Supplementary Online Content

Jerusalem G, de Boer RH, Hurvitz S, et al. Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor–Positive, HER2-Negative Advanced Breast Cancer (BOLERO-6): A Phase 2 Randomized Clinical Trial. *JAMA Oncology*. Published online June 3, 2018. doi:10.1001/jamaoncol.2018.2262

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

eMethods

Study Design and Participants

Everolimus was provided by Novartis as 5 mg tablets. Exemestane and capecitabine were supplied locally (or by Novartis if not commercially available) as 25 mg and 1250 mg/m^2 tablets, respectively.

Additional requirements were Eastern Cooperative Oncology Group (ECOG) performance status 0-2, adequate bone marrow, coagulation, liver and renal function, fasting serum cholesterol ≤300 mg/dL, and fasting triglycerides ≤2.5 × the upper limit of normal. Additional exclusion criteria included: prior treatment with strong inhibitors or inducers of isoenzyme cytochrome P450-3A for ≥7 days within 2 weeks of randomization, or treatment with sorivudine or any of its chemically related analogues within 4 weeks of randomization; another malignancy within 5 years of randomization (except adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell carcinoma, nonmelanomatous skin cancer, or a history of stage IA melanoma that has been cured), or current or historical central nervous system metastases; radiotherapy within 4 weeks of randomization, unless it was localized palliative radiotherapy, or radiotherapy for lytic lesions at risk of fracture completed ≥2 weeks before randomization; and hormone replacement therapy that was not discontinued before randomization, a known history of human immunodeficiency virus seropositivity, a severe and/or uncontrolled medical condition, bilateral diffuse lymphangitis, or active bleeding diathesis.

Procedures

Dose adjustments were permitted if a patient could not tolerate the scheduled dose. Up to two levels of everolimus dose adjustment from the starting dose (10 mg daily) were permitted in the event of severe or intolerable adverse reactions: 5 mg daily; 5 mg every other day. Capecitabine dose reductions were allowed in specific circumstances (see protocol). Interruption of everolimus or capecitabine monotherapy for ≥4 weeks resulted in permanent discontinuation of the study drug. Interruption of everolimus or exemestane for ≥4 weeks in patients randomized to receive everolimus plus exemestane resulted in permanent discontinuation of the drug, although monotherapy with the combination partner could continue until disease progression, unacceptable toxicity, or withdrawal of consent.

Interactive Response Technology (IRT) was used to randomize eligible patients in a 1:1:1 ratio to one of the three treatment arms, with randomization stratified by the presence or absence of visceral disease. A subject randomization list, produced by Novartis, was provided by the IRT provider using a validated system that automated the random assignment of subject numbers to randomization numbers. These randomization numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate

medication list was produced by, or under the responsibility of, Novartis Drug Supply Management, using a validated system that automated the random assignment of medication numbers to packs containing the study treatment. Randomization was performed with a block size of 6 to ensure 1:1:1 randomization within the strata. Each subject in the study was uniquely identified by a 9-digit subject number, which was a combination of her 4-digit center number and 5-digit subject number. The center number was assigned by Novartis to the investigative site. Upon signing the informed consent form, the subject was assigned a subject number by the investigator. At each site, the first subject was assigned subject number 1, and subsequent subjects were assigned consecutive numbers. The investigator or his/her staff contacted the IRT and provided the requested identifying information for the subject to register them into the IRT. A pre-randomization form was completed by each site and sent to Novartis for approval prior to randomizing subjects via IRT. Once assigned, the subject numbers for subjects were not reused. If the subject failed to be randomized for any reason, the IRT was required to be notified within 2 days that the subject was not randomized. The reason for not being randomized was entered on the Screening Log, and the Demography Case Report Form was also completed.

Sample Size Calculation

The primary objective was to estimate the HR of PFS for everolimus plus exemestane versus everolimus alone with approximately 150 PFS events. For this number of PFS events, the precision of HR estimation is illustrated by tabulating the approximate 90% CIs (Jennison and Turnbull 1999) for different values of hazard ratio from 0.55 to 0.75 by considering a relative precision of ±24% (see below).

Estimated HR	**Assuming 150 observed PFS events**	
	Lower bound of 90% CI for HR	**Upper bound of 90% CI for HR**
0.55	0.420	0.719
0.60	0.459	0.785
0.65	0.497	0.850
0.70	0.535	0.916
0.75	0.573	0.981

A total of 300 patients were planned for recruitment at a uniform rate over an 18-month enrollment period, and randomized with equal allocation to one of the three treatment arms. Assuming median PFS times of 7 months

in the everolimus plus exemestane arm (Baselga et al 2012), 4 months in the everolimus alone arm (Ellard et al 2009), and 6 months in the capecitabine arm (O'Shaughnessy et al 2012, Stocker et al 2007, Harbeck et al 2017, Kaufmann et al 2010, Robert et al 2011), the expected time to observe 150 PFS events in each of the two pairwise treatment comparisons was approximately 28 months after randomization of the first study patient (assuming approximately 10% of the study population would be lost to follow-up or would withdraw consent).

Interim Analysis

A planned interim analysis was performed after 75 PFS events had been observed per local assessment across the everolimus alone and everolimus plus exemestane arms, with the intent of allowing early termination of the everolimus alone arm in the event of far inferior efficacy versus the everolimus plus exemestane arm. A general guidance was to stop the everolimus alone arm if the observed HR was <0.20 (i.e., the everolimus alone arm was far inferior versus the everolimus plus exemestane arm). The proposed decision guidance yielded high probability to stop the control arm if the combination arm was highly superior (HR ≤0.1), while keeping the probability low if the superiority was not so extreme (HR ≥0.3). This interim analysis, included in amendment 2 of the protocol (Section 9.8.1), was endorsed by the DMC and SSC. Based on results of the interim analysis, the DMC recommendation was to continue the study as planned.

eTables

eTable 1. BOLERO-6 Recruitment Sites

Center country	Investigator name	Randomized
Russia	Prof. Lyudmila Manzyuk	17
United States	Dr Denise Yardley	12
United States	Dr Sibel Blau	12
Belgium	Prof. Guy Jerusalem	11
Turkey	Prof. Dr Mustafa Ozguroglu	11
Denmark	Dr Marianne Ewertz	9
Brazil	Dr Rodrigo Villarroel	8
Hungary	Dr Eva Padi	8
Malaysia	Dr Adlinda Alip	8
Brazil	Dr Roberto Hegg	7
Denmark	Dr Erik Jakobsen	7
Spain	Dr Antonio Gonzalez Martin	7
Lebanon	Dr Fadi Farhat	7
Russia	Dr Ekaterina Solovieva	7
Australia	Dr Yoland Antill	6
Denmark	Dr Peter Michael Vestlev	6
Argentina	Dr Guillermo Lerzo	5
Australia	Dr Richard de Boer	5
Spain	Dr Javier Cortes Castan	5
Spain	Dr Jose Angel Garcia Saenz	5
Lebanon	Dr Marwan Ghosn	5
Peru	Dr Hugo Fuentes	5
United States	Dr Timothy Panella	5
Argentina	Dr Luis Fein	4
Australia	Dr Gavin Marx	4
India	Dr Sudeep Gupta	4

Ireland	Dr Maccon Keane	4
Sweden	Dr Henrik Lindman	4
United States	Dr Sara Hurvitz	4
United States	Dr Patrick Dillon	4
United States	Dr Robert Weaver	4
Argentina	Dr Nora Mohr	3
Brazil	Dr Carlos Henrique Barrios	3
Brazil	Dr Andrea Juliana Gomes	3
Brazil	Dr Jorge Henrique Leal	3
Denmark	Dr Sven Langkjer	3
United Kingdom	Dr Grainne Dunn	3
India	Dr Tapti Sen	3
Ireland	Dr Linda Coate	3
Lebanon	Dr Nagi El-Saghir	3
Malaysia	Dr Flora Li Tze Chong	3
Sweden	Dr Ulrik Narbe	3
Turkey	Dr Binnaz Demirkan	3
United States	Dr Lowell Hart	3
Argentina	Dr Ruben Kowalyszyn	2
Argentina	Dra. Adriana Borello	2
Spain	Dr Manuel Borrego	2
United Kingdom	Dr Stephen Chan	2
Hungary	Dr Laszlo Landherr	2
India	Dr Senthil Rajappa	2
Ireland	Dr Janice Walshe	2
Lebanon	Dr Ghazi Nsouli	2
Peru	Dr Hernan Morón	2
Russia	Dr Svetlana Protsenko	2
Sweden	Dr Thomas Hatschek	2

Sweden	Dr Helena Granstam Bjorneklett	2
Sweden	Dr Maria Ekholm	2
Thailand	Dr Srila Samphao	2
Turkey	Prof. Dr Semra Paydas	2
United States	Dr Stanley Waintraub	2
United States	Dr Rajesh Belani	2
United States	Dr Samhita Chakraborty	2
United States	Dr Kevin Weibel	2
United States	Dr Robyn Young	2
United States	Dr Brooke Daniel	2
Australia	Prof. Michael Friedlander	1
Denmark	Dr Bent Ejlertsen	1
Denmark	Dr Sami Al-Rawi	1
United Kingdom	Dr Alison Humphreys	1
Hungary	Dr Zsolt Horvath	1
India	Dr Minish Jain	1
Lebanon	Dr Fady Nasr	1
Peru	Dr Alfredo Aguilar	1
Peru	Dra. Milagros Cavero	1
Sweden	Dr Antonis Valachis	1
Thailand	Dr Piti Pornpraserthsuk	1
Thailand	Dr Damnern Vachirodom	1
United States	Dr Corrine Zarwan	1
United States	Dr Karen Hunt	1
United States	Dr Gerardo Capo	1
United States	Dr Clyde Jones	1
United States	Dr Patrick Ward	1
United States	Dr Revati Rao	1

eTable 2. Baseline Patient Demographics and Disease Characteristics

Characteristic	Everolimus + Exemestane (n = 104)	Everolimus (n = 103)	Capecitabine (n = 102)
Age, years			
Median (range)	61 (32-86)	61 (38-88)	60 (35-84)
<65	65 (63)	64 (62)	69 (68)
≥65	39 (38)	39 (38)	33 (32)
Race, n (%)			
Caucasian	78 (75)	85 (83)	91 (89)
Asian	11 (11)	8 (8)	8 (8)
Native American	3 (3)	2 (2)	0
Black	1 (1)	2 (2)	0
Other	11 (11)	6 (6)	3 (3)
ECOG performance status, n (%)			
0	54 (52)	48 (47)	57 (56)
1	42 (40)	50 (49)	39 (38)
2	5 (5)	3 (3)	4 (4)
Missing	3 (3)	2 (2)	2 (2)
Metastatic site of cancer, n (%)			
CNS	0	1 (1)	1 (1)
Visceral[a] (excluding CNS)	69 (66)	66 (64)	63 (62)
Lung	32 (31)	30 (29)	30 (29)
Liver	44 (42)	43 (42)	42 (41)
Liver and lung	11 (11)	12 (12)	12 (12)
Other visceral	12 (12)	14 (14)	12 (12)
Bone	88 (85)	79 (77)	85 (83)
Bone-only	13 (13)	16 (16)	24 (24)
Other	67 (64)	61 (59)	60 (59)
Time since most recent recurrence			

or metastasis, months	96 (92)	97 (94)	97 (95)
<3	7 (7)	3 (3)	5 (5)
3-<6	1 (1)	3 (3)	0
≥6			
Number of metastatic sites, n (%)			
1-2	52 (50)	56 (54)	57 (56)
≥3	52 (50)	47 (46)	45 (44)
Type of lesion			
Target-only	3 (3)	10 (10)	7 (7)
Nontarget only	12 (12)	5 (5)	9 (9)
Bone-only	18 (17)	17 (17)	27 (26)
Target and nontarget	71 (68)	71 (69)	59 (58)
Any prior antineoplastic therapy[b]	104 (100)	103 (100)	102 (100)
Any prior radiotherapy	79 (76)	76 (74)	78 (76)
Any prior surgery	95 (91)	96 (93)	91 (89)
Prior NSAI	103 (99)	103 (100)	102 (100)
Prior chemotherapy			
Adjuvant/neoadjuvant only	47 (45)	43 (42)	55 (54)
Metastatic only	16 (15)	20 (19)	16 (16)
Both	8 (8)	15 (15)	5 (5)
Other prior therapy			
Fulvestrant	13 (13)	13 (13)	9 (9)
Targeted therapy	3 (3)	7 (7)	9 (9)
Other	4 (4)	5 (5)	3 (3)

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NSAI, nonsteroidal aromatase inhibitor.

[a] Lung, liver, heart, ovary, spleen, kidney, adrenal gland, malignant pleural, pericardial effusion, or malignant ascites, as collected on the Case Report Form.

[b] Any prior antineoplastic therapy was recorded in all settings.

eTable 3. First-Line Antineoplastic Therapies Initiated Following Treatment Discontinuation

No. (%)	Everolimus + Exemestane (n = 104)	Everolimus (n = 103)	Capecitabine (n = 102)
Overall	**81 (78)**	**83 (81)**	**81 (79)**
Capecitabine	20 (19)	20 (19)	8 (8)
Exemestane	5 (5)	10 (10)	10 (10)
Fulvestrant	5 (5)	14 (14)	10 (10)
Paclitaxel	5 (5)	2 (2)	2 (2)
Tamoxifen	5 (5)	2 (2)	3 (3)
Anastrozole	4 (4)	1 (1)	0
Bevacizumab + paclitaxel	3 (3)	1 (1)	0
Paclitaxel albumin	3 (3)	2 (2)	2 (2)
Doxorubicin	2 (2)	0	0
Fulvestrant + investigational drug	2 (2)	1 (1)	2 (2)
Bevacizumab + capecitabine	1 (1)	0	0
Bevacizumab + capecitabine + cyclophosphamide + exemestane	1 (1)	0	0
Capecitabine + docetaxel	1 (1)	0	0

Capecitabine + eribulin mesilate + tamoxifen	1 (1)	0	0
Capecitabine + gemcitabine hydrochloride non-drug	1 (1)	0	0
Capecitabine + zoledronic acid	1 (1)	0	0
Carboplatin	1 (1)	0	0
Cisplatin + gemcitabine	1 (1)	0	0
Cyclophosphamide + docetaxel	1 (1)	0	1 (1)
Cyclophosphamide + doxorubicin	1 (1)	0	0
Cyclophosphamide + doxorubicin + fluorouracil	1 (1)	0	0
Cyclophosphamide + epirubicin	1 (1)	2 (2)	0
Cyclophosphamide + fluorouracil	1 (1)	0	0
Cyclophosphamide + fluorouracil + methotrexate	1 (1)	0	0
Denosumab + fulvestrant	1 (1)	0	1 (1)
Docetaxel	1 (1)	1 (1)	2 (2)
Docetaxel + vinorelbine tartrate	1 (1)	1 (1)	0
Eribulin	1 (1)	1 (1)	1 (1)
Exemestane + fulvestrant	1 (1)	1 (1)	0
Exemestane + non-drug: radiotherapy	1 (1)	0	0
Fulvestrant + taselisib	1 (1)	0	0
Investigational drug + non-drug: radiotherapy	1 (1)	0	0

Letrozole + palbociclib	1 (1)	0	0
Non-drug: procedure surgical neoplasm	1 (1)	0	0
Tamoxifen citrate	1 (1)	0	0
Trastuzumab + vinorelbine tartrate	1 (1)	0	0
Vinorelbine tartrate	1 (1)	0	2 (2)
Anastrozole + bondronat	0	1 (1)	0
Anastrozole + everolimus	0	1 (1)	0
Anastrozole + zoledronic acid	0	0	1 (1)
Bevacizumab + paclitaxel albumin	0	0	1 (1)
Capecitabine + exemestane	0	1 (1)	0
Capecitabine + fulvestrant	0	0	1 (1)
Capecitabine + non-drug: radiotherapy	0	0	1 (1)
Capecitabine + ruxolitinib	0	1 (1)	0
Capecitabine + vinorelbine	0	1 (1)	0
Capecitabine + vinorelbine tartrate	0	3 (3)	0
Carboplatin + gemcitabine	0	1 (1)	1 (1)
Carboplatin + paclitaxel	0	0	2 (2)
Cyclophosphamide + epirubicin + fluorouracil	0	0	1 (1)
Cyclophosphamide + epirubicin + fluorouracil + zoledronic acid	0	1 (1)	0

Cyclophosphamide + methotrexate sodium	0	0	1 (1)
Denosumab + everolimus + exemestane	0	0	1 (1)
Docetaxel + paclitaxel	0	0	1 (1)
Docetaxel + zoledronic acid	0	1 (1)	0
Enzalutamide + exemestane	0	1 (1)	0
Epirubicin	0	0	1 (1)
Epirubicin + paclitaxel	0	0	1 (1)
Eribulin mesilate	0	1 (1)	0
Everolimus	0	1 (1)	0
Everolimus + exemestane	0	7 (7)	12 (12)
Everolimus + exemestane + non-drug: radiotherapy	0	0	1 (1)
Everolimus + fulvestrant	0	0	1 (1)
Exemestane + investigational drug	0	1 (1)	0
Fulvestrant + non-drug: radiotherapy	0	0	1 (1)
Fulvestrant + palbociclib	0	1 (1)	1 (1)
Fulvestrant + zoledronic acid	0	1 (1)	0
Gemcitabine	0	0	1 (1)
Gemcitabine hydrochloride	0	0	1 (1)
Letrozole	0	0	1 (1)

Non-drug: radiotherapy	0	0	2 (2)
Protein kinase inhibitors	0	0	1 (1)
Taselisib	0	0	1 (1)
Vinorelbine	0	0	1 (1)

eTable 4. Efficacy Analysis, Per Local Investigator Review (Full Analysis Set)

Parameter	Everolimus + Exemestane (n = 104)	Everolimus (n = 103)	Capecitabine (n = 102)
PFS event, No. (%)	80 (77)	74 (72)	68 (67)
Patients censored, No. (%)	24 (23)	29 (28)	34 (33)
HR[a] (90% CI) [95% CI]	–	0.74 (0.57-0.97) [0.54-1.02]	1.26 (0.96-1.66) [0.91-1.75]
Percentiles (90% CI) [95% CI], months			
25th percentile	3.9 (2.8-5.3) [2.8-5.3]	4.1 (2.8-4.3) [2.7-4.3]	4.2 (2.8-5.6) [2.8-5.7]
Median	8.4 (6.6-9.7) [5.7-9.7]	6.8 (5.5-7.2) [5.4-8.3]	9.6 (8.3-15.1) [7.1-16.6]
75th percentile	13.8 (11.1-17.0) [11.1-17.0]	11.0 (9.6-13.7) [9.5-13.8]	20.9 (17.9-24.3) [17.9-29.1]
Kaplan-Meier estimated PFS, % (90% CI) [95% CI]			
6 months	60 (51-67) [49-69]	52 (43-60) [41-62]	64 (54-72) [52-73]
12 months	32 (24-41) [23-42]	23 (15-31) [14-33]	47 (37-56) [36-58]
18 months	14 (8-21) [7-22]	11 (6-19) [5-20]	32 (23-41) [21-43]
24 months	12 (7-19) [6-21]	7 (3-13) [2-14]	18 (11-27) [10-28]
Best overall response, No. (%)			
Complete response	0	0	2 (2)
Partial response	21 (20)	12 (12)	21 (21)
Stable disease	38 (37)	52 (50)	29 (28)

Progressive disease	12 (12)	11 (11)	7 (7)
Non-complete response/non-progressive disease[b]	27 (26)	20 (19)	31 (30)
Unknown	6 (6)	8 (8)	12 (12)
ORR,[c]			
FAS, No. (%) [90% CI]	21 (20) [13.9-27.8]	12 (12) [6.9-18.2]	23 (23) [15.9-30.4]
Patients with target lesions at baseline, No./N (%) [90% CI]	21/74 (28) [19.9-38.2]	12/81 (15) [8.8-22.9]	23/66 (35) [25.1-45.6]
CBR,[d]			
FAS, No. (%) [90% CI]	59 (57) [48.2-65.0]	43 (42) [33.5-50.3]	53 (52) [43.4-60.5]
Patients with target lesions at baseline, No./N (%) [90% CI]	38/74 (51) [41.2-61.4]	32/81 (40) [30.4-49.2]	36/66 (55) [43.7-65.1]

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival.

[a] HR when comparing the everolimus alone or capecitabine arm with the everolimus plus exemestane arm. Obtained from the stratified Cox model.

[b] Non-complete response/non-progressive disease is for response assessment of patients with only nontarget lesions.

[c] Overall response rate = complete response + partial response.

[d] Clinical benefit rate = complete response + partial response + stable disease lasting ≥24 weeks.

eTable 5. Analysis of OS, Per Local Investigator Review (Full Analysis Set)

Parameter	Everolimus + Exemestane (n = 104)	Everolimus (n = 103)	Capecitabine (n = 102)
OS event, No. (%)	71 (68)	59 (57)	58 (57)
Patients censored, No. (%)	33 (32)	44 (43)	44 (43)
HR[a] (90% CI) [95% CI]	–	1.27 (0.95-1.70) [0.90-1.80]	1.33 (0.99-1.79) [0.94-1.89]
Percentiles (90% CI) [95% CI], months			
25th percentile	10.7 (8.4-14.3) [7.8-14.5]	12.0 (9.2-18.9) [8.6-19.4]	14.6 (11.3-20.8) [11.1-20.9]
Median	23.1 (19.5-28.0) [18.9-29.5]	29.3 (24.3-31.8) [23.1-35.8]	25.6 (23.8-33.4) [23.6-35.0]
75th percentile	NE (33.0-NE) [31.8-NE]	42.4 (41.6-NE) [41.6-NE]	NE (NE-NE) [40.2-NE]
Kaplan-Meier estimated OS, % (90% CI) [95% CI]			
12 months	73 (65-79) [63-80]	74 (66-81) [65-82]	82 (75-88) [73-89]
18 months	64 (55-71) [53-72]	68 (60-75) [58-76]	68 (60-76) [58-77]
24 months	48 (40-56) [38-58]	59 (50-66) [48-68]	59 (50-66) [48-68]

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

[a] HR when comparing the everolimus alone or capecitabine arm with the everolimus plus exemestane arm. Obtained from the stratified Cox model.

eTable 6. Dose Interruptions and Reductions

No. (%)	Everolimus + Exemestane (n = 104)		Everolimus (n = 103)	Capecitabine (n = 102)
	Everolimus	Exemestane		
Patients requiring dose interruption	70 (67)	29 (28)	56 (54)	71 (70)
1 dose interruption	32 (31)	22 (21)	26 (25)	25 (25)
≥2 dose interruptions	38 (37)	7 (7)	30 (29)	46 (45)
Reason for dose interruption				
As per protocol	0	0	1 (1)	1 (1)
Adverse event	66 (63)	20 (19)	55 (53)	64 (63)
Dosing error	13 (13)	8 (8)	8 (8)	14 (14)
Scheduling conflict	4 (4)	1 (1)	0	23 (23)
Dispensing error	0	3 (3)	0	2 (2)
Concomitant medication affecting drug exposure	1 (1)	1 (1)	0	1 (1)
Patients requiring dose reduction	47 (45)	0	41 (40)	68 (67)
1 dose reduction	37 (36)	0	35 (34)	30 (29)
≥2 dose reductions	10 (10)	0	6 (6)	38 (37)

Reason for dose reduction				
As per protocol	31 (30)	0	30 (29)	3 (3)
Adverse event	15 (14)	0	12 (12)	57 (56)
Dosing error	2 (2)	0	1 (1)	16 (16)
Scheduling conflict	1 (1)	0	0	5 (5)
Dispensing error	1 (1)	0	0	1 (1)
First dose lower than planned protocol dose	0	0	0	11 (11)
Missing	0	0	0	3 (3)

A patient with multiple occurrences of a reason for dose interruption or reduction was counted only once in that category. A patient with multiple reasons for dose interruption or reduction was counted only once in the total row.

eTable 7. Serious Adverse Events (≥1.5% Incidence in Any Arm), Regardless of Causality

No. (%)	Everolimus + Exemestane (n = 104)	Everolimus (n = 103)	Capecitabine (n = 102)
Any preferred term	**37 (36)**	**30 (29)**	**30 (29)**
Pneumonia	8 (8)	4 (4)	2 (2)
General physical health deterioration	4 (4)	0	0
Acute kidney injury	3 (3)	4 (4)	2 (2)
Urinary tract infection	3 (3)	1 (1)	1 (1)
Acute respiratory failure	2 (2)	0	0
Dyspnea	2 (2)	2 (2)	1 (1)
Hepatic failure	2 (2)	1 (1)	0
Nausea	2 (2)	0	0
Pneumonitis	2 (2)	3 (3)	0
Pulmonary embolism	2 (2)	1 (1)	2 (2)
Syncope	2 (2)	1 (1)	0
Vomiting	2 (2)	1 (1)	3 (3)
Abdominal pain	1 (1)	0	2 (2)
Anemia	1 (1)	3 (3)	1 (1)
Cancer pain	1 (1)	2 (2)	0
Dehydration	1 (1)	1 (1)	3 (3)
Diarrhea	1 (1)	2 (2)	3 (3)
Fatigue	1 (1)	0	2 (2)
Pleural effusion	1 (1)	1 (1)	2 (2)
Respiratory failure	1 (1)	3 (3)	1 (1)
Deep vein thrombosis	0	0	4 (4)
Hypokalemia	0	1 (1)	2 (2)
Hypotension	0	0	3 (3)

Stomatitis	0	2 (2)	1 (1)

eTable 8. Adverse Events Leading to Treatment Discontinuation (≥1.5% Incidence in Any Arm), Regardless of Causality

No. (%)	Everolimus + Exemestane (n = 104)	Everolimus (n = 103)	Capecitabine (n = 102)
Any preferred term	**18 (17)**	**20 (19)**	**21 (21)**
Pneumonitis	3 (3)	5 (5)	0
Stomatitis	2 (2)	3 (3)	3 (3)
Acute kidney injury	1 (1)	3 (3)	1 (1)
Blood creatinine increased	1 (1)	2 (2)	0
Vomiting	1 (1)	1 (1)	3 (3)
Diarrhea	0	1 (1)	4 (4)
Hyperglycemia	0	2 (2)	0
Nausea	0	2 (2)	1 (1)
Palmar-plantar erythrodysesthesia syndrome	0	0	5 (5)

eTable 9. Summary of Deaths

No. (%)	Everolimus + Exemestane (n = 104)	Everolimus (n = 103)	Capecitabine (n = 102)
All deaths (including on-treatment deaths)	71 (68)	59 (57)	58 (57)
Disease progression	67 (64)	53 (51)	53 (52)
Cardiac arrest	1 (1)	0	0
Cardiac failure acute	1 (1)	0	0
Cardio-respiratory arrest	0	1 (1)	0
Death	1 (1)[a]	1 (1)[b]	0
Lung infection	0	0	1 (1)
Septic shock	0	1 (1)	1 (1)
Metastases to liver	0	1 (1)	0
Cerebrovascular accident	0	0	1 (1)
Acute kidney injury	0	1 (1)	0
Pneumonia aspiration	1 (1)	0	0
Lung disorder	0	0	1 (1)
Respiratory failure	0	1 (1)	1 (1)
On-treatment deaths	9 (9)	5 (5)	2 (2)
Disease progression	6 (6)	2 (2)	0
Cardiac arrest	1 (1)	0	0
Cardiac failure acute	1 (1)	0	0
Death	1 (1)[a]	0	0
Acute kidney injury	0	1 (1)	0
Cardio-respiratory arrest	0	1 (1)	0
Cerebrovascular accident	0	0	1 (1.0)
Respiratory failure	0	1 (1)	0
Septic shock	0	0	1 (1.0)

On-treatment deaths are deaths that occurred up to 30 days after treatment discontinuation.

[a] Death occurred after a fall; [b] Cause of death unknown (occurred off-treatment).

eReferences

1. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520-529.

3. Ellard SL, Clemons M, Gelmon KA, et al. Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC clinical trials group IND.163. *J Clin Oncol*. 2009;27(27):4536-4541.

3. Harbeck N, Saupe S, Jäger E, et al. A randomized phase III study evaluating pegylated liposomal doxorubicin versus capecitabine as first-line therapy for metastatic breast cancer: results of the PELICAN study. *Breast Cancer Res Treat*. 2017;161(1):63-72.

4. Jennison C, Turnbull BW, (1999) Group Sequential Methods: Applications to Clinical Trials. (Book)

5. Kaufmann M, Maass N, Costa SD, et al. First-line therapy with moderate dose capecitabine in metastatic breast cancer is safe and active: results of the MONICA trial. *Eur J Cancer*. 2010;46(18):3184-3191.

6. O'Shaughnessy JA, Kaufmann M, Siedentopf F, et al. Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. *Oncologist*. 2012;17(4):476-484.

7. Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol*. 2011;29(10):1252-1260.

8. Stockler MR, Harvey VJ, Francis PA, et al. Capecitabine versus classical cyclophosphamide, methotrexate, and fluorouracil as first-line chemotherapy for advanced breast cancer. *J Clin Oncol*. 2011;29(34):4498-4504.