Supplementary Online Content

Munzone E, Regan MM, Cinieri S, et al. Efficacy of metronomic oral vinorelbine, cyclophosphamide, and capecitabine vs weekly intravenous paclitaxel in patients with estrogen receptor–positive, *ERBB2*-negative metastatic breast cancer: final results from the phase 2 METEORA-II randomized clinical trial. Published online July 13, 2023. *JAMA Oncol.* doi:10.1001/jamaoncol.2023.2150

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1
METEORA-II (MEtronomic TrEatment Option in Advanced bReast cAncer; IBCSG 54-16) Investigators and the International Breast Cancer Study Group (IBCSG) [a division of ETOP IBCSG Partners Foundation] Participants

IBCSG Scientific Committee Co-Chairs: M Colleoni (Co-Chair), A Di Leo† (Co-Chair), S Loi (Co-Chair)

ETOP IBCSG Partners Foundation Board: R Stahel (President), S Aebi, P Baas, M Colleoni, R Gelber, S Loi, K McGregor, S Peters, S Popat, R Rosell

ETOP IBCSG Partners Foundation Coordinating Center, Bern, Switzerland: A Hiltbrunner (Director), G Achille, A Carrer-Wagner, D Celotto, C Comune, A Gasca, N Giacomelli, R Kammler, R Pfister, H Roschitzki, B Ruepp, M Ruggeri, E Rugiati, M Schneider, J Schroeder, S Troesch

IBCSG Statistical Center, Division of Biostatistics, Dana-Farber Cancer Institute, Boston, MA, USA: M Regan (Director), C Bouzan, S Farah, R Gelber, R Shi, Z Sun

IBCSG Data Management Center, Frontier Science, Amherst, NY, USA: H Shaw (Director), L Blacher (former Director), C King, L Mundy, D Polizzi (Data Manager), M Greco, K Scott, R Starkweather

Trial Contact in Italy: R Ghisini

Funding: Pierre Fabre Pharma S.r.l., Fondazione Umberto Veronesi

Participating Centers and Principal Investigators of the 15 Centers Enrolling Patients

IBCSG
Istituto Europeo di Oncologia (IEO) IRCCS, Milan (E Munzone: 49 enrolled);
P.O. “Antonio Perrino”, Brindisi (S Cinieri: 22 enrolled);
Ospedale Infermi, UO Oncologia, Rimini (L Gianni: 6 enrolled);
Aviano Centro di Riferimento Oncologico (CRO), Aviano (F Puglisi: 5 enrolled);
Ospedale di Bolzano - Oncologia Medica, Bolzano (E Cretella: 4 enrolled);
ASST Settelaghi – Ospedale di Circolo e Fondazione Macchi, Varese (G Pinotti: 3 enrolled)
Italy (non-IBCSG centers)
Fondazione Policlinico Gemelli - Universita Cattolica del Sacro Cuore, Rome (R Masetti: 9 enrolled);
Santa Maria delle Croci Hospital, Ravenna (L Amaducci: 8 enrolled);
IRST IRCCS, Meldola (U De Giorgi: 6 enrolled);
Ospedale Treviglio, Treviglio (F Petrelli: 6 enrolled);
Ospedale Misericordia di Grosseto, Grosseto (C Bengala: 6 enrolled);
ASST di Cremona, Cremona (D Generali: 5 enrolled);
ASST Ovest Milanese Via Papa Giovanni Paolo II Legnano, Legnano (E Collovà: 5 enrolled);
A.O.U. di Bologna Policlinico S. Orsola-Malpighi, Bologna (C Zamagni: 4 enrolled);
A.O.U Città della Salute e della Scienza di Torino, Torino (M Donadio: 2 enrolled)

eMethods

The protocol will be available with the clinicaltrials.gov record of results (NCT02954055)

Eligibility

Pre- or postmenopausal women aged ≥18 years with histologically or cytological proven MBC, ER+/HER2- status according to local laboratory, were eligible. Patients may have received a maximum of one prior line of chemotherapy for advanced or MBC (if previously treated with a taxane in the neoadjuvant or adjuvant setting, the period from end of treatment to disease recurrence must have been >12 months). Patients were excluded if previously treated with taxanes, or capecitabine or vinorelbine or oral cyclophosphamide for MBC or if they received more than 2 lines of previous endocrine therapy for locally advanced or metastatic breast cancer (CDK4/6 inhibitors were allowed). Patients with measurable or non-measurable, but radiologically evaluable (except for skin lesions), disease according to RECIST 1.1 criteria were eligible.

Randomization

Randomization was stratified according to prior treatment for locally-advanced or MBC (no prior endocrine therapy or chemotherapy; prior endocrine therapy only; prior chemotherapy ± prior endocrine therapy) and ECOG performance status 0 versus 1, and implemented dynamic institutional balancing. The randomization process was implemented via an internet-based application hosted at the IBCSG Data Management Center, which participating sites accessed for patient registration and treatment assignment.

Treatment

The VEX regimen was vinorelbine 40 mg orally days 1, 3, 5/week, cyclophosphamide 50 mg/day orally, capecitabine 1500 mg/day orally. Those assigned paclitaxel were given intravenous paclitaxel 90 mg/m^2 days 1, 8, 15 of as 28-day cycle. Both regimens were administered in 28-day cycles until progression, lack of tolerability, or until further trial treatment was declined. Treatment could be delayed by a maximum of 3 weeks. Patients showing RECIST 1.1-defined progressive disease could continue with trial treatment at the discretion of the Investigator as long as that was considered to be in the best interest of the patient and no new anticancer treatment was initiated.

Study Assessments

Day 1 of every treatment cycle included physical examination, vital signs, hematology and biochemistry; hematology on day 15 of cycle 1 was also required for patients assigned VEX. During the COVID-19 pandemic, every-other-monthly visit by telemedicine was allowed for patients assigned VEX, and accounted for approximately 2% of all visits by 10% of patients.

Tumor measurements according to RECIST 1.1 criteria were assessed at baseline, and every 12 weeks (± 2 weeks) from randomization until first disease progression on the basis of clinical and radiological (by CT scan or MRI) tumor assessments; bone scan and FDG-PET was done if clinically indicated. Patients who discontinued treatment for reasons other than objective disease progression were followed for up to 1 year to record the subsequent date of first progression.

Adverse events (AE) were recorded and graded using the NCI CTCAE version 4.0, including 25 targeted AEs (for which any grade severity was to be reported) and any other medically-important AEs of grade 3 or higher, without regard to whether considered related to a trial medication. AEs were recorded between the first dose of trial medication until 28 days after the end of treatment date, and SAEs were collected until all treatment discontinuation (one or two of the VEX medications could be continued if one needed to be discontinued, but 63 of 67 patients' discontinuations were all 3 medications).

Endpoints

The primary endpoint was investigator-assessed time to treatment failure (TTF) defined as the interval between the date of randomization to the end of treatment date. For patients assigned paclitaxel, the end of treatment date was the date of last [IV] dose plus 7 days; for patients assigned VEX, it was the date when at least one of the three [oral] VEX drugs was taken for the last time. For those patients without end of treatment date, TTF was censored at the date of last treatment documentation (latest administration of paclitaxel or latest VEX cycle day 1 date). All instances of therapy delays were reviewed, and if treatment was re-initiated after more than 3 weeks protocol-defined maximum delay, then the end-of-treatment date was back-dated prior to the delay according to the definition.

The secondary endpoint PFS was defined as time from randomization until documented disease progression according to RECIST 1.1 criteria or death, whichever occurred first; the death must have occurred within an interval of time corresponding to the interval of tumor re-evaluations. For patients without progression, follow-up was censored at the date of last disease assessment.

Other secondary endpoints included disease control, defined as best overall response of complete or partial response (CR or PR), or stable disease (SD) lasting for at least 24 weeks. Overall survival (OS) was defined as the time from the date of randomization to death from any cause, or was censored at the date last known alive.

Survival follow-up was systematically updated for the database lock; the median follow-up was 28.7 months (interquartile range [IQR], 21.6-35.8 months).

Statistical Considerations

A sample size of 160 patients was planned to document 123 TTF events, assuming a median TTF of 4.5 months with paclitaxel improved to 7.5 months with VEX (hazard ratio [HR]=0.60) following exponential distributions, enrollment of 24 months plus 12 months additional follow-up, and comparison using logrank test with two-sided α=0.05 and desired power of 80%. One interim analysis of futility was conducted after approximately 60% information (75 TTF events) was documented using a one-sided boundary based on O'Brien-Fleming criteria. After more than 3 years of enrollment, discussions with the IBCSG Data and Safety Monitoring Committee led to early enrollment closure (after the Q4'2020 meeting), considering that the targeted 123 TTF events could be reached based upon enrollment to date (enrollment was 138 patients as of 2 Dec 2020). The IBCSG Data and Safety Monitoring Committee reviewed the trial at its twice-yearly meetings.

The TTF distributions were estimated using Kaplan-Meier method, with reporting of median, 6- and 12-month estimates, and compared using stratified log-rank test. The Cox proportional hazards model estimated a stratified hazard ratio (HR) with 95% confidence interval (CI), using the stratification factors from randomization. Subgroup analyses re-estimated HRs according to prior therapy for MBC, by use of treatment-by-covariate interaction in Cox models. The database lock was performed 4 December 2021.

Regulatory Conduct

All patients provided written informed consent. The study was approved by the local ethics and/or institutional review boards for all participating sites and the Italian health authority. The study was conducted according to principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4. doi: 10.1001/jama.2013.281053) and ICH Guidelines for Good Clinical Practice (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. Guideline for Good Clinical Practice E6(R1). 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf).

eResults, eTables and eFigures

eTable 1. Characteristics of the 133-patient METEORA-II efficacy analysis population.

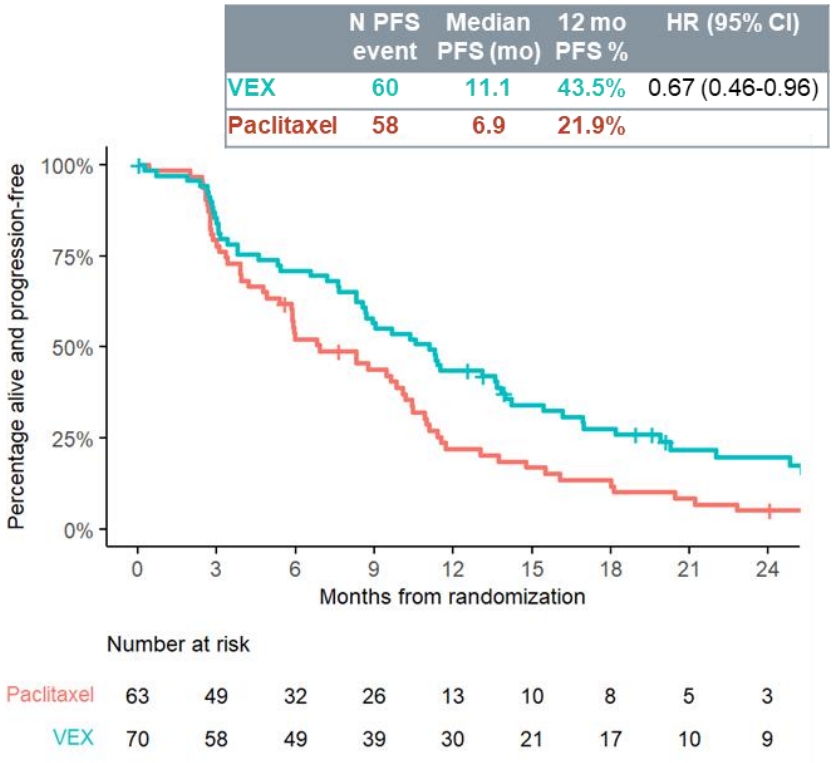
Characteristic	Treatment Assignment				Overall	
	Paclitaxel		VEX			
	N	%	N	%	N	%
N Patients in efficacy analysis population	*63*		*70*		*133*	
Months from MBC diagnosis to randomization, median	10.9	-	14.0	-	11.2	-
ECOG PS at randomization (stratification factor)						
0	49	77.8	56	80.0	105	78.9
1	14	22.2	14	20.0	28	21.1
Age at randomization						
<55	19	30.2	21	30.0	40	30.1
55-69	30	47.6	39	55.8	69	51.9
≥70	14	22.2	10	14.3	24	18.0
Type of evaluable disease						
Measurable	51	81.0	53	75.7	104	78.2
Non-measurable	12	19.0	17	24.3	29	21.8
ER status determination						
Primary lesion	31	49.2	42	60.0	73	54.9
Metastatic lesion	32	50.8	28	40.0	60	45.1
Prior treatment for MBC (stratification factor)						
No prior ET or CT	19	30.2	18	25.7	37	27.8
Prior ET only	35	55.6	40	57.1	75	56.4
Prior CT ± ET	9	14.3	12	17.1	21	15.8
Prior ET±CDK4/6 inhibitor use						
No prior ET	19	30.2	18	25.7	37	27.8
Prior ET & CDK46i unknown	1	1.6	2	2.9	3	2.3
ET, no CDK46i	13	20.6	18	25.7	31	23.3
ET+CDK46i just prior	26	41.3	29	41.4	55	41.4
ET, CDK46i previously	4	6.3	3	4.3	7	5.3

Randomization was stratified according to ECOG PS and prior treatment for MBC.
Abbreviations: VEX=vinorelbine+cyclophosphamide+capecitabine; PS=performance status; ER=estrogen receptor; ET=endocrine therapy; CT=chemotherapy; MBC=metastatic breast cancer

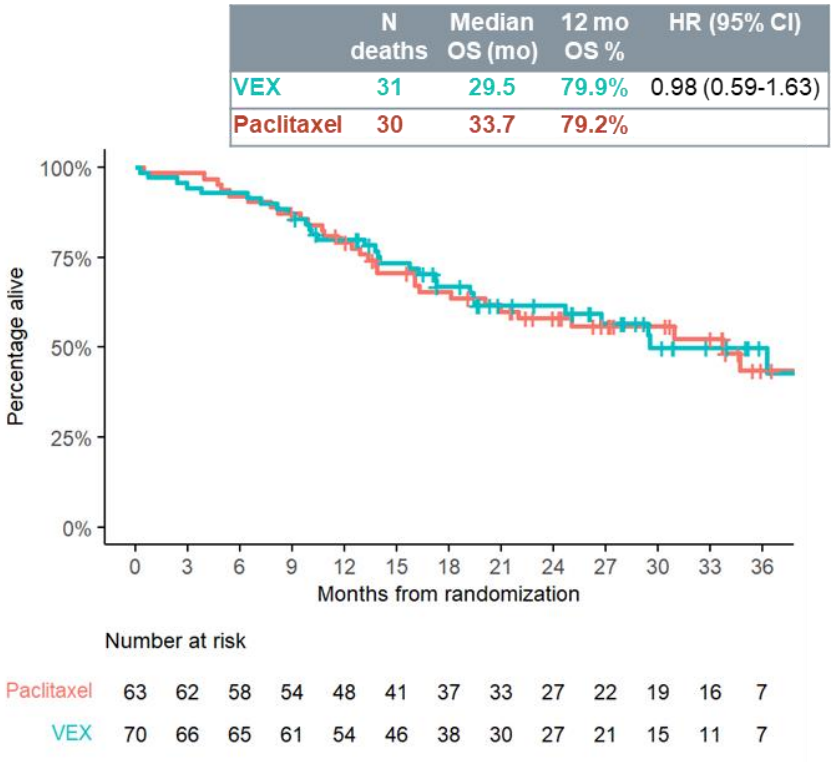
eFigure. METEORA-II Progression-free survival and overall survival.
Kaplan-Meier estimate of progression-free survival (PFS) and overall survival (OS) in the 133-patient efficacy analysis population, according to treatment assignment.

Abbreviations: VEX=vinorelbine+cyclophosphamide+capecitabine; PFS=progression-free survival; mo=months; HR=hazard ratio; CI=confidence interval.

(A)



(B)



eTable 2. METEORA-II subgroup analyses according to prior therapy. Kaplan-Meier estimates of median, 6 and 12-month time to treatment failure (TTF) and hazard ratio (HR) with 95% confidence interval (CI) of treatment effect.

		Time to Treatment Failure (TTF)									
Subgroup	**N Pts**	**N Event**	**Median (mo)**	**(95% CI)**	**6-mo (%)**	**95% CI**	**12-mo (%)**	**95% CI**	**HR**	**95% CI**	
No Prior ET or CT											
Paclitaxel	19	19	6.2	(3.7- | 8.5)	52.6	(28.7- | 71.9)	15.8	(3.9- | 34.9)			
VEX	18	18	7.6	(2.7-	14.2)	55.6	(30.5-	74.8)	38.9	(17.5-	60.0)	0.74	(0.38-	1.44)
Prior ET only														
Paclitaxel	35	33	5.6	(2.8- | 6.0)	34.3	(19.3- | 49.8)	3.4	(0.3- | 14.6)			
VEX	40	38	8.4	(5.4-	11.5)	55.0	(38.5-	68.8)	32.5	(18.8-	47.0)	0.52	(0.32-	0.84)
Prior CT±ET														
Paclitaxel	9	9	6.1	(2.6- | 10.6)	55.6	(20.4- | 80.5)	11.1	(0.6- | 38.8)			
VEX	12	11	6.9	(1.1-	16.3)	50.0	(20.8-	73.6)	33.3	(10.3-	58.8)	0.65	(0.27-	1.58)

		Time to Treatment Failure (TTF)									
Subgroup	**N Pts**	**N Event**	**Median (mo)**	**(95% CI)**	**6-mo (%)**	**95% CI**	**12-mo (%)**	**95% CI**	**HR**	**95% CI**	
No prior ET											
Paclitaxel	19	19	6.2	(3.7- | 8.5)	52.6	(28.7- | 71.9)	15.8	(3.9- | 34.9)			
VEX	18	18	7.6	(2.7-	14.2)	55.6	(30.5-	74.8)	38.9	(17.5-	60.0)	0.73	(0.38-	1.43)
ET without CDK4/6i*														
Paclitaxel	14	14	5.2	(2.6-	6.1)	35.7	(13.0-	59.4)	0	--				
VEX	20	19	7.6	(3.0-	15.9)	55.0	(31.3-	73.5)	45.0	(23.1-	64.7)	0.39	(0.19-	0.79)
ET+CDK4/6i														
Paclitaxel	30	28	5.6	(2.8- | 6.3)	40.0	(22.8- | 56.7)	8.0	(1.5- | 22.0)			
VEX	32	30	8.4	(3.8-	11.3)	53.1	(34.7-	68.5)	25.0	(11.8-	40.7)	0.63	(0.37-	1.06)

*Includes 3 patients with unknown prior ET and CDK4/6i.
Abbreviations: VEX=vinorelbine+cyclophosphamide+capecitabine; pts=patients; mo=months; ET=endocrine therapy; CT=chemotherapy

3.1 Protocol Treatment

At the time of the database lock, the median number of cycles was 6 (interquartile range [IQR], 3-12; range 1-50) overall (eTable 3); 74/133 (55.6%) patients had progression and 23.3% had AE as end-of-treatment reason (eTable 4). The cumulative paclitaxel doses, which VEX agent(s) were discontinued at TTF event, and dose modifications are summarized in eTables 5-8 below.
Dose modifications occurred more frequently in the VEX regimen than in paclitaxel (60% vs. 44%).

eTable 3. Number of cycles overall and according to treatment assignment, prior to TTF end-of-treatment date (or censoring date)

	N Pts	Min	Q1	Median	Q3	Max	N cycles received (sum)
Paclitaxel	63	1	3	6	9	50	466
VEX	70	1	3	9	16	36	737
Overall efficacy analysis population	133	1	3	6	12	50	1203

VEX=vinorelbine+cyclophosphamide+capecitabine; TTF=time to treatment failure; pts=patients

eTable 4. Reasons for TTF event end-of-treatment, overall and according to treatment assignment

	Treatment Assignment				Overall	
	Paclitaxel		VEX			
	N	%	N	%	N	%
Number of patients in efficacy analysis population	*63*	*100.0*	*70*	*100.0*	*133*	*100.0*
Reason for TTF event permanent discontinuation						
No TTF event	2	3.2	3	4.3	5	3.8
Progression	35	55.6	39	55.7	74	55.6
Adverse Event	16	25.4	15	21.4	31	23.3
Patient declined	1	1.6	3	4.3	4	3.0
Medical decision	8	12.7	8	11.4	16	12.0
Death	1	1.6	2	2.9	3	2.3

TTF=time to treatment failure

eTable 5. Cumulative number of paclitaxel doses and of dose administered, prior to TTF end-of-treatment date (or censoring date)

	N Pts	Min	Q1	Median	Q3	Max
Cumulative paclitaxel dose mg/m^2	63	90	720	1422	2168	10548
Cumulative paclitaxel doses	63	1	8	18	26	140
Paclitaxel relative dose intensity	63	0.33	0.78	0.88	0.96	1
Paclitaxel relative dose number	63	0.33	0.86	0.95	1.00	1

TTF=time to treatment failure; pts=patients

eTable 6. Paclitaxel treatment modifications, prior to TTF end-of-treatment date (or censoring date)

	N	%
N patients assigned paclitaxel in efficacy analysis population	*63*	*100.0*
Patients who had:		
Dose(s) reduced/increased	28	44.4
Dose(s) off schedule	23	36.5
Dose(s) not given	25	39.7

TTF=time to treatment failure

eTable 7. VEX agents stopped at TTF end-of-treatment date

	N	%
N patients assigned VEX in efficacy analysis population	*70*	*100.0*
Which VEX agent(s) stopped at TTF event		
On treatment	3	4.3
V only	2	2.9
E only	2	2.9
VEX	63	90.0

VEX=vinorelbine+cyclophosphamide+capecitabine; TTF=time to treatment failure

eTable 8. VEX treatment modifications prior to TTF event, prior to TTF end-of-treatment date (or censoring date)

	N	%
N patients assigned VEX in efficacy analysis population	*70*	*100.0*
Patients who had:		
V dose modification(s): <3x/week, 50% dose reduction, or not taken*	43	61.4
E dose modification(s): interruptions>3 days, every other day (50% dose reduction) or not taken*	41	58.6
X dose modification(s): interruptions>3 days, 1 table twice a day (67% dose reduction) or not taken*	42	60.0

VEX=vinorelbine+cyclophosphamide+capecitabine; TTF=time to treatment failure
*Not taken indicates a long interruption, restarted within protocol-specified time frame

eTable 9. Patients experiencing ≥1 targeted* AE

	Paclitaxel (95% CI)	VEX (95% CI)
Total patients experiencing ≥1 targeted AE	62 (98.4%) (91.5% - 100%)	65 (92.9%) (84.1% - 97.6%)
Total patients experiencing ≥1 targeted grade 3 or 4 AE	18 (28.6%) (17.9% - 41.3%)	30 (42.9%) (31.1% - 55.3%)
Total patients experiencing ≥1 targeted or other grade 3-5** AE	20 (31.7%) (20.9% - 44.8%)	41 (58.6%) (46.2% - 70.2%)

VEX=vinorelbine+cyclophosphamide+capecitabine; AE=adverse event.
*There were 25 targeted AEs, including those 23 listed in the Table and 2 not reported for any patients (heart failure, sinus bradycardia), for which any grade of severity was to be reported.
**Only medically-important (other) AEs of grade 3 or higher were to be reported, most of which were white blood cell decreases and liver function laboratory abnormalities. There were three deaths during study treatment (i.e., 'other' grade 5 AEs), 1 in the paclitaxel group and 2 in the VEX group (see eAppendix 2).

eAppendix 2

There were 3 deaths reported treatment, each during the first cycle of treatment. One patient with pleural metastatic disease died two weeks after starting VEX treatment, reported cause was pulmonary edema. One patient died at home during the first week of starting VEX, reported as sudden death cause unknown. One patient died within two weeks after starting paclitaxel attributed to rapid progression of disease, probably abdominal breast cancer metastasis.

A fourth patient developed a primary brain tumor (oligodendroglioma) about one year after starting the VEX regimen and died because of a venous sinus thrombosis; study treatment had been stopped 6 weeks earlier, and cause of death probably due to the extent of venous sinus thrombosis, secondary to the extent of the brain mass, but could not clearly be attributed to progression of disease.