human tumor cell lines, and *in vivo*, in congenitally immunodeficient 'nude' mice. In response to our request, the applicant conducted the following studies:

- *in vitro* effects of R-138727 and R-106583 on proliferation of human cell lines derived from lung, colon and prostate tumors; and
- *in vivo* effects of prasugrel on growth of human tumor xenografts derived from lung, colon and prostate in 'nude' mice.

The results are summarized in Dr. Belay Tesfamariam's review, dated 2/2/09:

- *In vitro:* Exposure of serum-starved human tumor cell lines (lung, colon and prostate) to prasugrel metabolites did not increase cell proliferation relative to starved cells stimulated to proliferate by addition of 10% fetal bovine serum.

- *In vivo:* In tumor-bearing 'nude' mice implanted with human lung, colon and prostate tumor cells, prasugrel did not enhance tumor growth rates.

Dr. Tesfamariam concluded: "In the context of the negative findings in the genotoxicity and the 2-year rodent carcinogenicity bioassays, these additional data on tumor progression assays add to the weight-of-evidence that prasugrel exhibits neither carcinogenic nor tumor progressing activity."

Analysis:

Prasugrel was associated with an excess number of new malignant tumors. Depending on whether risk is calculated from the analyses of the Division or those of the Sponsor, and depending on whether or not non-melanomatous skin cancers are included, the point estimate for relative risk is in the range of 1.2 - 1.5, with absolute risk in the range between 0.23% and 0.50% over the 12-month course of the study. The applicant's analyses do not show a statistically significant difference between treatment groups. Some of the Division's analyses demonstrate a nominally statistically significant difference between treatment groups, whereas others do not.

In deciding whether prasugrel plays a causal role in stimulating tumors, several factors merit consideration:

1. Mechanism

It is difficult to conceive of a mechanism through which prasugrel could cause or stimulate cancer development. One could posit that platelet aggregation and thrombosis (processes with which prasugrel interferes) provide natural defenses against tumor development and metastasis, that prasugrel is pro-angiogenic or mitogenic, or that it acts as a tumor cell growth factor; however, these concepts are purely speculative. There is a paucity of non-clinical data suggesting a role for prasugrel in tumor promotion.

2. Drug Class

It is noteworthy that prasugrel shares some similarities with clopidogrel, and there is no evidence that clopidogrel stimulated cancer development in its large development program. Therefore, if prasugrel were causing tumor stimulation, its effect is unique and not a class effect.

This would seem to make causality less likely. In the entire history of drug development, the only products thought to stimulate tumor development are the recombinant erythropoietins (Epoetin alfa; Darbepoetin alfa), and these are growth factors, whereas prasugrel is not.

3. Tumor Types

The distribution of tumor types was typical of a coronary artery disease patient population, and appeared little affected by prasugrel. According to United States Cancer Statistics, National Program of Cancer Registries, the leading types of cancer by incidence are: prostate, breast, lung/bronchial, and colorectal (http://apps.nccd.cdc.gov/uscs/, searched 7/2/08). In TAAL, the numbers of new non-benign tumors in these categories for prasugrel and clopidogrel were prostate: 11 versus 9; breast: 5 versus 1; lung/bronchial: 17 versus 13; and colorectal: 23 versus 10, respectively. Because females comprised only ~25% of the subjects enrolled in TAAL, the numbers of breast cancer cases would be roughly doubled if extrapolated to a 50% female population. Thus, if prasugrel is causally related to the excess tumors observed in TAAL, the stimulation appears to be fairly general in nature.

4. Carcinogenicity; Tumor Promotion

Considering the biology of the tumor types observed and the relatively brief (15-month) time frame of TAAL, it is simply not plausible for carcinogenicity to underlie these trends. Moreover, the results of prasugrel's carcinogenicity studies were not regarded to be positive (except by Dr. Marciniak, who held a minority view). Thus, if prasugrel *is* playing a role here, it is through enhancement of tumor progression and not carcinogenesis. The *in vitro* and *in vivo* data do not, however, support the hypothesis that prasugrel promotes tumor growth and/or progression.

5. Cancer Deaths

There were 27 and 19 cancer deaths in the prasugrel and clopidogrel groups, respectively, for a RR of 1.42 (95% CI: 0.79, 2.55). If cancer deaths in subjects with pre-existing cancers are included in the totals, the numbers of deaths are 33 and 21, respectively (RR=1.57, 95% CI: 0.91, 2.71). The applicant has argued that the imbalance is a byproduct of ascertainment bias. Because there were greater numbers of subjects with neoplasia-related adverse events in the prasugrel group (175) than the clopidogrel group (138), and because vital status was specifically sought for this subgroup of subjects, the imbalance in deaths would be expected to approximate 175/138 = 1.27. In fact, the RR for cancer deaths exceeds 1.27, although it is not strikingly different. Thus, the applicant's argument does provide some measure of reassurance. Nevertheless, deaths are always a reason for concern.

6. Multiplicity of Safety Analyses

Safety analyses are observational in nature and conducted without the benefit of pre-specified hypotheses or correction for multiplicity; therefore, there is always the possibility of a false positive finding. False positive results are, of course, *expected* under these circumstances. Beyond a mere association between prasugrel and excess cancers, therefore, biological plausibility, exposure-response, and other factors are helpful to support causality, and these factors seem to be missing here.

Conclusion:

In summary, by the Division's classification of non-benign tumors, there is a trend showing more adverse events of new, non-benign neoplasms in the prasugrel group than the clopidogrel group. The relative risk is 1.29, with 95% CI: 0.96, 1.72. The absolute risk is 0.33%, over a median follow-up of 12 months. However, given the lack of a plausible underlying mechanism of action, non-clinical data that fail to show tumor promotion, the multiplicity of safety analyses, the fact that fairly extensive data on a related drug (clopidogrel) show no signal, and the reality that only the erythropoietins have been shown to promote tumors, there is a good chance that these observations are spurious.

There is unanimous agreement within the Division that these findings should not stand in the way of prasugrel's approval, and the Office concurs with this position. However, there are differing opinions in the Division as to how labeling should be handled. There are some who argue that if there is a risk of tumor stimulation, it should be related to exposure. These individuals advocate placing a limit on the duration of prasugrel use to perhaps 30 days, with patients switching to clopidogrel at that point. Counter-arguments have been raised to this proposal: 1) Any proposed duration of treatment is necessarily arbitrary; 2) Switching involves logistical issues. Some patients will simply discontinue their thienopyridine, which could lead to stent thrombosis; 3) The strategy of switching from prasugrel to clopidogrel has not been tested. The pharmacodynamic effects of the change are not likely to be important, but the issues of logistics, as well as physician and patient acceptance, are key. For the majority of the review staff who believe more strongly that the imbalance is spurious, the exposure issue is moot, and they would not place any limitation on duration of use. I agree with the majority view on this issue.

Some have suggested a postmarketing requirement to study the tumor issue more carefully in a randomized controlled trial. This is consistent with the advice the Division received from the Division of Drug Oncology Products, Office of Oncology Drug Products, OND. The Division received advice from the Division of Epidemiology, OSE, that registry data are not likely to answer the question of cancer causality.

The Division has been in discussions with the applicant on a large outcome study (TABY), that could be used to assess the role of prasugrel in stimulating cancer. Specific areas under discussion include screening for cancer, identification of pre-existing tumors, and definitions and classification of tumors. This reviewer suggests that the completion of this study should be a post-marketing requirement under the Food and Drug Administration Amendments Act (FDAAA) of 2007, and that is the plan at this juncture.

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Ellis Unger
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