Results from CONTESSA: A Phase 3 study of tesetaxel plus a reduced dose of capecitabine versus capecitabine alone in patients with HER2-, hormone receptor + (HR+) metastatic breast cancer (MBC) who have previously received a taxane

Joyce O'Shaughnessy[1], Lee Schwartzberg[2], Martine Piccart[3], Hope S. Rugo[4], Denise A. Yardley[5], Javier Cortes[6], Michael Untch[7], Nadia Harbeck[8], Gail S. Wright[9], Igor Bondarenko[10], John Glaspy[11], Zbigniew Nowecki[12], Fadi Kayali[13], Arlene Chan[14], Christelle Levy[15], Mei-Ching Liu[16], Sung-Bae Kim[17], Julie Lemieux[18], Alexey Manikhas[19], Sara Tolaney[20], Elaine Lim[21], Andrea Gombos[3], Agostina Stradella[22], Mark Pegram[23], Peter Fasching[24], Laszlo Mangel[25], Vladimir Semiglazov[26], Veronique Dieras[27], Luca Gianni[28], Michael A. Danso[29], Jeff Vacirca[30], Stew Kroll[31], Joseph O'Connell[31], Kevin Tang[31], Thomas Wei[31] and Andrew Seidman[32]

[1]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX; [2]West Cancer Center, Memphis, TN; [3]Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium; [4]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [5]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; [6]IOB Institute of Oncology, Quironsalud Group, Madrid and Barcelona, Spain and Vall d´Hebron Institute of Oncology (VHIO), Barcelona, Spain; [7]Helios Hospital Berlin-Buch, Berlin, Germany; [8]Brustzentrum der Universität München (LMU), Munich, Germany; [9]Sarah Cannon Research Institute and Florida Cancer Specialists, New Port Richey, FL; [10]City Clinical Hospital No4, Dnipro, Ukraine; [11]University of California Los Angeles Hematology Oncology Center, Los Angeles, CA; [12]Narodowy Instytut Onkologii-Panstwowy Instytut Badawczy, Warsaw, Poland; [13]Florida Cancer Specialists, Fort Myers, FL; [14]Breast Cancer Research Centre-Western Australia and Curtin University, Perth, Australia; [15]Centre François Baclesse, Caen, France; [16]Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan; [17]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of; [18]CHU de Québec-Université Laval, Quebec, QC, Canada; [19]City Clinical Oncology Dispensary, St. Petersberg, Russian Federation; [20]Dana-Farber Cancer Institute, Boston, MA; [21]National Cancer Centre, Singapore, Singapore; [22]Institut Catala d'Oncologia Hospital Duran i Reynals, Barcelona, Spain; [23]Stanford Women's Cancer Center, Palo Alto, CA; [24]Universitätsklinikum Erlangen, Erlangen, Germany; [25]University of Pécs Institute Oncotherapy, Pécs, Hungary; [26]Petrov Research Institute of Oncology, St. Petersburg, Russian Federation; [27]Centre Eugène Marquis, Rennes, France; [28]I.R.C.C.S. Ospedale San Raffaele, Milan, Italy; [29]Virginia Oncology Associates, US Oncology, Norfolk, VA; [30]New York Cancer and Blood Specialists, New York, NY; [31]Odonate Therapeutics, Inc., San Diego, CA; [32]Memorial Sloan Kettering Cancer Center, New York, NY

Disclosures

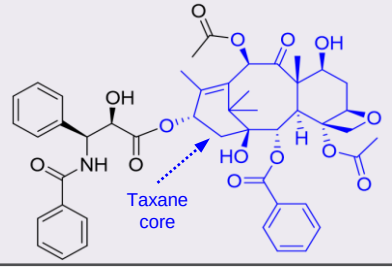
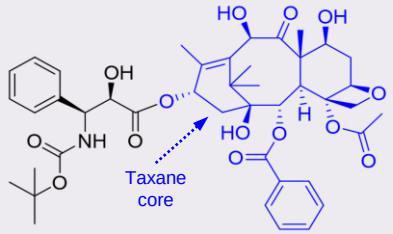
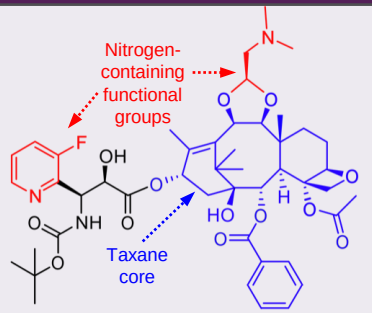
Dr. O'Shaughnessy has received consulting fees from AbbVie, Agendia, AstraZeneca, Celgene/Bristol-Myers Squibb Company, Eisai, Eli Lilly and Company, Genentech/Roche, Genomic Health, GRAIL, Heron Therapeutics, Immunomedics, Ipsen, Jounce Therapeutics, Novartis, Odonate Therapeutics, Pfizer, Puma Biotechnology and Seagen

Background and Rationale

- Chemotherapy regimens that offer robust efficacy while preserving patient quality of life are needed for patients with MBC
- Tesetaxel is a novel, oral taxane with Q3W dosing
- Tesetaxel demonstrated encouraging monotherapy activity in a Phase 2 trial in patients with HR positive, HER2 negative MBC[a]
  - Confirmed objective response rate (ORR) = 45%
- Based on 211 patients treated with tesetaxel at 27 mg/m^2 Q3W[b]
  - Grade ≥3 neuropathy = 3%
  - Grade 2 alopecia = 5%
  - No hypersensitivity reactions
- We present results of the protocol-specified primary analysis of CONTESSA, a Phase 3 study of tesetaxel plus a reduced dose of capecitabine vs. capecitabine alone in patients with HR positive, HER2 negative MBC who have previously received a taxane

[a] Seidman et al, 2018 ASCO Annual Meeting
[b] As monotherapy (N=180) or in combination with capecitabine at 1,750–2,500 mg/m^2 (N=31)

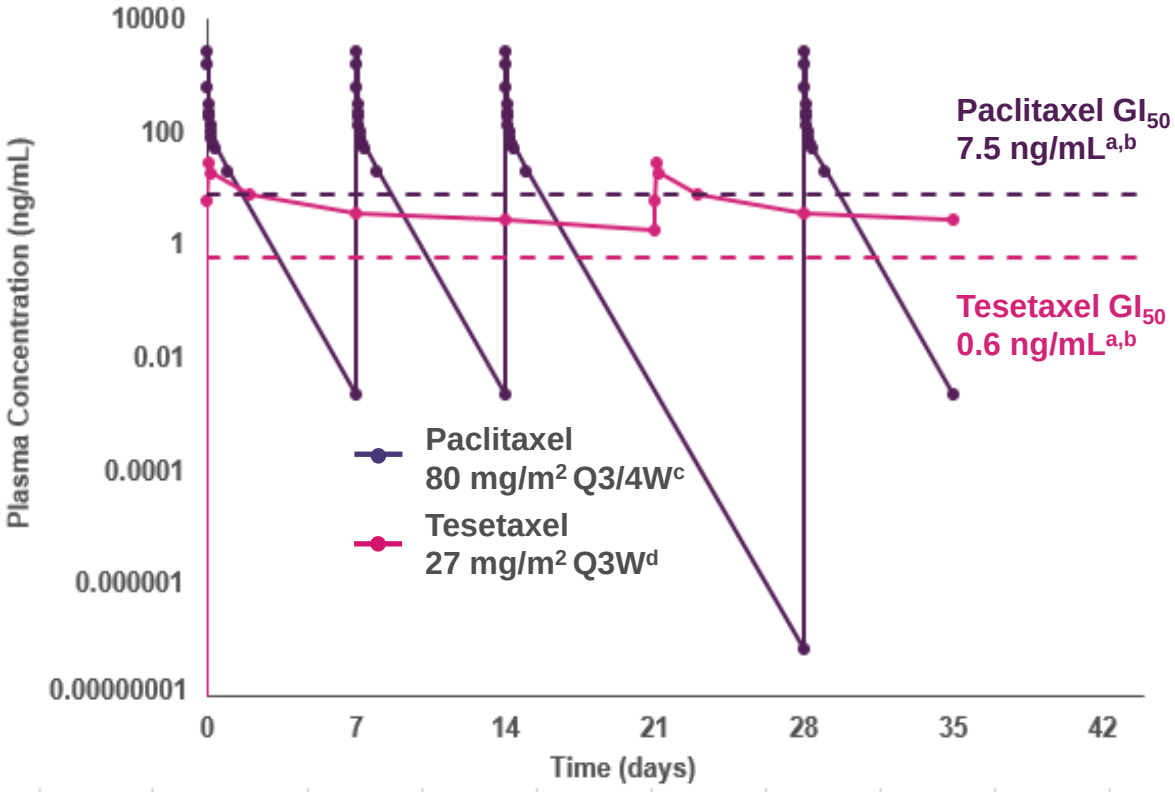
Chemical and Pharmacologic Properties of Paclitaxel, Docetaxel and Tesetaxel

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

* The P-glycoprotein (P-gp) efflux pump mediates gastric absorption as well as chemotherapy resistance

[a] Shanmugam et al, *Drug Development and Industrial Pharmacy* 2015;41(11):1864-1876
[b] McEntee et al, *Veterinary and Comparative Oncology* 2003;1(2):105-112
[c] At pH conditions similar to gastric fluid
[d] Montaseri, *Taxol: Solubility, Stability and Bioavailability* 1997
[e] Bharate et al, *Bioorganic & Medicinal Chemistry Letters* 2015;25(7):1561-1567
[f] Tan et al, *British Journal of Cancer* 2014;110(11):2647-54
[g] Taxotere (docetaxel) FDA prescribing information
[h] Lang et al, 2012 ASCO Annual Meeting, *Journal of Clinical Oncology* 2012;20(15 supp):2555

Tesetaxel Dosing and Administration



	Paclitaxel[e]	Tesetaxel
Route	Intravenous	Oral
Frequency	Once every 7 days	Once every 21 days
Dose	80 mg/m^2	27 mg/m^2 (2-5 capsules)
Anti-allergy Premedication	Yes[f]	No

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

[a] Shionoya et al, *Cancer Science* 2003;94(5):459-66
[b] Trock et al, *Journal of the NCI* 1997;89(13):917-31
[c] Tan et al, *British Journal of Cancer* 2014;110(11):2647-54
[d] Pharmacokinetic data from Studies 927A-PRT001, 927E-PRT003, 927E-PRT005, 927A-PRT006, and 927E-PRT007
[e] National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology 2020
[f] Corticosteroid + antihistamine + H_2 antagonist as per prescribing label

Study Design

Key Eligibility Criteria

- HR positive, HER2 negative MBC
- 0-1 prior chemotherapy regimens for MBC
- Prior taxane in the neoadjuvant or adjuvant setting required
  - No restriction on disease-free interval (DFI)
- Any number of prior endocrine therapies
- Any number of prior approved targeted therapies (*e.g.*, CDK 4/6 inhibitors, everolimus)
- Measurable disease per RECIST 1.1 or bone-only disease with lytic component

Multinational, Multicenter, Randomized

1:1 Randomization

Tesetaxel
27 mg/m² PO
Day 1 of a 21-day cycle

+

Capecitabine
1,650 mg/m² PO
(825 mg/m² BID)
Evening Day 1 to Morning Day 15
of a 21-day cycle

Treat until progressive disease or unacceptable toxicity

Capecitabine
2,500 mg/m² PO
(1,250 mg/m² BID)
Evening Day 1 to Morning Day 15
of a 21-day cycle

PO=oral dosing; BID=twice per day

Statistical Considerations

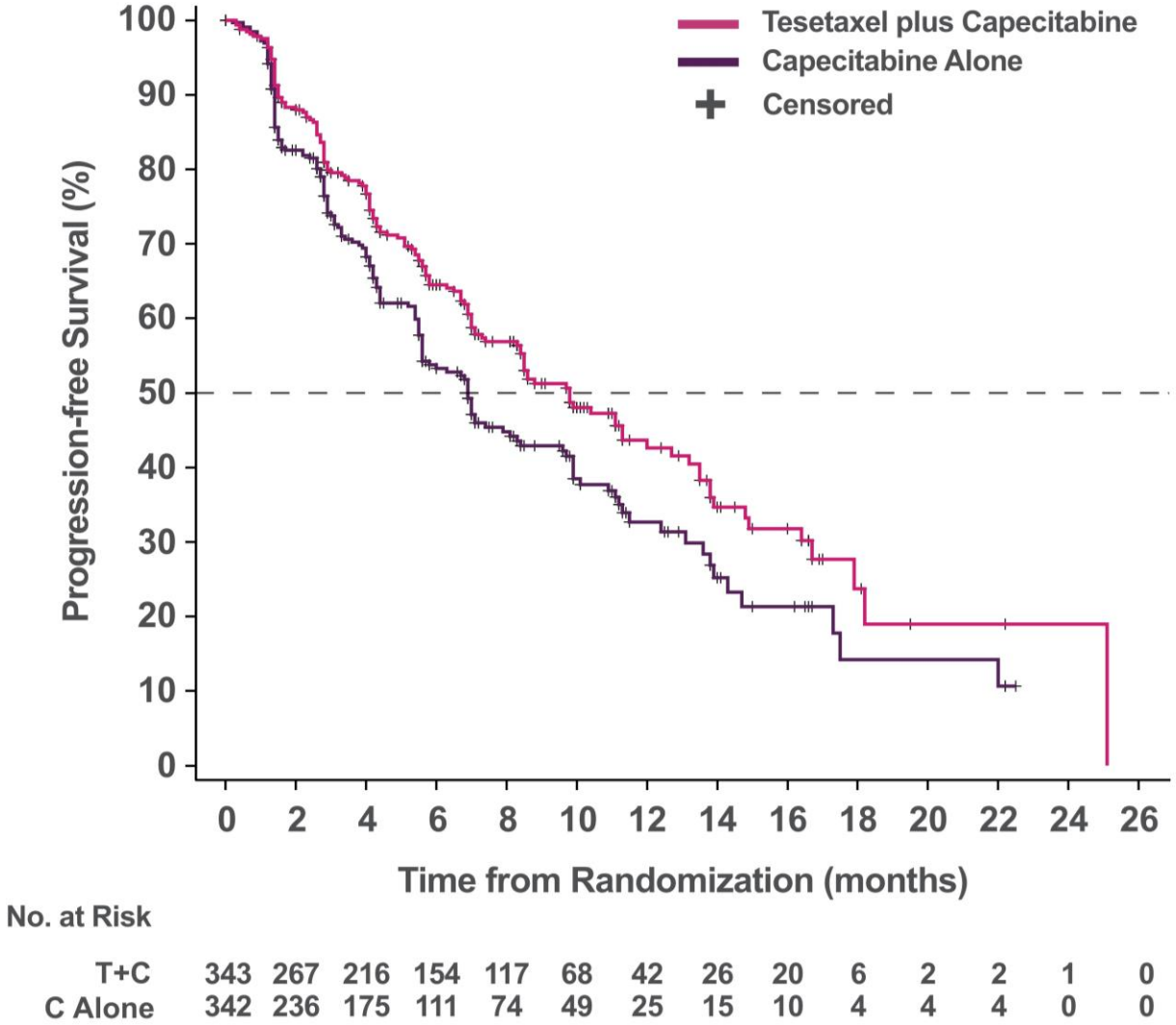
- Primary endpoint
  - Progression-free survival (PFS) as assessed by the Independent Radiologic Review Committee (IRC)
  - 90% power to detect a hazard ratio of 0.71 (median PFS difference of 2.5 months) by stratified log-rank test based on an expected 347 events
- Secondary endpoints
  - Overall survival (OS)
  - ORR as assessed by IRC[a]
  - Disease control rate (DCR) [ORR or stable disease of ≥24 weeks] as assessed by IRC[a]
- Stratified by the presence of visceral disease, geographic region and number of prior chemotherapy regimens for advanced disease
- Median follow-up = 13.9 months

[a] In patients with measurable disease

Baseline Characteristics

Baseline Characteristic	Tesetaxel plus Capecitabine (N=343)	Capecitabine Alone (N=342)
Median age, years (min, max)	56 (23, 85)	57 (29, 84)
Median time from initial diagnosis, **years** (min, max)	5.1 (0.9, 24.6)	5.2 (0.8, 24.0)
ECOG status, 0 / 1 / 2+	54% / 44% / 2%	59% / 39% / 2%
North America / Europe / Asia-Pacific	45% / 37% / 18%	45% / 38% / 17%
Prior therapy (neo/adjuvant or metastatic setting)		
Taxane	100%	99%
Anthracycline	84%	88%
Alkylator	93%	92%
Endocrine therapy	93%	90%
CDK 4/6 inhibitor	49%	51%
No. of prior chemo regimens for MBC, 0 / 1	92% / 8%	94% / 6%
DFI following prior taxane <24 months	33%	32%
Visceral disease	80%	78%
Common sites of disease		
Bone	70%	68%
Liver	60%	55%
Lung	38%	34%

PFS as Assessed by IRC

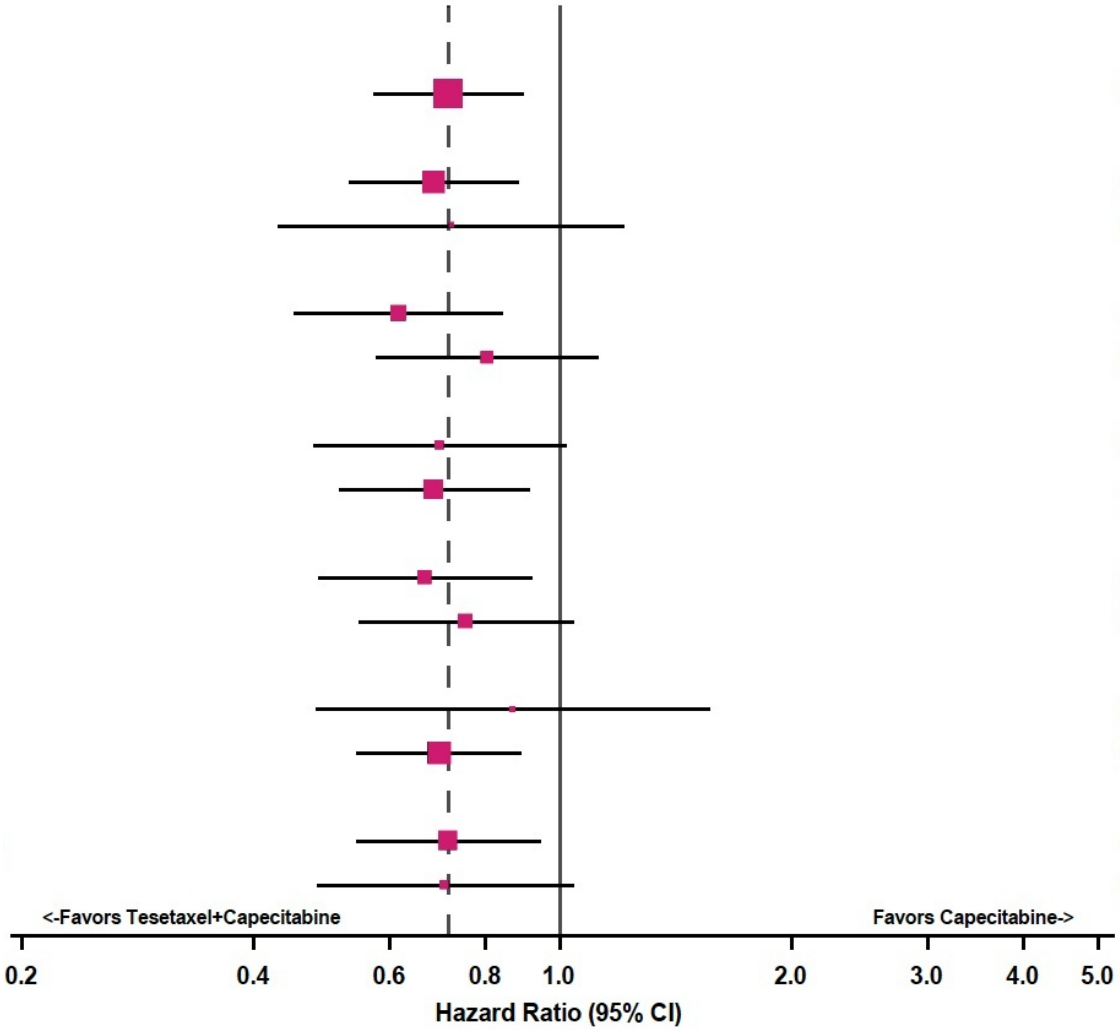


	Tesetaxel plus Capecitabine (N=343)	Capecitabine Alone (N=342)
Events	155	169
Median Months (95% CI)	9.8 (8.4 – 12.0)	6.9 (5.6 – 8.3)
	2.9-Month Improvement	
Hazard Ratio (95% CI)	0.716 (0.573 – 0.895)	
P-value	0.003	

CI=confidence interval

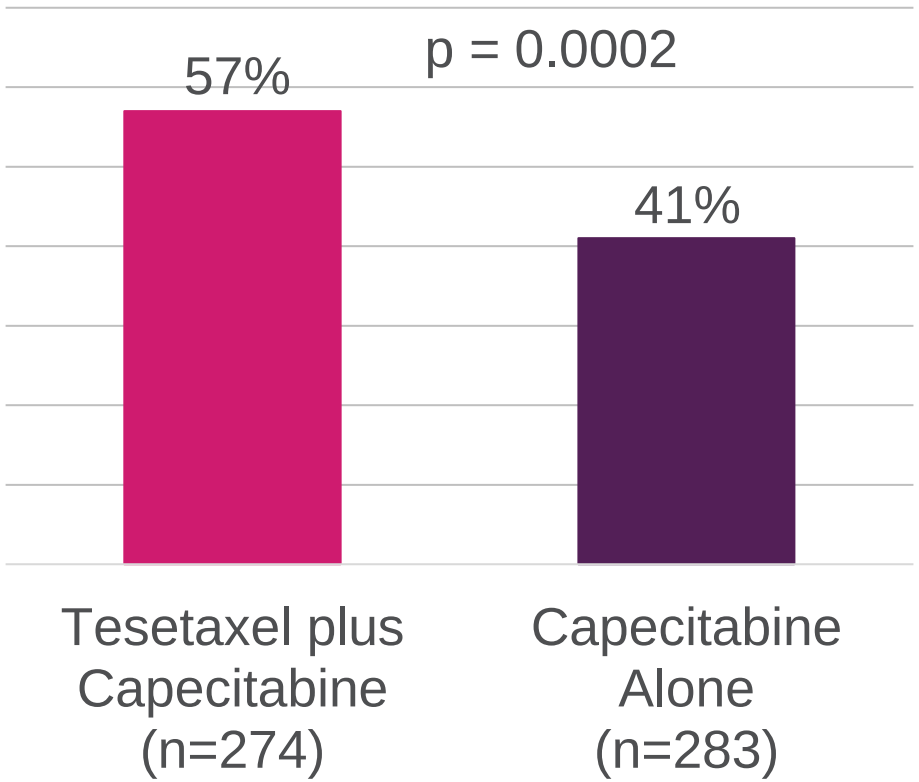
PFS as Assessed by IRC by Protocol-Specified Subgroups

Characteristics (N)	Hazard Ratio (95% CI)	P-value
Overall Treatment Group		
All (685)	0.72 (0.57 – 0.90)	0.003
Age (years)		
<65 (531)	0.69 (0.53 – 0.88)	0.003
≥65 (154)	0.72 (0.43 – 1.21)	0.217
Baseline ECOG		
0 (387)	0.62 (0.46 – 0.84)	0.002
≥1 (297)	0.80 (0.58 – 1.12)	0.197
DFI Following Prior Taxane		
<24 months (226)	0.70 (0.48 – 1.02)	0.063
≥24 months (459)	0.69 (0.52 – 0.91)	0.009
Prior CDK 4/6 Inhibitor		
No (345)	0.67 (0.49 – 0.92)	0.013
Yes (340)	0.76 (0.55 – 1.04)	0.086
Visceral or CNS Disease		
No (145)	0.87 (0.48 – 1.57)	0.641
Yes (540)	0.70 (0.55 – 0.89)	0.004
Geographic Region		
North America/Western Europe (456)	0.72 (0.54 – 0.94)	0.017
ROW (229)	0.71 (0.48 – 1.04)	0.079

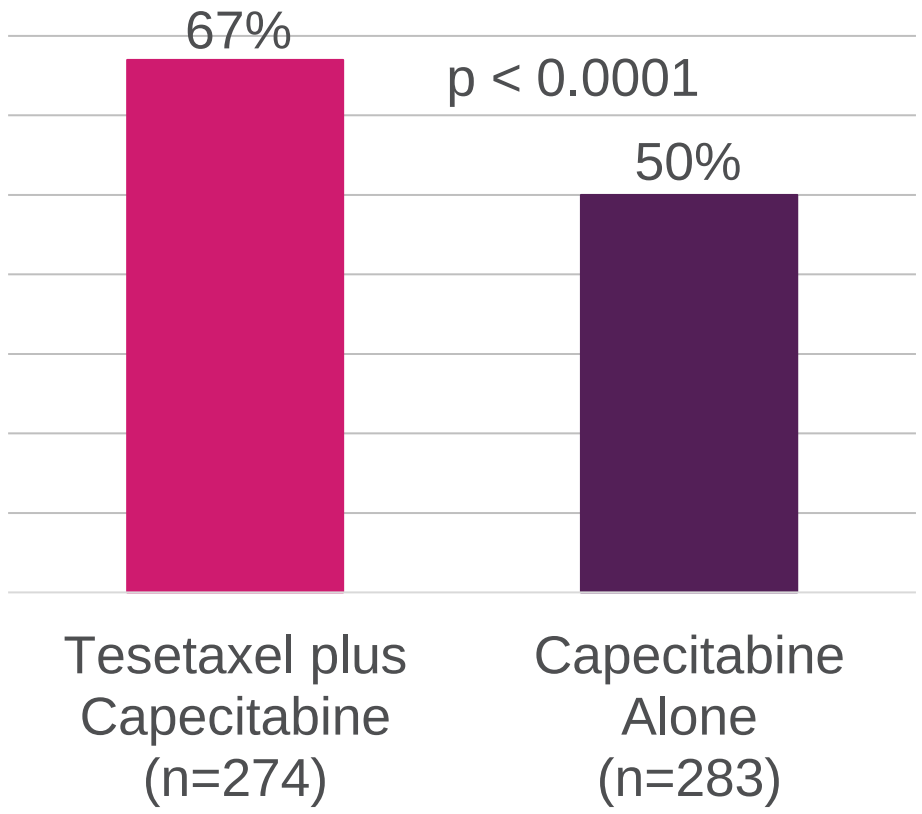


Secondary Endpoints

ORR as Assessed by IRC[a]



24-Week DCR as Assessed by IRC[a]



- OS data are immature; protocol-specified final analysis of OS is expected in 2022

[a] In patients with measurable disease

24-week DCR=ORR or stable disease of ≥24 weeks

All Grade Treatment-Emergent Adverse Events (TEAEs) That Occurred in ≥20% of Patients in Either Arm

System Organ Class	TEAE	Tesetaxel plus Capecitabine (N=337) (%)	Capecitabine Alone (N=337) (%)
Hematologic	Neutropenia	76.9	22.6
	Anemia	29.7	19.0
	Thrombocytopenia	20.5	6.2
Gastrointestinal	Nausea	62.6	42.7
	Diarrhea	61.1	46.9
	Constipation	33.2	15.1
	Vomiting	30.6	19.9
	Abdominal pain	21.7	17.2
	Stomatitis	20.5	29.1
Other	Hand-foot syndrome	50.7	66.2
	Neuropathy	48.1	13.6
	Fatigue	47.8	34.4
	Decreased appetite	28.8	19.3
	Alopecia*	28.2	2.4
	Hypokalemia	20.5	6.8

*Grade 2 alopecia (tesetaxel plus capecitabine vs. capecitabine alone): 8.0% vs. 0.3%

Note: Safety population includes 674 patients who were randomized and received study drug

Grade ≥3 TEAEs That Occurred in ≥5% of Patients in Either Arm

System Organ Class	TEAE	Tesetaxel plus Capecitabine (N=337) (%)		Capecitabine Alone (N=337) (%)	
		Grade 3	Grade 4	Grade 3	Grade 4
Hematologic	Neutropenia	32.6	38.3	7.4	0.9
	Febrile neutropenia	10.4	2.7	0.3	0.9
	Anemia	8.0	0.0	2.4	0.0
	Leukopenia	6.8	3.0	0.6	0.3
Gastrointestinal	Diarrhea	12.5	0.6	8.9	0.0
	Nausea	6.2	0.0	2.1	0.0
Other	Fatigue	8.6	0.0	4.5	0.0
	Hypokalemia	8.0	0.6	2.7	0.0
	Hand-foot syndrome	6.8	0.0	12.2	0.0
	Neuropathy[a]	5.3	0.6	0.9	0.0

No treatment-related hypersensitivity reactions

[a] Pooled term includes: paraesthesia, peripheral sensory neuropathy, polyneuropathy, neuropathy peripheral and peripheral motor neuropathy for all tables

Note: Safety population includes 674 patients who were randomized and received study drug

AEs Resulting in Treatment Discontinuation in ≥1% of Patients in Either Arm

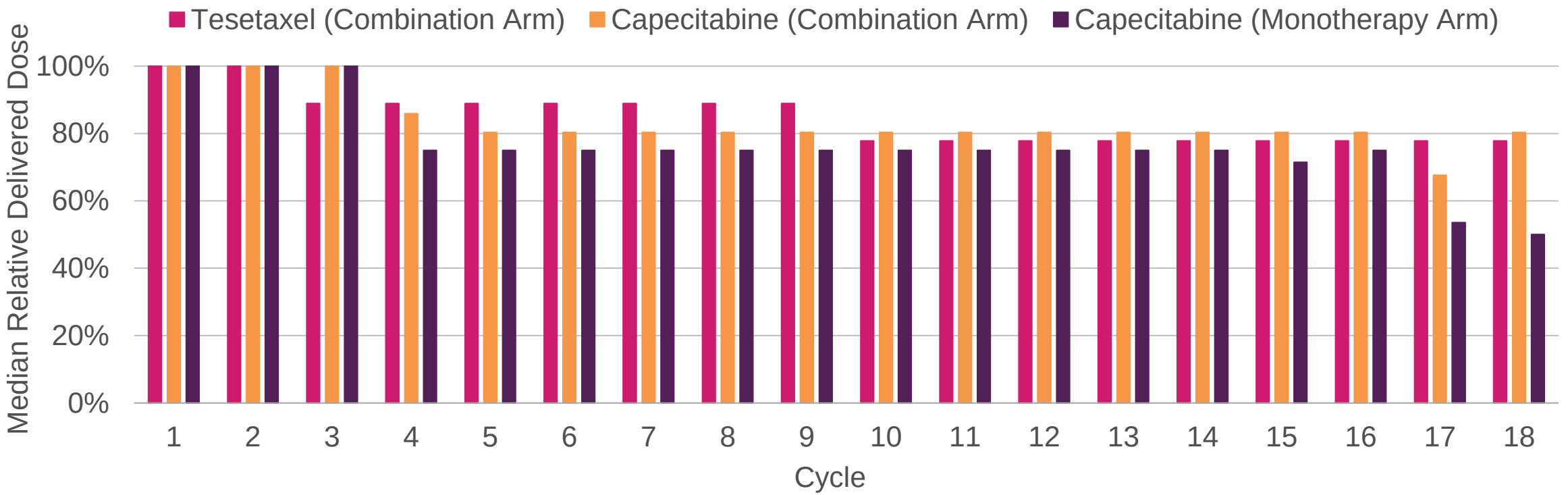
	Tesetaxel plus Capecitabine (N=337) (%)	Capecitabine Alone (N=337) (%)
Neutropenia or febrile neutropenia	4.2	1.5
Neuropathy	3.6	0.3
Sepsis or septic shock	1.8	0.6
Diarrhea	0.9	1.5
Hand-foot syndrome	0.6	2.1
Patients discontinuing treatment due to any AE[a]	23.1	11.9

[a] Includes 1.8% (6 patients) treatment-related deaths (5 sepsis, 1 cardiorespiratory arrest) in the tesetaxel plus capecitabine arm and 0.9% (3 patients) treatment-related deaths (2 septic shock, 1 colitis) in the capecitabine alone arm

Note: Patients may have discontinued treatment for multiple adverse events. One patient discontinued treatment for both febrile neutropenia and sepsis in the tesetaxel plus capecitabine arm and one patient discontinued treatment for both diarrhea and febrile neutropenia in the capecitabine alone arm.
Note: Safety population includes 674 patients who were randomized and received study drug

Relative Delivered Dose Intensity

	Tesetaxel (Combination Arm)	Capecitabine (Combination Arm)	Capecitabine (Monotherapy Arm)
Patients with dose reductions	76%	58%	61%
Primary reason for dose reduction	Neutropenia	Neutropenia	Hand-foot syndrome
Patients receiving G-CSF[a]	58% (Median = 2 cycles)		6%
Relative delivered dose intensity cycles 1-12	81%	79%	76%



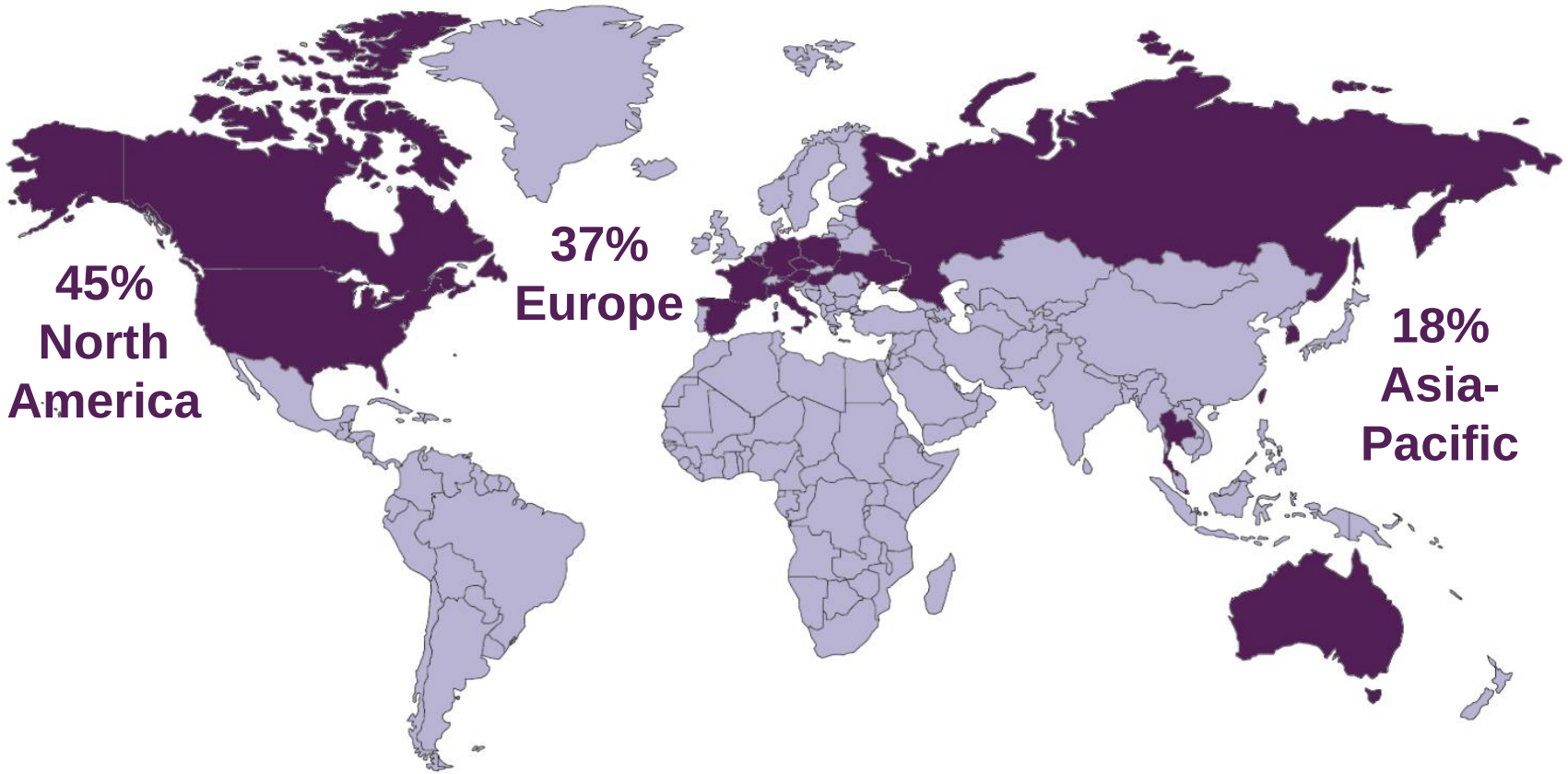
[a] G-CSF allowed only after occurrence of Grade ≥3 neutropenia or febrile neutropenia and only on capecitabine off days

Conclusions

- The all-oral regimen of tesetaxel plus a reduced dose of capecitabine significantly improved PFS vs. capecitabine alone
  - Median PFS was 9.8 months vs. 6.9 months, an improvement of 2.9 months
  - HR=0.716; p=0.003
- Neutropenia was the most frequent grade ≥3 TEAE
  - Generally manageable, primarily with dose reductions and G-CSF as needed
  - Treatment discontinuation due to neutropenia or febrile neutropenia was 4.2% for tesetaxel plus capecitabine vs. 1.5% for capecitabine alone
- Rates of grade ≥3 neuropathy (5.9%) and grade 2 alopecia (8.0%) were low
- Tesetaxel plus a reduced dose of capecitabine is a potential new treatment option for patients with HR positive, HER2 negative MBC

Acknowledgements

We thank the investigators, study team personnel, and especially the patients and their caregivers who made CONTESSA possible



Countries with enrolling clinical study sites

Country	Patients
United States	286
Ukraine	49
Spain	46
South Korea	42
Russia	34
France	33
Australia	30
Taiwan	25
Canada	23
Germany	22
Poland	21
Hungary	18
Belgium	15
Singapore	15
Austria	8
Thailand	8
Czech Republic	5
Italy	5
Total	**685**