Real-World Comparative Effectiveness of First-Line IBRANCE® (palbociclib) + Letrozole vs Letrozole Alone for HR+/HER2- mBC

HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer.

INDICATIONS

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 in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men, or
- fulvestrant in patients with disease progression following endocrine therapy

Please see Important Safety Information throughout and the full Prescribing Information for IBRANCE capsules and tablets and at www.IbranceHCP.com

IBRANCE® palbociclib

Real-world evidence can complement clinical trial findings by conducting evaluations in a heterogeneous population and among patients who would not have met clinical trial inclusion criteria[1,2]

Randomized clinical trials

- Designed to show **causality**[3]
- Patients **randomly** assigned to treatment or comparator[3,4]
- Data derived from prespecified, **protocol-defined, uniformly assessed endpoints**[4]
- Highly **monitored, controlled** environment[4]
- Measure the **efficacy** of an intervention (i.e., treatment performance under highly controlled conditions)[4]

Real-world observational studies

- Designed to assess associations and therefore **unable to determine causality**[2-4]
- Patients are **not randomized**; bias related to treatment selection and unobserved variables cannot be fully addressed[2,4]
- Real-world endpoints derived from assessments based on clinical judgment, with **variability in patient assessment and adherence**[4]
- Based on **routine clinical practice**, with broad patient populations that can result in varied outcomes[4]
- Measure the **effectiveness** of an intervention (i.e., treatment performance under real-world conditions)[4]

Observational retrospective analyses are not intended for direct comparison with clinical trials.

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.

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.

Study design: 2:1 randomized, double-blind, Phase 3 trial studying IBRANCE + letrozole vs placebo + letrozole in postmenopausal women receiving first-line treatment for estrogen receptor-positive (ER+)/HER2- mBC (N=666)[5†]

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

- 24.8 months of mPFS with IBRANCE + letrozole (n=444; 95% CI: 22.1–not estimable [NE]) vs **14.5 months** with 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%) in the IBRANCE + letrozole arm and 137 (61.7%) in the placebo + letrozole arm
- IBRANCE + letrozole reduced the risk of disease progression or death by 42% vs placebo + letrozole

Select secondary endpoints

- **Objective 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 (OS):** At the time of final analysis of PFS, OS data were not mature. Patients will continue to be followed for the final analysis

*Unless otherwise stated, PALOMA-2 data are based on the February 2016 data cut (final prespecified analysis).[5]
†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.[5]
‡ORR was defined as the number (%) of patients with confirmed complete response or partial response.[5]

Adverse reactions (ARs) reported in ≥10% of patients in PALOMA-2

	IBRANCE + letrozole (n=444)			Placebo + letrozole (n=222)		
AR (%)	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Neutropenia	80	56	10	6	1	1
Infections[§]	60	6	1	42	3	0
Leukopenia	39	24	1	2	0	0
Fatigue	37	2	0	28	1	0
Nausea	35	<1	0	26	2	0
Alopecia[‖]	33	N/A	N/A	16	N/A	N/A
Stomatitis[¶]	30	1	0	14	0	0
Diarrhea	26	1	0	19	1	0
Anemia	24	5	<1	9	2	0
Rash[#]	18	1	0	12	1	0
Asthenia	17	2	0	12	0	0
Thrombocytopenia	16	1	<1	1	0	0
Vomiting	16	1	0	17	1	0
Decreased appetite	15	1	0	9	0	0
Pyrexia	12	0	0	9	0	0
Dry skin	12	0	0	6	0	0
Dysgeusia	10	0	0	5	0	0

Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 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.
[‖]In the IBRANCE + letrozole arm, 30% of patients had Grade 1 alopecia, and 3% had Grade 2. In the placebo + letrozole arm, 15% of patients had Grade 1 alopecia, and 1% had Grade 2.
[¶]Stomatitis includes aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.
[#]Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

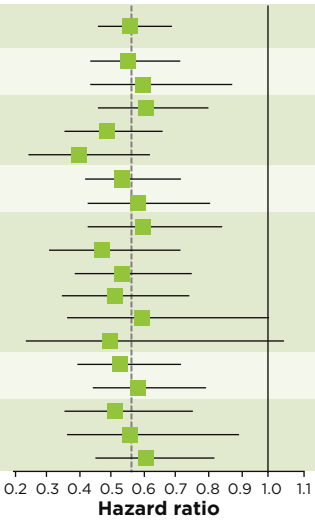
Updated Non-Prespecified Analysis of PFS*

- **27.6 months** of mPFS with IBRANCE + letrozole (n=444; 95% CI: 22.4–30.3) vs **14.5 months** with placebo + letrozole (n=222; 95% CI: 12.3–17.1); **HR=0.56** (95% CI: 0.46–0.69)[6]
- Number of PFS events: 245 (55.2%) in the IBRANCE + letrozole arm and 160 (72.1%) in the placebo + letrozole arm[7]

Updated Non-Prespecified Subgroup Analyses[6]

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 a particular subgroup.

Baseline factors		In favor of IBR+LET	In favor of PBO+LET	IBR+LET (n)	PBO+LET (n)	HR (95% CI)
All randomized patients (investigator assessed)				444	222	0.56 (0.46–0.69)
Age (years)	<65			263	141	0.55 (0.43–0.70)
	≥65			181	81	0.60 (0.43–0.86)
Site of metastatic disease	Visceral			214	110	0.62 (0.47–0.81)
	Nonvisceral			230	112	0.50 (0.37–0.67)
	Bone only			103	48	0.41 (0.26–0.63)
Prior endocrine therapy	Yes			250	126	0.54 (0.42–0.71)
	No			194	96	0.59 (0.43–0.80)
Disease-free interval	De novo metastases			167	81	0.61 (0.44–0.85)
	≤12 months			98	48	0.48 (0.32–0.72)
	>12 months			179	93	0.55 (0.40–0.76)
	>2 years			154	77	0.52 (0.36–0.75)
	>5 years			90	46	0.60 (0.36–1.00)
	>10 years			32	23	0.44 (0.19–1.03)
Prior chemotherapy	Yes			213	109	0.53 (0.40–0.71)
	No			231	113	0.59 (0.45–0.79)
Number of disease sites	1			138	66	0.52 (0.36–0.75)
	2			117	52	0.57 (0.37–0.89)
	≥3			189	104	0.61 (0.46–0.82)



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

Selected Adverse Events (AEs) Reported in an Updated Non-Prespecified Analysis of PALOMA-2[6]

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

The **most common selected AEs (≥10%, all causality)†** of any grade reported in an **updated non-prespecified analysis of PALOMA-2** for IBRANCE + letrozole vs placebo + 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 (ALT) increased (13% vs 6%), aspartate aminotransferase (AST) increased (12% vs 6%), and dysgeusia (10% vs 5%).

*Based on May 2017 data cut (non-prespecified analysis), with a median follow-up of 38 months.[6]
†Incidences of AEs reported in this updated non-prespecified analysis are all causality, and the AEs were selected based on their designation as ARs (treatment-related) in PALOMA-2 in the IBRANCE Prescribing Information.

Objective[2]

- To determine real-world effectiveness of first-line use of IBRANCE + letrozole vs letrozole alone in a cohort of women with HR+/HER2- mBC treated in routine clinical practice from across the United States

Methodology[2]

- Observational retrospective analysis of EHRs conducted using de-identified patient data from the Flatiron Health Analytic Database, which represents women treated in routine clinical practice from across the United States
  - The Flatiron Health Analytic Database is a longitudinal database that includes structured and unstructured EHRs from >280 cancer clinics, including approximately 800 sites of care, and represents 2.4 million patients with cancer actively being treated in the United States

Inclusion Criteria

- Women aged ≥18 years at mBC diagnosis with HR+/HER2- mBC before or up to 60 days after the metastatic diagnosis date
- A date of first prescription (index date) for IBRANCE + letrozole or letrozole alone as first-line therapy for mBC beginning on the date of the US FDA approval of IBRANCE, February 3, 2015, and extending 4 years to February 28, 2019
- A minimum potential follow-up for ≥3 months from the index date to the study cutoff date of May 31, 2019*

Exclusion Criteria

- Received prior treatment with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, aromatase inhibitors, fulvestrant, tamoxifen, raloxifene, or toremifene in the metastatic setting
- Had a first structured activity (a recording of vital information, a medication administration, a non-canceled drug order, or a reported laboratory test/result) >90 days after the mBC diagnostic date
- Received a CDK4/6 inhibitor as part of a clinical trial

Outcomes[2]

Real-world PFS (rwPFS) and OS were pre-planned endpoints

- **Primary: rwPFS†** defined as time in months from start of IBRANCE + letrozole or letrozole alone to death or disease progression (determined by the recorded assessment of the treating clinician based on radiology, laboratory evidence, pathology, or clinical assessment)
- **Secondary: OS‡** defined as number of months from start of IBRANCE + letrozole or letrozole alone to death due to any cause as recorded by Flatiron in the data extract

*The duration of follow-up was defined as the time in months from the start of IBRANCE + letrozole or letrozole alone to death or the data cutoff date of May 31, 2019, whichever came first. Median duration of follow-up was 24.2 months vs 23.3 months for patients who received IBRANCE + letrozole vs letrozole alone, respectively.[2]
†If patients did not die or have disease progression, they were censored at the date of initiation of next line of therapy for those with 2 or more lines of therapy or at their last visit during the study period (February 2015–May 2019) for patients with only 1 line of therapy.[2]
‡If patients did not die, they were censored at the study cutoff date of May 31, 2019.[2]

Observational retrospective analyses are not intended for direct comparison with clinical trials.

IBRANCE Indications

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 in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men, or
- fulvestrant in patients with disease progression following endocrine therapy

Statistical Analysis

- **Stabilized inverse probability treatment weighting (sIPTW)** was applied to patients to balance baseline demographic and clinical characteristics between the 2 cohorts[2]
  - sIPTW is a statistical approach increasingly used in observational retrospective real-world studies where randomization is not possible. Patients are weighted differently in the sample to create 2 cohorts that have balanced characteristics across the 2 arms[2,8]
  - This approach was used as the primary analysis[2]
- The **Kaplan-Meier method** and 95% CIs were used to estimate medians for rwPFS and OS[2]

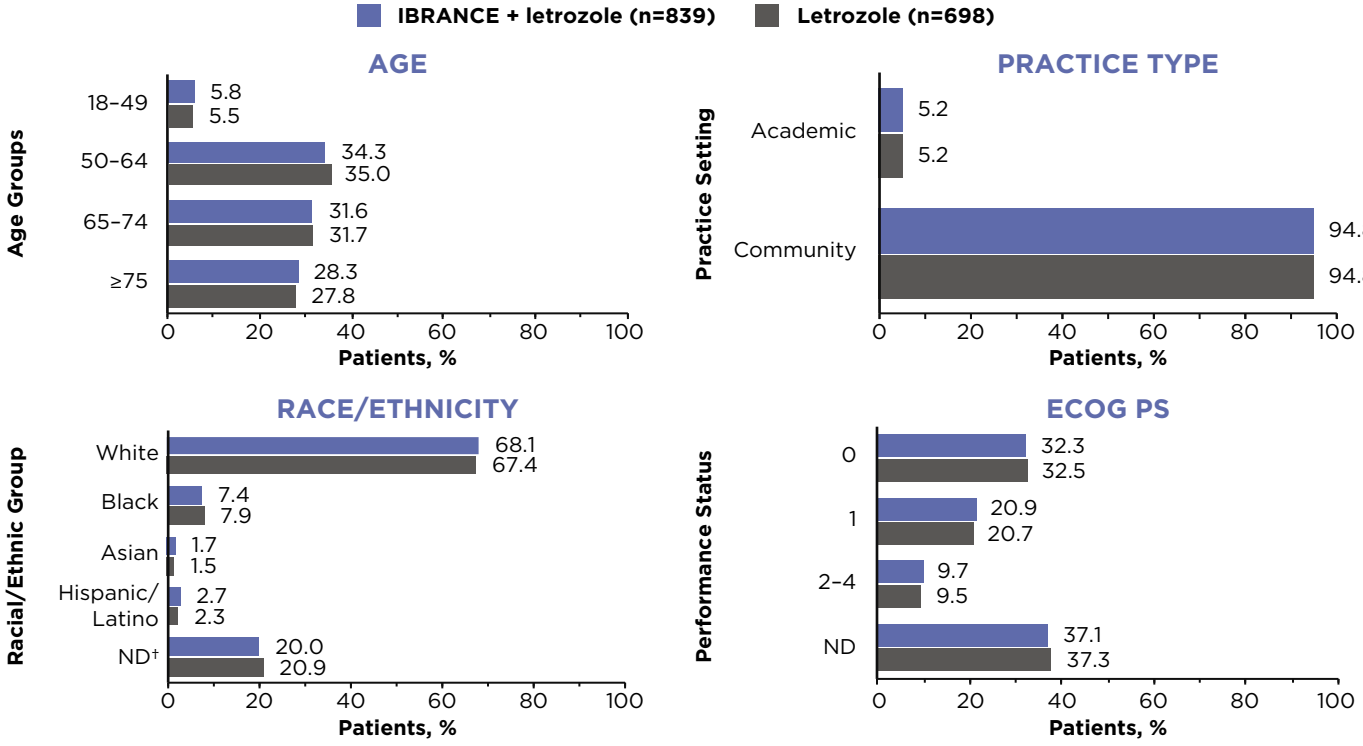
Study Limitations[2]

- **Observational retrospective database analyses** cannot conclude causality, are not intended for direct comparison with randomized controlled trials or other real-world studies, may have missing data or erroneous data entry, and incomplete capture of comorbid conditions and performance status
- **Bias related to treatment selection** and unobserved variables may confound these findings
- **Disease progression** was based on the individual treating physician's clinical assessment or interpretation of radiographic or pathologic results and not on standard criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST)
- **Significant censoring in the OS analysis** highlights the need for subsequent evaluation with longer follow-up
- **Subsequent treatment may have impacted OS outcomes,** and further research is warranted
- **Subgroup analyses are exploratory and are not sufficiently powered** to detect significant differences
- Findings from the Flatiron Health Analytic Database **should not be generalized** to other patient populations
- **Safety data were not collected** as part of the study

Observational retrospective analyses are not intended for direct comparison with clinical trials.

Baseline Demographic and Clinical Characteristics[2]

- A total of 1430 women with HR+/HER2- mBC taking IBRANCE + letrozole or letrozole alone were identified from the Flatiron Health Analytic Database according to the criteria noted on **page 5**
- sIPTW adjustment resulted in a sample of 1537, with 839 in the IBRANCE + letrozole group and 698 in the letrozole-alone group. Patient characteristics were generally balanced after sIPTW adjustment*
- **Patient menopausal status was not consistently available from the Flatiron Health Analytic Database and was not collected as part of this study. Per the FDA-approved Prescribing Information, IBRANCE is indicated for use in combination with an aromatase inhibitor as an initial endocrine-based therapy in postmenopausal women or in men with HR+/HER2- mBC**



*The balance in important prognostic baseline characteristics was assessed using a standardized differences approach, with a standardized difference of ≥0.10 considered indicative of practical significance.
†Race data were not known in the "not documented" race group.
ECOG PS=Eastern Cooperative Oncology Group performance status; ND=not documented.

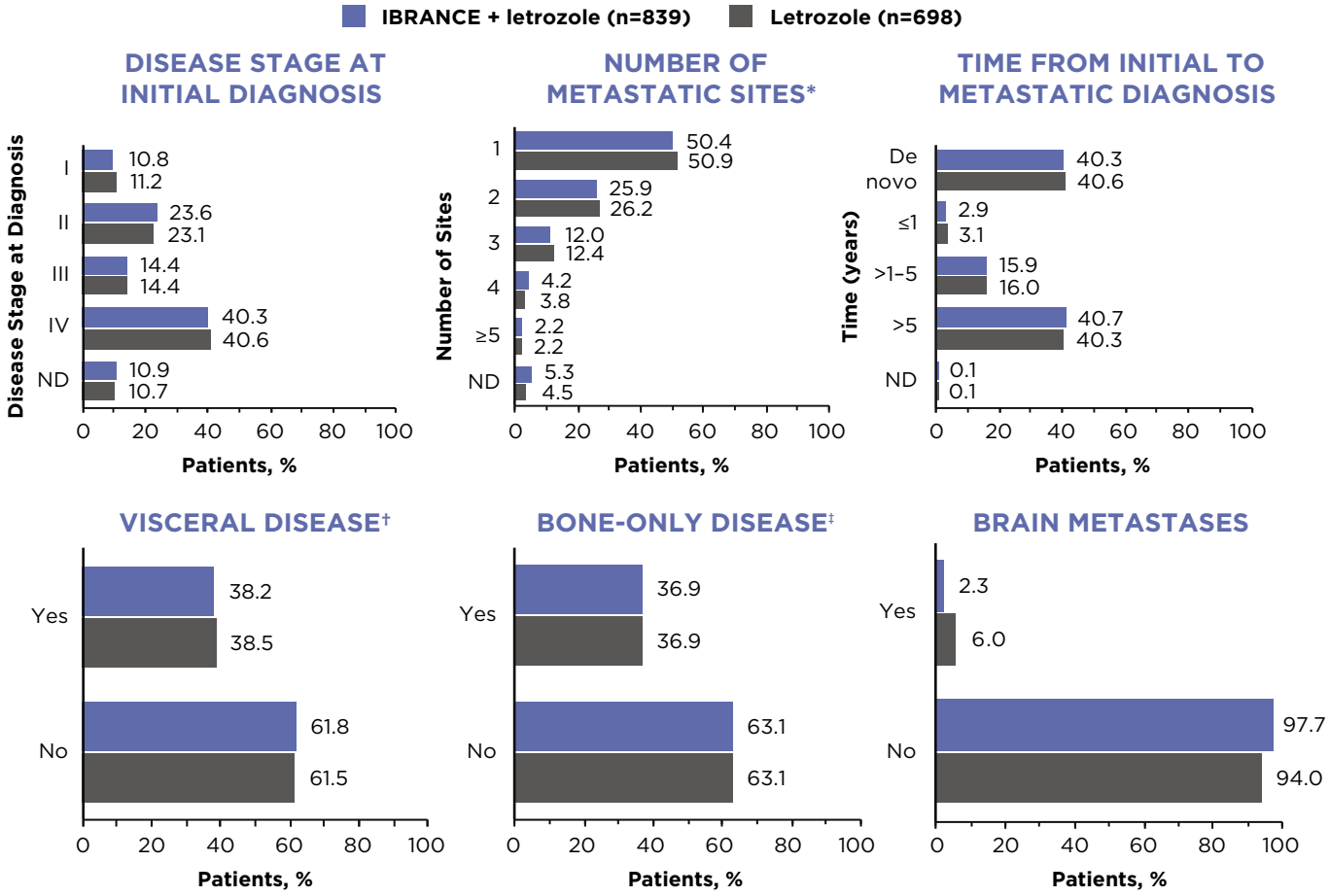
Observational retrospective analyses are not intended for direct comparison with clinical trials.

Important Safety Information (cont'd)

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.

Baseline Demographic and Clinical Characteristics (cont'd)[2]



*Multiple metastases at the same site were counted as 1 site (e.g., if a patient had 3 bone metastases in the spine, it was considered only 1 site).
†Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases.
‡Bone-only disease was defined as metastatic disease in the bone only.

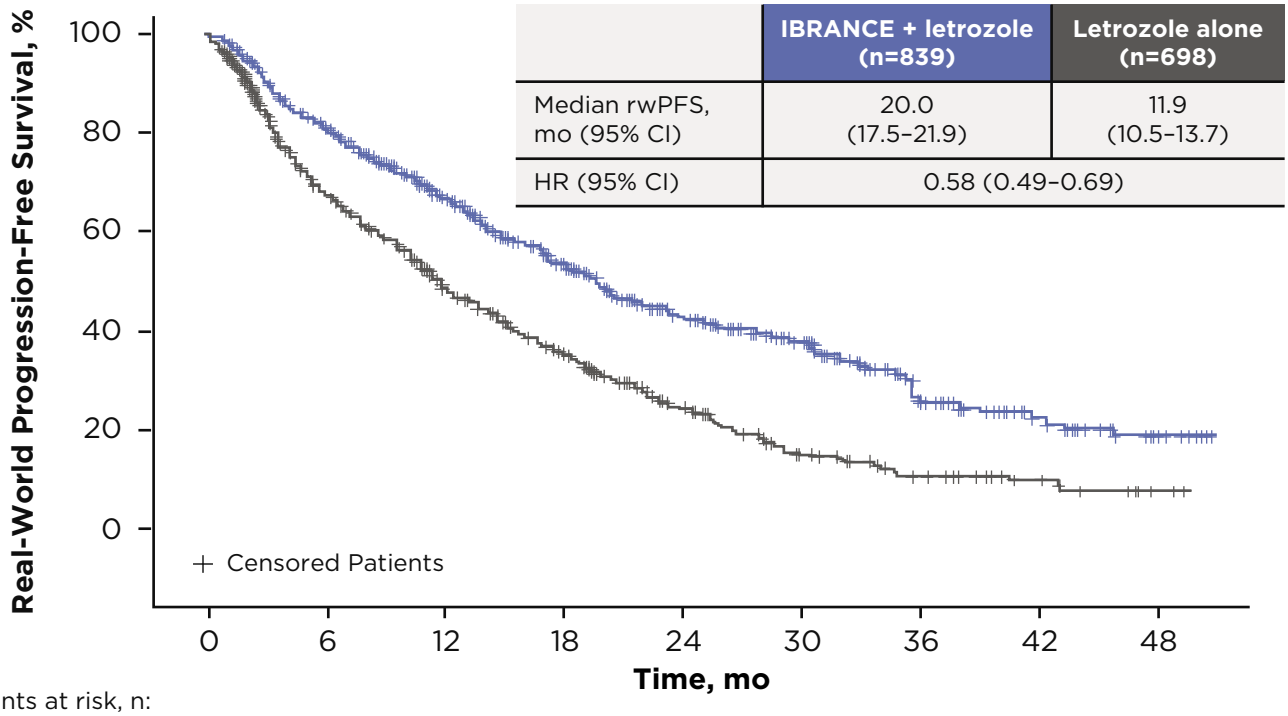
Observational retrospective analyses are not intended for direct comparison with clinical trials.

Important Safety Information (cont'd)

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.

Median follow-up*: 24.2 months (IQR: 14.2–34.9) for patients who received IBRANCE + letrozole and 23.3 months (IQR: 12.7–34.3) for patients who received letrozole alone.[2]

Primary Endpoint: Real-World Progression-Free Survival (rwPFS)[2*]



	IBRANCE + letrozole (n=839)	Letrozole alone (n=698)
Median rwPFS, mo (95% CI)	20.0 (17.5–21.9)	11.9 (10.5–13.7)
HR (95% CI)	0.58 (0.49–0.69)	

Patients at risk, n:									
IBRANCE + letrozole	839	637	442	300	191	130	62	29	8
Letrozole alone	698	369	241	159	95	47	23	10	2

- Median rwPFS was **20.0 months** (95% CI: 17.5–21.9) in the IBRANCE + letrozole group and **11.9 months** (95% CI: 10.5–13.7) in the letrozole-alone group; **HR=0.58** (95% CI: 0.49–0.69)

*sIPTW-adjusted patient population.
IQR=interquartile range.

Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality. Observational retrospective analyses are not intended for direct comparison with clinical trials.

Important Safety Information (cont'd)

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%).

Forest Plot of rwPFS by Subgroup[2]*

This graph below depicts subgroup analyses from an **observational retrospective analysis of EHRs from the Flatiron Health Analytic Database.** 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 real-world effectiveness in a particular subgroup.

Subgroups		In favor of IBR+LET	In favor of LET alone	IBR+LET (n)	LET alone (n)	HR (95% CI)
All patients				839	698	0.58 (0.49–0.69)
Age (years)	18–50			59	45	0.82 (0.48–1.39)
	51–69			424	355	0.55 (0.46–0.66)
	≥70			356	298	0.58 (0.46–0.74)
Race	White			586	483	0.53 (0.43–0.65)
	Black			63	55	0.35 (0.22–0.57)
	ND†			190	159	0.97 (0.73–1.29)
Stage at initial Dx	I or II			289	239	0.63 (0.50–0.79)
	III			121	101	0.53 (0.40–0.71)
	IV			338	283	0.58 (0.46–0.72)
	ND			91	74	0.55 (0.36–0.84)
ECOG PS at baseline	0			271	227	0.62 (0.47–0.83)
	≥1			257	210	0.54 (0.39–0.74)
	ND			311	260	0.59 (0.48–0.71)
Initial Dx to metastatic Dx (years)	De novo			338	283	0.57 (0.46–0.72)
	≤1			25	21	0.39 (0.15–0.99)
	>1–5			133	111	0.61 (0.44–0.83)
	>5			342	281	0.58 (0.47–0.72)
Metastatic sites	1			423	355	0.60 (0.49–0.73)
	2			217	183	0.66 (0.52–0.85)
	≥3			154	128	0.41 (0.29–0.58)
	ND			44	31	0.48 (0.30–0.75)
Disease sites	Bone-only disease			309	258	0.55 (0.45–0.68)
	No bone-only disease			530	440	0.60 (0.49–0.74)
	Brain metastases			19	42	0.72 (0.22–2.32)
	No brain metastases			820	656	0.59 (0.52–0.68)
	Visceral disease			320	269	0.55 (0.41–0.74)
	No visceral disease			518	429	0.60 (0.52–0.71)

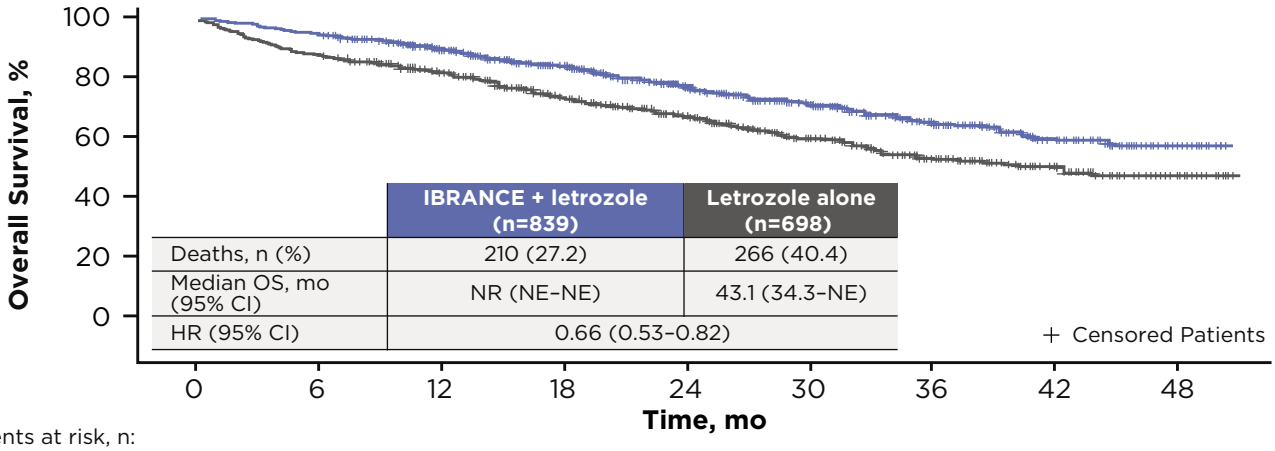
*sIPTW-adjusted patient population.
†Race data were not present in the "not documented (ND)" race group.
Dx=diagnosis; ND=not documented.

Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality. Observational retrospective analyses are not intended for direct comparison with clinical trials.

Important Safety Information (cont'd)

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%).

Secondary Endpoint: Overall Survival[2*]



	IBRANCE + letrozole (n=839)	Letrozole alone (n=698)
Deaths, n (%)	210 (27.2)	266 (40.4)
Median OS, mo (95% CI)	NR (NE–NE)	43.1 (34.3–NE)
HR (95% CI)	0.66 (0.53–0.82)	

Patients at risk, n:									
IBRANCE + letrozole	839	799	685	558	423	303	197	95	26
Letrozole alone	698	620	535	429	334	235	153	81	32

*sIPTW-adjusted patient population.
NR=not reached.

- In the real-world setting, median OS was not reached (95% CI: NE–NE) in the IBRANCE + letrozole group and was 43.1 months (95% CI: 34.3–NE) in the letrozole-alone group; HR=0.66 (95% CI: 0.53–0.82)
- Although median OS was reached in the letrozole-alone group, significant censoring in the OS analysis highlights the need for subsequent evaluation with longer follow-up
- In a landmark analysis at 2 years of follow-up, the OS rate was 78.3% in the IBRANCE + letrozole group and 68.0% in the letrozole-alone group

PALOMA-2 began in February 2013 and includes OS as a secondary endpoint. The planned number of events required for a final OS analysis has not been reached. Patients will continue to be followed for the final analysis.[6]

Mature OS data are available for PALOMA-3, which evaluated a different patient population than the PALOMA-2 trial or this real-world study. PALOMA-3 was a 2:1 randomized, double-blind, Phase 3 trial of women with HR+/HER2- mBC who progressed on or after endocrine therapy in the adjuvant or metastatic setting (N=521). PALOMA-3 studied IBRANCE 125 mg PO once daily taken 3 weeks on, 1 week off + fulvestrant 500 mg IM on Days 1, 15, 29, and monthly thereafter vs placebo + fulvestrant. The primary endpoint of PFS was met. A key secondary endpoint of OS showed a numerical difference in favor of IBRANCE + fulvestrant vs placebo + fulvestrant that did not reach statistical significance.[10]

Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality. Observational retrospective analyses are not intended for direct comparison with clinical trials.

Important Safety Information (cont'd)

The **most common adverse reactions (≥10%)** of any grade reported in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (83% vs 4%), leukopenia (53% vs 5%), infections (47% vs 31%), fatigue (41% vs 29%), nausea (34% vs 28%), anemia (30% vs 13%), stomatitis (28% vs 13%), diarrhea (24% vs 19%), thrombocytopenia (23% vs 0%), vomiting (19% vs 15%), alopecia (18% vs 6%), rash (17% vs 6%), decreased appetite (16% vs 8%), and pyrexia (13% vs 5%).

The **most frequently reported Grade ≥3 adverse reactions (≥5%)** in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (66% vs 1%) and leukopenia (31% vs 2%).

Lab abnormalities of any grade occurring in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were decreased WBC (99% vs 26%), decreased neutrophils (96% vs 14%), anemia (78% vs 40%), decreased platelets (62% vs 10%), increased aspartate aminotransferase (43% vs 48%), and increased alanine aminotransferase (36% vs 34%).

Please see Important Safety Information throughout and the full Prescribing Information for IBRANCE capsules and tablets and at www.IbranceHCP.com

IBRANCE® palbociclib

PALOMA-2 randomized clinical trial[5]

- PALOMA-2 was a 2:1 randomized, double-blind, Phase 3 trial studying IBRANCE + letrozole vs placebo + letrozole as first-line endocrine-based therapy in postmenopausal women with ER+/HER2- mBC (N=666)

Real-world observational retrospective analysis of EHRs[2]

- This was an observational retrospective analysis of EHRs conducted using de-identified patient data to determine real-world effectiveness of IBRANCE + letrozole vs letrozole alone as first-line treatment for HR+/HER2- mBC (N=1537; after sIPTW)

IBRANCE is the #1 prescribed FDA-approved oral combination treatment for HR+/HER2- mBC[7]

6+
YEARS
since initial FDA approval

15,000+
PRESCRIBERS
have chosen IBRANCE*

136,000+
PATIENTS
prescribed IBRANCE*

*Estimated data as of November 2020.

References:
1. Gyawali B, Parsad S, Feinberg BA, Nablan C. Real-world evidence and randomized studies in the precision oncology era: the right balance. *JCO Precis Oncol*. 2017;1:1-5. **2.** DeMichele A, Cristofanilli M, Brufsky A, et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2– metastatic breast cancer in US real-world clinical practice. *Breast Cancer Res*. Published online March 24, 2021. doi:10.1186/s13058-021-01409-8. **3.** Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. *J Natl Cancer Inst*. 2017;109(11):1-5. **4.** Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. *Clin Transl Gastroenterol*. 2014;5(1):e45. **5.** Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936. **6.** 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. **7.** Data on file. Pfizer Inc., New York, NY. **8.** Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679. **9.** Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17(4):425-439. **10.** Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.

Important Safety Information (cont'd)

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.

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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