2023 ASCO® ANNUAL MEETING

3-year invasive disease-free survival (iDFS) of the strategy-based, randomized phase II PHERGain trial evaluating chemotherapy (CT) de-escalation in human epidermal growth factor receptor 2-positive (HER2[+]) early breast cancer (EBC)

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Declaration of Interests

Dr. JAVIER CORTÉS MD PhD

- **Consulting/Advisor:** Roche , Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp&Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Expres2ion Biotechnologies
- **Honoraria:** Roche , Novartis , Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, Merck Sharp&Dohme, Daiichi Sankyo
- **Research funding to the Institution:** Roche, Ariad pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F.Hoffman-La Roche, Guardanth health, Merck Sharp&Dohme, Pfizer, Piqur Therapeutics, Puma C, Queen Mary University of London
- **Stock:** MEDSIR, Nektar Pharmaceuticals, Leuko (relative)
- **Travel, accommodation, expenses:** Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, Astrazeneca, Gilead
- **Patents:** *Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. ISSUED Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1. Licensed*

Background

- The introduction of HER2-directed therapies has dramatically improved the outcome of patients with HER2[+] EBC, leading to the investigation of different de-escalation strategies.[1, 2]
- Early metabolic evaluation using ^{18}F-FDG PET/CT helps to recognize patients with an increased probability of pathological complete response (pCR).[3]
- PHERGain trial assessed the opportunity of CT de-escalation with a response-adapted strategy in HER2[+] EBC based on i) an early metabolic response by ^{18}F-FDG PET/CT to neoadjuvant trastuzumab plus pertuzumab (HP) and ii) the pathological response.[4]

1. Bueno Muiño C, et al. (2022). *Cancers*, 14(3), 512.
2. Pernas S, et al. (2021). *JCO Oncol Pract*, 17(6), 320-330.
3. Gebhart G, et al. (2013). *J Nucl Med,* 54:1862-8
4. Pérez-García, JM, et al. (2021). *Lancet Oncol*, 22(6), 858-871

CT: chemotherapy; EBC: Early breast cancer; HER2: Human Epidermal Growth Factor Receptor 2; ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

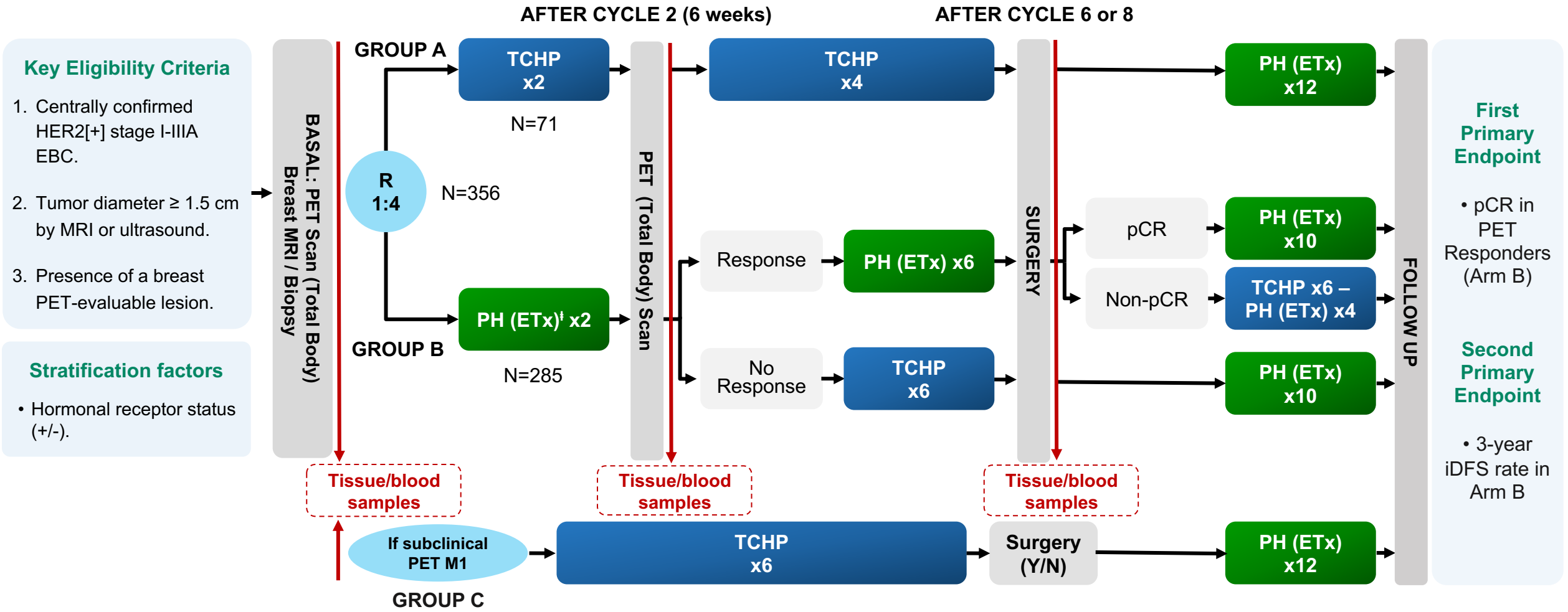
PHERGain Study Design

Key Eligibility Criteria

1. Centrally confirmed HER2[+] stage I-IIIA EBC.
2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.
3. Presence of a breast PET-evaluable lesion.

Stratification factors

- Hormonal receptor status (+/-).



First Primary Endpoint

- pCR in PET Responders (Arm B)

Second Primary Endpoint

- 3-year iDFS rate in Arm B

C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal), Adjuvant ETx up to 3 years from surgery; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; MRI: Magnetic resonance Imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin. ‡ All hormonal receptor-positive patients received ETx concomitantly with PH (except on chemotherapy).

- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0)

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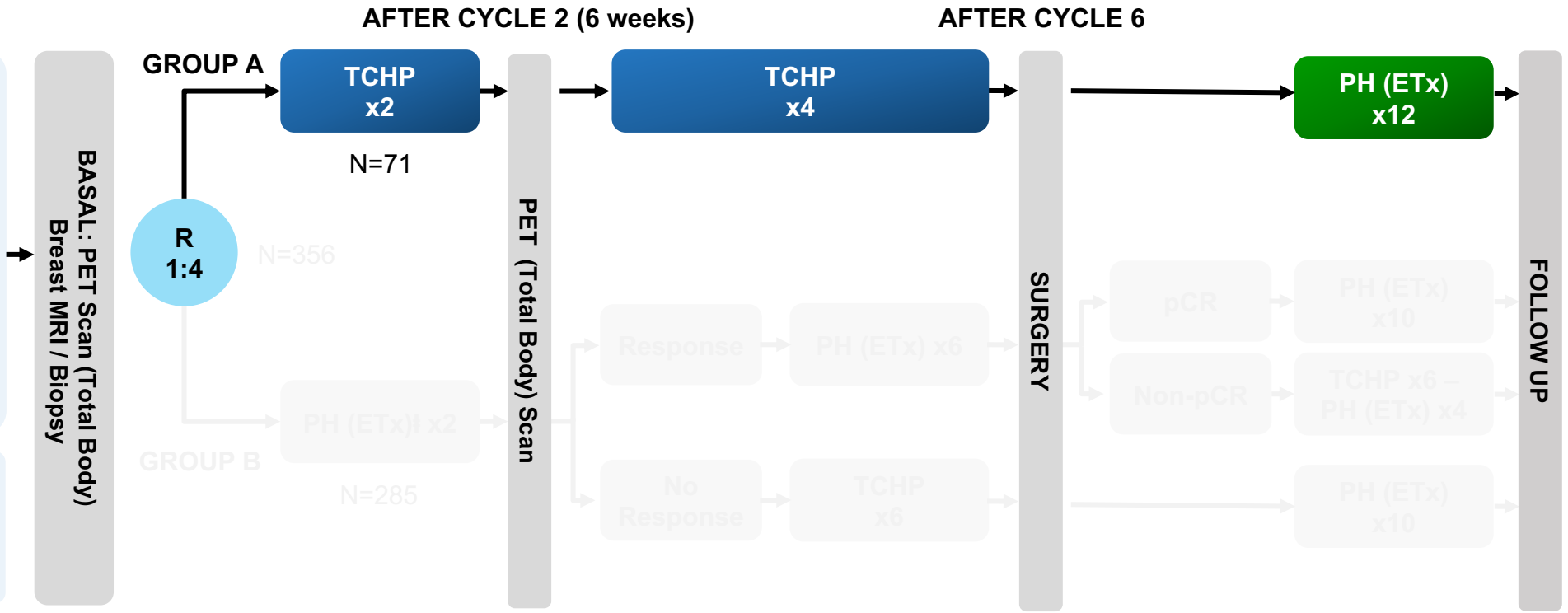

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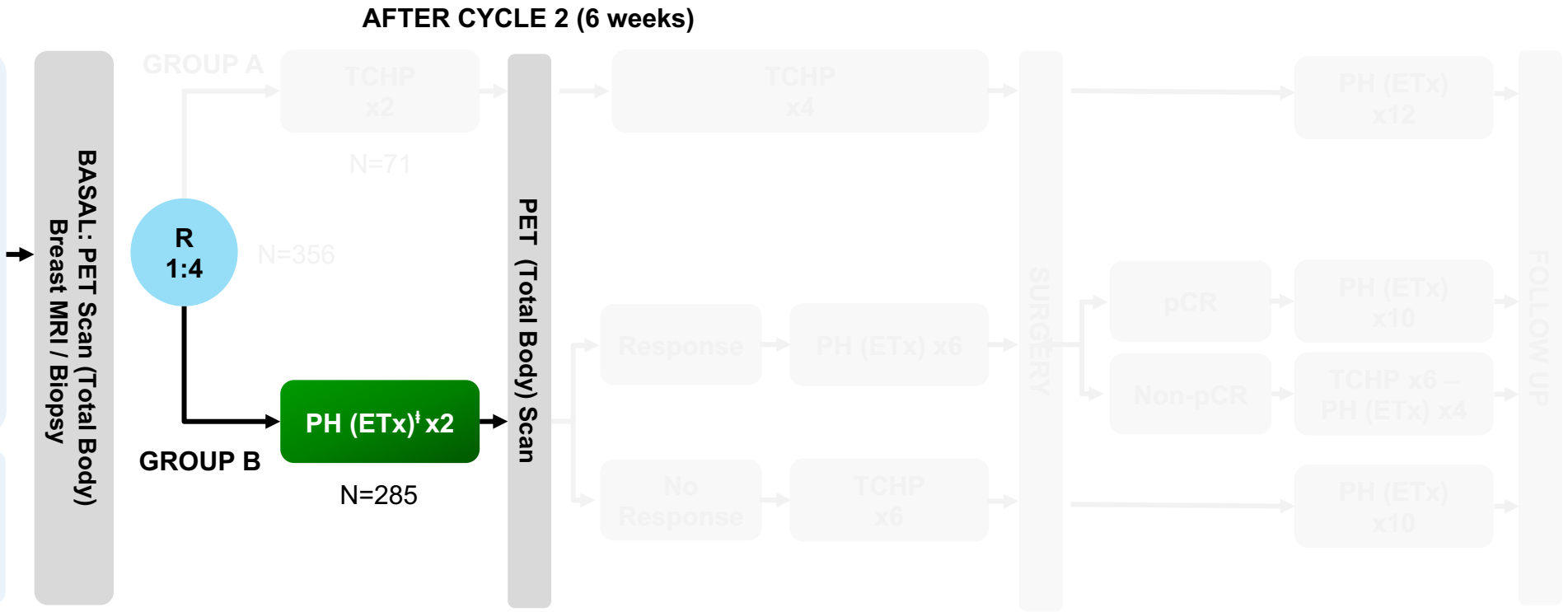

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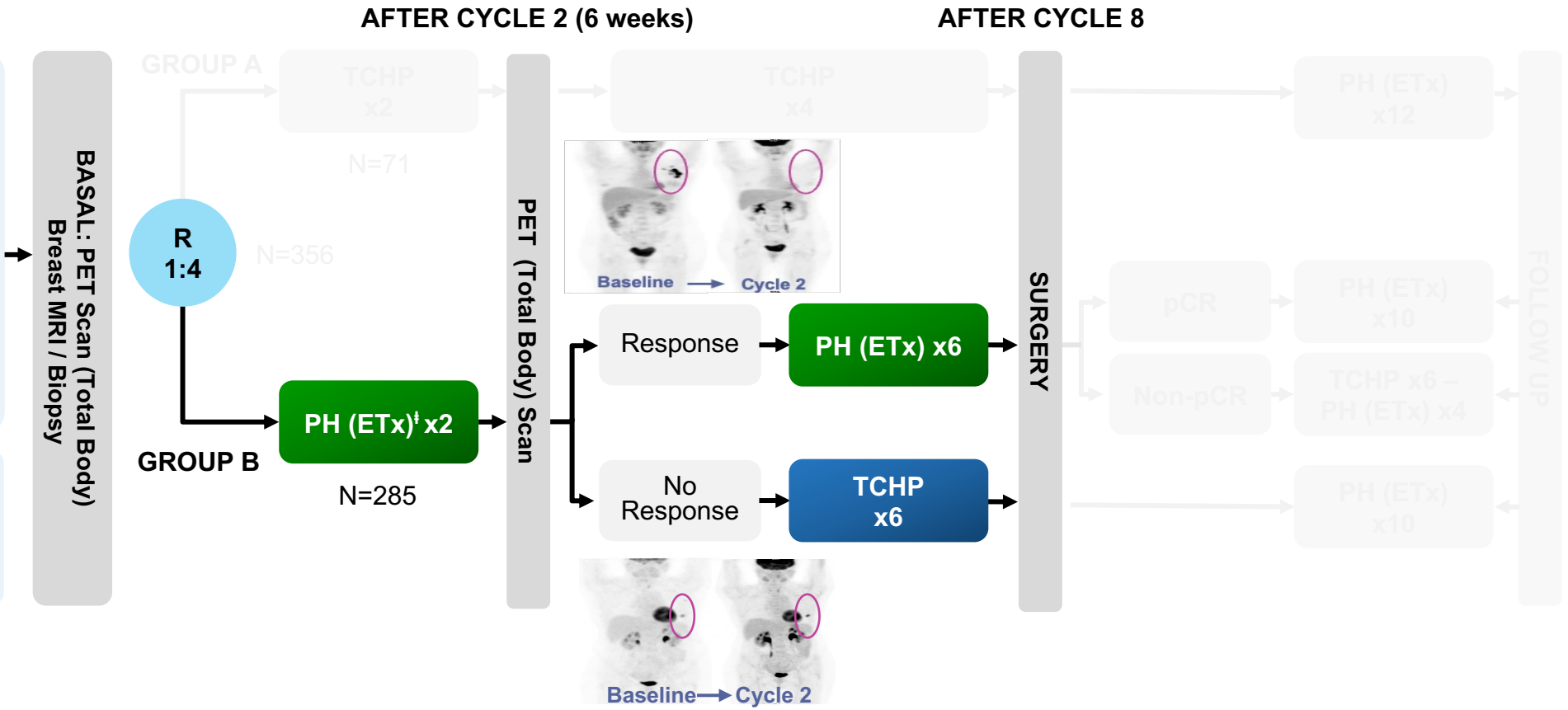

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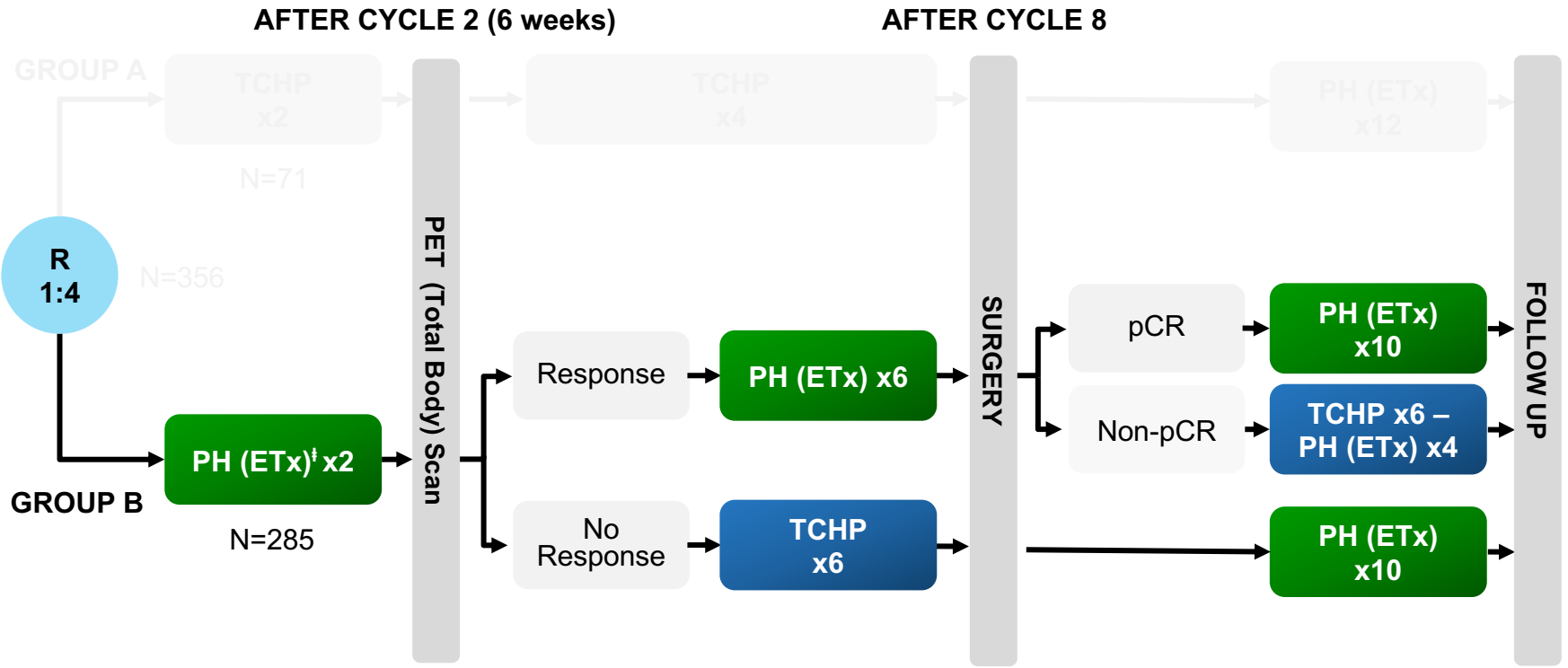

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- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0).

Key eligibility criteria

Inclusion criteria

- Stage I-IIIA invasive breast cancer.
- Tumor diameter ≥ 1.5 centimeter by MRI or ultrasound.
- At least one PET-evaluable breast lesion (SUV_{max} ≥ 1.5 x SUV_{mean} liver + 2 SD).
- Centrally confirmed HER2[+] breast cancer.
- Patient must have ER and PR status locally determined.

Exclusion criteria

- Previous chemotherapy, anti-HER2, radiotherapy, or endocrine therapy for invasive breast cancer.
- Evidence of metastatic disease by routine clinical assessment. Patients with subclinical M1 detected by PET will be included into Group C.

ER: Estrogen receptor; HER2: Human Epidermal Growth Factor Receptor 2; M1: Metastases; MRI: Magnetic resonance imaging; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; PR: Progesterone receptor; SD: Standard deviation; SUVmax: The maximum Standardized Uptake Value; SUVmean: The mean standardized uptake value.

Study Endpoints

Primary endpoints

- pCR (ypT0/isN0) in PET Responders (Group B)
- 3-year iDFS rate in Group B

Secondary endpoints

- pCR in Group A and Group B
- pCR by PET response / Other definitions of pCR
- Breast-conserving surgery
- Tumor response by MRI
- Optimal PET cut-off SUV_{max} for pCR
- 3-year iDFS in Group A
- 3-year DDFS in Group A and Group B
- 3-year EFS in Group A and Group B
- 3-year OS in Group A and Group B
- Long term outcomes per group
- Health-related quality of life
- Toxicity (CTCAE v4.0)

CTCAE v4.0: Common Terminology Criteria for Adverse Events version 4.0; DDFS: Disease-free survival; EFS: Event-free survival; iDFS: Invasive disease-free survival; OS: Overall survival; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response; SUV_{max}: The maximum Standardized Uptake Value

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3-year iDFS Primary Endpoint

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Stratification factors

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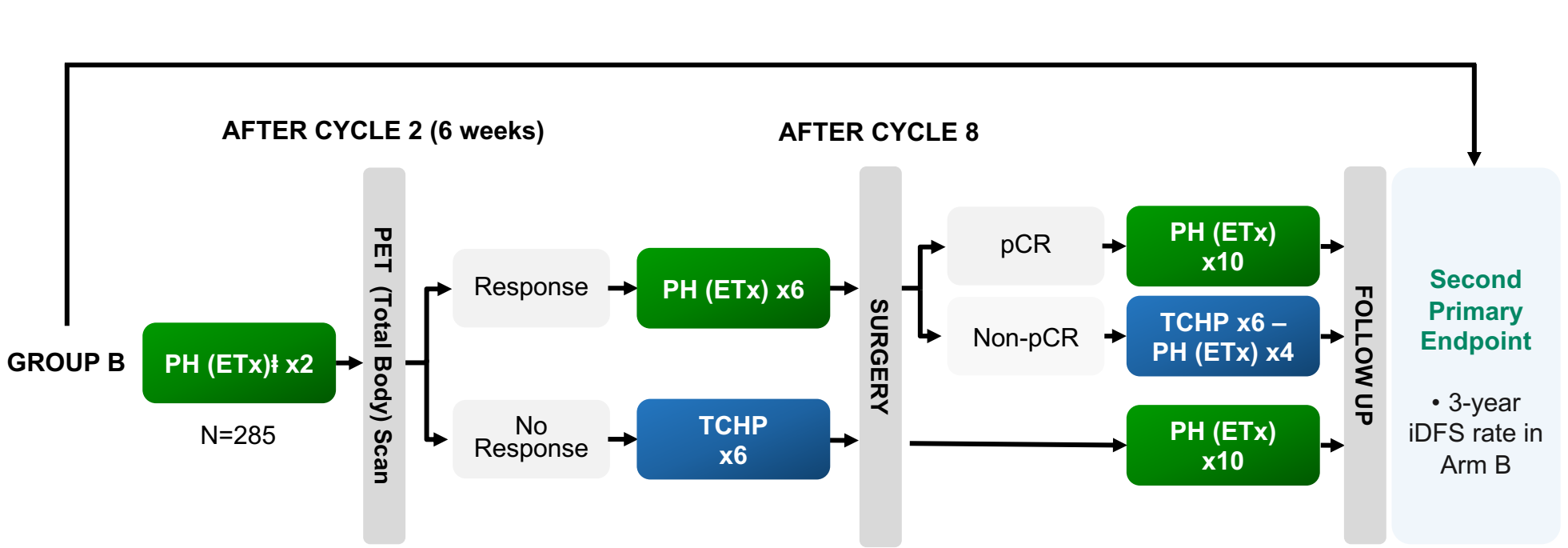

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3-year iDFS Primary Endpoint

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Stratification factors

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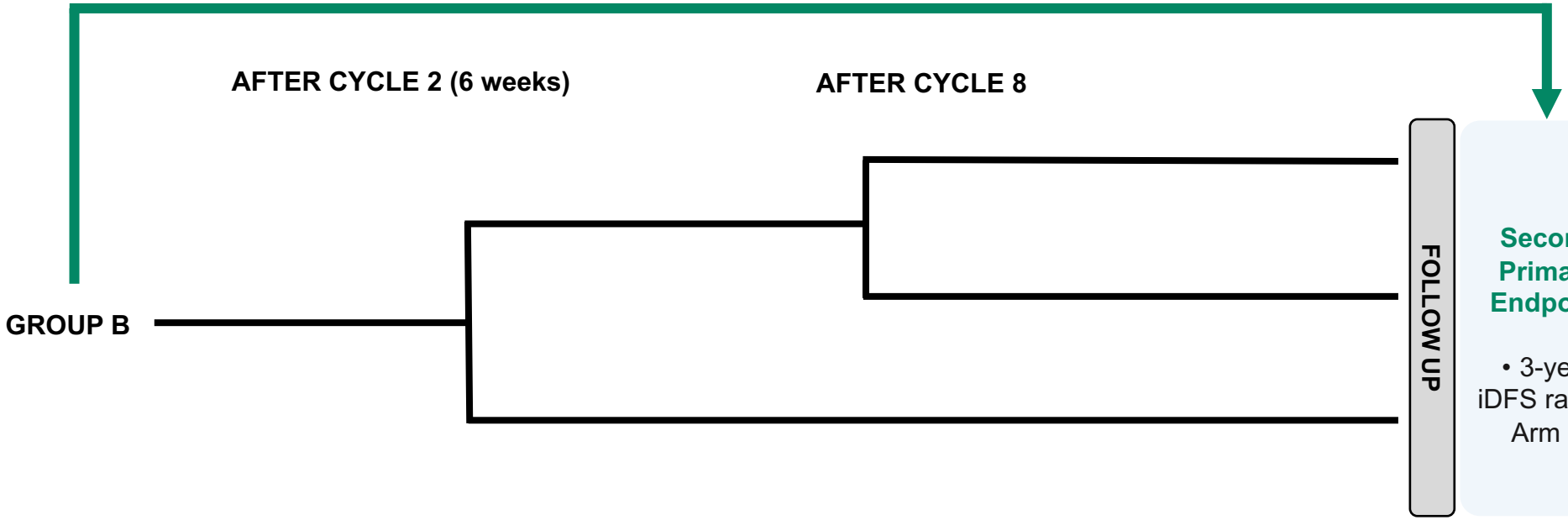
BASAL: PET Scan (Total Body) Breast MRI / Biopsy



Second Primary Endpoint

- 3-year iDFS rate in Arm B

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Statistical Considerations

First Primary Endpoint

- Decisions are based on one-sided exact binomial test (Null hypothesis: pCR ≤20%)
- This analysis was designed to attain an 80% power (Alternative hypothesis: pCR ≥30%) at α = 2.5% one-sided level.
- We considered a 10% dropout rate.

Second Primary Endpoint: 3-year iDFS assessed by investigator in patients with surgery (Group B)

- Decisions are based on one-sided exact binomial test (Null hypothesis: 3-year iDFS ≤89%)
- This analysis was designed to attain an 80% power (Alternative hypothesis: iDFS ≥95%) at α = 2.5% one-sided level.
- We considered a 25% dropout rate.

Safety assessed in all patients who received at least one dose of study treatment

iDFS: Invasive disease-free survival; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response.

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iDFS: Invasive disease-free survival; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response.

Summary of Analysis Population

356 patients randomized 1:4 from June 2017 to April 2019
Data cutoff: February 24, 2023
Median follow-up: 3.5 (0 to 5.3) years

Group A
Chemotherapy + Trastuzumab + Pertuzumab

- 71 allocated
- 68 (95.8%) started study treatment
- 63 (88.7%) had documented surgery

All randomized (N = 71)

- ITT set for 3-year iDFS: n = 63
- Safety-evaluable set: n = 68

Group B
Trastuzumab + Pertuzumab ± ET

- 285 allocated
- 283 (99.3%) started study treatment
- 267 (93.7%) had documented surgery

All randomized (N = 285)

- ITT set for primary analysis: n = 267
- Safety-evaluable set: n = 283

Baseline Characteristics

ITT population	Group A (N = 71)	Group B (N = 285)
Menopausal status		
Premenopausal	37 (52.1%)	146 (51.2%)
Postmenopausal	34 (47.9%)	139 (48.8%)
ECOG Performance status		
0	69 (97.2%)	264 (92.6%)
1	2 (2.8%)	21 (7.4%)
Histologically confirmed lesions		
Unifocal	56 (78.9%)	217 (76.1%)
Multifocal	15 (21.1%)	68 (23.9%)
Stage		
I	9 (12.7%)	24 (8.4%)
II	50 (70.4%)	219 (76.8%)
III	12 (16.9%)	42 (14.7%)

Data are *n* (%), unless otherwise specified.

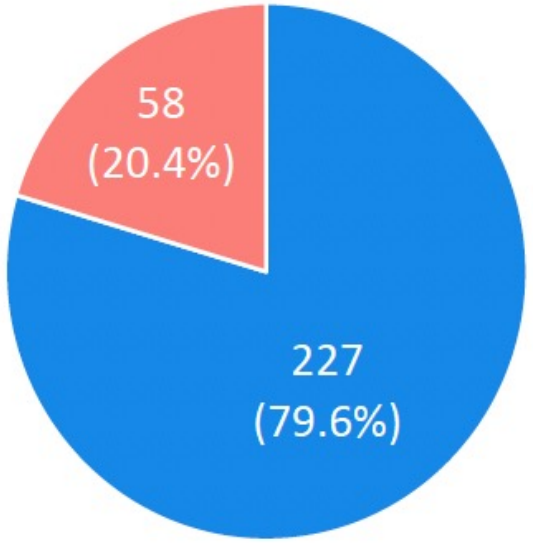
Baseline Characteristics (cont.)

ITT population	Group A (N = 71)	Group B (N = 285)
Nodal status		
Positive	32 (45.1%)	140 (49.1%)
Negative	39 (54.9%)	145 (50.9%)
Hormone receptor status		
ER-negative and PR-negative	27 (38.1%)	93 (32.6%)
ER-positive and/or PR-positive	44 (61.9%)	192 (67.4%)
HER2 IHC score and FISH analysis		
2+ and FISH-positive	13 (18.3%)	64 (22.5%)
3+	58 (81.7%)	221 (77.5%)

Data are *n* (%), unless otherwise specified.

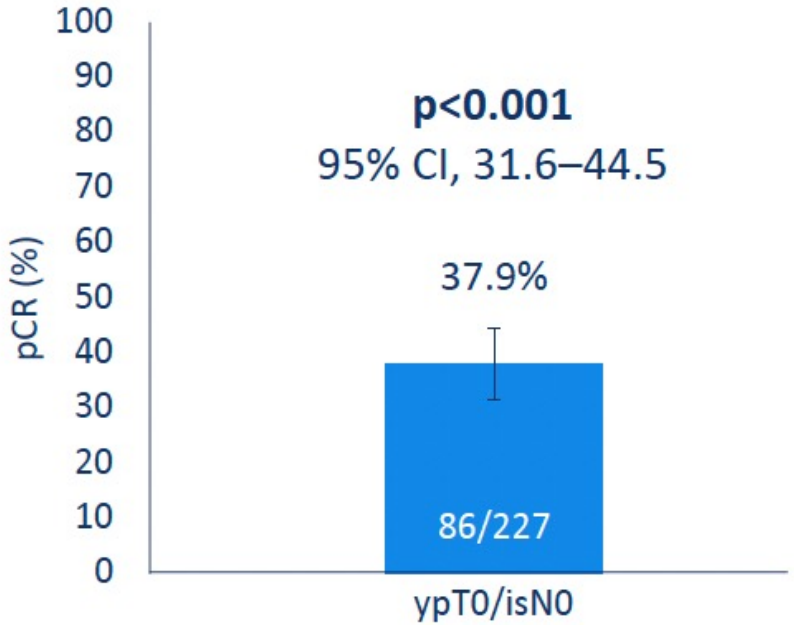
Primary Endpoint: pCR in ^{18}F-FDG-PET responders in group B

PET Responders and Non-Responders



PET Responder PET Non-Responder

pCR rate



Null hypothesis: pCR ≤20%

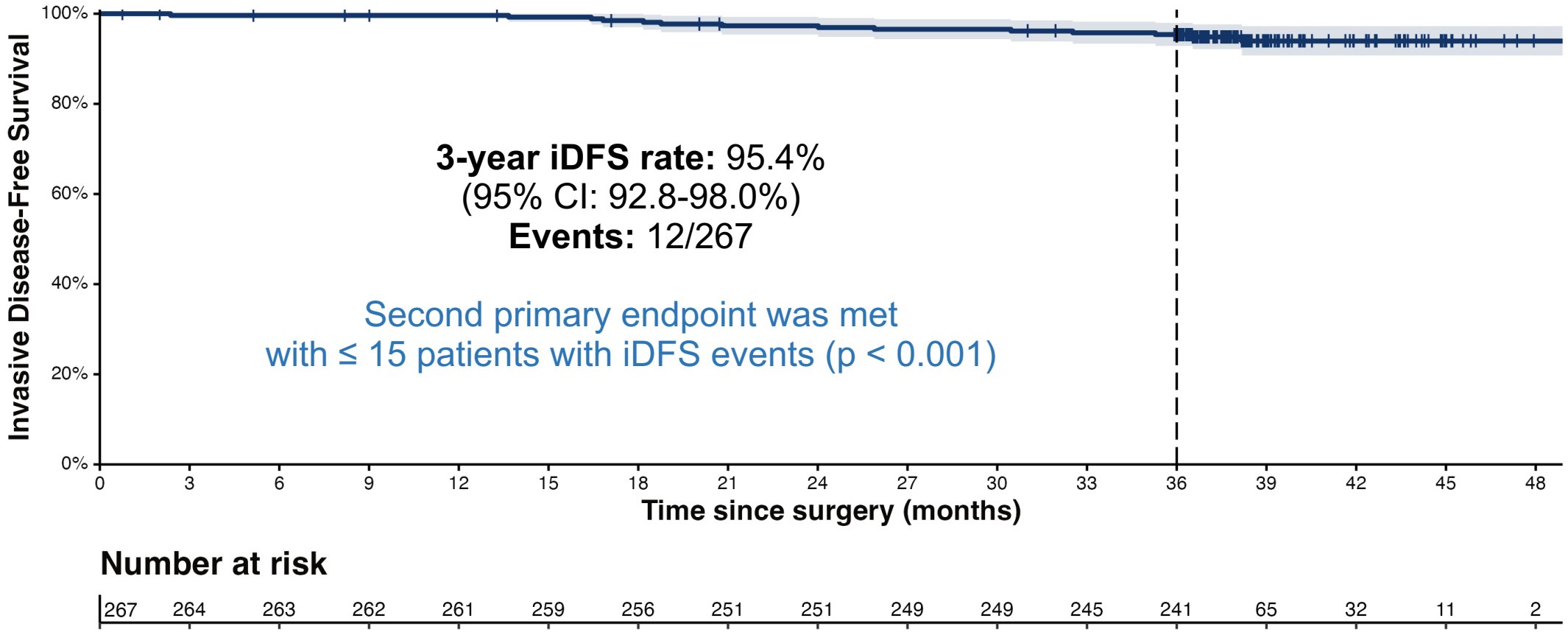
pCR was observed in patients with both HER2++ and HER2+++, pts with stage II and stage III, and pts ER+ and ER-.

Pérez-García, JM, et al. (2021). *Lancet Oncol*, 22(6), 858-871.

CI: Confidence interval; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response (ypT0/isN0).

Primary Endpoint: 3-year iDFS rate in group B

ITT population



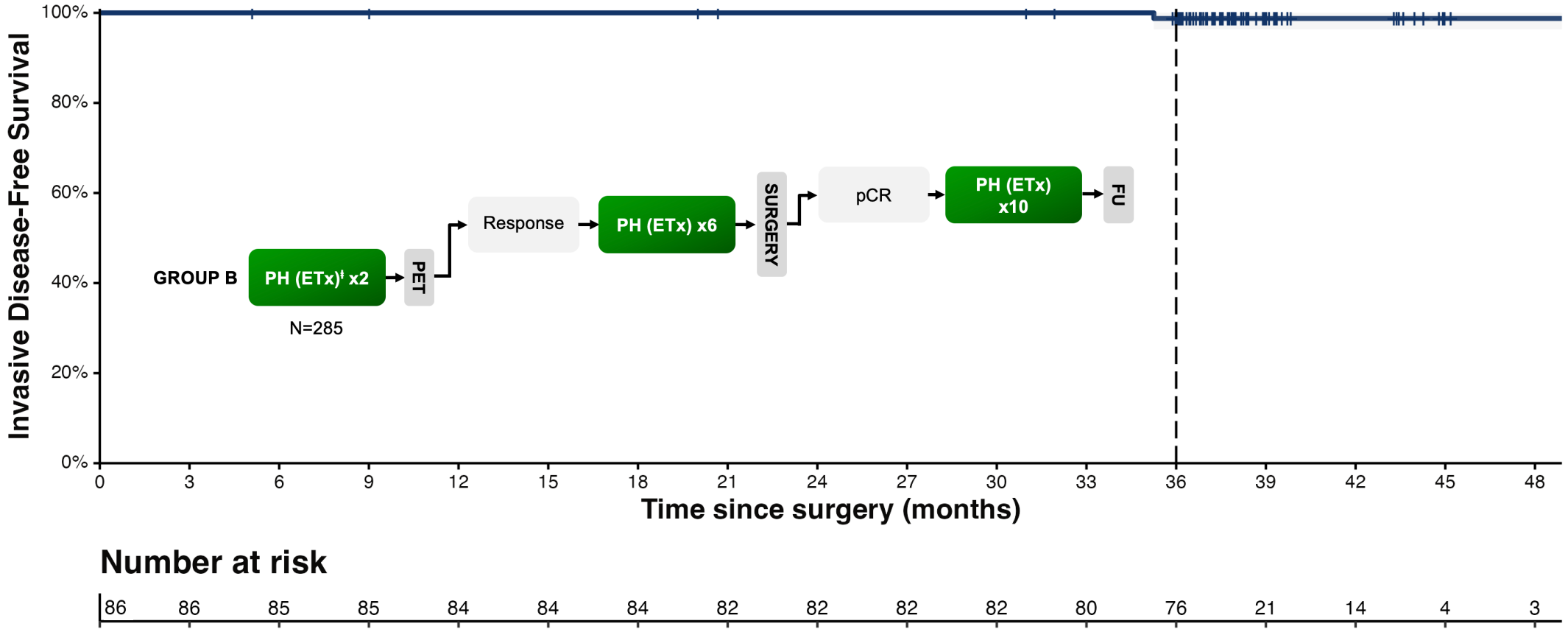
Primary Endpoint: 3-year iDFS events in group B

ITT population

3-year iDFS	Group B (N = 267)
iDFS events	**12 (4.5%)**
Relapse	**11 (4.1%)**
Ipsilateral invasive breast tumor recurrence	1 (0.4%)
Regional invasive breast cancer recurrence	2 (0.8%)
Contralateral invasive breast cancer	0 (0.0%)
Distant recurrence	8 (3.0%)
Non-related death without recurrence	**1 (0.4%)**

Data are *n* (%), unless otherwise specified.

Subgroup analysis:
3-year iDFS rate without CT in PET responders with pCR (n=86)



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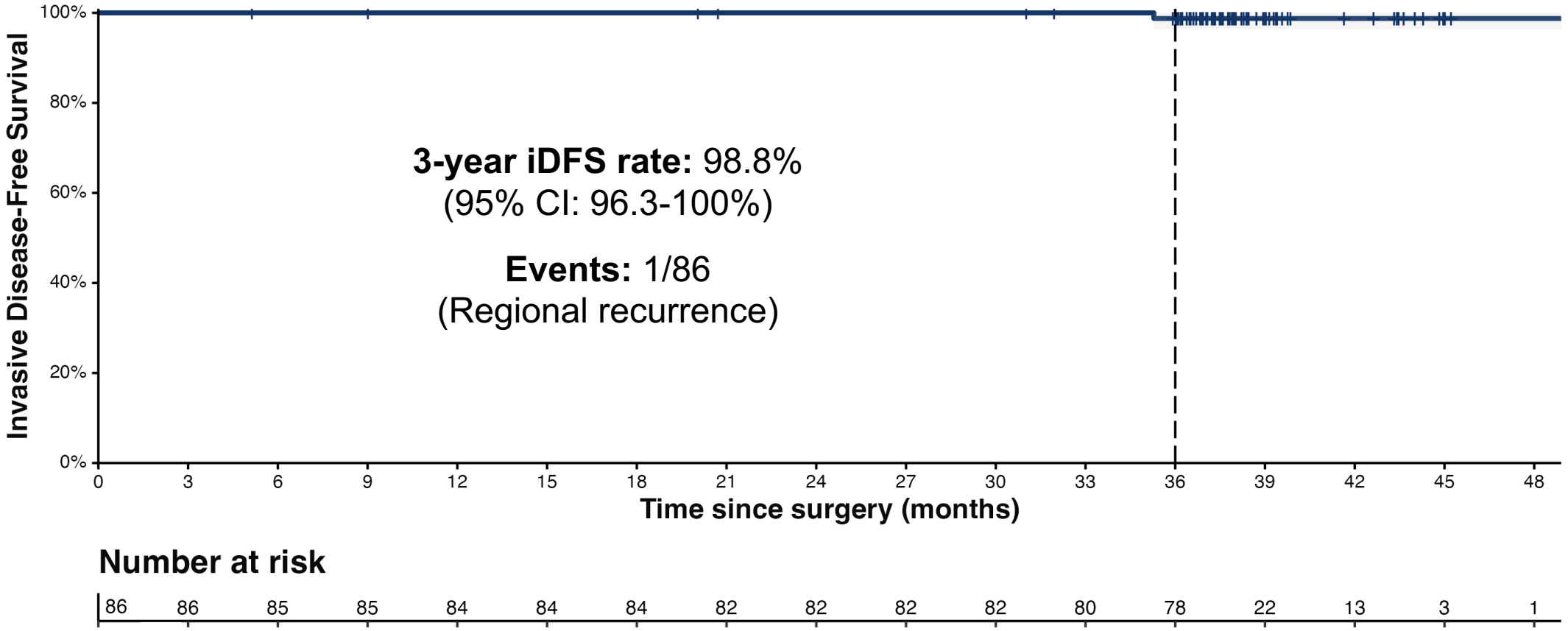
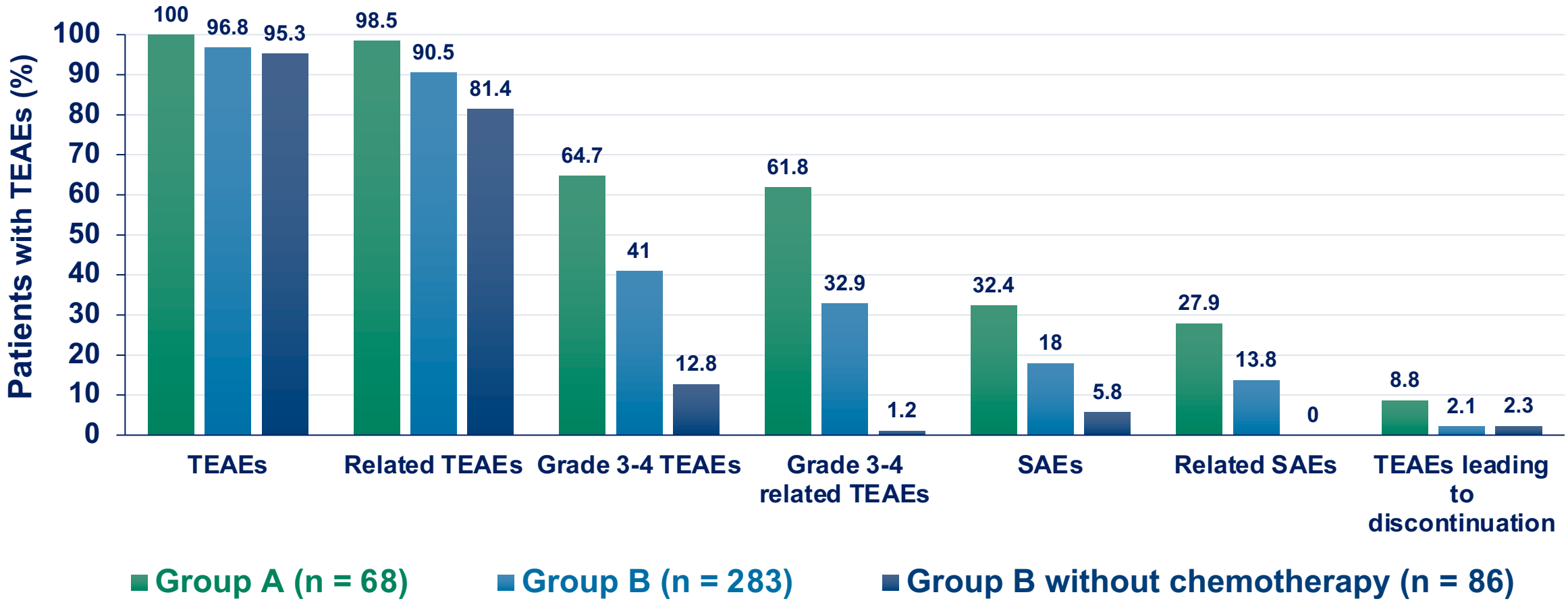


Efficacy Analysis: Summary of other efficacy endpoints

	Group A (n = 63)	Group B (n = 267)	Group B without CT (n = 86)
3-year iDFS	**98.3%**	**95.4%**	**98.8%**
(95% CI)	(95.1–100%)	(92.8–98.0%)	(96.3–100%)
3-year DDFS	**98.3%**	**96.5%**	**100%**
(95% CI)	(95.1–100%)	(94.3–98.8%)	(100–100%)
	(n = 71)	**(n = 285)**	**(n = 86)**
3-year EFS	**98.4%**	**93.5%**	**98.8%**
(95% CI)	(95.3–100%)	(90.7–96.5%)	(96.6–100%)
3-year OS	**98.4%**	**98.5%**	**100%**
(95% CI)	(95.3–100%)	(97.1–100%)	(100–100%)

None of these comparisons between the groups reached statistical significance.
iDFS and DDFS are defined from the time of surgery; EFS and OS are defined from randomization.

Safety Analysis: Summary of safety data



There was **no death** related to the study treatment.

Safety Analysis: TEAEs occurring in more than 20% of patients

	Group A n = 68		Group B n = 283		Group B without CT n = 86	
	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3
Any TEAEs	24 (35%)		155 (55%)		69 (80%)	11 (13%)
Haematological						
Anaemia	22 (32%)	5 (7%)	67 (24%)	21 (7%)	8 (9%)	0
Neutropenia	7 (10%)	19 (28%)	22 (8%)	22 (8%)	0	1 (1%)
Thrombocytopenia	14 (21%)	3 (4%)	34 (12%)	34 (12%)	0	0
Febrile neutropenia	0	14 (21%)	1 (0%)	1 (0%)	0	0
Non-haematological						
Fatigue	47 (69%)	11 (16%)	169 (60%)	19 (7%)	46 (53%)	0
Diarrhoea	45 (66%)	7 (10%)	177 (63%)	16 (6%)	48 (56%)	0
Nausea	38 (56%)	0	106 (37%)	5 (2%)	18 (21%)	0
Stomatitis	24 (35%)	6 (9%)	83 (29%)	3 (1%)	19 (22%)	0
Alopecia	23 (34%)	1 (1%)	77 (27%)	2 (1%)	4 (5%)	0
Vomiting	21 (31%)	1 (1%)	63 (22%)	5 (2%)	8 (9%)	0
Rash	14 (21%)	1 (1%)	70 (25%)	1 (0%)	19 (22%)	0
Arthralgia	20 (29%)	0	52 (18%)	0	23 (27%)	0
Dysgeusia	14 (21%)	0	40 (14%)	0	4 (5%)	0

Data are *n* (%). TEAEs: Treatment Emergent Adverse Events. No deaths occurred in the neoadjuvant setting.
Other grade 4 TEAEs in group A: Hyperthermia, Hypokalaemia, and Leukopenia. Other grade 4 TEAEs in group B: Gastrointestinal toxicity, Post procedural infection, and Thrombocytopenia.

Conclusions

- The PHERGain study also meets the second primary endpoint with a 3-year iDFS of 95.4% in patients in group B.
- These results are in line with those reported using the combination of CT and HER2-targeted therapies for the same patient population.
- No unexpected safety signals were identified.
- Among CT-free patients treated with trastuzumab and pertuzumab (group B with PET response and pCR), 3-year iDFS was 98.8%.
- This strategy identifies about one in three of HER2[+] EBC pts who can safely omit CT with significantly reduced toxicity.

CT: chemotherapy; EBC: Early breast cancer; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR, Pathological complete response (ypT0/isN0).

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