ESMO: Final Overall Survival Analysis: HER2-Positive Metastatic Breast Cancer Patients

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Press Release

First-line treatment with pertuzumab, trastuzumab, and docetaxel significantly improved overall survival.

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**Topic: Breast cancer / Anticancer agents & Biologic therapy**

In the CLEOPATRA study, first-line treatment with pertuzumab/trastuzumab/docetaxel significantly improved overall survival (OS) for patients with HER2-positive metastatic breast cancer compared with placebo/trastuzumab/docetaxel, providing a 15.7 month increase in the median values. The median OS of 56.5 months is unprecedented in first-line and this substantial improvement confirms the pertuzumab containing regimen as standard of care in this setting, reported Prof. Sandra Swain of the Medstar Washington Hospital Center, Washington Cancer Institute, Washington, USA during the Presidential Symposium 1 at ESMO Congress 2014 in Madrid, Spain.

In the CLEOPATRA study, 808 patients from 25 countries with HER2-positive metastatic breast cancer were randomised to receive first-line placebo/trastuzumab/docetaxel or
pertuzumab/trastuzumab/docetaxel. Randomisation was stratified by geographic region and neo/adjuvant chemotherapy.

The patients were eligible for the study if they had HER2-positive (centrally confirmed), metastatic, locally recurrent, or unresectable breast cancer, measurable or non-measurable disease; had received ≤ 1 hormonal regimen for metastatic breast cancer prior to randomisation, disease-free interval at least 12 months since prior neo/adjuvant treatment, and LVEF ≥ 50% at baseline.

The study primary endpoint was progression-free survival (PFS) independently assessed. Secondary endpoints included investigator-assessed PFS, objective response rate, safety, and OS. Final analysis was planned at 385 deaths, with two interim analyses at 165 and 267 deaths.

At primary analysis in May 2011, pertuzumab was shown to increase PFS significantly, with a strong trend to OS benefit. At a second interim analysis in May 2012, the OS was improved to a degree which was both statistically significant and clinically meaningful with hazard ratio (HR) 0.66 (p = 0.0008), but the median OS in patients who received pertuzumab was not reached.

In July 2012, the patients still on placebo were offered crossover to pertuzumab.

At ESMO 2014 the CLEOPATRA researchers reported results of a final prespecified OS analysis (February 2014). This OS analysis was planned when ≥385 deaths were reported. The log-rank test, stratified by prior treatment status and geographic region, was used to compare OS between arms, applying the threshold of p ≤ 0.0456. Subgroup analyses of OS were performed for stratification factors and other key baseline characteristics.

At median follow-up of 50 months (range 0 to 70 months), the statistically significant improvement in OS in favour of pertuzumab/trastuzumab/docetaxel arm was maintained (HR = 0.68, p = 0.0002). Median OS was 40.8 months in the placebo arm and 56.5 months in the pertuzumab arm, with difference of 15.7 months.

The OS benefit in predefined subgroups was consistent with previous observations. It is to be noted that following the previous report of OS benefit, 48 patients in the placebo arm crossed over to the pertuzumab arm.

The PFS in pertuzumab arm was 18.7 vs 12.4 months in placebo arm, HR 0.68 (p < 0.0001).

Median time on study treatment was 17.4 months in pertuzumab arm vs 11.4 months in placebo group.

**Conclusion**

The safety profile of pertuzumab/trastuzumab/docetaxel in the overall population and in patients who crossed over to the pertuzumab arm was consistent with the known safety profile of pertuzumab with more pronounced diarrhoea, rash, mucosal inflammation, pruritus, dry skin, and muscle spasm. No new safety concerns were seen with longer follow-up. There was no evidence of cumulative or late toxicity. The long-term cardiac safety profile was maintained.

Dr Lica Gianni, who discussed the study results, said that CLEOPATRA is an unquestionable therapeutic success with an unquestionable clinical implication: docetaxel/trastuzumab/pertuzumab is the new standard, not an option for first-line treatment of HER2-positive metastatic breast cancer. However, adjuvant trastuzumab was administered in only 10% of the study population. Dr Gianni said
that the therapeutic role and wide applicability of dual HER2-blockade with monoclonal antibodies is established but new therapeutic approaches to improve the overall results of CLEOPATRA should address the different biology and different drug sensitivity of subsets of HER2-positive tumours.

Improvements can be expected by addressing key features of HER2-positive breast cancer linked to different sensitivity in term of hormone receptor status (positive vs negative), PIK3CA status (wild type vs mutant), and immune environment.

The CLEOPATRA study did not allow endocrine therapy of patients with ER-positive tumours. Dual blockade of HER2 with pertuzumab/trastuzumab and concomitant endocrine therapy is feasible as shown by APHINITY study in the adjuvant setting. Dr Gianni wondered if the addition of endocrine therapy after the end of chemotherapy can increase the already large benefit observed in women with HER2-positive/ER-positive metastatic breast cancer patients enrolled in the CLEOPATRA study.

The PIK3CA status can be easily assessed on tumour biopsies or liquid biopsies. Many PI3K inhibitors are available and being tested in combination with standard HER2-directed therapy. T-DM1 is similarly active in HER2-positive tumours harbouring PIK3CA mutation. Therapies tailored according to PIK3CA mutational status of HER2-positive metastatic breast cancer should be tested.

Immune mechanisms and tumour lymphocyte infiltration are involved in the probability of pCR in HER2-positive breast cancer. There is a high expression of PDL1 and CTLA4 linked to residual disease in ER-negative tumours. Dr Gianni concluded that tests should be carried out to see if blocking of CTLA4 and/or PD1/PDL1 will be useful for some patients treated per the CLEOPATRA protocol.

Reference

Abstract 350O_PR - Final overall survival (OS) analysis from the CLEOPATRA study of first-line (1L) pertuzumab (Ptz), trastuzumab (T), and docetaxel (D) in patients (pts) with HER2-positive metastatic breast cancer (MBC) [1]

About the author

The European Society for Medical Oncology (ESMO) is the leading European professional organisation committed to advancing the specialty of medical oncology and promoting a multidisciplinary approach to cancer treatment and care.

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