on adrenocortical carcinoma (40) on non-small cell lung cancer (41) and on cancer of the head and neck (42) as cited.

An adverse event need not be life threatening in order to mandate dose modification. In a description of skin reactions from sorafenib and sunitinib, Lacouture et al. (43) detail the hand and foot skin reactions occurring with use of these drugs, and schemes for dose reduction. The hand and foot skin reactions include blisters, necrosis, pain, reduction in mobility, and loss of weight-bearing ability of feet. The recommended dose reduction is a 50% reduction in drug dose for at least 7 days, while the recommended drug delay is discontinuing the drug for at least 7 days. These recommendations are keyed to, or coupled with, a standard grading scale for skin reaction severity.

II. SAFETY DEFINITIONS

a. Definitions from U.S. and European regulatory agencies

The FDA's Guidance for Industry provides the following definitions for safety terms (44). The EMA also provides safety definitions, but these definitions may differ somewhat from those of the FDA (45). Investigators and medical writers need to compare safety definitions in these three sources: Code of Federal Regulations (CFR), ICH Guidelines, and FDA's Guidance for Industry.

Definitions for adverse events find a basis in the CFR. For example, 21 CFR 310.305(b) provides that adverse events include (46):

> *Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.*

[40] First International Randomized Ttrial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) Etoposide, Doxorubicin, Cisplatin and Mitotane vs. Streptozotocin and Mitotane. Collaborative Group for Adrenocortical Carcinoma Therapy-COACT-CLINICAL STUDY PROTOCOL. April 12, 2004.

[41] A Phase III Randomized Trial of Adjuvant Chemotherapy with or without Bevacizumab for Patients with Completely Resected Stage IB (>4 cm) – IIIA Non-Small Cell Lung Cancer (NSCLC). E1501. Revised April 2008.

[42] A Randomized Phase II Trial of Concurrent Radiation and Chemotherapy for Advanced Squamous Cell Carcinomas of the Head and Neck. RTOG 97-03. September 8, 1998.

[43] Lacouture ME, Wu S, Robert C, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Oncologist*. 2008;13:1001–1011.

[44] U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry. E6 Good clinical practice: consolidated guidance (April 1996).

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

[46] 21 CFR 310.305(b) (April 1, 2010 version).