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ORIGINAL REPORT

First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2–Positive and Hormone Receptor–Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial

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ABSTRACT

Purpose

To assess pertuzumab plus trastuzumab and an aromatase inhibitor (AI) in patients with human epidermal growth factor receptor 2 (HER2)–positive and hormone receptor–positive metastatic/locally advanced breast cancer (MBC/LABC).

Patients and Methods

The PERTAIN trial (NCT01491737) is an ongoing randomized, open-label, multicenter—80 sites and eight countries—phase II trial. Patients have HER2-positive, hormone receptor–positive MBC/LABC and no prior systemic therapy with the exception of endocrine. Random assignment was 1:1 to intravenous pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks) plus trastuzumab (8 mg/kg followed by 6 mg/kg every 3 weeks), and oral anastrozole (1 mg every day) or letrozole (2.5 mg every day), or trastuzumab and an AI. Induction intravenous docetaxel every 3 weeks or paclitaxel every week could be administered for 18 to 24 weeks at the investigator's discretion (decided before but given after random assignment). Primary end point was progression-free survival (PFS). Patients were stratified by whether they received induction chemotherapy and their time since adjuvant hormone therapy.

Results

One hundred twenty-nine patients were randomly assigned per arm (February 2012 to October 2014; intent-to-treat populations); 75 in one arm and 71 in the other were chosen to receive induction chemotherapy. Stratified median PFS was 18.89 months (95% CI, 14.09 to 27.66 months) in the pertuzumab plus trastuzumab arm and 15.80 months (95% CI, 11.04 to 18.56 months) in the trastuzumab arm (stratified hazard ratio, 0.65; 95% CI, 0.48 to 0.89; $P = .0070$). Serious adverse events (AEs) were reported for 42 (33.1%) of 127 and 24 (19.4%) of 124 patients in the safety populations of the pertuzumab plus trastuzumab and trastuzumab arms, respectively. Rates of grade ≥ 3 AEs were 64 (50.4%) of 127 and 48 (38.7%) of 124, respectively. There were no deaths as a result of AEs.

Conclusion

PERTAIN met its primary PFS end point. Pertuzumab plus trastuzumab and an AI is effective for the treatment of HER2-positive MBC/LABC. The safety profile was consistent with previous trials of pertuzumab plus trastuzumab.

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ASSOCIATED CONTENT

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Appendix
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Data Supplement
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INTRODUCTION

Clinical and laboratory evidence supports the hypothesis that human epidermal growth factor receptor 2 (HER2) and estrogen receptor (ER) bidirectional crosstalk contributes to resistance to hormonal and anti-HER2 therapies.[1-9] ER signaling can act as an escape mechanism, bypassing HER2 blockade downstream signaling—phosphatidylinositol 3-kinase, AKT, Ras, mitogen-activated protein kinase kinase, mitogen-activated protein kinase (signal transducer and activator of transcription)—to restore proliferation, migration,

differentiation, and apoptosis.[10] In HER2–positive and hormone receptor–positive metastatic breast cancer (MBC), adding trastuzumab or lapatinib to an aromatase inhibitor (AI) demonstrated improved efficacy versus AI alone.[4,11,12] Results of the CLEOPATRA, NeoSphere, and APHINITY trials demonstrated that comprehensive HER2 blockade—pertuzumab, trastuzumab, and chemotherapy—further improved outcomes in the metastatic, neoadjuvant, and adjuvant settings[13-17]; however, no study to date has prospectively tested the addition of pertuzumab in the context of standard palliative endocrine therapy.

We hypothesized that pertuzumab, trastuzumab, and an AI may offer additional benefits compared with trastuzumab plus an AI for HER2–positive and hormone receptor–positive MBC or locally advanced breast cancer (LABC). The PERTAIN trial is the first study to assess this combination, with or without chemotherapy, in this indication.

PATIENTS AND METHODS

Study Design

The PERTAIN trial (NCT01491737) is a randomized, two-arm, open-label, multicenter phase II trial, conducted across 80 sites and eight countries. Patients were randomly assigned 1:1 to pertuzumab plus trastuzumab and an AI—anastrozole or letrozole—or trastuzumab plus an AI (Fig 1) via an interactive voice response system (dynamic allocation of blocks to strata; block size of 4; sequence generated by Almac Clinical Technologies, San Francisco, CA). Investigators and sites enrolled patients and called the interactive voice response system to assign them to arms. Docetaxel/paclitaxel induction chemotherapy per product labeling was allowed at the investigator's discretion and administered after random assignment, the decision being made before random assignment, for 18 to 24 weeks in combination with trastuzumab (with or without pertuzumab) and before starting endocrine therapy. Stratification factors were "chosen to receive induction chemotherapy" (yes/no) and "time since adjuvant hormone therapy" (< 12 months/≥ 12 months/no prior hormone therapy).

Primary end point was progression-free survival (PFS; time since random assignment until first radiographically documented progression of disease or death from any cause, whichever occurs first). Secondary end points were overall survival (OS; time since random assignment to death, regardless of cause), overall response rate (ORR; best overall response recorded since the start of treatment until disease progression or recurrence, or death), clinical benefit rate (CBR; best confirmed response of partial response [PR], complete response [CR], or stable disease lasting ≥ 6 months), duration of response (DoR; date of initial confirmed PR/CR until date of progressive disease or death from any cause), time to response (TTR; date of first CR or PR relative to randomization date), safety and tolerability, and quality of life (QoL).

The PERTAIN trial is being conducted in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each patient.

Approval of the protocol and all amendments was obtained from an independent ethics committee for each participating site. An independent data monitoring committee monitored safety and made recommendations regarding the continuation of the study.

Patients

Key inclusion criteria included postmenopausal patients (fulfilling one or more National Comprehensive Cancer Network criteria[18]) with first-line HER2–positive and hormone receptor–positive disease (local laboratory assessment), one or more measurable lesions, and/or nonmeasurable disease (Response Evaluation Criteria In Solid Tumors [RECIST] v1.1[19]), Eastern Cooperative Oncology Group performance status of 0 to 1, left ventricular ejection fraction (LVEF) ≥ 50%, and life expectancy of ≥ 12 weeks. Key exclusion criteria included previous systemic nonhormonal anticancer therapy (MBC/LABC setting), disease-free interval of < 6 months from completion of systemic nonhormonal treatment in the neoadjuvant/adjuvant settings, previous approved/investigative anti-HER2 agents in any breast cancer setting, except trastuzumab and/or lapatinib in the neoadjuvant/adjuvant setting, disease progression while receiving trastuzumab and/or lapatinib in the adjuvant setting, or uncontrolled central nervous system metastases.

Procedures

Pertuzumab and trastuzumab were administered every 3 weeks intravenously (840 mg and 8 mg/kg loading doses followed by 420 mg and 6 mg/kg maintenance doses, respectively).

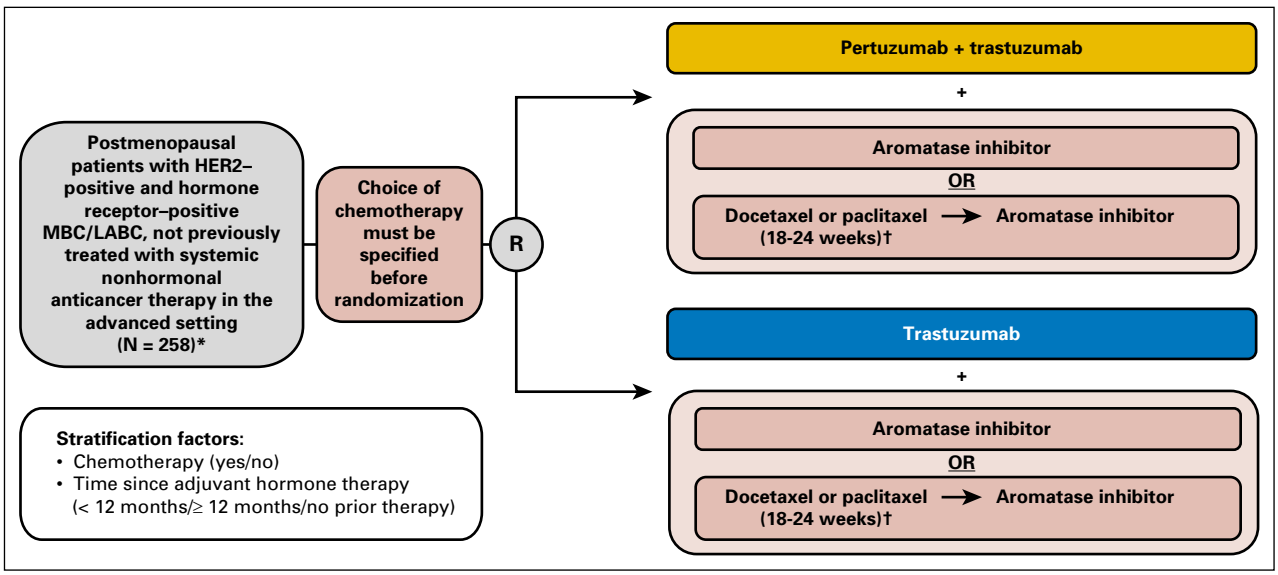

Fig 1. Study design. (*) One hundred sixty-five events to detect significant improvement in progression-free survival from 7 months to 10.8 months (hazard ratio, 0.645) with 80% power and a 2-sided log-rank test at an α level of .05. (†) Choice of chemotherapy must be specified before random assignment. Treatment was administered per product labeling. HER2, human epidermal growth factor receptor 2; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; R, random assignment.

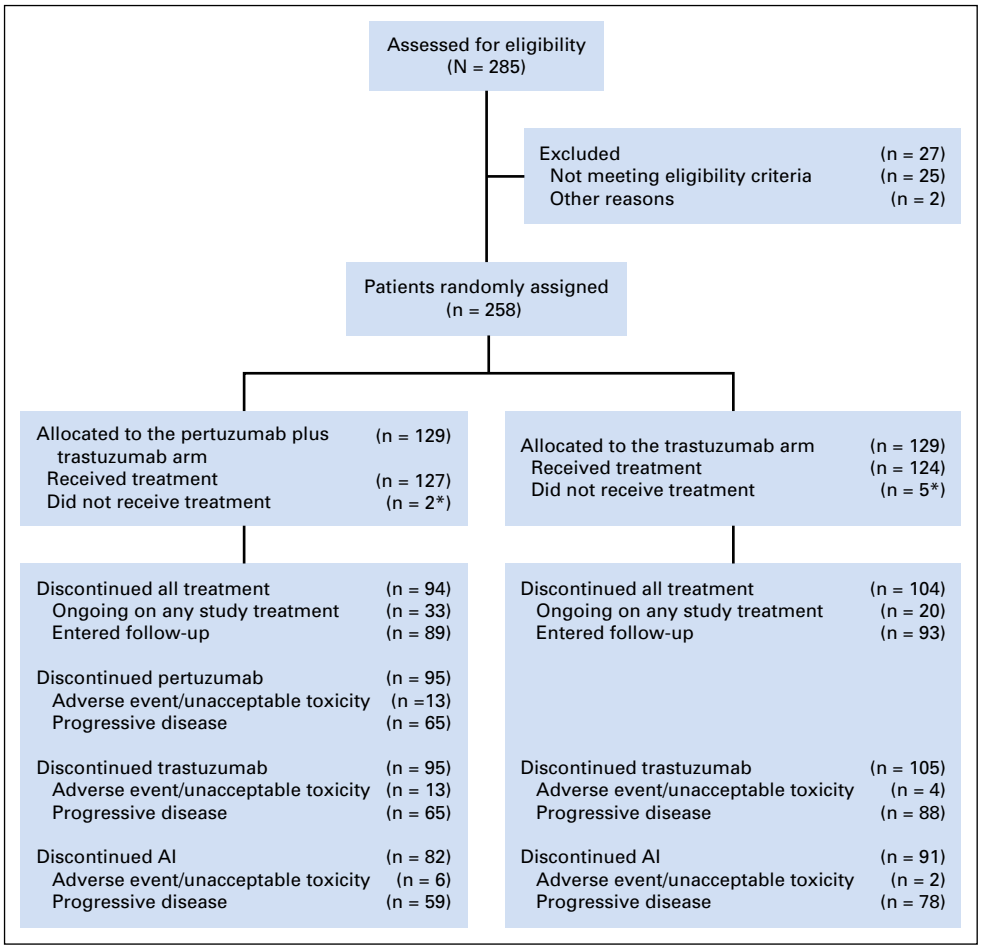

Fig 2. CONSORT diagram. (*) Incorrectly randomly assigned (n = 3), withdrawal of consent during screening procedures (n = 3), and investigator decision (n = 1). AI, aromatase inhibitor.

Anastrozole and letrozole were administered at 1 mg or 2.5 mg, respectively (oral, once daily). If the investigator decided to administer chemotherapy, docetaxel and paclitaxel were administered intravenously per product labeling every 3 weeks or every week, respectively, after random assignment. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. Pertuzumab and trastuzumab could be slowed, stopped, or delayed to assess or treat adverse events (AEs). No dose reductions were allowed. If any of the individual study medications were delayed for $\geq$ 1 day, all were delayed for the same timeframe. If a patient missed a pertuzumab dose for one cycle (two sequential administration times $\geq$ 6 weeks apart), a reloading dose was administered. If reloading was required for a given cycle, the three study therapies were administered on the same schedule as cycle 1. Subsequent maintenance pertuzumab was then administered every 3 weeks, starting 3 weeks later. If a patient missed a dose of trastuzumab by $\geq$ 1 week, reloading followed approved local product information and/or recognized clinical practice guidelines. If reloading was required for a given cycle, the three study therapies were administered on the same schedule as cycle 1. Subsequent maintenance doses were then administered every 3 weeks, starting 3 weeks later. Pertuzumab, trastuzumab, paclitaxel, and docetaxel were discontinued for confirmed congestive heart failure. Pertuzumab and trastuzumab were also discontinued for LVEF drops to $<$ 40% (confirmed within 3 weeks of assessment as being $<$ 40% or 40% to 45% and $\geq$ 10% below baseline). Taxane dose reductions were permitted for severe peripheral neurotoxicity.

Tumors were assessed (RECIST v1.1) at screening, every 3 cycles of anti-HER2 therapy $\leq$ 36 months, and every 6 cycles ($\pm$ 7 days of scheduled treatment day) thereafter for patients who remained progression-free after 36 months. Assessments continued during the safety follow-up visit—approximately 28 days after the end of study treatment—and during post-treatment follow-up visits every 3 months if disease progression was not established.

Assessments

AEs were assessed at screening, baseline, day –7 to day 1, during the treatment period, at the safety follow-up visit, and at post-treatment follow-up visits by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). LVEF was assessed locally by echo/multigated acquisition. Change from baseline was only calculated when the type of scan was the same as at baseline.

QoL was assessed before first study treatment and every 3 cycles of antibody treatment via the EQ-5D questionnaire (EQ-5D descriptive system and a Visual Analogue Scale [EQ VAS]).

Statistical Analysis

Adjusting for a withdrawal rate of approximately 10%, we planned to assign 250 patients randomly. A sample of 225 evaluable patients with 165 events was expected to provide 80% power to detect a significant improvement in median PFS, from 7.0 months with trastuzumab plus an AI to 10.8 months when adding pertuzumab (hazard ratio [HR], 0.645; two-sided log-rank test at an α level of .05; estimation [EAST version 5.2; Cytel, Cambridge, MA]). As some patients were scheduled to receive induction chemotherapy, median PFS in the trastuzumab arm was assumed to be higher than the 4.8 months found in the TAnDEM trial.[11]

PFS analysis was event driven (165 events required and 166 observed). Other end points were analyzed at this time, including preliminary OS (final analysis after a minimum follow-up of 60 months for all patients).

Table 1. Baseline Patient Demographics, Disease Characteristics, and Previous Systemic Therapies for Breast Cancer for the Intent-to-Treat Population

Characteristic	Pertuzumab Plus Trastuzumab Arm (n = 129)	Trastuzumab Arm (n = 129)
Female sex	129 (100)	129 (100)
Median age, years (range)	59 (35-87)	61 (31-89)
Age group, years		
< 65	86 (66.7)	86 (66.7)
≥ 65	43 (33.3)	43 (33.3)
< 75	108 (83.7)	102 (79.1)
≥ 75	21 (16.3)	27 (20.9)
World region		
Asia	10 (7.8)	16 (12.4)
Europe	82 (63.6)	70 (54.3)
North America	18 (14.0)	22 (17.1)
South America	19 (14.7)	21 (16.3)
ECOG PS at baseline*		
0	85 (65.9)	89 (69.0)
1	43 (33.3)	39 (30.2)
Stage at initial diagnosis†		
I	11 (8.5)	15 (11.6)
II	42 (32.6)	38 (29.5)
III	41 (31.8)	37 (28.7)
IV	34 (26.4)	39 (30.2)
Median time since initial BC diagnosis, months (range)	22.83 (0.3-365.8)	25.79 (0.3-327.1)
MBC/LABC at study entry		
LABC	8 (6.2)	7 (5.4)
MBC	121 (93.8)	122 (94.6)
Disease type at screening‡		
Visceral	94 (72.9)	88 (68.2)
Nonvisceral	35 (27.1)	41 (31.8)
No. of organs involved‡		
≥ 3	42 (32.6)	44 (34.1)
< 3	87 (67.4)	85 (65.9)
Induction chemotherapy		
Yes	75 (58.1)	71 (55.0)
No	54 (41.9)	58 (45.0)
ER and PgR score		
ER positive, PgR positive, or both positive	129 (100.0)	129 (100.0)
IHC HER2 expression score		
0§	0	1 (0.8)
1+	0	0
2+§	15 (11.6)	23 (17.8)
3+	108 (83.7)	100 (77.5)
Not performed§	6 (4.7)	5 (3.9)
Previous systemic therapy for BC‖	67 (51.9)	67 (51.9)
Chemotherapy setting		
Neoadjuvant	20 (15.5)	18 (14.0)
Adjuvant	51 (39.5)	41 (31.8)
Anthracyclines	53 (41.1)	36 (27.9)
Taxanes	33 (25.6)	36 (27.9)
Trastuzumab setting		
Neoadjuvant	10 (7.8)	8 (6.2)
Adjuvant	30 (23.3)	24 (18.6)
Hormonal therapy setting		
Neoadjuvant	1 (0.8)	1 (0.8)
Adjuvant	54 (41.9)	51 (39.5)
Other¶	2 (1.6)	4 (3.1)

NOTE. Data presented as No. (%) unless otherwise indicated. Time since initial diagnosis was calculated relative to date of randomization. All tumors with IHC results that were scored as IHC 0 or IHC 2+, or those that did not have IHC tests performed, were confirmed as ISH–positive. HER2 and ER/PgR testing were performed locally. Patients may be counted under more than one treatment setting for prior systemic therapy for BC (eg, neoadjuvant/adjuvant).

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IHC, immunohistochemistry; ISH, in situ hybridization; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; PgR, progesterone receptor; PS, performance status.

*Missing one patient in each arm. Both patients were randomly assigned but not treated.

†Unknown in one patient in the pertuzumab plus trastuzumab arm.

‡On the basis of baseline tumor assessment (target and nontarget lesions).

§All ISH–positive.

‖One patient in each arm received previous lapatinib, and one patient in the pertuzumab plus trastuzumab arm received previous bevacizumab.

¶Metastatic disease (n = 3), bone metastasis (n = 1), first-line metastatic (n = 1), and cancer treatment (n = 1).

Primary PFS analysis and OS analysis were based on the Kaplan-Meier approach, including stratification factors from the interactive voice or web response system. HR was from a stratified Cox proportional hazards regression model, including stratification factors from the interactive voice or web response system. For PFS subgroup analyses, HR for the pertuzumab plus trastuzumab arm compared with the trastuzumab arm (reference category) was from an unstratified Cox model. Median DoRs were unstratified on the basis of the Kaplan-Meier approach, with HR from a Cox proportional hazards regression model, including stratification factors from the interactive voice or web response system. Best overall response and CBR were assessed by numbers and proportions of responders and nonresponders in each arm; 95% CIs were computed using the Clopper-Pearson approach, and 95% differences in ORR between arms with associated 95% CIs were calculated using the Hauck-Anderson approach.

For PFS, DoR, and TTR, patients without events were censored at the time of the last evaluable tumor assessment, or, if they had no assessment, at the time of random assignment +1 day. For OS, patients without follow-up information were censored at the day of last study medication. Patients with no postbaseline information were censored at the time of random assignment +1 day.

The intent-to-treat (ITT) population is defined as all randomly assigned patients, and the safety population is defined as all patients who received one or more doses of study medication.

RESULTS

Population

From February 2012 to October 2014, 258 patients were randomly assigned—129 per arm (ITT population; Fig 2). The safety population consisted of 127 and 124 patients, respectively. Clinical cutoff was March 17, 2016, and median follow-up was 31 months. As demonstrated in Table 1, baseline patient demographics and disease characteristics in the ITT population were generally balanced between arms. One hundred forty-six patients

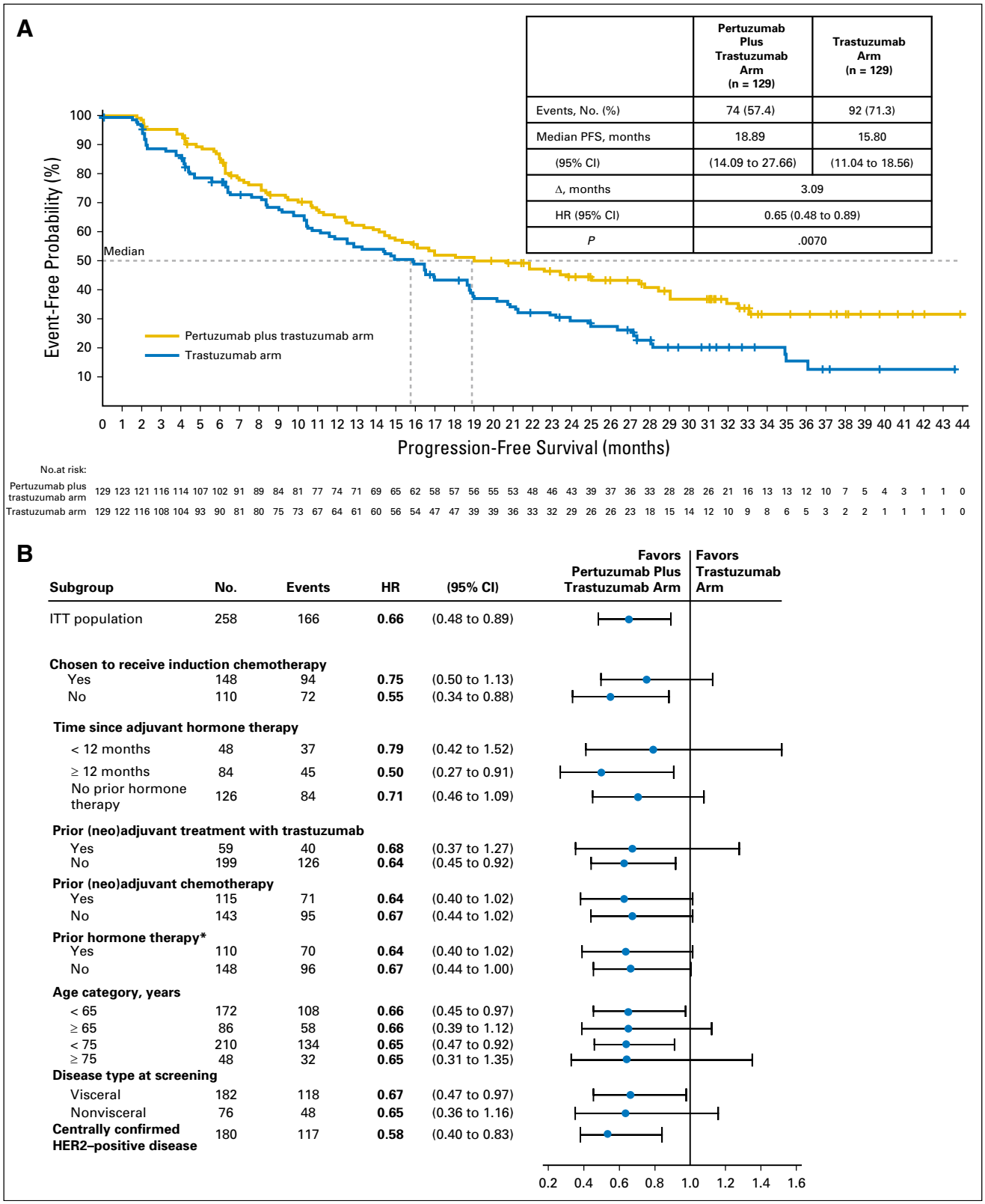

Fig 3. (A-D) Progression-free survival (PFS) in (A) the intent-to-treat (ITT) population, (B) subgroups, (C) patients who were chosen not to receive induction chemotherapy, and (D) patients who were chosen to receive induction chemotherapy. Primary analysis was based on the Kaplan-Meier approach, including stratification factors from the interactive voice or web response system (IXRS). Hazard ratio (HR) was from a stratified Cox proportional hazards regression model, including stratification factors from IXRS. For subgroup analyses, HR for the pertuzumab plus trastuzumab arm versus the trastuzumab arm (trastuzumab arm, reference category) was from an unstratified Cox model. (*) Prior hormone therapy includes treatment in neoadjuvant, adjuvant, and other settings. HER2, human epidermal growth factor receptor 2.

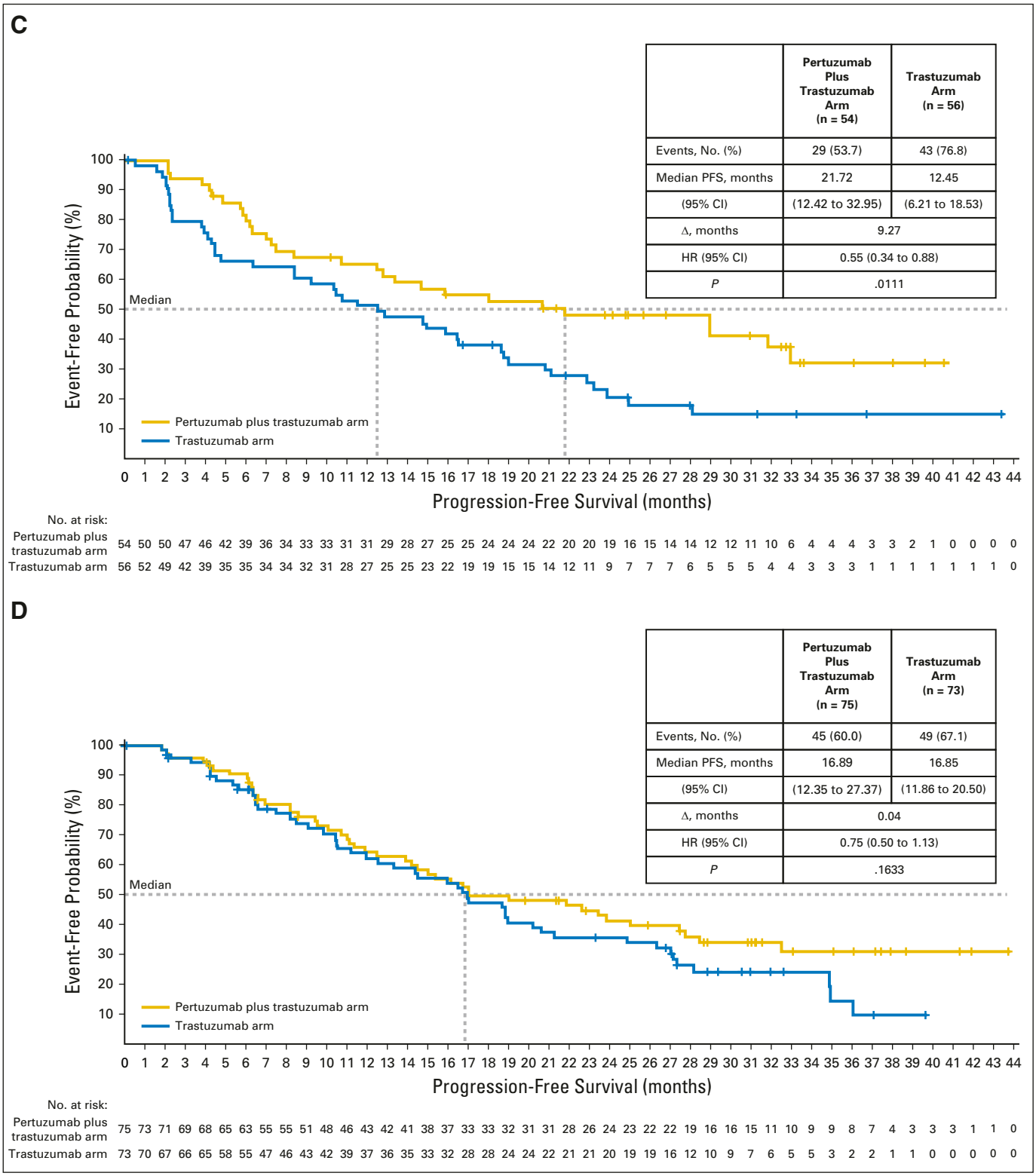

Fig 3. (Continued).

were chosen to receive induction chemotherapy (75 in the pertuzumab plus trastuzumab arm, and 71 in the trastuzumab arm), and 112 patients were not (54 and 58 patients, respectively; Appendix Table A1, online only).

PFS

Pertuzumab plus trastuzumab significantly improved PFS compared with trastuzumab (ITT: stratified median PFS, 18.89 months; 95% CI, 14.09 to 27.66 months versus 15.80 months; 95% CI,

11.04 to 18.56 months; stratified HR, 0.65; 95% CI, 0.48 to 0.89; $P = .0070$; Fig 3A).

Addition of pertuzumab was favorable for all predefined subgroups, and data generally supported the primary analysis (Fig 3B). Among patients who did not receive induction chemotherapy, unstratified HR was 0.55 (95% CI, 0.34 to 0.88), with a median PFS of 21.72 months (95% CI, 12.42 to 32.95 months) in the pertuzumab plus trastuzumab arm and 12.45 months (95% CI, 6.21 to 18.53 months) in the trastuzumab arm (Fig 3C). For patients who received induction chemotherapy, unstratified HR was 0.75 (95% CI, 0.50 to 1.13), with a median PFS of 16.89 months (95% CI, 12.35 to 27.37 months) in the pertuzumab plus trastuzumab arm and 16.85 months (95% CI, 11.86 to 20.50 months) in the trastuzumab arm (Fig 3D). Results for the "time since adjuvant hormone therapy" stratification factor are shown in Appendix Figure A1 (online only).

Secondary Efficacy End Points

One hundred nine patients in the pertuzumab plus trastuzumab arm and 106 in the trastuzumab arm had measurable disease at baseline. There was a nonsignificant, although numerically higher, proportion of responders in the pertuzumab plus trastuzumab arm (63.3% *v* 55.7% in the trastuzumab arm; $P = .2537$), mainly driven by CRs (7.3% *v* 0.9%, respectively). CBR was not significantly different between the arms (68.8% *v* 67.0%, respectively; $P = .7743$).

Median DoR in patients with confirmed CR/PR was significantly longer in the pertuzumab plus trastuzumab arm—27.10 months in 69 patients (95% CI, 14.13 months to not evaluable) versus 15.11 months in 59 patients (95% CI, 12.09 to 20.96 months) in the trastuzumab arm (unstratified HR, 0.57; 95% CI, 0.36 to 0.91; $P = .0181$; Fig 4). TTR was not significantly different between the arms—2.53 months in the pertuzumab plus trastuzumab arm (95% CI, 2.10 to 4.37 months) and 3.91 months in the trastuzumab arm (95% CI, 2.10 to 4.17 months; unstratified HR, 1.11; 95% CI, 0.78 to 1.57; $P = .5597$).

OS data are immature, as median has not been reached in either arm.

Treatment Exposure

Overall, patients in the pertuzumab plus trastuzumab arm had longer exposure to HER2-targeted therapy than those in the trastuzumab arm—a median of 18.0 pertuzumab and trastuzumab cycles (range, 1 to 65 cycles) and 15.5 trastuzumab cycles (range, 1 to 65 cycles), respectively. Median cycles of taxanes were balanced (6.0 cycles of docetaxel or paclitaxel [range, 0 to 8 cycles] in each arm [Appendix Table A2, online only]; results per induction chemotherapy subgroup are shown in Appendix Table A3, online only).

Safety

The safety profile during the study treatment period is shown in Table 2. Serious AEs were reported for 42 patients (33.1%) and 24 patients (19.4%) in the safety population of the pertuzumab plus trastuzumab and trastuzumab arms, respectively, and 64 patients (50.4%) and 48 patients (38.7%), respectively, had grade ≥ 3 AEs.

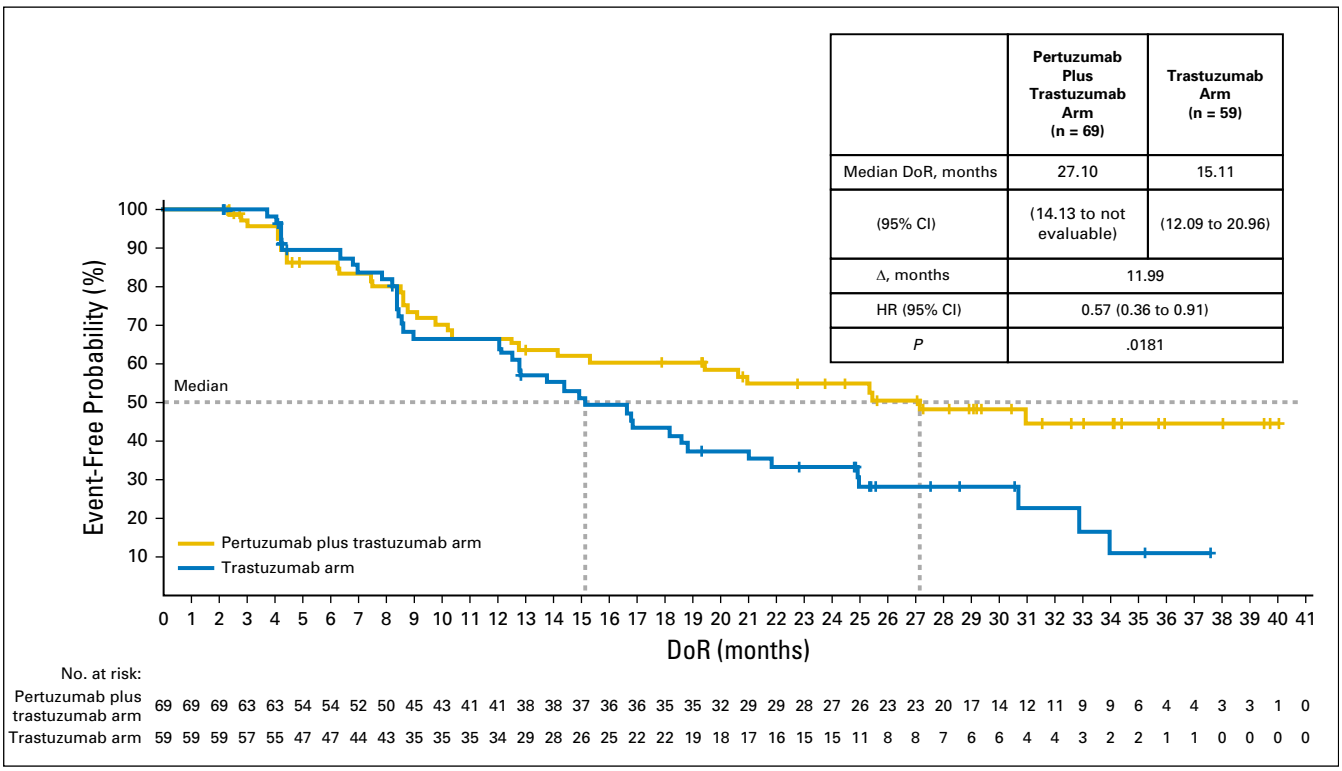

Fig 4. Duration of response (DoR; responders in the intent-to-treat population, unstratified). Median DoR was unstratified on the basis of the Kaplan-Meier approach, with the hazard ratio (HR) from a Cox proportional hazards model, including stratification factors from the interactive voice or web response system.

Table 2. Adverse Events in the Safety Population

Adverse Event	Pertuzumab Plus Trastuzumab Arm (n = 127)	Trastuzumab Arm (n = 124)
Any adverse event	122 (96.1)	122 (98.4)
Most common adverse events, all grades*		
Diarrhea	70 (55.1)	45 (36.3)
Alopecia	36 (28.3)	40 (32.3)
Nausea	41 (32.3)	32 (25.8)
Asthenia	39 (30.7)	31 (25.0)
Arthralgia	37 (29.1)	29 (23.4)
Edema peripheral	31 (24.4)	22 (17.7)
Vomiting	29 (22.8)	22 (17.7)
Anemia	26 (20.5)	18 (14.5)
Headache	22 (17.3)	14 (11.3)
Rash	22 (17.3)	11 (8.9)
Dyspnea	19 (15.0)	12 (9.7)
Decreased appetite	20 (15.7)	10 (8.1)
Dizziness	19 (15.0)	11 (8.9)
Bone pain	16 (12.6)	9 (7.3)
Anxiety	12 (9.4)	5 (4.0)
Muscle spasms	12 (9.4)	5 (4.0)
Dysuria	9 (7.1)	1 (0.8)
Hypersensitivity	7 (5.5)	0
Grade ≥ 3 adverse events†	64 (50.4)	48 (38.7)
Hypertension	13 (10.2)	14 (11.3)
Diarrhea	9 (7.1)	3 (2.4)
Neutropenia	4 (3.1)	8 (6.5)
Anemia	5 (3.9)	3 (2.4)
Asthenia	4 (3.1)	4 (3.2)
Febrile neutropenia	4 (3.1)	2 (1.6)
Pneumonia	5 (3.9)	1 (0.8)
Ejection fraction decreased	3 (2.4)	1 (0.8)
Hyperglycemia	1 (0.8)	3 (2.4)
Device-related infection	1 (0.8)	2 (1.6)
Hypertensive crisis	2 (1.6)	1 (0.8)
Hypokalemia	3 (2.4)	0
Hyponatremia	0	3 (2.4)
Left ventricular dysfunction	3 (2.4)	0
NYHA class I	1 (0.8)	0
NYHA class II	2 (1.6)	0
Leukopenia	1 (0.8)	2 (1.6)
Abdominal pain	1 (0.8)	1 (0.8)
Blood glucose increased	0	2 (1.6)
Erysipelas	1 (0.8)	1 (0.8)
Fatigue	2 (1.6)	0
Gastroenteritis	2 (1.6)	0
Mucosal inflammation	1 (0.8)	1 (0.8)
Neuropathy peripheral	2 (1.6)	0
Neutropenic sepsis	1 (0.8)	1 (0.8)
Paresthesia	2 (1.6)	0
Pulmonary embolism	1 (0.8)	1 (0.8)
Syncope	1 (0.8)	1 (0.8)
Weight increased	1 (0.8)	1 (0.8)
Serious adverse events	42 (33.1)	24 (19.4)
Adverse event leading to discontinuation of pertuzumab	13 (10.2)	—
Adverse event leading to interruption of pertuzumab	34 (26.8)	—

NOTE. Data are given as No. of patients (%).
Abbreviation: NYHA, New York Heart Association.
*Occurring in ≥ 20% of patients or with a ≥ 5% difference between arms.
†Adverse events listed occurred in more than one patient.

The most common AEs were diarrhea (70 patients [55.1%] in the pertuzumab plus trastuzumab arm and 45 [36.3%] in the trastuzumab arm), alopecia (36 [28.3%] and 40 [32.3%], respectively), and nausea (41 [32.3%] and 32 [25.8%], respectively), and the most common grade ≥ 3 AEs were hypertension (13 patients [10.2%] in the pertuzumab plus trastuzumab arm and 14 [11.3%] in the trastuzumab arm), diarrhea (nine [7.1%] and three [2.4%], respectively), neutropenia (four [3.1%] and eight [6.5%], respectively), and anemia (five [3.9%] and three [2.4%], respectively). Thirteen patients (10.2%) discontinued pertuzumab as a result of AEs, and 34 patients (26.8%) had pertuzumab interrupted because of AEs. AEs by induction chemotherapy subgroups are shown in Appendix Table A4 (online only). There were no deaths as a result of AEs.

In most patients, an LVEF of ≥ 45% was maintained during study treatment (86.6% of patients in the pertuzumab plus trastuzumab arm and 90.3% of patients in the trastuzumab arm). Mean LVEF by cycle is shown in Appendix Figure A2 (online only).

QoL

EQ VAS records remained stable in both arms across cycles, with a numerical improvement after cycle 45 that favored the pertuzumab plus trastuzumab arm (Appendix Fig A3A, online only). In all five EQ-5D descriptive domains, patients in the pertuzumab plus trastuzumab arm had numerically lower scores over all cycles (Appendix Figs A3B to A3F).

DISCUSSION

The PERTAIN trial is the first randomized phase II trial to investigate pertuzumab and trastuzumab with an AI for the treatment of patients with HER2–positive and hormone receptor–positive MBC or LABC. PERTAIN met its primary objective: this combination significantly improved PFS compared with trastuzumab plus an AI.

Pertuzumab and trastuzumab bind to different epitopes on HER2, which provides a more comprehensive signaling blockade and leads to greater activity compared with monotherapy.[20] Preclinical models have also suggested that this may inhibit HER2–estrogen receptor crosstalk more efficiently, enhancing the antitumor activity of tamoxifen or estrogen deprivation.[2,7] The PERTAIN trial builds on these preclinical findings and those of the recently reported phase III ALTERNATIVE trial of lapatinib plus trastuzumab plus an AI versus trastuzumab plus an AI,[21] but neither can confirm whether adding an AI to dual HER2 blockade is superior to dual blockade alone. Other studies of biologics in HER2–positive and hormone receptor–positive BC are ongoing.

The statistical plan assumed that PFS would reach 10.8 months in the pertuzumab plus trastuzumab arm and 7.0 months in the trastuzumab arm. These assumptions were derived from the results of the TAnDEM study of trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal patients with HER2–positive and hormone receptor–positive MBC.[11] PFS in the trastuzumab plus anastrozole arm of the TAnDEM trial was 4.8 months compared with 2.4 months in the anastrozole-alone arm (HR, 0.63; $P = .0016$).[11] As PERTAIN included optional induction chemotherapy, PFS was assumed to be longer than that in the TAnDEM trial.

Two additional studies that evaluated HER2-targeted therapy with an AI demonstrated longer median PFS than that reported in TAnDEM. The phase III eLEcTRA trial investigated the efficacy and safety of trastuzumab plus letrozole in HER2–positive and hormone receptor–positive MBC. Median time to progression increased from 3.3 months with letrozole to 14.1 months with trastuzumab plus letrozole; however, this was not statistically significant (HR, 0.67; 95% CI, 0.35 to 1.29; $P = .23$).[12] In a phase III study in first-line HER2–positive and hormone receptor–positive MBC, adding lapatinib to letrozole reduced the risk of disease progression (median PFS, 8.2 months *v* 3.0 months; HR, 0.71, 95% CI, 0.53 to 0.96; $P = .019$).[4] The results of PERTAIN are consistent with a trend of improving trastuzumab efficacy in clinical trials over time, which has been demonstrated in a recent analysis of 12 trials with 2,508 patients with previously untreated HER2–positive MBC.[22] Contributing factors for the overperformance of the trastuzumab arm might include increased quality of HER2 testing[23] and increasing health care professional experience with managing trastuzumab treatment over time. It should be noted that comparisons between the PERTAIN trial and earlier trials should be made with caution because of inherent differences, such as patient populations and treatments, between studies.

A potentially enhanced treatment effect was observed with pertuzumab, trastuzumab, and an AI versus trastuzumab plus an AI in some subgroups, including patients who did not receive induction chemotherapy after random assignment and in patients with a disease-free interval of ≥ 12 months since adjuvant hormone therapy. The subgroup of patients who were chosen by their physician to receive induction chemotherapy was generally younger, had more stage IV disease at initial diagnosis, had more visceral disease, had more organs involved (three or more), and had a shorter median time since initial diagnosis of breast cancer than those who did not receive induction chemotherapy after random assignment. In the CLEOPATRA study, patients who received pertuzumab, trastuzumab, and chemotherapy had significantly improved PFS[13]; however, as our results are from a subgroup analysis, it is difficult to draw conclusions and the studies cannot be directly compared. Additional studies may be needed to clarify these results.

The superior efficacy of pertuzumab plus trastuzumab and an AI was not associated with significantly improved ORR, although CRs were numerically higher in the pertuzumab plus trastuzumab arm. The significant increase in PFS may have been driven by the more sustained responses associated with pertuzumab, as shown by the significantly improved DoR. As aromatase inhibition in HER2–positive and hormone receptor–positive BC is prone to resistance generated by HER2 pathway activation, one possible explanation for the significant increase in PFS is the more comprehensive signaling blockade provided by pertuzumab and trastuzumab compared with trastuzumab alone. Identifying patients who are likely to gain the most benefit from the combination of endocrine therapy with pertuzumab and trastuzumab is important as, given our results, patients with HER2–positive and hormone receptor–positive disease may not always require a chemotherapy treatment that is associated with greater toxicity.

No new safety signals were identified with pertuzumab plus trastuzumab and an AI. Although there was a numerically higher incidence of grade ≥ 3 AEs in the pertuzumab plus trastuzumab arm, none was fatal. There were numerically more ejection fraction decreases and left ventricular dysfunction events in the pertuzumab plus trastuzumab arm; however, these were within the expected range, and LVEF remained stable over times for both arms. QoL records also demonstrate that the use of pertuzumab with trastuzumab and an AI maintains good QoL.

Strengths of the PERTAIN trial are the inclusion of a diverse patient population and the use of a standard-of-care control arm. A limitation is the small patient numbers in some subgroups, which do not enable strong conclusions to be drawn. In addition, PERTAIN was not designed to show differences between patients who received induction chemotherapy after random assignment and those who did not. The ability of investigators to choose which patients received induction therapy may have introduced selection bias and influenced these results.

In conclusion, PERTAIN met its primary PFS objective. Pertuzumab plus trastuzumab and an AI is effective for the treatment of patients with HER2–positive and hormone receptor–positive MBC or LABC. The safety profile was consistent with previous trials of pertuzumab plus trastuzumab.[13-17,24,25]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
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First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2–Positive and Hormone Receptor–Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial

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Appendix

The following investigators participated in the PERTAIN study:

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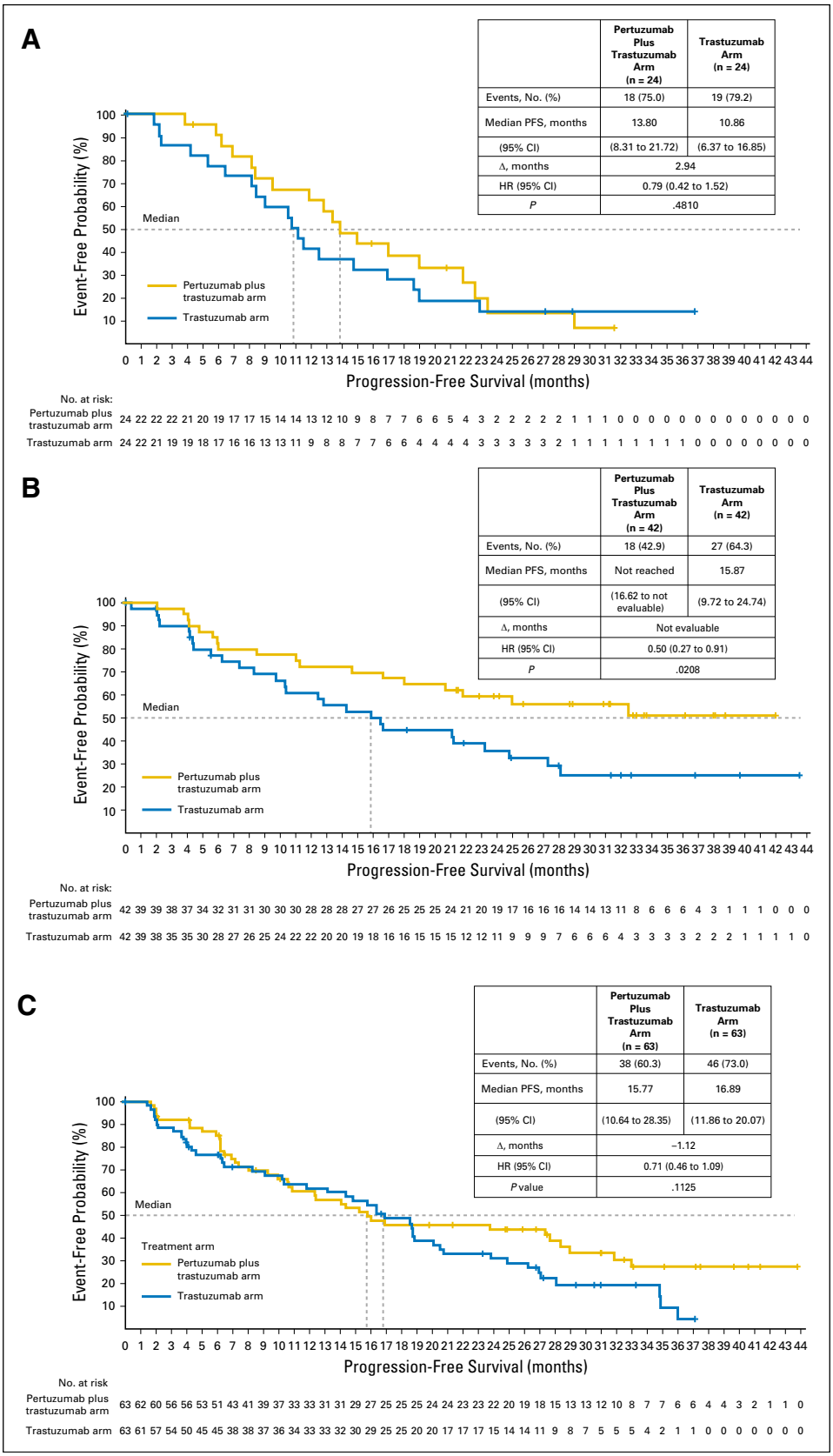


Fig A1. (A-C) Progression-free survival (PFS) in (A) patients with < 12 months since adjuvant hormone therapy, (B) patients with ≥ 12 months since adjuvant hormone therapy, and (C) patients with no adjuvant hormone therapy. Hazard ratio (HR) for the pertuzumab plus trastuzumab arm versus the trastuzumab arm (trastuzumab arm, reference category) was from an unstratified Cox model.

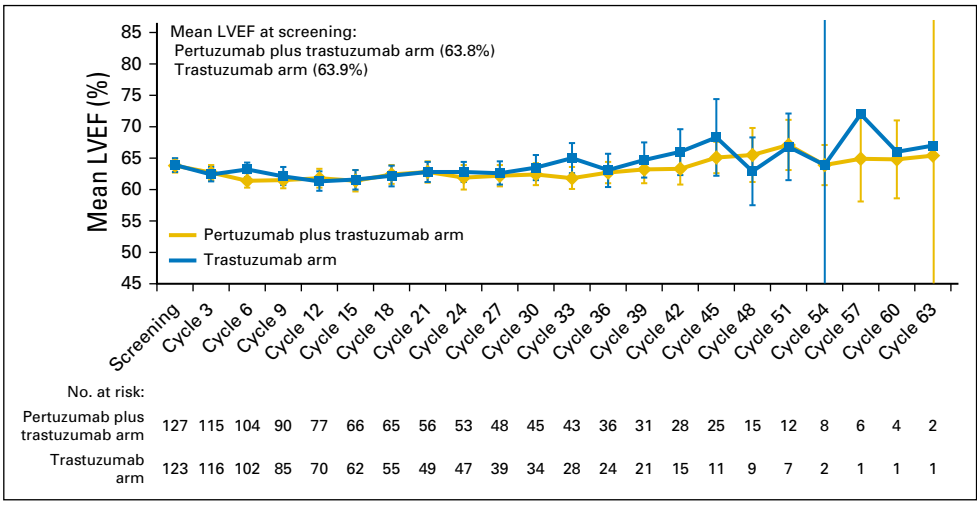
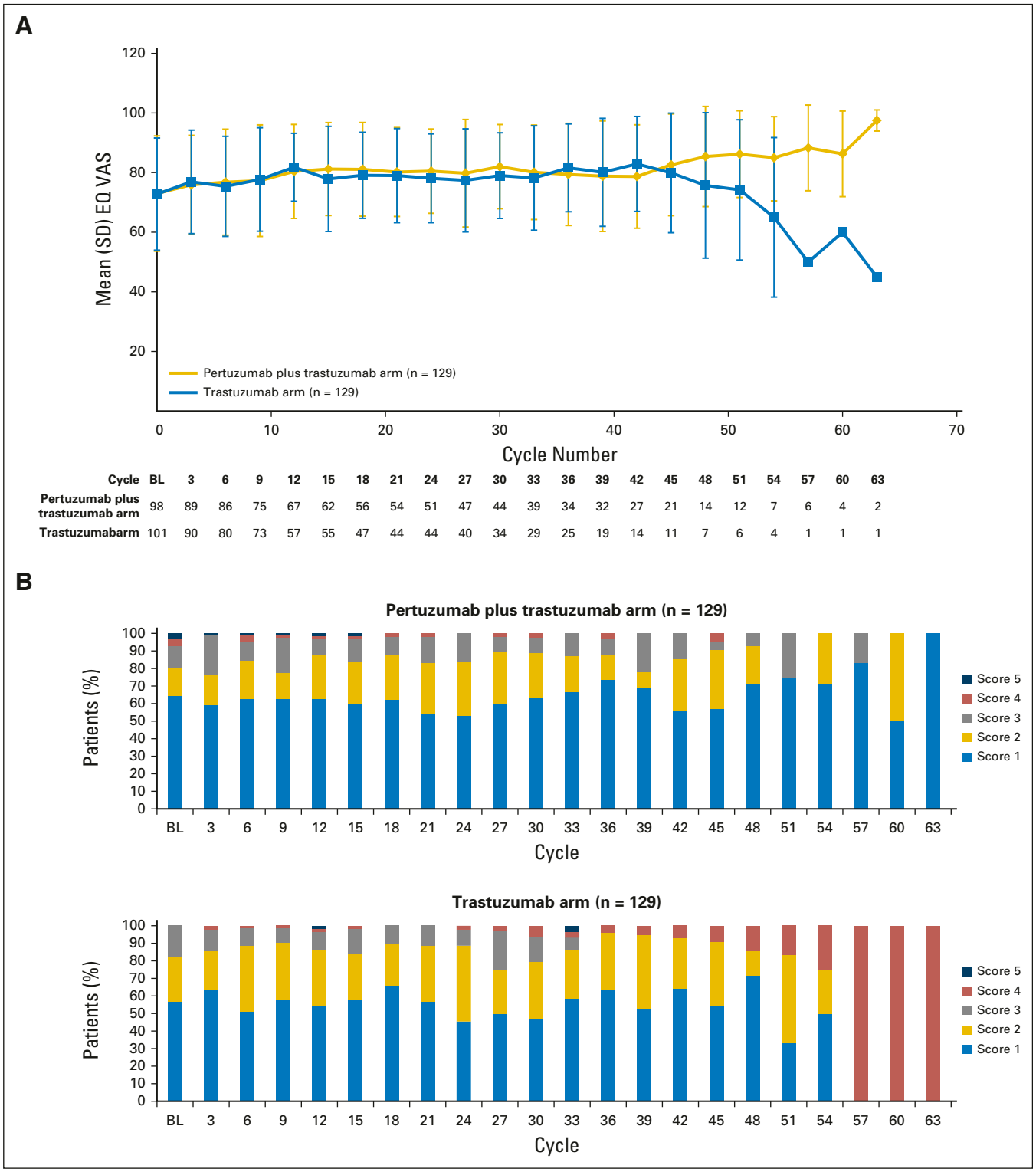


Fig A2. Mean left ventricular ejection fraction (LVEF) by cycle in the safety population.



Cycle	BL	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
Pertuzumab plus trastuzumab arm	98	89	86	75	67	62	56	54	51	47	44	39	34	32	27	21	14	12	7	6	4	2
Trastuzumabarm	101	90	80	73	57	55	47	44	44	40	34	29	25	19	14	11	7	6	4	1	1	1

Fig A3. (A) European Quality of Life (EQ) visual analog scale (VAS) by cycle. (B) Mobility. (C) Self-care. (D) Usual activities. (E) Pain/discomfort. (F) Anxiety/depression. Scores: 1, no problems; 2, slight problems; 3, moderate problems; 4, severe problems; and 5, extreme problems. BL, baseline; SD, standard deviation.

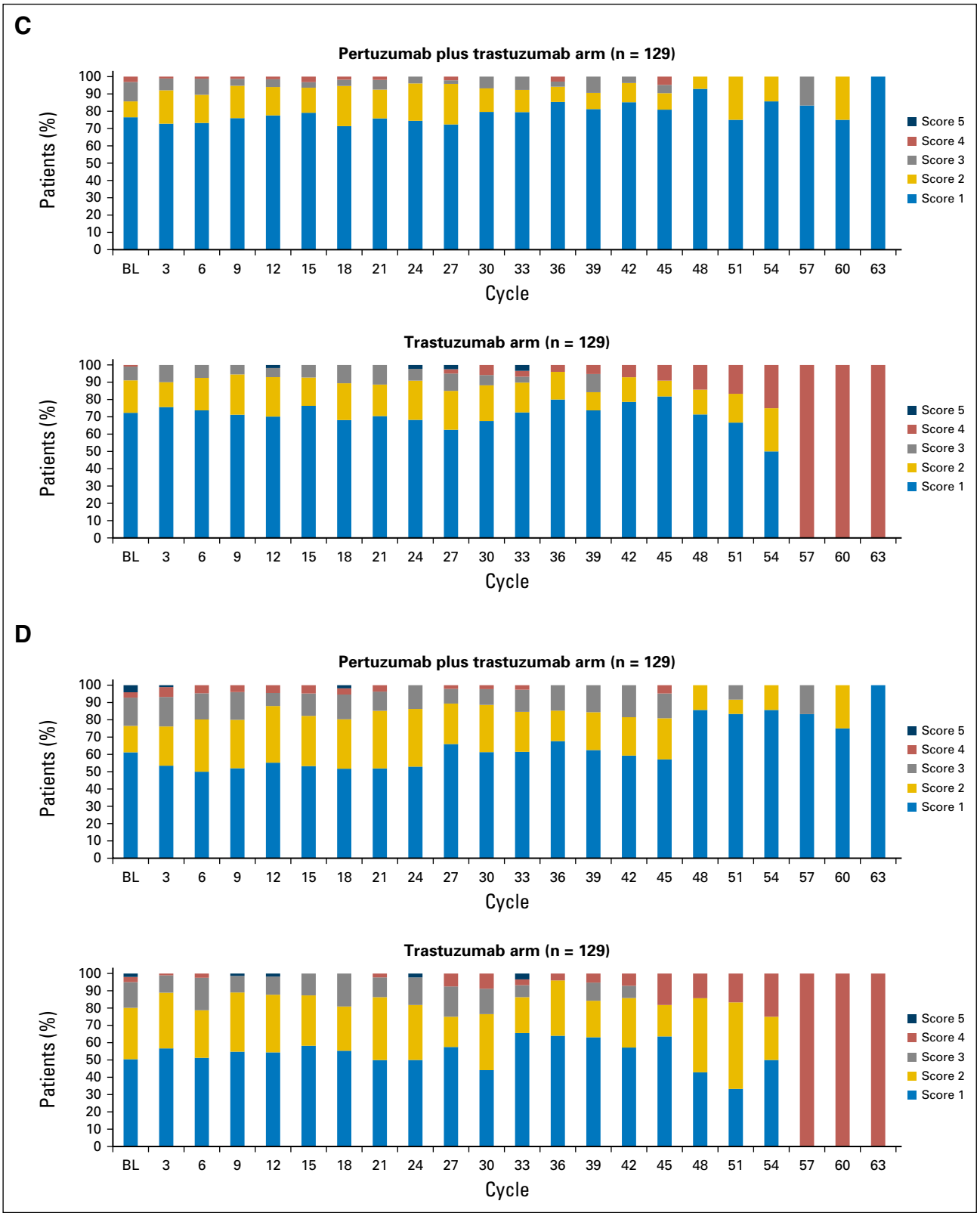


Fig A3. (Continued).

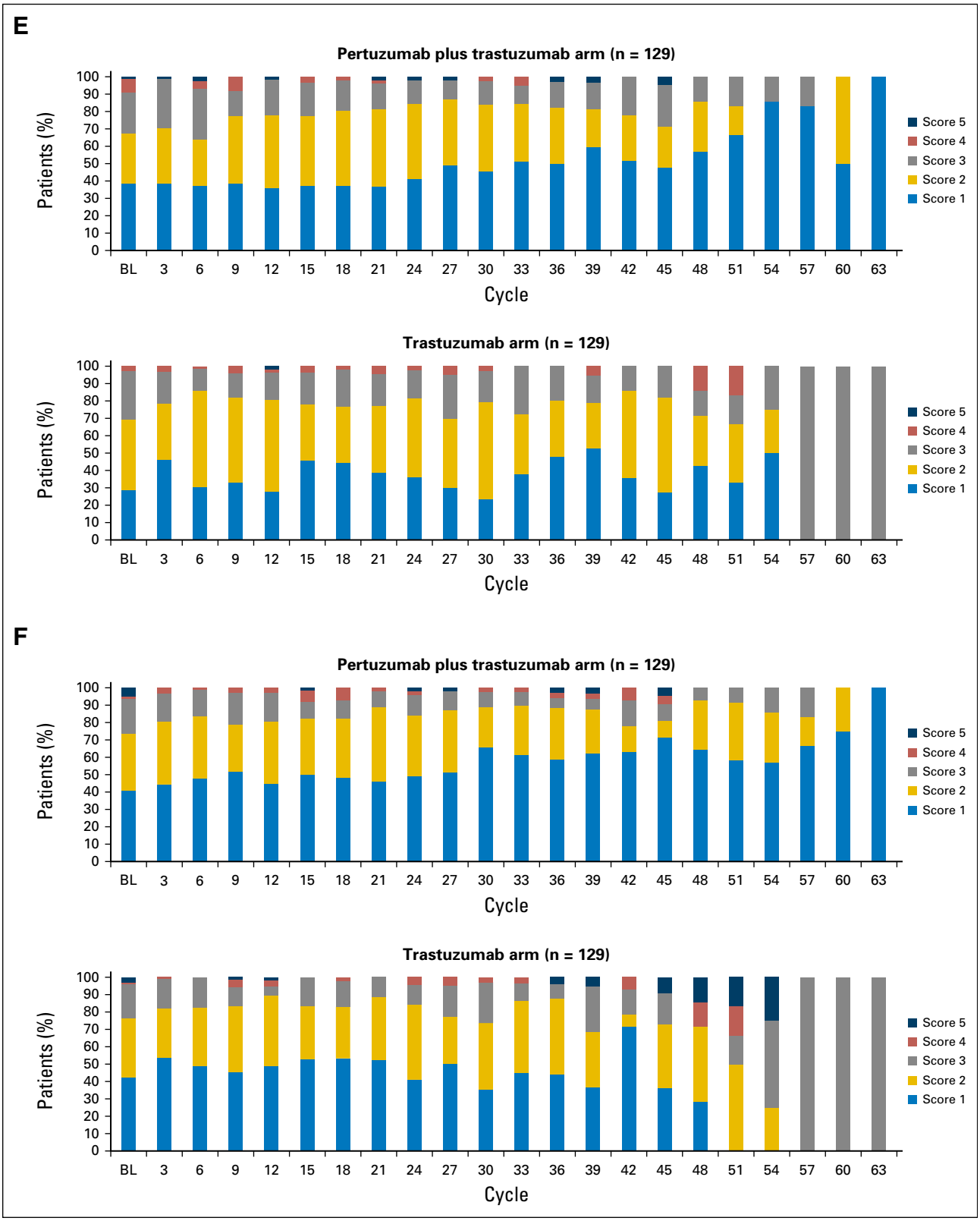


Fig A3. (Continued).

Table A1. Baseline Patient Demographics, Disease Characteristics, and Previous Systemic Therapies for Breast Cancer in Patients With and Without Induction Chemotherapy

Characteristic	With Induction Chemotherapy (n = 146)	Without Induction Chemotherapy (n = 112)
Female sex	146 (100)	112 (100)
Median age, years (range)	57 (35-77)	66.5 (31-89)
Age group, years		
< 65	122 (83.6)	50 (44.6)
≥ 65	24 (16.4)	62 (55.4)
< 75	137 (93.8)	73 (65.2)
≥ 75	9 (6.2)	39 (34.8)
World region		
Asia	14 (9.6)	12 (10.7)
Europe	81 (55.5)	71 (63.4)
North America	14 (9.6)	26 (23.2)
South America	37 (25.3)	3 (2.7)
ECOG PS at baseline*		
0	104 (71.2)	70 (62.5)
1	41 (28.1)	41 (36.6)
Stage at initial diagnosis†		
I	8 (5.5)	18 (16.1)
II	38 (26.0)	42 (37.5)
III	50 (34.2)	28 (25.0)
IV	49 (33.6)	24 (21.4)
Median time since initial BC diagnosis, months (range)	6.32 (0.3-232.3)	38.09 (0.3-365.8)
MBC/LABC at study entry		
LABC	10 (6.8)	5 (4.5)
MBC	136 (93.2)	107 (95.5)
Disease type at screening‡		
Visceral	110 (75.3)	72 (64.3)
Nonvisceral	36 (24.7)	40 (35.7)
No. of organs involved‡		
≥ 3	56 (38.4)	30 (26.8)
< 3	90 (61.6)	82 (73.2)
ER and PgR score		
ER-positive, PgR-positive, or both positive	146 (100.0)	112 (100.0)
IHC HER2 expression score		
0§	0	1 (0.9)
1+	0	0
2+§	13 (8.9)	25 (22.3)
3+	127 (87.0)	81 (72.3)
Not performed§	6 (4.1)	5 (4.5)
Previous systemic therapy for BC‖	68 (46.6)	66 (58.9)
Chemotherapy setting		
Neoadjuvant	26 (17.8)	12 (10.7)
Adjuvant	50 (34.2)	42 (37.5)
Anthracyclines	53 (36.3)	36 (32.1)
Taxanes	42 (28.8)	27 (24.1)
Trastuzumab setting		
Neoadjuvant	13 (8.9)	5 (4.5)
Adjuvant	33 (22.6)	21 (18.8)
Hormonal therapy setting		
Neoadjuvant	0	2 (1.8)
Adjuvant	53 (36.3)	52 (46.4)
Other¶	3 (2.1)	3 (2.7)

NOTE. Data presented as No. (%) unless otherwise indicated. Time since initial diagnosis was calculated relative to date of randomization. All tumors with IHC results that were scored as IHC 0 or IHC 2+, or those that did not have IHC tests performed, were confirmed as ISH–positive. HER2 and ER/PgR testing was performed locally. Patients may be counted under more than one treatment setting for prior systemic therapy for BC (eg, neoadjuvant/adjuvant).

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IHC, immunohistochemistry; ISH, in situ hybridization; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; PgR, progesterone receptor; PS, performance status.

*Missing one patient with induction chemotherapy in the pertuzumab plus trastuzumab arm and one patient without induction chemotherapy in the trastuzumab arm. Both patients were randomly assigned but not treated.

†Unknown in one patient in the pertuzumab plus trastuzumab arm with induction chemotherapy.

‡On the basis of baseline tumor assessment (target and nontarget lesions).

§All ISH–positive.

‖One patient in each arm received previous lapatinib (both in the with induction chemotherapy groups), and one patient in the pertuzumab plus trastuzumab arm received previous bevacizumab (without induction chemotherapy group).

¶Metastatic disease (n = 3), bone metastasis (n = 1), first-line metastatic (n = 1), and cancer treatment (n = 1).

Table A2. Treatment Exposure in the Safety Population

Treatment	Pertuzumab Plus Trastuzumab Arm	Trastuzumab Arm
Pertuzumab	(n = 127)	(n = 124)
Median No. of cycles (range)	18 (1-65)	—
Median exposure, months (range)	12.616 (0.03-44.22)	—
Median cumulative dose, mg (range)	7,980 (840-27,720)	—
Trastuzumab	(n = 127)	(n = 124)
Median No. of cycles (range)	18 (1-65)	15.5 (1-65)
Median exposure, months (range)	12.616 (0.03-44.22)	10.595 (0.03-44.45)
Median cumulative dose, mg (range)	110 (8-392)	95 (8-392)
Docetaxel	(n = 42)	(n = 37)
Median No. of cycles (range)	6 (0-8)	6 (0-8)
Median exposure, months (range)	3.515 (0.03-6.01)	3.515 (0.03-5.03)
Median cumulative dose, mg (range)	822.4 (129-1,464)	825 (160-1,407)
Paclitaxel	(n = 34)	(n = 33)
Median No. of cycles (range)	6 (0-8)	6 (0-8)
Median exposure, months (range)	3.910 (0.03-5.98)	3.943 (0-15.70)
Median cumulative dose, mg (range)	2,022.7 (138-3,706)	2,034 (0-3,790)
Anastrozole	(n = 32)	(n = 37)
Median No. of cycles (range)	13.5 (1-59)	14 (1-65)
Median exposure, months (range)	9.248 (0.69-41.49)	10.021 (0.69-45.11)
Median cumulative dose, mg (range)	14 (1-65)	14 (1-65)
Letrozole	(n = 85)	(n = 77)
Median No. of cycles (range)	18 (1-59)	17 (0-54)
Median exposure, months (range)	12.452 (0.66-40.71)	12.123 (0.99-37.49)*
Median cumulative dose, mg (range)	45 (3-148)	42.5 (0-135)

NOTE. Exposure is defined as (date of last dose of study treatment – date of first dose of study treatment) + 1, in months, where 1 month = 30.4375 days. Cumulative dose is defined as the sum of all doses of study treatment.
*(n = 76).

Table A3. Treatment Exposure According to Induction Chemotherapy Subgroups

Treatment	Pertuzumab Plus Trastuzumab Arm (n = 127)		Trastuzumab Arm (n = 124)	
	With Induction Chemotherapy	Without Induction Chemotherapy	With Induction Chemotherapy	Without Induction Chemotherapy
Pertuzumab	n = 74	n = 53	n = 0	n = 0
Median No. of cycles (range)	21 (2-65)	16 (1-59)	—	—
Median exposure, months (range)	14.505 (1.38-44.22)	10.875 (0.03-40.87)	—	—
Median cumulative dose, mg (range)	9,240 (1,680-27,720)	7,140 (840-25,200)	—	—
Trastuzumab	n = 74	n = 53	n = 69	n = 55
Median No. of cycles (range)	21 (1-65)	16 (1-59)	17 (1-55)	15 (1-65)
Median exposure, months (range)	14.489 (0.03-44.22)	10.875 (0.03-40.87)	11.203 (0.03-39.72)	10.119 (0.03-44.45)
Median cumulative dose, mg (range)	129 (8-392)	98 (8-358)	104 (8-332)	92 (8-392)
Docetaxel	n = 42	n = 0	n = 37	n = 0
Median No. of cycles (range)	6 (0-8)	—	6 (0-8)	—
Median exposure, months (range)	3.515 (0.03-6.01)	—	3.515 (0.03-5.03)	—
Median cumulative dose, mg (range)	822.4 (129-1,464)	—	825 (160-1,407)	—
Paclitaxel	n = 34	n = 0	n = 33	n = 0
Median No. of cycles (range)	6 (0-8)	—	6 (0-8)	—
Median exposure, months (range)	3.910 (0.03-5.98)	—	3.943 (0-15.70)	—
Median cumulative dose, mg (range)	2,022.7 (138-3,706)	—	2,034 (0-3,790)	—
Anastrozole	n = 16	n = 16	n = 16	n = 21
Median No. of cycles (range)	10.5 (1-42)	17 (3-59)	15 (3-49)	14 (1-65)
Median exposure, months (range)	6.801 (0.69-29.24)	12.025 (2.10-41.49)	10.793 (1.94-34.89)	9.265 (0.69-45.11)
Median cumulative dose, mg (range)	11 (1-65)	17 (3-59)	15 (3-49)	14 (1-65)
Letrozole	n = 48	n = 37	n = 41	n = 36
Median No. of cycles (range)	19.5 (1-59)	15 (1-52)	19 (0-45)	15 (3-54)
Median exposure, months (range)	13.667 (0.66-40.71)	10.743 (0.92-36.70)	13.536 (0.99-31.21)*	11.023 (2.04-37.49)
Median cumulative dose, mg (range)	48.8 (3-148)	37.5 (3-130)	50 (0-113)	37.5 (8-135)

NOTE. Exposure is defined as (date of last dose of study treatment – date of first dose of study treatment) + 1, in months, where 1 month = 30.4375 days. Cumulative dose is defined as the sum of all doses of study treatment.
*n = 40.

Table A4. Adverse Events in the Safety Population According to Induction Chemotherapy Subgroups

Adverse Event	Pertuzumab Plus Trastuzumab Arm (n = 127)		Trastuzumab Arm (n = 124)	
	With Induction Chemotherapy (n = 74)	Without Induction Chemotherapy (n = 53)	With Induction Chemotherapy (n = 69)	Without Induction Chemotherapy (n = 55)
Any adverse event	73 (98.6)	49 (92.5)	69 (100)	53 (96.4)
Grade ≥ 3 adverse events	49 (66.2)	15 (28.3)	33 (47.8)	15 (27.3)
Serious adverse events	28 (37.8)	14 (26.4)	15 (21.7)	9 (16.4)
Adverse event leading to discontinuation of pertuzumab	8 (10.8)	5 (9.4)	—	—
Adverse event leading to interruption of pertuzumab	25 (33.8)	9 (17.0)	—	—

NOTE. Data are given as No. of patients (%).