that rs301 and **rs13702** correlated with survival time of the patients to their leukemia, whereas no association with survival time was observed for rs328.

c. FDA's Decision-Making Process in Utilizing SNP Biomarkers in the FDA's Approval of Sofosbuvir

At the time of drug approval, FDA publishes its *Approval Letter* along with its *Medical Review*, *Pharmacological Review*, *Statistical Review*, and other reviews. This is from FDA's approval of sofosbuvir for the indication of hepatitis C virus (HCV) infections. This is for NDA 204671, which can be found on Mar. 2015 on FDA's website. The SNP was located on the human chromosome near the gene encoding *IL-28B*. In the list of baseline characteristics of all study subjects, the Sponsor had disclosed the genotype for each subject, that is, whether the subject was CC, CT, or TT. This refers to the nucleotide of interest near the *IL-28B* gene.

The FDA reviewer stated that:

> [a] genetic polymorphism near the IL28B gene is a strong predictor of SVR [Sustained Virologic Reponse] in patients receiving therapy with peginterferon and ribavirin. Numerous studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype.

The FDA reviewer merely observed the predictive value of the polymorphism, and refrained from making any further comment. The term *Sustained Virologic Response* (SVR) is conventional for studies on HCV, and it refers to reduction of viral RNA in the bloodstream to levels below 25 IU/mL blood as measures at 12 weeks after study drug cessation. The FDA reviewer's identification of the polymorphism indicates that it is identical with SNP **rs12979860**. This polymorphism is detailed below.

d. SNP That Is Upstream of *IL-28B* Gene and HCV Infections

Scientific background information on SNPs associated with the gene encoding *IL-28B* is disclosed here. SNP **rs12979860** is located about 1000 bases upstream of the gene encoding *IL-28B*. The *IL-28B* gene resides on chromosome 19. More specifically the gene resides at position 19q13 on chromosome 19.

In various people, this SNP can occur in three genotypes, homozygous for C (C/C), heterozygous (C/T), and homozygous for T (T/T).

People who are homozygous for C are twice as likely to respond to anti-HCV therapy than people homozygous for T (T/T), where therapy is with peginterferon alpha and ribavirin. Also, spontaneous recovery from HCV occurs at a two-and-a-half-times greater rate. Regarding subgroups, the variant that predicts greater risk of infection (T) is more common among Africans than in Caucasians, where the prevalence is 50–70% in Kenyans and Nigerians (206,207,208). The fact that SNP **rs12979860** has been characterized for its prognostic value (disease outcome in absence of therapy) and predictive value (disease outcome with a specific drug) indicates that it is a biomarker that can reasonably be included as an exploratory endpoint in a clinical trial.

[206]Thio CL, Thomas DL. Interleukin-28b: a key piece of the hepatitis C virus recovery puzzle. Gastroenterology 2010;138:1240–3.

[207]Thomas DL, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009;461:796–801.

[208]Howell CD, Gorden A, Ryan KA, et al. Single nucleotide polymorphism upstream of interleukin 28B associated with phase 1 and phase 2 of early viral kinetics in patients infected with HCV genotype 1. J. Hepatol. 2012;56. doi:10.1016/j.jhep.2011.10.004.