Randomized Phase II Study of the Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Cetuximab with Cisplatin versus Cisplatin Alone in Patients with Metastatic Triple-Negative Breast Cancer

BACKGROUND:
- Triple negative breast cancer (TNBC), defined by ER, PR, and HER2 receptor negative disease, accounts for 11%-17% of all breast cancers.
- Epidermal Growth Factor Receptors (EGFR) have been identified as a potential therapeutic target in triple-negative breast cancer by Corkery, Brown, Clynes, et al. in a study performed in 2009. Therefore, EFGR inhibitors such as cetuximab may be a rational drug choice to help treat the cancer and/or improve progression free and overall survival.

OBJECTIVE
- To evaluate the safety and efficacy of cisplatin plus cetuximab versus cisplatin alone in patients with mTNBC.

METHODS
- **Design**: Open label, randomized phase II trial, which was conducted in Europe, Australia, and Israel. Duration: June 2007-February 2009.
- **Inclusion criteria**: 18 y.o. or older; histologically confirmed diagnosis of Stage IV mTNBC; ER, PR, HER-2 negative receptor status which was determined locally; tumor receptor status of the primary lesion was permitted for inclusion; no more than one previous chemotherapeutic regimen for the treatment of metastatic breast cancer; at least one measurable lesion by MRI or CT according to RECIST, version 1.0; ECOG Performance status of 0-2 ; tumor tissue available for EGFR expression assessment
- **Exclusion criteria**: Prior therapy with a platinum agent or mitomycin; previous exposure to monoclonal antibody therapy, signal transduction inhibitors or EGFR-targeting therapy; known history of brain metastases; other cancers except for basal-cell skin carcinoma or preinvasive cervical carcinoma
- **Primary outcome measure**: Best overall response rate (ORR) defined as the proportion of patients with a confirmed complete response or partial response according to RECIST
- **Secondary outcome measures**: Progression-free survival, overall survival, time to response, and safety
- 181 patients were randomly assigned to treatment
  - 61 to receive cisplatin alone
    - 3 excluded from analysis due to significant deviations from Good Clinical Practice Guidelines
    - 58 patients were analyzed in this treatment group
    - 1 patient excluded from safety analysis as they did not receive the allocated intervention
  - 120 to receive cisplatin + cetuximab
    - 5 excluded from analysis due to significant deviations from Good Clinical Practice Guidelines
    - 115 patients were analyzed in this treatment group
    - 1 patient excluded from safety analysis as they did not receive the allocated intervention
- 180 patients needed to achieve a power of 80% with an alpha level of 0.10 to detect an increase of 18% in ORR with cisplatin plus cetuximab, an ORR of more than 20% in the cisplatin + cetuximab group, 2:1 randomization ratio, an 80% power for the rejection of both single null hypotheses, and a 5% dropout rate.
- Data handling method was intent-to-treat

RESULTS
- 173 patients were analyzed
- **Primary outcome measure**: 23 patients (20% of cisplatin + cetuximab group) achieved best ORR. (95% CI 13%-29%; Odds Ratio:2.13; 95% CI 0.81 to 5.59; p=.11)
- **Secondary outcome measures**: Progression free survival was 3.7 months in the cetuximab + cisplatin group compared to 1.5 months in the cisplatin alone group (Hazard ratio: 0.67; 95% CI 0.47 to 0.97; p=.032). Overall survival was 12.9 months in the cisplatin + cetuximab group compared to 9.4 months for cisplatin alone (Hazard ratio: 0.82; 95% CI 0.56 – 1.20; p = 0.31). Median time to response was 1.4 months in the cetuximab + cisplatin group and 1.3 months in the cisplatin alone group (Hazard ratio: 0.75; 95% CI 0.25-2.17; p = 0.60).
- **Author's conclusion:** The primary endpoint of the study was not met, although cisplatin plus cetuximab doubled the ORR achieved with cisplatin alone from 10-20% in patients with mTNBC.

STRENGTHS
- Study drugs used between the two groups were similar in terms of dose and duration of use and relatively similar to those used commonly in practice.
- The inclusion/exclusion criteria were appropriate to the patient population being studied.
- The authors acknowledged the study's shortcomings where appropriate.

LIMITATIONS
- Open-label and thus subject to bias
- It was not possible to accurately assess the impact of allowing patients to switch from cisplatin alone to cisplatin + cetuximab because response was not protocol-specified in these patients.
- Information pertaining to enrollment of patients was not clearly stated.
- Data from the analysis for predictive biomarkers of cetuximab activity were unavailable.
- Two null hypotheses were tested simultaneously.
- Information pertaining to how/when/where patients received treatment was not discussed.

CONCLUSION
- While this particular study did not meet its primary endpoint, it can serve as a basis for further studies. The findings associated with the increase in partial response, stable disease, progression, best ORR, and progression and median overall survival may indicate that EGFR inhibitors have a place in therapy for those diagnosed with mTNBC.
- Future studies should include those who are at any stage in mTNBC, not just stage IV so that the data collected can be extrapolated to the entire population affected by the disease. In doing so, we may learn that we can treat mTNBC sooner and may achieve better outcomes..

Reference: Baselga J, Gomez P, Greil R, Braga S, Climent MA, Wardley AM et al. Randomized Phase II Study of the Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Cetuximab With Cisplatin Versus Cisplatin Alone in Patients With Metastatic Triple-Negative Breast Cancer. J Clin Onc. 2013;31(20) 2586-91.

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