

## Disclosure Information

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- Chugai
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## Lifestyle Intervention and Effect on Disease-free Survival in Early Breast Cancer Patients: Interim Analysis from the Randomized SUCCESS C Study

Wolfgang Janni, Brigitte K. Rack, Thomas W.P. Friedl, Volkmar Müller, Ralf Lorenz, Mahdi Rezai, Hans Tesch, Georg Heinrich, Ulrich Andergassen, Nadia Harbeck, Fabienne Schochter, Amelie De Gregorio, Marie Tzschaschel, Jens Huober, Philip Hepp, Tanja N. Fehm, Andreas Schneeweiss, Werner Lichtenegger, Jens Blohmer, Dagmar Hauner, Matthias W. Beckmann, Lothar Häberle, Peter A. Fasching, Hans Hauner

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## Background:

Obesity and a low level of physical activity are associated with

- a higher risk of developing breast cancer <sup>1,2</sup>

<sup>1</sup> Pizot et al. *Eur J Cancer*. 52:138-54, 2016

<sup>2</sup> Reeves et al. *BMJ*. 335(7630):1134, 2007

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## Background:

Obesity and a low level of physical activity are associated with

- a higher risk of developing breast cancer <sup>1,2</sup>
- an increased risk for recurrence and reduced survival in breast cancer patients <sup>3-7</sup>

<sup>1</sup> Pizot et al. *Eur J Cancer*. 52:138-54, 2016

<sup>2</sup> Reeves et al. *BMJ*. 335(7630):1134, 2007

<sup>3</sup> Calle et al. *N Engl J Med*. 348(17):1625-38, 2003

<sup>4</sup> Ewertz et al. *J Clin Oncol*. 29(1):25-31, 2011 and *J Clin Oncol*.10;30(32):3967-75, 2012 .

<sup>5</sup> Chan et al. *Ann Oncol*. 25:1901-14, 2014

<sup>6</sup> Pan & Gray (EBCTCG) *J Clin Oncol* 32, Suppl. abstr 503 (ASCO 2015)

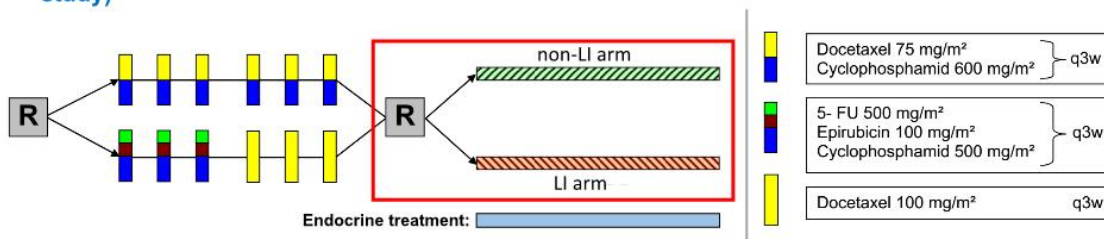
<sup>7</sup> Chlebowski RT, *Cancer*. 2018 Oct 8 [Epub ahead of print]

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## SUCCESS C – study design

(open-label, multicenter, 2x2 factorial design, randomized controlled Phase III study)



### First randomization:

3 cycles FEC100 followed by 3 cycles docetaxel vs. 6 cycles docetaxel / cyclophosphamide

### Second randomization for lifestyle intervention:

- **LI arm: Standardized and structured telephone and mail-based lifestyle intervention program with the aim of individual weight loss by diet and physical activity**
- **Non-LI arm: General recommendations for healthy lifestyle**

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## Methods: Lifestyle intervention

- **Intensified lifestyle intervention program (LI arm):**
  - ✓ 2-year standardized and structured telephone and mail-based intervention program (goals: individual weight loss, diet and physical activity)
  - ✓ intervention addressing behavioral and motivational issues related to weight management (maintaining motivation, emotional distress, time management)
    - 19 telephone contacts with trained lifestyle coaches
    - detailed patient workbook supplemented with mailings with focus on weight management
    - regular mailings of newsletters (weight loss intervention materials) at month 7 and 14
    - up to three additional telephone calls and mailings to address key issues or problems
- **General recommendations for healthy lifestyle (non-LI arm):**
  - ✓ standardized mail-based educational support focussing on healthy living (including mailings after completion of chemotherapy and at month 12)
  - ✓ 2-years of lifestyle information at regular intervals by either a newsletter or a lifestyle magazine

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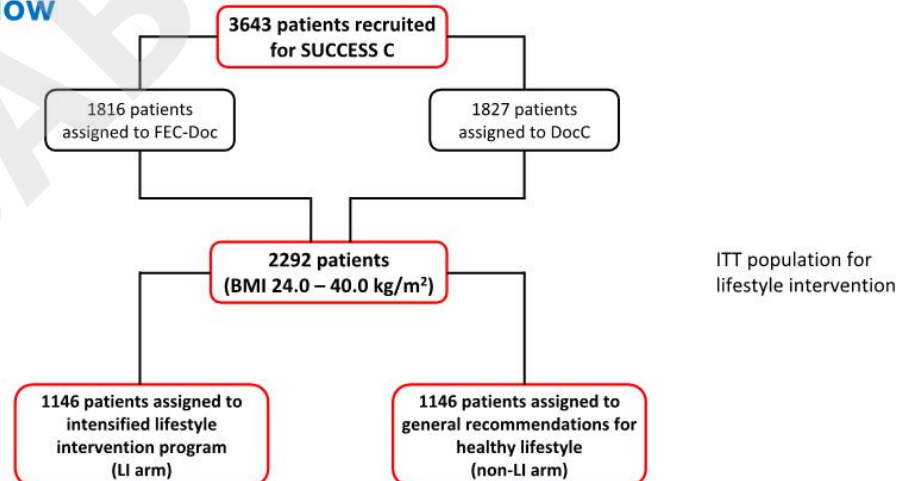
## Methods: Statistical analysis

- Univariable (Kaplan-Meier, Log-rank test) and multivariable (Cox regression) survival analysis
- Outcome analysed using disease-free survival (DFS) and overall survival (OS), defined according to STEEP criteria <sup>1</sup>
- Median observation time 64.2 months for DFS and 64.6 months for OS

<sup>1</sup> Hudis et al. *J Clin Oncol.* 2007; 25:2127-2132.

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## Patient flow



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## Patient characteristics (n = 2292)

Patients in the two randomization arms well balanced with regard to clinicopathological characteristics (all  $p > 0.10$ )

Patient and tumor characteristics*		LI arm (n = 1146)		non-LI arm (n = 1146)	
Age (years)		57.0	28 – 78	57.0	25 – 79
Body mass index (kg/m <sup>2</sup> )		28.2	23.7 – 40.2	27.9	24.0 – 40.4
Tumor size (n, %)	pT1	467	40.8	489	42.7
	pT2	594	51.8	583	50.9
	pT3/pT4	85	7.4	74	6.5
Nodal stage (n, %)	pN0	455	39.7	474	41.4
	pN+	691	60.3	671	58.6
Histological grading (n, %)	G1	84	7.3	69	6.0
	G2	567	49.5	601	52.4
	G3	495	43.2	476	41.5
Histological type (n, %)	ductal	925	80.7	909	79.3
	lobular	151	13.2	169	14.7
	other	70	6.1	68	5.9
Hormone receptor status (n, %)	negative	263	22.9	266	23.2
	positive	883	77.1	880	76.8
Menopausal status (n, %)	premenopausal	369	32.2	351	30.6
	postmenopausal	777	67.8	795	69.4
Adjuvant chemotherapy (n, %)	FEC-Doc	577	50.3	567	49.5
	DocC	569	49.7	579	50.5

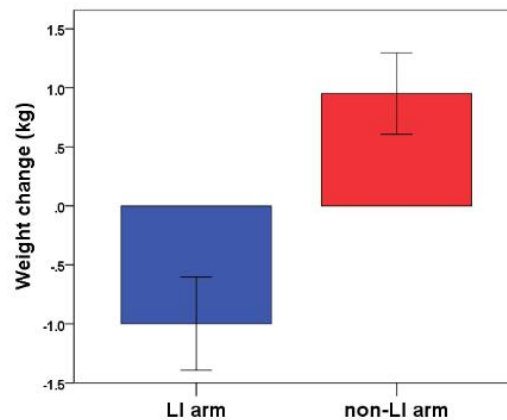
\* missing data in some categories

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## Weight change by lifestyle intervention arm – ITT analysis

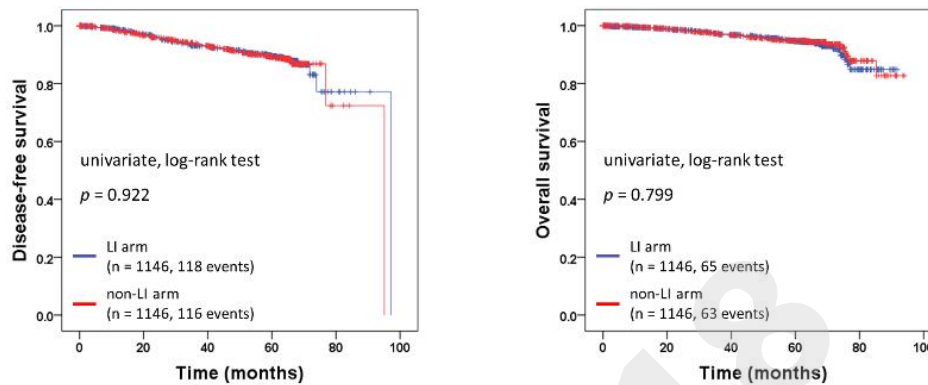
Intensified lifestyle intervention program was successful in reducing patients' weight (from start of LI intervention to 2-year follow up):

- LI arm (n = 828): weight **loss 1.0 kg** (95% CI -0.60 to -1.39)
- non-LI arm (n = 816): weight **gain 0.95 kg** (95% CI 0.61 to 1.30)



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## Disease-free survival (DFS) and overall survival (OS) by lifestyle intervention arm – ITT analysis



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## Disease-free survival (DFS) and overall survival (OS) by lifestyle intervention arm – ITT analysis

Multivariable Cox regression adjusted for age, body mass index, menopausal status, tumor size, nodal stage, histological grade, histological type, hormone receptor status, and adjuvant chemotherapy (i.e. first randomization)

- **DFS: Hazard ratio (LI arm vs. non-LI arm) 0.91 (95% CI 0.70 – 1.18);  $p = 0.48$**
- **OS: Hazard ratio (LI arm vs. non-LI arm) 0.90 (95% CI 0.63 – 1.28);  $p = 0.56$**

64.4 % of patients completed life style intervention

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## Explorative subgroup analysis: Completion of lifestyle intervention (yes/no)

### Definitions

- **Completer in the LI arm:**  
All patients who completed the final telephone-based interview approximately 24 months after the start of the intensified lifestyle intervention program
- **Completer in the non-LI arm:**  
All patients that did not meet any of the following criteria for non-completers
  - basic information on healthy living not received
  - objection to receive further information
  - withdrawal from the intervention

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## Explorative subgroup analysis: Completion of lifestyle intervention (yes/no)

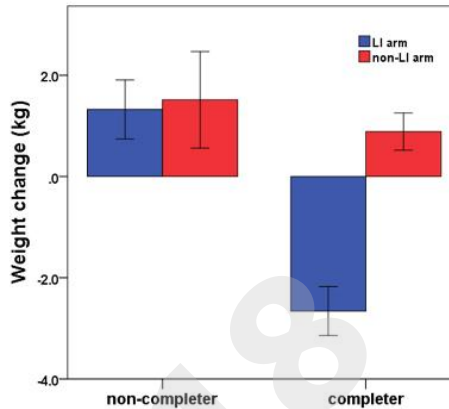
	completer	non-completer
LI arm	552 (48.2%)	594 (51.8%)
non-LI arm	925 (80.7%)	221 (19.3%)
Total	1477 (64.4%)	815 (35.6%)

In the LI arm a much lower proportion of patients completed the 2-year lifestyle intervention program compared to the non-LI arm

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## Explorative subgroup analysis: Completion of lifestyle intervention (yes/no)

Weight loss (from start of LI intervention to 2-year follow up) only observed in patients of the LI arm that completed the intensified lifestyle intervention program



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## Patient characteristics completer/non-completer LI arm (n = 1146)

There were moderate, but significant differences between completers and non-completer for age ( $p = 0.013$ ), grading ( $p = 0.043$ ) and hormone receptor status ( $p = 0.004$ )

\* missing data in some categories

§ significant differences ( $p < 0.01$ )

Patient and tumor characteristics*		completer (n = 552)		non-completer (n = 594)	
Age (years) §		56.0	30 – 78	58.0	28 – 77
Body mass index (kg/m <sup>2</sup> )		28.0	24.0 – 39.8	28.3	23.7 – 40.2
Tumor size (n, %)	pT1	245	44.4	222	37.4
	pT2	272	49.3	322	54.2
	pT3/pT4	35	6.3	50	8.4
Nodal stage (n, %)	pN0	207	37.5	248	41.8
	pN+	345	62.5	346	58.3
Histological grading § (n, %)	G1	48	8.7	36	6.1
	G2	284	51.4	283	47.6
	G3	220	39.9	275	46.3
Histological type (n, %)	ductal	441	79.9	484	81.5
	lobular	73	13.2	78	13.1
	other	38	6.9	32	5.4
Hormone receptor status § (n, %)	negative	106	19.2	157	26.4
	positive	446	80.8	437	73.6
Menopausal status (n, %)	premenopausal	191	34.6	178	30.0
	postmenopausal	361	65.4	416	70.0
Adjuvant chemotherapy (n, %)	FEC-Doc	281	50.9	296	49.8
	DocC	271	49.1	298	50.2

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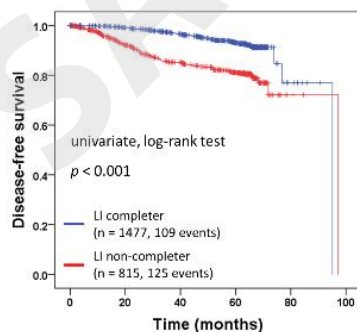
## Explorative subgroup analyses: Survival by lifestyle intervention arm

Patient cohort	Number of DFS events observed		
	completers	non-completers	total
LI arm	28/552 (5.1%)	90/594 (15.2%)	118/1146 (10.3%)
non-LI arm	81/925 (8.8%)	35/221 (15.8%)	116/1146 (10.1%)

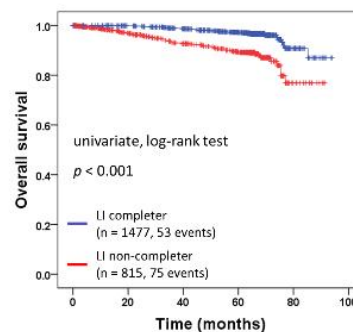
LI-arm: most DFS events observed in non-completers  
non-LI arm: most DFS events observed in completers

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## Explorative subgroup analysis: Completion of lifestyle intervention (yes/no)



DFS median observation time: completer: 64.4 months, non-completer: 58.9 months ( $p < 0.001$ )



OS median observation time: completer: 64.7 months, non-completer: 63.3 months ( $p < 0.001$ )

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## Patient characteristics completers only (n = 1477)

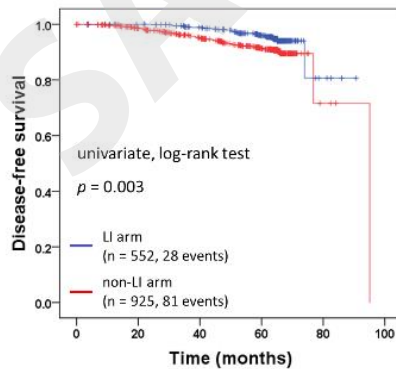
Completers in the two randomization arms well balanced with regard to clinicopathological characteristics (all  $p > 0.10$ )

\* missing data in some categories

Patient and tumor characteristics*		LI arm (n = 552)		non-LI arm (n = 925)	
Age (years)		56.0	30 – 78	57.0	25 – 79
Body mass index (kg/m <sup>2</sup> )		28.0	24.0 – 39.8	28.0	24.0 – 39.7
Tumor size (n, %)	pT1	245	44.4	393	42.5
	pT2	272	49.3	472	51.0
	pT3/pT4	35	6.3	60	6.5
Nodal stage (n, %)	pN0	207	37.5	384	41.5
	pN+	345	62.5	541	58.5
Histological grading (n, %)	G1	48	8.7	57	6.2
	G2	284	51.4	489	52.9
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Histological type (n, %)	ductal	441	79.9	732	79.1
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Menopausal status (n, %)	premenopausal	191	34.6	284	30.7
	postmenopausal	361	65.4	641	69.3
Adjuvant chemotherapy (n, %)	FEC-Doc	281	50.9	451	48.8
	DocC	271	49.1	474	51.2

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## Explorative subgroup analysis: Survival by lifestyle intervention arm (completers only)



Multivariable adjusted Cox regression  
**Hazard ratio (LI arm vs. non-LI arm)**  
**0.51 (95% CI 0.33 – 0.78);  $p = 0.002$**

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## Limitations of the study

- Low adherence to intensified life style intervention program
- Explorative and non-planned interim analysis (completers vs. non-completers)
- Patients in the non-LI arm may be less well documented
- Relatively low number of events
- Potential bias (health status, motivation) unaccounted for: 'Healthy participant effect'?

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## Summary

- Telephone-based intensified lifestyle intervention (LI arm) led to an average weight loss of 1.0 kg, while the patients in the control group with general lifestyle recommendations only (non-LI arm) gained on average 0.95 kg
- ITT analyses revealed no significant difference in DFS or OS between patients randomized to LI-arm vs non-LI arm ( $p=0.92$ ,  $p=0.88$  resp.)
- Only 48% of the patients assigned to intensified lifestyle intervention completed the program
- In an exploratory analysis, patients that completed the 2-year lifestyle program (LI and non-LI arm) had a significantly better DFS and OS compared to non-completers
- Analysis among completers suggests a higher weight loss (3.6kg difference) and significantly better DFS in patients in the LI arm compared to patients in the non-LI arm
- Bias in the exploratory analysis cannot be ruled out

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## Conclusion

- This analysis suggests that the completion of a systematic telephone-based lifestyle intervention program does positively impact body mass index and may improve outcome in overweight patients with early breast cancer, as indicated in previous studies
- However, based on a potential bias between completers and non-completers, the results of the exploratory interim analysis should be interpreted with appropriate caution
- Further analyses (long-term f/u, additional outcomes, predictive factors) are planned
- Results of further trials, such as BWEL, eagerly awaited

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Back up slide

## Explorative subgroup analyses: (completers only) Survival after the end of lifestyle intervention

Patient cohort	Number of DFS and OS events observed	
	DFS after end of LI	OS after end of LI
LI arm	24/552 (4.3%)	8 /552 (1.4%)
non-LI arm	49/925 (5.3%)	19/925 (2.1%)

Among completers, a (slightly) lower proportion of DFS and OS events was observed after the end of the lifestyle intervention in patients in the LI arm as compared to patients in the non-LI arm