Briefing Document

16 February 2000

Purpose of the Meeting

The ongoing registration trial, H3E-MC-JMCH (JMCH for brevity), has been modified through addition of folic acid for the purpose of promoting patient safety. The Medical Review Officer has stated that he does not support the addition of vitamins to an ongoing registration trial (FDA communications to Lilly on December 21, 1999 and January 6, 2000). The sponsor has sought a face-to-face meeting to come to agreement as to the implications of the action of adding folic acid to the pivotal registration trial and for supporting trials.

In addition, Lilly would like to discuss proposed modifications to our second-line NSCLC trial supporting the mesothelioma registration trial. This document includes the issues that we are seeking guidance on and background information related to these issues.

Rationale for Programmatic Intervention

Compound Overview and Link to Folate Metabolism

The antitumor activity of LY231514, a multitargeted antifolate, is derived from simultaneous and multiple inhibition of several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways. LY231514 has been found to inhibit cell growth by interfering with the action of the enzymes thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) by competing with the reduced folates 5,10-methylene tetrahydrofolate, dihydrofolate, and 10-formyl tetrahydrofolate for binding sites on the respective enzymes (Shih et al. 1997). Thus, the mechanism of action of LY231514 and other folic acid analogues such as methotrexate and lometrexol is critically linked to intracellular folate metabolism. The effects of antifolates are also significantly modulated by the formation of intracellular polyglutamates. Polyglutamates are retained within the cell for long periods thus increasing the potency of the antifolate. In addition the polyglutamate derivatives of LY231514 are significantly more potent inhibitors of TS and GARFT than the parent compound and may thus serve to enhance the action of the drug on these targets.

Preclinical and clinical studies evaluating the impact of dietary folic acid on the toxicity or efficacy of antifolates such as LY231514 and lometrexol have been reported. Because tumor tissue and normal tissue, such as bone marrow, presumably have different folate requirements, it is possible to decrease the toxicity to healthy tissue while maintaining antitumor effect through careful adjustment of folic acid intake. This has been shown in experimental systems for LY231514 and another antifolate, lometrexol (Worzalla et al. 1998; Alati et al. 1996) and in clinical trials with lometrexol (Young et al. 1992; Laohavinij et al. 1996). In addition, it has been clinically observed that the efficacy of low dose methotrexate used in the treatment of rheumatoid arthritis is not negatively affected by folic acid supplementation, while an improvement in toxicity is seen (Morgan et al. 1998).

Folinic Acid versus Folic Acid

If a patient receiving an antifolate experiences severe, life-threatening toxicity, standard medical treatment includes rescue with high doses of the reduced folate leucovorin (folinic acid). Because folates are not efficiently stored in the body, depletion and repletion can occur relatively quickly with supplementation. For example, megaloblastic hematopoeisis reverts to normal hematopoeisis within 12 to 48 hours of folinic acid supplementation (Antony 1991). Reversal of methotrexate toxicity by folinic acid is due

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