Indication

IBRANCE® (palbociclib) 125 mg capsules and tablets are indicated for the treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (mBC) in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men.

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Final prespecified analyses and updated non-prespecified analyses of selected subgroups from PALOMA-2, including visceral disease

Important Safety Information

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Inform patients to promptly report any fever.

Please see additional Important Safety Information throughout.
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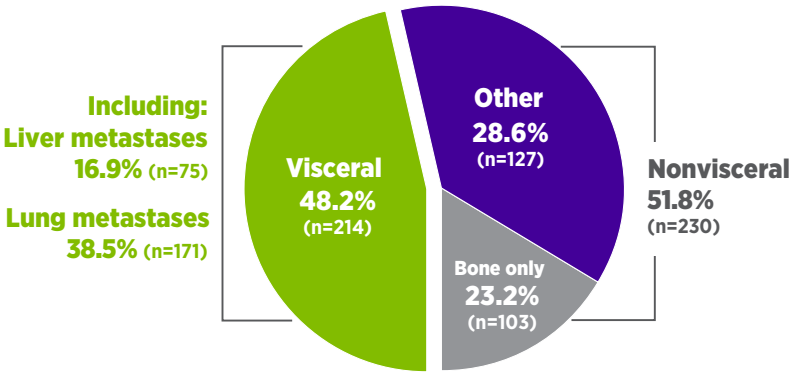
EVALUATED IN FIRST-LINE ER+/HER2- MBC PATIENTS WITH VARIOUS CHARACTERISTICS

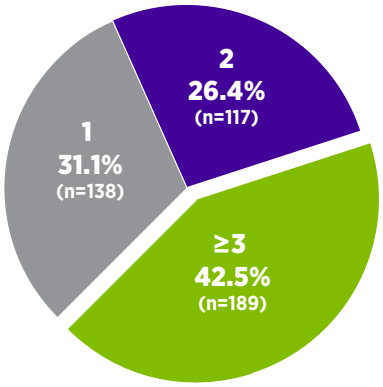
Selected baseline characteristics for the IBRANCE arm[1,2*]

There were no significant differences in baseline characteristics between the 2 treatment arms for the following characteristics: disease site, number of disease sites, disease-free interval, and prior hormonal therapy use in the adjuvant setting (**IBRANCE + letrozole n=444**; placebo + letrozole n=222).

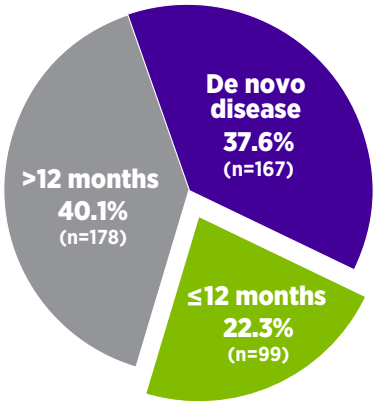
DISEASE SITE



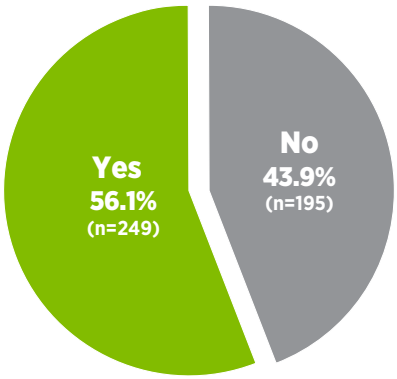
NUMBER OF DISEASE SITES



DISEASE-FREE INTERVAL (DFI)†



PRIOR HORMONAL THERAPY USED IN THE NEOADJUVANT/ ADJUVANT SETTING‡



ER+=estrogen receptor-positive.
*Patients were stratified by site of disease, by disease-free interval since completion of prior neoadjuvant or adjuvant therapy, and by the nature of prior neoadjuvant or adjuvant anticancer treatment received prior to their diagnosis of advanced breast cancer.[1]
†DFI was defined as the time from neoadjuvant or adjuvant therapy to recurrence.[1]
‡Patients who had received anastrozole or letrozole as a component of their adjuvant or neoadjuvant therapy were excluded from the study if they had disease progression while receiving the therapy or within 12 months after completing the therapy.[1]

Important Safety Information (cont.)

Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

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WARNINGS AND PRECAUTIONS FOR IBRANCE

Neutropenia

- **Neutropenia** was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant
- Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3
- One death due to neutropenic sepsis was observed in PALOMA-3
- Inform patients to promptly report any fever
- Monitor complete blood count (CBC) prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of the first 2 cycles, and as clinically indicated
- Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia

Interstitial lung disease (ILD)/Pneumonitis

- Severe, life-threatening, or fatal **interstitial lung disease (ILD) and/or pneumonitis** can occur in patients treated with CDK4/6 inhibitors, including IBRANCE when taken in combination with endocrine therapy
- Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3):
  - 1.0% of IBRANCE-treated patients had ILD/pneumonitis of any grade
  - 0.1% had Grade 3 or 4
  - No fatal cases were reported
- Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported
- Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea)
- In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient
- Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis

Embryo-fetal toxicity

- Based on the mechanism of action, IBRANCE can cause **fetal harm**
- Advise females of reproductive potential to use effective contraception during IBRANCE treatment and for at least 3 weeks after the last dose
- IBRANCE may **impair fertility in males** and has the potential to cause genotoxicity. Advise male patients to consider sperm preservation before taking IBRANCE. Advise male patients with female partners of reproductive potential to use effective contraception during IBRANCE treatment and for 3 months after the last dose
- Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise women **not to breastfeed** during IBRANCE treatment and for 3 weeks after the last dose because of the potential for serious adverse reactions in nursing infants

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MORE THAN 2 YEARS OF mPFS IN FIRST-LINE MBC

In a 2:1 randomized, double-blind, Phase 3 trial of postmenopausal women with ER+/HER2- mBC (N=666)[1*]

IBRANCE + letrozole demonstrated a compelling 10-month mPFS improvement vs placebo + letrozole[†]

Primary endpoint: Investigator-assessed progression-free survival (PFS)

24.8 months mPFS — **IBRANCE + letrozole** (n=444) (95% CI: 22.1-NE)

14.5 months mPFS — **placebo + letrozole** (n=222) (95% CI: 12.9-17.1)

- **HR=0.58** (95% CI: 0.46-0.72); *P*<0.0001
- Number of PFS events: 194 (43.7%) with IBRANCE + letrozole vs 137 (61.7%) with placebo + letrozole

CI=confidence interval; HR=hazard ratio; mPFS=median progression-free survival; NE=not estimable.
*PALOMA-2 studied IBRANCE 125 mg PO once daily taken 3 weeks on, 1 week off + letrozole 2.5 mg PO once daily vs placebo + letrozole in postmenopausal women with ER+/HER2- mBC with no prior treatment in the metastatic setting.[1]
[†]Unless otherwise stated, PALOMA-2 data are based on the February 2016 data cut (final prespecified analysis).[1]

Secondary endpoints[1]

- **Overall response rate (ORR)**[‡]: **55.3%** (95% CI: 49.9-60.7) of patients with measurable disease achieved an objective response with IBRANCE + letrozole vs **44.4%** (95% CI: 36.9-52.2) with placebo + letrozole (IBRANCE + letrozole n=338; placebo + letrozole n=171)
- **Overall survival**: At the time of final analysis of PFS, overall survival data were not mature. Patients will continue to be followed for the final analysis

[‡]ORR was defined as the number (%) of patients with confirmed complete response or partial response.[1]

IBRANCE + letrozole as initial mBC therapy delays the need for later lines of treatment, including hormonal agents and chemotherapies

Important Safety Information (cont.)

Severe, life-threatening, or fatal **interstitial lung disease (ILD) and/or pneumonitis** can occur in patients treated with CDK4/6 inhibitors, including IBRANCE when taken in combination with endocrine therapy. Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4, and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis.

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ADVERSE REACTIONS (≥10%) REPORTED IN PALOMA-2

	IBRANCE + letrozole (n=444)			placebo + letrozole (n=222)		
ADVERSE REACTION	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
INFECTIONS AND INFESTATIONS						
Infections*	60[†]	6	1	42	3	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
METABOLISM AND NUTRITION DISORDERS						
Decreased appetite	15	1	0	9	0	0
NERVOUS SYSTEM DISORDERS						
Dysgeusia	10	0	0	5	0	0
GASTROINTESTINAL DISORDERS						
Stomatitis[‡]	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Alopecia	33[§]	N/A	N/A	16[‖]	N/A	N/A
Rash[¶]	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

N/A=not applicable.
Grading according to *Common Terminology Criteria for Adverse Events* (CTCAE) 4.0.
*Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.
[†]Most common infections (≥1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.
[‡]Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.
[§]Grade 1 events – 30%; Grade 2 events – 3%.
[‖]Grade 1 events – 15%; Grade 2 events – 1%.
[¶]Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

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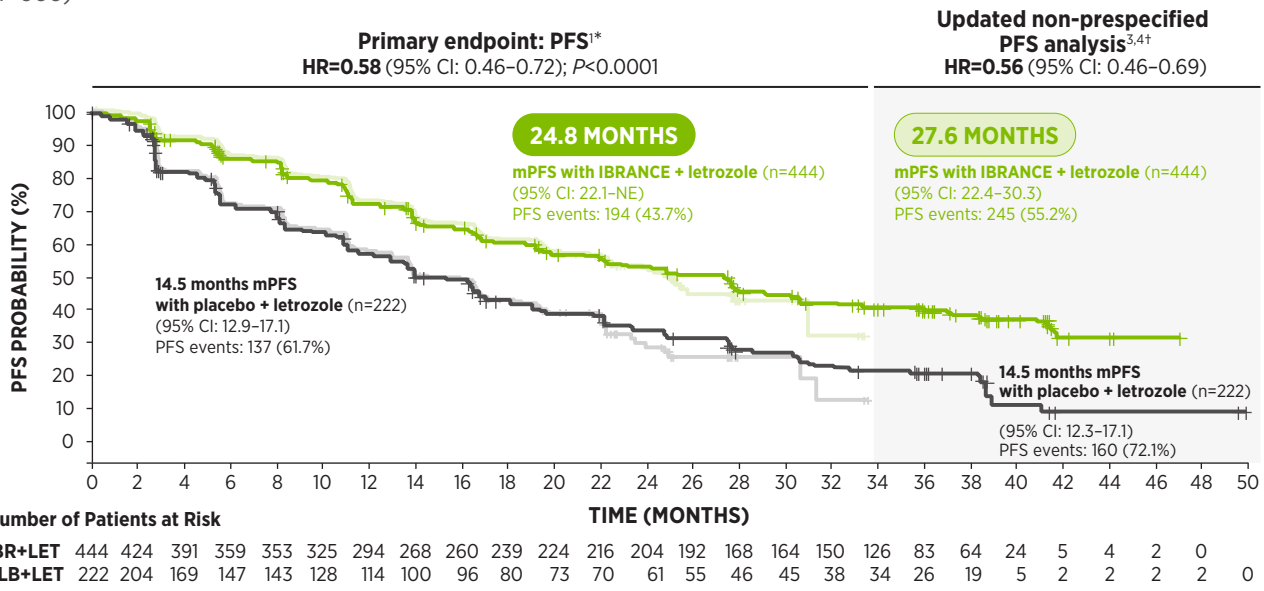
UPDATED NON-PRESPECIFIED PFS ANALYSES OF PALOMA-2

In a 2:1 randomized, double-blind, Phase 3 trial of postmenopausal women receiving first-line treatment for ER+/HER2- mBC (N=666)[1]



IBR=IBRANCE; LET=letrozole; PLB=placebo.

Treatment effect of IBRANCE + letrozole in an updated non-prespecified PFS analysis with an independent review of radiographs[4†]

In a blinded, independent central review of PFS in the intent-to-treat population

35.7 months mPFS (n=444)

vs **19.5 months mPFS** with placebo + letrozole (n=222); (95% CI: 27.7-38.9 vs 16.6-26.6); **HR=0.61** (95% CI: 0.49-0.77)

Review non-prespecified PFS analyses for selected subgroups on the following pages

Selected adverse events (AEs) reported in an updated non-prespecified analysis of PALOMA-2[4]

With an additional 15 months of follow-up, no new safety signals were observed for patients treated with IBRANCE + letrozole.†

The **most common selected adverse events (≥10%, all causality)**‡ of any grade reported in **an updated non-prespecified analysis of PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (82% vs 6%), infections (63% vs 45%), leukopenia (40% vs 2%), fatigue (40% vs 28%), nausea (37% vs 27%), alopecia (34% vs 16%), stomatitis (32% vs 15%), diarrhea (28% vs 21%), anemia (26% vs 10%), rash (20% vs 13%), thrombocytopenia (20% vs 1%), asthenia (18% vs 12%), decreased appetite (17% vs 9%), vomiting (17% vs 17%), dry skin (13% vs 7%), pyrexia (13% vs 9%), alanine aminotransferase increased (13% vs 6%), aspartate aminotransferase increased (12% vs 6%), and dysgeusia (10% vs 5%).

*Based on February 2016 data cut (final prespecified analysis).[1]
†Based on May 2017 data cut (non-prespecified analysis), with a median follow-up of 38 months.[4]
‡Incidences of AEs reported in this updated non-prespecified analysis are all causality and the AEs were selected based on their designation as Adverse Reactions (ARs, treatment-related) in PALOMA-2 in the IBRANCE Prescribing Information.[4]

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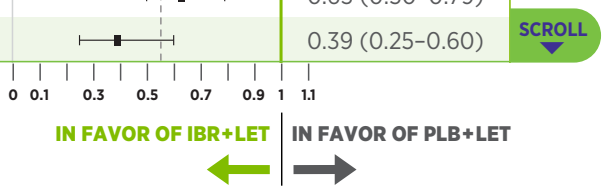
UPDATED NON-PRESPECIFIED PFS ANALYSES OF PALOMA-2

The graph below depicts subgroup analyses from the overall trial population in **an updated non-prespecified PFS analysis of PALOMA-2**. These analyses are considered exploratory. No adjustments were made for multiple comparisons in the subgroup analyses. Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups.[4]*

Baseline Factors	IBR+LET	PLB+LET	IBR+LET vs PLB+LET
	Patients, n (%)		HR (95% CI)
All randomized patients, IA	444 (100)	222 (100)	0.56 (0.46–0.69)
All randomized patients, BICR	444 (100)	222 (100)	0.61 (0.49–0.77)
Visceral disease	214 (48.2)	110 (49.5)	0.62 (0.47–0.81)
Nonvisceral disease	230 (51.8)	112 (50.5)	0.50 (0.37–0.67)
Bone-only disease	103 (23.2)	48 (21.6)	0.41 (0.26–0.63)
No bone-only disease†	341 (76.8)	174 (78.4)	0.62 (0.50–0.78)
TFI‡ >12 mo	179 (40.3)	93 (41.9)	0.55 (0.40–0.76)
TFI‡ ≤12 mo	98 (22.1)	48 (21.6)	0.48 (0.32–0.72)
TFI‡ >2 y	154 (34.7)	77 (34.7)	0.52 (0.36–0.75)
TFI‡ >5 y	90 (20.3)	46 (20.7)	0.60 (0.36–1.00)
TFI‡ >10 y	32 (7.2)	23 (10.4)	0.44 (0.19–1.03)
De novo metastatic	167 (37.6)	81 (36.5)	0.61 (0.44–0.85)
TFI from prior ET >12 mo	156 (35.1)	78 (35.1)	0.58 (0.41–0.82)
TFI from prior ET ≤12 mo	94 (21.2)	48 (21.6)	0.49 (0.33–0.73)
Measurable disease	338 (76.1)	171 (77.0)	0.63 (0.50–0.79)
Nonmeasurable disease§	106 (23.9)	51 (23.0)	0.39 (0.25–0.60)



Adapted from Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. 2019;174(3):719-729.
BICR=blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; IA=investigator assessed; TFI=treatment-free interval.
*Based on May 2017 data cut (non-prespecified analysis).[4]
†Per tumor site.[4]
‡Protocol-defined disease-free interval is equivalent to TFI in this analysis and refers to TFI since completion of prior (neo)adjuvant therapy and onset of metastatic disease or disease recurrence.[4]
§A few patients initially enrolled as having measurable disease were later found to have nonmeasurable disease beyond bone-only disease.[4]

Important Safety Information (cont.)

Based on the mechanism of action, IBRANCE can cause **fetal harm**. Advise females of reproductive potential to use effective contraception during IBRANCE treatment and for at least 3 weeks after the last dose. IBRANCE may **impair fertility in males** and has the potential to cause genotoxicity. Advise male patients to consider sperm preservation before taking IBRANCE. Advise male patients with female partners of reproductive potential to use effective contraception during IBRANCE treatment and for 3 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise women **not to breastfeed** during IBRANCE treatment and for 3 weeks after the last dose because of the potential for serious adverse reactions in nursing infants.

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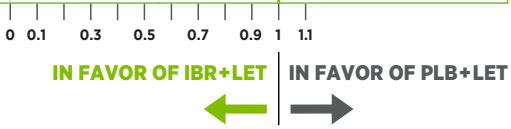
UPDATED NON-PRESPECIFIED PFS ANALYSES OF PALOMA-2 (cont.)

The graph below depicts subgroup analyses from the overall trial population in **an updated non-prespecified PFS analysis of PALOMA-2**. These analyses are considered exploratory. No adjustments were made for multiple comparisons in the subgroup analyses. Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups.[4*]

Baseline Factors	IBR+LET	PLB+LET	IBR+LET vs PLB+LET
	Patients, n (%)		HR (95% CI)
No prior ET with visceral disease	86 (19.4)	47 (21.2)	0.55 (0.36–0.85)
No prior ET without visceral disease	108 (24.3)	49 (22.1)	0.59 (0.38–0.92)
Prior ET in the adjuvant setting	250 (56.3)	126 (56.8)	0.54 (0.42–0.71)
No prior ET	194 (43.7)	96 (43.2)	0.59 (0.43–0.80)
Prior chemotherapy	213 (48.0)	109 (49.1)	0.53 (0.40–0.71)
No prior chemotherapy	231 (52.0)	113 (50.9)	0.59 (0.45–0.79)
Number of disease sites: 1	138 (31.1)	66 (29.7)	0.52 (0.36–0.75)
Number of disease sites: 2	117 (26.4)	52 (23.4)	0.57 (0.37–0.89)
Number of disease sites: ≥3	189 (42.6)	104 (46.8)	0.61 (0.46–0.82)
ECOG PS 0	257 (57.9)	102 (45.9)	0.65 (0.48–0.87)
ECOG PS 1/2	187 (42.1)	120 (54.1)	0.51 (0.39–0.68)
Age <65 y	263 (59.2)	141 (63.5)	0.55 (0.43–0.70)
Age ≥65 y	181 (40.8)	81 (36.5)	0.60 (0.43–0.86)



IN FAVOR OF IBR+LET | IN FAVOR OF PLB+LET

Adapted from Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. 2019;174(3):719-729.
BICR=blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; IA=investigator assessed; TFI=treatment-free interval.
*Based on May 2017 data cut (non-prespecified analysis).[4]
†Per tumor site.[4]
‡Protocol-defined disease-free interval is equivalent to TFI in this analysis and refers to TFI since completion of prior (neo)adjuvant therapy and onset of metastatic disease or disease recurrence.[4]
§A few patients initially enrolled as having measurable disease were later found to have nonmeasurable disease beyond bone-only disease.[4]

Important Safety Information (cont.)

The **most common adverse reactions (≥10%)** of any grade reported in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

The **most frequently reported Grade ≥3 adverse reactions (≥5%)** in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (66% vs 2%), leukopenia (25% vs 0%), infections (7% vs 3%), and anemia (5% vs 2%).

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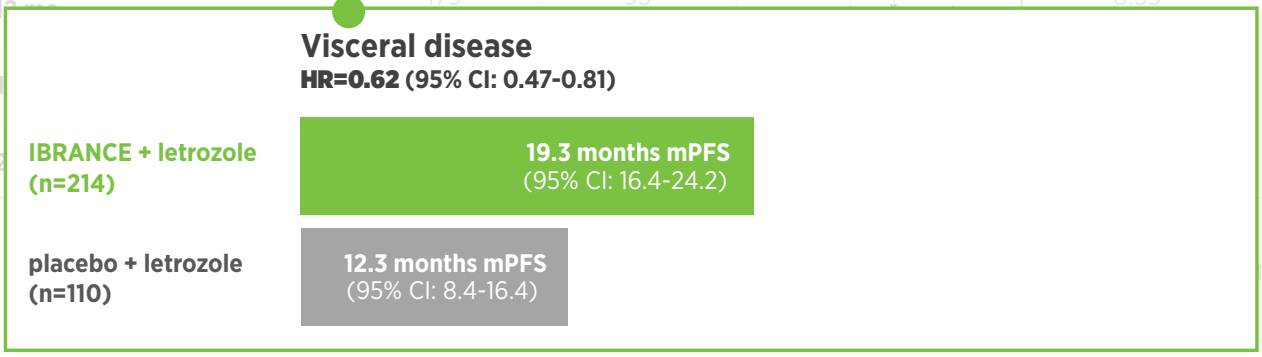
UPDATED NON-PRESPECIFIED PFS ANALYSES FOR IBRANCE + LETROZOLE BY DISEASE SITE

- **Intent-to-treat (ITT) population**: **27.6 months mPFS** with IBRANCE + letrozole (n=444) vs **14.5 months mPFS** with placebo + letrozole (n=222) (95% CI: 22.4-30.3 vs 12.3-17.1); **HR=0.56** (95% CI: 0.46-0.69)[4]

The figures below report the PFS for selected subgroups in **an updated non-prespecified analysis of PALOMA-2**. These analyses are considered exploratory. No adjustments were made for multiple comparisons in the subgroup analyses. Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups.[4]*

Updated non-prespecified PFS analyses: visceral disease[4]

Baseline Factors	IBR+LET Patients, n (%)	PLB+LET Patients, n (%)	IBR+LET vs PLB+LET HR (95% CI)
All randomized patients, BICR	444 (100)	222 (100)	0.61 (0.49–0.77)
Visceral disease	214 (48.2)	110 (49.5)	0.62 (0.47–0.81)
Nonvisceral disease	230 (51.8)	112 (50.5)	0.50 (0.37–0.67)
Bone-only disease	103 (23.2)	48 (21.6)	0.41 (0.26–0.63)
No bone-only disease	341 (76.8)	174 (78.4)	0.62 (0.50–0.78)
TFI >12 mo	179	93	0.55
TFI ≤1			
TFI >2			



*Based on May 2017 data cut (non-prespecified analysis).[4]

Important Safety Information (cont.)

Lab abnormalities of any grade occurring in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were decreased WBC (97% vs 25%), decreased neutrophils (95% vs 20%), anemia (78% vs 42%), decreased platelets (63% vs 14%), increased aspartate aminotransferase (52% vs 34%), and increased alanine aminotransferase (43% vs 30%).

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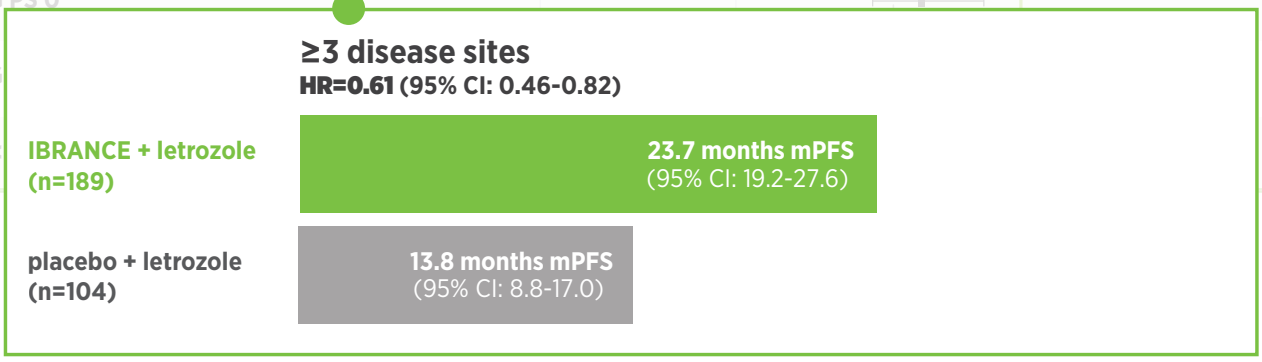
UPDATED NON-PRESPECIFIED PFS ANALYSES FOR IBRANCE + LETROZOLE BY NUMBER OF DISEASE SITES

- **Intent-to-treat (ITT) population**: **27.6 months mPFS** with IBRANCE + letrozole (n=444) vs **14.5 months mPFS** with placebo + letrozole (n=222) (95% CI: 22.4-30.3 vs 12.3-17.1); **HR=0.56** (95% CI: 0.46-0.69)[4]

The figures below report the PFS for selected subgroups in **an updated non-prespecified analysis of PALOMA-2**. These analyses are considered exploratory. No adjustments were made for multiple comparisons in the subgroup analyses. Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups.[4]*

Updated non-prespecified PFS analyses: ≥3 disease sites[4]

Baseline Factors	IBR+LET Patients, n (%)	PLB+LET Patients, n (%)	IBR+LET vs PLB+LET HR (95% CI)
Prior chemotherapy	213 (48.0)	109 (49.1)	0.53 (0.40–0.71)
No prior chemotherapy	231 (52.0)	113 (50.9)	0.59 (0.45–0.79)
Number of disease sites: 1	138 (31.1)	66 (29.7)	0.52 (0.36–0.75)
Number of disease sites: 2	117 (26.4)	52 (23.4)	0.57 (0.37–0.89)
Number of disease sites: ≥3	189 (42.6)	104 (46.8)	0.61 (0.46–0.82)
ECOG PS 0	257	102	0.65
ECOG			
Age <			



*Based on May 2017 data cut (non-prespecified analysis).[4]

Important Safety Information (cont.)

Avoid concurrent use of **strong CYP3A inhibitors**. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of **strong CYP3A inducers**. The dose of **sensitive CYP3A substrates** with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

Please see additional Important Safety Information throughout. Click for the full Prescribing Information for IBRANCE capsules and tablets or visit IBRANCEhcp.com.

IBRANCE® palbociclib

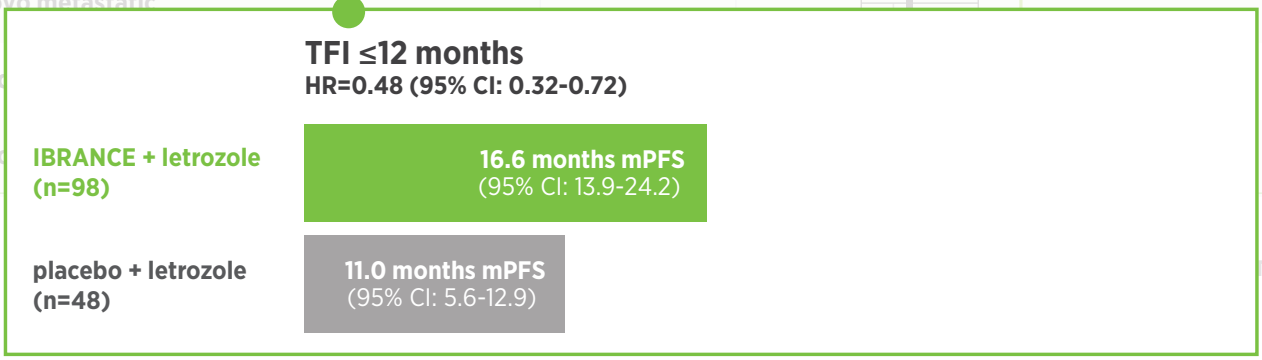
UPDATED NON-PRESPECIFIED PFS ANALYSES FOR IBRANCE + LETROZOLE BY TREATMENT-FREE INTERVAL

- **Intent-to-treat (ITT) population**: **27.6 months mPFS** with IBRANCE + letrozole (n=444) vs **14.5 months mPFS** with placebo + letrozole (n=222) (95% CI: 22.4-30.3 vs 12.3-17.1); **HR=0.56** (95% CI: 0.46-0.69)[4]

The figures below report the PFS for selected subgroups in **an updated non-prespecified analysis of PALOMA-2**. These analyses are considered exploratory. No adjustments were made for multiple comparisons in the subgroup analyses. Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups.[4]*

Updated non-prespecified PFS analyses: treatment-free interval (TFI) ≤12 months[4]

Baseline Factors	IBR+LET Patients, n (%)	PLB+LET Patients, n (%)	IBR+LET vs PLB+LET HR (95% CI)
TFI >12 mo	179 (40.3)	93 (41.9)	0.55 (0.40–0.76)
TFI ≤12 mo	98 (22.1)	48 (21.6)	0.48 (0.32–0.72)
TFI >2 y	154 (34.7)	77 (34.7)	0.52 (0.36–0.75)
TFI >5 y	90 (20.3)	46 (20.7)	0.60 (0.36–1.00)
TFI >10 y	32 (7.2)	23 (10.4)	0.44 (0.19–1.03)
De novo metastatic	167	81	0.61



*Based on May 2017 data cut (non-prespecified analysis).[4]

Important Safety Information (cont.)

For patients with **severe hepatic impairment** (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg. The pharmacokinetics of IBRANCE **have not been studied** in patients **requiring hemodialysis**.

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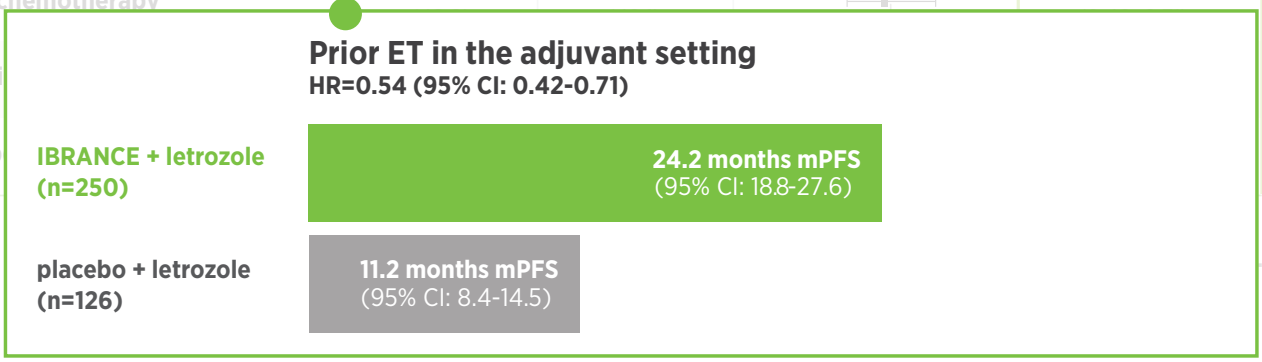
UPDATED NON-PRESPECIFIED PFS ANALYSES FOR IBRANCE + LETROZOLE BY TREATMENT HISTORY

- **Intent-to-treat (ITT) population**: **27.6 months mPFS** with IBRANCE + letrozole (n=444) vs **14.5 months mPFS** with placebo + letrozole (n=222) (95% CI: 22.4-30.3 vs 12.3-17.1); **HR=0.56** (95% CI: 0.46-0.69)[4]

The figures below report the PFS for selected subgroups in **an updated non-prespecified analysis of PALOMA-2**. These analyses are considered exploratory. No adjustments were made for multiple comparisons in the subgroup analyses. Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups.[4]*

Updated non-prespecified PFS analyses: prior endocrine therapy (ET) in the adjuvant setting[4]

Baseline Factors	IBR+LET Patients, n (%)	PLB+LET Patients, n (%)	IBR+LET vs PLB+LET HR (95% CI)
Nonmeasurable disease	106 (23.9)	51 (23.0)	0.39 (0.25–0.60)
No prior ET with visceral disease	86 (19.4)	47 (21.2)	0.55 (0.36–0.85)
No prior ET without visceral disease	108 (24.3)	49 (22.1)	0.59 (0.38–0.92)
Prior ET in the adjuvant setting	250 (56.3)	126 (56.8)	0.54 (0.42–0.71)
No prior ET	194 (43.7)	96 (43.2)	0.59 (0.43–0.80)
Prior chemotherapy	213	109	0.53
No pri			
Numb			



*Based on May 2017 data cut (non-prespecified analysis).[4]

Selected Safety Information

The **most common adverse reactions (≥10%)** of any grade reported in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

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MAKE IBRANCE YOUR PARTNER OF CHOICE

Hypothetical profiles of patients who may be appropriate for IBRANCE + aromatase inhibitor

Jean

- 62 years old; postmenopausal with HR+/HER2- mBC
- Was diagnosed with early breast cancer 6 years ago and received adjuvant anastrozole for 5 years
- Developed metastatic disease 6 months after her adjuvant hormonal therapy ended
- Has not had prior treatment for mBC
- Has metastases in the liver and lung

- 77 years old; postmenopausal with HR+/HER2- mBC
- Was diagnosed with early breast cancer 7 years ago and received adjuvant anastrozole for 5 years
- Developed metastatic disease 18 months after her adjuvant hormonal therapy ended
- Has not had prior treatment for mBC
- Has metastases in the lung

Helen

Visit IBRANCEhcp.com or contact your local IBRANCE representative to learn more

Selected Safety Information

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Inform patients to promptly report any fever.

References: 1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936. **2.** Finn RS, Turner NC, Mori A, et al. Palbociclib plus endocrine therapy in hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): updated summary of the PALOMA clinical programs. Poster presented at: the Florida Society of Clinical Oncology (FLASCO) Spring Meeting; May 10-12, 2018; Tampa, FL. **3.** Data on file. Pfizer Inc., New York, NY. **4.** Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. 2019;174(3):719-729.

Please see Important Safety Information throughout.
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