Chemotherapy (CT) De-Escalation using an FDG-PET/CT (PET) and Pathological Response-Adapted Strategy in HER2[+] Early Breast Cancer (EBC). PHERGAIN trial

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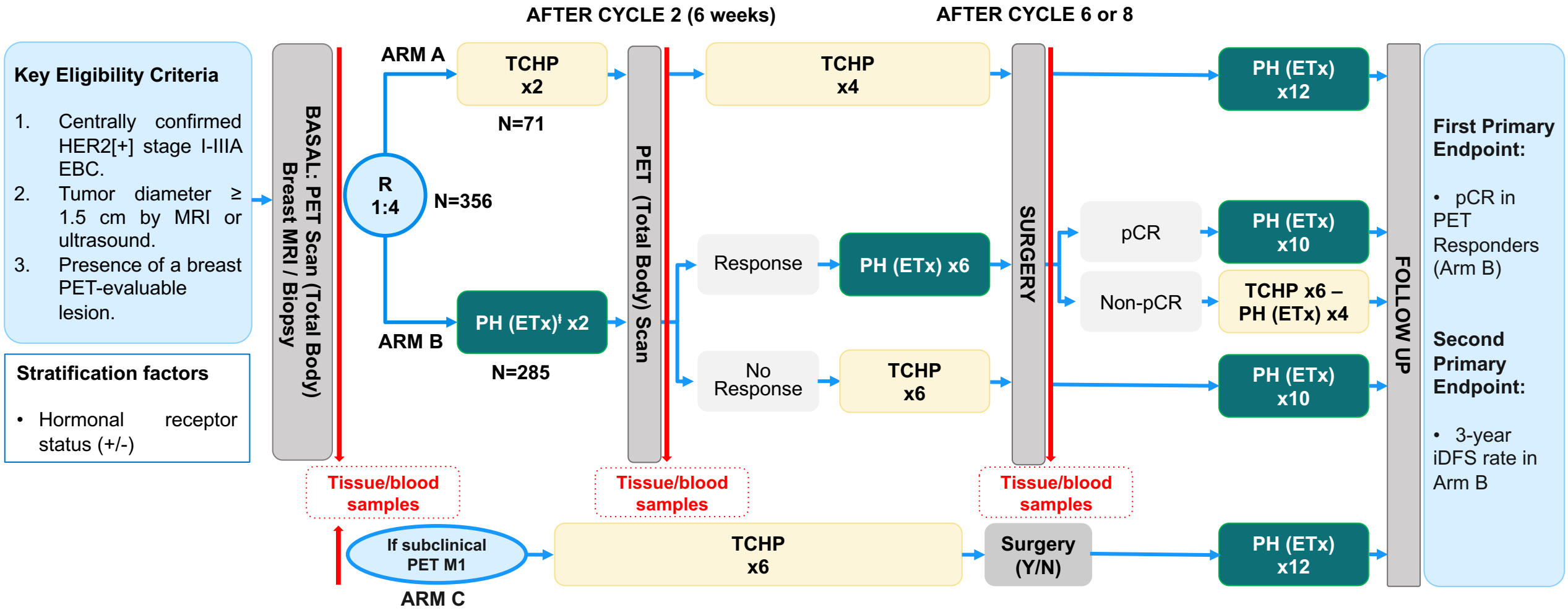
Background

- The introduction of HER2-directed therapies has dramatically improved the outcome of patients (pts) with HER2[+], leading to the investigation of different de-escalation strategies.
- The neoadjuvant scenario is the preferred setting to evaluate treatment de-escalation, considering the association between pathological complete response (pCR) and long-term outcome.[1]
- Chemotherapy (CT)-free dual blockade with trastuzumab-based regimens have shown promising pCR rates.[2-4]
- Early metabolic evaluation using ^{18}F-FDG PET/CT (PET) might help to recognize pts with an increased probability of pCR.[5]
- PHERGAIN trial assessed early metabolic response by PET to neoadjuvant trastuzumab plus pertuzumab (HP) and the opportunity of CT de-escalation with a response-adapted strategy in HER2[+] EBC.

1. Cortazar P et al. *The Lancet* 2014; 384:164-172
2. Llombart-Cussac A et al. *Lancet Oncol* 2017;18:545-554
3. Gianni L et al. *Lancet Oncol* 2012; 13:25-32
4. Nitz UA et al. *Ann Oncol* 2017; 28:2768-2772
5. Gebhart G, et al. *J Nucl Med.* 2013;54:1862-8.

PHERGAIN Study Design



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. ǂ All hormonal receptor-positive patients will receive 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).

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 (+/-)

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

R 1:4 N=356

ARM A → TCHP x2 N=71

ARM B → PH (ETx)[‡] x2 N=285

Tissue/blood samples

AFTER CYCLE 2 (6 weeks)

AFTER CYCLE 6 or 8

Tissue/blood samples

Tissue/blood samples

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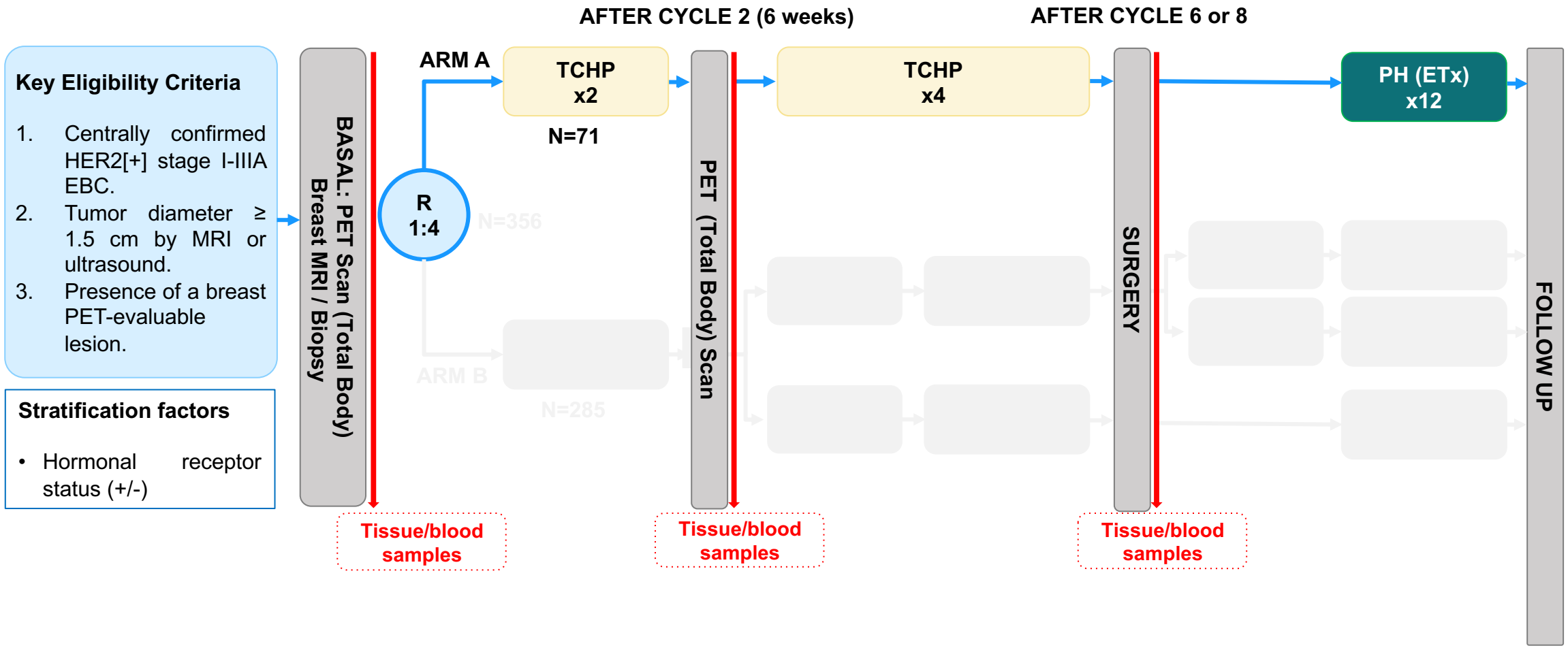

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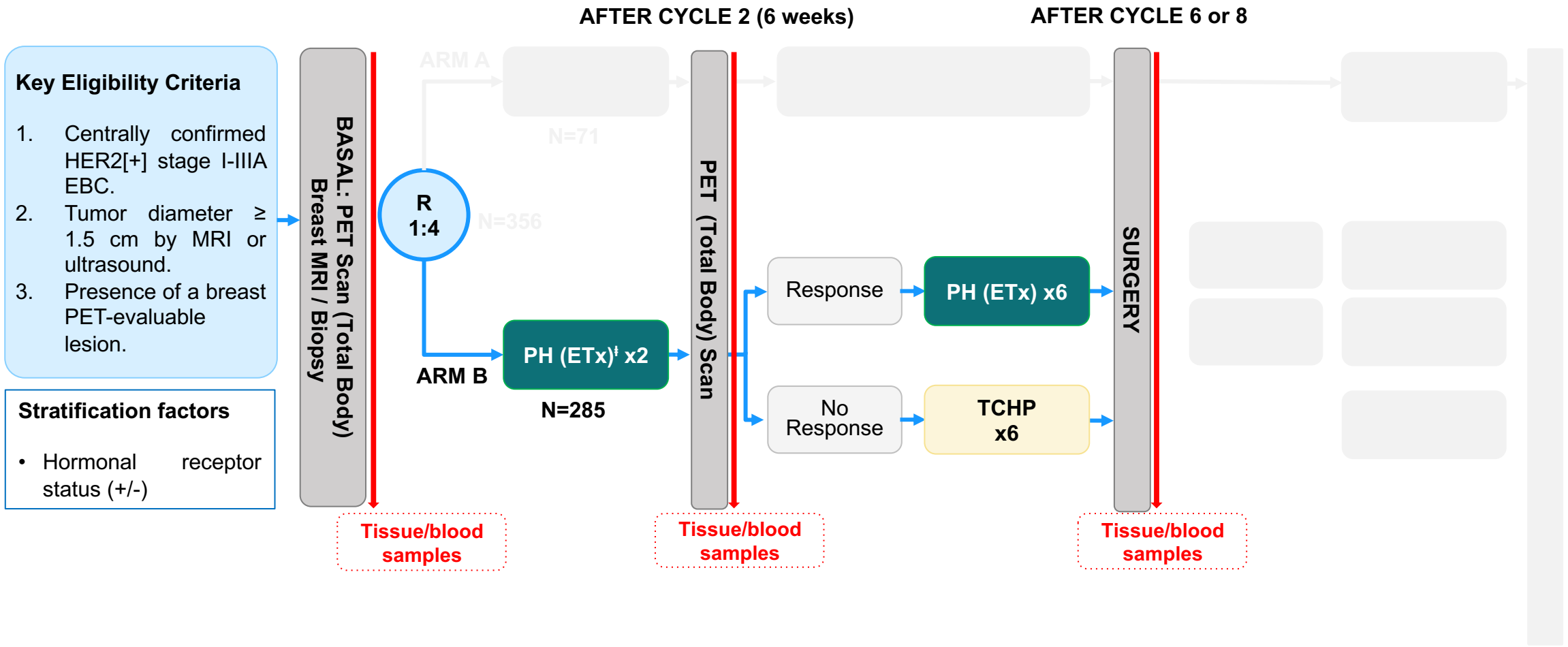

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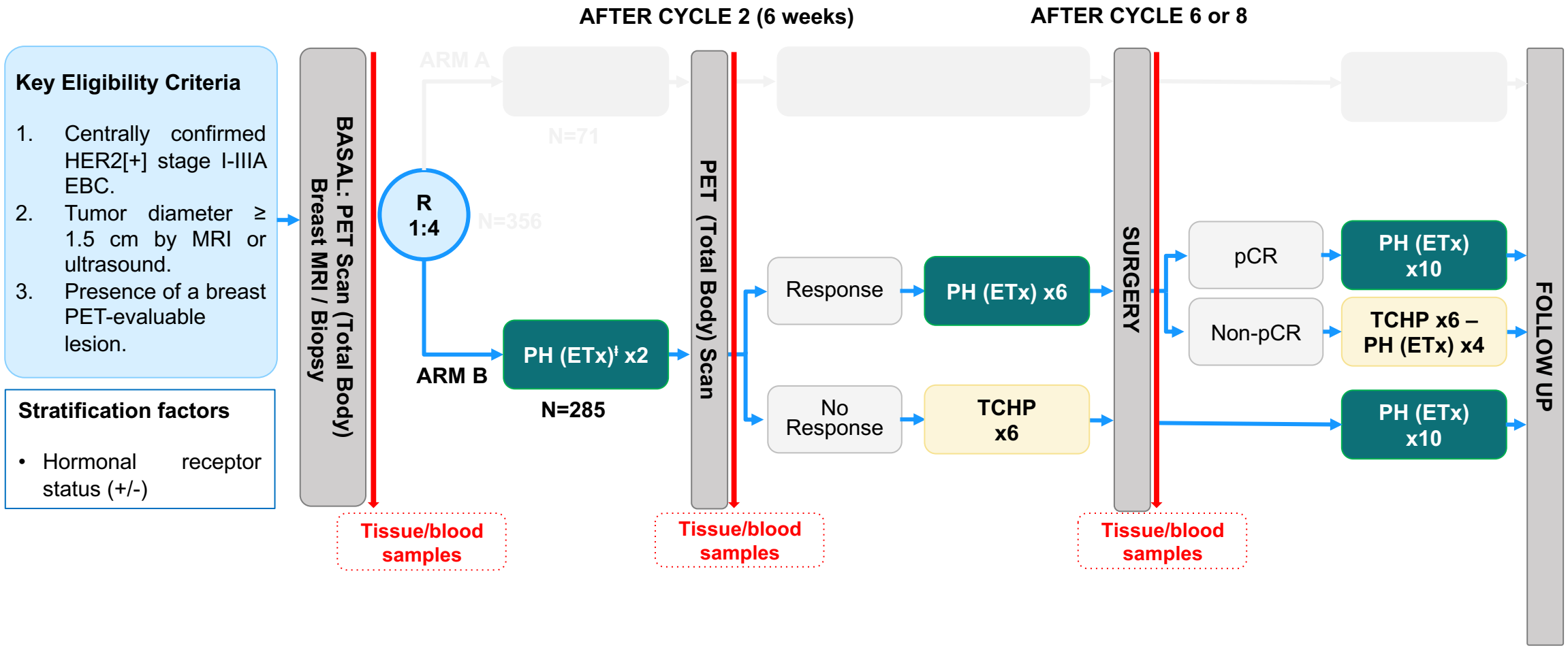

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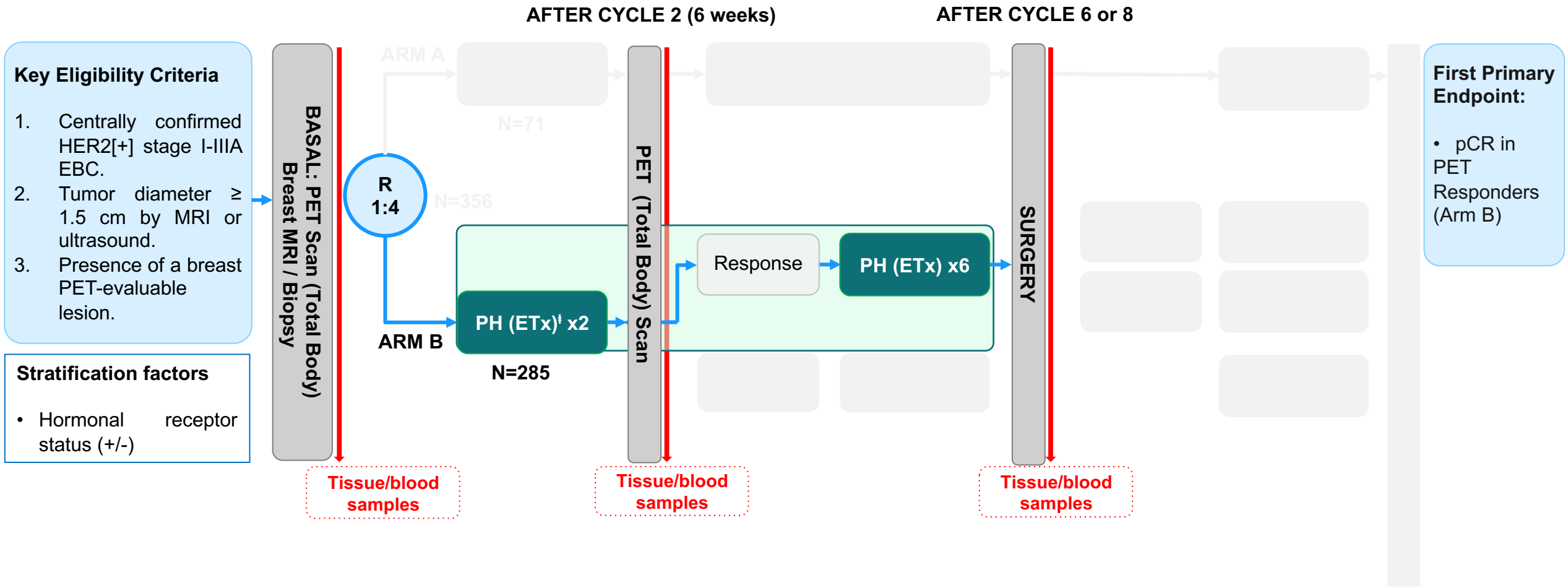

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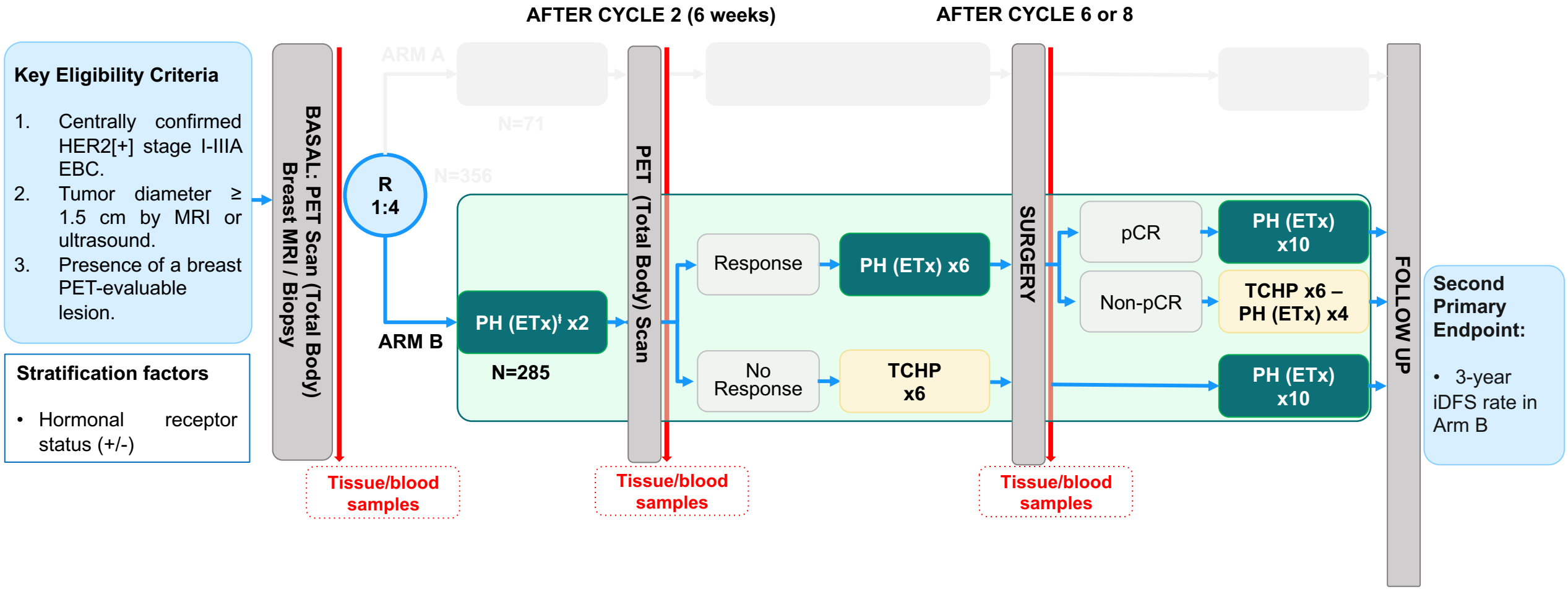

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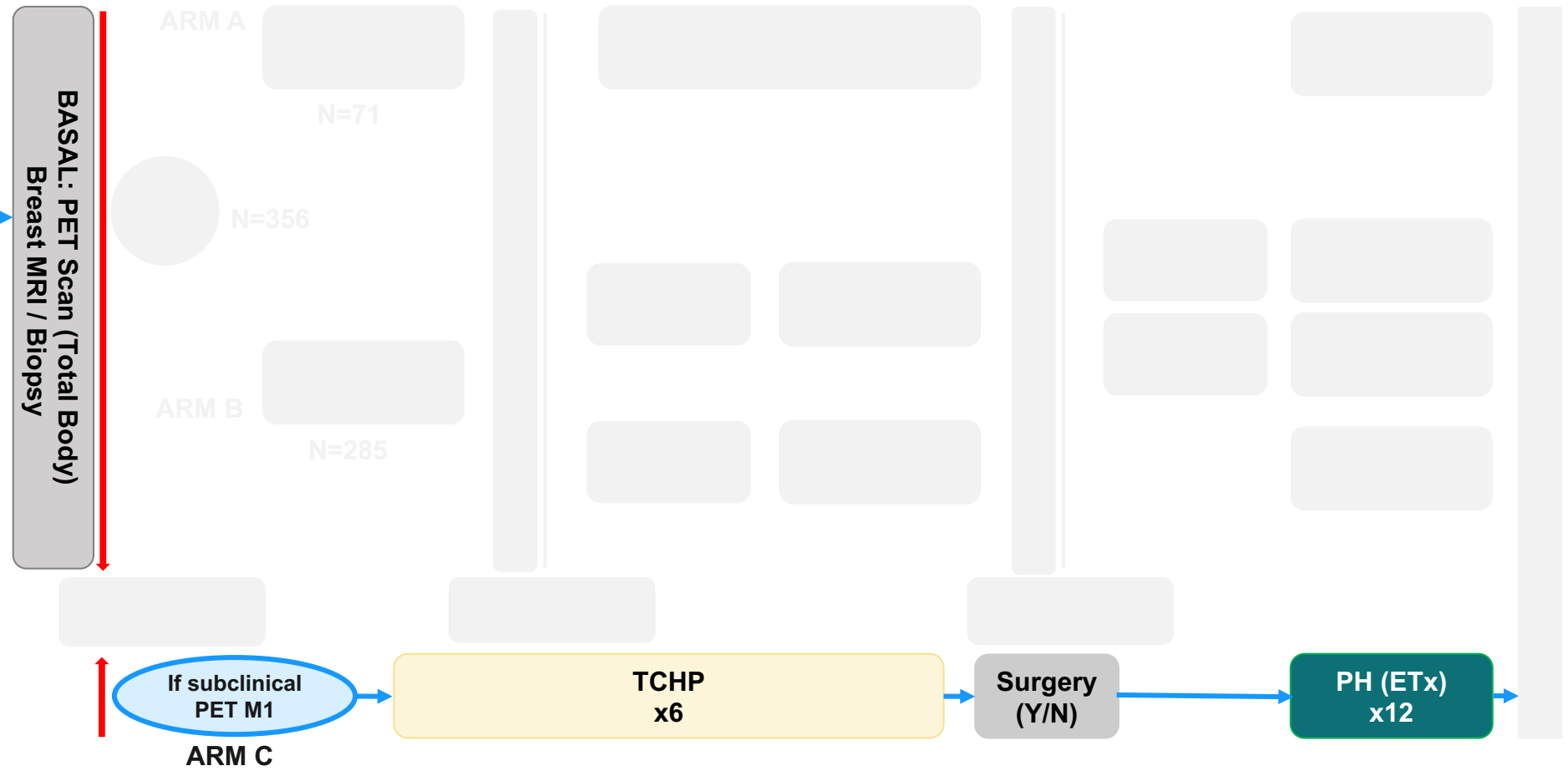

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Study Endpoints

CO-PRIMARY ENDPOINTS

- pCR (ypT0/isN0) in PET Responders (Arm B)[a]
- 3-year iDFS rate in Arm B

SECONDARY ENDPOINTS

- pCR in Arm A and Arm B
- pCR by PET response / Other definitions of pCR
- Breast-conserving surgery
- Tumor response by MRI
- Optimal PET cut-off SUV_{max} for pCR
- Long term outcomes per arm
- Health-related quality of life
- Toxicity (CTCAE v4.0) / Translational sub-studies

[a]Subjects without pCR data due to any reason were counted as non-pCR.

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

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Statistical Considerations

First Co-Primary Endpoint: pCR (ypT0/isN0) in the PET Responders (Arm B)

- 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 Co-Primary Endpoint: 3-year iDFS assessed by investigator in Arm 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

P-values for secondary endpoints are considered descriptive

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

Key Eligibility Criteria

Inclusion criteria:

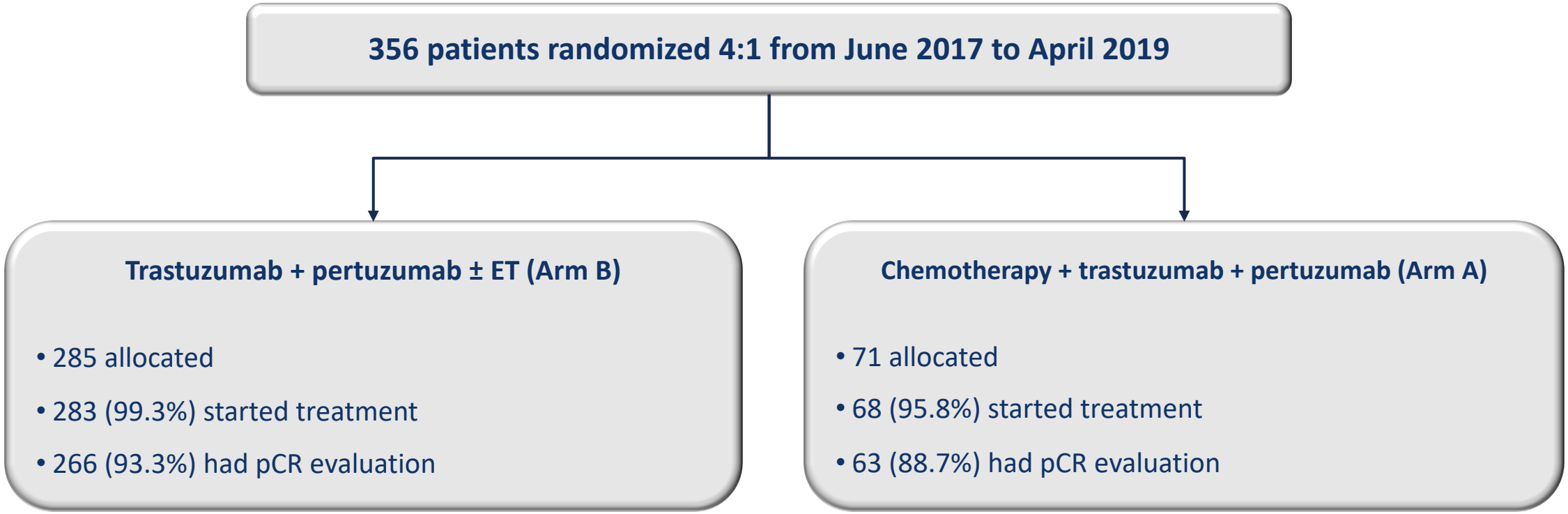
- Stage I-IIIA invasive breast cancer.
- Tumor diameter larger ≥ 1.5 centimeter by MRI or ultrasound.
- At least a PET-evaluable breast lesion (SUV_{max} ≥1.5 x SUV_{mean} liver + 2 SD).
- Centrally confirmed HER2-positive breast cancer.
- Patient must have ER and PR status locally determined.

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 Arm 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; SUV_{max}: The maximum Standardized Uptake Value; SUV_{mean}: The mean standardized uptake value.

Summary of Study Treatment and Analysis Populations



ET: Endocrine therapy; pCR: Pathological complete response.

Baseline Characteristics, ITT Population

Characteristics, n (%)		All subjects N=356	Arm B (HP) N=285	Arm A (TCHP) N=71
Age, median (range)		50 (20–82)	50 (25–77)	51 (20–82)
Postmenopausal	**No**	183 (51.4)	146 (51.2)	37 (52.1)
	Yes	173 (48.6)	139 (48.8)	34 (47.9)
Stage	**I**	33 (9.3)	24 (8.4)	9 (12.7)
	II	269 (75.6)	219 (76.8)	50 (70.4)
	IIIA	54 (15.2)	42 (14.7)	12 (16.9)
Node status	**-**	184 (51.7)	145 (50.9)	39 (54.9)
	+	172 (48.3)	140 (49.1)	32 (45.1)
HR status	**-**	120 (33.7)	93 (32.6)	27 (38.0)
	+	236 (66.3)	192 (67.4)	44 (62.0)

H: Trastuzumab SC; HR: Hormonal receptor; ITT: Intention to treat; ND: Not determined; P: Pertuzumab; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin.

Baseline Characteristics, ITT Population

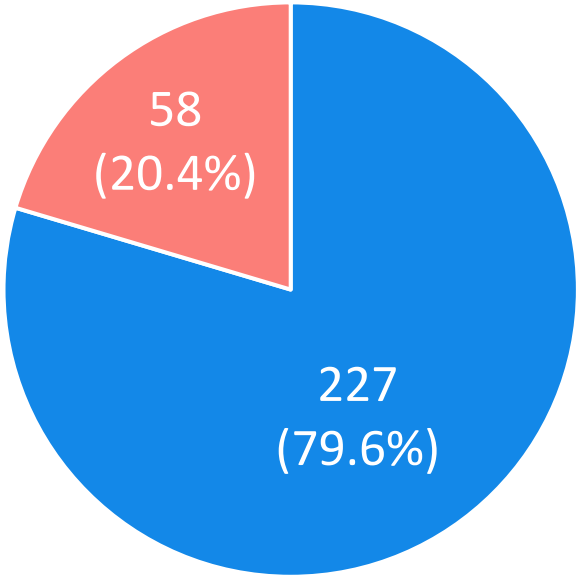
Characteristics, n (%)		All subjects N=356	Arm B (HP) N=285	Arm A (TCHP) N=71
HER2-IHC*	**2+**	77 (21.6)	64 (22.5)	13 (18.3)
	3+	279 (78.4)	221 (77.5)	58 (81.7)
Tumor Grade	**Gx**	52 (14.6)	43 (15.1)	9 (12.7)
	G1	6 (1.7)	6 (2.1)	0 (0)
	G2	138 (38.8)	109 (38.2)	29 (40.8)
	G3	160 (44.9)	127 (44.6)	33 (46.5)
SUV_{max} at baseline, median (range)		10.1 (3.4–54.6)	10.4 (3.4–54.6)	8.7 (3.6–34.5)

* Cases IHC 2+ resulted FISH-positive.

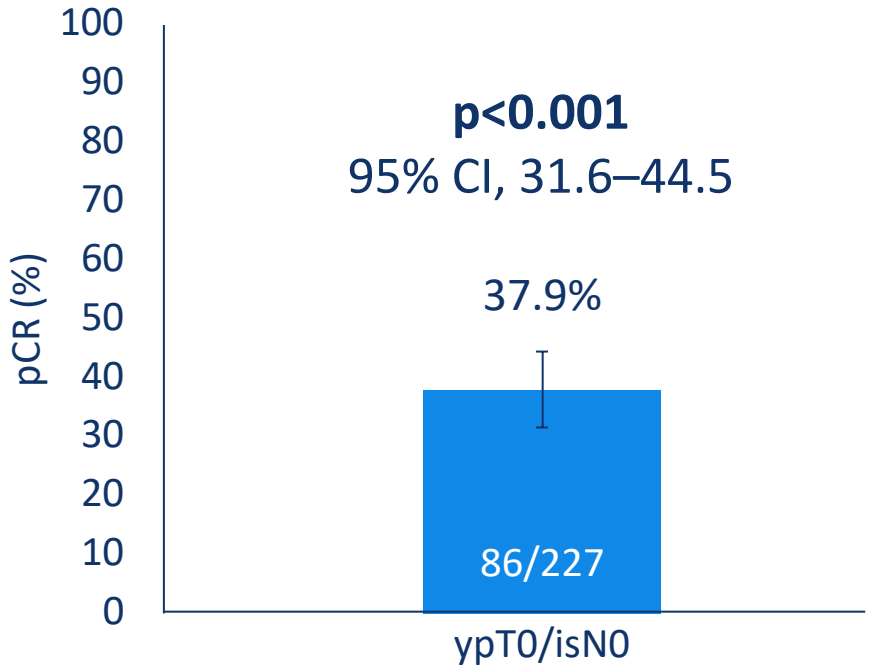
Gx: Histological tumor grade cannot be assessed; G1: Well differentiated; G2: Moderately differentiated; G3: Poorly differentiated/undifferentiated; H: Trastuzumab SC; HR: Hormonal receptor; IHC: Immunohistochemistry; P: Pertuzumab IV; SUV_{max}: The maximum Standardized Uptake Value; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin.

First Co-Primary: pCR in PET Responders (Arm B)

% of PET Responders and Non-Responders in Arm B



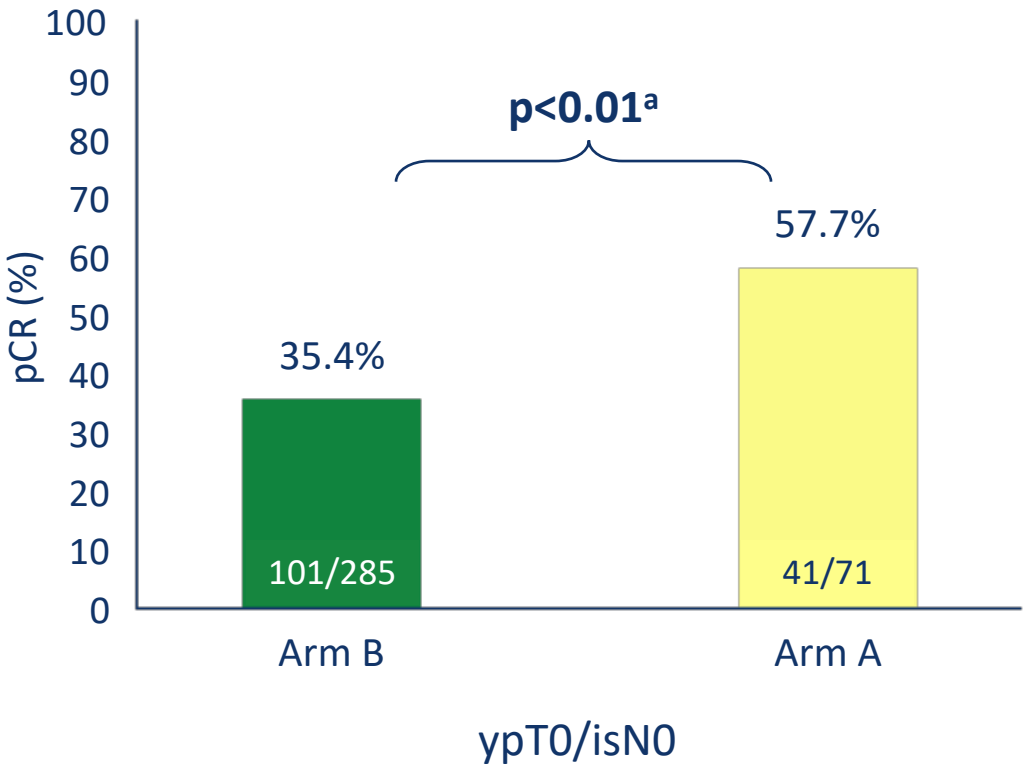
PET Responder PET Non-Responder

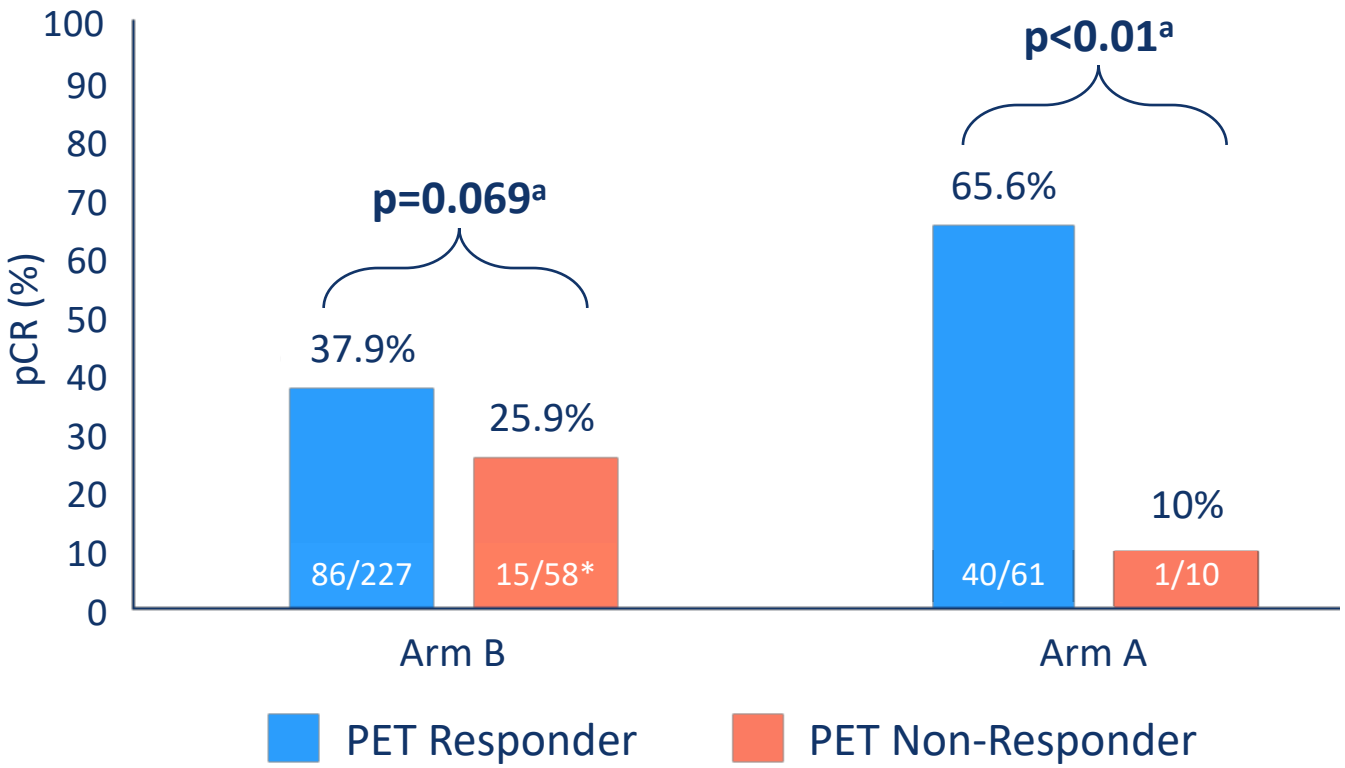


Null hypothesis: pCR ≤20%

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

pCR in Arm B and Arm A



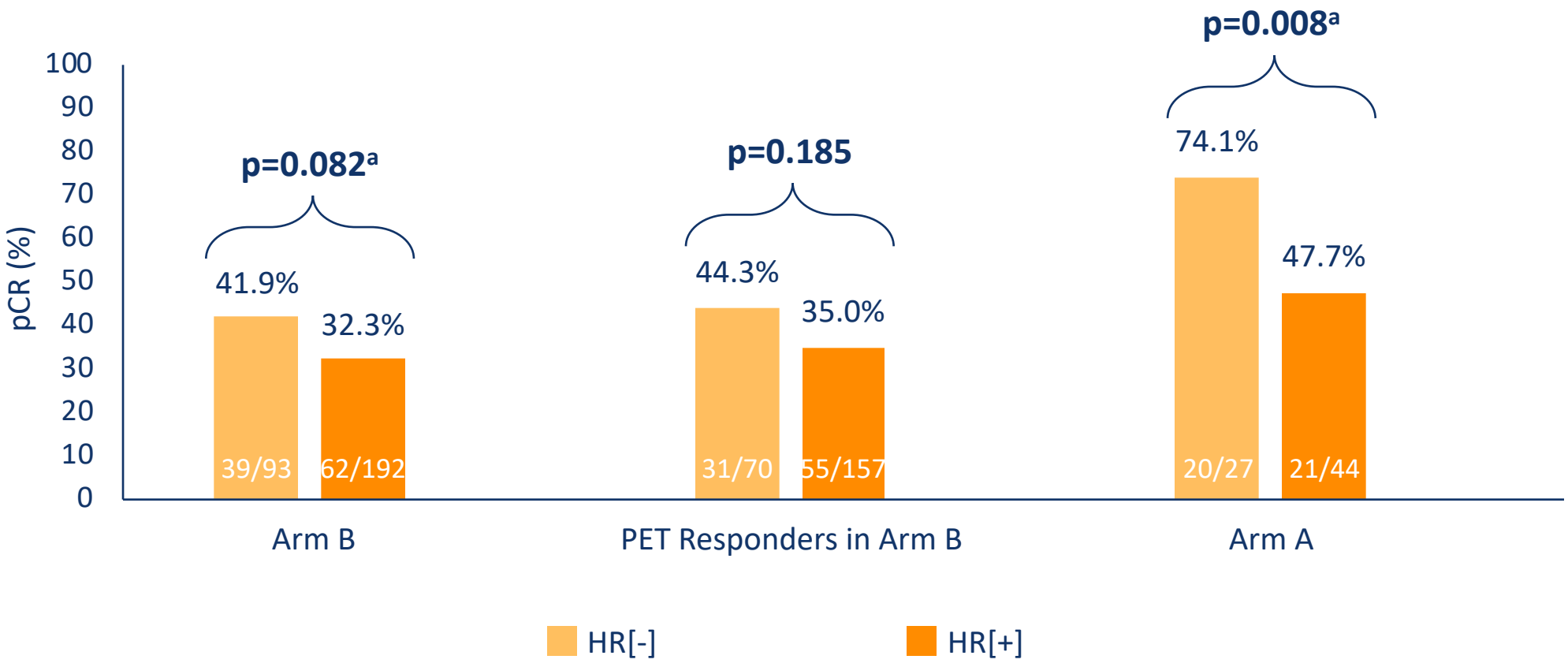


*These pts received TCHP.

[a]Logistic regression model adjusted by hormonal status, based on the Wald test.

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

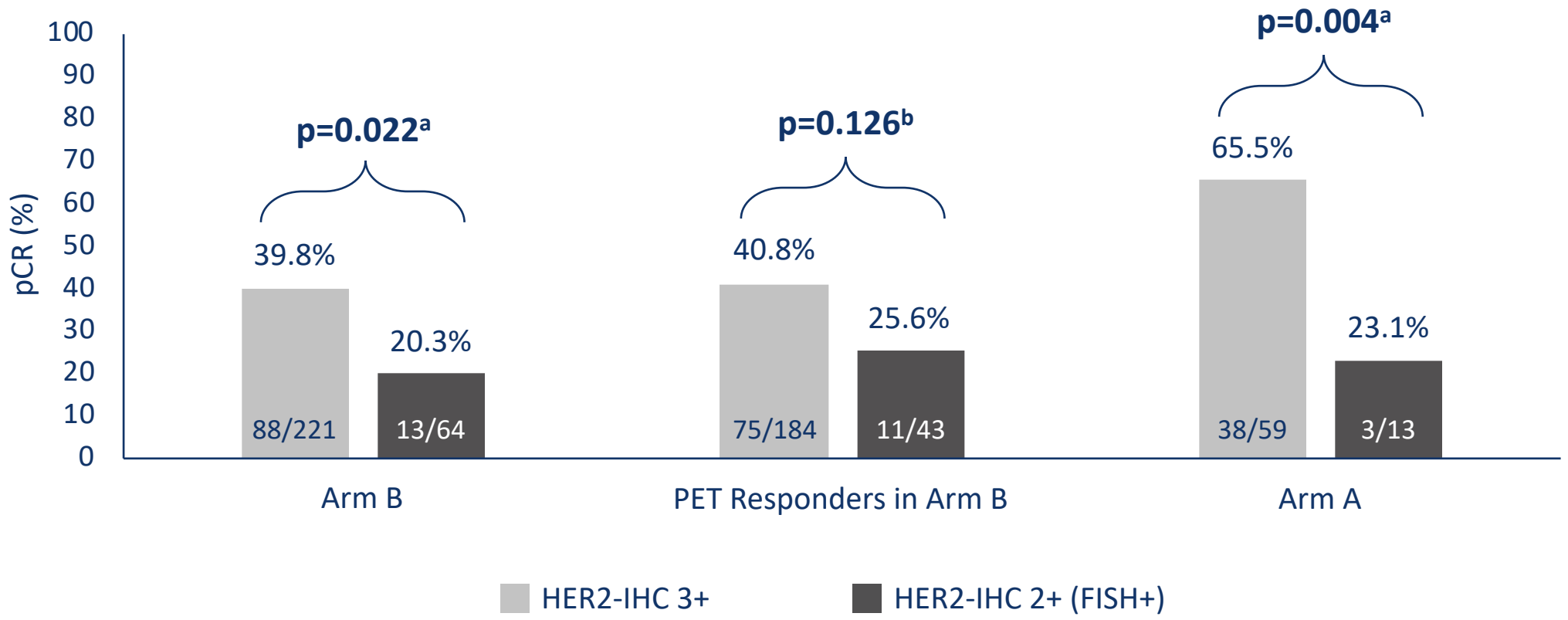
pCR According to HR Status in Arm B and Arm A



[a]Logistic regression model adjusted by PET response status, based on the Wald test.

HR: Hormone receptor; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response.

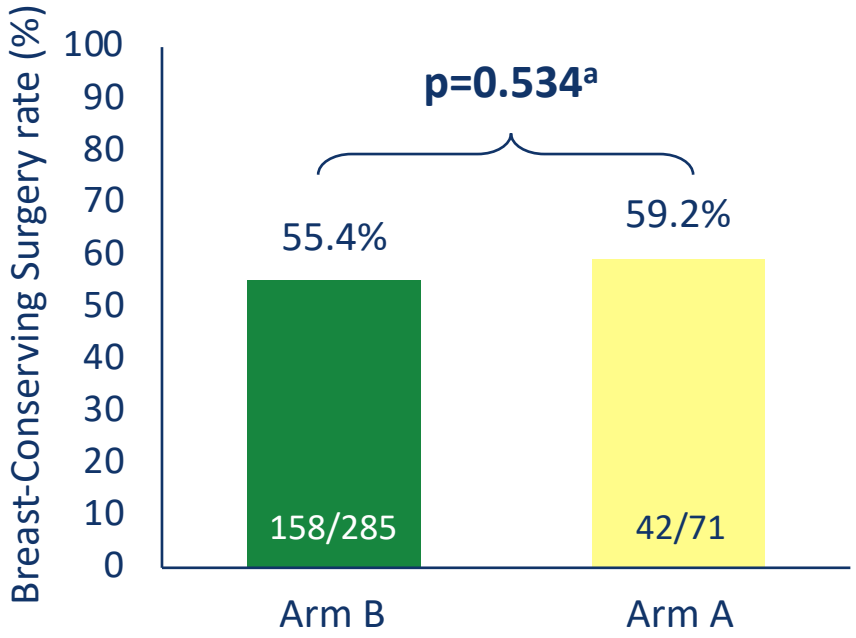
pCR According to HER2-IHC Status in Arm B and Arm A

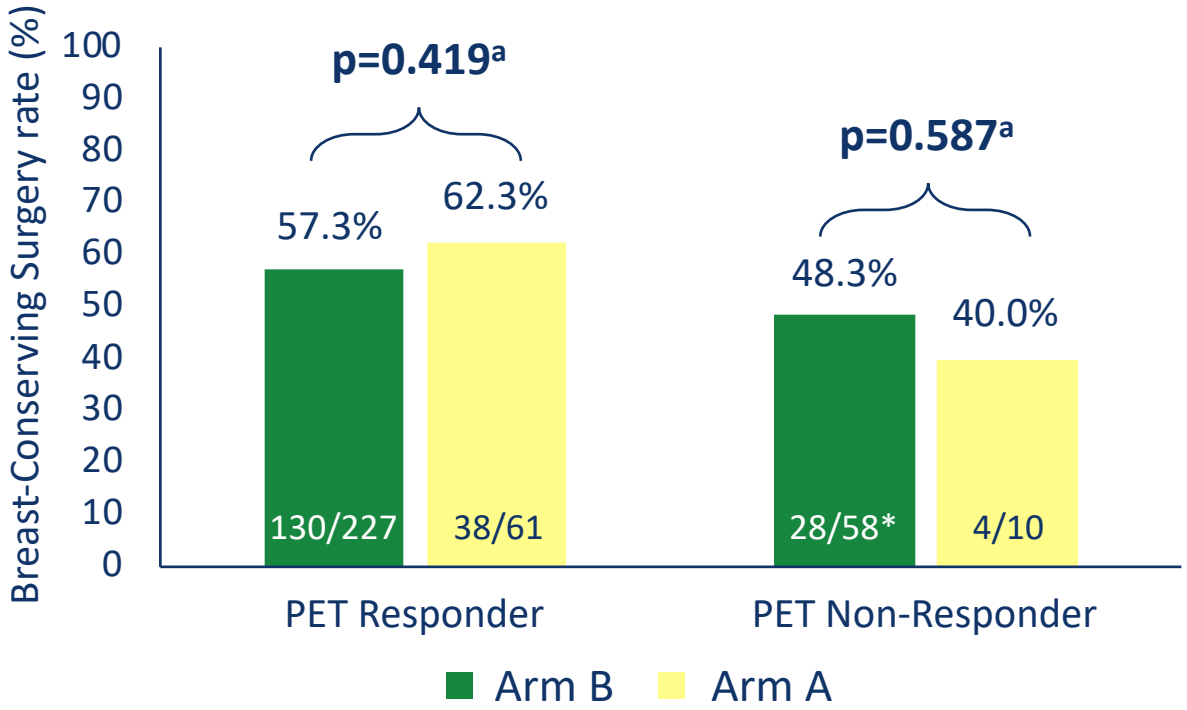


[a]Logistic regression model adjusted by PET response status, based on the Wald test. [b]Adjusted by hormonal status.

HER2: Human Epidermal Growth Factor Receptor; IHC: Immunohistochemistry; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response.

Breast-Conserving Surgery in Arm B and Arm A





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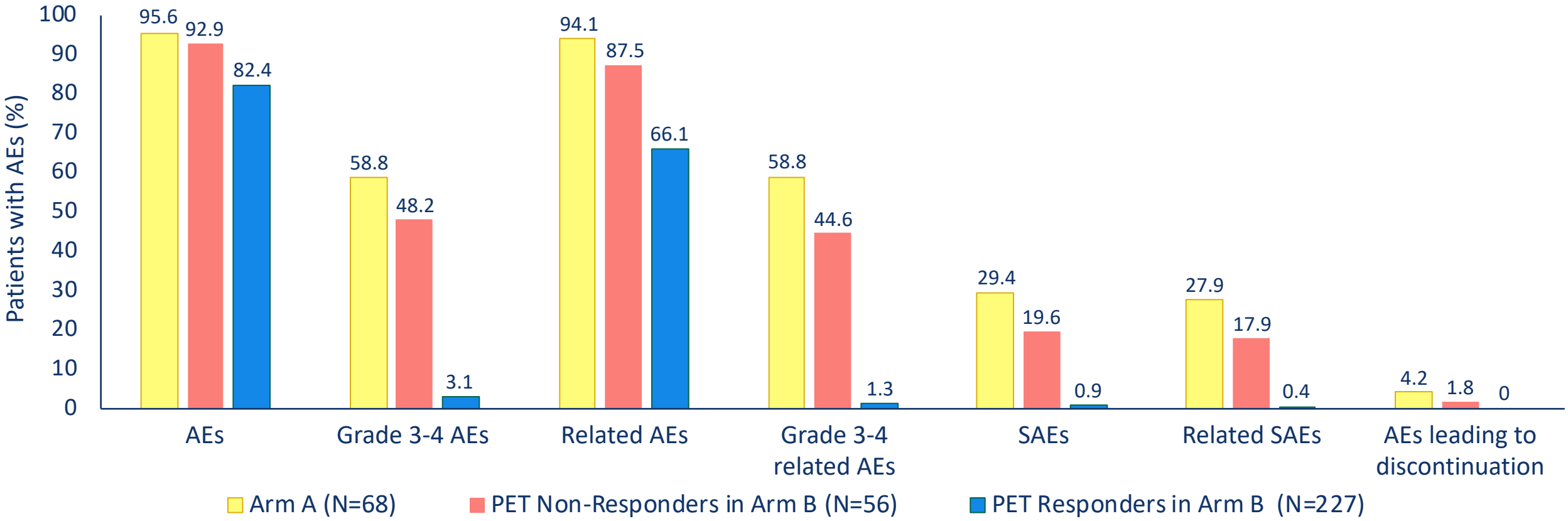
AEs of Any Grade in Neoadjuvant Stage



AEs: Adverse events; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; SAEs: Serious adverse events.

AEs with Incidence in ≥20% Patients

AE, n (%)	Arm A (N=68)		Non-Responder in Arm B (N=56)		Responder in Arm B (N=227)	
	Any	Grade 3-4	Any	Grade 3-4	Any	Grade 3-4
ANY	65 (95.6)	40 (58.8)	52 (92.9)	27 (48.2)	187 (82.4)	7 (2.6)
HAEMATOLOGIC						
Anemia	25 (36.8)	6 (8.8)	21 (37.5)	4 (7.1)	8 (3.5)	0 (0)
Neutropenia	20 (29.4)	16 (23.5)	16 (28.6)	9 (16.1)	4 (1.8)	0 (0)
Thrombocytopenia	15 (22.1)	3 (4.4)	13 (23.2)	2 (3.6)	0 (0.0)	0 (0)
Febrile neutropenia	14 (20.6)	14 (20.6)	11 (19.6)	10 (17.9)	0 (0.0)	0 (0)
NON-HAEMATOLOGIC						
Diarrhea	46 (67.6)	7 (10.3)	40 (71.4)	3 (5.4)	100 (44.1)	2 (0.9)
Nausea	36 (52.9)	0 (0)	23 (41.1)	2 (3.6)	34 (15.0)	0 (0)
Asthenia	30 (44.1)	6 (8.8)	30 (53.6)	4 (7.1)	48 (21.1)	0 (0)
Stomatitis	27 (39.7)	6 (8.8)	25 (44.6)	2 (3.6)	30 (13.2)	0 (0)
Alopecia	22 (32.4)	0 (0)	20 (35.7)	0 (0)	4 (1.8)	0 (0)
Vomiting	20 (29.4)	1 (1.5)	17 (30.4)	2 (3.6)	14 (6.2)	0 (0)
Fatigue	18 (26.5)	5 (7.4)	10 (17.9)	1 (1.8)	35 (15.9)	0 (0)
Dysgeusia	15 (22.1)	0 (0)	13 (23.2)	0 (0)	11 (4.8)	0 (0)

*There was not deaths in the study.

AEs: Adverse events.

Conclusions

- Nearly 40% of pts who started dual HER2 blockade with HP ± ET, and were PET-Responders, achieved a total pCR.
- PET identifies pts with HER2[+] EBC who are more likely to achieve a pCR with HP-based therapy.
- This CT-free strategy does not jeopardize breast conserving surgery in HER2[+] EBC pts.
- Omission of CT is associated with a more favorable toxicity profile.
- Follow-up is ongoing for 3-year iDFS endpoint. Depending on the results of this second co-primary endpoint, this strategy could select a group of HER2[+] EBC pts who would not need CT.

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