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Herceptin and Interleukin-12 combination therapy in patients with HER2/neu-overexpressing malignancies: a phase I trial

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We have observed that co-stimulation of natural killer (NK) cells with Interleukin-12 (IL-12) and Herceptin-coated Her2/neu-positive breast cancer cells leads to the secretion of large amounts of Interferon-gamma (IFN-g) and other potent immunomodulatory cytokines. We theorized that IL-12 would potentiate the anti-tumor actions of Herceptin and conducted an NCI-sponsored phase I trial using these two agents (T99-0032). Patients with metastatic Her2/neu-expressing malignancies (HER 1+, 2+, or 3+) received Herceptin on day 1 of each weekly cycle (4 mg/kg initially and 2 mg/kg thereafter). Beginning on week 3, patients also received intravenous injections of IL-12 on days 2 and 5. We have escalated the IL-12 component of this regimen within cohorts of three patients (30, 100, 300, or 500 ng/kg). Nine patients have been treated and those with stable disease or a clinical response at week 14 were allowed to continue therapy for one year. Seven patients had breast cancer, 1 had pancreatic cancer, and 1 had a neuroendocrine tumor. There has been one complete response in a patient with metastatic breast cancer (100 ng/kg dose level). A patient treated at the 300 ng/kg dose level experienced significant improvement in pain associated with widespread bony metastases, but progressed in L5 after 14 weeks and was removed from therapy. This regimen has been well tolerated with no reported Grade 3 or 4 toxicities. Fever, chills, and hypotension associated with IL-12 administration have been encountered, but have been easily managed. Correlative studies were conducted investigating cytokine levels and peripheral blood mononuclear cell (PBMC) activity in response to treatment. Of note, the only patient with measurable levels of serum IFN-g was the same one who experienced a complete clinical response. Analysis of this patient's PBMCs by Real-Time RT-PCR revealed an average 17-fold increase in IFN-g transcript. Intracellular cytokine staining showed significant production of IFN-g by both NK cells and T cells, whereas PBMCs of non-responders exhibited minimal production. Similar results were seen with levels of the anti-angiogenic factors IP-10 and MIG. These findings strongly suggest that immune modulation will enhance the anti-tumor efficacy of monoclonal antibody therapy.

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How much improvement in survival do early breast cancer patients require to consider endocrine therapy worthwhile?

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Purpose: Endocrine or hormonal therapies are increasingly used in the systemic treatment of early breast cancer. Each treatment intervention is begun in the belief that it will probably improve health more than it causes suffering, but trade-offs are often necessary. This study attempted to find out what trade-offs between quality and quantity of life are acceptable for patients

Methods: In this Patient Preference Interview (PPI) study, women who had previously taken part in a clinical trial of adjuvant endocrine therapy were asked (as part of a semi-structured interview) what minimum improvements in survival they would accept to balance their experience of endocrine therapy.

Results: The majority of the 84 women interviewed required an increase in survival time of an additional 3 and 5 years above expected survival without treatment (which would have been 5 or 15 years respectively). When considering 5-year survival rates respondents required an increase of 5% and 10% beyond expected 5-year survival rates of 80% or 60% respectively. These median acceptable benefits were higher than those in a similar study of adjuvant chemotherapy. There was some evidence to suggest that factors such as a longer duration of therapy and toxicity attributed to therapy influenced the required survival gains. Route of administration of treatment by tablets or injections had little influence on acceptable gains. Few respondents were willing to 'trade-of' any survival gains in order to avoid their worst side effect. Hypothetical survival rate questions had worse reliability than questions based on the individuals' expectations or choices made for a sister or best friend, which calls into question the validity of preference studies where 'trade-offs'are made on behalf of a hypothetical unknown person.

Conclusions: Patients were able to quantify the benefits which would make their treatment worthwhile, and such views should be considered when evaluating new treatments, as a bridge between survival and quality of life data.

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The ATAC (Arimidex™, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal (PM) patients (pts): Factors influencing the success of PT recruitment

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Purpose: The ATAC trial evaluates, in a randomized double-blind design, anastrozole (AN) alone or in combination with tamoxifen (TAM), relative to TAM alone as 5-year adjuvant treatment for PM pts with early breast cancer. To date, this trial is the largest adjuvant trial ever conducted in such pts. In approximately 30 months, the trial recruited over 9300 pts from 380 centres in 21 countries. A number of factors influencing the success of pt recruitment into this trial were highlighted in a questionnaire that was sent to all trialists.

Methods: This questionnaire included 11 statements rated for level of importance on a three-point scale.

Results: A total of 63% of the trialists returned the completed questionnaire. The top six motives for recruiting pts into the trial are included in the table.

	Very important (%)	Somewhat important (%)	Not important (%)
I found the scientific rationale of the trial attractive	84	15	1
I found the design easy to explain to the patients	79	18	3
Pragmatic design in line with standard practice	76	21	3
Infrastructure of the trial was well organised	70	26	4
The treatments were oral and relatively non toxic	69	28	3
Logical extension of earlier endocrine trials	67	29	4

Conclusions: Scientific rationale and pragmatism were leading reasons for inclusion of pts into the trial. A new questionnaire will solicit opinion from pt participants.

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Neoadjuvant chemotherapy with standard vs high dose of epirubicin plus filgrastim for locally advanced breast cancer. Report from the mexican oncology study group (MOSG)

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One research approach to improve the efficacy of tumor response and survival of patients with locally advanced breast cancer (LABC) is chemotherapy dose intensification. Purpose: Evaluate the response rate, toxicity and overall survival in 2 groups of LABC patients using different doses of Epirubicin as part of a FEC regimen. Inclusion criteria: naïve patients with LABC. All patients received 5-FU and Cyclophosphamide at 500 mg/m2 on day 1, and Epirubicin either 70 mg/mg2 (arm A) or 120 mg/mg2 (arm B) every 3 weeks. On arm A, G-CSF (Filgrastim) 5 μg/k/day was administered days 2-11 or until an ANC of 2,000 was obtained. Four cycles were followed by locorregional treatment Results: 236 patients were included from 02/98 until 03/01 (112 arm A and 124 arm B). Characteristics and results for arm A vs B were respectively: median age 45.4 vs 46.3 years; stage IIB 2% vs 5%, IIIA 48% vs 37%, III B 50% vs 58%; primary tumor 2 cm 3% vs 5%, 3 cm 56% vs 53%, 4 cm 34% vs 33%, > 5 cm 6% vs 9%; Karnofsky of 100%: