Disclosure of speaker

Dr. Hanusch Claus A.

- **Conducting trials with financial support:**

  Roche, Novartis, Pfizer, Boehringer Ingelheim, Amgen, Galena

- **Member of speakers´ bureau and Advisory board member:**

  Roche, Novartis, Pfizer, Boehringer Ingelheim, Amgen

Dual blockade with Afatinib and Trastuzumab as neoadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy efficacy and safety analysis

(DAFNE – GBG 70)

EudraCT-Nr.: 2011-004704-38

Claus Hanusch, Andreas Schneeweiss, Michael Untch, Stefan Paepke, Sherko Kümmel, Christian Jackisch, Jens Huober, Jörn Hilfrich, Bernd Gerber, Holger Eidtmann, Carsten Denkert, Serban Costa, Jens U. Blohmer, Sibylle Loibl, Nicole Burchardi, Gunter von Minckwitz

for the

GBG/AGO-B study groups

Presented at the 2014 ESMO. Presented data is the property of GBG and AGO-B.

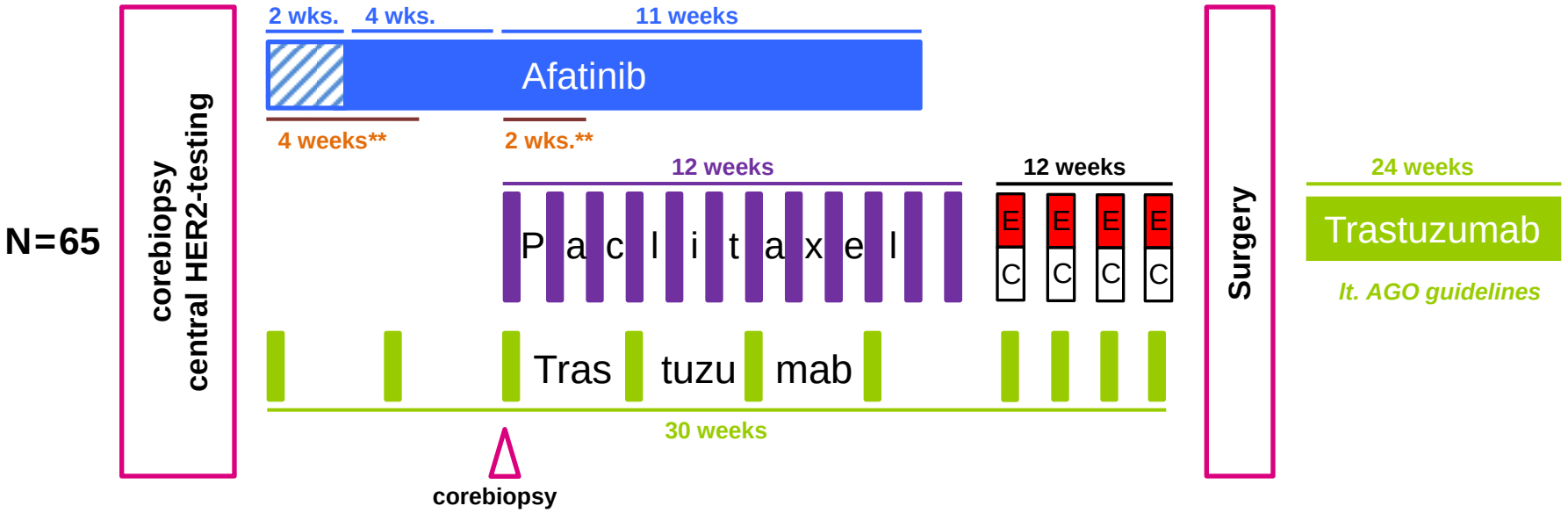
Introduction

- **Neoadjuvant standard therapy for primary breast cancer: anthracycline-taxane (AT)-containing chemotherapy (CT) ≥ 18 weeks (1).**
- **HER2 positive disease: addition of trastuzumab led to pathological complete response (pCR) rate of approx. 40% (2-4).**
- **AT chemotherapy plus dual blockage of HER2 receptor (e.g. trastuzumab + lapatinib/ trastuzumab + pertuzumab) can increase pCR rate further by approx. 20% (5,6).**
- **Afatinib, an irreversible ErbB-family blocker, has been tested for efficacy and safety (7).**

1. Current AGO Breast Commission recommendation (www.ago-online.org Vers. 2014 1D)
2. Untch M JCO 2011, 3. Gianni L Lancet 2010, 4. Untch M JCO 2010, 5. Baselga J Lancet 2012,
6. Gianni L Lancet 2012, 7. Schuler M BCRT 2012

Studydesign

multicenter, prospective, open-label phase II study



Afatinib: 20 mg daily (*during first 2 wks. every other day).
Trastuzumab: loading 8 mg/kg body weight, than 6 mg/kg q3w.
Paclitaxel: 80 mg/m^2 q1w.
Epirubicin: 90 mg/m^2 day 1 q22.
Cyclophosphamid: 600 mg/m^2 day 1 q22.

****Primary prophylaxis with loperamide 2x2mg daily was mandatory for the first 4 weeks of afatinib/trastuzumab and the first 2 weeks of paclitaxel.**

Selected Objectives

Primary:

- **pCR (ypT0/is ypN0)**

Secondary:

- **efficacy using other pCR definitions (ypT0 ypN0, ypT0 ypN0/+, ypTany ypN0) clinical response rates**
- **Rate and type of surgery**
- **compliance and toxicity**
- **Correlation of skin toxicity and diarrhoe and prespecified molecular markers with pCR**

Other objectives will be presented when data are fully analysed.

Key Eligibility Criteria

- **Unilateral primary breast cancer as confirmed by core biopsy**
- **Operable or locally advanced or inflammatory breast cancer (cT2 – cT4a-d).**
- **Centrally confirmed, positive HER2 status of core biopsy, HER2 positive: IHC 3+ or FISH/SISH ≥ 2.0.**
- **Centrally confirmed hormone receptor status (ER / PgR).**
- **Karnofsky performance status ≥ 80%.**
- **Normal cardiac function.**
- **Age ≥ 18**

Statistical Analysis*

Sample size calculation:

- **assumed pCR rate of AT plus concurrent trastuzumab: 40.0%**
- **Her2-status centrally reviewed: pCR rate increase 10% (8)**
- **Dual anti-Her2 blockade: pCR rate increase 20%**

Real pCR rate: assumed 70%

To exclude pCR rate of ≤55%: sample size of 65 patients

(2-sided one group χ^2-test, $\alpha = 0.1$, $1-\beta = 80\%$) (9)

8. Noske A, BCRT 2011

* SAS version 9.2 (SAS Institute Inc, Cary, NC)

Patients & Tumor Characteristics

Randomized patients (n)	**74**
Intent to treat population (n)	**65**
(recruited 5/2012-7/2013)	
age (median yrs/ range)	**50/29-73**
cT 2 (%)	**76.6**
cN 0 (%)	**51.6**
Tumor grade 3 (%)	**60**
HR-positive (%)	**70.8**

Compliance

Started treatment (n)	**65**
Discontinued all treatments early	**9**
➢adverse event	5
➢investigator‘s decision	1
➢patient’s wish	2
➢progressive disease	1
Discontinued afatinib treatment	**16**
➢adverse event	14
➢investigator‘s decision	1
➢patient’s wish	1
Completed planned treatment	**47**

Toxicity

SAEs (n) (in 16 patients)	**22**
Gastrointestinal (%)	**27.3**
Hematologic (%)	**18.2**
Infections (%)	**13.6**
Nervous system (%)	**9.1**
AEs of special interest (n)	**9**
Diarhea grade 3	**6**
Rashes grade 3	**1**
Renal failures grade 3	**2**
Grade 3-4 hematological	
Neutropenia (%)	**53.8**
Grade 3-4 non-hematological	
Diarrhea (%)	**7.7**

Efficacy primary objective

<u>pCR (ypT0/is ypN0):</u> **49.2%**

(32 of 65 pts.; 95 % CI: 38.5%-60.1%)

Efficacy secondary objectives (1)

pCR by other definitions:

ypT0, ypN0 **(21 of 65 pts.)**	**33.9%**
ypT0/is, ypN0/+ **(36 of 65 pts.)**	**55.4%**
ypTany, ypN0 **(54 of 65 pts.)**	**83.1%**

pCR and ER (hormonreceptorstatus) ypT0/is, ypN0:

ER+ (n= 46)	**43.5%**
ER- (n=19)	**63.2%**

(odds ratio 0.449; p=0.153)

Efficacy secondary objectives (2)

pCR and PIK3CA status:
(p=0.363)

Wild type	**54.2%**
(26 of 48 pts.)	
Mutation	**38.5%**
(5 of 13 pts.)	

pCR and LPBC (lymphocyte predominant breast cancer) status:
(p=0.0053)

without LPBC	**26,8%**
(15 of 56 pts.)	
With LPBC	**77.8%**
(7 of 9 pts.)	

pCR and skin toxicity or diarrhea: no association

Efficacy secondary objectives (3)

Clinical objective response rate at surgery: **96.3%**

Complete / partial response after 6 wks. of dual Her2 blockade: **5.3/ 36.8%**
(3/21 of 57 evaluable pts.)

Clinical signs of tumor progression after 6 wks. of dual Her2 blockade: **14%**
(8 of 57 evaluable pts.)

Breast-conserving surgery: **60%**

Conclusion

- **The DAFNE study did not meet its challenging primary endpoint to show a pCR rate of as high as 70% to suggest superior efficacy than other currently available regimes using dual Her2-blockade in breast cancer.**

- **The result does formally not support a subsequent phase III trial comparing this combination with other dual blockade regimen.**

- **Afatinib and trastuzumab in combination with anthracycline-taxane-based chemotherapy as given in the DAFNE study showed no new safety signals.**

- **However: results provide further support for the predictive value of LPBC and PIK3CA mutations in this treatment setting (10)**

10. Loibl S, JCO 2014

Acknowledgements

We would like to thank all participating patients and their families,

Mathias Uhlig, PhD and Datamanagment for their operative management of the study at GBG headquarters,

all sites and investigators that have participated in the study:

Düsseldorf (M. Rezai); Erlangen (P. Fasching); Greifswald (A. Belau); Heidelberg (A.Schneeweiss); Kassel (B. Conrad); Kiel (C. Schem); Magdeburg (J. Bischoff); München (C. Hanusch); Offenbach (C. Jackisch); Tübingen (E.-M. Grischke).

The study was financially supported by Boehringer Ingelheim, Germany.

Slides can be downloaded from www.germanbreastgroup.de.