Executive Summary

The sponsor submitted data from two studies which evaluated the combination of carboplatin every 3 weeks with irinotecan daily x 5 x 2 every 3 weeks. The first study is a Phase I dose finding study with pharmacokinetic evaluation conducted in 28 patients with refractory or relapsed solid tumors to establish the maximum tolerated dose (MTD). In the Phase II study, patients were randomized to receive either irinotecan 12 mg/m^2/day x 10 days in combination with carboplatin exposure (AUC) 4 mg/mL*min (Treatment A) or irinotecan 20 mg/m^2/day x 10 days every 21 days.

The pharmacokinetic information obtained from the Phase I study was found to be inconclusive because of the following reasons:

1. Only 33% of the measured carboplatin AUCs were within 30% of the target AUC of 4 mg/mL•h. However, a previous study showed that use of same formula (the modified Calvert formula) resulted in 68% of the measured carboplatin AUCs within 30% of the target AUC in the subset of patients with measured samples (Marina et al, Journal of Clinical Oncology, Vol 11, No 3 (March 1993)). It appears that this could be due to dosing errors as reported by the sponsor or unknown clinical reasons.
2. The AUC of irinotecan (18 mg/m^2) was 550 ng/mL•h in comparison to 294 ng/mL•h as observed in previous studies. No significant differences were observed for the metabolites of irinotecan (SN 38 and APC). The differences observed for irinotecan could be due to (a) sample size (N=5) (b) variability between studies.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the submitted information and has found the analysis performed by the sponsor inconclusive. Hence, no information should be added to the label.
The following information should be forwarded to the sponsor:

1. Whenever comparisons from across studies are made, a table clearly showing the comparison of pharmacokinetic parameters should be provided.
2. Discarding of data from analysis is discouraged. Prior information available in the literature should be utilized in order to maximize the information derived in the study. Use of other analysis methodology such as population pharmacokinetic analysis, may have enabled a much better interpretation of the study.

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