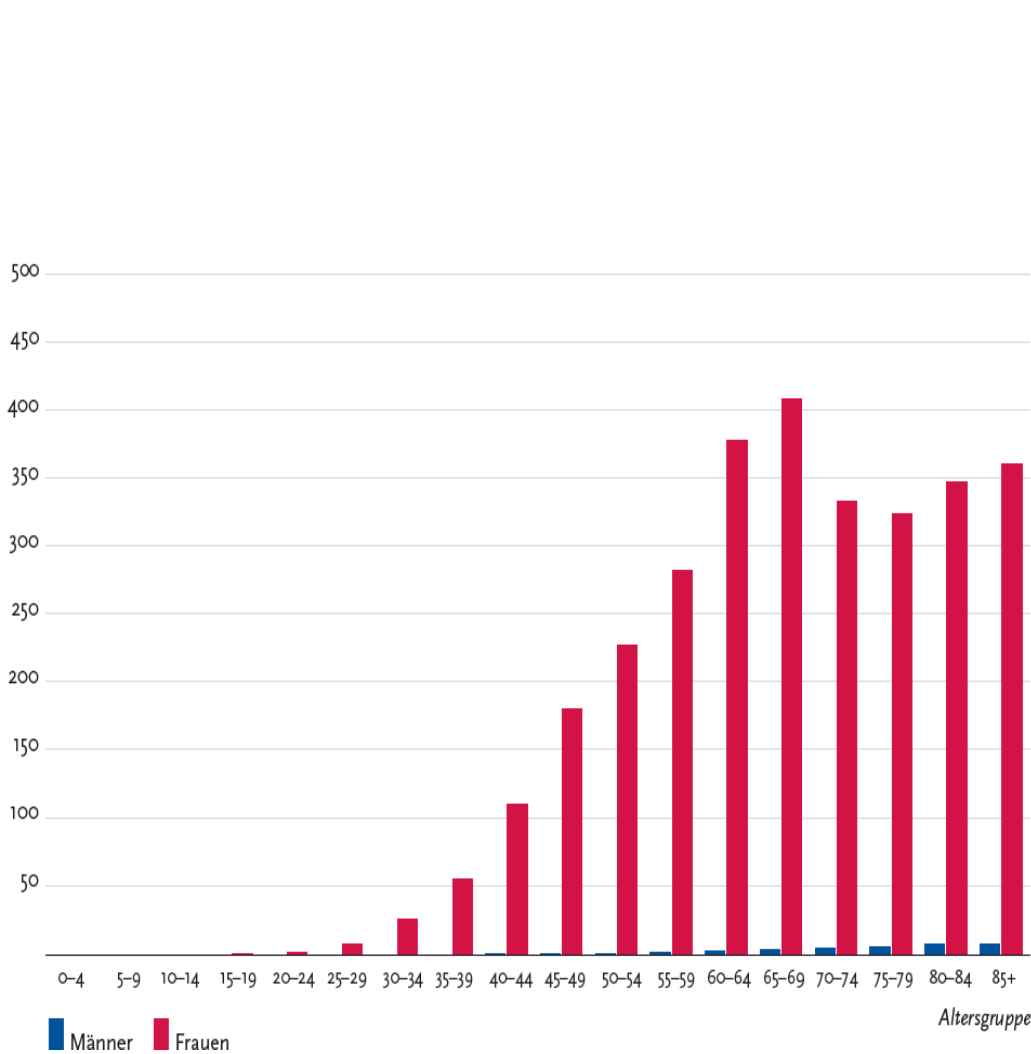
Fatima Cardoso [a,b,*], Sibylle Loibl [c], Olivia Pagani [d], Alessandra Graziottin [e], Pietro Panizza [f], Laura Martincich [g], Oreste Gentilini [h], Fedro Peccatori [i], Alain Fourquet [j], Suzette Delaloge [k], Lorenza Marotti [l], Frédérique Penault-Llorca [m], Anna Maria Kotti-Kitromilidou [n], Alan Rodger [o], Nadia Harbeck [p]

Incidence and Survival

A

Anders et al. JCO 2008

Survival in young breast cancer patients According to Subtypes

E ER-HER2- (*n* = 615)
- ≤40 (*n* = 110)
- 41–52 (*n* = 229)
- 53–64 (*n* = 137)
- ≥65 (*n* = 139)

Log-rank: $P = 0.69$
Log-rank test for $P_{trend} = 0.5$

B Luminal A (*n* = 975)
- ≤40 (*n* = 61)
- 41–52 (*n* = 325)
- 53–64 (*n* = 273)
- ≥65 (*n* = 316)

Log-rank: $P = 0.07$
Log-rank test for $P_{trend} = 0.42$

D HER2+ (*n* = 432)
- ≤40 (*n* = 69)
- 41–52 (*n* = 167)
- 53–64 (*n* = 103)
- ≥65 (*n* = 93)

Log-rank: $P = 0.42$
Log-rank test for $P_{trend} = 0.4$

C Luminal B (*n* = 879)
- ≤40 (*n* = 99)
- 41–52 (*n* = 247)
- 53–64 (*n* = 219)
- ≥65 (*n* = 314)

Log-rank: $P = 0.03$
Log-rank test for $P_{trend} = 0.006$

<= 40

17%   27%   21%   34%

nach Azim H et al. Clinical Cancer Res 2011

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Survival in women <40 years – POSH study

Copson E, et al. JNCI 2013

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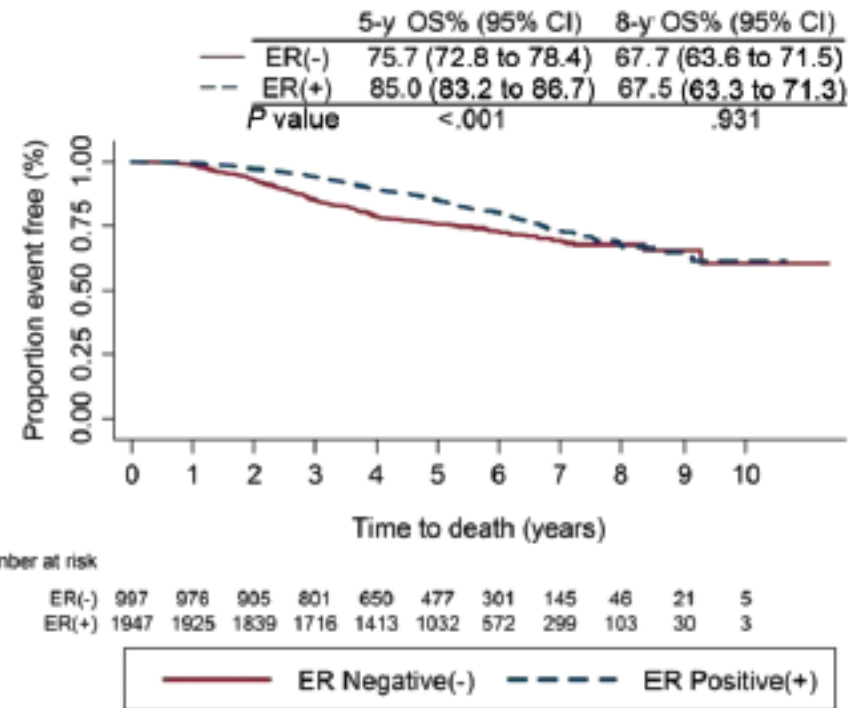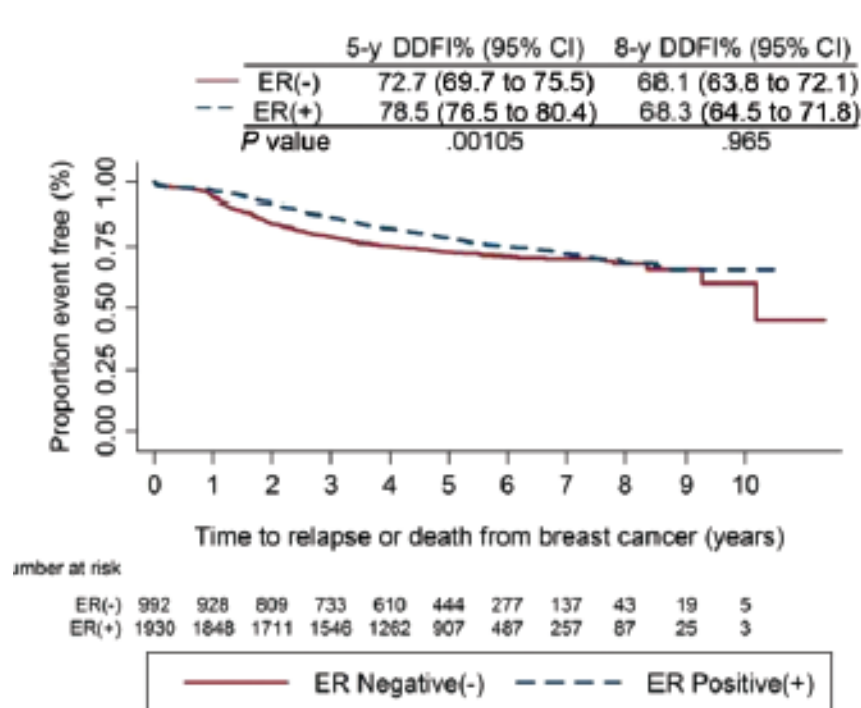
OS Hazards in ER-; ER+ women < 40 years – POSH study

Copson E, et al. JNCI 2013,
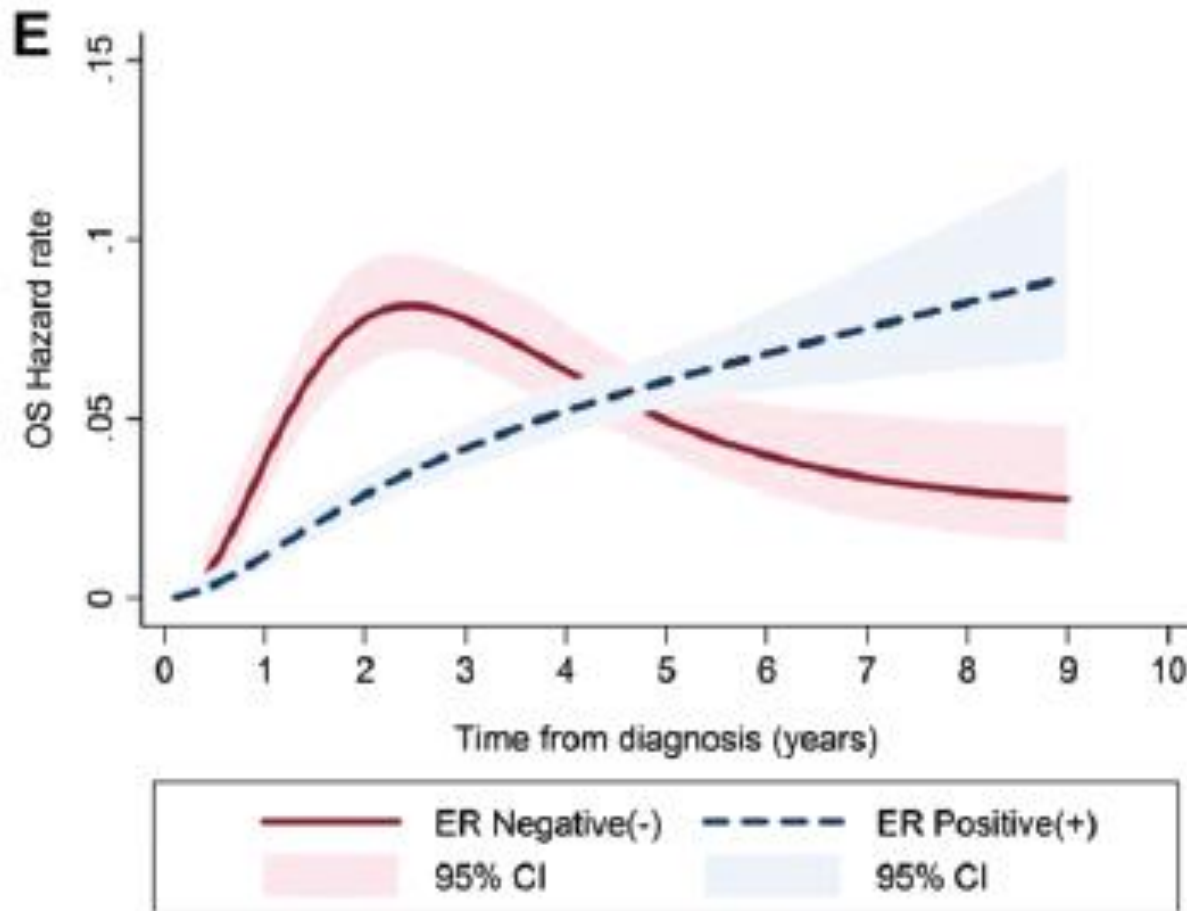
Do young women have a greater benefit from neoadjuvant therapy?

Rastogi J Clin Oncol 2008

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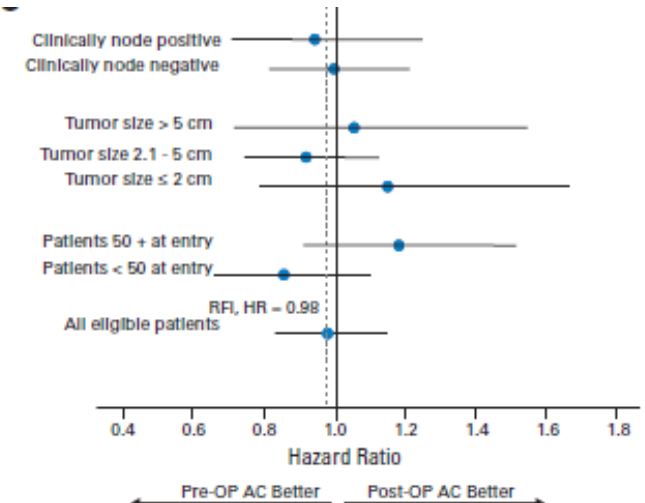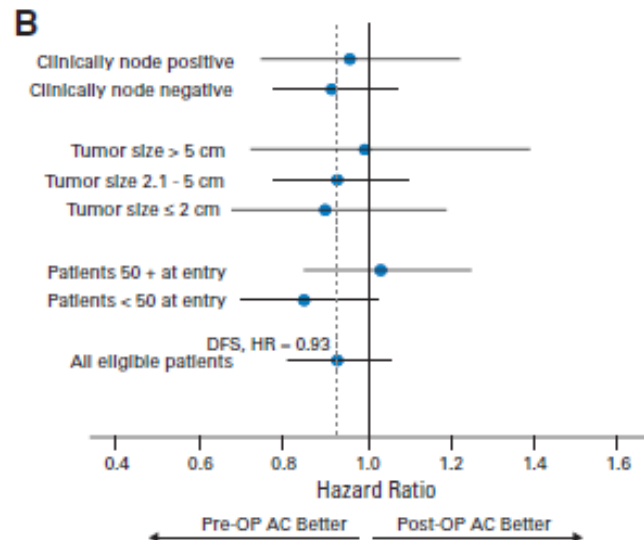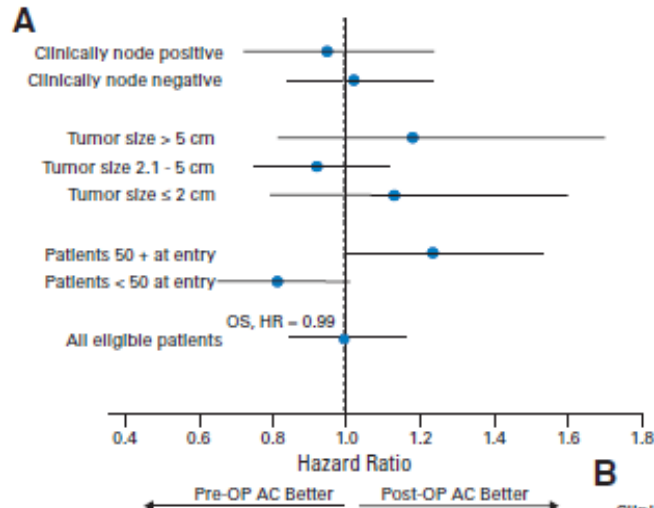
pCR rates overall and in subgroups

Loibl S, et al. Cancer Res 2012;72: #S3-1
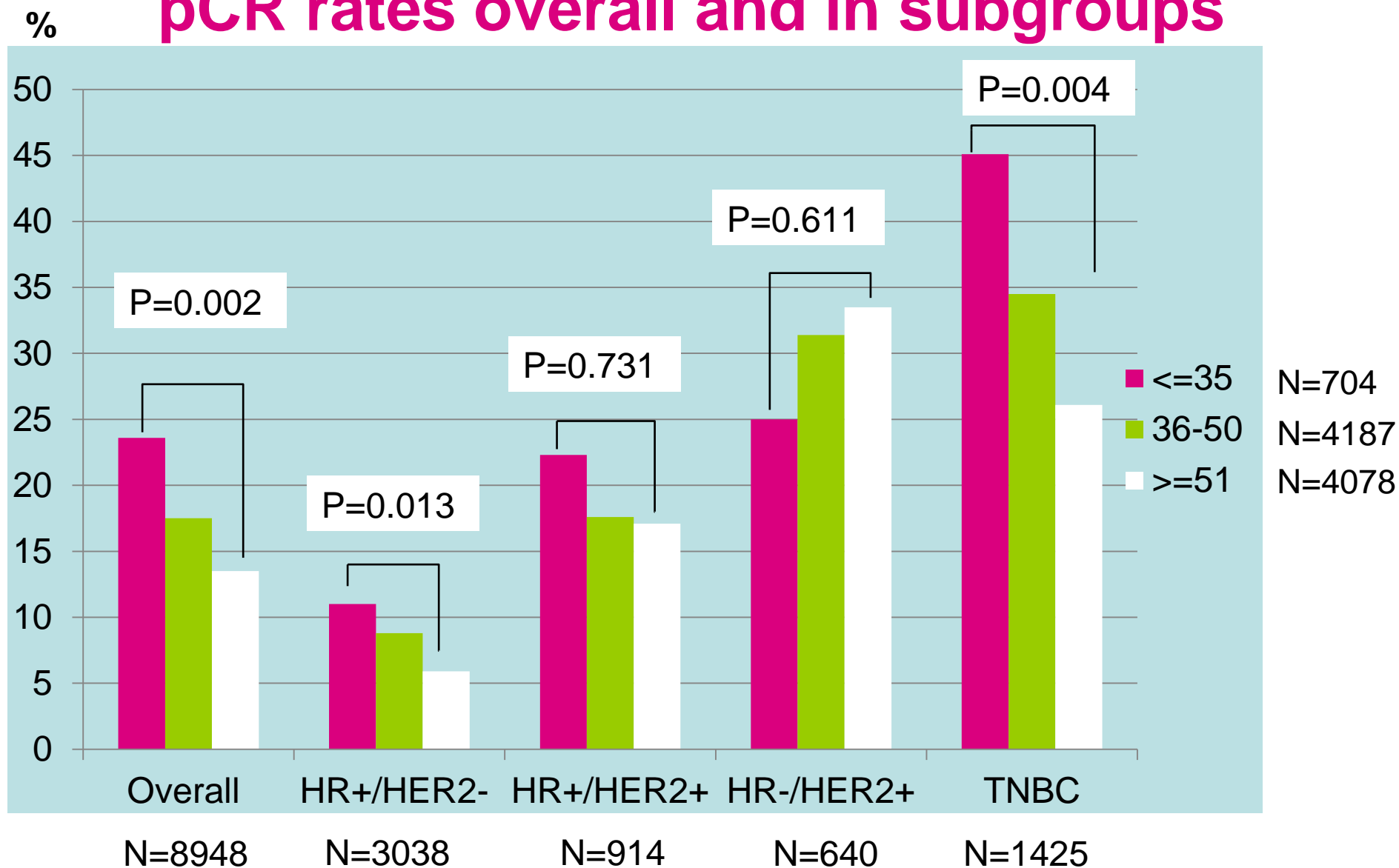
*adjusted for age, tumor size, nodal status, histological type, grading, trial

Survival in non-pCR patients

DFS

	HR	95% CI		p-value
age ≤ 35	1			0.003
age ≥36-50	0.75	0.62	0.90	0.002
age ≥51	0.74	0.62	0.88	0.001

LRFS

	HR	95% CI		p-value
age ≤ 35	1			<0.0001
age ≥36-50	0.67	0.51	0.87	0.003
age ≥51	0.55	0.42	0.72	<0.001

OS

	HR	95% CI		p-value
age ≤ 35	1			0.151
age ≥36-50	0.79	0.61	1.02	0.073
age ≥51	0.86	0.67	1.12	0.262

■ ≤35
■ 36-50
■ ≥51

Loibl S, et al. Cancer Res 2012;72: #S3-1
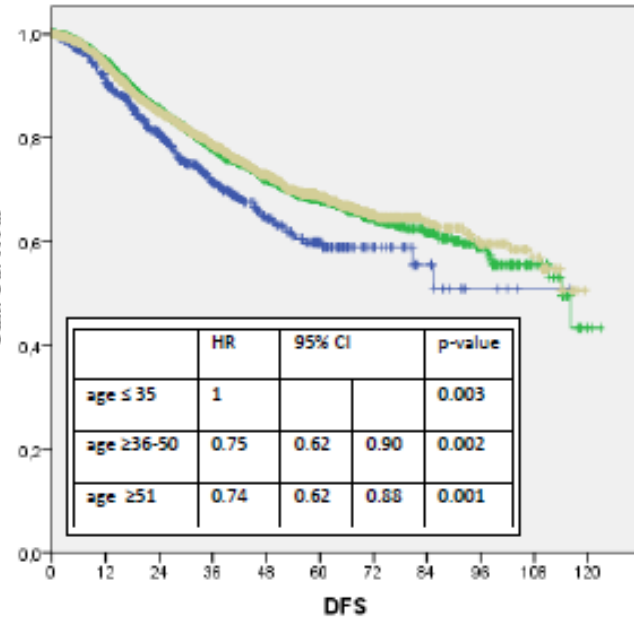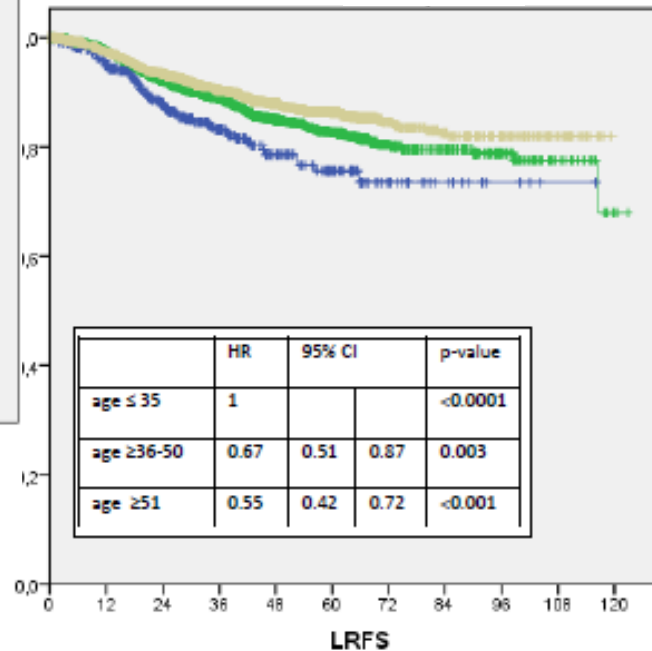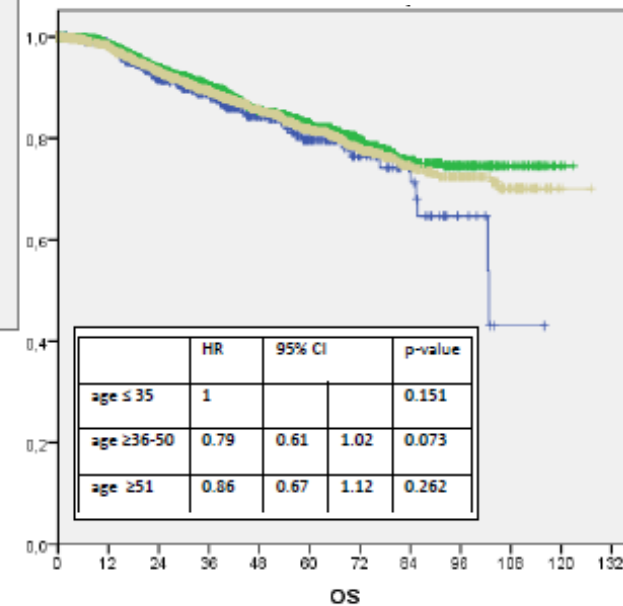
DFS in Different Subtypes by pCR and age

Loibl S, et al. Cancer Res 2012;72: #S3-1
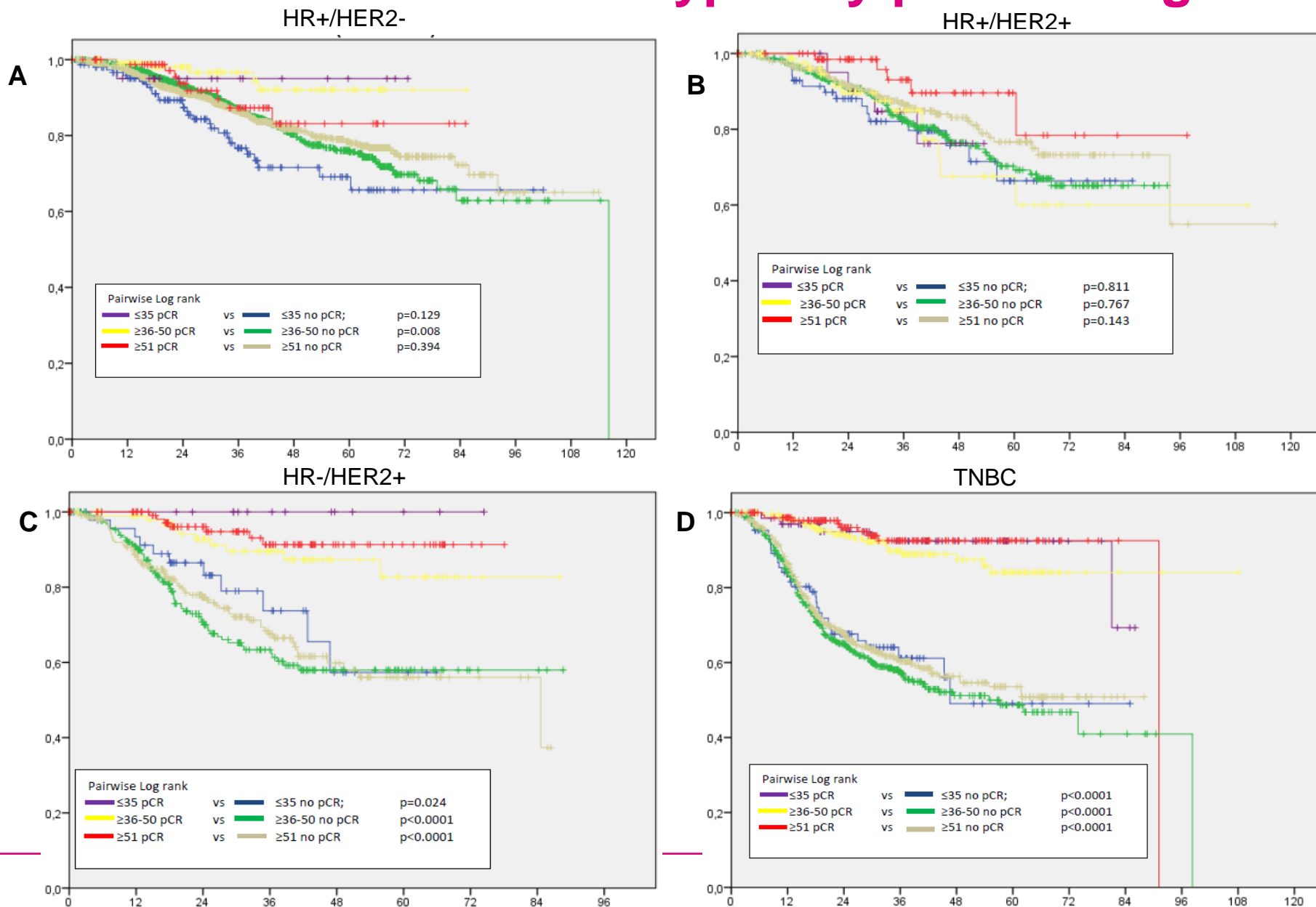
Who Should be Tested for BRCA1/2 Mutations?

Oxford LoE: 2b   GR: B   AGO: ++

Families with
at least three women with breast cancer independent of age or
at least two women with breast cancer, one < 51 yrs. or
at least one woman affected by breast and one by ovarian cancer or
at least one woman affected by breast and ovarian cancer or
at least two women affected by ovarian cancer or
at least one woman affected by bilateral breast cancer, first < 51 yrs. or
at least one woman affected by breast cancer < 36 yrs. or
at least one man affected by breast cancer and one additional relative affected by breast or ovarian cancer* #

* in one side of the family

#Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a mutation detection rate ≥ 10% in ~17.000 families tested by 2013

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

NCCN Guidelines - 2014

Affected persons – detailed criteria for breast cancer +

- All breast cancer $\leq$ 45
- Early onset ($\leq$50 yrs) breast cancer+
- Triple negative breast cancer – all $\leq$ 60, over 60 if +
- All multiple primaries
- All ovarian cancer
- All male breast cancer

Prevalence of BRCA mt depends on tumor type, family history and age at diagnosis

Table 2 Characteristics of women tested for germline *BRCA1* and *BRCA2* mutations

Characteristics	Triple negative n = 110				Not triple negative n = 321				P value
	n	BRCA1	BRCA2	Total (%)	n	BRCA1	BRCA2	Total (%)	
With family history									
Early onset, ≤35 years old	6	4	0	4 (66.7)	29	3	4	7 (24.1)	0.063[a]
>35 years old	32	9	3	12 (37.5)	161	7	13	20 (12.4)	0.0005[b]
Overall	38	13	3	16 (42.1)	190	10	17	27 (14.2)	<0.0001[b]
Without family history									
Early onset, ≤35 years old	25	7	0	7 (28.0)	71	3	4	7 (9.9)	0.045[a]
36 to 50 years old	47	3	1	4 (8.5)	60	1	3	4 (6.7)	1.000[a]
Overall	72	10	1	11 (15.3)	131	4	7	11 (8.4)	0.131[b]
All, regardless of family history or age	110	23	4	27 (24.5)	321	14	24	38 (11.8)	0.001[b]
Mean age at diagnosis (years)	40.6				42.0				0.172
Mean number of first-degree relatives	7.2				7.1				0.827
Mean number of affected (breast or ovarian) relatives, first or second degree	0.6				0.8				0.003
Prevalence of *BRCA1* mutations		20.9%				4.4%			<0.0001[b]
Prevalence of *BRCA2* mutations			3.6%				7.5%		0.158[b]

Phuah S-Y et al. Breast Cancer Res 2012 14:R142

Genetic Landscape

disease risk

high risk genes (OR >5.0)
(*BRCA1/2*)

moderately penetrant risk genes (OR 1.5 - 5.0)
(RAD51C, *ATM, BRIP1, CDH1, CHEK2, NBN, PALB2 , PTEN….)*

low risk variants / modifiers (OR/HR <1.5)
(*FGFR2, TOX3, 2q35, 11q15, SLC4A7, 5p12, MAP3K1…)*

Contribution of known genes to
familial aggregation of breast cancer

BRCA1 BRCA2 TP53
PTEN
ATM
CHEK2,
BRIP1,
PALB2
Other genes
familial risk factors
79 common
SNPs

frequency

- **Multi-gene sequencing identifies an additional ~10% with pathogenic germline mutations[1]**

- **DNA repair-targeted therapy is hypothesized to have a role in these patients with non-B1/2 germline HR alterations**

1. **Kurian AW, et al J Clin Oncol 2014**

Characteristics of patients with TNBC

		PM (N=146)	PMCb (N=148)
Age (median; yrs)		47.0	47.5
Tumor size (median; cm)		3.0	3.0
		%	**%**
cT 3 / 4		13.7	8.1
cN +		45.1	40.6
Grade 3		77.4	72.3
Family history for BC/OC*	(N=101)	34.9	33.8
g*BRCA 1* alteration	(N= 35)	13.0 ⎤	10.8 ⎤
g*BRCA* 2 alteration	(N= 6)	1.4 ⎬ 15.8	2.7 ⎬ 14.2
g*RAD50/51C* alteration	(N= 3)	1.4 ⎦	0.7 ⎦

*assessed by a checklist of the German BRCA consortium to identify women at risk for germline alterations of >10%

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pCR (ypT0 ypN0) in all Patients with TNBC

	gBRCA/RAD alteration	
	no (N=250)	**yes** (N=44)
no (N=193)	40.4% (69/171)	45.5% (10/22)
yes (N=101)	44.3% (35/79)	63.6% (14/22)

Family history for BC/OC

Prediction of Carboplatin Effect on pCR

%	PM (N=146)	PMCb (N=149)	OR	p
No risk factor	34.5	46.0	1.61	0.13
		Δ 11.5		
Family history of BC/OC without alteration	30.8	57.5	3.04	0.02
		Δ 26.7		
g*BRCA/RAD* alteration with/without family history	43.5	66.7	2.60	0.13
		Δ 23.2		

BRCA mutation carriers with triple negative breast cancer

Chromosom 17

17q25.2
17q24.3
17q24.1
17q23.2
17q22
17q21.32
17q21.2
BRCA1
17q12
q
p
17p12
17p13.2
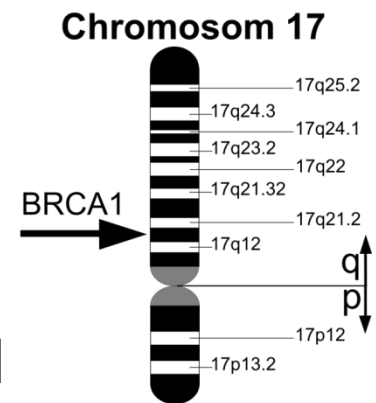
- **Responses to anthracycline and taxane-based neoadjuvant therapy in TNBC patients were significantly higher in BRCA1/2 carriers vs. non-carriers**

	BRCA1/2+ (N=44) N (%)	BRCA-WT (N=250) N (%)	p-value
pCR	28 (63%)	114 (45%)	**0.027**

- **Contrasts with retrospective U.S. series from Arun et al[1]**

	BRCA1/2+ (N=35) N (%)	BRCA-WT (N=42) N (%)	p-value
pCR	13 (37%)	13 (31%)	0.62

1 von Minckwitz G et al. J Clin Oncol 2014; 32:5s, (abstr 1005); 2 Arun B, et al. J Clin Oncol. 2011; 29:3739-3746

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Contralateral Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers

Table 2. Cumulative Risks and 95% CIs for Contralateral Breast Cancer Depending on Age at First Breast Cancer Observed in Relatives of Index Patients

Evaluation Time After First Breast Cancer According to Age	Risk by Mutation Group					
	BRCA1 (n · 675)		BRCA2 (n · 367)		Total (N · 1,042)	
	Cumulative Risk	95% CI	Cumulative Risk	95% CI	Cumulative Risk	95% CI
Age at first breast cancer, years						
· 40	n · 282		n · 97		n · 379	
5 years	14.2	9.1 to 19.3	3.8	0.0 to 8.9	11.7	7.6 to 15.8
10 years	30.7	22.7 to 38.7	20.7	6.4 to 35.0	28.3	21.2 to 35.4
15 years	42.6	32.4 to 52.8	20.7	6.4 to 35.0	37.8	29.0 to 46.6
25 years	62.9	50.4 to 75.4	63.0	32.8 to 93.2	62.5	50.5 to 74.5
40-50	n · 216		n · 122		n · 338	
5 years	7.3	3.0 to 11.6	7.9	2.2 to 13.6	7.5	4.2 to 10.8
10 years	10.6	5.1 to 16.1	12.8	5.2 to 20.4	11.5	7.0 to 16.0
15 years	17.7	9.3 to 26.1	18.9	8.1 to 29.7	18.2	11.5 to 24.9
25 years	43.7	24.9 to 62.5	48.8	22.7 to 74.9	45.4	30.1 to 60.7
· 50	n · 177		n · 148		n · 325	
5 years	7.9	2.8 to 13.0	3.1	0.0 to 6.6	5.5	2.4 to 8.6
10 years	7.9	2.8 to 13.0	9.2	1.8 to 16.6	8.4	4.1 to 12.7
15 years	13.4	4.6 to 22.2	16.7	1.0 to 32.4	14.5	6.5 to 22.5
25 years	19.6	5.3 to 33.9	16.7	1.0 to 32.4	19.5	7.3 to 31.7
Overall						
5 years	10.3	7.4 to 13.2	4.9	2.2 to 7.6	8.4	6.2 to 10.6
10 years	18.5	14.2 to 22.8	13.2	7.9 to 18.5	16.6	13.3 to 19.9
15 years	27.3	21.4 to 33.2	17.7	10.4 to 25.0	24.0	19.5 to 28.5
25 years	48.1	38.3 to 57.9	47.1	28.9 to 65.3	47.4	38.8 to 56.0

Graeser MK et al. J Clin Oncol 2009
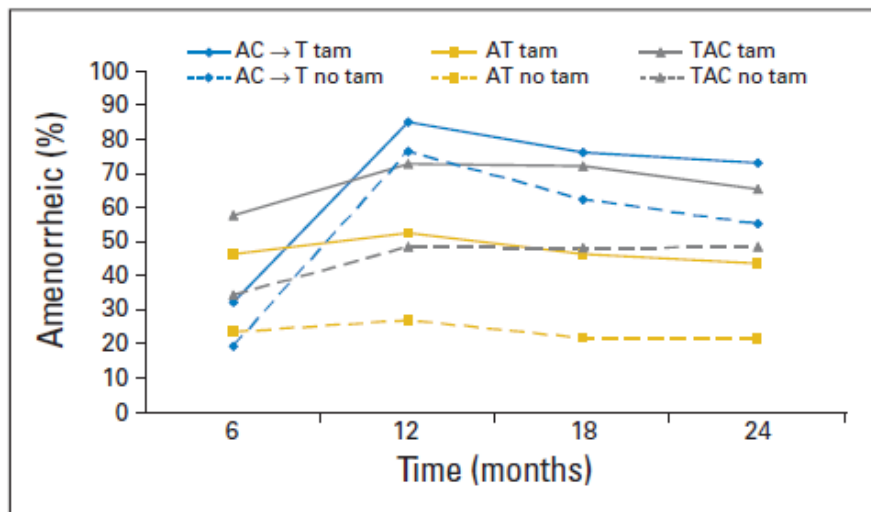
Fig 2. Rate of prolonged amenorrhea at each time point for chemotherapy and tamoxifen intention-to-treat groups. Excludes those who experienced amenorrhea for 3 months at baseline and those with a hysterectomy/oophorectomy or unknown status at each time point. A, doxorubicin; C, cyclophosphamide; T, docetaxel; tam, tamoxifen.

Ganz P et al. J Clin Oncol 2011; 29: 1110-16

Algorhythm for decision making of fertility preservation

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12-Month Landmark Analysis of Overall Survival and Disease-free Survival, According to Amenorrhea Status, and Average Dose Received per Patient.

A Overall Survival

Overall Survival (%) vs Years since 12 Mo after Randomization

Status	No. of Patients	No. of Events
Amenorrhea	1554	192
No amenorrhea	331	64

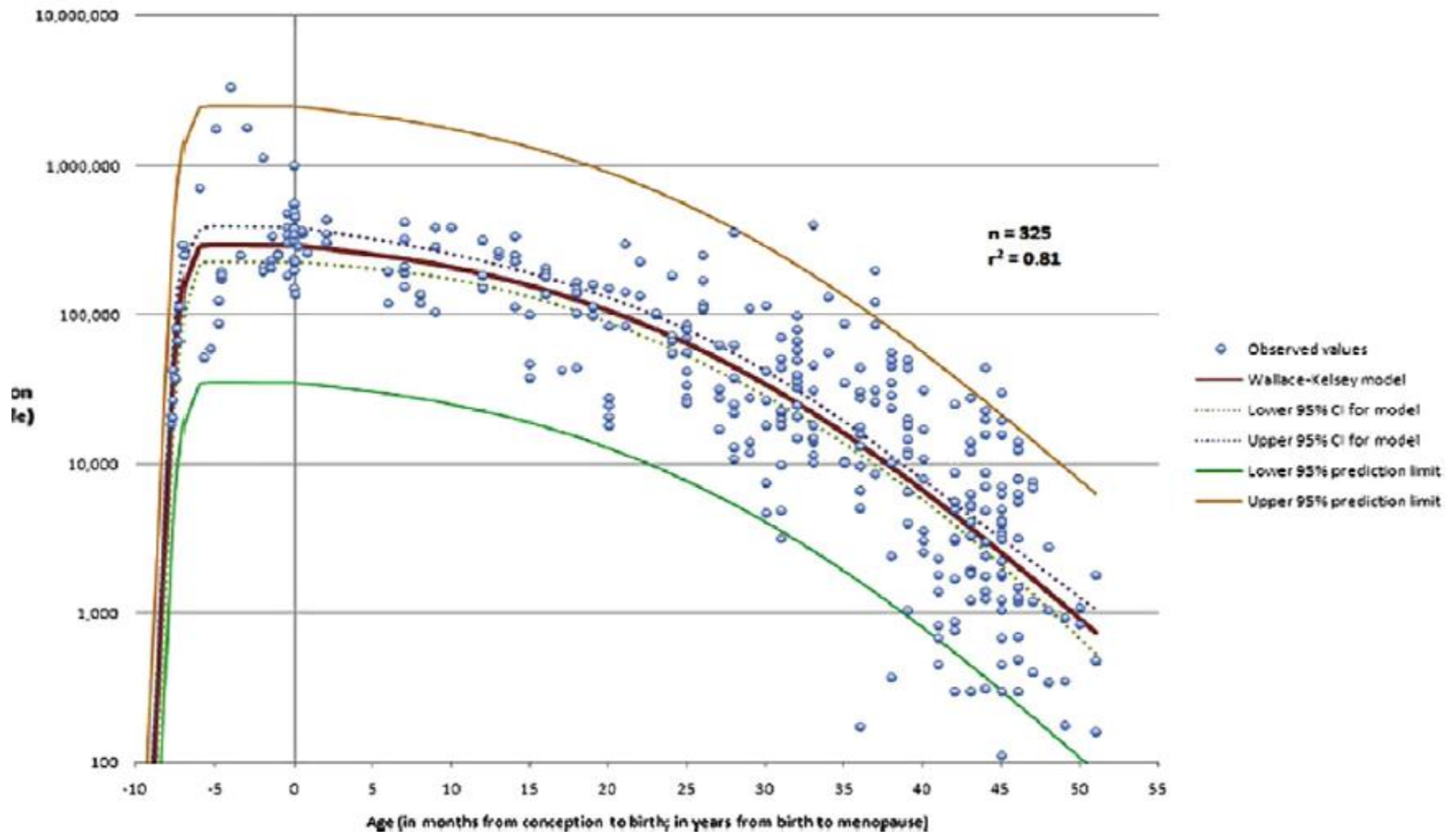Hazard ratio, 0.72
P=0.04

No. at Risk

Total	1885	1844	1774	1697	1334	903	633	307	29
Amenorrhea	1554	1523	1472	1409	1127	766	524	246	22
No amenorrhea	331	321	302	288	207	137	109	61	7

B Disease-free Survival

Disease-free Survival (%) vs Years since 12 Mo after Randomization

Status	No. of Patients	No. of Events
Amenorrhea	1515	304
No amenorrhea	322	103

Hazard ratio, 0.65
P<0.001

No. at Risk

Total	1837	1721	1618	1508	1166	786	541	264	25
Amenorrhea	1515	1429	1355	1272	996	676	454	215	18
No amenorrhea	322	292	263	236	170	110	87	49	7

C Average Dose Received per Patient, According to Study Drug, Estrogen-Receptor Status, and Treatment Group, for Patients with and without Amenorrhea

Tumor Status	Treatment Group	Amenorrhea Status	No. of Patients	Average Total Drug Dose per Patient (mg/m^2)		
				Doxorubicin	Cyclophosphamide	Docetaxel
ER-positive	Sequential ACT	Amenorrhea	430	236.3	2363.1	359.4
		No amenorrhea	34	236.2	2308.8	324.5
		Percent difference		0.1%	2.3%	9.7%
	Doxorubicin–docetaxel	Amenorrhea	376	210.3	0	272.6
		No amenorrhea	116	212.4	0	271.1
		Percent difference		−1.0%		0.6%
	Concurrent ACT	Amenorrhea	425	209.1	2087.6	271.6
		No amenorrhea	50	207.8	2075.7	261.4
		Percent difference		0.7%	0.6%	3.8%
ER-negative	Sequential ACT	Amenorrhea	137	235.8	2360.2	375.0
		No amenorrhea	19	240.0	2400.0	360.8
		Percent difference		−1.8%	−1.7%	3.8%
	Doxorubicin–docetaxel	Amenorrhea	79	209.8	0	267.2
		No amenorrhea	67	210.1	0	268.7
		Percent difference		−0.2%		−0.6%
	Concurrent ACT	Amenorrhea	107	208.9	2081.5	273.2
		No amenorrhea	45	206.4	2057.8	272.7
		Percent difference		1.2%	1.1%	0.2%

Swain SM et al. N Engl J Med 2010;363:2268-2270.

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Ovarian Reserve

Wallace WHB, Kelsey TW. PLoS ONE 5(1):e8772.
http://dx.doi.org/10.1371/journal.pone.0008772.
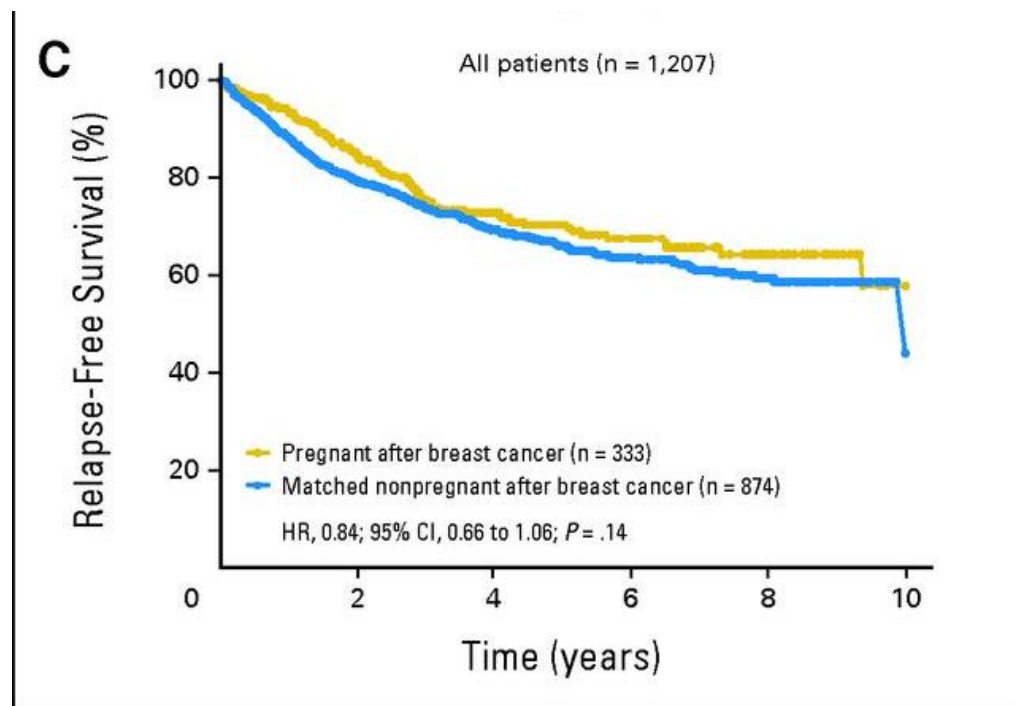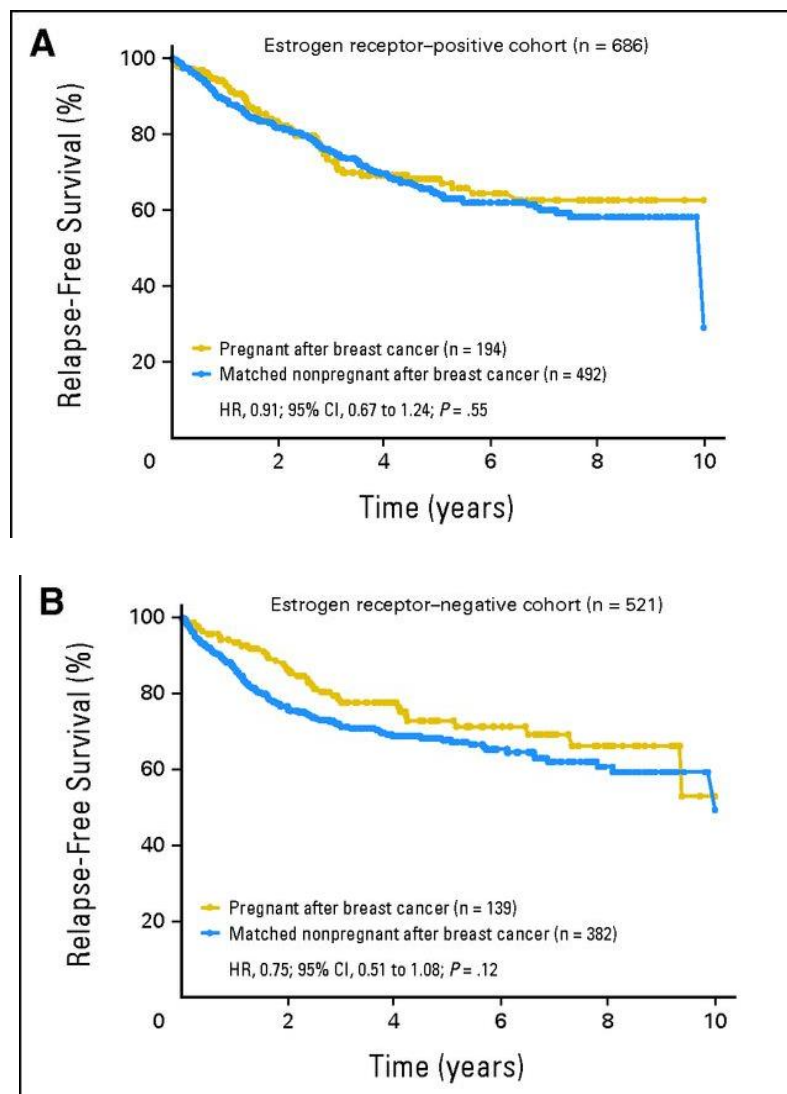
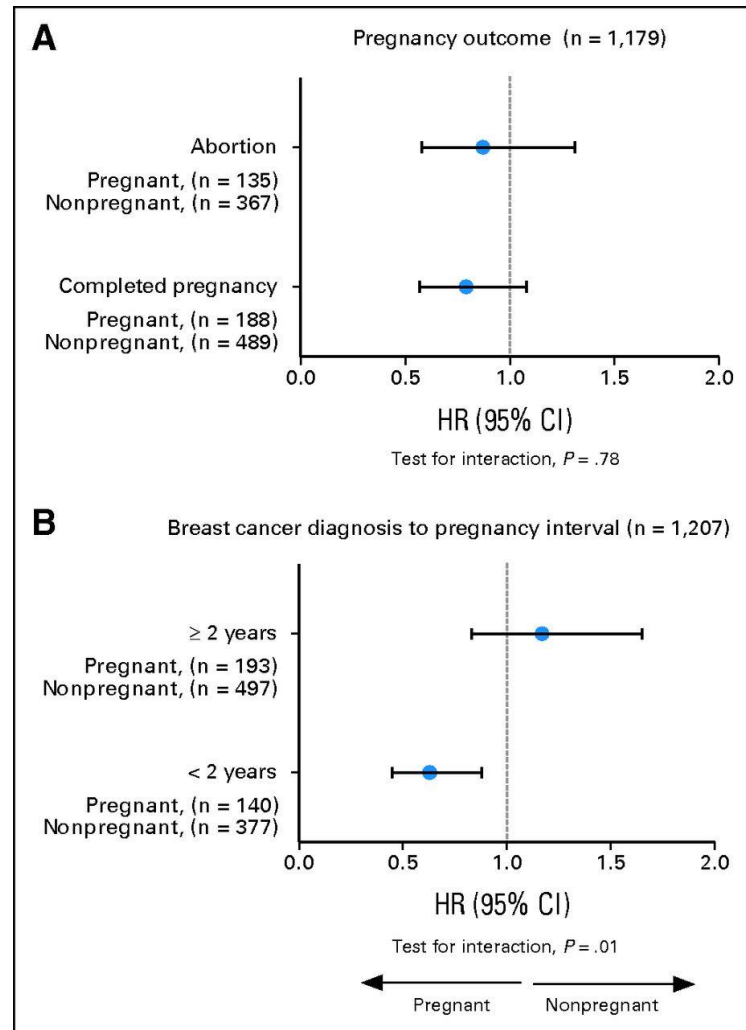# Differences in disease-free survival between the pregnant group and matched nonpregnant group.

Azim H A et al. JCO 2013;31:73-79

Forest plots of predefined subgroup analyses.

Azim H A et al. JCO 2013;31:73-79

Schwangerschaft nach *BRCA* 1/2 related Breast Cancer

Figure 4: Recurrence—free survival in subjects with and without a pregnancy after breast cancer. Follow—up from date of last birth
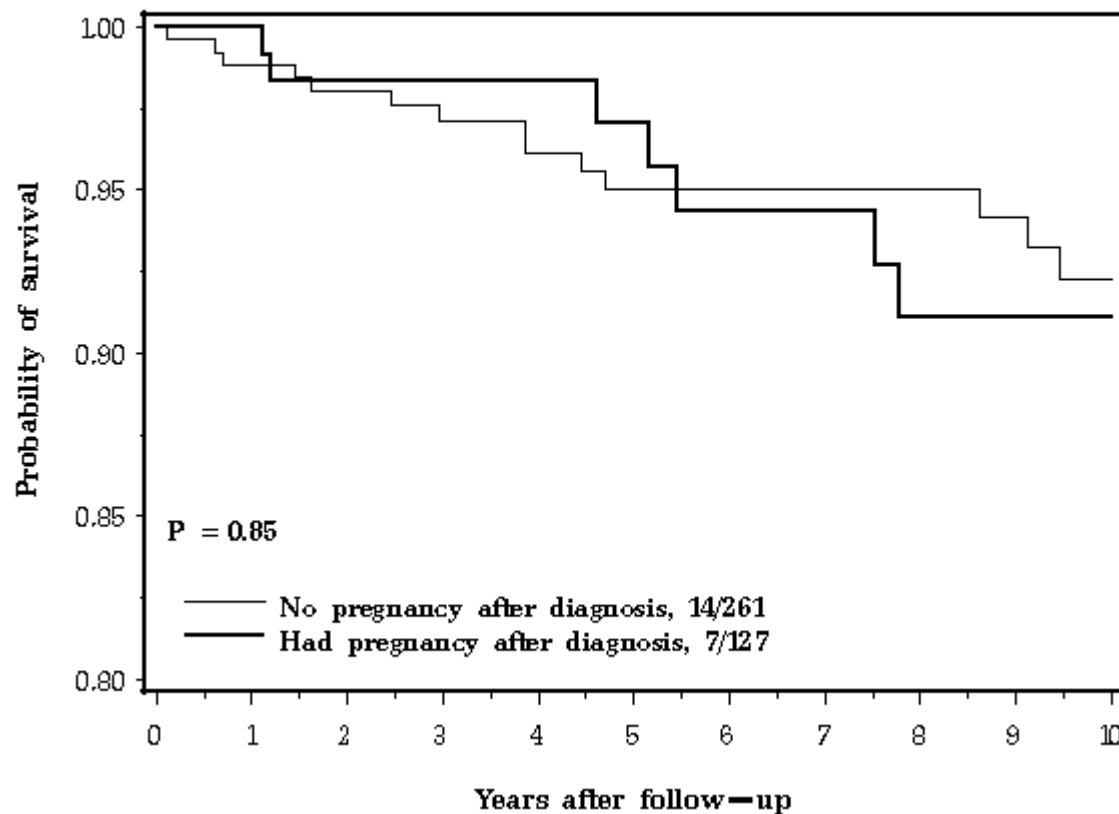
Programme for Young Patients Pregnancy Study

| <42 HR+ ET 18-30 months Childbearing | → | Stopp ET Wash-out period for Tamoxifen 3 months pregnancy IR of ET maximum 2 years Restart ET | → | 1. Risk of relapse 2. Factors predicting successfull pregnancy |
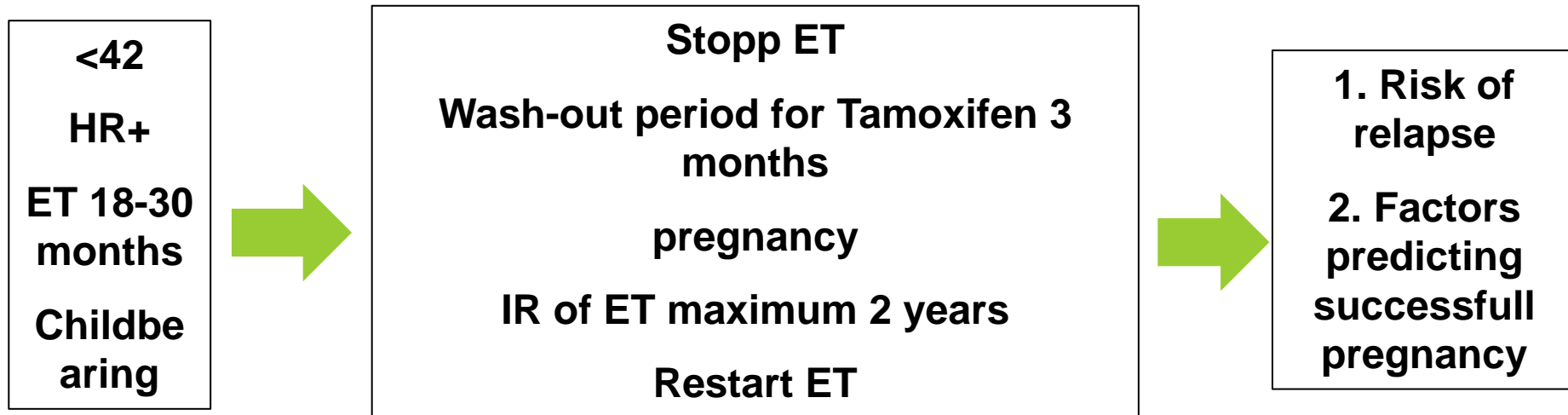
Breast Cancer in Young Women ≤ 35 Years

	Oxford / AGO LoE / GR		
› **Aggressive biological behavior**	2a	B	
› **Benefit from chemotherapy**	1b	A	++
› **Benefit from endocrine therapy**	1b	A	++
› **Endocrine therapy (TAM) if possible 5-10 y**	1b	B	++
› **Benefit from HER2 targeted therapy**	2b	B	++
› **Benefit from CT induced temporary amenorrhoea**	2b	B	+/-*
GnRHa as ovary protection 2 weeks prior CT	1a	A	-*
› **Surgery like ≥ 35 y (in particular BCT)**	2b	B	+
› **Stage II–III benefit from PMRT**	2b	C	+
› **Genetic and fertility counseling**	2b	B	++

Further Information

References

FORSCHEN
LEHREN
HEILEN

* Study participation recommended

Further
Information

References

FORSCHEN
LEHREN
HEILEN

Therapy of BRCA1/2-associated Breast Cancer+

Limited prospective cohort studies with short follow-up time

Oxford / AGO
LoE / GR

➢**Breast conserving therapy:**

  ➢**Adequate local tumor control (10 years observation)** **2a** **B**   **+**

➢**Systemic therapy according to sporadic breast cancer** **3a** **B**   **+**

➢**BRCA1 mutation status is predictive for chemotherapy response** **3b** **B**   **+**

➢**Platinum-based regimens** **3** **B**   **+/-***

➢**PARP inhibitor in breast cancer** **2b** **D**   **+/-***

  + Overall prognosis has to be considered   ***Study participation recommended**

Annual Incidence of Cancer during Pregnancy or Lactation,
proportions per year per 100,000 pregnancies
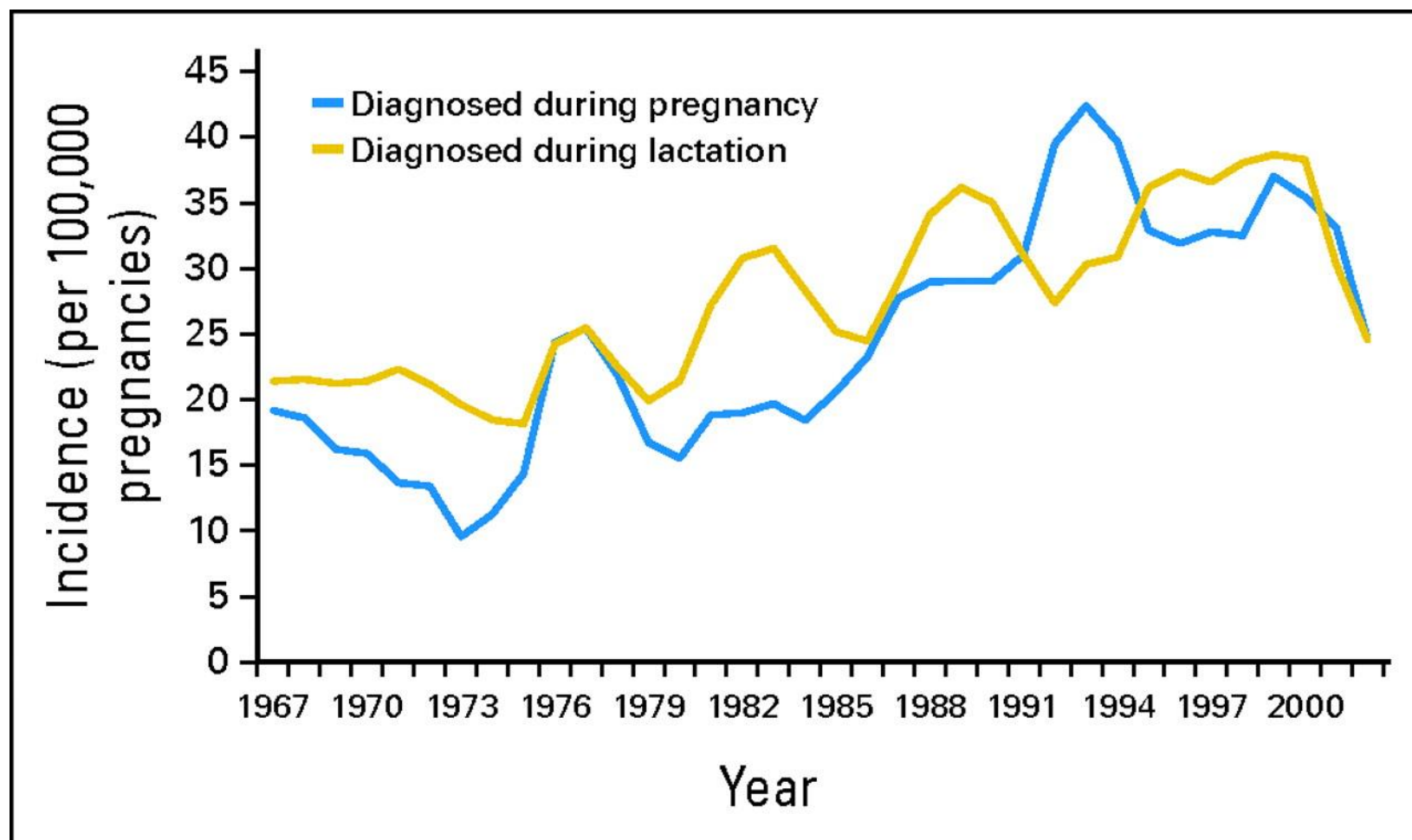
Stensheim, H. et al. J Clin Oncol; 2009; 27:45-51

BCP - Recruitment on 01.09.2014
n = 677

Germany n = 362 (total)   n = 321 (pregnant)   n = 41 (not pregnant)

Other Countries n = 315 (total)   n = 308 (pregnant)   n = 7 (not pregnant)

■ accrual no.

Prognosis of Women With Primary Breast Cancer Diagnosed During Pregnancy: Results From an International Collaborative Study

Frédéric Amant, Gunter von Minckwitz, Sileny N. Han, Marijke Bontenbal, Alistair E. Ring, Jerzy Giermek, Hans Wildiers, Tanja Fehm, Sabine C. Linn, Bettina Schlehe, Patrick Neven, Pieter J. Westenend, Volkmar Müller, Kristel Van Calsteren,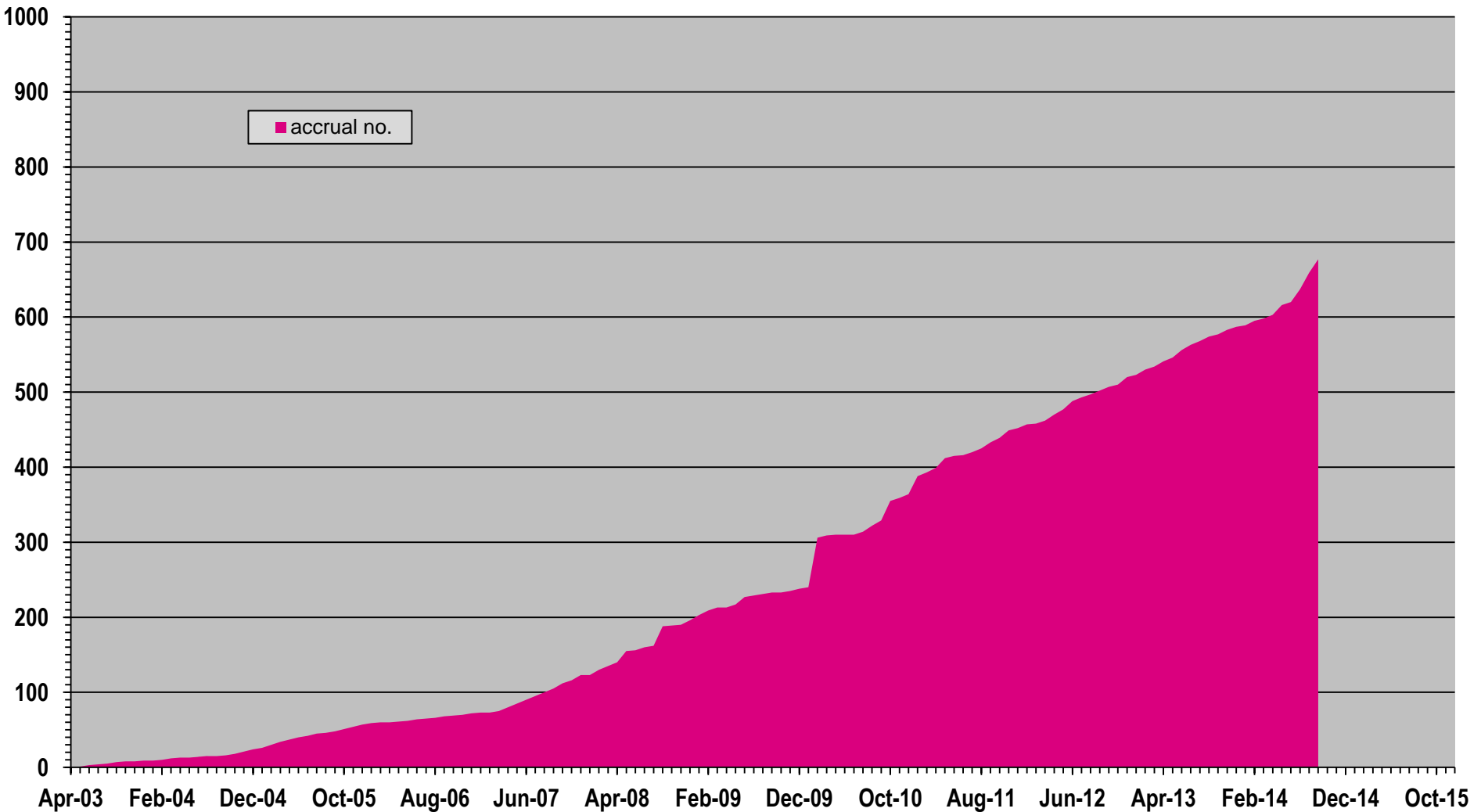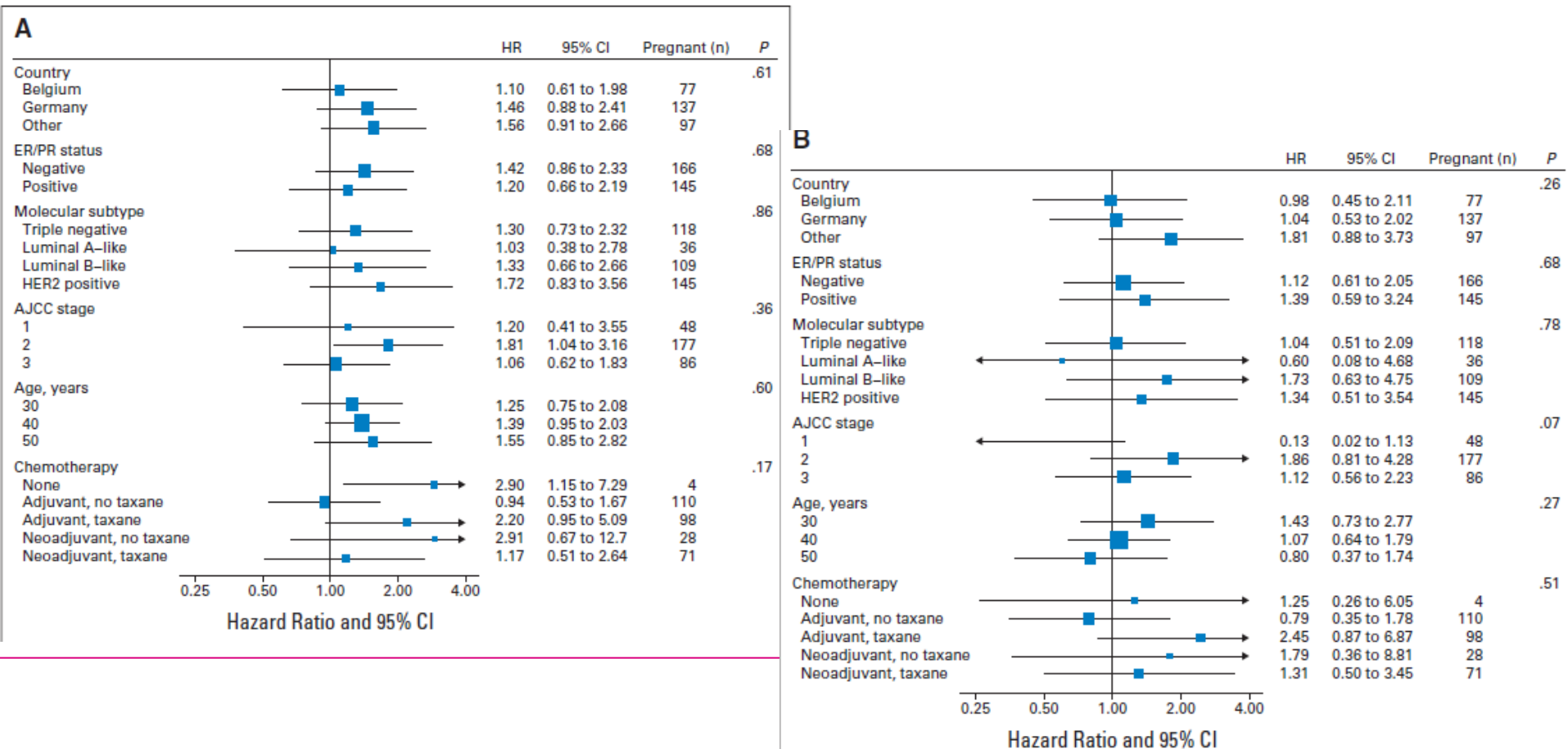 Brigitte Rack, Valentina Nekljudova, Nadia Harbeck, Michael Untch, Petronella O. Witteveen, Kathrin Schwedler, Christoph Thomssen, Ben Van Calster, and Sibylle Loibl

A

	HR	95% CI	Pregnant (n)	P
Country				.61
Belgium	1.10	0.61 to 1.98	77	
Germany	1.46	0.88 to 2.41	137	
Other	1.56	0.91 to 2.66	97	
ER/PR status				.68
Negative	1.42	0.86 to 2.33	166	
Positive	1.20	0.66 to 2.19	145	
Molecular subtype				.86
Triple negative	1.30	0.73 to 2.32	118	
Luminal A–like	1.03	0.38 to 2.78	36	
Luminal B–like	1.33	0.66 to 2.66	109	
HER2 positive	1.72	0.83 to 3.56	145	
AJCC stage				.36
1	1.20	0.41 to 3.55	48	
2	1.81	1.04 to 3.16	177	
3	1.06	0.62 to 1.83	86	
Age, years				.60
30	1.25	0.75 to 2.08		
40	1.39	0.95 to 2.03		
50	1.55	0.85 to 2.82		
Chemotherapy				.17
None	2.90	1.15 to 7.29	4	
Adjuvant, no taxane	0.94	0.53 to 1.67	110	
Adjuvant, taxane	2.20	0.95 to 5.09	98	
Neoadjuvant, no taxane	2.91	0.67 to 12.7	28	
Neoadjuvant, taxane	1.17	0.51 to 2.64	71	

Hazard Ratio and 95% CI (0.25 0.50 1.00 2.00 4.00)

B

	HR	95% CI	Pregnant (n)	P
Country				.26
Belgium	0.98	0.45 to 2.11	77	
Germany	1.04	0.53 to 2.02	137	
Other	1.81	0.88 to 3.73	97	
ER/PR status				.68
Negative	1.12	0.61 to 2.05	166	
Positive	1.39	0.59 to 3.24	145	
Molecular subtype				.78
Triple negative	1.04	0.51 to 2.09	118	
Luminal A–like	0.60	0.08 to 4.68	36	
Luminal B–like	1.73	0.63 to 4.75	109	
HER2 positive	1.34	0.51 to 3.54	145	
AJCC stage				.07
1	0.13	0.02 to 1.13	48	
2	1.86	0.81 to 4.28	177	
3	1.12	0.56 to 2.23	86	
Age, years				.27
30	1.43	0.73 to 2.77		
40	1.07	0.64 to 1.79		
50	0.80	0.37 to 1.74		
Chemotherapy				.51
None	1.25	0.26 to 6.05	4	
Adjuvant, no taxane	0.79	0.35 to 1.78	110	
Adjuvant, taxane	2.45	0.87 to 6.87	98	
Neoadjuvant, no taxane	1.79	0.36 to 8.81	28	
Neoadjuvant, taxane	1.31	0.50 to 3.45	71	

Hazard Ratio and 95% CI (0.25 0.50 1.00 2.00 4.00)

Comparison with other studies

**Table 4.** Outcome Rates of Breast Cancer During Pregnancy As Reported in Literature Since 1985*

| Study | Year | Total Patients | | | | | Follow-Up Period | DFS (%) | | OS (%) | | Authors' Conclusion |
| | | Pregnant | | Postpartum | | Nonpregnant | | | | | | |
		No.	%	No.	%	No.		Pregnant	Nonpregnant	Pregnant	Nonpregnant	
Nugent and O'Connell[17]	1985	19				155	5 years			57	56	No difference in OS
Greene[18]	1988	8				36	90 months			87.5	91.7	No difference in OS
Tretli et al[13]	1988	20	57	15	43	40	4 years			15	60	Worse survival for BCP
Guinee et al[12]	1994	26				139	5 years			40	74	Worse survival for BCP
Ezzat et al[19]	1996	28				84	7 years	37	33	57	61	No difference in DFS or OS
Ibrahim et al[20]	2000	72				216	47.5 months			67	58	No difference in DFS or OS
Bladström et al[11]	2003	94				7,779	10 years			43.9	68.6	Worse DFS and OS for BCP
Middleton et al[35]	2003	39					43 months	56		80		—
Ring et al[38]	2005	28					40.5 months	63		67		—
Hahn et al[37]	2006	57					38.5 months	70.2		77		—
Mathelin et al[15]	2008	18	45	22	55	61	10 years			72	97	Worse DFS and OS for BCP
Stensheim et al[22]	2008	59	56	46	44	13.106	4.9 years			56	69	No difference in OS
Beadle et al[21]	2009	51	49	53	51	668	91 months			62.6	64.6	No difference in OS
Halaska et al[23]	2009	16	50	16	50	32	142 months	81.3	62.5	87.5	71.9	No difference in DFS or OS
Cardonick et al[36]	2010	130					3.14 years			Stage I, 100; stage II, 86; stage III, 86; stage IV, 0		Survival for stages I to III seems similar to nonpregnant survival rates according to American Cancer Society Surveillance Research
Johansson et al[16]	2011	107	10	1,003	90	14.611						Worse survival for BCP
Azim et al[14]	2012	65				130	5 years	52.1	74.3	79.6	88.4	Significantly poorer DFS for BCP; no difference in OS observed
Current study		311				865	5 years	65	71	78	81	No difference in DFS or OS

NOTE. Table shows 17 studies with survival outcome of patients with BCP published since 1985; for studies making subdifferentiation between breast cancer during and after pregnancy (percentages specified), results of DFS and OS for postpartum and lactating patients with breast cancer are not shown, because this was not the aim of our study.[13,15,16,21-23]

Abbreviations: BCP, breast cancer during pregnancy; DFS, disease-free survival; OS, overall survival.
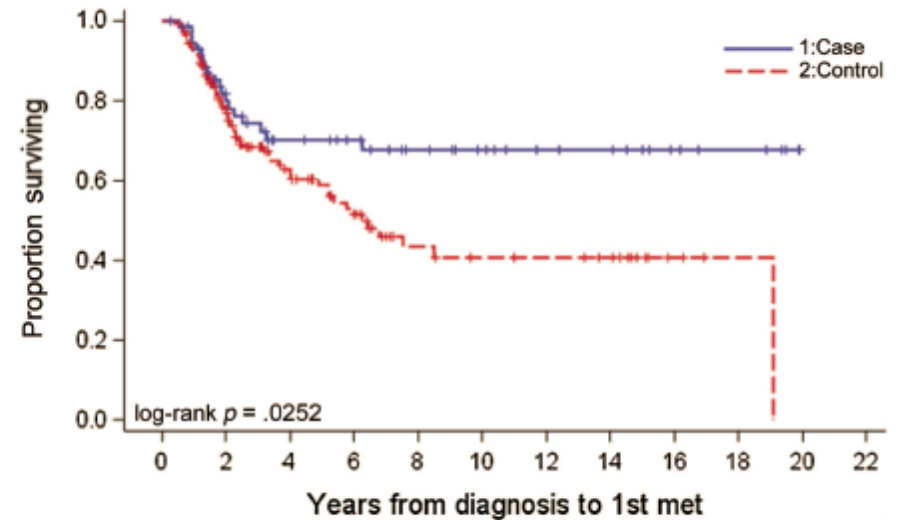
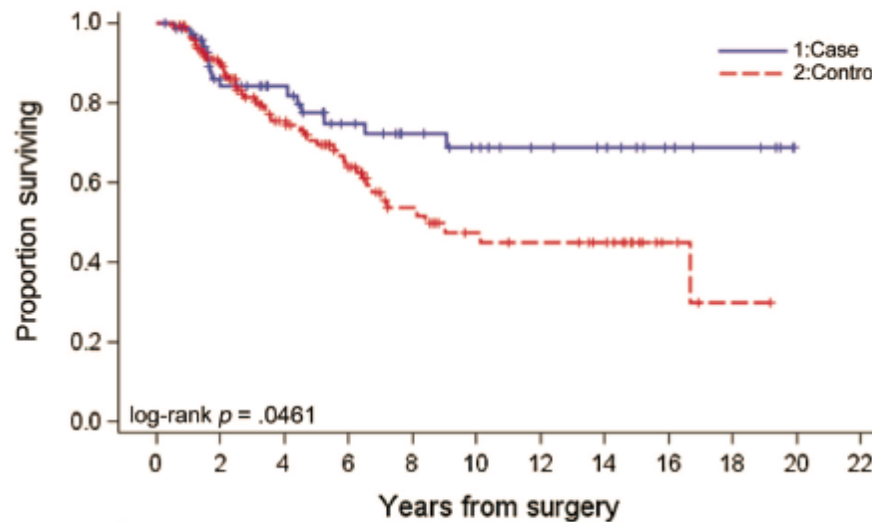*Postpartum breast cancer excluded.

A: Disease-Free Survival
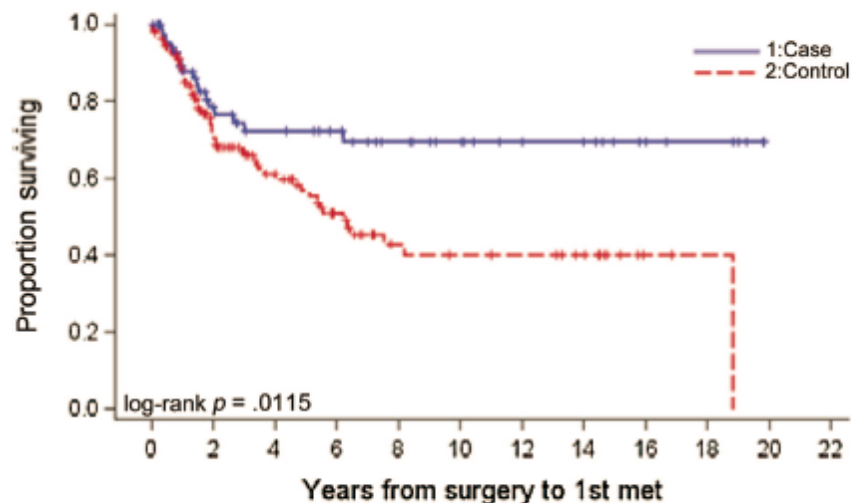
B: Progression-Free Survival

C: Overall Survival

Table 2. Cox proportional hazards regression models to predict survival

Variable	Level	Events	Total	Univariate model Hazard ratio HR	95% CI		p value	Multivariate model Hazard ratio HR	95% CI		p value
Disease-free survival (77 events/217 total)											
Study group	Nonpregnant	60	145	2.00	1.16	3.45	.0131	2.09	1.19	3.67	.0106
	Pregnant	17	72	1.00				1.00			
Age at diagnosis (yrs)		77	217	0.99	0.95	1.03	.5106	0.99	0.95	1.03	.7277
Year of diagnosis		77	217	1.00	0.96	1.05	.8463	0.99	0.94	1.03	.6318
Clinical cancer stage	Stage III	43	93	1.99	1.27	3.12	.0027	1.83	1.16	2.91	.0098
	Stage II or I	34	124	1.00				1.00			
Nuclear grade	Grade 3	61	169	1.44	0.83	2.50	.1986	1.41	0.79	2.53	.2453
	Grade 2 or 1	16	48	1.00				1.00			

Litton J et al. The Oncologist 2013

Mutations

	Patients diagnosed during pregnancy, *n* (%)	Patients not diagnosed during pregnancy, *n* (%)	*P* value
Total number	54 (100%)	113 (100%)	0.51
PIK3CA			
All	10 (18.6%)	26 (23%)	
Exon 9 mutations	3 (5.6%)	9 (8%)	
Exon 20 mutations	4 (7.4%)	12 (10.6%)	
Other *PIK3CA* mutations	3 (5.6%)	5 (4.4%)	
p53	2 (3.7%)	7 (6.2%)	0.51
MAP3K1	1 (1.9%)	2 (1.8%)	0.97
STK1	1 (1.9%)	0	0.15
RET	0	1 (0.9%)	0.49

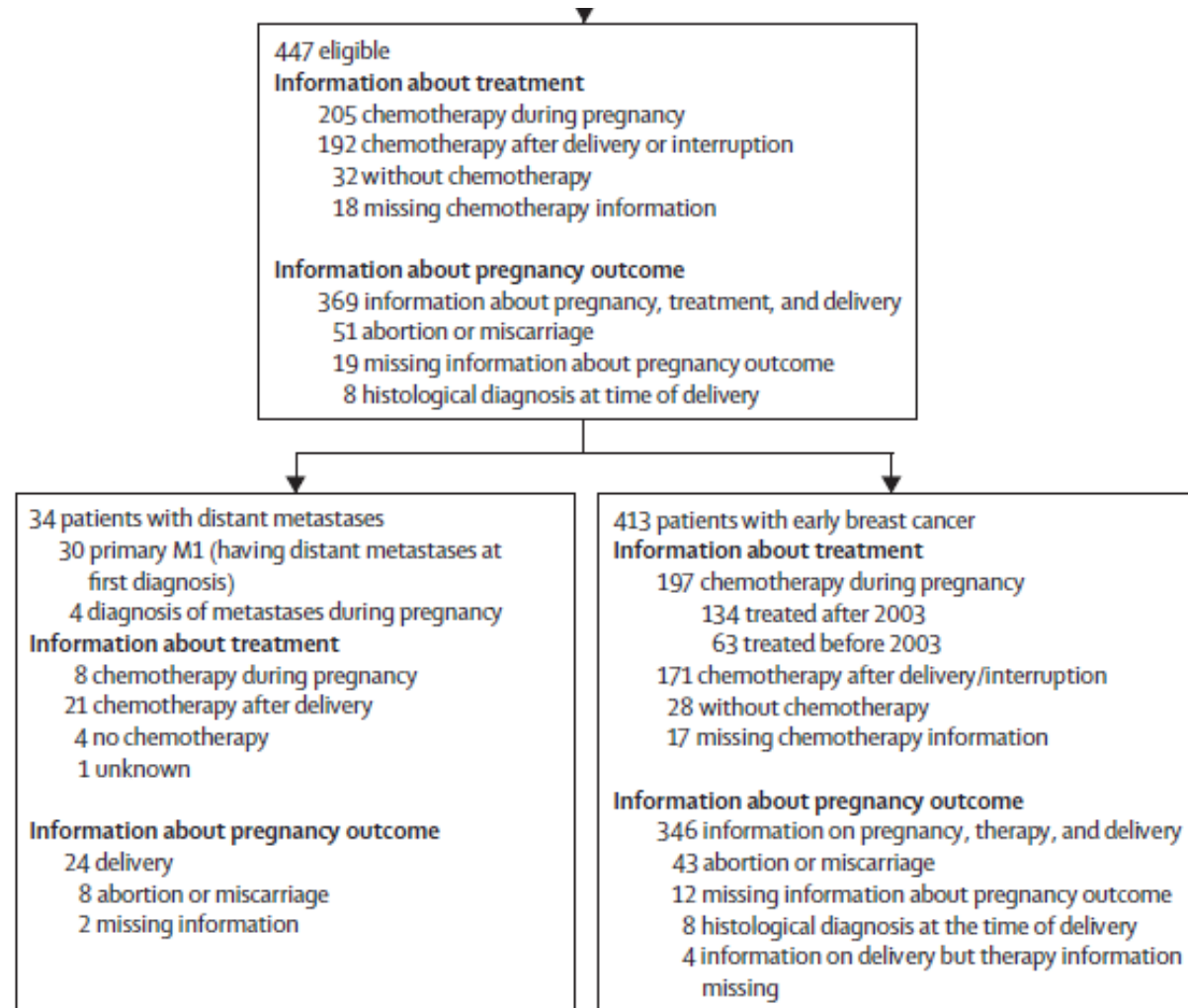Azim et al. Endor Rel Cancer 2014

PAM50 subtypes

Azim et al 2014
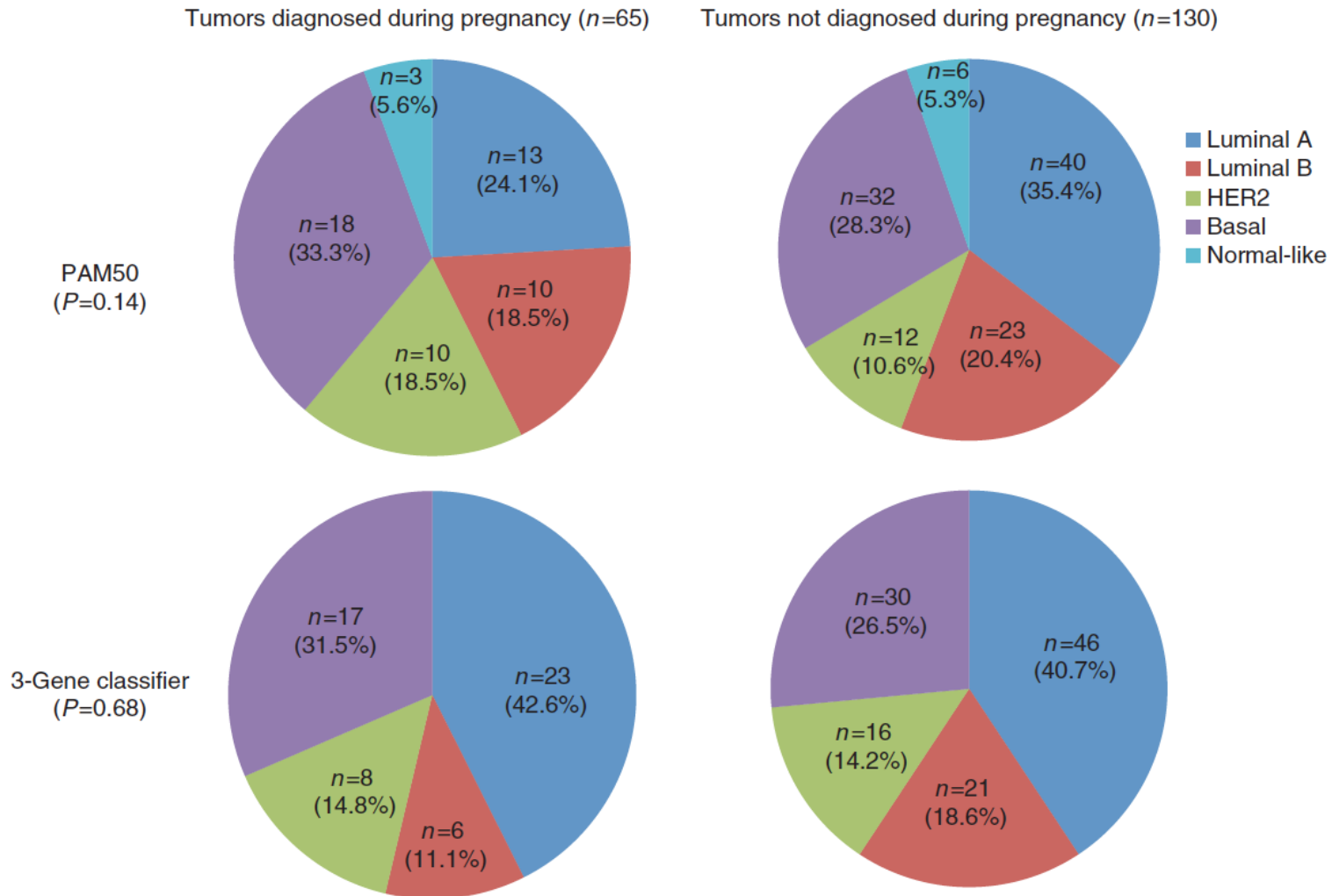
Treatment of breast cancer during pregnancy: an observational study

Sibylle Loibl, Sileny N Han, Gunter von Minckwitz, Marijke Bontenbal, Alistair Ring, Jerzy Giermek, Tanja Fehm, Kristel Van Calsteren,
Sabine C Linn, Bettina Schlehe, Mina Mhallem Gziri, Pieter J Westenend, Volkmar Müller, Liesbeth Heyns, Brigitte Rack, Ben Van Calster,
Nadia Harbeck, Miriam Lenhard, Michael J Halaska, Manfred Kaufmann, Valentina Nekljudova, Frederic Amant

447 eligible
Information about treatment
205 chemotherapy during pregnancy
192 chemotherapy after delivery or interruption
32 without chemotherapy
18 missing chemotherapy information

Information about pregnancy outcome
369 information about pregnancy, treatment, and delivery
51 abortion or miscarriage
19 missing information about pregnancy outcome
8 histological diagnosis at time of delivery

34 patients with distant metastases
30 primary M1 (having distant metastases at first diagnosis)
4 diagnosis of metastases during pregnancy
Information about treatment
8 chemotherapy during pregnancy
21 chemotherapy after delivery
4 no chemotherapy
1 unknown

Information about pregnancy outcome
24 delivery
8 abortion or miscarriage
2 missing information

413 patients with early breast cancer
Information about treatment
197 chemotherapy during pregnancy
134 treated after 2003
63 treated before 2003
171 chemotherapy after delivery/interruption
28 without chemotherapy
17 missing chemotherapy information

Information about pregnancy outcome
346 information on pregnancy, therapy, and delivery
43 abortion or miscarriage
12 missing information about pregnancy outcome
8 histological diagnosis at the time of delivery
4 information on delivery but therapy information missing

Loibl S et al. The Lancet Oncol 2012

Baseline characteristics

		All M0 % (N)	CHT during pregnancy % N=197	CHT after delivery % N=171
age median (range)		34 (23-51)	33 (25-43)	34 (23-51)
T status	1	21	17	20
	2	51	51	54
	3	21	21	23
	4 a-c	6	10	1
	4 d	2	2	2
Nodal status	N+	57	63	54
Histological type	Ductal	97	98	98
Grading	G3	76	79	72
ER	Negative	53	54	54
HER-2 status	positive	35	37	34
	missing	(62)		
	TNBC	33	32	37

Loibl S et al. The Lancet Oncol 2012

Patients´obstetrical characteristics

		All M0 % (N=413)	CHT during % (N= 197)	CHT thereafter % (N=171)
Time of diagnosis	week of gestation	24 weeks	20 weeks	30 weeks
	1st trimester	19	16	18
	2nd trimester	43	68	17
	3rd trimester	38	16	65
Pregnancy outcome	abortion /miscarriage*	11	n.a.	n.a.
Mode of delivery	Caesarean	45	47	45
Type of surgery	BCS	48	45	56

Loibl S et al. The Lancet Oncol 2012

Chemotherapy regimen applied

	Chemotherapy after delivery (N=171)	Chemotherapy during pregnancy (N=197*)
A(E)/C	16 (9%)	55 (28%)
FE(A)C	42 (25%)	34 (17%)
AC/EC-taxane	29 (17%)	46 (23%)
FE(A)C-taxane	19 (11%)	19 (10%)
CMF	16 (9%)	11 (6%)
AC/EC-CMF	4 (2%)	4 (2%)
FE(A)C-CMF	0 (--)	1 (1%)
A(E)mono-CMF	3 (2%)	4 (2%)
A(E)mono-taxane	0 (--)	4 (2%)
A(E)mono-taxane-CMF	1 (1%)	0 (--)
A(E)taxane	3 (2%)	0 (--)
A(E)taxane-CMF	1 (1%)	0 (--)
TAC	20 (12%)	0 (--)
dd E-P-C	4 (2%)	0 (--)
TC	1 (1%)	1 (1%)
Vinca alcaloid-based†	0 (--)	13 (7%)
Platinum-containing†	7 (4%)	2 (1%)
Other†	5 (3%)	3 (2%)

A=doxorubicin. C=cyclophosphamide. E=epirubicin. F=fluorouracil. CMF=cyclophosphamide, methotrexate, fluorouracil. T=docetaxel. P=paclitaxel. dd=dose-dense. Parenthesis mean "or" and solidi are "combined with"—eg A(E)/C=doxorubicin or epirubicin combined with cyclophosphamide. Data are n (%). *Not all agents were given during the course of pregnancy. †Some of these regimens contained taxanes.

Table 2: Chemotherapy regimens

Loibl S et al. The Lancet Oncol 2012

Taxanes during pregnancy

age (J)	therapy	start (SSW)	delivery (SSW)	cum dose mg/m²	weight(g)	remarks	Follow-up
30-42	Paclitaxel N=21	17-30	36 (30-38)	550 (300-1620)	2428 (1460-2800)	IUGR, Präeklampsie Anhydramnion* Anämie	15 (3-132) Monate
26-44	Docetaxel N=16	14-32	35 (32-40)	300 (175–570)	2245 (1490-3200)	Anhydramnios Preeclampsia ventriculomegalie	18 (9-36) Monate

* Simultaneous therapy with trastuzumab

Mir et al. Annals Oncol 2007; und 2010

Taxanes during pregnancy

GA dx (weeks)	Stage	GA chemo (weeks)	Neo/adj regimen	Toxicity	GA delivery (weeks)	BW (g)	Complications at birth: mother; infant	BD	Age at follow-up (months)	Medical issues
4	III	AC-13; D-24	Neo AC→D	Mouth sores	36	2438	None	No	54	Recurrent otitis media, myringotomy tubes
5	II	AC-14; P-25	Adj AC→P	None	34	2155	Preeclampsia; hyper-bilirubinemia	No	117	None
4	IIB	AC-12; P-21	Adj AC→P	None	30	1417	Preeclampsia; Apnea of prematurity, RDS, GERD	No	87	IgA deficiency, mild constipation
7,8	IIA	AC14; P-21	Adj AC→P	Neutropenia and PCP pneumonia	36	2580	Preterm labor and delivery	No	17	None
3.5	I	AC-13; P-20	Adj AC→P	Contractions	36	2835	PPROM	No	34	None
14	III	EC-18; D-30	EC→D	None	37	2410	None	No	16	None
13	III	AC-14; D-23	Neo AC→D	Cellulilitis of arm	37	2155	Meconium-stained fluid	No	61	Delayed speech
22.5	III	ED-24	Neo ED	None	37	2523	None	No		
14	III	AC-16; P-23; D-26	Neo AC→P→D	Allergic reaction to paclitaxel	36	2410	Neonatal neutropenia	Pyloric stenosis	2	None
17		AC-19; P-26; D-28	Neo AC→P→D	Hot flashes, nausea, tachycardia with paclitaxel	36	2892	None	No		
15.5	I	FAC-20; P-27	Neo FAC →P	Contractions	36	1956	IUGR	No	22	None
3	III	AC-14; P-22	Adj AC→P	None	37	2466	IUGR	No		

GA, gestational age; GA dx, gestational age at diagnosis in pregnancy; PPROM, premature rupture of membranes; RDS, respiratory distress syndrome; IUGR, intrauterine growth restriction (<10% for gestational

GA dx (weeks)	Stage	GA chemo (weeks)	Neo/adj regimen	Toxicity	GA delivery (weeks)	BW (g)	Complications at birth, mother; infant	BD	Age at follow-up (months)	Medical issues
7	I	8	Ca + P		36	1886	IUGR	No		
16	I	22	Cis + P		38	2608; 2623	Twin B: jaundice; hyperbilirubinemia	No	160	Twin A: none; Twin B: Tourette's syndrome, dyslexia, Asperger's syndrome and speech delay
18	I	24	Ca + P		39	3629		No	38	None

Cardonick et al. Annals Oncol 2012

Platinanaloga during pregnancy

**TABLE 3**
Evidence of Transplacental Transfer of Platinum Derivatives

Reference	Chemotherapy Regimen	Time Between the Last Cycle and Delivery	Gestational Age at Delivery, wk	Findings at Birth
Henderson 1993[35]	Cisplatin and cyclophosphamide followed by carboplatin (300 mg/m^2) and cyclophosphamide (no. of cycles NR)	NR	36	Platinum-DNA adducts on the placenta and maternal blood; no platinum-DNA adducts noted in the child's blood at 3 mo
Koc 1994[50]	Carboplatin (400 mg/m^2) for 3 cycles	9 wk	37	Normal CBC; normal serum creatinine; platinum-DNA adducts noted in cord blood lymphocytes and maternal lymphocytes
Elit 1999[28]	BEP over 5 d for 1 cycle	16 d	28	Normal leukocyte and platelet counts; cisplatin noted in the cord blood (0.80 μmol/L); cisplatin noted in the maternal blood (1.10 μmol/L)
Arango 1994[33]	Cisplatin (100 mg/m^2), and etoposide, and G-CSF for 4 cycles	3 d	35	Normal CBC; cisplatin noted in the blood of the neonate (40 μmol/L)

NR indicates not reported; CBC, complete blood cell count; BEP, bleomycin, etoposide, and cisplatin; G-CSF, granulocyte-colony-stimulating factor.

Mir et al. Cancer 2008

GBG
GERMAN
BREAST
GROUP

Platinum agents

Agent	Timing of birth[e] (No. of affected/total liveborn infants)				Spontaneous preterm birth[f]	Body weight at birth[g] (No. of affected/total liveborn infants)			Adverse health effects at follow-up[h]
	Early preterm	Late preterm	Term	Not specified	(No. of affected/ total liveborn infants)	SGA	Normal	Not specified	(No. of affected/ total offspring)
Busulfan	3% (1/29)	17% (5/29)	59% (17/29)	21% (6/29)	10% (3/29)	28% (8/29)	28% (8/29)	45% (13/29)	5% (1/22)
Carboplatin	38% (6/16)	38% (6/16)	6% (1/16)	19% (3/16)	6% (1/16)	13% (2/16)	81% (13/16)	6% (1/16)	7% (1/14)
Cisplatin	33% (34/102)	29% (30/102)	17% (17/102)	21% (20/102)	4% (4/102)	13% (13/102)	60% (61/102)	27% (28/102)	4% (3/68)
Cyclophosphamide	9% (37/400)	14% (56/400)	19% (74/400)	58% (233/400)	7% (27/400)	7% (28/400)	66% (263/400)	27% (109/400)	3% (8/284)

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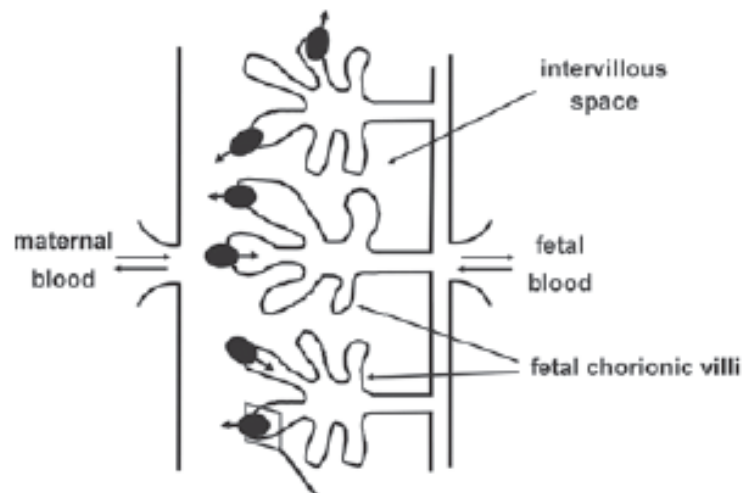
ABC transporters in placenta

GBG
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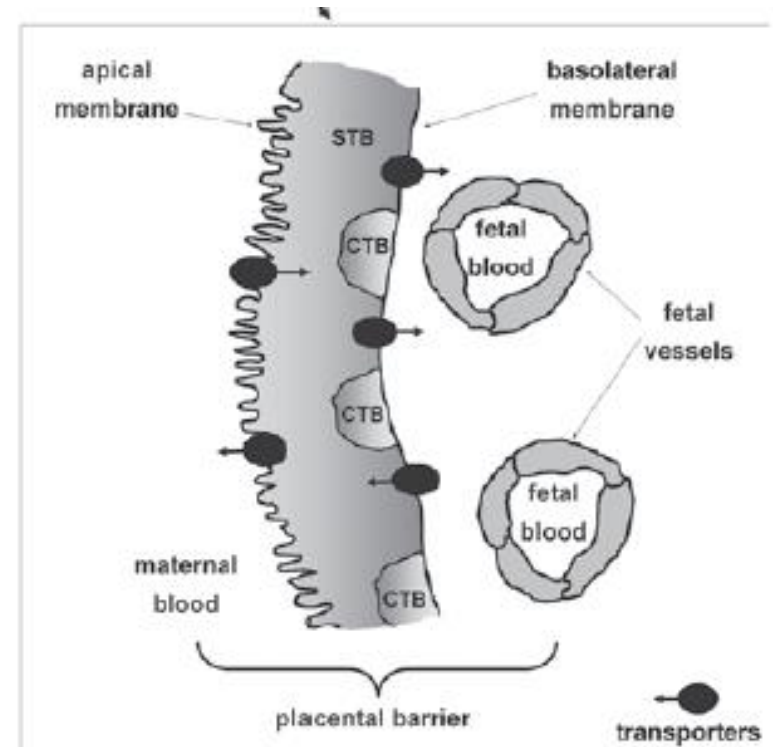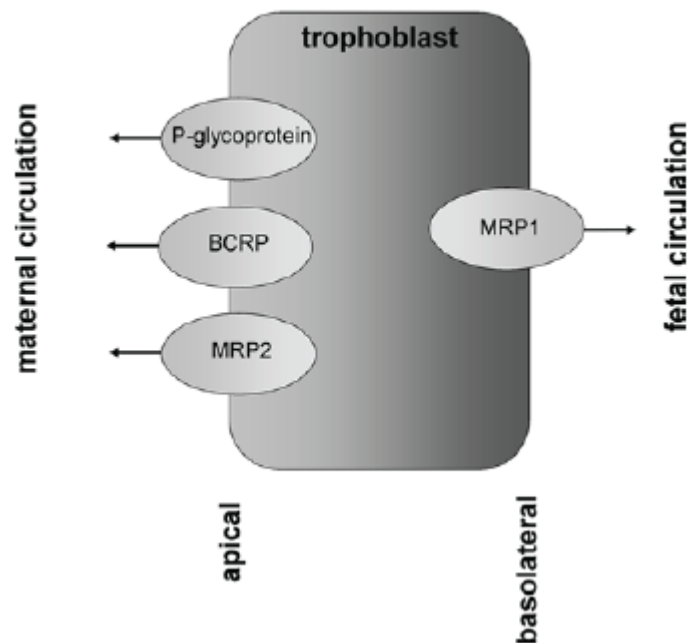
Transplacental transfer of cytotoxic agents

	Percent (SD)	Number of samples
Doxorubicin	7·5% (3·2)	6 (in 9 other fetal samples <LLQ)
Epirubicin	4·0% (1·6)	8 (in 3 other fetal samples <LLQ)
Carboplatin	57·5% (14·2)	7
Paclitaxel	1·4% (0·8)	7 (in 4 other fetal samples <LLQ)
Docetaxel	ND	9
4-OH-cyclophosphamide	25·1% (6·3)	3 (<LLQ in 1 fetal and maternal sample)
Vinblastine	18·5% (15·5)	9 (in 1 other fetal sample <LLQ)

LLQ=lower limit of quantification. ND=not detectable.

Table: Transplacental transfer of chemotherapeutic agents in pregnant baboons, from simultaneously collected maternal and fetal plasma samples[70,71]

Amant F, Loibl S, Neven P, Van Calsteren K. The Lancet 2012

Taxane PK analysis

The effect of pregnancy on volumes of distribution for doxorubicin, epirubicin, docetaxel and paclitaxel were estimated as fold-change of <1.32, <2.08, <1.37 and <4.21 respectively, with adequate precision (relative standard error [RSE] <37%). For doxorubicin, no gestational effect could be estimated on clearance. For epirubicin, docetaxel and paclitaxel a fold-change of 1.1 (RSE 9%), 1.19 (RSE 7%) and 1.92 (RSE 21%) were respectively estimated on clearance. Calculated dose adjustment-requirements for doxorubicin, epirubicin, docetaxel and paclitaxel were +5.5%, +8.0%, +16.9% and +37.8%, respectively. Estimated changes in infusion duration were marginal (<4.2%) except for paclitaxel (-21.4%).

Dose-Dense Chemotherapy

Table 4. Neonatal Outcomes

Chemotherapy Interval	Conventional Chemotherapy	Dose-Dense Chemotherapy	P
Gestational age (wk)	36 4/7	35 5/7	.60
Birth weight (g)	2,576	2,560	.64
IUGR (%)	7	0	>.99
Congenital anomalies (n)	3	1	.30
Neutropenia (%)	0	10	.09
Spontaneous preterm birth or preterm PROM (%)	17	30	.19

IUGR, intrauterine growth restriction; PROM, premature rupture of membranes.

Cardonick E, et al. Obstet Gynecol 2012

GBG

GERMAN
BREAST
GROUP

Birth weight according to gestational age

ANCOVA
P=0.018

Number of CHT cycles had no influence

Loibl S et al. The Lancet Oncol 2012
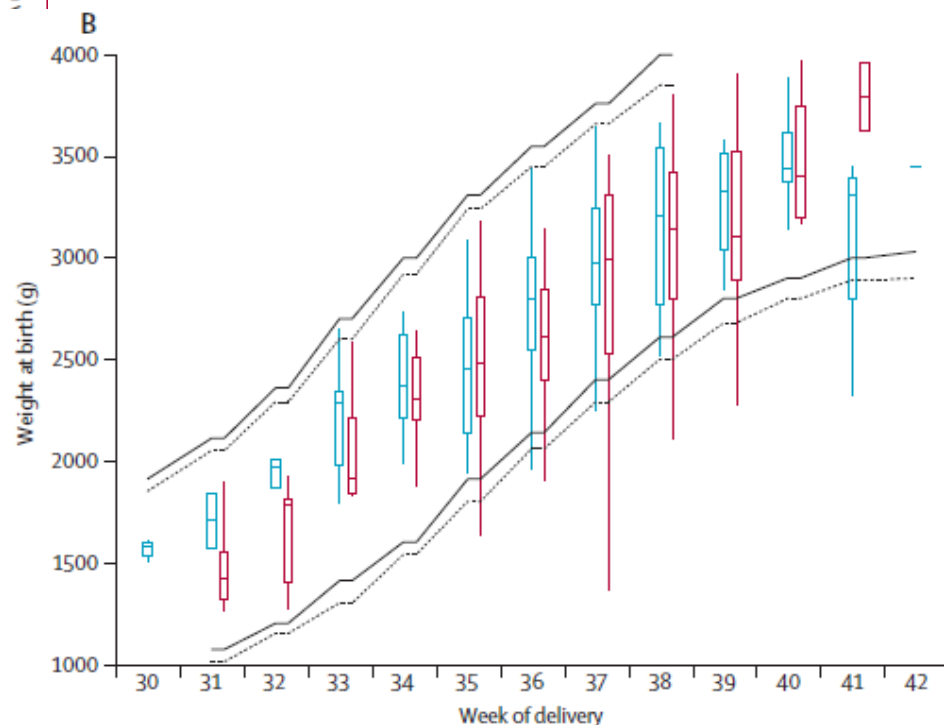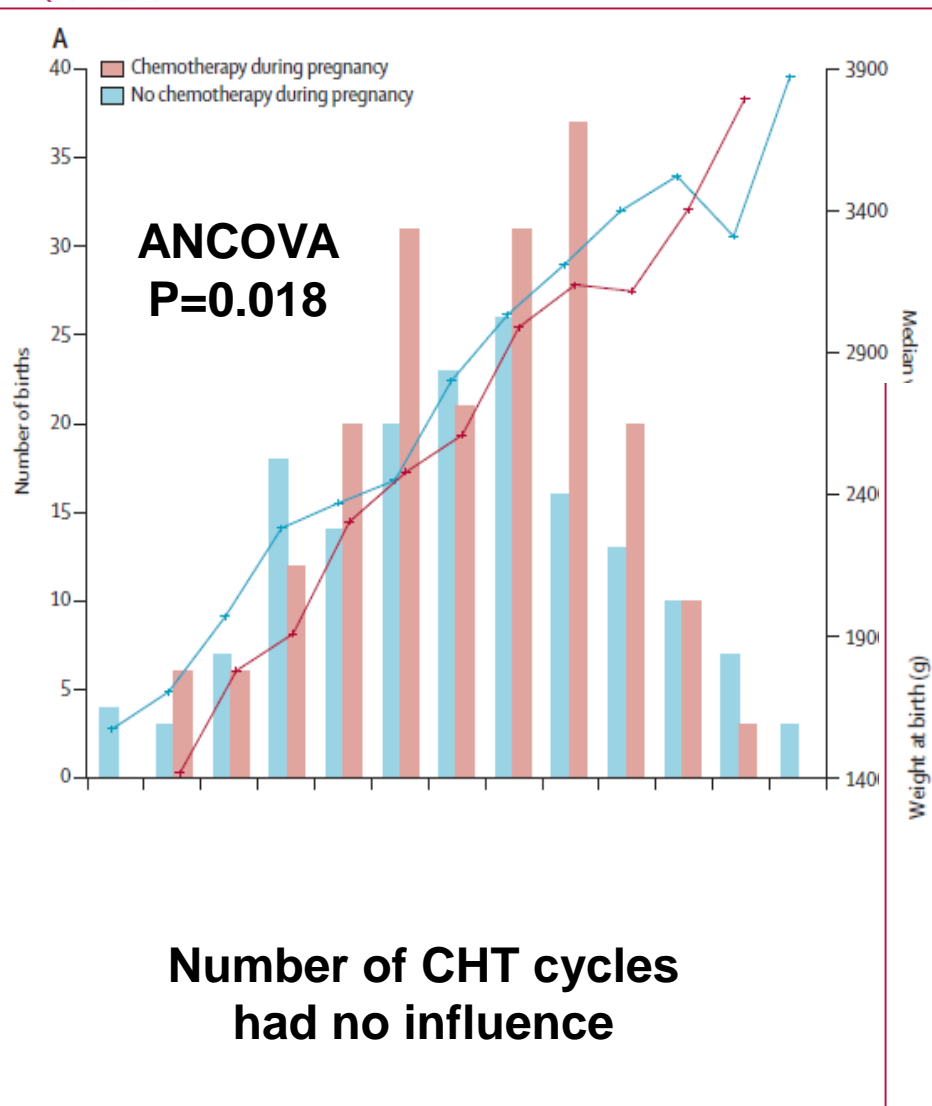
Reported Events in the Newborn
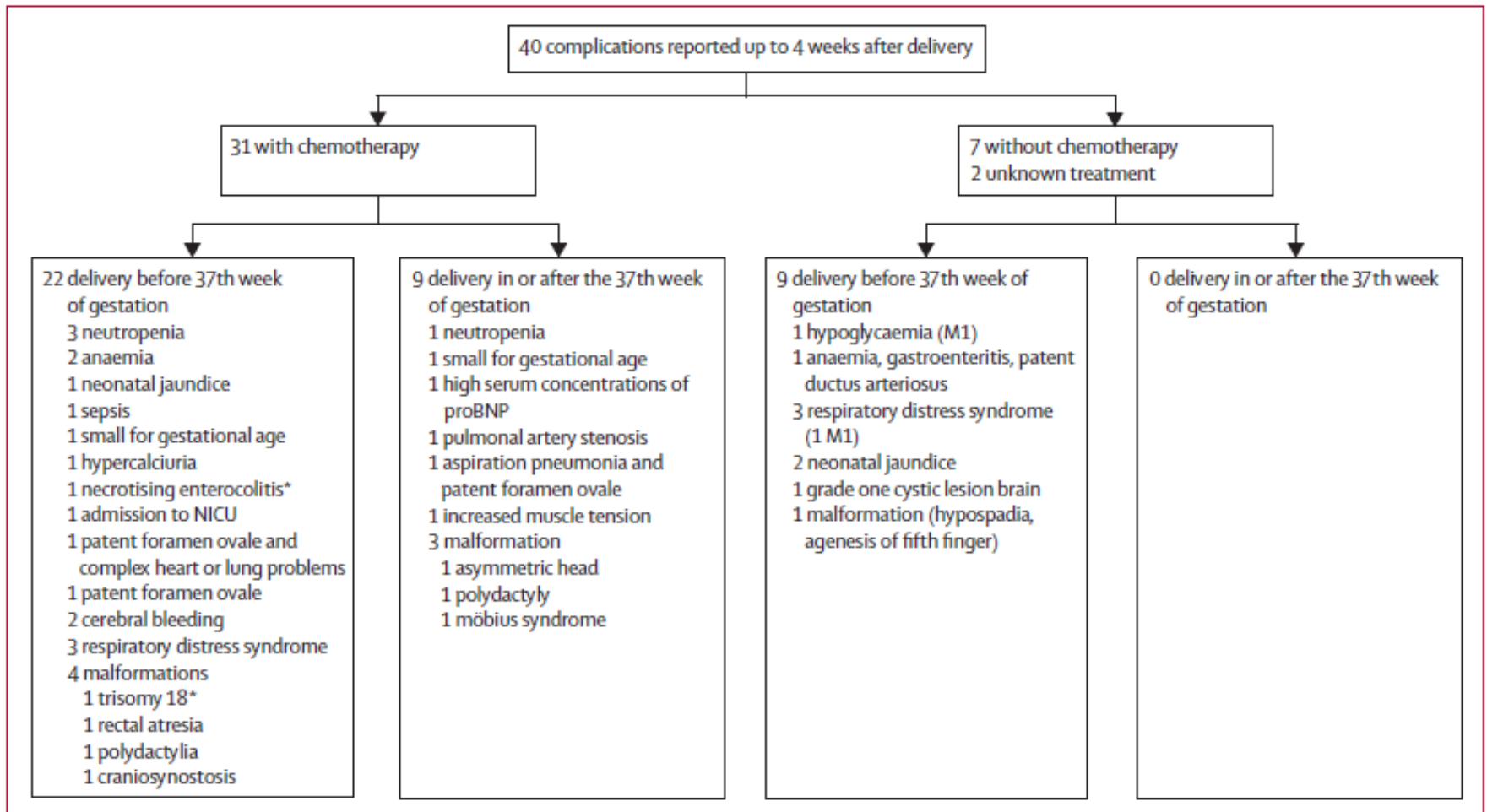
Figure 3: Adverse events in newborn babies up to 4 weeks after delivery

Loibl S et al. The Lancet Oncol 2012

Long term toxicity in children exposed to chemotherapy

Amant F et al. Lancet Oncol 2012
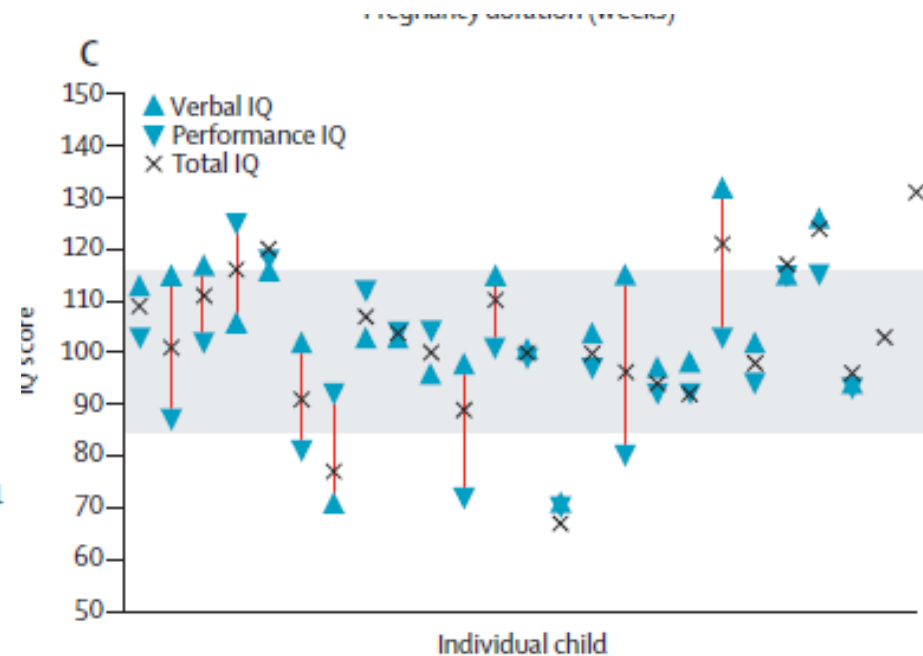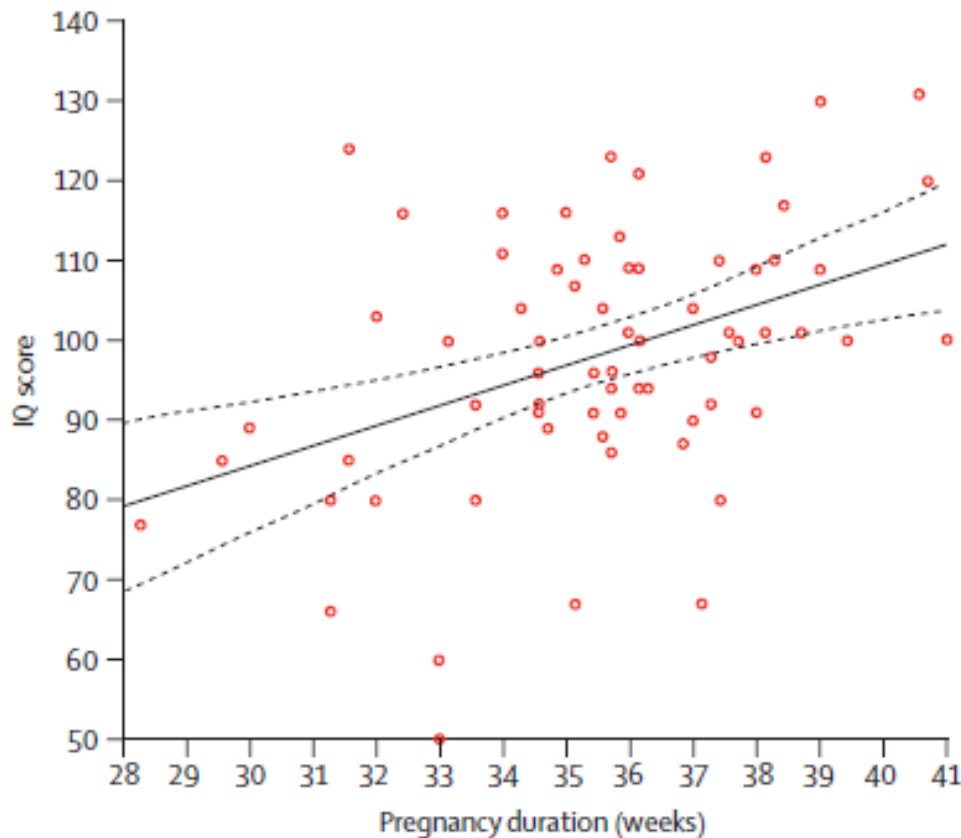
DFS in BCP with and w/o CHT during pregnancy

BCP Breast Cancer in Pregnancy

A

Disease-free survival (%)

— Chemotherapy during pregnancy
— No chemotherapy during pregnancy

p=0.537

Time (months)
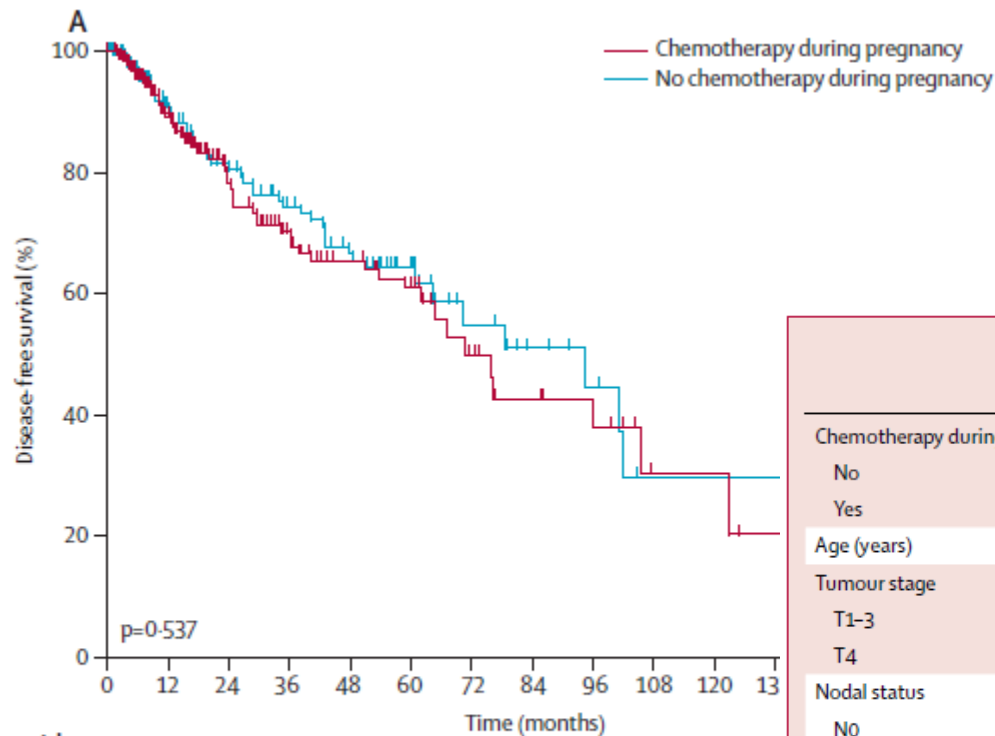
Number at risk

Chemotherapy during pregnancy	197	119	78	60	48	41	16	11	9	3	3	1
No chemotherapy during pregnancy	171	99	82	70	58	48	15	10	7	3	3	3

	Disease-free survival		Overall survival	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Chemotherapy during pregnancy				
No	1		1	
Yes	0·784 (0·504–1·22)	0·278	0·864 (0·454–1·64)	0·656
Age (years)	0·979 (0·929–1·03)	0·411	0·953 (0·887–1·02)	0·183
Tumour stage				
T1–3	1		1	
T4	5·66 (3·10–10·4)	<0·0001	4·44 (2·16–9·14)	<0·0001
Nodal status				
N0	1		1	
N+	2·75 (1·60–4·74)	<0·0001	6·57 (2·28–18·9)	<0·0001
Hormone receptor status				
ER/PgR negative	1		1	
ER/PgR positive	0·652 (0·415–1·02)	0·064	0·593 (0·314–1·12)	0·106

ER=oestrogen receptors. PgR=progesterone receptors.

Table 5: Multivariate analysis for disease-free and overall survival

Loibl S et al. The Lancet Oncol 2012

G B G
GERMAN BREAST GROUP

pCR rate in pregnant bc patients

Loibl S, et al. ASCO 2014
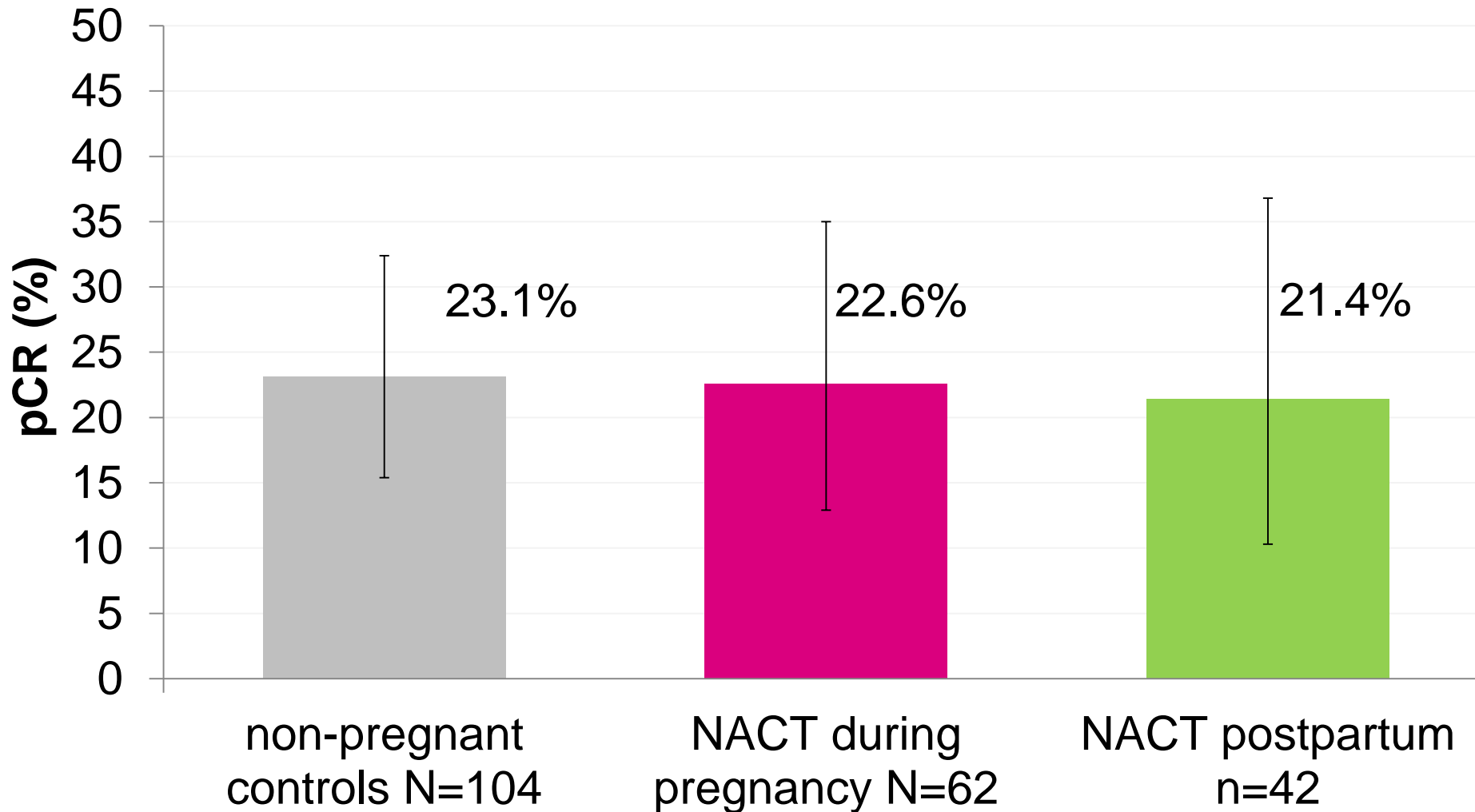
Trastuzumab during pregnancy

Table 1 Outcome of pregnancy in all three groups
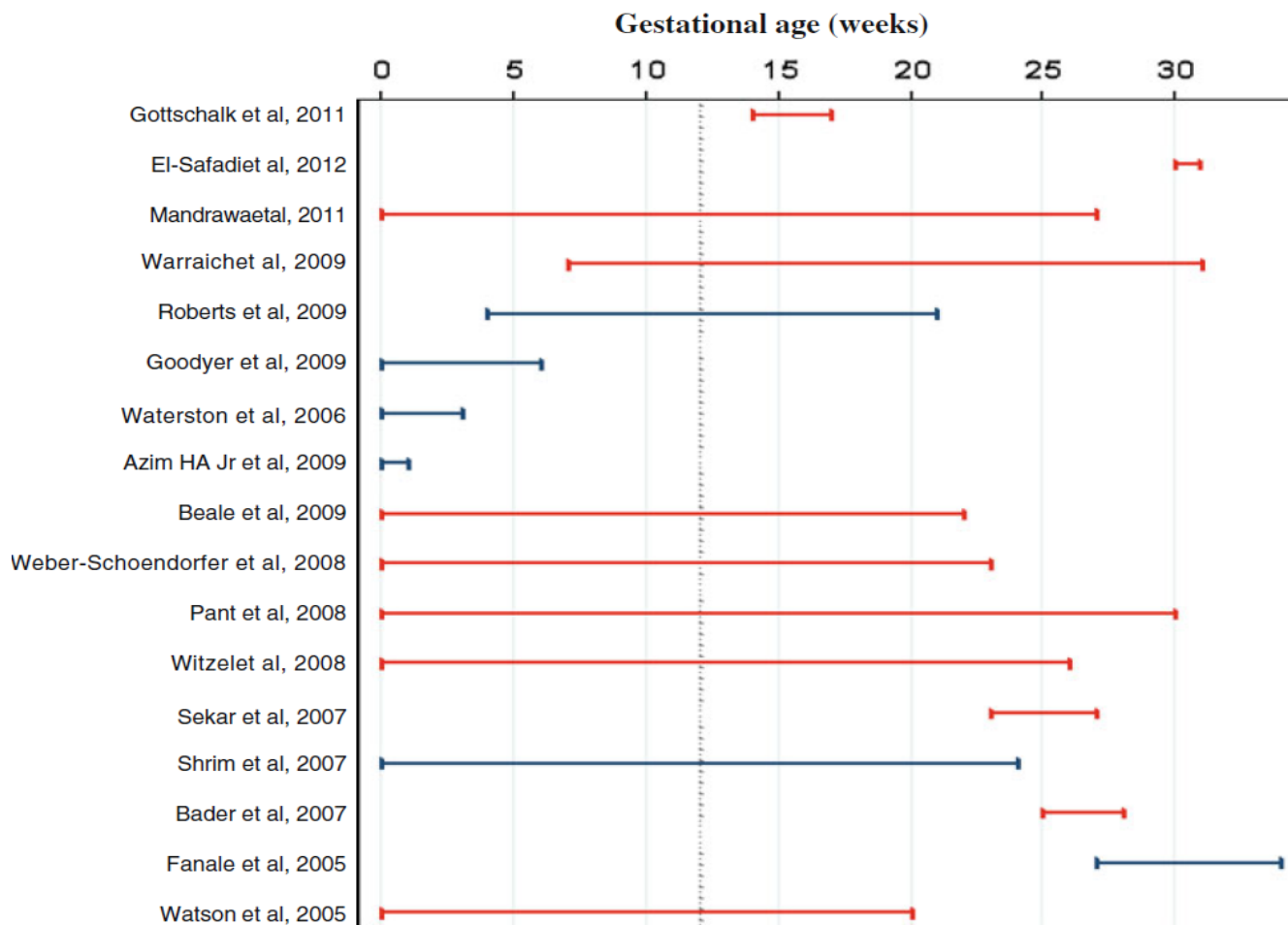
	Group 1 Pregnancy on trastuzumab and up to 3 months afterwards	Group 2 Pregnancy >3 months of trastuzumab	Group 3 Pregnancy with no exposure to trastuzumab
Number of patients (no. of pregnancies)	16 (16)	33 (45)[a]	9 (9)
Mean age at pregnancy in years (range)	32.5 (26–40)	34 (25–44)	35 (32–40)
Spontaneous abortion	4 (25%)	7 (16%)	0
Induced abortion	7 (44%)	4 (9%)	3 (33%)
Completed pregnancies	5 (31%)	30 (67%)	6 (67%)
Number of live births	5 (100%)	33 (100%)[b]	6 (100%)
Number of congenital anomalies	0	1	1
Number of oligohydramnios	0	0	0
Mean GW at delivery (range)	40 (39–40) ($n = 5$)	39 (36–41) ($n = 22$)	39 (38–41) ($n = 6$)
Mean Apgar score at 10 min (range)	10 (9–10) ($n = 3$)	9.6 (9–10) ($n = 18$)	9 (8–10) ($n = 6$)
Mean fetal weight in grams (range)	3,485 (2,940–4,180) ($n = 4$)	3,397 (2,200–4,500) ($n = 26$)	3197 (2,131–3,800) ($n = 6$)
Mean fetal length in cm (range)	50 (50–51) ($n = 3$)	52 (48–61) ($n = 18$)	49 (45–52) ($n = 5$)

GW gestational week

[a] Missing information on 4 pregnancies

[b] Three twin pregnancies

Azim H et al. BCRT 2012

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Trastuzumab during pregnancy

Panel: Checklist for care of pregnant patients with breast cancer

At diagnosis
- Confirm progressing pregnancy and define duration of pregnancy
- Exclude pre-existing fetal anomalies by ultrasonography before examinations or interventions

Obstetric follow-up during oncological treatment
- Consider intraoperative fetal monitoring from 24 to 26 weeks' gestation onwards, according to local policy
- Chemotherapy is possible during second or third trimester
  - Check for fetal wellbeing and general development
  - Check for preterm contractions
  - Check for intrauterine growth restriction
  - No chemotherapy after 35 weeks' gestation
- Radiotherapy is possible during first or second trimester
  - Check for fetal wellbeing and general development
  - Check for preterm contractions
  - Check for intrauterine growth restriction

Delivery
- Mode of delivery is determined by obstetric indications
- Timing of delivery
  - Preferably after 35–37 weeks' gestation
  - At least 3 weeks after last cycle of chemotherapy (delivered at 21 day intervals)
  - If preterm delivery is inevitable, fetal lung maturity is essential

Post-partum
- Examine placenta for metastatic disease
- Oncological treatment can be continued immediately after vaginal delivery, and a week after uncomplicated caesarean section
- Breastfeeding
  - If physiologically possible—eg, after radiotherapy
  - Contraindicated during and after chemotherapy

Malignancies in Pregnancy 2

Breast cancer in pregnancy

Frédéric Amant, Sibylle Loibl, Patrick Neven, Kristel Van Calsteren

Breast cancer staging and treatment are possible duri

General recommendations

- **To treat as closely as possible according to general recommendations for non-pregnant women**

- Prefer sequential regimen due to lower toxicity but equal efficacye.g. EC-Paclitaxel weekly

- Dose according to acutal weight – avoid underdosing

- Supportive treatment as indicated

- Observe pregnancy closely – Biometry once a cycle

- Treat within a multidisciplinary team including obstetricians, perinatologist, neonatologist

- Include the patients in public available registries

- Further information www.germanbreastgroup.de