

between the two groups except for slightly more males in the prasugrel group (75.4% vs. 73.5%). For details regarding TAAL conduct and patient characteristics, disposition, and other outcomes please see the primary clinical review.

For all of my analyses I worked from the raw data sets, checking for incomplete data against the case report forms (CRFs). The data submitted for TAAL were typical of most NDA submissions with four exceptions:

1. The original submission did not include the raw data corresponding to what the investigator originally recorded for CRF fields but only the final values that may have been changed through an iterative, multi-step data clarification process. In a few instances the data clarifications were bizarre, e.g., an initial recording of lung cancer (squamous cell cancer on a lung biopsy) was changed to squamous cell cancer and coded as skin cancer.
2. The CRFs employed a consecutive ID (E01, E02, etc.) for adverse events (AEs). The investigator was supposed to use the same ID for the same adverse event at subsequent visits despite recording AEs on different pages. Not surprisingly, investigators made mistakes and used the same ID on different pages for different AEs. The sponsor's computer system overwrote the old AE with a different AE if the investigator mistakenly used the same AE ID for different AEs, e.g., replacing "(L) breast cancer" (at baseline) with "no reflow". The sponsor at our request later submitted a data set providing the original and final descriptions for all AE IDs, but other overwritten AE fields (date of onset, severity, etc.) were not provided.
3. The CRFs collected cardiac and cardiac related baseline conditions with checkboxes on specific CRFs. For other non-cardiac baseline conditions, the CRF form was similar to the AE forms, including using the same AE IDs. The investigator was supposed to record only ongoing conditions, so not all histories of cancers were captured. The investigator was also supposed to re-record all baseline ongoing conditions at the final visit, indicating if the severity had changed. These directions were not followed perfectly. Some investigators recorded histories of cancers at baseline and baseline conditions at subsequent visits, and some repeated baseline conditions at multiple visits.
4. Coding of AEs was not very accurate. Coding for a few records were bizarre, e.g., "mycosis of the skin (fungi)" and "inguinal mycosis both groins" were coded as "mycosis fungoides". Transcriptions of handwritten entries also caused a few problems, e.g., "metastasis change", coded as "metastasis", was eventually resolved as "mental status change".

For all the above reasons, I have recoded all potential cancer adverse events using the original investigator terms and checked ambiguous data against the CRFs and against any additional data provided by the sponsor. The analyses below are based on the best available data, and I tried to assign derived variables without knowledge of treatment group.

Because I have refined the accuracy of assignments, the analyses in this review replace any of my preliminary analyses quoted in the original primary clinical review or in consults. Because this is a very complex submission, I may have a few remaining errors or I may have missed some additional information provided by the sponsor. However, please note that the results have changed little from my original analyses despite substantial refinements.

In the following analyses, when I refer to “solid cancers” I mean all malignancies excluding hematological malignancies, non-melanoma skin cancers, and primary brain tumors (malignant and benign). Non-melanoma skin cancers do not carry the same dire prognoses as most other adult malignancies, ascertainment may be erratic, and multiple cancers over years are not uncommon, making determination of new impossible. Skin cancers and neoplasms were less frequent in the prasugrel groups than in the control group in the mouse carcinogenicity study. Also, in the analyses below, I classified “squamous cell carcinomas” as skin cancers unless I found a record of a non-skin site. Brain tumors raise issues of metabolites crossing the brain-blood barrier and are sufficiently infrequent (1 new malignancy in this study) that including or excluding them does not change results significantly. Hematological malignancies also deserve separate treatment because their pathogenetic mechanisms differ from solid tumors, e.g., they are not dependent upon angiogenesis. Prasugrel also appears to have differential effects upon them in the rodent carcinogenicity studies.

For “new cancers”, I prospectively counted a cancer as new if the date of definitive diagnosis was after the randomization date. I believe this definition is most consistent with how incidence dates of cancers are usually determined and consistent with trying to detect tumor promoter effects. The sponsor has counted cancer cases for which there was a sign of a tumor (mass, x-ray lesion) preceding the randomization date as not treatment emergent (not new) regardless of whether the date of definitive diagnosis was after the randomization date. After internal discussions with other FDA staff and cancer case adjudication meetings with the sponsor, I have been persuaded to present additionally a modified definition that allows cases to be counted as recurrent cancers if the evidence is strong that the cancer was active prior to randomization, e.g., a fracture occurring prior to randomization that was biopsy proven after randomization to be a pathologic fracture due to metastatic prostatic cancer. I continue to have misgivings about this latter definition because of the subjectivity of determining whether the evidence is strong enough. Furthermore, solid cancer development is well established to be a lengthy process such that we have good reason to believe that all of the “new” solid cancers diagnosed in TAAL were present prior to randomization. Hence the most relevant measure is all new cancers plus recurrent ones having a new cancer-related event or intervention post-randomization, and I show the analyses for this latter categorization (“new and worse”) as well. I will note that, despite believing the latter to be most relevant, my prospective endpoint was new cancers because of a suspicion that combining new and worse cancers might produce a noisier endpoint.

Baseline Cancers

Before considering the cancer results, it is appropriate to examine the subjects’ baseline cancer data. TAAL was a large study, so substantial baseline imbalances should be rare, and demographics and other baseline characteristics were well-balanced between the two groups as noted above and detailed in the primary clinical reviewer’s review. The TAAL exclusion criteria did not exclude patients with cancer histories; investigators were to exclude patients only if the life

expectancy was reduced, i.e., less than 15 months. Furthermore, the protocol and case report forms did not require that investigators record the patients' histories of cancers; the investigators recorded "on-going" medical problems as discussed above. Hence no one can determine how many TAAL patients have a history of cancer (although, for patients who subsequently developed a cancer problem, the CRFs usually document whether the cancer had been diagnosed prior to randomization.) The statistics that are ascertainable are how many patients had an on-going cancer problem and the types of cancers that investigators considered to be on-going. Patients with any on-going malignancy or brain tumor were well-balanced between the two groups: clopidogrel 175 and prasugrel 174, about 2.6%. I show the breakdown by cancer site in Table 7.

Table 7: Patients with On-going Malignancies and Brain Tumors at Baseline in TAAL

site*	clopidogrel	prasugrel
bladder	12	8
brain	6	5
breast	13	12
cervix	5	1
colorectal	14	16
esophagus	1	0
eye	0	1
head & neck	2	4
kidney	3	4
leukemia	6	6
lung	7	9
lymphoma	14	5
melanoma	9	5
myelodysplasia	4	5
ovary	2	0
pituitary	0	2
prostate	46	61
sarcoma	0	1
skin	20	18
squamous	2	1
stomach	2	3
testis	3	3
thyroid	3	2
unknown	0	1
uterus	1	1
Total	175	174

* 8 clopidogrel and 4 prasugrel patients had multiple on-going cancers at baseline

Most sites are well-balanced between the two groups, with the exceptions of slight excesses of lymphomas, melanomas, and cervical cancers in the clopidogrel group and prostate cancers in the prasugrel group. None of the site imbalances are nominally statistically significant even ignoring the multiple comparisons. Patients with solid cancers excluding non-melanoma skin and brain were also reasonably well balanced between the two groups (clopidogrel 123 and prasugrel 132).

COMMENT: Baseline imbalances in patient characteristics or on-going cancers do not appear to explain the subsequent differences in cancer rates.

Investigator-Reported Cancers

Because the pre-specified data collection in TAAL was whether the investigator judged the cancer to be on-going and not whether the patient had a history of cancer, it should be informative to examine the rates of patients having subsequent cancer AEs for which the investigator did not report an on-going cancer of the same type at baseline. Most new cancer events were reported in patients who did not have a corresponding on-going cancer reported at baseline. The few new events in patients with the same cancer reported on-going at baseline were overwhelmingly in the prasugrel group (7 vs. 1). I show the new cancer events without a corresponding on-going cancer reported at baseline in Table 8 and the types of malignancies in Table 9.

Table 8: Investigator-Reported New Cancer Events without an On-going Cancer Reported at Baseline in TAAL

	clopidogrel	prasugrel	RR	p*
solid cancers except non-melanoma skin, brain	58	88	1.52	0.013
malignancies except non-melanoma skin	65	92	1.42	0.031
all malignancies including skin	81	108	1.33	0.050

*by Chi-square

Table 9: Types of Investigator-Reported Malignancies without an On-going Cancer Reported at Baseline in TAAL

	clopidogrel	prasugrel
bladder	6	6
breast	1	6
colorectal	9	21
esophagus	2	4
gall bladder	0	2
head & neck	2	1
kidney	3	2
leukemia	4	2
lung	11	17
lymphoma	1	2
melanoma	2	2
mesothelioma	0	1
myelodys	2	0
ovary	0	1
pancreas	2	2
prostate	11	11
sarcoma	0	2
skin	14	15
squamous	2	1
stomach	7	6
unknown	1	4
uterus	1	0
Total	81	108

The mortality rate was substantially higher for patients who experienced a new cancer event (excluding non-melanoma skin cancers), about 38% in the prasugrel group and 34% in the clopidogrel group vs. < 3% in patients without a new cancer event.

COMMENT: It should be very clear from Table 8 and the mortality statistics why these preliminary analyses of the investigator-reported cancers immediately raised serious concerns. Note that colorectal, breast, and lung cancer events are more frequent in the prasugrel group. Because TAAL CRFs did not capture histories of cancer and because the investigator reports of adverse events were inadequate to confirm malignancy in some cases, we and the sponsor scrutinized all potential cancer events and the sponsor collected operative reports, path reports, and follow-up information on these cases. The remainder of my analyses included these post-hoc data manipulations. However, note that the sponsor, in a "White Paper: Neoplasm" dated September 18, 2008 stated that "The Sponsors feel strongly that the neoplasm data should be analyzed as reported by the investigators." The above statistics are the neoplasm data as reported by the investigators; they are extremely concerning.

Reviewer-Adjudicated Cancers

The hypothesis I wished to test based on my interpretation of the rodent carcinogenicity studies was whether prasugrel is a promoter for a variety of solid cancers. Initially I decided to analyze as the primary analysis new cancers on the assumption that recurrent cancers or progression of existing cancers would introduce noise, i.e., cancers already poised to progress may not be affected as significantly by a cancer promoter. Of course, this assumption may not be valid, so as the secondary analysis I also planned to examine combined new and worse cancers.

Classifying a cancer as new requires a convention: Cancers may initially present as vague symptoms or masses that could be benign. They may be detected initially on imaging with uncertainty about the malignancy status. They usually eventually have a histologic diagnosis, but not always. I adopted the usual convention of counting a cancer as new if the date of first clinical diagnosis was after the randomization date. Two cases, both in the prasugrel group, had highly suspicious imaging (mammogram, chest x-ray) prior to randomization but refused further workup; I counted these cases as not new. A third case, also in the prasugrel group, had sclerotic changes on imaging suggestive of malignancy about the time of randomization with confirmation of malignancy shortly thereafter; I also counted this case as not new.

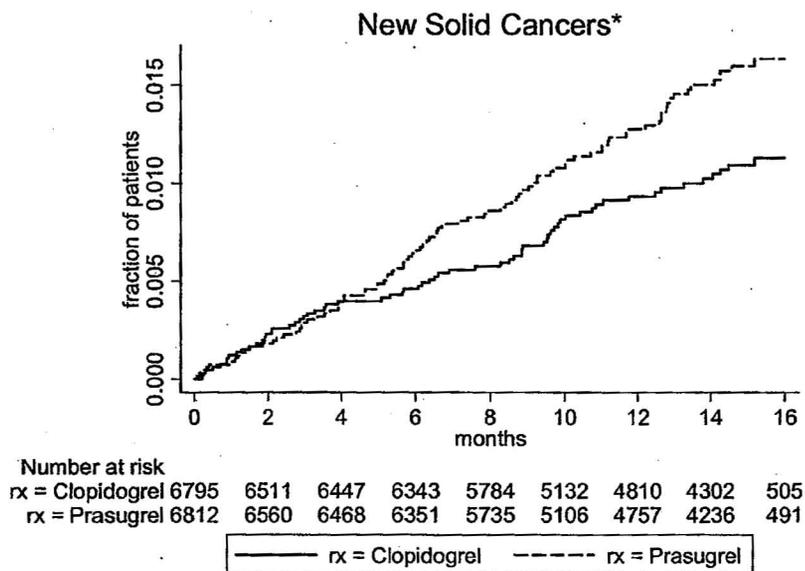
One relatively common neoplasm presented difficulties regarding malignancy status: Villous adenomas had varying histologic descriptions of mild dysplasia through severe dysplasia and invasive carcinoma. Differentiating severe dysplasia from carcinoma-in-situ is unreliable. (Terry, Neugut et al. 2002) Because severe dysplasia behaves similarly to carcinoma-in-situ (and in Japan and in an international guideline the two categories are lumped into one), I classified villous adenomas with severe dysplasia or carcinoma noted in the path report as new cancers. (Riddell 1999; Arumugam, Joseph et al. 2002; Stolte 2003)

Another site presented a different dilemma: squamous cancers near the lip could be classified as skin cancers if they primarily involve the skin and head and neck cancers if they involve the mucosa. The one such case in a prasugrel patient I counted as a skin cancer, hence excluded from my solid cancers analyses. Finally, there were two suspicious prasugrel cases for which the available data are inadequate: one a 55-year-old male who had an AE of "radiation burns" at day

104 and a “lesion removed from neck” at day 384; and the other a 71-year-old male who had an AE of “radiation burn on back” on day 30.

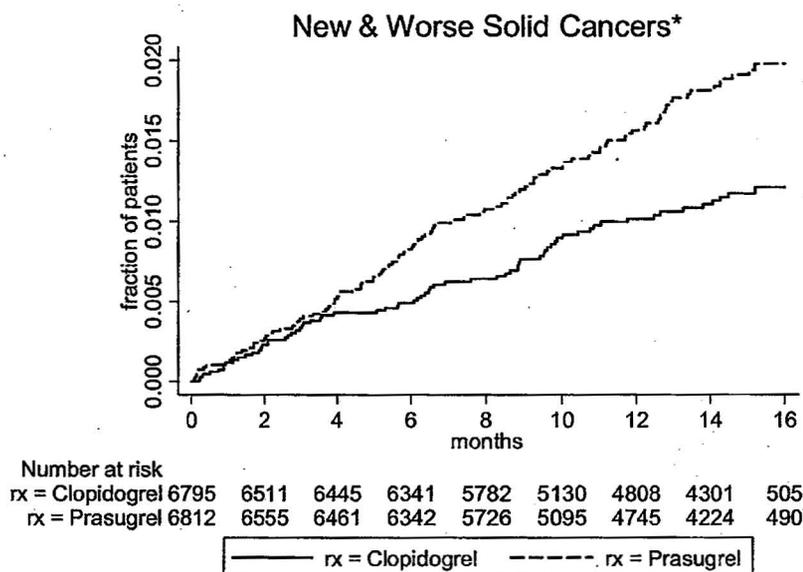
I show in Figure 5 the Kaplan-Meier (K-M) incidence plots by treatment for all new solid cancers (excluding non-melanoma skin and brain tumors) in TAAL by the conventions just discussed and in Figure 6 for new and worse solid cancers. I show the breakdown for new cancers and brain tumors by site and treatment in Table 10.

Figure 5: K-M Incidence Plot for New Solid Cancers (Excluding Skin and Brain) in TAAL



*excluding non-melanoma skin cancers and brain tumors; p = 0.024 by log rank

Figure 6: K-M Incidence Plot for New and Worse Solid Cancers (Excluding Skin and Brain) in TAAL



*excluding non-melanoma skin cancers and brain tumors; p = 0.0013 by log rank

Table 10: Numbers of New and Worse Malignancies by Site and Treatment in TAAL

site/patients	new		new and worse	
	clopidogrel	prasugrel	clopidogrel	prasugrel
bladder	7	7	8	8
breast	1	4	1	6
cervix	0	1	0	1
colorectal	10	22	10	22
esophagus	2	4	2	4
gall bladder	0	2	0	2
head & neck	2	1	2	1
kidney	4	5	4	6
liver	1	0	1	0
lung	12	15	14	19
melanoma	2	3	2	3
mesothelioma	0	1	0	1
ovary	0	2	0	2
pancreas	3	2	3	2
prostate	9	8	11	18
sarcoma	0	2	0	2
stomach	8	7	8	8
thyroid	0	1	0	2
unknown	2	5	2	5
uterus	1	0	1	0

site/patients	new		new and worse	
	clopidogrel	prasugrel	clopidogrel	prasugrel
solid cancers*	64	92	69	112
brain	1	0	1	0
leukemia	1	2	2	2
lymphoma	1	2	1	2
myelodysplasia	1	0	1	0
myeloma	0	1	0	1
skin	15	15	15	17
squamous	2	1	2	1
other malignancies	21	21	22	23

*excluding brain and non-melanoma skin

The relative risk a new solid cancer was about 1.44 and for a new or worse solid cancer was about 1.62 for prasugrel compared to clopidogrel. There was only one new brain malignancy and new hematologic and non-melanoma skin malignancies were relatively evenly distributed between the two groups. As with the investigator-reported cancers, new solid cancers were associated with a high mortality rate, about 30%, compared to <3% in patients without cancers. The mortality rate was slightly higher for patients with solid cancers in the prasugrel group such that there were substantially more deaths in prasugrel patients with new solid cancers (37 vs. 25) and in prasugrel patients with new and worse solid cancers (43 vs. 28).

COMMENT: Note the divergence of the K-M solid cancer incidence plots at four months with continuing divergence throughout the duration of the study. The divergence at four months would not seem to be a collection date artifact because the initial post-hospitalization visits were done at about 30, 90, and 180 days. It could be related to delaying doing invasive procedures after the ACS event.

New malignancies other than solid cancers excluding non-melanoma skin and brain appear to be balanced between the two groups. Including them dilutes the significance of the solid cancer findings but does not eliminate it: $p = 0.045$ by log rank for all new malignancies, $p = 0.0038$ for all new and worse malignancies.

For new solid cancers only colorectal appear clearly higher in the prasugrel group (with some suggestion that unknown primaries and breast may be higher as well.) For new and worse solid cancers the signal for breast cancer is stronger and prostate and lung cancers also are increased in the prasugrel group.

The high mortality rate in the patients with cancer, slightly higher in the prasugrel group, remains highly concerning. If, as the sponsor alleges, the differences are due to a detection bias due to more bleeding with prasugrel, we would expect the mortality rate from cancers with prasugrel to be lower than with clopidogrel. We would also expect the incidence curves to diverge initially and then converge. Observing slightly higher mortality in prasugrel new cancer patients and a continuing divergence of the incidence curves argues strongly against the TAAL findings being due to a detection bias.

Reconciliation of Cancers with Sponsor

Because of the serious implications of the above findings, we and the sponsor attempted to come to an agreement about the classification of non-skin cancer cases with ambiguous features. The changes from my classifications above were reclassifying all tubular adenomas with severe dysplasia as not malignant and reclassifying some cancer cases with signs or symptoms preceding the randomization date as not new. For four cases I may have differences in classification from the sponsor's:

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.

Using the classifications for the three solid cancer cases discussed above and the rest of the classifications reconciled with the sponsor, I count 86 new solid cancers in the prasugrel group and 61 in the clopidogrel group, for a relative risk for prasugrel of 1.41, $p = 0.038$ by log rank. For new and worse solid cancers the corresponding numbers are 110 and 67, for a relative risk for prasugrel of 1.64, $p = 0.0011$ by log rank. For new malignancies excluding non-melanoma skin the corresponding numbers are 90 and 65, for a relative risk for prasugrel of 1.38, $p = 0.043$ by log rank. It is only if non-melanoma skin cancers are included that the relative risk becomes nominally non-statistically significant (relative risk 1.29, $p = 0.08$ by my calculations.)

Table 11: Comparison of Reviewer’s and Reconciled New and Worse Solid Cancers (excluding Non-Melanoma Skin and Brain) in TAAL

	clopidogrel	prasugrel	relative risk	p*
new solid cancers (except non-melanoma skin and brain)				
investigator	58	88	1.52	0.013
reviewer	64	92	1.44	0.024
reconciled	61	86	1.41	0.038
new and worse solid cancers (except non-melanoma skin and brain)				
investigator	59	95	1.61	0.0035
reviewer	69	112	1.62	0.0013
reconciled	67	110	1.64	0.0011

*by log rank

COMMENT: While the numbers of total new solid cancers is reduced slightly by the reconciliation and the p value declines correspondingly, the relative risk remains about the same. For new and worse solid cancers there is virtually no change, and the relative risks among the three different classifications are remarkably similar. Because none of the solid cancers presenting as clinical problems in TAAL were really new, the new and worse cancer rates are the best measures of the promoter potential of prasugrel. I believe these statistics still document a serious potential problem for prasugrel.

The sponsor in “Supplemental Regulatory Response Concerning Neoplasms” dated November 7, 2008, rejects my conclusion that the data suggest a serious potential problem for prasugrel based predominantly on two arguments: (1) all malignancies, including skin cancers should be included in the analyses; and (2) “the higher incidence of nonbenign neoplasms observed in prasugrel-treated subjects results from detection/ascertainment bias related to the higher incidence of bleeding observed in prasugrel-treated subjects.”

The sponsor proposes several arguments for including skin cancers. I summarize each argument below in italics followed immediately by my response:

- *“Exclusion of any specific type of cancer would be post-hoc and subject to bias” and “The only scientific rationale to exclude a tissue from analysis is that the tissue has no exposure to the drug.”* However, my exclusion of skin cancers was done *pre hoc* based on my interpretation of the animal carcinogenicity studies (as well as experience with the SEER cancer registries, which similarly exclude non-melanoma skin cancers). A preliminary decision based on animal data is scientific—see Table 2 above for the evidence that, if anything, skin cancers were less frequent in the prasugrel treated mice than the control mice. Secondly, safety analyses are frequently post hoc. If a strong signal were detected for all malignancies, it would be greatly concerning just as this strong signal in solid cancers is greatly concerning, although the existing strong signal in solid cancers is doubly concerning because the analysis was pre-specified by me. Finally, for purposes of estimation of statistical significance of the TAAL cancer analyses, it makes no difference whether my interpretations of the animal carcinogenicity studies are reasonable or completely flawed.