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, Ellipes, 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

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 ¹⁸F-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 ¹⁸F-FDG PET/CT to neoadjuvant trastuzumab plus pertuzumab (HP) and ii) the pathological response.⁴


CT: chemotherapy; EBC: Early breast cancer; HER2: Human Epidermal Growth Factor Receptor 2; ¹⁸F-FDG PET/CT: ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography
### Key Eligibility Criteria

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

### Stratification factors
- Hormonal receptor status (+/−).

### Study Design

**GROUP A**
- **BASAL:** PET Scan (Total Body)
- **Breast MRI/Biopsy**
- **GROUP A:**
  - TCHP $x2$
  - PH (ETx)$^1 x2$
  - PH (ETx)$ x12$
  - N=71

**GROUP B**
- **PET (Total Body) Scan**
- **GROUP B:**
  - TCHP $x4$
  - PH (ETx)$ x6$
  - TCHP $x6$
  - N=285

**GROUP C**
- **Tissue/blood samples**
- **GROUP C:**
  - TCHP $x6$
  - Surgery (Y/N)
  - PH (ETx)$ x12$

**SURGERY**
- pCR
- Non-pCR
- TCHP $x6$ – PH (ETx)$ x4$
- PH (ETx)$ x10$

**FIRST PRIMARY ENDPOINT**
- pCR in PET Responders (Arm B)

**SECOND PRIMARY ENDPOINT**
- 3-year iDFS rate in Arm B

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### Abbreviations and Terms
- 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 $\geq 40\%$.
- pCR, Pathological complete response (ypT0/isN0)
Key Eligibility Criteria
1. Centrally confirmed HER2[+] stage I-IIIA EBC.
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Stratification factors
• Hormonal receptor status (+/-).

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: 18F-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).

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**PHERGain Study Design**

**Key Eligibility Criteria**

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2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.
3. Presence of a breast PET-evaluable lesion.

**Stratification factors**

- Hormonal receptor status (+/-).

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**Baseline: PET Scan (Total Body)**

**GROUP A**

- N=356
- TCHP x2
- PH (ETx) x2
- Basal: PET Scan (Total Body)
- Breast MRI / Biopsy

**GROUP B**

- N=285
- PH (ETx) x2

**AFTER CYCLE 2 (6 weeks)**

- Response
- PH (ETx) x6

- No Response
- TCHP x6

**AFTER CYCLE 8**

- PH (ETx) x12

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**PET RESPONDERS**: RECIST responders after cycle 2 with SUV\textsubscript{max} reduction ≥ 40%.

**pCR**, Pathological complete response (ypT0/isN0).

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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\textsuperscript{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).

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Stratification factors

- Hormonal receptor status (+/-).

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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-III A invasive breast cancer.
- Tumor diameter ≥ 1.5 centimeter by MRI or ultrasound.
- At least one PET-evaluable breast lesion ($\text{SUV}_{\text{max}} \geq 1.5 \times \text{SUV}_{\text{mean}}$ liver $+ 2 \text{ SD}$).
- 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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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; $SUV_{\text{max}}$: The maximum Standardized Uptake Value; DDFS: Disease-free survival; EFS: Event-free survival; OS: Overall survival
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3-year iDFS Primary Endpoint

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3. Presence of a breast PET-evaluable lesion.

Stratification factors
- Hormonal receptor status (+/-).

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

GROUP B

PET (Total Body) Scan

AFTER CYCLE 2 (6 weeks)

PH (ETx) x2

Response

PH (ETx) x6

No Response

TCHP x6

AFTER CYCLE 8

SURGERY

PH (ETx) x6 – PH (ETx) x4

pCR

Non-pCR

PH (ETx) x10

FOLLOW UP

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: 18F-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%.
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3-year iDFS Primary Endpoint

**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

**GROUP B**

- AFTER CYCLE 2 (6 weeks)
- AFTER CYCLE 8

**FOLLOW UP**

- 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:** 18F-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 will receive ETx concomitantly with PH (except on chemotherapy).*

- PET RESPONDERS: RECIST responders after cycle 2 with SUV\textsubscript{max} reduction ≥40%.
- pCR: Pathological complete response (ypT0/isN0).
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: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response.
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Safety assessed in all patients who received at least one dose of study treatment

iDFS: Invasive disease-free survival; PET: 18F-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

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

Data are n (%), unless otherwise specified.
### Baseline Characteristics (cont.)

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

Data are n (%), unless otherwise specified.
Primary Endpoint: pCR in \(^{18}\text{F-FDG-PET}\) responders in group B

PET Responders and Non-Responders

- **PET Responder**: 227 (79.6%)
- **PET Non-Responder**: 58 (20.4%)

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


CI: Confidence interval; PET: \(^{18}\text{F-fluorodeoxyglucose}\) positron emission tomography/computed tomography; pCR: Pathological complete response (ypT0/isN0).
Primary Endpoint: 3-year iDFS rate in group B
ITT population

3-year iDFS rate: 95.4%
(95% CI: 92.8-98.0%)
Events: 12/267

Second primary endpoint was met with ≤ 15 patients with iDFS events (p < 0.001)
Primary Endpoint: 3-year iDFS events in group B
ITT population

<table>
<thead>
<tr>
<th>3-year iDFS</th>
<th>Group B (N = 267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iDFS events</td>
<td>12 (4.5%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>11 (4.1%)</td>
</tr>
<tr>
<td>Ipsilateral invasive breast tumor recurrence</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Regional invasive breast cancer recurrence</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Contralateral invasive breast cancer</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>8 (3.0%)</td>
</tr>
<tr>
<td>Non-related death without recurrence</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise specified.
Subgroup analysis:
3-year iDFS rate without CT in PET responders with pCR (n=86)
Subgroup analysis:
3-year iDFS rate without CT in PET responders with pCR (n=86)

3-year iDFS rate: 98.8%
(95% CI: 96.3-100%)

Events: 1/86
(Regional recurrence)
**Efficacy Analysis: Summary of other efficacy endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 63)</th>
<th>Group B (n = 267)</th>
<th>Group B without CT (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year iDFS</td>
<td>98.3% (95.1–100%)</td>
<td>95.4% (92.8–98.0%)</td>
<td>98.8% (96.3–100%)</td>
</tr>
<tr>
<td>3-year DDFS</td>
<td>98.3% (95.1–100%)</td>
<td>96.5% (94.3–98.8%)</td>
<td>100% (100–100%)</td>
</tr>
<tr>
<td>3-year EFS</td>
<td>98.4% (95.3–100%)</td>
<td>93.5% (90.7–96.5%)</td>
<td>98.8% (96.6–100%)</td>
</tr>
<tr>
<td>3-year OS</td>
<td>98.4% (95.3–100%)</td>
<td>98.5% (97.1–100%)</td>
<td>100% (100–100%)</td>
</tr>
</tbody>
</table>

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**

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

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: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR, Pathological complete response (ypT0/isN0).
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