antiHER2 treatments in neoadjuvant to adjuvant setting of HER2 positive Breast Cancers

Joseph Gligorov MD, PhD

APHP Tenon, Paris, France
INSERM U938
Institut Universitaire de Cancérologie
Université Paris VI- Pierre & Marie Curie, Sorbonne Université
## Conflicts of interest

<table>
<thead>
<tr>
<th></th>
<th>Adv boards and speakers bureau</th>
<th>Travel support</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daïchi®</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eisai®</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Genomic Health ®</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ipsen®</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrogenics ®</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSD ®</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis ®</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Onxeo®</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer ®</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Roche Genentech ®</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Miss F, 47 years old

- Married, 3 kids (15, 12, 10)
- Teacher
- March 2012: Pain on left axillary region and self palpation of a lymph node.
- April 2012: goes to her general practitioner
General practitioner exam

• Tumour of the upper left quadrant of the breast (2 cm)
• Axillary lymph node with no other abnormalities
• Proposal:
  – Surgery First
  – Neoadjuvant treatment first
Breast Imaging

- Echography & mammography
- Tumour of the left upper quadrant
  - Tumour size evaluated at 25 mm
  - Axillary echography showing 2 abnormal lymph nodes
  - No additional suspect lesions
- Right breast considered to be normal
- Conclusion: Left breast ACR5
- Biopsy
Radiological biopsy and cytology

• Breast biopsy:
  – IDC Grade III, ER+, PgR-, HER2++, CISH positive

• Axillary puncture:
  – Presence of neoplastic cells
What would you do next?

1. Initiate neoadjuvant therapy: Anthracycline followed by THP
2. Initiate neoadjuvant therapy: TCHP X 6 cycles
3. Upfront surgery
4. Initiate neoadjuvant therapy: Anthracycline followed by TH
The neoadjuvant chemotherapy is as important for the oncologist as the white stick for a blind person.
Impact of neoadjuvant PH with chemotherapy on pCR rates in HER2-positive eBC

NeoSphere\(^1\)

<table>
<thead>
<tr>
<th>PH Regimen</th>
<th>pCR (%)</th>
<th>CI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>D, T</td>
<td>29.0</td>
<td>23.8-38.7</td>
<td>107</td>
</tr>
<tr>
<td>D, T, P</td>
<td>45.8</td>
<td>37.9-53.5</td>
<td>107</td>
</tr>
<tr>
<td>T, P</td>
<td>16.8</td>
<td>8.5-29.6</td>
<td>107</td>
</tr>
<tr>
<td>D, P</td>
<td>24.0</td>
<td>12.8-32.5</td>
<td>96</td>
</tr>
</tbody>
</table>

TRYPHAENA\(^2\)

<table>
<thead>
<tr>
<th>PH Regimen</th>
<th>pCR (%)</th>
<th>CI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEC + T, P x3 → D, T, P x3</td>
<td>61.6</td>
<td>53.5-68.5</td>
<td>72</td>
</tr>
<tr>
<td>FEC x3 → D, T, P x3</td>
<td>57.3</td>
<td>49.5-66.0</td>
<td>75</td>
</tr>
<tr>
<td>D, Cb, T, P x6</td>
<td>66.2</td>
<td>57.5-74.7</td>
<td>76</td>
</tr>
</tbody>
</table>

BERENICE

<table>
<thead>
<tr>
<th>Cohort</th>
<th>pCR (%)</th>
<th>CI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (THAC-TPH), n=199</td>
<td>61.9% (123/199)</td>
<td>53.5-69.7</td>
<td>199</td>
</tr>
<tr>
<td>B (FEC-DPH), n=201</td>
<td>60.7% (122/201)</td>
<td>52.5-68.0</td>
<td>201</td>
</tr>
</tbody>
</table>

Adapted from Sandra M. Swain et al Poster presentation, SABCS 2016

Cb, carboplatin; Ct, chemotherapy; D, docetaxel; FEC, 5-fluorouracil+epirubicin+cyclophosphamide; L, lapatinib; P, pertuzumab; T, trastuzumab.

Neoadjuvant therapy in International GL

St. Gallen Expert Consensus

The Panel strongly endorsed the use of neoadjuvant therapy for stage II or III, HER2 positive or triple-negative breast cancer as the preferred initial treatment approach, particularly when there is any suggestion that treatment response might enable de-escalation of surgery or radiotherapy.

For HER2 positive cancers, the Panel endorsed dual anti-HER2 neoadjuvant therapy with pertuzumab and trastuzumab with chemotherapy as a commonly administered option.

NCCN Breast Cancer Guidelines

Regimens for HER2-positive disease
Preferred regimens:
AC followed by T + trastuzumab
AC followed by T+ trastuzumab + pertuzumab
TCH
TCH + pertuzumab

2. NCCN Breast Cancer Guidelines. Version 1, 2018 – February 7, 2018
Case Study continue

• The patient received NA: AC-TPH

• Mammography and MRI: no evidence of residual tumor
What would you do next (multidisciplinary discussion)?

1. Lumpectomy and axillary dissection $\rightarrow$ complete adjuvant treatment + radiation

2. Mastectomy and axillary dissection $\rightarrow$ complete adjuvant treatment + radiation

3. Lumpectomy and SLND + removal of clipped node $\rightarrow$ complete adjuvant treatment + radiation
Case Study continue

- Lumpectomy and SLND + removal of clipped node

- At surgery- tpCR (breast and axilla)
Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis
NeoSphere: All patients are at risk of disease recurrence, whether or not they achieve a pCR

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PHT better</th>
<th>HT better</th>
<th>Events n (%)</th>
<th>HR (95% CI)</th>
<th>5-year PFS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL (N = 214)</td>
<td></td>
<td></td>
<td>36 (17)</td>
<td>0.69 (0.34–1.40)</td>
<td>86</td>
</tr>
<tr>
<td>tpCR (n = 65)</td>
<td></td>
<td></td>
<td>10 (15)</td>
<td>0.63 (0.17–2.38)</td>
<td>88</td>
</tr>
<tr>
<td>No tpCR (n = 149)</td>
<td></td>
<td></td>
<td>26 (17)</td>
<td>0.74 (0.32–1.70)</td>
<td>84</td>
</tr>
<tr>
<td>HR-positive (n = 100)</td>
<td></td>
<td></td>
<td>14 (14)</td>
<td>0.86 (0.27–2.75)</td>
<td>86</td>
</tr>
<tr>
<td>HR-negative (n = 114)</td>
<td></td>
<td></td>
<td>22 (19)</td>
<td>0.60 (0.24–1.48)</td>
<td>85</td>
</tr>
<tr>
<td>tpCR/HR-positive (n = 17)</td>
<td></td>
<td></td>
<td>2 (12)</td>
<td>- (-)</td>
<td>91</td>
</tr>
<tr>
<td>tpCR/HR-negative (n = 48)</td>
<td></td>
<td></td>
<td>8 (17)</td>
<td>0.78 (0.17–3.47)</td>
<td>87</td>
</tr>
<tr>
<td>No tpCR/HR-positive (n = 83)</td>
<td></td>
<td></td>
<td>12 (14)</td>
<td>0.93 (0.26–3.34)</td>
<td>85</td>
</tr>
<tr>
<td>No tpCR/HR-negative (n = 66)</td>
<td></td>
<td></td>
<td>14 (21)</td>
<td>0.51 (0.13–1.97)</td>
<td>83</td>
</tr>
</tbody>
</table>

Both tpCR and non-tpCR patients are at risk of relapse

12% of patients who achieved a pCR had experienced disease recurrence at 5 years, compared with 16% of those with residual disease

NEXT GENERATION TRIALS: IMPROVE OUTCOME OF NON-PCR PATIENTS
Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype

W. Fraser Symmans, Caimiao Wei, Rebekah Gould, Xian Yu, Ya Zhang, Mei Liu, Andrew Walls, Alex Bousamra, Maheshwari Ramineni, Bruno Sinn, Kelly Hunt, Thomas A. Buchholz, Vicente Valero, Aman U. Buzdar, Wei Yang, Abenaa M. Brewster, Stacy Moulder, Lajos Pusztai, Christos Hatzis, and Gabriel N. Hortobagyi

HER2 positive A/T

HER2 positive A/T + antiHER2

C

D

J Clin Oncol 2017; 35: 1049-61
Will you consider achieving pCR is enough to stop optimal targeted therapy in adjuvant setting?

1. Yes

2. No
What would you do next?

1. Continue Perjeta+Herceptin – to complete 18 cycles of HP
2. Continue Herceptin – to complete 18 cycles of H
3. Continue Perjeta+Herceptin – to complete 18 cycles of HP followed by a year of Neratinib
4. other
Katherine: Study Schema

Preoperative therapy:
- Trastuzumab/
- Taxane ± Anthracycline

Residual invasive tumor

- Trastuzumab
- T-DM1

Radiation per standard guidance; hormone therapy if ER- or PgR-pos

Conclusions

• In case of neoadjuvant treatment in HER2 positive disease
  – Using antiHER2 treatment is crucial
  – Like in adjuvant and metastatic disease trastuzumab is the backbone strategy of HER2 blockade
  – Dual blockade is superior and pertuzumab is actually the best and only approved option for optimizing neoadjuvant treatments and achieve best probability of pCR (FDA, EMEA, International guidelines)
  – Optimizing treatments strategies will need to better define the sensitive/resistant population and explore strategies of adjuvant post neoadjuvant trial (escalating and de-escalating)
What is the most important parameter that put the patient at high risk?

1. N+
2. Tumor size
3. HR-
4. High proliferation
5. Patients who were considered as neoadjuvant therapy
Are the initial prognostic parameters at the time of diagnosis important for treatment strategy in the adjuvant setting regardless of pCR status?

1. Yes
2. No
IMPACT OF FIRST GENERATION ADJUVANT TRIALS WITH TRASTUZUMAB
HER2-positive relapse rates still remain high despite the impact of Herceptin-based therapy

BCIRG 006: DFS final analysis (10.3 years’ MFU)

Although a large proportion of patients benefit from Herceptin, 1 in 4 patients will still experience recurrence or death despite 1 year of adjuvant Herceptin-based therapy.

BCIRG 006 ITT population had 71% node-positive patients

DFS, disease-free survival; ITT, intention-to-treat; MFU, median follow-up.

HERA: DFS event rate increases with increasing numbers of positive nodes

HERA 11-year FU: DFS events by nodal status with 1 year of adjuvant trastuzumab

The need to do more is particularly important for patients with Node+ or HR- HER2+ eBC disease facing a high risk of recurrence or death\(^1\)

BCIRG-006 10 year follow-up\(^2\)

HERA 11 year follow-up: Cumulative incidence of DFS event\(^3\)

\(~1\text{ in } 3\) of high risk patients Still relapse or die

\(^1\) Carter et al. (1989). Strasser-Weippl et al. (2015)\(^2\) Cameron D. et al., Lancet 2017; 389:1195–205, supplementary appendix. BCIRG 006 data cannot be shown for HR- disease as they are not published.
Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

Gunter von Minckwitz, M.D., Marion Procter, Ph.D., Evandro de Azambuja, M.D., Dimitrios Zardavas, M.D., Mark Benyunes, M.D., Giuseppe Viale, M.D., Thomas Suter, M.D., Amal Arahmani, Ph.D., Nathalie Rouchet, M.Sc., Emma Clark, M.Sc., Adam Knott, Ph.D., Istvan Lang, M.D., Christelle Levy, M.D., Denise A. Yardley, M.D., Jose Bines, M.D., Richard D. Gelber, Ph.D., Martine Piccart, M.D., and Jose Baselga, M.D., for the APHINITY Steering Committee and Investigators*
APHINITY is a Phase III adjuvant study investigating PERJETA–Herceptin + chemotherapy

- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second non-breast primary cancers included, DFS, OS, RFI, DRFI, safety and HRQoL
- **Stratification factors:** Chemotherapy regimen, HR status, nodal status, geographic region, Protocol version (A vs. B)

DFS, disease-free survival; DRFI, distant relapse-free interval; HR, hormone receptor; HRQoL, health-related quality of life; IDFS, invasive disease-free survival; OS, overall survival; RFI, relapse-free interval.

APHINITY met the primary efficacy objective: IDFS

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>No. of patients at risk</th>
<th>PERJETA–Herceptin (n = 2400)</th>
<th>Placebo–Herceptin (n = 2404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>2400</td>
<td>171 (7.1)</td>
<td>210 (8.7)</td>
</tr>
<tr>
<td>2 years</td>
<td>2309</td>
<td>170 (7.1)</td>
<td>211 (8.7)</td>
</tr>
<tr>
<td>3 years</td>
<td>2275</td>
<td>170 (7.1)</td>
<td>208 (8.7)</td>
</tr>
<tr>
<td>4 years</td>
<td>2236</td>
<td>169 (7.1)</td>
<td>206 (8.7)</td>
</tr>
</tbody>
</table>

Stratification factors are: nodal status and protocol version, intended adjuvant chemotherapy and central hormone receptor status

* The p-value shown in this table is based on stratification factor data taken from the eCRF.
In a sensitivity analysis based on stratification factor data from the IxRS system (FDA Preferred Analysis), the p-value from the stratified log-rank test was 0.0471. Hazard ratio was estimated by Cox regression.

19% reduction of the risk of an IDFS event with PERJETA–Herceptin vs. Herceptin (HR 0.81; 95% CI 0.66, 1.00; p = 0.0446)

APHINITY: The positive outcome of the study was driven by results in patients with disease at high risk of recurrence.

Hazard ratios were estimated by Cox regression.

Baseline HRQoL scores were maintained throughout treatment, except for a decline at the end of taxane treatment. 

Mean EORTC QLQ-C30 global health status by treatment regimen, ITT population

* Indicates time points where there was a clinically meaningful change in absolute score.

# Improving eBC standard-of-care treatment modalities

## INTRODUCTION of a First Generation

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>CMF vs. no chemo</th>
<th>Anth + taxane vs. anth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk*1</td>
<td>0.70</td>
<td>0.84</td>
</tr>
</tbody>
</table>

## IMPROVEMENT of a Second Generation

<table>
<thead>
<tr>
<th>Endocrine therapy</th>
<th>Tam 5 years vs. no tam</th>
<th>AI 5 years vs. tam 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk*2</td>
<td>0.50</td>
<td>0.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-HER2 therapy</th>
<th>Trastuzumab vs. observation</th>
<th>APHINITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk*3</td>
<td>0.52</td>
<td>0.81</td>
</tr>
</tbody>
</table>

* Analysis conducted at different time points.


* Relative risk * indicates statistical significance.

9.9 – 12% improvement in recurrence rate for new modalities\(^1,3,4\)

0.5 – 3.6% improvement in recurrence rate for improving a modality\(^1,5\)
Based on APHINITY, the FDA and CHMP support the use of adjuvant PERJETA–Herceptin for 18 cycles in high-risk HER2-positive eBC

**PERJETA Prescribing Information**

Indicated for use in combination with trastuzumab and chemotherapy as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer and the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence. Following surgery, patients should continue to receive PERJETA and trastuzumab to complete 1 year of treatment (up to 18 cycles).

**CHMP opinion: PERJETA label extension**

PERJETA is indicated for use in combination with trastuzumab and chemotherapy in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence. PERJETA should be administered in combination with trastuzumab for a total of 1 year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first) as part of a complete regimen for early breast cancer and regardless of the timing of surgery.

3. PROPOSED PERJETA SmPC 2018.
Treatment improvement by adding PERJETA to Herceptin therapy in APHINITY was classified as Grade B on the ESMO-MCBS

ESMO-MCBS guidelines categorised the APHINITY data (HR 0.81; 95% CI = 0.66, 1.00) as a ‘Group B intervention’ in the curative setting, which means they correspond to a substantial improvement.

CI, confidence interval; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HR, hazard ratio.

APHINITY: Treatment improvement by adding PERJETA to Herceptin in node-positive subgroup (planned analysis) was classified as Grade A on the ESMO-MCBS scale.

ESMO-MCBS guidelines categorised the APHINITY data in node-positive disease (HR 0.77; 95% CI = 0.62, 0.96)\textsuperscript{4} as a ‘Group A intervention’ in the curative setting, which means they correspond to a meaningful clinical benefit.

International guidelines recommend the APHINITY regimen in patients with tumours at high risk of recurrence

Recommendations in the adjuvant setting:
Dual blockade with PERJETA–Herceptin for HER2-positive patients at high risk of relapse

St. Gallen Expert Consensus¹
High risk due to lymph node involvement or HR-negativity

ASCO Guidelines³
High-risk, such as node-positive disease

NCCN Breast Cancer Guidelines²
If node-positive (HR-positive and HR-negative disease)

AGO Guidelines⁴
Node-positive or HR-negative disease

² NCCN Breast Cancer Guidelines. Version 1, 2018 – February 7, 2018;

AGO, Arbeitsgemeinschaft Gynäkologische Onkologie E.V.; ASCO, American Society of Clinical Oncology; HR, hormone receptor; NCCN, National Comprehensive Cancer Network.
FDA / EMA labels and international guidelines support the continuation of Pertuzumab-Trastuzumab from neoadjuvant to adjuvant for patients with high-risk of recurrence

**NCCN Breast Cancer Guidelines**

**Adjuvant systemic treatment recommendations after neoadjuvant therapy:** If HER2-positive, complete up to one year of HER2-targeted therapy with trastuzumab ± pertuzumab in node-positive, HR-positive or HR-negative tumours. HER2-targeted therapy may be administered concurrently with radiation therapy and with endocrine therapy if indicated.

**AGO Breast Cancer Guidelines**

After Neoadjuvant therapy, complete Pertuzumab treatment for 1 year if N+ or HR-
Extenet: Phase III trial of Neratinib in HER2+ Early Breast Cancer

- Primary endpoint: invasive disease-free survival
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, central nervous system (CNS) metastases, OS, safety
- Other analyses: biomarkers, health outcome assessment (FACT-B, EQ-5d)

ExteNET: iDFS By Hormone Receptor Status

**HR-Positive Subgroup**

<table>
<thead>
<tr>
<th>Months After Randomization</th>
<th>Invasive Disease-Free Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>98.1%</td>
</tr>
<tr>
<td>24</td>
<td>96.1%</td>
</tr>
<tr>
<td>36</td>
<td>95.4%</td>
</tr>
<tr>
<td>48</td>
<td>93.6%</td>
</tr>
<tr>
<td>60</td>
<td>92.6%</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.60 (0.43–0.83)
Two-sided \( P = .002 \)

**HR-Negative Subgroup**

<table>
<thead>
<tr>
<th>Months After Randomization</th>
<th>Invasive Disease-Free Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>97.5%</td>
</tr>
<tr>
<td>24</td>
<td>94.7%</td>
</tr>
<tr>
<td>36</td>
<td>91.8%</td>
</tr>
<tr>
<td>48</td>
<td>90.8%</td>
</tr>
<tr>
<td>60</td>
<td>89.9%</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.95 (0.66–1.35)
Two-sided \( P = .762 \)

No. at risk
Neratinib: 818, 767, 731, 706, 642, 571, 585, 588, 564, 544, 523
Placebo: 815, 779, 750, 719, 647, 581, 587, 556, 551, 542, 525

No. at risk
Neratinib: 604, 658, 541, 520, 484, 407, 400, 391, 384, 376, 362
Placebo: 605, 575, 548, 529, 495, 448, 444, 435, 427, 416, 402

Intention-to-treat population. Cut-off date: March 1, 2017
## ExteNET: Adverse Events (≥10% of Patients)

<table>
<thead>
<tr>
<th>n (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>781 (55.5)</td>
<td>561 (39.8)</td>
<td>1 (0.1)</td>
<td>476 (33.8)</td>
<td>23 (1.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>579 (41.1)</td>
<td>26 (1.8)</td>
<td>0</td>
<td>301 (21.4)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>359 (25.5)</td>
<td>23 (1.6)</td>
<td>0</td>
<td>276 (19.6)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>322 (22.9)</td>
<td>47 (3.3)</td>
<td>0</td>
<td>107 (7.6)</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Abdominal pain, general</td>
<td>314 (22.3)</td>
<td>24 (1.7)</td>
<td>0</td>
<td>141 (10.0)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>269 (19.1)</td>
<td>8 (0.6)</td>
<td>0</td>
<td>269 (19.1)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>201 (14.3)</td>
<td>11 (0.8)</td>
<td>0</td>
<td>93 (6.6)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>205 (14.6)</td>
<td>5 (0.4)</td>
<td>0</td>
<td>100 (7.1)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>166 (11.8)</td>
<td>3 (0.2)</td>
<td>0</td>
<td>40 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>157 (11.2)</td>
<td>1 (0.1)</td>
<td>0</td>
<td>44 (3.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>143 (10.2)</td>
<td>3 (0.2)</td>
<td>0</td>
<td>125 (8.9)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>84 (6.0)</td>
<td>2 (0.1)</td>
<td>0</td>
<td>158 (11.2)</td>
<td>4 (0.3)</td>
</tr>
</tbody>
</table>

*Antidiarrheal prophylaxis to minimize neratinib-related diarrhea was not protocol-mandated.*

Case Study continue

Patient continue HP with concurrent radiation following surgery to complete up to 18 cycles of HP
Conclusions

- There is still some residual risk of distance recurrence in adjuvant setting for HER2 positive disease optimally treated with anthracyclines and taxanes.

- APHINITY trial is positive, but not in pN- population for the moment.

- The population that might benefit more from adjuvant pertuzumab is high risk HER2 positive disease and regardless time of surgery (pN+ and/or eligible for neoadjuvant strategies).

- EXTENET trial is positive, but in a non planned subgroup analysis, and with an efficacy/safety ratio that is not in favour of neratinib.
THANKS