Table 5: Exposure (Mean AUC_{0-24} µg·h/mL) for Main/Active Metabolites in the Prasugrel Carcinogenicity Studies (Compared to Human 0.3/0.05 for 10 mg Daily Dose)

	Female				Male			
	10	30	100	300	10	30	100	300
Mouse		23/6	85/26	201/68		23/2	87/16	206/41
Rat	4/7	18/28	43/59		4/5	7/14	22/58	

Main human metabolite R-106583/active metabolite R-138727

In addition to the neoplasms, the similar findings to the two other hepatic histologic findings found in the mouse study were also observed in the rat study as shown in Table 6.

Table 6: Other Hepatic Histologic Findings in the Prasugrel Rat Carcinogenicity Study

Group	Female				Male			
	Control	10	30	100	Control	10	30	100
Diffuse hypertrophy	0	0	0	15	0	0	0	20
Altered cell focus, eosinophilic	27	31	31	36	43	41	44	51

COMMENT: The rat carcinogenicity does not support the mouse study in suggesting that prasugrel is carcinogenic. Alone it might be interpreted as suggesting that prasugrel has a protective effect, e.g., the lower rates of leukemia. There are some similarities between the two studies for other findings, such as the endometrial polyps and the hepatocytic hypertrophy. There are also definite differences in exposure, both regarding the higher high dose exposure in the mice and the different ratios of active to main metabolite.

Because of the highly significant difference in hepatic adenomas, the moderately suggestive trend in hepatic cancers, the weakly suggestive trends in intestinal and lung cancers, the supportive data of the altered cell foci, and the absence of any tumors showing a clear reverse trend, I would still interpret the mouse study as suggestive of a carcinogenic effect of prasugrel in one species. The difference in measured exposures between the mouse and humans is not completely reassuring because we have no idea of what metabolite could be carcinogenic. The rat study is not supportive of carcinogenicity but neither does it contradict the possibility. However, by itself the results of the mouse study do not prohibit approval—the critical issue is what the human studies show. Regardless, these studies are very useful for hypothesis generation: The hypothesis they suggested to me is that prasugrel may be a tumor promoter for a variety of solid cancers—it is this hypothesis that I tested in my initial analysis of the TAAL study data.

Cancer Adverse Events in TAAL

The only human study in the submission large and long enough to provide any insight into cancer rates is TAAL. Hence I limit my analyses to that study.

TAAL (or TRITON) was a large, international, multicenter, randomized, double-blind, double dummy, active-controlled (vs. clopidogrel) of prasugrel in patients with ACS undergoing PCI. The labeled regimen for clopidogrel (300 mg loading, 75 mg maintenance) was compared to prasugrel 600 mg loading, 10 mg maintenance. About 13,608 patients (74% male) were randomized 1:1 and followed for 6-15 months. Baseline characteristics were well-balanced

between the two groups except for slightly more males in the prasugrel group (75.4% vs. 73.5%). Patients with a baseline history of cancer were balanced overall between the two groups (about 2.8% in each—but please see the discussion below regarding problems with determining baseline history.) 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 the same ID for these cases, 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 or available.

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. 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 active 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 even 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 clarifications 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. There will be some cases for which the sponsor may prefer an alternative assignment, e.g., I assigned two

cases with a history of prostate carcinoma but who later during the study underwent radiation therapy for it as worsened, while the sponsor assigned them as stable because the crude, three level severity scale had not changed.

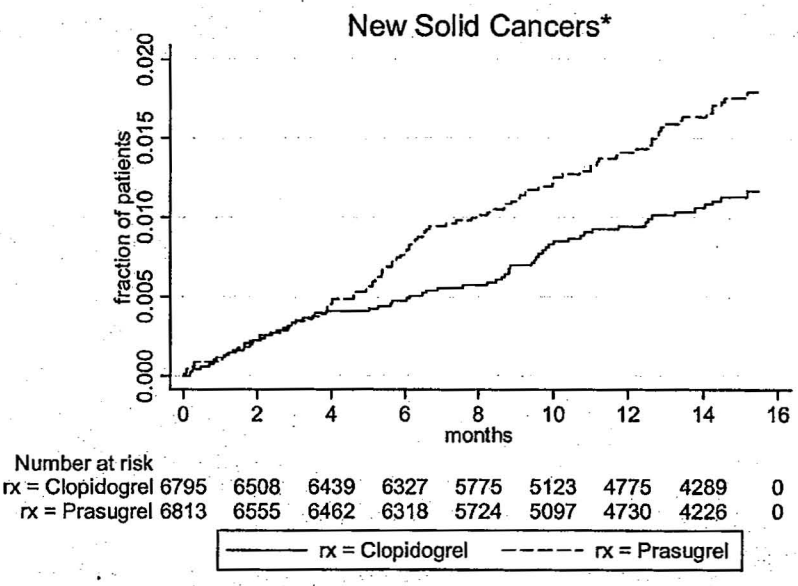
Because I have refined the accuracy of assignments, the analyses in this review replace any of my preliminary analyses quoted in the original primary clinical review or in consults. Because this is a very complex submission, I may have a few remaining errors or I may have missed some additional information 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 very erratic, and multiple cancers over years are not uncommon, making determination of new impossible. 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 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 counted a cancer as new if the date of definitive diagnosis was after the randomization date. I believe my 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. For example, one case has a left breast mass noted on randomization but a left breast cancer adverse event recorded on day 181. While the sponsor argues that severity has not changed, I have counted this case as a new breast cancer. As a sensitivity analysis related to this issue, I also analyzed all new cancers plus recurrent ones having a greater severity post-treatment.

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. I show the Kaplan-Meier (K-M) incidence plots by treatment for all new solid cancers (excluding non-melanoma skin and brain tumors) in TAAL in Figure 5. I show the breakdown for new cancers and brain tumors by site and treatment in Table 7.

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



*excluding non-melanoma skin cancers and brain tumors; p = 0.005 by log rank

Table 7: Numbers of New First Cancers and Brain Tumors by Site and Treatment in TAAL

	clopidogrel	prasugrel
patients	6,696	6,682
bladder	8	7
breast	1	5
cervix	0	1
colorectal	9	22
esophagus	2	5
gall bladder	0	2
head & neck	2	1
kidney	4	4
liver	1	0
lung	13	21
melanoma	3	3
mesothelioma	0	1
ovary	0	2
pancreas	3	2
prostate	9	10
sarcoma	0	3
stomach	8	7
thyroid	0	1
unknown	2	5

	clopidogrel	prasugrel
uterus	1	0
total new solid cancers	66	102
brain	1	0
pituitary	0	2
skin	15	13
squamous	2	1
leukemia	2	2
lymphoma	1	2
myelodysplasia	2	0
myeloma	0	1

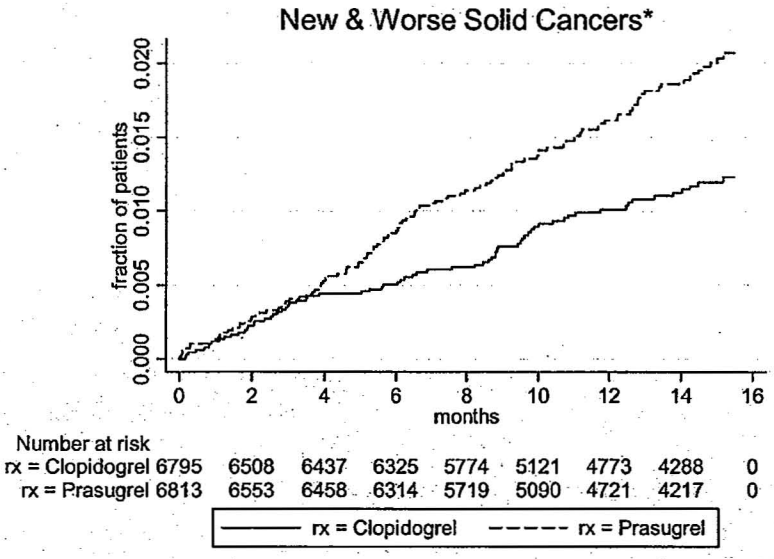
There were 102 new solid cancers in the prasugrel group compared to 66 in the clopidogrel group, a relative risk of about 1.5 for prasugrel.

COMMENT: Note the divergence of the K-M all 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. Such delays should affect clopidogrel and prasugrel patients similarly. The shape of the clopidogrel curve is the opposite of what I would expect due to delayed diagnostic procedures: The clopidogrel rate is higher for the first four months and then decreases slightly. The curves are more consistent with an earlier ascertainment of cancers that were clinically apparent but undiagnosed at the time of the ACS event with the differences in rates with routine surveillance manifesting later in the trial. However, speculations about the reasons for the shapes of the curves are not as important as the substantial divergence in the curves.

The breakdown by sites shows substantial differences in numbers of cancers for most major solid tumors, particularly colorectal, lung, and breast. There are not balancing substantial increases in cancers with clopidogrel for any sites, also suggesting that the differences are not random variations.

Because baseline cancer status was recorded erratically in TAAL and hence determining whether a post-treatment cancer AE was the occurrence of a new cancer was difficult for some cases, I also analyzed new and worse solid cancers combined. I show the incidence plot for new and worse solid cancers in Figure 7 and the distribution of cancer types for new and worse solid cancers in Table 8.

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 = 0.0005 by log rank

Table 8: Numbers of New and Worse Solid Cancers by Site and Treatment in TAAL

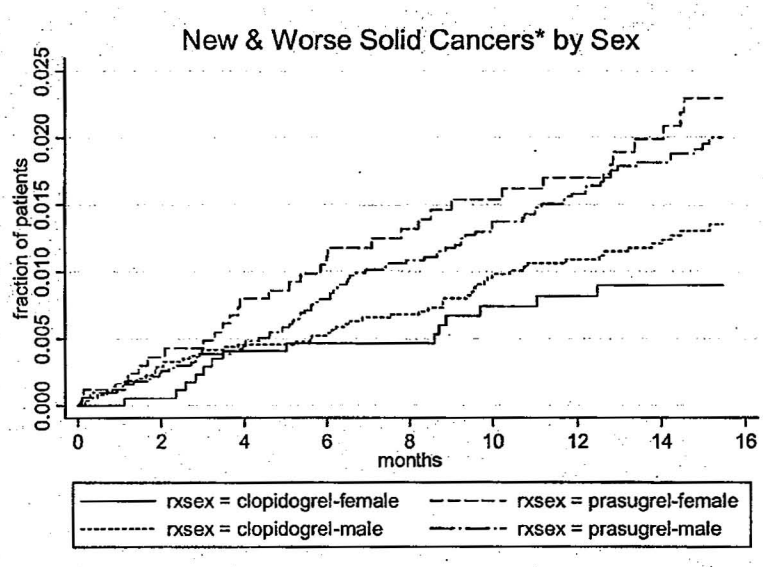
	clopidogrel	prasugrel
bladder	9	8
breast	1	6
cervix	0	1
colorectal	9	22
esophagus	2	5
gall bladder	0	2
head & neck	2	1
kidney	4	5
liver	1	0
lung	15	21
melanoma	3	4
mesothelioma	0	1
ovary	0	2
pancreas	3	2
prostate	10	19
sarcoma	0	3
stomach	8	8
thyroid	0	2
unknown	2	5
uterus	1	0
Total	70	117

I identified 15 prasugrel and 4 clopidogrel cases that had reasonable documentation of worsening of a cancer diagnosed before randomization. (I did not determine the worsened cancer cases for skin and hematologic malignancies and brain tumors). As a comparison of Table 7 to Table 8 shows, the difference in worse cancers is largely attributed to worsened prostate cancers in the prasugrel group. Because of the relatively small number of worsened cancers compared to new and worsened cancers are also more frequent with prasugrel, the incidence plots for new (Figure 5) and new and worse cancers (Figure 6) look very similar, but the p value decreases to 0.0005.

COMMENT: The analysis of new and worsened solid cancers is even more concerning than that for new solid cancers alone. However, they both are very similar, and their similarity may even be greater than labels of new vs. worse suggest: As discussed previously, TAAL investigators were not to record baseline conditions that were not active. Some of the cancer cases that I have classified as "new" are likely "worse" (or recurrent). Regardless, a new cancer or worsening of an old cancer is a major, frequently life-threatening event for a patient.

Based on preliminary analyses of all solid cancers by sex, the primary clinical reviewer has noted that increases in new solid cancers with prasugrel were greater in women than in men. I show the incidence plots for new and worsened cancers by sex in Figure 7. Note that TAAL patients were predominantly male (74%).

Figure 7: K-M Incidence Plot for New and Worse Solid Cancers (Excluding Skin and Brain) by Sex in TAAL



*excluding non-melanoma skin cancers and brain tumors

There is one confounding factor regarding the analyses by sex: While overall rates of histories of cancer were balanced between the two groups, there were variations by sex as shown in Table 9.

Table 9: Histories of Cancer at Baseline by Treatment and Sex in TAAL

	female	male	both
Clopidogrel	2.7%	2.9%	2.8%
Prasugrel	2.1%	3.0%	2.8%

However, neither sex nor history of cancer (excluding skin) at baseline is a significant baseline cofactor in a Cox regression for new solid cancers as shown in Table 10.

Table 10: Cox Regression of New Solid Cancers in TAAL

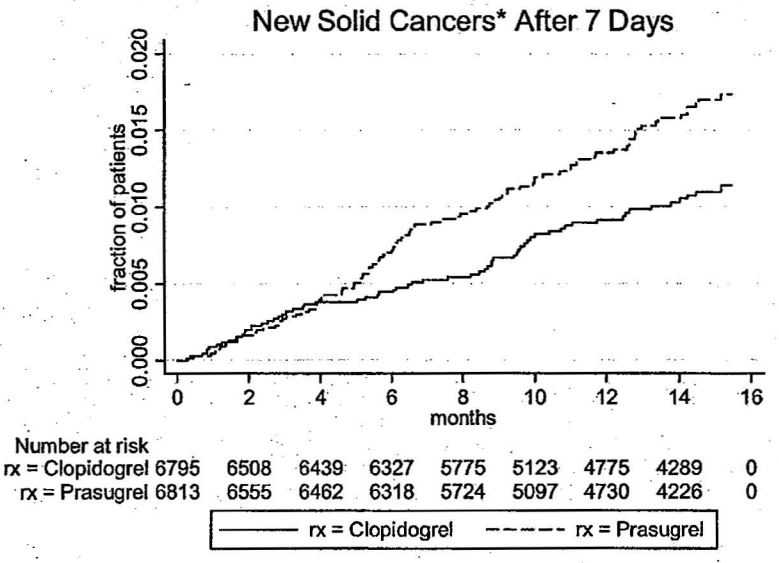
```
Cox regression -- Breslow method for ties

No. of subjects =        13608                     Number of obs    =     13608
No. of failures =          168
Time at risk    =  170889.4051
                                                   LR chi2(4)       =     48.34
Log likelihood  =   -1545.7538                     Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   prasugrel |   1.554438   .2456262     2.79   0.005     1.140433    2.118737
        male |   1.222776    .220994     1.11   0.266      .858041    1.742552
         age |   1.046035   .0076065     6.19   0.000     1.031232     1.06105
   cancer hx |   1.137233   .4758623     0.31   0.759     .5008106    2.582409
------------------------------------------------------------------------------
```

COMMENT: There is some variation in new and worsened cancer rates by sex, with females on clopidogrel having the lowest rate and females on prasugrel having the highest. The incidence plot in females on clopidogrel appears particularly erratic, with a low rate for the first two months, catching up with males by four months, and then falling behind later in the trial. I'd attribute this variation to random variation in this small subgroup. The imbalance in baseline history of cancers in women treated with prasugrel is interesting. The Cox regression results do not confirm that it is important, although I still wonder if it is contributing to the highly divergent results in women. Overall I don't judge there to be strong evidence for a variable effect by sex.

There is no biologic plausibility for cancers diagnosed shortly after randomization to be related to study drug. There were reasonable numbers of cancer AEs in TAAL in the immediate months following randomization as shown in the incidence plots above. During internal discussions within the Division of the cancer findings in TAAL, we discussed excluding cancers for some short, arbitrary period after randomization to eliminate completely biologically implausible incident cancers. The primary clinical reviewer presents several incidence plots that I generated that exclude cancers diagnosed within the first seven days after randomization. I show such an analysis for all solid new solid cancers, censoring seven cases (4 prasugrel, 3 clopidogrel) diagnosed in the first seven days, in Figure 8.

Figure 8: K-M Incidence Plot for New Solid Cancers (Excluding Skin and Brain) in TAAL



*excluding non-melanoma skin cancers and brain tumors; p = 0.007 by log rank

COMMENT: Not surprisingly, given the superimposed incident curves for the first four months, whether one excludes or includes very early solid cancers makes little difference in the analysis. Because a 7-day (or 14-day, or any length) exclusion is arbitrary, the occurrences of non-study drug related cancers should be reasonably balanced by the randomization, and handling these cases differently breaks the randomization, I would not exclude early cancers from the analyses. The one complicating factor is the possible effect of bleeding that I address next.

The sponsor has argued that the differences may be due to an ascertainment bias: Prasugrel causes more bleeding than clopidogrel at the dosages used in TAAL, so the sponsor hypothesizes that prasugrel caused earlier bleeding of existing cancers leading to increased rates of detection. They hypothesize this effect particularly for gastrointestinal (GI) and genitourinary (GU) cancers, but they also argue that bleeding at any site may lead to a visit or hospitalization that leads to earlier detection of cancers at any site. They have presented a diverse set of tables and graphs alleging to support this hypothesis. The tables are diverse regarding the types of neoplasms included (frequently both malignant and benign), the accuracy of the cancer diagnoses (the sponsor's diagnoses have been refined since the original submission including skin mycoses classified as mycosis fungoides), and the type and severity of bleeding. Bleeding reporting is complicated because there appear to be three sources: (1) bleeds recorded on the AE CRFs; (2) bleeds recorded on the bleeding endpoint CRFs; and (3) some bleeds adjudicated by the Clinical Endpoint Committee (CEC) that are not recorded on the AE or bleeding endpoint CRFs. I can not reproduce all of the sponsor's analyses here, but I will provide my own analyses that are most relevant to this issue and that use the all available data for the cancer events and the bleeding events from all three sources. Because most common bleeds (epistaxis, bruises, etc.) would not initiate a cancer workup, I analyzed bleeds that would be likely to initiate a cancer workup (GI, hemoptysis, hematuria, vaginal, breast) as well as all bleeds and site-specific bleeds.

For patients with new solid cancers, 53% of the prasugrel and 41% of the clopidogrel patients had a preceding bleed of any type. About 32% in each group had a preceding bleed of a type likely to lead to a cancer workup. I show the rates of site-specific prior bleeds for the solid cancers for which bleeding is a common presentation, plus breast cancer because its rates are different in the two treatment groups, in Table 11.

Table 11: New Solid Cancers and Site-Specific Prior Bleeds in TAAL

	new cancers		# with prior site specific bleed		% with prior site specific bleed	
	clopidogrel	prasugrel	clopidogrel	prasugrel	clopidogrel	prasugrel
breast	1	5	0	0	0%	0%
colorectal	9	22	5	12	56%	55%
gi*	19	34	10	17	53%	50%
lung	13	21	0	2	0%	10%
urinary	12	11	8	7	67%	64%
uterine	1	1	1	1	100%	100%

*includes colorectal, stomach, esophagus but not pancreas, liver, gall bladder

COMMENT: In any of the analyses above of new solid cancers and prior bleeding I do not find a strong signal that prasugrel produced an ascertainment bias for detecting new cancers. The sponsor's analyses that suggest such a bias include neoplasms other than solid cancers and benign tumors and the common bleeds such as epistaxis, ecchymoses, and superficial hematomas that are unlikely to lead to a cancer search.

To explore further the hypothesis of ascertainment bias due to bleeding, I performed the following analyses: I show the K-M incident plot for GI/GU cancers in Figure 9, for non-GI/GU cancers in Figure 10, for GI cancers alone in Figure 11, and for GU cancers alone in Figure 12. (For these analyses I have not counted ovarian or testicular cancers as GU cancers or pancreas, gall bladder, or liver cancers as GI cancers because they do not usually present by bleeding.)