the analyses, the difference between groups can be statistically significant. These two issues are discussed in detail, below.

Ascertainment Bias:
The sponsor's original argument was that neoplasms discovered in subjects with antecedent bleeding events should be excluded from analyses, because they could have been ascertained as a result of the bleeding event, or discovered because of investigator-patient contact, laboratory studies, or imaging investigations initiated in response to the bleeding event. Given that the RR of bleeding was quantitatively similar to the RR of cancer, this was an attractive hypothesis. The Division rejected this argument in favor of a more restricted view: that neoplasms with antecedent bleeding in the same organ system as the tumor (or new or worsened anemia in cases of GI or GU tumors) might be excluded:

1. respiratory (lung and bronchus/other respiratory)
2. GU (kidney and urethral/bladder/gynecologic)
3. GI (colorectal/esophagus/stomach)

The Division extracted all adverse events in subjects with neoplasms, and assessed the temporal sequence of adverse events involving bleeding, anemia, and iron deficiency for each case. Where antecedent bleeding was reported in one of the three organ systems listed above, or when the development or worsening of anemia (or iron deficiency) might lead to a search for occult blood loss (i.e., for the GU and GI systems), the neoplasms were excluded.

The Division and sponsor exchanged interpretations, and the sponsor presented the results of their analysis at a face-to-face meeting on September 24, 2008 (presentation slides were submitted to the dossier on October 3, 2008). Table 19 was developed based on the sponsor's Slide #20, with one difference: the sponsor excluded 5 additional cases with respiratory tumors who had antecedent anemia; for reasons noted above, these cases are restored in Table 19. Irrespective of whether cases with antecedent bleeding or anemia are counted, the RR is 1.4. From these analyses, there is no support for the sponsor's contention that ascertainment bias was responsible for the imbalance in malignancies.

Table 19: Sensitivity Analysis: Effect of Removal of Neoplasia Cases Related to Bleeding or Anemia in the Gastrointestinal, Genitourinary, and Pulmonary Systems

	Prasugrel			Clopidogrel			RR
	N	n	%	N	n	%	
Gastrointestinal (colorectal/ esophagus/ stomach)							
total	6741	32	0.47	6716	19	0.28	1.7
with bleed	6741	25	0.4	6716	14	0.2	1.8
without bleed	6741	7	0.1	6716	5	0.1	1.4
Genitourinary (kidney and urethral/ bladder/ gynecologic)							
total	6741	13	0.2	6716	12	0.2	1.1
with bleed	6741	7	0.1	6716	8	0.1	0.9
without bleed	6741	6	0.1	6716	4	0.1	1.5
Respiratory							
total	6741	16	0.2	6716	13	0.2	1.2
with bleed	6741	3	0.0	6716	3	0.0	1.0
without bleed	6741	13	0.2	6716	10	0.1	1.3
All 3 Systems							
total	**6741**	**61**	**0.9**	**6716**	**44**	**0.7**	**1.4**
with bleed	**6741**	**35**	**0.5**	**6716**	**25**	**0.4**	**1.4**
without bleed	**6741**	**26**	**0.4**	**6716**	**19**	**0.3**	**1.4**

Cancer Mortality: Cancer mortality is another important issue, and one that bears importantly on the question of ascertainment bias. The sponsor's "Supplemental Regulatory Response Concerning Neoplasms" of May 9, 2008 summarized cancer deaths, as follows:

For subjects with pre-existing non-benign neoplasms (n=28 for prasugrel; n=10 for clopidogrel), there were 6 and 2 deaths due to malignancy in the prasugrel and clopidogrel groups, respectively (Table 8 of sponsor's Supplemental Response, shown below in Table 20, top panel). For subjects with non-benign neoplasms that were considered to be new, there were 27 and 19 cancer deaths in the prasugrel and clopidogrel groups, respectively, for a RR of 1.42 (Table 14 of sponsor's Supplemental Response, shown below in Table 20, bottom). Overall, therefore, for subjects with non-benign neoplasms (new or pre-existing), there were 33 and 21 cancer deaths in the prasugrel and clopidogrel groups, respectively (RR=1.57, 95% C.I. 0.91 to 2.71).

Table 20: Sponsor's Accounting of Malignancy Deaths – Top: Subjects with Pre-existing Non-Benign Neoplasms; Bottom: Subjects with New Non-Benign Neoplasm

Table 8. Vital Status of Subjects With a Pre-existing Non-Benign Neoplasm

			Pras	Clop
Total			28	10
Vital Status	Primary Cause of Death	Subcategory		
ALIVE			17	6
DEAD	CARDIOVASCULAR		1	0
	NON-CARDIOVASCULAR	MALIGNANCY	6	2
		OTHER	0	1
	UNKNOWN CAUSE		1	1
	TOTAL DEAD		8	4
UNKNOWN			3	0

Source: l0463_fqvitj11_vital.rtf

Table 14. Vital Status of Subjects With a New Non-Benign Neoplasm

			Pras	Clop
Total			100	84
Vital Status	Primary Cause of Death	Subcategory		
ALIVE			58	54
DEAD	CARDIOVASCULAR		1	3
	NON-CARDIOVASCULAR	MALIGNANCY	27	19
		OTHER	6	2
	UNKNOWN CAUSE		1	1
	TOTAL DEAD		35	25
UNKNOWN			7	5

Source: l0463_fqvitj11_vital.rtf

The sponsor commented as follows:

"The proportion of subjects diagnosed with a new nonbenign neoplasm that died due to malignancy was similar between treatment groups (27 of 100 subjects, 27% prasugrel; 19 of 84 subjects, 23% clopidogrel)."

Although the numbers of events are small, the imbalance in cancer deaths is concerning. The fact that similar proportions of subjects with cancer had a fatal outcome is not reassuring. Moreover, the additional deaths in the prasugrel group argue against the influence of ascertainment bias, given that ascertainment of death should be complete and unbiased.

Reconciled Analyses:
The Division and sponsor reached agreement on the classification of all neoplasia in October, 2008. Table 21 shows the reconciled tabulation of "new" non-benign neoplasms, and is numerically identical to the Sponsor's Table 7.2 on page 122 of their "Cardiovascular and Renal Drugs Advisory Committee Briefing Document." Using this categorization, the K-M frequencies of new, non-benign neoplasms were 1.82% versus 1.54% for the prasugrel and clopidogrel groups, respectively, for a RR of 1.18 (log-rank p = 0.28). If non-melanomatous skin tumors are excluded, the corresponding frequencies are 1.70% and 1.29%, for a RR of 1.31, log-rank p = 0.09. The Kaplan-Meier time-to-event analyses are shown in Figure 20. The top panel shows the results of the analysis that includes all subjects, and the bottom panel shows the results of analyses with clinically less important non-melanomatous skin cancers omitted.

Because of the relatively small numbers of events, the results are sensitive to the categorization of only a few cases. Moreover, some aspects of the categorization, conducted post-hoc and with knowledge of treatment assignment, were extremely difficult. These complexities are exemplified by the following cases, identified by Dr. Marciniak in his December 31, 2008, review:

1. A 68-year-old male in the prasugrel group was hospitalized after more than a year on-study with an enlarged hard, anechoic nodular liver and sepsis. The patient died before a biopsy was done and no autopsy was done. The investigator reported the event as a malignancy and the CEC adjudicated the event as a malignancy death. I believe this case should be classified as a new malignancy while the sponsor proposes to reclassify it as not malignant.

2. A 44-year-old male in the clopidogrel group had an event reported of "recurrent bladder tumor" at about 3 months with a clear history of prior bladder tumors. I believe this case should be classified as a not new, but worse, cancer while the sponsor proposes to reclassify it as new because the initial diagnosis of bladder tumor was six years prior to randomization, although the operative report refers to a "history of superficial bladder tumors" and it is not recorded whether there were any other recurrences. The surgeon gave a clinical diagnosis of "superficial bladder cancer," although the investigator reported the event and history as histology unknown and a path report was not submitted.

3. A 73-year-old female in the clopidogrel group had a rectal polyp removed that showed high-grade dysplasia. Because all other adenomas with severe dysplasia were classified as not malignant, I believe this case should be classified as not malignant, while at last reconciliation the sponsor classified this case as malignant.

4. A 75-year-old female in the prasugrel group had low back pain at randomization but was not tentatively diagnosed as multiple myeloma until 3 months later. Low back pain is a non-specific symptom, so I believe this case should be classified as a new malignancy.

Table 21: New Non-Benign Neoplasms – Sponsor/FDA Reconciliation 10/08

neoplasm location	prasugrel n=6741	clopidogrel n=6716	
brain	0	1	
endocrine	1	0	
oral cavity and pharynx	1	2	
breast	3	1	
lung and bronchus	16	12	
other respiratory/thoracic	1	0	
any GI site	34	24	
colorectal, stomach, esophagus	30	20	
colorectal	19	10	
esophagus	4	3	
stomach	7	7	
pancreas	2	3	
liver	0	1	
gallbladder/biliary	2	0	
any GU site	19	20	
kidney	6	3	
bladder	5	8	
prostate	8	9	
gynecologic	2	1	
malignant melanoma	3	2	
non-melanomatous skin	6	13	
endocrine	1	0	
any hematologic	3	3	
leukemia	1	1	
lymphoma	2	1	
other hematologic	0	1	
metastasis unknown primary	2	0	
other unknown primary	0	1	
unknown	2	0	
all	**94**	**80**	RR = **1.18**
all, excluding non-melanomatous skin	**88**	**67**	RR = **1.31**

Dr. Marciniak analyzed the neoplasia data independently, classifying cases as new or worse based on his review of the case report forms. His Kaplan-Meier incidence plots for new solid tumors and new or worse solid tumors are shown in Figure 21. Note that the analyses exclude non-melanomatous skin cancer, hematological malignancies, and brain tumors. The log-rank p-value for new solid cancers is 0.024; for new or worsened cancers, the p-value is 0.0013.

Dr. Marciniak also reviewed the data from the clopidogrel development program, and found no apparent effect of clopidogrel on cancer rates. CURE showed a doubling in the rate of colorectal cancer with clopidogrel compared to placebo (16 versus 8), but this was not observed in CAPRIE or CHARISMA. Clopidogrel was associated with excess lung cancer in CURE (12 versus 7) and CREDO (5 versus 0), but not in the larger CAPRIE (72 versus 74) or CHARISMA Studies (70 versus 63).

The Division also sought the expertise of the Division of Drug Oncology Products, and their consult team (B. S. Mann, J. R. Johnson, and P. Cortazar) highlighted the following points (paraphrased here):

1. In terms of supporting the concept that prasugrel causes cancer, no analyses based on TAAL can be conclusive:
   a. TAAL was not designed to compare the cancer incidences between study arms, so the Type I error rate for this exploratory significance testing is essentially unknown.
   b. The absence of cancer at entry was not a requirement. There was no baseline cancer screening evaluation of study subjects.
   c. The clinical significance of the statistical findings obtained by combining of different cancers in the comparisons is hard to interpret given differing etiologies and natural histories of the diverse types of cancers.

2. There are no data in TAAL to support a belief that prasugrel is a "promoter" in humans. Given the absence of a well defined cancer screening at study entry, short drug exposure to the study drugs (6 to 15 months), and no specified follow up to detect specific cancers, the cancers diagnosed on study are more likely to be incidental.

3. To determine whether worsening of cancer was related to study drugs or was spontaneous, one would need to study the progress of known cancers when exposed to study drugs and a placebo to address this issue. Such trials are not possible in humans for clinical, statistical, and ethical reasons.

Figure 20: New, Non-Benign Neoplasms – Top: All; Bottom: Excluding Non-Melanomatous Skin

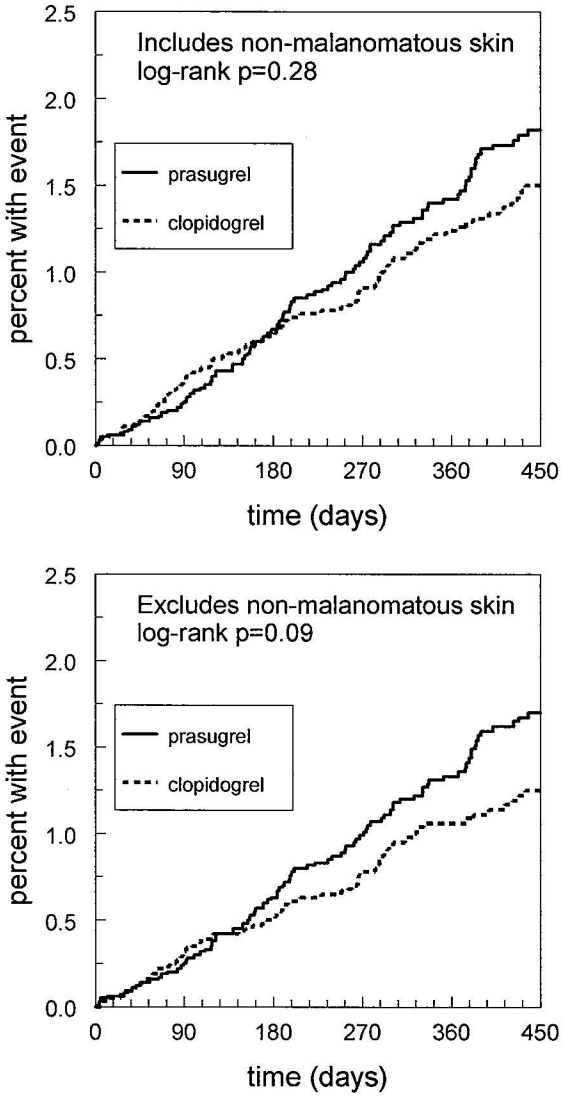
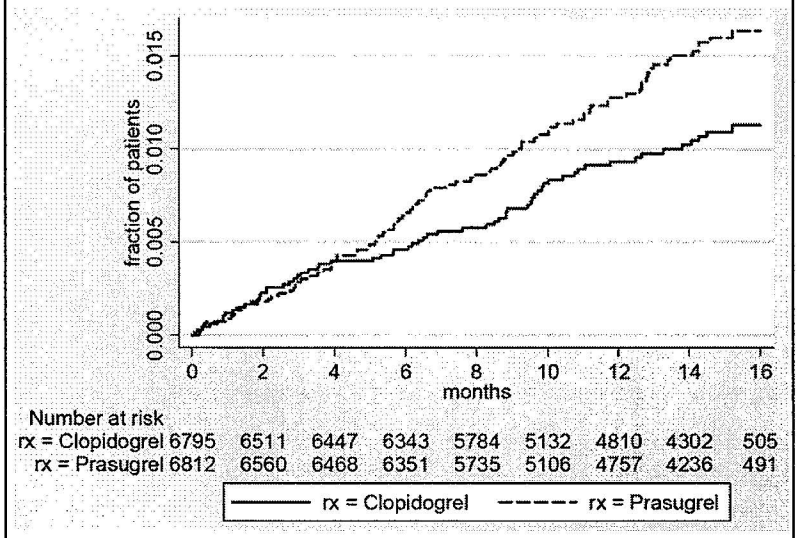
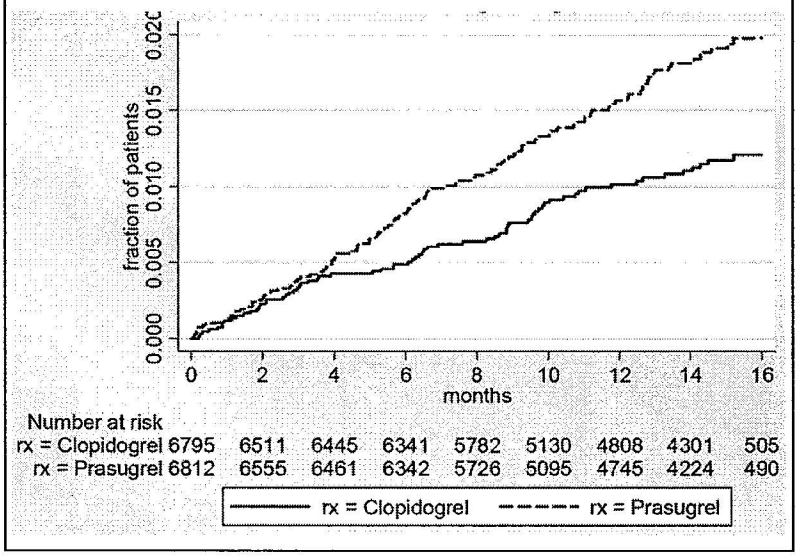


Figure 21: Solid Cancers, Excluding Non-Melanoma Skin and Brain – Top: New; Bottom: New and Worse





4. Epidemiologic comparison with the SEER data may be helpful; however, the results are of limited value and likely to be inconclusive as the study population in TAAL is drawn from several different countries. SEER data come from US populations from selected cities/regions.

5. A definitive study would require a screened population (cancer free) of adequate size, randomly assigned to the study treatments and followed up for adequate time.

Cancer – Conclusions: Prasugrel was associated with an excess number of new malignant tumors.

There are two principal interpretations of the neoplasia data: the RR and statistical significance turn on whether or not non-melanomatous skin cancers are included in the analyses. Some in the Division would exclude non-melanomatous skin cancers, because they are cured by excision and their clinical significance differs greatly from that of other cancer types. Others do not believe that exclusion is justified, because their biology is seemingly similar to other cancers, and because exclusion was performed post-hoc (of course, this is true of most safety analyses). If cases of non-melanomatous skin cancer are excluded from the counts, the RR is 1.3 and almost reaches statistical significance; with Dr. Marciniak's classification, RR is 1.4 and the p-value reaches 0.024. When all tumors, including non-melanomatous skin cancers are considered, the RR is only 1.2 and not statistically significant.

Because safety analyses are observational in nature and conducted without the benefit of pre-specified hypotheses or correction for multiplicity, 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.

There is a paucity of non-clinical data suggesting a role for prasugrel in tumor stimulation. One could hypothesize an indirect mechanism, that platelet aggregation and thrombosis provide natural defenses against tumor development and metastasis, and that prasugrel interferes with these processes. Alternatively, one could posit a more direct mechanism, wherein prasugrel is pro-angiogenic, mitogenic, or it acts as a tumor cell growth factor; however, all of this is purely speculative.

Considering the diverse biologies of these tumor types and the relatively brief 15-month time frame of TAAL, it is simply not plausible for carcinogenicity effects to underlie the imbalance in cancer cases (moreover, the results of carcinogenicity studies in the prasugrel development program were not positive). If in fact prasugrel is causally related to the excess cancers, a tumor stimulatory effect is much more likely. Of note, there is no separation of the curves through 5 or 6 months, and the delay would seem consistent with stimulation. The time course of the incidence of new tumors (Figure 20) is consistent with some of the observations with exogenous erythropoietins in patients with cancer.[5]

Given that prasugrel and clopidogrel share similarities in their mechanisms of action, Dr. Marciniak re-visited the large clopidogrel outcome trials, CAPRIE, CREDO, CURE, and CHARISMA, with a combined sample size of over 39,000 subjects. He found no consistent trends suggesting that clopidogrel is a cancer stimulator. This is reassuring, actually. Had clopidogrel been associated with a slight increase in cancer rates verses placebo, it would suggest a class effect, which would make a stronger case for a causal role of prasugrel in cancer.

Although the sponsor maintains that the imbalance was largely due to ascertainment bias, that is, that excess bleeding in the prasugrel group drew attention to excess tumors, the Division does not agree. When cases with antecedent bleeding are completely removed from the analyses, the RR of neoplasia remains principally the same.

Overall, there are reasons to be both reassured and concerned:

Reasons to be reassured: Given the varied tumor types under consideration and apparent time course of effect, a generalized stimulatory effect seems most plausible. As such, the analyses should focus on all tumor types. With the inclusion of non-melanomatous skin cancers, RR is not importantly different from unity. The lack of an identifiable mechanism of action and the multiplicity of potential safety issues analyzed should also assuage apprehension, at least to some extent. An additional reason to be reassured is that even if prasugrel is deemed to be causative, the absolute risk of cancer, based on all of the analyses above, is 0.3 to 0.6% (based on point estimates). To place this risk into perspective with efficacy (Table 6), prasugrel was associated with a 2.1% absolute reduction in the triple efficacy endpoint, primarily due to a reduction in non-fatal myocardial infarction. Thus, for each 1000 patients treated with prasugrel, one might expect to prevent 21 non-fatal myocardial infarctions at a cost of 3-6 cancers (if, in fact the drug is causally related to cancer). This trade seems advantageous, at least for many patients.

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[5] Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *JCO*. 2005; 23:1-13.

Reasons for concern: The fact that cancer deaths go against prasugrel (27 for prasugrel versus 19 for clopidogrel, RR = 1.42) is reason for consternation. The consideration of death as an endpoint largely removes sources of bias from the analyses. In addition, if there is a 0.3 to 0.6% risk of cancer, the risk is per year. This has to be extrapolated over the length of treatment. The efficacy (prevention of non-fatal MI) is largely front-loaded, but the risk of cancer would presumably continue.

This reviewer suggests a precaution in labeling regarding the excess cancers and cancer deaths. The labeling should suggest that consideration be given to use of alternative agents in patients with known cancer, but I would not go as far as to suggest that patients without a history of cancer switch to other agents after some arbitrary period in time (see below). A postmarketing requirement to study the issue more carefully in a randomized controlled trial may be worth considering. The sponsor is presently conducting a large outcome trial of prasugrel in subjects with ACS managed without PCI, and the data from this trial may suffice. The advice we have received from the Division of Epidemiology, OSE is that because of the limitations of registry data, including missing data, typically low and possibly biased enrollment, and the absence of controls, a registry is not likely to answer the question of cancer etiology.

In addition, the Division requested *in vitro* and *in vivo* tumor progression studies, and the sponsor submitted preliminary results one week ago.

7.4.16. QT Prolongation

The sponsor performed a thorough QT study in normal volunteers (Study TAAP), which was deemed negative and largely adequate by the Division's Interdisciplinary Review Team for QT Studies (S. Balakrishnan, Y. Chen, J. Zhang, N. Mehrotra, and C. Garnett). TAAP was a single-center, randomized, three-period crossover study wherein 60 healthy volunteers received either an 80-mg single dose of prasugrel or placebo. Subjects also received a single 400-mg oral dose of moxifloxacin, administered open label. Delta QTcF for moxifloxacin was 10.7 ms, with 90% C.I. 8.3 ms, 13.0 ms, demonstrating assay sensitivity, i.e., the study was adequately designed and conducted to detect an effect of a QT-prolonging drug on the QT interval. For prasugrel 80 mg, ΔQTcF was 2.1 ms, 90% C.I. -1.3 ms, 5.4 ms. Because the upper limit of the two-sided C.I. for the mean difference between prasugrel and placebo was <10 ms, the threshold for regulatory concern (per ICH E14 Guideline), the study was considered negative in the context of a positive moxifloxacin control.

The review team identified two key study limitations: 1) the 80-mg dose used in the study did not adequately emulate "worst-case" scenarios (based on intrinsic and extrinsic factors) for the 60-mg LD, although it did cover the expected high exposure scenario for the 5-or 10-mg MD; and 2) the ECG sampling schedule did not capture the t_{max} for metabolites, except for R-106583.

Because the lack of a QT effect observation could have been a result of dose and/or timing of ECG sampling, the QT Team compared R-119521 and R-106583 exposures achieved in TAAL to those achieved in TAAP, and concluded that prasugrel is unlikely to prolong QT interval after clinically relevant exposures.

In light of the QT Team's conclusion, and given that QT effects are inherently less important when the benefit of a drug is improvement in a cardiovascular outcome, no additional evaluation is needed for QT.