assigned. This incorrect treatment was only identified during the audit procedures of the pharmacy after the blind was broken (78).

k. Exclusion of study subjects who failed to take drug long enough to have the expected efficacy – the Krainick-Strobel study

In a study of breast cancer with letrozole, Krainick-Strobel et al. (79) used a modified ITT analysis and PP analysis. The modified ITT analysis excluded both untreated patients and those who took study medication for less than four months, which was the minimum treatment duration for clinically sound assessment of tumor shrinkage. The authors stated that a valid assessment of letrozole efficacy, in terms of tumor shrinkage, required at least four months of treatment. The PP analysis excluded all patients with major protocol violations, these being defined as: (1) an interval of more than 30 days between the last dose of letrozole and breast surgery; (2) the patient's refusal to undergo surgery; (3) deviation from clinically relevant selection criteria; and (4) any treatment with prohibited medication.

The Krainick-Strobel study is distinguished in that the subjects evaluated for efficacy were defined separately than the subjects evaluated for safety. In other words, all subjects receiving study drugs (no matter the duration) were evaluated for safety (32 subjects), whereas subjects evaluated for efficacy were 29 subjects (modified ITT group) and 25 subjects (per protocol group).

l. Excluding subject who dropped out because of adverse events, and because of the bad flavor of the study drug – the Kreijkamp-Kaspers study

In a study of plant estrogen supplements on bone mineral density, Kreijkamp-Kaspers et al. (80) used both modified ITT analysis and per protocol analysis. The ITT population was 202 subjects. The modified ITT population was fewer, namely, 175 subjects, and these were subjects who received an analysis at baseline, and at least one additional analysis. The per protocol population was even fewer, and consisted of the 153 subjects who had completed the entire treatment protocol. Thus, following randomization, the steady dropout of subjects due to gastrointestinal distress, aversion to the taste of the study drug, had the consequence that the modified ITT group was only 175 subjects, and the PP group was only 153 subjects.

[78] Berek JS. E-mail of August 10, 2010.

[79] Krainick-Strobel UE, Lichtenegger W, Wallwiener D, et al. Neoadjuvant letrozole in postmenopausal estrogen and/or progesterone receptor positive breast cancer: a phase IIb/III trial to investigate optimal duration of preoperative endocrine therapy. *BMC Cancer.* 2008;8:62.

[80] Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *J Am Med Assoc.* 2004;292:65–74.