CONTESSA TRIO: A Multinational, Multicenter, Phase 2 Study of Tesetaxel plus 3 Different PD-(L)1 Inhibitors in Patients with Metastatic Triple-Negative Breast Cancer (TNBC) and Tesetaxel Monotherapy in Elderly Patients with HER2- Metastatic Breast Cancer (MBC)

San Antonio Breast Cancer Symposium® - December 10-14, 2019
OT1-08-08

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Background

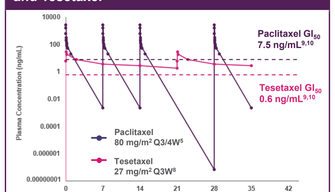
- Chemotherapy regimens for patients with MBC that offer robust efficacy while preserving patient quality of life are needed
- Tesetaxel is a novel taxane with several properties that make it unique (**Table 1**), including:
  - Oral administration with a low pill burden
  - A long (~8-day) terminal plasma half-life ($t_{1/2}$) in humans, enabling infrequent, once-every-3-weeks (Q3W) dosing (**Figure 1**)
  - No observed hypersensitivity reactions
  - Preclinical evidence of central nervous system (CNS) penetration
  - Significant activity against chemotherapy-resistant tumors
- More than 600 patients have been treated with tesetaxel in clinical studies

Table 1: Tesetaxel's Unique Pharmacologic Properties

Molecule	Paclitaxel	Docetaxel	Tesetaxel
Structure			
Substantially effluxed by P-gp pump[a]	Yes	Yes	No
Oral bioavailability in preclinical studies	8%[1]	18%[2]	56%
Solubility (μg/mL)[b]	0.3[3]	0.5[4]	41,600
Terminal plasma half-life in humans ($t_{1/2}$)	0.5 days[5]	0.5 days[6]	8 days[7]

[a] The P-glycoprotein (P-gp) efflux pump mediates gastric absorption as well as chemotherapy resistance
[b] At pH conditions similar to gastric fluid

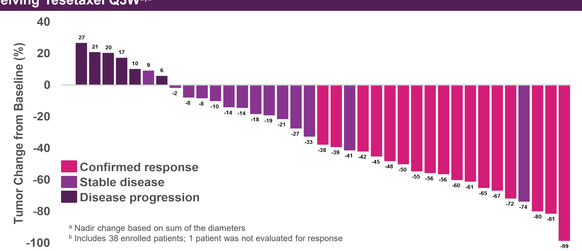
Figure 1: Pharmacokinetic Profiles of Paclitaxel and Tesetaxel



Note: The graph above includes median plasma concentrations through Day 1 and simulated data thereafter for paclitaxel and geometric mean plasma concentrations through Day 21 and simulated data thereafter for tesetaxel.
GI_{50}=concentration of drug required to inhibit growth by 50%; Q3/4W=once per week for 3 of 4 weeks; Q3W=once every 3 weeks

- In a multicenter, Phase 2 study, 38 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 (**Figure 2**)[11]

Figure 2: Study TOB203 Tumor Change from Baseline in Target Lesions for HR Positive Patients Receiving Tesetaxel Q3W[a,b]



[a] Nadir change based on sum of the diameters
[b] Includes 38 enrolled patients; 1 patient was not evaluated for response

Table 2: Ongoing Tesetaxel Clinical Studies

Study Name	Phase	N	Patient Population	Regimen
CONTESSA	3	600	HER2 negative, HR positive MBC with prior taxane	Tesetaxel + capecitabine vs. capecitabine
CONTESSA 2	2	125	HER2 negative, HR positive MBC with no prior taxane	Tesetaxel + capecitabine
CONTESSA TRIO Cohort 1	2	90-150	Metastatic TNBC	Tesetaxel + nivolumab vs. tesetaxel + pembrolizumab vs. tesetaxel + atezolizumab
CONTESSA TRIO Cohort 2	2	40-60	Elderly (≥ 65 years old) with HER2 negative MBC	Tesetaxel monotherapy

Study Design (Cohort 1)

- Nivolumab and pembrolizumab (PD-1 inhibitors) and atezolizumab (a PD-L1 inhibitor) are approved for the treatment of multiple types of cancer
- Atezolizumab, in combination with nab-paclitaxel, was recently approved in the U.S. for the treatment of metastatic TNBC (**Figure 3**)[12]
- Tesetaxel plus a PD-(L)1 inhibitor may provide patients with an alternative treatment option requiring fewer infusion center visits than the currently approved atezolizumab plus nab-paclitaxel dosing regimen (**Figure 4**)

Figure 3: Atezolizumab Plus Nab-paclitaxel PFS Results in Patients with PD-L1 Expression ≥ 1%

	PD-L1 Expression ≥ 1%[a]	
	Atezolizumab in combination with nab-paclitaxel	Placebo in combination with nab-paclitaxel
Progression-Free Survival[b,c] Events (%) Median, months	(n=185) 136 (74) 7.4 (6.6, 9.2)	(n=184) 151 (82) 4.8 (3.8, 5.5)
Stratified Hazard ratio (95% CI)[d] p-value	0.60 (0.48, 0.77) <0.0001	

[a] PD-L1 expression in tumor-infiltrating immune cells (IC)
[b] As determined by investigator assessment
[c] Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[d] Stratified by presence of liver metastases, and by prior taxane treatment

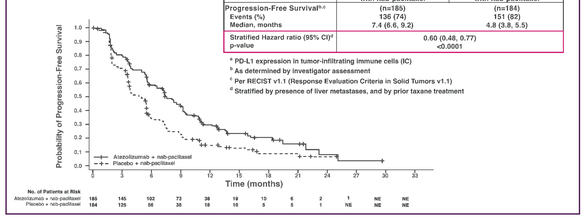


Figure 4: Infusion Schedules for Atezolizumab Plus Nab-paclitaxel and a PD-(L)1 Inhibitor Plus Tesetaxel

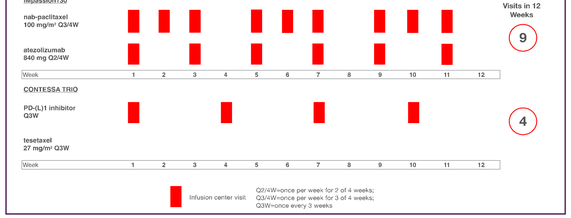
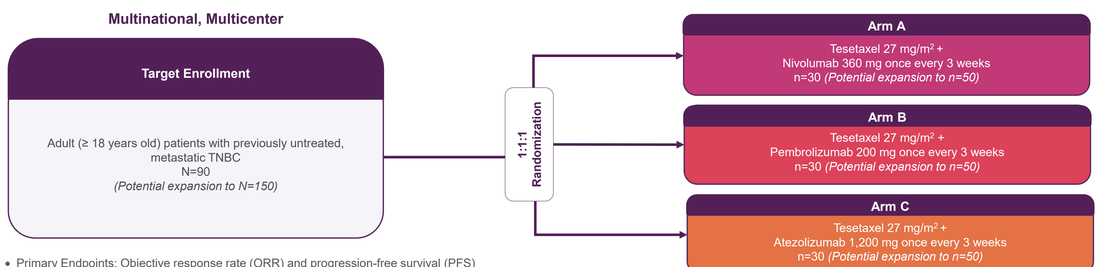


Figure 5: Study Design



- Primary Endpoints: Objective response rate (ORR) and progression-free survival (PFS)
- Secondary Endpoints: Duration of response (DoR) and overall survival (OS)
- Exploratory Endpoints: ORR and PFS by PD-L1 expression, CNS ORR, CNS DoR

Table 3: Key Eligibility Criteria[a]

Patients are ELIGIBLE if they:	Patients are NOT ELIGIBLE if they:
1. Have HER2 negative MBC; *de novo* patients are allowed	1. Have previously received chemotherapy for MBC
2. Have a most recent biopsy that is HR negative	2. Have HER2 positive breast cancer
3. Have a disease-free interval of at least 12 months after completion of systemic neoadjuvant or adjuvant chemotherapy, if applicable	3. Have had prior PD-(L)1/PD-L2 or CTLA-4 inhibitor
4. Received a taxane in the (neo)adjuvant setting or are taxane-naïve	4. Have certain autoimmune or inflammatory conditions, active infections, or are using certain immunosuppressive agents
5. Have CNS metastases (allowed but not required)	
6. Have an adequate, newly obtained or archival core or excisional biopsy of a not-previously-irradiated tumor lesion obtained since completion of any systemic therapy for central determination of PD-L1 status. Metastatic tumor biopsy preferred; PD-L1 status determination is not required for enrollment or randomization	

[a] All patients must meet full eligibility criteria as stipulated in the Study ODO-TE-B202 Protocol

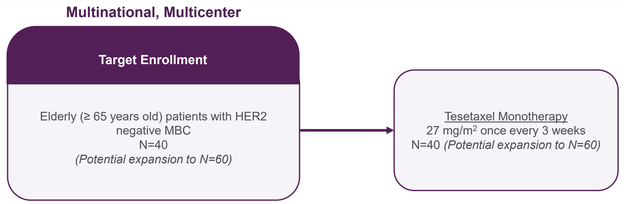
Table 4: Comparison of 3 Approved PD-L1 Diagnostic Assays

PD-L1 Assay \ PD-(L)1 Inhibitor	Nivolumab	Pembrolizumab	Atezolizumab
Dako 28-8	Approved Assay for Nivolumab	Exploratory	Exploratory
Dako 22C3	Exploratory	Approved Assay for Pembrolizumab	Exploratory
Ventana SP142	Exploratory	Exploratory	Approved Assay for Atezolizumab

- Each of the 3 PD-(L)1 inhibitors being combined with tesetaxel has an approved PD-L1 diagnostic assay
- Tumors from each patient will be tested with all 3 PD-L1 diagnostic assays
- Efficacy results for each of the 3 PD-(L)1 inhibitor combinations will be assessed for correlation with the results of each of the 3 approved PD-L1 diagnostic assays

Study Design (Cohort 2)

Figure 6: Study Design



- Primary Endpoint: ORR
- Secondary Endpoints: PFS, DoR, OS
- Exploratory Endpoints: ORR by receptor subtype, CNS ORR, CNS DoR

Table 5: Key Eligibility Criteria[a]

Patients are ELIGIBLE if they:	Patients are NOT ELIGIBLE if they:
1. Have HER2 negative MBC; *de novo* patients are allowed	1. Have previously received chemotherapy for MBC
2. Have a disease-free interval of at least 12 months after completion of systemic neoadjuvant or adjuvant chemotherapy, if applicable	2. Have HER2 positive breast cancer
3. Received a taxane in the (neo)adjuvant setting or are taxane-naïve	
4. Have CNS metastases (allowed but not required)	
5. Have had prior endocrine therapy with or without a cyclin-dependent kinase 4/6 inhibitor (allowed but not required) unless endocrine therapy is not indicated; any prior targeted therapies are permitted; there is no limit on the number of prior endocrine therapies	

[a] All patients must meet full eligibility criteria as stipulated in the Study ODO-TE-B202 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 TRIO is a multinational, Phase 2 study of tesetaxel plus three different PD-(L) 1 inhibitors in patients with metastatic TNBC and tesetaxel monotherapy in elderly patients with HER2 negative MBC
- The primary efficacy endpoints are ORR and PFS for Cohort 1 and ORR for Cohort 2
- In March 2019, the study was initiated with planned enrollment of approximately 90 patients (potential expansion to 150 patients) across 13 countries

References

1. Shanmugam et al, *Drug Development and Industrial Pharmacy* 2015;41(11):1864-1876
2. McEntee et al, *Veterinary and Comparative Oncology* 2003;1(2):105-112
3. Montaseri, *Taxol: Solubility, Stability and Bioavailability* 1997
4. Bharate et al, *Bioorganic & Medicinal Chemistry Letters* 2015;25(7):1561-1567
5. Tan et al, *British Journal of Cancer* 2014;110(11):2647-54
6. Taxotere (docetaxel) prescribing label
7. Lang et al, 2012 ASCO Annual Meeting, *Journal of Clinical Oncology* 2012;20 (15 supp):2555
8. Pharmacokinetic data from Studies 927A-PRT001, 927E-PRT003, 927E-PRT005, 927A-PRT006, and 927E-PRT007
9. Shionoya et al, *Cancer Science* 2003;94(5):459-66
10. Trock et al, *Journal of the NCI* 1997;89(13):917-31
11. Seidman et al, *Journal of Clinical Oncology* 36, 2018 (suppl; abstr 1042; poster #123)
12. Tecentriq (atezolizumab) prescribing label