> treatment-related lymphocytosis is an **expected and frequent pharmacodynamic phenomenon** observed with initiation (or re-initiation) of ibrutinib. Ibrutinib associated treatment-related lymphocytosis generally occurs within the first few weeks of therapy, peaks within the first few months, and resolves slowly.

6. Potential Confusion in Defining Adverse Events

Defining terms used to characterize drug safety is not a trivial issue. Ioannidis et al. (61) find that some publications use the terms *side effects* and *adverse effects* to mean the same thing, thus creating confusion. Regarding this inappropriate use of terms, Ioannidis et al. (62) complain that, some authors use the term *adverse events* synonymously with *side effects*. What is inappropriate is that the term *side effects* implies that the drug causes the side effect while, in contrast, the term adverse effects does not imply causality.

Moreover, ICH Guidelines (63) expressly recommend not using the term, side effect, writing that, "[t]he old term 'side effect' has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction."

The CFR distinguishes between adverse events that are "expected" and that are "anticipated." To quote from 21 CFR §312.32(a),

> Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure … [u]nexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

To repeat, "expected" is not synonymous with "anticipated."

b. Classification of Adverse Events as Induced by Disease Versus Induced by the Study Drug

This distinguishes between AEs due to the disease and drug-induced AEs. This particular example is from the Council for International Organizations of Medical Sciences (CIOMS). The example provided by CIOMS concerns the AE of skin eruptions (64):

> In diagnosing a cutaneous eruption that may be an adverse drug reaction it is important to decide whether the eruption is due to the disease, primarily due to the drug, or due possibly to an interaction between the disease and the drug. Cutaneous reactions frequently occur when patients are receiving a number of drugs, and thus etiological relationship may be difficult to assess. When patients take drugs for a febrile disorder [increased body temperature] that ultimately proves to be an infection, an eruption may be due to the underlying disorder or the prescribed drug.

This concerns AEs that are accidents, such as accidents occurring when using machinery. Where a subject enrolled in a clinical study is

[61]Ioannidis JP, Evans SJ, Gøtzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann. Intern. Med. 2004;141:781–8.

[62]Ioannidis JP, Evans SJ, Gøtzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann. Intern. Med. 2004;141:781–8.

[63]ICH Topic E 2 A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; June 1995.

[64]Bankowski Z, Bruppacher R, Crusius I, Gallagher J, Kremer G, Venulet J. Reporting adverse drug reactions. Geneva: Council for International Organizations of Medical Sciences; 1999. 146 pp.