Interim Overall Survival Analysis of APHINITY:
A randomized multi-center, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo
Presenter: Helen Analo, MD

Interim Overall Survival Analysis of APHINITY
A randomised multi-center, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer
**APHINITY: A Phase III adjuvant study investigating the benefit of pertuzumab when added to trastuzumab + chemotherapy**

- **Central confirmation of HER2 status (N = 4895)**
- **Chemotherapy + trastuzumab + pertuzumab (N = 2400)**
- **Chemotherapy + trastuzumab + placebo (N = 2405)**

- Randomization and treatment with 6 weeks of surgery
- Anti-HER2 Hormone (FAC + 4 treatments after the 6th week of surgery)

* Standard anthracycline or non-anthracycline (TaxO) regimens were allowed: 3 x 4 FEC (or FAC) + 3 x 4 Tax + 4 AC (or EC) + 4 x 4 Tax + 4 Tax

- **Primary endpoint:** DFS (APHINITY definition differs from STOP definition)
- **Secondary endpoint:** OS with 2' tumors non-breast primary cancer included: DL, DL, MP, CML, myeloblasts, and MCL
- **Histological features:** histologic grade, geographic region, National Cancer Inst NCI.
- **Clinical cut off date (2017):** At the time of the primary analysis was 13 June 2016, median follow-up of 45.4 months.

---

**APHINITY primary analysis showed benefit of adjuvant pertuzumab in HER2 +ve early stage breast cancer after 45.4 months of median FU (2017)**

- **DFS (%)**
  - Pertuzumab + placebo (339.7%)
  - Pertuzumab + chemotherapy (333.6%)
- **No. of patients at risk**
  - Pertuzumab + placebo (304.6)
  - Pertuzumab + chemotherapy (304.6)
- **Time (months)**
  - No. of months (12, 24, 36, 48)
- **DFS (%)**
  - Pertuzumab + placebo (339.7%)
  - Pertuzumab + chemotherapy (333.6%)
- **Median follow-up, months**
  - Pertuzumab + placebo (45.4)
  - Pertuzumab + chemotherapy (45.4)

---

**Pertuzumab in combination with trastuzumab was approved for high risk HER2 +ve early breast cancer patients (APHINITY primary analysis 2017)**

- **Node-positive subgroup**
  - DFS (%)
- **Hormone receptor-negative subgroup**
  - DFS (%)

---

[Image credit: Allegheny Health Network]
Methods

- 2nd interim analysis of OS: pre-planned, time-driven, 2.5 years from primary analysis (PA), where 50% of the target events were anticipated.
  - Median follow-up time is 74.1 months, 28.7 months longer than at the PA.
  - P-value of 0.0012 is required for statistical significance for this interim OS analysis.
  - There are now 272 deaths (103 more than at the PA).
  - This is 42.5% of the 640 deaths needed for definitive OS analysis.
- Updated descriptive analyses of DFS and cardiac safety were also performed.
  - There are now 508 patients with an DFS event (127 more than at the PA).

Results

Baseline characteristics were balanced between 2 arms in APHINITY
Baseline characteristics were balanced between 2 arms in APHINITY

APHINITY Interim Overall Survival Analysis 74.1 months median FU, OS by treatment regimen (ITT population)

APHINITY Updated descriptive analysis, 74.1 months median FU
Time to first IDFS event by treatment regimen (ITT population)
Clinical benefit of adjuvant dual-HER2 blockade with chemotherapy

<table>
<thead>
<tr>
<th>Population</th>
<th>Hazard ratio (95% CI) for IDFS at 6 years from randomisation</th>
<th>OS difference after 74.1 months of median FU did not reach statistical significance.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Analysis: median for 5+6 months, 2011</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>Hazard ratio: 0.64 (0.44-0.93)</td>
<td></td>
</tr>
<tr>
<td>LN positive</td>
<td>Hazard ratio: 0.77 (0.42-0.96)</td>
<td></td>
</tr>
<tr>
<td>LN negative</td>
<td>Hazard ratio: 1.33 (0.69-1.86)</td>
<td></td>
</tr>
<tr>
<td>HR positive</td>
<td>Hazard ratio: 0.86 (0.66-1.13)</td>
<td></td>
</tr>
<tr>
<td>HR negative</td>
<td>Hazard ratio: 0.76 (0.58-1.04)</td>
<td></td>
</tr>
</tbody>
</table>

APHINITY Updated descriptive analysis Cardiac Safety, 74.1 months median FU

No new cardiac safety issues emerged.

Primary cardiac event:
- Heart failure: New York Heart Association class III or IV + (VF) drop
- Cardiac death: There were 2 cardiac deaths for each arm

One additional primary cardiac event (heart failure) was reported in the pertuzumab arm.

Secondary Cardiac Event:
- Asymptomatic or mildly symptomatic (NYHA class I) VF drop
- One additional patient in each arm had a secondary cardiac event.

Conclusions
APHINITY 2nd Interim Analysis Overall Survival

Fewer deaths seen in pertuzumab (P) compared to placebo arm.
After 74.1 months median FU, 6-year OS percent were 94.8% (P) vs. 93.9% (placebo)
0.9% difference (95% CI [0.5, 2.2]; hazard ratio 0.85 [0.67, 1.07])
Follow-up is very important to determine OS benefit of P.

APHINITY Updated descriptive analysis of IDFS and safety

Clinical benefit of P in HER2+ early BC is strengthened in node+ve patients.
• Hazard ratio 0.72 (0.59-0.87); 6-year IDFS percent 87.9% (P) vs 83.4% (placebo)
• Difference of 4.5% (95% CI 1.8, 7.1)
• No benefit of P can be claimed in the node-ve population.

After 74.1 months median FU, the benefit of P is seen regardless of HR status.
• 0.73 (0.59 - 0.92) - Hazard ratio for HR+ve patients
• 0.83 (0.63 - 1.01) - Hazard ratio for HR-ve patients

No new cardiac safety issues emerged at this interim analysis.
• Incidence of primary cardiac event remains <1% in both arms (0.8% P vs. 0.3% placebo).
• One additional primary cardiac event (heart failure) was reported in the P arm.