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**Comparison of two Phase II trials evaluating three dosing regimens of fulvestrant in Japanese vs non-Japanese postmenopausal women with advanced breast cancer (FINDER1 and FINDER2)**

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**Background:** Data from the **F**aslodex **In**vestigation of **D**ose evaluation in **E**strogen **R**eceptor-positive (ER+) advanced breast cancer studies (FINDER 1 and 2) have been compared to identify population differences in terms of efficacy, safety and drug exposure between Japanese (J) or non-Japanese (NJ) patients treated with 3 different dose regimens of fulvestrant.

**Material and Methods:** Postmenopausal women with ER+ advanced breast cancer (FINDER1, J; FINDER2, NJ) who had recurred or progressed following prior endocrine therapy were randomised 1:1:1 to receive fulvestrant 250 mg/month (approved dose [AD]); 250 mg plus loading dose (LD, 500 mg on Day 0, then 250 mg on Days 14, 28 and every month thereafter); and 500 mg (high dose [HD], 500 mg/month plus 500 mg on Day 14 of Month 1). Treatment continued until disease progression or any other criterion for discontinuation was met. The primary endpoint was: objective response rate (ORR); secondary endpoints included time to progression (TTP), clinical benefit rate (CBR), tolerability (adverse events [AEs]) and pharmacokinetics. This investigation examined whether or not there were any significant differences in efficacy/tolerability and drug exposure between J and NJ patients.

**Results:** In total, 144 patients were randomised to FINDER1 and 143 patients to FINDER2. Demographic characteristics were similar within each study, with no significant differences between studies. ORR rates (%) for fulvestrant AD, LD and HD were 11.1%, 17.6% and 10.6%, respectively, in FINDER1; and 8.5%, 5.9% and 15.2%, respectively, in FINDER2. In FINDER1, CBRs for AD, LD and HD were 42.2%, 54.9% and 46.8%, respectively; in FINDER2: 31.9%, 47.1% and 47.8%, respectively. The number of progression events and median TTP were similar within and across the two trials for each dosing regimen. The pharmacokinetics of fulvestrant appeared to be similar in J and NJ patients and was predictable across the 3 dosing regimens within each study. Fulvestrant was well tolerated; there was no relationship between dose and ethnicity in terms of number of AEs/serious AEs, treatment-related AEs or AEs leading to discontinuation.

**Conclusions:** There were no significant differences detected in the efficacy, tolerability and pharmacokinetics of 3 fulvestrant dosing regimens in J (FINDER1) vs NJ patients (FINDER2). Therefore, ethnicity is unlikely to have an impact on the success of fulvestrant treatment of postmenopausal women with advanced breast cancer.

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**Inhibition of fatty acid synthase by amentoflavone suppresses HER2/neu (erbB2) oncogene expression in breast cancer cells**

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**Purpose:** Fatty acid synthase (FASN) is a potential therapeutic target to treat cancer and obesity, and highly elevated in 30% of HER2-overexpressing breast cancers. A molecular link between FASN and HER2 oncogene is a marker for poor prognosis in breast cancers. Considerable interest has been developed in searching for novel FASN inhibitors as a therapeutic target for HER2-overexpressing breast cancers.

**Materials and Methods:** SKBR3 and MDA-MB-231 human breast cancer cell lines were obtained from ATCC. Amentoflanone was purchased from Sigma-Aldrich® (>99.0% HPLC). FASN activity was measured by the incorporation of [$^3$H]acetyl-CoA into fatty acids. Using western blotting, cell growth and proliferation inhibition assay, and caspase3-dependent poly-ADP ribose polymerase (PARP) cleavage assay, we characterized the pharmacological effects of amentoflavone on HER2-regulated signaling pathways and apoptosis.

**Results:** In this study, amentoflavone, a naturally occurring flavonoid, was found to be effective in suppressing FASN expression and lipogenesis in HER2-overexpressing breast cancer cells, while HER2 expression was dramatically down-regulated by amentoflavone. Amentoflavone inhibited cellular proliferation and induced apoptosis in HER2-overexpressing cancer cells. Moreover, amentoflavone inhibited phosphorylation of Akt and p70S6K, and decreased phosphorylation of p38, Erk1/2, and JNK. The use of pharmacological inhibitors revealed that the modulation of Akt, p70S6K, and MAPK phosphorylation was required amentoflavone-induced FASN inhibition.

**Conclusion:** These findings provide evidence of an active role of FASN as the key molecular sensor of energy balance in HER2-overexpressing breast cancer cells, suggesting that amentoflavone may act as the potential chemopreventive or chemotherapeutic agent for breast cancers that overexpress HER2.

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**Silibinin enhances UVB-induced cytotoxicity of ERa positive breast cancer cells**

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**Background:** Silibinin is a major active constituent of silymarin, the mixture of flavonolignans extracted from blessed milk thistle and has anticancer effects in various malignancies including prostate, intestinal tract, skin, and bladder. Recently, it has been reported that silibinin plays an important role in breast cancer cells. In addition, a recent study showed that silibinin enhances apoptosis in response to UVB-induced damage in human keratinocytes. Thus, we investigated the effect of silibinin in ERa positive breast cancer cells and whether the combination of silibinin and UVB synergistically affect to cytotoxicity.

**Materials and Methods:** An effect of silibinin on cell viability in ERa positive breast cancer (MCF-7) cells was determined using MTT assay and the expression of PARP, p53, and PTEN were detected by Western blotting.

**Results:** Silibinin induced dose- and time-dependent loss of MCF-7 cells viability. Interestingly, silibinin up-regulated p53 expression and induced apoptotic cell death of MCF-7 cells, which was identified by PARP cleavage. Moreover, silibinin enhanced UVB-induced cytotoxicity in MCF-7 cells.

**Conclusions:** These findings suggest that silibinin might be an important supplementary treatment agent in ERa positive breast cancer.

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**Recombinant anti-HER2 antibody production in bacterial host**

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**Background:** A few years ago, common therapeutic methods for breast cancer treatment were surgery, chemotherapy, and radiation, but these methods affect both normal and malignant tissues. On the other hand, targeted cancer therapies focus on specific cancer receptors that influence the growth and proliferation of cancer cells. In recent years, recombinant monoclonal antibodies and derivatives have emerged as targeted therapy agents. In some cases, over expression of Human Epidermal growth factor Receptor 2 (HER2) on the cell surface of breast cancer cells has been observed, that can be associated with more aggressive or treatment-resistant cancers. Thus, anti-HER2 antibodies can be used successfully.

**Material and Methods:** The cDNA, encoding the amino acid sequence of the anti-her2 antibody, was designed and synthesized. Heavy and light chains of antibody inserted into a polycistronic expression vector. Expression vector transformed to the bacterial host and transformants were cultured in suitable medium. Produced antibody was assayed by conventional methods.

**Results:** Polycistronic expression vectors were constructed for the antibody chains and transformed into the bacterial host. Whole cell lysates were detected by visualization of heavy and light chains bands by SDS-PAGE under reducing condition, and assembled antibody was observed under Non-reducing condition. Other conventional assays showed other related results, respectively.

**Conclusions:** Bacterial hosts have several advantages as an antibody producing system. They can consider as economic, labor saving devices rather than expensive mammalian cells. This study demonstrates that, full length antibodies and antibody fragments can be successfully expressed in bacterial hosts. Bacterial host-produced antibodies bound to cancer receptors with similar affinity to that of antibodies produced in mammalian cells.