DESIREE - A multicenter, randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer

Sibylle Loibl[1,2], Jenny Furlanetto[1], Jana Barinoff[3], Dirk Bauerschlag[4], Daniel Herr[5], Kristina Lübbe[6], Nico Maass[4], Volkmar Müller[7], Christoph Mundhenke[4], Marcus Schmidt[8], Kathrin Schwedler[9], Marc Thill[3], Ioannis Gkantiragas[1], Nicole Burchardi[1], Gunter von Minckwitz[1]

[1]German Breast Group, Neu-Isenburg; [2]Sana Klinikum, Offenbach; [3]Agaplesion Markus Krankenhaus, Frankfurt am Main; [4]Universitätsklinikum Schleswig-Holstein, Kiel; [5]Universitätsklinikum Würzburg; [6]Diakoniekrankenhaus Henriettenstiftung, Hannover; [7]Universitätsklinikum Hamburg-Eppendorf; [8]Universitätsfrauenklinik Mainz; [9]Kantonsspital Luzern

OT-03-08

Background

- The BOLERO-2 study demonstrated a relevant benefit for everolimus in addition to exemestane in patients who progressed during/after a non steroidal aromatase inhibitor (NSAI), which led to approval of everolimus in this indication. However, in routine use a high rate of intolerability due to side effects is reported. The most common side effect of everolimus is mucositis with a reported high rate of intolerability especially during the first 12 weeks of treatment. Mucositis is also considered to be the leading cause for treatment discontinuation not related to tumor progression.[1,2]
- In the neoadjuvant GeparQuinto study, a dose-escalation schema was successfully used to improve tolerability of everolimus together with cytotoxic agents.[3]
- DESIREE study aims to evaluate the tolerability of an induction dose escalation of everolimus in patients with advanced or metastatic breast cancer (Figure 1).

Figure 1: DESIREE study design

N=156

R

EVEROLIMUS 10mg

Weeks 1-3:	**4 x 2,5mg/day (blinded)**
Weeks 4-24:	**10mg/day (open-label)**

EVEROLIMUS DOSE-ESCALATED

Weeks 1:	**1 x 2,5mg Verum + 3 x placebo/day;**
Weeks 2:	**2 x 2,5mg Verum + 2 x placebo/day;**
Weeks 3:	**3 x 2,5mg Verum + 1 x placebo/day;**
Weeks 4-24:	**10mg/day (open-label)**

- **Treatment will be given until 24 weeks of treatment are completed, disease progression, unacceptable toxicity of the study drug, or withdrawal of consent of the patient**

Main inclusion criteria:

1. Histological confirmed hormone receptor-positive (ER/PR>1%), HER2-negative carcinoma of the breast.
2. Postmenopausal women
3. Locally advanced or metastatic stage of disease not amenable to curative treatment by surgery or radiotherapy alone.
4. No indication for chemotherapy (e.g. symptomatic visceral metastasis)
5. Disease progression following prior therapy with NSAI, defined as:
   a. Recurrence while on, or following completion of an adjuvant treatment with letrozole or anastrozole, or
   b. Progression while on or following completion of letrozole or anastrozole treatment for advanced breast cancer/metastatic breast cancer.

Objectives

Primary Objective:

Cumulative rate of stomatitis grade 2-4 (WHO's oral toxicity scale (OTS); Figure 2) at 12 weeks after start of treatment using a conventional and a dose-escalating schema of everolimus in combination with exemestane

Secondary Objectives:

- cumulative rate of stomatitis grade 2-4 (WHO´s OTS)
- cumulative rate of stomatitis grade 1 and any grade (WHO´s OTS) at 12 and 24 weeks after start of treatment
- rate of patients on 10mg daily at 12 weeks and 24 weeks after start of everolimus treatment
- clinical benefit rate at 24 weeks after start of everolimus treatment
- safety with regard to other organ signs and symptoms
- time to grade ≥2 mucositis/stomatitis
- cumulative dose at 4 weeks
- relative dose intensity for everolimus
- quality of life using the FACT-B questionnaire and the QSDQ

Other objectives:

- Potential biomarkers predicting safety and compliance will be determined after completion of study treatment

Materials and Methods

DESIREE (NCT02387099) is a randomized, double-blind, phase II study of everolimus in addition to exemestane in patients who progressed during or after NSAI.

Patients will be randomized in a 1:1 ratio to receive either everolimus 10 mg/day (week 1-3: 4x2.5 mg/day, blinded; week 4-24: 10mg/day, open according to label) or an escalating dose of everolimus as follows: week 1: 1x2.5 mg verum + 3x placebo/day; week 2: 2x2.5 mg verum + 2x placebo/day; week 3: 3x2.5 mg verum + 1x placebo/day; week 4-24: 10 mg/day (open according to label) (Figure 1).

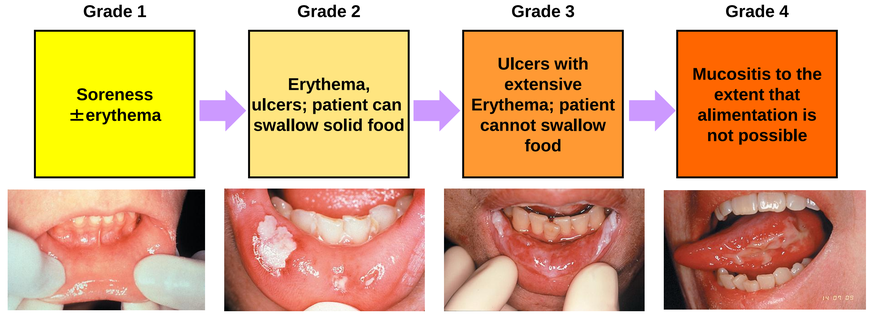
Statistical methods:

156 evaluable patients (78 in each arm) are required to detect a clinically relevant difference of 20% in the mucositis rate between treatment arms using a continuity-corrected χ2-test on a significance two sided level alpha of 0.2 and a power of 90%. The rate was estimated to be 40% and 20% in the control arm and the treatment arm, respectively.

Results

- The study will be conducted in up to 60 German centers. Recruitment has started in June 2015. Enrollment is planned to be completed within 24 months.
- So far 14 patients in 8 centers have been recruited (as of 01.12.2015).

Fígure 2: WHO oral toxicity scale



Adapted from Patrick J. Stiff, MD, Loyola University Medical Center

Conclusions

The combination of everolimus and exemestane has shown to improve the outcome of patients with metastatic breast cancer. In the DESIREE trial a dose-escalating schema will be employed to enhance patient compliance and tolerability necessary to achieve an adequate dose-intensity.

References

1. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366:520-9.
2. Rugo HS, Pritchard KI, Gnant M, et al. Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. Ann Oncol. 2014;25:808-15.
3. Huober J, Fasching PA, Hanusch C, et al. Neoadjuvant chemotherapy with paclitaxel and everolimus in breast cancer patients with non-responsive tumours to epirubicin/cyclophosphamide (EC) ± bevacizumab - results of the randomised GeparQuinto study (GBG 44). Eur J Cancer. 2013;49:2284-93.

Presented at: San Antonio Breast Cancer Symposium - December 8-12, 2015

This presentation is the intellectual property of the author/presenter. Contact them at publications@gbg.de for permission to reprint and/or distribute.