CONTESSA: A Multinational, Multicenter, Randomized, Phase 3 Registration Study of Tesetaxel in Patients (Pts) with HER2-, Hormone Receptor + (HR+) Locally Advanced or Metastatic Breast Cancer (MBC)

Poster Board #184a
Abstract TPS1106

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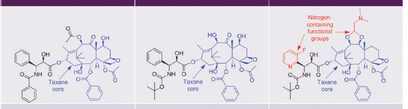
Background

- Chemotherapy regimens for patients with MBC that offer robust efficacy while preserving patient quality of life are needed
- Tesetaxel is a novel taxane that is taken orally Q3W with a low pill burden, no history of hypersensitivity reactions and improved activity against chemotherapy-resistant tumors[1,2]
- Tesetaxel's improved pharmacologic properties include: (1) high oral bioavailability; (2) high solubility; and (3) a long (~8-day) half-life (**Table 1** and **Figure 1**)

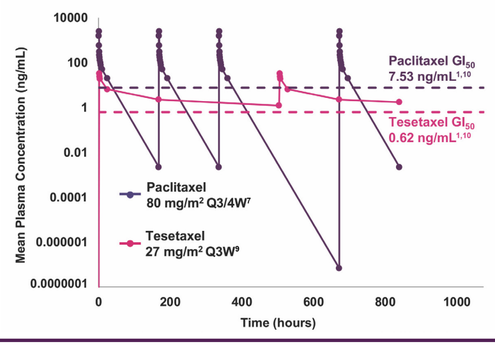
Table 1: Tesetaxel's Unique Pharmacologic Properties

Molecule	Paclitaxel	Docetaxel	Tesetaxel
Structure			
Substantially effluxed* by P-gp pump**	Yes	Yes	No
Oral bioavailability in preclinical studies	8%[3]	18%[4]	56%
Solubility (µg/mL)***	0.3[5]	0.5[6]	41,600
Terminal half-life in humans	11 hours[7]	11 hours[8]	193 hours

*At therapeutic concentrations
**The P-glycoprotein (P-gp) efflux pump mediates gastric absorption as well as chemotherapy resistance
***At pH conditions similar to gastric fluid

Figure 1: PK Profiles of Paclitaxel and Tesetaxel

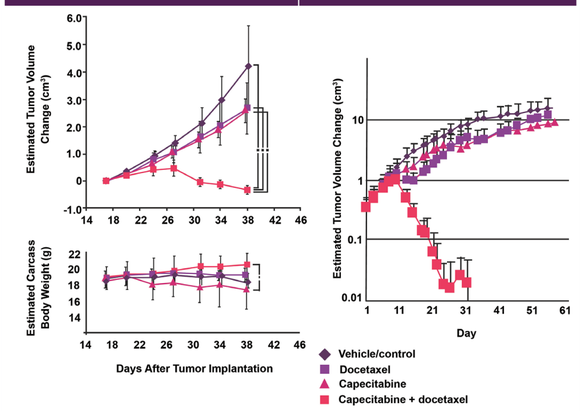
Mean Plasma Concentration (ng/mL) vs. Time (hours) for Paclitaxel and Tesetaxel



- 559 patients have been treated with tesetaxel in prior clinical studies (496 monotherapy; 63 in combination with capecitabine)
- In a multicenter, Phase 2 study, HER2 negative, HR positive MBC patients receiving tesetaxel as a single agent achieved a confirmed response rate of 45% (44% in patients with no prior taxane exposure and 45% in patients with prior taxane exposure) with a low incidence of Grade ≥3 neuropathy and Grade 2 alopecia (2018 ASCO Annual Meeting Poster Board #123, Abstract 1042) (**Figure 2**)

- Preclinical and clinical studies support the effectiveness of a reduced dose of capecitabine when combined with a taxane; taxanes potentiate capecitabine's antitumor activity by up-regulating tumor levels of thymidine phosphorylase, the enzyme essential for the activation of capecitabine[10,11] (**Figure 3**)

Figure 3: Preclinical Evidence of Synergy when Combining a Taxane with Capecitabine



* Capecitabine dosed 5 times every 7 days; docetaxel dosed once every 7 days
** Capecitabine dosed on Days 1-14 and 22-36; docetaxel dosed on Days 8 and 29

- In a Phase 1 study, tesetaxel plus a reduced dose of capecitabine was generally well tolerated with minimal overlapping toxicity (Grade ≥3 neuropathy was 6%; Grade ≥3 hand-foot syndrome was 6%; Grade ≥3 diarrhea was 6%; no Grade 2 alopecia; and no hypersensitivity reactions)

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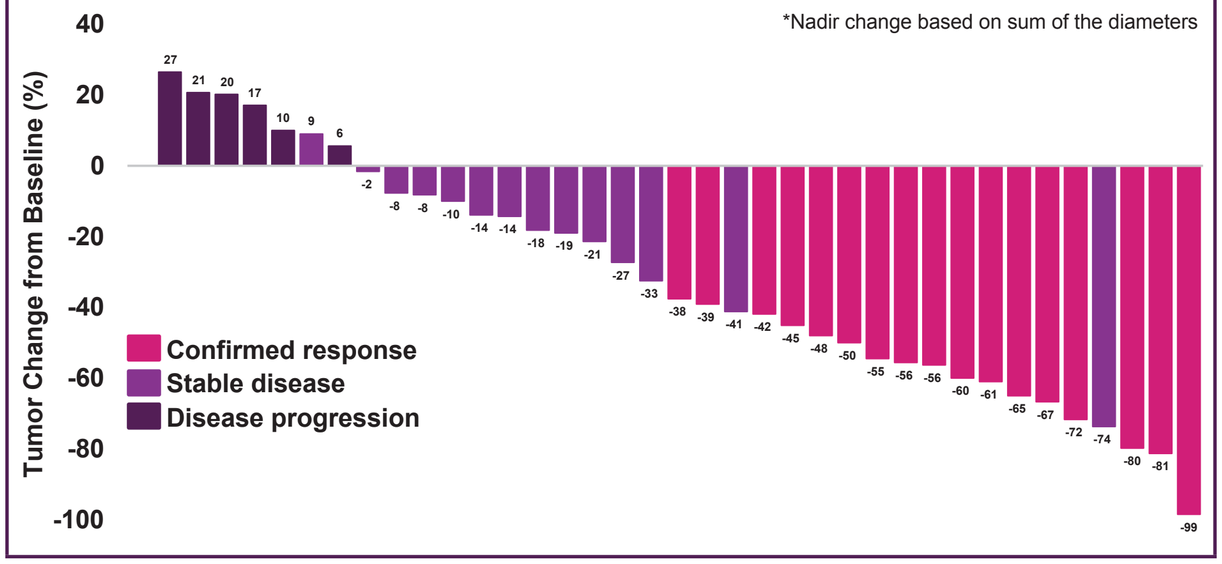
Study Hypothesis and Objective

Figure 4: Study Hypothesis and Objective

Hypothesis	Objective
The all-oral regimen of tesetaxel plus a *reduced dose* of capecitabine will lengthen PFS while being well-tolerated as compared to capecitabine alone	Establish a new, all-oral treatment option with an improved benefit-risk profile

Figure 2: Study TOB203 Tumor Change from Baseline in Target Lesions for HR Positive Patients Receiving Tesetaxel Q3W*



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Study Design

- CONTESSA is a multinational, multicenter, randomized, Phase 3 registration study of tesetaxel plus a reduced dose of capecitabine vs. the approved dose of capecitabine alone in patients with HER2 negative, HR positive MBC (NCT03326674) (**Figure 5**)
- Key eligibility criteria are outlined in **Table 2**
- Eligible patients are stratified according to:
  - Disease status (presence vs. absence of visceral disease)
  - Geographic region (North America/Western Europe vs. Rest of World)
  - Number of prior chemotherapy regimens for advanced disease (0 vs. 1)
- Tesetaxel and capecitabine dose reductions will be made in consideration of the known toxicity profile of each drug
- Capecitabine monotherapy arm dose reductions
  - Capecitabine monotherapy arm to start at the FDA-approved dose
  - Capecitabine dose reductions due to occurrence of adverse events should follow capecitabine prescribing information
- Patients will be treated until documentation of progressive disease, evidence of unacceptable toxicity or other decision to discontinue treatment
- Patient-reported outcomes (PROs), as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), are additional endpoints
- Safety endpoints include adverse events, including deaths and other serious adverse events, and clinical laboratory abnormalities
- An Independent Data Monitoring Committee (IDMC) will periodically perform safety analyses; the IDMC will also perform an interim PFS futility analysis (after 100 PFS events)

Figure 5: Study Design

Target Enrollment

Patients with HER2 negative, HR positive MBC who have received no more than one chemotherapy regimen for advanced disease and have received a taxane in the neoadjuvant or adjuvant setting. Where indicated, patients must have received endocrine therapy with or without a CDK 4/6 inhibitor.
N=600

1:1 Randomization

Multinational, Multicenter, Randomized

Tesetaxel 27 mg/m²
Day 1 of a 21-day cycle
+
Capecitabine 1,650 mg/m²
(825 mg/m² BID)
Days 1-14 of a 21-day cycle

Treated until progressive disease or unacceptable toxicity

Capecitabine 2,500 mg/m²
(1,250 mg/m² BID)
Days 1-14 of a 21-day cycle

BID = twice per day

Primary Endpoint: PFS assessed by Independent Radiologic Review Committee (IRC)

- Designed (with 90% statistical power) to detect a 42% improvement in PFS (hazard ration=0.71)

Secondary Endpoints: Overall survival, objective response rate assessed by IRC and disease control rate assessed by IRC

Table 2: Key Eligibility Criteria*

Key Inclusion Criteria	Key Exclusion Criteria
1. Have HER2 negative and ER or PR positive (≥1% ER positive or PR positive) locally advanced or metastatic breast cancer 2. Received a taxane in the neoadjuvant or adjuvant setting 3. Received any number of endocrine therapies (*e.g.*, 0, 1, 2, 3+) 4. Received any number of targeted therapies (*e.g.*, palbociclib, everolimus) with endocrine therapy (*e.g.*, 0,1, 2, 3+) 5. For locally advanced or metastatic breast cancer, received: • No prior chemotherapy; or • One prior non-taxane, non-capecitabine chemotherapy (*e.g.*, gemcitabine, doxorubicin)	1. Have HER2 positive or triple-negative breast cancer 2. Did not receive a taxane in the neoadjuvant or adjuvant setting 3. Have *de novo* locally advanced or metastatic breast cancer 4. Previously received a taxane for locally advanced or metastatic breast cancer 5. Previously received capecitabine

*All patients must meet full eligibility criteria as stipulated in the Study ODO-TE-B301 Protocol

Study Highlights

- Chemotherapy regimens for patients with MBC that offer robust efficacy while preserving patient quality of life are needed
- Tesetaxel is a novel taxane that is taken orally Q3W with a low pill burden, no history of hypersensitivity reactions and improved activity against chemotherapy-resistant tumors
- In a multicenter, Phase 2 study, HER2 negative, HR positive MBC patients receiving tesetaxel as a single agent achieved a confirmed response rate of 45% with a low incidence of Grade ≥3 neuropathy and Grade 2 alopecia
- CONTESSA is a multinational, multicenter, randomized, Phase 3 registration study of tesetaxel plus a reduced dose of capecitabine vs. the approved dose of capecitabine alone in patients with HER2 negative, HR positive MBC
- Study enrollment was initiated in December 2017, with planned enrollment of approximately 600 patients across 20 countries
- The primary efficacy endpoint is PFS assessed by IRC

References

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