

### **l. Excluding Subjects Who Failed to Receive the Assigned Treatment Because of a Mistake by the Healthcare Provider—The Berek Study**

In a study of ovarian cancer, Berek et al. (80) analyzed the data by modified ITT analysis. Modified ITT analysis was conducted only on subjects who received at least one dose of study treatment. Thus, subjects not exposed to any treatment were excluded from the analysis. According to the authors, the study was blinded using a third-party pharmacist who prepared the treatment infusion bags. A few of the subjects were incorrectly started on and completed a full series of the opposite treatment than assigned. This incorrect treatment was only identified during the audit procedures of the pharmacy after the blind was broken (81).

### **m. Exclusion of Study Subjects Who Failed to Take Drug Long Enough to Have the Expected Efficacy—The Krainick-Strobel Study**

In study of breast cancer with letrozole, Krainick-Strobel et al. (82) 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 4 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 4 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 to 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 (PP group).

### **n. 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. (83) used both modified ITT analysis and PP 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 PP population were even fewer, and consisted of the 153 subjects who had completed the entire treatment protocol. Thus, following randomization,

<sup>80</sup>Berek JS, Taylor PT, Gordon A, et al. Randomized, placebo-controlled study of oregovomab for consolidation of clinical remission in patients with advanced ovarian cancer. *J. Clin. Oncol.* 2004;22:3507–16.

<sup>81</sup>Berek JS. E-mail of August 10, 2010.

<sup>82</sup>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.

<sup>83</sup>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.